JCN Open Access ORIGINAL ARTICLE

pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2015;11(4):364-371 / http://dx.doi.org/10.3988/jcn.2015.11.4.364

Preoperative Coronary Stenosis Is a Determinant of Early Vascular Outcome after Carotid Endarterectomy

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Background and Purpose The benefit of carotid endarterectomy (CEA) is directly influenced by the risk of perioperative adverse outcomes. However, patient-level risks and predictors including coronary stenosis are rarely evaluated, especially in Asian patients. The aim of this study was to determine the relationship between the vascular risk factors underlying CEA, including coronary stenosis, and postoperative outcome.

Methods One hundred and fifty-three consecutive CEAs from our hospital records were included in this analysis. All patients underwent coronary computed tomography angiography before CEA. Data were analyzed to determine the vascular outcomes in patients with mild-to-moderate vs. severe coronary stenosis and high vs. standard operative risk, based on the criteria for high operative risk defined in the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial. The vascular outcome was defined as the occurrence of postoperative (≤30 days) stroke, myocardial infarction (MI), or death.

Results An adverse vascular outcome occurred in 8 of the 153 CEAs, with 6 strokes, 2 MIs, and 3 deaths. The vascular outcome differed significantly between the groups with mild-to-moderate and severe coronary stenosis (p=0.024), but not between the high- and standard-operative-risk groups (stratified according to operative risk as defined in the SAPPHIRE trial). Multivariable analysis adjusting for potent predictors revealed that severe coronary stenosis (odds ratio, 6.87; 95% confidence interval, 1.20–39.22) was a significant predictor of the early vascular outcome.

Conclusions Severe coronary stenosis was identified herein as an independent predictor of an adverse early vascular outcome.

Key Words carotid endarterectomy, coronary artery disease, coronary angiography, risk assessment.

INTRODUCTION

Atherosclerosis is common in the intracranial artery than the extracranial artery in Asian patients; as a result, carotid endarterectomy (CEA) has not frequently been performed in Korea. However, according to a recent nationwide, hospital-based stroke registry study in Korea, it appears that the prevalence of intracranial cerebral artery disease has been declining, while that of extracranial disease has been increasing.[1,2]

Prospective randomized studies have demonstrated that CEA reduces the incidence of stroke in symptomatic patients with ipsilateral carotid artery stenosis of ≥50%, and in asymptomatic patients with internal carotid stenosis of ≥70%.[3,4] However, there is a trend toward minimizing intervention for asymptomatic carotid stenosis in favor of medical treatment because of the significant advances in such therapies for vascular disease.[5,6] The ultimate goal of the treatment of carotid artery disease is prolongation of healthy life; there-

Received February 9, 2015
Revised May 7, 2015
Accepted May 8, 2015

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fore, caution is necessary when selecting an invasive treatment approach, and perioperative complications should be prevented wherever possible for interventions such as CEA. Decision-making regarding CEA is dependent upon whether the postoperative risk of stroke, myocardial infarction (MI), or death exceeds the risk of these outcomes under medical management. Defining the relationship between various risk factors and outcomes after CEA is important for appropriate patient selection for this procedure. Several studies have shown that certain risk factors are associated with adverse postoperative vascular outcomes such as stroke, MI, or death after CEA.[7-9]

A link between carotid and coronary arterial diseases has been proposed. Atherosclerosis of the carotid arteries often occurs concomitantly with coronary stenosis, and both diseases are believed to be associated with similar risk factors and pathological mechanisms. Atherosclerotic stroke occurs as a result rupture of atherosclerotic plaques at the site of arterial occlusion or in the proximal relevant arteries, and may be directly relevant to atherosclerotic diseases in other organs.[10] Furthermore, coronary artery disease (CAD) is a very important cause of death during the perioperative and follow-up periods after CEA.[11-14] However, the relationship between preoperative coronary stenosis and postoperative vascular outcome in patients treated by CEA is not well understood.

The aim of this study was to determine whether preoperative coronary stenosis can influence early outcomes after CEA, and to identify the factors that may affect major adverse events (MAEs) following that procedure.

