Executive Summary

Economic evaluation of carotid artery stenting as compared to endarterectomy for patients with carotid artery stenosis

☐ Background

Carotid artery stenosis is a narrowing or constriction of the inner surface of the carotid artery and is serious because it can cause a stroke. 30% of the cause of stroke is from this disease and occurrence of this disease is rapidly increasing in Korea because of the lifestyle changes. The narrowing of the carotid arteries is most commonly related to atherosclerosis, and it is closely related with adult diseases, such as hypertension, hyperlipidemia, and diabetes. Not all patients have symptoms; carotid artery disease may be asymptomatic or symptomatic. It is considered that 2–3% of asymptomatic carotid stenosis patients have the risk of stroke, and 10–17% of symptomatic patients have the risk of stroke.

Carotid steonsis is conventionally treated by carotid endarterectomy (CEA) as a preventive treatment of stroke, and patients with and without neurological symptoms are selectively treated with this treatment method. Carotid-artery stenting (CAS) was developed as an option for patients who are high risk for CEA or patients who has high risk because of carotid lesions located at or above the level of the second cervical vertebra. Clinical guideline in Korea recommends (Level of Evidence 1b, Classification of Recommendation A) that CAS indicated as an alternative to CEA for symptomatic patients who have more than 50% stenosis and the anticipated rate of stroke or mortality is less than 6% (Clinical Research Center For Stroke, 2011).

Therefore, this study evaluated the clinical effectiveness and cost-effectiveness in the target patients with symptomatic carotid artery stenosis (more than 50% stenosis) who can undergo CAS as an alternative to CEA for carotid artery stenosis. The four detailed topics to achieve the object of this study are the following: first, the utilization trends (2008-2012) of the treatments (CEA and CAS) in patients with symptomatic carotid artery stenosis in Korea by using national health insurance claims database provided HIRA; second, the comparative effectiveness of the CEA

and CAS based on systematic reviews in patients with symptomatic carotid artery stenosis; third, the comparative effectiveness of the CEA and CAS based on retrospective chart review of patients with symptomatic carotid artery stenosis (>50%) collected from five hospitals in Korea (2008-2011); fourth, the cost-utility analysis of CEA versus CAS in patients with symptomatic carotid artery stenosis.

☐ Utilization Trends of Patients with Symptomatic Carotid Artery Stenosis in Korea

The utilization trend was analyzed from the database of Health Insurance Review and Assessment Service (HIRA; Seoul, Korea) between 1 January 2008 and 31 December 2011. The number of patients with symptomatic carotid artery stenosis among the patients who received CAS or CEA were 6,622. The number of patients who received a carotid intervention is increasing since 2008, and the result appeared that about 80% among all symptomatic carotid stenosis patients received CAS annually (Figure 1).

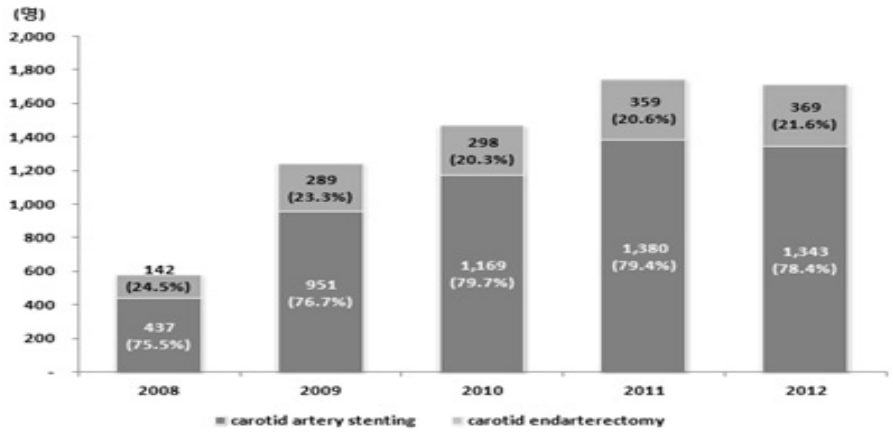

Figure 1. Trends in CEA and CAS utilization from 2008-2012

Most of the patients undergoing the carotid intervention (CEA or CAS) were male and the average age of patients who received CAS was 69.95 (±8.71) years while that of patients who received CEA was 68.08 (±7.91) years – there was not much difference between the groups.

As a result of the comparison treatment cost and the length of hospital stay for both procedures, the treatment cost per hospitalization for CAS KRW 7,538,590, which was more expensive than CEA (KRW 5,742,767), but length of hospital stay

for CEA was 14.3 days in average, which was slightly longer than CAS (13.4 days).

