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Mid-Term Meta-Analysis Results of Carotid Artery Stenting and Carotid Endarterectomy Based on Randomized Controlled Studies

Randomize Kontrollü Çalışmalara Dayalı Karotis Arter Stentleme ve Karotis Endarterektominin Orta Dönem Metaanalizi Bulguları

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ABSTRACT Objective: A comprehensive of published randomized controlled trials (RCTs) was performed to evaluate the mid-term safety of carotid artery stenting (CAS) versus carotid endarterectomy (CEA) for both asymptomatic and asymptomatic carotid stenosis. **Material and Methods:** In this research, trails published from 1994 until December 31, 2021 was performed using ScienceDirect, Pubmed, Web of Science, Sage, Ebscohost, Scopus and Cochrane Central electronic databases. Major end points (any stroke, myocardial infarction, and all-cause mortality) were extracted from the publications. We calculated pooled risk ratios (RRs) and 95% confidence intervals (CIs) using a fixed-effects model. The Q and I2 statistic were used as a measure of heterogeneity. **Results:** Twelve trials involving 8,301 (4,498 with CAS; 3,803 with CEA) patients were included in the meta-analysis. When compared with CAE, stenting was associated with a significantly increased risk of mid-term any stroke (RR=1.397; 95% CI: 1.159-1.684; p<0,001) but a significantly decreased risk of mid-term myocardial infarction (RR=0,487; 95% CIs: 0.302-0.786; p=0,003). No difference was found in mid-term all-cause mortality (RR=1,009; 95% CIs: 0.904-1.126; p=0,869) between the 2 interventions, yet with a minor trend toward superiority favoring CEA. No evidence of significant heterogeneity was found in any of the analysis. **Conclusion:** CAE was found to be superior to stenting in term of any stroke, whereas CAS was associated with a lower risk of mid-term myocardial infarction. But for robust results, further studies are needed to address the relative effectiveness of CAS versus CAE in the future.

Keywords: Carotid stenosis; meta-analysis; randomized control trials

ÖZET Amaç: Bu araştırmada, yayımlanmış randomize kontrollü çalışmaların (RKÇ) sonuçları kullanılarak semptomatik veya asemptomatik karotis stenozou tedavisinde kullanılan karotis arter stentleme (KAS) ve karotis endarterektomi (KAE) yöntemlerinin orta dönem meta-analitik sonuçları değerlendirilmiştir. **Gereç ve Yöntemler:** Araştırmada ScienceDirect, Pubmed, Web of Science, Sage, Ebscohost, Scopus ve Cochrane Central elektronik veri tabanları kullanılarak, 1994 yılından 31 Aralık 2021 tarihine kadar yayımlanan RKÇ'ler analiz edilmiştir. Araştırmada tedavi sonrası yöntemlerin; inme, miyokard infarktüsü ve tüm ölüm nedeni değerlendirilmiştir. Risk Oranı (RO) ölçütü seçilerek hesaplanan etki büyüklüğü, Sabit Etkiler Modeli kullanılarak %95 güven aralığında (GA) hesaplanmıştır. Q ve I2 istatistikleri verilerin heterojenlik varsayımlarında ve verilerin analizinde kullanılmıştır. **Bulgular:** Toplam 8.301 (KAS=4.498; KAE=3.803) hastayı içeren 12 çalışma analize dâhil edilmiştir. KAE ile karşılaştırıldığında KAS yöntemi, orta dönem inme riskinde istatistiksel olarak önemli bir atış ile sonuçlanırken [risk oranı "risk ratio (RR)"=1,397; %95 GA: 1,159-1,684; p<0,001]; tam tersine miyokard infarktüsü bakımından istatistiksel bir azalma ile sonuçlanmıştır (RR=0,487; %95 GA: 0,302-0,786; p=0,003). Araştırmada, orta dönem tüm nedenlere bağlı ölüm oranlarında (RR=1,009; %95 GA: 0,904-1,126; p=0,869) 2 müdahale arasında hiçbir fark bulunmazken, elde edilen sonuç KAE lehine olmuştur. Analizde homojenlik varsayımları sağlanmıştır. **Sonuç:** Araştırmada, inme ve miyokard infarktüsü bakımından tedavi yöntemleri farklı sonuçlar üretirken, tüm ölüm nedenleri bakımından bir fark gözlenmemiştir. Tedavi yöntemlerinin birbirlerinin alternatifi olmaktan ziyade birbirlerini tamamlayan yöntemler olarak kullanılması önerilmektedir.

