Prospective evaluation of the relationship between C-reactive protein, D-dimer and progression of peripheral arterial disease

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Objective: Elevated levels of C-reactive protein (CRP) and D-dimer (DD) have been associated with the presence and progression of various forms of atherosclerotic disease, particularly coronary heart disease. We hypothesize that there is a relationship between elevated levels of baseline CRP and DD and progression of peripheral arterial disease (PAD) in patients with symptomatic PAD. The current study is a prospective evaluation of this hypothesis.

Methods: Between 1996 and 2003, 384 subjects were enrolled in a National Institutes of Health-sponsored blinded, prospective trial evaluating the effects of multiple atherosclerotic risk factors on progression of symptomatic PAD. Baseline levels of CRP and D-dimer were obtained in 332 subjects. Subjects were followed every 6 months with clinical history and exam, ankle-brachial pressure index (ABI), and carotid artery duplex scanning (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 included each of the components of the primary end point. The relationship between time to the various endpoints and baseline CRP and DD levels was examined by life-table analysis and Cox proportional hazards analysis.

Results: Adequate baseline samples for CRP and DD were available in 332 subjects (mean age, 67 years; 57.8% men) with mean follow-up of 38.4 months (range, 1 to 99 months). Mean baseline levels (± SD) for CRP were 0.8 ± 1.14 (range, 0.03 to 13.0), and mean DD levels were 227.4 ± 303.3 (range, 1.9 to 2744.8). Progression, as defined by the primary end point, 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 the lowest values (lowest tertile) (P = NS, log-rank test, for all comparisons). By univariate analysis, subjects with elevated DD (highest tertile) were significantly more likely to die from any cause compared with subjects with the lowest DD values (lowest tertile) (P = .03, log-rank test). They were, however, no more likely to reach any of the other progression end points, including the primary end point (P = NS, log-rank test for all other comparisons). Multivariate analysis showed that DD level was a significant independent variable associated with occurrence of myocardial infarction (hazard ratio, 2.3; P = .02).

Conclusions: In subjects with symptomatic PAD, elevated baseline DD, a marker of thrombotic activity, was significantly associated with the occurrence of myocardial infarction. This study did not confirm a relationship between progression of PAD and baseline DD or CRP during the first 3 years. Baseline DD and CRP do not provide useful risk stratification in patients at high risk for progression of symptomatic PAD. Future studies should evaluate serial levels of these markers to assess their utility in predicting progression of symptomatic PAD. (J Vasc Surg 2006;43:772-80.)

Atherosclerosis is the leading cause of death and disability in developed countries. Despite considerable research effort, the cause of this important disease process remains unknown. Current efforts are focused on identifying risk factors that predispose patients to atherosclerosis. Well-known risk factors that have been found to increase the risk of developing symptomatic atherosclerosis include diabetes mellitus, smoking, hypertension, and hypercholesterolemia, among others.1

More recent studies have investigated the influence of alternative risk factors on the development of atherosclerotic arterial disease.2-5 Nutritional factors such as elevated homocysteine levels have been shown to be associated with the presence of atherosclerotic arterial disease and its progression.5 Lipid markers such as lipoprotein(a) and apolipoprotein A-1 are associated with premature atherosclerotic disease.5 Inflammatory markers such as C-reactive protein (CRP) and fibrinogen as well as thrombotic markers such as fibrin D-dimer (DD) and tissue plasminogen activator are now known to be associated with both ischemic heart disease and peripheral vascular disease.4,8

CRP is a plasma protein that is a marker for systemic inflammation. Single, elevated CRP levels have been associated with an increased risk of ischemic heart disease.6 It has also been shown that when CRP levels are decreased with statins, the risk for ischemic coronary events is also decreased.7 A study of the association between CRP and peripheral vascular disease (PAD) found that increased levels of serum CRP were an independent predictor of the development of symptomatic PAD.8 Elevated levels of serum CRP are related to the development of cerebrovascular disease.9 CRP levels can be lowered by removal of atherosclerotic plaque by carotid endarterectomy.10
Fibrin DD is a marker of cross-linked fibrin turnover and fibrinolysis. Fibrinolysis is a normal part of the inflammatory response, and studies suggest that elevated DD levels may be a measure of the severity of atherosclerosis. Elevated levels of DD have been associated with the presence of both coronary heart disease and PAD. DD levels have also been found to be inversely associated with functional performance in patients with and without PAD. Few studies have evaluated the relationship between these inflammatory and prothrombotic markers and the progression of atherosclerotic vascular disease. We hypothesize a relationship exists between elevated levels of baseline CRP and DD and the progression of PAD in patients with PAD. The current study is a prospective evaluation of this hypothesis.

