Original Paper

Ipsilateral Infarct in Newly Diagnosed Cervical Internal Carotid Artery Atherosclerotic Occlusion

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Key Words

Carotid artery diseases · Stroke · Risk factors · Hydroxymethylglutaryl-CoA reductase inhibitors · Antihypertensive agents

Abstract

Objective: We aimed to determine factors associated with recent infarct (RI) in patients with newly identified atherosclerotic cervical internal carotid artery occlusion (CICAO). **Methods:** This was a retrospective review of consecutive patients who underwent cervical CT angiography from 2002 to 2006 at a single tertiary center. RI was defined by positive diffusion-weighted imaging/apparent diffusion coefficient magnetic resonance imaging (MRI) in the correspondent CICAO territory. Subjects were dichotomized into those with a RI versus patients with no RI (No-RI). **Results:** Of 2,459 patients with cervical CT angiograms in the study period, 108 (4.4%) had complete medical records and brain MRI and were included. The mean age was 64 ± 13 years, 58% were men, and 62 (57%) had a RI. The demographics of the RI and No-RI patients were comparable, with the exception that those with RI had a lower frequency of coronary artery disease (CAD, 13 vs. 54%; $p < 0.01$) and dyslipidemia (38 vs. 69%; $p < 0.01$). The use of antiplatelets was not statistically different between the groups (56 vs. 71%; $p = 0.1$). Subjects with RI were less likely on statins (21 vs. 56%; $p < 0.01$) and antihypertensives (9 vs. 71%; $p < 0.01$). Multivariate regression revealed that CAD, the use of statins, and the use of antihypertensives were associated with No-RI CICAO presentation. **Conclusion:** The use of statins and antihypertensives is associated with a decreased risk of RI atherosclerotic CICAO.

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Introduction

Cervical internal carotid artery occlusion (CICAO) is an important cause of ischemic stroke [1]. The risk of ipsilateral recurrent stroke in the territory of CICAO has been reported to be as high as 5.9% per year [2–4]. Advancing age, underlying hyperlipidemia, and hypertension have been associated with higher rates of recurrent ischemia [2, 5], while the use of statins and antihypertensive medications has been associated with reduced stroke risks [6, 7]. However, the factors predisposing atherosclerotic CICAO patients to an initial infarct have not been well studied. We aimed to determine factors associated with recent infarct (RI) in patients with newly identified atherosclerotic CICAO.

Materials and Methods

Inclusion and Exclusion

We performed a retrospective review of consecutive patients who presented to the Albany Medical Center, Albany, N.Y., USA, with a new diagnosis of CICAO by CT angiogram (CTA) from January 2002 to November 2006. Patients with atherosclerotic extracranial CICAO were identified from a neuroradiology database that included all patients who underwent a cervical CTA. CICAO had to be at the level of the bulb; mid-cervical or petrocervical occlusions were excluded. The sample included both inpatient and outpatient CTA studies. The indications for testing included the evaluation of a transient ischemic attack, stroke, mental status changes, preoperative evaluation, suspected aneurysms, or arterial dissections. Patients with magnetic resonance imaging (MRI) of the brain performed within 4 weeks of the presentation were included. MRI was reviewed to delineate the location and lateralization of RI, if present. The sample was dichotomized into patients with RI versus those without RI (No-RI). RI was defined by an MRI with a hyperintense lesion in diffusion-weighted imaging and a compatible apparent diffusion coefficient hyperintense signal in the correspondent CICAO territory compared to the corresponding contralateral area [8] and could be symptomatic or silent [9]. Since studies of the cerebral circulation were not systematically available, the CICAO territory was defined as the areas vascularized by the middle and/or anterior cerebral arteries. The degree of stenosis as per CTA was estimated by the NASCET criteria [10]. In patients with bilateral CICAO, the CICAO with recent stroke was used as the dependent side. The study was approved by the local Committee on Research Involving Human Subjects.

Baseline presenting symptoms, demographics, initial National Institutes of Health Stroke Score, laterality of CICAO, and home medication intake at the time of CICAO diagnosis were recorded. Evaluated vascular risk factors included tobacco use, diagnosis of hypertension, hyperlipidemia, coronary artery disease [CAD; angina or prior myocardial infarction (MI)], previous transient ischemic attack or ischemic stroke (defined as events that had occurred 4 weeks prior to the CICAO diagnosis), atrial fibrillation, hypercoagulable states, and diabetes mellitus.

