JAMA | Original Investigation

Balloon Angioplasty vs Medical Management for Intracranial Artery Stenosis
The BASIS Randomized Clinical Trial

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IMPORTANCE Previous randomized clinical trials did not demonstrate the superiority of endovascular stenting over aggressive medical management for patients with symptomatic intracranial atherosclerotic stenosis (sICAS). However, balloon angioplasty has not been investigated in a randomized clinical trial.

OBJECTIVE To determine whether balloon angioplasty plus aggressive medical management is superior to aggressive medical management alone for patients with sICAS.

DESIGN, SETTING, AND PARTICIPANTS A randomized, open-label, blinded end point clinical trial at 31 centers across China. Eligible patients aged 35 to 80 years with sICAS defined as recent transient ischemic attack (<90 days) or ischemic stroke (14-90 days) before enrollment attributed to a 70% to 99% atherosclerotic stenosis of a major intracranial artery receiving treatment with at least 1 antithrombotic drug and/or standard risk factor management were recruited between November 8, 2018, and April 2, 2022 (final follow-up: April 3, 2023).

INTERVENTIONS Submaximal balloon angioplasty plus aggressive medical management (n = 249) or aggressive medical management alone (n = 252). Aggressive medical management included dual antiplatelet therapy for the first 90 days and risk factor control.

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of any stroke or death within 30 days after enrollment or after balloon angioplasty of the qualifying lesion or any ischemic stroke in the qualifying artery territory or revascularization of the qualifying artery after 30 days through 12 months after enrollment.

RESULTS Among 512 randomized patients, 501 were confirmed eligible (mean age, 58.0 years; 158 [31.5%] women) and completed the trial. The incidence of the primary outcome was lower in the balloon angioplasty group than the medical management group (4.4% vs 13.5%; hazard ratio, 0.32 [95% CI, 0.16-0.63]; $P < .001$). The respective rates of any stroke or all-cause death within 30 days were 3.2% and 1.6%. Beyond 30 days through 1 year after enrollment, the rates of any ischemic stroke in the qualifying artery territory were 0.4% and 7.5%, respectively, and revascularization of the qualifying artery occurred in 1.2% and 8.3%, respectively. The rate of symptomatic intracranial hemorrhage in the balloon angioplasty and medical management groups was 1.2% and 0.4%, respectively. In the balloon angioplasty group, procedural complications occurred in 17.4% of patients and arterial dissection occurred in 14.5% of patients.

CONCLUSIONS AND RELEVANCE In patients with sICAS, balloon angioplasty plus aggressive medical management, compared with aggressive medical management alone, statistically significantly lowered the risk of a composite outcome of any stroke or death within 30 days or an ischemic stroke or revascularization of the qualifying artery after 30 days through 12 months. The findings suggest that balloon angioplasty plus aggressive medical management may be an effective treatment for sICAS, although the risk of stroke or death within 30 days of balloon angioplasty should be considered in clinical practice.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03703635

JAMA. 2024;332(13):1059-1069. doi:10.1001/jama.2024.12829
Published online September 5, 2024.

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Intracranial atherosclerotic stenosis (ICAS) is a major etiology of stroke worldwide, especially in East and South Asia, accounting for up to 50% of all ischemic stroke.[1] Symptomatic ICAS (sICAS), defined as a recent transient ischemic attack (TIA) or ischemic stroke attributed to a 70% to 99% atherosclerotic stenosis of a major intracranial artery, has a 7.2% to 15.1% risk of recurrent stroke within 1 year despite aggressive medical management.[2-4] Patients with sICAS and border zone infarction or poor collateral circulation may be vulnerable, with a risk of recurrent stroke within 1 year of up to 37%.[5]

Three randomized clinical trials (RCTs) did not demonstrate the superiority of intracranial stenting over aggressive medical management for sICAS.[2-4] The Stenting vs Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) and Vitesse Intracranial Stent Study for Ischemic Stroke Therapy (VISSIT) trials demonstrated that aggressive medical management was superior to self-expanding stenting and balloon-expanding stenting for sICAS.[2,3,6] The China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS) trial showed no significant difference in the risk of stroke or death between self-expanding stenting and aggressive medical management for sICAS.[4]

Balloon angioplasty has been investigated for secondary stroke prevention in sICAS patients in observational studies.[7-10] Meta-analyses suggest that submaximal balloon angioplasty may have lower rates of periprocedural complications than stenting and a high probability of being effective for secondary stroke prevention.[7-10]

The Balloon Angioplasty for Symptomatic Intracranial Artery Stenosis (BASIS) trial investigated whether balloon angioplasty plus aggressive medical management is superior to aggressive medical management alone for secondary stroke prevention in patients with sICAS.

Key Points

Question Is balloon angioplasty plus aggressive medical management superior to aggressive medical management alone for the treatment of severe symptomatic intracranial atherosclerotic stenosis (sICAS)?

Finding In this randomized clinical trial that included 501 patients, the composite outcome of any stroke or death within 30 days or an ischemic stroke or revascularization of the qualifying artery after 30 days through 12 months occurred in 4.4% of patients in the balloon angioplasty group and 13.5% of patients in the aggressive medical management group, a statistically significant difference.

Meaning The findings suggest that balloon angioplasty plus aggressive medical management may be an effective treatment for sICAS, although the risk of stroke or death within 30 days of balloon angioplasty should be considered in clinical practice.

Methods

Trial Design

BASIS was an investigator-initiated, multicenter, randomized, open-label, blinded end point trial conducted at 31 comprehensive stroke centers across China. The institutional review boards of Beijing Tiantan Hospital and each site approved the trial protocol. Because China is a multiethnic country, ethnicity was assessed in this study and defined by self-report of participants with an open-ended question. All patients or their legally authorized representatives provided written informed consent. The annual volume of balloon angioplasty by the neurointerventionists in BASIS was more than 50 cases. The neurointerventionists received standard technique training from the lead center at regular intervals. Details of the study protocol and statistical analysis plan are provided in Supplement 2.

Participants

Eligible patients were aged 35 to 80 years; had primary or recurrent sICAS (a recent TIA [<90 days] or ischemic stroke [14-90 days] before enrollment attributed to 70%-99% atherosclerotic stenosis of a major intracranial artery) while receiving at least 1 treatment, including antithrombotic drug or vascular risk factor management; had severe atherosclerotic stenosis (70%-99% according to the Warfarin Aspirin Symptomatic Intracranial Disease method[11]); and normal distal artery involving the internal carotid (C4-C7 segments), middle cerebral (M1 segment), vertebral (V4 segment), or basilar arteries.

