Silent Brain Infarcts Following Cardiac Procedures: A Systematic Review and Meta-Analysis

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Background—Silent brain infarcts (SBI) are increasingly being recognized as an important complication of cardiac procedures as well as a potential surrogate marker for studies on brain injury. The extent of subclinical brain injury is poorly defined.

Methods and Results—We conducted a systematic review and meta-analysis utilizing studies of SBIs and focal neurologic deficits following cardiac procedures. Our final analysis included 42 studies with 49 separate intervention groups for a total of 2632 patients. The prevalence of SBIs following transcatheter aortic valve implantation was 0.71 (95% CI 0.64-0.77); following aortic valve replacement 0.44 (95% CI 0.31-0.57); in a mixed cardiothoracic surgery group 0.39 (95% CI 0.28-0.49); coronary artery bypass graft 0.25 (95% CI 0.15-0.35); percutaneous coronary intervention 0.14 (95% CI 0.10-0.19); and off-pump coronary artery bypass 0.14 (0.00-0.58). The risk ratio of focal neurologic deficits to SBI in aortic valve replacement was 0.22 (95% CI 0.15-0.32); in off-pump coronary artery bypass 0.21 (95% CI 0.02-2.04); with mixed cardiothoracic surgery 0.15 (95% CI 0.07-0.33); coronary artery bypass graft 0.10 (95% CI 0.05-0.18); transcatheter aortic valve implantation 0.10 (95% CI 0.07-0.14); and percutaneous coronary intervention 0.06 (95% CI 0.03-0.14). The mean number of SBIs per patient was significantly higher in the transcatheter aortic valve implantation group (4.58 ± 2.09) compared with both the aortic valve replacement group (2.16 ± 1.62, P=0.03) and the percutaneous coronary intervention group (1.88 ± 1.02, P=0.03).

Conclusions—SBIs are a very common complication following cardiac procedures, particularly those involving the aortic valve. The high frequency of SBIs compared with strokes highlights the importance of recording this surrogate measure in cardiac interventional studies. We suggest that further work is required to standardize reporting in order to facilitate the use of SBIs as a routine outcome measure. (***J Am Heart Assoc***. 2019;8:e010920. DOI: 10.1161/JAHA.118.010920.)

Key Words: cardiac surgery • magnetic resonance imaging • silent brain infarction • transapical aortic valve implantation

Stroke after cardiac surgery is one of the most devastating outcomes for both patients and doctors. It is considered one of the most significant complications perioperatively, but the risk of clinically evident stroke remains low. In conventional coronary artery bypass graft (CABG) the rate of stroke approaches 2%, whereas in anaortic off-pump coronary artery bypass (OPCAB), the rate has been reported at less than

0.4%.[1] For aortic valve replacement procedures, stroke rates are higher, recently reported as 5.1% for surgical aortic valve replacement (AVR) and 5.3% in transcatheter aortic valve implantation (TAVI).[2] There is, however, significant variability related to the risk level of individual study populations.[3]

Acute brain injury after cardiac surgery exists on a broad spectrum ranging from major stroke to subclinical brain injury, which includes postoperative cognitive dysfunction (POCD) and silent brain infarcts (SBI). SBIs are clinically silent, radiologically diagnosed infarcts, and although they can be defined by a number of magnetic resonance imaging (MRI) sequences, density-weighted imaging (DWI) is the preferred technique due to its ability to demonstrate small ischemic lesions as bright hyperintensities that are evident within a few hours of onset of ischemia and generally disappear within 14 days.[4,5]

Although the initial insult is clinically silent, SBIs have been linked to significant morbidity. The risk of subsequent stroke has been shown to increase more than 5 times when SBIs are present,[6] which may simply reflect associated undescribed risk

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Clinical Perspective

What Is New?

- Silent brain infarcts are strongly associated with cardiac procedures, particularly those involving the aortic valve.

What Are the Clinical Implications?

- Silent brain infarcts present as a potentially important surrogate marker for brain injury in studies of cardiac procedures.

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factors or possibly indicate an associated reduced threshold for further cerebral ischemic injury. Additional associated sequelae include cognitive dysfunction, increased risk of dementia,[7] psychiatric disturbances,[8] and reduced quality of life.

Subtle POCD has been a known but poorly defined complication of cardiac procedures, and although an association with SBIs has been hypothesized, the evidence to date is inconclusive, with conflicting data presented across a number of relatively small studies.[9] A difficulty faced in quantifying the true incidence of POCD and SBI is the wide variation in both the definitions used for POCD and the radiological diagnostic techniques used to measure SBIs, respectively.[10,11]

SBIs may have a role as a tool to measure brain injury post–cardiac surgery as the incidence of SBIs postoperatively is far greater than that of overt stroke.[9] SBIs may therefore have a role as a standard outcome measure in cardiovascular interventional trials. The purpose of this systematic study and meta-analysis was: (1) to report the prevalence of SBI following common cardiac procedures using standardized criteria, with prevalence defined as the proportion of this postoperative population who are noted to have DWI evidence of SBIs within the first 14 days; (2) to evaluate the effect of procedural and patient-related risk factors; (3) to test if SBI frequency is proportionally related to the incidence of postoperative stroke, thus adding weight to the use of SBI as a more sensitive marker for procedure-related brain injury; and (4) to assess the association between POCD and SBIs.

Methods

The authors declare that all supporting data are available within the article.

Search Strategy

Electronic databases PubMed and Google Scholar were searched for relevant studies. Search terms included "cardiac surgery," "cardiac surgical procedures," "coronary artery bypass," "aortic valve," "replantation," "transcatheter aortic valve replacement," "percutaneous coronary intervention,"

"silent," "brain infarction," "DWI lesions," "magnetic resonance imaging," and "brain injury." Reference lists of appropriate studies were also examined for relevant literature.

Inclusion Criteria

Studies were included that specifically utilized DWI in the early postoperative period following cardiac procedures to assess for acute cerebral ischemic lesions. Inclusion criteria included (1) DWI following open cardiac surgical procedures (CABG, OPCAB, AVR, mitral valve repair (MVR), and mixed procedures), TAVI, and percutaneous coronary intervention (PCI); (2) MRI performed within 14 days of the procedure; (3) assessment for focal neurologic deficits indicating stroke or transient ischemic attack (TIA), performed postoperatively; (4) age >18 years; and (5) English language studies.

Of the included studies, only patients who had postoperative DWI imaging were included in the analysis.

Studies comparing the use of embolic protection devices during TAVI were excluded, as were studies utilizing other imaging techniques such as susceptibility-weighted MRI or gradient-echo MRI.

Data Extraction

Extraction included first author and first author/corresponding author's institution to avoid the potential of including a single cohort twice. Data points included baseline characteristics, total number of patients scanned, total number of patients with new postoperative SBIs, number of SBIs per patient, and early postoperative focal neurologic deficit. When reported, the volume of individual lesions and the total lesion load per patient were collected. Neurocognitive testing and subsequent results were also included to assess for a potential correlation between imaging findings and neurocognitive decline.

Statistical Analyses

For studies that reported data as median and range,[12-18] a technique described by Hozo et al[19] was utilized to calculate an estimate of the mean and SD. For data reported as median and IQR,[20,21] the mean and SD were estimated according to calculations per Luo et al[22] and Wan et al,[23] respectively. For comparison of means 1-way ANOVA was performed with post hoc Tukey honestly significant difference (HSD) utilized for specific significance values reported. SPSS v23 (IBM, Armonk, NY) and interactive statistics[24] were used for descriptive statistics and comparison of means.

A meta-analysis of prevalence was performed for both SBI and focal neurologic deficits (FND) in addition to a meta-analysis estimating the risk ratio between SBI and FND. Both were performed on the Microsoft Excel plug-in, MetaXL (www.epigear.com; Sunrise Beach, Queensland, Australia). Because the multiple procedural groups in our analysis displayed a high

heterogeneity, the inverse variance heterogeneity estimate was utilized. This method of meta-analysis has been proposed as a replacement for the random effects method due to its ability to more accurately estimate statistical error and to provide more valid CIs.[25] Publication bias is demonstrated by Funnel plots.

Author B.I. had full access to the collected study data and takes responsibility for data integrity and integrity of the data analysis. The requirement for informed consent by subjects was waived for this study type.

Results

A total of 902 studies were initially identified, from which 42 studies were included in this analysis (Figure 1). These comprised 49 separate intervention groups: 7 AVR, 9 CABG, 2 OPCAB, 5 mixed cardiothoracic surgery (CTSx; studies that did not differentiate among CABG, AVR, mitral valve repair, Tricuspid valve repair, and combined valve replacement and coronary artery bypass procedures), 16 TAVI, and 10 PCI. Taken together they accounted for a total of 2632 patients, of whom 951 patients were identified to have new postoperative SBI, and 67 patients were found to have an early postoperative FND.

