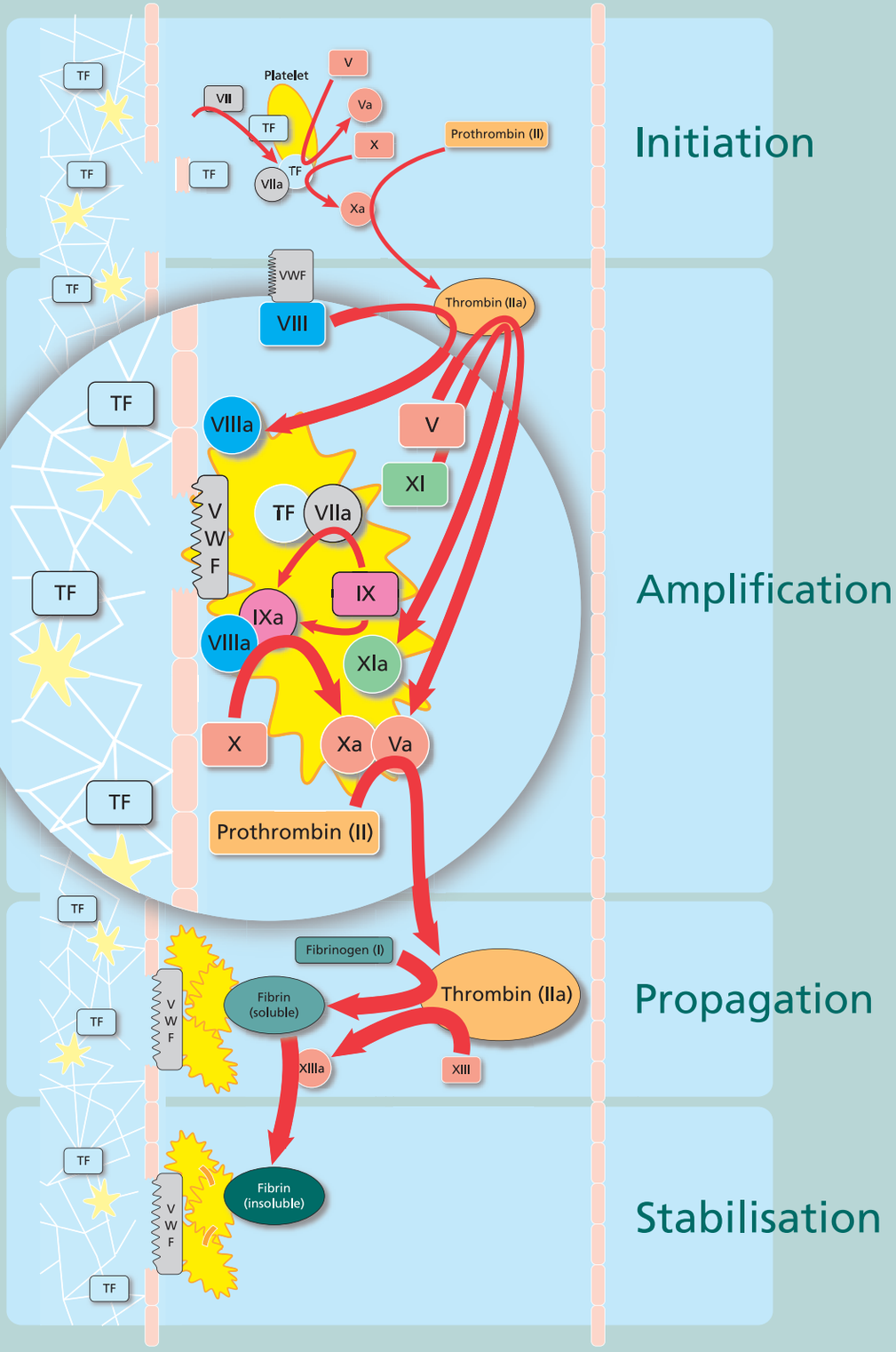
Coagulation Disorders: Pathogenesis & Therapies



Biotherapies for Life™ CSL Behring

Dear Reader,

The second brochure of a comprehensive series of educational materials may serve physicians, pharmacists, medical students, nurses and other health care professionals as a short introduction to the pathogenesis and treatment approaches of coagulation disorders.

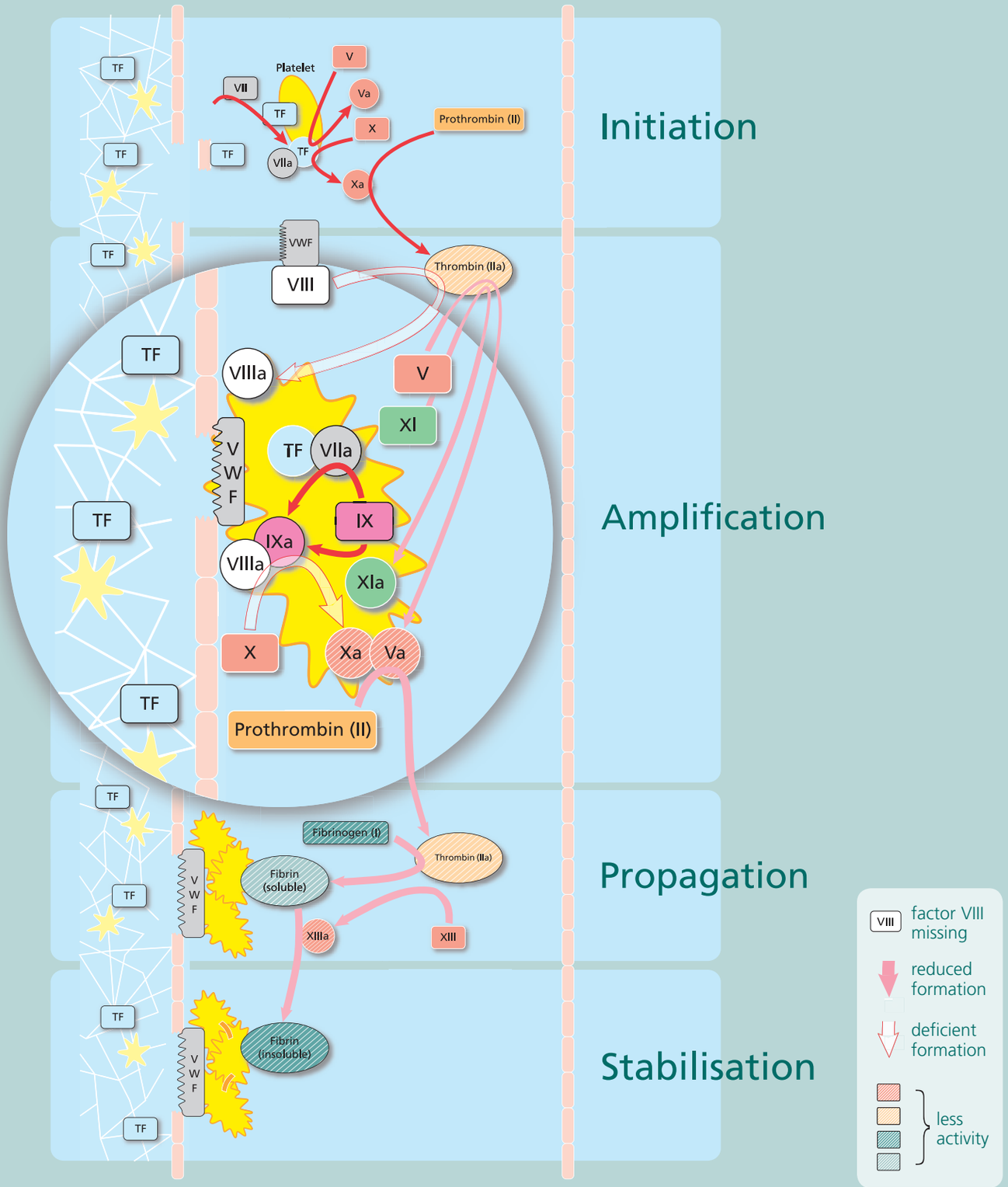
We thank Professor Klaus T. Preissner (Giessen, Germany) for his expertise and creativity in developing this innovative educational guide.

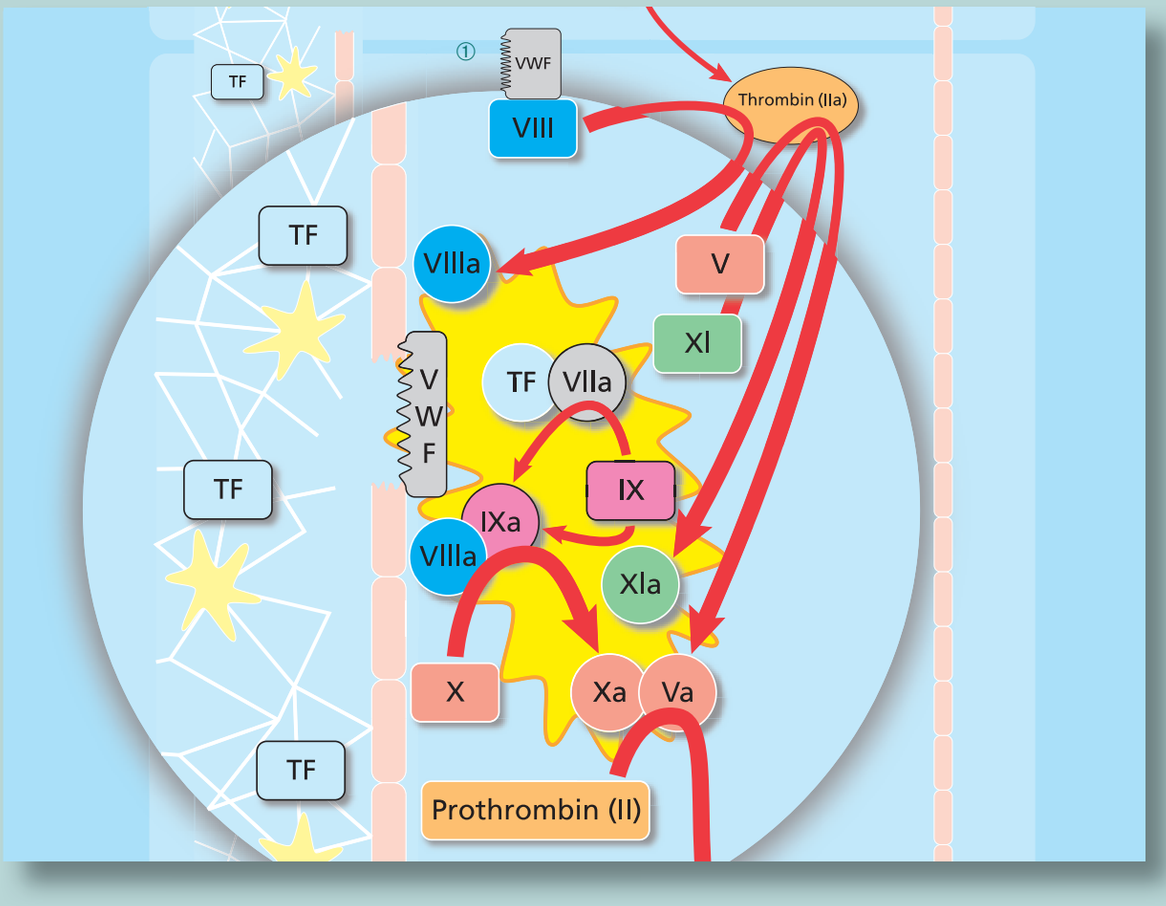
Yours sincerely,
CSL Behring Team

Marburg, Germany

Haemophilia A (factor VIII deficiency)

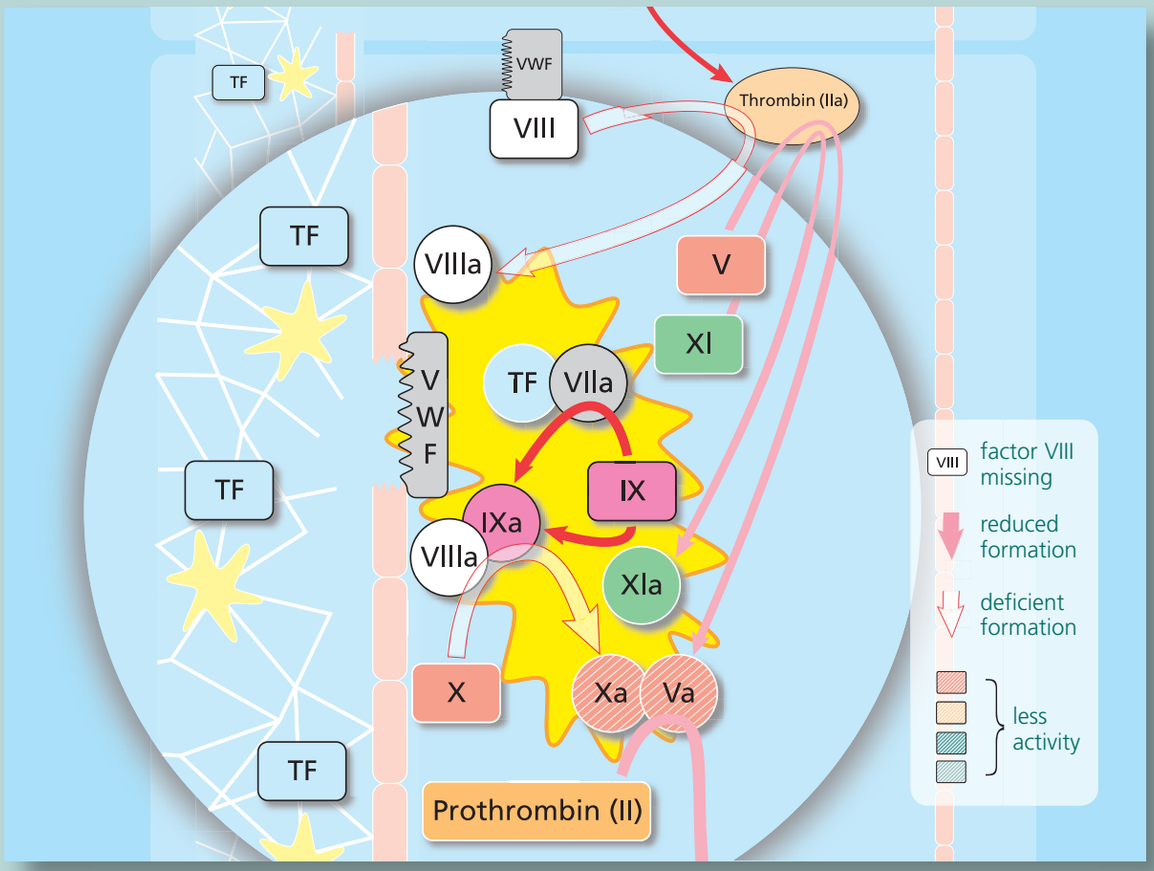
Disorders, treatment approaches, and CSL Behring products





