Anticoagulation therapy in acute coronary syndromes according to current guidelines

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Abstract

Appropriate anticoagulant treatment, together with antiplatelet co-therapy, plays an important role in effective treatment of patients with acute coronary syndrome (ACS). There is a wide range of anticoagulants, from the oldest therapeutic agent – unfractionated heparin (UFH) – through low-molecular-weight heparin (LMWH), to selective inhibitors of factor Xa such as fondaparinux and direct inhibitors of thrombin such as bivalirudin. Patients with ACS require different anticoagulation therapy depending on treatment strategy. Individualization of anticoagulation therapy includes stratification of both the risk of bleeding and the risk of ischaemic complications. Current guidelines generally recommend comparable anticoagulant strategy; however, there are some differences in indications, classes of recommendation and levels of evidence of anticoagulants. This article summarizes current guidelines on anticoagulation therapy in acute coronary syndrome with or without persistent ST-segment elevation.

Key words: acute coronary syndrome, anticoagulation, bivalirudin, fondaparinux, heparins.

Background

Patients with acute coronary syndrome (ACS) are at greater risk of cardiovascular events, particularly re-infarction or death. Anticoagulation therapy significantly decreases the risk of cardiovascular events and additional benefits occur when accompanied by antiplatelet drugs. On the other hand, with decreasing blood coagulation capacity the risk of haemorrhagic complications increases. Among patients with ACS, major bleeding (according to TIMI classification [1]) in the acute phase results in significantly increased 30-day and long-term mortality. In the group of patients with ACS the goal of anticoagulation therapy must be balanced between highest efficacy and acceptable risk of bleeding [2, 3].

Both European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend different anticoagulation therapy among patients with ST-segment elevation myocardial infarction (STEMI) and with unstable angina/non-ST-segment elevation myocardial infarction (UA/NSTEMI) [3-6]. Recommended agents are unfractionated heparin (UFH), low-molecular-weight heparins (LMWH), fondaparinux and bivalirudin.

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Both STEMI and UA/NSTEMI patients require anticoagulation therapy depending on early invasive strategy, conservative treatment, and intended reperfusion strategy – primary percutaneous coronary intervention (PCI), fibrinolytic therapy or no reperfusion. ESC and ACA/AHA guidelines differ in indications, classes of recommendation and levels of evidence of anticoagulants. The objective of this article is to present and compare ESC and ACC/AHA recommendations in anticoagulation treatment and indicate differences between them.

Antithrombotic options

Unfractionated heparin

Unfractionated heparin has a long history of successful clinical use. It is a heterogeneous mixture of polysaccharides with a molecular weight of 2-30 kDa. Unfractionated heparin accelerates factor-Xa inhibition (anti-Xa activity) by binding to antithrombin and inhibits factor-IIa (anti-IIa activity) by bridging antithrombin and factor-IIa molecules. Anti-Xa and anti-IIa activity rates are similar. As UFH is poorly absorbed by subcutaneous injection the intravenous route is preferred. The UFH bolus leads to immediate anticoagulation, followed by infusion which maintains coagulation cascade inhibition. The therapeutic window is narrow so it is necessary to monitor UFH activity by either activated partial thromboplastin time (aPTT; 1.5-2.5 times the upper normal limit) or by activated coagulation time (ACT) [3, 4].

Unfractionated heparin is well known with confirmed efficiency in mortality reduction. The effect of UFH stops rapidly with infusion ending and can be reversed with protamine, which becomes important in case of bleeding. However, disadvantages of UFH are nonlinear pharmacokinetics and the requirement for activity monitoring, indirect thrombin inhibition (clot-bound thrombin is not inhibited), and the risk of heparin-induced thrombocytopenia (HIT) occurrence leading to thrombosis. Moreover, for 24 h from UFH infusion ending the risk of coagulation process reactivation remains increased [3, 7].

Low-molecular-weight heparin

Low-molecular-weight heparin is a mixture of heparin fraction with a molecular weight of 2-10 kDa with increased anti-Xa to anti-IIa activity leading to greater inhibition of thrombin production. Anti-Xa activity is a result of pentasaccharide sequence binding with antithrombin. Anti-Xa to anti-IIa activity index is dependent on molecular weight and decreases with enlargement of its medium molecular weight. Among LMWHs enoxaparin has the highest anti-Xa to anti-IIa activity index. Low-molecular-weight heparin dosing in ACS is body mass adjusted [3].