METHODS

Patient selection. The Homocysteine and Progression of Atherosclerosis Study (HPAS) is a prospective, randomized, blinded clinical research study conducted at Oregon Health & Science University (OHSU) using the combined facilities of the Division of Vascular Surgery and the General Clinical Research Center. This study began in 1991 as a long-term follow-up study of patients with symptomatic PAD designed to examine the relationship between homocysteine levels, progression of symptomatic PAD, and vitamin treatment.

HPAS has been divided into two phases. The first phase was a prospective observational study of the relationship between homocysteine level, other risk factors, and progression of symptomatic PAD. The results of the first phase of HPAS have been reported previously. The second phase of HPAS is a prospective, randomized, double-blinded clinical trial of folate (4 mg/day) vs placebo to prevent progression of symptomatic PAD. The results of this treatment trial with respect to the influence of the treatment assignment (folate vs placebo) are being reported separately. Subjects for the present report were those participating in the treatment trial, the second phase of HPAS.

Patients were recruited for participation in HPAS if they had symptomatic PAD in at least one lower extremity, as indicated by claudication, bypass surgery, rest pain, or ischemic ulcer with vascular laboratory evidence of PAD (ankle-brachial index [ABI] <0.90), or symptomatic cerebral vascular disease (transient ischemic attack, stroke, carotid surgery with carotid stenosis >16% diameter reduction at the symptomatic site), or both. Subjects were not included unless at least one leg or carotid artery had not undergone surgery. Patients with unstable disease (limb-threatening ischemia, repeated transient ischemic attacks) were not enrolled until they had been treated and attained a stable status.

HPAS is fully approved by the Institutional Review Board of OHSU and by the Advisory Committee of the OHSU General Clinical Research Center. All subjects gave informed consent for participation.

Baseline clinical data. Before participation in the randomized treatment trial, all subjects provided their medical history and had a physical examination, laboratory testing, and vascular laboratory testing of the lower extremities and carotid arteries. Lower-extremity testing included segmental limb pressures and ankle pressure (ABI) response to treadmill walking. Carotid artery testing was performed with duplex ultrasound scanning (CDS) using the University of Washington criteria for diagnosis of carotid artery stenosis: category A, 0% stenosis; category B, 1% to 16% stenosis; category C, 17% to 49% stenosis; category D, 50% to 79% stenosis; category D+, 80% to 99% stenosis; category E, occluded.

C-reactive protein and D-dimer testing. CRP and DD levels were determined from blood samples obtained at baseline. High-sensitivity CRP and DD assays were performed by the OHSU General Clinical Research Center Core Laboratory. Quality control samples were included in each assay (2 for CRP, 4 for DD) at concentrations throughout the assay range. CRP levels were measured by using the automated Immulite chemiluminescent system (Diagnostic Products Corporation, Los Angeles, Calif). The interassay coefficient of variation ranged from 6.5% to 7.8%. DD levels were measured by a modified commercially available electroimmunoassay kit (Trinity Biotech USA, St. Louis, Mo). The interassay coefficient of variation ranged from 5.4% to 10.2%.

Follow-up. After baseline data accumulation and randomization, subjects were seen every 6 months. An interval history and physical examination was performed and vascular laboratory testing was repeated at each follow-up visit.

Treatment. Subjects underwent standard management of PAD. Nonoperative management included antiplatelet therapy with aspirin or clopidogrel, lipid lowering treatment, smoking cessation counseling, and the recommendation for daily walking exercise.

