

vincingly demonstrated that antibiotic treatment of post-Lyme disease symptoms is not in the best interests of patients.⁵ Our article summarizes the consensus among clinicians who practice evidence-based medicine, such as Drapkin, whom we thank for his comments.

Henry M. Feder, Jr., M.D.

University of Connecticut Health Center
Farmington, CT 06030
hfeder@nso2.uhc.edu

for the Ad Hoc International Lyme Disease Group

1. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical

assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006;43:1089-134. [Erratum, *Clin Infect Dis* 2007; 45:941.]

2. Klemperer 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.

3. Zoschke DC, Skemp AA, Defosse DL. Lymphoproliferative responses to *Borrelia burgdorferi* in Lyme disease. *Ann Intern Med* 1991;114:285-9.

4. Aguero-Rosenfeld ME, Wang G, Schwartz I, Wormser GP. Diagnosis of Lyme borreliosis. *Clin Microbiol Rev* 2005;18:484-509.

5. Halperin J. Prolonged Lyme disease treatment: enough is enough. *Neurology* (in press).

Primary Percutaneous Coronary Intervention

TO THE EDITOR: Several studies have evaluated the role of combination medical therapies administered upstream of primary percutaneous intervention (PCI). As noted in the review of the time to treatment in PCI, by Nallamothu et al. (Oct. 18 issue),¹ these trials have failed to demonstrate a survival benefit from either full-dose fibrinolysis plus PCI or reduced-dose fibrinolysis in combination with glycoprotein IIb/IIIa antagonists plus PCI in patients with ST-elevation myocardial infarction. However, there is evidence of improved outcomes with early administration of glycoprotein IIb/IIIa antagonists as compared with administration in the catheterization laboratory.² A Thrombolysis in Myocardial Infarction (TIMI) flow grade of 2 or 3 was significantly more frequent in the group in which glycoprotein IIb/IIIa antagonists were administered early than in the late-administration group, and there was a trend toward a reduction in mortality.² A TIMI flow grade of 2 or 3 before PCI is associated with a decrease in adverse events and improved 1-year outcomes.^{2,3} Other studies have revealed decreased 30-day mortality and reinfarction rates with the use of the glycoprotein IIb/IIIa inhibitor abciximab.⁴ Thus, these data support early administration of glycoprotein IIb/IIIa inhibitors to improve outcomes in patients undergoing primary PCI.

Roger Kapoor, M.D., M.B.A.

John R. Kapoor, M.D., Ph.D.

Stanford University
Stanford, CA 94305

1. Nallamothu BK, Bradley EH, Krumholz HM. Time to treatment in primary percutaneous coronary intervention. *N Engl J Med* 2007;357:1631-8.

2. Montalescot G, Borentain M, Payot L, Collet JP, Thomas D. Early vs late administration of glycoprotein IIb/IIIa inhibitors in

primary percutaneous coronary intervention of acute ST-segment elevation myocardial infarction: a meta-analysis. *JAMA* 2004;292:362-6.

3. Mehta RH, Harjai KJ, Cox D, et al. Clinical and angiographic correlates and outcomes of suboptimal coronary flow in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention. *J Am Coll Cardiol* 2003; 42:1739-46.

4. De Luca G, Suryapranata H, Stone GW, et al. Abciximab as adjunctive therapy to reperfusion in acute ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. *JAMA* 2005;293:1759-65.

TO THE EDITOR: In their review of primary PCI, Nallamothu et al. reaffirm the importance of the time to treatment and underscore the point that the superiority of PCI over thrombolysis is limited in time, "reaching equipoise between 60 and 120 minutes." Therefore, facilitated PCI by means of pretreatment with tissue plasminogen activator (t-PA) was seen as a logical option. But as the authors emphasize, this combination actually increased mortality. The incompatibility of t-PA with PCI may be related to t-PA's procoagulant effect and the significant rate of coronary reocclusion.¹ In contrast, prourokinase follows another fibrinolytic paradigm² and has a very different mode of action.³ Indeed, prourokinase caused no measurable thrombin generation and little reocclusion (1.4%),⁴ indicating that the above complications should not be seen as an inevitable accompaniment of all thrombolytic agents.

Therefore, it is surprising that in their discussion of future challenges, the authors do not include a thrombolytic agent that is compatible with PCI. Surely, the optimal reperfusion strategy would be immediate thrombolysis followed by PCI, thereby also addressing the critical issue

of microvascular perfusion. This possibility may not be beyond reach.

