


# Meta-analysis of the outcomes of treatment of internal carotid artery near occlusion

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**Background:** Guidelines recommend treating patients with an internal carotid artery near occlusion (ICANO) with best medical therapy (BMT) based on weak evidence. Consequently, patients with ICANO were excluded from randomized trials. The aim of this individual-patient data (IPD) meta-analysis was to determine the optimal treatment approach.

**Methods:** A systematic search was performed in MEDLINE, EMBASE and the Cochrane Library databases in January 2018. The primary outcome was the occurrence of any stroke or death within the first 30 days of treatment, analysed by multivariable mixed-effect logistic regression. The secondary outcome was the occurrence of any stroke or death beyond 30 days up to 1 year after treatment, evaluated by Kaplan–Meier survival analysis.

**Results:** The search yielded 1526 articles, of which 61 were retrieved for full-text review. Some 32 studies met the inclusion criteria and pooled IPD were available from 11 studies, including some 703 patients with ICANO. Within 30 days, any stroke or death was reported in six patients (1.8 per cent) in the carotid endarterectomy (CEA) group, five (2.2 per cent) in the carotid artery stenting (CAS) group and seven (4.9 per cent) in the BMT group. This resulted in a higher 30-day stroke or death rate after BMT than after CEA (odds ratio 5.63, 95 per cent c.i. 1.30 to 24.45;  $P = 0.021$ ). No differences were found between CEA and CAS. The 1-year any stroke- or death-free survival rate was 96.1 per cent for CEA, 94.4 per cent for CAS and 81.2 per cent for BMT.

**Conclusion:** These data suggest that BMT alone is not superior to CEA or CAS with respect to 30-day or 1-year stroke or death prevention in patients with ICANO. These patients do not appear to constitute a high-risk group for surgery, and consideration should be made to including them in future RCTs of internal carotid artery interventions.

\*Members of the NEON study group are co-authors of this study and are listed in *Appendix S1* (supporting information) Data presented to the European Society for Vascular Surgery Congress, Valencia, Spain, September 2018, the Munich Vascular Conference, Munich, Germany, December 2018, and the International Stroke Conference, Honolulu, Hawaii, USA, February 2019

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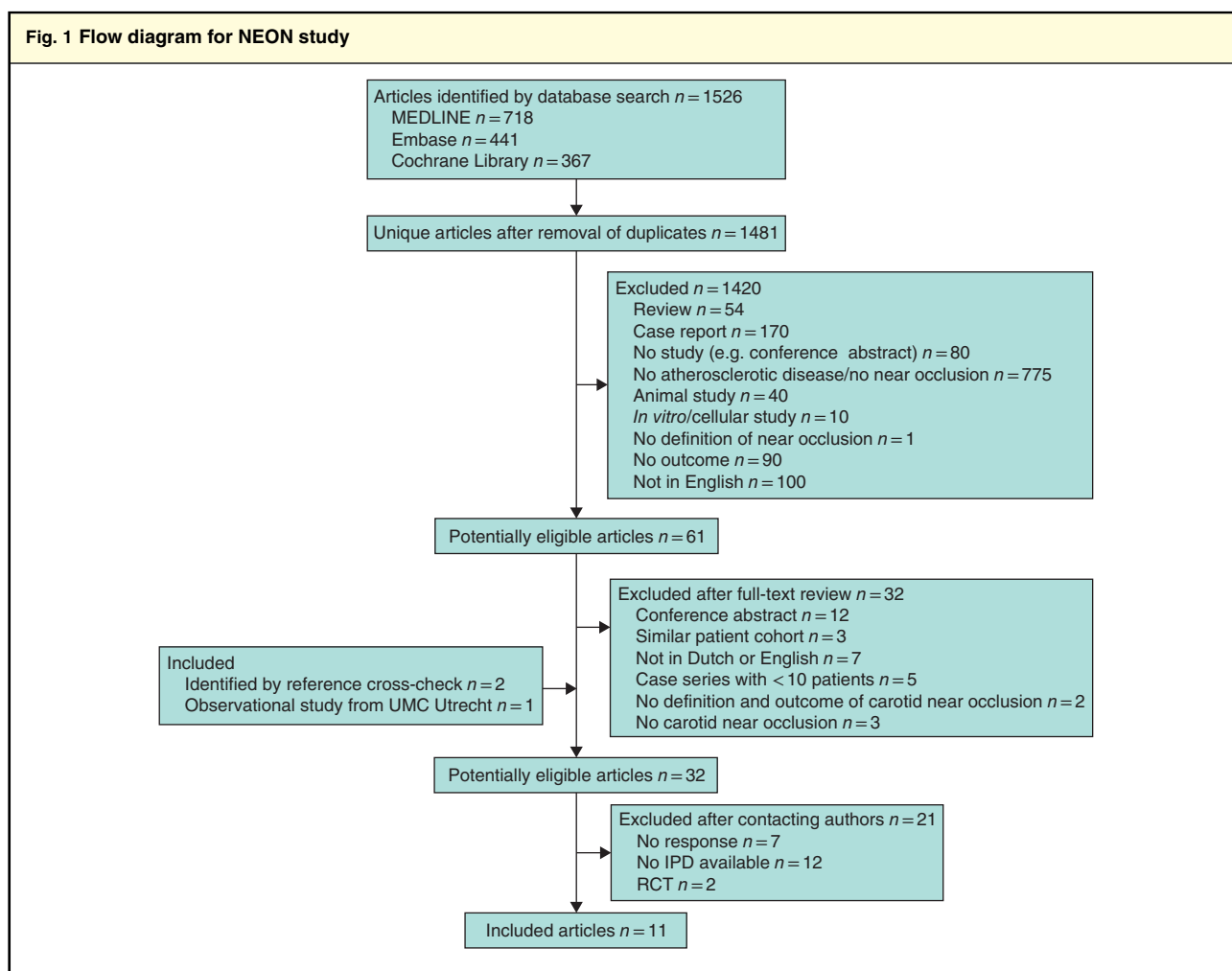
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## Introduction

