

ORIGINAL ARTICLE

## Antibiotic Treatment of *Chlamydia pneumoniae* after Acute Coronary Syndrome

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### ABSTRACT

#### BACKGROUND

*Chlamydia pneumoniae* has been found within atherosclerotic plaques, and elevated titers of antibody to this organism have been linked to a higher risk of coronary events. Pilot studies have suggested that antibiotic treatment may reduce the risk of cardiovascular events.

#### METHODS

We enrolled 4162 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days and evaluated the efficacy of long-term treatment with gatifloxacin, a bactericidal antibiotic known to be effective against *C. pneumoniae*, in a double-blind, randomized, placebo-controlled trial. Subjects received 400 mg of gatifloxacin daily during an initial 2-week course of therapy that began 2 weeks after randomization, followed by a 10-day course every month for the duration of the trial (mean duration, 2 years), or placebo. The primary end point was a composite of death from all causes, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke.

#### RESULTS

A Kaplan–Meier analysis revealed that the rates of primary-end-point events at two years were 23.7 percent in the gatifloxacin group and 25.1 percent in the placebo group (hazard ratio, 0.95; 95 percent confidence interval, 0.84 to 1.08;  $P=0.41$ ). No benefit was seen in any of the prespecified secondary end points or in any of the prespecified subgroups, including patients with elevated titers to *C. pneumoniae* or C-reactive protein.

#### CONCLUSIONS

Despite long-term treatment with a bactericidal antibiotic effective against *C. pneumoniae*, no reduction in the rate of cardiovascular events was observed.

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**A**LTHOUGH EPIDEMIOLOGIC STUDIES have identified numerous risk factors for atherosclerosis, many patients do not exhibit such risk factors, and this has prompted a search for additional contributors to the progression of the disease.<sup>1</sup> Infection with various pathogens has been implicated in the development of coronary artery disease. Specifically, *Chlamydia pneumoniae* has been associated with a doubling of the risk of atherosclerosis or myocardial infarction.<sup>2-7</sup> The organism has been detected in human atheroma,<sup>5,6</sup> and animal models have shown that new infection with *C. pneumoniae* results in more extensive atherosclerosis.<sup>7-10</sup> Although not all studies show a significant relationship between IgG titers to *C. pneumoniae* and coronary events, a meta-analysis of more than 20 studies suggests that such a relationship does exist.<sup>11</sup>

Given the potential etiologic relationship between *C. pneumoniae* and cardiac events, there has been great interest in the treatment of patients who have coronary artery disease with antibiotics that are effective against chlamydia. The results of some initial pilot trials were promising,<sup>12,13</sup> but more recent, larger studies have shown mixed results.<sup>14-17</sup> In the largest study, patients were treated with azithromycin, a bacteriostatic antibiotic, for three months. Although no benefit was seen after a mean duration of 2.5 years of follow-up, a reduction in the rate of death or myocardial infarction was seen at 6 months,<sup>15</sup> suggesting that long-term treatment with antibiotics might be effective in the prevention of cardiovascular events. In addition, because *C. pneumoniae* has a unique life cycle that includes a long, dormant intracellular phase, long-term treatment would allow better potential eradication of this organism from the vasculature.

Accordingly, the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction (PROVE IT–TIMI) 22 trial was set up as a two-by-two factorial design to compare long-term treatment with gatifloxacin with that of placebo for the prevention of death or major cardiovascular events in patients who had recently had an acute coronary syndrome. The study also compared standard and intensive statin therapy for the reduction of low-density lipoprotein cholesterol; the results of that comparison have been previously reported.<sup>18</sup> Gatifloxacin is a quinolone antibiotic with bactericidal activity against *C. pneumoniae* and has been shown to prevent atherosclerosis in an animal model.<sup>19</sup>

## METHODS

### PATIENTS

As previously described, between November 15, 2000, and December 22, 2001, 4162 patients underwent randomization at 349 sites in eight countries.<sup>18</sup> Men and women who were at least 18 years of age were eligible for inclusion if they had been hospitalized for an acute coronary syndrome — either acute myocardial infarction (with or without electrocardiographic evidence of ST-segment elevation) or high-risk unstable angina — within the preceding 10 days. Patients had to be in stable condition and were to be enrolled after a percutaneous revascularization procedure if one had been planned. Exclusion criteria were as previously reported.<sup>18</sup> The protocol was approved by the relevant institutional review boards, and written informed consent was obtained from all patients.

