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Cerebral Protection During Transcatheter Aortic Valve Implantation: An Updated Systematic Review and Meta-Analysis

Luca Testa, MD, PhD; Azeem Latib, MD; Matteo Casenghi, MD; Riccardo Gorla, MD; Antonio Colombo, MD; Francesco Bedogni, MD

***Background*—**The use of embolic protection devices (EPD) may theoretically reduce the occurrence of cerebral embolic lesions during transcatheter aortic valve implantation. Available evidence from single studies is inconclusive. The aim of the present meta-analysis was to assess the safety and efficacy profile of current EPD.

***Methods and Results*—**Major medical databases were searched up to December 2017 for studies that evaluated patients undergoing transcatheter aortic valve implantation with or without EPD. End points of interest were 30-day mortality, 30-day stroke, the total number of new lesions, the ischemic volume per lesion, and the total volume of lesions. Eight studies involving 1285 patients were included. The EPD delivery success rate was reported in all studies and was achieved in 94.5% of patients. The use of EPD was not associated with significant differences in terms of 30-day mortality (odds ratio 0.43 [0.18–1.05], *P*=0.3) but it was associated with a lower rate of 30-day stroke (odds ratio 0.55 [0.31–0.98], *P*=0.04). No differences were detected with respect to the number of new lesions (standardized mean difference −0.19 [−0.71 to 0.34], *P*=0.49). The use of EPD was associated with a significantly smaller ischemic volume per lesion (standardized mean difference, −0.52 [−0.85 to −0.20], *P*=0.002) and smaller total volume of lesions (standardized mean difference, −0.23 [−0.42 to −0.03], *P*=0.02).

***Conclusions*—**The use of EPD is not associated with a reduced rate of mortality and new ischemic cerebral lesions. The use of EPD during transcatheter aortic valve implantation seems to be associated with a lower 30-day stroke rate, although this result is driven by a single nonrandomized study. The use of EPD is associated with a smaller volume of ischemic lesions, and smaller total volume of ischemic lesions. **(*J Am Heart Assoc*. 2018;7:e008463. DOI: 10.1161/JAHA.117.008463.)**

Key Words: aortic valve stenosis • stroke • transcutaneous aortic valve implantation

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In the past decade, transcatheter aortic valve implantation (TAVI) triggered a paradigm shift in the treatment of patients with severe symptomatic aortic stenosis.[1–6] Nonetheless, along with groundbreaking efficacy results, data concerning the risk of cerebrovascular complications have been consistently reported in studies using either diffusion-weighted magnetic resonance imaging (DW-MRI) or high-intensity transient signals as assessed by transcranial Doppler.[7–10] Embolic protection devices (EPDs) have been ideated and introduced with the aim of reducing such an inherent risk, but they have been tested in relatively small populations, providing inconclusive results. We thus aimed at summarizing, by means of a meta-analytic approach, the available evidence concerning the safety and efficacy profile of current EPDs in the setting of TAVI.

Materials and Methods

Search Strategy and Inclusion Criteria

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure as the present article is a systematic review and meta-analysis; thus, the source data are available for consultation, reproduction, and analysis on web-based medical libraries. EMBASE, PubMed, Web of Science Core Collection, and the Cochrane Library were searched up to December 2017. The search terms used were transcatheter aortic valve implantation OR TAVI OR transcatheter aortic valve replacement OR TAVR AND embolic protection device. No language restriction was applied. Abstracts and unpublished studies presented in conferences were excluded. Single-arm studies that evaluated the

From the Department of Cardiology, IRCCS Pol. S. Donato, S. Donato Milanese, Milan, Italy (L.T., M.C., R.G., F.B.); Interventional Cardiology Unit, San Raffaele Scientific Institute, EMO-GVM Centro Cuore Columbus, Milan, Italy (A.L., A.C.).

An accompanying Data S1 is available at http://jaha.ahajournals.org/content/7/10/e008463/DC1/embed/inline-supplementary-material-1.pdf

Correspondence to: Luca Testa, MD, PhD, Department of Cardiology, IRCCS Pol. S. Donato, S. Donato Milanese, Milan, Italy. E-mail: luctes@gmail.com

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Clinical Perspective

What Is New?

- The percentage of patients experiencing brain damage assessed by means of diffusion-weighted magnetic resonance imaging following transcatheter aortic valve implantation is significantly higher than those having a clinically relevant cerebrovascular event.

What Are the Clinical Implications?

- The available literature does not support the routine use of cerebral protection in patients undergoing transcatheter aortic valve implantation: it should be considered in selected patients who are at high risk of embolization from the aortic valve, root, and arch.

feasibility of performing TAVI with EPD were also excluded. A flow diagram is shown in Figure 1.

The PRISMA[11] (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist is provided in Data S1.

We included studies that evaluated 1 or more of the following outcomes: EPD delivery success, stroke, death, new-silent ischemic lesions as assessed by DW-MRI, neurocognitive function as assessed by Mini-Mental State Examination, Montreal Cognitive Assessment, Center for Epidemiological Studies Depression Scale, or National Institutes of Health Stroke Scale.

