Impact of Viral and Bacterial Infectious Burden on Long-Term Prognosis in Patients With Coronary Artery Disease

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Background—The number of infectious pathogens to which an individual has been exposed (infectious burden) may correlate with coronary artery disease (CAD). In a prospective study, we evaluated the effect of 8 pathogens and the aggregate pathogen burden on the risk for future fatal cardiac events among patients with angiographically documented CAD.

Methods and Results—In 1018 patients, IgG or IgA antibodies to herpes simplex virus types 1 and 2, cytomegalovirus, Epstein-Barr virus, Haemophilus influenzae, Chlamydia pneumoniae, and Helicobacter pylori were determined. Moreover, highly sensitive C-reactive protein was measured. Follow-up information on cardiovascular events was obtained (mean 3.1 years, maximum 4.3 years). Seropositivities to Epstein-Barr virus (P = 0.001), H pylori (P = 0.002), and herpes simplex virus type 2 (P = 0.045) were independently associated with the future risk of cardiovascular death. An increasing number for pathogen burden was significantly predictive of the long-term prognosis (P < 0.0001). Infectious burden divided into 0 to 3, 4 or 5, and 6 to 8 seropositivities was associated with an increasing mortality of 3.7%, 7.2%, and 12.6%, respectively. Patients seropositive to >5 pathogens compared with those seropositive to <4 pathogens had a 5.1 (1.4 to 18.3) higher risk of future cardiac death. This result was mainly driven by the pathogen burden of seropositivities to Herpesviridae (P < 0.0001). The prognostic impact of total or viral pathogen burden was independent of the C-reactive protein level.

Conclusions—These results support the hypothesis that the number of infectious pathogens to which an individual has been exposed independently contributes to the long-term prognosis in patients with documented CAD. (Circulation. 2001;104:25-31.)

Key Words: infection ■ inflammation ■ prognosis ■ atherosclerosis ■ coronary disease

Several classic risk factors for the development of coronary artery disease (CAD) have been identified. However, these factors may explain only the high prevalence of CAD in part.1 Injury to the vessel wall and the associated inflammatory response are now generally recognized as essential components of atherogenesis.2 However, the stimuli that initiate and sustain the inflammatory process have not been fully identified. A candidate trigger of both inflammatory3 and autoimmune4 responses is infection, which might be a source of chronic local or systemic inflammation.

Several retrospective and cross-sectional studies have shown an association between previous infections with Chlamydia pneumoniae, herpes simplex virus (HSV), cytomegalovirus (CMV), Helicobacter pylori, hepatitis A, or respiratory tract infection and the presence of CAD or the risk for acute coronary events, but other studies have not shown such an association.5–8 The results of prospective studies regarding an association between seropositivity to infectious agents and future cardiac events have also been disparate.9–15 Recently, Epstein et al12 formally introduced the concept of infectious burden and demonstrated that the number of infectious pathogens to which an individual has been exposed is related to the presence of CAD. Zhu and colleagues16,17 could show an association between infectious burden and the risk of future cardiac events.

Viral infections might differ from bacterial infections regarding their latent state, and Herpesviridae especially exert direct proatherogenic effects on injured vessel walls.3 In the

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*The Appendix lists the AtheroGene Investigators.

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present study, we prospectively evaluated the impact of the aggregate number of infectious pathogens on long-term prognosis in patients with CAD. Furthermore, the relative contribution of viral and bacterial infections on the long-term outcome and the interaction with an inflammatory process was studied.

