Parenteral anticoagulants in heart disease: Current status and perspectives (Section II)

Position Paper of the ESC Working Group on Thrombosis – Task Force on Anticoagulants in Heart Disease

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Summary

Anticoagulants are a mainstay of cardiovascular therapy, and parenteral anticoagulants have widespread use in cardiology, especially in acute situations. Parenteral anticoagulants include unfractionated heparin, low-molecular-weight heparins, the synthetic pentasaccharides fondaparinux, idraparinux and idrabiotaparinux, and parenteral direct thrombin inhibitors. The several shortcomings of unfractionated heparin and of low-molecular-weight heparins have prompted the development of the other newer agents. Here we review the mechanisms of action, pharmacological properties and side effects of parenteral anticoagulants used in the management of coronary heart disease treated with or without percutaneous coronary interventions, cardioversion for atrial fibrillation, and prosthetic heart valves and valve repair. Using an evidence-based approach, we describe the results of completed clinical trials, highlight ongoing research with currently available agents, and recommend therapeutic options for specific heart diseases.

Keywords

Parenteral anticoagulants, coagulation, heart disease, coronary heart disease, heart failure, atrial fibrillation

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Introduction

Drugs that interfere with blood coagulation (anticoagulants) are a mainstay of cardiovascular therapy, and parenteral anticoagulants, mostly used in acute situations, are widely used in cardiology. Classical anticoagulants, such as unfractionated heparin (UFH) and low-molecular-weight heparins (LMWH), have several shortcomings, which have prompted, in recent years, the development of an unprecedented number of new agents. A Task Force of coagulation experts and clinical cardiologists appointed by the European Society of Cardiology (ESC) Working Group on Thrombosis will review the entire topic of anticoagulants in heart disease. The present report complements the recent Task Force document on the use of antiplatelet agents in cardiovascular disease (1), and updates a previous comprehensive document on anticoagulants in heart disease published in 2007 (2).

Section II, presented here, logically follows Section I, dedicated to general mechanisms of coagulation and targets of anticoagulants (3). Here we provide an overview of the pharmacology of parenteral anticoagulants and of their clinical applications, ending with a list of boxed recommendations for their use in general and in specific cardiological settings, including percutaneous coronary interventions (PCI), acute coronary syndromes (ACS), cardioversion of atrial fibrillation (AF), and prosthetic heart valves and valve repair.
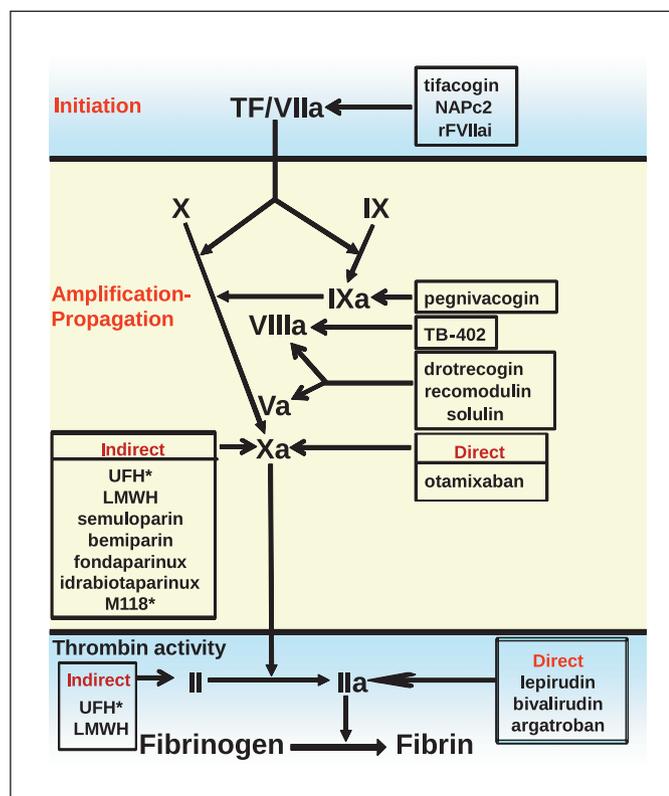
Figure 1: Targets of parenteral anticoagulants. Besides the indirect thrombin inhibitors unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH, including the ultra-low molecular-weight heparin semuloparin and bemiparin, and the engineered heparin derivative M118), direct thrombin inhibitors bind directly to thrombin and prevent fibrin formation as well as thrombin-mediated activation of FV, FVIII, FXI and FXIII. They also prevent thrombin-mediated activation of platelets, of inflammation, of anti-fibrinolysis, as well as of the anticoagulant protein C / protein S / thrombomodulin pathway. These include recombinant hirudin (lepirudin), bivalirudin and the low-molecular-weight compound argatroban. Drugs that target coagulation proteases involved in the amplification phase include agents that block FIXa (such as the DNA aptamer pegnivacogin), 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; recomodulin and solulin, both recombinant soluble derivatives of human thrombomodulin). Blockers of the propagation phase include FXa inhibitors. At variance from the parenteral indirect FXa inhibitors, such as UFH, LMWH, and pentasaccharide derivatives (fondaparinux, idrabiotaparinux), which exert their effects equally on thrombin and on FXa (UFH), prevalently on FXa (LMWH) or exclusively on FXa (fondaparinux, biotaparinux), all by potentiating the natural inhibitor antithrombin (antithrombin III, AT), direct FXa inhibitors have non-AT-mediated effects. One such direct FXa inhibitor (otamixaban) has reached phase II experimentation. To target the initiation of coagulation, inhibitors towards the TF/FVIIa complex have been developed, such as recombinant TFPI (tifacogin), recombinant nematode anticoagulant protein (NAP)c2, active site-inhibited recombinant (r) FVIIa (rFVIIai) and monoclonal antibodies against TF. *UFH and M118, besides inhibiting thrombin and FXa, also interfere with FIXa and FVIIa.

Future Sections will deal with vitamin K antagonists (Section III), new anticoagulants in acute coronary syndromes (Section IV), and special situations (Section V).

Targets of parenteral anticoagulants

The targets of parenteral anticoagulants in current use or in development are depicted in ▶Figure 1. A detailed description of coagulation targets has been provided in Section I of this series (3).
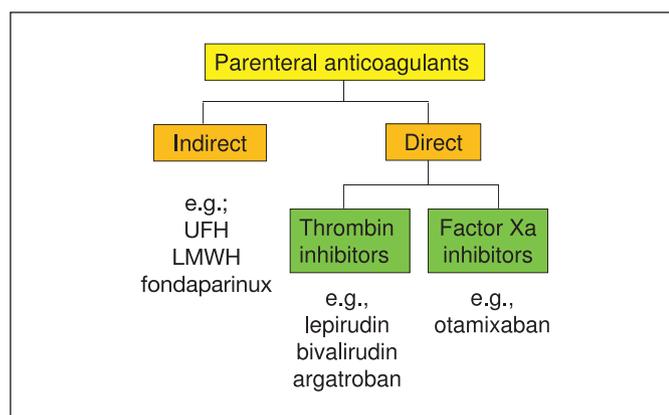

Figure 2: A rational classification of the main currently available parenteral anticoagulants, based on their mode of action (direct vs indirect).

Here we will provide a brief summary only related to parenteral anticoagulants.

The *indirect* thrombin inhibitors include UFH and LMWH, including the ultra-low-molecular-weight heparins (ULMWH) semuloparin and bemiparin and the engineered heparin-derivative M118. *Direct* thrombin inhibitors bind directly to thrombin and prevent fibrin formation as well as thrombin-mediated activation of factor (F)V, FVIII, FXI and FXIII. They also prevent thrombin-mediated activation of platelets, of inflammation, of anti-fibrinolysis, as well as of the anticoagulant protein C/protein S/thrombomodulin pathway. The direct thrombin inhibitors block thrombin bound to fibrin in addition to thrombin in plasma (5). These include recombinant hirudin (lepirudin), bivalirudin and the low-molecular-weight compound argatroban.

Blockers of the propagation phase include FXa inhibitors. At variance from the *parenteral indirect* FXa inhibitors, such as UFH, LMWH, and pentasaccharide derivatives (fondaparinux, idrabio-taparinux), which exert their effects equally on thrombin and on FXa (UFH), prevalently on FXa (LMWH) or exclusively on FXa (fondaparinux, biotaparinux), all by potentiating the natural inhibitor antithrombin (antithrombin III, AT), *direct* FXa inhibitors have non-AT-mediated effects. One such *direct* FXa inhibitor (otamixaban) has reached phase II experimentation.

Of note, UFH and M118, besides inhibiting thrombin and FXa, also interfere with FIXa and FVIIa.

