ON-LINE APPENDIX

Ovid MEDLINE in-process and other nonindexed citations and Ovid MEDLINE from 1946 to Present (March 9, 2016) are the following:

1) exp Carotid Stenosis/

2) exp Carotid Arteries/

3) Carotid Artery Diseases/

4) (LRNC or ((calcinosis or calcium or calcification or athero$ or steno$ or occlus$ or ulcer$ or plaque$ or intraplaque or h?emorrhag$ or IPH or narrow$ or obstruct$ or constrict$ or bruit$ or lipid or fibrous or culprit or lesion$) adj3 (extracranial or carotid or cerebr$ or brain))).tw.

5) (steno$ occlus$ or stenoocclus$).tw.

6) or/1–5

7) Angiography/

8) Cerebral Angiography/

9) Tomography, X-Ray Computed/

10) (angiograph$ or angiogram$).tw.

11) (comput$ adj3 tomograph$).tw.

12) (CT or CTA or CTCA).tw.

13) or/7–12

14) 6 and 13

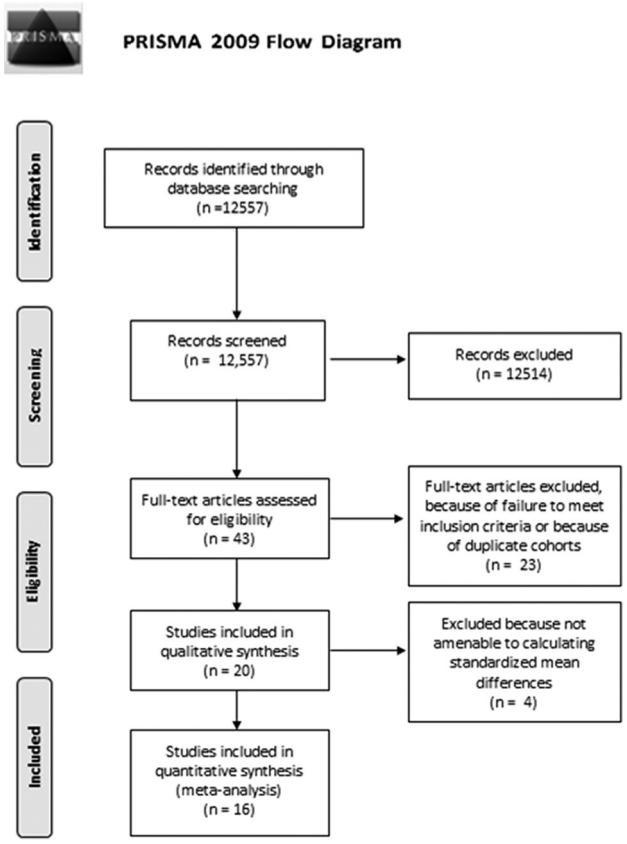
15) limit 14 to "causation-etiology (best balance of sensitivity and specificity)"

16) (animals not (humans and animals)).sh.

