WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 8, Issue 13, 295-305. Research Article ISSN 2277– 7105

CEREBRAL EMBOLIC PROTECTION DURING TRANSCATHETER AORTIC VALVE REPLACEMENT (TAVR): CLINICAL EVENT META-ANALYSIS

Ziad Eidhah Sharaf Alzahrani*[1], Abdullah Ali Saeed Alzahrani[2], Abdulaziz Ibrahim Abbas Alghamdi[3], Abdulmohsin Ahmed Ali Alghamdi[4], Abdulraheem Ahmad Abdulraheem Alghamdi[5], Abdulrahman Mohammed Hassan Alzahrani[6], Majed Abdullah Mohammed Almuafa[7], Alabbas Saleh Abbas Alghamdi[8], Razan Mahmoud A. Alshaheen[9], Abdulhamid Mahmoud A. Alshaheen[10]

[1,2,3,4,5,6,7,8]Medical Intern, Albaha, Albaha University, Saudi Arabia.

[9,10]Medical Intern, Arar Northern Boarder University, Saudi Arabia.

Article Received on
15 Oct. 2019,

Revised on 05 Nov. 2019,
Accepted on 25 Nov. 2019,

DOI: 10.20959/wjpr201913-16367

***Corresponding Author**
Ziad Eidhah Sharaf Alzahrani
Medical Intern, Albaha, Albaha University, Saudi Arabia.

ABSTRACT

Background & Purpose: Cerebral protection devices gain cerebral protection either through a filtering system (a landing net extracting emboli from the circulation), or a deflection system (alternating the route of the emboli away from the cerebral circulation to the systemic circulation). The Aim of this work is to provide cumulative data about the effect of Cerebral Embolic Protection (EP) During Transcatheter Aortic Valve Replacement (TAVR) on cardiac patients. ***Methods:*** A systematic search was performed of PubMed, Cochrane library Ovid, Scopus & Google scholar to identify Cardiology RCTs, clinical trials, and comparative studies, which studied the outcome of EP group versus Control group of TAVR patients. A meta-analysis was done using fixed and random-effect methods. The primary outcome was death or stroke event. The secondary outcome was rate of new ischemic lesions. ***Results:*** A total of 6 studies were identified involving 1185 patients, with 656 patients in EP group, and 529 patients in Control group. Regarding primary outcome measures, the fixed-effects model of the meta-analysis study showed highly significant decrease in death or stroke events in EP group compared to Control group ($p = 0.003$). Regarding secondary outcome measures, the fixed-effects model of the meta-analysis study showed non-significant difference in new ischemic lesions in EP group compared to Control group ($p > 0.05$). ***Conclusion:*** To conclude, use of EP seems to be related to

reductions in mortality rate and related to early clinical neurological effectiveness in patients undergoing TAVR.

KEYWORDS: Cerebral Embolic Protection, TAVR.

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is increasingly used to deal with patients with extreme symptomatic aortic valve stenosis who're considered inoperable or too high a threat for surgical aortic valve replacement (SAVR). regardless of its medical gain, TAVR is related to the risk of clinically happen temporary or irreversible neurological impairment.[1]

Stroke following transfemoral aortic valve replacement is a critical problem substantially increasing acute and long-time period morbidity and mortality. With careful neurological exam, stroke rates have been stated of up to 10.0% following TAVR.[2]

Embolic Protection (EP) is an approach to prevent embolization of thrombotic or calcific debris all through transcatheter aortic valve replacement (TAVR). Randomized controlled trials (RCT) investigating the efficacy and safety of EP devices were underpowered for clinical endpoints.[3]

Cerebral protection devices gain cerebral protection either through a filtering system (a landing net extracting emboli from the circulation), or a deflection system (alternating the route of the emboli away from the cerebral circulation to the systemic circulation).[4]

Transcatheter aortic valve implantation (TAVI) techniques have been associated with silent ischemic cerebral embolism as assessed via diffusion-weighted magnetic resonance imaging (DW-MRI) or high- intensity temporary signals as assessed by way of transcranial Doppler. Embolic protection devices (EPD) would possibly lessen the threat of cerebral embolic ischemic lesions, both clinically evident cerebrovascular accidents or silent ischemic lesions in patients undergoing TAVI. nevertheless, the efficacy of EPD inside the TAVI setting has only been investigated in research with relatively small sample sizes.[5]

Aim of the study: The Aim of this work is to provide cumulative data about the effect of Cerebral Embolic Protection (EP) During Transcatheter Aortic Valve Replacement (TAVR) on cardiac patients.