Drugs that target coagulation proteases involved in the amplification phase include agents that block FIXa (such as the DNA aptamer pegnivacogin), FVIIIa (TB-402) or jointly FVa/FVIIIa, co-
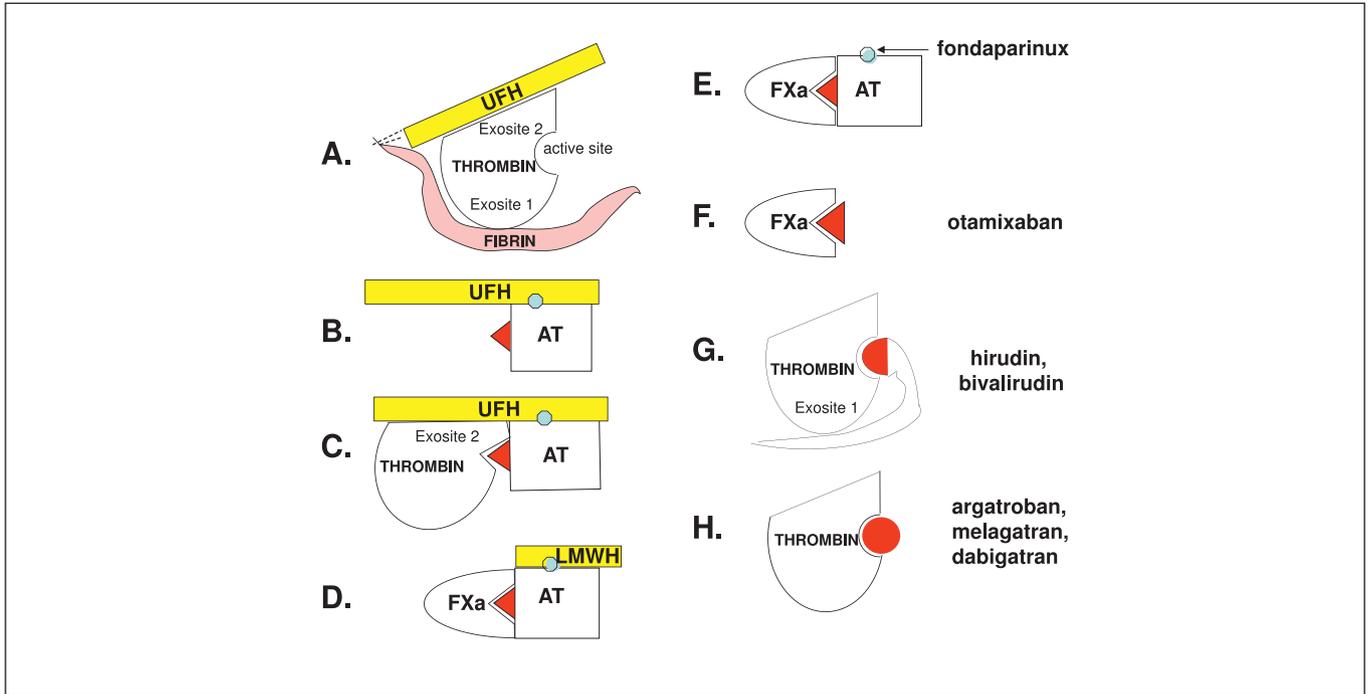
Figure 3: Mechanisms of action of the different thrombin inhibitors.
A) The ternary UFH/thrombin/fibrin complex increases the affinity of thrombin for its fibrin substrate and lessens the ability of the heparin-antithrombin (AT) complex to inhibit thrombin. Heparin binding to thrombin occurs through a domain of the thrombin molecule termed exosite 2, while binding of thrombin to its substrate fibrinogen, allowing the steric configuration of the complex necessary for thrombin to exert its enzymatic action, occurs through a thrombin domain known as exosite 1. UFH and LMWH (this latter not shown in this context) both possess the pentasaccharide unit (azure dot) necessary for their interaction with AT (B). The UFH/AT complex is able to block thrombin active site, with AT blocking the active site and UFH keeping thrombin in the proper steric configuration (through its binding to exosite 2) for AT to exert its action (C). Short chains of LMWH do not bind to exosite 2 of thrombin, contrary to the longer UFH chains. However, all LMWH/AT complexes can still bind to factor Xa (D). The synthetic pentasaccharides fondaparinux and idraparinux, like LMWH, bind and activate AT, and allow AT to efficiently inhibit FXa (E). The direct parenteral FXa inhibitor otamixaban blocks the active site of FXa (F). Hirudin and bivalirudin bind to thrombin via the active site as well as exosite 1, displacing thrombin from fibrin (G). The recombinant bivalent direct thrombin inhibitors lepirudin and hirudin inhibit thrombin active site, but also bind the fibrinogen binding site (exosite I) (G). The synthetic direct thrombin inhibitors argatroban, melagatran and dabigatran (these latter being the active metabolites of the oral prodrugs ximelagatran and dabigatran etexilate, respectively) bind only to thrombin active site, without displacing thrombin from its substrate (H).

factors that are critical for the generation of thrombin (drotrecogin, which is a recombinant form of human activated protein C; recomodulin and solulin, both recombinant soluble derivatives of human thrombomodulin).

Of the above drugs, only heparin, LMWH, fondaparinux, idrabiotaparinux and bivalirudin have reached phase III clinical testing in heart disease (www.clinicaltrials.gov). Only these agents will therefore be further reviewed.

A rational classification of currently available parenteral anticoagulants, based on their mechanism of action, is presented in ►Figure 2.

Parenteral anticoagulants – general pharmacology

All anticoagulants, in general, and therefore also parenteral anticoagulants, inhibit either thrombin action or thrombin generation. Understanding the pharmacology of currently available anticoagulants is closely related to the modes of inhibition of thrombin and FXa. Thrombin has an active site, which is flanked by two positively-charged exosites. Exosite 1, the substrate binding domain, mediates thrombin's interaction with its substrates, such as fibrinogen, whereas exosite 2 is the heparin-binding domain. ►Figure 3 displays the mechanisms of action of the different parenteral anticoagulants, as detailed below.

Heparin derivatives

The heparin derivatives in current use include UFH, LMWH and synthetic pentasaccharides. These drugs are administered by intravenous infusion or injection, or subcutaneous injection, and are classified as indirect anticoagulants because they require antithrombin (AT), a plasma cofactor, to exert their anticoagulant activity (►Figure 2 and ►Figure 3). Heparin derivatives bind to AT, a naturally occurring serine protease inhibitor, and enhance its capacity to inhibit activated coagulation factors including FXa and thrombin. Each of the heparin derivatives will be briefly described.

Unfractionated heparin

As an agent discovered almost 90 years ago, UFH is the prototype of the heparin derivatives. Heparin is a natural product that can be isolated from beef lung or porcine intestinal mucosa. Because of the risk of transmission of prion disease from bovine tissues, most of the heparin used today is derived from porcine intestinal tissue (6).

Mechanism of action

Heparin consists of a family of highly sulfated polysaccharide chains, ranging in molecular weight from 3,000 to 30,000 g/mol (Dalton, Da) with a mean of 15,000 Da, which corresponds to about 45 saccharide units (6). Only one third of the heparin chains possess the unique pentasaccharide sequence that binds AT with high affinity, However, it is only this fraction that is responsible for most of the anticoagulant activity of heparin (6). Heparin chains lacking this pentasaccharide sequence have minimal anticoagulant activity when given in the usual prophylactic or therapeutic doses. With higher doses, however, heparin chains with or without a pentasaccharide sequence can activate heparin cofactor II, a second plasma cofactor (7). Unlike AT, heparin cofactor II only inhibits thrombin (7). At even higher concentrations, heparin attenuates factor Xa generation in an AT- and heparin cofactor II-independent fashion (8, 9).

Heparin catalyses thrombin inhibition by AT by simultaneously binding to both AT, via its pentasaccharide sequence, and thrombin, in a charge-dependent fashion. Formation of this ternary heparin/AT/thrombin complex bridges the inhibitor and the enzyme together and accelerates their interaction (6). Thrombin then cleaves the reactive center loop of AT to form a covalent thrombin/AT complex. Heparin dissociates from this complex and is able to activate additional AT molecules (▶ Figure 3A-C).

Only heparin chains consisting of 18 or more saccharide units, which correspond to a molecular weight of about 5,400 Da, are of sufficient length to bridge AT to thrombin. However, shorter pentasaccharide-containing heparins can catalyse FXa inhibition by AT because this reaction does not require bridging. Instead, to catalyse FXa inhibition, heparin needs only to bind to AT via its pentasaccharide sequence (6). This binding evokes conformational changes in the reactive centre loop of AT that accelerate its interaction with FXa. Heparin also induces the release of tissue factor pathway inhibitor (TFPI) (10), which inhibits the FVIIa–tissue factor complex (11). In an AT-dependent fashion, heparin also inhibits other coagulation factors, including FXII, FXI, FIX, and also VIIa (12). However the clinical relevance of these properties for the anticoagulant effects of heparin are uncertain.

Pharmacokinetics

UFH must be given parenterally. The preferred routes are by continuous intravenous (i.v.) infusion or by subcutaneous (s.c.) injection. When given subcutaneously for treatment of thrombosis, higher doses of heparin than those administered by i.v. infusion are needed to overcome the fact that the bioavailability of heparin after s.c. injection is only about 30% (6). The anticoagulant response of treatment doses of s.c. heparin is highly variable among individuals (13). Therefore, we recommend against the use of s.c. UFH, even as a bridging therapy for short-term use, after interruption of a vitamin K antagonist (VKA). In case the non-recommended s.c. route is used, monitoring of the activated partial thromboplastin time (aPTT), as for i.v. heparin, should be done, but in this case the longer half-life of s.c. compared with i.v. heparin renders such route of administration a poorer choice.

In the circulation, a number of plasma proteins compete with AT for heparin binding, thereby reducing its anticoagulant activity. The levels of these heparin-binding proteins vary among patients. This phenomenon contributes to the variable anticoagulant response to heparin and to the phenomenon of heparin resistance (6). Heparin also binds to endothelial cells and macrophages, a property that further complicates its pharmacokinetics.

Heparin is cleared through a combination of a rapid saturable phase and a slower, first-order mechanism (6). The saturable phase of clearance likely reflects heparin binding to endothelial cells and macrophages. Once bound, heparin is internalised and depolymerised. When the cellular binding sites are saturated, heparin enters the circulation, where it is cleared more slowly via the kidneys. At therapeutic doses, a large proportion of heparin is cleared through the rapid saturable mechanism (6).

The complex kinetics of heparin clearance renders the anticoagulant response to UFH non-linear at therapeutic doses, with both the peak activity and duration of effect increasing disproportionately with increasing doses. Thus, the apparent half-life of UFH increases from 30 minutes (min) after an i.v. bolus of 25 IU/kg to 60 min with a bolus of 100 IU/kg and to 150 min with a 400 IU/kg bolus (6).

