JAMA | Original Investigation

The CASSISS Randomized Clinical Trial

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IMPORTANCE Prior randomized trials have generally shown harm or no benefit of stenting added to medical therapy for patients with symptomatic severe intracranial atherosclerotic stenosis, but it remains uncertain as to whether refined patient selection and more experienced surgeons might result in improved outcomes.

OBJECTIVE To compare stenting plus medical therapy vs medical therapy alone in patients with symptomatic severe intracranial atherosclerotic stenosis.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, open-label, randomized, outcome assessor–blinded trial conducted at 8 centers in China. A total of 380 patients with transient ischemic attack or nondisabling, nonperforator (defined as nonbrainstem or non–basal ganglia end artery) territory ischemic stroke attributed to severe intracranial stenosis (70%-99%) and beyond a duration of 3 weeks from the latest ischemic symptom onset were recruited between March 5, 2014, and November 10, 2016, and followed up for 3 years (final follow-up: November 10, 2019).

INTERVENTIONS Medical therapy plus stenting (n = 176) or medical therapy alone (n = 182). Medical therapy included dual-antiplatelet therapy for 90 days (single antiplatelet therapy thereafter) and stroke risk factor control.

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of stroke or death within 30 days or stroke in the qualifying artery territory beyond 30 days through 1 year. There were 5 secondary outcomes, including stroke in the qualifying artery territory at 2 years and 3 years as well as mortality at 3 years.

RESULTS Among 380 patients who were randomized, 358 were confirmed eligible (mean age, 56.3 years; 263 male [73.5%]) and 343 (95.8%) completed the trial. For the stenting plus medical therapy group vs medical therapy alone, no significant difference was found for the primary outcome of risk of stroke or death (8.0% [14/176] vs 7.2% [13/181]; difference, 0.4% [95% CI, −5.0% to 5.9%]; hazard ratio, 1.10 [95% CI, 0.52-2.35]; $P = .82$). Of the 5 prespecified secondary end points, none showed a significant difference including stroke in the qualifying artery territory at 2 years (9.9% [17/171] vs 9.0% [16/178]; difference, 0.7% [95% CI, −5.4% to 6.7%]; hazard ratio, 1.10 [95% CI, 0.56-2.16]; $P = .80$) and 3 years (11.3% [19/168] vs 11.2% [19/170]; difference, −0.2% [95% CI, −7.0% to 6.5%]; hazard ratio, 1.00 [95% CI, 0.53-1.90]; $P > .99$). Mortality at 3 years was 4.4% (7/160) in the stenting plus medical therapy group vs 1.3% (2/159) in the medical therapy alone group (difference, 3.2% [95% CI, −0.5% to 6.9%]; hazard ratio, 3.75 [95% CI, 0.77-18.13]; $P = .08$).

CONCLUSIONS AND RELEVANCE Among patients with transient ischemic attack or ischemic stroke due to symptomatic severe intracranial atherosclerotic stenosis, the addition of percutaneous transluminal angioplasty and stenting to medical therapy, compared with medical therapy alone, resulted in no significant difference in the risk of stroke or death within 30 days or stroke in the qualifying artery territory beyond 30 days through 1 year. The findings do not support the addition of percutaneous transluminal angioplasty and stenting to medical therapy for the treatment of patients with symptomatic severe intracranial atherosclerotic stenosis.

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page 529

page 543

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Key Points

Question Among patients with transient ischemic attack or ischemic stroke due to symptomatic severe intracranial atherosclerotic stenosis, does performing angioplasty and stenting 3 weeks or more after the index event along with standard medical therapy reduce the risk of stroke or death compared with medical therapy alone?

Findings In this randomized clinical trial that included 358 patients, the risk of stroke or death within 30 days or stroke in the qualifying artery territory beyond 30 days through 1 year occurred in 8.0% in the percutaneous transluminal angioplasty and stenting group vs 7.2% in the medical therapy alone group, a difference that was not statistically significant.

Meaning The findings do not support the addition of percutaneous transluminal angioplasty and stenting to medical therapy for the treatment of patients with symptomatic severe intracranial atherosclerotic stenosis.

