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Dextran as an adjunct in Carotid Endarterectomy: A Systematic Review and Meta Analysis

Duarte José da Silva Vieira

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Dextran as an adjunct in carotid endarterectomy: A Systematic Review and Meta Analysis

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ASSINALE APENAS UMA DAS OPÇÕES:

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UC Dissertação - DECLARAÇÃO DE TRANSPARÊNCIA RELATIVAMENTE À UTILIZAÇÃO DE FERRAMENTAS DE CHATBOT GENERATIVO BASEADAS EM LARGE LANGUAGE MODELS

Eu, Duarte José da Silva Vieira, abaixo assinado, nº mecanográfico 201906372, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro que:

☒ Não procedi à utilização de ferramentas de chatbox generativo baseadas em large language models para nenhuma das tarefas no contexto do meu trabalho de Dissertação ou Monografia

☐ Procedi à utilização de ferramentas de chatbox generativo baseadas em large language models no contexto do meu trabalho de Dissertação ou Monografia, encontrando-se todas as interacções (prompts e respostas) transcritas em anexo bem como a indicação das aplicações utilizadas.

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Dedicatória

Dedico este trabalho primeiramente aos meus pais, cuja presença constante, amor, ensinamentos contribuiram para os fundamentos de todo o meu percurso. Estendo também esta dedicatória a toda a minha família, que sempre me apoiou incondicionalmente.

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A cada um de vocês, deixo aqui a prova da minha profunda gratidão e reconhecimento.

Dextran as an Adjunct in Carotid Endarterectomy: A Systematic Review and Meta-analysis

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ABSTRACT

BACKGROUND

Carotid endarterectomy (CEA) is a widely used surgical procedure to prevent stroke in patients with carotid artery stenosis. Dextran, an antithrombotic agent with antihemostatic properties, has been proposed as an adjunctive therapy to reduce thromboembolic complications during CEA. However, its effectiveness and safety remain controversial. This systematic review and meta-analysis aim to assess the incidence of thromboembolic and haemorrhagic complications in patients undergoing CEA with dextran administration.

MATERIALS AND METHODS

A systematic search was conducted in MEDLINE, Scopus, and Web of Science for studies evaluating the postoperative effects of dextran in CEA patients. Random-effects meta-analysis was performed to estimate the pooled incidence of adverse events, and heterogeneity was assessed through meta-regression analysis. The quality of the included studies was evaluated using the National Heart, Lung, and Blood Institute (NHLBI) Study Quality Assessment Tool for observational studies and the Cochrane Risk of Bias 2 tool for randomized controlled trials (RCTs).

RESULTS

Ten studies, including a total of 149,540 patients, met the inclusion criteria. Of these, nine were observational cohort studies (six retrospective and three prospective), while one was an RCT. The meta-analytical incidence of stroke following CEA with dextran was 0.7% (95% CI: 0.3%–1.1%), with moderate heterogeneity (I^2 = 50.79%, p = 0.002). Meta-regression analysis indicated that geographic region significantly contributed to heterogeneity (p = 0.010), while other clinical covariates, such as diabetes, hypertension,

and coronary artery disease, were not associated with significant variations in outcomes. Dextran was primarily administered selectively to high-risk patients, with variations in dosing protocols across studies.

CONCLUSION

The use of dextran in CEA was associated with a low incidence of thromboembolic events. However, some heterogeneity among studies highlights the need for further large-scale RCTs to clarify its efficacy and safety. Given the potential risks of dextran, including haemorrhage and renal complications, individualized patient selection and standardized administration protocols are recommended.

INTRODUCTION

Carotid endarterectomy (CEA) is a surgical procedure commonly performed to reduce the risk of complications such as stroke or transient ischaemic attack (TIA), which typically result from carotid artery stenosis. The procedure involves opening the blood vessel, after which the surgeon removes the plaque responsible for stenosis of the artery. Thromboembolic stroke is a major cause of morbidity and mortality in patients following CEA. The usage of transcranial Doppler monitoring (TCD), followed by dextran administration, has been shown to reduce embolization rates. [1]

In medical practice, various adjuncts are used as supplements to anticoagulant therapy, such as polygeline (acting as plasma substitutes with anticoagulant properties),[2] gelatin-based colloid solutions (preventing clot formation)[3] , and pentastarch or hydroxyethyl starch (plasma expanders with mild antithrombotic effects)[4, 5].

The most commonly used, dextran, a complex branched glucan, has demonstrated antihemostatic properties, including the inhibition of platelet adhesion and aggregation, interference with fibrin polymerization, inhibition of erythrocyte aggregation, reduction of blood viscosity, and enhancement of fibrinolysis. Consequently, it has been theorized to lower the risk of complications associated with CEA and has traditionally been used, although the extent of its usage varies amongst surgeons. [1, 6]

As a supportive treatment, dextran is used in combination with other anticoagulants. Its simultaneous use with heparin or low molecular weight heparin may enhance the anticoagulant effect of both by inhibiting platelet aggregation and prolonging clotting times. Dextran interacts with vitamin K antagonists and direct oral anticoagulants, amplifying their anticoagulant action. Dextran may also amplify the antiplatelet effect of

aspirin. Using dextran during thrombolytics increased risk of hemorrhage. Concurrent use is avoided unless absolutely required.

Numerous reports have documented complications associated with dextran use, including haemorrhage, volume overload, allergic reactions, anaphylactic shock, thrombocytopenia, acute renal failure and haemodilution. [7-9]

Hence, the impact of using dextran as an adjunct in CEA requires further investigation, as guidelines are not well established. The goal of this systematic review is to provide greater insight into the benefits and risks of dextran use in CEA.

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 the AMSTAR -2 critical appraisal tool [10, 11]. Ethical approval from an institutional review board was not obtained due to the nature of this study. The review protocol has been registered at Prospero (reference: CRD42024593605).

Selection Criteria

The inclusion criteria encompassed all original studies conducted in humans, except for systematic reviews, and case series with fewer than 15 patients, that assessed the incidence of postoperative adverse events following CEA. No exclusion criteria were applied based on publication language or date.

Search strategy

A systematic search was conducted in three databases – PubMed, Scopus, and Web of Science – in September 2024. The query and keywords are presented in Supplemental

Table 1. Additionally, the references of the included primary studies and relevant systematic reviews were screened to identify any further articles of potential interest.

Study selection and data extraction

After duplicates removal, two authors (DSV and JRN) independently selected studies. Any disagreements were resolved through the intervention of a third author (APN). First, studies were screened by title and abstract, and those remaining were assessed to full text eligibility. Exclusion criteria included patients undergoing synchronous cardiac surgery, carotid stenting, or carotid reintervention. Efforts were made to contact authors to obtain full texts that were not publicly available. The selected studies were carefully reviewed to avoid duplicate populations.

Data from included studies were independently extracted by two authors (DSV and JRN) using a standardized form. Extracted data included the year of publication, country and centre of recruitment, study design, recruitment period, number of participants undergoing CEA, participants' age and gender, prevalence of cardiovascular comorbidities, and carotid symptomatic status (Table 1 and 2).

Assessment of study quality

For qualitative assessment, the Cochrane Risk of Bias-2 tool was used for randomized clinical trials, while the National Heart, Lung, and Blood Institute (NHLBI) Study Quality Assessment Tool was applied for observational cohort and cross-sectional studies (2013). Two authors (DSV and JRN) independently conducted the assessment, and any disagreements were resolved by consensus following a third-party review (APN).

Quantitative synthesis

A random-effects meta-analysis (using the restricted maximum likelihood method) of log-transformed proportions was conducted to calculate the meta-analytical pooled

incidence of stroke among participants. Pooled estimates and 95% confidence intervals (95% CI) were backtransformed into their original scale to easier 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 indicative of substantial heterogeneity. Sources of heterogeneity were explored through leave-one-out sensitivity analysis and univariable meta-regression models. Assessed covariates included the publication year, participants' mean age, percentage of male participants, and prevalence of arterial hypertension, dyslipidaemia, diabetes, or coronary artery disease (CAD). Other factors included the percentage of symptomatic patients and proportion of patients using antiplatelet drugs.

