

Nitinol double-layer stent versus closed single-layer stent: a systematic review

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INTRODUCTION

The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field to standardize how to conduct and to assist in the reasoning and decision-making of doctors. The information provided by this project must be critically evaluated by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical condition of each patient.

About 10–15% of all ischemic strokes (STROKES) originate from stenosis at the level of the internal carotid artery. In patients with carotid disease, the goal of carotid revascularization is the prevention of stroke (recurrent). For more than 50 years, carotid endarterectomy (CEA) has been considered the standard treatment for severe asymptomatic and symptomatic carotid stenoses. The carotid artery stent (CAS) has emerged in the past 20 years as a minimally invasive alternative to surgery¹. It is recognized that the stent itself can substantially increase embolic protection in CAS through adequate plate scaffolding, since the distal embolic protection device (EPD) has been removed. The ideal properties of a carotid stent are a well-balanced blend of high flexibility and conformability, accommodating tortuous anatomy, as well as high plate coverage, preventing delayed embolization of debris. The structure of the stents is characterized by annular rings sequentially aligned by bridges, and the drawing can be open cell or closed cell, depending on the density of the bridges between the rings. Open-cell design stents present some free segments of adjacent rings, allowing greater adaptation to vessel anatomy, but with lower plate coverage and increased risk of tissue prolapse. Closed-cell design stents are characterized by higher

bridge interconnection density, which reduces their conformability and increases the likelihood of bed position, but at the same time offers greater plate coverage. A hybrid configuration with an open-cell design of the proximal and distal segments combined with a closed-cell design of the central segments was also developed²⁻⁵.

Another carotid double-layer mesh stent design allows high flexibility to accommodate tortuous anatomies while conveying the properties of the scaffold for optimal plate coverage. This technology is characterized by an internal layer of micromesh for plate coverage and an outer layer of self-expanding nitinol for scaffolding, offering the flexibility that characterizes open-cell design stents².

The impact of the design of the self-expanding stent on the clinical outcome after CAS is the objective of this evaluation.

OBJECTIVE

This study aimed to evaluate the efficacy and safety of carotid angioplasty stent micromesh design and double layer of nickel/titanium alloy (nitinol) implantation, with closed-cell stent (single-layer) of nitinol or stainless steel, both procedures using distal EPDs.

METHODS

Clinical doubt: What is the impact of stent design on clinical outcome after CAS with EPD, comparing double-layer nitinol stent versus closed-cell stent (single layer), nitinol or stainless steel?

The eligibility elements of the studies are as follows:

1. Patient with carotid stent and indication of CAS.

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2. CAS with EPD, use of double-layer stent (nitinol) compared with closed-cell stent (single layer) of nitinol or stainless steel.
3. Outcomes—new brain lesions detected and adverse events (neurological and cardiac complications) related to procedure.
4. Excluding outcomes—intermediaries.
5. Phase III randomized controlled trial (RCT) or cohort studies.
6. No period or language limit.
7. Full-text available for access.
8. Follow-up time: 1-month post-procedure.

The search for evidence will be carried out in the Virtual Scientific Information Base MEDLINE using the following search strategy: (Carotid Stenosis OR Carotid Stenoses OR Carotid Artery Diseases) AND (Carotid Stenting OR Stent*) AND (nitinol OR dual-layer OR double layer OR double layer OR micromesh OR Casper OR Roadsaver) AND Random*; CENTRAL/Cochrane: (Carotid Stenosis OR Carotid Stenoses OR Carotid Artery Diseases) AND (Carotid Stenting OR Stent*) AND (nitinol OR dual-layer OR double layer OR double layer OR micromesh OR Casper OR Roadsaver); and ClinicalTrials.gov: (Carotid Stenting OR Stent) AND (nitinol).

The search was carried out until June 2022, and a systematic review was carried out according to PRISMA recommendations⁶.

Two authors independently performed the data extraction, followed by a cross-check of the data. From the studies, the following data were extracted: author's name and year of publication, study population, intervention and comparison methods, absolute number of events, number and average size of new ischemic brain lesions, mean number of microembolic signs (MES), adverse events, and follow-up time.

