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Short-Term Outcomes of Carotid Artery Stenting versus Carotid Endarterectomy in the Treatment of Carotid Stenosis: An Up-Dated Meta-Analysis of Randomized Controlled Trials

Karotis Stenozu Tedavisinde Karotis Arter Stentleme ve Karotis Endarterektomi Yöntemlerinin Kısa Dönem Sonuçları: Randomize Kontrollü Çalışmaların Güncel Bir Meta-Analizi

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ABSTRACT

Aim: Carotid artery stenting is thought to result in better outcomes when compared to carotid endarterectomy. To evaluate this hypothesis, a far-reaching of published randomized controlled trials were performed to evaluate the short-term outcomes of carotid artery stenting versus carotid endarterectomy for patients undergoing carotid artery stenosis.
Material and Methods: A comprehensive search of trials published from 1994 until December 31, 2022, was performed using Science Direct, PubMed, Web of Science, Sage, Ebscohost, Scopus, and Cochrane Central electronic databases. Major endpoints (any stroke, myocardial infarction, and all-cause mortality) were extracted from the publications. Pooled risk ratio (RR) and 95% confidence interval (CI) were calculated using a fixed-effects model.
Results: 21 trials involving 15518 patients (8514 with stenting, 7004 with endarterectomy) were included in the meta-analysis. Stenting was associated with a significantly increased risk of short-term any stroke (RR=1.555, 95% CI: 1.307-1.851, p<0.001) yet a significantly decreased risk of short-term myocardial infarction (RR=0.458, 95% CI: 0.319-0.660, p<0.001) when compared with endarterectomy. No significant difference was found in all-cause mortality between the two interventions (RR=1.277, 95% CI: 0.835-1.952, p=0.259), but with a trend toward superiority favoring endarterectomy.
Conclusion: Endarterectomy was found to be superior in terms of any stroke and partially regarding all-cause mortality, whereas stenting was found to be superior in terms of myocardial infarction. Yet for robust results, further studies are needed to address the relative effectiveness of stenting versus endarterectomy in the future.
Keywords: Carotid endarterectomy; meta-analysis; randomized controlled trials; short-term outcomes; carotid artery stenting.

ÖZ

Amaç: Karotis arter stentlemenin karotis endarterektomiye kıyasla daha iyi sonuçlar ürettiği düşünülmektedir. Bu hipotezi sınamak için, karotis arter stenozu geçiren hastalarda karotis arter stentleme ve karotis endarterektominin kısa süreli sonuçlarını değerlendirmek üzere yayınlanmış randomize kontrollü çalışmaların geniş kapsamlı değerlendirmesi yapıldı.
Gereç ve Yöntemler: Science Direct, PubMed, Web of Science, Sage, Ebscohost, Scopus ve Cochrane Central elektronik veri tabanları kullanılarak 1994'ten 31 Aralık 2022'ye kadar yayınlanmış olan denemelerin kapsamlı bir araştırması yapıldı. Yayınlardan temel sonlanım noktaları (herhangi bir inme türü, miyokard enfarktüsü ve tüm nedenlere bağlı ölüm) çıkarıldı. Sabit etkiler modeli iler etki büyüklüğü risk oranı (RO) ve %95 güven aralığı (GA) hesaplandı.
Bulgular: Bu meta-analizine 15518 hastayı (8514 stentleme, 7004 endarterektomi) içeren 21 çalışma dahil edildi. Endarterektomi ile karşılaştırıldığında, stentleme, kısa süreli herhangi bir inme riskinde anlamlı derecede artma (RR=1,555; %95 GA: 1,307-1,851; p<0,001), ancak kısa süreli miyokard enfarktüsü riskinde ise azalma (RR=0,458; %95 GA: 0,319-0,660; p<0,001) ile ilişkiliydi. İki müdahale arasında tüm nedenlere bağlı ölüm açısından anlamlı bir fark yokken (RR=1,277; %95 GA: 0,835-1,952; p=0,259) endarterektomi lehine üstünlük eğilimi vardı.
Sonuç: Endarterektominin herhangi bir inme türü açısından ve kısmen de tüm nedenlere bağlı ölüm açısından üstün olduğu, stentlemenin ise miyokard enfarktüsü açısından üstün olduğu görüldü. Ancak daha sağlam sonuçlar için gelecekte stentlemenin endarterektomiye karşı göreceli etkinliğini ele alan daha fazla çalışmalara ihtiyaç vardır.
Anahtar kelimeler: Karotis endarterektomi; meta-analizi; randomize kontrollü çalışmalar; kısa-dönem sonuçlar; karotis arter stentleme.

