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ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ
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Μεταπτυχιακή Διπλωματική Εργασία

" Perioperative Risk of Myocardial Infarction after Carotid Endarterectomy and Carotid Stenting. Systematic Review and Meta-analysis of Randomized Control Trials. "

υπό

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Υπεβλήθη για την εκπλήρωση μέρους των
απαιτήσεων για την απόκτηση του
Διπλώματος Μεταπτυχιακών Σπουδών
«Υπερηχογραφική Λειτουργική Απεικόνιση για την πρόληψη & διάγνωση των αγγειακών παθήσεων»

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Τίτλος εργασίας στα ελληνικά:
Περιεγχειρητικός κίνδυνος εμφράγματος του μυοκαρδίου μετά από επεμβάσεις ενδαρτηρεκτομής και αγγειοπλαστικής καρωτίδων. Συστηματική ανασκόπηση και μεταανάλυση τυχαιοποιημένων κλινικών μελετών

ΕΥΧΑΡΙΣΤΙΕΣ

Θα ήθελα να ευχαριστήσω θερμά τον επιβλέποντα καθηγητή μου κ. Μουλακάκη Κωνσταντίνο, για την βοήθεια και την καθοδήγηση που προσέφερε για την εκπόνηση της διπλωματικής μου εργασίας, καθώς και τον καθηγητή κ. Γιαννούκα Αθανάσιο και τους λοιπούς καθηγητές –ιατρούς που συμμετείχαν στο εκπαιδευτικό πρόγραμμα του μεταπτυχιακού προγράμματος.

Contents

Abstract

Background and aim: The aim of this study is to identify the significance of periprocedural myocardial infarction (PMI) after carotid revascularization, in order to assess the safety of carotid artery stenting (CAS) and carotid endarterectomy (CEA) through systematic review and meta-analysis.

Methods: Electronic databases were searched [PubMed, Cochrane Central Register of Controlled Trials (CENTRAL)] from 2000 till 2023. The research should include randomized control trials comparing the perioperative events (30-day results) after carotid angioplasty and endarterectomy. All the trials should refer to the perioperative risk of myocardial infarction, in order to assess its' importance in the safety of each method.

Results: Twelve randomized control trials (RCTs) were included in the review. Not all contributed to each analysis. The risk of periprocedural stroke is reduced in endarterectomy compared to stenting [(OR:1,6, confidence interval:1,3-2,1) p<0,05], while periprocedural myocardial infarction (MI) was more frequent after CEA favoring stenting [OR: 0,4, CI 95%: 0,2-0,7, p< 0,05]. The periprocedural rates of mortality had no great difference between angioplasty and endarterectomy, although endarterectomy has lower risk of death [OR: 1,1, CI (0,6-2,1), p= 0,68]. The composite endpoint of stroke, MI or death is favoring endarterectomy as safer treatment [(OR: 1,3, CI:1-1,5), p<0,05] with significant difference.

Conclusions: Perioperative risk of myocardial infarction is lower in stenting, although the data do not demonstrate raise in mortality rates. Some of the trials do not include definitions of myocardial infarction, probably underestimating the rates of PMI. Carotid and cardiac artery disease share the same risk factors. Future trials should search thoroughly the incidence of PMI, in order to assess the safety of each treatment for carotid disease.

Key words: carotid endarterectomy, carotid stenting, myocardial infarction, systematic review, meta-analysis

Περίληψη

Σκοπός: Σκοπός της παρούσας μελέτης είναι να προσδιορίσει τη σημασία του περιεπεμβατικού κινδύνου εμφράγματος του μυοκαρδίου μετά από επαναγγείωση καρωτίδων, προκειμένου να αξιολογηθεί η ασφάλεια της αγγειοπλαστικής καρωτίδων και της καρωτιδικής ενδαρτηρεκτομής μέσω συστηματικής ανασκόπησης και μετα ανάλυσης.

Μέθοδοι: Έγινε αναζήτηση σε ηλεκτρονικές βάσεις δεδομένων [PubMed, Cochrane Central Register of Controlled Trials (CENTRAL)] από το 2000 έως το 2023. Η έρευνα θα πρέπει να περιλαμβάνει τυχαιοποιημένες δοκιμές ελέγχου που συγκρίνουν τα περιεγχειρητικά συμβάντα (αποτελέσματα 30 ημερών) μετά από καρωτιδική αγγειοπλαστική και ενδαρτηρεκτομή. Όλες οι μελέτες θα πρέπει να αναφέρονται στον περιεγχειρητικό κίνδυνο εμφράγματος του μυοκαρδίου, προκειμένου να εκτιμηθεί η σημασία του για την ασφάλεια της κάθε μεθόδου.

Αποτελέσματα: Δώδεκα τυχαιοποιημένες δοκιμές ελέγχου συμπεριλήφθηκαν στην ανασκόπηση. Δεν συνέβαλαν όλες σε κάθε ανάλυση. Ο περιεγχειρητικός κίνδυνος εγκεφαλικού επεισοδίου είναι μειωμένος στην ενδαρτηρεκτομή σε σύγκριση με την αγγειοπλαστική [(OR:1,6, CI:1,3-2,1) p<0,05], ενώ ο περιεγχειρητικός κίνδυνος εμφράγματος του μυοκαρδίου ήταν πιο συχνός μετά από ενδαρτηρεκτομή, ευνοώντας την αγγειοπλαστική [OR: 0,4, CI 95%: 0,2-0,7, p< 0,05]. Τα περιεγχειρητικά ποσοστά θνησιμότητας δεν είχαν μεγάλη διαφορά μεταξύ αγγειοπλαστικής και ενδαρτηρεκτομής, αν και η ενδαρτηρεκτομή έχει μικρότερο κίνδυνο θανάτου [OR: 1,1, CI (0,6-2,1), p= 0,68]. Το σύνθετο τελικό σημείο εγκεφαλικού επεισοδίου, εμφράγματος ή θανάτου ευνοεί την ενδαρτηρεκτομή ως ασφαλέστερη θεραπεία [(OR: 1,3, CI:1-1,5), p<0,05] με σημαντική διαφορά.