All included studies were prospective cohort studies and used DWI to identify new cerebral ischemic lesions (Table 1).[26–33] Imaging was performed within the first 14 postoperative days in all patients, with the majority of patients being scanned within the first postoperative week. Thirty-one studies were performed with 1.5T MRI, and 4 studies with 3T MRI; 7 studies did not report on the MRI magnetic field strength.

Baseline characteristics of each procedural group are demonstrated in Table 2. The TAVI group was significantly older than all other groups, as was the AVR group (with the exception of the TAVI group being older still). The mean age of patients with new postoperative DWI lesions was older than those without, although this difference was nonsignificant (71.94 $\pm$ 7.27 years versus 66.51 $\pm$ 9.48 years, P=0.08).

Prevalence of preexisting atrial fibrillation was significantly higher in the TAVI group as compared with the CABG group (37.17% versus 5.81%, P=0.05); however, only 2 CABG study groups reported on the presence of preexisting atrial fibrillation. Diabetes mellitus was more common in the PCI group as compared with the mixed CTSx group (45.31% versus 4.4%, P=0.02). The proportion male was significantly less in the TAVI group as compared with the CABG, OPCAB, and PCI groups (49.97% versus 79.60%, P≤0.01; 49.97% versus 78.37%, P=0.03; 49.97% versus 70.3%, P≤0.01, respectively). No other significant differences in baseline characteristics were identified among groups.

The pooled postoperative prevalence rate of SBIs in the early postoperative period is shown in Figure 2. Rates of new postoperative SBIs varied from 0.14 (95% CI 0.0-0.58) for the OPCAB group to 0.71 (95% CI 0.64-0.77) for the TAVI group. The pooled postoperative prevalence of stroke varied from 0.00 (95% CI 0.00-0.001) for PCI, to 0.09 (95% CI 0.03-0.16) for AVR (Figure 3).

The funnel plots for the pooled prevalence meta-analysis of SBIs are shown in Figure 4, and that for the pooled prevalence meta-analysis of FNDs is shown in Figure 5. Funnel plots were not utilized for the OPCAB group because only 2 studies were included.

Of the patients with new postoperative DWI lesions, the mean number of lesions was 3.38 $\pm$ 2.01 per patient across all procedural groups (Table 3). There was a statistically significant difference in mean lesion size among groups as determined by 1-way ANOVA (F[4,30] = 4.473, P=0.006). The results of the post hoc Tukey HSD are demonstrated in Table 3.

TAVI patients had significantly more lesions than AVR (4.58 $\pm$ 2.09 versus 2.16 $\pm$ 1.62, P=0.03) and PCI patients (4.58 $\pm$ 2.09 versus 1.88 $\pm$ 1.02, P=0.03). The mean volume of individual SBI lesions was reported in only 9 studies with a mean single-lesion size of 114 mm^3 (range 24-760 mm^3). The mean volume of total SBI lesion load per patient was also reported in only 9 studies with a mean volume of 1585.87 mm^3 (range 132-8830 mm^3). Of the 9 studies reporting individual lesion volume and total lesion load per patient, 6 were TAVI, 1 CABG, 1 AVR, and 1 mixed CTSx.

In the meta-analysis (Figure 6) comparing the risk ratio of FND to SBI, the overall risk ratio was 0.13 (95% CI 0.11-0.16) across all procedures. There was a significant difference between the risk ratio for AVR and that for PCI (risk ratio 0.22, 95% CI 0.15-0.32 versus 0.06, 95% CI 0.03-0.14; P=0.02). Of the other procedural groups, the risk ratio for CABG was 0.10 (95% CI 0.05-0.18), TAVI 0.10 (95% CI 0.07-0.14), and mixed CTSx 0.15 (95% CI 0.07-0.33). There were no other significant differences in risk ratios among these groups.

The funnel plots for the meta-analysis assessing the risk ratio of FND to SBIs are shown in Figure 7. Again funnel plots were not utilized for the OPCAB group because only 2 studies are included.

A total of 13 studies reported on a variable array of clinical neurocognitive measures pre- and postoperatively to assess for correlation with DWI lesions (Table 4). Only 3 studies[37,46,47] utilized all 4 core neuropsychological tests (Rey auditory verbal learning test, trail-making A, trail-making B, and grooved-pegboard test) as recommended in a previously published consensus statement of POCD after cardiac surgery.[59] All studies performed preoperative cognitive testing at baseline, but only 8 studies performed postoperative testing at least 3 months following the operation.
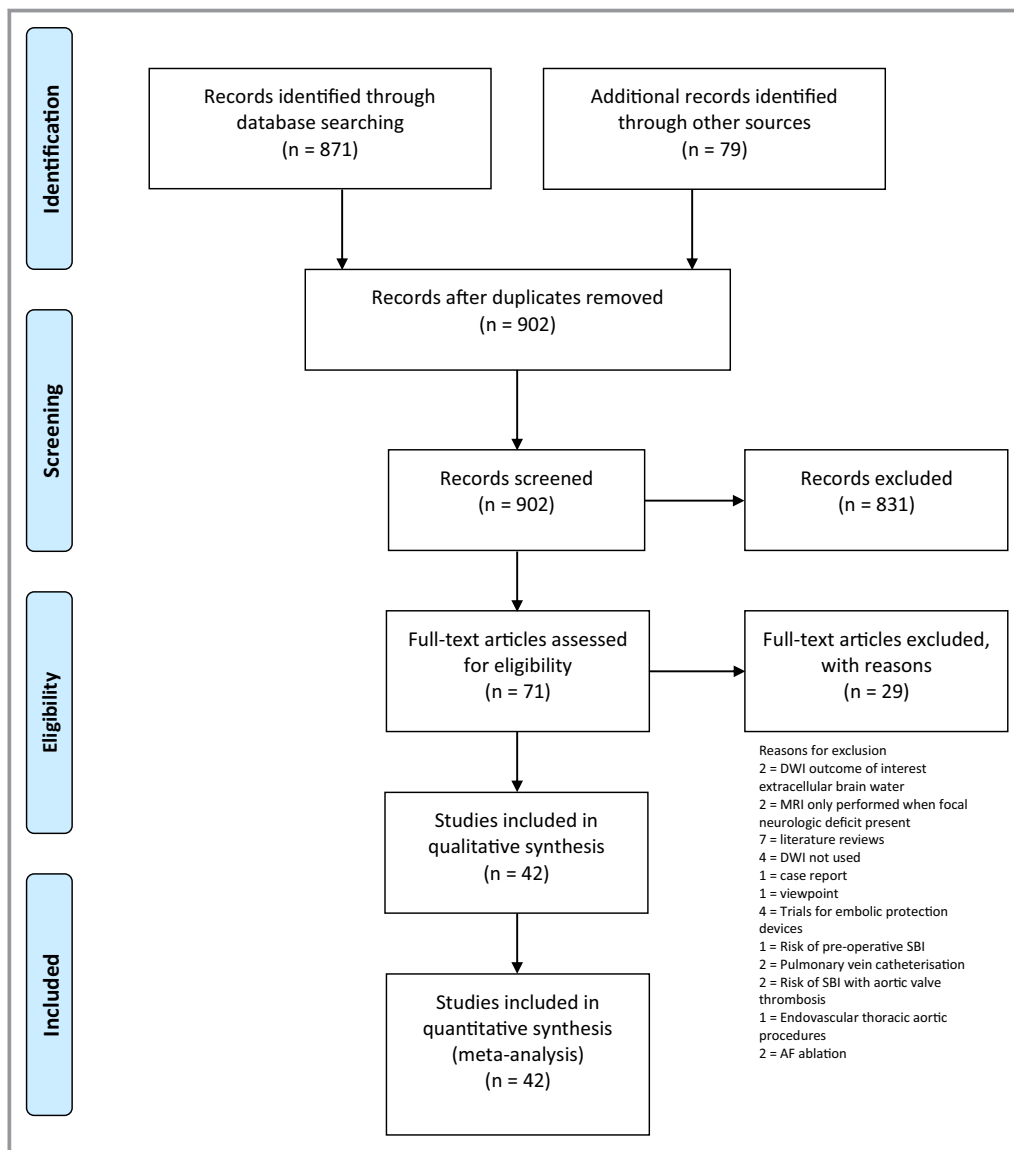
Figure 1. PRISMA flow diagram. AF indicates atrial fibrillation; DWI, density-weighted imaging; MRI, magnetic resonance imaging; SBI, silent brain infarct.