### STUDY PROTOCOL

The protocol specified that patients receive standard medical and interventional treatment, including aspirin at a dose of 75 to 325 mg daily, with or without clopidogrel or warfarin, for acute coronary syndromes. Eligible patients underwent randomization in a 1:1 ratio to receive 400 mg of gatifloxacin daily or placebo, to be administered in a double-blind fashion. Subjects in the gatifloxacin group received an initial 2-week course of therapy beginning at the visit on day 15, followed by a 10-day course every month for the duration of the trial. The duration of follow-up ranged from 18 to 32 months, with a mean duration of 2 years. In addition, in a two-by-two factorial design, as previously reported,<sup>18</sup> patients also underwent randomization to receive 40 mg of pravastatin or 80 mg of atorvastatin daily.

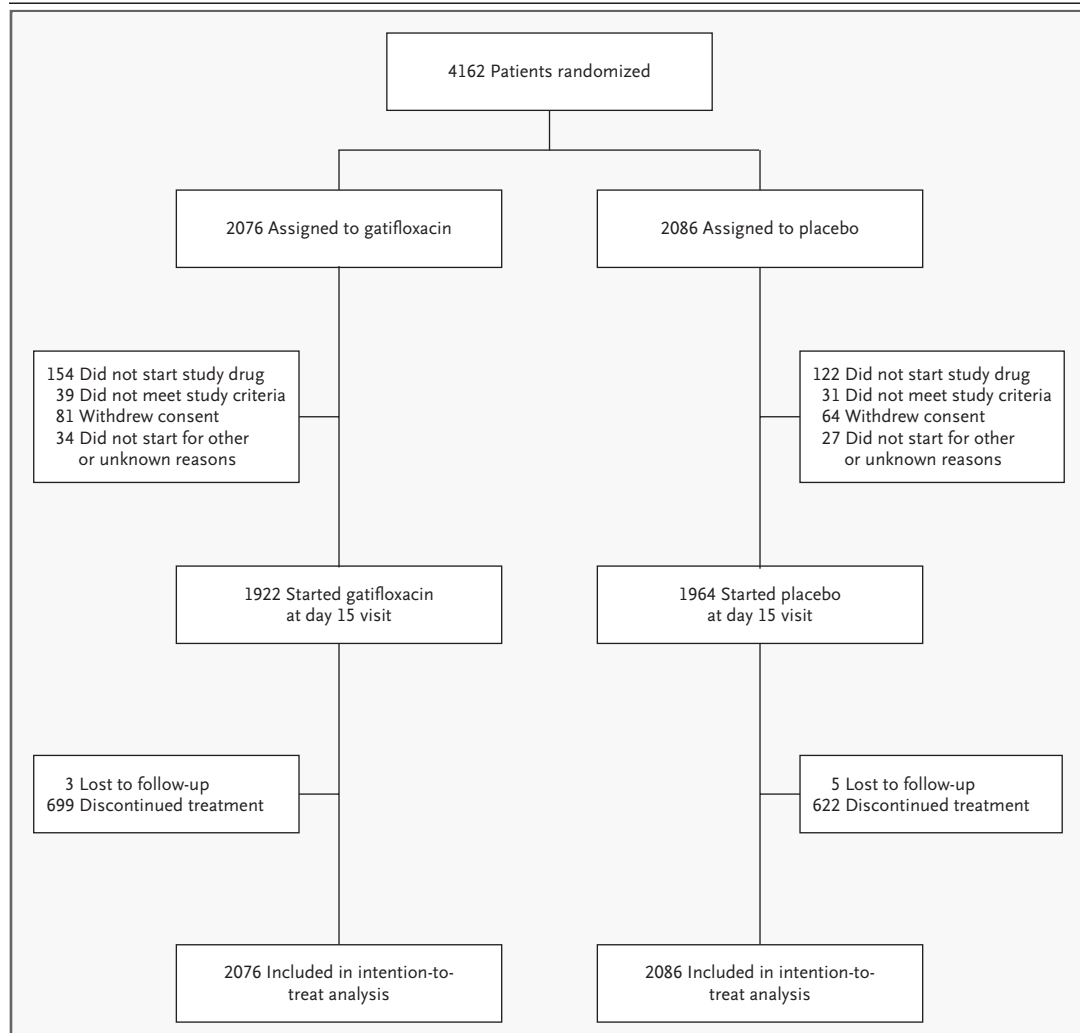
Patients were seen for follow-up visits at 30 days, 4 months, and every 4 months thereafter until a final visit in August or September of 2003. Patients who discontinued treatment with the study drug during the trial were followed by telephone contact. Blood samples for the measurement of antibodies to *C. pneumoniae* were obtained at baseline, at 4 months, and at the final visit and underwent assay at a central core laboratory; samples for the assay (by Denka Seiken) for high-sensitivity C-reactive protein were obtained at these times and also at 30 days. In a substudy at selected centers, blood samples were obtained at baseline and at four months for assessment by polymerase

