Editorial

Impact of Acquired von Willebrand Syndrome in Severe Aortic Stenosis

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Aortic stenosis is the most common valvular disease in developed countries, and it is an increasing public health issue[1]. Normal aortic valve is composed of 3 leaflets, each of which is a thin, smooth, flexible, and mobile structure[2]. However, in aortic stenosis, these leaflets are thickened, fibrosed, and calcified, resulting in reduced leaflet mobility and progressive valvular obstruction[1]. Although lipid levels and inflammation may be important in the initiation phase, self-perpetuating processes of calcification are predominantly responsible for driving disease progression in the propagation phase[1]. There is an increasing evidence that senile lesions of aortic valve leaflets have several features, which are morphologically similar to atherosclerosis because of overlapping clinical factors in atherosclerosis including inflammation[3]. The pathogenesis of aortic stenosis shares various similarities with that of atherosclerosis[4-6].

In this condition, Heyde's syndrome, i.e., aortic stenosis associated with gastrointestinal bleeding, was first reported in 1958[7]. In the clinical settings, we often experience severe aortic stenosis patients with positive fecal occult blood test, in whom the bleeding improves after surgical therapy. In the current issue of *Journal of Atherosclerosis and Thrombosis*, Tamura *et al.* have demonstrated that >2/3 of the patients with severe aortic stenosis have shown the loss of large von Willebrand factor multimer, that most patients have hematologically shown acquired von Willebrand syndrome type IIA, that 38.7% of them had definite/possible Heyde's syndrome, that the loss of large von Willebrand factor multimer was correlated with the severity of aortic stenosis, and that anemia complicated with aortic stenosis was improved after successful aortic valve replacement, which was associated with the recovered large von Willebrand factor multimer[8]. The current study clearly demonstrated the mechanism regarding the gastrointestinal bleeding associated with severe aortic stenosis.

Recently, transcatheter aortic valve implantation has been developed and performed worldwide; this procedure is less invasive compared with open-heart surgery[9], which successfully achieved the primary objective and demonstrated the functional and anatomical effectiveness in patients with severe aortic stenosis[10]. Although heparin is required as the choice of anticoagulant for several cardiac surgical procedures, including open-heart aortic valve replacement and transcatheter aortic valve implantation, the acquired von Willebrand syndrome complicated with severe aortic stenosis is currently treated by surgical aortic valve replacement, with no therapeutic strategy for the loss of large von Willebrand factor multimer. Therefore, the new concept of therapeutic approach for such patients may be hopefully developed in the near future, as described in **Fig. 1**.

Conflicts of Interest

None.

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References

1) Pawade TA, Newby DE, Dweck MR. Calcification in Aortic Stenosis: The Skeleton Key. J Am Coll Cardiol 2015; 66: 561-577
2) Rajamannan NM, Evans FJ, Aikawa E, Grande-Allen KJ, Demer LL, Heistad DD, Simmons CA, Masters KS, Mathieu P, O'Brien KD, Schoen FJ, Towler DA, Yoganathan AP, Otto CM. Calcific aortic valve disease: not simply a degenerative process: A review and agenda for research from the National Heart and Lung and Blood Institute Aortic Stenosis Working Group. Executive summary: Calcific aortic valve disease-2011 update. Circulation 2011; 124: 1783-1791

