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Article in *Journal of Periodontology* · August 2008

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Inflammation, C-Reactive Protein, and Atherothrombosis

Paul M Ridker*† and Josh D Silvertown‡

Atherothrombosis of the coronary and cerebral vessels is understood to be a disorder of inflammation and innate immunity, as well as a disorder of lipid accumulation. From a vascular biology perspective, the processes of cellular adhesion, monocyte and macrophage attachment, and transmigration of immune cells across the endothelium are crucial steps in early atherogenesis and in the later stages of mature plaque rupture, particularly the transition of unstable plaque at the time of acute thrombosis. There is abundant clinical evidence demonstrating that many biomarkers of inflammation are elevated years in advance of first ever myocardial infarction (MI) or thrombotic stroke and that these same biomarkers are highly predictive of recurrent MI, recurrent stroke, diabetes, and cardiovascular death. In daily practice, the inflammatory biomarker in widest use is high-sensitivity C-reactive protein (hsCRP); when interpreted within the context of usual risk factors, levels of hsCRP <1, 1 to 3, and >3 mg/l denote lower, average, and higher relative risk for future vascular events. Risk-prediction models that incorporate hsCRP, such as the Reynolds Risk Score, have been developed that improve risk classification and the accuracy for global risk prediction, particularly for those deemed at “intermediate risk” by usual algorithms, such as the Framingham Risk Score. With regard to cerebral vessels, increased biomarkers of inflammation, including hsCRP, have been associated with increased stroke risk as well as an increased rate of atherosclerosis progression in the carotid vessels. Although the proportion of variation in hsCRP explained by genetic factors may be as large as 20% to 40%, diet, exercise, and smoking cessation remain critical tools for risk reduction and CRP reduction. Statin therapy reduces hsCRP in a largely low-density lipoprotein (LDL)-independent manner, and the “anti-inflammatory” properties of these agents have been suggested as a potential mechanism beyond LDL reduction for the efficacy of these agents. The ongoing multinational Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial of 17,802 initially healthy men and women with low levels of LDL cholesterol but increased levels of hsCRP will help to define whether vascular protection can be achieved with statin therapy, even in the absence of hyperlipidemia. Targeted anti-inflammatory therapies are being developed that may provide a direct method of translating the biology of inflammation into new clinical treatments across multiple vascular beds. This article summarizes data supporting a role for inflammation in cardiovascular disease and offers the possibility that other disorders characterized by inflammation, such as periodontal disease, may have an indirect role by influencing the risk, manifestation, and progression of vascular events. *J Periodontol* 2008;79:1544-1551.

KEY WORDS

Cardiovascular disease; cholesterol; myocardial infarction; periodontal disease; Reynolds Risk Score; statin.

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Evidence supporting a link between periodontal disease (PD) and cardiovascular disease (CVD) is accumulating in the literature. Data derived from a meta-analysis of five prospective cohort studies, five case-control studies, and five cross-sectional studies suggested a positive correlation between PD and coronary heart disease (CHD).¹ After adjusting for risk factors, such as smoking, diabetes, alcohol intake, obesity, and blood pressure, subjects with PD had a 1.14- to 1.59-fold greater risk for developing CHD compared to those without PD. Although the mechanism underlying this association is not clearly understood, it was reported that specific bacteria (*Aggregatibacter actinomycetemcomitans* [previously *Actinobacillus actinomycetemcomitans*] and *Porphyromonas gingivalis*) that colonize periodontal pockets are also present in human atherosclerotic plaques and can gain access to the circulation through oral tissue.^{2,3} These pathogens produce lipopolysaccharide, which, in turn, induces macrophages to secrete cytokines (interleukin [IL]-1 α and -1 β and tumor necrosis factor [TNF]) that play important roles in atherothrombogenesis.⁴

