ORIGINAL ARTICLE

Near-Occlusion is a Common Variant of Carotid Stenosis: Study and Systematic Review

Elias Johansson, *Allan J. Fox*

ABSTRACT: ***Background:*** Symptomatic carotid near-occlusion is often described as rare. Recent studies have shown that near-occlusions are overlooked, especially near-occlusion without full collapse (with a small but normal-appearing distal internal carotid artery). ***Objective:*** To assess the prevalence of near-occlusion among symptomatic ≥50% carotid stenosis, incidence of symptomatic near-occlusion, and review the literature. ***Methods:*** Prospective controlled single-center cross-sectional study. Consecutive cases with symptomatic ≥50% carotid stenosis were examined with computed tomography angiography (CTA). The CTAs were assessed for near-occlusion by two observers. A systematic literature review was performed with emphasis on how study design affects prevalence estimate. ***Results:*** Totally, 186 patients with symptomatic ≥50% carotid stenosis were included, 34% ($n = 63$, 95% CI 27, 41) had near-occlusion. The incidence of symptomatic near-occlusion was 3.4 (95% CI 2.5, 4.2) per 100,000 person-years. Inter-rater κ was 0.71. The average prevalence of near-occlusion among symptomatic ≥50% carotid stenosis was higher in studies with good design (30%, range 27%–34%) than studies without good design (9%, range 2%–10%). ***Conclusions:*** Near-occlusion is common variant of symptomatic ≥50% carotid stenosis, both in the current study and in all previous studies of good design. Studies that suggest that near-occlusion is rare have had methodological issues.

RÉSUMÉ : La quasi-occlusion, forme courante de sténose carotidienne – Étude et revue systématique. ***Contexte*** **:** La quasi-occlusion carotidienne symptomatique est souvent présentée comme une forme rare d'obstruction. D'après des études récentes, les quasi-occlusions passent inaperçues, surtout celles non accompagnées d'un d'affaissement complet (artère carotide interne distale petite mais d'apparence normale). ***Objectifs*** **:** L'étude visait à évaluer la prévalence de la quasi-occlusion dans les cas de sténose carotidienne de ≥ 50 %, symptomatique ainsi que l'incidence de la quasi-occlusion symptomatique, et à examiner la documentation médicale. ***Méthode*** **:** Il s'agit d'une étude transversale, prospective et comparative, de type unicentrique. Des cas consécutifs de sténose carotidienne de ≥ 50 %, symptomatique ont d'abord été examinés à l'angiographie par tomodensitométrie, puis deux observateurs ont évalué les images quant à l'existence de quasi-occlusion. L'équipe de recherche a aussi procédé à une revue systématique de la documentation, tout particulièrement en ce qui concerne l'influence du plan d'étude sur l'évaluation de la prévalence. ***Résultats*** **:** Ont été inclus dans l'étude 186 patients présentant une sténose carotidienne de ≥50 %, symptomatique; dans 34 % des cas (n = 63, IC à 95 % : 27-41 %), il s'agissait de quasi-occlusion. L'incidence de la quasi-occlusion symptomatique était de 3,4 pour 100 000 personnes-années (IC à 95 % : 2,5-4,2), et la valeur kappa interévaluateurs, de 0,71. La prévalence moyenne de la quasi-occlusion parmi les cas de sténose carotidienne de ≥ 50 %, symptomatique était plus élevée dans les études bien conçues (30 %; plage : 27-34 %) que dans les études de qualité médiocre (9 %; plage : 2-10 %). ***Conclusion*** **:** La quasi-occlusion est une forme courante de sténose carotidienne de ≥ 50 %, symptomatique, et ce, tant dans l'étude ici présentée que dans toutes les études antérieures bien conçues. Celles dont les résultats donnent à penser que la quasi-occlusion est une forme rare souffrent d'une démarche méthodologique douteuse.