chain reaction for the presence of DNA of *C. pneumoniae*.

The dosage of the study drug could be reduced to a five-day course per month if patients had symptoms of drug intolerance, including diarrhea or nausea. The trial continued until reports of 925 events had been received at the coordinating center, after which all patients were asked to return for a final visit. Eight patients (0.2 percent) were lost to follow-up (Fig. 1).<sup>20</sup>

**END POINTS**

The measure of the primary efficacy outcome was the time from randomization until the first occurrence of a component of the primary end point—death from all causes, myocardial infarction, documented unstable angina that required rehospitalization, revascularization with either percutaneous coronary intervention or coronary-artery bypass surgery (if these procedures were performed at least 30 days after randomization), or stroke;



**Figure 1. Numbers of Patients Who Were Randomly Assigned to a Treatment Group, Who Started the Assigned Treatment, and Who Discontinued Treatment or Were Lost to Follow-up.**

Treatment was discontinued in 699 patients in the gatifloxacin group and 622 in the placebo group for the following reasons: withdrawal of consent to treatment, 178 in the gatifloxacin group and 169 in the placebo group; withdrawal of consent to follow-up, 26 and 27, respectively (data on these patients were censored at the time they withdrew consent); discovery of a violation in protocol, 14 and 6; abnormality on electrocardiogram, 5 and 3; creatinine clearance of less than 40 milliliters per minute, 0 and 3; need for contraindicated medication, 17 and 20; drug-related side effects, 159 and 106; lack of compliance with protocol requirements, 56 and 58; other adverse events, 158 and 139; and other reasons, 86 and 91.

the definitions of these events have been previously reported.<sup>18</sup> Secondary end points were the risk of death from coronary heart disease, nonfatal myocardial infarction, or revascularization (if performed at least 30 days after randomization) and the risk of death from coronary heart disease or of nonfatal myocardial infarction, as well as the individual components of the primary end point. Prespecified subgroup analyses were performed among patients with elevated *C. pneumoniae* antibody titers and according to quintiles of C-reactive protein levels at baseline as well as sex, smoking status, and the presence or absence of diabetes mellitus.

#### STATISTICAL ANALYSIS

We compared the results of treatment with gatifloxacin with those of placebo using Kaplan–Meier analyses of event rates as well as Cox proportional-hazards ratios over the duration of follow-up. On the assumption that there would be a two-year event rate of 24 percent in the placebo group during an average of two years of follow-up, a total of 2000 patients per group was considered necessary to yield 925 primary end points and give the study 94 percent power to detect a 19 percent reduction in the primary end point. This was based on a hypothesis that treatment with antibiotics would lead to a 20 percent reduction in events; however, because we were starting treatment with the drug on day 15, and no benefit could be derived before this, a 19 percent overall reduction of risk would be expected. Allocation of treatment was based on a central randomization system in which treatment was assigned according to the method of randomized permuted blocks of patients, stratified according to center. Two interim assessments of efficacy and safety were carried out by an independent data and safety monitoring board. Rules for early cessation due to the superiority of either treatment were not prespecified.

