Management of adjunctive antithrombotic therapy in STEMI patients treated with fibrinolysis undergoing rescue or delayed PCI

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Summary
Although primary percutaneous coronary intervention (PCI) is the recommended method of reperfusion in patients presenting with ST-segment elevation myocardial infarction (STEMI), fibrinolysis remains a beneficial alternative in patients who cannot be reperfused timely with primary PCI, and is still the preferred revascularisation strategy in many parts of the world where PCI facilities are unavailable. Because fibrinolysis is known to activate platelets and promote thrombin activity, concomitant administration of antiplatelet and anticoagulant therapies is needed to lower the risk for re-occlusion and to support mechanical interventions in patients undergoing rescue or delayed PCI. However, the addition of oral antiplatelet and parenteral anticoagulant drugs on top of fibrinolysis may come at the price of an increased risk of bleeding. The current availability of several antiplatelet and anticoagulant therapies often leads to questions about the optimal selection in STEMI patients treated with fibrinolysis. This article appraises current evidences for the management of adjunctive antiplatelet and anticoagulant therapies in patients with STEMI undergoing fibrinolysis followed by rescue or delayed PCI.

Keywords
Antiplatelet agents, antithrombin, fibrinogen / fibrin

Introduction
Practice guidelines in both the United States (US) and Europe advocate primary percutaneous coronary intervention (PCI) as the recommended method of reperfusion in patients presenting with ST-segment elevation myocardial infarction (STEMI), when expert operators can perform it in a timely fashion (1–3). However, when a STEMI patient without cardiogenic shock is seen at a non-PCI-capable hospital and transfer for primary PCI is not feasible within 120 minutes (min) from the first medical contact due to unavoidable delays, fibrinolysis remains a class I (level of evidence B) indication to be performed possibly within 30 min of hospital arrival or in the prehospital setting (2). If fibrinolysis is successful, patients should nonetheless be transferred for coronary angiography and eventually revascularised within 3–24 hours (h) (no sooner than 3 h after administration of thrombolytic therapy). In contrast, if thrombolysis proves to be unsuccessful due to re-occlusion or evidence of failed reperfusion, patients should be urgently transferred to a PCI-capable hospital for rescue PCI. In the absence of contraindications and when primary PCI is not possible, fibrinolysis also has a role (class IIa level of evidence C) when STEMI patients present within 12–24 h from symptoms onset with clinical and/or electrocardiographic evidence of ongoing ischaemia and haemodynamic instability or a large area of myocardium at jeopardy (1).

Reperfusion approaches for patients with STEMI have evolved over the past years. Definitions of different reperfusion strategies for patients with STEMI, including the use of fibrinolysis, are provided in Table 1 (4). Although prioritisation of primary PCI is the target of ongoing initiatives that are effectively increasing the number of mechanical reperusions after STEMI (5), fibrinolysis remains the reperfusion strategy in a vast proportion of STEMI patients in Europe, with large variations in practice patterns across countries (6). Because fibrinolysis is known to activate platelets and promote thrombin activity, concomitant administration of antiplatelet and anticoagulant therapies is needed to lower the risk for re-occlusion, which occurs in 5–15% of successfully recanalized arteries, and to support mechanical interventions in patients undergoing rescue or delayed PCI (7). Importantly, the addition of oral antiplatelet and parenteral anticoagulant drugs on top of fibrinolysis occurs in several STEMI scenarios and may come at the price of an increased risk of bleeding (Figure 1). The current availability of several antiplatelet and anticoagulant therapies often leads to questions about the optimal selection in STEMI patients treated with fibrinolysis. On this background, this article reviews the current evidence for the management of adjunctive antiplatelet and anticoagulant therapies in patients with STEMI undergoing fibrinolysis followed by rescue or delayed PCI.

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Fibrinolytic drugs

Details of the currently available thrombolytic agents, including 90-min patency rates after administration, are given in ▶Table 2 (8–12). Streptokinase is a protein secreted by several species of streptococci that can bind and activate human plasminogen, with no fibrin specificity and a half-life of 23–29 min (13). In contrast, newer fibrin-specific fibrinolytic agents, including tenecteplase, reteplase and alteplase, are recombinant tissue plasminogen activators that directly bind to fibrin and selectively promote conversion of thrombus-bound plasminogen to plasm. Among these latter, tenecteplase owns the highest fibrin specificity and has the longest half-life (20 min vs 15 and 4–8 min of reteplase and alteplase, respectively) (13). Importantly, the effect on coagulation after intravenous administration of lytics may persist for hours after discontinuation due to a decrease in plasma level of fibrinogen paralleled by an increase in the amount of circulating fibrin degradation products. The next sections discuss the use of fibrinolytic drugs in the setting of facilitated PCI and pharmacoinvasive strategies.

