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Review

Borderzone Infarcts and Recurrent Cerebrovascular Events in Symptomatic Intracranial Arterial Stenosis: A Systematic Review and Meta-Analysis

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Background and Purpose Intracranial arterial stenosis (ICAS)-related stroke occurs due to three primary mechanisms with distinct infarct patterns: (1) borderzone infarcts (BZI) due to impaired distal perfusion, (2) territorial infarcts due to distal plaque/thrombus embolization, and (3) plaque progression occluding perforators. The objective of the systematic review is to determine whether BZI secondary to ICAS is associated with a higher risk of recurrent stroke or neurological deterioration.

Methods As part of this registered systematic review (CRD42021265230), a comprehensive search was performed to identify relevant papers and conference abstracts (with ≥20 patients) reporting initial infarct patterns and recurrence rates in patients with symptomatic ICAS. Subgroup analyses were performed for studies including any BZI versus isolated BZI and those excluding posterior circulation stroke. The study outcome included neurological deterioration or recurrent stroke during follow-up. For all outcome events, corresponding risk ratios (RRs) and 95% confidence intervals (95% CI) were calculated.

Results A literature search yielded 4,478 records with 32 selected during the title/abstract triage for full text; 11 met inclusion criteria and 8 studies were included in the analysis (n=1,219 patients; 341 with BZI). The meta-analysis demonstrated that the RR of outcome in the BZI group compared to the no BZI group was 2.10 (95% CI 1.52–2.90). Limiting the analysis to studies including any BZI,

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the RR was 2.10 (95% CI 1.38–3.18). For isolated BZI, RR was 2.59 (95% CI 1.24–5.41). RR was 2.96 (95% CI 1.71–5.12) for studies only including anterior circulation stroke patients.
Conclusion This systematic review and meta-analysis suggests that the presence of BZI secondary to ICAS may be an imaging biomarker that predicts neurological deterioration and/or stroke recurrence.

Keywords Borderzone Infarct; Stroke; Recurrence; Intracranial arterial diseases; Intracranial atherosclerosis

Introduction

Intracranial atherosclerotic disease (ICAS) is a common cause of stroke worldwide,[1] accounting for up to 50% of ischemic strokes in China[2] and nearly 10% of ischemic strokes in the United States[3] and Europe.[4] It is associated with a high risk of recurrence in medically treated patients, particularly early after the initial event.[5-9] ICAS causes ischemic stroke either by distal embolization, perforator disease, and/or by impaired blood flow/perfusion across a highly stenotic artery.[1,10-14] Studies have shown that in medically treated patients with symptomatic ICAS, certain biomarkers of impaired distal blood flow or perfusion are associated with increased stroke recurrence.[15-19]

Borderzone infarct (BZI) pattern indirectly implies blood flow impairment[20,21] and perfusion delay[19,22] distal to the arterial stenosis. Several studies have shown that BZI is associated with an increased risk of recurrence in patients with symptomatic ICAS related to possible hemodynamic impairment.[18,23-26] Such studies, however, were small, observational, underpowered, mostly single-center based and were subject to confounding bias.

We performed a systematic review and meta-analysis to evaluate the hypothesis that BZI is associated with a higher risk of recurrent ischemic stroke or neurological deterioration compared to other ICAS-related infarct patterns such a perforator disease or artery-to-artery embolism.

Methods

Study design

This is a systematic review and meta-analysis registered in International Prospective Register of Systemic Reviews (PROSPERO, CRD42021265230) and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 (Supplementary Table 1). As this study used published de-identified data, ethics approval was waived by the Lifespan Institutional Review Board. Data from this study is available upon request to the corresponding author.

Inclusion and exclusion criteria

We included retrospective or prospective observational studies (manuscripts or conference abstracts) of patients 18 years or older with an ischemic stroke in the setting of ICAS. Studies with fewer than 20 patients and those with full texts in languages other than English were excluded during the initial screening. Duplicate studies and those not reporting the association between infarct pattern and our study outcome were excluded during the second stage of study selection.

Primary predictor

The primary predictor was the presence of BZI, either in isolation (isolated BZI) or along with other infarct patterns.

Outcome

The outcome was recurrent cerebrovascular events during follow-up defined as new or worsening neurological symptoms caused by: (1) new distinct infarct (recurrent ischemic stroke) or (2) extension of the existing infarct (neurological deterioration). This outcome does not include transient ischemic attack.[27]

Search criteria

A comprehensive search was performed by a health science librarian (RM) using combinations of vocabulary, title, and abstract keywords in MEDLINE (via PubMed), Scopus (Elsevier), Cochrane Library, and Web of Science Core Collection (Clarivate Analytics). The search was performed from the conception of the above databases until October 18, 2021, with an updated search on March 15, 2022. An additional targeted search of conference abstracts for the International Stroke Conference, European Stroke Organization Conference, and the American Academy of Neurology was performed using the Web of Science's conference search field on June 13, 2022. The search was conducted using the name of the conference in combination with the term "intracranial stenosis" in all fields. The complete search strategy for all databases is presented in Supplementary Table 2.

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Screening

The search results were then imported into Abstrackr (http://abstrackr.cebm.brown.edu),[28] which each study screened for eligibility independently by two of seven reviewers (SY, AS, BM, SKB, CO, DC, and FF). Disagreements were resolved by a third reviewer. Potentially eligible abstracts were then screened in detail using the full text if available, and for excluded abstracts, the reasons for exclusion were recorded.

