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Comparative analysis of cerebrovascular events in transcatheter and surgical aortic valve replacement: a systematic review and meta-analysis of randomised trials

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KEYWORDS

- aortic stenosis
- clinical research
- stroke
- TAVI

Abstract

Aims: Transcatheter aortic valve replacement (TAVR) has become the procedure of choice for inoperable patients and a safe alternative to surgical aortic valve replacement (SAVR) among moderate-risk patients. We used meta-analysis to compare the incidence of cerebrovascular events amongst patients undergoing TAVR and SAVR in randomised controlled trials (RCT).

Methods and results: Our search revealed five RCT published between 2011 and 2017 with a total of 5,414 patients. Data were summarised as Mantel-Haenszel relative risk (RR) and 95% confidence intervals (CI). The risk of major stroke (RR 0.89, 95% CI: 0.53-1.51), all strokes (RR 0.85, 95% CI: 0.59-1.22) and all cerebrovascular events (RR 0.94, 95% CI: 0.75-1.17) was comparable between patients undergoing TAVR and SAVR at 30 days of follow-up. The risk of all strokes (RR 0.92, 95% CI: 0.69-1.22), major stroke (RR 0.92, 95% CI: 0.62-1.37) and all cerebrovascular events (RR 1.03, 95% CI: 0.79-1.33) was comparable between TAVR and SAVR at one year of follow-up. The incidence of major stroke (RR 1.02, 95% CI: 0.64-1.61), all strokes (RR 1.12, 95% CI: 0.78-1.62) and all cerebrovascular events (RR 1.23, 95% CI: 0.91-1.66) was comparable between TAVR and SAVR between 30 days and one year of follow-up.

Conclusions: In our meta-analysis of RCT comparing TAVR and SAVR, we showed comparable risk of major stroke, all stroke and all cerebrovascular events.

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Abbreviations

CI	confidence interval
NOTION	Nordic Aortic Valve Intervention Trial
PARTNER	Placement of Aortic Transcatheter Valves Trial
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
RR	relative risk
SAVR	surgical aortic valve replacement
SURTAVI	Surgical Replacement and Transcatheter Aortic Valve Implantation trial
TAVR	transcatheter aortic valve replacement
TIA	transient ischaemic attack

Introduction

Transcatheter aortic valve replacement (TAVR) has become the treatment of choice for inoperable patients with symptomatic, severe aortic stenosis and is a viable alternative to surgical aortic valve replacement (SAVR) for high and intermediate surgical risk patients. However, there are several adverse effects associated with TAVR, prime among them being stroke and transient ischaemic attack (TIA)[1-7]. At 30 days, around 4% of patients undergoing TAVR experience strokes and 5.7% of patients experience a stroke and/or TIA[8]. A sub-analysis of the CoreValve trial (and Continued Access Study) demonstrated that the incidence of stroke may be over 8% at one year[9].

While acute cerebrovascular events (stroke and TIA) are undoubtedly significant adverse events after TAVR, there are several areas of uncertainty related to their occurrence. The comparative incidence of stroke in patients undergoing TAVR and SAVR has often been questioned. The landmark PARTNER trial (2011) reported a higher incidence of neurological events in patients undergoing TAVR as compared to SAVR[5]. In stark comparison, the SURTAVI trial (2017) showed that patients undergoing SAVR had a greater incidence of stroke at 30 days (5.6% vs. 3.4%) and one year (6.9% vs. 5.4%)[10]. Also, it has been shown that the risk for post-TAVR stroke may be biphasic, with early and late strokes having different pathophysiology. Existing meta-analyses have focused on traditional temporal endpoints of 30 days and one year and the comparative risk in between these time points needs to be evaluated[11-13]. Additionally, recent literature suggests that patients undergoing TAVR may have an increased risk of subclinical leaflet thrombosis as compared to SAVR patients, which may be associated with stroke and TIA, although this has not been established[14,15]. We aimed to compare the incidence of cerebrovascular events at 30 days, one year and between 30 days and one year amongst patients undergoing TAVR and SAVR in randomised controlled trials (RCT) using meta-analysis. We also systematically reviewed the reporting of cerebrovascular endpoints and risk factors for cerebrovascular events among the individual RCT.

Methods

SEARCH STRATEGY AND INCLUSION CRITERIA

We included all randomised trials comparing neurological outcomes in TAVR and SAVR with a minimum one year of follow-up. Our search strategy and inclusion criteria are detailed in **Supplementary Appendix 1** and **Figure 1**.

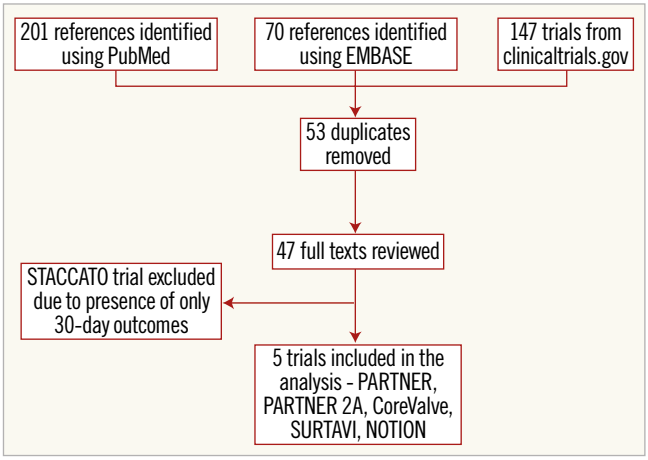

Figure 1. *Description of the search strategy for the meta-analysis.*

STUDY ENDPOINTS

The primary outcome of interest for our study was all strokes at one-year follow-up. Secondary outcomes included: (1) major stroke at 30 days, (2) all stroke (a composite of major and minor strokes) at 30 days, (3) all cerebrovascular events (a composite of all major strokes, minor strokes and TIA) at 30 days, (4) all stroke (a composite of major and minor strokes) at one year, (5) all cerebrovascular events (a composite of all major strokes, minor strokes and TIA) at one year, (6) major stroke between 30 days and one year, (7) all strokes (a composite of major and minor strokes) between 30 days and one year, and (8) all cerebrovascular events (a composite of all major strokes, minor strokes and TIA) between 30 days and one year. The terms major stroke/disabling stroke and minor stroke/non-disabling stroke are used interchangeably in this paper.

