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ORIGINAL ARTICLE

Cardiac damage after carotid intervention: a meta-analysis after a decade of randomized trials

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Abstract
Purpose This study synthesizes evidence from randomized controlled trials of the past decade regarding the relative safety of carotid endarterectomy (CEA) versus carotid angioplasty and stenting (CAS) as concerns postoperative cardiac damage.
Methods We searched Medline, Embase, and Cochrane Central through November 2013 to December 2013. We determined trial eligibility and extracted descriptive, methodological, and outcome data related to cardiac damage after open or endovascular treatment. Cardiac damage was defined as evidence of symptomatic or asymptomatic myocardial ischemia/infarction.
Results Nine trials (5,959 patients) were eligible for enrollment in this review. CAS was associated with a decreased risk for cardiac damage in all trials (pooled RR = 0.37; 95 % CI = 0.22–0.61, $I^2 = 11$ %, $P = 0.0001$), and specifically in the latest two randomized trials that show fewer methodological flaws (RR = 0.39; 95 % CI = 0.23–0.69, $P = 0.03$). CAS was associated with 11.5 fewer cardiac events (from 14.7 fewer to 6.3 fewer) compared to CEA.
Conclusions Compared to open surgery, CAS is associated with significantly decreased risk for symptomatic and asymptomatic cardiac damage postoperatively. Therefore, a standardized troponin measurement after CEA should be further evaluated in future studies.

Keywords Carotid intervention · Cardiac damage · Carotid endarterectomy · Carotid stenting · Silent myocardial ischemia

Introduction

Carotid endarterectomy (CEA) has been the gold standard for effective treatment of patients with advanced symptomatic and asymptomatic carotid disease for many years [1, 2]. Nevertheless, carotid angioplasty with stenting (CAS) has been introduced in the last decades as a less invasive therapeutic method [3, 4]. Therefore, several randomized trials have been conducted comparing the main outcomes between CEA and CAS, including postoperative cardiac events [5–8]. Furthermore, in patients with a higher cardiac risk such as patients with coronary artery disease [9, 10], hemodynamic changes are observed perioperatively [11] that could lead to myocardial ischemia or even to myocardial infarction (MI) [12, 13].

Most of the trials so far comparing CEA and CAS have concluded that CEA is related to a lower stroke rate but higher risk for MI postoperatively [5–8]. However, because stroke was the primary endpoint in almost all trials, the exact postoperative cardiac damage has not been extensively studied, especially in the older trials. Moreover, many studies have tried recently to focus on the assessment and detection of 'silent' myocardial ischemia and have correlated it with early and late mortality [15, 16]. However, so far as we know, no meta-analysis has yet been conducted focusing on silent myocardial ischemia and pooling all data referring to asymptomatic cardiac damage

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from randomized trials. Therefore, our aim is to evaluate the effects of CEA and CAS on postoperative symptomatic and asymptomatic cardiac damage to make useful conclusions concerning the perioperative management of such surgical patients.

Methods

Prospective studies that enrolled patients with symptomatic or asymptomatic carotid artery disease and allocated them randomly either to open surgery or to endovascular treatment were eligible for this meta-analysis. Only studies that included clinical results of well-defined postoperative or post-interventional myocardial damage were included [5–8, 16–20]. Studies were included regardless of size, language, or country of publication.

The main outcome of interest was cardiac damage, expressed in all trials by measurement of postoperative incidence of myocardial infarction or ischemia. Definition of myocardial infarction/ischemia, according to the guidelines of the American College of Cardiology (ACC) and European Society of Cardiology, has evolved recently with the introduction of cardiac enzymes into clinical practice [21]. Therefore, studies that defined cardiac damage either clinically or using cardiac biomarkers were included.

Absolute effects were estimated using pooled risks and median control event rates from patient undergoing CEA in the included trials. The GRADE framework was used to determine the quality of evidence [22]. We conducted subgroup analyses as well, based on patients' neurological symptoms preoperatively, use of protective devices, and stopping trials prematurely.

