Spontaneous reperfusion in STEMI: Its mechanisms and possible modulation

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ABSTRACT

Patients with transient ST-segment elevation myocardial infarction or spontaneous reperfusion, which occurs in approximately 20% of patients with ST-segment elevation myocardial infarction (STEMI), have smaller infarcts and more favorable clinical outcomes than patients without spontaneous reperfusion. Understanding the mechanisms underlying spontaneous reperfusion is therefore important since this may identify possible novel therapeutic targets to improve outcomes in patients with STEMI.

In this review, we discuss some of the possible determinants of spontaneous reperfusion including pro-thrombotic profile, endogenous fibrinolytic status, lipoprotein(a) (Lp[a]), inflammatory markers, and neutrophil extracellular traps (NETs). Effective (rapid) endogenous fibrinolysis, as assessed in whole blood *in vitro*, using a point-of-care technique assessment of global thrombotic status, has been strongly linked to spontaneous reperfusion. Lp(a), which has a high degree of homology to plasminogen, may impair fibrinolysis through competitive inhibition of tissue plasminogen activator-mediated plasminogen activation as well as tissue plasminogen activator-mediated clot lysis and contribute to pathogenic clot properties by decreasing fibrin clot permeation. NETs appear to negatively modulate clot lysis by increasing thrombin fiber diameter and inhibiting plasmin-driven lysis of plasma clots.

There are limited data that oral anticoagulation may modulate endogenous fibrinolysis but antiplatelet agents currently appear to have no impact. Phase III trials involving subcutaneous $P2Y_{12}$ or glycoprotein IIb/IIIa inhibitors, oral factor XIa inhibitors, interleukin-6 inhibitors, and apolipoprotein(a) antisense oligonucleotides in patients with cardiovascular disease are ongoing. Future studies will be needed to determine the impact of these novel antithrombotic, anti-inflammatory, and lipid-lowering therapies on endogenous fibrinolysis and spontaneous reperfusion.

Key words: acute coronary syndrome, endogenous fibrinolysis, global thrombosis test, lipoprotein(a), spontaneous reperfusion

INTRODUCTION

Despite optimal medical and interventional treatments, morbidity and mortality from acute coronary syndrome (ACS) remain significant.

ACS represents myocardial ischemia or infarction, most commonly caused by a decrease in myocardial blood supply due to temporary or persistent coronary artery occlusion. Conventionally, ACS is divided into three clinical categories according to the presence or absence of ST-segment elevation on the initial electrocardiogram, with or without dynamic changes, and the presence or absence of a rise in high-sensitivity cardiac troponin concentration [1]. In ST-segment elevation myocardial infarction (STEMI), cardiac symptoms such as chest pain are associated with ST-segment elevation on the electrocardiogram, coupled with a rise in high-sensitivity cardiac troponin. This occurs due to complete cessation of blood flow in a main epicardial coronary artery or one of its branches, most often due to disruption of an atherosclerotic plaque leading to thrombotic vessel occlusion. Generally, the vessel stays

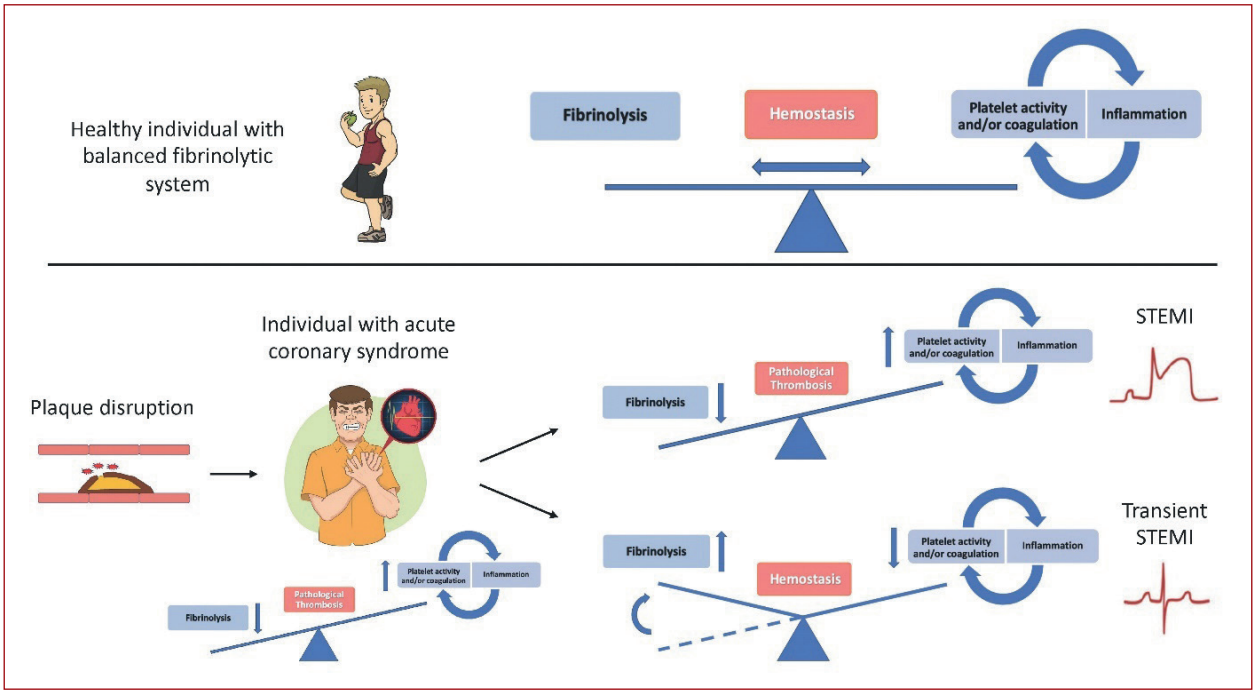

Figure 1. Mechanistic alterations underlying ST-segment elevation myocardial infarction (STEMI) and transient STEMI

occluded, and lasting myocardial necrosis occurs unless the vessel patency is restored, whether by mechanical or pharmacological means.

Transient STEMI (t-STEMI) or spontaneous reperfusion, which occurs in approximately 20% of patients with STEMI, is generally defined as spontaneous ST-segment improvement on electrocardiogram and/or the achievement of initial thrombolysis in myocardial infarction grade 2-3 flow in the infarct-related artery (IRA) before primary percutaneous coronary intervention (PPCI) and typically coincides with resolution or improvement of symptoms (Figure 1) [2, 3]. For patients presenting with persistent ST-segment elevation, immediate reperfusion of the occluded coronary artery with primary percutaneous coronary intervention (PCI) is recommended [1]. However, the optimal management of patients with t-STEMI is less well defined.

In the TRANSIENT trial, 141 patients with t-STEMI were randomized to immediate PCI (n = 70) versus delayed PCI (n = 71) and followed up for the primary outcome of median infarct size as assessed by cardiac magnetic resonance imaging [4]. The study demonstrated that an immediate invasive strategy did not reduce infarct size compared with a delayed invasive strategy (1.3%; interquartile range [0.0%–3.5%] vs. 1.5% [0.0%–4.1%]; $P = 0.48$). In data drawn from the Acute Coronary Syndrome Israeli Survey, 405 (17%) patients with ST-segment elevation-acute coronary syndrome in Killip class 1 were not treated with PPCI because of evidence of spontaneous reperfusion (≥70% reduction in ST-segment elevation on consecutive electrocardiograms and ≥70% resolution of pain) [5]. The intervention in patients with evidence of spontaneous reperfusion was performed at a median of 26 hours after admission. There were no significant differences in in-hospital mortality (1% vs. 2%; $P = 0.4$), 30-day major cardiac events (4% vs. 4%; $P = 0.9$), and mortality at 30 days (1% vs. 2%) and 1 year (4% vs. 4%; $P = 0.72$) between the two cohorts, which demonstrates that deferring immediate intervention seems to be safe in patients with clinical indices of spontaneous reperfusion. On the other hand, a more recent article by Koc et al. [6] showed that 25% of t-STEMI patients still had an occluded IRA on initial angiography. All patients enrolled had a field diagnosis of STEMI and were transported directly for PPCI. The STEMI was considered transient if no residual ST-segment elevations were present on admission to the catheterization laboratory.

There is a substantial amount of evidence that patients with spontaneous reperfusion have smaller myocardial infarcts and better clinical outcomes than those patients without spontaneous reperfusion [7]. Understanding the mechanisms underlying spontaneous reperfusion is, therefore, important since this may identify possible novel therapeutic targets to improve outcomes in patients with STEMI.

In this review, we discuss potential mechanisms of t-STEMI, prognostic tools, biomarkers, and potential future therapeutic targets to enhance spontaneous reperfusion.

