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#### ORIGINAL RESEARCH

# Efficacy and safety of stenting for elderly patients with severe and symptomatic carotid artery stenosis: a critical meta-analysis of randomized controlled trials

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Correspondence: Yugang Jiang Department of Neurosurgery, Second Xiang-Ya Hospital of Central South University, No 139, Renmin Road, Changsha 410011, Hunan Province, People's Republic of China Tel +86 731 8529 5888 Fax +86 731 8529 5888 Email ygjiangmd@163.com **Objective:** To investigate both short-term and long-term therapeutic efficacy and safety of carotid artery stenting (CAS) and carotid artery endarterectomy (CEA) for elderly patients with severe and symptomatic carotid artery stenosis.

**Methods:** PubMed, EMBASE, Cochrane Library, Clinical Trials Register Centers, and Google Scholar were comprehensively searched. After identifying relevant randomized controlled trials, methodological quality was assessed by using Cochrane tools of bias assessment. Meta-analysis was performed by RevMan software, and subgroup analyses according to different follow-up periods were also conducted.

**Results:** Sixteen articles of nine randomized controlled trials containing 6,984 patients were included. Compared with CEA, CAS was associated with high risks of stroke during periprocedural 30 days (risk ratio [RR]=1.47, 95% confidence interval [CI]: 1.15–1.88), 48 months (RR=1.37, 95% CI: 1.11–1.70), and >48 months (RR=1.76, 95% CI: 1.34–2.31). There was no significant difference in the aspects of death, disabling stroke, or death at any time between the groups. For other periprocedural complications, CAS decreased the risk of myocardial infarction (RR=0.44, 95% CI: 0.26–0.75), cranial nerve palsy (RR=0.09, 95% CI: 0.04–0.22) and hematoma (RR=0.31, 95% CI: 0.14–0.68) compared with CEA, while it increased the risk of bradycardia or hypotension (RR=8.45, 95% CI 2.91–24.58).

**Conclusion:** Compared with CEA, CAS reduced hematoma, periprocedural myocardial infarction, and cranial nerve palsy, while it was associated with higher risks of both short-term and long-term nondisabling stroke. And they seemed to be equivalent in other outcome measures. As regards to its minimal invasion, it should be applied only in specific patients.

**Keywords:** symptomatic carotid artery stenosis, carotid artery stenting, carotid artery endarterectomy

## Introduction

According to the latest statistic from the American Heart Association, stroke ranks third among all the death causes, and every 4 minutes someone dies of stroke. Of all the strokes, 87% are ischemic, and people from 55 to 75 years of age who have a risk of stroke is 14% for men and 20% for women in the USA.<sup>1</sup>

Carotid artery stenosis and occlusive diseases induced by many factors are important causes of ischemic stroke, and they often lead to immediate death although they count approximately 10%–15% of all the strokes.<sup>2</sup> Symptomatic patients with a >50% stenosis of vessel lumen was considered to be of high risk, and need to adopt aggressive treatments.<sup>3</sup> Among the kinds of methods, carotid artery endarterectomy (CEA) was established as an effective option that periprocedural stroke/death

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http://dx.doi.org/10.2147/CIA.S91721

Clinical Interventions in Aging 2015:10 1733-1742

© 2015 Ouyang et al. This work is published by Dove Medical Press Limited, and licensed under Creative Commons Attribution — Non Commercial (unported, v3.0) permission from Dove Medical Press Limited, provided the work is properly attributed. Permissions beyond the scope of the License are administered by Dove Medical Press Limited, provided the work is properly attributed. Permissions beyond the scope of the License are administered by Dove Medical Press Limited, Information on how to request permission may be found at: http://www.dovepress.com/permissions.pp is <6% for symptomatic and <3% for asymptomatic patients, and 10-year risk of stroke after CEA is approximately 2% per year.<sup>4,5</sup> Carotid artery stenting (CAS) that emerged in the past 2 decades has also gradually developed to be an important and minimally invasive alternative. Compared with CEA, it was supposed to enhance recovery, reduce complication, and achieve cosmetic effect,<sup>3</sup> and CAS was performed increasingly in clinical practice during the past few years.

However, therapeutic efficacy and safety of CAS compared with CEA were still uncertain. Up-to-date, a series of randomized controlled trials (RCTs) were designed and performed with various participants and follow-up periods.<sup>6–21</sup> As insufficient statistical test power existed in single trials, the results and conclusions across the trials were controversial and confusing. Meanwhile, due to the lack of long-term results of follow-up longer than 2 years, current meta-analyses based on periprocedural and short-term data<sup>22,23</sup> were not enough to provide valid and comprehensive evidence. Recently, in 2014 and 2015, many large-scale and multicenter RCTs stratified and published their long-term results ranged from postoperative 2–10 years.<sup>11,17,18</sup>

It was necessary to take them together, and all the relevant RCTs involving short-term and long-term results could enhance our current knowledge and findings. So we conducted this critical and updated meta-analysis to conclude the comparative outcomes of CAS and CEA for carotid artery stenosis treatment.

## Methods

### Literature search

A comprehensive search was performed on the databases including PubMed (1966.01–2015.05), EMBASE (1974.01– 2015.05), and Cochrane Library (2015 Issue 5), as well as Clinical Trials Register Centers (up to 2015.05). Search terms were as follows: ("carotid artery" OR "vertebrobasilar" OR "cerebral" OR "craniocerebral" OR "head and neck") AND ("angiostenosis" OR "stenosis" OR "obstruct" OR "endothelial thicken" OR "occlusive disease") AND ("stent" OR "stenting"). Medical subject headings were also used. Related articles, the references of relevant trials, and reviews were also screened to identify potential publications. Google Scholar was also searched for the lasted published articles.

## Inclusion and exclusion criteria

Literature search results were first imported to citation manager software, and after duplication removed titles and abstracts were carefully scanned. At last, potential publications were further assessed by reading full-texts. Publications were included if 1) RCTs investigated the therapeutic efficacy and safety of CAS and CEA in carotid artery stenosis; 2) symptomatic patients >60 years, and with a severe carotid artery stenosis >50% of the luminal diameter, or asymptomatic patients with a >60% stenosis were participants; 3) preoperative aspirin was begun at least 72 hours before CAS or CEA and was continued indefinitely in both groups. Standard CEA was performed, and the stent used was self-expanding-nitinol stent with an emboli-protection device; and 4) primary outcomes should at least include stroke, death, or both of them. Secondary outcomes should include other complications such as transient ischemic attack, cranial nerve palsy, hematoma, restenosis, infection, and artery thrombosis. Meeting abstracts, reviews, non-RCTs, and non-English published papers were excluded.

## Data collection and quality assessment

Reviewers extracted baseline characters of the included trials, which contained the first author, published year, case, average age, interventions, stenosis severity, diagnosis determination methods, and follow-up period. Data of outcomes were extracted in a predesigned table for pooled analysis. Methodological quality was assessed by the tool of bias assessment provided by Cochrane Collaboration, which was based on six items:<sup>23</sup> randomization, allocation concealment, participant, outcome assessment blinding, incomplete outcomes, selective reporting, and other bias. All data extraction and quality assessment were performed by two reviewers independently. Any disagreements were resolved by a third reviewer.

## Statistical analysis

Meta-analysis was performed by using RevMan software (version 5.3, the Cochrane Collaboration, Copenhagen, Denmark). Subgroup analyzes were performed to identify important clinical characters, and all the analyzes were first performed based on clinical homogeneity. After that,  $\chi^2$  and  $I^2$  statistical tests were used to judge and present the statistical heterogeneity across the trials. A homogeneity was considered when  $I^2 \leq 50\%$ , and fixed-effects model was chosen. Random-effects model was chosen when a heterogeneity existed,  $I^2 > 50\%$ . Risk ratio (RR) and mean difference with their respective 95% confidence intervals (CIs) were presented for pooled effect size. Invested funnel plots were used to assess the risks of publication bias.

The meta-analysis was reported mainly according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement.<sup>24</sup> It did not involve any ethic issues.

## Results

## Trial inclusion and quality assessment results

Finally, 16 articles<sup>6-21</sup> of nine trials containing 6,984 patients were included. There were 3,511 cases in the CAS group and 3,473 cases in the CEA group. Flow diagram of trial selection from initial search result to final decision is shown in Figure 1. The baseline characteristic of the included trials was presented in Table 1. Except three trials included both symptomatic and few asymptomatic patients, 67,14,19,20 the others only included symptomatic patients. The three trials included patients who suffered >50% internal carotid artery (ICA) stenosis, 6,7,18-20 and the four trials included patients who suffered >70%ICA stenosis.<sup>8,9,13,15–17</sup> Follow-up ranged from postprocedural 30 days to 10 years.

