Chapter 3
Anticoagulation Therapy. Heparins, Factor II and Factor Xa Inhibitors

Ana Muñiz-Lozano, Fabiana Rollini, Francesco Franchi, and Dominick J. Angiolillo

Introduction and General Considerations

Atherosclerotic disease is a progressive and diffuse disease which may affect any arterial vasculature [1]. Coronary artery disease (CAD) starts in the late teens under the form of fatty streaks and progress with age, until atherosclerotic plaques are developed. Thrombotic complications of atherosclerotic plaques occur mostly following rupture, fissure or superficial endothelial cell erosion [2]. This leads to activation of the platelet cascade, characterized by adhesion, activation, and aggregation, as well as activation of the extrinsic pathway of the coagulation cascade which ultimately results in thrombin generation. Thrombus formation can be subclinical, and thus favor plaque progression, or clinical, and thus leading a clinical manifestation of an acute coronary syndrome (ACS) [1, 2]. Nonocclusive thrombi typically lead to a non-ST elevation ACS (NSTE-ACS) and occlusive thrombi to

A. Muñiz-Lozano, MD • F. Rollini, MD • F. Franchi, MD
D.J. Angiolillo, MD, PhD (✉)
Department of Cardiology,
University of Florida College of Medicine-Jacksonville,
655 West 8th Street, Jacksonville, FL 32209, USA
e-mail: dominick.angiolillo@jax.ufl.edu

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a ST-elevation myocardial infarction (STEMI) [1–3]. The absence or presence of cardiac biomarkers allows to differentiate NSTE-ACS patients into two categories: unstable angina (UA) or non-ST elevation myocardial infarction (NSTEMI). In the setting of percutaneous coronary interventions (PCI), plaque rupture is iatrogenically induced. Therefore, these patients are also exposed to the risk of intraprocedural thrombotic complications which warrant specific therapies.

The extensive procoagulant and prothrombotic actions of thrombin underlie its key role in the setting of ACS, given that it represents the last step of coagulation as it converts fibrinogen to clottable fibrin by releasing fibrinopeptides A and B [4]. Moreover, thrombin is also the most potent naturally occurring platelet agonist and therefore has been considered as a pharmacological target in order to prevent the formation of fibrin- and platelet-rich thrombi induced by thrombin. The mechanism of generation of acute platelet-rich thrombus and promoting vascular healing after arterial injury has been broadly described [5–10]. On the platelet surface, thrombin binds to its specific receptor on platelets ultimately leading to the expression of activated glycoprotein IIb/IIIa (GP IIb/IIIa) receptors. Via the GP IIb/IIIa receptor platelets are cross-link activated by ligands such as fibrinogen forming platelet aggregates. Moreover such platelet aggregates increase the surface area for the prothrombinase complex by providing a phospholipid membrane platform on which a complex of activated factors V and X and calcium ions can form contributing to thrombus formation [7] and amplifying thrombin generation. Thrombin becomes resistant to inactivation by the heparin/antithrombin complex when bound to fibrin, fibrin degradation products or subendothelial matrix [8–10].

Given that this central role of thrombin in arterial thrombogenesis, therapeutic agents have been developed to target either thrombin or modulators of thrombin generation within the coagulation cascade (Fig. 3.1). These include a variety of agents available for parenteral administration, used in combination with antiplatelet therapies (discussed in details elsewhere in this book), used in ACS and PCI setting

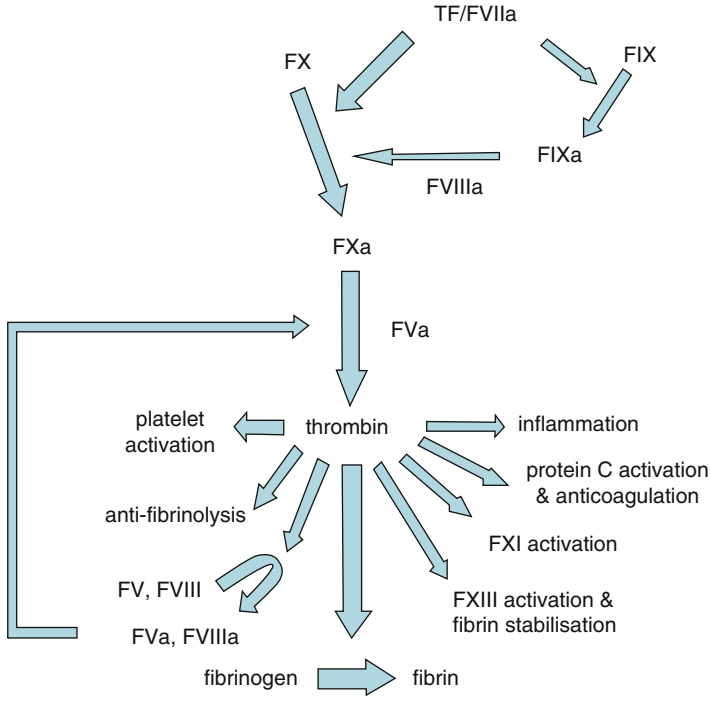


FIGURE 3.1 Central role of thrombin in thrombosis and haemostasis. Thrombin is a crucial enzyme that has numerous biological actions. Its main role regards the generation of fibrin by the excision of fibrinogen, but additionally it promotes platelet activation and aggregation by binding protease-activated receptors (PARs)-1 and –4 existing in platelets and multiple cell types exerts. Moreover, thrombin also intensifies clotting by activating coagulation factor (F) XI and the cofactors FV and FVIII into FVa and FVIIIa, respectively; and it stabilizes clots by activating FXIII. In addition, thrombin has pro-inflammatory actions and also exerts anti-fibrinolytic actions, given that it provides a molecular link between coagulation and inhibition of fibrinolysis by activating thrombin activatable fibrinolysis inhibitor (TAFI). Furthermore, thrombin promotes the activation of protein C and protein S, two natural vitamin K-dependent anticoagulant proteins that stop the coagulation cascade by blocking FVa and FVIIIa (Reproduced from De Caterina et al. [11])

which may be chosen depending on the level of ischemic and hemorrhagic risk of the patient as well as their planned early management (conservative vs. invasive). Indeed, not only the choice of therapy by also timing of administration and cessation are key determinant of short and long-term outcomes. Given that ACS patients persist with elevated thrombin levels following an ACS event, there also has been an emerging interest on adding oral anticoagulant therapy to standard antiplatelet regiment for long-term secondary prevention of ischemic event. In this chapter, we provide an overview of the basic principles of pharmacology, rationale for use, indications, contraindications, dosing considerations and side effects of currently available anticoagulant therapies are summarized and recent advances in the field provided.

Anticoagulant Therapy: Classification

The classification of anticoagulant agents is based primarily on the target coagulation enzyme which is inhibited. Most clinically available anticoagulant therapies block factor (F) II or thrombin and FX. Each class of inhibitors blocking a specific target can then be classified according to its mechanism of action to exert its inhibitory effects as direct or indirect, based on the need of a co-factor without which these agents would provide minimal or null effects (Fig. 3.2). Finally, anticoagulant therapies can be classified according to their route of administration (parenteral or oral).In the setting of ACS and PCI, parenteral agents are used and include a variety of thrombin inhibitors (direct and indirect). Anti-X inhibitors are also used in ACS patients, mostly medically managed, although to a lesser extent than thrombin inhibitors and currently only an indirect anti-X inhibitor for parenteral use is clinically available. These agents are described in details below.

Thrombin Inhibitors

Thrombin inhibitors can be classified into two broad categories according to the presence or absence of a plasma cofactor needed to exert its effects: indirect and direct thrombin inhibitors (DTIs). Details of these agents are described below.

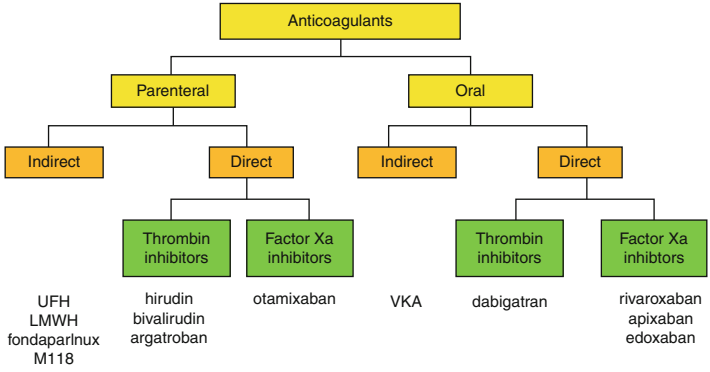


FIGURE 3.2 Currently available anticoagulants according their mode of action and route of administration (Reproduced from De Caterina et al. [11])

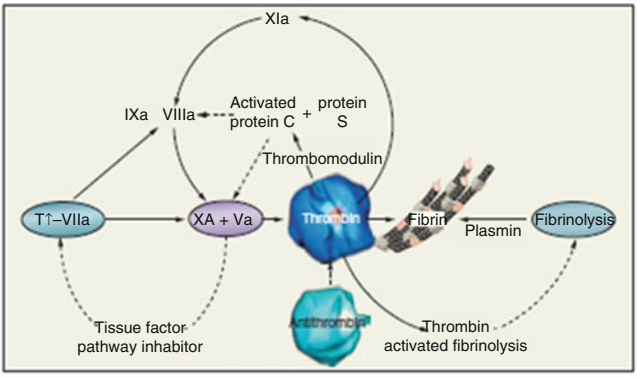
Indirect Thrombin Inhibitors

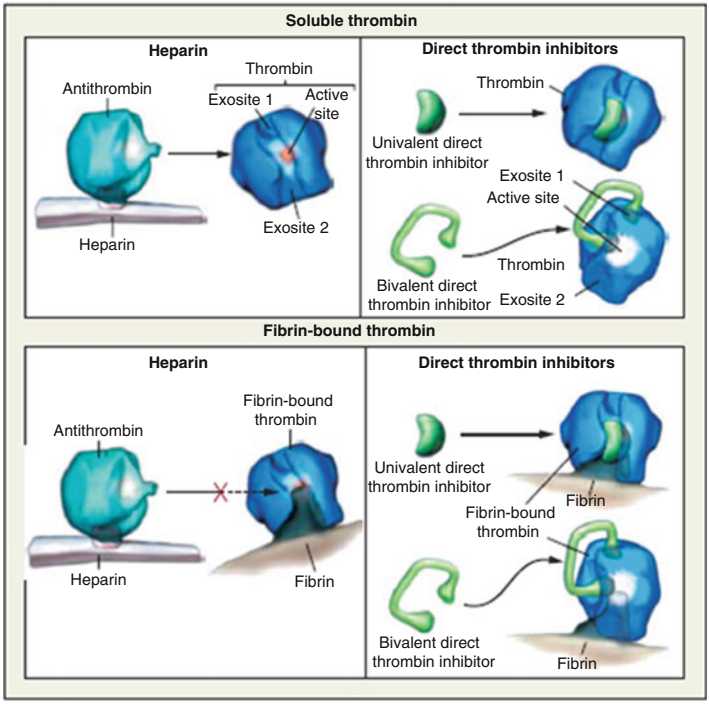
Indirect thrombin inhibitors include unfractionated heparin (UFH) and low-molecular weight heparin (LMWH), which in the absence of the cofactor antithrombin (AT), an endogenous inhibitor of several activated clotting factors have minimal or no intrinsic anticoagulant activity.