Subgroup analyses were conducted to separately evaluate studies in which participants underwent general anaesthesia versus regional anaesthesia. The potential for publication bias was assessed using funnel plots.

All statistical analysis was performed using Open Meta®.

RESULTS

Search Results

After the database search and duplicate removal, a total of 135 studies were screened. Following title and abstract screening, 114 studies were excluded. Twenty-one studies proceeded to full-text assessment, during which 10 studies were excluded, and one study could not be retrieved (Figure 1).

Comprehensive reasons for exclusion during full-text assessment included: multiple articles from the same patient population (N=6), incorrect patient population (N=1), irrelevant outcome (N=3), and unavailable full-text despite contacting the respective author (N=1).

Thus, a total of 10 published articles were included in this systematic review. [1, 6-9, 12-16]

Description of Studies

Nine of the 10 studies were observational cohorts' studies, six retrospective and three prospective. The remaining study was a randomized controlled trial (RCT). The included studies were conducted across three different countries spanning three continents- two from North America,[7, 8] six from Europe,[1, 9, 13-16] and two studies from Oceania [6, 12].

A total of 149,540 patients were assessed, with study sample sizes ranging from 19 participants [1] to 140,893 participants [8] The mean participant age was 70 years, and 60.1% (n=89 909) were male.

Demographics and comorbidities of the included study population are presented in Table 2.

Main findings and meta-analysis

The meta-analytical incidence of stroke after CEA with dextran was 0.7% (Figure 2) [95% CI: 0.3%–1.1%], with moderate heterogeneity observed (I^2 = 50.79%p = 0.002), indicating tolerable variability among the included studies.

In all leave-one-out sensitivity analyses and univariable meta-regression models, substantial heterogeneity persisted.

Regarding the meta-regression analysis, the following covariates showed no significant association with outcomes: gender, diabetes mellitus (DM), hypertension (HTA), coronary artery disease (CAD), smoking, and symptomatic carotid stenosis. These findings suggest that these clinical factors did not significantly influence the proportion of adverse events across studies. Detailed results are presented in Supplementary Figure 1.

Meta-regression by continent

The meta-regression analysis identified a statistically significant association between continent and the proportion of adverse events (p = 0.010).

The adjusted model yielded an intercept coefficient of 0.004 (95% CI: 0.001–0.007, p = 0.009), suggesting regional variations in the reported incidence of events.

The omnibus p-value for the model was 0.010, confirming that the continent significantly contributed to the observed heterogeneity among the included studies. North America presented a single study with an increased stroke rate compared to the remaining.[8]

Dextran Administration Approaches

Dextran administration across studies was primarily selective, targeting high-risk patients undergoing CEA [7]. Most protocols utilized TCD to identify patients with significant embolization (e.g., >25 emboli in 10 minutes or >50 per hour) or severe stenosis [1]. Dextran was administered intraoperatively or postoperatively, often as a bolus followed by infusion. A notable exception was observed in the study by Farber et al.,[7] where dextran was administered to 5% of patients without specific embolization criteria, reflecting a less selective approach.

Studies quality

The risk of bias in the selected articles is displayed in Figures 3 and 4. The risk of bias for each observational cohort is individually shown in Figure 2a, while the risk of bias for the RCT is displayed in figure 3a. The overall judgement per evaluated item regarding observational cohorts is presented in Figure 2b, whereas that for the RCT is shown in Figure 3b.

All studies included in this review exhibited an overall low risk of bias both cohorts and RCT. The items most frequently associated with high risk of bias amongst observational cohorts included sample size justification and statistical adjustment for confounding

factors. For the RCT, high or unclear risk patterns were noted in essential domains, such as allocation concealment and outcome measurement.

DISCUSSION

This systematic review and meta-analysis demonstrated that dextran administration during CEA was associated with a low incidence of stroke (0.7%), with moderate heterogeneity among included studies. The findings suggest that dextran may be beneficial in reducing thromboembolic events; however, significant variability in study methodologies and patient selection criteria limits definitive conclusions.

The primary finding of this study—the low incidence of stroke associated with dextran use—supports its potential as an adjunct therapy during CEA. While dextran can decrease embolic signals detected via transcranial Doppler, studies show it fails to significantly lower stroke rates and is associated with severe complications such as anaphylaxis, hemorrhage, myocardial infarction (MI), congestive heart failure (CHF), renal failure, and prolonged hospital stays [7, 8]. In contrast, dual antiplatelet therapy (DAPT), combining aspirin and clopidogrel, has proven more effective in reducing post-operative embolization and stroke risk without the adverse cardiac effects linked to dextran. A study demonstrated that preoperative DAPT reduced high-rate embolization to 0.4%, compared to 3.2% in historical controls using dextran[15]

For asymptomatic patients undergoing CEA, the risks associated with dextran administration may outweigh its benefits. DAPT provides a safer alternative, minimizing complications while maintaining efficacy in stroke prevention. This highlights a shift away from dextran in favor of therapies with better safety profiles and comparable or superior outcomes.

Dextran exerts its protective effects through multiple physiological mechanisms that contribute to the reduction of thromboembolic events during carotid endarterectomy. As a branched polysaccharide, dextran interferes with coagulation by inhibiting platelet aggregation and adhesion, reducing blood viscosity, and enhancing fibrinolysis. These effects collectively prevent the formation of microthrombi, which are a major cause of perioperative stroke. Additionally, dextran's ability to interfere with fibrin polymerization further contributes to its antithrombotic profile.[7, 8] Another key aspect of dextran's protective mechanism is its role in improving blood flow properties. By reducing erythrocyte aggregation and increasing capillary perfusion, dextran helps maintain adequate cerebral oxygenation and prevents hypoperfusion-related ischemic events. Furthermore, dextran has been shown to decrease endothelial activation and reduce inflammatory responses, which may play a role in limiting vascular complications following CEA [1, 6, 7].

A key observation from this review is the variability in dextran administration protocols across studies. Most studies employed a selective approach, administering dextran only to high-risk patients identified via TCD monitoring, particularly those exhibiting high embolization rates. In contrast, some studies, such as Farber et al.[7] reported a non-selective approach, administering dextran to a broader patient population without stringent embolization criteria. These discrepancies in dextran administration highlight the lack of standardized guidelines, making direct comparisons challenging. The impact of dextran may therefore be contingent upon specific patient selection strategies.

Meta-regression analysis revealed that the continent in which the study was conducted significantly influenced the incidence of adverse events ($p = 0.010$). This finding suggests that regional variations in perioperative management, patient selection criteria, and institutional practices may contribute to heterogeneity in outcomes. Studies from Europe

tended to report lower adverse event rates, potentially reflecting more stringent patient selection and perioperative monitoring protocols. Conversely, studies from North America and Oceania exhibited higher variability in outcomes, which may be attributed to differing dextran administration strategies and institutional guidelines. These regional discrepancies further emphasize the necessity of establishing universal, evidence-based recommendations for dextran use in CEA.

Other findings, such as the lack of significant associations between patient comorbidities (e.g., diabetes, hypertension, coronary artery disease) and stroke incidence, suggest that dextran's benefits may be independent of traditional cardiovascular risk factors. However, the significant regional variations identified through meta-regression underscore the influence of institutional practices and geographical differences in patient management.