Low-molecular-weight heparins are a group of therapeutic agents with a long history of use in clinical practice. The main advantages of LMWH are almost complete absorption after subcutaneous injection and more predictable anticoagulation effect related to dose. LMWH compared with UFH has more consistent anticoagulation, longer half-life (administered twice daily) and lower risk of heparin-induced thrombocytopenia. Monitoring of anticoagulant activity is unnecessary except in a group of patients with increased risk of bleeding such as patients with higher age, lower body weight and renal dysfunction. Low-molecular-weight heparins are eliminated by the renal route, so dose adjustment is required among patients with renal dysfunction. Among patients with glomerular filtration rate (GFR) < 30 ml/min/1.73 m^2 LMWHs are contraindicated. Using LMWH it is important to consider that the subcutaneous route is easier to use but the anticoagulation effect is more difficult to reverse [3, 7].

Fondaparinux

Fondaparinux is a selective inhibitor of factor Xa. This is a synthetic pentasaccharide modelled after the antithrombin-binding sequence of UFH. Fondaparinux is administered subcutaneously, has a long half-life (15 h), a predictable anticoagulant response and is administered using a fixed dose. In ACS, a 2.5 mg fixed dose is recommended. Fondaparinux has no antigenicity, does not cross the placenta and HIT antibodies. It is eliminated mainly by the renal route. It is contraindicated if creatinine clearance is lower than 30 ml/min. Clinical trials showed decreased bleeding complications versus UFH or LMWH. One of the disadvantages is that it is difficult to monitor. Also thrombosis on catheters has been noted when using only fondaparinux in the cath lab so it is not recommended as the sole anticoagulant to support PCI [3-6].

Bivalirudin

Bivalirudin is a direct thrombin inhibitor. Inactivating both fibrin-bound and fluid-phase factor-IIa, bivalirudin inhibits thrombin-induced fibrinogen to fibrin conversion. Linear pharmacokinetics, high specificity to thrombin and high correlation between dose administered intravenously and APPT make the anticoagulant effect predictable and easy to monitor. The main advantage of bivalirudin is its safety.

Bivalirudin appears to be more effective than UFH in risk reduction of adverse cardiac events (death, myocardial infarction or repeat revascularization) and bleeding, and safer than UFH in combination with GP IIb/IIIa inhibitors among patients undergoing PCI in ACS. Currently bivalirudin

is recommended for urgent and elective PCI and treatment of HIT complicated by thrombosis [3].

Anticoagulation therapy in ST-elevation myocardial infarction

ESC Guidelines

Among STEMI patients undergoing PCI UFH is the anticoagulation treatment recommended by ESC (class I-C). According to ESC experts there is a lack of randomized clinical trials (RCT) comparing heparin vs. placebo in this group of patients. Strong conviction of anticoagulation therapy's necessity in STEMI prevents absence of heparin in a control group. Despite the low level of evidence UFH is indicated as the standard anticoagulant during PCI in STEMI. Unfractionated heparin is administered as an intravenous bolus (usual dose 100 U/kg weight or 60 U/kg weight if administered with GP IIb/IIIa inhibitor). It is recommended to monitor ACT during UFH therapy (range 250 to 350 s or 200 to 250 if administered with GP IIb/IIIa inhibitor). Low-molecular-weight heparins, due to limited evidence, are not recommended during PCI in STEMI patients [3].

Bivalirudin is recommended by ESC guidelines in STEMI patients undergoing PCI (class IIa-B) due to the Harmonizing Outcomes With Revascularization and Stent in Acute Myocardial Infarction (HORIZONS-AMI) trial, where bivalirudin with GP IIb/IIIa inhibitor was compared to UFH/LMWH with GP IIb/IIIa inhibitor. Use of bivalirudin resulted in 40% reduction of major bleeding ($p < 0.001$) and 1% lower 30-day mortality ($p < 0.0047$) despite higher risk of acute stent thrombosis ($p < 0.001$) [5, 6, 8]. Bivalirudin is administered as an intravenous bolus (0.75 mg/kg weight) with following infusion (1.75 mg/kg weight/h). Routine ACT or APTT monitoring is not required [3].

