



Anticoagulants in heart disease: current status and perspectives[†]

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[‡]The content of parts of this position paper overlaps with that of the forthcoming guidelines on NSTEMI-ACS, and unavoidably, some sections are similar, for the sake of consistency, between these documents.

Vitamin K antagonists	901	NYHA	New York Heart Association
Management of bleeding complications	901	NSTE-ACS	non-ST elevation acute coronary syndromes
Unfractionated heparin and low-molecular weight heparins	901	OASIS	Organization to Assess Strategies for Ischemic Syndromes
Pentasaccharides	901	PAR	protease-activated receptor
Direct thrombin inhibitors	902	PCI	percutaneous coronary intervention
Vitamin K antagonists	902	POCT	point-of-care test(s)
Special situations	902	PF4	platelet factor-4
Vitamin K antagonists in pregnant patients with artificial heart valves	902	PT	prothrombin time
Renal failure and haemodialysis	902	SK	streptokinase
Surgery, percutaneous coronary interventions, biopsies, and dental procedures	902	STEMI	ST elevation acute myocardial infarction
Cancer	903	TAFI	thrombin-activatable fibrinolysis inhibitor
Anticoagulant therapy in combination with other drugs interfering with haemostasis	904	TF	tissue factor
Anticoagulant therapy in combination with antiplatelet therapy	904	TFPI	tissue factor pathway inhibitor
Anticoagulant therapy in combination with fibrinolytic therapy	904	TIMI	Thrombolysis In Myocardial Infarction
Current needs and future developments	906	TM	thrombomodulin
Acknowledgements	906	TNF	tumor necrosis factor
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		UFH	unfractionated heparin
		VKA	vitamin K antagonist
		VTE	venous thromboembolism
		WHO	World Health Organization

List of Abbreviations

ACCP	American College of Chest Physicians
ACS	acute coronary syndrome(s)
ACT	activated clotting time
AF	atrial fibrillation
ALAT	alanine amino transferase
APC	activated protein C
APSAC	anisoylated plasminogen streptokinase activator complex
aPTT	activated partial thromboplastin time
ASIS	active site-inhibited seven (FVIIa)
AT	antithrombin, formerly antithrombin III
CABG	coronary artery bypass graft
CD	cluster of differentiation
CDSS	computerized decision support system
CHF	chronic heart failure
CrCl	creatinine clearance
ECAA	European Society of Cardiology
F	factor
FDA	Food and Drug Administration
GFR	glomerular filtration rate
GP	glycoprotein
GUSTO	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
HIT	heparin-induced thrombocytopenia
ICH	intracranial hemorrhage
IL	interleukin
INR	International Normalized Ratio
ISI	International Sensitivity Index
ISTH	International Society on Thrombosis and Haemostasis
LDL	low-density lipoproteins
LMWH	low molecular weight heparin
MI	myocardial infarction
MNPT	mean normal prothrombin time
NAPC2	nematode anticoagulant peptide C2

Preamble: purposes and scope of the task force

Drugs interfering with blood coagulation are a mainstay of cardiovascular therapy. Despite their widespread use, there are a number of unmet needs for current parenteral and oral anticoagulants in cardiovascular diseases. This therapeutic area is undergoing unprecedented changes with the clinical introduction of new drugs. This document, initiated by a committee appointed by the European Society of Cardiology (ESC) Working Group on Thrombosis, intends therefore:

- to review the current mechanism of action, pharmacological properties, indications, side effects, ongoing trials, and areas of current investigations for drugs interfering with coagulation as applied to atherothrombosis and arterial thrombo-embolism in heart disease, namely:
 - coronary heart disease and percutaneous coronary interventions (PCIs);
 - atrial fibrillation (AF);
 - artificial heart valves;
 - chronic heart failure (CHF);
- to do so with a 'pharmacologically based' approach rather than a 'disease-oriented' one, complementary with what other Guidelines Groups and Task Forces have done or are in the process of doing in indicating and recommending therapeutic options for specific cardiovascular diseases;
- to do so by putting together a group of coagulation experts and clinical cardiologists, mostly—but not exclusively—from Europe.

This document is intended to follow-up on the Task Force Document on the use of antiplatelet agents in cardiovascular disease, proposed by the committee of experts appointed similarly by the ESC Working Group on Thrombosis¹ and is intended to be regularly updated. The Writing Committee of this document has decided against issuing graded recommendations on the use and dosing of drugs, because this might conflict with the task of guidelines, some of which are being finalized at the same time by the ESC.

Blood coagulation

Haemostasis

When a blood vessel is damaged, the site of disruption must be rapidly sealed to prevent blood loss. Haemostasis requires the formation of an impermeable platelet and fibrin plug at the site of injury. Preventing clot propagation through the vascular tree also requires localizing platelets and coagulation at the site of injury. The clot is later dissolved by another protease reaction, fibrinolysis, which also prevents the vessel from being occluded by the clot during its formation. In order for the blood to stay fluid within the circulation, a delicate balance between the carefully regulated systems of coagulation and fibrinolysis is needed. Disturbances in either system will cause a tendency towards thrombosis or bleeding, respectively.²

Arterial thrombosis

Arterial thrombosis can occur from at least two main different mechanisms, endothelial erosion or plaque rupture.³⁻⁵ Superficial erosion or denudation of the endothelial cells lining the plaque accounts for about 25% of all cases of fatal coronary thromboses. Plaque rupture causes ~75% of major coronary thromboses. Plaque rupture results in the exposure of thrombogenic material, e.g. collagen and tissue factor (TF), to the flowing blood. Upon plaque rupture, the lipid gruel, containing TF, and the underlying connective tissue matrix are exposed to the blood, leading to the activation of platelets and the coagulation system as well as to the simultaneous release of vasoactive substances. This induces thrombus formation and vasoconstriction, which may cause myocardial ischaemia and acute coronary syndromes (ACS).

Tissue factor

Today coagulation is considered to be a highly regulated reaction that takes place on cell surfaces.^{6,7} The main initiator of coagulation is TF, a transmembrane glycoprotein (GP). TF is a member of the class II cytokine receptor superfamily, and functions both as the receptor and as the essential cofactor for factors (F) VII and VIIa. Assembly of the TF/FVIIa complex on cellular surfaces leads to the activation of FX and initiates coagulation. TF is constitutively expressed in cells surrounding blood vessels and large organs to form a haemostatic barrier, but can also be induced in vascular cells in response to a number of inflammatory stimuli, such as adhesion molecules [among which P-selectin and CD40 ligand (CD40L)], cytokines, and oxidized/modified low density lipoproteins (LDLs).⁸ Total lethality in homozygous TF knock-out mice embryos provides convincing evidence for TF to be indispensable for life. In addition to its role in haemostasis, the TF/FVIIa complex has been shown to elicit intracellular signalling resulting in the induction of various genes, thus explaining its role in various biological functions, such as embryonic development, cell migration, inflammation, apoptosis, and angiogenesis.⁹⁻¹¹

Tissue factor pathway inhibitor

TF pathway inhibitor (TFPI) is a potent serine protease inhibitor of TF/FVIIa-induced coagulation. It functions by neutralizing the catalytic activity of FXa and, in the

presence of FXa, by feedback inhibition of the TF/FVIIa complex.¹² TFPI contains three Kunitz-type domains: the first domain binds to FVIIa and the second to FXa. The third domain is involved in binding of TFPI to lipoproteins. The C-terminal end of TFPI is required for the binding to cell surfaces (¹³ and references therein). The primary site of synthesis of TFPI is the vascular endothelium,¹⁴ but also a number of other cell types have been reported to be production sites, including platelets. *In vivo*, ~80% of plasma TFPI circulates in complex with plasma lipoproteins. A major pool of TFPI, free TFPI, is associated with the endothelial surface and is released into circulating blood upon the intravenous (i.v.) administration of unfractionated heparin (UFH) as well as after the subcutaneous (s.c.) injection of low molecular weight heparins (LMWHs).¹⁵

Cellular control of coagulation

The cell surface-based coagulation process can be currently described in three overlapping phases: initiation, amplification, and propagation.^{7,16,17} The process starts on TF-exposing cells and continues on the surfaces of activated platelets.

The initiation phase is localized to TF-bearing cells that are exposed from the subendothelial tissue to flowing blood upon vascular injury. The proteolytic TF/FVIIa complex activates small amounts of FIX and FX. On TF-exposing cells, FXa then associates with FVa to form the prothrombinase complex (*Figure 1*). FVa derives from several sources, including activated platelets adhering at injury sites, as well as from plasma, where FV can be activated by FXa. The prothrombinase complex then cleaves prothrombin to generate small amounts of thrombin, the enzyme responsible for clot formation. The concentration of TF/FVIIa complex and of TFPI regulates the duration of this initiation phase. When a certain amount of FXa has been generated, it is bound by TFPI, and a quaternary complex with TF and FVIIa is formed.

In contrast to FXa, FIXa is not inhibited by TFPI, and only slowly inhibited by antithrombin (AT). FIXa moves in the fluid phase from TF-bearing cells to nearby platelets at the injury site.

In the amplification phase, low concentrations of thrombin activate platelets adhering to the injury site to release FV from their α -granules. A positive feedback loop is initiated, whereby thrombin activates released FV, and FVIII bound to von Willebrand factor. Such activated factors bind to platelet surfaces, which provide enough scaffolding for the large-scale thrombin generation that occurs during the propagation phase. Thrombin also activates FXI bound to platelets (*Figure 1*). The role of FXIa, a member of the intrinsic pathway of coagulation, can be considered as a booster of FIXa production on the platelet surface and thus increases thrombin generation.¹⁷

In the propagation phase, the phospholipid surface of activated platelets acts as a cofactor for the activation of the FVIIIa-FIXa complex (termed 'Xase') and of the FVa-FXa complex ('prothrombinase'), which accelerate the generation of FXa and thrombin, respectively. In addition, FXIa bound to the platelet surface activates FIX to form more Xase. FXa, thus produced, associates rapidly with FVa on the platelet surface, resulting in a burst of thrombin, ultimately leading to the bulk cleavage of fibrinogen to fibrin. Soluble fibrin is

finally stabilized by FXIIIa, also activated by thrombin, to form a fibrin network, i.e. a thrombus (Figure 1).

Thrombomodulin (TM), a transmembrane molecule expressed on endothelial cells, also binds thrombin, and the thrombin-TM complex activates the protein C anticoagulation system. Activated protein C limits the FXa/FVa activity on the endothelial surface of the injured vessel and thus the propagation of coagulation reactions.¹⁷ However, the burst of thrombin also induces activation of the carboxypeptidase thrombin-activatable fibrinolysis inhibitor (TAFI), which removes the plasmin(ogen)-binding C-terminal lysine residues, and thereby increases the resistance of the clot to lysis.

Possible targets of coagulation inhibitors (anticoagulants) are depicted in Figure 2.

Classical targeting of coagulation is done with heparins and vitamin K antagonists (VKAs). To target the initiation phase of coagulation, a number of drugs that inhibit the activity of TF/FVIIa complex are under evaluation, including recombinant TFPI (tifagasin), recombinant nematode anticoagulant (NAPC2), and active site-inhibited FVIIa (ASIS). Under development are a number of novel drugs targeting TF-FVIIa (Figure 2).

Drugs directed to target coagulation proteases that drive the propagation phase include agents that block the coagulation proteases FIXa or FXa, directly or indirectly. These drugs decrease thrombin formation. On the other hand, activated protein C and soluble TM are aimed to inactivate the cofactors FVa and FVIIIa that are critical for the generation of thrombin. FIXa blockers include monoclonal antibodies and active site inhibitors. However, these new drugs have not yet (<http://www.clinicaltrials.gov>) reached phase III and will not be further reviewed here. The synthetic pentasaccharides mediate an indirect, AT-dependent, inhibitory effect on FXa. A number of orally active direct FXa inhibitors are under clinical testing in phase II studies. One advantage with these inhibitors is the capacity to block not only free FXa, but also FXa within the prothrombinase complex at the platelet surface. Other possible advantages of these

inhibitors are that they target a molecule, FXa, which has fewer functions outside coagulation compared with thrombin, they have a wider therapeutic window than thrombin inhibitors, and they do not apparently lead, upon discontinuation, to the rebound hypercoagulability that is regularly observed upon stopping thrombin inhibitors.

New inhibitors of fibrin formation are direct thrombin inhibitors (DTIs) that bind to thrombin and block its interaction with substrates, preventing the formation of fibrin and activation of platelets and FV, FVIII, FXI, and FXIII. These drugs may also inhibit thrombin-induced intracellular signal transduction pathways, including thrombin-induced platelet activation. The DTIs also block thrombin bound to fibrin in addition to thrombin in plasma.¹⁸

Cross-talk between coagulation and inflammation

Coagulation and inflammation are integrated processes through a network of components.^{19–21} They contribute together to diseases, as illustrated by the thrombus formation on ruptured atherosclerotic plaques, which contain abundance of inflammatory cells. Coagulation proteases modulate inflammation by activation of protease-activated receptors (PARs) and also by TM and binding of activated protein C to endothelial protein C receptor.^{22,23} PARs are seven transmembrane domains, G protein-coupled receptors expressed on a variety of cells, such as platelets, endothelial cells, and leukocytes. Platelets express PAR1 and PAR4, to which thrombin binds and thereby induces the activation of platelets, the expression of P-selectin and CD40L, and the release of inflammatory cytokines and growth factors. Cross-talk between the cells in platelet-leukocyte complexes via P-selectin and CD40L leads to TF-expression and further cytokine release. PAR1 may also bind the ternary complex TF/FVIIa/FXa. PAR2 cannot bind thrombin, but TF/FVIIa complex and FXa can activate this receptor.²⁴ Binding of the different coagulation proteases to the PARs results in the upregulation of a number of genes involved in inflammation, including interleukin (IL)-8 and tumor

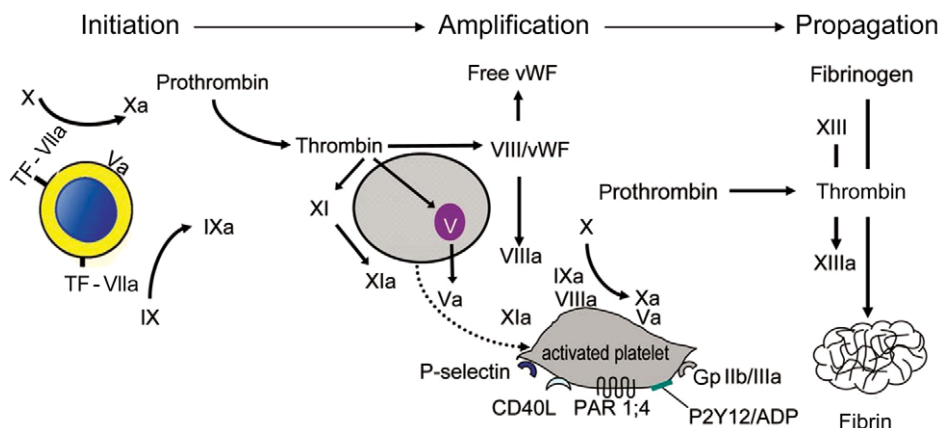


Figure 1 Scheme of current concepts on the coagulation process. The cell surface-based coagulation process includes three overlapping phases; upon vascular injury, TF-expressing cells and microparticles are exposed to the coagulation factors in the lumen of the vessel and thereby initiate thrombosis. In the initiation phase, the TF/FVIIa complex initiates blood coagulation. Platelets, which are partially activated by vascular injury, such as plaque rupture, are recruited and adhere to the site of injury. The TF/FVIIa complex further activates the coagulation FIX-IXa and X-Xa and trace amounts of thrombin are generated. In the amplification phase, this small amount of thrombin is a signal for further platelet activation and aggregation. On the surface of platelets, thrombin activates FV, FVIII, and FXI. In the propagation phase, FVIIIa forms a complex with FIXa (Xase) and FVa forms a complex with FXa (prothrombinase) on the platelet surface, which accelerate the generation of FXa and thrombin, respectively. When FXa associates with FVa, it is protected from TFPI and AT. In the propagation phase, a burst of thrombin is generated, which is sufficient for the clotting of fibrinogen and formation of a fibrin meshwork. A thrombus is formed.

