

# Prevalence of carotid webs in patients with acute ischemic stroke due to intracranial large vessel occlusion

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## ABSTRACT

**Background and purpose** To investigate the prevalence of symptomatic carotid web in patients with acute ischemic stroke due to intracranial large vessel occlusion, to determine the clinical and imaging profile of patients with carotid web as well as their association with ischemic stroke, and to determine the interobserver agreement in the assessment of carotid webs.

**Methods** All patients (n=500) of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) in whom the carotid bifurcation could be assessed (n=443) were included. The presence of a carotid web at the carotid bifurcations was evaluated at computed tomographic (CT) angiography. Demographics, clinical characteristics, and imaging baseline characteristics were presented by descriptive statistics for patients with an identified carotid web. Interobserver agreement in the detection of carotid webs was examined by using kappa statistics.

**Results** Eleven (2.5%) carotid webs were found at the symptomatic side and two (0.5%) carotid webs were found at the asymptomatic side. Ten (91%) patients with a symptomatic carotid web were female. Nine patients with a symptomatic carotid web did not have major risk factors or other causes for ischemic stroke (82%). Fair to good interobserver agreement ( $\kappa$  0.72) was observed for diagnosing carotid webs at CT angiography.

**Conclusion** Carotid webs at the symptomatic carotid bifurcation were observed in 2.5% of the patients with acute ischemic stroke due to large vessel occlusion and were mostly diagnosed in female patients with a fair to good interobserver agreement.

## INTRODUCTION

Identification of the cause of acute ischemic stroke is important for treatment and secondary prevention<sup>1,2</sup>. However, in 14%–36% of patients with acute ischemic stroke, the cause of stroke cannot be identified<sup>1,3-5</sup>. Previous research showed that patients who have sustained cryptogenic ischemic stroke have a cumulative risk of 21.3% of recurrent ischemic stroke after first-ever stroke after 20 years of follow-up<sup>6</sup>. This finding suggests that the underlying cause persists.

Earlier studies showed sex differences in acute ischemic stroke. Female patients have a less favorable functional outcome after ischemic stroke, and also after adjustment for age, than do male patients<sup>7-9</sup>. These findings emphasize the importance of identifying the cause of ischemic stroke to further optimize stroke management. In several recent case series, carotid webs were identified as a possible cause of ischemic stroke in a predominantly female population<sup>10,11</sup>.

Radiologically, carotid webs are thin, circumferential filling defects arising from the posterior wall of the proximal internal carotid artery bulb at computed tomographic (CT) angiography<sup>10,12,13</sup>. Histologic examination of carotid webs shows fibrous intimal hyperplasia without atherosclerotic characteristics. Carotid webs are often diagnosed as either atypical or intimal fibromuscular dysplasia without evidence of fibromuscular dysplasia in other vessels<sup>10,11,14</sup>. In previous case series, carotid webs have been related to recurrent ischemic strokes especially in young female patients, possibly caused by the altered hemodynamic patterns they induce<sup>10-12,14</sup>. The same studies also found no other major risk factors or causes of acute ischemic stroke suggesting that a carotid web could be a cause of ischemic stroke.

The association between large vessel occlusions and carotid webs at the symptomatic carotid bifurcation is still unclear. Previous studies distinguished between carotid webs and small protruding lesions<sup>10</sup>. These protruding lesions are the main differential diagnosis of carotid webs and appear less prominent than do carotid webs at CT angiography. They are smaller and assumed to be less thrombogenic than are carotid webs<sup>10</sup>. The interobserver agreement in identifying a carotid web or a small protruding lesion has not been evaluated.

The primary aim of this study was to investigate the prevalence of symptomatic carotid web in patients with acute ischemic stroke due to intracranial large vessel occlusion. The secondary aim was to determine the clinical and imaging profile of patients with carotid web as well as their association with ischemic stroke. Our final aim was to determine the interobserver agreement in the assessment of carotid webs.