Unfractionated Heparin

Mechanism of Action and Pharmacokinetic/ Pharmacodynamic Profile

UFH is a highly sulfated glycosaminoglycan composed by a heterogeneous mixture of variable molecular weight polysaccharide molecules. The structure and the mechanism of action of heparin are described in Fig. 3.3. UFH is administrated through anintravenous (IV) or subcutaneous (SC) route because its polysaccharide chain is degraded in gastric acid. UFH should not be administrated intramuscularly because of the danger of hematoma generation. UFH is metabolized primarily by the liver (by heparinase to uroheparin, which has only small AT activity) and partially metabolized by the reticuloendothelial system [13].


XIa
IXa
VIIIa
Activated protein C
+
protein S
Thrombomodulin
T↑–VIIa
XA + Va
Thrombin
Fibrin
Plasmin
Fibrinolysis
Tissue factor pathway inhabitor
Antithrombin
Thrombin activated fibrinolysis


Soluble thrombin
Heparin
Antithrombin
Thrombin
Exosite 1
Active site
Exosite 2
Heparin
Direct thrombin inhibitors
Thrombin
Univalent direct thrombin inhibitor
Exosite 1
Active site
Thrombin
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Exosite 2
Fibrin-bound thrombin
Heparin
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Fibrin-bound thrombin
Heparin
Fibrin
Direct thrombin inhibitors
Univalent direct thrombin inhibitor
Fibrin
Fibrin-bound thrombin
Bivalent direct thrombin inhibitor
Fibrin

Figure 3.3 Mechanism of thrombin generation and action of direct thrombin inhibitors (DTIs) as compared with heparin. (**a**) Tissue-factor expression by endothelial cells and the activation of factors XI, IX, and VIII are crucial to formation of fibrin. During the coagulation cascade the molecule of thrombin is the cornerstone. Natural anticoagulant mechanisms regulate the formation of the clot limiting the hemostatic process to the location of the injury to the vessel. (**b**) The transformation of AT from a slow to a very fast thrombin inhibitor causes a conformational change by the binding of pentasaccharide to AT. A ternary complex (UFH:AT:thrombin), composed by AT and thrombin, joined by UFH longer chains (>18 saccharide units) acting as a bridge between both molecules, leads to a greater inhibition of thrombin compared with FXa. In this way, UFH fibrin formation and inhibits thrombin-induced activation of platelets, factor V, and factor VIII, thereby preventing thrombus propagation (Reproduced from Di Nisio M et al. [12])

After administering an IV bolus followed by continuous IV infusion, an immediate anticoagulant effect can be achieved, which underscores this route of administration in patients with ACS. SC administrations (10 % lower bioavailability than IV) delay 1 hour (h) the anticoagulant effect of UFH, achieving the peak plasma levels at 3 h [14, 15]. After entering in the bloodstream, the binding of UFH to a number of plasma proteins, endothelial cells, macrophages, and von Willebrand factor (vWF), takes places, reducing its anticoagulant activity, leading to heparin resistance, and inhibiting vWF-dependent platelet function [16–19] The variability of anticoagulant response, particularly in patients with thromboembolic disorders, and its complex pharmacokinetic (PK) profile, is caused by the heterogeneity of UFH properties [16]. Clearance of UFH takes place by a saturable depolymerization process produced by the binding of UFH to endothelial cells and macrophages [20, 21]. A non saturable renal clearance, a slower elimination pathway, occurs mostly with supraclinical doses of UFH [22].

The PK profile of UFH explains why the intensity and duration of anticoagulant response results nonlinear to therapeutic doses of UFH and increases excessively with cumulative dose. In line with this, an IV bolus of 100 U/kg increases the biological half-life of UFH from 30 min (after an IV bolus of 25 U/kg) to 60 min, and a bolus of 400 U/kg for 30–150 min [14, 22–24]. The anticoagulant effect of UFH lasts just a few hours after cessation of UFH due to the fast clearance. In fact, it is possible to reactivate the coagulation process and because of an increase of thrombin activity after cessation a phenomenon called "heparin rebound" may occur, despite concomitant aspirin treatment [25, 26]. Changing from IV to SC dosing before interruption of UFH could mitigate this effect [27, 28].

The heterogeneous binding properties to several cells and proteins confer UFH other biologic effects in addition to its anticoagulant effects, such as alteration of platelet function, an increase in vessel wall permeability, a suppression of smooth muscle cell proliferation. Inhibition of osteoblast formation and osteoclast activation has also been described by *in vitro* studies of UFH [28–35]. Clinically the most relevant non anticoagulant effect of UFH is its potential to induce immune-mediated platelet activation known as heparin-induced thrombocytopenia (HIT) [24, 36, 37].In comparison with LMWH,UFH causes more frequently thrombocytopenia (defined as a platelet count <100,000/μL or a 50 % reduction in baseline platelet count), with an approximate incidence of 0.3 %. The phenomenon of inadequate response to UFH is described by heparin resistance, demanding higher than usual doses of UFH to acquire the desired anticoagulant effect. More rapid clearance of UFH [38], increased heparin-binding proteins [17], AT deficiency, or increased factor VIII levels [39] can explain this phenomenon.

Indications

The benefit of UFH in the setting of ACS, particularly UA/NSTEMI, has been extensively demonstrated in many trials establishing it as a class IA therapy concomitantly with

platelet inhibitors [40, 41]. Metaanalyses of six relatively small randomized, placebo-controlled trials with UFH for treatment of UA/NSTEMI have led to guideline recommendations for UFH use in ACS [42–48] (Table 3.1).

For STEMI patients undergoing PCI the use bivalirudin with or without prior treatment with UFH is considered preferable to UFH andglycoprotein IIb/IIIa inhibitors (GPI) [49, 50] (Table 3.2). However, during PCI or combined with fibrinolytic therapy in the setting of STEMI adjunctive anticoagulation with UFH has been also demonstrated in clinical trials, but the use of SC or IV UFH as an adjunct to streptokinase (SK) remains controversial. UFH is recommended in high-thrombotic-risk patients SK-treated [49, 50].

Dosages, Monitoring and Reversal

Based on evidence-based guideline recommendations and available clinical trial data [49, 50], initial dosing of UFH in patients with ACS should start with an IV weight-based bolus followed by continuous IV infusion [40]. At each institution, because of the laboratory variation, nomograms should be performed in order to reach activated partial thromboplastin time (aPTT) values in the target range, for many aPTT reagents [40, 49]. In a patient with ACS, UFH is usually initiated at time of clinical presentation. For UA/NSTEMI, an initial IV bolus of 60–70 U/kg (maximum 4,000 U) followed by continuous infusion of 12–15 U/kg/h (maximum 1,000 U/h is recommended) [40, 49]. For STEMI patients on non-SK fibrinolytic therapy regimens, the dosing of UFH is at the lower end of this range (Table 3.1) [51]. Given that higher aPTT responses to UFH have been related with older age, low body weight, and female sex, these factors should be particularly considered in dosing decisions. Also smoking and diabetes should be considered because have been associated with an attenuated response to UFH [52, 53]. Higher than usual doses of UFH to obtain the desired anticoagulant effect are needed when the phenomenon of inadequate response to UFH occurs because of a heparin resistance [17]. Higher doses of UFH, [54, 55] prolonged or repeated exposure, [56]

Table 3.1 Guidelines recommendations on anticoagulant therapy in unstable angina and non ST-elevation myocardial infarction patients

			During PCI		
		Initial medical treatment	**Patient received initial medical treatment**	**Patient did not receive initial medical treatment**	**After PCI**
2012 ACCF/AHA Guideline for the management of UA/NSTEMI* [40]	Bivalirudin	0.1 mg/kg bolus, 0.25 mg/kg/h infusion	0.5 mg/kg bolus, increase infusion to 1.75 mg/kg/h	0.75 mg/kg bolus, 1.75 mg/kg/h infusion	No additional treatment or continue infusion for up to 4 h
	Enoxaparin	LD of 30 mg IV bolus may be given MD = 1 mg/kg SC every 12 h; extend dosing interval to 1 mg/kg every 24 h if estimated creatinine clearance less than 30 ml/min	Last SC dose less than 8 h: 0.5–0.75 mg/kg no additional treatment Last SC dose greater than 8 h: 0.3 mg/kg IV bolus	IV bolus	No additional treatment
	Fondaparinux	2.5 mg SC once daily. Avoid for creatinine clearance less than 30 mL/min	50–60 U/kg IV bolus of UFH is recommended by the OASIS 5 Investigators	50–60 U/kg IV bolus of UFH is recommended by the OASIS 5 Investigators	No additional treatment
	Unfractionated heparin	LD of 60 U/kg (max 4,000 U) as IV bolus MD of IV infusion of 12 U/kg/h (max 1,000 U/h) to maintain aPTT at 1.5–2.0 times control (approximately 50–70 s)	IV GPI planned: target ACT 200 s No IV GPI planned: target ACT 250–300 s for HemoTec; 300–350 s for Hemochron	IV GPI planned: 60–70 U/kg No IV GPI planned: 100–140 U/kg	No additional treatment

2011 ESC Guideline for the management of UA/ NSTEMI** [11, 41]	Bivalirudin	If immediate invasive strategy is planned, bivalirudin without a GPI should be considered the anticoagulant of choice over UFH or enoxaparin, particularly in patients with a high risk of bleeding, provided that optimal DAPT with aspirin plus an ADP receptor blocker is given (Class I, LOE B) Bivalirudin plus provisional GPI are recommended as an alternative to UFH plus GPI in patients with an intended urgent or early invasive strategy, particularly in patients with a high risk of bleeding (Class I, LOE B)		Discontinuation of anticoagulation should be considered after an invasive procedure unless otherwise indicated (Class IIa, LOE C)
	Enoxaparin	For conservative or non-immediate invasive strategies 1 mg/kg twice daily is recommended when fondaparinux is not available (Class I, LOE B)		
	Fondaparinux	2.5 mg subcutaneously daily is preferred over other anticoagulants (Class I, LOE A) if planned: 1. A non-immediate invasive strategy or 2. A conservative strategy (treatment should be maintained until clinical discharge) (Class I, LOE A)	85 IU/kg IV bolus of UFH (adapted to ACT) or 60 IU in the case of concomitant use of GPI (Class I, LOE B)	