Multiple studies have examined the potential side effects of dextran in patients undergoing CEA. While some publications have not reported significant complications, others have noted important adverse events. For instance, Levi et al.[6] observed seven wound hematomas in patients who received dextran, and both Farber et al. and Moore et al.[7, 8] found associations between dextran use and an increased risk of perioperative cardiovascular complications, such as myocardial infarction and congestive heart failure. Although the exact mechanism underlying these complications may stem from dextran's antihemostatic and plasma-volume–expanding properties, these findings underscore the possible importance of careful risk–benefit assessment and support the use of selective administration protocols—particularly in high- cardiovascular risk patients. It is noteworthy that none of the studies specifically reported increased renal complications [7, 8]. The absence of reported renal complications could suggest that current protocols for dextran administration during CEA may be relatively safe for renal function. Some

studies mention the specific heparin protocol which consists on the administration of unfractionated heparin prior to carotid artery clamping. [1, 6, 12, 13]

This study has several limitations. The heterogeneity in study designs, dextran administration protocols, and patient selection criteria complicates direct comparisons. Additionally, most included studies were observational, with some risk of bias due to inadequate statistical adjustments and sample size limitations.

Future research should focus on large-scale, well-designed RCTs to establish standardized protocols for dextran use in CEA and clarify its risk-benefit profile. Until then, clinicians should weigh its potential benefits against the associated risks and consider selective administration based on individual patient profiles.

CONCLUSION

This systematic review and meta-analysis provide insight into the role of dextran as an adjunct in carotid endarterectomy. The findings suggest that dextran administration is associated with a very low incidence of stroke and may offer protective benefits in high-risk patients. However, concerns regarding variations in dosing protocols warrant caution in its widespread use.

This study highlights the need for further research to mitigate intraoperative stroke risk. Future large-scale randomized controlled trials should focus on defining optimal dextran dosage, evaluating short-term safety, and assessing its overall impact on patient outcomes. Until robust evidence is available, dextran should be used selectively, with careful consideration of individual patient risk factors to balance its benefits and risks effectively.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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REFERENCES

1. Lennard NS, Vijayasekar C, Tiivas C, Chan CW, Higman DJ, Imray CH. Control of emboli in patients with recurrent or crescendo transient ischaemic attacks using preoperative transcranial Doppler-directed Dextran therapy. Br J Surg. 2003;90(2):166-70.
2. Singh A, Ali S, Shetty R. Effectiveness and Safety of Polygeline in Patients with Hypovolemia due to Trauma. J Emerg Trauma Shock. 2017;10(3):116-20.
3. Charlesworth M, Shelton CL. Should intravenous gelatins have a role in contemporary peri-operative and critical care? Anaesthesia. 2020;75(2):266-9.
4. Golparvar M, Saghaei M, Hamidi H, Sajedi P, Kashefi P, Aghadavoudi O, et al. Comparative evaluation of the effects of hydroxyethyl starch on coagulation state of patients during brain tumor surgeries in comparison to crystalloids by thromboelastography. J Res Med Sci. 2014;19(1):8-12.
5. Van der Linden P, Ickx BE. The effects of colloid solutions on hemostasis. Can J Anaesth. 2006;53(6 Suppl):S30-9.
6. Levi CR, Stork JL, Chambers BR, Abbott AL, Cameron HM, Peeters A, et al. Dextran reduces embolic signals after carotid endarterectomy. Ann Neurol. 2001;50(4):544-7.
7. Farber A, Tan TW, Rybin D, Kalish JA, Hamburg NM, Doros G, et al. Intraoperative use of dextran is associated with cardiac complications after carotid endarterectomy. J Vasc Surg. 2013;57(3):635-41.
8. Moore JM, Garg K, Laskowski IA, Maldonado TS, Mateo RB, Babu S, et al. Intraoperative Infusion of Dextran Confers No Additional Benefit after Carotid Endarterectomy but Is Associated with Increased Perioperative Major Adverse Cardiac Events. Ann Vasc Surg. 2023;97:8-17.
9. Saedon M, Singer DR, Pang R, Tiivas C, Hutchinson CE, Imray CH. Registry report on kinetics of rescue antiplatelet treatment to abolish cerebral microemboli after carotid endarterectomy. Stroke. 2013;44(1):230-3.
10. McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM, Clifford T, et al. Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. JAMA. 2018;319(4):388-96.
11. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008.
12. Dunne VG, Besser M, Ma WJ. Transcranial Doppler in carotid endarterectomy. J Clin Neurosci. 2001;8(2):140-5.
13. Naylor AR, Hayes PD, Allroggen H, Lennard N, Gaunt ME, Thompson MM, et al. Reducing the risk of carotid surgery: a 7-year audit of the role of monitoring and quality control assessment. J Vasc Surg. 2000;32(4):750-9.
14. Robless PA, Tegos TJ, Okonko D, Mansfield AO, Nicolaides AN, Mikhailidis DP, et al. Platelet activation during carotid endarterectomy and the antiplatelet effect of Dextran 40. Platelets. 2002;13(4):231-9.
15. Sharpe RY, Dennis MJ, Nasim A, McCarthy MJ, Sayers RD, London NJ, et al. Dual antiplatelet therapy prior to carotid endarterectomy reduces post-operative embolisation and thromboembolic events: post-operative transcranial Doppler monitoring is now unnecessary. Eur J Vasc Endovasc Surg. 2010;40(2):162-7.
16. Sharpe RY, Walker J, Bown MJ, Naylor MB, Evans DH, Naylor AR. Identifying the high-risk patient with clinically relevant embolisation after carotid endarterectomy. Eur J Vasc Endovasc Surg. 2009;37(1):1-7.

Table 1 – Study characteristics

Author	Journal	Pub. Year	Study design	Study center	Recruitment period	Sample size	GRADE Evaluation	No. CEA
Saedon M et al.	Stroke	2013	Cohort	University Hospitals Coventry and Warwickshire NHS Trust	2000-2010	Spontaneous Resolution: 54 Tirofiban: 40 Dextran: 34 (n= 128)	★★☆☆	Spontaneous Resolution: 54 Tirofiban: 40 Dextran: 34 (n= 128)
Moore, JM et al.	Annals of Vascular Surgery	2023	Retrospective Cohort	VQI	2008 to 2022	Dextran: 9935 / No Dextran: 130,958 (n = 140893)	★★☆☆	140893
Farber, A et al.	Journal of Vascular Surgery	2013	Retrospetive Cohort	VSGNE	2003–2010	Dextran: 334 / No dextran: 6307 (n=6641)	★★☆☆	6641
Levi, CR et al.	Annals of Neurology	2001	RCT	Austin and Repatriation Medical Centre and Warringal Private Hospital	N/A	Dextran: 72 / No Dextran: 69 (n=141)	★★★☆	141
Dunne, VG et al.	Journal of Clinical Neuroscience	2001	Retrospective Cohort	Royal Prince Alfred Hospital	1996-1999	30	★★☆☆	32
Sharpe, RY et al.	Eur J Vasc Endovasc Surg	2010	Prospective Audit	Leicester Royal Infirmary	2006-2009	297	★★☆☆	297
Sharpe, RY et al.	Eur J Vasc Endovasc Surg	2009	Prospective Audit	Leicester Royal Infirmary	1995-2006	821	★★☆☆	821
Lennard, NS et al.	The British journal of surgery	2003	Prospective Cohort	Coventry and Warwickshire University Hospitals	1998-2001	19	★★☆☆	19
Naylor, AR et al.	Journal of vascular surgery	2000	Prospective Audit	Leicester Royal Infirmary	1995-1999	500	★★☆☆	500
Robless, PA et al	Platelets	2002	Prospective Cohort	St Mary's Hospital	N/A	40	★★☆☆	40

CEA – Carotid endartectomy; RA – Regional Anesthesia; NA – information not available; VQI – Vascular Quality Iniciative; VSGNE -Vascular Surgery Group of New England.