Methods

Study Population

Between November 1996 and July 1998, 1018 consecutive patients who had been admitted to the Department of Medicine II of the University Clinic Mainz for diagnostic angiography because of symptoms of suspected CAD and in whom a diameter stenosis of at least 30% was diagnosed in a major coronary artery were included in the present study. Patients with no evidence of CAD as defined above and with evidence of concomitant diseases, in particular, valvular heart disease, cardiomyopathy, known malignant diseases, and febrile conditions, had been excluded. Diabetes mellitus was diagnosed in patients who had previously undergone dietary treatment or received additional oral antidiabetic or insulin medication or who had a current fasting blood sugar level >125 mg/dL, hypertension was diagnosed in patients who had received antihypertensive treatment or had been diagnosed as hypertensive (blood pressure >160/90 mm Hg), and hyperlipoproteinemia was diagnosed in patients who had been given lipid-lowering medication or had a history of cholesterol levels >240 mg/dL. Smoking was classified as current smoking, past smoking (stopped between 4 weeks and <40 years ago), or never smoking (never smoked or stopped smoking ≥40 years ago). Acute coronary syndrome was defined as acute myocardial infarction or unstable angina (Braunwald class B or C). A total of 1010 (99.2%) of the 1018 patients were followed up for a mean of 3.1 (maximum 4.3) years. Patients either presented at our clinic (87.2%) or were interviewed by telephone by trained medical staff. Follow-up information was obtained about death from cardiovascular causes (n=78), death from causes not related to heart disease (n=22), and nonfatal myocardial infarction (n=61). Information about the cause of death or clinical events was obtained from hospital or general practitioner charts.

Study participants had German nationality. The study was approved by the ethics committee of the University of Mainz. Participation was voluntary, and each study subject gave written informed consent.

Infectious Serology and Laboratory Methods

Blood was drawn from all study subjects under standardized conditions after an overnight fasting period before coronary angiography was performed. Samples were stored at −80°C until analysis.

The serum of each study subject was tested for specific IgG class antibodies against CMV, HSV-1, HSV-2, Epstein-Barr virus (EBV), C. pneumoniae, Mycoplasma pneumoniae, Haemophilus influenzae, and H. pylori as well as IgA class antibodies against C. pneumoniae, M. pneumoniae, H. pylori, and EBV by using quantitative in vitro ELISA or indirect immunofluorescence (C. pneumoniae and H. influenzae) (EUROMMUN). A value of >20 relative units per mL in the IgG ELISA and a ratio of >1 in the IgA ELISA were considered positive according to the manufacturer’s instructions. Concerning indirect immunofluorescence, the starting dilution was 1:100, and specific fluorescence patterns at or above these dilutions were considered positive. C-reactive protein (CRP) was determined immediately by use of routine methods.

Statistical Considerations

Highest versus lowest pathogen burden groups were compared by χ²-test (categorical variables) or Student t test (continuous variables). For skewed distribution (CRP), logarithmically transformed variables were tested. Survival was assessed by Cox regression and the Kaplan-Meier method. For adjusted survival analysis, Cox regression was applied; variables included all univariate predictive variables and those variables possibly confounding or being confounded by infectious serology tested, such as smoking and HDL cholesterol. Adjusted estimates of risks for each unit increase in pathogen burden are presented as hazard ratio risks (HRRs) and 95% CIs. First, pathogen burden was entered as a single ordinal covariate in the Cox regression models; further groups of seropositivities were stratified into low, middle, and high pathogen burden. Additionally, analyses were performed separately for Herpesviridae and bacterial infections. All statistical tests used are reported with 2-tailed probability values; P<0.05 was considered to be significant. All computations were carried out by using SPSS, version 10.0.

Results

Baseline Characteristics

Table 1 demonstrates patient characteristics according to low or high pathogen load. The mean age of the entire study population was 62±10 years; 73.5% were male patients.

Univariate Predictors of Mortality From Cardiovascular Causes

As shown in Table 2, CRP was strongly associated with mortality from cardiovascular causes (HR 1.3 for logarithmically transformed continuous variables, P=0.001). Further univariate predictors were age, history of diabetes, left ventricular ejection fraction, and statin intake at enrollment. Both angiographic features, ie, the number of diseased vessels and the number of stenoses >30%, were predictors of future fatal cardiovascular events. Interestingly, history of hyperlipidemia paradoxically predicted lower risk after CAD diagnosis. This may be explained by a higher percentage of statin prescription in this patient cohort. Therefore, we preferred to include the variable statin intake instead of history of hyperlipidemia in multivariate analyses.