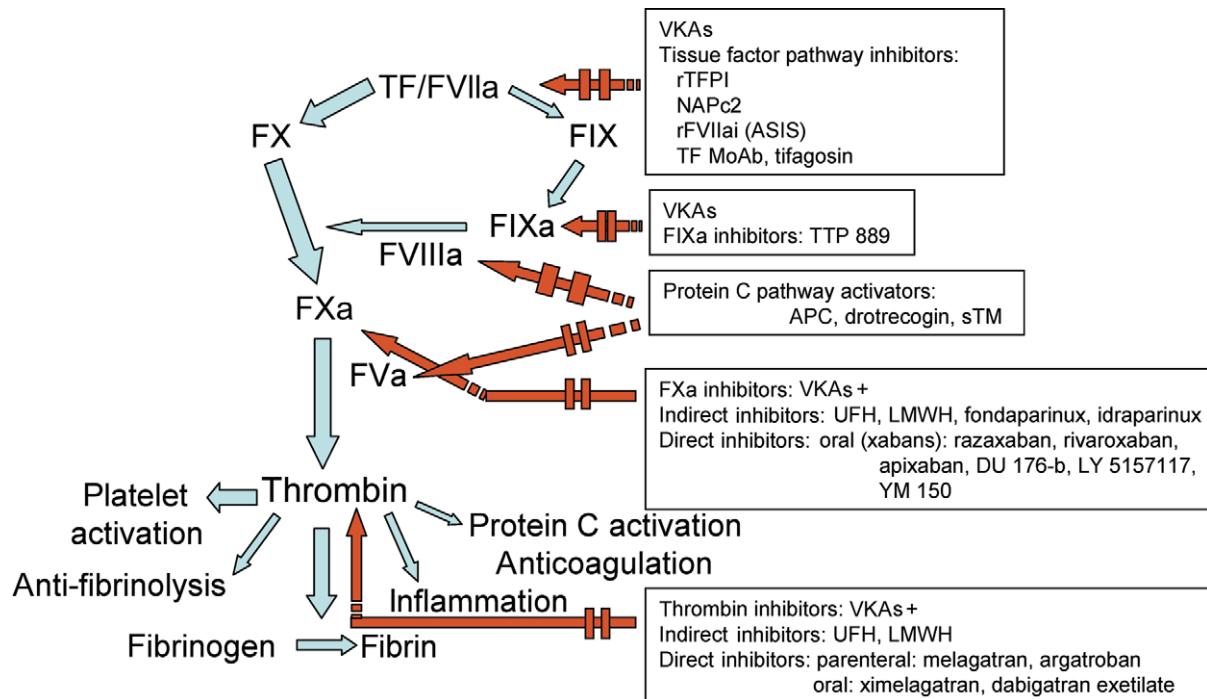


Figure 2 Targets of coagulation inhibitors (anticoagulants). To target the initiation of coagulation, inhibitors towards the TF/FVIIa complex have been developed, such as recombinant TFPI (Tifagosin), recombinant nematode anticoagulant protein(NAP)C2, active site-inhibited recombinant (r) FVIIa (ASIS), and monoclonal antibodies against TF. Blockers of the propagation phase include FIXa and FXa inhibitors. FXa inhibitors include UFH and LMWHs, which exert their effects equally on thrombin and on FXa (UFH) or prevalently on FXa (LMWHs), both by potentiating the natural inhibitor AT (antithrombin III). They are therefore indirect FXa inhibitors. The new synthetic pentasaccharides also exert their effects through the interaction with AT, but exert an effect exclusively on FXa. These drugs include fondaparinux and idraparinux. A number of oral direct (i.e. non-AT-mediated) FXa inhibitors are in clinical trials. Thrombin inhibitors include the indirect inhibitors UFH and LMWHs. DTIs 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 and thrombin-mediated inflammation and anti-fibrinolysis, as well as thrombin-mediated inhibition of coagulation through the activation of the protein C/protein S/TM pathway. Parenteral DTIs include hirudin, bivalirudin, and argatroban. Oral direct inhibitors are pro-drugs that generate an active compound able to bind directly to the catalytic site of thrombin: examples include ximelagatran (now withdrawn from development), as well as dabigatran exetilate and AZD0837, now under evaluation.

necrosis factor- α (Figure 3). On the basis of these findings, new drugs that will prevent activation of these PARs are under development.

Epidemiology of anticoagulant therapy in heart disease

Coronary heart disease

Population-based surveys conducted in Europe during 1999–2001 have shown that most (>90%) patients presenting with an ACS receive aspirin during hospital admission and that most (~80%) also receive either unfractionated heparin (UFH) or low molecular weight heparins (LMWHs), with the proportions receiving these two forms of heparin approximately equal.^{25–27} The frequency of use of heparin varies little according to the presence of ST-elevation on admission or by final diagnosis [Q-wave myocardial infarction (MI), non-Q-wave MI, or unstable angina], but there is considerable variation in usage between European countries. At hospital discharge, most patients (>90%) receive an anti-thrombotic agent, generally aspirin, but in one survey around 6% were prescribed warfarin and around 9% LMWHs.²⁷ The most recent cardiological survey of European prescribing practice, the EUROASPIRE-II study, examined treatment of patients who had undergone a coronary procedure (coronary bypass surgery or PCIs) or who had been hospitalized with acute MI or myocardial ischaemia.²⁸ On

admission, around one half were taking an antiplatelet agent and 7% an anticoagulant (which must be supposed to have been oral in most instances). On discharge, 90% were taking an antiplatelet regimen and 12% an anticoagulant regimen [which could have been an oral anticoagulant or a subcutaneous (s.c.) LMWH]. There was evidence of variation in the frequency of use of anticoagulants between European countries.

Non-valvular atrial fibrillation

The Euro Heart Survey on Atrial Fibrillation examined prescribing patterns among European cardiology practices during 2003–04.²⁹ Most patients surveyed had a risk factor for stroke, and hence an oral anticoagulant was indicated. Around 80% of those with persistent or permanent AF received an anticoagulant, and 50% of those with paroxysmal did so. Only around 4% of patients with persistent or permanent AF did not receive any antithrombotic therapy. These rates are likely to be an overestimate of the use of anticoagulants in general practice. In a survey of UK-based general practitioners in 2003, around 40–50% of patients were taking warfarin (which was up from around 20–25% in 1994), whereas the remainder were taking an antiplatelet regimen.³⁰ However, only around one half of those at very high risk of stroke were taking warfarin, so there remains ample scope for better targeting of therapy.

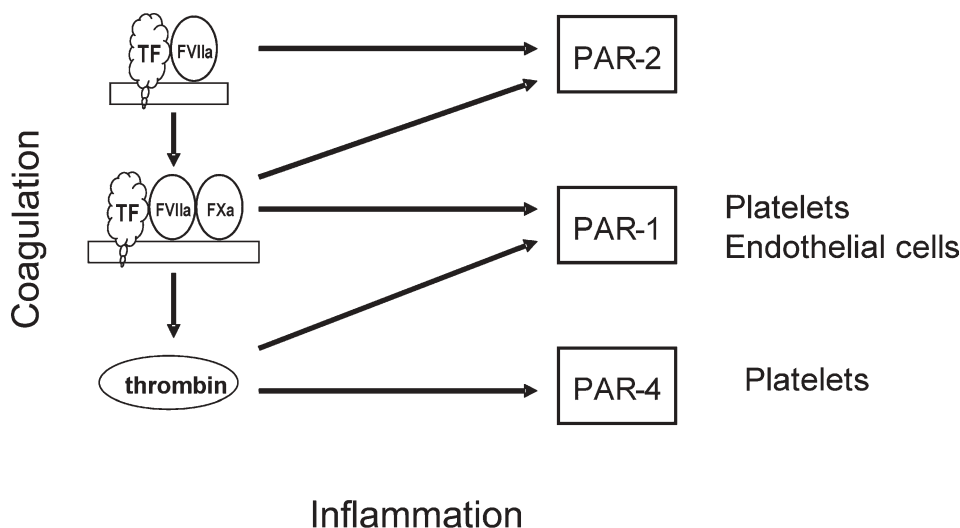


Figure 3 Cross-talk between coagulation and inflammation. Coagulation proteases modulate inflammation by binding to PARs, which mediate intracellular signalling, resulting in the induction of genes involved in inflammation. PARs are expressed on a variety of cells, among which platelets, monocytes/macrophages, and endothelial cells.

Prosthetic heart valves

Oral anticoagulants are widely prescribed and used in patients with prosthetic heart valves and irregularly recommended and used in patients with rheumatic mitral stenosis in sinus rhythm, but there is little data on the consistency of use and on how closely available recommendations are followed in different countries³¹ (see <http://americanheart.org/downloadable/heart/1150461625693ValvularHeartDisease2006.pdf>).

Heart failure

In the PRIME-II trial of ibopamine in CHF [New York Heart Association (NYHA) functional classes III and IV], drug use was surveyed among 1825 patients in 13 participating countries.³² Overall, 43% of patients were taking anticoagulants, but the proportion varied from 19% in France to 70% in the Netherlands. There was indirect evidence that anticoagulants were being used instead of antiplatelet therapy, since in areas of high anticoagulant use there was lower-than-average use of antiplatelet therapy. These data suggest the need for further randomized trials to establish whether oral anticoagulant therapy is preferable to aspirin among suitable patients with heart failure.

Parenteral anticoagulants: general pharmacology

Thrombin has an active site and two exosites, one of which, exosite 1, binds to its fibrin substrate, orientating it towards the active site. *Figure 4* displays the mechanisms of action of the different thrombin inhibitors described here below.

Heparin derivatives

The heparin derivatives in current use include UFH, LMWHs, and the synthetic pentasaccharide derivatives fondaparinux and idraparinux. These are all parenteral drugs that must be administered by i.v. or s.c. injection, and they are classified as indirect anticoagulants because they require a plasma cofactor (essentially AT) to exert their anticoagulant

activity. Thus, heparin derivatives bind to AT in plasma, a naturally occurring serine protease inhibitor, and enhance its capacity to inhibit 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 its derivatives. It is a natural product that can be isolated from beef lung or porcine intestinal mucosa. Because of the danger of transmission of prion disease from bovine tissues, most of the heparin used today is from porcine intestinal tissue.³³

Mechanism of action

Heparin consists of a family of highly sulfated polysaccharide chains ranging in molecular weight from 3000 to 30 000 with a mean of 15 000, which corresponds to about 45 saccharide units.³³ Only one-third of the heparin chains possess a unique pentasaccharide sequence that exhibits high affinity for AT, and it is this fraction that is responsible for most of the anticoagulant activity of heparin.³³ Heparin chains lacking this pentasaccharide sequence have minimal anticoagulant activity when heparin is given in the usual prophylactic or therapeutic doses. With higher doses, heparin chains with or without a pentasaccharide sequence activate heparin cofactor II, a second plasma cofactor.³⁴ Unlike AT, however, heparin cofactor II only inhibits thrombin.³⁴ At even higher concentrations, heparin attenuates FXa generation in an AT- and heparin cofactor II-independent fashion.^{35,36}

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.³³ The arginine reactive centre of AT then binds covalently to the active site serine of thrombin to form a stable thrombin/AT complex. Heparin dissociates from this complex and is able to activate additional AT molecules (*Figure 4A–C*).

Only heparin chains consisting of 18 or more saccharide units, which correspond to a molecular weight of about

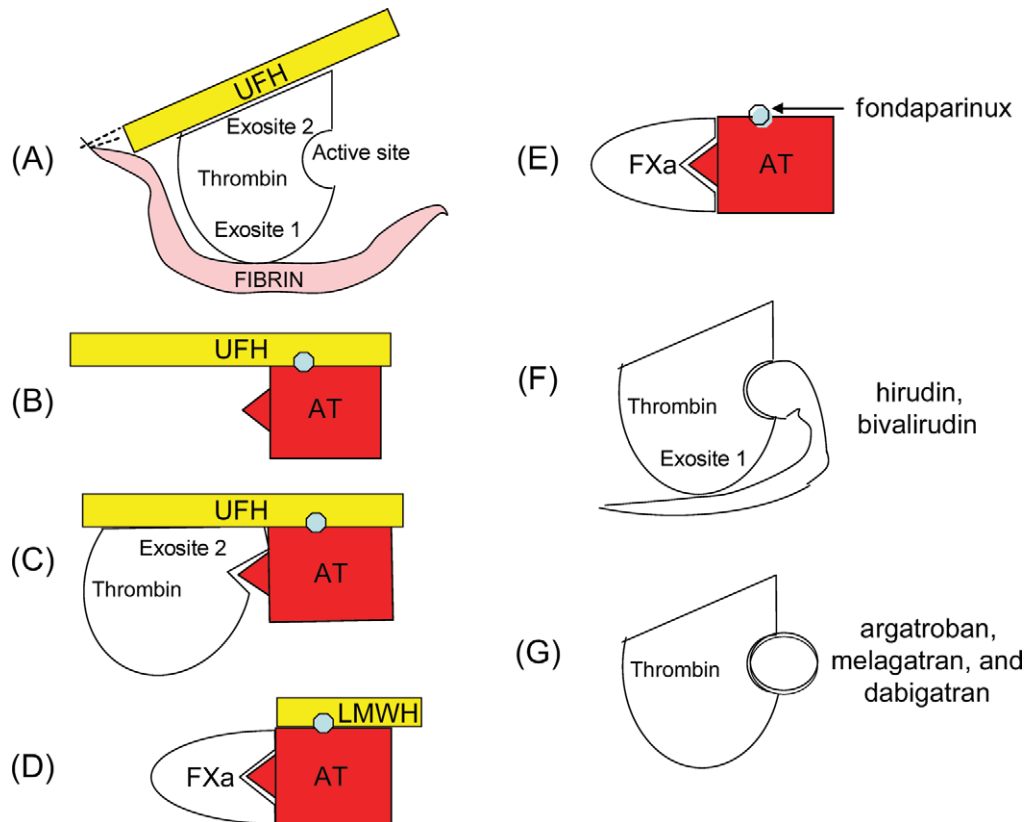


Figure 4 Mechanisms of action of the different thrombin inhibitors. (A) The ternary UFH/thrombin/fibrin complex increases the affinity of thrombin for its fibrin substrate and lessens the ability of the heparin-AT complex to inhibit thrombin. Heparin binding to thrombin occurs through a domain of the thrombin molecule termed exosite 2, whereas binding of thrombin to its substrate fibrin, allowing the steric configuration of the complex necessary for thrombin to exert its enzymatic action, occurs through a thrombin domain known as exosite 1. (B) UFH and LMWHs (the latter is not shown in this context) both possess the pentasaccharide unit (azure dot) necessary for their interaction with AT. 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 LMWHs 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 LMWHs, bind and activate AT and allow AT to efficiently inhibit FXa (E). Hirudin and bivalirudin bind to thrombin via the active site as well as exosite 1, displacing thrombin from fibrin (F). The synthetic DTIs argatroban, melagatran and dabigatran bind only to the active site, without displacing thrombin from its substrate (G).

5400, are of sufficient length to bridge AT to thrombin. However, shorter pentasaccharide-containing heparin 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.³³ This binding evokes conformational changes in the reactive centre arginine of AT that accelerate its interaction with FXa.

Pharmacokinetics

UFH must be given parenterally. The preferred routes are by continuous i.v. infusion or by s.c. injection. When given s.c. 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%.³³ This is, however, highly variable among individuals.³⁷ The committee therefore recommends against the use of s.c. UFH, even as a bridging therapy for the short-term use after interruption of VKAs.

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.³³ 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.³³ The saturable phase of clearance likely reflects heparin binding to endothelial cells, platelets, and macrophages. Once bound, heparin is internalized and depolymerized. When the cellular binding sites are saturated, heparin enters the circulation, from where it is cleared more slowly via the kidneys. At therapeutic doses, a large proportion of heparin is cleared through the rapid saturable mechanism.³³

The complex kinetics of heparin clearance render 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 min after an i.v. bolus of 25 U/kg to 60 min with a bolus of 100 U/kg and to 150 min with a 400 U/kg bolus.³³

Dosing and monitoring

The efficacy of UFH for the initial treatment of venous thrombo-embolism (VTE) is critically dependent on the dose.^{38,39} Heparin can be given in fixed or weight-adjusted

doses, and nomograms have been developed to facilitate dosing.³⁹ 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.

Because the anticoagulant response to UFH varies among patients, UFH therapy is monitored and the dose is adjusted based on these results. The test most often used to monitor heparin is the activated partial thromboplastin time (aPTT). The activated clotting time (ACT) is used to monitor the higher doses of UFH given to patients undergoing PCIs or cardiopulmonary bypass surgery.

A retrospective 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.⁴⁰ On the basis of this study, an aPTT ratio (calculated by dividing the reported therapeutic aPTT range by the control value for the reagent) of 1.5–2.5 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 2.0–3.0.⁴¹ The committee agrees with the ACCP statement that the therapeutic range should be adapted to the reagent used.³³ The committee recommends against the use of a fixed aPTT target in seconds for any therapeutic indications of UFH.

Side effects

Bleeding is the major complication of heparin therapy and will be dealt with in a specific paragraph together with management of bleeding with other anticoagulants (discussed subsequently).

Other complications of heparin include heparin-induced thrombocytopenia (HIT) and osteoporosis. HIT is caused by antibodies that are 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 of the IgG subclass, can activate the platelets.^{42,43} 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 prothrombotic condition.^{42,43}

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.³³ It is not clear whether heparin-induced osteoporosis is reversible when heparin treatment is stopped.

Low molecular weight heparins

LMWHs are gradually replacing UFH for most indications. Like UFH, LMWHs are natural products that are derived from UFH by chemical or enzymatic depolymerization.³³ LMWHs have pharmacological and biological advantages over heparin that render them more convenient to administer and less likely to cause HIT.^{33,44}

Mechanism of action

As fragments of heparin, the *mean* molecular weights of LMWH preparations are about one-third that of heparin and range from about 4000 to 5000, which corresponds to about 15 saccharide units. Like UFH, LMWHs are heterogeneous and consist of polysaccharide chains that range in molecular weight from 2000 to 9000. About one-fifth of the chains possess a pentasaccharide sequence, and the anticoagulant activity of LMWHs is restricted to this fraction^{33,44} (Figure 4).

A number of LMWH preparations are available for clinical use. Each is prepared using a different method of depolymerization, and each has a unique molecular weight profile that endows it, at least to some extent, with distinct pharmacokinetic and anticoagulant properties. Consequently, the various LMWH preparations are not interchangeable.

Like UFH, LMWHs 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 50–75% 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-Xa to anti-IIa 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 ratio of 1^{33,44} (Table 1). LMWHs have been shown to reduce significantly the release of von Willebrand factor, which has been shown to be a predictor of outcome in non-ST-elevation ACS (NSTEMI-ACS) and in ST-elevation acute myocardial infarction (STEMI),⁴⁷ when compared with UFH.⁴⁸ LMWHs also produce enhanced release of TFPI, which inhibits the factor VIIa–TF complex.⁴⁹ However, the clinical relevance of these properties is uncertain.

