Management of internal carotid artery near-occlusion: the need for updated evidence

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Abstract: Near occlusion of internal carotid artery (ICA) is a rare and easily misdiagnosed condition and the decision for revascularisation still remains controversial. We conducted an updated meta-analysis in order to investigate outcomes after carotid endarterectomy (CEA), carotid artery stenting (CAS) or best medical treatment (BMT) in patients with near-occlusion of the ICA. We also aimed to investigate the role of time as a potential moderator of the near-ICA occlusion—stroke rate association. A multiple electronic health database search on articles published up to November 2019 was performed. The pooled stroke rate after CEA, CAS and BMT were calculated. We also investigated transient ischemic attack (TIA), stroke-related death, myocardial infarction (MI), any cause of death and ICA restenosis crude rates (%). A total of 33 articles were finally deemed eligible. The pooled stroke rate was 1.52% [95% confidence interval (CI): 0.09–4.02%] after CEA, 1.80% (95% CI: 0.61–3.40%) after CAS and 8.39% (95% CI: 3.39–14.80%) after BMT. Out of 896 CEA patients, we recorded 22 TIAs (2.5%), 33 all-cause deaths (3.7%), 5 stroke-related deaths (0.6%) and 6 MIs (0.7%). Concerning outcomes after 603 CAS patients, we recorded 7 TIAs (1.2%), 56 all-cause deaths (9.3%), 4 stroke-related deaths (0.7%) and 22 MIs (3.6%). Among 263 patients who were treated with BMT, we found 16 TIAs (6.1%), 10 all-cause deaths (3.8%), no stroke-related death, and no MI. Crude restenosis rate during follow-up was 9.0% (54/601) for CEA and 4.1% (24/592) for CAS patients. No significant effect of publication year upon stroke rate after CEA was recorded. However, there was a significant reversed association between pooled stroke rate after CAS and publication year (P=0.05). A statistically significant reversed association between pooled stroke rate after BMT and publication year was also recorded (P<0.01). The results of this updated meta-analysis revealed high stroke rate for patients with near-occlusion of ICA who treated only with BMT, while intervention seemed to be safe and effective. A downward trend in the stroke rates over time after CAS and BMT was also discovered. These highlight that patients with near-occlusion of ICA should be included and investigated in future studies.

Keywords: Carotid artery; near occlusion; meta-analysis; string sign; stroke

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Background

Stroke is the fifth leading cause of death and a major cause of serious long-term disability for adults (1). The degree of internal carotid artery (ICA) stenosis is one of the most important factors, affecting the decision whether subsequent intervention is warranted, as it is directly linked to the risk of stroke. More specifically, an increased degree of ICA stenosis has been associated with a higher risk for ipsilateral stroke, based on the findings of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) (2,3). This study showed a high stroke incidence in medically treated patients, while carotid artery endarterectomy (CEA) was proved as beneficial. However, a later sub-analysis of this study, yielded a 1-year stroke rate of 11% in the patients with almost complete occlusion of the ICA, contrary to 35% in the patients with less than 94% ICA stenosis (3), making the indication for surgical intervention in the first population rather unclear. Further analysis of the three most important randomized controlled trials (RCTs) comparing CEA with best medical treatment (BMT), namely NASCET, European Carotid Surgery Trial (ECST) and the Symptomatic Veterans Affairs Co-operative Study (SVACS) Trial, showed that the benefit conferred by CEA increased with increasing stenosis severity, with the exclusion of "near-occlusion". More specifically, patients with chronic near occlusion (defined as a 95–99% stenosis with distal ICA collapse or a narrow calibre lumen with "trickle flow") gained no obvious benefit from CEA (4,5).

Since the original publication of the three RCTs, many other studies have focused on the optimal treatment of patients with near ICA occlusion in the form of CEA, carotid artery stenting (CAS) or BMT. A recent European Society for Vascular Surgery (ESVS) Guidelines document (6) on the management of carotid artery disease recommended conservative treatment in symptomatic patients with a chronic ICA near-occlusion, unless associated with recurrent ipsilateral symptoms despite optimal medical therapy. However, this recommendation did not take into consideration the "real-world", non-randomized studies, and it was based on rather outdated data. Furthermore, a recent individual patient meta-analysis (7), concluded 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 near ICA occlusion. Similarly, a previous review by our team (8), which included five articles on BMT and CEA, eight articles on CEA, and eleven articles on CAS published up to December 2014 provided with evidence that an intervention is probably indicated for patients with near-total ICA occlusion. However, during the last 5 years, many more studies were added to the literature, thus making an update pertinent.

The aim of this study was to update our early systematic review in order to investigate outcomes after CEA, CAS or BMT in patients with near-occlusion of the ICA. We also aimed to investigate the role of time as a potential moderator of the near-ICA occlusion—stroke rate association.