Facilitated PCI vs primary PCI

Using lytics to restore a Thrombolysis in Myocardial Infarction (TIMI) flow 3 before angioplasty in STEMI patients with long delays to primary PCI seems an intuitively beneficial approach to
broaden the window of opportunity in which effective mechanical reperfusion may be achieved. Upstream administration of glycoprotein IIb/IIIa inhibitors (GPI) has also been advocated as a potentially effective therapy in this setting, and remains a class IIb recommendation in selected patients undergoing transfer for primary PCI in current European guidelines for myocardial revascularisation (14). Notably, the 2011 US guidelines for PCI assigned a class III recommendation for precatheterisation laboratory administration of GPI as part of an upstream strategy for STEMI patients undergoing PCI (1). Conversely, the 2013 STEMI US guidelines upgraded this recommendation to IIb, warning that GPI “should be used with great caution, if at all, after full-dose fibrinolytic therapy, given the high rates of bleeding and intracranial haemorrhage, particularly in the elderly” (15).

Early phase clinical investigations evaluating surrogate markers (e.g. TIMI flow) initially supported the rationale for facilitated strategies in the setting of PCI for STEMI (16, 17). However, establishment of TIMI 3 flow with lytics or GPI does not necessarily correspond to optimal myocardial reperfusion, and it may come at the expenses of bleeding, which make clinical investigations mandatory to fully appreciate the net benefit of pharmacological reperfusion strategies before primary PCI (18). With this background, the concept of facilitated PCI has been hampered primarily by two large randomised phase III clinical trials. In the Assessment of the Safety and Efficacy of a New Treatment Strategy With Percutaneous Coronary Intervention (ASSENT-4 PCI) trial, STEMI patients (N=1,667) were randomised 1–3 h before catheterisation to facilitated PCI with full-dose tenecteplase or primary PCI alone on top of antithrombotic co-therapy with aspirin 150–325-mg, clopidogrel 300-mg if a stent was deployed, and a single intravenous bolus of unfractionated heparin (UFH) (19). The trial, originally intended to enroll 4,000 patients, was prematurely interrupted due to the observed increased rate of major adverse events in the investigational arm, including death or heart failure (primary endpoint) and intracranial haemorrhages. Surprisingly, ischaemic events not attributed to bleeding (i.e. reinfarction and target vessel revascularisation) were also increased in the facilitated PCI arm, a finding that can be partly explained by the relatively low use of thienopyridines (63 %) and GPI (10 %) in patients who received tenecteplase. In addition, patients who are more likely to benefit by a facilitated approach (i.e. those presenting early after the onset of symptoms but with long expected delays to primary PCI) were largely under-represented in the ASSENT-4 PCI trial (17).

In the Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events (FINESSE) trial, STEMI patients (N=2,452) with anticipated time delay ranging from 1-4 h to catheterisation were randomised to facilitated PCI with abciximab, facilitated PCI with half-dose reteplase plus abciximab and primary PCI with abciximab administered at the time of PCI (20). The trial was interrupted at 82 % of the originally estimated enrollment due to financial constraints and slow recruitment. Differently from patients randomised to facilitated PCI in the ASSENT-4 PCI trial, those corresponding in the FINESSE trial received adequate platelet inhibition with abciximab in all the three groups, but the study failed to show any difference in the primary 90-day composite endpoint of all-cause mortality, readmission for heart failure, ventricular fibrillation or cardiogenic shock, while TIMI non-intracranial major bleedings were significantly increased in patients who received facilitated PCI with abciximab and half-dose reteplase as compared with those undergoing standard primary PCI. At one-year, there was no difference in mortality among the three groups, despite a favourable trend (p=0.09) with combination lytic/abciximab treatment versus primary PCI was observed in patients presenting with anterior STEMI (21). In view of the above, guidelines do not currently support the practice of facilitated PCI over rapid transfer for primary PCI (1, 2).
Pharmacoinvasive strategy vs fibrinolysis

Although subtle, the difference between “pharmacoinvasive strategy” and “facilitated PCI” must be emphasised. In facilitated PCI, the decision to perform PCI is already taken before fibrinolysis, while in a pharmacoinvasive strategy PCI represents just an invasive backup, with patients routinely transferred to PCI-capable centres for rescue PCI in case of failed fibrinolysis or nonurgent coronary angiography to establish the need for additional revascularisation of the culprit lesion (22). Differently from facilitated PCI, the benefit of a pharmacoinvasive strategy has been validated versus fibrinolysis in several clinical trials, in particular the Combined Abciximab Re-teplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI) and Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI) trials (23, 24).