Revascularization for lower-extremity ischemia was performed for disabling claudication or limb-threatening ischemia and was performed by the investigators according to principles published previously. Carotid endarterectomy was recommended for asymptomatic progression to high-grade carotid stenosis or development of hemispheric symptoms in association with >50% carotid stenosis.

Definition of disease progression. In the HPAS study, progression of disease includes both lesion-defined parameters (vascular laboratory) and event-defined parameters (clinical events). The primary study end point is a composite that includes ABI progression, CDS progression, stroke, myocardial infarction, amputation, and death from cardiovascular disease. Secondary end points included each of the components of the primary end point. Nonfatal progression, as determined by means of symptoms, was documented during patient interviews at regular 6-month follow-up visits, by hospital discharge diagnoses, and by communication with primary care physicians. Death from any cause was also an end point. Cause of death was determined from autopsy reports when available or from hospital discharge summaries or death certificates. Vascular laboratory progression of lower-extremity disease was defined as a decrease in ABI of >0.15, and CDS progres-
sion was defined as an increase in carotid stenosis of at least one category.

Data analysis. Data are expressed as means ± SD and ranges.

Univariate analysis: For CRP and DD, subjects with the highest one third of values were compared with those with the lowest one third of values, for time to the primary and each of the secondary end points by life-table methods. Life tables were compared by log-rank testing.

Multivariate analysis: Hazard ratios (HR) with 95% confidence intervals (CI) for time to the primary and secondary end points as dependent variables were calculated using a Cox proportional hazards model for censored data. Log-CRP and log-DD were placed into the model as independent variables, and the model was fully adjusted for other independent variables including age, gender, diabetes mellitus, hypertension, log-cholesterol, log-homocysteine level, and smoking. The variables CRP, DD, cholesterol, and homocysteine were all highly skewed; the use of log-transformations reduced the skewness and improved the fit of the models. Because the ranges of values for log-cholesterol and log-homocysteine were small, we obtained hazard ratios corresponding to an increase of .10 on the log-scales (ie, an approximate 10% increase on the original scales). Blinded randomization group for the treatment trial (folate vs placebo) was also entered into the model as an independent variable.

RESULTS

Subjects. From August 1996 through November 2003, 384 subjects were entered into the study and were randomized. Of these, 361 subjects returned for at least one follow-up visit. Adequate baseline samples for CRP and DD were available in 332 subjects, and these comprised the current study group. Mean age was 67.2 ± 9.1 years, and 57.8% of subjects were male. Symptomatic lower-extremity disease was present at baseline in 270 subjects (82%), and symptomatic cerebrovascular disease was present in 140 subjects (43%). Eighty-eight subjects (27%) had both symptomatic lower-extremity disease and cerebrovascular disease. Mean lowest ABI was 0.75 ± 0.24. Median worst carotid stenosis was 17% to 49% diameter reduction (UW class C). Thirty-one percent of subjects were current smokers, and >80% of subjects had been smokers at some point in time. Additional risk factors for atherosclerosis present at study entry are listed in Table I.

Follow-up. The mean follow-up period for the 332 subjects in the study group was 38.4 ± 20.4 months (range, 1 to 99 months).

Nonfatal clinical progression. Nonfatal myocardial infarction occurred in 13 subjects (3.9%), 11 subjects (3.3%) had a stroke, and there were two amputations (0.6%) (Fig 1).

Vascular laboratory progression. A decrease in ABI >0.15 occurred in 76 subjects (22.9%). An increase in carotid artery stenosis of one category occurred in 98 subjects (29.5%). Some progression of disease by vascular laboratory criteria (ABI, CDS, or both) occurred in 142 subjects (42.8%) (Fig 1).

Survival. Eighty-three subjects (11.4%) died during the follow-up period. Fifty percent of all deaths (19 subjects, 5.7% overall) were attributed to cardiovascular etiology (Fig 1).

Primary composite end point. During follow-up, 161 subjects (48.5%) reached the primary composite end point. When any death was substituted for cardiovascular death, 175 subjects met the combined end point (52.7%) (Fig 1).