Knipp et al (2004)[52] demonstrated a significant decline in the verbal learning test (p=0.012) at 3 months post-CABG, however this was not correlated to the presence of new SBI. Similarly, in another study of CABG patients, this same group demonstrated a 23% decline in cognitive function after 3 months, not correlated to new SBIs.[52] Gerriets et al[56] demonstrated a significant correlation between SBIs and cognitive decline in the attention domain at postoperative days 2 to 4, and although there was a decline in verbal and visual memory at 3 months, this was not correlated to new SBIs. Barber et al[47] demonstrated a significant association to postperative cognitive decline and the presence of post-operative SBIs at 6 weeks following AVR (OR 37.49 95% CI 4.01–350.18), with an additional association shown between the ischemic burden and the degree of cognitive dysfunction.

In a study of both CABG and PCI by Schwarz et al,[15] the presence of postoperative SBI was correlated with a reduced performance in verbal and visual memory at 3 months. Two studies[12,49] did not demonstrate the presence of POCD at 3 months postoperatively. Although Lund et al[37] demonstrated a significant association between SBI and POCD following left heart catheterization, this was demonstrated only in the first postoperative day.

Discussion

Brain injury associated with cardiac surgery exists on a spectrum from clinically overt stroke and TIA to subtle POCD and SBI. The latter 2 categories have been shown to occur at much higher rates than the former ones, and although not as

Table 1. Included Study Characteristics

Author	Year	Procedure	Institution	Country	Study Design	No. Participants (Postoperative MRI)	SBI	FND	MRI Strength	MRI Follow-Up (Postoperative Day)
Kahlert[13]	2010	TAVI	University hospital, Essen	Germany	Prospective cohort compared with retrospective cohort	32	27	0	1.5T	2 to 5
Ghanem[14]	2010	TAVI	University of Bonn	Germany	Prospective cohort	22	16	2	1.5T	2.2±0.4
Arnold[26]	2010	TAVI	University Hospital Erlangen	Germany	Prospective cohort	25	17	2	1.5T	6±2
Rodés-Cabau[27]	2011	TAVI	Laval University	Canada	Prospective cohort	60	41	2	1.5T	4±1
Astarci[28] (group 1)	2011	TAVI	University Hospital Saint-Luc	Belgium	Prospective cohort	35	32	0	3T	2 to 5
Fairbarin[29]	2012	TAVI	University of Leeds	UK	Prospective cohort	31	24	2	1.5T	5±1.55
Ghanem[30]	2012	TAVI	University of Bonn	Germany	Prospective cohort	39	28	4	1.5T	3±1
Ghanem[16]	2013	TAVI	University of Bonn	Germany	Prospective cohort	56	36	0	1.5T	3±1
Alassar[12] (group 2)	2015	TAVI	St Georges Hospital, London	UK	Prospective cohort	62	47	1	NA	6
Samim[31]	2015	TAVI	University medical centre, Utrecht	The Netherlands	Prospective cohort	42	38	1	3T	1 to 5
Uddin[17] (group 2)	2015	TAVI	University of Leeds	UK	Prospective cohort	70	54	2	1.5T	1 to 7
Altisent[18] (group 2)	2016	TAVI	Universitat Autònoma de Barcelona	Spain	Prospective cohort	40	18	0	1.5T	6.5±3.5
Lansky[20]	2016	TAVI	Yale University School of Medicine	USA	Prospective cohort	34	32	8	NA	4±2
Fanning[21]	2016	TAVI	The Prince Charles Hospital	Australia	Prospective cohort	30	18	1	1.5T	3±1
Ghanem[32]	2017	TAVI	University Hospital Bonn	Germany	Prospective cohort	27	17	0	NA	1 to 3
Knipp[33]	2013	TAVI	University Hospital, Essen	Germany	Prospective cohort	28	7	0	1.5T	Predischarge
Hamon[34]	2007	PCI	University Hospital of Caen	France	Prospective cohort	41	2	0	1.5T	1
Murai[35]	2008	PCI	Osaka Medical College	Japan	Prospective cohort	101	26	0	3T	3±1
Schwarz[15] (Group 1)	2011	PCI	Justus Liebig University Giessen	Germany	Prospective cohort	75	1	0	1.5T	2 to 4
Deveci[36]	2016	PCI	Cukurova University	Turkey	Prospective cohort	30	12	0	1.5T	1
Lund[37]	2005	PCI	Rikshospitalet University Hospital	Norway	Prospective cohort	42	5	1	1.5T	1
Busing[38]	2005	PCI	University Hospital Mannheim	Germany	Prospective cohort	48	7	0	1.5T	1 to 2
Ohi[39]	2013	PCI	Gifu Uni versity Graduate School of Medicine	Japan	Prospective cohort	111	20	0	1.5T	1 to 7
Hamon[40]	2012	PCI	University Hospital of Caen	France	Prospective cohort	160	24	2	1.5T	1 to 2
Kim[41]	2012	PCI	University of Ulsan College of Medicine	Republic of Korea	Retrospective cohort	272	45	0	NA	1 to 7
Kim[42]	2011	PCI	Keimyung University Dongsan Medical Center	Republic of Korea	Prospective cohort	197	20	0	3T	1 to 1

Continued

Table 1. Continued

Author	Year	Procedure	Institution	Country	Study Design	No. Participants (Postoperative MRI)	SBI	FND	MRI Strength	MRI Follow-Up (Postoperative Day)
Friday[43]	2005	OPCAB	Lankenau Hospital	USA	Prospective cohort	16	5	0	1.5T	4 to 14
Djaiani[44] (group 2)	2006	OPCAB	University of Toronto	Canada	Case-control	13	0	0	NA	3 to 7
Folyd[45] (group 2)	2006	Mixed CTSx	Hospital of the University of Pennsylvania	USA	Prospective cohort	34	0	0	1.5T	6±2
Cook[46]	2007	Mixed CTSx	Hospital of the University of Pennsylvania	USA	Prospective cohort	50	16	4	1.5T	4.5±1.5
Barber[47]	2008	Mixed CTSx	University of Auckland	New Zealand	Prospective cohort	36	15	1	1.5T	1 to 5
Knipp[48]	2017	Mixed CTSx	University hospital, Essen	Germany	Prospective cohort compared with retrospective cohort	36	19	0	1.5T	Predischarge
Knipp[49]	2005	Mixed CTSx	University Clinic of Essen	Germany	Prospective cohort	30	14	0	1.5T	5.0±1.4
Bendszus[50]	2002	CABG	University of Wurzburg	Germany	Prospective cohort	35	9	0	1.5T	3
Restrepo[51]	2002	CABG	Johns Hopkins	USA	Prospective cohort	13	4	1	NA	4±1.6
Knipp[52]	2004	CABG	University Hospital, Essen	Germany	Prospective cohort	29	13	0	1.5T	Predischarge
Djaiani[53]	2004	CABG	Toronto General Hospital	Canada	Prospective cohort	50	8	1	NA	3 to 7
Djaiani[44] (group 1)	2006	CABG	University of Toronto	Canada	Case-control	13	8	1	NA	3 to 7
Knipp[54]	2008	CABG	University clinic of Essen	Germany	Prospective cohort	39	20	0	1.5T	Predischarge
Schwarz[15] (group 2)	2011	CABG	Justus Liebig University Giessen	Germany	Prospective cohort	39	7	0	1.5T	2 to 4
Nah[55]	2014	CABG	University of Ulsan College of Medicine	South Korea	Prospective cohort	127	35	4	1.5T	3
Gerriets[56]	2010	CABG	Justus Liebig University Giessen	Germany	Prospective cohort	86	13	0	1.5T	1 to 3
Stolz[57]	2004	AVR	Kerckhoff Klinik	Germany	Prospective cohort		14	3	NA	1 to 6
Folyd[45] (group 1)	2006	AVR	Hospital of the University of Pennsylvania	USA	Prospective cohort	37	6	2	1.5T	6±2
Astarci[28] (group 2)	2011	AVR	University Hospital Saint-Luc	Belgium	Prospective cohort	13	1	0	3T	2 to 5
Alassar[12] (Group 1)	2015	AVR	St Georges Hospital, London	UK	Prospective cohort	32	23	1	NA	6
Uddin[17] (group 1)	2015	AVR	University of Leeds	UK	Prospective cohort	38	17	1	1.5T	1 to 7
Altisent[18] (group 1)	2016	AVR	Universitat Autònoma de Barcelona	Spain	Prospective cohort	27	11	0	1.5T	9±3
Messe[58]	2015	AVR	Hospital of the University of Pennsylvania	USA	Prospective cohort	129	79	20	1.5T	6.35±2.25

AVR indicates aortic valve replacement; CABG, coronary artery bypass graft; FND, focal neurological deficit; Mixed CTSx, mixed cardiothoracic surgical group; MRI, magnetic resonance imaging; NA, not available; OPCAB, off-pump coronary artery bypass; PCI, percutaneous coronary intervention; SBI, silent brain infarct; TAVI, transcatheter aortic valve implantation.