All efficacy analyses were based on the intention-to-treat principle. Estimates of hazard ratios and associated 95 percent confidence intervals for the comparison of gatifloxacin with placebo were obtained with the Cox proportional-hazards model, with randomized treatment as the covariate and stratification according to statin group. With the two-by-two factorial design, a test for interaction with statins was carried out, and no interaction was found with the groups receiving treatment with statins. The investigators designed the trial and had free and complete access to the data. The study was

designed by the TIMI Study Group. Data coordination was performed by the Nottingham Clinical Research Group.<sup>18</sup> Investigators from TIMI, the sponsor, and Nottingham performed data analysis jointly, and all groups vouch for the data.

## RESULTS

The two groups of enrolled patients were similar (Table 1). Their average age was 58 years, and 22 percent were women. Before their index event, 38 percent of patients had evidence of previous cardiovascular disease, and 18 percent had diabetes mellitus. As their index event, approximately one third had high-risk unstable angina, one third had myocardial infarction associated with electrocardiographic ST-segment elevation, and one third had myocardial infarction without such elevation. Sixty-nine percent of patients had undergone percutaneous coronary intervention for treatment of their index acute coronary syndrome before randomization. Concomitant medications were administered to patients during the treatment period as follows: aspirin, 93 percent; warfarin, 8 percent; clopidogrel or ticlopidine, 72 percent initially and

**Table 1. Baseline Characteristics of the Patients.\***

Characteristic	Gatifloxacin (N=2076)	Placebo (N=2086)
Age — yr	58.1±11.2	58.3±11.2
Male sex — no. (%)	1638 (78.9)	1613 (77.3)
White race — no. (%)†	1875 (90.3)	1901 (91.1)
Diabetes mellitus — no. (%)	394 (19.0)	340 (16.3)
Hypertension — no. (%)	1059 (51.0)	1032 (49.5)
Current smoker — no. (%)	756 (36.4)	773 (37.1)
Prior cardiovascular disease — no. (%)	798 (38.4)	789 (37.8)
Index event — no. (%)		
Unstable angina	610 (29.4)	608 (29.1)
Myocardial infarction without ST-segment elevation	763 (36.8)	741 (35.5)
Myocardial infarction with ST-segment elevation	702 (33.8)	736 (35.3)
Body-mass index‡	29.5±5.6	29.5±5.9
PCI for index event — no. (%)§	1436 (69.2)	1441 (69.1)

\* Plus–minus values are means ±SD. None of the differences between groups were statistically significant.

† Race was assessed by the local investigator.

‡ Body-mass index is defined as the weight in kilograms divided by the square of the height in meters.

§ PCI denotes percutaneous coronary intervention.

20 percent at one year; beta-blockers, 85 percent; angiotensin-converting-enzyme (ACE) inhibitors, 69 percent; and angiotensin-receptor blockers, 14 percent. The study drug was administered for an average of 1.6 years in the gatifloxacin group and 1.7 years in the placebo group. By one year, 74.4 percent of patients in the gatifloxacin group and 80.0 percent of those in the placebo group were taking the study drug. There were 3025 and 3272 patient-years of exposure to gatifloxacin and placebo, respectively.