The term internal carotid artery near occlusion (ICANO) is used for severe stenosis of the internal carotid artery with collapse of the artery distal to the stenosis. It has been referred to previously as a ‘string sign’ or ‘subtotal occlusion’<sup>1</sup>. It is a relatively rare disease with a prevalence of less than 10 per cent among patients with significant carotid artery stenosis<sup>2</sup>. Although carotid endarterectomy (CEA) is the standard treatment for symptomatic

significant carotid artery stenosis, the optimal treatment for patients with ICANO remains to be determined.

Guidelines<sup>3</sup> recommend treating patients with ICANO with best medical therapy (BMT). However, this recommendation is based on level III and class C evidence provided by a *post hoc* reanalysis of pooled data from the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST)<sup>4</sup>, published in 2003. Consequently, patients with



UMC, University Medical Centre; IPD, individual-patient data.

ICANO were excluded from RCTs of carotid interventions.

A recently published meta-analysis<sup>5</sup> investigating treatment efficacy in patients with ICANO proved inconclusive. The aim of the present meta-analysis was to pool all individual-patient data (IPD) from studies of treatment of ICANO to determine the optimal treatment approach for these patients.

## Methods

The study protocol defining the process for obtaining patient-level data and the preplanned analyses was designed by the core study group and approved by all collaborating authors of the NEON (treatment of carotid artery NEar OcclusionN) study group. The meta-analysis was reported in accordance with the PRISMA statement<sup>6</sup>.

## Search strategy and study selection

A systematic search was performed in MEDLINE, EMBASE and Cochrane databases in June 2016, and updated in January 2018. Synonyms for 'internal carotid artery near occlusion' were used to identify all relevant articles. The full search strategy can be found in *Table S1* (supporting information). Two researchers assessed full-text eligibility independently based on title and abstract screening. Judgement differences were resolved by discussion with the senior author. The reference lists of the included articles were screened for missing articles.

Studies were eligible if they reported on: a minimum of ten patients with ICANO due to atherosclerosis; criteria used to diagnose ICANO; and treatment approach and outcomes. Excluded were animal studies, reviews, and articles in languages other than Dutch and English.