Patients were ineligible if they received thrombolytic therapy within 24 hours before enrollment, had worsening neurological deficits within 24 hours before enrollment, had other intracranial arteries with severe stenosis (70%-99%) apart from the qualifying artery, had stenosis greater than 50% of the parent artery to the qualifying artery, had perforator stroke (except for severe stenosis of the supplying artery with hemodynamic compromise),[12] or with baseline modified Rankin Scale (mRS) score of 3 or above. Detailed inclusion and exclusion criteria are in the study protocol.[13]

Randomization and Blinding

The trial used an interactive web response system for central randomization stratified by centers with permuted blocks (block size: 4). Eligible patients were randomized 1:1 into the balloon angioplasty or aggressive medical management group. All end point events were reported and adjudicated by the clinical event adjudication committee, who were unaware of the trial group assignments (eFigure 1 in Supplement 1). A neuroimaging core lab of independent neuroradiologists masked to all clinical information assessed the imaging.

Procedure

Both groups underwent the same aggressive medical management after enrollment, including aspirin 100 mg daily for the entire follow-up period and clopidogrel 75 mg daily for the first 90 days after enrollment. Clopidogrel could be replaced with ticagrelor or cilostazol for patients with clopidogrel resistance defined as platelet aggregation rate of adenosine diphosphate greater than 40% or loss-of-function allele CYP2C19.[14] Vascular risk factor management included blood pressure goal

at or below 140 mm Hg/90 mm Hg, target low-density lipoprotein cholesterol (<70 mg/dL), diabetes management (hemoglobin A1C <7.0%), and lifestyle modification, including smoking cessation and physical activity. Patients in the balloon angioplasty group were recommended to undergo balloon angioplasty with a dedicated intracranial balloon under general anesthesia (the Neuro RX [China Food and Drug Administration registration number: 20163773491] and Neuro LPS [National Medical Products Administration registration number: 20203030576] Intracranial Balloon Dilation Catheter [Sinomed Inc]) within 3 business days after randomization. Submaximal balloon angioplasty was recommended, which was defined as a balloon inflation diameter 50% to 70% of the proximal artery diameter. Details of the procedure and periprocedural management are in the study protocol.

Patients were followed by the on-site neurologist at baseline, the day of angiography, discharge, 30 ± 7 days, 90 ± 7 days, 6 months ± 14 days, 1 year ± 30 days, and up to 3 years (at 6-month intervals after 1 year). At each follow-up, the participants' medications and risk factor management were evaluated. As the primary outcome follow-up was completed, we report the 1-year results of the BASIS trial.

Outcomes

Primary Outcome

The primary outcome was any stroke or death within 30 days after enrollment or after balloon angioplasty of the qualifying lesion or any ischemic stroke in the qualifying artery territory or revascularization of the qualifying artery after 30 days through 12 months following enrollment. We defined ischemic stroke as a new focal, sudden-onset neurologic deficit from a cerebral infarct confirmed via computed tomography (CT) or magnetic resonance imaging (MRI). We defined symptomatic intracranial hemorrhage (sICH) as subarachnoid, parenchymal, or intraventricular hemorrhage identified on brain MRI or CT, which led to new neurologic symptoms (consciousness level change, headache, or focal symptoms) lasting more than 24 hours or a seizure. If sICH occurred within 30 days after enrollment or 30 days after balloon angioplasty, we considered it a primary outcome. Revascularization of the culprit artery was considered a primary outcome if it occurred from 30 days through 1 year after enrollment and fulfilled 1 of the following criteria: (1) acute revascularization: acute qualifying artery occlusion with neurological deficit requiring intravenous thrombolysis, intra-arterial thrombolysis, mechanical thrombectomy, or balloon/stent angioplasty; or (2) elective revascularization: neurologic symptom-driven revascularization, including balloon angioplasty or stent implantation if the participant fulfilled 1 of the following conditions: (i) ischemic stroke caused by the culprit artery stenosis: a new focal neurological deficit of sudden onset attributed to the territory of the culprit artery, confirmed as a recurrent stroke on brain CT or MRI; or (ii) hard TIA, which was defined as culprit artery stenosis that caused recurrent TIA in the territory of the index artery lasting longer than 10 minutes, or new disabling neurological symptom (limb weakness/numbness, dysarthria, diplopia, or dystaxia) compared with baseline.

Secondary Outcomes

Secondary outcomes were: (1) any stroke or all-cause death within 30 days after enrollment or after balloon angioplasty of the qualifying lesion during follow-up; (2) any stroke in the territory of the qualifying artery or all-cause death within 90 days and 1 year; (3) any stroke outside the territory of the qualifying artery within 90 days and 1 year; (4) 90-day and 1-year mRS scores (scores range from 0 to 6, with higher scores indicating greater disability); (5) revascularization of the qualifying artery within 1 year; (6) restenosis of the qualifying artery within 1 year (defined as stenosis >70% or increased by 30% on follow-up neurovascular imaging); (7) composite of stroke, myocardial infarction, or vascular death within 1 year; (8) quality of life assessment (EuroQol-5-Dimensions Scale questionnaire) at 1 year (scores range from 0 to 100, with 0 indicating the worst possible quality of life and 100, the best possible quality of life); (9) any stroke in the territory of the target artery or all-cause death within 24 and 36 months after enrollment; (10) any stroke outside of the territory of the target artery within 24 and 36 months after enrollment; (11) mRS at 24 months; (12) combined events such as stroke, myocardial infarction, and vascular death within 24 and 36 months after enrollment; and (13) neurological improvement assessed by mRS score at 36 months. Outcomes at 24 and 36 months are not reported.

Adverse Events and Procedural Complications

All adverse events were confirmed by the clinical-event adjudication committee (eFigure 1 in Supplement 1). Adverse events included nervous system disorders; sICH; asymptomatic intracranial hemorrhage; any intracranial hemorrhage; disabling stroke (defined as mRS score ≥2 at 1 year); vascular and lymphatic system disorder; metabolic and nutritional disease; infection; various surgical and medical operations; respiratory, thoracic, and mediastinal disorder; gastrointestinal disorder; injury and poisoning; benign, malignant, and unexplained tumors (including cystic and polypoid); and reproductive system and breast disease. Procedural complications included vasospasm, arterial dissection, pseudoaneurysm, arterial occlusion, arterial perforation, arterial rupture, hemorrhage, and thrombosis.

