The goals of the initial management of ST-segment elevation myocardial infarction include swift restoration of flow within the occluded coronary artery, prevention of early reinfarction, and avoidance of complications of reperfusion therapy. The selection of the reperfusion strategy, either the preferred percutaneous coronary intervention (PCI) or fibrinolysis, is usually driven by institutional access to primary PCI. Thus, the decision that clinicians most commonly grapple with at the time of the patient’s presentation is the selection of adjunctive anticoagulant and antiplatelet therapy. In this issue of the Journal, Stone and colleagues report on a large, randomized trial that tested an anticoagulant agent in primary PCI.

When performed rapidly by an experienced team, primary PCI restores flow in the culprit artery in more than 95% of patients and, as compared with fibrinolysis, reduces the risk of reinfarction by more than 50%, but with a higher risk of extracranial bleeding. Thus, the goals of antithrombotic therapy for primary PCI differ from those for fibrinolysis, which fails to restore coronary flow or culminates in early reocclusion in approximately 20% of patients. Antithrombotic therapy in primary PCI is focused on minimizing the thrombotic complications of mechanical intervention. Only modest absolute reductions in early spontaneous reinfarction are possible because the absolute risk is 3% or less. Although antithrombotic therapy facilitates improved flow before angiography, the effect appears to be small if the pretreatment is brief.

Current guidelines for ancillary antithrombotic therapy recommend that patients who are undergoing primary PCI receive aspirin and a loading dose of clopidogrel, generally 600 mg, before or at the time of PCI. On the basis of expert consensus, unfractionated heparin is recommended in patients undergoing primary PCI (class I [treatment should be administered], according to the American College of Cardiology/American Heart Association guidelines). The glycoprotein IIb/IIIa-receptor inhibitor abciximab, which is administered intravenously, has been evaluated in seven randomized, placebo-controlled trials involving a total of approximately 4000 patients undergoing primary PCI, with mixed results. In aggregate, these trials suggest that abciximab treatment is associated with a reduction in reinfarction and in mortality at 30 days (odds ratio for reinfarction, 0.56; 95% confidence interval [CI], 0.33 to 0.94; and odds ratio for mortality, 0.68; 95% CI, 0.47 to 0.99). Few data are available for the glycoprotein IIb/IIIa inhibitors eptifibatide and tirofiban in primary PCI. Taking into consideration observations from PCI in unstable angina and non–ST-elevation myocardial infarction, abciximab is recommended as reasonable (class IIa [it is reasonable to administer treatment]) and eptifibatide or tirofiban is considered to be possibly useful (class IIb [treatment may be considered]) to support primary PCI. In clinical practice in the United States, administration of unfractionated heparin and a glycoprotein IIb/IIIa antagonist is the most common ancillary regimen for primary PCI.

A large, randomized trial of the pentasaccharide factor Xa inhibitor fondaparinux in patients with ST-segment elevation myocardial infarction, including 3789 patients who were undergoing primary PCI, revealed a possible hazard related to catheter thrombosis. Therefore, fondaparinux is not recommended as the sole anticoagulant for primary PCI. Evaluation of low-molecular-weight heparins in patients undergoing primary PCI has not been sufficient to allow recommendation of the use of these agents for this indication.

The direct thrombin inhibitor bivalirudin is a short-acting anticoagulant that, when administered for a short interval during PCI, has been found to reduce bleeding as compared with heparin plus a glycoprotein IIb/IIIa inhibitor. The trial of bivalirudin in primary PCI reported by Stone et al. addressed an important and untested hypothesis. Strengths of the trial include a large sample, a well-defined population that is relevant to clinical practice, and a comparison of bivalirudin with a treatment that is representative of contemporary practice. The primary result, that bivalirudin alone reduced a composite end point of major bleeding and major cardiovascular events by 24% at 30 days owing to a 40% reduction in the primary bleeding end point, is compelling with respect to the potential for bivalirudin as antithrombotic therapy in this setting.
There are several aspects of the trial design and results that merit careful consideration, since they affect the strength of the findings and the potential application in clinical practice and reveal trade-offs between the efficacy of antithrombotic therapy and the risk of bleeding. First, the limitation of an open-label design requires emphasis, since this study design weakens the conclusiveness of any analysis of end points, such as bleeding and ischemic events, for which there may be bias in reporting by the local investigator on the basis of treatment. However, the consistency of the reduction in bleeding across multiple definitions and trials bolsters this finding as a qualitative conclusion. Second, the effect of the administration of another antithrombin agent (unfractionated heparin) in approximately 65% of the patients shortly before PCI warrants consideration. Bivalirudin was tested as monotherapy in only 615 patients. In this group, major cardiovascular events occurred in 7.2% of the patients, as compared with 5.2% of the patients who received heparin plus a glycoprotein IIb/IIIa inhibitor (relative risk, 1.39; 95% CI, 0.85 to 2.28), with interaction testing suggesting heterogeneity (P<0.1). Even with cautious interpretation of this interaction testing, the administration of unfractionated heparin before enrollment to the majority of patients in the study mitigates the strength of the results with respect to clinical practice in which bivalirudin might be used as monotherapy. Third, the duration of treatment before PCI was not reported and is relevant to the effect of glycoprotein IIb/IIIa antagonists in ST-segment elevation myocardial infarction. It is not clear whether the findings of this study apply when a period of treatment before PCI is necessary, such as during the common practice of transferring patients to a different hospital for a difference in survival. The finding of a possible decrease in deaths with bivalirudin alone is interesting and supports the continued pursuit of an optimal balance in the trade-off between bleeding and thrombotic complications, as well as a clearer understanding of whether our clinical responses to bleeding may be detrimental.

Stone and colleagues have substantially increased the experience with bivalirudin in a new setting. Although their study is a single open-label trial with limitations and observations that call for additional investigation, their findings indicate that bivalirudin warrants consideration among the alternatives for ancillary antithrombotic therapy in patients undergoing primary PCI.
Preliminary Results of Gene Therapy for Retinal Degeneration
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In this issue of the Journal, two groups of investigators — Bainbridge et al.¹ and Maguire et al.² — describe the first results of separate clinical trials investigating the short-term safety and preliminary efficacy of gene therapy for Leber’s congenital amaurosis. Both groups present short-term data (12 months and 5 months, respectively) on three patients with Leber’s congenital amaurosis in each study; the patients were enrolled in trials of recombinant adeno-associated viral delivery of the human retinal pigment epithelium-specific 65-kDa protein gene (RPE65), which was administered as a subretinal injection during vitrectomy.

Originally described by Leber in 1869, Leber’s congenital amaurosis has the earliest onset of all inherited retinal dystrophies causing congenital blindness; it is also the most severe form.³⁻⁵ Infants with Leber’s congenital amaurosis have profound visual impairment or blindness at birth. However, the visual impairment is usually recognized only later, when parents note the infant’s inability to track objects or light. Severe visual impairment persists throughout childhood, resulting in an inability to read or ambulate independently, and finally in total blindness by the third or fourth decade of life. Other findings include nystagmus (roaming eye movements), abnormal pupillary responses, and flat or nearly undetectable signals on electroretinography (ERG). The appearance of the retina is normal early on but progresses to a pigmentary retinopathy over time. There is no treatment for Leber’s congenital amaurosis.

Most cases of Leber’s congenital amaurosis are