METHODS

Subjects

Routine preoperative coronary evaluation by coronary computed tomography angiography (CCTA) was adopted at our hospital in July 2007. Patients who underwent CEA after that time were included in this study. One hundred and seventy-three consecutive CEAs were performed by a single experienced surgeon at Kyung Hee University Hospital between July 2007 and December 2013. Twenty procedures were excluded because of a lack of CCTA data; further evaluation was not needed in these patients because their electrocardiography and echocardiography findings were normal and they had no cardiac symptoms. This study ultimately included 141 patients who underwent a total of 153 CEA procedures (12 patients underwent bilateral CEA for separate ipsilateral symptomatic events or severe stenosis). Patients with neurological symptoms referable to the ipsilateral carotid territory within 6 months before surgery were classified as symptomatic. Surgery was indicated for symptomatic patients with a carotid stenosis of ≥50% or severe ulceration of the carotid artery, and for asymptomatic patients with a carotid stenosis of ≥70%. All surgeries were performed under general anesthesia, and simultaneous electroencephalography was performed and monitored during the procedure to determine the status of intraluminal shunting.

This study was approved by an independent ethics committee at Kyung Hee University Medical Center (KMC IRB 1414-02).

Risk factors and outcome measurement

Data on patient demographics, surgical indications, operative details, and postoperative outcomes were obtained from hospital records. Postoperative MAEs included any episodes of stroke, MI, or death within 30 days after the operation. Upon appearance of new neurological symptoms or signs, strokes were identified and confirmed by formal neurological examination by neurologists, and by brain imaging. The association between these outcomes and various demographic and preoperative factors that could influence their likelihood were evaluated. These included age, sex, hypertension, dyslipidemia, diabetes mellitus, other cerebral arterial lesions (occlusion or ≥50% stenosis), smoking, and atrial fibrillation.

Definitions of high and standard coronary and operative risks

CCTA was performed prior to CEA and the results used to determine coronary risk; this was in turn used to predict postoperative outcome. The degree of coronary stenosis, as assessed by CCTA, was determined using the scoring system described by Cury et al.,[15] which defines three categories of stenosis: mild (0–40%), moderate (41–70%), and severe (71–100%). Patients were examined using a 64-channel multidetector computed tomography (MDCT) system (Brilliance 64, Philips Medical Systems, Best, The Netherlands). All quantitative measurements were made in a semiautomatic maneuver using the FD10 software provided with Allura 9 (Philips, Eindhoven, The Netherlands) in orthogonal projections at end-diastole, when this was possible. In addition, the severity of coronary stenosis was determined by coronary angiography (CAG) and graded by an experienced angiographer. The degree of stenosis of each of the three major blood vessels (left anterior descending artery, left circumflex artery, and right coronary artery) was graded by both CCTA and CAG. The presence of severe stenosis in at least one of the three vessels resulted in classification into the high-coronary-risk (HCR) group. If the results of the two tests were inconsistent, those obtained using CAG were prioritized; for example, a subject with severe stenosis based on CCTA and with mild-to-moderate stenosis based on CAG was categorized into the standard-coronary-risk (SCR) group.

The high-operative-risk (HOR) and standard-operative-risk (SOR) groups were also defined using the following criteria for high risk in the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial: significant cardiac disease (congestive heart failure, abnormal stress test, or need for open-heart surgery), severe pulmonary disease, contralateral carotid occlusion, contralateral laryngeal nerve palsy, previous radical neck surgery/radiation, tracheostomy, recurrent carotid stenosis, or age greater than 80 years.[16] The SOR group included all procedures not included in the HOR group.

Statistical analysis

The data are presented as mean±SD or median (interquartile range) values (for continuous variables), or as the number (%) of subjects (for categorical variables). Categorical variables were compared using Fisher's exact test, and continuous variables were compared using Student's *t*-test and Wilcoxon's rank-sum test. Preoperative variables positively associated with postoperative outcome at $p<0.2$ were included in a multivariable analysis using logistic regression with Firth's bias correction estimation method. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). The threshold for statistical significance was set at $p<0.05$ (two-sided).