In CARESS-in-AMI, STEMI patients (N=600) received a combination of half-dose reteplase and abciximab on top of aspirin and heparin at a non PCI-capable hospital and were randomly assigned to immediate transfer to the nearest interventional centre for PCI or to standard management in the local hospital with transfer only in case of clinically indicated rescue PCI (21). In the pharmacoinvasive strategy arm, 97% of patients underwent coronary angiography and 86% were treated with PCI (vs 30% in the standard care/rescue PCI group). The primary outcome, a composite of death, reinfarction or refractory ischaemia at 30 days, was significantly reduced by 60% in patients who were immediately transferred for PCI, and there were no differences in major bleeding and strokes between the two groups.

In the TRANSFER-AMI trial, STEMI patients (N=1,059) were treated with tenecteplase on top of aspirin and UFH/enoxaparin at non-PCI centres and subsequently randomised to immediate transfer to another hospital and PCI (with the goal of performing coronary angiography and PCI of the infarct-related artery within 6 h after fibrinolysis) or standard treatment, including clinically indicated rescue PCI (22). Similarly to the CARESS-in-AMI trial, the primary endpoint, a composite of death, reinfarction, recurrent ischaemia, new or worsening congestive heart failure, or cardiogenic shock within 30 days, occurred less frequently in the pharmacoinvasive arm, with a relative risk reduction of 36%, and there were no significant differences between the groups in the incidence of major bleeding. In view of the above, the pharmacoinvasive strategy is currently recommended by the US and European guidelines as compared to fibrinolysis alone (1, 2).

Pharmacoinvasive strategy vs primary PCI

A recent trial supported the use of a pharmacoinvasive strategy as an alternative to primary PCI in selected patients who are treated with fibrinolysis and are only given urgent PCI on arrival at the hospital if the ECG shows they had not reperfused. In the STRategic Reperfusion Early After Myocardial Infarction (STREAM) trial, STEMI patients (N=1,892) presenting within 3 h after the onset of symptoms who were unable to undergo primary PCI within 1 h were randomised to fibrinolysis with tenecteplase and transport to a PCI-capable hospital coupled with timely coronary angiography, or primary PCI (25) In the fibrinolysis group, urgent angiography was performed in approximately one third of the patients, while angiography within 24 h followed by additional revascularisation was performed in the remainder of the patients under nonurgent circumstances. This avoided the situation of doing PCI with fibrinolysis on board (which has been associated with adverse outcomes in the ASSENT-4 and FINESSE trials) in the majority of patients. The primary composite endpoint of death, shock, congestive heart failure, or reinfarction at 30 days was similar between the two groups. There was a significant increase in intracranial haemorrhage in the fibrinolysis group, which led to the dose of tenecteplase being halved in elderly patients relatively early on in the course of the trial, after which the intracranial haemorrhage rate in the fibrinolysis group was not significantly different from the PCI group. One-year results from the STREAM trial have recently confirmed that a pharmacoinvasive strategy of pre-hospital fibrinolysis with timely coronary angiography results in similar mortality after STEMI compared with standard primary PCI (26).
findings generally support the guideline recommendations about the 120-min window for transfer PCI, but in those systems where timely primary PCI is not possible, a pharmaco-invasive therapy for STEMI as part of a carefully dose-adjusted algorithm may be a valuable option.

Rationale for administration of concomitant antithrombotic therapies on top of thrombolysis

Fibrinolysis has been advocated to promote a prothrombotic environment, which might be responsible for ischaemic complications when primary PCI is performed (27). Thrombolytic therapy is well known to promote thrombin activity and activate platelets (28, 29). Platelet activation after lytics application may reflect a direct mechanism mediated by plasmin or independent mechanisms by exposed subendothelial collagen at the site of the coronary lesion or by procoagulant systems on the clot surface (i.e. fibrin-bound thrombin) (Figure 2) (30, 31). The activation of the haemostatic system is considered to play a pivotal role in preventing or impairing fibrinolysis-induced reperfusion and in producing early re-occlusion, which underscores the need for combining lytic therapy with adjunctive antithrombotic drugs. Indeed, some degree of transient activation of coagulation still occurs in response to thrombolytic therapy despite heparin administration, because heparin mostly acts on circulating thrombin, while being less effective on clot-bound thrombin (32, 33). Importantly, the primary component of thrombus in STEMI is fibrin, which becomes more pronounced over time and may be more exposed after lysis (34). These issues could partly explain why facilitated PCI has been associated with a detrimental net clinical effect. In the ASSENT-4 PCI trial, compared with patients undergoing primary PCI, patients who underwent facilitated PCI showed more patency in the infarct-related artery at the first angiogram (73.7% vs 33.4%, p < 0.001) but higher thrombus burden (19.7% vs 13.4%, p = 0.002), defined as residual TIMI thrombus grade ≥2 and/or distal embolisation and/or slow flow (35). The presence of residual thrombus was associated with impaired tissue reperfusion and a significantly worse outcome at 90 days, particularly in patients who underwent facilitated PCI. Notably, as mentioned above, a thrombus resistant to fibrinolysis is highly organised and richer in fibrin due to the longer time interval from symptom onset to first balloon inflation, thereby being more likely to cause distal obstruction after subsequent mechanical fragmentation during PCI (36). Because these findings from the ASSENT-4 PCI trial were observed in the context of suboptimal pharmacotherapy, the importance of best-practice administration of adjuvant antithrombotic drugs in patients undergoing rescue or delayed PCI is reinforced.