Methods

We conducted a systematic review and meta-analysis according the published recommendations of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group (9). Our literature review included the electronic health databases of Medline, Ovid and the Cochrane Database of Systematic Reviews. We focused on articles evaluating treatment options, including BMT, CEA or CAS for patients with near total ICA occlusion. For that reason, we used MeSH (medical subject heading) terminology with keywords: "carotid", "critical stenosis", "internal carotid artery", "near total occlusion", "sub-occlusion", "pre-occlusion", "pseudo-occlusion", "string sign", "slim sign". Articles describing ligation of the ICA due to near total ICA occlusion were excluded. Two independent reviewers (CN Antonopoulos, A Giosdekos) performed the literature review and the data extraction of articles published in English up to November 2019. From all eligible articles, along with baseline characteristics, we focused on outcomes after application of the treatment (CEA, CAS or BMT), including, transient ischemic attack (TIA), stroke, stroke-related death, myocardial infarction (MI), any cause of death and ICA restenosis. After extraction of the number of patients with outcome events (used as numerator) and the total number of patients included in each study (used as denominator), we presented outcome rates for each study as crude rates (% percentage). For the outcome of "stroke" we also calculated crude outcome rate with 95% confidence intervals (95% CIs). The corresponding rate was thereafter transformed into quantities according to the Freeman-Tukey variant of the arcsine square root transformed proportion (10). The pooled effect estimate of stroke, was calculated as the back-transformation of the weighted mean of the transformed proportion, using inverse arcsine variance weights for the fixed effects model or DerSimonian-Laird weights in case of
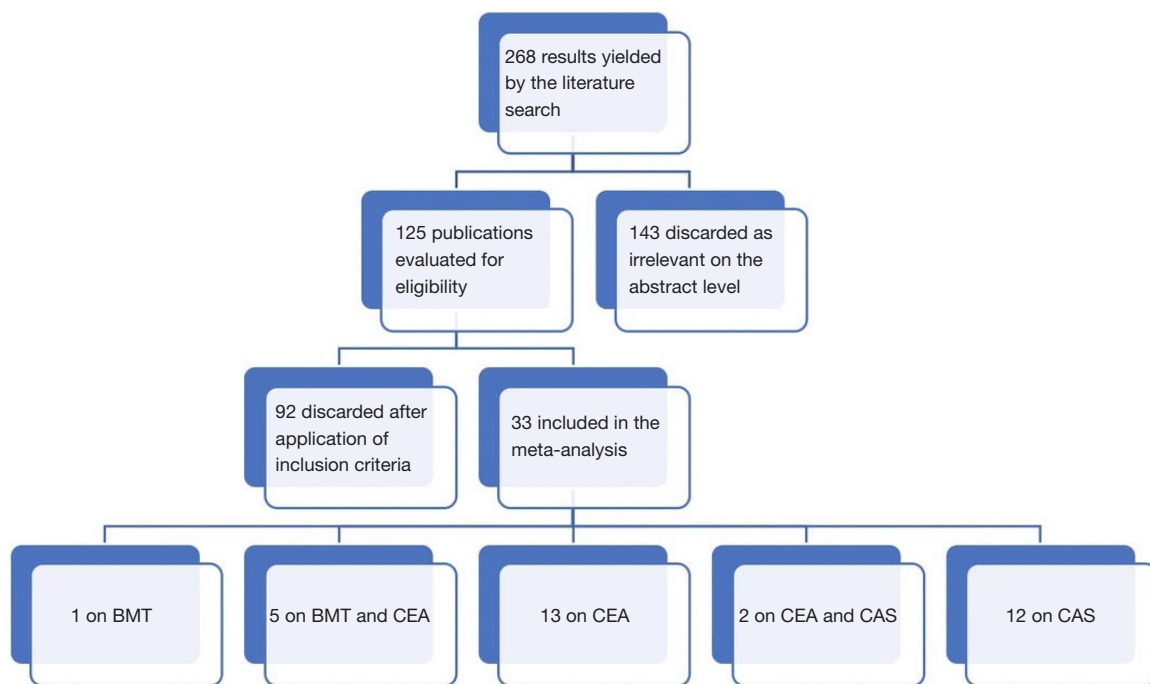
Figure 1 Flow chart. BMT, best medical treatment; CEA, carotid endarterectomy; CAS, carotid artery stenting.

random effects model (11). We assessed the heterogeneity among studies with the Cochran Q score (reported as I^2), while publication bias was assessed with Egger's regression test and funnel plot. Thereafter, we performed a meta-regression analysis in order to investigate the role of publication year as a potential modifier upon the effect estimate of stroke, with the aim to explore the effect of time by means of improvements in each one of the treatment arms upon stroke rate. The meta-analysis was conducted using Stata 14.2 (StataCorp, College Station, TX, USA).