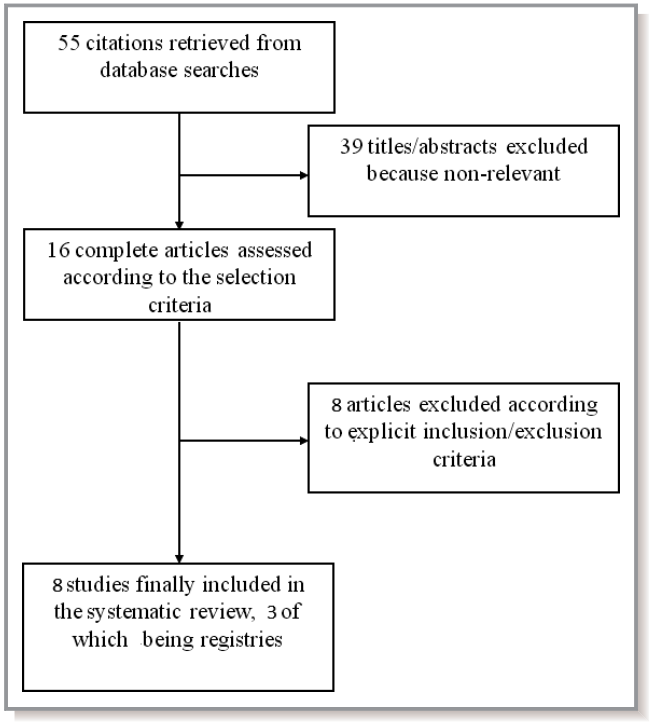

Figure 1. Flow diagram showing the study search.

End points were calculated at 30 days and in accordance with Valve Academic Research Consortium-2 definitions.[12]

Validity Assessment

Two unblinded reviewers (L.T., A.L.) appraised the internal validity of included studies, none involved in any of the included studies, with divergences resolved by consensus, according to the methods of The Cochrane Collaboration.[13] Specifically, we adjudicated explicitly the risk for selection, performance, attrition, and adjudication biases, and expressed as low risk of bias (A), moderate risk of bias (B), high risk of bias (C), or incomplete reporting leading to inability to ascertain the underlying risk of bias (D).[13]

Data Analyses

We used RevMan (Review Manager version 5.1.7, Nordic Cochrane Center) to perform random-effects meta-analysis using the Mantel–Haenszel method to determine pooled odds ratio (OR) of EPD compared with non-EPD for dichotomous data. Standardized mean difference (SMD) was used to assess differences in continuous outcomes. The standardized mean difference is used as a summary statistic in meta-analysis when the studies all assess the same outcome but measure it in a variety of ways. In this circumstance it is necessary to standardize the results of the studies to a uniform scale before they can be combined. We thus made the choice of using the standardized mean difference because the MRI scans have been done with different machines (1.5 and/or 3 T), different protocols of acquisition, and as a consequence, a source of heterogeneity was clearly envisionable. Analyses were performed on an intention-to-treat approach. When only median and interquartile range were available, we estimated mean and SD using formulas proposed by Wan et al.[14]

When only 95% confidence interval was available, normal distribution was assumed when sample size was $\geq$100, and we calculated SD using the equation proposed by the *Cochrane Handbook*.[13]

The I^2 statistic was used to assess the heterogeneity across studies.

Cohen K scores between the 2 reviewers with respect to title/abstract and full-text screening were 0.78 and 0.70, respectively, indicating moderate agreement.

The likelihood of publication bias was assessed graphically by generating a funnel plot for the combined end point of major adverse cardiovascular events and mathematically by means of Egger's test (P for significant asymmetry <0.1).[13]

Subgroup analyses were performed to determine whether the type of bioprosthesis and the design of the study influenced the treatment effect. Two-sided P values of 0.05 were considered statistically significant.

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Table 1. Features of Included Studies

	N	Type of Valve	Type of EPD	Time Frame Imaging Assessment	Outcomes
Rodés-Cabau et al; PROTAVI-C pilot study[15] (2014)	40	Edwards SAPIEN-XT	Embrella Embolic Deflector	Periprocedural TCD d ≤7 and 30 DW-MRI	HITS Patients with new lesions: d ≤7 Patients with single lesions Patients with multiple lesions Lesion volume, per lesion Lesion volume, per patient Patients with any post-TAVI lesions: d 30
Lansky et al[16] (2015)	85	Edwards SAPIEN-XT Medtronic CoreValve	TriGuard	D 4 and 30 DW-MRI	Freedom from ischemic lesions (ITT): d 4 New brain lesions: d 30 Single lesion volume Maximum lesion volume
Wendt et al[17] (2015)	30	Edwards SAPIEN-XT	Embol-X Trans-aortic	D 7 DW-MRI	New brain lesion Lesion volume
Samim et al; DEFLECT II Pilot Study[18] (2015)	52	Edwards SAPIEN Medtronic CoreValve	TriGuard HDH	D 4 DW-MRI	Patients with new lesions Patients with single lesions Patients with multiple lesions Lesions per patient Mean lesion volume per patient
Van Mieghem et al; MISTRAL-C[19] (2016)	65	EdwardsSAPIEN 3 SAPIEN-XT Medtronic CoreValve St Jude Portico BAV only	Claret Sentinel	Periprocedural TCD d 5 and 30 DW-MRI	HITS Single lesion volume Total lesion volume
Haussig et al; CLEAN-TAVI[20] (2016)	100	Medtronic CoreValve	Claret Montage	Periprocedural TCD D; 2, 7, and 30 DW-MRI	HITS New lesion (d 2) Total lesion number: d 2 Total lesion volume: d 2 Total lesion number: d 7 Total lesion volume: day 7
Kapadia et al; SENTINEL[21] (2017)	359	SAPIEN-XT SAPIEN-3 CoreValve Evolut-R	Claret Sentinel	D 2–7	Total lesion number: d 2 to 7 Total lesion volume: d 2–7
Seeger et al[22] (2017)	560	SAPIEN-3 Lotus Evolut R	Claret Sentinel	D 7	Mortality Stroke

