Essential Guide to Blood Coagulation

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2nd Edition

Edited by

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WARNING: Always check that the prescribed dose is reasonable!

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Preface

The Swedish edition of this book, *Coagulation News*, has existed for many years. The English edition has been largely rewritten to include additional medical topics and recent developments in the field.

Essential Guide to Blood Coagulation is a practical guide to laboratory diagnosis and treatment of hemostatic disorders. The book covers both the stable and the acute stages of hereditary and acquired bleeding and thrombotic disorders. This edition includes a much revised chapter on new anticoagulants and a new chapter on antiplatelet drugs.

The book has been edited in cooperation with physicians now or previously employed at the Karolinska University Hospital and by doctors working at Danderyd Hospital and Södersjukhuset, Stockholm, Sweden.

Essential Guide to Blood Coagulation will appeal to interns, hematologists, anesthesiologists, cardiologists, neurologists, pediatricians, laboratory doctors, gynecologists, surgeons, primary care physicians, dentists, and students. It can also be used by nurses, hospital chemists, biomedical technicians, and midwives.

Jovan P. Antovic, Margareta Blombäck

Abbreviations

ACoTS	Acute coagulopathy of trauma and shock
ACS	Acute coronary syndrome
ACT	Activated clotting time
ADH	Antidiuretic hormone
ADP	Adenosine diphosphate
AFLP	Acute fatty liver of pregnancy
APC	Activated protein C
APT	Activated partial thromboplastin
ASA	Acetylsalicylic acid
AUC	Area under the concentration curve
AVK	Anti-vitamin K drugs
BMI	Body mass index
CABG	Coronary artery by-pass grafting
CAD	Coronary artery disease
CRP	C-reactive protein
CT	Computed tomography
DES	Drug-eluting stent
DIC	Disseminated intravascular coagulation
DVT	Deep venous thrombosis
ECT	Ecarin clotting time
EDA	Epidural anesthesia
EDTA	Ethylene-diamine-tetra-acetic acid
eGFR	Estimated glomerular filtration rate
ET	Essential thrombocytosis
ETP	Emergency trauma packages
HELLP	Hemolysis, elevated liver enzymes, low platelet counts
HIT	Heparin-induced thrombocytopenia
HRT	Hormone replacement therapy
HUS	Hemolytic uremic syndrome
INR	International normalized ratio
ISI	International sensitivity index
ITP	Idiopathic thrombocytopenic purpura

IUFD	Intrauterine fetal death
IV	Intravenous
LA	Lupus anticoagulant
LDA	Low-dose aspirin
LMH	Low molecular weight heparin
MOF	Multiple organ failure
MPHV	Mechanical prosthetic heart valve
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
NOAC	New oral anticoagulant drug
NSAID	Nonsteroidal anti-inflammatory drug
NSTEMI	Non ST-elevation myocardial infarction
OC	Oral contraceptives
PAI-1	Plasminogen activator inhibitor
PCC	Prothrombin-complex concentrate
PCI	Percutaneous coronary intervention
PCR	Polymerase chain reaction
PE	Pulmonary embolism
POCT	Point-of-care test
PT	Prothrombin time
PTA	Percutaneous transluminal angioplasty
PVT	Portal vein thrombosis
rt-PA	Recombinant tissue plasminogen activator
SC	Subcutaneous
SLE	Systemic lupus erythematosus
SSRI	Selective serotonin re-uptake inhibitor
STEMI	ST-elevation myocardial infarction
TAFI	Thrombin activatable fibrinolysis inhibitor
TAR	Thrombocytopenia with absent radius
TAT	Thrombin-antithrombin
TDM	Therapeutic drug monitoring
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
TIA	Transient ischemic attack
TM	Thrombomodulin
t-PA	Tissue plasminogen activator
TSH	Thyroid-stimulating hormone
TTP	Thrombotic thrombocytopenic purpura
UFH	Unfractionated heparin
VKA	Vitamin-K antagonist
VTE	Venous thromboembolism
VWD	von Willebrand disease
VWF	von Willebrand factor

GENERAL HEMOSTASIS

PART 1

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Schematic presentation of the hemostatic system

Nils Egberg

CHAPTER 1

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The formation of fibrin via a series of reactions within the coagulation system is central in the hemostatic process (Figure 1.1). Coagulation is initiated *in vivo* mainly through exposure of tissue factor, TF, on damaged tissue or endothelium. Activated monocytes can also expose TF. TF binds FVII/VIIa (a = activated). The TF-FVIIa complex initiates coagulation by activating FIX and FX. The activated FX transforms prothrombin into thrombin. The process continues, mainly as surface-bound enzymatic reactions, where activated platelets probably offer the phospholipid surface to which coagulation factors (enzymes as well as co-factors) can bind, for example by means of Ca^2 bridges. Moreover, the coagulation inhibitors (antithrombin, activated protein C (APC)) quickly react with non-surface connected enzymes and co-factors, which help to limit the spread of fibrin formation. Thrombin cleaves off fibrinopeptides A and B to form fibrin monomers, which then polymerize and cross-link, by the action of FXIII, to form an insoluble fibrin network.

The formation of thrombin is accelerated initially by a positive feedback, whereby the thrombin activates FVIII and FV in order to produce more thrombin. Thrombin also promotes coagulation by activating platelets and endothelium.

The physiological importance of the contact activation system for blood coagulation is partly unclear. It has been suggested that when the FXII initiated coagulation is activated *in vivo* it could lead to excessive fibrin formation resulting in thromboembolic manifestations.

The thrombin specificity is modified by its binding to the endothelial receptor thrombomodulin (TM). The TM–thrombin complexes then

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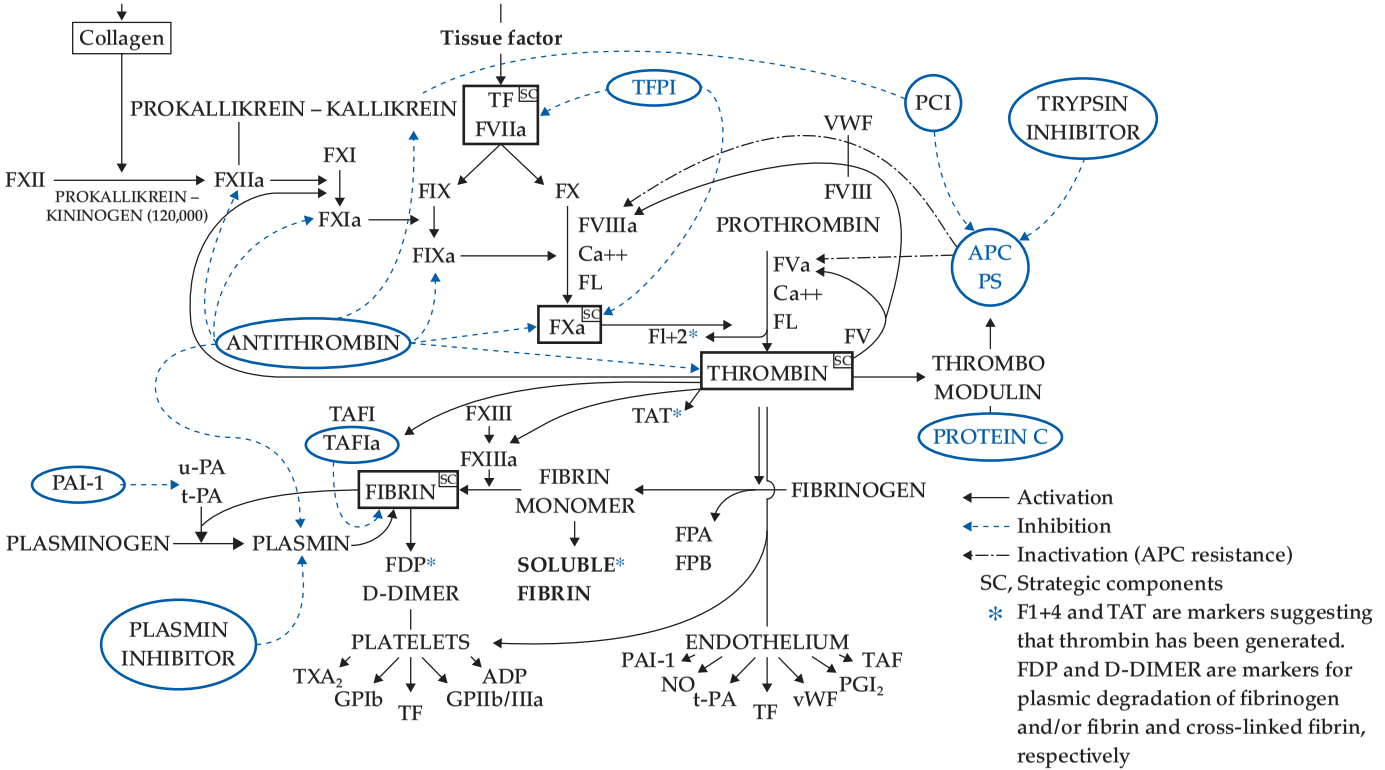

Figure 1.1 Cell and tissue injury.

activate protein C into APC, which then decomposes FVIIIa and FVa. Consequently, thrombin is involved both in the *stimulation and inhibition* of the hemostatic process.

A model for cell-associated blood coagulation has also been proposed where the reaction sequence has been divided into three stages:

1 The **initiation phase** where a small amount of thrombin is generated via the TF-induced pathway to activate platelets and coagulation co-factors FV and FVIII to their activated forms.
2 The **priming phase (amplification phase)** where coagulation factors bind to receptors and phosphatidylserine-enriched surfaces such as activated platelets.
3 The **propagation phase** where thrombin is formed via both the contact and TF pathways in order to generate large amounts of thrombin that will transform fibrinogen to fibrin.

Antithrombin and APC are the most important coagulation inhibitors. Another is tissue factor pathway inhibitor (TFPI) but its physiological role is not yet entirely clear. Antithrombin inhibits thrombin by irreversible complex binding, thrombin-antithrombin (TAT) complexes. In a similar way, antithrombin also inhibits most of the activated coagulation factors, except for FVIIa, with different affinities. Heparin accelerates the reaction about 500 times.

It has recently been discovered that thrombin also has antifibrinolytic effects. It activates thrombin activatable fibrinolysis inhibitor (TAFI) to its active form, thereby inhibiting fibrinolysis.

The activation of fibrinolysis is probably secondary to the activation of coagulation. Tissue plasminogen activator (t-PA) is released from the endothelium and transforms plasminogen into plasmin. The reaction is substantially accelerated by the presence of fibrin, and plasmin formation normally occurs only locally on and in a fibrin clot. Plasmin breaks down fibrin and fibrinogen into a number of fragments, fibrin(ogen) degradation products, for example X, Y, D and E fragments, and cross-linked fibrin fragments, fibrin D-dimers. t-PA is inhibited by the release of plasminogen activator inhibitor (PAI-1) from the endothelium. Free plasmin, not bound to fibrin, is rapidly inhibited by the plasmin inhibitor. Plasmin inhibitor and plasmin form an enzymatically inactive complex.

Proposals for sampling instructions

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CHAPTER 2

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Points to note prior to sampling

The concentrations of components of the hemostatic system often vary with the patient's condition, for example infection, emotional stress, physical exertion (e.g. rush to keep an appointment), lipid concentration in plasma, etc. Sampling conditions should be standardized as far as possible to minimize sources of error (see [1] and following).

- *Sitting up/lying down.* Due to changes in hydrostatic pressure, the concentrations of high molecular proteins and blood cells vary according to whether the patient is sitting up or lying down (hematocrit is as much as 15% higher when sitting up). A new balance is reached fairly quickly (after 15–20 min).
- *Diurnal variations* occur for several factors such as PAI-1, which peaks late at night.
- *Acute phase reactants.* Many hemostatic components, such as FVIII, von Willebrand Factor (VWF), PAI-1 and fibrinogen, are acute phase reactants (i.e. increased by inflammation, infection, surgery, etc.).
- *Intraindividual variations* occur mainly for FVIII and VWF but also for FVII. Thus, mental stress and physical activity increase the concentrations of FVIII and VWF many times over.
- *Smoking and age* affect the levels of several coagulation factors (e.g. VWF and fibrinogen are increased).
- *Estrogen.* High-dose contraceptives (and other hormone drugs) also affect coagulation and fibrinolysis (e.g. FVIII, VWF and fibrinogen are

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increased and antithrombin, protein C and FVII are lowered at high levels of estradiol).

- *Influence of blood group.* The level of FVIII is about 30% lower in blood group O and the difference for VWF (earlier known as FVIII R:Ag) is somewhat greater. Consequently, levels near the lower reference limit of these factors imply that the patient can be a normal variant or have mild von Willebrand disease (VWD).

Sampling time and patient preparation

See recommendations by ISTH/SSC Subcommittee on Women's Health Issues [1].

The patient should be calm and relaxed, arrive at the sampling room without hurrying and sit down there for a while (15–20 min) before samples are drawn.

The patient should have fat-fasted since midnight, or for at least 6 hours. Samples should be taken before 10 am with the patient sitting down. In an investigation for bleeding diathesis, the patient should not have taken **acetylsalicylic acid** (ASA) or clopidogrel for the previous 7–10 days or other antiphlogistic nonsteroidal anti-inflammatory drugs (NSAIDs) for the previous 1–3 days. If these drugs have been prescribed, they should not be withdrawn without consulting the physician in charge.

In an investigation of bleeding tendency, fertile women should preferably be sampled during menstrual days 1–4. It is then easier to diagnose a suspected mild VWD. Contraceptives and other hormone drugs should have been withdrawn, if possible, for at least 2 months, preferably 3 months. In women who have been pregnant, a deficiency cannot be determined exactly until breastfeeding has ceased and menstruation has become regular. If these recommendations are not followed, mild defects may not be detected.

To monitor the effect of heparin (unfractionated heparin (UFH)/low molecular weight heparin (LMH)) by determining anti-FXa, samples should be drawn 3 hours after an injection in patients receiving "low-dose" prophylactic treatment (1 injection per day) and prior to an injection in "high-dose" treatment (2 injections per day). In treatment that is not prophylactic, samples are usually taken prior to next injection.

A coagulation investigation after a thromboembolic complication should be performed, if possible, not less than 3 months after the latest event in order to avoid an acute phase reaction. For example, the amount of antithrombin decreases about 25% after 4–5 days of i.v. UFH/LMH treatment. Separate coagulation factor analyses cannot always be performed, since UFH/LMH interferes with the test systems. During vitamin-K antagonist (VKA) treatment, it is not possible to determine the basic

levels of the vitamin K-dependent coagulation factors prothrombin, FVII, FIX and FX or the coagulation inhibitors protein C and protein S. If the diagnosis of a hereditary defect is an urgent matter, investigate parents or other relatives with a similar history. The medication could also be changed from VKA drugs to UFH/LMH at least 2 weeks prior to sampling combined with a short break in heparin treatment just before sampling.

If the patient is being treated with VKA drugs or UFH/LMH, you must consider the above. Consult a coagulation expert.

New antithrombotic agents, for example FXa and thrombin inhibitors, will most likely interfere with many functional coagulation assays and should preferably be withdrawn before investigation. However, consult the doctor in charge of the patient about how to proceed.

Mutation analyses, for instance of the FV Leiden mutation in the factor V gene 1691G>A and of the prothrombin gene mutation (2021G>A), can of course be performed regardless of whether the patient is on treatment.

Referrals for coagulation analyses

Remember to:

- provide a short case history, your question, results of any earlier analyses and list the analyses that you require;
- state the sender's name with full address, and include the name of your hospital and who is to be invoiced;
- always give your telephone/fax number/email if you want a quick reply;
- always state the date and time of the blood sampling and whether the patient is on VKA drugs, UFH/LMH (even just an occasional flush), or other anticoagulants;
- state if the patient has received a transfusion of blood, plasma or blood products during the past month.

Sampling

Analyses of plasma

- The sample should be taken by direct vein puncture, not from heparinized catheters or from an infusion apparatus for administering heparin (see also section on "Technique"). Stasis should be moderate (or nil) and the blood should flow easily.
- Samples that cannot be analyzed right away must be centrifuged etc. (see section on "Technique") and the plasma frozen in 3–4 portions of 0.6 mL for each analysis in small plastic tubes at -70°C.

- The outcome of coagulation analyses can be markedly affected by the sampling conditions.
- *For an investigation of thrombosis and bleeding,* usually four citrate tubes, each containing 5 mL, are taken and the plasma is separated into nine small plastic tubes each containing 0.6 mL. For a single analysis, take one citrate tube and separate the plasma into 3–4 small tubes. *When sampling from small children,* special 2 mL citrate tubes can be used. Separate the plasma into as many tubes as possible, each containing 0.3 mL.
- *For mutation (DNA) analyses,* use one EDTA whole-blood plastic tube (5 mL) (if only glass tubes are available, the blood should be transferred to plastic tubes prior to freezing).
- *For DNA analyses in children,* use one EDTA whole-blood plastic tube, about 2 mL whole blood (for handling, see earlier point on sampling).

Technique

1. The patient should be sitting up. If this is not possible, remember to have the patient in the same position next time so that the results can be compared. Also see above.
2. Take the sample by direct vein puncture, not by an indwelling cannula, with minimal stasis. If an indwelling cannula has to be used, discard the first 5–10 mL of the blood. The first tube cannot be used for coagulation analyses.
3. The blood should flow fast. If not, note the deviations, for instance on the referral.
4. Use 5 mL vacuum tubes intended for coagulation tests (currently siliconized vacuum tubes), containing 0.5 mL of 0.109 mol/L trisodium citrate (9 parts of blood + 1 part of trisodium citrate), pH 7.4. (If blood is taken in open tubes, the proportions of blood to citrate should be the same.) Note that only filled tubes (±10% deviation) are accepted for further handling. For DNA, see section on "Sampling" above.
5. Important to mix citrate and blood properly. Tilt the tubes 5–10 times.
6. Centrifuge citrated blood samples as soon as possible (preferably within 30 min) at 15°C; or alternatively, at room temperature for 15 min at 2000 *g* (alternatively, 10 min at 3000 *g*). Samples for determination of heparin (UFH/LMH) with anti-FXa method (N.B. remember to state any medication that the patient is being treated with), of lupus anticoagulant and of platelet microparticles must be centrifuged *twice* in order to obtain platelet-free plasma. Note that this plasma can also be used for testing other hemostasis components, such as APC resistance, and for research analyses of plasma samples.

7 Centrifuging twice involves pipetting the plasma after the first centrifugation into a new empty tube, which is then centrifuged for 15 min at 2000 *g*. The supernatant after the second centrifuging is the test material, that is, platelet-free plasma.
8 Collect the plasma, *no closer to the cells than 10 mm* (do not disturb the platelets). If there is only one tube of citrate blood, divide the plasma into 0.3–0.6 mL portions in small plastic tubes. If there are several tubes of citrated blood, mix the plasma from all the tubes in a separate plastic tube before dividing the plasma into portions, in order to avoid variations in the measured values.
9 Try to get two tubes for freezing for each analysis. Since additional assays often have to be performed, be sure to freeze the plasma in at least four extra small tubes in order to avoid new sampling. Note this on the referral to the sampling unit.
10 Label the tubes with the date, time, number and name or other identification.
11 Use a rubber band to bundle all the tubes for each patient.
12 Deep-freeze the plasma at -70°C within 1 hour after sampling.

For DNA investigation (genetic analyses)

Analyses of factor V Leiden (1691G>A), prothrombin (2021G>A), FVIII and VWF mutations, are done with the DNA from nucleated cells from EDTA blood. EDTA blood can withstand storage in a refrigerator at 6°C for about 3 days. It can also be frozen provided the blood (if it arrives in a glass tube) is transferred first to a plastic tube. One EDTA tube (5 mL) with whole blood is enough for several mutation assays. Note that the patient should be identified as for blood group testing.

Reference

1 Blombäck M, Konkle BA, Manco-Johnson MJ, *et al.*; ISTH SSC Subcommittee on Women's Health Issues. Preanalytical conditions that affect coagulation testing, including hormonal status and therapy. *J Thromb Haemost* 2007; 5:855–858.

Laboratory investigations

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CHAPTER 3

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Nomenclature

The nomenclature in this book has been adapted from the usage at the Karolinska University Laboratory. It is essentially the nomenclature recommended by the Scientific and Standardization Committee (SSC)/International Society on Thrombosis and Haemostasis (ISTH), International Union of Pure and Applied Chemistry (IUPAC) and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC).

The most common assays of hemostasis are listed in Box 3.1. The "investigation kit" proposed below may be a suitable starting point. If the analyses do not indicate pathology, additional analyses can be performed. Alternatively, if the patient's symptomatology is indefinite, the investigation can end here.

In the event of problems in interpreting the analyses or deciding what to do next, contact your own coagulation laboratory or the hospital's coagulation unit in order to discuss.

Box 3.1 Frequently used assays of hemostatic function and hemostatic components

Screening analyses

Pt-bleeding time	P-APT time
B-platelet aggregation (Multiplate®)	P-fibrinogen
CB/B-platelet count	P-fibrin D-dimer
	P-soluble fibrin
	P-antifactor Xa

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CB/P-PT(INR)	P-antithrombin
P-factor VIII	Heparin/PF4 antibodies (ID-PaGIA)
Special analyses	
Coagulation factors	**Platelet function**
P-prothrombin (FII), factor VII, factor X	P-platelet aggregation
P-factor V	P-factor VIII P-heparin/PF4 antibodies (HIT) IgG specific ELISA
P-factor IX	**Fibrinolysis**
P-factor XI	P-plasminogen
P-factor XII	P-antiplasmin (plasmin inhibitor)
P-factor XIII	P-t-PA
P-VWF activity, antigen	P-PAI-1
Anticoagulants	
P-Coag surface-induced antibody – circulating anticoagulants (screening)	
P-factor VIII, antibody	
P-factor IX, antibody	**Markers for coagulation activation**
P-VWF, antibody	P-TAT complex
P-lupus anticoagulants (DRVVP and lupus sensitive APT time)	P-prothrombin fragment 1 + 2
Protein C anticoagulant system	**DNA analyses: genetic investigations**
P-protein S (free or total)	Hemophilia, VWD
P-protein C	Factor V genotype (1691G>A)
P-APC resistance	Prothrombin, genotype (20210G>A)

Notes

- P, measurement made in plasma; S, measurement made in serum; Pt, sample analyzed directly on patient; CB, capillary blood sampling; B, whole blood measurements.
- Strictly speaking, the Roman figure should be preceded by the words "coagulation factor," for example "coagulation factor VIII." If there is no risk of a misunderstanding, however, this can be abbreviated to, for instance, "factor VIII" or "FVIII."
- The prefix "anti-" was often used for inhibitors but nowadays this is done only for components that are antibodies. There are two exceptions: antithrombin (III), which for historical reasons has kept its name, though III has been dropped; and α2-antiplasmin, which has usually kept its former name (the recommendation would be "plasmin inhibitor").
- The old abbreviations of the following components are used in this manual because coagulation specialists have not yet reached a consensus about more appropriate solutions.

APT time. Should instead be an abbreviation of "coagulation surface-induced time," i.e. the time of activation on a surface.

P-PT, prothrombin time. Should instead be an abbreviation of "coagulation, tissue factor induced time." It denotes the coagulation time obtained when tissue factor is added to the sample, and measures the sum of the coagulation factors prothrombin (FII) + FX + FVII. The laboratories have currently agreed to use P-PT(INR), as is done in this manual.

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SSC/ISTH. Nomenclature of quantities and units in thrombosis and haemostasis. *J Thromb Haemost* 1994; **71**:375–394.

Properties and units in the clinical laboratory sciences. V. Properties and units in thrombosis and haemostasis. *Pure Appl Chem* 1997; **69**(5):1043–1079.

An updated version can be found at: www.IUPAC.ORG/publications/pac/1997/pdf/6905x1043.pdf (last accessed November 2012).

Reference intervals for laboratory investigations

Consult your laboratory.

Screening analyses

Screening analyses undertaken in hemostatic contexts are usually performed in general clinical chemistry laboratories. They are available 24 h daily and include CB/B-PLT, P-APT time, CB/P-PT(INR), P-fibrinogen and, if applicable, Pt-bleeding time. P-fibrin D-dimer is used for ruling

out venous thromboembolism (VTE). If disseminated intravascular coagulation (DIC) is suspected, usually P-fibrin D-dimer and P-antithrombin are also measured (P-factor VIII can also be determined). P-heparin/PF4 antibodies (ID-PaGIA) are used for screening and ruling out heparin-induced thrombocytopenia (HIT) diagnosis.

Pt-Bleeding time

Reflects a defect in primary hemostasis, for example blood vessel and platelet function. Bleeding time is usually measured with an incision on the lower arm (modified Ivy – ask your laboratory).

Note: Measurement of bleeding time is difficult to standardize and must therefore be performed by skilled personnel. Several investigations show that it cannot be used to predict bleeding during surgery. There is an intraindividual variation in bleeding time. Bleeding time increases with decreasing EVF (hematocrit), for example during pregnancy (normally not above the upper reference range). So-called isolated increased bleeding time also occurs (all other tests normal). Properly taken anamnestic data may be more important for the diagnosis of bleeding tendency than bleeding time. Therefore Pt-bleeding time is not used in all laboratories as a routine screening test for bleeding disorders.

Other proposed analyses when bleeding time is increased in spite of normal platelet count

Exclude drug effects (ASA, clopidogrel, NSAID). Complete with the following:

- VWF antigen/functional assay
- confirm the increased bleeding time
- in severe cases, possibly also platelet function tests, for example platelet aggregation test.

Treatment with desmopressin can shorten bleeding time and improve hemostasis, see Chapter 4.

B-Platelet aggregation (Multiplate)

Several whole blood platelet function assays which can give potentially more valid information about platelets function than Pt-bleeding time have recently become available. Multiple impedance aggregometry (Multiplate) is in use as a routine analysis at Karolinska University Laboratory and available 24 h.

The method is generally used as a screening of platelet function (hereditary or acquired platelet functions disorders) and monitoring of treatment with antiplatelet drugs (ASA, clopidogrel, prasugrel, GP IIb/IIIa antagonists). It enables rapid control or exclusion of drug- or disease-related platelet function disorders in trauma or before surgery.

B/CB-PLT (platelet particle concentration = platelet count)

A sufficient number of platelets is a requirement for good primary hemostasis.

Thrombocytopenia is a condition in which platelet count is below 150×10^9/L. It can be hereditary or acquired (see Chapter 4). An increased risk for bleeding is rare at platelet count above 50×10^9/L. The risk of bleeding is often increased at lower levels than that (particularly below 20 and especially below 10×10^9/L). Platelet concentrate is usually needed at considerably lower levels. The risk of bleeding increases as platelet function decreases and/or fibrinolysis increases.

Thrombocytosis is a condition in which platelet count is above 400×10^9/L and may be associated with either thrombosis or bleeding risk.

P-APT time

Reflects a defect in the part of the hemostatic system initiated by surface activation, previously called the "intrinsic coagulation system." Increased activated partial thromboplastin (APT) time is seen in deficiencies of FXII (all levels), FXI, prokallikrein, FIX, FVIII, FX, FV, prothrombin, and fibrinogen. In the latter deficiencies, the APT time does not increase unless the deficiencies are severe or moderately severe. The APT time can be normal even at factor concentrations 15–30% of normal (0.15–0.30 IU/mL).

Specific coagulation factor analyses should be performed if a disturbance is suspected clinically even though APT time is normal.

APT time is *not prolonged* in deficiency of FVII or FXIII.

APT time is *often prolonged* in the presence of lupus anticoagulant/phospholipid antibodies. Other acquired circulating inhibitors (associated both with bleeding or thrombosis) may induce prolongation of APT time. APT time is also prolonged during the treatment with standard heparin and may therefore be used for monitoring of such treatment (1.5–2-fold increase of APT time recommended as target therapeutic values).

Interpretation of prolonged APT time is not always easy and may be a problem even if the patient's clinical status (presence of bleeding or thrombosis) is known. However, prolonged APT time may commonly be found during routine preoperative screening in patients without known clinical abnormalities. In such cases mixing test (performance of APT time in mixtures of the patient's and normal pool plasma after incubation) may give additional information and enable a differentiation between factor deficiency (if APT time normalizes in mixture) or circulating inhibitor (e.g. lupus anticoagulant) if normalization does not occur.

B/CB prothrombin complex

Reflects a defect in the system or systems activated by the tissue factor. This used to be called the "extrinsic coagulation system."

The so-called prothrombin complex consists of prothrombin (FII), FVII, FIX and FX. These coagulation factors are formed in the liver and for their synthesis are dependent on vitamin K. The common methods in Scandinavia and Japan measure the sum of the above-mentioned factor activities, except for factor IX. The prothrombin complex (PC) can be determined in blood (B), capillary blood (cB) and plasma (P).

Prothrombin time (PT) methods vary throughout the world. Most laboratories use simple thromboplastin reagents (Quick "plain reagents"), in which case the test is also dependent on the contents of FV and fibrinogen in the patient's plasma. Adsorbed bovine plasma containing these factors is added to the Owren reagent ("combined reagents"). The combined reagents are mostly easier to standardize.

PT(INR)

Because all reagents, Quick as well as Owren reagents, contain different thromboplastins, the characteristics of these measuring methods tend to differ. However, the numerical value of a test can be compared with another test with the aid of an international thromboplastin standard, against which every new reagent must be calibrated.

This procedure enables us to express test results as an international normalized ratio (INR). Log INR = ISI × log patient's coagulation time/reference plasma's coagulation time. Alternatively, INR = (patient's coagulation time/reference plasma's coagulation time)^{ISI}.

The International Sensitivity Index (ISI) is an experimentally obtained value for every reagent-instrument combination in use. The ISI value for thromboplastin reagents is recommended to be close to 1.0, which is ideal. INR was adopted by the SSC of the ISTH in 1999. The reference value for PT(INR) is <1.2 (equivalent to over 67% on the earlier percentage scale). An alternative INR calibration for the Owren type of PT by means of plasma calibrators with assigned INR values was suggested by Lindalhl *et al.* (2004)[1].

A full list of all comparisons can be found on the Equalis web site: www.equalis.se/INR.

PT determinations expressed in INR are internationally accepted only for control of VKA treatment under stable conditions. Experience indicates that results expressed as INR can also be used for estimating liver function or other types of influence on the measurement system.

Spontaneous increase or decrease in PT(INR)

Check liver status. Complete with FVII, FX and FII (prothrombin) determinations, and determination of cardiolipin antibodies/lupus anticoagulant. If results disagree, contact a coagulation specialist.

Intravenous injection of vitamin K will normalize P-PT(INR) at deranged adsorptions and in VKA treatment. Note that the full effect occurs after at least 12–16 h in adults but after just a couple of hours in newborns. Normalization seldom occurs if the liver is damaged.

Note that increased PT(INR) can indicate a corresponding fall in FVII, to which the test is normally most sensitive. On the other hand, deficiency of prothrombin or FX can be more serious than shown by PT(INR) (e.g. FX 0.20 U/mL = PT(INR) 1.3).

P-fibrinogen

Decreased concentration of fibrinogen (below 1 g/L) can cause bleeding. It may occur due to increased consumption/degradation in serious DIC or due to decreased synthesis in evident damage to the liver.

Hereditary fibrinogen deficiency or fibrinogen with an abnormal structure (e.g. with replacement of a specific amino acid due to a mutation) can also cause a bleeding tendency but is very rare. In these cases there is a prolonged thrombin and/or batroxobin time.

In fibrinolytic (thrombolytic) therapy the fibrinogen level *usually decreases*. In certain situations the therapeutic effect of fibrinolytic therapy can be monitored and evaluated by measuring fibrinogen. Note that the samples must be analyzed without delay so that the fibrinolytic process does not continue *ex vivo* and result in a "falsely" low fibrinogen level.

Elevated concentration of fibrinogen in plasma is observed, for example, in an inflammatory reaction (acute phase protein). The elevation lasts longer postoperatively, for instance, than is the case with other acute phase proteins, like C-reactive protein (CRP) and orosomucoid, due to differences in the regulation of biosynthesis and elimination from the blood. An elevated level is also normally seen in *pregnancy.*

An elevated level is associated with an increased risk of myocardial infarction and cerebral thrombosis. Very high levels can be seen in, for example, sepsis. *Note*: sepsis may be associated with DIC and a single fibrinogen value may be falsely normal in spite of significant consumption. Repeated measurements of fibrinogen concentrations should therefore be made.

Several hereditary mutations that can cause a venous thrombosis are also described.

Fibrinogen detection is based on the method in which thrombin is added in excess, and the clotting time is measured (Claus method). Rapidly formed fibrin polymerizes into a visible clot. Changes in absorbance at clot formation are registered using a spectrophotometer. The time needed for clot formation is inversely proportional to the concentration of fibrinogen in the sample.

Immunological methods for fibrinogen determination using both mono- and polyclonal antibodies and based on nephelometry are also available but they measure fibrinogen concentration which does not necessarily correspond with the activity.

International calibration standards for fibrinogen are available.

S-Soluble fibrin (SF/FM)

Fibrin monomers (FM) are formed after fibrinopeptides A and B have been cleaved off by thrombin. Some fibrin monomers will not polymerize to fibrin clots and can be measured in the circulation. Soluble fibrin (SF) is another name for FM and circulating oligomers of FM. When coagulation proceeds there is a polymerization of fibrin, which is then stabilized by the coagulation factor XIIIa, enzymatically cross-linking fibrin molecules.

SF can be used as a marker for early activation of the coagulation and may have better specificity for intravascular coagulation than the D-dimer (which is a product of plasmin degradation of cross-linked polymerized fibrin). SF should be analyzed in hypercoagulable conditions, for example sepsis, multiple trauma, surgery, malignancy, or pregnancy complications. It may also be analyzed in patients on Extra Corporal Membrane Oxygenation. SF may be a useful marker for diagnosis and monitoring of disseminated intravascular coagulation (DIC). The immunological automated quantitative turbidimetric SF assay based on latex agglutination is currently available.

S-FDP/P-fibrin D-dimer

A marker of hypercoagulation and fibrinolysis, which reflects increased fibrinolytic degradation of increased amounts of intravascular fibrin.

Fibrin D-dimer is primarily *a marker of increased coagulation.* Fibrinolysis is seldom so suppressed that fibrin D-dimer levels are not elevated in connection with an ongoing coagulation activity. Fibrin(ogen) degradation products (FDP) are fibrinolytic products from fibrin as well as fibrinogen. Fibrin D-dimer is a specific degradation product of cross-linked fibrin – an elevated level is present at fibrin formation followed by fibrinolysis. Levels of D-dimer are frequently elevated in medically severely sick patients, post-traumatically and postoperatively, as well as in DIC and in pregnancy toxicosis. High levels of degradation products of fibrin or fibrinogen (e.g. in thrombolytic treatment) inhibit platelet function and can therefore contribute to an increased bleeding tendency. Elevated levels of fibrin D-dimer are also almost always observed in DVT/LE.

The great value of this test in thrombosis diagnosis is the high probability with which a negative test can exclude thrombosis in outpatients, especially in combination with a clinical calculation of probability of the type score-based diagnostic algorithm (compare Wells' score) (www.sbu.se). An increased fibrin D-dimer level is, however, more difficult to evaluate and cannot be used to predict the presence of a thrombosis.

Automated quantitative turbidimetric assays based on latex agglutination with a sensitivity level similar to that of ELISA (up to 99%) are widely available for the detection of D-dimer. However, some methods for measuring D-dimer have a relatively high detection limit and do not identify the minor elevations that sometimes occur in a thrombotic disease. Contact your laboratory concerning the detection limit (and the clinical prediction capacity). It is desirable to have a detection level of about 100 μg/L, which is above the upper reference limit in healthy individuals. However, D-dimer methods are poorly standardized and numerical values from different methods can usually not be compared.

Note that the outcome of the test also depends on the examined population, the patient's age, the duration of the thrombosis and its extent. The fibrin D-dimer level is normally elevated (up to twice) during *pregnancy* (see Chapter 14). The level is even more elevated in pre-eclampsia but not so evident in intrauterine growth defect. The level rises with age (for instance, the level is 2–5 times higher in those over 60 years than in younger individuals). In severely ill (hospitalized) patients, the test is of little value for diagnosing thrombosis. The half-life in healthy individuals is normally 15–30 h.

P-antithrombin

Antithrombin is the most important inhibitor of the coagulation enzymes thrombin and FXa, but also of FXIIa, FXIa, and FIXa. Some studies indicate that antithrombin also inhibits kallikrein and plasmin. The physiologic importance of this is not clear.

The activity of antithrombin increases dramatically in the presence of UHF and LMH.

Hereditary deficiency leads to an increased risk of thrombosis. Acquired deficiency, also leading to increased risk of thrombosis, is seen in DIC, sepsis, obstetric complications, heparin treatment for more than 4–5 days, liver damage (antithrombin is synthesized in the liver), malignancy, high-dose estrogen treatment and nephrosis. The level may be slightly elevated during VKA treatment. Antithrombin levels in plasma do not change during a normal pregnancy. However, the level often decreases in pre-eclampsia.

Both antigen and activity of antithrombin can be measured. Antigen is usually determined in special coagulation laboratories using antibody based latex agglutination assays. Both thrombin- and factor Xa-based methods are used for determination of the activity. Neither of them is fully sensitive to all potential mutations behind type II deficiency but it has been shown that the FXa-based method (which is in use in our laboratory) may be more appropriate for routine use.

P-anti-Xa analysis to be used in monitoring heparin and LMH treatment

P-heparin or P-LMH-heparin is the former name of an assay that is now called anti-factor Xa because several similar anticoagulant drugs (e.g. new oral Xa inhibitors rivaroxaban, apixaban) can be measured with the same test system. The assay measures the inhibiting effect of UFH, LMH, etc. on FXa using a chromogenic substrate. However, in order to obtain relevant values for different LMH, the assay mostly has to be calibrated against the corresponding anticoagulant drug and/or LMH.

P-heparin/HPF4 for screening of heparin/PF4 antibodies in HIT with ID-PaGIA HPF4 method

Heparin-induced thrombocytopenia (HIT) is a severe, potentially limb- and life-threatening immune-mediated adverse drug reaction to unfractionated heparin and/or low molecular weight heparin (see Chapter 16). ID-PaGIA HPF4 assay with high-density polymer particles coated with heparin/PF4 complex, which reacts with antibodies in plasma, is a rapid screening method and in combination with clinical 4Ts score may be used for ruling out HIT diagnosis. (4T score: thrombocytopenia, time (after exposure to heparin), thrombotic manifestations, thrombocytopenia due to other possible causes.)

Special analyses

Coagulation factors

P-prothrombin (FII), P-factor VII (FVII), P-factor X (FX)

Low levels are mostly found in connection with VKA treatment, liver damage and, in the case of FX, sometimes in amyloidosis. A pronounced hereditary deficiency is very rare for FX and prothrombin but entails a severe bleeding tendency. Hereditary FVII deficiency is somewhat more common but even its severe form seldom leads to bleeding symptoms and does not seem to protect against thrombosis.

P-factor VII and P-factor VII activated

An increased concentration of FVII has been reported to increase the risk of myocardial infarction. The significance of FVII and activated FVII (FVIIa) has not, however, been sufficiently documented.

P-factor V (FV)

Total or partial hereditary FV deficiency is rare. Total deficiency leads to bleeding symptoms similar to those in severe hemophilia.

P-factor VIII (FVIII)

A low level of FVIII is present in patients with hemophilia type A, carriers of this disease, all patients with severe VWD as well as many with a moderate or mild form.

A consumption-dependent deficiency is often found in DIC with bleeding. FVIII analysis is relatively quick and should be performed if there is a severe bleeding. The possibility of an anticoagulant should be considered if severe bleeding is inexplicable or a prolonged APT time is discovered by chance. These anticoagulants are often turned against FVIII. They should always be assessed when FVIII is low or undetectable in patients who have previously been considered healthy, with no bleeding disorders.

The concentration of FVIII roughly doubles in a normal pregnancy.

As an inflammatory reaction the levels of FVIII and VWF often increase in parallel. Elevated levels of these factors, due to inflammation or other causes, probably favors coagulation and is associated with an increased risk of DVT/LE. It is also an independent predictor of recurrence. An elevated FVIII level is sometimes inherited but no genetic explanation has been found.

P-factor IX (FIX)

A low FIX level is present in patients with hemophilia B, in carriers of this disease, and in patients with liver damage, etc. (see earlier section on prothrombin complex and Chapter 4).

P-factor XI (FXI)

Factor XI deficiency is common in Jews of east European origin. The disorder often leads to an increased bleeding risk, above all in surgery, especially oral or of the prostate.

P-factor XII (FXII), P-prokallikrein, P-kininogen

A partial or total deficiency of one of these factors does not lead to an increased bleeding risk. The APT time is moderately to strongly prolonged (in FXII deficiency). Some of these patients may have an increased

risk of thrombosis. These disorders need to be diagnosed in order to avoid an unnecessary investigation of the prolonged APT time and thus delay, for example an acute operation.

P-factor XIII (FXIII)

Hereditary FXIII deficiency is rare. The severe form (total deficiency) often shows symptoms in the neonatal period, such as persistent bleeding from the umbilicus. Spontaneous intracranial bleeding may occur. Decreased fertility and an increased frequency of abortions have been reported in patients with FXIII deficiency. Acquired partial FXIII deficiency has been described in chronic inflammatory intestinal disorders. FXIII is of importance in the healing of wounds.

P-VWF

The von Willebrand factor (VWF) partly functions as a carrier protein for FVIII and circulates in the blood in complex with FVIII. VWF also binds to platelet receptor complex GPIb/IX/V and thereby adheres platelets to endothelial and other cells that expose VWF. To some extent VWF also contributes to agglutination of platelets. Traditionally VWF is analyzed as protein/antigen (VWF:Ag) or functionally (VWF:Rco or VWF:CB). Recently a new functional assay was introduced where VWF binds to and agglutinates latex particles carrying antibodies to GPIbA coupled with recombinant GPIbA (the receptor for VWF on platelets). The assay is denoted VWF GPIbA activity. Generally functional assays are to be preferred for determination of VWF.

VWF is *decreased* in patients with VWD. In severe cases, the factor is only detectable with a sensitive ELISA technique. The ratios FVIII/VWF:Ag and VWF:Ag/VWF:Rco are normally about 1.0. An elevation of FVIII/VWF:Ag ratio is common in mild VWD and can be used as one way of diagnosing the disease, especially if the level is close to the lower reference limit. On the other hand, the ratio is often decreased in carriers of hemophilia A and always in mild and moderate forms of hemophilia A. VWF:Ag/VWF:Rco or VWF:GPIbA is usually elevated in type 2VWD.

The inter- and intraindividual variations are very wide for VWF and for FVIII and diagnosis can be difficult, especially of mild VWD. Often 2–3 samples have to be taken at various times especially if not recommended rules are used. (See also Chapter 2.) In normal fertile women, there is some variation during the menstrual cycle and samples are preferably drawn during the first 4 days of a menstrual cycle. It is also most important that the patient arrives at the laboratory in a calm and unrushed state (avoid physical and psychologic stress). A FVIII/VWF quotient of 1.6 or more confirms the diagnosis. However, not all patients with a mild

form of the disease have such a quotient. An acquired decreased VWF level is seen, for instance, in certain forms of myeloproliferative diseases.

Elevated VWF levels often appear in inflammatory reactions (acute phase reactant). VWF is synthesized in endothelial cells in the blood vessels. High levels of VWF are therefore a good marker of endothelial damage; levels may be very high in vasculitis, for example. Some studies have found that high concentrations are associated with an increased risk of myocardial infarction. The Leiden Thrombophilia Study indicated that high levels are also a risk factor for DVT/LE. High levels of FVIII and VWF can be seen in liver cirrhosis (the FVIII/VWF:Ag ratio decreases in DIC). Very high levels of VWF are often seen in sepsis and correlate with a poor prognosis. In a normal pregnancy, VWF concentrations increase about four times. Levels may be very high in pregnancy toxicosis.

Anticoagulants

P-coagulation surface-induced antibody (screening for coagulation factor inhibitors)

Activated partial thromboplastin (APT) time is measured in different dilutions of patient plasma in normal plasma. The diluted samples are measured immediately and then after 2 h of incubation at 37°C. The test requires that the patient's APT time is prolonged at least 5 sec more than the upper reference level. An APT time that is substantially prolonged in a mixture containing only 10% of the patient's plasma is a strong indication that the patient's plasma contains antibodies which disturb the coagulation process. The antibodies are usually directed against FVIII.

P-factor VIII, antibody

In a test system for measuring FVIII, the dilutions of patient plasma in normal plasma are measured immediately and after incubation for 2 h at 37°C. The result is expressed in Bethesda units.

Note: the Nijmegen method, which is a modification of the Bethesda method, is more sensitive for low inhibitor titer but is not **currently** widely used.

