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PERIPHERAL

Cerebral Embolic Lesions Detected With Diffusion-Weighted Magnetic Resonance Imaging Following Carotid Artery Stenting

A Meta-Analysis of 8 Studies Comparing Filter Cerebral Protection and Proximal Balloon Occlusion

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ABSTRACT

OBJECTIVES The aim of this meta-analysis was to evaluate and compare the efficacy of the 2 different neuroprotection systems in preventing embolization during carotid artery stenting (CAS), as detected by diffusion-weighted magnetic resonance imaging (DW-MRI).

BACKGROUND Data from randomized and nonrandomized studies comparing both types of embolic protection devices revealed contrasting evidence about their efficacy in neuroprotection, as assessed by the incidence of new ischemic lesions detected by DW-MRI.

METHODS Eight studies, enrolling 357 patients, were included in the meta-analysis. Our study analyzed the incidence of new ischemic lesions/patient, comparing filter cerebral protection and proximal balloon occlusion.

RESULTS Following CAS, the incidence of new ischemic lesions/patient detected by DW-MRI was significantly lower in the proximal balloon occlusion group (effect size [ES]: −0.43; 95% confidence interval [CI]: −0.84 to −0.02, $I^2 = 70.08$, $Q = 23.40$). Furthermore, following CAS, the incidence of lesions at the contralateral site was significantly lower in the proximal protection group (ES: −0.50; 95% CI: −0.72 to −0.27, $I^2 = 0.00$, $Q = 3.80$).

CONCLUSIONS Our meta-analysis supports the concept that the use of proximal balloon occlusion compared with filter cerebral protection is associated with a reduction of the amount of CAS-related brain embolization. The data should be confirmed by a randomized clinical trial. (J Am Coll Cardiol Intv 2014;7:1177–83) © 2014 by the American College of Cardiology Foundation.

Carotid artery stenting (CAS) is a validated treatment to reduce the incidence of stroke among patients with moderate-to-severe symptomatic carotid stenosis (1,2), as well as among those with severe asymptomatic carotid stenosis (3,4). According to guideline recommendations, CAS has shown noninferiority to carotid endarterectomy in the prevention of stroke (5). However, because of the occurrence of periprocedural neurological ischemic events, current guidelines recommend the use of embolic protection devices (EPDs) during CAS (1).

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ABBREVIATIONS AND ACRONYMS

CAS = carotid artery stenting

CI = confidence interval

DW-MRI = diffusion-weighted magnetic resonance imaging

EPD = embolic protection device

ES = effect size

Among the EPDs that are in clinical use, proximal EPDs have the advantage of providing cerebral embolic protection during all phases of the endovascular intervention (6). The use of endovascular clamping, a proximal EPD, during CAS has been demonstrated to be particularly safe and efficient in large registries and clinical trials (7,8). Moreover, the use of proximal EPDs has been associated with a reduced amount of cerebral embolic signals when compared with distal protection devices (6).

Diffusion-weighted magnetic resonance imaging (DW-MRI) has been shown to be a sensitive tool in identifying new ischemic cerebral lesions caused by emboli during CAS. Data from randomized and nonrandomized studies comparing both types of EPDs revealed contrasting evidence about their efficacy in neuroprotection, as assessed by the incidence of new ischemic lesions detected by DW-MRI (9–16).

Therefore, the aim of this meta-analysis was to evaluate and compare the efficacy of the 2 different neuroprotection systems in preventing embolization during CAS, as detected by DW-MRI.

METHODS

STUDY SELECTION. The study was designed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) requirements (17). MEDLINE, Cochrane (Cochrane Database of Systematic Reviews), Web of Science, and SCOPUS database were searched for studies published until December 2013. Studies were identified using the major medical subject heading "carotid artery stenting or CAS" AND "DW-MRI or magnetic resonance imaging" AND "distal embolic protection device or filter or distal cerebral protection" AND "proximal embolic protection device or flow reversal or proximal cerebral protection." Citations were screened at the title and abstract level, and retrieved as a full report if they reported data on the comparison of CAS outcomes, defined as new ischemic lesions detected at DW-MRI, between a filter cerebral protection group and a proximal balloon occlusion group. No language limitations were applied. The full texts and bibliography of all potential studies also were retrieved in detail to seek additional relevant studies.

