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Reviews

Carotid Endarterectomy versus Carotid Stenting or Best Medical Treatment in Asymptomatic Patients with Significant Carotid Stenosis: A meta-analysis☆

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ABSTRACT

Background: This meta-analysis aimed to evaluate randomized trials (RTs) that compare outcomes among asymptomatic patients with significant carotid stenosis undergoing carotid endarterectomy (CEA) versus carotid stenting (CAS) or best medical treatment (BMT).

Material and methods: The Pubmed, Embase, Scopus and Cochrane Library databases were systematically searched to identify eligible studies. Data were analyzed by using the StatsDirect Statistical software (Version 2.8.0, StatsDirect Ltd). Odds ratios (OR) were used to determine effect size, along with 95% confidence interval (CI). PRISMA guidelines for conducting meta-analyses were utilized.

Results: Overall, 10 RTs including 8771 asymptomatic patients were evaluated. Compared to CAS, 30-day all stroke risk was found to be lower after CEA (pooled OR = 0.56; CI 95% [0.312–0.989]; $P = 0.046$). However, other early and late outcomes were not different between CEA and CAS. Furthermore, 30-day all stroke (pooled OR = 3.43; CI 95% [1.810–6.510]; $P = 0.0002$), death (pooled OR = 4.75; CI 95% [1.548–14.581]; $P = 0.007$) and myocardial infarction (MI) (pooled OR = 9.18; CI 95% [1.668–50.524]; $P = 0.011$) risks were higher after CEA compared to BMT, as expected. Additionally, 30-day all stroke/death and all stroke/death/MI risks were higher after CEA compared to BMT as well. Regarding long-term results, ipsilateral stroke risk was lower after CEA compared to BMT (pooled OR = 0.46; CI 95% [0.361–0.596]; $P < 0.0001$) although death due to stroke risk was not different (pooled OR = 0.57; CI 95% [0.223–1.457]; $P = 0.240$). Unfortunately, no study comparing CAS to BMT was found.

Conclusions: CEA is associated with a lower early all stroke risk compared to CAS although other early or late outcomes did not show any difference between the two methods. Additionally, CEA seems to have a benefit over BMT against long-term ipsilateral stroke, although early outcomes are worse after CEA. No studies are available comparing CAS to BMT alone.

Contents

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1. Introduction

Several therapeutic strategies have been recommended for patients with significant asymptomatic carotid stenosis, including carotid endarterectomy (CEA), carotid artery stenting (CAS) and best medical treatment (BMT). Major randomized trials (RTs) of the 1990s have found a small benefit favoring the open surgery over BMT alone in such patients [1.2], although most trials comparing CEA with CAS have reported significant differences regarding perioperative outcomes, mainly in symptomatic patients. [3,4] However, comparative data remain controversial for asymptomatic patients and current guidelines on proper management are still inconclusive. [5]

Regarding the comparison between CEA and CAS, the majority of recently published guidelines prefer open repair for patients with significant asymptomatic stenosis and a low perioperative surgical risk. [5] However, there is still uncertainty considering the safety and efficacy of the endovascular method, because of limited trial-based evidence data on such patients. [5] Additionally, pooled data comparing CEA with BMT are still lacking although there is growing evidence from non-randomized studies that improvements in BMT during the last decade may have reduced the annual risk of stroke in asymptomatic patients to the extent that no further intervention could be of any benefit. [6]

Therefore, aim of this review is to collect and analyze all RTs comparing CEA to CAS or BMT for asymptomatic patients with significant stenosis as far as major outcomes are concerned.

2. Materials and methods

2.1. Data sources and search

We systematically searched Pubmed, Embase, Scopus and Cochrane Library (during the period June–July 2017) for RTs published online prior to July 2017 comparing CEA to CAS or BMT among patients with significant asymptomatic carotid stenosis. This review was conducted according to established methods for systematic reviews in cardiovascular medicine (PRISMA criteria) [7]. The following medical subject terms were utilized for the online search: (i) 'randomized trial' plus (ii) 'asymptomatic carotid stenosis' plus(iii) 'carotid endarterectomy' or 'carotid angioplasty ± stenting' or 'best medical treatment'. In addition to searching databases, reference lists of all included studies, meta-analyses and reviews were manually evaluated, including unpublished data. Only studies published in English were included in this review. References from eligible articles or textbooks were also reviewed to identify further potential sources.

2.2. Data extraction – outcomes – definitions

Three authors independently completed data extraction after following search criteria and quality assessment. Disagreements were resolved by consensus or after review by the senior author of the study, when necessary. Data was obtained from tables, graphs and text as well. When data were presented in percentage, the absolute values were calculated. For each study, the following data were collected: first author, year of publication, country of publication, number of patients randomized, number of asymptomatic patients, duration of follow-up, basic demographics/comorbidities (sex, age, degree of stenosis, vascular risk factors), medications used after intervention, technique used for CEA/CAS, evaluation method and rate of early (30-day all stroke, death, myocardial infarction (MI), all stroke/death and all stroke/death/MI) and late(after 30-days ipsilateral stroke, death due to stroke) major outcomes.

Early outcomes were defined as outcomes recorded during the first 30 postoperative days for patients undergoing CEA or CAS, and during the corresponding 30-day period (as defined by each separate trial) for patients treated with BMT. Late outcomes were defined as outcomes recorded during follow-up, after the first 30-day postoperative period. Significant asymptomatic carotid stenosis was defined as the stenosis indicated for treatment according to the criteria provided by each separate trial. All stroke rate was defined as the rate for all types of stroke in total, when reported separately (fatal or non-fatal, disabling or non-disabling).

2.3. Quality assessment

Three authors independently reviewed study eligibility and quality. Disagreements were resolved by consensus or after review by the senior author of the study, when necessary. The quality of each study was assessed using well established criteria for randomized studies [7], specifically evaluating: collection of data, aim of the studies, incomplete outcome data, statistical analysis and other sources of bias. Quality of each study was evaluated and reported as high, medium or low, based on design and methodology of study according to the aforementioned criteria [7]. When asymptomatic patients represented a subgroup of a given RT, quality for the trial overall was assessed.

2.4. Study selection – exclusion criteria

Studies included in this meta-analysis met the following criteria: RTs comparing at least one early (30-day) major outcome (30-day all stroke, death, myocardial infarction (MI), all stroke/death and all stroke/death/MI) or one late (after 30 days) major outcome (after 30-days ipsilateral stroke, death due to stroke) between asymptomatic patients with significant carotid stenosis undergoing CEA and patients undergoing CAS, or treated with BMT.