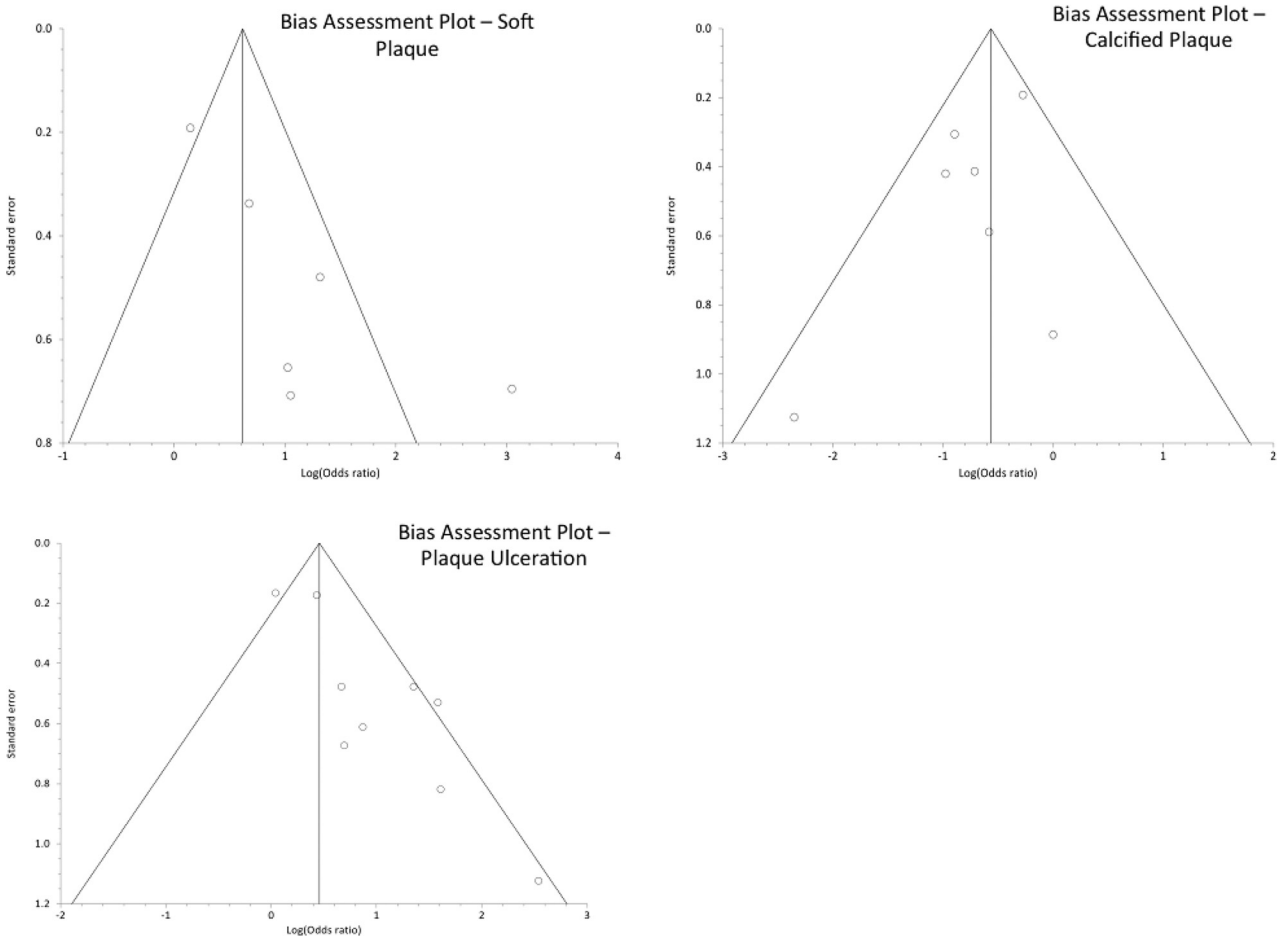
17) 16 not 17

INCLUDED STUDIES

1. Nandalur KR, Baskurt E, Hagspiel KD, et al. **Calcified carotid atherosclerotic plaque is associated less with ischemic symptoms than is noncalcified plaque on MDCT.** *AJR Am J Roentgenol* 2005;184:295 CrossRef Medline
2. Miralles M, Merino J, Busto M, et al. **Quantification and characterization of carotid calcium with multi-detector CT-angiography.** *Eur J Vasc Endovasc Surg* 2006;32:561–67 CrossRef Medline
3. Serfaty JM, Nonent M, Nighoghossian N, et al; CARMEDAS Study Group. **Plaque density on CT: a potential marker of ischemic stroke.** *Neurology* 2006;66:118–20 CrossRef Medline
4. Nandalur KR, Hardie AD, Raghavan P, et al. **Composition of the stable carotid plaque: insights from a multidetector computed tomography study of plaque volume.** *Stroke* 2007;38:935–40 CrossRef Medline
5. Uwatoko T, Toyoda K, Inoue T, et al. **Carotid artery calcification on multislice detector-row computed tomography.** *Cerebrovasc Dis* 2007;24:20–26 CrossRef Medline
6. Saba L, Sanfilippo R, Pascalis L, et al. **Carotid artery wall thickness and ischemic symptoms: evaluation using multi-detector-row CT angiography.** *Eur Radiol* 2008;18:1962–71 CrossRef Medline
7. Wintermark M, Arora S, Tong E, et al. **Carotid plaque computed tomography imaging in stroke and nonstroke patients.** *Ann Neurol* 2008;64:149–57 CrossRef Medline
8. de Weert TT, Cretier S, Groen HC, et al. **Atherosclerotic plaque surface morphology in the carotid bifurcation assessed with multidetector computed tomography angiography.** *Stroke* 2009;40:1334–40 CrossRef Medline
9. Romero JM, Babiarz LS, Forero NP, et al. **Arterial wall enhancement overlying carotid plaque on CT angiography correlates with symptoms in patients with high grade stenosis.** *Stroke* 2009;40:1894–96 CrossRef Medline
10. Saba L, Mallarini G. **Fissured fibrous cap of vulnerable carotid plaques and symptomaticity: are they correlated? Preliminary results by using multi-detector-row CT angiography.** *Cerebrovasc Dis* 2009;27:322–27 CrossRef Medline
11. Saba L, Montisci R, Sanfilippo R, et al. **Multidetector row CT of the brain and carotid artery: a correlative analysis.** *Clin Radiol* 2009;64:767–78 CrossRef Medline
12. Eesa M, Hill MD, Al-Khathaami A, et al. **Role of CT angiographic plaque morphologic characteristics in addition to stenosis in predicting the symptomatic side in carotid artery disease.** *AJNR Am J Neuroradiol* 2010;31:1254–60 CrossRef Medline
13. Hokari M, Kuroda S, Yasuda H, et al. **Lumen morphology in mild-to-moderate internal carotid artery stenosis correlates with neurological symptoms.** *J Neuroimaging* 2011;21:348–54 CrossRef Medline
14. Horie N, Morikawa M, Ishizaka S, et al. **Assessment of carotid plaque stability based on the dynamic enhancement pattern in plaque components with multidetector CT angiography.** *Stroke* 2012;43:393–98 CrossRef Medline
15. Magge R, Lau BC, Soares BP, et al. **Clinical risk factors and CT imaging features of carotid atherosclerotic plaques as predictors of new incident carotid ischemic stroke: a retrospective cohort study.** *AJNR Am J Neuroradiol* 2013;34:402–09 CrossRef Medline
16. Grimm JM, Schindler A, Schwarz F, et al. **Computed tomography angiography vs 3 T black-blood cardiovascular magnetic resonance for identification of symptomatic carotid plaques.** *J Cardiovasc Magn Reson* 2014;16:84 CrossRef Medline
17. Gupta A, Baradaran H, Kamel H, et al. **Evaluation of computed tomography angiography plaque thickness measurements in high-grade carotid artery stenosis.** *Stroke* 2014;45:740–45 CrossRef Medline
18. Gupta A, Mtui EE, Baradaran H, et al. **CT angiographic features of symptom-producing plaque in moderate-grade carotid artery stenosis.** *AJNR Am J Neuroradiol* 2015;36:349–54 CrossRef Medline
19. van Dijk A, Truijman M, Hussain B, et al. **Intraplaque hemorrhage and the plaque surface in carotid atherosclerosis: the Plaque at RISK study (PARISK).** *AJNR Am J Neuroradiol* 2015;36:2127–33 CrossRef Medline
20. Wang P, Wang Y, Zhang G, et al. **Study on the carotid atherosclerotic plaque of patients suffering from ischemic cerebrovascular disease by 64 slices CT.** *Eur Rev Med Pharmacol Sci* 2015;19:3480–85 Medline



ON-LINE FIG 1. Study selection flow diagram adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses group statement.



ON-LINE FIG 2. Funnel plots for 3 of the meta-analyses to evaluate publication bias. On the x-axis, individual study effect sizes expressed as odds ratios are shown, and on the y-axis, the standard of error of each study is shown. Larger and more precise studies are plotted near the top, while smaller, less precise studies are plotted near the bottom, with a wider distribution. Without any publication bias, the studies would be symmetrically distributed on both sides of the pooled odds ratio line.