☐ A Systematic Review: Comparative Effectiveness between CAS and CEA in Patients with symptomatic Carotid Stenosis

By using existing systematic review, clinical effectiveness of CEA and CAS in patients with symptomatic carotid artery stenosis was compared. The research question in this systematic review was: "Dose CAS has significantly different risk of peri-procedural stroke or death compared with CEA in patients with symptomatic carotid artery stenosis?"

Among the four systematic reviews in accordance with the key question of this study, an article published by Bonati et al. (2012) was finally selected because it was evaluated as a good methodological quality through AMSTAR (assessment of multiple systematic reviews). There was no other randomized control trial (RCT) published after the study by Bonati et al. (2012). We excluded obviously irrelevant studies (excluding the studies in patients with asymptomatic carotid stenosis, a study that cannot extract symptomatic and asymptomatic patients separately, non-comparative study, and non-English study) from 15 RCT included in the systematic review (Bonati et al., 2012). Therefore 11 RCTs involving 5,621 patients with available outcome data that fulfilled the inclusion criteria was included. Main results of meta-analysis were shown <Table 1>.

Table 1. CAS or CEA for symptomatic carotid stenosis

	CAS	CEA	Meta-analysis result (Reference group: CEA)				
			RR	95%	lower	95%	upper
Peri-procedure outcome (within 30 days after treatment)							
Death	26/1,943	15/1,938	1.72		0.90		3.30
Any stroke	206/2,621	120/2,598	1.72		1.28		2.30
Major stroke1)	83/2,611	57/2,588	1.43		1.03		2.00
Myocardial infarction (MI)	11/2,555	25/2,539	0.46		0.23		0.93
Death or any stroke	227/2,669	132/2,661	1.75		1.31		2.33
Death or any stroke or MI	144/1,727	100/1,715	1.43		1.12		1.83
Post-procedure outcome (until the end of follow-up)							
Death	93/1,793	75/1,784	1.25		0.86		1.81
Any stroke	207/2,461	142/2,437	1.44		1.1		1.89
Major stroke1)	68/1,629	50/1,627	1.3		0.9		1.88
Death or any stroke	184/2,200	128/2,178	1.4		1.02		1.93
Death or any stroke or MI	152/1,624	107/1,610	1.42		1.04		1.94
Peri-procedure complication							
Restenosis	14/614	2/600	3.71		0.31		44.48
Hemorrhage	29/1,853	42/1,828	0.75		0.19		2.91
Cranial nerve palsy	7/1,853	103/1,828	0.1		0.05		0.2

1) Major stroke: Major, fatal, or disabling stroke

The risk of stroke of any severity, occurring between randomization and 30 days following the procedure was significantly higher in CAS group compared with the CEA group (RR: 1.72, 95% CI: 1.28-2.30). There was also significant difference in the major stroke (major, fatal or disabling stroke), and two combined outcome measures of 'death or any stroke', and 'death or any stroke or myocardial infarction (MI)' between CEA and CAS (Table 1). The risk of myocardial infarction (MI) up to 30 days after treatment was lower in patients assigned to CAS than in CEA groups (RR: 0.46, 95% CI: 0.23-0.93). There was a non-significant increase in all-cause mortality up to 30 days after treatment among patients randomized to CAS compared with those assigned CEA (RR: 1.72, 95% CI: 0.90-3.30). According to the major results during follow-up period after the treatment, the risk of any stroke, 'death or any stroke', and 'death or any stroke or myocardial infarction (MI)' was significantly higher in CAS compared with CEA. In case of the other complications related with the treatment, rates of cranial nerve palsy were significantly reduced among patients treated CAS compared with CEA (RR: 0.1, 95% CI: 0.05-0.2). The overall comparison did not showed higher restenosis or hemorrhage rates among patients assigned CAS compared with CEA patients.

☐ A Multi-center, Retrospective Chart Review: Comparative Effectiveness between CAS and CEA in Korean Patients with Symptomatic Carotid Stenosis

In this study, peri-procedure and post-procedure outcome of CAS was compared with those of CEA in patient with carotid artery stenosis in Korea. Between January 2008 and December 2011, 677 patients (CEA patients=331, CAS patients=346) with symptomatic carotid artery stenosis (≥50%) who underwent carotid intervention were enrolled in this study at five hospitals (Inha University Hospital, Samsung Medical Center, Asan Medical Center, Chonnam National University Hospital, and Severance Hospital).

