No-Reflow: Is the “Great Challenge” Getting Smaller?

– New Evidence From Pleiotropic Drugs –

Giancarla Scalone, MD; Giampaolo Niccoli, MD, PhD

The no-reflow phenomenon still represents a “great challenge” in the management of patients with ST segment elevation myocardial infarction (STEMI). It negates the benefits of coronary reopening, thus playing a crucial role in the prognosis of these patients. Indeed, no-reflow is associated with an adverse outcome related to adverse remodelling after STEMI¹ and, more importantly, to higher mortality.² The no-reflow phenomenon is considered a dynamic process characterized by multiple pathogenetic components: (1) distal atherothrombotic embolization; (2) ischemic injury; (3) reperfusion

injury; and (4) susceptibility of coronary microcirculation to injury.³ Each of these mechanisms is variably involved in the pathogenesis of no-reflow in the individual patient. Therefore, assessment of these multiple components might guide the development of personalized forms of prevention and treatment. Over the past years, many targets of therapy have been identified. In this context, prevention of distal embolization of thrombotic/plaque material has been the focus of trials employing thrombus aspiration.^{4,5} Furthermore, several studies have assessed the beneficial effect on microcirculation of drugs given

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Institute of Cardiology, Catholic University of the Sacred Heart, Rome, Italy

Mailing address: Giampaolo Niccoli, MD, PhD, Department of Cardiovascular Sciences, Catholic University of the Sacred Heart, L.go A. Gemelli, 8, Rome 00168, Italy. E-mail: gniccoli73hotmail.it

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by either the systemic or intracoronary route, targeting different cellular types as platelets⁶ or neutrophils,⁷ or acting as vasodilators.^{8,9} Ultimately, the strategies are designed to reduce microvascular obstruction and to activate intracellular cardioprotective mechanisms.¹⁰ Notably, the modulation of “no-reflow” by risk factors has suggested that some subgroups (diabetic patients) should be managed more aggressively.¹¹ Finally, over the recent few years, identification of the mechanisms responsible for “no-reflow” reversibility has become a new field of research.¹² However, although considerable effort is being given to applying these therapeutic strategies in real-world practice, there is weak evidence of an objective clinical improvement in this setting. In this regard, our sense is that they are usually given indiscriminately, without careful detection of the different mechanisms for each patient.

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In this issue of the Journal, Lee et al¹³ assess whether cilostazol, in addition to conventional dual antiplatelet therapy with clopidogrel and aspirin, is able to improve the clinical outcome of patients with acute myocardial infarction (AMI) and no-reflow. This represents an interesting topic, because cilostazol might influence the no-reflow phenomenon, blocking multiple pathogenetic components: ischemia-reperfusion-related injury, distal embolization and microcirculation damage (Figure). Indeed, because of its pleiotropic effects, cilostazol might be applicable in a wider range of cases, without detection of specific mechanisms in each case. Furthermore, cilostazol seems safe and available in the clinical practice, with a similar side-effect profile of aspirin and clopidogrel.

The most important issue reported by the authors is the specific effect of cilostazol in decreasing cardiac mortality at 1, 6 and 12 months of follow-up in the no-reflow patients. The Kaplan-Meier curves for the probability of survival are separated within the first month, and then gradually become linear. The authors suggest that this behavior might be partially explained by the suggested effect of cilostazol on the recovery of the sequelae of the no-reflow phenomenon beyond antirestenotic and antithrombotic effects. However, as also specified by the authors, the study does not provide information about rehospitalization for heart failure during the follow-up period. Indeed, no-reflow phenomenon is mostly characterized by unfavorable ventricular remodeling and heart failure; this effect is usually prominent at least 6 months after AMI.

Taken together, these promising results underline that blocking multiple mechanisms of the no-reflow phenomenon might provide an objective improvement in the clinical outcome of patients with AMI. In this context, the solution to the “great challenge” of no-reflow might come from the use of safe and pleiotropic drugs that are able to ensure a more complete blunting of

the pathogenetic mechanisms.

Disclosures

Nothing to declare.

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