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Atherosclerosis

Prognostic Factors for Neurologic Outcome in Patients with Carotid Artery Stenting

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Background: Carotid artery stenting (CAS) is a valid treatment for patients with carotid artery stenosis. The long-term outcome and prognostic factors in Asian population after CAS are not clear. This study aimed to identify the prognostic factors among Asian patients who have undergone CAS.

Methods: We retrospectively analyzed 246 patients with CAS. Annual carotid duplex ultrasound was used to identify restenosis. Peri-procedural complications, restenosis, neurologic outcomes, and mortality were recorded. Cox regression analyses were used to identify prognostic factors.

Results: The mean follow-up time was 49.2 months. Procedural success was achieved in 237 patients (98.3%), and protection devices were used in 208 patients (84.5%). Within 30 days of CAS, 13 (4.3% per procedure) peri-procedural complications occurred. During the follow-up period, 24 (9.7%) patients developed restenosis, and 37 (15.0%) developed ischemic strokes. In a multiple logistic regression analysis, head and neck radiotherapy [hazard ratio (HR) = 9.9, 95% confidence interval (CI), 3.38-29.1, p < .001], stent diameter (HR = 0.72, 95% CI, 0.58-0.89, p = .003), and predilatation (HR = 3.08 95% CI, 1.21-7.81, p = .018) were independent predictors for restenosis. In Cox regression analysis, hypercholesterolemia (HR = 0.25, 95% CI, 0.07-0.94, p = .04), head and neck radiotherapy (HR = 6.2, 95% CI, 1.8-21.3, p = .004), and restenosis (HR = 3.6, 95% CI, 1.1-11.18, p = .04) were predictors for recurrent ipsilateral ischemic stroke.

Conclusions: CAS provides reliable long-term results in Asian patients with carotid stenosis. Restenosis is associated with an increased rate of recurrent stroke and should be monitored carefully following CAS.

Key Words: Carotid artery disease • Prognosis • Cerebrovascular disease

INTRODUCTION

Carotid artery stenosis contributes to 20% of all ischemic strokes in Western countries.[1] In patients with asymptomatic carotid artery stenosis, the annual risk of ipsilateral ischemic stroke was approximately 2-5%.[2,3] In patients with symptomatic carotid artery stenosis (with a history of stroke or transient ischemic attack), the rate of recurrent ischemic stroke has been reported to be approximately 21% within the first 72 hours after the index event, followed by a gradual reduction to the level of an asymptomatic lesion.[4]

To treat carotid artery stenosis, carotid artery stenting (CAS) is now regarded as an established alternative to carotid endarterectomy (CE), especially in patients with elevated surgical risk.[5] CAS with a distal protective device has been shown to reduce procedural embolic events.[6,7] In the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST), 2502 patients with symptomatic or asymptomatic carotid stenosis were randomized to undergo CAS or CE. The primary endpoints (stroke, myocardial infarction or death) were not significantly different between treatment groups.[8] A meta-analysis on the outcome after carotid artery stenting

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revealed a higher risk of peri-procedural stroke rate in older patients.[9]

The rate of restenosis after CAS has been reported to range from 6.4 to 11.1%, depending on the cutoff point for restenosis and the duration of follow-up.[10,11] In the CREST trial, the rate of restenosis (defined as reduction of diameter > 70%, assessed by duplex ultrasonography) 2 years after CAS or CE was also comparable between groups (6.0% in CAS group vs 6.3% in the CE group).[12] Restenosis after CAS has been proposed as an independent predictor for recurrent ischemic stroke.[13] The data on the restenosis and long-term outcome after CAS in Asian population are minimal.[14] In general, Asian populations have a higher stroke rate and a lower prevalence of carotid artery stenosis compared with Western populations.[15,16] The predictors for restenosis and long-term outcome might not be the same as those in the Western populations. To fill this gap, we designed a retrospective study to identify the patient and procedural factors contributing to the development of restenosis and recurrent ischemic stroke in an Asian population.

MATERIALS AND METHODS

Patients

We analyzed the patients who received CAS in the Department of Cardiology at a tertiary teaching hospital in Taiwan from January 2001 to December 2006 retrospectively. All patients 18 years of age or older who received unilateral or bilateral carotid artery stenting for symptomatic or asymptomatic carotid artery stenosis during the study period were enrolled. Symptomatic lesions with a stenosis diameter of 60-99%, or asymptomatic lesions with a stenosis diameter of 80-99% were considered eligible for CAS. A patient was considered symptomatic as defined in the North American Symptomatic Carotid Endarterectomy Trial (NASCET).[17] The conditions associated with high risk for carotid endarterectomy were recorded according to Cutlip et al., except in those patients with severe pulmonary disease – pulmonary function tests were not performed.[18]