Exclusion criteria included: (i) types of publication other than RTs such as non-randomized clinical studies, reviews, letters, meta-analyses, case reports/series (<10 patients) or editorials, (ii) RTs randomizing <50 patients in total (combined when mixed population), (iii) studies not referring to humans, (iv) abstracts from conferences not published as full articles, (v) studies published in a language other than English, and (vi) RTs comparing the incidence of major early or late outcomes among symptomatic only patients. RTs in which the randomized groups did not have an equal opportunity to receive anticoagulation or antiplatelet therapies in the post-operative period were excluded. No exclusion was made based on the use of embolic protection devices (EPDs). Early terminated trials were not excluded, given that they provided adequate data for analysis for the already randomized cohort of patients. When early and late outcomes of one trial were reported in separate publications, both studies were combined and evaluated to extract the proper data for analysis, without any duplication.

After applying the selection/exclusion criteria, 10RTs (6 trials comparing CEA to CAS, 3 trials comparing CEA to BMT, and 1 trial comparing

CEA to CAS or BMT) [1–4,8–18] were identified as appropriate for analysis and overall 1656 studies were excluded (Fig. 1). All included trials were published between 1993 and 2016 (Table 1).

2.5. Statistical analysis

Meta-analysis was carried out utilizing the StatsDirect Statistical software (Version 2.8.0, StatsDirect Ltd). Odds ratios (OR) were used to determine effect size, along with 95% confidence interval (CI). Inter-study variations and heterogeneities were estimated using Q-statistic with $P < 0.05$ indicating a statistically significant heterogeneity. The present meta-analysis also quantified the effect of heterogeneity by using the I^2 index (range, 0–100%), which represents the proportion of inter-study variability attributed to heterogeneity, rather than to chance. The effect size was calculated based on random effects for sensitivity analysis. Chi-square test with Yate's correction was utilized for comparing categorical variables between the two groups of patients. Statistical analysis for comparison between groups was conducted only when at least two studies provided adequate data. The *P* values were two-sided, and $P < 0.05$ was considered to indicate a statistically significant difference. All statistical analyses were conducted using the absolute values and not percentages. Risk of bias was also assessed applying the Habbord-Egger test, and generating funnel plots. Finally, all event rates in the included trials are reported on an intent-to-treat basis.

3. Results

In this meta-analysis, overall 8771 asymptomatic patients (total number of patients included in the trials = 10,764) were evaluated. In the 7 trials comparing CEA to CAS [3,4,8–12,15–18], overall 3435 asymptomatic patients (CEA: $n = 1348$ and CAS: $n = 2087$) were included, and in the 4 trials comparing CEA to BMT [1,2,10,13,14], overall 5539 asymptomatic patients (CEA: $n = 2799$ and BMT: $n = 2740$) were included. None of the trials evaluated was found to be of low quality, according to aforementioned criteria. Table 1 lists basic characteristics of all included trials, and Table 2 compares epidemiologic data among patient groups for all RTs. In trials comparing CEA to CAS, most of the risk factors did not differ between the two groups, except for

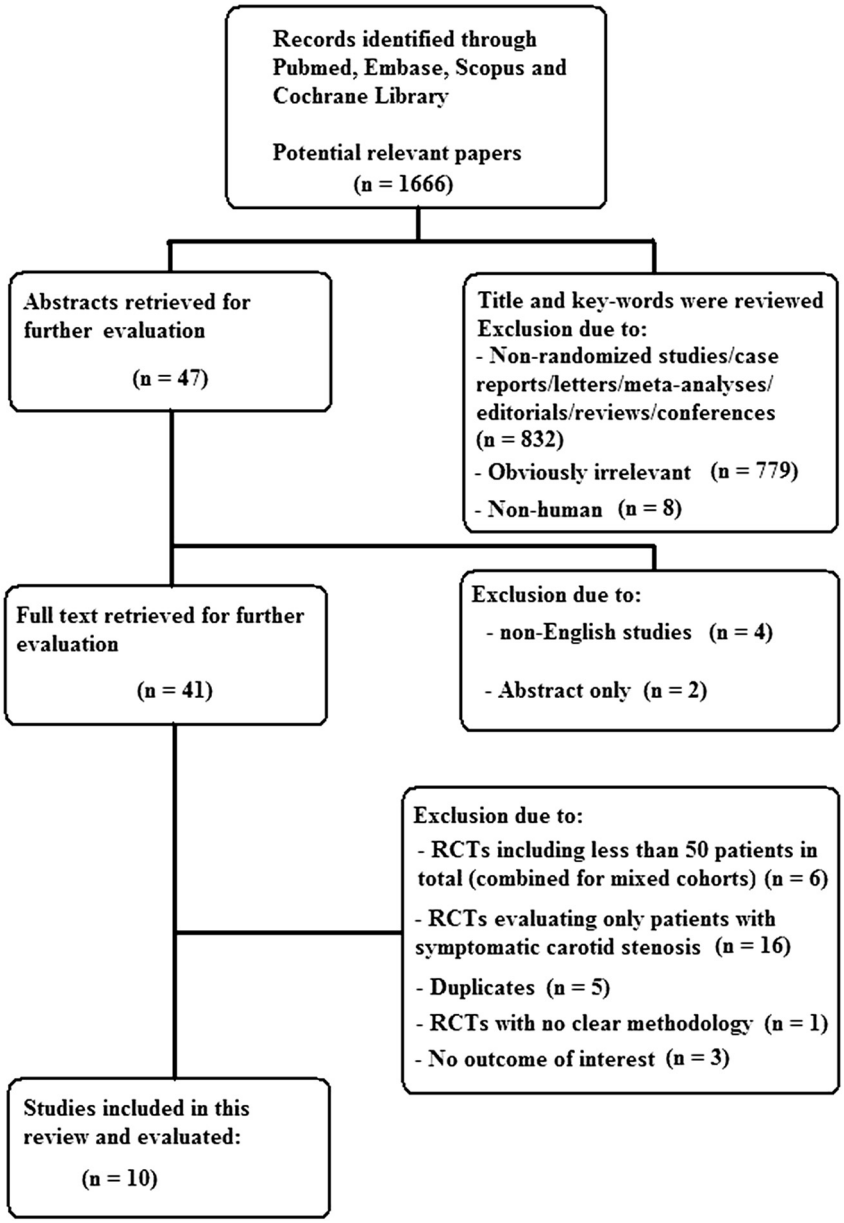

Fig. 1. Study selection - Flow chart of study selection (RTs, randomized controlled trials).