SENSITIVITY ANALYSIS

We further explored the heterogeneity in each primary and secondary analysis by means of sensitivity analysis using the "one study removal" method, wherein the effect of removal of individual studies on the overall results was assessed.

DATA ABSTRACTION AND INDIVIDUAL STUDY QUALITY APPRAISAL

Details of the data abstraction strategy, review of study protocols and risk of bias of included studies using the standardised criteria defined in the Cochrane Handbook for Systematic Reviews of Interventions is provided in **Supplementary Appendix 2** and **Supplementary Table 1**[16].

STATISTICAL ANALYSIS

Categorical dichotomous data were summarised across treatment arms using the Mantel-Haenszel risk ratio (RR) along with 95%

confidence intervals (CI). We evaluated heterogeneity of effects using Higgins' I-squared (I^2) statistic. A fixed effects model was used except in cases where heterogeneity was significant (defined as I^2 >25%). If the heterogeneity was significant, a random effects model was used. A cut-off of 25% was used as values >25% signify moderate to severe heterogeneity and indicate that variability across studies cannot be attributed to chance[17]. To address publication bias, we used Egger's test[18,19]. Funnel plot analysis was not carried out as the number of included studies was small (<10). Comprehensive Meta-Analysis v. 3.3.070 (Biostat, Englewood, NJ, USA) was used for the meta-analysis. A two-tailed p-value of 0.05 was considered significant for all our analyses.

Results

Our search results yielded five RCT published between 2011 and 2017 with a total of 5,414 patients (TAVR 2,755, SAVR 2,659)[4,5,10,20,21]. Details of the individual RCT are included in **Table 1**. A detailed description of stroke risk factors among individual studies is available in **Supplementary Table 2**. Details of definition, scheduled neurological checks and handling of neurological events in individual studies are provided in **Table 2**. Throughout this study, the first PARTNER trial[5] is referred to simply as the PARTNER trial, whereas the second PARTNER trial[4] is referred to as the PARTNER 2A trial.

1. Primary outcome (all strokes at one year of follow-up). There was no significant difference between patients undergoing TAVR and SAVR (RR 0.92, 95% CI: 0.69-1.22, I^2=42%) **(Figure 2)**.
2. Secondary outcomes at 30 days **(Figure 3A-Figure 3C)**. The incidence of major stroke (RR 0.89, 95% CI: 0.53-1.51, I^2=55%), all strokes (RR 0.85, 95% CI: 0.59-1.22, I^2=44%) and all cerebrovascular events (RR 0.94, 95% CI: 0.75-1.17), I^2=47%) was comparable between patients undergoing TAVR and SAVR.
3. Secondary outcomes at one year **(Figure 4A, Figure 4B)**. The incidence of major stroke (RR 0.92, 95% CI: 0.62-1.37, I^2=51%) and all cerebrovascular events (RR 1.03, 95% CI: 0.79-1.33, I^2=46%) was comparable between TAVR and SAVR.
4. Secondary outcomes between 30 days and one year **(Figure 5A-Figure 5C)**.
   The incidence of major stroke (RR 1.02, 95% CI: 0.64-1.61, I^2=24%), all strokes (RR 1.12, 95% CI: 0.78-1.62, I^2=9%) and all cerebrovascular events (RR 1.23, 95% CI: 0.91-1.66, I^2=21%) was comparable between TAVR and SAVR.

SENSITIVITY ANALYSIS (Supplementary Figure 1)

Sensitivity analysis using the "one study removal" method did not result in any significant changes in effect on any of the outcomes except (1) all strokes at 30 days and (2) all cerebrovascular events at one year. For the outcome of all strokes at 30 days of follow-up, we observed that, after exclusion of the PARTNER trial, the risk was significantly reduced in patients undergoing TAVR (RR 0.76, 95% CI: 0.59-0.98). Exclusion of the other studies individually for this outcome did not alter the overall effect. For the outcome of all cerebrovascular events between 30 days and one year, exclusion of the CoreValve trial showed that patients undergoing TAVR had an increased risk of all cerebrovascular events (RR 1.42, 95% CI: 1.01-2.02) between 30 days and one year. Exclusion of both CoreValve and PARTNER trials resulted in a borderline increased risk of all cerebrovascular events (RR 1.41, 95% CI: 0.98-2.03). Exclusion of the other studies individually for this outcome did not alter the overall effect.

Table 1. Baseline information about the studies comparing transcatheter aortic valve replacement and surgical aortic valve replacement.