Results

After an initial search in the literature, we identified 268 potentially eligible studies. Review of the titles and abstracts evidenced that 143 were irrelevant. After applying exclusion criteria, 92 studies were excluded and finally 33 articles participated in the meta-analysis. More specifically, the literature review revealed 13 articles on CEA (12-24), 12 articles on CAS (25-36), 5 studies on BMT and CEA (37-41), 2 studies on CEA and CAS (42,43) and 1 study on BMT (44) (*Figure 1*: flow chart). The demographic characteristics of the 33 eligible studies included in our study are presented in *Tables 1,2*. Among the patients who received CAS almost 76% were symptomatic, the mean age

was 69 years, embolic filter devices were used in 75.2% of the cases and the mean follow up was 20.5 months. Among the patients who were treated with CEA, about 80% were symptomatic, the mean age was 65.8 years, patch applied in 34% of the cases and the mean follow up was 26.2 months. It should be mentioned that in 7 patients (18,37,38) the ICA was ligated and thus they were excluded from the further analysis. Out of 896 CEA patients, we recorded 22 TIAs (2.5%), 33 all-cause deaths (3.7%), 5 stroke-related deaths (0.6%) and 6 MIs (0.7%). Concerning outcomes after 603 CAS patients, the respective number of events and crude rates were 7 TIAs (1.2%), 56 all-cause deaths (9.3%), 4 stroke-related deaths (0.7%) and 22 MIs (3.6%). Among 263 patients who were treated solely with BMT, the events and crude rates were 16 TIAs (6.1%), 10 all-cause deaths (3.8%), no stroke-related death, and no MI, although only one study reported on the last outcome. Crude restenosis rate during follow-up was 9.0% (54/601) for CEA and 4.1% (24/592) for CAS patients.

The pooled stroke rate after CEA was 1.52% (95% CI: 0.09–4.02%; *Figure 2*), while the respective rate for CAS was 1.80% (95% CI: 0.61–3.40%; *Figure 3*). Evaluation of the eligible studies reporting stroke rates after BMT only, revealed a pooled stroke rate of 8.39% (95% CI: 3.39–14.80%; *Figure 4*). No significant effect of publication year

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Table 1 Eligible studies on carotid endarterectomy (CEA) and best medical treatment (BMT)

Author	Year	Study period	N with near total ICA occlusion	N on CEA	N on BMT	Gender (%males)	Mean age (years)	Symptomatic (%)	Patch use (%)	FU (M)
Archie, *et al.* (24)	1994	July 1981 to December 1999	17	17	–	58.80	68	100.00	76.50	27
Ascher, *et al.* (37)	2002	July 1999 to April 2001	13	8	5	66.70	73	83.30	100.00	8
Berman, *et al.* (12)	1994	March 1984 to December 1992	91	91	–	59.30	N.d.	75.80	80.20	21
Bowman, *et al.* (38)	2009	February 2003 to January 2008	10	1	8	100.00	72	0	0	12
Desole, *et al.* (13)	2015	January 2006 to December 2013	33	33	–	78.80	70	57.60	61.00	32
Fox, *et al.* (39)	2005	NASCET/ECST	262	148	114	80.40	N.d.	65.50	N.d.	36
Fredericks, *et al.* (14)	1990	January 1978 to January 1988	26	26	–	73.10	61.1	69.20	N.d.	8
Garcìa-Pastor, *et al.* (44)	2017	January 2010 to May 2016	77	–	77	N.d.	N.d.	100.00	N.d.	3
Greiner, *et al.* (15)	2004	1983–2001	40	40	–	67.50	56	72.50	0	48
Hirata, *et al.* (16)	2014	January 2001 to December 2007	17	17	–	88.20	70.5	76.50	0	20.2
Kim, *et al.* (42)	2019	January 2010 to December 2018	23	23	–	76.00	65.4	100.00	N.d.	12
Kniemeyer, *et al.* (17)	1996	1984–1996	76	76	–	78.90	60.6	89.50	100.00	73
Meershoek, *et al.* (18)	2018	January 2008 to June 2017	15	15	–	70.00	65	100.00	100.00	23
Ogata, *et al.* (19)	2011	January 1994 to September 2005	28	28	–	82.10	70.7	53.60	0	26
O'Leary, *et al.* (40)	1989	July 1978 to July 1988	25	25	9	88	66	92	0	34
Pulli, *et al.* (20)	1997	1992–1997	24	24	–	N.d.	N.d.	N.d.	N.d.	24
Radak, *et al.* (41)	2010	2003–2006	309	259	50	59.50	64	100.00	0	12
Regina, *et al.* (21)	1997	1985–1997	15	15	–	N.d.	N.d.	N.d.	13.30	50.4
Ringelstein, *et al.* (22)	1983	N.d.	7	7	–	N.d.	58.1	100.00	N.d.	N.d.
Samson, *et al.* (23)	1999	N.d.	5	5	–	N.d.	N.d.	N.d.	N.d.	N.d.
Yan, *et al.* (43)	2019	January 2012 to June 2017	92	38	–	92.10	66.5	92.10	52.60	28.3

