Proximal occlusion versus distal filter for cerebral protection during carotid artery stenting: a meta-analysis of MRI studies

Salvatore Cassese, MD

Deutsches Herzzentum, Technische Universität München

Munich, Germany

Disclosure

- Nothing to disclose

Background

Proximal occlusion (PO) and distal filter (DF) serve for cerebral embolic protection during carotid artery stenting (CAS)

The incidence of new cerebral lesions at diffusion-weighted magnetic resonance imaging (DW-MRI) represents a surrogate endpoint for embolization, though the clinical impact is controversial

Purpose

To perform a meta-analysis of DW-MRI studies comparing PO and DF during CAS

Methods

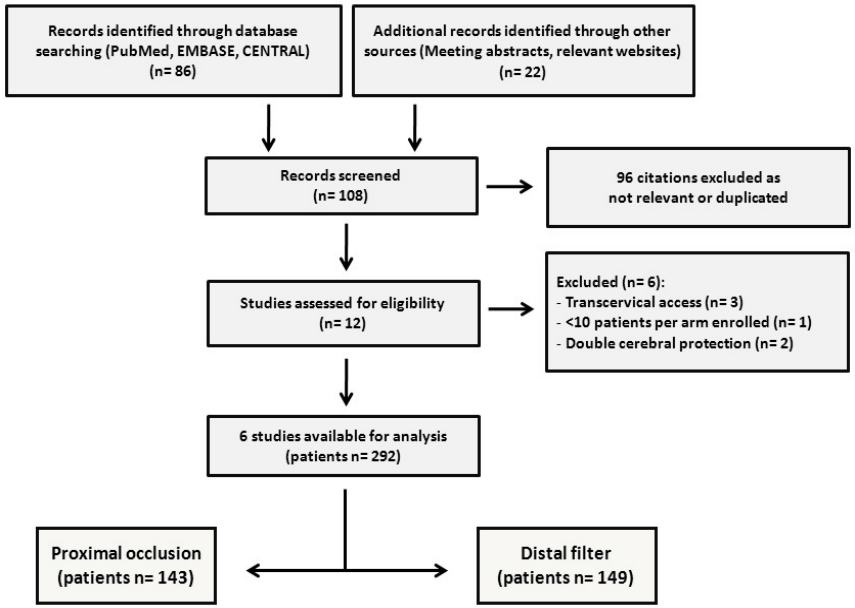
Medline, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), scientific session abstracts and relevant websites were searched for studies comparing PO versus DF for cerebral protection during CAS
Search terms: “carotid”, “stenosis”, “stent(s)”, “cerebral protection”, “embolic protection device”, “proximal occlusion”, “clamping”, “filter” “distal filter”, “magnetic resonance imaging (MRI)”, “diffusion-weighted (DW)-MRI”, “trial”, and “randomized trial”

Inclusion criteria: (1) transfemoral protected CAS; (2) routine DW-MRI before and after CAS (not only in case of complication); (3) ≥30-day clinical follow-up
Exclusion criteria: (1) vessel treated other than internal carotid artery; (2) device used for cerebral embolic protection other than PO or DF; (3) <10 patients per arm enrolled; (4) duplicated data

Primary outcome: the incidence of new cerebral lesions at DW-MRI
Secondary outcomes: the incidence of new ipsilateral and new contralateral cerebral lesions at DW-MRI and death/cerebrovascular events (CVE)
Outcomes were evaluated as per protocol definitions

Odds ratio (OR) and 95% confidence interval [95% CI] served as summary statistics; statistical analysis was performed using the RevMan (Review Manager [RevMan] Version 5.1, The Cochrane Collaboration, Copenhagen, Denmark), and Stata 11.2 (STATA Corp, College Station, Texas, USA) software packages

Results



Study	Pat, n	Age, yrs	M, %	DM, %	Sten, %	Symp, %
Bijuklic et al.	62	71.7	77	29	89.0	40
Cano et al.	60	67.7	67	40	83.6	69
de Castro-Afonso et al.	44	69.0	63	40	66.3	82
El-Koussy et al.	33	68.0	71	N/R	N/R	56
Montorsi et al.	53	68.8	79	25	85.0	11
Zwenneke Flach et al.	44	66.0	85	12	N/R	100

A total of 292 patients received protected CAS

PRISMA flow chart for the study selection process. PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

Main characteristics of patients enrolled among studies included in the meta-analysis

Overall mean values are reported; N/R: not reported

A total of 274 patients (93.8%) received DW-MRI after CAS at 48 hours [24-48]) follow-up