Carotid artery stenting protocol

Patients were given a combination of 75 mg clopidogrel and 100 mg aspirin daily for at least 7 days before CAS. This treatment regimen continued for a minimum of 3 months after CAS. Diagnostic cerebral angiography was performed via the femoral artery under local anesthesia. Digital subtraction angiography was performed before CAS in all patients. The diameter of the internal carotid artery, common carotid artery, and the stenotic segment of the internal carotid artery were measured from the digital subtraction angiography. The internal carotid artery (ICA) to common carotid artery (CCA) diameter ratio was defined as the ratio between normal segment diameters of these two arteries. The percentage diameter stenosis was calculated according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method (diameter stenosis % = (1 - diameter of the stenotic segment/distal normal segment of internal carotid artery) $\times$ 100%).[19] Additionally, coronary artery angiography was performed routinely in all patients, and renal arteriography was performed if renal artery stenosis was suspected.

CAS was performed after heparinization and an activated clotting time > 200 seconds was achieved. The use of an embolic protection device was strongly encouraged, but prophylactic atropine or a temporary pacemaker was not routinely provided. A self-expanding carotid stent was deployed with or without pre-dilatation, but post-dilatation was mandatory to achieve stent apposition and expansion. Predilatation was performed according to the judgment of the operator, primarily for the safety of protection device deployment. A final ipsilateral intracranial angiogram was performed to document the absence of distal embolization. Procedural success was defined as the successful deployment of a stent covering the entire lesion with a residual diameter stenosis < 20%.

Clinical evaluation and follow-up

After the procedure, all patients were transferred to the intensive care unit for overnight hemodynamic and neurological monitoring. Systolic blood pressure was maintained between 100 and 140 mmHg.

A neurologic evaluation was performed 24 hours post-CAS and on the day of discharge. A minor stroke was defined as a new neurologic event that persisted for more than 24 hours, but completely resolved or returned to baseline within 30 days with a change of the

National Institutes of Health Stroke Scale (NIHSS) by 2 to 3 points. A major stroke was defined as a new neurologic event that persisted after 3 days with a change of the NIHSS by at least 4 points. An ipsilateral stroke was defined as a stroke affecting the cerebral hemisphere supplied by the treated carotid artery. Periprocedural complications were defined as any neurologic deficit within 30 days after carotid artery stenting.

Patients were followed-up every 3 months in the clinic, where their assessments included meticulous neurological examinations. A carotid duplex ultrasound exam was scheduled annually after the patients' index procedure for monitoring in-stent restenosis, and all carotid duplex ultrasounds were performed by an experienced vascular ultrasonographer using a Philips Sonos 5500 cardiology ultrasound system at our hospital. Peak systolic velocity of the internal carotid artery (PSV) within the stent was measured. A PSV greater than 175 cm/s has been demonstrated to be correlated to a luminal reduction of more than 50%.[20] Restenosis was defined as a reduction of vessel diameter by more than 50% according to PSV. Patients lost to follow-up were contacted by telephone.

Statistical analysis

Continuous data are presented as mean ± standard deviation (SD), and categorical data are reported as numbers and percentages. Logistic regression analysis was performed to examine the development of periprocedural neurologic complications. Univariate and multivariate Cox regression analysis were performed to examine the development of restenosis, recurrent ipsilateral ischemic stroke, all ischemic stroke, and all-cause mortality. Restenosis-free day was defined as the time from the date when the index procedure was performed to the date when restenosis over 50% was first detected by ultrasonography. A 2-tailed p-value < 0.05 was considered to demonstrate statistical significance for all analyses. Statistical analyses were performed using SPSS version 16.0 software package (SPSS Inc., Chicago, Illinois, USA).

RESULTS

A total of 246 patients underwent 301 carotid artery stenting procedures during the study period. The mean patient follow-up time was 49.2 months, with a median of 48 months [interquartile range (IQR): 34.4, 67.1]. Only 16 patients were lost to follow-up during the study period. One hundred and forty-nine patients (60.5%) underwent carotid stenting for symptomatic stenosis. Baseline characteristics are shown in Table 1. Procedural success was achieved in 237 patients (98.3%). Protection devices were used in 208 patients (84.5%), including filter wire [n = 137 (56.9%)], Percu-Surge [n = 46 (19.1%)], Neuroshield [n = 12 (5%)], and Emboshield [n = 13 (5.4%)]. The stent diameter was 9.1 ± 1.3mm; the stent to CCA diameter ratio was 1.15 ± 0.23. There were 13 (4.3%) periprocedural complications within 30 days of CAS. During the overall follow-up period, 37 patients (15%) developed ischemic strokes: 20 ipsilateral ischemic stroke and 21 contralateral ischemic stroke episodes (with 4 patients developed both ipsilateral and contralateral stroke). The ischemic stroke-free survival rate for the whole study group is shown in Figure 1. Ipsilateral ischemic stroke-free survival rate at 1, 3, 5, and 7 years after CAS were 94.6%, 93.6%, 90.4%, and 90.4%, respectively.