Methods

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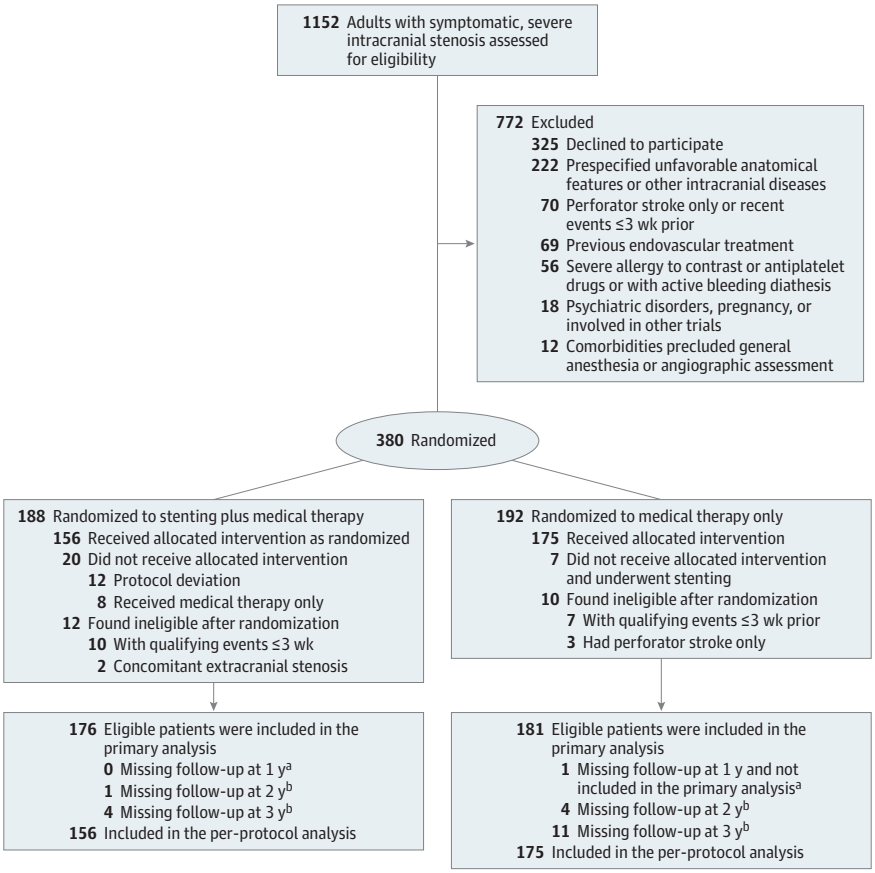

[a] Primary outcome was assessed up to 1 year.

[b] Time points at which some secondary outcomes were assessed.

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Results

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h ( ) (,) (**Figure 1**). O h , , (h h h) - (**Table 1**). Th (SD)
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Characteristic	No. (%) Percutaneous transluminal angioplasty and stenting group (n = 176)	Medical therapy alone group (n = 182)
Age, mean (SD), y	56.7 (9.4)	55.9 (9.8)
Sex		
Male	128 (72.7)	135 (74.2)
Female	48 (27.3)	47 (25.8)
Ethnicity[a]		
Han	172 (97.7)	179 (98.4)
Non-Han	4 (2.3)	3 (1.6)
Medical history[b]		
Hypertension	117 (66.5)	125 (68.7)
Diabetes	57 (32.4)	44 (24.2)
Coronary artery disease	19 (10.8)	19 (10.4)
Lipid disorder	18 (10.2)	21 (11.5)
Peripheral artery disease	0 (0.0)	1 (0.5)
Received antiplatelet therapy prior to latest qualifying event	49 (27.8)	48 (26.4)
Received statin therapy prior to latest qualifying event	19 (10.8)	20 (11.0)
Alcohol history		
Former	25 (14.2)	22 (12.1)
Current	30 (17.0)	32 (17.6)
Smoking history		
Former	39 (22.2)	38 (20.9)
Current	41 (23.3)	50 (27.5)
Qualifying event		
TIA[c]	87 (49.4)	77 (42.3)
Stroke	89 (50.6)	105 (57.7)
Artery-to-artery embolism	57 (64.0)	58 (55.2)
Isolated hemodynamic compromise[d]	18 (20.2)	22 (21.0)
Mixed mechanism	14 (15.7)	25 (23.8)
Time from latest ischemic event to randomization, median (IQR), d	34.5 (27.0-65.5)	36.0 (28.0-68.0)
TIA	33.0 (25.0-52.0)	33.0 (28.0-57.0)
Stroke	38.0 (27.0-75.0)	40.0 (29.0-72.0)
Symptomatic qualifying artery		
Middle cerebral artery (M1)	65 (36.9)	79 (43.4)
Basilar artery	50 (28.4)	52 (28.6)
Intracranial vertebral artery	46 (26.1)	34 (18.7)
Intracranial internal carotid artery	15 (8.5)	17 (9.3)
Stenosis of symptomatic qualifying artery[e]		
% Stenosis, median (IQR)	78.5 (74.1-82.6)	76.6 (73.2-80.9)
Distribution, % stenosis		
70-79	105 (59.7)	130 (71.4)
80-89	65 (36.9)	46 (25.3)
90-99	6 (3.4)	6 (3.3)

(continued)

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Characteristic	No. (%) Percutaneous transluminal angioplasty and stenting group (n = 176)	Medical therapy alone group (n = 182)
NIHSS score, median (IQR)[f]	0.0 (0.0-1.0)	0.0 (0.0-0.0)
mRS score, median (IQR)[g]	0.0 (0.0-1.0)	0.0 (0.0-1.0)

Abbreviations: mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

[a] Ethnicity was self-reported.