Table 2 – Populations demographics and risk factors

Author	Mean age	Male	Arterial Hypertension	Dyslipidemia	Diabetes Mellitus	Smoking History	Coronary artery disease	Carotid territory symptoms
Moore, JM et al.	Dextran: 71 / No Dextran: 70.7	Dextran: 5947 (4.2%) / No Dextran: 79,527 (56.4%) (n= 85 474) (61%)	Dextran: 8834 (6.3%) / No Dextran: 116,968 (82.5%) (n= 125 802) (89.2%)	N/A	Dextran: 3057 (2.2%) / No Dextran: 41,281 (29.3%) (n= 44338) (31.5%)	Dextran: 2515 (1.8%) / No Dextran: 33,778 (24%) (n= 36 293) (25.8%)	Dextran: 2542 (1.8%) / No Dextran: 34,034 (24.2%) (n= 36 576) (26%)	Dextran: 2447 (1.7%) / No Dextran: 38,055 (27%) (n= 40052) (28.4%)
Farber, A et al.	Dextran: 70 / No Dextran: 70	Dextran: 217 (3.3%) / No Dextran: 3784 (57%) (n=4001) (60.2%)	Dextran: 274 (4.1%) / No Dextran: 5550 (83.6%) (n=5824) (87.7%)	N/A	Dextran: 104 (1.6%) / No Dextran: 1955 (29.4%) (n=2059) (31%)	Dextran: 264 (4.0%) / No Dextran: 5046 (76%) (n=5310) (80%)	Dextran: 94 (1.4%) / No Dextran: 2081 (31.3%) (n=2175) (32.8%)	1660 (25%) symptomatic
Levi, CR et al.	Dextran: 69 / No Dextran: 69.5	Dextran: 50 (35.4%) / No Dextran: 52 (36.9%) (n= 102) (72.3%)	N/A	N/A	Dextran: 8 (5.7%) / No Dextran: 10 (7.1%) (n= 18) (12.8%)	Dextran: 13 (9.2%) / No Dextran: 8 (5.7%) (n=21) (14.9%)	Dextran: 28 (19.9%) / No Dextran: 32 (22.7%) (n=60) (42.6%)	N/A
Saedon M et al.	Spontaneous Resolution: 71 / Tirofiban: 74 / Dextran: 69	Spontaneous Resolution: 36 (28.1%) / Tirofiban: 27 (21.1%) / Dextran: 22 (17.2%) (n=85) (66.4%)	Spontaneous Resolution: 47 (36.7%) / Tirofiban: 31 (24.2%) / Dextran: 27 (21.1%) (n=105) (82%)	N/A	Spontaneous Resolution: 16 (12.5%) / Tirofiban: 10 (7.8%) / Dextran: 6 (4.7%) (n=32) (25%)	Spontaneous Resolution: 12 (9.4%) / Tirofiban: 13 (10.2%) / Dextran: 9 (7%) (n=34) (26.6%)	Spontaneous Resolution: 24 (18.8%) / Tirofiban: 14 (11%) / Dextran: 14 (11%) (n=52) (40.6%)	N/A
Dunne, VG et al.	64	22 (68.8%)	22 (68.8%)	20 (62.5%)	8 (25%)	11 (34.8%)	18 (56.2%)	15 TIA (46.9%), 6 Amaurosis Fugax (18.8%), 8 Stroke (25%) (n=29) (90.6%)
Sharpe, RY et al.	69	204 (68.7%)	N/A	N/A	N/A	N/A	N/A	253 (84.9%) symptomatic
Sharpe, RY et al.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lennard NS et al.	38-86	13 (68.4%)	N/A	N/A	1 (5.3%)		8 (42.1%)	N/A
Naylor AR et al.	N/A	N/A	310 (62%)	N/A	74 (14.8%)	N/A	123 (24.6%)	421 (84.2%)
Robless, PA et al.	68	30 (75%)	25 (62.5%)	12 (30%)	10 (25%)	16 (40%)	13 (32.5%)	36 (90%)

CEA – Carotid Endarterectomy; N/A – Information Not Available

Table 3 – Pre-operative characteristics

Author	Ipsilateral stenosis	Contralateral stenosis	Antiplatelet therapy	Anticoagulation	General anaesthesia	Regional anaesthesia	Intraoperative Anticoagulation protocol	Dextran administration protocol
Moore, JM et al.	Dextran: 4864 / No Dextran: 58,957	N/A	Aspirin: Dextran: 8144 / No Dextran: 109,736// Inibidor P2Y12: Dextran: 3027 / No Dextran: 46,335	N/A	Dextran: 9569 / No Dextran: 120,856 (n=130 425)	N/A	N/A	Dextran was administred intraoperatively A total of 7.1% of patients received Dextran (n=9935)
Farber, A et al.	N/A	N/A	Dextran: 291 / No Dextran: 5676 (n=5967)	N/A	Dextran: 248 / No Dextran: 5613 (n=5838)	N/A	N/A	Dextran was administered in 5% of patients (n = 334)
Levi, CR et al.	N/A	N/A	N/A	N/A	N/A	N/A	Heparinization (UFH)	N/A
Saedon M et al.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Dextran as well as tirofiban was administered in patients showing a MES value >= reported by TCD
Dunne, VG et al.	N/A	13	30	N/A	32	N/A	N/A	Dextran 40 was administered in patients with high post-operative embolization >=50
Sharpe, RY et al.	241 >70%	29	N/A	N/A	297	N/A	N/A	Patients with increased post-operative embolization (>25 emboli in 10 minutes) received dextran
Sharpe, RY et al.	N/A	N/A	N/A	N/A	821	N/A	N/A	Patients with increased post-operative embolization (>25 emboli in 10 minutes) received dextran
Lennard NS et al.	N/A	N/A	N/A	N/A	1	18	Heparinization (UFH)	Dextran infusion was given to patients with stenosis >= 70% and microemboli on TCD or 2 or more TIA in 30 days. 20ml bolus followed my infusion at 20ml/h
Naylor AR et al.	317 (>70%)	88	N/A	N/A	125	N/A	Heparinization (UFH)	Dextran was given selectively to high post-operative embolization patients (>50 emboli per hour during the 3 hour TCD)
Robless, PA et al.	N/A	N/A	N/A	N/A	40	N/A	N/A	Patients with >50 signs of embolization (HITS) in 30 minutes received Dextran

CEA – Carotid Endarterectomy; D – Intraoperative Dextran; NA – Information Not Available; TCD - Transcranial Doppler; TIA – Transient Ischemic Attack; UFH – Unfractionated Heparin

Table 3 – Pre-operative characteristics

Author	Ipsilateral stenosis	Contralateral stenosis	Antiplatelet therapy	Anticoagulation	General anaesthesia	Regional anaesthesia	Intraoperative Anticoagulation protocol	Dextran administr
Moore, JM et al.	Dextran: 4864 / No Dextran: 58,957	N/A	Aspirin: Dextran: 8144 / No Dextran: 109,736// Inibidor P2Y12: Dextran: 3027 / No Dextran: 46,335	N/A	Dextran: 9569 / No Dextran: 120,856 (n=130 425)	N/A	N/A	Dextran was administre A total of 7.1% of patients rec
Farber, A et al.	N/A	N/A	Dextran: 291 / No Dextran: 5676 (n=5967)	N/A	Dextran: 248 / No Dextran: 5613 (n=5838)	N/A	N/A	Dextran was administere (n = 33
Levi, CR et al.	N/A	N/A	N/A	N/A	N/A	N/A	Heparinization (UFH)	N/A
Saedon M et al.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Dextran as well as tirofiban was administere reported by
Dunne, VG et al.	N/A	13	30	N/A	32	N/A	N/A	Dextran 40 was administered in patients w >=50
Sharpe, RY et al.	241 >70%	29	N/A	N/A	297	N/A	N/A	Patients with increased post-operative emb received de
Sharpe, RY et al.	N/A	N/A	N/A	N/A	821	N/A	N/A	Patients with increased post-operative emb received de
Lennard NS et al.	N/A	N/A	N/A	N/A	1	18	Heparinization (UFH)	Dextran infusion was given to patients with TCD or 2 or more TIA in 30 days. 20ml b
Naylor AR et al.	317 (>70%)	88	N/A	N/A	125	N/A	Heparinization (UFH)	Dextran was given selectively to high post- emboli per hour during
Robless, PA et al.	N/A	N/A	N/A	N/A	40	N/A	N/A	Patients with >50 signs of embolization (HI