Data extraction

Extracted data included details of each study: age, sex, follow-up duration, BZI definition, outcome definition, ischemic stroke location (anterior circulation vs. posterior circulation), and outcome rates between the two groups (BZI vs. non-BZI). Data was extracted independently by two of four investigators (EDG, LS, AD, and SD), with disagreements resolved by a third investigator followed by consensus between the three investigators. Due to missing raw data in one study,[25] the corresponding author was contacted and provided raw data for inclusion in the data synthesis. In addition, further analysis of data from one study[29] was done by authors (SY and AK).

Risk of bias assessment

Risk of bias was assessed (by MA and LP) for all studies (all observational) using the Risk of Bias in Nonrandomized Studies (ROBINS-I) tool.[30] The ROBINS-I tool assesses bias based on confounding, participant selection, classification of intervention, deviations from intervention, missing data, outcome measurement, and selection of the reported results.

Publication bias assessment

Publication bias was assessed in analyses including at least 10 studies[31] using both the Egger's test[32] and inspection of the funnel plot.

Data synthesis

We summarized the results both narratively and quantitatively when possible. We calculated risk ratios as the data allowed. When at least two studies were sufficiently similar, a pairwise meta-analysis was performed using a random effects model. The appropriateness of the meta-analysis was determined based on clinical/methodological (characteristics of the studies and definitions of predictors/outcomes) as well as statistical heterogeneity using I^2 values using the Cochrane Handbook[33] (0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; and 75% to 100%: considerable heterogeneity). We conducted subgroup analyses stratified based on (1) definition of BZI (any BZI vs. isolated BZI), (2) location of ICAS (anterior circulation vs. anterior and posterior circulation), (3) definition of outcome (neurological deterioration, recurrent ischemic stroke, or both), and (4) follow-up duration (≤90 days vs. >90 days). These analyses were prespecified in our meta-analysis protocol.

Results

Search and screening results

Among the 4,478 records generated by the initial search, 32 abstracts were selected and after detailed review, 10 met the inclusion criteria and an additional conference abstract was selected yielding 11 studies. Reasons for exclusion included no information on BZI (12 records), no information on association between BZI and study outcome (5 records), no information on study outcome (1 record), and duplicate records (4 records) (Figure 1).

Risk of bias assessment

The risk of bias assessment is shown in Figure 2. All retrospective studies had at least moderate bias in most of the seven domains, the prospective study and those with retrospective analysis of prospective studies had low to moderate bias in most domains.

Risk of publication bias assessment

Since all analyses included <10 studies, publication bias using Egger's test was not performed.[31]

Characteristics of studies and results of systematic review

The characteristics of included studies are shown in Table 1.

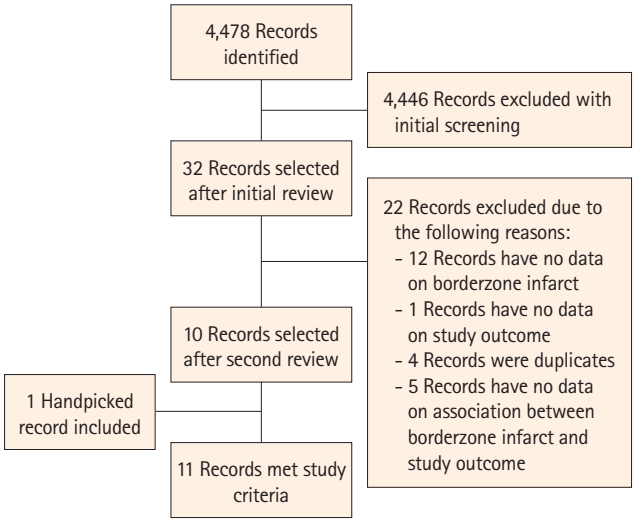

Figure 1. Study selection flow chart.

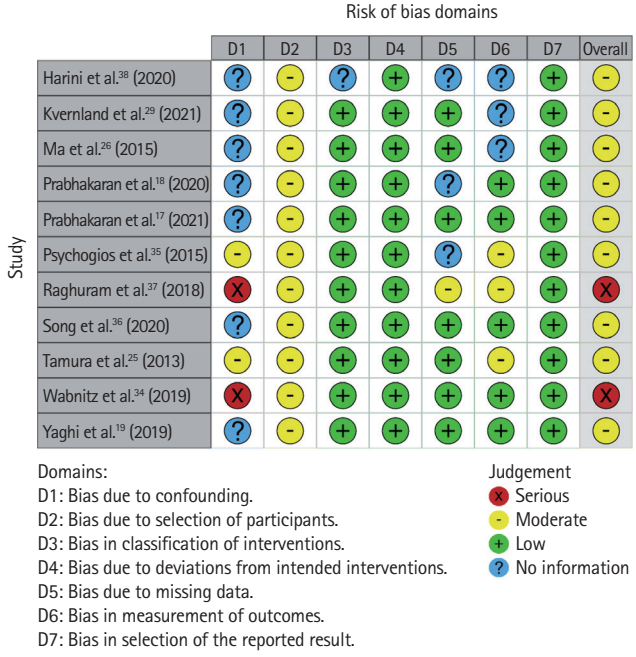

Figure 2. Risk of bias assessment using the Risk of Bias in Nonrandomized Studies (ROBINS-I) tool.