On-line Table 1: Patient characteristics[a]

Study No.	Study First Author and Year	Study Design	Major Inclusion Criteria	Country	No. of Subjects	No. of Arteries	Mean Age (SD) (yr)	Men (No.) (% male)	Degree of Carotid Stenosis Enrolled (mean)	Type of Controls	HTN (%)	DM (%)	AFIB (%)	CAD (%)	HLD (%)	Smoking History (%)
1	Nandalur 2005[1]	Retrospective	ICA stenosis ≥60% on CTA; patients with restenosis after CEA, non-atherosclerotic causes of stenosis, known cardiac thrombus, or small vessel lacunar infarcts were excluded	United States	31	36	Range, 45–93	18 (58.1)	≥60%	Asymptomatic patients and contralateral arteries	74.2	16.1	NA	48.4	HLD: 67.7; statin use: 54.8	54.8
2	Miralles 2006[2]	Retrospective	Patients scheduled for CTA to evaluate ICA for suspected stenosis of >60%; exclusion criteria: age >80 years, previous ipsilateral CEA, and nonspecific or vertebrobasilar symptoms	Spain	26	26	NA	NA	>60%	Asymptomatic patients	80.8	42.3	NA	38.5	57.7	46.2
3	Serfaty 2006[3]	Prospective	Patients with stenosis degree of >50% on Doppler US	France	141	132	68 (range, 46–94)	53.7	>50% (81.8%)	Asymptomatic patients and contralateral arteries	48.9	21.1	NA	NA	40.1	34.6
4	Nandalur 2007[4]	Retrospective	Inclusion criteria: patients with ≥50% ICA stenosis secondary to atherosclerosis on CTA; exclusion criteria: conflicting causes of neurologic symptoms, previous CEA with restenosis and tandem lesions	United States	102	102	69 (11.2)	62 (60.8)	≥50% (80.3%)	Asymptomatic patients	73.5	27.5	NA	42.2	61.8	54.9
5	Uwatoko 2007[5]	Retrospective	Patients scheduled to have CEA or CAS with the following: 1) carotid stenosis of ≥70%, or 50%–69% with repeat ischemic cerebrovascular events or severe ulcerative atheroma; 2) mRS of ≤2; 3) small or no brain infarction on MRI; and 4) absence of significant occlusive disease (≥70% in diameter) distal to the carotid stenosis	Japan	84	84	70.25 (6.80)	74 (88.1)	≥50% (81.75%)	Asymptomatic patients	69	46.4	NA	NA	34.5	69
6	Saba 2008[6]	Retrospective	Inclusion criteria: a given clinical indication for CTA of ICA; patients with intracranial masses, cardiac thrombus, posterior circulation symptoms, stenosis from nonatherosclerotic causes, or complete occlusion of a carotid vessel were excluded	Italy	217	217	68 (11.2)	158 (72.8)	NA	Asymptomatic patients	66.8	26.3	NA	48.8	59.9	44.7
7	Wintermark 2008[7]	Retrospective	Consecutive patients admitted to the emergency department who had carotid CTA	United States	90	130	66 (16)	77 (56.6)	Any	Asymptomatic patients and contralateral arteries	NA	NA	NA	NA	NA	NA
8	de Weert 2009[8]	Prospective	Consecutive patients with ischemic cerebrovascular disease, including amaurosis fugax or focal cerebral ischemia	the Netherlands	404	808	62 (14)	60%	Any	Asymptomatic patients and contralateral arteries	71	15	NA	26	78	48
9	Romero 2009[9]	Retrospective	Patients with ≥70% ICA stenosis on CTA	United States	75	75	NA	NA	≥70% (81.0%)	Asymptomatic patients	NA	NA	NA	NA	NA	NA
10	Saba 2009 *CVD*[10]	Retrospective	Patients who underwent CTA after a previous Doppler US showing stenosis >50% and/or a plaque alteration	Italy	132	264	64 (range, 37–84)	96 (73)	>50%	Asymptomatic patients and contralateral arteries	38.6	10.6	NA	40.9	NA	NA
11	Saba 2009 *Clin Radiol*[11]	Retrospective	Inclusion criteria: 1) patients with stenosis >70%; 2) symptomatic patients with stenosis >50% with presence, on Doppler US and CTA, of intraplaque hemorrhage, fissuration, or irregular surface; and 3) symptomatic patients with ulceration; exclusion criteria: contraindications to iodinated contrast media, patients with re-stenosis after CEA, tandem lesions, carotid occlusion, or atrial fibrillation	Italy	112	112	69.51 (10.7)	80 (71.4)	>50% and symptomatic patients with ulceration regardless of the degree of stenosis	Asymptomatic patients	63.4	25.9	None	57.1	60.7	58.9

