Prevalence of Carotid Artery Disease among Ambulatory Patients with Coronary Artery Disease

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ABSTRACT: **Background:** Concomitant carotid artery disease (CaAD) in patients with coronary artery disease (CAD) is associated with worse cardiac and neurologic outcomes. The reported prevalence and risk factors for concomitant CaAD in CAD patients varied among previous studies.

Objectives: To examine these factors in ambulatory patients with CAD and well-documented cholesterol levels treated with cholesterol-lowering medications.

Methods: We retrospectively analyzed prospectively collected data from 325 unselected patients with CAD (89 women, mean age 68.8 ± 9.9 years) undergoing routine evaluation at the coronary clinic of our hospital.

Results: The low density lipoprotein-cholesterol (LDL-C) was ‹ 100 mg/dl in 292 patients (90%). Age at onset of CAD symptoms was 59.4 ± 10.8 years. Carotid stenosis ≥ 50% was seen in 83 patients (25.5%) and between 30% and 49% in 55 patients (17%) (duplex method). Carotid stenosis was significantly associated with hypertension ($P = 0.032$), peripheral arterial disease ($P = 0.002$) and number of coronary arteries with ≥ 50% stenosis ($P = 0.002$), and showed a borderline association with age at CAD onset ($P = 0.062$) and diabetes mellitus ($P = 0.053$). On linear regression analysis, independent predictors of CaAD were peripheral vascular disease (OR 3.186, 95%CI 1.403–7.236, $P = 0.006$), number of coronary arteries with ≥ 50% stenosis (OR 1.543, 95%CI 1.136–2.095, $P = 0.005$), and age at CAD onset (OR 1.028, 95%CI 1.002–1.054, $P = 0.003$). None of the variables studied predicted freedom from CaAD.

Conclusions: Carotid atherosclerosis is very common in stable ambulatory patients with CAD regularly taking statins. The risk is higher in patients with peripheral arterial disease, a greater number of involved coronary arteries, and older age at onset of CAD.

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KEY WORDS: coronary artery disease (CAD), concomitant carotid artery disease (CaAD), stroke, ≥ 50% stenosis

Atherosclerotic disease affecting the extracranial portion of the carotid artery accounts for 15%–20% of all events of stroke, the third leading cause of death in industrialized nations and a major cause of long-term disability [1-4]. Carotid artery disease (CaAD) is also associated with continued neurologic events over time [5] and serves as a predictor of increased risk of myocardial infarction and non-stroke vascular death [1,6]. There is a well-established association between disease of the carotid arteries and disease of the coronary arteries, which is not surprising given the involvement of atherosclerosis in both and the proximity of these two arterial beds [6]. Much of the current data on concomitant CaAD in patients with CAD were derived from candidates for aortocoronary bypass grafting (CABG) [7-13], who often undergo carotid evaluation because severe CaAD can induce intraoperative stroke [7,8]. The reported prevalence rates of concomitant CaAD in this patient group are variable, reaching 36% [9-11], and there appears to be a striking relationship between the extent of CAD and the risk of CaAD [12]. The risk factors for the development of CaAD are similar to those for CAD [1], namely, advanced age, smoking, hypertension, diabetes mellitus, hypercholesterolemia, and possibly, ethnic origin [13]. The risk factors for concomitant CaAD in patients with CAD are less clear and, as data from candidates for aortocoronary bypass surgery show, may include peripheral vascular disease, previous stroke, and unstable angina [10,14].

However, data on concomitant CaAD in ambulatory patients with stable CAD are more limited [12,15], even though this is a much larger group in whom CaAD poses an increased lifetime risk of stroke. In addition, little is known about the prevalence of concomitant CaAD in patients with CAD treated with statins, which have been found to reduce the risk of CaAD-associated stroke [16]. Therefore, the aim of the present study was to examine the prevalence and risk factors of CaAD in ambulatory patients with CAD in the statin era.