Sample Size Calculation

The sample size was initially planned at 802 patients (401 per group) under the assumption of a composite event rate of the primary outcome in the aggressive medical management group of 12% based on the 1-year results of the SAMMPRIS trial,[2] with a projected 50% relative risk reduction in the balloon angioplasty group and 1 interim analysis. According to more recent studies and the investigators' clinical practice in China, the composite event rate in the aggressive medical management group was 15%[3,15] and 7%[9,16] in the balloon angioplasty group. With the updated data of event rates and considering the difficulty in enrolling patients related to the COVID-19 pandemic and insufficient funding, on December 29, 2021, the data and safety monitoring board recommended to forgo the interim analysis and reestimate the sample size at 512 (256 per group) for a power of 80%, a 2-sided type I error rate of .05,

and a 10% attrition rate. The institutional review board approved the amendments and updated protocol on February 15, 2022. During the reestimation process of the sample size, the centralized blinded end point assessment results remained inaccessible to the investigators, ensuring that the reestimation did not rely on any interim data from the trial.

Statistical Analysis

The main analyses were performed in the primary analysis population, defined as all eligible patients who received the treatment, analyzing patients in the groups to which they were randomized. Per-protocol and as-treated analyses were conducted as sensitivity analyses. Differences between groups of the composite primary outcome during the 1-year follow-up were assessed using Kaplan-Meier plots and compared via log-rank test. The hazard ratio (HR) and its 95% CIs were calculated by a Cox proportional hazards model. Center-effect adjustment was not considered for the primary analysis. The proportional hazards assumption was affirmed by the Schoenfeld residual-based test (P = .12), but the survival curves of the 2 groups crossed at 30 days. Thus, we provided a post hoc landmark analysis over 30 days and presented 3 components of the composite primary outcome in addition to the main analysis. In the landmark analysis, the outcomes of the composite primary end point were delineated at the 30-day mark. All subgroup analyses in the forest plot were prespecified.[13] Participants were censored at their last follow-up, at 1 year, or at the time of withdrawal if a clinical event had not occurred. If there were multiple events, the time to the first event was adopted. Similar approaches were used for comparison of secondary outcomes. Shift analysis was planned of the mRS at 90 days and 12 months between the 2 groups, using ordinal logistic regression. Because the proportional odds assumption was not met, we switched to an assumption-free ordinal analysis approach. A generalized odds ratio (OR) was calculated via the Wilcoxon-Mann-Whitney test. Missing data were handled by censoring at the last follow-up. Apart from 2 patients who died prematurely, all participants completed the 1-year follow-up. When calculating the incidence difference of specific events, missing cases were assumed to have not experienced the event.

All statistical analyses were performed by 2-sided tests. A 2-sided P value of <.05 was considered statistically significant. A provision for correcting for multiplicity was not planned when conducting tests for secondary outcomes. Results are reported as point estimates with 95% CIs. The widths of the CIs were not adjusted for multiplicity and therefore should not be used to infer definitive treatment effects for secondary outcomes.

We performed post hoc analyses including (1) analyzing individual components of composite outcomes, (2) landmark analysis of the primary end point, (3) center-effect adjustment results for the primary end point, (4) incidence differences between 2 treatments of all end points, and (5) comparing the rate of a composite outcome of any stroke or all-cause death within 30 days or after balloon angioplasty of the qualifying lesion or any qualifying artery ischemic stroke beyond 30 days through 1 year between 2 treatments.

An independent data and safety monitoring committee, including an independent statistician and academic members, supervised the trial to ensure it was consistent with ethical standards and patient safety. The Department of Biostatistics at the Peking University Clinical Research Institute, Institute of Advanced Clinical Medicine, conducted the statistical analysis with SAS software, version 9.4 (SAS Institute).

Results

Patient Population

From November 2018 to April 2022, 1409 patients were assessed for eligibility and 512 underwent randomization: 256 were assigned to receive aggressive medical management and 256 were assigned to receive balloon angioplasty. Eleven patients were excluded due to consent withdrawal, leading to 501 patients for the primary analysis, with 252 in the aggressive medical management group and 249 in the balloon angioplasty group (**Figure 1**). Of the enrolled patients, 51.5% (258/501) were from the lead center.