Pharmacokinetics

LMWHs have pharmacokinetic advantages over UFH. The bioavailability of LMWHs after s.c. injection is over 90%, likely reflecting the better absorption of shorter heparin chains from the s.c. injection site. LMWHs produce a more

Table 1 Various LMWHs and their respective antiXa/IIa ratio

	Anti-Xa (IU/mg dry substance)	Anti-IIa (IU/mg dry substance)	Ratio
Enoxaparin ¹	103	25	4.1
Nadroparin ¹	104	30	3.5
Reviparin ²	127	36	3.5
Dalteparin ^{1,4}	167	64	2.6
Tinzaparin ¹	100	54	1.9
Certoparin ¹	106	45	2.4
UFH ³	193	193	1.0

Anti-Xa activity measured using an amidolytic assay (chromogenic substrate S-2222).

Anti-IIa activity measured using aPTT.

1. European Pharmacopoeia Commission (March 1994).

2. Knoll Pharma.

3. see ref.⁴⁵

4. see ref.⁴⁵

predictable anticoagulant response than UFH because the shorter heparin chains exhibit reduced affinity for heparin binding proteins in the plasma. In addition, LMWHs have a longer half-life than UFH and the half-life is dose-independent. These phenomena reflect reduced binding of LMWHs to the endothelium.

LMWHs are cleared via the kidneys and the drug can accumulate in patients with impaired renal function.

Dosing and monitoring

Typically, LMWHs are given in fixed or weight-adjusted doses without monitoring. However, monitoring is recommended in obese patients, in those with renal insufficiency, and when therapeutic doses of LMWHs are required during pregnancy. When monitoring is required, the anti-Xa level is the recommended test.³³ LMWHs also slightly prolong the aPTT, but this occurs to a much lesser extent than with UFH, and the aPTT cannot be used for monitoring.³³

Recent studies suggest that LMWHs 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 over 30 did not find any increase in major bleeding when LMWHs were administered in this fashion.⁵⁰ Appropriate dosing of LMWHs in patients with renal sufficiency is less clear. There is an inverse relationship between creatinine clearance and anti-Xa levels^{51,52} and the risk of bleeding complications with LMWHs is higher in patients with impaired renal function.^{50,53} In patients with severe renal insufficiency, UFH may be a better choice than LMWHs.

Side effects

Like any anticoagulant, the major side effect of LMWH treatment is bleeding. This is dealt with below in a specific paragraph (discussed subsequently).

HIT is less common with LMWHs than with UFH.^{42,54} This reflects the fact that LMWHs have lower affinity for platelets and cause less PF4 release than UFH. In addition, if PF4 is released, the lower affinity of LMWHs for PF4 results in the formation of fewer heparin/PF4 complexes, the antigenic target of HIT antibodies.⁴² However, LMWHs can form complexes with PF4 that are capable of binding HIT antibodies. This phenomenon likely explains the cross-reactivity with LMWHs in patients with HIT. Therefore, LMWHs should not be used as an alternative to heparin in patients with suspected or established HIT.

The risk of osteoporosis is lower with LMWHs than with heparin. This probably reflects the lower affinity of LMWHs for bone cells. In small clinical trials, LMWHs did not appear to reduce bone density when given in prophylactic or treatment doses.⁵⁵⁻⁵⁷

Pentasaccharides: fondaparinux and idraparinux

A new heparin derivative is fondaparinux, a synthetic analogue of the pentasaccharide sequence present in UFH and LMWHs that mediates their interaction with AT.^{58,59} Fondaparinux shares all the pharmacological and biological advantages of LMWHs over UFH. However, compared with LMWHs, fondaparinux selectively inhibits FXa, without specific inhibition of thrombin activity. As a synthetic molecule, fondaparinux is highly standardized and has no antigenic properties. A derivative of fondaparinux, termed idraparinux, is a synthetic, long-acting, highly sulfated analogue of fondaparinux, with prolonged half-life.

Mechanism of action

Fondaparinux has a molecular weight of 1728.^{58,59} Compared with the natural heparin-derived pentasaccharide, its structure has been modified so as to enhance its affinity for AT. The specific anti-Xa activity of fondaparinux is about seven-fold higher than that of LMWHs (about 700 anti-Xa U/mg and 100 anti-Xa U/mg, respectively). Fondaparinux reversibly binds to AT, producing irreversible 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 4).

The bioavailability of fondaparinux after s.c. injection is 100%, higher than LMWHs and much higher than UFH. The drug is rapidly absorbed 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^{58,60} and should therefore not be given to patients with a creatinine clearance of <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.^{58,59} It does not bind to other plasma proteins, a finding that explains why it produces a more predictable anticoagulant response than heparin.

Like fondaparinux, idraparinux is a selective indirect FXa inhibitor.⁶¹ The idraparinux affinity for AT is more than 10-fold higher than that of fondaparinux. The higher affinity for AT probably explains its long plasma half-life, similar to that of AT, i.e. around 80 h. The anti-FXa activity and inhibition of thrombin generation of idraparinux are dose-dependent.

Dosing

Fondaparinux is given s.c. once daily in fixed doses. A dose of 2.5 mg is used in patients with non-ST-elevation and ST-elevation ACS and for thromboprophylaxis in medical and orthopaedic surgery patients. A dose of 7.5 mg is used for treatment of VTE. Because of the long half-life, idraparinux can be given s.c. once a week.⁶¹

Monitoring

Fondaparinux and idraparinux have not been monitored in the clinical studies that evaluated their utility. Both drugs have little or no effect on routine tests of coagulation, such as the aPTT or ACT.⁶² These tests are therefore unsuitable to monitor the clinical use of these drugs. If monitoring is required, their anticoagulant activity can be measured with anti-Xa assays using fondaparinux or idraparinux as the reference standard.

Side effects

Besides bleeding (see the specific paragraph below), side effects of fondaparinux and idraparinux are largely unknown. In contrast to UFH or LMWHs, fondaparinux does not cause HIT and has actually been used successfully to treat HIT. It also has been used successfully in a patient who had urticarial reactions at the LMWH injection sites. Finally, although patient data are lacking, *in vitro* and *in vivo* studies suggest that fondaparinux will have less effect on bone than UFH or LMWHs.^{63,64}

Table 2 A comparison of relevant pharmacological properties of the different thrombin inhibitors in current clinical use

	UFH	LMWH	Pentasaccharides	DTIs
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 DTIs)
Predictability of pharmacological effect	–	++	++	++
Inhibition of thrombin generation	++	++	++	+
Inhibition of thrombin activity	+++	+	–	+++
Inhibition of bound-thrombin	–	–	–	+++
Rebound of thrombin generation after discontinuation	+++	++	–	++
Platelet activation	+++	+	–	–
Immune thrombocytopenia	+++	+	–	–
Decreased bone density	+++	+	–	–

Properties are semiquantitatively graded as –: absent; ±: barely present; +: present-to a low degree; ++: present-to an intermediate degree; +++: present-to a high degree.

Parenteral direct thrombin inhibitors

In contrast to indirect thrombin inhibitors, such as UFH, LMWHs, and the heparin-derived pentasaccharides, which act by catalysing the naturally occurring thrombin inhibition by AT and/or heparin cofactor II, DTIs 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 aggregation (Figure 4F). By interfering with these feedback mechanisms, DTIs also interfere with thrombin generation.

Hirudins are polypeptides first isolated from the salivary glands of the medicinal leech. Hirudins are bivalent inhibitors that typically bind both to the active site and the fibrin-binding site of thrombin (Figure 4F). Consequently, they 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 i.v., and of 120–180 min by s.c. injection. There are two commercially available recombinant hirudin preparations, desirudin and lepirudin. Lepirudin, with a half-life of 90 min, is approved for the i.v. use in HIT. There is no selective antagonist that can reverse over-anticoagulation with hirudins.

Bivalirudin, formerly known as hirulog, is a 20-amino acid, synthetic version of hirudin and is—like original molecules—a bivalent inhibitor of thrombin (Figure 4F). However, bivalirudin is slowly released from thrombin, restoring active site function of the enzyme. Bivalirudin has a half-life of 25 min and is degraded primarily by a combination of hepatic metabolism and proteolytic cleavage. Only a small proportion is eliminated via the kidney. There is no selective antagonist that can reverse the anticoagulant action of bivalirudin.

Argatroban is a small, synthetic, univalent molecule that competitively and reversibly inhibits the active site of free and fibrin-bound thrombin (Figure 4G). It has a half-life of 45 min and is metabolized in the liver via a process that generates three active intermediates. There is no selective antagonist that can reverse the anticoagulant action of argatroban. As a class, DTIs have potential biological and pharmacokinetic advantages over heparins. Unlike UFH and LMWHs, DTIs inactivate fibrin-bound thrombin, in addition to fluid-phase thrombin. Consequently, DTIs may attenuate thrombus accretion more effectively. In addition, DTIs produce a more predictable anticoagulant effect than

heparins because they do not bind to plasma proteins and are not neutralized by PF4 (Table 2). Three parenteral DTIs have been licensed in North America and Europe for limited indications. Hirudin and argatroban are approved for the treatment of HIT, whereas bivalirudin is licensed as an alternative to heparin in patients undergoing PCIs.

Compared pharmacological properties of unfractionated heparin, low-molecular weight heparins, pentasaccharides, and direct thrombin inhibitors

A comparison of the pharmacological properties of the main classes of thrombin inhibitors is shown in Table 2.

The AT action of UFH is limited by variable efficacy and stability, mainly due to a poor bioavailability when given s.c., non-specific protein binding, neutralization by PF4, and a lack of efficacy on fibrin-bound thrombin.⁴⁹ Moreover, UFH exhibits prothrombotic properties related to platelet activation⁶⁵ and thrombin generation rebound after discontinuation.³³

LMWHs have a more predictable pharmacological profile than UFH, removing the need for therapeutic drug monitoring. This is mainly due to reduced non-specific protein binding and reduced neutralization by PF4. Limiting the amplification of clotting formation by inhibiting thrombin generation is a possible theoretical advantage. Various LMWHs differ according to their anti-Xa:anti-IIa ratio (Table 1) as well as to other biological effects.

Fondaparinux and idraparinux have features that distinguish them from LMWHs. Because they are too short to bridge AT to thrombin, fondaparinux and idraparinux enhance the rate of FXa inactivation by AT, thereby blocking thrombin generation, but have no effect on thrombin activity. Both agents have almost complete bioavailability after s.c. injection. Neither fondaparinux nor idraparinux interact with plasma proteins other than AT. Consequently, these drugs produce a predictable anticoagulant response that eliminates the need for routine coagulation monitoring.⁶⁶

DTIs (Figure 4F and G, Table 2) do not bind to plasma proteins, providing a more predictable pharmacological response than UFH. They are not affected by PF4 and are active against fibrin-bound thrombin. However, because they exert a direct action on thrombin, in a 1:1

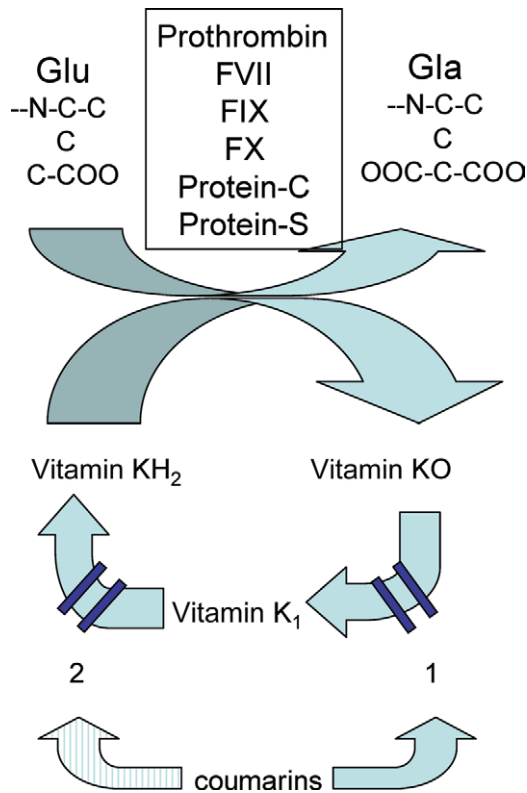


Figure 5 Mechanism of action of coumarinic VKAs. Coumarinic VKAs exert their anticoagulant effect by interfering with the cyclic interconversion of vitamin K and its 2,3 epoxide (vitamin K epoxide), modulating the γ -carboxylation of glutamate residues (Gla) on the N-terminal regions of vitamin K-dependent proteins, including the coagulation factors FII (prothrombin), FVII, FIX, and FX, as well as of the anticoagulant proteins C and S. Vitamin K1 (phylloquinone) is reduced to the reduced form of vitamin K (vitamin KH₂) by two warfarin-sensitive enzymes (KO-reductase to K-reductase) and the nicotinamide adenine dinucleotide-dependent reductase system that is insensitive to warfarin. The γ -carboxylation is required for the activity of all the above-mentioned factors, and treatment with coumarins results in the hepatic production of partially carboxylated and decarboxylated proteins with reduced coagulant activity. Carboxylation allows a calcium-dependent conformational change in such coagulation proteins that promotes binding to cofactors on phospholipid surfaces. The inhibition of the γ -carboxylation of the regulatory anticoagulant proteins C and S has the potential to be procoagulant. However, under most circumstances the anticoagulant effect of the coumarins is dominant. Carboxylation requires vitamin KH₂, molecular oxygen, and carbon dioxide. The oxidation-reduction reaction between vitamin KH₂ and vitamin K epoxide involves a reductase pair. The first, vitamin K epoxide reductase (1), is sensitive to coumarins, whereas vitamin K reductase (2) is less sensitive. Therefore, the anticoagulant effect of VKAs can be overcome by low doses of vitamin K1. Glu designates the amino acid glutamine, Gla the amino acid glutamic acid (modified from ref. 67).

stoichiometric fashion, the amount of thrombin inhibited is proportional to the concentration of the DTI. This is the main limitation of their action, as increasing their concentration to achieve a greater inhibition of thrombin is associated with prohibitive bleeding rates.⁴⁹

Vitamin K antagonists: general pharmacology

Mechanism of action

VKAs exert their anticoagulant effect by interfering with the γ -carboxylation and thereby activation of the vitamin K-dependent coagulation factors II, VII, IX, and X⁶⁷ (Figure 5).

Vitamin K anticoagulant therapy: interference with foods and drugs

Environmental factors such as drugs and diet can importantly alter the pharmacokinetics and pharmacodynamics of VKAs.⁶⁷ Influence on absorption, clearance, and plasma protein binding of VKAs or their effect on the synthesis of vitamin K-dependent coagulation factors has been documented for numerous drugs and food. Change of dosage of VKAs and a more frequent control of the international normalized ratio (INR) are important in the management of the increased risk of bleeding and thrombo-embolic complications, when interaction may occur. The direction of interaction and the supporting level of evidence have been reviewed recently.^{67,68}

Laboratory control

The prothrombin time (PT) assay is sensitive to the inhibition of factors the carboxylation of which is inhibited by VKAs, and has been used for decades to monitor the intensity of oral anticoagulant therapy. The PT is performed by adding calcium and thromboplastin to citrated plasma. The PT monitoring of VKA treatment is not standardized when simply expressed in seconds or as a simple raw ratio of the value of patient's plasma (in seconds) to that of plasma from healthy control subjects (also in seconds). Dosage of warfarin, the main oral anticoagulant drug, has been shown to differ significantly in different countries,^{69,70} depending on the thromboplastin used to perform the PT. As a result, there was a great risk of bleeding from overdose and of ineffective treatment from underdosage. The problem was shown to be due largely to the use of different thromboplastins. Thromboplastins indeed vary in responsiveness to a reduction in the vitamin K-dependent coagulation factors. An unresponsive ('insensitive') thromboplastin produces less prolongation of the PT for a given reduction in vitamin K-dependent clotting factors than a responsive ('sensitive') one. To meet the challenge of the lack of standardization, the World Health Organization (WHO) in 1983 produced a 'gold standard' by the introduction of a PT standardization scheme based on the INR.^{69,71} The responsiveness of a thromboplastin was measured by assessing its international sensitivity index (ISI). Highly sensitive thromboplastins (ISI, approximately 1.0), which are composed of human or rabbit TF produced by recombinant technology and defined phospholipid composition, are now available. Reporting of PT values is now done by converting the PT ratio measured with the local thromboplastin into an INR, calculated as follows:

$$\text{INR} = (\text{patient PT}/\text{geometric mean normal PT})^{\text{ISI}}$$

or

$$\log \text{INR} = \text{ISI} (\log \text{observed PT ratio})$$

where ISI denotes the ISI of the thromboplastin used at the local laboratory to perform the PT measurement. The ISI reflects the responsiveness of a given thromboplastin to the reduction of the vitamin K-dependent coagulation factors compared with the primary WHO international reference preparations, so that the more responsive the reagent, the lower the ISI value.⁶⁷

The history of standardization of the PT has been reviewed by Poller,⁷² and the reader is referred to this review for a detailed discussion of principles and implementation. The INR system of PT standardization was, however, originally based on manual determination of PT and envisaged the assignment of a single ISI value for each batch of thromboplastin reagent.^{69,70} However, in recent years, the manual PT has been almost universally replaced by coagulometers, and many studies have shown that the ISIs of thromboplastin reagents differ according to the type of instrument used.⁷³⁻⁷⁶ Some manufacturers have introduced 'instrument-specific' ISIs, but this does not overcome the problem completely because of the many possible instrument/reagent combinations and because ISIs often differ with the same thromboplastin even among instruments of the same type. ISI calibration with local PT system (i.e. thromboplastin/coagulometer combination), therefore appears essential. ISI calibration using the WHO-recommended procedure is not usually possible in routine hospital laboratories for a variety of reasons, including the requirement for manual PT testing with a WHO reference standard thromboplastin. WHO standard thromboplastin is not readily available to routine hospital laboratories. Furthermore, the WHO procedure requires a sample of 60 fresh plasmas from stabilized orally anticoagulated patients, and 20 fresh plasmas from normal subjects (see *Table 3* for definitions of terms).