Anahtar Kelimeler: Karotis stenozu; metaanalizi; randomize kontrollü çalışmalar

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Diseases such as cerebrovascular and cardiovascular, have become the main cause of disabilities and mortality over the world. Carotid artery stenosis-an atherosclerosis disease-is a leading cause of neurological and cardiological morbidity and mortality.[1] Carotid artery stenting (CAS) and carotid endarterectomy (CEA) are 2 essential surgical prosedures applied to manage carotid stenosis. Although, CEA has been considered as the "golden standart" in operation of carotid artery stenosis so far, CAS has progressively become the recent prosedure as an alternative to CAE.[2-5] It was previously indicated that 20-25% nearly all type of stroke incidents are resulted from carotid stenosis.[6] Likewise, approximately 63% individuals with carotid artery stenosis were found to be associated with cardiac events especially in terms of myocardial infarction.[7] Besidas that, death (all-cause morality) is measured generally after both CAS and CAE. At the worldwide level, occurrence of carotid artery stenosis disease is predicted to be 1.5% in 2020.[1]

Despite the observed increase in utilization of CAS prosedure in terms of widespread use of tools in carotid artery stenosis, increased in physicians' clinical knowledge, and patients preferences, the ultimate effect of CAS with CEA precudures remain debatable most notably in mid-term and long-term outcomes.[5,6] In this reseach, we systematically reviewed the randomized controlled trials (RCTs) comparing outcomes of CAS versus CEA in both symptomatic and asymptomatic carotid stenosis in terms of mid-term (post-operaif beyond 30 days) outcomes of any stroke, all-cause mortality, and myocardial infarction.

MATERIAL AND METHODS

In this study, Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines was operated as a handbook.[8]

DATA SOURCES AND SEARCH STRATEGY

An across-the-board literature was searched from 1994 (when metal stents placed in 2 patients with carotid artery stenosis at first) to December 31, 2021 for all RCTs that compared CAS with CEA in the operation of carotid stenosis reported mid-term outcomes.[5] Most popular databases such as ScienceDirect, Pubmed, Web of Science, Sage, Ebscohost, Scopus and Cochrane Central was searched. While searching in databases key terms as "carotid artery stenosis", "endarterectomy", "stenting", "randomized controlled trial", "stroke", "death", "mortality", and "myocardial infarction" was entered. PRESS (Peer Review of Electronic Search Strategies) 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] Upon searching in title and the abstract, then we reviewed the studies as full text. In case of confliction, eventual solution was executed via discussion. In this review, mainly, articles published in English language were taken into consideration but, the searching was not merely restricted to publications in English.

STUDY SELECTION

The predefined criteria that meet the study qualification are the eligible RCTs were included in analysis: (i) participants with symptomatic or asymptomatic stenosis; (ii) trials with or without embolic protection device; (iii) participants with symptomatic stenosis of ≥50% and asymptomatic stenosis of ≥60%; (iv) participants aged ≥18 years); (v) participants who have not previously been treated for carotid artery stenosis.

QUALITY ASSESSMENT

Defined elements such as trial eligibility, data extraction, and evaluated the risk of bias of individual trials assessed independently by 3 researchers. Data was extracted by using National Collaborating Centre for Methods and Tools.[10] For every RCTs, we extracted the year of publication, study type (single or multiple center), total number of patients, median length of follow-up, mean age, the proportion of symptomatic and a symptomatic patients, degree of stenosis, surgical risk, the use of embolic protection devices (EPDs), and outcomes to be analyzed.

The quality of studies were assessed by the Cochrane Collaboration assessment tools.[11] More specifically we analyzied included studies in terms of "sequence generation", "allocation concealment", "blinding of outcome assessment", "incomplete outcome data", "selective outcome reporting", and "other potential sources of bias." For each sub-di-

mention of Collaboration assessment tools every study assigned to a score of high, low, or unclear through risk of bias (Robvis) assessment tool.[12]

As for the outcomes, all data endpoints extracted and classified from individual studies according to included criteria. Outcomes definitions were adopted from the original papers. Although none of the trials had blinding of participants or personnel due to nature of the trials, all individual studies were defined by authors as having a low risk of randomization bias.