Author name (year of publication)	Study name	Study duration	Number of patients	Valve used TAVR	EuroSCORE TAVR	EuroSCORE SAVR	Primary outcome
Smith et al (2011)	Transcatheter versus surgical aortic valve replacement in high-risk patients (PARTNER)	May 2007-Aug 2009	699	SAPIEN	29.3±16.5	29.2±15.6	Death from any cause at 1 year
Adams et al (2014)	Transcatheter aortic valve replacement with a self-expanding prosthesis (CoreValve)	Feb 2011-Sep 2012	747	CoreValve	17.7±13.1	18.6±13.0	Death from any cause at 1 year
Thyregod et al (2015)	Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis (NOTION)	Dec 2009-Apr 2013	276	CoreValve	8.4±4.0	8.9±5.5	Composite of rate of death from any cause, stroke, or myocardial infarction at 1 year
Leon et al (2016)	Transcatheter or surgical aortic valve replacement in intermediate-risk patients (PARTNER 2)	Dec 2011-Nov 2013	2,032	SAPIEN XT	5.8±2.1#	5.8±1.9#	Composite of death from any cause or disabling stroke at 2 years
Reardon et al (2017)	Surgical or transcatheter aortic valve replacement in intermediate-risk patients (SURTAVI)	June 2012-June 2016	1,660	CoreValve	11.9±7.6	11.6±8.0	Composite of death from any cause or disabling stroke at 24 months

STS risk score. SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement

Table 2. Detailed description of definition, scheduled neurological assessment and handling of neurological outcomes amongst individual randomised trials.

Name of trial	Definition of neurological events	Handling of neurological endpoints	Standardised follow-up in the first year
Smith et al (PARTNER)	TIA: defined as an FND, which was fully reversible at 24 hours in the absence of new imaging findings of infarction or other primary medical cause. Stroke: (1) FND ≥24 hrs (2) FND <24 hrs with imaging findings of acute infarction	Retrospective analysis of events by the CEC, which included neurologist	- NIHSS at baseline by physician, PA or NP; no specified person to perform discharge, 30 d, 6 mo, 1 yr follow-up. - MMSE at baseline
Adams et al (CoreValve)	VARC	Any patient with evidence of a neurological event should have a neurology consult and an imaging study if deemed necessary by the neurologist. Also retrospective analysis of events by the CEC which included neurologist	- NIHSS at baseline, post procedure, discharge, 1 mo, 6 mo, 1 year
Thyregod (NOTION)	VARC2	When a neurological lesion was suspected, an independent neurologist conducted a formal neurological examination, and cerebral imaging studies were performed.	- No mention of follow-up neurological assessments.
Leon et al (PARTNER 2)	VARC2	All neurological events and sub-classifications were assessed by an independent CEC. All neurological testing was completed by a neurologist or neurology fellow.	- NIHSS at baseline, post procedure and discharge assessments by neurologist/ neurology fellow. 1 mo, 6 mo, 1 yr assessments by dedicated certified personnel - Designated sites representing at least 50% of the projected trial enrolment will ensure that the protocol neurological examinations will be administered by a dedicated neurologist or neurology fellow - mRS for any person with a previous stroke at baseline and post-procedure by neurologist or neurology fellow - Barthel index immediately prior to MRS.
Reardon et al (SURTAVI)	VARC2	All the patients were seen by a trained neurologist or stroke specialist, and neurologic events were adjudicated by a neurologist on the clinical events committee.	- NIHSS at baseline, post procedure, discharge, 1 mo, 6 mo, 1 yr - MMSE at baseline, discharge, 1 yr - mRS at baseline - Additional testing (visual, gait, hand function, writing, drawing) baseline, discharge, 1yr

CEC: clinical events committee; FND: focal neurological deficit; NIHSS: National Institutes of Health Stroke Scale; MMSE: mini mental state examination; mRS: modified Rankin Scale; NP: nurse practitioner; PA: physician assistant; VARC: Valve Academic Research Consortium

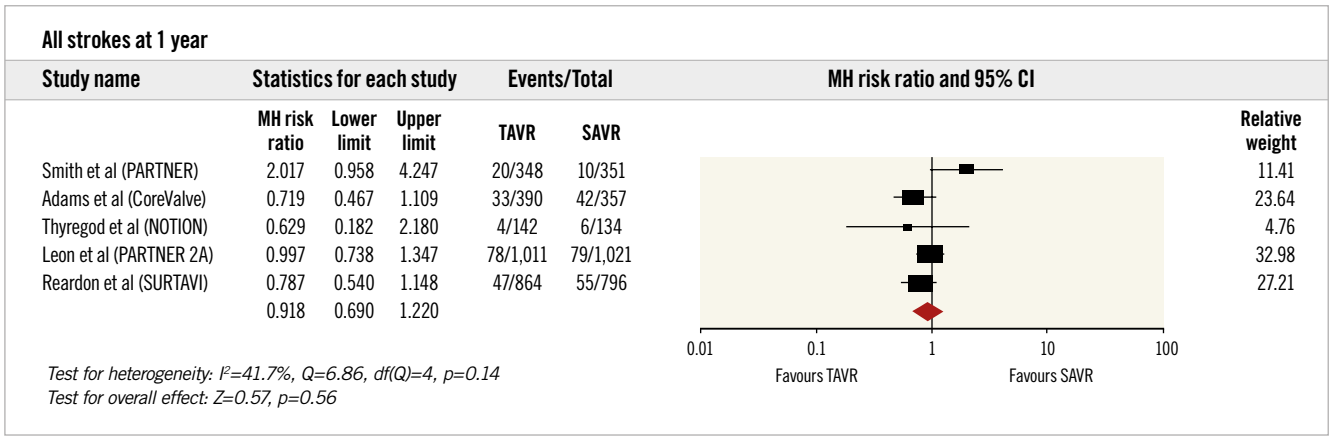

Figure 2. *Forest plot comparing risk of all strokes in patients undergoing transcatheter and surgical aortic valve replacement. The diamond indicates the overall summary estimate for the analysis. The centre of the diamond represents the point estimate and the width represents the 95% confidence interval.*