METHODS

This review was carried out using the standard methods mentioned within the Cochrane handbook and in accordance with the (PRISMA) statement guidelines.[6]

Identification of studies

An initial search carried out throughout the PubMed, Cochrane library Ovid, Scopus & Google scholar using the following keywords: Cerebral Embolic Protection, TAVR.

We will consider published, full text studies in English only. Moreover, no attempts were made to locate any unpublished studies nor non-English studies.

Criteria of accepted studies

Types of studies

The review will be restricted to RCTs, clinical trials, and comparative studies, either prospective or retrospective, which studied the outcome of EP group versus Control group of TAVR patients.

Types of participants: TAVR patients.

Types of outcome measures

Death or stroke event (1ry outcome)

Rate of new ischemic lesions (2ry outcome)

Inclusion criteria

English literature.

Journal articles.

Between 2015 until 2017.

Describing TAVR with either EP group or Control group.

Human studies.

Exclusion criteria

Articles describing other types of cardiac interventions.

Irrelevance to our study.

Methods of the review

Locating studies

Abstracts of articles identified using the above search strategy will be viewed, and articles that appear of fulfill our inclusion criteria will be retrieved in full, when there is a doubt, a second reviewer will assess the article and consensus will be reached.

Data extraction

Using the following keywords: Cerebral Embolic Protection, TAVR, data will be independently extracted by two reviewers and cross-checked.

Statistical analysis

Statistical analysis done using MedCalc ver. 18.11.3 (MedCalc, Ostend, Belgium). Data were pooled and odds ratios (ORs) as well as standard mean differences (SMD), were calculated with their 95 per cent confidence intervals (CI). A meta-analysis was performed to calculate direct estimates of each treatment, technique or outcome. According to heterogeneity across trials using the I^2-statistics; a fixed- effect model ($P \geq 0.1$) or random-effects model ($P < 0.1$) was used.

Study selection

We found 150 records; 110 were excluded based on title and abstract review; 40 articles are searched for eligibility by full text review; 17 articles cannot be accessed or obtain full text; 8 studies were reviews and case reports; 9 were not describing functional outcome; leaving 6 studies that met all inclusion criteria (Fig. 1).

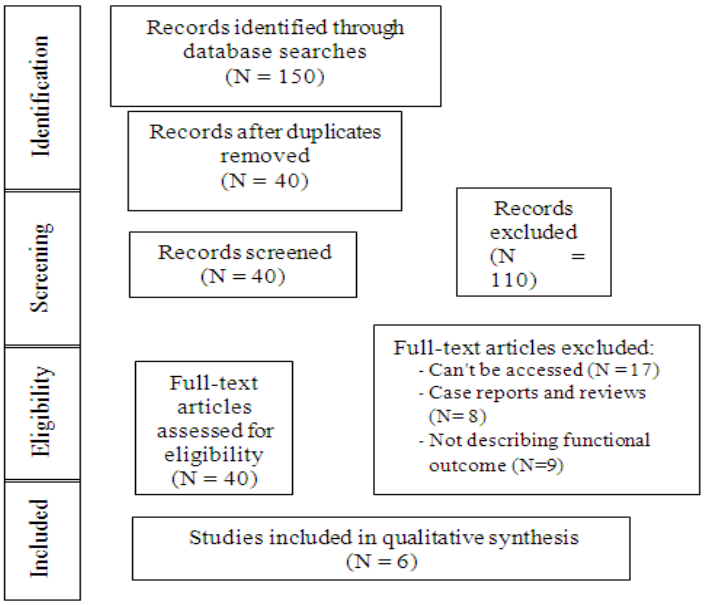

Figure 1: Flow chart for study selection.

RESULTS

Descriptive analysis of all studies included (Tables 1, 2)

Table 1: Patients and study characteristics.

N	Author	TAVR access site	Total	Number of patients		Age (average years)	Male (%)
				EP group	Control group		
1	***Lansky et al., 2015***	Femoral	85	46	39	82	45
2	***Wendt et al., 2015***	Transaortic	30	14	16	82	40
3	***Van Mieghem et al., 2016***	---	65	32	33	82	52
4	***Haussig et al., 2016***	Femoral	100	50	50	80	43
5	***Kapadia et al., 2017***	Femoral	345	234	111	---	---
6	***Seeger et al., 2017***	Femoral	560	280	280	80	45

#Studies were arranged according to publication year.

