Periodontal Disease and Coronary Heart Disease

A Reappraisal of the Exposure

James D. Beck, PhD; Paul Eke, PhD, MPH, PhD; Gerardo Heiss, MD, MPH, PhD; Phoebus Madianos, DDS, PhD; David Couper, PhD; Dongming Lin, MS; Kevin Moss, AS; John Elter, DMD, PhD; Steven Offenbacher, DDS, PhD, MMSc

Background—Results from studies relating periodontal disease to cardiovascular disease have been mixed. Residual confounding by smoking and use of clinical measures of periodontal disease rather than measures of infection have been 2 major criticisms. The aims of this study were to investigate relationships between prevalent coronary heart disease (CHD) and 2 exposures, (1) clinical periodontal disease and (2) IgG antibodies to 17 oral organisms, and to evaluate the role of smoking in these relationships.

Methods and Results—Our study is based on a subset of participants in the Atherosclerosis Risk in Communities (ARIC) Study, who received a complete periodontal examination during visit 4 (1996–1998). The exposures were periodontal status and serum IgG antibody levels against 17 periodontal organisms, and the outcome was prevalent CHD at visit 4. Multivariable analyses indicate that periodontal status is not significantly associated with CHD in either ever smokers or never smokers. Similar analyses evaluating antibodies indicate that high antibodies (above the median) to Treponema denticola (odds ratio [OR] = 1.7; 95% CI, 1.2 to 2.3), Prevotella intermedia (OR = 1.5; 95% CI, 1.1 to 2.0), Capnocytophaga ochracea (OR = 1.5; 95% CI, 1.1 to 2.1), and Veillonella parvula (OR = 1.7; 95% CI, 1.2 to 2.3) are significantly associated with CHD among ever smokers, whereas Prevotella nigrescens (OR = 1.7; 95% CI, 1.1 to 2.6), Actinobacillus actinomycetemcomitans (OR = 1.7; 95% CI, 1.2 to 2.7), and Capnocytophaga ochracea (OR = 2.0; 95% CI, 1.3 to 3.0) were associated with CHD among never smokers.

Conclusions—Clinical signs of periodontal disease were not associated with CHD, whereas systemic antibody response was associated with CHD in ever smokers and never smokers. These findings indicate that the quality and quantity of the host response to oral bacteria may be an exposure more relevant to systemic atherothrombotic coronary events than clinical measures. (Circulation. 2005;112:19-24.)

Key Words: antibodies ■ coronary disease ■ epidemiology ■ risk factors ■ smoking

Periodontitis is a chronic infection by oral bacteria that affects the supporting structures of the teeth.1 A mechanism has been proposed whereby the burden of bacterial pathogens, antigens, endotoxins, and inflammatory cytokines of periodontitis contributes to the process of atherogenesis and thromboembolic events. In response to infection and inflammation, susceptible individuals may exhibit greater expression of local and systemic mediators and may thereby be at increased risk for a myocardial infarction or stroke.2

Case-control, cross-sectional, and longitudinal studies have found that periodontitis is associated with coronary heart disease (CHD) and cerebrovascular disease, even after adjustment for a variety of potential confounders of these associations.3–26 However, other studies have found either nonsignificant positive trends or no association after adjustment for variables considered to be confounders.27–31 Concerns about the validity of the periodontitis–cardiovascular disease associations have been expressed. A review by Danesh32 noted that studies were based on clinical measures of periodontal disease and did not have direct measures of the infection, such as bacterial counts or systemic antibody levels to oral pathogens.

A second criticism focuses on the role of smoking, which is a risk factor for both periodontal disease and heart disease and must be considered as a confounder.33 Most studies have adjusted for smoking by means of multivariable analyses, an approach open to bias due to residual confounding. As for other morbidities, it has been suggested that statistical adjustment is insufficient to control for smoking and that stratification is needed.33 In the present study we examined the relationship between 2 types of periodontitis measures (clinical and antibody) and prevalent CHD after stratification by...
smoking status and adjustment for other potential confounders.

