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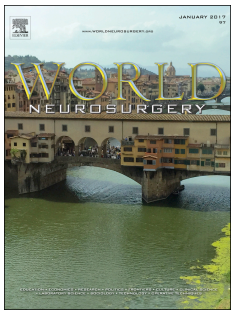

Carotid Artery Endarterectomy (CEA) vs. Carotid Artery Stenting (CAS) for Restenosis after CEA: A Systematic Review and Meta-analysis

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Carotid Artery Endarterectomy (CEA) vs. Carotid Artery Stenting (CAS) for Restenosis after CEA: A Systematic Review and Meta-analysis

Abstract

Background: Carotid artery restenosis may occur following ipsilateral carotid endarterectomy (CEA). It remains unclear whether carotid artery stenting (CAS) or a repeat CEA (redoCEA) is the best treatment strategy for carotid artery restenosis.

Objective: We sought to find whether CAS or redoCEA is the optimal therapy for post-endarterectomy carotid restenosis.

Methods: This study was performed according to the PRISMA and MOOSE guidelines. Eligible studies were identified through a search of PubMed, Scopus and Cochrane until July 20, 2017. A meta-analysis was conducted with the use of random effects modeling. I-square was used to assess for heterogeneity.

Results: Thirteen studies involving 4,163 patients were included. The risk for any type of cranial nerve (CN) injury was higher in the redoCEA group (OR: 13.61; 95% CI: 5.43 – 34.16; I^2 =3.3%). Periprocedural/short-term (within 30 days) stroke, transient ischemic attack (TIA), myocardial infarction (MI), temporary CN injury and death rates were similar between the two revascularization approaches. During a median follow-up of 28 months CAS was associated with significantly lower risk for long-term recurrent carotid artery restenosis, when defined as stenosis >60% (OR: 2.16; 95% CI: 1.13 – 4.12; I^2 =0%) or as stenosis >70% (OR: 2.31; 95% CI: 1.13 – 4.72; I^2 =0%). No difference was identified in long-term target lesion revascularization rates between redoCEA and CAS.

Conclusions: Patients with carotid restenosis after CEA can safely undergo both CAS and CEA with similar risks of periprocedural stroke, TIA, MI and death. However, patients treated with CAS have a lower risk for a new restenosis and periprocedural CN injury.

Keywords: carotid artery endarterectomy; carotid artery stenting; recurrent stenosis; restenosis

Introduction

Carotid endarterectomy (CEA) is the gold standard for treatment of both symptomatic and asymptomatic carotid atherosclerotic disease. [1–3] Carotid angioplasty with stenting (CAS) is a less invasive alternative approach to CEA.[4,5] CAS is currently reserved for patients with high surgical risk, including those with post-endarterectomy stenosis. Published data support that CAS is associated with lower periprocedural MI rates at the cost of a higher periprocedural stroke rate.[6–8] However, advancement in endovascular technologies and increasing operator experience has led to improved outcomes and lower rates of complications with CAS.[9–11]

Incidence of carotid artery restenosis (defined as stenosis> 50%) after a first CEA ranges from 6% to 36% in published series. [12]Carotid restenosis can occur early (up to two years after the primary intervention) or late (greater than two years).[13,14] The pathogenesis of early carotid restenosis involves an inflammatory reaction leading to the formation of a plaque rich in fibroblasts and smooth muscle cells, a phenomenon named myointimal hyperplasia.[13,15] Late carotid restenosis is mainly attributed to recurrence/progression of carotid atherosclerotic disease.[14,16]

Carotid restenosis after CEA can be treated with repeated CEA (redoCEA) or CAS. From a technical standpoint, the presence of scar tissue increases the complexity of the redoCEA approach, leading to a higher complication rate compared to primary CEA.[12,17] With the addition of emerging endovascular technologies, CAS is increasingly utilized for these patients with promising results.[5,18–20] Given the absence of randomized controlled trials (RCTs) on the topic, available outcome data are based on real-world studies. Our aim with this meta-analysis is to quantitatively synthesize the best available real-world data from studies comparing redoCEA vs. CAS for carotid restenosis.

Methods

This review protocol has been registered in the PROSPERO International Prospective Register of systematic reviews:

http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017075004

Both the systematic review and meta-analysis were performed according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines.[21]

Search strategy and selection criteria

Systematic literature searches were conducted in PubMed, Scopus and Cochrane Central. The algorithm used for PubMed was the following: (endarterectomy OR CEA) AND carotid AND (recurrent stenosis OR restenosis OR re-operation OR reintervention OR redo). The search was conducted by two independent investigators (PT, SG). Disagreements were resolved by a third investigator (DGK). The references of the included studies were also manually reviewed in order to identify further potentially eligible articles.