Συμπεράσματα: Ο περιεγχειρητικός κίνδυνος εμφράγματος του μυοκαρδίου είναι χαμηλότερος στην αγγειοπλαστική, αν και τα δεδομένα δεν καταδεικνύουν αύξηση των ποσοστών θνησιμότητας. Ορισμένες από τις δοκιμές δεν περιλαμβάνουν ορισμούς του εμφράγματος του μυοκαρδίου, πιθανώς υποτιμώντας τα ποσοστά περιεγχειρητικά. Η καρωτιδική και καρδιακή αρτηριακή νόσος μοιράζονται τους ίδιους παράγοντες κινδύνου. Οι μελλοντικές δοκιμές θα πρέπει να ερευνήσουν

διεξοδικά τη συχνότητα εμφάνισης περιεγχειρητικού εμφράγματος, προκειμένου να αξιολογηθεί η ασφάλεια κάθε θεραπείας για την καρωτιδική νόσο

Λέξεις-κλειδιά: ενδαρτηρεκτομή καρωτίδων, αγγειοπλαστική καρωτίδων, έμφραγμα μυοκαρδίου, συστηματική ανασκόπηση, μετα-ανάλυση

INTRODUCTION

Stroke is one of the most common causes of death worldwide. Carotid artery stenosis is responsible for 20% of ischemic strokes and transient ischemic attacks, which can present with variant neurological symptoms such as amaurosis fugax, dysarthria, aphasia, numbness or weakness of extremities [1,2]. Ultrasonography as noninvasive diagnostic modality helps in detection of asymptomatic carotid stenosis, which can be treated under circumstances [3]. Carotid Endarterectomy (CEA) was for many years the gold standard surgical procedural for the treatment of carotid stenosis in symptomatic and asymptomatic patients. Carotid artery stenting refers to percutaneous angioplasty as an alternative to endarterectomy in high risk patients, who cannot undergo surgery. Stenting is performed widely the last two decades and is no inferior to endarterectomy, regardless the patient symptom status. Trials have been conducted for the safety of each technique, comparing CEA to CAS for periprocedural stroke, myocardial infarction and death. There has been debate whether myocardial infarction should be included as endpoint in large randomized trials, because the main purpose of conducting this kind of trials was the elimination of stroke and mortality rates after each procedure. However, periprocedural MI is associated with high risk of mortality after vascular surgery and endovascular procedures [4,5]. This was confirmed by a long- term study, in which MI was responsible for two to three times the late mortality compared to patients with no periprocedural events [6]. Data show that CAS has a greater risk for stroke, while periprocedural risk of myocardial infarction (MI) is more often after CEA in randomized control trials (RCTs).

PMI often occurs within the first 24-48 hours after the procedure, as a result of unstable coronary plaque rupture or as severe coronary artery disease (CAD) [7]. It can present as Acute Coronary Syndrome (Type I MI) with thrombotic occlusion of the coronary artery. This is the result of hyperactivity of sympathetic system which includes vasoconstriction, hemodynamic instability and rupture of unstable coronary plaque leading to thrombosis [8]. The second type of myocardial infarction (Type II MI) is a mismatch between myocardial oxygen demand and supply. This occurs when the stress of the procedure is more than the burden the coronary arteries can afford due to stable but obstructive coronary plaques [9]. Type II MI is the most frequent type of MI after non-cardiac surgery, although Type I is recognized in many

cases. MI can present with typical symptoms including chest pain, ischemic electrocardiographic changes (ECG) or elevation of cardiac biomarkers [10]. Many non-cardiac surgeries are accompanied with biomarker elevation without other symptoms. The cardiac biomarker elevation is predictive of intermediate and long-term morbidity and mortality. The elevation of TnI alone following vascular surgery is a stronger predictor of death than the presence of diabetes, congestive heart failure and coronary artery disease [11]. Periprocedural MI can be a fatal endpoint for patients undergoing carotid revascularization and increases future mortality and mortality. PMI must be considered in carotid revascularization when choosing strategy for symptomatic and asymptomatic patients, since decreasing the incidence makes the procedure safer.

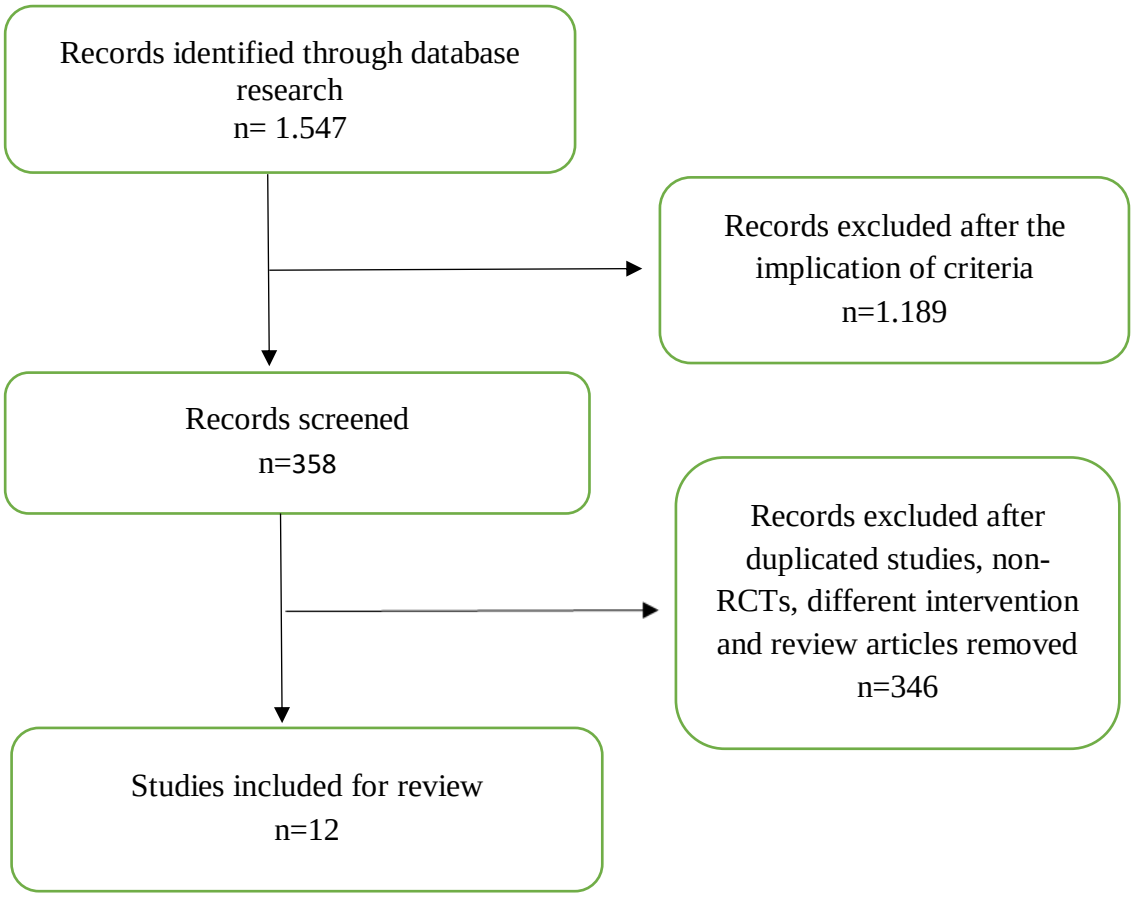
METHODS

Search Strategy

The research was detailed and included the Cochrane Central Register of Controlled Trials (CENTRAL) and PubMed. The keywords used for the research were: carotid angioplasty, carotid stent, carotid endarterectomy, myocardial ischemia, cardiac ischemia, myocardial infarct, cardiac infarct. The research included randomized control trials (RCTs) released from 2000 till 2023. The publication language was English. Reviews, meta-analyses and other studies were checked in order to identify all the eligible studies for the review. The selection included only randomized control trials comparing carotid stenting with endarterectomy. Non randomized trials, single arm studies, case series and letters were excluded.