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On-line Table 1: Continued

Study No.	Study First Author and Year	Study Design	Major Inclusion Criteria	Country	No. of Subjects	No. of Arteries	Mean Age (SD) (yr)	Men (No.) (% male)	Degree of Carotid Stenosis Enrolled (mean)	Type of Controls	HTN (%)	DM (%)	AFIB (%)	CAD (%)	HLD (%)	Smoking History (%)
12	Eesa 2010[12]	Retrospective	Patients who presented with hemispheric ischemic symptoms and/or TIA, who also had a CTA that included imaging of both ICAs within 24 hr of admission	Canada	673	1346	65.8 (15.2)	408 (60.6)	Any	Contralateral artery	59.6	16.9	14.1	Recent MI: 1.5	29	35.5
13	Hokari 2011[13]	Prospective	Patients who had >30% ICA stenosis on US or MRA; exclusions: patients with allergy, renal failure, and found to have stenosis ≥70% on CTA	Japan	52	67	71.1 (range, 54–88)	48 (92.3)	30%–69% (52.6%)	Asymptomatic patients and contralateral arteries	NA	NA	NA	NA	NA	NA
14	Horie 2012[14]	Prospective	Patients with >50% carotid stenosis on CTA	Japan	51	59	70.4 (8.72)	46 (90.2)	>50% (77.3%)	Asymptomatic patients and contralateral arteries	78.4	27.5	NA	33.3	Using statins: 56.9	29.4
15	Magge 2013[15]	Retrospective	Patients with suspicion of acute stroke and no history of significant renal insufficiency or contrast allergy undergoing cervical CTA who also had follow-up brain imaging at least 14 days after baseline CTA; patients with remote infarcts in a carotid distribution, a CEA, and diagnoses that predisposed to brain infarcts independent of carotid atherosclerosis were excluded	United States	329	658	64.9 (16.2)	117 (36)	Any	Asymptomatic patients and contralateral arteries	70.8	31.9	NA	NA	56.6	15.8
16	Grimm 2014[16]	Prospective	1) Ischemic stroke <15 days before both CTAs; 2) >50% atherosclerotic plaque in the ICA of the symptomatic side as determined by US	Germany/Switzerland	20	40	69.9 (8.8)	15 (75)	>50%	Contralateral artery	70	20	NA	15	60	Current smoker: 25%; former smoker: 35%
17	Gupta 2014[17]	Retrospective	1) Unilateral high-grade extracranial ICA stenosis (70%–99%) identified on CTA; 2) documentation available in the electronic medical records to determine whether stroke or TIA had occurred before the CTA; 3) detailed medical record documentation of preexisting vascular risk factors; exclusion: complete ICA occlusions	United States	76	76	75.11 (9.16)	48 (63.2)	≥70% (81.96%)	Asymptomatic patients	92.1	17.1	13.2	39.7	85.6	68.6
18	Gupta 2015[18]	Retrospective	1) Moderate-grade (50%–69%) extracranial ICA stenosis as measured on CTA; 2) adequate documentation in the electronic medical records to determine whether stroke or TIA occurred before CTA; 3) detailed medical record of preexisting vascular risk factors	United States	68	72	74.1 (10.5)	60.3	50%–69% (58.3%)	Asymptomatic patients and contralateral arteries	87.5	23.6	27.8	48.6	70.8	57.3
19	van Dijk 2015[19]	Prospective	Patients with a TIA or minor stroke in the ICA territory and a 30%–60% stenosis of the ipsilateral ICA; exclusion criteria: probable cardiac source of embolism, a clotting disorder, severe comorbidity, standard contraindications for MR imaging, a documented allergy to MR imaging or CT contrast agents, or a renal clearance of <30 mL/min	the Netherlands	78	149	67 (9)	57 (73)	30%–69%	Contralateral artery	72.0	24	NA	21	HLD 55%; statin use: 46%	26
20	Wang 2015[20]	Prospective	Patients with carotid atherosclerosis; patients with severe intracranial arterial stenosis, cardiogenic cerebral embolism, and other intracranial primary and secondary diseases excluded	China	100	200	62.48 (5.97)	70 (70%)	Any	Asymptomatic patients and contralateral arteries	65	17	NA	NA	NA	NA

Note:—HTN indicates hypertension; DM, diabetes mellitus; AFIB, atrial fibrillation; CAD, coronary artery disease; HLD, hyperlipidemia; CEA, carotid endarterectomy; NA, not applicable.

[a] References in on-line tables are from the Appendix.

On-line Table 2: CTA protocols

No.	Study First Author and Year	CT Scanner Platform	No. of Rows	Axial Section Thickness	mAs/kV	FOV	Scan Coverage	Contrast Type	Contrast Amount	Bolus-Tracking Used?	Plaque Features Determined on Axial Sections?	Plaque Features Determined on Reformations? If Yes, What Type?	No. of Readers	Reproducibility of Plaque Feature Assessment ICC (95% CI)	If Reproducibility Calculation Was Performed, What Was κ?
1	Nandalur 2005[1]	LightSpeed Ultra and LightSpeed 16[a]	8- and 16-row MDCT scanners	1.25 mm	NA	NA	Aortic arch to supraventricular white matter	Nonionic	120 mL at 4 mL/s	Yes	Yes	No	2	NA	NA
2	Miralles 2006[2]	Somatom Sensation 4[b]	4-row MDCT scanner	1.25 mm	NA	12 cm	C2–C6 level	Nonionic	120 mL at 4 mL/s	NA	No	Semitransparent 3D reconstructions	2	NA	NA
3	Serfaty 2006[3]	NA	In 4 centers: multisection CT; in 1 center: single-section spiral CT	1–1.25 mm or 3 mm	NA	NA	NA	Iodine contrast media	80–100 mL at 3–4 mL/s	NA	Yes	Coronal and sagittal multiplanar reconstruction images	2	0.72 (90.61–0.80)	NA
4	Nandalur 2007[4]	LightSpeed 16	16-section scanner	1.25 mm	350 mAs/120 kV(peak)	NA	Aortic arch to supraventricular white matter	Omnipaque[c] 300	100–125 mL at 4.0–4.5 mL/s	Yes	Yes	Multiplanar reconstructed images	2[h]	0.998–0.999	NA
5	Uwatoko 2007[5]	MultiSpeed Ultra 16x[a]	16-row MDCT scanner	0.625 mm	Auto-mAs/120 kV(p)	NA	NA	Omnipaque 300	3.0 mL/s	NA	Yes	Cross-sectional and longitudinal	2	NA	NA
6	Saba 2008[6]	Somatom Marconi MX8000[b]	4-row MDCT scanner	3.2 mm	180–200 mAs/120–140 kV(p)	11–19 cm	C7 level to as cephalic as possible	Nonionic iodinated	110–130 mL at 4–6 mL/s	No	Yes	No	2	0.923	NA
7	Wintermark 2008[7]	GE Healthcare	16-section CT scanner	0.625 mm	240 mA/120 kV(p)	NA	Midchest to vertex	Omnipaque 300	70 mL at 4 mL/s	Test bolus technique	No	Automated classifier computer algorithm	1	NA	NA
8	de Weert 2009[8]	Sensation 16[b]	16-section MDCT scanner	1.0 mm	180 mAs/120 kV(p)	100 mm	Ascending aorta to the intracranial circulation	320 mg/mL iodixanol	80 mL at 4 mL/s	Yes	No	Multiplanar reformatting software to evaluate in oblique planes	2[h]		$\kappa = 0.84–1$, depending on plaque feature
9	Romero 2009[9]	GE Healthcare	16-section helical scanners	2.5 mm	220–250 mA/140 kV(p)	NA	C6 vertebral body through circle of Willis	Nonionic contrast	100–140 mL at 3 mL/s	No	Yes	No	2	Interobserver agreement: 96%	$\kappa = 0.9$
10	Saba 2009 *CVD*[10]	Somatom[b]; MX8000[d]	4-row MDCT	1.6 mm	180–210 mAs/120 kV(p)	12–19 cm	C7 level to as cephalic as possible	Iopromide, Ultravist 370[e]	100–130 mL at 4–6 mL/s	No	Yes	No	2	Interobserver agreement: 95.45%	$\kappa = 0.781$ (0.660–0.902)
11	Saba 2009 *Clin Radiol*[11]	MX 8000[d]	4-row spiral MDCT	3.2 mm	180–200 mAs/120–140 kV(p)	11–19 cm	C7 level to as cephalic as possible	Iopromide, Ultravist 370	110 mL at 4–6 mL/s	No	Yes	No	2	Interobserver agreement: 91.96%	$\kappa = 0.876$ (0.799–0.954)
12	Eesa 2010[12]	LightSpeed Plus;[a] Somatom Sensation 64[b]	4- and 64-row CT	1.25 mm	NA	NA	Aortic arch to the vertex	NA	90–120 mL at 5 mL/s	Yes	Yes	Coronal and sagittal	2	NA	NA
13	Hokari 2011[13]	LightSpeed VCT[a]	64-section CT scanner	0.625 mm	240 mA/120 kV(p)	NA	Midchest to the vertex	Iopamidol 300,[f] Omnipaque 300	240 mg/kg at 20 mg I/kg/s	Test bolus technique	No	Reformatted axial images, maximum intensity projections, vessel analysis software	1	NA	NA
14	Horie 2012[14]	Aquilion 64[g]	64-row MDCT	0.5 mm	300 mA/120 kV(p)	15 cm	Aortic arch to head	Iohexol, Omnipaque	70 mL at 3.5 mL/s	Yes	Yes	No	2	NA	NA
15	Magge 2013[15]	GE Healthcare	16- and 64-row CT	0.625 mm	240 mA/120 kV(p)	NA	Midchest to the vertex	Iohexol, Omnipaque	70 mL at 4 mL/s	Test bolus technique	No	CT-based automated classifier computer algorithm	1	NA	NA

