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Silent cerebral injury after transcatheter aortic valve implantation and the preventive role of embolic protection devices: A systematic review and meta-analysis

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ABSTRACT

Background: The aims of this study were: 1) to evaluate silent cerebral injury detected by cerebral diffusion weighted magnetic resonance imaging (DW-MRI) after transcatheter aortic valve implantation (TAVI); and 2) to assess the efficacy of embolic protection devices (EPDs) on DW-MRI endpoints.
Methods: We included in a pooled analysis 25 prospective studies reporting post-procedural cerebral DW-MRI data after TAVI (n = 1225). Among these studies, we included in a meta-analysis 6 studies investigating TAVI performed with versus without EPDs (n = 384). Primary endpoints were the number of new lesions per patient and the total lesion volume, while secondary endpoints were the number of patients with new lesions and the single lesion volume.
Results: The main pooled DW-MRI outcomes were: patients with new ischemic lesions, 77.5% (95% confidence interval = 71.7–83.3%); total lesion volume, 437.5 mm^3 (286.7–588.3 mm^3); single lesion volume, 78.1 mm^3 (56.7–99.5 mm^3); and number of new lesions per patient, 4.2 (3.4–5.0). The use of EPDs was associated with a significant reduction in total lesion volume (mean difference [95% confidence interval] = −111.1 mm^3 [−203.6 to −18.6 mm^3]; p = 0.02) and single lesion volume (−12.1 mm^3 [−18.3 to −6.0 mm^3]; p = 0.0001) after TAVI.
Conclusions: Silent cerebral injury occurs in the majority of patients undergoing TAVI and DW-MRI allows a precise characterization of new ischemic brain lesions. EPDs reduce the total and single volume of such lesions detected after the procedure, although the number of new lesions per patient and the number of patients with new lesions are not significantly reduced by such devices.

1. Introduction

Since the first case in 2002 [1], transcatheter aortic valve implantation (TAVI) has emerged as the treatment of choice for high-risk and inoperable patients with severe symptomatic aortic stenosis [2–5]. Although recent randomized trials have shown similar outcomes compared to surgical treatment in intermediate- or low-risk patients [6,7], one of the greatest barriers to TAVI extending into younger and lower risk subjects is the occurrence of cerebral injury.

Cerebrovascular events (CVEs) after TAVI mainly occur during an early high hazard phase in the first days following implantation [8]. A meta-analysis of approximately 10,000 patients indicated a stroke rate of 3.3% (±1.8%) at 30 days, with half of subacute events occurring in the first 24 h after TAVI [9]. Most acute ischemic CVEs result from embolization of aortic debris or thrombotic material during or after the procedure [10]. Importantly, the occurrence of stroke post-TAVI has been associated with a higher 30-day, 1-year, and 2-year mortality [9,11–13]. Despite the introduction of next-generation transcatheter

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valves, a recent meta-analysis showed a major stroke rate of 2.4% at 30 days [14] and PARTNER IIA trial reported a 30-day stroke rate of 5.5% after TAVI [6], confirming that acute neurological events still represent a major issue.

Several studies have shown that the incidence of silent cerebral injury is dramatically higher than that of clinically apparent CVEs. Brain diffusion-weighted magnetic resonance imaging (DW-MRI) allows the mapping of areas suffering from acute ischemia, which appear hyperintense as the result of a reduction in water diffusion rate [15]. The prognostic significance of this subclinical brain injury remains controversial, and a clear correlation between cerebral microinfarcts post-TAVI and long-term cognitive decline or behavioral changes has not been established. However, in various clinical contexts the occurrence of silent brain lesions has been linked to a higher incidence of stroke [16,17] or cognitive impairment and dementia [18–20].

Given the early risk of neurological injury during or after TAVI, the use of cerebral protection filters or embolic deflection systems seems logical. The relatively small incidence of clinically apparent CVEs makes them difficult to use as endpoints in clinical trials, shifting the attention to subclinical cerebral damage [21]. All studies evaluating embolic protection devices (EPDs) have focused on the assessment and characterization of new brain ischemic lesions on DW-MRI as the main efficacy endpoints [22].

Therefore, we aimed to perform a systematic review and pooled analysis of all studies reporting DW-MRI outcomes after TAVI, and subsequently a meta-analysis of studies evaluating EPDs during TAVI, with a special focus on the impact of such devices on DW-MRI endpoints.

