Comparison of Carotid Artery Stenting Performance between Cardiologists and Neuroradiologists: One Medical Center's Experience

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Abstract-

Purpose: To report the experience of carotid artery angioplasty with stenting (CAS) by cardiologists (CV) and neuroradiologists (NR) in an area with less incidence of extracranial artery stenosis.

Methods: From 1999 to 2008, 210 patients with 231 stents were collected by claim records from the administrative office and reviewed by one independent neurologist. Outcome measures were peri-procedural adverse events (AE), restenosis and recurrent ipsilateral stroke (RS) rate, categorized into treatment groups by either CV or NR.

Results: The average age was 69.0 years and 82.9 % of the patients were men. 63.8% of the patients with 62.8% stents were treated by CV and the remaining 36.2% of patients with 37.2% stents were done by NR. Symptomatic CAS was evident in 70.1% of the CV cases and 83.0% in NR treated patients (P = 0.017). The peri-procedural AE rate was 31.6%; 35.9% in CV group and 24.4% in the NR group (P = 0.071). RS rate was 4.8% in 663.3 days; 4.1% in 920.8 days in the CV group and 5.8% in 354.2 days in the NR group (P = 0.865). The restenosis rate was 10.9% in 630.5 days; 5.4% in the CV group in 224.8 days and 20.6% in the NR group in 817.8 days (P = 0.007).

Conclusions: The restenosis and recurrent stroke rates after carotid artery stenting in Taiwan appears to be consistent with other published and well organized trials. Measures to minimize peri-procedural AR rates are definitely warranted.

Key Words: Carotid artery angioplasty with stenting, Peri-procedural adverse event, Restenosis, Recurrent ipsilateral stroke.

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INTRODUCTION

In Taiwan, the prevalence of significant carotid lesions is 8%-32% in patients with hemispheric strokes, which, it has been believed, was less than western countries. Among patients with large-artery atherosclerosis, only 27% had significant extracranial internal carotid artery (ICA) disease whereas 69% had intracranial vessel stenoses[1].

For patients with extracranial carotid artery stenosis, Carotid endarterectomy (CEA) or Carotid artery angioplasty with stenting (CAS) is a complementary treatment to medical therapy depending on patients' risk categories as well as whether the diseased vessels are symptomatic or asymptomatic. CEA is the standard treatment in patients who are candidates for surgery with symptomatic atherosclerotic carotid stenosis >70%[2,3]. CAS is an alternative treatment in high risk patients with the same safety profile as CEA[4]. However, except for lower risk of cranial nerve injury, CAS is believed to be neither safer nor associated with a better short-term outcome as compared to CEA in treating carotid artery stenosis[5,6]. Nevertheless, CAS is continually developing into a safer and more efficacious therapy for stroke prevention[7,8]. In a treatment trial reported in 2004, the study was prematurely halted because of increased resistance from clinicians and patients randomized to the non-CEA group[4]. At present, CAS is not inferior to CEA and may be considered as the treatment of choice among patients with symptomatic severe stenosis (>70%) in whom the stenosis is difficult to access surgically, and where medical conditions are present that greatly increase the risk for surgery, or where other specific circumstances exist such as radiation-induced stenosis or restenosis after CEA. CAS is reasonable when performed by surgeons with established periprocedural morbidity and mortality rates of 4% to 6%, similar to that observed in trials of CEA and CAS[3].

Though less incidence of carotid stenosis was reported, CAS attracts a lot of interest and is assessed as a safe and effective treatment in the management of stroke in Asia[9,10]. Its effectiveness and safety in different subspecialties has never been evaluated in large case series in a purely Asian population. Physicians interested in performing CAS represent a variety of subspecialties with different backgrounds, experience, and expertise. In Taiwan, CAS is usually performed by cardiologists (CV) and neuroradiologists (NR) with no substantial preference difference in clinical practice. The stents used might be the same; however, the preparation before procedures, the dilatation procedures, the care plans after the procedures, and the alertness to peri-procedural adverse events (AE) may be very different.