P-factor IX, antibody

In a test system for measuring FIX, the dilutions of patient plasma in normal plasma are measured immediately and after incubation for 2 h at 37°C. The result is expressed in Bethesda units.

P-VWF, antibody

In a test system for measuring functional VWF (VWF:GPIbA), the dilutions of patient plasma in normal plasma are measured after incubation for 2 h at 37°C.

P-lupus anticoagulant

Thromboembolic manifestations caused by so-called lupus anticoagulants (LA) or phospholipid antibodies are seen fairly frequently. These antibodies are directed against phospholipids such as cardiolipin and phosphatidylserine in cell membranes, bound, for example to β2-glycoprotein 1. Apart from primary antiphospholipid syndrome these lupus anticoagulants may develop in pregnancy in particular and secondarily in autoimmune disorders like SLE, rheumatic arthritis, Sjögren syndrome, and in infectious diseases, above all in bacterial infections; in HIV they occur in 60–80%. The phospholipid antibodies interfere with many coagulation tests and often generate a prolonged APT time. APT time (as well as other coagulation tests) is normalized after addition of excess amount of phospholipids. It is not clear how these antibodies interact with the hemostatic system *in vivo* and cause thrombosis formations. (*Note:* If frozen plasma is used for this test, the plasma should be centrifuged twice in order to minimize the number of platelets in the sample. Fragments of platelets after freezing will bind the antiphospholipid antibodies.)

Since no single test has optimum sensitivity for all types of LA two types of tests are carried out (LA Screen (DRVVT) and LA sensitive APT time (LA APTT)), with subsequent confirmation (LA Confirm (addition of phospholipids to DRVVT) and LA insensitive APT time (APTT FS) respectively). If either of the two tests is positive, the results are reported as positive; this approach provides a higher diagnostic sensitivity compared to the acknowledged the use of the previous mixing test.

The recommended algorithm for diagnosis of presence of LA (used at Karolinska University Laboratory) is presented in Figure 3.1.

P-, S-phospholipid antibodies (PA)

This test indicates an immunochemical presence of antibodies directed against cardiolipin and/or β2-glycoprotein 1 in plasma or serum. The presence of phospholipid antibodies does not always lead to a positive lupus anticoagulant result and vice versa. To confirm a diagnosis of antiphospholipid syndrome, the LA and/or PA must be detected at least twice, in tests conducted at least 12 weeks apart.

Protein C anticoagulant system

P-protein S

Protein S is a vitamin K-dependent protein, which is a co-factor to protein C. Protein S in plasma is linked to a considerable extent to the C4b-binding protein. This makes it easy to differentiate between free and total protein S. The free protein S fraction is physiologically active. Hereditary protein S deficiency generates an increased risk of thrombosis. Decreased levels are observed in vitamin K deficiency, liver damage, VKA treatment,

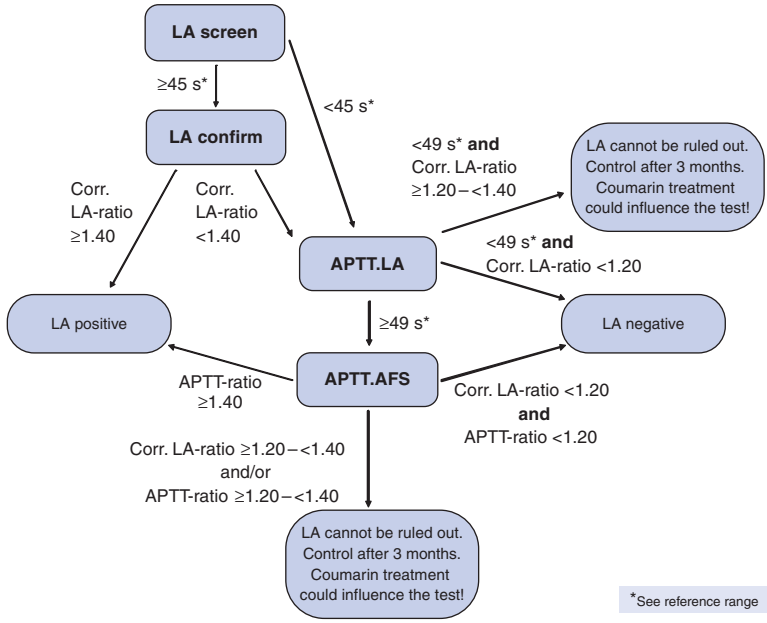

Figure 3.1 Recommended algorithm for diagnosing the presence of lupus anticoagulants (LA). Corr. = Patient plasma clotting times as well as ratios of patient plasmas at confirmation tests should be corrected according to the current clotting time of a reference plasma. (Courtesy of Karolinska University Laboratory.)

DIC, and in pregnancy and hormonal treatment (replacement and/or contraceptives). At present, properly standardized methods are available only for detecting free and total protein S antigen. An analysis of free protein S is sufficient to determine whether an individual is sick. Functional methods are being developed.

P-Protein C

Protein C is a vitamin K-dependent coagulation inhibitor. Hereditary protein C deficiency generates an increased risk of thrombosis. An acquired deficiency is observed in connection with vitamin K deficiency, VKA treatment, liver damage and DIC. APC acts among other things through degradation of activated FVIII and FV.

P-activated protein C resistance

Activated protein C (APC) resistance is the most common known reason for a hereditary venous thromboembolic disorder in which APC cannot link to and degrade the mutant form of FVa and it usually depends on a hereditary mutation in the FV gene (1691G>A), named FV Leiden mutation. This defect is present in more than 90% of patients with APC resistance.

APC resistance can be measured with the original functional method (the ratio of APT time with and without addition of APC) where intraindividual differences between sampling occasions make it necessary to perform confirming assays, for instance in connection with pregnancy or anticoagulant therapy. We now have a more secure method that can be used during VKA and heparin treatment (dilute samples with FV-deficient plasma). APC resistance cannot be determined correctly if the patient's APT time is initially prolonged, as is the case, for instance, in the presence of phospholipid antibodies. Individuals with a so-called acquired APC resistance (no mutation but a positive result of the original APC assay) may also have an increased tendency to thrombosis.

The DNA diagnosis using PCR technique gives a more adequate answer than the conventional measurement of APC resistance. The analysis of the Leiden mutation 1691G>A cannot, of course, detect an acquired APC resistance. If this is suspected (e.g. in pregnancy), a functional analysis must be performed.

Platelet function

P-platelet aggregation (Pt-agg)

One reason for performing Pt-agg may be a prolonged capillary bleeding time or mucous bleedings in spite of normal platelet count and VWF levels. Functional platelet defects are the most common hemostatic defects. In the test, ADP, adrenaline, collagen, ristocetin, and arachidonic acid are added to the patient's platelets, often making it possible to judge which type of functional defect is present. However, the sensitivity of the test is limited – mainly severe defects, such as Glanzmann thromboasthenia and Bernhard–Soulier syndrome, are clearly pathologic.

For many years platelet aggregation has also been evaluated by impedance aggregometry performed on whole blood. For an alternative, see Multiplate.

P-heparin-induced platelet aggregation (HIPA)

This is used in HIT (heparin-induced thrombocytopenia) diagnosis. It measures activation of platelets in healthy donor washed platelets after the addition of patient plasma and heparin (concentration 0.1–1 IU/mL). The sensitivity of this method is good (>90%) while the specificity for detecting clinically relevant (pathogenic) antibodies is higher than with commercially available antigen assays (see below) As the assay is sometimes difficult to evaluate, and even though special equipment as for serotonin release assay is not needed, it is usually performed in special laboratories only. The majority of laboratories therefore perform an ELISA test.

P-heparin antibodies ELISA

This detects circulating IgG, IgA and IgM antibodies against heparin/PF4 complex. Since only some antibodies (e.g. IgG) are of clinical importance, sensitivity to all three subclasses of antibodies decreases assay specificity (50–93%). At the same time, the sensitivity of this method is high (>97%) with a negative predictive value of >95%. Therefore negative results obtained with ELISA may be used for ruling out a HIT diagnosis, while positive results should be combined with clinical findings and/or the above functional assay. The introduction of IgG-specific assay improved specificity in the recognition of reactive heparin induced platelets antibody but confirmation with functional assay still has to be done in certain patients.

The algorithm for the diagnosis of HIT using PaGIA, IgG-specific ELISA and HIPA together with clinical 4Ts score is given in Chapter 16.

Fibrinolysis

P-plasminogen

Hereditary plasminogen deficiency is very rare and is connected with thromboembolic events. An acquired plasminogen deficiency is present in liver disease, often in connection with thrombolytic treatment, and occasionally in DIC. Plasma concentration of plasminogen is usually determined by means of plasmin-sensitive chromogenic substrates after activation of plasmin by, for example, streptokinase.

P-plasmin inhibitor (α_2-antiplasmin)

The protein is a weak acute phase reactant. It is often consumed in DIC. Low levels are seen above all in liver diseases and in connection with thrombolytic treatment. Hereditary total deficiency is very rare and, as a result of increased fibrinolysis, leads to a severe bleeding disorder, including muscle and joint bleeding, similar to those in severe hemophilia. Plasmin inhibitor can also be determined by chromogenic assays where excess plasmin is added to the sample and residual plasmin activity measured.

P-plasminogen activator, tissue type (t-PA)

The t-PA, normally present in plasma, is released from the endothelial cells of the vessels. It activates plasminogen to plasmin in the presence of fibrin. A decreased release of this activator (measured as activity) entails a decreased fibrinolytic capacity. In order to assess the situation, t-PA can be measured before and after a provocation (e.g. venous stasis, 1-desamino-8-D-arginine vasopressin (DDAVP) or physical effort). In plasma, the largest component of t-PA, measured as an antigen, consists of an enzymatically inactive complex with PAI-1.

An elevated level of the antigen indicates an increased risk of arterial complications, including myocardial infarction. At present, this analysis is not recommended for investigating DVT/LE but can be performed in investigations of arterial thromboembolism. The level increases with age. To determine the plasma level t-PA in the sample, is allowed to activate plasminogen added to the system in the presence of fibrin monomers. Plasmin generated is measured with a chromogenic plasmin-sensitive substrate.

P-plasminogen activator-inhibitor-1 (PAI-1) (P-tissue plasminogen activator inhibitor-1)

An increased concentration of PAI-1 causes reduced activity of t-PA and thereby worsens the fibrinolytic function. An elevated concentration of PAI-1 is associated with an increased risk of DVT/LE as well as myocardial infarction. Elevated levels are often seen in obesity, physical inactivity, high levels of blood lipids (especially triglycerides) and in the so-called metabolic syndrome (insulin resistance). PAI-1 is an acute phase reactant, often increasing parallel to CRP. Therefore, high levels are also present in many intensive care patients but often decrease quickly after adequate treatment. High levels inhibit fibrinolytic activity and can possibly contribute to poor "revascularization" of the microcirculation and organ damage. High levels correlate to a poorer prognosis. The level is elevated about five times in pregnancy. PAI-1 levels are often elevated in pre-eclampsia. In severe pre-eclampsia, the increased resistance in the placental circulation is correlated with a further increase in PAI-1.

The diurnal variation is quite large, above all in individuals who are homozygous for the 4G allele in the well-known 4G/5G polymorphism in the promotor region of the PAI-1 gene. The plasma concentration peaks during the second half of the night. Sampling should be done between 7 and 10 am (i.e. as early as possible). This must also be remembered when collecting control materials.

Total PAI-1 deficiency has been associated with postoperative bleedings in several studies.

An ELISA-like assay is available where t-PA has been bound to a plastic surface. Thereafter PAI-1 from the sample is allowed to react with the bound t-PA. After washing a monoclonal enzyme linked antibody against PAI-1 is added and after subsequent addition of a suitable enzyme substrate the concentration of PAI-1 could be estimated. This assay gives good information of the available functional PAI-1 level in plasma. (There are also latent and inactive forms of PAI-1 in plasma.)

Markers of coagulation activation (hypercoagulation markers)

See also under fibrin D-dimer and soluble fibrin.

Activating peptides: general remarks

Peptides, small protein fragments, are released from the proenzyme in the activation of several enzymes in the coagulation and fibrinolytic systems. Their presence is subsequently a good marker of activation. However, their concentrations are low as a rule, they have a very short half-life in the circulation and sampling difficulties lead to elevated values. To date, we know most about fibrinopeptide A (FPA) but determination is complex and sampling has to be faultless. One activating peptide that has proved to be relatively useful is prothrombin fragment 1+2. Peptides split off from FIX and FX have also been described as possible markers/predictors.

P-prothrombin fragment 1+2 (F1+2)

The level is elevated in increased coagulation activation, including DIC. The assay has been used in many studies. The half-life in circulation under normal conditions is 60–90 min.

Note: when TAT complex and F1+2 are used to monitor severely ill patients, higher reference values apply to intensive care patients and pregnant women.

P-thrombin-antithrombin (TAT) complex

Thrombin-antithrombin complex is formed when free thrombin is circulating. Elevated levels have been shown, for example, in DVT/PE and DIC. The method is time-consuming and treatment with antithrombin concentrate containing TAT complex makes the result difficult to evaluate. The half-life in the circulation is normally about 15 min.

Note that the upper reference limit for TAT complex and F1+2 increases 2–3 times with age. Problems in sampling often lead to falsely high values.

DNA analyses

All assays are performed in whole blood-leukocyte DNA extraction (B Lkc).

DNA-based diagnosis of hemophilia A and B

The DNA-based diagnosis of hemophilia A and B are used to identify or exclude women as carriers of a defect gene. Mothers, daughters, sisters, aunts and female cousins of a patient with hemophilia should

be investigated, in order to give those with a disposition good genetic advice. The purpose is to offer possibilities of prenatal diagnosis, if the carrier wishes to become or is pregnant. DNA diagnosis is especially important in women who have a son with hemophilia and in daughters of hemophiliacs. The investigation should be performed before a pregnancy, if possible. A DNA diagnosis is often much more reliable than coagulation analysis. In order to confirm that a person is a carrier, it is important to have a blood sample for comparison from a family member with hemophilia or from another relevant relative.

A mutation has been identified in the FVIII gene (inversion mutation in intron 22) causing severe hemophilia. This is found in almost 45% of severely ill hemophilia A patients attending the Stockholm Hemophilia Center. These families can now be offered a better direct genetic diagnosis. A rare (5%) inversion mutation in intron 1 has also been described in severely ill hemophiliacs. This mutation can be analyzed at special coagulation and/or genetic laboratories.

Embryo DNA from a chorionic villus (part of the placenta) biopsy is used in prenatal diagnosis. The investigation is normally performed in pregnancy week 10–11. For patients and potential carriers where the inversion mutations of intron 22 and intron 1 are not found and for patients and carriers who suffer from mild or moderate hemophilia A, a direct sequencing of the 26 exons of the FVIII gene can be performed in order to find the disease causing mutation. In families where a disease causing mutation is identified only the affected exon is sequenced in carriers.

DNA-based diagnosis in VWD

With the help of direct mutation screening at the genetic laboratory in co-operation with the coagulation laboratory, it is possible to identify the mutations in the VWF gene in most patients with severe VWD (type 3). It is possible to verify that this form usually appears when both parents have one mutation each. The patient can be homozygous, that is, a recipient of the same mutation from both parents, or compound heterozygous, that is, carry two different mutations, one from each parent. However, international studies have shown that most patients with mild VWD are heterozygous for one mutation in the VWF gene. But even heterozygous individuals can develop phenotypically severe forms. For patients with VWD type 2 mutations in many different exons are described, for type 2A, 2B and 2M mutations in exon 28 are most common while for type 2N mutations in exons 18–20 are most common. Sequencing of theses exons can be used to verify findings from multimeric assays and is performed in our laboratory. In families where the mutations have been identified, conditions favor a reliable diagnosis and embryonal diagnosis can be performed when desired. In practice, this is not yet a clinical routine.

DNA-based diagnosis in other hereditary bleeding disorders

DNA assays are performed in many laboratories. Information can be obtained from the coagulation units.

DNA-based diagnosis in thromboembolic disorders

Mutation 1691G>A in the factor V gene is known as the Leiden mutation. The frequency of the FV Leiden mutation (1691G>A) is about 5% in Caucasians while it is almost absent in Chinese. In patients with this mutation, the risk of developing DVT/LE is increased about seven times, while for those who are homozygous for this mutation the risk is increased more than 50-fold. This means that many heterozygous individuals will be asymptomatic for the rest of their lives. See also APC resistance.

Mutation 20210G>A in the prothrombin gene

This mutation (polymorphism) is present in about 2% of the normal population and is a weak but independent risk factor for DVT/LE. It leads to slightly elevated levels of prothrombin. The exact mechanism is not yet known.

Mutation analyses: other

Many mutations leading to thromboembolic complications have been identified, for example in antithrombin and protein C genes. Consult a coagulation specialist to discuss the possibilities for analyses.

Global hemostatic assays and bedside methods

Endogenous thrombin potential (ETP)

Thrombin generation is measured after the addition of a suitable trigger (tissue factor, phospholipids, and calcium) and the amount of generated thrombin is plotted against time to construct a thrombin generation curve (thrombogram), from which additional parameters are calculated, that is, lag time, peak height, time to peak, and the area under the thrombin generation curve – ETP. Both chromogenic and fluorogenic substrate may be used.

Overall hemostatic potential (OHP)

A quick and simple method has been developed in the coagulation research unit, whereby it is possible to determine the total coagulation balance (OHP), hypercoagulation (OCP = overall coagulation potential) and the fibrinolytic potential (OFP = overall fibrinolytic potential) in plasma. For details see He *et al.* [2]. This is still only a research analysis which is performed in citrated plasma.

Thromboelastography (TEG®)/ROTEM®)

By following the change in elasticity during clot formation with a mechanical detection system, the assay provides data about clot formation and its physical strength and stability, in addition to any dissolution. Recently a new portable TEG instrument (ROTEM coagulation analyzer) was introduced. The preferred sample is citrated whole blood but plasma can also be used for experimental work.

Point-of-care tests (POCT) also used as a routine

Today, a number of small instruments are available for measuring the concentrations of some parameters on the ward, in outpatient clinics and even at home. These instruments are usually used for APT time and PT(INR). The Coagucheck is such an instrument available for self-testing of PT(INR).

Several POCT for determination of D-dimer are also available and their analytical profile primary sensitivity and NPV are similar to other laboratory methods. The instruments may be used for D-dimer only or some other tests (troponin, CRP, pro-BNP) may be performed simultaneously.

Other bedside methods have been developed for intensive care and surgical departments. Whole blood is normally used. The result is a graphic picture of the coagulation-hemostatic process. The curves can be interpreted to indicate whether or not there is an influence on the primary and/or secondary hemostasis.

Apart from TEG/ROTEM, REOROX® and Sonoclot® are also used. They are built on different analytical principles and different reagents are used. Systems for controlling reproducibility, etc. are often lacking. Neither is the interpretation always properly standardized and it depends to a great extent on personal experience.

Useful components in research studies

Fibrin-gel structure

Some small investigations have revealed an abnormally tight fibrin-gel network in young patients with myocardial infarction, in other patients with cardiac artery disorders, in stroke patients and in uncontrolled diabetes. The fibrin network becomes more porous during treatment with relatively low doses of ASA. So far, this method is only suitable for scientific investigations.

P-plasmin-plasmin inhibitor complex

The complex forms upon inactivation of free plasmin. It indicates an ongoing fibrinolytic activation. It is a good predictor of elevated primary and secondary fibrinolysis, particularly useful in promyelocytic leukemia and prostate cancer.

P-t-PA-PAI complex

An increase in this complex is a better marker of DVT/LE, and above all of myocardial infarction, than an increase in t-PA antigen.

P-thrombin time

Thrombin time is prolonged in the presence of heparin (UFH, LMH), high concentrations of fibrinolytic products, low fibrinogen concentrations and hereditary fibrinogen dysfunction.

P-ecarin clotting time

Ecarin is snake venom which activates prothrombin directly. Modification of method using chromogenic substrate is currently under evaluation and is promising for monitoring direct thrombin inhibitors. It is not sensitive to the presence of heparin (UFH, LMH).

P-C1-esterase inhibitor

The C1-esterase inhibitor is the only inhibitor of C1-esterase in the complement system, but is also an inhibitor of kallikrein and FXIIa. Consequently the concentration is often decreased in DIC.

P-elastase

Elastase is released from active granulocytes. It degrades, for example, fibrinogen and fibrin into different FDPs, for instance fibrin D-dimer. Thus, the fibrinolytic activity is not always caused by plasmin. Very high levels are often present in DIC, correlating with a poor prognosis. One elastase inhibitor has recently been discovered.

P-heparin co-factor II (HC II)

Heparin co-factor II is a thrombin inhibitor similar to antithrombin, but it inhibits only thrombin, not other coagulation proteases. Dermatan sulfate couples to HC II and therefore its affinity to thrombin increases in the same way as UFH/LMH increases the affinity of antithrombin. HC II is an inhibitor of thrombin in the connective tissue rather than in the circulation. Decreased levels are seen in liver damage, obstetric complications and DIC. Hereditary thromboembolic deficiencies have been described but family studies have yielded conflicting information about such a deficiency. The test is only performed in special cases.

P-plasminogen activator inhibitor 2 (PAI-2)

Plasminogen activator inhibitor 2 is an inhibitor of fibrinolysis that is produced in the placenta and is only present in the blood in pregnancy. The level in the mother is significantly correlated with the function and

weight of the placenta, as well as with the growth of the fetus (not correlated with the severity of the pre-eclampsia).

P-protein C inhibitor

The protein C inhibitor is attracting more and more attention, being an inhibitor of APC but also a very important inhibitor of kallikrein. The activity increases in the presence of heparin. The level is decreased in DIC. (It is also important in male reproduction.) The level decreases in pregnancy.

P-APC-protein C inhibitor (PCI) complex

The protein C system is essential for keeping blood vessels open, free from thrombi. It is activated in any thromboembolic situation. However, a great deal of the formed APC is quickly inhibited by PCI. Complexes of APC-PCI therefore are found in the circulation in thromboembolic situations. An ELISA method for the assay of these complexes has been developed at the clinical chemistry laboratory in Malmö and preliminary studies have shown promising results, that is, increased levels of APC-PCI have been found in patients with DIC, thromboembolism, pre-eclampsia, etc. The method is expected to become commercially available in the near future.

P-TAFI

Thrombin activatable fibrinolysis inhibitor is an enzyme (also called carboxypeptidase B, R, or U) that has been described relatively recently as an inhibitor of fibrinolysis and can be regarded as a link between coagulation and fibrinolysis. The proenzyme is activated by the thrombin/thrombomodulin complex, after which the enzyme splits off the carboxyterminal lysin and arginine residues from the formed fibrin. The fibrin "co-factor" activity, affecting t-PA, disappears, plasmin cannot easily form and thereby fibrinolysis is down-regulated. There are large interindividual variations but no gender differences. TAFI is decreased *in vitro* in hemophilia (does not easily generate thrombin, so fibrinolysis increases). TAFI levels are increased in APC resistance (more thrombin is generated and thereby inhibits fibrinolysis). TAFI is decreased *in vivo* in liver cirrhosis and in DIC. Several studies describe an increase in cardiovascular disorders and stroke (acute phase reactant?).

P-VWF cleaving protease = ADAMTS-13

Only the large VWF multimers are active in hemostasis. The size of VWF is regulated by proteolytic degradation of the binding 842Tyr-843Met in the A2 domain of the VWF via a metalloprotease, the

proform of which, ADAMTS-13, is normally present in plasma. The importance of the enzyme is reflected in the disease thrombotic thrombocytopenic purpura (TTP), a condition with a deficiency or decreased function of ADAMTS-13, with extra large multimers and microthromboembolic complications. It is possible that the high VWF levels found in patients with a stable ischemic cardiac disorder are due not only to endothelial damage but also to lower ADAMTS-13 activity. The same may be the case in many situations with high VWF levels. In hereditary TTP there is a deficiency of the proenzyme. In noncongenital TTP, the apparent deficiency is due to an inhibitor (IgG) of the protease.

Patients with the hemolytic uremic syndrome (HUS) do not have a severe VWF protease deficiency but antibodies have developed against the protease (see Chapter 16).

Determination of the concentration of ADAMTS-13 is not a routine procedure but may be of interest to distinguish TTP from other thrombotic microangiopathies. However, all available assays (primarily ADAMTS-13 activity and anti ADAMTS-13 antibodies but also ADAMTS-13 antigen and determination of VWF multimers) are not standardized and are limited to specialized laboratories only and therefore the starting of the treatment does not strictly require determination of ADAMTS-13.

P-tissue factor pathway inhibitor (TFPI)

Tissue factor pathway inhibitor is a FXa-dependent inhibitor of the FVIIa tissue factor complex. The importance of TFPI for the development of thromboembolic events and DIC is still rather uncertain.

P-tissue factor (TF)

Tissue factor is exposed in tissue damage, endothelial damage and on or by white blood cells, especially monocytes, in inflammatory reactions. New methods have been developed for the determination of this factor.

Platelet-activating predictors

P-thromboglobulin (β-TG), P-platelet factor 4 (PF4)

These are two platelet-specific peptides stored in the α granules. Strong platelet stimulation is accompanied by release of the content of α granules into the surrounding plasma. When increased intravascular platelet activation leads to platelet aggregation, increased levels of the two substances are found. Measurements of these two components have been difficult to evaluate, possibly due to *ex vivo* release of these components during blood sampling and handling of the samples.

Platelet P-selectin (CD62P) or P-soluble P-selectin

P-selectin is a receptor structure in the α granules membrane. Platelet activation and release of the α granules content expose the granule membrane on the platelet surface. This antigen structure can be demonstrated with flow cytometry. Soluble P-selectin is composed of P-selectin which has been cleaved off enzymatically from the membrane or has not been attached to the granule membrane. It is a useful marker of platelet activation.

PLT-fibrinogen, PLT-VWF

Platelet activation involves the activation of receptors on the surface of the platelets which bind to fibrinogen (receptor GPIIb/IIIa) and VWF (receptor GPIb/IX), respectively. With flow cytometry, fibrinogen and VWF can be detected on the platelet surface as markers of elevated intravascular platelet activation.

Microparticles (MP)

Microparticles are subcellular structures – microvesicles (<1 μm) released from different cells after activation and/or apoptosis. It has been shown that different types of MP are increased in different atherothrombotic diseases. MPs are also associated with inflammation and complement activation. Flow cytometry seem to be the most appropriate method for their testing; however, there are still methodological and standardization problems with analyses of MP.

Other non-hemostatic variables of importance

P/S-CRP

An elevated level of CRP is an activity marker of inflammatory disease and also helps to distinguish bacterial infection from other infections and inflammatory stages. CRP has proved to be more efficient for this purpose than, for example, sedimentation rate and white blood cell counts, including differential counts. CRP, using a highly sensitive method (hsCRP), has proved to be a powerful predictor of future cardiovascular disease (myocardial infarction and stroke) in both women and men.

The combination of total cholesterol and CRP in the upper quartiles leads to a greatly increased risk of future cardiovascular disorder. A CRP level above 2 mg/L multiplies the risk.

S-cytokines

The most important cytokines to analyze in trauma, infection and sepsis are the interleukins IL-1, IL-6, and TNF-α. These have a number of pro-inflammatory effects and contribute pathophysiologically in the above-mentioned conditions. They interact with the coagulation system by

potentiating the release of tissue factor from monocytes and damaged endothelium.

P-homocysteine

An elevated level of homocysteine in plasma was described as correlating with venous thrombosis, as well as arterial disorder. However, recent studies have questioned its importance and therefore homocysteine should be considered as a risk marker rather than a cause of disorders. The most common cause of acquired hyperhomocysteinemia is a deficiency of vitamin B12 or folic acid.

About 5% of the population has a hereditary cause – a homozygous mutation (677C>T) in the methylenetetrahydrofolic reductase gene – the enzyme becomes thermo-unstable. Hyperhomocysteinemia interacts additively with conventional risk factors like hypertension, smoking, and hypercholesterolemia.

P-thrombomodulin (TM)

A few rare hereditary TM defects have been described but analysis of TM has not yet proved to be of any importance for investigating thromboembolic disorders. On the other hand, increased levels in plasma can be a marker of vasculitis.

P-fibronectin

Fibronectin (previously called cold-insoluble globulin) is a protein produced by endothelial cells, fibroblasts and cells belonging to the reticuloendothelial system. It acts as an extracellular matrix protein and can bind to collagen, heparin, heparan sulfate, and fibrin. When coagulation is activated, half of it binds to fibrin. An increase is a marker of vasculitis. In DIC in severely ill intensive care patients, decreasing levels of fibronectin correlate with a poor prognosis. In pregnancy toxicosis, an elevated level appears before clinical signs.

S-lipoprotein (a) (Lp(a)), P-apolipoprotein

Lipoprotein (a) is an independent risk factor for cardiovascular disorders and cerebrovascular ischemic stroke. It forms a complex with apolipoprotein(a) and LDL. The structure is similar to that of plasminogen. High levels of Lp(a) in plasma are linked to premature coronary syndrome and cerebrovascular insult risk.

P-apolipoprotein A1 (ApoA1) and P-apolipoprotein B (ApoB) concentrations can nowadays be measured in most laboratories with sufficient precision for clinical use and at competitive costs. The ratio P-ApoB/P-ApoA1 has been shown to be a superior marker for risk evaluation of cardiovascular events. The ratio performs better than cholesterol/

triglycerides and LDL/HDL ratios in large multinational and multiethnic studies. Target ratios are 0.8 for men and 0.7 for women.

Combinations of assays suggested for various hemostatic abnormalities

With the aim of helping clinicians in their choice of appropriate tests for the detection of hemostatic abnormalities, Karolinska University laboratory offers several "packages".

- Bleeding tendency: Fibrinogen, VWF activity, FVIII and FIX (CRP as a help for correct estimation of VWF and FVIII levels).
- Venous thrombosis: FV-gene mutation Leiden/APC-resistance (FV1691 G>A), Prothrombin (FII)-gene mutation (FII20210G>A), Protein C (activity), Protein S free, antithrombin. FVIII, lupus anticoagulant.
- Cardiolipin antibodies and β-2 glycoprotein 1-antibodies.
- Heredity for venous thrombosis: FV-gene mutation Leiden/APC-resistance (FV1691 G-A), Prothrombin (FII)-gene mutation (FII20210G-A), Protein C (activity), Protein S, free, antithrombin.
- Arterial thrombosis: Fibrinogen, lipoprotein (a), CRP, PAI-1, Lupus anticoagulant and Cardiolipin antibodies and β-2 glycoprotein 1-antibodies.

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BLEEDING DISORDERS

PART 2

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Hereditary bleeding disorders

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CHAPTER 4

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General remarks about hemophilia A and B

Classical hemophilia is a rare disease and occurs in about 14 : 100 000 men. Hemophilia A is 4–5 times more common than hemophilia B. Hemophilia is classified as severe, moderate, or mild, depending on the degree of deficiency of FVIII or FIX. About half or more of the patients have a severe or moderate form. The disease is X-linked, but in about 50% of newborns with hemophilia, it was not previously known in the family. Joint and muscle bleedings are characteristics of the severe form of hemophilia. Joint bleedings can occur spontaneously or after a minor trauma. Such bleedings are usually very painful. Without adequate treatment, these bleedings cause synovitis, an increased risk of repeated bleedings in the joint and eventually hemophilic arthropathy, with limited mobility and chronic pain. Most elderly men with severe hemophilia have marked functional impairments. Younger patients who have had prophylactic treatment with factor concentrates from an early age usually have good joint and muscle functions. Patients with severe and moderate forms, with or without known heredity, are usually diagnosed at an early age. Mild forms of hemophilia are often not diagnosed before adulthood. Patients with mild hemophilia suffer from bleedings after surgery, tooth extraction or after trauma.

Regular controls at a hemophilia center are recommended for patients with hemophilia, including those with mild forms. For severe and moderate hemophilia it is recommended that coagulation status and general health be checked 1–2 times a year. Children should be checked by a

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coagulation-competent pediatrician. For milder forms, controls are conducted every 2–3 years.

Specialists in infectious disease, orthopedic surgeons, dentists, physiotherapists, and social workers, all specialized in treating hemophiliacs act as consultants to the coagulation centers for patients needing their help.

Note: The amount of coagulation factors is now expressed in international units (kIU/L) or in units per mL (U/mL). The former is used by laboratories that have adopted an international standard. Previously the amount was expressed as a percentage; 100% indicated a normal level and is equivalent to 1 kIU/L or 1 U/mL.

***Hemophilia A** – FVIII deficiency
– *severe* form: less than 0.01 U/mL FVIII
– *moderate* form: 0.01–0.05 U/mL FVIII
– *mild* form: 0.06–0.40 U/mL FVIII.

***Hemophilia B** – FIX deficiency
– *severe* form: less than 0.01 U/mL FIX
– *moderate* form: 0.01–0.05 U/mL FIX
– *mild* form: 0.06–0.40 U/mL FIX.

General remarks about von Willebrand disease

Von Willebrand disease (VWD) is caused by a quantitative or a qualitative deficiency of von Willebrand factor (VWF) that entails a primary hemostatic defect with bleeding symptoms, above all from mucous membranes. A mild form of VWD is the most common type of hereditary bleeding tendency, occurring in about 1% (or more or less depending on the criteria used). Severe forms are rare, but can cause serious bleeding symptoms resembling those in severe hemophilia. VWD is inherited autosomally, that is, it occurs in both men and women.

VWD is subdivided into three main types:

1 *Type 1* (earlier type I) is a quantitative defect with a decreased level of VWF, which in other respects is normally structured (normal multimeric pattern); the level of FVIII can also be decreased. There are mild to moderate forms of VWD type 1. The patients are probably heterozygous with regard to gene defect. The ratio of FVIII/VWF levels is usually high.
2 *Type 2* (earlier type II) comprises all the qualitative defects of VWF that cause bleeding symptoms. FVIII may be normal or decreased. Most patients have an abnormal multimeric pattern of VWF and may be either homozygous or heterozygous with respect to a defect gene. About 20 subtypes have been identified. VWD type 2A lacks the largest multimers. In VWD type 2B, the VWF often has a heightened affinity to platelets, which leads to aggregation and thrombocytopenia. Type 2N lacks

the ability to bind FVIII, which means that levels of FVIII are very low and may therefore lead to a false diagnosis of hemophilia A.

3 *Type 3* (earlier type III) patients have no or very low plasma levels of VWF. The clinical manifestations resemble severe hemophilia. As a consequence of the low levels of VWF, levels of FVIII are also low since VWF carries FVIII in the circulation. No multimers can be detected.

*__von Willebrand disease__ – VWF deficiency

Approximate clinical classification:

– *severe* form type 3 (earlier III): VWF less than 0.05 U/mL, FVIII less than 0.10 U/mL, bleeding time prolonged (more than 10 min)
– *moderate* form: VWF 0.05–0.2 U/mL, FVIII decreased, bleeding time prolonged
– *mild* form: VWF 0.2–0.5 U/mL, FVIII often somewhat decreased, bleeding time prolonged or normal.

Values were previously expressed as a percentage; 100% indicated a normal level and is equivalent to 1 kIU/L or 1 U/mL.

Factor concentrates used for treatment of hemophilia A and B and VWD in Sweden in 2012

General remarks about factor concentrates

The appropriate factor concentrate for each patient is decided at the hemophilia center. The type of concentrate is usually maintained for an individual patient, but can of course be altered as new drugs are developed. Alterations in dosing and/or type of concentrate should not be made outside the hemophilia center.

Modern factor concentrates are either of recombinant type or, if plasma derived, treated with at least one method of virus-inactivation. Donors of blood and plasma are carefully tested for HIV and hepatitis. Patients who start treatment with coagulation factor concentrates today are usually given a recombinant drug.

Hemophilia A Factor VIII concentrates:

Advate (Baxter)*, Helixate® NexGen (CSL Behring)*, Immunate (Baxter), Kogenate® Bayer (Bayer)*, Octanate® (Octapharma), Recombinate (Baxter)*, ReFacto AF®/Xyntha® (Genetics/Pfizer)*

Factor VIII concentrate: In the patient, the yield of the FVIII activity in the concentrate is about 100%.

1 IU FVIII/kg bodyweight increases the plasma concentration by 0.02 IU/mL.

The half-life of FVIII is normally 10–14 h in adults (6–10 h in children

*concentrates developed with biotechnology, using recombinant technique. The others are produced from plasma.

under 5 years). *Note* that in trauma, serious infection, sepsis, when the patient is bleeding, and after surgery the half-life may be very short: 2–4 h.

Example: For serious bleeding in a patient with severe hemophilia, 70 kg bodyweight and a desired FVIII level of 1.00 IU/mL, give $50 \times 70 = 3500$ IU.

Hemophilia B Factor IX concentrates:
BeneFIX® (Wyeth)*, Immunine (Baxter), Mononine® (CSL Behring), Nanofix® (Octapharma)

Factor IX concentrate: The yield in the patient is normally only about 60% (the remaining amount is distributed extravasally), so *1 IU FIX/kg bodyweight increases the plasma concentration by about 0.01 IU/mL.*

The half-life is usually close to 24 h (shorter for children). *Note* that, as with FVIII, the half-life is shorter in trauma, serious infection, sepsis, when the patient is bleeding, and after surgery.

Example: For treating a moderate bleeding in a patient with severe hemophilia B, bodyweight 70 kg, and a desired FIX level of 0.5 U/mL, give 3500 IU FIX.

Von Willebrand disease factor concentrates with VWF 2012:
Haemate® (CSL Behring), Wilate® (Octapharma)

The available factor concentrates contain both FVIII and VWF. They are labeled mainly after their FVIII content, that is, 1000 U of Haemate contains 1000 U of FVIII and 2400 U of VWF. Nine hundred U of Wilate contains 900 U of FVIII and 800 U of VWF. The yield is initially 100% with respect to FVIII. (See earlier section on hemophilia A.) If dosing continues the FVIII concentration will, since a person with VWD *does not* have an impaired production of FVIII, remain elevated as long as there is enough VWF available. The half-life of VWF is usually 15–17 h.

Treatment strategy in severe forms of hemophilia and VWD

Home/self-treatment

Many patients with severe or moderate hemophilia have learned how to administer factor concentrate intravenously themselves at home. Advice concerning treatment and dosage of the concentrates can be obtained from the coagulation unit. Persons treated as outpatients or at the emergency unit are requested to bring their own concentrates, if possible.

Treatment in trauma and acute bleedings

Patients with severe forms of hemophilia and VWD run a high risk of morbidity and mortality if adequate treatment with factor concentrates is not given for bleedings or trauma. Treatment with plasma is not sufficient. If nothing else is available, however, treatment for a serious bleeding or

trauma can start with fresh or fresh-frozen plasma and tranexamic acid, pending rapid delivery of concentrate.

In the event of an **accident, head trauma, abdominal trauma,** or **gastrointestinal bleeding**, patients are instructed to go to a hospital. Immediate treatment with factor concentrates in these cases is usually urgent and should begin, if possible, at home or at the site of the accident. **The coagulation doctor on duty should always be contacted immediately.**

Important rules for initial treatment with factor concentrates

The requisite amount of factor concentrate is calculated from:

*desired level in plasma (U/mL)

*bodyweight (kg)

The calculated volume is rounded up to the nearest whole bottle or ampoule.

Note: if B-EVF (hematocrit) is low, correct the volume upwards if erythrocyte concentrate is not given.

Recommendations for desired initial plasma concentrations at different types of bleedings

A single treatment is not sufficient in more severe forms of hemophilia and should be repeated in relation to the magnitude of the trauma for several days or longer (possibly weeks). **About further treatment, contact the coagulation doctor on duty.**

The bleedings listed below are regarded as severe and should be treated *immediately* with factor concentrate as follows:

FVIII concentrate 40–50 IU/kg bodyweight or FIX concentrate 70–80 IU/kg bodyweight.

Head trauma, abdominal trauma, severe external injury, suspected retroperitoneal bleeding

- Desired initial plasma concentration: 0.8–1.2 U/mL
- **Trauma to the head** may cause intracranial bleeding even in mild forms of bleeding disorders

Gastrointestinal bleeding

- Desired initial plasma concentration:
  - *minor* 0.4–0.6 U/mL
  - *severe* 0.8–1.2 U/mL

Suspected bleeding in the throat and face region

- Desired initial plasma concentration: 0.8–1.2 U/mL

Muscle bleedings in iliopsoas

- Risk of compression of the femoral nerve. Immobilization and a high leg position initially are recommended
- Desired initial plasma concentration: 0.8–1.2 U/mL

Muscle bleeding in the calf or lower arm

- Risk of compartment syndrome
- Desired initial plasma concentration: 0.8–1.2 U/mL

Joint and other types of muscle bleedings

Symptoms at joint and muscle bleedings			
	Minor	**Moderate**	**Severe**
Pain	+/–	+	++
Swelling	–	(+)	+
Restricted movement	(+)	+	++
Nerve involvement	–	–	+

The symptoms of minor joint bleeding can be a pricking or creeping feeling of discomfort that remains or gets worse. "Trust the patient!" A serious joint bleeding can be extremely painful.

In addition to treatment with factor concentrate, it is recommended that the affected leg be rested. Cooling can have a favorable effect on bleeding and pain.

Desired initial plasma concentration:

– *minor* symptoms 0.3 U/mL
– *moderate* symptoms 0.4 U/mL
– *severe* symptoms 0.6–0.8 U/mL

Maintenance treatment:

– Minor bleeding: continue conventional prophylaxis (see section on "Prophylaxis against joint bleedings"
– Otherwise: give 20–40 IU/kg bodyweight once per 24 h (possibly twice per 24 h in hemophilia A) for 2–6 days, depending on the degree of bleeding, or until there is no discomfort. Always contact the coagulation unit for advice.

Conventional prophylaxis thereafter. For severe joint bleeding with remaining synovitis or repeated bleeding symptoms, increase the intensity of the prophylaxis.

All patients with moderate to severe forms of hemophilia are provided with an individual care plan containing personally calculated instructions as to dosage and intervals for different types of bleeding.

Prophylaxis against joint bleedings

In most patients with a severe form of hemophilia or VWD, regular prophylactic treatment with factor concentrate begins at 1–2 years of age. *Usually* 20–40 IU/kg bodyweight is given initially once a week. The frequency is increased as soon as possible to twice per week (hemophilia B) or 3–4 times

per week (hemophilia A) and in some cases daily prophylaxis with a lower dose of FVIII is administered. Similar principles apply to **severe forms** of VWD. Bleeding prophylaxis is maintained during the growing period, after which some patients continue with regular prophylaxis while others turn to "on-demand treatment", depending on the frequency and intensity of the bleeding symptoms. As a result of this treatment, most patients with severe hemophilia now reach adult age without damage to joints and muscles.

Physiotherapy is recommended for patients with severe forms in order to prevent invalidity after bleedings and further immobilization in those who already have joint damage.

Regular exercise of various kinds (gymnastics, swimming, and other sports) is important, even for those with intact joints, in order to maintain good muscle strength and good coordination. Physical training is coordinated with treatment with factor concentrate.

Home treatment has much reduced the need for hospital care and permitted a significantly better life.

Surgery in patients with bleeding disorders

Both major elective surgery and minor surgery with a high risk of bleeding **should** be performed in a hospital with a coagulation laboratory and a coagulation unit.

Daily contact with the coagulation doctor on duty is also important in every case!

Remember that surgery always has to be preceded by prophylactic treatment with factor concentrate (or with desmopressin in special mild cases of VWD). A schedule should be drawn up in cooperation with the coagulation unit at least one week prior to a planned operation. It is important that the schedule is followed in every respect. After surgery, the patient **should** be monitored with analyses of the factor that he/she is lacking because the *in vivo* consumption of factors varies between individuals and between different kinds of surgery. It follows that the schedule may need to be adjusted. For half-lives, see FVIII, FIX, and VWF.

Tooth extraction in a hemophilia patient

Tooth extraction in a hemophilia patient is conducted in cooperation with a coagulation unit and its consulting dentist. Prior to the extraction, treatment with factor concentrate should be given as well as tranexamic acid (Cyklokapron) both locally as a mouthwash, and on the scar and orally, which reduces the need for hemostatic factor concentrates.

Mild hemophilia patients (i.e. not severe or moderate hemophilia A/hemophilia B/VWD or a serious platelet function disorder) only need to use a mouthwash, possibly in combination with desmopressin (not active in hemophilia B).

Caution in patients with bleeding disorders

- **High blood pressure combined with bleeding disorders can cause brain hemorrhage.** Monitor blood pressure continuously in severe hemophilia/VWD/defective platelet function. *The same applies to patients with moderate and, in many cases, mild forms.* If blood pressure is high, it should be treated without delay.
- Arterial punctures and intramuscular injections should be avoided.
- Epidural/spinal anesthesia should *not* be given to patients with bleeding disorders.
- Do not take blood samples from the femoral vein in small children with a suspected bleeding disorder.
- **Bleeding after a vein puncture** is stopped by compression until the bleeding is brought to a standstill.
- **Drugs** containing *ASA*, long-term *NSAID* drugs, dextran and heparin (UFH and LMH), and thrombin or Xa inhibitors can cause serious/life-threatening bleeding in more severe bleeding disorders.