Keywords: Stroke, Carotid stenosis, Carotid near-occlusion, Prevalence, Incidence

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Introduction

Carotid near-occlusion is a severe variant of carotid stenosis in which the artery distal to the stenosis is reduced in size.[1–3] This is thought to be a physiological reaction to the stenosis-caused reduction in blood volume and blood pressure beyond a stenosis. Near-occlusions can be subdivided into full collapse (threadlike distal artery, Figure 1A) and without full collapse (small but normal-appearing distal artery, Figure 1B).[1–2] Only stenosis without near-occlusion (conventional stenosis) should be assessed as percent when using NASCET grading.[4] In patients with symptomatic stenosis, near-occlusion should be separated from conventional stenosis as recommended management differs.[5–6]

Carotid ultrasound has poor sensitivity for near-occlusion (13%).[7] Although near-occlusions can be assessed by computed tomography angiography (CTA), only 20% of near-occlusions are detected when CTAs are assessed in routine practice.[8] Many seem to apply the criteria for NASCET stenosis quantification with percent

From the Department Clinical Science, Umeå University, Umeå, Sweden and Wallenberg Center for Molecular Medicine (WCMM), Umeå University, Umeå, Sweden (EJ); and Department of Medical Imaging, Sunnybrook Health Science Center, University of Toronto, Toronto, Canada (AJF)

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Correspondence to: Elias Johansson, Department Clinical Science, Umeå University, Umeå, Sweden. Email: elias.johansson@umu.se

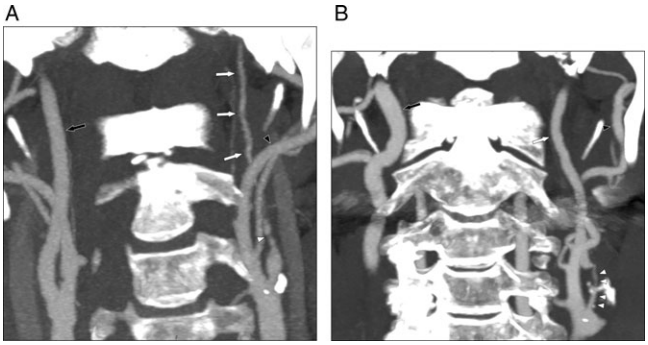

Figure 1. *Two cases of left-sided near-occlusion. (A) Near-occlusion with full collapse. After severe stenosis (white arrowhead), the distal left ICA is very narrow (white arrows), clearly smaller than right ICA (black arrow) and smaller than left ECA (black arrowhead). (B) Near-occlusion without full collapse. After a severe stenosis (white arrowheads), the distal left ICA is normal-appearing (white arrow). However, distal left ICA is smaller than distal right ICA (black arrow) and similar to left ECA (black arrowhead). ECA: external carotid artery. ICA: internal carotid artery.*

to all cases, but forget that NASCET called for assessment for near-occlusion before any measurements be done because whenever the ICA lumen is reduced from near occlusion, percent ratio calculations will be fallacious.[4] Thus, near-occlusion seems to be often overlooked in routine practice, especially those without full collapse.[7–8] As near-occlusion with full collapse less often undergoes revascularization than conventional stenosis, studies requiring treatment, such as large randomized trials, will likely underestimate the prevalence of near-occlusion.[3,9] Therefore, near-occlusions might not be 'rare', as they are often described to be.[10–15] Systematic reviews and meta-analyses of near-occlusion either do not present a prevalence estimate,[1–2] present near-occlusion as 'rare',[11–12,15] 'relatively rare',[15–17] as ≤10% of 'cases' (of varying definition),[15–20] or as 20% of ≥70% stenosis.[17] In consecutive studies assessing near-occlusion prognosis, the prevalence of near-occlusion among symptomatic ≥50% carotid stenosis has been 27%–31%, but with possible selection bias.[9,21] No study has aimed to estimate the prevalence of symptomatic near-occlusion among patients with symptomatic ≥50% carotid stenosis. No systematic review has assessed how such prevalence is affected by study design (selection, modality, and near-occlusion definition). No estimate of incidence of symptomatic near-occlusion has been made.

Aims

The aims of this study were to assess the prevalence of symptomatic near-occlusion among symptomatic ≥50% carotid stenosis, the incidence of symptomatic near-occlusion, and perform a systematic review focusing on the impact of study design on near-occlusion prevalence estimate.