Physiology of FVIII and vWF 1/3

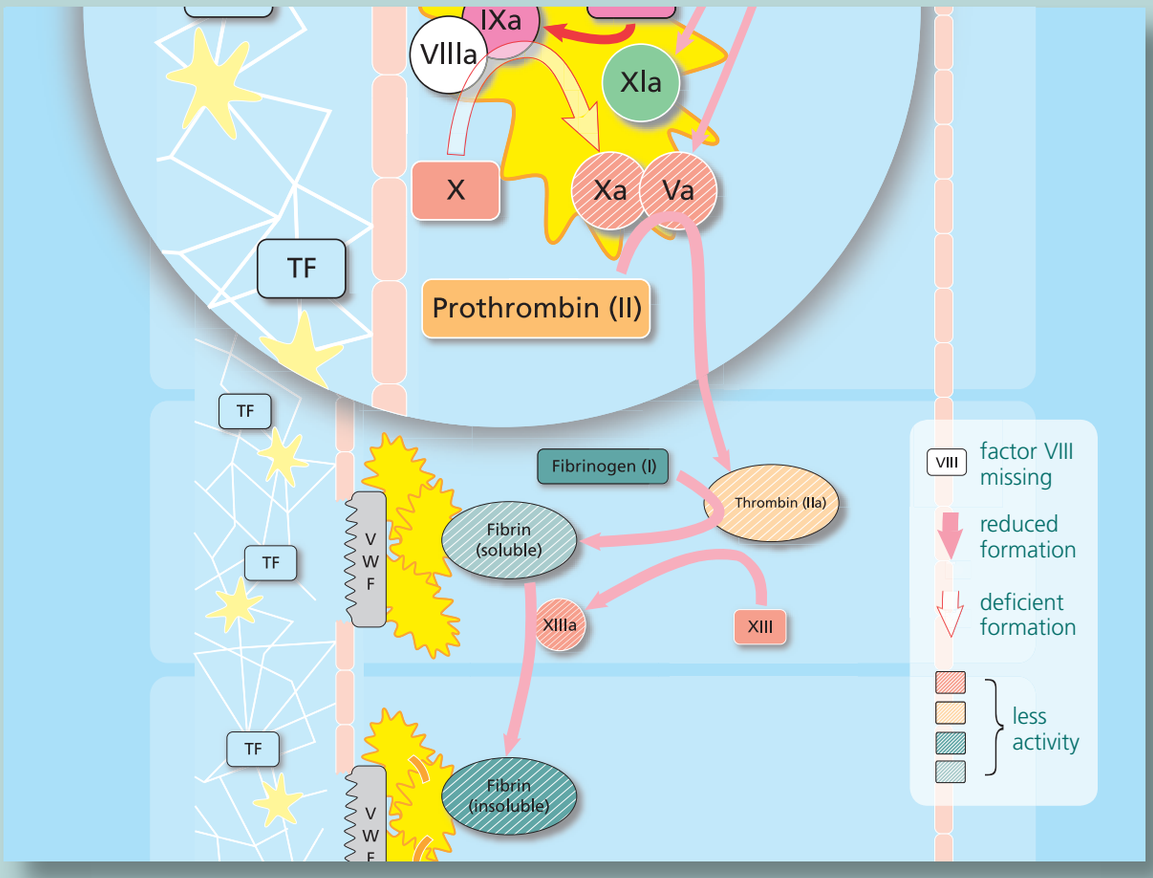
Factor VIII (FVIII) is a glycoprotein that operates as a cofactor in the intrinsic activation of factor X (FX), performing the function of an accelerator protein. The gene coding for FVIII is located on the X chromosome and FVIII is synthesised primarily in the liver. FVIII circulates in the blood in a tightly-bound complex with von Willebrand factor (VWF/FVIII complex) which stabilizes FVIII.
① The VWF/FVIII complex has physiological advantages for the FVIII molecule:
Firstly, VWF protects FVIII from premature splitting and inactivation by proteases such as activated protein C (APC) or activated factor X (FXa), and also against premature proteolytic activation by thrombin. Excessive amounts of circulating activated FVIII may represent a risk of occurrence of thrombotic events. However, in complex with VWF, levels of activated FVIII in the circulation are reduced and, therefore, the risk of thrombosis is not high at physiological conditions.
Secondly, VWF acts as a carrier protein transporting FVIII, well-protected and non-activated, to all parts of the body, and leads to an accumulation of the trace protein FVIII at sites of vessel injury, where immobilized VWF is involved in platelet adhesion and aggregation. Once released from its carrier protein, FVIII can be activated by thrombin with the effect of accelerating factor X formation with subsequent thrombin generation necessary for effective blood clotting to occur.



Haemophilia A (factor VIII deficiency) 2/3

Haemophilia A is one of the most common forms of hereditary plasma coagulopathy. It is the result of a recessive gene mutation on the X chromosome and is characterised by a deficiency of coagulation-promoting FVIII, in which the residual activity is less than 1% of normal in its severe forms. Haemophilia A affects about 1 in 10,000 individuals and is only manifested clinically in males – with a few exceptions. About one-third of cases are due to new mutations in the factor VIII gene.
The clinical symptoms depend on the degree of severity of the reduction in FVIII activity, designated FVIII-coagulant (FVIII:C). Patients with a severe deficiency (FVIII:C <1% of normal) may experience spontaneous haemorrhage in the joints and soft tissue, which in most cases leads to recurrent severe arthropathy and impaired movement. With moderate haemophilia A (FVIII:C about 1–5%), haemorrhage and haemarthrosis are less frequent and usually only occur after trauma. Patients with a slight deficiency (FVIII:C >5%) usually exhibit haemorrhage only after severe trauma or major surgery. Haemophilia A is manifested clinically in early childhood, usually from the crawling stage onward. The site and frequency of bleeds can vary with increasing age.

Bowen DJ. Haemophilia A and haemophilia B: molecular insights. Mol Pathol. 2002;55:1-18.
Bolton-Maggs PH, Pasi KJ. Haemophilias A and B. Lancet. 2003;361:1801-1809.

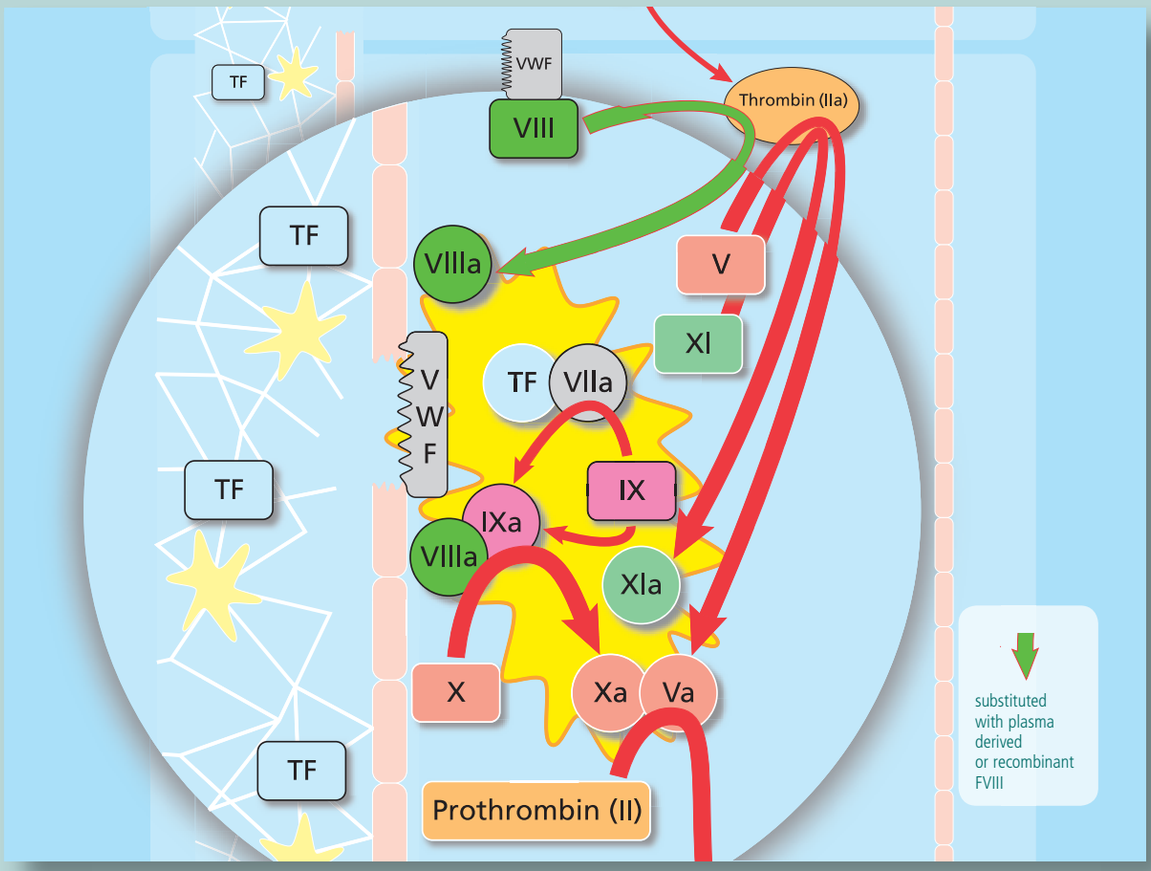


Haemophilia A (factor VIII deficiency) 3/3

Diagnosis of haemophilia A is made on the basis of:

- patient´s history (including family history) and physical examination in patients with suspected haemophilia (individuals with spontaneous bleeding).
- laboratory investigations including platelet count, bleeding time, and the coagulation panel consisting of prothrombin time (PT) and activated partial thromboplastin time (aPTT). Typically, the aPTT will be prolonged, but all other tests will be normal.
- specific assays for FVIII and FIX that will establish the differential diagnosis between haemophilia A and haemophilia B.

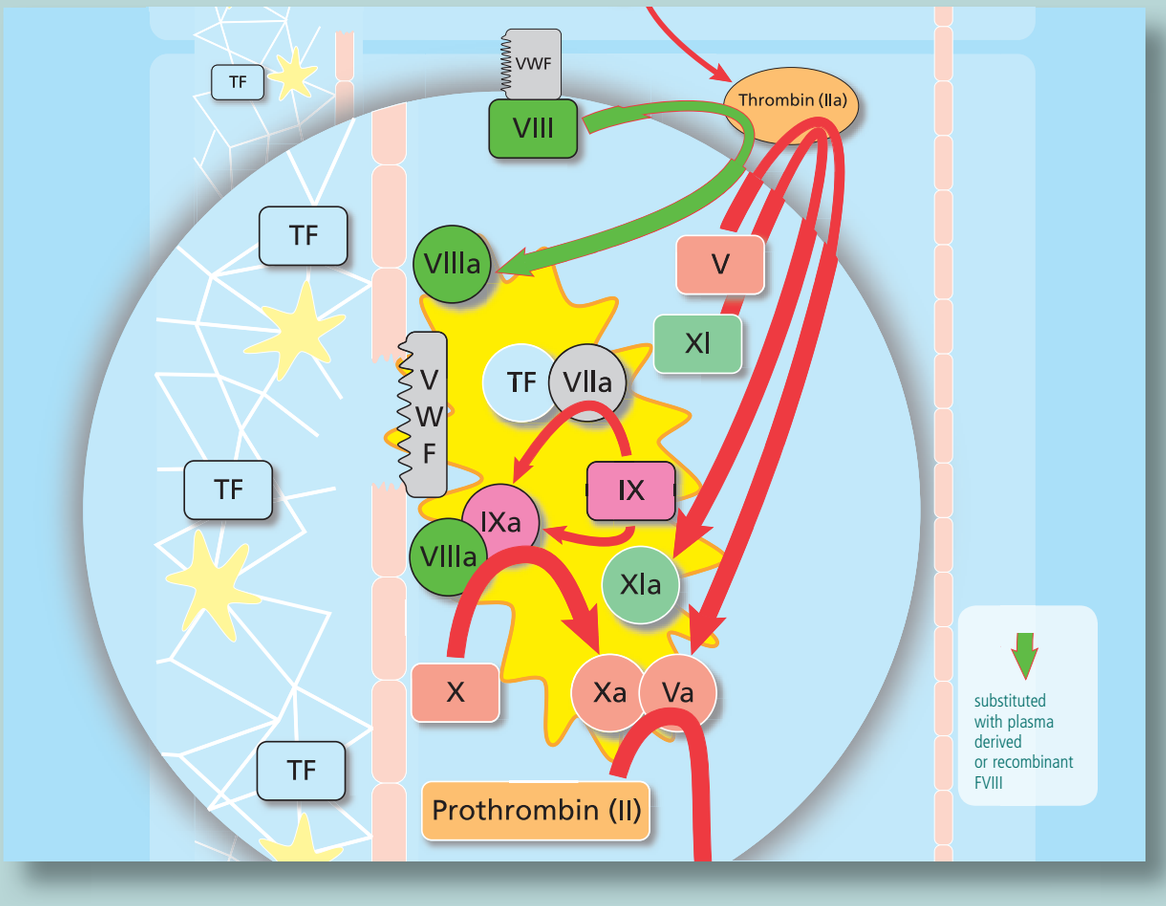
Peyvandi F, Kaufman RJ, Seligsohn U, et al. Rare bleeding disorders. Haemophilia. 2006;12 Suppl 3:137-142. Mannucci PM. Back to the future: a recent history of haemophilia treatment. Haemophilia. 2008;14 Suppl 3:10-18.



Treatment approaches for Haemophilia A 1/3

Haemophilia A is a complex disorder in terms of diagnosis and management. Optimal management requires more than just the treatment and prevention of acute bleeding. Patients should ideally be managed by a multidisciplinary team in a comprehensive care centre. All staff members should have expertise and experience in treating patients with bleeding disorders. The centre should have access to a coagulation laboratory, appropriate clotting factor concentrates, and a blood bank.
The general principles of care for persons with haemophilia A include early treatment of acute bleeds, prevention of bleeding, and home therapy to manage uncomplicated mild or moderate bleeding episodes and prophylaxis.
Patients with FVIII:C levels >5% may be treated with desmopressin acetate (DDAVP) administered either intravenously or nasally. DDAVP was developed as a synthetic analogue of vasopressin (antidiuretic hormone) modified to reduce its pressor (blood pressure increasing) activity. DDAVP was found to increase VWF and FVIII levels in normal individuals, and in patients with mild to moderate VW-disease or mild haemophilia A, based on its ability to induce exocytosis of Weibel-Palade granules from the vascular endothelium.