This report will attempt to describe 10 years of experience doing CAS in a tertiary referral hospital in Taiwan, with a focus on reporting the peri-procedural AE, recurrent ipsilateral stroke (RS) rate, restenosis rate and exploring the performance of the two specialties.

METHODS

Patients treated with CAS from March 1999 to March 2008 were retrospectively collected by claim records from the study hospital's administrative office. The study hospital is a 2,400-bed non-profit proprietary hospital, which serves as a tertiary referral hospital in a catchment area with 3 million people. The hospital provides medical centre-level healthcare in Southern Taiwan treating all kinds of cerebrovascular diseases. Patients suffering from acute cerebrovascular diseases are usually admitted from the Emergency Department and were treated mainly by neurologists. Patients usually received Carotid Doppler Sonography (CDS) in the acute admission phase. When carotid artery stenosis of more than 50% was found, cerebral angiograms would be offered as a routine practice and CEA or CAS would be suggested. CV, NR and neurologists in this study were all board-certified, experienced in stroke management and actively involved in clinical trials and stroke risk factor studies[1,11-14].

Patients were categorized into 2 groups as those treated by CV or NR. The medical indication for the CAS was retrospectively reviewed by one independent neurologist (YSW) using the best available data. Seven vascular risk factors were identified in each patient and were included in the comorbidities. Degree of stenosis

reported by treating physicians from cerebral angiograms before CAS was retrospectively collected without modification, though validation of the degree of the stenosis was attempted but not successful by one neurologist (YSW).

Symptomatic diseased vessels were defined if the diseased vessels were ipsilateral to symptoms related to transient ischemic attack or infarct, or appropriate image findings corresponded to cerebral infarct. Others would be classified as asymptomatic.

The peri-procedural period was defined as any time from during stenting procedure to within 3 days after procedure with one exception: Any intracranial hemorrhage within 7days. AE were retrospectively identified by one independent neurologist (YSW), including all kinds of events needing medical attention in the peri-procedure period; such as: Stroke, transient ischemic attack, acute myocardial infarction, intracerebral hemorrhage, bradycardia, hypotension, catheter related infection, catheter related dissection, vasospasm, contrast related nephropathy, paroxysmal atrial fibrillation, ventricular flutter, ventricular tachycardia post cardioversion, hematoma, bleeding, seizure, and syncope.

Outcome events were defined as restenosis/occlusion and RS at follow up period. Restenosis was defined as intrastent restenosis over 50% by CDS as peak systolic velocity over 175 cm/s suggested by the retrospectively applied uniform post stenting criteria[15]. RS was defined as sudden onset neurological deficits with corresponding infarction identified by appropriate neuroimage and ascertained retrospectively by one neurologist. Uncertain cases were adjudicated by two other neurologists (KCC and TYT).

As a hospital-based observation study, there was no uniform scheduled CDS follow up after CAS. Times and frequencies of CDS after CAS were also explored in this study.

Chi-square test was used to determine any significant differences in attributes studied in relation to characteristics of patients, peri-procedural AE and outcome events. Log Rank test was used to explore the difference between the percentage of peri-procedural AE and outcome events in NR and CV treated vessels. Cox regression was used to analyze the factors associated with outcome events. In the Cox regression, variables used in univariate analysis were entered simultaneously into the models. All significant tests were two-tailed and differences were considered to be statistically significant at a $P < 0.05$ level. All analyses were done using SPSS version 11.5 for Windows (SPSS Inc.).

RESULTS

In 10 years, 231 treated vessels in 210 patients were found in this hospital. The mean patient age was 69.0± 8.3 years old and 174 (82.9%) were men. (Table 1) Hypertension was present in 175 (83.3%) patients, previous stroke in 144 (68.1%), hyperlipidemia 138 (65.7%), cardiovascular disease 125 (59.0%), diabetes mellitus 72 (34.0%), current smoker 62 (29.2%), and atrial fibrillation/paroxysmal atrial fibrillation 11 (5.2%). Previous stroke was found more in patients treated by NR. Coronary artery disease was found more in patients treated by CV. Patients with post-radiotherapy were treated more by NR.