Methodological quality assessment result was shown in Figure 2. The overall quality was good, whereas the item of blinding of participants and personnel was under unclear risk of bias. As a comparison of surgery, the procedure of CAS and CEA was really different, and blinding of participants and personnel was hard to realize.

## Primary periprocedural and follow-up results

#### Death

According to the different follow-up period, a subgroup analysis including periprocedural 30 days, postprocedural 24, 48, and >48 months was conducted. Meta-analysis results



Figure | Flow diagram of trials selection. Abbreviation: RCTs, randomized controlled trials.

arudy Cou	untry	Case (T/C, n)	Mean age (T/C,	Sex (M/F	:, n)	Intervention	Severity	Symptomatic	Determination	Follow-up (T/C)
			years)	F	υ	(T/C)		(T/C)		
Gurm et al, <sup>6</sup> USA Yadav et al <sup>7</sup>	_	167/167	72.5±8.3/72.6±8.9	111/54	112/55	CAS/CEA	>50% ICA stenosis	28%/30%	Angiography/doppler	Final 3 years
Hoffmann et al <sup>8</sup> Switz	zerland	10/10	69±8.6/71±5.9	8/2	1/6	CAS/CEA	>70% ICA stenosis	%001/%001	Angiography/doppler	48.  ±2 .3/43.5± 9.5
Steinbauer Gerr	many	43/44	67.9±9.1/68.4±6.6	R	NR	CAS/CEA	>70% ICA stenosis	%001/%001	Ultrasound/	monus 66±14.2/64±12.1 months
et al <sup>y</sup> Mas et al <sup>10-12</sup> Fran	ce	265/262	70/69	206/59	188/74	CAS/CEA	>60% ICA stenosis	%001/%001	angiography Angiography/MRA/	7.1 (IQR 5.1–8.8) years
SPACE <sup>13</sup> Gerr	many	607/589	68.1±8.2/68.7±8.7	436/171	422/167	CAS/CEA	>70% ICA stenosis	%001/%001	ultrasound Ultrasound	Final 2 years
CAVATAS <sup>14</sup> Mult	ticenter	251/253	68/68	174/77	178/75	CAS/CEA	Determined by	88/%16	Angiography/MRA/	5 (IQR 2–6)/5 (2–6) months
Brooks et al <sup>15-17</sup> USA		53/51	70/66	NR	NR	CAS/CEA	>70% ICA stenosis	%001/%001	Angiography	>10 years
ICSS <sup>18</sup> UK		853/857	70±9	601/252	606/251	CAS/CEA	>50% ICA stenosis	%001/%001	Doppler ultrasound	4.2 (IQR 3.0–5.2) years
Silver, <sup>19</sup> USA Brott et al <sup>20</sup> Cana	v and	1,262/1,240	68.9±9.0/69.2±8.7	806/456	832/408	CAS/CEA	>50% ICA stenosis	53.9%/53.7%	Angiography/ ultrasonography/MRA	Median 2.5 years

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Figure 2 Summary of methodological quality assessment results.

in fixed-effects model showed that there was no significant difference between CAS and CEA during periprocedural 30 days ( $l^2$ =0%, RR=1.22, 95% CI: 0.69–2.14, P=0.50), postprocedural 24 months ( $l^2$ =0%, RR=0.99, 95% CI: 0.71–1.37, P=0.93), 48 months ( $l^2$ =0%, RR=1.07, 95% CI: 0.89–1.29, P=0.48), and >48 months ( $l^2$ =0%, RR=1.23, 95% CI: 1.00–1.52, P=0.05), as shown in Figure 3.

#### Stroke

According to the different follow-up period, a subgroup analysis including periprocedural 30 days, postprocedural 24, 48, and >48 months was conducted. Meta-analysis results in fixed-effects model showed that CAS was associated with a higher stroke incidence during periprocedural 30 days ( $I^2$ =37%, RR=1.62, 95% CI: 1.31–2.00, P<0.0001), 48 months ( $I^2$ =0%, RR=1.37, 95% CI: 1.11–1.70, P=0.003), and >48 months ( $I^2$ =20%, RR=1.76, 95% CI: 1.34–2.31, P<0.0001) than CEA, whereas there was no significant difference between the groups during postprocedural 24 months ( $I^2$ =0%, RR=1.08, 95% CI: 0.80–1.47, P=0.60), as shown in Figure 4.

Subgroup analysis of the long-term effects also included periprocedural stroke incidence. To avoid a repeated analysis of periprocedural stroke incidence in postprocedural 24, 48, and >48 months, another subgroup analysis excluding periprocedural incidence was also conducted. It revealed that there was no significant difference between CAS and CEA during periprocedural 30 days to postprocedural 24 ( $I^2$ =0%, RR=0.98, 95% CI: 0.60–1.60, P=0.94) months and 48 months ( $I^2$ =0%, RR=1.07, 95% CI: 0.78–1.47, P=0.67). While, during periprocedural 30 days to postprocedural >48 months, the difference was statistically significant ( $I^2$ =44%, RR=1.58, 95% CI: 1.11–2.23, P=0.01).

#### Myocardial infarction

Subgroup analysis including periprocedural 30 days, postprocedural 12 and 36 months was performed. Metaanalysis results in fixed-effects model showed that compared with CEA, CAS achieved a decreased incidence of myocardial infarction (MI) during periprocedural 30 days ( $I^2$ =0%, RR=0.44, 95% CI: 0.26–0.75, P=0.003), whereas the difference between the groups did not reach statistical significance during postprocedural 12 months ( $I^2$ =0%, RR=0.41, 95% CI: 0.15–1.08, P=0.07) and 36 months (RR=0.64, 95% CI: 0.29–1.44, P=0.28), as shown in Figure 5.

#### Disabling stroke and death

Subgroup analysis including periprocedural 30 days, postprocedural 24, and >24 months was performed. Metaanalysis results in the fixed-effects model showed that there was no significant difference between the groups during periprocedural 30 days ( $l^2=0\%$ , RR=1.19, 95% CI: 0.85–1.67, P=0.32), postprocedural 24 months ( $l^2=50\%$ , RR=1.30, 95% CI: 0.93–1.82, P=0.13), and >24 months ( $l^2=48\%$ , RR=1.02, 95% CI: 0.84–1.22, P=0.87), as shown in Figure 6.

#### Other major complications

Compared with CEA, CAS was associated with a significant decrease in periprocedural cranial nerve palsy (P=0%, RR=0.09, 95% CI: 0.04, 0.22, P<0.00001) and hematoma (P=41%, RR=0.31, 95% CI: 0.14, 0.68, P=0.003), whereas it was associated with a significant increase in bradycardia or hypotension (P=0%, RR=8.45, 95% CI: 2.91–24.58, P<0.0001). Besides, there was no significant difference in aspects of transient ischemic attack (P=11%, RR=1.58, 95% CI: 0.93–2.68, P=0.09), restenosis (P=0%, RR=2.22,

Study or subgroup	Experim Events	ental Total	Control Events	Total	Weight	Risk ratio M–H, fixed, 95% Cl	Risk ratio M–H, fixed, 95% Cl
Periprocedural 30 days							
Gurm et al6	2	167	4	167	18.5%	0.50 (0.09, 2.69)	
EVA-3S <sup>10</sup>	2	261	3	259	13.9%	0.66 (0.11, 3.93)	
SPACE <sup>13</sup>	6	607	5	589	23.5%	1.16 (0.36, 3.79)	
CAVATAS <sup>14</sup>	7	251	4	253	18.4%	1.76 (0.52, 5.95)	
Brooks et al <sup>17</sup>	0	53	1	51	7.1%	0.32 (0.01, 7.70)	• • • • • • • • • • • • • • • • • • •
Brott et al <sup>20</sup> Subtotal (95% CI)	9	1,262 <b>2,601</b>	4	1,240 <b>2,559</b>	18.7% <b>100%</b>	2.21 (0.68, 7.16) <b>1.22 (0.69, 2.14)</b>	•
Total events	26		21				
Heterogeneity: $\chi^2$ =3.55, <i>di</i> Test for overall effect: <i>Z</i> =0	f=5 ( <i>P</i> =0.6 .68 ( <i>P</i> =0.5	52); /²=0% 50)	6				
Postprocedural 24 mont	hs						
Gurm et al <sup>6</sup>	31	167	35	167	55.2%	0.89 (0.57, 1.37)	
SPACE <sup>13</sup>	32	607	28	589	44.8%	1.11 (0.68, 1.82)	
Subtotal (95% CI)		774		756	100%	0.99 (0.71, 1.37)	<b>•</b>
Total events	63		63				
Heterogeneity: $\chi^2$ =0.45, <i>di</i> Test for overall effect: <i>Z</i> =0	f=1 ( <i>P</i> =0.5 .09 ( <i>P</i> =0.9	60); /²=0% 93)	0				
Postprocedural 48 mont	hs						
Gurm et al <sup>6</sup>	31	167	35	167	19.1%	0.89 (0.57, 1.37)	
EVA-3S <sup>10</sup>	13	265	6	262	3.3%	2.14 (0.83, 5.55)	
CAVATAS <sup>14</sup>	59	251	59	253	32.0%	1.01 (0.74, 1.38)	-
Brott et al <sup>20</sup>	94	1,262	83	1,240	45.6%	1.11 (0.84, 1.48)	<b>₽</b>
Subtotal (95% CI)		1,945		1,922	100%	1.07 (0.89, 1.29)	•
lotal events	197		183				
Heterogeneity: $\chi^2$ =2.98, <i>di</i> Test for overall effect: <i>Z</i> =0	f=3 ( <i>P</i> =0.3 .71 ( <i>P</i> =0.4	9); /²=0% 18)	0				
>Postprocedural 48 mon	iths						
Steinbauer et al9	5	43	3	44	2.2%	1.71 (0.43, 6.70)	
Brooks et al <sup>17</sup>	5	90	1	83	0.8%	4.61 (0.55, 38.66)	<u> </u>
ICSS <sup>18</sup>	153	853	129	857	97.0%	1.19 (0.96, 1.48)	
Subtotal (95% CI)		986		984	100%	1.23 (1.00, 1.52)	•
Total events	163		133				
Heterogeneity: $\chi^2$ =1.79, da Test for overall effect: Z=1	f=2 ( <i>P</i> =0.4 .93 ( <i>P</i> =0.0	1); /²=0% 05)	0				
							++

