Original Articles

PROVE-IT TIMI 22 Study

Potential Effects on Critical Pathways for Acute Coronary Syndrome

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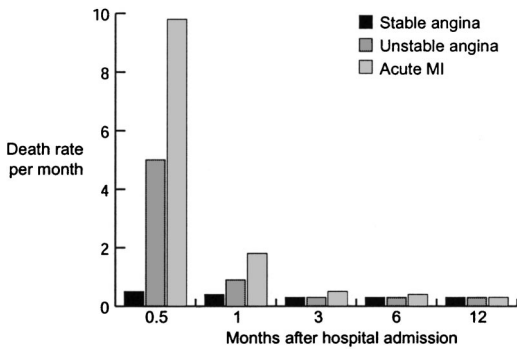From the Cardiovascular Division, Brigham and Women's Hospital, Boston, MA.

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Acute coronary syndrome (ACS), defined as acute myocardial infarction (MI) or unstable angina (UA), is a major cause of morbidity and mortality, and is the most prevalent cause of death in patients who have been hospitalized for the treatment of medical conditions.[1] In the United States alone, more than 1.9 million suspected cases of UA or acute MI occur each year, and approximately 515,000 deaths annually from coronary heart disease (CHD).[2] Most fatalities after acute MI or UA occur within the first 30 days; however, by 90 days, death rates are comparable with those of patients with stable angina[3] (Fig. 1). Therefore, maximizing therapeutic protection immediately after ACS is important in this patient population.

Recent advances in treatment, including antiplatelet and antithrombotic therapy, have reduced ACS-related morbidity and mortality. New guidelines incorporating these treatments have been published by the American College of Cardiology and the American Heart Association (ACC/AHA).[4] However, mortality rates remain high, and more effective treatments are still needed. This article reviews completed and ongoing studies on the efficacy of 2 potential ACS therapies—statins and antibiotics—that are currently under evaluation.

STATINS FOR THE TREATMENT OF CORONARY HEART DISEASE

A series of intervention studies have established the benefit of cholesterol-reducing statins for the prevention of fatal and nonfatal cardiovascular events in populations with stable atherosclerotic disease.[5–7] In addition, statin treatment has been shown to reduce mortality in patients with a range of cholesterol levels who have a history of MI and UA.[5–8] Statins have also been proven effective in reducing the incidence of CHD in people who are hypercholesterolemic,[9] those with no history of CHD who have normal cholesterol levels,[10] and those at high risk of developing CHD, including the elderly.[8,11,12]

The Adult Treatment Panel III[13] and ACC/AHA guidelines[4] now recommend that CHD patients with low-density lipoprotein cholesterol (LDL-C) levels >130 mg/dL or higher should be prescribed a lipid lowering drug in combination with intensive therapeutic lifestyle changes to reduce cholesterol levels. Preliminary observations suggest that compliance may be improved by administration of lipid-lowering therapy before discharge from the hospital.[4]

CURRENT STATIN THERAPY IN ACUTE CORONARY SYNDROME

Secondary CHD prevention studies initiating statin treatment more than 3 months after the acute cardiac event have demonstrated efficacy and safety in this setting[6,7] (Fig. 2); however, recurrence in ACS is most likely to occur shortly after the initial event, and the risk of death is highest within the first 30 days after acute MI or UA[3] (Fig. 1). Preliminary trials have shown that early treatment with statins after ACS can be safe and effective in reducing coronary events. For

FIGURE 1. Most fatalities occur within the first 30 days after acute MI or UA; however, by 90 days, death rates are comparable with those observed in patients with stable angina.[3]

example, the results of the Lipid-Coronary Artery Disease (L-CAD) study[14] indicated that pravastatin administered immediately after ACS for 6 months was well tolerated, reduced coronary atherosclerosis, and may have generated clinical benefit, although patient numbers were small and no definitive conclusions could be drawn from this trial.