Table 1
Basic characteristics of included studies.

Study, Year	Country	Patients (Asymptomatic/total)	Asymptomatic (CEA/CAS) or (CEA/BMT)	Criteria of asymptomatic stenosis	Follow-up time (maximum)	Quality of trial
CEA vs CAS						
CREST [3,18], 2010	USA, Canada	1181/2502	587/594	≥60% DSA, ≥70% DUS or ≥80% CTA/MRA	10 years	High
Brooks et al. [8,15], 2004	USA	85/85	42/43	≥80% DSA	10 years	Medium
SAPPHIRE [4,16], 2004	USA	237/334	120/117	>80% US	3 years	High
CAVATAS [9,17], 2001	Europe, Canada Australia	16/504	7/9	US, CTA, MRA or DSA No threshold reported in the study	10 years	High
SPACE-2 [10], 2016	Germany	400/513	203/197	70–99% U/S [ECST criteria]	Early terminated (initial goal: 5 years)	Medium
ACT-I [11], 2016	USA	1453/1453	364/1089	70–99% U/S or DSA	5 years	High
Kuliha [12], 2015	USA	63/150	25/38	>70% U/S and CTA	30 days	Medium
CEA vs BMT						
ACST-1 [2,14], 2004	USA, Canada, Brazil, Tunisia, Europe	3120/3120	1560/1560	≥60% U/S	5–10 years	High
VACSG [13], 1993	USA	444/444	211/233	>50% DSA	96 months; 48 months (mean)	Medium
ACAS [1], 1995	USA	1659/1659	825/834	≥60% CEA: U/S + DSA BMT: U/S	5 years; 2.7 years (mean)	High
SPACE-2 [10], 2016	Germany	316/513	203/113	70–99% U/S [ECST criteria]	Early terminated (initial goal: 5 years)	Medium

CEA, carotid endarterectomy; CAS, carotid angioplasty and stenting; BMT, best medical treatment; DSA, digital subtraction angiography; U/S, ultrasound; CTA, computed tomography arteriography; USA, United States of America; MRA, magnetic resonance arteriography; ECST, European Carotid Surgery Trial; CREST, Carotid Revascularization Endarterectomy versus Stenting Trial; SAPPHIRE, Stenting and Angioplasty with Protection in Patients at HIgh Risk for Endarterectomy; CAVATAS, Carotid and Vertebral Artery Transluminal Angioplasty Study; SPACE-2, Stent-Protected Angioplasty Versus Carotid Endarterectomy-2; ACT-1, Asymptomatic Carotid Trial-1; ACST-1, Asymptomatic Carotid Surgery Trial-1; VACSG, Veterans Affairs Cooperative Study Group; ACAS, Asymptomatic Carotid Atherosclerosis Study.

Study, Year	Exclusion criteria	Medical treatment after procedure	Technique	Major Endpoints criteria
CEA vs CAS				
CREST [3,18], 2010	Stroke severe to assess endpoints, chronic AF, paroxysmal AF within 6 months or needing anticoagulants, MI within 30 days or unstable angina	Aspirin 325 mg qd/bid plus clopidogrel 75 mg qd or ticlopidine 250 mg bid for 30 days at least (after CAS) Aspirin 325 mg or ticlopidin 250 mg bid, clopidogrel 75 mg qd, aspirin 81 mg qd or aspirin plus dipyridamole bid for one year at least (after CEA)	CEA: Selective use of shunt (57%) and patch (62%) CAS: RX Acculink stent plus RX Accunet embolic-protection device when possible	Stroke: neurologic evaluation (0, 18, 48 h, one month, every 6 months), NIHSS, modified Ranking scale, TIA-Stroke Questionnaire MI: Enzymes (0, 6–8 h), ECG (0, 6–48 h, one month)
Brooks et al. [8,15], 2004	Allergy/sensitivity to aspirin, heparin or clopidogrel History of bleeding diathesis or coagulopathy or cardiac arrhythmias	Aspirin 325 mg plus clopidogrel 75 mg qd (both CAS and CEA)	CAS: predilation, no protection device, either 10X20mm Wallstent or a 10X38mm Dynalink stent CEA: not reported	Stroke: neurological evaluation before and after treatment (not specified), Rankin and Barthel scores MI: not reported
SAPPHIRE [4,16], 2004	Ischemic stroke within previous 48 h, presence of intraluminal thrombus, total occlusion of target vessel, vascular disease precluding use of catheter-based techniques, intracranial aneurysm >9 mm in diameter, need for more than two stents, history of bleeding disorder, percutaneous or surgical intervention planned within next 30 days, life expectancy <1 year, ostial lesion of common carotid artery or brachiocephalic artery	Aspirin 81/325 mg qd indefinetily (both groups) Plus clopidogrel 75 mg qd for 2–4 weeks (CAS)	CEA: customary technique for each surgeon CAS: self-expandable nitinol stent (Smart or Precise, Cordis®) with an emboli-protection device (Angioguard or Angioguard XP, Cordis®).	Stroke: NIHSS, Barthel index and Rankin scale within 24 h and daily until discharge, and at follow-up visits. CT imaging for deficits >48 h MI: CPK > 2 times the normal limit, and CPK-MB levels increase.
CAVATAS [9,17], 2001	unsuitable for surgery because of medical or surgical risk factors, patients unwilling to undergo either procedure, were unable to give informed consent, or if they had a disabling stroke with no useful recovery of function within the region supplied by the treatable artery, angiography showing thrombus in the carotid artery, severe intracranial carotid artery stenosis beyond the skull base, or a stenosis unsuitable for endovascular treatment	aspirin (minimum dose 150 mg daily) or an alternative antiplatelet + heparin for 24 h, only antiplatelet for the rest of follow-up	CAS: balloon angioplasty only (before 1994) plus stenting (from 1994) Stents: Wallstent® (Schneider, USA), Streker® (Medi-Tech, USA), and Palmaz® (Johnson and Johnson, USA) CEA: not reported	Stroke: modified Rankin grade (score worse than 3) MI: not reported