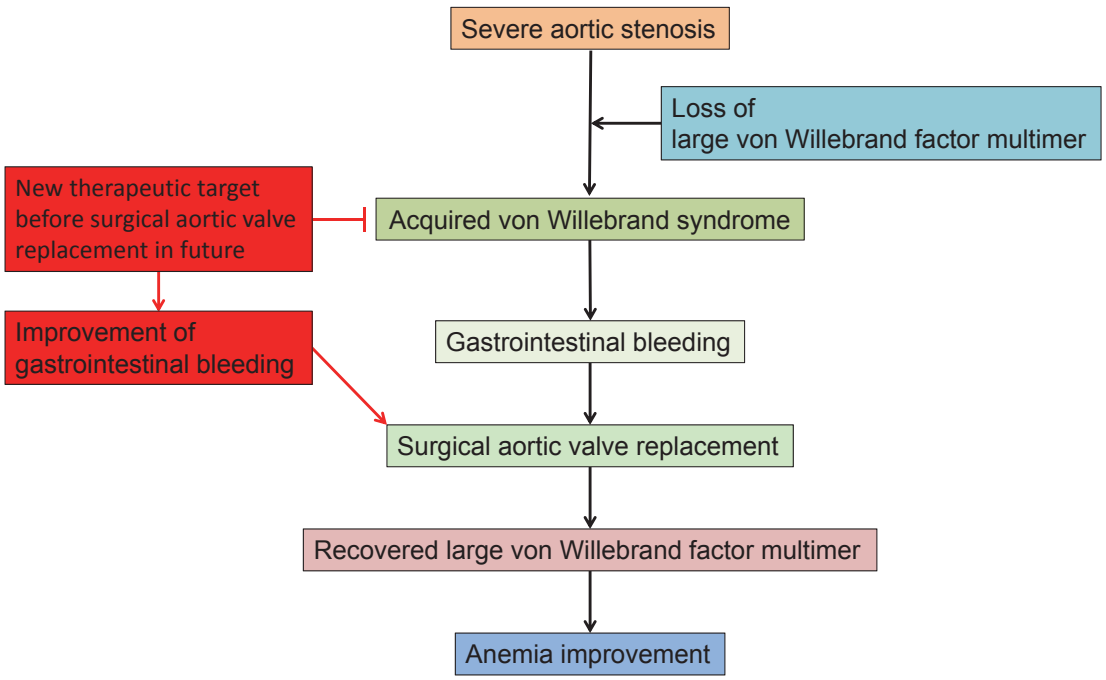

Fig. 1. Concept of new approach for acquired von Willebrand syndrome.

Patients with severe aortic stenosis, who have lost the large von Willebrand multimer, have gastrointestinal bleeding before surgical aortic valve replacement in the current situation (black arrows pathway). After the new therapy is developed for acquired von Willebrand syndrome in the near future, surgical therapy can be safely performed after anemia improvement (red arrows pathway).

3) Saladze T, Gogiashvili L, Tsagareli Z, Bakhutashvili Z, Kavtaradze T. Histological and Immunohistochemical Studies of Atherosclerotic and Senile Calcific Aortic Valve Stenosis. Georgian Med News 2015; 244-245: 94-99
4) Fukumoto Y, Shimokawa H, Ito A, Kadokami T, Yonemitsu Y, Aikawa M, Owada MK, Egashira K, Sueishi K, Nagai R, Yazaki Y, Takeshita A. Inflammatory cytokines cause coronary arteriosclerosis-like changes and alterations in the smooth-muscle phenotypes in pigs. J Cardiovasc Pharmacol 1997; 29: 222-231
5) Fukumoto Y, Libby P, Rabkin E, Hill CC, Enomoto M, Hirouchi Y, Shiomi M, Aikawa M. Statins alter smooth muscle cell accumulation and collagen content in established atheroma of watanabe heritable hyperlipidemic rabbits. Circulation 2001; 103: 993-999
6) Kaida H, Tahara N, Tahara A, Honda A, Nitta Y, Igata S, Ishibashi M, Yamagishi S, Fukumoto Y. Positive correlation between malondialdehyde-modified low-density lipoprotein cholesterol and vascular inflammation evaluated by 18F-FDG PET/CT. Atherosclerosis 2014; 237: 404-409
7) Heyde E. Gastrointestinal bleeding in aortic stenosis. N Engl J Med 1958; 259: 196
8) Tamura T, Horiuchi H, Imai M, Tada T, Shiomi H, Kuroda M, Nishimura S, Takahashi Y, Yoshikawa Y, Tsujimura A, Amano M, Hayama Y, Imamura S, Onishi N, Tamaki Y, Enomoto S, Miyake M, Kondo H, Kaitani K, Izumi C, Kimura T, Nakagawa Y: Unexpectedly High Prevalence of Acquired von Willebrand Syndrome in Patients with Severe Aortic Stenosis as Evaluated with a Novel Large Multimer Index. J Atheroscler Thromb, 2015; 22: 1115-1123
9) Dvir D, Webb JG. Transcatheter aortic valve-in-valve implantation for patients with degenerative surgical bioprosthetic valves. Circ J 2015; 79: 695-703
10) Sawa Y, Saito S, Kobayashi J, Niinami H, Kuratani T, Maeda K, Kanzaki H, Komiyama N, Tanaka Y, Boyle A, Zhang A, Moore BJ, de Medeiros R; MDT-2111 Japan Investigators. First clinical trial of a self-expandable transcatheter heart valve in Japan in patients with symptomatic severe aortic stenosis. Circ J 2014; 78: 1083-1090