INTRODUCTION

Cerebrovascular and cardiovascular diseases have become the leading cause of disability and mortality globally. Thus, the great and still growing burden of cerebrovascular and cardiovascular diseases on healthcare systems indicates an urgent need for preventive measures (1-3). Carotid artery stenosis (CS), an atherosclerosis disease, is a major cause of neurological and cardiological morbidity and mortality. The prevalence of CS disease was estimated to be 1.5% globally in 2020 (1).

Carotid artery stenting (CAS) was progressively preferred as a chance to carotid endarterectomy (CEA) for the operation of patients with CS in the 1994s onwards (2,3). Stroke is a leading cause of death worldwide (4), yet it was previously noted that about 20-25% of nearly all types of strokes are caused by CS (5). On the other hand, individuals with CS are at high risk of developing cardiovascular disease as well (1). In a review, it was indicated that approximately 63% of individuals with CS were found to be associated with cardiac events (6). In this regard, myocardial infarction is measured as another primary disease outcome in the treatment of CS. Likewise, mortality is generally measured after both CAS and CEA (1). In addition to these major outcomes mentioned here, of course, there are other complications such as restenosis, cranial nerve palsies, transient ischemic attack, cognitive decline, bleeding, etc. being tested after CAS and CEA treatment techniques (7).

CAS and CEA are feasible options for patients with symptomatic or asymptomatic CS. Even though higher side effects and death rates were associated with CAS than CEA in the early studies, developments such as new endovascular technologies, cerebral embolic protection device (EPD), and, trials with their larger sample sizes issued lately have improved efficacy with CAS. Yet, the exact role of CAS versus CEA in the treatment of CS remains controversial, according to some studies (8-12). Therefore, in this paper, we aimed to compare the risks and benefits of CAS and CEA with a particular focus on the short-term outcomes of any stroke, all-cause mortality, and myocardial infarction, which are frequently observed and measured immediately after operation.

MATERIAL AND METHODS

In this study, the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist and guidelines were used as a handbook (13).

Data Sources and Search Strategy

A wide-ranging literature search was carried out from 1994 (when Morris et al. first deployed metal stents in two patients with CS) to December 31, 2022, for all randomized controlled trials (RCTs) that compared CAS with CEA in the treatment of CS and reported peri- and post-procedural outcomes. We searched Science Direct, PubMed, Web of Science, Sage, Ebscohost, Scopus, and Cochrane Central electronic databases and keyword search terms for “carotid artery stenosis”, “carotid stenosis”, “endarterectomy”, “stenting”, “randomized controlled trial”, “controlled trial” “stroke”, “death”, “mortality”, and “myocardial infarction”. All search databases were screened using the advanced search options specific to those databases. For instance, while searching PubMed, we utilized medical subject headings (MeSH) terms. Moreover, the Peer Review of Electronic Search Strategies (PRESS) guideline, which focuses on the quality of the database search and is the core element in the health technology assessment, was used systematically for searching databases (9). All the studies were initially examined according to title, abstract, and finally the complete body text by researchers. In cases of disagreement, resolution was achieved through discussion. Finally, the articles were merely restricted to English.

Study Selection

The population, intervention, comparison, outcome, and study design (PICOS) criteria identified by researchers were used to construct a set of inclusion and exclusion guidelines. Eligible trials that met the subsequent predefined criteria were included in the analysis by consensus. Trials that meet the requirements are (i) RCTs of participants with symptomatic or asymptomatic CS comparing CAS with CEA, (ii) trials with or without EPD, (iii) participants with symptomatic CS of ≥50% and asymptomatic CS of ≥60%, (iv) participants aged ≥18 years, (v) participants who have not previously been treated for CS, and (vi) participants reporting the 30-day peri- and post-procedural any stroke, all-cause mortality, and myocardial infarction.

Non-randomized controlled trials, animal trials, and all other forms of studies were excluded. Participants who had coronary bypass concurrently with the CS and only those who underwent balloon angioplasty were also excluded. Additionally, the surgical risk conditions of participants and gender terms were disregarded as results of insufficient studies.