N, total number of patients; CEA, carotid endarterectomy; BMT, best medical treatment; FU, follow-up; N.d., not defined; M, months; NASCET, North American Symptomatic Carotid Endarterectomy Trial; ECST, European Carotid Surgery Trial.

upon stroke rate after CEA was recorded (P>0.05; *Figure 5*). However, meta-regression analysis showed a significant reversed association between pooled stroke rate after CAS and publication year (P=0.05; *Figure 6*). A statistically significant and reversed association between pooled stroke rate after BMT and publication year was also recorded (P<0.01; *Figure 7*).

Discussion

Our systematic review and meta-analysis focused on patients with near-occlusion of the ICA. We analyzed 33 eligible studies, including 896 CEA, 603 CAS and 263 BMT patients. We estimated a pooled rate of 1.5% for

CEA, 1.8% for CAS and 8.4% for BMT, highlighting a higher stroke rate for patients who were not offered any carotid intervention. We also found a significant reversed association between pooled stroke rate after CAS or BMT with publication year. The latter may underline the potential improvements in carotid stenting technique, along with optimization and better adherence to medical treatment over time for the subgroup of patients with near-occlusion of the ICA.

The term pseudo occlusion of the ICA was first used by Lippman *et al.* (45), in 1970 and was defined as the presence of a very tight stenosis of the ICA with an extremely narrow residual lumen and a collapsed distal portion induced by hypoperfusion. Angiographically, it resembles a thin

Table 2 Eligible studies on carotid artery stenting (CAS)

Authors	Year	Study period	N	Gender (% males)	Mean age (years)	Symptomatic (%)	EPD use (%)	Pre-dilatation (%)	FU (M)
Akkan, *et al.* (25)	2018	2004–2014	182	72.50	70.2	56.00	60.50	100.00	64
Barker, *et al.* (26)	2010	April 1999 to June 2009	9	66.70	66	100.00	66.70	100.00	12
Choi, *et al.* (27)	2010	2005–2010	48	85.40	69	100.00	N.d.	N.d.	6
Gonzales, *et al.* (28)	2011	March 2000 to March 2009	116	85.30	65.8	90.50	79.30	100.00	36
Kim, *et al.* (42)	2019	January 2010 to December 2018	10	50.00	66.2	100.00	N.d.	N.d.	12
Nikas, *et al.* (29)	2010	October 2006 to August 2007	25	84.00	70.9	80.00	96.00	68.00	12
Ruiz-Salmeron, *et al.* (32)	2013	January 2008 to March 2012	54	83.30	67	74.10	53.70	N.d.	1
Son, *et al.* (34)	2013	January 2010 to July 2012	24	83.30	69.5	75.00	95.70	36.40	17
Spacek, *et al.* (35)	2012	November 2006 to November 2009	19	68.40	72	57.90	84.20	55.60	6
Terada, *et al.* (36)	2006	1991–2003	20	100.00	69.1	85.00	95.00	100.00	25
Razuk, *et al.* (31)	2010	N.d.	13	N.d.	N.d.	61.50	100.00	76.90	12
Sakamoto, *et al.* (33)	2013	April 2008 to September 2012	14	100.00	75.4	71.40	64.30	N.d.	17
Oka, *et al.* (30)	2013	July 2006 to June 2012	15	93.30	70.6	66.70	100.00	N.d.	38
Yan, *et al.* (43)	2019	January 2012 to June 2017	54	92.60	68.1	96.30	100.00	6.50	28.3

N, total number of patients; EPD, embolic protection device; FU, follow-up; N.d., not defined; M, months.

string and several terms have been used so far to describe this entity: "string sign", "pseudoocclusion", "incomplete occlusion", "near occlusion", "subtotal occlusion", "slim sign", "small distal ICA" or "poststenotic narrowing". Four angiographic criteria were suggested by Fox *et al.* (39) to define near total ICA occlusion: (I) reduction in ICA diameter compared with the ipsilateral external carotid artery (ECA), (II) obviously reduced diameter of the ICA compared with the opposite ICA, (III) intracranial collaterals seen as a cross-filling of contralateral vessels or ipsilateral contrast dilution and (IV) delayed cranial arrival of ICA contrast compared with that of the ECA.