There were 134 (63.8%) patients who received 145 (62.8%) stents treated by CV, and 76 (36.2%) patients who received 86 (37.2%) stents treated by NR. Symptomatic CAS procedures were identified in 103 (70.1%) and 73 (83.0%) treated vessels by CV and NR, respectively ($P = 0.017$).

Peri-procedural AE was found in 31.6% of patients. There was no difference in peri-procedural AE between two groups, except that hypotension was found more in patients treated by CV. (Table 2)

RS was identified in 4.8 % (11/231) of stent cases in a mean of 663.3 days (median 463, 25%-75% 78-734) after stenting. The RS rate was 4.1% (6/145) in 920.8 days (528.0, 107.3-1712.5) after stenting by CV and 5.8% (5/86) in 354.2 days (463.0, 45.0-609.0) after stenting by NR (Log Rank Test, $P = 0.865$). (Fig. 1) Demographics of patients with and without RS were compared but no contributing factors were identified in the Cox regression model. (Table 3)

In our study, the Kaplan-Meier estimates of severe (≥ 70%) ICA stenosis with symptomatic ipsilateral

Table 1. *Baseline patient demographics* *(N=210)*

	Total	NR	CV	*P* value
	N(%)	N(%)	N(%)	
Patients	210	76(36.2)	134(63.8)	
Male	174(82.9)	63(82.9)	111(82.8)	0.991
Age, yr (mean ± SD)	69.0±8.3	67.5±8.7	69.8±7.9	0.054
Post-radiotherapy number	16(6.9)	11(12.8)	5(3.4)	0.007*
Comorbidities				
Hypertension	175(83.3)	61(80.3)	114(85.1)	0.369
Previous stroke	143(68.1)	63(82.9)	80(59.7)	0.001*
Hyperlipidemia	138(65.7)	46(60.5)	92(68.7)	0.233
Coronary artery disease	125(59.5)	20(26.3)	105(78.4)	<0.001*
Diabetes mellitus	72(34.3)	24(31.6)	48(35.8)	0.534
Current smoking	62(29.5)	23(30.3)	39(29.1)	0.860
Atrial fibrillation	12(5.7)	3(3.9)	9(6.7)	0.543
Stents	231	86(37.2)	145(62.8)	
Side (person)				0.450
Left	88(41.9)	29(38.2)	59(44.0)	
Right	101(48.1)	37(48.7)	64(47.8)	
Bilateral	21(10.0)	10(13.2)	11(8.2)	
Symptomatic (176)				0.118
> 70%	130(73.9)	48(65.8)	82(79.6)	
50-69%	44(25.0)	24(32.9)	20(19.4)	
< 50%	2(1.1)	1(1.4)	1(1.0)	
Asymptomatic (55)				
> 60%	45(81.8)	10(76.9)	35(83.3)	0.685

Table 2. *Peri-procedural adverse events*

	Total	NR	CV	*P* value
		N(%)	N(%)	
Stent number	231	86(37.2)	145(62.8)	
Mortality	0(0.0)	0(0.0)	0(0.0)	
Morbidity				
Stroke/Transient ischemic attack	29(12.6)	7(8.1)	22(15.2)	0.119
Ipsilateral anterior circulation stroke	13(5.6)	4(4.7)	9(6.2)	0.772
Major	2(0.9)	1(1.2)	1(0.7)	1.000
Minor	11(4.8)	3(3.5)	8(5.5)	0.751
Acute myocardial infarction	1(0.4)	1(1.2)	0(0.0)	0.372
Intracranial hemorrhage	2(0.9)	2(2.3)	0(0.0)	0.138
Bradycardia	19(8.2)	4(4.7)	15(10.3)	0.128
Hypotension	31(13.4)	5(5.8)	26(17.9)	0.009*
Others*	20(8.7)	7(8.1)	13(9.0)	0.829
Total	73(31.6)	21(24.4)	52(35.9)	0.071

*Others including: catheter related infection, (catheter related) dissection, vasospasm, contrast related nephropathy, paroxysmal atrial fibrillation, ventricular flutter, ventricular tachycardia post cardioversion, hematoma, bleeding, seizure, or syncope.