(continued)

Table 3.1 (continued)

	Initial medical treatment	During PCI		After PCI
		Patient received initial medical treatment	Patient did not receive initial medical treatment	
Unfractionated heparin	For high-risk patients in whom an immediate invasive strategy is planned, UFH is preferred over LMWH or fondaparinux because of its shorter half-life and potential for complete reversal with protamine sulphate should bleeding occur (Class IIa B) For conservative or non-immediate invasive strategies if fondaparinux or enoxaparin are not available, UFH with a target aPTT of 50–70s or other LMWHs at the specific recommended doses are indicated (Class I, LOE C)	IV bolus under ACT guidance (ACT 250–350 s, or 200–250 s if a GPI is given) or weight-adjusted (usually 70–100 IU/kg, or 50–60 IU/kg) in combination with a GPI In patients with previous IV infusion of UFH: a further IV bolus of UFH adapted according to the ACT values and use of GPI		

LOE level of evidence, *ACT* activated clotting time, *aPTT* activated partial thromboplastin time, *GPI* glycoprotein IIb/IIIa receptor inhibitors, *LMWH* low molecular weight heparin, *PCI* percutaneous coronary intervention, *UFH* unfractionated heparin, *IU* international unit, *IV* intravenous, *SC* subcutaneous, *U* units, *UA/NSTEMI* unstable angina/non–ST-elevation myocardial infarction, *DAPT* dual antiplatelet therapy, *ADP* adenosine diphosphate

2012 ACCF/AHA Guideline for the management of UA/NSTEMI* [40]

- For conservatively managed patient who develops a need for PCI:

  (A) If fondaparinux was given for initial medical treatment an IV bolus of 50–60 U/kg of UFH is recommended (the safety of this drug combination is not well established).

  (B) If enoxaparin was the initial medical treatment additional IV enoxaparin is an acceptable option.

- For patients managed by an initial conservative strategy, enoxaparin and fondaparinux are more convenient because of their SC administration (compared with an IV infusion of UFH) and their lower association with heparin-induced thrombocytopenia (compared with UFH).

2011 ESC Guideline for the management of UA/NSTEMI** [11, 41]

- It is not recommended (Class III):
  - The use of SC UFH as an anticoagulation strategy, even as short-term bridging therapy (LOE B).
  - The use of a fixed aPTT target in seconds when using UFH for any therapeutic indication (LOE B).
  - The interchange of the various LMWH preparations (LOE B).
  - The crossover (switching) between heparins (UFH and LMWH) (LOE B).
  - The use of fondaparinux for prevention or treatment of thrombosis during pregnancy, unless the patient has a history of HIT (LOE B).
  - The use of LMWH as alternatives to heparin in patients with suspected or established HIT (LOE A).

(continued)

- In patients with chronic kidney disease:
  - Moderate (CrCl 30–60 ml/min): reducing enoxaparin to 75 % of the usual dose (Class IIa, LOE B).
  - Severe or end-stage (CrCl ≤15–30 ml/min):
    - UFH over LMWH and over fondaparinux (Class I A).
    - The IV infusion dose of bivalirudin should be reduced from 1.75 to 1 mg/kg/h
  - Haemodialysis: The IV infusion dose of bivalirudin should be reduced from 1.75 to 0.25 mg/kg/h
- Regarding monitoring:
  - The therapeutic range for UFH should be adapted to the aPTT reagent used (Class IIa, LOE B).
  - The anticoagulant activity of LMWH or fondaparinux can be measured with anti-FXa assays, using the appropriate reference calibrator (Class I, LOE B).

Table 3.2 Guidelines recommendations on anticoagulant therapy in ST-elevation myocardial infarction patients

	Undergoing primary percutaneous coronary intervention	**Receiving fibrinolytic therapy**
2013 ACCF/AHA guideline for the management of STEMI [49]	**UFH**: Class I LOE C With GPI planned: 50- to 70-U/kg IV bolus to achieve therapeutic ACT With no GPI planned: 70- to 100-U/kg bolus to achieve therapeutic ACT.	**UFH**: To support reperfusion Weight-based IV bolus and infusion adjusted to obtain aPTT of 1.5–2.0 times control for 48 h or until revascularization. IV bolus of 60 U/kg (maximum 4,000 U) followed by an infusion of 12 U/kg/h (maximum 1,000 U) initially, adjusted to maintain aPTT at 1.5–2.0 times control (approximately 50–70 s) for 48 h or until revascularization. To Support PCI After Fibrinolytic Therapy Continue UFH through PCI, administering additional IV boluses as needed to maintain therapeutic ACT depending on use of GPI. ACT recommended without GPI: 250–300 s (HemoTec device) or 300–350 s (Hemochron device). [Class I LOE C]
	Bivalirudin: Class I LOE B 0.75-mg/kg IV bolus, then 1.75-mg/kg/h infusion with or without prior treatment with UFH. An additional bolus of 0.3 mg/kg can be given if needed. Reduce infusion to 1 mg/kg/h with estimated CrCl <30 mL/min. [Class I LOE B] Preferred over UFH with GPI in patients at high risk of bleeding. [Class IIa LOE B] Preferred over UFH with GPI in patients at high risk of bleeding. [Class IIa LOE B]	**Bivalirudin**: Not recommended.

(continued)

TABLE 3.2 (continued)

Undergoing primary percutaneous coronary intervention	Receiving fibrinolytic therapy
Enoxaparin: Not recommended.	**Enoxaparin**: To support reperfusion [Class I LOE A] <75 years: 30 mg IV bolus, followed in 15 min by 1 mg/kg SC every 12 h (max. 100 mg for the first 2 doses). ≥75 years: no bolus, 0.75 mg/kg SC every 12 h (maximum 75 mg for the first 2 doses). CrCl <30 mL/min: 1 mg/kg SC every 24 h. Duration: For the index hospitalization, up to 8 days or until revascularization. To Support PCI After Fibrinolytic Therapy Continue enoxaparin through PCI: No additional drug if last dose within previous 8 h 0.3-mg/kg IV bolus if last dose 8–12 h earlier. [Class I LOE B]
Fondaparinux: Class III LOE B Not recommended as sole anticoagulant for primary PCI	**Fondaparinux**: To support reperfusion [Class I LOE B] Initial dose 2.5 mg IV, then 2.5 mg SC daily starting the following day, for the index hospitalization up to 8 days or until revascularization. Contraindicated if CrCl <30 mL/min. To Support PCI After Fibrinolytic Therapy Not recommended as sole anticoagulant for primary PCI [Class III LOE C]

2012 ESC Guidelines for the management of AMI in patients presenting with ST-segment elevation [50]	An injectable anticoagulant must be used in primary PCI. Class I LOE C.	
	Bivalirudin: Class I LOE B With GPI restricted to bailout is recommended over UFH and a GPI. 0.75 mg/kg IV bolus followed by IV infusion of 1.75 mg/kg/h for up to 4 h after the procedure as clinically warranted. After cessation of the 1.75 mg/kg/h infusion, a reduced infusion dose of 0.25 mg/kg/h may be continued for 4–12 h as clinically necessary.	**Bivalirudin**: Not recommended.
	Enoxaparin: with or without routine GPI. Class IIb LOE B May be preferred over UFH. 0.5 mg/kg IV bolus.	**Enoxaparin**: Preferred over UFH for patients <75 years of age and have an estimated CrCl >30 ml/min [Class IIa LOE B]. <75 years: 30 mg IV bolus followed 15 min later by 1 mg/kg SC every 12 h until hospital discharge for a maximum of 8 days (the first two doses should not exceed 100 mg). >75 years: no IV bolus; start with first SC dose of 0.75 mg/kg with a maximum of 75 mg for the first two SC doses. In patients with CrCl <30 mL/min, regardless of age, the SC doses are given once every 24 h.

(continued)

TABLE 3.2 (continued)

Undergoing primary percutaneous coronary intervention	Receiving fibrinolytic therapy
UFH: with or without routine GPI. Class I LOE C Must be used in patients not receiving bivalirudin or enoxaparin. 70–100 U/kg IV bolus when no GPI is planned. 50–60 U/kg IV bolus with GPI.	**UFH**: Agent of choice for patients >75 years of age or with a CrCl <30 ml/min. [Class I LOE B] 60 U/kg IV bolus with a maximum of 4,000 U followed by an IV infusion of 12 U/kg with a maximum of 1,000 U/h for 24–48 h. Target aPTT: 50–70 s or 1.5–2.0 times that of control to be monitored at 3, 6, 12 and 24 h.
Fondaparinux: Class III LOE B Not recommended for primary PCI.	**Fondaparinux**: As effective and safe as UFH, provided CrCl is >30 ml/min. [Class IIa LOE B] 2.5 mg IV bolus followed by a SC dose of 2.5 mg once daily up to 8 days or hospital discharge.

ACC American College of Cardiology Foundation/American Heart Association, *ESC* European Society of Cardiology, *STEMI* ST-elevation myocardial infarction, *AMI* acute myocardial infarction, *UFH* unfractionated heparin, *GPI* glycoprotein IIb/IIIa inhibitor, *LOE* level of evidence, *IV* intravenous, *PCI* percutaneous coronary intervention, *CrCl* creatinine clearance

and concomitant use of fibrinolytic [57–59] or GPI [60] have been associated with an increase of the hemorrhagic and non-hemorrhagic complications. During UFH infusion platelet count and hemoglobin should be measured at least once a day. More than a 20 % of patients could have a mild, clinically insignificant drop in their platelet count (above 100,000/μL). All UFH therapy (included IV flush) should be immediately interrupted if there is a drop in platelet count (suspecting HIT). Moreover a screening for anti–platelet factor-4 antibodies, followed by the more definitive serotonin release assay, is also required [56, 61, 62]. Reversal of UFH effects can be achieved with protamine, a small arginine-rich (e.g. cationic) nuclear protein purified from fish sperm. An IV bolus of 1 mg of protamine could be used to rapidly neutralize 100 U of UFH, reversing its anticoagulant effect [63, 64].

In the setting of PCI, the recommended dosage of IV UFH depends on prior exposure to anticoagulant therapy [65] (Table 3.2). In patients who have received prior anticoagulant therapy, if IV GPI are planned, UFH should be added as needed (e.g., 2,000–5,000 U) to achieve an ACT of 200–250 s. If IV GPI are not planned, the additional UFH should aim to achievean ACT of 250–300 s for HemoTec, 300–350 s for Hemochron. Without prior anticoagulant therapy, if IV GPI are planned, a 50–70 U/kg bolus should be administrated to achieve an ACT of 200–250 s. However, if IV GPI are not planned, the bolus dose may be 70–100 U/kg to achieve target ACT of 250–300 s for HemoTec, 300–350 s for Hemochron. Full-dose anticoagulation is no longer used after successful PCI procedures [65].