To avoid the above-mentioned constraints, laboratories may now calibrate their own local system (i.e. instrument/reagent combination) using certified plasmas supplied by manufacturers or reference laboratories. A working group of the International Society of Thrombosis and Haemostasis, Subcommittee on Control of Anticoagulation, has very recently worked out guidelines on preparation,

certification, and use of certified plasmas, and these are intended to provide guidance to both manufacturers and users of certified plasmas.⁷⁷

Currently, there is one procedure for local calibration with certified plasmas, which is a modification of the WHO method of ISI determination. In a European Concerted Action on Anticoagulation (ECAA) study of lyophilized plasmas and of individual VKAs, it has been shown that the number of 60 lyophilized abnormal samples required for a full WHO calibration can be reduced to 20 if combined with results from seven lyophilized normal plasmas.⁷⁸ Further reductions below this number were associated with decreased precision of the calibration line and hence increased variability of the INR.⁷⁹ However, the use of pooled VKA plasmas may reduce the scatter of values from individual plasmas,⁷⁹ and with pooled plasmas and repeat testing it is possible to use an even lower number. For example, acceptable precision has been achieved with six pooled VKA plasmas containing at least 50 patient samples in each pool and two pooled normal plasmas if these were analysed on at least three different days.⁸⁰

In the other procedure, named 'direct' INR determination, certified plasmas are used to calculate a line relating log (PT) to log (INR),⁷⁷ and the use of orthogonal regression^{77,81} (*Table 3*). External quality control for INR performances are available with a number of national and international schemes, including that from the WHO.

Dosing

World-wide increase in the use of VKA treatment in recent years has followed the publication of studies demonstrating its value in a widening spectrum of clinical disorders. Improved benefit/risk ratio has resulted from the increased use of lower-dose VKA administration, pioneered in the UK and the Netherlands, combined with the introduction of the WHO INR system of laboratory control.^{69,70} With such a great increase in demand, medical, technical, nursing, and administrative staff in hospitals and clinics in many countries are being overwhelmed by the numbers of patients requiring regulation of anticoagulant dosage, with an increasing tendency to devolve management to community-based centres. One possible way of preserving standards achieved in specialized centres is by the computerization of anticoagulant dosages. The ECAA computerized dosage study is the first multicentre randomized evaluation of the safety and effectiveness of computerized treatment with VKAs.⁸² The results of this study favour computer dosage, with a highly significant overall benefit in achieving the target INR in the clinical groups randomized to this modality at the five centres in that study.⁸²

The usual practice is to start with the expected maintenance dose (stabilization period) and adjust the daily dose according to the INR results from blood samples taken over the following 5-7 days. Because there is a delay before the onset of the clinical effects of warfarin, heparin should be given concomitantly in the initial stages of treatment if patients are thrombosis-prone or carriers of a thrombosis. Once the patient has achieved the target INR, treatment is continued with a maintenance dose (stable period) of warfarin. Time in therapeutic range varies considerably both in the stabilization and in the stable periods. In the ECAA computer study, the time in the

Table 3 Definitions and nomenclature of test reagents and indices for VKA monitoring⁷⁷

Certified plasma	Plasma with assigned PT (in seconds) or INR value.
ISI calibration	Determination of ISI according to 1999 WHO Guidelines
Mean normal prothrombin time (MNPT) according to 1999 WHO Guidelines	The geometric (logarithmic) mean of the PTs of the healthy adult population. For practical purposes, the geometric mean of the PT calculated from at least 20 fresh samples from healthy individuals, including those of both sexes, is a reliable approximation of MNPT
Test system	Combination of thromboplastin and instrument for PT determination
Local test system ISI calibration	Determination of local test system ISI using certified plasmas
'Direct' INR determination	Alternative approach to INR determination using certified plasmas without employing an ISI and MNPT

therapeutic range varied in the stabilization period between 44 and 69%, and in the stable period between 26 and 70%. In daily clinical practice, the success figures are likely to be considerably lower.⁸²

Thus, there is a clear need for improvement. Patients must undergo periodic blood tests to ensure that their target INR is maintained. With long-term treatment after a stabilization period of 3–4 weeks, the interval between laboratory tests can be increased to 4–6 weeks or even longer. The dose of VKAs required to achieve the desired INR can be estimated using algorithms and treatment tables. Computerized decision support systems (CDSS) have been developed in order to simplify the process of anticoagulation monitoring and to improve the dosing decisions. CDSS systems can also help in identifying patients with inadequate INR control, and in addition suggest intervals for the re-testing.⁸² The reliability of the CDSS systems is currently being evaluated in the European Action on Anticoagulation (EAA), the successor to the ECAA, under the EC Quality of Life and Management Programme, entitled 'Cost-Effectiveness of Computer-Assisted Anticoagulant Dosage', using the clinical endpoints of bleeding and thrombosis, and not only the surrogate endpoints of time in the therapeutic range. This is a randomized clinical endpoint trial of computer-assisted oral anticoagulant dosage. It is a massive study aiming at recruiting 16 000 patient-years at 33 expert centres across the European Union. The EAA has already recruited over 12 000 patient-years, which makes it by far the largest clinical study ever undertaken in the field of oral anticoagulation. Upon completion, this trial should have a major impact on the clinical management of VKA administration.

Point-of-care testing and prothrombin time monitors

The high demand for VKAs have increased the interest for new testing procedures, such as the determination of the INR at the point of care on whole blood samples. There is a general consensus that these procedures do not need the technical expertise of traditional methods. However, both optimal calibration and quality control systems and connection with expert centres are mandatory in order to keep an acceptable quality standard and ensure the transferability to a higher order of calibration (discussed subsequently). Point-of-care test (POCT) monitors must, however, give dependable INR values because the safety and effectiveness of treatment with VKAs depends on keeping patients within the target INR ranges. Thrombotic events increase disproportionately at INR <2.0 and bleeding complications at INR >4.5.

It has been shown that it is possible to calibrate home PT monitors to conform to the WHO standard.⁸³ To find out how accurately two POCT systems, the CoaguChek Mini and the TASPT-NC (RapidPointCoag), measured INRs at 10 ECAA centres, such systems were tested and compared on 600 patients on long-term warfarin therapy.⁸⁴ The mean INR displayed differed by 21.3% between the two POCT monitoring systems. The INR on one system was 15.2% higher, on the average, than the 'true' INR, but on the other system it was 7.1% lower. The percentage difference between the mean displayed INR and the 'true' INR at individual centres also varied considerably with both systems. Reliable

quality assessment procedures have been developed,⁸⁵ and their feasibility was recently evaluated in the Netherlands within the framework of the European Concerted Action on Thrombosis.^{86,87} In Germany, such devices are claimed to be currently in use in 100 000 households for self-testing and self-dosage. It has been estimated that if half of the patients in Europe currently treated with VKAs were to adopt self-monitoring systems, over 1 000 000 devices would be in use within the next 5 years. A comparable expansion may also take place in North America and, in time, in other parts of the developed world. For patients, there is the greater convenience of testing at home or at a local community clinic. In general, such a system would provide savings of time and transportation costs. However, these POCT PT monitors also need appropriate control regarding calibration, quality control, and reference with expert centres. Moreover, the quality control scheme needs to be adequate to ensure accordance with the WHO PT standardization. The same holds true for hospital routine laboratories. Simplified procedures have been developed in order to improve local ISI calibration and also to ensure accordance with the WHO procedure and a coherent reference system in terms of INR.⁷⁷ These policies should result in a decrease in the bleeding risks, and better prevent or cure thrombosis, in the daily clinical practice.

Self-management of oral anticoagulation

In the self-management of oral anticoagulation, the patients themselves—using a finger stick sample of capillary blood inserted into a point-of-care monitoring device such as the CoaguCheck—perform a PT test. They then decide themselves whether a dosing adjustment of the anticoagulant is necessary. Prior to participating in a self-management of oral anticoagulation programme, patients have to follow an intensive training course on how to use the point-of-care device, on the management of their diet (content of vitamin K in various foods), drug interactions of VKAs, effect of excessive alcohol consumption, etc. In Germany, over 100 000 patients on long-term VKAs participate in self-management of oral anticoagulation programmes. In many other European countries, this form of VKA control is catching on. In a recent meta-analysis of 14 randomized trials of self-management of oral anticoagulation, significant reductions were found for thrombo-embolic events (OR 0.27; 95% CI 0.12–0.59) and death (0.37; 0.16–0.85), but not for major bleeding (0.93; 0.42–2.05). In 11 studies INR values were more often in the desired therapeutic range in the self-management of oral anticoagulation arm.⁸⁸ However, it should be underlined that only highly selected groups of patients were included with a high level of compliance and capability to operate the coagulometer. In addition the studies exhibited various methodological problems and were not weighted in the meta-analysis. A major positive element of self-management of oral anticoagulation is the empowerment of the patient, the better insight of factors that might influence VKA therapy, and a feeling of security⁸⁹ (reviewed in Ansell *et al.*⁶⁷ and Siebenhofer *et al.*⁹⁰). All these elements eventually result in a better quality of life.⁹¹ Despite these promising aspects, there is a need for high-quality randomized controlled studies involving well-defined clinical and laboratory endpoints.

Oral direct thrombin inhibitors: general pharmacology

The oral DTIs evaluated in phase III so far, ximelagatran and dabigatran etexilate, are synthetic low molecular weight peptidomimetics that bind directly and reversibly to the catalytic site of the thrombin molecule^{92–96} (Figure 4D). They are administered orally as pro-drugs, which are rapidly metabolized to the active compound; ximelagatran is converted to melagatran in several organs, including the liver, the lungs, the intestine, and the kidneys, whereas dabigatran etexilate is rapidly and completely converted to dabigatran primarily by serum esterase-catalysed hydrolysis. Pharmacokinetic data for dabigatran etexilate in healthy volunteers show peak plasma levels within 2–3 h after oral administration^{97,98} and a half-life in healthy subjects of 3–4 h for melagatran and around 12–14 h in patients for dabigatran.⁹⁹ Both are eliminated primarily by the kidney, therefore plasma concentrations are increased for both compounds in patients with impaired renal function (creatinine clearance, CrCl <50 mL/min). The therapeutic window, however, is fairly wide, and they have therefore been tested in fixed doses (ximelagatran 24 or 36 mg bid; dabigatran etexilate 110 and 150 mg bid), in patients with a glomerular filtration rate (GFR) above 30 mL/min.^{92–95}

In long-term use, ximelagatran has been associated with transient elevations of liver function tests [alanine amino transferase (ALAT) three or more times the upper normal limits] in around 8% of patients, in the majority of cases occurring between 1 and 6 months after the start of treatment, which also led to protocol-mandated cessation of treatment in a non-trivial proportion of patients.¹⁰⁰ It was therefore decided to withdraw ximelagatran from the market and terminate its development. The withdrawal was triggered by new patient safety data with an adverse event report of serious liver injury in a clinical trial. The long-term treatment with dabigatran etexilate has been evaluated so far only in a limited number of patients. On the basis of current information, ALAT elevations (more than three times the upper limit of normal) have only been observed in ~2% of patients,¹⁰¹ but no severe hepatic events (ALAT more than three times the upper limit of normal + bilirubin more than two times the upper limit of normal) have occurred.

The oral DTI AZD0837 is a pro-drug, which is metabolized to the active thrombin inhibitor via an intermediate form. On the basis of encouraging results from the first phase IIa study, further development of AZD0837 is continuing, with the decision to develop this product through an extended release formulation for prophylaxis of thrombo-embolic events.

Parenteral anticoagulants: clinical indications

Unfractionated heparin

A pooled analysis of six trials in patients with NSTEMI-ACS testing short-term UFH vs. placebo or untreated controls showed a 33% significant risk reduction of death and MI (OR 0.66, 95%CI 0.44–0.99, $P = 0.045$).³³ The risk reduction for MI accounted for practically all of the beneficial effect. In trials comparing the association of heparin plus aspirin vs. aspirin alone in NSTEMI-ACS, a trend towards a benefit was observed in favour of the heparin–aspirin combination, but

at the cost of an increase in bleeding. Recurrence of events after interruption of UFH explains why this benefit is not maintained over time, unless the patient was revascularized before the interruption of UFH.¹⁰² On the basis of this currently available (admittedly relatively weak) evidence, it is now generally acknowledged that UFH should be recommended in the treatment of NSTEMI-ACS.

Adjunctive UFH use in the setting of STEMI, together with the use of fibrinolytic agents, has a narrow therapeutic window. UFH adjunct to streptokinase (SK) does not reduce mortality at 35 days or 6 months, but leads to an increase in major or severe bleedings (ISIS-3 and GISSI-2). The evidence for the use of UFH with tissue-plasminogen activator (t-PA) is somewhat stronger,¹⁰³ and became standard therapy after the superiority of front-loaded tPA with UFH over SK was demonstrated in the GUSTO-I trial.¹⁰⁴ I.v. UFH using a bolus of 60 U/kg (maximum 4000 U) followed by a maintenance infusion of 12 U/h (maximum 1000 U) for 48 h is recommended with t-PA and other fibrin-specific fibrinolytic agents.¹⁰⁵

UFH is the most commonly used anticoagulant during PCI. ACT monitoring is used in this case because the required level of anticoagulation is beyond the range that can be measured using aPTT. Several retrospective studies^{106–108} and randomized trials^{109,110} have shown UFH to reduce ischaemic complications. On the basis of these data, UFH in a dose of 60–100 IU/kg and a target ACT between 250 and 350 s are recommended.¹¹¹ A target of 200 s is advocated for UFH dosing in conjunction with a GP IIb–IIIa inhibitors.^{112–114} After completion of the PCI procedure, UFH is not indicated, as continued treatment does not reduce ischaemic complications and is associated with a higher risk of bleeding.^{115,116}

Low molecular weight heparins

Non-ST-elevation acute coronary syndromes

The efficacy of LMWHs in aspirin-treated patients suffering from NSTEMI-ACS has been evaluated vs. placebo, showing a pronounced reduction in the risk of death and MI associated with a modest increase in the risk of bleeding.^{117,118} More trials have tried to establish the respective efficacy and safety of various LMWHs in comparison with UFH (Table 4). Dalteparin and nadroparin did not show any superiority over UFH in aspirin-treated patients.^{119,120} Enoxaparin has been studied extensively in several trials [Thrombolysis in Myocardial Infarction (TIMI) 11B, ESSENCE, INTERACT, ACUTE 2, AtoZ, SYNERGY].^{121–126} The meta-analysis of these six trials, totalling 21 946 patients, and testing enoxaparin vs. UFH head-to-head showed no significant difference between the two compounds for death at 30 days (3.0 vs. 3.0%, OR 1.00, 95%CI 0.85–1.17).¹²⁷ However, a slight reduction in the combined endpoint of death or MI at 30 days was observed in favour of enoxaparin vs. UFH (10.1 vs. 11.0%, respectively, OR 0.91, 95%CI 0.83–0.99). No significant difference in blood transfusions was observed (OR 1.01, 95%CI 0.89–1.14) or for major bleeding (OR 1.04, 95%CI 0.83–1.30) at 7 days after randomization in the overall population, as well as in the population of patients who received no anti-thrombin therapy prior to randomization.

In the SYNERGY trial, which analysed 9978 high-risk patients planned to undergo early revascularization, no significant difference was observed in terms of death and MI at

Table 4 Randomized controlled comparative trials between LMWHs and UFH in addition to aspirin (ASA) in NSTEMI-ACS including more than 300 patients in each group

Study, publication year, (number of patients) reference	Tested treatment	Control treatment	Background treatment	Death+MI 30 days test/control (%), <i>P</i> -level	More than moderate bleeding test/control (%), <i>P</i> -level
FRIC, 1997 (1482) ¹¹⁹	Dalteparin	UFH	ASA	4.3/4.7, N.S.	1.6/1.4, N.S.
ESSENCE, 1997 (3171) ¹²²	Enoxaparin	UFH	ASA	6.1/7.7, N.S.	3.3/6.5, N.S.
TIMI 11B, 1998 (3910) ¹²⁸	Enoxaparin	UFH	ASA	7.4/8.3, N.S.	1.0/0.6, N.S.
FRAX.I.S., 1998 (2317) ¹²⁰	Nadroparin	UFH	ASA	8.6/7.9, N.S. (3 months)	1/1, N.S.
INTERACT, 2003 (746) ¹²³	Enoxaparin	UFH	ASA, eptifibatide	5.0/9.0, <i>P</i> = 0.03	2.0/3.1, N.S.
A to Z, 2003 (3629) ¹²⁴	Enoxaparin	UFH	ASA	7.4/7.9, N.S.	1.0/0.8, N.S.
SYNERGY, 2004 (9978) ¹²⁶	Enoxaparin	UFH	ASA, clopidogrel	14.0/14.5, N.S.	13.0/13.6, N.S.

30 days.¹²⁶ However, in this study, using the current standard treatment strategies with a high rate of invasive procedures, there was a trend towards an excess of bleeding with enoxaparin when compared with UFH, according to the TIMI definition of major bleeding.¹²⁶

LMWHs have been used in combination with various therapies: aspirin, thienopyridines, and GP IIb/IIIa inhibitors without initial safety concerns. The association of LMWHs and GP IIb/IIIa inhibitors has been tested in several older randomized trials^{123–125,129–131} and, more recently, also in trials (ACUTE 2, INTERACT, and SYNERGY) better reflecting current standards of treatments.^{123–125} Overall, few safety concerns have been reported about the risk of bleeding with LMWHs (mostly enoxaparin) in association with GP IIb/IIIa inhibitors in comparison with UFH plus GP IIb/IIIa inhibitors.

