

EDITORIALS



Improving Reperfusion in Patients with Myocardial Infarction

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A little over 50 years ago, my father had a heart attack. He was driven to the hospital by friends after having “indigestion” for 2 days. He spent 2 weeks as an inpatient on an unmonitored rehabilitation ward and was treated principally with warfarin and digitalis. He was lucky and survived, but in that era, more than 20% of patients with an acute myocardial infarction died. Fast-forward to today, when public education about early recognition of symptoms, emergency transport, monitored coronary care units, and early reperfusion by means of primary percutaneous coronary intervention (PCI) have markedly reduced mortality from acute myocardial infarction to less than 5%.

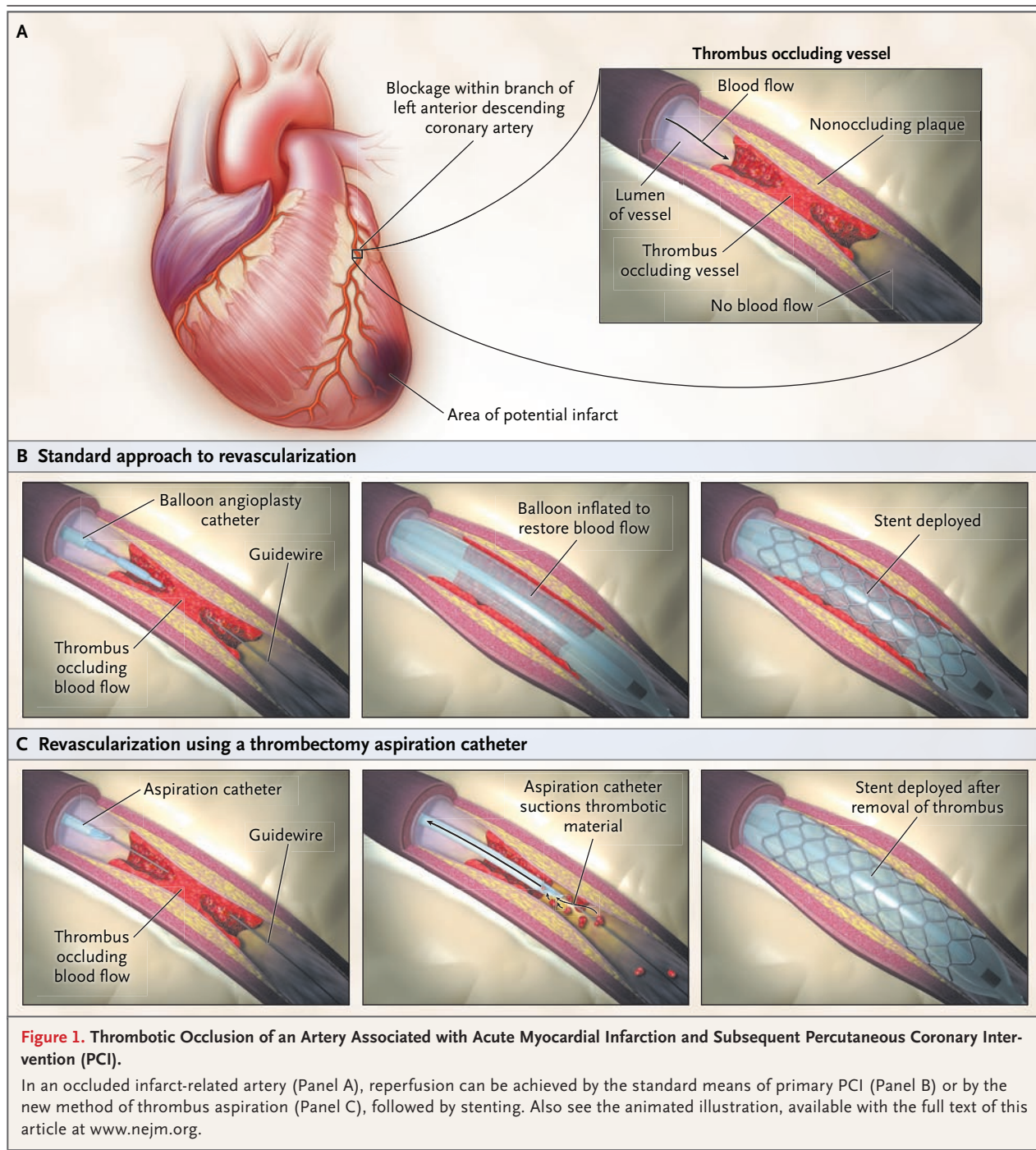
Major contributors to this remarkable improvement in outcome are based on pathological studies^{1,2} showing thrombotic occlusion of an artery associated with acute myocardial infarction (Fig. 1A), in parallel with diagnostic and therapeutic advances from cardiac catheterization laboratories. By performing coronary angiography during evolving myocardial infarction, DeWood et al.³ observed total coronary-artery occlusion in patients with acute myocardial infarction, with frequent, early, spontaneous reperfusion. Coincidentally, angiographic features of the thrombus were characterized, helping to identify the role of clots in acute coronary syndromes.^{4,5}