Methods

The Atherosclerosis Risk in Communities (ARIC) Study is a prospective investigation of the etiology and natural history of atherosclerosis and of clinical cardiovascular disease in 4 US communities. A probability sample of 15,792 community-dwelling residents aged 45 to 64 years at baseline took part in an evaluation of cardiovascular risk factors and their sequelae. The ARIC clinical examination included anthropometry including waist-to-hip ratio, blood pressure, cognitive function, ECG, clinical chemistries, plasma lipids, medications, and health questionnaires. The Dental ARIC, an ancillary study, was conducted at ARIC visit 4 during 1996–1998. Human subjects participated in the study after providing informed consent to a protocol that was reviewed and approved by the University of North Carolina School of Dentistry Committee on Research Involving Human Subjects.

The cross-sectional Dental ARIC Study consisted of an oral examination; collection of gingival crevicular fluid, dental plaque, and serum; and interviews. Persons requiring antibiotic prophylaxis for periodontal probing were excluded.

The outcome was prevalent, manifest CHD. The ARIC Study collected self-reported physician-diagnosed CHD before enrollment into the study (1987–1989) and abstracted hospital records for all hospitalizations reported (yearly) by the cohort members followed by validation of the discharge diagnoses according to standardized criteria. Unequivocal ECG signs of myocardial infarction during any of the 3 examination visits that preceded the dental study were also considered prevalent CHD at visit 4. Any events occurring during visit 4 but after the dental examination were not included in this analysis.

Two measures of periodontal exposures were used: clinical periodontal disease and serum IgG antibody levels to 17 selected periodontal organisms. Clinical measures included probing depth and cementoenamel junction measures relative to the gingival margin on 6 sites for all teeth. Clinical attachment level was calculated from the sum of probing depth and cementoenamel junction scores. Periodontal examiners at the ARIC centers were calibrated to a standard examiner, and the percent agreement for clinical attachment level within 1 mm between each examiner and the standard examiner ranged from 83.2% to 90.2%. Weighted κ statistics ranged from 0.76 to 0.86, indicating excellent agreement, and intraclass correlation coefficients ranged from 0.76 to 0.90, indicating excellent to outstanding agreement. Our case definition of periodontal disease was independently derived during a meeting by indicating excellent to outstanding agreement. Our case definition of periodontal disease was independently derived during a meeting by indicating excellent to outstanding agreement. Similar criteria. Unequivocal ECG signs of myocardial infarction during any of the 3 examination visits that preceded the dental study were also considered prevalent CHD at visit 4. Any events occurring during visit 4 but after the dental examination were not included in this analysis.

This 3-level definition is as follows: (1) severe periodontitis: ≥2 interproximal sites (not on same tooth) with ≥6-mm clinical attachment level and ≥1 interproximal site with probing depth ≥5 mm; (2) initial periodontitis: ≥2 interproximal sites with 4- or 5-mm clinical attachment level (not on same tooth) and no interproximal sites with clinical attachment level ≥6 mm; and (3) healthy/gingivitis: individuals not meeting the above definitions. IgG antibody levels to 17 oral organisms (Porphyromonas gingivalis, Prevotella intermedia, Prevotella nigrescens, Tannerella forsythensis [formerly Bacteroides forsythus], Treponema denticola, Fusobacterium nucleatum, Actinobacillus actinomycetemcomitans, Campylobacter rectus, Eikenella corrodens, Micromonas (Pep- tostrepptococcus) micros, Veillonella parvula, Capnocytophaga ochracea, Selenomonas noxia, Actinomyces viscosus, Streptococcus intermedius, Streptococcus sanguinis, and Streptococcus oralis) represent the other exposure. Serum samples were frozen at −80°C, transported on dry ice to our laboratory, and stored in aliquots at −80°C. The samples were assayed for IgG antibody levels directed against the aforementioned periodontal organisms with the use of the checkerboard immunoblotting technique described by Sakellari et al. See the online-only Data Supplement for additional details.

Periodontal organisms selected were representatives from clusters of organisms reported to be associated with periodontal infections by Socransky et al. Absolute measures of systemic antibody to these periodontal organisms were categorized into dichotomous variables (high or low) with the median score for each organism used as the cutoff point. The median value was used rather than the upper quartile because stratification on smoking resulted in similar point estimates of association but much wider CIs because of small cell sizes when high antibody was defined as the highest quartile.