Side Effects and Contraindications

Bleeding is the main side effect related with the use of IV UFH, but recent trials demonstrated that this is <3 % [66]. However, higher heparin dosages, concomitant use of antiplatelet drugs or oral anticoagulant, and increasing age (>70 years) increases the bleeding risk [66]. As stated above, the development of HIT (usually between 5 and 15 days after the

initiation of UFH) is another important problem associated with heparin therapy. Patients who have a previous exposition to heparin may have a more rapid onset [36, 37, 61].An alternative antithrombin drug must be chosen in the setting of HIT. The development of osteoporosis and rare allergic reactions less commonly have been described with long-term use of heparin.

Low-Molecular-Weight Heparin

Mechanism of Action and Pharmacokinetic/ Pharmacodynamic Profile

Because of the many known limitations associated with the use of UFH (nonspecific binding, the production of antiheparin antibodies that may induce thrombocytopenia, continuous IV infusion, and the necessity for frequent monitoring), LMWHs, potent inhibitors of both thrombin (anti-IIa effects) and FXa have been developed [55]. These heparins do not require monitoring due to their more rapid and predictable absorption, anticoagulant response and greater than 90 % bioavailability [67]. Anti-Xa levels peak 3–5 h after a SC dose of LMWH [68, 69]. Fewer platelet agonist effects less often associated with HIT also characterize LMWHs. After 3–6 h following a SC dose a renal elimination (largely dose-independent) takes place, leading to prolonged anti-Xa effect and linear accumulation of anti-Xa activity in patients with a creatinine clearance (CrCl) <30 ml/min [70–72]. The anticoagulant effect of LMWHs can be measured via anti-FXa levels, with a target peak anti-Xa level 0.6–1.0 U/mL derived from studies of venous thromboembolism treatment [73, 74].

Depolymerization of the polysaccharide chains of UFH originates LMWHs, producing fragments ranging from 2,000 to 10,000 Da [68, 69, 75]. The unique pentasaccharide sequence needed to bind to AT is contained by these shorter chain lengths, that are too short (<18 saccharides) to form the ternary complex crosslinking AT and thrombin. Consequently,

the primary effect of LMWHs is limited to AT-dependent FXa inhibition. LMWHs result in a FXa:thrombin inhibition ratio ranging from 2 to 4:1, in comparison to UFH where the ratio of FXa:thrombin inhibition is 1:1 [76]. Also compared to UFH, LMWHs have a more favorable and predictable pharmacokinetic profile because of its reduced binding to plasma proteins and cells [68].

Enoxaparin is the most studied and developed LMWH preparation in clinical trials of UA/NSTEMI, STEMI and PCI. The main difference among LMWHs is their molecular weight and therefore the relative anti-Xa:anti IIa ratio. Enoxaparin has a mean molecular weight of 4,200 Da with anti-Xa:anti-IIa ratio of 3.8; dalteparin with a mean molecular weight of 6,000 Da has an anti-Xa: anti-IIa ratio of 2.7 [69]. The preferential binding ratio to FXa over thrombin, less plasma protein binding, attenuated platelet activation, lower risk of HIT, and reduced binding to osteoblasts are the theoretical pharmacologic advantages of LMWH over UFH [35, 69, 77–79].

In the majority of clinical settings routine monitoring of anti-FXa levels is not necessary due to the predictable anticoagulant response to LMWHs. The Thrombolysis in Myocardial Infarction 11A (TIMI 11A) trial assessed the PK and pharmacodynamic (PD) properties of enoxaparin including an enoxaparin clearance of 0.733 L/h, a distribution volume of 5.24 L, and an elimination half-life of 5 h [80]. Enoxaparin clearance modeled and predicted hemorrhagic complications and was significantly related to patient weight and CrCl. A 27 % decrease in enoxaparin clearance was correlated with CrCl <30 mL/min, causing a 3.8-fold increased risk of major hemorrhage [81].In patients with CrCl <30 mL/min, the dose of enoxaparin needs to be adjusted and reduced in half (e.g. 1 mg/kg/day). Age, female sex, lower body weight, reduced renal function, and interventional procedures can increase the risk of bleeding with LMWH which is highly dose-related [80].

The probability of LMWHs to origin anti–platelet factor-4 antibody formation is about three times lower than UFH [56,

82] and produces less frequently HIT in patients who have anti-platelet factor-4 antibodies, although LMWHs are similarly reactive as UFH in activation assays of washed platelets using serum from HIT patients [56, 83]. Also osteopenic effect is lower compared with UFH [84]. Protamine sulfate (1 mg per each 1 mg of enoxaparin within 8 h) may be used to neutralize the anti-IIa effect of LMWH when hemorrhagic complications, but it is variable and uncertain the grade to which the anti-Xa activity of LMWH is neutralized by protamine [85].

Indications

The safety and efficacy of LMWHs has been demonstrated in patients with UA/NSTEMI and STEMI, and also in patients undergoing PCI [40, 49, 86]. LMWH with UFH have been directly compared in 9 randomized trials [87–95] in UA/NSTEMI patients. No significant differences in death or MI were observed in patients treated with LMWH compared with UFH in two studies using dalteparin [87, 88] and one with nadroparin [89]. Enoxaparin's greater anti-Xa-to-anti-IIa ratio when compared with dalteparin, and the extension of its antithrombotic actions to include inhibition of platelet aggregation by blocking the release of vWF could be the reasons of the greater severity of the disease in the patients enrolled in the reported studies [96].

A meta-analysis by Petersen et al. [97] that pooled the data from six trials evaluating 21,946UA/NSTEMI patients randomized to enoxaparin or UFH, showed significant reductions in the combined endpoint of death/MI by 30 days favoring enoxaparin over UFH, particularly in patients who had not received any antithrombin before randomization [97]. There were no significant differences in major bleeding or blood transfusion within the first week of therapy.

The largest and most recent trial comparing enoxaparin to UFH, randomized 10,027 high-risk patients with UA/NSTEMI undergoing an early invasive strategy using

guideline recommended aspirin, clopidogrel and GPI [90]. The primary composite end point of death or MI at 30 days, was no different between enoxaparin and UFH (14 % vs. 14.5 %; OR 0.96; 95 % CI, 0.86–1.06). Enoxaparin compared to UFH produced significantly higher TIMI major bleeding (P = 0.008). Anticoagulant switching effects due to pre-randomization anticoagulant use and time- rather than ACT-guided sheath removal in the enoxaparin arm were potential causes of the increased bleeding with enoxaparin [90]. Enoxaparin, but not the other LMWHs, is preferred over UFH for the medical management of UA/NSTEMI in the ACC/AHA guidelines [40]. The greatest benefit is described in patients with elevated troponin values.

As adjunctive pharmacotherapy for STEMI patients receiving fibrinolytic therapy, the safety and efficacy of enoxaparin versus UFH has been assessed in 2 trials. Added to fibrinolytic therapy, enoxaparin diminished the risk of in-hospital reinfarction or refractory ischemia compared to UFH, but at the expense of an increased the rate of intracranial hemorrhage (ICH) among patients over the age of 75 [49, 98, 99].

STEMI patients receiving thrombolytic therapy to enoxaparin or UFH for at least 48 h were randomized in the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction-TIMI 25 (ExTRACT-TIMI 25) trial (n = 20,506) [51]. Patients with impaired renal function defined (CrCl <30 mL/min) received a reduced dose of enoxaparin (1 mg/kg SC q.d.) and also patients older than 75 did not receive bolus of enoxaparin and receive a lower SC dose of 0.75 mg/kg b.i.d). The risk of death and reinfarction at 30 days associated with enoxaparin compared with UFH was significantly reduced (p = 0.001). Enoxaparin was associated with a significant increase of TIMI major bleeding compared with UFH (2.1 % vs. 1.4 %; P < 0.001). In conclusion, the type of fibrinolytic agent and the age of the patient did not affect the net clinical benefit (absence of death, non-fatal infarction, or ICH) which favored enoxaparin (10.1 % vs. 12.2 %; P < 0.001) [100, 101].

Dosages

UA/NSTEMI patients should receive anticoagulant therapy in addition to antiplatelet therapy as soon as possible after clinical presentation [40, 49] (Table 3.1). Enoxaparin (1 mg/kg SC b.i.d) has demonstrated to be effective for patients in whom an invasive or conservative strategy is selected. As previously mentioned, it is particularly important to adjust the dose of enoxaparin in patients with renal insufficiency (CrCl <30 mL/min), reducing it to 1.0 mg/kg SC daily. LMWH should be continued without loading of UFH if it has been started upstream.

Numerous routes of administration of LMWH can be used in the setting of a PCI: (a) the first dosing regimen option is 1 mg/kg SC b.i.d.; the last dose of SC LMWH has to be administered within 8 h of the procedure and it is also important to warrant that at least 2 SC doses of LMWH are given before the procedure to ensure balanced state; (b) a 0.3 mg/kg bolus of IV enoxaparin is recommended at the time of PCI if the last dose of enoxaparin was given 8–12 h before PCI, (c) another dosing regimen option at the time of PCI is 1 mg/kg enoxaparin IV (if no GPIis used) or 0.75 mg/kg (if a GPI is used) [40, 49]. The STEEPLE (SafeTy and Efficacy of Enoxaparin in PCI patients, an internationaL randomized Evaluation) study found safe the IV dose of 0.5 mg/kg for elective PCI [102].

In the setting of patients with STEMI treated with fibrinolysis if renal function is preserved (<2.5 mg/dL [220 μmol/L] in male patients and <2.0 mg/dL [175 μmol/L] in female patients), we recommend the use of enoxaparin over UFH, continued up to 8 days (Class IIa, LOE B). The recommended dosing for enoxaparin depends on the age: 30-mg IV bolus followed by 1 mg/kg SC q12 h (maximum of 100 mg for the first two SC doses) for <75 years; and no IV bolus, 0.75 mg/kg SC q12 h (maximum of 75 mg for the first two SC doses) for age >75 years. Enoxaparin should be given before fibrinolytic administration. The continuation of enoxaparin therapy after discharge has not be demonstrated to be beneficial [49], and for

this reason enoxaparin regimen uses to be maintained during hospitalization or until day 8 (whatever come first). Regardless of age, if the CrCl is <30 mL/min the dosage of 1 mg/kg subcutaneously every 24 h may be used.