Berntorp E, Boulyjenkov V, Brettler D, et al. Modern treatment of haemophilia. Bull World Health Organ 1995;73:691-701.
Dargaud Y, Negrier C. Haemophilia therapies. Expert Opin Biol Ther. 2007;7:651-663.



Treatment approaches for Haemophilia A 2/3

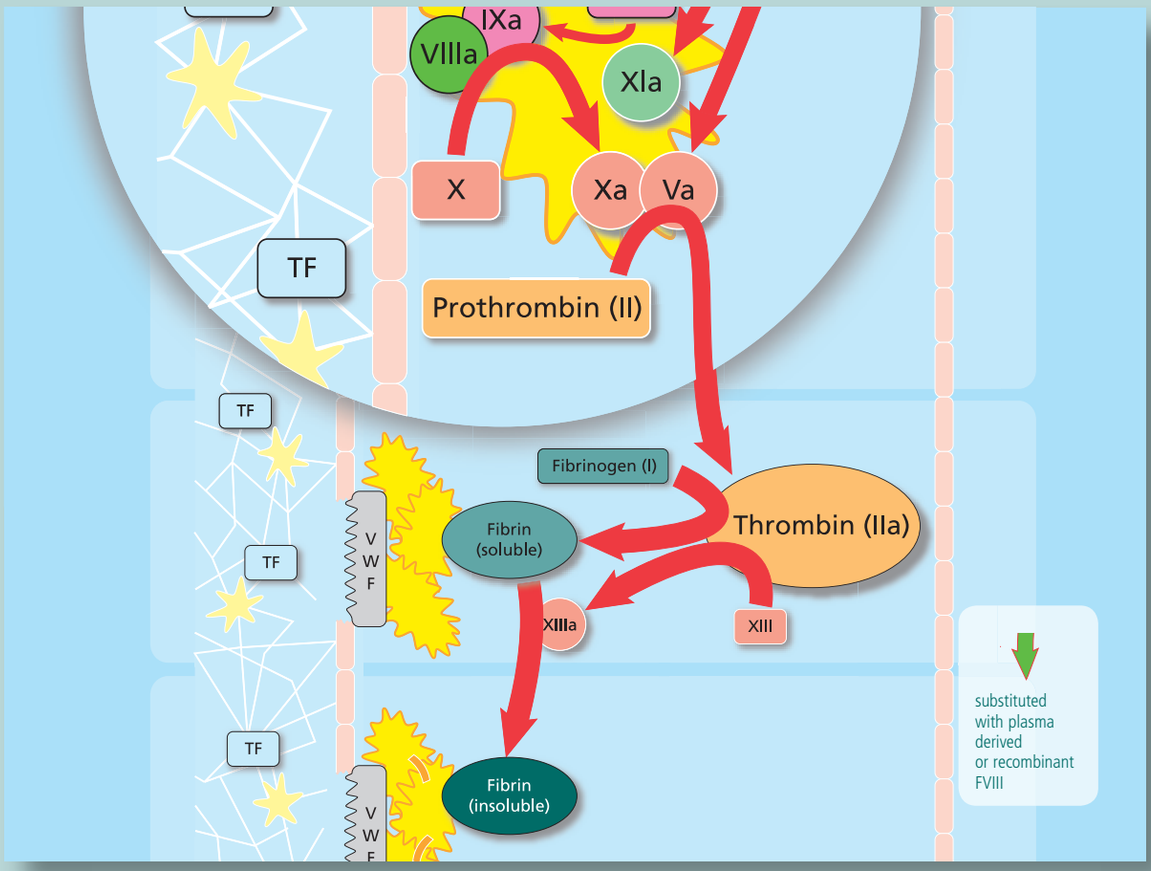
In patients with mild haemophilia A, who exhibit an inadequate response to DDAVP, and in patients with moderate or severe haemophilia A, FVIII replacement therapy with plasma-derived FVIII (pdFVIII) or recombinant FVIII (rFVIII) concentrates is indicated. Different factor supplementation regimens are in use for different clinical situations:

- substitution 'on-demand' in case of acute bleeding
- prophylactic substitution to prevent bleeding and its complications.

Haemophilia specialists have agreed on the definition of 'primary prophylaxis' as a long-term, continuous treatment starting before the age of 2 years and/or prior to any clinically evident bleeding into joints. 'Secondary prophylaxis' is more diverse. An international conference on prophylactic therapy for severe haemophilia generated an updated definition of prophylaxis:

- on-demand therapy – treatment in case of bleeding
- primary prophylaxis – long-term continuous (46–52 weeks/year up to adulthood) treatment determined by age, starting before 2 years of age and prior to clinically evident joint bleeding

Leissinger C, Becton D, Cornell C Jr, Cox Gill J. High-dose DDAVP intranasal spray (Stimate) for the prevention and treatment of bleeding in patients with mild haemophilia A, mild or moderate type 1 von Willebrand disease and symptomatic carriers of haemophilia A. Haemophilia 2001;7:258-266.
Berntorp E, Astermark J, Björkman S, et al. Consensus perspectives on prophylactic therapy for haemophilia: summary statement. Haemophilia 2003;9:1-4.



Treatment approaches for Haemophilia A 3/3

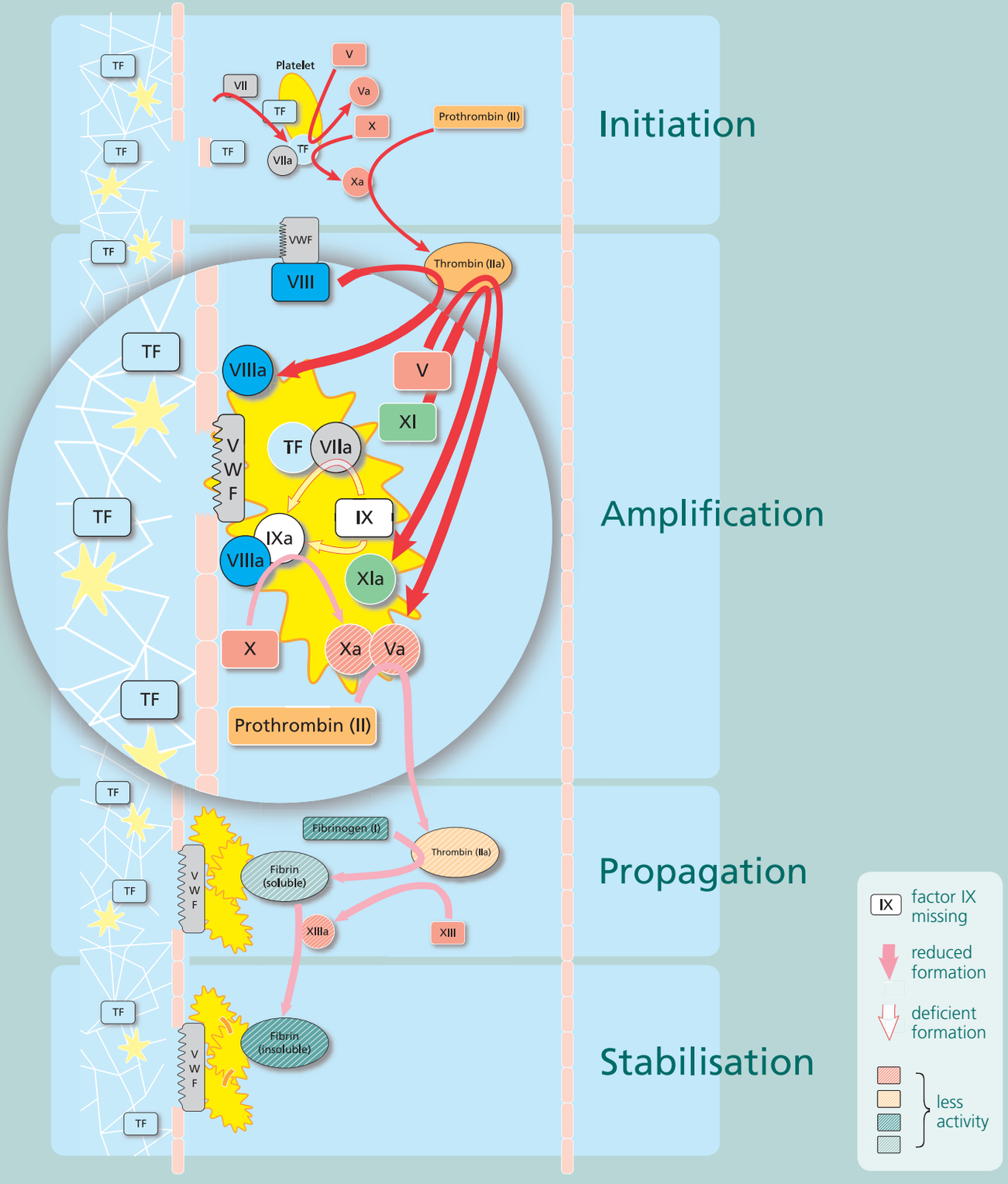
- primary prophylaxis determined by first bleed – long-term continuous treatment starting prior to the onset of joint damage (no more than one joint bleed), irrespective of age
- secondary prophylaxis – long-term continuous treatment not fulfilling the criteria for primary prophylaxis
- short-term prophylaxis (e.g., before surgery or athletic activity) – short-term treatment to prevent bleeding.

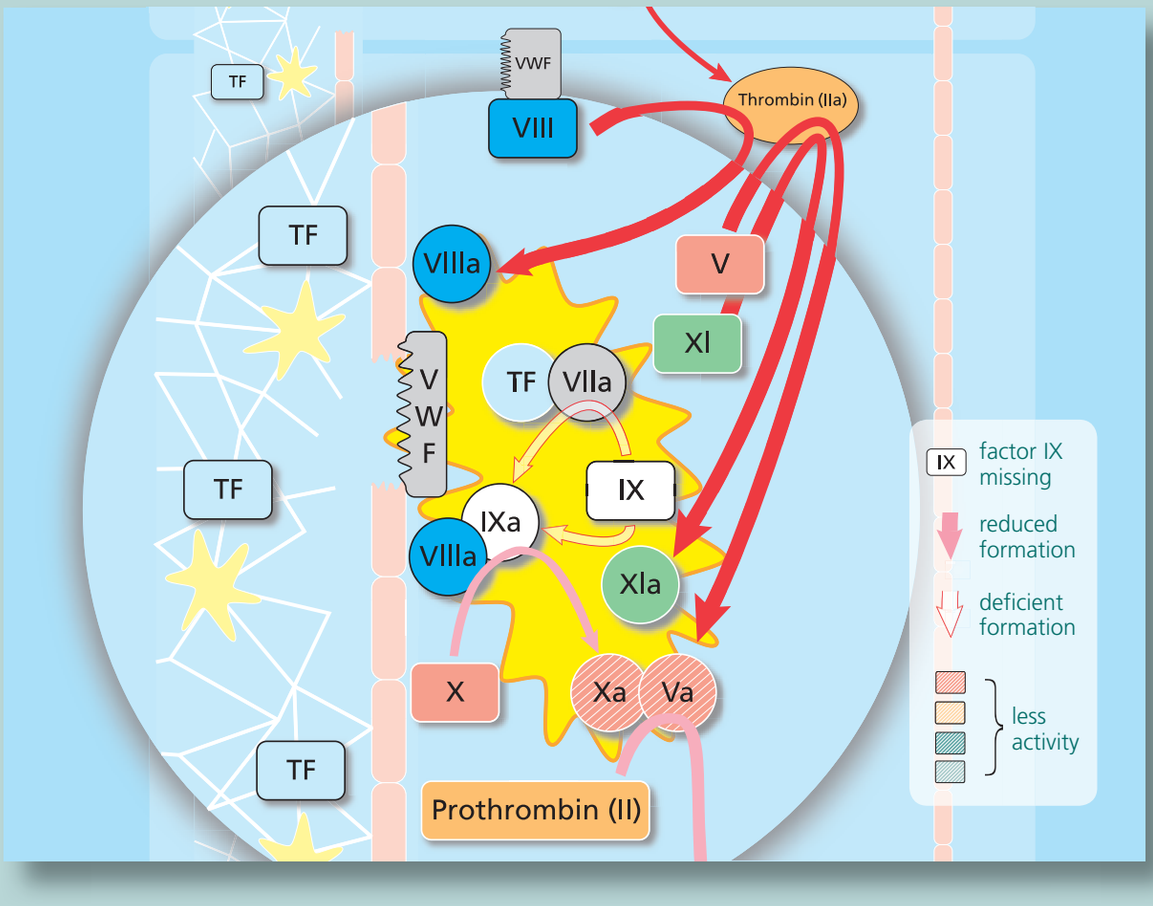
Bleedings that are considered mild and moderate in severity can be managed by 'self-infusion' or home therapy. Patients are trained to self-administer the factor concentrate by infusion according to their individually adjusted treatment regimen. Most patients are candidates for home therapy – with the exception of haemophilia patients with inhibitors, or patients where the home situation does not allow the patient to take responsibility for the treatment. Home therapy with coagulation factor usually commences when a child is between 3 and 5 years old. Home treatment must be supervised closely by a haemophilia centre.

Berntorp E, Boulyjenkov V, Brettler D, et al. Modern treatment of haemophilia. Bull World Health Organ 1995;73:691-701.
Coppola A, Di Capua M, De Simone C. Primary prophylaxis in children with haemophilia. Blood Transfus. 2008;6 Suppl 2:s4-11.