TRANSIENT STEMI AND CLINICAL OUTCOMES

Among patients with a diagnosis of acute myocardial infarction with elevated cardiac biomarkers, a number of studies have demonstrated that patients presenting with

Table 1. Studies reporting transient STEMI due to spontaneous reperfusion

Study/year	Patients (n)	Criteria for spontaneous reperfusion	SR (%)	Clinical outcomes between patients with and without spontaneous reperfusion
Kanji et al. (2023) [17]	801	Angiographic (TIMI 2–3)	18.5	Spontaneous reperfusion was associated with a longer occlusion time (435 seconds vs 366 seconds; P <0.001) and a shorter lysis time (1257 seconds vs. 1616 seconds; P < 0.001), lower troponin, and better LVEF Significantly lower MACE rates were observed in patients with spontaneous reperfusion compared with those without spontaneous reperfusion, at 30 days, 1 year, and a mean follow-up of 629 days (4.1% vs. 10.6%; P = 0.01), with 65% lower MACE rate in patients with spontaneous reperfusion at maximal follow-up (HR, 0.35; 95% CI, 0.14–0.97; P = 0.02), driven by a lower incidence of cardiovascular death (HR, 0.38; 95% CI, 0.15–0.95; P = 0.04)
Alici et al. (2022) [18]	1641	Angiographic (TIMI 3)	14.6	LVEF value was significantly higher in the SR group compared to the non-spontaneous reperfusion group (41.01 ± 7.51 vs. 36.01 ± 6.63; P = 0.02) In-hospital mortality rate was significantly lower in the spontaneous reperfusion group compared to the non-SR group (0% vs. 6.7%; P <0.001)
Demirkiran et al. (2022) [20]	407	Complete resolution of ST-segment elevations as well as symptoms on arrival to the hospital, with or without initial treatment of sublingual nitrate, heparin, $P2Y_{12}$ inhibitor, and/or aspirin	42	t-STEMI patients demonstrated the highest LVEF and the most preserved global LV strain (longitudinal, circumferential, and radial) across the three groups (overall P ≤0.001) The CMR-defined infarction was less frequently observed in t-STEMI than in STEMI patients (77 [65%] vs. 124 [98%]; P <0.001] A smaller infarct size was seen in t-STEMI compared to STEMI patients (1.4 g [0.0–3.9] vs. 13.5 g [5.3–26.8]; P <0.001)
Koc et al. 2022 [6]	299	Complete resolution of ST-segment elevations up to the isoelectric line prior to PPCI initiation	6.7	Patients with spontaneous reperfusion had a higher LVEF (59.9 ± 6.3% vs. 51.6 ± 10.2%; P <0.001) Survival did not differ between the t-STEMI and STEMI groups over a median follow-up period of 5.6 years
Janssens et al. (2021) [19]	251	Complete resolution of ST-segment elevations and symptoms before revascularization therapy was initiated	56.2	CMR revealed microvascular obstruction less frequently (4.2% vs. 34.6%; P <0.001) and smaller infarct size (1.4%; interquartile range [IQR], 0.0–3.7% vs. 8.8%; IQR, 3.9–17.1% of the LV, P <0.001) with a better preserved LVEF (57.8 ± 6.7% vs. 52.5 ± 7.6%; P <0.001) Fibrinolysis was more efficient in t-STEMI, as demonstrated by a reduced clot lysis time (89 ± 20% vs. 99 ± 25%; P = 0.03)

Abbreviations: CI, confidence interval; CMR, cardiac magnetic resonance; HR, hazard ratio; IQR, interquartile range; LV, left ventricle; LVEF, left ventricular ejection fraction; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; t-STEMI, transient STEMI

signs of spontaneous reperfusion have better in-hospital [8–11] and long-term clinical outcomes [9, 12–16] compared to those without spontaneous reperfusion.

Since an earlier review of this topic [7], several articles concerning spontaneous reperfusion in the setting of STEMI have been published reinforcing the previous evidence base that patients with spontaneous reperfusion have more favorable outcomes compared to those without spontaneous reperfusion [6, 17–20]. A summary of these studies reporting clinical outcomes with t-STEMI is shown in Table 1. One of the major determinants of infarct size is duration of ischemia, therefore intuitively, spontaneous reperfusion would be expected to lead to improved clinical outcomes compared to those seen in patients with persistent ST-segment elevation due to shorter ischemia time.

RISK SCORES THAT PREDICT SPONTANEOUS REPERFUSION

The PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy (PRECISE-DAPT) is a simple five-item risk score, which provides a standardized tool for predicting the risk of bleeding in patients on dual antiplatelet therapy after PCI [21]. The PRECISE-DAPT score's clinical components include age, creatinine clearance, hemoglobin, white-blood-cell count, and previous spontaneous bleeding. A score equal to or above 25 indicates a high bleeding risk and, therefore, advocates a short period of dual antiplatelet therapy. Beyond estimating bleeding risks, a recent study suggests that the PRECISE-DAPT score in patients with STEMI is independently linked to the likelihood of IRA patency before PPCI (PRECISE-DAPT score 10 [3–46] vs. 14 [3–50]; P <0.01). A study by Saylik et al. [22] showed that among 204 STEMI patients undergoing PPCI, a higher PRECISE-DAPT score was associated with higher intracoronary thrombus burden.

The CHA_2DS_2-VASc score is a simple scoring system developed for estimating cardioembolic thrombosis risk in patients with non-valvular atrial fibrillation and to guide recommendations for anticoagulation [23]. Alici et al. [18] recently demonstrated that the CHA_2DS_2-VASc score was significantly lower in patients with spontaneous reperfusion compared to those without spontaneous reperfusion (mean CHA_2DS_2-VASc score 1.36 ± 0.64 vs. 2.01 ± 0.80; P <0.001) [18]. The receiver operating characteristic analysis indicated that the CHA_2DS_2-VASc score at a cut-off value of ≤1 may predict spontaneous reperfusion with 56.1% sensitivity and 73.3% specificity (area under the curve 0.703, 95% confidence interval: 0.681–0.725; P <0.001).

Therefore, risk stratification tools such as PRECISE-DAPT and CHA_2DS_2-VASc, which can be calculated easily and in a timely fashion, could provide important prognostic information and may also serve to identify patients who are very unlikely to have spontaneous reperfusion and who require a higher level of monitoring.

MECHANISMS OF SPONTANEOUS REPERFUSION

Although spontaneous reperfusion is associated with improved outcomes, its pathophysiology remains unclear. There are several determinants that influence spontaneous reperfusion. Studies have highlighted the importance of the extent, severity, and location [24] of coronary artery disease as well as plaque morphology [25]. By identifying clinical characteristics of patients with spontaneous reperfusion and establishing relationships between this cohort of patients and potentially modifiable determinants described below, we could implement a variety of strategies to identify patients at risk of future cardiovascular events and personalize management not only to reduce the risk of an event occurring but reduce the severity of any sequelae following coronary occlusion.

Endogenous fibrinolysis

Once a thrombus begins to form in an artery, the natural protective enzymes that can break down the clot before it causes lasting damage also become activated. The natural protective enzymes that break down a clot form the "endogenous fibrinolytic system", which is a physiological protective mechanism in healthy individuals that is imperative for the prevention of occlusive thrombus formation and lasting vessel occlusion. When the balance is altered in favor of platelet activation and/or coagulation, or if endogenous fibrinolysis becomes less efficient, pathological thrombosis can occur (Figure 1). A number of proteins and enzymes are involved in fibrinolysis and include those that potentiate fibrinolysis, such as tissue plasminogen activator, urokinase-type plasminogen activator, and thrombomodulin as well as those that inhibit fibrinolysis like plasminogen activator inhibitor-1, thrombin activatable fibrinolysis inhibitor, α1-antiplasmin, and α2-macroglobulin.

Until recently, endogenous fibrinolysis has been difficult to measure. The value of measuring individual fibrinolysis activity markers such as tissue plasminogen activator, plasminogen activator inhibitor-1, or thrombin activatable fibrinolysis inhibitor is very limited in aiding diagnosis and risk stratification in the individual patient, based on the weak prognostic values obtained in some studies and the lack of power in others. Measuring the antigen or activity level of enzymes requires highly specialist laboratory expertise, is not widely available, and it takes a long time to obtain the results. Serum D-dimer is a fibrin degradation product that detects ongoing fibrinolysis and is, therefore, useful in diagnosing hypercoagulable states; however, the prognostic value of D-dimer remains controversial in the context of ACS. Elevated concentrations of D-dimer have been reported in several clinical settings [26], and as a non-specific acute-phase marker, its clinical utility is limited. The relative importance of each of these aforementioned biomarkers compared to the others is unclear and, therefore, one cannot build a picture of the overall endogenous fibrinolytic status by measuring individual markers alone [27, 28]. Furthermore, no clinically significant difference in whole blood assays has been observed or reported in any studies involving spontaneous reperfusion in the setting of STEMI.