The Fluvastatin on Risk Diminishing After Acute Myocardial Infarction (FLORIDA) study[15] investigated the effect of early initiation of treatment with statins after acute MI, and reported that 12 months of treatment with fluvastatin had no significant effect on ischemia; however, the trial was underpowered for the evaluation of this end point. In contrast, the Myocardial Ischemia Reduction
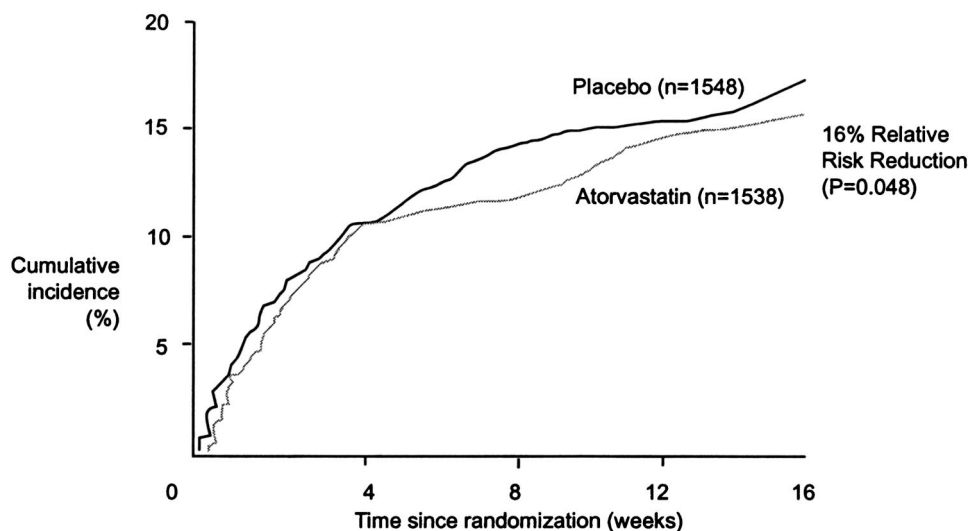
With Aggressive Cholesterol Lowering (MIRACL) trial,[16] which investigated the effect of aggressive lowering of cholesterol in patients with ACS, showed that short-term (4 months) treatment with high-dose atorvastatin (80 mg/d) was well tolerated and effectively reduced the primary composite end point of CHD death, nonfatal MI, resuscitated sudden cardiac death, or emergency rehospitalization for recurrent ischemia by 16% (reduction in absolute event rate, 2.6%; $P = 0.048$) (Fig. 3). The secondary end point of stroke was reduced by 50% (reduction in absolute event rate, 0.8%; $P = 0.045$).[16] Aggressive treatment with atorvastatin reduced LDL-C levels to an average of 72 mg/dL in this patient population. The results of MIRACL suggest that atorvastatin 80 mg is effective during the early stages of ACS and that these effects can be observed within 4 months, and in some cases as early as 1 month, after treatment is initiated. The study then raised the question of whether the aggressive LDL-C lowering was needed to achieve this benefit, or whether it could be accomplished with any statin therapy.

LOW-DENSITY LIPOPROTEIN CHOLESTEROL: IS LOWER BETTER?

The relationship between the degree of LDL-C lowering and the magnitude of risk
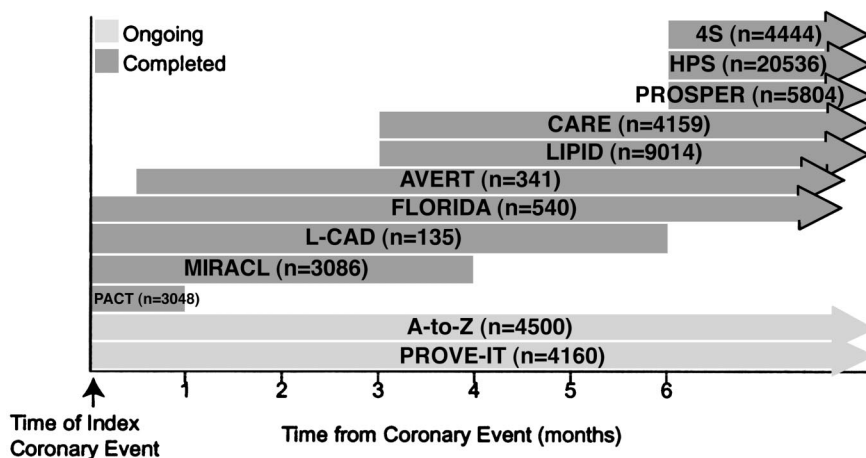
FIGURE 2. Time of initiation and duration of statin therapy in a range of clinical trials investigating the efficacy of statins for the secondary prevention of CHD (http://www.timi.org, http://www.clinicaltrialresults.org).