Concerns for administration of concomitant antithrombotic therapies of top of thrombolysis

Bleeding complications, in particular intracranial haemorrhage, represent the major concern with fibrinolytic therapy. This is even more worrisome in patients who receive combined antiplatelet agents on top of thrombolysis and those with independent factors of intracranial haemorrhage with fibrinolytic therapy (e.g. low weight, high blood pressure, prior stroke) (37). Therefore, adding antiplatelet and anticoagulant therapies on top of thrombolysis requires preliminary assessment of the individual risk of ischaemia and bleeding, as well as careful drug selection in view of the available evidences. The following sections will discuss the evidence base for the use of different antiplatelet and anticoagulant therapies for patients undergoing rescue or delayed PCI.

Antiplatelet therapies for rescue or delayed PCI

Guidelines recommend the administration of aspirin and clopidogrel in patients with STEMI who receive fibrinolytic therapy (Table 3 and Table 4) (1). These agents should be given before or with the fibrinolytic agent. US guidelines (1) suggest aspirin to be given at the loading dose of 162-325 mg, followed by a low daily dose (i.e. 81 mg) aspirin indefinitely thereafter. European Society of Cardiology (ESC) guidelines (2) recommend oral aspirin with a starting dose 150–500 mg orally, or i.v. aspirin 250 mg if oral ingestion is not possible.

Based on US guidelines (1), clopidogrel should be administered with a 300-mg loading dose only in patients below 75 years, and then maintained for at least 14 days and up to one year at the dose of 75 mg daily; in patients ≥75 years, clopidogrel should be started at the 75 mg daily dose without a loading dose. For patients undergoing PCI within 24 h of fibrinolysis, a 300-mg loading dose of clopidogrel should be given to patients who did not receive a previous loading dose, while a 600-mg loading dose should be preferred for patients undergoing PCI more than 24 h from fibrinolysis. Also for patients undergoing PCI, prasugrel (60-mg loading dose, followed by 10-mg daily) may be considered as an alternative to clopidogrel in patients without a history of prior stroke or transient ischaemic attack who did not receive a previous loading dose of clopidogrel at the time of fibrinolysis, but only if the coronary anatomy is known and no sooner than 24 h from administration of a fibrin-specific agent or 48 h from administration of a non-fibrin-specific agent (Table 3). ESC guidelines (2) simply recommend administering a 300 mg loading dose of clopidogrel in patients aged ≤75 years, followed by a maintenance dose of 75 mg/day (Table 4), whereas the use of prasugrel is not recommended. Ticagrelor has currently no recommendation in patients who have undergone prior thrombolysis both in the US and ESC guidelines (1, 2), but several investigations are ongoing to assess its role (NCT01950416; NCT02048085) (1).

