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FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2021/2022

Ana Filipa Fonseca da Silva

Incidência de lesão miocárdica em doentes submetidos a endarterectomia carotídea: uma revisão sistemática

Incidence of myocardial injury in patients submitted to carotid endarterectomy: a systematic review

MARÇO, 2022

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Mestrado Integrado em Medicina

Área: Angiologia e Cirurgia Vascular

Tipologia: Dissertação

Trabalho efetuado sob a Orientação de:

Doutor João Rocha Neves

E sob a Coorientação de:

Dr. José Paulo Andrade

Trabalho organizado de acordo com as normas da revista:
International Journal of Surgery

MARÇO, 2022

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DESIGNAÇÃO DA ÁREA DO PROJECTO

Angiologia e Cirurgia Vascular

TÍTULO DISSERTAÇÃO/MONOGRAFIA (riscar o que não interessa)

Incidence of myocardial injury in patients submitted to carotid endarterectomy: a systematic review

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À minha família, que me apoiou durante todo o meu percurso.

Aos meus amigos, que tornaram esta viagem

tão mais memorável.

INCIDENCE OF MYOCARDIAL INJURY IN PATIENTS SUBMITTED TO CAROTID ENDARTERECTOMY: A SYSTEMATIC REVIEW

Running Title: *Myocardial injury in carotid endarterectomy review*

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

ABSTRACT

BACKGROUND

Myocardial injury following noncardiac surgery (MINS) is associated with higher mortality and major adverse cardiovascular event rates in the short- and long-term in patients undergoing carotid endarterectomy (CEA). However, its incidence is still unclear in this subset of patients. Therefore, this systematic review with meta-analysis aims to determine MINS incidence in patients undergoing CEA.

MATERIALS AND METHODS

Three electronic databases MEDLINE, Scopus, and Web of Science were used to search for studies assessing MINS occurrence in the postoperative setting of patients undergoing CEA. The incidence of MINS was pooled by random-effects meta-analysis, with sources of heterogeneity being explored by meta-regression. Additionally, the incidence of MINS regarding subgroups of patients, general anesthesia (GA) vs. regional anesthesia (RA), was also analyzed. Assessment of studies' quality was performed using National Heart, Lung, and Blood Institute (NHLBI) Study Quality Assessment Tool for Observational Cohorts and Cross-Sectional Studies, and Risk of Bias 2 tools.

RESULTS

Twenty studies were included, with a total of 117,933 participants. Four were randomized controlled trials (RCT), while the remaining were cohort studies. All observational cohorts had an overall high risk of bias, except for Pereira Macedo et al. As three of them had repeated populations, only data from the most recent one was considered. On the other hand, all RCT had an overall low risk of bias. In patients under regional anesthesia, the incidence of MINS in primary studies ranged between 2% and 15.3%, compared to

0-42.5% for general anesthesia. The meta-analytical incidence of MINS after CEA was 6.3% [95% CI 2.0%-10.6%], but severe heterogeneity was observed (I^2 = 99.1%).

CONCLUSION

MINS appears to be relatively common among patients undergoing CEA. The observed severe heterogeneity points to the need for further larger studies adopting consistent definitions of MINS and equivalent cutoff values.

Keywords: myocardial damage, postoperative troponin elevation, carotid revascularization, postoperative cardiovascular events

HIGHLIGHTS

- Incidence of MINS within 30-days after CEA ranges from 2 to 15.3% under RA
- Studies are strongly heterogeneous regarding MINS definitions and cutoff values
- Consistent methodology towards standardized definitions is strongly recommended
- The prognostic relevance of MINS is still unclear and poorly understood
- RCTs should be carried out regarding preventing measures and management of MINS

1. INTRODUCTION

Some patients submitted to noncardiac surgery may experience troponin elevation in the first thirty postoperative days, resulting from myocardial injury (1). Myocardial injury following noncardiac surgery (MINS) resembles a type two myocardial infarction (MI). It is defined by troponin rising and/or falling patterns, without referred symptoms and/or electrocardiographic findings (2). Established perioperative non-ischemic diagnosis, such as pulmonary embolism, sepsis, and cardioversion, does not fulfill the criteria for MINS (1). Selective troponin assessment in patients with a cardiovascular risk superior to 5% evaluated by Revised Cardiac Risk Index is recommended (3, 4). The high-sensitivity cardiac troponin, troponins I and T are the current best biomarkers in accessing myocardial injury through troponin assays (2, 5, 6).

The occurrence of MINS withstands a substantial damaging impact on the prognosis of the patients. A prospective cohort study has previously described a 17-fold increased risk of non-fatal MI in vascular patients (7). Additionally, these patients have shown a 10-fold increased risk of mortality at 30-days after surgery.

Available literature reporting incidence of MINS, which includes vascular surgeries amongst heterogeneous samples of noncardiac surgical patients, ranges from 8 to 25% (7-9). One in every five patients undergoing vascular surgery develop MINS (7). However, the incidence of MINS has not been systematically assessed for each type of vascular surgery. Such is the case for carotid endarterectomy (CEA), which is considered the gold-standard treatment for carotid-stenosis. In short and long-term follow-up, adverse events such as major adverse cardiovascular events (MACE), MI, or acute heart failure also appear to be more common in patients submitted to CEA, who have experienced troponin elevation than those who had not (10-12).

Therefore, the present systematic review aims to assess MINS incidence in patients submitted to CEA with or without RA.

2. MATERIALS AND METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for a Systematic Review and Meta-analysis (PRISMA) Statement and Assessing the methodological quality of systematic reviews (AMSTAR) (13, 14). An institutional review board's ethical approval was not obtained due to the nature of this study. The review protocol has been registered at Prospero (reference: CRD42021224429).

2.1 Selection Criteria

Inclusion criteria consisted of all original cohort or experimental studies performed in humans (except for systematic reviews and case series under 20 patients), in which the incidence of MINS after CEA was assessed. Exclusion criteria comprised patients undergoing synchronous cardiac surgery, carotid stenting, or carotid reintervention. No exclusion criteria based on the publication language or date were applied.

2.2 Search strategy

A systematic search was performed in three databases – Pubmed, Scopus, and Web of Science – in September 2021. The query and keywords are shown in supplemental Table B.1. Additionally, the references of the included primary studies and relevant available systematic reviews were screened to search for any further articles of possible interest.

2.3 Study selection and data extraction

After duplicates removal, two authors (JPM and AFS) have independently participated in studies selection; any disagreement was solved by the intervention of a third author (JRN). First, studies were selected by title and abstract, and the remaining ones were eligible for full-text assessment. The same samples studied in multiple original articles

were only included once. Efforts were made to contact the authors to obtain the full texts that were not publicly available.

Data from included studies were independently extracted by two authors (AFS, JPM). Data were extracted using a purposely-built form on the year of publication, country and center of recruitment, study design, recruitment time, number of participants undergoing CEA, participants' age and gender distribution, frequency of cardiovascular comorbidities, and symptomatic carotid status. In addition, data related to each study's MINS cutoff and troponin kit used was retrieved, as well as the incidence and definition of MINS.

2.4 Assessment of study quality

Concerning qualitative assessment, the Cochrane Risk of Bias-2 tool was used for randomized clinical trials (15), and the National Heart, Lung, and Blood Institute (NHLBI) Study Quality Assessment Tool was used for observational cohort and cross-sectional studies (2013) (16). This assessment was independently performed by two authors (JPM and AFS), and when disagreements were observed, decisions were made by mutual consensus after a third-party review (JRN).

2.5 Quantitative synthesis

A random-effects meta-analysis (using the restricted maximum likelihood method) of log-transformed proportions to calculate the meta-analytical pooled incidence of MINS among participants was performed. Pooled estimates and 95% confidence intervals (95%CI) were back-transformed into their original scale to simplify their interpretation. Heterogeneity was assessed using the Q-Cochran *p*-value and the I^2 statistic – a *p*-value<0.10 and an $I^2 \geq 50\%$ were considered to represent substantial heterogeneity. Sources of heterogeneity were assessed by leave-one-out sensitivity analysis and

univariable meta-regression models. Assessed covariates included the publication year, participants' mean age, percentage of male participants, percentage of patients with arterial hypertension, dyslipidemia, diabetes, or coronary artery disease (CAD), percentage of symptomatic patients, percentage of patients using antiplatelet drugs, troponin T levels, troponin I levels, and CK-MB. Subgroup analyses were also performed with separate analyses of studies in which participants were under general anesthesia or regional anesthesia. The possibility of publication biases was assessed using funnel plots.