0.005 0.1 1 10 200 **Favors (experimental)** Favors (control)

Figure 3 Meta-analysis of periprocedural and postprocedural death. Abbreviations: M–H, Mantel–Haenszel; Cl, confidence interval.

95% CI: 0.51–9.60, *P*=0.29), arterial occlusion or thrombosis (*P*=23%, RR=1.49, 95% CI: 0.42–5.27, *P*=0.54), and infection (*P*=0%, RR=0.60, 95% CI: 0.08, 4.54, *P*=0.62), as shown in Figure 7.

#### Hospital stay

Three trials<sup>7,8,17</sup> reported the data of hospital stay, and the meta-analysis in random-effects model showed that there was no significant difference between CAS and CEA ( $l^2$ =62%, mean difference =-2.08, 95% CI: -4.47 to -0.32, P=0.09).

#### Publication bias

Inverted funnel plots indicated that low risks of publication bias existed in the outcomes of death, stroke, and other major complications (Figure 8).

## Discussion

The critical meta-analysis including 16 articles of nine RCTs with follow-up periods ranged from procedural 30 days to postprocedural 10 years. The pooled analysis altered that CAS was associated with increased risks of stroke compared with CEA during periprocedural 30 days and after postprocedural 4 years. And it confirmed the findings that higher risks of nondisabling stroke and bradycardia or hypotension, and a lower risk of MI were associated with CAS than CEA in the periprocedural period.

The estimated stroke rates were 6.19%, 9.79%, 9.56%, and 12.89%, respectively, at postprocedural 30 days, 2 years, 4 years and >4 years in the CAS group, compared with 3.82%, 9%, 6.97%, and 7.33% in the CEA group. Due to the loss to follow-up and the reduction of available cases, total stroke rate of both was increasing during follow-up period,

