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## Clopidogrel for the Hot Patient

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### Keywords

Editorials; flammation; platelets; stents; clopidogrel

Inflammation plays a critical role in the initiation, progression, and clinical complications of atherosclerosis.<sup>1</sup> Experimental evidence indicates that lesion formation is dependent on heterotypic interactions among immune cells, endothelial cells, and platelets. An emerging paradigm is the linkage between inflammation and thrombosis—namely, inflammation can beget thrombosis, and thrombosis can amplify inflammation. Inflammation itself promotes oxidative stress and endothelial dysfunction, resulting in deficiencies of endogenous antithrombotic factors such as nitric oxide, pro-s-tacyclin, and thrombomodulin.

Proinflammatory and prothrombotic cellular responses can also be triggered by soluble and cell adhesion signaling molecules. In particular, signaling by the CD40/CD40 ligand (CD40L) system may serve as a pivotal link between inflammation and thrombosis.<sup>2</sup> CD40L and CD40 are expressed on endothelial and smooth muscle cells as well as monocytes and have been implicated in various inflammatory responses to vascular injury.<sup>3</sup> Binding of CD40L to CD40 on endothelial cells upregulates the expression of inflammatory adhesion molecules (eg, vascular cell adhesion molecule-1 and intercellular adhesion molecule-1), tissue factor, and matrix metalloproteinases,<sup>4–6</sup> and it is required for atherosclerotic lesion formation.<sup>5</sup> Interestingly, platelets are the most abundant peripheral blood source of CD40L, which binds to glycoprotein IIb/IIIa and promotes thrombosis.<sup>7</sup> Indeed, platelets are now considered to be essential for atherosclerotic lesion initiation and lesion growth because of the delivery of platelet-derived proinflammatory factors (eg, RANTES [regulated upon activation, normal T cell expressed, and secreted] and platelet factor-4) to monocytes and the vessel wall.<sup>8,9</sup>

This linkage between inflammation and thrombosis has led to the hypotheses that antiinflammatory therapies may limit thrombosis and that antithrombotic therapies may reduce vascular inflammation.<sup>10</sup> Percutaneous coronary intervention (PCI) is known to

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#### Disclosures

Dr Simon serves on advisory boards or as a consultant for Accumetrics, Cordis/Johnson & Johnson, Daiichi-Sankyo, The Medicines Company, Medtronic Vascular, Portola, Sanofi-Aventis, and Schering-Plough and serves on the speaker's bureau for Accumetrics, Cordis/Johnson & Johnson, Daiichi-Sankyo, Lilly, The Medicines Company, Sanofi-Aventis, and Schering-Plough.

induce platelet activation, thrombosis, and a systemic inflammatory response as evidenced by a rise in the plasma levels of acute-phase reactants such as C-reactive protein (CRP), cytokines, chemokines, and soluble forms of adhesion molecules.<sup>11</sup> Failure to normalize CRP after PCI has been associated with increased rates of restenosis and target vessel revascularization.<sup>12</sup> Potent platelet inhibition during PCI with a glycoprotein IIb/IIIa inhibitor attenuates the rise of proinflammatory factors including CRP, tumor necrosis factor- $\alpha$ , soluble CD40L, and RANTES.<sup>11,13,14</sup> Oral antiplatelet therapy with clopidogrel has been shown to reduce soluble CD40L levels in patients with acute coronary syndromes and to improve systemic endothelial nitric oxide bioavailability in patients with coronary artery disease.<sup>15,16</sup>