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On-line Table 2: Continued

No.	Study First Author and Year	CT Scanner Platform	No. of Rows	Axial Section Thickness	mAs/kV	FOV	Scan Coverage	Contrast Type	Contrast Amount	Bolus-Tracking Used?	Plaque Features Determined on Axial Sections?	Plaque Features Determined on Reformations? If Yes, What Type?	No. of Readers	Reproducibility of Plaque Feature Assessment ICC (95% CI)	If Reproducibility Calculation Was Performed, What Was κ?
16	Grimm 2014[16]	Bright Speed S (GE), Aquilion (Toshiba), Somatom Definition Flash and Somatom Definition AS+ and Sensation 64 (All Siemens)	NA	0.625 mm	NA	NA	Aortic arch to cranium	Nonionic iodinated contrast	0.35–0.50 g iodine per kg at 4.5–6 mL/s	NA	Yes	Volume-rendered reconstructed images	2	NA	NA
17	Gupta 2014[17]	LightSpeed Pro-16 or HD-750[a]	16-row helical scanner	0.625 mm	Auto-mAs/120 kV(p)	NA	Aortic arch to C1 ring	Nonionic iodinated contrast	90 mL at 4–5 mL/s	Yes	Yes	No	2[h]	Interreader correlation coefficients = 0.93, 0.91, and 0.88	NA
18	Gupta 2015[18]	LightSpeed Pro-16 or HD-750[a]	16-row helical scanner	0.625 mm	Auto-mAs/120 kV(p)	NA	Aortic arch to C1 ring	Nonionic iodinated contrast	90 mL at 4–5 mL/s	Yes	Yes	No	2[h]	Interreader correlation coefficients = 0.96–0.97	NA
19	van Dijk 2015[19]	NA	16-, 64-, or 128-section MDCT	1.0 mm	150–180 mAs/120 kV(p)	120–160 mm	Ascending aorta to the intracranial circulation	Iodinated contrast agent (300–320 mg/mL)	80–85 mL at 4–5 mL/s	Yes	Yes	Multiplanar reformatting; oblique, coronal, and sagittal planes	2 with 3rd reader resolving discrepancies	Yes	$\kappa = 0.46$
20	Wang 2015[20]	GE Healthcare	64-section CT scanner	0.625 mm	200–230 mAs/100–120 kV(p)	NA	Aortic arch to calvarium	350 g/L nonionic contrast agent iohexol[c]	80 mL at 4.5–5 mL/s	Yes	Yes	No	2	NA	NA

Note:—NA indicates data not available; MDCT, multidetector CT; ICC, intraclass coefficient.

[a] GE Healthcare, Milwaukee, Wisconsin.

[b] Siemens.

[c] Iohexol; GE Healthcare, Piscataway, New Jersey.

[d] Philips Healthcare, Best, the Netherlands.

[e] Bayer HealthCare, Berlin, Germany.

[f] Isovue; Bracco, Princeton, New Jersey.

[g] Toshiba Medical Systems, Tokyo, Japan.

[h] Two independent readers were used with one evaluating a subset of the total number of arteries analyzed.

On-line Table 3: Clinical definitions for ischemic stroke and transient ischemic attack