Among the 11 studies included, 1 was prospective,[17] 3 were retrospective analyses of prospectively collected data,[18,26,34] and 7 were retrospective studies.[19,25,29,35-38] The primary outcome was early neruological deteroriation in 2 studies,[25,26] and it was one of the few primary outcomes reported in 2 other studies.[19,29] The definition of BZI was any infarct involving the borderzone area in 5 studies[17-19,25,29] or infarct(s) isolated to the borderzone territory in 4 studies,[34,35,37,38] and unclear in 2 studies.[26,36] The outcome was captured in-hospital in 2 studies,[25,26] within 90 days from index event in 5 studies,[17-19,29,38] and beyond 90 days in 4 studies.[34-37] All studies except 1 study,[38] demonstarted an association between BZI and: (1) recurrent stroke,[18,19,29,34-37] (2) recurrent infarct,[17] or (3) neurological deterioration.[25,26]

Association between borderzone infarct and recurrent cerebrovascular events

Recurrent cerebrovascular events were assessed in 8 studies[18,19,25,26,29,34,35,37] and 3 studies were not included in the data synthesis (1 study[17] due to outcome being recurrent infarct and 2 studies[36,38] due to not providing raw data for event rates across the two groups). The 8 studies included a total of 1,219 patients with 341 BZI. The weighted proportion of patients with BZI was 28.0% (25.5%–30.6%). When compared to non-BZI, BZI was associated with a higher risk of recurrent cerebrovascular events (RR 2.10, 95% CI 1.52–2.90, *P* for Cochran Q: <0.01, I^2=38.68%) (Figure 3A).

Subgroup analyses by definition of borderzone infarct

In a subgroup analysis limited to studies assessing any BZI as the predictor (n=325 patients, 4 studies),[18,19,25,29] there was an association between any BZI and recurrent cerebrovascular events (RR 2.10, 95% CI 1.38–3.18, *P* for Cochran Q: <0.01, I^2=0%) (Figure 3B). Furthermore, when the analysis was limited to studies assessing isolated BZI as the predictor (n=679 patients, 4 studies),[25,34,35,37] the association between BZI and recurrent cerebrovascular events was statistically significant (RR 2.59, 95% CI 1.24–5.41, *P* for Cochran Q: 0.02) but there was substantial statistical heterogeneity (I^2=66.19%) across included studies (Figure 3C).

Subgroup analyses by outcome definition and timing

In a subgroup analysis limited to studies whose outcome was defined as recurrent ischemic stroke during follow-up (n=854 patients, 4 studies),[18,34,35,37] we found an association between BZI and recurrent ischemic stroke (RR 2.03, 95% CI 1.19–3.47, *P* for Cochran Q: 0.01, I^2=60.95%) (Figure 4A). Furthermore, in a subgroup analysis limiting studies to those where the outcome encompassed neurological detrioration[19,29] or was limited to in-hospital neurological deterioration outcome[25,26] (n=365 patients, 4 studies), there was an association between BZI and recurrent ischemic stroke (RR 2.27, 95% CI 1.52–3.38, *P* for Cochran Q: <0.01, I^2=8.95%) (Figure 4B). The association between BZI and recurrent cerebrovascular events was present in studies assessing in-hospital outcomes (n=289 patients, 2 studies)[25,26] (RR 2.44, 95% CI 1.21–4.91, *P* for Cochran Q: 0.01, I^2=48.68%) (Figure 4C) and short term recurrent cerebrovascular events (within 90 days) (n=288 patients, 3 studies[18,19,29] (RR 2.10, 95% CI 1.38–3.18, *P* for Cochran Q: <0.01, I^2=0%) (Figure 4D). There was no association between BZI and long-term outcome (>90 days)[34,35] (n=603 patients, 2 studies) (RR 1.55, 95% CI 0.79–3.04, *P* for Cochran Q: 0.20, I^2=47.47%) (Figure 4E).

Subgroup analysis limiting to studies including anterior circulation stroke

In a subgroup analysis limited to studies including only anterior circulation stroke (n=214 patients, 4 studies),[19,25,29,34] there was an association between BZI and recurrent ischemic stroke (RR 2.96, 95% CI 1.71–5.12, *P* for Cochran Q: <0.01, I^2=0%) (Figure 3D).

Sensitivity analysis

Sensitivity analysis stratifying by continent of published study yielded similar findings (Supplementary Figure 1).