[b] Medical history was collected at the baseline visit, based on a combination of self-reports from patients, medicated conditions, and laboratory results.

[c] TIA was a clinical diagnosis without imaging.

[d] Isolated hemodynamic compromise refers to strokes with an arterial border zone or "watershed" pattern.

[e] Stenosis was quantified on the basis of a reading of the angiogram by the site interventionist on the criteria of the WASID trial.[18]

[f] NIHSS score ranges from 0 to 42, with higher scores indicating worse neurologic deficits.

[g] mRS score ranges from 0 to 6, with higher scores indicating worse function deficits (0 indicates no deficit and 6 indicates death).

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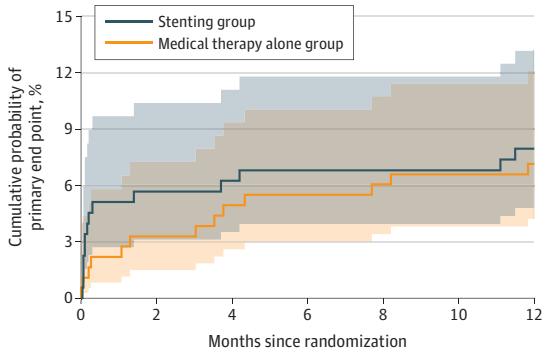

The primary outcome was stroke or death within 30 days after enrollment or stroke in the qualifying artery territory beyond 30 days through 1 year. One patient lost to follow-up within 1 year in the control group was treated as censored data. All other patients were followed up to event or 1 year. *P* = .82 for log-rank testing between the stenting and medical therapy alone groups with center as stratification factor.

P = .) (**Figure 2** **Table 2**). Th - (. % / . % / HR, . % CI, . - . *P* = .) (F S).

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	No./total (%)				
	Percutaneous transluminal angioplasty and stenting group (n = 176)	Medical therapy alone group (n = 181)[a]	Incidence difference, % (95% CI)[b]	Hazard ratio (95% CI)[b]	*P* value[c]
Components of the primary outcome	14/176 (8.0)	13/181 (7.2)	0.4 (−5.0 to 5.9)	1.10 (0.52 to 2.35)	.82
Stroke or death within 30 d after enrollment[d]	9/176 (5.1)[e]	4/181 (2.2)[f]			
Stroke in territory of qualifying artery beyond 30 d through 1 y[d]	5/176 (2.8)	9/181 (5.0)			
Secondary outcomes					
Stroke in the same territory within 2 y	17/171 (9.9)[g]	16/178 (9.0)[h]	0.7 (−5.4 to 6.7)	1.10 (0.56 to 2.16)	.80
Stroke in the same territory within 3 y	19/168 (11.3)[i]	19/170 (11.2)[j]	−0.2 (−7.0 to 6.5)	1.00 (0.53 to 1.90)	>.99
Disabling stroke or death within 3 y	19/168 (11.3)[k]	15/166 (9.0)[l]	2.0 (−4.6 to 8.6)	1.28 (0.65 to 2.52)	.49
Any stroke, TIA, cardiovascular events related to stenting or medical therapy within 3 y	24/169 (14.2)[m]	31/172 (18.0)[n]	−4.1 (−12.0 to 3.7)	0.76 (0.45 to 1.30)	.31
Death within 3 y	7/160 (4.4)[o,p]	2/159 (1.3)[q,r]	3.2 (−0.5 to 6.9)	3.75 (0.77 to 18.13)	.08
Stroke-related death[d]	4/160 (2.5)	2/159 (1.3)			
Nonstroke-related death[d]	3/160 (1.9)	0/159 (0)			

Abbreviation: TIA, transient ischemic attack.

[a] One participant randomized to the medical therapy alone group was not included due to missing outcome data. See Figure 1.

[b] Adjusted for site effect.

[c] Log-rank test adjusted for site effect.

[d] Post hoc analysis.

[e] There were 5 ischemic stroke and 4 hemorrhagic strokes. Of the 4 symptomatic hemorrhagic strokes, 1 was periprocedural subarachnoid hemorrhage immediately after percutaneous transluminal angioplasty and stenting (probably related to guidewire perforation); 1 was periprocedural parenchymal and subdural brain hemorrhage evident immediately after percutaneous transluminal angioplasty and stenting (probably related to guidewire perforation); 1 was cerebellar and occipital hemorrhage that occurred 3 days after percutaneous transluminal angioplasty and stenting (probably related to reperfusion); and 1 was subarachnoid hemorrhage within 24 hours after percutaneous transluminal angioplasty and stenting (probably related to reperfusion). A total of 2 of these hemorrhages were fatal (1 developed massive cerebral infarction and brain hernia, and 1 had parenchymal brain hemorrhage), and 2 were nondisabling (1 cerebellar and occipital hemorrhage and 1 subarachnoid hemorrhage).