Procedural & periprocedural complications

Periprocedural neurological complications developed in 13 patients. These included 5 ipsilateral major strokes, 4 ipsilateral minor strokes, 1 contralateral major stroke, 2 contralateral minor strokes, and 1 intracranial hemorrhage (Table 2). Using a multivariate logistic analysis, the following factors were found to be associated with the development of periprocedural neurological complications: diabetes [odds ratio (OR) 5.1 (95% confidence interval (CI) 1.3-19.7), p = .02], ICA to CCA ratio over 0.7 [OR 0.23 (95% CI 0.07-0.84), p = .03] and stent to CCA ratio [OR 0.15 (95% CI 0.03-0.69), p = .02] (Table 3).

Restenosis

Twenty-four (9.7%) of the patients developed restenosis > 50% during follow-up as diagnosed by an ultrasound PSV > 175 cm/s. The average diameter stenosis of restenotic lesions was 71.5 (17.6%). Patients with restenosis had a higher rate of recurrent ipsilateral ischemic stroke (25% vs. 6.3%, p = .001) and all ischemic stroke (33.3% vs. 13.1%, p = .008), compared with patients without restenosis. Restenosis was first detected at 8.6 months (median; IQR: 2.1, 42) after CAS. The level

Table 1. Baseline characteristics

Baseline characteristics	N = 246
Demographic data	
Age, mean (SD)	72.8 (8.6)
Sex (M/F)	199/47
Hypertension, n (%)	208 (84.5)
Diabetes, n (%)	89 (36.2)
Hypercholesterolemia, n (%)	119 (48.4)
Smoking, n (%)	136 (55.7)
History of coronary artery disease, n (%)	96 (39.3)
History of transient ischemic attack, n (%)	38 (15.4)
History of stroke, n (%)	103 (41.9)
History of radiotherapy, n (%)	14 (5.7)
High risk for carotid endarterectomy	130 (51.8)
Other atherosclerotic stenosis	
Common carotid artery, n (%)	25 (10.1)
Vertebral artery, n (%)	116 (47.1)
Intracranial lesion, n (%)	29 (11.9)
Subclavian artery, n (%)	41 (16.7)
Coronary artery, n (%)	166 (67.5)
Renal artery, n (%)	53 (21.5)
Angiographic and procedural	
Bilateral stenting, n (%)	47 (19.1)
Use of Protection device, n (%)	208 (84.5)
Common carotid artery diameter (mm), mean (SD)	7.75 (0.83)
Internal carotid artery diameter (mm), mean (SD)	5.58 (0.64)
Internal carotid artery to common carotid artery diameter ratio, mean (SD)	72.4 (7.4)
Lesion length (mm), mean (SD)	18.9 (7.37)
Lesion stenosis (%), mean (SD)	87.2 (15.2)
Predilatation, n (%)	83 (34.6)
Predilatation diameter (mm), mean (SD)	3.93 (1.33)
Predilatation pressure (bar), mean (SD)	6.89 (2.83)
Stent type, close, n(%)	187 (76%)
Stent diameter (mm), mean (SD)	9.14 (1.27)
Stent length (mm), mean (SD)	27.0 (7.0)
Stent to CCA diameter ratio, mean (SD)	1.15 (0.23)
Post-dilatation, n (%)	216 (90.4)
Post-dilatation diameter (mm), mean (SD)	5.71 (0.62)
Post-dilatation pressure (bar), mean (SD)	7.75 (2.57)
Procedure success, n (%)	237 (98.3)
Residual stenosis (%), mean (SD)	8.7 (6.5)
External carotid artery jailed by stent, n (%)	218 (90.5)
Medications	
Aspirin, n (%)	221 (90.1)
Clopidogrel, n (%)	240 (98.8)
Beta-blocker, n (%)	74 (30.4)
Angiotensin converting enzyme inhibitor, n (%)	13 (5.4)
Angiotensin II receptor blocker, n (%)	77 (31.7)
Calcium channel blocker, n (%)	55 (22.6)
Diuretics, n (%)	23 (9.5)
Statin, n (%)	88 (36.2)
Fibrate, n (%)	8 (3.3)

CCA, common carotid artery; SD, standard deviation.