Analyses of Seropositivities and Future Death From Cardiac Causes

Table 3 demonstrates the associations of baseline pathogen IgG and IgA antibodies with future fatal cardiovascular events. Of all evaluated pathogens, only IgG seropositivity to HSV-2 and IgA seropositivity to EBV as well as H. pylori revealed an independent significant association with future cardiovascular death.

Pathogen Burden and Future Cardiac Mortality

For analysis of the association between future death from cardiovascular causes and the aggregate number of anti-pathogen antibodies, we used IgG seropositivities to HSV-1 and -2, CMV, and H. influenzae, as well as IgA seropositivities to H. pylori, C. pneumoniae, M. pneumoniae, and EBV. An increasing pathogen burden was significantly predictive of the long-term prognosis in a dose-response manner (P<0.0001, fully adjusted) (Figure 1). As demonstrated in Table 4, relative hazard risk ratios increased with increasing numbers of seropositivities. Because of the limited numbers of subjects with very low and very high pathogen burden, we stratified patients into groups with 0 to 3, 4 or 5, and 6 to 8 numbers of seropositivities. The mortality in these groups amounted to 3.7%, 7.2%, and 12.6%, respectively. In the fully adjusted model, patients seropositive to >5 pathogens
revealed a 5.1 (1.4 to 18.3) increase in risk for future fatal events compared with the reference group of patients with <4 seropositivities ($P$ for trend $<0.002$, fully adjusted).

Further analyses were performed separating seropositivities into Herpesviridae and bacterial infections (Table 4). The overall dose-response relationship between pathogen burden and future fatal cardiovascular events was mainly driven by seropositivities to Herpesviridae ($P$, $0.0001$). The hazard risk ratio for individuals with 3 and 4 seropositivities compared with patients with 2 seropositivities was 6.4 (95% CI 2.1 to 19.6). The corresponding Kaplan-Meier survival estimates to these analyses are presented in Figure 2.

### Pathogen Burden and Combined End Point of Myocardial Infarction and Death From Cardiovascular Causes

The relationship between the combined end point of myocardial infarction and death from cardiovascular causes and total pathogen burden was somewhat attenuated in the fully adjusted model (1.9-fold increase in risk for >5 compared with <4 pathogens, 95% CI 1.4 to 18.3). However, the relationship between aggregate number of Herpesviridae and combined end point remained highly significant (2.3-fold increase in risk for >2 compared with <2 pathogens, 95% CI 1.2 to 4.4; $P=0.008$).

### Association Between CRP Level, Pathogen Burden, and Future Cardiac Death

To evaluate a possible interaction between pathogen burden, CRP, and future death from cardiovascular causes, we re-
peated analyses with respect to high (>0.5 mg/dL) or low (≤0.5 mg/dL) CRP levels. Figure 3a and 3b demonstrates the association of total pathogen burden with future fatal cardiovascular events, which was independently significant in both subgroups irrespective of the CRP level. Then the association is shown between the aggregate number of seropositivities to bacterial infections (Figure 3c and 3d) or Herpesviridae (Figure 3e and 3f) among both CRP groups. The strongest association between infectious burden and future fatal cardiovascular events was observed for the aggregate number of Herpesviridae among patients with low CRP levels (P < 0.0001, fully adjusted; HR 5.6, 95% CI 2.3 to 13.9). These data provide evidence that Herpesviridae predict risk independent of CRP, whereas bacterial infections are predictive in patients with elevated CRP levels only.