CLEAN-TAVI indicates Claret Embolic Protection and TAVI; DEFLECT I, SMT Embolic Deflection CE Mark Trial; DEFLECT II, A Study to Evaluate the Safety and Performance of the TriGuard HDH in Patients Undergoing TAVR; DEFLECT III, A Prospective, Randomized Evaluation of the TriGuard HDH Embolic Deflection Device During TAVI; DW-MRI, diffusion-weighted magnetic resonance imaging; HITS, high-intensity transient signal; ITT, Intention to treat; MISTRAL-C, MRI Investigation in TAVI With Claret; PROTAVI-C, Prospective Randomized Outcome Study in Patients Undergoing TAVI to Examine Cerebral Ischemia and Bleeding Complications; TAVI, transcatheter aortic valve implantation; TCD, transcranial Doppler.

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Results

Study Population

Eight studies have been included, totaling 1285 patients[15–22] (Figure 1). Five studies were randomized controlled trials[17–21]; the remaining 3 were registries.[15,16,22] The mean age was 81.7 years, and 50.2% were female. Atrial fibrillation was present at baseline in 30.6% of the patients. A previous stroke was diagnosed in 94 patients (12.9%). See Tables 1 and 2 for more details.

Quality Assessment

A complete description is shown in Table 3.

Risk of bias was assessed for Randomized Studies using ACROBAT (A Cochrane Collaboration Risk of Bias Tool) and Non-Randomized Studies of Intervention using the ACROBAT-NRSI.[13] Overall, the quality of evidence was actually low, with a significant risk of bias, although the visual examination of the funnel plot (Figure 2) did not suggest a publication bias, and the *P* of significance for the Egger's test was 0.7.

Table 2. Cognitive Impairment Assessment

	Assessment Definitions	Outcomes
Rodés-Cabau et al; PROTAVI-C pilot study[15] (2014)	MMSE MoCA	MMSE: baseline MMSE: d 30 MoCA: baseline MoCA: d 30
Lansky et al[16] (2015)	NIHSS MoCA	NIHSS worsening: d 30 MoCA worsening: d 30
Wendt et al[17] (2015)	No neurocognitive assessment	N/A
Samim et al; DEFLECT II Pilot Study[18] (2015)	NIHSS	NIHSS worsening
Van Mieghem et al; MISTRAL-C[19] (2016)	MoCA MMSE CES-D NIHSS	MMSE worsening MoCA worsening CES-D worsening NIHSS worsening
Haussig et al; CLEAN-TAVI[20] (2016)	New neurological symptom assessed by a NIHSS-trained specialist	NIHSS worsening: d 2 NIHSS worsening: d 7 NIHSS worsening: d 30
Kapadia et al; SENTINEL[21] (2017)	Neurocognitive function (attention, executive function, processing speed, verbal and visual memory, mental status, depression)	Δ overall composite score: d 2–7 Δ overall composite score: d 30 Δ overall composite score: d 90
Seeger et al[22] (2017)	N/A	N/A

CES-D indicates Center for Epidemiological Studies-Depression scale; CLEAN-TAVI, Claret Embolic Protection and TAVI; DEFLECT I, SMT Embolic Deflection CE Mark Trial; DEFLECT II, A Study to Evaluate the Safety and Performance of the TriGuard HDH in Patients Undergoing TAVR; DEFLECT III, A Prospective, Randomized Evaluation of the TriGuard HDH Embolic Deflection Device During TAVI; EPD, embolic protection devices; ITT, Intention to treat; MISTRAL-C, MRI Investigation in TAVI With Claret; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; N/A, Not applicable; NIHSS, National Institutes of Health Stroke Scale; PROTAVI-C, Prospective Randomized Outcome Study in Patients Undergoing TAVI to Examine Cerebral Ischemia and Bleeding Complications.

Clinical Outcomes at 30-Day Follow-Up

The EPD delivery success rate was reported in all studies and was achieved in 94.5% of patients, ranging from 64% to 100%. All-cause mortality occurred in 1.9% of the patients treated with the use of an EPD; 2.8% in patients without. The incidence of stroke was 4.8% in patients treated with the use of EPD and 6% in patients without the use of EPD.