Baseline plasma C-reactive protein and D-dimer levels. The mean baseline plasma CRP level for all subjects was 0.8 ± 1.1 mg/L. Mean baseline DD level for all subjects was 227.4 ± 303.3 µg/mL. Baseline values for these and other relevant laboratory tests are listed in Table II.

Univariate analysis

By life table, there were no significant differences between subjects with the highest vs lowest tertiles of baseline CRP and DD with respect to myocardial infarction, stroke, amputation, carotid progression, ABI progression, cardiovascular death, or the primary composite end point. Death from any cause was significantly more likely to occur in subjects with elevated baseline DD levels (lowest tertile, 6.8% vs highest tertile, 15.5%; P = .03, log-rank
Table II. Selected baseline laboratory values in 332 subjects

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Mean ± SD (reference range)</th>
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</thead>
<tbody>
<tr>
<td>High-sensitivity C-reactive protein level (mg/L)</td>
<td>0.8 ± 1.1 (0-1.0)</td>
</tr>
<tr>
<td>Fibrin D-dimer level (µg/mL)</td>
<td>227 ± 303 (0-130)</td>
</tr>
<tr>
<td>Fasting serum cholesterol level (mg/dL)</td>
<td>199 ± 38 (0-199)</td>
</tr>
<tr>
<td>Plasma homocysteine level (nmol/mL)</td>
<td>12 ± 6 (4-12)</td>
</tr>
<tr>
<td>Plasma creatinine level (mg/dL)</td>
<td>1.3 ± 1.4 (0.7-1.3)</td>
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</table>

test). Figs 2 and 3 show the univariate, life-table curves for death from cardiovascular disease, death from any cause, and occurrence of the primary end point comparing the highest vs lowest tertiles of subject values for baseline DD and baseline CRP.

Multivariate analysis

Although randomization group (folate vs placebo) was not independently associated with the primary or any of the secondary end points (P = NS for all comparisons, data not shown), we retained randomization group in the multivariate model as it was instrumental in the design of the study and allowed us to adjust for any undetected effects of treatment assignment.

No significant differences in end-point occurrence were associated with age or gender (P = NS for all associations, data not shown). Age and gender were retained in the multivariate model because of their known influence on outcome of atherosclerotic disease from other studies. As expected, diabetes mellitus, hyperlipidemia, and hyperhomocysteinemia were all shown by Cox proportional hazards analysis to be significantly associated with one or more aspects of disease progression, as assessed by clinical progression, vascular laboratory progression, or death (Figs 4 to 7, Table III). These factors were therefore retained in the multivariate model.

Nonfatal clinical progression. Baseline DD level was significantly associated with the development of myocardial infarction (HR, 2.3; 95% CI, 1.12 to 4.76; P = .03) (Fig 4). Diabetes mellitus was also significantly associated with myocardial infarction (HR, 6.3; 95% CI, 1.59 to 25.28; P = .009) (Table III). No relationship was found between baseline CRP and myocardial infarction (HR, 0.63; 95% CI, 0.32 to 1.22; P = .17). No significant associations were found between baseline DD, baseline CRP, and stroke or amputation, or both (data not shown).

Vascular laboratory progression. There was no significant association between baseline CRP and DD and progression of ABI or CDS, or both (data not shown). Diabetes mellitus (HR, 1.82; 95% CI, 1.04 to 3.18; P = .03) and homocysteine (HR, 2.33; 95% CI, 1.17 to 4.61, P = .02) were associated with ABI progression (Table III). Cholesterol (HR, 3.78; 95% CI, 1.10 to 12.96, P = .03) was associated with CDS progression (Table III).

Survival. Baseline DD and CRP levels had no significant association with the risk of death from any cause (P = .50 for DD; P = .41 for CRP), or with death from cardiovascular disease (P = .15 for DD; P = .64 for CRP). Homocysteine (HR, 4.12; 95% CI, 1.76 to 9.64; P = .001) and cholesterol (HR, 14.77; 95% CI, 1.70 to 128.2; P = .01) were associated with death from any cause. Figs 5 and 6 show the hazard ratios associated with cardiovascular death and death from any cause for the factors included in the multivariate model.