ST-elevation acute myocardial infarction treated with fibrinolytics

ASSENT-3, with an open-label design, compared enoxaparin with UFH after fibrinolytic therapy with tenecteplase, and in addition tested this LMWH against half-dose tenecteplase with UFH in combination with a 12 h infusion of abciximab.¹³² There was a lower incidence of the composite of 30-day mortality, in-hospital re-infarction, with in-hospital 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 1-year follow-up demonstrated no difference in mortality rates among the three groups.¹³² 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 endpoint as shown in ASSENT-3, but here the risks of ICH (2.2 vs. 0.97%; *P* = 0.048) and of major bleeding (4 vs. 2.8%; *P* = 0.17) in the enoxaparin group were increased.¹³³ The risk for ICH and major bleeding was mainly confined to patients >75 years of age. In a meta-analysis of the combined ASSENT-3 and ASSENT-3 PLUS trials, there was an excess in major systemic bleeding evident with enoxaparin (3.3 vs. 2.4%, *P* = 0.01). Whereas 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 the pre-hospital ASSENT-3 PLUS trial (6.7 vs. 0.8%,

P = 0.013).¹³⁴ A trend to more major bleedings in patients treated with LMWHs for 4–8 days compared with UFH (given for 2–4 days) is also found in a meta-analysis of all (*n* = 6) randomized trials performed before 2005, but this was compounded by significantly greater efficacy on re-infarction.¹³⁵

In the EXTRACT-TIMI 25 trial, 20 506 patients with STEMI scheduled to undergo fibrinolysis were randomized to receive either enoxaparin throughout the index hospitalization or weight-based UFH for at least 48 h.¹³⁶ Patients >75 years of age did not receive the i.v. bolus of enoxaparin and only had 75% of the s.c. injection dose. At 30 days, death and nonfatal recurrent MI occurred in 4.5% of the UFH patients and 3.0% of the enoxaparin patients (*P* < 0.001), but the risk of major bleeding was increased in the enoxaparin-treated patients (2.1 vs. 1.4%, *P* < 0.001), and fatal bleeds were also increased (0.55 vs. 0.33%, relative risk 1.64; 95% CI 1.07–2.51).^{136,137} The incidence of ICH was 0.8% and 0.7% in the enoxaparin and UFH groups, respectively.¹³⁶ The composite of death, non-fatal re-infarction, or non-fatal ICH (a measure of net clinical benefit) occurred in 12.2% of patients given UFH and 10.1% of those given enoxaparin (*P* < 0.001).

Elective percutaneous coronary interventions

In elective PCIs, several studies have examined the use of i.v. LMWHs in patients not previously treated by any form of anticoagulant. Small and/or non-comparative trials have shown the feasibility of a single i.v. bolus of enoxaparin 1, 0.75, and 0.5 mg/kg in patients undergoing PCI with or without the administration of GP IIb/IIIa inhibitors. In a small study,¹³⁸ two doses of dalteparin (40 or 60 IU/kg i.v.) in combination with abciximab were compared in patients undergoing PCI. The patients who received the higher dose had less procedural thrombosis and a lower incidence of major bleeding than those with the lower dose. A close relation between the rise in aPTT and ACT was seen in patients receiving dalteparin 80 IU/kg with or without abciximab.¹³⁸ Major PCI studies with dalteparin have not been performed. A meta-analysis of the data from randomized studies comparing the use of i.v. LMWHs and i.v. UFH in patients undergoing PCIs found no difference in the occurrence of ischaemic events and a non-significant trend toward a reduction in major bleeding with LMWHs.¹³⁹ In the randomized STEEPLE trial (Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized

Evaluation), a single i.v. bolus of enoxaparin (0.5 or 0.75 mg/kg) was evaluated in comparison with UFH in 3528 patients treated mostly on an elective basis.¹⁴⁰ Enoxaparin was used as a single i.v. bolus before the start of PCI, without anticoagulation monitoring, with a similar dose with or without GP IIb/IIIa inhibitors. Enoxaparin 0.5 mg/kg significantly reduced the primary endpoint of non-coronary artery bypass graft (CABG)-related bleeding compared with an ACT-adjusted UFH regimen (5.9 vs. 8.5%, $P=0.01$). This arm was prematurely terminated because a significant difference in mortality was observed, at an interim analysis, between the two enoxaparin arms, whereas no difference was observed with the control UFH arm. This finding was, however, not confirmed in the final analysis. The enoxaparin 0.75 mg/kg arm also showed a trend to reduced bleeding (6.5 vs. 8.5%, $P=0.051$). In terms of ischaemic events, there were no significant differences among the three groups.¹⁴⁰

Percutaneous coronary interventions in the setting of acute coronary syndromes

Few studies evaluated LMWH management in the transition from medical to interventional therapy. Collet *et al.*¹⁴¹ examined the safety and efficacy of performing PCI in the setting of NSTEMI-ACS on enoxaparin therapy without interruption of, or addition of, anticoagulation for PCI. The only rule was to perform PCI within 8 h of the last s.c. enoxaparin injection, when anti-Xa levels are still sufficiently elevated. Four hundred and fifty-one consecutive patients with NSTEMI-ACS received at least 48 h treatment with s.c. enoxaparin (1 mg/kg/12 h), and 293 (65%) underwent coronary angiography within 8 h of the morning enoxaparin s.c. injection with PCI in 132 (28%), with no further enoxaparin. The mean anti-Xa activity at the time of catheterization was >0.5 IU/mL in 97.6% patients. There were no instances of in-hospital acute vessel closure or urgent revascularization following PCI. Recent data from more than 350 patients indicate that anti-Xa levels similar to those found after 48 h of s.c. treatment are achieved after just two s.c. doses of enoxaparin.¹⁴²

In the open-label, observational NICE-3 study,¹³¹ 628 NSTEMI-ACS patients were treated with enoxaparin s.c. 1 mg/kg plus abciximab, eptifibatid, or tirofiban at standard doses. Forty-three patients received enoxaparin alone. The following in-hospital clinical outcomes were observed: death: 1 and 0%; MI: 3.5 and 4.7%; urgent revascularization: 2.7 and 9.3%; and the combined outcome death/MI/urgent revascularization: 7.0 and 14%, respectively, in patients receiving enoxaparin plus one of the GP IIb/IIIa inhibitors vs. those receiving enoxaparin only. In the 283 patients undergoing PCI, the incidence of non-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 described above, comparing enoxaparin and UFH in almost 10 000 NSTEMI-ACS patients managed with current early invasive strategy, 92% patients underwent coronary angiography, PCI was performed in 47%, and 57% received GP IIb/IIIa inhibitors. The main result was that enoxaparin was non-inferior to UFH for the treatment of high-risk patients with NSTEMI-ACS concerning ischaemic events, but was associated with an increased risk of major bleeding. When stratifying by pre-randomization therapy, enoxaparin had some benefit

on ischaemic events among patients without anticoagulant therapy before randomization (12.6 vs. 14.8% for death and MI at 30 days) without any difference in bleeding.¹²⁶

UFH should be preferred in high-risk NSTEMI-ACS patients with planned invasive strategy because of its shorter half-life and easier reversibility. However, switching from UFH to a 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. If the patient is already being treated with a LMWH, the following management (tested in trials with enoxaparin) is recommended: in patients undergoing PCI within 8 h of the previous s.c. dose, no additional anticoagulation is required; when PCI is performed within 8–12 h following an s.c. LMWH injection, supplemental treatment with a lower dose either of i.v. LMWH bolus (enoxaparin 0.3 mg/kg i.v. bolus) or of UFH could be given. There is so far no conclusive evidence on the use of LMWHs in the setting of primary PCI for STEMI.

Pentasaccharides

Fondaparinux

In ACS, fondaparinux was first evaluated in two dose-finding phase II trials in NSTEMI-ACS, PENTUA¹⁴³ and STEMI-PENTALYSE,¹⁴⁴ respectively, and in two phase II elective PCI studies.^{145,146} These studies identified the lowest dose of 2.5 mg s.c. once daily to be the safest, with at least similar efficacy as higher dosages. This dose was therefore carried forward into the two large-scale phase III trials.

In the Organization to Assess Strategies for Ischemic Syndromes (OASIS)-5 trial, 20 078 patients with NSTEMI-ACS were randomized to s.c. fondaparinux 2.5 mg qd vs. s.c. enoxaparin 1 mg/kg body weight bid for a mean of 6 days.¹⁴⁷ The primary efficacy outcome of death, MI, or refractory ischaemia at 9 days was 5.8% with fondaparinux compared with 5.7% with enoxaparin, which satisfied the pre-specified criterion for non-inferiority ($P=0.007$). Major bleeds were halved with fondaparinux (2.2%) compared with enoxaparin (4.1%, $P<0.001$). The composite outcome of death, MI, refractory ischaemia, or major bleeding therefore favoured fondaparinux (7.3%) compared with enoxaparin (9.0%, $P<0.001$). Major bleeding was an independent predictor of long-term mortality, which was lower with fondaparinux (5.8 vs. 6.5% at 6 months, $P=0.05$). At 6 months, also the composite outcome of death, MI, or strokes was significantly reduced (11.3 vs. 12.5%, $P=0.007$). There were low rates of catheter-related thrombi, but these were higher with fondaparinux than with enoxaparin (0.9 vs. 0.4%, $P<0.001$) and a trend to more clinical PCI-related coronary complications (9.5 vs. 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 procedure-related complications of death, MI, or bleeding were significantly lower with fondaparinux than with enoxaparin (16.6 vs. 20.6%, $P<0.001$). Thus, the trial demonstrated that fondaparinux was equivalent to enoxaparin in reducing ischaemic events at 9 days, but with a substantially lower rate of major bleeding, which translated into a significantly lower long-term (6 months) mortality and morbidity. The conclusions from the OASIS-5 are that in NSTEMI-ACS fondaparinux 2.5 mg qd is the first

anti-thrombotic treatment that reduces the risk of bleeding, lowers long-term morbidity, and improves survival compared with today's standard treatment. At PCI, there is a slightly increased risk of catheter-related thrombi, which seems avoidable by pre-treatment with UFH at the procedure.

The OASIS-6 trial evaluated the effect of fondaparinux, given for up to 8 days, compared with standard adjuvant anticoagulant treatment in 12 092 patients with STEMI.¹⁴⁸ The trial had a complicated design with two strata. In stratum I with no indication for UFH, 5658 STEMI patients were randomized to fondaparinux vs. placebo. In stratum II, 6434 patients were randomized to fondaparinux for 8 days vs. UFH for up to 48 h, followed by placebo for up to 8 days. Both strata contained subgroups with and without reperfusion treatments and also with the use of different types of reperfusion, i.e. SK (73% of thrombolysis), urokinase, t-PA agents, and primary PCI. In the overall population, the endpoint of death or re-infarction at 30 days was significantly reduced from 677 (11.2%) of 6056 patients in the control group to 585 (9.7%) of 6036 patients in the fondaparinux group ($P = 0.008$). The benefit was, however, only seen in stratum I (no indication for UFH), with 11.2 vs. 14.0% ($P < 0.001$) in the fondaparinux vs. placebo groups, respectively. In contrast, there were no significant differences in stratum II (patients with indications for UFH): 8.3 vs. 8.7% in the fondaparinux and UFH groups, respectively. In the 3768 patients treated with primary PCI, who all were in stratum II, there was no benefit—and actually a trend to harm—of fondaparinux, with a 30-day rate of death or MI of 6.1% with fondaparinux vs. 5.1% in the UFH group ($P = 0.19$). There was a higher rate of guiding 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 2666 patients in stratum II (with an indication for UFH and without primary PCI), fondaparinux tended to be superior to UFH in preventing death or re-infarction at 30 days, with event rates of 11.5 and 13.8%, respectively ($P = 0.08$). There was a trend to fewer severe bleedings with fondaparinux combining both strata, and interestingly, severe bleeds were even less common with fondaparinux than with placebo in stratum I patients. The conclusions of the OASIS-6 trial are that: first, in acute STEMI without indication for UFH fondaparinux is more effective and as safe as no anticoagulant treatment regardless of whether any reperfusion treatment is used or not; secondly, in STEMI patients treated with thrombolysis, fondaparinux is at least as effective and as safe as UFH, although at present a claim of superiority is doubtful; thirdly, in STEMI patients treated with primary PCI, fondaparinux used as the only anticoagulant seems associated with a risk of harm, based on an increased rate of coronary complications. This risk seems avoidable by pre-treatment with UFH before PCI.

Idraparinux

This drug has been developed for long-term anticoagulation. The AMADEUS (AF trial of Monitored, Adjusted Dose VKA, comparing Efficacy and safety with Unadjusted SanOrg34006/ idraparinux) enrolled patients with AF at high risk of stroke with an indication for VKAs. Patients were randomized to

receive idraparinux 2.5 mg once weekly s.c. or VKAs (INR 2–3) for 6–24 months. This trial has been prematurely interrupted for safety reasons (unpublished results).

Intravenous direct thrombin inhibitors

Bivalirudin was approved in the European Union in 2004 to be used as an anticoagulant during PCI. The clinical programme pertinent to the PCI indication consisted of five studies. An early open-label, dose-finding trial in patients undergoing PCI ($n = 279$) indicated that the incidence of abrupt vessel closure at 24 h was low in patients receiving bivalirudin in doses of 0.45–0.55 mg/kg bolus followed by 1.8–2.2 mg/kg/h infusion.¹⁴⁹ A dose of 1 mg/kg bolus followed by a 4 h infusion of 2.5 mg/kg/h was consequently brought forward and compared with high-dose UFH in a randomized, double-blind study in 4098 patients requiring urgent PCI because of unstable or post-infarction angina [Bivalirudin Angioplasty Trial (BAT)].¹⁵⁰ In a Food and Drug Administration (FDA)-endorsed analysis of the results of the BAT trial, done on the entire intention-to-treat cohort of 4312 patients with more complete follow-up information and a more contemporary definition of MI, there was a suggestion that bivalirudin significantly reduced the combined endpoint of death, MI, or repeat revascularization in the entire cohort at 7 days (OR 0.78, 95% CI 0.62–0.99, $P = 0.04$) and at 90 days (OR 0.82, 95% CI 0.70–0.96, $P = 0.01$).¹⁵¹ Major bleeding events were significantly less frequent with bivalirudin than with heparin (3.5 and 9.3%, respectively; $P < 0.001$).

These studies were completed by 1993, and therefore reflected the standard of care in PCI at the time. Two randomized trials [The Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial (CACHET)¹⁵² and the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events (REPLACE)¹⁵³] were undertaken to gain experience with bivalirudin at revised, lower doses and to estimate the rate of complications with bivalirudin used with provisional GP IIb/IIIa inhibitors in the contemporary PCI setting.

The clinical efficacy and safety of the revised dose (0.75 mg/kg bolus followed by 1.75 mg/kg/h) was demonstrated in a large double-blind trial, REPLACE-2, in patients undergoing elective or urgent PCI. UFH plus GP IIb/IIIa inhibitors were compared with bivalirudin. For the latter arm GP IIb/IIIa inhibitors were added only if complications occurred during the PCI procedure. The trial demonstrated that the intra-procedural administration of bivalirudin with provisional GP IIb/IIIa blockade (required in 7.2% of patients) provides similar protection from acute ischaemic events with significantly fewer haemorrhagic complications as a regimen of UFH plus planned GP IIa/IIIb inhibition during elective or urgent PCI.¹⁵⁴ Among the 6010 patients (both stable and unstable) randomized in this trial, the composite ischaemic endpoint of death, MI, or urgent repeat revascularization by 30 days occurred in 7.6 and 7.1% of those treated with bivalirudin and heparin plus GP IIa/IIIb, respectively, meeting the formal criteria for non-inferiority. Major in-hospital bleeding rates were significantly reduced with bivalirudin (from 4.1 to 2.4%).¹⁵⁴ It should, however, be pointed out that ACT values higher than those recommended by the guidelines were used in the control arm of the study, which might have favoured the study drug in

this comparison. The substantial equivalence of bivalirudin in comparison with heparin plus GP IIa/IIIa blockade was sustained at 6 months and 12 months of follow-up, with a non-significant trend towards a lower mortality in the bivalirudin group.¹⁵⁵

Recently, the results of the ACUITY trial were published.¹⁵⁶ This study randomized 13 819 patients with moderate/high-risk unstable angina or NSTEMI-ACS undergoing an invasive strategy to one of three treatment groups—standard combination treatment with either UFH or enoxaparin with GPIIb/IIIa inhibitor (*n* = 4603) or bivalirudin with GPIIb/IIIa inhibitor treatment (*n* = 4604) or bivalirudin alone (*n* = 4612). Concerning the two arms with GPIIb/IIIa inhibition, there was a subrandomization to starting this treatment either upstream or in the catheterization laboratory. The randomization was stratified for pre-treatment prior to angiography with a thienopyridine (clopidogrel in the vast majority of cases), which was used in ~64% of patients. Coronary angiography was performed in 99%, PCI in 57%, CABG in 11%, and 33% of patients had no procedure. In the comparison between the respective standard combination treatment (heparin and a GPIIb/IIIa inhibitor) and the combination of bivalirudin and GPIIb/IIIa, there was neither any difference in the ischaemic composite endpoint (death, MI, or unplanned revascularization) at 30 days (7.3 and 7.7%, respectively), nor major bleeding (5.7 and 5.3%, respectively). Concerning the comparison between the respective standard combination treatment and bivalirudin alone, there was no difference in the ischaemic composite endpoint (7.3 and 7.8%), but a lower bleeding rate (5.7 and 3.0%, *P* < 0.001). Therefore, the net clinical outcome (ischaemic events+major bleeds) at 30 days was significantly lower in the bivalirudin alone group compared with the standard combination (10.1 vs. 11.7%, *P* = 0.015), and consistently in favour of bivalirudin across all pre-defined subgroups such as age classes, gender, presence of diabetes, presence of reduced renal function, etc. Among patients pre-treated with a thienopyridine, the net clinical outcome was 9.2 vs. 12.2% in the bivalirudin alone group vs. standard combination treatment. In patients without clopidogrel pre-treatment, the corresponding event rates were 11.3 vs. 11.1%. Although there is always a risk of random findings with multiple subgroup analyses, this finding might indicate a positive ‘additive’ effect when combining a thienopyridine with bivalirudin. There were no differences in efficacy or safety results in relation to the randomization to upstream treatment with GP IIb/IIIa inhibition. In conclusion, the ACUITY trial results show that bivalirudin is non-inferior to UFH in moderate-to-high risk NSTEMI-ACS receiving GP IIb/IIIa inhibitors. Bivalirudin alone in comparison with UFH together with GP IIb/IIIa inhibition was associated with significantly less bleeding, although the rate of ischaemic events in the overall population was similar. The lesser bleeding rate, at variance from OASIS-5, here did not translate into reduced hard endpoints at 30 days. At the current state of knowledge, it can only be concluded that bivalirudin is at least as effective and safe as UFH with and without GP IIb/IIIa inhibition in moderate-to-high risk NSTEMI-ACS patients.