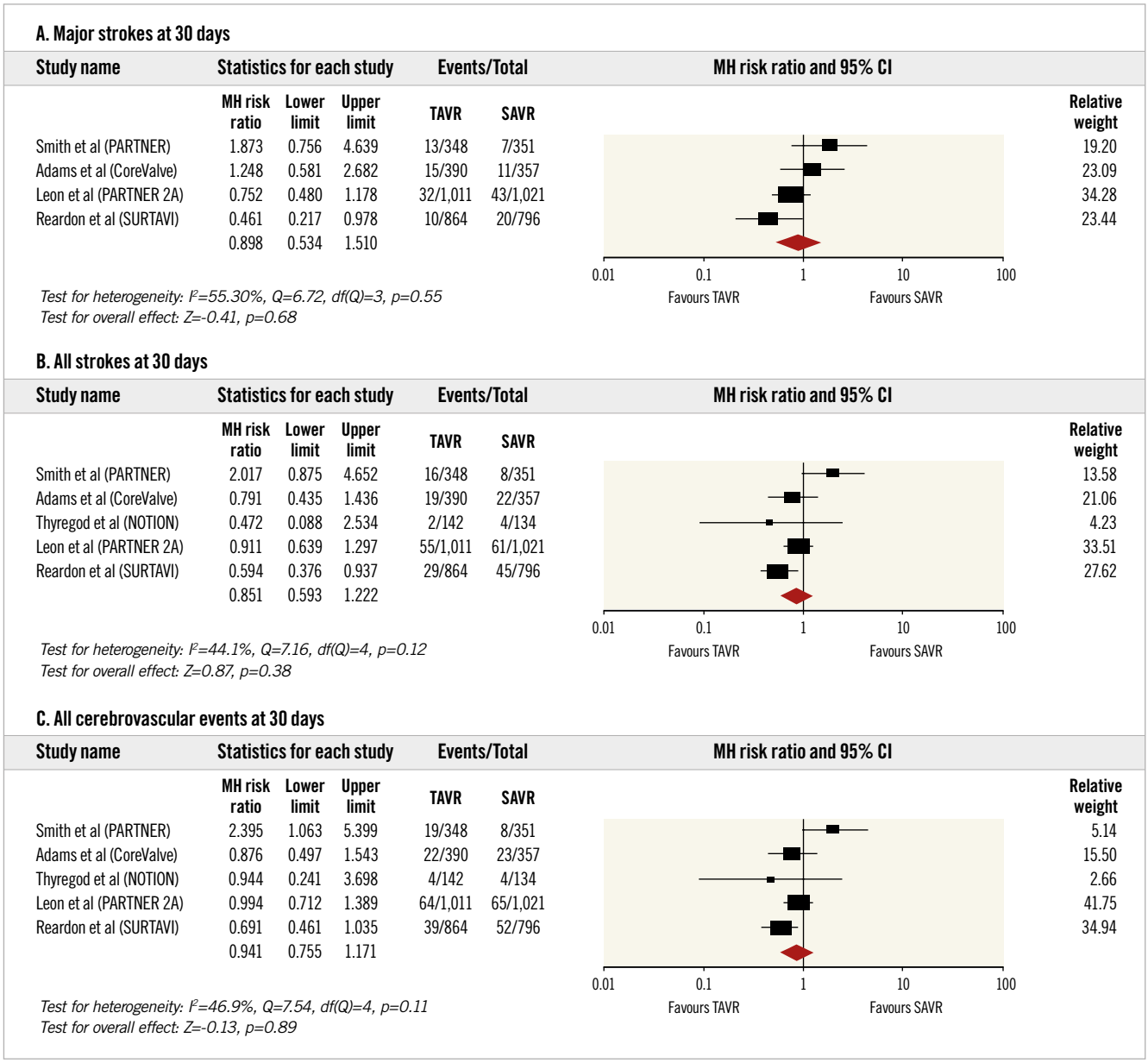

Figure 3. *Forest plots comparing risk of events in patients undergoing transcatheter and surgical aortic valve replacement at 30 days. A) Risk of major stroke. B) Risk of all stroke. C) Risk of all cerebrovascular events. The diamond indicates the overall summary estimate for the analysis. The centre of the diamond represents the point estimate and the width represents the 95% confidence interval.*

PUBLICATION BIAS

Egger's test did not reveal evidence of publication bias for any of the other primary, secondary or supplementary analyses.

Discussion

In this meta-analysis of five RCT with over 5,400 patients randomised to TAVR and SAVR we showed that major strokes, all strokes, and all cerebrovascular events were comparable between the two groups at 30 days, one year and between 30 days and one year. Additionally, our sensitivity analyses revealed that removal of the PARTNER trial resulted in a lower risk of all strokes in patients undergoing TAVR, whereas removal of the CoreValve study resulted in an increased risk of all cerebrovascular events between 30 days and one year in those undergoing TAVR. To the best of our knowledge, this is the most up-to-date comparative analysis of cerebrovascular events in TAVR and SAVR. Also, it is the most comprehensive review of trial protocols with regard to cerebrovascular event definition, detection, and monitoring **(Table 2)**.