Most of the remarkable improvements have occurred over the 30 years since the introduction of coronary angioplasty.⁶ Rentrop et al.⁷ demonstrated that reperfusion with the use of mechanical or thrombolytic revascularization could avert evolving infarction. Most recently, the recognized importance of early and complete reperfusion by means of PCI has led to a strategy of using

PCI as the preferred therapy for acute myocardial infarction, with a goal of reestablishing flow within 90 minutes after presentation (i.e., a door-to-balloon time of <90 minutes), provided that this can be achieved without major delays in transport.⁸ Thus, the improvement in outcomes for patients with acute myocardial infarction is principally due to earlier, more effective mechanical resolution of thrombotic occlusion of a coronary artery to maximally and quickly restore effective myocardial perfusion.

Technically, the current method of primary PCI is to cross the occlusion with a balloon catheter, which, after a brief period of inflation, reestablishes flow. Subsequently, one or more stents are placed to provide stable revascularization (Fig. 1B). The initial inflation expedites reperfusion and provides visualization of the occluded segment for accurate stent sizing. However, as a consequence of manipulations of the balloon and stent, distal clot embolization occurs, at times visibly reducing distal reperfusion through the occlusion of macrovessels and microvessels. Reduced distal flow is indicated by slow coronary flow (Thrombolysis in Myocardial Infarction flow grade 2), incomplete resolution of the injury seen on the electrocardiogram, abnormal myocardial blush, or any combination of these. Abnormal blush (represented by a low blush grade) reflects slow or absent washout of injected contrast medium within the reperfused arterial system. Each of these indicators has been associated with a less favorable long-term prognosis.⁹

In this issue of the *Journal*, Svilaas et al.¹⁰ describe passing a guidewire through the occluded infarct-related artery, but instead of then opening the artery with a balloon, a small catheter is



advanced into the occluded segment. Direct aspiration of the occluding thrombus is then performed (Fig. 1C; also see the animated illustration available with the full text of this article at www.nejm.org). After aspiration, stenting was performed, without balloon dilation beforehand in the majority of patients, unless the stent

could not be delivered. Conceptually, this technique limits the embolization of distal clots, thus improving distal myocardial perfusion.

To test this hypothesis, Svilaas et al. randomly assigned 1071 patients to undergo initial aspiration with stenting or conventional primary PCI with the use of a balloon and stent. They

used the ST-segment characteristics on electrocardiography as well as the myocardial blush grade to assess the efficacy of clot extraction before stenting on distal perfusion. There was a clear correlation between the resolution of electrocardiographic changes and improvement in myocardial blush scores: complete resolution of ST-segment elevation, the absence of persistent ST-segment deviation, and myocardial blush grade of 0 or 1 were all significantly more frequent in the patients who underwent aspiration than in those who underwent conventional PCI. In addition, histological assessment of the aspirate from nearly three quarters of the patients who underwent aspiration revealed platelet thrombi, consistent with current understanding of the role of such thrombi in the pathophysiological characteristics of acute myocardial infarction.

Clinical outcome at 30 days was significantly related to the extent of myocardial reperfusion. Mortality was higher among patients with persistent abnormalities in myocardial blush than among patients with improved myocardial distal-bed perfusion. The frequencies of other adverse events were similar to that of death.

Reasons for the reported benefit of reduced embolization in patients who underwent aspiration seem related to enhanced distal-bed perfusion. Neumann et al.¹¹ showed that increases in ejection fraction correlated with improved peak Doppler flow velocity in patients receiving a platelet glycoprotein IIb/IIIa inhibitor that minimizes distal thrombotic occlusion of small vessels. The significance may be that maintaining arterial flow limits apoptosis and potentially adverse remodeling,¹² thus providing a mechanism for the favorable outcomes associated with improved microvascular reperfusion.