A study was considered eligible for this meta-analysis if it fulfilled all of the predefined inclusion criteria: i) randomized controlled trials (RCTs) or prospective and retrospective real-world studies comparing redoCEA vs. CAS for treatment of carotid artery restenosis after primary CEA; ii) studies that reported quantitative data on clinical outcomes of interest; iii) studies published in English, up to July 20th 2017. Studies reporting on irrelevant outcomes were excluded. When duplicate studies were identified, the most recent study was included unless the earliest version reported more relevant outcomes.

Data extraction and risk of bias assessment

Two reviewers, blind to each other (PT, SG), independently extracted the relevant data from the eligible studies. All disagreements were resolved following discussion and final decision was reached by consensus with the addition of a

third reviewer (DGK). The primary outcome was incidence of stroke within 30 days of procedure. Secondary outcomes were TIA, cranial nerve (CN) injuries, MI and death within 30 days, and long-term target carotid artery recurrent restenosis (tertiary restenosis) and target lesion revascularization (TLR). Sensitivity analyses of all outcomes were conducted by excluding the largest study from the analysis. Risk of bias assessment was performed by two investigators (PT, SG) with the Robins-I tool for non-randomized studies.[22]

Statistical synthesis and analysis

Odds ratios (ORs) with the corresponding 95% confidence intervals (CIs) were used for the outcomes. The random effects model was used to account for heterogeneity among studies. Heterogeneity was assessed with the Higgins I-square (I^2).[23] I^2 greater than 75% indicated significant heterogeneity.[23] A forest plot was used to graphically display the effect size in each study and the pooled estimates. A p value <0.05 was considered significant. STATA 14.1 (StataCorp, College Station, Texas) was used as statistical software.

Results

Search results

Literature search yielded 2,426 potentially relevant records after duplicates were removed. After screening titles and abstracts, 95 articles were retrieved for full-text evaluation. Thirteen studies met the predetermined search criteria and were included in this meta-analysis as shown in the PRISMA flow diagram **(Figure 1).**

Characteristics of the eligible studies

All 13 studies were real-world and included a total of 4,163 patients.[14,24–35] Overall, four studies were assessed as having a low risk of bias[24,25,28,31] and nine as

having a moderate risk of bias **(Supplementary Table A).**[14,26,27,29,30,32–35] Detailed patient and study characteristics are presented in **Table 1**. The main indications for revascularization across the included studies were a symptomatic restenotic carotid artery with a stenosis >50% or an asymptomatic restenotic artery with a stenosis >80%. However, different indications were utilized by a few studies: i) asymptomatic stenosis >60%[34], ii) asymptomatic stenosis >70%[24], iii) symptomatic or asymptomatic stenosis >70%[31] and iv) symptomatic or asymptomatic stenosis >80%.[35]

The main CEA techniques used in the surgical group included CEA with patch angioplasty (76.1%), carotid artery interposition grafting (16%) primary closure CEA (3.7%), eversion CEA (1.2%) and carotid artery bypass (1.2%). The transfemoral approach was the main percutaneous approach used by interventionalists. Five out of six studies specified the type of stent used for CAS; in these studies, the authors reported partial or exclusive utilization of the carotid WALLSTENT.[24,26,29,31,34] Only two (out of the four studies that reported data on neuroprotection) used neuroprotection consistently in their CAS group.[27,35]

Early periprocedural outcomes (within 30 days)

Patients in the redoCEA group were at a significantly higher risk for CN injuries (OR: 13.61; 95% CI: 5.43 – 34.16; I^2 =3.3%) **(Figure 2A)**. The prevalence of CN injuries (any type) among patients who underwent redoCEA was 6% (N=84/1,389). In contrast, the prevalence of permanent only CN injuries was 1.3% (N=5/371), but only a part of the studies provided data regarding the permanence of CN injuries. Specifically, 87.5% (N=35/40) of these injuries were transient with most of them being reversible within six months. Analysis of permanent only CN injuries did not reach statistical significance (OR: 4.28; 95% CI: 0.93 – 19.74; I^2 =0%) **(Figure 2B).** Overall, 2.3% (N=40/1,678) of patients in the redoCEA group and 1.7% (N=43/2,485) in the CAS group suffered stroke. There were no differences in stroke rates (pooled OR: 1.28; 95% CI: 0.82 – 2.00; I^2 =0%) between CAS and redoCEA (**Figure 3A**), neither for patients with symptomatic carotid