Table 1 Overview of included studies

Reference	Inclusion period	Study type	Criteria for ICANO*	No. of patients			
				CEA	CAS	BMT	Any stroke or death within 30 days
Regina <i>et al.</i> <sup>8</sup>	1985–1997	Prospective	NASCET	15	0	0	2 (13)
Radak <i>et al.</i> <sup>9</sup>	2003–2006	Prospective	NASCET	259	0	50	CEA: 2 (0.8) BMT: 1 (2)
González <i>et al.</i> <sup>10</sup>	2000–2009	Prospective	NASCET	0	116	0	0 (0)
Ogata <i>et al.</i> <sup>11</sup>	1994–2005	Retrospective	NASCET	28	2	4	CEA: 1 (4) CAS: 0 (0) BMT: 0 (0)
Oka <i>et al.</i> <sup>12</sup>	2006–2012	Prospective	NASCET	0	15	0	1 (7)
Son <i>et al.</i> <sup>13</sup>	2010–2012	Retrospective	NASCET	0	24	0	0 (0)
Sakamoto <i>et al.</i> <sup>14</sup>	2008–2012	Retrospective	Rothwell	0	14	0	0 (0)
Johansson <i>et al.</i> <sup>15</sup>	2007–2009	Prospective	Bartlett	15	0	5	CEA: 0 (0) BMT: 4 (80)
Matsuda <i>et al.</i> <sup>16</sup>	2002–2013	Retrospective	NASCET	0	56	0	4 (7)
García-Pastor <i>et al.</i> <sup>17</sup>	2010–2016	Prospective	NASCET	0	0	83	2 of 77 (3)†
Meershoek <i>et al.</i> <sup>18</sup>	2008–2017	Retrospective	NASCET	17	0	0	1 (6)

Values in parentheses are percentages. \*North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria<sup>2,19</sup>: recognition of two or more of the following: delayed contrast arrival; evidence of collaterals; internal carotid artery (ICA)-to-ICA comparison of diameter reduction; ICA-to-external carotid artery (ECA) comparison of diameter reduction. Rothwell criteria<sup>20</sup>: severe ICA stenosis with distal ICA narrowing; an ICA/common carotid artery ratio of less than 0.40 in men and under 0.45 in women. Bartlett<sup>21</sup>: adapted from NASCET criteria; diagnosis of near occlusion by CT angiography, based on notable stenosis of the carotid bulb; and the presence of distal ICA calibre reduction in comparison to its expected size, the contralateral ICA and the ipsilateral ECA. †No information on outcome was available for six of 83 patients. ICANO, internal carotid artery near occlusion; CEA, carotid endarterectomy; CAS, carotid artery stenting; BMT, best medical treatment.

Corresponding authors of all eligible studies were contacted by e-mail, and asked to participate in this study by sending their IPD in a predefined spreadsheet. If there was no response after 2 weeks, the corresponding authors were contacted again, with a maximum of four attempts. If there was still no response to these e-mails, the other authors of the paper (first author, senior author, other co-authors) were contacted similarly, a maximum of three times.

### Data extraction and study outcomes

After data examination and quality assessment (for discrepancies between published and shared data), data were extracted from the IPD files received and pooled into a single database.

Owing to differences in study design, analyses in this IPD meta-analysis were based on observational studies; the two RCTs were used for additional literature support.

Study, patient and outcome characteristics were collected. Patient characteristics comprised: demographics (age, sex); clinical characteristics (symptom status, type of treatment, medical history); and drug use and antiplatelet therapy. Study characteristics comprised: year of study publication; number of included patients; and definition of ICANO.

The primary outcome of the present study was the occurrence of any stroke or death within 30 days. The secondary outcome measure was the occurrence of any stroke or death beyond 30 days until 1 year after treatment. Rates of restenosis, technical failure and cranial nerve injury were also assessed.

### Study quality assessment

The Newcastle–Ottawa Scale for observational studies<sup>7</sup> was used to assess the quality of included studies. Average quality was defined as 4 of 6 points, or 6–7 of 9 points. Good quality was defined as 5–6 of 6 points, or 8–9 of 9 points.

### Statistical analysis

Baseline characteristics of the treatment groups were compared using the  $\chi^2$  test for categorical variables, and the non-parametric Mann–Whitney *U* test for continuous data. The CEA group was used as the reference group.  $\chi^2$  tests were used to investigate differences between the distribution of baseline characteristics in the event and no-event groups. For the primary outcome, a multi-variable mixed-effect logistic regression analysis was