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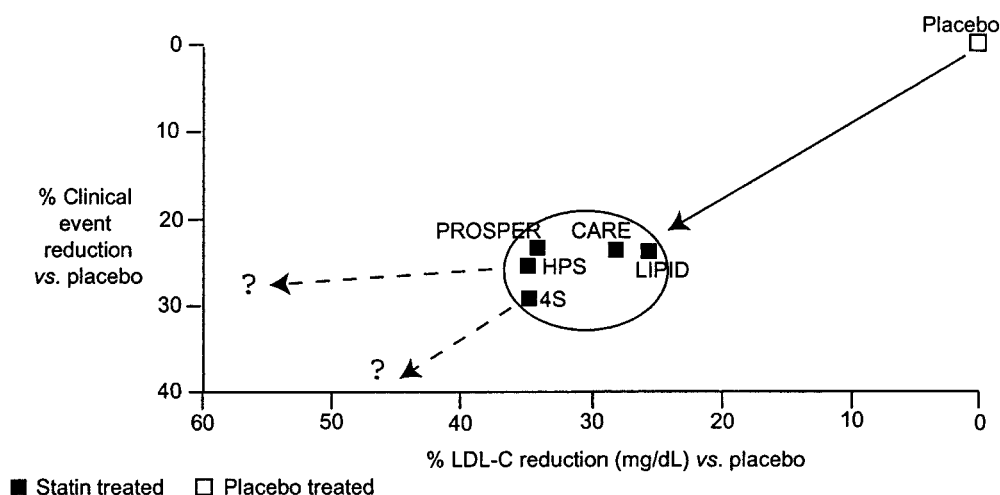*Volume 2, Number 3*
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FIGURE 3. In the MIRACL study, treatment with atorvastatin (80 mg daily) resulted in a 16% relative risk reduction in the composite primary end point of death, nonfatal MI, resuscitated cardiac arrest, worsening angina, and urgent rehospitalization (adapted from *JAMA*).[16]

reduction remains unclear. In clinical practice, it is widely accepted that titration of the dose of a statin to achieve an LDL-C target is required to manage hypercholesterolemia. However, none of the clinical end point trials to date have tested the value of achieved LDL-C targets; all have used a fixed dose and have generated similar results (when appropriately powered). When compared with placebo, the observed clinical event reduction (CHD death and nonfatal MI) in the major statin trials[5–7,9,11] appears to be similar and consistent (24%–31%) despite differences in percent LDL-C lowering (25%–35%) (Fig. 4). The results suggest that there are no significant differences in clinical event rates when lowering LDL-C between 25% and 35%. Therefore, the benefit seen in these trials may have little to do with the LDL-C achieved and more to do with the reduction in overall patient risk, regardless of the statin chosen. Further trials, such as Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) Thrombolysis in Myocardial Infarction (TIMI) 22, are currently ongoing to determine whether differences exist in clinical event rates with more aggressive (>35%) LDL-C lowering.

ONGOING STUDIES ON THE EVALUATION OF STATINS FOR ACUTE CORONARY SYNDROME

Studies to date have investigated the effect of statins on the ACS patient population over the short term. However, 2 trials that will investigate the efficacy of statins over the long term, the Aggrastat to Zocor (A-to-Z) TIMI 21 trial[17] and the PROVE-IT TIMI 22 trial,[18] are ongoing.

The A-to-Z trial (TIMI 21) is an international, randomized, multicenter study designed to investigate whether the early use of an aggressive dose of a statin (40 mg/d simvastatin for 30 days, followed by 80 mg/d for approximately 14 months) is superior to the accepted care regimen of a lower dose of statin started 3 to 6 months after an acute event (placebo for 4 months, followed by simvastatin 20 mg/d). It also investigates whether low molecular weight heparin is more effective or is associated with an improved safety profile compared with unfractionated heparin when used as an adjunct to baseline treatment. The trial is therefore the key follow-up trial to the MIRACL study, because it aims to confirm the early benefit of treatment with statins. The 4-month placebo period at the beginning of the trial in the

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FIGURE 4. The correlation between CHD events and LDL-C: the maximum degree of LDL-C lowering required for significantly greater clinical event reduction is currently unknown.

accepted care arm is of note, because ACC/AHA unstable angina guidelines[4] recommend initiation of lipid lowering at hospital discharge for all patients with ACS. The aim of the recommendation is to ensure that all patients with ACS receive treatment with lipid-lowering drugs, because observations made by the Swedish Registry of Cardiac Intensive Care[19] and by the Cardiovascular Hospitalization Atherosclerosis Management Program (CHAMP)[20] suggest that administration at discharge may improve compliance. Because all the patients enrolled in the A-to-Z trial will eventually receive treatment with statins, compliance is assured, and the risk of undertreatment will be minimized.

PROVE-IT TIMI 22, which is also an international multicenter trial, is testing the hypothesis that a lower absolute LDL-C level in patients with ACS is associated with reduced risk of cardiovascular disease (CVD) events, while also evaluating the relative efficacy and safety of aggressive LDL-C lowering. This goal can be accomplished by comparing the effect of a reduction in LDL-C levels to approximately 100 mg/dL with pravastatin (40 mg), or to 75 mg/dL with atorvastatin (80 mg), on the primary composite end point of all-cause death, MI, UA requiring hospitalization, revascularization occurring 30 days or more after randomization, and stroke. The primary hypothesis is that the 2 treatment strategies will be clinically equivalent—that is, that the benefit of statins in ACS will not be affected by the degree of LDL-C lowering. In addition, the role of *Chlamydia pneumoniae* infection on CVD risk will be examined by also randomizing patients to receive the antibiotic gatifloxacin or placebo.

The PROVE-IT TIMI 22 study is unique because it is the first to evaluate the clinical equivalence of 2 statins. Clinical equivalence can be claimed when the upper 95% confidence interval of the estimate of relative risk between 2 agents is within a prespecified range. PROVE-IT adopts a stringent definition of clinical equivalence, which corresponds to an upper 95% confidence interval of 1.17 relative risk difference at 2 years between pravastatin 40 mg and atorvastatin 80 mg (Fig. 5). The prespecified analysis uses the Cox proportional hazards model, and hazard ratio corresponding to a relative risk of 1.17 at 2 years is 1.198.[21] In terms of absolute event rates, equivalence translates into a difference of <1.2% between the patients taking pravastatin and atorvastatin (assuming a 22% event rate with atorvastatin). The sample size of 4160, duration of 2 years (6 times the follow-up period of the MIRACL trial[16]), and generation of 925 events is sufficient to generate 87% power to demonstrate that the
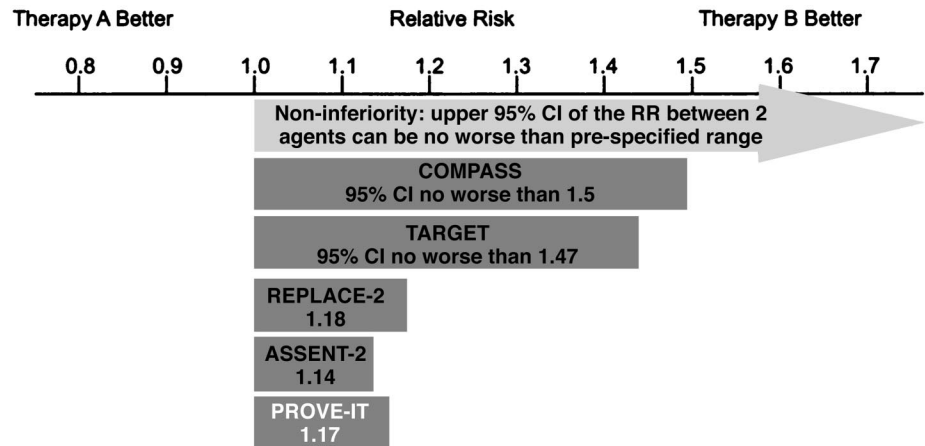
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FIGURE 5. The definition of clinical equivalence in a range of trials that evaluated treatment of patients with ACS (http://www.timi.org, http://www.clinicaltrialresults.org).

relative 2-year cardiovascular event risk of pravastatin relative to atorvastatin is equivalent. Therefore, compared with previous or ongoing statin trials in ACS, PROVE-IT TIMI 22 is unrivaled, because it has both the longest duration and the highest number of endpoints (Fig. 6).

ANTIBIOTICS FOR THE TREATMENT OF ACUTE CORONARY SYNDROME

Chlamydia pneumoniae is an obligate intracellular bacterium associated with community-acquired pneumonia, bronchitis, and sinusitis. Retrospective evidence from the

Helsinki Heart Study first suggested an association between *C. pneumoniae* seropositivity and CVD.[22] Since then, this link has been supported by the majority of 18 epidemiologic studies, involving a total of approximately 2700 patients.[23] The consistency in the findings of these studies, which have generally reported a 2-fold or greater odds ratio, supports the existence of a real association between *C. pneumoniae* and CHD (Fig. 7). In addition, a composite of 13 pathology studies have reported the presence of chlamydial DNA, antigens, or elementary bodies in 52% of atheromatous lesions in human
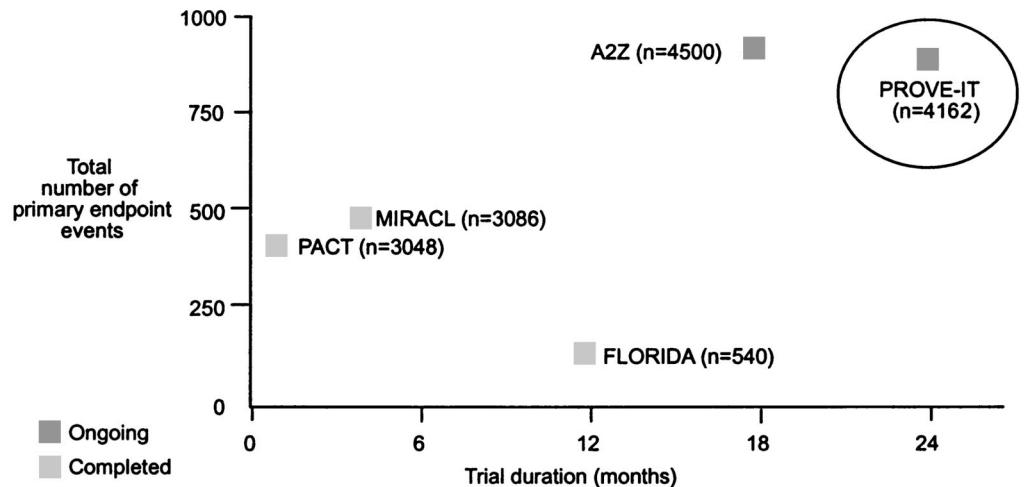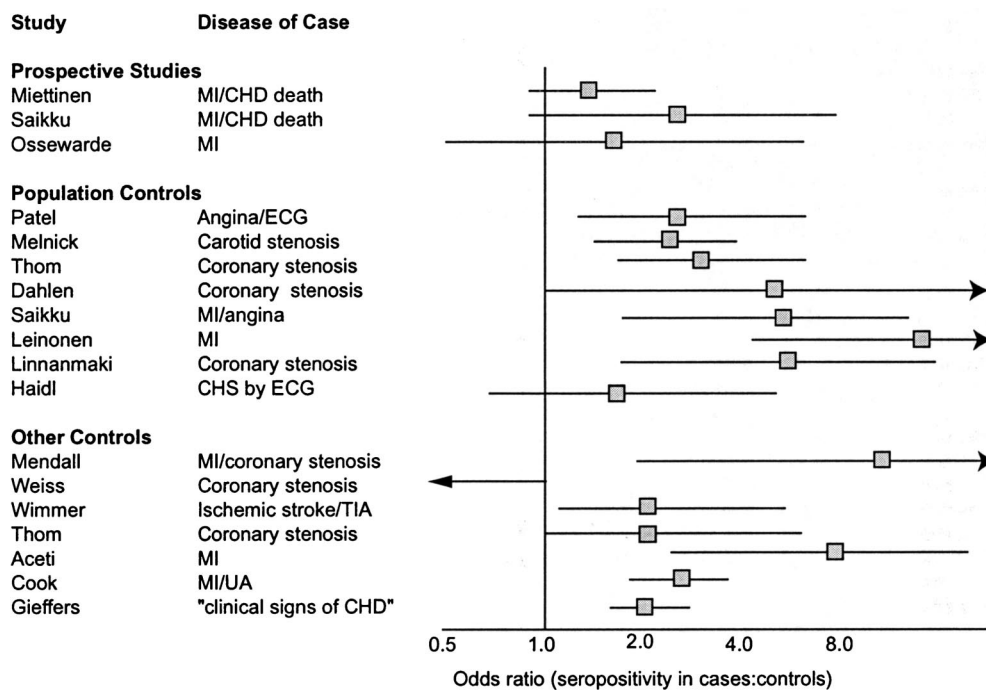

FIGURE 6. PROVE-IT TIMI 22 is superior to previous or ongoing statin trials in ACS, because it has the combination of the longest duration and the highest number of end points (http://www.timi.org, http://www.clinicaltrialresults.org).

FIGURE 7. Epidemiologic studies of *C. pneumoniae* seropositivity and vascular disease; the consistency of the findings supports the existence of a real association between *C. pneumoniae* and CHD (adapted from Danesh).[23] Reprinted with permission from Elsevier (*The Lancet*, 1997, Vol 350, pp. 430–6).

arterial tissue, compared with 5% of control samples.[23] A study by Roivainen et al[24] found that circulating immune complexes and antibodies against *C. pneumoniae* were associated with an increased risk for future coronary events in dyslipidemic men. This finding suggests that the inflammatory reaction to *C. pneumoniae* may be a factor in the pathophysiology of atherosclerosis. However, the risk factors for infection are not fully understood, and prospective studies, which are less likely to be affected by selection bias, have been small.[23] Therefore, further investigations are required to evaluate fully the role of *C. pneumoniae* in CVD.

A number of preliminary trials investigating the effect of short-term macrolide antibiotic treatment in patients with and without raised antibody titers against *C. pneumoniae* have failed to demonstrate consistently that treatment targeted against infection prevents cardiovascular events.[25–27] However, these studies have been insufficiently powered to evaluate this end point.

Also, short-term treatment may not effectively combat infection because of the biphasic life cycle of *Chlamydia*, which allows it to persist in host tissues. Therefore, randomized trials to investigate the effects of longer-term treatment are needed to evaluate fully the efficacy of antibiotics for the prevention of CVD.

The first placebo-controlled, early intervention trial that investigated moderate-term (3 months) antibiotic treatment of patients with CVD was the Weekly Intervention With Zithromax for Atherosclerosis and Its Related Disorders (WIZARD) trial[28] (Fig. 8). The benefits of therapy with azithromycin were not sustained over the observation period of 2 to 4 years, but treatment was shown to reduce all-cause mortality and recurrent MI significantly at 6 months follow-up.