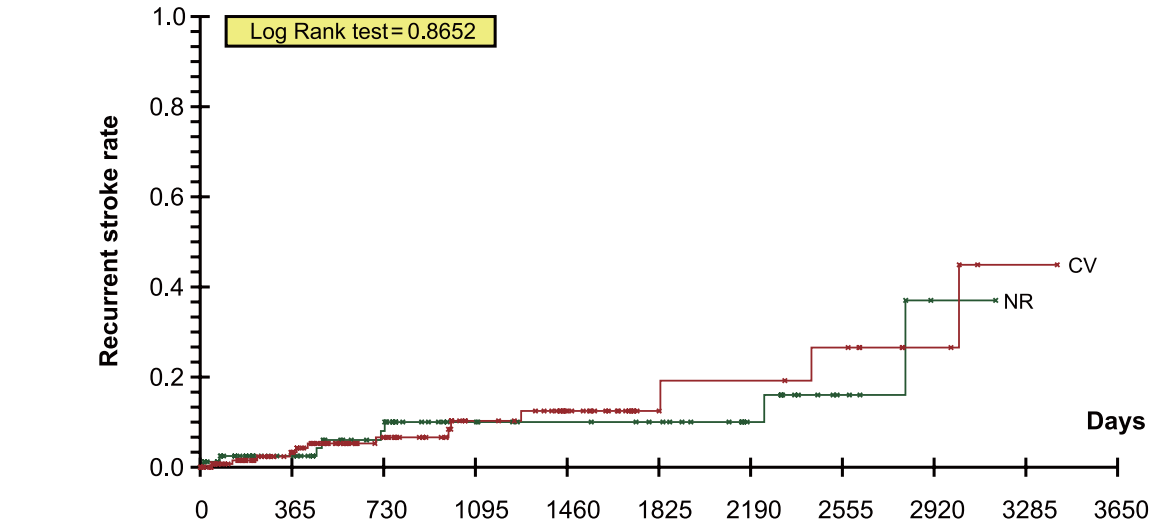
Table 3. *Demographics of patients with recurrent stroke or not*