Patient demographic and clinical data are shown in <Table 2>. The average age of the total patients was 68.3 (range: 24-92 years), and there were 570 males (84.2%) and 107 female (15.8%). There was no difference in age and gender between two groups. The mean follow-up duration was 499.9 days. The ratio of symptomatic carotid artery stenosis with more than 70% of stenosis was 90.2% in CAS group and 75.5% in CEA group - the degree of stenosis in the CAS group was slightly higher more than CEA. 96.8% of 346 patients underwent CAS by Embolic Protection Devices (EPDs).

Table 2. Patient demographic and clinical data

	Total (N=677)		CAS (N=346)		CEA (N=331)	
	n	(%)	n	(%)	n	(%)
Age						
Mean ± SD	68.3	±8.3	68.5	±8.6	68.2	±7.8
[min, max]	[24	92]	[24	92]	[42	86]
Younger than 70 yrs	340	(50.2)	170	(49.1)	170	(51.4)
70 yrs or older	337	(49.8)	176	(50.9)	161	(48.6)
Gender						
Male	570	(84.2)	295	(85.3)	275	(83.1)
Female	107	(15.8)	51	(14.7)	56	(16.9)
Follow-up period						
No. of patient	653		337		316	
Mean ± SD	499.9	±246.8	518.4	±237.0	480.1	±255.8
Degree of stenosis						
< 70%	115	(17.0)	34	(9.8)	81	(24.5)
≥ 70%	562	(83.0)	312	(90.2)	250	(75.5)
CAS with EPD						
Yes			335	(96.8)	-	
No			11	(3.2)	-	

Table 3. Clinical outcomes after CAS and CEA

	CAS (N=346)		CEA (N=331)		p-value[2]
	n	rate(%)[1]	n	rate(%)[1]	
Peri-procedure outcome(within 30 days after treatment)					
Death	2	(0.59)	1	(0.31)	1.000†
Stroke	17	(4.99)	6	(1.89)	0.026
Major	7	(2.06)	1	(0.30)	0.069†
Minor	10	(2.94)	5	(1.59)	0.256
MI	1	(0.30)	0	(0.00)	1.000†
Post-procedure outcome(up to 2 years after treatment)					
Death	5	(1.57)	1	(0.31)	0.217†
Stroke	24	(7.27)	14	(5.05)	0.126
Major	14	(4.46)	6	(2.40)	0.086
Minor	11	(3.25)	9	(3.00)	0.743

1) Kaplan-Meier method

2) Chi-square test, † : Fisher's exact test

Among peri-procedure outcomes, 30-day stroke rate was inferior in CAS group to

CEA group, and it was statistically significant (4.99% vs. 1.89%, p=0.026, chi-test). There was no significant difference between CAS and CEA for death and MI within 30 days after treatment. As a result of the analysis in the whole period (up to 2 years) after treatment, the incidence rate of death, stroke, and myocardial infarction in CAS group was higher than the CEA group, but it was not a statistically significant difference (Table 3). Peri-operative complications (infection or hemorrhage) was less common with CAS than CEA (2 patients in CAS, 4 patients in CEA), and revascularization was done in 1 patient of CAS and 1 patients of CEA group during the follow-up. Rates of cranial nerve palsy were significantly reduced among patients treated CAS compared with CEA groups (p-value< 0.001, chi-test).

We also performed subgroup analysis by degree of stenosis and age. First, as a result of the subgroup analysis based on 70% of stenosis, the rate of death, stroke, and myocardial infarction was higher in CAS group (312 patients) even in the high risk group with > 70% carotid stenosis (562 patients), and rate of major stroke was statistically inferior in CAS group to CEA group. For the patient group with less than 70% of stenosis (115 patients), 30-day stroke rate was higher in CAS (34 patients), but 2-years stroke rate was higher in CEA (81 patients), and the difference was not statistically significant. The rate of complications, the secondary outcomes, was higher CEA group than CAS in more and less than 70% stenosis group, and only the cranial nerve palsy showed statistically significant difference in more than 70% stenosis group.

Second, as a result of age subgroups analysis (younger than 70 years, 340 patients, 70 years or older, 337 patients), in 70 years or older groups, the rate of death, stroke, and myocardial infarction was higher in CAS group, but it was not statistically significant. In CAS group, younger than 70 years old (340 patients), the rate of major and minor stroke was higher, but the death rate was higher in CEA group; the result was not statistically significant.