Currently, the use of bivalirudin in STEMI patients undergoing primary PCI in comparison to using UFH with a GPIIb/IIIa is being tested in a large randomized controlled trial (HORIZONS).

Table 5 Randomized aspirin-controlled studies of warfarin plus aspirin in ACS, coronary bypass surgery and PCIs

After ACS Study (reference)	Year	n	INR target	INR reached	Aspirin dose (mg/day)	Death/re-infarction		RR	P-value	FU (months)
						Warfarin+aspirin	Aspirin			
ATACS ¹⁶⁶	1994	214	2.0-3.0	2.03	163	4/105 (3.8%)	9/109 (8.3%)	0.46 (0.14-1.49)	0.22	3
CARS ¹⁶⁷	1997	8803	1 mg qd	1.01	80	173/2 028 (8.6%) ^a	332/3 393 (9.8%)	0.87 (0.73-1.04)	0.18	14
OASIS-2 ¹⁶⁸	2001	3712	3 mg qd	1.05	80	328/3 382 (9.7%)	137/1 864 (7.4%)	0.99 (0.90-1.09)	0.065277778	14
CHAMP ¹⁶⁹	2002	5059	2.0-2.5	n.a.	n.a.	129/1 848 (7.0%)	700/2 537 (27.6%)	0.95 (0.75-1.20)	0.052083333	5
APRICOT-2 ¹⁷⁰	2002	300	1.5-2.5	1.09	160/80 ^b	725/2 522 (28.8%)	10/147 (6.8%)	1.04 (0.95-1.14)	0.38	33
ASPECT-2 ¹⁷¹	2002	668	2.8-4.5	2.06	80	4/153 (2.6%)	10/147 (6.8%)	0.41 (0.11-1.57)	0.17	3
WARIS-2 ¹⁷²	2002	2414	2.0-3.0	2.04	80	19/332 (5.7%)	29/336 (8.6%)	0.64 (0.37-1.13)	0.19	12
LoWASA ¹⁷³	2004	3.3	2.0-3.0	2.02	160/75 ^b	181/1 208 (15.0%) ^c	241/1 206 (20.0%) ^c	0.71 (0.58-0.86)	0.0005	48
Total		24 470	1.25 mg qd	n.a.	75	466/1 659 (28.1%) ^c	473/1 641 (28.8%) ^c	0.98 (0.88-1.09)	0.046527778	60
After coronary bypass surgery						2 029/13 237 (15.3%)	1 931/11 233 (17.2%)	0.89 (0.84-0.94)	0.00001	
Post-CABG ¹⁶⁰	2000	1351	<2.0	1.04	325	123/674 (18.2%)	178/677 (26.3%)	0.69 (0.57-0.85)	0.001	90
Before and after PCIs										
BAA5 ¹⁶¹	2000	1058	2.1-4.8	2.07	100	20/530 (3.7%)	31/528 (5.1%)	0.65 (0.50-0.84)	0.12	12

n.a., not analysed; FU, follow-up.

^aEstimate for 14 months follow-up.

^bThe aspirin alone/comparison groups.

^cIncluding stroke.

Vitamin K antagonists

After the 2004 publication of the ACCP Guidelines on Antithrombotic Drugs, 67 new data have become available on VKAs in the long-term prevention and treatment of cardiovascular disease.

Coronary heart disease

Major complications of coronary heart disease are usually caused by coronary plaque rupture followed by coronary thrombosis. Besides antiplatelet therapy, oral anticoagulation with VKAs has shown to be effective in the prevention of coronary thrombosis.

Primary prevention

Primary prevention of coronary heart disease with warfarin, with a mean INR intensity of 1.5 reduced the risk of fatal MI by 39%, with an acceptable bleeding risk in over 2500 healthy high-risk males.¹⁵⁷

Acute coronary syndromes

Several major old studies have demonstrated the benefit of VKAs in patients with a previous MI.¹⁵⁸ VKAs on top of antiplatelet therapy with aspirin vs. aspirin alone have been studied in at least eight randomized controlled trials in patients who survived ACS, both with STEMI and with NSTEMI-ACS (Table 5). For these indications, adding VKAs to antiplatelet therapy does not seem to show benefit when the INR reached is below 2.0. When INR is above 2.0, there is a significant reduction of re-infarction and death, with acceptable safety.¹⁵⁹

Two of these studies (ATACS and OASIS-2, Table 5) were performed in only NSTEMI-ACS patients.

Coronary bypass graft surgery

Combining low-intensity warfarin (INR <2.0) with aspirin (325 mg daily) after CABG has only been studied in one single large long-term trial. The combination does not seem to lead to better graft patency, but on the long term, unexpectedly, it led to a highly significant 35% reduction in all-cause mortality and 24% in non-fatal MI¹⁶⁰ (Table 5).

Percutaneous coronary interventions

Early and late complications of PCIs are probably related to the occurrence of peri-procedural coronary thrombosis. Therefore, VKAs (essentially warfarin) have been evaluated in the prevention of these sequelae. One trial in over 1000 patients compared aspirin 80 mg daily plus warfarin (INR 2.1–4.8), started at least 1 week before PCI, with aspirin alone on peri-procedural outcomes, the angiographic outcome at 6 months and clinical events at 1 year, when trial medication was discontinued.¹⁶¹ Death, MI, stroke, or urgent revascularization were significantly diminished by warfarin by 47% at 30 days and 29% at 1 year (Table 5). Bleeding was increased: there was a 1% excess of major peri-procedural bleeding and 1% excess major bleeding during the follow-up, but life-threatening bleeding was similar. Interestingly, the clinical benefit of VKAs was shown not only in non-stented, but also in stented patients, in whom—by protocol—warfarin was switched to ticlopidine.

Atrial fibrillation

The yearly incidence of stroke in patients with AF is about 5%,¹⁶² which is five times higher than that in comparable populations in sinus rhythm. The stroke risk largely depends on the underlying heart disease. In 'lone' AF (absence of heart disease) the stroke risk is only 0.5%/year,¹⁶³ whereas in AF associated with rheumatic valvular heart disease, especially mitral valve stenosis, it is very high. Oral anticoagulation with VKAs (warfarin, acenocoumarol, and phenprocoumon) has been shown effective in the prevention of thrombo-embolism in patients with valvular and non-valvular AF.¹⁶⁴ Severe bleeding with warfarin is seen in one out of 100 patients per year, which is double the risk of stroke in lone AF. Therefore, anticoagulation is only indicated in AF patients with a stroke risk of 2% or more per year, calculated as summarized in Table 6.¹⁶⁵ For patients with low risk, aspirin 75–325 mg daily is recommended. For patients with one moderate-risk factor either aspirin or VKAs are recommended. For patients with any high-risk factor or more than one moderate-risk factor, VKAs are recommended. The target INR should be between 2.0 and 3.0. In patients with AF with high risk of stroke, VKAs have been recently shown to be superior to the combination of aspirin and clopidogrel in the large open-labeled randomized ACTIVE-W, including 3335 patients randomized to clopidogrel plus aspirin and 3371 randomized to VKA. The study was stopped early due to clear evidence of superiority of VKAs, especially in those already taking oral anticoagulation therapy at the time of enrolment. There were however no differences in total mortality between the arms.¹⁷⁴

Artificial heart valves

The development of artificial heart valves with better flow profiles has diminished haemolysis and the development of valve thrombosis. Although always indicated, the desirable intensity of oral anticoagulation with VKAs has been adjusted down in recent ESC guidelines,¹⁶⁵ which is summarized in Table 7.¹⁷⁵

Table 6 Grading of thrombo-embolic risk in intermittent (paroxysmal) or permanent/persistent atrial fibrillation

High-risk patients (approximately >6 major thrombo-embolic events/100 patients/year)
Previous stroke, TIA or systemic embolism
Mitral stenosis
Prosthetic heart valve
Intermediate-risk patients (approximately 2–6 major thrombo-embolic events/100 patients/year)
Age >75 years
Hypertension
Heart failure
Left ventricular ejection fraction <35%
Diabetes mellitus
Low-risk patients (approximately <2 major thrombo-embolic events/100 patients/year)
Female gender
Age 65–74 years
Coronary artery disease
Thyrotoxicosis

TIA, transient ischaemic attack.
Source: Fuster *et al.*¹⁶⁵

Table 7 Recommendations for target intensity of anticoagulation with vitamin K antagonists in patients with mechanical heart valves

	Without risk factors	With risk factors
Adjust target INR to intracardiac conditions and prosthesis thrombogenicity	SR LA <50 mm MV gr 0 LV normal SEC 0 AVR	AF LA >50 mm MV gr + EF <35% SEC + MVR, TVR, PVR
Prosthesis thrombogenicity (as determined by valve thrombosis rates)	Low 2.5 Medium 3.0 High 3.5	3.0 3.5 4.0

Low: Medtronic Hall, St Jude Medical (without Silzone), Carbomedics AVR; medium: bileaflet valves with insufficient data, Bjork-Shiley valves high: Lillehei Kaster, Omniscience, Starr Edwards. SR, sinus rhythm; LA, left atrium; MVgr, mitral valve gradient; LV, left ventricle; EF, ejection fraction; SEC, spontaneous echo contrast; AVR, MVR, TVR, PVR, aortic, mitral tricuspid and pulmonary valve replacement, respectively. From Butchart *et al.*, 2005.¹⁷⁵

Heart failure

In patients with CHF caused by either dilated cardiomyopathy or ischaemic heart disease, there is a cardio-embolic risk of 1.5–4.5%/year, with the highest risk related to very low EF and severe clinical heart failure. There are no major randomized studies demonstrating the beneficial effect of VKAs in these patients, and the WATCH trial,¹⁷⁶ which was planned to randomize more than 5000 patients, was prematurely stopped because of problems with patient recruitment. In post-infarction patients, the cardio-embolic risk is especially high in patients with ejection fraction <30%^{177,178} and patients with persisting or protruding thrombus.¹⁷⁹ Also in dilated cardiomyopathy, ventricular thrombi increase the risk of thrombo-embolism.¹⁸⁰

On the basis of the available data, VKA treatment should be considered in patients with CHF in case of very low ejection fraction, severe clinical heart failure, ventricular thrombi, and prior cardio-embolic episodes. In addition, VKAs are strongly recommended in patients with CHF and AF.

In conclusion, oral anticoagulation in the form of VKAs is likely helpful in the secondary prevention of ischaemic events after MI in patients taking aspirin, although not widely used and still with an uncertain risk/benefit ratio. VKAs are currently indicated, and are standard treatment, in patients with artificial heart valves and in those with AF at medium-to-high thrombo-embolic risk. VKAs should be considered in patients with CHF with very low EF, severe clinical heart failure, ventricular thrombi, and prior thrombo-embolic episodes.

Oral direct thrombin inhibitors: clinical developments

The clinical efficacy of ximelagatran in preventing stroke and thrombo-embolic events in AF when compared with warfarin at INR 2–3 was evaluated in one open-label (SPORTIF-III) and one double-blind (SPORTIF-V) prospective randomized trial

including altogether 7329 patients.^{181–183} The event rates in SPORTIF III were 1.64 vs. 2.30%, corresponding to a difference of –0.66% (95% CI –1.4, 0.13) and in SPORTIF V were 1.61 vs. 1.16%, corresponding to a difference of +0.45% (95% CI = –0.13, 1.03). These results were not considered to fulfil the current US FDA requirements to prove non-inferiority in efficacy. In addition, in the trials of prevention of venous thrombo-embolic disease, there was a suspicion of a slightly raised risk of MI in patients on ximelagatran in comparison with LMWHs and/or warfarin. These two findings, in combination with evidence of liver toxicity, prevented the registration at the first application in the USA in 2004. Finally, on 14 February 2006, the company developing ximelagatran decided to withdraw it from the market (for the indications in orthopaedic surgery) and terminate its further development. The withdrawal was triggered by new patient safety data with an adverse event report of serious liver injury in a clinical trial. Concerning dabigatran etexilate in the indication of stroke prevention in AF, only the results from a small randomized dose-finding phase II trial in around 430 patients are available.¹⁸⁴ These results are encouraging, as they have formed the basis for a large phase III programme (RE-LY), randomizing 15 000 patients with AF in a direct comparison of dabigatran etexilate with warfarin.

Long-term oral thrombin inhibition with ximelagatran has also been evaluated in a dose-finding trial comparing four different bid doses (24, 36, 48, and 60 mg) with placebo on top of routine treatment with aspirin, in 1883 post-MI patients without early revascularization procedures (ESTEEM).¹⁸⁵ The results showed a significant 24% relative reduction in death, MI, and severe recurrent ischaemia on all tested doses of ximelagatran, with no dose-effect relationship.¹⁸⁵ There was, as expected, a low, but dose-related, increased risk of total bleeding, with around a 50% increase on the lowest dose, and a doubling on the highest dose, in comparison with placebo. The occurrence of transient elevation of liver enzymes was similar to other long-term studies with the compound.¹⁰⁰ As ximelagatran has been withdrawn and all further development terminated, any further evaluation of the promising concept of oral thrombin inhibition in coronary artery disease needs to be performed with other compounds.

In conclusion, oral thrombin inhibition is a promising concept for anticoagulation that might replace VKAs in all indications. The clinical results with the first available compound ximelagatran were encouraging, showing similar anticoagulant efficacy as warfarin at INR 2–3, at a somewhat lower risk of bleeding.

Oral Factor Xa inhibitors: clinical developments

After the results with the parenteral fondaparinux proved the concept of the antithrombotic effect due to FXa inhibition, a number of oral FXa inhibitors have entered clinical development. These agents have a molecular weight of ~500 Da, are direct inhibitors of FXa, as they do not require a plasma cofactor for their action, and are selective for FXa, as their K_i is at least 5000 times lower than that for any other serine protease. The direct inhibitors of FXa are inhibitors of the catalytic site of FXa. It has been shown that the direct inhibitors of FXa can inhibit FXa both in the fluid phase and in the context of the prothrombinase complex. The clinical relevance of this biochemical feature is unclear.

Clinical data are currently available for at least four oral inhibitors of FXa: razaxaban,¹⁸⁶ rivaroxaban (BAY 59 7939),^{187,188} LY 5157117¹⁸⁹, and YM 150¹⁹⁰. Other oral inhibitors of FXa are known to be under clinical development, including apixaban and DU 176-b. The available clinical data are related to the assessment of the efficacy and safety of the oral inhibitors of FXa in phase II studies on the prevention of VTE after major orthopaedic surgery. Rivaroxaban is currently under evaluation in two phase II studies in the treatment of deep vein thrombosis. In general, these agents have shown a reasonably large therapeutic window. Doses of rivaroxaban between 20 and 30 mg once a day^{187,188} and of LY 5157117 between 100 and 150 mg once a day¹⁸⁹ have been proved to be as effective as enoxaparin in the prevention of deep vein thrombosis after major orthopaedic surgery without being associated with excessive bleeding.

The currently available clinical data on the oral inhibitors of FXa only derive from short-term studies (maximum 10 days of drug administration). Thus, only after the presentation of long-term studies it will be possible to draw any conclusion of the potential hepatotoxicity of these compounds. The favourable results achieved by the oral inhibitor of FXa in studies on the prophylaxis of VTE in major orthopaedic surgery promoted the development of these compounds in indications where a prolonged administration is required. In particular, studies on the prevention of stroke in patients with AF, and at least one (with apixaban) in ACS are either planned or ongoing.

Bleeding risk and bleeding management during anticoagulant therapy

General risk factors for bleeding

By their very mode of action, all anticoagulants are endowed with a certain risk for haemorrhagic complications. With all anticoagulants currently in use, the bleeding risk is dose-related. Age >70 years was found to be a risk factor for major bleeding with UFH, LMWHs, VKAs, and probably with all other anticoagulants. Recent surgery, trauma, or invasive procedures also increase the bleeding risk.³³ Table 8 lists

Table 8 Bleeding risk categories in patients undergoing surgery or procedures

Low risk	High risk
Diagnostic endoscopy	Major intra-abdominal surgery
Cataract surgery	Major vascular surgery
Oral surgery/dental extraction	Major orthopaedic surgery
Arthrocentesis	Prostatectomy or bladder surgery
Cutaneous surgery	Neurosurgical procedures
Hernia repair	Heart valve replacement
Scrotal surgery	Coronary artery bypass graft surgery
Coronary angiography	Major intrathoracic surgery
	Major cancer surgery
	Pacemaker insertion/implantation
	Biopsy in a non-compressible tissue
	Puncture in a non-compressible artery

surgical interventions associated with a low and high risk for bleeding complications. Underlying diseases contributing to a higher risk of bleeding include hypertension, cerebrovascular disease, ischaemic stroke, serious heart disease, cancer, and renal failure. Occult pathological lesions, particularly in the gastrointestinal or genito-urinary tracts were found in about 30% of bleeding patients exhibiting a prothrombin ratio ≥ 2.5 .