	Recurrent stroke			Restenosis		
	Yes	No	*P*	Yes	No	*P*
	N(%)	N(%)		N(%)	N(%)	
Patients						
Male	10(90.9)	179(81.4)	0.694	13(68.4)	176(83.0)	0.124
Age, yr (mean ± SD)	69.5±7.8	69.2±8.3	0.875	66.9±9.8	69.4±8.1	0.221
Post-radiotherapy	0(0.0)	16(7.3)	1.000	1(5.3)	15(7.1)	1.000
Comorbidities						
Hypertension	11(100)	183(83.2)	0.220	17(89.5)	177(83.5)	0.746
Previous stroke	10(90.9)	146(66.4)	0.109	16(84.2)	140(66.0)	0.105
Hyperlipidemia	7(63.6)	146(66.4)	1.000	14(73.7)	139(65.6)	0.473
Coronary artery disease	9(81.8)	128(58.2)	0.207	10(52.6)	127(59.9)	0.536
Diabetes mellitus	6(54.5)	71(32.3)	0.187	6(31.6)	71(33.5)	0.866
Current smoking	4(36.4)	63(28.6)	0.734	6(31.6)	61(28.8)	0.796
Atrial fibrillation	0(0)	12(5.5)	1.000	3(15.8)	9(4.2)	0.065
Stents	114.8)	220(95.2)		19(8.2)	212(91.8)	
Side (person)			0.970			0.539
Left	5(45.5)	83(41.7)		6(33.3)	82(42.7)	
Right	5(45.5)	96(48.2)		9(50.0)	92(47.9)	
Bilateral	1(9.1)	20(10.1)		18(9.4)	3(16.7)	
Symptomatic (176)			0.866			0.125
> 70%	4(66.7)	126(74.1)		13(76.5)	117(73.6)	
50-69%	2(33.3)	42(24.7)	3(17.6)	41(25.8)		
< 50%	0(0)	2(1.2)		1(5.9)	1(0.6)	
Asymptomatic (55)						
> 60%	4(80.0)	41(82.0)	1.000	1(50.0)	44(83.0)	0.333
Morbidity						
Stroke/Transient ischemic attack	2(18.2)	27(12.3)	0.633	1(5.3)	28(13.2)	0.481
Acute myocardial infarction	0(0)	1(0.5)	1.000	0(0)	1(0.5)	1.000
Intracranial hemorrhage	0(0)	2(0.9)	1.000	0(0)	2(0.9)	1.000
Bradycardia	0(0)	19(8.6)	0.606	1(5.3)	1(8.5)	1.000
Hypotension	2(18.2)	29(13.2)	0.646	3(15.8)	28(13.2)	0.726
Others*	0(0)	20(9.1)	0.605	1(5.3)	19(9.0)	1.000
Total	4(36.4)	69(31.4)	0.745	3(15.8)	70(33.0)	0.122

ischemic strokes up to 2 years after CAS and any peri-procedural stroke or death were 9.8%; with 12.2% by CV and 6.3% by NR (*P*=0.201). (Supplemental Fig. 1) The 30 days MI, stroke and death rate was 8.7%; with 9.7% by CV and 7.0% by NR (*P*=0.509). Among symptomatic patients, the 30 days MI, stroke and death rate was 9.0%; with 10.7% by CV and 8.2% by NR (*P*=0.753).

After stenting, 174 (75.3%) treated vessels were evaluated for restenosis, including 111 (76.6%) by CV and 63 (73.3%) by NR (*P* = 0.576). The mean observation period was 1145 days (928, 449-1698); with 1015 days (793, 428-1444) by CV, and, 1374 days (1243, 525-2311) by NR (*P*=0.013). There was no difference in demographics or peri-procedural AE among 174 evaluated vessels and 57 treated but not evaluated vessels.

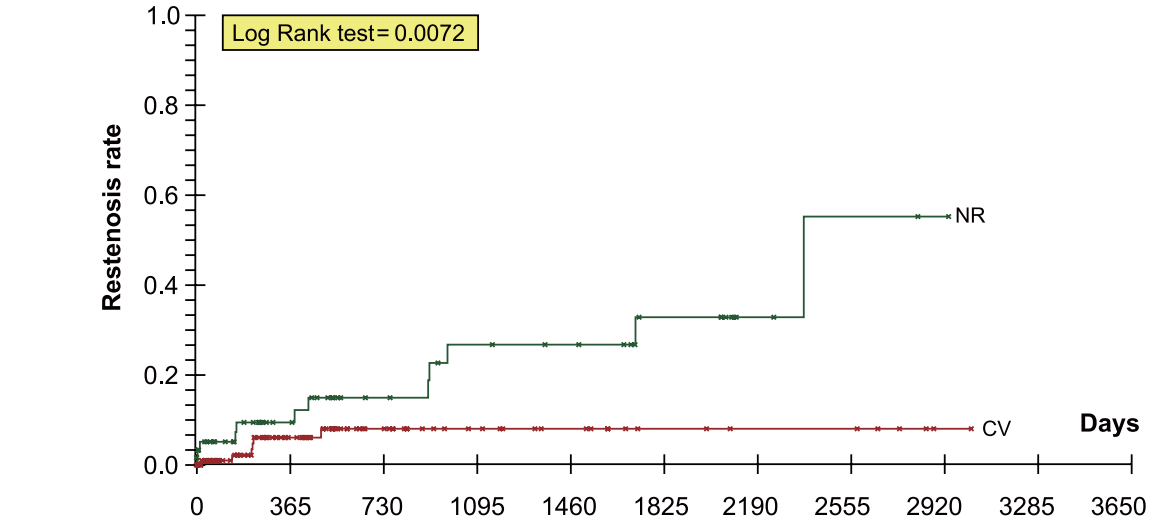
In these 174 evaluated vessels, CDS was first evaluated at 217 days (74, 22-230) after stenting; at 203 days (91, 25-233) after stenting by CV and 241 days (58, 10-205) by NR (*P*=0.557). CDS was re-evaluated in every 535 days in each patient (360, 210-753), 520 days (361, 208.3-750) by CV and 562 days (359, 211-770) by NR