Table 2. Baseline Characteristics

	1. CABG	2. OPCAB	3. AVR	4. TAVI	5. Mixed CTSx	6. PCI	P-Value														
							1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6	2 vs 3	2 vs 4	2 vs 5	2 vs 6	3 vs 4	3 vs 5	3 vs 6	4 vs 5	4 vs 6	5 vs 6
Age, y	65.51±8.06	70.3±6.4	70.76±9.31	81.76±5.76	66.44±10.54	67.13±9.8	0.05	<0.01	<0.01	0.84	0.02	>0.99	0.00	0.23	0.39	<0.01	<0.01	<0.01	<0.01	<0.01	0.92
Male, %	79.6	78.37	62.76	49.97	69.61	70.3	>0.99	0.24	<0.01	0.74	0.06	0.62	0.03	0.95	0.83	0.41	0.96	0.99	0.06	0.03	>0.99
Smoking, %	42.9	12.5	36.6	21.91	44.41	41.17	NR	0.99	0.35	>0.99	>0.99	NR	NR	NR	NR	0.82	0.99	>0.99	0.37	0.26	>0.99
HTN, %	75.25	68.27	71.93	79.5	52.6	57.6	>0.99	>0.99	>0.99	0.45	0.52	>0.99	0.97	0.93	0.98	0.99	0.76	0.87	0.19	0.18	>0.99
Prior CVA, %	9.36	12.5	11.23	19.78	11.18	9.75	NR	0.53	>0.99	>0.99	>0.99	NR	NR	NR	NR	0.7	>0.99	>0.99	0.56	0.19	>0.99
Diabetes mellitus, %	34.72	40.38	22.37	28.77	14.4	35.18	0.98	0.53	0.86	0.44	>0.99	0.94	0.68	0.06	0.99	0.93	0.9	0.44	0.19	0.76	0.02
Cholesterol, %	65	67.31	62.75	63.54	52.19	45.31	>0.99	>0.99	>0.99	0.98	0.75	>0.99	>0.99	0.98	0.87	>0.99	>0.99	0.91	0.98	0.67	>0.99
Preexisting AF, %	5.81	NA	21.93	37.17	24.75	16.62	NR	0.71	0.05	0.49	0.86	NR	NR	NR	NR	0.56	>0.99	0.99	0.6	0.11	0.91

AF indicates atrial fibrillation; AVR, aortic valve replacement; CABG, coronary artery bypass graft; CVA, cerebrovascular accident; HTN, hypertension; Mixed CTSx, mixed cardiothoracic surgical group; NA, not available; OPCAB, off-pump coronary artery bypass; PCI, percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation.

acutely catastrophic for patients, they can significantly reduce quality of life and predispose to longer-term neurologic dysfunction. The importance of these subtle brain injuries is 2-fold: they are a significant surgical complication that, combined, may affect more than 50% of patients postoperatively with long-term consequences, and they present an important outcome measure for studies of neuroprotective techniques due to high rates of occurrence.

This systematic review and meta-analysis primarily reports on pooled prevalence rates of early postoperative SBIs and FND following common cardiac surgical and interventional procedures.

In our study the early postoperative stroke/TIA rates are in line with commonly reported figures for procedural groups, although the AVR group rate of 9% was higher than expected. This finding could be traced back to a specific AVR study that had been included, which reported a stroke rate of 17%[58] and carried a weighting of 44% in the meta-analysis. Excluding this study from the analysis resulted in the prevalence rate of FND following AVR decreasing to 5%.

There is significant variability in the postoperative prevalence rate of SBIs with regard to the procedural group. The TAVI and AVR groups report the highest rates, 74% and 58%, respectively, demonstrating that SBIs are very common following procedures involving the aortic valve and manipulation of the aorta. This is in accordance with the suspected etiology of SBIs being in part due to microemboli as a result of direct disruption of atherosclerotic plaque in the ascending aorta. Increased levels of proximal thoracic aortic atheroma have been shown to be associated with higher rates of intraoperative cerebral embolism as evident on transcranial Doppler and higher rates of SBIs postoperatively following AVR.[53] TAVI presents a particularly high-risk procedure for embolism due to a number of factors. Most studies to date have focused on high-risk surgical populations with severe aortic stenosis. This population is thus likely to have increased proximal aortic atherosclerosis beause this is well correlated with the amount of aortic valve calcium and stenosis severity.[60] For TAVI, the intra-aortic catheter and in-situ valve expansion inside calcific aortic valves pose individual risks for embolic phenomenon.[61]

With this considered, it can be seen why neurologic injury has been the Achilles heel of TAVI to date, with the high rate of embolic events mostly limiting its application in clinical practice to either inoperable or high–surgical risk patients.[61]