RESULTS

Patient characteristics

One hundred and fifty-three CEA procedures were performed in 141 patients. The baseline characteristics of those patients are given in Table 1. Only the preexistence of severe coronary stenosis significantly affected the postoperative outcome. Preoperative CCTA was performed before CEA in all patients, and CAG was performed in 68 CEAs (44.4%). CAG was performed in 39 of the 57 subjects with severe coronary stenosis based on CCTA. Of those, 35 subjects (89.7%) had severe coronary stenosis based on CAG, and were treated with a percutaneous coronary intervention (PCI). In 96 subjects without severe coronary stenosis based on CCTA, 29 subjects underwent CAG in response to a history of chest pain or a positive stress test. Of those, 17 subjects (58.6%) were observed to have coronary stenosis based on CAG. Of the 52 procedures in subjects with severe coronary stenosis based on CAG, preoperative PCI was performed in 44 procedures. Eight subjects did not undergo PCI because of long-

Table 1. Baseline characteristics of all subjects undergoing carotid endarterectomy

	Major adverse events		*p*
	No (*n*=145)	Yes (*n*=8)	
Age, years	68.6±6.6	65.1±6.6	0.149
Male (%)	123 (84.8)	6 (75.0)	0.612
Hypertension (%)	126 (86.9)	8 (100.0)	0.597
Diabetes mellitus (%)	61 (42.1)	3 (37.5)	>0.999
Dyslipidemia (%)	89 (61.4)	4 (50.0)	0.712
Atrial fibrillation (%)	4 (2.8)	1 (12.5)	0.238
Other cerebral vessel severe (>50%) stenosis (%)	62 (42.8)	4 (50.0)	0.727
Current smoker (%)	43 (29.7)	3 (37.5)	0.697
Preoperative statin (%)	109 (75.2)	6 (75.0)	>0.999
Ipsilateral TIA or stroke within 6 months (%)	78 (53.8)	7 (87.5)	0.077
High operative risk (SHAPPIRE) (%)	12 (8.3)	1 (12.5)	0.517
Stenosis degree (NASCET), %	74.8±15.5	75.2±12.9	0.945
Severe coronary stenosis (%)	63 (43.4)	7 (87.5)	0.024
Preoperative NIHSS score (median, IQR)	1 (0–3)	0 (0–4)	0.564
Preoperative mRS score (%)			0.744
0	55 (37.9)	4 (50.0)	
1	35 (24.1)	1 (12.5)	
2	24 (16.6)	1 (12.5)	
3	18 (12.4)	2 (25.0)	
4	13 (9.0)	0 (0.0)	

Except where indicated otherwise, the data are mean±SD, numbers of patients (%), or median (IQR) values. *p* values were calculated using Student's *t*-test, Fisher's exact test, or Wilcoxon's rank-sum test, as appropriate.
IQR: interquartile range, mRS: modified Rankin Scale, NASCET: North American Symptomatic Carotid Endarterectomy Trial, NIHSS: National Institutes of Health Stroke Scale, SHAPPIRE: Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy, TIA: transient ischemic attack.

segment stenosis, or other specific reasons, such as patient refusal. The patterns of the coronary lesions revealed by preoperative coronary workups are summarized in Fig. 1.

Early outcomes

Postoperative (≤30 days) MAEs occurred in eight CEA procedures (5.2%): six strokes (3.9%), two MIs (1.3%), and three deaths (2.0%; caused by one major stroke and two MIs). The early outcome differed significantly between the HCR and SCR groups (p=0.024). There were no statistically significant differences between the HOR and SOR groups, as defined in the SAPPHIRE trial, with respect to stroke (p=0.418), death (p=0.235), MI (p>0.999), or all MAEs (p=0.517). Vocal cord palsy was the only minor complication that differed signifi-