Patients at risk

NR	86	62	46	31	27	24	15	6	1	0
CV	145	103	68	43	31	14	12	10	5	1

Figure 1. Recurrent stroke with patients at risk.



Patients at risk

NR	72	38	24	15	12	7	3	2	1
CV	102	50	26	15	12	5	2	2	1

Figure 2. Restenosis with patients at risk

(*P*=0.579).

By uniform post stenting criteria, among 174 treated and evaluated vessels, restenosis was identified in 10.9% in 630.5 days (231, 146-929) after stenting. The restenosis rate was 5.4 % in 224.8 days (225, 115.3-298) after stenting by CV, while 20.6 % in 817.8 days (449, 88.5-1374) by NR (*P*=0.007). Accordingly, restenosis was usually found at 1.8 times (median: 2.0, 25%-75%: 1.0-2.0) CDS examinations after stenting in follow-up period. (Fig. 2) Demographics of patients with restenosis or not were compared but no contributing factors were identified by Cox regression model. (Table 3)

DISCUSSION

This was a long term follow up of a large sample size evaluation of CAS cases derived from clinical practice in a tertiary referral hospital in Taiwan where incidence of CAS was thought to be low. This observational study might very well represent a generalized perspective on carotid revascularization and more closely represents its "real world" outcomes. Our results should add substantial information to help patients and physicians to treat stenotic carotid arteries with CAS in daily practice. This study also explored some of the outcome differences of medical specialties in performing CAS.

This study was limited by its observational nature. Our results were somewhat imperfect based on several issues including: A lack of a general agreement on the eligibility criteria for CAS, preparation before procedures, technique of CAS, dilatation procedures, description of residual stenosis after CAS, assessment time points, or care plan after the procedures. Variability in medical specialty alertness to various peri-procedural AE might also have existed. As expected, these two specialties used different stenosis evaluation criteria, though NASCET criteria were preferred.

By a retrospective design and an intensive audition of AE, the peri-procedural AEs were identified higher than 30% in our study. Fortunately, most of these AE were transient and easily managed medically. As hypotension was found more in the CV patients, the causal relationship of the optimal dilatation with possible carotid body stimulation and also the higher incidence of concurrent coronary artery disease in this group of patients was speculated[9,16-18]. Unfortunately, residual stenosis was not routinely reported and the images of post dilatation were not always recorded. In our study, peri-procedural AE were not related to outcome events in univariate and multivariate analyses.

In our study, 2 patients with intracranial hemorrhage were assessed as suffering from hyperperfusion syndrome. They presented as sudden onset of ipsilateral headache around 1 week. Brain MRI indicated brain edema over the hemisphere on the stenting side along with intracerebral hemorrhage. However, our study might underestimate the incidence of hyperperfusion syndrome due to the retrospective study design. Though hyperperfusion syndrome might not be easily defined and clearly clarified by our study design, further prospective surveillance study of CAS in this hospital is warranted in order to clarify the incidence and the impact of the hyperperfusion syndrome after CAS.