Victor Gurewich, M.D.

Beth Israel Deaconess Medical Center
Boston, MA 02215
vgurewic@bidmc.harvard.edu

1. Fitzgerald DJ, Fitzgerald GA. Role of thrombin and thromboxane A2 in reocclusion following coronary thrombolysis with tissue-type plasminogen activator. *Proc Natl Acad Sci U S A* 1989;86:7585-9.
2. Pannell R, Black J, Gurewich V. Complementary modes of action of tissue-type plasminogen activator and pro-urokinase by which their synergistic effect on clot lysis may be explained. *J Clin Invest* 1988;81:853-9.
3. Liu JN, Gurewich V. A comparative study of the promotion of tissue plasminogen activator and pro-urokinase-induced plasminogen activation by fragments D and E-2 of fibrin. *J Clin Invest* 1991;88:2012-7.
4. Weaver DA, Hartmann JR, Anderson JL, Reddy PS, Sobolski JC, Sasahara AA. New recombinant glycosylated prourokinase for the treatment of patients with acute myocardial infarction. *J Am Coll Cardiol* 1994;24:1242-8.

TO THE EDITOR: Nallamothu et al. note that fibrinolytic therapy remains a practical option for many patients with ST-elevation myocardial infarction when there is no immediate access to a catheterization laboratory. Despite data showing the superiority of primary PCI over thrombolysis, aspects of prehospital fibrinolysis should be mentioned. Because the benefit of thrombolysis is maximal during the first 2 hours after the onset of symptoms, and most patients with ST-elevation myocardial infarction present to hospitals without on-site PCI facilities, transport delays may limit the benefits of PCI ("time is myocardium"). Data from the Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) trial showed that in the group of patients treated with prehospital thrombolysis who were randomized less than 2 hours after the onset of symptoms, as compared with the primary-PCI group, there was a trend toward lower 30-day mortality, and cardiogenic shock was less frequent (occurring in 1.3% of patients, vs. 5.3% in the primary-PCI group; $P=0.032$).¹ Prehospital thrombolysis is safe, may shorten the time until reperfusion therapy by about 60 minutes,² and is associated with a fourfold increase in aborted myocardial infarction, as compared with in-hospital treatment.³ Patients with ST-segment myocardial infarction who were treated with facilitated PCI after prehospital fibrinolysis had improved tissue perfusion and smaller infarcts, with a trend toward a better clinical outcome.⁴

Sebastian Szabo, M.D.

Thomas Oikonomopoulos, M.D.

Hans Martin Hoffmeister, M.D., Ph.D.

Städtisches Klinikum Solingen
42653 Solingen, Germany
krisztinaszb@aol.com

1. Steg PG, Bonnefoy E, Chabaud S, et al. Impact of time to treatment on mortality after prehospital fibrinolysis or primary angioplasty: data from the CAPTIM randomized clinical trial. *Circulation* 2003;108:2851-6.
2. Chittari MS, Ahmad I, Chambers B, Knight F, Scriven A, Pitcher D. Retrospective observational case-control study comparing prehospital thrombolytic therapy for ST-elevation myocardial infarction with in-hospital thrombolytic therapy for patients from same area. *Emerg Med J* 2005;22:582-5.
3. Lamfers EJ, Hooghoudt TE, Hertzberger DP, Schut A, Stolwijk PW, Verheugt FW. Abortion of acute ST segment elevation myocardial infarction after reperfusion: incidence, patients' characteristics, and prognosis. *Heart* 2003;89:496-501.
4. Thiele H, Engelmann L, Elsner K, et al. Comparison of pre-hospital combination-fibrinolysis plus conventional care with pre-hospital combination-fibrinolysis plus facilitated percutaneous coronary intervention in acute myocardial infarction. *Eur Heart J* 2005;26:1956-63.

THE AUTHORS REPLY: Kapoor and Kapoor highlight the potential role of glycoprotein IIb/IIIa inhibitors in a "facilitated" approach, when used "upstream" of PCI. We agree that this strategy has been associated with improvements in TIMI flow grades but note the inconclusive data in regard to a clinical benefit.¹ Indeed, the Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) trial investigators recently reported that upstream administration of abciximab did not provide an additional clinical benefit when compared with in-laboratory administration.²

Gurewich points out the existing limitations of fibrinolytic-therapy drugs that have been combined with PCI in contemporary trials. His observation that some drugs in this class (e.g., prourokinase) may be better suited for use with PCI because of diminished procoagulant effects is provocative, particularly given the higher rates of reinfarction noted with tenecteplase plus PCI in the Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction (ASSENT) 4 trial.³ However, recent results from the FINESSE and ASSENT-4 trials may make it challenging to pursue this area further.