DATA EXTRACTION STATISTICAL ANALYSIS

In the statistical analysis, the effect size of risk ratios (RR) and 95% confidence intervals (CIs) were used to estimate the pooled effect size for outcomes. A probability value of 0.05 was accepted as statistical significance. Q-test was used for the presence of heterogeneity among studies. If the Q-test was greater than the degrees of freedom (df), this would indicates the existence of heterogeneity. Afterwards, in order to calculate the heterogeneity between the RCTs, I^2 statistic was used. $I^2 \geq 50\%$ was accepted to represent heterogeneity.[13] The fixed-effects model (FEM) that represents low heterogeneity or random-effects model that represents high heterogeneity applied according to the results of the heterogeneity. Finally, a funnel plot and weighted regression test of Egger was performed in case of publication bias. Investigating the effect of outlier studies on the overall effect size a sensitivity analysis was conducted. For the analysis, Comprehensive Meta-Analysis v2.0 (CMA) software imposed. CMA, developed by Biostat, Inc. was founded in 1986 with funding from the National Institutes of Health in the United States.

ETHICS COMMITTEE APPROVAL

Since the analysis were based on published studies, no ethics committee permission or patient consent were required.

RESULTS

SEARCH RESULTS AND PATIENT CHARACTERISTICS

Based on databases searching, we primarily identified 1,045 relevant studies. After complete evaluation (removing duplicates, abstracts, titles, reviews, protocols, costs etc.), 81 papers finally met the inclusion criteria, and 12 of potential RCTs (mid-term) that compared CAS to CEA were chosen for the analysis (Figure 1).

Table 1 summarizes the design features and the characteristics of the individual studies. 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 He art Association Guidelines) taken into consideration.

These 12 studies enrolled a total of 8,301 (4,498 for CAS, 3,803 for CEA) participants. The sample sizes of included trials waried between 19 and 2,289 patients. Of these patients, 5,001 are symptomatic with a percent of approximately 61% of the studies included, 8 of them are Multiple-center RCTs. The mean age (68.9) of the patients ranged from 65.4 to 72.6 years, and median follow-up durations ranged from 12 to 60 month. Majority of patients had high or moderate surgical risk. In addition, EPD were used in most of the patients especially those published in recent years. The incidence of mid-term outcomes after CAS and CAE was also given in Table 1. There are 12 studies that compare any stroke and all-cause mortality, and 8 compared myocardial infarction.

QUALITY ASSESSMENT AND RISK OF BIAS

The possibility risk of bias in each trial evaluated by the study researcher and evaluators according to the Cochrane Collaboration guidelines. While the included trials were high-quality randomized trials, some studies had no data about the risk of bias. As a result, the trials included in the analysis had significant performance bias (Figure 2).

MID-TERM ANY STROKE

For mid-term of any stroke after treatment, the FEM was applied as a results of Q statistical indicating an exact homogeneity of trials (Q: 9.746; df(Q):11; I^2=0.001%; p<0.553). Since the Q statistic is lower than df, we have some evidence that the true effect size does not vary between studies. And also $I^2 \leq 50\%$, then, there is no significant heterogeneity. Upon applied FEM, CAS was associated with a significantly