**Discussion**

There is consistent evidence that inflammation plays a crucial role in the pathogenesis of atherosclerosis. Inflammatory cell infiltration is observed in atherosclerotic plaques at virtually all stages, and many studies have linked serum markers of inflammation, such as the level of CRP to future cardiac events in healthy individuals as well as in patients with stable or unstable angina.18,19

The evidence of infectious pathogens contributing to the atherosclerotic process includes seroepidemiological data, direct identification of Herpesviridae and C pneumoniae in the atherosclerotic plaque, experimental models demonstrating an acceleration of atherosclerosis by Herpesviridae or C pneumoniae, and induction of proatherogenic properties by infectious agents.3

It is hypothesized that infectious agents exert their effects by inducing a local or systemic inflammatory response and/or by infection-induced autoimmune response involving molecular mimicry.

It has been shown that the aggregate number of pathogens to which an individual had been exposed might be involved in the pathogenesis of atherosclerosis. This concept has been referred to as infectious burden and was demonstrated in a cross-sectional as well as prospective study recently.3,16,17 Increasing numbers of infectious pathogens were associated with future death from overall causes and nonfatal myocardial infarction. This association was described independent of CRP levels.

In the present study, we selected 8 pathogens because of the following 2 main characteristics: They are obligate intracellular pathogens, except for H influenzae and

### Table 3. Seropositivity to Various Pathogens and Risk of Fatal Cardiovascular Event

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Positive Serology, %</th>
<th>Causes (n = 78)</th>
<th>Survivors (n = 932)</th>
<th>Univariate</th>
<th>Adjusted*</th>
<th>HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV, IgG</td>
<td>80.8</td>
<td>70.7</td>
<td>0.06</td>
<td>0.3</td>
<td>1.4 (0.7–3.0)</td>
<td></td>
</tr>
<tr>
<td>HSV-1, IgG</td>
<td>94.9</td>
<td>92.7</td>
<td>0.5</td>
<td>0.3</td>
<td>3.0 (0.4–22.4)</td>
<td></td>
</tr>
<tr>
<td>HSV-2, IgG</td>
<td>25.6</td>
<td>13.5</td>
<td>0.003</td>
<td>0.045</td>
<td>2.0 (1.01–4.0)</td>
<td></td>
</tr>
<tr>
<td>EBV, IgG</td>
<td>100</td>
<td>98.7</td>
<td>0.3</td>
<td>0.98</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>EBV, IgA</td>
<td>27.8</td>
<td>13.8</td>
<td>0.001</td>
<td>0.001</td>
<td>2.8 (1.5–5.0)</td>
<td></td>
</tr>
<tr>
<td>C pneumoniae, IgG</td>
<td>84.6</td>
<td>84.7</td>
<td>0.99</td>
<td>0.9</td>
<td>0.9 (0.5–2.0)</td>
<td></td>
</tr>
<tr>
<td>C pneumoniae, IgA</td>
<td>46.2</td>
<td>48.6</td>
<td>0.7</td>
<td>0.4</td>
<td>0.8 (0.4–1.4)</td>
<td></td>
</tr>
<tr>
<td>H pylori, IgG</td>
<td>77.8</td>
<td>80.6</td>
<td>0.6</td>
<td>0.3</td>
<td>0.7 (0.4–1.4)</td>
<td></td>
</tr>
<tr>
<td>H pylori, IgA</td>
<td>41.0</td>
<td>27.7</td>
<td>0.01</td>
<td>0.002</td>
<td>2.5 (1.4–4.4)</td>
<td></td>
</tr>
<tr>
<td>M pneumoniae, IgG</td>
<td>57.7</td>
<td>59.9</td>
<td>0.8</td>
<td>0.6</td>
<td>0.8 (0.5–1.5)</td>
<td></td>
</tr>
<tr>
<td>M pneumoniae, IgA</td>
<td>16.7</td>
<td>12.3</td>
<td>0.3</td>
<td>0.3</td>
<td>1.5 (0.7–3.2)</td>
<td></td>
</tr>
<tr>
<td>H influenzae, IgG</td>
<td>82.1</td>
<td>74.1</td>
<td>0.1</td>
<td>0.5</td>
<td>1.3 (0.7–2.7)</td>
<td></td>
</tr>
</tbody>
</table>

Because of incomplete data of CRP and ejection fraction, total was 795 for the adjusted analyses.