CTA Technique

CTAs were performed on a GE Lightspeed VCT 64 slice scanner using an intravenous contrast bolus of 100 ml Omnipaque-350. An axial noncontrast head CT was performed first at 5-mm slice thickness followed by a helical contrasted axial CTA at 0.625-mm slice thickness intervals.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences 20.0 (SPSS, Chicago, Ill., USA). Results are reported as the mean $\pm$ standard deviation and proportions. Between-group comparisons (RI vs. No-RI CICAO) for categorical variables were performed by the χ^2 test or Fisher's exact test, as appropriate. The Kolmogorov-Smirnov test was performed to evaluate normality. Continuous variables were compared by the independent t test or the Mann-Whitney U test, as appropriate. Multivariate logistic regression analysis with the variable selection method was performed and included variables with $p < 0.1$ on univariate analysis. Statistical significance was set at $p < 0.05$.

Table 1. Baseline characteristics of patients with CICA0

	Total (n = 108)	RI CICA0 (n = 62)	No-RI CICA0 (n = 46)	p value
Age, years	63.9±13.2	62.6±12.2	65.5±12.1	0.23
Male	63 (58)	34 (55)	29 (63)	0.43
Race				0.84
White	100 (92)	57 (92)	43 (94)	
Black	6 (6)	4 (6)	2 (4)	
Hispanic	1 (1)	0 (0)	1 (2)	
Asian	1 (1)	1 (2)	0 (0)	
CICA0 lateralization (left)	55 (50)	33 (53)	22 (48)	0.69
Diabetes	30 (27)	22 (35)	8 (17)	0.05
Dyslipidemia	56 (51)	24 (38)	32 (69)	<0.01
Smoking	66 (61)	41 (66)	25 (54)	0.23
Prior TIA	31 (28)	15 (24)	16 (34)	0.28
Prior stroke	36 (33)	17 (27)	19 (41)	0.15
Hypertension	94 (87)	55 (88)	39 (84)	0.57
Coronary disease	36 (30)	8 (13)	25 (54)	<0.01
Hypercoagulability	6 (5)	2 (3)	4 (8)	0.39
Atrial fibrillation	26 (24)	12 (19)	14 (30)	0.25
Contralateral ICA				
<50% stenosis	82 (76)	49 (79)	33 (71)	0.49
≥50% stenosis/occlusion	26 (24)	13 (21)	13 (28)	0.49
Vertebral artery occlusion (any side)	11 (10)	3 (5)	8 (17)	0.05
Antiplatelets	68 (63)	35 (56)	33 (71)	0.10
Aspirin	44 (40)	18 (29)	26 (56)	<0.01
Clopidogrel	34 (31)	22 (35)	12 (26)	0.40
Aspirin/dipyridamole	4 (3)	2 (3)	2 (4)	1.00
Warfarin	17 (17)	9 (14)	8 (17)	0.79
Statin	39 (36)	13 (21)	26 (56)	<0.01
Antihypertensive medication	39 (36)	6 (9)	33 (71)	<0.01

Results are shown as means ± standard deviations; percentages are shown within parentheses. TIA = Transient ischemic attack.

Results

Out of 2,459 patients who underwent cervical CT angiography, a total of 144 patients (5.8%) were diagnosed with atherosclerotic CICA0. One hundred and eight (4.4%) of the 144 patients had an available MRI and complete medical records. The overall age of the subjects was 64 ± 13 years, and over half (58%) were men.

Sixty-two subjects (57%) had RI CICA0 at presentation. Thirty patients (48%) had cortical strokes, 27 (44%) had cortical and subcortical strokes, while only 5 (8%) had isolated subcortical strokes. The demographics of the RI CICA0 group were comparable to those of the No-RI group, with the exception that those with RI had a lower prevalence of CAD and dyslipidemia (table 1) on univariate analysis. The use of antiplatelet therapy was not different between the two groups. Individuals with RI were less likely on statin and antihypertensive therapy (table 1). Only 28 patients were concomitantly on statin and antihypertensive therapy (6% in the RI vs. 52% in the No-RI group; $p < 0.01$). Five percent of the patients with RI also had recent contralateral or posterior circulation RI, compared to 62% of the No-RI patients ($p < 0.01$).