Eligible Studies

The eligible studies were randomized control trials of angioplasty compared with endarterectomy in symptomatic and asymptomatic patients of any age. The studies had to refer to the periprocedural myocardial infarction as endpoint after stenting and endarterectomy. The results of the research using the keywords above included 1.547 records. The selection criteria were applied and 12 RCT's met the criteria and were included in the review.



RESULTS

The baseline characteristics of the RCTs, inclusion criteria of each study and the demographic characteristics of the patients included in the RCTs are shown in Table 1, Table 2 and Table 3. The 12 RCT's have enrolled 11.153 patients, of whom 5.204 (46%) patients were randomized to CEA and 5.949 (53%) patients were randomized to CAS. Four of the trials have included patients with symptomatic carotid artery disease (Kentucky 2001[13] [Carotid angioplasty and stenting vs carotid endarterectomy trial], EVA 3-S[16] [Endartectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis], BACASS[17] [Basel Carotid artery stenting vs carotid endarterectomy], and the ICSS[19] [Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis] trials), four trials have both symptomatic and asymptomatic participants (CAVATAS [12] [Carotid and Vertebral Artery Transluminal Angioplasty Study], Sapphire[15] [Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy], CREST[18] [Carotid Revascularization Endarterectomy versus Stenting Trial] and Kuliha[20] trials) and four trials have enrolled exclusively asymptomatic patients (Kentucky 2004 [14] [Carotid angioplasty and stenting vs carotid endarterectomy for treatment of asymptomatic carotid stenosis trial], ACT-1[21] [Asymptomatic Carotid Trial], Mannheim/Karmeli[22] and ACST-2[23] [Second asymptomatic carotid surgery trial] trials). An embolic protection device (EPD) has been used in most of them, with the exception of CAVATAS[12], Kentucky 2001[13] and Kentucky 2004[14] trials. The demographics of the RCTs show that most of the patients are men, >60 years and hypertension (HTN) is the more frequent risk factor for carotid artery stenosis unlike diabetes mellitus (DM) and cardiac artery disease (CAD).

Table 1

Characteristics of selected randomized clinical trials included in the review

Study (year)	No. of patients	Symptomatic/ Asymptomatic	CEA	CAS	EPD(%)
CAVATAS (2001) [12]	504	488/16	253	251	0
Kentucky (2001) [13]	104	104/0	53	51	0
Kentucky (2004) [14]	85	0/85	42	43	0
Sapphire (2004) [15]	334	96/238	167	167	95,6
EVA -3S (2006) [16]	527	527/0	262	265	92
Bacass (2008) [17]	20	20/0	10	10	100
Crest (2010) [18]	2502	1.326/1.176	1240	1262	96
ICSS(2010) [19]	1713	1713/0	858	855	73
Kuliha (2014) [20]	150	87/63	73	77	96
ACT 1(2016) [21]	1453	0/1453	364	1089	97,8
Mannheim (2017) [22]	136	0/136	68	68	100
ASCT-2 (2021) [23]	3625	0/3625	1814	1811	100

Table 2

Inclusion criteria of selected randomized control trials

Study (year)	Inclusion criteria
CAVATAS (2001) [12]	>50% symptomatic or asymptomatic stenosis of the common carotid artery, carotid bifurcation, or internal carotid artery needed treatment and was suitable for both carotid endarterectomy and endovascular treatment
Kentucky (2001) [13]	>70% symptomatic stenosis of the ipsilateral carotid bifurcation as determined by the NASCET criteria
Kentucky (2004) [14]	>80% asymptomatic stenosis of internal carotid artery with digital subtraction angiography – documented as determined by NASCET criteria

Sapphire (2004) [15]	>50% symptomatic carotid stenosis of the luminal diameter or >80% asymptomatic stenosis and at high surgical risk
EVA -3S (2006) [16]	60-99% symptomatic carotid stenosis as determined by the NASCET criteria and hemispheric or retinal transient ischemic attack or non-disabling stroke within 120 d before enrollment
Bacass (2008) [17]	Symptomatic high- grade internal carotid artery stenosis (70-99% on duplex ultrasonography and on magnetic resonance angiography)
Crest (2010) [18]	>50% symptomatic carotid stenosis on angiography and > 70% on US, CTA, MRA symptomatic stenosis or >60% asymptomatic carotid stenosis on angiography and >70%
ICSS(2010) [19]	>50% symptomatic carotid artery stenosis by the NASCET criteria
Kuliha (2014) [20]	>70% stenosis of internal carotid artery (symptomatic or asymptomatic) detected by duplex ultrasonography and confirmed using CT angiography (CTA)
ACT 1(2016) [21]	> 70% asymptomatic bifurcation carotid stenosis, as determined by ultrasonographic or angiographic criteria
Mannheim (2017) [22]	>70% asymptomatic carotid stenosis detectable by duplex ultrasound and confirmed by CTA or MRA without previous ipsilateral carotid procedure
ASCT-2 (2021) [23]	>60% asymptomatic carotid artery stenosis

Table 3

Demographic characteristics of the patients

Study (year)	**Male (%)**	**Age Mean, y**	**HTN (%)**	**CAD(%)**	**DM(%)**
CAVATAS (2001)[12]	352 (69,5)	67	276 (55,5)	187 (38,5)	67 (13)
Kentucky (2001) [13]	NK	68	48 (46,5)	36 (35,5)	16 (15,5)
Kentucky (2004) [14]	NK	68	32 (38)	23 (27,5)	5 (6)

Sapphire (2004) [15]	219(67)	72,5	285(85,4)	267(80,6)	88(26,4)
EVA -3S (2006) [16]	391(69,5)	69,5	380(73)	NK	124(24)
Bacass (2008) [17]	17(85)	70	15(75)	6(30)	6 (30)
Crest (2010) [18]	1629 (74)	69	2.151(86)	1.050(42)	750(30)
ICSS(2010) [19]	1207(70)	70	1.1.82 (69)	307(18)	371 (22)
Kuliha (2014) [20]	105(70)	65	131(87)	57(38)	65 (43)
ACT 1(2016) [21]	873(60)	67	1.313(90)	767(52)	506 (33)
Mannheim (2017) [22]	93(62)	68	115 (84)	67(49)	65(48)
ASCT-2 (2021) [23]	2545(70)	70	2.299(64)	1.301(35)	1.085(30)

Periprocedural outcomes of RCTs comparing CAS and CEA

The periprocedural period was defined as the time from randomization to 30 days' post procedure. The incidence of periprocedural outcomes of interest in all RCTs is shown in Table 4.