INCLUSION CRITERIA. Studies were included if they:

1. Reported data on comparison of CAS outcomes, defined as the incidence of new ischemic lesions and number of new ischemic lesions per patient (lesions/patient), between a filter cerebral protection group and a proximal balloon occlusion group; and
2. New ischemic lesions were detected by DW-MRI.

EXCLUSION CRITERIA. Studies were excluded if any of the following criteria applied:

1. Duplicate publication, subgroup studies of a main study;
2. The outcome of interest was not clearly reported or was impossible to extract or calculate from the published results.

DATA EXTRACTION. Two reviewers independently screened studies for fulfilment of inclusion criteria. Reviewers compared selected trials, and discrepancies were resolved by consensus. The quality of the trials was not evaluated because this practice has been previously discouraged (18).

STUDY ENDPOINTS. The primary endpoint evaluated was the incidence of new ischemic lesions/patient during a CAS procedure with filter cerebral protection or proximal balloon occlusion. Publication bias was assessed by plotting the study results against the precision of the study (funnel plots) for each outcome. Symmetry of the funnel plots was tested using the trim and fill method. Of the 193 studies identified by the initial search, 12 were retrieved for more detailed evaluation, and 8 studies were included in the study (**Figure 1**).

STATISTICAL ANALYSIS. Mean, SD, and p values were used. Overall estimates of effect (effect size [ES]) were calculated with a random effects model (19). Statistical significance was set at $p < 0.05$ (2-tailed). Heterogeneity was assessed by a Q statistic and I^2 test. Significant heterogeneity was considered present for p values <0.10 or an I^2 >50%. Data analysis was performed using ProMeta 2.0 (Internovi, Cesena, Italy). For verification of the robustness of the results, sensitivity analyses were performed to test the influence of potential effect modifiers, including mean age, age >80 years, male sex, symptomatic carotid artery disease, smoking status, diabetes, coronary artery disease, chronic obstructive pulmonary disease, peripheral artery disease, hypertension, dyslipidemias, prior myocardial infarction, prior stroke, prior transient ischemic attack, and study publication year.

RESULTS

CHARACTERISTICS OF INCLUDED CLINICAL TRIALS. Of the 193 studies identified by the initial search, 12