## MATERIAL AND METHODS

### Patients

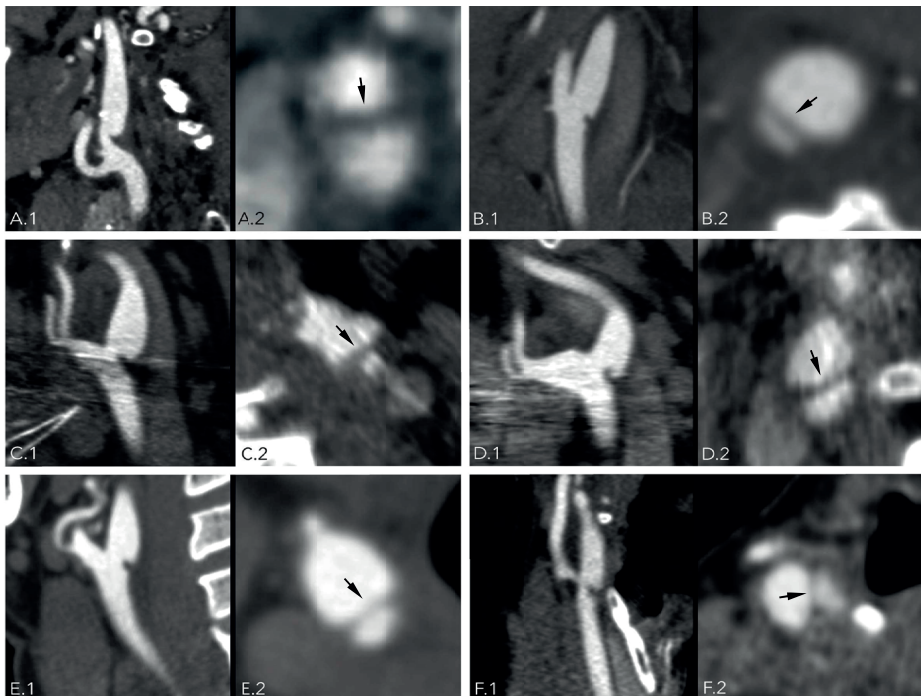
Data of the 500 patients from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) was used. The study protocol was approved by a central medical ethics committee and the research board of each participating center. All patients or their legal representatives provided written informed consent. Included patients were age 18 years or older, had a minimal score of 2 on the National Institutes of Health Stroke Scale at baseline, and had a radiologically confirmed proximal intracranial arterial occlusion. Intra-arterial treatment (intra-arterial thrombolysis, mechanical treatment, or both) had to be possible within 6 hours after stroke onset<sup>15</sup>. Patients with a carotid dissection or extracranial occlusion were not excluded. Treatment was randomly assigned between patients to intra-arterial treatment plus usual care or usual care only. Usual care could include intravenous alteplase before inclusion. Patients were excluded from the present study if CT angiograms were missing (n=3); if the carotid bifurcation was not scanned (n=24); if CT angiograms were of poor quality because of technical artifacts, movements artifacts, or poor contrast supply (n=28); or in case of a carotid stent (n=2). The remaining patients (n=443) were included in the current study (Suppl. Figure 1).