This not only highlights the fact that a "global" assessment of thrombotic status is preferable but also that there is a need for a novel biomarker that can identify STEMI patients with a low likelihood of spontaneous reperfusion. There are currently 2 methods to assess global endogenous fibrinolysis, namely viscoelastic tests such as the rotational thromboelastometry ROTEM® (Pentapharm GmbH, Munich, Germany) or thromboelastography (Haemonetics Ltd., Coventry, UK), which assesses thrombus formation and lysis at low shear rates, more akin to venous thrombosis, and the Global Thrombosis Test (Thromboquest Ltd., London, UK), which assesses thrombus formation and lysis under arterial flow conditions of high shear [29–31].

Studies have shown that impaired endogenous fibrinolysis is an independent predictor of recurrent heart attack, stroke, and death in patients with ACS [12, 32]. The less efficient the endogenous fibrinolysis, the greater the cardiovascular risk. In a recent prospective study, blood from STEMI patients (n = 801) was tested pre-PCI to assess *in vitro,* point-of-care, occlusion times, and endogenous lysis times using the Global Thrombosis Test [17]. It showed that individuals with spontaneous reperfusion (defined as infarct-related artery thrombolysis in myocardial infarction flow grade 3 before PCI) demonstrated more rapid endogenous fibrinolysis than patients without spontaneous reperfusion. Specifically longer occlusion time, reflecting lower platelet reactivity and a shorter lysis time, reflecting more efficient endogenous fibrinolysis, were significantly associated with spontaneous reperfusion. Notably, there were no differences in clinical characteristics or antiplatelet therapy before angiography between patients with and without spontaneous reperfusion. Furthermore, among patients with spontaneous reperfusion, those with complete ST-segment resolution had more rapid endogenous fibrinolysis times and had reduced platelet reactivity than those with only partial ST-segment resolution. Over a 4-year follow-up period, patients with spontaneous reperfusion experienced fewer major adverse cardiovascular events than those without (4.1% vs. 10.6%; $P = 0.01$). The frequency of subsequent major adverse cardiovascular events was lowest in individuals with both spontaneous reperfusion and complete ST-segment resolution (1.5% vs. 10.1%; $P = 0.03$).

Clot structure

The formation of fibrin clots that are relatively resistant to lysis represents the final step in the process of blood coagulation and thrombosis. The assessment of clot structure can provide information about clot permeability as well as susceptibility to lysis [33]. There is significant evidence indicating that abnormal fibrin properties, which enhance the resistance of clots to lysis, represent a novel risk factor for arterial and venous thrombotic events [34]. Patients

with coronary artery disease have been shown to have clots that are less permeable and with longer lysis time than clots formed from blood taken from healthy subjects [35]. Moreover, patients with ACS have been shown to have denser clot structure (greater fibrin concentration), lower clot permeability, faster clot polymerization, and prolonged lysis time compared to patients with stable angina, and these features correlated with raised C-reactive protein (CRP) and oxidative stress [36]. There have been no studies comparing the clot structure of patients with and without spontaneous reperfusion. An important limitation of using clot structure to reflect the susceptibility to fibrinolysis is that fibrin clots are created from plasma, rather than whole blood, and therefore do not take account of cellular components that can also have a major impact on properties of a thrombus *in vivo*.

Platelet reactivity

Platelet activation, leading to enhanced platelet aggregation, contributes to an increased risk of cardiovascular events in patients with coronary disease. The main determinants of platelet activation and aggregation in stenosed arteries are shear stress and wall shear stress. Poor platelet inhibition (in response to antiplatelet agents) in the early phase of ACS and PCI is associated with increased risk of recurrent ischemic events including acute stent thrombosis [37]. In a meta-analysis of randomized controlled trials, reducing high platelet reactivity in ACS was associated with a reduction of major ischemic complications [38].

Capranzano et al. [39] assessed the relationship between platelet reactivity, using the VerifyNow assay, with spontaneous reperfusion in STEMI patients. High on-treatment platelet reactivity was shown to be associated with lower rates of pre-PCI thrombolysis in myocardial infarction flow grade 2 or 3 and higher rates of thrombus score grade 3/4 (29.8% vs. 52.1%; $P = 0.02$) compared with that observed in patients without high on-treatment platelet reactivity (32.5% vs. 51.1%; $P = 0.04$).

Ticagrelor and prasugrel have been shown to reduce circulating platelet activation markers in ACS [40] as well as chronic coronary syndrome [41]. Nevertheless, the ATLANTIC (Administration of Ticagrelor in the Cath-Lab or the Ambulance for New ST-Elevation Myocardial Infarction to Open the Coronary Artery) study showed that prehospital administration of ticagrelor does not improve pre-PCI coronary flow, compared to ticagrelor administration in hospital [42]. The cause of persistently increased platelet activation, despite antiplatelet medication, may be multifactorial. Opioid medication utilized for pain management in patients with ACS has been shown to delay the onset of action of $P2Y_{12}$ inhibitors [43]. Another explanation for this is that the effectiveness of clopidogrel depends on its conversion to an active metabolite, which is accomplished by the cytochrome P450 2C19 enzyme and individuals who have either 1 or 2 loss-of-function copies of the cytochrome *P450 2C19* gene (defined at intermediate and poor metabolizers respectively) will have significantly reduced enzyme activity and cannot activate clopidogrel, which means the drug will have a reduced antiplatelet effect.

In another study of patients with STEMI receiving aspirin and clopidogrel, the prevalence of high on-treatment platelet reactivity was lower in patients with spontaneous reperfusion than in those without spontaneous reperfusion (15.9% vs. 66.7%; $P = 0.01$) [44]. Patients with spontaneous reperfusion have also been shown to have reduced platelet reactivity, as measured under conditions of high shear using the Global Thrombosis Test, compared to patients without spontaneous reperfusion [17].

Interaction between inflammation and fibrinolysis

The active inflammatory process involved in the formation of atherosclerotic plaques is well described [45], and there is also increasing evidence of complex, bi-directional cross-talk between inflammation and coagulation pathways [46, 47]. Exposure of blood to tissue factor, either through plaque rupture or release from circulating monocytes, results in activation of coagulation, resulting in thrombin and ultimately fibrin generation, as well as platelet activation. These coagulation factors have additional inflammatory effects. Binding of tissue factor, thrombin, and other activated coagulation proteases to specific protease-activated receptors on inflammatory cells may induce the release of proinflammatory cytokines and chemokines, which can further modulate coagulation and fibrinolysis [46–48].

The main inhibitor of fibrinolysis in the circulation is plasminogen activator inhibitor-1, and increased levels have been linked to myocardial infarction [49]. Not only are high CRP levels associated with elevated plasminogen activator inhibitor-1 levels in several conditions such as sepsis, inflammation, and myocardial infarction, but in experimental models, proinflammatory cytokines liberated during inflammation, including CRP, interleukin-6, and tumor necrosis factor alpha, directly influence plasminogen activator inhibitor-1 synthesis [50, 51]. Incubation of human aortic endothelial cells with CRP induced a time- and dose-dependent increase in plasminogen activator inhibitor-1 expression and activity [51], and a reduction in tissue plasminogen activator activity [52], showing a direct effect on fibrinolytic status. There is a direct functional relationship between plasminogen activator inhibitor-1 and CRP and a correlation between CRP and endogenous fibrinolysis time or plasma clot lysis time [32]. In a retrospective study evaluating 998 STEMI patients who underwent emergency coronary angiography, 229 (22.95%) patients had evidence of spontaneous reperfusion (defined as infarct-related artery thrombolysis in myocardial infarction flow grade 3 before PCI) [53]. CRP levels were significantly lower in patients with spontaneous reperfusion than in those without spontaneous reperfusion (3.48 mg/dl vs. 5.48 mg/dl; $P = 0.01$). Furthermore, multivariate logistic regression, adjusted for

age, sex, cardiovascular risk factors, antiplatelet therapy, time to angiography, and hematological variables, demonstrated that CRP level was an independent predictor of spontaneous reperfusion (odds ratio 0.92; 95% confidence interval, 0.87–0.99; $P = 0.02$).

Neutrophil extracellular traps

Atherosclerosis is triggered by the damage of vascular endothelial cells and neutrophils are the first line of inflammatory cells to be activated and recruited to these damaged endothelial cells. Neutrophils can release neutrophil extracellular traps (NETs), which are web-like chromatin structures composed of deoxyribonucleic acid, histones, and granule proteins that promote arterial thrombosis by providing a scaffold for platelets, red blood cells, extracellular vesicles, and clotting factors, such as von Willebrand factor and tissue factor [54].