All statistical analyses were performed using software R (metafor package).

3. RESULTS

3.1 Search Results

After the database search and duplicate exclusion, a total of 165 studies were screened. Upon selection by title and abstract, 118 studies were excluded. Forty-seven studies were eligible for full-text assessment, and, during this process, 26 studies were excluded, and one was not retrieved (Figure A.1). Comprehensive reasons for exclusion upon full-text assessment were: patients undergoing synchronous cardiac surgery, carotid stenting, or carotid reintervention (N=9), absence of assessment of MINS (N=17), and absence of full-text even after contacting the respective author (N=1). Thus, a total of 20 published articles were included in this systematic review (10-12, 17-31) (Table B.2).

3.2 Description of Studies

Sixteen of the 20 studies included in this systematic review were observational cohorts, five of them being retrospective (20, 24, 28, 29, 32). However, two studies had repeated samples that were subsequently included in a more recent article, and therefore only data from the latter was considered (11, 33, 34). The other four studies were randomized controlled trials (RCT) (23, 30, 31, 35). The included publications were performed in 10 different countries within three continents - six from North America (17, 21-23, 27, 29), nine from European countries (10-12, 18, 20, 25, 26, 28, 30), and three studies from Asia (19, 24, 31). A total of 117,933 patients were assessed, with a minimum of 40 (19) and a maximum of 75,319 (17) patients per study. The mean participants' age was 69.2 years old. The percentage of male participants was 40.7% (n=48,029). Demographics and comorbidities of the populations included in the studies were gathered and are available in Table B.3. Data related to periprocedural setting, such as type of anesthesia and previous use of antiplatelet/anticoagulation therapy, is displayed in Table B.4.

MINS was defined according to the Fourth Universal Definition of Myocardial Infarction in six of the studies (2, 10, 18, 19, 22, 28, 31), while Grobben et al. and Garcia et al. (12, 21) followed the Third Universal Definition, which is similar to the former one. The Vascular Quality Initiative database used in one of the included studies defined MINS according to their criteria, which, likewise, are comparable to the Fourth Universal Definition (17). Tyson et al. (29) determined the diagnosis of MI as a troponin I value equal or above to 0.6 ng/mL or CK-MB is >6.3 ng/mL together with correlation with electrocardiographic changes. Galyfos et al. (11) and Kwon et al. (24) followed the British Cardiac Society international guidelines of MI definition (24, 36), while Motamed et al. (26) conformed to the definition of the Joint European Society of Cardiology/American College of Cardiology guidelines (37). Feringa et al used the lower reference limit of detection (> 0.03 ng/ml) of the kit to define troponin elevation only (20). Hye et al. (22) used troponin I, T, and CK-MB for the assessment of MINS, while Tyson et al. (29) recurred to troponin I and CK-MB markers. Troponin I and hSTnI were both used by Pereira-Macedo et al. (10). Troponin I alone was used in thirteen articles (11, 12, 17-19, 21, 23-27, 30, 31), and only one article (20) used troponin T alone. Two articles did not specify which biomarkers were used (17, 28). Additionally, Jellish et al., Leblanc et al., Walsh et al., and Shukla et al. (23, 25, 27, 30) did not state any MINS definitions. Troponin measurement kits were retrieved as displayed in Table B.5.

3.3 Main findings and meta-analysis

The incidence of reported MINS within 30-days after CEA in primary studies ranged from 0 and 42.5%. Considering only patients submitted to RA, a range of 2 to 15.3% was observed in the occurrence of MINS, while among patients submitted to GA, such range was 0% to 42.5%.

Concerning short- and long-term outcomes in patients that experienced MINS, available data was sparse but further withdrawn and displayed in Tables B.6 and B.7.

The meta-analytical incidence of MINS after CEA was 6.3% [95% CI 2.0%-10.6%]. However, severe heterogeneity was found (I^2 = 99.1%; Q-Cochran *p*-value<0.001). In all results of leave-one-out sensitivity analysis and of univariable meta-regression models, severe heterogeneity was described (I^2>90%) (Table C.1 and C.2). Additionally, subgroup analysis regarding the use of general anesthesia vs. regional anesthesia has shown similar high heterogeneity (above 98 and 96%, respectively). Studies related to general anesthesia have reached a prevalence of 4.5%, whereas regional anesthesia accounted for 2.2% of MINS, in the meta-analysis (Table C.1).

3.4 Studies quality

The risk of bias of the selected articles is displayed in figures A.2-A.5. The risk of bias for each observational cohort is individually displayed in figure A.2, while the risk of bias for each RCT is displayed in figure A.3. The overall judgment per evaluated item regarding observational cohorts is shown in figure A.4, whereas the one regarding RCT is shown in figure A.5.

All observational cohorts had an overall high risk of bias, except for Pereira Macedo et al. (38). On the other hand, all RCT had an overall low risk of bias (21, 23, 39, 40). The items most frequently associated with a high risk of bias amongst observational cohorts included sample size justification, power description, variance and effect estimates, exposure assessment, key potential confounding variables measurement, and statistical adjustment for their impact.

3.5 Publication bias

A funnel plot regarding publication bias is displayed in figure A.6. The funnel plot displays an asymmetric pattern – while funnel plot asymmetry is expected in cases of severe heterogeneity, publication bias cannot be excluded.

4. DISCUSSION

The present systematic review has found a meta-analytical incidence of MINS after CEA of 6.3%, with a range between 0 and 42.5%. However, severe heterogeneity was found and not accounted for by sensitivity analysis or meta-regression models.

MINS has been the subject of increasing interest to clinical researchers. In fact, despite being an asymptomatic troponin elevation finding that occurs within 30-days after noncardiac surgery, several studies have shown that its prognostic effect might be deleterious for the patients at short and long-term periods, which turns this topic into a focus of concern in clinical practice (1, 7, 10, 12). The diagnostic criteria for MINS diverge from the criteria for MI, and its occurrence may be pathophysiologically explained by oxygen supply or demand imbalance in the postoperative period (2). For vascular surgery, it is known that the surgical procedure itself is considerably associated with a higher risk of cardiovascular events (41). Additionally, a previous meta-analysis regarding vascular surgery has found that MINS was a predictor of all-cause postoperative mortality at 30 days (42). Such systematic review has identified a 15.5% incidence of patients experiencing myocardial lesion after vascular surgery (42).

However, the incidence of MINS after CEA is not widely reported. Likewise, its therapeutic approach and prognostic potential are not well established. Due to its likely impact on prognosis, management of MINS is vital, and it is a major concern of clinical research. Nonetheless, how to manage these patients is still a challenge. The recently published MANAGE trial found a protective effect of the administration of dabigatran 110 mg twice daily on significantly lowering the risk of major vascular adverse events without significantly increasing the risk of major bleeding (43).

Regarding CEA and the occurrence of postoperative MINS on the present systematic review, only three cohort studies – Cnotliwy et al. (18), Pereira-Macedo et al. (10), and Leblanc et al. (25) have performed CEA under RA while other ten studies, including all the randomized control trials, executed CEA under GA (11, 12, 19, 21, 23, 24, 26, 29-31). Two studies did not specify the anesthetic approach (20, 28). The remaining three studies performed both RA and GA but did not discriminate MINS incidence between the two procedures (17, 22, 27). The samples of the studies whose patients were submitted to RA are small, ranging from 50 to a maximum of 150 individuals, which compromises the precision of the results. On the other hand, most of the studies were performed under GA, assessing larger samples of patients.

Since RA is reasonable in clinical practice and may be associated with fewer adverse effects, it is expected to have a lower incidence of troponin elevation. Furthermore, GA stands for a more challenging hemodynamic management, which could prompt myocardial blood flow imbalances. However, the GALA trial suggests that no differences in MI occurrence are expected between CEA patients submitted to RA or those submitted to GA, as well as in the postoperative quality of life, length of hospital stay, stroke, or death (44). Nevertheless, the incidence of MINS has not been widely studied, and the impact of the anesthetic approach is still unclear.