Pain-killing drugs allowed in hemophilia

Analgesics (pain killers)

Pain killers: paracetamol (Alvedon®, Panodil®), codeine (Citodon) – and possibly morphine etc. – do not increase the risk of bleeding. The morphine group of analgesics should be prescribed with caution in view of the risk of addiction.

Antiflogistics (against inflammation)

Treatment should be planned together with a coagulation expert. Non-steroidal anti-inflammatory drugs (NSAIDs) are normally contra-indicated. In special situations – and in cooperation with a coagulations expert, drugs with a short half-life can be used for short-term treatment. COX-2-inhibitors (Celebra, Arcoxia) do not affect platelet function and are especially adequate for patients with chronic synovitis for short-term treatment. At time of writing, however, the Swedish Medical Products Agency warns against long-term treatment with these drugs.

Other important issues in more severe forms of hemophilia and VWD

Inhibitors

Always contact the coagulation unit.

If treatment with factor concentrates does not have the expected clinical effect (i.e. the patient has an increased number of bleedings), it should be followed by taking samples before and after injection of factor concentrate to determine the level of the factor in question and the presence of a

possible inhibitor, that is, antibodies against the coagulation factor that is deficient in the patient. Antibodies develop after a varied number of treatments (usually <50) in 30–35% of patients with the more severe forms of hemophilia A and in 2–5% of those with hemophilia B. Patients with VWD may also develop antibodies. In the above cases, the inhibitors have to be neutralized with concentrate before a desired hemostatic concentration is obtained. This is not possible at high levels of antibodies. Activated concentrates, such as FEIBA (Baxter), are used for patients with hemophilia A.

Another form of treatment for these patients is the elimination of antibodies by means of a daily supply of a high dose of the deficient factor (so called immune tolerance treatment). Moreover, treatment with recombinant FVIIa (rVIIa, NovoSeven®, Novo Nordisk) has been shown to stop severe bleedings, including joint bleedings, irrespective of the level of antibodies. It is therefore useful in surgery. rVIIa can be used in cases of hemophilia A, hemophilia B, and VWD.

Risk of hepatitis

Patients with bleeding disorders are recommended vaccination against hepatitis A and B if future treatment with blood products or factor concentrates is expected.

Antibodies against hepatitis C are present as a consequence of previous treatment with factor concentrates and/or plasma in up to 90% of patients with severe or moderate hemophilia treated before 1989, and also in some elderly patients with mild hemophilia. Moreover, many patients developed antibodies against hepatitis B before vaccination was introduced. Most of the patients that were infected with hepatitis C and who have not been cured or become spontaneously seronegative have had intermittently increased levels of transaminases and a chronic hepatitis C infection. Some have suffered/suffer from serious late complications, such as liver cirrhosis and hepatocellular cancer. Liver transplantation has been performed in recent years to save life and this has simultaneously cured hemophilia A as well as B but not VWD. A current treatment for hepatitis C, effective in about 60% of the patients, is pegylated interferon and ribavirin.

Treatment principles for different types of bleeding disorders (severe, moderate, and milder forms of hemostatic defects)

Hematuria

Withdraw treatment with tranexamic acid (Cyklokapron, Tranon).

Minor hematuria: Prednisolon 0.5 mg/kg bodyweight per 24 h for 5 days, followed by 0.25 mg/kg bodyweight per 24 h for 5 days can be considered. Copious fluid intake.

Massive hematuria: Possibly factor concentrate in order to obtain a factor level of about 0.3 U/mL. As much rest as possible. Copious fluid intake. Contact the coagulation doctor on duty for advice.

For patients with *mild* hemophilia A or VWD: try desmopressin (see section "Treatment with desmopressin").

Nose bleeding

Usual local measures, for example blood-stilling cotton and mucous membrane softeners. Give tranexamic acid (Cyklokapron). For persistent bleeding, give factor concentrate (for patients with *severe or moderate hemophilia and VWD*) and contact the coagulation doctor on duty.

Experience shows that etching and similar measures should be used very restrictively. Laser treatment can be a more adequate alternative for recurrent bleeding.

For patients with *mild* hemophilia A or VWD, try desmopressin (see section "Treatment with desmopressin").

Gum bleeding

Gum bleedings are often caused by poor oral hygiene and associated gingivitis. Local treatment and regular control by a dentist and/or dental hygienist. Mouthwash with solution of tranexamic acid (as used for i.v. injection: Cyklokapron [100 mg/mL] 5 mL with 5 mL water). Rinsing for 1–2 min every 8th hour, or as needed, helps to reduce bleeding.

Menorrhagia

Tranexamic acid (Cyklokapron) and/or oral contraceptives (OC). Factor concentrates may be needed in severely ill cases.

Treatment with desmopressin is not helpful in either severe VWD type 3 or in VWD type 2B (see section "Treatment with desmopressin").

Pregnancy and delivery

Contact a coagulation doctor in order to plan bleeding prophylaxis well in advance. FVIII and VWF increase during the latter part of pregnancy. In patients with mild VWD and hemophilia A carriers, levels are usually normal during the last trimester. This should be verified, preferably after week 32. Patients with more severe VWD need treatment before delivery and may need several weeks of treatment with factor concentrate after delivery. Epidural-spinal anesthesia cannot be used, due to the risk of bleeding.

We recommend that the route of delivery should be chosen according to regular obstetric guidelines and that, when possible, the least traumatic approach is used. We therefore advocate against the use of vacuum extraction or forceps.

Treatment with tranexamic acid

Treatment with fibrinolysis inhibitors (Cyklokapron, Tranon (the latter only available as tablets)) is often effective in mild, moderate, and severe hemophilia patients (most often as an additional treatment), as well as in all patients with VWD or with platelet function defects. They are useful in: mucous membrane bleedings, nose bleedings, gum bleedings, intestinal bleedings, menorrhagia, other bleedings, at tooth extractions, and in surgery. In mild forms of hemophilia A, VWD, or thrombocytopathia they are often combined with desmopressin (DDAVP). In more severe bleeding disorders they are used in combination with coagulation factor concentrate.

Dosage: Injection of tranexamic acid (Cyklokapron 10 mg/kg bodyweight i.v.) or mixture 20 mg/kg bodyweight orally every 8th hour. In Sweden the drug can also be purchased in tablet form (Cyklo-F) without a prescription. The mixture is sold under the name tranexamic acid as an *ex tempore* preparation.

Contraindication

Macroscopic hematuria is an important contraindication to tranexamic acid (Cyklokapron, Tranon) due to the risk of urethral clotting and thus a possible hydronephrosis.

Rare bleeding disorders

Hereditary deficiency of all remaining coagulation factors (fibrinogen, II, V, VII, X, XI, XII, and XIII) are known. Their prevalence in severe form in the general population is low and ranges from 1/500 000 to 1/3 000 000. They are, except for certain variants of dysfibrinogenemias, inherited as autosomal recessive disorders so both men and women can be affected. Homozygous genotype results in very low levels of the missing coagulation factor and the clinical picture is usually that of severe hemophilia. Heterozygous carriers of the trait are in many cases asymptomatic since a factor level of approximately 0.20 IU/mL is usually sufficient to prevent bleeding symptoms in everyday life. However, as in persons with mild hemophilia A and B, they can bleed excessively if subjected to trauma or surgery. Exceptions to this rule are FXI deficiency where the correlation between the clinical phenotype and factor level is poor, that is, a person with near normal FXI levels can bleed easily, and FVII deficiency, where homozygous patients can have a milder bleeding tendency. Furthermore, FXII deficiency and some of the dysfibrinogenemias *do not* exhibit an increased bleeding tendency. These conditions are rare and diagnosis requires special laboratory analysis. For treatment/prophylaxis, factor concentrates are available for fibrinogen, FII, FVII, FX, FXIII (license

required for FX, FXIII) but not for FV or FXI deficiency (plasma). It is therefore strongly recommended that bleeding, pregnancy, delivery, and preoperative treatment are managed in cooperation with a coagulation specialist.

Severe platelet function defect (e.g. Glanzmann thrombasthenia)

Glanzmann thrombasthenia is a very rare disorder. Note that most of the principles for treatment outlined earlier should also be observed in this disease. However, FVIII or FIX concentrates are of no use in these patients, who especially during childhood display a pronounced tendency to mucous membrane bleedings and hematomas. The diagnosis is confirmed by a markedly prolonged bleeding time and by studying receptors and platelet aggregation capacity. Severe forms of platelet function defect with little or no response to desmopressin treatment should be handled in consultation with a coagulation expert. In acute bleeding situations these patients are primarily treated with leucocyte-filtered platelet transfusion (in order to reduce the risk of platelet antibodies) in combination with tranexamic acid (except in hematuria). However, there is a risk that repeated treatments with platelets will lead to the development of HLA antibodies, and such treatment should be restricted to clear indications. Recombinant FVIIa (NovoSeven, Novo Nordisk) has resulted in effective hemostasis in a number of cases and is licensed in Europe for use in patients with Glanzmann disease.

Mild hemostatic defects

General remarks

Bleeding disorders in a mild form are found in 3–5% of the population in several countries, usually presenting as a mild form of VWD, or a mild platelet function disorder, causing an increased bleeding tendency. These hemostatic disorders are characterized by mucous membrane bleedings and spontaneous bruises, whereas joint and muscle bleedings are rare. Examples are individuals who experience bleeding in connection with an intake of ASA or NSAID, postoperative bleedings and bleeding after a tooth extraction, with no surgical explanation for the bleeding. Such disorders are also present in persons with frequent nosebleeds, gastrointestinal bleeding, or menorrhagia, where no pathologic anatomic explanation can be found. Brain hemorrhage can also develop in such patients.

Treatment (general)

- *First and foremost, provide accurate information.*
- The patient should avoid ASA and NSAIDs.

- Patients who are diagnosed with a milder hemostatic defect normally return to their regular physician after initial investigation. Contact with a specialized coagulation unit is thereafter taken when necessary.
- The risk of having a serious bleeding is probably low. It can, however, occur and is most probable after trauma, surgery or in conjunction with disease (peptic ulcer etc.). Bleeding/risk of bleeding should therefore always be considered in these situations. **Special care should be taken with head trauma, since a subdural hematoma can develop slowly.**

Treatment with desmopressin

Desmopressin (Octostim® (Ferring)) is a synthetically produced peptide, modified according to a natural hormone in the body called antidiuretic hormone (ADH).

Desmopressin induces endothelial cell release of VWF and FVIII and can improve the interaction between defective platelets and the vessel wall. Desmopressin is therefore effective at various bleedings in patients with *type 1 VWD*, in *primary or secondary platelet function defects*, and in mild hemophilia A. Treatment with desmopressin should almost always be combined with tranexamic acid (except in hematuria).

Desmopressin has no effect in:

- hemophilia B;
- severe deficiency of VWF or FVIII (VWD type 3 and severe hemophilia A), as neither VWF nor FVIII is stored in the endothelium in these patients. The effect in moderate hemophilia is usually not enough to achieve hemostasis;
- the serious platelet function defect, Glanzmann thrombasthenia;
- VWD type 2B; desmopressin can induce thrombocytopenia and should *not* be used.

If the patient fails to respond to the treatment, contact the coagulation unit.

Octostim 0.3 µg/kg bodyweight i.v. increases the plasma levels of VWF and FVIII 2–3 times resulting in a well-documented effective treatment of *mild forms of VWD and hemophilia A* (FVIII deficiency), including in carriers of this disease. Octostim may also have some effect in moderate forms of these diseases, but is then often insufficient to achieve good hemostasis.

The effect of desmopressin should be tested prior to planned surgery. The intraindividual response is relatively constant, but 10% do not respond with improved hemostasis and a shortening of the bleeding time. Responders to the treatment (cause unknown) cannot be identified in advance.

For such an investigation, desmopressin (Octostim) is usually given at 0.2–0.3 µg/kg bodyweight subcutaneously near the umbilicus, with control of the bleeding time after 1 hour.

For treatment desmopressin is usually given subcutaneously and in some cases intravenously; dose Octostim 0.2–0.3 µg/kg bodyweight (see manufacturer's instructions).

Desmopressin (Octostim) can also sometimes be administrated as a nasal spray, 150 µg per dose, for example in *menorrhagia* in patients with mild VWD or with a platelet function defect. In these cases it is mostly combined with tranexamic acid.

Desmopressin treatment can be repeated if necessary after 6–12 h.

Contraindications and side-effects of desmopressin

Desmopressin is not recommended in patients with an untreated hypertension, unstable angina, or after a myocardial infection.

If considered during pregnancy or at delivery, a discussion with an obstetrician and/or coagulation expert is advised. In women with mild VWD or platelet function disorder, the bleeding risk during pregnancy occurs mainly postpartum, and desmopressin is therefore usually given after delivery. (See Chapter 14.)

In all patients and especially in *young children* and *pregnant women*, the risk of fluid retention and hyponatremia should be considered, especially at repeated doses. Seizures are associated with desmopressin treatment and it should be used with great caution in children under two years of age.

With repeated doses of desmopressin, the fluid balance and S-Na should always be monitored, regardless of the patient's age, and only isotonic fluids may be used.

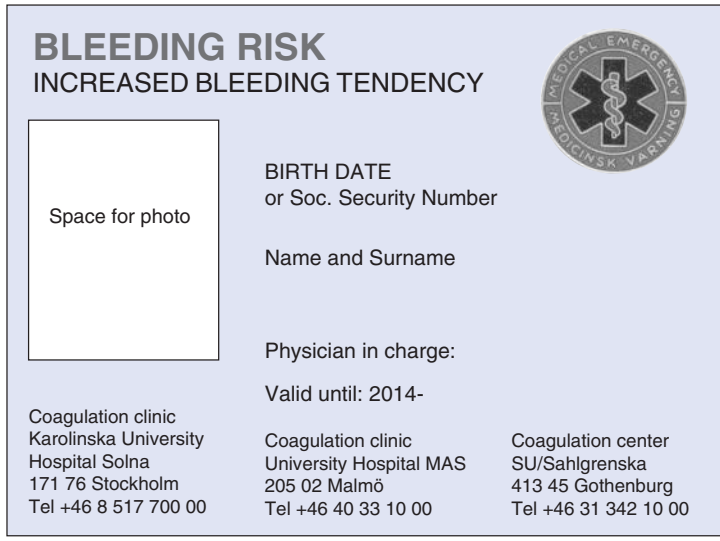
Blood sampling in bleeding disorders

When sampling blood from patients with bleeding disorders, it is important to note that most patients who have been treated with blood products have had hepatitis B, and many, including some teenagers, will have chronic hepatitis C. Moreover, some adults have been exposed to HIV contamination through treatment with concentrate. ***Follow the rules from your hospital's hygiene committee concerning blood sampling, identification of tubes, etc.***

Bleeding risk charts

Individuals in whom a hereditary bleeding disorder has been diagnosed are required to wear a bleeding risk chart. These charts are individually designed and differ between coagulation centers (Figure 4.1).

(a)



(b)

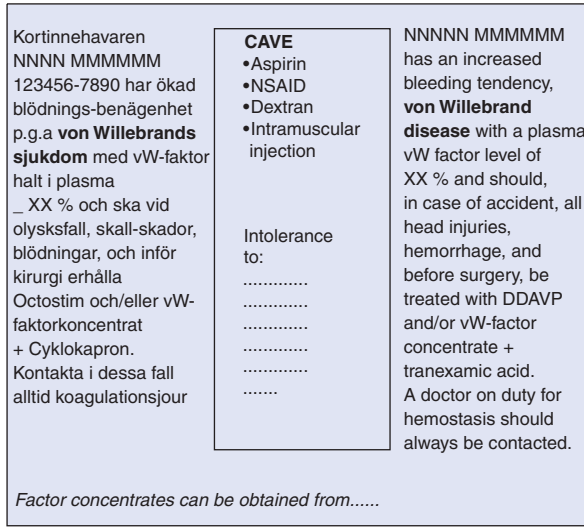


Figure 4.1 **(a)** Front side of a risk chart for anyone with a risk of bleeding. **(b)** Reverse side of a risk chart for a moderate or mild form of von Willebrand disease.

Critical bleeding

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CHAPTER 5

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Introduction

Serious bleeding implies general massive bleeding or a critical bleed in a vital organ, such as in the brain, the throat or in a muscle with life- and limb-threatening compartment syndrome. It is of vital importance to take action against causes of serious bleeding at an early stage to prevent hemostatic failure and fatal outcome. Bleeding may be aggravated by renal and liver failure, malignancy, bleeding disorders, and ongoing treatment with anticoagulant and antiplatelet drugs.

Definition of massive bleeding

A massive bleeding is usually defined in terms of blood loss during a certain period of time or numbers of packed red blood cells given to replace the loss, that is:

- replacement of one blood volume within 24 h
- replacement of more than 50 % of the blood volume within 3 h
- one unit of packed red blood cells per 10 kg bodyweight per hour.

Transfusion coagulopathy

Less than 3% of trauma patients in civilian medical care suffer a massive bleeding and are in shock with a pronounced coagulopathy, *acute coagulopathy of trauma and shock* (ACoTS), on arrival at an emergency ward.

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Trauma in combination with a massive bleeding and circulatory shock causes a massive activation of the coagulation system and platelets, and has an influence on the vascular endothelial function.

Massive obstetrical bleedings are associated with an acute coagulopathy, characterized by a significantly increased fibrinolysis in combination with consumption and proteolysis of fibrinogen and other coagulation factors.

In massive bleeding that requires substantial blood transfusion, several factors contribute to the development of a *transfusion coagulopathy* which becomes absolute, if not compensated when bleeding continues:

- dilution of coagulation factors due to endogenous fluid influx from extra vascular compartments and fluid resuscitation;
- consumption of platelets and proteolysis of coagulation factors;
- disturbances in the coagulation process due to citrate-induced hypocalcemia;
- hypothermia below 36°C (97°F);
- acidosis with pH less than 7.2;
- hematocrit below 0.30 and hemoglobin lower than 90–100 g/L;
- fibrinolysis.

Recommendations to obtain optimal hemostasis

Keep the patient warm. Body temperature below 36°C (97°F) impairs hemostasis. The platelet function deteriorates, the coagulation process slows down and the fibrinolytic activity increases. This calls for preheated infusion solutions, a warm room and covering the patient with warm blankets or similar.

Keep hematocrit above 0.30. A low hematocrit alters the flow conditions (shear rate) in small vessels and capillaries. The platelets cease to circulate in a laminar layer just beneath and in close contact with the endothelium, leading to impaired capillary hemostasis.

Correct acidosis A decreased pH (and base excess) impairs platelet function and the coagulation process. A pronounced hemostatic dysfunction is observed at a pH below 7.2.

Avoid hypocalcemia below 1 mmol/L. Blood transfusions are anticoagulated with citrate and a potential complication is hypocalcemia due to accumulation of citrate, which binds calcium. Consider that calcium is crucial for activation of the other coagulation factors.

Keep the patient calm and free from pain. Pain and anxiety are stress factors that might impair the body's hemostatic capacity.

Management

- Inform the local blood bank.
- Draw blood samples for blood count, PT(INR), APTT, fibrinogen, creatinine, arterial blood gas analysis, and blood grouping.
- There is no universal test for measuring hemostasis but bedside instruments may be useful for a quick estimate, for example point-of-care instrument for PT(INR) in patients on coumarins; viscoelastometric tests for general assessment of clot formation, TEG and ROTEM; and platelet function test for patients on antiplatelet drugs, such as Multiplate.
- Repeat tests for hemostasis frequently until bleeding is under control.
- Do not wait for laboratory results before starting treatment.
- Consider administration of tranexamic acid intravenously at an early stage.

Role of massive transfusion protocols in massive bleeding

At trauma centers, new protocols for resuscitation are being implemented, as a result of a paradigm shift. These protocols are valid even in patients with massive bleeding of other etiologies. Most trauma centers start transfusion with emergency trauma packages (ETP) delivered from the local blood bank containing packed red blood cells, plasma and platelets. The proportions of given units of packed red blood cells, plasma and platelets varies between blood banks depending on how much each blood product contains (i.e. in the United States 1 : 1 : 1, in Denmark 5 : 5 : 2, and in Sweden 4 : 4 : 1). Some centers in Europe use coagulation factor concentrates (prothrombin complex concentrate (PCC), fibrinogen, FXIII) in early treatment to diminish use of plasma.

During continuous bleeding, aim for the following levels

- Hematocrit above 0.30
- Platelet count above 50–100 $\times 10^9$/L
- PT(INR) below 1.5
- APT time shorter than 1.5 times of the reference value
- Fibrinogen concentration above 2 g/L.

Choice of plasma

Some blood centers supply both fresh-stored (no more than 2 weeks in a refrigerator) and fresh-frozen plasma. The concentrations of some coagulation factors are only slightly lower in fresh-stored plasma than in fresh-frozen plasma. Defrosting the fresh-frozen plasma takes about 45 min while in an acute setting the fresh-stored plasma is preferable due to its quick access.

Local procedures

Consider endoscopic or endovascular treatment to achieve control of the bleeding. It can be done with selective embolization or clotting, or covered stents. Such stents are also used in rupturing aneurysm of the aorta and other major vessels. Angiography also provides an opportunity for stabilizing the circulation with an occluding aorta balloon and for creating a respite for other actions.

Additional treatment

In certain situations, treatment with plasma and platelet concentrate is not sufficient to achieve full hemostasis and optimize the coagulation.

Fibrinogen concentrate

Fibrinogen concentrates (Riastap®), ampoules contain 1 g. *In vivo* recovery after administration is about 85%. In an adult weighing 70 kg and with a plasma volume of 3 L, 1 g of fibrinogen will increase the concentration of fibrinogen by 0.3 g/L.

Prothrombin complex concentrate (PCC)

PCC can be used if plasma treatment fails to have a sufficient effect on PT(INR) and in situations where a volume burden with plasma should be avoided in order to reverse elevated PT(INR). This may be the case in patients with an excessive consumption of coagulation factors, in patients with liver failure or in patients being treated with coumarins.

For dose and reversal of increased PT(INR) see Chapter 7.

Recombinant factor VIIa

Recombinant FVIIa (NovoSeven) is a prohemostatic drug. NovoSeven accelerates platelet activation and thrombin formation locally on an injured vessel. NovoSeven has a short half-life of 2–3 h, and a clearance corresponding to 30–35 mL/min. In children under 10 years of age the half-life may be shorter and clearance faster.

The use of recombinant VIIa has in some cases been associated with thromboembolic complications. The risk of complications has to be weighed against the expected benefit in the individual situation. There are still no conclusive studies in massive bleeding in connection with trauma. The hemostatic effect of NovoSeven is diminished

in pronounced acidosis (pH below 7.2), at low fibrinogen concentrations (less than 1.0 g/L) and presumably also when platelet count is low.

Concentrates of other coagulation factors

Factor XIII is essential to stabilize fibrin. Occasionally plasma concentration drops to levels which are critical for optimal hemostasis, that is, below 25–30% of normal, and administration of FXIII concentrate (Fibrogammin®) might be of value. But so far there have been no clinical studies to support this.

In occasional cases, addition of FVIII and VWF can be required when levels of the factor in question have been found to be low.

For factor concentrates and dosages, see Chapter 4.

Cryoprecipitates

In many countries cryoprecipitates are used to compensate for coagulation defects. Cryoprecipitates contain high amounts of fibrinogen, FXIII, FVIII, and VWF.

Tranexamic acid

Tranexamic acid inhibits activation of fibrinolysis, by inhibiting activation of plasminogen to plasmin. It is excreted via the kidneys with a half-life of 80 min and delayed when renal function declines. Note that tranexamic acid can cause clot formation in kidneys, urethra, and bladder during ongoing bleeding in the urinary tract.

Desmopressin

Desmopressin might be useful if there is a simultaneous endogenous or acquired platelet function defect. Desmopressin is often combined with tranexamic acid.

For dosage and special considerations for treatment, see Chapter 4.

Local hemostatic drugs

Local hemostatic drugs can be helpful in serious bleeding. They are available in various forms as biologic tissue glues. Tranexamic acid can also be used as a local hemostatic drug, for example in bleeding from the mouth, nose, rectum, or a wound.

Complicating factors

Kidney failure

Impaired kidney function often causes a prolonged bleeding time, due to a low hematocrit, and also to platelet and endothelial dysfunction. This can partly explain an increased sensitivity to platelet-inhibiting drugs and bleeding tendency. Paradoxically, there is also an increased risk of thromboses.

Desmopressin may be tried for hemostasis in severe bleedings.

Liver failure

As liver failure progresses the hemostatic balance becomes altered and fragile with reduced synthesis of prohemostatic coagulation factors as well as of the inhibitors. Thrombocytopenia and platelet dysfunction may also be present. This is reflected by increased PT(INR) and decreased levels of fibrinogen and antithrombin. In serious bleeding with coexistent liver failure, it may be relevant to treat with vitamin K, plasma, PCC, fibrinogen, fibrinolysis inhibitors, and platelet transfusion.

Reduced vitamin K absorption

In certain situations, vitamin K deficiency can contribute to elevation of PT(INR), due to defective intestinal resorption and cholestasis. In serious bleeding consider treatment with vitamin K intravenously.

Malignancies

Blood malignancies, such as promyelocytic leukemia, as well as disseminated cancer and prostate cancer, may initiate fibrinolytic activity, with a low fibrinogen concentration and increased levels of fibrin D-dimers. Besides affecting fibrin, the fibrinolytic activity degrades coagulation factors V, VIII, XIII, the large multimeric forms of VWF.

In serious bleeding, treatment with fibrinolysis-inhibiting drugs is essential and may be combined with plasma, fibrinogen concentrate, platelets transfusion or VWF.

Ongoing treatment with antiplatelet and anticoagulant drugs

The combination of treatments may result in an additive and potent inhibition of hemostasis. See Chapter 10.

Investigation of increased bleeding tendency

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CHAPTER 6

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Introduction

When investigating an increased bleeding tendency, a detailed history is important. With regard to sampling, a number of screening analyses are of primary interest.

If the patient presents with only small, shallow bruises, has no heredity and the screening analyses are normal, there is generally no need for further investigations. However, if the patient has a manifest history of bleeding and/or heredity, a coagulation specialist should be consulted even if the screening analyses appear to be normal.

Diagnosis

The keystone of the diagnosis is the history of bleeding (Box 6.1), which is often more instructive than many laboratory analyses. The history is informative preoperatively and in connection with an investigation of hemostatic defects. Further investigation is usually based on the bleeding history and the results of screening analyses.

Evaluating a case history can be difficult and calls for experience to distinguish between what may be normal as opposed to definitely pathologic. Spontaneous muscle or joint bleeding is almost always associated with severe hemophilia or other total coagulation factor deficiencies, sometimes also with severely defective platelet function. If nose bleeds or bleeding after tooth extraction or menorrhagia has required medical treatment, they are also more likely to indicate a hemostatic defect. Frequent bleedings, perhaps of various origins, also indicate a hemostatic defect. If

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a close relative is known to have a verified specific defect, measurement of the factor in question is usually mandated.

Box 6.1 Suggested questions for bleeding history (yes/no)

Do you bruise easily?

Do you often have nose bleeds?

Do you bleed abnormally from a cut or other wound?

Do your gums often bleed?

Have you had any muscle bleedings?

If yes, what was the cause?

Have you had any joint bleedings?

If yes, what was the cause?

Have you had a tooth extracted?

If yes, did you bleed for more than 5 hours afterwards?

Have you undergone any surgery?

If yes, what for?

Have you bled abnormally after surgery?

Have you been given blood or plasma for bleeding from surgery?

Do you have plentiful menstrual bleeding (menorrhagia)?

Have you had a delivery?

Have you had abnormal bleeding after a delivery/abortion?

If so, did you receive transfusion of blood or plasma?

Which drugs do you use (including contraceptives)?

Do you suffer from any liver, kidney or blood disease?

Heredity – have any of your relatives had problems with bleeding after surgery, delivery, tooth extraction, or other severe bleeding?

Laboratory tests

Recommended screening analyses include platelet count, PT(INR), APT time, fibrinogen and bleeding time.

Note: testing of bleeding time requires skilled personnel in order obtain reliable results (see also Chapter 3).

Reasons for pathologic screening analyses and further actions

Causes of prolonged bleeding time

- Bleeding time lengthens during pregnancy (normally not above the upper reference limit) and is prolonged in connection with decreasing extravascular fluid. Diseases involving the connective tissue can result in prolonged bleeding time.
- Drug effects (ASA, clopidogrel, NSAID, antiepileptics, and certain antidepressive drugs).
- Thrombocytopenia (platelet count below 80×10^9/L). For causes, see below. The number of platelets is crucial for adequate primary hemostasis. Levels above 50×10^9/L are usually sufficient but bleeding time can be prolonged even at 80×10^9/L.
- For patients with a bleeding time of more than 900 sec, who do not respond to desmopressin (Octostim) (see also Chapter 4), request an investigation with certain special platelet tests (a referral to a coagulation unit is advisable).

To investigate thrombocytopenia when a coagulation disorder is not likely, contact a hematologist. In this context, hemostatic disorders include the following.

- *von Willebrand disease (VWD)*. However, bleeding time may be normal in a mild form of VWD. Analyze VWF (VWF functional (VWF:RCo or VWF:GPIbA) and VWF antigen) and FVIII, and calculate the ratios FVIII/VWF:Ag and VWF:Ag/VWF:RCo or VWF:GPIbA.
- *Acquired platelet function defects* due to liver damage, kidney damage, autoimmune disease such as SLE, platelet inhibitory drugs, increased fibrinolysis.
- *Hereditary platelet function disorders*, for example Glanzmann thrombasthenia and Bernard–Soulier syndrome.
- *Disseminated intravascular coagulation (DIC)*. Platelets are consumed as a result of extensive activation of coagulation. Peripheral bleedings (e.g. ecchymoses and bleeding in the gums) already indicate a platelet function defect and therefore bleeding time measurements are not necessary. See Chapter 16.
- Bleeding time may be prolonged in FV and FXI deficiency.

Causes of thrombocytopenia

Investigation and treatment of thrombocytopenia is normally handled by a hematologist. In the rare situations where the underlying diagnosis is made of a primary coagulation disorder, such as VWD type 2B or Bernard–Soulier syndrome, further treatment

is managed in a specialized coagulation unit. Discussion with a coagulation specialist is usually of value in emergency conditions such as DIC, HIT.

So-called pseudothrombocytopenia is often caused by platelet aggregation in EDTA tubes. Check platelet count in citrate tubes or heparin tubes for comparison.

Hereditary thrombocytopenias

- Isolated (autosomal dominant)
- Combined with qualitative defect (e.g. Bernard–Soulier (see above), May–Hegglin, Wiscott–Aldrich)
- Combined with other defects (e.g. VWD type 2B, Fanconi syndrome)
- Thrombocytopenia with absent radius (TAR).

Acquired thrombocytopenia

Increased peripheral destruction

- Idiopathic thrombocytopenic purpura (ITP)
- Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). See Chapter 16
- Drugs (i.e. heparin). See Chapter 16 (HIT).

Reduced production

- Aplastic anemia
- Malignant blood diseases
- Metastases to bone marrow from tumors
- Drugs
- Megaloblastic anemia, B12 or folate deficiency
- Alcohol damage to bone marrow.

Abnormal distribution

- Sequestering in an enlarged spleen.

Causes of prolonged activated partial thromboplastin time (APT time)

Check that the sampling was not done with a heparinized needle and/or that the patient is treated with low molecular or standard heparin (LMH/UFH).

Possible causes

- UFH treatment (LMH can also cause some prolongation of APT time)
- VKA treatment
- Hemophilia A/B; often also in more severe forms of VWD

- FXI deficiency
- FXII deficiency (APT time often greatly prolonged). By itself, this deficiency does not lead to an increased bleeding tendency
- Deficiency of any of the coagulation factors II (prothrombin) and FX can also cause a prolonged APT time; such deficiencies are usually demonstrated better in a PT(INR) analysis
- Circulating anticoagulants (antibodies against a coagulation factor)
- Lupus anticoagulant/phospholipid antibodies
- Severe liver insufficiency
- Disseminated intravascular coagulation (DIC). See Chapter 16.

APT time is *not* prolonged in deficiency of FVII or FXIII.

Note that a normal APT time does not rule out mild coagulation disorders, such as mild hemophilia A or B or VWD. So if a disorder is still suspected clinically even though APT time is normal, a specific coagulation factor investigation should be performed.

Causes of elevated PT(INR)

- Liver damage/disease with defective synthesis of coagulation factors
- VKA treatment: Waran® (warfarin), Sintrom® (acenocoumarol), Marcoumar® (phenprocoumon) or treatment with thrombin or Xa inhibitors
- Vitamin K deficiency (resorption disorder), intravenous nutrition for more than 5 days, long-term antibiotic treatment
- Hereditary coagulation defect (FVII, FX, FII (prothrombin))
- Amyloidosis (can cause acquired FX deficiency)
- Antibodies against any of above-mentioned factors or against tissue factor. A pronounced lupus anticoagulant sometimes elevates PT(INR)
- Newborns and healthy children up to 2 years of age have elevated PT(INR) values
- Seriously ill and prematurely born children have abnormally high PT(INR) values compared with healthy newborns
- Disseminated intravascular coagulation. See Chapter 16.

Investigation of bleeding tendency: practical aspects

Elective investigation in non-acute bleeding tendency

Referrals for consultation can be sent to coagulation specialists in the local or referral hospital. The referral must include the bleeding history and results of screening tests.

Preoperative investigation

A preoperative investigation is required in order to avoid unnecessary bleeding complications. Take a bleeding history and, if this is positive, screening samples. In urgent cases, contact the on-call coagulation doctor. If the patient has thrombocytopenia only, contact a hematologist.

Acute investigation in postoperative or post-traumatic bleeding

For patients with a known bleeding disease, always *immediately* contact the on-call coagulation doctor at the referral hospital or the patient's regular center for proposals concerning sampling and treatment. See Chapter 4.

For other patients, first determine hemoglobin platelet count, APT time, PT(INR), and fibrinogen.

THROMBOEMBOLIC DISORDERS

PART 3

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Venous thrombosis and pulmonary embolism

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CHAPTER 7

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Introduction

In a US study the average yearly incidence of first lifetime venous thromboembolism among white people between 1966 and 1990 was 117 per 100 000 people. Similar results have been found in the EU with an incidence of 183 per 100 000 people. The incidence increases exponentially with age for men and women, for both deep venous thrombosis (DVT) and pulmonary embolism (PE) commonly named venous thromboembolism (VTE). Of the patients with venous thrombosis, 20–30% have either had a surgical event in the past month or have recently had a leg injury requiring a cast or other immobilization. A known malignancy is present in at least 15–20%.

With advancing age, other thrombogenic factors play an increasingly important role (venous status, obesity, reduced mobility, pregnancy, malignancies, autoimmune conditions, and hormonal treatment). Several hereditary coagulation disorders are associated with an increased risk of thrombosis. More needs to be known about the causes of hereditary venous thromboembolism; identified defects account for only about 50% of cases.

Incidence of thrombosis in different clinical materials

The figures mentioned in Table 7.1 refer to the frequency of spontaneous DVT when thrombosis prophylaxis is not given. The ratio of symptomatic to asymptomatic DVT is approximately 1 : 10. Prophylaxis is nowadays an established practice in connection with surgery.

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Table 7.1 Average frequency of asymptomatic and symptomatic DVT and PE diagnosed in well-controlled studies of more than 10 000 patients.

	Percentage
Medicine	
Stroke	20–50 (in the paretic leg)
Acute myocardial infarction	5–30
Surgery	
Elective hip surgery	59
Hip fracture surgery	53
General surgery	29
Neurosurgery	29
Gynecologic surgery	19
Prostate surgery, transurethral	11
Average frequency of lethal PE	
All kinds of surgery	0.8
Hip fracture surgery	7.1
Elective hip surgery	2.4
Trauma (different types)	1.0
Stroke	1–2
Infectious disorders	0.7
Acute internal medicine	0.4

There is no up-to-date information about the incidence of DVT and severe PE in patients with acute myocardial infarction.

Venous thrombosis

Diagnosis

Clinical suspicion

Risk factors for DVT, besides age, are a previous VTE, recent surgery, trauma, recent immobilization, pregnancy, oral contraceptives of combination types, postmenopausal hormone replacement (HRT) or

Table 7.2 Medical history/clinical findings in DVT (Wells' score).

	Points
Cancer treatment during the past 6 months	+1
Lower leg paralysis or plastering	+1
Recent immobilization for more than 3 days or major surgery within the past 12 weeks	+1
Local tenderness over the deep venous system	+1
Swelling of the entire leg	+1
Calf >3 cm thicker than the other calf, measured 10 cm below tuberositas tibiae	+1
Pitting edema only in the leg with symptoms	+1
Enlarged superficial collateral veins	+1
Earlier documented venous thrombosis	+1
Other diagnosis at least as plausible as DVT	–2

Total points: <1 p = low probability; 1–2 p = medium probability; >2 p = high probability of DVT.

estrogen treatment in prostate cancer, infection, or malignancy (Table 7.2). VTE can also be due to hereditary defects.

The cardinal symptoms are swelling, burden pain and sometimes, when resting, pain in the thrombotic leg, where an enlarged vein structure and palpation soreness are often observed, sometimes also inflamed superficial veins (thrombophlebitis). Slight fever is a common sign. The more proximal the DVT, the greater is the risk of PE. More than half of all cases of proximal DVT have PE with or without symptoms. Corresponding symptoms are sometimes seen in an arm affected by a venous thrombosis, and such venous thrombosis may also cause PE.

Differential diagnoses

Erysipelas, *Borrelia* infection, ruptured Baker cyst, ruptured Achilles tendon, bruised or ruptured muscle, venous insufficiency, cardiac failure, hypoalbuminemia, etc. An instrument for standardizing anamnestic statements and estimating the probability of a diagnosis of DVT is provided by the Wells' score (see Table 7.2).

Tools for confirming or excluding clinical suspicion of venous thrombosis

Ultrasound diagnostics (ultrasound with Doppler, mapping the flow)

A noninvasive method was shown in meta-analyses to have a sensitivity of 96% and a specificity of 93%, compared with phlebography, in DVT with symptoms. In asymptomatic DVT the sensitivity is considerably lower (less than 60%). For DVT in the veins of the lower leg, the sensitivity is about 89%.

Phlebography (venography)

This is still used as a reference in comparative studies of different methods for diagnosing DVT (in both upper and lower extremities). A *direct finding* is a picture of a thrombosis surrounded by contrast. An *indirect finding* is failure of contrast to fill the veins; however, this may be due to causes other than a thrombosis.

Limitations: Distinguishing a new thrombosis from older clots in phlebographic images can be difficult. The method cannot always exclude DVT proximal of the inguinal ligament because of intestinal content, obesity, degree of contrast filling, etc.

Computed tomography (CT)

Computed tomography can demonstrate a thrombosis in sizeable veins, for example vena cava superior and inferior, vv iliaca, vv axillaris, vv subclavia, and thromboses in splanchnic vessels.

Limitations: CT is often suboptimal for diagnosis of venous thrombosis in cerebral sinus, since the image is symmetric and difficult to evaluate.

Note that if your investigation requires intravenous injection of contrast (e.g. phlebography and CT), it should be avoided in kidney failure and/or in treatment with certain drugs (metformin).

Magnetic resonance angiography

Magnetic resonance (MR) angiography can visualize a thrombosis in all large veins. It may be the method of choice for diagnosing DVT during pregnancy, if ultrasound examination fails to confirm the diagnosis. MR is a priority method for confirming clots in cerebral vein sinus. One advantage is that it provides some information even without injection of contrast or at least requires less contrast than phlebography.

Limitations: MR is not always available and is not yet established for DVT examinations. The usual contraindications for MR technique apply.

Analysis of D-dimer

There are various methods for analyzing fibrin D-dimer, with a wide range of sensitivity and specificity. Plasma levels of fibrin D-dimer do not

differ between women and men. It is primarily a negative predictor, that is, an unelevated level, together with low clinical probability, may be a basis for excluding thrombosis.

Limitations: The result is difficult to evaluate. Not enough is known about D-dimers in recurrent thrombosis. In hospitalized elderly people and patients with multiple illnesses the level is often increased without a confirmed venous thrombosis. Pregnancy often causes a spontaneous increase in D-dimer levels. Bleeding and inflammation may cause an increase.

Vein thrombosis in the arm

This group consists of about 4–10% of all vein thrombosis. Mostly you will find factors increasing the risk of VTE, for example hormones, trauma, hereditary thrombophilia. A small group seems to be missing a trigger factor (idiopathic thrombosis). Treatment studies are lacking and the most common treatment is as for vein thrombosis in the leg.

Vein thrombosis in v portae, v hepatica (Budd–Chiari syndrome) and v mesenterica

These types of vein thrombosis are often associated with other diseases such as blood malignancies, cancer, but also more "trivial" inflammatory diseases in connection with the liver, gallbladder, and pancreas. The diagnosis is often confirmed with ultrasound (Doppler) or CT scan and first line of treatment is LMH.

Superficial thrombophlebitis

Inflammatory conditions may be found in superficial veins because of endothelial damage in connection with local trauma, peripheral vein needle, infection, drugs that irritate vessels, etc.

Varicose veins seem to increase the risk of phlebitis. Venous thrombophlebitis is a secondary phenomenon in Behçet's disease, Buerger disease (thromboangiitis obliterans), and malignancy. Such a thrombophlebitis can occur together with DVT, and therefore a strict physical examination is important.

Phlebitis in v saphena magna or parva, emptying directly into the deep venous system, is a possible source of PE. With the clinical sign of this superficial phlebitis, it may also be necessary to exclude DVT as well as PE in the patient, because the treatment will be different.

Pulmonary embolism

Clinical suspicion

Given a clinical suspicion of PE, prompt and adequate action is critical. Risk factors for PE are previous venous thromboembolism and besides

this principally the same factors as for DVT risks (see Table 7.1 and section on Venous Thrombosis). Some patients have a known heredity for VTE.

The cardinal symptom of PE is impaired physical capacity with symptoms of breathlessness (dyspnea). The symptoms can appear relatively suddenly but can also fluctuate and worsen over time (usually within a week). Various types of arrhythmia, dizziness, chest pain, and retrosternal non-precise discomfort may occur. Ten percent or less of the patients have complaints such as pleuritic pain or hemoptysis. The symptoms can often be related to lung function, that is, in patients suffering from pulmonary emphysema, symptoms become dramatic more quickly than in healthy, often young, patients with no pulmonary disorder.

Among patients with symptomatic PE, phlebography or ultrasound examination confirms an asymptomatic DVT in the legs in 40–60%. These findings support a clinical suspicion of PE, which must be considered in the choice of therapy, for example thrombolysis. Attempts have also been made to create a system for scoring the diagnostic probability of PE. The example in Table 7.3 is taken from a report by the Swedish Council on Health Technology Assessment (SBU).

Table 7.3 Medical history/clinical findings in PE.

	Points
Age 60–75 years	+1
Age above 79 years	+2
Recurrence of earlier embolism	+2
Surgery in the past 12 weeks	+3
Heart rate at rest above 100/min	+1
pCO_2 less than 4.8 kPa	+2
Pulmonary X-ray	
Atelectasis	+1
Unilateral elevation of diaphragm	+1
PaO_2 below 6.5 kPa	+4
6.5–7.99	+3
8.0–9.49	+2
9.5–11.0	+1

Total points: <5 p = low probability; 5–8 p = medium probability; >8 p = high probability of PE.

Tools for confirming or excluding clinical suspicion of PE

Pulmonary X-ray

The X-ray image is a means of revealing cardiac factors (heart failure etc.) that would explain the symptoms. It can also provide information about other differential diagnoses (pneumothorax, tumor, emphysema, etc.) and can be a guide in the evaluation of a perfusion scintigram, especially if it shows infiltration and/or emphysema.

Pulmonary scintigraphy

A complete pulmonary scintigraphic examination includes investigation of both perfusion of the lung with perfusion scintigraphy and ventilation of the lung with ventilation scintigraphy. The combination of defective perfusion and normal ventilation is a sign *mismatch*, which is a classic criterion of PE.

The results of the perfusion scintigram can be divided into three clinical categories.

1 *Normal perfusion* excludes PE (except in rare cases with an isolated and not totally occlusive thrombosis/embolus in a main pulmonary vessel).
2 *Inconclusive perfusion image*, requiring further complementary examination of the defect image. Provided a contraindication for contrast X-ray is not present, it may be cost-effective to avoid ventilation scintigraphy in favor of the recommended "CT lung" with spiral technique (see (**3**)).
3 *Clinically conclusive perfusion image*. In most cases this requires simultaneous access to a ventilation scintigram (alternatively, CT lung examination) and a pulmonary X-ray.