Haemophilia B (factor IX deficiency)

Disorders, treatment approaches, and CSL Behring products





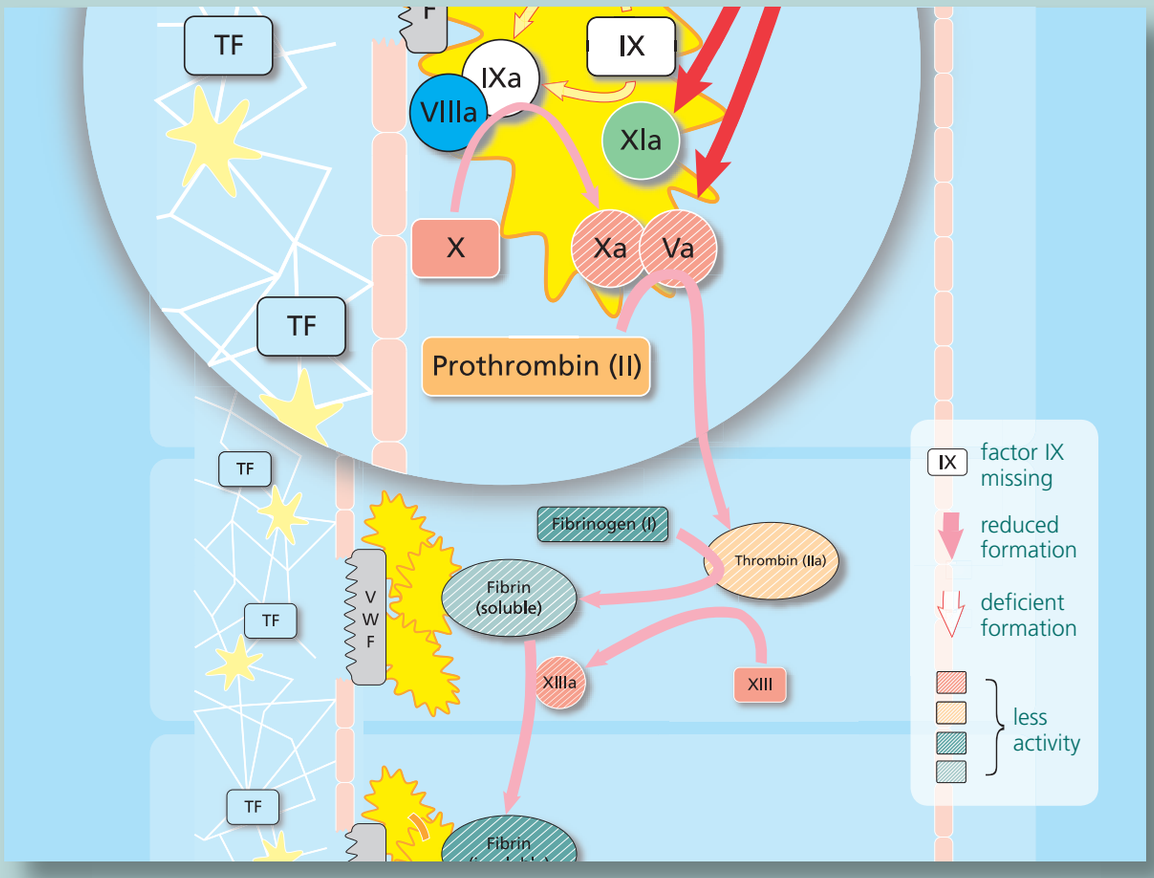
Physiology of Factor IX

Factor IX (FIX) is a vitamin K-dependent coagulation factor, which is synthesised in the liver. The coagulation function of FIX lies in the intrinsic activation of factor X (FX). Activated factor IX (FIXa) is a serine protease which, in the presence of activated factor VIII (FVIIIa), phospholipids, and calcium ions, splits and thus activates FX, starting the terminal phase of blood coagulation (fibrin formation).

Haemophilia B (factor IX deficiency) 1/3

Haemophilia B is a congenital coagulation disorder characterised by a lack, or deficiency, of FIX. It was distinguished from haemophilia A for the first time in 1947. The incidence of haemophilia B is estimated to be 10–15% of all people with haemophilia, or 1–2 cases per 100,000 individuals.

Pavlovski A. Contribution to the pathogenesis of hemophilia. Blood 1947;2:185-191.
Peyvandi F, Kaufman RJ, Seligsohn U, et al. Rare bleeding disorders. Haemophilia. 2006;12 Suppl 3:137-142.



Haemophilia B (factor IX deficiency) 2/3

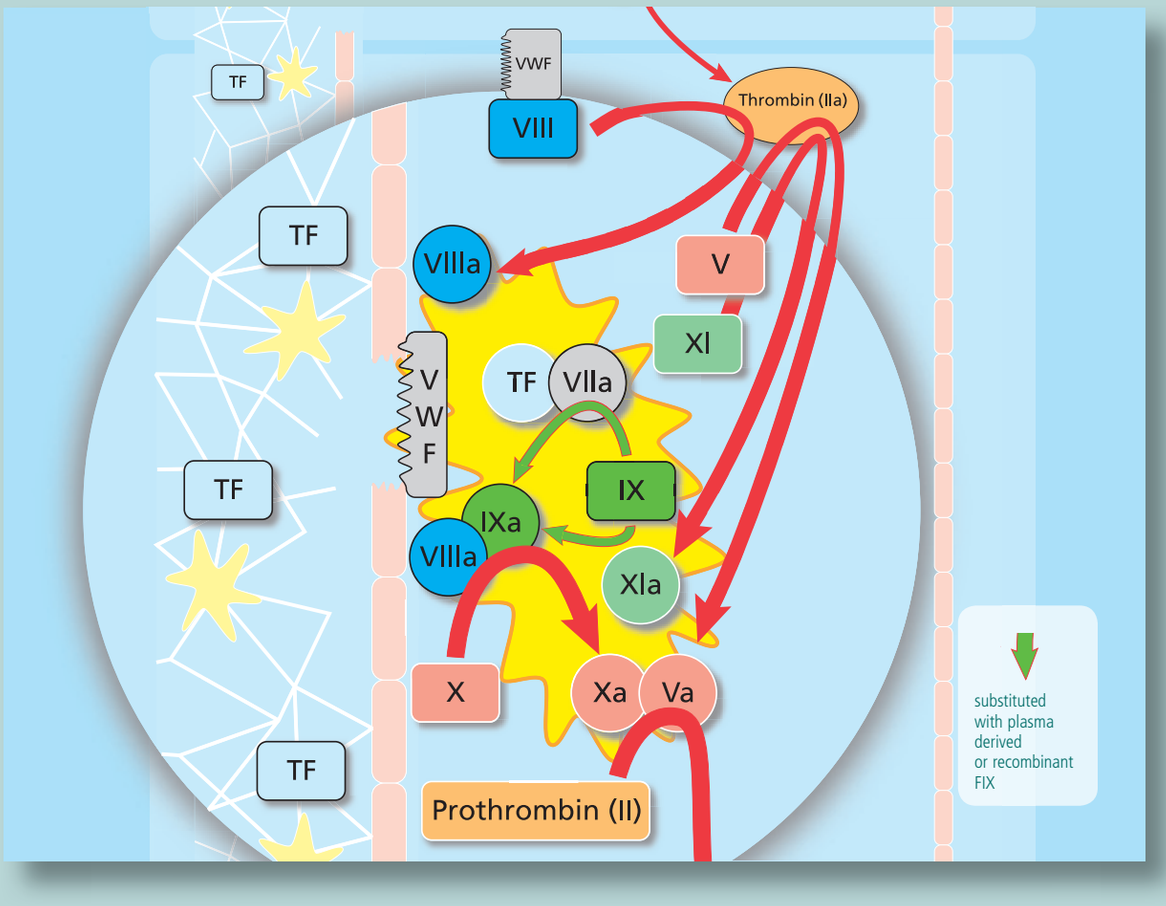
Haemophilia B is an X-linked recessive disorder, and one-third of all cases is due to a spontaneous mutation. The clinical symptoms depend on the severity of the FIX deficiency: In patients with a severe deficiency (FIX <1%), spontaneous bleeding occurs in the joints and soft tissue, which usually leads to severe arthropathy and impaired movement. In moderate haemophilia B (FIX 1–5%), bleeding and haemarthrosis are less frequent, and are usually only found in post-trauma situations. Patients with a mild deficiency (FIX >5%) usually only bleed after severe trauma or major surgery.

Haemophilia B (factor IX deficiency) 3/3

The concentration of FIX (expressed as FIX:Ag) does not always correlate with FIX coagulation activity in haemophilia B patients. Immunological methods are used to distinguish among three main types of haemophilia B: Haemophilia B–, with a complete deficiency of FIX:Ag; haemophilia B, with a reduced concentration of FIX:Ag; and haemophilia B+, with a normal FIX:Ag concentration (10% of haemophilia B patients). Haemophilia B is manifested clinically in early childhood, usually from the crawling stage onwards; the site and frequency of bleeds can vary with increasing age.

Diagnosis of haemophilia B is based on clinical history and examination, and laboratory studies including prothrombin time (PT), activated partial thromboplastin time (aPTT), and platelet count. Assessment of FIX levels and the presence of FIX inhibitors is also important.

Wong T, Recht M. Current options and new developments in the treatment of haemophilia. Drugs. 2011;71:305-320.



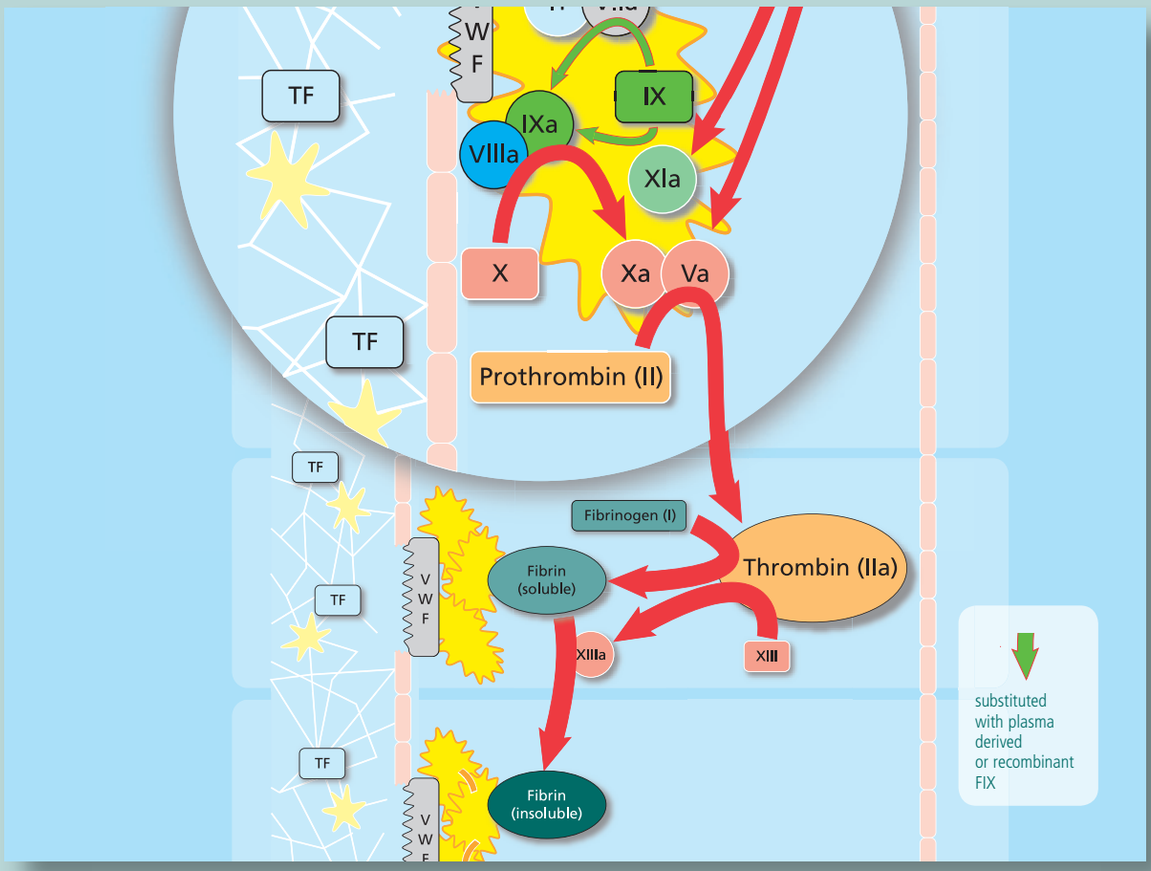
Treatment approaches for Haemophilia B 1/5

In order to prevent and treat haemophilia B-related haemorrhages, the patient is given FIX in the form of an appropriate FIX concentrate. The desired minimum activity of FIXa and the dosage depend on the site and severity of the bleeding. The need to begin treatment as soon as possible is based on the knowledge that the later the treatment is started, the more serious the consequences of the haemorrhage will be.

Deficient FIX can be replaced by a FIX-containing product. Most commonly, FIX concentrates in various forms are utilised; these are heat-treated and lyophilised commercially-produced agents. FIX concentrate products include pure coagulation FIX products, or FIX complex concentrates. In addition, a recombinant FIX concentrate exists.

Treatment approaches for Haemophilia B 2/5

There have been repeated reports on thrombosis occurring in haemophilia B patients after treatment with early prothrombin complex concentrates (PCC) or with less pure FIX concentrates. The cause of this phenomenon was thought to include the high plasma levels of factors II, VII, and X that result from PCC infusion (as haemophilia B patients can replenish these themselves, and these factors are contained in PCC), the activated FIX (FIXa) and activated FX (FXa) content of PCC, and the platelet phospholipid content of PCC. The risk of thrombosis and of disseminated intravascular coagulation (DIC) are thought to be largely eliminated by the use of pure coagulation products, which contain only traces of other coagulation proteins and, in particular, no detectable activated coagulation factors or phospholipids. Modern PCC have not been associated with increased thromboembolic events when used as indicated.



Treatment approaches for Haemophilia B 3/5

Fresh frozen plasma (FFP) should only be used for the emergency treatment of life-threatening bleeding when FIX products are not available.