Data Extraction and Quality Assessment

Pre-specified data elements were extracted and evaluated independently by the all three researchers of the present study. For each included RCT, study characteristics such as year of publication, study type (single- or multi-center), total number of randomized patients, median length of follow-up, mean age, the proportion of symptomatic and asymptomatic participants, degree of stenosis, surgical risk, the use of EPD, and outcomes to be analyzed were classified.

The quality evaluation of the included studies and the risk of bias (Risk Of Bias VISualization, Robvis) before analysis were assessed by the Cochrane Collaboration assessment tools. More specifically, we evaluated each RCT’s sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other potential sources of bias. For each domain, every study was assigned a score of high, low, or unclear risk of bias (14,15).

Data Synthesis and Statistical Analysis

The main outcomes whose impacts were examined in our study are the incidence of any stroke, all-cause mortality, and myocardial infarction just after the operation. All outcomes in the analysis were limited to the information provided in each trial. For data analysis, we used Comprehensive Meta-Analysis (CMA) v.2.0 software. For the pooled effect size, the risk ratio (RR)-widely employed in health science- and 95% confidence interval (CI) were utilized in estimating results. $p<0.05$ were considered statistically significant. The Cochran Q-test was used to determine the presence of heterogeneity among studies. If the Q statistic was greater than the degree of freedom (df), this would indicate the existence of heterogeneity. For heterogeneity between the RCTs, the Higgins I^2 statistic was used. I^2 represents significant heterogeneity, provided that $I^2 \geq 50\%$ is taken to represent significant heterogeneity. In the present study, as no evidence of significant heterogeneity was found in any analyses, the fixed-effect model (FEM) was applied. Finally, publication bias was evaluated using both the visually funnel plot along with the trim and fill statistic and the weighted regression test of Egger. Eventually, a sensitivity analysis was performed to evaluate the impact of higher-weight individual studies on the summary for any stroke, myocardial infarction, and all-cause mortality separately.

RESULTS

Search Results

Based on database searching, we initially identified 1,045 potentially relevant studies. After removing duplicates, abstracts, titles, reviews, protocols, costs, etc. Finally, 86 papers were predicted to meet the inclusion criteria. After a thorough screening and full-text readings by researchers, 21 strictly eligible trials comparing CAS with CEA were included in the meta-analysis (Figure 1).

Patient Characteristics and Quality Assessment

The design features and clinical characteristics of the individual studies are summarized in Table 1. In all included studies, basic criteria in individual studies and some institutions' guidelines (e.g., Peripheral Artery and Vein Diseases-National Treatment Guidelines, American Society of Cardiologists, American Heart Association Guidelines) were taken as references. Those 21 studies enrolled 15,519 (8,514 for CAS, 7,004 for CEA) Participants. Of these patients, 9,721 are asymptomatic, accounting for approximately 62.6% of the studies included, and 12 of them are multi-center RCTs. The mean age (68.2) of the patients was in the range of 63.0 to 72.6 years, and median follow-up durations ranged from 1 to 60 months. The majority of patients had high or moderate surgical risk. In addition, EPD was used in most of the patients, especially those published in recent years. The incidence of short-term outcomes after CAS and CEA was also given in Table 1. In the end, we found 21 studies comparing any stroke and all-cause mortality and 19 comparing myocardial infarction.

When analyzing the visual risk of bias (Robvis) of included trials, the quality of randomization was found to be high. As shown in Figure 2, however, some studies had no data about the risk of bias pointed out with yellow dots. Due to the nature of CAS and CEA treatment procedures, none of the trials involved blinding of participants or personnel. Yet, all individual studies were defined by the authors, who carried out the individual studies, as having a low risk of randomization bias.

Any Post-Procedural Stroke

A FEM was applied as the Q statistics for heterogeneity indicated an obvious trend for homogeneity (Q: 15.561, df(Q):20, I^2=0.001%, p=0.743) among the trials, indicating that most of the variance reflects sampling error. Upon performing FEM, CAS was associated with a significantly higher incidence of any stroke when compared to CEA (RR=1.555, 95% CI: 1.307-1.851, p<0.001). It could be said that the risk of any stroke after treatment in