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Discussion

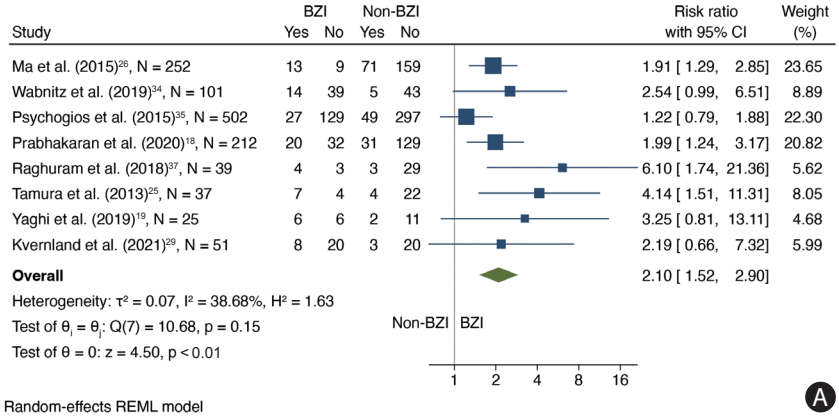
Summary of findings

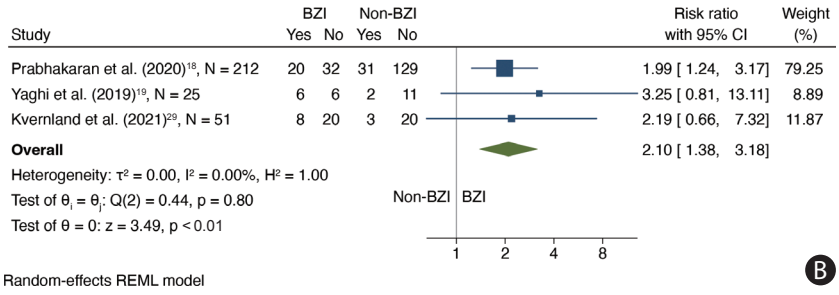
This systematic review and meta-analysis suggests that BZI may be associated with an increased risk of recurrent cerebrovascular events compared with other infarct patterns. The association seemed to be more pronounced in studies assessing early as opposed to long-term recurrent cerebrovascular events. Further-

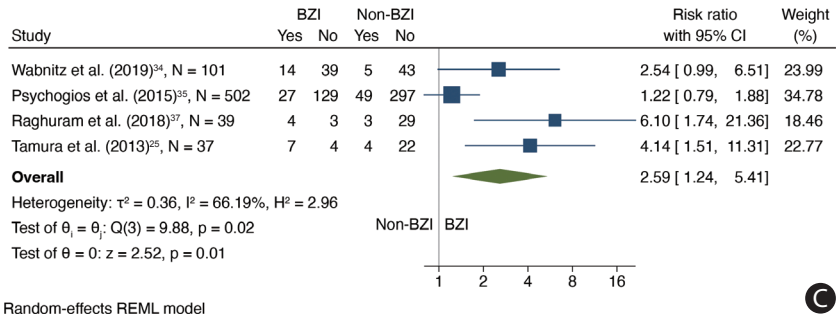
Table 1. Characteristics of 11 studies included

Study	Country	Sample size	Age, sex, follow up	Outcome	Association between BZI & outcome
Ma et al. 2015[26]	China	252	Mean age 65 y 63% men Median follow-up: 16 days	BZI definition: N/A Outcome: in-hospital deterioration	Yes
Wabnitz et al. 2019[34]	USA	101 (anterior circulation only)	N/A Median follow-up: 32 months	BZI definition: cortical borderzone occurred between ACA/MCA or MCA/PCA; internal borderzone infarct when between lenticulostriate arteries and superficial perforators Outcome: recurrent ischemic stroke in affected territory	Yes
Psychogios et al. 2015[35]	Greece	502	Mean age 66 y 79% men Mean follow-up: 56 months	BZI definition: involving cortical or internal borderzone areas Outcome: recurrent ischemic stroke within 10 years	Yes
Prabhakaran et al. 2020[18]	USA	212	Mean age 68 y % men N/A Follow-up: 3 months	BZI definition: any infarct involving the borderzone area Outcome: recurrent ischemic stroke at 90 days	Yes
Prabhakaran et al. 2021[17]	USA	89 (59 anterior circulation)	Mean age 64 y 61% men Follow-up: 6–8 weeks	BZI definition: lesions in the corona radiata or centrum semiovale adhering to the internal borderzone and in the cortical borderzone regions between the middle and anterior or middle and posterior cerebral arteries Outcome: recurrent infarct on 6–8 week MRI	Yes
Song et al. 2020[36]	China	60	Mean age 58 y 72% men Median follow-up: 12 months	BZI definition: infarct involving internal borderzone (corona radiata or centrum semiovale) and cortical borderzone (ACA/MCA or MCA/PCA) Outcome: relevant vessel recurrent stroke within 12 months	Yes
Raghuram et al. 2018[37]	USA	39 (anterior circulation only)	Mean age 62 y 66% men Follow-up: N/A	BZI definition: N/A Outcome: recurrent stroke during follow-up	Yes
Harini et al. 2020[38]	India	178	Mean age 61 y % men N/A Follow-up: 3 months	BZI definition: N/A Outcome: recurrent stroke	No
Tamura et al. 2013[25]	Japan	37*	Mean age 71 y 66% men Follow-up: 7 days	BZI definition: cortical borderzone occurred between ACA/MCA or MCA/PCA; internal borderzone infarct when between lenticulostriate arteries and superficial perforators Outcome: neurological deterioration within 7 days	Yes
Yaghi et al. 2019[19]	USA	25 (anterior circulation only)	Mean age 65 y 48% men Follow-up: 90 days	BZI definition: infarct involving internal borderzone (corona radiata or centrum semiovale) and cortical borderzone (ACA/MCA or MCA/PCA) Outcome: recurrent cerebrovascular events within 90 days	Yes
Kvernland et al. 2021[29]	USA	51 (anterior circulation)	Mean age 70 y 56% men Follow-up: 90 days	BZI definition: any infarct affecting the borderzone (internal or cortical) territory Outcome: recurrent cerebrovascular events within 90 days	Yes

BZI, borderzone infarct; y, years; N/A, not available; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; MRI, magnetic resonance imaging.
*Tamura et al.[25] included 44 patients, of whom 7 were excluded during the analysis as communication with authors revealed that 7 patients in their study population had mixed infarcts.