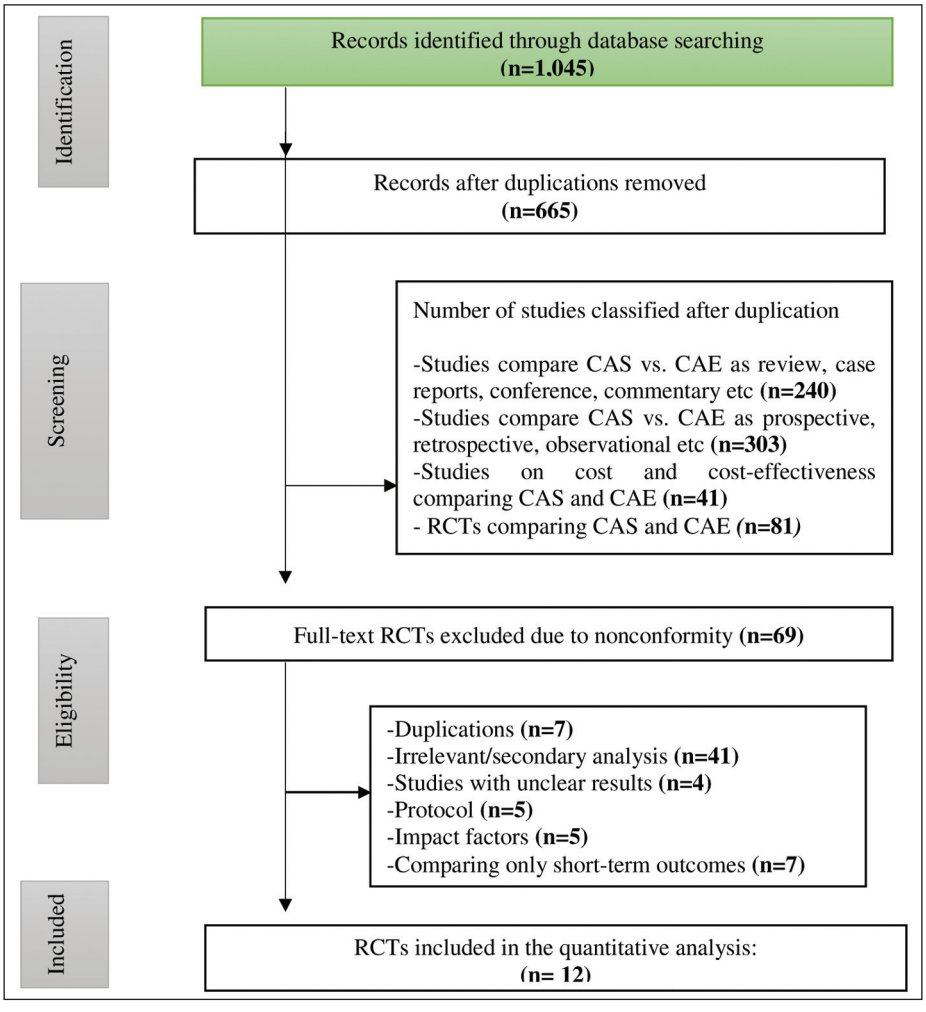

FIGURE 1: Flowchart of the study selection process.[8]
CAS: Carotid artery stenting; CAE: Carotid endarterectomy; RCTs: Randomized controlled trials.

higher incidence of any stroke comparing to CAE (RR=1.397; 95% CI: 1.159-1.684; p<0.001). It can be said that the risk of any stroke after treatment in the CAE group is about 40% less than treatment in CAS (Figure 3). In other words, being treated by CAE might be safer and effective than CAS in terms of mid-term any stroke.

As for bias for any stroke, distribution of funnel plot and the result of an Egger's test (p<0.418) indicated no publication bias and showing robust reliability of results. According to Duval and Tweedie's trim and fill statistic, complete symmetry will be achieved if 2 imaginary studies (black circles) are added to the right side of the funnel plot. In the sensitivity analysis by excluding the study with the highest sample, the results revealed no particular strong influence on the effect size (RR of 1,489; with 95% CIs).

MID-TERM MYOCARDIAL INFARCTION

In the study, since there was no heterogeneity for the myocardial infarction, between CAS and CAE prosedures (Q: 1.157; df(Q):7; I^2=0.000%; p=0.982), a FEM was applied for analyzing the results. After the analysis as the effect size, CAE was associated with a statistically significant higher risk of myocardial infarction (RR=0.487; 95% CIs: 0.302-0.786; p=0.003) when compared with CAS (Figure 4). This findings also shows that the risk of myocardial infarction could be reduced almost 51% if treated with CAS.

TABLE 1: Characteristics and clinical mid-term outcomes of included RCTs comparing CAS and CAE.

Studies	Study design	Population CAS/CAE (yotal)	Mean age (years)	Any stroke (CAS/CAE)	Myocardial infarction (CAS/CAE)	All-cause mortality (CAS/CAE)	Follow-up (month)	*Sympt/ asympt	Degree of stenosis (%)	Surgical risk	Use of EPD
Yadav et al. (2004)[14]	Multiple-center RCTs	158/148 (306)	72.6	4/6	1/2	10/16	12	89/217	Sympt≥ 50% Asympt≥ 80%	High	Yes
Steinbauer et al. (2008)[15]	Single-center RCTs	43/44 (87)	68.3	4/2	0/1	0/0	12	87/0	Sympt≥ 60%	Low	No
SPACE Group (2008)[16]	Multiple-center RCTs	557/545 (1,102)	67.9	16/12	-	24/20	24	1102/0	Sympt≥ 70%	High	Mixed
Hoffmann et al. (2008)[17]	Single-center RCTs	10/9 (19)	70.0	0/0	0/0	0/0	48	19/0	Sympt≥ 70%	High	Yes
Liu et al. (2009)[18]	Single-center RCTs	23/23 (46)	65.4	0/0	0/1	0/0	18	Not available	Sympt≥ 50% Asympt≥ 70%	Not available	Mixed
CAVATAS Group (2009)[19]	Multiple-center RCTs	239/242 (481)	67.0	49/27	-	95/99	60	434/47	Sempt≥ 50% Asempt≥ 50%	Moderate	No
Brott et al. (2010)[3]	Multiple-center RCTs	1,175/1,114 (2289)	69.0	53/46	10/26	85/79	48	1208/1081	Sympt≥ 50% Asympt≥ 60%	Moderate	Mixed
Mas et al. (2014)[20]	Multiple-center RCTs	245/254 (499)	69.7	19/22	11/19	84/92	60	499/0	Sempt≥ 60%	Moderate	Yes
ICSS Group (2015)[21]	Multiple-center RCTs	752/811 (1563)	70.0	56/39	-	120/119	60	1563/0	Sympt≥ 50%	High	Mixed
Rosenfield et al. (2016)[22]	Multiple-center RCTs	1,031/342 (1373)	67.8	102/17	-	134/38	60	0/1373	Asympt≥ 70%	High	Yes
Mannheim and Karmeli (2017)[23]	Single-center RCTs	68/68 (136)	69.2	1/0	0/0	4/4	60	0/136	Asympt≥ 70%	Moderate	Yes
Reiff et al. (2020)[24]	Multiple-center RCTs	197/203 (400)	70.0	3/3	0/1	2/5	12	0/400	Asympt≥ 70%	Moderate	Mixed
Summation		**4498/3,803 (8,301)**	**68.9**	**307/174**	**22/50**	**558/472**	**-**	**5,001/ 3,254**			