A wide variability exists in reporting of stroke risk across studies. Often, the reporting of these adverse events is dependent on identification by treating clinicians in retrospective studies or

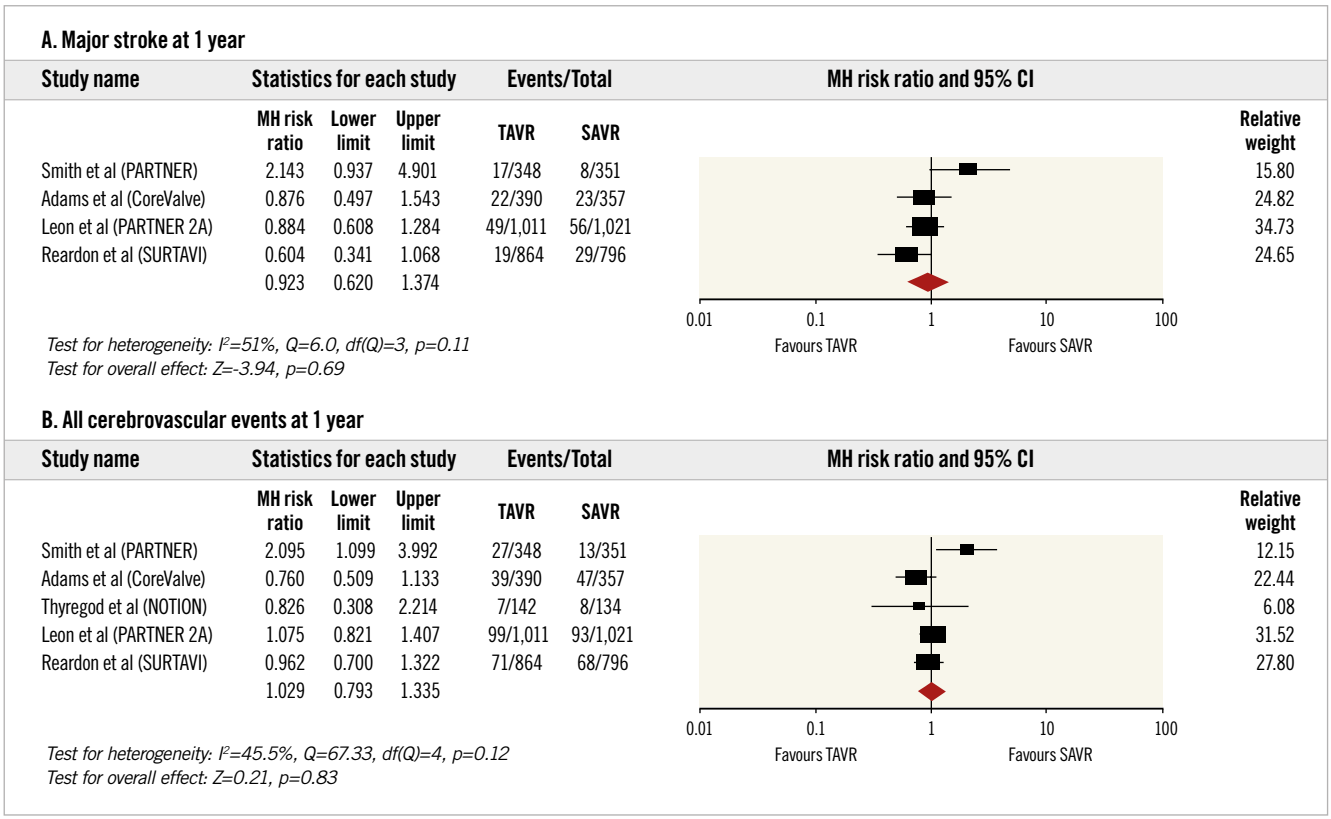

Figure 4. *Forest plots comparing risk of major stroke and all cerebrovascular events in patients undergoing transcatheter and surgical aortic valve replacement at one year. A) Risk of major stroke. B) Risk of all cerebrovascular events. The diamond indicates the overall summary estimate for the analysis. The centre of the diamond represents the point estimate and the width represents the 95% confidence interval.*

based on self-reporting of events in prospective registries. In fact, in a sub-analysis of the CoreValve trial, Kleiman et al noted that the 8.4% one-year incidence of stroke in their report was markedly higher than the 4.1% in the TVT registry (one year) and 3.9% in the FRANCE registry (six months)[9,22,23]. For this reason, we chose to analyse only RCT wherein a clear structure, comparative baseline risk and thorough protocol-based reporting of clinical events would allow us to investigate the true incidence of stroke and systematically to investigate differences in trial protocols that could result in differential reporting of cerebrovascular events.

In a comprehensive analysis of neurological events in the PARTNER trial, it was shown that the probability of stroke at 30 days was 3.8% in the transfemoral cohort and 2.7% in the transapical cohort. Thereafter, it increased slowly to 5.4% and 6.9% for the transfermoral cohort, and 4.1% and 7% for the transapical cohort at 1 year and 3 years, respectively[9,24]. Furthermore, it has been suggested that procedural and anatomical factors may be responsible for this early stroke risk[24]. The risk for stroke in patients randomised to the TAVR arm was substantially higher in the PARTNER trial, whereas in SURTAVI the incidence of cerebrovascular events was lower in the TAVR group at 30 days, and one year of follow-up[5,10]. In the PARTNER trial, although the increased risk of major stroke at one year in patients undergoing TAVR did not reach statistical significance, the risk of all cerebrovascular events was significantly increased in the TAVR arm (8.3% vs. 4.3%, p=0.04). This was probably driven by the increased rates of TIA in the TAVR cohort. Of note, our sensitivity analysis revealed that risks of cerebrovascular events are in fact lower in the TAVR group after removal of the PARTNER trial. There are several possible reasons for these findings. PARTNER was the only trial amongst those included in our analysis that did not require neurological evaluation in patients with stroke/TIA to be completed by a trained neurologist and/or a neurology fellow. Additionally, baseline National Institutes of Health Stroke Scale (NIHSS) assessment was completed in this study by a physician (not necessarily a neurologist) or by a nurse practitioner/physician assistant. In comparison, this assessment was carried out by a neurologist/neurology fellow in the PARTNER 2A trial **(Table 2)**. These differences in trial methodology could perhaps have introduced an ascertainment bias. It is also important to recognise that the PARTNER trial did not require routine post-procedural NIHSS evaluation (first follow-up in the absence of stroke was at the time of discharge). This, if present, may have allowed enhanced identification of subtle neurological findings and therefore reduced the risk for ascertainment bias for early stroke. These findings should also be kept in mind while designing future clinical trials, and post-procedural evaluation for stroke should form part of standard protocol for studying cerebrovascular events in trials evaluating cardiovascular procedures.

