CORRESPONDENCE

Acute Coronary Syndromes

TO THE EDITOR: The Timing of Intervention in Acute Coronary Syndrome (TIMACS) trial reported on by Mehta et al. (May 21 issue)[1] showed that a routine early-intervention strategy was not superior to a delayed-intervention strategy for the prevention of the composite primary outcome of death, myocardial infarction, or stroke. There was no evidence of an early hazard associated with early intervention. The authors consider a potentially important finding that in a prespecified subgroup of high-risk patients, early intervention appeared to provide a significant benefit, mainly due to an increased accumulation of events in the delayed-intervention group from 30 days to 6 months after randomization. This is a striking observation, since the percentage of patients who underwent angiography and subsequent revascularization per protocol was virtually similar at 30 days in both groups. The authors do not address this finding and do not provide us with an explanation of this difference in the late accumulation of events. Therefore, we contend that this could be a spurious finding due to a subgroup analysis, albeit prespecified, in which the overall primary outcome of the TIMACS trial was negative.

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1. Mehta SR, Granger CB, Boden WE, et al. Early versus delayed invasive intervention in acute coronary syndromes. N Engl J Med 2009;360:2165-75.

TO THE EDITOR: Mehta et al. do not show any significant difference between early and delayed intervention in patients with acute coronary syndrome. In their study, 9.9% of patients in the early-intervention group received intervention more than 24 hours after randomization and 20.5% of patients in the delayed-intervention group received intervention less than 36 hours after randomization. The authors used an intention-to-treat principle for their analysis. One of the limitations of intention-to-treat analysis is that interpretation becomes difficult if large proportions of patients cross over to the opposite treatment groups.[1] Although there was no actual crossover in this study, it would be interesting to note whether any difference between the two groups would be present if a treatment-received analysis was used to estimate the difference between the two groups. It would also be interesting to note the risk profile and average time of intervention among patients who did not receive intervention as per protocol to see whether this was the reason the study did not show any significant result.

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1. Heritier SR, Gebski VJ, Keech AC. Inclusion of patients in clinical trial analysis: the intention-to-treat principle. Med J Aust 2003;179:438-40.

TO THE EDITOR: In their editorial, Hillis and Lange[1] report that low-risk patients should receive unfractionated heparin for 2 to 5 days. However, unfractionated heparin has pharmacologic limitations that may affect efficacy and safety. Frequent monitoring of activated partial-thromboplastin time is necessary to achieve optimal anticoagulation levels. Enoxaparin and fondaparinux are options for anticoagulation with either superior efficacy[2] or better safety[3] and with a different pharmacodynamic profile than unfractionated heparin. As compared with unfractionated heparin, enoxaparin has greater bioavailability, providing a more stable and predictable anticoagulation, and fondaparinux has a more favorable tolerability, particularly regarding the risk of major bleeding. Both allow fixed dosing without the need for monitoring, and they facilitate a longer duration of treatment. Furthermore, both regimens are class I recommendations in the American College of Cardiology–American Heart Association (ACC–AHA) guidelines for patients in whom a conservative strategy is selected.[4]

In addition, although Hillis and Lange recommend the discontinuation of anticoagulation treatment in high-risk patients after successful percutaneous coronary intervention (PCI), they suggest the use of glycoprotein IIb/IIIa inhibition for 12 to 24 hours after PCI. What is the current rationale for this recommendation?

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1. Hillis LD, Lange RA. Optimal management of acute coronary syndromes. N Engl J Med 2009;360:2237-40.
2. Petersen JL, Mahaffey KW, Hasselblad V, et al. Efficacy and bleeding complications among patients randomized to enoxaparin or unfractionated heparin for antithrombin therapy in non-ST-segment elevation acute coronary syndromes: a systematic overview. JAMA 2004;292:89-96.
3. The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med 2006;354:1464-76.
4. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2007;116(7):e148-e304. [Erratum, Circulation 2008;117(9):e180.]

TO THE EDITOR: Hillis and Lange summarize the evidence-based treatment strategies for patients with acute coronary syndrome. However, they do not mention the role of angiotensin-converting–enzyme (ACE) inhibitors, which have been recommended by the ACC–AHA joint guidelines for the treatment of patients with unstable angina and non–ST-elevation myocardial infarction[1] and by the European Society of Cardiology guidelines for the diagnosis and treatment of non–ST-segment elevation acute coronary syndrome.[2] Both sets of guidelines strongly recommend (level of evidence A, class I) that ACE inhibitors should be initiated during the course of hospitalization in patients with diabetes, hypertension, or a left ventricular ejection fraction of less than 40%; these recommendations are not as strong for all other patients (level of evidence A, class IIa).