SPACE-2 [10], 2016	nonatherosclerotic stenosis, stenosis following radiotherapy, previous CEA/CAS in the treated artery, additional higher grade intracranial or intrathoracic stenosis, intracranial bleeding within the last 90 days, known intracranial angioma/aneurysm, pre-existing disability (modified Rankin scale 41), contraindications for heparin, aspirin, clopidogrel or contrast media, indication for anticoagulation, life expectancy of ≥5 years, recent history of a malignancy, major surgery planned within 8 weeks after randomization, no double enrollment	CEA: Aspirin or clopidogrel (not specified dosage) CAS: Aspirin plus clopidogrel (not specified dosage) for at least 6 weeks	CAS: selective use of cerebral protecting devices or stents CEA: not reported	Stroke: NIHSS, modified Rankin score MI: ECG
ACT-I [11], 2016	Stroke or TIA within 180 days prior to randomization, participation to another trial, inability to understand or cooperate, intracranial hemorrhage within 1 year prior to procedure, dementia or neurological illness, prior reaction to anesthesia or contrast media, intolerance to antiplatelets, low hematocrit or platelet count, bleeding diathesis or coagulopathy, history of GI bleeding, MI within previous 30 days, estimated survival <3 years, high-risk surgical candidate, non-surgical candidate for CEA, severe vascular disease, intraluminal thrombus, excessive calcification, occlusion or string sign ipsilaterally, tandem lesions >60%, other devices required.	All patients: aspirin 325 mg qd CAS: plus clopidogrel 75 mg qd for 30 days	Closed-cell, nitinol stents with a tapering diameter (Xact, Abbott Vascular) plus distal embolic protection (Emboshield, Emboshield Pro, or Emboshield NAV6, Abbott Vascular). CEA: shunt or patch at the surgeon's discretion	Stroke: NIHSS, Modified Rankin score MI: not specified
Kuliha [12], 2015	Not reported	CEA: aspirin 100 mg qd plus clopidogrel 75 mg qd (for 5 days only) CAS: aspirin 100 mg qd	CEA: shunt according to protocol (not specified) CAS: cerebral FilterWire EZ protection device, stent and strategy at the discretion of the surgeon	Stroke: NIHSS, modified Rankin score, MRI, MMSE score MI: Troponin T > 2fold the normal limit or ECG changes
CEA vs BMT				
ACST-1 [2,14], 2004	Previous ipsilateral CEA, poor surgical risk, probable cardiac source of emboli, any life-threatening condition other than carotid stenosis	Both groups: antiplatelet, antihypertensive, lipid-lowering therapy (not specified)	Shunting: optional Anesthesia: optional	Stroke: modified Rankin score, CT MI: not reported
VACSG [13], 1993	Previous cerebral infarction, previous CEA with restenosis, previous extracranial to intracranial bypass, high surgical risk, long-term anticoagulation, intolerance of aspirin or long-term aspirin therapy at high dose, life expectancy <5 years, surgically inaccessible lesion, noncompliance, refusal to participate.	Both arms: high-dose aspirin (initially 650 mg bid)	CEA: at surgeon's discretion	Stroke/TIA: neurological evaluation according to definitions established by the Advisory Council of the National Institutes of Neurological and Communicative Disorders and Stroke. MI: not specified
ACAS [1], 1995	cerebrovascular events in the distribution of the study carotid artery or in that of the vertebrobasilar arterial system; symptoms referable to the contralateral cerebral hemisphere within the previous 45 days; contraindication to aspirin therapy; a disorder that could seriously complicate surgery; or a condition that could prevent continuing participation or was likely to produce disability or death within 5 years.	Both groups: aspirin 325 mg qd Plus antihypertensive, lipid-lowering, antidiabetic therapy, ethanol and tobacco cessation.	Surgical technique and anesthesia: at surgeon's discretion	Stroke: deficit >24 h, Endpoint Review Committee criteria
SPACE-2 [10], 2016	*as above	BMT: risk factors' treatment, lipid-lowering and antiplatelet treatment (not specified) CEA: *as above	*as above	*as above

TIA, transient ischemic attack; MI, myocardial infarction; ECG, electrocardiogram; CPK-MB, Creatine Phosphokinase-MB; CEA, carotid endarterectomy; CAS, carotid angioplasty and stenting; BMT, best medical treatment; CT, computed tomography; USA, United States of America; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; MMSE, Mini-Mental State Examination, bid: twice a day; qd, once a day.
CREST, Carotid Revascularization Endarterectomy versus Stenting Trial; SAPPHIRE, Stenting and Angioplasty with Protection in Patients at HIgh Risk for Endarterectomy; CAVATAS, Carotid and Vertebral Artery Transluminal Angioplasty Study; SPACE-2, Stent-Protected Angioplasty Versus Carotid Endarterectomy-2; ACT-1, Asymptomatic Carotid Trial-1; ACST-1, Asymptomatic Carotid Surgery Trial-1; VACSG, Veterans Affairs Cooperative Study Group; ACAS, Asymptomatic Carotid Atherosclerosis Study.

Table 2
Baseline characteristics of patients.

CEA vs CAS																	
Trials	CREST [3,18]		ACT-1 [11]		SAPPHIRE [4,16]		Brooks et al. [8,15]		Kuliha et al. [12]		SPACE-2 [10]		CAVATAS [9,17]		Total		*P* value
	CEA	CAS	CEA	CAS	CEA	CAS	CEA	CAS	CEA	CAS	CEA	CAS	CEA	CAS	CEA	CAS	
Randomized patients (n)	587	594	364	1089	120	117	42	43	25	38	203	197	7	9	1348	2087	
Age, mean (SD)	69.6 (9.7)	69.0 (8.0)	67.9 (6.9)	67.7 (7.0)	NR	NR	69.9	66.6	NR	NR	70.7 (7.0)	69.8 (8.0)	NR	NR	69.3	68.3	NS
Male gender	396	379	207	667	NR	NR	NR	NR	NR	NR	151	143	NR	NR	754	1189	NS
HT	516	524	326	987	NR	NR	41	35	NR	NR	177	177	NR	NR	1060	1723	NS
DM	198	194	118	388	NR	NR	5	7	NR	NR	51	59	NR	NR	372	648	NS
Smoking (past or current)	130	155	71	266	NR	NR	37	40	NR	NR	134	130	NR	NR	372	591	NS
Dyslipidemia	535	533	320	980	NR	NR	8	9	NR	NR	155	158	NR	NR	1018	1680	NS
CAD	NR	NR	186	581	NR	NR	20	35	NR	NR	69	72	NR	NR	275	688	0.007
Ipsilateral stenosis ≥ 70%	539	551	364	1089	0	0	42	43	25	38	203	197	NR	NR	1173	1918	0.001
Contralateral carotid stenosis	NR	NR	162	441	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	162	441	–