A comprehensive literature search of the most popular electronic databases (Medline, Embase, and Cochrane Central) was conducted during a timeframe of 2 months (November 2013–December 2013), using the following keywords and terms: "carotid intervention," "cardiac damage," "carotid endarterectomy," "carotid stenting," and "myocardial infarction." Descriptive, methodological, and outcome statistics of each study were extracted.

During this meta-analysis, we assessed relative risks and heterogeneity of treatment effect among trials. The I^2 statistics represent the proportion of heterogeneity of treatment effect across trials that were not attributable to chance or random error. A value >50 % reflects significant heterogeneity caused by real differences in study populations, protocols, intervention, and outcomes.

Results

From this extended research, we identified nine eligible randomized controlled trials (RCTs), published between 2001 and 2013. The total body of those trials enrolled 5,959 patients, of which 2,993 belonged to the CAS group and 2,966 to the CEA group. The majority of patients were symptomatic (74 %) preoperatively. Although there were methodological limitations noted in RCTs before 2008 (concerning allocation concealment, blinded outcome assessment, etc.), the latest trials (after 2008), which include 72 % of all patients, do not have these limitations. Table 1 describes all features of the nine RCTs and their methodological quality. No trials ongoing during this research were included in this review.

Meta-analysis

Compared to CEA, stenting was associated with decreased risk for cardiac damage, with almost no heterogeneity observed between the studies (pooled RR = 0.37; 95 % CI = 0.22–0.61, I^2 = 11 %, P = 0.0001). Data focusing on asymptomatic cardiac troponin elevation were sparse and only extracted from the latest trials (after 2008). Using the median event rate observed in patients who underwent CEA across all RCTs as a control event incidence, we estimated the risk difference per 1,000 patients. Results are summarized in Tables 2 and 3 with the associated quality of evidence (Fig. 1).

Subgroup and sensitivity analysis

We found no significant treatment–subgroup interaction for subgroups, based on whether the patient had neurological symptoms preoperatively, the use of protecting devices, or stopping the trial prematurely. No significant treatment interactions based on severity of stenosis, patient gender, presence of symptoms, or relationships between cardiac damage and former electrocardiographic signs were established as well.

When analysis was restricted to the two most recent studies [International Carotid Stenting Study (ICSS) [6] and Blackshear et al. [16], which showed fewer methodological limitations and were generated with more contemporary techniques and skill], we again found CAS to be associated with a significant reduction of risk of cardiac damage in comparison with CEA (RR = 0.39; 95 % CI = 0.23–0.69, P = 0.03). Furthermore, the latter correlation was made taking into account postoperative events of biomarkers only elevation (asymptomatic myocardial ischemia/infarction) in the these two studies.

Table 1 Description of included trials

Trials	No. of patients	Mean age (years)	Percent (%) asymptomatic	Degree of stenosis (%)
CAVATAS [5]	504	67.0	3	NR
SAPPHIRE [19]	334	72.6	71	>50, >80[a]
EVA-3S [17]	527	69.7	0	>60
Motamed [20]	150	72 (CAS), 70 (CEA)	47	NR
TESCAS-C [8]	166	63	Mixed, % unclear	>50, >70[b]
BACASS [7]	20	NR	0	>70
Steinbauer [18]	87	69	0	>70
ICSS [6]	1713	70	0	>70 (CTA/MRI)
Blackshear (CREST) [16]	2502	61	47	>50 (angio) >70 (US)

Trials	Follow-up (months)	Definition of myocardial infarction (MI)	Allocation concealment	Early termination
CAVATAS [5]	36	NR	No	No
SAPPHIRE [19]	36	CPK > 2 × normal and CPK-MB (+)	Yes	For slow enrollment
EVA-3S [17]	6	At least 2 of: pain/biomarkers > 2 × normal/ECG changes	No	For futility and harm
Motamed [20]	44 ± 12	Trop *I* > 1.5 ng/ml	Yes	No
TESCAS-C [8]	6	NR	Probably not	No
BACASS [7]	45	NR	Yes	No
Steinbauer [18]	64–66	NR	No	No
ICSS [6]	3	Trop > 2 × upper limit of lab + symptoms/ECG signs	Yes	No
Blackshear (CREST) [16]	48	Trop > 2 × upper limit of lab ± symptoms/ECG signs	Yes	No