Primary composite end point. Baseline CRP and DD had no significant independent association with time to the primary composite end point (HR, 1.07; 95% CI, 0.91 to 1.25; P = .44 for DD; HR, 0.90; 95% CI, 0.75 to 1.08; P = .26 for CRP) (Fig 7). Homocysteine (HR, 1.65; 95% CI, 1.00 to 2.73; P = .05) was associated with occurrence of the primary end point. Fig 7 shows hazard ratios associated with the various risk factors included in the multivariate model for the primary composite end point.

DISCUSSION

Except for a significant association between baseline DD and myocardial infarction (P = .04), the hypothesis tested by this study was not confirmed. Consistent with the findings of the first phase of the HPAS study, elevated baseline levels of homocysteine were significantly associated with an increased risk of achieving the composite end point, which included death from vascular disease, myocardial infarction, ABI decrease, CDS progression, stroke, and amputation. In the present analysis, a similar association was not present related to baseline DD or CRP levels.

The association between baseline DD and myocardial infarction is consistent with previous studies which have shown that elevated plasma levels of inflammatory and thrombotic markers, such as CRP and DD, are associated with the development of ischemic heart disease. Lowe et al were able to show an association between DD and baseline evidence of heart disease; however, the strength of this association was reduced in a multivariate analysis. Pai et al were able to show a moderate, but significant, independent relationship between CRP levels and risk of coronary disease (relative risk, 1.79).

There are several possible explanations for the fact that our study showed no association between baseline CRP and progression and minimal association between DD and progression. First, the sample size may have been too small to allow for statistical significance. The widths of the confidence intervals provide information about the precision of the hazard ratio estimators, and wide confidence intervals suggest larger sample sizes are needed. This is suggested by the fact that other well-established risk factors for progression of atherosclerotic disease (diabetes mellitus smoking, hypertension, cholesterol, age, gender) were associated with some but by no means all of the study end points.

Second, the length of follow-up may have been too short to allow an adequate number of clinical events to occur. Although one half of the subjects experienced an end point event, most of the end points occurring in this study were asymptomatic progression of disease detected.
in the vascular laboratory. The number of symptomatic events, including myocardial infarction, stroke, amputation, and death was small. Symptomatic progression of atherosclerotic disease has been associated with CRP and DD in published reports, but this relationship has not been previously examined for asymptomatic vascular-laboratory-detected progression. The current results suggest there may be little relationship.

Although previous studies of PAD patients have suggested higher event rates than were recorded in this study, the entry criteria for stable disease and the well-known beneficial effects of participation in a randomized trial may have selected/influenced the event rate in a negative direction. Alternately, the end points included in the analysis may not have been sensitive to CRP or DD levels. Had we chosen clinical end points such as the onset of rest pain, ischemic tissue loss, or evidence of plaque rupture, the findings may have been different.

Our findings that DD levels were minimally associated with the progression of symptomatic PAD are consistent with those of the Edinburgh Artery Study.14 In that study >1500 men and women were followed for 5 years in an attempt to detect the onset of PAD and determine whether elevated levels of DD were related to the progression of symptomatic PAD. These authors showed that DD levels were higher in patients who had worsening ischemia; how-

![Fig 2. Life-table survival curves for death from cardiovascular disease and death from any cause for highest vs lowest tertiles of D-dimer levels.](image)

![Fig 3. Life-table survival curves for the primary composite end point (ankle-brachial index decrease, carotid duplex progression, vascular death, myocardial infarction, stroke, amputation) for highest vs lowest tertiles of D-dimer and C-reactive protein (CRP) levels.](image)
ever, they found no factors that were predictive of disease progression by multivariate analysis. Despite the paucity of research showing an influence of inflammatory mediators on the progression of PAD, numerous studies show an association between these markers of inflammation and thrombosis and the presence of PAD. Elevated levels of CRP have been shown to be independently associated with the presence of PAD. The Physician’s Health Study found that elevated levels of CRP at baseline were an independent predictor of the development.
of PAD in asymptomatic subjects. Similarly, elevated DD levels have been shown to be independently related to the presence of claudication and to the severity of PAD as measured by the ABI. In addition, elevated levels of DD and CRP have been shown to be associated with increased functional impairment, decreased activity levels, and more rapid functional decline in patients with PAD. McDermott et al have also shown that patient-reported
Table III. Hazard ratios (with 95% confidence intervals) for relationship between log C-reactive protein and log D-dimer and study end points

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MI, Myocardial infarction; ABI, ankle-brachial index; CRP, C-reactive protein.