PATIENTS AND METHODS

The study sample included 325 unselected patients with angiographically documented CAD attending the coronary clinic of a community hospital between 1 January 2011 and 31 December 2013. All underwent carotid artery examination as part of their routine evaluation. The patients' prospectively collected data were derived by file review and analyzed retro-

spectively, as follows: patient age and gender, age at onset of CAD, coronary risk factors (diabetes mellitus, hypertension, hypercholesterolemia, smoking habits, and family history of premature CAD), and relevant co-morbidities, including hypothyroidism, peripheral arterial disease, and history of CABG. Use of statins and plasma levels of creatinine and low and high density lipoprotein-cholesterol (LDL-C, HDL-C) were recorded from the hospital's computerized laboratory database. To avoid selection bias, patients with known CaAD or previous stroke and homozygotes for familial hypercholesterolemia were excluded. The results of the patients' coronary angiograms were reviewed to determine the number of coronary vessels with ≥ 50% luminal stenosis and presence of left main coronary artery luminal stenosis > 40%.

Diabetes mellitus was defined as fasting plasma glucose > 125 mg/dl, glycated hemoglobin level > 6.5%, or taking anti-diabetic medications. Hypertension was defined as systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, or taking antihypertensive medications. Hypercholesterolemia was defined as level of LDL-C > 70 mg/dl or HDL-C < 40 mg/dl. Smoking was defined as current or recent (< 1 year) smoking of > 10 cigarettes daily. Family history of premature CAD was defined as onset of CAD in a first-degree male relative at age < 55 years or a first-degree female relative at age < 65 years.

All the patients underwent coronary angiography at our laboratory using standard techniques. Severity of coronary stenosis and number of involved coronary arteries were assessed by skilled operators. Left ventricular systolic function was assessed by echocardiography and categorized as follows: normal (ejection fraction > 55%, category 1), mild or moderate left ventricular dysfunction (category 2), and left ventricular dysfunction of more than moderate severity (category 3).

The extracranial carotid arteries were examined at the hospital or in the community by experienced sonographers using duplex ultrasound. The findings were classified according to the severity of the stenosis in the more severely affected carotid artery. Carotid luminal stenosis of 30–49% was classified as mild CaAD, luminal stenosis of 50–69% as moderate CaAD, and luminal stenosis of ≥ 70% as severe CaAD. To assess the possible impact of the duration of atherosclerosis, we calculated the time (by patient age) from onset of CAD symptoms to the carotid artery examination.

Nominal data were described as numbers and percentages, and continuous data as means and standard deviations. Comparisons of continuous parameters between groups were performed with Student's *t*-test, and of nominal parameters with chi-square and Spearman tests. A *P* value of < 0.05 was considered significant. SPSS software was used for statistical analyses. Univariate analysis was applied to examine the effect of risk factors on the prevalence of CaAD. Factors found to be significant were entered into a linear regression model to identify those with an independent effect. For analysis of risk factors, patients were divided into two groups by degree of CaAD [9,12,13,17,18]: carotid stenosis ≥ 50% and 0–49%.

RESULTS

The sample consisted of 325 patients (27% women) aged 34–90 years. Age at onset of CAD symptoms ranged from 33 to 87 years (mean 68.8 ± 9.9 years). Carotid artery stenosis of ≥ 50% was identified in 83 patients (25.5%) and stenosis of 30–49% in an additional 55 patients (17%). Twelve patients (4%) had left main CAD, 125 (38%) triple-vessel CAD, 92 (28%) double-vessel CAD, and 96 (29%) single-vessel CAD. All patients except 6 were treated with statins; 292 patients (90%) had a plasma LDL-C level < 100 mg/dl. Table 1 compares patients with carotid artery stenosis ≥ 50% to those with stenosis < 50% or no stenosis. Patients with carotid stenosis ≥ 50% had a significantly higher frequency of hypertension ($P = 0.032$) and concomitant peripheral arterial disease ($P = 0.002$), a significantly greater number of coronary arteries with ≥ 50% stenosis ($P = 0.002$), and a tendency to older age at onset of CAD ($P = 0.068$) and higher rate of diabetes mellitus ($P = 0.053$). No significant effect was found for age at carotid artery examination, gender, level of HDL-C, family history of CAD, previous CABG, level of plasma creatinine, and time from diagnosis of CAD to carotid artery examination. On linear regression analysis, peripheral arterial disease

Table 1. Rates of risk factors in patients with vs without carotid artery stenosis ≥ 50%

