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Comparative effects of 10-mg versus 80-mg Atorvastatin on high-sensitivity C-reactive protein in patients with stable coronary artery disease: results of the CAP (Comparative Atorvastatin Pleiotropic effects) study.

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Abstract

BACKGROUND: The major beneficial effect of statins- reducing the risk for coronary events-has primarily been ascribed to reductions in low-density lipoprotein cholesterol (LDL-C) but may in part be related to a direct antiinflammatory action (ie, decreased high-sensitivity C-reactive protein [hs-CRP] concentration). OBJECTIVES: The objectives of this CAP (Comparative Atorvastatin Pleiotropic Effects) study were to compare the effects of low- versus high-dose atorvastatin on hs-CRP concentrations and to determine the relationship between changes in LDL-C and hs-CRP concentrations in patients with coronary artery disease (CAD), low-grade inflammation, and normal lipoprotein concentrations. METHODS: This multicenter, prospective, randomized, double-blind, double-dummy study was conducted at 65 centers across Canada and Europe. Patients with documented CAD, low-grade inflammation (hs-CRP concentration, 1.5-15.0 mg/L), and a normal-range lipid profile (LDL-C concentration, 1.29-3.87 mmol/L [50-150 mg/dL]; triglyceride [TG] concentration, <4.56 mmol/L [<400 mg/dL]) were randomly assigned to receive 26-week double-blind treatment with atorvastatin 10 or 80 mg QD. Investigators were to aim for the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) LDL-C target of <2.59 mmol/L (<100 mg/dL). The primary end point was the percentage change from baseline in hs-CRP, as measured at baseline and weeks 5, 13, and 26 using high-sensitivity, latex microparticle-enhanced immunoturbidimetric assay. Changes from baseline in LDL-C, as measured directly in serum at the same time points, were also calculated. The secondary efficacy variables included the percentage changes from baseline in lipid parameters (LDL-C, high-density lipoprotein cholesterol [HDL-C], total cholesterol [TC], TG, apolipoprotein B, non-HDL-C, and TC:HDL-C ratio) at 5, 13, and 26 weeks of treatment. Tolerability was assessed using physical examination, including vital sign measurement, and laboratory analyses. RESULTS: A total of 339 patients were enrolled (283 men, 56 women; mean age, 62.5 years; weight, 81.3 kg; 10-mg/d group, 170 patients; 80-mg/d group, 169). No significant differences in baseline demographic or clinical data were found between the 2 treatment arms. In the 10-mg group, hs-CRP was decreased by 25.0% at 5 weeks and remained stable thereafter (%Delta at week 26, -24.3%; $P < 0.01$). In the 80-mg group, hs-CRP was decreased by 36.4% at 5 weeks and continued to be decreased over the study period (%Delta, -57.1% at week 26; $P < 0.001$ vs baseline). At 5 weeks, LDL-C was decreased by 35.9% in the 10-mg group and by 52.7% in the 80-mg group ($P < 0.001$ between groups) and remained stable thereafter (%Delta at week 26, -34.8% and -51.3%, respectively; $P < 0.001$ between groups). The NCEP ATP III LDL-C target of <2.59 mmol/L (<100 mg/dL) was reached in 77.1% of patients treated with atorvastatin 10 mg and 92.3% of those treated with 80 mg ($P < 0.001$). Dual targets of hs-CRP <2 mg/L and LDL-C <1.81 mmol/L (<70 mg/dL) were reached in a significantly greater proportion of patients in the 80-mg group compared with the 10-mg group (55.6% vs 13.5%; $P < 0.001$). The decrease in hs-CRP was largely independent of baseline LDL-C and change in LDL-C. Two serious adverse events were reported by the investigator as treatment related: acute hepatitis in the 10-mg group and intrahepatic cholestasis in the 80-mg group, in 2 patients with multiple comorbidities. Two deaths occurred during the study, both in the atorvastatin 80-mg group (1, myocardial infarction; 1, sudden death), neither of which was deemed treatment related by the investigator. CONCLUSIONS: In these patients with documented CAD, evidence of low-grade inflammation, and normal range lipid profiles, the effects of atorvastatin on changes in hs-CRP were dose dependent, with the high dose (80 mg) being associated with significantly greater reductions in hs-CRP concentrations. Both doses were associated with a significant and progressive decline in hs-CRP largely independent of changes in LDL-C, HDL-C, and TG. Clinical Trials Identification Number: NCT00163202.

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