[f] There were 4 ischemic strokes and 0 hemorrhagic strokes. Of the 4 ischemic strokes, 2 were disabling, 2 were nondisabling, and none were fatal.

[g] One missing follow-up and 4 died.

[h] Four missing follow-up and 0 died.

[i] Four missing follow-up and 4 died.

[j] Eleven missing follow-up and 1 died.

[k] Eight missing follow-up, including 4 with primary outcomes (but no disabling stroke or death).

[l] Sixteen missing follow-up, including 5 with primary outcomes (but no disabling stroke or death).

[m] Four missing follow-up and 3 died.

[n] Ten missing follow-up and 0 died.

[o] Sixteen missing follow-up, including 12 with primary outcomes.

[p] The causes of death in the percutaneous transluminal angioplasty and stenting group were as follows: brain hemorrhage (n = 2), ischemic stroke (n = 2), sudden cardiac arrest (n = 1), intrahepatic cholangiocarcinoma (n = 1), and aortic artery aneurysm (n = 1).

[q] Twenty-three missing follow-up, including 12 with primary outcomes.

[r] The causes of death in the medical management group were as follows: ischemic stroke (n = 1) and brain hemorrhage (n = 1).

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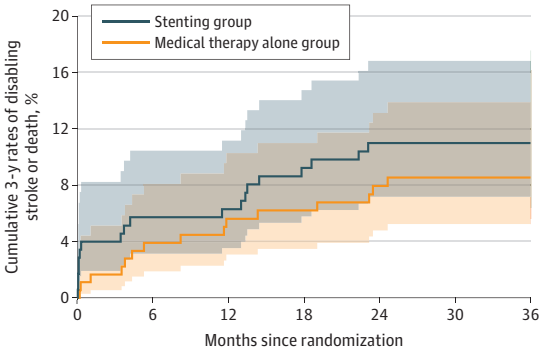

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Medical therapy alone group	182	170	166	162	159	151	151
Stenting group	176	163	162	155	152	149	149

The median time of observation was 36.0 months (IQR, 36.0-36.0) for the stenting group and 36.0 months (IQR, 36.0-36.0) for the medical therapy alone group. *P* = .49 for log-rank testing between stenting group and medical therapy alone group with center as stratification factor.

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Discussion

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Conclusions

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Author Contributions: Dr Jiao had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Gao, T. Wang, D. Wang, and Liebeskind are co-first authors.
Concept and design: Gao, T. Wang, D. Wang, Shi, Li, Zhao, Cai, W. Wu, He, Yu, Zheng, Dmytriw, Krings, Jiao.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Gao, T. Wang, D. Wang, Shi, Li, Zhao, Cai, W. Wu, He, Yu, Zheng, Dmytriw, Jiao.
Critical revision of the manuscript for important intellectual content: Gao, T. Wang, D. Wang, Liebeskind, H. Wang, Y. Wu, Dmytriw, Krings, Derdeyn, Jiao.
Statistical analysis: H. Wang.
Obtained funding: Gao, Dmytriw, Jiao.
Administrative, technical, or material support: Gao, T. Wang, D. Wang, Liebeskind, Shi, Li, Zhao, Cai, W. Wu, He, Yu, Zheng, Jiao.
Supervision: Gao, Liebeskind, H. Wang, Krings, Jiao.

Conflict of Interest Disclosures: Dr Liebeskind reported consultancy to the imaging core laboratories of Cerenovus, Genentech, Medtronic, Stryker, and Rapid Medical Inc during the conduct of the study. Dr Krings reported receiving personal fees from Stryker, Medtronic, Cerenovus, Penumbra, Stereotaxis, and Cranmed and royalties from Thieme and being a stockholder of Marblehead Inc outside the submitted work. Dr Derdeyn reported consultancy to Penumbra Inc, NoNO Inc, and Euphrates Vascular Inc. Dr Jiao reported receiving grants from the Ministry of Science and Technology of the People's Republic of China (2011BAI08B04) and Stryker Neurovascular during the conduct of the study, as well as grants from Ministry of Science and Technology of the People's Republic of China (SQ2016YFSF110141) outside the submitted work. No other disclosures were reported.

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Data Sharing Statement: See Supplement 5.

Additional Contributions: We thank the patients and their families for participating in this trial.

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