Studies^{5,6} reported that elevated cell- and cytokine-mediated markers of inflammation, including C-reactive protein (CRP), fibrinogen, and various cytokines, are associated with PD. The same elevated proinflammatory factors in PD have also been linked with atherothrombogenesis. The connection between vascular events and PD is further supported by evidence showing that oral bacteria can cause platelet aggregation and thromboembolic events by upregulating the expression of platelet aggregation-associated protein.⁷

Given that PD and CVD are correlated and potentially share similar hallmarks of inflammation, it is relevant to review available data supporting a role for inflammation in CVD. This article focuses on epidemiological data linking inflammation to atherothrombosis, highlighting recent advances in establishing new biomarkers and understanding the role of genetics in the inflammatory process, and suggests new pathways for treatment.

BIOMARKERS FOR PREDICTION OF VASCULAR EVENTS

Cardiovascular (CV) Events

In many ways, atherosclerosis is a chronic inflammatory disorder, and plasma markers of inflammation may have clinical usefulness in the detection and assessment of risk for vascular events. In a large prospective study⁸ involving just less than 15,000 healthy men, IL-6 levels were significantly elevated among the 202 men who subsequently experienced an MI compared to age-matched controls. In another prospective study involving >28,000 subjects, healthy middle-aged women who subsequently developed CV events ex-

hibited increased levels of soluble P-selectin,⁹ soluble CD40L,¹⁰ or macrophage-inhibitory cytokine-1¹¹ compared to matched controls. TNF- α is another factor associated with CV disorders. Plasma concentrations of TNF- α were measured from 272 patients who developed recurrent non-fatal MI or another CV event.¹² TNF- α levels were persistently elevated among post-MI patients at increased risk for recurrent coronary events. All of these data indicate that baseline levels of the inflammatory biomarkers discussed above pose as potential biomarkers indicative of future risk for CV events, such as MI, stroke, coronary revascularization, and CV death, and they could be novel targets for CVD prevention.

However, one of the factors with the strongest evidence as a biomarker for predicting CV events is high-sensitivity CRP (hsCRP). When measured in the blood with a high-sensitivity assay, hsCRP proved to be a strong, independent predictor of future MI and stroke among apparently healthy asymptomatic men.¹³ The relative risk for first MI and ischemic stroke increased significantly with each increasing quartile of baseline concentrations of CRP. This study showed that inflammation, as reflected in the concentration of hsCRP, preceded the onset of CV events, confirming the hypothesis that atherothrombosis is, at least in part, an inflammatory disorder. Although hsCRP levels correlated with the greatest risk for cardiovascular events, elevations of other biomarkers found to be significantly associated with vascular events included Lp(a) lipoprotein, homocysteine, IL-6, total cholesterol, serum amyloid A, apolipoprotein B-100, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and the ratio of total cholesterol/HDL cholesterol.¹² In 2002, data derived from a 10-year cohort of 27,939 healthy women revealed further support for CRP as an indicator for CV risk.¹⁴ A direct comparison of CRP and LDL cholesterol showed that CRP is a stronger predictor for CV events and death compared to LDL cholesterol. Data from this study also enabled the investigators to calculate survival curves associated with CRP levels and LDL cholesterol. Women in the high CRP/low LDL cholesterol subgroup were at higher absolute risk than those in the low CRP/high LDL cholesterol subgroup (Fig. 1A). Even after adjustment for all components of the Framingham Risk Score, including age, smoking status, categorical levels of blood pressure, presence or absence of diabetes mellitus (DM), and HDL and LDL cholesterol levels, quintiles of CRP remained an independent prognostic factor of risk. Moreover, increasing levels of CRP were associated with an increased risk for CV events at all levels of estimated 10-year risk (Fig. 1B). These observations highlight the need for physicians to look beyond the traditional reliance on using LDL cholesterol as a