Table 4

Outcome Event Rate in the RCTs

Study (year)	30-Day Death		30-Day Stroke		30-Day MI		30-Day MI, Stroke or Death	
	CAS	CEA	CAS	CEA	CAS	CEA	CAS	CEA
CAVATAS (2001) [12]	7(2,8)	4(1,6)	18(7,1)	21(8,3)	0(0)	3(1,2)	25(9,9)	28(11,1)
Kentucky (2001) [13]	0(0)	1(2)	0(0)	0(0)	0(0)	1(2)	0(0)	1(2)
Kentucky (2004) [14]	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	NK	NK
Sapphire (2004) [15]	2(1,2)	4(2,4)	6(3,6)	5(3)	4(2,4)	10(5,9)	8(4,8)	10(5,9)
EVA -3S (2006) [16]	2(1)	3(1,1)	23(8,7)	7(2,7)	1(0,4)	2(0,8)	26(9,8)	12(4,6)
Bacass (2008) [17]	0(0)	0(0)	0(0)	1(10)	0(0)	0(0)	0(0)	1(10)
Crest (2010) [18]	9(0,7)	4(0,3)	52(4)	29(2,3)	14(1)	28(2,3)	66(5,2)	56(4,5)

ICSS(2010) [19]	1(0,1)	1(0,1)	58(7)	27(3,3)	3(0,4)	5(0,6)	61(7,4)	33(4)
Kuliha (2014) [20]	0(0)	0(0)	2 (2,7)	1(1,7)	0(0)	0(0)	2(2,7)	1(1,7)
ACT 1(2016) [21]	1(0,1)	1(0,1)	30(2,8)	5(1,4)	5(0,5)	3(0,9)	36 (3,3)	9(2,6)
Mannheim (2017) [22]	0	0	2 (2,9)	1 (1,4)	0	0	2(2,9)	1 (1,4)
ASCT-2 (2021) [23]	2 (0,1)	2(0,1)	61(3,6)	41(2,4)	5 (0,3)	12(0,7)	68 (3.9)	55(3,2)

Periprocedural MI in the RCTs

The carotid revascularization trials tend to inform for the risks of each procedure by outlining the outcome events after CEA and CAS. The events of stroke, myocardial infarction and death are the main outcomes, in order to evaluate the safety of endarterectomy and stenting for carotid artery stenosis. Periprocedural myocardial infarction is one of the most significant outcomes and in some cases can be fatal, leading to death. Most of the trials include the incidence of periprocedural myocardial infarction, but each of these sets a different definition including symptoms, electrocardiographic changes and biomarker elevation. A small range of trials includes only the outcomes, without providing a definition. The available data concerning the definitions of each study are shown in Table 5.

CAVATAS

CAVATAS [12] is an international multicenter study, including symptomatic and asymptomatic patients for endovascular treatment and surgery. 504 participants were randomized between CEA and CAS. There was no definition of periprocedural MI, but it was included as outcome. 3 (1,2) patients had myocardial infarction after CEA in contrast to CAS, which had no events. Stroke had a greater incidence after CEA (8,3 versus 7,1), making CAS a safer treatment for carotid revascularization. All myocardial infarctions were defined as no fatal.

Kentucky

The Kentucky [13-14] trials are two single center randomized trials. The first trial included 104 symptomatic patients, who had signs and symptoms of cerebral ischemia within the last 3 months, while the second trial had 84 participants without

symptoms with a carotid stenosis >80%. None of the studies provided a definition of myocardial infarction. The first trial recorded one myocardial infarction after CEA leading to death. The second trial had no events.

Sapphire

The Sapphire [15] trial included both symptomatic and asymptomatic patients with high surgical risk. The majority of the patients randomized to the trial were asymptomatic and the eligibility criteria were >60% stenosis in the symptomatic group and >80% stenosis for the asymptomatic group. The definition included only biomarker elevation (CK) twofold the normal limit and a positive CK-MB and was the first trial to require PMI ascertainment. The perioperative incidence of myocardial infarction was higher after endarterectomy in contrast to angioplasty (5,9 versus 2,4), while stenting had a greater percentage of stroke incidence (3,6 vs 3). There was no data about myocardial infarctions leading to death.

BACASS

BACASS[16] is a single center study with 20 participants. The patients were randomized between endarterectomy and stenting and the trial included symptomatic and asymptomatic carotid stenosis. There was no definition of myocardial infarction and there was no perioperative event, except of an ipsilateral stroke, which leaded to death.

EVA 3-S

The randomized trial EVA-3S [17] was a multicenter study which included only symptomatic patients with stenosis >70% (NASCET criteria). The trial had 527 participants which were randomized between angioplasty and endarterectomy. EVA -3S was the first study to specify periprocedural myocardial infarction as an endpoint. The event of myocardial infarction should fulfill two of the following criteria (chest pain, biomarker elevation, electrocardiographic changes) and there were more periprocedural events after endarterectomy compared to stenting (0,8 vs 0,4). The trial had a great incidence of periprocedural strokes after CAS (8,7 vs 2,7) but low mortality rates (1,1 vs 1). No myocardial infarction was reported to lead to death.

CREST

CREST [18] is a multicenter trial, in which 2,502 symptomatic and asymptomatic patients were randomized between endarterectomy and stenting. The trial included PMI as primary endpoint and was defined as CK-MB or TNI elevation, chest pain or ischemic electrocardiographic changes. CREST reported a higher risk of PMI in CEA compared to CAS (2,3 vs 1) and similar mortality rates in both arms (0,3 vs 0,7). One periprocedural myocardial infarction in CREST was reported to lead to death. On the other hand, CAS has higher risk of stroke compared to CEA (4 vs 2,3).

ICSS

The International Carotid Stenting Study (ICSS) [19] was a multicenter randomized trial which included 1.713 patients with >50% symptomatic carotid artery stenosis by the NASCET criteria. Despite the fact that the study provided definition of myocardial infarction including chest pain >30′, biomarker elevation and specific ECG changes, periprocedural myocardial infarction was a secondary endpoint without protocol driven ascertainment of ECG's and biomarkers resulting in low PMI rates compared to other trials. The reported results included increased PMI events after CEA compared to CAS (0,6 vs 0,4). In ICSS, fatal MI events occurred in 3 of 853 patients (0.4%) with CAS, and 5 nonfatal MIs occurred in 821 patients with CEA (0.6%). The trial reported high risk of periprocedural stroke after CAS compared to CEA (7 vs 3,3), although mortality was low in both arms (0,1).

Kuliha

The Kuliha trial [20] is a single center trial, which randomized 150 symptomatic and asymptomatic patients between CEA and CAS. The study included myocardial infarction as endpoint, which was defined as elevation of cardiac enzymes or ischemic electrocardiogram. However, there was no event of PMI and the trial reported periprocedural stroke with a higher incidence after CAS (2,7 vs 1,7).