The PARTNER trial reported an increased rate of stroke postoperatively and at 1 year for TAVI as compared with AVR.[62] When all neurologic injuries (stroke and TIA combined) were compared, there was a further separation in the rate of reported neurologic injury between TAVI and AVR at 1 year (8.7% versus 4.3%, respectively) and 2 years (11.2% versus 6.5%, respectively).[63] More recent studies, likely due to the advent of newer-generation devices and more collective
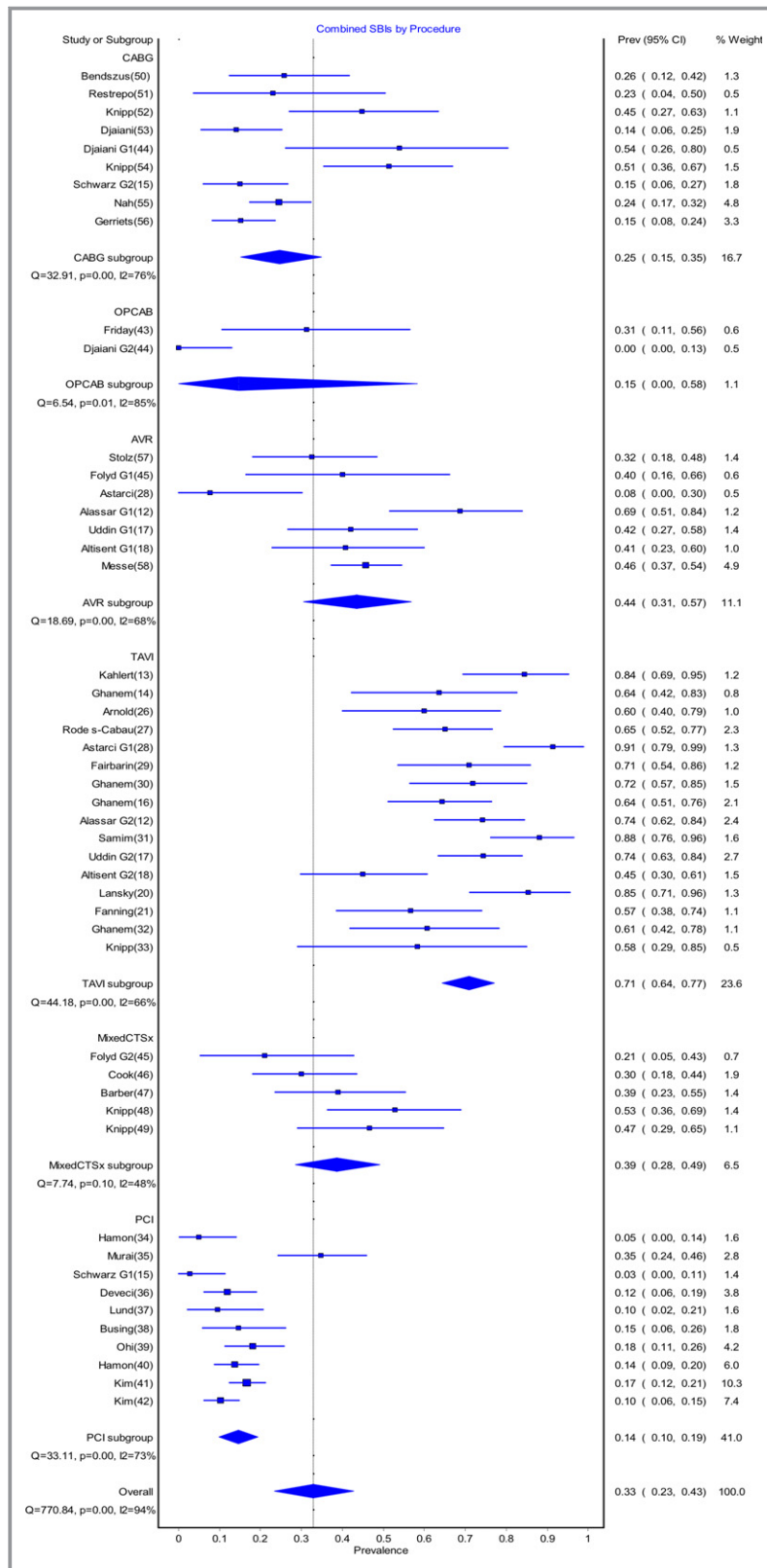
Figure 2. Pooled prevalence of silent brain infacts (SBIs) post–cardiac proce-dures. AVR indicates aortic valve replacement; CABG, coronary artery bypass graft; MixedCTSx, mixed cardiothoracic surgical group; OPCAB, off-pump coronary artery bypass; PCI, percutaneous coronary intervention; Prev, prevalence; TAVI, tran-scatheter aortic valve implantation.
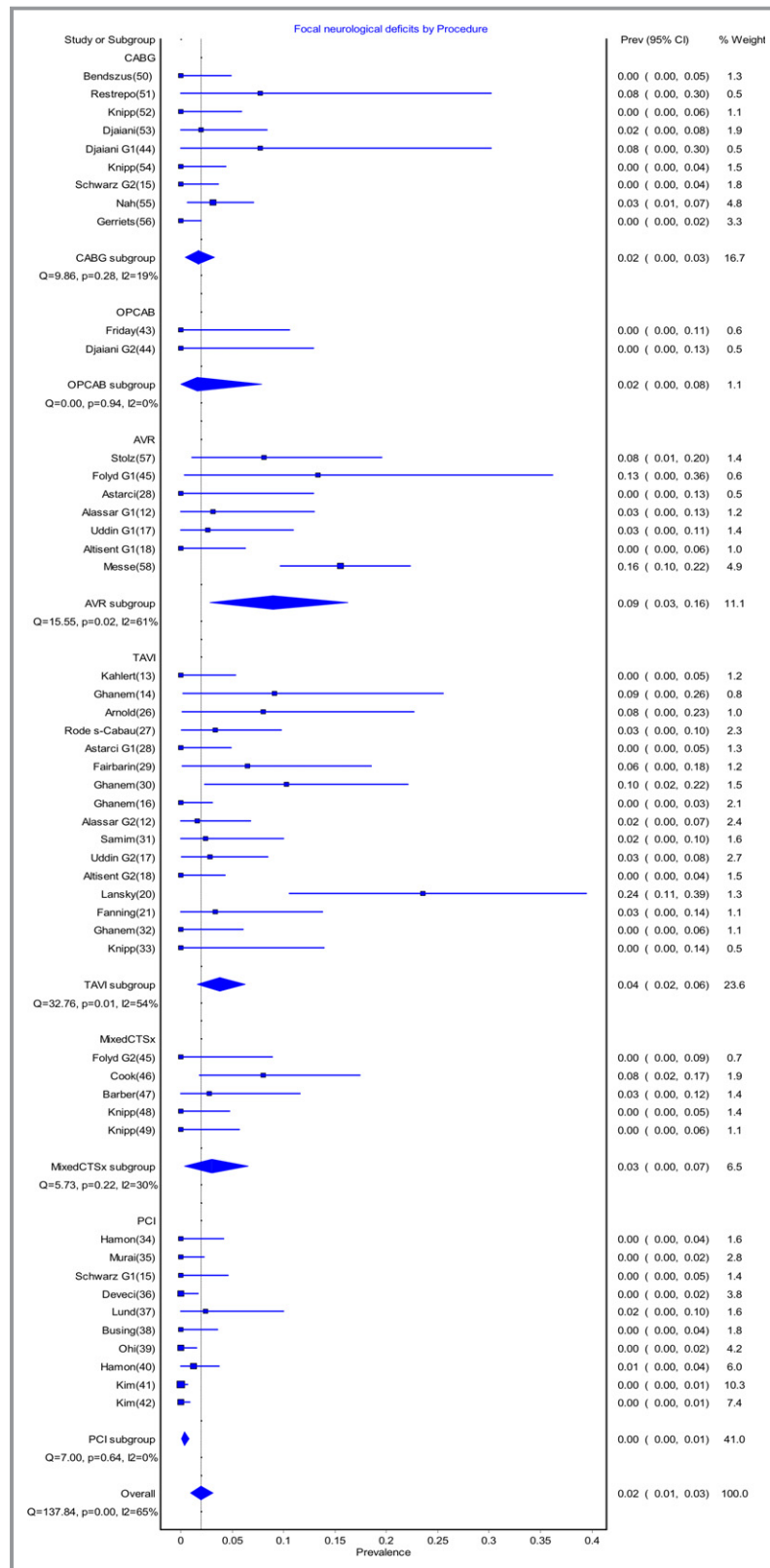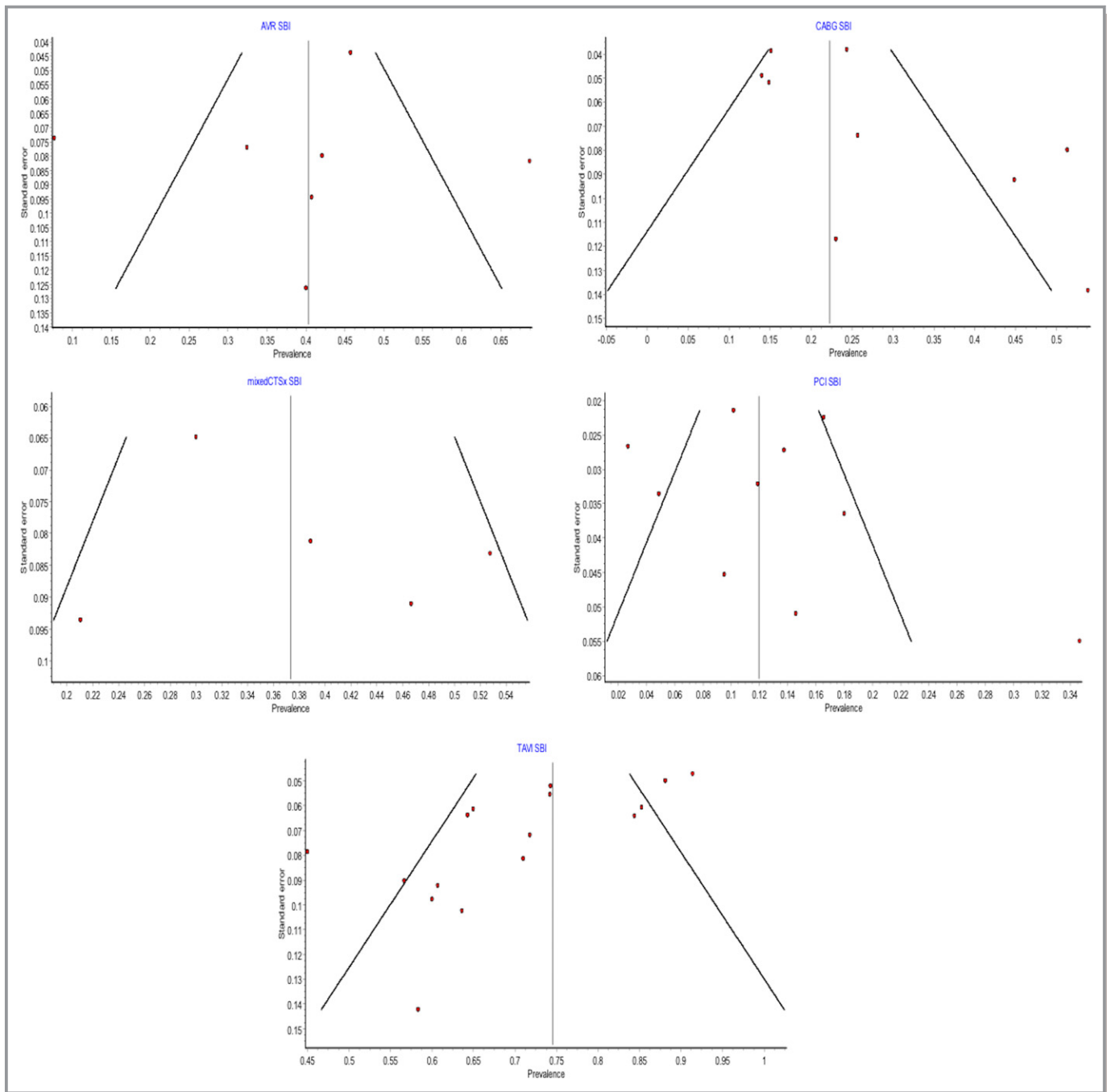
Figure 3. Pooled prevalence of focal neurologic deficits post–cardiac procedures. AVR indicates aortic valve replacement; CABG, coronary artery bypass graft; Mixed CTSx, mixed cardiothoracic surgical group; OPCAB, off-pump coronary artery bypass; PCI, percutaneous coronary intervention; Prev, prevalence; TAVI, transcatheter aortic valve implantation.