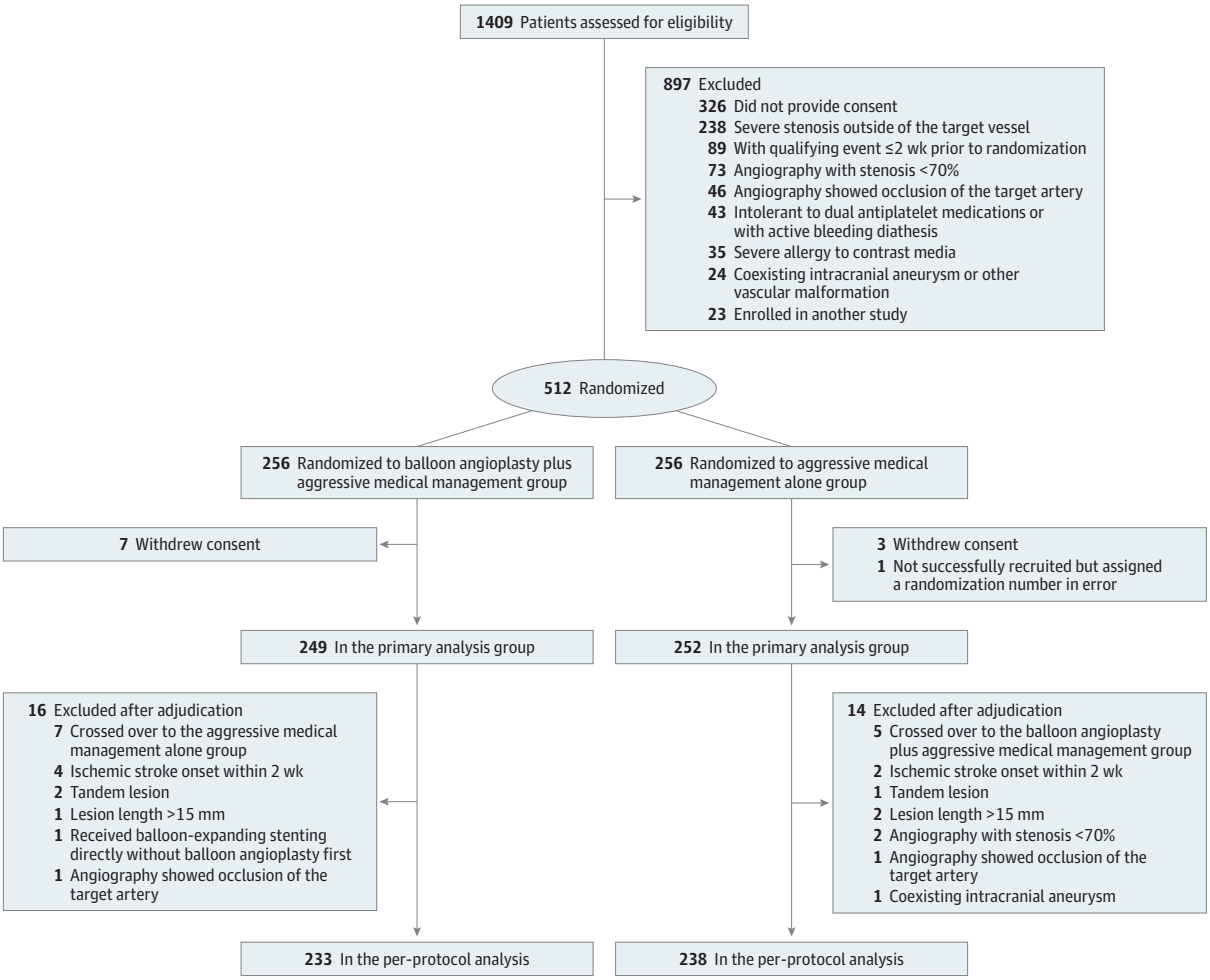
Baseline demographic and clinical characteristics were similar in the 2 groups (**Table 1**; eTable 1 in Supplement 1). The patients' median (IQR) age was 58.0 (52.0-65.0) years, 343 (69.1%) were male, and 494 (98.6%) were Han Chinese. The qualifying event was TIA in 78 patients (15.6%) and ischemic stroke in 423 patients (84.4%). Of the 423 patients with ischemic stroke, 135 (31.9%) had artery-to-artery embolism, 69 (16.3%) had isolated border zone infarct, 42 (9.9%) had perforator stroke, and 177 (41.8%) had mixed mechanism. Additionally, 100 patients with mixed mechanism had border zone infarct for a total of 169 patients (40.0%) with border zone infarct, of whom 40.9% were in the aggressive medical management group and 39.1% were in the balloon angioplasty group. The median (IQR) time from last TIA or ischemic stroke to randomization was 34 (21-53) days and 32 (22-51) days in the balloon angioplasty and aggressive medical management groups, respectively. The degree of stenosis was 60%-69% in 2 patients (0.4%), 70%-79% in 289 patients (57.6%), 80%-89% in 163 patients (32.5%), 90%-99% in 45 patients (9.0%), and 100% in 2 patients (0.4%) (Table 1). For patients in the balloon angioplasty group, the median (IQR) days from enrollment and randomization to the procedure was 2 (1-2) days. Vascular risk factor control was closely monitored, and the target metrics achieved at 3 months and 1 year are illustrated in eTables 2 and 12 in Supplement 1. The proportion of patients receiving antiplatelet and statin medicine at baseline, 3-month, and 1-year follow-up is presented in eTable 3 in Supplement 1.

Outcomes

Primary Outcome

In the primary outcome analysis, the balloon angioplasty group experienced a lower rate of stroke or death within 30 days after enrollment or after balloon angioplasty of the qualifying lesion or an ischemic stroke in the qualifying artery territory or revascularization of the qualifying artery after 30 days through 12 months following enrollment compared with the

Figure 1. Flowchart of Recruitment, Randomization, and Follow-Up in the BASIS Trial



aggressive medical management group (4.4% vs 13.5%; HR, 0.32 [95% CI, 0.16-0.63]; $P < .001$). In the balloon angioplasty group, 1 patient had acute revascularization due to acute qualifying artery occlusion and 2 patients underwent elective revascularization due to hard TIA. In the aggressive medical management group, 1 patient had acute revascularization due to acute qualifying artery occlusion, 10 had elective revascularization due to hard TIA, and 10 had elective revascularization due to ischemic stroke caused by the qualifying artery stenosis (eTable 5 in Supplement 1). The per-protocol and as-treated sensitivity analyses showed similar results as the primary analyses (eTables 8 and 9 in Supplement 1).

Subgroup analyses for prespecified baseline factors with rates of the primary outcome at 1 year are shown in **Figure 2**. Point estimates of subgroup analyses favored balloon angioplasty plus aggressive medical management.

Secondary Outcomes

The rate of any stroke or all-cause death within 30 days after enrollment was 3.2% and 1.6% in the balloon angioplasty and aggressive medical management groups, respectively (HR, 2.05 [95% CI, 0.62-6.81]; $P = .24$) (**Table 2**). The rate of any stroke in the territory of the qualifying artery or all-cause death within 1 year (3.2% vs 9.1%; HR, 0.35 [95% CI, 0.16-0.78]; $P = .01$), the rate of the qualifying artery revascularization within 1 year (1.6% vs 9.5%; HR, 0.16 [95% CI, 0.06-0.47]; $P < .001$), and the rate of combined events (stroke, myocardial infarction, and vascular death) within 1 year (4.0% vs 10.3%; HR, 0.38 [95% CI, 0.19-0.80]; $P = .01$) were all lower in the balloon angioplasty group than in the aggressive medical management group. Balloon angioplasty was associated with a shift in the distribution of the 90-day mRS score (generalized OR, 1.21 [95% CI, 1.03-1.38]; $P = .01$) and 1-year mRS score (generalized OR, 1.26 [95% CI, 1.06-1.45]; $P = .01$) toward better outcomes than aggressive medical management alone (Table 2). The restenosis rate of the qualifying artery within 1 year in the balloon angioplasty group was 15.7%, and 2.0% of patients had a TIA or stroke clearly related to restenosis (eTable 4 in Supplement 1).