Feng et al. (19) have found an association between MINS and symptomatic carotid stenosis (defined by authors as >70% of the luminal diameter on color duplex ultrasonography), and ST-segment changes consistent with ischemia. However, none of these associations were confirmed by multivariable logistic regression analysis. Moreover, they have detected significant changes in hemodynamic parameters such as higher cardiac output and stroke volume indexes and lower diastolic and mean arterial pressures in patients with abnormal cardiac troponin.

In the study of Grobben et al. (12), the 34 patients that experienced troponin elevation after CEA had a significantly higher prevalence of chronic kidney disease (glomerular filtration rate < 45 mL/min), symptomatic presentation, and primary/bovine patch closure than the patients with no troponin elevation. However, only 26 of those 34 patients were diagnosed with MINS, while the remaining patients were diagnosed with perioperative MI. Since the reported baseline characteristics were not discriminated between these two groups of patients with troponin elevation, extrapolation could result in an overestimating effect. Four percent of MINS patients experienced short-term MACE (1 stroke), defined as the composite of MI, stroke, and cardiovascular death, and 8% at 1.8 years follow-up (4% stroke, 4% cardiovascular death, and 12% all-cause mortality).

In Pereira-Macedo et al. (10), chronic heart failure was independently associated with the occurrence of MINS with a 4-fold increased risk in patients submitted to RA, whereas coronary artery disease (CAD) was not confirmed as a statistically significant risk factor. CAD is currently the leading cause of heart failure (45) and plays an important role in postoperative myocardial events in vascular patients (46, 47). The majority of patients enrolled for vascular surgery had a prior history of CAD. Biccard et al. which studied a large prospective cohort also did not confirm CAD as a risk factor for incidence of MINS in vascular patients (7). Therefore, it can be suggested that CAD may present significant interaction and act as a confounding factor.

Only two studies (Pereira-Macedo et al. and Grobben et al.) (10, 12) have assessed the impact of MINS at short and long-term follow-up. Both have found a substantial potential role of MINS in the occurrence of cardiovascular events. However, in Grobben et al. (12), results should be carefully scrutinized since only 26 patients of the 34 with troponin elevation had experienced the full criteria of MINS. Nevertheless, Pereira-Macedo et al.

(10) have found a significant impact regarding the occurrence of MACE and acute MI at 52 months follow-up.

Seven of the papers did not offer information regarding the equipment utilized, and considering their respective definitions of MINS it is challenging to interpret the results. Indeed, when a kit is identified, a cutoff of troponin detection is established along with the definition of MINS used by the authors. According to the Fourth Universal Definition of MI, MINS is defined by a rising of cardiac troponins with at least one value above the 99th percentile upper reference limit (2). Centers that did not mention the cutoff limits inferred MINS diagnosis according to their institution protocols, which conveys some inconsistency amid the selected studies. Therefore, the derived outcomes should be judiciously revised. When the definition of MINS varied from the current guidelines, interpretation of the results considered this issue to avoid erratic analysis.

This study faced many limitations worth noting. First, few articles were eligible for this systematic review, and the majority of those had a small sample size without sample justifications and power descriptions, which led to low precision of obtained results and consequently might affect external validity. Moreover, there was severe heterogeneity amongst studies regarding most baseline patient characteristics, study designs, and methodology, prompting a high diversity of MINS definitions and troponin kits used. In fact, differences between primary studies were so extensive that, in meta-regression, any single variable could be identified, which could possibly account for most heterogeneity. The authors were not able to perform multivariable meta-regression models on account of the insufficient number of included primary studies. Few other short- and long-term outcomes were assessed, such as stroke, MI, MACE, or death, which deprived the study of MINS association with other outcomes.

This systematic review exposes the need for large cohorts and RCTs that implement standardized methodology and apply consistent definitions of MINS, with a primary aim to assess the incidence and effect of MINS in patients undergoing CEA to validate the current findings in the literature and further uncover the existing gaps of knowledge. Furthermore, observational cohorts should avoid the frequent bias detected in this study by presenting sample size justification, power description, variance and effect estimates, exposure assessment, key potential confounding variables measurement, and statistical adjustment for their impact.

In truth, the potential impact of MINS might predispose clinicians to adapt their strategies for better management of these patients. Nonetheless, more studies regarding the prevention and management of MINS are crucial to avoid further harm to the patients at short and long periods.

5. CONCLUSION

The incidence of MINS within 30-days after CEA ranged between 0 and 42.5% in the present systematic review. However, inferring results should be cautiously interpreted due to a significant heterogeneity amongst the selected studies and the diversity of study designs and methodology. Henceforward, additional research with a consistent and internationally defined methodology is required to provide valid results and assess the true incidence and risk factors of MINS in this subset of patients, with or without RA, as well as its appropriate management.

6. FUNDING

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

7. CONFLICT OF INTEREST STATEMENT

None.

8. PROVENANCE AND PEER REVIEW

Not commissioned, externally peer-reviewed.

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APPENDIX A

Figure A.1 – Flow-diagram according to PRISMA statement regarding the process of identification and selection of the studies

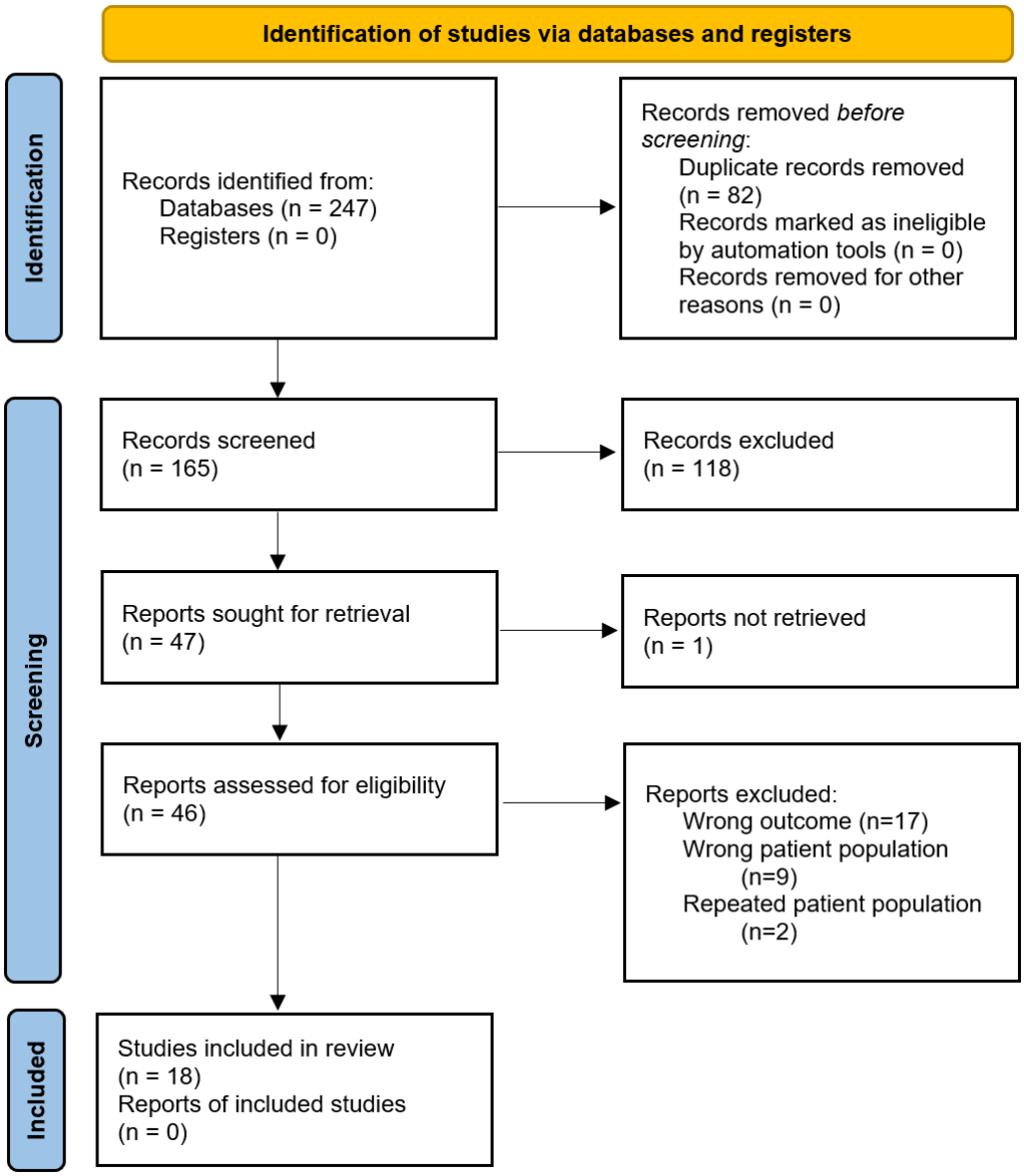


Figure A.2 – Risk of bias of all observational studies included in the systematic review, displayed by article

