



Endogenous fibrinolysis in STEMI: important before and after primary PCI

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This editorial refers to ‘Impaired endogenous fibrinolysis in ST-segment elevation myocardial infarction patients undergoing primary percutaneous coronary intervention is a predictor of recurrent cardiovascular events: the RISK PPCI study’[†], by M. Farag *et al.*, on page 295.

One of the most convincing clinical papers suggesting a causal role of an obstructing intraluminal thrombus in patients with an ST-segment elevation acute myocardial infarction (STEMI) is almost 40 years old.¹ In that study, Marcus DeWood and colleagues reported on the coronary angiograms of STEMI patients made early after onset of symptoms. In the 126 patients evaluated within 4 h, the percentage total occlusion was 87%. In 57 patients studied 12–24 h after symptom onset, this proportion decreased significantly to 65%. Comments and editorials following the publication of this important study that started a new era have focused on the presence of thrombus obstructing the infarct coronary artery. At that time, this was a key finding confirming similar observations in small numbers of patients. Still, no explanation was provided for the 13% of patients without complete occlusion evaluated within 4 h after onset of symptoms or for the 35% open vessels in those studied in the 12–24 h time window. The possibility of a role for coronary spasm was cautiously put forward by DeWood *et al.* We now know that endogenous fibrinolysis is the key mechanism responsible for early patency before any treatment and for the increasing proportion of open vessels later on in STEMI patients. In a study performed ~8 years later, the European Cooperative Study Group reported 83% patency (TIMI flow grades 2 and 3) of the infarct artery 10–22 days after i.v. recombinant tissue-type plasminogen activator, a rate only slightly higher than the 77% found in control patients who did not receive fibrinolytic therapy.² Both groups received the same antithrombotic treatment including heparin and aspirin. In a subpopulation of 99 patients from this trial, our group evaluated the culprit lesion.³ No differences in stenosis length, minimal luminal diameter, and geometric area obstruction were found. Taken together, these data strongly suggest that

endogenous fibrinolysis can act as a powerful but often slow ‘recanalization’ mechanism in a significant proportion of STEMI patients. More recently, it has become clear that impaired endogenous fibrinolysis or ‘hypofibrinolysis’ could also play a role in clinical outcomes after an acute coronary syndrome (ACS) and in the risk of developing a new myocardial infarction.^{4,5} In addition, a recent prospective substudy from the PLATO (Study of PLATelet Inhibition and Patient Outcomes) trial showed that fibrin clots that are resistant to lysis predict outcome after ACS, independent of the type of P₂Y₁₂ inhibitor given.⁶ Although the relationship between outcome and hypofibrinolysis was independent of known biomarkers in this PLATO substudy, delayed lysis was nevertheless clearly associated with these markers, which might to some extent explain their prognostic power.

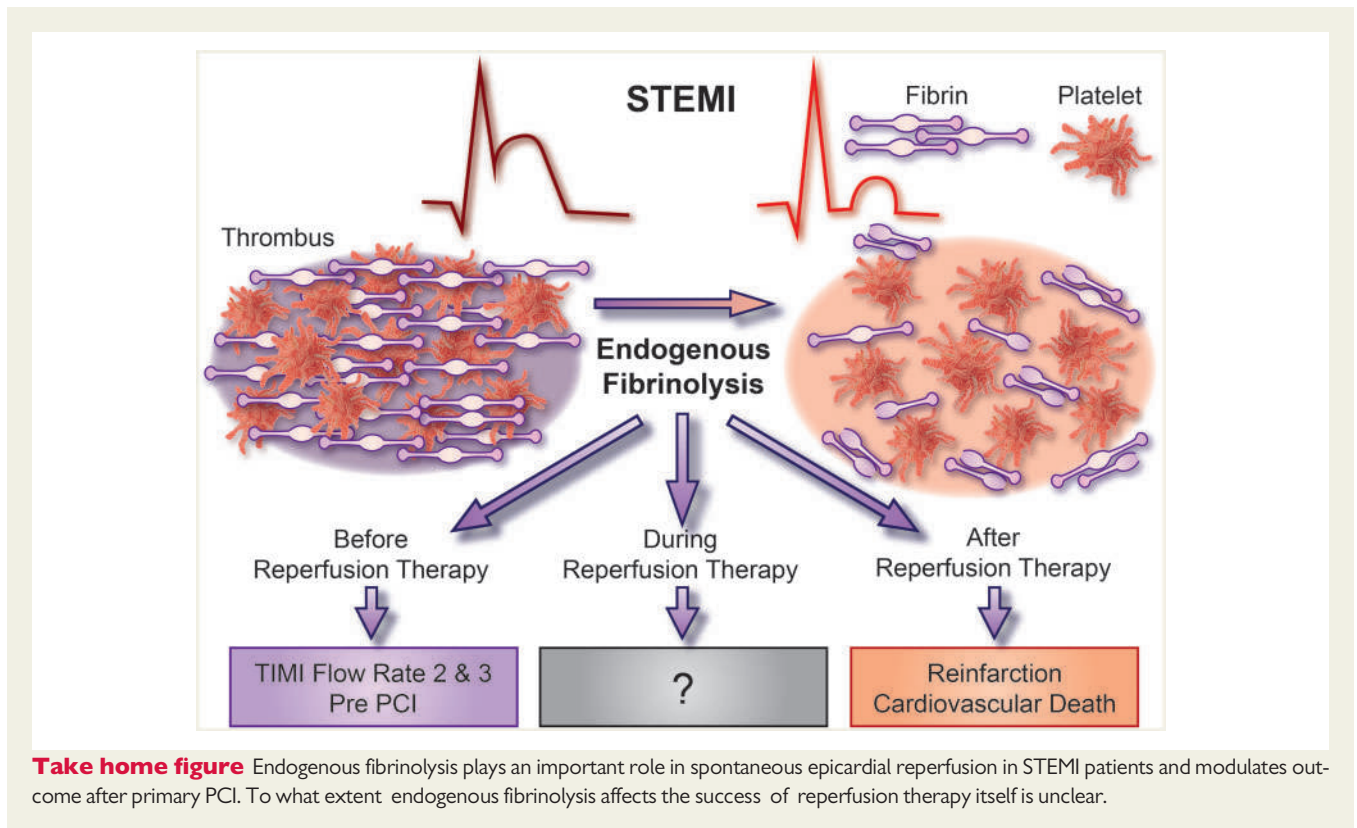
In this issue of the *European Heart Journal*, Gorog and colleagues from the RISK PPCI (RISK model to predict adverse outcomes after Primary Percutaneous Coronary Intervention) study now report on the effect of the level of endogenous fibrinolysis on outcome in STEMI patients ($n = 496$) undergoing PPCI.⁷ They found that endogenous fibrinolysis, measured using a point-of-care Global Thrombosis Test (GTT) at the time of presentation, was impaired in 14% of patients ($n = 70$) and was independently predictive of new major cardiovascular events during follow-up. Although numbers were relatively small, patients with impaired fibrinolysis were six times more likely to experience a new myocardial infarction. Cardiovascular mortality at 30 days was 1.6% (7/426) vs. 25.7% (18/70) in patients with vs. without impaired fibrinolysis. Patients with poorer fibrinolysis tended to have a higher baseline risk profile which might in part have contributed to this large difference. Interestingly, STEMI patients with an open vessel at the time of PPCI had faster clot lysis times as assessed by the GTT. In a parallel electron microscopy study, impaired fibrinolysis appeared to be accompanied by an increasing density of the fibrin network in the thrombi of these patients. Being a small and single-centre clinical study with only 36 patients experiencing a major cardiovascular event during follow-up, these results of course need to be interpreted cautiously. Still, the