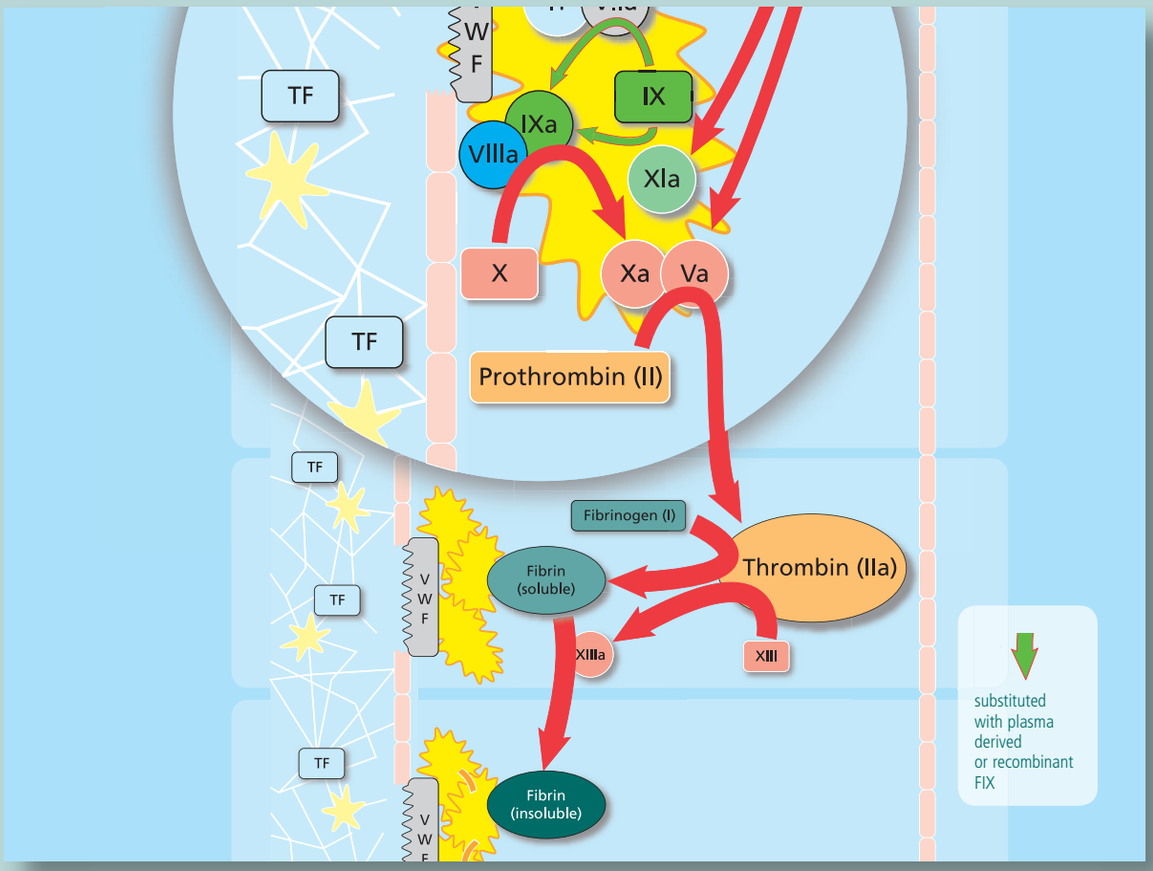
Antifibrinolytics inhibit local fibrinolysis, thereby maintaining clots and decreasing rebleeding. These agents, including aminocaproic acid and tranexamic acid, can be employed as a primary or adjunctive therapy in patients also treated with plasma-derived or recombinant FIX concentrate.

Different factor supplementation regimens are in use for different clinical situations:
- substitution 'on-demand' in case of acute bleeding
- prophylactic substitution to prevent bleeding and its complications.

Treatment approaches for Haemophilia B 4/5

Bleedings that are considered mild and moderate in severity can be managed by 'self-infusion' or home therapy. Patients are trained to self-administer the factor concentrate by infusion according to their individually adjusted treatment regimen. Most patients are candidates for home therapy – with the exception of haemophilia patients with inhibitors, or patients where the home situation does not allow the patient to take responsibility for the treatment.

Scharrer I. The need for highly purified products to treat hemophilia B. Acta Haematol 1995;94:2-7.
Monahan PE, Di Paola J. Recombinant factor IX for clinical and research use. Semin Thromb Hemost. 2010;36:498-509.
Franchini M, Mannucci PM. Inhibitors of propagation of coagulation (factors VIII, IX and XI): a review of current therapeutic practice. Br J Clin Pharmacol. 2011;72:553-562.



Treatment approaches for Haemophilia B 5/5

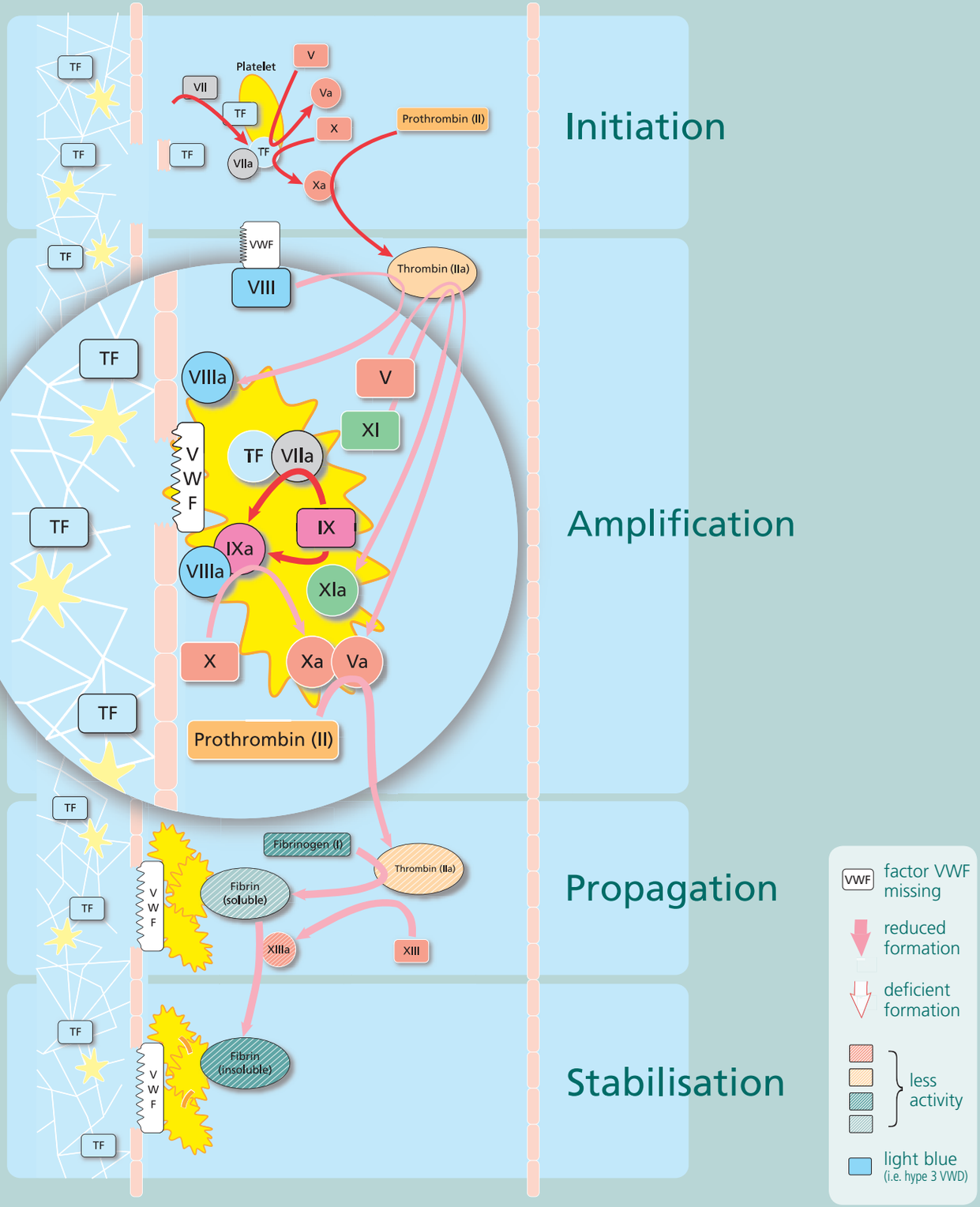
Haemophilia specialists have agreed on the definition of 'primary prophylaxis' as a long-term, continuous treatment starting before the age of 2 years and/or prior to any clinically evident bleeding into joints. 'Secondary prophylaxis' is more diverse. An international conference on prophylactic therapy for severe haemophilia generated an updated definition of prophylaxis:

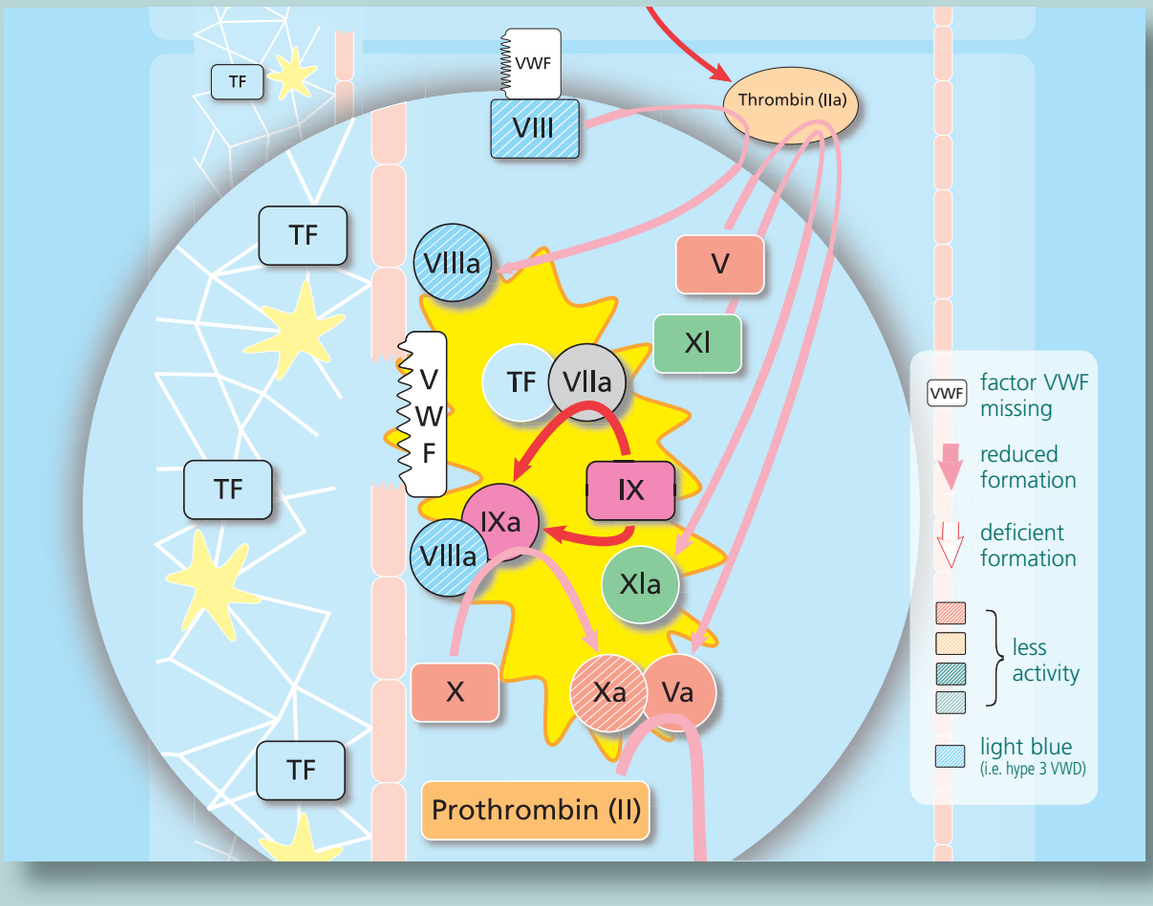
- on-demand therapy – treatment in case of bleeding
- primary prophylaxis – long-term continuous (46–52 weeks/year up to adulthood) treatment determined by age, starting before 2 years of age and prior to clinically evident joint bleeding
- primary prophylaxis determined by first bleed – long-term continuous treatment starting prior to the onset of joint damage (no more than one joint bleed), irrespective of age
- secondary prophylaxis – long-term continuous treatment not fulfilling the criteria for primary prophylaxis
- short-term prophylaxis (e.g., before surgery or athletic activity) – short-term treatment to prevent bleeding.

Berntorp E, Astermark J, Björkman S, et al. Consensus perspectives on prophylactic therapy for haemophilia: summary statement. Haemophilia 2003;9:1-4.
Morfini M. Secondary prophylaxis with factor IX concentrates: continuous infusion. Blood Transfus. 2008;6 Suppl 2:s21-25.
Manco-Johnson MJ. Advances in the care and treatment of children with hemophilia. Adv Pediatr. 2010;57:287-294.

von Willebrand disease

Disorders, treatment approaches, and CSL Behring products





Physiology of von Willebrand Factor

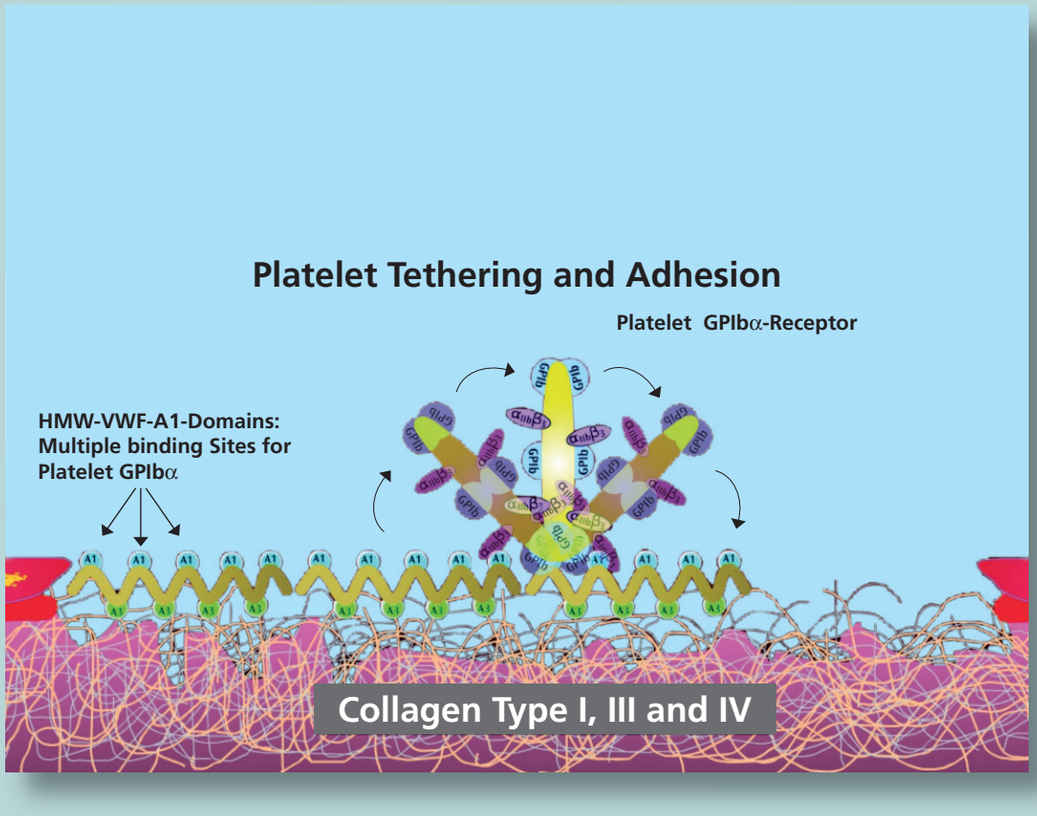
von Willebrand factor (VWF) is synthesised only in endothelial cells and megakaryocytes and is found (a) as a circulating glycoprotein in a tightly-bound complex with factor VIII (VWF/FVIII complex), (b) deposited in the subenthelial cell matrix, and (c) stored in specific granules of endothelial cells and platelets. The physiological function of VWF lies in primary haemostasis. The high molecular weight (HMW) multimers, in particular, are important for initial platelet adhesion and aggregation under shear stress and flow conditions.