All angioplasties were performed with stenting, except in CAVATAS (only 26 %)

Angio angiography, *CTA* computed tomography angiography, *MRI* magnetic resonance imaging, *NR* not reported, *US* ultrasound, *Trop* troponin, *Lab* laboratory, *NR* not reported

[a] Stenosis was >50 % in symptomatic patients and >80 % in asymptomatic patients

[b] Stenosis was >50 % in symptomatic patients and >70 % in asymptomatic patients

Table 2 Random effects meta-analysis comparing carotid angioplasty and stenting (CAS) with carotid endarterectomy (CEA) relative to myocardial damage

Trials	Risk ratio	Lower limit	Upper limit	Events/total (CAS)	Events/total (CEA)
CAVATAS [5]	0.14	0.01	2.77	0/251	3/253
SAPPHIRE [19]	0.40	0.13	1.25	4/167	10/167
EVA-3S [17]	0.45	0.05	5.42	1/265	2/262
Motamed [20]	0.25	0.15	2.16	1/75	4/75
TESCAS-C [8]	0.51	0.05	5.54	1/82	2/84
BACASS [7]	0	–	–	0/20	0/20
Steinbauer [18]	0.34	0.01	8.14	0/43	1/44
ICSS [6]	0.09	0	1.63	3/828	5/821
Blackshear (CREST) [16]	0.66	0.27	1.61	22/1,262	40/1,240
Pooled	0.37 ($P = 0.0001$)	0.22	0.61	32/2,993	67/2,966

Table 3 Absolute risk difference (RD) per 1,000 patients

Outcome	RD (95 % CI)	Quality of evidence	Interpretation
Cardiac damage	−11.5 (−14.7 to −6.3)	High	CAS is associated with 11.5 fewer cardiac events (range, from 14.7 fewer to 6.3 fewer)

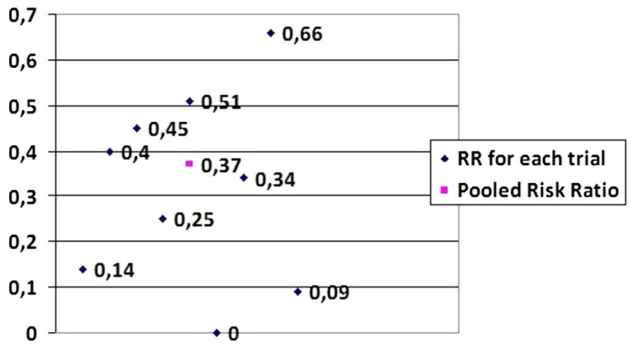

Fig. 1 Risk ratio (*RR*) and pooled risk ratio of all trials

Discussion

The present meta-analysis presents evidence concerning differences in postoperative cardiac damage between CEA and CAS, both for patients with severe carotid artery stenosis and history of cerebral ischemia (symptomatic patients) and for asymptomatic patients. The current study highlights the superiority of endovascular treatment regarding the occurrence of postoperative cardiac events and underlines the increasing prevalence of asymptomatic cardiac damage, especially after open carotid stenosis treatment.

First, regarding formerly published reviews, this analysis adds two more studies-RCTs in comparison to the recent Murad et al. meta-analysis [23] and the recent Yavin et al. meta-analysis [24]. In the latter reviews, the writers presented 13 and 12 RCTs, respectively, in which they compared the two methods so far as basic outcomes are concerned (stroke, MI, death). In these two studies, Murad et al. compared seven trials and Yavin et al. eight trials, respectively, so far as MI is concerned. Furthermore, in the Liu et al. meta-analysis of 2012, data from only six studies were used to extract results concerning postoperative myocardial infarction [25]. In our study, however, data were extracted from all nine enrolled studies. Finally, in comparison to the Wang et al. meta-analysis [26] from 2013, we studied trials that enrolled both symptomatic and asymptomatic patients with carotid stenosis, explaining this way the larger number of included patients in our study (5,959 vs. 3,873 patients).