Variable	CaAD(-)* n=242	CaAD(+)* n=83	*P* value
Gender (males), %	74.0	68.7	0.351
Smoking, %	31.0	33.7	0.643
Hypertension, %	59.1	72.3	0.032
Diabetes mellitus, %	33.9	45.8	0.053
Family history, %	42.1	32.5	0.122
Hypercholesterolemia, %	78.5	72.3	0.246
Peripheral vascular disease, %	5.8	16.9	0.002
Prior CABG, %	33.9	44.6	0.081
No. of involved coronary arteries, mean ± SD	2.1 ± 0.9	2.4 ± 0.9	0.002
LV function category (1-3), mean ± SD	1.2 ± 0.5	1.2 ± 0.4	0.191
HDL-C (mg/dl), mean ± SD	44.1 ± 13.3	49.9 ± 3.4	0.327
Creatinine (mg/dl), mean ± SD	1.1 ± 0.8	1.1 ± 0.4	0.876
Age at carotid examination (yr), mean ± SD	68.4 ± 9.9	69.9 ± 9.5	0.236
Age at onset of CAD (yr), mean ± SD	58.7 ± 10.7	61.3 ± 10.9	0.062
Age difference (yr), mean ± SD†	9.3 ± 6.5	8.2 ± 6.7	0.181
No. of risk factors, mean ± SD	2.5 ± 1.1	2.6 ± 1.1	0.430

*CaAD(-) = carotid stenosis < 50% or no stenosis, CaAD(+) = carotid stenosis of ≥ 50%
†Difference between age at onset of CAD and age at evaluation for CaAD

[odds ratio (OR) 3.186, 95% confidence interval (95%CI) 1.403–7.236, $P = 0.006$], number of coronary arteries with ≥ 50% stenosis (OR 1.543, 95%CI 1.136–2.095, $P = 0.005$), and age at onset of CAD (OR 1.028, 95%CI 1.002–1.054, $P = 0.0033$) were independent predictors of concomitant CaAD. None of the variables studied effectively predicted freedom from CaAD.

DISCUSSION

The results of the present study reveal a very high prevalence of CaAD among a group of ambulatory statin-treated patients with CAD. Concomitant peripheral vascular disease, hypertension, and older age at onset of CAD were associated with increased risk of concomitant CaAD. However, we could not identify subgroups of patients who were not at risk. To the best of our knowledge, this is the first report on the prevalence of CaAD among patients with CAD that examined the possible effect of the age at onset of CAD and that included data on statin use and subsequent plasma LDL-C levels. The sample included only ambulatory patients with stable CAD who had no history of stroke or CaAD. Thus, the CaAD in our patients was newly diagnosed. Inclusion of patients with known CaAD in the sample would have increased the prevalence rate.

The association between CAD and CaAD demonstrated in the present study is consistent with previous findings in ambulatory patients with CAD [12,15] and in other populations of CAD patients [7,9-11]. However, an exact comparison of the results may not be possible, owing at least in part to the strong effect of left main or triple-vessel CAD and differences in the definition of CAD. For example, in a recent study by Steinvil et al. [12] of 1405 candidates for non-emergent coronary angiography, only 17% of the patients with CAD had carotid stenosis of at least moderate severity, but they defined CAD as a luminal diameter stenosis > 70%. Moreover, 42% of their patients with CAD had left main or triple-vessel disease, and the rates of CaAD were 31% in patients with left main disease, 18% in patients with triple-vessel CAD, 13% in patients with double-vessel disease, and 6% in patients with single-vessel disease [12]. By contrast, Tanimoto and co-authors [15] reported a 25.4% prevalence of carotid stenosis in Japanese patients scheduled for coronary angiography for suspected CAD. They defined CAD as coronary stenosis > 50%. The prevalence of triple-vessel CAD among their patients was 33%, and the rates of CaAD were 36% in patients with triple-vessel CAD, 21.4% in patients with double-vessel CAD, and 14.5% in patients with single-vessel CAD. The results of the present study are compatible with these findings, showing a 25.2% prevalence of CaAD among patients with CAD of whom 42% had left main or triple-vessel disease, defined as luminal diameter stenosis ≥ 50%. The number of involved coronary arteries was a significant predictor of CaAD in our patients as well.