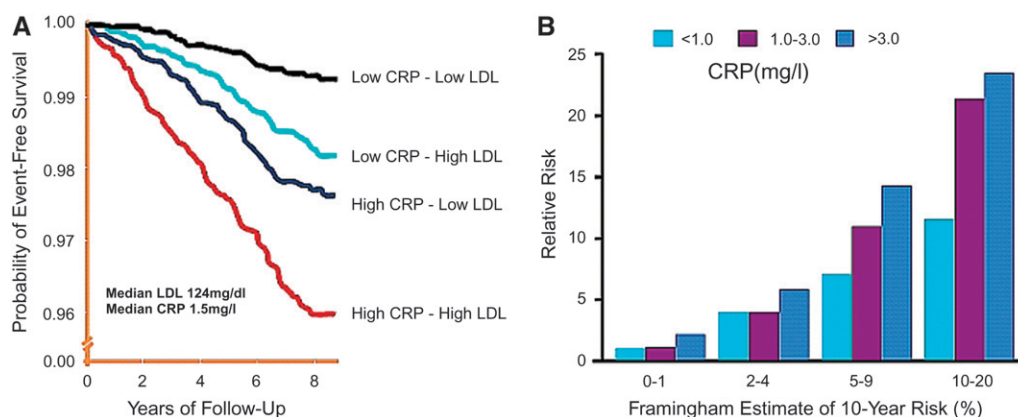


Figure 1.

The CRP level is a stronger predictor of CV events than the LDL cholesterol level and adds prognostic information supported by the Framingham Risk Score. **A)** Event-free survival among women ($N = 27,939$) with CRP and LDL cholesterol levels above or below the median for the study population.¹⁴ **B)** Multivariable-adjusted relative risks for CV disease according to CRP levels and the estimated 10-year risk based on the Framingham Risk Score, currently defined by the National Cholesterol Education Program and according to CRP levels and categories of LDL cholesterol.¹⁴ Copyright 2002 Massachusetts Medical Society. All rights reserved.

predictor of CV events and possibly consider new biomarkers, such as CRP.¹⁴

Since these reports, studies based on many more population cohorts have corroborated the usefulness of hsCRP as a predictor of MI, ischemic stroke, and CV death: a general population cohort from Britain;¹⁵ the Women's Health Initiative (WHI) observational cohort;¹⁶ the Honolulu Heart Study;¹⁷ the Nurses Health Study (NHS);¹⁸ the Health Professionals Follow-Up Study (HPFUS);¹⁸ the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA)-Augsberg cohort;^{19,20} the Atherosclerosis Risk in Communities (ARIC) study;²¹ the Cardiovascular Health Study (CHS);²² the Strong Heart Study (SHS);²³ the Kuopio Ischemic Heart Disease Risk Factor Study;²⁴ and the Evaluation for Prevention of Ischemic Complications (EPIC)-Norfolk cohort.²⁵

Based on these large population studies, the Centers for Disease Control and Prevention and the American Heart Association issued the first set of clinical guidelines for hsCRP in 2003. It was suggested that hsCRP levels of <1, 1 to 3, and >3 mg/l be used to represent lower, moderate, and higher vascular risk within the context of other risk factors typically used for global risk prediction.²⁶ Of interest, hsCRP levels measured in individuals exhibiting very low (<0.5 mg/ml) or very high levels (>10 mg/ml) of hsCRP have clinical significance. Once believed to be false positives, individuals with levels >10 mg/ml were found to be at "high risk" for CV events.²⁷ Although unproven, it is tempting to think that these extremely high levels could be the result of the contribution of chronic inflammation from other inflammatory disorders, such as arthritis or PD.

In all of the epidemiologic studies noted above, hsCRP levels were measured only once at baseline. In theory, because hsCRP levels might vary over time as part of the acute-phase response, this limitation might bias the risk estimates toward the null and lead to an underestimation of risk. Multiple studies demonstrated that the year-to-year and decade-to-decade variability of hsCRP is actually quite similar to that of cholesterol. Nonetheless, in clinical practice, it is recommended to repeat hsCRP measures if the initial value is >8 mg/l.