For all randomized patients, Kaplan–Meier estimates of the event rates for the primary end point at two years were 23.7 percent in the gatifloxacin group and 25.1 percent in the placebo group (Fig. 2), representing a hazard ratio of 0.95 (95 percent confidence interval, 0.84 to 1.08;  $P=0.41$ ). The risk associated with the secondary end point of death due to coronary heart disease, myocardial infarction, or revascularization also was not significantly reduced among patients receiving gatifloxacin, with a rate of 20.4 percent as compared with 21.6 percent among those receiving placebo (hazard ratio, 0.95; 95 percent confidence interval, 0.84 to 1.09;  $P=0.48$ ). The risk of death due to coronary heart disease or myocardial infarction was also not significantly reduced in the gatifloxacin group, at 7.6 percent as compared with 8.0 percent in the placebo group (hazard ratio, 0.97;  $P=0.78$ ). There was no reduction in the individual components of the primary end point among patients treated with gatifloxacin (Fig. 3).

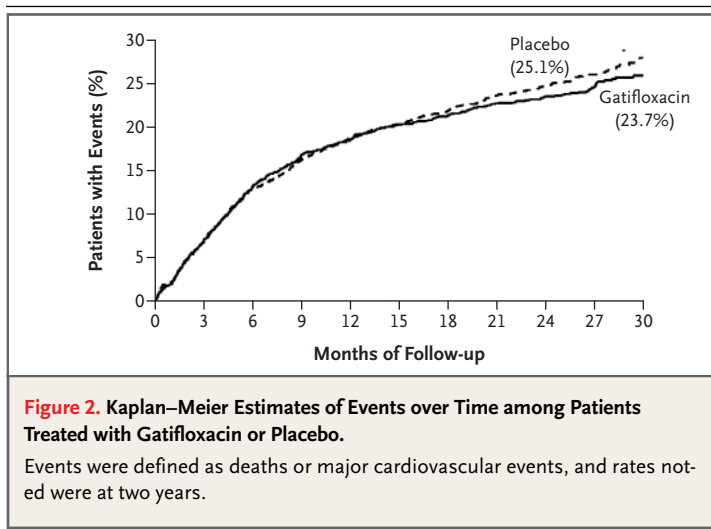
No benefit from gatifloxacin was observed among prespecified clinical subgroups in terms of

either the primary end point (Fig. 4) or the secondary end point of death from coronary heart disease or myocardial infarction (data not shown). Testing of baseline IgG antibody titers to *C. pneumoniae* did not identify a subgroup of patients who benefited from antibiotic treatment (Fig. 4), including the 5 percent of patients who had the highest baseline titers (greater than 1:512) (data not shown). There was no effect of gatifloxacin on antibody titers over the trial period. In the placebo group, there was a decrease in antibody titers over time, with the percentage of patients in whom titers were elevated falling from 64.6 percent at baseline to 52.4 percent at the final visit ( $P<0.001$ ). An identical pattern was seen in the gatifloxacin group, with a fall from 64.0 percent at baseline to 53.5 percent at the final visit ( $P<0.001$ ). The  $P$  value for interaction was not significant, and thus treatment with gatifloxacin did not influence antibody titers to *C. pneumoniae*. In the substudy that assessed the presence of DNA for *C. pneumoniae* in peripheral mononuclear blood cells, only 6 of 171 patients in the placebo group (3.5 percent) and 6 of 172 in the gatifloxacin group (3.5 percent) were positive at baseline. At four months, among 80 patients who received gatifloxacin and 89 who received placebo with follow-up blood samples, 3 (3.8 percent) and 4 (4.5 percent), respectively, were positive ( $P$  not significant).

Use of levels of C-reactive protein at baseline to define subgroups according to either the median level of 12.1 mg per liter (Fig. 4) or according to quintile did not identify any subgroups that had a benefit from gatifloxacin. Over the duration of the trial, there were no differences in achieved C-reactive protein levels between patients receiving gatifloxacin and those receiving placebo; in each group, the level was 1.7 mg per liter at four months and 1.8 mg per liter at the final visit ( $P$  not significant for either time).