CEA – Carotid Endarterectomy; D – Intraoperative Dextran; NA – Information Not Available; TCD - Transcranial Doppler; TIA – Transient Ischemic Attack; UFH – Unfractionated Heparin

Table 4 – Post-operative outcomes in the first month

Author	Stroke	Stroke/ Death	Death	MI	MACE	MACE definition	Post-operative adverse events
Moore, JM et al.	Dextran: 85 / No Dextran: 1175 (n=1260)	Dextran: 105 / No dextran: 1419 (n=1524)	Dextran: 23 / No Dextran: 349 (n=372)	Dextran: 61 / No Dextran: 463 (n=524)	Dextran: 160 / No Dextran: 1817 (n=1977)	MI, CHF, Dysrhytmia	N/A
Farber, A et al.	N/A	Dextran: 4 / No Dextran: 63 (n= 67)	N/A	Dextran: 8 / No Dextran: 63 (n = 71)	N/A	N/A	N/A
Levi, CR et al.	N/A	N/A	N/A	N/A	N/A	N/A	7 patients with wound hematoma
Saedon M et al.	Spontaneous resolution: 0 / Tirofiban: 1 / Dextran: 0 (n=1)	N/A	N/A	Spontaneous resolution: 1 / Tirofiban: 1 / Dextran: 2 (n=4)	N/A	N/A	N/A
Dunne, VG et al.	8	N/A	N/A	N/A	N/A	N/A	N/A
Sharpe, RY et al.	3	3	0	N/A	N/A	N/A	N/A
Sharpe, RY et al.	N/A	21	N/A	N/A	N/A	N/A	N/A
Lennard NS et al.	1	N/A	N/A	N/A	N/A	N/A	N/A
Naylor AR et al.	4	11	6	N/A	N/A	N/A	N/A
Robless, PA et al.	2	2	0	0	N/A	N/A	N/A

CEA – Carotid Endarterectomy; CHF – Congestive Heart Failure; D – Intraoperative Dextran; LOS – Length Of Stay; MACE – Major Adverse Cardiovascular Events; MI - Myocardial Infarction; NA – Information Not Available; TCD – Transcranial Doppler.

Table 5 – Other outcomes

Author	Other outcomes	Long-term outcomes	Long-term follow up time	Long-term MI	Long term Stroke	Long term MACE	Long term all cause mortality
Moore, JM et al.	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Farber, A et al.	N/A	N/A	1 year	N/A	Dextran: 0,4% No Dextran: 0,8%	N/A	2.5% (167) dextran vs. 3.2% (202) no dextran
Levi, CR et al.	Reduction in embolic signals	N/A	N/A	N/A	N/A	N/A	N/A
Saedon M et al.	N/A	N/A	N/A	Dextran: 2 Tirofiban: 1	Dextran: 1 Tirofiban: 1	N/A	N/A
Dunne, VG et al.	Dextran-40 reduced embolic loads	N/A	N/A	N/A	N/A	N/A	N/A
Sharpe, RY et al.	Dextran reduced embolic signals	N/A	N/A	N/A	N/A	N/A	N/A
Sharpe, RY et al.	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lennard NS et al.	Dextran controlled emboli and symptoms preoperatively	N/A	N/A	N/A	N/A	N/A	N/A
Naylor AR et al.	Reduction of embolic signals	N/A	N/A	N/A	N/A	N/A	N/A
Robless, PA et al.	N/A	N/A	N/A	N/A	N/A	N/A	N/A

MACE – Major Adverse Cardiac effects; MI – Myocardial Infarction

Supplementary Table 1 – Search query – keywords

Bibliographic source	**Search term**	**No of reports 23 September 2024**
Pubmed	(Dextran OR Dextran-40 OR Dextran-70 OR Dextran-sulphate OR "Dextran derivatives") AND ("Endarterectomy" Or "Endarterectomy, Carotid" OR "Carotid Endarterectomy" OR "Carotid Endarterectomies")	47
ISI	(Dextran OR Dextran-40 OR Dextran-70 OR Dextran-sulphate OR "Dextran derivatives") AND ("Endarterectomy" Or "Endarterectomy, Carotid" OR "Carotid Endarterectomy" OR "Carotid Endarterectomies")	47
Scopus	(Dextran OR Dextran-40 OR Dextran-70 OR Dextran-sulphate OR "Dextran derivatives") AND ("Endarterectomy" Or "Endarterectomy, Carotid" OR "Carotid Endarterectomy" OR "Carotid Endarterectomies")	123

Search strategy used in PubMed, ISI, and Scopus databases, combining keywords related to Dextran and Carotid Endarterectomy.

Supplementary table 2 - Meta-regression analysis of covariates associated with adverse event proportions.

Covariates	**Odds ratio**	**Lower Bound**	**Upper Bound**	**Std. Error**	**p-Value**
Continent	1,002002001334	1,00100050016671	1,00400801067734	< 0.001	0,01
Male	1	1	1	< 0.001	0,54
AHT	1	1	1	< 0.001	0,811
DM	1	1	1	< 0.001	0,754
CAD	1	1	1	< 0.001	0,746
Smoking	1	1	1	< 0.001	0,134
Symptomatic carotid stenosis	1	1	1	< 0.001	0,787

Odds Ratios (OR) with 95% confidence intervals (CI), standard errors, and p-values for each covariate. Significant associations are considered at $p < 0.05$.

Supplementary Table 3 Covariates used in the adjusted models

Author	Covariables used in adjusted models
Moore, JM et al.	MI, CHF, Hemodynamic instability, Hypotension, HTN
Farber, A et al.	COPD, General anaesthesia, Eversion endarterectomy, Shunt use, Gender (male), Hypertension, Coronary artery disease, Clopidogrel
Levi, C.R. et al.	NA
Saedon, M. et al.	Family History
Dunne, V.G. et al.	NA
Sharpe, R.Y. et al.	NA
Naylor AR et al.	Intimal flaps, Luminal thrombus
Robless, PA et al.	NA
Sharpe, R.Y. et al.	NA
Lennard, N.S. et al.	NA

CHF - Congestive Heart Failure-; COPD – Chronic Obstructive Pulmonary Disease; HTN - Hypertension; MI – Myocardial infarction; NA - Information Not Available

Legends

Figure 1 – PRISMA flow chart illustrating the number of records included and excluded at various screening and reviewing steps, leading to final list of records for data extraction and meta-analysis.

Figure 2: Forest plot of adverse event proportions across studies. Squares represent study estimates (size ∝ weight), horizontal lines show 95% CIs, and the diamond indicates the pooled estimate. The red dashed line marks the overall proportion (I^2 = 50.79%, p = 0.002).