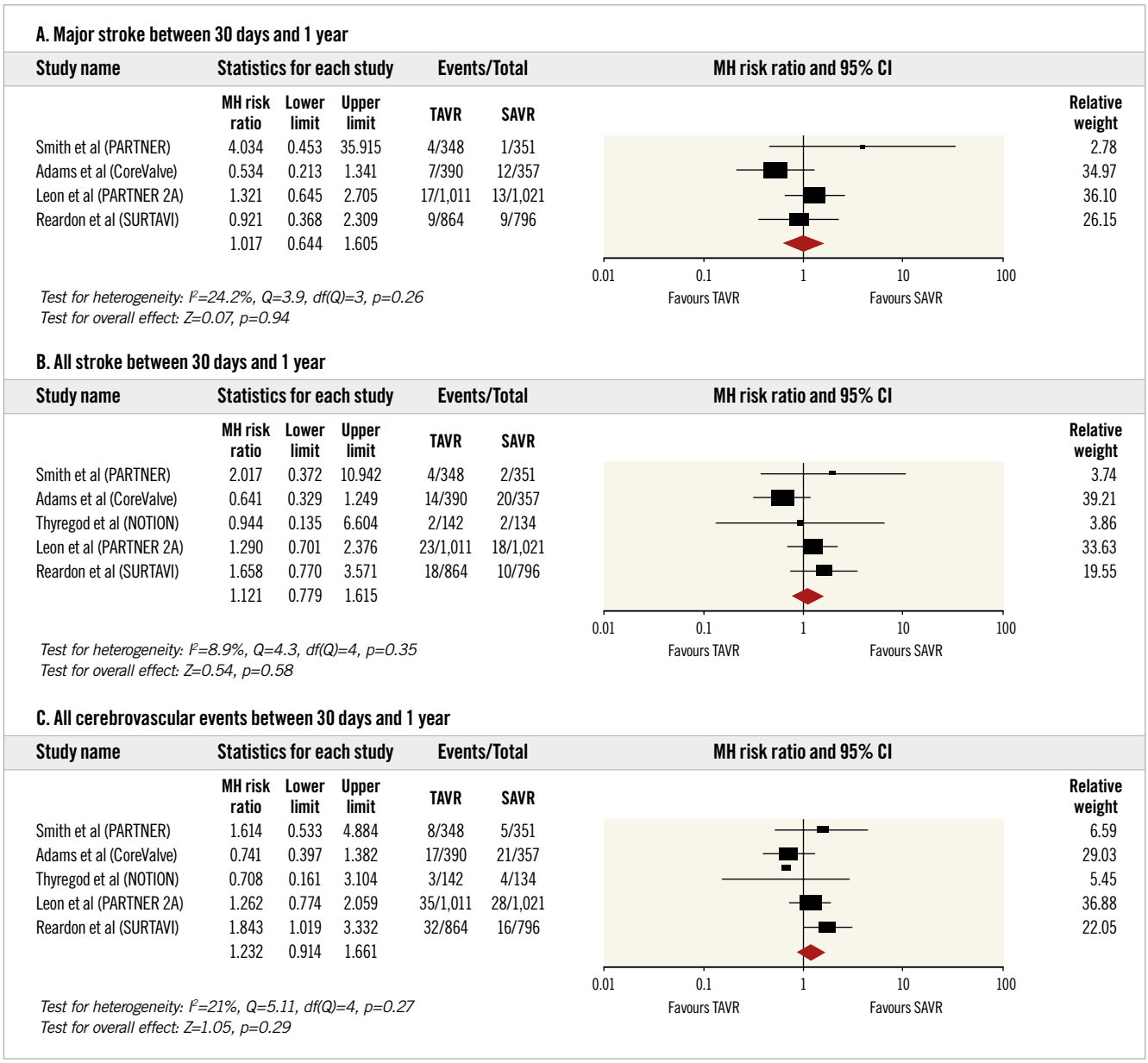

Figure 5. *Forest plots comparing risk of events in patients undergoing transcatheter and surgical aortic valve replacement between 30 days and one year of follow-up. A) Risk of major stroke. B) Risk of all stroke. C) Risk of all cerebrovascular events. The diamond indicates the overall summary estimate for the analysis. The centre of the diamond represents the point estimate and the width represents the 95% confidence interval.*

We also found that, with removal of the CoreValve study, there was an increased risk of all cerebrovascular events in patients undergoing TAVR (p=0.045) between 30 days and one year of follow-up. With additional removal of the PARTNER trial, the increased risk remained of borderline significance (p=0.07). Since the risk of major stroke and all strokes does not change with sensitivity analysis, we can postulate that this increased risk is due to a higher incidence of TIA in patients undergoing TAVR. It is possible that this increased risk of TIA is secondary to subclinical leaflet thrombosis occurring between 30 days and one year. In a recently published report from the SAVORY and RESOLVE registries, Chakravarty and colleagues reported a significantly higher incidence of subclinical leaflet thrombosis in patients undergoing TAVR, which was subsequently associated with a higher risk for TIA[15]. Additionally, it is possible that the microembolic nature of cerebrovascular events after TAVR may result in early recovery of neurological function and therefore an increased risk of TIAs rather than major or minor strokes.