#### TOLERABILITY AND SAFETY

As expected, the side effects of diarrhea and nausea or vomiting associated with antibiotic treatment were significantly more common among patients receiving gatifloxacin (8.1 percent had diarrhea, and 7.3 percent nausea or vomiting;  $P=0.01$ ) than among those receiving placebo (6.1 percent and 5.5 percent, respectively;  $P=0.02$ ). Slight changes in blood glucose levels were noted in the gatifloxacin group, as previously reported with this agent.<sup>21</sup> Among patients who did not have diabetes mellitus



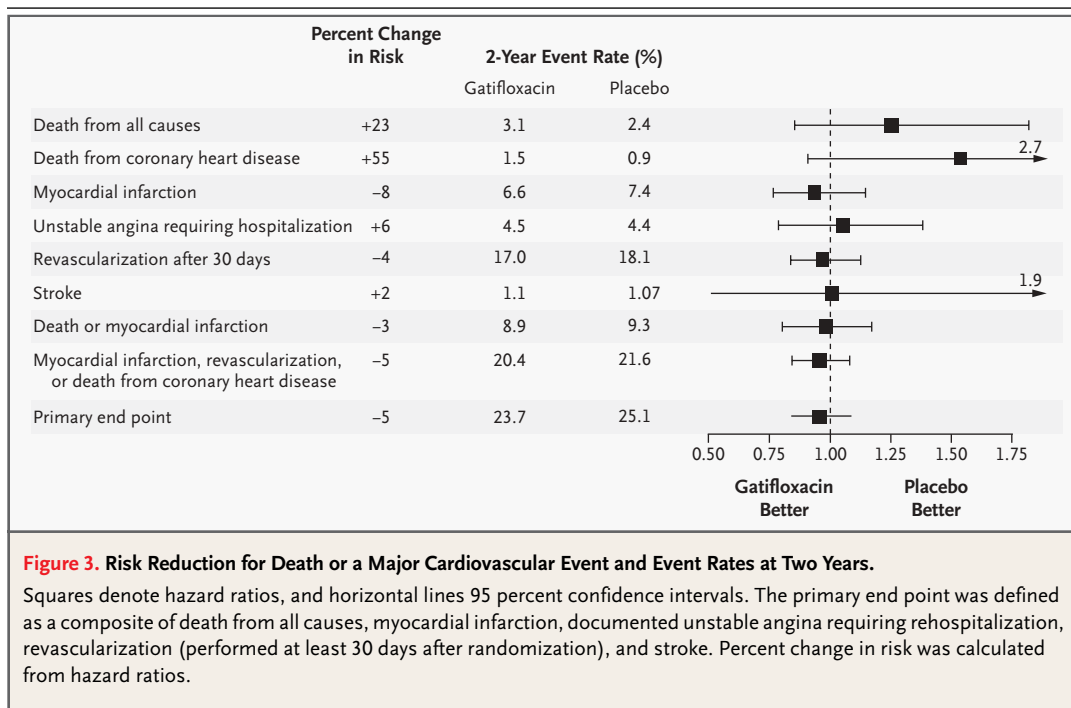
at baseline, new-onset diabetes (defined as the presence of one or more nonfasting serum glucose values of  $\geq 200$  mg per deciliter, two or more nonfasting serum glucose values of  $\geq 140$  mg per deciliter, or two or more fasting serum glucose values of  $\geq 126$  mg per deciliter) tended to develop more frequently in patients treated with gatifloxacin than in those given placebo (4.6 percent vs. 3.4 percent,  $P=0.08$ ). Among patients with diabetes, there were trends toward more patients who were treated with gatifloxacin having episodes of hyperglycemia than patients who were treated with placebo (30.7 percent vs. 25.4 percent,  $P=0.11$ ) and toward more patients who were treated with gatifloxacin having episodes of hypoglycemia (2.6 percent vs. 1.5 percent,  $P=0.32$ ). Conversely, fewer upper respiratory tract infections developed in patients receiving the monthly courses of gatifloxacin than in patients receiving placebo (10.9 percent vs. 14.8 percent,  $P<0.001$ ), and fewer sinus infections developed in patients in the gatifloxacin group than in those in the placebo group (4.6 percent vs. 6.5 percent,  $P=0.01$ ).