Table 2. Multivariate logistic regression analyses for factors associated with CICA0 presenting with RI

	OR	95% CI	p value
Model No. 1			
Dyslipidemia	0.62	0.19–2.05	0.39
CAD	0.17	0.03–0.75	0.02
Diabetes	1.72	0.49–6.02	0.39
Aspirin	0.74	0.18–2.93	0.67
Antihypertensive medication	0.04	0.01–0.15	<0.01
Model No. 2			
Dyslipidemia	0.63	0.23–1.70	0.36
CAD	0.17	0.04–0.64	<0.01
Diabetes	3.00	0.98–9.14	0.05
Aspirin	0.89	0.28–2.84	0.85
Statin	0.28	0.11–0.73	0.01

The variables ‘statin therapy’ and ‘antihypertensive therapy’ were significantly correlated ($\rho = 0.59$; $p < 0.001$). Therefore, two multivariate models including either statin or antihypertensive therapy as part of the covariates were performed. Multivariate logistic regression analysis revealed that CAD, statin therapy, and antihypertensive therapy were inversely associated with symptomatic CICA0 (table 2).

In order to evaluate whether the independent negative association of CAD with RI CICA0 was due to a higher prevalence of statin therapy in the No-RI CICA0 group, sensitivity analyses were performed. Multivariate logistic analysis for predictors of statin use revealed that CAD was not independently associated with statin therapy (OR 2.0, 95% CI 0.5–8.5; $p = 0.30$).

Discussion

Although statin use and antihypertensive therapy have been previously demonstrated to benefit patients with symptomatic CICA0 for secondary stroke prevention [6, 7], we were able to demonstrate that pretreatment with statin and antihypertensive medications in patients with CICA0 is associated with asymptomatic No-RI presentation.

Overall, statin use was low (39%) in our series, likely because CICA0 was newly diagnosed and because aggressive statin treatment was less common in ischemic stroke before 2006 [11]. Nevertheless, our findings indicate that statin is associated with a lower risk of symptomatic CICA0 at the time of diagnosis. This class of medication has been shown to prevent recurrent stroke in nonselected ischemic stroke patients [11]. Evidence of the effect of statin specifically on primary prevention in cervical carotid occlusion is scarce [1]. Powers et al. [6] compared risk factors in two groups of patients with recent ischemic symptoms from ICA occlusion and ipsilateral increased oxygen extraction fraction and followed them up for 2 years (22 patients studied from 1992 to 1997, and 98 from 2002 to 2010); the reduced stroke risk observed in the more recent cohort was independently associated with the higher proportion of patients on lipid-lowering therapy at baseline. Our findings further support their conclusions, as we demonstrated an objective association between statin use and lower chances of CICA0 presenting with RI.

The etiology of ischemic stroke in patients with CICA0 may be related to hemodynamic insufficiency, impaired microembolus washout, embolism from the area distal to the occlusion, or from stump emboli entering the external carotid artery through collateral channels into the ICA territory [4]. Statins have been shown to prevent stroke in patients with ICA stenosis,

possibly by stabilizing atherosclerotic plaques [12]. However, since strokes in CICA0 are unlikely to be atheroembolic, the mechanism through which it may benefit patients in this context is unclear [13]. The use of statins has been linked to enhanced collateralization in patients presenting with large vessel intracranial occlusions and may explain, in part, this potential benefit in CICA0 [14, 15]. Statins have been shown to reduce carotid intima-media thickness, exert antioxidant, anti-inflammatory, and antiplatelet effects, and protect the endothelial lining of blood vessels by interacting with nitric oxide synthase [16]. Moreover, it has been speculated that statins promote angiogenesis, endogenous cell proliferation, neurogenesis, and new synapse formation [17]. These pleiotropic cerebrovascular effects of statins may explain the association of statins with asymptomatic CICA0 in our cohort.

Antihypertensive medication use was observed in <10% of CICA0 patients with RI compared to 71% of patients with No-RI, implying that antihypertensive medication may have a beneficial impact on the course of asymptomatic CICA0. A study of a cohort predominantly composed of patients with carotid stenosis >75% or complete occlusion revealed that antihypertensive treatment was associated with significantly reduced recurrent stroke risk [7]. In patients with recently symptomatic CICA0 and hemodynamic cerebral ischemia (Carotid Occlusion Surgery Study cohort), controlled hypertension ($\leq 130/85$ mm Hg) was associated with a reduced risk of subsequent ischemic stroke [18]. In clinical practice, physicians may be reluctant to treat hypertension to lower blood pressure targets because of concerns about reducing cerebral perfusion pressure in the setting of carotid high-grade stenosis or occlusion. While this is particularly important in the acute stroke scenario, our findings corroborate the idea that chronic blood pressure treatment is associated with asymptomatic CICA0 status at diagnosis. The mechanisms underlying this effect are unclear. Untreated hypertensive disease is known to affect endothelial function, generating enhanced leukocyte-endothelial cell adhesion, endothelial barrier dysfunction, reversed angiogenesis (rarefaction) and platelet hyperreactivity, and impaired vasomotor reactivity [19]. Antihypertensive treatment may, therefore, maximize arterial vasomotor function in collateral cerebral and craniocervical blood vessels.

