

# Relationship between Baseline Levels of C-Reactive Protein, D-Dimer, and Progression of Atherosclerotic Vascular Disease in Patients with Symptomatic Arterial Disease

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## Purpose

C-reactive protein (CRP) is a plasma protein and a marker of inflammation. Elevated CRP levels are associated with an increased risk of ischemic heart disease. CRP is also an independent predictor of symptomatic peripheral arterial disease (PAD and is related to development of cerebrovascular disease). Fibrin D-dimer (DD) is a marker of fibrinolysis. Fibrinolysis is a normal part of the inflammatory response. Elevated DD levels may also reflect severity of atherosclerosis in that they have been associated with coronary heart disease and PAD.

Although CRP and DD are associated with the presence of atherosclerotic vascular disease, the relationship between these inflammatory and pro-thrombotic markers and the progression of atherosclerotic vascular disease is unknown. We studied this relationship by prospectively assessing baseline levels of CRP, DD and subsequent progression of atherosclerotic vascular disease in a cohort of patients with symptomatic arterial disease.

## Methods

Between 1996 and 2003, 384 subjects were enrolled in a National Institutes of Health trial evaluating atherosclerotic risk factors and progression of symptomatic PAD. Baseline levels of CRP and DD were obtained in each subject at study entry. Follow-up was every 6 months with clinical history, physical examination, ankle brachial indices (ABI) and carotid duplex scans (CDS). The primary study end point was a composite of ABI progression, CDS progression, stroke, myocardial infarction, amputation and death from cardiovascular disease. Secondary end points were each component of the primary end point. Time to end points and baseline CRP and DD levels were examined with life-table and Cox proportional hazards analysis.

## Results

Baseline values of CRP and DD were obtained in 332 subjects (mean age 67 years; 57.8% men). Mean follow-up was 38.4 months (range 1 to 99). Mean baseline CRP levels were 0.787 (range 0.03 to 13.0, SD  $\pm$  1.14). Mean DD levels were 227.4 (range 1.9 to 2744.8, SD  $\pm$  303.3). As defined by the primary end point progression of vascular disease occurred in 48.5% of subjects. Subjects with elevated CRP (highest tertile) were no more likely to have any of the progression end points than those with lowest values (lowest tertile) ( $p = ns$ , log rank test, for all comparisons). Subjects with elevated DD (highest tertile) were more likely to die from any cause compared to subjects with the lowest DD values (lowest tertile) ( $p = .03$ , log rank test). Subjects with elevated DD were, however, no more likely to reach any other end point including the primary end point ( $p = ns$ , log rank test for all other comparisons).

DD level was a significant independent variable associated with myocardial infarction ( $p = .04$ ). There was a weak association between DD level and cardiovascular death ( $p = .09$ ).

## Conclusions

Overall, in subjects with symptomatic PAD, death from cardiovascular cause was slightly more likely in those with elevated baseline DD. DD was significantly associated with the occurrence of MI. This study did not confirm a relationship between progression of PAD and baseline DD or CRP. Baseline DD and CRP do not provide useful risk stratification in patients at risk for progression of symptomatic PAD. Future studies should evaluate serial levels of these markers to assess their ability to predict PAD progression.