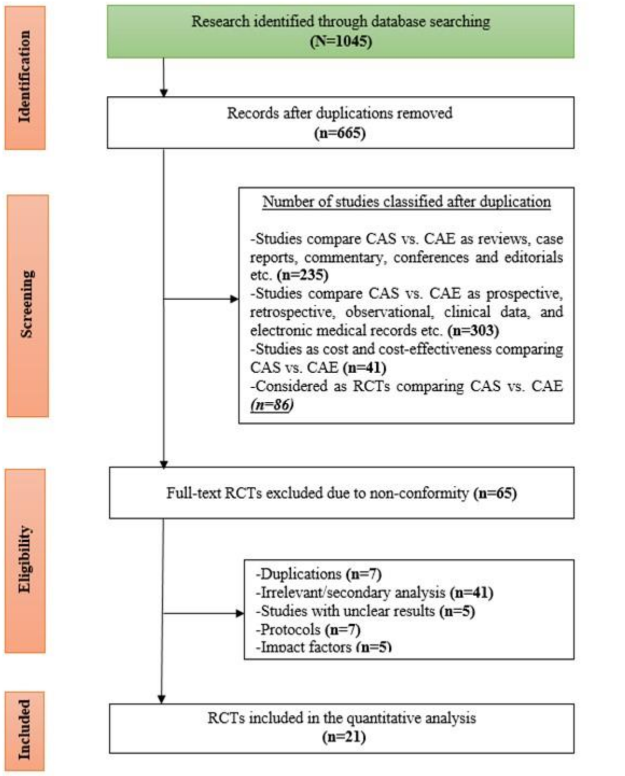

Figure 1. Flowchart of the study selection process
CAS: carotid artery stenting, CEA: carotid endarterectomy, RCT: randomized controlled trial

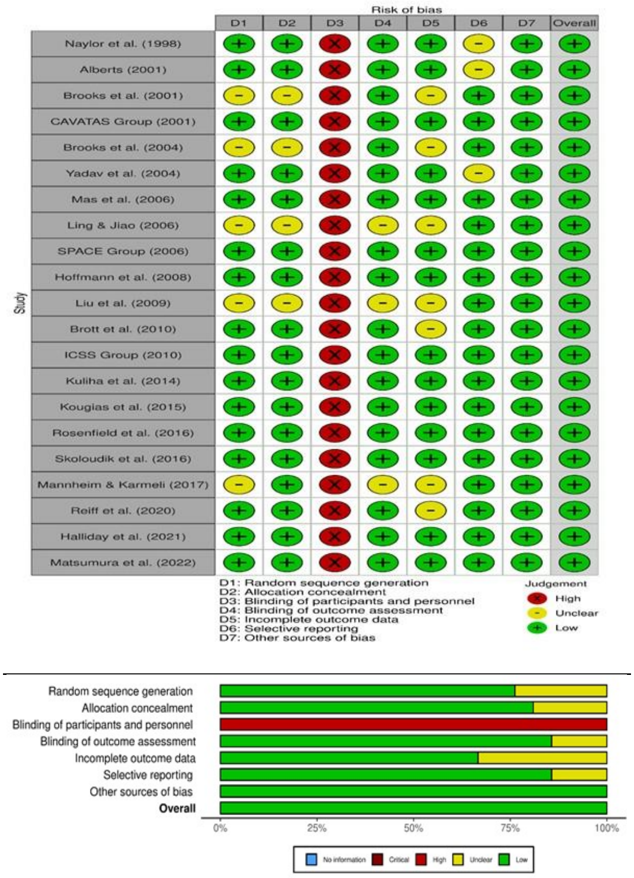

Figure 2. Risk of bias graph for randomized controlled trials (upper panel) and risk of bias summary of randomized controlled trials (lower panel)

Table 1. Characteristics and clinical outcomes of including randomized controlled trials comparing carotid artery stenting and carotid endarterectomy

