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Antithrombin treatment strategies for patients with ST-elevation myocardial infarction

Summary

Appropriate antithrombotic therapy in patients with ST-elevation myocardial infarction (STEMI) helps reducing major cardiovascular events and bleeding complications. The majority of patients presenting with STEMI in Switzerland are referred for early reperfusion therapy. Primary percutaneous coronary intervention (PCI) has become the preferred reperfusion strategy and replaced the use of fibrinolysis in many hospitals. Optimal antithrombotic treatment is particularly important during mechanical intervention at the thrombotic coronary occlusion site due to activation of platelets and the clotting cascade.

The combination of aspirin, clopidogrel, and glycoprotein IIb/IIIa inhibitors is recommended for STEMI patients undergoing primary PCI. Unfractionated heparin has been used for many years as antithrombin of choice in these patients; it is usually started at the time of presentation and is continued during PCI. The direct thrombin inhibitor bivalirudin has emerged as promising antithrombotic agent for primary PCI, and a bivalirudin alone strategy without GP IIb/IIIa inhibitor may be especially useful for elderly patients or those with increased risk of bleeding. Antithrombotic treatment regimens for STEMI patients managed conservatively or with fibrinolysis differ from those undergoing primary PCI. Extended-duration therapy with either enoxaparin or fondaparinux for up to 8 days has emerged as antithrombotic regimen of choice for patients not undergoing primary PCI.

This article intends to serve as a practical guide to interventional cardiologists and other interested physicians managing patients with STEMI. Current options of anticoagulant drug regimens are summarized from a practical point of view, with special attention to the primary management strategy.

Key words: myocardial infarction; anticoagulation

Conflict of interest:
Dr. Kucher received a honorarium from Sanofi-Aventis for participating at the Expert Consensus Meeting on antithrombotic treatment in patients with ST-elevation myocardial infarction, held on March 11th, 2007, in Berne, Switzerland.

Introduction

The clinical outcome of patients with ST-elevation myocardial infarction (STEMI) has dramatically improved since the introduction of fibrinolysis and primary percutaneous coronary intervention (PCI). Although fibrinolysis is still the most common method of reperfusion worldwide, rapid transfer to a cardiac catheterisation laboratory with primary PCI has evolved as the preferred reperfusion therapy in Switzerland. Well-balanced antithrombotic therapy is especially important for a successful and stable recanalisation of the thrombotic coronary occlusion site without an increase in severe bleeding complications.

International consensus guidelines on antithrombotic treatment in the STEMI setting are updated on a regular basis [1, 2], and provide rather general than practical recommendations for the various antithrombotic treatment regimens. The authors have reviewed the available evidence of antithrombin treatment regimens during an expert consensus conference (see acknowledgement). In accordance with a recently published article on the antithrombotic management of patients with Non-ST elevation myocardial infarction [3], this article provides practical dose schemes of various antithrombic treatment strategies in STEMI patients with special attention to the primary management strategy: primary PCI, fibrinolysis or conservative management without reperfusion.

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Unfractionated heparin

Primary PCI

Unfractionated heparin (UFH) is the most commonly used antithrombin agent in STEMI patients referred for primary PCI. Advantages of UFH include its long history of use, low cost, and rapid reversibility by protamin in case of bleeding complications. UFH is immunogenic by binding to platelet factor 4 with the risk of heparin-induced thrombocytopenia. Because of its inconsistent effect in individual patients, UFH requires close anticoagulant monitoring. UFH is administered upstream prior to coronary angiography as intravenous bolus and a continuous infusion (fig. 1). In most patients, additional UFH is administered during primary PCI according to the activated clotting time (ACT) obtained during coronary angiography.

Primary PCI with UFH usually requires combination with GP IIb/IIIa inhibitors. Dose regimens for the GP IIb/IIIa inhibitors tirofiban, eptifibatide and abciximab are given on the table 1. Note that tirofiban requires dose-halving with a creatinin clearance of less than 30 ml per minute, while abciximab does not need dose adjustment with renal insufficiency.