NETs and their individual components appear to modulate clot lysis and data suggest that the permeability of plasma clots was reduced by about 50% in the presence of DNA or histones. This is in part due to increased thrombin fiber diameter but also due to inhibition of plasmin-driven lysis of plasma clots [55]. Increased concentrations of histones have been shown to markedly impair fibrinolysis *in vitro*, and the addition of DNA further prolongs lysis time [56]. The effects of histones and DNA in isolation were subtle and suggest that histones affect clot structure, whereas DNA alters the way clots are lysed. DNase, an enzyme that breaks up extracellular DNA, can nullify these effects and has been shown to accelerate tPA-induced lysis (measured as percent of baseline thrombus weight per time point) in clots obtained from patients with STEMI undergoing PPCI [57]. In the same study performed by Mangold et al., coronary NET burden was inversely correlated with ST-segment resolution ($r = –0.608$; $P = 0.003$) and positively with cardiac magnetic resonance imaging-measured infarct size ($r = 0.689$; $P = 0.003$). Moreover, culprit lesion site DNase activity was inversely correlated with coronary thrombus NET burden ($r = –0.623$; $P < 0.0001$) as well as cardiac magnetic resonance imaging-measured infarct size ($r = –0.475$; $P = 0.008$) and positively with ST-segment resolution ($r = 0.579$; $P = 0.001$)

Blasco et al. [58] recently demonstrated that the presence of NETs in coronary thrombi was associated with a worse prognosis soon after STEMI. NETs were detected in 51% of coronary thrombi aspirated from 406 patients with STEMI and their presence was strongly associated with recurrent adverse cardiovascular events in the first 30 days after infarction (hazard ratio 2.82; $P = 0.01$), particularly reinfarction (odds ratio 2.28; $P = 0.03$).

NETs also enhance blood coagulation, not only by activating the intrinsic pathway of coagulation but also by degrading tissue factor pathway inhibitor, the major extrinsic coagulation pathway inhibitor. NETs can impair smooth muscle cells and the death of smooth muscle cells and foam cells, together with the degradation of the extracellular matrix, results in thinning of the fibrous cap and the formation of rupture-prone vulnerable plaques [59].

Such evidence provides the rationale for NET-targeted strategies to improve thrombolysis, particularly in the setting of STEMI.

Lipoprotein (a)

Lipoprotein (a) (Lp[a]), is a low-density lipoprotein (LDL) particle bound to apolipoprotein(a). Elevated levels of Lp(a) have been shown to be associated with increased risk of cardiovascular events in patients with established cardiovascular disease irrespective of LDL cholesterol levels [60]. Lp(a) levels vary among the general population from ≤0.2 to ≥250 mg/dl but have been shown to remain stable throughout an individual's life [61].

Lp(a) may exert its adverse effects by negatively impacting endogenous fibrinolysis. Plasmin is an important enzyme present in blood that degrades many plasma proteins, including fibrin clots. Lp(a) has a high degree of homology to plasminogen (a pro-enzyme that is cleaved to form plasmin) and may cause thrombosis by competitively inhibiting tissue plasminogen activator-mediated plasminogen activation and tissue plasminogen activator-mediated clot lysis. Furthermore, Lp(a) stimulates the activity of plasminogen activator inhibitor-1, which is the major inhibitor of the fibrinolytic system. Undas and co-workers have shown that elevated plasma Lp(a) levels are associated with pathogenic clot properties, namely decreased fibrin clot permeation and impaired susceptibility to fibrinolysis, both in apparently healthy subjects and patients with advanced coronary artery disease [62].

A study conducted in patients with myocardial infarction receiving thrombolytic therapy showed that Lp(a) levels were not related to the reperfusion outcome of thrombolysis [63]. However, among those patients who did not receive thrombolysis, the spontaneous reperfusion rate was significantly higher in patients with low Lp(a) levels compared to those with high Lp(a) levels. Lp(a) levels were shown to be significantly higher in patients with persistent occlusion compared with those with spontaneous reperfusion of the IRA in the early phase of ACS [64]. More recently, Sankhesara et al. [65] have shown elevated Lp(a) levels to be associated with greater thrombus burden in younger STEMI patients. The findings of these studies accord with the thrombotic and anti-fibrinolytic properties of Lp(a).

POTENTIAL THERAPEUTIC TARGETS

Endogenous fibrinolysis

Despite optimal contemporary treatments with PPCI and antithrombotic medications, studies have shown that impaired endogenous fibrinolysis is an independent predictor of adverse cardiovascular outcomes in patients with ACS [12, 32].

The study conducted by Kanji et al. [17] provides insights into the role of the endogenous fibrinolytic system in

thrombotic coronary artery occlusion and the likelihood of spontaneous restoration of coronary artery patency prior to mechanical or fibrinolytic therapy intervention. Therefore, measurement of endogenous fibrinolysis using the Global Thrombosis Test may be a novel target for pharmacological intervention and could in the future allow targeting of potent antithrombotic medications to high-risk patients.

Clot structure

The PLATO sub-study demonstrated that impaired fibrin clot properties, such as fibrin network architecture and susceptibility to fibrinolysis, independently predict adverse clinical outcomes following ACS [32]. Clot structure assessment can provide us with an abundance of information with regard to what therapeutic interventions can potentially break down resistant clots in life-threatening events or even favorably modify fibrin clot structure to prevent future cardiovascular events. Zabczyk et al. [33] have recently summarized the studies that have already reported effects of conventional therapeutic interventions on fibrin clot properties. Of the current conventional secondary prevention drugs for cardiovascular disease, aspirin can increase clot permeability at all doses in healthy individuals [66], statins can increase clot permeability and clot maximum absorbency as well as reduce clot lysis time [67, 68], and anti-hypertensive medications (monotherapy with quinapril, losartan, amlodipine, hydrochlorothiazide, or bisoprolol) can increase clot permeability and reduce clot lysis time [69]. With regard to anti-diabetic medication, metformin has been shown to decrease clot lysis time *in vitro* [70], and insulin has been shown to increase clot permeability in type 1 diabetics after 4–6 months of treatment [71]. Future studies utilizing novel therapeutic interventions could incorporate clot structure assessment to gain a better mechanistic understanding if a favorable clinical outcome is achieved.

Lipoprotein (a)

Until recently, Lp(a) has been considered a non-modifiable cardiovascular risk factor as few therapies are available to sufficiently reduce Lp(a) levels. New data, however, have shown that novel cholesterol-lowering treatments, namely proprotein convertase subtilisin/kexin type 9 inhibitors [72], inclisiran (a long-acting silencing ribonucleic acid) [73] and antisense oligonucleotides [74] can reduce Lp(a) levels by approximately 25%, 20%, and 80% respectively. The FOURIER trial was a randomized trial of evolocumab versus placebo inpatients with established atherosclerotic cardiovascular disease [72]. Lp(a) was measured at baseline in 25 096 patients and at 48 weeks, evolocumab significantly reduced Lp(a) by a median of 26.9%. In the ODYSSEY OUTCOMES trial, alirocumab reduced Lp(a) levels by 23% from baseline to month 4, compared to placebo. In the ORION-10 and ORION-11 trials, a total of 1561 and 1617 patients with elevated LDL-cholesterol levels, respectively. were randomly assigned in a 1:1 ratio to receive either inclisiran or placebo [73]. The median reduction in Lp(a) levels was 21.9% and 18.6% from the baseline in the ORION-10 and ORION-11 trials, respectively. In a phase I/IIa trial assessing 30 patients with elevated Lp(a) levels, administration of the antisense oligonucleotide IONIS-APO(a)-LRx in a multiple-ascending-dose phase, resulted in mean reductions in Lp(a) of 66% in the 10 mg group, 80% in the 20 mg group, and 92% in the 40 mg group (P <0.001 for all vs. placebo) at day 36 [74].

The pivotal role played by Lp(a) in thrombus formation and stability provides the rationale for employing Lp(a) lowering therapies to prevent atherothrombosis. Phase III studies (NCT04023552 and NCT05581303) involving antisense oligonucleotides (i.e., pelacarsen and olpasiran) are currently ongoing to assess whether Lp(a) reduction translates to improved cardiovascular outcomes. Additionally small interfering ribonucleic acid therapies targeting Lp(a) messenger ribonucleic acid are also under development [75]. Whether these drugs, in addition to reducing Lp(a), can also enhance endogenous fibrinolysis and, therefore, increase the likelihood of spontaneous reperfusion following STEMI will require further assessment.

$P2Y_{12}$ and glycoprotein IIb/IIIa inhibitors

Despite significant advances in antiplatelet therapy for ACS, oral $P2Y_{12}$ inhibitors have failed to demonstrate either improved patency or reduced mortality when administered in the prehospital setting [76]. Furthermore, although potent intravenous glycoprotein IIb/IIIa inhibitors (abciximab, tirofiban, and eptifibatide) have been shown to reduce the incidence of death and recurrent ACS in high-risk patients undergoing PCI compared with unfractionated heparin, they block all circulating platelets resulting in increased frequency of major bleeding complications [77]. Thus, there is a need for antiplatelet agents that achieve rapid and potent platelet inhibition to restore patency of the IRA in the prehospital setting without unreasonably high bleeding risk.

Selatogrel is a novel, potent, reversible, and selective $P2Y_{12}$ inhibitor administered subcutaneously undergoing clinical trial evaluation. Results from preclinical, phase I and II trials have confirmed that the agent provides sustained and reversible $P2Y_{12}$ platelet inhibition with an acceptable safety profile [78–81]. Zalunfiban, a novel subcutaneously administered glycoprotein IIb/IIIa inhibitor designed for prehospital administration, has been shown to achieve rapid, high-grade platelet inhibition that exceeds that of $P2Y_{12}$ inhibitors and also has a rapid offset of action to minimize the risk of bleeding [82].

