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*J. Am. Coll. Cardiol.* 1999;33;1294-1304

**This information is current as of October 12, 2008**

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# Pravastatin Therapy in Hyperlipidemia: Effects on Thrombus Formation and the Systemic Hemostatic Profile

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- OBJECTIVES** The study sought to determine the effects of lipid-lowering with pravastatin on the systemic fibrinolytic profile and on thrombus formation under dynamic flow conditions.
- BACKGROUND** Lowering cholesterol (C) decreases clinical events in coronary artery disease (CAD) patients, but an analysis of the effects of lipid-lowering on the entire hemostatic and thrombotic profile has not been conducted.
- METHODS** We prospectively studied 93 stable patients with untreated low-density lipoprotein cholesterol (LDL-C) >145 mg/dl. The CAD patients received pravastatin, and non-CAD patients were randomized to pravastatin versus placebo (double-blind). Thrombus formation upon an injured vascular surface was assessed in a substudy of 40 patients with a previously validated ex vivo perfusion chamber system. Systemic hemostatic markers and thrombus formation were evaluated at baseline, three and six months.
- RESULTS** Placebo produced no changes in either the lipid profile, any of the hemostatic markers, or the ex vivo thrombus formation. Both pravastatin groups (CAD and non-CAD) showed decreased LDL-C by 30% within 6 weeks (188 to 126 mg/dl,  $p < 0.001$  vs. baseline), and decreased plasminogen activator inhibitor-1 at 3- and 6-month follow-up compared to baseline (15% to 18% decrease at 3 months and 21% to 23% at 6 months). For the tissue plasminogen activator antigen, CAD and non-CAD groups showed significant decreases at 6 months compared to baseline (10% and 13%, respectively). No significant changes were observed with treatment in *d*-dimer, fibrinopeptide A, prothrombin fragment F<sub>1,2</sub>, factor VIIa, von Willebrand factor, or C-reactive protein. Fibrinogen levels were significantly increased at 6 months compared to baseline, though still below the upper normal limit. In the perfusion chamber substudy, there was a decrease in thrombus area in non-CAD patients treated with pravastatin at both 3 and 6 months compared to baseline (by 21% and 34%, respectively). The CAD patients showed decreases in thrombus formation by 13% at 3 months, and by 16% at 6 months. The change in LDL-C correlated modestly with the change in thrombus formation ( $r = 0.49$ ;  $p < 0.01$ ).
- CONCLUSIONS** Pravastatin therapy significantly decreased thrombus formation and improved the fibrinolytic profile in patients with and without CAD. These early effects may, in part, explain the benefit rendered in primary and secondary prevention of CAD. (J Am Coll Cardiol 1999;33:1294-304) © 1999 by the American College of Cardiology

Hyperlipidemia has been identified as a major risk factor for the development of coronary artery disease (CAD) (1), and lipid-lowering has been proven beneficial for the primary

and secondary prevention of CAD (2-4). Reduction of low-density lipoprotein cholesterol (LDL-C) has been associated with decreased progression and occasionally with regression of CAD (5-10), but the most profound effect of such intervention is the marked decrease in ischemic events (2-4,11,12).

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The development of acute coronary syndromes has mainly been attributed to thrombus formation upon a fissured, disrupted, or eroded plaque (13-15). The lipid-

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Manuscript received June 12, 1998; revised manuscript received October 29, 1998, accepted January 5, 1999.