# Possible Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves

**TO THE EDITOR:** Makkar et al. (Nov. 19 issue)[1] report possible subclinical leaflet thrombosis in up to 40% of patients involved in a clinical trial of transcatheter aortic-valve replacement (TAVR). In contrast, we found a relatively low incidence (7%) of possible subclinical valve leaflet thrombosis among patients in our series in which 255 patients underwent TAVR with the use of a CoreValve prosthesis.

A retrospective review of our series (unpublished data) showed that in 104 patients, cardiac computed tomography (CT) at a median of 7 days after implantation (range, 3 to 87) (in 51 patients), transesophageal echocardiography at a median of 45 days (range, 7 to 421) after implantation (in 76 patients), or both (in 23 patients) was performed. In 101 patients, the findings were deemed to be interpretable. Of these patients, 52% were receiving dual antiplatelet therapy, 19% aspirin or thienopyridine monotherapy, and 29% oral anticoagulation.

A definite thrombus was identified in three patients (3%; one patient each on days 31, 44, and 87 after implantation). All three patients were receiving continuous dual antiplatelet therapy. An additional four patients (4%) had hypoattenuated leaflet thickening (two patients on day 7 after implantation and one patient each on days 8 and 47 after implantation). We hypothesize that besides the antithrombotic strategy, the valve type (bovine vs. porcine) and design (intraannular vs. supraannular) might also be related to the occurrence of thrombosis, at least in self-expandable nitinol frames.

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1. Makkar RR, Fontana G, Jilaihawi H, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. N Engl J Med 2015;373:2015-24.
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**TO THE EDITOR:** Makkar et al. describe the phenomenon of reduced leaflet motion in patients who had received bioprosthetic aortic valves. An in vitro study by Ducci et al.[1] showed that TAVR produced substantial alteration of the flow pattern in the sinuses of Valsalva, creating regions of blood stasis that could lead to thrombus formation. This abnormal condition is not observed after conventional surgical aortic-valve replacement because the complete resection of the calcified leaflets allows preservation of the natural geometry and vortex dynamics of the aortic root. Moreover, with the use of TAVR implants, there is often angular or rotational misalignment with the sinuses and coronary ostia; this could further impair local blood flow.

The data reported by Makkar et al. and Ducci et al. suggest that the use of bioprosthetic valves per se is not sufficient to guarantee correct leaflet dynamics and avoid the need for anticoagulation. This finding may be particularly alarming in light of what has been clinically observed with surgical bioprostheses.[2-4] The data reported by Ducci and colleagues need to be taken into account when considering the use of TAVR in patients who cannot be treated with anticoagulants and in lower-risk patients.

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1. Ducci A, Tzamtzis S, Mullen MJ, Burriesci G. Hemodynamics in the Valsalva sinuses after transcatheter aortic valve implantation (TAVI). J Heart Valve Dis 2013;22:688-96.
2. Colli A, Verhoye JP, Heijmen R, Antunes M. Low-dose acetyl salicylic acid versus oral anticoagulation after bioprosthetic aortic valve replacement: final report of the ACTION Registry. Int J Cardiol 2013;168:1229-36.
3. Colli A, Mestres CA, Castella M, Gherli T. Comparing warfarin to aspirin (WoA) after aortic valve replacement with the St. Jude Medical Epic heart valve bioprosthesis: results of the WoA Epic pilot trial. J Heart Valve Dis 2007;16:667-71.
4. Colli A, Marchetto G, Salizzoni S, et al. The TRIBECA study: (TRI)fecta (B)ioprosthesis (E)valuation versus (C)arpentier Magna-Ease in (A)ortic position. Eur J Cardiothorac Surg 2016;49:478-85.
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**TO THE EDITOR:** Makkar et al. found that reduced aortic-valve leaflet motion commonly occurred after TAVR or surgical aortic-valve replacement, probably because of leaflet thrombosis. An analysis of their CT images showed that most leaflets with reduced motion were facing the noncoronary sinus of Valsalva. With identification of the location of the thrombosed leaflet, we can hypothesize that a mechanism responsible for this observation was the lack of coronary-bound blood flow in the noncoronary sinus. We have previously found that lack of coronary-bound blood flow in the noncoronary sinus was associated with stasis and reduced wall shear stress in the sinus[1]; theoretically, this could have increased the risk of thrombosis of the noncoronary leaflet.

Two additional factors that may contribute to this observation in TAVR are the misalignment of the prosthetic leaflets and the native sinuses of Valsalva and the abnormal location of the leaflets relative to the aortic annulus. Reduced flow in a coronary sinus because of a partially occluded coronary artery may also place the leaflet at risk for thrombosis. Studies to corroborate or refute this hypothesis are lacking.

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1. Moore BL, Dasi LP. Coronary flow impacts aortic leaflet mechanics and aortic sinus hemodynamics. Ann Biomed Eng 2015; 43:2231-41.

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**TO THE EDITOR:** Makkar et al. present data describing subclinical leaflet thrombosis in bioprosthetic aortic valves. Although this phenomenon may be real, the potential link to neurologic events is unclear, and the trial shows neither a causal nor a temporal link between imaging findings and clinical events.