### Clinical and radiological data

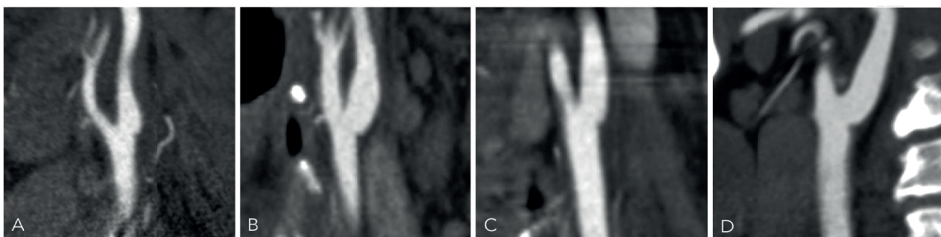
Demographics and clinical information were obtained and have been described previously<sup>15</sup>. The presence of atrial fibrillation was evaluated by using clinical information or electrocardiogram during hospitalization. Patients with a carotid web or protruding lesion at the symptomatic side were additionally evaluated for the identification of other potential causes of ischemic stroke according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria<sup>16</sup>. Carotid bifurcations at CT angiography were evaluated with respect to the presence of carotid webs and small protruding lesions in multiplanar reconstruction view. Carotid webs were defined as thin, linear filling defects arising from the posterior wall of the proximal internal carotid artery bulb at sagittal CT angiography as described previously<sup>10,11</sup>. A carotid web was confirmed if a septum was also seen at axial CT angiography (Figure 1). If an axial septum could not be visualized, then the lesion was classified as a small protruding lesion<sup>10</sup> (Figure 2).

An experienced neuroradiologist (B.E., with 7 years of experience with carotid CT angiography) evaluated the presence or absence of carotid webs or small protruding lesions in the symptomatic as well as the asymptomatic carotid bifurcation at baseline CT angiography. Carotid bifurcations with high-grade stenosis (>50% according to North American Symptomatic Carotid Endarterectomy Trial criteria) or occlusion were considered as arteries without a carotid web or small protruding lesion<sup>17</sup>. Patients with

a carotid web or protruding lesion were additionally evaluated for the presence of atherosclerotic calcification in the extra- and intracranial arterial vessels, namely, the aortic arch, brachiocephalic artery, right common carotid artery, right carotid bifurcation, right extracranial internal carotid artery, right intracranial internal carotid artery, left common carotid artery, left carotid bifurcation, left extracranial internal carotid artery, and left intracranial internal carotid artery. The bifurcation was defined as 3 cm below and above the branch. In addition, we evaluated the extracranial carotid arteries of patients with a carotid web and small protruding lesions for radiologic features of fibromuscular dysplasia such as string of beads sign, S curves, and 360° loops.



**Figure 1: A–F.** Sagittal and axial CT angiograms of six carotid webs in the carotid bifurcation. Arrows in the internal carotid artery indicate the carotid web.



**Figure 2: A–D.** Sagittal CT angiograms of small protruding lesions in the carotid bifurcation.

## Interobserver agreement

To assess interobserver agreement in identifying carotid webs, a second experienced neuroradiologist (A.v.E., with 4 years of experience with carotid CT angiography) independently analyzed all patients with a carotid web or small protruding lesion, as well as an extra data set of 50 randomly selected CT angiograms. The random selection was taken from CT angiograms with an extracranial carotid artery without dissection, high-grade stenosis (>50%), or occlusions and severe calcifications (upper quartile of volume of calcification) at the symptomatic bifurcation. This was done to ensure that the randomly selected CT angiograms did not include obvious cases regarding the absence of webs or protruding lesions. Both observers were not blinded for the symptomatic side because this information could be extracted from the CT angiogram.

## Statistical analysis

Demographic data and clinical information were presented as medians and interquartile ranges because of a nonnormal distribution. Differences in baseline values between patients with and patients without a carotid web or protruding lesion at the symptomatic carotid bifurcation were tested with the Fisher exact test or Mann-Whitney U test. Conditional logistic regression was used to compare the proportion of carotid webs at the symptomatic and asymptomatic bifurcation. The 95% confidence interval (CI) and corresponding odds ratio were calculated by using the "survival" package (version 2.38–3) of R statistical software (version 3.2.3; Foundation for Statistical Computing, Vienna, Austria). Cohen kappa ( $\kappa$ ) statistic was used to define the level of interobserver agreement in the identification of carotid webs at the carotid bifurcation and square-weighted Cohen kappa value was calculated for evaluating the ordering in small protruding lesions and carotid webs with the use of the "IRR" package (version 0.84). A two-sided p-value <0.05 was considered to indicate statistical significance.