Table 2: Summary of outcome measures in all studies.

N	Author	Primary outcome		Secondary outcome	
		Death or stroke event		New ischemic lesions	
		EP group	Control group	EP group	Control group
1	***Lansky et al., 2015***	2	4	26	23
2	***Wendt et al., 2015***	0	0	8	11
3	***Van Mieghem et al., 2016***	1	4	16	13
4	***Haussig et al., 2016***	4	5	---	---
5	***Kapadia et al., 2017***	16	11	---	---
6	***Seeger et al., 2017***	6	19	4	13

The included studies published between 2015 and 2017. Regarding the TAVR access site, 4 studies (out of 6 studies) had femoral access, while 1 study had transaortic access.

Regarding patients' characteristics, the total number of patients in all the included studies was 1185 patients, with 656 patients in EP group, and 529 patients in Control group.

The average age of all patients was (81 years), with average (45%) male patients.

Meta-analysis of outcome measures

Data were divided into two groups:

EP group

Control group

Meta-analysis study was done on 6 studies which described and compared the 2 different groups of patients; with overall number of patients (N=1185).

Patients who achieved outcome measures were pooled:

Each outcome was measured by

Odds Ratio (OR)

Death or stroke event (1ry outcome)

Rate of new ischemic lesions (2ry outcome)

Regarding primary outcome measure, We found 6 studies reported death or stroke event with total number of patients (N=1185).

I^2 (inconsistency) was 0% with non-significant Q test for heterogeneity ($p > 0.05$), so fixed-effects model was carried out; with overall OR= 0.46 (95% CI 0.28 to 0.77).

The fixed-effects model of the meta-analysis study showed highly significant decrease in death or stroke events in EP group compared to Control group ($p = 0.003$).

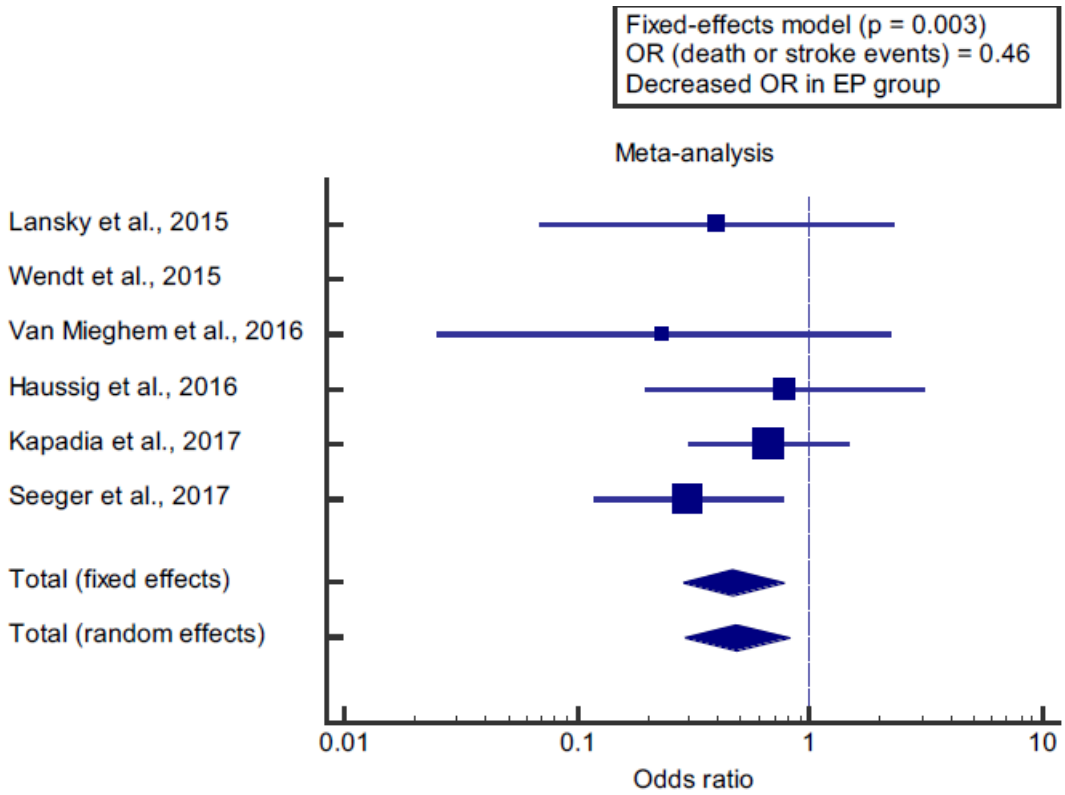

Figure 2: Forest plot of (death or stroke events) on EP group vs Control group – Odds ratio.