Stroke and Ischemic Events

Inflammatory processes are also a risk for stroke and cerebral small-vessel disease. In a population-based sample of elderly people (60 to 90 years old), hsCRP levels were associated with the presence and progression of periventricular and subcortical white matter lesions.²⁸ In another study,²⁹ CRP levels were measured from 591 and 871 healthy men and women, respectively. Over a 14-year follow-up, 196 ischemic strokes and transient ischemic attacks occurred. After adjustment for other risk factors, men and women in the highest quartiles of CRP levels had a two- and three-fold greater risk for stroke, respectively. The investigators were careful to note that elevated CRP levels may not be the result of the disease, but they could be produced in response to tissue injury, infectious agents, inflammation, and/or immunological and environmental stimuli. CRP levels are known to be greater in smokers, obese individuals, individuals with abnormal fibrinolytic activity (plasmin-antiplasmin complex), and individuals with subclinical atherosclerosis. This "marker versus mechanism" debate remains open and in need of further research.³⁰ Overall, these data support the view that CRP, as a marker of low-level inflammation, predicts an increased risk for CV events in otherwise healthy individuals. Considering the inflammatory nature of these diseases, it is not surprising that there was a significant reduction of risk for MI in subjects with high baseline CRP levels who were treated with the anti-inflammatory drug aspirin.¹³

Diabetes Mellitus

Patients with type 2 DM are at an increased risk for atherosclerosis. Evidence is accumulating in the literature supporting a role for inflammation in the pathogenesis of DM, thereby possibly linking the manifestation or progression of diabetes with a number of inflammatory disorders.

Similar to CVD, hsCRP is a predictor of risk for type 2 DM. In a cohort of 27,628 women free of diagnosed DM, baseline levels of hsCRP and IL-6 were significantly higher among cases than controls (both $P < 0.001$).³¹ Later studies investigating a direct association between hsCRP, inflammation, and DM used exogenous injections of recombinant human CRP (rhCRP). Following a bolus injection of rhCRP (1.25 mg/kg), markers of inflammation (IL-6 and -8, serum albumin A protein, and type II secretory phosphatase A₂) and coagulation markers (prothrombin F1 + 2) were significantly elevated compared to controls.³² In another study³³ conducted by the same research team, similar rhCRP bolus injections administered to healthy male subjects resulted in increased gluconeogenesis and subsequent plasma glucose levels. These investigators detected a decrease in insulin and an increase in norepinephrine/cortisol hormone levels known to abrogate and induce glucose metabolism, respectively.

Growing evidence for a role of CRP in DM led another group to investigate CRP as a prognostic marker for the metabolic syndrome. The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP-III)³⁴⁻³⁶ suggested that the metabolic syndrome is characterized by the presence of at least three of the following: abdominal obesity, elevated levels of triglycerides, reduced levels of HDL cholesterol, high blood pressure, and a high fasting glucose level. These parameters put patients with the metabolic syndrome at an increased risk for diabetes and CV events.³⁵ In a recent study³⁷ of a cohort of 14,719 apparently healthy women, assessment of hsCRP levels contributed prognostic information on the risk for the metabolic syndrome. The data presented in this study suggested that hsCRP levels should be included by the ATP-III as a parameter for metabolic syndrome as an indicator for CV (and diabetic) risk.

Taken together, the above evidence lends further credence for the need to develop strategies aimed at decreasing vascular risk among individuals with elevated levels of CRP.