Zalunfiban and selatogrel represent an exciting new generation of platelet antagonists that may be administered easily *via* subcutaneous injection at first medical contact in patients with STEMI. The ongoing phase III studies, CeleBrate (NCT04825743) and SOS-AMI (NCT04957719) will provide more definitive answers and shed further light on whether these medications might increase the frequency of "spontaneous" reperfusion and improve outcomes.

Anticoagulants

The mainstay of pharmacological treatment for ACS patients is dual antiplatelet therapy. Anticoagulants (including vitamin K antagonists, non-vitamin K antagonist oral anticoagulants, fondaparinux, and heparin) have been shown to alter fibrin clot structure by increasing clot permeability and altering clot density [83, 84]. Pilot data have also shown that in patients with atrial fibrillation, treatment with non-vitamin K antagonist oral anticoagulants showed a trend to enhance endogenous fibrinolysis as well as a favorable effect on reducing platelet reactivity [85].

Among the non-vitamin K antagonist oral anticoagulants, rivaroxaban is the only one to successfully undergo phase III evaluation in ACS patients in combination with dual antiplatelet therapy. The ATLAS ACS-2 TIMI 51 study showed that the addition of even very low-dose anticoagulant (rivaroxaban 2.5 mg twice daily) to dual antiplatelet therapy in patients with a recent ACS significantly reduced the primary endpoint of cardiovascular death, myocardial infarction or stroke, compared with placebo, and also reduced the rates of death from cardiovascular causes (2.7 vs. 4.1%; P <0.01) and from any cause (2.9 vs. 4.5%; P <0.01); however, this came at a price of increased major bleeding and intracranial hemorrhage [86].

Factor XI is the zymogen of a plasma protease, factor Xa, that contributes to thrombin generation during blood coagulation which may potentially lead to vessel occlusion and pathological manifestations of thrombosis [87]. Factor XI-directed strategies are proposed to reduce thrombosis with minimal effect on hemostasis due to its limited role in the initiation phase of the extrinsic pathway and therefore, in theory, they might be safer than rivaroxaban in ACS patients. Circulating factor XIa has been shown to be associated with prothrombotic plasma fibrin clot phenotype, represented by low permeability and impaired susceptibility to lysis, suggesting additional pathways that factor XIa inhibitors could act as novel antithrombotic agents in coronary artery disease [88]. There is already a phase III clinical trial underway (NCT05754957) assessing the efficacy and safety of the addition of factor XIa inhibitor milvexian versus placebo to standard-of-care in patients with recent ACS. Again, whether such patients with ACS given milvexian, on top of dual antiplatelet therapy, will have a lower frequency of subsequent ischemic events, and whether this could be driven by enhanced spontaneous reperfusion remains to be seen.

Anti-inflammatory therapies

The most important inflammatory mediators that play a significant role in the atherosclerotic process are the cytokines, interleukin-1 beta and interleukin-6 chemokines, interferon-gamma, and tumor necrosis factor alpha.

The LoDoCo trial [89] and COLCOT trial [90] showed that among patients with a recent myocardial infarction, colchicine at a dose of 0.5 mg daily led to a significantly lower risk of ischemic cardiovascular events than placebo. The CANTOS study showed for the first time that isolated treatment with canakinumab targeting interleukin-1 beta inhibition can reduce the risk of cardiovascular events in patients post-ACS [91]. However, this came at the price of an increased risk of fatal infection or sepsis (incidence rate, 0.31 vs. 0.18 events per 100 person-years; P = 0.02). Furthermore, canakinumab is extremely expensive (approximately £12 000 per injection) and is not cost-effective for prevention of recurrent cardiovascular events in patients with a prior myocardial infarction [92]. This has highlighted the need for the development of other novel therapeutic strategies as well as for a more appropriate cohort of patients more likely to respond to anti-inflammatory therapies.

Although prompt reperfusion of the infarct-related artery results in reduced infarct size and more favorable outcomes in STEMI patients, paradoxically the restoration of blood flow itself may also lead to further myocardial damage thought to be *via* the generation of reactive oxygen species, intracellular calcium overload, and acidosis [93]. Up to 50% of the viable myocardium loss may be attributed to the reperfusion injury and the associated inflammatory response [93]. Interleukin-6 levels are substantially elevated after myocardial infarction contributing to both the inflammatory process as well as reperfusion injury [94, 95]. The ASSAIL-MI trial was a randomized, double-blind, placebo-controlled trial, where 200 STEMI patients were assigned randomized in a 1:1 fashion to promptly receive a single infusion of 280 mg tocilizumab or placebo [96]. The primary endpoint was the myocardial salvage index as measured by cardiac magnetic resonance imaging after 3–7 days. The study demonstrated that tocilizumab increased myocardial salvage in patients with STEMI (69.3 ± 19.3% vs. 63.6 ± 20.58%; P = 0.04).

ARTEMIS (NCT06118281) is a phase-III, double-blind, randomized control trial scheduled to start patient recruitment in mid-2024 and will compare an interleukin-6 inhibitor (ziltivekimab) to placebo in patients with acute myocardial infarction (STEMI or NSTEMI) and evidence of type I myocardial infarction on coronary angiography. This trial will try to determine whether ziltivekimab reduces cardiovascular event rates. Whether such chronic maintenance therapy can enhance and favorably modulate thrombo-inflammatory status and reduce future vascular occlusion will be eagerly awaited.

CONCLUSION

Patients with spontaneous reperfusion in the setting of STEMI experience more favorable outcomes and reduced mortality. A biomarker that can identify patients with STEMI with a low likelihood of spontaneous reperfusion would justify the use of more potent antithrombotic medications in such patients, in a personalized fashion, avoiding unnecessary treatment in those with spontaneous reperfusion and improving outcomes for those with persistent vessel

occlusion. Assessment of endogenous fibrinolysis in whole blood appears to be the most promising biomarker available at present and provides pathophysiologically relevant information. Future studies will be needed to assess the impact of novel antithrombotic, anti-inflammatory, and lipid-lowering therapies currently in development on endogenous fibrinolysis and spontaneous reperfusion.