Figure 4. Funnel plots assessing interstudy bias for pooled prevalence of silent brain infarcts. AVR indicates aortic valve replacement; CABG, coronary artery bypass graft; mixedCTSx, mixed cardiothoracic surgical group; PCI, percutaneous coronary intervention; SBI, silent brain infarct; TAVI, transcatheter aortic valve implantation.

procedural experience report similar rates of perioperative stroke between these interventions[64]; however, the rates of SBIs remain significantly higher following TAVI. We hypothesize this may increase the vulnerability of this population to medium- and long-term stroke and TIA. Although the majority of clinically overt neurologic injuries occur within the first 30 days of TAVI, there is evidence of an ongoing stroke and TIA risk long term.[61]

For the mixed CTSx group, which consisted of a mixture of CABG only, valve only, or simultaneous valve and CABG operations, the prevalence rate of SBIs of 36% may reflect the decreased risk of cerebral embolism seen in the coronary artery bypass operations because they involve less manipulation of the ascending aorta. Moreover, prevalence of SBIs fell further for isolated CABG (26%), OPCAB (14%), and PCI (15%). This is supported by evidence that anaortic OPCAB, in
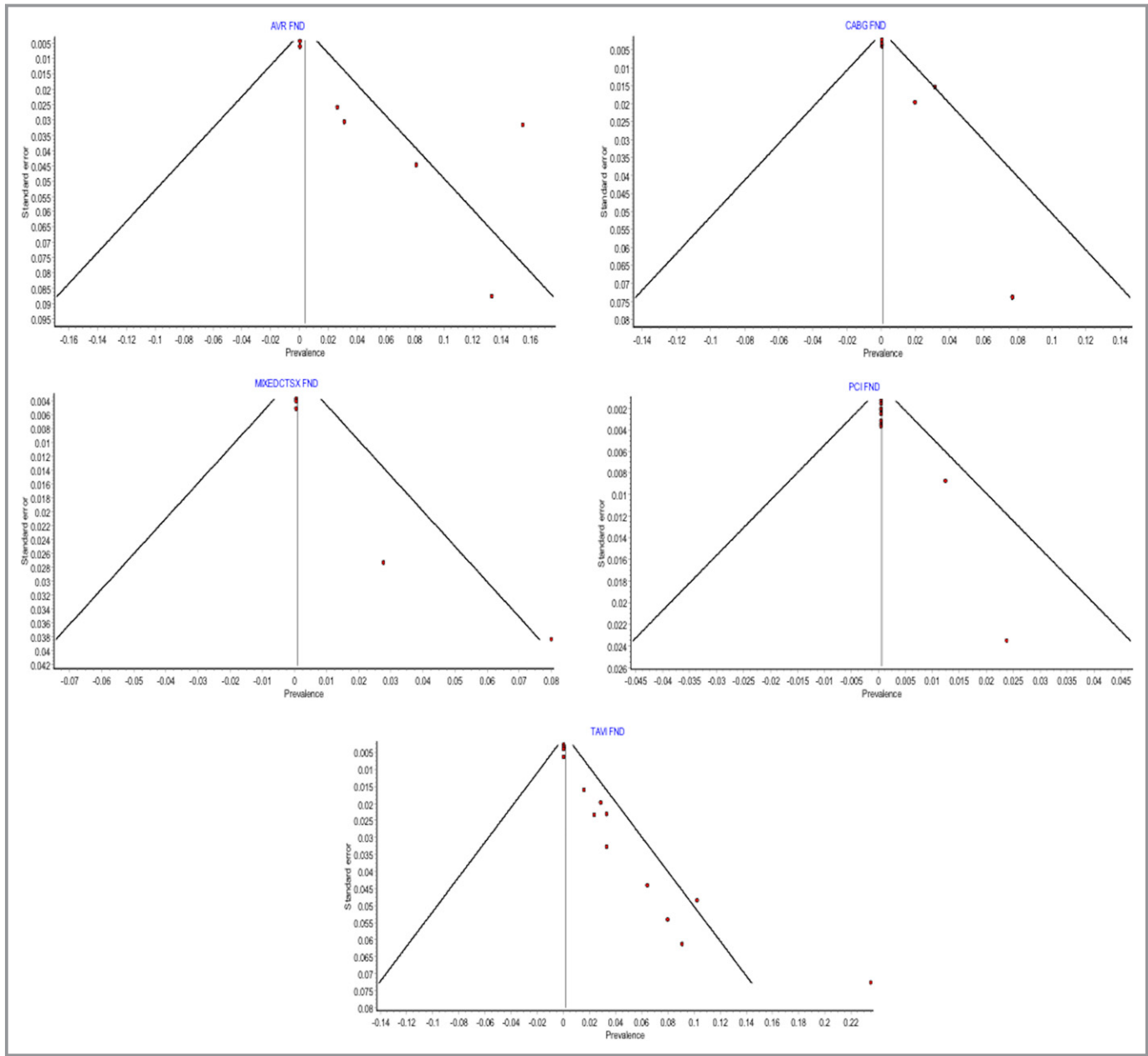
Figure 5. Funnel plots assessing interstudy bias for pooled prevalence of focal neurologic deficits. AVR indicates aortic valve replacement; CABG, coronary artery bypass graft; FND, focal neurologic deficits; MIXEDCTSX, mixed cardiothoracic surgical group; PCI, percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation.

which there is no manipulation or cross-clamping of the aorta, reduces the rates of clinically overt neurologic injury as compared with conventional CABG.[65] In this analysis only 2 studies reporting on OPCAB were available, and neither was performed with the anaortic technique.[43,44] Further studies are required to evaluate the risk of SBIs in anaortic OPCAB as compared with techniques involving clamping of the aorta or cardiopulmonary bypass.

Although the stroke rate following PCI has been shown to be negligible, the rate of SBI that we report remains not insignificant at 15%. The main mechanism is again thought to relate to atheroma disruption by guide wires in the ascending aorta resulting in cerebral embolism.[66] Subsequently, procedural time is a predictor of SBI risk in this population.[38]

SBIs have been shown to occur at significantly higher rates than strokes or TIAs, which has resulted in their becoming a potential surrogate measure of brain injury associated with cardiac procedures. Obtaining adequate statistical power remains a challenge in trials studying postoperative stroke and TIA due to low rates of occurrence. This is highlighted by

Table 3. Mean Number of SBIs Per Patient for Procedural Groups

Procedural Group	Number of SBIs (Mean±SD)	P-Value				
		AVR	CABG	Mixed CTSx	PCI	TAVI
AVR	2.16±1.62	···	>0.99	0.77	>0.99	0.09
CABG	2.11±0.25	>0.99	···	0.82	>0.99	0.88
Mixed CTSx	3.38±0.72	0.77	0.82	···	0.67	0.7
PCI	1.88±1.02	>0.99	>0.99	0.67	···	0.33
TAVI	4.58±2.09	0.03	0.09	0.7	0.03	···
Total	3.38±2.01	···	···	···	···	···

AVR indicates aortic valve replacement; CABG, coronary artery bypass graft; Mixed CTSx, mixed cardiothoracic surgical group; PCI, percutaneous coronary intervention; SBI, silent brain infarct; TAVI, transcatheter aortic valve implantation.

Aggarwal et al,[67] who performed a large registry trial that included more than 700 000 patients and evaluated the incidence and risk of stroke following PCI. They reported a stroke rate of 0.22%—an event rate too low for the data to be utilized in developing a predictive model.

This can be further highlighted by calculating the sample size that would be required of a hypothetical cohort study to compare the risk of brain injury associated with traditional CABG versus anaortic OPCAB. Data from a network meta-analysis recently published by 1 of our authors (M.P.V.) showed the rate of stroke following CABG to be 1.8% versus 0.4% for anaortic OPCAB.[65] With these stroke rates, a randomized controlled trial comparing these techniques would require a total sample size of 1744, with a power of 80% and an absolute error of 5%. Maintaining these parameters but changing the outcome measure to SBI—utilizing a hypothetical rate of SBI for anaortic OPCAB of 10% and our reported SBI rate in CABG of 25%— would require the total sample size to be 200.