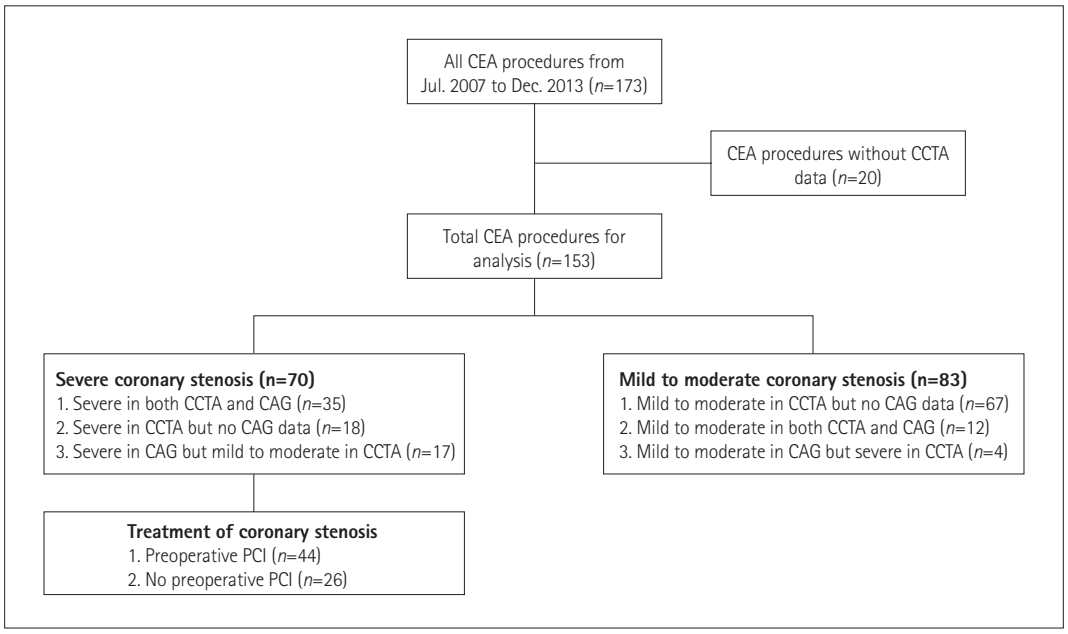

Fig. 1. Preoperative coronary workups for all procedures (n=153). CAG: coronary angiography, CCTA: coronary computed tomography angiography, CEA: carotid endarterectomy, PCI: percutaneous coronary intervention.

Table 2. Early outcome (≤30 days) stratified according to severity of coronary stenosis

	Severity of coronary stenosis		p	Operative risk defined by SAPPHIRE criteria		p
	Mild to moderate (n=83)	Severe (n=70)		Standard (n=140)	High (n=13)	
Major vascular complications	1 (1.2)	7 (10.0)	0.024	7 (5.0)	1 (7.7)	0.517
Death	0 (0.0)	3 (4.3)	0.094	2 (1.4)	1 (7.7)	0.235
Stroke	1 (1.2)	5 (7.1)	0.094	5 (3.6)	1 (7.7)	0.418
Myocardial infarction	0 (0.0)	2 (2.9)	0.208	2 (1.4)	0 (0.0)	>0.999
Minor complications	12 (14.5)	13 (18.6)	0.493*	22 (15.7)	3 (23.1)	0.447
Seizure	2 (2.4)	1 (1.4)	>0.999	2 (1.4)	1 (7.7)	0.235
Hypoglossal palsy	1 (1.2)	0 (0.0)	>0.999	1 (0.7)	0 (0.0)	>0.999
Vocal cord palsy	1 (1.2)	6 (8.6)	0.048	6 (4.3)	1 (7.7)	0.470
Facial palsy	1 (1.2)	1 (1.4)	>0.999	2 (1.4)	0 (0.0)	>0.999
Hematoma	2 (2.4)	1 (1.4)	>0.999	3 (2.1)	0 (0.0)	>0.999
Wound infection	2 (2.4)	0 (0.0)	0.498	2 (1.4)	0 (0.0)	>0.999
Other (fall-down fracture, acute renal failure, pericardial effusion, headache, pneumothorax)	5 (6.0)	4 (5.7)	>0.999	8 (5.7)	1 (7.7)	0.560

Data are n (%) values.
*p was calculated using Fisher's exact test and chi-square test.
SHAPPIRE: Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy.

cantly between the HCR and SCR groups (Table 2). No significant differences were found in early outcome between vascular territories of coronary stenosis (Table 3). Four MAEs (15.4%) occurred in 26 procedures in patients with severe coronary stenosis who received PCI prior to CEA, and 3 MAEs (6.8%) occurred in 44 patients with severe coronary stenosis who did not receive PCI. However, the difference was not statistically significant because both the sample size and number of events were small (p=0.411).

Candidate variables for multivariable analysis using logistic regression were identified, including age, atrial fibrillation, neurological symptoms (transient ischemic attack or stroke) referable to the ipsilateral carotid territory within 6 months, and the existence of severe coronary stenosis. The time interval between CEA and the manifestation of neurological symptoms did not differ significantly between the groups (Table 4). The HOR group (based on the SAPPHIRE definition) did not exhibit a significantly high rate of MAEs. The independent predictors of a poor outcome after multivariable regression analysis are given in Table 5. Severe coronary stenosis was associated with a sevenfold higher risk of occurrence of postoperative MAEs (p=0.030).