	<b>CEA</b> (n = 334)†	<b>CAS</b> (n = 227)	<b>P</b> (CEA versus CAS)‡	<b>BMT</b> (n = 142)	<b>P</b> (CEA versus BMT)‡
<b>Age (years)*</b>	66 (59–71)	71 (64–76)	< 0.001§	69 (61–75)	0.001§
<b>Sex ratio (M : F)</b>	242 : 92	199 : 28	< 0.001	115 : 27	0.049
<b>Symptoms</b>					
Asymptomatic	17 (5.1)	40 (17.6)	< 0.001	2 (1.4)	0.060
TIA or amaurosis fugax	191 (57.2)	65 (28.6)	< 0.001	60 (42.3)	< 0.001
Stroke	126 (37.7)	122 (53.7)	< 0.001	80 (56.3)	< 0.001
<b>Hypertension</b>	260 (77.8)	182 (80.2)	0.357	105 (73.9)	0.357
<b>Diabetes mellitus</b>	95 (28.4)	88 (38.8)	0.007	52 (36.6)	0.077
<b>Smoking</b>	125 (37.4)	117 (51.5)	< 0.001	60 (42.3)	0.507
<b>Best medical treatment</b>					
Antiplatelet/anticoagulant					
Aspirin monotherapy				67 (47.2)	
Aspirin + clopidogrel				20 (14.1)	
Clopidogrel monotherapy				33 (23.2)	
Aspirin + persantin				3 (2.1)	
Anticoagulant therapy				11 (7.7)	
Aspirin + anticoagulant				7 (4.9)	
Unknown				1 (0.7)	
Statin					
Yes				121 (85.2)	
Unknown				4 (2.8)	
Antihypertensive treatment					
Yes				106 (74.6)	
Unknown				4 (2.8)	

Values in parentheses are percentages unless indicated otherwise; \*values are median (i.q.r.). †Reference group. CEA, carotid endarterectomy; CAS, carotid artery stenting; BMT, best medical treatment; TIA, transient ischaemic attack. ‡ $\chi^2$  test, except §Mann–Whitney *U* test.

	<b>Stroke or death within 30 days</b>	
	<b>Odds ratio</b>	<b>P</b>
<b>Treatment</b>		
CEA	1.00 (reference)*	0.266
CAS	0.62 (0.06, 6.11)	0.682
BMT	5.63 (1.30, 24.45)	0.021
<b>Confounders</b>		
Sex (M versus F)	0.35 (0.12, 1.02)	0.054
Age (per year)	0.99 (0.94, 1.05)	0.816
TIA/amaurosis fugax (yes or no)	0.67 (0.15, 3.11)	0.613
Stroke (yes or no)	1.02 (0.25, 4.22)	0.978

Values in parentheses are 95 per cent confidence intervals. Outcome analyses were based on 696 patients because no data on the primary (and secondary) outcomes were available for seven patients. \*The odds for carotid endarterectomy (CEA) were 0.09 (0.00 to 6.31). CAS, carotid artery stenting; BMT, best medical treatment; TIA, transient ischaemic attack. A multivariable mixed-effect logistic regression analysis was performed with correction for potential confounders (centre of inclusion, age, sex, symptom status and index event).

undertaken with correction for potential confounders. For this analysis, baseline characteristics with  $P < 0.200$  were included as potential confounders, or potential confounders were predefined on the basis of clinical relevance and availability (less than 25 per cent missing values)

by members of the core study group. These clinically relevant confounders were: centre of inclusion, age, sex, symptom status and index event. Primary outcomes are reported as odds ratios (ORs) with 95 per cent confidence intervals.  $P < 0.050$  was considered statistically significant. A Kaplan–Meier survival analysis for time to any stroke or death was undertaken for the secondary outcome. No statistical tests were performed on the secondary outcome.

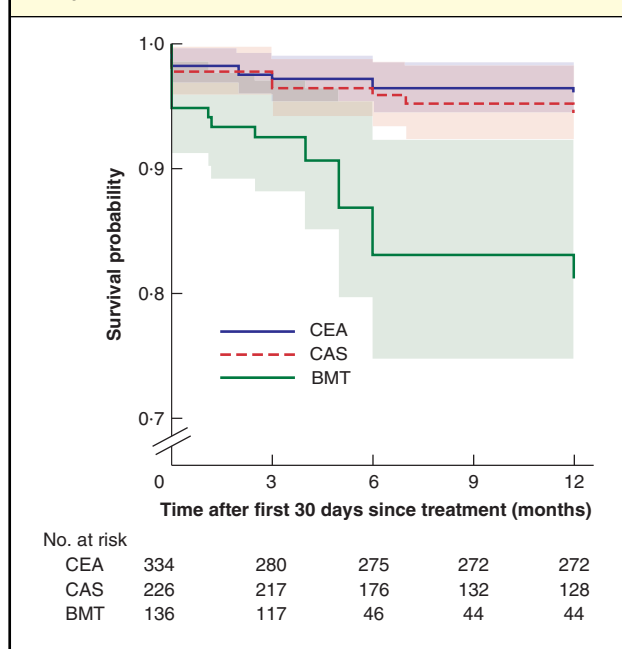
SPSS® version 20.0 (IBM Armonk, New York, USA) and R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses.