All the aforementioned meta-analyses conclude that CAS leads to fewer MIs compared to CEA. Even when both procedures are performed by vascular surgeons only, Timaran et al. found that the periprocedural risks still vary (lower stroke with CEA and lower MI with CAS), although CAS and CEA might have similar net outcomes (combined death/stroke/MI) [27]. However, in our study, we focused on the impact of asymptomatic myocardial damage as a short-term outcome after carotid treatment. Therefore, compared to other large-scale reviews such as the studies of Economopoulos et al. [28] and Guay et al. [29], we included the study of Blackshear et al. [16] in place of the recent Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) [30]. Blackshear et al. collected all data from the CREST trial and analyzed the results relative to asymptomatic postoperative cardiac damage ('silent' myocardial ischemia) and biomarkers only elevation.

According to recent guidelines [31] regarding the diagnosis and management of perioperative myocardial

ischemia, perioperative MI is the most common major vascular complication after noncardiac surgery and is associated with a poor prognosis and high 30-day mortality. Furthermore, most patients with a perioperative MI will not experience ischemic symptoms [31]. Therefore, routine biomarker measurement is recommended on the first days after major surgery, especially for high-risk patients [31]. However, the results of this meta-analysis concur with our formerly published clinical study showing that asymptomatic myocardial ischemia after CEA is high, independent of the surgical risk of patients [32]. Therefore, our results suggest that perhaps the aforementioned recommendations should be further evaluated for intermediate cardiac risk procedures such as CEA as well.

The strength of this review stems from the systematic and comprehensive research of databases, and the accurate protocol of filtering and analyzing the separate trials and extracting outcome data. There seems to be very little heterogeneity of estimations in our review, although most outcome data were derived from symptomatic patients. Furthermore, this study has the advantage of including the most recent trials and those with fewer methodological faults, in comparison to older reviews [23, 24, 33]. Finally, this review incorporates data regarding the 'silent' postoperative cardiac damage that has been strongly correlated with clinical outcomes, as mentioned previously [31].

However, there are limitations, deriving mainly from inability to evaluate patient-level covariates that are essential for conducting meaningful subgroup analyses. Such further analyses could demonstrate differential overlaps or benefit of CAS versus CEA in particular subgroups, according to gender, age, or other patient characteristics. As demonstrated in our review, CAS is associated with less cardiac damage, although there is a lack of data concerning the clinical symptoms and consequences of myocardial ischemia described in the included trials/RCTs, and thus the estimated decrement in quality of life is not quite accurate in our review.

The higher prevalence of cardiac damage after CEA, shown in our study, indicates the need for stratifying patients with cardiac problems/coronary artery disease before deciding on the proper therapeutic method, so that the best choice with the fewest complications is made [34, 35]. However, to define the best treatment for carotid stenosis, it is important that trials in the future should include a non-intervention arm that receives the best available medical management; this would preserve a true equipoise. An adequate medical treatment strategy may trump myocardial damage as a primary outcome. Finally, another important issue for future research is to include the measurement of nonclinical cardiac damage by establishing a standardized protocol of biomarker detection postoperatively [36–38].

In conclusion, CAS is associated with a lower risk of both clinical and 'silent' myocardial damage in patients with carotid artery disease in comparison to CEA. Standardized troponin measurements after CEA are justified, especially for patients of high cardiac risk. Future studies focusing on cardiac morbidity after CEA or CAS must include separately as a secondary endpoint the assessment of cardiac troponin elevation, asymptomatic myocardial infarction, and symptomatic myocardial infarction with electrocardiographic alterations.

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Conflict of interest There was no conflict of interest.

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