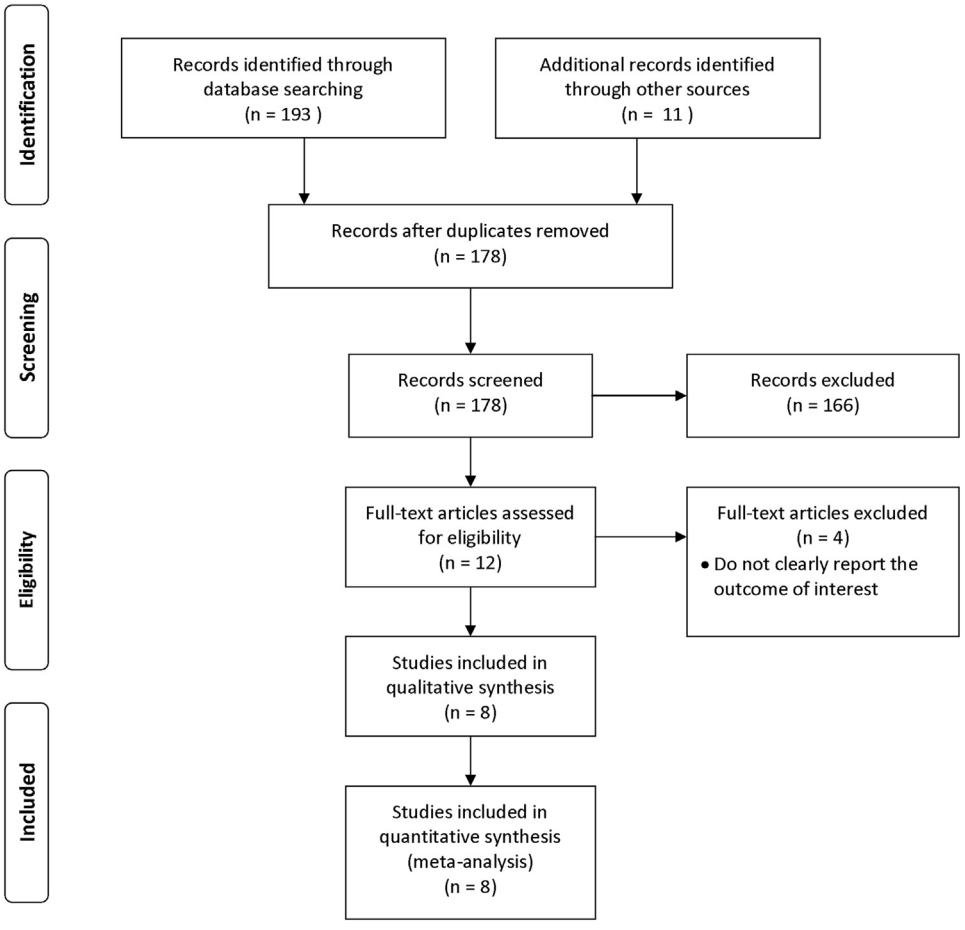

FIGURE 1 Meta-Analysis Flow Chart

Flow diagram demonstrating study selection for meta-analysis (PRISMA [Preferred Reporting Items for Systematic Reviews and Meta-Analyses] diagram).

were retrieved for more detailed evaluation. Four studies were subsequently excluded, and therefore, 8 studies were finally included in the analyses, enrolling 357 patients (Figure 1). No significant limitations were identified for 8 studies, 5 of which were randomized trials (9,11,12,14,15), whereas 3 were nonrandomized comparisons (13,16,20) (Table 1).

INCIDENCE OF NEW ISCHEMIC LESIONS/PATIENT AT DW-MRI. The number of new ischemic lesions/patient detected by DW-MRI was significantly lower in the proximal balloon occlusion group (ES: −0.43; 95% confidence interval [CI]: −0.84 to −0.02, $I^2 = 70.08$, $Q = 23.40$) (Figure 2).

INCIDENCE OF NEW ISCHEMIC LESIONS AT THE CONTRALATERAL SITE AT DW-MRI. Following CAS, the incidence of new ischemic lesions detected at the contralateral site by DW-MRI was significantly lower in the proximal protection group (ES: −0.50; 95% CI: −0.72 to −0.27, $I^2 = 0.00$, $Q = 3.80$) (Figure 3).

META-REGRESSION ANALYSIS. Meta-regression analysis showed no relationship between all the analyzed modifiers and both the incidence of new ischemic lesions and the number new ischemic lesions/patient. These results should be considered with caution, given the limited number of reports, which weakens the meta-regression analysis itself.

SENSITIVITY ANALYSIS. Results were confirmed when meta-analyses were repeated, removing 1 study at a time.

PUBLICATION BIAS. The trim and fill method did not show any publication bias in any of the analyses performed.

TABLE 1 Baseline Characteristics of Selected Studies Included in the Meta-Analysis

First Author (Ref. #)	Year	N	Age (yrs)	Age >80 yrs	CAD (%)	COPD (%)	Diabetes (%)	Dyslipidemia (%)	Hypertension (%)	Male (%)	PAD (%)	Previous MI (%)	Previous Stroke (%)	Previous TIA (%)	Smoking (%)	Symptomatic (%)
Bijuklic et al. (12)	2012	62	71.7	19.5	56.4	N/A	29.0	83.9	98.4	77.4	N/A	N/A	N/A	N/A	14.8	40.3
Cano et al. (14)	2013	60	67.7	5.0	70.0	6.7	40.0	78.2	93.3	66.6	48.3	N/A	N/A	N/A	N/A	25.0
Castro-Afonso et al. (15)	2013	40	69.1	N/A	N/A	N/A	40.0	70.0	97.5	62.5	N/A	15.0	22.5	15.0	32.5	82.5
El-Koussy et al. (9)	2007	44	67.7	N/A	N/A	N/A	N/A	N/A	N/A	70.0	N/A	N/A	N/A	N/A	N/A	56.8
Flach et al. (20)	2007	33	66	N/A	45.4	N/A	12.1	66.6	54.5	84.8	N/A	N/A	N/A	N/A	60.6	N/A
Leal et al. (13)	2012	64	67.6	3.1	N/A	N/A	45.3	50.0	68.7	90.6	14.1	17.2	25.0	43.7	37.5	68.7
Montorsi et al. (11)	2011	35	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Taha et al. (16)	2009	19	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Not applicable (N/A) indicates that the data are not shown in the primary study or are not obtainable; otherwise, the analysis was conducted only in a subgroup of the entire study population.
CAD = coronary arterial disease; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; PAD = peripheral arterial disease; TIA = transient ischemic attack.