Periprocedural 30 days         Gurm et al*       6       167       5       167       3.9%       1.20 (0.37, 3.86)         Hoffmann et al*       0       10       1       11, 2%       0.33 (0.02, 7.32)         EVA.35 <sup>10</sup> 23       261       7       259       5.4%       3.26 (1.42, 7.47)         SPACE <sup>10</sup> 44       607       37       589       29.1%       1.15 (0.76, 1.76)         CAVATAS <sup>14</sup> 26       251       22       253       17.0%       1.19 (0.69, 2.04)         ICSS <sup>16</sup> 59       837       27       836       20.9%       2.18 (1.40, 3.41)       +         Brott et al*       52       1.262       29       1.76 (1.13, 2.76)       5       5         Subtotal (95% CI)       3.395       3.354       100%       1.62 (1.31, 2.00)       +         Ordal events       210       128       +       +       +       +         Postprocedural 24 months       100       0.51, 1.98)       1.09 (0.51, 1.98)       +       +         Gurm et al*       15       167       15       167       1.07 (0.51, 1.98)       +       +         Postprocedural 24 months       80       72       +	Study or subgroup	Experim Events	ental Total	Control Events	Total	Weight	Risk ratio M–H, fixed, 95% Cl	l	Risk ratio M–H, fixe	o ed, 95% Cl	
Gurm et all <sup>®</sup> 6       167       5       167       3.9%       1.20 (0.37, 3.86)         Hoffmann et all <sup>®</sup> 0       10       1       10       1.2%       0.33 (0.02, 7.32)         EVA-3S <sup>®</sup> 23       261       7       259       5.4%       3.26 (1.42, 7.47)         SPACE <sup>®</sup> 44       607       37       589       29.1%       1.15 (0.76, 1.76)         CAWATAS <sup>**</sup> 26       251       22.253       17.0%       1.19 (0.69, 2.04)         ICSS <sup>®</sup> 59       837       27       836       20.9%       2.18 (1.40, 3.41)         Brott et all <sup>®</sup> 52       1.260       22.8%       1.76 (1.13, 2.76)       1.44         Subtotal (95% CI)       3.395       3.354       100%       1.62 (1.31, 2.00)         Postprocedural 24 months       210       128       128       128         Beterogeneity: 2 <sup>+</sup> 29.8, <i>d.</i> , <i>d.</i> 9 ( <i>P</i> =0.79); <i>P</i> =0.76       3.07 (0.13, 73.30)       44       0.7%         Subtotal (95% CI)       817       72       320 (10.0%, 1.08 (0.80, 1.47)       100 (0.51, 1.98)         Subtotal (95% CI)       817       72       122 (1.00, 51, 1.98)       1.68 (0.80, 1.47)       1.77         Total events       80	Periprocedural 30 days	;									
Hoffmann et al <sup>B</sup> 0       10       1       10       1.2%       0.33 (0.02, 7.32)         EVA.3S <sup>10</sup> 23       261       7       259       5.4%       3.26 (1.42, 7.47)         SPACE <sup>10</sup> 44       607       37       589       221       253       17.0%       1.19 (0.69, 2.04)         ICSS <sup>16</sup> 59       837       27       836       20.9%       2.18 (1.40, 3.41)	Gurm et al6	6	167	5	167	3.9%	1.20 (0.37, 3.86)				
EVA.3S <sup>10</sup> 23       261       7       259       5.4%       3.26 (1.4.2, 7.47)         SPACE <sup>10</sup> 44       607       37       589       29.1%       1.15 (0.76, 1.76)         CAVATAS <sup>14</sup> 26       251       22       253       17.0%       1.19 (0.69, 2.04)         ICSS <sup>10</sup> 52       1.262       29       2.16 (1.4.3, 2.41)	Hoffmann et al <sup>8</sup>	0	10	1	10	1.2%	0.33 (0.02, 7.32)				
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	EVA-3S <sup>10</sup>	23	261	7	259	5.4%	3.26 (1.42, 7.47)			<b>_</b>	
CAVATAS <sup>14</sup> 26       251       22       253       17.0%       1.19 (0.69, 20.4)         ICSS <sup>18</sup> 59       837       27       836       20.9%       2.18 (1.40, 3.41)         Brott et al <sup>105</sup> 52       1.262       29       1.240       22.6%       1.76 (1.13, 2.76)         Subtotal (95% CI)       3,395       3,354       100%       1.62 (1.31, 2.00)         Total events       210       128       128       128         Heterogeneity: $\chi^2=0.58, df=6$ (P=0.14); P=37%       128       100%       1.62 (1.31, 2.00)         Postprocedural 24 months       15       167       15       167       20.4%         Subtotal (95% CI)       817       800       100%       1.08 (0.51, 1.98)         Subtotal (95% CI)       817       800       100%       1.08 (0.80, 1.47)         Total events       80       72       1.22       1.240       26.2%       1.38 (1.03, 1.63)         Subtotal (95% CI)       817       262       12.7%       1.92 (1.10, 3.6)	SPACE <sup>13</sup>	44	607	37	589	29.1%	1.15 (0.76, 1.76)		_	-	
$ \begin{array}{ c c c c c c }  c c c c c c c c c c c c $	CAVATAS <sup>14</sup>	26	251	22	253	17.0%	1.19 (0.69, 2.04)		<del>.</del>		
Brott et al <sup>PD</sup> 52       1,262       29       1,240       22.6%       1.76 (1.13, 2.76)         Subtotal (95% CI)       3,395       3,354       100%       1.62 (1.31, 2.00)         Total events       210       128         Heterogeneity: x <sup>2</sup> =9.58, d <sup>2</sup> =6 (P=0.14); l <sup>2</sup> =37%, Test for overall effect: Z=4.43 (P<0.00001)	ICSS <sup>18</sup>	59	837	27	836	20.9%	2.18 (1.40, 3.41)				
Subtoal (95% CI)       3,395       3,354       100%       1.62 (1.31, 2.00)         Total events       210       128         Heterogeneity: $\chi^2=9.58, dr=6$ ( $P=0.14$ ); $P=37\%$ 128         Postprocedural 24 months       15       167       15         Gurn et al <sup>0</sup> 15       167       15       167         Steinbauer et al <sup>0</sup> 1       43       0       44       0.7%         Subtotal (95% CI)       817       800       100%       1.09 (0.78, 1.53)         Subtotal (95% CI)       817       800       100%       1.08 (0.80, 1.47)         Total events       80       72       Heterogeneity: $\chi^2=0.47, dr=2$ ( $P=0.79$ ); $P=0\%$ 72         Heterogeneity: $\chi^2=0.47, dr=2$ ( $P=0.79$ ); $P=0\%$ 72       102 (1.10, 3.36)       1.04 (0.51, 1.98)         FVA-35 <sup>10</sup> 33       251       27       253       20.0%       1.23 (0.76, 1.99)         Brott et al <sup>10</sup> 15       167       1.240       56.2%       1.38 (1.03, 1.63)         Subtotal (95% CI)       1.945       1.922       1.03( 1.63, 1.63)       1.945         Total events       186       1.945       1.92       1.37 (1.11, 1.70)         Total events       186       134	Brott et al <sup>20</sup>	52	1,262	29	1,240	22.6%	1.76 (1.13, 2.76)				
Total events       210       128         Heterogeneity: $\chi^2=9.58$ , $df=6$ ( $P=0.14$ ); $P=37\%$ rest for overall effect: Z=4.43 ( $P=0.0001$ )         Postprocedural 24 months         Gurm et al <sup>6</sup> 15       167       10       0.051, 1.98)         Steinbauer et al <sup>6</sup> 1       43       0       44       0.7%       3.07 (0.13, 73.30)         SPACE: <sup>13</sup> 64       607       57       589       78.9%       1.09 (0.78, 1.53)         Subtotal (95% CI)       817       800       100%       1.08 (0.80, 1.47)         Total events       80       72         Heterogeneity: $\chi^2=0.77$ , $df=2$ ( $P=0.79$ ); $P=0\%$ rest for overall effect: Z=0.53 ( $P=0.60$ )         Postprocedural 48 months       80       72         Gurm et al <sup>6</sup> 15       167       15       167 (1.1%         CAVATAS <sup>14</sup> 33       265       17       262       12.7%       1.92 (1.10, 3.36)         CAVATAS <sup>14</sup> 33       251       27       253       20.0%       1.23 (0.76, 1.99)       Portocella (1.2, 0.2, 1.9)       Portocella	Subtotal (95% CI)		3,395		3,354	100%	1.62 (1.31, 2.00)			•	
Heterogeneity: $\chi^{2}=9.58$ , $dr=6$ ( $P=0.14$ ); $P=37\%$ Test for overall effect: Z=4.43 ( $P<0.0001$ ) Postprocedural 24 months Gurm et al <sup>6</sup> 15 167 15 167 20.4% 1.00 (0.51, 1.98) Steinbauer et al <sup>9</sup> 1 43 0 44 0.7% 3.07 (0.13, 73.30) SPACE <sup>13</sup> 64 607 57 589 78.9% 1.09 (0.78, 1.53) Subtotal (95% CI) 817 800 100% 1.08 (0.80, 1.47) Total events 80 72 Heterogeneity: $\chi^{2}=0.47$ , $df=2$ ( $P=0.79$ ); $P=0\%$ Test for overall effect: Z=0.53 ( $P=0.60$ ) Postprocedural 48 months Gurm et al <sup>6</sup> 15 167 15 167 11.1% 1.00 (0.51, 1.98) EVA-35 <sup>10</sup> 33 265 17 262 12.7% 1.92 (1.10, 3.36) CAVATAS <sup>14</sup> 33 265 17 262 12.7% 1.92 (1.10, 3.36) CAVATAS <sup>14</sup> 33 265 17 262 12.7% 1.92 (1.10, 3.36) CAVATAS <sup>14</sup> 33 265 17 262 12.7% 1.93 (1.03, 1.83) Subtotal (95% CI) 1,945 1,922 100% 1.37 (1.11, 1.70) Total events 186 134 Heterogeneity: $\chi^{2}=2.40$ , $df=3$ ( $P=0.49$ ); $P=0\%$ Test for overall effect: Z=0.33 ( $P=0.49$ ); $P=0\%$ Test for overall effect: Z=2.93 ( $P=0.003$ ) Postprocedural 48 months Steinbauer et al <sup>69</sup> 4 42 0 42 0.7% 9.00 (0.50, 162.10) Brooks et al <sup>17</sup> 4 90 0 883 0.7% 8.31 (0.45, 151.99) ICSS <sup>16</sup> 119 853 72 857 98.6% 1.66 (1.26, 2.19) Subtotal (95% CI) 985 982 100% 1.76 (1.34, 2.31) Total events 127 72	Total events	210		128							
Test for overall effect: $Z=4.43$ (P<0.00001)	Heterogeneity: $\chi^2$ =9.58,	df=6 (P=0.14)	; <b>/</b> ²=37%								
Postprocedural 24 months         Gurm et al <sup>6</sup> 15       167       15       167       20.4%       1.00 (0.51, 1.98)         Steinbauer et al <sup>9</sup> 1       43       0       44       0.7%       3.07 (0.13, 73.30)         Subtotal (95% CI)       817       800       100%       1.08 (0.80, 1.47)         Total events       80       72         Heterogeneity: $\chi^{2}=0.47, df=2$ ( $P=0.79$ ); $I^{2}=0\%$ Total events       80       72         Postprocedural 48 months         Gurm et al <sup>6</sup> 15       167       15.167       11.1%       1.00 (0.51, 1.98)         EVA-35 <sup>10</sup> Call of the colspan="4">Colspan="4"         Colspan="4">Co	Test for overall effect: Z=	4.43 ( <i>P</i> <0.000	001)								
Gurm et al <sup>6</sup> 15       167       15       167       20.4%       1.00 (0.51, 1.98)         Steinbauer et al <sup>9</sup> 1       43       0       44       0.7%       3.07 (0.13, 73.30)         SPACE <sup>13</sup> 64       607       57       589       78.9%       1.09 (0.78, 1.53)         Subtotal (95% CI)       817       800       100%       1.08 (0.80, 1.47)         Total events       80       72         Heterogeneity: $\chi^2=0.47, df=2$ (P=0.79); P=0%       72         Postprocedural 48 months       72         Gurm et al <sup>6</sup> 15       167       15       167       1.00 (0.51, 1.98)         EVA.35 <sup>10</sup> 33       265       17       262       12.7%       1.92 (1.10, 3.36)         CAVATAS <sup>14</sup> 33       251       27       253       20.0%       1.23 (0.76, 1.99)         Brot et al <sup>20</sup> 105       1.262       75       1.240       56.2%       1.38 (1.03, 1.83)         Subtotal (95% CI)       1.945       1.922       100%       1.37 (1.11, 1.70)       •         Postprocedural 48 months       134       -       -       -       •         Steinbauer et al <sup>6</sup> 4       2       0       42 <td>Postprocedural 24 mor</td> <td>nths</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	Postprocedural 24 mor	nths									