New cerebral lesions at DW-MRI after CAS were observed in 129 patients (49.0%)

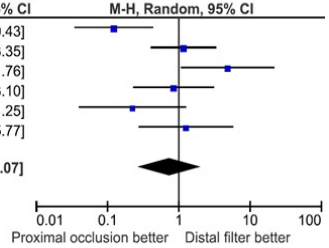
Clinical follow-up was to 90 days [30-360]

Death/CVE occurred in 11 patients (3.7%)

A. New cerebral lesions

Study or Subgroup	Proximal occlusion Events	Total	Distal filter Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bijuklic et al.	14	31	27	31	17.6%	0.12 [0.03, 0.43]
Cano et al.	20	30	19	30	19.1%	1.16 [0.40, 3.35]
de Castro-Afonso et al.	10	21	3	19	15.9%	4.85 [1.08, 21.76]
El-Koussy et al.	7	25	6	19	17.3%	0.84 [0.23, 3.10]
Montorsi et al.	2	14	9	21	14.3%	0.22 [0.04, 1.25]
Zwenneke Flach et al.	4	10	8	23	15.7%	1.25 [0.27, 5.77]
Total (95% CI)		**131**		**143**	**100.0%**	**0.74 [0.26, 2.07]**
Total events	57		72			

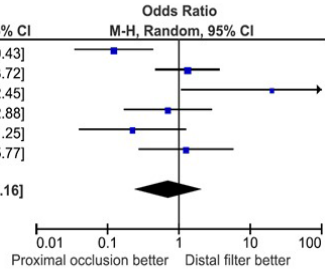
Heterogeneity: Tau² = 1.14; Chi² = 16.86, df = 5 (P = 0.005); I² = 70%
Test for overall effect: Z = 0.57 (P = 0.57)



B. New ipsilateral cerebral lesions

Study or Subgroup	Proximal occlusion Events	Total	Distal filter Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bijuklic et al.	14	31	27	31	19.1%	0.12 [0.03, 0.43]
Cano et al.	19	30	17	30	20.9%	1.32 [0.47, 3.72]
de Castro-Afonso et al.	7	21	0	19	9.1%	20.17 [1.06, 382.45]
El-Koussy et al.	5	25	5	19	18.0%	0.70 [0.17, 2.88]
Montorsi et al.	2	14	9	21	15.7%	0.22 [0.04, 1.25]
Zwenneke Flach et al.	4	10	8	23	17.2%	1.25 [0.27, 5.77]
Total (95% CI)		**131**		**143**	**100.0%**	**0.72 [0.24, 2.16]**
Total events	51		66			

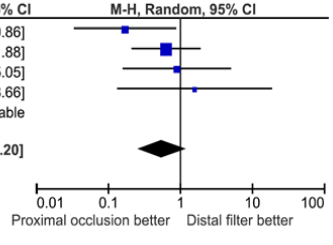
Heterogeneity: Tau² = 1.25; Chi² = 16.08, df = 5 (P = 0.007); I² = 69%
Test for overall effect: Z = 0.59 (P = 0.55)



C. New contralateral cerebral lesions

Study or Subgroup	Proximal occlusion Events	Total	Distal filter Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bijuklic et al.	2	31	9	31	22.4%	0.17 [0.03, 0.86]
Cano et al.	8	30	11	30	47.9%	0.63 [0.21, 1.88]
de Castro-Afonso et al.	3	21	3	19	19.8%	0.89 [0.16, 5.05]
El-Koussy et al.	2	25	1	19	9.8%	1.57 [0.13, 18.66]
Zwenneke Flach et al.	0	10	0	23		Not estimable
Total (95% CI)		**117**		**122**	**100.0%**	**0.55 [0.25, 1.20]**
Total events	15		24			

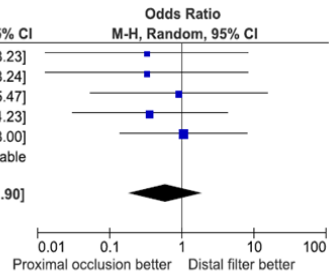
Heterogeneity: Tau² = 0.02; Chi² = 3.08, df = 3 (P = 0.38); I² = 2%
Test for overall effect: Z = 1.51 (P = 0.13)