Table 3. Preoperative coronary stenosis and early outcome after carotid endarterectomy

	Major adverse events	p
LAD stenosis (+)	5/47 (10.6)	0.059
LAD stenosis (-)	3/109 (2.8)	
LCX stenosis (+)	3/33 (9.1)	0.371
LCX stenosis (-)	5/120 (4.2)	
RCA stenosis (+)	3/39 (7.7)	0.421
RCA stenosis (-)	5/114 (4.4)	

Data are n (%) values. p was calculated by Fisher's exact test.
LAD: left anterior descending artery, LCX: left circumflex artery, RCA: right coronary artery.

DISCUSSION

In this study, postoperative (≤30 days) MAEs occurred following 8 of 153 CEA procedures (5.2%). The key finding of this study is that severe coronary stenosis, confirmed by CCTA and CAG, is an independent predictor of postoperative adverse vascular events after CEA.

Several factors thought to complicate the CEA procedure and to increase the risk of postoperative death and morbidity were investigated in this study. Several other attempts have been made to identify the modifiable risk factors associated with postoperative adverse outcomes in patients undergoing CEA. However, most of those studies did not analyze coronary stenosis. Instead, previous studies have focused primarily on the clinical symptoms and medical history of risk factors, such as CAD (history of MI, angina, previous coronary revascularization), elevated creatinine level, and pulmonary disease.[9,17] One study demonstrated that preoperative CAG in randomized patients without any evidence of CAD was the only independent variable capable of predicting the occurrence of postoperative coronary ischemia after CEA.[18] The validity and usefulness of some studies is limited by the absence of multivariable analyses.[19,20] To build on this previous research, the quantitative data concerning coronary stenosis generated by CCTA and CAG were analyzed in the present study, with the aid of multivariable analyses.

CCTA is used increasingly for the evaluation of CAD. Several publications using 64-slice CT have demonstrated high accuracy for detection of coronary stenosis, in comparison with invasive angiography.[21,22] Despite good sensitivity and specificity for detecting significant CAD patients, there is

Table 4. Early outcome (≤30 days) stratified by symptom onset

	Major adverse events		p
	No (n=145)	Yes (n=8)	
Symptomatic <1 month (n=67)	61 (91.0)	6 (9.0)	0.075
Symptomatic 1–6months (n=18)	17 (94.4)	1 (5.6)	
Symptomatic >6 months (n=15)	15 (100.0)	0 (0.0)	
Asymptomatic (n=53)	52 (98.1)	1 (1.9)	

Data are n (%) values. 'Symptomatic' means neurological symptoms (stroke or transient ischemic attack) referable to the ipsilateral carotid territory. p was calculated using exact Wilcoxon's rank-sum test.

Table 5. Multivariable analysis of early (≤30 days) outcome adjusted by potential predictors

	Adjusted OR	95% CI	p
Age	0.94	0.86–1.03	0.200
Ipsilateral TIA or stroke within 6 months	4.19	0.72–24.44	0.112
Severe coronary stenosis (%)	6.87	1.20–39.22	0.030

p was calculated by logistic regression using Firth's bias correction estimation method. Potential variables were selected based using a threshold of p<0.2 in Table 1.
CI: confidence interval, OR: odds ratio, TIA: transient ischemic attack.

common disagreement on the severity of coronary stenosis between MDCT and the current gold standard (i.e., conventional angiography). Although the negative predictive values are remarkably consistent among studies, the positive predictive values are not, ranging from 64% to 91% in a patient-level analysis among the three major multicenter studies.[23-25] The high negative predictive value makes CCTA an attractive tool with which to rule out CAD. In the present study, the positive predictive value of CCTA was high. However, for 96 procedures performed in patients with mild-to-moderate stenosis of the coronary artery on CCTA, severe coronary stenosis was confirmed in 17 of 29 who also submitted to CAG. This finding may be explained by several factors. First, the CAG procedure was performed only in patients with angina or positive stress test results. Second, while many studies designed to evaluate the accuracy of CCTA in comparison with conventional angiography were performed to identify significant stenosis (≥50%) of the coronary artery tree, we adopted the scoring system used in a previous study, which defined severe stenosis as lying in the range 71–100%. Thus, some patients with stenosis of between 50% and 70% on CCTA would probably be considered to have severe coronary stenosis based on CAG. Variability among readers, poorer spatial resolution of MDCT, inconsistency of conventional angiography readings, and limitations associated with the use of a two-dimensional technique are additional potential reasons for the discrepancy. Direct inspection of the plaque by CT imaging allows detection of CAD, assessment of total atherosclerotic plaque burden, assessment of the number and location of stenoses, and plaque characterization. Therefore, many studies suggest that CCTA is a strong and independent predictor capable of defining the risk of CAD and adverse outcomes, in addition to reducing the need for CAG in particular patients with suspected CAD and either inconclusive or nondiagnostic stress test results.[26]