Steinbauer et al <sup>0</sup> 1       43       0       44 $0.7\%$ $3.07$ ( $0.13, 73.30$ )         SPACE <sup>13</sup> 64 $607$ $57$ $589$ $78.9\%$ $1.09$ ( $0.78, 1.53$ )         Subtotal (95% CI)       817       800 $100\%$ $1.08$ ( $0.80, 1.47$ )         Total events $80$ $72$ Heterogeneity: $\chi^2=0.47$ , $d=2$ ( $P=0.79$ ); $P=0\%$ $72$ Test for overall effect: $Z=0.53$ ( $P=0.60$ ) $72$ Postprocedural 48 months $15$ $167$ $11.1\%$ $1.00$ ( $0.51, 1.98$ )         EVA-3S <sup>10</sup> 33       265 $17$ $262$ $12.7\%$ $1.92$ ( $1.10, 3.36$ )         CAVATAS <sup>14</sup> 33       251 $27$ $253$ $20.0\%$ $1.23$ ( $0.76, 1.99$ ) $P$ Brott et al <sup>20</sup> 105 $1,262$ $75$ $1,240$ $56.2\%$ $1.38$ ( $1.03, 1.83$ ) $P$ Subtotal (95% CI) $1,945$ $1,922$ $100\%$ $1.37$ ( $1.11, 1.70$ ) $T$ Total events       186       134 $P=0.003$ $P=0.003$ $P=0.003$ $P=0.003$ $P=0.003$ $P=0.003$ $P=0.003$ $P=0.003$ $P=$	Gurm et al6	15	167	15	167	20.4%	1.00 (0.51, 1.98)				
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Steinbauer et al9	1	43	0	44	0.7%	3.07 (0.13, 73.30)				
Subtotal (95% Cl)       817       800       100%       1.08 (0.80, 1.47)         Total events       80       72         Heterogeneity: $\chi^2=0.47$ , $df=2$ (P=0.79); I^2=0%       72         Postprocedural 48 months       900       100%       1.00 (0.51, 1.98)         EVA-3S <sup>10</sup> 33       265       17       262       12.7%       1.92 (1.10, 3.36)         CAVATAS <sup>14</sup> 33       251       27       253       20.0%       1.28 (1.03, 1.83)         Subtotal (95% Cl)       105       1,262       75       1,240       56.2%       1.38 (1.03, 1.83)         Subtotal (95% Cl)       1,945       1,945       1,922       100%       1.37 (1.11, 1.70)         Total events       186       134       134       144       146       147         Heterogeneity: $\chi^2=2.40$ , $df=3$ (P=0.49); I^2=0%       1.38 (0.05, 162.10)       1.37 (1.11, 1.70)       1.37 (1.11, 1.70)         Steinbauer et al <sup>10</sup> 4       90       0       83       0.7%       8.31 (0.45, 151.99)       1.66 (1.26, 2.19)         Subtotal (95% Cl)       985       982       100%       1.76 (1.34, 2.31)       1.76 (1.34, 2.31)	SPACE <sup>13</sup>	64	607	57	589	78.9%	1.09 (0.78, 1.53)		-	-	
Total events       80       72         Heterogeneity: $\chi^2=0.47$ , $df=2$ (P=0.79); $l^2=0\%$ 72         Postprocedural 48 months       72         Gurm et al <sup>6</sup> 15       167       11.1%       1.00 (0.51, 1.98)         EVA-3S <sup>10</sup> 33       265       17       262       12.7%       1.92 (1.10, 3.36)         CAVATAS <sup>14</sup> 33       251       27       253       20.0%       1.23 (0.76, 1.99)         Brott et al <sup>20</sup> 105       1.262       75       1.240       56.2%       1.38 (1.03, 1.83)         Subtotal (95% CI)       1,945       1,922       100%       1.37 (1.11, 1.70)         Total events       186       134         Heterogeneity: $\chi^2=2.40$ , $df=3$ (P=0.49); l <sup>2</sup> =0%       1.34         Test for overall effect: Z=2.93 (P=0.003)	Subtotal (95% CI)	• •	817		800	100%	1.08 (0.80, 1.47)			•	
Heterogeneity: $\chi^{2=0.47}$ , $df=2$ (P=0.79); $l^{2=0\%}$ Test for overall effect: Z=0.53 (P=0.60) Postprocedural 48 months Gurm et al <sup>6</sup> 15 167 15 167 11.1% 1.00 (0.51, 1.98) EVA-3S <sup>10</sup> 33 265 17 262 12.7% 1.92 (1.10, 3.36) CAVATAS <sup>14</sup> 33 251 27 253 20.0% 1.23 (0.76, 1.99) Brott et al <sup>20</sup> 105 1.262 75 1.240 56.2% 1.38 (1.03, 1.83) Subtotal (95% Cl) 1,945 1.922 100% 1.37 (1.11, 1.70) Total events 186 134 Heterogeneity: $\chi^{2=2.40}$ , $df=3$ (P=0.49); $l^{2=0\%}$ Test for overall effect: Z=2.93 (P=0.03) Postprocedural 48 months Steinbauer et al <sup>9</sup> 4 42 0 42 0.7% 9.00 (0.50, 162.10) Brooks et al <sup>17</sup> 4 90 0 83 0.7% 8.31 (0.45, 151.99) ICSS <sup>16</sup> 119 853 72 857 98.6% 1.66 (1.26, 2.19) Subtotal (95% Cl) 985 982 100% 1.76 (1.34, 2.31)	Total events	80		72							
Test for overall effect: $Z=0.53$ ( $P=0.60$ )         Postprocedural 48 months         Gurm et al <sup>6</sup> 15       167       15       167       11.1%       1.00 (0.51, 1.98)         EVA-3S <sup>10</sup> 33       265       17       262       12.7%       1.92 (1.10, 3.36)         CAVATAS <sup>14</sup> 33       251       27       253       20.0%       1.23 (0.76, 1.99)         Brott et al <sup>20</sup> 105       1,262       75       1,240       56.2%       1.38 (1.03, 1.83)         Subtotal (95% CI)       1,945       1,922       100%       1.37 (1.11, 1.70)         Total events       186       134         Heterogeneity: $\chi^2=2.40$ , $df=3$ ( $P=0.49$ ); $I^2=0\%$ Image: Steinbauer et al <sup>9</sup> 4       42       0.7%       9.00 (0.50, 162.10)       Image: Steinbauer et al <sup>9</sup> 4       90       0       83       0.7%       8.31 (0.45, 151.99)       Image: Steinbauer et al <sup>9</sup> 119       853       72       857       98.6%       1.66 (1.26, 2.19)       Image: Steinbauer et al <sup>9</sup> Image: Steinbauer et al <sup>9</sup> 127       72	Heterogeneity: $\gamma^2=0.47$ .	df=2 (P=0.79):	/²=0%	. –							
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Test for overall effect: Z=	0.53 ( <i>P</i> =0.60)									
Gurm et al <sup>6</sup> 15       167       15       167       11.1%       1.00 (0.51, 1.98)         EVA-3S <sup>10</sup> 33       265       17       262       12.7%       1.92 (1.10, 3.36)         CAVATAS <sup>14</sup> 33       251       27       253       20.0%       1.23 (0.76, 1.99)         Brott et al <sup>20</sup> 105       1,262       75       1,240       56.2%       1.38 (1.03, 1.83)         Subtotal (95% CI)       1,945       1,922       100%       1.37 (1.11, 1.70)         Total events       186       134         Heterogeneity: $\chi^2$ =2.40, <i>df</i> =3 ( <i>P</i> =0.49); <i>I</i> <sup>2</sup> =0%       -         Fest for overall effect: Z=2.93 ( <i>P</i> =0.003)       -         Postprocedural 48 mont+       -         Steinbauer et al <sup>9</sup> 4       42       0       42       0.7%       9.00 (0.50, 162.10)         Brooks et al <sup>17</sup> 4       90       0       83       0.7%       8.31 (0.45, 151.99)       -         ICSS <sup>18</sup> 119       853       72       857       98.6%       1.66 (1.26, 2.19)       -         Subtotal (95% CI)       985       982       100%       1.76 (1.34, 2.31)       -       - <td>Postprocedural 48 mor</td> <td>nths</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	Postprocedural 48 mor	nths									
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Gurm et al <sup>6</sup>	15	167	15	167	11.1%	1.00 (0.51, 1.98)			<u>.</u>	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	EVA-3S <sup>10</sup>	33	265	17	262	12.7%	1.92 (1.10, 3.36)				
Brott et al <sup>20</sup> 105       1,262       75       1,240       56.2%       1.38 (1.03, 1.83)         Subtotal (95% Cl)       1,945       1,945       1,922       100%       1.37 (1.11, 1.70)         Total events       186       134         Heterogeneity: $\chi^2$ =2.40, df=3 (P=0.49); I <sup>2</sup> =0%       1.34       1.37 (1.11, 1.70)         Postprocedural 48 montb-       V       V       9.00 (0.50, 162.10)         Brooks et al <sup>17</sup> 4       90       0       83       0.7%       8.31 (0.45, 151.99)         ICSS <sup>18</sup> 119       853       72       857       98.6%       1.66 (1.26, 2.19)         Subtotal (95% Cl)       985       982       100%       1.76 (1.34, 2.31)	CAVATAS <sup>14</sup>	33	251	27	253	20.0%	1.23 (0.76, 1.99)		_		
Subtotal (95% Cl)       1,945       1,922       100%       1.37 (1.11, 1.70)         Total events       186       134         Heterogeneity: $\chi^2$ =2.40, df=3 (P=0.49); I²=0%       134         Test for overall effect: Z=2.93 (P=0.003)       -         >Postprocedural 48 months         Steinbauer et al <sup>9</sup> 4       42       0.7%       9.00 (0.50, 162.10)         Brooks et al <sup>17</sup> 4       90       0       83       0.7%       8.31 (0.45, 151.99)         ICSS <sup>16</sup> 119       853       72       857       98.6%       1.66 (1.26, 2.19)         Subtotal (95% Cl)       985       982       100%       1.76 (1.34, 2.31)       Image: Content of the second s	Brott et al <sup>20</sup>	105	1,262	75	1,240	56.2%	1.38 (1.03, 1.83)				
Total events       186       134         Heterogeneity: x²=2.40, df=3 (P=0.49); l²=0%       134         Test for overall effect: Z=2.93 (P=0.003)       >         >Postprocedural 48 months       >         Steinbauer et al <sup>9</sup> 4       42       0.7%       9.00 (0.50, 162.10)         Brooks et al <sup>17</sup> 4       90       0       83       0.7%       8.31 (0.45, 151.99)         ICSS <sup>16</sup> 119       853       72       857       98.6%       1.66 (1.26, 2.19)         Subtotal (95% CI)       985       982       100%       1.76 (1.34, 2.31)           Total events       127       72	Subtotal (95% CI)		1,945		1,922	100%	1.37 (1.11, 1.70)			٠	
Heterogeneity: $\chi^2$ =2.40, df=3 (P=0.49); I <sup>2</sup> =0%         Test for overall effect: Z=2.93 (P=0.003)         >Postprocedural 48 months         Steinbauer et al <sup>9</sup> 4       42       0.7%       9.00 (0.50, 162.10)         Brooks et al <sup>17</sup> 4       90       0       83       0.7%       8.31 (0.45, 151.99)         ICSS <sup>18</sup> 119       853       72       857       98.6%       1.66 (1.26, 2.19)         Subtotal (95% CI)       985       982       100%       1.76 (1.34, 2.31)           Total events       127       72	Total events	186		134						-	
>Postprocedural 48 months           Steinbauer et al <sup>9</sup> 4         42         0.7%         9.00 (0.50, 162.10)           Brooks et al <sup>17</sup> 4         90         0         83         0.7%         8.31 (0.45, 151.99)           ICSS <sup>18</sup> 119         853         72         857         98.6%         1.66 (1.26, 2.19)           Subtotal (95% CI)         985         982         100%         1.76 (1.34, 2.31)         Image: Control of the second s	Heterogeneity: $\chi^2$ =2.40, Test for overall effect: Z=	df=3 (P=0.49); 2.93 (P=0.003	; /²=0% 3)								
Steinbauer et al <sup>9</sup> 4       42       0       42       0.7%       9.00 (0.50, 162.10)         Brooks et al <sup>17</sup> 4       90       0       83       0.7%       8.31 (0.45, 151.99)         ICSS <sup>18</sup> 119       853       72       857       98.6%       1.66 (1.26, 2.19)         Subtotal (95% Cl)       985       982       100%       1.76 (1.34, 2.31)         Total events       127       72	>Postprocedural 48 mc	onths									
Brooks et al <sup>17</sup> 4         90         0         83         0.7%         8.31 (0.45, 151.99)           ICSS <sup>18</sup> 119         853         72         857         98.6%         1.66 (1.26, 2.19)           Subtotal (95% Cl)         985         982         100%         1.76 (1.34, 2.31)         ▲           Total events         127         72<	Steinbauer et al9	4	42	0	42	0.7%	9.00 (0.50, 162.10)				
ICSS <sup>18</sup> 119       853       72       857       98.6%       1.66 (1.26, 2.19)         Subtotal (95% Cl)       985       982       100%       1.76 (1.34, 2.31)         Total events       127       72	Brooks et al17	4	90	0	83	0.7%	8.31 (0.45, 151.99)			<u></u>	
Subtotal (95% CI)         985         982         100%         1.76 (1.34, 2.31)           Total events         127         72	ICSS <sup>18</sup>	119	853	72	857	98.6%	1.66 (1.26, 2.19)				
Total events 127 72	Subtotal (95% CI)		985		982	100%	1.76 (1.34, 2.31)			<b>*</b>	
	Total events	127		72							
Heterogeneity: $\chi^2$ =2.49, <i>df</i> =2 ( <i>P</i> =0.29); <i>l</i> <sup>2</sup> =20% Test for overall effect: <i>Z</i> =4.05 ( <i>P</i> <0.0001)	Heterogeneity: $\chi^2$ =2.49, Test for overall effect: Z=	df=2 ( <i>P</i> =0.29); 4.05 ( <i>P</i> <0.000	; /²=20% )1)								
								0.005	0.1	1 10	
								Eavore (	U.I experimental)	Favors (con	200 trol)