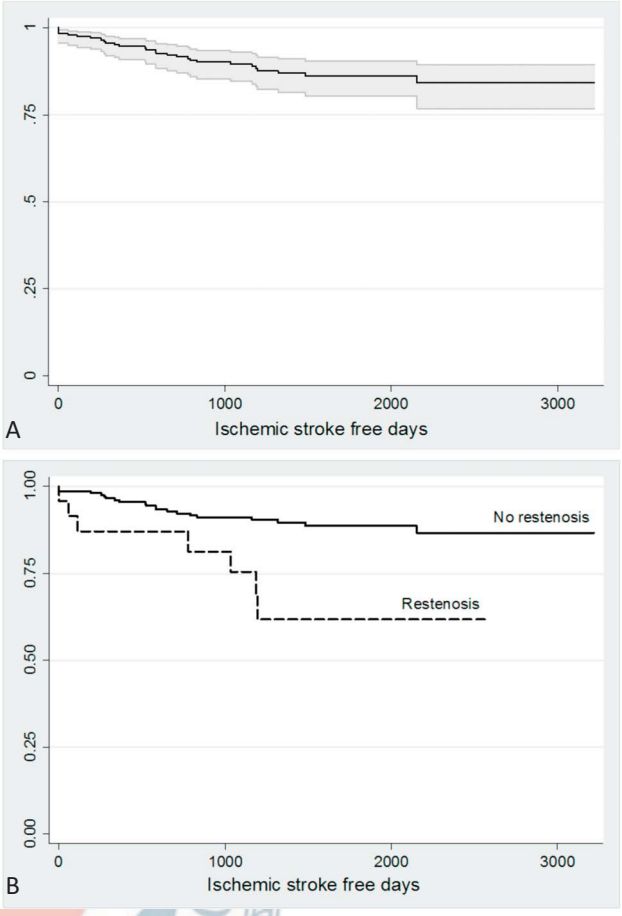

Figure 1. *The ipsilateral ischemic free Kaplan-Meier survival curve. (A) The overall population and (B) by the presence of restenosis > 50%.*

Table 2. Neurologic complications or myocardial infarction

Clinical events	N (%), per procedure
Periprocedural neurologic complications or MI, n (%)	13 (4.3)
Ipsilateral major ischemic stroke	5 (1.7)
Ipsilateral minor ischemic stroke	4 (1.3)
Contralateral major ischemic stroke	2 (0.6)
Contralateral minor ischemic stroke	1 (0.3)
Intracranial hemorrhage	1 (0.3)
Myocardial infarction	0 (0)
Neurologic complications or MI during follow-up (after 30 days), n (%)	47 (15.6)
Ipsilateral major ischemic stroke	6 (1.9)
Ipsilateral minor ischemic stroke	5 (1.7)
Contralateral major ischemic stroke	17 (5.6)
Contralateral minor ischemic stroke	1 (0.3)
Intracranial hemorrhage	9 (3)
Myocardial infarction	9 (3)

Table 3. Univariate and multivariate logistic regression analysis, for the development of periprocedural neurologic complications

Risk factors	Univariate analysis			Multivariate analysis[a]		
	Odds ratio	95% CI	p	Odds ratio	95% CI	p
Age	1.03	0.96-1.11	.9	1.05	0.95-1.14	.27
Sex, male	0.77	0.20-2.93	.71	0.81	0.2-3.5	.79
Diabetes	3.0	0.95-9.47	.06	5.3	1.33-19.7	.02
Symptomatic	0.4	0.11-1.48	.17			
Lesion stenosis > 90%	0.46	0.15-1.4	.17			
CTO over Contralateral carotid artery	1.66	0.34-7.95	.53			
Intracranial lesion	2.36	0.61-9.15	.21			
Stent, close design	0.68	0.17-2.61	.57			
Protection device	0.38	0.11-1.31	.13			
Pre-dilation	0.94	0.27-3.22	.93			
Bilateral stenting	0.68	0.15-3.2	.63			
ICA to CCA diameter ratio > 0.7	0.34	0.11-1.04	.06	0.24	0.07-0.84	.03
Stent to CCA ratio	0.13	0.03-0.56	.006	0.14	0.03-0.69	.02

[a] Multivariate analysis: using periprocedural complication as the dependent variable, the age, sex, diabetes, dyslipidemia, internal carotid artery diameter to common carotid artery diameter over 70% and stent to common carotid artery diameter ratio as independent variables.