Carotid atherosclerotic disease and CAD have common vascular risk factors and often exist simultaneously [20, 21]. The prevalence of ischemic heart disease in patients with carotid atherosclerosis is relatively high. MI at baseline was reported in 13% of the COSS trial patients, while MI or angina was reported in 32 and 19% of the NASCET and European Carotid Surgery Trial (ECST) patients, respectively [22, 23]. Thirty percent of our sample presented with CAD, which was independently associated with No-RI CICA0 status. Our analyses indicated that this finding was not solely explained by a higher use of statins and may potentially represent a referral selection bias in our sample (since patients with CAD may have been sent for asymptomatic carotid disease screening more frequently). Conversely, the prevalence of 62% contralateral and posterior circulation strokes in the No-RI patients indicates that this group was constituted predominantly by patients with ischemic cerebrovascular disease.

Our study is also limited by its retrospective and cross-sectional design. Thirty-six patients had incomplete medical records or no brain MRI and were therefore not incorporated into the analyses, which may have led to selection bias. The interval between symptom occurrence and MRI was 0–28 days; therefore, some patients with subacute stroke may have been inaccurately classified as not having had a recent stroke. However, this would lead to regression to the mean and only impact statistical power, which was not a concern in this study. The timing between symptom onset and CTA and MRI was not recorded. Regrettably, we did not have access to and could not evaluate dosing, nor the statin subtype or antihypertensive class. Patients with asymptomatic carotid occlusion have been demonstrated to have a lower risk of subsequent stroke compared to symptomatic CICA0 patients [24, 25]. Therefore, we cannot exclude the possibility that the two groups studied had a different

biological substrate and represent distinct disease processes. However, our findings may indicate that the more benign prognosis of CICA0 may, in part, relate to an initial symptomatic presentation predisposed by suboptimal medical therapy.

Conclusion

The use of statins and antihypertensive medication is associated with No-RI atherosclerotic CICA0 status. Our findings reinforce the accrued evidence pointing to important benefits of these therapeutic agents in ischemic cerebrovascular disease and extend these results to a specific population of patients with atherosclerotic CICA0.

Disclosure Statement

Scott D. Newsome received consultant fees from Biogen-Idec and Genzyme and research support (paid directly to the institution) from Biogen-Idec and Novartis. Randall C. Edgell is consultant to Penumbra Inc., and Dileep R. Yavagal is consultant to Boston Scientific, Micrus, Abbott Vascular, and Coaxia and has received travel support from Abbott Vascular, Inc. None of the other authors have any conflicts of interest.