ESC guidelines contraindicate fondaparinux in STEMI patients qualified for PCI (class III-B). No clinical benefits were found for its administration in this group; there is even a non-significant higher risk of death or recurrent infarction at 30 days.

Among STEMI patients undergoing fibrinolytic therapy the choice of anticoagulant in the ESC guidelines depends on the fibrinolytic agent used. In the case of alteplase, reteplase or tenecteplase, the ESC guidelines favour enoxaparin (class I-A) because of the best prevention of death or non-fatal infarction and the lowest risk of intracranial haemorrhage (especially in the absence of renal dysfunction and age lower than or equal to 75 years old). Enoxaparin should be administered as an intravenous bolus (30 mg) after 15 min followed by subcutaneous injection (1 mg/kg weight dose) repeated every 12 h until discharge but not longer than 8 days. The first two subcutaneous injections should not exceed 100 mg. In patients 75 years old or over no intravenous bolus is administered, subcutaneous dose is 0.75 mg/kg and the first two subcutaneous injections should not exceed 75 mg. Among patients with creatinine clearance of less than 30 ml/min (severe renal dysfunction) subcutaneous injections are administered every 24 h. If enoxaparin is not available UFH should be administered (class I-A) as an intravenous bolus (60 U/kg weight with a maximum dose of 4000 U) followed by an infusion (12 U/kg weight/h but not more than 1000 U/h). The first aPTT control is recommended after 3 hours, then after 6, 12 and 24 h.

In the case of using streptokinase in fibrinolytic therapy ESC guidelines recommend fondaparinux (class IIa-B), enoxaparin (class IIa-B) or UFH (class IIa-C) in the schema presented above. In the Sixth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-6) international, double-blind, randomized trial fondaparinux was superior to placebo or heparin, reducing risk of death and reinfarction by about 20% [9]. Fondaparinux should be used as an intravenous bolus of 2.5 mg followed by subcutaneous injection of 2.5 mg every 24 h up to 8 days or hospital discharge.

Among STEMI patients without reperfusion therapy ESC guidelines recommend the same anticoagulation treatment as in patients with fibrinolytic therapy – fondaparinux, enoxaparin, or UFH (all classes I-B) [3].

ACC/AHA Guidelines

ACC/AHA recommends for patients undergoing fibrinolytic therapy anticoagulant treatment for a minimum of 48 h and preferably for up to 8 days or to hospital discharge (class I-C). However, if anticoagulation therapy is continued for longer than 48 h, regimens other than UFH should be administered to prevent HIT occurrence (class I-A). It is observed that prolonged anticoagulant therapy is beneficial in long-term observation, probably because of a multifactor mechanism. The same time limits are suggested in the ESC guidelines but reading the ACC/AHA guidelines it is much more obvious.

Among patients with fibrinolytic therapy ACC/AHA recommends enoxaparin (class I-A), fondaparinux (class I-B) or UFH (class I-C; on condition that treatment is not continued longer than 48 h). ACC/AHA guidelines differ from ESC guidelines in classes of recommendation of anticoagulant regimens. Suggested dosages are very similar to those proposed by the ESC.

Among patients undergoing PCI ACC/AHA guides how to administer anticoagulant during intervention according to prior anticoagulant treatment.

If prior treatment was UFH it should be continued by additional boluses during intervention (class I-C). Also possible is bivalirudin addition (class I-C).

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For prior treatment with enoxaparin if the last subcutaneous injection was administered within 8 h before intervention no additional injection is needed; if longer than 8 h before, an additional intravenous bolus of 0.3 mg/kg weight is necessary (class I-B).

Patients treated with fondaparinux need additional intravenous treatment with an anticoagulant possessing anti-IIa activity (class I-C). Due to the high risk of catheter thrombosis fondaparinux should never be administered as the only anticoagulant in patients undergoing PCI (class I-C).

ACC/AHA guidelines mention a new LMWH – reviparin. This fact is supported by the Cardiovascular risk Reduction by Early Anemia Treatment with Epoetin beta (CREATE) trial – a randomized, double-blind trial comparing reviparin with placebo in more than 15 thousand patients with STEMI enrolled in Asia [10]. In the reviparin group the risk of composed end point (death/ infarction/stroke) was lower than in the placebo group (differences were more significant in the non-reperfused cohort) but the risk of life-threatening bleeding was also increased. Because data about reviparin used alone in PCI patients are still unavailable, when administrating reviparin an additional anticoagulant would be necessary, e.g. UFH or bivalirudin [6].