CEA vs BMT											
Trials	ACST-1 [2,14]		ACAS [1]		SPACE-2 [10]		VACSG [13]		Total		*P* value
	CEA	BMT	CEA	BMT	CEA	BMT	CEA	BMT	CEA	BMT	
Randomized patients (n)	1560	1560`	825	834	203	113	211	233	2799	2740	
Age, mean (SD)	NR	NR	NR	NR	70.7 (7.0)	68 (7.0)	64 (6.8)	64.7 (6.7)	67.5 (6.8)	66.7 (6.8)	NS
Male gender	NR	NR	545	550	151	87	NR	NR	696	637	NS
HT	NR	NR	528	534	177	102	63	64	768	700	NS
DM	NR	NR	206	175	51	40	30	27	287	242	NS
Smoking (past or current)	NR	NR	231	200	134	91	95	91	460	382	0.015
Dyslipidemia	NR	NR	NR	NR	155	91	NR	NR	155	91	–
CAD	NR	NR	569	576	69	40	58	50	696	666	NS
Ipsilateral stenosis ≥ 70%	NR	NR	NR	NR	203	113	NR	NR	203	113	–
Contralateral carotid stenosis	NR	NR	NR	NR	NR	NR	NR	NR	–	–	–

CEA, carotid endarterectomy; CAS, carotid angioplasty and stenting; BMT, best medical treatment; NR, not reported; NS, non significant; SD, standard deviation; DM, diabetes mellitus; CAD, coronary artery disease; HT, hypertension.
ACST-1, Asymptomatic Carotid Surgery Trial-1; VACSG, Veterans Affairs Cooperative Study Group; ACAS, Asymptomatic Carotid Atherosclerosis Study.
CREST, Carotid Revascularization Endarterectomy versus Stenting Trial; SAPPHIRE, Stenting and Angioplasty with Protection in Patients at HIgh Risk for Endarterectomy; CAVATAS, Carotid and Vertebral Artery Transluminal Angioplasty Study; SPACE-2, Stent-Protected Angioplasty Versus Carotid Endarterectomy-2; ACT-1, Asymptomatic Carotid Trial-1.

coronary artery disease (CAD) (CEA: 45.2% vs CAS: 51.8%; $P = 0.007$) and carotid artery stenosis ≥70% (CEA: 87.5% vs CAS: 92.3%; $P = 0.001$). Additionally, in trials comparing CEA to BMT, only smoking (CEA: 37.1% vs CAS: 32.3%; $P = 0.015$) was different between the two groups.

Table 3 lists early and late outcomes evaluated in this meta-analysis for all trials. In trials comparing CEA to CAS, 30-day all stroke risk was found to be marginally lower after CEA compared to CAS (pooled OR = 0.56; CI 95% [0.312–0.989]; $P = 0.046$). However, 30-day MI (pooled OR = 1.87; CI 95% [0.859–4.072]; $P = 0.115$) and death (pooled OR could not be calculated due to very small number of events) risks were found to be no different between the two methods. Additionally, 30-day all stroke/death (pooled OR = 0.59; CI 95% [0.335–1.026]; $P = 0.062$) and all stroke/death/MI risks (pooled OR = 1.029; CI 95% [0.627–1.688]; $P = 0.910$) were also not different between CEA and CAS. Regarding the follow-up (maximum duration = 10 years),

Table 3
Early and late outcomes in asymptomatic patients with carotid artery stenosis.

Trials	30-day outcomes (postoperative)					Outcomes during follow-up (after 30 days)	
	Any stroke	Death	MI	Any Stroke/Death	Any Stroke/Death/MI	Ipsilateral Stroke	Death due to stroke
CEA vs CAS							
CREST [3,18] (587/594)	8/15	0/0	13/7	8/15	21/22	20/21	NR
Brooks et al. [8,15] (42/43)	0/0	0/0	0/0	0/0	0/0	0/6	1/5
SAPPHIRE [4,16] (120/117)	NR	NR	NR	NR	12/6	9/11	4/3
CAVATAS [9,17] (7/9)	0/0	0/0	0/0	0/0	0/0	NR	NR
SPACE-2 [10] (203/197)	4/5	0/0	NR	4/5	NR	NR	NR
ACT-1 [11] (364/1089)	5/30	1/1	3/5	6/31	9/36	42/34	NR
Kuliha et al. [12] (25/38)	0/0	0/0	0/0	0/0	0/0	NR	NR
Total (1348/2087)	17/50	1/1	16/12	18/51	42/64	71/72	5/8
CEA vs BMT							
VACSG [13] (211/233)	5/1	4/1	4/0	9/2	13/2	18/29	¼
ACAS [1] (825/834)	10/2	1/1	1/0	11/3	12/3	41/83	6/9
SPACE-2 [10] (203/113)	4/0	0/0	NR	4/0	NR	NR	NR
ACST-1 [2,14] (1560/1560)	25/9	15/2	10/0	40/11	50/11	38/92	NR
Total (2799/2740)	44/12	20/4	15/0	64/16	75/16	97/204	7/13

MI, myocardial infarction; CEA, carotid endarterectomy; CAS, carotid angioplasty and stenting; BMT, best medical treatment, NR, not reported; NS, non significant.
CREST, Carotid Revascularization Endarterectomy versus Stenting Trial; SAPPHIRE, Stenting and Angioplasty with Protection in Patients at HIgh Risk for Endarterectomy; CAVATAS, Carotid and Vertebral Artery Transluminal Angioplasty Study; SPACE-2, Stent-Protected Angioplasty Versus Carotid Endarterectomy-2; ACT-1, Asymptomatic Carotid Trial-1; ACST-1, Asymptomatic Carotid Surgery Trial-1; VACSG, Veterans Affairs Cooperative Study Group; ACAS, Asymptomatic Carotid Atherosclerosis Study.