Pulmonary scintigraphy has been superseded by CT with spiral technique. However, in cases where contrast injection would be inappropriate, ventilation scintigraphy can be a necessary adjunct to perfusion scintigraphy, provided the scintigraphic image can be evaluated by a professional.

Limitations: Compared to CT, pulmonary scintigraphy is expensive (gamma-camera, staff, isotope, etc.). The evaluation calls for a high level of skill and experience, and even then the interobserver variation is considerable.

CT with spiral technique (spiral CT)

Several studies have shown that lung CT is capable of excluding acute PE that would demand treatment, and no high frequency of recurrence has been observed during 3 months' follow-up. Moreover, the latest scanners provide significantly better image resolution. A great advantage of this method is the lower interobserver variability, especially compared with scintigraphy.

Pulmonary angiography
This "gold standard" method is expensive and is being superseded by spiral CT for PE diagnosis.

Limitation: Angiography laboratories are not available in every hospital. The examination requires a specialized team with high competence in evaluating images.

Magnetic resonance angiography
This method has not yet been fully evaluated for PE diagnosis.

Echocardiography
Echocardiography is a valuable method for evaluating myocardial loading. A skilled examiner can extract information about the dimensions (dilation) of the right ventricle, and indirectly estimate the pressure in the right ventricle and pulmonary artery. Echocardiographic findings are important parameters for judging the need for thrombolysis or, in rare cases, thoracic surgery. The right ventricle burden may have causes other than PE. A right ventricle burden confirmed by echocardiography may be an indication for continued investigation of a possible PE. Note that an unconfirmed right ventricle burden does not rule out a submassive/massive PE.

Electrocardiography (ECG)
No specific ECG changes are present in PE. Arrhythmia, not infrequently atrial fibrillation, and/or a sign of right ventricle burden may lead to suspicion of PE. In combination with a clinical suspicion, these findings warrant further investigation.

Cardiac enzymes
Elevated levels of cardiac enzymes (troponin, creatine kinase, pro-brain natriuretic peptide, and brain natriuretic peptide) may sometimes appear as a sign of a cardiac burden in the absence of coronary disease. In PE patients an increased troponin level may also be sign of micro myocardial infarctions in the right ventricle of the heart.

Arterial blood gas
For diagnosing PE, both the sensitivity and specificity of blood gas analysis are low. A normal pO_2 is found in about 15% of PE patients, but pO_2 may be decreased due to many other reasons than PE in patients with respiratory symptoms. However, arterial blood gas may be useful to estimate the demand of oxygen in the PE patient.

Treatment of VTE

Nonpharmacologic treatment of lower-leg DVT

The patient should not be immobilized unless there are special reasons, such as intense pain, manifest edema, a fracture, etc. In order to avoid late symptoms, such as venous insufficiency and post-thrombotic syndrome, with a risk of developing venous ulcers (especially leg ulcers), the patient should start to use a compression stocking class 0–1 in the acute phase. After 4–6 weeks, when the leg is no longer swollen, it is recommended that the patient try a compression stocking class 2 (in exceptional cases, class 3). For lower-leg DVT, the compression stocking should not cover the knee. The basic recommendation is to wear the stocking in the daytime for at least 12 months. If the DVT is minor and confined to the lower leg without symptoms, the stockings can perhaps be used for a shorter time. Use should be prolonged if symptoms are still present after 12 months or the medical history or physical status indicate signs of venous insufficiency. A compression stocking loses its elasticity and effectiveness over time and should be replaced every 6 months.

In rare cases compression treatment is difficult or impossible, for instance if the patient has a severe arterial insufficiency with intermittent claudication and possibly pain at rest. However, the treatment is usually tolerable if the popliteal artery can be palpated.

Blood sampling prior to pharmacologic/surgical treatment of VTE

The following blood tests should precede start of anticoagulation. However, normally it is not necessary to have the *results of the analyses* before start of treatment.

- *B-Hb and B-EVF*. Low levels can imply suspected bleeding or other disease and should lead to caution concerning anticoagulation treatment. High levels can indicate myeloproliferative disease (polycythemia vera) as an etiology to the thrombosis.
- *B-PLT*. Low levels can indicate a hematologic disorder with an increased risk of bleeding and should lead to caution concerning anticoagulation treatment. However, an arbitrary rule is that B-PLT 80×10^9/L or above is sufficient to keep primary hemostasis intact. High levels can also indicate a hematologic disorder and an increased level (platelet count significantly above 1000×10^9/L) can be a risk of thrombosis.
- *P-APT time*. A prolonged APT time can occasionally indicate a specific coagulation factor deficiency but is primarily a marker of phospholipid antibodies/lupus anticoagulant and an increased risk of thrombosis. During treatment with UFH as well as with LMH, APT time can be prolonged or slightly prolonged, respectively. Vitamin-K antagonists (VKA) such as warfarin medication may somewhat prolong the APT time by decreasing coagulation factors prothrombin, FIX, and FX.

- *PT(INR)*. The basic level of PT(INR) can be important for the choice of drugs for treating venous thrombosis and PE. Spontaneously elevated PT(INR) is seen in impaired liver function, alcoholism, vitamin K deficiency, primary or secondary liver malignancy, etc. Spontaneously elevated PT(INR) implies an increased bleeding risk but does not necessarily mean that the patient is protected against venous thrombosis. On occasion, one may see patients with a healthy liver but a hereditary deficiency of coagulation factor VII or X, resulting in spontaneously increased level of PT(INR). Bleeding is usually rare in patients with hereditary deficiency of FVII and more common in those with deficiency of FX.
- *S-creatinine*. Several anticoagulation drugs (LMH, fondaparinux, dabigatran etexilat, etc.) are dependent on adequate kidney function. As a marker of kidney failure, S-creatinine may therefore be important to analyze for the dosing of these drugs (clearance below 30 mL/min should lead to restriction and dose reduction of UFH, LMH, thrombin, and FXa inhibitors).

Treatment involving surgery

Pharmacologic treatment for DVT aims primarily at eliminating the risk of PE by reducing the likelihood of increasing an existing thrombosis.

- *Surgical thrombectomy* is used in rare cases, for example isolated DVT in the iliac veins in pregnant women or, in special cases, thrombectomy in the pulmonary arteries.
- *Vena cava filter*. A temporary or permanent filter in the v cava can be used in special cases to reduce the risk of PE when conventional medication is wholly or partly ruled out (contraindication of anticoagulants in proximal DVT (less than 1 week old), serious bleeding complications during ongoing anticoagulant treatment of proximal DVT (1 week to 1 month old), and certain cases of PE in spite of adequate treatment). There are no studies supporting decreased mortality when treating with v cava filter. Permanent v cava filter should be used with high restriction and in very special cases!
- *Stenting* involves placing a plastic or metal tubular structure in a vessel with a narrow lumen in order to prevent turbulence and/or stoppage in the blood flow. Stenting is still in the experimental stage for treating thrombosis in large veins.

Drug treatment in deep vein thrombosis and PE

Anticoagulation is the standard treatment for preventing progression of VTE, leaving the rest to the body's fibrinolytic system. The drugs in use are UFH, LMH, thrombin inhibitors, inhibitors of FXa, and VKA drugs.

If proximal venous thrombosis or PE is strongly suspected clinically and it is estimated that the diagnosis will not be confirmed within 3 h, the patient should, *without waiting for an objective diagnosis*, be given UFH 5000 IU i.v. or LMH s.c.

Subcutaneous LMH is currently the method of choice for patients with VTE. Patients with venous thromboses and, nowadays, certain PE patients are treated with LMH in open-care units. One side-effect of treatment with LMH is, of course, bleeding. The bleeding risk is increased in patients with reduced renal function. Thrombocytopenia (HIT type 2) is rare in treatment with LMH, but LMH should not be prescribed for patients with a confirmed HIT type 2.

Several LMH are registered for treatment and available for s.c. injection. Dalteparin is recommended in a dose of 200 anti-FXa U/kg bodyweight daily and tinzaparin in a dose of 175 anti-FXa U/kg bodyweight daily. For enoxaparin, the dose is 1 mg/kg bodyweight twice daily or 1.5 mg/kg bodyweight daily in uncomplicated cases.

Treatment with LMH as above can be effective and safe without laboratory monitoring. When LMH is used at the same time as the start of VKA treatment, it should accompany the latter for at least 5 days and until PT(INR) reaches a therapeutic level, usually 2.0–3.0.

If renal function is impaired (clearance less than 30 mL/min), LMH may accumulate in the patient. UFH can be an alternative because it is possible to monitor with APT time.

LMH can affect APT time differently, depending on the type of analysis, so APT time cannot be used to monitor treatment with LMH.

If LMH is used despite impaired renal function, the concentration can be checked by analyzing anti-FXa. This should be done 3–4 h after the injection of LMH and the level of anti-FXa should be in the range 0.5–1.2 U/mL. If anti-FXa is above 1.2 U/mL, the patient has accumulated LMH and the dose should be reduced. A single daily dose of LMH is preferable to twice daily if renal function is impaired. If reduction of the dose is indicated, the dose should be reduced by at least 30–50%.

Treatment of DVT in patients with malignancy

There is a known malignancy in 15–20 % of patients with venous thrombosis. Monitoring of VKA drugs is liable to be difficult in these patients, due to defective liver function, metastases, etc. Today there is evidence that these patients can be treated with dalteparin alone. The recommended treatment regimen is a full dose of dalteparin during the first month, followed by a reduction to 75% of the full dose. Continuous treatment is often recommended in these patients, with a regular check-up at least every 6–12 months.

UFH

When a strong clinical suspicion of acute PE or DVT is present, especially proximal to the knee joint, an immediate bolus i.v. injection should be provided initially, without waiting for a definite diagnosis. The bolus dose is usually 5000 IU i.v. If the diagnosis is confirmed and UFH is chosen, a continuous i.v. infusion of 400–500 IU/kg bodyweight per day is suggested. APT time should be checked once a day, preferably at the same time every day (in extensive VTE or a risk of bleeding, the first control is performed within 12 h). An APT time within the desired range (according to your local laboratory) is the aim; the target range may differ between different laboratories. Heparin treatment should be continued for at least 5 days after the beginning of medication with VKA drugs and until PT(INR) has reached the therapeutic level, usually 2.0–3.0.

Treatment of superficial thrombophlebitis

Treatment depends on the location and degree of the phlebitis. NSAIDs and Hirudoid can both be used in minor phlebitis. For phlebitis in v saphena magna or parva, we recommend treatment with LMH (full dose for at least 2 weeks). An alternative treatment for phlebitis in these large veins may occasionally still be surgery. In secondary phlebitis, treatment of the underlying cause is obviously required.

Bleeding complications in treatment with UFH and LMH

Bleeding can occur during treatment with LMH as well as with UFH. Both drugs have a short half-life and for moderate bleeding it is sufficient to withdraw the drug.

Bleeding from the injection site, nose, or gums is treated locally as the first option (a compress moistened with tranexamic acid, mouthwash with tranexamic acid injection solution diluted 1 + 1 with water, or mouthwash with tablets of tranexamic acid, dissolved in water). Blood-stilling cotton can be used for nose bleeding.

UFH can be neutralized with protamine, 1 mg of which neutralizes 100–150 IU heparin. A maximum of 50 mg protamine should be given i.v. If needed, one additional dose may be given i.v. to reach a desired APT time. It is important to allow an interval of about 3 h between the two injections of protamine.

The dose should be chosen so that only half of the circulating amount of heparin is neutralized. *Caution is required because a surplus of this antidote causes platelet aggregation and thereby thrombocytopenia, which can increase the risk of bleeding.*

LMH affects platelet function less than UFH does. However, protamine does not neutralize LMH to the same degree as it does for UFH. An overdose of LMH may also induce thrombocytopenia (see caution

in previous paragraph) and in that way lead to bleeding complications. Protamine 1 mg is said to neutralize the prolongation of coagulation time (APT time) caused by 100 U anti-FXa.

Desmopressin might be considered for serious bleeding related to treatment with UFH/LMH (UFH causes platelet inhibition and prolongation of bleeding time). Treatment with UFH/LMH can then be continued if the bleeding stops.

Thrombolytic treatment

Thrombolytic treatment should perhaps be used more frequently in treatment of VTE. A drawback is the difficulty of selecting the appropriate patients for this risky treatment. The treatment is performed either systemically or locally, via radiologic intervention with special catheters. However, *thrombolysis is not recommended as a first treatment option even in PE*, unless the patient is hemodynamically unstable (American College of Chest Physicians (ACCP), Evidence-Based Clinical Practice Guidelines, July 2004). Drugs that are appropriate for thrombolysis of VTE are t-PA, which has replaced streptokinase. In addition, but without evidence, reteplase and tenecteplase can be used, for example if t-PA is not available.

An objectively visualized VTE is required in routine thrombolytic treatment of VTE. Blood samples should be drawn prior to the treatment for analyses of fibrinogen, Hb, PLT, PT(INR), APT time, creatinine, and blood group.

Thrombolytic treatment and thus the increased risk of bleeding must be weighed in every case against the value of rapid thrombolysis and the possibility of preventing post-thrombotic disorders in the long run. Take advice from a skilled colleague before initiating the treatment! **Prior to treatment, consider possible actions in the event of bleeding complications.**

Thrombolytic therapy in venous thrombosis

Thrombolytic treatment may be considered in patients with a thrombosis that is still fresh (especially thrombosis with a history below 3–4 days). The treatment may be relevant for thrombosis in large veins and the upper and lower legs, as well as in the cerebral venous sinus. In exceptional cases, thrombolysis can be considered in body vessels (vv cava, portae, hepatica, renales, etc.). Thrombolysis is less likely to be successful in a total as opposed to a partial occlusion. **The treatment is associated with a risk of serious bleeding complications.**

"Local thrombolysis" or surgery can be an option for a thrombosis of short duration. In exceptional cases it may be worth considering the use of a "v cava filter" prior to thrombolysis.

Thrombolytic therapy in pulmonary embolism

Thrombolytic treatment may be considered in acute or subacute massive PE. *It is not recommended as a first treatment option if the patient is hemodynamically stable.*

Criteria for unstable hemodynamic state when thrombolysis is being considered

Objectively confirmed PE and at least two of the following criteria.

- Hypotension with systolic blood pressure <100 mmHg
- Elevated troponin
- At least two of the "triad of death": dyspnea (SO_2 <95% + dyspnea), syncope, heart rate > systolic blood pressure
- Peripheral oxygen saturation = SO_2 <95% in patients with previously healthy lungs
- Affected right ventricle confirmed by echocardiogram
- High BNP (>500 pg/mL).

Indications may suggest immediate commencement of thrombolytic treatment in patients with hypotension and shock.

Before starting thrombolytic treatment of PE, an objective diagnosis is desired, as follows.

- Echocardiography to determine whether the right ventricle is affected.
- Spiral CT of thorax with confirmed embolus, or
- Pulmonary angiography with confirmed embolus, or
- Perfusion and ventilation scintigraphy with a "high probability" of acute PE.

Thrombolytic drugs

Recombinant tissue plasminogen activator (rt-PA)

Recombinant plasminogen activator has been tested in a variety of doses and regimens in order to arrive at the optimal dosage.

Treatment with UFH in connection with rt-PA should be stopped ½–1 h prior to thrombolysis of PE by infusion of rt-PA. The infusion of UFH may be resumed immediately or within 1–2 h after the completion of rt-PA.

Several studies have shown that in massive PE, short-term treatment with a high dose of rt-PA normalizes hemodynamics much more quickly than treatment with UFH alone. If the patient does not show clear signs of improvement within 24 h, one must either consider another reason for the disorder or repeat the thrombolytic treatment.

Bleeding complications in thrombolytic treatment

- Treatment should be stopped
- The effect on coagulation is corrected by supplying plasma
- Tranexamic acid

- Samples should be drawn for analysis of fibrinogen levels. Low levels (P-fibrinogen below 1 g/L) should be dealt with by adding fibrinogen concentrate.

VKA drugs

Vitamin-K antagonist (VKAs) should be administered together with UFH/LMH or as soon as the diagnosis has been confirmed. VKA drugs are not used in pregnancy on this indication; see Chapter 14.

Monitoring the treatment can be difficult in patients with alcoholism, drug abuse, malabsorption, severe liver function disorder, malignancy, etc.

The most common VKA drug in the Western world is warfarin. Some patients are sensitive to the color in the pills, indigo carmine (E132). Itching or temporary skin exanthema occurs in rare cases. In these patients, prescribe warfarin without indigo carmine. Alternatives to warfarin include acenocoumarol and phenprocoumon (Table 7.4).

Note that head injury or onset of acute focal neurology in patients on VKA or other anticoagulant treatment *always indicates a suspected intracranial bleeding* and requires a neuroradiologic examination (CT of the brain) and may require immediate adequate treatment. *Note* also that in connection with head trauma, several days may pass before symptoms appear because bleeding may take time to develop.

Intensity of treatment

Traditionally, treatment with VKA drugs commonly aims for PT(INR) in the range 2.0–3.0. There is now evidence in favor of less intense treatment for some venous thrombosis with a low risk. The range aimed for in low-intensity treatment is PT(INR) 1.5–2.0. There is, however, still no clear evidence that low-intensity treatment in high-risk patients reduces the risk of thrombosis relapse. Neither is it yet certain that the risk of bleeding is reduced to a greater extent than with treatment of an ordinary intensity (PT(INR) 2.0–3.0).

Table 7.4 VKA drugs.

	Tablet dose mg	Half-life (h)	Protein binding %
Warfarin	2.5	35–45	98–99
Warfarin without E132	2.5	35–45	98–99
Acenocoumarol*	1.0	9	98.7
Phenprocoumon	3.0	160	99.6

*Also a metabolite, has a VKA effect, and elimination of the drug is dependent on kidney function.

A change from hospital to outpatient care with less frequent monitoring increases the risk of deviations from the goal range of PT(INR). It is therefore desirable to check PT(INR) within a week after discharge from hospital. If it is then within the therapeutic range, the interval between tests may be lengthened successively, but to no more than 6–8 weeks.

The duration of treatment with VKA drugs is designed to reduce the risk of recurrence. There is no evidence that this treatment reduces mortality. The optimal medication time after VTE has been shown to be longer than was earlier assumed. Most patients are probably helped by 6 months of medication after the first VTE. In patients with distal thrombosis and an eliminated risk factor (e.g. postsurgical thrombosis), medication time can usually be shortened to 3 months (if a coagulation investigation is indicated, it is advisable to await its result before discontinuing the treatment).

Table 7.5 shows some mechanisms for interaction with VKA drugs, and their effect on PT(INR).

It may be necessary to extend medication time beyond 6 months in the event of remaining risk factors, such as malignancy, a deficiency of

Table 7.5 Mechanisms for interaction with VKA drugs.

Reason	PT(INR)
Interactions with drugs	Increases or decreases
Increased vitamin K intake (spinach, broccoli, sauerkraut, etc.)	Decreases
Decreased food intake (vitamin K)	Increases
Parenteral nutrition for a long time	Increases
Decreased absorption	Decreases
Forgotten to take the tablet	Decreases
Hypermetabolism, increased physical activity	Decreases
Infection with fever	Decreases
Immobilization, decreased physical activity	Increases
Liver disorder (illness, addiction)	Increases
Ginko biloba	Increases
Curbicin (may be due to vitamin E)	Increases
Hypericum	Decreases
Kan Jang®	Decreases
Strawberries	Decreases

any of the coagulation inhibitors antithrombin, protein C, or protein S, presence of cardiolipin antibodies or lupus anticoagulant – in particular with co-existing systemic lupus erythematosus and possibly also if FVIII is elevated (over 2.3 IU/mL). Moreover, presence of the very common FV Leiden mutation (1691G>A), causing APC resistance, or the prothrombin mutation (20210G>A) in heterozygous forms, seems to extend the risk of a thrombosis relapse little and accordingly they do not indicate a prolonged treatment. Homozygosity for one or a combination of the above-mentioned defects obviously means a greatly increased risk of recurrence and therefore indicates prolonged treatment. Irrespective of the outcome of the investigation of the coagulation system, clinical circumstances, such as extended venous insufficiency, obesity, immobilization, or decreased pulmonary function, can be a relative indication of a prolonged treatment time. Recurrence of thrombosis in the same leg extends the risk of post-thrombotic complications and is thereby also a relative indication of a prolonged anticoagulation.

After a second VTE event, it seems obvious to provide a prolonged secondary prophylaxis, but medication for more than a couple of years is associated with a gradual increase in the risk of serious bleeding. An alternative to consider in this situation is to lower the intensity of treatment to the goal range of PT(INR) 1.5–2.0, for which there is some support concerning DVT prophylaxis. For patients with a very high risk of recurrence, for instance with malignancy or severe thrombophilic defects, there is a lack of evidence at present for lowering the intensity of treatment with VKA drugs.

If a remaining risk makes it desirable to continue to give VKA drugs after a second recurrence, the treatment should be reconsidered yearly. At reconsideration, compliance, contraindications, any incident that has occurred, etc. should be weighed against the benefit of the treatment, and an active decision should be made to continue or interrupt the treatment.

Termination of treatment with VKA drugs

Treatment of VTE patients with VKA drugs can be ended without first reducing the dose. This is apparent from a great deal of experience and there is no evidence that abrupt discontinuation of treatment can lead to any form of complication. If the patient is to be treated with platelet inhibitor (ASA), there should be an interval of at least 2–3 days between the last VKA dose and the first ASA dose in order to avoid the risk of bleeding due to drug interaction. Note that there are now some rather new studies indicating that ASA has an effect on DVT secondary prophylaxis.

Note: **please study all possible interactions when you prescribe an additional drug to a patient being treated with a VKA drug.**

High PT(INR) during VKA treatment

Measures to be taken when PT(INR) diverges from goal range without simultaneous bleeding

- *PT(INR) above 6*. Administer liquid vitamin K 1–3 mg per os (p.o.) or i.v. Reduce dose of VKA. Check PT(INR) within 2 days (over a weekend, within 3 days). Particular caution as a high bleeding risk is present.
- *PT(INR) 4–6*. Possibly administer liquid vitamin K 1–3 mg p.o. or i.v. Reduce dose of VKA. Check PT(INR) within 2 days (over a weekend, within 3 days).
- *PT(INR) 3–4*. Adjust VKA dosage. Check PT(INR) soon after.
- *PT(INR) 2–3*. Traditional goal range for PT(INR) in anticoagulation treatment.

Divergence from PT(INR) goal range accompanied by minor bleeding

- *PT(INR) above 4*. Reverse PT(INR) to a therapeutic goal range, e.g. with vitamin K 1–3 mg p.o. or i.v. Reduce dose of VKA. Check PT(INR) the next day.
- *PT(INR) 3–4*. Reverse PT(INR) to a therapeutic goal range, for example with vitamin K 1–3 mg p.o. or i.v. Adjust VKA dosage. Check PT(INR) soon after.
- *PT(INR) 2–3*. Traditional goal range for PT(INR). Consider vitamin K 1–3 mg p.o. and dose adjustment, depending on the type of bleeding.

Serious or major bleeding in patients on VKA drugs

- Immediately consider reversing PT(INR) to below 1.5.

Reversing PT (INR) in treatment with VKA drugs

High doses of vitamin K create a resistance to VKA drugs, so repeated small doses (1–3 mg) are preferable. (Vitamin K injection liquid may be administered per os. The same amount in mg as you wish to inject intravenously. If given per os, remove the needle of the injection syringe and give the drug perorally.) It takes 6–8 h for the effect of vitamin K to materialize, which in most cases is too slow in an acute situation. The effect lasts about 24 h after the dose has been given.

Factor concentrates for reversing VKA should be dosed according to weight and current and desired PT(INR). With these drugs, the patient receives coagulation factors directly without volume loading and the drug takes effect promptly. The PT(INR) may be checked about 10 min after the dosage, to estimate if the amount of factor concentrate given is sufficient or not. The effect diminishes after 6–8 h, so simultaneous administration of vitamin K may be indicated for acute reversal of PT(INR).

Plasma (not necessarily fresh-frozen) is dosed by weight, current and desired PT(INR). A disadvantage is that acute reversal of PT(INR) in

elderly patients is liable to result in volume loading, with a risk of cardiac failure. The preparations (blood grouping, basic tests, and thawing of plasma) often cause an unacceptably long delay. The effect of plasma diminishes after about 6 h.

Hemostatic treatment with other drugs (desmopressin) and other factor concentrates, including recombinant FVII, etc.
See Chapters 4 and 5.

Elective adjustment of PT(INR) in preparation for risk situations (e.g. tooth extraction, surgery, etc.)
Tooth encroachment (extraction etc.)
PT(INR) below 2.4 is recommended and can be obtained by reducing the VKA dose in good time (this time differs between different VKA drugs with different half-lives) before the day of the operation. *Check PT(INR) prior to the operation*. Local hemostatics include tranexamic acid tampon and/or mouthwash, suture, etc. Restore the therapeutic level of PT(INR) as soon as there is no contraindication.

Intramuscular injection is contraindicated. For such injections to be safe, PT(INR) must be reduced below 1.5.

Intramuscular vaccinations are contraindicated without reversing PT(INR) in patients on VKA treatment. However, most vaccines can be injected subcutaneously; when in doubt about this, consult a vaccination unit.

Local anesthesia
PT(INR) should be below 2.4. Reduce the VKA dose as in dental surgery.

Minor surgery
PT(INR) below 2.0 is recommended. Reduce the VKA dose and monitor PT(INR). When PT(INR) is below 2.0, supplement with LMH (dalteparin 5000 U s.c. or enoxaparin 40 mg s.c. or tinzaparin 4000 U s.c.) × 1. This LMH dose is maintained until VKA treatment is reinstituted.

Major surgery and surgery with a high bleeding risk
This includes liver biopsy, spinal-epidural anesthesia, lumbar puncture, gastroscopy/coloscopy with biopsy, joint puncture, abdominal, prostate or orthopedic surgery, etc. PT(INR) below 1.5 is recommended. Reduce the VKA dose and monitor PT(INR). When PT(INR) is below 2.0, supplement with LMH as above until PT(INR) after surgery has returned to the therapeutic level.

Note that when surgery under spinal-epidural anesthesia is planned, LMH in prophylactic dosage should be administered *at least 10 h prior to surgery*, often the evening before the surgery.

If PT(INR) needs to be adjusted prior to acute surgery, see the section on reversing PT(INR).

Low levels of PT (INR)

Monitoring therapy as follows in patients treated prophylactically with VKA drugs, for example patients with a mechanical cardiac valve prosthesis or during the first 3 postoperative months in patients receiving a biologic cardiac valve prosthesis.

PT(INR) 1.8–2.0	Adjust the dose of the VKA drug	
PT(INR) 1.6–1.7	Weight below 60 kg	Dalteparin 5000 U s.c. × 1 or Enoxaparin 40 mg s.c. × 1 or Tinzaparin 4500 U s.c. × 1
	Weight above 60 kg	Dalteparin 10 000 U s.c. × 1 or Enoxaparin 80 mg s.c. × 1 or Tinzaparin 10 000 U s.c. × 1

Extra dose VKA drug + increased maintenance dose unless the low PT(INR) is due to a missed dose.

PT(INR) 1.3–1.5	Dalteparin 200 U/kg bodyweight	s.c. × 1 or
	Enoxaparin 1.5 mg/kg bodyweight	s.c. × 1 or
	Tinzaparin 175 U/kg bodyweight	s.c. × 1

Increase the dose of the VKA drug. Continued outpatient treatment with frequent monitoring of PT(INR).

PT(INR) below 1.3 Consider hospitalization for observation. LMH in full dose or UFH infusion. Adjust the dose of VKA to a therapeutic PT(INR).

Intoxication with VKA drugs

Be sure that intoxication is present. This can normally be done by checking PT(INR). Evaluating PT(INR) must be done in relation to the effect of the VKA drug being used. The longer the half-life, the longer it takes for PT(INR) to be affected. At the same time, the duration of the effect increases with the drug's half-life (see Table 7.4).

If the patient is bleeding, begin treatment without waiting for laboratory results.

- Check if the patient is bleeding.
- Check PT(INR), APT time, and B-Hb.
- Give active charcoal in repeated doses.

- Consider antidote (vitamin K) when the PT(INR) result is known.
- Consider factor concentrate.
- Consult coagulation specialist on call.

Bleeding during treatment with UFH/LMH, thrombin-, and FXa- inhibitors

- Stop the treatment, including UFH.
- Check B-Hb, platelet count, APT time, PT(INR) (if simultaneous VKA treatment).
- Check APT time, for instance every 4 h.
- Consider injection of protamine 10 mg/mL. Give 50 mg = 5 mL i.v. during 10 min (50 mg neutralizes about 5000 U of UFH). The dose can be repeated with caution when needed.
- For serious bleeding, factor concentrate and/or plasma can be administered.
- When APT time has reached the therapeutic level, and provided the patient does not bleed, UFH can be reinstituted at an adjusted dose if treatment is to be continued.

LMH

Dalteparin, enoxaparin, and tinzaparin have no effective antidote. Bleeding can be somewhat reduced with protamine, which can be administered in the same way as for bleeding due to UFH.

Bleeding during treatment with thrombin inhibitors or with FXa- inhibitors

These new antithrombotic drugs do not yet have a known antidote. Bleeding requires symptomatic treatment. See Chapter 5.

Primary prophylaxis against VTE

Thrombosis prophylaxis is recommended in surgery for patients over 45 years of age who are to have surgery for more than half an hour.

There are a variety of methods for preventing VTE. Mechanical methods alone are less effective than drug prophylaxis, and the effect of mechanical methods against PE has not been documented. There are indications, in particular cases, that a filter in vena cava inferior can be used as prophylaxis against PE in patients for whom pharmacologic treatment is contraindicated or liable to lead to complications. A cava filter can be applied percutaneously for both temporary and permanent use.

Physical prophylaxis in connection with surgery

Exercise treatment and early postoperative mobilization are important for diminishing the postoperative risk of thrombosis. Bedridden patients should be told to flex their feet up and down regularly and to advance to a bed-bicycle, a chair-bicycle, and walking exercises as soon as possible. Exercise treatment by itself is not sufficient to prevent thromboembolism.

Thromboses often occur while surgery is in progress, so it is advisable to improve the venous return by elevating the foot of the bed and using graded compression stockings or intermittent mechanical calf muscle compression during surgery.

Drug prophylaxis in patients with a medical diagnosis

Patients with a known bleeding tendency should not be given LMH or UFH as a routine. On the other hand, a known bleeding tendency (e.g. just a prolonged capillary bleeding time etc.) does not necessarily indicate a decreased risk of DVT as a postoperative complication.

Patients with medical diseases with a moderate or high risk of VTE may be treated with LMH 5000 IU dalteparin or 40 mg enoxaparin once daily.

Drug prophylaxis in surgery

Low molecular weight heparin (half-lives: dalteparin i.v. 2 h, s.c. 4 h; enoxaparin s.c. 4 h; tinzaparin s.c. 1.5 h) is the predominant prophylactic method in surgery. Treatment with LMH starts pre- or postoperatively and is given as dalteparin s.c. in doses of 5000 anti-FXa units/day or as enoxaparin 40 mg/day. In order to reduce the risk of bleeding, the drug prophylaxis should start 10–12 h prior to surgery (normally the previous evening), followed by one injection every evening. In general surgery, the treatment is recommended for **at least** 7–10 days, possibly for as long as the patient is immobilized. In high-risk surgery, the postoperative prophylaxis may be prolonged for 3–7 weeks, especially in patients whose risk profile includes malignancy or an earlier venous thrombosis.

For surgery under spinal or epidural anesthesia, thrombosis prophylaxis can be started pre- or postoperatively.

- *Preoperative start*. Provided kidney function is normal, it is recommended that epidural anesthesia is not performed until at least 10 h after discontinuing LMH prophylaxis.
- *Postoperative start*. We recommend that thrombosis prophylaxis is given as soon as surgical hemostasis permits, preferably as soon as 6 h after surgery.

Thrombin- and FXa inhibitors

The prodrug *dabigatran etexilat* is an oral thrombin inhibitor which in clinical trials has shown non-inferior results as compared to warfarin, both in acute treatment and secondary prophylaxis of DVT as well as of PE.

In the pipeline are several different new drugs in the group of oral FXa inhibitors. **Rivaroxaban** is the first, and in clinical trials has shown non-inferior results in the treatment of DVT as well as of PE. It has already been registered for these diagnoses as an indication, as acute treatment as well as secondary prophylaxis, and as prophylaxis against thrombosis in connection with orthopedic surgery.

Other drugs in the anti-FXa group are **apixaban, edoxaban**, etc., not yet for clinical use.

Fondaparinux (half-life 17–21 h) is a pentasaccharide and may be handled as a FXa inhibitor. It is registered for thrombosis prophylaxis in major orthopedic surgery. The drug should be used with great caution if kidney function is impaired. Laboratory monitoring is not normally required. The concentration of the drug can be assessed by analyzing anti-FXa. Fondaparinux has been reported to induce formation of antibodies but it is still uncertain if it can cause clinical HIT type 2. The drug does not have a specific antidote. However, it seems that its effect might be partially reversed by recombinant FVII.

For HIT see also Chapter 16. For rivaroxaban and dabigatran, see Chapter 11.

Dextran

Dextran is a plasma expander with flow-enhancing and antihemostatic properties that provides protection against thrombosis and PE. In order to counteract anaphylactic reactions, 20 mL of hapten-inhibiting low molecular dextran should be given first, followed after a few minutes by 500 mL dextran as an i.v. infusion. Caution is required in elderly patients with latent heart failure (cardiac overloading) and in dehydrated patients (risk of kidney damage). The use of dextran as protection against venous thrombosis nowadays is used less frequently, and is replaced by other more effective treatment.

VKA drugs

Vitamin-K antagonist drugs have a prophylactic antithrombotic effect in connection with surgery. However, as such treatment is difficult to monitor, it entails a greater risk of bleeding compared to treatment with LMH, UFH, or dextran.

Investigation of thromboembolic tendency

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CHAPTER 8

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Introduction

A coagulation investigation concerning biochemical thrombophilic disorders should be considered above all in relatively young patients (arbitrary limit, below 50 years of age) and in patients with heredity for venous thromboembolism. The investigation can be done on blood samples drawn at a coagulation unit or at a laboratory.

The coagulation investigation is usually undertaken after an acute episode, most often after three months or more. However, DNA analysis of mutations can be undertaken during the acute phase. The outcome of the coagulation investigation may be influenced by acute phase reactants, estrogen medication (oral contraceptives, HRT), VKA drugs, etc. The result can influence the decision about further treatment with vitamin-K antagonists and the investigation should therefore preferably be completed before making a final decision about the length and type of treatment.

In the first instance, a coagulation investigation in DVT/PE concerns the possible presence of APC resistance, FV Leiden (1691G>A) mutation, prothrombin (20210G>A) mutation, deficiencies of antithrombin, protein C or protein S. In certain cases the investigation can be extended to detect rare defects in fibrinogen and FVIII. The presence of phospholipid antibodies, such as cardiolipin antibodies, and lupus anticoagulant may also be related to the thrombotic disorder and should be included in the investigation. Modern studies do not support analyzing homocysteine in the investigation of coagulation concerning thrombophilia, but homocystinuria should be taken as a possible underlying cause of venous and arterial thromboembolism in younger patients.

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In "unexplainable" (idiopathic) DVT/PE, particularly in elderly patients, remember that phospholipid antibodies can occur both in cancer and in autoimmune disorders.

Box 8.1 Thrombosis history

- Have you had a thrombosis in the leg/arm?
- Have you had a thrombosis/embolus in the lung (PE)?
  - How many times?
  - When?
  - Reason for the thrombosis
  - After surgery, fracture, confinement to bed, pregnancy, contraceptives
  - Drugs? Other disease? Unknown?
  - What treatment did you receive?
- Do you have, or have you had, varices?
- Has any close relative had venous thromboses, thrombophlebitis, PE?
  - Which relatives and which condition?
- What drugs are you using?

Venous thromboembolism

Possible hereditary defect

Determine APC resistance = B(Lkc) mutation factor V gene (1691G>A), B(Lkc) mutation prothrombin gene (2021G>A), P-antithrombin, P-protein C, P-protein S free.

It is usually best to order all these analyses simultaneously. A deficiency of the coagulation inhibitors – a low level of antithrombin, protein C, or protein S – is often hereditary.

Abnormal fibrinogen, thrombomodulin, and plasminogen can also in rare cases be a cause of DVT/PE.

Investigation prior to prescribing oral contraceptives or postmenopausal HRT

Women who have had DVT/PE or who have heredity for VTE should be investigated and OCs with estrogen should not be prescribed. Check first if there is a known defect in relatives with DVT/PE.

No useful screening method is available at present to easily identify women with an increased risk of DVT/PE, but the above-mentioned investigation may be used in certain cases. If no defect has been found, there may still be a risk of DVT/PE, but at least the known risk factors have been excluded.

Acquired defects

Analyze P-antithrombin, P-protein C, P-protein S free, P-lupus anticoagulant, P-cardiolipin antibodies. For physiologic changes during pregnancy see Chapter 16.

Phospholipid antibodies and lupus anticoagulant

Thromboembolic complications due to the presence of phospholipid antibodies directed against cell membrane phospholipids (e.g. cardiolipin antibodies, antibodies against phosphatidylserine and lupus anticoagulant) occur in particular in pregnancy and also secondary to autoimmune disorders such as SLE, rheumatoid arthritis, and Sjögren syndrome, as well as in infectious diseases, especially bacterial infections (60–80% in HIV). Phospholipid antibodies lower the levels of many coagulation factors in the test systems.

Arterial thromboembolism

Analyze P-fibrinogen, P-factor VIII, P-VWF, P-PAI-1, P-homocysteine, P-lipoprotein(a). Note, however, that the first four are also known to be acute phase reactants.

Many studies have found that high levels of the above-mentioned components are associated with an increased risk of arterial thromboembolism. Some have also shown high levels of FVII and the presence of phospholipid antibodies (lupus anticoagulant/cardiolipin antibodies) in arterial thromboembolism. In addition, levels of other nonhemostatic components, such as S-CRP, are high.

Disseminated intravascular coagulation

Suspected or manifest DIC

For interpretations etc., see Chapter 16.

Indicators of DIC:

- *degree of hypercoagulation:* P-soluble fibrin, P-fibrin D-dimer
- *degree of consumption:* P-APT time, P-PT(INR), P-fibrinogen, B-PLT, P-antithrombin
- *degree of fibrinolysis:* P-fibrin D-dimer, P-fibrinogen.

Analyze trends! New bedside methods are being introduced. See Chapter 3.

Hypercoagulation (not acute DIC)

- P-soluble fibrin, P-fibrin D-dimer
- P-thrombin–antithrombin complex, P-prothrombin fragment 1+2 (analyses for research purposes).

Heart disease

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CHAPTER 9

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Ischemic heart disease

Stable ischemic heart disease

Prophylaxis against myocardial infarction in patients with stable angina pectoris and/or a previous myocardial infarction: ASA 75 mg once daily is the treatment of choice. In case of ASA intolerance or ASA allergy, use clopidogrel 75 mg once daily.

VKA, for example warfarin, may be used in secondary prophylaxis of myocardial infarction, especially in patients where there are other concomitant indications for VKA such as atrial fibrillation, cardiac valve prosthesis, or venous thromboembolism.

Unstable angina pectoris/non ST-elevation myocardial infarction (NSTEMI)

For signs of instability, such as repeated attacks of chest pain, combined with ECG changes and/or an increase in troponin, platelet-inhibiting treatment should be given in the form of ASA 300–500 mg as a loading dose followed by 75–160 mg once daily. ASA treatment should be given long term and re-evaluated at least yearly; continued treatment should be based on a positive benefit–risk analysis. Note that in patients with coronary artery stents the indication for long-term ASA treatment is strong (often considered as a "life-long" treatment).

Additional treatment with P_2Y_{12}-receptor antagonists should also be given; either as ticagrelor (loading dose 180 mg, i.e. two 90 mg tablets) followed by 90 mg twice daily for one year, or in fragile patients and/or in patients with an increased bleeding risk, as clopidogrel (loading dose

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of 300–600 mg) followed by one tablet of 75 mg once daily for at least 3 months.

In the acute stage combine the above-mentioned platelet-inhibiting drugs with LMH (dalteparin s.c. 120 IU/kg bodyweight per 12 h or enoxaparin s.c. 1 mg/kg per 12 h), or fondaparinux (2.5 mg s.c. once daily; in the case of renal insufficiency defined as creatinine clearance between 20–50 mL/min, 1.5 mg s.c. once daily). In patients with severe renal insuffiency (i.e. creatinine clearance below 20 mL/min) give enoxaparin s.c. 1 mg/kg once daily.

In case of persistent instability despite treatment given as above, refer the patient without delay to coronary angiography. If coronary angiography cannot be performed urgently – consider treatment with a short-acting glycoprotein IIb/IIIa receptor (GPIIb/IIIa) antagonist such as tirofiban or eptifibatide until coronary angiography can be performed. The clinical experience in combining ticagrelor with GPIIb/IIIa receptor antagonists is, however, limited.

Parenteral anticoagulation should be terminated after revascularization with percutaneous coronary intervention (PCI). In patients who are planned to have coronary artery bypass grafting (CABG) parenteral anticoagulation should continue until 24 h prior to surgery while treatment with P_2Y_{12} receptor antagonists should be interrupted 3 days before surgery for ticagrelor, and 5 days before surgery for clopidogrel. Treatment with ASA should continue throughout the surgical procedure.

ST-elevation myocardial infarction (STEMI)

Direct coronary intervention (primary PCI) is the first choice in treatment of an acute ST-elevation infarct. An oral bolus dose of 300–500 mg ASA should be given acutely, regardless of the treatment outlined in the following. Ticagrelor (loading dose 180 mg, i.e. two 90 mg tablets) followed by 90 mg twice daily for one year should be given to all patients scheduled for primary PCI. Prasugrel (60 mg as bolus followed by 10 mg once daily) is another option but is associated with a higher bleeding risk, especially in patients >75 years of age, weighing <60 kg, or with a previous stroke or TIA.

If for some reason ticagrelor or prasugrel is not at hand in patients scheduled for primary PCI, clopidogrel should be given at a loading dose of 600 mg. If primary PCI is not available, thrombolysis should be strongly considered. Contraindications for thrombolysis include ischemic stroke in the previous two months, previous intracerebral bleeding, or ongoing internal bleeding. In patients planned for thrombolysis a bolus dose of 300 mg clopidogrel (in addition to ASA) is recommended followed by 75 mg once daily for 3–12 months.

The use of ticagrelor (or prasugrel) in patients intended for thrombolysis is not recommended due to increased risk of bleeding.

Thrombolysis in STEMI

Prior to thrombolysis always check that ASA (bolus 300–500 mg), and preferably also clopidogrel (bolus 300 mg), have been given.

Tenecteplase is given as a weight-adjusted i.v. bolus dose, followed by LMH (enoxaparin 30 mg i.v. *and* 1 mg/kg bodyweight [maximum 100 mg] s.c. or fondaparinux [2.5 mg s.c. daily, the first dose given i.v.]). Continue with ASA (75–160 mg × 1), and LMH (enoxaparin 1 mg/kg bodyweight × 2 s.c. in keeping with the above) or fondaparinux (2.5 mg s.c. daily) for up to 7 days or until the patient is discharged from the hospital. Thereafter, ASA 75 mg once daily only. Beneficial effects of clopidogrel treatment (75 mg daily) in the setting of thrombolytic treatment have been shown for up to 8 days after the reperfusion treatment, and this should preferably be given as well. Data on the use of ticagrelor or prasugrel in this setting are not available.

An alternative to tenecteplase is streptokinase 1.5 million units in 250 mL of physiologic NaCl solution i.v. during 1 h. Continue prophylaxis with ASA 75 mg once daily long term, and in combination with clopidogrel 75 mg daily during one week. LMH is given only on special indications.

Percutaneous coronary intervention (PCI) in ischemic heart disease

ASA and clopidogrel

Regardless of the indication, all patients should be prescribed ASA 75 mg once daily starting a few days prior to PCI. If this has not been prescribed, a bolus dose of ASA of 300–500 mg orally should be given on the day of PCI, followed by ASA 75 mg once daily. Notably, ASA treatment should be given long term and re-evaluated at least yearly; continued treatment should be based on a positive benefit–risk analysis. Note that in patients with coronary artery stents the indication for long-term ASA treatment is strong.

In addition, clopidogrel should be given as a bolus dose of 600 mg (8 tablets) at least 2 h prior to PCI. Depending on the procedure (whether coronary stenting is performed, and if so, what type of stents are implanted) clopidogrel should be prescribed at 75 mg once daily for 1–12 months. The use of ticagrelor or prasugrel for PCI and coronary stenting in patients with stable ischemic heart disease has up to now not been documented in large clinical trials. However, the development in this field is rapid, thus guidelines and treatment principles have to be updated continuously.