VWF also functions as a carrier protein to transport FVIII molecules to the site of blood vessel injury and enables the spatio-temporal activation of FVIII. When bound in a complex, VWF protects the FVIII molecule from rapid proteolysis in plasma. Unbound FVIII is unstable and characterised by a very short half-life, resulting in very low plasma FVIII levels.

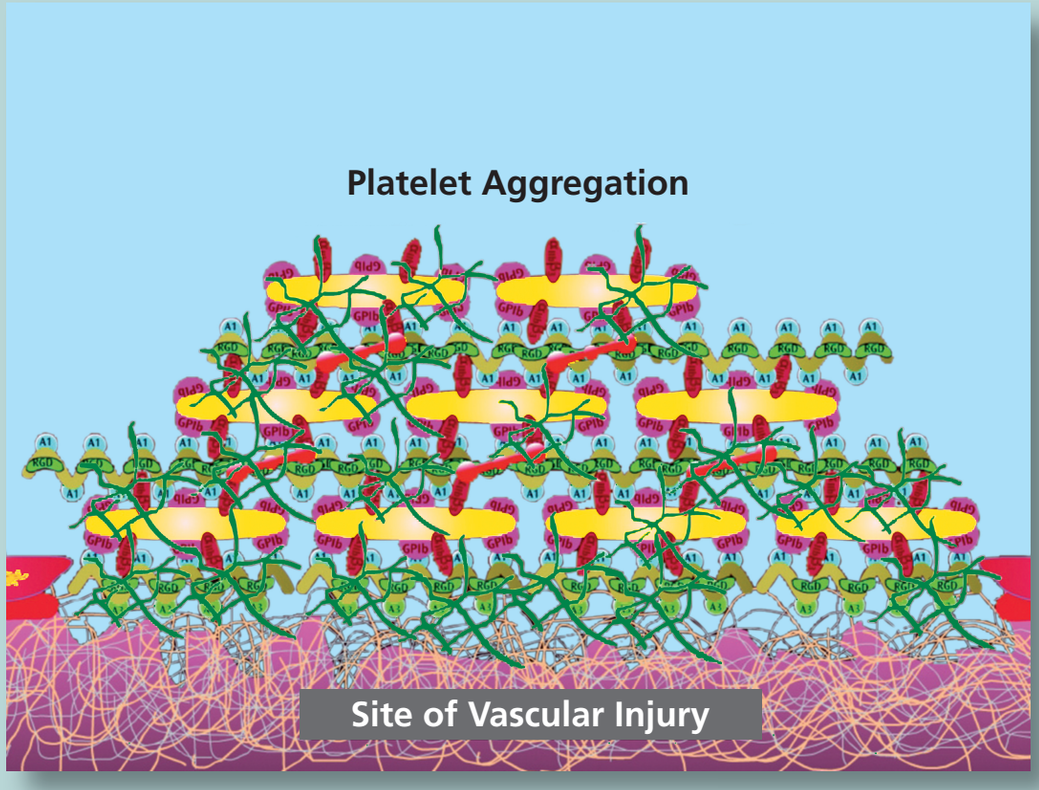
VWF, present in the vessel wall connective tissue, is essential to achieve effective primary haemostasis under dynamic conditions, but not in capillary vascular beds. It promotes initial platelet adhesion to the injured vessel wall, allowing further stabilization through contacts of activated platelets with collagen fibres and other adhesive proteins in the subendothelium.

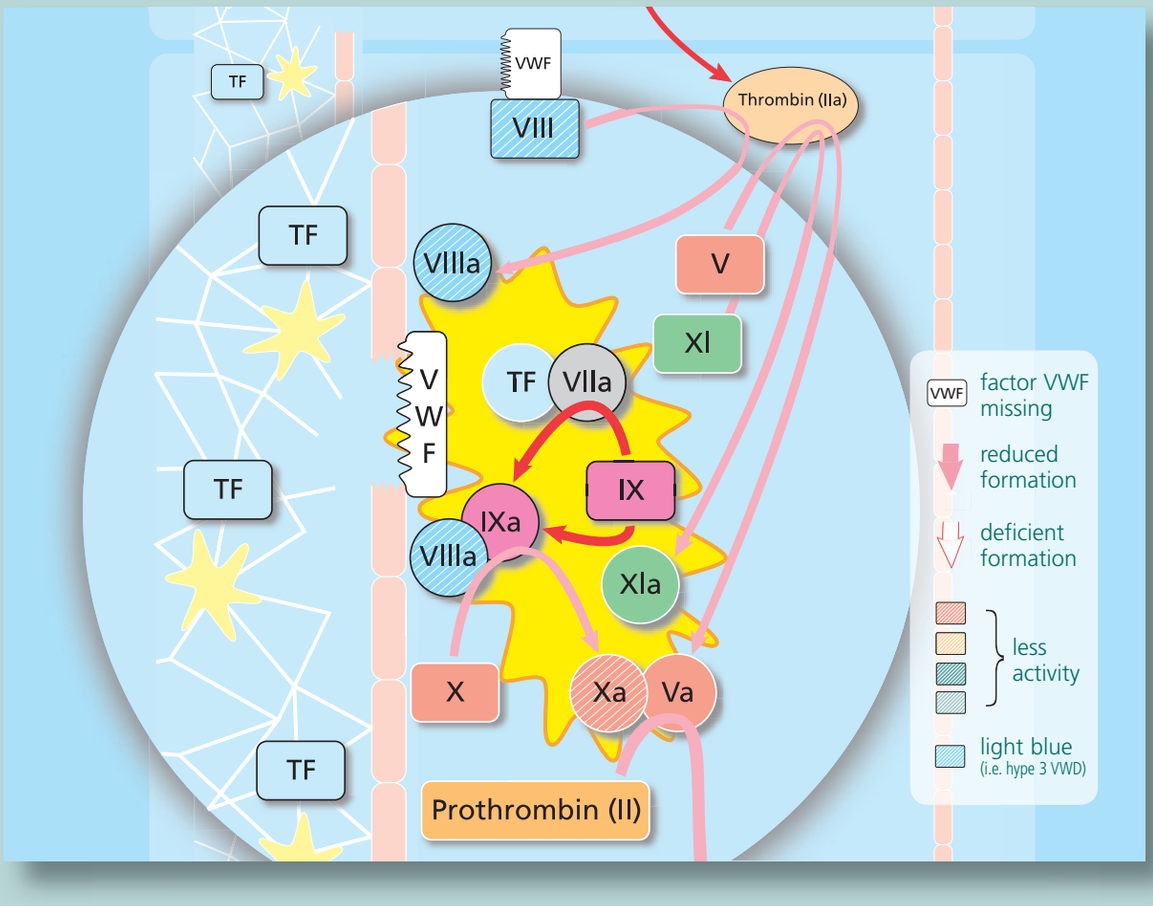
Also, platelet-to-platelet aggregation during thrombus formation (mediated primarily by fibrinogen bridges) can be reinforced by VWF.

Budde U, Drewke E, Mainusch K, Schneppenheim R. Laboratory diagnosis of congenital von Willebrand disease. Semin Thromb Hemost. 2002;28:173-190.



Formation of a haemostatic patelet plug



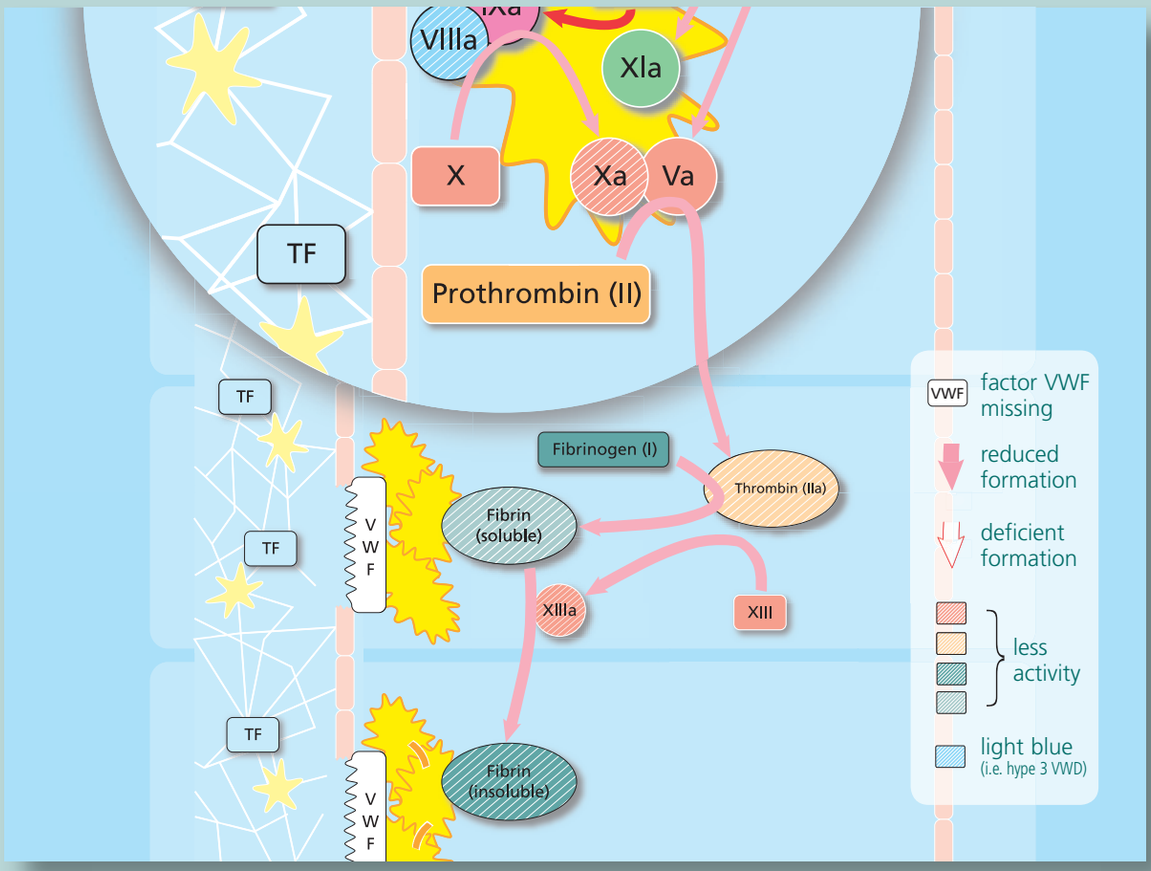


von Willebrand disease (VWD) 1/2

von Willebrand disease (VWD) is the most common bleeding disorder, affecting approximately 1% of the general population. Under normal circumstances, the vast majority of these individuals remain asymptomatic. The prevalence of VWD patients requiring regular therapy is in the same range as that of haemophilia (approximately 1:10,000 of the general population). The gene for VWF is located on the short arm of chromosome 12; mutations in the gene may lead to quantitative or qualitative defects of VWF. The mode of inheritance is mainly autosomal dominant and only occasionally autosomal recessive, affecting males and females with almost the same frequency. The clinical picture depends on the type of mutation, the level of gene expression, and the residual functional activity of the glycoprotein.

VWD is a phenotypically heterogeneous coagulopathy for which more than 20 distinct subtypes or variants of subtypes have been identified. Type 1 is the most frequent type of VWD, occurring in approximately 55–70% of diagnosed patients. The quantity of VWF is reduced in type 1 VWD, but the function of the glycoprotein is normal. Patients with VWD type 2 demonstrate qualitative defects of VWF, and many different type 2 subtypes exist. Type 3 is the most severe form of VWD, as VWF is virtually absent.

Sadler JE, Budde U, Eikenboom JC, et al. Update on the pathophysiology and classification of von Willebrand disease: a report of the Subcommittee on von Willebrand Factor. J Thromb Haemost. 2006;4:2103-2114.
Castaman G, Montgomery RR, Meschengieser SS, Haberichter SL, Woods AI, Lazzari MA. von Willebrand's disease diagnosis and laboratory issues. Haemophilia. 2010;16 Suppl 5:67-73.
Tiede A, Rand JH, Budde U, Ganser A, Federici AB. How I treat the acquired von Willebrand syndrome. Blood. 2011;117:6777-6785.