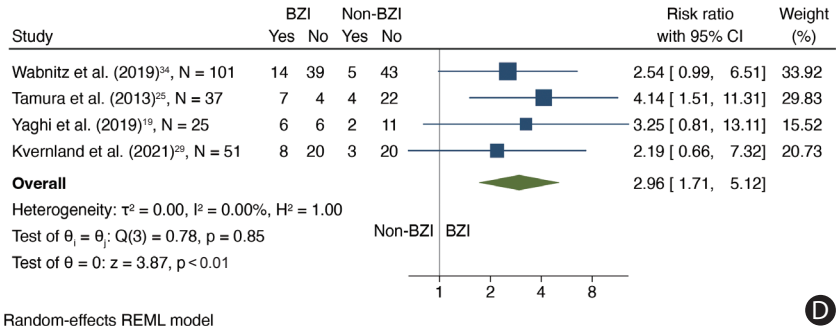


Figure 3. Forest plot showing association between BZI and recurrent cerebrovascular events. (A) Association between BZI and recurrent cerebrovascular events. (B) Association between any BZI and recurrent cerebrovascular events. (C) Association between isolated BZI and recurrent cerebrovascular events. (D) Association between BZI and recurrent cerebrovascular cerebrovascular events in patients with anterior circulation. BZI, borderzone infarct; CI, confidence interval; REML, restricted maximum likelihood.

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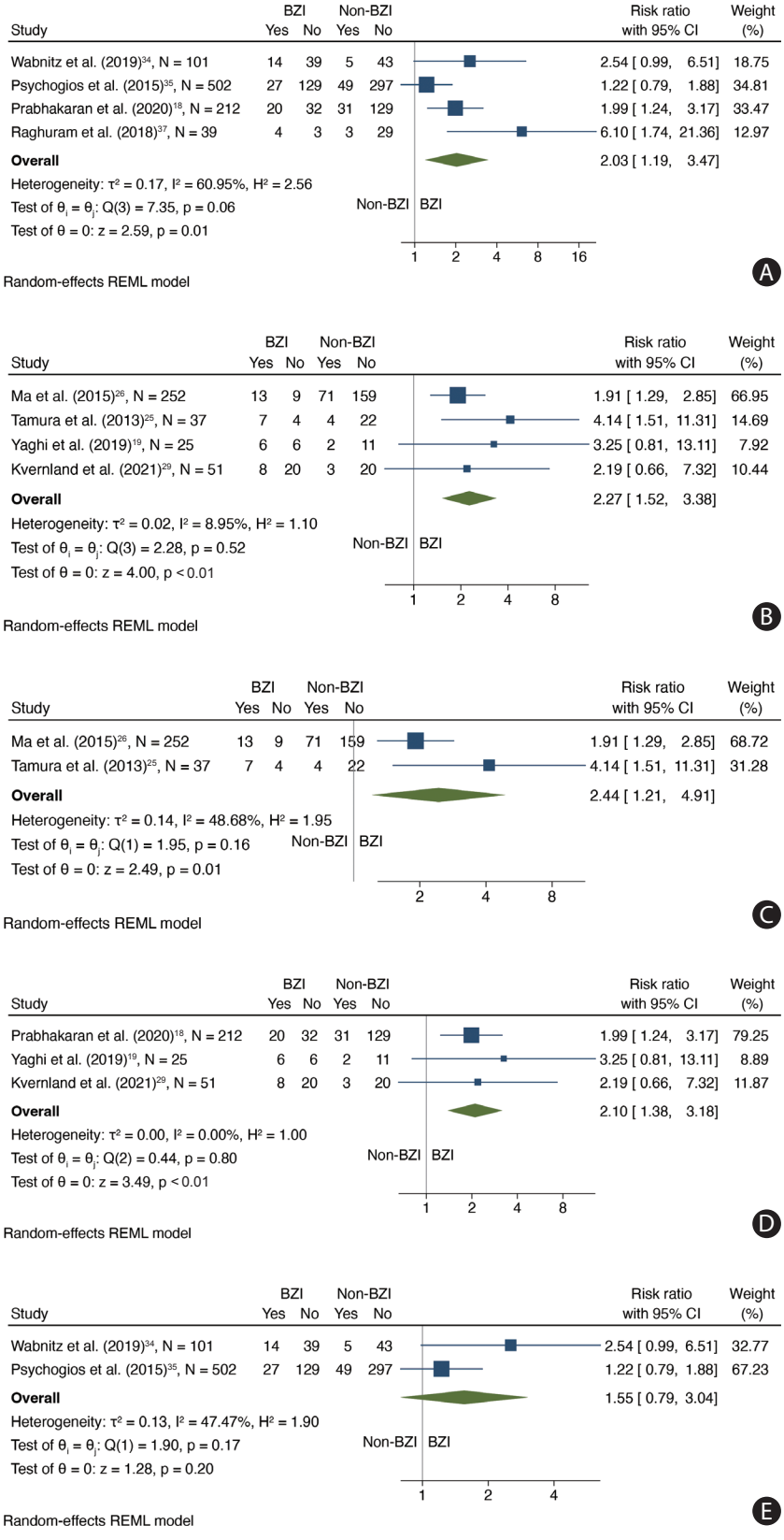

Figure 4. Forest plot showing subgroup analyses by outcome definition and timing. (A) Association between BZI and recurrent ischemic stroke. (B) Association between BZI and recurrent cerebrovascular events in studies whose outcome included or was limited to in-hospital neurological deterioration outcome. (C) Association between BZI and in-hospital recurrent cerebrovascular events. (D) Association between BZI and recurrent cerebrovascular events within 90 days. (E) Association between BZI any recurrent cerebrovascular events in studies with >90-day follow-up. BZI, borderzone infarct; CI, confidence interval; REML, restricted maximum likelihood.

more, the effect size was larger when limiting the studies to anterior circulation only and to those defining BZI as the presence of one or more infarct involving the borderzone territory even when occurring in conjunction with non-BZI.