In this issue of *Circulation: Cardiovascular Interventions*, Dosh et al<sup>17</sup> explore the relationship among clopidogrel therapy, inflammation, and major adverse cardiovascular events after PCI. The investigators used baseline high-sensitivity CRP (hs-CRP) and pregnancy-associated plasma protein-A (PAPP-A) levels as biomarkers of inflammation in patients undergoing elective PCI. Blood samples were obtained through a substudy of the CREDO (Clopidogrel for the Reduction of Events During Observation) trial. The main CREDO trial was designed to evaluate the benefit of long-term (12 months) treatment with clopidogrel (75 mg daily versus placebo) after PCI and to determine the benefit of initiating clopidogrel as a preprocedure loading dose (300 mg single dose versus placebo).<sup>18</sup> Both groups received clopidogrel (75 mg daily) for 28 days after PCI and aspirin (81 to 325 mg daily, at the discretion of the investigator) throughout the study. Levels of hs-CRP and PAPP-A were divided into tertiles for data analyses. There was no significant correlation between hs-CRP and PAPP-A levels. Event rates and unadjusted hazard ratios for tertiles 2 and 3 of hs-CRP and PAPP-A levels were found to be similar. Subsequently, the upper 2 tertiles for each biomarker (ie, hs-CRP  $\geq 1.5$  mg/L and PAPP-A  $\geq 0.79$  mIU/L) were combined for comparison against tertile 1 (ie, hs-CRP  $< 1.5$  mg/L and PAPP-A  $< 0.79$  mIU/L). Patients with hs-CRP levels in the second and third tertiles had an increased composite incidence of death, myocardial infarction, or stroke compared with patients with levels in the first tertile (at the 28th day, 8.0% versus 5.1%,  $P=0.04$ ; at 1 year, 11.4% versus 6.4%,  $P=0.003$ ). Similar associations were observed for patients with PAPP-A levels (at the 28th day, 8.1% versus 5.0,  $P=0.07$ ; at 1 year, 10.2% versus 6.8%,  $P=0.06$ ). Treatment with clopidogrel reduced the 1-year, but not the 28-day, composite end point for patients in tertiles 2 and 3 as compared with patients in tertile 1 (for hs-CRP, 9.1% versus 13.5%,  $P=0.04$ ; for PAPP-A, 7.3% versus 13.1%,  $P=0.01$ ). Importantly, there was no benefit of clopidogrel compared with placebo for patients in the first tertile hs-CRP or PAPP-A levels.

These tantalizing data suggest that clinical evidence of inflammation not only predicts major cardiovascular events in patients receiving PCI but also defines the patients who will benefit from clopidogrel therapy. These findings from CREDO are similar to the observation in the FRISC (Framingham and Fast Revascularization During Instability in Coronary Artery Disease) II trial that the clinical benefits of an invasive compared with conservative treatment strategy in patients with unstable angina/non-ST-segment-elevation myocardial infarction is limited to patients who had evidence of inflammation on the basis of IL-6

levels.<sup>19</sup> Similarly, the benefit of aspirin therapy for the primary prevention of myocardial infarction was greatest in apparently healthy men with evidence of baseline inflammation.<sup>20</sup>

The finding that the beneficial effects of clopidogrel are limited to patients with evidence of baseline inflammation has important clinical implications. The optimal duration of dual antiplatelet therapy after PCI with bare metal or drug-eluting stents is unknown, and it is the subject of intensive clinical investigation. The benefits of prolonged dual anti-platelet therapy with respect to ischemic events (cardiovascular death, myocardial infarction, and stroke) must be weighed in the context of an expected annual bleeding risk of 3.0% to 4.9% associated with dual antiplatelet therapy compared with 1.9% to 3.7% with aspirin alone.<sup>21</sup> Biomarker assessment of inflammation may assist the physician in identifying patients at higher risk for ischemic events. Inflammatory biomarker substudies from the Dual Antiplatelet Therapy trial (NCT00977938) testing the efficacy and safety of 12 versus 30 months of dual antiplatelet therapy in patients undergoing PCI with either drug-eluting or bare metal stents are, therefore, eagerly awaited.

The study by Dosh et al<sup>17</sup> raises several questions: (1) Were other inflammatory biomarkers investigated in addition to hs-CRP and PAPP-A? (2) Will inflammatory biomarkers be useful in patients with drug-eluting and bare metal stents? (3) Does more potent P<sub>2</sub>Y<sub>12</sub>-receptor blockade with drugs such as prasugrel, ticagrelor, or elinogrel have more profound antiinflammatory effects which could favorably impact the progression of atherosclerosis and longer term clinical events? (4) Is there a relationship between baseline inflammatory status and stent thrombosis or restenosis? We look forward to studies addressing these questions and are confident that leveraging the biological interactions between inflammation and thrombosis will improve clinical outcomes.

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