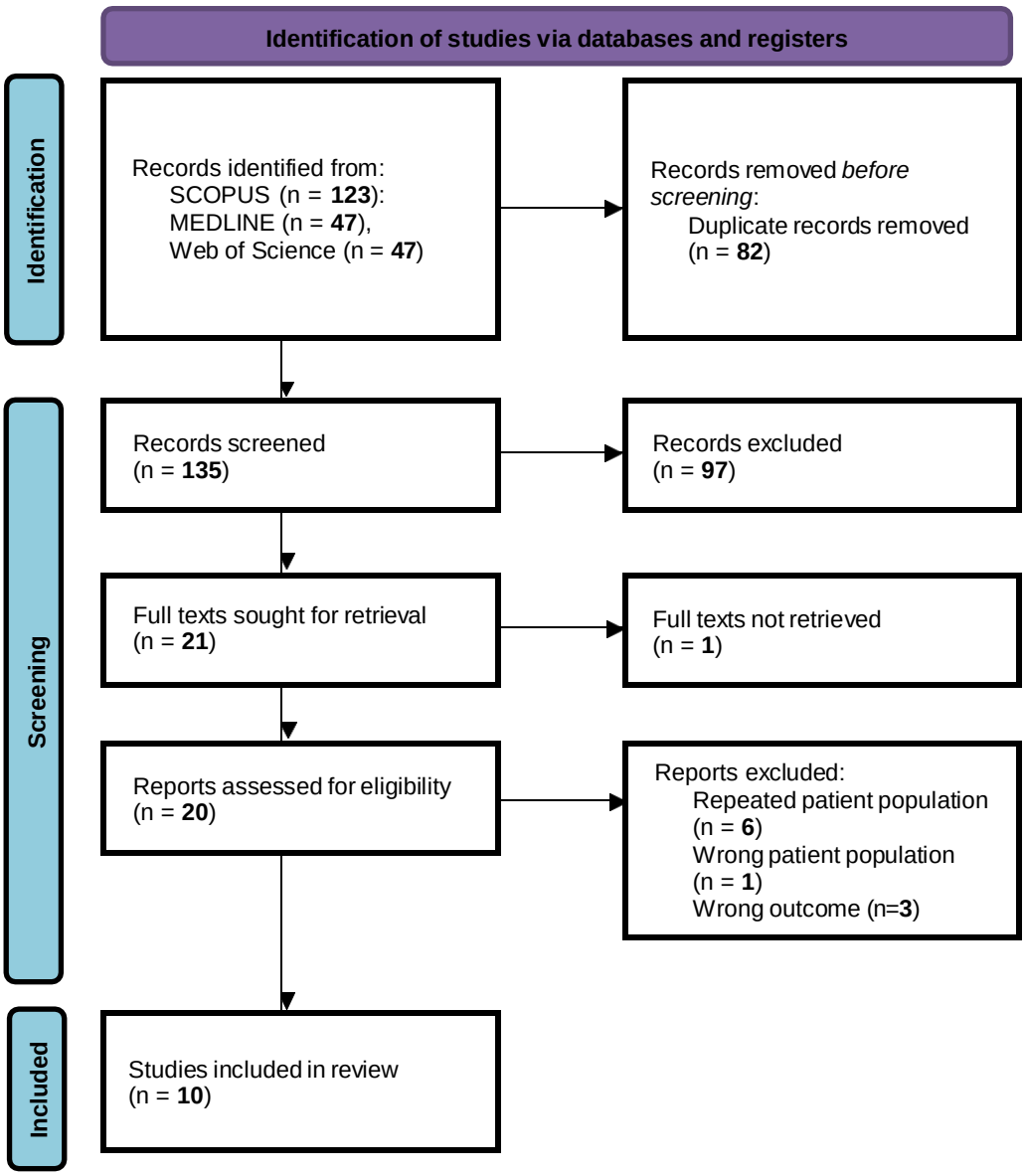
Figure 3a: Risk of bias for each observational cohort individually, using National Heart, Lung, and Blood Institute (NHLBI) Study Quality Assessment Tool.

Figure 3b: Overall judgment of bias for each evaluated item regarding observational cohorts, using National Heart, Lung, and Blood Institute (NHLBI) Study Quality Assessment Tool.

Figure 4a: Risk of bias for each randomized controlled trial (RCT) individually, using Rob2 evaluation tool.

Supplemental Figure 1: Meta-regression plot assessing the association between adverse event proportions and study continent. Each circle represents a study, with size proportional to study weight. The blue line indicates the estimated trend, suggesting potential regional differences in post-CEA outcomes.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



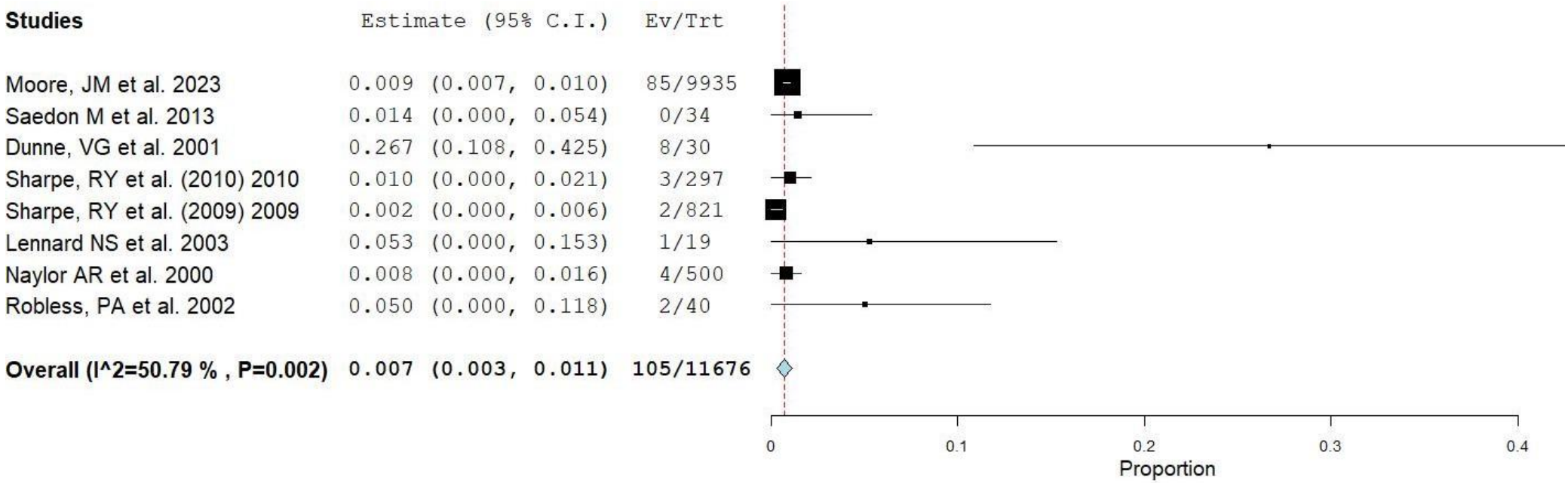
*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

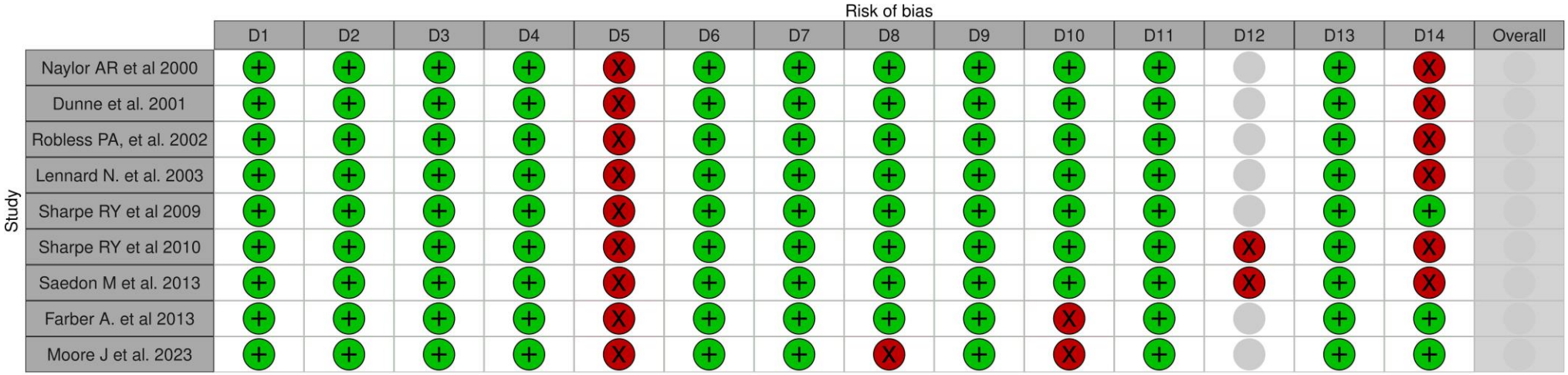
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Fig 1. PRISMA flow chart illustrating the number of records included and excluded at various screening and reviewing steps, leading to final list of records for data extraction and meta-analysis.