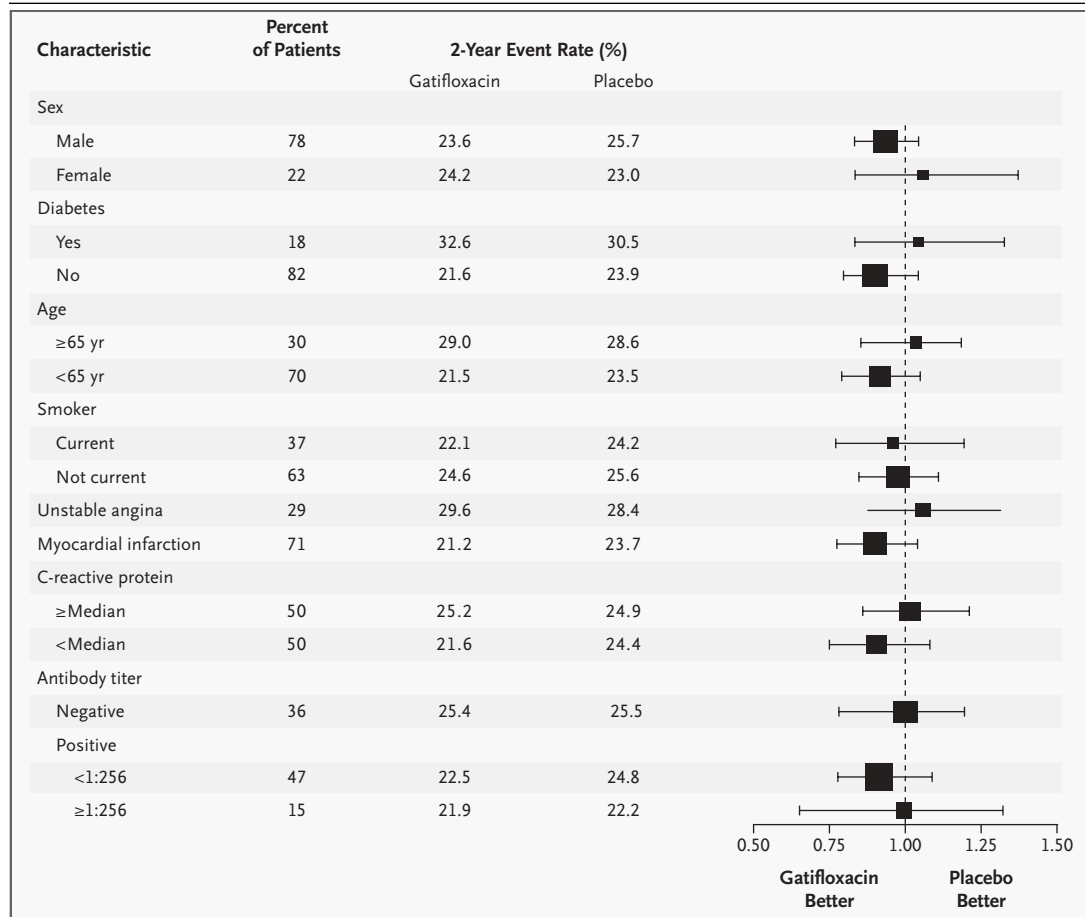
#### DISCUSSION

Although there is evidence to suggest that *C. pneumoniae* has a role in the development of atheroscle-

rosis, we were not able to detect a benefit from long-term antibiotic therapy in patients who had recently been hospitalized for an acute coronary syndrome. These results are in agreement with those of Grayston et al., reported elsewhere in this issue of the *Journal*.<sup>22</sup> There was no reduction in the primary end point, the secondary end points, or any of the individual components of the primary end point as a result of antibiotic treatment. None of the prespecified subgroups, distinguished by high-risk clinical characteristics, C-reactive protein levels, antibody titers to *C. pneumoniae*, or the presence of *C. pneumoniae* within peripheral mononuclear blood cells, showed any benefit from the antibiotic treatment. Thus, our findings suggest that for patients who have had a recent acute coronary syndrome and who have established cardiovascular disease, antibiotic therapy is not effective in reducing the risk of recurrent cardiovascular events. When these findings are juxtaposed with the significant benefit of intensive statin therapy as compared with standard statin therapy that was observed in the same trial,<sup>18</sup> the results reinforce the importance of using proven therapies for secondary prevention in this population.