*Adjusted for age, sex, presence or absence of ever smoking, diabetes, HDL cholesterol (continuous variable), number of stenoses, invasive treatment, antihypertensive treatment and statin intake at enrollment, CRP (logarithmically transformed continuous variables), and ejection fraction (≤30%).

![Figure 1. Percentage of mortality from cardiovascular causes according to pathogen burden, which was based on IgG seropositivities to HSV-1, HSV-2, CMV, H influenzae, and IgA seropositivities to C pneumoniae, M pneumoniae, H pylori, and EBV.](http://circ.ahajournals.org/)

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M pneumoniae, and they all develop persistent antibodies targeted to the pathogen. Furthermore, 6 pathogens produce a lifelong latent (Herpesviridae) or persistent infection, whereas H influenzae and M pneumoniae are not known to provoke a persistent infection although they establish a lifelong persistence of antibodies. In all pathogens, we determined anti-IgG antibodies; in some pathogens, additional IgA antibodies were measured because of the nearly 100% prevalence of IgG (EBV) and because of reports suggesting that IgA antibodies might reflect more recent and/or repeated infectious episodes (C pneumoniae, H pylori, and M pneumoniae). 20

The results of the present study confirm and extend previous findings. Three (H pylori, HSV-2, and EBV) of 8 infectious pathogens were identified as being independently predictive of future death from cardiovascular causes. Interestingly, neither IgG nor IgA antibodies to C pneumoniae were associated with future cardiovascular events. It cannot be ruled out that measurement of antibodies to C pneumoniae provides the wrong tool to determine the association between this pathogen and cardiovascular events. However, our data do not support the implicit assumption of several prospective trials testing the effect of macrolide antibiotics on future cardiac event rates in patients with atherosclerosis. 21 On the other hand, our results show for the first time that prior infection to EBV may influence the course of atherosclerosis. EBV is an obligate intracellular pathogen with lifelong persistence in B cells. If infections do play a role in atherogenesis and if, at least in part, infection-induced autoimmune responses contribute to this process, EBV could be a candidate trigger. Virus-induced antigens are part of B-cell membranes and can so far stimulate T-cell activity. On the other hand, EBV-containing T cells have been recently demonstrated in atherosclerotic abdominal aneurysms. 22 Regardless of the mechanism, EBV shows the strongest association of all single pathogens with future events. This may suggest that a variety of pathogens sharing these characteristics may play a role in atherogenesis.

Most important, increasing numbers of infectious serologies were identified as independent risk factors for future cardiac death. Furthermore, stratified analyses in patients with low and high CRP levels demonstrated that the association of pathogen burden with future cardiovascular death remained independently significant in both groups.

### TABLE 4. HRRs of Future Death From Cardiovascular Disease According to Numbers of Seropositivities Among Patients With Documented CAD in 3 Cox Regression Models

