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Antithrombin treatment of patients with acute coronary syndromes undergoing percutaneous coronary intervention

Summary

Antithrombotic therapy in patients with acute coronary syndromes (ACS) targets activated platelets, thrombin, and certain clotting factors, and has been shown to improve clinical outcomes, including recurrent myocardial infarction and cardiovascular death. The majority of patients presenting with ACS in Switzerland are referred for coronary angiography and percutaneous coronary intervention (PCI) using an early invasive strategy. Optimal antithrombotic treatment is particularly important during mechanical intervention at the coronary culprit lesion due to the activation of the clotting cascade following stent mediated arterial injury. The combination of aspirin, clopidogrel, and glycoprotein IIb/IIIa inhibitors is recommended for high-risk ACS patients undergoing 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. Several shortcomings of unfractionated heparin have resulted in the development of a variety of novel anticoagulants, including low molecular weight heparins, fondaparinux, and bivalirudin.

Several antithrombotic drug regimens are now available to treat ACS patients and have been included in international consensus guidelines. This article is intended to serve as a practical guide to interventional cardiologists and other interested physicians treating patients with ACS who are managed with an early invasive strategy. Current options of anticoagulant drug regimens are summarised from a practical point of view, with special attention to the upstream antithrombotic treatment prior to referral to the cardiac catheterisation laboratory. Unfractionated heparin (UFH) still is the antithrombotic agent of choice for patients with urgent PCI or haemodynamic instability. Enoxaparin can be used as an alternative to UFH as upstream treatment and as antithrombotic agent during PCI. Fondaparinux is especially useful as upstream

treatment if PCI is delayed for several hours; however, UFH is needed during PCI in patients on fondaparinux. Bivalirudin is useful during PCI in elderly patients or those with an increased bleeding risk.

Key words: anticoagulation; thrombosis; acute coronary syndrome; percutaneous coronary intervention

Introduction

Plaque rupture with intracoronary thrombosis is the underlying mechanism in the majority of patients with acute coronary syndromes (ACS). Thrombosis is the result of platelet activation and aggregation, in addition to release of tissue factor and several coagulation factors. A critical step in thrombus formation is thrombin because it engenders (1.) the conversion of fibrinogen to fibrin, (2.) self-amplification via activation of the intrinsic clotting pathway, and (3.) direct platelet activation. Unfortunately, thrombin activity persists when bound to fibrin, and therefore, thrombin-rich coronary clot may be a nidus for ongoing thrombus formation and can cause recurrent myocardial infarction and cardiovascular death.

The European [1] and North American [2] consensus guidelines on antithrombotic treatment in the ACS setting are updated on a regular basis, and provide rather general than practical recommendations for the various drug regimens. The authors have reviewed the available evidence of antithrombin treatment regimens during a recent expert consensus

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conference. This article provides practical dose schemes of various antithrombin treatment strategies in ACS patients who are managed with an early invasive strategy, with special attention to the therapy that has been initiated at presentation prior to referral to the cardiac catheterisation laboratory.

Unfractionated Heparin (UFH)

Mechanism of action

UFH is a thrombin inhibitor of animal origin and acts primarily by forming a ternary complex with thrombin and antithrombin. Therefore, its action depends on antithrombin levels. It also binds to factor Xa with an anti-Xa/anti-IIa activity of 1:1. Only a minority of the heparin chains contain the active pentasaccharide sequence that binds to antithrombin. Heparin also exhibits prothrombo-

