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High Platelet Reactivity on Clopidogrel Therapy Correlates With Increased Coronary Atherosclerosis and Calcification

A Volumetric Intravascular Ultrasound Study

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OBJECTIVES This study sought to evaluate the relationship between platelet reactivity and atherosclerotic burden in patients undergoing percutaneous coronary intervention (PCI) with pre-intervention volumetric intravascular ultrasound (IVUS) imaging.

BACKGROUND Atherosclerosis progresses by the pathologic sequence of subclinical plaque rupture, thrombosis, and healing. In this setting, increased platelet reactivity may lead to more extensive arterial thrombosis at the time of plaque rupture, leading to a more rapid progression of the disease. Alternatively, abnormal vessel wall biology with advanced atherosclerosis is known to enhance platelet reactivity. Therefore, it is possible that by either mechanism, increased platelet reactivity may be associated with greater atherosclerotic burden.

METHODS This study included patients who underwent PCI with pre-intervention IVUS imaging and platelet reactivity functional assay ($P2Y_{12}$ reaction units) performed >16 h after PCI, after the stabilization of clopidogrel therapy (administered before PCI). Platelet reactivity >230 $P2Y_{12}$ reaction units defined high on-treatment platelet reactivity (HPR).

RESULTS Among 335 patients (mean age 65.0 years, 71% men), there were 109 patients with HPR (32.5%) and 226 without HPR (67.5%), with HPR being associated with diabetes and chronic renal insufficiency. By IVUS analysis, patients with HPR had significantly greater target lesion calcium lengths, calcium arcs, and calcium indexes. Furthermore, patients with HPR tended to have longer lesions and greater volumetric dimensions, indicating higher plaque volume, larger total vessel volume, and also greater luminal volume, despite similar plaque burden. By multivariate analysis controlling for baseline clinical variables, HPR was the single consistent predictor of all IVUS parameters examined, including plaque volume, calcium length, and calcium arc.

CONCLUSIONS Increased platelet reactivity on clopidogrel treatment, defined as >230 $P2Y_{12}$ reaction units, is associated with greater coronary artery atherosclerotic disease burden and plaque calcification. (J Am Coll Cardiol Img 2012;5:540–9) © 2012 by the American College of Cardiology Foundation

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Enhanced platelet reactivity plays a pivotal role in arterial ischemic events, acute coronary syndromes, and complications of percutaneous coronary intervention (PCI) (1). In addition, the complex interactions among platelets, inflammatory cells, vascular cells, and chemokines also play a major role in atherosclerotic plaque and neointimal formation (2,3). Putative mechanisms whereby platelets may promote atherosclerosis include: 1) releasing chemokines and their precursors, which trigger the atherogenic recruitment of vascular cells or modulate processes such as angiogenesis or lipoprotein metabolism; 2) inducing chemokine secretion by endothelial and other vascular cells; and 3) binding and presenting vascular cell–derived chemokines to trigger arrest of circulating mononuclear cells (2,4–8). Huo et al. (9) showed that the injection of activated platelets exacerbated atherosclerotic lesion formation, a process involving platelet surface receptors that facilitate mononuclear cell recruitment. The deposition of the most abundant platelet chemokine, platelet factor-4, has been correlated with lesion severity and symptomatic atherosclerosis, suggesting that persistent platelet activation may contribute to the evolution of vascular lesions and supporting the rationale for long-term antiplatelet therapy in patients at risk for atherosclerosis (10). These observations not only extend the current view of platelets as being responsible for adhesion to the endothelium and propagation of endovascular thrombosis but also suggest that activated platelets play an important role in promoting the atherosclerotic process itself, in particular the stages relating to acute coronary syndromes. Furthermore, it is also well described that alterations in the vascular wall or situations inducing high shear stress may lead to secondary platelet activation (11,12). Therefore, as either a primary cause or a secondary consequence, there is a strong rationale to expect that platelet activation may be associated with atherosclerotic plaque burden.

Antiplatelet therapy is a cornerstone of cardiovascular disease management and secondary prevention (13). Significant reductions in ischemic complications in a wide range of patients with coronary artery disease have been demonstrated in major randomized controlled trials by the use of dual-antiplatelet therapy with a thienopyridine plus aspirin (14,15). However, clopidogrel nonresponsiveness (characterized as high on-treatment platelet reactivity [HPR]) (16) has been recognized to correlate with adverse events after acute coronary syndromes and PCI (17–24). Because most patients with known coronary artery disease are receiving long-term antiplatelet therapy, assessment of platelet reactivity and ascertainment of HPR status are relevant to clinical practice and patient outcomes. Importantly, a recent meta-analysis demonstrated that HPR is associated with long-term cardiovascular events after PCI, including death, myocardial infarction, and stent thrombosis (24). Although it is widely assumed that this is due to increased thrombotic events, a preliminary study recently reported that HPR may be associated with increased coronary artery atherosclerotic burden as assessed by cine angiography (25). In the present study, we sought to extend these findings and determine if HPR, as an indicator of high residual platelet reactivity in patients receiving clopidogrel, correlates with more extensive atherosclerotic disease as determined by volumetric intravascular ultrasound (IVUS) imaging, the gold-standard imaging modality for the assessment of atherosclerotic burden and calcification.

ABBREVIATIONS AND ACRONYMS

CSA = cross-sectional area

EEM = external elastic membrane

HPR = high on-treatment platelet reactivity

IVUS = intravascular ultrasound

PCI = percutaneous coronary intervention

METHODS

Patient population, PCI, and IVUS image acquisition. We analyzed 335 consecutive patients who underwent PCI with pre-intervention IVUS imaging and who had platelet function testing performed on the day after PCI. Only a single culprit target lesion and associated target vessel per patient were included in this study. IVUS of other vessels was not clinically indicated and was not performed. Key enrollment criteria were as follows: guideline-appropriate requirement for PCI, typically based on severe disease, positive stress test results, or presentation with unstable coronary syndromes; age >18 years; and signed informed consent. Exclusion criteria were as follows: presentation with ST-segment elevation myocardial infarction; serum creatinine ≥2.0 mg/dl;

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