Nitinol Double Layer Stent versus Closed Single Layer Stent: Systematic Review

Antônio Silvinato[1.2], Idevaldo Floriano[1], Wanderley Marques Bernardo[2.3]

[1]Evidence-Based Medicine, Cooperative Baixa Mogiana, Mogi-Guaçu (SP) Brazil
[1.2]Evidence-Based Medicine, Brazilian Medical Association, São Paulo (SP) Brazil.
[2.3]School of Medicine, University of São Paulo, São Paulo, Brazil

Summary

Objective: To evaluate the efficacy and safety in the use of double layer nitinol stent, compared to the closed cell carotid artery stent (CAS) (single layer), in carotid artery angioplasty, both procedures with the use of distal embolic protection devices (EPD). **Methods:** We conducted this systematic review following *the preferred reporting items for systematic reviews and meta-analyses* (PRISMA), researching in the scientific databases: Mediline/PubMed, Central Cochrane and ClinicalTrials.gov. We performed the meta-analysis of randomized clinical trials through software revman 5.4 software for some outcomes. **Results:** 16 studies were retrieved, of which 2 met the eligibility criteria, with 140 patients undergoing carotid angioplasty. The risk of overall study bias was considered non-severe. We found no significant difference to use double layer nitinol stent and single layer for outcomes: risk of new ischemic brain lesions, mean number of new ischemic brain lesions and mean (in mm) size of new ischemic brain lesions, (RD = -0.06, 95%CI -0.26 to 0.15; p = 0.59), (RD = -0.40, 95%CI -1.09 to 0.29; p = 0.26), (RD = -1.10, IC95% -3.20 to 1.00; p = 0.30). In another study, there was also no statistical difference for the outcomes: mean number of micro brain embolization [mean (SD), RD = -2.80, 95% CI -5.96 to 0.36; p = 0.08)], stent restenosis (RD = -0.04, | IC95% -0.14 to 0.06, p = 0.44). Meta-analysis of two randomised controlled trials (RCTs) showed no difference for major cardiac and cerebrovascular events (DR = 0.02, 95%CI -0.05 to 0.08, p = 0.63, I^2 = 42%). **Conclusion:** The double layer nitinol stents showed no difference for the outcomes that evaluated efficacy and safety when compared to single layer during CAS under distal EPD.

Introduction

Ten to fifteen percent 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 has emerged in the last 20 years as a minimally invasive alternative to surgery [1]. It is recognized that

the stent itself can substantially increase embolic protection in CAS through adequate plate scaffolding, since the distal embolic protection device 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 developed [2-5].

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 stents [2].

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

OBJECTIVE

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) nitinol or stainless steel, both procedures using distal embolic protection devices.

METHOD

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:

1. Patient with carotid stent and indication of CAS;
2. CAS with EPD, use of double layer stent (nitinol) compared with closed cell stent (single layer), nitinol or stainless steel;
3. Outcomes - new brain lesions detected, adverse events (neurological and cardiac complications) related to procedure;
4. Excluding outcomes – intermediaries;
5. Phase III randomized clinical 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 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*; search strategy 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 recommendations [6].

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

We will be assessed the risk of bias for randomized clinical trials level using ROB 2 tool [7], plus other key elements, and expressed as very severe, severe or non-severe. For cohort studies, the tool currently recommended by the Cochrane Collaboration used to assess the risk of bias in estimates of effectiveness and safety in non-randomized robins-i (Risk Of Bias In Non-randomised Studies – of Interventions) intervention studies [8]. ROBINS-I evaluates seven domains of bias, classified by moment of occurrence. The bias risk assessment will be conducted by two independent reviewers (AS and IF), and in case of disagreements, a third reviewer (WB) may deliberate on the assessment. The quality of the evidence will be extrapolated from the risk of bias and obtained from the study(s) (if was or no meta-analysis) using the terminology GRADE [9] by software GRADEpro [10] in very low, low, moderate and high degree of evidence.