We agree with Szabo and colleagues that prehospital fibrinolytic therapy is safe and effective when delivered within organized emergency-medical-service (EMS) systems that are capable of making a rapid diagnosis and treating eligible patients

outside the hospital. However, several barriers — unrelated to the clinical benefit — continue to prevent the practical application of this strategy in the United States. These include limited funding and infrastructure within EMS systems in general, as well as concerns about legal liability and reimbursement.⁴ In addition, EMS systems with enough volume to justify dedicating resources to overcome these barriers are likely to be in urban areas where there is the potential for rapid access to primary PCI.⁵

Brahmajee K. Nallamothu, M.D., M.P.H.
Ann Arbor Veterans Affairs Medical Center
Ann Arbor, MI 48109

Elizabeth H. Bradley, Ph.D.

Harlan M. Krumholz, M.D., S.M.

Yale University
New Haven, CT 06520
harlan.krumholz@yale.edu

1. Montalescot G, Borentain M, Payot L, Collet JP, Thomas D. Early vs late administration of glycoprotein IIb/IIIa inhibitors in primary percutaneous coronary intervention of acute ST-segment elevation myocardial infarction: a meta-analysis. *JAMA* 2004;292:362-6.
2. Ellis SG. The Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) trial. Presented at the European Society of Cardiology Annual Congress, Vienna, September 1-5, 2007. abstract.
3. Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) Investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet* 2006;367:569-78.
4. Welsh RC, Ornato J, Armstrong PW. Prehospital management of acute ST-elevation myocardial infarction: a time for reappraisal in North America. *Am Heart J* 2003;145:1-8.
5. Nallamothu BK, Bates ER, Wang Y, Bradley EH, Krumholz HM. Driving times and distances to hospitals with percutaneous coronary intervention in the United States: implications for prehospital triage of patients with ST-elevation myocardial infarction. *Circulation* 2006;113:1189-95.

The Normal Hematocrit Study — Follow-up

TO THE EDITOR: We previously reported in the *Journal* the results of a randomized, prospective study comparing outcomes of normal versus low hematocrit values in 1233 patients with congestive heart failure or ischemic heart disease who were undergoing hemodialysis and receiving treatment with epoetin alfa; 618 patients were randomly assigned to the normal-hematocrit group, and 615 to the low-hematocrit group.¹ The primary end point was the length of time to death or a first nonfatal myocardial infarction. The editors of the *Journal* requested that we now provide supplemental data, including end-point events that occurred after the data set was analyzed by the independent data and safety monitoring committee, as reported in the previous article. This invitation was prompted by a presentation by the Food and Drug Administration on September 11, 2007, in which higher numbers of patients and events than were reported in the article were discussed.

The data and safety monitoring committee recommended termination of the study after 29 months (median duration of treatment, 14 months). The committee was convened on June 3, 1996, and reviewed data for the 1233 patients available as of March 31, 1996; these data were the basis for the article. There were 183 deaths and 19 first nonfatal myocardial infarctions among the patients in the normal-hematocrit group (target hematocrit, 42%) versus 150 deaths and 14 nonfatal

myocardial infarctions among the patients in the low-hematocrit group (target hematocrit, 30%) (Table 1). Although the difference in event-free survival between the groups did not reach the prespecified statistical stopping boundary, the results were clearly heading in a direction that threatened the safety of the patients in the normal-hematocrit group. In addition, the incidence of vascular-access thrombosis was significantly higher in the normal-hematocrit group (39%) than in the low-hematocrit group (29%). We concluded that a target hematocrit value of 42% in this patient population cannot be recommended.

The treatment intervention was halted on June 24, 1996, by which time a total of 1265 patients had been randomly assigned to a study group: 634 to the normal-hematocrit group and 631 to the low-hematocrit group. In the 3 months between March 31, 1996, and June 24, 1996, there were 25 additional deaths and 1 additional nonfatal myocardial infarction in the normal-hematocrit group, as compared with 23 additional deaths and 2 additional nonfatal myocardial infarctions in the low-hematocrit group. When these events are included, the risk ratio for death or myocardial infarction again fails to cross the prespecified statistical boundary for significance in this fourth analysis (Table 1).

Patients were followed for 1 year after cessation of the study intervention. Hematocrit values