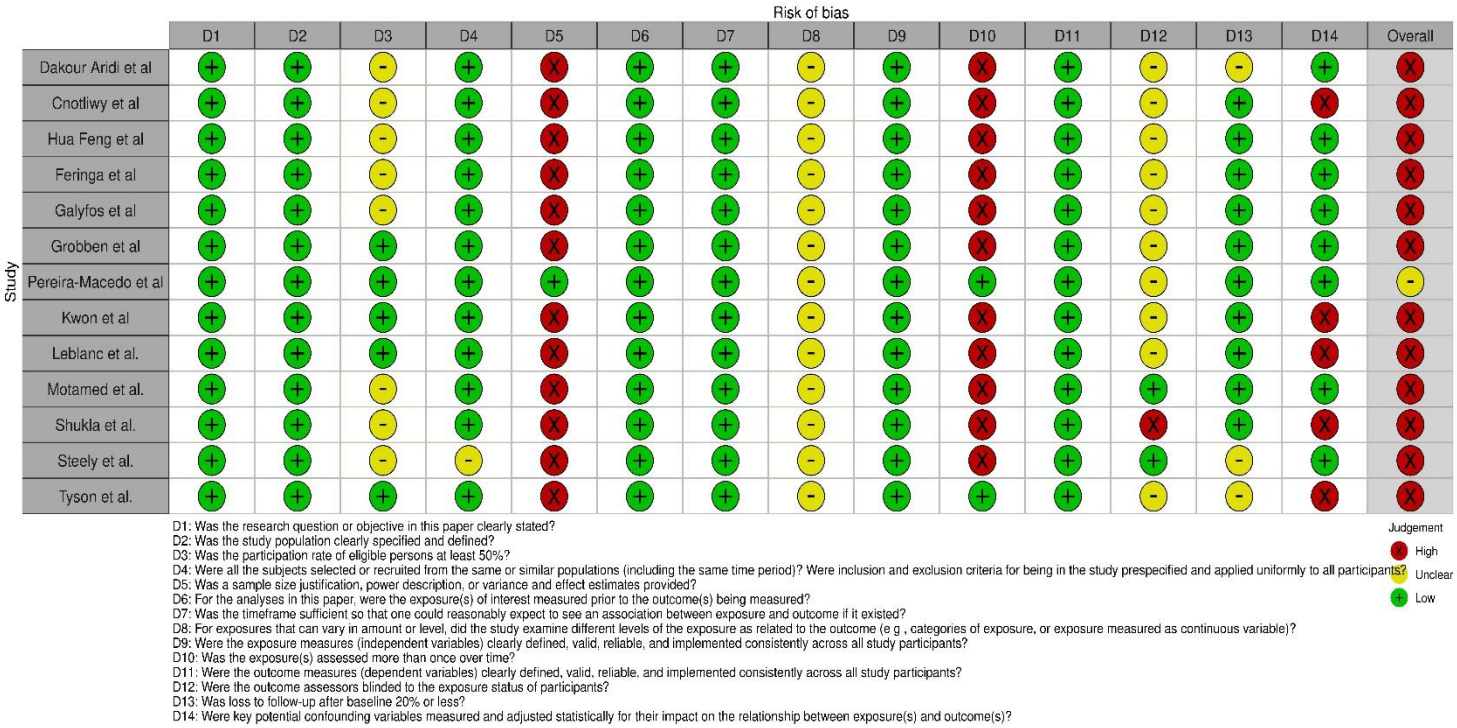


Figure A.3 – Risk of bias of included RCTs, displayed by article.

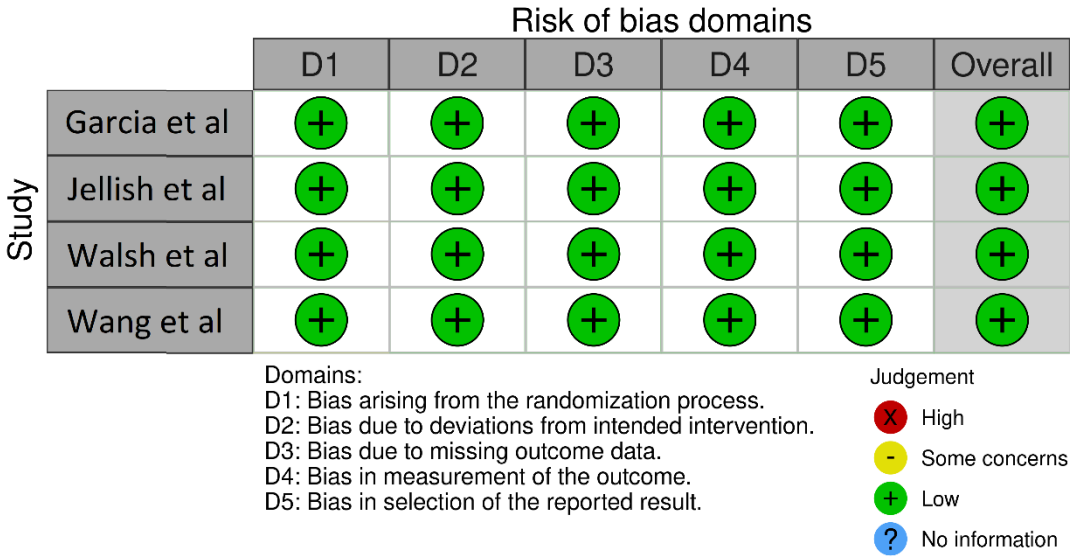
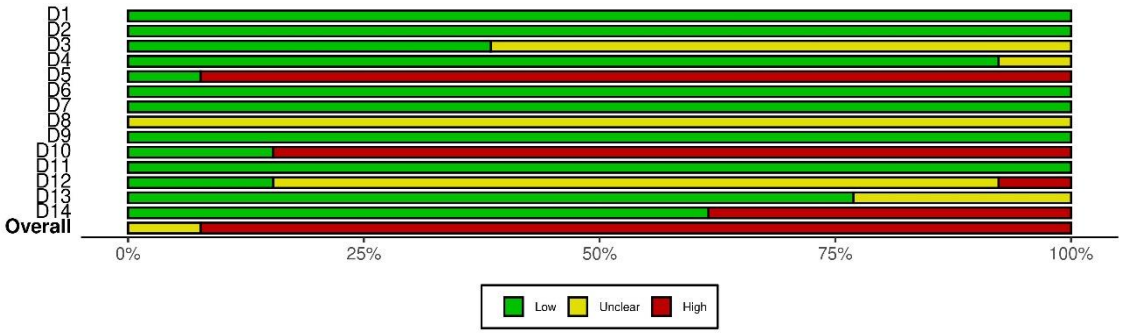


Figure A.4 – Risk of bias of all included observational studies, displayed by item



D1: Was the research question or objective in this paper clearly stated?
D2: Was the study population clearly specified and defined?
D3: Was the participation rate of eligible persons at least 50%?
D4: Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
D5: Was a sample size justification, power description, or variance and effect estimates provided?
D6: For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
D7: Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
D8: For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
D9: Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
D10: Was the exposure(s) assessed more than once over time?
D11: Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
D12: Were the outcome assessors blinded to the exposure status of participants?
D13: Was loss to follow-up after baseline 20% or less?
D14: Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Figure A.5 – Risk of bias of all included RCTs, displayed by item