Participants were defined as never smokers, former smokers, or current smokers by standardized interview. The former and current categories were further divided into light or heavy smokers, with light smokers reporting >0 but <20 pack-years of smoking and heavy smokers reporting ≥20 pack-years of smoking. This scheme resulted in a 5-level categorization of smoking that simultaneously takes into account both the intensity and the immediacy of smoking exposure. This variable was used in multivariable models that were not stratified by smoking status. For purposes of stratification, a dichotomy of never smokers and ever (current and former) smokers was used. Education was divided into basic (<12 years), intermediate (12 to 16 years), or advanced (17 to 21 years) and was included to adjust for socioeconomic status. Age in years at visit 4 was included, and a variable representing race/ethnicity (black or white) and ARIC center was designed to control for the ethnic, regional, and examiner differences in the ARIC cohort. A total of 49 individuals who were not black or white or who were blacks seen in Minnesota or Washington County, Md (n=49), were excluded because their numbers were too small to be represented in the race/ethnicity/ARIC center variable. See the online-only Data Supplement for additional details.

Statistical Analysis

Statistical significance was set at 0.05, and the unit of analysis was the person. Frequency distributions, means, empirical distribution functions, and standard errors were determined to describe the data. Bivariate relationships were assessed by t tests or Kolmogorov-Smirnov tests for continuous variables and Cochran Mantel-Haenszel χ² statistics and odds ratios (ORs) and 95% CIs for categorical variables. Multivariable modeling was performed with the use of binary logistic regression. Potential confounders were based on the literature and our previous findings on the relationship between clinical periodontal disease and CHD. Covariates that were significant main effects in the multivariable logistic regression models (Tables 1 and 2) or that confounded the association between antibodies and CHD by at least 5% were retained in the models. We checked for multicollinearity among the 17 antibodies using the collinearity diagnostics in SAS PROC REG. The antibody distributions were dichotomized at the median. The best score option in PROC Logistic was used to identify the best single antibody model and the best 2 antibodies model. In this procedure, the covariates were forced into the model, and the antibodies were then eligible to enter. The score option uses the branch and bound algorithm to find a specified number of models with the highest likelihood score (χ²) statistic for all possible model sizes, from 1-, 2-, and 3-effect models, and so on, up to the single model containing all of the explanatory effects. See the online-only Data Supplement for additional details.

Finally, the analyses of relationships between the 17 antibodies and CHD by necessity involved multiple tests of significance. Hence, type 1 error could exist. There are a number of methods to correct for multiple testing, but we have opted for not adjusting the levels of nominal statistical significance for multiple testing but to make readers aware of the need to consider the statistical significance of these associations with caution.

Results

Of all ARIC cohort members examined at baseline (1987–1989), 86.2% responded to a screening interview to determine eligibility for the oral examination. Of those screened, 15% were edentulous, and 17% were ineligible because they had a medical contraindication to periodontal probing. Among those eligible, 13% refused the dental examination. A
TABLE 1. Multivariable Logistic Model for Association Between Clinical Periodontal Status and Prevalent CHD (n=4846)