*Sympt: Symptomatic; Asympt: Asymptomatic; EPD: Embolism protection device; RCTs: Randomized controlled trials; CAS: Carotid artery stenting; CAE: Carotid endarterectomy

There was no evidence of big-size study effects by of funnel plots and by Egger's regression test (p<0.134). Yet, for the exact symmetry, while considering Duval and Tweedie's trim and fill statistic, about 4 imaginary studies (black circles) are needed to the left side of the funnel plot. Moreover, the consistency of our main findings has been confirmed by sensitivity analysis. The odds of mid-term myocardial infarction remained significantly in favors of CAS when data from the most number of trial was omitted (RR of 0.645; with 95% CIs).

MID-TERM ALL-CAUSE MORTALITY

There was no confirmed heterogeneity in terms of all-cause mortality (Q:4.931; df(Q):11; I^2=0.001%; p<0.934) thus, a FEM was applied. Compared with CAS, CEA was associated with a non-significant reduction in the risk of all-cause mortality. In other words, the pooled results (RR=1,009; 95% CIs: 0,904-1,126; p=0,869) indicates that the difference in all-cause mortality for mid-term results between the CAS and CAE groups was not meaningful (Figure 5). There was no evidence of big-size study effects by funnel plots and by Egger's regression test (p<0.472). According to the trim and fill statistics, when 2 virtual studies (black circles) are added to the right side of the funnel graph, the desired symmetry would be achieved. A sensitivity analysis of all-cause mortality demonstrated that exclusion of trials with the highest weight did greatly affect the overall result of the all-cause mortality in favors of CAS (RR of 0.996; with 95% CIs).

All the funnel plots for mid-term any storke, myocardial infarction and all-cause mortality with Duval and Tweedie's trim and fill statistic (indicated with black spots) demonstrated in Figure 6 from left to right side, respectively.

DISCUSSION

In this systematic review and meta-analysis we aimed at executing the mid-term results of