Implications for clinical practice

The finding that the presence of a BZI is associated with recurrent cerebrovascular events, particularly in the first 90 days, is noteworthy. In patients with ICAS, BZI indirectly implies impaired blood flow,[20,21] impaired clearance of emboli,[39] or perfusion delay[19,22] across a stenosed artery. Although medical treatment can help stabilize atherosclerotic plaques and reduce the risk of thrombosis and embolization, it is unlikely to improve blood flow/perfusion in the affected territory in the acute setting. Thus, medical treatment may not be effective in preventing early recurrent stroke or neurological deterioration in patients with impaired distal blood flow/perfusion.

Endovascular trials of ICAS such as the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS)[7] and the Vitesse Intracranial Stent Study for Ischemic Stroke Therapy (VISSIT)[8] trials raised safety concerns with regard to endovascular treatment. These trials selected patients based on the degree of intracranial stenosis rather than based on blood flow/perfusion status. In fact, a *post hoc* analysis of SAMMPRIS[34] not only showed that the presence of BZI in medically treated patients was associated with increased recurrence risk but also that patients with BZI had fewer events when treated with stenting versus medical treatment. More recently, the China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS) trial showed randomized patients with symptomatic 70%–99% ICAS excluding those with perforator infarct.[40] CASSISS showed no significant difference in recurrence risk between medical treatment and endovascular treatment.[40] Similar to VISSIT and SAMMPRIS, CASSISS was not limited to patients with impaired perfusion/flow.

Therefore, given the high risk of recurrence in patients with symptomatic ICAS and BZI and a potential mechanistic benefit from reperfusion, studies testing the safety and efficacy of angioplasty with or without stenting in patients with symptomatic ICAS and BZI are needed.

Limitations

There are several limitations to our study. First, we restricted studies to the English language. Given that ICAS is more prevalent in Asia, we may have missed relevant studies published in languages other than English. Second, our assessment of the studies suggested a high risk of bias, which could have impacted our results. Third, the definition of BZI and outcomes varied across the studies. However, our findings were largely consistent in various subgroups stratified based on various definitions of BZI and outcomes, suggesting that this limitation is unlikely to have impacted our findings. Fourth, we did not examine time-to-event data since this information was unavailable in the included studies. Fifth, we pooled studies with different design (retrospective vs. prospective, single-center vs. multi-center). Sixth, given the small number of studies included, we are unable to rule out the potential for publication bias. Finally, other factors that can contribute to recurrence such as plaque stability and lesion multiplicity were not captured in our study. Thus comprehensive meta-analyses addressing these issues can help understand the pathophysiology of recurrent cerebrovascular events in ICAS.

Conclusions

In this systematic review and meta-analysis, in patients with symptomatic ICAS, BZI is associated with recurrent cerebrovascular events, particularly in the early period after the index event. Given the limitations of the identified evidence, our findings should be interpreted with caution pending confirmation by prospective studies with core lab adjudication.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2023.00185.

Funding statement

None

Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: SD, LS, RJM, EG, BMG, AD, EM, SY. Study design: SD, LS, RJM, EG, AD, EM, SY. Methodology: SD, LS, RJM, EG, AD, EM, SY. Data collection: SD, AS, FHF, DC, BM, SKB, CO, MA, AK, LP. Investigation: SD, LS, RJM, EG, AD, EG, AD, EM, SY. Statistical analysis: LS, LP, SY. Writing—original draft: SD, LS, RJM, SY. Writing—review & editing: SD, JES, TN, EG, BMG, KF, PK, SP, DSL, JGR, ADH, GT, SY. Approval of final manuscript: all authors.

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Supplementary Table 1. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			Page
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	3
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	2
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	3
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	4
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	4
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	4

Supplementary Table 1. Continued

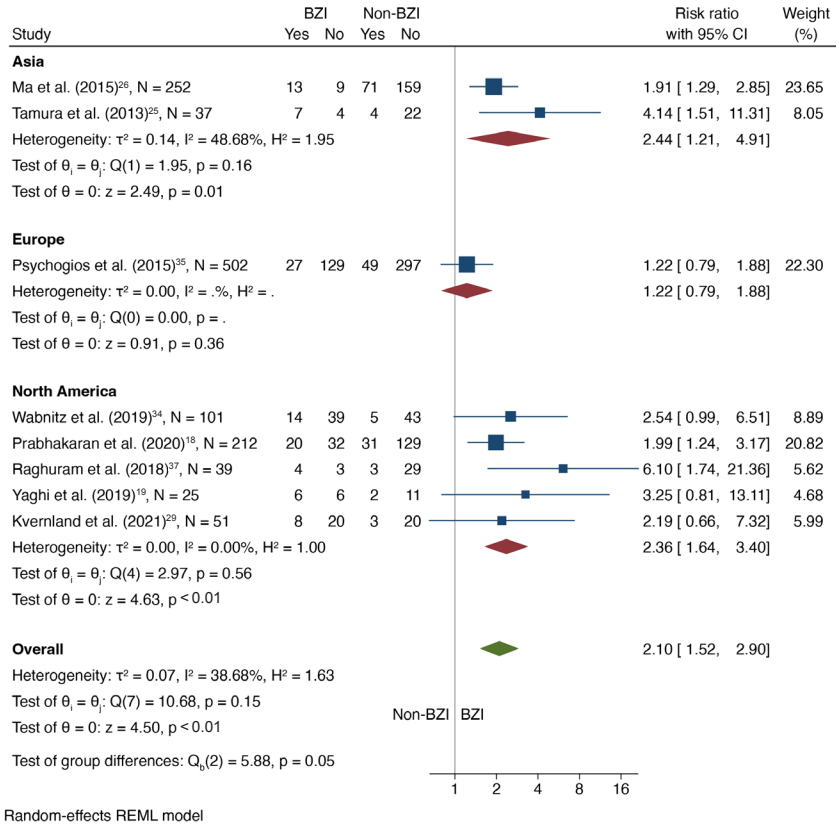
Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	3-4
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	3-4
Study characteristics	17	Cite each included study and present its characteristics.	3-4
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	3-4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	3-4
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	3-4
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	3-4
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	3-4
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	3-4
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	3-4
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	3-4
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	5-6
	23b	Discuss any limitations of the evidence included in the review.	8
	23c	Discuss any limitations of the review processes used.	8
	23d	Discuss implications of the results for practice, policy, and future research.	8
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	2
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	8
Competing interests	26	Declare any competing interests of review authors.	8
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	2