Apart from PROVE-IT, there is only 1 other large trial currently ongoing that aims to investigate further the efficacy of long-term antibiotic therapy in patients with CVD. The Azithromycin and Coronary Events
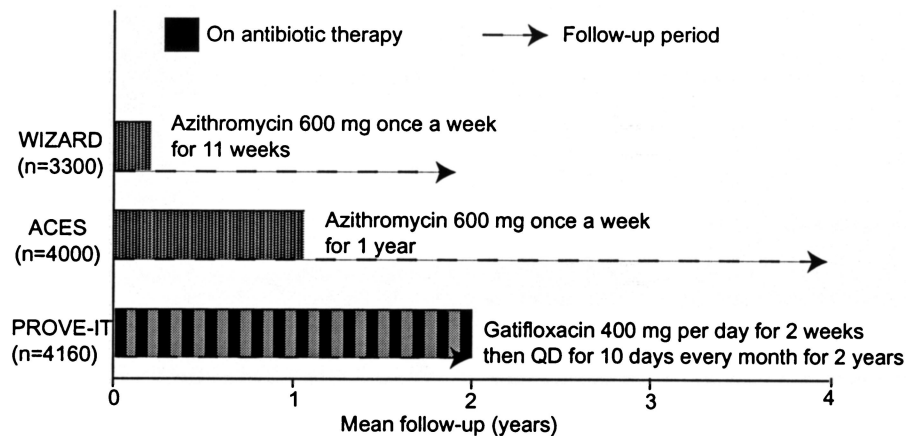
FIGURE 8. Duration of antibiotic therapy and duration of follow-up for the WIZARD, ACES, and PROVE-IT trials.

(ACES) study[29] (Fig. 8) is investigating the effect of macrolide treatment in patients with stable CVD receiving treatment with 600 mg azithromycin orally once a week for 1 year. Patients will be followed up for 4 years. The trial is scheduled for completion in October 2003. In contrast, the PROVE-IT trial,[19] which uses long-term quinolone antibiotic therapy (gatifloxacin) in the ACS population, is investigating the effectiveness of this therapy in reducing cardiac events and to study long-term antibiotic resistance and the adverse event profile in patients post ACS (Fig. 8). It will also determine the role of *C. pneumoniae* as a marker and investigate the role of statins in acute disease. Gatifloxacin was chosen because it has bactericidal activity against *C. pneumoniae* and a favorable safety profile.

CONCLUSION

Lowering cholesterol levels can reduce the risk of coronary events in high-risk patients and in those with chronic CHD. Current ACC/AHA guidelines recommend that lipid levels are managed through diet, or by treatment with lipid-lowering drugs such as statins, if LDL-C levels are >130 mg/dL. Although previous studies suggest that the percentage decrease in cholesterol levels is important in reducing risk at high baseline LDL-C levels, there is currently no evidence to demonstrate that

reducing cholesterol levels below 100 mg/dL in the majority of patients has additional benefit. However, guidelines continue to recommend a target LDL-C level of <100 mg/dL. Early treatment with statins may have some clinical benefit in patients with ACS; however, because preliminary trials were underpowered, further studies are required to investigate fully the effects of treatment. Two ongoing ACS trials, A-to-Z and PROVE-IT TIMI 22, will provide information on the efficacy and safety of early and long-term use of statins in ACS. PROVE-IT TIMI 22, which is superior to previous trials because of its longer duration and higher number of end points, is designed to determine whether reducing LDL-C to 100 mg/dL provides a benefit similar to that of a lower level of approximately 75 mg/dL.

Chlamydia pneumoniae has been implicated in the development of CHD; however, the results of preliminary trials investigating the effect of antichlamydial antibiotics have been inconsistent. The benefits of short-term therapy reported in WIZARD were not sustained over the long term, but this finding may have been a result of persistent infection in the host and the short duration of antibiotic therapy. The ACES and PROVE-IT studies aim to investigate the efficacy of long-term antibiotic therapy in patients with CVD and ACS, respectively.

Clearly, the results of the ongoing studies discussed in this article could have major implications for the treatment of patients with ACS and CHD. In the event of positive outcomes, guidelines should be amended to incorporate new therapies into critical pathways for the management of ACS.

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