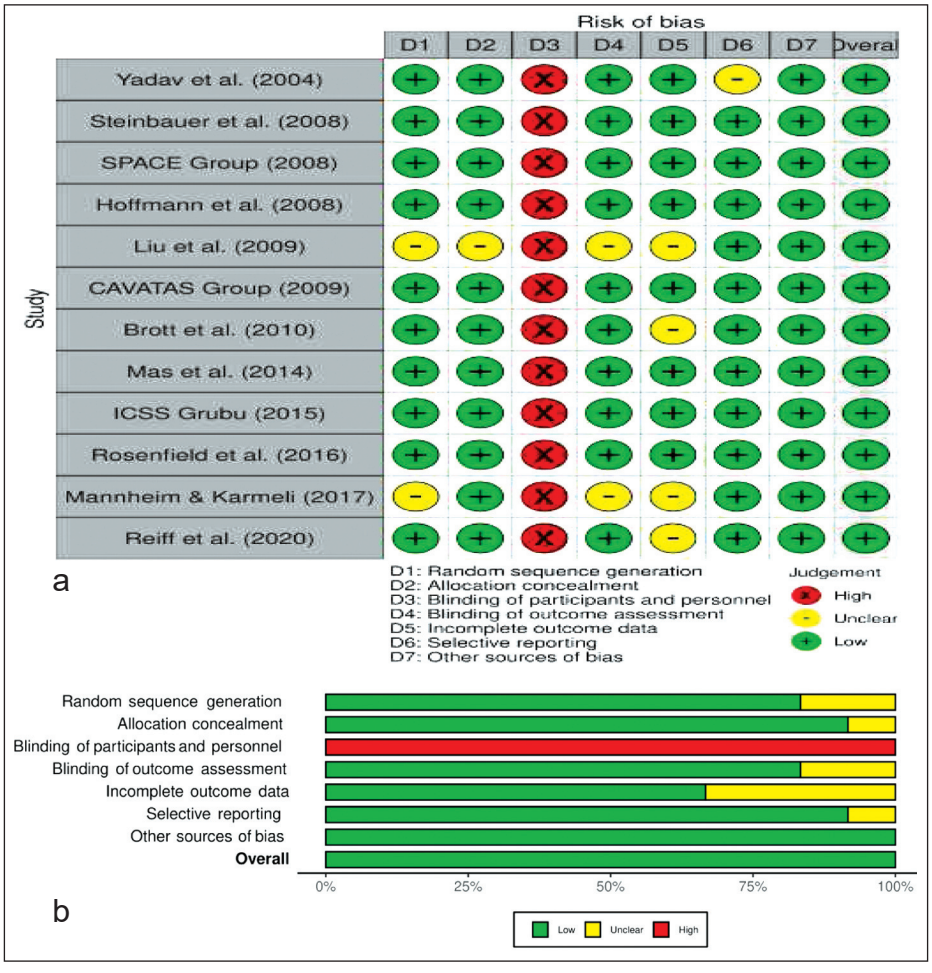

FIGURE 2: Risk of bias graph for RCTs and risk of bias summary of RCTs.
RCTs: Randomized controlled trials.

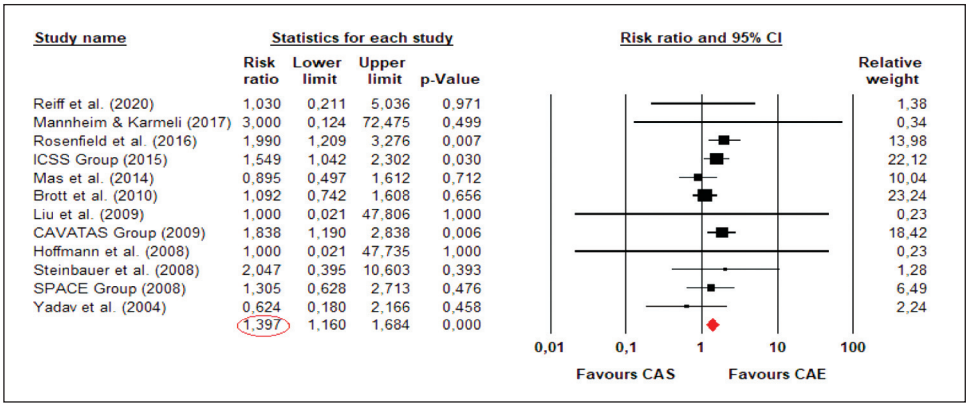

FIGURE 3: Mid-term forest plot of risk ratio (RR) of any stroke.
CI: Confidence interval; CAS: Carotid artery stenting; CAE: Carotid endarterectomy.

safety and efficacy of CAS and CAE with perspective of RCTs in carotid artery stenosis. In this up-dated meta-analysis, which tested mid-term of any stroke, myocardial infarction, and all-cause mortality CAS was associated with a relatively higher rate of any stroke after the procedure that makes CAE superior to CAS. Yet,

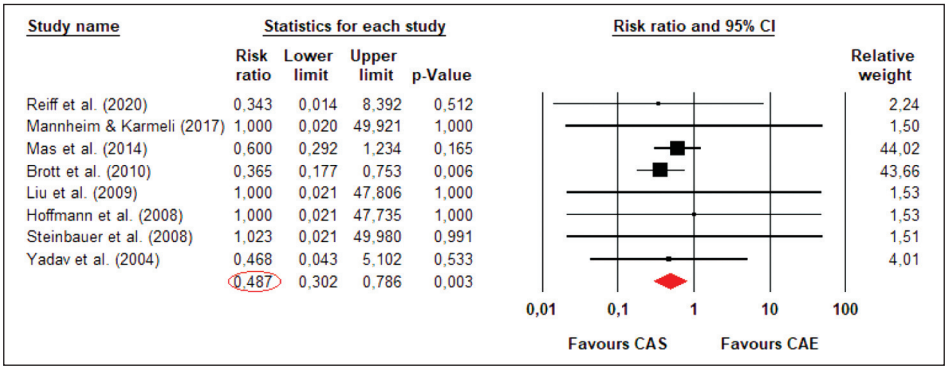

FIGURE 4: Mid-term forest plot of risk ratio (RR) of myocardial infarction.
CI: Confidence interval; CAS: Carotid artery stenting; CAE: Carotid endarterectomy.