Dosing and monitoring

The efficacy of UFH for the initial treatment of venous thromboembolism (VTE, not covered here) has been found to be critically dependent on the dose (14, 15). Heparin can be given in fixed or weight-adjusted doses, and nomograms have been developed to facilitate dosing (15). The doses of UFH recommended for the treatment of ACS are lower than those typically used to treat VTE. Because heparin can bind to fibrin, this difference may reflect the smaller thrombus burden in arterial thrombosis compared with venous thrombosis. A heparin bolus of 60 to 70 IU/kg (maximum 5,000 U) followed by an infusion of 12 to 15 IU/kg/h (maximum 1,000 U/hour [h]) is recommended for NSTE-ACS (16). Even lower doses of heparin are recommended when heparin is given in conjunction with fibrinolytic agents for treatment of STEMI. Here, the bolus is about 60 IU/kg (maximum 4,000 U), and the infusion is 12 IU/kg/h (maximum of 1,000 IU/kg/h) (16).

Because the anticoagulant response to UFH varies among patients, UFH therapy is monitored and the dose is adjusted based on test results. The test most often used to monitor heparin is the aPTT. The activated clotting time (ACT) is used to monitor the higher doses of UFH given to patients undergoing PCI or cardiopulmonary bypass surgery, because at such higher doses the aPTT becomes prolonged to the point of becoming unmeasurable and unreliable.

A prospective study done many years ago suggested that an aPTT ratio between 1.5 and 2.5 was associated with a reduced risk for recurrent VTE (17). Based on this study, an aPTT ratio (calculated by dividing the reported therapeutic aPTT range by the control value for the reagent) of 1.5 to 2.5 was adopted as the therapeutic range for UFH. However, the clinical relevance of this therapeutic range is uncertain because it has never been validated in prospective studies and because the aPTT reagents and coagulometers have changed over the years. With most aPTT reagents and coagulometers in current use, therapeutic heparin levels correspond to an aPTT ratio of 2.0 to 3.0 (18). The Task Force endorses the American College of Chest Physicians (ACCP) statement that the therapeutic range of UFH should be adapted to the aPTT reagent used (6, 16). The Task Force recommends against the use of a fixed aPTT target in seconds for any therapeutic indication of UFH.

Side effects

Bleeding is the major complication of heparin therapy and treatment with other anticoagulants. This complication and the neutralisation of UFH by protamine sulphate will be dealt with in a separate review article of this series.

Other complications include heparin-induced thrombocytopenia (HIT) and osteoporosis. HIT (recently reviewed in [19] and [20]) is caused by antibodies directed against a neoepitope on platelet factor 4 (PF4) that is exposed with the formation of heparin/PF4 complexes. By binding to Fc receptors on the platelet, these antibodies, which are mainly of the IgG subclass, can activate platelets (21, 22). Activated platelets are then removed from the circulation, which causes thrombocytopenia. In addition, activated platelets and microvesicles arising from them can provide a surface onto which clotting factors assemble to promote thrombin generation. This phenomenon likely explains why HIT is a dangerous prothrombotic condition (21, 22).

Osteoporosis is a complication of long-term treatment with therapeutic doses of heparin. This appears to be the result of heparin binding to osteoblasts with subsequent osteoclast activation (6). It is not clear whether heparin-induced osteoporosis is reversible when heparin treatment is stopped.

Low-molecular-weight heparins

LMWH are gradually replacing UFH for most indications. Like UFH, LMWH are natural products that are derived from UFH by chemical or enzymatic depolymerisation (6). LMWH have pharmacological and biological advantages over heparin that render them more convenient to administer and less likely to cause HIT or osteoporosis (6, 23).

Mechanism of action

As fragments of heparin, the mean molecular weights of LMWH preparations are about one-third that of heparin and range from 2300 to 5,000 Da, which corresponds to about 8 to 15 saccharide units. Like UFH, LMWH are heterogeneous. About one-fifth of the chains possess a pentasaccharide sequence, and the anticoagulant activity of LMWH is restricted to this fraction (6, 23) (►Figure 3D).

A number of LMWH preparations are available for clinical use. Each is prepared using a different method of depolymerisation, and each has a unique molecular weight profile that endows it, at least to some extent, with distinct pharmacokinetic and pharmacodynamic (anticoagulant) properties. In addition, currently no international standard for LMWH exists, and every single producer declares its own units, leading to different dosing of every LMWH. Consequently, the various LMWH preparations are not interchangeable. The use in any specific setting should be restricted to those LMWH that have been demonstrated effective and safe in that specific setting.

Like UFH, LMWH produce their anticoagulant effects by activating AT and accelerating the rate at which it inhibits FXa and thrombin. Because only pentasaccharide-containing chains composed of at least 18 saccharide units are of sufficient length to bridge AT to thrombin, at least 50 to 75% of LMWH chains are too short to catalyse thrombin inhibition. However, these short chains retain the capacity to promote FXa inhibition because this reaction does not require bridging. Consequently, LMWH preparations have greater capacity to promote FXa inhibition than thrombin inhibition, and have anti-FXa to anti-FIIa activity ratios that range from 2:1 to 4:1 depending on their molecular weight profiles. In contrast, by definition, UFH has an anti-Xa to anti-IIa activity ratio of 1 (6, 23). The relevance of the anti-Xa to anti-IIa activity ratio, which varies considerably among various LMWH, in explaining differential efficacy and safety profiles of the various LMWH is, however, questioned at the moment.

LMWH have been shown to attenuate the release of von Willebrand factor (24), which has been shown to be a predictor of outcome in non-ST elevation ACS (NSTE-ACS) and in ST-elevation myocardial infarction (STEMI) (25). Like UFH (10), LMWH also induce the release of TFPI, which inhibits the FVIIa–tissue factor complex (11). However, the clinical relevance of these properties is uncertain.

Pharmacokinetics

LMWH have pharmacokinetic advantages over UFH. The bioavailability of LMWH after s.c. injection is over 90%, likely reflecting the better absorption of shorter heparin chains from the subcutaneous injection site. LMWH produce a more predictable anticoagulant response than UFH because the shorter heparin chains exhibit reduced affinity for heparin binding proteins in the plasma. In addition, LMWH have a longer half-life than UFH, and the half-life is dose-independent. These phenomena reflect reduced binding of LMWH to the endothelium. Different LMWH with different median chain lengths have different half-lives: LMWH with longer chain lengths are generally endowed with shorter half lives than LMWH with shorter chain length, and therefore are less prone to accumulation.

LMWH are cleared via the kidneys and therefore can accumulate in the plasma of patients with impaired renal function.

Dosing and monitoring

Typically, LMWH are given in fixed or weight-adjusted doses without monitoring. However, monitoring may be used in obese patients, in those with renal insufficiency and when therapeutic doses of LMWH are required during pregnancy. When monitoring is required, the anti-Xa level is the recommended test (6). Since, however, every LMWH is different, LMWH monitoring by the use of anti-Xa levels requires calibration towards the specific LMWH used for therapy. LMWH may produce some prolongation of the aPTT, but their effect on the aPTT is less than that of UFH, and the aPTT cannot be used for monitoring (6).

Some studies suggest that LMWH can be given in weight-based doses to obese patients, and a meta-analysis that included data on 921 patients with a body mass index (BMI) over 30 did not find any increase in major bleeding when LMWH were administered in this fashion (26). Appropriate dosing of LMWH in patients with renal insufficiency is less clear. There is an inverse relationship between creatinine clearance and anti-FXa levels (27, 28), and the risk of bleeding complications with LMWH is higher in patients with impaired renal function (26, 29). In patients with severe renal insufficiency, UFH is, in most cases, a better choice than LMWH.

Side effects

Like any anticoagulant, the major side-effect of LMWH treatment is bleeding, which will be dealt with in a separate article of this series.

HIT is less common with LMWH than with UFH (19, 21, 30). This reflects the fact that LMWH have lower affinity for platelets and cause less PF4 release than UFH. In addition, if PF4 is released, the lower affinity of LMWH for PF4 results in the formation of fewer heparin/PF4 complexes, the antigenic target of HIT antibodies (21). However, LMWH can form complexes with PF4 that are capable of binding HIT antibodies. This phenomenon likely explains the cross reactivity with LMWH in patients with HIT. Once HIT antibodies are formed, there is 100% cross reactivity with LMWH, therefore LMWH cannot avoid HIT sensitisation nor can be used for HIT therapy. LMWH should therefore not be used as an alternative to UFH in patients with suspected or established HIT.

The risk of osteoporosis is lower with LMWH than with UFH. This probably reflects the lower affinity of LMWH for bone cells. In small clinical trials, LMWH did not appear to reduce bone density when given in prophylactic or therapeutic doses (31-33).

Synthetic pentasaccharides

Fondaparinux

Fondaparinux is a synthetic analog of the pentasaccharide sequence present in UFH and LMWH that mediates their interaction with AT (34, 35). Fondaparinux shares all the pharmacological and biological advantages of LMWH over UFH. However, in contrast to LMWH, fondaparinux only inhibits FXa because it is too short to bridge AT to thrombin (36). As a synthetic molecule, fondaparinux is highly standardised and has low (but not absent) potential of forming complexes with PF4 and therefore scarce antigenic properties.

Mechanism of action

Fondaparinux has a molecular weight of 1,728 Da (34, 35). The structure of fondaparinux has been modified to enhance its affinity for AT. Thus, the specific anti-Xa activity of fondaparinux is about 7-fold higher than that of LMWH (about 700 vs 100 anti-Xa U/mg). Fondaparinux reversibly binds to AT, producing conformational changes at the reactive centre loop of AT that enhance its reactivity with FXa by at least two orders of magnitude. As the molecule is too short to bridge AT to thrombin, fondaparinux has no effect on AT-mediated thrombin inhibition (►Figure 3E).

Pharmacokinetics

The bioavailability of fondaparinux after s.c. injection is 100%, which is higher than that of LMWH. Fondaparinux is rapidly absorbed after s.c. injection, and has a half-life of about 17 h in young subjects and 21 h in the elderly. This difference in half-life likely reflects the reduced renal function in the elderly. Fondaparinux is excreted unchanged in the urine (34, 37), and should therefore not be given to patients with a creatinine clearance of less than 30 ml/min.