<table>
<thead>
<tr>
<th>Variables in Model</th>
<th>OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy/gingivitis</td>
<td>1.00</td>
</tr>
<tr>
<td>Initial periodontitis</td>
<td>0.92 0.68–1.22</td>
</tr>
<tr>
<td>Severe periodontitis</td>
<td>1.26 0.90–1.76</td>
</tr>
<tr>
<td>Age at visit 4 (5-year intervals)</td>
<td>1.32 1.18–1.48</td>
</tr>
<tr>
<td>Gender (female=0, male=1)</td>
<td>3.05 2.22–4.19</td>
</tr>
<tr>
<td>Race/center (reference: Jackson blacks)</td>
<td>1.32 0.83–2.12</td>
</tr>
<tr>
<td>North Carolina blacks</td>
<td>0.60 0.73–3.50</td>
</tr>
<tr>
<td>Minnesota whites</td>
<td>1.25 0.78–2.01</td>
</tr>
<tr>
<td>Washington County, Md, whites</td>
<td>1.21 0.76–1.94</td>
</tr>
<tr>
<td>Smoking status (reference: never smoker)</td>
<td>1.0</td>
</tr>
<tr>
<td>Current heavy</td>
<td>1.51 1.01–2.28</td>
</tr>
<tr>
<td>Current light</td>
<td>0.20 0.03–1.50</td>
</tr>
<tr>
<td>Former heavy</td>
<td>1.79 1.32–2.44</td>
</tr>
<tr>
<td>Former light</td>
<td>0.94 0.67–1.32</td>
</tr>
<tr>
<td>Diabetes (no=0, yes=1)</td>
<td>1.29 0.97–1.72</td>
</tr>
<tr>
<td>Hypertension (no=0, yes=1)</td>
<td>2.01 1.54–2.61</td>
</tr>
<tr>
<td>Waist-to-hip ratio (Z score)</td>
<td>0.93 0.79–1.09</td>
</tr>
<tr>
<td>HDL cholesterol level (mg/dL, SD)</td>
<td>0.77 0.66–0.91</td>
</tr>
<tr>
<td>LDL cholesterol level (mg/dL, SD)</td>
<td>0.82 0.72–0.94</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
</tr>
<tr>
<td>&lt;12 y</td>
<td>1.49 1.04–2.15</td>
</tr>
<tr>
<td>12–16 y</td>
<td>1.19 0.91–1.56</td>
</tr>
<tr>
<td>≥17 y (referent)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Bold type indicates that CI does not include 1.0.

At least 68% of the participants had a detectable antibody level for each of the 17 organisms. At least 86% of participants had detectable antibody scores for P gingivalis, T forsythensis, and T denticola, which are strongly associated with chronic periodontitis. Antibodies to P intermedius, M micros, P nigrescens, and A actinomycetemcomitans were detected in >90% of the individuals, and V parvula was least likely to be detected at 68.6% (data not shown; see online-only Data Supplement). Significant unadjusted associations were seen between high antibody level (median or above) against all organisms except S sanguinis, S intermedius, and A viscosus and prevalent CHD. The strongest associations were seen for M micros (OR=1.7; 95% CI, 1.3 to 2.1) and C ochracea (OR=1.8; 95% CI, 1.4 to 2.8). The lower confidence limits for a number of the significant antibodies were close to 1.0. Evaluation of multicollinearity among the 17 antibodies resulted in a condition index close to 8.7, indicating collinearity levels that were not troublesome.

Because there were a number of significant unadjusted associations between high antibodies and CHD, we further evaluated antibody-CHD associations by means of a series of logistic regression models adjusting for covariates that were either significant main effects in the model or that conferred the antibody-CHD association by at least 5%. In addition, we stratified the participants according to whether or not they had ever smoked (Table 2). The antibody-CHD patterns for ever smokers and never smokers appear to differ.
Antibody to *T denticola*, which with *P gingivalis* and *T forsythia* is strongly associated with chronic periodontitis, was significantly related to CHD in smokers, whereas none of those antibodies were significant in never smokers. However, there is a positive trend, and the ORs are similar to those in ever smokers. In ever smokers, antibody to *P intermedia* was significantly related to CHD (OR = 1.5), and high antibodies to *C ochracea* and *V parvula* were associated with CHD (ORs = 1.5 and 1.7, respectively). Among never smokers, antibody to *P nigrescens* was associated with CHD. In addition, high antibodies to *A actinomycetemcomitans* and *C ochracea* were related to prevalent CHD. Because space limits presentation of the 34 full models, significant main effects among the covariates in the ever smokers were age (5-year increments), gender (male), hypertension (yes), and pack-years of smoking, and both HDL and LDL cholesterol were negatively associated with CHD. For never smokers, significant main effects were age (5-year increments), gender (male), diabetes (yes), and hypertension (yes), and both HDL and LDL cholesterol were negatively associated with CHD. Analyses of antibodies as log-transformed, continuous variables produced patterns similar to those of antibodies dichotomized at the median (not shown). For example, all 3 antibodies significant in Table 2 for never smokers also were significant as continuous variables plus *P intermedia*. For ever smokers, antibodies to *M micros*, *F nucleatum*, *S noxia*, *C ochracea*, and *V parvula* were significant.