Makkar and colleagues report three total strokes (two with reduced leaflet motion and one with normal leaflet motion), all of which occurred within 24 hours after the index procedure. Attributing these events to findings on CT that was performed at a subsequent time point (in two of the patients) is problematic. In addition, "significant" differences in rates of neurologic events were driven by three transient ischemic attacks (TIAs), which are difficult to adjudicate and probably multifactorial in this patient population.

As physicians who care for patients who have aortic stenosis, we have concerns that overreaction to these findings may lead to the use of aggressive anticoagulation regimens in elderly patients who are at high risk for bleeding. Although these findings warrant further study, at present the link to clinical events is weak and therefore major changes to clinical practice are premature.

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**THE AUTHORS REPLY:** We agree with Miljoen et al., Colli et al., and Hatoum et al. that the cause of leaflet thrombosis may be multifactorial, including but not limited to local flow dynamics in the aortic root after valve replacement, the antithrombotic strategy, the valve type and design, and perhaps implantation techniques. The hypothesis proposed by Hatoum et al. regarding stasis in the noncoronary sinus due to lack of coronary flow is certainly interesting, but it was not substantiated in our trial, since we observed this finding in multiple leaflets, irrespective of the location of the leaflet in relation to the coronary artery. Trials to elucidate the relative contribution of these factors to the pathogenesis of this phenomenon are lacking.

Kodali et al. raise a few issues. Multiple studies have confirmed the presence of subclinical leaflet thrombosis in both transcatheter and explanted surgical aortic valves.[1-4] We agree that

the cause of neurologic events (strokes or TIAs) in patients undergoing TAVR, especially in the immediate postprocedural period, is multifactorial. Hence, as we noted in our article, any association of subclinical leaflet thrombosis with neurologic events is "preliminary and inconclusive." Nonetheless, the significantly increased rate of TIAs, all of which occurred late and after CT studies, requires further investigation.

Routine anticoagulation in patients after TAVR cannot be recommended at present, given the high risk of bleeding in the current TAVR population and the uncertain clinical significance of this finding. However, these findings provide a sound rationale for some of the planned trials of various antithrombotic regimens after TAVR and call into question current guidelines regarding dual antiplatelet therapy. The response of the Food and Drug Administration — to incorporate CT imaging substudies in the upcoming trials of TAVR that involve low-risk patients — is appropriate. Given the findings of our trial, identification of elevated aortic-valve gradients, heart failure, or thromboembolic events in patients with bioprosthetic aortic valves should prompt physicians to consider CT to rule out valve thrombosis.

Colli and colleagues suggest caution in the use of TAVR in low-risk patients or those who cannot receive anticoagulants without adverse effects. The pivotal trials that established the net clinical benefit of TAVR involved high-risk patients who were not the most appropriate candidates for anticoagulation. Although our imaging findings are thought provoking, the expansion of TAVR should be guided primarily by large randomized trials or registries that are focused on clinical outcomes and that measure net clinical benefit. Our trial may stimulate further research on antithrombotic strategies after TAVR.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Leetmaa T, Hansson NC, Leipsic J, et al. Early aortic transcatheter heart valve thrombosis: diagnostic value of contrast-enhanced multidetector computed tomography. Circ Cardiovasc Interv 2015;8(4):e001596.
2. Latib A, Naganuma T, Abdel-Wahab M, et al. Treatment and clinical outcomes of transcatheter heart valve thrombosis. Circ Cardiovasc Interv 2015;8(4):e001779.
3. Egbe AC, Pislaru SV, Pellikka PA, et al. Bioprosthetic valve thrombosis versus structural failure: clinical and echocardiographic predictors. J Am Coll Cardiol 2015;66:2285-94.
4. Pache G, Schoechlin S, Blanke P, et al. Early hypo-attenuated leaflet thickening in balloon-expandable transcatheter aortic heart valves. Eur Heart J 2015 October 7 (Epub ahead of print).

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## Ibrutinib for Chronic Lymphocytic Leukemia

**TO THE EDITOR:** It is not surprising that Burger et al. (Dec. 17 issue)[1] report positive results in the Study of Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia (RESONATE-2), a randomized trial of ibrutinib versus chlorambucil in older patients with chronic lymphocytic leukemia (CLL). Chlorambucil has served as a comparator in trials of bendamustine, alemtuzumab, ofatumumab, and obinutuzumab, and longer durations of progression-free survival have been reported with each agent.[2-5] In addition, these trials have shown longer durations of overall survival with the use of ibrutinib and obinutuzumab.[1,2]

We reviewed our experience in the Connect CLL Disease Registry (ClinicalTrials.gov number, NCT01081015). This prospective observational study, which was conducted from March 2010 through January 2014, involved 1494 patients with CLL in the United States. We observed that only 40 of 889 patients with CLL (4.5%) received chlorambucil monotherapy as first-line therapy, and event-free survival with this agent was inferior to that with all other commonly used first-line regimens, even after adjustment for the patient's age, performance status, and Charlson comorbidity index score (hazard ratio for disease progression, relapse, or death, 2.7; 95% confidence interval, 1.3 to 3.7; P=0.008). Because of the superiority of alternative first-line regimens and the infrequent use of chlorambucil monotherapy, we do not think that chlorambucil monotherapy should serve as a comparator regimen in future studies of CLL.