Article information

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REFERENCES

1. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J Acute Cardiovasc Care. 2024; 13(1): 55–161, doi: 10.1093/ehjacc/zuad107, indexed in Pubmed: 37740496.
2. Wang J, He SY. Clinical and angiographic characteristics of patients with spontaneous reperfusion in ST-segment elevation myocardial infarction. Medicine (Baltimore). 2020; 99(10): e19267, doi: 10.1097/MD.0000000000019267, indexed in Pubmed: 32150062.
3. Christian TF, Milavetz JJ, Miller TD, et al. Prevalence of spontaneous reperfusion and associated myocardial salvage in patients with acute myocardial infarction. Am Heart J. 1998; 135(3): 421–427, doi: 10.1016/s0002-8703(98)70317-5, indexed in Pubmed: 9506327.
4. Lemkes JS, Janssens GN, van der Hoeven NW, et al. Timing of revascularization in patients with transient ST-segment elevation myocardial infarction: a randomized clinical trial. Eur Heart J. 2019; 40(3): 283–291, doi: 10.1093/eurheartj/ehy651, indexed in Pubmed: 30371767.
5. Fefer P, Beigel R, Atar S, et al. ACSIS (Acute Coronary Syndrome Israeli Survey) Study Group. Outcomes of patients presenting with clinical indices of spontaneous reperfusion in ST-elevation acute coronary syndrome undergoing deferred angiography. J Am Heart Assoc. 2017; 6(7): e004552, doi: 10.1161/JAHA.116.004552, indexed in Pubmed: 28743786.
6. Koc L, Mikolaskova M, Novotny T, et al. Primary percutaneous coronary intervention is appropriate in transient ST-elevation myocardial infarction. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2022; 166(2): 180–186, doi: 10.5507/bp.2021.005, indexed in Pubmed: 33542543.
7. Farag M, Peverelli M, Spinthakis N, et al. Spontaneous reperfusion in patients with transient ST-elevation myocardial infarction-prevalence, importance and approaches to management. Cardiovasc Drugs Ther. 2023; 37(1): 169–180, doi: 10.1007/s10557-021-07226-7, indexed in Pubmed: 34245445.
8. Hashimoto T, Ako J, Nakao K, et al. Pre-Procedural thrombolysis in myocardial infarction flow in patients with ST-segment elevation myocardial infarction. Int Heart J. 2018; 59(5): 920–925, doi: 10.1536/ihj.17-518, indexed in Pubmed: 30158385.
9. Blondheim DS, Kleiner-Shochat M, Asif A, et al. Characteristics, management, and outcome of transient ST-elevation versus persistent ST-elevation and non-ST-elevation myocardial infarction. Am J Cardiol. 2018; 121(12): 1449–1455, doi: 10.1016/j.amjcard.2018.02.029, indexed in Pubmed: 29699746.
10. Fefer P, Hod H, Hammerman H, et al. Relation of clinically defined spontaneous reperfusion to outcome in ST-elevation myocardial infarction. Am J Cardiol. 2009; 103(2): 149–153, doi: 10.1016/j.amjcard.2008.08.050, indexed in Pubmed: 19121427.
11. Bainey KR, Fu Y, Wagner GS, et al. Spontaneous reperfusion in ST-elevation myocardial infarction: comparison of angiographic and electrocardiographic assessments. Am Heart J. 2008; 156(2): 248–255, doi: 10.1016/j.ahj.2008.03.018, indexed in Pubmed: 18657653.
12. Farag M, Spinthakis N, Gue YX, et al. 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. Eur Heart J. 2019; 40(3): 295–305, doi: 10.1093/eurheartj/ehy656, indexed in Pubmed: 30380032.
13. Shavadia JS, Granger CB, Alemayehu W, et al. Novel biomarkers, ST-elevation resolution, and clinical outcomes following primary percutaneous coronary intervention. J Am Heart Assoc. 2020; 9(13): e016033, doi: 10.1161/JAHA.120.016033, indexed in Pubmed: 32552321.
14. Brener SJ, Mehran R, Brodie BR, et al. Predictors and implications of coronary infarct artery patency at initial angiography in patients with acute myocardial infarction (from the CADILLAC and HORIZONS-AMI Trials). Am J Cardiol. 2011; 108(7): 918–923, doi: 10.1016/j.amjcard.2011.05.022, indexed in Pubmed: 21764028.
15. Rimar D, Crystal E, Battler A, et al. Improved prognosis of patients presenting with clinical markers of spontaneous reperfusion during acute myocardial infarction. Heart. 2002; 88(4): 352–356, doi: 10.1136/heart.88.4.352, indexed in Pubmed: 12231590.
16. Lee CW, Hong MK, Lee JH, et al. Determinants and prognostic significance of spontaneous coronary recanalization in acute myocardial infarction. Am J Cardiol. 2001; 87(8): 951–954; A3, doi: 10.1016/s0002-9149(01)01427-8, indexed in Pubmed: 11305984.
17. Kanji R, Gue YX, Memtsas V, et al. Biomarkers of thrombotic status predict spontaneous reperfusion in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol. 2023; 81(19): 1918–1932, doi: 10.1016/j.jacc.2023.03.388, indexed in Pubmed: 37164525.
18. Alıcı G, Barman HA, Atıcı A, et al. The impact of lesion complexity and the CHA2DS2-VASc score on spontaneous reperfusion in patients with ST-segment elevation myocardial infarction. Int J Clin Pract. 2022; 2022: 8066780, doi: 10.1155/2022/8066780, indexed in Pubmed: 35685511.
19. Janssens GN, Lemkes JS, van der Hoeven NW, et al. Transient ST-elevation myocardial infarction versus persistent ST-elevation myocardial infarction. An appraisal of patient characteristics and functional outcome. Int J Cardiol. 2021; 336: 22–28, doi: 10.1016/j.ijcard.2021.05.018, indexed in Pubmed: 34004231.
20. Demirkiran A, van der Hoeven NW, Janssens GN, et al. Left ventricular function, strain, and infarct characteristics in patients with transient ST-segment elevation myocardial infarction compared to ST-segment and non-ST-segment elevation myocardial infarctions. Eur Heart J Cardiovasc Imaging. 2022; 23(6): 836–845, doi: 10.1093/ehjci/jeab114, indexed in Pubmed: 34195800.
21. Costa F, van Klaveren D, James S, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet. 2017; 389(10073): 1025–1034, doi: 10.1016/S0140-6736(17)30397-5, indexed in Pubmed: 28290994.
22. Şaylık F, Akbulut T. The association of PRECISE-DAPT score with thrombus burden in patients with ST-segment elevation myocardial infarction. Acta Cardiol. 2022; 77(5): 449–455, doi: 10.1080/00015385.2021.1954747, indexed in Pubmed: 34309488.
23. Siddiqi TJ, Usman MS, Shahid I, et al. Utility of the CHA2DS2-VASc score for predicting ischaemic stroke in patients with or without atrial fibrillation: a systematic review and meta-analysis. Eur J Prev Cardiol. 2022; 29(4): 625–631, doi: 10.1093/eurjpc/zwab018, indexed in Pubmed: 33693717.
24. Leibowitz D, Gerganski P, Nowatzky J, et al. Relation of spontaneous reperfusion in ST-elevation myocardial infarction to more distal coronary culprit narrowings. Am J Cardiol. 2008; 101(3): 308–310, doi: 10.1016/j.amjcard.2007.08.036, indexed in Pubmed: 18237590.
25. Guo J, Chen J, Wang G, et al. Plaque characteristics in patients with ST-segment elevation myocardial infarction and early spontaneous reperfusion. EuroIntervention. 2021; 17(8): e664–e671, doi: 10.4244/EIJ-D-20-00812, indexed in Pubmed: 33495143.
26. Lippi G, Bonfanti L, Saccenti C, et al. Causes of elevated D-dimer in patients admitted to a large urban emergency department. Eur J Intern Med. 2014; 25(1): 45–48, doi: 10.1016/j.ejim.2013.07.012, indexed in Pubmed: 23948628.
27. Gorog DA. Prognostic value of plasma fibrinolysis activation markers in cardiovascular disease. J Am Coll Cardiol. 2010; 55(24): 2701–2709, doi: 10.1016/j.jacc.2009.11.095, indexed in Pubmed: 20538163.