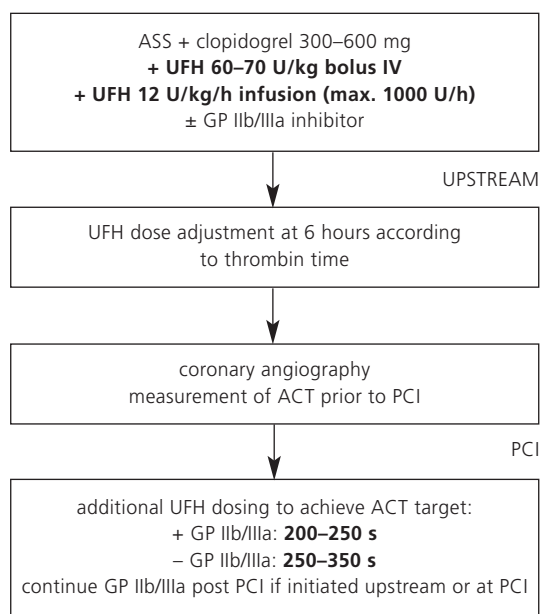
genic properties by binding thrombin and fibrin at the same time. These UFH-thrombin-fibrin complexes cannot be inactivated by heparin and potentially increase the affinity of thrombin for fibrin. UFH shows variable and non-linear dose response, and its effect cannot be well predicted in the individual patient. The main reasons for its inconsistent action include (1.) poor bioavailability, (2.) unspecific protease and cell binding, complex formation with platelet factor-4, (3.) GP IIb/IIIa receptor activation, and (4.) rebound of thrombin formation after drug discontinuation. The inconsistent action of UFH mandates regular dose adjustments and close anticoagulant monitoring by measuring the thrombin time during upstream treatment or monitoring of the activated clotting time (ACT) during PCI in the catheterisation laboratory.

Antithrombotic strategy

In Switzerland, UFH is still the most commonly used antithrombotic agent during PCI. Advantages and disadvantages of UFH are listed in table 1. A typical dose regimen for patients who are referred for an early invasive strategy is shown in figure 1.

Figure 1

The classical antithrombotic strategy using unfractionated heparin. Note that anticoagulant monitoring of upstream-UFH with the thrombin time or activated thromboplastin time is recommended, if PCI is delayed for more than 6 hours. At presentation, acetylsalicylic acid (ASS) is administered at a dose of 500 mg (per os, or IV) and clopidogrel at a dose of 300 mg or 600 mg. The 600 mg dose is preferable to the 300 mg dose for patients who are rapidly transferred to the catheterisation laboratory (within less than 6 hours). Clopidogrel should be withheld in patients who are scheduled for coronary bypass surgery.



Glycoprotein IIb/IIIa inhibitors

GP IIb/IIIa inhibitors are established for the management of high-risk ACS patients. Debates continue whether GP IIb/IIIa inhibitors should be initiated upstream or at initiation of PCI in patients with high-risk ACS. Dose regimens for the GP IIb/IIIa inhibitors tirofiban, eptifibatid and abciximab are given in table 2. 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.

Table 1

Advantages and disadvantages of UFH in the management of patients with acute coronary syndrome.

Advantages	disadvantages
Long history of use	inconsistent effect in individual patients
Effect rapidly reversible by protamine	requires close anticoagulant monitoring
Agent of choice in haemodynamically unstable patients or those undergoing urgent coronary angiography	partially thrombogenic, especially after discontinuation
Low cost	route of administration by infusion
No dose adjustment in patients with renal insufficiency	immunogenic by binding to platelet factor-4 with the risk of heparin-induced thrombocytopenia
	requires dose reduction when combined with GP IIb/IIIa inhibitors

Table 2

ACS dose regimens for the GP IIb/IIIa inhibitors tirofiban, eptifibatide and abciximab.

Dose regimen	bolus	infusion
Tirofiban initiated upstream	0.4 µg/kg/min in 30 min	0.15 µg/kg/min IV for 48–96 h
Tirofiban initiated in catheterisation	25 µg/kg 3-min-bolus IV	0.15 µg/kg/min IV for 18 h
Laboratory:		
high dose		
Tirofiban initiated in catheterisation	10 µg/kg 3-min-bolus IV	0.15 µg/kg/min IV for 18 h
low dose		
Eptifibatide initiated either upstream or in catheterisation laboratory	180 µg/kg bolus IV (second bolus after 10 min for PCI)	2 µg/kg/min IV for 72–96 h
Abciximab initiated either upstream or in catheterisation laboratory	0.25 mg/kg bolus IV	0.125 µg/kg/min IV for 12–24 h