All of the patients included in the SAPPHIRE trial, were required to have at least one coexisting condition that potentially increased the risk posed by CEA.[16] The SAPPHIRE study showed a combined death, stroke, or MI rate of 4.8% for carotid stenting and 9.8% for CEA on an intention-to-treat basis, and concluded that for patients for whom surgery poses an increased risk, carotid artery stenting with the aid of an emboli-protection device was not inferior to CEA with respect to the prevention of a poor postoperative outcome. In our study, no statistically significant difference was found between the SOR and HOR groups. These results raise the question as to whether the HOR group, as defined in the SAPPHIRE trial, is truly representative of patients at a high risk of CEA. Four other large studies did not find increased morbidity and mortality for high-risk patients,[27-30] and the present results also challenge this concept of a high-risk group of patients for CEA. While the high-risk definition of the SAPPHIRE trial adopted conventional operative risk in general anesthesia, coronary stenosis was used in the present study as a single surrogate marker of advanced atherosclerosis. We believe that coronary stenosis is a potent direct and indirect marker for polyvascular disease. The increasing burden of atherosclerosis is very important with respect to predicting vascular outcome after CEA.[27,31] Although no significant differences were found in the early outcome between vascular territories of coronary stenosis, the outcome for patients with left anterior descending artery stenosis exhibited a trend toward a high prevalence of MAE. Further validation in a large-scale study is required.

The 30-day incidence of stroke or death in the present study was 5.2%, a rate that is similar to those found in previous clinical trials for symptomatic (3.9–6.5%) and asymptomatic (3.1%) patients.[3,32-34] For about half (55.6%) of the procedures, the patients were symptomatic before undergoing CEA. Furthermore, the incidence of MI was 1.3%, which is lower than that found in the Carotid Revascularization Endarterectomy versus Stenting (CREST) study (2.4%), and higher than those found in the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST) (0.4% and 0.9%, respectively).[3,14,34] The 30-day mortality rate among the procedures in the present study (2.0%) differed from that in the ACAS (0.1%), the North American Symptomatic Carotid Endarterectomy Trial (1.1%), and the ACST (1.1%).[3,32] Most studies have found variable rates of perioperative mortality and MAEs, based on varying definitions of outcomes and events. These divergent findings may be attributable to several variables, such as surgeon volume, institutional practices, and operative technique.[35,36] In addition, it seems that even clinically insignificant myocardial injury can have a deleterious effect on survival. The CREST study also highlighted the complications of perioperative cerebral infarction in coronary stenosis patients and perioperative ischemic heart disease in CEA patients.[14] Patients with CAD are at high risk of postoperative myocardial complications.[37]

In the present study population, 18 procedures were performed on patients with evidence of severe coronary stenosis based on CCTA did not undergo CAG. Of these, four patients suffered from acute MI (n=1) or postoperative stroke (n=3) after CEA, and one patient died during the postoperative period. Although the optimal cardiac evaluation process prior to CEA is a matter of debate, these results have practical implications. It is not possible to know whether these MAEs could have been prevented if those patients had undergone carotid artery stenting instead of CEA, or PCI before CEA.

The findings of this study should be considered in the light

of two key limitations. First, it had a retrospective observational design and a small sample, and second, patients with severe stenosis in both carotid arteries or severe coronary disease were usually assigned to carotid artery stenting. Therefore, many patients with HOR were excluded before CEA. However, for about half of all procedures (70/153), the patients with a HCR according to our study criteria.

The incidence of major vascular events was higher in patients with severe coronary stenosis than in those with traditional HOR. We suggest that the occurrence of postoperative vascular events could be estimated and minimized by thorough preoperative screening and appropriate management of coronary stenosis before CEA.

Conflicts of Interest

The authors have no financial conflicts of interest.

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