PCI in NSTEMI

ASA and ticagrelor (clopidogrel as second choice) in bolus doses and in daily doses as indicated in the section "ASA and clopidogrel" should be given. Patients should be on anticoagulating treatment with LMH s.c or fondaparinux s.c. in doses outlined above (see section "Unstable angina pectoris/NSTEMI") unless PCI is performed acutely.

A bolus dose of UFH (50–100 U/kg i.v.) or bivalirudin (in doses described in section "Primary PCI") are used as decided by the interventionist.

Primary PCI

ASA and ticagrelor (prasugrel as second choice, clopidogrel as third choice) in bolus doses as indicated in section "ASA and clopidogrel" should be given in combination with LMH (enoxaparin 40 mg i.v.) or UFH (50–100 U/kg i.v.) or bivalirudin (see following).

GPIIb/IIIa-receptor antagonists could be used, especially if the procedure is complicated with intracoronary thrombus formation and/or embolization, acute occlusions, and major dissections affecting coronary blood flow.

Bivalirudin should be used in patients with increased bleeding risk. The drug is given as an i.v. bolus dose of 0.75 mg/kg followed by an i.v. infusion of 1.75 mg/kg/h which is continued as long as the PCI procedure is ongoing; the infusion can be prolonged for 2–4 h in complicated cases as decided by the interventionist. GPIIb/IIIa antagonists are not used concomitantly with bivalirudin.

Coronary artery stenting

Dual platelet inhibition with ASA (bolus dose of 300–500 mg followed by 75–160 mg daily) and a P_2Y_{12} receptor antagonist is mandatory in coronary stenting. In patients with acute coronary syndrome (unstable angina, NSTEMI, or STEMI) ticagrelor (180 mg bolus followed by 90 mg twice daily for one year) is the drug of choice, whereas in patients with stable ischemic heart disease clopidogrel is still the P_2Y_{12} receptor antagonist best documented in clinical trials. If a drug-eluting stent (DES) has been implanted, the P_2Y_{12} receptor antagonist used should be prescribed for at least 12 months regardless of the indication. If the patient has an increased risk of bleeding, the duration of treatment of the P_2Y_{12} receptor antagonist could be shortened to 6 months. Of note, DES should preferably *not* be implanted in patients with increased risk of bleeding, for example patients with a strong indication for simultaneous treatment with VKA.

Importantly, in case of surgery ASA treatment should continue if possible. This is especially important in patients who have coronary stents implanted. If ASA treatment must be interrupted, as in neurosurgery or

in surgery of the posterior part of the eye, the patient should be put on ASA again as soon as possible after the surgical procedure.

Note: before surgical procedures on patients with coronary artery stents are performed, consult a cardiologist.

Diabetes mellitus

In patients with diabetes and unstable angina pectoris/non ST-elevation myocardial infarction/ST-elevation myocardial infarction, ticagrelor (first choice) or prasugrel (second choice) should be used in doses as described in the section on unstable angina/non-ST elevation myocardial infarction.

For elective PCI, abciximab may be given if the interventionist considers that the PCI procedure will be more complicated than normal, such as lengthy interventional procedure, several stent implants, etc.

Secondary prophylaxis against arterial embolism

For an anterior wall myocardial infarction with a visible left ventricle thrombus and/or substantially reduced left ventricle function, treatment with an oral vitamin-K antagonist (VKA, e.g. warfarin) should be considered for 3 months or until the thrombus is not visible on echocardiographic examinations or MRI. Of note, data on warfarin following acute myocardial in the absence of coronary stents are rather strong, thus warfarin could be prescribed long term instead of ASA. This is especially the case in the presence of severely reduced left ventricle function and/or atrial fibrillation. In selected high-risk patients warfarin and ASA could be combined but with great caution as the bleeding risk is considerably increased. Regular re-evaluation of this combined treatment is important.

In case of immobilization consider giving LMH (enoxaparin 40 mg × 1 s.c or dalteparin 5000 IU × 1 s.c.) during a shorter period if the patient is not receiving VKA treatment.

Triple therapy

Patients with a strong indication for VKA who undergo PCI with coronary artery stenting need to receive "triple therapy" (i.e. VKA and ASA in combination with clopidogrel) during a limited time period. During triple therapy the patient should be treated at an outpatient clinic specialized in VKA treatment, PT(INR) should be within 2.0–2.5 and checked weekly. The ASA dose should be 75 mg daily and the patient should be given a proton pump inhibitor. Notably, there is very limited experience with P_2Y_{12} receptor antagonists other than clopidogrel when combining with VKA treatment. It is recommended that in patients who are anticipated to receive triple therapy, bare metal stents (BMS) should be implanted (instead of DES) in order to reduce the duration of triple antithrombotic treatment.

The duration of triple therapy depends on the indication for PCI (stable or unstable ischemic heart disease), the type of coronary stent (BMS or DES), indication for VKA (mechanical heart valve, atrial fibrillation, or left ventricle mural thrombus), and the bleeding risk of the patient.

- PCI due to unstable ischemic heart disease: preferably 3 months triple therapy
- DES: at least 3 months therapy (if high bleeding risk, the duration may be reduced to 4 weeks); if BMS: 4 weeks of triple therapy
- If possible the combination of VKA and ASA should be continued for 12 months.

Regarding patients who receive triple therapy and in whom the indication for VKA treatment is atrial fibrillation, see also section following on "Atrial fibrillation".

Atrial fibrillation

The occurrence of atrial fibrillation doubles the risk of mortality in the total patient population. The risk is partly related to the underlying heart disease and thromboembolic complications secondary to the arrhythmia, whereas the risk strictly associated with atrial fibrillation itself is probably of minor importance.

The treatment should be adjusted to traditional risk factors. The treatment of atrial fibrillation aims at *either* rhythm control, that is, an attempt to convert to a sinus rhythm, and anti-arrhythmic treatment in order to maintain the sinus rhythm, *or* frequency control, that is, acceptance of the fibrillation with an adequate ventricular frequency regulation (about 70–90 beats/min at rest) and adequate antithrombotic treatment. Studies have shown that neither morbidity nor mortality differs between rhythm and frequency control.

In atrial fibrillation there is an elevated risk of embolization and stroke which increases depending on clinical risk factors, the strongest risk factors being previous ischemic stroke, TIA or embolism, and age ≥75 years. As suggested by the European Society of Cardiology some simple scoring systems can be used to better stratify patient risk and the need for anticoagulation. $CHADS_2$ score is the simplest scheme and in this scoring system five different clinical factors are included: cardiac failure (1 point), hypertension (1 point), age ≥75 years (1 point), diabetes mellitus (1 point), and stroke (i.e. ischemic stroke/TIA, 2 points). If the calculated score is 1–2 or higher, treatment with VKA (e.g. warfarin) is indicated.

Recently, a more comprehensive risk scoring scheme has been presented, namely, the CHA_2DS_2-VASc score. This scheme simplifies risk

scoring in patients with atrial fibrillation in the "lower risk range", that is, a $CHADS_2$ score of 0–1.

In the CHA_2DS_2-VASc scoring system the following factors are included: cardiac failure (1 point), hypertension (1 point), age ≥75 years (2 points), diabetes mellitus (1 point), stroke (ischemic stroke/TIA, 2 points), vascular disease (ischemic heart disease, peripheral artery disease, aortic plaque, 1 point), age 65–74 years (1 point), sex (female sex, 1 point). In patients with a risk score of ≥1, VKA (with, for example, warfarin) should be considered.

It should be emphasized that ASA (at any dose) does not confer any important protection against cardiac embolization in patients with atrial fibrillation.

Planned electroconversion

If atrial fibrillation has been present for more than 48 h an VKA (e.g. warfarin) should be given daily and PT(INR) values should be between 2.0–3.0 for more than 3 weeks prior to conversion. The treatment with VKA should continue for at least 4–6 weeks after a successful regularization of the heart rhythm. If there is indication of oral anticoagulation according to CHADS/CHADS VASc scores as outlined in the section "Atrial fibrillation", anticoagulation should continue long term and its indication be re-evaluated at least yearly irrespective of result of regularization, as silent episodes of atrial fibrillation and/or relapses are common.

Regarding the use of dabigatran for planned electroconversion, it is recommended that this approach at present be used in low-risk patients and as a part of research and development.

Cardiac valve prosthesis

Embolism prophylaxis with VKA (e.g. warfarin) during 3 months in the case of a biologic valve may be considered but is not mandatory. In patients with mechanical valves "life-long treatment" with VKA is mandatory. If embolism occurs in spite of VKA treatment at therapeutic PT(INR) levels, either increase the therapeutic range somewhat (especially if the previous range was PT(INR) 2.0–3.0, increase it to 2.5–3.5) or add ASA 75 mg daily or dipyridamole 75 mg × 3 (data on the latter drug are, however, somewhat weak).

Note that there are at present no clinical studies on new oral anticoagulants (NOACs), including dabigatran, in patients with mechanical heart valves. Thus, NOACs should not be used to prevent thromboembolism in patients with mechanical heart valves.

New oral anticoagulants in the treatment of heart disease

Dabigatran, an oral direct thrombin inhibitor, has been approved for use in atrial fibrillation; oral Xa inhibitors (rivaroxaban and apixaban) will also be approved for treatment of atrial fibrillation, and perhaps also in the treatment of ischemic heart disease, in the near future (see also Chapter 11).

At present, warfarin before dabigatran is recommended, especially in patients with atrial fibrillation and concomitant ischemic heart disease as there is positive documentation for warfarin in ischemic heart disease, and no such data are available on dabigatran. In fact, a slight overrepresentation of acute myocardial infarction has been reported in some large trials of oral direct thrombin inhibitors. Dabigatran may be considered in patients with atrial fibrillation where the bleeding risk is expected to be low (as there is no antidote), and for those in whom repeated testing may be inconvenient.

It is expected that more information will appear in the near future regarding NOACs and how they should be used in patients with heart disease.

Note: As stated above, NOACs, including dabigatran, should not be used in patients with mechanical heart valves. In such patients VKA, for example warfarin, are the drugs of choice.

Questions about the above-mentioned treatments should be referred to the cardiologist on duty. It is recommended that interruption of antithrombotic treatment in patients with established heart disease should not be done without consulting a cardiologist.

Antiplatelet drug therapy and reversal of its effects

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CHAPTER 10

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Introduction

About 5–10% of citizens in the Western world are on treatment with antiplatelet drugs as primary or secondary prophylaxis against acute coronary syndromes and ischemic stroke. Antidepressive agents, that is, selective serotonin re-uptake inhibitors (SSRI s), are also commonly used and can inhibit platelet function. Self-medication using "over-the-counter" drugs containing ASA or NSAIDs, or herbs and health supplements known to affect platelets is even more common. The most important adverse effect of antiplatelet drug treatment is the occurrence of spontaneous bleeding or bleeding during surgery.

The documentation on reversal of antiplatelet drug treatment is presently weak and there are no evidence-based guidelines on the issue. In addition, there are no specific antidotes.

Our recommendations are based on the mode of action of different antiplatelet drugs together with expert opinions and a few published studies.

ASA

ASA is an irreversible directly acting platelet inhibitor with a short half-life (20–30 min). The drug acts through irreversible inhibition of the enzyme COX-1 which is necessary in the synthesis of thromboxane. The

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reoccurrence of platelet COX-1 activity is dependent on the formation and reoccurrence of new platelets with intact COX-1. The bone marrow releases platelets to the circulation continuously. Approximately 10–15% of the platelet pool is renewed daily. Thus, within 2–3 days after discontinuation of ASA therapy in a patient with a normal platelet count there will be around $40–60 \times 10^9$/L new platelets with an intact and functional COX-1 in the circulation.

ADP (P_2Y_{12}) receptor antagonists

The ADP receptor (P_2Y_{12}) antagonists have in general a stronger platelet inhibitory effect than ASA. Presently there are three P_2Y_{12} receptor antagonists in clinical use, namely clopidogrel, prasugrel and ticagrelor (see Table 10.1). In addition, ticlopidine (the oldest of the P_2Y_{12} receptor antagonists) is still registered in Sweden but due to high risk for serious hematological adverse effects its use is very limited.

Clopidogrel and prasugrel are prodrugs which are metabolized to active metabolites that irreversibly bind to and block the platelet P_2Y_{12} receptor. Discontinuation should be done at least 5 days in advance of surgical procedures if intact platelet function is considered necessary (see Table 10.1).

Ticagrelor is a direct and reversible inhibitor of the P_2Y_{12} receptor and the platelet-inhibiting effect of the drug is consequently dependent on its actual plasma concentration. In patients on treatment with ticagrelor 90 mg twice daily (i.e. the dose documented in pivotal trials) discontinuation of treatment is generally recommended at least 3–5 days prior to larger surgical procedures. The somewhat shorter discontinuation time period for ticagrelor compared to clopidogrel and prasugrel is due to the reversible action of the drug (see Table 10.1). It should be emphasized that there may be considerable interindividual variations in drug half-life and platelet turnover. Guidance regarding discontinuation time and when sufficient platelet function is obtained following drug withdrawal may be achieved through platelet function testing in the individual patient.

GPIIb/IIIa receptor antagonists

These drugs bind to and block the GPIIb/IIIa receptor, that is, the receptor to which fibrinogen (and to a certain extent VWF) binds and promotes aggregation. Presently there are three different types of GPIIb/IIIa antagonist available for clinical use; all of them are parenteral drugs and their use is restricted to PCI procedures in patients with CAD. The antagonists are abciximab (a chimeric antibody) and the two low molecular weight compounds tirofiban and eptifibatide.

Table 10.1 Antiplatelet agents.

	ASA	Clopidogrel	Prasugrel	Ticagrelor
Mechanism of platelet inhibition	Irreversible COX-1 inhibition	Irreversible inhibition of P_2Y_{12} receptor	Irreversible inhibition of P_2Y_{12} receptor	Reversible inhibition of P_2Y_{12} receptor
Type of drug	Active per se	Prodrug	Prodrug	Active per se (active metabolite also contributes to platelet inhibition)
T1/2 active drug or active metabolite	20–30 min	Short, T1/2 not reported**	2–15 hours**	6–12 hours (both parent drug and active metabolite)**
Discontinuation until surgery	2–3 days*	5–7 days**	5–10 days**	3–5 days**
Degree of platelet inhibition	+	++	+++	+++
No. of platelet transfusion concentrates in intracranial and/or critical bleeding	0–1	1–2	1–2	1–2***
No. of platelet transfusion concentrates in neurosurgery	1	2	2	2***
No of platelet transfusion concentrates in urgent surgery	0	1	1	1***
Comments	Platelet inhibiting effect can partly be reversed by desmopressin (DDAVP)	In patients with intracranial bleeding, critical bleeding, or if high-risk surgery in patients on treatment (i.e. with high concentration of active metabolite and/or high concentration of active drug in the circulation) platelet transfusion may need to be repeated several times. This may especially be the case for ticagrelor.		
Consider using platelet function tests				

*In patients with high risk, ASA treatment should not be interrupted before surgery, and should be restarted early postoperatively. Note that bridging with heparin/LMH does not protect against coronary stent thrombosis.
**Individual variations in half-life (T1/2) of drugs and/or active metabolites. Note that T1/2 of clopidogrel or prasugrel does not reflect the duration of inhibition of platelet function due to the irreversible nature of the drug's action on the P_2Y_{12}receptor.
***Due to its reversible inhibition, free ticagrelor, still in circulation will also inhibit transfused platelets.

Source: Based in part on data from Sarode, R. *Transfusion* 2012; **52**:695.

Phosphodiesterase inhibitors and other antiplatelet compounds

Dipyridamole and cilostazol are phosphodiesterase inhibitors with antiplatelet and vasodilating properties. Some beneficial effects of treatment with dipyridamole have been documented in ischemic stroke. Regarding cilostazol the clinical documentation is much less extensive than for the other antiplatelet drugs mentioned above. These phosphodiesterase inhibitors confer a low bleeding risk. Fish oils and several herbs are also known to cause platelet inhibition but they are weak inhibitors. In spite of this, we recommend treatment interruption before surgery associated with a high bleeding risk, and for plastic and cosmetic surgery.

NSAIDs are weak and reversible platelet inhibitors and should be interrupted according to their half-life and at least 24 h before surgery.

Combined antithrombotic treatment

The anti-hemostatic effect of a platelet-inhibiting drug is significantly increased if it is combined with another platelet-inhibiting drug with a different mode of antiplatelet action (so-called dual antiplatelet treatment), and even more increased when combined with an anticoagulating drug. The highest bleeding risk is present in patients who receive dual antiplatelet treatment in combination with an anticoagulating drug (so called "triple therapy").

Benefit–risk assessment

In the early period after acute coronary syndrome (ACS), especially after coronary artery stenting, patients are at high risk of cardiovascular complications. Therefore surgery which requires interruption of antithrombotic treatment should be avoided.

Elective surgery should preferably be postponed, and urgent elective surgery be performed only after consultation with a cardiologist. Similarly patients with a recent stroke or newly inserted arterial stent in a carotid artery, or intracerebral or peripheral medium-sized arteries, are at high risk for stent thrombosis until stent endothelialization has occurred. In coronary artery stents it is generally considered that endothelialization of stents takes 1–3 months. In drug-eluting stents (DES) endothelialization takes longer, up to one year or even more.

Patients who are treated with platelet inhibitors should be discussed in a team made up of a senior general surgeon – or neurosurgeon, an anesthesiologist, a hemostasis consultant and a cardiologist or neurologist in the acute phase of a critical bleeding, when requiring urgent surgery, and in *due time* before any elective surgical procedure is performed.

Consideration has to be given not only to the type of antiplatelet drug and its effect but also to the individual patient's risk for bleeding, risk for thrombosis, indication for antiplatelet treatment, and type and indication of surgery.

The bleeding risk in a particular patient is dependent not only on treatment with anticoagulants or antiplatelet drugs but also on individual risk factors for bleeding such as old age, low body weight, anemia, renal or hepatic failure, blood disorders, thrombocytopenia (platelet count $< 100 \times 10^9$/L) and malignancy.

Even a weak antiplatelet drug like ASA can lead to serious bleeding during surgery in a patient with a high bleeding risk and especially if combined with an anticoagulant drug like LMH. Of note, SSRIs may also inhibit platelet function. Oral steroids increase the risk of upper gastrointestinal bleeding, and should if possible be avoided. Neurosurgery, urologic surgery and surgical interventions in closed anatomical spaces including some ophthalmic surgery also carry increased risk. In these kinds of surgery even ongoing treatment with ASA or other weak platelet inhibitors should be interrupted before the intervention. In other types of general or orthopedic surgical interventions and in patients with no other bleeding risk factors, the small extra bleedings can often be handled by compression, careful surgical hemostasis and/or application of local "hemostatic" agents.

Platelet transfusion

To date there have been no randomized clinical trials performed to evaluate platelet transfusion therapy in the treatment of antiplatelet drug-related bleedings, but *in vitro* studies and some clinical reports are in favor of a positive effect. Many centers have included platelet transfusion as a treatment option in their guidelines. In patients with an active antiplatelet drug or active metabolites present in plasma – which in theory would also make transfused platelets dysfunctional – platelet transfusion still seems to be of value. *In vitro* data indicate that one platelet concentrate would be enough in bleedings related to ASA, whereas transfusions with two platelet concentrates (in some situations to be repeated within 24–48 h), is advocated in patients on P_2Y_{12} receptor antagonist who bleed or are undergoing major surgery (see Table 10.1).

Point-of-care instruments for rapid platelet function testing (Chapter 3) may be of help to assess platelet function in the patient and determine if the patient is on antiplatelet treatment, type of drug and the response to treatment. Information on how platelet function reacts to "hemostatic" treatments can also be obtained.

Additional comments on Table 10.1:

- Discontinuation of antiplatelet drug treatment in patients with coronary artery stents should be performed after consultation with a cardiologist. In severe, life-threatening bleeding, however, stopping the bleeding must be given highest priority.
- Platelet transfusion in patients on P_2Y_{12} receptor antagonists may need to be repeated 1–2 times within 24–48 h if patient is still bleeding.
- Intracranial hemorrhage – the most feared bleeding complication – is seen in 0.2–0.4% of patients treated with ASA and/or clopidogrel. In-hospital mortality is high, around 15–25%.
- Increase of intracranial hemorrhage volume during the first 6–12 hours, as is often seen in patients treated with anticoagulants or antiplatelet agents, is a strong predictor of poor outcome if left untreated. Similarly, intact hemostasis is necessary in neurosurgical procedures. Platelet transfusion to reverse ADP receptor antagonists, especially ticagrelor in intracranial hemorrhages are still a matter of discussion.
- Recombinant factor VIIa has platelet stimulating effects *in vitro* but there are few clinical data on its reversal of bleeding in patients on platelet inhibitors. The use of factor VIIa may in some cases be afflicted with thrombotic complications. It has been used in patients with severe intracranial hemorrhages but the documentation is weak.
- Anti-fibrinolytic drugs (see Chapter 5) may also be of value in critical bleeding in patients on antiplatelet agents. In addition, they are used in patients on antiplatelet treatment who are undergoing cardiac surgery.

New oral anticoagulants: focus on currently approved oral factor Xa and thrombin inhibitors

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CHAPTER 11

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Clinical pharmacology of NOACs

Rivaroxaban

Rivaroxaban (Xarelto®, Bayer HealthCare AG) is an oral low molecular weight direct factor Xa (FXa) inhibitor. Rivaroxaban inhibits FXa by binding to its active site. The inhibition is dose dependent and can be measured by prolongation of prothrombin time PT(INR). Data from phase I studies show that 15 mg of rivaroxaban reduces FXa activity by 35% and increases PT(INR) 1.4-fold compared with basal levels. The prolongation of PT(INR) is strongly correlated to plasma levels of rivaroxaban ($r = 0.935$), with little interindividual variability. Thus, the determination of PT(INR) seems to be a useful tool for therapeutic monitoring of rivaroxaban treatment, if necessary. The method is, however, not in current routine clinical use.

After oral administration, rivaroxaban is rapidly absorbed, with **80%** bioavailability. Maximal plasma concentrations are achieved with 2.5–4 h. After multiple dosing, the half-life is 5–9 h in healthy volunteers and 9–13 h in the elderly (average 65 years). Elimination is dependent on the absorption rate; with a 10 mg dose, the half-life has been reported to be 7–11 h. No significant circulating active metabolite has been identified. About one third of an ingested dose of rivaroxaban is renally excreted

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in an unchanged form. The remaining two-thirds are metabolized in the liver. Elimination is reduced in old age, in cases of decreased renal function and in the presence of strong inhibitors of CYP3A4 (e.g. azole antimycotics such as ketoconazole and protease inhibitors such as ritonavir). In patients with severe renal insufficiency (creatinine clearance <30 mL/min), plasma concentrations of rivaroxaban have been reported to be increased by 64% and PT(INR) was prolonged by 144% ($P < 0.001$) compared with control subjects. Patients with creatinine clearance below 30 mL/min and those with significant liver disease or ongoing medication with strong CYP3A4 inhibitors/inducers were excluded in the phase III studies.

Preclinical data indicate that recombinant activated factor VII (rFVIIa) could potentially be used for partial reversal of the effects of rivaroxaban. In a rat mesenteric model of bleeding, rFVIIa was administered after a high dose of rivaroxaban (2 mg/kg). A dose of rFVIIa at 400 μg/kg reduced the bleeding time by nearly 50% and partially reversed the prolongation of PT(INR) and total thrombin activity, without affecting rivaroxaban dependent FXa inhibition. These preclinical data must, however, be confirmed in clinical trials to establish their clinical relevance. One small clinical study including 12 healthy volunteers may indicate that prothrombin complex concentrate (PCC, Cofact, 50 IU/kg) may possibly reverse the effect of rivaroxaban (20 mg twice daily) on prothrombin time and endogenous thrombin potential.

Apixaban

Apixaban (Eliquis®, Bristol-Myers Squibb and Pfizer) is an oral low molecular weight direct factor Xa (FXa) inhibitor, and is a refinement of the predecessor razaxaban that went into Phase II. Apixaban displays many pharmacologic similarities to rivaroxaban, see above. Apixaban is primarily metabolized to the inactive metabolite O-desmethyl apixaban sulfate . The half-life of the parent drug is 8–13 h. Metabolic pathways are believed to include desmethylation, hydroxylation, and sulphation exerted through several CYP enzymes, particularly CY3A4. This may provide opportunities for interactions with other drugs. In phase I studies, strong inhibitors of CYP3A4 gave increased plasma concentrations of apixaban, while the risk of impact from other drugs appears low. Excretion is by both feces and urine, which makes the medication less susceptible to organ dysfunction. Only a small fraction is excreted in the bile. Active liver disease and creatinine clearance <30 mL/min appears to have been exclusion criteria in clinical studies and may therefore become contraindicated.

Dabigatran

Dabigatran etexilate (Pradaxa®, Boehringer Ingelheim Pharma GmbH) is the orally bioavailable prodrug of dabigatran. After oral administration, dabigatran etexilate is rapidly absorbed and converted to dabigatran by esterase-catalyzed hydrolysis in plasma and in the liver. Dabigatran is a potent, competitive, and reversible direct inhibitor of thrombin. Peak dabigatran plasma concentrations occur 0.5–2 h after oral administration. The mean terminal half-life of dabigatran has been reported to be 12–14 h in healthy volunteers and 14–17 h in patients undergoing major orthopedic surgery. The half-life was independent of dose. Most (80%) of the drug is excreted unchanged by the kidneys. The average absolute bioavailability of dabigatran is low, at 6.5%. In healthy volunteers and in patients, the interindividual variability of C_{max} and the area under the concentration curve (AUC), expressed as a coefficient of variation, was high, approximately 80%, whereas in healthy volunteers intraindividual variability was close to 30%.

Exposure to dabigatran (AUC) was approximately 2.7-fold higher in subjects with moderate renal insufficiency (creatinine clearance 30–50 mL/min) and approximately six times higher in subjects with severe renal insufficiency (creatinine clearance 10–30 mL/min) than in those without renal insufficiency. In elderly subjects, the AUC was increased by 40–60% and C_{max} by more than 25% compared with young subjects. Exposure in female patients is about 40–50% higher than in male patients.

Dabigatran etexilate and dabigatran are not metabolized by the cytochrome P450 system and have no effects *in vitro* on human cytochrome P450 enzymes. Therefore, no cytochrome P450-related drug interactions are expected with dabigatran. Amiodarone inhibits the transport protein P-glycoprotein and dabigatran etexilate is a substrate for this transport protein. In the presence of amiodarone the AUC and C_{max} of dabigatran have been reported to increase by 60% and 50%, respectively.

There are currently no specific coagulation tests adapted for accurate and sensitive evaluation of thrombin inhibition in routine clinical use. The effects of dabigatran have been assessed using APT time, PT(INR), and thrombin time (TT). Measurement of ecarin clotting time (ECT), a test which is better adapted to thrombin inhibition but is not in current practice in clinical laboratories, has also been used. A curvilinear relationship has been shown between dabigatran plasma concentrations and APT time which is why this test may not be suitable for the precise quantification of the anticoagulant effect of dabigatran. The PT(INR) assay has been found to lack sensitivity within the clinically relevant dabigatran plasma concentration range and showed high variability, and is not considered a suitable tool. The TT assay exhibited a linear relationship

with dabigatran plasma concentrations, with a high level of sensitivity. However, this assay might be too sensitive for clinically relevant dabigatran plasma concentrations and the reagents used for determining TT in different laboratories are not standardized. A standardized and modified TT assay, of suitable sensitivity, could be a useful tool for monitoring dabigatran. The same goes for the ECT assay, which has been shown to be sensitive to dabigatran and which displayed a linear relationship with drug plasma concentrations over the full range of concentrations.

In summary, the pharmacokinetic characteristics of dabigatran, namely, low bioavailability (6.5%) with great interindividual variability, the concentration–effect relationship, and the bleeding risks strongly suggest that drug monitoring is needed, especially in subgroups at increased risk (see section on clinical aspects later).

There is no antidote to dabigatran.

Possibility of and need for therapeutic monitoring of NOACs

For short-term treatment indications, for example the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery, there is a need for therapeutic drug monitoring (TDM), especially in patients among whom there is a risk of higher drug exposure increasing the risk of bleeding. Such patients may include the elderly, those with low bodyweight or impaired renal or hepatic function, and those on co-medication with possibly interacting drugs. In possible future long-term indications, for example stroke prevention in atrial fibrillation, and other situations when TDM is warranted will arise. Such situations include drugs added to ongoing anticoagulant treatment and concomitant disease acquired during treatment. Furthermore, a periodical sample to check treatment compliance could sometimes be indicated – such information is provided by PT(INR) testing in connection with warfarin treatment.

Tests for therapeutic monitoring of the new anticoagulants are not in clinical use today. However, for rivaroxaban and apixaban, anti-FXa assays or a clinically adapted and reliable prothrombin time assay could be used. For dabigatran, among coagulation tests, it is probably either a clinically adapted and standardized ECT or TT assay that will provide the best information. Alternatively, plasma levels of either drug may be used.

Clinical aspects of NOACs

Thrombotic vascular disease is a leading cause of mortality and morbidity worldwide, and is no longer confined to the Western world. Over

recent years new antithrombotic drugs, "blood thinners", have been developed and new treatment strategies are being proposed that may be more efficacious and secure than the earlier ones.

More than half a century ago, in the 1940s and 1950s, clinical trials, first with heparin and then with vitamin-K antagonists (VKA), were presented; some decades later low molecular heparin (LMH) was introduced as prophylaxis and treatment of thrombosis in different vascular areas and settings.

Although clinical interest in these anticoagulant drugs was great, serious and frequent unexpected bleeding complications, which were difficult to manage and predict, soon became a growing problem and hampered for some time the initial enthusiasm for treatment.

Since then we have learned to monitor these anticoagulants better, with standardized clotting tests, and to predict and handle bleeding complications, and thus their clinical use has increased substantially.

In contrast to LMH, warfarin is a cheap and very effective antithrombotic drug (daily medical cost is about US$0.35). However, the attendant cost for warfarin treatment and controls is about 10 times higher. Worldwide sale of warfarin is now more than one billion US$ corresponding to more than five million patient years in treatment annually.

However, the complexity of oral anticoagulation with warfarin makes many clinicians reluctant to start VKA treatment. Treatment is difficult to carry through, afflicted with serious bleeding complications, and other drawbacks. Even in special anticoagulant clinics, with experienced personal staff, as well as in clinical trials with selected patients, intracranial bleedings (with poor prognosis) occurred in about 0.3–0.7% (patient years), other major bleeding complication in 2–4%, and minor bleeding in 10–15%. To establish good control of treatment every single patient has to be monitored regularly by a clotting test (PT(INR)), which is not possible in many parts of the world and VKA treatment might be interacted by a lot of other drugs, medications, and way of living. A new era began in the mid-1980s when Astra (now Astra Zeneca) started a project to devise an oral alternative to warfarin and LMH. In the late 1990s their final product, ximelagatran, an orally active thrombin inhibitor and prodrug of melagatran, more than 10 years ahead of other NOACs, was shown in clinical trials to be a noninferior alternative to VKA in atrial fibrillation, to LMH as prophylaxis against PE and venous thrombosis in elective orthopedic surgery, and as a potential treatment following myocardial infarction and acute coronary syndrome.

There was tremendous disappointment worldwide when some years later ximelagatran was withdrawn from the market because of liver toxicity.

Currently, more than 20 NOACs for oral administration once or twice daily, targeting one or another of the coagulation factors have been tried, or are in ongoing phase II and II large multicenter clinical trials in fixed doses, or regulated by age and renal function with carefully selected patients for treatment and prophylaxis of PE and venous thrombosis in different settings, prophylaxis in atrial fibrillation, and for treatment of coronary heart disease.

Most trials include between 5000 and 20 000 patients recruited from 30–40 countries in different parts of the world without regular monitoring.

Positive results of these trials will impact significantly on "real-world" clinical practice. Irrespective of the results, the trials will focus clinicians on the fact that atrial fibrillation is not a benign arrhythmia, and treatment and prophylaxis of venous thrombosis, PE, and arterial thrombotic disease can be improved.

Most advanced in clinical trials to date are one thrombin inhibitor (dabigatran) and three inhibitors directed against factor Xa (rivaroxaban, apixaban, edoxaban).

A standardized and fixed-dose regimen that does not necessitate close and regular monitoring and has fewer interactions with other drugs, makes therapy with these new drugs easier than standard therapy with warfarin.

There is ongoing debate on whether any NOAC, or any class of NOAC is better or more secure than the others in different clinical settings. So far, no head-to-head comparisons have been made, and when different trials are compared, it has not been possible to answer this question.

Results of clinical trials

Summary

- *In comparison with warfarin, NOACs have been shown to be at least noninferior, coequal, or even better (apixaban, dabigatran high dose) as prophylaxis against ischemic stroke and peripheral arterial embolism in patients with atrial fibrillation. In addition, the risk of intracranial hemorrhage and possibly the risk of death (apixaban) may be decreased.*
- *Compared with LMH, NOACs have been shown to be noninferior or even superior (rivaroxaban) against venous thrombosis and pulmonary embolism after elective orthopedic knee and hip surgery in short term or prolonged prophylaxis, inferior (more bleeding complications) to LMH as prophylaxis in medical patients (rivaroxaban); in trials they have shown comparable results with standard treatment for acute venous thrombosis and pulmonary embolism (rivaroxaban, dabigatran) and with similar safety profiles.*
- *In combination with antiplatelet treatment for coronary heart disease adequate data is still missing or contradictory. Bleeding complications when anticoagulant and antiplatelet treatment is combined seems, so far, to be unsafe because of hemorrhages.*

Dabigatran, which has been approved in the United States and Canada and some other countries since November 2010, and rivaroxaban in the United States and Europe since December 2011, are now approved in most countries as prophylaxis against stroke and peripheral embolism in atrial fibrillation and as venous thromboprophylaxis in elective orthopedic hip and knee surgery.

Rivaroxaban has also been approved (2012) for treatment of acute and long-term treatment of venous thrombosis and pulmonary embolism. Apixaban is so far approved as venous thrombo-prophylaxis after elective orthopedic surgery and atrial fibrillation. Edoxaban (Lixiana®) has been approved in Japan as venous thrombo-prophylaxis in elective orthopedic surgery.

National and local guidelines for NOACs vary, due to differences in national health systems, dependence on health insurance, and the way that national and local expert committees have graded results of clinical trials in comparison with how well general care with warfarin is performed in their individual countries and regional areas.

In Sweden, the daily medication cost of NOACs is about 10 times more expensive than warfarin and about equal with LMH.

In some countries medication is free, in others it is subsidized by the state or by regional aid for special groups of patients. In other countries it is paid for by individual health insurance.

The American College of Chest Physicians (ACCP) 2012 guidelines recommend dabigatran in favor of adjusted doses with VKA. The European Society of Cardiology (ESC) new guidelines (2012) recommend either well-controlled VKA treatment or any of the new oral anticoagulants (NOACs). Scottish and Swedish national guidelines only recommend dabigatran as an alternative when warfarin is clinically inconvenient. The ACCP and Sweden do not recommend a general pharmacologic prophylaxis in medical patients and to date recommend LMH in favor of NOACs in elective orthopedic surgery. Many countries such as the Netherlands and Denmark (and parts of Sweden) have well-organized general warfarin care centralized to coagulation centers. Many patients (between 15 and 40% long-term users) self-monitor PT(INR) with a point-of-care (POC) instrument; the results can be directly connected to the anticoagulation center. In other countries warfarin care is decentralized and very few patients use POC instruments (e.g. in the United States, Sweden, and in many other countries it is less than 1%).

NOACs are anticoagulants and as such are afflicted with a risk of inducing and worsening hemorrhages in patients on treatment. Also, the risk for bleeding complication is pronounced in combination with any platelet-inhibiting therapy without significant improvement of antithrombotic effect.

Now, in 2012 (i.e. only a few years after approval for general use) there are repeated reports of serious unexpected bleeding complications and warnings that these new drugs are difficult to handle and predict.

NOACs differ with respect to side-effects, pharmacokinetics, and their dependence on an intact renal function for elimination. No clotting test or other test to determine plasma concentration has been evaluated for clinical use to regulate dosages in different critical situations or in patients with extraordinary high risk for thrombosis or bleeding, and currently there are no specific antidotes to reverse the anticoagulation effect. So far we are unaware of long-term effects and still uncertain about universal applicability in the real world of results from clinical trials. Clinical trials are ongoing to solve such questions but until then we have to rely on proposals, guidelines and recommendations from international, national, regional, and local expert groups on special considerations, individual drugs, how to handle clinical situations, and how to follow patients on treatment with NOACs.

In Sweden most patients starting on treatment with a NOAC are followed using a national register, Journalia (www.journalia.se), AuriculA (www.auricula.se), or with data from computer-based patient journals. To ensure that clinicians register patients continuously some regional authorities subsidize the cost of medication. The Swedish Society on Thrombosis and Haemostasis (www.ssth.se) has written clinical recommendations for treatment with NOACs (dabigatran and rivaroxaban are now available in an English version) in different clinical situations.

Some characteristics of the individual NOACs

Summary

- ***Dependence on intact renal function for elimination***
  Dabigatran is mostly eliminated by the kidneys (80–85%), rivaroxaban and apixaban (25–35%). These NOACs are not recommended for use when the estimated renal function is below 30% (estimated glomerular filtration rate (eGFR)). Clinical trials have only studied patients with no severe renal dysfunction. Many cases of serious bleeding complications reported when using dabigatran are caused by the fact that fixed doses have been given irrespective of decreased renal function.
- ***Laboratory tests to measure anticoagulant activity or plasma concentration***
  Ordinary clotting test, APT time, PT(INR), POC instruments for PT(INR), ACT, thromboelastography (TEG), and thromboelastometry (ROTEM) tests are not sensitive to therapeutic concentrations of NOACs, and commercial clotting reagents vary considerably in sensitivity to NOACs. New tests are being tried, such as ecarin clotting time (ECT) or modified thrombin time to measure dabigatran, and modified

anti-FXa assay and prothrombinase-induced clotting time (PiCT) to measure factor Xa inhibitors. It is also now possible (at Karolinska University Hospital, Stockholm, Sweden) to measure plasma concentration of dabigatran.

- Compared with warfarin, there have been a greater number of **gastrointestinal hemorrhages** reported with NOACs (dabigatran, rivaroxaban); this is possibly due to a direct (indirect by dabigatran via P-glucoprotein efflux transporter) effect on the gastrointestinal mucosa.
- ***Dyspepsia and intestinal irritability*** occurred in some patients (5–10%) after starting dabigatran. This was possibly due to tartaric acid in the pellets; symptoms became persistent if they did not disappear after several weeks of taking the tablets with food.
- A slight increase (2–3 per 1000 patient years) in ***myocardial infarctions*** has been registered during treatment with dabigatran. This was also observed with ximelagatran. The increase is not impressive but so far there is no good explanation for this observation.
- In clinical trials for **atrial fibrillation**, dabigatran and apixaban included patients with a low mean $CHAD_2$ score of 2.1 in comparison with rivaroxaban, which included higher risk patients, mean $CHAD_2$ score 3.5, and more elderly patients.
- NOACs have not been tried and are not recommended in renal insufficiency, in children, during pregnancy, in patients with artificial heart valve prosthesis, in patients with advanced malignancies, hepatic insufficiency, or other serious inflammatory or immunologic disorders. Nor has there been much experience of treating older (>80 years) people.
- Warfarin has a long offset time and a few doses missed are not of great clinical significance. NOACs have short offset and onset times, and the clinical significance of missed doses is unknown. Missing doses may possibly have a rebound effect in acute situations.

Considerations to be taken when using NOACs in some emergency situations

Summary

- ***Non-urgent medical procedures, requiring dose adjustment***
  Consideration should be given to elimination of the drug. In general, about 15% anticoagulation effect remains when administration is stopped after three half-times, and less than 5% after five half-times.

  For **dabigatran** renal function is of great significance. The half-life of the drug is about 15 h in normal renal function (>eGFR 50 mL/min) and prolonged to more than 24 h when eGFR is <30 mL/min. Administration should be stopped at least 24, 48, or 96 h or more before surgery or any other invasive procedure, dependent on eGFR and type

of surgery. If coexisting severe liver insufficiency exists these times should be even longer, probably doubled. Normal APT time does not exclude a certain remaining anticoagulation effect.

Rivaroxaban and **apixaban** are less dependent on renal elimination and the half-life time (6–14 h) does not vary very much until eGFR is <30 mL/min. Administration should be stopped between 48 and 96 h or more before major surgery, dependent on eGFR and liver function. Normal PT(INR) does not exclude a certain remaining anticoagulation effect.

- ***Urgent medical procedures requiring optimal hemostasis.***
  There are no specific antidotes for NOACs. Verify when (and if) the last dose was taken and if NOACs are combined with platelet-inhibiting therapy. Determine creatinine and calculate eGFR, hemoglobin and platelet counts. If ECT, thrombin time, anti-factor Xa or plasma concentration assays are not available, use an ordinary clotting test. A normal APT time (dabigatran) or a normal PT(INR) (factor Xa inhibitors) exclude high concentrations of the drug but do not exclude the possibility of a certain effect remaining. Select an experienced surgeon, contact the blood delivery clinic in advance, neutralize platelet active drugs if present (platelet transfusion, 2 units), be prepared for any bleeding complications that may develop during surgery, use tranexamic acid and local hemostatics. Prothrombin complex concentrate (PCC) (10–30 units per kg bodyweight) may be tried for reversing factor Xa inhibitors. Discuss hemostatic disorders with the local hospital unit in advance. A significant remaining dabigatran concentration might be considerably reduced by 2–3 h in acute hemodialysis prior to surgery.
- ***Postoperatively***
  Different regimens may be used dependent on type of surgery, other disorders, complications, and indication for NOAC. In uncomplicated operations, NOACs can be started on the first, second or third day, preferably with a lower dose the first day and until hemostasis is secured. In other situations it may be more convenient, for a period of time, to exchange NOACs with LMH.
- ***Serious bleeding during treatment with NOACs***
  All types of bleeding during NOAC treatment should be regarded as serious. Critical bleedings should be handled in the usual way, including tranexamic acid and trying to stop the bleed locally by compression, endoscopic or endovascular methods. Although PCC, activated PCC (FEIBA), NovoSeven, and plasma have been used to try to reverse NOACs, there are currently no recommendations, with the exception that PCC may be the first choice in reversing factor Xa inhibitors, and that hemodialysis might be a first choice in reversing a high plasma concentration of dabigatran.

Stroke and transient ischemic attack

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CHAPTER 12

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Antithrombotic secondary stroke prevention

Intracranial bleeding must always be excluded with computed tomography (CT) or magnetic resonance imaging (MRI) of the brain prior to a decision to initiate antithrombotic treatment. Acetylsalicylic acid (ASA) 75–100 mg daily (first day 300–500 mg as a bolus dose) is recommended as soon as neuroradiologic imaging has excluded hemorrhage. Higher doses of ASA provide no better prevention but increase the risk of gastrointestinal side-effects. If thrombolysis is given, a CT scan excluding hemorrhage should be performed 24 h after administration of rt-PA and before ASA is given. The preventive effect of ASA may be improved by combining it with dipyridamole (Persantine), but this is often avoided during the first days because of limited safety data from the acute phase. Commonly occurring initial headache may be avoided by starting with one capsule of dipyridamole before sleep for at least 5 days before a full dose is given. Clopidogrel (Plavix®) 75 mg is an alternative to the combination of dipyridamol and ASA in the long term for secondary antithrombotic prevention. Patients with stents require combination therapy using ASA combined with clopidogrel for a limited time (3–12 months), otherwise the combination is not recommended due to the risk of intracerebral hemorrhage.

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Atrial fibrillation and TIA or stroke

Secondary prophylaxis with VKA should always be considered in ischemic stroke or transient ischemic attack (TIA) due to atrial fibrillation. If warfarin is used, the PT(INR) range to aim for is 2.0–3.0. Check PT(INR) regularly. Moreover, VKAs should be considered in TIA or stroke after recent (<3 months) acute myocardial infarction, and in other kinds of cardiac embolism.

VKA treatment can start immediately after TIA and minor cerebral infarction. In more extensive cerebral infarction of cardiac origin, wait for about 10–14 days and begin the treatment after renewed CT of the brain to exclude bleeding.

There are no definite guidelines for the duration of secondary prophylactic treatment. Platelet inhibitory treatment is often given for life. VKA treatment continues as long as atrial fibrillation persists or until there is a serious risk of complications. After an acute myocardial infarction, the treatment may often be discontinued after a few months and changed to antiplatelet treatment. Note that VKA and ASA should normally not be given in combination.

New oral anticoagulants (NOACs), now becoming available for use in TIA and stroke caused by atrial fibrillation, may offer an alternative to warfarin, although experience from their use is still limited.