The use of EPD was not associated with significant differences in terms of 30-day mortality (OR 0.43 [0.18–1.05], P=0.3).

The use of EPD was associated with a lower rate of 30-day stroke (OR 0.55 [0.31–0.98], P=0.04), with this result driven by the registry of Seeger et al (Figure 2). The number needed to treat to save 1 stroke was 33. No differences were detected when restricting the analysis to randomized controlled trials (Figure 3).

We recalculated all the outcomes by means of a fixed-effect model. The results were consistent with those obtained with the random effect: 30-day mortality OR 0.44 (0.19–1.00), P=0.05 and 30-day stroke (OR 0.53 [0.31–0.92], P=0.03). We opted to present the data with the random effect in order to provide more conservative and reliable results.

DW-MRI Assessment

The overall incidence of new lesions was 88%: 86% in patients with the use of EPD and 91% in patients without EPD. The total volume of lesions was 88 to 466 mm^3 in patients with EPD and 168 to 800 mm^3 in patients without EPD. The meta-analysis showed no differences in terms of number of new lesions: (standardized mean difference −0.19 [−0.71 to 0.34]; P=0.49). On the other hand, the use of EPD was associated with a significantly smaller volume per lesion (standardized mean difference, −0.52 [−0.85 to −0.20]; P=0.002) and smaller total volume of lesions (standardized mean difference, −0.23 [−0.42 to −0.03], P=0.02) (Figure 4). In registry studies, the use of EPD seemed detrimental with respect to the number of new lesions (Figure 4A). The analysis according to the type of valve showed that the beneficial effect of the EPD is mainly driven by the benefit in patients treated with a self-expanding valve (Figure 5).

Neurocognitive Assessment

Patients were assessed by the Montreal Cognitive Assessment before and after TAVI in 2 studies,[15–17] and the proportion of patients with EPD showing worsening neurocognitive function ranged from 10.7% to 27.3% and from 22.7% to 33.3% in patients without EPD. Three studies[17,19,20] used the National Institutes of Health Stroke Scale, and the proportion of patients with EPD showing worsening neurocognitive function ranged from 0% to 17.9% and from 4.5% to 22.5% in patients without EPD. The Mini-Mental State Examination was used in 1 study[15] and did not show differences between EPD versus without EPD strategies (Table 2).

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Table 3. Risk of Bias Assessed for Randomized Studies Using ACROBAT and for Nonrandomized Studies of Intervention Using the ACROBAT-NRSI[13]

Randomized Controlled Trials							
	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessors	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias
Lansky et al[16]	Unclear (inadequate description)	Unclear (unclear concealment)	Unclear (inadequate description)	Low (outcome assessors were blinded)	Unclear (missing data were handled by a modified ITT with a high rate of loss to follow-up)	Unclear (cannot be ruled out)	Unclear (funding source was acknowledged)
Wendt et al[17]	Low (computer-generated scheme)	Low (appropriate allocation concealment)	Unclear (inadequate description)	Unclear (inadequate description)	Unclear (inadequate description)	Unclear (cannot be ruled out)	Unclear (stopped early, not because of data-dependent process)
Van Mieghem et al; MISTRAL-C[19]	Unclear (inadequate description)	Unclear (unclear concealment)	Low (double-blind)	Low (outcome assessors were blinded)	Unclear (missing data were handled by ITT with a high rate of loss to follow-up)	Unclear (cannot be ruled out)	Unclear (funding source was acknowledged)
Haussig et al; CLEAN-TAVI[20]	Unclear (inadequate description)	Low (appropriate allocation concealment)	Low (double-blind)	Low (outcome assessors were blinded)	Low (missing data were handled by a modified ITT with a high rate of loss to follow-up)	Unclear (cannot be ruled out)	Unclear (funding source was acknowledged)
Kapadia et al; SENTINEL[21]	Unclear (inadequate description)	Unclear (unclear concealment)	Low (double-blind)	Low (outcome assessors were blinded)	Low (performed ITT)	Unclear (cannot be ruled out)	Unclear (funding source was acknowledged)

Nonrandomized Comparative Studies							
	Pre-Intervention		At Intervention	Postintervention			
	Bias Because of Confounding	Bias in Selection of Participants Into the Study	Bias in Measurement of Interventions	Bias Because of Departures From Intended	Bias Because of Missing Data	Bias in Measurement of Outcome	Bias in Selection of the Reported Results
Rodés-Cabau et al; PROTAVI-C pilot study[15]	Moderate (adjustment for confounder not reported)	Low (multiple centers, a representative sample)	Low (prospective recording of data)	Moderate (no contamination nor co-interventions reported)	Moderate (imbalance in proportion of missing across groups)	Moderate (blinding of outcome assessors not reported)	Moderate (all outcomes reported
Samim et al; DEFLECT II Pilot Study[18]	Moderate (adjustment for confounder not reported)	Moderate (single center and potential selection bias)	Moderate (retrospectively comparing to the control with an inadequate description of confounding adjustment)	Moderate (no contamination nor co-interventions reported)	Moderate (unclear missing data)	Low (blinding of outcome assessors was reported)	Moderate (all outcomes reported)
Seeger et al[22]	Low-to-moderate (Propensity Score done)	Low-to-moderate (Propensity Score done)	Low (adequate description of confounding adjustment)	Moderate (no contamination nor co-interventions reported)	Low (no missing data)	Moderate (blinding of outcome assessors not reported)	High (only 2 outcomes reported)