ACT-1

The Asymptomatic Carotid Stenosis trial [21] randomized 1.453 patient with asymptomatic carotid disease between angioplasty and endarterectomy. There was no definition of PMI, although it was included as composite primary endpoint with stroke and death. The trial results haven't shown a great difference in the incidence of PMI between the two methods, but CAS had higher percentages (0,5 vs 0,9). ACT -1 is the

first trial, which reports higher risk of PMI after angioplasty compared with other trials. The reason might be that CAS included more patients in randomization compared with CEA (1089 vs 364). The periprocedural stroke rate was higher after CAS (2,8 vs 1,4), while mortality rates were similar in both arms (0,1)

Mannheim

The Mannheim trial [22] is a single center trial with 136 participants, which were equally randomized in CEA and CAS. Periprocedural myocardial infarction was defined as clinical symptoms or biomarker elevation. There were no events of PMI or death, except for the periprocedural stroke, which was higher after stenting (2,9 vs 1,4).

ACST -2

ACST-2 [23] was a multicenter study with 3.625 participants with asymptomatic carotid stenosis. The trial included myocardial infarction as primary endpoint and it was defined as chest pain, elevation of cardiac biomarkers or electrocardiographic changes. CEA had a greater rater of PMI compared to CAS (0,7 vs 0,3), while CAS had a higher risk of periprocedural stroke as in other trials (3,6 vs 2,4). The trial did not demonstrate results about the association between mortality and myocardial infarctions. There was no difference in periprocedural rates of death between CEA and CAS.

Table 5

Definition of Myocardial Infarction in the selected RCTs

Study (year)	Myocardial Infarction
CAVATAS (2001) [12]	Not available
Kentucky (2001) [13]	Not available
Kentucky (2004) [14]	Not available
Sapphire (2004) [15]	Myocardial infarction was defined as creatine kinase level higher than two times the upper limit of normal with a positive MB fraction
EVA -3S (2006) [16]	Myocardial infarction was defined by at least two of the following criteria: typical chest pain lasting 20 minutes or more; serum levels of creatine kinase, creatine kinase MB, or troponin at least twice the upper limit of the normal range; and new Q wave on at least two

	adjacent derivations or predominant R waves in V1 (R wave ≥1 mm >S wave in V1).
Bacass (2008) [17]	Not available
Crest (2010) [18]	Myocardial infarction was defined by a creatine kinase MB or troponin level that was twice the upper limit of the normal range or higher according to the center′s laboratory, in addition to either chest pain or symptoms consistent with ischemia or ECG evidence of ischemia, including new ST segment depression or elevation of more than 1 mm in two or more contiguous leads
ICSS(2010) [19]	Myocardial infarction was defined by the presence of two of the following three criteria: specific cardiac enzymes more than twice the upper limit of normal; history of chest discomfort for at least 30 min; or the development of specific abnormalities (e.g., Q waves) on a standard 12-lead electrocardiograph.
Kuliha (2014) [20]	Myocardial infarction defined as greater than twofold increase in cardiac troponin T level or electrocardiographic evidence of ischemia
ACT 1(2016) [21]	Not available
Mannheim (2017) [22]	Myocardial infarction defined by relevant clinical symptoms with elevated enzymes
ASCT-2 (2021) [23]	Confirmation of a myocardial infarction required at least two of three criteria: symptoms, biomarker elevation, or electrocardiogram changes.

PMI Risk Factors

The high prevalence of coronary artery disease with peripheral arterial disease and the mortality rates following PMI make the cardiac evaluation during major vascular surgeries of great importance. The key is the recognition of the factors that increase the risk of PMI, in order to reduce the mortality rates in high-risk patients. Age greater than 70, diabetes mellitus (DM), coronary artery disease (CAD) and hypertension (HTN) are the main risk factors for periprocedural myocardial infarction [8]. Most of the PMIs are asymptomatic and routine biomarker assessment

in high risk patients is recommended prior and up to 72 hours after all major no cardiac surgeries [6]. The randomized control trials which were selected in the review provide the demographic characteristics of the patients. Peripheral arterial disease and coronary arterial disease share the same risk factors. Most of the participants in the trials are male, while the mean age of the majority of the patients is 70 years old. Age has been associated with increased surgical risk, due to more comorbidities in older patients. CREST[18], EVA-3S[16] and ICSS[19] reported increased stroke risk with increasing age among patients [27,28]. These data suggest that patient selection factors, especially age should be considered in high risk patients when they are randomized between endarterectomy and stenting. Hypertension is one of the most frequent risk factors recognized in the participants. Five trials (Sapphire[15], Crest[18], Kuliha[20], ACT-1[21] and Mannheim[22] trials) include patients with hypertension up to 90% of the participants, while the percentages in the other trials are lower. Coronary arterial disease is recognized in all trials. The Sapphire trial has the highest percentage of CAD up to 80%, and ACT-1 is following with 52%. Diabetes mellitus is also present in the majority of the patients participating in the trials, playing a significant role in carotid arterial disease.