For patients with STEMI undergoing PCI after receiving fibrinolytic therapy with enoxaparin, if the last SC dose was given within the prior 8 h, no additional enoxaparin should be administered; if the last SC dose was given between 8 and 12 h earlier, enoxaparin 0.3 mg/kg IV should be administered (Class I, LOE B) (Table 3.2). These recommendations are based on the analysis of patients who underwent PCI in the ExTRACT TIMI 25 trial [103] as well as on the Enoxaparin as adjunctive antithrombin therapy for ST-elevation myocardial infarction: results of the ENTIRE-TIMI 23 trial [104]. This trial demonstrated that enoxaparin was associated with similar TIMI 3 flow rates as UFH at an early time point, with similar risk of major hemorrhage and greater benefit over UFH regarding to ischemic events through 30 days (P = 0.005) [104].

Side Effects and Contraindications

Patients with contraindications to anticoagulant therapy such as active bleeding, significant thrombocytopenia, recent neurosurgery, ICH, or ocular surgery should not receive LMWH. Patients with bleeding diathesis, brain metastases, recent major trauma, endocarditis, and severe hypertension required to be treated with particular caution. Less major bleeding compared with UFH has been associated with enoxaparin in acute venous thromboembolism. In the setting of ACS, neither UFH nor LMWH are associated with an increase in major bleeding, but in ischemic stroke the both agents are associated with an increase in major bleeding [105]. Hemorrhagic complications could occur due to LMWH, particularly in patients with renal dysfunction (who should receive an adjusted dose of enoxaparin). To neutralize the anti-IIa effect of LMWH, protamine sulfate may be administered, although the degree of neutralization of the anti-Xa

activity of LMWH is variable and uncertain. In patients with documented or suspected HIT,LMWH are not recommended for use because they can induce it.

Direct Thrombin Inhibitors

The direct thrombin inhibitors (DTIs) bind to thrombin and inhibit its capacity to transform fibrinogen to fibrin, to intensify its own generation through activation of FV, FVIII, and FIX, and to function as a potent platelet agonist [106]. Importantly, DTIs not only block free thrombin, but also inhibit thrombin bound to fibrin in contrast to indirect thrombin inhibitors [12, 107–109] (Fig. 3.3). These properties are indeed important and provide a rationale for their clinical use in the setting of ACS and PCI. The anticoagulant effect of DTIs in healthy volunteers can be reversed by recombinant factor VIIa, although the short half-life of these agents normally avoids the necessity for active reversal [110]. Three DTI's are approved for clinical use (lepirudin, argatroban, and bivalirudin) and described below.

Hirudin (lepirudin)

Mechanism of Action and Pharmacokinetic/ Pharmacodynamic Profile

Hirudin is among the most potent of the natural thrombin inhibitors. It is a 65-amino acid polypeptide located in the salivary glands of the leech *Hirudo medicinalis*. Lepirudin is a recombinant form of hirudin that irreversibly inhibits thrombin [111]. Several biochemical and molecular biological techniques have been used to study the specific nature of the hirudin-thrombin interaction. The thrombin time (TT) and the aPTT are the most frequently used measures for the anticoagulant activity of hirudin. Bleeding time is not significantly altered by hirudin which does not have direct effects on platelet aggregation or secretion.

Indications

In UA/NSTEMI a single dose of UFH with a single dose of hirudin were compared in both the TIMI-9 and the Global Utilization of Strategies to Open Occluded Coronary Arteries (GUSTO) II trials [57, 58]. Both trials used high doses of hirudin (0.6 mg/kg bolus followed by 0.2 mg/kg/h) and weight-adjusted heparin. An unacceptably high rate of ICH in both treatment arms forced to terminate prematurely both trials. Using lower doses of both hirudin (0.1 mg/kg bolus followed by 0.1 mg/kg/h) and heparin (not weight adjusted), both trials were continued as TIMI-9b [57] and GUSTO IIb [59]. The TIMI-9b trial showed similar efficacy of heparin and hirudin as adjunctive therapies for SK or t-PA in individuals with acute Q-wave MI without differences in bleeding [57]. The GUSTO IIb trial showed a marginally significant benefit of hirudin over heparin early after infarction in individuals with both Q wave and non–Q-wave MI, which lessened over time [59]. Additionally, results from the Organisation to Assess Strategies for Ischemic Syndromes (OASIS-2) trial showed that recombinant hirudin may be useful when compared with heparin in preventing cardiovascular death, MI, and refractory angina with an acceptable safety profile in patients who have UA/NSTEMI and who receive aspirin [112]. This study (n = 10,141) randomized patients to receive UFH or hirudin (0.4 mg/kg bolus, 0.15 mg/kg/h infusion) for 72 h. This study demonstrated a nonsignificant difference between hirudin and UFH in the primary outcome of cardiovascular death or MI at 7 days: 3.6 % vs.4.2 % had experienced cardiovascular death or new MI (P = 0.077). However, hirudin was associated with a significantly increased risk of major, but not life-threatening, bleeding [112].

A pooled analysis of the OASIS, GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries)-2B, and TIMI-9B trials showed superiority of hirudin compared with UFH for the prevention of death or MI at 30–35 days [112]. However, the only approved clinical application for this agent is in the treatment of HIT recombinant hirudin (lepirudin). Because of a reduced risk

for new thromboembolic complications, lepirudin-treated patients had consistently lower incidences of combined endpoints primarily when compared with historical controls [12].

Dosage

The dosage of IV hirudin is 0.15 mg/kg/h infusion with or without 0.4 mg/kg initial bolus [113]. Monitoring is required and it has a narrow therapeutic window. During treatment with lepirudin, aPTT ratios of 1.5:2.5 produce optimal clinical efficacy with a moderate risk for bleeding, aPTT ratios lower than 1.5 are subtherapeutic, and aPTT levels greater than 2.5 are associated with high bleeding risk. The plasma half-life of hirudins is 60 min following IV injection [114]. Renal clearance is the predominant way of elimination of this drug. Adjustment of dose of lepirudin is recommended for patients with severe renal impairment (<30 ml/min) reducing the dose by a factor of six compared with that given to patients with normal renal function. Monitoring of aPTT should be necessary to further adjust if it exceeds two times baseline. In moderate (CrCl 31–60 ml/min) and mild renal impairment (CrCl 61–90 ml/min) adjustment is not recommended initially but if peak aPTT exceeds two times baseline it is necessary to reduce the dose by half [114].

Side Effects and Contraindications

In settings where anticoagulation is contraindicated hirudin should not be used. In the setting of concomitant anticoagulation or platelet inhibitors, the risk of bleeding with hirudin is increased. In patients with renal dysfunction hirudin should not be used (given that it is renally cleared). Antibody formation to hirudin can be induced for this agent in up to 40 % of patients, presenting anaphylaxis after a re-exposure [113].

Argatroban

Mechanism of Action and Pharmacokinetic/ Pharmacodynamic Profile

Argatroban or (2R,4R) 4-methyl-[N2-(3-methyl-1,2,3,4-tetrahydro-8-quinolinyl) sulfonyl]-2-piperidine carboxylic acid is a small-molecule with potent direct competitive thrombin inhibiting effects [12]. This drug is a synthetic N2-substituted arginine derivative that binds to the catalytic site of thrombin with high affinity. Itbinds noncovalently and rapidly to both clot-bound and soluble thrombin, forming in that way a reversible complex [115, 116]. Argatroban is metabolized via the cytochrome P450 3A4 pathway in the liver with a half-life of 45 min. Rapid restoration of normal hemostasis on cessation of therapy is allowed by the reversible binding of the agent. Argatroban has a predictable dose response that correlates with changes in anticoagulant parameters.

Indications

The use of argatroban has been evaluated primarily as adjunctive therapy with fibrinolytics, in the treatment of HIT, or in patients undergoing PCI [40, 49]. At present there are still limited data with argatroban and it is approved only for use in HIT [117].

Dosages

Argatroban is administered in individuals with unstable angina at a dose of 0.5–5.0 μg/kg/min for 4 h. Dose adjustment with renal impairment is unnecessary, but in patients with renal failure it should be used with caution [118].

Side Effects and Contraindications

Argatroban should not be used in patients who have contraindications to anticoagulant therapy. Argatroban metabolism occurs in the liver. The maximum concentration and half-life of argatroban are increased approximately two- to threefold and clearance is one fourth in patients with hepatic impairment compared with healthy volunteers.

Bivalirudin

Mechanism of Action and Pharmacokinetic/ Pharmacodynamic Profile

Bivalirudin is a 20-amino acid polypeptide and is a synthetic version of hirudin [119]. Its amino-terminal D-Phe-Pro-Arg-Pro domain, which interacts with active site of thrombin, is linked via 4 Gly residues to adodecapeptide analogue of the carboxy-terminal of hirudin (thrombinexosite) [120] (Fig. 3.3). Bivalirudin forms a 1:1 stoichiometric complex with thrombin, but once bound, the amino terminal of bivalirudin is cleaved by thrombin, thereby restoring thrombin activity [121].

The half-life of bivalirudin is 25 min [122]. Its clearance is mediated by proteolysis, hepatic metabolism, and renal excretion [123]. Severe renal impairment prolongs the half-life of bivalirudin, and dose adjustment is required for dialysis [124]. Bivalirudin is not immunogenic, in contrast to hirudin, although antibodies against hirudin can cross-react with bivalirudin, the clinical consequences of which are unknown [113].

Indications and Dosage

The use of bivalirudin is supported by wide clinical trial experience. These include supstream treatment in patients with UA/NSTEMI [125, 126],across the spectrum of patients of patients undergoing PCI, including patients with STEMI

undergoing primary PCI as an alternative to UFH plus GPI [127], in patients undergoing CABG [128], and in HIT [129]. The recommended dose in PCI is a bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/h for up to 4 h after the procedure as clinically warranted. After cessation of the 1.75 mg/kg/h infusion, a reduced infusion dose of 0.25 mg/kg/h may be continued for 4–12 h as clinically necessary.

Evidence for Use: UA/NSTEMI

Bivalirudin and UFH were compared in the Randomized Evaluation in Percutaneous Coronary Intervention Linking Angiomax to Reduced Clinical Events 2(REPLACE-2) study [130]. This trial (n = 6,010) enrolled patients undergoing urgent or elective PCI who were randomized to receive bivalirudin with provisional GPI or UFH with planned GPI. The study demonstrated the noninferiority of bivalirudin compared to UFH plus GPI regarding ischemic end point sand showed also a significant association with less major and minor bleeding [130].