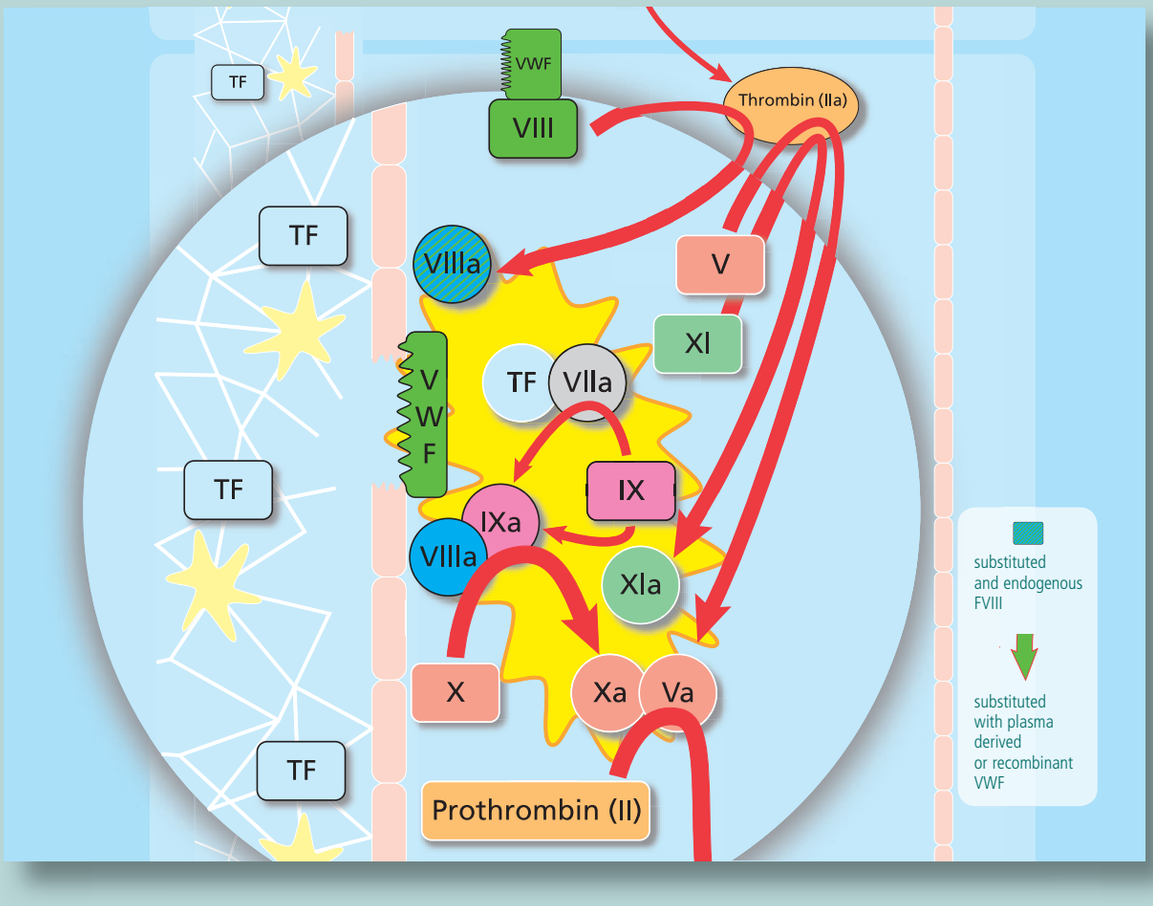
von Willebrand disease (VWD) 2/2

About 70% of patients symptomatic for VWD have milder forms of VWD, while 30% have a moderately severe to severe form. The main clinical sign of VWD is bleeding from mucocutaneous membranes. Gastrointestinal bleeding due to colonic angiodysplasia is a well-recognised complication of VWD. It occurs in VWD subtypes associated with a reduction of the haemostatically active HMW multimers of VWF. Joint bleeds also occur, but are much less frequent than in patients with haemophilia. Women tend to be clinically more affected due to menstrual bleeding, which may be intensified (hypermenorrhoea) and prolonged (menorrhagia), and painful (dysmenorrhoea).
In VWD type 1 and type 2 there may be a tendency to bleed in spite of only minimal pathological changes in laboratory parameters. In severe forms of VWD (mainly the rare type 3), patients may experience spontaneous bleeding into joints, in addition to mucosal bleeding.

The diagnosis of VWD consists of three elements:

- personal and familial history, including a detailed bleeding history, and physical examination
- laboratory investigation
- genetic testing – autosomal dominant or recessive inheritance; in de novo mutations of the VWF gene, the family history will be negative.

Lak M, Peyvandi F, Mannucci PM. Clinical manifestations and complications of childbirth and replacement therapy in 385 Iranian patients with type 3 von Willebrand disease. Br J Haematol 2000;111:1236-1239.
Makris M. Gastrointestinal bleeding in von Willebrand disease. Thromb Res 2006;118:13-17.



Treatment approaches for von Willebrand disease 1/2

Due to the multiple interactions of VWF with platelets, endothelial cells, and coagulation proteins, VWD might be considered a more complex disease than haemophilia. Optimal management of VWD requires more than prevention or treatment of acute bleeding. Severe cases, especially, should be managed by multidisciplinary teams in comprehensive care centres. The centre should have access to a coagulation laboratory and blood bank, and be able to diagnose and classify VWD. Appropriate factor concentrates as well as desmopressin (1-deamino-8-D-arginine vasopressin; DDAVP) to induce release of VWF from endothelail cells should also be available.

Treatment approaches for von Willebrand disease 2/2

Any therapy of VWD aims at increasing or supplementing the missing proteins, either prophylactically or on-demand at the time of bleeding. As VWD is a complex disease with a broad variety of genetic defects and clinical severity, a wide range of therapeutic measures other than substitution of plasma-derived VWF/FVIII concentrate may be implemented. These measures include hormones, antifibrinolytic treatments, or DDAVP. DDAVP should be the first treatment option in all mild forms of VWD, but, in the case of insufficient response or existing contraindications to DDAVP, therapy with a VWF/FVIII concentrate is the treatment of choice.

Mannucci PM. Treatment of von Willebrand's Disease. N Engl J Med 2004;351:683-694.
Federici AB. Management of inherited von Willebrand disease in 2006. Semin Thromb Hemost 2006;32:616-620.

Adjunctive Therapies

Desmopressin

Desmopressin acetate (DDAVP) was developed as a synthetic analogue of vasopressin/ADH (antidiuretic hormone), modified to reduce its pressor (blood pressure increasing) activity. DDAVP was found to increase VWF activity (expressed as ristocetin cofactor activity; VWF:RCo) and FVIII activity (expressed as FVIII:C; otherwise known as FVIII-coagulant) in normal individuals, and in patients with mild to moderate VWD or mild haemophilia A. Since DDAVP releases VWF from endothelial storage sites (designated Weibel-Palade bodies), it is used primarily to treat patients with mild type 1 and type 2 VWD, while patients with more severe forms of VWD either do not respond or the response is insufficient. DDAVP may be administered subcutaneously, intravenously, or nasally for the treatment of mild to moderate VWD and mild haemophilia A.

Hormones

In women, it has been shown that VWF activity and FVIII activity both increase after administration of oestrogens. Oestrogen–progesterone oral contraceptive pills, vaginal rings, or intrauterine devices releasing these hormones, may be sufficient to control mild menorrhagia.

Antifibrinolytics

Aminocaproic acid and tranexamic acid interfere with the lysis of newly formed clots by saturating the binding sites on plasminogen and t-PA, thereby preventing their attachment to fibrin and making plasminogen unavailable within the forming clot. Antifibrinolytics given locally or systemically are often used to control mouth or nose bleeding, bleeding following dental extractions, and menorrhagia. Antifibrinolytics may be combined with DDAVP or clotting factor concentrates.

Local procedures

In milder forms of VWD, when DDAVP cannot be used, and especially in dentistry (e.g., tooth extraction), fibrin sealant, oral aminocaproic acid, tranexamic acid either via intravenous administration or as a haemostatic mouthwash, may be effective alternatives to factor concentrate substitution.

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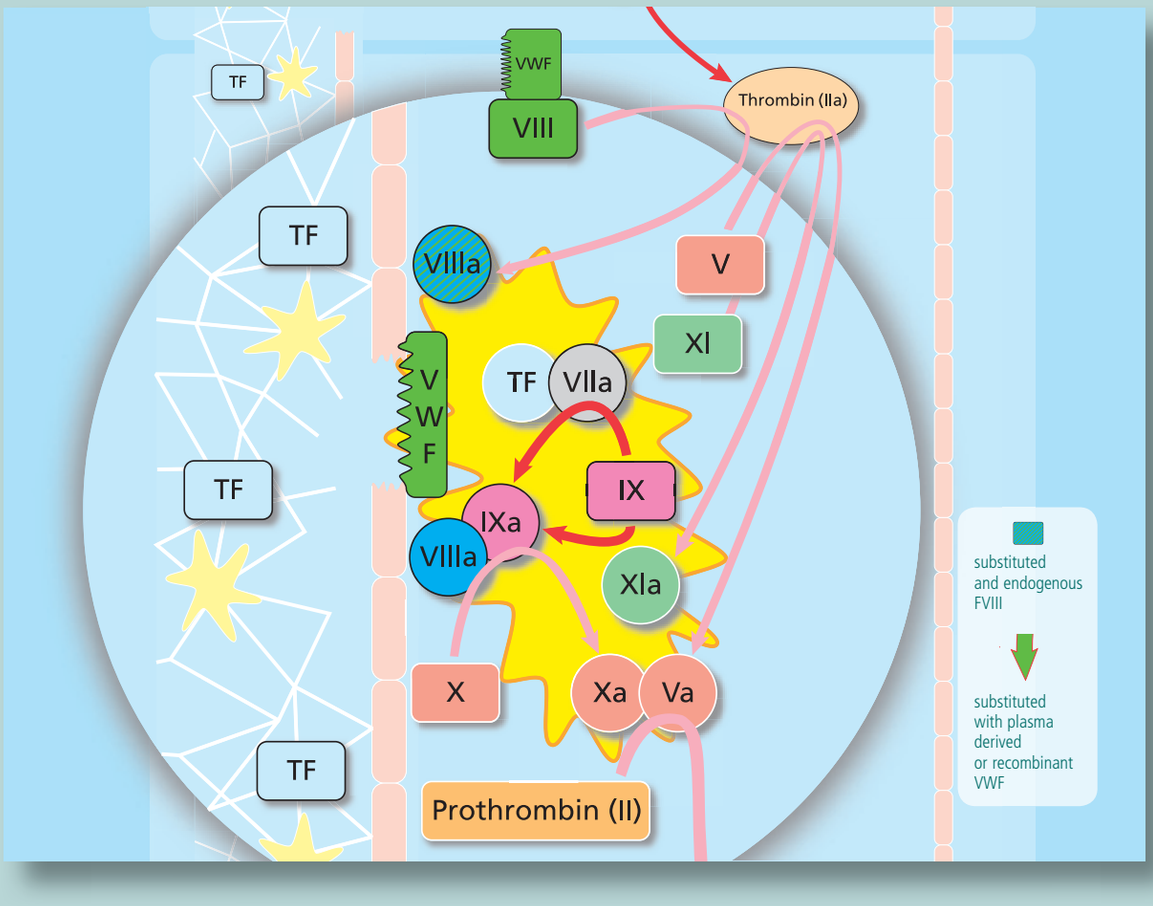

Supplementation of von Willebrand factor and factor VIII 1/3

Cryoprecipitate contains VWF along with FVIII, in addition to some factor XIII and fibrinogen. It is produced from screened donor plasma, but is rarely subjected to any virus elimination or inactivation process. Once cryoprecipitate was found to contain the VWF/FVIII complex, it was used to treat patients with VWD and haemophilia A. However, the VWF in both cryoprecipitate and the early FVIII concentrates undergo proteolysis, resulting in loss of some of the HMW VWF multimers, which are clinically most effective. As a result, clinical efficacy was often poor and treatment failures occurred. Today, cryoprecipitate is no longer the first choice, but is still used in some countries.

The first choice for treatment and prophylaxis of DDAVP-unresponsive VWD-patients are virus-inactivated VWF/FVIII concentrates containing high amounts of VWF with a multimer distribution as close to normal plasma as possible.

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Supplementation of von Willebrand factor and factor VIII 2/3

On-demand therapy and short-term prophylaxis

Different factor supplementation programmes are used for VWD substitution: 'On-demand' schemes in cases of bleeding, or prophylaxis schemes to prevent bleeding and its complications. Supervised self-infusion may be possible if the patient is taught and monitored by an experienced treatment centre. Because of the relatively small number of patients on prophylaxis, large clinical outcome studies on the prophylactic use of VWF/FVIII concentrate are not yet available.

VWF/FVIII concentrates are indicated in type 3 VWD, type 2B (as DDAVP can precipitate transient thrombocytopenia), and in all patients with type 1 and type 2 VWD, who are not responsive to DDAVP or who may have contraindications to its use, such as low or high age, hyponatraemia, and renal impairment. Although the minimal VWF activity level to maintain sufficient haemostasis in VWD has not yet been determined in prospective studies, preliminary retrospective data suggest that VWF:RCo levels >0.30 IU/ml (30%) are associated with a low incidence of spontaneous mucosal bleeding.

Supplementation of von Willebrand factor and factor VIII 3/3

Prophylaxis of bleeding in von Willebrand disease

Some patients with severe VWD (mostly type 3) have recurrent episodes of mucosal or joint bleeding that are similar to those seen in haemophilia. These bleeds can hamper daily activities, and can lead to joint impairment (arthropathy). Arthropathy has also been reported in patients with VWD type 2N (in which the VWF/FVIII complex cannot be formed), particularly if the FVIII activity is <10%, and in severe type 1 VWD, where the VWF/FVIII:C level may also be quite low. Persistent bleeding into joints can result in pain, joint degeneration, swelling, and reduced range of motion. In this situation, prophylaxis is recommended. However, little retrospective or prospective data on secondary long-term prophylaxis in VWD are available. The guidance for prophylactic regimens in VWD is, therefore, based upon prophylaxis in haemophilia. Prophylaxis reduces the days in hospital and the need for transfusion.