Methods

Prospective Study

A prospective controlled single-center study performed between February 2018 and March 2020. Cases with suspected symptomatic carotid stenosis (local admissions or by referral) assessed at Umeå Stroke Centre were included. All patients in Northern Sweden with suspected carotid stenosis aimed or revascularization are preoperatively assessed at this center, with 11 referring hospitals. Based on population data from the Swedish Bureau of Statistics, 1,869,135 person-years transpired during the study period in the study area. The study was approved by the regional ethics board in Umeå. All patients provided informed consent, written whenever possible.

Clinical exclusion criteria (applied before approaching patients for consent) were severe co-morbidity or major stroke as presenting event, making carotid revascularization clearly unfeasible. Only obviously unfeasible cases were excluded in this fashion, i.e., cases that underwent revascularization or were reasonable candidates were included, even when revascularization was not performed. CTA exclusion criteria were kidney failure and contrast allergy. Of included patients, analyses were restricted to those with symptomatic ≥50% stenosis on CTA (including near-occlusion, but not occlusion). Symptomatic was defined as having a recent (<6 months) ipsilateral ischemic stroke, TIA, amaurosis fugax, or retinal artery occlusion.

CTA was performed using various protocols at the referring hospitals or the department of radiology at the University hospital of Northern Sweden. All CTAs were reviewed by one observer (EJ). All cases with suspected near-occlusion and controls were reviewed by a second observer (AF) blinded to first reviewer. Both observers had near-occlusion expertise. Cases of disagreement handled by consensus discussion. As in previous studies, near-occlusion was sought prior to measurements for stenosis quantification.[4] Near-occlusion was diagnosed when a severe carotid stenosis was the most reasonable cause for a small distal internal carotid artery (ICA).[9,22] This was assessed by systematic interpretation of residual stenosis diameter, distal ICA diameter, distal ICA diameter compared to contralateral ICA (ICA ratio) and distal ICA diameter compared to ipsilateral external carotid artery (ECA ratio).[9,22] ICA asymmetry associated with Circle of Willis variation that mimic near-occlusion was recognized.[22] A conservative approach was used, diagnosing near-occlusion only when sufficiently certain. Among near-occlusions, those with a thread-like appearance of the distal artery were considered as full collapse. Occlusion was defined as no contrast seen beyond the stenosis. Conventional stenoses were graded with percent according to NASCET method, i.e., comparing smallest stenosis lumen diameter with the distal ICA well beyond the bulb.[4] Very severe stenoses, with less dense lumen opacity than the lumen proximal and distal (likely artery diameter ≤0.6 mm, the voxel size), were arbitrarily assigned to have a 0.5 mm diameter when visible and 0.2 mm when not visible.

Systematic Review

A previous systematic review of near-occlusion including articles published until December 2014[1–2] was updated by using the same search strategy until October 2020. PubMed search was performed with the terms "carotid near-occlusion," "carotid pseudo-occlusion," "carotid string sign," "carotid slim sign," "carotid critical stenosis," "small distal carotid artery," "narrow distal carotid artery," "carotid preocclusive stenosis," "carotid pre occlusive stenosis," "carotid subtotal stenosis," "carotid sub total stenosis," "carotid subtotal occlusion," "carotid sub total occlusion," "carotid functional occlusion," "carotid sub-