## RESULTS

### Prevalence, demographics and imaging characteristics of carotid webs

We found 11 (2.5%; 95% CI: 1.3%, 4.5%) carotid webs at the symptomatic bifurcation and two carotid webs (0.5%; 95% CI: 0.08%, 1.8%) at the asymptomatic bifurcation (odds ratio, 10; 95% CI: 1.28, 78.12; p 0.028). One patient had a carotid web both at the symptomatic and asymptomatic bifurcation (case 8; Figure 1, C and D). None of the webs were treated.

As shown in Table 1, carotid webs in the symptomatic carotid artery were significantly more often observed in female patients (n=10) than in male patients (n=1; p <0.001) and more prevalent in the symptomatic carotid artery at the right side (p 0.03). The

median age (59 years; interquartile range, 46–67 years) of patients with a carotid web at the symptomatic carotid bifurcation did not differ significantly ( $p$  0.08) from patients without a carotid web at the symptomatic carotid bifurcation. Smoking and diabetes were not observed in patients with a carotid web. A description of all patients with a carotid web can be found in Table 2. In our data, one patient with a carotid web at the symptomatic side had a history of ischemic stroke in the ipsilateral hemisphere and was undergoing antiplatelet treatment (case 1). However, no possible cause of stroke could be observed during the previous and current stroke. In total, nine patients with a symptomatic carotid web did not have major risk factors or other causes for ischemic stroke according to the TOAST criteria (82%). In two patients, medium and high cardio-embolic risk factors for acute ischemic stroke were identified.

**Table 1.** Demographics and clinical characteristics

	Patients without carotid web at symptomatic side (n=432)	Patients with carotid web at symptomatic side (n= 11)	P-value
Age (median [IQR])	66 [56 – 76]	59 [46 – 67]	0.08
Sex (male)	260 (58.7%)	1 (9.1%)	<0.001
Left-hemisphere stroke	230 (51.9%)	2 (18.2%)	0.03
History of ischemic stroke	45 (10.2%)	1 (9.1%)	1.00
Smoking	124 (28%)	0	0.04
Diabetes	56 (12.6%)	0	0.37
Atrial fibrillation	115 (26%)	2 (18.2%)	0.73
Myocardial infarction	64 (14.4%)	0	0.38
Systolic blood pressure (mmHg)	143 [130 – 160]	143 [116 – 154]	0.50
Location intracranial occlusion			0.50
ICA (with possible involvement M1)	118 (27.3%)	4 (36.4%)	
M1/M2/A1/A2	314 (72.7%)	7 (63.6%)	
Allocated treatment (intra-arterial treatment)	199 (44.9%)	8 (72.3%)	0.12

Continuous and ordinal variables are reported as medians and interquartile ranges. Dichotomous variables are reported as absolute values and percentages.

In total, 11 patients with a carotid web underwent CT angiography from the aortic arch to the top of the internal carotid artery (intracranial carotid T). One patient underwent incomplete CT angiography without depiction of the aortic arch. In six of the 11 (54.5%) patients with a carotid web, calcifications were observed in at least one vessel location. Two patients with symptomatic carotid web and one patient with asymptomatic carotid web had calcifications at the carotid bifurcation. In one patient, we observed a 360° loop of the symptomatic internal carotid artery.