artery disease (**Figure 3B**), nor for patients with asymptomatic carotid artery disease (**Figure 3C**). In this study, 2.1% (N=7/330) of patients in the redoCEA group and 3.8% (N=13/341) in the CAS group suffered TIA. Similarly, no statistically significant differences were found between CAS and redoCEA groups in TIA rates (OR: 0.62; 95% CI: 0.24 – 1.60; I^2 =0%) **(Figure 3D)**. In total, 1.2% (N=16/1,289) of patients in the redoCEA group and 0.9% (N=20/2,127) in the CAS group suffered MI. Also, 1% (N=15/1,377) of patients in the redoCEA group and 0.5% (N=12/2,249) in the CAS group died. No statistically significant differences were found in periprocedural MI or mortality rates (for MI; OR: 1.32; 95% CI: 0.71 – 2.44; I^2 =0% and for mortality; OR: 1.82; 95% CI: 0.94 – 3.53; I^2 =0%) **(Figure 4).**

Late outcomes

Overall, 8.5% (N=26/328) of patients in the redoCEA group vs. 4.2% (N=16/380) in the CAS group developed tertiary restenosis >60% and 8.1% (N=24/295) in the redoCEA group vs. 3.5% (N=12/336) in the CAS group developed tertiary restenosis >70%. Tertiary carotid restenosis, defined as recurrent restenosis > 60% (OR: 2.16; 95% CI: 1.13 – 4.12; I^2 =0%) **(Figure 7A)** or >70% (OR: 2.31; 95% CI: 1.13 – 4.72; I^2 =0%) were significantly higher in the CEA group **(Figure 7B)**, during a median follow-up of 28 months. In total, 7.9% (N=28/351) of patients in the redoCEA group vs. 5.5% (N=21/379) in the CAS group underwent a TLR procedure. TLR rates were similar in the two groups (OR: 1.08; 95% CI: 0.34 – 3.50; I^2 =61.1%) **(Figure 8).**

Sensitivity analysis by excluding the largest study

Patients in the redoCEA group were at a statistically significant risk of CN injuries (OR: 9.84; 95% CI: 3.73 – 25.95; I^2 =0%). No differences were identified in terms of death (OR: 1.13; 95% CI: 0.34 – 3.82; I^2 =0%), MI (OR: 1.38; 95% CI: 0.29 – 6.58; I^2 =0%), and stroke (OR: 1.15; 95% CI: 0.58 – 2.26; I^2 =0%). **(Figure 6)**

Discussion

We conducted a meta-analysis of 13 real-world comparative studies. The main findings of this study were that: i) CAS group had a lower incidence of CN injury ii) the two treatment approaches were similarly safe in terms of periprocedural stroke, TIA, MI and death rates; iii) CAS was associated with decreased restenosis risk (defined as either 60% or 70% stenosis) in the follow-up; however, without a significant difference in the risk of TLR.

CAS has emerged as an alternative to open surgical therapy for high-risk patients with carotid artery stenosis including restenosis after CEA, heart failure or hostile neck anatomy.[36–39] Even though redoCEA can be a technically challenging procedure, there is no evidence suggesting that periprocedural adverse event rates in patients with carotid restenosis are lower in the CAS group.[40,41] However, given the lack of dedicated RCTs for those patients comparing the two treatment strategies, it is unknown whether such a difference exists. Prior RCTs such as NASCET (North American Symptomatic Carotid Endarterectomy Trial) and ACAS (Asymptomatic Carotid Atherosclerosis Study) excluded patients with restenotic carotid artery lesions. The only RCT that included patients with CEA restenosis was the SAPPHIRE trial (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy); however, no sensitivity analysis for these patients was performed. [42]

Apart from CN palsy, the periprocedural adverse event rates were similar between the two groups. However, it is important to note the majority of CN injuries in this study were temporary and the risk for a new permanent CN palsy did not reach statistical insignificance. Our results regarding periprocedural event rates are in agreement with those of previous meta-analyses and the new guidelines by the European Society for Vascular Surgery (ESVS).[4,17,40] We also proceeded to sensitivity analyses of all outcomes by excluding the largest study (Arhuidese 2017), to further validate our results. Similarly, the periprocedural adverse event rates were no different between redoCEA and CAS, with the exception of CN palsy. However, according to the meta-analysis from Sardar et al. on CEA vs. CAS for primary carotid stenosis, periprocedural stroke was

significantly higher in the CAS group (OR: 2.07; 95% CI: 1.56-2.75) while periprocedural MI and CN palsy were lower in the CAS group (MI; OR: 0.45; 95% CI: 0.27-0.75, CN palsy; OR: 0.07; 95% CI: 0.04-0.14).[6,7] It is unknown if our inability to detect a difference between the two arms is due to a real effect or because of the retrospective design and lack of randomization in the included real-world studies. The explanation for our inability to find a difference between the two groups might be that de novo carotid atherosclerosis and carotid stenosis are different disease entities, with different pathogeneses, plaque composition and periprocedural embolic potential.[43–46]