Unfractionated heparin and low-molecular weight heparins

With UFH, there appears to be a relationship of bleeding risk with prolonged aPTT or ACT. In one study, it was found that a 10 s increase in the aPTT resulted in a 7% increase in the risk of bleeding (reviewed in Levine *et al.*¹⁹¹). Meta-analyses of studies comparing LMWHs with UFH for the treatment of VTE or ACS suggest that LMWHs have a benefit–risk profile that is comparable to—or slightly better than—that of UFH.^{192,193} Patients who have taken aspirin in addition to heparins bleed more during cardiovascular interventions. Therapy with thrombolytics and GP IIb/IIIa antagonists also increase the heparin-associated bleeding risk.

Pentasaccharides

For treatment of NSTEMI-ACS in the huge OASIS-5 trial, fondaparinux, at a daily dose of 2.5 mg (a prophylactic dose), resulted in a bleeding rate of 2.2%, whereas enoxaparin at a dose of 1 mg/kg twice daily (a therapeutic dose) produced 4.1% major bleeds.¹⁴⁷ It is likely that the reduced bleeding seen with fondaparinux in this setting reflects the low dose used, because the bleeding risk with fondaparinux was clearly dose-related in the ASPIRE trial.¹⁴⁵ The bleeding rate in the fondaparinux group receiving 2.5 mg daily was 3.4% and that in the 5 mg daily group was 9.6%.¹⁴⁵ Clinical results using the very-long-acting idraparinux (half-life of about 80 h) in cardiovascular medicine are not yet available. In the phase II PERSIST trial, 659 patients with deep vein thrombosis were randomized to receive one s.c. weekly injection of 2.5, 5, 7.5 or 10 mg of idraparinux or warfarin adjusted to attain an INR of 2.0–3.0. There was a clear dose–response for major bleeding with idraparinux ($P = 0.003$). However, the lowest weekly dose of 2.5 mg of idraparinux was as effective as warfarin in the secondary prevention of deep vein thrombosis and was not associated with major bleeding.¹⁹⁴

Direct thrombin inhibitors

Bleeding with the use of the parenteral DTI bivalirudin was evaluated in several studies. A meta-analysis of the BAT, CACHET, REPLACE-1, and two other trials compared bivalirudin with UFH-based regimens. The following incidences were significantly lower in the bivalirudin groups: death (0.1 vs. 0.2%; $P = 0.049$), revascularization (2 vs. 2.7%; $P = 0.02$), and major bleeding (2.7 vs. 5.8%; $P < 0.001$) (reviewed in Moen *et al.*¹⁹⁵).

Ximelagatran, a synthetic oral DTI now withdrawn from development also provoked less bleeding than VKAs or LMWHs in several trials (reviewed in Mohapatra *et al.*¹⁹⁶). Dabigatran etexilate, an oral DTI with a longer half-life but lower bioavailability than ximelagatran, has been studied in 1973 patients undergoing total hip or knee replacement (BISTRO II trial). In this double-blind study, patients were randomized to dabigatran etexilate 50 mg bid, 150 mg

bid, 300 mg qd, 225 mg bid or enoxaparin 40 mg qd. A significant dose-dependent decrease in VTE was observed with increasing doses of dabigatran. Composite major or clinically significant bleeding in the 50 mg bid group (2.6%) was lower than in the enoxaparin group (4.6%) and the incidence of VTE was 5.0 and 5.6% respectively.⁹⁷ Results of a phase II trial with dabigatran in AF (PETRO) have not yet been published. Preliminary data suggest that dabigatran might have a favourable risk/benefit ratio.

Vitamin K antagonists

The major complication of VKAs is bleeding (reviewed in Levine *et al.*¹⁹¹). In randomized controlled studies, major bleeding in patients exhibiting an INR of 2.0–3.0 is quite low (in five large AF studies: 1.3 vs. 1.0% in the control group¹⁹⁷). The bleeding risk is increased considerably in patient groups with a target INR >3.0. In one study, the risk for ICH doubled with each increase of approximately 1 INR units.¹⁹⁸ The importance of the intensity of anticoagulation with VKAs as a determinant of bleeding is particularly well illustrated in the Leiden anticoagulation study,¹⁹⁹ where target ranges were reduced for three indications in 1998. In over 400 patients with mechanical heart valves, the INR target range was reduced from 3.6–4.8 to 3.0–4.0, and in over 1800 patients treated for AF or cerebral ischaemia the INR target range was lowered from 3.0–4.5 to 2.5–3.5. This resulted in a 30% overall reduction in major bleeding episodes from 3.6 to 2.7/100 patients/year and, in the higher target group, from 6.1 to 3.0/100 patients/year (50% reduction).¹⁹⁹ Although a high INR (>3.0) is epidemiologically related to a strongly increased rate of bleeding, in the individual patient, an increased INR without bleeding does not indicate the need of an antidote.

Many drugs interact with or enhance the bleeding risk of VKAs, the most common being aspirin. Representative of many similar studies is the Veterans Administration study, in which 5059 survivors of acute MI were randomized to warfarin (target INR 1.5–2.5) plus aspirin treatment vs. aspirin alone. In the combination therapy group, major bleeding occurred in 1.28%/year, and in the aspirin alone group in 0.72%/year.¹⁶⁹ Many other drugs and natural substances interact with VKAs. The reader is referred for this to a recent review.²⁰⁰

Several studies have reported a higher incidence of haemorrhagic complication in the early phase of treatment with VKAs, where probably the fluctuations of the INR are larger. These fluctuations diminish with increased duration of VKA treatment. The incidence of haemorrhagic complication appears also to be higher in patients treated by family physicians than in patients followed by an anticoagulation clinic or practicing self-management of oral anticoagulation.^{88,201,202}

Management of bleeding complications

The treatment of choice of major bleeding due to anticoagulant therapy is the administration of a specific rapidly acting antidote. This is unfortunately not available for many of the currently used anticoagulants. The availability of a specific antidote is particularly desirable for anticoagulants with long half-lives. In the absence of a specific antidote, bleeding may be reduced or stopped by the administration of

fresh frozen plasma, prothrombin complex preparations or activated blood coagulation FVII (FVIIa), but there is recent evidence that the administration of recombinant FVIIa can be associated with increased risk of thrombotic events.²⁰³ Because LMWHs, the pentasaccharides, and DTI are mostly cleared by the kidney, acute haemodialysis should be considered in patients with renal failure.

Unfractionated heparin and low-molecular weight heparins

In UFH-treated patients with bleeding episodes, the anticoagulant effects can be reversed with i.v. protamine sulfate, a cationic protein derived from fish sperm that binds heparin to form a stable salt. Each mg of protamine sulfate neutralizes about 100 U of UFH. Patients with a history of fish allergy and those who have received protamine-containing insulin may suffer allergic reactions to protamine.³³ The risk of anaphylactoid reactions can be reduced by administering the drug slowly.²⁰⁴

Controversy exists concerning the neutralization of UFH after open-heart surgery with cardiopulmonary bypass.²⁰⁵ Overneutralization of UFH with protamine may cause decreased platelet aggregation, probably due to inhibition of the platelet membrane GP Ib-von Willebrand factor interaction necessary for normal haemostasis.^{206,207} Protamine itself produces a haemostatic defect by prolonging blood clotting times.²⁰⁸ The half-life of protamine sulfate is quite short (about 5 min).²⁰⁹ UFH binds reversibly to a number of proteins and endothelial cells, but protamine does not. After neutralization of high doses of circulating UFH (half-life about 90 min) after cardiopulmonary bypass, protein- and tissue-bound UFH is released slowly and produces a heparin rebound.²¹⁰ Ideally, after cardiopulmonary bypass or off-pump coronary artery bypass surgery, protamine corresponding to about half of the heparin administered should be given by slow (2–3 min) injection. A control of the ACT is indicated. ACT should reverse to pre-heparin values. To prevent heparin rebound, it is recommended that a continuous infusion with 20–25 mg of protamine per hour is then administered by continuous infusion for 6 h.²¹⁰

When bleeding occurs with LMWHs, there is no proven method for neutralizing fully its anticoagulant effects. Protamine sulfate reverses all of the anti-IIa activity of LMWHs, but only about 60% of the anti-Xa activity because protamine sulfate does not bind to shorter heparin chains.⁵⁰ In such cases, 1 mg neutralizes 100 anti-Xa units of LMWHs. A full dose of protamine sulfate should be given if the LMWH was administered within 8 h, whereas a lower dose can be used if more than 8 h have elapsed since the last LMWH injection. If the bleeding continues, a second injection of protamine sulfate can be given; this dose of protamine sulfate should be half that of the first. Furthermore, there is a case report of the successful use of recombinant FVIIa to control bleeding in a post-operative patient with renal failure who was receiving a LMWH.²¹¹

Pentasaccharides

If major bleeding occurs with fondaparinux or idraparinux, there is no specific antidote. Protamine sulfate does not bind to these pentasaccharides, and therefore this agent is of no value. Recombinant FVIIa reverses the anticoagulant effects of fondaparinux and of idraparinux in healthy

volunteers,^{60,212,213} but the usefulness of this agent in patients with major haemorrhage has only been documented in single cases.²¹⁴ The ongoing development of a biotinylated idraparinux derivative should allow the quick neutralization of the compound by the i.v. administration of avidin.

Direct thrombin inhibitors

No antidote exists for DTIs. Theoretically, it should be possible to construct an inactive thrombin molecule with intact binding sites for hirudin, ximelagatran, and dabigatran. Vitamin K-dependent clotting factor concentrates were more effective than FVIIa to counteract the bleeding tendency in animals treated with very high doses of DTIs.²¹⁵

Vitamin K antagonists

Over-anticoagulation with VKAs is best treated with vitamin K-derivatives (Konakion, phytomenadion, or phytonadion) given orally or by i.v. injections. S.c. administration is to be avoided.²¹⁶ However, in order to be active, these drugs must induce the synthesis of functional vitamin K-dependent clotting factors, and therefore act slowly. For rapid action in cases with serious bleeding, it is better to transfuse fresh-frozen plasma or plasma fractions containing vitamin K-dependent clotting factors (prothrombin complexes, such as Feiba[®] or Autoplex[®]).²¹⁷ FVIIa also has been effective to stop major bleeding.

Special situations

Vitamin K antagonists in pregnant patients with artificial heart valves

Pregnant women with an indication for oral anticoagulation with VKAs for artificial heart valves must interrupt VKAs in early pregnancy and switch to a s.c. LMWH according to current guidelines,¹⁷⁵ as summarized in *Table 9*.^{218,219}

Renal failure and haemodialysis

Patients with renal dysfunction, renal failure, and haemodialysis have an increased risk of thrombotic cardiovascular events and a substantially raised cardiovascular mortality. They also have a raised risk of bleeding complications both with and without anticoagulant treatments. Since many anticoagulant drugs are renally excreted, patients with renal failure are often excluded from clinical trials of new antithrombotic agents. Therefore, our knowledge on the effects of anticoagulant treatment on event rates and risk of bleeding in this patient group is limited. Of the routinely used anticoagulants, UFH, LMWHs, fondaparinux, bivalirudin, and the newer oral DTIs are all renally excreted. Dose reduction and close monitoring of anticoagulation by the appropriate means (i.e. aPTT, ACT, or anti-Xa

Table 9 Anticoagulation in pregnant patients with artificial heart valves

First 12 weeks	LMWH ^a bid
Weeks 12–35	Warfarin (INR 2.0–3.0)
Week 35 to delivery	LMWH ^a bid
After delivery	Restart warfarin (INR 2.0–3.0) in 4–8 h

^aAnti-Xa level of 1.0 U/mL 4 h after dosing, or 0.6 U/mL pre-dosing.

activity according to the drugs used) are needed at a GFR <30 mL/min.^{220–222} Even in patients with moderately reduced GFR (30–50 mL/min), a cautious approach is recommended, considering the opportunity of monitoring the anticoagulant response. VKAs can commonly be managed with the standard dosing, as the anticoagulant response is influenced by many other factors and always adjusted by frequent INR controls.²²² Although it might seem safer to use UFH, which is easily monitored by the aPTT, there are no clinical trials indicating any difference in bleeding complications with LMWHs, provided that adequate dose adjustments are performed.^{223,224}

Surgery, percutaneous coronary interventions, biopsies, and dental procedures

Oral anticoagulant therapy with VKAs for patients needing surgery or invasive procedures may be problematic because many patients require discontinuation of VKAs in the peri-procedural and peri-operative period to reduce the risk of bleeding. Surgery and procedures can be safely performed with an INR <1.5, but in patients with a high risk of thrombo-embolism the simple discontinuation of oral therapy with VKAs may not be acceptable during the period (5 days in the case of warfarin) necessary for the effect of the antithrombotic therapy to subside.

Some of these patients may need bridging therapy with a LMWH s.c. to minimize the risk of thrombo-embolism. This strategy has been shown to be feasible, safe,^{225–228} and with significantly lower cost than with the use of weight-adjusted i.v. UFH.²²⁹ The thrombo-embolic risk in different patient groups is shown in *Table 10*. For patients with a low risk of thrombo-embolism, oral therapy with VKAs can be withheld in the peri-procedural period, whereas high-risk patients require continuous anticoagulation involving 'bridging' during periods of sub-therapeutic levels of anticoagulation with VKAs.

On the other hand, it has to be considered that the risk of bleeding during anticoagulant therapy with VKAs varies in relation to specific operations and procedures (*Table 8*), when strategies for anticoagulation are planned. During procedures with a low bleeding risk, such as diagnostic endoscopy, cataract surgery, arthrocentesis, coronary

Table 10 Thrombo-embolic risk profile in patients undergoing surgery, PCIs, biopsies, and dental procedures

Low risk	High risk
Biological prosthetic heart valve (>3 months)	Mechanical prosthetic heart valve
Mitral valve repair (>3 months)	Biological prosthetic heart valve (<3 months)
AF without any high ^a or without ≥1 moderate risk factor(s) ^b	Mitral valve repair (<3 months)
VTE (>3 months) and mild thrombophilia	VTE (<3 months) and severe thrombophilia ^c

^aPrior ischaemic stroke, transient ischaemic attack or systemic embolism, mitral stenosis or prosthetic heart valve.

^bAge >75 years, hypertension, heart failure, left ventricular ejection fraction <35%, diabetes mellitus.

^cActive cancer, antiphospholipid antibody, AT deficiency, protein C or S deficiency, homozygous FV Leiden, or prothrombin 20210 mutation.

arteriography, and oral surgery/dental extractions, an alteration of oral anticoagulant therapy with VKAs is not needed. However, in high-risk situations, such as major cancer or vascular surgery, neurosurgical procedures, as well as diagnostic endoscopy, arterial punctures or biopsies in organs where compression is not possible, oral anticoagulant therapy with VKAs must be discontinued and 'bridging therapy' with a s.c. LMWH in either standard prophylactic and/or therapeutic dosages (Table 11) has to be initiated.

Table 11 Bridging therapy of VKAs with LMWHs in high- and low-risk patients/procedures

Low thrombo-embolic risk	Procedures with low bleeding risk
Discontinue VKA therapy 5 days before procedure ^a Standard LMWH prophylaxis administered peri-procedurally Start VKAs on the day of surgery Stop LMWH with INR in therapeutic range or after at least 5 days	Continue VKA therapy with INR in therapeutic range
High thrombo-embolic risk	Procedures with high bleeding risk
Discontinue VKA therapy 5 days before procedure ^a Start a therapeutic LMWH 3 days before procedure with last dose 24 h before procedure Standard LMWH prophylaxis administered peri-procedurally Post-procedural start of VKAs on the day of surgery and LMWH on day 1, 2 or 3, depending on haemostasis Stop LMWH when INR in therapeutic range (after at least 5 days)	Discontinue VKA therapy and treat with a LMWH as described for low- or high-risk patient

^aFor phenprocoumon 4 days, for acenocoumarol 2 days.

In patients with a high risk of bleeding, oral anticoagulant therapy with warfarin is stopped 5 days before surgery (Table 11). In patients with a low risk of thrombo-embolism, warfarin therapy is re-started on the day of surgery. Standard prophylactic LMWHs may be used and should be continued until a therapeutic INR is obtained during warfarin therapy or warfarin has been resumed for at least 5 days. In patients with a high risk of thrombo-embolism, a therapeutic LMWH is started 3 days before surgery and the last dose administered 24 h before surgery. Depending on haemostasis, a therapeutic LMWH can be started 1, 2, or 3 days after surgery and warfarin on the day of surgery. Prophylactic LMWHs can be used 12 h before and in the evening after surgery. LMWH therapy is continued until a therapeutic INR is obtained during warfarin therapy. Phenprocoumon, which has a longer therapeutic half-life than warfarin, is stopped 7 days before surgery.

Cancer

Cancer patients have an increased risk of spontaneous VTE and of thrombo-embolic complications during surgery.²³⁰ Cancer chemotherapy and radiotherapy also increase the risk of VTE.^{231,232} In cancer patients, the risk of bleeding and thrombo-embolic complications are increased during oral anticoagulant therapy with VKAs, and it is more difficult to keep the INR in the therapeutic range than in patients without cancer.^{233,234} Anorexia, vomiting, drug interactions, thrombocytopenia, and interruption of anticoagulant therapy in relation to procedures are important for the increased risk and monitoring difficulties in cancer patients.