DISCUSSION

This meta-analysis suggests that the use of proximal balloon occlusion during CAS is associated with a significant reduction of the number of distal embolizations, when compared with the use of distal EPDs. A significant reduction in the number of distal embolizations is also evident at the site contralateral to the target vessel.

It is accepted that EPDs lower the risk of stroke with CAS. In theory, proximal EPDs may provide better neuroprotection for 2 important reasons (6):

1. A proximal EPD affords neuroprotection throughout all phases of the procedure, including initial lesion crossing, whereas distal EPDs must cross the lesion before neuroprotection can be afforded; and
2. A proximal EPD is able to capture particulate debris with higher efficiency.

DW-MRI is a valuable tool for the detection of focal brain ischemia in the acute stage. It has been used for the detection of cerebral embolism after acute ischemic neurological events and for the detection of silent ischemic brain lesions after carotid endarterectomy, stenting, and diagnostic cerebral angiography (21). Importantly, the occurrence of new cerebral lesions using DW-MRI should be considered a surrogate marker of embolization because the greater part of these lesions remained asymptomatic and did not have a prognostic impact at 30 days of follow-up (22). However, it should be considered that currently, because of the small incidence of CAS-related symptomatic lesions, it is difficult to establish the superiority of one EPD compared with another on the basis of the ability to reduce clinically relevant neurological events.

The use of proximal protection has been inconsistently reported to be a valid tool to reduce the occurrence of post-CAS new lesions. Subcohort analysis from a 53-patient randomized trial, comparing Mo.Ma (Invatec, Roncadelle, Italy) versus FilterWire (Boston Scientific, Natick, Massachusetts) protection for the treatment of extracranial carotid atherosclerosis, showed robust reduction in the occurrence of new ischemic lesions when proximal protection was used, with a 42.8% (9 of 21) rate in the filter group and 14.3% (2 of 14) in the Mo.Ma group (11). Similarly, another 62-patient randomized trial comparing the use of proximal versus distal protection for CAS reported a dramatic difference between proximal and distal protection in the proportion of patients with new ischemic lesions (45.2% vs. 87.1%, $p < 0.001$) (5).

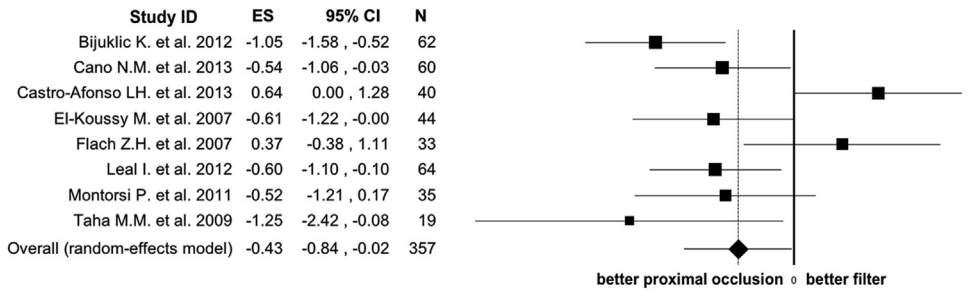

FIGURE 2 Incidence of New Ischemic Lesions/Patient at DW-MRI

Forrest plot representing the pooled estimate analysis for overall incidence of new ischemic lesions/patient detected at diffusion-weighted magnetic resonance imaging (DW-MRI). CI = confidence interval; ES = effect size.

A recent comparative trial between a filter device (Angioguard, Cordis, East Bridgewater, New Jersey) and the Mo.Ma system showed a lack of a significant difference in the proportion of patients with new ischemic lesions (63.3% vs. 66.7%; p = NS). Despite this, the number of ischemic cerebral lesions per patient was significantly lower in the Mo.Ma group (a median of 6 lesions per patient vs. a median of 10 in the Angioguard group, $p < 0.001$). One patient had a minor stroke during CAS (1.66%) in the Angioguard group (14).