Anticoagulation therapy in unstable angina/non-ST-elevation myocardial infarction

ESC Guidelines

In the current ESC guidelines (2007) a lot of attention is focused on anticoagulation therapy. Prevention of major bleeding complications is assumed to be important as bleeding increases the risk of death in long-term observation. The necessity to individualize anticoagulation therapy, including stratification of both the risk of bleeding and the risk of ischaemic complications (class I-B), and the chosen revascularization strategy (class I-B) come from the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial. OASIS-5 authors comparing enoxaparin with fondaparinux in UA/NST-ACS patients observed higher frequency of bleeding complications in 9 days after ACS in the group of patients treated with enoxaparin. It resulted in higher mortality in 1.5-year follow-up [11].

Among patients selected for early invasive strategy (PCI) anticoagulation treatment should be immediately initiated. The preferred anticoagulant seems to be bivalirudin (class I-B) or UFH (class I-C), possibly enoxaparin (class IIa-B) [12]. Priority of bivalirudin is a result of the Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial, where a bleeding risk reduction was observed in the bivalirudin group compared with the UFH/LMWH group [13]. In the case of prior anticoagulant therapy it should be continued during PCI if bivalirudin (class I-B), UFH (class I-C) or enoxaparin (class IIa-B) is used. According to recent data no additional UFH infusion is recommended as was suggested in previous guidelines. Moreover, similar to management in STEMI an additional enoxaparin intravenous bolus of 0.3 mg/kg weight is required only if the last dose was administered previous to 6-8 h before PCI [12]. Responsible for lower recommendations for enoxaparin than UFH is, among other trials, the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial [14], which showed a strong trend in bleeding with enoxaparin use compared with UFH. For prior treatment with fondaparinux an additional intravenous bolus of UFH (100 U/kg weight or 50 U/kg weight if administered with GP IIb/IIIa inhibitor) is required to reduce the risk of catheter thrombosis by UFH anti-IIa activity (class IIa-C).

In an early conservative strategy the favoured anticoagulant is fondaparinux (class I-A). Its leading role was established mostly by the OASIS-5 study (described above), which proved its higher efficacy/safety index than enoxaparin in a conservative strategy of UA/NSTEMI treatment [11]. Enoxaparin, with a lower efficacy/safety index than fondaparinux, can be used only if the risk of bleeding is low (class IIa-B). Other LMWH and UFH, with an unknown efficacy/safety index compared to fondaparinux, have a lower class of recommendation than fondaparinux (class IIa-B).

ESC recommendations allow one to stop anticoagulation treatment in UA/ NSTEMI patients within 24 h after an invasive intervention (class IIa-C). In a conservative strategy with fondaparinux or enoxaparin the anticoagulant can be continued up to hospital discharge (class I-B) [4].

ACC/AHA Guidelines

ACC/AHA guidelines confirm that immediate antiplatelet and anticoagulant treatment is essential among UA/NSTEMI patients and depends on the treatment strategy. In UA/NSTEMI management (favoured regimens) ACC/AHA recommendations differ from ESC recommendations.

Among patients selected for an initial invasive strategy enoxaparin and UFH are indicated as preferred anticoagulants (class I-A). Bivalirudin and fondaparinux have class I-B recommendations and are indicated as acceptable options for enoxaparin and UFH. ACC/AHA guideline authors mention a number of trials comparing UFH and enoxaparin, suggesting their similar efficacy and safety, such as the Efficacy and Safety of Subcutaneous Enoxaparin in Unstable Angina and Non-Q-Wave

MI (ESSENCE) trial [15, 16], the Thrombolysis In Myocardial Ischemia trial, the phase 11B (TIMI 11B) trial [17], and the Antithrombotic Combination Using Tirofiban and Enoxaparin (ACUTE II) trial.