Post Hoc Outcomes and Analyses

The post hoc analysis showed that the rate of any ischemic stroke in the qualifying artery territory beyond 30 days through 1 year following enrollment (0.4% vs 7.5%) and the

Table 1. Demographic and Clinical Characteristics of Patients at Baseline

Variable	Balloon angioplasty group (n = 249)	Aggressive medical management group (n = 252)
Age, median (IQR), y	58.0 (52.0-65.0)	58.0 (52.0-65.0)
Sex, No. (%)		
Male	172 (69.1)	171 (67.9)
Female	77 (30.1)	81 (32.1)
Medical history, No. (%)		
Hypertension	181 (72.7)	185 (73.4)
Hyperlipidemia	176 (70.7)	191 (75.8)
Diabetes	82 (32.9)	87 (34.5)
Received antiplatelet therapy before latest qualifying event, No. (%)	118 (47.4)	113 (44.8)
Received statin therapy before latest qualifying event, No. (%)	123 (49.4)	126 (50.0)
Current smoking, No. (%)	60 (24.1)	66 (26.2)
Qualifying event, No. (%)		
Transient ischemic attack	34 (13.7)	44 (17.5)
Ischemic stroke[a]	215 (86.4)	208 (82.5)
Artery-to-artery embolism	78 (36.3)	57 (27.4)
Isolated border zone infarct	37 (17.2)	32 (15.4)
Perforator stroke	18 (8.4)	24 (12)
Mixed mechanism	82 (38.1)	95 (45.7)
Qualifying artery, No. (%)		
Middle cerebral artery	143 (57.4)	154 (61.1)
Basilar artery	73 (29.3)	72 (28.6)
Internal carotid artery	21 (8.4)	8 (3.2)
Vertebral artery	12 (4.8)	17 (6.8)
mRS score 0-1 at admission, No. (%)[b]	227 (91.2)	231 (91.7)
NIHSS score at admission, median (IQR)[c]	0 (0-2)	0 (0-2)
NIHSS score at admission, No. (%)[c]		
0-1	186 (74.7)	187 (74.2)
2-4	51 (20.5)	51 (20.5)
5-10	12 (4.8)	14 (5.6)
Stenosis of symptomatic artery, No. (%)[d]		
60%-69%	0	2 (0.8)
70%-79%	140 (56.2)	149 (59.1)
80%-89%	83 (33.3)	80 (31.7)
90%-99%	25 (10.4)	20 (7.9)
100%	1 (0.4)	1 (0.4)
Time from last ischemic event to randomization, median (IQR), d	34.0 (21.0-53.0)	32.0 (22.0-51.0)
Transient ischemic attack	33.0 (21.0-56.0)	33.0 (19.0-47.0)
Ischemic stroke	34.0 (20.0-51.0)	32.0 (22.0-51.0)

Abbreviations: mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

[a] Artery-to-artery embolism: infarcts distal to the stenotic vessel in the territory of the relevant artery, usually multiple, scattered, and often associated with perfusion deficits throughout the territory of the stenotic vessel; isolated border zone infarct: border zone pattern in the presence of 1 or more lesions in the internal border zone region (corona radiata or centrum semiovale) and/or in the cortical border zone region (between middle cerebral artery and anterior cerebral artery or middle cerebral artery and posterior cerebral artery territories without other mechanisms); perforator stroke: in the presence of subcortical lesions in the distribution of perforating vessels that originate at the site of stenosis (perforator stroke with severe stenosis of supplying artery combined with hemodynamic compromise or poor collaterals was enrolled in the BASIS trial); and mixed mechanism: a combination of any of the above patterns.

[b] mRS scores range from 0-6, with higher scores indicating greater disability.

[c] Scores on the NIHSS, an ordinal scale to evaluate the severity of stroke, range from 0-42, with higher scores indicating greater neurologic deficit.

[d] The stenosis degree was assessed according to the Warfarin Aspirin Symptomatic Intracranial Disease method.

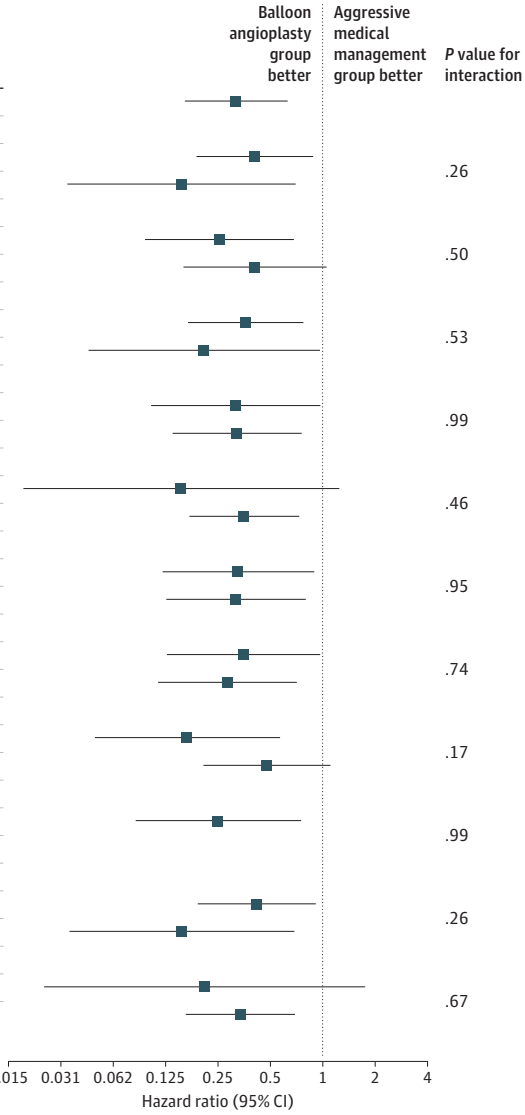
rate of the qualifying artery revascularization beyond 30 days through 1 year following enrollment (1.2% vs 8.3%) was lower in the balloon angioplasty group than in the aggressive medical management group (Table 2, **Figure 3**). Additionally, the post hoc analysis adjusting for center effect showed that the result was similar to the main analysis (HR, 0.32 [95% CI, 0.16-0.62]; *P* = .001) (eTable 6 in Supplement 1), and no interaction effect on the primary outcome between different centers and treatment options was found (*P* for interaction = .10) (eTable 7 in Supplement 1). Moreover, after removing revascularization from the composite outcome, the rate of any stroke or all-cause death within 30 days after enrollment or after balloon angioplasty of the qualifying lesion or any ischemic stroke from the qualifying artery beyond 30 days through 1 year following enrollment was lower in the balloon angioplasty group than the aggressive medical management group (3.6% vs 9.1%; HR, 0.39 [95% CI, 0.18-0.85]; *P* = .01) (eTable 10 in Supplement 1).