Regarding secondary outcome measure, We found 4 studies reported new ischemic lesions with total number of patients (N=740).

I^2 (inconsistency) was 38% with non-significant Q test for heterogeneity (p > 0.05), so fixed-effects model was carried out; with overall OR= 0.75 (95% CI 0.45 to 1.26).

The fixed-effects model of the meta-analysis study showed non-significant difference in new ischemic lesions in EP group compared to Control group (p > 0.05).

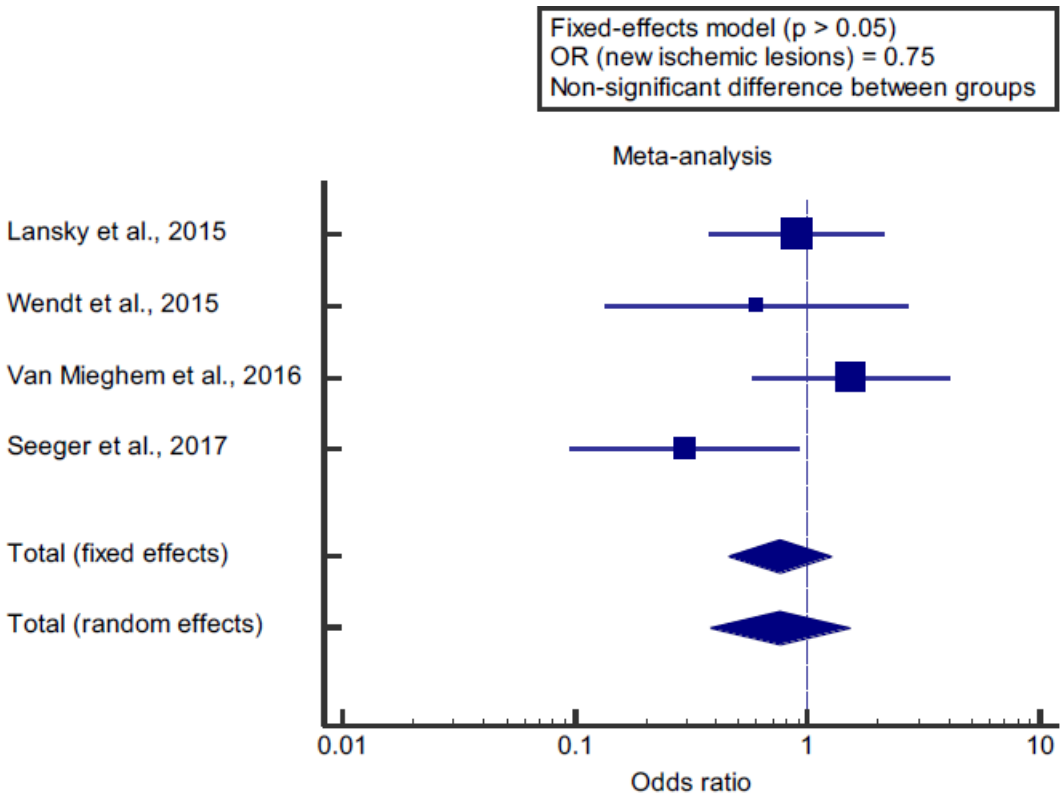

Figure 3: Forest plot of (new ischemic lesions) on EP group vs Control group – Odds ratio.

DISCUSSION

The Aim of this work is to provide cumulative data about the effect of Cerebral Embolic Protection (EP) During Transcatheter Aortic Valve Replacement (TAVR) on cardiac patients.

The included studies published between 2015 and 2017. Regarding the TAVR access site, 4 studies (out of 6 studies) had femoral access, while 1 study had transaortic access.

Regarding patients' characteristics, the total number of patients in all the included studies was 1185 patients, with 656 patients in EP group, and 529 patients in Control group.

The average age of all patients was (81 years), with average (45%) male patients.

Regarding Meta-analysis of outcome measures Data were divided into two groups **(EP group and Control group)**.

Meta-analysis study was done on 6 studies which described and compared the 2 different groups of patients; with overall number of patients (N=1185).