The results for categorical outcomes will be expressed through the difference in risk between the CAS procedure with EPD between double nitinol layer stent and closed cell stent (single layer) of nitinol or stainless steel. If the difference in risk (DR) between the groups is significant (95% confidence) this will be expressed accompanied by the 95% Confidence Interval (95% CI) and the necessary number to treat (NNT) or to produce damage (NNH). For continuous measurements, the results will be the difference of the mean (DM) with confidence intervals (CI) 95%.

If there is more than one study included with common outcomes, these will be aggregated through the meta-analysis, using the RevMan 5.4 software [11], the overall difference in risk or average, with 95% confidence intervals (CI) the final measure used to support the synthesis of evidence, which will answer 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($I^2 > 50\%$) effect after the evaluation of heterogeneity results. Heterogeneity was also calculated using the value I^2.

STUDIES INCLUDED

Database searching identified 16 citations. We removed 14 records, and we selected by title and abstract 2 studies [12,13], which evaluated the CAS with EPD with double nitinol

layer stent and closed cell stent (single layer) of nitinol or stainless steel. The two studies were assessed because they met the eligibility criteria, for analysis of the full text. Both were ECRs and were included to support this evaluation, whose characteristics are described in Table 2 (ANNEXES). The number of excluded studies and the reasons are available in Figure 1.