Although the study by Svilaas et al. reports encouraging results for coronary-thrombus extraction, previous extraction trials of different designs have had various results. Caveats regarding the trial by Svilaas et al. include the fact that it was a single-center study performed by highly experienced interventionalists who had a low failure rate with regard to delivering the catheter. It is unknown whether more general use will demonstrate similar safety and favorable outcomes. Furthermore, there is concern that such catheters can dissect or damage the arterial segment, necessitating longer stents, which could increase the risk of late restenosis. In addition, some operators believe that direct stenting with-

out multiple balloon inflations reduces the risk of distal emboli. In the trial by Svilaas et al., the majority of patients in the thrombus-aspiration group had stents placed directly, whereas the majority in the conventional-PCI group had balloon angioplasty followed by stenting, which might have increased the relative incidence of embolization in the conventional-PCI group.

In addition, current guidelines of the American College of Cardiology, the American Heart Association, and the Society for Cardiovascular Angiography and Interventions emphasize the door-to-balloon time as the primary temporal marker of quality. If strategies involving thrombus extraction evolve to become a primary reperfusion strategy, quality indicators must encompass reperfusion by multiple methods, specifically balloon inflation or catheter placement through the occlusion as interchangeable markers of reperfusion.

Potential adverse issues aside, on the basis of the data of Svilaas et al., thrombus extraction is conceptually sound and appears to reduce the risk among patients undergoing primary PCI. With the current low risk of death associated with early reperfusion in patients with acute myocardial infarction, refinements can be expected to make only small, albeit clinically significant, improvements in outcome. Thrombus aspiration appears to be such a favorable improvement.

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Pharmacogenomic Biomarkers for Prediction of Severe Adverse Drug Reactions

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The accumulating knowledge of human genomic variation is being used for the development of personalized medicine, with the aims of decreasing the number of adverse drug reactions and increasing the efficacy of drug treatment. Considerable pharmacogenomic research has focused on understanding the molecular mechanisms behind adverse drug reactions and finding biomarkers that identify people at risk.

Serious adverse drug reactions have been shown to cause or contribute to 6 to 7% of all hospitalizations, a 2-day increase in the average length of hospitalization, and 100,000 deaths annually in the United States — and may, according to some estimates, cost about as much as the drug treatment itself.¹ During the period 1998–2005, the numbers of reported adverse drug reactions and deaths related to such reactions have increased, both by a factor of about 2.6.² Adverse drug reactions are also a major problem during the development of a drug. In total, approximately 4% of all new medical agents are withdrawn from the market owing to adverse drug reactions.¹ During the period 1995–2005, at least 34 drugs were withdrawn, mainly as a result of hepatotoxic or cardiotoxic effects — notably, cerivastatin, nefazodone, rofecoxib (Vioxx), terfenadine, and troglitazone.³

The search for pharmacogenomic biomarkers that could be used to identify patients at increased risk for drug-related toxic effects has often focused on variation within genes encoding drug-metabolizing enzymes. Altered enzymatic activity can lead to elevated levels of the substrate drug, or alternatively, increased amounts of a reactive metabolite, either of which could have toxic effects.

For immune-mediated toxic effects, much focus has been placed on the major-histocompatibility-complex class I genes. A review of pharmacogenomic biomarkers reveals only a limited number of potentially useful examples (Table 1), with the highest specificity seen among the HLA allelic variants. Thus, many more biomarkers remain to be identified. Unfortunately, much of the existing research in this area has been hampered by limitations in study design, such as poorly defined case and control groups, the use of retrospective and nonblind study protocols, and nonoptimal selection of gene variants. In addition, polygenic influences on many adverse drug reactions, instances of treatment with multiple drugs, and variation in the severity of clinical

Table 1. Pharmacogenomic Biomarkers as Predictors of Adverse Drug Reactions.

Gene or Allele	Relevant Drug	Specificity of Biomarker	Percent of Patients with an Adverse Reaction to Drug*
<i>TPMT</i> (mutant)	6-Mercaptopurines	Very good	1–10
<i>UGT1A1</i> *28	Irinotecan	Good	30–40
<i>CYP2C9</i> and <i>VKORC1</i>	Warfarin†	Good	5–40
<i>CYP2D6</i> (mutant)	Tricyclic anti-depressants	Relatively good	5–7
<i>HLA-B</i> *5701	Abacavir	Very good	5–8
<i>HLA-B</i> *1502	Carbamazepine	Very good	10
<i>HLA-DRB1</i> *07 and <i>DQA1</i> *02	Ximelagatran	Good	5–7

* Percentages are of affected whites except that for *HLA-B**1502, which is the percentage of affected Asians.

† Carriage of the *CYP2C9* and *VKORC1* alleles affects warfarin dosing.