Regarding primary outcome measure; We found 6 studies reported death or stroke event with total number of patients (N=1185).

The fixed-effects model of the meta-analysis study showed highly significant decrease in death or stroke events in EP group compared to Control group (p = 0.003) which came in agreement with ***Seeger et al. 2019***[2] and disagreement with ***Bagur et al. 2017***[5] and with ***Giustino et al. 2016.***[7]

Seeger et al. 2019[2] reported that although, all-cause mortality and all-stroke were significantly lower (2.06% vs. 6.00%, odds ratio 0.34, 95%, relative risk reduction 66%, P = 0.0013).

Bagur et al. 2017[5] reported that Meta-analyses evaluating embolic protection device (EPD) versus without EPD strategies could not confirm or exclude any differences in terms of clinically evident stroke (relative risk, 0.70; P=0.26) or 30-day mortality (relative risk, 0.58; P=0.30).

Giustino et al. 2016[7] reported that Risk for overt stroke and all-cause mortality were non-significantly lower in the embolic Protection group.

Regarding secondary outcome measure; We found 4 studies reported new ischemic lesions with total number of patients (N=740).

The fixed-effects model of the meta-analysis study showed non-significant difference in new ischemic lesions in EP group compared to Control group (p > 0.05) which came in agreement with ***Samim et al. 2015***[8] and disagreement with ***Haussig et al. 2016.***[9]

Samim et al. 2015[8] reported that Post-TAVR Cerebral Diffusion Weighted-Magnetic Resonance Imaging (DWI) revealed new ischemic lesions in all patients in the Embrella group and in 35 (95%) cases in the TAVR-only group. Lesions were typically multiple in both groups with a significantly higher number of lesions in the Embrella group: a median of

9.0 lesions in the Embrella group and 5.0 lesions in the TAVR-only group (P > 0.05).

Haussig et al. 2016[9] reported that For the first hierarchical secondary end point, new lesion volume after TAVI was lower in the filter group (242 mm3) vs in the control group (527 mm3) (difference, 234 mm3; P = 0.001).

CONCLUSION

To conclude, use of EP seems to be related to reductions in mortality rate and related to early clinical neurological effectiveness in patients undergoing TAVR

ACKNOWLEDGMENTS

Conflict of interest

None.

Authorship

All the listed authors contributed significantly to conception and design of study, acquisition, analysis and interpretation of data and drafting of manuscript, to justify authorship.

Funding

Self-funding.

REFERENCES

1. Samim, M.; van der Worp, B.; Agostoni, P.; Hendrikse, J.; Budde, R. P. J.; Nijhoff, F.; Ramjankhan, F.; Doevendans, P. A.; Stella, P. R. TriGuard ™ HDH Embolic Deflection Device for Cerebral Protection during Transcatheter Aortic Valve Replacement: Use of Cerebral Protection Device in TAVR. *Cathet. Cardiovasc. Intervent,* 2017; *89*(3): 470–477. https://doi.org/10.1002/ccd.26566.
2. Seeger, J.; Kapadia, S. R.; Kodali, S.; Linke, A.; Wöhrle, J.; Haussig, S.; Makkar, R.; Mehran, R.; Rottbauer, W.; Leon, M. Rate of Peri-Procedural Stroke Observed with Cerebral Embolic Protection during Transcatheter Aortic Valve Replacement: A Patient-Level Propensity-Matched Analysis. *European Heart Journal,* 2019; *40*(17): 1334–1340. https://doi.org/10.1093/eurheartj/ehy847.
3. Giustino, G.; Sorrentino, S.; Mehran, R.; Faggioni, M.; Dangas, G. Cerebral Embolic Protection During TAVR: A Clinical Event Meta-Analysis. *J Am Coll Cardiol*, 2017; *69*(4): 465–466. https://doi.org/10.1016/j.jacc.2016.12.002.