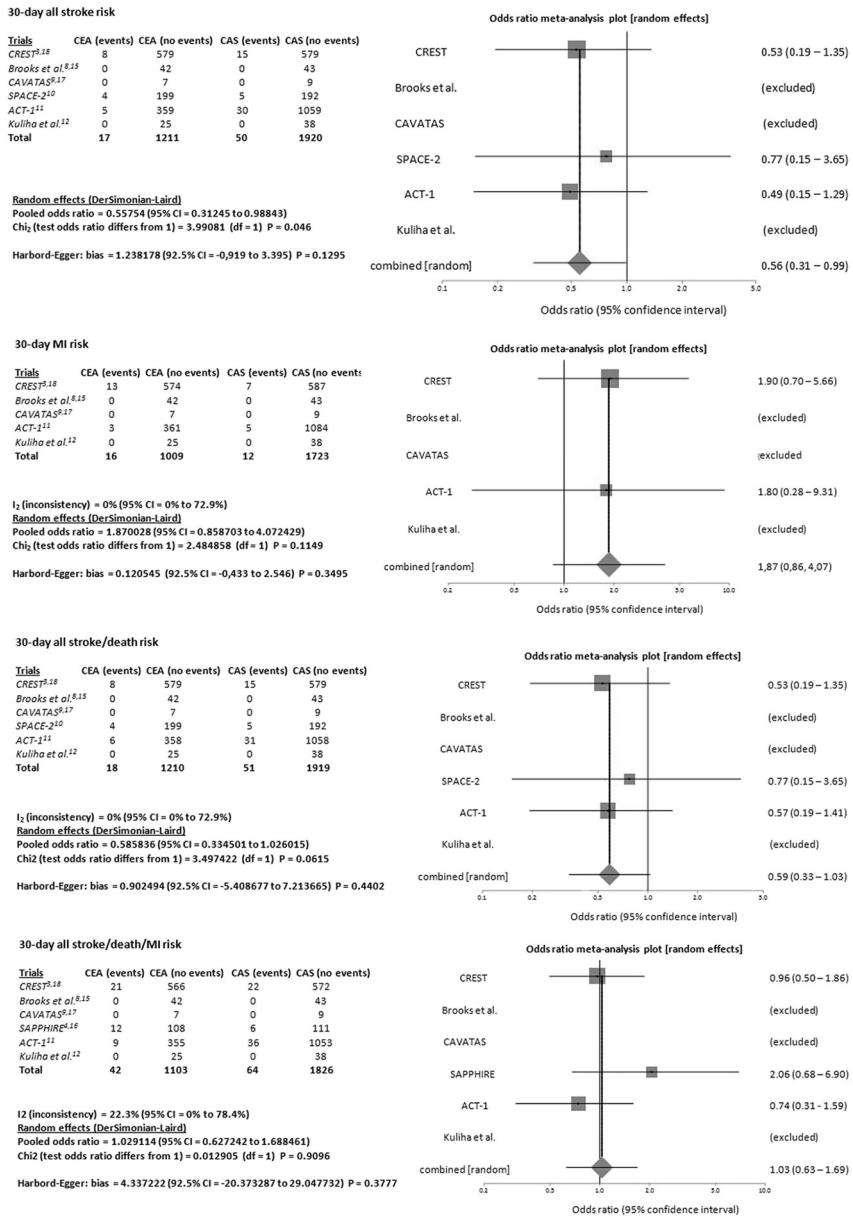

Fig. 2. Early outcomes in asymptomatic patients undergoing CEA versus CAS (CEA, carotid endarterectomy; CAS, carotid angioplasty and stenting).

ipsilateral stroke (pooled OR = 1.071; CI 95% [0.332–3.452]; $P = 0.909$) and death due to stroke (pooled OR = 0.33; CI 95% [0.031–3.634]; $P = 0.367$) risks were not different between the two methods as well (Figs. 2 and 4).

Regarding trials comparing CEA to BMT, 30-day all stroke (pooled OR = 3.43; CI 95% [1.810–6.510]; $P = 0.0002$), death (pooled OR = 4.75; CI 95% [1.548–14.581]; $P = 0.007$) and MI (pooled OR = 9.18; CI 95% [1.668–50.524]; $P = 0.011$) risks were all higher after surgery compared to conservative treatment. Concerning the combined risks, 30-day all stroke/death (pooled OR = 3.94; CI 95% [2.278–6.809]; $P < 0.0001$) and all stroke/death/MI (pooled OR = 4.85; CI 95% [2.817–8.355]; $P < 0.0001$) risks were higher after surgery as well. Regarding long-term results (maximum duration 10 years), ipsilateral stroke risk was lower after surgery compared to BMT (pooled OR = 0.46; CI 95% [0.361–0.596]; $P < 0.0001$) although death due to stroke risk was not different (pooled OR = 0.57; CI 95% [0.223–1.457]; $P = 0.240$) (Figs. 3 and 4).

Heterogeneity was low for all statistical analysis and Harbord-Egger tests showed low bias risks for all analyses except for the long-term death due to stroke risk (only two trials analyzed). Regarding potential risk factors for major outcomes, data were scarce to conduct further multivariate analysis in order to calculate potential overall predictors. Only three trials reported potential risk factors, namely one trial comparing CEA to CAS and two trials comparing CEA to BMT. The VSCSG trial [13] reports that history of contralateral symptomatic events (RR = 1.17; CI 95% [0.67–1.84]) and no history of any symptomatic event (RR = 0.84; CI 95% [0.59–1.18]) had no effect on outcomes. In the ACAS trial [1], the authors found that there was no difference among gender, age and degree of stenosis as far as primary outcomes were concerned ($P > 0.05$). Finally, in the ACST-1 trial [2,14], the effect of gender, age and initial carotid stenosis were evaluated, with male gender being the most important predictor of benefit for CEA (Risk reduction: 8.21% (95% CI 5.64–10.78); $P < 0.0001$).