2. Methods

2.1. Search strategy and study selection

All prospective studies reporting data from post-procedural DW-MRI after TAVI (last update December 24th, 2015) were evaluated for inclusion in the pooled analysis investigating the frequency and features of embolic events. We excluded studies with less than five patients and studies with overlapping populations. Two authors (MP, MC) independently searched PubMed, Embase, BioMedCentral, Google Scholar, and the Cochrane Central Register of Controlled Trials. In addition, we employed backward snowballing and searched abstracts from 2014 and 2015 relevant scientific meetings (Transcatheter Cardiovascular Therapeutics, American Heart Association, American College of Cardiology, European Society of Cardiology, EuroPCR, and PCR London Valves). The search strategy for PubMed is available as Supplemental Material. For studies evaluating the use of EPDs during TAVI, only patients enrolled in the arm without EPD and performing post-procedural DW-MRI were considered in the pooled analysis.

To address the effect of EPDs, we aimed to include in the meta-analysis any randomized controlled trial (RCT), prospective study, and study including consecutive patients performed in subjects undergoing TAVI with versus without EPDs and reporting post-procedural DW-MRI outcomes. Studies comparing the EPD group with a historical control group were excluded. All patients included in the meta-analysis were symptomatic for severe aortic stenosis and considered suitable for TAVI.

2.2. Data extraction

Two investigators (MP, MC) independently evaluated studies for possible inclusion. Non-relevant articles were excluded based on title and abstract. Two authors (EAM, MC) independently assessed study eligibility and extracted data on study design, measurements, patient characteristics, and outcomes. Conflicts about data extraction were discussed and resolved with another author (MP).

2.3. Outcomes

In the meta-analysis, we evaluated as primary endpoints both the number of new lesions per patient and the total lesion volume per patient (mm^3). Secondary endpoints were the number of patients with new lesions and the single lesion volume (mm^3). Early safety endpoints were all-cause mortality, acute kidney injury, major vascular complications, and life-threatening bleeding.

2.4. Statistical analysis

2.4.1. Pooled analysis

For the weighted meta-analysis of single arm studies computation was performed with Meta-analyst Beta 3.13 (Tufts Evidence-based Practice Center, Boston, Massachusetts). Outcomes were divided into dichotomous and non-dichotomous. Cumulative event rates were obtained and reported, for dichotomous outcomes, from a pooled analysis among selected studies. Pooled estimate rates and 95% confidence intervals (CIs) were obtained using a binary random-effects model, according to DerSimonian and Laird [23]. Non-dichotomous outcomes were compared by means of a continuous random-effects model, also in accordance with DerSimonian and Laird [23]. When data was available only as median and interquartile range, mean and standard deviation were calculated [24]. To assess heterogeneity across studies, we used Cochrane Q statistic to compute I^2 (a heterogeneity p-value ≤ 0.1 was considered significant). I^2 values of less than 25%, 25–50%, or more than 50% indicated low, moderate, or high heterogeneity, respectively.

Search strategy, study selection, data extraction, and data analysis were performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25].

2.4.2. Meta-analysis

Computation was performed with RevMan (Review Manager version 5.3, The Nordic Cochrane Center, The Cochrane Collaboration, Copenaghen, 2014) and Stata (version 14.1, Stata Corp., College Station, Texas). Pooled odds ratios (ORs) for categorical variables (dichotomous outcomes) and pooled mean differences for continuous variables (non-dichotomous outcomes) were calculated using a random-effects model. When data was available only as median and interquartile range, mean and standard deviation were calculated [24]. Hypothesis of statistical heterogeneity was tested by means of Cochran Q statistic and I^2 values [26]. Statistical significance was set at p-value < 0.05 (two-sided). Publication bias was assessed for primary endpoints using funnel plots comparing mean difference estimates with standard error. Egger's linear regression method was used to detect funnel plot asymmetry [27]. Analysis for primary and secondary endpoints was stratified by type of EPD (protection filter and deflection system) and type of valve (balloon-expandable and self-expanding device) with formal interaction test. A sensitivity analysis including only studies with a randomized design (RCTs) was also performed.

Search strategy, study selection, data extraction, and data analysis were performed in accordance with The Cochrane Collaboration and the PRISMA guidelines [25].

3. Results

3.1. Pooled analysis of DW-MRI studies

Nineteen full manuscripts [28–46] and 6 studies selected from recent scientific meetings [47–52] were included in the final pooled analysis (Fig. 1) for a total of 1225 patients who underwent TAVI with the self-expanding CoreValve (Medtronic, Minneapolis, Minnesota), balloon-expandable SAPIEN/XT/3 (Edwards Lifesciences, Irvine, California), or other prostheses (Table 1). The mean age was 81.6 years (95% CI: 80.9–82.3 years), mean Society of Thoracic Surgeons