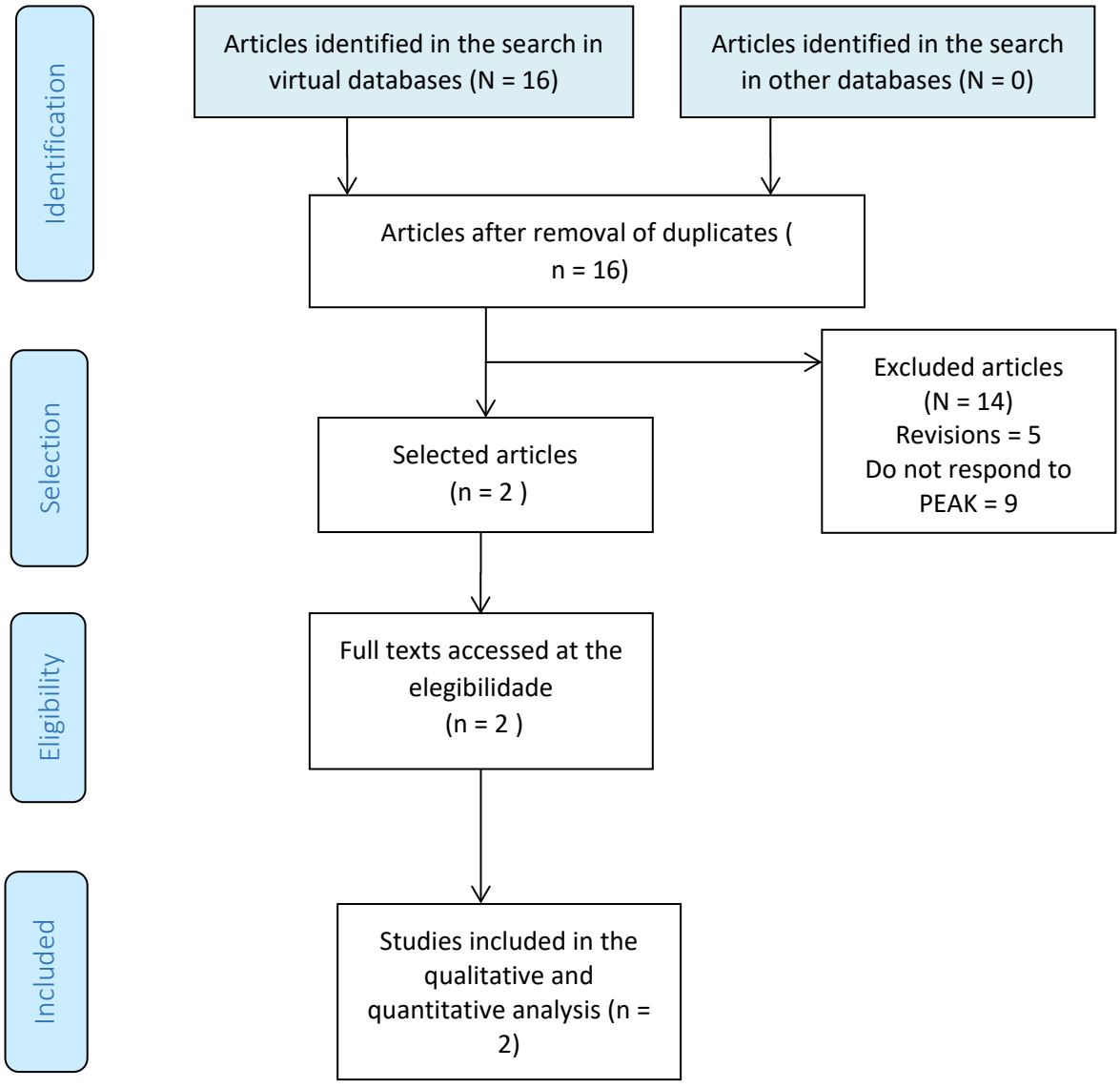

Figure 1. Evidence retrieval and selection diagram

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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: 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 cardiac and cerebrovascular adverse events (MACCE) and restenosis in-stent, in a follow-up 1 – 3 and 6 months after the procedure (Table 1- APPENDIX).

Regarding the risk of bias of the 2 RCTs (12-13) included, one did not describe randomization, it had uncertain blinded allocation, was not blinded to the evaluator and did not analyze by intention-to-treat (ITT). The o
overall risk of bias could be considered non-severe (Table 1).

Table 1. Risk of bias from RCTs studies included

RISK OF VIESES IN RANDOMIZED CLINICAL TRIALS										
STUDY	**Random**	**Blind folded allocation**	**Double blind**	**Appraiser Blinding**	**Losses < 20%**	**Characteristic prog.**	**Outcome**	**ITT**	**Simple size calculation**	**Early interruption**
Vanzin JR, 2020 [12]										
Montorsi P, 2020 [13]										

Biases of the included ECRs studies (red = absence; green = presence; yellow = risk of unclear bias), ITT = analysis by intention of treatment, Prog. = prognostic.

RESULTS OF THE STUDIES INCLUDED

One study [12], 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 efficacy and safety in a follow-up of up to 3 months.

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 for the outcomes: mean number of new ischemic brain lesions (RD = -0.40, 95%CI -1.09 to 0.29; p = 0.26); average (in mm) size of new ischemic brain lesions (RD = -1.10, 95% CI -3.20 to 1.00; p = 0.30).

One study [13] 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 hours, 30 days and 6 months after CAS.

There was no difference in the mean number of cerebral microembolization [mean (DS)], evaluatedby monitoring with transcranial doppler [number of microembolizations signals (MES)], in the stages of stent implantation, dilation and recovery of the distal embolic protection device, including spontaneous MES (29% of patients), DR = -2. 80, IC95% -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, | IC95% -0.14 to 0.06, NNT = NS, p = 0.44).

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

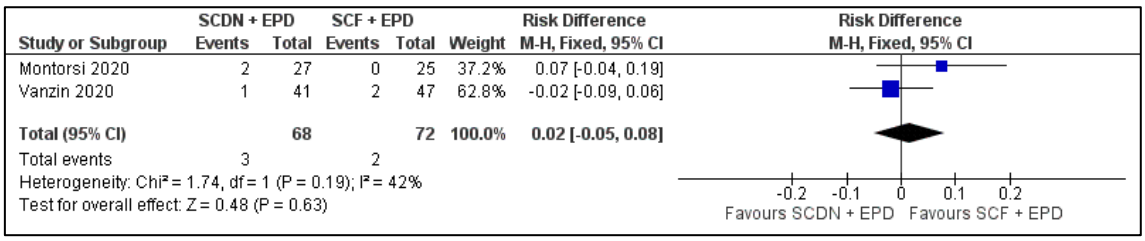

Figure 2. Forest plot comparison: 1 Double Layer stent of Nitinol versus Closed Cell Stent, outcome: 1.5 MACCE (major cardiac and cerebrovascular adverse events).