Fondaparinux produces a predictable anticoagulant response and exhibits linear pharmacokinetics when given in s.c. doses ranging from 2 to 8 mg (34, 35). It does not bind to other plasma proteins, a finding that explains why it produces a more predictable anticoagulant response than UFH and even the different LMWH.

Dosing

Fondaparinux is given subcutaneously once daily in fixed doses. A dose of 2.5 mg is used in patients with non-ST-elevation ACS and ST-elevation myocardial infarction (STEMI), and for thromboprophylaxis in medical or orthopaedic surgery patients. A dose of 7.5 mg is used for treatment of VTE. The dose can be reduced to 5 mg daily or increased to 10 mg daily for patients with low or high body weight, respectively.

Monitoring

Fondaparinux was not monitored in the clinical studies that evaluated its utility. The drug has little or no effect on routine tests of coagulation, such as the prothrombin time (PT), aPTT or ACT (38). These tests are therefore unsuitable for monitoring. If monitoring is required, the anticoagulant activity of fondaparinux can be measured with anti-FXa assays, using fondaparinux as a calibrator.

Side-effects

Besides bleeding, side effects of fondaparinux include oedema, injection site reaction (bleeding, rash, and pruritus), and gastrointestinal effects (constipation, nausea, vomiting). In contrast to UFH or LMWH, fondaparinux rarely causes HIT, and has actually been used successfully to treat HIT (39). It also has been used successfully in a patient who had urticarial reactions at the LMWH injec-

tion sites (39). There are limited data on fondaparinux use in pregnancy. Therefore, unless the patient has a history of HIT, fondaparinux should not be used for prevention or treatment of thrombosis during pregnancy. Finally, although patient data are lacking, *in vitro* and *ex vivo* studies suggest that fondaparinux is less likely to cause osteoporosis than UFH or LMWH (40, 41).

Idraparinux and idrabiotaparinux

Like fondaparinux, idraparinux is a fully synthetic selective indirect FXa inhibitor (42). The idraparinux affinity for AT is more than 10-fold higher than that of fondaparinux. Because of the lack of an antidote, a subsequent evolution in the area of synthetic pentasaccharides has been the development of a biotinylated derivative of idraparinux, termed idrabiotaparinux, which can be effectively removed from the circulation with an injection of avidin, complexing the biotin hook of the molecule (43). An egg white protein, avidin binds the biotin moiety with high affinity and the avidin/idrabiotaparinux complex is then rapidly cleared by the kidneys.

Mechanism of action and pharmacokinetics

The higher affinity for AT probably explains the long plasma half-life of both idraparinux and idrabiotaparinux, similar to that of antithrombin, i.e. around 80 h. The anti-FXa activity and inhibition of thrombin generation of both drugs is dose-dependent.

At the time of this writing the development of idrabiotaparinux in atrial fibrillation has been interrupted for excess bleeding (44), while it continues for VTE, with some promises (45). For this reason, neither idraparinux nor idrabiotaparinux will be discussed here in greater detail.

Parenteral direct thrombin inhibitors

In contrast to indirect thrombin inhibitors, which act by catalysing AT and/or heparin cofactor II activation, direct thrombin inhibitors bind directly to thrombin and block its interaction with substrates, thus preventing fibrin formation, thrombin-mediated activation of FV, VIII, XI, or XIII, and thrombin-induced platelet activation (►Figure 3G and H). By interfering with these feedback mechanisms, direct thrombin inhibitors also reduce further thrombin generation. Another important property of direct thrombin inhibitors is their ability to inactivate fibrin-bound thrombin. In contrast, fibrin-bound thrombin is resistant to inhibition by the AT-heparin or heparin cofactor II-heparin complex. The inability to inhibit fibrin-bound thrombin may be an important limitation of indirect thrombin inhibitors because fibrin-bound thrombin is an important mediator of thrombus expansion.

Hirudin

Hirudin is a 65-amino-acid protein originally extracted from the salivary glands of the medicinal leech (*Hirudo medicinalis*). Recombinant forms of hirudin are available and include lepirudin and desirudin, which differ slightly in their amino acid composition.

Hirudins are bivalent inhibitors that bind both to the active site and the fibrinogen/fibrin-binding site of thrombin (►Figure 3G) to form an essentially irreversible 1:1 hirudin/thrombin complex. They are cleared via the kidney, with a half-life of 90-120 min when given intravenously and 120-180 min after s.c. injection; the half-life may be prolonged in patients with severe renal impairment. There is no specific antidote for the hirudins. Lepirudin is approved for the i.v. use in HIT (46). Subcutaneous desirudin is approved for thromboprophylaxis after elective hip arthroplasty.

Bivalirudin

Bivalirudin is a 20-amino acid, synthetic analogue of hirudin. Like hirudin, bivalirudin is a bivalent inhibitor that interacts with both the active site and the substrate binding site of thrombin (►Figure 3G). However, once in complex with thrombin, bivalirudin is slowly cleaved, thereby restoring the active site function of the enzyme. The reversible nature of the bivalirudin/thrombin complex endows bivalirudin with a superior safety profile to that of hirudin. Bivalirudin has a half-life of 25 min after i.v. injection, and is partly degraded and partly excreted by the kidney (20%). Because of the renal excretion, the half-life is prolonged in patients with renal impairment. Bivalirudin does not bind to plasma proteins and is removed by haemodialysis. Although there is no need for routine monitoring, global coagulation tests like the aPTT, ACT or PT are non-linearly prolonged, and therefore are unable to predict over- or underdosing. Drug monitoring can, however, be performed by use of the dose-linear ecarin clotting time. There is no specific antidote for bivalirudin (47).

Argatroban

Argatroban is a small, synthetic molecule that competitively and reversibly inhibits the active site of free and fibrin-bound thrombin. Because it only interacts with the active site of thrombin, argatroban is considered an univalent inhibitor (►Figure 3H). Argatroban has a half-life of 45 min and is mainly cleared by the liver via a process that generates three active intermediates. The anticoagulant effect of argatroban is usually monitored with the aPTT or the ACT. Argatroban also prolongs the PT, which can complicate the transitioning of patients from argatroban to a VKA. Because of its metabolism, dosing precautions are recommended in patients with hepatic dysfunction; dose adjustment is not usually required in those with renal impairment, which renders argatroban an attractive choice for such patients. No specific antidote for argatroban is available.

As a class, direct thrombin inhibitors have potential biologic and pharmacokinetic advantages over heparins. Unlike UFH and LMWH, direct thrombin inhibitors inactivate fibrin-bound thrombin in addition to fluid-phase thrombin. Consequently, direct thrombin inhibitors may attenuate thrombus accretion more effectively. In addition, direct thrombin inhibitors produce a more predictable anticoagulant effect than heparins because they do not bind to plasma proteins and are not neutralised by PF4 or dependent on AT. Because one of the pleiotropic effects of thrombin is to

	UFH	LMWH	Pentasaccharides	DTI
Presence of cofactor required	+++	+++	+++	-
Renal clearance of clinical relevance	±	++	+	++
Non-specific protein binding	+++	+	-	-
Bioavailability by s.c. or oral administration	+ (for s.c. UFH)	++	+++	+ (for oral DTI)
Predictability of pharmacological effect	+	++	++	++
Inhibition of thrombin generation	++	++	++	+ (*)
Inhibition of thrombin activity	+++	+	-	+++
Inhibition of bound-thrombin	-	-	-	+++
Rebound of thrombin generation after discontinuation	+++	++	-	++
Specific antidote available	+++	-	-**	-
Platelet activation	+++	+	-	-
Immune thrombocytopenia	+++	+	-	-
Decreased bone density	+++	+	-	-

UFH: unfractionated heparin; LMWH: low molecular weight heparins; DTI: direct thrombin inhibitors. Properties are semiquantitatively graded as -: absent; ±: barely present; +: present-to a low degree; ++: present-to an intermediate degree; +++: present-to a high degree; *: only feedback activation (amplification) is interfered; **: available for idrabiotaparinux.

Table 1: A comparison of relevant pharmacological properties of the different parenteral thrombin inhibitors in current clinical use (information on oral direct thrombin inhibitors is included for comparison).

promote cell proliferation and wound healing, there has been concern that wound healing may be impaired with the use of the direct thrombin inhibitors, but this has not been substantiated so far.

Three parenteral direct thrombin inhibitors have been licensed in North America and Europe for limited indications. Hirudin, lepirudin and argatroban are approved for the treatment of HIT, whereas bivalirudin, in addition, is also licensed as an alternative to heparin in patients with ACS undergoing percutaneous coronary interventions (PCI) (see below).

A comparison of the pharmacological properties of the main classes of thrombin inhibitors is shown in ►Table 1.

Comparative clinical indications
UFH and LMWH vs control
Primary PCI in STEMI patients

Because anticoagulation is believed to be absolutely necessary during PCI, the safety and efficacy of UFH or LMWH vs placebo have not been tested in randomised trials of STEMI patients undergoing PCI (48, 49).

NSTE-ACS with or without PCI

A pooled analysis of six randomised trials in patients with NSTE-ACS treated with short-term UFH plus aspirin compared with aspirin alone (50-55) showed a 33% relative risk (RR) reduction in death or MI during treatment (RR 0.67, 95% confidence interval [CI] 0.44-1.02), with a trend toward an increased rate of major bleeding (RR 1.99, 95% CI 0.52-7.65) (56). A meta-analysis that also included the FRISC trial (57), which compared in-hospital

dalteparin with placebo, yielded a more definite risk reduction in death or MI up to seven days in favour of anticoagulation (odds ratio [OR] 0.53, 95% CI 0.38-0.73), but with an approximately two-fold increase in the rate of major bleeding (OR 2.3, 95% CI 0.97-5.4) (58). In the FRISC 2 trial, long-term (up to 3 months) administration of LMWH compared with placebo did not confer additional efficacy on top of aspirin, but increased the rate of major bleeding (59). Based on this evidence, anticoagulant therapy is generally recommended in hospital for up to seven days in patients with NSTE-ACS not receiving PCI. Anticoagulation is safely stopped at the end of the procedure in patients undergoing PCI.