**Table 2.** Demographics and clinical characteristics

Case number	Gender	Age	Symptomatic hemisphere	Location intracranial occlusion	History of ischemic stroke	Smoking
<i>CAROTID WEB – SYMPTOMATIC SIDE</i>						
1	F	45	Right	M1	Yes	-
2	M	77	Right	M1	-	-
3	F	67	Right	M1	-	-
4	F	47	Left	ICA-T	-	-
5	F	44	Right	ICA-T	-	-
6	F	66	Right	M2	-	-
7	F	45	Right	ICA-T	-	-
8	F	60	Left	ICA-T	-	-
9	F	59	Right	M1	-	-
10	F	84	Right	M1	-	-
11	F	46	Right	M1	-	-
<i>CAROTID WEB – ASYMPTOMATIC SIDE</i>						
8	F	60	Right	ICA-T	-	-
12	F	73	Left	M1	-	-
<i>SMALL PROTRUDING LESIONS – SYMPTOMATIC SIDE</i>						
13	F	60	Left	ICA-T	-	Yes
14	M	97	Right	ICA-T	-	-
15	M	49	Left	M1	-	-
16	F	51	Right	M1	-	Yes
17	F	44	Left	M1	-	-
18	F	67	Left	M2	-	Yes
19	F	46	Right	M1	-	-
20	M	60	Right	M1	-	-
<i>SMALL PROTRUDING LESIONS – ASYMPTOMATIC SIDE</i>						
21	F	61	Right	M1	-	-
22	M	42	Left	ICA-T	-	-
3	F	67	Right	M1	-	-
23	M	80	Right	M1	-	Yes
24	F	79	Right	M1	-	-
25	F	50	Left	ICA-T	-	Yes
26	F	69	Left	ICA-T	-	-
9	F	59	Right	M1	-	-

\* Calcifications at the symptomatic side or aortic arch on CTA.  
IAT, intra-arterial treatment



Diabetes	Atrial fibrillation	Myocardial infarction	Hypertension	Systolic blood pressure (mmHg)	Calcifications*	Allocated treatment
-	-	-	Yes	113	-	IAT
-	Yes	-	Yes	117	Yes	No IAT
-	-	-	Yes	153	Yes	No IAT
-	-	-	-	126	-	IAT
-	-	-	Yes	143	-	IAT
-	-	-	-	155	Yes	IAT
-	-	-	-	113	-	No IAT
-	-	-	-	115	-	IAT
-	-	-	-	150	Yes	IAT
-	Yes	-	Yes	180	Yes	IAT
-	-	-	Yes	173	-	IAT
-	-	-	-	115	-	NA
-	-	-	Yes	130	Yes	NA
-	-	-	-	112	-	No IAT
-	-	-	-	128	Yes	No IAT
-	-	-	-	145	-	IAT
-	-	-	Yes	136	-	IAT
-	-	-	-	117	-	No IAT
-	-	-	Yes	140	Yes	No IAT
-	-	-	-	125	-	IAT
-	-	-	-	157	Yes	IAT
-	-	-	-	134	Yes	NA
-	Yes	-	-	110	-	NA
-	-	-	Yes	153	Yes	NA
-	Yes	Yes	Yes	66	Yes	NA
-	-	-	Yes	225	Yes	NA
-	-	-	-	130	Yes	NA
-	Yes	-	-	125	Yes	NA
-	-	-	-	150	Yes	NA

## Prevalence, demographics and imaging characteristics of small protruding lesions

We observed eight small protruding lesions at the symptomatic carotid bifurcation and eight at the asymptomatic carotid bifurcation (odds ratio, 1.0; 95% CI: 0.33, 3.06;  $p > 0.99$ ) in 16 patients. Two patients (case 3 and 9) had a carotid web at the symptomatic bifurcation and also a small protruding lesion at the asymptomatic side. The median age (56 years; interquartile range, 48–62 years) of patients with a small protruding lesion at the symptomatic carotid bifurcation did not differ significantly ( $p 0.10$ ) from patients without a small protruding lesion or carotid web at the symptomatic carotid bifurcation. Most of the patients with a small protruding lesion at the symptomatic side were female ( $n=5$ ;  $p 0.28$ ). No other differences were found between patients with and patients without small protruding lesions in the symptomatic carotid artery. None of the patients with a symptomatic protruding lesion had a history of previous stroke. One patient with a symptomatic protruding lesion had a medium risk of cardioembolism because of mitral valvular insufficiency. In 10 patients (62.5%) with a protruding lesion, calcifications were observed in at least one vessel location. One patient with a symptomatic protruding lesion and three patients with an asymptomatic protruding lesion had a calcification at the carotid bifurcation. In one patient, we observed an S curve in the symptomatic internal carotid artery.