D. Death/CVE

Study or Subgroup	Proximal occlusion Events	Total	Distal filter Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bijuklic et al.	0	31	1	31	13.3%	0.32 [0.01, 8.23]
Cano et al.	0	30	1	30	13.3%	0.32 [0.01, 8.24]
de Castro-Afonso et al.	1	21	1	19	17.2%	0.90 [0.05, 15.47]
El-Koussy et al.	1	25	2	19	22.7%	0.35 [0.03, 4.23]
Montorsi et al.	2	26	2	27	33.5%	1.04 [0.14, 8.00]
Zwenneke Flach et al.	0	10	0	23		Not estimable
Total (95% CI)		**143**		**149**	**100.0%**	**0.58 [0.18, 1.90]**
Total events	4		7			

Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 4 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.90 (P = 0.37)

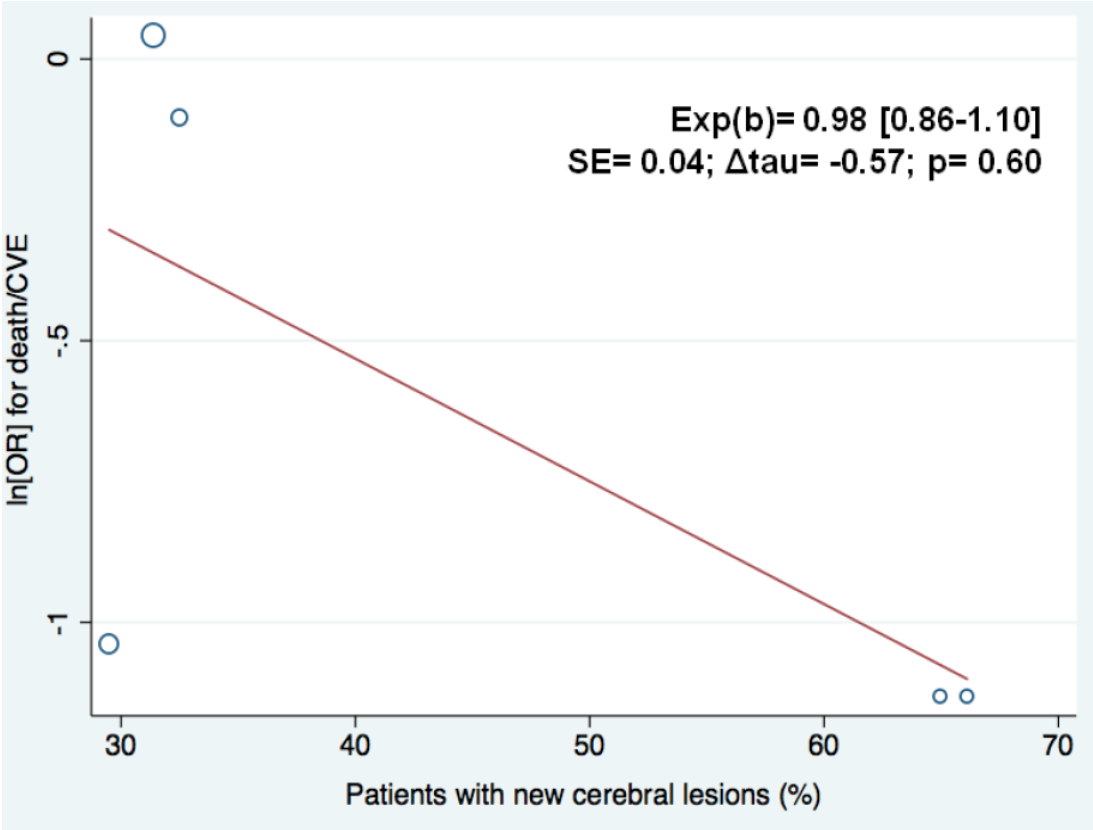


The Mantel-Haenszel random effects model (DerSimonian and Laird) was used to obtain pooled OR
The Breslow-Day χ^2 test and the I^2 statistic were used to test heterogeneity across the studies
As a guide, I^2 values <25% indicated low, 25–50% moderate, and >50% high heterogeneity