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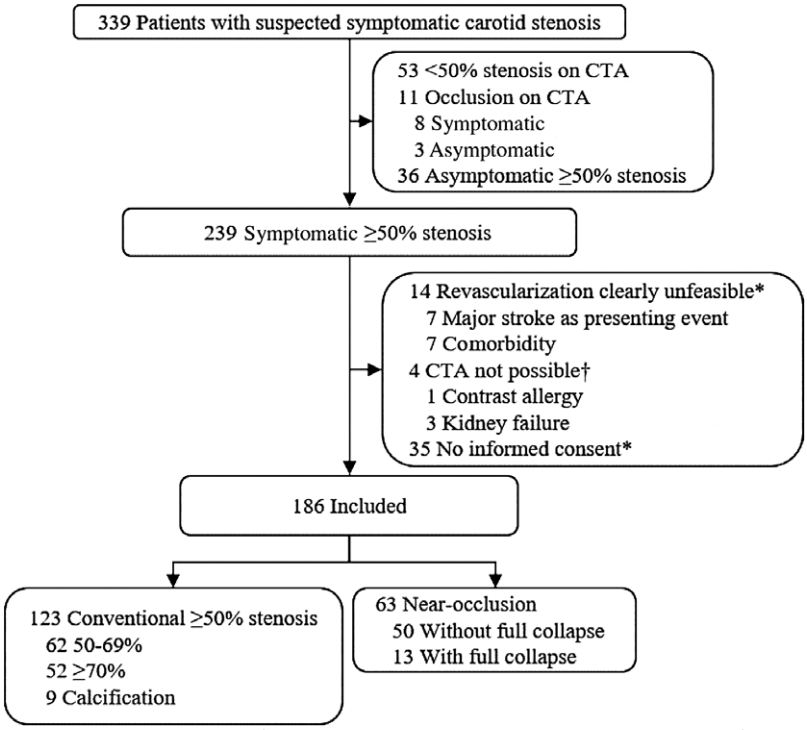

Figure 2. Study flow chart. *≥50% stenosis on either CTA or carotid ultrasound. †≥50% stenosis on carotid ultrasound.

occlusion," "carotid hypoplasia," "carotid incomplete occlusion," and "carotid hairline," without search restrictions. Reference lists were checked for additional articles. One observer (EJ) performed all steps of the review. We required data on >10 cases, English language, allowing for prevalence assessment of near-occlusion among ≥50% and/or ≥70% carotid stenosis by NASCET grading.

We recognized that the use of ultrasound alone,[7] omitting near-occlusion without full collapse[1–3] and requiring treatment[9] or clinical selection to multiple exams, would likely affect near-occlusion prevalence estimate. Therefore, we defined *good design* as a consecutive sample without additional selection criteria (such as revascularization or requiring multiples exams), use of an angiographic technique and that near-occlusion without full collapse was clearly included in the definition of near-occlusion. Prevalence was analyzed separately for those with and without good design and by share of symptomatic cases. Articles with overlapping and/or pooled data were handled so that no patient was assessed several times for the same modality. However, patients examined with several modalities were assessed for each separate modality whenever feasible. The systematic review was performed according to PRISMA guidelines.

Statistics

Where appropriate we used mean, standard deviation (SD), 95% confidence intervals (95% CI), κ values, 2-sided χ^2-test with exact calculation method, and t-test. Calculations were performed with IBM SPSS 26.0. A $p < 0.05$ was considered statistically significant.

Results

Prospective Study

Of 339 patients with suspected carotid stenosis, 239 had symptomatic ≥50% carotid stenosis, of which 186 (78%) were included, Figure 2. Baseline findings are presented in Table 1. Of the 186 included patients, 34% (95% CI 27, 41) had near-occlusion. Of the 115 patients with symptomatic ≥70% stenosis, 55% (95% CI 46, 64) had near-occlusion. Of the 123 patients with conventional ≥50% stenosis, the ipsilateral distal ICA was visibly smaller than contralateral ICA in 29 (24%). These smaller distal ICAs were assessed to be caused by coinciding anatomical variant ($n = 11$), loops/kinks ($n = 3$), coinciding intracranial severe ICA stenosis ($n = 1$), and unclear (suspicion of near-occlusion, but insufficient features for a certain diagnosis, $n = 14$). Inter-rater agreement was 88%, κ 0.71 (95% CI 0.64, 0.79). The incidence of symptomatic near-occlusion was 3.4 (95% CI 2.5, 4.2) per 100,000 person-years.