Near occlusion of the ICA is a relative rare condition with incidence varying from 0.5% to 2% (46). Ultimately, total ICA occlusion will occur in 40% of the patients within 12 months (40) and cerebrovascular or cardiac events are more frequent in patients with near-total ICA occlusion, compared with patients with carotid artery stenosis (20). Although CEA is the gold standard for significant symptomatic carotid artery stenosis, the treatment management of patients with near ICA occlusion remains

controversial. Furthermore, a near occlusion of the ICA can be easily misdiagnosed and misclassified as complete ICA occlusion. Current ESVS guidelines (6) recommend BMT for this specific group of patients. This recommendation was based on evidence from *post hoc* analyses of the North American Symptomatic Endarterectomy Trial (NASCET), the ECST and the Veterans Affairs trial, which reported that the risk of stroke in patients with near occlusion of ICA was low with medical treatment and there was no surgical benefit (4). However, these trials were performed in the 1990s and this recommendation is based on level III and class C evidence. Furthermore, SVS Guidelines (47) do not discriminate treatment between high grade and near occlusion ICA patients. What is more, some patients with near-total ICA occlusion may progress to total occlusion with BMT alone and this may hamper the hemodynamic reservoir of the brain vascular bed, which might be especially important in case of contralateral ICA occlusion. Our study indicated lower stroke rates after CEA and CAS, compared to medical therapy. This is in line with a recent individual patient meta-analysis (7). Although it finally
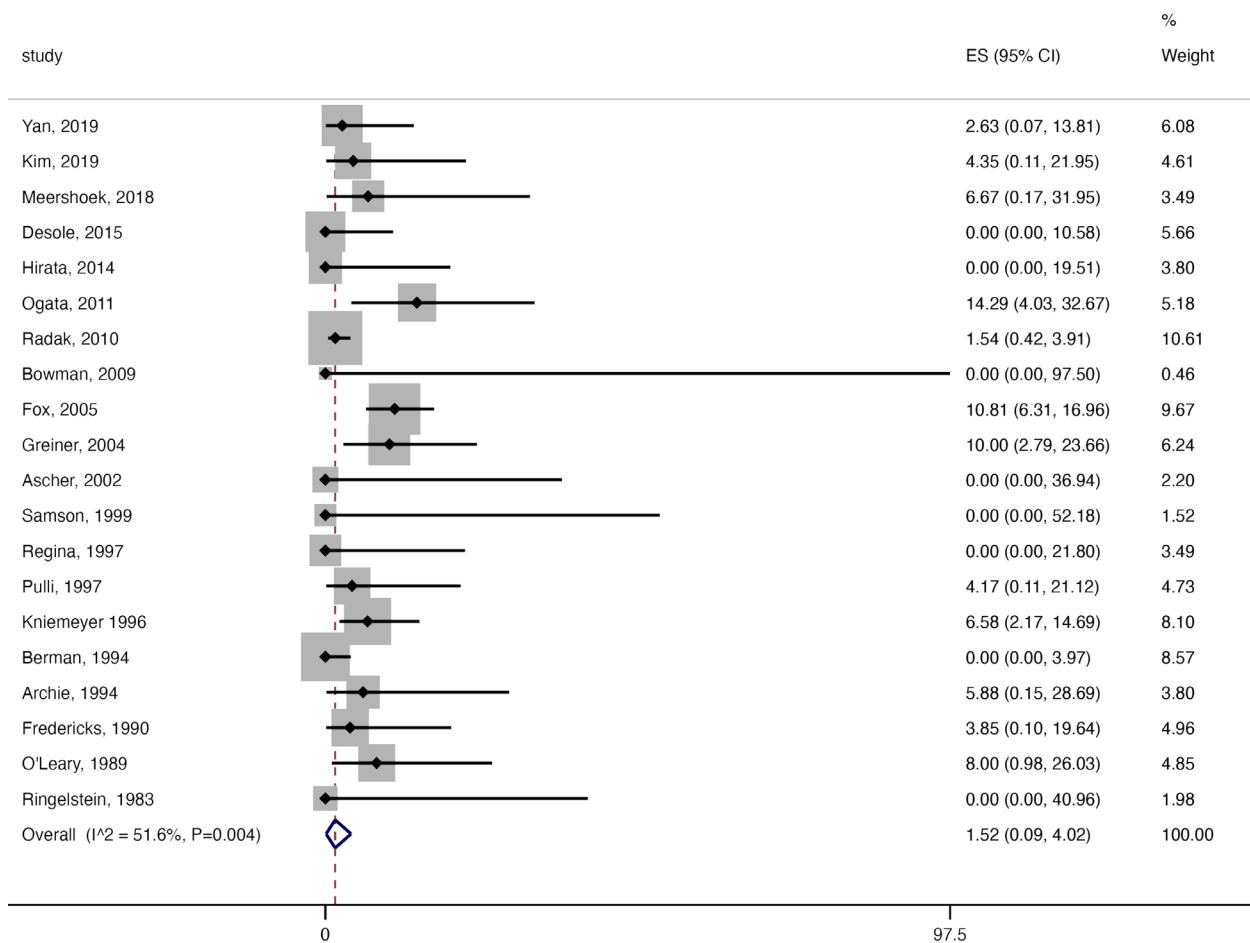
Figure 2 Forest plot presenting the meta-analysis of stroke rates after carotid endarterectomy (CEA). Event rates in the individual studies are presented as squares with 95% confidence intervals (CIs) presented as extending lines. The pooled event rate with its 95% CI is depicted as a diamond. ES, effect estimate.