Study No.	Study First Author and Year	Ischemic Stroke Definition	Transient Ischemic Attack Definition	How Was Symptomatic Status Adjudicated?
1	Nandalur 2005[1]	An episode of neurologic dysfunction, such as hemiparesis, hemiparesthesia, dysarthria, dysphagia, or monocular blindness, caused by focal brain or retinal ischemia with persistent clinical signs/symptoms and imaging characteristics, also attributed to carotid disease	A brief episode of neurologic dysfunction, such as hemiparesis, hemiparesthesia, dysarthria, dysphagia, or monocular blindness, caused by focal brain or retinal ischemia and without evidence of acute infarction appropriate to carotid disease	NA
2	Miralles 2006[2]	NA	NA	NA
3	Serfaty 2006[3]	A carotid artery was considered symptomatic only if the patient had ipsilateral symptoms	A carotid artery was considered symptomatic only if the patient had ipsilateral symptoms	Senior neurologist adjudicated symptomatic status with relation to each carotid artery
4	Nandalur 2007[4]	An episode of neurologic dysfunction, such as hemiparesis, hemiparesthesia, dysarthria, dysphagia, or monocular blindness caused by focal brain or retinal ischemia with persistent clinical signs/symptoms and imaging characteristics, also appropriate to carotid disease	A brief episode of neurologic dysfunction, such as hemiparesis, hemiparesthesia, dysarthria, dysphagia, or monocular blindness caused by focal brain or retinal ischemia and without evidence of acute infarction appropriate to carotid disease	NA
5	Uwatoko 2007[5]	Symptomatic ischemic stroke in the territory of the affected carotid artery in the preceding 6 mo	TIA or transient monocular blindness in the territory of the affected carotid artery in the preceding 6 mo	NA
6	Saba 2008[6]	If the episode of neurologic dysfunction lasted >24 hr, the ischemic neurologic episode was classified as stroke	TIA was defined as a brief (<24 hr) episode of neurologic dysfunction, such as dysarthria, dysphasia, hemiparesis, hemiparesthesia, or monocular blindness	Patient medical records were reviewed by 1 observer trained to identify ischemic stroke based on neurologic symptoms and neurologic charts
7	Wintermark 2008[7]	Patients with carotid stroke were defined as those who had an acute infarct in a carotid distribution and the likely mechanism of stroke was large-artery atherosclerosis	NA	On the basis of review of the imaging studies by a neuroradiologist, degree of carotid stenosis, and test results available in patients' charts, patients were categorized as "patients with carotid stroke" if they had an acute infarct in a carotid distribution and the likely mechanism of stroke was large-artery atherosclerosis
8	de Weert 2009[8]	An ischemic stroke was defined as a sudden focal neurologic deficit confined to an area of the brain perfused by a specific artery that lasted 24 hr or that was accompanied by a relevant infarct on the CT	TIA was defined as a sudden, focal neurologic deficit that was presumed to be of vascular origin and was confined to an area of the brain perfused by a specific artery and that lasted 24 hr without a relevant infarct (one that explains the deficit) on CT; amaurosis fugax was defined as sudden, focal neurologic deficit that was presumed to be of vascular origin and confined to the eye	NA
9	Romero 2009[9]	Anterior circulation stroke ipsilateral to the stenosed carotid artery, based on clinical presentation and positive DWI or CT findings at follow-up within 1 mo of CTA	Anterior circulation TIA ipsilateral to the stenosed carotid artery, based on clinical presentation within 1 mo of CTA	Diagnosis of stroke was based on admission clinical presentation and positive DWI or CT findings at follow-up
10	Saba 2009 *CVD*[10]	If the episode of neurologic dysfunction lasted >24 hr, the ischemic neurologic episode was classified as stroke	TIA was defined as a brief (<24 hr) episode of neurologic dysfunction, such as dysarthria, dysphasia, hemiparesis, or hemiparesthesia; amaurosis fugax was defined as acute onset of transient, partial, or complete monocular loss of vision	NA

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On-line Table 3: Continued

Study No.	Study First Author and Year	Ischemic Stroke Definition	Transient Ischemic Attack Definition	How Was Symptomatic Status Adjudicated?
11	Saba 2009 *Clin Radiol*[11]	If the episode of neurologic dysfunction lasted >24 hr, the ischemic neurologic episode was classified as stroke	TIA was defined as a brief (<24 hr) episode of neurologic dysfunction, such as dysarthria, dysphasia, hemiparesis, hemiparesthesia, or monocular blindness	NA
12	Eesa 2010[12]	Hemispheric ischemic symptoms	TIA including amaurosis fugax	By stroke neurologist; a baseline NIHSS score was documented on admission
13	Hokari 2011[13]	Stroke in the territory of ipsilateral ICA within 6 mo of CTA imaging	TIA, including amaurosis fugax in the territory of ipsilateral ICA within 6 mo of CTA	NA
14	Horie 2012[14]	Anterior circulation stroke within 2 wk of radiologic evaluation with consistent clinical presentation at admission and positive DWI findings	Transient symptoms in anterior circulation within 2 wk of radiologic evaluation	Based on clinical presentation at admission and positive DWI findings at follow-up
15	Magge 2013[15]	Acute infarction in a patient in whom carotid stenosis was likely etiology for stroke via stroke classification	NA	Patients who developed a brain infarct in a carotid distribution on follow-up brain imaging that was not present on the baseline brain CT were considered symptomatic patients with "carotid infarcts"
16	Grimm 2014[16]	Acute lesion on DWI with a corresponding acute neurologic deficit of >24-hr duration ipsilateral to carotid stenosis	NA	Carotid artery was classified as symptomatic if the artery was ipsilateral to the DWI lesion
17	Gupta 2014[17]	Permanent episode of neurologic dysfunction caused by focal brain or retinal ischemia	Transient episode of neurologic dysfunction caused by focal brain or retinal ischemia	History of ipsilateral TIA or stroke and preexisting vascular risk factors were determined by the consensus of 2 stroke neurologists after a detailed examination of the electronic medical record
18	Gupta 2015[18]	Permanent episode of neurologic dysfunction caused by focal brain or retinal ischemia	Transient episode of neurologic dysfunction caused by focal brain or retinal ischemia	History of ipsilateral TIA or stroke and preexisting vascular risk factors were determined by the consensus of 2 study investigators after a detailed examination of the electronic medical record, with any disagreements in assessment resolved by consensus
19	van Dijk 2015[19]	Minor strokes were defined as episodes of temporary and focal cerebral dysfunction of vascular origin, lasting for >24 hr or a nondisabling stroke with a mRS score of ≤3	TIA was defined as an episode of temporary and focal cerebral dysfunction of vascular origin, lasting for a maximum of 24 hr, leaving no persistent neurologic deficits; amaurosis fugax was defined as a sudden loss of vision of presumed vascular origin and confined to 1 eye	NA
20	Wang 2015[20]	Acute cerebral infarction in the distribution of the carotid artery	TIA in the distribution of the carotid artery	NA

Note:—NA indicates not applicable.