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Supplementary Table 2. Database search strategies

Database	Search strategy
PubMed MEDLINE; search from inception Date run: October 18, 2021 and updated March 15, 2022 Results: 2,233	((((((((cerebral[tiab]) OR (intracranial[tiab])) AND ((((((arteriosclerosis[tiab]) OR (arterioscleroses[tiab])) OR (arteriosclerotic[tiab])) OR (atherosclerosis[tiab])) OR (atherosclerоses[tiab])) OR (atherosclerotic[tiab]))) OR (((symptomatic[tiab]) AND (intracranial[tiab])) AND (((stenosis[tiab]) OR (stenoses[tiab])) OR (stenotic[tiab])))) OR (((intracranial[tiab]) AND (atherosclerotic[tiab])) AND (disease*[tiab]))) OR (((((stenosis[tiab]) OR (stenoses[tiab])) OR (stenotic[tiab]))) AND (intracranial[tiab]))) OR ("Intracranial Arteriosclerosis"[Mesh])) OR (ICAD[tiab])) OR (sICAS[tiab])) AND ((((((((((((cerebral[tiab]) OR (subcortical[tiab])) OR (cortical[tiab])) OR (borderzone[tiab])) OR (border zone[tiab])) OR (territorial[tiab])) OR (mixed[tiab])) OR (watershed[tiab])) OR (perforator[tiab])) AND ((((infarction[tiab]) OR (infarctions[tiab])) OR (infarct[tiab])) OR (infarcts[tiab]))) OR (((((stroke[tiab]) OR (infarct[tiab])) OR (infarction[tiab])) OR (lesion[tiab])) AND ((pattern[tiab]) OR (patterns[tiab])))))) OR (stroke[tiab]) AND (((((recurrence[tiab]) OR (recurrences[tiab])) OR (recurring[tiab])) OR (recurs[tiab])) OR (recur[tiab]))) OR ("Cerebral Infarction"[Mesh]))
Scopus (Elsevier); search from inception Translation Tool: Translated from PubMed using SR Accelerator Polyglot Tool Date Run: October 18, 2021 and updated March 15, 2022 Results: 1,440	((((((((TITLE-ABS(cerebral)) OR (TITLE-ABS(intracranial))) AND ((((((TITLE-ABS(arteriosclerosis)) OR (TITLE-ABS(arterioscleroses))) OR (TITLE-ABS(arteriosclerotic))) OR (TITLE-ABS(atherosclerosis))) OR (TITLE-ABS(atherosclerоses))) OR (TITLE-ABS(atherosclerotic)))) OR (((TITLE-ABS(symptomatic)) AND-(TITLE-ABS(intracranial))) AND (((TITLE-ABS(stenosis)) OR (TITLE-ABS(stenoses))) OR (TITLE-ABS(stenotic))))) OR (((TITLE-ABS(intracranial)) AND (TITLE-ABS(atherosclerotic))) AND (TITLE-ABS(disease*)))) OR (((((TITLE-ABS(stenosis)) OR (TITLE-ABS(stenoses))) OR (TITLE-ABS(stenotic)))) AND (TITLE-ABS(intracranial)))) OR (INDEXTERMS("Intracranial Arteriosclerosis"))) OR (TITLE-ABS(ICAD))) OR (TITLE-ABS(sICAS))) AND ((((((((((((TITLE-ABS(cerebral)) OR (TITLE-ABS(subcortical))) OR (TITLE-AB-S(cortical))) OR (TITLE-ABS(borderzone))) OR (TITLE-ABS("border zone"))) OR (TITLE-ABS(territorial))) OR (TITLE-ABS(mixed))) OR (TITLE-ABS(watershed))) OR (TITLE-ABS(perforator))) AND ((((TITLE-ABS(infarction)) OR (TITLE-ABS(infarctions))) OR (TITLE-ABS(infarct))) OR (TITLE-ABS(infarcts)))) OR (((((TITLE-ABS(stroke)) OR (TITLE-ABS(infarct))) OR (TITLE-ABS(infarction))) OR (TITLE-ABS(lesion))) AND ((TITLE-ABS(pattern)) OR (TITLE-ABS(patterns))))) OR (TITLE-ABS(stroke)) AND ((((((TITLE-ABS(recurrence)) OR (TITLE-ABS(recurrences))) OR (TITLE-ABS(recurring))) OR (TITLE-ABS(recurs))) OR (TITLE-ABS(recur)))) OR (INDEXTERMS("Cerebral Infarction")))