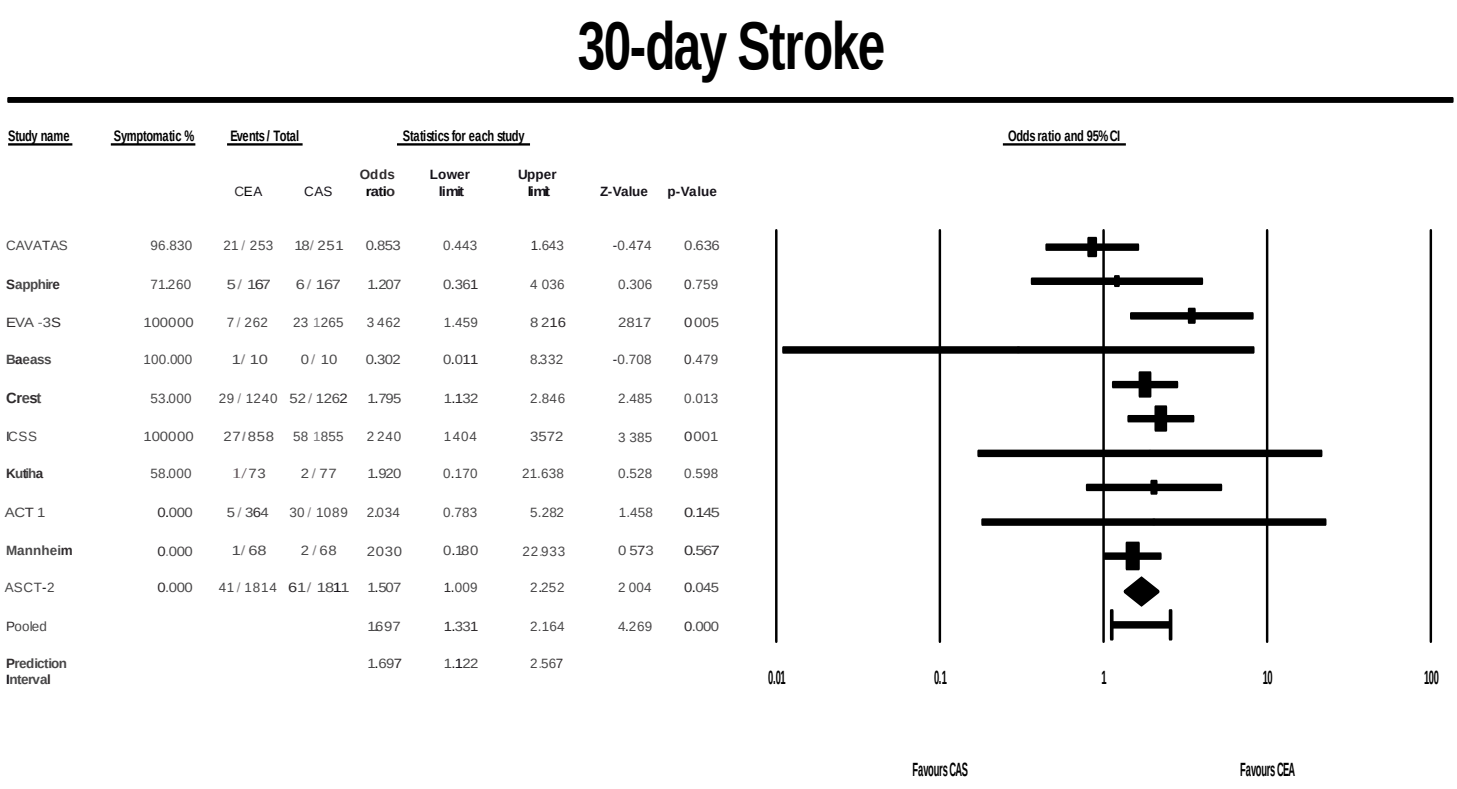
Statistical analysis

Periprocedural Stroke

The outcome analysis included ten studies [12, 15-23]. Seven studies had both symptomatic and asymptomatic patients and three of the studies only asymptomatic patients. A total of 10.964 patients were included in the analysis on stroke, of which 5.109 were randomized to endarterectomy and 5.855 were randomized to stenting. The odds ratio (OR) for periprocedural stroke was significantly in favor of endarterectomy compared to stenting [OR: 1,6, 95% confidence interval 1,3-2,1, p<0,05). Only the CAVATAS [12] study favored CAS compared to CEA with no significant difference (OR: 0,8, CI 95%: 0,4-1,6, P: 0,6). Two RCTs (Kentucky studies[13,14]) did not include the stroke incidence between the two treatments. The test for overall effect is Z= 4,2 (p<0,05), which indicates a significant difference between CEA and CAS. The I squared test is 11% (p: 0,342), which demonstrates low heterogeneity between the studies. The data are shown on table 6.

Table 6

Forrest plot of periprocedural Stroke



The I-squared statistic is 11% p 0.342

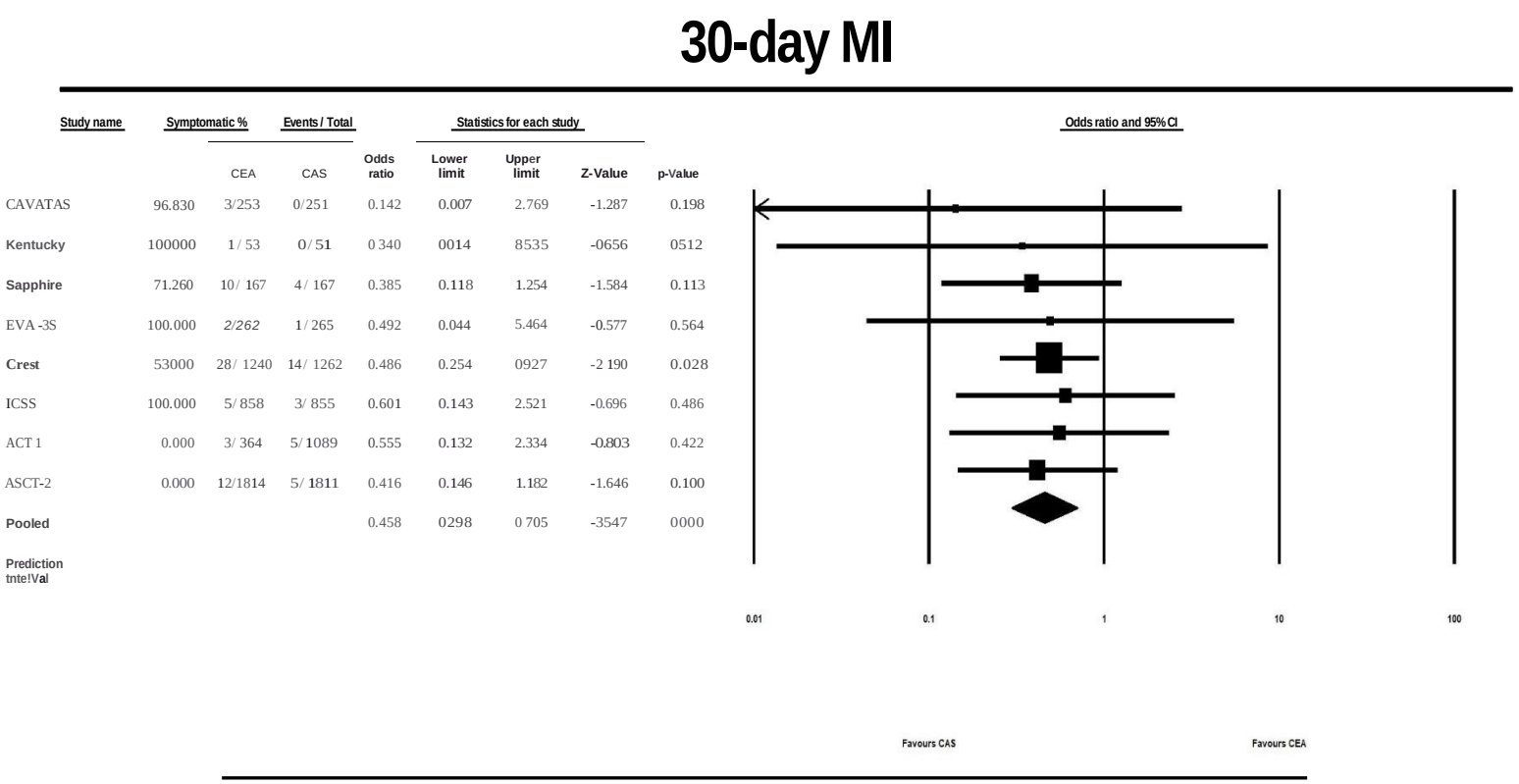
Peripocedural Myocardial infarction

The outcome event of periprocedural MI was reported in eight studies [12-13, 15-16, 18-19, 21,23], which included both symptomatic and asymptomatic patients. The analysis included 10.762 patients. 5.011 patients were randomized to CEA and 5.711 were randomized to CAS. Four of the studies (Kentucky[14], BACASS[17], Kuliha[20] Mannheim[22]) had no report of events of PMI. All of the trials in the analysis reported lower periprocedural risk of myocardial infarction among patients undergoing stenting compared to endarterectomy, as demonstrated by the pooled data [OR: 0,4, CI 95%: 0,2-0,7, p< 0,05]. CREST study was the only trial with significant difference in the reported results (OR: 0,48, CI: 0,25-0,92, p=0,02). The overall

effect was Z: -3,5 (p: 0<0,05). The analysis had no heterogeneity as indicated by the I squared test= 0% (p=0,98). The data are shown on table 7.