REYNOLDS RISK SCORE

Whether to add hsCRP to traditional risk-prediction models, like the Framingham Risk Score, remains a topic of current research. To address this issue, a se-

ries of 35 risk factors were evaluated at baseline among 25,558 initially healthy women (>45 years old) who were followed for future cardiovascular events over a 10-year period. Using these data, a new risk-prediction algorithm, the Reynolds Risk Score, was developed and validated. In brief, of the new biomarkers of risk, the most important additions were hsCRP and parental history of MI before age 60 years. When these two novel factors were added to the usual risk markers, the Reynolds Risk Score proved to be more accurate than the Framingham Risk Score, particularly for those at "intermediate risk." In this critical group (where 70% of all events occur), almost half of all participants were predicted to be at higher or lower risk than anticipated when the Reynolds Risk Score was used, and in almost all cases, this reclassification was correct.³⁰ Because United States and European treatment guidelines suggest that statin therapy be considered an option for those with 10-year risk estimates of >10% or >20%, respectively,^{38,39} the application of the Reynolds Risk Score should allow more accurate targeting of statin prescriptions to those patients with the most appropriate level of risk, thereby minimizing toxicity and maximizing benefit and cost efficacy. Considering that ~8 to 10 million women in the United States have a 10-year risk estimated at 5% to 20%, application of these data could have an immediate effect on CV prevention. Two ongoing analyses, one in the Framingham data itself and one in a large prospective cohort of men, are being conducted to address the generalizability of these data.

STATINS

Statins have potent lipid-lowering and anti-inflammatory properties. When 3,745 patients with acute coronary syndrome (ACS) were treated with statins in the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 trial, levels of LDL cholesterol and hsCRP were decreased.⁴⁰ Treated subjects who achieved a target level of hsCRP ≤ 2 mg/l had a significant improvement in event-free survival, an effect independent of achieved levels of LDL cholesterol. Subjects who achieved LDL cholesterol levels ≤ 70 mg/dl and hsCRP levels ≤ 2 mg/l had a particularly low risk for recurrent MI or death resulting from MI compared to subjects with one or both of those biomarker above the given threshold values. These findings were corroborated in the multinational Aggrastat-Zocor trial, which reinforced the significance of hsCRP as an indicator of risk and inflammation.⁴¹ Data from these two studies are illustrated in Figure 2.

The potential role of hsCRP as a method to define high-risk individuals for statin therapy is also being evaluated in the Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating

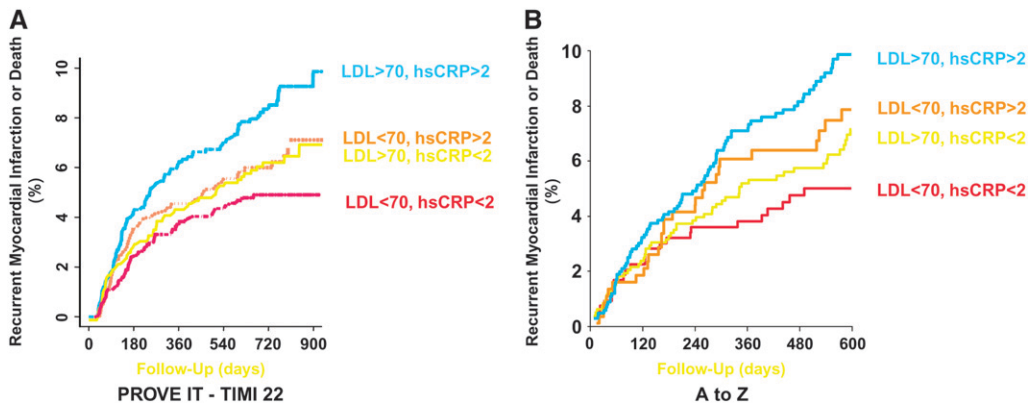


Figure 2.

Clinical importance of achieving levels of LDL cholesterol ≤ 70 mg/dl and hsCRP ≤ 2 mg/l following the initiation of statin therapy in two independent studies. Cumulative incidence of recurrent MI or death from coronary causes, according to the achieved levels of LDL cholesterol and hsCRP shown in the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT – TIMI 22) trial⁴⁰ (A) and Aggrastat-Zocor study (A to Z) (B).⁴¹ A: Copyright 2005 Massachusetts Medical Society. All rights reserved. B: Reprinted with permission from Lippincott Williams & Wilkins.