Systematic Review

The article search resulted in 664 title matches. After screening and reference list checks, 144 articles were assessed of which 12 were included; 13 when also considering the current study. Three studies presented data on ≥50% stenosis,[7,21,23] five on ≥70% stenosis,[24–28] and the current study and four previous studies did both.[3,9,29–30]

In studies with >90% symptomatic cases, the average prevalence of near-occlusion among ≥50% stenosis was 30% (range 27%–34%) in studies with good design and 9% (range 2%–10%) in studies without good design (Table 2,

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Table 1. Baseline features

	Conventional ≥50% stenosis ($n = 123$)	Near-Occlusion ($n = 63$)	$p^{\S}$
Age mean (SD)	74 (7)	73 (7)	0.44
Women *n* (%)	44 (36)	16 (25)	0.19
Smallest stenosis diameter in mm mean (SD)*	1.3 (0.5)	0.6 (0.3)	<0.001
Distal ICA diameter in mm mean (SD)	4.0 (0.7)	2.4 (1.1)	<0.001
ICA ratio mean (SD)†	1.02 (0.59)	0.57 (0.26)	<0.001
ECA ratio mean (SD)	1.67 (0.43)	0.92 (0.42)	<0.001
50%–69% stenosis *n* (%)‡	62 (54)	NA	-
Full collapse	NA	13 (21)	-
Contralateral ≥50% stenosis *n* (%)	36 (29)	16 (25)	0.61

ECA: external carotid artery. ECA ratio: ipsilateral distal ICA/ipsilateral ECA diameter. ICA: internal carotid artery. ICA ratio: ipsilateral/contralateral distal ICA diameter. NA: not applicable. SD: standard deviation.

*10 missing data due to severe calcification in stenosis.

†6 missing data due to contralateral occlusion.

‡9 missing data due to severe calcification, but sufficiently certain ≥50%.

§2-sided χ^2-test for categorical data. t-test for continuous data.

Table 2. Systematic review of studies with >90% of stenoses where symptomatic. Separated by studies with and without design. Good design required consecutive symptomatic cases without additional selection, study-assessed angiography, and clear recognition of near-occlusion without full collapse

Study	Year	Modality	Why not good design	Prevalence among ≥50%	Prevalence among ≥70%
Good design					
Johansson et al.[21]	2015	CTA + CA	-	31 (20–42) [23/74]	NR
Gu et al.[9]	2020	CTA	-	27 (23–32) [99/365]	46 (39–53) [99/215]
Current		CTA	-	34 (27–41) [63/186]	55 (46–64) [63/115]
All with good design				30 (26–33) [185/625]	49 (44–55) [162/330]
Not good design					
Paciaroni et al.[24]	2003	CA	Without full collapse not clearly included	NR	2 (0–5) [2/104]
Fox et al.*[3]	2005	CA	Only treatable cases (randomized trial)	10 (9–11) [262/2718]	22 (19–24) [262/1216]
Gonzalez et al.†[25]	2011	CA	Only treated cases	NR	16 (13–19) [116/720]
Ruiz-Salmerón et al.[26]	2013	CA	Only treated cases	NR	36 (27–45) [40/111]
Oka et al.‡[27]	2013	CA	Only treated cases and without full collapse not clearly included	NR	20 (9–31) [10/50]
Fanous et al.[29]	2015	CA	Only treated cases and without full collapse not clearly included	5 (2–7) [10/221]	6 (2–10) [10/167]
Johansson et al.[21]	2015	Ultrasound	Ultrasound based	2 (0–5) [5/204]	NR
All without good design				9 (8–10) [277/3143]	20 (18–22) [264/1320]

CA: conventional angiography. CTA: computed tomography angiography. NR: not reported.

Outcomes presented as percent (95% confidence interval) [n/N].

*1 Randomized trial, requiring patient to be treatable, but treated according to allocation. Denominator extracted from Rothwell et al.[33].

†91% symptomatic cases, all other studies in the table had only symptomatic cases.

‡Cases with asymptomatic stenosis also studied and presented separately, excluded in this analysis.

Figure 3). The average prevalence of near-occlusion among ≥70% symptomatic stenosis was 49% (range 46%–55%) in studies with good design (Table 2).