Table 7

Forrest plot of periprocedural myocardial infarction



The I-squared statistic is 0% p 0.985

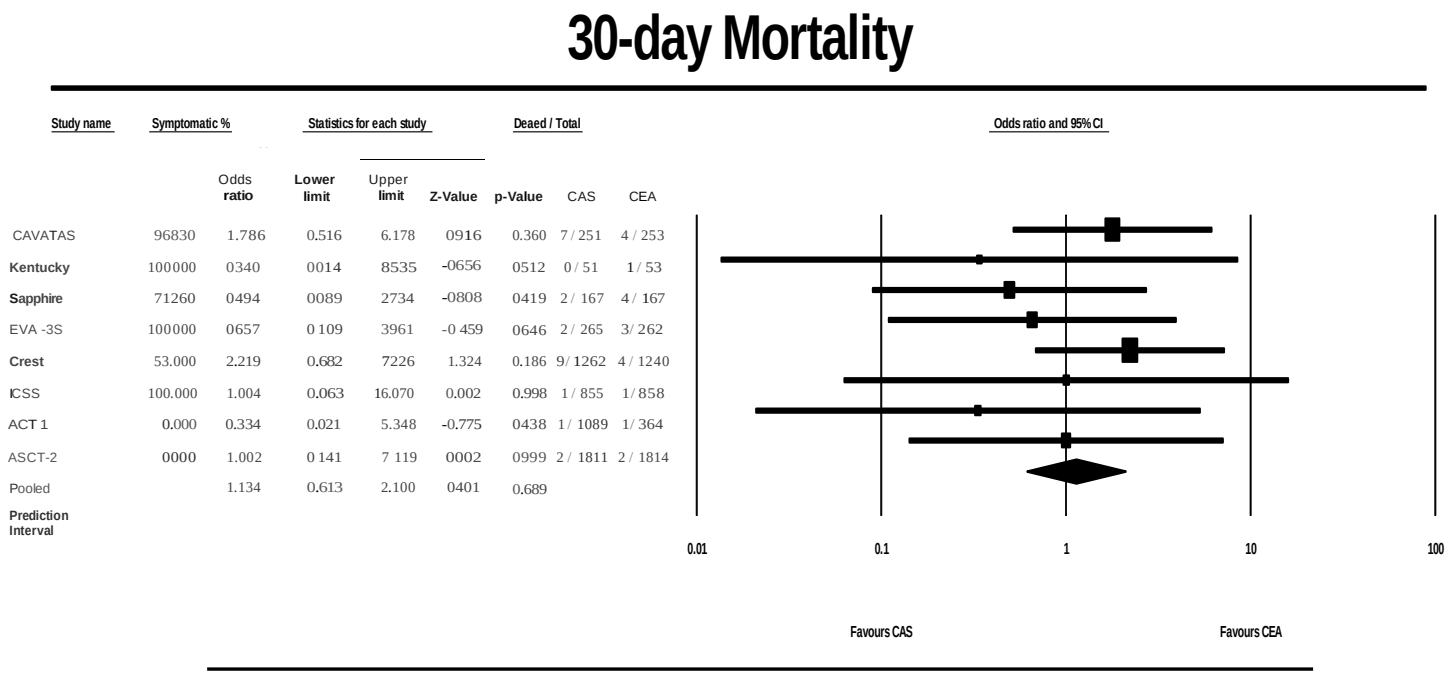
Periprocedural mortality

The analysis included outcomes from eight studies [12-13, 15-16, 18-19, 21,23]. A total of 10.742 symptomatic and asymptomatic patients were included in the analysis of mortality and were randomized as 5.011 in endarterectomy and 5.751 in the stenting group. According to the pooled data, periprocedural mortality was lower in the endarterectomy treatment group compared to stenting, although there was no significant difference between the two treatments [OR 1,1, 95% confidence interval 0,6-2,1, p:0,68]. Four of the studies demonstrated lower mortality risk after stenting (Kentucky[13], Sapphire[15], EVA 3S[16], ACT I[21]), while CAVATAS[12] and Crest[18] reported lower mortality rates after endarterectomy. Two studies reported no

difference in the mortality rates. Four studies had no reference in mortality rates. The test for overall effect indicates Z= 0,4 (p=0,68) and the test had no heterogeneity as indicated by I squared = 0% (p=0,742). Data are demonstrated on table 8.