CCA, common carotid artery; CTO, chronic total occlusion; ICA, internal carotid artery.

of residual stenosis immediately following CAS did not correlate with the severity of restenosis (Pearson correlation r = 0.12, p = .06) or the development of restenosis (Spearman's correlation r = 0.08, p = .24). A univariate Cox regression analysis was performed to identify variables that may contribute to the development of restenosis. Results revealed that lesion length, stent length, stent diameter, predilatation, and a history of head and neck radiotherapy were significant predictors of restenosis development. Close-type stent design was associated with reduced restenosis in univariate Cox analysis. A multivariate logistic regression analysis was applied using the variables previously identified as significant from the univariate analysis. The following parameters were significant and were independent predictors for the development of restenosis: patients with a history of head and neck radiotherapy [hazard ratio (HR) = 6.32 (95% CI 3.00-13.3), p < .001]; predilatation [HR = 2.03 (95% CI 1.19-3.43), p = .008] and stent diameter [HR = .82 (95% CI .71-.95), p = .009] (Table 4). Interactions between predilatation and stent diameter or lesion length were not significant.

Long term results

The cumulative ischemic stroke-free survival curve was shown in Figure 1A. Univariate analyses for ipsilateral stroke, any ischemic stroke, all-cause mortality, and any ipsilateral stroke or death were performed

Table 4. Multivariate cox regression analysis for the development of restenosis

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
Age	0.98	0.93-1.02	.4	1.01	0.97-1.03	.58
Sex	0.56	0.23-1.36	.2	0.83	0.44-1.59	.27
History of radiotherapy	6.3	2.3-17.2	< .001	6.32	3.00-13.3	< .001
Lesion diameter stenosis (%)	1.04	1.0-1.08	.03			
Stent diameter (mm)	0.76	0.65-0.89	.001	0.82	0.71-0.95	.009
Stent type, close	0.56	0.33-0.96	.04			
Predilatation	2.73	1.21-6.16	.016	2.03	1.19-3.43	.008
Stent coverage of bifurcation	0.34	0.13-0.88	.026			

CI, confidence interval; HR, hazard ratio.

using a Cox proportional hazard analysis. The following variables were significantly associated with ipsilateral ischemic stroke: hypercholesterolemia, history of head and neck radiotherapy, and restenosis. To avoid the possible impact of periprocedural complication on this analysis, we excluded patients with periprocedural complication and repeated the Cox regression analysis. All results remained valid after excluding patients who developed periprocedural complications (Supplementary Table 1-1 and 1-2). Multivariate Cox regression analysis revealed the following significant correlations: ipsilateral ischemic stroke was correlated with hypercholesterolemia [HR = .25 (95% CI .07-.94), p = .04], a history of head and neck radiotherapy [HR = 6.2 (95% CI 1.8-21.3), p = .004], and restenosis with diameter stenosis > 50% [HR = 3.6 (95% CI 1.1-11.8), p =.04]; any ischemic stroke was correlated with a history of head and neck radiotherapy, [HR = 4.25 (95% CI, 1.55-11.7), p = .005] and bilateral stenting [HR = 2.92 (95% CI, 1.28-6.67, p = .011]; ipsilateral stroke or death was correlated with age (HR = 1.06 95% CI, 1.02-1.1, p = .003), radiotherapy [HR = 3.07 (95% CI, 1.27-7.45), p = .01], and "equal or more than 3" vascular sites of atherosclerosis vascular sites of atherosclerosis [HR = 1.41 (95% CI, 1.12-1.76), p =.003]. The multivariate analysis performed after excluding patients with periprocedural complications revealed similar results (Table 5).

DISCUSSION

The current investigation demonstrated the short-term and long-term safety and clinical efficacy of CAS in an Asian population. Important predictors for the development of periprocedural complications, restenosis and recurrent stroke were also identified. A history of head and neck radiotherapy, the performance of predilatation before stent implantation, and smaller stent diameter were associated with a higher rate of restenosis. It was noted that restenosis and a history of head and neck radiotherapy were associated with a higher rate of recurrent stroke.

Previous studies have identified several factors contributing to the development of periprocedural complications, including advanced age, initial presenting symptoms, lesion length, and the absence of hyperlipidemia.[19,20-23] Our results extended this list by identifying diabetes, ICA to CCA diameter ratio, and stent to CCA