Enoxaparin

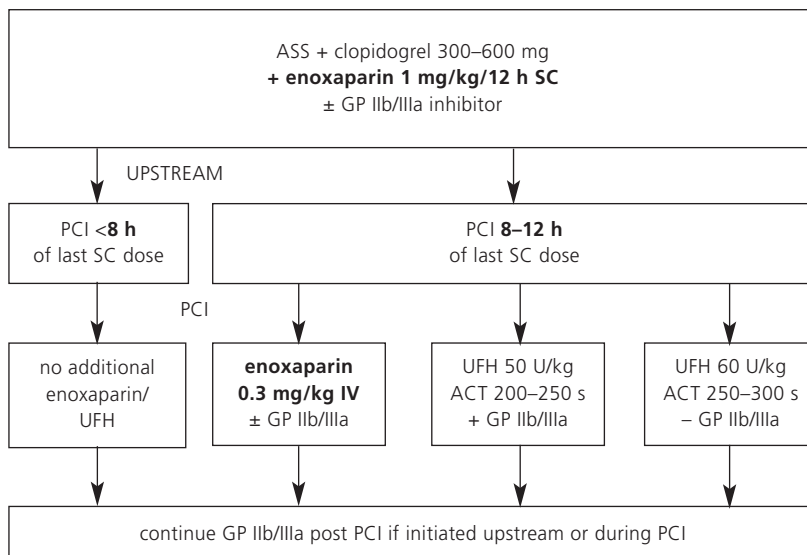
Mechanism of action

Low molecular weight heparins (LMWH) are of animal origin and contain depolymerised UFH chains. Because LMWH contain more pentasaccharides than UFH, they exhibit greater anti-Xa activity. Among the LMWH, the anti-Xa/anti-IIa ratio is highest for enoxaparin (3.8:1). In contrast to UFH, the favorable pharmacodynamic profile of LMWH is responsible for a consistent action in individual patients. Monitoring of the anti-Xa activity is therefore recommended only in obese or elderly patients as well as in those with renal insufficiency.

Antithrombotic strategy

Intravenous enoxaparin is currently used in several Swiss tertiary care hospitals during PCI if it was given subcutaneously as upstream antithrombotic agent. Enoxaparin is the only low molecular weight heparin that covers the entire spectrum of antithrombin therapy in the ACS setting, regardless of the treatment strategy. The other available LMWH preparations have not been fully studied in ACS patients with an early invasive strategy and are therefore not recommended from current European and North American consensus guidelines. Many physicians use enoxaparin as initial anticoagulant in patients with ACS due to its ease of administration (subcutaneous injections) without the need of monitoring. In contrast to other LMWH, established dosing recommendations (fig. 2) for the intravenous administration of enoxaparin in the catheterisation laboratory during PCI are available, without the need for switching anticoagulant regimens. Around 60% anti-Xa activity of enoxaparin may be neutralised by protamine.

In a systematic review of available data, enoxaparin is more effective than UFH in ACS patients who are managed conservatively. In patients who are managed with an early invasive strategy, enoxaparin is as effective and safe as UFH. As with UFH, enoxaparin can safely be used in combination with GP IIb/IIIa inhibitors without an increase in major bleeding complications. In contrast to UFH, no dose adjustment of enoxaparin is necessary with concomitant therapy with GP IIb/IIIa inhibitors. During initial upstream therapy, a dose reduction of enoxaparin is warranted in patients with a creatinin clearance of less than 30 ml per minute.

**Figure 2**

The ACS enoxaparin strategy. Note that the enoxaparin strategy does not require any anticoagulant monitoring. Switching from enoxaparin SC upstream to UFH iv in the catheterisation laboratory should generally be avoided because it may increase the risk of bleeding complications. However, if IV enoxaparin is not available in the catheterisation laboratory, UFH in slightly reduced doses may be used. In patients who have received the last enoxaparin upstream injection more than 12 hours ago, the IV enoxaparin dose should be increased to 0.75 mg/kg for PCI. In patients with creatinin clearance of less than 30 ml per minute, the enoxaparin dose needs to be adjusted to 1 mg/kg/24h SC during initial upstream therapy. See figure 1 for ASS and clopidogrel management.

