Does Uncontrolled Platelet Activation Promote Coronary Artery Disease?*

Meinrad Gawaz, MD

Platelets play a critical role in the development of intracoronary thrombosis. Recent discoveries have documented that platelets augment chronic vascular inflammation and remodeling of the arterial wall resulting in progression of atherosclerosis (1,2). Dual antiplatelet therapy consisting of aspirin and adenosine diphosphate receptor inhibitor has become the cornerstone of preventing thromboischemic events in patients undergoing coronary stenting (3). High on-treatment platelet activity (HPR) after percutaneous coronary intervention is associated with enhanced occurrence of cardiovascular events and death (4–6). Clinical studies have shown that an increase in activation of circulating platelets is associated with the severity of coronary artery disease and progression of atherosclerosis (1,2,7). HPR correlates with coronary plaque burden and calcification as assessed by cardiac computed tomography (8). Further, systemic platelet activation is associated with progression of carotid artery disease in patients with diabetes (9) and cardiac transplant vasculopathy (10) within 1 year.

The effect of dual antiplatelet therapy in patients with coronary artery disease is highly variable and dependent on comorbidity (11,12). HPR is influenced by various clinical risk factors including diabetes mellitus, increased body mass index, left ventricular ejection fraction, renal failure, acute coronary syndrome, advanced age, and congestive heart failure (13,14). Previously, a simple clinical risk score, PREDICT (Residual Platelet Aggregation after Deployment of Intracoronary Stent), has been developed to identify patients with coronary artery disease at risk for HPR (15,16). The score encompasses different variables including acute coronary syndrome, older age, diabetes mellitus, and renal and left ventricular function impairment. After weighing these variables according to their effects size in multivariate analysis, the score ranged from 0 to 9 with higher score levels being significantly associated with both HPR and cardiovascular outcome. Thus, morbidity has a major impact of individual responsiveness on antiplatelet drugs.

In this issue of JACC, Yun et al. (17) have presented the results of a subgroup analysis derived from the ADAPT-DES (Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents) study (18). The ADAPT-DES study was a prospective, multicenter registry of a large cohort of patients (n = 8,582) that were successfully treated with drug-eluting stents (18). All patients received a dual antiplatelet therapy consisting of aspirin and clopidogrel as post-intervention antithrombotic prevention. The authors have assessed the issue of HPR using the VerifyNow P2Y12 assay (Accumetrics, San Diego, California) and its impact on clinical prognosis in these patients. HPR was related to stent thrombosis and myocardial infarction and was inversely associated with bleeding, a finding that has been confirmed by others previously.

In the present study, the authors have evaluated the impact of platelet reactivity on atherosclerotic burden and plaque morphology in a subgroup of patients derived from the ADAPT-DES study. Using intracoronary ultrasound, the authors have analyzed plaque burden of 909 culprit lesions from 773 patients. The authors found that HPR was observed more commonly in elderly patients, female patients, patients with diabetes, acute coronary syndrome, 3-vessel disease, high body mass index, and those having a history of heart failure and showing reduced...
left ventricular ejection fraction. Most strikingly, HPR was associated with atherosclerotic plaque burden and a higher incidence of vulnerable fibroatheroma. The results of the current study do not allow drawing a definite conclusion as to whether platelet reactivity is a causal mechanism for development and progression of coronary artery disease. However, the findings of the present study are compelling and require further scientific efforts to disclose the role of platelets for vascular inflammation, atherogenesis, and the development of vulnerable atherosclerotic plaques.

Coronary artery disease is considered as a chronic inflammatory disease influenced by circulating cells, including platelets (1,2). Platelet adhesion to the carotid artery occurs early during atherogenesis, which, in turn, leads to several steps in the development of atherosclerosis exemplified by the release of proinflammatory cytokines, chemoattractants, and enhanced monocyte/macrophage infiltration (19). Chronic inhibition of systemic platelet activation therefore reduces leukocyte accumulation and attenuates the progression of atherosclerotic lesions in mice (19). Platelets may mediate such effects by means of inflammatory mediators released after adhesion and activation. Indeed, platelet-derived cytokines and chemokines such as CXCL12 are found in atherosclerotic plaques, where they express biologic activities that may contribute to several aspects of the disease (20). Further, platelets are critical in development of monocyte-derived macrophage generation (21,22) and are a major source for oxidized low-density lipoprotein cholesterol and formation of foam cells at site of vulnerable plaques (23). Testing platelet reactivity might disclose individuals not only at risk for coronary thrombosis, but might also reveal platelet activation markers for ongoing platelet-driven systemic vascular inflammation, which in turn influences atheroprecession and occurrence of vulnerable plaques in the long term among patients with coronary artery disease. Extensive clinical studies are needed to analyze the impact of platelet function on disease progression, which might be accomplished by the ADAPT-DES research consortium. If on-treatment platelet reactivity as assessed by platelet function testing discloses patients at risk for accelerated disease progression, then an individualized antiplatelet strategy using alternative antiplatelet drugs such as prasugrel, ticagrelor, or vorapaxar or a prolonged duration of dual antiplatelet therapy (24,25) might be a promising future strategy to control progression of coronary artery disease.

REFERENCES


REPRINT REQUESTS AND CORRESPONDENCE: Dr. Meinrad Gawaz, Department of Cardiology, University of Tübingen, Otfried-Mueller-Strasse 10, 72076 Tübingen, Germany. E-mail: meinrad.gawaz@med.uni-tuebingen.de.


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