4. Vlastra, W.; Vendrik, J.; Koch, K. T.; Baan, J.; Piek, J. J.; Delewi, R. Cerebral Protection Devices during Transcatheter Aortic Valve Implantation. *Trends in Cardiovascular Medicine*, 2018; *28*(6): 412– 418. https://doi.org/10.1016/j.tcm.2018.01.007.
5. Bagur, R.; Solo, K.; Alghofaili, S.; Nombela-Franco, L.; Kwok, C. S.; Hayman, S.; Siemieniuk, R. A.; Foroutan, F.; Spencer, F. A.; Vandvik, P. O.; et al. Cerebral Embolic Protection Devices During Transcatheter Aortic Valve Implantation: Systematic Review and Meta-Analysis. *Stroke*, 2017; *48*(5): 1306–1315. https://doi.org/10.1161/STROKEAHA.116.015915.
6. Liberati, A.; Altman, D.; Tetzlaff, J.; Mulrow, C.; Gøtzsche, P.; Ioannidis, J.; Clarke, M.; Devereaux, P.; Kleijnen, J.; Moher, D. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Healthcare Interventions. *Bmj.*, 2009; *339*.
7. Giustino, G.; Mehran, R.; Veltkamp, R.; Faggioni, M.; Baber, U.; Dangas, G. D. Neurological Outcomes With Embolic Protection Devices in Patients Undergoing Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Am Coll Cardiol Intv.*, 2016; *9*(20): 2124–2133. https://doi.org/10.1016/j.jcin.2016.07.024.
8. Samim, M.; Agostoni, P.; Hendrikse, J.; Budde, R. P. J.; Nijhoff, F.; Kluin, J.; Ramjankhan, F.; Doevendans, P. A.; Stella, P. R. Embrella Embolic Deflection Device for Cerebral Protection during Transcatheter Aortic Valve Replacement. *The Journal of Thoracic and Cardiovascular Surgery*, 2015; *149*(3): 799-805.e2. https://doi.org/10.1016/j.jtcvs.2014.05.097.
9. Haussig, S.; Mangner, N.; Dwyer, M. G.; Lehmkuhl, L.; Lücke, C.; Woitek, F.; Holzhey, D. M.; Mohr, F. W.; Gutberlet, M.; Zivadinov, R.; et al. Effect of a Cerebral Protection Device on Brain Lesions Following Transcatheter Aortic Valve Implantation in Patients With Severe Aortic Stenosis: The CLEAN-TAVI Randomized Clinical Trial. *JAMA*, 2016; *316*(6): 592. https://doi.org/10.1001/jama.2016.10302.

Papers included in our meta-analysis

- Lansky, A.J., Schofer, J., Tchetche, D., Stella, P., Pietras, C.G., Parise, H., Abrams, K., Forrest, J.K., Cleman, M., Reinöhl, J. and Cuisset, T., 2015. A prospective randomized evaluation of the TriGuard™ HDH embolic DEFLECTion device during transcatheter aortic valve implantation: results from the DEFLECT III trial. *European heart journal*, *36*(31): 2070-2078.

- Wendt, D., Kleinbongard, P., Knipp, S., Al-Rashid, F., Gedik, N., El Chilali, K., Schweter, S., Schlamann, M., Kahlert, P., Neuhäuser, M. and Forsting, M., 2015. Intraaortic protection from embolization in patients undergoing transaortic transcatheter aortic valve implantation. *The Annals of thoracic surgery*, *100*(2): 686-691.
- Van Mieghem, N.M., van Gils, L., Ahmad, H., Van Kesteren, F., Van Der Werf, H.W., Brueren, G., Storm, M., Lenzen, M., Daemen, J., van den Heuvel, A.F. and Tonino, P., 2016. Filter-based cerebral embolic protection with transcatheter aortic valve implantation: the randomised MISTRAL-C trial. *EuroIntervention*, *12*(4): 499-507.
- Haussig, S., Mangner, N., Dwyer, M.G., Lehmkuhl, L., Lücke, C., Woitek, F., Holzhey, D.M., Mohr, F.W., Gutberlet, M., Zivadinov, R. and Schuler, G., 2016. Effect of a cerebral protection device on brain lesions following transcatheter aortic valve implantation in patients with severe aortic stenosis: the CLEAN-TAVI randomized clinical trial. *Jama*, *316*(6): 592-601.
- Kapadia, S.R., Kodali, S., Makkar, R., Mehran, R., Lazar, R.M., Zivadinov, R., Dwyer, M.G., Jilaihawi, H., Virmani, R., Anwaruddin, S. and Thourani, V.H., 2017. Protection against cerebral embolism during transcatheter aortic valve replacement. *Journal of the American College of Cardiology*, *69*(4): 367-377.
- Seeger, J., Gonska, B., Otto, M., Rottbauer, W. and Wöhrle, J., 2017. Cerebral embolic protection during transcatheter aortic valve replacement significantly reduces death and stroke compared with unprotected procedures. *JACC: Cardiovascular Interventions*, *10*(22): 2297-2303.