If an initial conservative strategy is selected, acceptable anticoagulant regimens are enoxaparin (class I-A), UFH (class I-A) and fondaparinux (class I-B). Usually enoxaparin or fondaparinux is preferable to UFH, unless CABG is planned within 24 h (class IIa-B). If a patient is in increased risk of bleeding, fondaparinux is favoured due to its efficacy/safety index being higher than heparins (class I-B). Enoxaparin recommendations do not include other LMWHs, because data on their use among UA/NSTEMI patients are limited.

An important part of ACC/AHA guidelines is definitive anticoagulant therapy instructions for patients planned for coronary artery bypass graft (CABG) as a post-angiography management strategy. According to the guidelines, the only regimen recommended for CABG is UFH (class I-B). Other anticoagulants should be replaced by UFH: enoxaparin 12 to 24 h before, fondaparinux 24 h before and bivalirudin 3 h before CABG (all class I-B).

Among patients undergoing a conservative strategy of UA/NSTEMI treatment without angiography or stress tests anticoagulant therapy should be continued for 48 h (if UFH is used) and up to 8 days or until hospital discharge (if enoxaparin or fondaparinux is used; class I-A). After uncomplicated PCI anticoagulant therapy should not be continued (class I-B). For patients with coronary artery disease diagnosed in acute phase angiography and selected for medical treatment UFH should be administered for 48 h or until hospital discharge (if given before angiography; class I-A), enoxaparin and fondaparinux – for up to 8 days or until hospital discharge (if given before angiography; class I-B). Bivalirudin can be continued or discontinued depending on the discretion of the clinician for 72 h at a dose of 0.25 mg/kg weight/h (if given before angiography; class I-B) [6].

To summarize, patients with ACS require different anticoagulation therapy depending on treatment strategy. Treatment should be individualized based on invasive or non-invasive strategy and risk stratification of both bleeding risk and ischaemic complications. Current ESC and ACC/AHA guidelines are mainly comparable regarding anticoagulant strategy; however, there are some differences in indications, classes of recommendation and levels of evidence. Comparisons of ESC and ACC/AHA guidelines regarding anticoagulants in STEMI and UA/NSTEMI are presented in Tables I and II.

Table I. Comparison of ESC and ACC/AHA guidelines regarding anticoagulants in STEMI

Indication/therapy	ESC		ACC/AHA	
	Class	LOE	Class	LOE
Adjunctive therapy for primary PCI				
Heparin	I	C	I	C
Bivalirudin	IIa	B	I	C
Fondaparinux	III	B	III*	C
Fibrinolytic therapy with alteplase, reteplase and tenecteplase				
Enoxaparin	I	A	The same as for fibrinolytic therapy with streptokinase	
UFH	I+	A		
Fibrinolytic therapy with streptokinase				
Enoxaparin	IIa	B	I§	A
Fondaparinux	IIa	B	I§	B
UFH	IIa	C	I§	C‖
Antithrombotic treatment without reperfusion therapy				
Fondaparinux	I	B	IIa	B
Enoxaparin	I‡	B	IIa	C
UFH	I‡	B	Non-UFH regimen recommended	

LMWH – low-molecular-weight heparin, LOE – level of evidence, PCI – percutaneous coronary intervention, UFH – unfractionated heparin *as the sole anticoagulant to support PCI, +if enoxaparin not available, ‡ if fondaparinux not available, §generally for fibrinolytic therapy, ‖if more than 48 h change to other than UFH [4, 5]

Table II. Comparison of ESC and ACC/AHA guidelines regarding anticoagulants in UA/NSTEMI

Indication/therapy	ESC		ACC/AHA	
	Class	LOE	Class	LOE
Adjunctive therapy for initial invasive strategy				
Bivalirudin	I	B	I	B
UFH	I	C	I	A
Enoxaparin	IIa	B	I	A
Fondaparinux	–	–	I	B
Adjunctive therapy for initial conservative strategy				
Fondaparinux	I	A	I*	B
Enoxaparin	IIa	B	I	A
UFH	IIa	B	I+	A

LMWH – low-molecular-weight heparin, LOE – level of evidence, PCI – percutaneous coronary intervention, UFH – unfractionated heparin *preferable if increased risk of bleeding, +enoxaparin or fondaparinux is preferable to UFH when an initial conservative strategy is selected, unless coronary artery bypass graft is planned within 24 h [3, 6]

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