Aspirin

The benefit of adding aspirin to thrombolysis is known since the landmark International Study of Infarct Survival 2 (ISIS-2) study, in which 17,187 patients were randomised to streptokinase, aspirin, both, or neither (38). Streptokinase and aspirin resulted the most effective treatment strategies in reducing mortality, with an
Table 3: ACC/AHA Guidelines recommendations for the management of antithrombotic therapy in STEMI patients undergoing fibrinolysis with or without rescue or delayed PCI.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fibrinolysis</th>
<th>Rescue or Delayed PCI</th>
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<td><strong>Antiplaletet therapies</strong></td>
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| Aspirin               | • Aspirin (162– to 325-mg loading dose) should be administered to patients with STEMI who receive fibrinolytic therapy (Class I, LOE A).<sup>1</sup>  
  • Aspirin should be continued indefinitely (Class I, LOE A).  
  • It is reasonable to use aspirin 81 mg per day in preference to higher maintenance doses after fibrinolytic therapy (Class IIa LOE B).<sup>2</sup> | • After PCI, aspirin should be continued indefinitely (Class I, LOE A).  
  • After PCI, it is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses (Class IIa LOE B).<sup>2</sup> |
| Clopidogrel           | • Clopidogrel (300-mg loading dose for patients <75 years of age, 75-mg dose for patients >75 years of age) should be administered to patients with STEMI who receive fibrinolytic therapy (Class I LOE A).  
  • Clopidogrel (75 mg daily) should be continued for at least 14 days (Class I, LOE A) and up to 1 year (Class I, LOE C) in patients with STEMI who receive fibrinolytic therapy. | • A 300-mg loading dose of clopidogrel should be given before or at the time of PCI to patients who did not receive a previous loading dose and who are undergoing PCI within 24 hours of receiving fibrinolytic therapy (Class I, LOE C).  
  • A 600-mg loading dose of clopidogrel should be given before or at the time of PCI to patients who did not receive a previous loading dose and who are undergoing PCI more than 24 hours after receiving fibrinolytic therapy (Class I, LOE C).  
  • A dose of 75 mg daily of clopidogrel should be given after PCI (Class I, LOE C). |
| Prasugrel             | • Not recommended (no data available).                                       | • Prasugrel, in a 60-mg loading dose, is reasonable once the coronary anatomy is known in patients who did not receive a previous loading dose of clopidogrel at the time of administration of a fibrinolytic agent, but prasugrel should not be given sooner than 24 hours after administration of a fibrin-specific agent or 48 hours after administration of a non–fibrin-specific agent (Class Ia LOE B).  
  • Prasugrel, in a 10-mg daily maintenance dose, is reasonable after PCI (Class Ia LOE B).  
  • Prasugrel should not be administered to patients with a history of prior stroke or transient ischaemic attack (class III LOE B). |
| Ticagrelor            | • Not recommended (no data available).                                       | • Not recommended (no data available).                                               |
| GP IIb/Ill receptor antagonists | • Not recommended.                                                        | • Not recommended.                                                                   |
| **Anticoagulant therapies** |                                                                              |                                                                                       |
| UFH                   | • UFH administered as a weight-adjusted intravenous bolus and infusion to obtain an activated partial thromboplastin time of 1.5 to 2.0 times control, for 48 hours or until revascularisation (Class I, LOE C).<sup>3</sup> | • For patients with STEMI undergoing PCI after receiving fibrinolytic therapy with intravenous UFH, additional boluses of intravenous UFH should be administered as needed to support the procedure, taking into account whether GP IIb/Ill receptor antagonists have been administered (Class I, LOE C). |
| LMWH                  | • Enoxaparin administered according to age, weight, and creatinine clearance, given as an intravenous bolus, followed in 15 minutes by subcutaneous injection for the duration of the index hospitalisation, up to 8 days or until revascularisation (Class I, LOE A).<sup>4</sup> | • For patients with STEMI undergoing PCI after receiving fibrinolytic therapy with enoxaparin, if the last subcutaneous dose was administered within the prior 8 hours, no additional enoxaparin should be given; if the last subcutaneous dose was administered between 8 and 12 hours earlier, enoxaparin 0.3 mg/kg IV should be given (Class I, LOE B). |
| Fondaparinux          | • Fondaparinux administered with initial intravenous dose, followed in 24 hours by daily subcutaneous injections if the estimated creatinine clearance is greater than 30 ml/min, for the duration of the index hospitalisation, up to 8 days or until revascularisation (Class I, LOE B).<sup>5</sup> | • Fondaparinux should not be used as the sole anticoagulant to support PCI. An additional anticoagulant with anti-II activity should be administered because of the risk of catheter thrombosis (Class III, LOE C). |
| Bivalirudin           | • Not recommended.                                                          | • Not recommended (no data available).                                               |

Abbreviations: GP = Glycoprotein; LOE = Level Of Evidence; PCI = Percutaneous Coronary Intervention; UFH = Unfractionated Heparin. Reproduced and adapted from O’Gara et al. (1).
additive effect in the combination group. Reinfarction was higher with streptokinase alone, unless aspirin was added in combination. Early initiation of aspirin before or at the time of thrombolysis should be preferred over late initiation, according to a relatively small observational study (39).