Study	Year	Study Design	Population CAS/CEA (Total)	Mean Age (Year)	Any Stroke (CAS/CEA)	Myocardial Infarction (CAS/CEA)	All-cause Mortality (CAS/CEA)	Follow-up (Month)	Sym/Asy	Degree of Stenosis (%) (Sym/Asy)	Surgical Risk	Use of EPD
SPACE Group (10)	2006	MC	561/550 (1111)	67.9	42/34	0/0	4/5	24	1111/0	≥70/-	high	mixed
Alberts MJ. (16)	2001	MC	107/112 (219)	68.3	4/1	-	9/4	24	219/0	≥60/-	low	no
Naylor et al. (17)	1998	SC	7/10 (17)	67.2	5/0	-	0/0	1	17/0	≥70/-	moderate	yes
Brooks et al. (18)	2001	SC	53/51 (104)	68.0	0/0	0/1	0/1	24	104/0	≥70/-	low	no
Kougias et al. (19)	2015	SC	29/31 (60)	69.2	0/0	0/0	0/0	6	0/60	-/≥80	moderate	yes
CAVATAS Group (20)	2001	MC	240/246 (486)	67.0	18/21	0/3	7/4	60	437/49	≥50/≥50	moderate	no
Brooks et al. (21)	2004	SC	43/42 (85)	68.2	0/0	0/0	0/0	48	0/85	-/≥80	high	no
Yadav et al. (22)	2004	MC	159/151 (310)	72.6	5/5	3/10	1/3	36	91/219	≥50/≥80	high	yes
Mannheim et al. (23)	2017	SC	68/68 (136)	69.2	2/1	0/0	0/0	60	0/136	-/≥70	moderate	yes
Mas et al. (24)	2006	MC	247/257 (504)	69.7	22/9	1/2	2/3	6	504/0	≥60/-	moderate	yes
Liu et al. (25)	2009	SC	23/23 (46)	65.4	2/1	0/1	0/0	18	NA	≥50/≥70	NA	mixed
Ling et al. (26)	2006	MC	82/84 (166)	63.0	2/3	1/2	1/2	6	NA	≥50/≥70	moderate	yes
Hoffmann et al. (27)	2008	SC	10/10 (20)	70.0	0/1	0/0	0/0	24	20/0	≥70/-	high	yes
Reiff et al. (28)	2020	MC	197/203 (400)	70.0	5/5	0/0	0/0	60	0/400	-/≥70	moderate	mixed
ICSS Group (29)	2010	MC	828/821 (1649)	70.0	58/24	3/5	11/4	4	1649/0	≥50/-	high	mixed
Brott et al. (30)	2010	MC	1184/1118 (2302)	69.0	52/29	14/28	9/4	48	1217/1085	≥50/≥60	moderate	mixed
Kuliha et al. (31)	2014	SC	77/73 (150)	65.5	2/1	0/0	0/0	1	87/63	≥70/≥70	high	yes
Rosenfield et al. (32)	2016	MC	1032/343 (1375)	67.8	30/5	5/3	1/1	60	0/1375	-/≥70	high	yes
Školoudík et al. (33)	2016	SC	136/106 (242)	66.3	3/1	0/0	0/0	1	126/116	≥70/≥70	high	yes
Halliday et al. (34)	2021	MC	1811/1814 (3625)	69.5	61/41	5/8	2/2	60	0/3625	-/≥60	high	yes
Matsumura et al. (35)	2022	MC	1620/891 (2511)	68.0	43/13	9/15	2/2	48	0/2511	-/≥70	high	yes
Summation			**8514/7004 (15518)**	**68.2**	**356/198**	**41/88**	**50/35**	**-**	**5582/9721**			

CAS: carotid artery stenting, CEA: carotid endarterectomy, MC: multi-center randomized controlled trial, SC: single-center randomized controlled trial, Sym: symptomatic, Asy: asymptomatic, EPD: embolic protection device, NA: not available the CEA group is approximately 55% less than treatment in CAS (Figure 3). In other words, being treated by CEA might be safer and more effective than CAS in terms of short-term any stroke.

As for publication bias for any stroke, a funnel plot distribution, and the result of an Egger's test (p=0.904) suggest that there was no publication bias, which indicates the results could be reliable. According to Duval and Tweedie's trim and fill statistic, complete symmetry will be achieved if only one imaginary study (red circles) is added to the right side of the funnel plot. Sensitivity analysis was performed by exclusion of trials that contributed the most number of patients (higher weight). After the exclusion of these trials, the results revealed no particular strong influence, while the effect size partly came down (RR=1.541, 95% CI: 1.283-1.705).

Post-Procedural Myocardial Infarction

Due to the lower heterogeneity (Q: 3.504, df(Q):18, I^2=0.001%, p<0.001) for myocardial infarction, a FEM statistic was applied. The pooled results (RR=0.458, 95% CI: 0.319-0.660, p<0.001) show that CEA was associated with a higher risk of myocardial infarction compared with CAS (Figure 4). These findings also show that the risk of myocardial infarction for post-operation could be reduced by almost 54% if treated with CAS.