Thrombolysis in stroke

Thrombolysis with IV rt-PA (Actilyse) is indicated when CT of the brain has excluded bleeding, the treatment can be started within 4.5 h of symptom onset, and no other contraindications are found. Treatment should be given at a stroke unit with experience of this kind of treatment. Patients with very severe symptoms (National Institutes of Health stroke score above 24) or a CT scan showing extensive ischemia, usually defined as infarction exceeding one third of the volume of the middle arterial territory or one half of the anterior or posterior artery territories, should not be treated; neither should patients with an earlier brain hemorrhage, head trauma or other serious disease. A high blood pressure (>180/110) that can not be pharmacologically lowered is another contraindication. Treatment beyond 4.5 h, supported by multimodal neuroimaging indicating reduced focal perfusion with limited established infarct, is currently evaluated in randomized controlled trials. Patients on VKA treatment should not be treated with thrombolysis unless, in case of warfarin, PT(INR) is ≤1.7. An exclusion list must be checked prior to a decision about treatment. The time of onset is crucial; if this is uncertain, the

last time-point without symptoms is noted. In selected cases of unsuccessful intravenous thrombolysis or when there are contraindications for thrombolysis mechanical thrombus extraction or intra-arterial, local thrombolysis may be an alternative. Although earliest possible recanalization should be aimed for, time limits are less documented compared to intravenous thrombolysis. Treatment decisions are usually based on multimodal neuroimaging of mismatch between perfusion defects and manifest lesion.

The effect of thrombolysis diminishes rapidly with time after onset. The treatment is given as an intravenous infusion with a dose of rt-PA (Actilyse) of 0.9 mg/kg bodyweight for 1 h. The effect of successful treatment often appears during the infusion or within the subsequent first hour but may also do so successively during the first 24 h. The treatment is associated with a risk of bleeding complications, which can be serious. If intracranial bleeding is suspected during the treatment (a sudden change for the worse, with increasing neurologic symptoms, decreased consciousness, headache), discontinue the treatment. If the bleeding is superficial, local compression is performed. If necessary, give refrigerated (stored up to 1 week) or fresh-frozen plasma. Factor VIIa (NovoSeven), prothrombin complex concentrate (PCC) and tranexamic acid (Cyklokapron), may be considered. Contact the coagulation specialist on duty. Accumulating data indicate that bleeding almost exclusively occurs after the treatment has been finished, thus close observation of the patient is needed for the first 24 h.

Secondary antithrombotic prophylaxis may start 24 h after the end of the treatment and after a CT of the brain has excluded hemorrhage.

SITS International (https://sitsinternational.org) is recommended as a globally available tool for documentation and quality development of stroke thrombolysis and mechanical thrombectomy.

Cerebral venous thrombosis and dissection of precerebral arteries

Treatment with unfractionated heparin (UFH) and simultaneous initiation of VKA treatment is recommended, provided there are no contraindications. Hemorrhagic stroke secondary to sinus thrombosis is not considered to be a contraindication for UFH but may require that a slightly lower APT time is aimed for. Local fibrinolysis may be considered in cerebral venous thrombosis with progressive neurologic symptoms and/or reduced consciousness. Patients with this condition should be managed at comprehensive stroke centers with capacity for neuroradiologic interventions.

Recurrent TIA

Randomized controlled trials provide no support for treatment with heparin, although it is still sometimes used if the symptoms are suspected to be thromboembolic. The treatment should be avoided, in particular in recurrent lacunar TIA, when the disorder is not primarily thromboembolic and the safety of anticoagulation treatment has not been confirmed.

Prophylactic treatment against DVT and PE

A pronounced paresis after stroke entails a risk of DVT and PE. If paresis persists after the first 24 h, consider preventive treatment with LMHs.

For advice concerning treatment, also in intracranial bleeding and laboratory analyses, contact the neurologist on duty and a specialist in coagulation.

Peripheral artery surgery

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CHAPTER 13

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Prophylaxis against reocclusion in peripheral vascular surgery or percutaneous transluminal angioplasty (PTA)

Treatment with ASA is used to decrease risk of occlusion of the arterial reconstruction. It also has a prophylactic effect against future consequences of coronary heart disease.

ASA (75–160 mg per 24 h) should start soon after surgery. If the patient is already on this dosage of ASA, it should be continued during open surgery and PTA. Clopidogrel (75 mg × 1) may be prescribed. Note that clopidogrel causes an increased bleeding tendency and should, if possible, be discontinued before open surgery; this is also important for carotid surgery. If epidural anesthesia is used, clopidogrel should be discontinued 5 days and vitamin-K agonists (VKA) 2 days before intervention.

Peri- and postoperative treatment

Intraoperatively, UFH 35–70 IU/kg bodyweight i.v., reversal with protamine is seldom needed, or LMH 70 IU/kg bodyweight i.v. Dextran is used in connection with surgery but should be dosed with caution, due to the risk of fluid overload leading to heart failure.

Postoperatively after open surgery, LMH prophylaxis against DVT should be used. After intervention, ASA as above. If arterial reconstruction after open surgery is associated with a high risk of occlusion, VKA drugs (warfarin) can be used. When synthetic grafts are used in open surgery or when stents are used at PTA, VKA should be substituted with ASA + clopidogrel.

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Thrombolysis in acute ischemia

In acute leg ischemia, local thrombolysis is often used. This is usually the case in acute thrombosis caused by arteriosclerotic disease. A catheter with multiple side holes is inserted through an introducer into the groin for local infusion of rt-PA into the thrombosis. A thrombus in the superficial femoral artery can usually be lysed with less than 20 mg rt-PA. The thrombolytic agent is given in repeated doses of 2 mg and can be followed by a slow infusion of 2 mg/h. Fibrinogen levels are checked with the same routines as for other thrombolytic treatments. The thrombolytic treatment is discontinued if the level of fibrinogen falls below 1 g/L. If thrombolysis is successful, the arterial stenosis that caused the thrombosis is often visualized and can be treated with PTA with or without stenting. In order to reduce the risk of bleeding at the point of insertion, the introducer in the groin is left *in situ* until thrombolysis is completed.

Questions concerning the above-mentioned treatments should be addressed to the vascular surgeon on duty.

SPECIAL HEMOSTASIS

PART 4

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Hemostasis in obstetrics and gynecology

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CHAPTER 14

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Introduction

Thrombosis and hemorrhage are major complications for pregnant women. Pregnancy is accompanied by changes in the expression of coagulation and fibrinolytic proteins that favor a balance towards clot formation. Increased activation of the coagulation cascade contributes to a reduction in hemorrhage risk that could otherwise be detrimental to fetal and maternal health. From early pregnancy an increase in thrombin generation is evident as measured by global tests, prothrombin fragment 1+2 and thrombin-antithrombin (TAT) complexes. Levels of pro-coagulant factors: VII, VIII, X, fibrinogen, VWF increase. Levels of endogenous anticoagulant protein S decrease. Antithrombin and protein C levels remain unaltered, and acquired resistance to activated protein C develops. Proteins in the fibrinolytic system that inhibit fibrinolysis are upregulated thereby further favoring coagulation. Fibrinolysis is diminished as levels of tissue plasminogen activator fall and levels of PAI-1 rise.

For hemostatic variables during normal pregnancy and coagulation factors at different stages of pregnancy see Tables 14.1 and 14.2.

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Table 14.1 Hemostatic variables (indices) during normal pregnancy.

Variable	Pregnancy week 12–15	Pregnancy week 24	Pregnancy week 35	Delivery (n = 16)	5 weeks Postpartum (n = 19)	Breast-feeding (n = 12–14)	Ref. values
B-platelet count (× 109/L)	275±64	256±49	244±52	246±54	243±61	267±57	150–400
P-fibrinogen (g/L)	3.7±0.6	4.4+1.2	5.4±0.8	5.7±0.7	3.1±0.7	3.1±1.0	2.1–4.2
P-PT (%)*	120±27	140±27	130±27	144±30	102±8.7	90±18	70–130
P-antithrombin (IU/mL)	1.02±0.10	1.07±0.14	1.07±0.11	1.06±0.14	1.09±0.16	1.08±0.12	0.85–1.25
P-protein C (U/mL)	0.92±0.13	1.06±0.17	0.94±0.2	1.01±0.20	1.03±0.14	0.91±0.17	0.68–1.25
P-protein S, total (U/mL)	0.83±0.11	0.73±0.11	0.77±0.10	0.77±0.11	0.93±0.11	1.00±0.18	0.70–1.70
P-protein S, free (U/mL)	0.26±0.07	0.17±0.04	0.14±0.04	0.12±0.05	0.19±0.06	0.25±0.06	0.20–0.50
P-fibrin, soluble (nmol/L)	9.2±8.6	11.8±7.7	13.4±5.2	17.2±13.9	9.4±4.4	9.7±6.2	<15
P-TAT (µg/L)	3.1±1.4	5.9±2.6	7.1±2.4	8.2±2.5	1.9±0.5	2.1±0.7	<2.7
P-fibrin D-dimer (µg/L)	91±24	128±49	198±59	266±101	84±14	81±34	<80
P-PAI-1 (AU/mL)	7.4±4.9	14.9±5.2	37.8±19.4	33.3±14.5	6.0±3.1	8.1±4.9	<15
P-PAI-2 (µg/L)	31±14	84±16	160±31	150±45	3.0±8.7	1.3±1.9	<5
S-cardiolipin antibodies pos. results	2/25	2/25	3/23		2/16	2/11	0

*For transformation to INR see www.equalis.se (last accessed November 2012). See Chapter 3.
P, plasma; TAT, thrombin–antithrombin complex; PAI, plasminogen activator inhibitor.
Data are presented as mean ± SD. Unless otherwise indicated, 24–26 women were investigated during pregnancy.

Source: Reproduced from Bremme *et al. Obstet Gynecol* 1992: **80**:132–137, with permission from LWW.

Table 14.2 Some coagulation factors (% of normal) at different stages of pregnancy (mean ± 95% ranges). n = 60

	Week of pregnancy			8 w	
	11–15	21–25	31–35	postpartum	Breastfeeding
Factor VII	111 (60–206)	150 (80–280)	162 (84–312)	94	91
Factor X	103 (62–69)	115 (74–177)	123 (78–194)	91	92
Factor V	93 (46–188)	82 (36–185)	82 (34–195)	80	84
Factor II*	125 (70–224)	125 (73–214)	115 (74–179)	106	107
FVIII:C	122 (53–833)	141 (44–453)	185 (69–499)	86	109
VWF	133 (56–318)	167 (66–427)	262 (95–718)	93	78

* Prothrombin.

Source: Modified from Stirling *et al*. *Thromb Haemost* 1984; **52**:176–182.

Thrombosis during pregnancy

Venous stasis develops from early pregnancy owing to the effect of progesterone on the vessel wall. The pregnant uterus obstructs venous return through the pelvic veins and the decrease in flow is most pronounced in the common femoral veins. In 85% of cases the thrombosis is in the left leg due to compression of the left iliac vein by the iliac arteries.

Deep venous thrombosis (DVT) and pulmonary embolism (PE) occur in 0.5–1 out of 1000 pregnancies. The risk of DVT/PE is highest in the puerperium. Pelvic thromboses, especially on the left side, are more frequent during the later part of pregnancy and in the puerperium.

Pulmonary embolism is one of the most common causes of maternal death, with an approximate incidence of 1–2 deaths per 100 000 deliveries. The risk of lethal PE is greatest during the first few weeks postpartum, especially after acute caesarean section. A higher frequency of cases with venous thromboembolism (VTE) has been reported in pre-eclampsia. Post-thrombotic complaints are reported in 30–60% of women with a history of deep venous thrombosis in connection with pregnancy vs 22% in unaffected legs. The risk of recurrence, especially after DVT/PE in connection with an earlier pregnancy or during treatment with contraceptives, is somewhat uncertain, but retrospective studies state it to be 0–13%.

Women with hereditary or acquired thrombophilia (a biochemically verified increased risk of thrombosis, i.e. deficiencies in

antithrombin, protein C or protein S, or with APC resistance with or without FV Leiden mutation, with phospholipid antibodies or lupus anticoagulant) have an increased risk of DVT/PE and obstetric complications. The risk is possibly also increased in the presence of the 20210G>A polymorphism of the prothrombin gene and in hyperhomocysteinemia.

Recent data have shown that thrombophilia increases the frequency of placental thrombosis and infarction, leading to intrauterine growth retardation. The frequency is also increased in obstetric complications such as intrauterine embryonic death, habitual abortion, placental rejection, and preeclampsia. This shows that thrombophilic factors should be investigated in women with DVT/PE, though not less than 3 months after delivery or 2 months after withdrawal of combined oral contraceptives. Reference values for nonpregnant women can be obtained not less than 1 month after the end of breastfeeding. The investigation (or at least analyses of antithrombin and Leiden mutation) is recommended for women with thrombophilia in first-degree relatives (parents, siblings, or children) and in women with defined thrombophilia in second-degree relatives.

Diagnosis of DVT and PE during pregnancy

Suspected venous thrombosis in the leg ought to be investigated by compression ultrasonography. However, thromboses located only in the lower leg are difficult to diagnose by this method, so in certain cases complementary duplex Doppler investigation or phlebography is needed. Phlebography, with its semi-invasive character, should only be used in exceptional cases because of the iodine contrast and radiation load.

Phlebography involves relatively little radiation of the fetus, while an incorrect diagnosis can have major consequences. Table 14.3 describes the radiation dose to the fetus. A radiation dose of 0.7 mSv is comparable to the basic radiation received per year by the fetus and the lower limit when deformities can occur has been stated to be 50–150 mSv. Deformities can arise in the fetus at weeks 2–8 (organogenesis) and with regard to deformities of the CNS, at weeks 8–25.

If ultrasonography is negative and a high level of clinical suspicion exists, the patient should remain anticoagulated and ultrasonography should be repeated after 1 week or an alternative diagnostic test should be used. If repeated investigation is negative, stop treatment.

Computed tomography (CT) or MRA can also be considered to diagnose an isolated iliac vein thrombosis and to evaluate a vena cava thrombosis.

If a massive PE is suspected, pulmonary artery CT is performed first (without previous pulmonary X-ray in order to avoid unnecessary

Table 14.3 Calculated and estimated mean effective radiation doses to patient and fetus in radiologic investigations for diagnosing VTE and for other common purposes. Individual variation may be considerable.

Investigation	Effective dose to patient (mSv)	Effective dose to fetus (mSv)
Pulmonary scintigraphy		
– perfusion only	1.5	0.2
– perfusion and ventilation	2.4	1
Pulmonary X-ray	0.1	<0.1
Pulmonary arteriography	6.6	<0.1
CT thorax	7.5	<0.1
Spiral CT thorax	2.5	<0.1
CT leg	0.8	<0.1
Phlebography (unilateral)	3.5	3
Colon	10	10
Urography	4	3
Lumbar spine	1.8	2.5
Pelvic measurement	0.5	0.5
Natural annual background radiation	1	0.7
Bone density (whole body)	0.01–0.3	
Mammography	3.0	

Source: Modified from SBU (Swedish Council on Health Technology Assessment).

radiation of the fetus). Suspicion of a submassive PE leads in the first place to duplex Doppler investigation of the legs. If thrombosis is found in the legs, further investigation of the pulmonary arteries does not affect the clinical handling.

The value of a negative D-dimer test result has not yet been assessed in pregnancy but it may possibly support a negative result in CT, ultrasonography, or duplex Doppler investigation.

Women could be advised that investigation with scintigraphy carries a slightly higher risk of childhood cancer compared with CT but a lower risk of maternal breast cancer.

In CT of the pulmonary arteries, smaller, subsegmental PE may be missed, so a negative result should be combined with ultrasonographic or duplex Doppler investigation of the legs in order to exclude DVT/PE for certain. The fetal radiation dose is less than 10% of that with scintigraphy and therefore there is a three times lower risk of childhood cancer.

When PE exerts a hemodynamic effect, clinical evaluation is important. In massive PE, the hemodynamic effect can be evaluated by means of echocardiography.

Assay of the natriuretic peptides BNP and pro-BNP, which can now be carried out as acute tests in many hospitals, has proved to be very useful, together with determination of troponin in nonpregnant individuals, for evaluating the degree of right ventricle involvement in massive PE and the results correlate with prognosis and right ventricle involvement as determined by echocardiography.

Circulating concentrations of thyroid-stimulating hormone (TSH) ought to be assessed 1 month after investigation in all women who have undergone iodine contrast investigation. They should also be investigated in all newborn children.

Breastfeeding can continue after phlebography whether or not iodine or gadolinium contrast medium has been used, as only a negligible amount passes to the mother's milk. In lung scintillation, reduced doses of isotopes are used. There should be a pause in breastfeeding for 12 h after the investigation.

The recommendation by the EANM (European Association of Nuclear Medicine) is that V/Q SPECT should become the gold standard for the diagnosis of PE in all patients and should be used in preference to CT.

Furthermore, MRI in the diagnosis of PE during pregnancy is becoming more advanced and may become the first choice. It does not require contrast medium, is independent of kidney function and contrast intolerance, and there is no irradiation. For the time being, however, MRI has not been evaluated sufficiently but is safe during pregnancy.

The choice of technique will depend on local availability. Pulmonary scintigraphy is not available in every hospital and usually not outside regular hours. Therefore CT is recommended but it also has advantages including better sensitivity and specificity and it can identify other pathology, such as aortic dissection. Thoracic CT has been reported to increase the lifetime risk of breast cancer by 14% in the mother.

Treatment with anticoagulation

Unfractionated heparin (UFH) does not pass through the placenta. The need for heparin varies during pregnancy. Compared with APT time, methods used to measure anti-FXa activity are more sensitive to the anticoagulation effect of heparin. Using an anti-FXa method, it can be

noted that less heparin is required to maintain a detectable anticoagulation effect. Side-effects of heparin treatment are bleeding complications resulting from high doses as well as obstetric complications, and osteoporosis in long-term treatment, with vertebral fractures in about 1–2% of cases. Heparin-induced osteoporosis seems to be reversible.

Low molecular weight heparin (LMH) has many advantages over UFH. It does not pass across the placenta, is more bioaccessible and is at least as good at preventing thrombosis. It is given once a day, leads to fewer bleeding complications, a reduced risk of heparin-induced thrombocytopenia (HIT), and probably a reduced risk of osteoporosis compared with UFH. There have been case reports of symptomatic osteoporosis occurring with LMH. Risk factors that make women susceptible to this complication remain to be identified. The frequency of adverse skin reactions appears reduced in patients receiving LMH. Skin lesions are benign, but HIT should be excluded. However, monitoring by means of APT time is generally not possible as it is not sensitive enough; an anti-FXa method is required.

LMH is recommended for prevention and treatment of VTE, rather than UFH.

Vitamin-K antagonist (VKA) drugs pass through the placenta and have a teratogenic effect, primarily during pregnancy weeks 6–12. Bleeding complications can occur in both mother and fetus, but because the synthesis of coagulation factors is low in the fetus, the effect on fetal coagulation is more pronounced. VKA have also been linked to an increased risk of pregnancy loss. Such drugs should therefore not be given during pregnancy, but might have to be considered if the need for anticoagulation therapy is extremely great, as in patients with artificial heart valves.

Low-dose aspirin (LDA): the use of aspirin as a thromboprophylax in pregnancy has never been tested in controlled studies but it is safe and can be used in the presence of phospholipid antibodies.

The use of thrombolytic therapy is reserved for life-threatening maternal thromboembolism. Only minimal transplacental passage is described, but the number of cases is small.

The new oral anticoagulants cannot be recommended for use in pregnancy and women who take these drugs and wish to be pregnant are advised to change to VKA and then change to LMH, depending on the diagnosis.

Fondaparinux is used in heparin intolerance. From limited data fondaparinux appears efficacious in pregnancy, but due to bleeding risk, care is required when used in heparin intolerance.

Treatment of acute DVT/PE during pregnancy

Blood sampling before anticoagulation treatment (with UFH/LMH) should include analyses of APT time, platelet count, PT(INR), phospholipid antibodies, lupus anticoagulant, antithrombin, protein C, protein S,

homocysteine and mutation 1691G>A in the FV gene (FV Leiden), and polymorphism 20210G>A in the prothrombin gene. Sampling to test kidney and liver function is recommended in addition to analyses of hemoglobin (HB), platelet count, and serum homocysteine. At PT(INR) >1.2, serum creatinine >170 µmol/L, platelet count $<70 \times 10^9$ and prolonged APT time, anticoagulation treatment should be individualized. Note that a prolonged APT time can result from the presence of lupus anticoagulant, which can increase the risk of thromboembolism.

Unfractionated heparin (5000–10 000 IU; 75 IU/kg bodyweight) is given intravenously prior to diagnostic examinations. The higher dose might be considered if PE is suspected. When DVT/PE is verified, give an intravenous continuous infusion of UFH (10 000 IU UFH per 100 mL [100 U/mL] NaCl solution), usually at a drop rate of 10–20 mL/h (24 000–48 000 IU per 24 h = 250 IU/kg bodyweight per 12 h) (Table 14.4) is indicated for massive pulmonary thromboembolism or in situations where rapid reversibility may be required and initially at vena cava or sinus thrombus. Considering the short half-life of heparin, the infusion ought to start within an hour after the bolus dose has been given. The same infusion drop equipment should not be used for more than 12 h owing to the risk of contamination. Twice the upper value of APT time is 70–140 sec when the reference value is 35 sec; check after 4–6 h.

Table 14.4 Suggestions for dosage and dilutions of heparin.

	Corresponds to		Corresponds to
1 mL/h	2400 U/24 h	11 mL/h	26 400 U/24 h
2 mL/h	4800 U/24 h	12 mL/h	28 800 U/24 h
3 mL/h	7200 U/24 h	13 mL/h	31 200 U/24 h
4 mL/h	9600 U/24 h	14 mL/h	33 600 U/24 h
5 mL/h	12 000 U/24 h	15 mL/h	36 000 U/24 h
6 mL/h	14 400 U/24 h	16 mL/h	38 400 U/24 h
7 mL/h	16 800 U/24 h	17 mL/h	40 800 U/24 h
8 mL/h	19 200 U/24 h	18 mL/h	43 200 U/24 h
9 mL/h	21 600 U/24 h	19 mL/h	45 600 U/24 h

Dilute heparin to 10 000 U/100 mL NaCl.

The patient should be in bed for the first 24 h and then mobilized with a graded support stocking on the affected lower leg in the event of massive thrombosis or PE.

Thromboses located only in the lower leg can be treated by LMH, 10 000 IU s.c. twice daily, without UFH intravenously. However, UFH is given initially to women with PE; or with sinus- or vena cava thrombosis. After 24 h of infusion treatment and clinical improvement, change to subcutaneous treatment twice daily with LMH: dalteparin 125 IU/kg bodyweight. The level of anti-FXa should be about 0.3–0.4 IU/mL before the next injection and above 0.6 IU/mL 3 h after an injection and should not exceed 1.3 IU/mL. The level should be checked once after 24 h of treatment, followed by a check-up and dose adjustment once a week when a stable level has been established.There is good evidence that active treatment of VTE is completed with 3 months of VKA therapy.

LMHs are used in pregnancy and a longer time period may be needed to complete the treatment of VTE with LMH compared with VKA therapy. Patients with VTE and pregnancy have a higher risk of recurrence and such patients are usually maintained on treatment as long as pregnancy stands. However, it is reasonable to suspect that patients with isolated distal VTE may not need full dosage for as long as those who have more extensive thrombosis.

LMHs: several centers favor a full dose or three-quarters of a full-dose treatment with LMH throughout the pregnancy. The latter modified dosing regimen is recommended for pregnant women with increased risk of bleeding or osteoporosis and, of course, those near delivery. If the VTE occurs early in pregnancy, it may be appropriate to reduce dosage to a high prophylactic dose after 6 months. Treatment should be continued until delivery. Note that the anticoagulation effect is reinforced and prolonged at the end of pregnancy, especially in high-dose treatment. The dose may therefore sometimes need to be lowered as delivery approaches and definitely at delivery (see section "Treatment at partus and postpartum"). Therefore, it is recommended to test anti-FXa every second week and platelet count once a month; more often near delivery.

Treatment at partus and postpartum

- *If less than 1 month has passed* since the thrombotic event, reduce the LMH dose to 2500 IU every 12 hours during delivery. A vena cava filter has been used in cases with a risk of recurrence of PE and more intensive anticoagulation treatment is contraindicated.
- *If more than 1 month has passed*, you can wait for 24 h after the last injection before the above-mentioned dosage is given. The

dosage (2500 IU twice daily) is continued until the infant has been delivered.
- Antithrombin concentrate is given in cases with hereditary antithrombin deficiency or if the level of antithrombin is below 0.5 IU/mL.
- *Postpartum:* VKA treatment (e.g. warfarin) starts as soon as hemostasis has been established. LMH at the same dose as during pregnancy is given for 5–7 days until the VKA treatment has a therapeutic effect. The treatment is given for at least 3 months in cases of uncomplicated lower leg thrombosis and for at least 6 months in cases of pelvic thrombosis or PE, but should always continue for at least 6 weeks postpartum. A compression stocking should be used during the day for 2 years.
- Advise the patient not to start a new pregnancy until 6–12 months after the thrombosis treatment has been completed.

Note: Oral VKA drugs, such as warfarin, are contraindicated during pregnancy, unless the patient has a mechanical heart valve prosthesis or is allergic to heparin/heparinoids and danaparoid (Orgaran) or fondaparinux (Arixtra) cannot be used (see HIT, Chapter 16). Treatment of a pregnant woman with UFH or LMH is not associated with complications in the child.

Allergy against LMH is usually evidenced as an itching redness around the injection site. In the first instance, change to another LMH drug.

After prophylactic/low-dosage LMH there does not seem to be any risk of osteoporosis. Women who have been treated with UFH or LMH at high doses should be offered investigation of bone mineral content.

Breastfeeding

Treatment with VKA, UFH, or LMH or LDA does not exclude breastfeeding of fully developed children. If the child is premature a neonatologist needs to be informed.

Special cases

- *Pelvic thrombosis*. Surgery, including thrombectomy and an AV fistula, has not been shown to give a better result than conventional long-term anticoagulation treatment. For circulatory disturbances in the leg, phlegmasia alba dolens, contact a vascular surgeon.
- *Massive pulmonary embolism*. Thrombolytic therapy may be indicated for a life-threatening massive PE.
- *Cerebral infarction*. Treat in consultation with a neurologist. Thrombolytic therapy may be indicated for sinus thrombosis and TIA or cerebral thrombosis (see Chapter 12).
- *Retinal thrombosis*. Treat in consultation with an ophthalmologist.

Heart disease: treatment of women with mechanical heart valve prostheses

Treatment should be given in a department with established cooperation between cardiologists, physiologists, obstetricians, and coagulation experts.

VKA should be continued until pregnancy is achieved; if requiring long-term VKA treatment and attempting pregnancy and therefore a candidate for LMH substitution, it is suggested to perform frequent pregnancy tests and start LMH when a pregnancy test is positive. The mother is best protected with VKA treatment throughout the pregnancy, but in 30% of cases this will lead to pathologic consequences. Treatment with VKA in pregnancy weeks 6–12 can be associated with significant risk to the fetus, including spontaneous abortion and skeletal deformity, frequency 6.4 % (warfarin embryopathy with nasal hypoplasia and epiphyseal puncture). In addition, VKA treatment during pregnancy may be associated with fetal hemorrhage, including intracranial bleeding and minor neurological dysfunction. VKA at a daily dose >5 mg is a significant predictor ($P < 0.001$) for poor fetal outcome. Such treatment entails a risk of minimal brain damage throughout pregnancy, probably as a result of the bleeding risk.

Several approaches are acceptable, for example LMH throughout pregnancy with full treatment dosage or LMH until the 13th week, followed by VKA alone until a few weeks prior to delivery.

The decision should be influenced by patient preference. However, in very high-risk cases (older generation prosthesis in the mitral position, history of thromboembolism, or associated atrial fibrillation), VKA and a change to LMH close to delivery is suggested (Table 14.5). High-risk cases should have additional ASA (75–100 mg/day) and regular investigations by echocardiography. No data have been published on skeletal decalcification when high-dose LMH is given throughout pregnancy. If VKA is used, the dose should be adjusted to a target PT(INR) of 3.0 (range 2.5–3.5); the lower level to be used in women with an aortic valve. If LMH is used, a therapeutic level should be used (see section on 'Treatment of acute DVT/PE during pregnancy'). Adequate protection throughout pregnancy may not be achieved in pregnant women with a mechanical valve.

Young women with native valve disease who are planning a pregnancy in the future should undergo a thorough risk assessment to decide whether an intervention is necessary before pregnancy and eventually to define its timing and the type of surgical therapy. Pregnancy in women with a bioprosthesis is associated with early and late structural valve deterioration leading to high reoperation rate.

Table 14.5 Recommended approach to anticoagulation therapy for women with a mechanical prosthetic heart valve (MPHV) during pregnancy.

Higher risk	Lower risk
Old-generation MPHV in mitral position or in tricuspid position, atrial fibrillation, history of VTE	New-generation MPHV in mitral position and in aortic position
Warfarin (PT(INR) 3.0–3.5) until 35–36 weeks of pregnancy followed by LMH (see below) to parturition + ASA 75 mg/day	LMH s.c. 12 h (trough anti-Xa 0.4–0.5 IU /mL, peak anti-Xa <1.5 IU/mL) to parturition
or	or
LMH s.c. 12 h (trough anti-Xa 0.5–0.6 IU/mL, peak anti-Xa <1.5 IU/mL), until 12 weeks followed by warfarin (INR 3.0–3.5) until 35–36 weeks of pregnancy followed by LMH (see above) to parturition + ASA 75 mg/day	LMH s.c. 12 h (see above) until 12 weeks followed by warfarin (PT(INR) 2.5–3.0) until 35–36 weeks of pregnancy followed by LMH (see above) to parturition

Active LMH anticoagulation prophylaxis during pregnancy may be required in cyanotic heart disease due to the thromboembolic risk because of polycythemia, and in atrial fibrillation and heart dysfunction.

Thromboprophylaxis in obstetrics and gynecology

Short-term prophylaxis during pregnancy is required in cases of strict immobilization, such as orthopedic immobilization (e.g. plaster) of the lower legs or that associated with major surgery and trauma. Active prophylaxis should be considered when flying (the day of the flight and the following day), if the flight lasts more than 4 h or the woman has risk factors such as BMI over 35–40 kg/m^2, duplex pregnancy, thrombophilia, or a clear family history of thromboembolism. Other recommendations include: exercising the legs, walking in the cabin, avoiding dehydration, minimizing intake of alcohol/coffee and, above all, use of support stockings. Knee stockings alone are only sufficient for women with normal pregnancy and no risk factors. An alternative is active prophylaxis with low-dose ASA, but this is less effective than low-dose prophylaxis with dalteparin (LMH).

Risk factors for VTE in pregnancy and puerperium include medical co-morbidities such as SLE, cancer, inflammatory conditions, nephritic syndrome, sickle cell disease, heart or lung disease, gross varicose veins,

paraplegia, multiple pregnancy, pre-eclampsia, cesarean section, postpartum hemorrhage, hyperemesis, OHSS (ovarian hyperstimulation syndrome), systemic infection, long-distance travel. Consider antenatal prophylaxis with LMH with 3 or more persisting risk factors.

In thrombophilia, even without DVT/PE, always consider thrombosis prophylaxis in situations associated with an increased risk of thrombosis, such as immobilization, pronounced varices, obesity, severe pre-eclampsia, caesarean section, and complicated delivery.

In acquired thrombophilia with lupus anticoagulant established on two different occasions (with at least a 12-week interval) or with cardiolipin antibodies IgG (GPL) or IgM (MPL) at medium or high titer (>40 GPL/MPL) established on two different occasions, or with β2-glycoprotein 1 antibody titer >99th percentile, the diagnosis is antiphospholipid syndrome (APS) together with the presence of clinical criteria such as vascular thrombosis (arterial, venous or small vessel thrombosis in any tissue or organ) or pregnancy morbidity (three or more unexplained consecutive spontaneous abortions before week 10; unexplained fetal death after week 10; delivery before week 34 because of pre-eclampsia or placental insufficiency). The recommended treatment is at least low-dose aspirin (LDA) besides LMH in those with earlier VTE.

Available evidence suggests that LDA during the second and third trimester is safe for the fetus and clinicians should use this agent for maternal indications. Although its safety during the first trimester remains uncertain, there is no clear evidence of harm to the fetus. If the indication is clear, clinicians should offer LDA to first-trimester patients.

Thromboprophylaxis during pregnancy, partus, and postpartum

For low and high prophylactic doses see Table 14.6.

Thromboprophylaxis

- should be *considered* at partus and postpartum when there is no previous DVT/PE, but thrombophilia and a clear family history of DVT/PE. *Note* that, in addition to antithrombin deficiency (see below), active prophylaxis may be necessary antenatally in combined or homozygous forms of prothrombin mutation 20210G>A and FV Leiden mutation, if additional risk factors are present.
- is *mandatory* at partus and postpartum for women without thrombophilia and with no family history but with earlier DVT/PE elicited by factors such as surgery, sepsis, fractures, etc.
- should be *considered* during the second and third trimesters and is *mandatory* during partus and postpartum in women without thrombophilia but with earlier verified DVT/PE in connection with pregnancy or during oral contraceptive treatment or with other risk factors, such as marked obesity.

Table 14.6 Thromboprophylactic doses of LMH antenatally and postnatally.

Low prophylactic dose per kg weight	
Weight (kg)	**dalteparin**
<50	2500 units × 1
50–90	5000 units × 1
91–130	7500 units × 1
131–170	5000 units × 2
>170	7500 units × 2
High prophylactic dose per kg weight	
Weight (kg)	**dalteparin**
50–90	5000 units × 2
91–131	7500 units × 2
Treatment dose	**125 units/kg/12 h**

- is *mandatory* throughout pregnancy, during partus and postpartum in women with:
  - ongoing DVT/PE during the current pregnancy (LMH high-dose prophylaxis)
  - ongoing treatment with VKA drugs (LMH high-dose prophylaxis)
  - inherited antithrombin deficiency (LMH high-dose prophylaxis)
  - recurrent DVT/PE (LMH high-dose prophylaxis)
  - DVT/PE and thrombophilia FV Leiden mutation or other thrombogenic mutations, such as prothrombin 20210G>A mutation, protein C deficiency, protein S deficiency, or with phospholipid antibodies/lupus anticoagulant.

In the presence of additional risk factors, high-dose/intermediate-dose prophylaxis may be needed in combined or homozygous forms of prothrombin and Leiden mutations.

The risk of first VTE during pregnancy and the puerperium in asymptomatic double heterozygous carriers of FV Leiden and prothrombin 20210G>A is low and similar to that of single mutation carriers. Therefore, management of pregnancy in terms of antithrombotic prophylaxis can be similar in double heterozygous and single mutation carriers. Both in single heterozygotes and in asymptomatic double heterozygous carriers, antithrombotic prophylaxis appears to be justified only in the puerperium.

General comments on thromboprophylaxis

The risk of venous thromboembolism appears to arise early in pregnancy; therefore, when antepartal prophylaxis is used, it should be commenced in the first trimester.

- Coagulation analyses *before* treatment: APT time, platelet count, PT(INR), phospholipid antibodies/lupus anticoagulant and other analyses, if they have not been investigated earlier.
- Treatment with *compression stockings* should start as soon as pregnancy is apparent. This is also recommended for women with an increased risk of thrombosis without earlier DVT/PE. Compression stockings are used as early as possible in pregnancy and up to 12 weeks postpartum. A knee stocking is usually sufficient; stocking class I is recommended, and for chronic problems, use a class II stocking.
- In antithrombin-deficient women treatment with LMH (s.c.) *should begin as early in pregnancy as practical* and as soon as a pregnancy test is positive. Thrombosis prophylaxis in cases of a moderately increased risk of recurrence is given with LMH (s.c.), using one-dose administration (= low-dose prophylaxis) in the morning. A dose in the evening has the same effect but is not practical when blood has to be sampled. In cases of a greatly increased risk, two-dose administration (= high-dose prophylaxis) is suggested.
- In the presence of *phospholipid antibodies/lupus anticoagulant*, additional treatment with ASA should be given. Corticosteroid treatment is currently recommended only in active SLE. Folic acid should be given in hyperhomocysteinemia. (Note that levels of homocysteine normally decrease during pregnancy.) If there is no normalization, add B6 and B12 and investigate MTHFR (methylenetetrahydrofolate reductase) polymorphism.
- One of the laboratory criteria to be met is persistent lupus anticoagulant (LA), defined as LA positivity that must be confirmed in samples 12 weeks apart. However, LA detection in patients who are under treatment with heparin and/or VKA 12 weeks later is problematic. If LMH is used for treatment, the interference is less. Note that it is important to test for LA before starting treatment.
- With previous *cerebral venous thrombosis*, LMH prophylaxis is started early in pregnancy with the addition of ASA if a phospholipid antibodies/LA test is positive. Arterial cerebral thrombosis is always treated with ASA, with the addition of LMH in thrombophilia.

Thromboprophylaxis for women of medium weight (50–90 kg) can be given at the initial dose throughout pregnancy. If bodyweight is below 50 kg or above 90 kg, we recommend after 2–3 weeks to control anti-FXa activity once. The aim is an anti-FXa activity corresponding to 0.20–0.45 IU/mL 3 hours after an injection. With adequate anti-FXa

activity, further controls are not necessary unless there is an abnormal weight increase, or obstetric complications. Dose adjustments should be made in steps of 2500 IU per 24 h and checked after 1–2 weeks. APT time and platelet count should be checked 2–3 weeks after the start of thromboprophylaxis and in pregnancy week 34.

When treated with LMH, control platelet count after 2 weeks as HIT may occur. If platelet count is unexpectedly decreased (by 50% from baseline), see Chapter 16. Suspicion of HIT is strong if there is no other reason for the thrombocytopenia or if thrombosis is increasing.

Thromboprophylaxis at birth

Most pregnant women on anticoagulation treatment can be delivered vaginally. It is recommended that the delivery takes place in a clinic with specialist interest and knowledge.

On arrival at the delivery department, APT time, platelet count, PT(INR) and antithrombin should be checked to evaluate the risk of bleeding and the possible need for antithrombin concentrate. Note the time of the latest injection of LMH.

In spontaneous labor, give LMH (dalteparin), 2500 IU s.c. 24 h after the previous LMH dose and thereafter every 12 h until the infant is delivered. At induction of delivery, the morning dose of LMH is reduced to 2500 IU.

After partus, give the same dose of LMH as the patient had prior to delivery, 2–4 hours after partus if no excessive bleeding is present. If bleeding is present, reduce the dosage.

Thromboprophylaxis in the puerperium

Postpartum, LMH (dalteparin) s.c. of 5000 IU per 24 h, is given for at least 6 weeks in the morning or evening, depending on when partus occurred. The interval after the last dose during partus should not exceed 12 h. Monitoring by means of anti-FXa determinations is not needed unless there is an absolute indication. If prolonged thromboprophylaxis (more than 6 weeks) is planned, consider changing to VKA treatment. LMH is given until PT(INR) is 2.0–3.0 for at least 2 days and VKA treatment has been given for 5 days. Bone density measurement is recommended as soon as possible postpartum after high-dose prophylaxis (two-dose) and/or simultaneous cortisone treatment. In extended osteopenia, consider continued thromboprophylaxis with VKA and follow-up of bone density 1 year after delivery. Refer to an endocrinologist thereafter if needed.

With a greatly increased risk, two-dose prophylaxis (= high-dose prophylaxis) should be used.

For all other pregnant women with thrombophilia and no prior VTE, antepartal clinical surveillance is suggested plus postpartal anticoagulants. At present, complete thrombophilia investigation is carried out. If

the father has a family history of thrombosis, he ought to be investigated with regard to thrombophilic factors.

Thromboprophylaxis in antithrombin deficiency

Thromboprophylaxis should start as early as possible in pregnancy. A measurable anticoagulation effect for 24 h is desired. Dalteparin is given at 5000–7500 IU s.c. twice daily with an anti-FXa level of 0.1– 0.2 IU/mL immediately prior to the injection (Table 12.7). Anti-FXa should be checked every second week and during the last 2 months, every week.

During delivery, in early puerperium and with obstetric complications, it is recommended to normalize the inhibitory capacity with antithrombin concentrate. An adequate dose of antithrombin (AT) is calculated in IU as follows: (a) kg × (desired AT level minus the current AT level, both in IU/mL) × 100, or (b) kg × (desired AT level minus the current AT level, both in %). Desired level: 1.0–1.4 IU/mL or 100–140%.

When the antithrombin level has been normalized, the dose of dalteparin can be reduced. In view of the risk of bleeding, when treatment with antithrombin concentrate is combined with high-dose LMH, treatment with VKA drugs can wait until a couple of days after partus. During the following week, the antithrombin concentration in plasma should exceed 80%. Prophylactic anticoagulation treatment should continue for 3 months postpartum, or for longer if the woman has had an earlier DVT/PE.

The infant should be investigated after birth for antithrombin deficiency and treated on suspicion of hereditary antithrombin deficiency.

Ongoing treatment with VKA drugs and with recurrent DVT/PE history

If the patient is on VKA treatment (warfarin etc.), it is recommended to plan pregnancy in advance so that when a test confirms the pregnancy, a change to LMH can be made *before* pregnancy week 6. Note that VKA must be withdrawn.

Thromboprophylaxis should start as early as possible in the pregnancy. A measurable anticoagulation effect in 24 h is desirable. Give dalteparin at 5000–7500 IU s.c. twice daily, aiming for an anti-FXa level of 0.1–0.2 IU/mL immediately prior to an injection. Anti-FXa should be monitored every month up to week 32, every second week up to the last month, and during the last month, every week (Table 12.7).

If anti-FXa is below 0.1 IU/mL, increase the evening dose in the first place by 2500 IU dalteparin.

On arrival at the delivery department, check APT time, PT(INR), antithrombin and platelet count. Note the time of the last LMH injection. In order to make regional anesthesia possible in spontaneous labor,

Table 14.7 Summary of guidelines for thromboprophylaxis in women with previous venous thromboembolism (VTE) and/or thrombophilia.

Risk	History	Prophylaxis
Very high Requires special management by experts in hemostasis and pregnancy	• Previous VTE on long-term warfarin • Antithrombin deficiency • Previous recurrent VTE	Recommend antenatal high-dose LMH and at least 6 weeks postnatal LMH/warfarin
	• Antiphospholipid syndrome with or without previous VTE	Minimum ASA. Previous VTE recommend antenatal and at least 6 weeks postnatal prophylactic LMH (special location high dose LMH can be recommended). Obstetric APS without VTE can be recommended high dose LMH
High Needs to be discussed with experts in hemostasis and pregnancy	• Previous unprovoked VTE • Previous estrogen-provoked VTE • Previous VTE + thrombophilia • Previous VTE + family history • Asymptomatic thrombophilia (for antithrombin deficiency see above) with combined defects and homozygous FVL combined with other risk factors	Recommend antenatal and 6 weeks postnatal prophylaxis with LMH
Intermediate Needs to be discussed with experts in hemostasis and pregnancy	• Single previous VTE associated with transient risk factor no longer present without thrombophilia, family history or other risk factors	Consider antenatal LMH (but not routinely recommend). Recommend 6 weeks postnatal prophylaxis with LMH
	• Asymptomatic thrombophilia without other risk factors (for antithrombin deficiency see above)	Postnatal prophylaxis with LMH. Recommend 7 days (or 6 weeks if family history or other risk factors present)

wait for 24 h and thereafter reduce the LMH dose to half, twice daily; for instance, reduce the dalteparin dose to 2500 IU/mL twice daily. Women treated with low-dose ASA due to acquired thrombophilia, SLE nephritis or stroke should remain on this dose.

On induction/caesarean section, omit the evening dose to prepare for regional anesthesia/catheterization in the morning. High-dose prophylaxis should be resumed as soon as possible after postoperative supervision. Women on VKA prior to pregnancy can resume this treatment 1–2 days after delivery, but it may be an advantage to wait for 2–3 weeks and continue with high-dose LMH instead.

Thromboprophylaxis at caesarean section

The puerperium is the time of maximal risk of pregnancy-associated VTE. A thrombosis risk assessment should be performed in all women undergoing caesarean section to determine the need for thromboprophylaxis.

The risk of thromboembolism in an elective caesarean section is low in an uncomplicated pregnancy with no risk factors and similar to that seen in low-risk surgical patients for whom no routine thromboprophylaxis other than early mobilization is recommended. Support stockings are recommended. Routine thromboprophylaxis is not justified and cannot be recommended on the basis of caesarean section alone.

Prophylaxis with LMH should be considered for patients presenting with major risk factors such as previous VTE, thrombophilia, ongoing infection, severe pre-eclampsia, immobilization, immobility with strict bed rest for >4 days prior to surgery, large amount of blood loss, dehydration, sickle cell anemia, inflammatory intestinal disorder, nephrotic syndrome or SLE, and heart disease and other co-morbid medical conditions.

In the case of minor risk factors such as obesity (BMI >35 kg/m^2), multiple pregnancy, postpartum hemorrhage, pre-eclampsia, the presence of at least two or one together with emergency cesarean section, thromboprophylaxis must be considered.