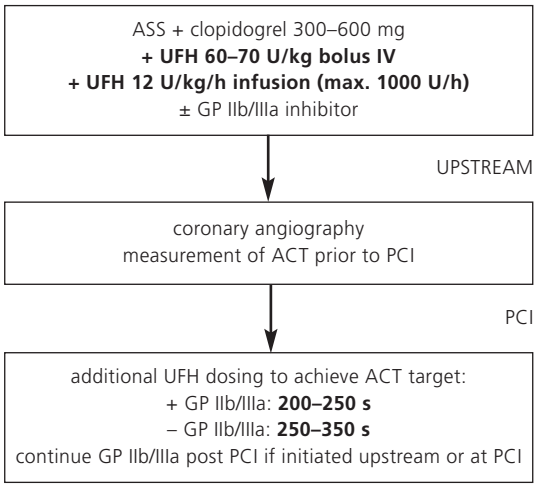

Figure 1
The classical antithrombotic strategy using unfractionated heparin for STEMI patients undergoing primary PCI. At presentation, acetylsalicylic acid is administered at a dose of 500 mg (per os, or IV) and clopidogrel at a dose of 300 mg or 600 mg. Intravenous UFH is given as bolus and infusion. The UFH dose during PCI will be adjusted according to the ACT target. Note that the ACT target depends on the use of glycoprotein IIb/IIIa inhibitors.

Fibrinolysis or conservative management

In STEMI patients, thrombin activity is enhanced and plays a key role in promoting thrombus formation. Paradoxically, fibrinolysis further worsens the prothrombotic state and platelet activation by releasing a pool of trapped thrombin during the course of clot lysis [4]. Although UFH impedes thrombin activity associated with thrombolysis, it does not inhibit thrombin generation, which in turn predicts subsequent thrombotic events [5]. Both, enoxaparin and fondaparinux inhibit the coagulation cascade earlier and may therefore prove more effective than UFH in STEMI patients managed with fibrinolysis.

According to current international consensus guidelines [1, 2], UFH may still be used for patients not undergoing primary PCI. However, it is now recommended to administer UFH no longer than 48 hours due to he risk of heparin-induced thrombocytopenia [1, 2, 6]

Bivalirudin

Primary PCI

In STEMI patients managed with primary PCI, a bivalirudin alone strategy appears as effective as but safer than a strategy with UFH plus GP IIb/IIIa inhibitors. The risk of severe bleeding complications is lower with bivalirudin as compared with UFH plus GP IIb/IIIa inhibitors [7]. Most STEMI patients receive UFH as initial antithrombin at presentation prior to referral to the catheterisation laboratory (fig. 2). If a bivalirudin strategy is chosen, no UFH infusion is required during a rapid transport to the catheterisation laboratory. Of note, bivalirudin can be combined with GP IIb/IIIa inhibitors in case of giant thrombus, distal embolisation, or no reflow (bail-out indication), without an increase in major bleeding complications [7, 8]. Because of the small risk of acute stent thrombosis <24 hours with a bivalirudin alone strategy, it appears useful to initiate clopidogrel pre-treatment (preferably 600 mg) already at presentation. Due to the

Table 1
Dose regimens for the GP IIb/IIIa inhibitors tirofiban, eptifibatide and abciximab.

Dose regimen	bolus	infusion
Tirofiban	25 mg/kg 3-min-bolus IV	0.15 mg/kg/min IV for 18 h
Eptifibatide	180 mg/kg bolus IV (second bolus after 10 minutes for PCI)	2 mg/kg/min IV for 72–96 h
Abciximab	0.25 mg/kg bolus IV	0.125 mg/kg/min IV for 12–24 h

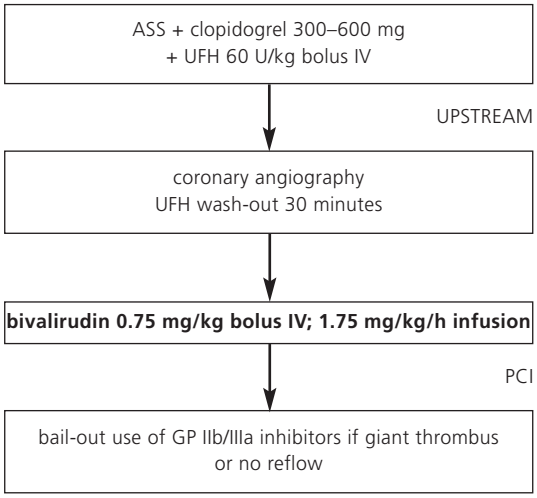

Figure 2
The bivalirudin alone strategy for patients undergoing primary PCI. Upstream treatment is initiated using an intravenous UFH bolus. If the patient is rapidly transferred to the catheterisation laboratory, no additional UFH infusion is administered. A wash-out period of UFH of 30 minutes is recommended before starting bivalirudin. Bivalirudin does not require anticoagulant monitoring nor does it need dose reduction with renal insufficiency. In dialysis patients, the infusion rate but not the bolus should be reduced to 0.25 mg/kg/h. Note that bivalirudin can be safely combined with GP IIb/IIIa inhibitors during PCI in case of giant thrombus, distal embolisation, or no reflow phenomenon.
See figure 1 for ASS and clopidogrel management.

short half-life of 25 minutes, it appears also useful to continue the bivalirudin infusion after conclusion of the PCI procedure until the complete amount of the bivalirudin vial (250 mg) has been used.