On-line Table 4: Test characteristics for plaque features that could not be included in the meta-analysis

Study No.	Study First Author and Year	Plaque Feature	Mean (SD) Ipsilateral to Symptoms	No. of Vessels Ipsilateral to Symptoms	Mean (SD) Vessels Contralateral to Symptoms	No. of Vessels Contralateral to Symptoms
1	Nandalur 2005[1]					
2	Miralles 2006[2]	HU	401.92 (359.92)	13	686.92 (234.76)	13
3	Serfaty 2006[3]					
4	Nandalur 2007[4]	Calcified plaque (mm^3)	76 (69)	35	114 (118)	67
		Noncalcified plaque (mm^3)	510 (486)	35	334 (333)	67
5	Uwatoko 2007[5]					
6	Saba 2008[6]					
7	Wintermark 2008[7]	Calcium volume (mm^3)	20.4 (7.3)	40	21.0 (6.1)	50
		Lipid volume (mm^3)	24.9 (3.1)	40	13.9 (3.5)	50
8	de Weert 2009[8]					
9	Romero 2009[9]					
10	Saba 2009 *CVD*[10]					
11	Saba 2009 *Clin Radiol*[11]					
12	Eesa 2010[12]					
13	Hokari 2011[13]					
14	Horie 2012[14]	HU (early phase)	53.0 (19.4)	33	59.2 (19.7)	18
15	Magge 2013[15]	Volume of calcium (mm^3)	89.57 (4.17)	14	79.37 (64.28)	14
		Volume of lipids (mm^3)	15.79 (13.36)	14	13.43 (11.60)	14
16	Grimm 2014[16]	Calcification volume (mm^3)	0.0820 (0.159)	20	0.0735 (0.077)	18
		HU	48.9 (15.6)	20	61.8 (15.6)	18
17	Gupta 2014[17]	Soft-plaque thickness	4.51 (1.46)	42	2.01 (1.65)	34
		Hard-plaque thickness	2.10 (1.22)	42	3.25 (1.51)	34
		HU	48.6 (33.5)	42	47.4 (24.7)	34
18	Gupta 2015[18]	Soft-plaque thickness	3.45 (1.54)	20	1.41 (0.97)	52
		Hard-plaque thickness	1.19 (0.92)	20	2.69 (1.04)	52
19	van Dijk 2015[19]	Calcium volume (mm^3)	24.2	78	17.2	71
20	Wang 2015[20]					

On-line Table 5: Study plaque definitions

Study No.	Study First Author and Year	Abnormal Plaque Feature	Definition of Abnormal Plaque Feature
1	Nandalur 2005[1]	Soft plaque	Median density of ≤50 HU
		Calcified plaque	Median density >130 HU
2	Miralles 2006[2]	HU	Threshold of calcium density = 420 HU
3	Serfaty 2006[3]	Calcified plaque	Calcified plaque present
4	Nandalur 2007[4]	Calcified plaque (mm^3)	Plaque area was calculated by subtracting lumen area from outer vessel wall cross-sectional area for each section, then multiplying by section increment; calcified volume was determined by manually tracing calcified plaque on each section then multiplying by section increment
		Noncalcified plaque (mm^3)	Noncalcified volume was calculated by subtracting calcified volume from total volume
5	Uwatako 2007[5]	Carotid calcification volume (cm^3)	Calcified area was calculated for 7 axial 15-mm-thick sections around the bifurcation; the volume of calcification was determined by multiplying the calcified area by section thickness
6	Saba 2008[6]	Carotid artery wall thickness	Wall thickness of the CCA was measured at its thickest point on the distal wall of the CCA, where there was no evidence of plaque between the leading edge of the opacified lumen vessel and the external visible limit of artery wall
7	Wintermark 2008[7]	Plaque ulceration	Concave irregularities in contour of the carotid lumen
		Calcium volume (mm^3)	Computer algorithm that segments inner and outer contours of carotid artery wall distinguished histologic components with HU thresholds
		Lipid volume (mm^3)	Computer algorithm that segments inner and outer contours of carotid artery wall distinguished histologic components with HU thresholds
8	de Weert 2009[8]	Plaque ulceration	Plaques were classified as ulcerated if extension of contrast material was present beyond the vascular lumen into surrounding plaque
9	Romero 2009[9]	Carotid wall enhancement	Carotid wall enhancement present if >50% of carotid wall circumference enhanced at the level of maximum stenosis; a minimum mean difference of >10 HU between enhancing 50% of the target ICA wall circumference and contralateral ICA wall
10	Saba 2009 *CVD*[10]	Fissured fibrous cap	Fissured fibrous cap was defined as the following: 1) the presence of an "in plus" image, 2) whose dimension was <1 mm in depth with 3) an angle of ≥230° with the lumen, and 4) presence of atherosclerotic plaque into which the in plus image projects
11	Saba 2009 *Clin Radiol*[11]	Fatty plaques	Plaque with a density value <50 HU
		Calcified plaques	Plaque with a density value <120 HU
12	Eesa 2010[12]	Hypodense plaque	Hypoattenuated
		Plaque ulceration	Ulcerated plaque
		Extensive calcification	Extensive calcification within plaque
13	Hokari 2011[13]	Plaque ulceration	Presence of large, obvious excavations and/or plaque with multiple cavities or a cavernous appearance on CTA MIP images of luminal sagittal reconstruction view
		Lumen morphology	Lumen morphology at the level of maximal stenosis identified on reformatted axial image at maximum stenotic level; the shape was classified into 4 types: circular, elliptical, crescentic, and multilobular; regular lumen = circular or elliptical; irregular lumen = crescentic or multilobular
14	Horie 2012[14]	Plaque ulceration	Outpouching of contrast into the plaque at least 2 mm deep on CTA
		HU	Mean HU in the ROI at 3 axial sections, including the most stenotic site and 3 mm proximally and 3 mm distally, was measured at 2 phases (early and delayed phases), excluding severely calcified portions of plaque
15	Magge 2013[15]	Carotid artery wall thickness	Computer algorithm segment inner and outer contours of carotid artery wall; maximum wall thickness measured as greatest distance from lumen-intima interface to outer edge of adventitia
		Lipid cluster maximal size (mm^3)	Computer algorithm that segments inner and outer contours of carotid artery wall distinguished histologic components with HU thresholds
		Calcium cluster maximal size (mm^3)	Computer algorithm that segments inner and outer contours of carotid artery wall distinguished histologic components with HU thresholds
16	Grimm 2014[16]	Calcified plaque	Average HU for noncalcified plaques associated with lipid-rich necrotic core was <60 HU; calcified plaques had average of >130 HU
		Noncalcified plaque	
		Calcification volume (mm^3)	Calcification volume calculated with standard plug-in on syngo MultiModality Workplace[a]
		Plaque ulceration	Outpouching of contrast material into or adjacent to the plaque of ≥1 mm