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subjects, n</th>
<th>Deaths From Cardiovascular Causes, n (%)</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total pathogen burden (8 infectious agents)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–3*</td>
<td>190</td>
<td>7 (3.7)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>…</td>
</tr>
<tr>
<td>4 or 5</td>
<td>598</td>
<td>43 (7.2)</td>
<td>1.7 (0.8–3.9)</td>
<td>1.7 (0.8–3.9)</td>
<td>2.4 (0.7–7.9)</td>
<td>…</td>
</tr>
<tr>
<td>6–8</td>
<td>222</td>
<td>28 (12.6)</td>
<td>2.7 (1.1–6.4)</td>
<td>2.8 (1.2–6.7)</td>
<td>5.1 (1.4–18.3)</td>
<td>…</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.002</td>
<td>0.01</td>
<td>0.017</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 or 1*</td>
<td>458</td>
<td>26 (5.7)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>370</td>
<td>35 (9.5)</td>
<td>1.6 (0.9–2.6)</td>
<td>1.6 (0.95–2.7)</td>
<td>1.8 (0.94–3.5)</td>
<td>1.8 (0.94–3.5)</td>
</tr>
<tr>
<td>3</td>
<td>158</td>
<td>15 (9.5)</td>
<td>1.5 (0.8–2.9)</td>
<td>1.9 (0.95–3.6)</td>
<td>2.2 (0.93–5.1)</td>
<td>…</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>2 (8.3)</td>
<td>1.3 (0.3–5.4)</td>
<td>1.6 (0.4–6.9)</td>
<td>1.1 (0.1–9.2)</td>
<td>2.1 (0.9–4.8)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.2</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Herpesviridae</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 or 1*</td>
<td>263</td>
<td>9 (3.4)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>549</td>
<td>40 (7.3)</td>
<td>1.8 (0.8–3.7)</td>
<td>1.8 (0.9–3.7)</td>
<td>2.5 (0.8–7.4)</td>
<td>2.5 (0.8–7.4)</td>
</tr>
<tr>
<td>3</td>
<td>179</td>
<td>25 (14.0)</td>
<td>3.6 (1.6–8.1)</td>
<td>3.6 (1.6–8.0)</td>
<td>6.1 (1.9–19.3)</td>
<td>…</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>4 (21.1)</td>
<td>4.7 (1.3–17.8)</td>
<td>4.1 (1.0–16.5)</td>
<td>8.7 (1.1–67.9)</td>
<td>6.4 (2.1–19.6)</td>
</tr>
<tr>
<td>P for trend</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.001</td>
<td>&lt;0.0001</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

Model 1 included age, sex, and presence or absence of risk factors diabetes, ever smoking, and HDL cholesterol as continuous variables. Model 2 further adjusted for number of stenoses, invasive treatment, and antihypertensive and statin medication at time of enrollment. Model 3 (n=817) further included LVEF (<30%) and logarithmically normalized CRP levels.

*Patients in this group served as control group.
†Patients with 3 or 4 seropositivities were combined into 1 group because of small numbers.
On the other hand, several prospective studies have revealed contradictory results.9,12,14,23 These disparate results may have been reached for several reasons: In contrast to the present study, each of these studies was restricted to a highly homogeneous, apparently healthy population. Despite the advantage of such highly selected populations (eg, elimination of various confounders), these populations may not necessarily represent other populations (eg, those with proven atherosclerotic disease). Furthermore, most of these studies determined only IgG antibodies, and last, evaluation of Herpesviridae was mostly restricted to anti-CMV IgG alone.

Although prospective in design, the present study shares the limitations of nonrandomized observational studies, ie, unsuspected selection biases and possible confounding. However, the association of infectious burden and mortality remained stable after adjustment for multiple potentially confounding variables. Nonetheless, the present study cannot unequivocally prove a causal relationship between infectious agents and the atherosclerotic process.

In conclusion, our data provide strong evidence that infections play a role in atherogenesis, at least as covariates to preexisting CAD risk factors. An increasing pathogen load (infectious burden) was independently related to future death from cardiovascular causes in patients with CAD. Because there is growing evidence that a variety of pathogens are participating in the development and/or acceleration of at least preexisting atherosclerosis (even by secondary immune or autoimmune mechanisms), it seems questionable whether specific antibiotic therapy to 1 or 2 specific pathogens will be useful in determining the infectious hypothesis and in improving patient outcome.

Appendix

The AtheroGene Group consisted of the following members:
Hans-Jürgen Rupprecht, Stefan Blankenberg, Christoph Bickel, Christine Espinola-Klein, Jürgen Meyer (II Medical Clinic, Johannes Gutenberg University Mainz, Germany); Laurence Tiret, Odette Poirier, Viviane Nicaud, Jean-Louis Georges, François Cambien (INSERM U525, Paris, France); and Gerd Hafner and Wilfried...
AtheroGene recruitment centers were located at II Medical Clinic, Johannes Gutenberg University, Mainz, and at Bundeswehrkrankenhaus Koblenz, Germany.

References

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