4. Discussion

The present review confirmed that CEA is associated with a lower early all-stroke risk compared to CAS in asymptomatic patients with

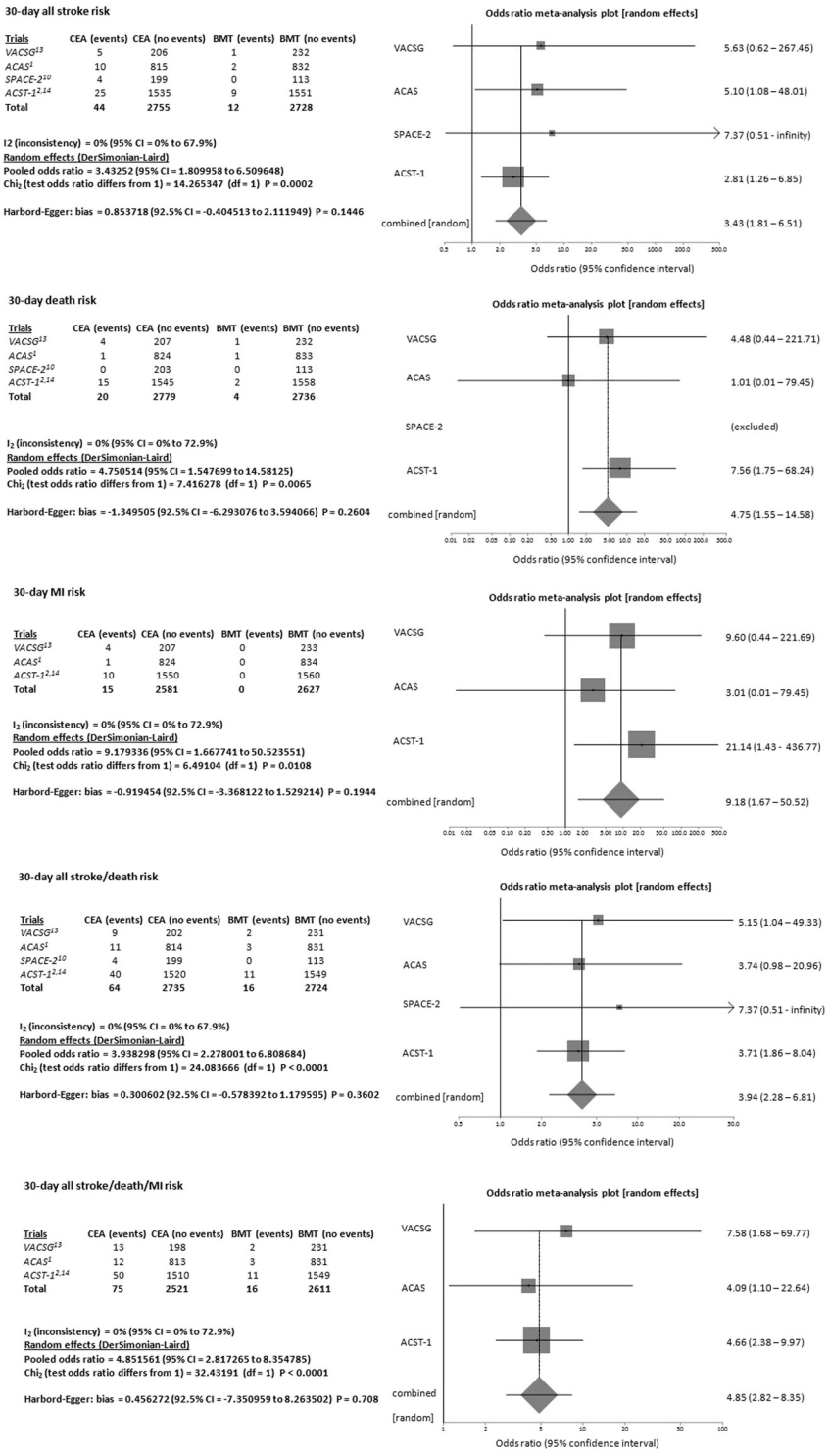

Fig. 3. Early outcomes in asymptomatic patients undergoing CEA versus BMT (CEA, carotid endarterectomy; BMT, best medical treatment).

significant stenosis although there is no difference regarding long-term risks for ipsilateral stroke and death related to stroke. Compared to BMT, CEA shows definitely a higher early complications' risk although open surgery seems to have a protective effect against long-term ipsilateral stroke, with no difference concerning death related to stroke during follow-up.

Regarding the comparison between open and endovascular repair, perioperative stroke risk seems to be slightly higher after CAS in asymptomatic patients although 30-day death or MI risks show no difference. Several meta-analyses have concluded that perioperative stroke or death risk is higher after CAS compared to CEA, although the vast majority of these reviews have evaluated RTs of mainly symptomatic populations [19]. Additionally, we have found in the past that perioperative MI risk is lower after CAS compared to open surgery although almost 80% of the evaluated patients were also symptomatic [20]. This could be justified as symptomatic carotid disease is associated with a higher overall cardiovascular risk, increasing the risk for cardiac events during an open repair [21,22]. Furthermore, the annual stroke risk for asymptomatic patients is significantly lower [23], and pooled data on their prognosis after treatment is limited.