None of the four studies with mixed (48%)[30] or no data reported on share of symptomatic cases[7,23,28] had good design. The prevalence of near-occlusion among ≥50% stenosis was

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Table 3. Systematic review of studies that were mixed symptomatic and asymptomatic, or did not present data on symptom status. None had good design

Study	Year	Modality	Why not good design	Prevalence among ≥50%	Prevalence among ≥70%
Mansour et al.[23]	1995	CA	Without full collapse not clearly included	13 (8–17) [30/240]	NR
Mansour et al.[23]	1995	Ultrasound	Ultrasound based	4 (2–7) [12/267]	NR
Anzidei et al.[30]	2009	CA	Without full collapse not clearly included	4 (0–8) [4/101]	5 (0–10) [4/77]
Ogata et al.[28]	2011	CA	Without full collapse not clearly included	NR	10 (7–13) [34/337]
Khangure et al.*[7]	2018	CTA	Requiring both CTA and ultrasound	31 (20–42) [23/74]	NR
Khangure et al.*[7]	2018	Ultrasound	Requiring both CTA and ultrasound and ultrasound based	5 (0–11) [4/74]	NR

CA: conventional angiography. CTA: computed tomography angiography. NR: not reported.
Outcomes presented as percent (95% confidence interval) [n/N].
*Overlapping cases better presented in Johansson et al.[21] excluded.

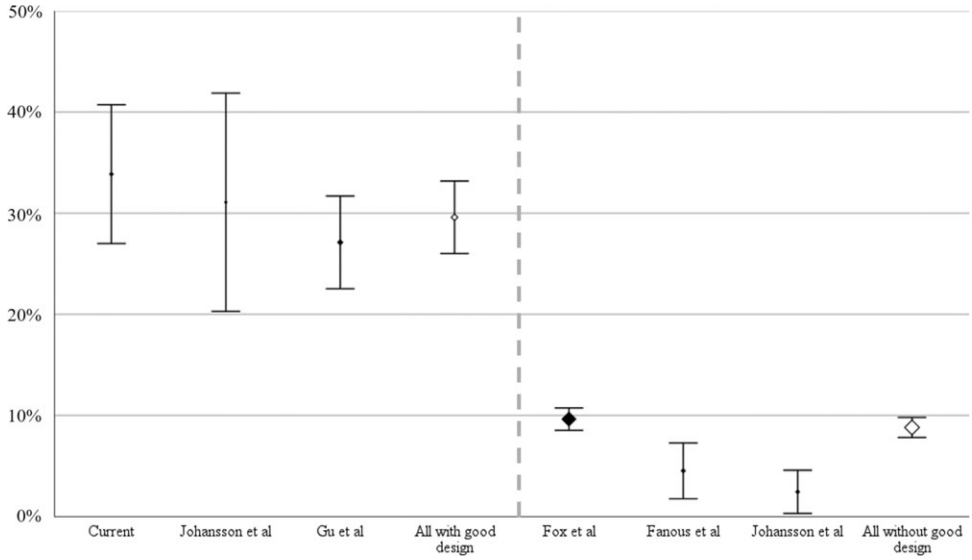

Figure 3. *Forest plot of prevalence of near-occlusion among symptomatic ≥50% stenosis. Studies to the left of the dashed line had good design, to the right did not have good design. Error bars denote 95% confidence interval. Diamond area is proportional to number of patients. Study references are same as in Table 2.*

31% when the only design flaw was requiring two exams and ranged 5%–13% when for other design flaws (Table 3).

Discussion

The main findings of this study were a high prevalence of near-occlusion among symptomatic ≥50% carotid stenosis, and that similar high prevalence has been reported in all previous studies with good design, but was lower in studies without good design. Additionally, we made the first estimate of the incidence of symptomatic near-occlusion.