Table 8

Forrest plot of periprocedural mortality



The I-squared statistic is 0% p 0.742

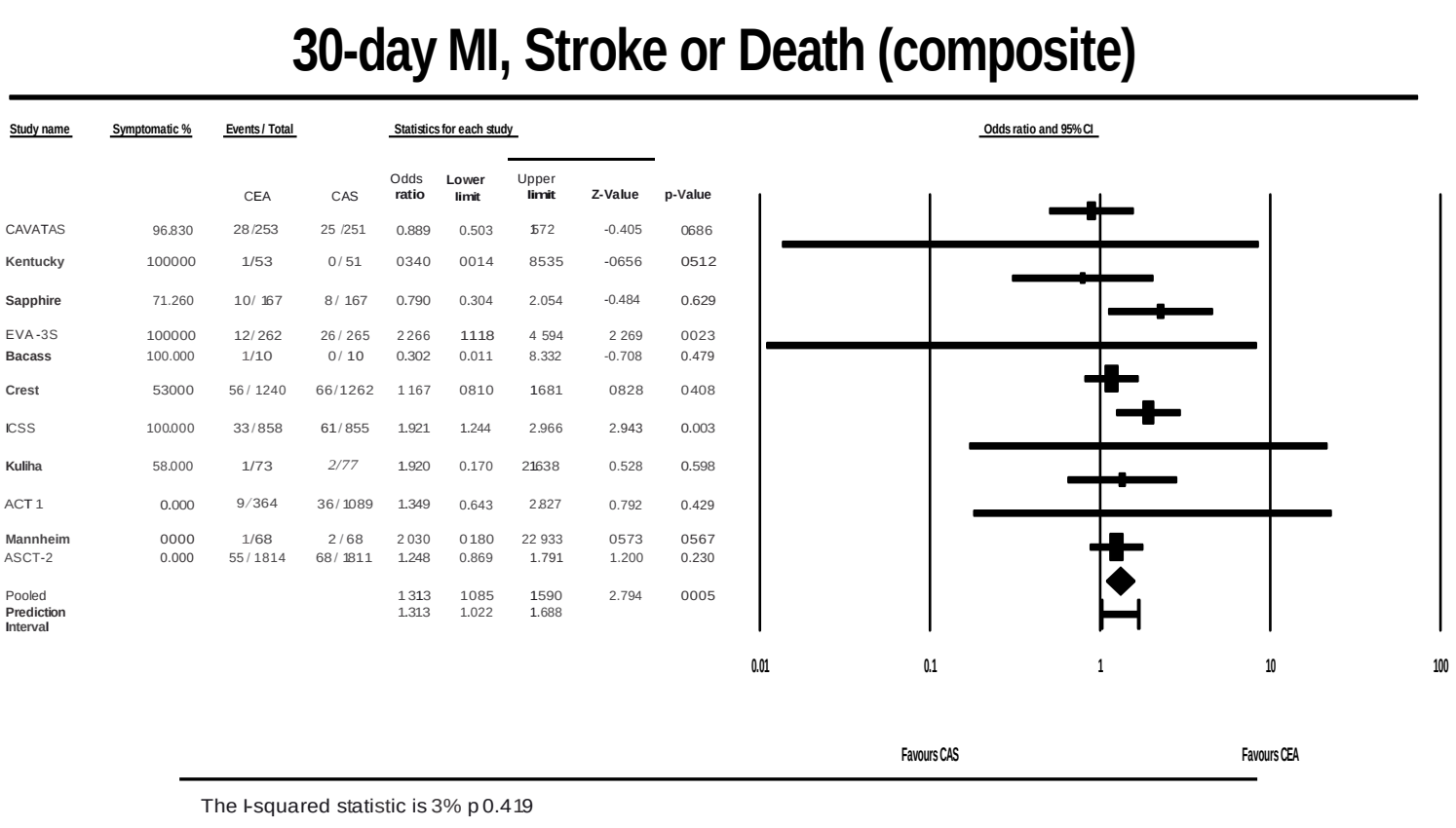
Periprocedural composite endpoint of Stroke, MI or Death

The outcome analysis included eleven studies [12-13,15-23] with a total of 11.048 participants. 5.162 patients were randomized to endarterectomy, while 5.886 were randomized to stenting. The pooled data demonstrated endarterectomy as a safer treatment compared to stenting with significant difference (OR: 1,3, 95% CI: 1-1,5, p<0,05). Among the trials, EVA 3-S[16] and ICSS[19] demonstrated endarterectomy as safer treatment with significant difference(p<0,05). Only two of the trials (CAVATAS[12,] Sapphire[15]) had lower risk of composite endpoint after stenting but with no significant difference (p:0,68, p:0,62 respectively). Four of them (Kentucky[13], Bacass[17], Kuliha[20] and Mannheim[22]) had very few events in the

treatment arms and could not be analyzed and one trial had no events and was not included. The overall effect is Z= 2,7 (p<0,005) and the test of heterogeneity was low [I squared =3% (p=0,4)]. Data are demonstrated on table 9.

Table 9

Forrest plot of composite periprocedural endpoint of MI, Stroke or Death



Limitations

The analysis has some potential limitations. The selected studies should refer to periprocedural myocardial infarction as endpoint. The number of trials including this endpoint was small and the selection included some trials with small amount of participants or events. As a result, the data were heterogeneous. Heterogeneity is found in many aspects of the trials. The stenting technique is not the same in all trials. Those in the early stage used devices no longer in use and without protection. The analysis included trials with no use of cerebral protection device, which could affect the risk of periprocedural stroke in the stenting arm in these trials. However, the amount of patients randomized to stenting in these trials is small and two (Kentucky [13-14]) of these reported no events of stroke. There is also variety in the baseline characteristics of the patients included in the trials. One of the trials (EVA-3S [16]) was stopped earlier, because of concerns in the safety. Another limitation is the variation in the definitions of myocardial infarction between the trials and the number of patients included in each of them. There has been a great variety in the cardiac biomarkers used in each of them, while some of them report events without providing definition of myocardial infarction (CAVATAS[12], Kentucky[13,14], BACASS[17]). However, the diagnosis is based on parameters (clinical symptoms, biomarker elevation, ECG changes) and the estimation of risk of MI has not been severely affected. The same limitation is recognized in strokes, as most of the trials include both major and minor events in their results. Another limitation is the fact, that not all trials provide data about the fatal MIs and there cannot be exacted results about the mortality rates of PMIs. Moreover, the analysis was based on data abstracted from publications and not individual patient data. One of the studies (Kentucky[14]) was included due to the reference in periprocedural myocardial infarction, although there were no reported events and did not offer data for statistical analysis.

CONCLUSIONS

The study shows that carotid endarterectomy had fewer harmful events compared to stenting. The periprocedural risk of stroke at 30 days is significantly reduced with endarterectomy [(OR: 1,6, confidence interval:1,3-2,1) p<0,05], although most of the trials included in the analysis used cerebral protection devices in almost all participants in the stenting treatment (Table 1). Only three trials (CAVATAS[12], Kentucky[13,14]) had no use of protection devices. When carotid stenting was introduced as treatment, it was combined with high risk of periprocedural stroke and the technique was modified, in order to include cerebral protection devices. Nevertheless, the analysis demonstrates higher incidence of stroke with stenting, even if some of these strokes are minor.

The opposite results are reported in the incidence of myocardial infarction. The analysis demonstrated that periprocedural MI is more frequent after open endarterectomy. Carotid stenting is much safer treatment technique and only few events were reported. This is related with the antiplatelet therapy, the type of anesthesia performed in each procedure (general anesthesia in CEA vs local anesthesia in CAS) [24] and the prothrombotic state, which is higher in endarterectomy [25]. However, the myocardial infarction incidence was not associated with high mortality rates, because there were only few events mentioned as fatal in the studies included in the analysis (Kentucky, Crest, ICSS). As mentioned above, no cardiac surgeries (including carotid artery treatment) are associated with higher incidence of myocardial infarction, because atherosclerosis is a systematic disease [26]. Coronary arterial disease is recognized in participants in most of the included trials, which is the main risk factor for myocardial infarction in carotid surgery. However, the number of studies including MI as endpoint are few compared with the trials including stroke and mortality, making essential the inclusion of MI in future trials for more accurate results.

Death as endpoint is included in all studies of the analysis. The study demonstrated lower mortality risk after endarterectomy compared with stenting, but there was no significant difference [OR:1,1, CI 95% 0,6-2,1, p=0,68]. The two treatment groups have similar death rates. The composite endpoint of stroke, myocardial infarction or death is higher in stenting compared to endarterectomy, which is proven to be safer [(OR: 1,3, CI: 1-1,5, p<0,05] and the difference is significant. Despite the periprocedural risk of MI, the overall outcome is favoring endarterectomy as safer

treatment for carotid disease. The future trials should focus on reducing stroke and myocardial infarction for the improval of the two treatments.

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