Though the AE were high, the results of our daily practice might be compatible with large multicenter trials. As compared with the SPACE study, the Kaplan-Meier estimates of severe (≥ 70 %) ICA stenosis with symptomatic ipsilateral ischemic strokes within 2 years after CAS, including any peri-procedural strokes and deaths was 9.4%-9.5%[19], which is compatible with the 9.8 % seen in our study. When compared with CAVATAS, SAPPHIRE, EVA-3S, and SPACE[4,20-22], the 30 days stroke rate with a range of 3.2 ~ 9.2 %, certainly brackets the 8.2 % seen in our series.

Our results offered important clinical practice data regarding the follow up rate and the use of CDS after CAS in a relative long observation period. There is no general agreement for the timing and frequency of CDS after CAS. In our study, 75.3 % treated vessels were evaluated at least once by CDS after CAS with no difference in both groups. Most of our patients had the first CDS at 7.1 months (217 days) after CAS. The evaluation of CDS was once in every 1.5 years (535 days) in both groups. Restenosis was found at 1.8 times (median: 2.0, 25%-75%: 1.0-2.0) CDS examinations after stenting in

follow-up period. Immediate poststenting CDS might provide valuable baseline values for further follow-up comparisons[15,23]. Scheduled CDS follow-up of treated vessels to document restenosis at 30 days, 6 months, and annually during the first 5 years post-procedure would be a feasible strategy to assess the long-term effects of treatment[19,24]. However, based on previous reports and the findings of our study, the positive yield of CDS follow-up would be low for the first year post-stenting, as most restenosis occurred 1.7 years after CAS[19,24]. The incidence of restenosis seemed to be highest in the first 2 years after CAS[24], though observations after 2 years were less available in the literature.

Restenosis was identified in 10.9% of our patients, with 5.4% in patients treated by CV and 20.6% in patients treated by NR (P = 0.007). However, the data showed that CV treated vessels had restenosis earlier than vessels treated by NR (224.8 days vs. 817.8 days, P = 0.034). No causality factors could be identified for restenosis from our data by Cox regression model. Furthermore, long-term restenosis depended on many factors, not merely CAS intervention. Medication including antiplatelets, co-morbidities and their control may without a doubt affect the incidence of restenosis. Therefore, we cannot conclude directly that there is significant difference of restenosis rates or time periods between the two specialties. Based on the literature, most restenotic vessels were asymptomatic and not associated with recurrent stroke. The early occurrence of restenosis caused by intima hyperplasia other than progressive atherosclerosis might be a possible explanation[19,25,26].

From our results, both CV and NR specialists were capable of doing CAS. However, there were differences in methodologies of each specialty. A transfemoral approach was the usual method used by NR. A transbrachial approach had been developed by the CV specialists in this hospital to perform CAS as an alternative for patients unsuitable to femoral arterial access and endarterectomy[7,27]. In our study, peri-procedural AE didn't decline with time. (Supplemental Fig. 2) We concur with the recommendation that endovascular physician specialists be employed to rigorously apply the lessons learned from previous well-designed trials to avoid treating patients who are at higher risk for complications with CAS[8]. For example, patients with heavily calcified plaques, a complex aortic arch, excessively tortuous vessels, or internal carotid arteries with lumen diameters smaller than 3 mm are likely better served with endarterectomy[28-36]. The reasons for the persistent peri-procedural morbidity was not clear from the results of our study. As a result, we recommend mandatory sustained surveillance for AE in CAS patients.

In conclusion, by means of retrospective case analysis, this study reported the outcome experience of CAS patients as performed by two specialties in a part of the world with notably less incidence of extracranial artery stenosis. Even though there is a lower incidence, the RS and restenosis rates following CAS, our outcomes appear to conform with well organized trials. Measures to minimize the peri-procedural AE are definitely warranted.

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