Table 4. Clinical Effectiveness: Comparison with the Previous Studies

F/U Period	Result	Systematic Review						Retrospective Chart Review			
		CAS			CEA			CAS (n=346)		CEA (n=331)	
		N	event	%	N	event	%	event	%	event	%
Short term F/U (within 30 days)	Death	1,943	26	1.34	1,938	15	0.77	2	0.58	1	0.30
	Stroke	2,621	206	7.86	2,598	120	4.62	17	4.91	6	1.81
	Major	2,611	83	3.18	2,588	57	2.20	7	2.02	1	0.30
	Minor							10	2.89	5	1.51
	MI	2,555	11	0.43	2,539	25	0.98	1	0.29	0	0.00
	peri-operative infection							2	0.58	3	0.91
	Cranial nerve palsy							0	0.00	12	3.63
Long term F/U (From 30 days)	Deaths	1,545	142	9.19	1,519	139	9.15	3	0.87	0	0.00
	Strokes	1,502	33	2.20	1,475	36	2.44	8	2.31	9	2.72
	Major	615	14	2.28	607	10	1.65	7	2.02	5	1.51
	Minor							1	0.29	4	1.21
	Revascularization: Retrospective studies			3.00			1.00	1	0.29	4	1.21
	CREST			4.00			6.10				

☐ Quality of Life in the Health States related with Carotid Artery Intervention

For cost utility analysis, the utility index for health states related with carotid artery intervention was surveyed by face-to-face interview. Health states was classified in accordance with the major health states in Markov model for cost-utility analysis: no major adverse events (stroke or myocardial infarction) after CEA or CAS, myocardial infarction and stroke (minor or major stroke).

The utility index without major adverse events after treatment was surveyed by using the time trade off (TTO) and EQ-5D-3L against 400 general populations after providing a virtual scenario which is a comprehensive general description of health status of the carotid artery stenosis patient. The 5th Korea National Health and Nutrition Examination Survey (KNHNES) in 2012 data were used for the utility of myocardial infarction, and 465 patients in the stroke registry of Seoul National University Bundang hospital were analyzed for the utility index of stroke per severity.

Table 5. Utility Index by Health States

Health states	Mean	SD	Source of data (Instrument)
No major adverse events			
After initial treatment	0.79	±0.10	Survey (TTO)
After revascularization	0.61	±0.13	
Myocardial infarction	0.77	±0.05	Korea National Health and Nutrition Examination Survey (EQ-5D-3L)
Minor stroke	0.79	±0.06	Patient registry (EQ-5D-3L)
Major stroke	0.41	±0.48	

As a result of TTO survey, the utility index of health states without major adverse events after CEA or CAS was 0.79 (±0.10). However, utility index of health states without major adverse event after the revascularization due to restenosis was lower, 0.61 (±0.13. The utility index of major adverse events by health states was as follow: the utility index was 0.77 (±0.05) for myocardial infarction, 0.79 (±0.06) for minor stroke and 0.41 (±0.48) for major stroke. Consequentially, utility index of health states without major adverse events after treatment was similar with minor stroke after treatment, and followed by myocardial infarction, major stroke in an order. In case of revascularization due to restenosis, respondents of TTO survey evaluated that the lower utility index due to the high risk of stroke and myocardial infarction compared with the initial treatment.

□ Cost-utility analysis of CAS as compared to CEA for patients with symptomatic carotid artery stenosis in Korea

The cost-utility analysis of CAS versus CEA was conducted for the patients with symptomatic carotid artery stenosis (≥50% stenosis) from Korean healthcare system perspectives. We used the Markov model to compare the expected costs and quality-adjusted life years (QALYs) during the 15 years of time horizon period. The health status was comprised of five states such as no major adverse events (NMAEs), myocardial infarction, major stroke, minor stroke, and death. The cycle length was 1 year. The incremental cost per the additional QALY gained of CAS compared to CEA was calculated. All future costs, and QALYs were discounted at 5% per year, consistent with current guidelines.

Transition probability and clinical outcomes were estimated based on the retrospective cohort study with a medical chart review for 677 subjects with symptomatic carotid artery stenosis in Korea. We applied the utility index of Markov health states from the survey using TTO or EQ-5D.