Alternative treatment regimens with LMWHs have been tested in three studies comparing s.c. LMWHs with VKAs in cancer patients with VTE or pulmonary embolism.²³⁵⁻²³⁷ Altogether, these studies demonstrated less VTE recurrence and lower risk of bleeding with LMWHs than with VKAs during a treatment period of 3-6 months (Table 12).

In addition, LMWH treatment may influence tumour growth and metastasis in cancer patients,²³⁸ and may thus prolong survival in these patients.²³⁹⁻²⁴¹ Therefore, a tight INR control during therapy with VKAs or an alternative treatment regimen with a LMWH are recommended in cancer patients.

Table 12 LMWHs vs. VKAs for treatment of VTE

Number (n) of patients	LMWH treatment (daily)	Treatment duration	Thrombo-embolic complications	Bleeding complications	Reference
n = 167 (post-hoc analysis) DVT	Tinzaparin 175 IU/kg × 1 s.c.	3 months	Tinzaparin 6.3%; VKA 11.5%, P < 0.05	Tinzaparin 6.3%, VKA 8.0%, NS	237
n = 146 DVT and PE	Enoxaparin 1.5 mg/kg × 1 s.c.	3 months	VTE+bleeding: Enoxaparin 10.5%; VKAs 21.1%, P = 0.09	Enoxaparin 7.0% (0/5 fatal); VKAs 16.0% (6/12 fatal); NS	235
n = 676 DVT and PE	Dalteparin 200 IU/kg for 1 month; then reduced by 25%	6 months	Dalteparin 8.0%; VKAs 15.8%; RR 0.48 (95% CI 0.3-0.77; P = 0.002)	Dalteparin 6.0%; VKAs 4%; NS	236

DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; NS, not significantly different.

Anticoagulant therapy in combination with other drugs interfering with haemostasis

Anticoagulant therapy in combination with antiplatelet therapy

Although mechanistically sound, the combination of VKAs and antiplatelet therapy has not been convincingly shown to have a favourable benefit/risk profile for the long-term management of coronary heart disease patients. Aspirin increases the risk of warfarin-associated bleeding by inhibiting platelet function.¹⁹¹ The size of this increased risk depends on the intensity of anticoagulation as well as on the daily dose of aspirin.¹⁹¹ Although aspirin completely blocks thromboxane(TX)_A₂-dependent platelet function at any dose in excess of 30 mg daily, its deleterious effects on the gastroduodenal mucosa are clearly dose-dependent.²⁴² Thus, daily doses in the range of 75–100 mg do not produce significantly more gastroduodenal ulcer lesions than placebo²⁴³ and double the risk of upper gastrointestinal bleeding largely through the impairment of primary haemostasis.²⁴² In contrast, higher doses of aspirin dose-dependently increase the risk of upper gastrointestinal bleeding by inducing new mucosal lesions as well as by inhibiting platelet function.²⁴²

Concomitant use of aspirin and VKAs has been associated with a higher risk of bleeding, even in patients treated with warfarin with a mean INR <2.0.^{157,167,169} In a large randomized trial in patients with a recent MI, the rate of spontaneous major haemorrhage during the first year of therapy was increased to 1.4% in patients treated with 3 mg of warfarin (INR 1.2) and aspirin 80 mg/day, compared with 0.7% in patients treated with aspirin 160 mg/day ($P = 0.01$).¹⁶⁷ In a primary prevention trial in approximately 5000 men at high risk for coronary heart disease, the rate of haemorrhagic stroke was 0.09%/year in those treated with low-dose warfarin (INR 1.5) plus aspirin 75 mg/day; 0.01%/year in those treated with low-intensity warfarin alone, and 0.02%/year in those treated with low-dose aspirin alone.¹⁵⁷ Similarly, in a trial that compared warfarin (INR 1.8) plus 81 mg of aspirin with 162 mg of aspirin alone in approximately 5000 patients with a recent MI, major bleeding was more common in the warfarin and aspirin group than in the aspirin-only group (1.28 vs. 0.72 events/100 persons/year of follow-up, respectively; $P < 0.001$).¹⁶⁹ The percentage of patients with a recent MI who suffered a serious bleed was also doubled by the combination of 1.25 mg of warfarin and 75 mg of aspirin vs. 75 mg of aspirin alone in the recently reported LoWASA study.¹⁷³ Interestingly, in three separate trials after MI,^{167,169,173} the increased risk of major bleeds was recorded in the face of no differences in the rates of major vascular events, suggesting that the threshold for the intensity of anticoagulation with warfarin to increase the risk of bleeding in aspirin-treated patients may be somewhat lower than the threshold for protecting against arterial thrombosis.¹⁷²

In a literature survey of 14 articles reporting on the combination of aspirin and VKAs (mostly warfarin) vs. aspirin alone, enrolling 25 307 patients, Andreotti *et al.*²⁴⁴ recently reported that the combination of aspirin and VKAs, pooling data irrespective of the achieved INR, did not significantly affect the risk of major adverse events (all-cause death, non-fatal MI, and non-fatal thrombo-embolic stroke) when compared with aspirin alone [OR 0.96 (0.90–1.03),

$P = 0.30$], but increased the risk of major bleeds OR 1.77 (1.47–2.13), $P < 0.00001$. However, in studies with INR of 2–3, aspirin plus VKAs was associated with a significant reduction of major adverse events [OR 0.73 (0.63–0.84), $P < 0.0001$, number needed to treat to avoid one major adverse event=33], albeit at an increased risk of major bleed [OR 2.32 (1.63–3.29), $P < 0.00001$; number needed to harm by causing one major bleed=100]. In both analyses, intracranial bleeding was not significantly increased by aspirin plus VKA when compared with aspirin alone. Therefore, for patients recovering from an ACS, a combined strategy of aspirin plus warfarin at INR values of 2–3 doubles the risk of major bleeds, but is nonetheless superior to aspirin alone in preventing major adverse events. Whether this combined regimen is also superior to a 'double' antiplatelet strategy with aspirin plus clopidogrel or to newer evolving treatments warrants further investigation.

In a small trial combined treatment with clopidogrel, aspirin, and VKAs in ACS patients gave more major bleeding complications than clopidogrel and aspirin in combination.²⁴⁵ In a population-based observational cohort study using linked administrative databases, triple therapy in elderly patients after a myocardial infarction only gave a small increase in bleeding risk.²⁴⁶ In a retrospective analysis of 66 PCI-treated patients who received aspirin in combination with clopidogrel for 4 weeks and continued treatment with warfarin, six patients (9.2%) experienced bleeding events.²⁴⁷ These results were later confirmed in a separate study of 107 consecutive patients.²⁴⁸ In patients receiving a drug-eluting stent, treatment with aspirin and clopidogrel for a period of at least 12 months is necessary to reduce the risk of stent thrombosis, whereas the treatment period may be shortened to 1 month if bare metal stents are used. Thus, such latter type of stents may be a better choice in patients who need continued treatment with VKAs.

In patients who are treated with a combination of aspirin and dipyridamole because of a previous stroke or transient ischaemic attack, treatment with VKAs may be indicated for other reasons. In these patients, dipyridamole is usually suspended, as the risk and benefit of these three drugs in combination is unknown. Dipyridamole has no documented effect in patients with coronary heart disease, and in patients with ACS and/or PCI with stent implantation dipyridamole treatment is stopped and dual platelet inhibition with aspirin and clopidogrel initiated. Treatment with dipyridamole can be resumed when clopidogrel is stopped.

Further prospective trials are needed to evaluate safety and efficacy of long-term treatment with dual platelet inhibition in combination with VKAs.

Anticoagulant therapy in combination with fibrinolytic therapy

In patients with acute MI treated with SK, no clear advantage was seen by the adjunctive treatment of i.v. UFH in the GISSI-2, ISIS-3 and GUSTO-I trials.²⁴⁹ The evidence for the use of UFH with t-PA is only slightly stronger.¹⁰³ In the GUSTO-I trial, the combination of front-loaded t-PA with UFH was found to be superior to SK and resulted in five fewer deaths, three fewer re-infarctions, and one less pulmonary embolism per 1000 patients treated. It has to be remarked, however, that the study did not include a

t-PA-only group.¹⁰⁴ As a consequence of GUSTO-I, however, later clinical trials, such as GUSTO-IIb, TIMI-9B, COBALT, and GUSTO-III, all utilized a 5000 U bolus of adjunctive UFH, followed by 1000 U/h of UFH. However, the incidence of ICH in these studies still was unacceptably high (0.7–0.9%), and later studies began using body weight-adjusted UFH doses (reviewed in Menon *et al.*²⁴⁹). The most recent recommendation of the seventh ACCP conference on antithrombotic and thrombolytic therapy for patients with AMI treated with alteplase, tenecteplase, or reteplase is 60 U/kg UFH as a bolus, but maximally 4000 U, followed by 12 U/kg/h (1000 U maximum) for 48 h, adjusted to maintain the aPTT in the 50–75 s range (Grade 1C). However, in a meta-analysis of UFH trials, UFH has not been shown to prevent death or re-infarction in STEMI patients receiving thrombolytic therapy and aspirin.¹³⁵

In the HERO-2 trial, the effect of bivalirudin vs. UFH together with 1.5 million units of SK and 150–325 mg of aspirin was examined in 17 073 patients with STEMI. Bivalirudin did not reduce mortality at 30 days compared with UFH. It did, however, reduce the rate of re-infarction within 4 days by 30%. Small increases were seen in mild and moderate bleeding in the bivalirudin arm.²⁵⁰ No further trials were undertaken with bivalirudin in STEMI.

Of the four randomized, double-blind studies comparing LMWHs with placebo in STEMI patients undergoing thrombolytic therapy with SK, three (AMI-SK, FRAMI, BIOMACS II) resulted in favourable outcomes in the LMWH group; due to the limited size of these studies, few outcome parameters (death and re-infarction at 7 and 30 days) were significantly different in the LMWH group compared with placebo (reviewed in Eikelboom *et al.*¹³⁵). The large randomized, double-blind, placebo-controlled CREATE study in 15 570 STEMI patients from China and India administered the LMWH reviparin twice a day (<50 kg: 3436 IU; 50–75 kg: 5153 IU; >75 kg: 6871 IU). The choice of the thrombolytic agents was left to the investigator; SK, UK, and t-PA were used. Most patients (97%) received aspirin, 55% clopidogrel, or ticlopidine. Thrombolytic therapy was given to 73% and direct PCI was used in 6% of patients. At 30 days, the death rate was 9.8% in the reviparin group and 11.3% in the placebo arm (95% CI 0.79–0.95), re-infarction 2.0 vs. 2.5% (0.62–0.95), stroke 1.0 vs. 0.8 (0.89–1.73), and life-threatening bleeding at 7 days 0.7 vs. 0.3% ($P < 0.001$). The authors concluded that the small absolute increase of life-threatening bleeding was outweighed by the reduction in mortality and re-infarction without a substantial increase in the overall stroke rate.²⁵¹

Until 2003, six studies were reported comparing LMWHs with UFH in STEMI patients treated with thrombolysis (ASSENT-2, ASSENT-3, ASSENT-3 PLUS, HART II, ENTIRE-TIMI and Baird *et al.*). In five studies, therapeutic doses of enoxaparin were given, in one dalteparin was used. Thrombolytic agents included SK or anisoylated plasminogen SK activator complex in one, t-PA in two, and tenecteplase (TNK) in three studies. A meta-analysis of these six studies revealed a significant (45%) reduction in re-infarction and a non-significant reduction in death at day 7 in patients treated with a LMWH. Similar results were obtained at 30 days. There was a non-significant increase of strokes at day 7, and a significant increase in minor bleeding, as well as a small increase in major bleeding in the LMWH arm (reviewed in Eikelboom *et al.*¹³⁵).

In the EXTRACT-TIMI 25 trial, 20 506 patients with STEMI were randomly allocated to receive enoxaparin throughout the index hospitalization or i.v. UFH for 48 h. All patients were to receive aspirin, and—at the discretion of treating physicians—SK, TNK, t-PA, or reteplase according to the manufacturer's instructions. The primary efficacy endpoint was death or non-fatal re-infarction through 30 days. This occurred in 12% in the UFH group and in 8.9% in the enoxaparin group (17% reduction in relative risk; $P < 0.001$). Major bleeding was more common in the enoxaparin arm (2.1%) than in the UFH group (1.4%; $P < 0.001$). The composite of death, non-fatal re-infarction, and non-fatal ICH (a measure of net clinical benefit) occurred in 12.2% of patients given UFH and in 10.1% of those given enoxaparin ($P < 0.001$).¹³⁶

One study evaluated the effect of fondaparinux in conjunction with thrombolysis. In the double-blind OASIS-6 trial, 12 092 patients with STEMI were randomized to fondaparinux, 2.5 mg once daily for 8 days, or placebo or UFH for 48 h followed by placebo for up to 8 days. Forty-five percent of patients were given a fibrin-specific thrombolytic agent, and 31% underwent primary PCI. Death or re-infarction at days 9 and 30 were lower in the fondaparinux than in the placebo/UFH group (7.4 vs. 8.9%, $P = 0.003$; 9.7 vs. 11.2%, $P = 0.08$). Severe haemorrhage was less common in the fondaparinux arm compared with the placebo/UFH groups (1.0 vs. 1.3%).¹⁴⁸ A subanalysis within the group of patients being treated with fibrinolysis ($n > 3000$) showed that there was no difference whether the fondaparinux patients got SK or fibrin-specific lytics.

Thus, in treatment regimens using thrombolytic therapy, a clear tendency appears to exist in replacing UFH with LMWHs, particularly enoxaparin, given for up to 1 week. Results with fondaparinux are also encouraging.

Finally, one study, the Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis (APRICOT)-2 trial evaluated the impact of a prolonged anticoagulation regimen as adjunctive to aspirin in the prevention of reocclusion and recurrent ischaemic events after fibrinolysis for STEMI.¹⁷⁰ Here, 308 patients receiving aspirin and i.v. heparin had a patent infarct-related artery (TIMI grade 3 flow) at coronary angiography <48 h after fibrinolytic therapy. They were randomly assigned to standard heparinization and continuation of aspirin alone or to a 3-month combination of aspirin with moderate-intensity VKAs, including continued heparinization until the target INR of 2.0 to 3.0 was reached. Angiographic and clinical follow-up were assessed at 3 months. Median INR was 2.6 (25–75th percentiles 2.1–3.1). Reocclusion (\leq TIMI grade 2 flow) was observed in 15% of patients receiving aspirin and VKAs compared with 28% in those receiving aspirin alone [relative risk (RR), 0.55; 95% CI 0.33–0.90; $P < 0.02$]. TIMI grades 0–1 flow rates were 9% and 20%, respectively (RR 0.46, 95% CI 0.24–0.89; $P < 0.02$). Survival rates free from re-infarction and revascularization were 86 and 66%, respectively ($P < 0.01$). Bleeding (TIMI major and minor) was infrequent: 5 vs. 3% ($P = \text{NS}$).¹⁷⁰ Therefore, as adjunctive to aspirin, a 3-month regimen of moderate-intensity VKAs, including heparinization until the target INR is reached, markedly reduces reocclusion and recurrent events after successful fibrinolysis. This conceptual study provides a mechanistic rationale to further investigate the role of prolonged anticoagulation after fibrinolytic therapy.

Current needs and future developments

Anticoagulants are a mainstay of cardiovascular therapy, both in the acute phase (mainly heparins) and in the long term (VKAs). They have allowed the take-off of cardiac surgery, permitting extracorporeal circulation, and are important adjuvant therapy in the performance of PCIs and in the management of ACS. Despite these certain merits, currently available anticoagulants have several shortcomings, including potentially improvable rates of bleeding and additional side effects not necessarily linked to their activity in inhibiting coagulation. Especially of concern is the use of VKAs. These drugs, despite widespread diffusion, remain problematic, mainly for the narrow therapeutic window, the extent of interactions with foods and other drugs, the need of frequent monitoring and adjustments of dosages, and poor patients' acceptance. Pharmacological research is currently making new anticoagulants available, of which the pentasaccharides and DTIs (including orally active molecules) have reached extremely promising phase III development. This document has been finalized a few months after the announcement that one such drug, the orally active DTI ximelagatran, has been voluntarily withdrawn by the manufacturer from further development, after having already been approved for the prevention of deep vein thrombosis in the setting of orthopaedic surgery, and after having been favorably tested in large phase II and phase III trials in NSTEMI-ACS and AF, due to hepatic side effects. Although the committee supports this prudent decision by the manufacturer, this leaves many hopes for alternative drugs unfulfilled. It is expected that newly developed orally active DTIs, similar to ximelagatran in terms of pharmacodynamic and pharmacokinetic properties, but potentially better tolerated, will not make their appearance on the market before 3 years from now. An even longer wait will probably be necessary for orally active FXa inhibitors, for which phase-III trials in heart disease are just starting. The committee underscores the therapeutic relevance of this area of pharmacological research and welcomes clinical trials of a number of newcomers, including the pentasaccharides, oral FXa inhibitors and DTIs. Eighty-three years after the first clinical use of heparin,²⁵² and 66 years after the clinical introduction of VKAs,²⁵³ we are at the verge of an unprecedented pharmacological revolution in this area, whereby safer drugs with low potential for food and drug interaction and simple, fixed dosing, without need of monitoring, are being evaluated. There are now several research developments that will likely lead to drugs finally able to meet many of the current needs. For the moment, the cardiologist needs to master currently available drugs, understanding mechanism of action, side effects, relative advantages, and management problems in depth. The cardiologist also needs to be aware of new developments and, while remaining alert in scrutinizing new drugs for the balance between real advantages and new problems connected with their use, should actively participate in the ongoing discussion on proper comparisons with older generation drugs.

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