Figure 4 Meta-analysis of periprocedural and postprocedural stroke. Abbreviations: M–H, Mantel–Haenszel; CI, confidence interval.

while CAS was always having a higher rate than CEA. In order to investigate the long-term effect of them, we further conducted a subgroup analysis including isolated data during procedural 30 days to final follow-up. The results revealed that CAS had a higher rate of stroke after postprocedural 4 years, based on the fact that there was no significant difference in outcomes of death and disabling stroke all the time. So it was clear that CAS had higher risks of nondisabling stroke during short-term of periprocedural 30 days, long-term of >postprocedural 4 years, and overall period of follow-up, while a comparable risk during mid-term with CEA.

And CAS was demonstrated to achieve less cranial nerve palsy than CEA. However, it is hard for the patients in CEA group to identify a cranial nerve palsy from a stroke, so the actual stroke rate in CAS group might be even higher. Although the underlying mechanism was unclear, several studies reported that the increased incidence of stroke was mainly occurring in the contralateral carotid or vertebrobasilar territory.14,25 As is known, carotid artery and vertebrobasilar artery anastomoses each other through the circle of Willis (coW), and both the structure and function of coW are very important for blood supply of the whole brain. On the whole, local carotid artery surgeries may have different effects on the function of coW,<sup>26</sup> and these different influences might be the major causes of therapeutic differences. A study including 139 patients reported that after carotid revascularization, the average diameter of ipsilateral precommunicating anterior cerebral artery (A1) increased 0.1 mm, while ipsilateral and contralateral posterior communicating artery (PCoA) decreased 0.12 mm and 0.08 mm.<sup>25</sup> But, CAS led to much more diameter changes than CEA, with a maximum increase of 0.16 mm and decrease of 0.09 mm. After revascularization

Favors (control)

Study or subgroup	Experin Events	nental Total	Contro Events	l Total	Weight	Risk ratio M–H, fixed, 95% C	I	Risk ratio M–H, fixed, 95% Cl
Periprocedural 30 days								
Gurm et al6	4	167	10	167	22.9%	0.40 (0.13, 1.25)		
EVA-3S <sup>10</sup>	1	261	2	259	4.6%	0.50 (0.05, 5.44)		
CAVATAS <sup>14</sup>	0	251	3	253	8.0%	0.14 (0.01, 2.77)		
Brott et al <sup>20</sup>	14	1,262	28	1,240	64.6%	0.49 (0.26, 0.93)		
Subtotal (95% CI)		1,941		1,919	100%	0.44 (0.26, 0.75)		•
Total events	19		43					
Heterogeneity: $\chi^2$ =0.70, or Test for overall effect: Z=	df=3 (P=0. 3.01 (P=0	.87); /²=( .003)	0%					
Postprocedural 12 mon	iths							
Gurm et al6	5	167	12	167	89.0%	0.42 (0.15, 1.16)		
Steinbauer et al9	0	43	1	44	11.0%	0.34 (0.01, 8.14)	_	
Subtotal (95% CI)		210		211	100%	0.41 (0.15, 1.08)		-
Total events	5		13					_
Heterogeneity: $\chi^2$ =0.01, or Test for overall effect: Z=	<i>df</i> =1 ( <i>P</i> =0. 1.81 ( <i>P</i> =0	.91); /²=( .07)	0%					
Postprocedural 36 mon	iths							
Gurm et al6	9	167	14	167	100%	0.64 (0.29, 1.44)		
Subtotal (95% CI)		167		167	100%	0.64 (0.29, 1.44)		
Total events Heterogeneity: not applic Test for overall effect: 7=	9 able 1 07 ( <i>P</i> =0	28)	14			,		
		,						
							0 001	

Figure 5 Meta-analysis of periprocedural and postprocedural myocardial infarction. Abbreviations: M–H, Mantel–Haenszel; CI, confidence interval.

stenosis in carotid artery was eliminated, A1 perfusion was increased, and PCoA perfusion was back to normal. Although they were relatively small changes, they had marked hemo-dynamic effects.<sup>27</sup>