Table 5. Multivariate Cox regression analysis of prognostic parameters

Risk factors	Ipsilateral ischemic stroke			All ischemic stroke			Ipsilateral ischemic stroke or all-cause death		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
For all patients									
Age	1.02	0.96-1.08	.67	0.98	0.94-1.02	.45	1.06	1.02-1.1	.003
Sex	0.54	0.15-1.97	.36	0.86	0.33-2.25	.77	1.03	0.53-2.01	.92
Hypercholesterolemia	0.25	0.07-0.94	.04	(-)			(-)		
Radiotherapy	6.2	1.8-21.3	.004	4.25	1.55-11.7	.005	3.07	1.27-7.45	.01
Restenosis > 50%	3.6	1.1-11.8	.04	1.83	0.68-4.96	.23	1.8	0.88-3.69	.11
Bilateral stenting	(-)			2.92	1.28-6.67	.011	(-)		
Number of vascular stenosis sites ≥ 3[a]	(-)			2.24	0.95-5.25	.06	1.41	1.12-1.76	.003
For patients without periprocedural complications									
Age	1.02	0.96-1.1	.47	0.98	0.94-1.02	.46	1.07	1.03-1.1	.001
Sex	0.52	0.14-1.92	.33	0.87	0.33-2.27	.79	1.07	0.53-2.16	.83
Hypercholesterolemia	0.24	0.06-0.91	.04	(-)			(-)		
Radiotherapy	6.1	1.76-20.8	.004	4.21	1.53-11.5	.005	3.33	1.36-8.12	.008
Restenosis > 50%	3.42	1.03-11.3	.04	1.81	0.67-4.87	.24	1.8	0.87-3.7	.11
Bilateral stenting	(-)			2.96	1.3-6.74	.01	(-)		
Number of vascular stenosis sites ≥ 3[a]	(-)			2.25	0.96-5.27	.06	1.52	1.21-1.91	< .001

[a] Vascular sites: atherosclerosis over carotid artery, vertebral artery, intracranial artery, coronary artery, peripheral artery and renal artery.
(-): Factor not included in the model.
CI, confidence interval; HR, hazard ratio.

diameter ratio as independent predictors for periprocedural complications. ICA to CCA ratio indicates the discrepancy of vessel size, which has been reported to contribute to complications immediately post CAS.[24] Other procedures or device-related factors such as predilatation, post-dilatation, the pressure used during dilatation, stent design, and the use of protective devices did not influence the occurrence of periprocedural complications.

Although debate remains regarding the benefit of protective devices during CAS,[25] recently the use of protective devices has increased around the globe, as well as in our medical center.[26] After July 2002, the rate of protective device use increased from 31% to 98% as reported in our study. The use of protective devices was not associated with a lower rate of periprocedural complications, restenosis or recurrent stroke in our study, probably due to a high rate of use.

We found a strong association between restenosis and recurrent stroke in our study. This result is similar to those in previous studies in symptomatic patients undergoing carotid artery stenting.[13] Furthermore, we identified 3 factors that were associated with higher rate of restenosis: pre-dilatation, small stent diameter and a history of head and neck radiotherapy. Although still not fully understood, the restenosis process is initiated after the vascular injury by balloon dilatation, followed by several proliferative responses including vascular smooth muscle proliferation, extracellular matrix deposition, and neointimal hyperplasia.[27] The performance of pre-dilatation or increased pressure post-dilatation may increase endothelial damage, which may lead to a higher rate of restenosis. Residual stenosis after carotid artery stenosis has been proposed as a possible mechanism of restenosis; however, we could not find a significant correlation between residual stenosis with the development of restenosis.

Few studies have reported long-term results after CAS, especially in an Asian population. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) study reported a 24.6% composite primary endpoint (myocardial infarction, stroke, and death) 3 years following CAS.[28] After a mean follow-up of 47.23 $\pm$ 28.5 months, Parlani et al. reported six-year survival rates from any-cause mortality were 76.0% in diabetic and 80.8% in nondiabetic populations after CAS.[29] We demonstrated an all-cause mortality of 19.1%, similar to published reports. Myocardial infarction developed in 9 (3.7%) patients (none in the periprocedural period). The relatively high mortality rate may reflect the increased age of the current patient population and the higher burden of cardiovascular diseases in this patient group. In the CREST trial, the 4-year death or stroke rate was 6.4% (median follow-up time = 2.5 years).[8] In a single center study, Eskandari et al. reported the freedom from all strokes at 12, 24, 36, and 48 months was 99.2%, 97.6%, 96.7%, and 96.7%, respectively.[30] Consistent with our current results, Randall MS et al. has also reported the ipsilateral stroke rate for patients undergoing CAS (n = 563) was 7.0% and 9.5% at the 1-year and 4-year period, respectively,[13] as well as patient registry data from the UK.[31] Overall, our data support the notion that CAS results in a durable long-term solution in an Asian population.

The current results demonstrate that a history of head and neck radiotherapy was a significant predictor for restenosis and recurrent stroke, but did not increase the rate of periprocedural complications. The ipsilateral ischemic stroke-free survival rate at 3 years for patients with and without a history of radiotherapy was 71% and 92.8%, respectively. The pathogenesis of radiation-induced vasculopathy is a topic that remains unresolved, and whether it is an accelerated form of atherosclerosis or a distinct disease entity due to vasa vasorum insult is not clear.[32] However, the clinical characteristics of radiation-induced vasculopathy seem to be different from classical atherosclerosis. Recent observational studies showed higher rates of restenosis in patients with radiation-induced carotid stenosis treated with stenting.[33-35] Further studies are needed to elucidate the best treatment in this special subgroup.