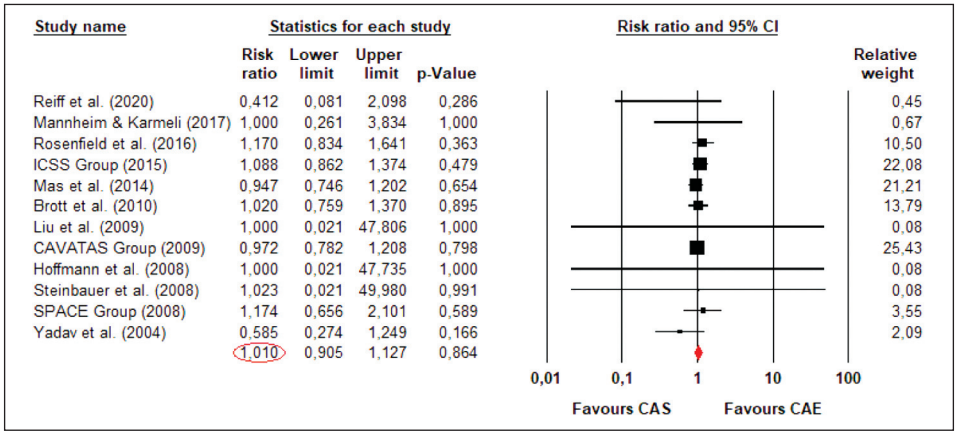

FIGURE 5: Mid-term forest plot of risk ratio (RR) of all-cause mortalit.
CI: Confidence interval; CAS: Carotid artery stenting; CAE: Carotid endarterectomy.

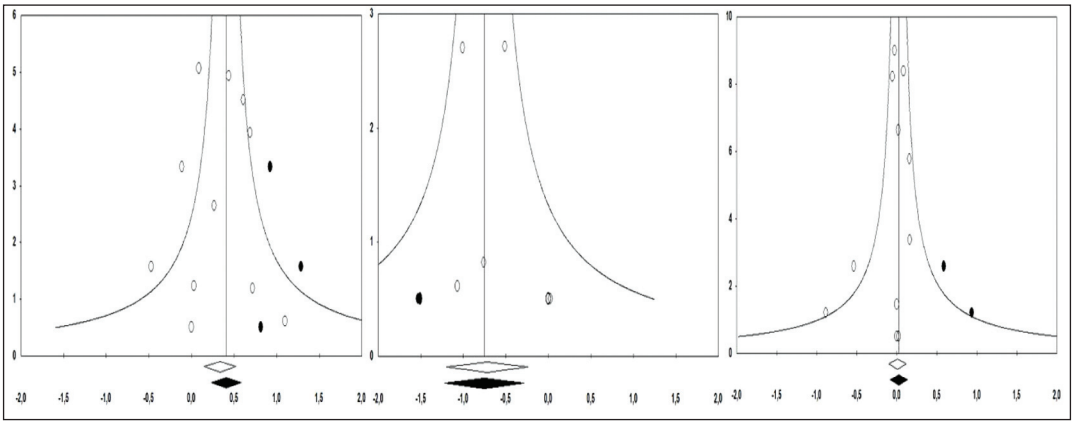

FIGURE 6: Funnel plots of the incidence of any stroke, myocardial infarction, and all-cause mortality from left to right, respectively.

when it comes to myocardial infarction the opposite situation has been observed. That's to say CAS was associated with a significant reduction in the occurrence, and makes CAS superior over CAE. Both procedures have similar effect on all-cause mortality in spite of with a minor trend toward superiority favoring CEA.

TABLE 2: Summary findings of studies on clinical-efficacy of CAS vs CAE.