There was no evidence of big-size study effects (publication bias) of funnel plots or Egger's regression test (p=0.116). Yet, for the exact symmetry, while considering Duval and Tweedie's trim and fill statistic, about four imaginary studies (red circles) are needed on the left side of the funnel plot. A sensitivity analysis also confirmed the consistency of our main findings. The odds of 30-day myocardial infarction remained in favor of CAS when data from the most number of trials was omitted (RR=0.514, 95% CI: 0.352-0.730).

Post-Procedural All-Cause Mortality

Since the homogeneity terms for 30-day all-cause mortality were met in the study (Q: 9.445, df(Q): 20, I^2=0.001%, p=0.977) we applied the FEM statistic. Compared with CAS, CEA was associated with a non-significant reduction in the risk of all-cause mortality (Figure 5). In other words, no significant difference in all-cause mortality was observed between the CAS group and the CEA group after operation (RR=1.277, 95% CI: 0.835-1.952, p=0.259).

However, the funnel plot distributions and the result of Egger's test (p=0.007) suggest that there was a publication bias and that the results are questionable in terms of reliability. According to the trim and fill statistics, when 10 virtual studies (red circles) are added to the right side of the funnel graph, the desired symmetry will be achieved. In addition to publication bias, a sensitivity analysis of all-cause mortality demonstrated that the exclusion of trials with the highest weight did not greatly affect the overall result of all-cause mortality in favor of CAS (RR=1.252, 95% CI: 0.702-1.452). Therefore, it is beneficial to be more careful and cautious when interpreting pooled effect size related to all-cause mortality. All the funnel plots of outcomes are demonstrated in Figure 6.

DISCUSSION

Aiming to summarize the effectiveness of CAS versus CEA with the evidence from RCTs, CAS was found to be associated with a significantly higher rate of any stroke within 30 days after the operation. The higher rate of any stroke in the stenting group was likely attributed to the minor strokes in accordance with some recent trials' findings (26-30). On the other hand, it was found that CAS is superior to CEA just in the incidence of myocardial infarction for 30 days after operation. Furthermore, both procedures appeared equivalent in their effects on all-cause mortality, despite a trend toward the superiority of CEA. These results suggest that CEA has more favorable effects on short-term any stroke and partially all-cause mortality and should remain the treatment of choice for patients with CS.

Even though there has been an observed increased rate of any stroke with CAS and an increased rate of myocardial infarction with CEA, according to some studies (16-20,36-38), much of this conclusion could be