Patients in the redoCEA group were at a significantly higher risk for tertiary carotid stenosis > 60% and >70%. Tu et al. demonstrated that freedom from restenosis at 36 months was significantly higher in the CAS group (OR: 2.39; 95% CI, 1.13–5.07; P = .02).[17] Fokkema et al. did not find a CAS superiority in restenosis (stenosis > 70%) but this could be explained by the fact that their analysis included both comparative and single arm studies.[40] Our meta-analysis is the first to show that CAS could be the optimal strategy to avoid long term tertiary restenosis after post-endarterectomy restenosis and could help update clinical practice guidelines reported by the ESVS and the American Society for Vascular Surgery. This novel finding is particularly important and could potentially provide new insights in the management of patients with restenosis after CEA. In a meta-analysis of RCTs comparing long-term outcomes between CEA and CAS for patients with primary carotid artery stenosis, the overall incidence of long-term restenosis was 11.3% in the CAS group and 8% in the CEA group; however, this difference did not reach statistical significance.[8] RCTs in restenotic carotid arteries comparing the two groups could ideally provide more definitive answers.

Limitations

This meta-analysis of comparative real-world studies presents the largest number of patients with carotid restenosis after primary CEA. Our results however should be interpreted in the context of several limitations. First, periprocedural outcomes were similar between the two groups with the exception of CN palsy. Even if this finding could theoretically support that redoCEA use is safe for these patients, operators in the real-world studies were likely reluctant to treat patients with many comorbidities with CEA, which may represent selection bias. Second,

in the absence of RCTs, this was a meta-analysis of real-world studies, limited by their retrospective design and the non-blinded nature. Third, we were unable to adjust for patient specific data. Fourth, different operators and centers created heterogeneity in our pooled results. Finally, our long-term follow-up results are limited by the difference in the follow-up period among the included studies.

Conclusions

Despite the limitations, our study shows that for patients with carotid artery restenosis, CAS could lead to less CN palsies. However, CAS did not provide any benefit in other periprocedural complications. Interestingly, when a follow-up restenosis definition of 60% or 70% was used, CAS was associated with a lower restenosis risk. Future RCTs specifically designed to study patients with carotid artery restenosis will enable us to reach safer conclusions on the ideal management of carotid restenosis after CEA.

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Supplementary Material

Supplementary Table A. Risk of Bias Assessment for Observational Studies (Robins-I Tool)

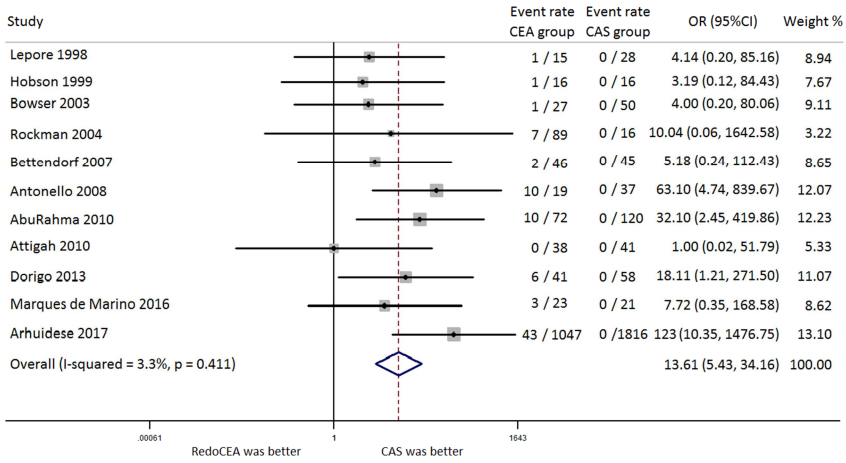
Table 1. Important baseline characteristics of patients enrolled in the included studies.