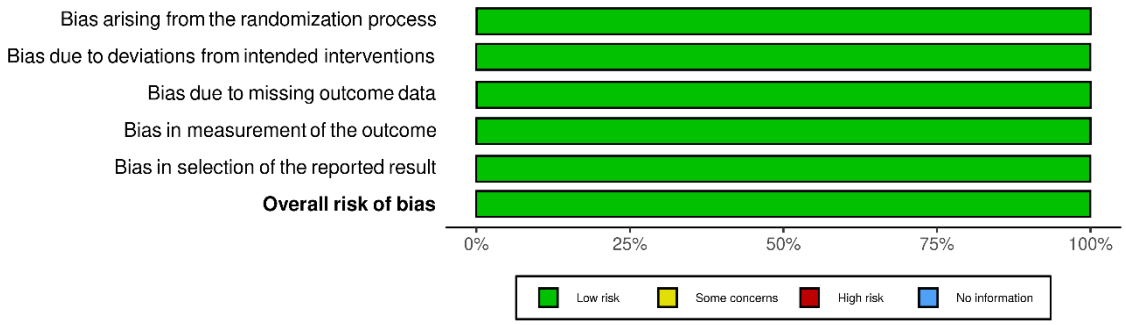
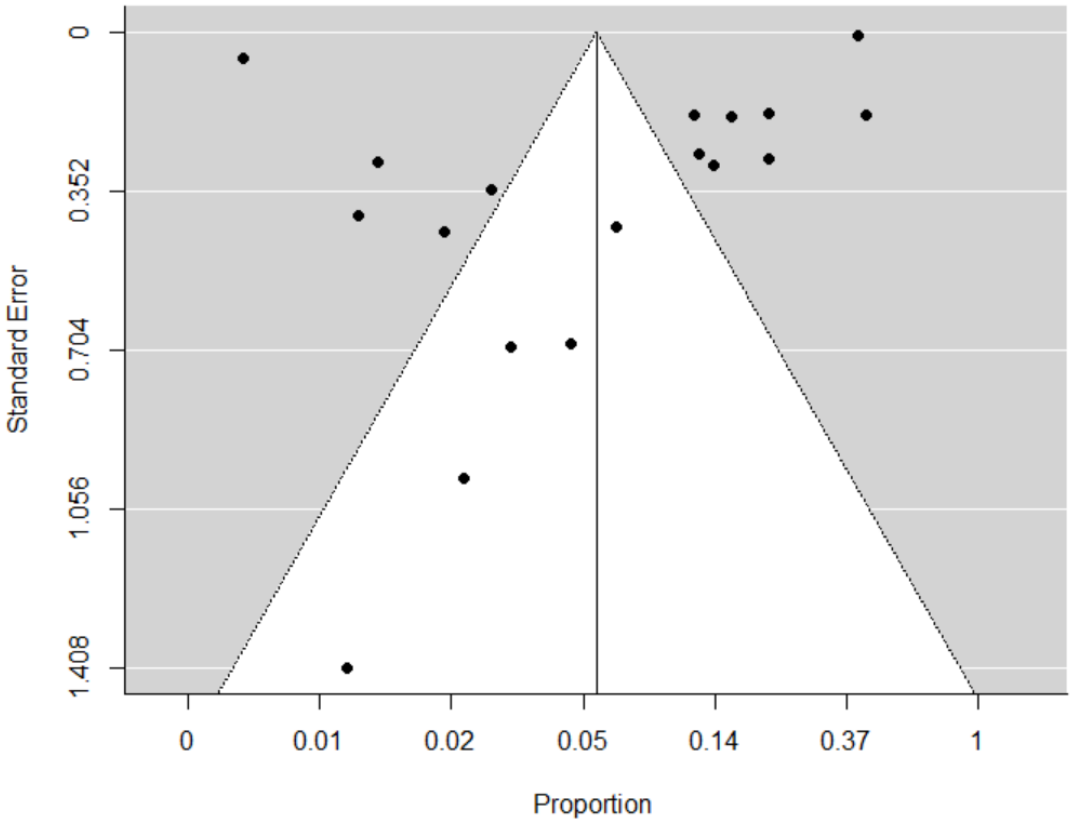


Figure A.6 – Funnel plot of publication bias assessment



APPENDIX B

Table B.1 – Search query – key words

Database	Fields	Search Terms
Pubmed	MeSH Terms	*Endarterectomy*
		Endarterectomy, Carotid
		Carotid endarterectomies
		Troponin
	Free text words	*Carotid endarterectomy (All fields)*
		Troponin (All fields)*
		Myocardial Injury (All fields)
		cTnT (All fields)
		cTnI (All fields)
	Limits	*None*
Scopus and Web of Science	Free text words	*Endarterectomy*
		Carotid endarterectomy (All fields)
		Carotid endarterectomies
		(All fields)
		Troponin (All fields)*
		Myocardial Injury (All fields)
		cTnT (All fields)
		cTnI (All fields)
	Limits	*None*

Table B.2 – Identification and summary description of the selected studies from where data were retrieved.

Author	**Journal**	**Publication Year**	**Study Design**	**Study Center**	**Recruitment Time**	**Sample Size (patients)**	**No. CEA**
Aridi et al.	Journal of Vascular Surgery	2017	Retrospective from a prospective database	Baltimore, USA multicenter, Johns Hopkins Bayview Vascular and Endovascular Research Center, USA	January 2003 - February 2017 (14 years)	75319	75319
Cnotliwy et al.	Acta Angiologica	2011	Prospective observational study	Pomeranian Medical University, Szczecin, Poland	NA	100	100
Feng et al.	Clinical and Applied Thrombosis/ Hemostasis	2013	Prospective observational study	XuanWu Hospital of Capital Medical University, China	May 2010 - March 2012 (22 months)	40	40
Feringa et al.	Coronary artery disease	2007	Retrospective from a prospective database	Erasmus Medical Center in Rotterdam	2005 - 2006 (1 year)	44	44

Galyfos et al.	Journal of Stroke and Cerebrovascular Diseases	2014	Prospective observational study	University of Athens Medical School, Hippocration Hospital, Athens	January 2003 - June 2013 (126 months)	324	324
Garcia et al.	Journal of the American Heart Association	2016	RCT	Minneapolis Veterans Affairs Healthcare System, USA	June 2011 - September 2015 (51 months)	49	49
Grobben et al.	European Journal of Vascular and Endovascular Surgery	2015	Prospective observational study	University Medical Center Utrecht, The Netherlands	January 2011 - December 2013 (3 years)	225	225
Hye et al.	Journal of Vascular Surgery	2016	Prospective, randomized, multicenter trial with	NA: 117 clinical centers in the United States and Canada	December 2000 - July 2008	1149	1149

			blinded endpoint adjudication				
Jellish et al.	Journal of neurosurgical anesthesiology	2003	RCT	Loyola University Medical Center, Maywood, Illinois, USA	NA	59	59
Pereira-Macedo et al.	International Journal of Surgery	2019	Prospective cohort	Portuguese tertiary care	January 2009 - January 2018 (9 years)	156	156
Kwon et al.	Journal of Neurosurgery	2016	Retrospective study of data from a prospective CEA registry	Asan Medical Center	January 2005 - December 2014 (10 years)	666	666
Leblanc et al.	Anesthesia Critical Care & Pain Medicine	2015	Prospective observational study	Institut Mutualiste Montsouris, French	April 2011 - May 2013 (25 months)	50	50

Motamed et al.	Journal of Vascular Surgery	2005	Prospective observational study	Single university Hospital, French	July 1998 - December 1999 (17 months)	75	75
Shukla et al.	Annals of Vascular Surgery	2019	Prospective observational study	Rural academic medical center of University of Vermont Medical Center	January 2016 - December 2016 (12 months)	78	78
Steely et al.	Annals of Vascular Surgery	2017	Retrospective from a prospective database	Multicenter VQI	January 2010 - December 2014 (4 years)	39118	39118
Tyson et al.	Annals of Vascular Surgery	2019	Retrospective from a prospective database	Single-center, NY	February 2011 - July 2015 (54 months)	289	289
Walsh et al.	Vascular and endovascular surgery	2010	RCT	Cambridge Vascular Unit	January 2006 - May 2008 (29 months)	70	70

Wang et al.	Chinese Medical Journal	2015	RCT	Single-center of Beijing, Xuan Wu Hospital, Capital Medical University	November 2011 - December 2013 (25 months)	122	122

Legend: CEA – carotid endarterectomy; RA – regional anesthesia

Table B.3 – Demographics and comorbidities of the population samples for each study.