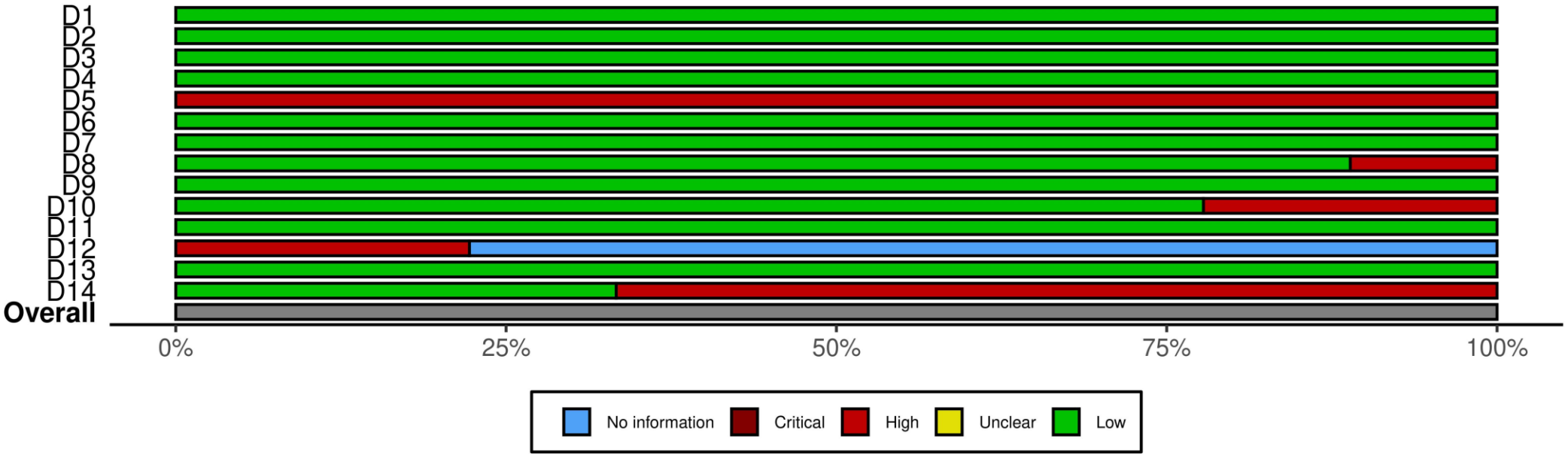
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

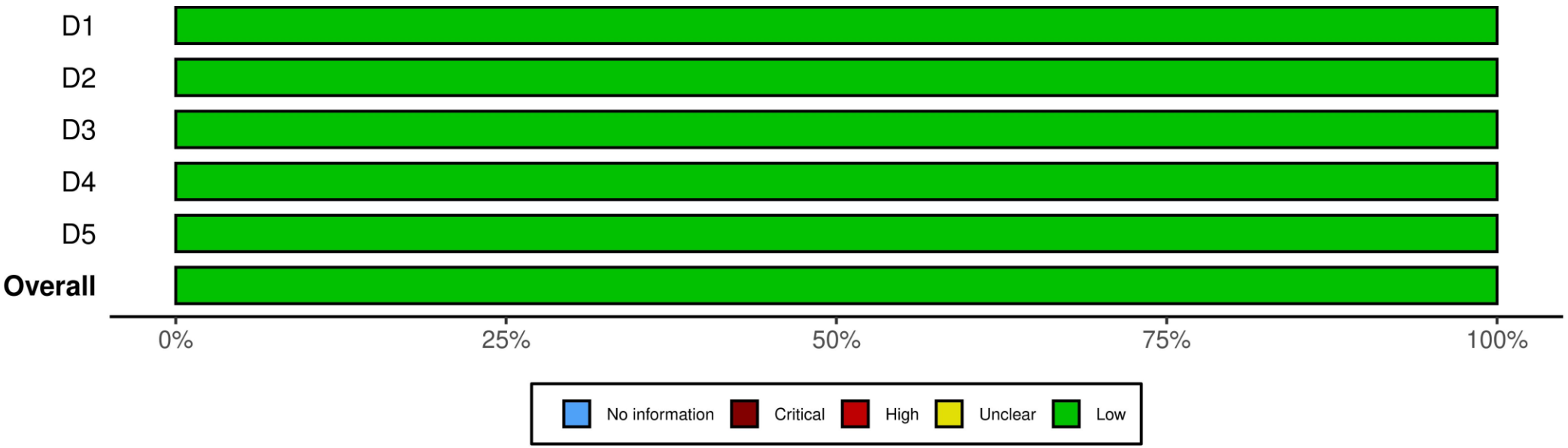
For more information, visit: http://www.prisma-statement.org/

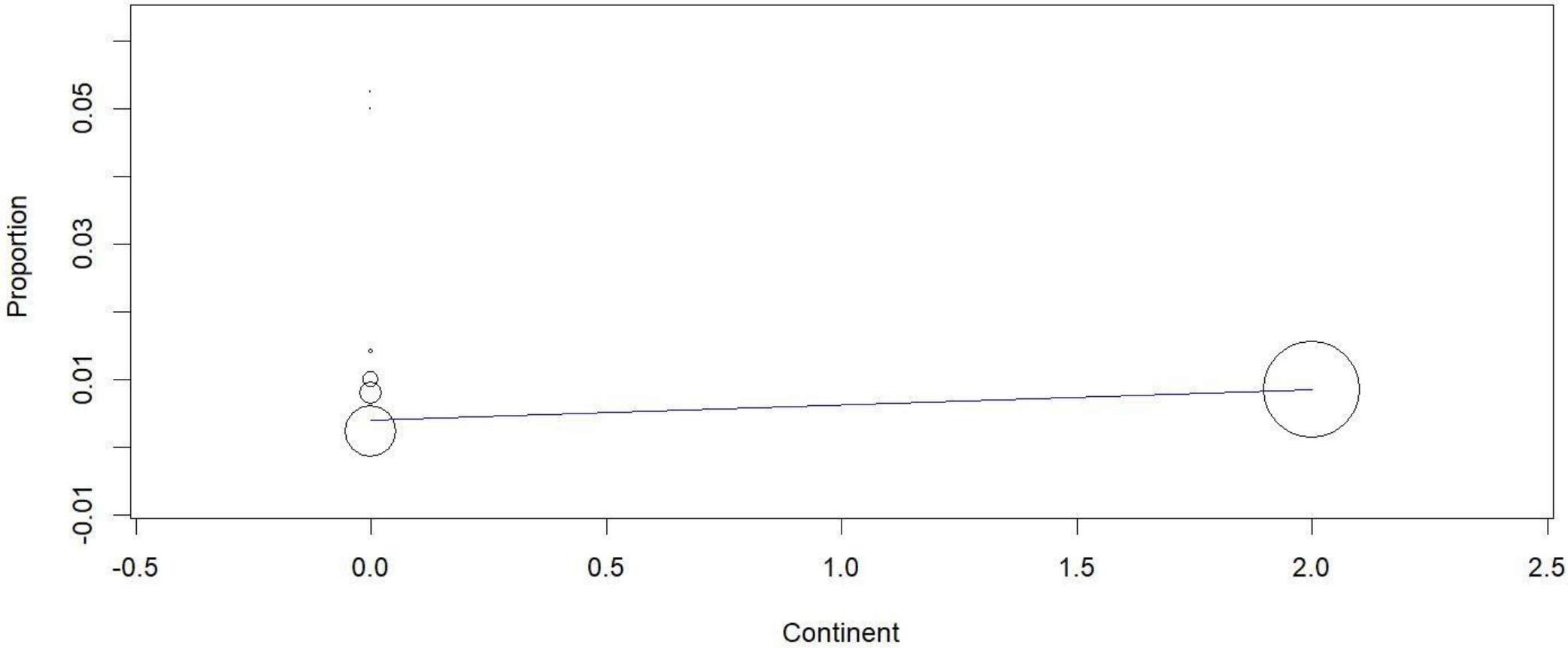

Studies
Estimate (95% C.I.)
Ev/Trt
Moore, JM et al. 2023
0.009 (0.007, 0.010)
85/9935
Saedon M et al. 2013
0.014 (0.000, 0.054)
0/34
Dunne, VG et al. 2001
0.267 (0.108, 0.425)
8/30
Sharpe, RY et al. (2010) 2010
0.010 (0.000, 0.021)
3/297
Sharpe, RY et al. (2009) 2009
0.002 (0.000, 0.006)
2/821
Lennard NS et al. 2003
0.053 (0.000, 0.153)
1/19
Naylor AR et al. 2000
0.008 (0.000, 0.016)
4/500
Robless, PA et al. 2002
0.050 (0.000, 0.118)
2/40
Overall (I^2=50.79 % , P=0.002)
0.007 (0.003, 0.011)
105/11676
0
0.1
0.2
0.3
0.4
Proportion



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?
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)?