In the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) study, patients with UA/NSTEMI (n = 13,189) were randomized to one of three antithrombotic regimens: UFH or enoxaparin plus GPI, bivalirudin plus GPI, or bivalirudin alone [125]. Compared with UFH plus a GPI, bivalirudin plus a GPI, was associated with noninferior 30-day rates of the composite ischemia end point (7.7 and 7.3 %, respectively), major bleeding (5.3 and 5.7 %), and the net clinical outcome end point (11.8 and 11.7 %). Compared with UFH plus a GPI, bivalirudin alone was associated with a noninferior rate of the composite ischemia end point (7.8 and 7.3 %, respectively; $P = 0.32$) and significantly reduced rates of major bleeding (3.0 % vs. 5.7 %; $P < 0.001$) and the net clinical outcome end point (10.1 % vs. 11.7 %; $P = 0.02$). Essentially, compared with UFH bivalirudin in addition to GPI presented similar rates of ischemia and bleeding, but bivalirudin alone was also associated with significantly lower rates of bleeding [125].

However, the ACUITY trial presented some important limitations that need to be addressed: first, not all patients were pretreated with clopidogrel (and used inconsistent dosing) and two thirds of them were already receiving some anticoagulant before randomization and, with the resultant variability among the treatments before and during the study. Moreover the election of type of GPI and UFH/LMWH was left at the discretion of physician. Lastly, the ACUITY trial has been also criticized because of its quite liberal definition of bleeding, particularly concerning the definition of major bleeding [125].

The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 4 (ISAR REACT 4) trial [126] was a double-blind randomized trial which design tried to overcome the aforementioned limitations of the ACUITY trial. The same GPI (abciximab) was used and all patients received a 600-mg-clopidogrel pretreatment. In addition, less liberal definitions of major bleeding were considered (presence of intracranial, intraocular, or retroperitoneal hemorrhage; a decrease in the hemoglobin level of >40 g/L plus either overt bleeding or the need for transfusion of 2 or more units of packed red cells or whole blood). Specifically, the ISAR REACT 4 trial compared abciximab and heparin versus bivalirudin in NSTEMI patients undergoing PCI ($n=1,721$) showing that such regimen compared to bivalirudin increased the risk of bleeding in NSTEMI patients undergoing PCI ($P=0.02$) and failed to decrease the rate of ischemic events ($P=0.76$) [126]. Current guidelines for UA/NSTEMI recommend to omit administration of an IV GPI if bivalirudin is selected as the anticoagulant and at least 300 mg of cvs. lopidogrel was administered at least 6 h earlier than planned catheterization or PCI (Class IIa, LOE B) [40, 65] (Table 3.1).

Evidence for Use: STEMI

In the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarctions (HORIZONS-AMI) trial, [127] STEMI patients ($n=3,602$) who presented within 12 h after onset of symptoms were randomized to UFH plus

GPI or to treatment with bivalirudin alone for primary PCI. At 30 days, compared with UFH plus GPI, bivalirudin alone demonstrated lower rates of death (P = 0.047) and major bleeding (P < 0.001), leading to a significantly lower rate of net adverse clinical events (P = 0.005). The rates of cardiac mortality (P = 0.005) and all-cause mortality (P = 0.037) were significantly lower in the bivalirudin alone treatment group after 1 year (p = 0.001) [131] and 3 years (P = 0.03) [132]. Regarding stent thrombosis (ST), the study found that within the first 24 h ST occurred more commonly in patients on bivalirudin compared with those assigned to heparin plus a GPI [127]. Nevertheless, between 24 h and 1 year, ST was more frequent in the heparin plus GPI group than in the bivalirudin group (46 vs. 36 ST events, respectively). Thus, at the end of the 1-year follow-up, the rate of ST was similar in the two groups (3.1 % vs. 3.5 %, respectively, P =0.53) [131]. However, the hazard ratio for death within the first month was greater after major bleeding than after reinfarction or ST [127]. In a post-hoc analysis, mortality and major bleeding were shown to be significantly higher after in-hospital ST compared with out-of-hospital ST (p < 0.01 for both events). Randomization to UFH plus GPI (vs. bivalirudin) was additionally correlated with increased mortality after ST [133].

Another post-hoc analysis of this study [134] showed that 600-mg-clopidogrel loading dose compared with 300 mg had significantly lower 30-day unadjusted rates of definite or probable ST (1.7 % vs. 2.8 %, p = 0.04), as well as lower mortality (p = 0.03) and reinfarction (p = 0.02), and, without higher bleeding rates. Bivalirudin monotherapy resulted in similar reductions in net adverse cardiac event rates with both doses (p-interaction = 0.41). However, a 600-mg-clopidogrel loading dose was an independent predictor of lower rates of 30-day major adverse cardiac events (p = 0.04) [134].

In the setting of STEMI, current guidelines recommended bivalirudin over UFH and a GPI, restricting the use of GPI to bailout (Class I, LOE B) [49, 50]. In patients at high risk of bleeding the American guidelines recommended bivalirudin preferred over UFH with GPI (Class IIa, LOE B) [49] (Table 3.2).

Factor Xa Inhibitors

Fondaparinux

Mechanism of Action and Pharmacokinetic/ Pharmacodynamic Profile

Fondaparinux is a selective indirect FXa inhibitor. This compound, with a molecular weight of 1,728 Da, is a synthetic analog of the unique AT-binding pentasaccharide sequence found in UFH. It binds reversibly to AT and provokes an irreversible conformational change at the reactive site of AT that increases its reactivity with FXa [135]. Fondaparinux is available to activate additional AT molecules after being released from AT, but it does not increase the rate of thrombin inhibition by AT because it is too short to bridge AT to thrombin. Fondaparinux does not have any inhibitory action against thrombin that is already formed, even though it inhibits FXa-dependent thrombin generation [113]. After SC injection the bioavailability is 100 % [136, 137]. The elimination half-life is 17 h with primary renal clearance. Fondaparinux is contraindicated in patients with severe renal impairment [40, 113, 138]. The anticoagulant response of fondaparinux is predictable and its PK profile is linear when it is given in SC doses of 2–8 mg or in IV doses ranging from 2 to 20 mg that result in anti-Xa activity that is roughly 7 times that of LMWHs [136, 137]. Its minimal nonspecific binding to plasma proteins it is likely to be the reason of its excellent bioavailability and predictable anticoagulant response [139].

Even if monitoring is not required, the anticoagulant effect of fondaparinux can be measured in anti-FXa units. Fondaparinux does not affect other parameters of anticoagulation, including aPTT, activated clotting time, or prothromb in time [138] and does not induce the formation of UFH:platelet factor-4 complexes and does not cross-react with HIT antibodies. Therefore, it is unlikely that induces HIT [140]. Not with Standing fondaparinux is not labeled for treatment of HIT, it has been used successfully to treat HIT

patients [141, 142].It is unlikely that fondaparinux induces osteoporosis because it has no effect on osteoblasts [143]. In pregnancy, fondaparinux has not been studied enough, but it does not seem to cross the placental barrier [144].

Dosing, Monitoring, Reversal

Fondaparinux 2.5 mg daily was shown to have the best efficacy/safety profile when compared with 4-, 8-, and 12-mg doses of fondaparinux and with enoxaparin 1 mg/kg b.i.d based on a dose-ranging study of fondaparinux versus enoxaparin in the setting of UA/NSTEMI involving 1,147 patients [145].

There are no data about coagulation monitoring as part of the clinical development of this drug, but currently it is not recommended. Also in patients with severe renal impairment (CrCl <30 mL/min), fondaparinux has not been adequately studied. However, it is established that in patients with moderate renal impairment (30–50 mL/min) fondaparinux dose should be reduced in half or low-dose heparin should be used in place of fondaparinux [113].To assess the anticoagulant effect of fondaparinux it is possible to measure anti-Xa levels, but the standard therapeutic level is unknown. It is important to highlight that protamine is not able to reverse the anticoagulant effect of fondaparinux. Recombinant factor VIIa may be given to achieve the reversal of the anticoagulant effect of fondaparinux if life-threatening bleeding takes place due to this agent [146].

Indications

Evidence for Use: UA/NSTEMI

The large-scale OASIS-5 trial (n = 20,078) evaluated the efficacy and safety of fondaparinux (2.5 mg SC daily) compared with enoxaparin (1 mg/kg SC b.i.d) in patients with UA/NSTEMI [147]. Fondaparinux demonstrated to be noninferior vs. enoxaparin in the primary outcome of

combined death, MI, or refractory ischemia at 9 days was achieved (P = 0.007), with less incidence of major bleeding (P < 0.001). Fondaparinux showed a superior net clinical benefit (composite of death, MI refractory ischemia, or major bleeding) compared with enoxaparin (P < 0.001). Compared with enoxaparin, fondaparinux also demonstrated significantly a reduction in mortality at 6 months (P = 0.05). Nevertheless, more catheter-related thrombus formation occurred with fondaparinux in the group of patients who underwent PCI (P < 0.001), showing that anticoagulation with fondaparinux alone is not enough for PCI, therefore another anticoagulant with FIIa activity (such as UFH) must be coadministered [147].

The main disadvantage of fondaparinux in this trial was the excess of catheter thrombosis seen in patients undergoing PCI (0.9 % vs. 0.4 % with enoxaparin), which has limited the widespread use of the drug in this setting. For that reason the OASIS investigators conducted The Fondaparinux Trial With UFH During Revascularization in ACS (FUTURA/OASIS-8) trial (n = 2,026) in order to evaluate the safety of 2 dose regimens of adjunctive IV UFH during PCI in high-risk patients with NSTEMI initially treated with fondaparinux [148]. Patients received either low-dose UFH (50 U/kg, regardless of use of GPI) or standard-dose UFH (85 U/kg or 60 U/kg with GPI), adjusted by activated clotting time. In terms of preventing peri-PCI major bleeding or major vascular access-site complications, low fixed-dose of UFH was not superior to standard ACT-guided UFH. Thrombotic events were not significantly different between the treatment groups (P = 0.27). Catheter thrombosis rates were very low (0.5 % in the low-dose group and 0.1 % in the standard-dose group, P = 0.15) [148].

Based on the above, current guidelines recommended 2.5 mg SC once daily as having the most favorable efficacy-safety profile with respect to anticoagulation (Class I, LOE A), avoiding its use for CrCl <30 mL/min. During PCI, at present2012 American guidelines recommend an additional 50–60 IU/kg IV bolus of UFH [40] while European guidelines recommend a 85 IU/kg IV bolus of UFH (adapted to ACT) or 60 IU in the case of concomitant use of GPI (Class I, LOE B) [41] (Table 3.1).