Fibrinolysis or conservative management

Currently, bivalirudin has no role for STEMI patients managed conservatively or with fibrinolysis.

Enoxaparin

Primary PCI

In the absence of large randomised controlled trials, enoxaparin has not been recommended for patients managed with primary PCI.

Fibrinolysis or conservative management

In a systematic review of available data, enoxaparin is more effective than UFH with a higher risk of major bleeding complications in STEMI patients who are managed with fibrinolysis [9, 10]. Overall, the benefit/risk ratio defined as death, recurrent myocardial infarction and major bleeding is in favour of enoxaparin [11, 12]. Enoxaparin is recommended for up to 8 days or until discharge (whatever comes first) in STEMI patients managed conservatively or with fibrinolysis. In case of subsequent PCI during the index hospitalisation, intravenous enoxaparin can be used during the intervention, depending on the time of the last subcutaneous injection (fig. 3). Due to the lack of data, other low-molecular weight heparins than enoxaparin are not recommended for this indication.

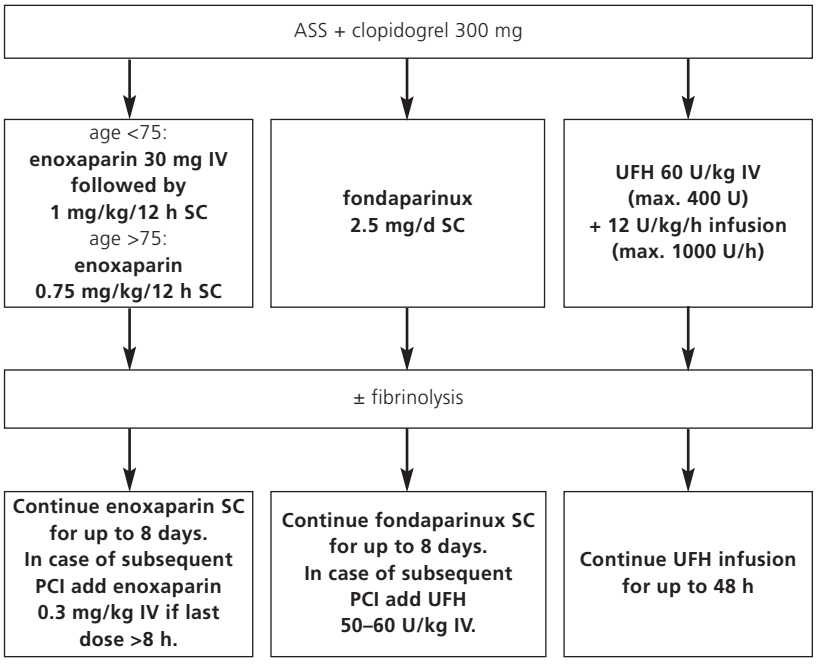

Figure 3
Antithrombotic treatment regimens for STEMI patients not undergoing primary PCI. These regimens apply for patients managed conservatively or with fibrinolysis. Note that the enoxaparin IV bolus is omitted and the SC dose reduced in patients >75 years of age. In patients with creatinin clearance of less than 30 ml per minute, the enoxaparin dose needs to be adjusted to 1 mg/kg/24 h SC. Fondaparinux 2.5 mg once daily is an alternative to enoxaparin. The first dose is given intravenously at presentation, whereas all other doses are administered subcutaneously. Note that fondaparinux should not be administered in patients with creatinin clearance of less than 20 ml per minute. If UFH is chosen as antithrombotic agent, it should be administered for no more than 48 hours due to the risk of heparin-induced thrombocytopenia. Be aware that the dosing regimens for enoxaparin, fondaparinux, and UFH are identical for patients with and without fibrinolysis.
In case of subsequent PCI during the index hospitalisation, switch of antithrombotic agents during PCI is generally discouraged. In patients who have received the last enoxaparin upstream injection more than 8 hours ago, 0.3 mg/kg enoxaparin IV is given during PCI. If the last enoxaparin SC injection is more than 12 hours ago, the IV enoxaparin dose should be increased to 0.75 mg/kg for PCI. In patients who have received upstream fondaparinux, the use of UFH is recommended during PCI. In case of UFH upstream use, PCI should be performed either with UFH or with bivalirudin (see fig. 2). See figure 1 for ASS and clopidogrel management.