We assessed the risk of bias for RCTs level using the RoB 2 tool⁷, plus other key elements, and expressed it as very severe, severe, or non-severe. For cohort studies, the tool ROBINS-I (Risk of Bias In Non-randomized Studies of Interventions), recommended by the Cochrane Collaboration, was used to assess the risk of bias in estimates of effectiveness and safety in non-randomized intervention studies⁸. ROBINS-I evaluates seven domains of bias, classified by the moment of occurrence. The bias risk assessment was conducted by two independent reviewers (AS and IF), and in case of disagreements, a third reviewer (WB) deliberated on the assessment. The quality of the evidence was extrapolated from the risk of bias, and it was obtained from the study/studies (if was or

no meta-analysis) using the terminology GRADE⁹ through the GRADEpro software¹⁰ for very low, low, moderate, and high degree of evidence.

The results for categorical outcomes were expressed as the difference in risk (DR) between the CAS procedure with EPD between double-layer nitinol stent and closed-cell stent (single layer) of nitinol or stainless steel. If DR between the groups was significant, the result was expressed with 95% confidence interval (95%CI) and the number needed to treat (NNT) or number needed to harm (NNH). For continuous measurements, the results were the difference of the mean (DM) with 95%CI.

If more than one study was included with common outcomes, the results were aggregated through the meta-analysis, using the RevMan 5.4 software¹¹, and the overall DR or DM, with 95%CI as the final measure used to support the synthesis of evidence, which answers the clinical doubt of this evaluation. The estimated size of the combined effects was performed by a model of fixed effect ($I^2 \leq 50\%$) or random effect ($I^2 > 50\%$) after the evaluation of heterogeneity results. Heterogeneity was also calculated using the I^2 value.

STUDIES INCLUDED

Database searching identified 16 citations. We removed 14 records, and we selected 2 studies with regard to title and abstract^{12,13}, which evaluated the CAS with EPD with double-layer nitinol stent and closed-cell stent (single layer) of nitinol or stainless steel. The two studies were assessed since they met the eligibility criteria for analysis of the full text. Both were RCTs and were included to support this evaluation, whose characteristics are described in ANNEX Table 1. The number of excluded studies and the reasons are available in Figure 1.

The population included was 140 participants in the 2 RCTs, submitted to carotid angioplasty with stent implantation and distal brain protection device. This population was followed to measure the outcomes such as new ischemic brain lesions assessed by a diffusion-weighted resonance imaging (DW-MRI); average number of new ischemic brain lesions; average (mm) size of new ischemic brain lesions; brain microembolization in the stages of stent implantation, dilation and recovery of EPD; major adverse cardiac and cerebrovascular events (MACCE); and restenosis in-stent, in a follow-up of 1, 3, and 6 months after the procedure (ANNEX Table 2).

Regarding the risk of bias of the 2 RCTs (12–13) included, a study by Montorsi et al.(13) did not describe randomization;