Bivalirudin

Mechanism of action

Bivalirudin is a direct thrombin inhibitor and exhibits reversible and bivalent binding of thrombin (active site and exosite 1). Therefore, bivalirudin displaces thrombin from its fibrin substrate. Bivalirudin has an excellent pharmacodynamic profile with consistent action in individual patients. It is currently the only approved agent that is independent of antithrombin levels. In contrast to UFH, it also inhibits clot-bound fibrin. In addition, it is the only agent with strong inhibition of thrombin-mediated platelet activation. There is no binding to non-specific protease or platelet factor-4. The short elimination half-life of 25 minutes makes bivalirudin an attractive antithrombotic agent for PCI on one side but requires an infusion if prolonged activity is desired on the other side.

Antithrombotic strategy

Bivalirudin was just recently approved by the Swiss authorities, and a few PCI centers have started to gain experience with this antithrombotic agent. Among intermediate-risk ACS patients, a bivalirudin-alone strategy appears as effective as but safer than a strategy with UFH/LMWH + GP IIb/IIIa inhibitors. The risk

of severe bleeding complications appears to be lower with bivalirudin as compared to with UFH + GP IIb/IIIa inhibitors. More data are required to prove that bivalirudin can replace GP IIb/IIIa inhibitors with high-risk non-ST elevation myocardial infarction. Of note, bivalirudin can be combined with GP IIb/IIIa inhibitors (bail-out indication), without an increase in major bleeding complications.

Because of its recent introduction and cost, bivalirudin is not yet commonly used as upstream treatment in patients with ACS. Most patients receive UFH or enoxaparin as initial antithrombin prior to referral to the catheterisation laboratory (fig. 3). A wash-out period of these upstream agents is required (UFH 30 minutes, enoxaparin 8 hours) before bivalirudin can be safely administered for PCI. If these wash-out periods are respected by the interventional cardiologist, bivalirudin potentially has a role in the cardiac catheterisation laboratory, particularly in elderly ACS patients or in those with an increased risk of bleeding.

Fondaparinux

Mechanism of action

Fondaparinux is a synthetic pentasaccharide, which selectively binds and inhibits factor Xa. Similar to UFH and LMWH, inhibition of factor Xa is achieved via binding to antithrombin. Similar to enoxaparin, fondaparinux also inhibits clot-bound fibrin and there is partial inhibition of thrombin-mediated platelet activation. In contrast to the short half-life of enoxaparin (270 minutes) that mandates a twice-daily regimen, fondaparinux has a half-life of approximately 18 hours. Therefore, a once-daily regimen of fondaparinux in a dose of 2.5 mg subcutaneously is sufficient. No specific antidote is available for fondaparinux. In patients with creatinin clearance of less than 30 ml per minute, fondaparinux should not be used.

Antithrombotic strategy

The reduction in bleeding complications with fondaparinux among intermediate-risk and high-risk ACS patients translated into a significant reduction in mortality in the clinical trials. The convincing safety profile makes fondaparinux a promising anticoagulant choice for patients with ACS, who are primarily managed conservatively. However, among patients who were managed with PCI, an increased rate of catheter thrombosis was reported with