We found that absence of hypercholesterolemia was associated with periprocedural complications, similar to previous reports.[13,19] We also found that the presence of hypercholesterolemia was associated with a reduced incidence of recurrent stroke (univariate analysis), although not significantly after multivariate analysis. These results may be explained by the aggressive use of statins in patients with hypercholesterolemia, although the analysis of statin use in our study population did not reveal a significant correlation with any adverse outcomes.[36]

Study limitations

As a retrospective analysis, our study is not without limitations. Because this study was conducted in a single center with a modest overall patient number, the generalizability of the results may be limited. Due to the limited sample size, further subgroup analyses such as different type of diabetes or different type of protection device was not conducted. The rate of statin use (36%) in our patients, which may be perceived as lower than expected, was primarily influenced by national health insurance regulations in Taiwan. Lastly, the timing of restenosis development could not be estimated accurately by the annual ultrasound follow-up.

CONCLUSIONS

Our study showed that CAS for symptomatic and asymptomatic carotid stenosis is safe and provides established long-term outcomes in an Asian population. Predilatation before stent implantation and a history of head and neck radiation are two predictors for the development of restenosis after CAS. Restenosis after CAS has a major influence on the rate of long-term recurrent stroke and should be monitored carefully following carotid artery stenting.

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SUPPLEMENT

Supplementary Table 1-1. Univariate cox regression of prognostic parameters (for all patients)

Risk factors	n	Ipsilateral stroke			All ischemic stroke			Ipsilateral stroke or death		
		HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Age	-	1.03	0.96-1.1	.39	0.99	0.94-1.02	.5	1.06	1.02-1.1	.001
Sex, male	199	0.57	0.18-1.8	.34	0.81	0.33-2.01	.66	1.01	0.53-1.95	.96
BMI > median	143	0.5	0.17-1.43	.2	1.24	0.57-2.7	.58	0.89	0.53-1.49	.65
Symptomatic	143	1.78	0.61-5.12	.29	1.34	0.63-2.81	.44	0.78	0.46-1.31	.36
Hypertension	208	2.46	0.32-18.8	.38	1.57	0.47-5.2	.46	0.89	0.46-1.71	.72
Diabetes	89	0.77	0.24-2.45	.66	1.1	0.5-2.37	.82	1.19	0.69-2.03	.53
Hypercholesterolemia	119	0.26	0.07-0.92	.04	0.79	0.38-1.67	.54	0.69	0.42-1.15	.16
Smoking	96	0.42	0.11-1.52	.19	0.62	0.29-1.33	.22	0.79	0.45-1.34	.38
Coronary artery disease	166	1.84	0.51-6.6	.35	2.34	0.89-6.2	.09	1.34	0.76-2.36	.3
Radiotherapy	14	8.27	2.58-26.5	< .001	6.12	2.46-15.3	< .001	2.92	1.24-6.86	.01
Diameter stenosis > 90%	158	0.67	0.23-1.96	.47	1.07	0.48-2.36	.87	0.96	0.56-1.63	.87
Contralateral CTO	25	0.67	0.08-5.14	.7	0.3	0.04-2.21	.24	1.03	0.47-2.27	.94
Intracranial lesion	29	1.49	0.33-6.67	.6	2.44	0.98-6.02	.05	1.04	0.44-2.44	.92
Stent: close	189	0.94	0.26-3.36	.93	0.95	0.38-2.35	.91	1.03	0.55-1.9	.93
Stent length	-	1.01	0.94-1.08	.77	0.99	0.93-1.04	.74	1.0	0.97-1.03	.85
Stent diameter	-	0.95	0.66-1.36	.78	1.02	0.77-1.37	.85	1.05	0.85-1.3	.63
Protection device	208	1.14	0.25-5.12	.86	0.91	0.34-2.41	.84	1.12	0.58-2.19	.73
Predilatation	83	0.73	0.23-2.3	.61	0.59	0.25-1.39	.23	1.3	0.76-2.21	.35
Coverage of bifurcation	218	0.65	0.14-2.89	.57	0.65	0.22-1.87	.42	1.97	0.7-5.52	.2
Stent to ICA ratio	-	0.64	0.19-2.08	.46	1.51	0.42-5.44	.52	0.62	0.35-1.09	.09
Stent to CCA ratio	-	2.22	0.11-44.7	.6	2.71	0.29-25.2	.38	0.53	0.23-1.21	.13
Bilateral stenting	51	3.81	1.34-10.9	.01	3.61	1.71-7.6	.001	1.03	0.55-1.96	.9
Restenosis ≥ 50%	24	5.88	1.96-17.6	.002	3.76	1.59-8.89	.002	2.34	1.19-4.65	.01
Number of vascular stenosis sites ≥ 3	53	1.53	0.99-2.36	.05	1.42	1.04-1.94	.026	1.46	1.17-1.8	< .001