PREDICTORS OF CaAD IN PATIENTS WITH CAD

Previous studies identified several potential independent predictors of concomitant CaAD in patients with CAD: age [12,14,15], peripheral vascular disease [14], history of cerebrovascular accident [12,14], unstable angina [14], the extent of CAD [12,15], previous CABG [16], smoking status [12], and diabetes mellitus [12]. However, the risk of CaAD was high even in the absence of these factors, and even the association with age had no clear threshold. Our evaluation of the predictive value of various clinical, biochemical, demographic, and anatomic variables identified only peripheral vascular disease, extent of CAD, and age at onset of CAD (OR 1.028, 95%CI 1.002–1.054, $P = 0.0033$) as independent predictors of CaAD. We did not find a significant association with actual patient age but rather with older age at onset of CAD symptoms. The possible relationship between age at CAD onset and the development of concomitant CaAD has not yet been addressed in the literature. We examined this issue because although atherosclerosis develops and becomes more widespread over time, earlier onset of CAD might indicate a more aggressive course or risk factors. Our findings show that earlier onset of CAD was weakly protective against CaAD. Whether this results from a difference in risk factors is unclear, because age at onset was an independent predictor, and specific risk factors for early onset of CAD, for example familial hypercholesterolemia, hyperhomocysteinemia and genetic factors, were either excluded or not examined. The possibility of a lower susceptibility to CaAD in patients with earlier onset of CAD needs to be confirmed by further research. Nevertheless, our data clearly demonstrate that the time between onset of CAD symptoms and carotid evaluation was comparable in patients with and without CaAD. This may support the hypothesis that the risk of concomitant CaAD is related to factors determining the extent of CAD rather than its duration.

The relationship with peripheral vascular disease and the lack of effect of most risk factors may suggest that patients with atherosclerosis in more than one arterial bed may be at higher risk of involvement of additional arterial beds that are direct ramifications of the aorta. Importantly, this process is not related to the traditional risk factors.

We defined carotid stenosis by a cutoff of 50%, as in most previous studies that examined the prevalence and risk factors of concomitant CaAD and CAD. However, we also examined the prevalence of mild CaAD in our patients given that the rate of progression of carotid disease in these patients is not much slower than in patients with moderate CaAD [18]. For example, Ballotta et al. [18] found that after a mean follow-up of 4.1 years, carotid artery disease progressed in 34.3% of patients with carotid luminal diameter stenosis of 30%–49% and in 47.9% of those with stenosis of 50%–69%. In our study, the inclusion of patients with mild carotid artery stenosis in the analysis yielded a very high prevalence of CaAD (42.5%). This finding is consistent with the report by Steinvil et al. [12] where

only 42% of patients had patent carotid arteries. Together, our findings underscore the very high prevalence of potentially clinically significant CaAD among patients with CAD and the potential value of screening for these patients to prevent long-term neurologic complications.

STATINS AND CaAD IN PATIENTS WITH CAD

Statins may delay the progression of atherosclerosis and reduce the risk of stroke in patients with CAD [19]. Only very limited data are available on statin use or LDL-cholesterol levels in terms of the risk of CaAD in patients with CAD. All but six of our patients were taking statins, and 90% of them had reached the LDL-C target for CaAD (< 100 mg/dl). Although we did not have information on the duration of statin use, we assume it was long term, since the diagnosis of CAD in our patients, and presumably the initiation of statin therapy, preceded the diagnosis of CaAD by 8.2 ± 6.7 years. Thus, our study probably shows for the first time that CaAD is very common in patients with CAD despite the effective widespread use of statins.

STUDY LIMITATIONS

Some of our patients underwent duplex carotid ultrasound in the community. This might have resulted in difficulty comparing the results. However, similar diagnostic criteria were used in all tests and most of them were performed by operators who were staff members at our hospital. Thus, all test results were comparable.

CONCLUSIONS

The results of the present study show that carotid atherosclerosis is common in ambulatory patients with CAD who are treated effectively with statins. The risk is higher in patients with hypertension, peripheral arterial disease, older age at onset of CAD, and many involved coronary arteries, but remains substantial even in patients without these factors.