Limitations

While our meta-analysis provides insight into the neurological events following TAVR and SAVR, there are several limitations to

our analysis. First, this is a meta-analysis performed on study-level data and therefore individual patient risk of cerebrovascular events could not be addressed. Second, given the limited number of studies, we were unable to explore the effect of baseline patient and procedural characteristics (such as valve and access type) on outcomes using meta-regression techniques. It is for the same reason that we were unable to carry out subgroup analysis by TAVR access and valve type. Third, the earliest time point of 30 days in our study may be marginally beyond the time frame for early phase of stroke risk (<10 days) as suggested by current literature[9]. Additionally, both changes in valve technology over time and operator experience may have impacted on the results but could not be accounted for in this analysis. However, we feel that our selective analysis of only randomised patients (with comparable baseline characteristics), large pooled sample size of patients, standardised definitions of neurological outcomes amongst individual studies, and extensive subgroup and sensitivity analysis provide robustness to our study.

Conclusions

In our meta-analysis of RCT comparing TAVR and SAVR, we showed that the risk of major stroke, all stroke and all cerebrovascular events is comparable between the two groups at 30 days and one year.

Impact on daily practice

Our meta-analysis will allow interventional cardiologists to inform their patients undergoing TAVR adequately of their risk of cerebrovascular events. This will be of special value in risk versus benefit discussions in patients who may be potential surgical candidates.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Search strategy and inclusion criteria.

Supplementary Appendix 2. Data abstraction and individual study quality appraisal.

Supplementary Table 1. Risk of bias assessment among various studies.

Supplementary Table 2. Risk factors for cerebrovascular events in individual studies.

Supplementary Figure 1. Sensitivity analysis.

The supplementary data are published online at: http://www.pcronline.com/eurointervention/134th_issue/11

Supplementary data

Supplementary Appendix 1. Search strategy and inclusion criteria

Search strategy

A computerised literature search of all publications of PubMed, EMBASE and ClinicalTrials.gov was carried out. We then manually searched the reference lists of included articles. This was last assessed as up-to-date on 1 April 2017 **(Figure 1)**.

Search terms included varying combinations of the following keywords: “transcatheter aortic valve replacement”, “transcatheter aortic valve implantation”, “surgical aortic valve replacement”, “severe aortic stenosis” “stroke” “cerebrovascular event”, “transient ischaemic attack”.

Inclusion criteria

The Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (PRISMA) of reporting systematic reviews and meta-analyses was applied to the methods for this study [15].

The following inclusion criteria were used:

1. RCT comparing TAVR and SAVR.
2. Studies which included data on both 30-day and one-year outcomes.
3. Studies on all TAVR valve types and TAVR approaches.

The following exclusion criteria were used:

1. Non-randomised trials, prospective registries and other observational studies.
2. Studies where data pertaining to the primary outcome of all strokes at one year could not be obtained.

3. Conference abstracts and studies in languages other than English.

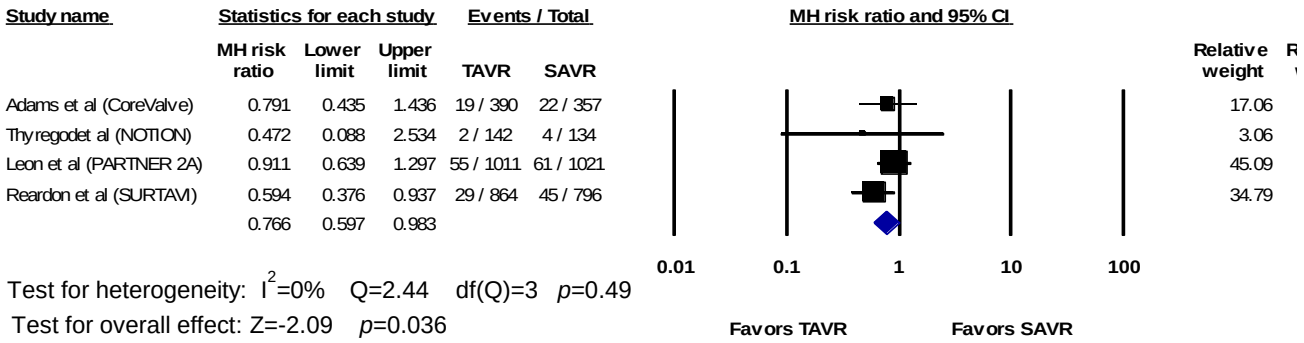
Supplementary Appendix 2. Data abstraction and individual study quality appraisal.

Two authors (D. Mohananey, P. Sengodan) abstracted data from all included studies on to a standardised worksheet. The following data were collected: name of author, study title, year of publication, TAVR access site, study period, number of patients included, valve type, percentage of certain baseline variables (age, male gender, atrial fibrillation, renal failure, previous stroke, diabetes mellitus, previous pacemaker). Information on European System for Cardiac Operative Risk Evaluation Score (EuroSCORE), antiplatelet therapy, percentage of patients with new atrial fibrillation and new pacemaker placement was also collected. Additionally, we abstracted data on individual study definition of strokes, handling of neurological clinical events and details of scheduled neurological checks as part of the trial protocol. All included studies except the NOTION trial had protocol data available online as part of the publication. For the NOTION trial, the protocol publication was reviewed separately [14]. Also, data required for comparative analysis of all outcomes were abstracted. Intention-to-treat analysis was used to obtain data wherever available.