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1. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/ non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2007;116(7):e148-e304. [Erratum, Circulation 2008;117(9):e180.]
2. Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J 2007;28:1598-660.

THE AUTHORS REPLY: We agree with Damman et al. that subgroup analyses should be interpreted with caution. The prespecified analysis in the TIMACS trial that showed a greater benefit of early intervention in patients at high risk is supported by a statistically significant test for interaction (P=0.01), which is a relatively stringent test. Damman et al. incorrectly suggest that the benefit of early intervention in the high-risk patients was mainly due to a late accumulation of events. As early as 1 week after randomization, there was an emerging benefit of the early invasive strategy in patients at high risk (5.8% in the early-intervention group vs. 8.0% in the delayed-intervention group; hazard ratio, 0.73; 95% confidence interval [CI], 0.45 to 1.18), with no apparent difference in outcomes in the group at low-to-intermediate risk (3.5% in the early-intervention group vs. 3.3% in the delayed-intervention group; hazard ratio, 1.08; 95% CI, 0.68 to 1.73). Moreover, a similar finding of a greater benefit in high-risk patients was also observed in the secondary outcome of death, myocardial infarction, or refractory ischemia.

In response to Rathod: TIMACS was a pragmatic effectiveness trial designed to evaluate two management strategies, and an intention-to-treat approach is the correct method to analyze the results of such trials.[1,2] Performance of clinically indicated early intervention for valid, protocol-defined reasons in patients randomly assigned to the delayed strategy was an integral component of that strategy, and it would not be appropriate to exclude such patients. Moreover, a "treatment-received" analysis, as Rathod suggests, is flawed because it introduces bias that invalidates the essential value of randomization by excluding persons on the basis of a differing clinical course after randomization.[1,2] Finally, the protocol-defined criteria for crossover (i.e., new myocardial infarction, hemodynamic instability with a high risk of death, and refractory ischemia) included components of the primary or secondary outcome and thus are already reflected in the main results of the trial. For these reasons, we believe that a treatment-received analysis would not be helpful in interpreting the results of the trial.

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1. Altman DG. Randomisation. BMJ 1991;302:1481-2.
2. Schulz KF, Grimes DA. Sample size slippages in randomised trials: exclusions and the lost and wayward. Lancet 2002;359: 781-5.

THE EDITORIALISTS REPLY: We agree with Cequier et al. that unfractionated heparin has limitations. However, in patients with acute coronary syndrome who are considered to be at low risk for a cardiac event, unfractionated heparin and enoxaparin have similar efficacy in preventing death and myocardial infarction,[1] and the former is much less expensive than the latter. Although the systematic review by Petersen et al.[2] suggests that the use of enoxaparin is associated with a modest reduction in nonfatal myocardial infarction and no difference in mortality as compared with unfractionated heparin, the trial populations in the review were not identical with respect to their baseline characteristics, in that, by design, the later trials included higher-risk patients. Fondaparinux has not received approval by the Food and Drug Administration for the treatment of patients with acute coronary syndromes, and its safety and efficacy in patients undergoing PCI are not well established.[3] After successful PCI, discontinuation of anticoagulant therapy is recommended, since its continued use offers no proven benefit in further reducing cardiac events and is associated with increased bleeding, particularly at the site of catheterization. In contrast, therapy with a glycoprotein IIb/IIIa inhibitor is ineffective in reducing cardiac events if it is discontinued immediately after PCI[4]; as a result, continued infusion for 12 to 24 hours is recommended.

As Shojai notes, the evidence supporting the use of ACE inhibitors in patients with acute coronary syndromes and concomitant pulmonary congestion or left ventricular systolic dysfunction (ejection fraction, ≤0.40) in the absence of hypotension or known contraindications to these agents is strong. In addition, the benefits of ACE inhibitors in improving ischemic outcomes have been the subject of study in patients with stable coronary artery disease. However, since ACE inhibitors have not been tested directly in patients with acute coronary syndromes, we chose not to recommend their routine use.

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1. Morrow DA, Antman EM, Tanasijevic M, et al. Cardiac troponin I for stratification of early outcomes and the efficacy of enoxaparin in unstable angina: a TIMI-11B substudy. J Am Coll Cardiol 2000;36:1812-7.
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3. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2007;116(7):e148-e304. [Erratum, Circulation 2008;117(9):e180.]
4. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high risk coronary angioplasty. N Engl J Med 1994;330:956-61.