Still we cannot rule out the conclusion that the much more changes caused by CAS increased the higher risk of stroke than CEA because of the insufficient data and limitations from the study.<sup>25</sup> While the other study demonstrated that the coW is

Favors (experimental)

Study or subgroup	Experin Events	nental Total	Contro Events	l Total	Weight	Risk ratio M–H, fixed, 95%	Risk ratio CI M–H, fixed, 95% CI
Periprocedural 3	0 days						
EVA-3S <sup>10</sup>	8	261	3	259	5.2%	2.65 (0.71, 9.86)	
SPACE <sup>13</sup>	45	607	39	589	68.8%	1.12 (0.74, 1.69)	
CAVATAS <sup>14</sup>	16	251	15	253	26.0%	1.08 (0.54, 2.13)	
Subtotal (95% CI	)	1,119		1,101	100%	1.19 (0.85, 1.67)	٠
Total events	69		57				
Heterogeneity: $\chi^2$	=1.58, df=	=2 (P=0.4	5); /2=0%	, D			
Test for overall eff	ect: Z=0.9	99 (P=0.3	2)				
Postprocedural 2	24 month	s					
Gurm et al6	9	167	13	167	23.0%	0.69 (0.30, 1.58)	
EVA-3S <sup>10</sup>	31	265	16	262	28.5%	1.92 (1.07, 3.42)	
SPACE <sup>13</sup>	34	549	27	534	48.5%	1.22 (0.75, 2.00)	-
Subtotal (95% CI	)	981		963	100%	1.30 (0.93, 1.82)	•
Total events	74		56				
Heterogeneity: $\chi^2$	=4.04, df=	=2 (P=0.1	3); /2=50	%			
Test for overall eff	ect: Z=1.	53 ( <i>P</i> =0.1	3)				
>Postprocedural	24 mont	hs					
EVA-3S <sup>10</sup>	9	265	4	262	3.2%	2.22 (0.69, 7.13)	
CAVATAS <sup>14</sup>	117	251	121	253	96.8%	0.97 (0.81, 1.17)	
Subtotal (95% CI	)	516		515	100%	1.02 (0.84, 1.22)	▼
Total events	126		125				
Heterogeneity: $\chi^2$ Test for overall effective	=1.93, <i>df</i> ect: Z=0.	=1 ( <i>P</i> =0.1 16 ( <i>P</i> =0.8	7); /²=48 37)	%			
							0.005 0.1 1 10 200
							Favors (experimental) Favors (control)

Figure 6 Meta-analysis of periprocedural disabling stroke and death. Abbreviations: M–H, Mantel–Haenszel; CI, confidence interval.

Study or subgroup	Experi Events	mental Total	Contro Events	l Tota	Weight I	Risk ratio M–H, fixed, 95% C	Risk ratio I M–H, fixed, 95% Cl
Transient ische	mic atta	ck					
Steinbauer et al9	3	43	2	44	9.6%	1.53 (0.27, 8.74)	
EVA-3S <sup>10</sup>	6	261	2	159	12.1%	1.83 (0.37, 8.95)	
CAVATAS <sup>14</sup>	22	251	16	253	77.8%	1.39 (0.75, 2.58)	-
Brooks et al <sup>17</sup>	1	53	0	511	0.5%	28.44 (1.17, 689.70	
Subtotal (95% C	;I)	608		967	100%	1.58 (0.93, 2.68)	•
Total events Heterogeneity: $\chi$ Test for overall effective	32 <sup>2</sup> =3.36, c ffect: Z=1	f=3 (P=0 1.70 (P=0	20 .34); /²=1 .09)	1%			
Periprocedural	cranial r	nerve pals	sy				
Gurm et al <sup>6</sup>	0	167	8	167	14.9%	0.06 (0.00, 1.01)	
Steinbauer et al <sup>9</sup>	0	43	1	44	2.6%	0.34 (0.01, 8.14)	
EVA-3S <sup>10</sup>	3	261	20	259	35.2%	0.15 (0.04, 0.49)	
CAVATAS <sup>14</sup>	0	251	22	253	39.3%	0.02 (0.00, 0.37)	
Brooks et al <sup>17</sup>	0	53	4	51	8.0%	0.11 (0.01, 1.94)	
Subtotal (95% C	;I)	775		774	100%	0.09 (0.04, 0.22)	•
Total events Heterogeneity: $\chi$ Test for overall effective	3 ²=2.46, c ffect: Z=	lf=4 (P=0 5.25 (P<0	55 .65); /²=0 .00001)	)%			
Hematoma							
Steinbauer et al <sup>9</sup>	1	43	6	44	22.9%	0.17 (0.02. 1.36)	
EVA-3S <sup>10</sup>	1	261	2	259	7.8%	0.50(0.05, 5.44)	and set
CAVATAS <sup>14</sup>	3	251	17	253	65.4%	0.18 (0.05, 0.00)	
Brooks et al <sup>17</sup>	3	53	1	51	3.9%	2 89 (0 31 26 85)	
Subtotal (95% C	;I)	608	•	607	100%	0.31 (0.14, 0.68)	•
Total events Heterogeneity: $\chi$ Test for overall e	8 ²=5.12, c ffect: Z=2	1f=3 (P=0 2.94 (P=0	26 .16); /²=4 .003)	1%			
Restenosis							
Gurm et al <sup>6</sup>	2	167	1	167	40.1%	2.00 (0.18, 21.85)	
Hoffmann et al8	1	10	1	10	40.1%	1.00 (0.07, 13.87)	
Steinbauer et al9	2	43	0	44	19.8%	5.11 (0.25, 103.51)	
Subtotal (95% C	;I)	220		221	100%	2.22 (0.51, 9.60)	
Total ovents	, 5		2			(*** ) * * * )	
Heterogeneity: $\chi$ Test for overall effective	<sup>2</sup> =0.66, c ffect: Z= <sup>-</sup>	f=2 (P=0 1.06 (P=0	.72); /²=0 .29)	)%			
Arterial occlusion	on or thr	ombosis					
EVA-3S <sup>10</sup>	4	261	1	259	25.1%	3.97 (0.45, 35.27)	
CAVATAS <sup>14</sup>	0	251	2	253	62.2%	0.20 (0.01, 4.18)	
Brooks et al17	1	53	0	51	12.7%	2.89 (0.12, 69.32)	
Subtotal (95% C	;I)	565		563	100%	1.49 (0.42, 5.27)	-
Total events Heterogeneity: $\chi$ Test for overall e	5 ²=2.61, c ffect: Z=0	lf=2 (P=0 0.62 (P=0	3 .27); /²=2 .54)	23%			
Infection							
Steinbauer et al9	0	43	1	44	59.6%	0.34 (0.01, 8.14)	
EVA-3S <sup>10</sup>	1	261	1	259	40.4%	0.99 (0.06, 15.78)	
Subtotal (95% C	;I)	304		303	100%	0.60 (0.08, 4.54)	
Total events	1		2				
Heterogeneity: $\chi^2$ Test for overall effective	<sup>2</sup> =0.25, c ffect: Z=0	df=1 (P=0 0.49 (P=0	.62); /²=0 .62)	)%			
Bradycardia or	hypoten	sion					
EVA-3S <sup>10</sup>	11	261	0	259	14.1%	22.82 (1.35, 385.31	)
Brooks et al17	19	53	3	51	85.9%	6.09 (1.92, 19.35)	
Subtotal (95% C	;I)	314		310	100%	8.45 (2.91, 24.58)	
Total events	30		3				
Heterogeneity: x	<sup>2</sup> =0.78, c	df=1 (P=0	.38); /²=0	)%			
Test for overall e	ffect: Z=3	3.92 (P<0	.0001)				
							0.001 0.1 1 10 1,000
							Favors (experimental) Favors (control)

Figure 7 Meta-analysis of other periprocedural complications. Abbreviations: M–H, Mantel–Haenszel; Cl, confidence interval.

plastic,<sup>28</sup> except for inborn variation, stenting would alter the flow pattern, and nearly one-third of the subjects adopted CAS had a blockade of A1, PCoA or precommunicating posterior cerebral artery (P1) at postprocedural 1 week.<sup>29</sup> Meanwhile, our meta-analysis mainly included patients of >50% ipsilateral stenosis, and most of them were symptomatic, who had high possibilities of variant structure and impaired function of coW compared with asymptomatic patients, although detailed



Figure 8 Inverted funnel plots indicating low risks of publication bias. Notes: (A) Death; (B) stroke. Abbreviations: RR, risk ratio; SE, standard error.

information is absent. Therefore, hemodynamic instability such as bradycardia or hypotension together with significantly altered coW flow pattern may to some extent explain the difference risk of nondisabling stroke between CAS and CEA.