Cardioversion of AF

Cardioversion of atrial fibrillation (AF) entails increased risk of thromboembolism. Therefore, anticoagulation is considered mandatory before elective cardioversion for AF of >48 h or unknown duration, even in patients at low risk of thromboembolic events who would not receive long-term anticoagulation otherwise (60). Thromboprophylaxis is recommended for electrical and pharmacological cardioversion of AF >48 h (60).

Based on observational cohort studies, treatment with a VKA (international normalised ratio [INR] 2.0–3.0) is currently recommended for at least three weeks before cardioversion, continuing treatment for a minimum of four weeks after cardioversion because of risk of thromboembolism due to post-cardioversion left atrial/left atrial appendage dysfunction (so-called "atrial stunning") (60). In patients with a definite AF onset <48 h, however, cardioversion can be performed immediately under the cover of either UFH administered i.v. [e.g. with an i.v. bolus of 80 IU/kg, followed by a continuous i.v. infusion adjusted to an activated partial thromboplastin time of twice the control value (initially 18 IU/

kg/h); or s.c. LMWH (60)]. If the patient has risk factors for stroke, oral anticoagulation (OAC) should be started after cardioversion and continued lifelong. In such cases, using a VKA, UFH or LMWH should be continued until the INR is at the therapeutic level (2.0–3.0 in most cases). With the novel oral anticoagulants (the direct thrombin inhibitor dabigatran etexilate, and the FXa inhibitors rivaroxaban and apixaban), initial experience of cardioversion is being accrued. Because of the rapid onset of the anticoagulant effect with these agents, it would be logical to expect no need for bridging with either UFH or a LMWH, but data on this for recent-onset AF are at the moment extremely limited (4). We recommend peri-cardioversion heparin treatment also in patients without cardioembolic risk factors and in whom long-term OAC is not indicated, although this is not evidence-based.

For patients with definite atrial fibrillation duration of 48 h or less and no risk factors for thromboembolism (i.e. CHA_2DS_2-VASc score = 0) undergoing cardioversion with successful restoration of sinus rhythm, we recommend no continuation of any anticoagulant therapy after cardioversion, since the risk of stroke in such patients appears not to be different from that of the normal population (60).

The mandatory three-week period of OAC prior to cardioversion can be shortened if transesophageal echocardiography (TEE) reveals no left atrium or left atrial appendage thrombus. A TEE-guided cardioversion strategy is recommended as an alternative to three-week pre-cardioversion anticoagulation if experienced staff and appropriate facilities are available. It is also indicated when early cardioversion is needed (e.g. in case of haemodynamic instability) or when pre-cardioversion oral anticoagulation is not indicated due to patient choice or potential bleeding risks, or when there is a high risk of left atrium or left atrial appendage thrombus. If no left atrium or left atrial appendage thrombus is detected on TEE, UFH (or LMWH) should be started prior to cardioversion and continued thereafter until the target INR is achieved with OAC. If TEE detects a thrombus in the left atrium or left atrial appendage, treatment with a VKA (INR 2.0–3.0) is required for at least three weeks and TEE should be then repeated to decide on whether to proceed or not to cardioversion (60).

Bridging to non-cardiac surgery in patients with a cardiac prosthetic valve or after valve repair

The temporary cessation of oral anticoagulation for another operative procedure is a common cause of prosthetic valve thrombosis in patients carrying such (especially mechanical) valves. The latter will be dealt with separately in a following document of this Task Force.

Current American (61) and European (62) guidelines are in agreement that in situations of high risk of valve thrombosis i.v. UFH should be commenced when the INR falls below 2.0, maintained until 4-6 h before the operation, restarted as soon as possible afterwards, and continued until the INR is again therapeutic (61, 62).

However, there is disagreement about the management of patients at low risk of valve thrombosis, which the American guide-

lines define as patients with a bileaflet aortic prosthesis and no risk factors. In these patients they recommend stopping the VKA until the INR is <1.5, omitting heparin, and restarting the VKA 24 h after the procedure. They base this recommendation on a calculation of embolic risk, estimating the risk for three days of omitting anticoagulation to 0.08-0.16%, figures too low to warrant any therapy (61). There are, however, several concerns with this approach, which assumes that the perioperative risk of valve thrombosis is similar to the risk in a steady-state condition.

The ESC guidelines therefore recommend that, if it is essential to interrupt anticoagulation for any operative procedure, in any patient with a mechanical valve, i.v. UFH should be employed to cover the period that the INR is subtherapeutic (62). For many minor procedures in which bleeding is readily controlled by local measures, including dental treatment, anticoagulation interruption is unnecessary.

LMWH vs UFH

STEMI treated with PCI

The safety and efficacy of LMWH (mostly enoxaparin) have been compared with those of UFH in STEMI patients treated with either primary or secondary (i.e. following fibrinolysis) PCI. Four of 10 studies involve post-hoc analyses of larger randomised trials (ASSENT-3, CLARITY-TIMI 28, ExTRACT-TIMI 25, FINESSE); three are retrospective analyses of prospective registries (MITRA-plus, KAMIR, e-PARIS); two are relatively small non-randomised prospective studies (63). Despite the different nature of the studies, there is general consistency with a lower rate of death or MI at 30 days with enoxaparin than with UFH, without a significant increase in major bleeding rates (defined in most studies using the TIMI criteria) (63). In ATOLL (65), the most recent study of this kind and the only randomised trial specifically designed for this patient group, 910 STEMI patients presenting within 12 h of symptom onset were randomised to receive, before primary PCI, an i.v. bolus of enoxaparin (0.5 mg/kg with or without glycoprotein IIb/IIIa inhibitors (GPI), followed by s.c. injections) or UFH (ACT-adjusted 50-70 IU/kg with GPI, 70-100 IU/kg without GPI, followed by i.v. or s.c. administration). All patients received aspirin and clopidogrel. Patients who received any anticoagulant before randomisation were excluded. The primary end point was the 30-day incidence of death, complication of MI, procedure failure or major bleeding. The main secondary end point was the composite of death, recurrent ACS or urgent revascularisation. Compared with UFH, enoxaparin resulted in a non-significantly lower rate of the primary end point (28% vs 33.7%, RR 0.83, 95% CI 0.68-1.01, p=0.06) and a significantly lower rate of the main secondary end point (6.7% vs 11.3%, RR 0.59, 95% CI 0.38-0.91, p=0.015). Death or complication of MI was also reduced with enoxaparin (7.8% vs 12.4%, RR 0.63, 95% CI 0.42-0.94, p=0.02). Rates of bleeding were not different between groups. The net clinical benefit (death, complication of MI or major bleeding) was reduced with enoxaparin (10.2% vs 15%; p=0.03) (63). Thus, enox-

Table 2: Randomised comparative trials between low-molecular-weight heparins (LMWH) and unfractionated heparin (UFH) in addition to aspirin (ASA) in NSTE-ACS including more than 300 patients in each group.

Study, Publication year (no. patients) [ref.]	Tested treatment	Control treatment	Background treatment	Death + MI test / control, P-level	Major bleeding test /control, P-level
FRIC, 1997 (1,482) [71]	dalteparin	UFH	ASA	8.2 % / 8.3 %, N.S. (at 45 days)	1.6 % / 1.4 %, N.S. (at 45 days)
ESSENCE, 1997 (3,171) [72, 73]	enoxaparin	UFH	ASA	6.2 % / 8.2 %, N.S. (at 43 days)	6.5 % / 7.0 %, N.S. (at 30 days)
TIMI 11B, 1998 (3,910) [72, 74]	enoxaparin	UFH	ASA	7.9 % / 8.9 %, N.S. (at 43 days)	4.4 % / 2.5 %, P=0.02 (at 43 days)
FRAX.I.S, 1999 (2,317) [75]	nadroparin	UFH	ASA	8.6 % / 7.9 %, N.S. (3 months)	0.7 % / 1 %, N.S. (at 6 days)
INTERACT, 2003 (746) [76]	enoxaparin	UFH	ASA, eptifibatide	5.0 % / 9.0 %, P=0.03 (at 30 days)	5.3 % / 8.7 %, N.S. (at 30 days)
SYNERGY, 2004 (9,978) [77]	enoxaparin	UFH	ASA, clopidogrel	14.0 %/14.5 %, N.S. (at 30 days)	9.1 % / 7.6 %, N.S. (P=0.008) (in-hospital)
A to Z, 2004 (3,960) [78]	enoxaparin	UFH	ASA	7.4 %/7.9 %, N.S. (at 30 days)	0.9 % / 0.4 %, P=0.05 (at 30 days)

aparin may provide some benefit over UFH in STEMI patients undergoing PCI.