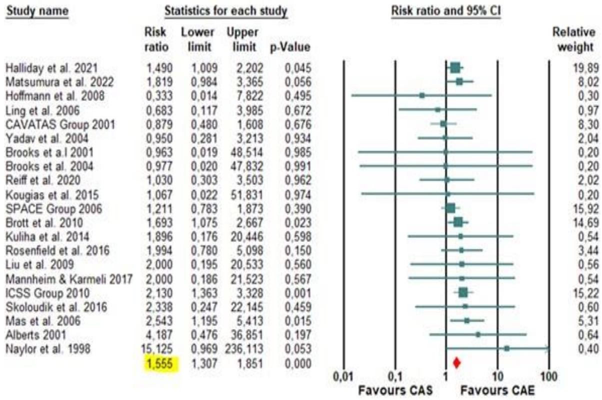

Figure 3. Forest plot of risk ratio of any stroke

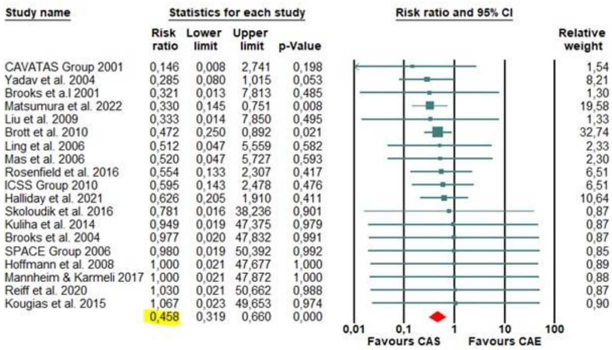

Figure 4. Forest plot of risk ratio of myocardial infarction

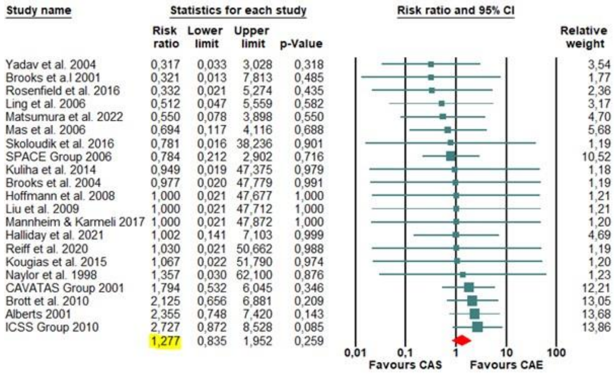

Figure 5. Forest plot of risk ratio of all-cause mortality

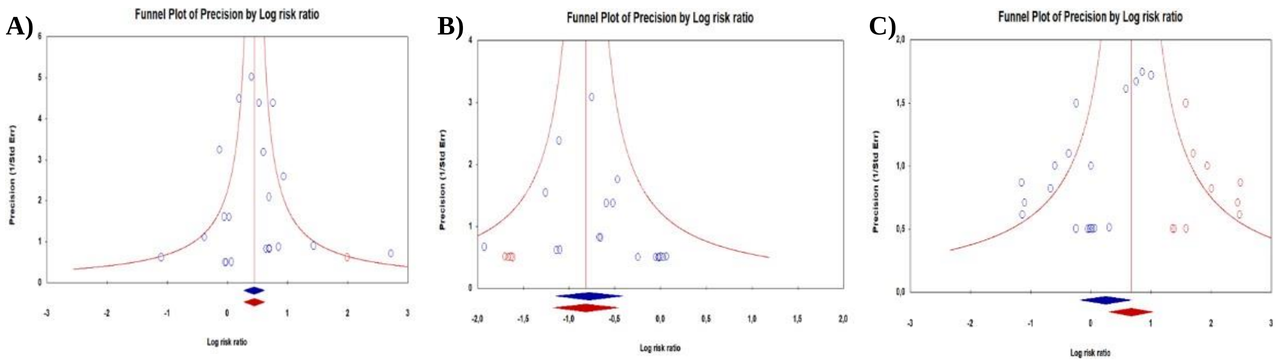

Figure 6. Funnel plots of the incidence of **A)** any stroke, **B)** myocardial infarction, and **C)** all-cause mortality

based on the majority of the symptomatic population. Yet, this gap may be attributable to the nature of the CAS and CEA techniques as well as the asymptomatic. Furthermore, as reported in some studies (10,20,36) surgical risk level might have also contributed to the expected outcomes in this study.

Technological advances in CAS and the use of distal EPD as well as mesh-covered stents might have reduced the incidence of post-procedural stroke in patients undergoing CAS but have not yet reached a comparative effectiveness over CEA (39). As for CEA, advances in preoperative cardiac evaluation, anesthesia, and quality improvement through standardized outcome analysis are areas of focus to reduce the risk of post-operative complications (40,41) Therefore, it could be said that our findings are in concordance with those views.

In this study, although we obtained results parallel to those of previous studies for patients with both symptomatic and asymptomatic CS at large, the current meta-analysis is the first far-reaching review with pooled outcomes from 21 RCTs. A summary comparison outcome of individual RCTs and some previous meta-analytical studies with similar design characteristics to the current study results are shown in Table 2.

Several limitations of this current study should be underlined. To begin with, as the number of trials included in the analysis was not enough, it was thus overlooked to perform subgroup analysis in terms of patient type (symptomatic or asymptomatic), use of an EPD, stent type, surgical risk, etc. Secondly, our conclusions were based on evidence predominantly from asymptomatic patients. Third, studies with both small and large samples included in this review may have affected the effect size. Therefore, all these limitations may have reduced the scientific precision of research. Thirdly, the differences in patient characteristics within the individual studies, and being both symptomatic and asymptomatic traits of studies might have affected outcomes. Another limitation is that the possible consequences of long-term results on the effectiveness of the methods are not included in the study. On the other hand, our study also has several strengths. Firstly, it is a comprehensive study conducted by different databases; data collection, summary methods, reporting biases, and explicit quality assessment represent the strengths of this work. Besides, the homogeneity across trials did reach a level of statistical significance, reinforcing the consistency of our findings. Taken together, the current analysis suggests that CAS and CEA seem to be complementary rather than competing modes of therapy with careful patient selection. Over and above, CEA is a reasonably safe treatment for CS in terms of any stroke and all-cause mortality in short-term results whereas CAS is a reasonable procedure for short-term myocardial infarction.