BMI, body mass index; CCA, common carotid artery; CI, confidence interval;CTO, chronic total occlusion; HR, hazard ratio; ICA, Internal carotid artery; Vascular stenosis sites: atherosclerosis over carotid artery, vertebral artery, intracranial artery, coronary artery, peripheral artery and renal artery.

Supplementary Table 1-2. Univariate cox regression of prognostic parameters (for patients without periprocedural complications)

Risk factors	n	Ipsilateral stroke			All ischemic stroke			Ipsilateral stroke or death		
		HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Age	-	1.03	0.96-1.1	.37	0.98	0.94-1.02	.51	1.07	1.03-1.11	< .001
Sex, male	189	0.56	0.17-1.78	.33	0.93	0.34-2.05	.69	1.07	0.54-2.12	.84
BMI > median**	132	0.51	0.17-1.49	.22	1.27	0.58-2.76	.54	0.83	0.49-1.41	.5
Symptomatic	100	1.72	0.59-4.96	.32	1.31	0.62-2.75	.47	0.76	0.44-1.3	.32
Hypertension	197	2.43	0.31-18.6	.39	1.53	0.46-5.1	.48	0.93	0.47-1.86	.85
Diabetes	81	0.77	0.24-2.48	.67	1.1	0.5-2.39	.8	1.21	0.7-2.1	.5
Hypercholesterolemia	118	0.25	0.07-0.89	.03	0.77	0.37-1.63	.5	0.68	0.4-1.14	.15
Smoking	91	0.42	0.11-1.51	.18	0.62	0.29-1.33	.22	0.85	0.49-1.46	.56
Coronary artery disease	157	1.84	0.51-6.61	.35	2.33	0.88-6.15	.09	1.51	0.83-2.72	.17
Radiotherapy	14	8.07	2.51-25.9	< .001	6.1	2.42-15	< .001	3.06	1.3-7.22	.01
Diameter stenosis > 90%	152	0.65	0.22-1.87	.42	1.03	0.46-2.3	.9	0.91	0.52-1.59	.76
Contralateral CTO***	23	0.7	0.09-5.38	.74	0.31	0.04-2.33	.26	0.94	0.42-2.27	.95
Intracranial lesion	26	1.56	0.35-6.96	.56	2.6	1.05-6.41	.04	1.17	0.5-2.74	.72
Stent: close	181	0.93	0.26-3.32	.91	0.92	0.37-2.28	.86	0.96	0.52-1.79	.91
Stent length	-	1.01	0.94-1.09	.7	0.99	0.93-1.05	.85	1.01	0.98-1.05	.53
Stent diameter	-	0.95	0.66-1.37	.8	1.02	0.77-1.37	.85	1.06	0.86-1.31	.56
Protection device	199	1.08	0.24-4.8	.91	0.84	0.32-2.25	.74	1.13	0.57-2.28	.72
Predilatation	79	0.77	0.22-2.32	.59	0.58	0.24-1.38	.22	1.16	0.67-2.0	.6
Coverage of bifurcation	209	0.66	0.15-2.95	.59	0.65	0.22-1.89	.43	1.95	0.69-5.49	.2
Stent to ICA ratio	-	0.6	0.18-.99	.4	1.49	0.39-5.67	.55	0.66	0.35-1.23	.2
Stent to CCA ratio	-	2.02	0.09-42.4	.65	2.52	0.26-24.4	.42	0.62	0.24-1.56	.31
Bilateral stenting	49	3.83	1.34-10.9	.01	3.67	1.74-7.7	.001	0.99	0.52-1.93	1.0
Restenosis ≥ 50%	23	5.73	1.91-17.1	.002	3.7	1.57-8.8	.003	2.47	1.24-4.9	.01
Number of vascular stenosis sites ≥ 3	50	1.53	0.99-2.53	.05	1.42	1.04-1.94	.03	1.56	1.25-1.93	< .001

BMI, body mass index; CCA, common carotid artery; CI, confidence interval; CTO, chronic total occlusion; HR, hazard ratio; ICA, Internal carotid artery; Vascular stenosis sites: atherosclerosis over carotid artery, vertebral artery, intracranial artery, coronary artery, peripheral artery and renal artery.