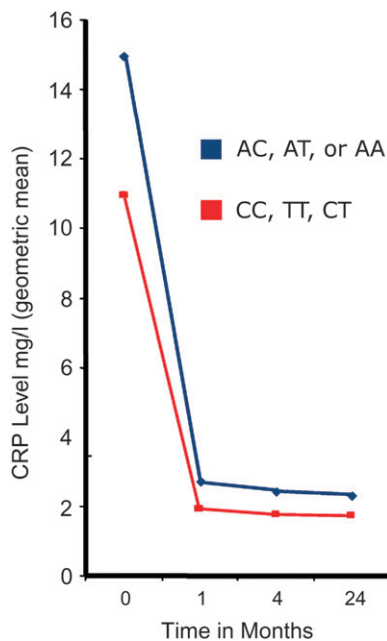


Figure 3.

CRP levels during and after acute ischemia according to the SNP $-286C>T>A$. The geometric mean of CRP levels is shown at each time point on a logarithmic scale. Comparison of CRP values from subjects with one or two copies of the A allele to subjects with no copies of the A allele revealed differences that persisted in the chronic phase after ischemia.⁴⁵ Reprinted with permission from Blackwell Publishing.

Rosuvastatin (JUPITER) trial. JUPITER was developed to investigate whether long-term treatment with a statin (rosuvastatin, 20 mg/day) would decrease the rate of vascular events among apparently healthy men and women with currently acceptable levels of

LDL cholesterol (<130 mg/dl) and elevated levels of hsCRP (≥ 2 mg/l) compared to placebo.⁴² Based on these parameters, these patients normally do not qualify for statin therapy because of low levels of LDL cholesterol but are at increased CV risk because of elevated levels of hsCRP. Owing to its unique design, JUPITER will increase understanding of inflammation in vascular disease and provide crucial data regarding the usefulness of statin therapy in primary prevention among women (especially those with below-average levels of LDL cholesterol).

GENETIC ANALYSIS OF CRP

Common polymorphisms among patients with CVD revealed by sequencing of the *CRP* gene may explain why some individuals have varying levels of plasma hsCRP and may be predisposed to CVD. In 2005, Miller et al.⁴³ sequenced the *CRP* gene from patients involved in three different trials. Four minor alleles ($-757T>C$, $IVS1+29A>T$, $1444C>T$, and both minor alleles of $-286C>T>A$) of the *CRP* gene were associated with higher hsCRP in all three cohorts, whereas two minor alleles ($1059G>C$ and $1846G>A$) were associated with lower levels of hsCRP. None of the single nucleotide polymorphisms (SNPs) were associated with the risk for MI or stroke. However, in 2006, a study⁴⁴ from the laboratory of Leslie Lange aimed to answer whether SNPs in the *CRP* gene are associated with plasma hsCRP and CVD events. The results summarized in their article suggested a genetic basis might underlie the relationship between hsCRP concentration and CVD risk in older adults. Specifically, the $790>T$ allele was associated with an increased risk for MI in black subjects, the $1919>T$ allele was associated with an increased risk for stroke and CVD mortality in white subjects, and the minor alleles of 2667 and 3872 SNPs were associated with a decreased risk for CVD mortality in white subjects. In another study,⁴⁵ variants in the *CRP* gene were examined to assess whether there is any SNP association with plasma hsCRP levels after an ACS (Fig. 3). Among 1,827 American subjects of European origin with acute coronary ischemia, variants in the putative promoter

region, $-757T>C$ and $-286C>T>A$, were associated with the highest hsCRP elevations after ACS. Subjects with two copies of the A allele of SNP $-286C>T>A$ had median hsCRP values of 76.6 mg/l compared to 11.1 mg/l in subjects with no copies of the rare variant ($P<0.0001$) after ACS.