Analyses of the relationship between the presence of multiple high antibody titers to oral organisms and CHD with the use of the best score option in logistic regression and with adjustment for all covariates revealed that the best-fitting 2-variable antibody model for ever smokers was a combination of *T denticola* and *V parvula* (not shown). Individuals with high antibody levels to both *T denticola* and *V parvula* have a CHD prevalence of 11.0% compared with a prevalence of 5.3% for individuals with low antibodies to both organisms (OR = 2.0; 95% CI, 1.4 to 2.9). The best-fitting model for a combination of 2 antibody titers and CHD in never smokers included *P nigrescens* and *C ochracea*. Individuals with high antibody levels to both *P nigrescens* and *C ochracea* have a CHD prevalence of 6.6% compared with a prevalence of 2.6% for individuals with low antibodies to both organisms (OR = 2.3; 95% CI, 1.4 to 4.0).

**Discussion**

Study findings indicate that our a priori clinical case definition of periodontitis was not significantly associated with an increased prevalence of CHD after adjustment for a number of CHD risk factors. This is consistent with other studies. Studies reporting on this association have used a variety of definitions of periodontal disease as an exposure, and our own work has used >1 definition. Because there is almost no information on which clinical periodontal measures and their severity may be related to systemic conditions, the range of exposures reported in the literature may be one reason for the inconsistency in findings. Our study obtained detailed clinical periodontal measures, meaning that we could explore a variety of clinical definitions as they may relate to CHD, which we did.

A strength of this study is that we used a clinical definition that was independently derived by a group interested in surveillance of periodontal disease in the United States. Interestingly, the prevalence of severe periodontitis as defined in this study was ≈16%, which is similar to national estimates for this condition. However, this definition and others that we have previously published (and some that we have not published) were not associated with prevalent CHD, and we are persuaded that such an association does not exist in this study population.

In earlier publications we reviewed evidence indicating that the chronic inflammatory burden of periodontal infection and the host response provide the basis for the observed associations between periodontal disease and atherosclerosis and CHD. The results of this study lend support to our original working model, and they support and extend the findings of Pussinen et al, who found associations between elevated *A actinomycetemcomitans* and *P gingivalis* antibody titers and CHD, after adjusting for age and several CHD risk factors. Support for our findings also comes from studies that indicate that several periodontal organisms, including *P gingivalis*, *T denticola*, *S sanguinis*, and *A actinomycetemcomitans*, have been detected directly within the atherosclerotic plaque lesion of the vessel wall. Furthermore, periodontal organisms such as *P gingivalis* have been reported to invade human coronary artery cells and induce several pathological responses, and long-term systemic challenge with *P gingivalis* was reported to accelerate atherogenic plaque progression.

We are aware of uncertainties in the interpretation of high antibody titers to oral organisms in relation to periodontal disease. The antibody response varies between individuals, and immune system response to an organism can be influenced by the individual’s genetic and immunological background, previous exposure to the organisms, and the dose, timing, route, and immunogenic characteristics of the antigenic challenge. Systemic exposures that originate from local infection may imply an insufficient local response to prevent systemic entry, as well as factors that promote acute episodes of periodontal disease activity, such as smoking. The immune response to infection may also undergo age-related changes that result in loss of response and functional capacity. Hence, we controlled for age and stratified on smoking status.

High antibody titers could represent a response to an active phase of infection in subjects with periodontitis but could also reflect a host response to an oral pathogen that confers protection to an individual without periodontal disease. The premise for this study was the assumption that an antibody response merely indicates systemic exposure to an oral organism. The distribution of periodontopathic organisms in gingival plaque is closely related to antibody levels to the intact bacteria in serum. For example, studies have shown a direct relationship between the serum anti-*P gingivalis* IgG levels and subgingival colonization by *P gingivalis* consistent with a systemic antibody response as a reflection of the host response to infections by periodontal organisms. Increases in systemic antibody response to organisms have also been associated with episodes of periodontal disease activity. Longitudinal studies have shown that elevation in systemic antibody specificities to periodontal organisms is an indicator
of periodontal disease recurrence,\textsuperscript{49} although it is not a sensitive marker for initial periodontitis.\textsuperscript{50} High antibody titers to \textit{T. forsythensis} have also been reported to be significantly higher in periodontitis patients.\textsuperscript{51} Finally, although the role of antibodies to periodontal organisms in host immune protection against infections by periodontal organisms is not fully elucidated, it appears that antibody level is not a good quantitative indicator for periodontal disease. Nonetheless, antibody to periodontopathic organisms appears to be a reliable index measure for systemic exposure to these organisms. Thus, we conservatively interpret the results of this study to indicate that systemic exposure to oral organisms is related to the prevalence of detected CHD.