included data only from 11 studies, after exclusion of 21 eligible studies due to unavailable data, this study concluded 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 near ICA occlusion, which was also supported by others (48-50). Furthermore, the authors of two meta-analyses (7,51) also underlined that consideration should made to include patients with near occlusion in future RCTs. As a result, it is obvious that no consensus on the management of this group of patients has yet been reached and there is need for updated evidence.

The result of our new updated meta-analysis depicts that the stroke rates after CEA have remained relatively stable. However, stroke rates after CAS have decreased, which may correspond to improvements in CAS material, technique

and learning curve. Interestingly, Smout et al. (52), reported that in high volume CAS units, it may take almost 2 years before the stroke/death rates fall below an arbitrary 5% threshold. As a result, currently, near occlusion of the ICA can be successfully treated by endovascular procedures by an experienced team, although wire manipulation in ICA with near occlusion may still increase the risk for ipsilateral stroke. On the other hand, stroke rates after BMT have also substantially decreased over time, which is mainly attributed to great improvements in medical therapy. Apparently, BMT has improved significantly over the past 25 years, due to new antiplatelet and anticoagulation therapy and a high-intensity statin therapy. Taken as a whole, the current optimum medical therapy includes smoking cessation, blood pressure control, diabetes mellitus control, antiplatelet
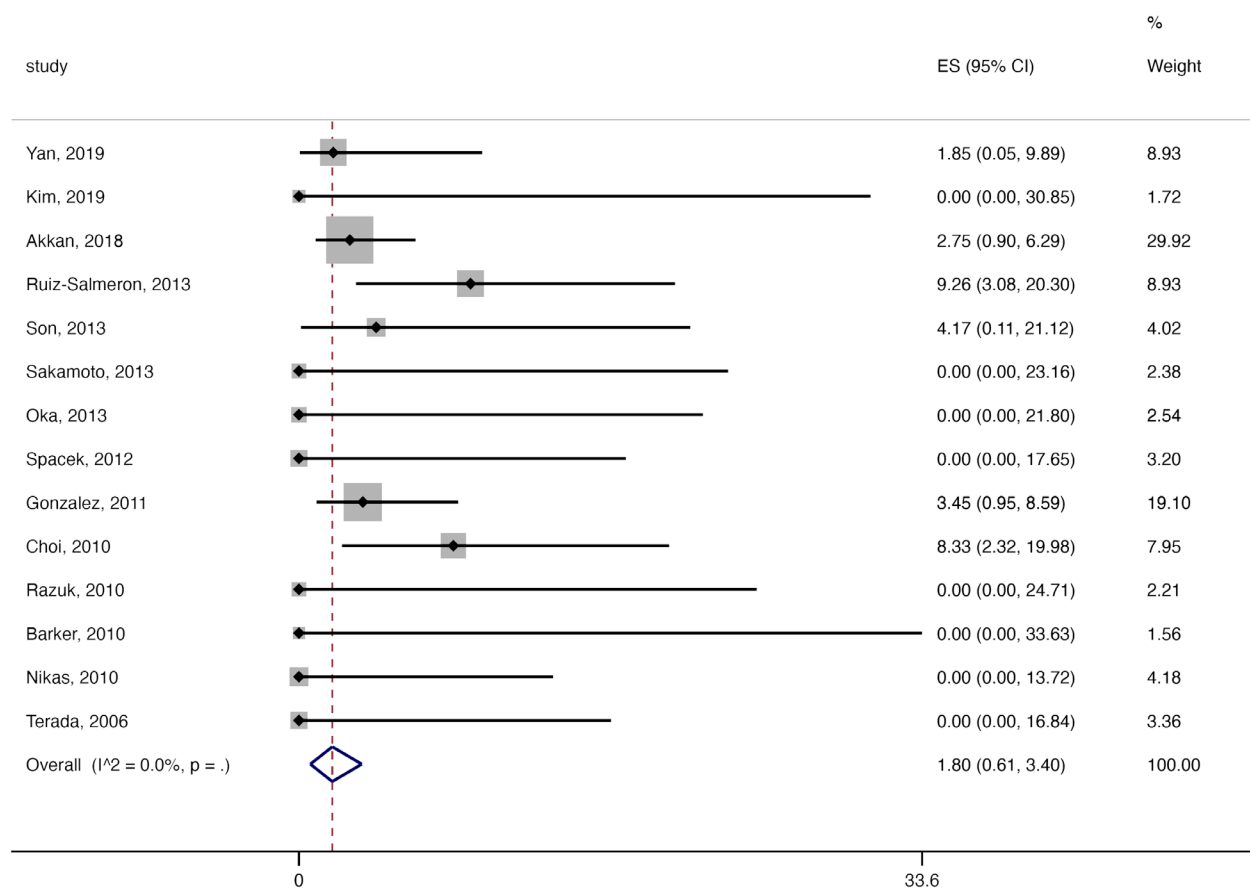
Figure 3 Forest plot presenting the meta-analysis of stroke rates after carotid artery stenting (CAS). Event rates in the individual studies are presented as squares with 95% confidence intervals (CIs) presented as extending lines. The pooled event rate with its 95% CI is depicted as a diamond. ES, effect estimate.