## Results

### Study selection

The search yielded 1526 articles, of which 61 were retrieved for full-text review (Fig. 1). Some 32 studies met the inclusion criteria, and the authors asked for their IPD. Eleven studies with IPD available were included in the meta-analysis (Fig. 1)<sup>8–18</sup>, including an observational study<sup>18</sup> from University Medical Centre Utrecht. Of the remaining 21 studies, IPD could not be retrieved because the authors did not respond (7; response rate 78 per cent), IPD were not available (12), or the study was an RCT (2). An overview of the included studies is shown in Table 1.

**Fig. 2 Kaplan–Meier curves for any stroke- or death-free survival after the first 30 days of treatment for internal carotid artery near occlusion**



CEA, carotid endarterectomy; CAS, carotid artery stenting; BMT, best medical treatment.

The methodological quality was good in eight studies and average in three (*Table S2*, supporting information).

### Study population

The total patient cohort consisted of 703 patients, of whom 334 (47.5 per cent) had been treated with CEA, 227 (32.3 per cent) had undergone carotid artery stenting (CAS) and 142 (20.2 per cent) had received BMT. Regarding CEA technique, 268 patients had been treated by eversion CEA, 58 by longitudinal CEA, five by graft interposition, and in three patients the internal carotid artery was ligated as there was no perioperative back-bleeding. No IPD on CAS procedural characteristics were available. Patients in the BMT group received antiplatelet therapy (100 per cent), antihypertensive therapy (74.6 per cent) and statins (85.2 per cent) (*Table 2*). Baseline characteristics were not distributed evenly between the three treatment groups. The CEA group included younger patients, and a smaller proportion of men, patients with diabetes and smokers than the CAS and BMT groups. The index event was less often stroke in the CEA group.

Comparing the distribution of baseline characteristics between groups with and without any stroke or death within 30 days, although not statistically significant, there was a higher proportion of men in the group without any

stroke or death within 30 days (*Table S3*, supporting information). Assessing the distribution of sex in the three treatment groups, an equal distribution was observed (*Fig. S1*, supporting information).

### Stroke or death within 30 days

In the entire cohort, any stroke or death within 30 days was reported in 18 patients (2.6 per cent): six patients (1.8 per cent) in the CEA group, five (2.2 per cent) in the CAS group and seven in the BMT group (*Table 1*). After adjustment for possible confounders (centre of inclusion, age, sex, symptom status and index event), this difference was statistically significant for BMT *versus* CEA, with higher stroke or death rates after BMT (OR 5.63, 95 per cent c.i. 1.30 to 24.45;  $P=0.021$ ). No differences were found between CAS and CEA (OR 0.62, 0.06 to 6.11;  $P=0.682$ ), nor between BMT and CAS (OR 9.08, 0.78 to 106.37;  $P=0.079$ ). Regarding potential confounders, none of the variables were statistically significant (*Table 3*). Male sex was borderline significant and showed a trend towards a lower risk of stroke or death within 30 days (OR 0.35, 0.12 to 1.02;  $P=0.054$ ).

### Stroke or death during 1-year follow-up

In total, 38 patients died, 22 from a cardiovascular cause. The 1-year any stroke-free survival rate was 97.8 per cent for CEA, 97.3 per cent for CAS and 93.3 per cent for BMT. *Fig. 2* shows Kaplan–Meier curves for any stroke- or death-free cumulative survival during 1-year follow-up in the three treatment groups. The 1-year any stroke- or death-free survival rate was 96.1 per cent for CEA, 94.4 per cent for CAS and 81.2 per cent for BMT. Visual assessment revealed no difference between the curves for CEA and CAS. There seemed to be a higher rate of any stroke or death in the BMT group in this time frame of 1 year.

### Other outcomes

Rates of restenosis, technical failure and cranial nerve injury after CEA and CAS are shown *Table S4* (supporting information). There seemed to be no difference in patency between CEA and CAS.