Our meta-analysis also revealed that CAS had a significant high risk of stroke than CEA on long-term effects. In the current analysis, patients had an average age more than 67 years, and studies demonstrated that age was an independent predictor of stroke in CAS other than CEA.<sup>18,30,31</sup> Patients >70 years old had a significantly increased risk of CAS in aspects of procedural stroke or death or ipsilateral stroke. After 48 months, patients including in the metaanalysis had an average age of nearly 71–72 years. So taking everything together, we may conclude that no matter to adopt or already adopted CAS, patients aged >70 years would suffer higher risk than CEA.

For other major complications, CAS significantly reduced the incidence of local hematoma. There was no significant difference in the aspects of infection, artery occlusive thrombosis, infection, restenosis, transient ischemic attack, and hospital stay. So as a minimally invasive surgery, CAS did not have obvious advantages than CEA, except for a decreased incision size, while clinically it seemed to be difficult for surgeons to perform a reoperation in recurrent patients who had undergone CAS.

Although the overall quality of the included RCTs was good, some other limitations existed: 1) stent material and type were not reported in detail, and different stent might have its special characters;<sup>32</sup> 2) an accurate diagnosis of MI should be based on symptom, electrocardiogram, and Q-wave situation. However, most of the studies did not report a standard



diagnosis method, and this might lead to potential bias; 3) surgeon's experience may to affect the therapeutic effects. While, it was still without confirmed conclusions;<sup>33</sup> 4) most of the patients were symptomatic, so the results and conclusions were mainly based on data of symptomatic patients. Their comparative efficacy on asymptomatic patients was inconclusive; 5) Stenosis location and coW structure may be the most important factors to influence future clinical judgment and choice, whereas currently RCTs did not involve them; and 6) only on one study performed cost analysis, while it only compared medical cost and did not add the cost of stent.<sup>15</sup> Actually, CAS had a higher total cost than CEA.

## Conclusion

CAS reduced hematoma, periprocedural MI, and cranial nerve palsy, while it was associated with a higher risk of nondisabling stroke of both short-term and long-term period in elderly patients with severe and symptomatic carotid stenosis. After considering age and survival time, we suggest that the choice on CAS or CEA in symptomatic patients should take into account coW situation, financial condition, and cosmetic requirement.

## Disclosure

The authors report no conflicts of interest in this work.

## References

- Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics–2014 update: a report from the American Heart Association. *Circulation*. 2014;129(3):e28.
- Schneider AT, Kissela B, Woo D, et al. Ischemic stroke subtypes: a population-based study of incidence rates among blacks and whites. *Stroke*. 2004;35(7):1552–1556.

- Guay J. Endovascular stenting or carotid endarterectomy for treatment of carotid stenosis: a meta-analysis. *J Cardiothorac Vasc Anesth.* 2011;25(6):1024–1029.
- Chaturvedi S, Bruno A, Feasby T, et al. Carotid endarterectomy an evidence-based review: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology[J]. *Am J Ophthalmol.* 2006;141(1):238–239.
- European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST)[J]. *Lancet*. 1998;351(9113):1379–1387.
- Gurm HS, Yadav JS, Fayad P, et al. Long-term results of carotid stenting versus endarterectomy in high-risk patients[J]. N Engl J Med. 2008;358(15):1572–1579.
- Yadav JS, Wholey MH, Kuntz RE, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients[J]. *N Engl J Med.* 2004;351(15):1493–1501.
- Hoffmann A, Engelter S, Taschner C, et al. Carotid artery stenting versus carotid endarterectomy–a prospective randomised controlled single-centre trial with long-term follow-up (BACASS)[J]. *Neurol Psychiatr.* 2008;159:84–89.
- Steinbauer MGM, Pfister K, Greindl M, et al. Alert for increased longterm follow-up after carotid artery stenting: results of a prospective, randomized, single-center trial of carotid artery stenting vs carotid endarterectomy[J]. J Vasc Surg. 2008;48(1):93–98.
- Mas JL, Trinquart L, Leys D, et al. Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial: results up to 4 years from a randomised, multicentre trial[J]. *Lancet Neurol.* 2008;7(10):885–892.
- Mas JL, Arquizan C, Calvet D, et al. Long-term follow-up study of endarterectomy versus angioplasty in patients with symptomatic severe carotid stenosis trial[J]. *Stroke*. 2014;45(9):2750–2756.
- Mas JL, Chatellier G, Beyssen B, et al. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis[J]. N Engl J Med. 2006;355(16):1660–1671.
- Eckstein HH, Ringleb P, Allenberg JR, et al. Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial[J]. *Lancet Neurol.* 2008;7(10): 893–902.
- 14. Ederle J, Bonati LH, Dobson J, et al. Endovascular treatment with angioplasty or stenting versus endarterectomy in patients with carotid artery stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): long-term follow-up of a randomised trial[J]. *Lancet Neurol.* 2009;8(10):898–907.
- Brooks WH, McClure RR, Jones MR, Coleman TC, Breathitt L. Carotid angioplasty and stenting versus carotid endarterectomy: randomized trial in a community hospital[J]. J Am Coll Cardiol. 2001;38(6): 1589–1595(7).
- Brooks WH, Mcclure RR, Jones MR, Coleman TL, Breathitt L. Carotid angioplasty and stenting versus carotid endarterectomy for treatment of asymptomatic carotid stenosis: a randomized trial in a community hospital[J]. *Neurosurgery*. 2004;54(2):318–325.

- Brooks WH, Jones MR, Gisler P, et al. Carotid Angioplasty With Stenting Versus Endarterectomy: 10-Year Randomized Trial in a Community Hospital[J]. *JACC Cardiovasc Interv*. 2014;7(2):163–168.
- Bonati LH, Dobson J, Featherstone RL, et al. Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the International Carotid Stenting Study (ICSS) randomised trial.[J]. *Lancet*. 2015;385(14):529–538.
- Silver FL. Safety of stenting and endarterectomy by symptomatic status in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST).[J]. *Stroke.* 2011;54(3):280.
- Brott TG, Hobson RW, Howard G, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis[J]. N Engl J Med. 2010;363(1):11–23.
- Murad MH, Shahrour A, Shah ND, Montori VM, Ricotta JJ. A systematic review and meta-analysis of randomized trials of carotid endarterectomy vs stenting[J]. J Vasc Surg. 2011;53(3):792–797.
- Bonati LH, Lyrer P, Ederle J, et al. Percutaneous transluminal balloon angioplasty and stenting for carotid artery stenosis[J]. *Cochrane Database Syst Rev.* 2012;9:CD000515.
- Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions, 5.1. 0 (updated March 2011). The Cochrane Collaboration 2011[J]. Available from: www.cochrane-handbook.org; 2011.
- Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement[J]. Syst Rev. 2015;4(1):1.
- Bost RBC, Hendrikse J, Algra A, et al. Effects of carotid endarterectomy or stenting on arterial diameters in the circle of Willis[J]. *J Stroke Cerebrovasc Dis.* 2014;23(4):699–705.
- Cassot F, Vergeur V, Bossuet P, Hillen B, Zagzoule M, Marc-Vergnes JP. Effects of Anterior Communicating Artery Diameter on Cerebral Hemodynamics in Internal Carotid Artery Disease A Model Study[J]. *Circulation*. 1995;92(10):3122–3131.
- Cao Q, Zhang J, Xu G. Hemodynamic Changes and Baroreflex Sensitivity Associated with Carotid Endarterectomy and Carotid Artery Stenting[J]. *Interv Neurol.* 2014;3(1):13–21.
- Chuang YM, Guo W, Lin CP. Appraising the plasticity of the circle of Willis: a model of hemodynamic modulation in cerebral arteriovenous malformations[J]. *Eur Neurol.* 2010;63(5):295–301.
- Chuang YM, Lin CP, Wong HF, et al. Plasticity of circle of Willis: a longitudinal observation of flow patterns in the circle of Willis one week after stenting for severe internal carotid artery stenosis[J]. *Cerebrovasc Dis.* 2009;27(6):572–578.
- Economopoulos KP, Sergentanis TN, Tsivgoulis G, Mariolis AD, Stefanadis C. Carotid artery stenting versus carotid endarterectomy a comprehensive meta-analysis of short-term and long-term outcomes[J]. *Stroke*. 2011;42(3):687–692.
- Bonati L. Stenting or Endarterectomy for patients with symptomatic carotid stenosis[J]. *Neurol Clin*. 2015;33(2):459–474.
- He D, Liu W, Zhang T. The Development of Carotid Stent Material[J]. Interv Neurol. 2014;3(2):67–77.
- Bangalore S, Kumar S, Wetterslev J, et al. Carotid artery stenting vs carotid endarterectomy: meta-analysis and diversity-adjusted trial sequential analysis of randomized trials[J]. *Arch Neurol*. 2011;68(2):172–184.

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