therapy and aggressive statin medication. Lifestyle changes are also very important such as a balanced diet and moderate exercise.

In addition, we need to highlight the difference between the near occlusion of the ICA with or without collapse of the distal ICA. Initially, near occlusion was defined in association with full collapse of the distal ICA, which is often referred as a string sign. Near occlusion with full ICA collapse is well-known with a threadlike lumen while without collapse refers to a smaller calibre of the vessel than the original size but without having this characteristic threadlike appearance (46). Unfortunately, many studies have not separated these two entities as it seems that the possibility of near occlusion without full collapse has not been fully recognised. Johansson *et al.* (46,53) detected that patients with a symptomatic ICA near occlusion with full collapse had a very high risk of ipsilateral ischemic stroke recurrence, whereas those without full collapse

had a low risk. According to this study, the 90-day risk of recurrent stroke was 0% for patients with near-occlusion without full collapse but 43% for patients with near-occlusion with full collapse (53). This result challenges the current guidelines, which suggest BMT without highlighting the difference between near occlusion with or without collapse.

Our study has some limitations, which should be reported. Firstly, differences in design among the eligible studies make heterogeneity among studies an inherent limitation. Secondly, the retrospective nature of the eligible studies, along with the lack of control group should be acknowledged. Diversity in follow-up period and definitions of near total occlusion might have also been reflected upon the pooled effect estimates. Discrimination of data between symptomatic and asymptomatic patients along with near ICA occlusion with and without full collapse was not feasible and as a result no further subgroup analysis was possible.
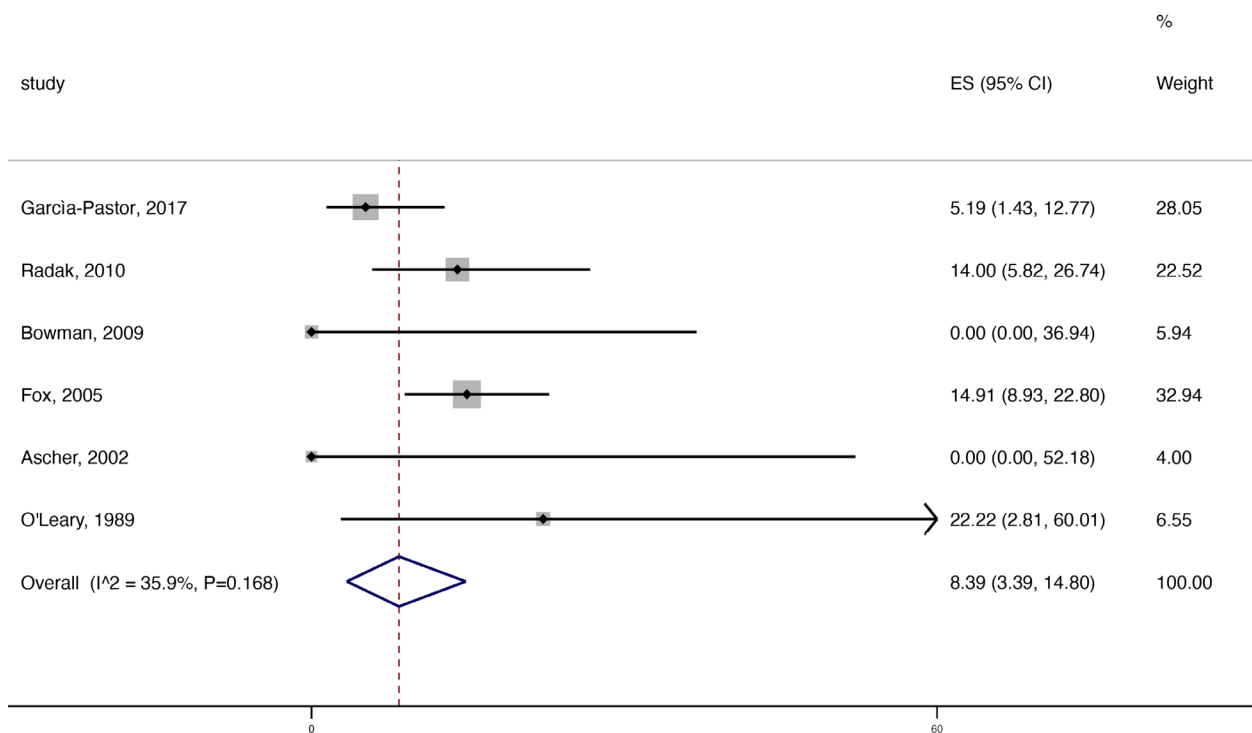
Figure 4 Forest plot presenting the meta-analysis of stroke rates after best medical treatment (BMT). Event rates in the individual studies are presented as squares with 95% confidence intervals (CIs) presented as extending lines. The pooled event rate with its 95% CI is depicted as a diamond. ES, effect estimate.
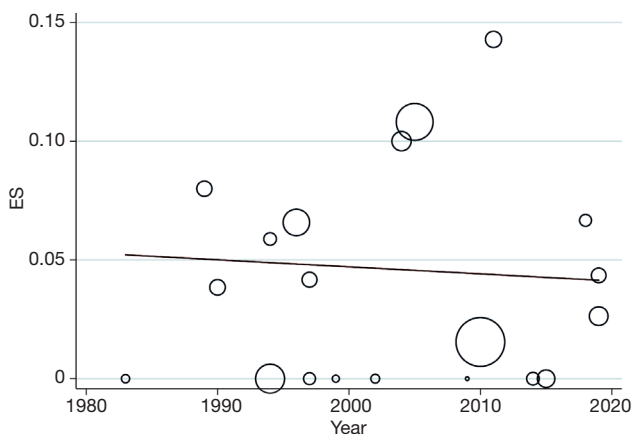