The costs were categorized into procedural costs and post-procedural costs related to complication. The procedural costs including the index procedure, diagnostic procedures / laboratory tests, anesthesia, and drug costs were calculated based on resource use and unit cost for each component. Also, the post-procedural costs for treatment of stroke, myocardial infarction, and cranial nerve palsy were estimated using the claims data by HIRA. Because physician visits were not significant difference between two groups, and the average age of the subjects was over aged 68 years, transportation costs and patient time costs were not considered in this study. As a result, the procedural costs per event were about KRW 2,360,000 higher for CAS (KRW 3,670,000 for CEA versus KRW 6,030,000 for CAS). Within 30-days, initial hospitalization costs for patients with NMAEs were about KRW 340,000 higher for CEA, which showed longer length of stays than CAS (KRW 1,520,000 for CEA versus KRW 1,180,000 for CAS). The post-procedural costs for treatment of stroke, and myocardial infarction was applied equally to both CEA and CEA.

For symptomatic patients with carotid artery stenosis over 50%, the cost-utility analysis demonstrated that over a 15-year time horizon CEA was associated with a 0.22 QALY gained (6.49 QALYs for CAS versus 6.71 QALYs for CEA) and net cost savings of about KRW 1,690,000 (KRW 7,980,000 for CAS versus KRW 7,980,000 for CEA). In other words, the base case analysis showed that CEA for patients with symptomatic stenosis had a slightly better benefit than CAS, with lower costs.

Subgroup analysis was performed for degree of stenosis (70%), age (70 years old) and physicians with adequate training. The results for subjects with ≥70% stenosis were similar to the base-case; For subjects with <70% stenosis, CAS (about KRW 6,520,000) was less expensive than CEA (KRW 11,840,000), and had 1.05 longer QALYs (7.15 QALYs for CAS versus 6.01 QALYs for CEA). Also, CAS for the patients younger than 70 years old was associated with the higher costs of KRW 450,000, and the 0.27 QALYs increased as compared with CEA. Meanwhile, the analyses for the patients over aged 70, and those treated by physicians with

adequate training were consistent with the base case analysis. Subgroup analysis showed that CAS became the cost-effectiveness alternative for the patients under the age of 70, and <70% stenosis.

Recently, clinical practice guideline in Korea and foreign countries recommends that the CAS can be the alternative treatment for the CEA in symptomatic patients with ≥ 50% carotid artery stenosis. But previous economic evaluation studies assessed in foreign countries reported that CAS was not cost-effectiveness or it was dominated by CEA for symptomatic patients with both higher costs and lower effectiveness (Table 6). This study assessed based on the domestic data also showed a consistent result.

Table 6. Economic evaluation in foreign countries

	Study population & Comparator	Methods and Results	Data Source
Janssen et al. (2008)	• Symptomatic with ≥ 70% stenosis • CAS vs. CEA	• Cost-Utility analysis/Time horizon: 10 years • CEA dominant	ECST, Cochrane SR
Young et al. (2010)	• Symptomatic over aged 70 • CAS vs. CEA	• Cost-Utility analysis/Time horizon: Lifetime • CEA dominant.	CREST, SAPPHIRE, EVA-3S, SR
Mahoney et al. (2011)	• Symptomatic in surgical high risk group • CAS with EPD vs. CEA	• Cost-Utility analysis/Time horizon: Lifetime • ICER of CAS compared to CEA=$204,229: CAS, no cost-effectiveness (ICER=$6,555 in asymptomatic stenosis: CAS, cost-effectiveness)	SAPPHIRE
Vilain et al. (2012)	• Symptomatic and asymptomatic • CAS vs. CEA	• Cost-Utility analysis/Time horizon: 10 years • CAS with higher costs of $524 and lower QALYs of 0.008: CAS, dominated by CEA	CREST

☐ Conclusions

The incidence rate of carotid artery stenosis is also increasing in Korea. Among the patients with carotid artery stenosis, symptomatic carotid artery stenosis patient with higher risk of stroke (≥ 50% of stenosis) were selected as subjects for this study. The rate of death, stroke, myocardial infarction, and complications related with the CEA and CAS in patients with symptomatic carotid artery stenosis was compared by a systematic reviews and retrospective chart review. As a result, death and stroke in CEA was less occurred while complications were occurred more. As a result of cost-effectiveness analysis, the effectiveness difference of CEA and CAS was not that large, but CEA was less expensive than CAS, CEA was cost-effective option for carotid artery stenosis. To generalize these results to national level, the large-scale prospective, multicenter, randomized control trial should be conducted, and these comparative effectiveness research (CER) can provide the evidence of proper use of CEA and CAS.

Key Words: Carotid Artery Stenosis, Carotid Endarterectomy, Carotid Artery Stenting, Cost-benefit Analysis