Author	**Mean age**	**Male n(%)**	**Arterial Hypertension n(%)**	**Dislipidemia n(%)**	**Diabetes Mellitus n(%)**	**Smoking History n(%)**	**Coronary Artery Disease n(%)**	**Carotid territory symptoms n(%)**
Aridi et al.	71.1	45498 (60.4)	66 821 (88.7)	60275 (80.0)	26325(35.0)	57007 (75.7)	20710 (27.5)	23091 (30.7)
Cnotliwy et al.	69.4	66 (66.0)	85 (85.0)	NA	35 (35.0)	NA	47 (47.0)	61 (61.0)
Feng et al.	67.0	32 (80.0)	31 (77.5)	27 (67.5)	14 (35.0)	25 (62.5)	6 (15.0)	40 (100)
Feringa et al.	64.0	34 (77.3)	18 (40.9)	29 (65.9)	6 (13.6)	29 (65.9)	13 (29.5)	NA
Galyfos et al.	67.3	207 (64.0)	289 (89.0)	168 (52.0)	93 (29.0)	171 (53.0)	NA	143 (44.0)
Garcia et al.	NA	49 (100)	NA	NA	NA	NA	NA	NA

Grobben et al.	73.0	164 (73.0)	188 (83.6)	182 (81.0)	57 (25.3)	67 (29.8)	NA	202 (89.7)
Hye et al.	69.1	769 (67.0)	989 (86.1)	986 (85.8)	355 (30.9)	299 (26.0)	588 (51.1)	611 (53.2)
Jellish et al.	70.7	34 (58.0)	NA	NA	NA	NA	NA	NA
Pereira-Macedo et al.	69.6	119 (76.3)	133 (85.3)	127 (81.4)	62 (39.7)	79 (50.6)	57 (36.5)	62 (39.7)
Kwon et al.	68.7	573 (86.0)	498 (74.8)	NA	239 (35.9)	424 (63.7)	45 (6.8)	364 (54.7)
Leblanc et al.	72.0	37 (74.0)	NA	NA	NA	NA	14 (28.0)	10 (20.0)
Motamed et al.	72.0	63 (84.0)	58 (77.3)	NA	14 (18.7)	40 (53.3)	NA	42 (56.0)
Shukla et al.	NA	53 (68.0)	67 (86.0)	78 (100)	26 (33.3)	63 (80.7)	20 (25.6)	47 (60.3)
Steely et al.	NA	NA	NA	NA	NA	NA	NA	NA
Tyson et al.	70.2	172 (59.5)	267 (92.4)	232 (80.6)	NA	225 (78.0)	NA	NA
Walsh et al.	68.9	49 (70.0)	44 (62.9)	62 (88.6)	15 (21.4)	38 (54.3)	23 (32.8)	42 (60.0)

Wang et al.	66.2	110 (90.2)	82 (67.2)	20 (16.4)	32 (26.2)	61 (50.0)	22 (18.0)	122 (100)

Legend: NA – unavailable data

Table B.4 – Relevant data related to the surgical setting: presence of contralateral disease, antiplatelet and anticoagulation therapies, and type of anesthesia

Author	**Contralateral Stenosis n(%)**	**Antiplatelet Therapy n(%)**	**Dual Antiplatet Therapy n(%)**	**Anticoagulation n(%)**	**General anestesia n(%)**	**Regional anestesia n(%)**
Aridi et al.	NA	62519 (83.0)	NA	5687 (75.5)	68635 (91.1)	6684 (8.9)
Cnotliwy et al.	NA	NA	NA	NA	12 (12.0) *	100 (100) *
Feng et al.	9 (22.5)	19 (47.5)	NA	NA	40 (100)	0 (0.0)
Feringa et al.	NA	41 (93.2)	NA	NA	NA**	NA**
Galyfos et al.	NA	324 (100)	NA	NA	324 (100)	0 (0.0)
Garcia et al.	NA	NA	NA	NA	49 (100)	0 (0.0)
Grobben et al.	50 (22.2)	196 (87.1)	NA	NA	225 (100)	0 (0.0)
Hye et al.	NA	NA	NA	NA	1038 (90.3)	111 (9.7)
Jellish et al.	NA	NA	NA	NA	59 (100)	0 (0.0)

Pereira-Macedo et al.	NA	156 (100)	0 (0.0)	156 (100)	0 (0.0)	156 (100)
Kwon et al.	NA	363 (54.5)	NA	NA	375 (56.3)	0 (0.0)
Leblanc et al.	NA	50 (100)	4 (8.0)	6 (12.0)	0 (0.0)	50 (100)
Motamed et al.	NA	52 (69.0)	NA	NA	39 (52.0)	NA
Shukla et al.	NA	78 (100)	20 (25.6)	5 (6.4)	77 (99.0)	NA
Steely et al.	NA	NA	NA	NA	NA	NA
Tyson et al.	NA	250 (86.5)	NA	NA	289 (100)	0 (0.0)
Walsh et al.	NA	63 (90.0)	18 (25.7)	NA	70 (100)	0 (0.0)
Wang et al.	NA	NA	NA	NA	122 (100)	0 (0.0)

Legend: NA – unavailable data

* - 12 conversions of RA to GA during the intervention

** - combination of GA and RA

Table B.5 – MINS definitions, troponin cutoff values, and troponin kits used in the centers.

Author	MINS n(%)	MINS definition	Troponin T vs I	Troponin kit	Kit troponin limit
Aridi et al.	285 (3.8)	Troponin rise alone was reported if there was a rise in cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and in the absence of the six qualifying criteria for MI or sudden death as defined by the VQI.	NA	NA	One value above the 99th percentile upper reference limit
Cnotliwy et al.	12 (12.0)	Myocardial infarction and sudden cardiac death are defined according to the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction.	Trop I	VIDAS Troponin I Ultra immunoassay and VIDAS BLUE analyzer, bioMerieux INC., Durham	NA
Feng et al.	17 (42.5)	Myocardial injury is indicated if the cTnI concentration is above 0.04 ng/mL.	Trop I	AxSYM Troponin-I ADV assay (Abbott Laboratories) on a routine AxSYM analyzer	Myocardial injury >0.04 ng/mL; Myocardial ischemia

					0,05-1.5 ng/mL; Myocardial infarction >1.5 ng/mL
Feringa et al.	2 (4.5)	Troponin T levels were measured on postoperative days 1, 3, 7 or before discharge and whenever clinically indicated by ECG changes, consistent with myocardial ischemia or infarction.	Trop T	Electrochemiluminescence immunoassay on the Elecsys 2010 (Roche Diagnostics, Mannheim, Germany)	Lower limit positive detection >0.03 ng/ml
Galyfos et al.	8 (2.4)	Postoperative cTnI values ranging from .05 ng/mL to .5 ng/mL were classified as MIsch and cTnI values over 0.5 ng/mL as MIn, even in the absence of symptoms, according to international guidelines. The occurrence of MIsch or MIn was defined as cardiac damage.	Trop I	Architect; Abbott Corporation Ltd, North Chicago, IL	cTnI normal value cutoff was .05 ng/mL
Garcia et al.	10 (21.0)	Proportion of subjects with a detectable increase in cardiac troponin I (cTnI) within 72 hours of vascular surgery and the distribution of such	Trop I	Abbott ARCHITECT cTnI assay; Siemens Dimension Vista cTnI assay	> 0.028 lg/L; > 0.021 lg/L, respectively

increases. A detectable increase was defined as having 1 postoperative cTnI measurement above the preoperative cTnI with at least 1 of the postoperative values above the 99th percentile for the assay. We also evaluated the proportion of patients meeting the Third Universal Definition of MI. According to this definition a MI is present when there is evidence of myocardial necrosis (ie, rise and fall of cardiac biomarker) and one of the following (s): symptoms of myocardial ischemia, developing of pathological Q waves or new ischemic changes (1-mm horizontal or downsloping STdepression, new 2-mm-deep T-wave inversion, ≥1 mm STsegment elevation in 2 contiguous leads, or new left bundle branch block) in the electrocardiogram (ECG), imaging evidence of new

		loss of viable myocardium or new regional wall motion abnormality, and/or identification of an intracoronary thrombus by angiography or autopsy.			
Grobben et al.	26 (11.0)	Patients were classified as troponin only in case of troponin elevation without angina or ischemic changes on the ECG (based on the most recent definition of MI - 3rd universal definition).	Trop I	Third generation AccuTnI assay (Beckman Coulter, Brea, CA)	Upper reference limit of 60 ng/L
Hye et al.	12 (10.4)	Cardiac ischemia was biomarker elevation alone were included in the analysis and were labeled as biomarkerþ-only MI.	Trop T, I and CK-MB	NA	CK myocardial band (CK-MB) or troponin levels were two or more times the upper limit of the local site laboratory's normal value.