Study	Country	Patients total, (N)	RedoCEA group, (N)	CAS group, (N)	Age mean, yrs	Males, %	Sx patients prior to procedure, %	CAD, %	HTN, %	Diabetes, %	Dyslipidemia, %	TIA Hx, %	Stroke Hx, %	Current or prior smoker, %	RedoCEA group: time interval from 1st CEA to 2nd intervention, mean (SD), months	CAS group: time interval from 1st CEA to 2nd intervention, mean (SD), months
Lepore 1998	USA	43	15	28	68	70	28	51	58	25.5	NA	25.5	NA	53	58	83
Hobson 1999	USA	32	16	16	65	47	50	NA	NA	NA	NA	NA	NA	NA	NA	14
Bowser 2003	USA	77	27	50	69	NA	62	57	88	20	66	30	22	67.5	83 (15)	50 (8)
Rockman 2004	USA	105	89	16	63	57	42	50	73	26	NA	NA	NA	46	NA	NA
Bettendorf 2007	USA	91	46	45	68	43	32	47	86	28.5	81	NA	NA	81	NA	NA
Sagic 2007	Serbia	50	33	17	NA	74	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Antonello 2008	Italy	56	19	37	76	91	73	34	71	27	NA	21	18	62.5	44	43
AbuRahma 2010	USA	192	72	120	NA	51	NA	NA	82	37	60	NA	NA	60	NA	NA
Attigah 2010	Germany	79	38	41	64	77	45.5	47	14	32	82	NA	NA	23	85 (10)	54 (9)
Dorigo 2013	Italy	99	41	58	68.5	70	23	27	88	22	64	20	3	83	75 (42)	42 (38)
Fokkema 2014	USA	432	212	220	69	61	100	37	92	32	83	25	8	88	NA	NA
M. de Marino 2016	Spain	44	23	21	68.5	68	18	66	79.5	60	64	NA	NA	91	39	27
Arhuidese 2017	USA & Canada	2,863	1,047	1,816	70.2	56	33	33	92	35.5	NA	20	12	32	NA	NA

*CAD: coronary artery disease,CAS: carotid artery stenting, CEA: carotid endarterectomy, Hx: history, HTN: hypertension, N: number of patients, NA: not available, Sx: symptomatic, SD: standard deviation, TIA: transient ischemic attack

Figure 2. This forest plot presents the comparison between redoCEA and CAS in terms of:

A. Cranial nerve injury within 30 days



B. Permanent cranial nerve injury within 30 days

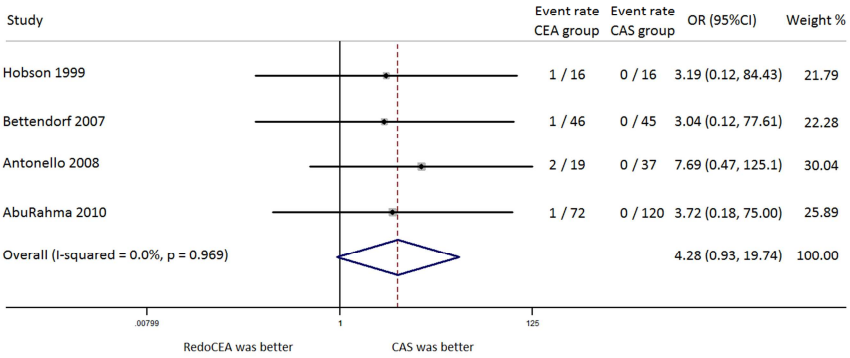
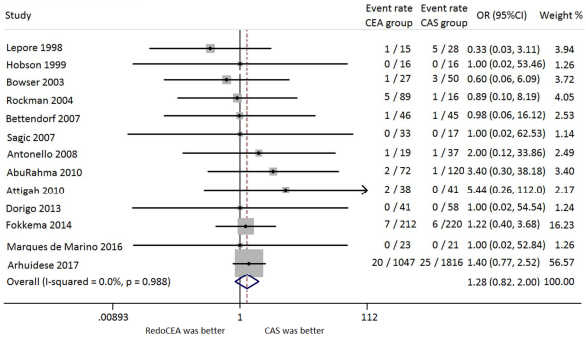
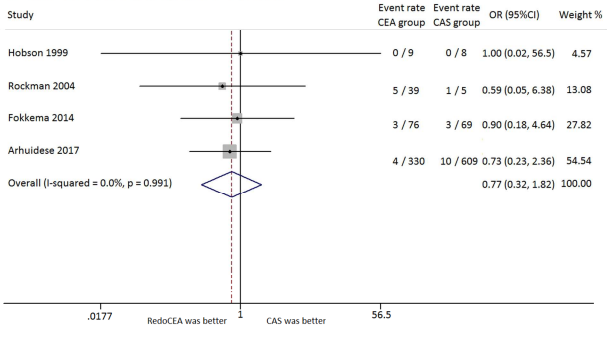


Figure 3. This forest plot presents the comparison between redoCEA and CAS in terms of:

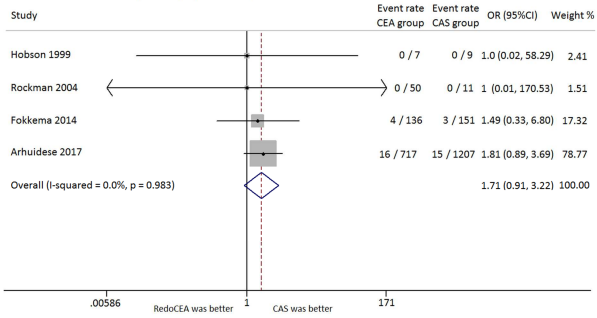
A. Stroke within 30 days



B. Stroke within 30 days in symptomatic patients



C. Stroke within 30 days in asymptomatic patients



D. TIA within 30 days

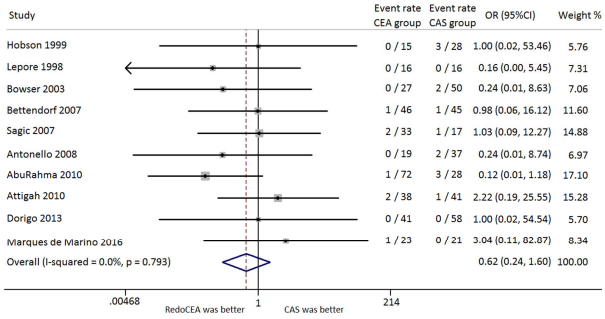
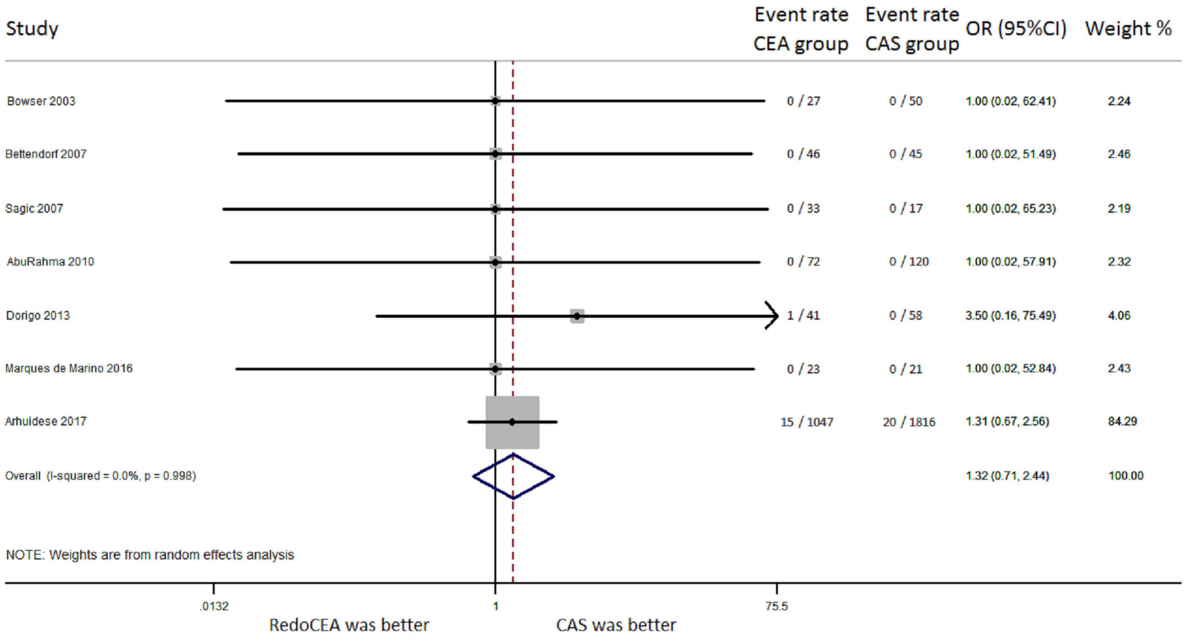


Figure 4. This forest plot presents the comparison between redoCEA and CAS in terms of:

A. MI within 30 days



B. Death within 30 days

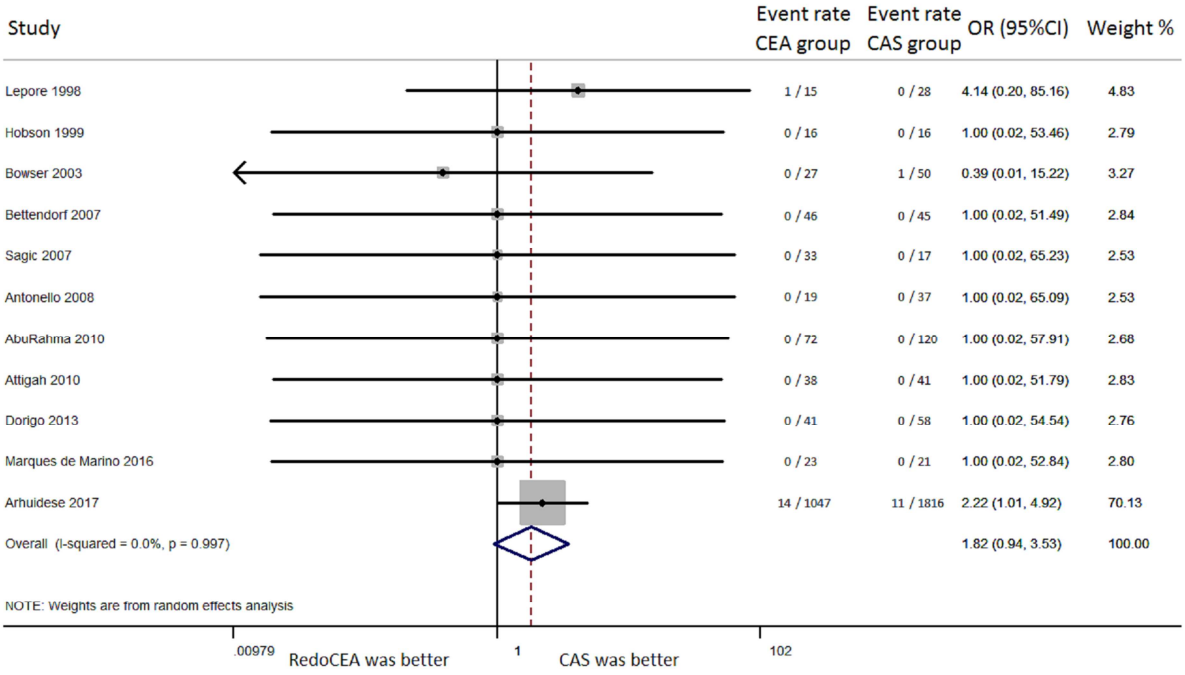


Figure 1: PRISMA searchflow diagram *(last search: 07/20/2017)*

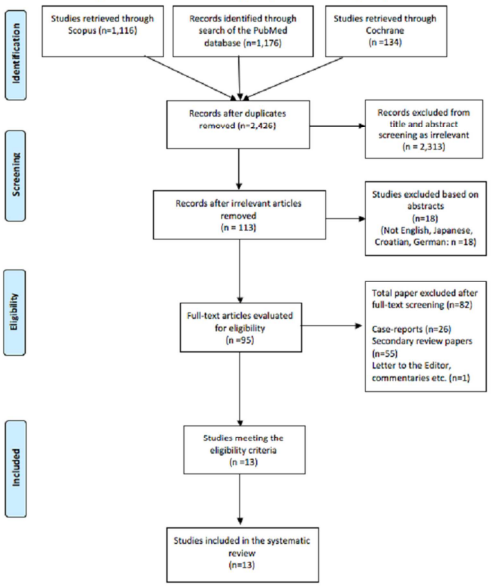
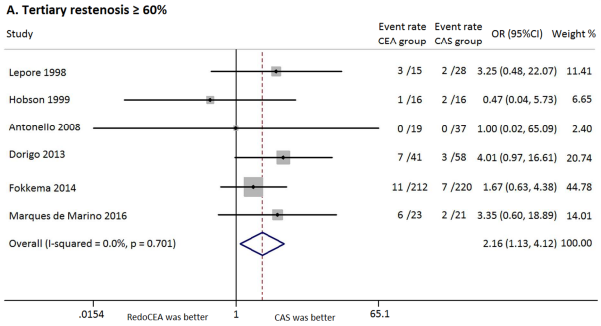
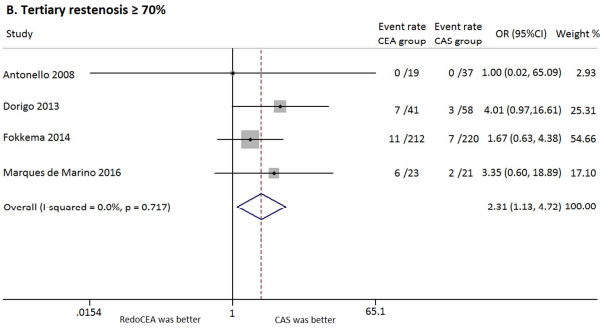


Figure 5. This forest plot presents the comparison between redoCEA and CAS in terms of:

A. Tertiary restenosis ≥ 60%



B. Tertiary restenosis ≥ 70%



C. Target lesion revascularization

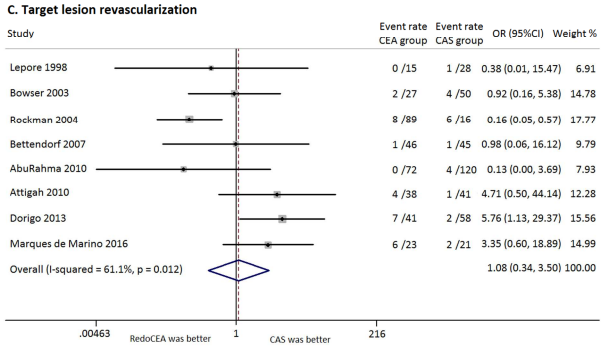
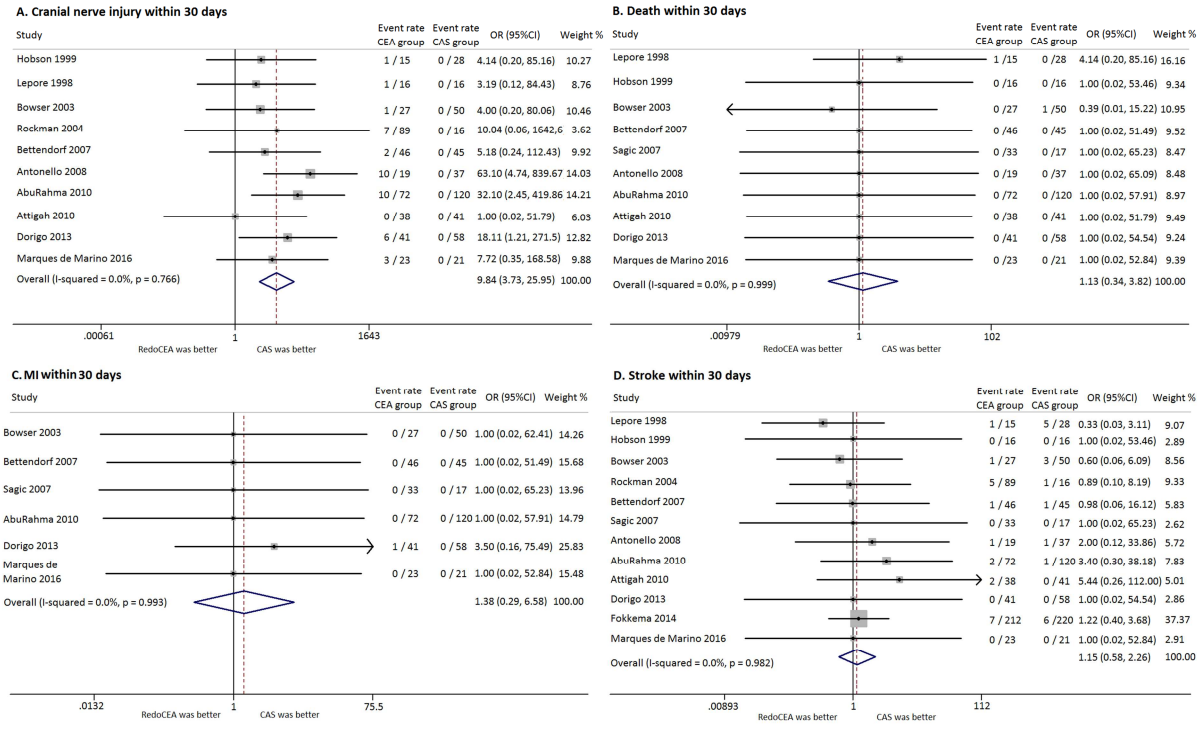


Figure 6. This forest plot presents the comparison between redoCEA and CAS by excluding the largest study in terms of:



Highlights:

- Restenosis is not an uncommon CEA-related complication
- It is unclear whether CAS or redoCEA is the optimal approach for restenosis after CEA
- CAS and redoCEA have similar risks for periprocedural stroke, TIA, MI and death
- RedoCEA is associated with a higher risk for CN injuries and long-term restenosis

Abbreviation List:

ACAS: Asymptomatic Carotid Atherosclerosis Study

CAS: Carotid Artery Stenting

CEA: Carotid Endarterectomy

CI: Confidence Injuries

CN: Cranial Nerve

MI: Myocardial Infarction

NASCET: North American Symptomatic Carotid Endarterectomy Trial

OR: Odds Ratio

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

RCT: Randomized Controlled Trial

RedoCEA: Repeat Carotid Endarterectomy

SAPPHIRE: Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy

TIA: Transient Ischemic Attack

TLR: Target Lesion Revascularization

To: The Editorial Board of *"World Neurosurgery"*

Thessaloniki, Greece

December 20th, 2017

On behalf of the authors of this study, I declare:

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2) This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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