Variable	Subgroup	Study, n	New cerebral lesions OR [95% CI]	p_{int}	New ipsilateral cerebral lesions OR [95% CI]	p_{int}
Study size, patients	≤48	4	1.65 [0.58-4.68]	0.08	1.70 [0.35-8.21]	0.32
	>48	2	0.33 [0.07-1.50]		0.41 [0.04-4.28]	
RCT	Yes	5	0.67 [0.20-2.26]	0.53	0.66 [0.17-2.47]	0.53
	No	1	1.25 [0.27-5.77]		1.25 [0.27-5.77]	
Experienced center	Yes	4	0.63 [0.13-3.06]	0.63	0.69 [0.12-3.99]	0.79
	No	2	0.99 [0.37-2.68]		0.91 [0.32-2.58]	
PO type	Without AV-shunt	4	0.43 [0.14-1.31]	0.47	0.42 [0.13-1.36]	0.15
	With AV-shunt	2	2.48 [0.66-9.37]		3.84 [0.23-63.79]	
DF type	Concentric	2	0.39 [0.04-3.51]	0.43	0.41 [0.04-4.28]	0.51
	Eccentric	4	1.07 [0.33-3.45]		1.01 [0.25-4.13]	
Stent design	Closed-cell	2	1.07 [0.05-22.02]	>0.99	1.82 [0.02-182.06]	0.83
	Open-cell	3	1.07 [0.52-2.20]		1.10 [0.53-2.29]	
Sensitivity of imaging	1.5-Tesla scanner	4	0.41 [0.13-1.25]	0.07	0.38 [0.13-1.13]	0.12
	3-Tesla scanner	2	2.14 [0.53-8.59]		3.70 [0.25-55.52]	
Median age, years	≤68.4	3	1.07 [0.52-2.20]	0.53	1.10 [0.53-2.29]	0.65
	>68.4	3	0.50 [0.05-5.07]		0.60 [0.05-7.81]	
Average of males, %	≤74	2	2.14 [0.53-8.59]	0.07	3.70 [0.25-55.52]	0.12
	>74	4	0.41 [0.13-1.25]		0.38 [0.13-1.13]	
Average of diabetics, %	≤29	3	0.31 [0.08-1.30]	0.054	0.31 [0.08-1.30]	0.11
	>29	2	2.14 [0.53-8.59]		3.70 [0.25-55.52]	
Average of baseline stenosis, %	≤84.3	2	2.14 [0.53-8.59]	**0.003**	3.70 [0.25-55.52]	**0.03**
	>84.3	2	0.15 [0.05-0.42]		0.15 [0.05-0.42]	
Average of symptomatic patients, %	≤62.5	3	0.29 [0.08-0.98]	**0.02**	0.26 [0.09-0.77]	**0.01**
	>62.5	3	1.75 [0.74-4.15]		1.89 [0.57-6.29]	

Sensitivity analysis for endpoints with significant heterogeneity

Odds ratios OR [95% CI] are used as summary statistics; p-values for interaction (p_{int}) between treatment effects and subgroups of interest are derived using the Mantel-Haenszel random effects model (DerSimonian and Laird). The median values are used to define cut-offs for trial size, age, prevalence of males, diabetics, symptomatic patients, and for grade of baseline stenosis. RCT: randomized controlled trial; PO: proximal occlusion; DF: distal filter; AV: arterio-venous



Meta-regression analysis of new cerebral embolization and death/cerebrovascular events

The relationship between death/cerebrovascular events (CVE), measured as the natural logarithm of odds ratio – ln(OR) – for death/CVE and the incidence of new cerebral embolization is investigated with a weighted random effect meta-regression analysis. The size of circles is proportional to the weight of each study in the fitted random-effects meta-regression. Exp(b) is presented with pertinent [95% CI] whilst the symbol Δ refers to "change". A p value <0.05 indicates significance. SE: standard error

Limitations

- The majority of the studies included are not powered for clinical outcomes
- The risk estimates derived by studies in which patients were treated with different devices
- The experience of centers in CAS (cut-off of >50 CAS/year) did not modify treatment effect
- The confidence of operators with specific devices has not routinely been reported within studies included
- A longer follow-up would be desirable for assessing the clinical and neurocognitive impact of new cerebral lesions at DW-MRI
- Only one trial among those included performed a supplemental 3-month MRI after CAS: the reversibility of new cerebral lesions after CAS cannot be adequately assessed

Conclusions

- At DW-MRI 48 hours after protected CAS one half of patients present new embolic cerebral lesions, though the large majority of events are asymptomatic
- The use of PO versus DF does not influence the risk of new cerebral lesions after CAS, neither ipsilateral nor contralateral
- There is significant modification of treatment effect by high-grade baseline stenosis and by symptoms
- The use of PO versus DF during protected CAS does not impact the risk of death/CVE