SUMMARY OF EVIDENCE

Quality of evidence - GRADE (annex)

In patients with carotid stenosis: angioplasty with nitinol double layer stent implantation versus stent (nitinol or chromium-cobalt alloy) single closed cell layer, and distal brain protection device for both:
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 SMS. Moderate evidence quality.
- at the risk of significant in-stent restenosis at 6 months. Moderate evidence quality.
- at the risk of major cardiac and cerebrovascular events (ipsilateral stroke, transient ischemic event, myocardial infarction) at 3- 6-month evaluations. High evidence quality.
- at the average number of new ischemic brain lesions, at 3 months. High evidence quality
- at in the average size of new ischemic brain lesions, up to 3 months. High evidence quality.

Conclusion: The double layer nitinol stents showed no difference for the outcomes that evaluated efficacy and safety when compared to closed cell stents during CAS under distal DPS.

Authors' contribution:

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

Conflict of interest:

None conflict of interest

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ANNEXES

Table 2. Characteristics of the included studies

DESCRIPTIVE TABLE OF THE CHARACTERISTIC OF STUDIES IN THERAPY					
STUDY	**POPULATION**	**INTERVENTION**	**COMPARISON**	**Outcome**	**FOLLOW-UP TIME**
Vanzin JR, 2020	Study with a total 88 patients; age in years 73.5± 6.9; symptomatic ICA stenosis ≥50%*, asymptomatic ICA stenosis ≥70%*, symptoms defined as ischemic stroke, transient ischemic attack 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 6:00 a.m. and 24:00 after the procedure. A new neurological evaluation was performed at a 3-month follow-up.
Montorsi P, 2020	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 myocardial infarction 72 h before CAS, and concomitant sources of potential cerebral embolization that would confound neurological	**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: Endpoints included in hospital and 30-day major adverse cardiac and cerebrovascular events (MACCE) (death, all stroke, retinal embolism, and myocardial infarction), technical and clinical success, target vessel ECA patency on angiography at the end of CAS and on Doppler ultrasound	The measurements of the outcomes were repeated within 24 hours, 30 days and 6 months post-CAS.

	assessment. Anatomic exclusion criteria were contralateral carotid occlusion without detectable ipsilateral posterior communicating artery, isolated hemisphere of the target vessel, target vessel external carotid artery (ECA) occlusion, intracranial, significant (>50%) stenosis of the ipsilateral common carotid artery (CCA), and/or CCA >50% stenosis below bifurcation.			at 1, 30, and 180 days of follow-up, and significant in stent restenosis at 6 months.	

* Based on the criteria defined by NASCET, ECA, external carotid artery; CCA, common carotid artery; ICA, internal carotid artery; MI, myocardial infarction; NIHSS, National Institutes of Health scale score; MRS, modified Rankin scale; TCD, transcranial Doppler; MACCE, major adverse cardiac and cerebrovascular events; MES**,** microembolic signs; EPD, distal embolic protection devices; ALO, transient ischemic attack; DW-MRI, diffusion-weighted magnetic resonance imaging; CRF, chronic renal failure; MRI, magnetic resonance imaging

Table 3. Quality of evidence (GRADE)

Summary of Results:

Dual Layer nitinol + EPD stent compared to Closed Cell Stent + EPD for carotid stenosis

Participants or population: Carotid stenosis

Context: Efficacy and safety

Intervention: Stent Double Layer 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 Nº of participants: 52(1 ECR)	-	-	-	MD **2.8 lower** (5.96 lower to 0.36 higher)	⨁⨁⨁◯ Moderate[a]
Major 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]

Outcome Nº of participants (studies)	Relative Effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty
		Control	Intervention	**Difference**	

*The risk in the intervention group (and its 95% confidence interval) 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

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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.

Explanations
a. It does not describe randomization; uncertainty in blinded allocation; without blinding of the evaluator; did not analyze by ITT