28. Krychtiuk KA, Speidl WS, Giannitsis E, et al. Biomarkers of coagulation and fibrinolysis in acute myocardial infarction: a joint position paper of the Association for Acute CardioVascular Care and the European Society of Cardiology Working Group on Thrombosis. Eur Heart J Acute Cardiovasc Care. 2021; 10(3): 343–355, doi: 10.1093/ehjacc/zuaa025, indexed in Pubmed: 33620437.
29. Okafor ON, Gorog DA. Endogenous fibrinolysis: An important mediator of thrombus formation and Cardiovascular risk. J Am Coll Cardiol. 2015; 65(16): 1683–1699, doi: 10.1016/j.jacc.2015.02.040, indexed in Pubmed: 25908074.
30. Kanji R, Leader J, Memtsas V, et al. Measuring thrombus stability at high shear, together with thrombus formation and endogenous fibrinolysis: First experience using the global thrombosis test 3 (GTT-3). Clin Appl Thromb Hemost. 2023; 29: 10760296231181917, doi: 10.1177/10760296231181917, indexed in Pubmed: 37551011.
31. Gorog DA, Lip GYH. Impaired spontaneous/endogenous fibrinolytic status as new cardiovascular risk factor?: JACC review topic of the week. J Am Coll Cardiol. 2019; 74(10): 1366–1375, doi: 10.1016/j.jacc.2019.07.030, indexed in Pubmed: 31488274.
32. Sumaya W, Wallentin L, James SK, et al. Fibrin clot properties independently predict adverse clinical outcome following acute coronary syndrome: a PLATO substudy. Eur Heart J. 2018; 39(13): 1078–1085, doi: 10.1093/eurheartj/ehy013, indexed in Pubmed: 29390064.
33. Ząbczyk M, Ariëns RAS, Undas A. Fibrin clot properties in cardiovascular disease: from basic mechanisms to clinical practice. Cardiovasc Res. 2023; 119(1): 94–111, doi: 10.1093/cvr/cvad017, indexed in Pubmed: 36662542.
34. Kietsiriroje N, Ariëns RAS, Ajjan RA. Fibrinolysis in acute and chronic cardiovascular disease. Semin Thromb Hemost. 2021; 47(5): 490–505, doi: 10.1055/s-0040-1718923, indexed in Pubmed: 33878782.
35. Siniarski A, Baker SR, Duval C, et al. Quantitative analysis of clot density, fibrin fiber radius, and protofibril packing in acute phase myocardial infarction. Thromb Res. 2021; 205: 110–119, doi: 10.1016/j.thromres.2021.06.024, indexed in Pubmed: 34298252.
36. Undas A, Szułdrzynski K, Stepien E, et al. Reduced clot permeability and susceptibility to lysis in patients with acute coronary syndrome: effects of inflammation and oxidative stress. Atherosclerosis. 2008; 196(2): 551–557, doi: 10.1016/j.atherosclerosis.2007.05.028, indexed in Pubmed: 17640649.
37. Stone GW, Witzenbichler B, Weisz G, et al. ADAPT-DES Investigators. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. Lancet. 2013; 382(9892): 614–623, doi: 10.1016/S0140-6736(13)61170-8, indexed in Pubmed: 23890998.
38. Piccolo R, Galasso G, De Luca G, et al. Relationship between changes in platelet reactivity and ischemic events following percutaneous coronary intervention: a meta-regression analysis of 30 randomized trials. Atherosclerosis. 2014; 234(1): 176–184, doi: 10.1016/j.atherosclerosis.2014.02.024, indexed in Pubmed: 24657388.
39. Capranzano P, Capodanno D, Bucciarelli-Ducci C, et al. Impact of residual platelet reactivity on reperfusion in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Eur Heart J Acute Cardiovasc Care. 2016; 5(5): 475–486, doi: 10.1177/2048872615624849, indexed in Pubmed: 26758542.
40. Chyrchel B, Kruszelnicka O, Surdacki A. Endothelial biomarkers and platelet reactivity on ticagrelor versus clopidogrel in patients after acute coronary syndrome with and without concomitant type 2 diabetes: a preliminary observational study. Cardiovasc Diabetol. 2022; 21(1): 249, doi: 10.1186/s12933-022-01685-4, indexed in Pubmed: 36397167.
41. Paszek E, Natorska J, Ząbczyk M, et al. Therapy with ticagrelor/prasugrel is associated with enhanced fibrinolysis and suppressed platelet activation as compared to clopidogrel in chronic coronary syndrome. Kardiol Pol. 2023; 81(11): 1130–1133, doi: 10.33963/v.kp.97391, indexed in Pubmed: 37718582.
42. Montalescot G, van 't Hof AW, Lapostolle F, et al. Prehospital ticagrelor in ST-segment elevation myocardial infarction. N Engl J Med. 2014; 371(11): 1016–1027, doi: 10.1056/NEJMoa1407024, indexed in Pubmed: 25175921.
43. Moore CH, Lukas JG, Cave BE, et al. Challenges of combining opioids and P2Y inhibitors in acute coronary syndrome: should the future be opioid free? Curr Probl Cardiol. 2021; 46(4): 100781, doi: 10.1016/j.cpcardiol.2020.100781, indexed in Pubmed: 33453543.
44. Ferreiro JL, Homs S, Berdejo J, et al. Clopidogrel pretreatment in primary percutaneous coronary intervention: prevalence of high on-treatment platelet reactivity and impact on preprocedural patency of the infarct-related artery. Thromb Haemost. 2013; 110(1): 110–117, doi: 10.1160/TH13-01-0057, indexed in Pubmed: 23615769.
45. Wolf D, Ley K. Immunity and inflammation in atherosclerosis. Circ Res. 2019; 124(2): 315–327, doi: 10.1161/CIRCRESAHA.118.313591, indexed in Pubmed: 30653442.
46. Foley JH, Conway EM. Cross talk pathways between coagulation and inflammation. Circ Res. 2016; 118(9): 1392–1408, doi: 10.1161/CIRCRESAHA.116.306853, indexed in Pubmed: 27126649.
47. Levi M, van der Poll T, Büller HR. Bidirectional relation between inflammation and coagulation. Circulation. 2004; 109(22): 2698–2704, doi: 10.1161/01.CIR.0000131660.51520.9A, indexed in Pubmed: 15184294.
48. Medcalf RL. Fibrinolysis, inflammation, and regulation of the plasminogen activating system. J Thromb Haemost. 2007; 5(Suppl 1): 132–142, doi: 10.1111/j.1538-7836.2007.02464.x, indexed in Pubmed: 17635719.
49. Juhan-Vague I, Pyke SD, Alessi MC, et al. Fibrinolytic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. ECAT Study Group. European Concerted Action on Thrombosis and Disabilities. Circulation. 1996; 94(9): 2057–2063, doi: 10.1161/01.cir.94.9.2057, indexed in Pubmed: 8901651.
50. Morrow GB, Whyte CS, Mutch NJ. A serpin with a finger in many PAIs: PAI-1's central function in thromboinflammation and cardiovascular disease. Front Cardiovasc Med. 2021; 8: 653655, doi: 10.3389/fcvm.2021.653655, indexed in Pubmed: 33937363.
51. Devaraj S, Xu DY, Jialal I. C-reactive protein increases plasminogen activator inhibitor-1 expression and activity in human aortic endothelial cells: implications for the metabolic syndrome and atherothrombosis. Circulation. 2003; 107(3): 398–404, doi: 10.1161/01.cir.0000052617.91920.fd, indexed in Pubmed: 12551862.
52. Singh U, Devaraj S, Jialal I. C-reactive protein decreases tissue plasminogen activator activity in human aortic endothelial cells: evidence that C-reactive protein is a procoagulant. Arterioscler Thromb Vasc Biol. 2005; 25(10): 2216–2221, doi: 10.1161/01.ATV.0000183718.62409.ea, indexed in Pubmed: 16123325.
53. Li J, Zhou Y, Zhang Y, et al. Admission homocysteine is an independent predictor of spontaneous reperfusion and early infarct-related artery patency before primary percutaneous coronary intervention in ST-segment elevation myocardial infarction. BMC Cardiovasc Disord. 2018; 18(1): 125, doi: 10.1186/s12872-018-0868-3, indexed in Pubmed: 29940881.
54. Thålin C, Hisada Y, Lundström S, et al. Neutrophil extracellular traps: villains and targets in arterial, venous, and cancer-associated thrombosis. Arterioscler Thromb Vasc Biol. 2019; 39(9): 1724–1738, doi: 10.1161/ATVBAHA.119.312463, indexed in Pubmed: 31315434.
55. Varjú I, Longstaff C, Szabó L, et al. DNA, histones and neutrophil extracellular traps exert anti-fibrinolytic effects in a plasma environment. Thromb Haemost. 2015; 113(6): 1289–1298, doi: 10.1160/TH14-08-0669, indexed in Pubmed: 25789443.
56. Longstaff C, Varjú I, Sótonyi P, et al. Mechanical stability and fibrinolytic resistance of clots containing fibrin, DNA, and histones. J Biol Chem. 2013; 288(10): 6946–6956, doi: 10.1074/jbc.M112.404301, indexed in Pubmed: 23293023.
57. Mangold A, Alias S, Scherz T, et al. Coronary neutrophil extracellular trap burden and deoxyribonuclease activity in ST-elevation acute coronary syndrome are predictors of ST-segment resolution and infarct size. Circ Res. 2015; 116(7): 1182–1192, doi: 10.1161/CIRCRESAHA.116.304944, indexed in Pubmed: 25547404.
58. Blasco A, Coronado MJ, Vela P, et al. Prognostic implications of neutrophil extracellular traps in coronary thrombi of patients with ST-elevation myocardial infarction. Thromb Haemost. 2022; 122(8): 1415–1428, doi: 10.1055/a-1709-5271, indexed in Pubmed: 34847588.
59. Dong Y, Zhang Y, Yang X, et al. Recent insights into neutrophil extracellular traps in cardiovascular diseases. J Clin Med. 2022; 11(22): 6662, doi: 10.3390/jcm11226662, indexed in Pubmed: 36431139.
60. Erqou S, Kaptoge S, Perry PL, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA. 2009; 302(4): 412–423, doi: 10.1001/jama.2009.1063, indexed in Pubmed: 19622820.