A major risk also exists with simultaneous hysterectomy, hereditary thrombotic disease, paralysis of the lower legs, and in the presence of phospholipid antibodies/lupus anticoagulant.

The first injection is given 2–4 h after the operation. For thromboprophylaxis, dalteparin (5000 IU × 1) together with mechanical prophylaxis with elastic stockings should be given until the fifth postoperative day or until full mobilization. The optimal duration of prophylaxis after ceasarean section is not established. Prophylaxis for 6–12 weeks postpartum may be indicated if major risk factors continue to exist in the puerperium.

Thromboprophylaxis at vaginal delivery

Prophylaxis to cover delivery should not be limited to those undergoing caesarean section. Age >40 years and BMI >35 kg/m^2 are important independent risk factors of postpartum VTE even after vaginal delivery. The combination of either of these risk factors with any other risk factor of VTE (pre-eclampsia, immobility, or inflammatory disorders) justifies the use of LMH for 3–5 days postpartum. Women who qualify for postpartum LMH prophylaxis can probably safely discontinue this after 3–5 days provided they are fully mobile.

Regardless of the mode of delivery and other risk factors for women with BMI >40, weight-based doses should be given for at least 7 days postpartum.

Blood sampling in children of women with severe forms of thrombophilia

The father should be analyzed with regard to the same deficiency as that of the mother and asked about a family history of thromboembolism.

In antithrombin deficiency in the mother, sample the child for analyzing the AT level at the same time as for phenylketonuria (PKU) if the child is otherwise healthy. After a traumatic delivery or if the child is affected, analyze AT immediately and contact a coagulation expert for discussion about treatment with antithrombin concentrate. Avoid use of any remaining IV ingoing catheter. Carry out ultrasonographic investigation of the head and of the aorta of a child with a decreased AT level.

Analyze AT level again at the age of 6 months.

If the woman has a deficiency of protein C or protein S, the child is sampled at the same time as for PKU.

Obstetric epidural/spinal analgesia (anesthesia)

Before delivery, it is important to make and document an individual plan. In low-dose prophylaxis with LMH, epidural anesthesia (EDA) can be used when APT time, PT(INR) and platelet count are normal and at least 10 h have passed since the injection of 5000 IU dalteparin given as a single dose. If only LMH (2500 IU SC) has been given after the beginning of labor, the time from injection to EDA/spinal anesthesia can be reduced, but it must be at least 6 h. The next prophylactic dose can be given 2 h after EDA/spinal anesthesia at the earliest, and the catheter is removed 10 and 6 h, respectively, after the last injection. A new injection is given at the earliest 2 h after EDA if the catheter is still in place.

In high-dose prophylaxis and treatment

In high-dose prophylaxis with a two-dose regime or treatment dosage, 24 h must have passed since the latest injection before EDA/spinal

analgesia can be allowed. Accumulation is to be expected in high-dose prophylaxis/treatment, so the anti-FXa level must be measured *exactly* as close to delivery if possible. When anti-FXa activity is known, EDA may be considered earlier if the trough value is below 0.1 IU/mL.

In ASA medication (75–160 mg)

Low-dose aspirin (ASA) medication should, if possible, be discontinued 2–3 days prior to planned EDA. If this is not advisable EDA can still be performed provided no other risk factors are present.

In platelet function deficiency

In platelet function deficiency, EDA/spinal anesthesia can be used if bleeding time is normal (tested in week 32). APT time, PT(INR), and platelet count should be normal. Spinal anesthesia for section can be performed if the bleeding time is only slightly prolonged (up to 600 sec measured as template bleeding time with a reference value below 420 sec). Spinal anesthesia is preferable in this situation. Epidural anesthesia should not be performed as a pain reliever in vaginal delivery if bleeding time is prolonged. Desmopressin treatment to make spinal anesthesia possible before section should not be carried out routinely. Consult coagulation and anesthesia specialists, and an obstetrician.

In pre-eclampsia

In pre-eclampsia, EDA/spinal anesthesia can be performed if platelet count is above 100×10^9/L. It is not necessary to control APT time and PT(INR) routinely. With platelet count at 80–100×10^9/L, EDA/spinal anesthesia can be considered if APT time, PT(INR), and bleeding time are normal. How early in advance the samples have to be drawn is often debated. This has to be considered from case to case. Mostly it is acceptable with samples drawn the same day, but sometimes it is necessary to draw and analyze samples just before the anesthesia.

In idiopathic thrombocytopenia purpura (ITP)

The same applies as in pre-eclampsia.

In von Willebrand disease

In many cases of VWD, EDA/spinal anesthesia is contraindicated. In patients with mild VWD type 1, when the levels of VWF have increased to >0.70 kIU/L during pregnancy, EDA/spinal anesthesia can be used if APT time, PT(INR), platelet count, and bleeding time are normal at the same time. These analyses are carried out in the third trimester and it is not necessary to repeat them routinely. The level of VWF decreases quickly after delivery and therefore a remaining epidural catheter ought to be removed 2 hours after partus (i.e. as in normal delivery).

In carriers of hemophilia A or B

Epidural/spinal anesthesia can be used if the levels of FVIII and FIX are >0.70 kIU/L and at the same time APT time, PT(INR), platelet count, and bleeding time are normal. These analyses are carried out in the third trimester/week 32 and need not be repeated thereafter.

In antiphospholipid syndrome (SLE)

If a prolonged APT time is due to the presence of LA, no further coagulation investigation is needed. If no LA is found, investigation of coagulation factors has to be carried out. However, planning before EDA/spinal anesthesia has to be carried out in all cases with prolonged APT time, together with a coagulation specialist. A necessary prerequisite before using EDA is that the woman has no bleeding history.

Complications during pregnancy

The hemostatic balance changes during pregnancy in order to prevent bleeding at delivery. Levels of most coagulation factors increase and fibrinolytic capability decreases (see Tables 14.1 and 14.2).

Hemophilia, VWD

During normal pregnancy, according to our experience, FVIII roughly doubles and VWF can increase up to fourfold. In patients with mild VWD and in hemophilia A carriers, levels are usually normal during the last trimester. The factor levels should be measured in pregnancy week 32 in hemophilia A carriers (FVIII) and in severe and mild VWD (VWF). Factor IX is not elevated at the end of pregnancy, so hemophilia B carriers may have a higher risk of bleeding.

Hemophilia A and B and severe forms of VWD are rare. Written recommendations concerning pregnancy and delivery are issued by the doctor in charge of the delivery in co-operation with the coagulation specialist. In hemophilia, ultrasonographic determination of the sex of the fetus is recommended. Section is not indicated routinely, only for a complicated or prolonged delivery. Vacuum extraction and scalp electrodes should be avoided. An umbilical cord test in infant boys with suspected or known hemophilia (analyses of FVIII/FIX) is recommended.

Patients with severe VWD need treatment before delivery and may need several weeks of treatment with factor concentrate after delivery. Carriers of mild VWD and hemophilia are treated with tranexamic acid Cyklokapron 500 mg, 3 tablets 3 times daily; if not per os, give i.v. at 10 mg/kg bodyweight) at the onset of labor, during delivery, and at least 1 week postpartum. For abnormal bleeding after delivery, give

desmopressin; be careful about repeating doses because of the possibility of electrolytic disturbances (see Chapter 4).

Idiopathic thrombocytopenia purpura

Assessment of platelet count is carried out initially in both EDTA and citrate tubes. For platelet count below 100×10^9/L, investigate the presence of hematologic malignancy together with a hematologist. Because isolated thrombocytopenia is present in SLE, at least the presence of LA and cardiolipin antibodies should be determined, and the development of pre-eclampsia should be taken into consideration. In the mother, platelet count should be followed during pregnancy.

If the woman does not have any symptoms and the number of platelets is above 50×10^9/L, there is no need for treatment during pregnancy or delivery.

Monitoring during pregnancy

- At platelet count $>150 \times 10^9$/L, monitor every second month.
- At platelet count $100–150 \times 10^9$/L, monitor each month.
- At platelet count $50–100 \times 10^9$/L, monitor every second week.
- At platelet count $<50 \times 10^9$/L, monitor each week.

There is probably no risk of spontaneous bleeding until platelet count is $10–20 \times 10^9$/L.

Treatment during pregnancy

Treatment during pregnancy should be considered if the platelet count is $<20 \times 10^9$ /L or there are bleeding complications. A platelet count $>50 \times 10^9$/L is aimed at, and before delivery/caesarean section, if possible $>100 \times 10^9$/L.

Intravenous immunoglobulin 0.4 g/kg/day for 3 days; alternatively 0.8–1 g for 1–2 days; effect within 1–3 days. There are few side-effects.

If treated with prednisolone 1 mg/kg/day for 7–10 days, the effect is slowly established but there are many side-effects. In treatment failure and platelet count $<10 \times 10^9$/L, splenectomy can be considered on vital indication.

Fibrinolytic inhibitor, tranexamic acid, can be given prophylactically at platelet count $<100 \times 10^9$/L.

Delivery

In the event of bleeding or a bleeding tendency in connection with delivery, platelet transfusions may be necessary. One unit, 300 mL, can be expected to increase platelet count by about 10×10^9/L. The effect does not last long (hours) so platelet concentrate should be given shortly before a planned operation.

An umbilical cord test (cordocentesis) is not usually recommended.

Check platelet count, APT time, and PT(INR) on admission to the delivery unit. Caesarean section should be performed according to obstetric indications. Bleeding complications in the child have not been proven to be related to the manner of delivery. Fetal thrombocytopenia, however, cannot be excluded. Avoid prolonged delivery and traumatic extraction. EDA can be used if platelet count is $>100 \times 10^9$/L and spinal anesthesia if platelet count is $>80 \times 10^9$/L. The risk of neonatal thrombocytopenia is greatest during the first few days after delivery.

The newborn infant

Circulating antibodies can cross the placenta during pregnancy and give rise to thrombocytopenia. ITP is not hereditary but it is important to inform the mother during pregnancy about the risk of transient thrombocytopenia in the child. Assess platelet count in the umbilical cord blood. A neonatology specialist should be informed and give an opinion about the platelet count after delivery and during the first 24 hours. Platelet counts should be monitored for 3 days and possible treatment with immunoglobulin should be given. The platelet level becomes normalized during the first few months.

Essential thrombocytosis/thrombocythemia (ET)

ET is a myeloproliferative disorder and is rare in women of childbearing age. The clinical course of ET is most often benign in the young. It should be remembered that around 85% of cases of thrombocytosis are reactive (bleeding, iron deficiency, malignancy, connective disease, splenectomy) rather than a primary phenomenon. Women with essential thrombocytosis have an increased risk of complications during pregnancy, possibly related to placental thromboses. However, platelet count can decrease during pregnancy. If platelet count is above 600×10^9/L, low-dose ASA medication is recommended. Cytostatics should be avoided during pregnancy, but interferon can be used for myelosuppression. Some patients with ET carry the JAK2V617F mutation.

Pre-eclampsia

For women with pre-eclampsia, the risk of the condition is increased 10-fold in the next pregnancy and is even higher if a previous pregnancy was associated with a medical risk factor or early/severe pre-eclampsia. Pre-eclampsia can occur without a clear cause but mainly if the woman develops high blood pressure.

For women with earlier severe or repeated pre-eclampsia, ablation, intrauterine growth retardation (IUGR), or unexplained intrauterine fetal death (IUFD), we recommend screening for hereditary thrombophilia,

phospholipid antibodies and hyperhomocysteinemia.Thrombophilia is not the cause of pre-eclampsia but it contributes to the disease.

Placental ablation, severe pre-eclampsia, and HELLP syndrome (hemolysis, elevated liver enzymes, low platelet counts) can cause severe disseminated intravascular coagulation (DIC). Total ablation is always accompanied by some form of coagulopathy. Coagulation disturbances in IUFD (intrauterine fetal death) are rare, but control of platelet count, fibrinogen and antithrombin levels is recommended before partus. If an acquired hemostasis disturbance is suspected, check on platelet count, APT time, PT(INR), antithrombin and fibrin D-dimer, with an additional test of fibrinogen in case of bleeding. Nowadays, thromboelastography (TEG) can give a complete picture of hemostatic function (platelet function, coagulation, and fibrinolysis).

Soluble fibrin, reflecting formation of thrombin, can be used to detect DIC at an early stage. In pregnancy, fibrin D-dimer analysis and global assays are useful (see Chapters 3 and 16).

Acute fatty liver of pregnancy (AFLP)

This is a rare condition almost always seen during the third trimester of pregnancy. Acute fatty liver of pregnancy is characterized by malaise, nausea, epigastric pain, and sometimes changes in mental status. Laboratory studies show moderate to severe abnormal liver function tests, hypoglycemia, and electrolyte imbalance. Coagulopathy ensues due to depressed clotting factor synthesis. Although the diagnosis of AFLP can be made clinically, confirmation can only be achieved by a liver biopsy.

Treatment should be aggressive in order to deliver as soon as possible.

Thrombotic thrombocytopenia purpura (TTP)

This is a rare disease characterized by a triad of microangiopathic hemolytic anemia (fragmented RBC in smears and elevated LDH), thrombocytopenia, and neurologic symptoms. The etiology has recently been shown to be due to severe deficiency of a VWF-cleaving protease, ADAMTS13. Two clinical forms have been described – acquired deficiency and congenital. The apparent higher incidence of TTP in pregnancy appears to be due to an overlap of a TTP-like syndrome with HUS, HELLP, and severe pre-eclampsia.

Prophylaxis against pre-eclampsia

General prophylaxis against pre-eclampsia with ASA has not proved to be of any value, except possibly in cases of early onset of severe pre-eclampsia (causing delivery prior to pregnancy week 34). However, studies have shown that low-dose ASA (LDA) can be used without risk during pregnancy. For women considered to be at high risk of

pre-eclampsia, low-dose ASA throughout pregnancy is recommended. It is therefore reasonable to give 75 mg ASA daily as prophylaxis to women with high blood pressure and either kidney disorders or diabetes, or with antiphospholipid syndrome, and furthermore to women with early-onset or severe or repeated pre-eclampsia.

For severe and early pre-eclampsia, LDA is recommended. New data recommend treatment not only in patients with antiphospholipid antibodies but also in patients with other types of thrombophilia because a better outcome is obtained if they are treated also with LMH. In patients with inherited thrombophilia and delivery before 34 pregnancy weeks adding LMH to LDA has to be considered. For women without thrombophilia it is less clear.

In patients with earlier severe pre-eclampsia with elective delivery or IUFD before week 34 and microvascular events in the woman (usually in the kidney or cerebral) and phospholipid antibodies (especially in the presence of LA and high levels of cardiolipin antibodies or β2-glycoprotein 1), a high-dosage prophylaxis program together with ASA is mandatory. When using ASA, treatment should start in or before pregnancy week 12. Several studies confirm the usefulness of treatment with folic acid (5 mg/day), but not with vitamin C (1000 mg/day) and vitamin E (400 IU/day) in high-risk populations.

The level of plasminogen activator inhibitor-1 (PAI-1), normally present in the blood, is increased in the mother in pre-eclampsia and is connected with increased resistance in the placental circulation. Plasminogen activator inhibitor-2 (PAI-2) forms in the placenta and is not present in the blood except during pregnancy. The level of PAI-2 in the mother is significantly correlated to placental function and weight and also to fetal growth, but it is not correlated to the severity of pre-eclampsia. Intrauterine growth inhibition is accompanied by reduced fibrinolysis, measured as lower levels of fibrin D-dimer compared with women with pre-eclampsia but no fetal growth inhibition. Levels of fibrin D-dimer are, however, higher than in healthy pregnant women.

Fibronectin has not been shown to be suitable for screening, although it probably indicates a pathologic development earlier than elevated blood pressure does. Besides fibronectin sFlt-1 (soluble fms-like tyrosine kinase-1), control of angiogenes, is shown to increase five weeks prior to the onset of pre-eclampsia and an increased ratio of sFlt-1/PLGF (placental growth factor) ratio strongly predicts the future onset of pre-eclampsia. The cytokine TNF-alfa is a strong candidate for mediating endothelial damage as recent reports suggest that serum concentrations are significantly higher already in the first trimester in pregnant women who are developing pre-eclampsia compared to controls.

Postpartum bleeding

The volume of blood in a highly pregnant woman is 5–6 liters. Blood flow in the spiral arteries increases to 600–800 mL/min at term.

A clinically massive loss of blood is defined as 50% of the total volume in 3 hours, or 150 mL/min. Blood loss equivalent to the total volume of the patient results in dilution of the platelet concentration to 40–50% of the original; after the loss of 1.5–2.0 blood volumes, the concentration of fibrinogen in the blood can fall to below 1 g/L and PT(INR) can rise above 1.5.

General procedures

Act promptly!

- Search for a local source of bleeding – first surgery and arterial ligation.
- Keep the patient warm, calm and free from pain.
- Take samples for PT(INR), platelet counts (PLT), APT time, fibrinogen, D-dimer and AT.
- Independently of the response from the laboratory, promptly administer tranexamic acid 10–20 mg/kg bodyweight IV. Dosage 3–4 times per 24 h i.v. in normal kidney function.
- If after 5 minutes massive bleeding continues, give 2–4 g of fibrinogen concentrate. An ampoule containing 1 g fibrinogen increases the concentration by 0.3 g/L.
- Thereafter give fresh-frozen plasma 15 mL/kg bodyweight and consider giving platelet concentrate.
- Prothrombin complex concentrate can be used if plasma treatment fails to have sufficient effect on PT(INR).
- If bleeding still continues, consider giving antithrombin concentrate if the level of antithrombin is <0.50 IU/L and platelet concentrate if platelet count $<50 \times 10^9$.
- The indication for transfusion at ongoing bleeding is HB <100 g/L but if the situation is stabilized at HB <80 g/L.
- Give LMH when bleeding is under control.

Recombinant factor VIIa NovoSeven is being increasingly proposed for massive bleeding despite a lack of clinical studies on its effect and safety. However, its use has also been associated with thromboembolic complications (see also Chapter 5).

Consider using NovoSeven:

- for blood loss of 1.5 times the total volume;
- when considering hysterectomy, so that extirpation of the uterus may be avoided;
- when planning selective embolization, so that embolism can be delayed or avoided.

Prior to administration of NovoSeven, the following should be fulfilled: hemoglobin concentration above 70 g/L, PT(INR) above 1.5, platelet count above 50×10^9/L, fibrinogen above 2.0 g/L, pH above 7.1.

If laboratory results are not known, give two units of platelet concentrate and fresh (frozen) plasma (10–20 mL/kg bodyweight).

Dosage of NovoSeven: give 0.1 mg/kg as an i.v. bolus during 2–3 min (7 mg to a 70 kg patient – round-off upwards). Combine this with tranexamic acid (10–20 mg/kg bodyweight). If there is no effect within 15–30 min, repeat the dose *once*.

Thromboprophylaxis in legal and spontaneous abortions

If the patient is in need of thrombosis prophylaxis during pregnancy but wants a legal abortion for medical or social reasons, LMH (dalteparin 5000 IU s.c. × 1) should be given as soon as possible. The medication should continue for 1–2 weeks after abortion.

For spontaneous or threatened miscarriage, the dose can be adjusted to 2500 IU twice daily.

Thromboprophylaxis in gynecologic surgery

The surgeon in charge decides which patient should have thrombosis prophylaxis and notes the prescription in the drug record on arrival. Indications include the following:

- all patients over 40 years of age undergoing laparotomy or similar operations;
- all patients regardless of age undergoing laparotomy or similar operations because of a malignant disease;
- all patients regardless of age having a reoperation within 30 days;
- risk factors that, regardless of age, should be taken into account as regards laparatomy and similar operations:
  - earlier thromboembolic disease
  - obesity (BMI above 30 kg/m^2)
  - extensive varices
  - long operation (more than 90 min)
  - ongoing medication with oral contraceptives or HRT
  - pregnancy
  - when taking oral contraceptives.

Prophylaxis consists of the following:

- *LMH* (dalteparin, 5000 IU), anti-FXa s.c. × 1, or enoxaparin (40 mg s.c. × 1) is given, starting in the evening prior to the operation day.

The treatment should continue for at least 5 days or for longer if immobilization continues. With a high risk of bleeding, the dose can be halved.

- *Dextran 60 + LMH*. Dextran 60 (1000 mL) is given preoperatively after 20 mL Dextran 1 to a patient who has not had LMH the previous evening. Postoperatively, LMH is given as above, starting on the first day after the operation.
- *Dextran 60 alone*. The patient is given 1000 mL Dextran 60 after 20 mL Dextran 1 during the operation and possibly on the first day after the operation.

Low molecular weight heparin is the first alternative in elective operations. Dextran 60 alone is suitable in most acute operations and in those with a low risk, for example in vaginal hysterectomy in a healthy woman over 40 years of age.

Oral contraceptive (OC) pills and hormone replacement therapy (HRT)

Some guidelines consider stopping OCs 6 weeks before elective surgery; it is less clear when to restart them. Women on OCs are generally at low risk for VTE and there is no evidence of any risk reduction by stopping treatment before elective surgery. When a patient is on OC LMH (s.c.) may be added as routine prophylaxis after surgery.

If it is possible, and there is enough time, it is important to inform the patient about advantages and disadvantages and also about alternative contraceptive methods.

For acute surgery or elective surgery while contraceptives are still in use, for plastering of lower leg fractures and for long-term immobilization, thrombosis prophylaxis with LMH should be given. Women with hormone substitution (HRT) already have additional risk factors indicating thrombosis prophylaxis.

Investigation before oral contraceptives, advice concerning oral contraceptives

For women 15–44 years old who are not on OCs, the risk for venous thrombosis is one per 10 000 per year. Observational studies showed a two- to sixfold increased risk of venous thrombosis, a two- to fivefold increased risk of myocardial infarction, a two- to fivefold risk of stroke, and a fourfold increased risk of peripheral artery disease in users of OCs compared to women not using OCs. Newer studies have demonstrated a threefold increased risk of VTE in users of medium- and low dose combined OCs with norethisterone, levonorgestrel, or noregistimate compared with non-users. In users of combined contraceptives with desogestrel, gestodone, drospirenone, or cyproteronacetat and

in users of vaginal rings a sixfold increased risk is demonstrated. The most serious complication is PE, present in 10% of these cases and fatal in 1–2%. This should be taken into consideration when OCs containing estrogen are prescribed for the first time, because for all combined OCs, the risk of thrombosis is greatest during the first year.

No screening method is yet available for adequate identification of women at risk prior to or during the use of OCs even though 25–40% of the women who develop thrombosis are APC-resistant (most of them have the FV Leiden mutation). Combined OCs are associated with a decreased sensitivity to APC, in certain cases to such an extent that the woman develops so-called acquired APC resistance. This type of APC resistance also carries an increased risk of venous thrombosis.

For women with earlier thrombosis, combined OCs are contraindicated. Nowadays, many of these women have undergone coagulation investigation.

Family history of VTE is important. Women who have a first-degree relative with thrombosis are advised to avoid OCs containing estrogen regardless of what coagulation investigation shows. Even women with several second-degree relatives should be advised to avoid OCs.

Screening women of a fertile age for thrombophilia is, however, not warranted without a clear family disposition.

Women with a known heterozygous form of APC resistance should avoid OCs containing estrogen, and for those with a homozygous form they should not be used. In hereditary thrombophilia, such as in antithrombin deficiency, OCs should not be given, neither should they be given to women with acquired thrombophilia, such as with lupus anticoagulant or significantly increased levels of cardiolipin antibodies.

Women with a strong fear of thrombosis should choose a contraceptive that does not contain estrogen. These women can of course undergo coagulation investigations, but what matters most is a thorough anamnesis and good information.

For most women with medical disorders, pregnancy is associated with risks other than the use of OCs. In addition, risks are related to age and body mass.

Methods other than combined (estrogen–progesterone) contraceptives (p-pills) should be considered in women as regards the following:

- age over 35 years and a smoker
- migraine headache and co-existing vascular risk factors, vascular disease or age over 35 years
- earlier thromboembolic disease
- coronary disease
- cerebrovascular disease

- chronic liver disease
- less than 3 weeks after delivery in a nonbreastfeeding woman (an intrauterine device is not suitable up to 6 weeks after delivery)
- diabetes mellitus with vascular disease or age over 35 years
- SLE and vascular disease, nephritis or phospholipid antibodies
- hypertriglyceridemia.

In the above-mentioned women, a contraceptive containing progesterone or a copper/hormone intrauterine device is safer than combined contraceptives. At present there are no scientific indications that contraceptives containing gestagens only increase the risk of venous or arterial thrombosis.

Finally, a low-dose pill with norethisterone, levonorgestrel, or norgestimate is recommended as first choice. In women predisposed to VTE progestogen-only contraception such as levonorgestrel-releasing intrauterine system (IUD) In women who are >35 years of age without cardiovascular risk (CVR) second-generation pills should be used and most importantly in women who are >35 years with CVR factors such as smoking, diabetes, hypertension, migraine with aura or hyperlipidemia, levonorgestrel-releasing intrauterine system should be considered.

Acute oral contraceptives (p-pills)

When acute p-pills (day-after pills) are administered, a high dose of steroid hormones (gestagen or a combination with estrogen) is given during a very short time. The risk of thrombosis has been investigated in just a few studies, none of which shows any risk of DVT/PE. There are no contraindications for acute p-pills that contain only gestagen, so these drugs can be chosen for women with an increased risk of thrombosis.

Investigation prior to postclimacteric substitution treatment

The risk of DVT/PE increases with age and for postmenopausal women it is approximately twice as high as for premenopausal women. Investigate anamnesis in the event of thromboembolic disease in first- or second-degree relatives. Hormone replacement therapy (HRT) increases the risk during the first year. This information should be given when prescribing HRT. Routine screening for thrombophilia is not indicated. HRT should be avoided in women with multiple DVT/LE risk factors in anamnesis.

There is no epidemiologic evidence that parenteral HRT is more advantageous than oral HRT, though comparative studies have shown that parenteral HRT leads to fewer effects on coagulation. Oral HRT should not be given to patients with earlier thrombosis with or without hereditary thrombophilia.

In women who have had DVT/PE, stroke/TIA or with a close family history of such conditions, an investigation of thrombophilia might

improve the assessment of risk. In those with no thrombosis but with known thrombophilia, HRT should be avoided in cases of antithrombin deficiency or a finding of several combined thrombophilias.

There are no epidemiologic studies, but published data indicate that regarding the risk of thrombosis, parenteral (transdermal or vaginal) hormone is safer than oral. Separate studies have shown that parenteral administration has less effect on coagulation inhibitors and it entails a loss of coagulation activation.

Selective estrogen receptor modulators (SERM), such as raloxifen and tamoxifen, have antiestrogenic effects on breast tissue and uterine mucous membranes, but they affect hemostasis in the same way as estrogens.

If DVT/PE develops during HRT, the HRT must be withdrawn. If the woman wishes to remain on HRT, prolonged anticoagulation therapy should be considered.

Investigation prior to artificial insemination (IVF)

The brief hormonal stimulation probably adds very little to the risk of thrombosis. Routine screening for thrombophilia in women undergoing assisted conception is not warranted, although testing may be helpful for those with a personal or family history of thrombosis. If the patient has had earlier thrombosis or high risk for VTE data are lacking regarding increased risk. Pre-conceptional counseling is important in this group before starting IVF. Anyway, women with low-risk "thrombophilias" or prior VTE associated with transient risk factors will have small benefit from prophylaxis. The risk may be higher in women with ovarian hyperstimulation syndrome (OHSS) with a reported incidence of thrombosis of up to 4.2%. Units carrying out IVF treatment should develop protocols for OHSS management available for patient and neighboring gynecology departments. At signs of overstimulation it is reasonable to start prophylaxis with LMH (dalteparin 5000 IU s.c. × 1) and continue for 12 weeks or more.

It is important to use methods with low risk for overstimulation especially in women with polycystic ovaries, in those developing multiple follicles, or in those with previous episodes of OHSS; furthermore, methods without hormone stimulation for groups with very high risk are needed.

Investigation in repeated miscarriages

Repeated miscarriages occur in 1% of all women. Thrombophilia is widespread in women who have had repeated miscarriages, above all in those who have never given birth (primary miscarriers). About 15%

of women with three or more miscarriages are found to have phospholipid antibody syndrome. By comparison, the prevalence of antiphospholipid antibodies in women with a low-risk obstetric history is less than 2%. The most common hereditary thrombophilia is caused by the FV Leiden mutation, which is present in about 28% of women with primary miscarriage. Women with repeated miscarriages may be assessed with regard to cardiolipin antibodies, β2-glycoprotein 1, lupus anticoagulant, FV Leiden mutation, prothrombin mutation, and levels of protein S, protein C, antithrombin and homocysteine even if treatment due to the investigation results is not obvious.

There is insufficient evidence to evaluate the effect of LMH to prevent a miscarriage in women with recurrent first-trimester miscarriage associated with inherited thrombophilia. But LMH during pregnancy in women with second-trimester miscarriage and inherited thrombophilias may improve outcome.

In patients with repeated miscarriages and phospholipid antibodies, treatment with low-dose ASA increases the probability of having a live-born child from 10 to 40%. Combined treatment with ASA and low-dose LMH increases this probability to 70%. Especially in the group with one or more cases of unexplained death of a normal fetus at or beyond the 10th week of gestation (late miscarriage), treatment with LMH should be considered. The pregnancies are still high risk, with complications during all trimesters, miscarriages, pre-eclampsia and inhibited growth, despite treatment and close supervision. Ongoing studies are aimed at clarifying treatment of miscarriage propensity in other thrombophilias.

Today women with Leiden mutations and earlier placental thrombosis ought to have thrombosis prophylaxis but women with an inexplicable propensity for miscarriage have a good prognosis in future pregnancies without pharmacologic intervention if TLC (tender loving care) is provided!

Investigation in menorrhagia (for treatment see Chapter 4)

Menorrhagia is experienced by 10–20% of women of fertile age. A number of studies indicate that this group has an increased frequency of a mild hemostatic defect, above all VWD type 1, and platelet function disorders.

Investigation of suspected coagulation disturbances include, in the first place, blood status, APT time, PT(INR), CRP, bleeding time, platelet count, FVIII, and VWF analyses (state blood group). Sampling should be carried out during cycle days 1–4, if possible.

Note that a levonorgestrel-releasing intrauterine system decreases menstrual bleeding by up to 97%.

Hemostasis in children

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CHAPTER 15

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Introduction

The hemostatic system, that is, endothelial function, coagulation, and fibrinolysis, is influenced by age. Though the hemostatic system is considered "immature" in young children, it is functionally adequate; bleeding or thromboses are rare in healthy full-term newborns. However, the neonatal hemostatic system lacks reserve capacity and can be affected in prematurely born or severely ill newborns.

The synthesis of coagulation factors starts during the first trimester of pregnancy and increases successively with the gestational age. Consequently, the measured plasma levels of these proteins should be related to prenatal as well as postnatal age. Coagulation factors do not pass through the placenta. At birth, concentrations of the vitamin K-dependent coagulation factors (FII, FVII, FIX, FX), FXI and FXII are about 50% of adult values (Table 15.1). Also, levels of the coagulation inhibitors antithrombin, protein C, and protein S are reduced. Consequently both formation and inhibition of thrombin are reduced in newborns. This is considered to be one of the factors contributing to the reduced thrombosis risk in children. The levels of FV, FVIII, FXIII, and VWF are the same at birth as in adults, or higher. Also, the fibrinolytic system differs in newborns with low plasminogen levels but increased levels of tissue plasminogen activator (t-PA) and plasminogen activator inhibitor (PAI-1). The hemostatic system matures during the first months of life. The concentrations of most of the components reach adult values by the age of 6 months in both premature and full-term children (Tables 15.1 and 15.2).

Essential Guide to Blood Coagulation, Second Edition. Edited by Jovan P. Antovic, Margareta Blombäck. © 2013 John Wiley & Sons, Ltd. Published 2013 by John Wiley & Sons, Ltd.

Table 15.1 Hemostasis variables in full-term children during the first 6 months compared with adults.

Variable	Day 1	Day 5	Day 30	Day 90	Day 180	Adults
Fibrinogen g/L	2.83 (1.67–3.99)*	3.12 (1.62–4.62)*	2.70 (1.62–3.78)*	2.43 (1.50–3.79)*	2.51 (1.50–3.87)*	2.78 (1.56–4.00)
Prothrombin (U/mL)	0.48 (0.26–0.70)	0.63 (0.33–0.93)	0.68 (0.34–1.02)	0.75 (0.45–1.05)	0.88 (0.60–1.16)	1.08 (0.70–1.46)
FV (U/mL)	0.72 (0.34–1.08)	0.95 (0.45–1.45)	0.98 (0.62–1.34)	0.90 (0.48–1.32)	0.91 (0.55–1.27)	1.06 (0.62–1.50)
FVII (U/mL)	0.66 (0.28–1.04)	0.89 (0.35–1.43)	0.90 (0.42–1.38)	0.91 (0.39–1.43)	0.87 (0.47–1.27)	1.05 (0.67–1.43)
FVIII (U/mL)	1.00 (0.50–1.78)*	0.88 (0.50–1.50)*	0.91 (0.50–1.57)*	0.79 (0.50–1.25)*	0.73 (0.50–1.09)	0.99 (0.50–1.49)
VWF (U/mL)	1.53 (0.50–2.87)	1.40 (0.50–2.54)	1.28 (0.50–2.46)	1.18 (0.50–2.06)	1.07 (0.50–1.97)	0.92 (0.50–1.58)
FIX (U/mL)	0.53 (0.15–0.91)	0.53 (0.15–0.91)	0.51 (0.21–0.81)	0.67 (0.21–1.13)	0.86 (0.36–1.36)	1.09 (0.55–1.63)
FX (U/mL)	0.40 (0.12–0.68)	0.49 (0.19–0.79)	0.59 (0.31–0.87)	0.71 (0.35–1.07)	0.78 (0.38–1.18)	1.06 (0.70–1.52)
FXI (U/mL)	0.38 (0.10–0.66)	0.55 (0.23–0.87)	0.53 (0.27–0.79)	0.69 (0.41–0.97)	0.86 (0.49–1.34)	0.97 (0.67–1.27)
FXII (U/mL)	0.53 (0.13–0.93)	0.47 (0.11–0.83)	0.49 (0.17–0.81)	0.67 (0.25–1.09)	0.77 (0.39–1.15)	1.08 (0.52–1.64)
Antithrombin (U/mL)	0.63 (0.39–0.87)	0.67 (0.41–0.93)	0.78 (0.48–1.08)	0.97 (0.73–1.21)*	1.04 (0.84–1.24)*	1.05 (0.79–1.31)
Protein C (U/mL)	0.35 (0.17–0.53)	0.42 (0.20–0.64)	0.43 (0.21–0.65)	0.54 (0.28–0.80)	0.59 (0.37–0.81)	0.96 (0.64–1.28)

*Values are indistinguishable from those of adults.

Source: Reproduced from Andrew *et al., Am J Pediatr Hematol Oncol* 1990; **12**:95, and Andrew *et al., Blood* 1987; **70**:165, with permission from the American Society of Hematology.

Table 15.2 Hemostasis variables in healthy pre-term children (30–36 weeks gestation) during the first 6 months of life compared with adults.

Variable	Day 1	Day 5	Day 30	Day 90	Day 180	Adult
Fibrinogen g/L	2.43 (1.50–3.73)	2.80 (1.60–4.18)	2.54 (1.50–4.14)	2.46 (1.50–3.52)	2.28 (1.50–3.60)	2.78 (1.56–4.00)
Prothrombin (U/mL)	0.45 (0.20–0.77)	0.57 (0.29–0.85)	0.57 (0.36–0.95)	0.68 (0.30–1.06)	0.87 (0.51–1.23)	1.08 (0.70–1.46)
FV (U/mL)	0.88 (0.41–1.44)	1.00 (0.46–1.54)	1.02 (0.48–1.56)	0.99 (0.59–1.39)	1.02 (0.58–1.46)	1.06 (0.62–1.50)
FVII (U/mL)	0.67 (0.21–1.13)	0.84 (0.30–1.38)	0.83 (0.21–1.45)	0.87 (0.31–1.43)	0.99 (0.47–1.51)	1.05 (0.67–1.43)
FVIII (U/mL)	1.11 (0.50–2.13)	1.15 (0.53–2.05)	1.11 (0.50–1.99)	1.06 (0.58–1.88)	0.99 (0.50–1.87)	0.99 (0.50–1.49)
VWFag (U/mL)	1.36 (0.78–2.10)	1.33 (0.72–2.19)	1.36 (0.66–2.16)	1.12 (0.75–1.84)	0.98 (0.54–1.58)	0.92 (0.50–1.58)
FIX (U/mL)	0.35 (0.19–0.65)	0.42 (0.14–0.74)	0.44 (0.13–0.80)	0.59 (0.25–0.93)	0.81 (0.50–1.20)	1.09 (0.55–1.63)
FX (U/mL)	0.41 (0.11–0.71)	0.51 (0.19–0.83)	0.56 (0.20–0.92)	0.67 (0.35–0.99)	0.77 (0.35–1.19)	1.06 (0.70–1.52)
FXI (U/mL)	0.30 (0.08–0.52)	0.41 (0.13–0.69)	0.43 (0.15–0.71)	0.59 (0.25–0.93)	0.78 (0.46–1.10)	0.97 (0.67–1.27)
FXII (U/mL)	0.38 (0.10–0.66)	0.39 (0.09–0.69)	0.43 (0.11–0.75)	0.61 (0.15–1.07)	0.82 (0.22–1.42)	1.08 (0.52–1.64)
Antithrombin, ag (U/mL)	0.38 (0.14–0.62)	0.56 (0.30–0.82)	0.59 (0.37–0.81)	0.83 (0.45–1.21)	0.90 (0.52–1.28)	1.05 (0.79–1.31)
Protein C, ag (U/mL)	0.28 (0.12–0.44)	0.31 (0.11–0.51)	0.37 (0.15–0.59)	0.45 (0.23–0.67)	0.57 (0.31–0.83)	0.96 (0.64–1.28)

The values, except for fibrinogen, are compared with a pooled normal plasma containing 1.0 U/ml.

Source: Reproduced from Andrew *et al.*, *Blood* 1988; **72**:1651, with permission from the American Society of Hematology.

From the eighteenth gestational week the number of platelets in fetuses is at the same level as in adults. The platelet function in newborns evaluated by aggregability to collagen and epinephrine is reduced. Nevertheless, newborns have a shorter bleeding time and a shorter "*in vitro* bleeding time" (closure time in platelet function analyzer PFA-100) than adults, which can be explained by high levels of VWF (especially the high molecular forms) and high hematocrit. Knowledge of the evolution of the hemostatic system is important for diagnosis and treatment of children with bleeding or thromboses.

In addition to medical and bleeding history accounting for age and sex, initial screening of children with bleeding symptoms includes complete blood count, APT time, and PT(INR) (Figure 15.1). Bleeding time which measures primary hemostasis is difficult to standardize and can only be performed if the child cooperates. For information on laboratory investigations, see Chapter 3.

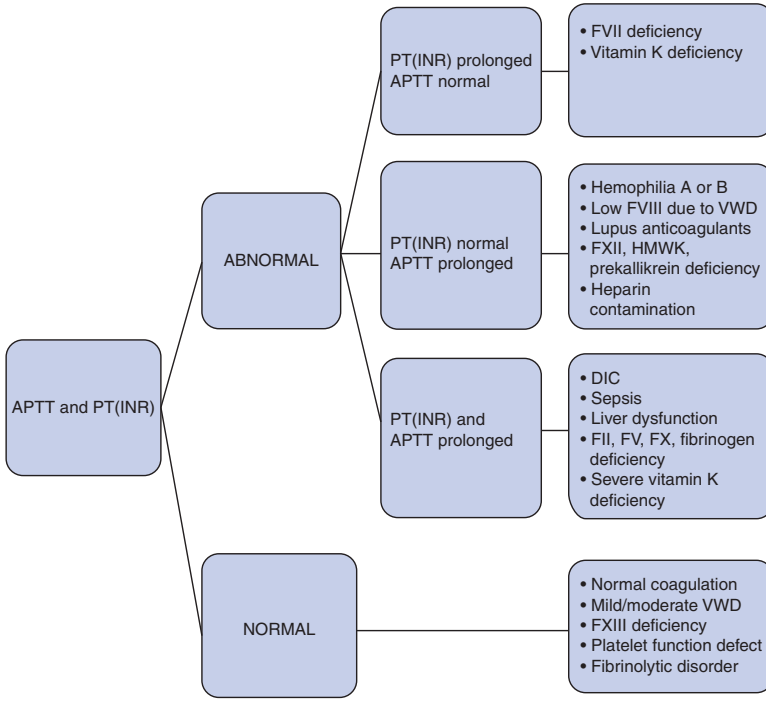

Figure 15.1 Initial coagulation screening analysis in children with bleeding tendency. PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; VWD, von Willebrand disease; HMWK, high molecular weight kininogen; DIC, disseminated intravascular coagulation

Bleeding disorders in children

Bleeding in newborns

The most common factors behind bleeding in newborns are acquired coagulation disturbances caused by asphyxia, infections, liver disease, or vitamin K deficiency. For information on disseminated intravascular coagulation (DIC), please see Chapter 16.

Vitamin K deficiency bleeding

Vitamin K is necessary for the post-translational modification of coagulation factors II, VII, IX and X, as well proteins S and C. The concentration of the vitamin K-dependent proteins in plasma is physiologically low at birth and these coagulation factors are inactive without vitamin K. Hemorrhagic disease of the newborn is caused by poor placental transfer of vitamin K, low vitamin K concentrations in breast milk, and scarce intestinal colonization by bacteria in newborns. Vitamin K deficiency is rarely seen in children fed with vitamin K supplemented formula. The bleeding symptoms vary but can be serious, for example intracranial or intestinal. Early forms beginning during the first 24 h are rare but frequently life threatening. They are typically seen in infants born to mothers on drugs that interfere with vitamin K metabolism, for instance phenytoin. The most common, "classic" form often presents during the second to third days of life in otherwise healthy, full-term breast-fed children. Bleeding commonly occurs in the umbilicus, gastrointestinal tract, skin, nose, after circumcision, and occasionally in the brain. Late forms starting after the first week, most often during weeks 2–8, are caused by dietary factors in combination with malabsorption or liver disease. The presenting bleeding symptom is often acute intracranial hemorrhage.

Intramuscular or subcutaneous injection of 1 mg vitamin K prevents the "classic" and late forms of this bleeding tendency and is administered routinely to newborns in most Western countries. With three oral doses of vitamin K the incidence of vitamin K deficiency bleeding fell to 2.8/100 000 and a weekly oral prophylaxis for three months prevents the "classic" and late forms as effectively as the injection. Oral prophylaxis is therefore effective in cases where injections are not desirable.

Laboratory diagnosis

Elevated PT(INR). More severe forms have a prolonged APT time (Figure 15.1).

Treatment

Vitamin K (Konakion®); 1 mg i.v. usually normalizes PT(INR) within a few hours.

In addition, plasma, or prothrombin complex concentrates providing a rapid reversal of vitamin K-dependent coagulopathy can be necessary for treatment of serious bleeding symptoms. Consult coagulation experts for dosage.

Hereditary bleeding tendency

In otherwise healthy children with bleeding symptoms, a hereditary bleeding disorder should be suspected bearing in mind that a negative family history does not exclude a hereditary bleeding disorder.

Coagulation factor deficiencies

Hemophilia A and B

The most common hereditary coagulation factor deficiencies are hemophilia A (FVIII deficiency) and hemophilia B (FIX deficiency). Both diseases are inherited sex-bound recessively. Today, fetal diagnosis can be offered to almost all possible or known carriers of hemophilia. Prevalence of hemophilia A is about 1/10 000 men and of hemophilia B about 1/30 000 men. Spontaneous mutations are common and seen in 50–60% of newly diagnosed boys with hemophilia A.

Diagnosis

Only 15–30% of newborns with hemophilia show bleeding symptoms during the neonatal period. Most bleedings are iatrogenic, caused by intramuscular injections (vitamin K), venous sampling (PKU test), or vacuum extraction at birth. Vacuum extraction increases the risk of intracranial bleeding in children with a bleeding disorder and should be avoided at the delivery of children with known heredity to hemophilia.

The most common presenting symptom is tendency to hematomas, observed when the child becomes more active. The hematomas are larger, darker and with a "bumpy" look compared with those in healthy children. In Sweden the mean age of diagnosis of severe hemophilia without family history is 9 months. The main symptoms of severe hemophilia are joint and muscle bleeds usually presenting at the age of 1–3 years.

Laboratory diagnosis

Activated partial thromboplastin (APT) time is prolonged. Note that mild forms of hemophilia can have a normal APT time for age. Decreased value of FVIII or FIX verifies the diagnosis. Mild hemophilia B can be difficult to diagnose at birth as newborns generally have low levels of FIX. Sampling should be repeated after 6 months of age.