In a recently reported genome-wide association study⁴⁶ of >6,400 women, the CRP locus proved relevant for CRP production as did some loci that are associated with weight homeostasis (LEPR) or with maturity-onset forms of diabetes (GCKR and HNF1). These provocative data suggested close genetic links among CRP, diabetes, and premature atherothrombosis. Taken as a group, the above studies suggested that between 20% and 40% of the population variance in CRP has a genetic basis.

BLOCKING PROINFLAMMATORY MEDIATORS

It is unknown whether inhibiting inflammation in general or CRP in particular will decrease the rate of vascular events. However, several approaches to anti-inflammatory therapy are being considered for clinical trial evaluation. With regard to inhibiting CRP itself, a provocative strategy was developed in 2006 by Pepys et al.⁴⁷ in a rodent model. They reported that treatment with a CRP inhibitor (1,6-bis(phosphocholine)-hexane) abrogated the increase in infarct size and cardiac dysfunction produced in rats given endogenous rhCRP. Whether such an inhibition might have similar effects in man is unknown. Other approaches to this problem include the use of novel IL-6 or TNF inhibitors. Alternatively, because low-dose methotrexate was shown to decrease parameters linked with systemic inflammation, including erythrocyte sedimentation rate, CRP concentrations, or signs of clinical inflammation,^{48,49} several investigators have begun to consider a test of the inflammatory hypothesis of atherothrombosis using this agent. As a chronic, progressive disease associated with systemic inflammation, rheumatoid arthritis (RA) is often treated with anti-inflammatory drugs, such as low-dose methotrexate.⁵⁰ In a non-randomized, observational cohort trial of subjects with RA, CV deaths were reduced by 70% among those treated with methotrexate.⁵¹ In light of the similarities between RA and atherosclerosis (such as the involvement of cytokines and elevated levels of CRP), conducting a trial comparing low-dose methotrexate to placebo in the secondary prevention of CVD would contribute significant understanding in this arena.

CONCLUSIONS

Given the potential role that inflammation plays in CVD, investigators are now beginning to question the direct and/or indirect influences that other inflammatory disorders may have on manifesting or aug-

menting the risk and progression for the disease. As a disease marked by inflammation, periodontitis may also be linked to incident CVD. Analogous to the studies discussed above, a randomized trial to test if a PD-preventative strategy can lead to a reduced incidence and/or risk for vascular events would be a worthy effort. By reducing the progression of PD, levels of inflammatory markers common to both diseases (i.e., IL-6, TNF, and hsCRP) would likely be decreased; carefully designed randomized trials based on this concept could then test whether such effects might, in turn, decrease the rates of vascular disease.

ACKNOWLEDGMENTS

The initial draft of this manuscript was developed by Dr. Silvertown, manager, Scientific Affairs and Program Development, Axon Medical Communications Group, based on a lecture given by Dr. Ridker at the symposium "Inflammation and Periodontal Diseases: A Reappraisal" in Boston, Massachusetts, in January 2008. The final manuscript submitted was reviewed and edited by Dr. Ridker. Dr. Ridker's research is supported by grants from the National Heart, Lung, and Blood Institute, Bethesda, Maryland; the National Cancer Institute, Bethesda, Maryland; the Donald W. Reynolds Foundation, Las Vegas, Nevada; and the Leducq Foundation, Paris, France, and by investigator-initiated grants from AstraZeneca, London, U.K.; Sanofi-Aventis, Paris, France; and Merck, Whitehouse Station, New Jersey. Dr. Ridker has served as a consultant to Dade Behring, Deerfield, Illinois; AstraZeneca; Merck; Schering Plough, Kenilworth, New Jersey; and Novartis, Basel, Switzerland, and is listed as a coinventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease.

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- Submitted May 7, 2008; accepted for publication May 30, 2008.