The overall stroke-to-SBI risk ratio for cardiac procedures we report of 0.13 is similar to that previously reported by Cho et al,[68] who report an overall risk ratio of 0.10 for cardiac procedures and cerebral angiography combined. Although the only significant difference in risk ratio was between AVR and PCI, the trend was toward a higher risk ratio for more invasive open surgical valve procedures, which made up the majority of the mixed CTSx group. Although they are useful as a guide to demonstrate some consistency between the occurrence of stroke and SBI, these rates do not take into account the number or size of DWI lesions.

Unfortunately, at present the utility of SBIs as a common outcome measure for surgical brain injury is limited by the current variability in definition and reporting. Of the 927 patients with SBI postoperatively, in only 427 patients were the actual number of lesions reported. Furthermore, the volume of individual lesions and/or the total lesion load was
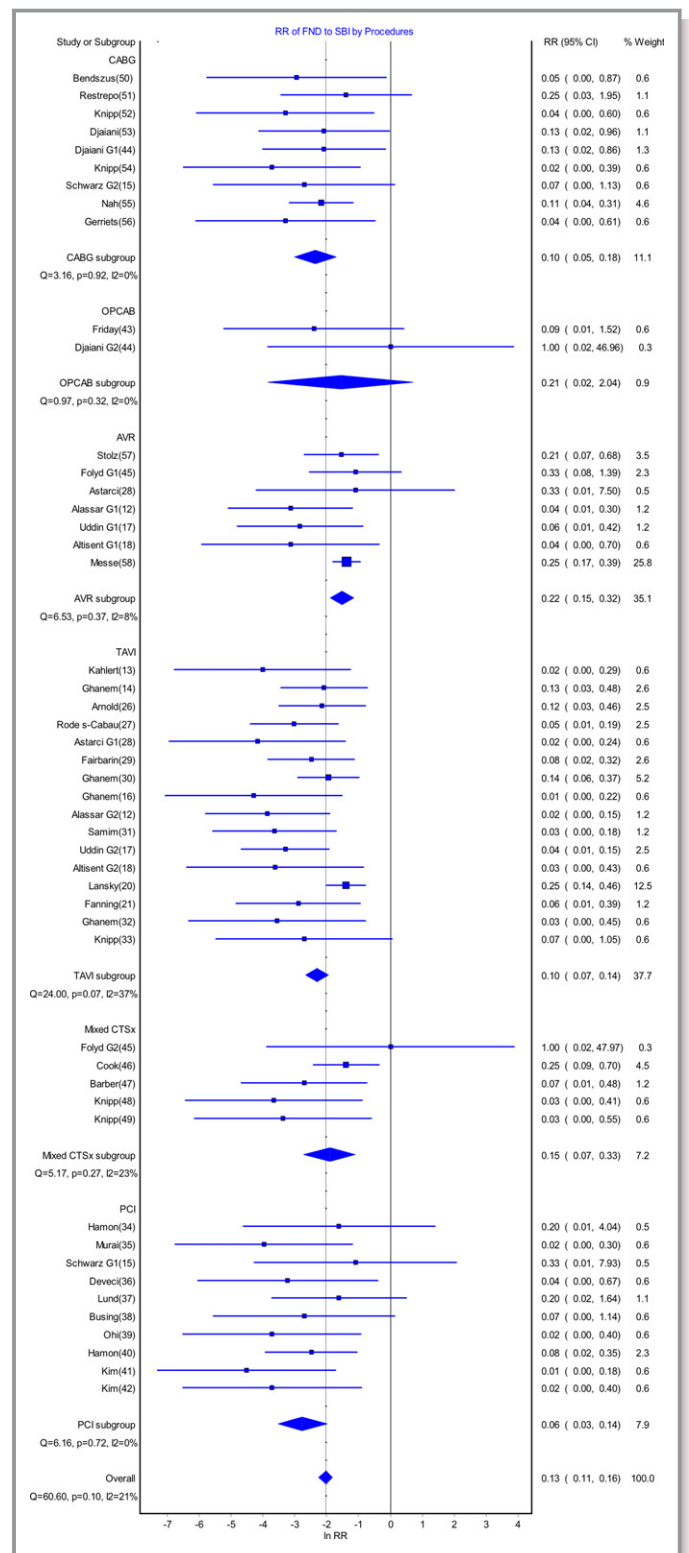

Figure 6. Meta-analysis demonstrating risk ratio of focal neurologic deficits (FNDs) to silent brain infarcts (SBIs) for cardiac procedures. AVR indicates aortic valve replacement; CABG, coronary artery bypass graft; Mixed CTSx, mixed cardiothoracic surgical group; OPCAB, off-pump coronary artery bypass; PCI, percutaneous coronary intervention; RR, risk ratio; TAVI, transcatheter aortic valve implantation.
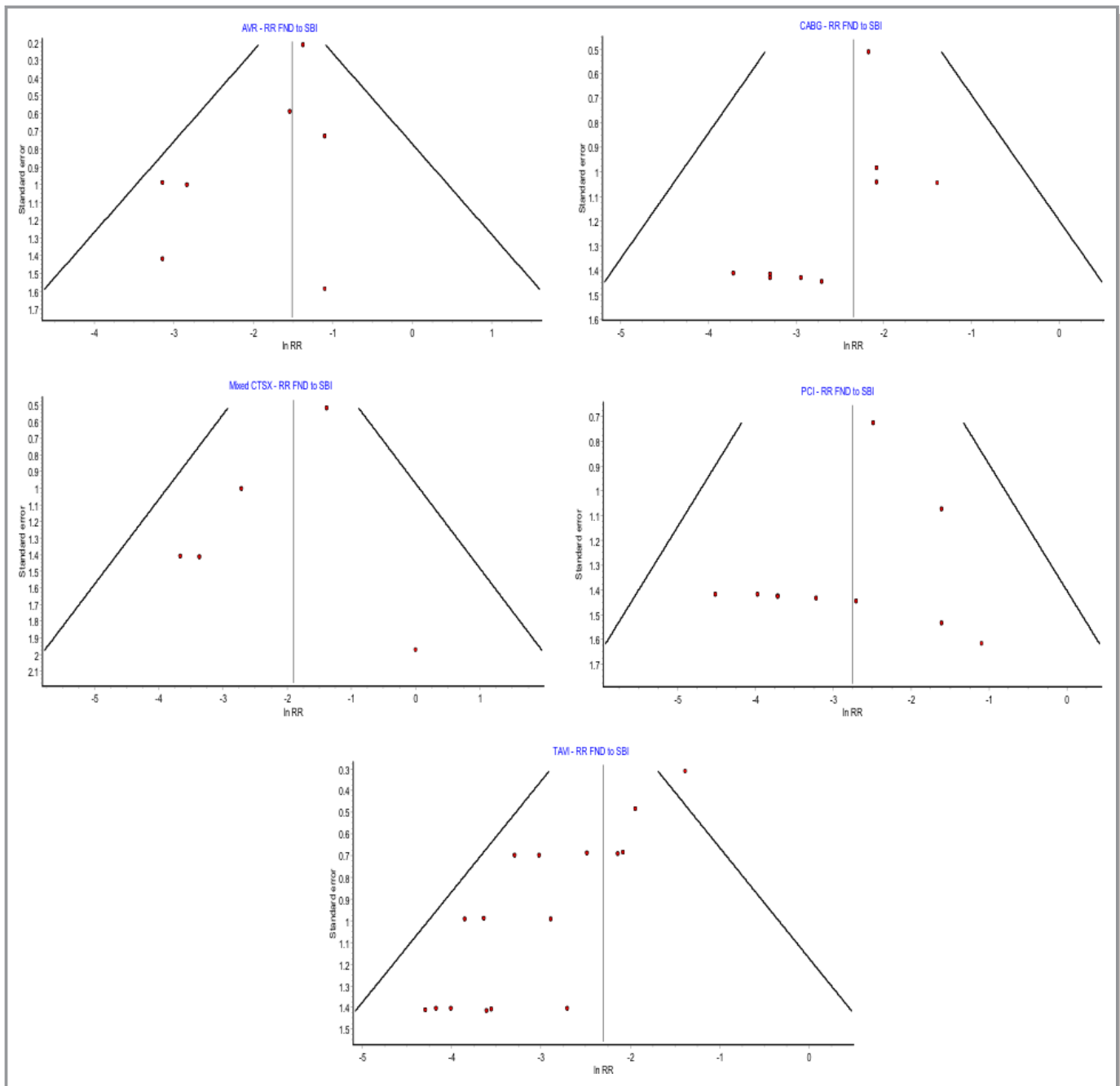
Figure 7. Funnel plots assessing interstudy bias meta-analysis comparing risk ratio of focal neurologic deficits (FNDs) to silent brain infarcts (SBIs). AVR indicates aortic valve replacement; CABG, coronary artery bypass graft; Mixed CTSX, mixed cardiothoracic surgical group; PCI, percutaneous coronary intervention; RR, risk ratio; TAVI, transcatheter aortic valve implantation.

only reported in 9 studies. The size and number of SBIs are likely to be important factors in determining the increased patient risk of future neurologic complications. In patients with acute ischemic stroke, DWI lesion volume in the middle cerebral artery territory has been shown to correlate with higher scores in the National Institutes of Health Stroke Scale[69] as well as with poorer long-term outcomes and increased risk of hemorrhagic transformation.[70] More closely

related, severe strokes have been associated with the presence of multiple coexisting SBIs.[71] Therefore, merely stating the presence of post-procedural SBIs gives little indication of the extent of neurologic injury sustained.