Main Findings

Our prevalence finding is likely much higher than what many perceive the prevalence of near-occlusion to be. This contrast between perceived and actual prevalence has several plausible causes. Near-occlusions are often overlooked on both ultrasound and when CTA are assessed in routine practice.[7–8] As presented in a previous literature review, many of the included and other studies have only included near-occlusion with full collapse (with a thread-like distal ICA, by some called 'string sign') in the definition of near-occlusion.[1–2] By doing so, near-occlusions without full collapse (with a small but normal-appearing distal ICA) are overlooked. To overlook near-occlusion without full collapse does not seem rational since 94% of near-occlusions were without full collapse in the large trials,[3] trial on which we base our guidelines.[5–6] Overlooking near-occlusion without full collapse does not seem to be by design, but a misunderstanding of how near-occlusion was diagnosed in the large trials.[2] Near-occlusion prevalence can also be underestimated by selection bias if studies require treatment[3,25–27,29] or several exams[7] for entry. The low share (6%) of full collapse among near-occlusions in large trials[3] compared to consecutive series (40%–42%)[9,21] was likely in part explained by requiring treatment in the trials. In our analysis, we defined good design in order to separately assess studies with and without these potential sources of bias. In studies with good design, the prevalence of near-occlusion was markedly higher than

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in studies without good design. Some of the studies in the review were designed for other aims but were also assessable for prevalence of near-occlusion, even if they did not include the more inclusive near-occlusion definition of both part and full collapse.

All three studies with good design had similar outcome. In the previous two studies, CTA was done by clinical selection (in 32%[9] and 71%[21] of respective populations), introducing the possibility of selection bias. The current study was designed in order to overcome this possible bias by ensuring that all eligible patients were examined with CTA. However, the current study also had possible selection bias as of 239 patients with symptomatic carotid stenosis, 78% were included, 15% were excluded by not providing informed consent, 6% were excluded due to clearly not candidates for revascularization, and 2% were excluded as angiography was not possible. With similar findings in all three studies, despite different types of selection, it seems unlikely that the high prevalence estimates were caused by selection bias.

Diagnostic Uncertainty in General

Separating near-occlusion and conventional stenosis is sometimes difficult. We used the state-of-the art approach, based on feature interpretation, similar to previous prognostic studies.[3,9,21] This approach has drawbacks as it requires experience. Although a conservative approach was used, some accentuation of near-occlusion cannot be excluded. Several conditions with small distal ICA similar to near-occlusion were accounted for. However, underestimation of near-occlusion is possible as there were many cases with unclear cause of small distal ICA. A previous study found similar issues with unclear cases.[22]

We had reasonable inter-rater reliability, similar to a previous study.[9] This was possibly and underestimation as most cases without near-occlusion suspicion were not assessed by both observers, and such cases would likely have above average agreement. More importantly, as this study was performed by collaborating experts, though in separate location, the assessed reliability was likely higher than when applied in routine practice.

Better diagnostic approaches for separating conventional stenosis and near-occlusion are warranted as near-occlusion is currently overlooked,[7–8] current state-of-the art has feasibility issues for routine practice use, and recommended management differs.[5–6] The high risk of recurrent stroke in near-occlusion with full collapse also warrants further clarification.[9,21] These method improvements could include physiological approaches, such as velocity distal to the stenosis on carotid ultrasound[31] or phase contrast MRI.[32] That near-occlusions are not rare but common should reasonably increase the priority of these studies.

Study Strengths and Weaknesses

The strengths of this study were prospective design situated at a stroke unit doing preoperative evaluations (not a revascularization clinic), steering cases to CTA, dedicated to near-occlusion analysis, and state-of-the art diagnostic approach. The sample size was moderate, but the 95% CI still excluded the possibility of near-occlusions being rare. As we did not assess cases that were clearly not eligible for revascularization, our findings are foremost applicable to cases eligible for revascularization. Some cases in referring hospitals might not have been sent and there was a moderate rate of refusing study participation. Only if such cases were more or less often near-occlusions than those included (which is unknown) would it would affect the prevalence estimate. However, some symptomatic near-occlusions in the study area during the study period might not have been included, why the incidence estimate was likely an underestimation.

Summary

Near-occlusion is a common variant of carotid near-occlusion. Previous assessments of near-occlusion being rare can be explained by suboptimal methodology.

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Disclosures

The authors have no conflicts of interest.

Statement of Authorship

EJ: Idea, concept, data collection, funding, analyses, and manuscript draft. AJF: Data collection, manuscript edit.

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