See Article page 1491.

Commentary: Subclinical valve thrombosis: A game-changer issue in transcatheter aortic valve replacement?

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CENTRAL MESSAGE

Heart teams should be aware of the incidence of subclinical valve thrombosis post-TAVR. A possible link to late stroke may influence the selection of patients for TAVR versus surgical AVR.

There is a growing interest in prosthetic valve thrombosis following transcatheter aortic valve replacement (TAVR). The high prevalence of subclinical valve thrombosis (SCVT) among nearly 1 in 5 patients post-TAVR,¹ the increasing use of high-resolution computed tomography (CT) for active SCVT screening, and a purported causal link between SCVT and early and late neurologic complications post-TAVR² have provided an impetus for accelerated research efforts in this area.

In this issue of the *Journal*, Woldendorp and colleagues³ conducted a meta-analysis of studies that systematically assessed SCVT after TAVR, with a focus on its prevalence, predisposing factors, clinical relevance, and therapeutic management. Among 3456 patients spanning 12 studies, SCVT occurred in 11.5%, whereas mean transprosthetic gradient was only slightly increased (2.2 mm Hg). Older age, depressed left ventricular function, and large prosthetic valve size (≥ 29 mm) were associated with SCVT. The striking main result of the study was that SCVT was independently associated with a nearly 3-fold increase in the risk of stroke during follow-up, compared with patients without SCVT (7.0% vs 2.6%, logistic odds ratio, 1.10, 95% confidence interval, 0.63-1.57, $P < .0001$). Moreover, they found an association between the use of oral anticoagulation (OAC) and a reduced risk of SCVT compared with patients on single or dual antiplatelet therapy (APT) (logistic odds ratio, -1.05, 95% confidence interval, -1.71 to -0.39,

$P < .0001$), with no significant differences between the 2 APT strategies.

The main strength of this systematic review is its inclusion of studies that used multidetector CT screening post-TAVR and standardized criteria for SCVT. This is in contrast to current literature, which is weakened by a lack of standardized definitions of SCVT across studies, as well as the use of low-sensitivity surveillance echocardiography in asymptomatic patients. This leads to a blurring of the lines between structural and nonstructural valve dysfunction and an underreporting of SCVT.⁴

The pathophysiology of SCVT remains elusive. The identification of robust clinical predictors of SCVT are needed, as systematic high-resolution CT screening of all recipients of TAVR remains problematic. Great variability in the onset of SCVT in relation to the TAVR procedure, the prevalence of renal failure precluding repeated contrast media injections, and cumulative radiation absorption in younger patients complicate longitudinal surveillance of SCVT. Older age and depressed ventricular function were 2 such predictors in the study by Woldendorp and colleagues,³ although of limited practical significance in the real world. The only prosthesis-related factor found to be associated with SCVT was large prosthetic valve size (≥ 29 mm), in accordance with a previous pooled study.⁵ Blood stasis, disturbances in periprosthetic blood flow patterns (native valve calcifications, valve-in-valve,

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perivalvular leaks, etc), or greater mechanical stress on the leaflets (crimping vs rigid stent) are all mechanisms that may explain differential rates of SCVT between TAVR and surgical AVR.^{2,4,6} Further investigations are needed to identify potential device- or procedural-related factors (eg, post-dilatation) that may help flag subgroups of patients at elevated risk for the development of SCVT.

A key question that remains unanswered is the clinical impact of SCVT. Early neurologic events are usually related to the procedure itself, whereas rates of subacute and late events are thought to be influenced by patient- or disease-specific factors and thromboembolic predisposing conditions.⁷ The main finding of this study is that SCVT was independently associated with a nearly 3-fold increase in the risk of stroke, in accordance with another recent meta-analysis.⁵ However, the timing of neurologic events was not consistently available across studies, making a direct causal relationship between SCVT and stroke impossible to establish, and diagnostic criteria of neurologic injury were not uniform. Also, the statistically significant association between SCVT and stroke after pooling the data was largely due to the results of only 2 studies, which had some overlap in the included patient populations.^{2,8}

Thromboembolic prophylaxis among patients undergoing TAVR remains controversial. As pointed out by the authors, an inverse correlation between a history of atrial fibrillation or a history of cerebrovascular disease and SCVT in their study could be explained by a more aggressive antithrombotic regimen in these patients, although these data were unavailable. Three to six months of double APT (or OAC + clopidogrel), and indefinite single APT (or OAC), are currently recommended, with the caveat that double APT has been shown to be associated with greater rates of bleeding, with no difference in ischemic event rates and hemodynamic changes, compared to single APT.^{9,10} The meta-analysis of Woldendorp and colleagues³ lends support to the notion of the efficacy of OAC in preventing SCVT. However, the risk of bleeding was not assessed and it remains a central concern, as shown in a recent randomized controlled trial.¹¹

The study by Woldendorp and colleagues³ provides a powerful word of caution that we cannot simply continue to ignore SCVT as an innocuous sequela of TAVR procedures, given the potential independent link between SCVT

and stroke. This review fits as a piece in the ongoing puzzle of prosthesis durability, which is incompletely elucidated for transcatheter valves. There is an urgent need to study the determinants of late hemodynamic performance and prosthetic durability, and this is all the more crucial as TAVR is moving toward first-line therapy for a large proportion of patients with aortic stenosis. Heart teams should be aware of the important issue of prosthetic valve thrombosis and integrate it when selecting patients and assessing the relative merits of TAVR versus surgical AVR on an individual basis. The extension of TAVR to lower-risk and younger patients and the potential risk of late strokes create some urgency to better understand the clinical relevance of SCVT and the role of antithrombotic medications and/or anticoagulation in patients undergoing TAVR.

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