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References

1. Brott TG, Halperin JL, Abbara S, et al; American College of Cardiology Foundation; American Stroke Association; American Association of Neurological Surgeons; American College of Radiology; American Society of Neuroradiology; Congress of Neurological Surgeons; Society of Atherosclerosis Imaging and Prevention; Society for Cardiovascular Angiography and Interventions; Society of Interventional Radiology; Society of NeuroInterventional Surgery; Society for Vascular Medicine; Society for Vascular Surgery. ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary. *Circulation* 2011; 124: 489-532.
2. Grau AJ, Welmar C, Buggle F, et al. Risk factors, outcome, and treatment in sub-types of ischemic stroke: the German data bank. *Stroke* 2001; 32: 2559-66.
3. Sacco RL, Kargman DE, Gu Q, Zamanillo MC. Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction. *Stroke* 1995; 26: 14-20.
4. Wityk RJ, Lehman D, Klag M, Coresh J, Ahn H, Litt B. Race and sex differences in the distribution of cerebral atherosclerosis. *Stroke* 1996; 27: 1974-80.
5. Bryan DS, Carson J, Hall H, et al. Natural history of carotid artery occlusion. *Ann Vasc Surg* 2013; 27: 186-93.
6. Rothwell PM. The interrelation between carotid, femoral and coronary artery disease. *Eur Heart J* 2001; 22: 11-14.
7. Ascher E, Hingorani A, Yorkovich W, Ramsey PJ, Salles-Cunha S. Routine preoperative carotid duplex scanning in patients undergoing open heart surgery: is it worthwhile? *Ann Vasc Surg* 2001; 15: 669-78.
8. Nylor AR, Mehta Z, Rothwell PM, Bell PR. Carotid artery disease and stroke during coronary artery bypass: a critical review of the literature. *Eur J Vasc Endovasc Surg* 2002; 23: 283-94.
9. Wanamaker KM, Moraca RJ, Nitzberg D, Magovern GJ Jr. Contemporary incidence and risk factors for carotid artery disease in patients referred for coronary artery bypass surgery. *J Cardiothorac Surg* 2012; 7: 78-82.
10. Chun LJ, Tsai J, Tam M, Prema J, Chen LH, Patel KK. Screening carotid artery duplex in patients undergoing cardiac surgery. *Ann Vasc Surg* 2014; 28: 1178-85.
11. Durand DJ, Perler BA, Rosenborough GS, et al. Mandatory versus selective preoperative carotid screening: a retrospective analysis. *Ann Thorac Surg* 2004; 78: 159-66.
12. Steinvil A, Sadeh B, Arbel Y, et al. Prevalence and predictors of concomitant carotid and coronary artery atherosclerotic disease. *J Am Coll Cardiol* 2011; 57: 779-83.
13. Greco G, Egorova NN, Moskowitz AJ, et al. A model for predicting the risk of carotid artery disease. *Ann Surg* 2013; 257: 1168-73.
14. Drohomirecka A, Koltowski L, Kwinecki P, Wronecki K, Chichon R. Risk factors for carotid artery disease in patients scheduled for coronary artery bypass grafting. *Kardiol Pol* 2010; 68: 789-94.
15. Tanimoto S, Ikari Y, Tanabe K, et al. Prevalence of carotid artery stenosis in patients with coronary artery disease in Japanese population. *Stroke* 2005; 36: 2094-8.
16. Streifler JY, Raphaeli G, Bornstein N, Molshatzki N, Tanne D, National Acute Stroke Israeli Registry Israel. Is the evaluation and treatment of transient ischemic attack performed according to current knowledge? A nationwide Israeli registry. *IMAJ* 2013; 15: 236-40.
17. Kazemi-Bajestani SM, Vlugt MJ, van der Leeuw FE, de Blankensteijn JD, Bredie SJH. A high prevalence of carotid artery stenosis in male patients older than 65 years, irrespective of presenting clinical manifestation of atherosclerotic disease. *Angiology* 2012; 64: 281-6.
18. Ballotta E, Da Giau G, Meneghetti G, Barbon B, Militello C, Baracchini C. Progression of atherosclerosis in asymptomatic carotid arteries after contralateral endarterectomy: a 10-year prospective study. *J Vasc Surg* 2007; 45: 516-22.
19. Sillesen H, Amarenco P, Hennerici MG, et al; Stroke Prevention by Aggressive Reduction in Cholesterol Levels investigators. 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: 3297-302.

"Let us remember: One book, one pen, one child, and one teacher can change the world"

Malala Yousafzai (born 1997), Pakistani activist for female education and the youngest-ever Nobel Prize laureate. She is known mainly for human rights advocacy for education and for women in her native area in Pakistan, where the local Taliban had at times banned girls from attending school. Yousafzai's advocacy has since grown into an international movement