Our trial differed from prior studies of antibiotics<sup>12-17</sup> in that it involved a large number of high-risk patients with acute coronary syndromes,





**Figure 4. Hazard Ratios for Death or a Major Cardiovascular Event, with Two-Year Event Rates, According to Baseline Characteristics.**

Squares denote hazard ratios, and horizontal lines 95 percent confidence intervals. None of the tests for interaction were significant. The median C-reactive protein level was 12.1 mg per liter.

among whom more than 1000 primary end points were observed; the trial thus had a more than 97 percent power to detect (or rule out) a benefit from antibiotic treatment of 19 percent and an 85 percent power to detect (or rule out) a benefit of 17 percent. In addition, we continued antibiotic treatment longer than any of the prior trials, using monthly courses of therapy throughout the two-year duration of the trial. We studied patients with acute coronary disease, the severity of which, it had been thought, would allow *C. pneumoniae* to be potentially active within coronary lesions. Finally, full-dose gatifloxacin, a bactericidal quinolone antibiotic known to be destructive to *C. pneumoniae*, was used, in contrast to the bacteriostatic macrolide antibiotics that were used in prior studies. Despite the long-term, full-dose antibiotic treatment,

no reduction in cardiac events was observed with antibiotic treatment in patients who had recently been hospitalized for an acute coronary syndrome.

In determining the potential reasons why antibiotic treatment was not effective, we assessed disease activity in several ways. The substudies point to an absence of active infection in the middle-aged patients with established coronary disease who were enrolled. With the use of serial antibodies to *C. pneumoniae*, no increase in titers was observed, as would be expected if patients had active infection with the organism. These findings were supported by the substudy that found that only 4 percent of patients had evidence of *C. pneumoniae* in their mononuclear blood cells (a marker that has been shown in other studies to be well correlated with the

presence of *C. pneumoniae* in arterial plaque).<sup>2,23</sup> Finally, there was no effect of antibiotic treatment on levels of C-reactive protein, a marker of inflammation, which might have been elevated by *C. pneumoniae*. Thus, the overall clinical results and the results of the three substudies within the trial suggest that patients were not actively infected with *C. pneumoniae* and that, accordingly, antibiotic therapy had no detectable effect.

Because the serologic and pathological evidence supports the likelihood of prior infection and the presence of *C. pneumoniae* within arterial plaque, it is possible that infection with *C. pneumoniae* is part of the initiation of atherosclerosis in the early decades of life but not an active part of the progression of disease later, when patients have established coronary artery disease. Indeed, the animal model that has shown a benefit of antibiotic therapy with either azithromycin or gatifloxacin is that of cholesterol-fed rabbits, in which antibiotic treatment at the time of initial infection can reduce the development of atherosclerosis.<sup>7,19</sup> No model of established vascular disease has been used to show that the use of antibiotics reverses or slows the progression of the disease. The situation may be similar to that of other infections such as those involving the Epstein-Barr virus, which is a well-established cause of Burkitt's lymphoma. However, among patients in whom the lymphoma develops, treatment is not with anti-

ral agents but, rather, with chemotherapeutic agents. Thus, it is possible that *C. pneumoniae* is a cause of early atherosclerosis but that once the process is established, with the appearance of cholesterol-laden plaque and inflammation, therapy with antichlamydial antibiotics is not effective.

Accordingly, the two components of the PROVE IT-TIMI 22 trial highlight the proven benefit of intensive statin therapy after acute coronary syndromes, as recently advocated in an update to the guidelines of the National Cholesterol Education Program.<sup>24</sup> Efforts toward secondary prevention in patients with these syndromes should be aimed at proven therapies, including antiplatelet therapy, treatment with beta-blockers and ACE inhibitors, and intensive lowering of lipid levels with the use of statins.

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