Protected TAVR

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ABSTRACT: Stroke is the most feared, unpredictable and underrecognized complication of transcatheter aortic valve replacement (TAVR) which has not deceased with the refinement of TAVR technology. It has significant impact on quality of life and socioeconomic impact. Cerebral atheroembolism is mainly responsible for these strokes. Cerebral embolic protection devices (CEPD) target to prevent or reduce this cerebral atheroembolism. SENTINEL CEPD in the only CEPD available in India. PROTECTED TAVR trial showed that SENTINEL CEPD has an excellent safety record and appears to prevent disabling stroke. However, the evidence for constant reduction in periprocedural stroke is inadequate.

KEYWORDS: TAVR, Stroke, Cerebral embolic protection devices, SENTINEL

INTRODUCTION:

Transcatheter aortic valve replacement (TAVR) via trans- femoral access is a standard therapy for patients with severe aortic stenosis (AS) in elderly across the entire surgical risk spectrum[1,2]. Though the rate of complications related to TAVR are on decreasing trend due to refinement of the technique, stroke rates remain the same at 2-4%[3,4]. However, the stroke rates are often underreported as neurological examination by neurologist and/ or imaging were not part of majority of clinical studies and not routinely done in clinical practice. It is devastating and the most feared complication of TAVR also from patients' perspective. It increases mortality and morbidity substantially and has significant impact on socioeconomic aspects and quality of life. Cerebral embolic protection devices (CEPD) were developed to mitigate TAVR-related stroke along with the burden of cerebral embolic debris and have been shown to be safe in various clinical settings. However, their true efficacy in stroke prevention during TAVR remains to be demonstrated.

CLINICAL MANIFESTATIONS OF STROKE RELATED TO TAVR

Major/ clinically disabling strokes are clinically apparent. However minor strokes, transient ischemic attacks and neurocognitive decline are subtle and are often undetected. Silent cerebral infarcts go undetected unless imaging is done.

ETIOLOGY AND TIMIMG OF STROKE DURING TAVR:

Peri procedural or early strokes are mainly caused by athero- or thromboembolic events provoked by the disruption of atheromatous or calcific debris arising during several

procedural steps. A prior history of stroke, arterial/valvular calcium burden, bicuspid aortic valves, aortic valve pre-/postdilatation and valve-in-valve procedures have been identified as risk factors for the same[3,5]. Late strokes may be related to calcified native valve disruption, incomplete endothelialisation of the valve stent, suboptimal antiplatelet effect, new-onset atrial fibrillation and patient's overall atherothrombotic burden. Reduced renal function, diabetes mellitus and increasing age were found to be related to the incidence of late stroke[6].

HISTOPATHOLOGY OF THE EMBOLIC DEBRIS

Cerebral embolic debris is generated in at least 99% of TAVI patients and includes pieces of calcium, valve and aortic tissue, myocardium, or other organic or foreign matter[7]. One in four patients have an average of 25 pieces of debris $\geq$0.5 mm headed to the brain. Debris of this size has the potential to occlude cerebral arteries (e.g., MCA, ACA, PCA, BA).

CEREBRAL EMBOLIC PROTECTION DEVICES (CEPD):

According to mechanism of action, CEPDs can be classified into 2 groups: devices that capture (totally or partially) debris within the aorta before it reaches the brain, renal or peripheral arteries; or deflectors of debris from the aortic arch and its branches. The former may be positioned along the aortic arch and/or descending aorta or within the brachiocephalic trunk and/or common carotid arteries, while the latter are typically positioned along the roof of the aortic arch.

Devices can also be classified into partial capture devices (SENTINEL), full capture devices (Emblok [Innovative Cardiovascular Solutions], Emboliner [Emboline], FLOWer [AorticLab]), primarily deflective devices with small capture capacity (TriGUARD 3 [Keystone Heart/Venus Medtech], ProtEmbo [Protembis], POINT-GUARD [Transverse Medical]), and deflection and capture devices (CAPTIS [Filterlex]).

Currently only SENTINEL is available in India for clinical use.

SENTINEL:

The SENTINEL Cerebral Protection System is a CE and USFDA approved device which consists of 2 polyurethane filters with 140 mm diameter pores fixed in a flexible nitinol radiopaque frame, advanced from a 6 Fr sheath through the right radial or right brachial artery and deployed into the ostia of brachiocephalic trunk and left common carotid artery. It is designed to capture emboli passing into the cerebral circulation in 2 of the 3 branches of the aortic arch, but not the left subclavian, leaving the left vertebral circulation unprotected. The Sentinel device has been studied in 4 RCTs, MRI Investigation in TAVI with Claret (MISTRAL-C) trial, The Claret Embolic Protection and TAVI (CLEAN-TAVI) trial, SENTINEL trial,

and the Stroke Protection with Sentinel During Transcatheter Aortic Valve Replacement (PROTECTED-TAVR) trial.

The US SENTINEL IDE Study[7] was a larger multicenter study in which the authors reported debris in 99% of the filters. Despite a numerical reduction in all-cause stroke at 30 days, statistical significance was not met. Also, the median total new lesion volume in protected territories evaluated by DW-MRI 2-7 days post-TAVR did not differ significantly between the control and the CEPD groups. The CEPD group demonstrated a reduction in stroke within 72 hours after TAVR (classified as procedural stroke by the Neurologic Academic Research Consortium [NeuroARC] definitions) when compared to the unprotected group (3.0% vs 8.2%; p=0.053).

The recently published PROTECTED TAVR trial[8] was the first randomized, open-label, multicenter, all-comer trial powered for clinical endpoints. It enrolled 3,000 patients undergoing transfemoral TAVR with all commercially available transcatheter heart valves, to receive TAVR plus the SENTINEL device (CEPD group: 1,501 patients) or TAVR with no CEPD (control group: 1,499 patients). The primary endpoint was all stroke (hemorrhagic, ischemic, or undetermined status; disabling or non-disabling) up to 72 hours post-TAVR procedure or hospital discharge using NeuroARC definitions. Successful device deployment was achieved in 94.4% of patients. SENTINEL use did not significantly reduce the incidence of stroke within 72 hours post-TAVR or before hospital discharge compared to the control group. Disabling stroke (a secondary endpoint) was less frequent in the CEPD group (0.5%) compared to the control group (1.3). The number needed to treat to prevent 1 disabling stroke was 125 patients. Although the device proved to be safe and a possible effect on disabling strokes (a secondary endpoint) was seen, clear clinical benefit is yet to be demonstrated.

ONGOING TRIALS:

The BHF PROTECT-TAVI[9] (British Heart Foundation Randomized Trial of Routine Cerebral Embolic Protection in Transcatheter Aortic Valve Implantation) (n=7,730), is an open label, outcome-adjudicated, multicenter, all-comer randomized clinical trial in the UK that will randomize patients undergoing TAVR by any access route to CEPD (with the SENTINEL CEPD) or no CEPD, with no specific exclusion criteria. The primary outcome measure is stroke at 72 hours post-TAVR. Amongst a range of secondary outcome measures, a cost-effectiveness analysis at 12 months will be performed. Results are expected by July 2026.

CONCLUSIONS:

Stroke following TAVR occurs at constant rate despite advancement of TAVR technology, is underrecognized and is the most feared complication with significant socioeconomic impact. It remains largely unpredictable with majority of periprocedural strokes due to cerebral embolization. Evidence of the same is present in majority of TAVR patients. SENTINEL CEPD has an excellent safety record and appears to prevent disabling stroke. However, the evidence for constant reduction in periprocedural stroke is inadequate. Ongoing and upcoming trials will address it further.

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