Evidence for Use: STEMI

In the OASIS-6 trial (n = 12,092), fondaparinux was evaluated as an alternative to standard adjunctive anticoagulation in patients with STEMI [149]. Patients received 2.5 mg SC daily for 8 day and it was compared with either no UFH (stratum I) or UFH infusion (stratum II) for 48 h. In approximately 25 % of patients primary PCI was performed. Approximately half the patients received fibrinolytic therapy, of whom 73 % received SK. In patients who received fondaparinux, the primary outcome of 30-day death or MI was significantly reduced (P = 0.008), although this was driven by patients in stratum I only. No significant benefit with fondaparinux was found in patients who underwent primary PCI or who were in stratum II. It is important to highlight that, compared with UFH, patients who underwent primary PCI with fondaparinux presented more catheter-related thrombi (P < 0.001), more coronary complications (P = 0.04), and a trend toward higher death or MI compared with UFH (P = 0.19).

Importantly, although European guidelines recommend using of fondaparinux in ACS [50], in the United States fondaparinux is not currently approved for such use by the FDA, as it is reflected in the current ACC guidelines for STEMI [49], because of the risk of catheter thrombosis (Class III, LOE: B) (Table 3.2).

As adjunctive antithrombotic therapy to support reperfusion with fibrinolytic therapy an initial IV dose of 2.5 mg of fondaparinux is recommended, and then 2.5 mg subcutaneously daily starting the following day for the index hospitalization up to 8 days or until revascularization. Fondaparinux is contraindicated if CrCl <30 mL/min [49] (Table 3.2).

Otamixaban

Otamixaban is a specific direct parenteral small molecule that inhibits clot-bound FXa which is inaccessible to large molecule or indirect inhibitors agent. Otamixaban is not still under advanced clinical investigation and not approved for clinical use. However, this agent has shown thus far promising results. Otamixaban has a very favorable PK/PD profile:

short acting (half-life30 min), weight based bolus (vs. infusion), no need for monitoring and no significant renal elimination (<25 %), but no antidote to otamixaban has been described [150].

In the Randomized, double-blind, dose-ranging study of otamixaban, a novel, parenteral, short-acting direct factor Xa inhibitor, in percutaneous coronary intervention (the SEPIA-PCI trial) [151], 947 patients were randomly assigned to either 1 of 5 weight-adjusted otamixaban regimens or weight-adjusted UFH before PCI. The study showed that otamixaban reduced the median change in prothrombin fragments 1 + 2 (F1 + 2) significantly more than UFH at the highest dose regimen (P = 0.008), without significant difference in the incidence of TIMI bleeding compared with UFH [151]. Posteriorly, another phase II study: the Otamixaban for the treatment of patients with non-ST-elevation acute coronary syndromes (SEPIA-ACS1 TIMI 42) trial (n = 3,241) assessed the dose response on death, MI, urgent revascularization or bail-out in patients with NSTE-ACS with encouraging results about safety and efficacy, concluding that otamixaban 0.105–014 mg/kg/h appeared to be best range for further study as a replacement of UFH and GPI [152]. The ongoing phase III Treatment of Acute coronary syndromes with Otamixaban (TAO) trial (n = 13,240) is evaluating the efficacy of otamixaban vs. UFH with and without eptifibatide on reduction of death or MI in patients with NSTE-ACS [153].

Oral Anticoagulant Therapy in ACS

The main reasons of the necessity of long term anticoagulation in ACS patients is the coexistence of another indication for anticoagulant therapy, such as atrial fibrillation (AF), left ventricular thrombus, advanced heart failure, deep venous thrombosis, prosthetic heart valves, or history of pulmonary embolism. The main risk in these patients remains the concomitant use of antiplatelet therapy and the consequent high risk of bleeding. Although, in the ACS population a considerable reduction in cardiovascular events

is obtained with long-term dual antiplatelet therapy (DAPT) using aspirin and a $P2Y_{12}$ platelet receptor, [154] the risk of a recurrent vascular event within 12 months is still high and underscores the necessity of better secondary prevention strategies. Given that levels of thrombin generation persist elevated in ACS patients [155], and given the role of thrombin on arterial thrombogenesis, long-term use of oral anticoagulant strategies have been considered for secondary prevention of coronary events. Initially, vitamin K antagonists (VKAs) have been studied, mostly in combination with aspirin. However, despite the proven efficacy of this strategy, bleeding rates were high. The development of novel oral anticoagulants (NOACs) characterized by a better safety profile compared with VKAs have led to reconsider long-term oral anticoagulant therapy in adjunct to standard of care antiplatelet therapy, including mostly DAPT with aspirin and clopidogrel, also known as "triple therapy". The role of oral anticoagulant therapy for secondary prevention of ischemic events is described below.

Vitamin K Antagonists

VKAs, warfarin and coumarin derivatives, have demonstrated to reduce the risk of recurrent ischemic events both in monotherapy and in combination with aspirin [156]. In the Warfarin-Aspirin Re-Infarction Study (WARIS II) study, in combination with aspirin or given alone, warfarin was superior to aspirin alone in reducing the incidence of composite events after an acute MI but was associated with a higher risk of bleeding [156]. In this study, the combination therapy targeted an international normalized ratio (INR) of 2–2.5 and the warfarin alone group had a target INR of 2.8–4.2. No reduction in the combined risk of cardiovascular death, reinfarction, or stroke was demonstrated using a fixed, low dose of warfarin added to aspirin in the long term after MI, but this combination reduced the risk of stroke (secondary endpoint). An increased risk of bleeding was also associated to the concomitant administration of aspirin and warfarin [157].

These bleeding rates are even higher in patients who are on DAPT with aspirin and clopidogrel, as have been studied mostly in patients with AF undergoing PCI [158–160], the details of which going beyond the scope of this chapter which is focused on the role of anticoagulants for secondary prevention of ischemic recurrences in ACS.

Currently available data based on around 20,000 patients from randomized clinical trials show that oral anticoagulant therapy (given in adequate doses) reduce the rates of re-infarction and thromboembolic stroke, but increasing significantly the rates of hemorrhagic events [161]. Nevertheless, even in controlled trials the use of warfarin, presents several difficulties. For example, in the WARIS II study the INR was below target in about one third of patients, and those over 75 years of age were excluded [161].

Novel Oral Anticoagulants for Secondary Prevention

Several classes of NOACs have been developed. These agents have been primarily studied in patients with AF [162–164] and characterized by more favorable safety profile, particularly a lower risk of ICH, with comparable or better efficacy compared with VKAs. These agents also have the advantage of less drug-drug and food-drug interactions and that they can be administered in fixed doses without routine coagulation monitoring.

There are some aspects that should be considered for the periprocedural management of NOACs, compared with warfarin, such as their shorter half-life or the fact that the onset of their effects is within 2 h, provided that intestinal absorption is normal. Table 3.3 summarizes the recommendations for NOACs in patients undergoing elective PCI. The current status of knowledge of NOACs for secondary prevention of ischemic events in ACS is described below.

Table 3.3 Elective PCI recommendations

Renal function (CrCl mL/min)	Half life (hours)	Timing of Procedure after last dose of NOAC
Dabigatran		
>50 mL/min	15 (12–34)	24 h
>30 to ≤50 mL/min	18 (13–13)	2 days
≥30 mL/min	27 (22–35)	4 days
Rivaroxaban		
>30 mL/min	12 (11–13)	24 h
≤30 mL/min	Unknown	2 days
Apixaban		
>50 mL/min	7–8	24 h
<30 to ≤50 mL/min	17–18	2 days

Adapted from: Stangier et al. [165]; Schulman et al. [166]; Spyropoulos et al. [167]

Oral Direct Thrombin Inhibitors

Ximelagatran

The Efficacy and Safety of the Oral Direct Thrombin Inhibitor Ximelagatran in Patients with Recent Myocardial Damage (ESTEEM) trial for the secondary prevention of ACS showed a 24 % relative reduction with ximelagatran plus aspirin treatment for 6 months in the risk of the primary composite end point of death, nonfatal MI, and severe recurrent ischemia versus aspirin alone, although this occurred at the expense of an increased risk of bleeding [168]. Ximelagatran was retrieved from the market due to safety concerns (hepatic toxicity), but did provide encouraging results for other NOACs to be tested for secondary prevention in ACS.

Dabigatran Etexilate

Dabigatran etexilate binds reversibly and directly to the catalytic site of thrombin. It is a synthetic low molecular weight eptidomimetic generated as a prodrug which immediately after absorption is biotranformed by an esterase-mediated hydrolysis to the active compound dabigatran [169–171] Table 3.4 summarizes the principal pharmacologic characteristics of dabigatran etexilate compared with the new FXa inhibitors [173].

The Dose Finding Study for Dabigatran Etexilate in Patients With Acute Coronary Syndrome (RE-DEEM) trial (n = 1,861) was a phase II study that showed a dose-dependent increase in clinically relevant bleeding events, with highest rates with dose regimens currently used in AF (110 mg and 150 mg b.i.d.) [174]. Despite higher dabigatran doses compared with lower doses and placebo group seemed to have some benefit, it was impossible to demonstrate an efficacy difference in cardiovascular death, nonfatal MI or nonhemorrhagic stroke because the lack of enough statistical power of the trial [174]. Phase III clinical testing of dabigatran in ACS has not been pursued.

Oral Direct Factor Xa Inhibitors

Rivaroxaban, apixaban and darexaban are the three oral direct FXa inhibitors that have been most studied over recent years. Table 3.4 summarize the principal pharmacologic characteristics and dosages of these drugs compared with dabigatran [173, 175].