STEMI treated with fibrinolysis

The open label ASSENT-3 trial compared enoxaparin with UFH after fibrinolytic therapy with full-dose tenecteplase. A third arm investigated UFH in combination with half-dose tenecteplase plus a 12 h infusion of abciximab (64). There was a lower incidence of the composite of 30-day mortality, in-hospital reinfarction or refractory angina in the enoxaparin and abciximab groups than in the UFH group. There were no significant differences in 30-day mortality, in-hospital intracranial haemorrhage (ICH) or major bleeding between the enoxaparin and UFH groups. The one-year follow-up demonstrated no differences in mortality among the three groups (64). The ASSENT-3 PLUS trial tested the efficacy and safety of pre-hospital treatment with enoxaparin or UFH in patients receiving tenecteplase, and demonstrated a similar difference in the efficacy end point, as shown in ASSENT-3, but the risk of ICH (2.2% vs 0.97%; p=0.048) and major bleeding (4% vs 2.8%; p=0.17) were higher in the enoxaparin group (66). The risk of ICH and major bleeding was mainly confined to patients >75 years of age. In a meta-analysis of the combined results from the AS-SENT-3 and ASSENT-3 PLUS trials there was an excess in major bleeding with enoxaparin (3.3% vs 2.4%, p=0.01). While the total ICH rate was not different between enoxaparin and UFH (1.3% vs 0.9%, p=0.258), an excess of ICH, primarily in females >75 years, occurred with enoxaparin in ASSENT-3 PLUS (6.7% vs 0.8%, p=0.013) (67). In a meta-analysis of all six randomised trials performed before 2005, although there was a trend to more major bleeding in patients treated with LMWH (for 4 to 8 days) than with UFH (for 2 to 4 days), this was offset by a reduction in reinfarction (68).

In the EXTRACT-TIMI 25 trial, 20,506 patients with STEMI scheduled to receive fibrinolytic therapy were randomised to receive either enoxaparin throughout the index hospitalisation or weight-based UFH for at least 48 h (69, 70). Patients over 75 years of age were not given an i.v. bolus of enoxaparin and received only 75% of the s.c. dose. At 30 days, death or non-fatal recurrent MI occurred in 4.5% of those given UFH and in 3.0% of the patients treated with enoxaparin (p<0.001). However, the rate of major bleeding was higher in patients given enoxaparin than in those treated with UFH (2.1 and 1.4%, respectively; p<0.001), as was the rate of fatal bleeds (0.55 and 0.33%, respectively; RR, 1.64; 95% CI, 1.07 to 2.51) (69, 70). The incidence of ICH was 0.8 and 0.7% in the enoxaparin and UFH groups, respectively (69, 70). The composite of death, non-fatal reinfarction, or non-fatal intracranial haemorrhage (a measure of net clinical benefit) occurred in 12.2% of patients given UFH and 10.1% of those given enoxaparin (p<0.001). Based on these data enoxaparin is a preferred alternative to UFH in patients with STEMI receiving fibrinolytic therapy <75 years of age and with an estimated creatinine clearance >30 ml/min. In the others, UFH remains the anticoagulant of choice.

NSTE-ACS

▶ Table 2 summarises the results of major trials that compared the efficacy and safety of LMWH vs UFH in patients with NSTE-ACS. Although dalteparin (71) and nadroparin (75) did not show superiority over UFH in aspirin-treated patients, a systematic overview (80) of the six trials comparing enoxaparin with UFH (TIMI 11B [72, 74], ESSENCE [72, 73], INTERACT [76], ACUTE 2 [79], A to Z [78], SYNERGY [77]), involving a total of 21,946 patients, showed a small but significant reduction in the combined end point of death or MI at 30 days in favour of enoxaparin (10.1 and

11.0%, respectively; OR 0.91, 95% CI 0.83-0.99), especially in the population who did not receive anticoagulant therapy prior to randomisation (OR 0.81, 95% CI 0.70-0.94) (80). The incidence of death at 30 days was similar with enoxaparin and UFH (3.0 and 3.0%, respectively; OR 1.00, 95% CI 0.85-1.17), as were rates of blood transfusion (OR 1.01, 95% CI 0.89-1.14) and major bleeding (OR 1.04, 95% CI 0.83-1.30) seven days after randomisation (80).

The SYNERGY trial, which compared s.c. enoxaparin (1 mg/kg every 12 h) with i.v. UFH (60 IU/kg bolus + 12 IU/kg/h adjusted to an aPTT of 1.5-2 times control or 50-70 seconds [s]) in 9,978 high-risk NSTE-ACS patients scheduled for early revascularisation, showed no significant difference in death or MI at 30 days, but there was more TIMI major bleeding with enoxaparin than with UFH (9.1% vs 7.6%, p=0.008) (77). The difference in bleeding may reflect the relatively low doses of UFH used in the trial. Patients with an estimated creatinine clearance <30 ml/min were excluded from SYNERGY. In such patients, enoxaparin doses should be either halved or the drug should be withheld (81).

Few studies have evaluated LMWH in the transition from medical to interventional therapy. Collet et al. (82) examined the safety and efficacy of performing PCI in NSTE-ACS patients receiving enoxaparin therapy. PCI was performed within 8 h of the last s.c. enoxaparin injection, and no additional anticoagulant therapy was given. In 451 consecutive patients with NSTE-ACS, who received at least 48 h of treatment with s.c. enoxaparin (1 mg/kg/12 h), 293 (65%) underwent coronary angiography within 8 h of receiving the morning dose of enoxaparin and 132 (28%) were not given additional enoxaparin. The mean anti-Xa activity at the time of catheterisation was over 0.5 IU/ml in 97.6% of the patients. There were no instances of in-hospital acute vessel closure or urgent revascularisation following PCI. More recent data from >350 patients indicate that anti-FXa levels similar to those found after 48 h of s.c. treatment are achieved after two s.c. doses of enoxaparin (10).

In the open-label, observational NICE-3 study (83), 628 NSTE-ACS patients were treated with enoxaparin (1 mg/kg twice daily [b.i.d.]) plus abciximab, eptifibatide or tirofiban at standard doses; 43 patients received enoxaparin alone. The following in-hospital clinical outcomes were observed in patients receiving enoxaparin plus a glycoprotein IIb/IIIa inhibitor (GPI) vs those receiving enoxaparin alone: death: 1 and 0%; MI: 3.5 and 4.7%; urgent revascularisation: 2.7 and 9.3%; and the combined outcome death/MI/urgent revascularisation: 7.0 and 14%, respectively. In the 283 patients undergoing PCI, the incidence of non-coronary artery bypass graft (CABG)-related major bleeding was 1.9%, comparable with that reported in trials administering UFH plus a GP IIb/IIIa inhibitor.

In the SYNERGY trial, which compared enoxaparin with UFH in almost 10,000 NSTE-ACS patients managed with a nearly invasive strategy, 92% patients underwent coronary angiography, and PCI was performed in 47%, of whom 57% received a GPI. Enoxaparin was non-inferior to UFH for the treatment of high-risk patients with NSTE-ACS in terms of ischaemic events, but was associated with an increased rate of major bleeding. When stratified by pre-randomisation therapy, enoxaparin had some benefit on ischaemic events among patients without anticoagulant therapy before randomisation (12.6% vs 14.8% for death and MI at 30 days), without any difference in bleeding (77).

In general, UFH is preferred to enoxaparin (the only LMWH studied in this setting) in high-risk NSTE-ACS patients with planned invasive strategy because of its shorter half-life and easier reversibility. However, switching from UFH to LMWH and vice versa should generally be avoided. If a LMWH has been administered prior to PCI, the administration of additional anticoagulant therapy depends on the timing of the last dose of LMWH. The following management (tested in trials with enoxaparin) is recommended: in patients undergoing PCI within 8 h of the last dose, no additional anticoagulation is required; when PCI is performed 8-12 h after the last dose, supplemental treatment with either a lower dose of i.v. LMWH (enoxaparin 0.3 mg/kg i.v. bolus), or UFH should be given.

Elective PCI

UFH is the standard anticoagulant therapy during PCI. The lack of randomised clinical trials of heparin vs placebo during PCI is due to the strong belief that anticoagulation therapy is an obligatory requirement during the procedure. Heparin is given as an i.v. bolus of 70–100 IU/kg (50–70 IU/kg if GPI are used). It is recommended to perform the procedure under ACT guidance: heparin should be given at a dose able to maintain an ACT of 250–350 s (200–250 s if GPI are used) (81), although such recommendations are based on circumstantial evidence and no ad hoc randomised trial (85). Since the two most widely used devices for ACT monitoring (Hemochron, ITC Technidyne Corp., more widely used; and Hemo-Tec, Medtronic) have different sensitivities to heparin, ACT measurements with these devices cannot be used interchangeably. Hemochron values are about 28% higher than HemoTec values. Therefore, when using the HemoTec device to monitor the ACT in guiding PCI a target range of 200 to 250 s is recommended in the absence of GPI, and correspondingly lower values if GPI are used (85). Higher doses of heparin, as tested even recently, do not apparently lead to better outcome and increase bleeding. In biomarker-negative patients undergoing PCI after clopidogrel loading, a dose of 100 U/kg UFH provided net clinical benefit compared with the historical control of 140 U/kg UFH in the ISAR-REACT 3 trial. The benefit was mostly driven by reduction in bleeding (86).

Several studies have examined the utility of i.v. LMWH in patients undergoing elective PCI who have not received an anticoagulant prior to the procedure. Small and/or non-comparative trials have shown the feasibility of a single i.v. bolus of enoxaparin (1.0, 0.75, or 0.5 mg/kg) in patients undergoing PCI with or without the co-administration of a GPI. A small study (84) compared two doses of dalteparin (40 or 60 IU/kg i.v.) in combination with abciximab; patients who received 60 IU/kg of dalteparin i.v. had a lower incidence of procedural thrombosis (0% vs 11.1%, p <0.01), more consistent antithrombotic effect (anti-FXa activity) and a similar incidence of major bleeding (3.7% vs 2.6%) compared with patients who received 40 IU/kg of i.v. dalteparin (84). A meta-analysis of the data from randomised studies comparing i.v.

LMWH with UFH in patients undergoing PCI found no difference in the rate of ischaemic events and a non-significant trend toward a reduction in major bleeding with LMWH (103). In the STEEPLE trial, an i.v. bolus of unmonitored enoxaparin (either 0.5 or 0.75 mg/kg) was compared with UFH in 3,528 patients treated mostly on an elective basis (87). At the 0.5 mg/kg dose, enoxaparin significantly reduced the primary end point of non-CABG-related bleeding compared with ACT-adjusted UFH (5.9 and 8.5%, respectively; p=0.01). However, randomisation into this arm of the study was stopped because of a significant increase in mortality compared with the higher dose enoxaparin regimen in the interim analysis, a finding not confirmed in the final analysis. There was a trend to less bleeding with the higher dose enoxaparin (0.75 mg/kg) compared with UFH (6.5 and 8.5%, respectively; p=0.051), but no significant difference in the rate of ischaemic events (87). Based on these data enoxaparin is a reasonable alternative to UFH in patients undergoing elective PCI, but without demonstrated superiority.