61. Cybulska B, Kłosiewicz-Latoszek L, Penson PE, et al. What do we know about the role of lipoprotein(a) in atherogenesis 57 years after its discovery? Prog Cardiovasc Dis. 2020; 63(3): 219–227, doi: 10.1016/j.pcad.2020.04.004, indexed in Pubmed: 32277995.
62. Undas A, Stepien E, Tracz W, et al. Lipoprotein(a) as a modifier of fibrin clot permeability and susceptibility to lysis. J Thromb Haemost. 2006; 4(5): 973–975, doi: 10.1111/j.1538-7836.2006.01903.x, indexed in Pubmed: 16689745.
63. Dagdelen S, Eren N, Akdemir I, et al. The effect of lipoprotein-a on thrombolytic therapy and spontaneous reperfusion in acute myocardial infarction. A comparative study. Int Angiol. 2002; 21(4): 384–389, indexed in Pubmed: 12518121.
64. Kim JW, Seo HS, Suh SY, et al. Relationship between lipoprotein(a) and spontaneous recanalization of infarct-related arteries in the early phase of acute myocardial infarction. Clin Cardiol. 2008; 31(5): 211–216, doi: 10.1002/clc.20143, indexed in Pubmed: 18473375.
65. Sankhesara DM, Lan NSR, Gilfillan P, et al. Lipoprotein(a) is associated with thrombus burden in culprit arteries of younger patients with ST-segment elevation myocardial infarction. Cardiology. 2023; 148(2): 98–102, doi: 10.1159/000529600, indexed in Pubmed: 36758526.
66. Antovic A, Perneby C, Ekman GJ, et al. Marked increase of fibrin gel permeability with very low dose ASA treatment. Thromb Res. 2005; 116(6): 509–517, doi: 10.1016/j.thromres.2005.02.007, indexed in Pubmed: 16181986.
67. Undas A, Celinska-Löwenhoff M, Löwenhoff T, et al. Statins, fenofibrate, and quinapril increase clot permeability and enhance fibrinolysis in patients with coronary artery disease. J Thromb Haemost. 2006; 4(5): 1029–1036, doi: 10.1111/j.1538-7836.2006.01882.x, indexed in Pubmed: 16689755.
68. Undas A, Topór-Madry R, Tracz W. Simvastatin increases clot permeability and susceptibility to lysis in patients with LDL cholesterol below 3.4 mmol/l. Pol Arch Med Wewn. 2009; 119(6): 354–359, indexed in Pubmed: 19694216.
69. Rajzer M, Wojciechowska W, Kawecka-Jaszcz K, et al. Plasma fibrin clot properties in arterial hypertension and their modification by antihypertensive medication. Thromb Res. 2012; 130(1): 99–103, doi: 10.1016/j.thromres.2011.08.022, indexed in Pubmed: 21917299.
70. Standeven KF, Ariëns RAS, Whitaker P, et al. The effect of dimethylbiguanide on thrombin activity, FXIII activation, fibrin polymerization, and fibrin clot formation. Diabetes. 2002; 51(1): 189–197, doi: 10.2337/diabetes.51.1.189, indexed in Pubmed: 11756340.
71. Jörneskog G, Hansson LO, Wallen NH, et al. Increased plasma fibrin gel porosity in patients with Type I diabetes during continuous subcutaneous insulin infusion. J Thromb Haemost. 2003; 1(6): 1195–1201, doi: 10.1046/j.1538-7836.2003.00301.x, indexed in Pubmed: 12871319.
72. O'Donoghue ML, Fazio S, Giugliano RP, et al. Lipoprotein(a), PCSK9 inhibition, and cardiovascular risk. Circulation. 2019; 139(12): 1483–1492, doi: 10.1161/CIRCULATIONAHA.118.037184, indexed in Pubmed: 30586750.
73. Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med. 2020; 382(16): 1507–1519, doi: 10.1056/NEJMoa1912387, indexed in Pubmed: 32187462.
74. Viney NJ, van Capelleveen JC, Geary RS, et al. Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials. Lancet. 2016; 388(10057): 2239–2253, doi: 10.1016/S0140-6736(16)31009-1, indexed in Pubmed: 27665230.
75. Koren MJ, Moriarty PM, Baum SJ, et al. Preclinical development and phase 1 trial of a novel siRNA targeting lipoprotein(a). Nat Med. 2022; 28(1): 96–103, doi: 10.1038/s41591-021-01634-w, indexed in Pubmed: 35027752.
76. Vlachojannis GJ, Wilschut JM, Vogel RF, et al. Effect of prehospital crushed prasugrel tablets in patients with ST-segment-elevation myocardial infarction planned for primary percutaneous coronary intervention: the randomized COMPARE CRUSH trial. Circulation. 2020; 142(24): 2316–2328, doi: 10.1161/CIRCULATIONAHA.120.051532, indexed in Pubmed: 33315489.
77. Labinaz M, Ho C, Banerjee S, et al. Meta-analysis of clinical efficacy and bleeding risk with intravenous glycoprotein IIb/IIIa antagonists for percutaneous coronary intervention. Can J Cardiol. 2007; 23(12): 963–970, doi: 10.1016/s0828-282x(07)70858-9, indexed in Pubmed: 17932572.
78. Baldoni D, Bruderer S, Krause A, et al. A new reversible and potent P2Y12 receptor antagonist (ACT-246475): tolerability, pharmacokinetics, and pharmacodynamics in a first-in-man trial. Clin Drug Investig. 2014; 34(11): 807–818, doi: 10.1007/s40261-014-0236-8, indexed in Pubmed: 25331625.
79. Storey RF, Gurbel PA, Ten Berg J, et al. Pharmacodynamics, pharmacokinetics, and safety of single-dose subcutaneous administration of selatogrel, a novel P2Y12 receptor antagonist, in patients with chronic coronary syndromes. Eur Heart J. 2020; 41(33): 3132–3140, doi: 10.1093/eurheartj/ehz807, indexed in Pubmed: 31994703.
80. Juif PE, Boehler M, Dobrow M, et al. Clinical pharmacology of the reversible and potent P2Y12 receptor antagonist ACT-246475 after single subcutaneous administration in healthy male subjects. J Clin Pharmacol. 2019; 59(1): 123–130, doi: 10.1002/jcph.1296, indexed in Pubmed: 30088663.
81. Ufer M, Huynh C, van Lier JJ, et al. Absorption, distribution, metabolism and excretion of the P2Y12 receptor antagonist selatogrel after subcutaneous administration in healthy subjects. Xenobiotica. 2020; 50(4): 427–434, doi: 10.1080/00498254.2019.1646440, indexed in Pubmed: 31322041.
82. Bor WL, Zheng KL, Tavenier AH, et al. Pharmacokinetics, pharmacodynamics, and tolerability of subcutaneous administration of a novel glycoprotein IIb/IIIa inhibitor, RUC-4, in patients with ST-segment elevation myocardial infarction. EuroIntervention. 2021; 17(5): e401–e410, doi: 10.4244/EIJ-D-21-00287, indexed in Pubmed: 34031019.
83. Undas A, Zabczyk M. Antithrombotic medications and their impact on fibrin clot structure and function. J Physiol Pharmacol. 2018; 69(4), doi: 10.26402/jpp.2018.4.02, indexed in Pubmed: 30415236.
84. Gauer JS, Riva N, Page EM, et al. Effect of anticoagulants on fibrin clot structure: A comparison between vitamin K antagonists and factor Xa inhibitors. Res Pract Thromb Haemost. 2020; 4(8): 1269–1281, doi: 10.1002/rth2.12443, indexed in Pubmed: 33313466.
85. Spinthakis N, Gue Y, Farag M, et al. Apixaban enhances endogenous fibrinolysis in patients with atrial fibrillation. Europace. 2019; 21(9): 1297–1306, doi: 10.1093/europace/euz176, indexed in Pubmed: 31505618.
86. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med. 2012; 366(1): 9–19, doi: 10.1056/NEJMoa1112277, indexed in Pubmed: 22077192.
87. Weitz JI, Fredenburgh JC. Factors XI and XII as targets for new anticoagulants. Front Med (Lausanne). 2017; 4: 19, doi: 10.3389/fmed.2017.00019, indexed in Pubmed: 28286749.
88. Paszek E, Malinowski KP, Ząbczyk M, et al. Elevated factor XIa as a modulator of plasma fibrin clot properties in coronary artery disease. Eur J Clin Invest. 2023; 53(9): e14007, doi: 10.1111/eci.14007, indexed in Pubmed: 37042848.
89. Tardif JC, Kouz S, Waters DD, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. N Engl J Med. 2019; 381(26): 2497–2505, doi: 10.1056/NEJMoa1912388, indexed in Pubmed: 31733140.
90. Bouabdallaoui N, Tardif JC, Waters DD, et al. Time-to-treatment initiation of colchicine and cardiovascular outcomes after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT). Eur Heart J. 2020; 41(42): 4092–4099, doi: 10.1093/eurheartj/ehaa659, indexed in Pubmed: 32860034.
91. Ridker PM, Everett BM, Thuren T, et al. CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med. 2017; 377(12): 1119–1131, doi: 10.1056/NEJMoa1707914, indexed in Pubmed: 28845751.
92. Sehested TSG, Bjerre J, Ku S, et al. Cost-effectiveness of canakinumab for prevention of recurrent cardiovascular events. JAMA Cardiol. 2019; 4(2): 128–135, doi: 10.1001/jamacardio.2018.4566, indexed in Pubmed: 30649147.
93. Hausenloy DJ, Yellon DM. Myocardial ischemia-reperfusion injury: a neglected therapeutic target. J Clin Invest. 2013; 123(1): 92–100, doi: 10.1172/JCI62874, indexed in Pubmed: 23281415.
94. Sawa Y, Ichikawa H, Kagisaki K, et al. Interleukin-6 derived from hypoxic myocytes promotes neutrophil-mediated reperfusion injury

in myocardium. J Thorac Cardiovasc Surg. 1998; 116(3): 511–517, doi: 10.1016/S0022-5223(98)70018-2, indexed in Pubmed: 9731794.
95. Gabriel AS, Martinsson A, Wretlind B, et al. IL-6 levels in acute and post myocardial infarction: their relation to CRP levels, infarction size, left ventricular systolic function, and heart failure. Eur J Intern Med. 2004; 15(8): 523–528, doi: 10.1016/j.ejim.2004.07.013, indexed in Pubmed: 15668089.
96. Broch K, Anstensrud AK, Woxholt S, et al. Randomized trial of interleukin-6 receptor inhibition in patients with acute ST-segment elevation myocardial infarction. J Am Coll Cardiol. 2021; 77(15): 1845–1855, doi: 10.1016/j.jacc.2021.02.049, indexed in Pubmed: 33858620.