Procedural Complications and Adverse Events

The rates of sICH were 1.2% and 0.4% and of asymptomatic intracranial hemorrhage, 1.2% and 0% in the balloon angioplasty and aggressive medical management groups, respectively. Disabling stroke was lower in the balloon angioplasty group than the aggressive medical management group (2.4% vs 7.1%; *P* = .02) (eTable 11 in Supplement 1). Within 30 days,

Figure 2. Subgroup Analyses of the Primary Outcome

Subgroup	No./total No. (%)		Hazard ratio (95% CI)
	Balloon angioplasty group	Aggressive medical management group	
Overall	11/249 (4.4)	34/252 (13.5)	0.32 (0.16-0.63)
Age, y			
<65	9/176 (5.1)	23/187 (12.3)	0.41 (0.19-0.88)
≥65	2/73 (2.7)	11/65 (16.9)	0.16 (0.03-0.70)
Sex			
Male	5/172 (2.9)	19/171 (11.1)	0.26 (0.10-0.68)
Female	6/77 (7.8)	15/81 (18.5)	0.41 (0.16-1.05)
Hypertension			
Yes	9/181 (5.0)	25/185 (13.5)	0.36 (0.17-0.77)
No	2/68 (2.9)	9/67 (13.4)	0.21 (0.05-0.96)
Diabetes			
Yes	4/82 (4.9)	13/87 (14.9)	0.32 (0.10-0.97)
No	7/167 (4.2)	21/165 (12.7)	0.32 (0.14-0.76)
Smoking			
Yes	1/60 (1.7)	7/66 (10.6)	0.15 (0.02-1.24)
No	10/189 (5.3)	27/186 (14.5)	0.35 (0.17-0.73)
eGFR, mL/min/1.73 m^2			
<60	5/88 (5.7)	16/96 (16.7)	0.33 (0.12-0.89)
≥60	6/161 (3.7)	18/156 (11.5)	0.32 (0.13-0.80)
Target vessel stenosis degree, %			
<80	5/140 (3.6)	15/151 (9.9)	0.35 (0.13-0.97)
≥80	6/109 (5.5)	19/101 (18.8)	0.28 (0.11-0.71)
BMI			
<25	3/110 (2.7)	17/110 (15.5)	0.17 (0.05-0.57)
≥25	8/139 (5.8)	17/142 (12.0)	0.48 (0.21-1.11)
Hypoperfusion[a]			
Yes	4/103 (3.9)	16/106 (15.1)	0.25 (0.08-0.75)
No	1/19 (5.3)	0/21	NA[b]
Lesion location			
Anterior circulation	9/164 (5.5)	21/162 (13.0)	0.42 (0.19-0.91)
Posterior circulation	2/85 (2.4)	13/90 (14.4)	0.16 (0.04-0.69)
Mechanism			
TIA	1/34 (2.9)	6/44 (13.6)	0.21 (0.03-1.75)
Ischemic stroke	10/215 (4.7)	28/208 (13.5)	0.34 (0.16-0.69)



BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); eGFR, estimated glomerular filtration rate; NA, not applicable; TIA, transient ischemic attack.

[a]Hypoperfusion was assessed by computed tomography perfusion.

[b]No events were observed in the aggressive medical management group, so the hazard ratio estimation was NA.

Stage 1: normal perfusion period: time to peak, mean transit time (MTT), relative cerebral blood flow, and relative cerebral blood volume (rCBV) remain unchanged compared with the contralateral side. Stage 2: compensation period: time to peak is prolonged, whereas MTT, relative cerebral blood flow, and rCBV are normal or slightly increased compared with the contralateral side. Stage 3: low perfusion: time to peak and MTT are prolonged, with decreased relative cerebral blood flow and basically normal or slightly decreased rCBV. Stage 4: time to peak and MTT are prolonged, with decreased relative cerebral blood flow and rCBV. Stages 3 and 4 are considered the decompensated stages, indicating hypoperfusion.

all-cause death occurred in 1 patient in the balloon angioplasty group due to sICH. Beyond 30 days to 1 year, 1 patient experienced all-cause death due to a motor vehicle crash in the aggressive medical management group (Table 2). Detailed adverse events are presented in eTable 11 in Supplement 1.

The rate of vasospasm was 1.2%; arterial dissection, 14.5%; pseudoaneurysm, 0.0%; arterial occlusion, 0.4%; arterial perforation, 0.4%; arterial rupture, 0.0%; hemorrhage, 0.4%; and thrombosis, 1.7% in the balloon angioplasty group (eTable 4 in Supplement 1).

Discussion

This randomized clinical trial demonstrated that in patients with a recent TIA within 90 days or ischemic stroke between 14 and 90 days prior attributed to a 70% to 99% atherosclerotic stenosis of a major intracranial artery, balloon angioplasty plus aggressive medical management resulted in a lower rate of a composite outcome of any stroke or all-cause death within 30 days after enrollment or after balloon angioplasty of the qualifying

