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EDITORIAL COMMENT

Cerebral Embolism

A Silent Iatrogenic Complication of TAVR That Needs Voiced Consideration*

Olivier Barthélémy, MD, Jean Philippe Collet, MD, PhD, Gilles Montalescot, MD, PhD

Transcatheter aortic valve replacement (TAVR) has rapidly and definitely changed the way patients with aortic stenosis are treated. Both the number of procedures and the indications have increased worldwide, allowing the inoperable patient to be treated, the high risk patient to be treated less invasively, and the intermediate risk patient to have the choice of an alternative to surgery (1–4). Clinical stroke or transient ischemic attack is not uncommon after aortic stenosis treatment, ranging in the randomized studies from 5% to 6% at 30 days to 8% to 10% at 1 year—one-half of them being major/disabling strokes (**Table 1**). Current registry data report a 3.5% stroke rate at 30 days, which represents almost a 50% decrease as compared to early experience with TAVR (5). In addition, stroke related to TAVR appears to be less frequent than stroke with surgical aortic replacement (3). However, clinical stroke is only the emerging part of the iceberg. Silent cerebral embolism (CE) following TAVR is the hidden part of this iceberg occurring in three-quarters of the cases, regardless of the device or vascular access used. If the prognosis impact of clinical stroke is well established (6), the potential long-term deleterious impact of silent CE remains unknown. Whereas silent brain infarctions are known to be associated with cognitive decline and dementia, long-term cognitive performance appears to be preserved in >90% of TAVR patients despite a high intrinsic risk for cognitive deterioration (7,8). However, poor information and the absence of long-term controlled evaluation keep the problem mostly invisible as TAVR indications now reach lower-risk and/or younger patients. Better understanding, detection, and identification of preventive measures of TAVR-related CE are needed.

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In this issue of the *Journal*, Van Belle et al. (9) present a cerebral magnetic resonance imaging (MRI) nested study as part of the BRAVO (Effect of Bivalirudin on Aortic Valve Intervention Outcomes)-3 randomized trial. The randomized, open-label BRAVO-3 trial did not show superiority of bivalirudin over unfractionated heparin on any of the 2 primary or main secondary endpoints, including major bleeding, in 802 high-risk or inoperable patients undergoing TAVR (10). Routine diffusion-weighed MRI was performed after TAVR and before discharge in 4 (178 patients) of the 31 centers participating in the study. Only 60 patients of this subgroup of 178 patients (34%) finally had an MRI performed, which is a serious limitation to the study. CE was identified in two-thirds of the patients by central core lab reading. Among those who underwent MRI, 29 patients were randomized in the bivalirudin arm versus 31 in the unfractionated heparin arm. The primary endpoint (proportion of patients with new cerebral emboli on MRI) did not

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From the Université Paris 06, ACTION Study Group, INSERM-UMRS 1166, Institut de Cardiologie, Pitié-Salpêtrière University Hospital Assistance Publique-Hopitaux de Paris (AP-HP), Paris, France. Dr. Barthélémy has received lecture fees from Sanofi. Dr. Collet has received research grants to the institution or consulting/lecture fees from AstraZeneca, Bayer, Bristol-Myers Squibb, Daiichi-Sankyo, Eli Lilly, Fédération Française de Cardiologie, Lead-Up, Medtronic, Merck Sharp & Dohme, Sanofi, and WebMD. Dr. Montalescot has received research grants to the institution or consulting/lecture fees from ADIR, Amgen, AstraZeneca, Bayer, Berlin Chimie, Boehringer Ingelheim, Bristol-Myers Squibb, Beth Israel Deaconess Medical, Brigham and Women's Hospital, Cardiovascular Research Foundation, Celladon, CME Resources, Daiichi-Sankyo, Eli Lilly, Europa, Elsevier, Fédération Française de Cardiologie, Fondazione Anna Maria Sechi per il Cuore, Gilead, Institute of Cardiometabolism and Nutrition (ICAN), Janssen, Lead-Up, Menarini, Medtronic, Merck Sharp & Dohme, Pfizer, Sanofi, Servier, The Medicines Company, TIMI (Thrombolysis In Myocardial Infarction) Study Group, WebMD. Deepak L. Bhatt, MD, served as Guest Editor for this paper.

differ between the 2 groups. The number of emboli per patient, the total volume of emboli or clinical neurological deficit at 48 h were also not different between the 2 groups. Although the study is grossly underpowered, the selection bias evident, and the number of patients too small to make any realistic conclusion, the topic is so sensitive and the lack of information so alarming that attention must be paid to these 60 patients representing 1 of the largest series in the field.

It is important to remind ourselves that approximately one-half of strokes occur during the TAVR procedure. Transcranial Doppler studies have suggested that CE occurs mainly during positioning and release of the prosthesis (11). Procedural CE have been shown to be of varied nature. Debris captured in embolic protection devices consists of fibrin, calcified material, and connective tissue from aortic wall or native leaflets (12). Isolated thrombus remains rare (about 20%). Thus, mechanical interaction between the calcified native valve and the device play a significant role in CE genesis, which is also favored by postdilation, multiple device repositioning, and small annulus size. Thus, in contrast to percutaneous coronary intervention, periprocedural anticoagulation to prevent CE may only be of marginal benefit. The other 50% of strokes occur after 24 h and may be linked to enhanced thrombogenicity (unendothelialized stent struts, vessel wall disruption, tissue factor released from the native valve, flow turbulences, paravalvular leak, and so on) or new onset of atrial fibrillation. They are out of reach of periprocedural anticoagulation but may well be prevented by adequate post-procedural anticoagulation. The height of irony is that antiplatelet therapy and not anticoagulation has been the rule after TAVR, a heritage from the coronary stent experience that is possibly not applicable to TAVR.

Consequently, from the little we know about TAVR-related CE, the prevention of periprocedural CE relies mainly on the combination of optimal technical delivery and targeted anticoagulation using unfractionated heparin to reach an activated clotting time >250 s. Protamine should be avoided unless a major bleeding complication occurs. The technical issues rely on better devices (catheter size reduction, better profile, and retroflex [balloon expandable prosthesis]), better delivery (direct TAVR and avoid multiple recaptures with self-expanding prosthesis), and possibly the development of "smooth" devices (e.g., the Direct Flow Medical prosthesis, Direct Flow Medical, Inc., Santa Rosa, California), all of which can reduce the initial aggression of the aorta. Another strategy, although not exclusive, would be the use of embolic protection devices. The randomized DEFLECT (A prospective randomized evaluation of the TriGuard HDH embolic DEFLECTion device during transcatheter aortic valve implantation) III trial showed that such a device was safe and reduced the volume and number of CE (13).

TABLE 1 Stroke Rates in TAVR Studies

		Event	TAVR	Control*	p Value
PARTNER Inoperable (1)	30 days	All stroke/TIA	6.7	1.7	0.03
		Major stroke	5.0	1.1	0.06
	1 year	All stroke/TIA	10.6	4.5	0.04
		Major stroke	7.8	3.9	0.18
PARTNER High-Risk (2)	30 days	All stroke/TIA	5.5	2.4	0.04
		Major stroke	3.8	2.1	0.20
	1 year	All stroke/TIA	8.3	4.3	0.04
		Major stroke	5.1	2.4	0.07
U.S. CoreValve Pivotal (3)	30 days	Stroke	4.9	6.2	0.46
		Major stroke	3.9	3.1	0.55
	1 year	Stroke	8.8	12.6	0.10
		Major stroke	5.8	7.0	0.59
PARTNER 2 (4)	30 days	Neurologic event	6.4	6.5	0.94
		Disabling stroke	3.2	4.3	0.20
	1 year	Neurologic event	10.1	9.7	0.76
		Disabling stroke	5.0	5.8	0.46

Values are percentages unless otherwise indicated. *Control: surgical aortic valve replacement or medical treatment.

PARTNER = Placement of Aortic Transcatheter Valve Trial; TAVR = transcatheter aortic valve replacement; TIA = transient ischemic attack.

The prevention of post-TAVR CE could rely on optimal antithrombotic therapy. Dual antiplatelet therapy for 1 to 6 months is commonly used after TAVR but is totally empirical (14). Whether short (3 or 6 months) anticoagulation is needed after TAVR is widely discussed. Indeed, leaflet endothelialization occurs only within 3 months of the procedure and several reports have shown leaflet motion abnormalities on 4-dimensional volume-rendered computed tomography scan, often resolving with full anticoagulation (15). Moreover, new onset of atrial fibrillation after TAVR has been reported in up to 30% of patients, arguing in favor of post-procedural anticoagulation. The absence of anticoagulation therapy has been associated with a higher rate of valvular hemodynamic deterioration. The hypothesis of modern effective anticoagulation after TAVR is now being tested in the ongoing ATLANTIS (Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis) (apixaban 5 mg × 2 vs. dual antiplatelet therapy or vitamin K antagonist) and GALILEO (Global Study Comparing a rivAroxaban-based Antithrombotic Strategy to an antipLatelet-based Strategy After Transcatheter aortIc vaLve rEplacement to Optimize Clinical Outcomes) (rivaroxaban + acetylsalicylic acid vs. dual antiplatelet therapy) trials.

In conclusion, the deafening silence of clinical research on this iatrogenic complication of TAVR shall not continue. CE will be less and less silent in clinical trial results and hopefully less and less frequent in the patients undergoing treatment with this breakthrough technology.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Gilles Montalescot, ACTION Study Group, Institut de Cardiologie, Pitié-Salpêtrière University Hospital, 47 Boulevard de l'Hôpital, 75013 Paris, France. E-mail: gilles.montalescot@psl.aphp.fr.

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