CONCLUSION

This study was designed to examine the safety and efficacy of compared with endarterectomy in patients with CS, with a particular focus on short-term outcomes. While stenting had a more favorable post-procedural outcome with respect to myocardial infarction, endarterectomy had a more favorable post-procedural any stroke outcome. For all-cause mortality, no significant differences were found between CAS and CEA, despite a trend toward superiority favoring CEA. The outcome-related all-cause mortality comparison of CAS and CEA must be interpreted cautiously, given the publication bias found. As a result, CAS may offer a viable alternative given its lower associated risk of myocardial infarction, whereas CEA offers a standard of care in the treatment of CS for the prevention of any stroke. To sum up, according to the findings, it could be said that CEA should be offered as the first alternative to CS, but more evidence is needed to reevaluate the absolute effectiveness of both techniques in terms of short-term results. For this assumption, further studies are needed to make a concrete comparison of CAS versus CEA in the future. Moreover, it is extremely important that, for payer institutions and policymakers it should be taken into consideration the economic effects of both procedures as well as intermediate and long-term outcomes.

Ethics Committee Approval: Since our study was not an experimental study including human or animal subject, ethics committee approval was not required.

Conflict of Interest: None declared by the authors.

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Author Contributions: Idea/Concept: İA, AEE; Design: İA, AEE; Data Collection/Processing: İA, İD; Analysis/Interpretation: İA, İD, AEE; Literature Review: İA; Drafting/Writing: İA; Critical Review: İD, AEE.

Table 2. Summary findings on the short-term clinical efficacy of carotid artery stenting versus carotid endarterectomy

Study	Year	Outcome	Pooled Effect	p
Sardar et al. (8)	2017	Any stroke	OR=2.07 (95% CI: 1.56-2.75)	**0.001**
		Myocardial infarction	OR=0.45 (95% CI: 0.27-0.75)	**0.002**
		All-cause mortality	OR=1.34 (95% CI: 0.60-3.02)	0.480
SPACE Group (10)	2006	Any stroke	OR=1.24 (95% CI: 0.79-1.95)	-
		All-cause mortality	OR=0.78 (95% CI: 0.15-3.64)	-
		Any stroke & all-cause mortality	OR=1.19 (95% CI: 0.71-1.92)	-
Kan et al. (12)	2018	Any stroke	RR=1.57 (95% CI: 1.25-1.97)	**0.001**
		All-cause mortality	RR=1.50 (95% CI: 0.83-2.74)	0.180
CAVATAS Group (20)	2001	Any stroke & all-cause mortality	HR=1.03 (95% CI: 0.64-1.64)	0.900
Mas et al. (24)	2006	Any stroke	RR=3.30 (95% CI: 1.40-7.50)	**0.004**
		Myocardial infarction	RR=0.50 (95% CI: 0.04-5.40)	0.620
		All-cause mortality	RR=0.70 (95% CI: 0.10-3.90)	0.680
ICSS Group (29)	2010	Any stroke	HR=2.13 (95% CI: 1.36-3.33)	**0.001**
		All-cause mortality	HR=2.73 (95% CI: 0.87-8.53)	0.072
		Any stroke & all-cause mortality	HR=1.83 (95% CI: 1.21-2.77)	**0.003**
Brott et al. (30)	2010	Any stroke	HR=1.79 (95% CI: 1.14-2.82)	**0.010**
		Myocardial infarction	HR=0.50 (95% CI: 0.26-0.94)	**0.030**
		All-cause mortality	HR=2.25 (95% CI: 0.69-7.30)	0.180
Yavin et al. (40)	2011	Any stroke	OR=1.72 (95% CI: 1.20-2.47)	**0.003**
		Myocardial infarction	OR=0.47 (95% CI: 0.29-0.78)	**0.003**
		All-cause mortality	OR=1.11 (95% CI: 0.56-2.18)	0.760
Murad et al. (41)	2008	Any stroke	RR=1.29 (95% CI: 0.73-2.26)	-
		Myocardial infarction	RR=0.43 (95% CI: 0.17-1.11)	-
		All-cause mortality	RR=0.61 (95% CI: 0.27-1.37)	-
Current study		Any stroke	RR=1.555 (95% CI: 1.307-1.851)	**0.001**
		Myocardial infarction	RR=0.458 (95% CI: 0.319-0.660)	**0.001**
		All-cause mortality	RR=1.277 (95% CI: 0.835-1.952)	0.259

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