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On-line Table 5: Continued

Study No.	Study First Author and Year	Abnormal Plaque Feature	Definition of Abnormal Plaque Feature
17	Gupta 2014[17]	Soft-plaque thickness	Maximum thickness of noncalcified plaque component on CTA axial section with greatest luminal narrowing
		Hard-plaque thickness	Maximum thickness of calcified plaque component on CTA axial section with greatest luminal narrowing
		HU	HU calculated from a ≥2-mm circular ROI placed within the noncalcified portion of the plaque on plaques >2 mm
18	Gupta 2015[18]	Soft-plaque thickness	Maximum thickness of noncalcified plaque component on CTA axial sections on which luminal-diameter stenosis was greatest
		Hard-plaque thickness	Maximum thickness of calcified plaque component on CTA axial sections on which luminal-diameter stenosis was greatest
19	van Dijk 2015[19]	Plaque ulceration	Extension of contrast material of >1 mm into atherosclerotic plaque on at least 2 orthogonal planes
		Calcium volume (mm^3)	Calculated with a custom-made plug-in for ImageJ software[b] threshold of 600 HU used to differentiate calcifications from luminal contrast material
20	Wang 2015[20]	Fatty plaque	Low-density area within plaque with <50 HU
		Calcified plaque	HU within plaque >120 HU
		Plaque ulceration	Ulcerated plaque

Note:—CCA indicates common carotid artery; *CVD*, *Cerebrovasc Dis*; *Clin Radiol*, *Clinical Radiology*.

[a] Siemens, Erlangen, Germany.

[b] National Institutes of Health, Bethesda, Maryland.

On-line Table 6: Test characteristics

No.	Study Author and Year	Plaque Feature	Overall Prevalence of Abnormal Plaque Feature by Artery (%)	No. of Arteries with Examined Plaque Feature with Ipsilateral Symptoms	No. of Arteries with Ipsilateral Symptoms without Examined Plaque Feature	No. of Arteries with Examined Plaque Feature without Ipsilateral Symptoms	No. of Arteries without Examined Plaque Feature without Ipsilateral Symptoms
1	Nandalur 2005[1]	Soft plaque	14/36 (38.9)	8	7	6	15
		Calcified plaque	10/36 (27.8)	1	14	9	12
2	Miralles 2006[2]						
3	Serfaty 2006[3]	Calcified plaque	26/134 (19.7)	4	26	22	80
4	Nandalur 2007[4]						
5	Uwatoko 2007[5]	Carotid calcification volume (cm^3)	78/84 (93)	15	85	15	32
6	Saba 2008[6]	CAWT	93/217 (42.9)	68	31	25	93
7	Wintermark 2008[7]	Plaque ulceration	28/80 (35.0)	17	23	11	29
8	de Weert 2009[8]	Plaque ulceration	21.3	89	261	83	375
9	Romero 2009[9]	Carotid wall enhancement	27/75 (36)	19	19	8	29
10	Saba 2009 *CVD*[10]	Plaque ulceration	30/264 (11.4)	12	24	11	85
11	Saba 2009 *Clin Radiol*[11]	Fatty plaques	43/112 (38.4)	36	40	7	29
		Calcified plaques	43/112 (38.4)	25	51	18	18
12	Eesa 2010[12]	Hypodense plaque	8.92	64	609	56	617
		Plaque ulceration	12.4	85	588	82	591
		Extensive calcification	8.92	53	620	68	605
13	Hokari 2011[13]	Plaque ulceration	27/67 (40.3)	8	6	19	34
		Lumen morphology	15/67 (22.4)	8	6	7	46
14	Horie 2012[14]	Plaque ulceration	16/51 (31.4)	12	21	4	14
15	Magge 2013[15]	CAWT	66.7%	10	2	50	28
16	Grimm 2014[16]	Calcified plaque	6/40 (15)	3	17	3	17
		Noncalcified plaque	19/40 (47.5)	12	8	7	13
		Plaque ulceration	9/40 (22.5)	8	12	1	19
17	Gupta 2014[17]	Soft-plaque thickness	52/76 (68.4)	39	3	13	21
18	Gupta 2015[18]						
19	van Dijk 2015[19]	Plaque ulceration	26/149 (17)	21	57	5	66
20	Wang 2015[20]	Fatty plaques	28.5	40	73	17	61
		Calcified plaques	74/200 (37)	34	79	40	38
		Plaque ulceration	10/200 (5)	8	88	2	102

Note:—CAWT indicates carotid artery wall thickness.

On-line Table 7: Risk of bias question results

Questions	Nandalur 2005[1]	Serfaty 2006[3]	Uwatoko 2007[5]	Saba 2008[6]	Wintermark 2008[7]	de Weert 2009[8]	Saba 2009 *CVD*[10]	Saba 2009 *Clin Radiol*[11]	Eesa 2010[12]	Hokari 2011[13]	Horie 2012[14]	Magge 2013[15]	Grimm 2014[16]	Gupta 2014[17]	van Dijk 2015[19]	Wang 2015[20]
Was the study sample prospectively selected to minimize the risk of selection bias?	−	+	−	−	−	+	−	−	−	+	+	−	+	−	+	+
Were the inclusion and exclusion criteria adequately described?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Was the primary objective of the study to assess whether the examined plaque feature was associated with ischemic presentations?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Were the investigators blinded to the location of the infarction or symptomatic status during carotid plaque evaluation?	+	+	+	+	+	NA	+	+	+	+	+	+	+	+	+	+
Did >1 investigator assess the presence of the plaque feature?	+	+	+	+	−	+	+	+	+	−	+	−	+	+	+	+
Was a measure of interreader reproducibility for plaque feature description reported?	−	+	−	+	−	+	+	+	−	−	−	−	−	+	+	−
Was the comparison of plaque features made with the asymptomatic, contralateral side?	+	+	−	−	+	+	+	−	+	+	+	+	+	−	+	+
Were plaque features corrected for degree of stenosis?	−	+	+	−	+	+	−	+	+	+	−	+	−	+	−	−

Note:—+ indicates that the answer is yes; − indicates that the answer is no; NA, not applicable.