Table 2. Study Outcomes

Study outcomes	Balloon angioplasty group (n = 249)	Aggressive medical management group (n = 252)	Incidence difference, % (95% CI)[a]	HR ratio (95% CI)	*P* value
Primary outcome, No. (%)[b]					
Any stroke or all-cause death within 30 d after enrollment or any ischemic stroke or revascularization of the qualifying artery beyond 30 d-1 y after enrollment[c]	11 (4.4)	34 (13.5)	−9.1 (−14.0 to −4.1)	0.32 (0.16 to 0.63)	<.001
Any stroke or all-cause death within 30 d after enrollment[d]	8 (3.2)	4 (1.6)	1.6 (−1.1 to 4.3)	2.05 (0.62 to 6.81)	
Any ischemic stroke of the qualifying artery beyond 30 d-1 y after enrollment[a]	1 (0.4)	19 (7.5)	−7.1 (−10.5 to −3.8)	0.05 (0.01 to 0.39)	
Revascularization of the qualifying artery beyond 30 d-1 y after enrollment[c,a]	3 (1.2)	21 (8.3)	−7.1 (−10.8 to −3.5)	0.14 (0.04 to 0.47)	
Secondary outcomes					
Any stroke or all-cause death within 30 d after enrollment, No. (%)[d]	8 (3.2)	4 (1.6)	1.6 (−1.1 to 4.3)	2.05 (0.62 to 6.81)	.24
Any stroke in the territory of the qualifying artery or all-cause death within 90 d after enrollment, No. (%)	7 (2.8)	10 (4.0)	−1.2 (−4.3 to 2.0)	0.72 (0.27 to 1.88)	.49
Any stroke outside the territory of the qualifying artery within 90 d after enrollment, No. (%)	2 (0.8)	0	0.8 (−0.3 to 1.9)	NA	.15
mRS score at 90 d, median (IQR)[e]	0 (0 to 0)	0 (0 to 1)	NA	1.21 (1.03 to 1.38)[f]	.01
Any stroke in the territory of the qualifying artery or all-cause death within 1 y after enrollment, No. (%)[g]	8 (3.2)	23 (9.1)	−5.9 (−10.1 to −1.7)	0.35 (0.16 to 0.78)	.01
Revascularization of the qualifying artery within 1 y after enrollment, No. (%)[c]	4 (1.6)	24 (9.5)	−7.9 (−11.9 to −4.0)	0.16 (0.06 to 0.47)	<.001
Any stroke outside the territory of the qualifying artery within 1 y after enrollment, No. (%)	3 (1.2)	4 (1.6)	−0.4 (−2.4 to −1.7)	0.76 (0.17 to 3.40)	.72
mRS score at 1 y, median (IQR)[e]	0 (0 to 0)	0 (0 to 1)	NA	1.26 (1.06 to 1.45)[f]	.01
Combined vascular events within 1 y, No. (%)	10 (4.0)	26 (10.3)	−6.3 (−10.8 to −1.8)	0.38 (0.19 to 0.80)	.01
Stroke	9 (3.6)	26 (10.3)	−6.7 (−11.1 to −2.3)		
Myocardial infarction	0	0	NA		
Vascular death	1 (0.4)	0	0.4 (−0.4 to 1.2)		
Quality of life assessment (EuroQol-5-Dimensions scale questionnaire) at 1 y, median (IQR)	100 (100 to 100)	100 (100 to 100)			.40

Abbreviations: HR, hazard ratio; mRS, modified Rankin Scale; NA, not applicable.

[a] Post hoc analysis.

[b] *P* value of log-rank test was <.001, and the primary outcome was a time-to-event composite outcome. When there were multiple events, only the first event was counted. For reporting individual components of the primary outcome, events were counted separately. The event number of the individual components does not add up to the total number of composite primary outcome events because 1 patient in the balloon angioplasty group and 10 patients in the aggressive medical management group had multiple events.

[c] Fulfills 1 of the following criteria to be considered for revascularization of the qualifying artery: (1) acute revascularization: acute qualifying artery occlusion accompanied by neurological deficit requiring intravenous thrombolysis, intra-arterial thrombolysis, mechanical thrombectomy, balloon/stent angioplasty, or intracranial-extracranial bypass; or (2) elective revascularization: neurologic symptom–driven revascularization, including balloon angioplasty, stent implantation, or intracranial-extracranial bypass.

[d] The proportion of any stroke within 30 days after enrollment was 2.8% (7/249) and 1.6% (4/252) in the balloon angioplasty and aggressive medical management groups, respectively, and the proportion of death within 30 days after enrollment was 0.4% (1/249) and 0% in the balloon angioplasty and aggressive medical management groups, respectively.

[e] mRS scores range from 0 to 6, with higher scores indicating greater disability.

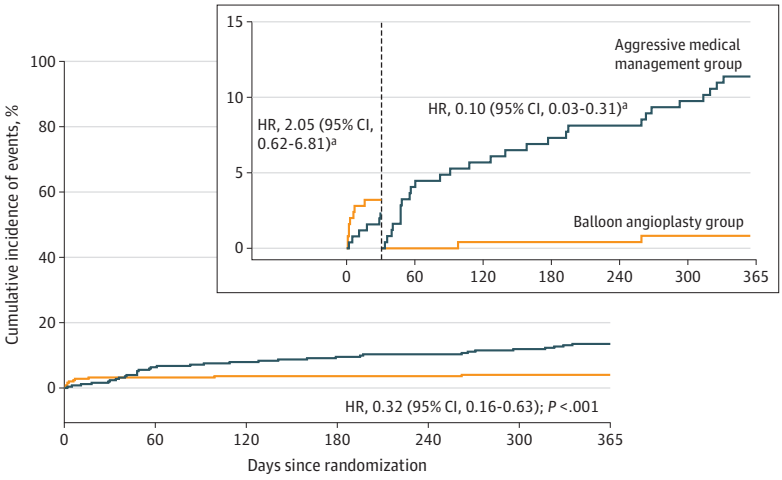
[f] mRS score at 90 days and 1 year stated as generalized odds ratio, with values >1 indicating that the balloon angioplasty group had a more favorable mRS shift toward better outcomes than the aggressive medical management group.

[g] Death within 1 year after enrollment occurred in 0.4% (1/249) and 0.4% (1/252) in the balloon angioplasty and aggressive medical management groups, respectively.

lesion or any ischemic stroke or revascularization of the qualifying artery beyond 30 days through 1 year after enrollment compared with aggressive medical management.

Unlike previous RCTs,[2-4] the BASIS trial is the first study to our knowledge to demonstrate that endovascular treatment is superior to aggressive medical management for secondary prevention of stroke in patients with sICAS. There may be several reasons for this. First, the study recommended submaximal balloon angioplasty with a dedicated intracranial balloon without stent implantation, with an easy navigation and technique, and a short procedure duration compared with balloon-expanding stenting or self-expanding stenting. Balloon angioplasty may reduce the risk of a "snowplowing effect" (balloon angioplasty or stenting mechanically displacing the atherosclerotic plaque into the ostia of side-branches, thus occluding side-branches), decreasing the perforator event rate.[8] Second, although balloon angioplasty may not achieve complete revascularization as easily as self-expanding stenting or balloon-expanding stenting, it can increase antegrade flow according to the Poiseuille law.[10,17,18] However, the main shortcoming of balloon angioplasty is arterial dissection, which was present in 14.5% of patients in

Figure 3. Cumulative Probability of the Primary Outcome According to Treatment Assignment



No. of patients at risk

Balloon angioplasty group	249	241	240	240	240	239	238
Aggressive medical management group	252	236	232	228	226	222	218

HR indicates hazard ratio.