### Discussion

This meta-analysis of IPD, including 703 patients from 11 studies of patients with ICANO, showed that BMT was not superior to CEA or CAS with respect to 30-day or 1-year



stroke or death prevention. The risk of stroke or death within 30 days after CEA was as low as 1.8 per cent.

There was no evidence that the outcomes after BMT alone were superior to those of either CAS or CEA. On the contrary, BMT was associated with a higher 30-day stroke or death rate of 4.9 per cent, compared with 2.2 per cent for CAS and 1.8 per cent for CEA. However, the number of events was small, preventing firm conclusions being drawn.

Medical therapy has improved significantly over the years. During the inclusion period of NASCET and ECST, BMT consisted of aspirin therapy in varying doses and anti-hypertensive treatment. Newer therapies including clopidogrel and statins were not available at that time. In the present IPD meta-analysis, even though all patients treated by BMT received antiplatelet therapy, 47.2 per cent still received aspirin monotherapy, 85.2 per cent received statins and 74.6 per cent were on antihypertensive treatment. The present analysis has shown that there remains room for improvement of BMT.

The effect of BMT compared with CEA in ICANO was based on a *post hoc* analysis of RCTs undertaken decades ago that were analysed on an intention-to-treat basis<sup>4</sup>. This analysis might have underestimated the benefit of endarterectomy in patients with ICANO, because of the high crossover rate to endarterectomy during follow-up in the medical treatment group in NASCET<sup>4</sup>. The lower medical stroke risk in ECST may have been due to the lower prevalence of some risk factors, such as older age, diabetes, ischaemic heart disease and hyperlipidaemia<sup>2</sup>. In addition, timing could have played a crucial role as only 35–45 per cent of the patients included in these two trials had been randomized within 1 month<sup>4</sup>. Hence, it is likely that patients with a chronic ICANO were included in these trials, and such patients may benefit more from BMT than patients with an acute ICANO. Unfortunately, information on the interval between the index event and study inclusion was not available from all studies for the present analysis.

The 30-day stroke or death rate of 1.8 per cent after CEA for patients with ICANO in the present analysis is similar to the rate of 2.7 per cent reported previously in patients with a symptomatic significant carotid artery stenosis who underwent CEA<sup>22</sup>. This suggests that patients with ICANO are not a high-risk subgroup for surgery. The high risk was based on the pooled analysis of NASCET and ECST, which reported a 30-day stroke or death risk of 5.4 per cent<sup>4</sup>. The low 30-day event rate in the present study could be due to better control of vascular risk factors in general, as in the early 1990s this 30-day event rate was 6.2 per cent in patients who underwent CEA for severe (more than 70 per cent) symptomatic carotid artery stenosis<sup>4</sup>, and decreased to 2.7 per cent in studies in which the

recruitment period ended beyond 2004<sup>22</sup>. Developments in revascularization techniques have also been made over recent years, especially for CAS. The 30-day stroke or death rate after CAS was 2.2 per cent in the present IPD meta-analysis, indicating that patients with ICANO could also be included in future RCTs focusing on CAS.

Several limitations have to be addressed. The numbers of each outcome in each treatment group were small, so the results should be interpreted with caution. Patients from the included studies originated from all over the world, creating a heterogeneous patient population with varying patient characteristics, treatment approaches and health-care systems, although correction was made for centre as a confounder in the logistic regression model. One study<sup>15</sup> reported an event within 30 days in four of five patients treated by BMT, potentially biasing the results. This was also dealt with by correcting for centre in the primary outcome analysis. No distinction was made between ICANO with *versus* without full collapse, or for single symptom *versus* recurrent symptoms. This is deemed a relevant distinction, as one study<sup>15</sup> reported a 28-day risk of recurrent stroke of 43 per cent in ICANO with full collapse (calculated using Kaplan–Meier derived risks, 4 patients), compared with 0 per cent among those without full collapse. However, another study<sup>17</sup> reported no significant differences between these two groups, and the ECST<sup>20</sup> concluded that full collapse was associated with a lower risk of stroke in medically treated patients. No separate subgroup analysis could be performed in the present review, because most studies made no distinction between patients with and without full collapse. Despite contact with the authors, information on the interval between neurological index event and treatment, type and intracerebral localization of post-treatment stroke, and who diagnosed the post-treatment stroke was not available for most studies. The use of different diagnostic modalities could have influenced the patients included. It would have been preferable to have reported outcomes on 5-year stroke- or death-free survival, but these data were not available.

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*Disclosure:* The authors declare no conflict of interest.

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### Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.