Fondaparinux

Primary PCI

Fondaparinux is not recommended in STEMI patients managed with primary PCI due to increased risk of cardiovascular events in comparison to treatment with UFH.

Fibrinolysis or conservative management

Similar to enoxaparin, fondaparinux is recommended in patients with STEMI, who are managed conservatively or with fibrinolysis, for up to 8 days or until discharge (whatever comes first) (fig. 3).

In case of subsequent PCI during the index hospitalisation, fondaparinux cannot be used as sole antithrombin agent during PCI due to an increased rate of guiding catheter thrombosis [13, 14]. Therefore, intravenous UFH is required during PCI of STEMI patients who received fondaparinux upstream to avoid this rare but potentially fatal complication, although more data are required to confirm the efficacy and safety of such a strategy [15].

Conclusions

For STEMI patients managed with primary PCI, UFH in combination with GP IIb/IIIa inhibitors currently remains the most often used antithrombotic treatment regimen. In elderly STEMI patients or those with an increased bleeding risk, a bivalirudin alone strategy is becoming an increasingly popular antithrombin strategy for primary PCI due to a marked reduction in bleeding complications without significant increase in thrombotic events.

For STEMI patients managed conservatively or with fibrinolysis, UFH is no longer standard treatment. For this indication, extended-duration enoxaparin or fondaparinux for up to 8 days have emerged as preferred antithrombin treatment options. In case of subsequent PCI, additional intravenous enoxaparin can be use during the intervention, whereas periprocedural UFH is required in patients who have received upstream fondaparinux.

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References

1 Antman EM, Hand M, Armstrong PW, et al. 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2008;117:296–329.

2 King SB, Smith SC, Hirshfeld JW, et al. 2007 Focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous Coronary Intervention: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. Circulation. 2008;117:261–95.

3 Kucher N, Windecker S, Mach F, et al. Antithrombin treatment of patients with acute coronary syndromes undergoing percutaneous coronary intervention. Kardiovaskuläre Medizin. 2008;11:7–11.

4 Merlini PA, Repetto A, Andreoli AM, et al. Effect of abciximab on prothrombin activation and thrombin generation in patients with acute myocardial infarction also receiving reteplase. Am J Cardiol. 2004;3:195–8.

5 Semeraro F, Piro D, Rossiello MR, et al. Profibrinolytic activity of the direct thrombin inhibitor melagatran and unfractionated heparin in platelet-poor and platelet-rich clots. Thromb Haemost. 2007;98:1208–14.

6 Joost A, Kurowski V, Radke PW. Anticoagulation in patients with heparin-induced thrombocytopenia undergoing percutaneous coronary angiography and interventions. Curr Pharm Des. 2008;14:1176–85.

7 Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med. 2008;358:2218–30.

8 Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. N Engl J Med. 2006;355:2203–16.

9 Murphy SA, Gibson CM, et al. Efficacy and safety of the low-molecular weight heparin enoxaparin compared with unfractionated heparin across the acute coronary syndrome spectrum: a meta-analysis. Eur Heart J. 2007;28:2077–86.

10 Giuseppe De Luca, MD, and Paolo Marino. Adjunctive benefits from low-molecular-weight heparins as compared to unfractionated heparin among patients with ST-segment elevation myocardial infarction treated with thrombolysis. A meta-analysis of the randomized trials. Am Heart J. 2007;154:1085.e1–1085.e6

11 Antman EM, Morrow DA, McCabe CH, et al. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. N Engl J Med. 2006;354:1477–88.

12 Sabatine MS, Morrow DA, Dalby A, et al. Efficacy and safety of enoxaparin versus unfractionated heparin in patients with ST-segment elevation myocardial infarction also treated with clopidogrel. J Am Coll Cardiol. 2007;49:2256–63.

13 Yusuf S, Mehta SR, Chrolavicius S, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med. 2006;354:1464–76.

14 Yusuf S, Mehta SR, Chrolavicius S, et. al. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. JAMA. 2006;295:1519–30.

15 Mehta SR, Granger CB, Eikelboom JW, et. al. Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: results from the OASIS-5 trial. J Am Coll Cardiol. 2007;50:1742–51.