Darexaban (YM150)

The safety, tolerability, and regimen of darexaban for the prevention of ischemic events in ACS were evaluated in The Study Evaluating Safety, Tolerability and Efficacy of YM150 in Subjects With Acute Coronary Syndromes (RUBY-1) trial [176]. The study did not find benefits regarding an addition of

TABLE 3.4 Pharmacological characteristics of oral direct thrombin inhibitors and oral direct factor Xa inhibitors

	Dabigatran etexilate	**Rivaroxaban**	**Apixaban**	**Darexaban**
Mechanism of action	Selective direct thrombin (FIIa) inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor
Prodrug	Yes	No	No	Yes
Oral bioavailability	6.5 %	80–100 %	50–66 %	5 %
Half-life (hours)	12–17	5–13	8–15	14–18
Excretion	Renal 80 % Fecal 20 %	Renal 66 % 36 % unchanged 30 % inactive metabolites Fecal-biliary 28 %	Renal 27 % Fecal 55 %	Renal 50 % Fecal 50 %
Time to maximum inhibition (hours)	0.5–2	1–4	1–4	1–1.5
Potential metabolic drug interactions	P-glycoprotein Inhibitors of P-gp: Verapamil, reduce dose Dronedarone: avoid Potent inducers of P-gp[c]: avoid	CYP3A4/ P-glycoprotein Potent inhibitors of CYP3A4 and P-gp[a]: avoid Potent inducers of CYP3A4[b]and P-gp: use with caution	CYP3A4/P-glycoprotein Potent inhibitors of and P-gp[a]: avoid Potent inducers of CYP3A4[b] and P-gp[c] use with caution	No drug-drug interactions with CYP3A4/ P-glycoprotein inhibitors and inducers

(continued)

Table 3.4 (continued)

	Dabigatran etexilate	Rivaroxaban	Apixaban	Darexaban
Reverse effect	Antidote not available Hemodialysis may remove 60 % Oral activated charcoal may adsorb it from the stomach. Inactivated or activated prothrombin complex concentrates or recombinant activated FVII may be useful if uncontrolled bleeding	Antidote not available Hemodialysis not effective (high plasma protein binding) Fresh frozen plasma, prothrombin complex concentrates, or activated FVII may reverse their effects		Antidote not available

Adapted from De Caterina et al. [172]
CYP cytochrome P450 isoenzyme, *F* factor, *P-gp* P-glycoprotein
[a]Potent inhibitors of CYP3A4 include antifungals (e.g. ketoconazole, intraconazole, voriconazole, posaconazole), chloramphenicol, clarithromycin, and protease inhibitors (e.g. ritonavir, atanazavir). P-gp inhibitors include verapamil, amiodarone, quinidine, and clarithromycin
[b]Potent CYP3A4 inducers include phenytoin, carbamazepine, phenobarbital, and St. John's wort
[c]P-gp inducers include rifampicin, St. John's wort (Hypericum perforatum), carbamazepine, and phenytoin

efficacy to DAPT in this setting, but showed an expected dose-related 2- to 4-fold increase in bleeding versus placebo as the only safety concern [176]. Darexaban development has been discontinued.

Apixaban

The phase II Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial found a dose-dependent interaction increased risk of bleeding complications with apixaban 2.5 mg b.i.d. and 10 mg q.d. Although apixaban was associated with a numerically lower incidence of cardiovascular death, MI, severe recurrent ischemia, or ischemic stroke it was not statistically significant [177]. APPRAISE-2 trial ($n = 7{,}392$) failed also to find similar benefits of adding a high dose of apixaban (5 mg b.i.d) to single or DAPT in a very-high-risk ACS population [178]. A greater number of intracranial and fatal bleeding events happened with apixaban than with placebo, without a significant reduction in recurrent ischemic events. Because of the wide CIs allow for either benefit or harm, the overall efficacy/safety balance of apixaban is still unknown.

Rivaroxaban

The Rivaroxaban in Combination With Aspirin Alone or With Aspirin and a thienopyridine in Patients With Acute Coronary Syndromes-TIMI 46 (ATLAS ACS-TIMI 46) trial [179], demonstrated either in patients receiving aspirin alone and in patients receiving DAPT, a rivaroxaban dose-dependent increased risk of clinically significant bleeding complications. However, the lower doses were associated with lowest bleeding risk and accompanied by an ischemic benefit. This set the basis for developing the phase III ATLAS ACS-2–TIMI 51 (ATLAS-2) trial ($n = 15{,}526$) demonstrated that both rivaroxaban regimens (2.5-mg and 5-mg b.i.d.) compared with placebo significantly reduced the primary efficacy composite of cardiovascular death, MI, or stroke ($p < 0.008$) [180, 181]. The 2.5-mg (but not 5-mg b.i.d.),

reduced cardiovascular and all-cause mortality. The 5 mg b.i.d. (but not 2.5-mg b.i.d.) reduced MI. Both dosages of rivaroxaban reduced significantly the risk of ST, as compared with placebo (P = 0.02), while the 2.5-mg b.i.d dose showed a nonsignificant but directionally consistent benefit for MI. The rates of non-CABG-related TIMI major bleeding and ICH with both doses were significantly increased, without a significant increase in fatal bleeding (P = 0.66) [180, 181].

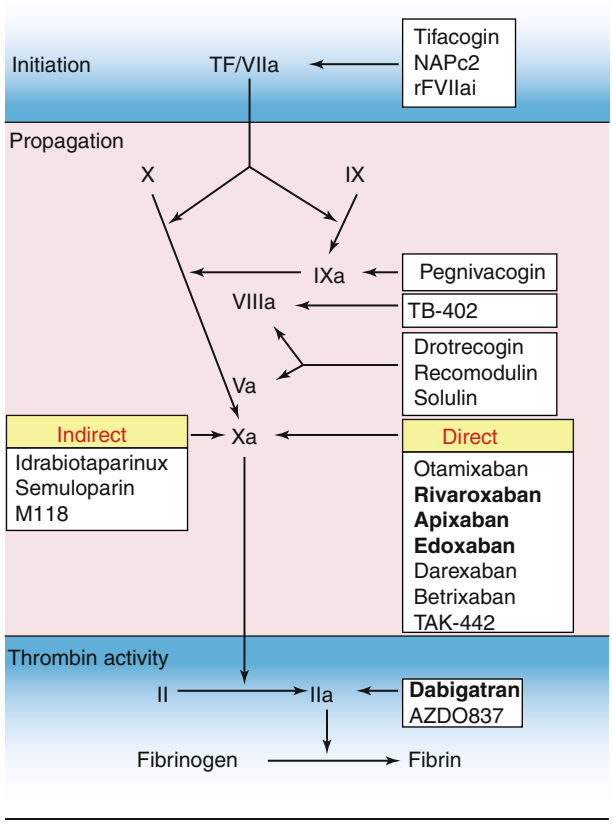
Current ESC Guidelines for the management of STEMI recommended considering the use of low-dose rivaroxaban (2.5 mg b.i.d) in selected patients who receive aspirin and clopidogrel, if the patient is at low bleeding risk (Class of recommendation IIb, LOE B) [50]. Rivaroxaban however is still not approved for clinical use in the United States.

Anticoagulants Under Clinical Development

Aptamers are small oligonucleotides that form unique sequence-dependent three-dimensional structures [182, 183] and can be developed to inhibit specific protein targets with high affinity and used as active drugs. Aptamers provide the code for their own complement (reversal agent), which can be developed and used to inhibit their function [183–185]. Reversal of aptamer activity can be titrated to the patient's clinical condition given that the degree of reversal is directly related to the molar ratio of administered components. The REG1 anticoagulation system is a novel, aptamer-based, FIXa inhibitor that is being described for use in patients undergoing PCI. This system consists of pegnivacogin, a single-stranded RNA factor IXa inhibitor, and its complementary reversal agent, anivamersen, which binds to and inactivates pegnivacogin with rapid kinetics [186]. Phase I [185–188] and phase II [189] studies investigated REG1 with encouraging results. Recently, the RADAR (A Randomized, Partially Blinded, Multicenter, Active-Controlled, Dose-Ranging Study Assessing the Safety, Efficacy, and Pharmacodynamics of the REG1 Anticoagulation System in

Patients with ACS) trial [190, 191] showed that at least 50 % anivamersen-mediated reversal of pegnivacogin was necessary to effectively diminish bleeding after early femoral sheath removal in invasively managed patients with ACS. To determine the safety and efficacy of REG1 more powered randomized clinical trials are needed. A large scale phase III clinical trial is currently planned.

Thrombin generation is also decreased by drugs that target coagulation proteases that drive the propagation phase. Coagulation proteases modulate inflammation by activating protease activated receptors (PARs), and by binding to other cell surface receptors, such as Thrombomodulin (TM) and endothelial protein C receptor (EPCR) [192, 193]. PAR-2 does not bind thrombin, but the tissue factor (TF)/FVIIa complex and FXa can activate this receptor [194]. Activation of PARs by the various coagulation proteases results in the upregulation of genes involved in inflammation, including interleukin (IL)-8 and tumour necrosis factor (TNF)-α. TF/FVIIa-induced signaling events can modulate cell fate and behaviour, rendering cells and tissues proliferative, pro-migratory, and resistant to apoptosis. Based on these findings, PAR inhibitors are under development and PAR-1-targeting drugs have undergone phase III clinical trial evaluation [195, 196]. In addition to the role of PARs in inflammation, additional cross-talk occurs at the level of FXa. This concept is highlighted by the recent demonstration that lufaxin, a FXa inhibitor from the salivary glands of blood-sucking arthropods, not only inhibits thrombosis in mice, but also attenuates oedema formation triggered by FXa injection into their paws [197]. Other anticoagulant therapies in development that block target coagulationproteases that drive the propagation phase, such as FVIIIa (TB-402), or jointly FVa/FVIIIa, cofactors that are critical for the generation of thrombin (drotrecogin, which is a recombinant form of human activated protein C and recomodulin and solulin, both of which are recombinant soluble derivatives of human thrombomodulin). Inhibitors toward the TF/FVIIa complex, such as recombinant TFPI (tifacogin), recombinant nematode anticoagulant



protein (NAP)C2, active site–inhibited recombinant (r) FVIIa inhibitors (rFVIIaI) and monoclonal antibodies against TFT have been developed to target the initiation of coagulation [107] (Fig. 3.4).

Conclusions

During the last decade antithrombotic treatment of ACS has changed very rapidly, particularly due to the development of new antiplatelet and anticoagulant agents. The coagulation

FIGURE 3.4 Targets of Novel Anticoagulants. Compared with the indirect thrombin inhibitors (such as the heparins), direct thrombin inhibitors (DTIs) bind directly to thrombin and prevent fibrin formation as well as thrombin-mediated activation of factor (F) V, FVIII, FXI, and FXIII. Hirudin, bivalirudin, and argatroban are the available parenteral DTIs. Oral DTIs including ximelagatran (withdrawn from development), AZD0837 (under evaluation), and dabigatran etexilate, are prodrugs that generate an active compound able to bind directly to the catalytic site of thrombin. Other agents block target coagulation proteases that drive the propagation phase: FIXa (DNA aptamer pegnivacogin), FVIIIa (TB-402), or jointly FVa/FVIIIa, cofactors for the generation of thrombin (drotrecogin, recomodulin and solulin). Inhibitors toward the tissue factor/FVIIa complex, such as recombinant TFPI (tifacogin), recombinant nematode anticoagulant protein (NAP)C2, active site–inhibited recombinant (r) FVIIa inhibitors (rFVIIaI) and monoclonal antibodies against TFT have been developed to target the initiation of coagulation (Reproduced from De Caterina et al. [172])

cascade offers numerous potential targets of treatment that allow interfering in many processes of haemostasis and thrombosis. Currently, there are a plethora of new parenteral and oral anticoagulants that are being developed and incorporated into clinical practice in the setting of ACS. Many of these are preferred over older treatment regimens because of their more favorable safety profile. However, others still require to be refined and ongoing clinical trials will provide more insights on the safety and efficacy of these strategies.

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