ACROBAT indicates A Cochrane Collaboration Risk of Bias Tool; ACROBAT-NRSI, A Cochrane Collaboration Risk of Bias Tool-non Randomised studies; ITT, Intention to treat; CLEAN-TAVI, Claret Embolic Protection and TAVI; DEFLECT II, A Study to Evaluate the Safety and Performance of the TriGuard HDH in Patients Undergoing TAVR; MISTRAL-C, MRI Investigation in TAVI With Claret; PROTAVI-C, Prospective Randomized Outcome Study in Patients Undergoing TAVI to Examine Cerebral Ischemia and Bleeding Complications.

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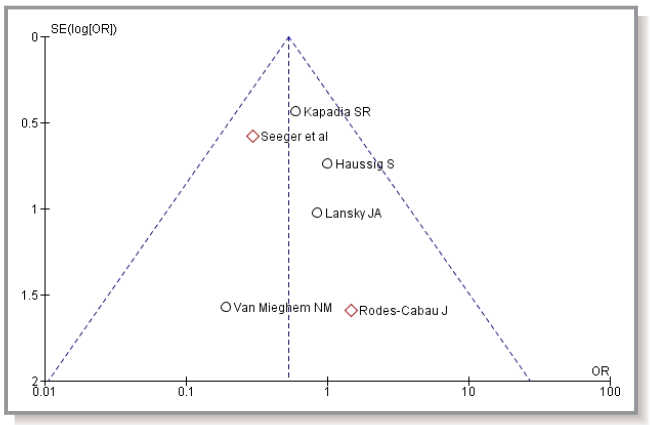

Figure 2. Funnel plot of included studies according to the rate of stroke. OR indicates odds ratio; SE, standard error.

Discussion

The results of the present meta-analysis can be summarized as follows:

1. The use of EPD during TAVI is not associated with reduced mortality.
2. The use of EPD during TAVI is associated with a lower rate of 30-day stroke: This result is driven by study registries and is not confirmed when considering randomized controlled trials separately.
3. The use of EPD during TAVI is not associated with a reduced rate of new lesions as assessed by MRI.
4. The use of EPD during TAVI is associated with a smaller volume of single lesions and smaller total volume of lesions.

Of note, all these point estimates are affected by very large confidence intervals, meaning that any conclusive statement would be rather inappropriate from a methodological point of view.

The issue of cerebrovascular complications in the context of the TAVI procedure is well known since the first reports, and it was confirmed by the major randomized trials that compared TAVI versus surgery in high- and moderate-risk patients.[1–6] These trials focused on the rate of "clinically relevant" cerebrovascular accidents and obviously prompted the ideation and introduction of EPD currently in use or under investigation.

On the other hand, the availability of these devices spurred the cardiological community to increase the use of MRI to assess patients after TAVI, thus leading to the publication of several randomized studies and/or registries specifically focusing on cerebral embolic protection.[15–21] All these studies, regardless of the design, arterial access, type of prosthesis, and the EPD, consistently showed that the rate of silent new ischemic cerebral lesions (as high as 80%) is much higher than the rate of clinically relevant cerebrovascular events (2–6%).[22] Long-term consequences of these lesions are still unclear, but increasing evidence suggests that they represent silent brain infarctions that could be related to memory loss, cognitive decline, and dementia.[23]

Of note, the evaluation of the neurocognitive function before and after TAVI can be challenging because it is critically affected by hemodynamic status and comorbidities; thus, the large set of tests usually implemented can be misleading and cause fatigue in the patients. As such, neurocognitive assessment would clearly benefit from a simplified and standardized approach that is lacking. Moreover, the timing of this evaluation is still controversial, as evident from the included studies (Table 2).

Our data suggest that the use of a self-expandable transcatheter bioprosthesis is possibly associated with a larger number and volume of brain lesions. This is possibly a consequence of the different technique and manipulation; specifically, the duration of the deployment could conceivably affect the amount of debris navigating from the aortic root.

The majority of available data come from studies that used 1.5-T MRI scanners while the MISTRAL-C (MRI Investigation in TAVI With Claret), CLEAN-TAVI (Claret Embolic Protection and TAVI), and SENTINEL used 3-T MRI scanners, although 11 patients in the CLEAN-TAVI underwent MRI in a 1.5-T scanner because of pacemaker dependency. Thus, particularly small emboli might have been missed with a 1.5-T MRI scanner, while the use of a 3-T MRI scanner may have led to an overestimation of the lesions. This issue, along with different MRI windows (up to 7 days after TAVI) determines a certain degree of heterogeneity in the detected volumes of ischemic lesions, given the time-dependent sensitivity of DW-MRI.