Values were obtained by means of multivariate Cox proportional hazards analysis adjusted for age, gender, randomization group, diabetes, smoking, hypertension, log-cholesterol, and log-homocysteine.

*Values significant at \( P < .05 \).
†Composite end point includes vascular death, myocardial infarction, stroke, amputation, ABI progression, carotid progression.
‡Variables were those determined at baseline.
§Hazard ratio estimates and confidence intervals correspond to an approximate 10% increase on the original (untransformed) scale.
**There were too few amputation end points to analyze (\( P \) values were 1.000 for all variables), therefore hazard ratios and confidence intervals not included.

Functional disability was greater in subjects with elevated CRP and DD. These findings were true for subjects with and without PAD.

The obvious question that arises when studying the effects of nonspecific markers of inflammation and thrombosis, such as DD and CRP, is the clinical relevance of these associations. Our data suggest little role for use of these markers as initial screening tests for the presence of PAD or for the risk of progression of symptomatic PAD.

CONCLUSION

Baseline DD levels were significantly associated with time to subsequent myocardial infarction in patients with symptomatic PAD. Baseline CRP was not related to any progression end point. Further research is needed to investigate the causative mechanisms involved, and larger prospective studies are needed to confirm the validity of these associations and determine the clinical utility of these measures.22

AUTHOR CONTRIBUTIONS

Conception and design: LMT, GLM, SEM
Analysis and interpretation: LMT, SEM, DP, RAS
Data collection: SEM, RAS, RU
Writing the article: SEM, LMT

Critical revision of the article: LMT, GLM, DP, RAS
Final approval of the article: LMT, SEM, DP, RAS
Statistical analysis: DP, RAS
Obtained funding: LMT
Overall responsibility: LMT

REFERENCES

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The study is a prospective evaluation of the relationship between C-reactive protein (CRP), and D-dimer (DD) and the progression of peripheral arterial disease (PAD). The authors are probing an important yet controversial clinical area. For the average reader, the presentation will be confusing and somewhat bewildering, as this article has been written for those who understand these types of trials and statistics. However, even the casual reader will be able to understand the fundamental questions and hypotheses. The authors studied 332 of 384 enrolled patients over a 7-year period. The patients were originally part of the Homocysteine and Progression of Atherosclerosis Study (HPAS). This trial started in 1991, and the first phase examined the relationship between the homocysteine level and progression of PAD. The second phase of the trial is a prospective, randomized, double-blind study examining the effects of folate vs placebo to prevent the progression of PAD.

The current study represents a secondary set of objectives derived from the second phase trial. The authors are presenting data that examined the relationship between time to the various end points and baseline CRP and DD levels. The data were examined by life-table analysis and Cox proportional hazards analysis. The data showed that in subjects with symptomatic PAD, death from a cardiovascular cause was slightly more likely in those with elevated baseline DD and that DD was significantly associated with the occurrence of myocardial infarction. However, the study did not find a relationship between progression of PAD and baseline DD or CRP. The findings of this study appear straightforward and are very important, as several other studies have suggested that DD and CRP as good markers to predict progression of PAD.

In summary, the study is extremely well designed and very well described. The study is important for two reasons. First, the authors have examined an important scientific and clinical question and have provided the reader with data showing that DD and CRP are not good markers of progression of PAD. These findings are contrary to several previous studies and as such are somewhat controversial. Second, this study is also important because it serves as an excellent example of how to design a clinical trial that has far reaching importance, yet examines very straightforward and simple hypotheses.

INVITED COMMENTARY

Stuart I. Myers, MD, Richmond, Va

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