Response to Letter Regarding Article, “Stent Thrombosis Late After Implantation of First-Generation Drug-Eluting Stents: A Cause for Concern”

We are grateful for the thorough comments by Agostoni et al and Kereiakes et al, which give us the opportunity to clarify our position. As Agostoni et al point out, important limitations exist in the measurements of luminal dimensions that may be magnified when the change in those dimensions are assessed by measurement of late loss (LL). Furthermore, there is variation in absolute quantitative coronary angiography (QCA) values according to core laboratories, which makes comparison of QCA data problematic. Regardless of these facts, QCA of lumen dimensions has long been the backbone of clinical studies in the field of restenosis. It has now become crucial to go beyond luminal measurements and to focus on both events that matter to the patient and their pathogenesis. For the patient, the clinical consequences of late stent thrombosis often are nonfatal myocardial infarction and death. Recently, late stent thrombosis and its consequences have become more the topic of committees dealing with the redefinition of end points and readjudication of events. Efforts by the Academic Research Consortium have indeed led to the introduction of new definitions and hence new analyses of pooled data by selected investigators and/or clinical research organizations. Although these efforts are valuable, they should not obscure the fact that the entire data set remains largely underpowered, so a robust answer to the raised concerns is simply not available yet. In addition, these efforts should not distract from necessary attempts to understand the biology of these late side effects, which seem to be the consequences of delayed healing and/or endothelial dysfunction. Our Figure 2 is a cartoon and was presented to illustrate a biological concept: Patients with vessel widening at follow-up (or positive remodeling: negative LL by QCA or late acquired malapposition by intravascular ultrasound) are likely to have an imperfect healing response with a higher risk for thrombosis as described by Virchow and consisting of an abnormal vessel wall lining (eg, incomplete in-stent endothelialization) and an abnormal blood-flow pattern (eg, slow flow secondary to positive vessel remodeling). The third component, altered blood constituents, is characterized by an increased blood thrombogenicity, which may occur after antplatelet therapy changes or as a consequence of systemic inflammation or dehydration. This hypothesis is supported by the finding of worse long-term outcomes in diabetic patients treated with drug-eluting stents, a group that experiences frequent and marked positive vessel remodeling, regardless of whether it is assessed by QCA (percentage of patients with negative LL) or by intravascular ultrasound (late acquired malapposition). It also is supported by the strikingly high rate of late acquired malapposition in patients presenting with DES thrombosis. Accordingly, the frequency distribution pattern of LL (eg, Gaussian, skewed, or biphasic) is irrelevant. What matters is the proportion of patients with negative LL, representing the “nonhealers” and captured by QCA by the area under the curve below the 0-point mark of the LL frequency distribution (Figure 3; DES, 40% to 50% versus BMS, 8% to 10%). We propose that this paradigm helps to identify a group of lesions at higher risk for late thrombosis, acknowledging that the positive predictive value in the individual patient will likely be very low because the events are rare and the biology may change over time.

The pathogenesis of late stent thrombosis remains complex, but we believe that its understanding can be clarified by keeping in mind the following concepts: (1) inflammation and imperfect healing are the primary site-specific causes and (2) the Virchow triad groups the following concepts: (1) inflammation and imperfect healing are the primary site-specific causes and (2) the Virchow triad groups the primary site-specific causes and (2) the Virchow triad groups the primary site-specific causes and (2) the Virchow triad groups the primary site-specific causes and (2) the Virchow triad groups the primary site-specific causes.

Disclosures

None.

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