D1
D2
D3
D4
D5
D6
D7
D8
D9
D10
D11
D12
D13
D14
Overall
0%
25%
50%
75%
100%
No information
Critical
High
Unclear
Low


D1
D2
D3
D4
D5
Overall
0%
25%
50%
75%
100%
No information
Critical
High
Unclear
Low


Proportion
0.05
0.03
0.01
-0.01
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
Continent

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page ("Dextran as an Adjunct in Carotid Endarterectomy: A Systematic Review and Meta-Analysis")
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract section
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction (section "INTRODUCTION"
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	**Materials and Methods**, subsection "Selection Criteria"
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	**Materials and Methods**, subsection "Search Strategy"
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	**Supplementary Table 1**; also mentioned in "Search Strategy
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	**Materials and Methods**, subsection "Study selection"
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	**Materials and Methods**, subsection "Data extraction"
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	**Materials and Methods** & Tables 1–5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	**Materials and Methods**, "Data extraction" and descriptive tables
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	**Materials and Methods**, subsection "Assessment of study quality"

Section and Topic	Item #	Checklist item	Location where item is reported
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	**Materials and Methods**, subsection "Quantitative Synthesis"
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	**Materials and Methods**, "Quantitative Synthesis"
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	**Materials and Methods**, "Quantitative Synthesis"
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	**Materials and Methods**, "Quantitative Synthesis"
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	**Materials and Methods**, "Quantitative Synthesis"
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	**Materials and Methods**, "Quantitative Synthesis"
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	**Materials and Methods**, "Quantitative Synthesis"
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	**Materials and Methods**, mention of funnel plots
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not strictly using GRADE, but see **Methods**, "Assessment of study quality,"
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	**Results**, subsection "Search Results" & **Figure 1** (PRISMA Flow Chart); reasons for exclusion are indicated.

Section and Topic	Item #	Checklist item	Location where item is reported
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	**Results**, subsection "Search Results", and **Figure 1 (PRISMA Flow Chart)**
Study characteristics	17	Cite each included study and present its characteristics.	**Results**, subsection "Description of studies" plus **Tables 1–5**.
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	**Results**, subsection "Studies quality". See **Figure 3a** and **Figure 3b** for observational cohorts and RCT risk of bias **(figure 4)**
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	**Results**, see **Tables 2–5** for summary statistics and outcome measures per study.
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	**Results**, "Main Findings and Meta-analysis" and "Meta-regression analysis" See **Figure 2 (Forest Plot)** for stroke incidence and **Supplemental Figure 1 (Meta-regression Plot)**
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	**Results**, "Main Findings and Meta-analysis" and "Meta-regression analysis" See **Figure 2 (Forest Plot)** for stroke incidence and **Supplemental Figure 1 (Meta-regression Plot)**
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	**Results**, "Main Findings and Meta-analysis" and "Meta-regression analysis"

Section and Topic	Item #	Checklist item	Location where item is reported
			See **Figure 2 (Forest Plot)** for stroke incidence and **Supplemental Figure 1 (Meta-regression Plot)**
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	**Results**, "Main Findings and Meta-analysis" and "Meta-regression analysis" See **Figure 2 (Forest Plot)** for stroke incidence and **Supplemental Figure 1 (Meta-regression Plot)**
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	**Results**, mention or discussion about funnel plot
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	**Results** and **Discussion** Not using formal GRADE, but quality and RoB discussed.
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	**Discussion** including clinical implications, limitations, and future directions.
	23b	Discuss any limitations of the evidence included in the review.	**Discussion** including clinical implications, limitations, and future directions.
	23c	Discuss any limitations of the review processes used.	**Discussion** including clinical implications, limitations, and future directions.
	23d	Discuss implications of the results for practice, policy, and future research.	**Discussion** including clinical implications, limitations, and future directions.
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	**Materials and Methods**, mention:

Section and Topic	Item #	Checklist item	Location where item is reported
			"Review protocol registered at PROSPERO (CRD42024593605)."
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	**Materials and Methods**, mention: "Review protocol registered at PROSPERO (CRD42024593605)."
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	**Materials and Methods**, mention: "Review protocol registered at PROSPERO (CRD42024593605)."
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	**Funding Sources** statement
Competing interests	26	Declare any competing interests of review authors.	Conflict of Interest Statement
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Data and materials available on request.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.
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Annals of Vascular Surgery

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Guide for authors

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About the journal

Aims and scope

The *International Journal of Vascular Surgery and Endovascular Therapies* is the Official publication for:

- Brazilian Society of Angiology and Vascular Surgery,
- Chilean Society for Vascular and Endovascular Surgery,
- Chinese Society for Vascular Surgery,
- Florida Vascular Society,
- French Society for Vascular and Endovascular Surgery,
- Southern California Vascular Surgical Society,
- Vascular & Endovascular Surgery Society, USA,
- Vascular Surgeons of Spanish Language,

- Georgia Vascular Society.

Annals of Vascular Surgery, is published ten times a year. The journal invites original manuscripts reporting clinical and experimental work in **vascular surgery** for peer review. Articles may be submitted for the following sections of the journal:

- Clinical Research (reports of clinical series, new drug or medical device trials)
- Basic Science Research (new investigations, experimental work)
- Case Reports (reports on a limited series of patients)
- General Reviews (scholarly review of the existing literature on a relevant topic)
- Developments in Endovascular and Endoscopic Surgery
- Selected Techniques (technical maneuvers)
- Historical Notes (interesting vignettes from the early days of vascular surgery)
- Editorials/Correspondence

Article types

Articles may be submitted for the following sections of the journal:

- Clinical Research (reports of clinical series, new drug or medical device trials)
- Basic Science Research (new investigations, experimental work)
- Basic Data
- General Reviews (scholarly review of the existing literature on a relevant topic)
- Developments in Endovascular and Endoscopic Surgery
- Historical Notes (interesting vignettes from the early days of vascular surgery)
- Research Letter (max. 1500 words, no abstract, at least 1 table and/or figure (max. 2 total), a maximum of 5 authors & 15 references, no supplementary material)
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[3] Strunk Jr W, White EB. The elements of style. 4th ed. New York: Longman; 2000.

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Reference to a website:

[5] Cancer Research UK. Cancer statistics reports for the UK, http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/; 2023 [accessed 13 March 2023].

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[6] Oguro M, Imahiro S, Saito S, Nakashizuka T. Mortality data for Japanese oak wilt disease and surrounding forest compositions [dataset]. Mendeley Data. 2015. https://doi.org/10.17632/xwj98nb39r.1.

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[7] Coon E, Berndt M, Jan A, Svyatsky D, Atchley A, Kikinzon E, et al. Advanced Terrestrial Simulator (ATS). Version 0.88 [software]. Zenodo; 2020 Mar 25. https://doi.org/10.5281/zenodo.3727209.

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