Jellish et al.	0 (0.0)	NA	Trop I	NA	Increment compared with preoperative values
Pereira-Macedo et al.	24 (15.3)	Myocardial injury after noncardiac surgery (MINS) is defined as a relevant myocardial injury due to ischemia occurring during or within 30 days after surgery. Myocardial injury after noncardiac surgery is defined by a rising pattern of cardiac troponin values with at least one value above the 99th percentile upper reference limit.	Trop I; hSTnI	Trop I chemiluminescent microparticle immunoassay (Architect Stat Troponin I, Abbot Laboratories, Wiesbaden, Germany) and a fourth-generation assay hSTnI (Abbot Laboratories, Wiesbaden, Germany)	Trop I: 0.032 μg/mL regardless of sex ; hsTnI27 ng/mL (male) or 11.4 ng/mL (female)
Kwon et al.	6 (1.0)	Cardiac damage was defined as postoperative elevation of the blood concentration of cardiac troponin I (0.05–0.5 ng/ml) in the absence of myocardial ischemia.	Trop I	NA	0.05–0.5 ng/ml

Leblanc et al.	1 (2.0)	CTnI up to 0.95 ng.ml-1 (day 2) without ECG changes.	Trop I	NA	cTnI up to 0.95 ng.ml-1
Motamed et al.	10 (13.3)	CTnI values of between 0.5 and 1.5 ng/mL were considered myocardial ischemia.	Trop I	Stratus analyzer (Dade, Massy, France). At the time of the study, the detection limit of the immunoassay was 0.1 ng/mL.	0.5 and 1.5 ng/mL
Shukla et al.	5 (6.4)	NA	Trop I	Immunoassay testing via monoclonal antibody binding with >0.034 ng/mL defined as abnormal (Ortho Clinical Diagnostics, Raritan, New Jersey).	>0.034 ng/mL
Steely et al.	15647 (0.4)	Troponin-only POMI was defined as troponin elevation beyond the normal upper limit without creatinine phosphokinase muscle brain elevation	NA	NA	NA

		and without other clinical signs, symptoms, or ECG changes consistent with myocardial infarction (MI).			
Tyson et al.	5 (1.7)	A patient was judged to have a myocardial infarction if the troponin-I level was greater than or equal to 0.6 ng/mL or CK-MB is >6.3 ng/mL (as per our institutional parameters). This was further qualified by the presence or absence of symptoms and changes on electrocardiography (EKG) or echocardiogram. A patient was judged to have an MI on EKG if the patient developed ST elevation, Q waves, or T wave inversion on postoperative EKG. Furthermore, echocardiogram findings of new wall motion abnormality, decreased ejection fraction, or new left ventricular dysfunction postoperatively indicated acute MI.	Trop I; CK-MB	NA	Trop I > 0.6 ng/mL or CK-MB > 6.3 ng/mL
Walsh et al.	2 (2.9)	Elevation in serum troponin I > 0.15 mg/dL	Trop I	NA	> 0.15 mg/dL

Wang et al.	25 (20.5)	The primary end-point was the rate of myocardial injury, as measured by cTnI. In the healthy population, the 99 percentile value of cTnI is 0.04 ng/ml; thus, the myocardial injury was defined as a cTnI > 0.04 ng/ml.	Trop I	AxSYM troponin I analyser (Abbott Laboratories, Longford, Ireland)	Lower limit of detection 0.02 ng/mL. MINS > 0.04

Legend: NA – unavailable data

Table B.6 – Short-term outcomes after CEA for patients who developed MINS

Author	**Stroke 30 days n(%)**	**Stroke/Death 30 days n(%)**	**Death 30 days n(%)**	**MI 30 days n(%)**	**MACE 30 days n(%)**	**MACE definition**	**Post-operative complications 30 days n(%)**
Aridi et al.	NA	NA	NA	NA	NA	NA	NA
Cnotliwy et al.	NA	NA	NA	NA	NA	NA	NA
Feng et al.	NA	NA	NA	0 (0.0)	NA	NA	NA
Feringa et al.	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Galyfos et al.	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA	NA
Garcia et al.	NA	NA	0 (0.0)	NA	NA	NA	NA
Grobben et al.	1 (3.8)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	Composite of MI, stroke and cardiovascular death	NA
Hye et al.	NA	NA	0 (0.0)	NA	NA	NA	NA
Jellish et al.	0 (0)	0 (0)	0 (0.0)	0 (0.0)	NA	NA	NA
Pereira-Macedo et al.	1 (4.1)	2 (8.3)	NA	1 (4.1)	1 (4.3)	Composite of MI, acute heart failure and all-cause mortality	NA

Kwon et al.	NA	NA	NA	NA	NA	NA	NA
Leblanc et al.	0 (0.0)	0 (0.0)	NA	0 (0.0)	NA	NA	NA
Motamed et al.	0 (0.0)	NA	NA	NA	NA	NA	NA
Shukla et al.	NA	NA	NA	NA	NA	NA	NA
Steely et al.	NA	NA	NA	NA	NA	NA	NA
Tyson et al.	NA	NA	NA	NA	NA	NA	NA
Walsh et al.	0 (0.0)	NA	NA	0 (0.0)	NA	NA	2 (2.9)
Wang et al.	NA	NA	NA	NA	NA	NA	NA

Legend: NA – unavailable data

Table B.7 – Long-term outcomes after CEA in patients who developed MINS

Author	Other outcomes	Long-term outcomes	Long-term follow-up time	Long-term MI n(%)	Long-term stroke n(%)	Long-term MACE n(%)	Long-term all-cause mortality n(%)
Aridi et al.	NA	NA	NA	NA	NA	NA	NA
Cnotliwy et al.	NA	NA	NA	NA	NA	NA	NA
Feng et al.	NA	NA	NA	NA	NA	NA	NA
Feringa et al.	NA	NA	1.2 years	0 (0.0)	NA	NA	NA
Galyfos et al.	NA	NA	2 years ± 2.2 months	NA	NA	NA	NA
Garcia et al.	NA	NA	6 months	NA	NA	NA	NA
Grobben et al.	NA	NA	1.8 years [IQR 1.0 -2.6]	0 (0.0)	1 (4.0)	2 (8.0)	3 (12.0)
Hye et al.	NA	NA	NA	NA	NA	NA	NA
Jellish et al.	NA	NA	NA	NA	NA	NA	NA

Pereira-Macedo et al.	NA	MI, stroke, MACE, all-cause mortality	52 months [49-54]	HR: 3.318. 95% CI:0.97–13.928. Breslow: P=0.025	HR: 2.133. 95% CI: 0.565–8.052 P=0.251	HR: 1.955. 95% CI: 1.01–4.132. Breslow: P=0.046	HR: 1.699 95% CI: 0.772–3.743. log rank: P=0.986)
Kwon et al.	NA	NA	NA	NA	NA	NA	NA
Leblanc et al.	NA	NA	NA	NA	NA	NA	NA
Motamed et al.	NA	NA	44 ± 12 months	NA	NA	NA	NA
Shukla et al.	NA	NA	NA	NA	NA	NA	NA
Steely et al.	NA	NA	NA	NA	NA	NA	NA
Tyson et al.	NA	NA	NA	NA	NA	NA	NA
Walsh et al.	NA	NA	NA	NA	NA	NA	NA
Wang et al.	NA	NA	NA	NA	NA	NA	NA