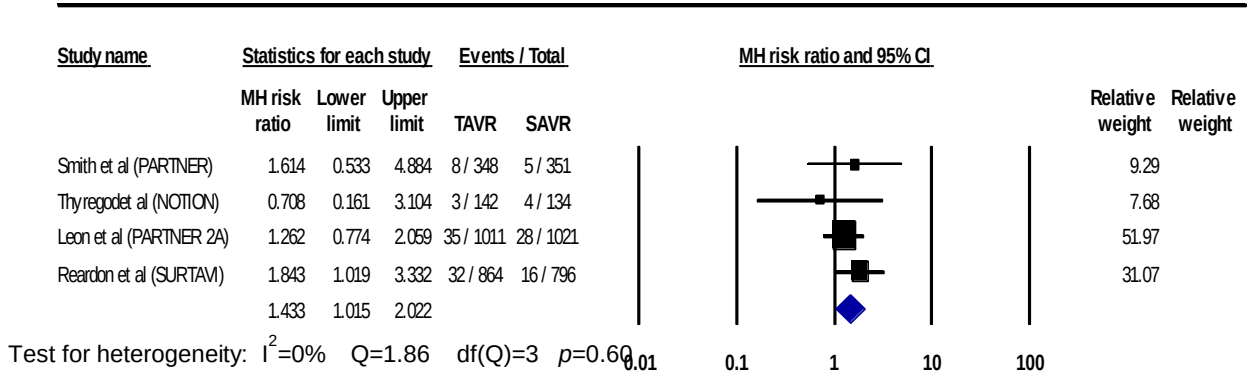
Two authors (D. Mohananey, P. Sengodan) independently assessed the risk of bias of included studies using the standardised criteria defined in the Cochrane Handbook for Systematic Reviews of Interventions **(Supplementary Table 1)**.

Supplementary Figure 1. Sensitivity analysis.

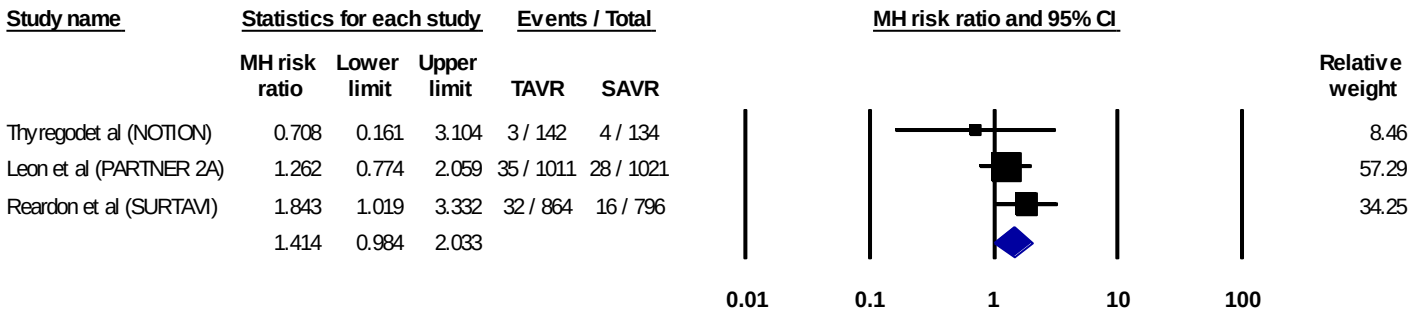
A. Effect of removal of PARTNER trial on all strokes at 30 days.



B. Effect of removal of CoreValve trial on all neurological events between 30 days and one year. (C) Effect of removal of PARTNER and CoreValve trials on all neurological events between 30 days and one year.



C. Effect of removal of PARTNER and CoreValve trials on all neurological events between 30 days and one year.



Test for heterogeneity: I^2=0% Q=1.81 df(Q)=2 *p*=0.40
Test for overall effect: Z=-1.83 *p*=0.070

Supplementary Table 1. Risk of bias assessment among various studies.

Study	Sequence generation	Allocation concealment	Blinding of participants, personnel, and outcome assessors	Incomplete outcome data and withdrawals	Free of selective reporting	Other sources of bias and commentaries
PARTNER	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
PARTNER 2A	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
CoreValve	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
NOTION	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
SURTAVI	Low risk	Low risk	High risk	Low risk	Low risk	Low risk

Supplementary Table 2. Risk factors for cerebrovascular events in individual studies.

Study	Previous CVA		CAD		Previous MI		Any renal failure		DM		HTN		Male		LVEF		PVD	
	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR
	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%
PARTNER	29.3	27.4	74.9	76.9	26.8	30	11.1	7	NA	NA	NA	NA	57.8	56.7	52.5±13.5	53.3±12.8	43	41.6
CoreValve	12.6	14	75.4	75.9	25.4	25.2	12.2	12.8	34.9	45.4	95.1	96.1	53.1	52.4	NA	NA	41.1	41.7
NOTION	16.6	16.3	NA	NA	5.5	4.4	1.4	0.7	17.9	20.7	71	76.3	53.8	52.6	NA	NA	4.1	6.7
PARTNER 2A	32.1	31	69.2	66.5	18.3	17.5	5	5.2	37.7	34.2	NA	NA	54.2	54.8	56.2±10.8	55.3±11.9	27.9	32.9
SURTAVI	6.6	7.2	62.6	64.2	14.2	13.4	NA	NA	34.1	34.8	92.8	90.8	57.6	55	NA	NA	30.8	29.9

CAD: coronary artery disease; CVA: cerebrovascular accident; DM: diabetes mellitus; HTN: hypertension; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NA: not available; NYHA: New York Heart Association; PVD: peripheral vascular disease; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement