JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 64, NO. 20, 2014

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER INC.

Letters

TAVR-Associated Prosthetic Valve Infective Endocarditis

Results of a Large, Multicenter Registry

In this study, we report the incidence, causes, and outcomes of prosthetic valve infective endocarditis (PIE) in 2,572 consecutive patients who underwent transcatheter aortic valve replacement (TAVR) (1,191 balloon-expandable transcatheter heart valves [THVs] [Edwards Sapien, Edwards Lifesciences Inc., Irvine, California], 1,343 self-expandable THVs [CoreValve, Medtronic, Minneapolis, Minnesota], and 38 other) in 14 centers between January 2008 and April 2013. Data were collected by retrospective review of hospital records using a standardized case report form conforming to the Valve Academic Research Consortium-2 criteria. All sites ensured ethics committee approval. We divided the onset of endocarditis into: 1) early-onset, diagnosed within 60 days of TAVR; 2) intermediate, between 60 and 365 days; and 3) late-onset, after 365 days (1–3). A total of 29 patients were identified with TAVR-PIE (incidence 1.13% [95% confidence interval: 0.76% to 1.62%]). Patients constituted a high-risk group characterized by advanced age (80 ± 6 years), high Society of Thoracic Surgeons score (13 ± 9), and Logistic EuroSCORE (23 ± 13). The majority (72%) had at least 1 pre-existing predisposing risk factor for infective endocarditis (IE), and 59% had >1 risk factor.

The majority (55%) of procedures were performed in a cardiac catheterization suite, 34% in a hybrid suite, and 11% in a surgical theatre. All patients received antimicrobial prophylaxis according to institutional practice. Incidence of TAVR-PIE was 1.1% (23 of 2,133) and 1.98% (6 of 303) after transfemoral and transapical TAVR, respectively. The incidence of TAVR-PIE was 1.93% (23 of 1,191) and 0.45% (6 of 1,343) after balloon-expandable and self-expandable THVs implantation, respectively. There was no evidence of a pattern or change in the onset of TAVR-PIE as experience with TAVR increased in the participating centers. Three patients underwent an aortic valve-in-valve procedure and were diagnosed with intermediate-onset TAVR-PIE. Overall median time to onset of IE symptoms was 158 days (range: 3 to 800 days). Diagnosis of early-onset TAVR-PIE was established in 28% (n = 8), intermediate-onset in 52% (n = 15) and late-onset in 20% (n = 6), resulting in a higher incidence within the first 12 months after TAVR (80%) and lower rates of late-onset (20%) if contrasted to surgical prosthetic valve endocarditis (PVE) (3). Patients commonly had a fever (76%), and heart failure was observed in one-third of the population, whereas 9 patients had embolic events during the course of IE (8 cerebrovascular accident [CVA] events and 1 ST-segment elevation myocardial infarction). Classic IE signs were infrequent. "Definite IE" was diagnosed in 83% (n = 24) and "possible IE" in the remaining. Blood cultures were positive in 73% (n = 21); the most common causes were *staphylococci* and *enterococci* in 50% of patients. **Table 1** summarizes pathogen information. Probable infective sources were identified in >70% of cases.

In the early-onset group, *staphylococcus aureus* and coagulase-negative *staphylococci* were the most prevalent (50%), suggesting nosocomial infections. Intermediate-onset IE is primarily healthcare-associated and *staphylococcal, enterococcal*, and *non-viridans* streptococcal species each accounted for 20%. Identified sources of bacteremia were iatrogenic (n = 3), recurrent bacteremia from systemic infections (n = 2), and systemic diseases (n = 4) (Osler-Weber-Rendu disease, colon cancer, advanced liver cirrhosis with previous IE, and advanced liver cirrhosis with drug-induced immune suppression). In the late-onset group, cultures grew *staphylococci* (33%) and *enterococci* (33%), which does not mirror the post-surgical late-onset PVE. Possible sources were recurrent bacteremia from healthcare-associated infections (n = 1), infected central catheter (n = 1), and colonic polyps (n = 1).

Although echocardiographic criteria are not easily applicable in PVE (4), especially with TAVR (5), combined transthoracic and transesophageal echocardiography yielded important findings in 86% (25 of 29) of patients, with prosthetic vegetations being the most common feature and mitral valve involvement evident in 14% (4 of 29).

Clinical follow-up was complete in all 29 patients (median 393 days [interquartile range: 191 to 785 days]), during which 62% (n = 18) died. Of these, 13 died during hospitalization for IE and 5 during

TABLE 1 Microbiological Etiology in Patients With TAVR-PIE Diagnosis

	All TAVR-PIE (n = 29)	Early-Onset (n = 8)	Intermediate-Onset (n = 15)	Late-Onset (n = 6)
Staphylococcus	9 (31)	4 (50)	3 (20)	2 (33)
S aureus	4 (14)	2 (25)	2 (13)	–
Coagulase-negative staphylococci	5 (17)	2 (25)	1 (6.5)	2 (33)
Enterococci	6 (21)	1 (13)	3 (20)	2 (33)
Streptococcus	4 (14)	–	4 (27)	–
Viridans group streptococci	1 (3.4)	–	1 (7)	–
Other streptococci	3 (10)	–	3 (20)	
HACEK	1 (3.4)	–	1 (7)	–
Non-HACEK gram negative bacteria*	1 (3.4)	–	1 (7)	–
Granulicatella adiacens	1 (3.4)	–	1 (7)	–
Polymicrobial†	1†	1†		–
Typical micro-organisms	13 (45)	2 (25)	9 (60)	2 (33)
Negative cultures	5 (17)	4 (50)	1 (7)	–
N/A	3 (10)	–	1 (7)	2 (33)

Values are n (%). *Escherichia coli. †Polymicrobial: 1 patient had blood cultures positive for E. faecalis and coagulase-negative staphylococci.