Legend: NA – unavailable data

APPENDIX C

Table C.1 – Meta-analysis results and subgroup analysis

Meta-analysis results	N studies	Proportion	CI_LB	CI_UB	Heterogeneity_I2	Heterogeneity_p-value
All studies	18	0.055	0.028	0.110	99.1	<0.001
General Anesthesia	12	0.045	0.018	0.113	98.1	<0.001
Regional Anesthesia	4	0.022	0.004	0.115	96.4	<0.001

Legend: CI – confidence interval; LB – lower bound; UB – upper bound

Table C.2 – Meta-Regression results

Meta-regression results	N studies	Odds Ratio	CI_LB	CI_UB	p-value	Heterogeneity_I2	Heterogeneity_p-value
Year	18	0.992	0.844	1.166	0.923	99.1	<0.001
Mean age	15	0.889	0.641	1.233	0.482	97.2	<0.001

Percent of males	17	1.073	1.020	1.129	0.007	94.8	<0.001
Percent of AHT	14	0.980	0.923	1.040	0.503	97.3	<0.001
Percent of dyslipidemia	11	0.979	0.941	1.018	0.283	97.8	<0.001
Percent of diabetes	13	0.984	0.880	1.100	0.774	97.8	<0.001
Percent of smokers	13	0.983	0.935	1.033	0.499	97.1	<0.001
Percent of CAD	11	0.990	0.918	1.067	0.787	98.2	<0.001
Percent of symptomatic	13	1.042	1.015	1.069	0.002	95.1	<0.001
Percent of antiplatelet use	12	0.987	0.941	1.035	0.581	97.3	<0.001
Troponin T	16	0.758	0.046	12.468	0.846	94.8	<0.001
Troponin I	15	1.440	0.374	5.542	0.596	94.5	<0.001
CKMB	16	0.268	0.022	3.310	0.304	94.3	<0.001

Legend: CI – confidence interval; LB – lower bound; UB – upper bound

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page and paragraph/ table #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1 - Paragraph 1 “Incidence of myocardial injury in patients submitted to carotid endarterectomy: a systematic review”
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 3 – Paragraphs 1-3; and Page 4 – Paragraph 1 “Myocardial injury following noncardiac surgery (…) and equivalent cut-off values.”
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 5 - Paragraphs 1-3 “Some patients submitted to noncardiac (…) than those who had not.”
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 6 - Paragraph 1 “Therefore, the present systematic review aims to assess the incidence of MINS in patients submitted to CEA with or without regional anesthesia (RA).”
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 7 - Paragraph 1 “The review protocol has been registered at Prospero (reference: CRD42021224429).”
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 7 - Paragraphs 2 and 3 “Inclusion criteria consisted in all (…) further articles of possible interest.”
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 7 - Paragraph 3 “A systematic search was performed in three databases – Pubmed, Scopus, and Web of Science –, in September 2021. The query and keywords are shown in supplemental Table B.1. Additionally, the references of the included primary

			studies and relevant available systematic reviews were screened to search for any further articles of possible interest."
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 31 - Table B.1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 7 – Paragraph 4 "After duplicates removal, two authors (JPM and AFS) have independently participated in studies selection; any disagreement was solved by the intervention of a third author (JRN). First, studies were selected by title and abstract, and the remaining ones were eligible for full-text assessment. The same samples studied in multiple original articles were only included once."
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 8 – Paragraph 1 "Data from included studies were independently extracted by two authors (AFS, JPM). Data were extracted using a purposely-built form on the year of publication, country, and center of recruitment, study design, recruitment time, number of participants undergoing CEA, participants' age, and gender distribution, frequency of cardiovascular comorbidities, and carotid symptomatic status. In addition, data related to each study's MINS cut-off and troponin kit used was retrieved, as well as the incidence and definition of MINS."
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 8 – Paragraph 1 "Data were extracted using a purposely-built form on the year of publication, country, and center of recruitment, study design, recruitment time, number of participants undergoing CEA, participants' age, and gender distribution, frequency of cardiovascular comorbidities, and carotid symptomatic status. In addition, data related to each study's MINS cut-off and troponin kit used was retrieved, as well as the incidence and definition of MINS."

Risk of bias in individual studies / Risk of bias across studies	12/ 15	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 8 – Paragraph 2 “Concerning qualitative assessment, the Cochrane Risk of Bias-2 tool was used for randomized clinical trials and the National Heart, Lung, and Blood Institute (NHLBI) Study Quality Assessment Tool was used for observational cohort and cross-sectional studies (2013). This assessment was independently performed by two authors (JPM and AFS), and when disagreements were observed, decisions were made by mutual consensus after a third-party review (JRN).”; Page 8 – Paragraph 3 “The possibility of publication biases was assessed using funnel plots.”
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 8 – Paragraph 3 “A random-effects meta-analysis (using the restricted maximum likelihood method) of log-transformed proportions to calculate the meta-analytical pooled incidence of MINS among participants was performed.”
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 8 – Paragraph 3 “Pooled estimates and 95% confidence (…)troponin I levels, and CK-MB.”; Page 9 – Paragraph 1 “All statistical analysis were performed using software R (metafor package).”
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 8 – Paragraph 3 “Subgroup analyses were also performed with separate analyses of studies in which participants were under general anesthesia or regional anesthesia.”
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 10 – Paragraph 1 “After the database search and (…) this systematic review (Table B.2).”; Paragraph 2 “However, two studies had repeated samples that were next included in a more recent article, and therefore only data from the latter was considered”; Figure A.1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 10 – Paragraph 2; and Page 11 – Paragraph 1 “Sixteen of the 20 studies (…) as displayed in Table

			B.5."; Tables B.2- B.5
Risk of bias within and across studies	19/ 22	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 12 – Paragraph 2 and 3 "The risk of bias of (…) statistical adjustment for their impact."; Page 13 – Paragraph 1 "A funnel plot regarding publication bias is displayed in figure A.6. The funnel plot displays an asymmetric pattern – while funnel plot asymmetry is expected in cases of severe heterogeneity, publication bias cannot be excluded." Figures A.2-A.6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 11 – Paragraph 1 "The incidence of reported MINS within 30-days after CEA in primary studies ranged from 0 and 42.5%. Considering only patients submitted to RA, a range of 2 to 15.3% was observed in the occurrence of MINS, while among patients submitted to GA such range was of 0% to 42.5%."; Page 12 – Paragraph 1 "Concerning short- and long-term outcomes in patients that experienced MINS, available data was sparse but further withdrawn and displayed in the Tables B.6 and B.7."; Table B.5-7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 12 – Paragraph 2 "The meta-analytical incidence of MINS after CEA was 6.3% [95% CI 2.0%-10.6%]. However, severe heterogeneity was found (I2 = 99.1%; Q-Cochran p-value<0.001). In all results of leave-one-out sensitivity analysis and of univariable meta-regression models, severe heterogeneity was described (I2>90%) (Table C.1 and C.2)." Table C.1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 12 – Paragraph 2 "In all results of leave-one-out sensitivity analysis and of univariable meta-regression models, severe heterogeneity was described (I2>90%) (Table C.1 and C.2). Additionally, subgroup analysis regarding the use of general anesthesia vs. regional anesthesia has shown similar high heterogeneity (above 98 and 96%, respectively). Studies related to general anesthesia have reached a prevalence of 4.5% whereas regional anesthesia

			accounted with 2.2% of MINS, in the meta-analysis (Table C.1).”; Tables C.1-C.2
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 14 – Paragraph 1 “The present systematic review has found a meta-analytical incidence of MINS after CEA of 6.3%, with a range between 0 and 42.5%. However, severe heterogeneity was found and not accounted by sensitivity analysis or meta-regression models.”
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 17 – Paragraph 2 “This study faced many limitations (…) MINS association with other outcomes.”
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 18 – Paragraphs 1 and 2 “This systematic review exposes the (…) at short and long periods.”
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 19 – Paragraph 2 “This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.”

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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