P2Y₁₂ inhibitors

Evidence for the efficacy of clopidogrel over aspirin in patients receiving fibrinolytic therapy for STEMI arises from the Clopidogrel as Adjunctive Reperfusion Therapy – Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI 28) trial, a study of 3,491 patients who received a fibrinolytic agent, aspirin, and heparin dispensed according to body weight and were scheduled to undergo angiography 48-192 h after the start of study medication (clopidogrel or placebo) (40). The rates of the primary efficacy endpoint, a composite of an occluded infarct-related artery (i.e. TIMI flow 0 or 1) on angiography or death or recurrent MI before angiography, was 15% in the clopidogrel group and 21.7% in the placebo group (p<0.001). At 30 days, clopidogrel reduced by 20% the composite endpoint of death from cardiovascular causes, recurrent MI, or recurrent ischaemia leading to the need for urgent revascularisation. Importantly, clopidogrel appeared to prevent re-occlusion rather than facilitating reperfusion (41). There were no differences in the incidence of major bleeding and intracranial haemorrhage between the two groups (40). It should be noted that patients >75 years were not included in the CLARITY-TIMI 28 trial, which makes uncertain the role of dual antiplatelet therapy with aspirin and clopidogrel (loaded with a 300-mg dose) in the elderly population treated with lytic therapy (37). In patients undergoing PCI (about half of the CLARITY-TIMI 28 population at 2-8 days from fibrinolysis), clopidogrel consistently improved the outcomes regardless of the duration of pretreatment or the use of additional GPI (42). This latter finding suggests that when clopidogrel is initiated early at the time of fibrinolysis, this could prevent the need for additional GPI if rescue PCI is necessary.

Limitations of clopidogrel include its broad variability in platelet inhibition, with low response in 5–40% of patients due to genetic, cellular, and clinical mechanisms (43). The link between poor responsiveness to clopidogrel and adverse ischaemic outcomes is well established (44). Prasugrel and ticagrelor exert more potent platelet inhibition compared with clopidogrel, but despite clear benefits demonstrated in phase III clinical testing they are still underused worldwide in clinical practice (45, 46). With this background, the net benefit of prasugrel or ticagrelor use in STEMI patients undergoing thrombolysis is uncertain and warrants specific investigations. In the TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with
Prasugrel–Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) of prasugrel vs clopidogrel for moderate to high risk patients with acute coronary syndromes intended for an invasive strategy, a subset of patients with STEMI received fibrinolytic therapy <24 h (for fibrin-specific agents) or <48 h (for non–fibrin-specific agents) before PCI (47, 48). In this cohort of STEMI patients, prasugrel significantly reduced by 35% the primary composite endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke, and was not associated with any significant increased risk of non-coronary artery bypass related TIMI major bleeding compared with clopidogrel (48). Fibrinolytic therapy within 24 h before randomisation was an exclusion criterion for enrollment in the Study of Platelet Inhibition and Patient Outcomes (PLATO) trial of ticagrelor, which is therefore currently not recommended in combination with aspirin and thrombolysis (49).

**Glycoprotein IIb/IIIa inhibitors**

Immediate platelet inhibition with intravenous administration of GPI has been advocated as a potential strategy to overcome some of the pitfalls of thrombolysis (50, 51). However, although effective in improving the patency rates, this benefit of this strategy is offset by the increased risk of major bleeding complications when GPI are used in combination with either a full- or reduced-dose thrombolysis, especially in patients undergoing early PCI and in the elderly (20, 52–58).

**Anticoagulant therapies for rescue or delayed PCI**

Based on guidelines, STEMI patients undergoing fibrinolysis should be given anticoagulant drugs for a minimum of 48 h and preferably for the duration of hospital stay, up to eight days or until revascularisation is performed (Table 3) (1). Recommended regimens include UFH (level of evidence C), enoxaparin (level of evidence A), and fondaparinux (level of evidence B). For patients who have received UFH or enoxaparin with fibrinolytic therapy, these agents may be continued uninterrupted through the PCI procedure. In contrast, fondaparinux should not be used as the only anticoagulant in patients referred for PCI, due to the enhanced risk of catheter thrombosis. Switching from enoxaparin to either UFH or bivalirudin is allowed, if the last enoxaparin dose was given at least 12 h before PCI, as well as switching from UFH to bivalirudin.

**Unfractionated heparin (UFH)**

UFH previously represented the standard anticoagulant therapy administered with fibrinolysis since The Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries I (GUSTO-I) trial (59). Although intravenous UFH does not increase per se the early patency rates of the infarct-related artery, it was found to increase the patency after administration of alteplase at later time-points already in the early nineties, by reducing the rate of re-occlusion (60, 61). However, the effectiveness of UFH is rather unpredictable due to its variable clearance and binding to cells and protein. In addition, UFH does not reduce thrombin generation associated with fibrinolysis and is relatively unable to inhibit clot-associated thrombin and factor X, which may result in rebound activation of the coagulation cascade upon cessation of the intravenous infusion (62).