A further source of heterogeneity in the interpretation of the data comes from the different EPDs. As such, the double-filter technology (the SENTINEL actually covers only 9 of 28 brain regions because of the dual blood supply of the posterior circulation) conceivably appears less effective as compared with the deflection technique of the TriGuard or Embrella devices, which are theoretically able to provide complete protection. On the other hand, although in a study registry with propensity-matched population, the SENTINEL devices were the only ones associated with a positive impact on stroke and mortality.[22]

There is no direct comparison between different EPDs; however, it is likely that no device can be completely protective against embolic material, and protection obviously depends on the position and stability of the device as well as the patient's anatomy. Of note, the positioning of the EPD itself can cause embolic debris. The manipulation of these devices, in terms of ease of use, fluoroscopy time, contrast media, and possible disturbance to the navigation of the

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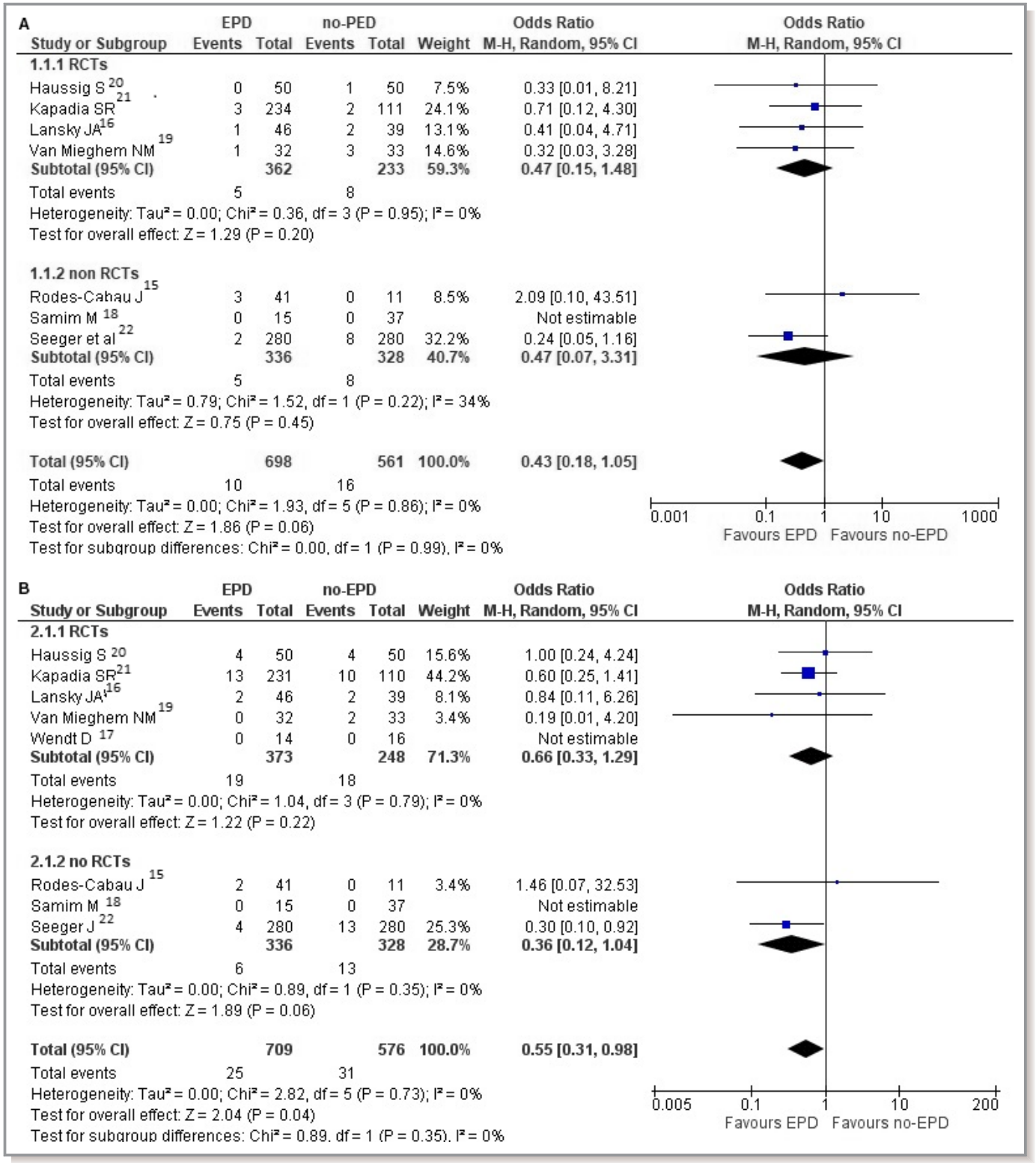

Figure 3. Meta-analysis of included studies with respect to 30-day all-cause mortality (A) and 30-day stroke (B). CI indicates confidence interval; EPD, embolic protection devices.

prosthesis in particular for transfemoral devices, is associated with a specific learning curve and it is impossible to make a thorough comparison.