## Interobserver agreement

The ground truth was defined by consensus reading between the most experienced reader (B.E.) with respect to the assessment of carotid webs and the first author based on the criteria published previously<sup>10</sup>. The first observer identified 13 carotid webs. The second observer missed one of these 13 carotid webs but detected another seven carotid webs. We observed a fair to good interobserver agreement (94.9%;  $\kappa 0.72$ ) for diagnosing carotid webs at CT angiography. The first observer identified 16 small protruding lesions. The second observer missed 10 of these 16 small protruding lesions but detected another 10 small protruding lesions. Poor agreement was observed for diagnosing small protruding lesions (87.2%;  $\kappa 0.30$ ). Between the diagnostic categories of small protruding lesion and carotid web, weighted agreement was slightly worse but still fair to good agreement (83.3%; weighted  $\kappa 0.664$ ).

## DISCUSSION

In our study, we observed symptomatic carotid webs at the carotid bifurcation in 2.5% of the patients with acute ischemic stroke due to intracranial large vessel occlusion. Carotid webs were observed significantly more often on the symptomatic side and significantly

more often in female patients. In most patients with a carotid web at the symptomatic side, other notable major risk factors or causes for stroke could not be identified. The diagnosis of carotid web was assessed with a fair to good interobserver agreement.

We studied the prevalence of carotid web in patients with acute ischemic stroke due to anterior large vessel occlusion. Previous literature suggests that carotid webs may be a cause of lacunar infarctions<sup>10, 12, 18</sup>. However, patients with lacunar infarctions were not included in our study. Further research will be necessary to investigate the potential association between carotid webs and lacunar infarctions. The prevalence of carotid webs in our study was higher compared with the earlier reported prevalence of 1.2% based on a hospital-based sample of patients suspected of having stroke<sup>10</sup>. As mentioned previously, our study was performed in patients with a radiologically confirmed intracranial arterial occlusion, which could explain the higher prevalence. Recently, a case-control study was published and reported an odds ratio estimate of 8.0 (95% CI: 1.2, 67) for the presence of a carotid web in patients with acute ischemic stroke versus control subjects<sup>19</sup>. Patients were selected from a registry of patients with ischemic stroke and included if stroke etiology was previously undetermined and age was younger than 60 years. In line with our study, in five of seven (71.4%) patients with a carotid web, no evidence of atherosclerotic disease at CT angiography was found. Among the patients with a carotid web, four of five (80%) patients were women.

In our population, carotid webs were more frequently observed at the symptomatic bifurcation and in female patients without cardiovascular risk factors or other causes for acute ischemic stroke. Proper detection of carotid webs could help to optimize stroke management. Several treatment options have been proposed, such as carotid endarterectomy and stent placement<sup>11-13, 18</sup>. Patients with acute ischemic stroke without other major risk factors might benefit from a timely and correctly diagnosed carotid web, although optimal treatment strategies need to be investigated in clinical trials.

Several patients had a small protruding lesion as defined by previous researchers<sup>10</sup>. In our study, we observed no difference in the frequency of small protruding lesions at the symptomatic versus asymptomatic carotid bifurcation. Nonetheless, small protruding lesions and carotid webs might be a continuum of the same disease process.

The interobserver agreement for diagnosing carotid webs at CT angiography was fair to good. However, patients with severe calcifications were excluded, possibly influencing the interobserver agreement. Disagreement might occur in cases with atherosclerotic characteristics by interpreting a carotid web as a complicated plaque or vice versa. Because of the radiologic aspect of carotid webs and small protruding lesions, they might be confused with a complicated ulceration or a floating thrombus. In addition, we examined the interobserver agreement of the main differential diagnosis of carotid webs, small protruding lesions, which showed poor agreement.