HACEK = Haemophilus species, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella species; N/A = cultures not available; PIE = prosthetic valve infective endocarditis; TAVR = transcatheter aortic valve replacement.

follow-up (1 patient treated medically had a relapse of endocarditis, 1 hemorrhagic CVA, 2 embolic CVA, and 1 recurrent sepsis). Three patients (3 of 29) underwent surgery and 1 underwent TAVR-in-TAVR (1 of 29), whereas the others were treated medically. In-hospital mortality for the surgical group was 67% (2 of 3); the surviving patient is still doing well, and the TAVR-in-TAVR patient is stable but with persistent severe mitral regurgitation. The only univariate predictor of all-cause mortality was the presence of chronic kidney disease (hazard ratio: 3.67; 95% confidence interval: 1.2 to 11.2; p = 0.023).

To our knowledge, this is the largest multicenter study to report the incidence of IE after TAVR. This complication is most commonly caused by *staphylococcal*, *enterococcal,* and *streptococcal* species. Our results suggest that the first year is a vulnerable period for infection of the THV, with a lower incidence of late-onset and higher incidence of intermediate-onset TAVR-PIE. Lack of complete endothelialization of the THV may have also contributed to the early infection post-TAVR.

In conclusion, despite timely and aggressive management, TAVR-PIE is associated with a very high mortality. Antimicrobial prophylaxis prior to any invasive procedure is recommended in all TAVR patients, even late after the procedure. In a post-TAVR patient with pyrexia and no obvious infectious source, clinicians should have a high index of suspicion of TAVR-PIE and perform a cautious search for potential causes of endocarditis. If diagnosed, these patients should be treated aggressively.

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http://dx.doi.org/10.1016/j.jacc.2014.09.021

JACC VOL. 64, NO. 20, 2014
NOVEMBER 18/25, 2014:2176–82

Please note: Dr. Latib is a consultant for Medtronic and Direct Flow Medical. Dr. Colombo is a minor shareholder in Direct Flow Medical. Dr. Glauber is a consultant for Sorin. Dr. Alfieri has received royalties from Edwards; and is a consultant for Symetis. Dr. Maisano is a consultant for Edwards, Medtronic, and St. Jude Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Latib and Naim contributed equally to this work.

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APPENDIX For a comprehensive list of the centers and physicians associated with this study, please see the online version of this article.

Coronary Myocardial Bridges

Pathophysiology and Clinical Relevance

The recent review by Corban et al. (1) highlights the limitations of the literature on myocardial bridges (MBs) and suggests the need for clearly defined terms and protocols. For example, to clearly establish the prevalence of MB, clinical identification should require 2 angiographic views obtained after nitroglycerin administration, rather than computed tomography (whose use should probably be limited to measuring length and depth). Chest pain, myocardial infarction, and sudden death are not systematically associated with MB of any anatomic severity; most MBs are benign. As Corban et al. (1) note, MBs actually prevent coronary artery disease (CAD) inside affected segments. Statements regarding pathophysiology, clinical indications, and adverse effects in MB require clearly defined inclusion and exclusion criteria (symptomatic or asymptomatic MB vs. MB with associated comorbidities that may influence clinical presentation, e.g., hypertrophic cardiomyopathy). To determine the cause of sporadic ischemic symptoms, workup must first rule out significant CAD; worsening of systolic, phasic arterial narrowing at MB sites (by dobutamine testing and angiography); and, especially, spasticity or endothelial dysfunction (by acetylcholine testing) (2–4).

Subselective intraluminal devices (e.g., pressure or Doppler wires, intravascular ultrasound catheters) should be generally avoided outside of experimental protocols because they can alter MB by inducing spasm and deforming the affected coronary segment (2,3). Incidentally, the "half-moon" sign associated with MB probably results from the fiberoptic probe bending at the MB site; it is not a true marker of MB severity (only of its presence).

Although fractional flow reserve has been advocated (1,2) as a measure of MB clinical severity and the prognosis of associated CAD, this measurement does not reveal the hemodynamic severity of MB, nor does it reflect prognosis, as it can in moderate atherosclerotic lesions. Definitive study of MB will require large, controlled, prospective, multicenter investigations with long-term, objective clinical follow-up. Anything less will only perpetuate the current state of confusion and uncertainty about this entity.

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http://dx.doi.org/10.1016/j.jacc.2014.07.992

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Myocardial Bridging

We were pleased to see a state-of-the-art review on myocardial bridging (1), but were surprised by the authors' failure to highlight several contemporary advances in the field.

First, it has become clear that traditional adenosine fractional flow reserve (FFR) is inadequate in testing the hemodynamic significance of a myocardial bridge (2). Because myocardial bridging creates a dynamic stenosis brought on by chronotropic and inotropic stimulation, simply dilating the artery