The issue of cerebral embolization while treating aortic valve stenosis is not exclusive to the transcatheter approach. Indeed, new cerebral ischemic lesions were reported in the

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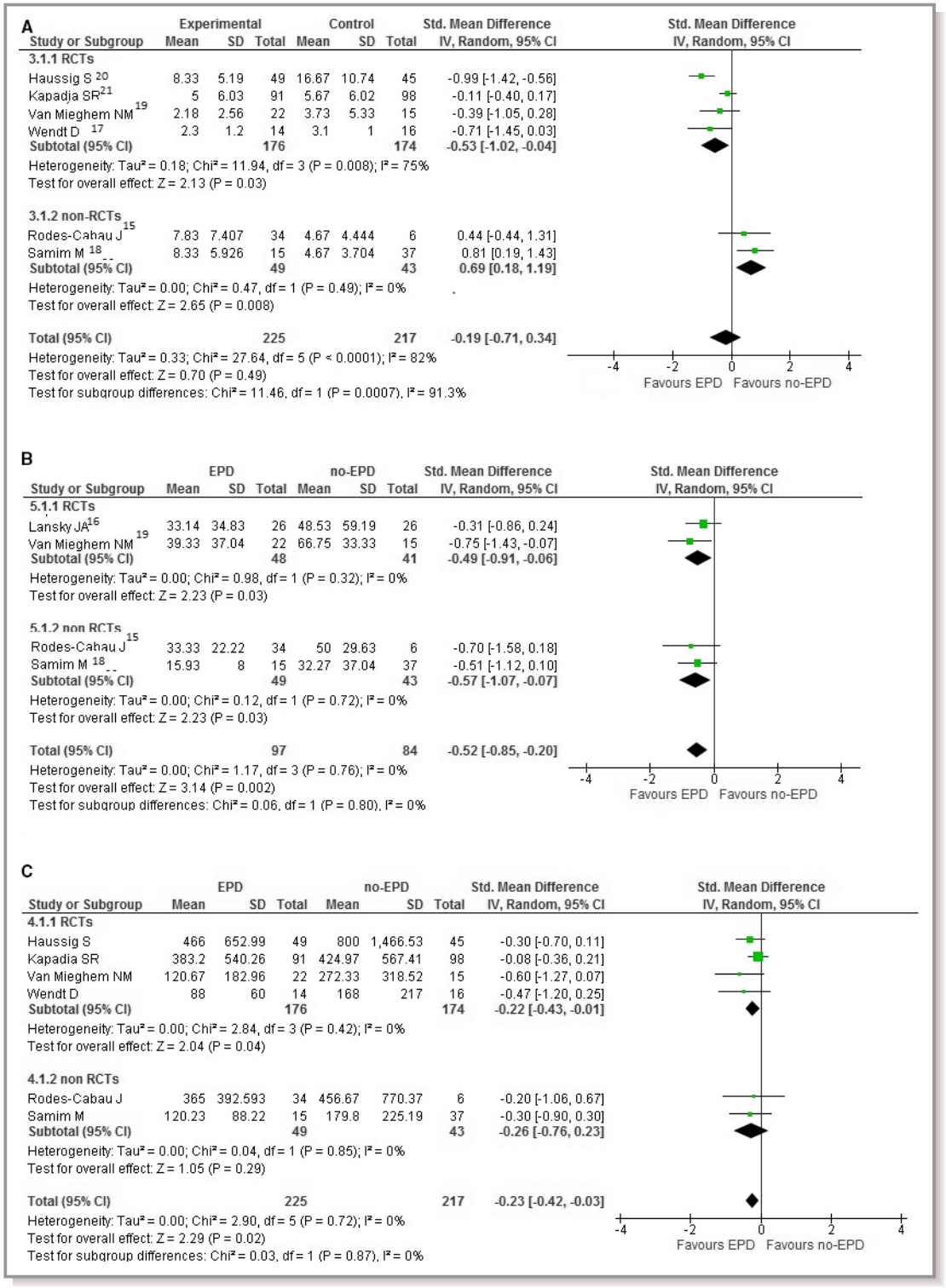

Figure 4. Meta-analysis of included studies with respect to the number of new lesions per patient (A); the volume per lesion (B), and the total volume of lesions per patient (C). CI indicates confidence interval; EPD, embolic protection devices; RCTs, randomized controlled trials.

surgical setting in up to 60% of patients: Lesions were often multiple and clinically silent.[24–28] One study suggested that they were of a smaller volume when compared with TAVI.[7,28]

Currently, the magnitude of this phenomenon is evident and the research in this field must proceed towards a robust demonstration of a "clinical" benefit from the reduction in