Cardioversion in AF

Because LMWH s.c. administration is more convenient than UFH infusion, s.c. LMWH has been a practical alternative to UFH for initiation of anticoagulation in patients with AF. A randomised study compared enoxaparin with the combination of a VKA (phenprocoumon) plus UFH until the INR was ≥2.0 in patients undergoing cardioversion of AF who were not already anticoagulated (99). Enoxaparin was given s.c. at an initial dose of 1 mg/kg body weight b.i.d. for 3-8 days, followed by a fixed dose of 40 mg b.i.d. in patients with a body weight <65 kg and 60 mg b.i.d. in patients with a body weight >65 kg for the rest of the study period. Study groups were then both anticoagulated for four weeks after cardioversion. The primary end point (a composite of all embolic and haemorrhagic events and all-cause mortality) occurred in 2.8% of patients in the group that received enoxaparin compared with 4.8% of patients in the group receiving UFH plus phenprocoumon. Thus, LMWH is non-inferior to conventional anticoagulation with UFH for prevention of ischaemic and thromboembolic events after cardioversion of AF.

Because of its cost, LMWH rarely is used in clinical practice as a substitute for long-term conventional anticoagulation. LMWH typically is used as a temporary bridge to therapeutic anticoagulation when therapy with a VKA is initiated, or in high-risk patients for a few days before and after an invasive procedure when anticoagulation with a VKA has been suspended.

Considerations on LMWH for cardioversion after TEE are similar to those given before for UFH.

Bridging to non-cardiac surgery in patients with a cardiac prosthetic valve or valve repair

Both American and European guidelines advise caution in the use of LMWH for bridging during interruption of OAC in patients with a cardiac prosthetic valve or after valve repair requiring oral anticoagulation and needing a surgical operation (61, 62). Al-

though it is acknowledged that this is a widespread practice, driven mainly by issues related to shortening stay in hospital and avoiding frequent monitoring with the aPTT, thus reducing costs, the safety of LMWH has not been established.

Synthetic pentasaccharides (fondaparinux) vs UFH and LMWH

Fondaparinux was first evaluated in two dose-finding phase II studies in NSTE-ACS and STEMI; PENTUA (91) and–PENTA-LYSE, respectively (92), and in two phase II elective PCI studies (88, 93). Based on the results of these studies, the lowest dose of fondaparinux tested, 2.5 mg s.c. once daily, was found to be the safest, and had efficacy that was at least as good as higher doses. This dose was therefore carried forward into the two large-scale phase-III trials. Since that dose was at the lower end of the dose spectrum so far explored, one may question whether dose finding has been truly appropriate.

STEMI treated with primary PCI or fibrinolytic therapy

The Organisation to Assess Strategies for Ischaemic Syndromes (OASIS)-6 trial compared fondaparinux, given for up to eight days, with standard adjuvant anticoagulant treatment in 12,092 STEMI patients (89). The trial had a complicated design with two strata. In stratum I, with no indication for UFH, 5,658 STEMI patients were randomised to fondaparinux or placebo. In stratum II, 6,434 patients with an indication for anticoagulation were randomised to fondaparinux for eight days or UFH for up to 48 h, followed by placebo for up to eight days. Both strata included subgroups that did or did not receive reperfusion therapy. Reperfusion therapy included primary PCI or fibrinolytic therapy, the latter predominantly with streptokinase. Overall, the end point of death or reinfarction at 30 days was significantly reduced with fondaparinux (from 11.2% to 9.7%; p=0.008). However, the benefit was restricted to stratum I, where fondaparinux was compared with placebo. In contrast, there was no significant difference in death or reinfarction between fondaparinux and UFH in stratum II (8.3 and 8.7%, respectively). In the 3,768 patients undergoing primary PCI, all of whom were in stratum II, fondaparinux was of no benefit over UFH, with a 30-day rate of death or MI of 6.1 and 5.1%, respectively (p=0.19). There was a higher rate of guide catheter thrombosis (22 vs 0; p<0.001) and more coronary complications (270 vs 225; p=0.04) with fondaparinux. However, among the 496 patients who received UFH prior to primary PCI, these differences were not noted. In the other 2,666 patients in stratum II (with an indication for UFH and without primary PCI), fondaparinux tended to be superior to UFH in preventing death or reinfarction at 30 days, with event rates of 11.5% and 13.8%, respectively (p=0.08). There was a trend to less major bleeds with fondaparinux, and the rate of major bleeds was lower with fondaparinux than with placebo in stratum I patients, a finding that is difficult to explain. Based on the results of the OASIS-6 trial (a) in STEMI patients without an indication for UFH, fondaparinux is more effective and at least as safe as no anticoagulant treatment regardless of

whether or not pharmacological reperfusion treatment is given; (b) in STEMI patients given fibrinolytic therapy fondaparinux is at least as effective and as safe as UFH; and (c) fondaparinux should not be used in STEMI patients undergoing primary PCI.

NSTE-ACS

In the OASIS-5 trial, 20,078 patients with NSTE-ACS were randomised to fondaparinux (2.5 mg once daily) or enoxaparin (1 mg/kg b.i.d) for a mean of six days (90). The primary efficacy outcome, a composite of death, MI or refractory ischaemia at nine days, occurred in 5.8% of patients treated with fondaparinux and in 5.7% of those given enoxaparin, which satisfied the pre-specified criterion for non-inferiority (p=0.007). The rate of major bleeding was 50% lower with fondaparinux than with enoxaparin (2.2 and 4.1%, respectively; p<0.001). Consequently, the composite outcome of death, MI, refractory ischaemia or major bleeding favoured fondaparinux over enoxaparin (7.3 and 9.0%, respectively; p<0.001). Major bleeding was an independent predictor of long-term mortality, which was lower with fondaparinux at six months than with enoxaparin (5.8 and 6.5%, respectively; p=0.05), as was the composite outcome of death, MI or stroke (11.3 and 12.5%, respectively; p=0.007). Although the rates of catheter thrombosis were low, these were higher with fondaparinux than with enoxaparin (0.9 and 0.4%, respectively; p<0.001), and there was a trend for more PCI-related coronary complications with fondaparinux compared with enoxaparin (9.5 and 8.6%; p=0.21). However, because of the lower rate of bleeding complications at the access site (3.3% vs 8.1%; p<0.001), the overall rate of procedure-related complications of death, MI or bleeding was significantly lower with fondaparinux than with enoxaparin (16.6% vs 20.6%; p<0.001). Thus, fondaparinux had an overall efficacy similar to that of enoxaparin at nine days, but produced significantly less major bleeding, which translated into a reduction in mortality at six months, albeit at the expense of an increased rate of catheter-associated thromboses. Therefore, fondaparinux is the first anticoagulant demonstrated to lower the risk of bleeding and to reduce mortality compared with enoxaparin. In fondaparinux-treated patients undergoing PCI, the slightly increased risk of catheter-related thrombosis was said to be largely preventable by supplemental UFH at the time of the procedure.

In the FUTURA-OASIS 8 trial 2,026 NSTE-ACS patients receiving fondaparinux who were undergoing PCI were randomised to receive i.v. either low-dose UFH, 50 IU/kg, regardless of use of GPI or standard-dose UFH, 85 IU/kg (60 IU/kg with GPI), adjusted by the ACT performed in a blinded fashion (95). There was no difference in the primary composite end point (major bleeding, minor bleeding or major vascular access site complications) between the two groups, but the net clinical benefit (major bleeding/target vessel revascularisation) favoured the use of the standard UFH dose. With the standard UFH dose, the incidence of catheter thrombosis was 0.1%. Therefore, based on the results of this study, a full UFH dose of 85 IU/kg (60 IU/kg if a GPI is given) is recommended in fondaparinux-treated NSTE-ACS patients undergoing PCI.

It is debatable whether fondaparinux, because of its safety, should be the preferred choice in NSTE-ACS treated invasively. The recent ESC Guideline recommendations are in such direction (96), downplaying the issue of stent thrombosis and arguing on its full preventability with additional full-dose UFH administration at the time of PCI. Such a choice is probably currently the best recommended strategy for patients (currently the majority) not proceeding to an immediate invasive treatment. If an immediate PCI in such patient is planned, we recommend bivalirudin or UFH as the preferred treatment.

Parenteral direct thrombin inhibitors vs UFH and LMWH

STEMI treated with primary PCI

The efficacy of bivalirudin in primary PCI was evaluated in the the Harmonizing Outcomes With Revascularisation and Stents in Acute Myocardial Infarction (HORIZONS AMI) trial (97), in which 3,602 patients with STEMI undergoing PCI were randomly assigned, in an unblinded fashion, to receive either bivalirudin (initial bolus of 0.75 mg/kg followed by an i.v. infusion of 1.75 mg/kg per h, discontinued after PCI) with provisional GPI, or UFH or enoxaparin plus planned GPI prior to primary PCI. The primary end point, the composite of major adverse cardiac events or major bleeding at 30 days, was significantly reduced with bivalirudin because of a 40% relative reduction in major bleeding (p<0.001). All-cause mortality at 30 days was 1% lower with bivalirudin (p<0.0047) and was maintained at three years (98). Acute stent thrombosis occurred more frequently (p<0.001), but no significant increase was present by 30 days; there was no difference in definite or probable stent thrombosis between the two study arms at one year and at three years (98).