Opposite results were recently observed in a similar single-center trial comparing flow-reversal EPD (n = 21) to filter EPD (n = 19); a significant reduction in the incidence (15.8% vs. 47.6%, p = 0.03), number (0.73 vs. 2.6, p = 0.05), and size (0.81 vs. 2.23 mm, p = 0.05) of new ischemic lesions were observed when filter EPDs were used (15).

This meta-analysis pooled all the available data and analyzed the incidence of new ischemic lesions detected at DW-MRI following CAS. We found that the number of lesions per patient who underwent proximal-protected CAS is lower when compared with distal-protected CAS. The association of proximal protection with a reduced distal embolization is consistent at the contralateral site.

STUDY LIMITATIONS. One of the most important pitfalls of the primary studies included in this meta-analysis is represented by the lack of information about the experience of physicians performing CAS procedures. It has now been clearly demonstrated that the number of procedures performed in catheterization laboratories influences the outcome of CAS procedures (23,24). A different level of experience on the use of specific EPDs might contribute to

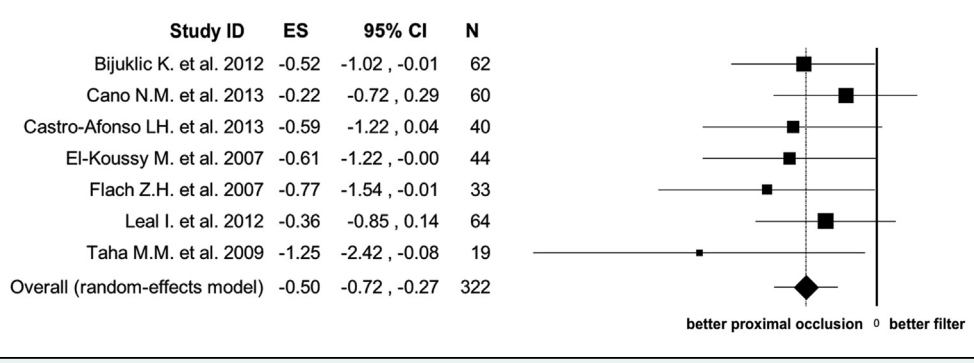

FIGURE 3 Incidence of New Ischemic Lesions at the Contralateral Site at DW-MRI

Forrest plot representing the pooled estimate analysis for overall incidence of new ischemic lesions at the contralateral site at DW-MRI. Abbreviations as in Figure 2.

justify, at least in part, the discrepancy between the studies.

It could be speculated that the differences in post-CAS distal embolization, highlighted by the analyzed studies, might be related to plaque echogenicity, stent design (25,26), and patient responsiveness to drug therapy (27). Unfortunately, these details have not been described in all the studies considered, precluding the possibility of evaluating the effect of these variables.

Furthermore, concerning the specific EPDs, despite all the studies comparing distal with proximal EPDs, there are some differences among the specific EPDs used. Regarding proximal EPDs, most of the studies included in the meta-analysis adopted the endovascular clamping system, whereas the use of the flow-reversal system was less common. However, even if it is not possible to demonstrate that these procedural differences justify the different outcomes, this hypothesis cannot be excluded.

CONCLUSIONS

Although our meta-analysis suggests a potential benefit by using proximal balloon occlusion compared with filter cerebral protection, it still remains unclear whether or not proximal balloon occlusion is superior to filter cerebral protection. However, although a large and well-designed randomized clinical trial is warranted to provide a definitive answer, the use of data from registries represents a valid alternative to draw provisional conclusions from data analysis. In this regard, it is important to acknowledge that registries provide a unique opportunity to generate hypotheses on contemporary disease evolution and treatment. The use of a registry is a tool able to advance science by spotlighting what really happens in actual medical practice, in contrast to the artificial environment of a controlled clinical trial. Finally, although randomized clinical trials often provide information on already established therapies, registries provide a picture of more modern therapy and help the evolution of them.

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KEY WORDS carotid artery stenting, cerebral ischemic lesions, diffusion-weighted magnetic resonance imaging, embolic protection device