**Enoxaparin**

Enoxaparin holds several advantages over UFH, including greater bioavailability after subcutaneous injection, increased anti-factor X activity, more efficient inhibition of thrombin generation and a more predictable anticoagulant response that does not mandate aPTT monitoring.

The relative efficacy and safety of enoxaparin versus UFH in the context of a contemporary pharmacoinvasive approach has been recently the object of a sub-analysis of the TRANSFER-AMI trial (63). At the time of fibrinolysis, enoxaparin and UFH were administered to 498 and 448 patients, respectively, and about half of patients in each group were randomised to the early invasive strategy. The primary endpoint was observed similarly in 11.9% of the patients who received enoxaparin and 11.6% of those who received UFH (adjusted odds ratio 0.95, 95% confidence interval 0.60–1.51, p=0.84).

However, the use of enoxaparin was associated with more access site-related (5.0% vs 2.9%, p=0.04) and mild bleeding (12.1% vs 7.8%, p=0.03). Of note, enoxaparin was associated with better outcomes compared with UFH when only one anticoagulant was used during the initial hospital stay, while mild bleedings were increased when transitioning from enoxaparin to UFH (63). This replicates similar findings from non-STEMI patients enrolled in the Superior Yield of the New Strategy of Enoxaparin, Revascularisation and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial, overall suggesting that crossover of UFH and enoxaparin should be avoided (64).

**Fondaparinux**

Similarly to enoxaparin, fondaparinux may be administered subcutaneously and does not require aPTT monitoring. In contrast to UFH and enoxaparin, fondaparinux does not bind to platelet factor 4 thereby reducing the risk of platelet activation and heparin-induced thrombocytopenia (HIT). In the Organisation for the Assessment of Strategies for Ischaemic Syndromes 6 (OASIS-6) trial, fondaparinux was compared to UFH or placebo in 12,092 patients with STEMI, mostly undergoing thrombolysis with streptokinase (65). Fondaparinux was associated with a significant 21% lower risk of death or MI at 30 days when compared with control, with no increase in bleeding and strokes. The primary efficacy outcome was driven by a significant reduction with fondaparinux vs placebo, whereas there was no difference in the comparison vs UFH. Importantly, among patients undergoing primary PCI in the OASIS-6 trial, guiding catheter thrombosis and coronary complications occurred more often with fondaparinux compared with control, especially in patients not using concurrent UFH, which led to the current class III recommendations for the use of fondaparinux as the sole anticoagulant to support PCI in STEMI (65).
Bivalirudin

Bivalirudin, a direct thrombin inhibitor with quick onset of action and short half-life, overcomes many of the limitations of heparins (66) First, differently to UFH, it does not bind to cells or plasma proteins other than thrombin, resulting in a predictable anticoagulant response. Second, it inhibits both circulating and clot-bound thrombin, and it contrasts thrombin-mediated platelet activation and aggregation. Finally, similarly to fondaparinux, it does not increase the risk of HIT. Inadequately inhibited thrombin at the site of the thrombus may be partly responsible for the pro-coagulant effect of fibrinolysis despite the use of

![Diagram](image_url)

**Figure 3: Practical algorithm for choice of antiplatelet agents in thrombolysed patients based on US and European Guidelines.** * it is reasonable to switch to prasugrel or ticagrelor in the chronic phase given their superior long-term benefits over clopidogrel.
heparin, hence the rationale for the use of bivalirudin in the setting of rescue or delayed PCI.

However, there are no adequately powered trials that demonstrate the clinical efficacy and safety of bivalirudin in this setting, while some encouraging data are available on the use of bivalirudin in combination with fibrinolysis as the only reperfusion strategy. In the Hirulog Early Reperfusion/Occlusion (HERO) trial, 412 STEMI patients were given aspirin and streptokinase and randomized to UFH, low-dose bivalirudin or high-dose bivalirudin (67). The primary endpoint of TIMI grade 3 flow of the infarct-related artery at 90–120 min was 35% with heparin, 46% with low dose bivalirudin and 48% with high-dose bivalirudin (p=0.023 for UFH vs bivalirudin; p=0.03 for UFH vs high-dose bivalirudin). Also, bivalirudin resulted in a significant reduction in major bleeding (40% access-related) and there were no differences among the three regimens in the rates of re-occlusion at 48 h and in the rates of death, cardiogenic shock or reinfarction at 35 days. In the subsequent, larger HERO-2 trial, 17,073 STEMI patients undergoing fibrinolysis with streptokinase were randomised to an intravenous bolus and 48-h infusion of either bivalirudin or UFH (68). Mortality at 30 days (primary endpoint) occurred in 10.8% of patients in the bivalirudin group and 10.9% of patients in the UFH group (p=0.85). Patients treated with bivalirudin had significantly fewer re-infarctions within 96 h, suggesting that early and more efficient inhibition of thrombin may counteract re-occlusion. Despite numerically less severe bleeding and intracranial haemorrhages with bivalirudin, small absolute increases were seen in mild and moderate bleeding.