Although the cross-sectional design allowed us to examine associations between multiple periodontal organisms and carotid atherosclerosis, no inference can be made about the antecedent-consequent nature of our results. Similarly, although serum antibody levels are stable over some time, it is unknown whether in our study population high levels of antibody to periodontal organisms are the result of incident, prior, or active reinfection. Thus, the temporal relationship between exposure to periodontal organisms and cardiovascular event cannot be addressed. Misclassification of event status can be expected to be minimal because disease status was defined and determined by standardized protocols and procedures were established by the ARIC Study and verified over the 9 years before the dental examination. Standardized and controlled protocols were also used in ARIC to obtain measures for the covariates included in our analyses. Although the validity of serum antibody measures for periodontal organisms could be influenced by cross-reactivity to other antigen-related species from nonoral sites, we know of no basis to suspect differential misclassification between cases and control for this reason, and we determined very weak associations between periodontal organisms from nonoral sites, we know of no basis to suspect differential misclassification between cases and control for this reason, and we determined very weak correlations between antibody measures for the most antigenically related species (eg, between \textit{Streptococcus} species) and a low percentage of concordance between high antibody levels to these closely related organisms in our study population. It may appear counterintuitive, but it is not unusual in cross-sectional studies that LDL cholesterol was negatively associated with prevalent CHD. Additional analyses (not shown) indicated that more than half of the individuals with prevalent CHD were taking cholesterol-lowering medications, which may account for the direction of the association.

The analyses of relationships between the 17 antibodies and CHD by necessity involved multiple tests of significance. Hence, type 1 error could exist. For example, Table 2 is a summary of 34 logistic regression models that resulted in 9 significant associations. With a significance level of 0.05, 1 or 2 significant associations can be expected by chance alone. We have opted for not adjusting the levels of nominal statistical significance for multiple testing but to make readers aware of the need to consider the statistical significance of these associations with considerable caution.

In this study population, the clinical signs of periodontal disease were not associated with CHD, whereas an indicator of systemic exposure to oral organisms (high antibody levels) was associated with prevalent CHD in current and former smokers as well as never smokers. Systemic exposure to >1 oral organism was related to a higher prevalence of CHD, especially in never smokers. These findings suggest that the quality and quantity of an individual’s host response to oral pathogens, which results in clinical expression of periodontal disease, may also be a more direct measure of periodontal disease as an exposure for CHD. Consequently, we believe that these findings are relevant for future research in that they indicate that clinical measures of periodontitis may not adequately represent the systemic burden of periodontal disease. Instead, future researchers may want to use measures that better capture the interplay of the infection, the host immune and inflammatory responses, and resulting clinical signs of this complex exposure that may affect general health.

**Acknowledgments**

The ARIC Study is performed as a collaborative study supported by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022 and grant R01-DE11551 from the National Institute of Dental and Craniofacial Research. The authors thank the staff and participants of the ARIC Study for their important contributions.

**Disclosure**

Dr Beck is principal investigator of the grant producing the data. Kevin Moss is on the research grant. Drs Offenbacher and Couper are co-investigators on the grant and Dr Heiss is an investigator on the parent ARIC study.

**References**


Periodontal Disease and Coronary Heart Disease: A Reappraisal of the Exposure
James D. Beck, Paul Eke, Gerardo Heiss, Phoebus Madianos, David Couper, Dongming Lin,
Kevin Moss, John Elter and Steven Offenbacher

Circulation. 2005;112:19-24; originally published online June 27, 2005;
doi: 10.1161/CIRCULATIONAHA.104.511998
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/112/1/19

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2005/06/07/CIRCULATIONAHA.104.511998.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located,
click Request Permissions in the middle column of the Web page under Services. Further information about
this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/