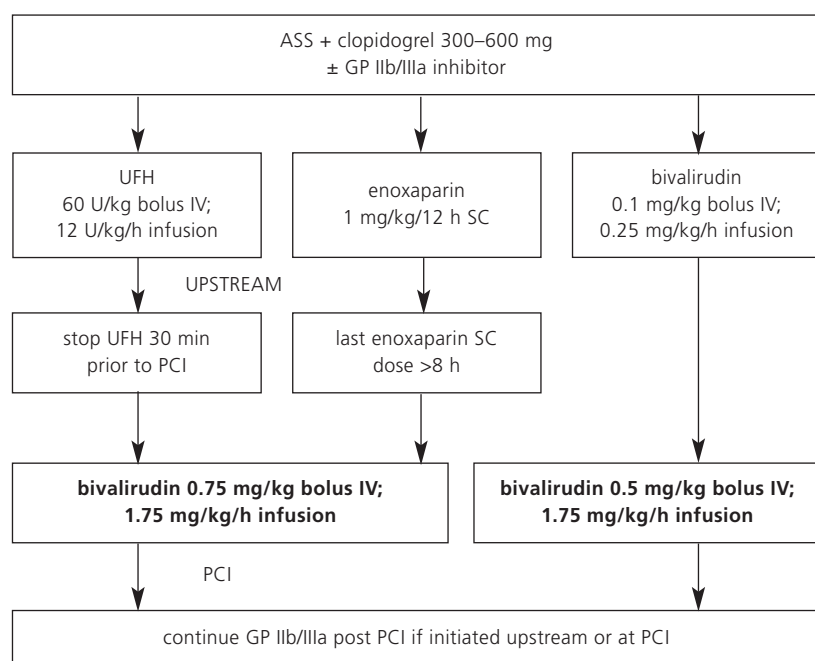
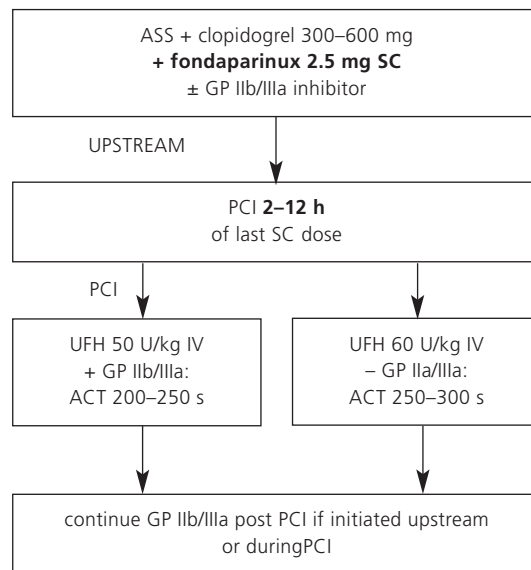


Figure 3

The ACS bivalirudin strategy. Bivalirudin does not require anticoagulant monitoring nor does it need dose reduction with renal insufficiency without dialysis. However, in dialysis patients, the infusion rate but not the bolus should be reduced to 0.25 mg/kg/h. Note, that wash-out periods for upstream treatment should be respected for safely starting bivalirudin in the catheterisation laboratory: UFH 30 minutes and enoxaparin 8 hours. See figure 1 for ASS and clopidogrel management as well as UFH upstream treatment.

Figure 4

The ACS fondaparinux strategy. Fondaparinux is recommended primarily in ACS patients with undecided or conservative management strategy. However, if an invasive strategy is chosen in a patient with upstream fondaparinux therapy, additional intravenous UFH is mandatory during PCI. Fondaparinux should not be used for patients with urgent PCI <2 hours. The proposed regimen requires confirmation of its safety and efficacy in a prospective trial of ACS patients managed with an early invasive strategy. See figure 1 for ASS and clopidogrel management.



the use of fondaparinux compared to patients treated with enoxaparin or unfractionated heparin. Thus, fondaparinux alone is not recommended as antithrombotic agent for PCI. A full dose of UFH iv on top of fondaparinux 2.5 mg sc may avoid this potentially severe complication during PCI without an increase in bleeding, but further studies are needed to confirm the safety and efficacy of such combination (fig. 4). Fondaparinux is not yet approved for patients with ACS by the Swiss authorities.

Perspective

Many novel anticoagulant drugs are in development. The majority of these drugs target factor Xa or thrombin and are currently in phase II or III programs. Some of these drugs are administered orally, such as rivaroxaban, a factor Xa inhibitor, or dabigatran, an oral direct thrombin inhibitor. Whether these new drugs are useful in the ACS setting has to be investigated.

There are also new drugs in development that inhibit platelets, such as the P2Y12 inhibitor prasugrel, or the first reversible ADP receptor antagonist AZD6140. These drugs may exhibit more consistent action on platelets than existing medications for the management of patients with ACS.

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