For SBIs to be utilized as a surrogate measure of brain injury, the number, volume, and locations of lesions should be reported. Additionally, the application of specific imaging criteria of SBIs, as has previously been suggested,[72] would

Table 4. Summary of Reported Cognitive Testing Batteries for Postoperative Cognitive Dysfunction and Association With SBIs

Study	Neurocognitive Domains Tested	Timing of Testing	Cognitive Decline	Association Between DWI Lesions and POCD
Bendszus (2002)[50]	1. Day-2 letter cancellation test 2. Benton visual retention test, instruction A 3. Trail-making test A* 4. Block design test from WAIS	1. Preoperatively 2. Postoperative days 3, 6, 9	Yes but no details given	Nil
Knipp (2004)[52]	1. Trail-making test A and B* 2. Zimmerman divided attention test 3. Wechsler Memory Scale 4. Verbal learning test* 5. Corsi block-tapping test 6. Horn performance test 55+ subsets 3 and 9	1. Preoperative 2. Discharge 3. 3 mo	1. Discharge: significant decline in Wechsler Memory Scale ($P=0.013$), Horn perforamce test 55+ subset 3 ($P=0.010$) and Trail-making B test ($P=0.021$) 2. 3 mo: Sigificant decline Verbal learning test ($P=0.012$)	Nil
Cook (2007)[46]	1. Rey AVLT* 2. Rey NVMT 3. Symbol-digit modalities test 4. Letter-cancellation task 5. Trail making A and B* 6. Grooved pegboard test* 7. Finger-tapping test	1. Preoperative 2. Discharge 3. 4 wk 4. 6 wk	1. Discharge: 88% of participant had cognitive decline 2. 4 and 6 wk: 30% had cognitive decline	Nil
Knipp (2008)[54]	1. Trail-making A and B* 2. Zimmerman joint attention test 3. Verbal learning test* 4. Wechsler Memory Scale revised digit span test (forward and backward) 5. Corsi block-tapping test 6. Horn performance test 55+ subsets 3 and 9	1. Preoperative 2. Discharge 3. 3 mo 4. 3 y	1. Discharge: 56% 2. 3 mo: 23% 3. 3 y: 1%	Nil
Barber (2008)[47]	Manual dexterity; Psychomotor speed; Executive function; Memory 1. Trail-making test parts A and B* 2. Grooved pegboard test* 3. Rey AVLT* 4. Letter-number sequencing test 5. Symbol-digit modalities test	1. Preoperative 2. 6 wk	63% had decline in 1 domain; 34% declined in 2	Yes, (OR 37.49, 95% CI 4.01-350.18)
Kahlert (2010)[13]	MMSE	1. Preoperative 2. Predischarge 3. 3 mo	Nil significant changes	NA
Schwarz (2011)[15]	1. WAIS digit symbol 2. Number cancellation test 3. SKT interference list 4. Regensburg word fluency test 5. NVLT	1. Preoperative 2. 3 mo	1. CABG patients: POCD in 7/10 tests 2. PCI patients: POCD in 2/10 tests As compared with controls*	Yes, SBI correlated with reduced performance in tests of verbal and visual memory

Table 4. Continued

Study	Neurocognitive Domains Tested	Timing of Testing	Cognitive Decline	Association Between DWI Lesions and POCD
	6. SKT pictoral memory test 7. VLMT*			
Ghanem (2013)[16]	1. Repeated battery for the assessment of neuropsychological status: attention, language, visuospatial/constructional abilities, memory domains tested 2. MMSE	1. Preoperative 2. 3 d 3. 3 mo 4. 1 y 5. 2 y	1. 3 days: POCD in 5.4% ($P<0.001$) 2. 2 years: 91% free from significant cognitive dysfunction	Nil
Alassar (2015)[12]	Overall cognition; Executive function; Processing speed Memory*Specific tests not mentioned	1. Preoperative 2. 3 mo	No improvement in cognitive function seen in AVR and TAVI groups at 3 mo	Nil
Ghanem (2017)[32]	MMSE	1. Preoperative 2. Within first 3 postoperative days 3. >30 mo postoperatively	Nonsignificant overall	Nonsignificant ($P=0.067$)
Lund (2005)[37]	1. Grooved pegboard test* 2. WAIS-R test 3. Trail-making part A and B* 4. Digit span (forward and backward) 5. Stroop color-word interference test 6. Rey AVLT* 7. Vocabulary and similarities (WAIS-R) 8. Controlled oral associated test 9. Rey Osterreiths complex figure test 10. Taylor complex figure test 11. Picture completion and block design (WAIS-R)	1. Preoperative 2. Postoperative day 1	Cognitive impairment seen in 16.7% defined as decline ≥20% in test scores in at least 2 of 12 tests	Yes, significant difference in 2 tests assessing learning and attention
Gerriets (2010)[56]	1. SKT 2. Trail-making A and B 3. Number cancellation 4. SKT interference list 5. Stroop color-word interference 6. Nonverbal learning test 7. SKT pictorial memory 8. VLMT short-term learning* 9. VLMT delayed recognition 10. Line tracing 11. WAIS block design	1. Preoperatively 2. Postoperative days 2-4 3. 3 mo	1. Postoperative days 2-4: all mean test scores decreased from baseline ($P<0.001$) 2. 3 mo: Most mean test scores returned to baseline except for the SKT visual memory test and verbal delayed recognition test ($P<0.001$)	Presence of postoperative SBIs correlated with decreased scores in letter-interference test and attention domain at postoperative day 2-4. Nil association of SBIs and POCD at 3 mo

AVLT indicates auditory verbal learning test; AVR, aortic valve replacement; CABG, coronary artery bypass graft; CD, cognitive dysfunction; DWI, diffusion-weighted imaging; MMSE, Mini-Mental State Exam; NVLT, non-verbal learning test; PCI, percutaneous coronary intervention; POCD, postoperative cognitive dysfunction; SBI, silent brain infarct; SKT, Syndrom Kurztest attention test; TAVI, transcatheter aortic valve implantation; VLMT, verbal learning and memory test; WAIS, Wechsler Adult Intelligence Scale; WAIS-R, revised WAIS.
*Tests recommended by Murkin et al[59] in the consensus statement for diagnosis of POCD.

increase the reproducibility for subsequent trials and thus comparability. Specific location of SBIs is also relevant as it may give clues as to the etiology of the lesions. A diffuse pattern of cerebral involvement would be consistent with an embolic source, whereas when present in watershed zones, cerebral hypoperfusion may be the likely factor involved.

We additionally performed a systematic review of POCD and its association with SBIs following cardiac procedures. Problems with the significant variability in the definitions of POCD led to the development of a consensus statement being published in 1995 outlining specific criteria that should be utilized when assessing for POCD.[59] A systematic review in 2010 found that there was poor uptake of this proposed criterion, with significant heterogeneity seen particularly in the definition of what constituted POCD and the contents of the neurocognitive test batteries per-formed.[10] Of the 13 studies that assessed for correlation between POCD and SBI in our review, there was low uptake of the consensus statement recommendations, making these results difficult to compare. Of the 4 studies that did report an association between POCD and DWI lesions, the measurement of POCD within 4 days of the procedure largely nullifies the significance of these results without repeat testing at 3 months (or more) postoperatively. Early POCD is difficult to diagnose due to multiple confounders such as anesthetic agents, analgesia, and delirium impacting on the cognitive state acutely. Without the application of consistent criteria and strict definitions, the prevalence and risk factors of POCD will be unable to be accurately measured; nor will treatment options nor preventative techniques be able to be proven.

SBIs are shown to be very common complication of cardiac procedures. Increased understanding of these lesions demon-strates that they are likely not as "silent" as their name would suggest. The common occurrence of lesions perioperatively also presents them as a potential surrogate marker for neuroprotective studies. At present, however, inconsistencies in how these are defined and reported limit their clinical and research applicability.

Disclosures

None.

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