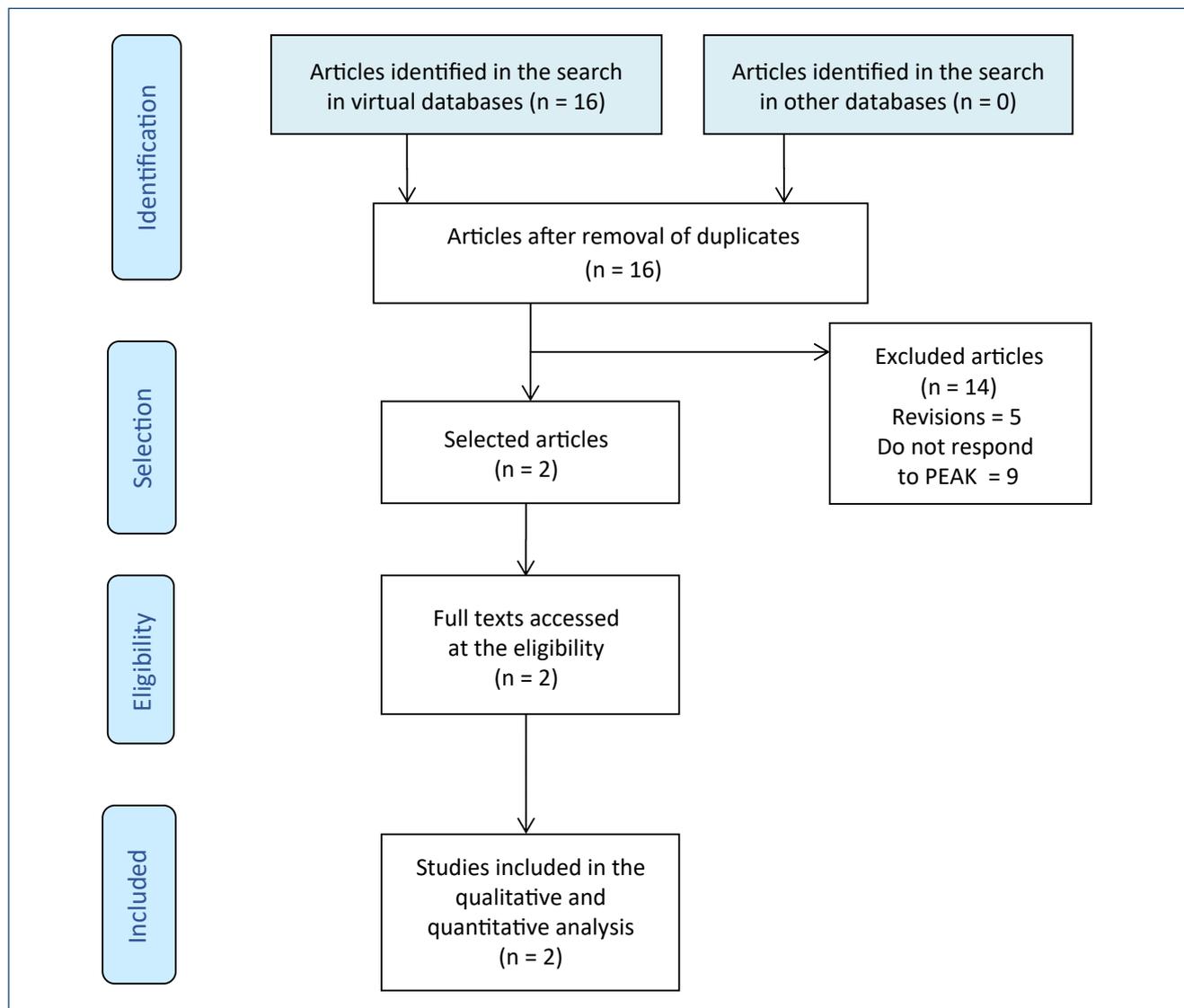


Figure 1. Evidence retrieval and selection diagram. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;6(7):e1000097. <https://doi.org/10.1371/journal.pmed1000097>

Table 1. Risk of bias from randomized controlled trials included.

Study	Risk of bias in randomized clinical trials									
	Random	Blind-folded allocation	Double blind	Appraiser blinding	Losses <20%	Characteristic prognostic	Outcome	Intention-to-treatment	Simple size calculation	Early interruption
Vanzin et al. ¹²	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
Montorsi et al. ¹³	Yellow	Yellow	Red	Red	Green	Green	Green	Red	Green	Green

Biases of the included ECRs: red indicates absence; green indicates presence; yellow indicates risk of unclear bias.

it had uncertain blinded allocation, was not blinded to the evaluator, and did not analyze by intention-to-treat (ITT); while Vanzin et al. did not show bias. The overall risk of bias could be considered non-severe (Table 1).

RESULTS OF THE STUDIES INCLUDED

One study¹², with a total of 88 participants, compared the double-layer nitinol stent (n=41) and single-layer closed-cell stent (n=47), plus EPD, evaluating the efficacy and safety in a follow-up of up to 3 months.

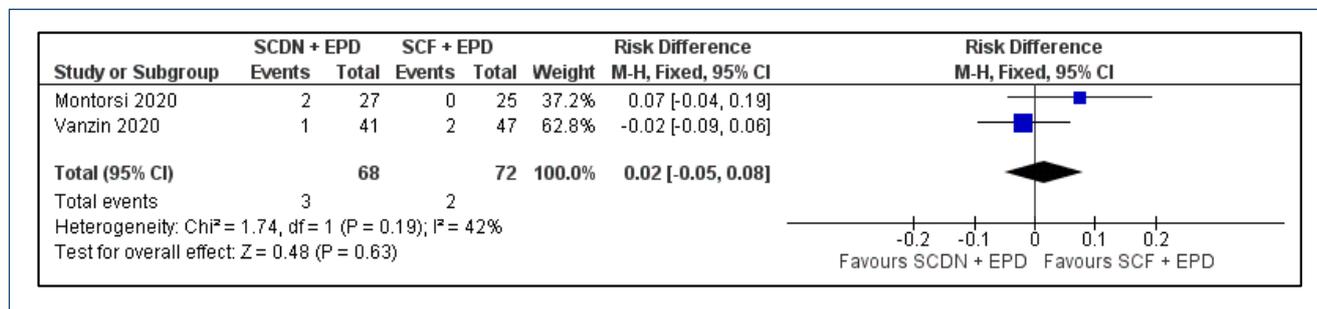


Figure 2. Forest plot comparison: double-layer stent of nitinol versus closed-cell stent, outcome: 1.5.