Treatment

In severe hemophilia, preventive treatment with factor concentrates (prophylaxis) should start at the age of 1 year before the child has

experienced joint bleeds (primary prophylaxis). Primary prophylaxis is more effective in preventing arthropathy than secondary prophylaxis or on-demand treatment. Children are preferably treated with recombinant factor concentrates to minimize the risk of viral transmission. Prophylaxis is usually initiated with one injection (250–500 IU) per week. As soon as possible, from a technical and psychological point of view, the treatment intensity is increased to 3–4 times per week in hemophilia A and twice per week in hemophilia B. Local pain-relief with EMLA® (Lidocain-Prilocain) ointment has made it easier to perform intravenous injections and blood sampling by a peripheral vein in children.

Home treatment, that is, treatment performed by the parents, is established as soon as possible, usually after 9–12 months of treatment and training in the pediatric outpatient clinic. Children with recurring bleeding symptoms and those in whom peripheral vein injections have not been successful receive an implantable venous access system (Port-A-Cath®). Early onset of prophylaxis has enabled most children to grow up without permanent joint damage. Quality of life has improved with less (or no) absence from school and the possibility of joining in physical activities with children of the same age.

Tranexamic acid (Cyklokapron®) is used for minor bleeding symptoms, especially in mucous membranes. Recommended oral dose is 20 mg/kg three times daily. For intravenous treatment the recommended dose is 10 mg/kg three times a day.

Operations in children with hemophilia can today be performed for the same indications as in healthy children. However, they should be performed in hospitals with coagulation expertise.

The most serious complication of treatment with factor concentrates is the development of antibodies against the deficient coagulation factor. Most hemophilia centers screen routinely children with prophylaxis for such inhibitors. Antibodies against FVIII occur in 20–30% of children with severe hemophilia A. They often appear early (after less than 50 injections). Antibodies against FIX are rare (3%) but in contrast to the FVIII inhibitors, administration of FIX concentrate to these patients can result in serious allergic reactions, even anaphylaxis. Risk factors associated with the development of inhibitors include type and severity of hemophilia, severe gene defects such as large deletions and family history of inhibitors. Development of inhibitors should be suspected in any patient with no or a poor response to FVIII or FIX concentrate.

High levels of antibodies against FVIII or FIX prevent treatment of bleeds and effective prophylaxis. Treatment of bleeding symptoms is possible with by-passing agents, recombinant FVII (NovoSeven®) and plasma-derived activated prothrombin complex concentrate (FEIBA®). The management of bleeds with bypassing agents is extremely expensive

and inhibitor patients have an increased risk of disability and life-threatening bleeds. Therefore the aim of treatment is to eliminate the inhibitors. This can be achieved by desensitization or immune tolerance. Doctor Brackman in Bonn was the first to demonstrate the elimination of inhibitors in hemophilia A patients by daily administration of high doses of FVIII. Different treatment regimes have been used thereafter with varying results (40–80% success rate in hemophilia A and 13–31% in hemophilia B).

Von Willebrand disease

Severe forms of VWD can cause bleeding problems during the neonatal period. The most common (i.e. mild) forms are difficult to diagnose at this age, as high levels of FVIII and VWF are physiologic during the neonatal period. These patients are usually diagnosed later in life due to epistaxis, hematomas, or menorrhagia.

Blood sampling is appropriate after 6 months of age in children with known heredity to VWD.

Laboratory diagnosis and treatment

See Chapters 3 and 4.

Rare hereditary coagulation factor deficiencies

The mode of inheritance for rare hereditary coagulation factor deficiencies is usually autosomal recessive. In severe deficiency of fibrinogen, FVII, FX and FXIII, bleeding symptoms are frequent in the neonatal stage. Bleeding from the umbilical cord is seen in >80% of children with severe FXIII deficiency and is also common in severe FX deficiency. Both deficiencies are associated with a significant risk of intracranial bleedings during childhood. FXIII deficiency also leads to muscle bleeds, impaired wound-healing, and increased frequency of repeated spontaneous abortions.

Laboratory diagnosis

For evaluation of APT time and PT(INR) see Chapter 3 and Figure 15.1. Please note that FXIII deficiency does not affect APT time or PT(INR). The diagnoses are established by analyses of the respective factors.

Treatment

Substitution with plasma (10–15 mL/kg) or, if available, replacement therapy with the deficient factor concentrate (e.g. fibrinogen, FXIII, FVII, prothrombin-complex concentrate). Treatment is given at bleeding or as prophylaxis, depending on the frequency and characteristics of the bleeding.

Platelet function defect

Symptoms are similar to those in VWD and should be suspected in children with epistaxis or with a tendency to hematomas and mucous membrane bleeding. Such defects are often hereditary. More severe forms are rare (e.g. Glanzmann thrombasthenia and Bernard–Soulier syndrome) and often present during the first year of life.

Diagnosis

APT time and PT(INR) are normal (Figure 15.1). Platelet count can be normal (Glanzmann thrombasthenia) or decreased (Bernard–Soulier syndrome). Please note that platelet count can also be low in VWD type 2B.

In vivo bleeding time, which can be used as a screening test for platelet function defects by experienced personnel, is prolonged. Alternatively, *in vitro* bleeding time such as PFA-100 can be used as a screening test provided that platelet count and hematocrit are sufficient. However, normal bleeding time does not completely exclude platelet function defect.

Light microscopy of May-Grünwald-Giemsa stained blood smear can reveal presence of large/giant platelets in, for example, Bernard–Soulier syndrome. Specific tests including flow cytometry analysis of platelet surface protein and aggregation responses can be performed at specialized coagulation laboratories.

Treatment

Treatment of platelet function defects resembles treatment of VWD. Tranexamic acid usually has a good effect either alone or used in conjunction with other therapy. Many patients with mild platelet function defect respond to desmopressin. Response is variable in Bernard–Soulier and poor in Glanzmann thrombasthenia. Desmopressin can be administered in small children intravenously, subcutaneously or in older children also by nasal spray. However, younger children are especially sensitive to fluid retention and hyponatremia and therefore desmopressin should be avoided in children under 2 years of age. Platelet transfusion is effective but should be reserved to more serious bleedings or surgical procedures as development of alloantibodies to missing glycoproteins in Bernard–Soulier and Glanzmann thrombasthenia can lead to poor responses to subsequent platelet transfusions. Recombinant FVIIa (NovoSeven) can be used in severe platelet function defects where desmopressin and/or platelet transfusions alone are not effective.

Acquired bleeding tendency

Thrombocytopenia

Although the number of platelets in healthy newborns is comparable with adults thrombocytopenia is common in severely ill newborns. Most

frequent symptoms are bleedings in mucous membranes and hematomas. Tranexamic acid (Cyklokapron) usually has a good effect on these symptoms. Platelet infusion is needed at low platelet levels (below 20×10^9/L) and serious bleedings or in combination with other factors predisposing to bleeding.

Idiopathic thrombocytopenic purpura

Idiopathic thrombocytopenic purpura (ITP) is caused by autoimmune antibodies against glycoproteins of the platelet membranes. Incidence in the Nordic countries is 4–5/100 000 children. The median age at diagnosis is 4 years. The disease often starts after a viral infection. Mild bleeding symptoms, such as mucosal bleeding and hematomas, are common. Intracranial bleedings rarely occur. In children, ITP is usually self-limiting; three out of four children have normal platelet counts after 6 months of diagnosis.

Patients with ITP are usually investigated by hematologists. Most patients with acute ITP have an uneventful course and do not need intervention. Mild symptoms can be treated with tranexamic acid (see Chapter 4). When necessary, treatment of acute ITP with steroids, intravenous γ-globulin or anti-RhD can raise the platelet counts. Platelet transfusions should only be given in cases with severe bleeding symptoms in combination with other treatments. Splenectomy or rituximab can be considered in chronic ITP with recurrent or serious bleeds. Experiences of oral thrombopoietin receptor agonists in children are limited.

Purpura fulminans

Purpura fulminans is a rare disorder characterized by dermal microvascular thrombosis. Neonatal purpura fulminans can be congenital or acquired. Congenital purpura fulminans is due to homozygous protein C or S deficiency whereas the acquired forms are mainly due to severe infections and associated consumptive coagulopathy leading to relative deficiency of protein C and/or S. The clinical picture of rare autoimmune mediated acquired protein S deficiency after varicella infection in children can also mimic congenital protein S deficiency.

Neonatal purpura fulminans is a life-threatening condition which can progress rapidly to multiorgan failure caused by thrombotic occlusion of small and medium-sized blood vessels. Diagnosis of congenital purpura fulminans is based on clinical picture, undetectable levels of protein C or S (below 0.05 U/mL), and heterozygous deficiency in parents. Treatment of congenital purpura fulminans is replacement therapy with fresh-frozen plasma (10–20 ml/kg twice daily) or protein C concentrate. Treatment of the underlying cause is crucial in severe acquired deficiencies of protein C and S, although replacement therapy has also been used.

Hemolytic uremic syndrome and thrombotic thrombocytopenic purpura
See Chapter 16.

Bleeding tendency secondary to liver or kidney disease
See Chapter 5.

Thromboembolic disorders in children

Thrombotic diseases in children are different from those of adults in many ways. The incidence is significantly lower. Therefore thromboprophylaxis is seldom considered necessary for children before puberty in connection with, for example, orthopedic surgery. Children with hereditary prothrombotic risk factors do not usually develop thrombosis until adolescence or adulthood.

Recommendations concerning diagnosis and treatment have to a great extent been based on experience in adults. Acquired risk factors, such as malignancy, infection, heart disease, or indwelling catheters, are common in children with thrombosis. Newborns have about 50% of adult levels of the three natural anticoagulants, antithrombin, protein C, and protein S, which makes it difficult to diagnose hereditary deficiencies in children before 6 months of age (Table 15.1). Also the presence of FV Leiden or prothrombin mutation may increase the thrombosis risk.

The treatment of thrombosis is also affected by lower thrombin generation in children and by low levels of plasminogen in newborns. Transient antiphospholipid antibodies, especially lupus anticoagulant and anticardiolipin, are commonly observed in children after infections. However, several studies have shown an increased presence of antiphospholipid antibodies in children with a thrombotic disease and idiopathic cerebral ischemia. There is an ongoing discussion on whether or not this is a risk factor for thrombosis in children or an epiphenomenon.

Venous thrombosis

An underlying disease is usually present in children who develop venous thrombosis and it is increasingly recognized in the pediatric population as a complication of improved treatment strategies for previously lethal childhood diseases. The incidence of symptomatic venous thrombosis was first reported to be 0.07/10 000 children and 5.3/10 000 hospitalized children aged 1 month to 18 years in Canada, with a peak incidence in infants younger than 1 year of age. The majority of the children have several risk factors. The most important risk factor is an indwelling catheter observed in up to 90% of patients with venous thrombosis during

the neonatal period and in 30–60 % of patients with venous thrombosis during childhood. Central venous catheters (CVCs) inserted in jugular or subclavian veins explain why thrombosis in the upper venous system is so common in children (60%) compared with adults (2%). There are no differences in incidence between the sexes before puberty. In adolescence the thrombosis rate is higher in girls due to pregnancy and oral contraceptives of combination types.

The impact of inherited hypercoagulable states in venous thrombosis in children is poorly defined, and the prevalence ranges from 10 to 60% in different studies, being significantly higher in older children with spontaneous episodes of thrombosis. Inherited risk factors including FV Leiden, prothrombin gene mutation, deficiencies of antithrombin (AT), protein S and protein C, as well as increased level of plasma lipoprotein (a) have been associated with increased risk of thrombosis in children. A positive family history of thrombosis has been shown to predict congenital thrombotic disorder. Prophylaxis against venous thrombosis is rarely given to children with a known hereditary risk factor but no previous thrombosis before puberty. The current knowledge is not sufficient to give recommendations, but prophylaxis can be beneficial for children with the highest risks such as AT deficiency or combined inherited risk factors.

The risk of recurrence in children is reported to be about 8% after a follow-up of one year and 13% after 3 years. Accurate information is not available on the incidence and risk factors for post-thrombotic symptoms, estimated risk ranges from 10 to 70%. The mortality directly related to thrombosis or pulmonary embolism is suggested to be 2.2–4.2%.

Thrombotic complications related CVCs can be asymptomatic or manifest as loss of CVC patency, sepsis, acute swelling, superior vena cava syndrome, and prominent collateral circulation. Venous thromboses without relation to CVC are most commonly seen in the femoral, iliac, or popliteal veins. Presenting symptoms are the same as in adults.

Renal vein thrombosis is the most common type of non-catheter-related VTE during the neonatal period and accounts for 20% of all thromboembolic events in newborns. Symptoms in newborns include palpable resistance in the flank, hematuria, proteinuria, and thrombocytopenia. Renal vein thrombosis in children is often secondary to nephritic syndrome, systemic lupus erythematosus, or renal transplantation. Children usually present with acute symptoms like diarrhea, vomiting and dehydration but renal vein thrombosis may also have an insidious onset with no symptoms from the kidneys.

Portal vein thrombosis (PVT) is the most common thrombosis in the hepatic venous system. Neonatal PVT is mostly related to intensive care

with umbilical catheterization and sepsis. Liver transplantation, splenectomy, chemotherapy, and infections are associated with PVT in older children.

The incidence of pulmonary embolism (PE) in children is not known but possibly underestimated. PE may be silent or present with similar symptoms as in adults. In younger children the symptoms may be unspecific. Children with PE most often have multiple risk factors for thrombosis such as CVC, immobility, cancer, heart disease, infection, and oral contraceptive use in females. The Wells' score and D-dimer measurement have not been proven useful in the diagnosis of PE in children.

Diagnosis

Imaging: Ultrasound Doppler is usually the first option but phlebography might be needed. Computed tomography (CT)/MRI are often helpful for diagnosis in larger central vessels. For physical and radiologic investigations, see Chapter 7.

Treatment

The choice of medication and length of treatment are based on studies in adults with a thrombotic disease. Both UFH and LMH are used but there has been a gradual increase in the use of LMH due to more predictable pharmacokinetics, reduced requirement for monitoring, and possibly fewer complications. In the case of invasive procedures, UFH is discontinued at least an hour and LMH 10–24 h earlier. For dosing of UFH and LMH, please see Table 15.3.

Unfractionated heparin

Evaluation of the effect of UFH in newborns is difficult because of their developing hemostatic system and low levels of antithrombin, possibly resulting in less effect. Half-life for UFH is 1–2 h in older children, but has been reported to be as low as 25 min in newborns. UFH may be used as initial therapy where a rapid reversal of anticoagulation is required.

Low molecular weight heparin

Pharmacokinetic studies on LMH in children have been performed primarily with enoxaparin (Clexane®) but dalteparin (Fragmin®) and tinzaparin (Innohep®) are also used in children. LMH is administered subcutaneously. It is excreted through the kidneys and can consequently accumulate in kidney failure (clearance below 30 mL/min). LMH does not affect the APT time to the same degree as UHF. The effect of anticoagulation is preferably monitored by determining anti-FXa about 3–4 h after the third-fourth injection with a target level is 0.5–1.0 anti-FXa. Half-life for subcutaneous LMH is 3–4 h.

Table 15.3 Antithrombotic therapy with UFH and LMH in children.

Medication	Dose	Monitoring frequency and parameters
UFH i.v.		**APTT**
>1 month of age	Loading dose 75 IU/kg, maintenance 20–30 IU/kg/h	4 h after loading dose or change of infusion rate, otherwise once daily: 60–85 sec or 1.5–2.5 × normal upper reference value
		Anti-FXa
		0.3–0.7
LMH s.c.		
Enoxaparin		
<2 months of age	1.5 mg/kg × 2 (prophylactic dose 0.75 mg × 2)	
>2 months of age	1.0 mg/kg × 2 (prophylactic dose 1.0 mg × 1 or 0.5 mg × 2)	**Anti-FXa** 3–4 h following dose: 0.5–1.0 (prophylaxis 0.2–0.4)
Dalteparin		
<2 months of age	150 U/kg × 2	10–12 h following dose: 0.3–0.5 (prophylaxis 0.1–0.3)
>2 months of age	Initially 100 U/kg × 2 thereafter 200 U/kg × 1 or 100 U/kg × 2 (prophylactic dose 70–100 U/kg × 1)	
Tinzaparin		
0–2 months of age	275 U/kg × 1	
2 months–10 years	200–250 U/kg × 1	
>10 years	175 U/kg × 1	

Vitamin-K antagonists (VKAs)

The effect of VKAs is mediated by competitive blocking of the vitamin K metabolism. This leads to decreasing plasma levels of FII, FVII, FIX and FX, and consequently an elevated PT (INR) within 1–3 days of beginning treatment. The treatment is usually given orally once a day, but can be given intravenously. The most commonly used VKA in children is warfarin.

Newborns have physiologically low levels of vitamin K-dependent coagulation factors and are seldom treated with VKA drugs with the exception of newborns with congenital heart disease and prophylactic VKA treatment.

Dosage: Day 1: 0.2 mg/kg (max 10 mg/dose), maintain this dose day 2–3 or until PT(INR) is >1.4. Thereafter 50% of the initial dose until PT(INR) is in the therapeutic interval. The dose is therefore usually reduced to 25% of the initial dose. If PT(INR) is over 3.5, the dose is reduced after 1–2 days' interruption of treatment with the drug. Older children and teenagers often need a lower dose (0.1 mg/kg). Therapeutic target level of PT(INR) is 2.0–3.0.

Thrombolytic treatment

Thrombolytic drugs act by transforming endogenous plasminogen to plasmin. Since newborns have a reduced level of plasminogen (about 50% that of adults) such drugs may be less effective. Currently tissue plasminogen activator (t-PA) alteplase (Actilyse®) is recommended for thrombolytic treatment in connection with recent (under 2 weeks) life- or limb-threatening thromboses such as a massive PE with hemodynamic compromise, or extended vena cava thrombosis in children who do not respond to treatment with UFH or LMH. In minor studies, Actilyse 0.1–0.5 mg/kg/h for 6 h has been used. Lower doses for a longer treatment period up to 3 days have also been effective. Usually the treatment is combined with UFH and plasma. Always consult coagulation experts. The thrombolytic effect can be followed by measuring fibrinogen and fibrin D-dimer. The same contraindications apply as in adults (see Chapter 12). Bleeding complications are common in children (68%); bleeding necessitating blood transfusion occurs in 39%. For treatment of bleeding in connection with thrombolysis, see Chapter 12.

Duration of anticoagulation treatment

The recommended treatment of newborns is usually UFH or LMH, the length of the treatment has traditionally been shorter compared to that for older children. Following the first thrombosis or PE in older children, treatment with LMH or VKAs for 3–6 months is recommended after initial treatment with UFH/LMH.

Long-term treatment, usually with a VKA drug and a yearly evaluation of continuing therapy, may be necessary for children with recurrence or serious thrombotic disease, including remaining risk factors. In children, monitoring of PT(INR) is recommended at least every fourth week.

Bleeding complications during treatment with UFH, LMH, and warfarin

Protamine neutralizes the anticoagulation effect of UFH and to some degree the effect of LMH. One mg protamine neutralizes 100–150 units

of UFH. The effect is temporary and can be monitored with APT time when using UFH. Protamine should only be used in patients with serious bleeding symptoms. See Chapter 7. To reverse a high PT(INR) see Chapter 7. Please note that PT(INR) reversal is faster in newborns. Prothrombin complex concentrates, recombinant FVII, and plasma can be used to reverse the effect of VKAs in case of severe bleeding symptoms or need of acute surgery.

Investigation of prothrombotic risk factors

An investigation can usually be performed 3–6 months after the thrombosis. A symptomatic venous thrombosis in children most often has a multifactorial genesis. Hereditary or acquired deficiencies of coagulation inhibitors antithrombin, protein C, protein S (free fraction), presence of FV mutation (1691G>A), prothrombin polymorphism (20210G>A), increased levels of homocysteine and lipoprotein (a), or acquired phospholipid antibodies have all been associated with increased risk of venous thrombosis.

Heparin-induced thrombocytopenia

The incidence of heparin-induced thrombocytopenia (HIT) in UFH-treated children is not known. In connection with cardiac surgery the incidence of clinical HIT in infants and children exposed to UFH is 1.3%. HIT in LMH-treated children is rare. HIT should be considered in any child who develops unexpected thrombocytopenia during heparin treatment. The clinical course appears to be similar in children and adults (see Chapter 16). Argatroban is recommended for adults with HIT and in need of anticoagulation and can be considered for children as well. The clearance of argatroban depends on liver function. Bivalirudin or danaparoid can be considered as alternatives for children with liver dysfunction. Always consult coagulation experts.

Sinus venous thrombosis

The etiology of cerebral venous sinus thrombosis in children is unclear, and the importance of prothrombotic risk factors generating the disease is not known. Half of children with a sinus thrombosis develop secondary cerebral infarction as a result of rapid thrombotic development and a total venous occlusion. Fifty percent of these cases are found in newborns and preschool children. The symptoms are often discrete and develop over several days (headache, nausea, apathy). Seizures are common in the youngest children. Newborns show a tense fontanelle and possibly enlarged scalp veins and swollen eyelids.

The majority of children (65%) have at least two risk factors, such as otitis media, sinusitis, trauma, dehydration, heart failure, or asparaginase

treatment. Rheumatoid arthritis, SLE, and chronic intestinal disease are more common in older children. Acquired and hereditary prothrombotic risk factors possibly contribute to the origin of sinus thrombosis. The most common of these risk factors is the presence of antiphospholipid antibodies. Mortality is still about 10%. Fifty to 75% of children recover. The remaining patients have neurologic sequelae.

Diagnosis
Best performed by MRI. See Chapter 7.

Treatment
Most of the children receive anticoagulation treatment with UFH/LMH followed by VKA for 3–6 months. The recommendations are based on studies in adult patients. Newborns without large cerebral bleeding symptoms can be treated with UFH or LMH for 6 weeks to 3 months. Newborns with significant secondary hemorrhage can be treated with supportive care only with careful radiologic monitoring of the thrombosis and anticoagulation in case of thrombus extension. Local thrombolytic treatment has been used in a few patients with progressive symptoms in spite of anticoagulation treatment.

Arterial thrombosis

Arterial thrombosis is rare in otherwise healthy children. An incidence as high as 8.5/10 000 hospitalizations has been reported in an Australian tertiary pediatric hospital. It usually occurs in connection with arterial catheterization in cardiac disorders and in newborns with an umbilical arterial catheter.

Recommendations concerning diagnosis and treatment of arterial thromboses are based on studies in adults. Preventive treatment with UFH is often administered in connection with heart catheterization. A bolus dose with 100–150 U/kg reduced thromboembolic complications from 40 to 8%. Long-term treatment with warfarin or ASA is usually recommended in children with complicated heart disease or after heart surgery.

The incidence of thromboembolism in connection with an umbilical arterial catheter varies between 10 and 60% depending on examination techniques. The symptoms depend on the extension of the thrombosis. Many newborns are asymptomatic, while others show a serious ischemia in lower limbs and other organs (1–5%). Prophylactic treatment with low doses of UFH (0.5 units/mL at 1 mL/h) is recommended for newborns with an arterial catheter. In case of symptomatic arterial catheter-related thrombosis, treatment with UFH is recommended in addition to removal of the catheter. In connection with aorta thrombosis, thrombolysis with t-PA (Actilyse®) may be required.

Children with Kawasaki disease are treated with high doses of ASA (80–100 mg/kg/day) during the first weeks, and thereafter with a lower dose (1–5 mg/kg/day) during the following 6–8 weeks or longer.

Stroke

Stroke in children is rare compared with adults. The incidence is stated to be about 2–8 per 100 000 children/year. The ratio of arterial ischemic stroke to sinus thrombosis is 3 : 1. A third of the children with stroke are affected during the neonatal period. The incidence of stroke during childhood seems to increase, probably due to improved imaging diagnosis and increased survival of children with severe heart diseases, malignancies, and pronounced prematurity.

Ischemic stroke

Pediatric ischemic stroke differs from adult stroke in several ways: etiologies are different, cerebral location is often different, and recovery is generally better. It can be divided into two categories: neonatal occurring within the first 28 days of life, and childhood strokes. In 25% of embolic strokes, the source of embolism is the heart, for example atrial septal defect or open foramen ovale with a right-to-left shunt or cardiac surgery. Most cases with ischemic stroke are found in newborns and small children. The incidence of perinatal arterial ischemic store is estimated to be 1 : 2300–5000 live births, 10 times higher compared to later in childhood. The most common presenting symptoms in perinatal stroke are seizures, apnoeic attacks, lethargy, and poor feeding. Small children suffer from headache, nausea, and fever. In older children, seizures and focal neurological defects such as hemiparesis are the most common symptoms.

Diagnosis

CT, MRI, and angiography.

Treatment

The risk/benefit ratio of antithrombotic treatment of stroke in children is not known. There are currently no controlled studies. About 35–65% of children with arterial ischemic stroke are treated with UFH, LMH, VKA (warfarin), or ASA. Thrombolytic treatment is rare. Children are rarely diagnosed within 4.5 h of the first symptom, which is recommended in adults for this type of treatment. The risk of bleeding complications in children receiving thrombolytic treatment has not been evaluated. In newborns, which have the highest incidence of stroke, less effect can be expected due to low levels of plasminogen.

Table 15.4 Risk factors for ischemic stroke in infants and older children.

Infants	Children and adolescents
Maternal- or pregnancy-related factors Maternal conditions (autoimmune disorders, prothrombotic disorders, anticardiolipin antibodies, pre-eclampsia, sickle cell disease, cocaine abuse) Growth restriction in the uterus and placental dysfunction such as chorioamnionitis and placental vasculopathy Twin-to-twin transfusion syndrome **Delivery related** Birth injury of head or neck with cervical arterial dissection **Perinatal and neonatal factors** Birth asphyxia, prothrombotic disorders, polycythemia, congenital heart disease and cardiac surgery, ECMO, catheterizations, meningitis, systemic infection	**Heart-related factors** Congenital heart disease, cardiac catheterization and surgery, angiography, ECMO, myocarditis, cardiomyopathy **Hematological disturbances and vascular abnormalities** Acquired and inherited prothrombotic disorders, cervicocephalic arterial dissection, sickle cell disease, hemoglobinopathies, systemic lupus erythematosus vasculitis, postvaricella angiopathy and idiopathic focal cerebral arteriopathy, hematologic malignancy, polycythemia **Infections** Meningitis, central nervous system infection Systemic infection with septic embolism **Medicines** Oral contraceptives, asparaginase, cocaine, steroids **Miscellaneous** Metabolic diseases and hyperlipidemia, trauma

Anticoagulation with UFH/LMH for 3 months is recommended for newborns with a cardioembolic source. Otherwise treatment of neonatal arterial ischemic stroke has traditionally been supportive. For older children UFH/LMH for 5–7 days or until the cause of the stroke has been established and thereafter ASA (2–5 mg/kg /day) is recommended, based on studies in adults. In children with cardiac embolic sources, warfarin is often the drug of choice for long-term prophylaxis.

Prognosis

Retrospective studies show neurologic sequelae in three-quarters of the children. In one study 37% of the children were shown to totally recover,

46% showed mild to moderate neurologic sequelae, and 16% had more severe sequelae. The risk of recurrence is related to underlying risk factors (Table 15.4). Recurrence in newborns is low, 1.2% within 5 years, mostly confined to patients with congenital heart disease or prothrombotic abnormalities. For older children the recurrence risk is considerably higher, 20–40% and is associated with, for example, vasculopathy or a combination of risk factors.

Emergency conditions associated with coagulation: DIC, HIT and TTP/HUS

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CHAPTER 16

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Disseminated intravascular coagulation

Definition

Disseminated intravascular coagulation (DIC) was defined by the DIC Subcommittee of the Scientific and Standardization Committee of the International Society of Hemostasis and Thrombosis in 2001 as follows: "DIC is an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which, if sufficiently severe, can produce organ dysfunction" [1].

Pathophysiology

Disseminated intravascular coagulation is induced by numerous factors in which tissue damage, endothelial damage, or damage to blood cells have a central role. Examples of cell-damaging mediators are endo- and exotoxins from bacteria, antigen–antibody complexes, cytokines released from macrophages and monocytes, proteases released from white blood cells, etc.

Tissue factor is exposed on and/or released from damaged tissue, endothelial cells, or monocytes. The amount of released tissue factor is related to subsequent coagulation activation. DIC is characterized by a primary hypercoagulation phase with disseminated intravascular fibrin formation and microembolism.

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Soluble fibrin complexes in the circulation precipitate and form, together with platelets (and leukocytes), thromboemboli in the microcirculation, resulting in organ damage. All organ systems can be affected: kidneys, lungs, and the central nervous system are particularly sensitive. Microembolism is considered to be one component of the syndrome, usually characterized by a progressive development of multiple organ failure (MOF). The hypercoagulation results in consumption of coagulation factors, inhibitors, and platelets. Consumption is faster than synthesis.

Secondarily, there is also a physiologic activation of other proteolytic enzyme systems, including formation of elastase and plasmin, leading to an increased fibrinolysis, with degradation of fibrinogen, fibrin, other coagulation factors and receptors on the platelet surface. The stimulation of fibrinolysis results in raised concentrations of fibrin(ogen) degradation products (FDP), including fibrin D-dimers, which inhibit fibrin formation and platelet aggregation. A paradoxical combination of microembolism and bleeding (thrombohemorrhagic syndrome) may occur.

Secondary activation of, for example, complement and kallikrein-kinin systems is of great pathophysiologic importance and possibly also for therapy.

In certain cases, inhibition of fibrinolysis occurs simultaneously with activation of the coagulation system. There are specific diseases in which fibrinolysis may dominate, for example acute promyelocytic leukemia (M3).

Examples of conditions triggering DIC

Sepsis, trauma (including burns and heat stroke) and particularly head and multitrauma, obstetric complications such as abruptio placentae, cancer, toxins (e.g. snake venom), immunologic/allergic disorders, vascular disorders (e.g. aneurysm).

The clinical picture

Typical symptoms of DIC emanate from the most sensitive organs, that is, the central nervous system, kidneys, lungs, skin, and mucous membranes. Symptoms may be mild at an early stage, but fulminant multiorgan failure may occur in later stages, including significant cerebral symptoms, acute lung failure (acute respiratory distress syndrome), renal failure, and also necrosis of skin and mucous membranes due to microthrombosis. Coagulation activation associated with microthrombosis may be unrecognized in the early stages and/or misdiagnosed as complications of underlying disease, and suspicion of DIC may be established only when bleedings occur. Petechial bleedings and ecchymoses as well as mucosal bleeding from gums etc. and bleedings from venous punctures and catheter sites are the most common findings. Gastrointestinal bleeding may occur as well as intracranial bleedings.

In **septic shock**, a severe form of DIC, powerful activation of the coagulation system often occurs very quickly, mainly through upregulation of tissue factor from damaged endothelium and monocytes. Fibrinolysis is inhibited. In meningococcal sepsis, for example, blue-black confluent skin changes are found, due to a combination of necrosis and bleeding.

Laboratory diagnosis of DIC

Disseminated intravascular coagulation develops in stages and the diagnosis (and treatment) differs accordingly.

1 Generalized activation of coagulation, with intravascular formation of soluble fibrin.
2 Consumption of platelets, coagulation factors, and inhibitors. Secondary fibrinolysis.
3 Microembolism and/or bleeding in various organs.
4 Multiple organ failure may develop as a result of uninhibited DIC.

Laboratory values change. Repeat the analyses to identify trends.

- *Platelet count* decreases due to consumption.
- *APT time* is prolonged after consumption. Pathologic test results occur relatively late in the process, when general factor deficiency such as of FVIII and/or fibrinogen has reached about 30% of normal values.
- *Low EVF* (Hct <20%) leads to prolonged P-APT time.
- *PT(INR)* increases as the vitamin K-dependent coagulation factors are consumed. Liver failure may interfere with the evaluation of laboratory data. Pathologic test results occur relatively late in the process, when general factor deficiency has reached about 30% of normal values.
- *Fibrinogen* may drop, due to rapid fibrin formation and degradation, but its level can also be normal or high, especially in an infection, since fibrinogen is an acute phase reactant. At a level below 1 g/L bleeding often starts. Therefore repetitive measurements of fibrinogen should be performed. Fibrinogen <0.5 g/L results in a prolonged APT time.
- *Fibrin D-dimer* usually increases, indicating fibrin formation followed by subsequent fibrinolysis.
- *Antithrombin* is consumed as a result of increased thrombin formation. It also can drop due to being dependent on liver function.
- *Soluble fibrin*, an intermediate stage between fibrinogen and stable (cross-linked) fibrin, increases when the formation of fibrin is stimulated.

Treatment monitoring

Use laboratory tests to evaluate progress and treatment. Repeat testing 2–4 times daily. Platelet count, APT time, PT(INR), fibrinogen, fibrin D-dimer, antithrombin, 2–3 times per day.

If bleeding symptoms are present, fibrinogen and FVIII concentrations need to be analyzed. Special tests may be suggested by coagulation specialists.

Treatment

It is mandatory to treat the underlying cause of DIC, for example treatment of infection, fracture stabilization, emptying of abscesses, debridement of necrotic tissue, delivery induction or caesarean section in obstetric complications, etc. Without treatment and cure of the cause, DIC will not subside.

As this treatment policy is now more widely applied, DIC does not occur so often.

General treatment for sepsis

General recommendations focus on rapid diagnosis and treatment of the cause, that is, give adequate antibiotics in combination with shock therapy and support of vital functions. No tranexamic acid as fibrinolysis is usually impaired.

Specific treatment of coagulation disturbances (for dosages see Table 16.1)

The specific treatment of DIC is mainly based on clinical experience and physiologic considerations arising from studies in animals. However, the positive effects of various treatment options in animal studies have not

Table 16.1 Proposed dosages in the treatment of coagulation disturbances in DIC.

Drug	Dose
Plasma	10–15 mL/kg bodyweight
Antithrombin	(kg bodyweight × (1.0 U/mL – actual AT level) × 100, i.v.)
Prothrombin complex concentrate	10 U/kg i.v. (PT(INR) decreases by about 50%)
Tranexamic acid (Cyklokapron)	10 mg/kg i.v. may be repeated × 3. Stop when the bleeding has ceased. Be cautious in kidney damage. Dose adjustment
Other factor concentrates	Contact coagulation expert
Platelet concentrate	Contact coagulation expert
Dalteparin (Fragmin®)	2500–5000 IU/d s.c. as thromboprophylaxis
Enoxaparin (Clexane®)	20–40 mg/d s.c. as thromboprophylaxis

been confirmed in human studies, probably because patients with DIC are so heterogeneous and the causes of DIC are multifactorial.

Substitution of acquired deficiencies of inhibitors of coagulation, fibrinolysis, and kallikrein is usually initially achieved with plasma transfusion. If volume needs to be limited, plasma may be replaced by inhibitor and/or factor concentrates. Platelet count may be transfused if platelet count is very low ($<20 \times 10^9$/L) in combination with persistent bleeding. Discuss with the coagulation specialist. For details see below.

When DIC subsides, antithrombotic treatment (LMH) may be considered.

Caution

- LMH creates an increased bleeding tendency, which should be considered in particular if platelet count is low (below 20×10^9/L) and there is ongoing bleeding.
- Patients with traumatic brain injury may be given LMH in prophylactic doses 24 h after injury if there is no obvious ongoing bleeding or contraindication. Brain injury is a potent activator of coagulation.
- LMH can cause thrombocytopenia due to antibodies against platelet factor 4. See below.
- Accumulation of heparins may occur in renal and hepatic insufficiency. Consider dose reduction if increased creatinine level or pathologic liver tests.
- The plasma activity of heparin can be monitored by measuring anti-FXa.

Fresh-stored (less than 2 weeks) or fresh-frozen plasma

This is the first option *in* bleeding. The plasma is given to supply coagulation, fibrinolysis, and other protease inhibitors. In the absence of dilution, a general inhibitory deficiency may be presumed if antithrombin levels are low. Fifteen mL plasma/kg bodyweight will increase the levels of inhibitors and coagulation factors by about 10–15%.

Antithrombin concentrate

The half-life of antithrombin is normally 3 days, but in DIC it can be 4–24 h.

A large randomized study (KyberSept), did not show any significant effects on **septic patients** of treatment with antithrombin concentrate. However, there is a relatively long clinical experience with antithrombin treatment in patients with septic shock and severe progressive coagulopathy despite large plasma supply. Appropriate patients for this type of treatment may be those with fulminant septic shock caused by meningococci or pneumococci and symptoms of coagulopathy in the form of purpura or other bleedings.

A low antithrombin level per se is not an indication for antithrombin treatment. Heparin should be avoided together with antithrombin infusion due to the increased risk of bleeding.

Note that the combination of LMH and substitution of antithrombin may lead to an amplified anticoagulation effect and increased bleeding.

Coagulation factor concentrates

These can be used in severe DIC with consumption of the factors, especially FVIII, fibrinogen, and FXIII. Factor concentrates should preferably not be substituted until the pathologic consumptive hypercoagulation ("fuel on the fire") has ceased and there is still bleeding due to low levels of factors. Patients needing factor concentrate often have a spontaneously prolonged APT time.

- *Vitamin K-dependent factor concentrates*. Non-activated prothrombin complex concentrates of factors II, VII, IX, X, protein C, and protein S are used in serious bleedings as well as when PT(INR) exceeds 1.6 (preferred level in surgical hemostasis) or plasma treatment is not sufficient. The effect is instantaneous and lasts for 6–12 h.
- *Fibrinogen concentrate* is used in serious bleedings, at fibrinogen concentrations <1 g/L and when plasma administration is not sufficient or difficult to perform. One gram of the concentrate increases the fibrinogen level by 0.3 g/L in an adult. For full hemostasis effect a level of 2 g/L or more is needed if the patient is bleeding. Half-life (normally 4.5 days) is shorter in massive hypercoagulation including consumption and degradation.
- *VWF/factor VIII concentrate* (Haemate). In conditions involving massive fibrinolysis, not only fibrinogen is degraded but also FVIII, VWF, and FXIII. A low FVIII level causes a prolonged APT time and low VWF causes a prolonged bleeding time and worsened primary hemostasis. Haemate may be indicated in massive fibrinolysis and/or serious bleeding problems that are not improved by plasma (and eventually platelet concentrate).

Dextran, ASA and NSAID

These may potentiate the risk of bleeding by inhibiting platelet function.

Tranexamic acid (Cyklokapron)

If, in spite of plasma supply, severe bleeding continues with a low fibrinogen level and continuously high fibrin D-dimer levels, this indicates fibrinolysis. Tranexamic acid 10–15 mg/kg bodyweight i.v. during protective LMH treatment may be an option, possibly in repeated doses. Be restrictive in the event of simultaneous massive coagulation activation and in thrombosis. There is a risk that lysis of the microthromboses will cease, followed by remaining organ damage.

In **septic coagulopathy**, treatment with fibrinolysis inhibitors, for example tranexamic acid, should be avoided because fibrinolysis is often already inhibited.

Local treatment

Biologic tissue glue, Tisseel®, contains mainly fibrinogen, fibronectin, FXIII, aprotinin, and thrombin. Tranexamic acid locally may be effective. The i.v. preparation is diluted 1 + 1 with physiologic NaCl solution.

Heparin-induced thrombocytopenia

HIT type 1

Heparin-induced thrombocytopenia 1 is a nonimmunologically conditional benign form of thrombocytopenia occurring during treatment with UFH/LMH. It does not require treatment. It needs to be differentiated from "false thrombocytopenia" which can be diagnosed by measuring platelet count in a test tube with EDTA and comparing it with a tube containing citrate.

HIT type 2

Heparin-induced thrombocytopenia type 2 (usually named HIT only) is a severe, potentially limb- and life-threatening immune-mediated adverse drug reaction to UFH and/or LMH which occurs in up to 3% of treated patients. In spite of thrombocytopenia, which occurs typically 5–10 days after the initiation of heparin treatment, bleeding is uncommon, while thromboembolic complications are the main clinical problem in patients with HIT.

Heparin-induced thrombocytopenia is caused by the formation of antibodies that activate platelets following heparin administration, with a complex of heparin and platelet factor 4 (PF4) as a principal antigen. The complex links to the FcγRII receptor on the surface of the platelet. In this way, platelet activation and aggregation are induced, leading to thrombosis.

Heparin-induced thrombocytopenia is a condition where the diagnosis of HIT primarily remains clinical, supported by confirmatory laboratory testing. The pretest clinical probability scoring system (4Ts) seems to be a valuable tool for HIT diagnosis (Table 16.2).

Diagnosis

A significant decrease in platelet count is a clinical criterion of suspected HIT type 2. It usually occurs when treatment with UFH/LMH has been in progress for 5–14 days. If the patient has been treated with UFH/LMH during the previous 3 months, thrombocytopenia may occur immediately at the start of therapy.

Other reasons for thrombocytopenia should be excluded.

Laboratory diagnosis of HIT relies on the detection of antibodies against heparin/PF4 complex in plasma or serum with functional and/or immunologic methods (see Chapter 3).

Table 16.2 The pretest clinical probability (4Ts) score.

	Points (0, 1 or 2 for each category: maximum possible score = 8)		
	2	**1**	**0**
Thrombocytopenia	50% fall or platelet nadir 20–100 × 10^9/L	30–50% fall or platelet nadir 10–20 × 10^9/L	Fall <30% or platelet nadir <10 × 10^9/L
Timing of platelet count fall or other sequelae	Clear onset between day 5–day 10; or <1 day (if heparin exposure within past 100 days)	Consistent with immunization but not clear (e.g. missing platelet counts) or onset of thrombocytopenia after day 10	Platelet count fall too early (without recent heparin exposure)
Thrombosis or other sequelae (e.g. skin lesions)	New thrombosis; skin necrosis; post-heparin bolus acute systemic reaction	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis not yet proven	None
Other cause for thrombocytopenia not evident	No other cause for platelet count fall is evident	Possible other cause is evident	Definite other cause is present

Pretest clinical probability score: 6–8, high; 4–5, intermediate; 0–3, low.

Source: Reproduced from Lo, GK *et al. J Thromb Haemost* 2006; **4**:759–765, with permission from John Wiley & Sons.

Treatment

Patients being treated with UFH/LMH need anticoagulation in spite of suspected HIT type 2 as they have a paradoxically increased risk of both venous and arterial thrombosis despite decreased platelet count. VKA drugs should not immediately be substituted for UFH/LMH because there is a risk of skin necrosis, and they should not be given before platelet count is stable at over 100 × 10^9/L.

Argatroban is licensed in many countries for HIT type 2. Danaparoid (currently not available in Sweden) can be used but there is a small risk of cross-reactivity with UFH/LMH with a rise in antibody formation and platelet aggregation. The clearance rates of danaparoid and fondaparinux are dependent on renal function, while the clearance of argatroban is dependent on the patient's liver function.

If HIT type 2 is suspected, consult coagulation experts concerning alternative treatment.

The new oral anticoagulants (thrombin inhibitors and FXa inhibitors) may on theoretical grounds be considered in cases of HIT but they are not licensed for use in patients with HIT.

Thrombotic microangiopathies

Thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome

In both thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS), platelets are consumed as platelet aggregates are formed by the interaction of platelets with VWF. The most likely reason is endothelial damage, but the pathogenesis is not totally clear. A large multimer variant of VWF, normally degraded by a metalloprotease (ADAMTS-13), has been observed in plasma in TTP. The cause of TTP is infection or autoimmunity (isolated cases); for HUS, it is most often infection (especially Shiga toxin-producing *E. coli* in children).

Acquired TTP and HUS are idiopathic in about 80%, and in 20% of TTP secondary to another condition, for example infection, cancer, cytostatic and immunosuppressive treatment, bone marrow transplantation, and pregnancy. Congenital TTP with deficiency of ADAMTS-13 may occur (recurrent cases).

The clinical picture includes thrombocytopenia, hemolytic anemia (elevated LD, increased numbers of reticulocytes, elevated bilirubin, and reduced haptoglobin), fragmented erythrocytes in peripheral blood (so-called schistocytes), kidney failure (worse in HUS), fever (mostly in TTP), and neurologic symptoms (particularly in TTP). Diarrhea is frequent when the cause is infection. Coagulation factors are usually not affected, in contrast to DIC. Determination of the ADAMTS-13 is performed in special laboratories.

Treatment is based on fresh-frozen plasma and plasmapheresis (in hereditary deficiency there are additional possibilities). In autoimmune TTP, chemotherapy and/or treatment with rituximab may be necessary to prevent recurrence. Without treatment, the prognosis is poor; with plasmapheresis, however, 80% remission has been reported in idiopathic TTP.

Contact a hematologist, coagulation expert or blood center for advice.

Reference

1 Taylor FB, Jr, Toh CH, Hoots WK, *et al*. Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH). Towards definition, clinical and laboratory criteria and a scoring system for disseminated intravascular coagulation. *Thromb Haemost* 2001;**86**:1327–1330.

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