Our study had several limitations. First, because of small numbers of patients with carotid web, there is a lack of statistical power that could influence the magnitude of associations. Adjusted regression analyses would cause estimation uncertainty and are performed. Hence, exact tests were more accurate in our study and applied for analysis. However, true associations can still be exaggerated. Second, the interobserver agreement was limited, resulting in uncertainty regarding the assessment of observed carotid webs but particularly small protruding lesions. Third, 20% of the symptomatic carotid bifurcations were stenosed (>50% according to North American Symptomatic Carotid Endarterectomy Trial criteria) or occluded by atherosclerotic lesions<sup>17</sup>, which might have obscured the presence of carotid webs at CT angiography. However, in most patients in whom the carotid bifurcation was obscured, atherosclerotic vessel disease was more plausible as a cause of ischemic stroke. In line with this, previous research showed an absence of atherosclerotic characteristics in histopathologic reports after surgical excision of carotid webs<sup>10,11</sup>. Therefore, patients with a significant stenosis (>50%) or occlusion were assumed to have no underlying carotid web in the carotid bifurcation. Fourth, all carotid webs were identified with CT angiography only. There was no validation with digital subtraction angiography or histopathologic examination. Finally, no long-term follow-up to determine the frequency of recurrent strokes among patients with a carotid web was available.

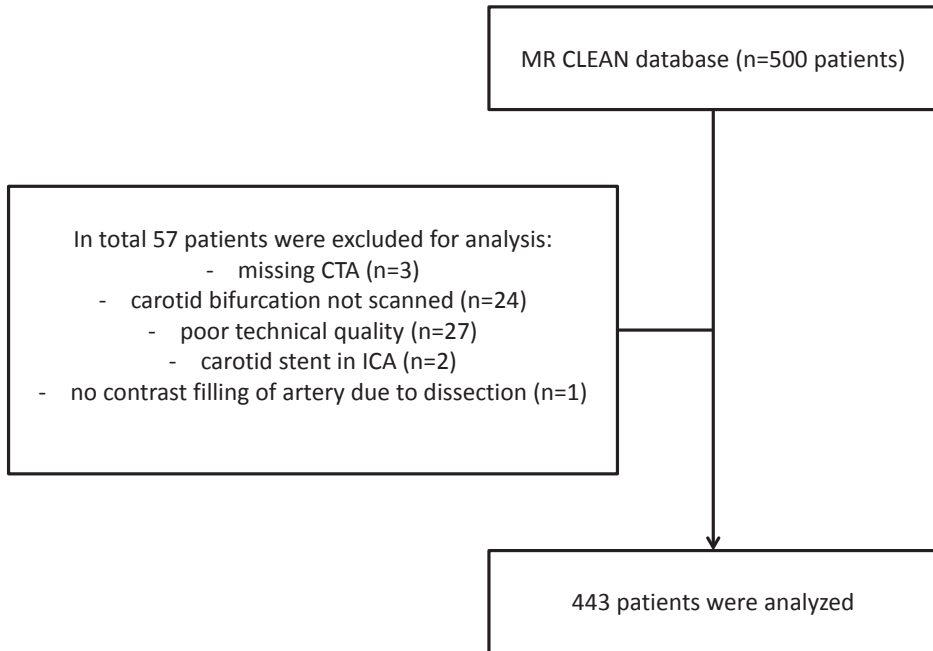
In conclusion, our results showed a relatively high prevalence of carotid webs in patients with large vessel occlusion stroke compared with previous studies. In addition, there was a pronounced difference in the prevalence of carotid webs in favor of the symptomatic side. Most patients with carotid web were female and did not have any other cardiovascular risk factors. Interobserver agreement for diagnosing carotid webs at CT angiography is fair to good. These findings suggest that carotid webs can be recognized with a good agreement between observers at CT angiography and may play a role in the pathogenesis of large vessel occlusion strokes in specific patient populations.

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## SUPPLEMENTAL DATA



**Suppl. Figure 1:** Flowchart of included patients in the study. CTA, CT angiography. ICA, internal carotid artery.