There was no difference in the risk of new ischemic brain lesions evaluated by magnetic resonance imaging in the diffusion sequence (DWI-MR) (RD=-0.06, 95%CI -0.26 to 0.15; NNT=NS; p=0.59).

There was also no difference in the outcomes such as mean number of new ischemic brain lesions (RD=-0.40, 95%CI -1.09 to 0.29; p=0.26) and average (in mm) size of new ischemic brain lesions (RD=-1.10, 95%CI -3.20 to 1.00; p=0.30).

One study¹³ including a total of 52 participants compared the double-layer nitinol stent (n=27) and closed-cell stent (n=25), plus EPD, with outcome measurements at 24 h, 30 days, and 6 months after CAS.

There was no difference in the mean number of cerebral microembolization [mean (SD)], evaluated by monitoring with transcranial Doppler (number of MES), in the stages of stent implantation, dilation, and recovery of the distal EPD, including spontaneous MES (29% of patients) (RD=-2.80, 95%CI -5.96 to 0.36; p=0.08).

There was also no difference in the risk of significant in-stent restenosis (PSV>330 cm/s with stenosis >80% of the diameter) at 6 months (RD=-0.04, 95%CI -0.14 to 0.06, NNT=NS, p=0.44).

Two studies^{12,13} that compared the double-layer nitinol stent (n=25) and single-layer closed-cell stent (n=47), plus EPD, presented data for the outcome MACCE (ipsilateral stroke, transient ischemic event, and myocardial infarction) at follow-up of 3–6 months. There was no difference in MACCE risk (RD=0.02, 95%CI -0.05 to 0.08, NNH=NS, p=0.63, I²=42%) (Figure 2).

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Summary of evidence and quality of evidence: TOOL GRADE

In patients with carotid stenosis, angioplasty with nitinol double-layer stent implantation versus stent (nitinol or chromium-cobalt alloy) single closed-cell layer are adopted, both procedures using distal brain protection device.

Showed no difference

- At the risk of new ischemic brain damage up to 3 months. High evidence quality.
- At the average number of brain microembolizations in the stages of stent implantation, dilation, and recovery of EPD, including spontaneous MES. Moderate evidence quality.
- At the risk of significant in-stent restenosis at 6 months. Moderate evidence quality.
- At the risk of MACCE (ipsilateral stroke, transient ischemic event, and myocardial infarction) at 3- to 6-month evaluations. High evidence quality.
- At the average number of new ischemic brain lesions at 3 months. High evidence quality.
- At the average size of new ischemic brain lesions up to 3 months. High evidence quality.

CONCLUSION

The double-layer nitinol stents showed no difference in the outcomes that evaluated efficacy and safety when compared to closed-cell stents during CAS under distal EPD.

AUTHORS' CONTRIBUTIONS

AS, IF, and WMB contributed to study conception, data collection, statistical analysis, and data interpretation. **AS and IF** contributed to manuscript writing. **AS, IF, and WMB** contributed to critical review and approval of the final version.

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ANNEXES

Table 1. Characteristics of the included studies.