Based on these results, bivalirudin is now approved by the European Medicines Agency (EMA) as an anticoagulant for patients undergoing PCI, including STEMI patients undergoing primary PCI. In STEMI patients undergoing PCI, bivalirudin – with provisional GPI - should be the anticoagulant of choice because of its net clinical benefit over UFH or enoxaparin with GPI. Bivalirudin is given as an i.v. bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/h, and is not titrated according to the ACT. The drug is usually terminated at the end of the procedure.

The use of bivalirudin in the prehospital treatment of STEMI is currently being tested in the EUROMAX trial.

NSTE-ACS

Patients enrolled in the early trials with bivalirudin did not receive either GPI or clopidogrel. The efficacy and safety of bivalirudin alone or with GPI compared with UFH or enoxaparin given with GPI was tested in the ACUITY trial, which included 13,819 patients with moderate-to-high risk ACS undergoing PCI (100, 101). The primary end point was a composite of death, MI, or unplanned revascularisation for ischaemia at 30 days. Bivalirudin was begun before angiography, with an i.v. bolus of 0.1 mg/kg and

an infusion of 0.25 mg/kg/h. Before PCI, an additional i.v. bolus of 0.5 mg/kg was administered, and the infusion was increased to 1.75 mg/kg/h. All antithrombotic agents were discontinued according to the protocol at the completion of angiography or PCI, but could be continued at low doses at the discretion of the operator. Bivalirudin alone was non-inferior to UFH or enoxaparin plus a GPI at 30 days (7.8 and 7.3 %, respectively; RR 1.08, 95% CI 0.93-1.24), while the rate of major bleeding was significantly lower with bivalirudin (3.0 vs 5.7 %, RR 0.53, 95% CI 0.43-0.65). Bivalirudin was associated with a significantly lower rate of non-CABG major bleeding in all age groups, but the absolute difference was greatest in patients aged 75 years or older (5.8 vs 10.1 %). The

ACUITY trial highlights the importance of clopidogrel pretreatment for patients given bivalirudin who are not treated with a GPI, because subgroup analysis showed a higher rate of ischaemic outcomes if clopidogrel was not given before angiography or PCI. In the ISAR-REACT 4 trial the combination of abciximab plus heparin was not superior to bivalirudin in preventing ischaemic end points, but was associated with more bleeding in NSTEMI-ACS patients undergoing PCI (102). Based on such results, and because of its net clinical benefit, bivalirudin without a GPI should now be considered the anticoagulant of choice in patients with NSTE-ACS treated with PCI, particularly in patients with a high risk of bleed-

Boxed Recommendations

Classes of Recommendations and Levels of Evidence are given according to the European Society of Cardiology (ESC) Practice Guidelines. For laboratory tests, Levels of Evidence are graded from A – full consensus based on converging data – to C – expert opinion.

General recommendations

- We recommend against the use of s.c. UFH as an anticoagulation strategy, even as short-term bridging therapy [III B].
- The therapeutic range for UFH should be adapted to the aPTT reagent used [IIa B].
- We recommend against the use of a fixed aPTT target in seconds when using UFH for any therapeutic indication [III B].
- In patients with severe kidney disease (creatinine clearance 15-30 ml/min) or end-stage kidney disease (creatinine clearance <15 ml/min), we recommend UFH over LMWH and over fondaparinux [I A].
- In patients with moderate kidney disease (creatinine clearance 30-60 ml/min), we recommend reducing enoxaparin to 75% of the usual dose [IIa B].
- The i.v. infusion dose of bivalirudin should be reduced from 1.75 to 1 mg/kg/h if the creatinine clearance is <30 ml/min and to 0.25 mg/kg/h in case of haemodialysis .
- In patients with suspected or established HIT we recommend against LMWH as alternatives to heparin [III A].
- The various LMWH preparations are not interchangeable [III B]. The use in any specific setting should be restricted to those LMWH that have been demonstrated to be effective and safe in that specific setting.
- We recommend against crossover (switching) between heparins (UFH and LMWH) whenever possible [III B].
- If monitoring or assessment is required, the anticoagulant activity of LMWH or fondaparinux can be measured with anti-FXa assays, using the appropriate reference calibrator [I B].
- Unless the patient has a history of HIT, we recommend against the use of fondaparinux for prevention or treatment of thrombosis during pregnancy [III B].

Percutaneous coronary interventions (PCI)

- UFH is the anticoagulant therapy of choice for patients undergoing elective PCI [I B].
- In elective PCI, UFH is given as an i.v. bolus at a usual starting dose of 70–100 IU/kg (50–70 IU/kg if a GPI is used). We recommend anticoagulation monitoring using the ACT, adjusting the UFH dose to maintain an ACT with the Hemochron device of 250–350 s (200–250 s if a GPI is used) [IIa B].
- When using the HemoTec device to monitor the ACT during UFH therapy for PCI, a target range of 200 to 250 s is recommended in the absence of GPI, and correspondingly lower values (170–200 s) if a GPI is used [IIa B].
- In patients undergoing elective PCI, enoxaparin is a reasonable alternative to UFH [IIa B].
- If a LMWH has been administered prior to PCI, the administration of additional anticoagulant therapy should depend on the timing of the last dose of LMWH. If PCI is performed within 8 h of the last dose, no additional anticoagulation is required. If PCI is performed 8-12 h after the last dose, supplemental treatment with either a lower dose of i.v. LMWH (enoxaparin 0.3 mg/kg i.v. bolus; data for other LMWH are lacking) or UFH should be given [IIa B].
- Discontinuation of anticoagulation should be considered immediately after an invasive procedure unless otherwise indicated [IIa C].

Acute coronary syndromes (ACS)

- In STEMI patients undergoing PCI, we recommend bivalirudin with a provisional GPI over UFH or enoxaparin with a systematic GPI [I B].
- In STEMI patients undergoing primary PCI, enoxaparin (0.5 mg/kg i.v. followed by s.c. treatment) may provide some benefit over UFH [IIb B].
- In STEMI patients undergoing primary PCI, we recommend against the use of fondaparinux [III B].

- In STEMI patients receiving fibrinolytic therapy who are <75 years of age and have an estimated creatinine clearance >30 ml/min, enoxaparin is preferred over UFH [IIa B].
- In STEMI patients receiving fibrinolytic therapy who are >75 years of age or with a creatinine clearance <30 ml/min, we recommend UFH as the agent of choice [I B].
- In STEMI patients given fibrinolytic therapy, fondaparinux is as effective and safe as UFH, provided creatinine clearance is >30 ml/min [IIa B].
- When using UFH for ACS, we recommend a bolus of 60 to 70 IU/kg (maximum 5,000 IU) followed by an infusion of 12 to 15 IU/kg/h (maximum 1,000 IU/h) in order to double the baseline aPTT [I B].
- When using UFH in conjunction with a fibrinolytic agent for STEMI patients, we recommend lower UFH doses: a bolus of 60 IU/kg (maximum 4,000 IU) followed by an infusion of 12 IU/kg/h (maximum of 1,000 IU/h) [I B].
- In patients with NSTE-ACS in whom an 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 dual antiplatelet therapy with aspirin plus an ADP receptor blocker is given [I B].
- For high-risk NSTE-ACS 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 [IIa B].
- In NSTE-ACS patients in whom a non-immediate invasive strategy is planned, we recommend fondaparinux (2.5 mg s.c. daily) over other anticoagulants, provided creatinine clearance is >30 ml/min, because of its more favourable efficacy–safety profile [I A].
- In fondaparinux-treated NSTE-ACS patients undergoing PCI, we recommend administration of full-dose UFH at the time of the procedure (85 IU/kg bolus or 60 IU/kg if a GPI is given) [I B].
- In NSTE-ACS patients in whom a conservative strategy is planned, we recommend fondaparinux (2.5 mg s.c. daily) over other anticoagulants, provided creatinine clearance is >30 ml/min, because of its more favourable efficacy–safety profile [I A], and we recommend that such treatment be continued until hospital discharge [I A].

Cardioversion of atrial fibrillation (AF)

- In patients with definite AF lasting 48 h or less, cardioversion can be immediately performed under either i.v. UFH (e.g. i.v. bolus of 80 IU/kg, followed by a continuous i.v. infusion, initially of 18 IU/kg/h and adjusted to achieve an aPTT of twice the control value) or s.c. LMWH [IIa B].
- For patients with definite AF lasting 48 h or less who have undergone successful cardioversion, we recommend continued long-term anticoagulation after the procedure if there are risk factors for thromboembolism [I B]; in such patients, we recommend initiation of a VKA and continuation of UFH or a LMWH until a therapeutic INR (2-3 in most cases) is achieved. In non-valvular AF, long-term anticoagulation with a direct thrombin inhibitor or with a direct FXa inhibitor, instead of a VKA, should be considered [IIa B]. In such cases no bridging with UFH or a LMWH should be performed [IIa C].
- LMWHs are non-inferior to conventional anticoagulation with UFH for prevention of ischaemic and thromboembolic events around cardioversion of AF [IIa B].
- For patients with definite atrial fibrillation lasting 48 h or less who have undergone successful cardioversion and who have no risk factors for thromboembolism (i.e. CHA_2DS_2-VASc score = 0), we recommend discontinuation of anticoagulant therapy immediately after cardioversion [IIa B].

Prosthetic heart valves and valve repair

- In patients with a prosthetic heart valve requiring an oral anticoagulant in whom a surgical operation requiring full haemostasis is planned, we recommend bridging with i.v. UFH; the latter should be started after stopping oral anticoagulation with a VKA, when the INR falls below 2.0, continued until 4-6 h before the operation, restarted (together with the VKA) as soon as possible afterwards, and continued until the INR is again therapeutic [IIa B].
- We favour bridging with UFH over a LMWH in such situations because of the shorter half-life, potential for complete reversal with protamine sulfate should bleeding occur, and larger experience with UFH vs LMWH [IIa C].

ing, in whom, however, optimal dual antiplatelet therapy with aspirin and clopidogrel has to be given (96).

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