Cochrane Library; search from inception Date Run: October 18, 2021 and updated March 15, 2022 Translation Tool: Translated from PubMed using SR Accelerator Polyglot Tool Results: 391	((((((((cerebral:ti,ab) OR (intracranial:ti,ab)) AND ((((((arteriosclerosis:ti,ab) OR (arterioscleroses:ti,ab)) OR (arteriosclerotic:ti,ab)) OR (atherosclerosis:ti,ab)) OR (atherosclerоses:ti,ab)) OR (atherosclerotic:ti,ab))) OR (((symptomatic:ti,ab) AND (intracranial:ti,ab)) AND (((stenosis:ti,ab) OR (stenoses:ti,ab)) OR (stenotic:ti,ab)))) OR (((intracranial:ti,ab) AND (atherosclerotic:ti,ab)) AND (disease*:ti,ab))) OR (((((stenosis:ti,ab) OR (stenoses:ti,ab)) OR (stenotic:ti,ab))) AND (intracranial:ti,ab))) OR ([mh "Intracranial Arteriosclerosis"])) OR (ICAD:ti,ab)) OR (sICAS:ti,ab)) AND ((((((((((((cerebral:ti,ab) OR (subcortical:ti,ab)) OR (cortical:ti,ab)) OR (borderzone:ti,ab)) OR ("border zone":ti,ab)) OR (territorial:ti,ab)) OR (mixed:ti,ab)) OR (watershed:ti,ab)) OR (perforator:ti,ab)) AND ((((infarction:ti,ab) OR (infarctions:ti,ab)) OR (infarct:ti,ab)) OR (infarcts:ti,ab))) OR (((((stroke:ti,ab) OR (infarct:ti,ab)) OR (infarction:ti,ab)) OR (lesion:ti,ab)) AND ((pattern:ti,ab) OR (patterns:ti,ab)))) OR (stroke:ti,ab) AND ((((((recurrence:ti,ab) OR (recurrences:ti,ab)) OR (recurring:ti,ab)) OR (recurs:ti,ab)) OR (recur:ti,ab))) OR ([mh "Cerebral Infarction"]))
Web of Science Core Collection (Clarivate Analytics); full database search; search from inception Date Run: October 18, 2021 and updated March 15, 2022 Translation Tool: Translated from PubMed using SR Accelerator Polyglot Tool Results: 2,593	(TI=((((((((((cerebral) OR (intracranial)) AND ((((((arteriosclerosis) OR (arterioscleroses)) OR (arteriosclerotic)) OR (atherosclerosis)) OR (atherosclerоses)) OR (atherosclerotic))) OR (((symptomatic) AND (intracranial)) AND (((stenosis) OR (stenoses)) OR (stenotic)))) OR (((intracranial) AND (atherosclerotic)) AND (disease*))) OR ((((((stenosis) OR (stenoses)) OR (stenotic))) AND (intracranial))) OR ("Intracranial Arteriosclerosis")) OR (ICAD)) OR (sICAS)) AND ((((((((((((cerebral) OR (subcortical)) OR (cortical)) OR (borderzone)) OR ("border zone")) OR (territorial)) OR (mixed)) OR (watershed)) OR (perforator)) AND ((((infarction) OR (infarctions)) OR (infarct)) OR (infarcts))) OR (((((stroke) OR (infarct)) OR (infarction)) OR (lesion)) AND ((pattern) OR (patterns)))) OR (stroke) AND ((((((recurrence) OR (recurrences)) OR (recurring)) OR (recurs)) OR (recur))) OR ("Cerebral Infarction")))) OR AB=((((((((((cerebral) OR (intracranial)) AND ((((((arteriosclerosis) OR (arterioscleroses)) OR (arteriosclerotic)) OR (atherosclerosis)) OR (atherosclerоses)) OR (atherosclerotic))) OR (((symptomatic) AND (intracranial)) AND (((stenosis) OR (stenoses)) OR (stenotic)))) OR (((intracranial) AND (atherosclerotic)) AND (disease*))) OR ((((((stenosis) OR (stenoses)) OR (stenotic))) AND (intracranial))) OR ("Intracranial Arteriosclerosis")) OR (ICAD)) OR (sICAS)) AND ((((((((((((cerebral) OR (subcortical)) OR (cortical)) OR (borderzone)) OR ("border zone")) OR (territorial)) OR (mixed)) OR (watershed)) OR (perforator)) AND ((((infarction) OR (infarctions)) OR (infarct)) OR (infarcts))) OR (((((stroke) OR (infarct)) OR (infarction)) OR (lesion)) AND ((pattern) OR (patterns)))) OR (stroke) AND ((((((recurrence) OR (recurrences)) OR (recurring)) OR (recurs)) OR (recur))) OR ("Cerebral Infarction")))
Web of Science Core Collection (Clarivate Analytics); conference targeted search; search from inception Date Run: June 13, 2022 Results: 159	(((CF=(International stroke conference)) OR CF=(European stroke conference)) OR CF=(American Academy of Neurology)) AND ALL=('intracranial stenosis')



Supplementary Figure 1. Forest plot showing sensitivity analysis stratifying by continent. BZI, borderzone infarct; CI, confidence interval; REML, restricted maximum likelihood.

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