Descriptive table of the characteristics of studies in therapy					
Study	Population	Intervention	Comparison	Outcome	Follow-up Time
Vanzin et al. ¹²	Study with a total of 88 patients; age in years: 73.5±6.9; symptomatic ICA stenosis ≥50%, asymptomatic ICA stenosis ≥70%, symptoms defined as ischemic stroke, TIA, or amaurosis. Excluded: Total occlusion of the target carotid artery; ischemic stroke < 14 days before CAS; MI < 6 months; major surgery 30 days before or planned for 30 days after stent; severe CRF; intractable hemorrhagic diathesis or hypercoagulability state; high or medium risk for cardioembolism and contraindication for antiplatelet therapy.	Double-layer nitinol stent+EPD (n=41)	Single-layer stent, closed cell+EPD (n=47)	Primary: Incidence, number, and size of new ischemic brain lesions. Secondary: Stroke, TIA, and MI (up to 3 months).	MRI and neurological evaluation between 06:00 and 24:00 after the procedure. A new neurological evaluation was performed at a 3-month follow-up.
Montorsi et al. ¹³	Included 104 patients (age 72.4±9) at high risk, with lipid-rich plaque; de novo carotid artery stenosis either symptomatic (Doppler peak systolic velocity [PSV] ≥130 cm/s and >50% stenosis) or asymptomatic (Doppler PSV≥230 cm/s and >70% stenosis). Excluded: Evolving acute or recent disabling stroke, history of major disabling stroke (modified Rankin scale score ≥3), acute MI 72 h before CAS, and concomitant sources of potential cerebral embolization that would confound neurological assessment. Anatomic exclusion criteria were contralateral carotid occlusion without detectable ipsilateral posterior communicating artery, isolated hemisphere of the target vessel, target vessel ECA occlusion, intracranial, significant (>50%) stenosis of the ipsilateral CCA, and/or CCA >50% stenosis below bifurcation.	GROUP 1 Double-layer nitinol stent+EPD (n=27) GROUP 3 Double-layer nitinol stent+proximal protection (n=27)	GROUP 2 Single-layer stent (chromium-cobalt alloy) and closed cell+EPD (n=25) GROUP 4 Single-layer stent (chromium-cobalt alloy) and closed cell+proximal protection (n=25)	Primary: Cerebral microembolization evaluated by monitoring with TCD (number of microembolic signals). Secondary: End points included in-hospital and 30-day MACCE (death, all stroke, retinal embolism, and MI), technical and clinical success, target vessel ECA patency on angiography at the end of CAS and on Doppler ultrasound at 1, 30, and 180 days of follow-up, and significant in-stent restenosis at 6 months.	The measurements of the outcomes were repeated within 24 h, 30 days, and 6 months post-CAS.

¹Based on the criteria defined by NASCET. ECA: external carotid artery; CCA: common carotid artery; ICA: internal carotid artery; MI: myocardial infarction; TCD: transcranial Doppler; MACCE: major adverse cardiac and cerebrovascular events; EPD: embolic protection device; TIA: transient ischemic attack; DW-MRI: diffusion-weighted magnetic resonance imaging; CRF: chronic renal failure; MRI: magnetic resonance imaging.

Table 2. Summary of evidence and quality of evidence: TOOL GRADE.

Summary of results: Double-layer nitinol+EPD stent compared to closed-cell stent+EPD for carotid stenosis					
Participants or population: Carotid stenosis					
Context: Efficacy and safety					
Intervention: Double-layer stent of nitinol+EPD					
Comparison: Closed-cell stent+EPD					
Outcome no. of participants (studies)	Relative effect (95%CI)	Anticipated absolute effects (95%CI)			Certainty
		Control	Intervention	Difference	
New ischemic brain lesions (DW-MRI). Number of participants: 88 (1 ECR)	RR 0.87 (0.53 para 1.44)	44.7%	38.9% (23.7 para 64.3)	5.8% less (21 less to 19.7 more)	⊕⊕⊕⊕ High
Average number of new ischemic brain lesions in the number of participants: 88 (1 ECR)	-	-	-	MD 0.4 lower (1.09 lower to 0.29 higher)	⊕⊕⊕⊕ High
Average size (mm) of new ischemic brain lesions in participants: 88 (1 ECR)	-	-	-	MD 1.1 smaller (3.2 lower to 1 higher)	⊕⊕⊕⊕ High
Cerebral microembolization N° of participants: 52 (1 ECR)	-	-	-	MD 2.8 lower (5.96 lower to 0.36 higher)	⊕⊕⊕○ Moderate ^a
Major adverse cardiac and cerebrovascular events (MACCE) In the participants: 140 (2 ECRs)	RR 1.46 (0.28 para 7.52)	2.8%	4.1% (0.8 para 20.9)	1.3% more (2 less to 18.1 more)	⊕⊕⊕⊕ High
Significant in-stent restenosis no. of participants: 52 (1 ECR)	RR 0.31 (0.01 para 7.26)	4.0%	1.2% (0 for 29)	2.8% less (4 less to 25 more)	⊕⊕⊕○ Moderate ^a

^aThe risk in the intervention group (and its 95%CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI). CI, confidence interval; MD: mean difference; RR: risk ratio.

GRADE: Working group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