[a]The survival curves of the 2 groups crossed at 30 days (dashed line), so a post hoc landmark analysis was provided over 30 days in addition to the main analysis.

the BASIS trial, and is comparable to prior literature.[9] In the BASIS trial, rescue stenting was allowed for arterial dissection with impaired distal blood flow (modified treatment in cerebral infarction, <2b) and 71.4% of patients with dissection underwent rescue stenting.

Third, there were differences in the enrolled populations of the SAMPPRIS, VISSIT, CASSISS, and BASIS trials. The median (IQR) interval between symptom onset and patient enrollment with ischemic stroke in the BASIS trial was beyond 14 (34 [20-51]) days, which was longer than that in the SAMPPRIS (7 [4-16] days) and VISSIT (9 [0-42] days) trials and shorter than that in the CASSISS trial (38 [27-75] days).[2-4] Endovascular treatment administered too early could lead to a higher risk of periprocedural complications. However, delay in endovascular treatment may miss a therapeutic window.[2-4,6,10] Additionally, the proportion of ischemic stroke of the qualifying event in the experimental group of the BASIS trial was 86%, which was higher than that in the SAMMPRIS (63%), VISSIT (62%), and CASSISS (51%) trials. However, the proportion of border zone ischemic infarct in the experimental group was comparable between the BASIS and SAMMPRIS trials (39% vs 37%) and higher than that in the CASSISS trial (20%), which indicated that the CASSISS trial enrolled patients with a lower risk of recurrent stroke. Previous studies reported that a border zone infarct was associated with a high risk of recurrent stroke.[5,19-21] However, the proportion with border zone infarct among those with ischemic stroke in the aggressive medical management group was higher in the BASIS trial than the CASSISS trial (40.9% vs 21.0%), and the 1-year event rate of the aggressive medical management group was comparable between the BASIS and CASSISS trials (9.1% vs 7.2%). The low 1-year event rate suggests that patients in BASIS were receiving optimal medical therapy inspired by both the SAMMPRIS[2] and CHANCE-2 trial[14] results, and 47.6% (10/21) patients in the aggressive medical management group underwent revascularization due to hard TIA, which may decrease the risk of recurrent stroke.

Unlike prior RCTs, BASIS incorporated qualifying artery revascularization as one part of the composite primary outcome, which has been widely used as a clinical end point in coronary intervention trials[22] to assess the efficacy of stroke prevention of balloon angioplasty or aggressive medical management for sICAS. If the patient continued to experience stroke symptoms or infarct referrable to the territory in which they had sICAS, that indicated the patient may need to undergo revascularization to prevent ischemic progress, which could be another clinically relevant end point. Of note, after removal of the revascularization events from the composite primary outcome, the rate of any stroke or all-cause death within 30 days or after balloon angioplasty of the qualifying lesion or any qualifying artery ischemic stroke beyond 30 days through 1 year remained higher in the aggressive medical management group than in the balloon angioplasty group.

Another notable finding of this trial was that the risk of periprocedural composite primary outcome events was initially higher in the balloon angioplasty group than the aggressive medical management group, but was not statistically significant. The event rates later crossed at the 30-day point of the Kaplan-Meier curves (Figure 3), indicating that balloon angioplasty might increase the short-term risk of periprocedural complications. The numerically higher rates of sICH and any ICH in the balloon angioplasty group compared with the aggressive medical management group also confirmed this finding. However, the study found that balloon angioplasty was superior to aggressive medical management at 1-year follow-up, which may be explained by the benefit of balloon angioplasty related to hemodynamic improvement, thereby outweighing the risk of periprocedural complications. On the other hand, the majority of patients in the aggressive medical management group did not have a recurrent ischemic event,

nor require revascularization at 1 year (more than 85% of patients were event-free), which may also be perceived as a successful treatment for patients with sICAS.

Limitations

This trial has several limitations. First, the long-term effect of balloon angioplasty revascularization and restenosis of the qualifying artery remains unclear and may need longer-term follow-up. Second, more than half of the enrolled patients were from the lead center, which may limit the generalization of findings. However, a post hoc analysis adjusting for center effect showed that the result was similar to the main analysis (eTable 6 in Supplement 1). Another post hoc analysis was performed to explore the interaction effect on the primary outcome between different centers and treatment options, and no interaction effect was found (eTable 7 in Supplement 1). Third, the study did not assess drug-coated balloons or drug-eluting stents for sICAS. Fourth, as the study involved the Chinese population, findings may not be generalizable to other ethnic populations.

Conclusions

In patients with sICAS, balloon angioplasty plus aggressive medical management, compared with aggressive medical management alone, statistically significantly lowered the risk of a composite outcome of any stroke or death within 30 days or an ischemic stroke or revascularization of the qualifying artery after 30 days through 12 months. The findings suggest that balloon angioplasty plus aggressive medical management may be an effective treatment for sICAS, although the risk of stroke or death within 30 days of balloon angioplasty should be considered in clinical practice.

ARTICLE INFORMATION

Accepted for Publication: June 11, 2024.

Published Online: September 5, 2024. doi:10.1001/jama.2024.12829

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Conflict of Interest Disclosures: Dr Nguyen reported serving on the advisory boards of Brainomix and Aruna Bio and serving as the Associate Editor of *Stroke* for the American Stroke Association outside the submitted work. Dr Liebeskind reported serving in the core labs of Medtronic Imaging and Stryker Imaging outside the submitted work. Dr Yilong Wang reported receiving grants from Sanofi and Beijing Jialin Pharmaceutical Company for the INSPIRES trial during the conduct of the study. No other disclosures were reported.

Funding/Support: The BASIS trial was funded by Sino Medical Sciences Technology Inc; the National Natural Science Foundation of China (No. 82425101); Beijing Municipal Science & Technology Commission (No. Z231100004823036); Capital's Funds for Health Improvement and Research (2022-2-2045); National Key R&D Program of China (2022YFF1501500, 2022YFF1501501, 2022YFF1501502, 2022YFF1501503, 2022YFF1501504, 2022YFF1501505); Youth Beijing Scholar Program (No. 010); Beijing Laboratory of Oral Health (PXM2021_014226_000041); Beijing Talent Project - Class A: Innovation and Development (No. 2018A12); "National Ten-Thousand Talent Plan" - Leadership of Scientific and Technological Innovation; Beijing Outstanding Young Scientist Program (No. BJJWZYJH01201910025030).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: A full list of the BASIS Investigators appears in Supplement 3.

Data Sharing Statement: See Supplement 4.

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