Notably, signals of increased acute stent thrombosis have emerged in STEMI trials of bivalirudin vs heparin with or without GPI (69). The totality of the evidence in STEMI, however, suggests that bivalirudin still exert a certain degree of bleeding protection compared with heparin (regardless of GPI use) in patients undergoing primary PCI (70). Also, the acute risk of stent thrombosis might be mitigated by prolonged infusion (i.e. up to 4 h following PCI) at the PCI dosing regimen (71).

![Figure 4: Practical algorithm for choice of parenteral anticoagulants agents in thrombolysed patients based on US and European Guidelines.](/image)

* according to age, weight, and creatinine clearance. ** bivalirudin may represent a valuable alternative to heparins because of being very specific for thrombin, which is increased in this setting, as well as its established safety (i.e. low bleeding risk) profile.
Recommendations for clinical practice

Fibrinolytic therapy is beneficial in STEMI patients who cannot be reperfused timely with primary PCI, and is still the preferred revascularisation strategy in many parts of the world where PCI facilities are unavailable. However, after fibrinolysis, a strategy of rapid transfer to a PCI facility for rescue PCI in case of failure, or early invasive management with coronary angiography within 3–24 h is recommended by current clinical practice guidelines. Although stacked antithrombotic therapy with antiplatelet and anticoagulant drugs on top of fibrinolysis is required to maintain vessel patency, particularly among those undergoing PCI, this also increases the risk of bleeding complications. Therefore, strategies to minimize the risk of haemorrhagic complications are warranted in this high-risk cohort of patients. The reduced risk of bleeding complications associated with radial approach in general, makes preference towards this access route reasonable in patients treated with fibrinolysis undergoing rescue or delayed PCI (72). In line with practice guidelines, the adjuvant antiplatelet drugs of choice should be aspirin and clopidogrel, whereas routine administration of GPI should be avoided. Although not contraindicated, the use of the novel P2Y12 receptor inhibitors (prasugrel and ticagrelor) is generally not recommended in the early phase (24–48 h) after lytic therapy, although it is reasonable to switch to these agents after this time frame given their superior long-term benefits over clopidogrel. Ongoing studies will provide more insights on the safety of use novel P2Y12 receptor inhibitors in combination with lytics. Anticoagulant choices include UFH, enoxaparin, bivalirudin and fondaparinux, the latter in combination with UFH in case of PCI. Crossover with UFH and low-molecular-weight heparin is not recommended. Although there are no data deriving from large-scale experience, bivalirudin may represent a valuable alternative to heparins in patients undergoing PCI following treatment with fibrinolysis because of being very specific for thrombin, which is increased in this setting, as well as its established safety (i.e. low bleeding risk) profile. Pragmatic frameworks for the management of antithrombotic therapy in patients who have received thrombolysis are provided in ▶Figure 3 and ▶Figure 4.

Conclusions

Safety with antithrombotic therapy is a major concern in patients who have received fibrinolytic therapy, especially in patients at high risk for bleeding. As such, understanding strategies of antithrombotic management in patients undergoing rescue or delayed PCI is of paramount importance. The lack of studies performed specifically in patients who receive some of the currently available antithrombotic drugs, particularly prasugrel, ticagrelor and bivalirudin, lead to either no recommendation or sometimes-arbitrary assumptions. Overall, the choice and combination of antithrombotic therapies in this setting should be tailored to the individual risk of bleeding and low thrombotic risk.

Conflicts of interest

Dr. Davide Capodanno has received payments as an individual for consulting fee or honorarium from Eli Lilly, Daiichi Sankyo, The Medicines Company, AstraZeneca and Bayer. Dr. Dominick J. Angiolillo has received payments as an individual for: a) Consulting fee or honorarium from Bristol Myers Squibb, Sanofi-Aventis, Eli Lilly, Daiichi Sankyo, The Medicines Company, AstraZeneca, Merck, Abbott Vascular and PLx Pharma; b) Participation in review activities from CeloNova, Johnson & Johnson, St. Jude, and Sunovion. Institutional payments for grants from Bristol Myers Squibb, Sanofi-Aventis, Glaxo Smith Kline, Eli Lilly, Daiichi Sankyo, The Medicines Company, AstraZeneca, Gilead.

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