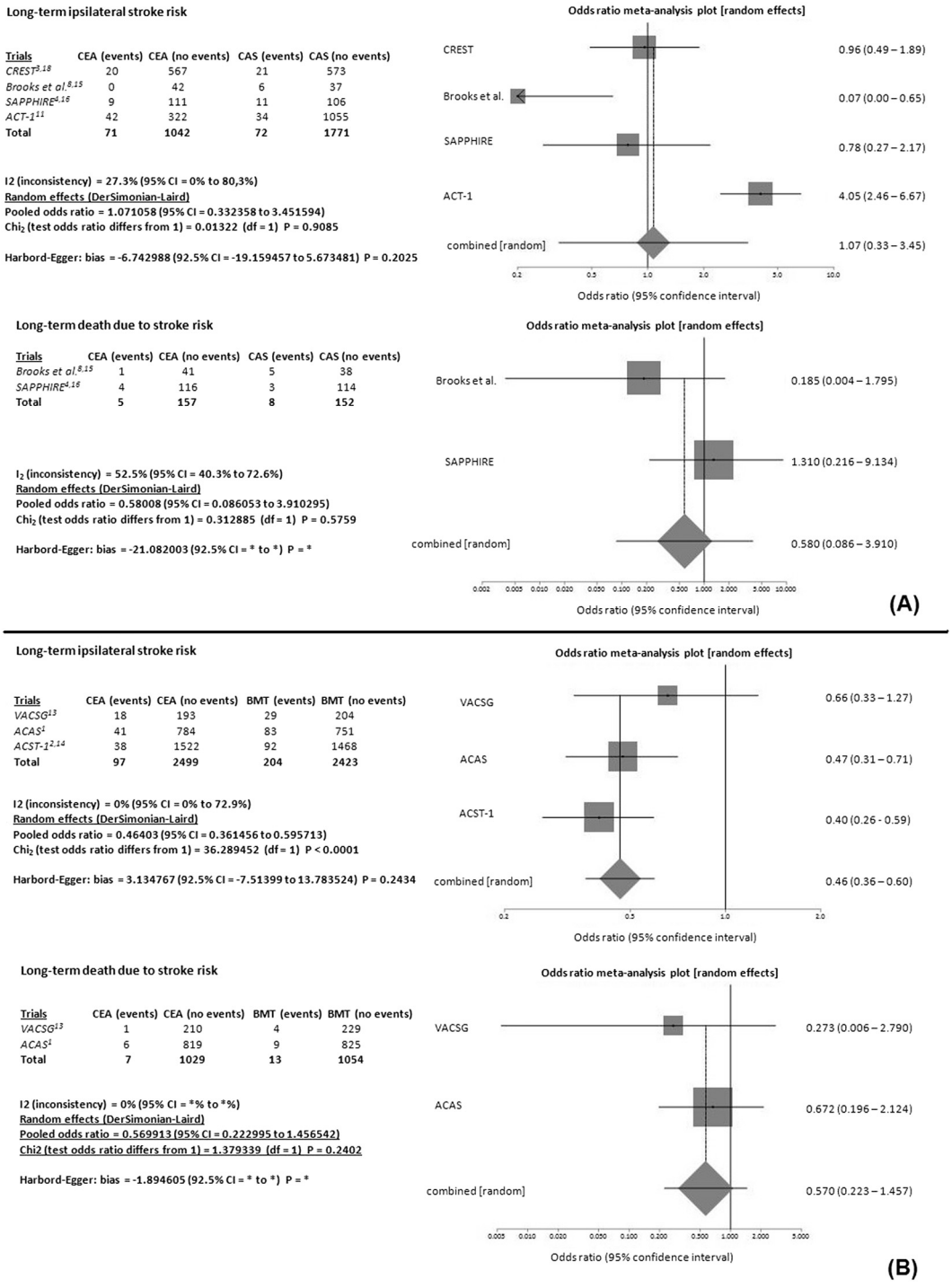

Fig. 4. (A) Long-term outcomes in asymptomatic patients undergoing CEA versus CAS (CEA, carotid endarterectomy; CAS, carotid angioplasty and stenting). (B) Long-term outcomes in asymptomatic patients undergoing CEA versus BMT (CEA, carotid endarterectomy; BMT, best medical treatment).

Concerning asymptomatic patients only, Moresoli et al. have found that periprocedural stroke and death risks are not different between CEA and CAS although they have not provided solid conclusions on long-term outcomes [24]. However, the present review has included a greater number of trials and patients, and has focused on more specific long-term outcomes such as ipsilateral stroke or death due to stroke, that would be of greater clinical interest. Regarding long-term results, no difference was found between the two methods, although symptomatic patients seem to increase after CAS the risk for all death or stroke during follow-up [25]. However, in a recent Cochrane review of mixed populations, the authors found also no increase in the incidence of ipsilateral stroke after the postoperative period (odds ratio = 0.93; 95% CI = 0.60–1.45), concurring with our results [26]. Finally, other studies have also tried to present pooled data on asymptomatic patients only. However, they have not meta-analyzed demographics or outcome data properly [27]. Recently, Kakkos et al. [28] have also evaluated asymptomatic patients, although there were trials included that did not provide adequate data on perioperative outcomes to perform meta-analysis.[29].

Comparing CEA to BMT, this review has shown that surgery is associated to an increased risk for early complications, as anticipated. However, CEA seems to reduce the ipsilateral stroke risk in the long-term,

without affecting the death due to stroke risk. Several other reviews have compared outcomes between surgery and conservative treatment although either they have not conducted proper meta-analysis [27] or they have not followed a proper methodology including ineligible trials [30]. In a recently published review [28], the authors have included the CASANOVA [31] and the MACE [32] trials, although the former trial has excluded patients with stenosis over 90% and the latter trial has randomized only half of the included patients. Additionally, the same review [30] has concluded that there is no benefit with CEA over BMT for long-term all stroke/death risk, although the more directly related to treatment risks for ipsilateral stroke or death due to stroke were not evaluated separately.

Furthermore, recent data indicate that there is a trend for significant fall of annual stroke rate with medical treatment only, although most of the data originate from non-randomized trials [6]. Additionally, one should underline that most of the RTs comparing CEA to BMT were published 10–20 years ago [1,12,13], and BMT has been significantly improved since then. Therefore, uncertainty remains concerning the debate on revascularization versus BMT alone for asymptomatic patients with significant stenosis, although the most recent recommendations support BMT alone for such patients under certain criteria [33]. Unfortunately, most of the included trials in the present review do not provide detailed description of BMT regimens in order to compare the effect of regimen improvement over the decades. Therefore, ongoing trials such as CREST-2 are anticipated in order to provide valuable information on the efficacy of BMT alone versus CEA or CAS [34].

Finally, our study has several potential limitations. First, there was some heterogeneity among RTs regarding the duration of follow-up, types of stents used for CAS and use of cerebral protection device. Secondly, data on exact antihypertensive or antiplatelet treatment for patients under BMT were not available in the included trials. However, this may limit the value of analysis slightly as the total number of patients is adequate, the quality of the included trials is medium to high level, and the calculated heterogeneity of data analysis (I^2) was low. Additionally, data provided in the individual trials were inadequate to conduct pooled multivariate analysis and evaluate potential predictors for adverse events, although conclusions regarding the effect of each treatment on early and late outcomes could be extracted. Furthermore, our search was restricted to studies published in English and therefore, our review could be affected by language bias.

5. Conclusions

In patients with significant asymptomatic carotid disease, CEA is associated with a lower early all stroke risk compared to CAS although there is no difference concerning risks for ipsilateral stroke and death related to stroke in the long-term. Additionally, open surgery has a benefit over BMT against long-term ipsilateral stroke, although surgery is associated with worse early outcomes. However, most of data on BMT derives from older studies, and ongoing RTs evaluating improved BMT regimens are anticipated. Finally, randomized data comparing CAS to BMT are still lacking.

Declaration of conflicting interests

The authors declare that there was no conflict of interests.

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