Studies	Outcomes	Pooled effect	p value
SPACE Group (2008)[16]	Any stroke	(HR=1.19; 95% CI: 0.83-1.73)	-
	All-cause mortality	(HR=1.14; 95% CI: 0.67-1.94)	0.63
CAVATAS Group (2009)[19]	Any stroke	(HR=1.66; 95% CI: 0.99-2.80)	-
	All-cause mortality	(HR=1.07; 95% CI: 0.82-1.40)	-
Brott et al. (2010)[3]	Any stroke	(HR=1.50; 95% CI: 1.05-2.15)	0.03
Mas et al. (2014)[20]	Any stroke	(HR=0.87; 95% CI: 0.43-1.77)	0.71
	All-cause mortality	(HR=1.08; 95% CI: 0.74-1.56)	0.69
	Myocardial infarction	(HR=1.40; 95% CI: 0.86-2.29)	0.17
Vincent et al. (2015)[28]	Any stroke	(OR=1.36; 95% CI: 1.16-1.61)	-
ICSS Group (2015)[21]	Any stroke	(HR=1.71; 95% CI: 1.28-2.30)	0.001
	All-cause mortality	(HR=1.17; 95% CI: 0.92-1.48)	0.19
Li et al. (2017)[29]	Any stroke	(OR=1.45; 95% CI: 1.22-1.73)	0.001
	All-cause mortality	(OR=1.09; 95% CI: 0.95-1.26)	0.21
Current study	Any stroke	(RR=1.397; 95% CI: 1.159-1.684)	0.000
	Myocardial infarction	(RR=0.487; 95% CI: 0.302-0.786)	0.003
	All-cause mortality	(RR=1.009; 95% CI: 0.904-1.126)	0.869

HR: Hazard ratio; OR: Odds ratio; CI: Confidence interval; CAS: Carotid artery stenting.

Even though the pooled effect of any stroke with CAS and myocardial infarction with CAE was higher, much of this conclusion could be based on the majority of the symptomatic (61%) population.[25,26] However, this difference is supposed to be linked to the natures of the CAS and CEA techniques, as well. Besides, surgical risk level also might contribute to the expected outcomes in this study.[27]

In this study, we got similar conclusion to those of previous studies both symptomatic and asymptomatic carotid stenosis. Although our mid-term results are similar to those of previous studies, current meta-analysis is the first far-reaching review with pooled outcomes from 12 RCTs. A summary outcomes of individual RCTs and previous meta-analytical studies with similar design characteristics to the current study are shown in Table 2.

LIMITATIONS AND STRENGTHS OF THIS STUDY

This current study has several limitations. First, since there was not enough studies on mid-term outcomes, it is overlooked to implement subgroup analysis such as patient type (symptomatic or asymptomatic), use of EPDs, different stents used, and surgical risk etc. Second, the conclusions was mainly based on evidence from symptomatic patients. Third, studies with both small and large samples included in this review may have affected the effect size. Thus, all these limitations may reduce the scientific and societal value of this research.

On the other hand, our study also has several strengths. Conducting a comprehensive search by different databases, data collection, summary methods, reporting biases, and explicit quality assessment represent the strengths of this work. Moreover, the homojenity across studies included in analysis reached the level of statistical significance, which strengthened the consistency of our outcomes. As a consequences, the outcomes we reached for CAS and CEA should be complementary rather than competing modes of provided that other variables remain constant.

CONCLUSION

This study was designed to examine the mid-term outcomes of CAS compared to CAE in patients with carotid artery stenosis. While stenting had more favorable mid-term outcome with respect to myocardial infarction, endarterectomy had more favorable mid-term any stroke outcome. For all-cause mortality, we found no significant differences as pooled estimated between CAS and CEA, despite with a minor

trend toward superiority favoring CEA. Thus, considering its lower risk, CAS may offer a well methot in treatment of myocardial infarction, whereas CEA offer a viable methot in the treatment of mid-term any stroke for patinets with carotid artery stenosis. Nonetheless, more evidence is needed to evaluate the comparative efficacy of both techniques. Thus, further studies are needed to address the relative outcomes of stenting versus endarterectomy in the future.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *İzzet Aydemir, İhsan Doğan, Afsun Ezel Esatoğlu;* ***Design:*** *İzzet Aydemir, Afsun Ezel Esatoğlu;* ***Control/Supervision:*** *İzzet Aydemir;* ***Data Collection and/or Processing:*** *İzzet Aydemir, İhsan Doğan, Afsun Ezel Esatoğlu;* ***Analysis and/or Interpretation:*** *İzzet Aydemir, Afsun Ezel Esatoğlu;* ***Literature Review:*** *İzzet Aydemir;* ***Writing the Article:*** *İzzet Aydemir;* ***Critical Review: References and Fundings:*** *İhsan Doğan, Afsun Ezel Esatoğlu.*

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