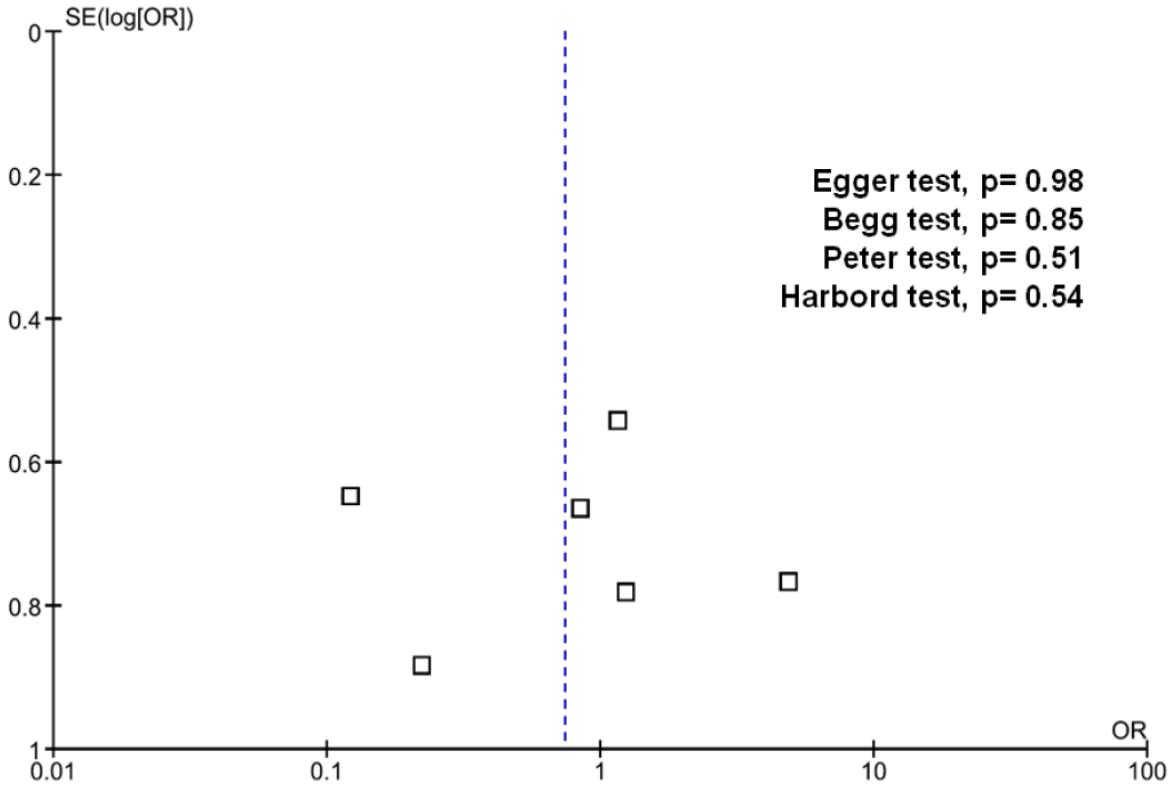
Thank you

Back-up slides

Study	Year	Stent	Embolic protection
Bijuklic et al.	2012	Cristallo Ideale, (Invatec/Medtronic Vascular Inc., Santa Rosa, California), hybrid-cell	Mo.Ma Ultra proximal cerebral protection versus Emboshield Protection System, (concentric-design)
Cano et al.	2013	Precise (Cordis, Johnson & Johnson, Bridgewater, New Jersey, US), open-cell	Mo.Ma Ultra proximal cerebral protection versus ANGIOGUARD RX Emboli Capture System (concentric-design)
de Castro-Afonso et al.	2013	Wallstent (Boston Scientific, Natick, MA, US), closed-cell	GORE Flow Reversal System† versus Filter Wire EZ Embolic Protection System (eccentric-design)
El-Koussy et al.	2007	Acculink (Guidant, Santa Clara, CA, USA), open-cell	Mo.Ma Ultra proximal cerebral protection versus Filter Wire EZ Embolic Protection System (eccentric-design)
Montorsi et al.	2011	Wallstent (Boston Scientific, Natick, MA, US), closed-cell	Mo.Ma Ultra proximal cerebral protection versus Filter Wire EZ Embolic Protection System (eccentric-design)
Zwenneke Flach et al.	2007	Acculink (Guidant, Santa Clara, CA, USA), open-cell*	Parodi Anti-Emboli System† versus Spider RX Embolic Protection Device (eccentric-design)

Devices used in the studies included in the meta-analysis

**Device predominantly used; †These two latter devices consisted of an extracorporeal arterio-venous shunt in addition to a cerebral flow-reversal system*



Funnel plot distribution of studies included in the meta-analysis according to primary outcome

The standard error (SE) of the logarithm of odds ratio (OR) – SE(log[OR]) – is plotted against the OR of new cerebral lesions
The absence of publication bias can be evaluated both visually and mathematically
A p value <0.05 indicates significance