References

- 1 Powers WJ: Management of patients with atherosclerotic carotid occlusion. *Curr Treat Options Neurol* 2011; 13:608–615.
- 2 Klijn CJ, van Buren PA, Kappelle LJ, Tulleken CA, Eikelboom BC, Algra A, van Gijn J: Outcome in patients with symptomatic occlusion of the internal carotid artery. *Eur J Vasc Endovasc Surg* 2000;19:579–586.
- 3 Klijn CJ, Kappelle LJ, Tulleken CA, van Gijn J: Symptomatic carotid artery occlusion. A reappraisal of hemodynamic factors. *Stroke* 1997;28:2084–2093.
- 4 Hankey GJ, Warlow CP: Prognosis of symptomatic carotid artery occlusion. *Cerebrovasc Dis* 1991;1:245–256.
- 5 Grubb RL Jr, Derdeyn CP, Fritsch SM, Carpenter DA, Yundt KD, Videen TO, Spitznagel EL, Powers WJ: Importance of hemodynamic factors in the prognosis of symptomatic carotid occlusion. *JAMA* 1998;280:1055–1060.
- 6 Powers WJ, Clarke WR, Grubb RL Jr, Videen TO, Adams HP, Derdeyn CP: Improved prognosis of medically treated hemodynamic cerebral ischemia is associated with more lipid-lowering therapy. Presented at the 2011 Meeting of the American Academy of Neurology, Honolulu, April 12, 2011.
- 7 Yokota C, Hasegawa Y, Minematsu K, Yamaguchi T: Effect of acetazolamide reactivity on [corrected] long-term outcome in patients with major cerebral artery occlusive diseases. *Stroke* 1998;29:640–644.
- 8 Schulz UG, Briley D, Meagher T, Molyneux A, Rothwell PM: Diffusion-weighted MRI in 300 patients presenting late with subacute transient ischemic attack or minor stroke. *Stroke* 2004;35:2459–2465.
- 9 Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MS, George MG, Hamdan AD, Higashida RT, Hoh BL, Janis LS, Kase CS, Kleindorfer DO, Lee JM, Moseley ME, Peterson ED, Turan TN, Valderrama AL, Vinters HV; American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Council on Nutrition, Physical Activity and Metabolism: An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; 44:2064–2089.
- 10 North American Symptomatic Carotid Endarterectomy Trial. Methods, patient characteristics, and progress. *Stroke* 1991;22:711–720.
- 11 Amarenco P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, Hennerici M, Rudolph AE, Silleesen H, Simunovic L, Szarek M, Welch KM, Zivin JA: Stroke prevention by aggressive reduction in cholesterol levels I: high-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006;355:549–559.
- 12 Della-Morte D, Moussa I, Elkind MS, Sacco RL, Rundek T: The short-term effect of atorvastatin on carotid plaque morphology assessed by computer-assisted gray-scale densitometry: a pilot study. *Neurol Res* 2011; 33:991–994.
- 13 Silleesen H, Amarenco P, Hennerici MG, Callahan A, Goldstein LB, Zivin J, Messig M, Welch KM: Stroke prevention by aggressive reduction in cholesterol levels I: atorvastatin reduces the risk of cardiovascular events in patients with carotid atherosclerosis: a secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. *Stroke* 2008;39:3297–3302.

- 14 Ovbiagele B, Saver JL, Starkman S, Kim D, Ali LK, Jahan R, Duckwiler GR, Vinuela F, Pineda S, Liebeskind DS: Statin enhancement of collateralization in acute stroke. *Neurology* 2007;68:2129–2131.
- 15 Lee MJ, Bang OY, Kim SJ, Kim GM, Chung CS, Lee KH, Ovbiagele B, Liebeskind DS, Saver JL: Role of statin in atrial fibrillation-related stroke: an angiographic study for collateral flow. *Cerebrovasc Dis* 2014;37:77–84.
- 16 Rajanikant GK, Zemke D, Kassab M, Majid A: The therapeutic potential of statins in neurological disorders. *Curr Med Chem* 2007;14:103–112.
- 17 Rodriguez-Yanez M, Agulla J, Rodriguez-Gonzalez R, Sobrino T, Castillo J: Statins and stroke. *Ther Adv Cardiovasc Dis* 2008;2:157–166.
- 18 Powers WJ, Clarke WR, Grubb RL Jr, Videen TO, Adams HP Jr, Derdeyn CP; COSS Investigators: Lower stroke risk with lower blood pressure in hemodynamic cerebral ischemia. *Neurology* 2014;82:1027–1032.
- 19 Granger DN, Rodrigues SF, Yildirim A, Senchenkova EY: Microvascular responses to cardiovascular risk factors. *Microcirculation* 2010;17:192–205.
- 20 Aboyans V, Lacroix P: Indications for carotid screening in patients with coronary artery disease. *Presse Med* 2009;38:977–986.
- 21 Jashari F, Ibrahim P, Nicoll R, Bajraktari G, Wester P, Henein MY: Coronary and carotid atherosclerosis: similarities and differences. *Atherosclerosis* 2013;227:193–200.
- 22 Fox AJ, Eliasziw M, Rothwell PM, Schmidt MH, Warlow CP, Barnett HJ: Identification, prognosis, and management of patients with carotid artery near occlusion. *AJNR Am J Neuroradiol* 2005;26:2086–2094.
- 23 Powers WJ, Clarke WR, Grubb RL Jr, Videen TO, Adams HP Jr, Derdeyn CP; COSS Investigators: Extracranial-intracranial bypass surgery for stroke prevention in hemodynamic cerebral ischemia: the Carotid Occlusion Surgery Study randomized trial. *JAMA* 2011;306:1983–1992.
- 24 Bornstein NM, Norris JW: Benign outcome of carotid occlusion. *Neurology* 1989;39:6–8.
- 25 Powers WJ, Derdeyn CP, Fritsch SM, Carpenter DA, Yundt KD, Videen TO, Grubb RL Jr: Benign prognosis of never-symptomatic carotid occlusion. *Neurology* 2000;54:878–882.