disease cases were missed, because serum samples were obtained from all of the nearly 11,000 study participants before and after the summer tick transmission season. Of the 30 additional patients who were identified with IgG seroconversion, 9 reported myalgias or arthralgias, sometimes with fever, during the period of seroconversion, but none reported gastrointestinal or respiratory symptoms.

The unexpected finding was that about 16% of the Lyme disease cases presented with systemic symptoms during summer without erythema migrans (1). A challenge for physicians is early recognition and treatment of such cases before the more debilitating and harder to treat later manifestations of the infection develop.

Drs. Stricker and Phillips are concerned about antibiotic treatment for chronic, post–Lyme disease syndrome (sometimes called chronic Lyme disease), the reliability of serologic tests, and the possible role of coinfection. None of these issues was addressed in our study. In our study, 7 patients, including 2 with coinfection, had arthralgias or fatigue that persisted for weeks or months after 3- or 4-week courses of oral doxycycline or amoxicillin. However, none of the 42 patients developed later manifestations of Lyme disease or chronic, post–Lyme disease syndrome. Moreover, long-term persistence of the spirochete has not been substantiated in any large series of patients treated with currently recommended antibiotic regimens (4,5). In a double-blind placebo-controlled trial that sought to determine whether patients with post–Lyme disease syndrome would benefit from additional 3-month courses of therapy (6), none had positive cultures or positive results by polymerase chain reaction before treatment, and no differences were noted in outcome between the antibiotic and placebo groups.

After several weeks of infection, the sensitivity and specificity of the IgG response to *B. burgdorferi* is high, using the two-test approach of enzyme-linked immunosorbent assay (ELISA) and Western blot (7). The new IgG VlsE peptide ELISA has been shown to be promising as an improved serologic test (8). Although these tests do not distinguish between active or past infection, they are reliable in showing exposure to *B. burgdorferi* in patients with systemic infection.

Patients with early Lyme disease who are infected with other tickborne agents, including *Babesia microti* or *Anaplasma phagocytophila*, may have more severe disease (9) or fatigue for months after treatment (10). However, neither babesiosis nor human anaplasmosis has been shown to cause chronic infection. As with patients infected with *B. burgdorferi* alone, there is no evidence that longer courses of antibiotic therapy are beneficial in coinfected patients.

Allen C. Steere, MD
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts

Vijay K. Sikand, MD
Tufts University School of Medicine
Boston, Massachusetts

1. Steere AC, Dhar A, Hernandez J, et al. Systemic symptoms without erythema migrans as the presenting picture of early Lyme disease. *Am J Med.* 2003;114:58–62.
2. Steere AC, Bartenhagen NH, Craft JE, et al. The early clinical manifestations of Lyme disease. *Ann Intern Med.* 1983;99:76–82.
3. Steere AC, Sikand VK, Meurice F, et al. Vaccination against Lyme disease with recombinant outer-surface protein A in adjuvant. *N Engl J Med.* 1998;339:209–215.
4. Nocton JJ, Dressler F, Rutledge BJ, et al. Detection of *Borrelia burgdorferi* DNA by polymerase chain reaction in synovial fluid in Lyme arthritis. *N Engl J Med.* 1994;330:229–234.
5. Nocton JJ, Bloom BJ, Rutledge BJ, et al. Detection of *Borrelia burgdorferi* DNA by polymerase chain reaction in cerebrospinal fluid in patients with Lyme neuroborreliosis. *J Infect Dis.* 1996;174:623–627.
6. Klempner MS, Hu LT, Evans J, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *N Engl J Med.* 2001;345:85–92.
7. Dressler F, Whalen JA, Reinhardt BN, Steere AC. Western blotting in the serodiagnosis of Lyme disease. *J Infect Dis.* 1993;167:392–400.
8. Liang FT, Steere AC, Marques AR, Johnson BJ, Miller JN, Philipp MT. Sensitive and specific serodiagnosis of Lyme disease by enzyme-linked immunosorbent assay with a peptide based on an immunodominant conserved region of *Borrelia burgdorferi* VlsE. *J Clin Microbiol.* 1999;37:3990–3996.
9. Krause PJ, Telford SR, Spielman A, et al. Concurrent Lyme disease and babesiosis: evidence for increased severity and duration of illness. *JAMA.* 1996;275:1657–1660.
10. Krause PJ, McKay K, Thompson CA, et al. Disease-specific diagnosis of coinfecting tickborne zoonoses: babesiosis, human granulocytic ehrlichiosis, and Lyme disease. *Clin Infect Dis.* 2002;34:1184–1191.

STATINS AND LOW-DENSITY LIPOPROTEIN CHOLESTEROL LEVELS

To the Editor:

It is well known that the types of patients, clinical presentations, and treatment outcomes in everyday medical practice can vary greatly from those in controlled clinical studies. Thus, it is not surprising that Frolkis et al (1) found that statins in clinical practice were associated with low-density lipoprotein (LDL) cholesterol reductions that were 20% less than the reductions projected by package insert guidelines (1). Although I agree with the authors' conclusion that physicians should be aware of this disparity, I am concerned that this will lead physicians to prescribe stronger initial doses of statins. This would be a mistake for several reasons.

It should be noted that 38% of patients in this study had LDL cholesterol reductions that were greater than 100% of the expected reductions. This explains the substantial number of patients who cannot tolerate standard initial statin doses, but who achieve their target LDL cholesterol levels without adverse effects

with lower doses. This is not unusual because 5 mg of atorvastatin and 10 mg of simvastatin (doses that are 50% lower than recommended initially by package inserts) reduce LDL cholesterol levels by 28% to 30% on average, which is enough for many patients with mild-to-moderate LDL cholesterol elevations (2,3). Indeed, dose-related adverse effects, such as myalgia and gastrointestinal discomfort, are major reasons why 50% of patients quit statin treatment within months of starting (4,5), and the incidence of liver enzyme elevations and liver toxicities are known to increase directly with the statin dosage (6,7). Thus, statin doses must be gauged to individual response and tolerance.

Moreover, that the majority of patients in the Frolkis study did not achieve expected LDL cholesterol reductions reflects a failure of the system, not of the drugs. Many of the patients required upward adjustments in their statin dosages but did not receive them. In everyday practice, clinicians must recognize that the projected LDL cholesterol reductions in package inserts are based on statistical means from studies, and that even in these studies individual responses vary considerably (8,9). Similar and even greater variability is seen with everyday patients. The key is for physicians to anticipate this variability and to adjust statin doses according to each patient's response. This often means an upward adjustment of dosage. In the 38% of patients who, because of genetic variations in metabolic enzyme functioning or other factors, have greater than expected reductions in LDL cholesterol levels, downward adjustments in dosage may sometimes be necessary to reduce dose-related adverse effects and maintain adherence.

Jay S. Cohen, MD
Departments of Family and Preventive Medicine, and Psychiatry
University of California, San Diego
La Jolla, California

1. Frolkis JP, Pearce GL, Nambi V, Minor S, Sprecher DL. Statins do not meet expectations for lowering low-density lipoprotein cholesterol levels when used in clinical practice. *Am J Med.* 2002;113:625–629.
2. Bakker-Arkema RG, Davidson MH, Goldstein RJ, et al. Efficacy and safety of a new HMG-CoA reductase inhibitor, atorvastatin, in patients with hypertriglyceridemia. *JAMA.* 1996;275:128–133.
3. *Physicians' Desk Reference.* 57th ed. Montvale, New Jersey: Medical Economics Company; 2003.
4. Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *JAMA.* 2002;288:462–467.
5. Benner JS, Glynn RJ, Mogun H, Newmann PJ, Weinstein MC, Avorn J. Long-term persistence in use of statin therapy in elderly patients. *JAMA.* 2002;288:455–461.
6. Roberts WC. The rule of 5 and the rule of 7 in lipid-lowering by statin drugs. *Am J Cardiol.* 1997;80:106–107.
7. Pasternak RC, Smith SC, Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol.* 2002;40:567–572.
8. Tuomilehto J, Guimaraes AC, Kettner H, et al. Dose-response of simvastatin in primary hypercholesterolemia. *J Cardiovasc Pharmacol.* 1994;24:941–949.
9. Steinhagen-Thiessen E. Comparative efficacy and tolerability of 5 and 10 mg simvastatin and 10 mg pravastatin in moderate primary hypercholesterolemia. Simvastatin Pravastatin European Study Group. *Cardiology.* 1994;85:244–254.

The Reply:

We appreciate Dr. Cohen's comments, but take issue with some of his conclusions and assertions. First, we disagree that it is "well known that . . . treatment outcomes in everyday medical practice can vary greatly from those in controlled clinical studies." In fact, that was the central purpose of our study. We are concerned that clinicians will uncritically adopt the treatment guidelines provided in package inserts, which have been derived from the ideal conditions of a randomized study. The disparity in our own clinical outcomes relative to those projections motivated our analysis.

Second, we are confused by Dr. Cohen's statement that the fact that a substantial proportion of our patients (38%) achieved low-density lipoprotein (LDL) cholesterol reductions that were greater than predicted by package insert parameters "explains" those patients "who cannot tolerate standard initial statin doses." We reported no data on tolerance or intolerance, and our results cannot address whether these patients would have achieved their individual target LDL cholesterol levels at lower doses.

Third, the studies that Dr. Cohen cites in support of his statement that "dose-related adverse effects, such as myalgia and gastrointestinal discomfort, are major reasons why 50% of patients quit statin treatment within months of starting" used data derived from large administrative databases of elderly subjects with free or low-cost medication. There were no individual clinical data available, and no information, as stated by the authors, on adverse events.

However, we agree that "statin doses must be gauged to individual response and tolerance"—which is, of course, our practice. Our report was confined, for purposes of generalizability, to patients receiving standard doses of the most commonly used statins, but each drug and dose were selected on the basis of each patient's risk status and LDL cholesterol level. This is related to our next area of confusion: Dr. Cohen's assertion that many of our patients "required upward adjustments in their statin dosages, but did not receive them." Again, the data we reported were primarily for the first follow-up visit, with the goal of examining initial LDL cholesterol reduction. We did report on a fraction of patients at a second follow-up visit that maintained the same dose. Although this reveals that LDL-lowering outcomes for the prescribed dose are similar to that of the initial follow-up visit, the basis for subsequently increasing or decreasing doses (which we certainly hope we did appropriately), or whether patients eventually achieved their LDL cholesterol targets, cannot be evaluated from our report or the data provided. Dr. Cohen does, however, raise