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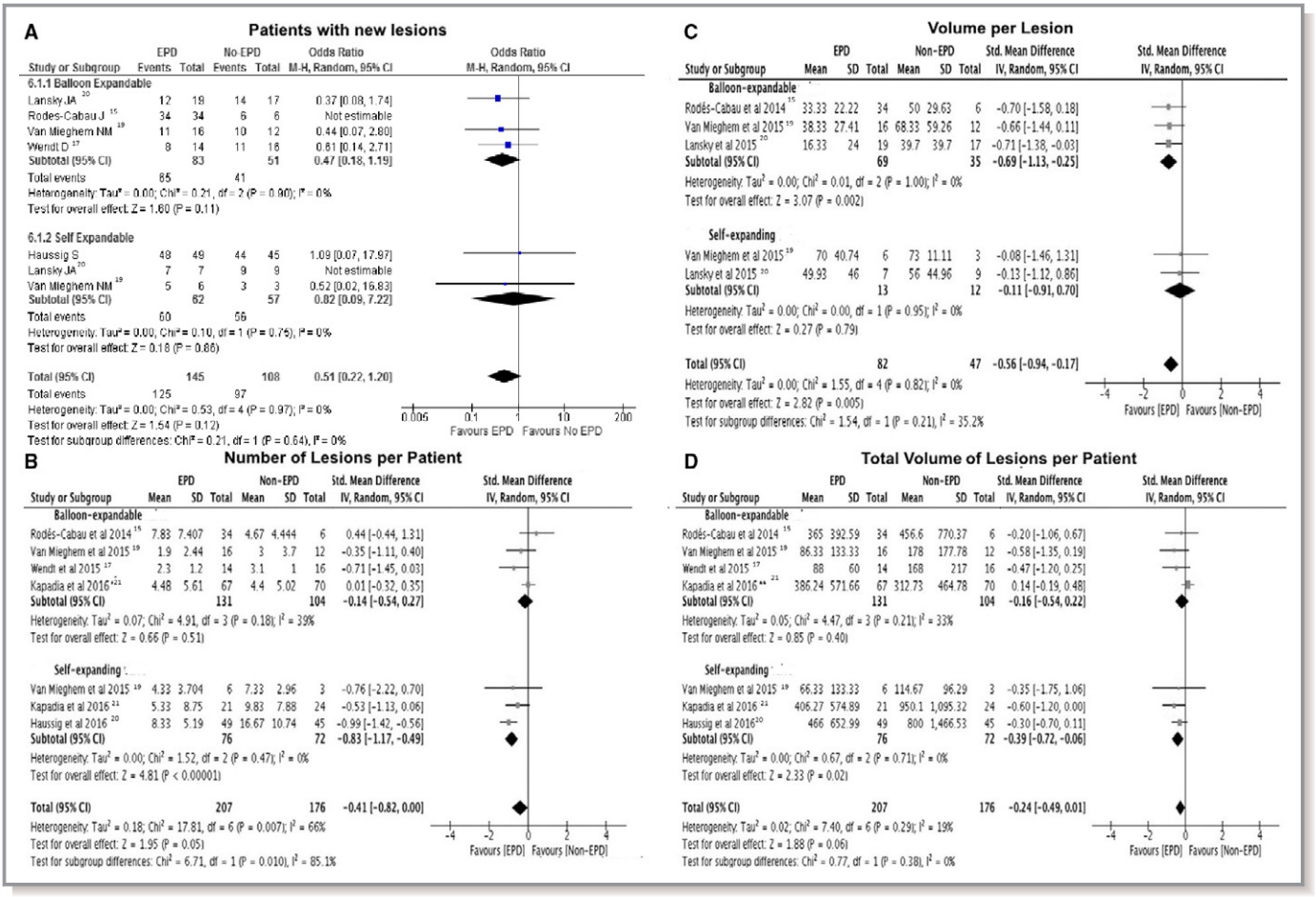

Figure 5. Meta-analysis of included studies, according to the type of transcatheter bioprosthesis, with respect to the number of new lesions per patient (A), the number of lesions per patient (B), the volume per lesion (C), and the total volume of lesions per patient (D). CI indicates confidence interval; EPD, embolic protection devices.

number and volume of ischemic cerebral lesions. Ideally, this benefit should be evident from large randomized controlled trials and appreciable at both short and long term (ie, an EPD should be able to reduce the rate of stroke in the periprocedural period [as suggested by the propensity-matched population analyzed at 7-day follow-up by Seeger et al[22]]) as well as to minimize the neurocognitive impairment after TAVI. Both issues are becoming even more crucial considering that TAVI is shifting towards younger and lower-risk patients.

Limitations

The main limitation of this meta-analysis comes from the small number and the quality of the studies. Patient-level data were not available, thus precluding any adjustments for possible confounders, and the wide confidence intervals make any conclusive statement possibly unreliable. Other sources of heterogeneity relate to the type of EPD, type of MRI scanner adopted, the timing of DW-MRI, and neurocognitive assessment.

Conclusions

The use of an EPD in the setting of TAVI is not associated with a reduction in the rate of overall mortality. The use of EPD, although according to evidence coming from a single nonrandomized study, seems able to reduce the rate of stroke.

The number of new ischemic cerebral lesions seems unaffected by the use of an EPD. However, the use of an EPD is associated with smaller volume of ischemic lesions, smaller total volume of ischemic lesions, and better neurocognitive parameters at follow-up. Available evidence is of low quality.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

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Data S1.



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

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