Figure 5 Forest plot presenting the meta-regression of stroke rates after carotid endarterectomy (CEA) with publication year.
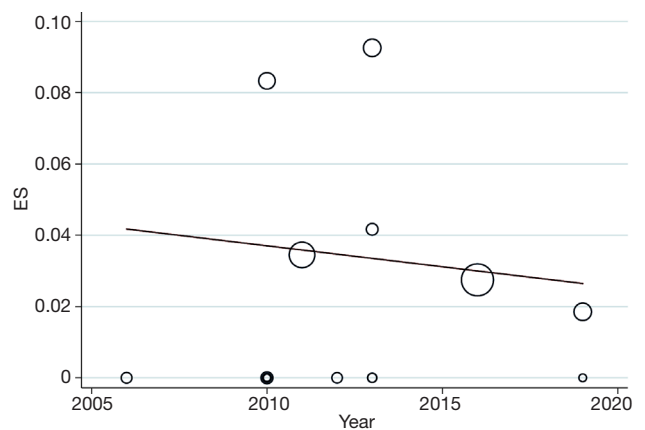

Figure 6 Forest plot presenting the meta-regression of stroke rates after carotid artery stenting (CAS) with publication year.

Conclusions

Near-occlusion of ICA is a rare and easily misdiagnosed condition and the treatment strategy still remains controversial. This updated meta-analysis depicts the high stroke rate for patients who treated only with BMT and

reinforce the opinion that both CEA and CAS seem to be safe and appropriate treatment for this group of patients. A downward trend in the stroke rates over time after CAS and BMT was also discovered. Patients with near-occlusion of ICA, with or without full collapse, need to be included and
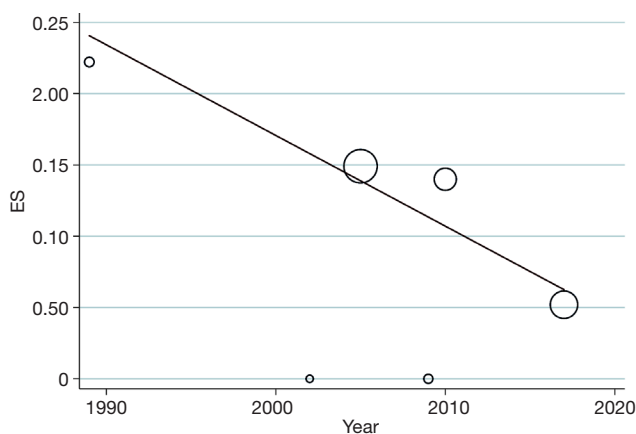
Figure 7 Forest plot presenting the meta-regression of stroke rates after best medical treatment (BMT) with publication year.

investigated in future RCTs.

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Footnote

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