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results lie perfectly in line with both historical and recent observations.

Clot formation and resolution is the result of complex interplay between prothrombotic, antithrombotic, and haemodynamic factors.⁸ In the current study, the level of endogenous fibrinolysis as measured by the GTT did not appear to vary much between measurements at baseline vs. at discharge and day 30, suggesting that the test is not significantly affected by antiplatelet or acute anticoagulant therapies. This finding, as well as being a relatively simple to use point-of-care test, greatly facilitates the test's usability as a marker in ACS patients in daily practice and probably in larger clinical trials as well. Although, as in the PLATO substudy, patients with high C-reactive protein levels were more likely to have impaired endogenous fibrinolysis, the GTT's reproducibility over time in the first month after the event would indicate that the extent of the infarct-related acute inflammation does not significantly alter the interpretation of the test.⁹ This needs to be confirmed in larger cohorts. Whether impaired fibrinolysis during the first month persists in these high-risk patients beyond this early post-ACS phase also remains unclear.

Whether markers of impaired endogenous fibrinolysis can also serve as a marker to guide the use of therapies is an intriguing question. Previous experience with platelet function monitoring tests underscores the necessity of exploring the applicability of hypofibrinolysis markers in the real world. While an impaired platelet response to antiplatelet agents seems to predict outcome, platelet function test-guided interventions have repeatedly been unable to demonstrate improved outcome in coronary artery disease patients, and are hence not recommended by guidelines.¹⁰⁻¹³ Nonetheless,

the present study opens up new possibilities to explore the ideal target populations for at least some of the increasingly prolific options for secondary prevention following an ACS. Low-dose rivaroxaban plus clopidogrel and aspirin for instance has been shown to improve outcome in the first year after an ACS in the ATLAS ACS 2-TIMI 51 Trial (Anti-Xa Therapy to Lower cardiovascular events in Addition to Standard therapy in subjects with Acute Coronary Syndromes—Thrombolysis In Myocardial Infarction 51) study,¹⁴ but this strategy has not been widely adopted in favour of the use of the more potent P₂Y₁₂ inhibitors prasugrel and ticagrelor. A lower dose of antiplatelet therapy (ticagrelor 60 mg b.i.d.) in PEGASUS-TIMI 54 (PrEvention with TicaGrelor of SecondAry Thrombotic Events in High-RiSk Patients with Prior AcUte Coronary Syndrome—Thrombolysis In Myocardial Infarction Study Group) and low-intensity anticoagulation (rivaroxaban 2.5 mg b.i.d.) in COMPASS (Cardiovascular Outcomes for People Using Anticoagulation StrategieS) have both been shown to improve outcome in stable or stabilized patients, but it remains unclear which particular patient would benefit the most from one of these two strategies.^{15,16} Assuming that impaired endogenous fibrinolysis persists beyond 30 days after ACS, a test like the GTT could potentially help to identify patients who could benefit most from long-term anticoagulant therapy.¹⁷

The authors of the present study are to be congratulated for their significant contribution helping to explain observations made 40 years ago by DeWood *et al.* We now know that endogenous fibrinolysis plays a crucial role in infarct-related patency in STEMI patients before reperfusion therapy as well as in outcome after primary PCI, although it remains less clear if and how these pathophysiological

processes interfere with the reperfusion process itself (*Take home figure*). The present study as well as the recent analysis from the PLATO trial do suggest it might be worthwhile to search for novel therapies that specifically target fibrin clot formation and degradation to improve the outcome of carefully phenotyped ACS patients.¹⁸

Conflict of interest: none declared.

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Corrigendum

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The author wishes to inform readers that the take home figure for this manuscript incorrectly listed the minimum stent area (MSA) in cm² rather than mm². The figure has been corrected online.