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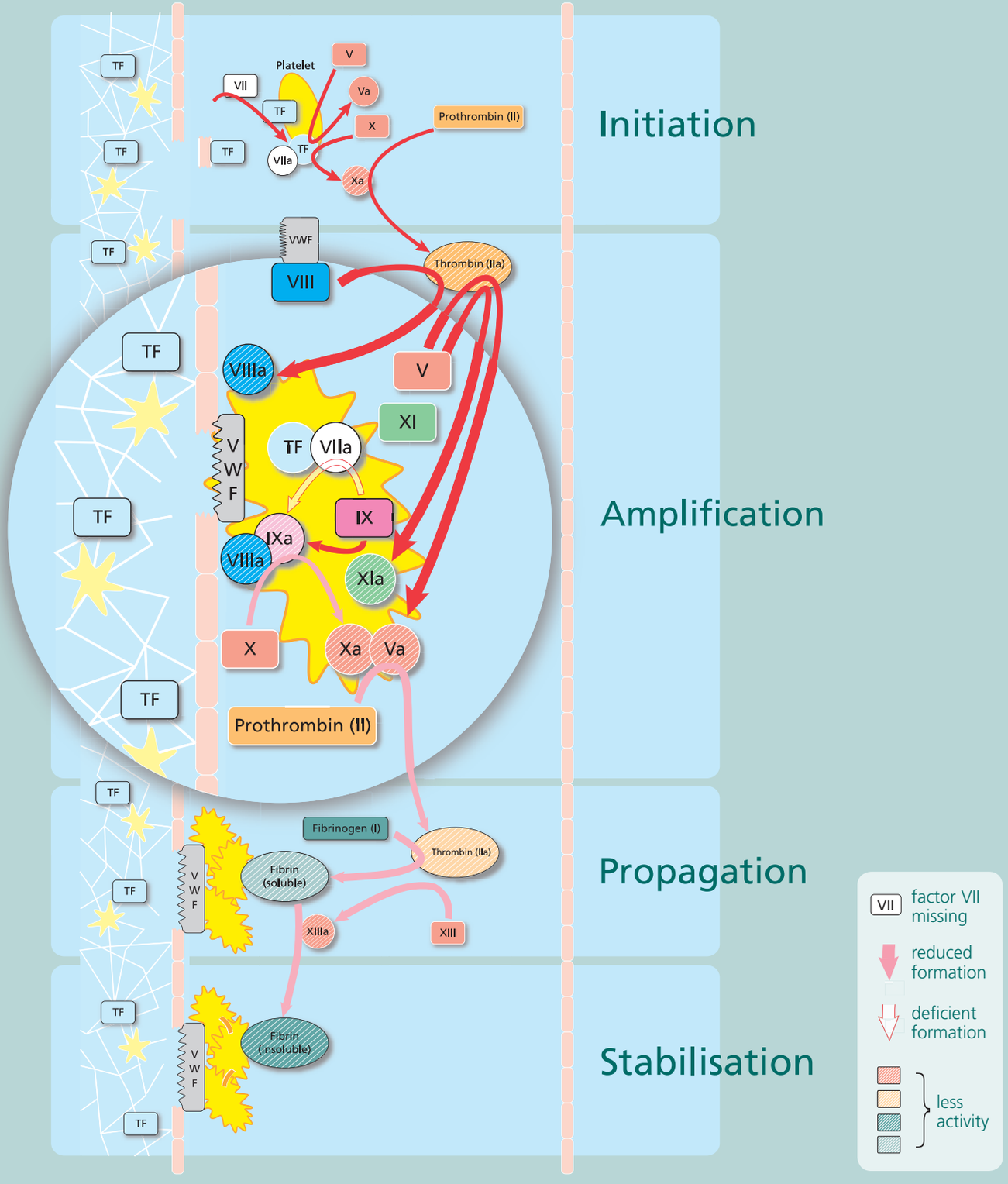
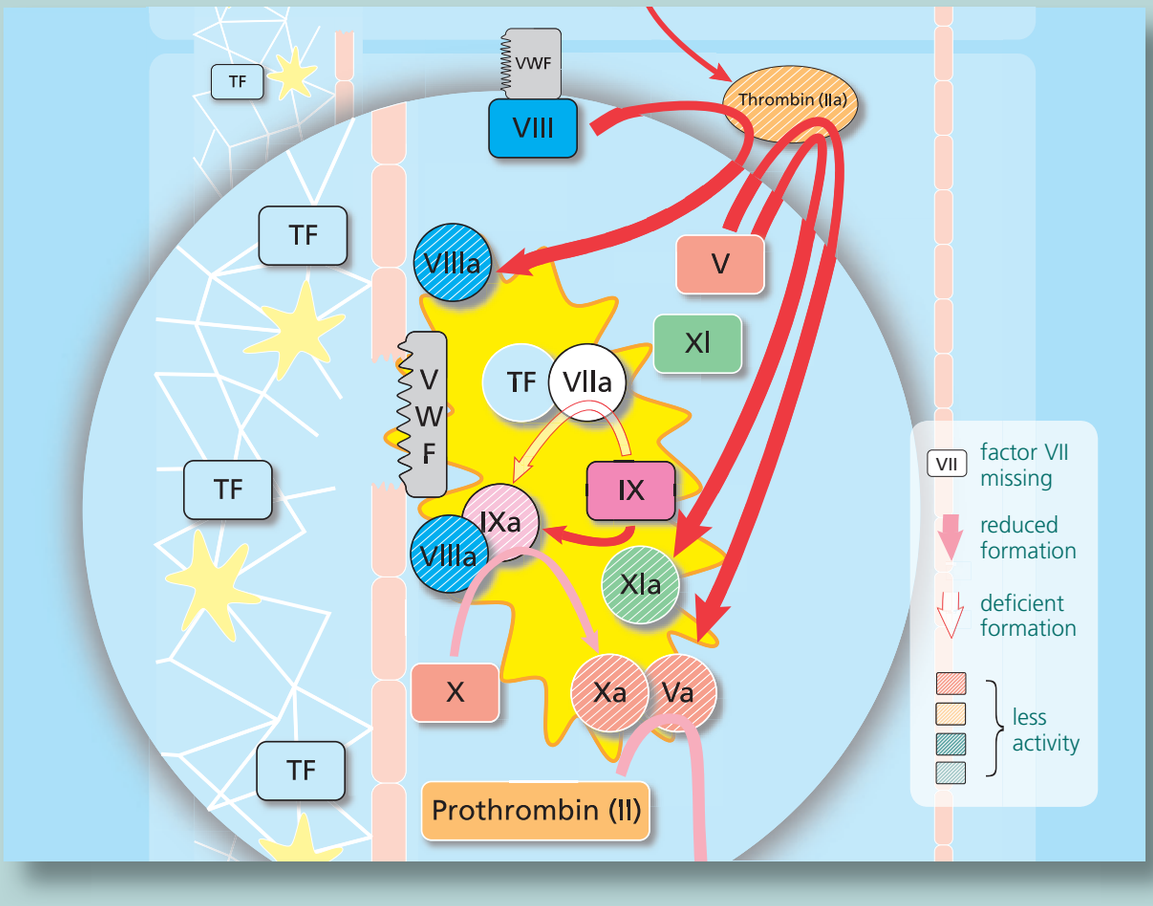
Factor VII deficiency

Disorders, treatment approaches, and CSL Behring products





Physiology of Factor VII

Factor VII (FVII) is one of the vitamin K-dependent coagulation factors (including factors II, VII, IX and X), that is contained in the prothrombin complex concentrate and is synthesised in the liver. It is a serine protease zymogen, and has a half life of 3–4 hours. When the vascular endothelium is damaged, the tissue factor (TF) in the deeper cell layers of the vessel wall (expressed on smooth muscle cells and fibroblasts) is exposed and binds to activated FVII (FVIIa), which normally circulates in minimal amounts, as well as to FVII, stimulating further conversion of FVII to FVIIa. The formation of the TF/FVIIa complex also causes rapid activation of factor X (FX) and (if available in larger quantities) of factor IX (FIX). The formation of the TF/FVIIa complex is, therefore, regarded as the initiating event of the in vivo coagulation cascade.

Disorders of Factor VII 1/2

Acquired factor VII deficiency

Acquired deficiency of FVII can occur following the use of coumarin oral anticoagulants (coumarins) such as warfarin, in the context of acquired deficiency of other vitamin K-dependent coagulation factors (FII, FIX and FX). Factors II, VII, IX, and X require carboxylation in the presence of vitamin K for their biological activity. Coumarins inhibit the vitamin K conversion cycle, and hence the production of functionally intact, calcium-binding coagulation factors. Other drugs associated with acquired FVII deficiency include cephalosporin and penicillin antibiotics. In addition, spontaneous acquired factor VII deficiency has been reported in myeloma, sepsis, and aplastic anaemia.

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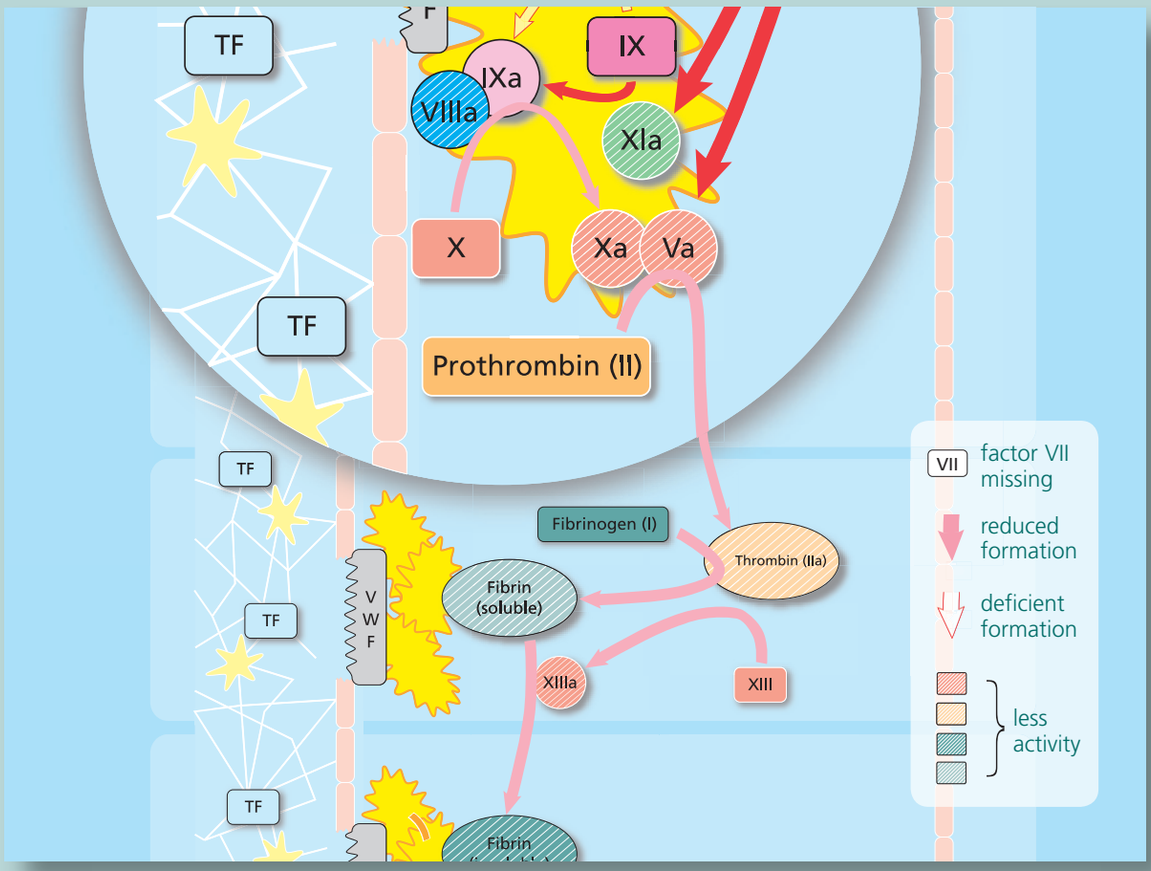

Disorders of Factor VII 2/2

Congenital factor VII deficiency

Congenital FVII deficiency has an incidence of one symptomatic individual per 500,000. It is also known as Alexander's disease. Clinical presentation of congenital FVII deficiency ranges from minor bleeding to severe and life-threatening haemorrhage, such as intracerebral or gastrointestinal bleeding. Symptom manifestations correlate poorly with FVII clotting levels, women tend to be more affected than men, and first presentation is often excessive surgical bleeding in previously undiagnosed individuals.

Laboratory diagnosis is based on the characteristic feature of an isolated, prolonged prothrombin time (PT).

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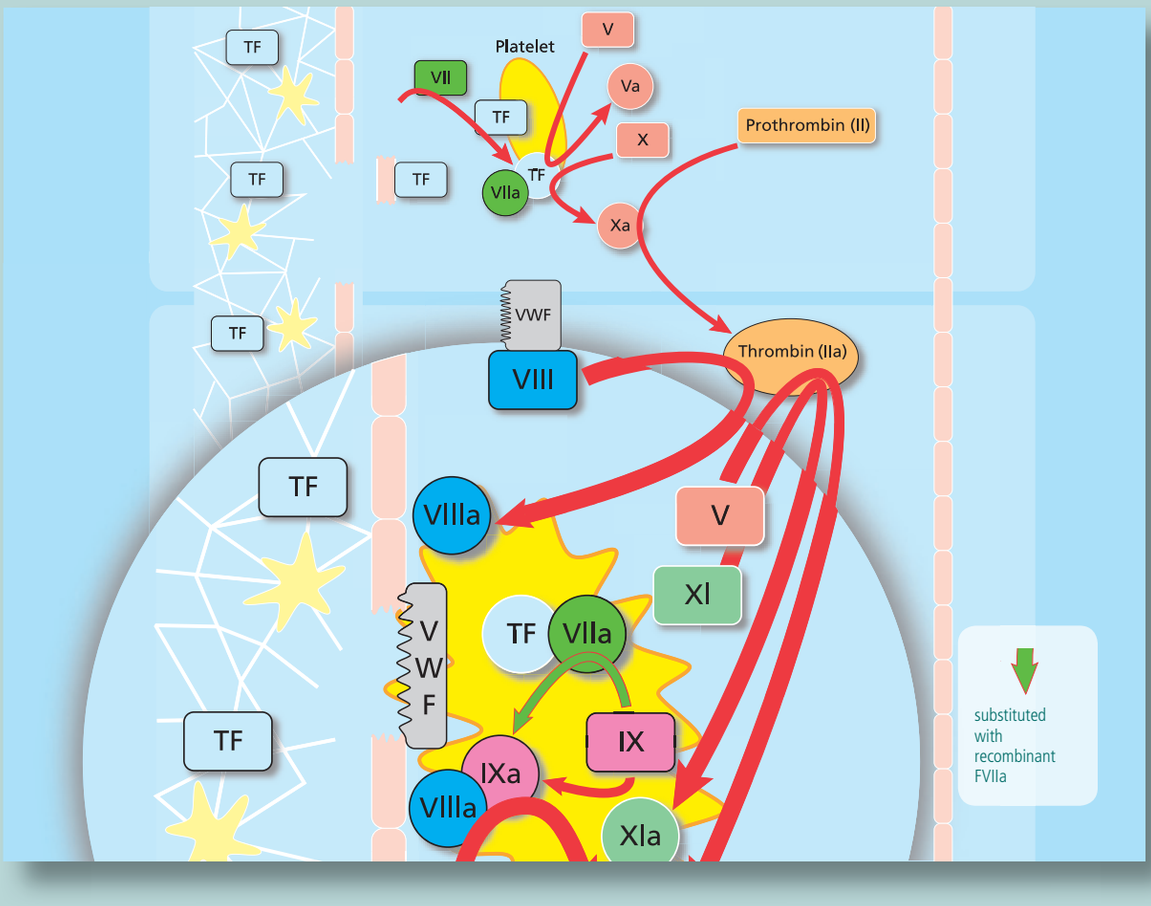

Treatment approaches for Factor VII deficiency 1/2

For both acquired and congenital FVII deficiency, the mainstay of treatment is FVII substitution therapy. Products employed in FVII substitution are fresh frozen plasma (FFP), prothrombin complex concentrate (PCC), plasma-derived FVII (pdFVII), and recombinant activated FVII (rFVIIa).

FFP is readily available, but its effectiveness is limited and its use carries a significant risk of circulatory overload. PCC contains all four vitamin K-dependent coagulation factors (II, VII, IX and X); both PCC and FFP can be associated with a risk of thrombotic events, as factors which the patients themselves can replenish are also supplied. PCC would be the treatment of choice for acquired FVII deficiency associated with, for example, coumarin anticoagulant use, as all coagulation factors require replacement in this situation.

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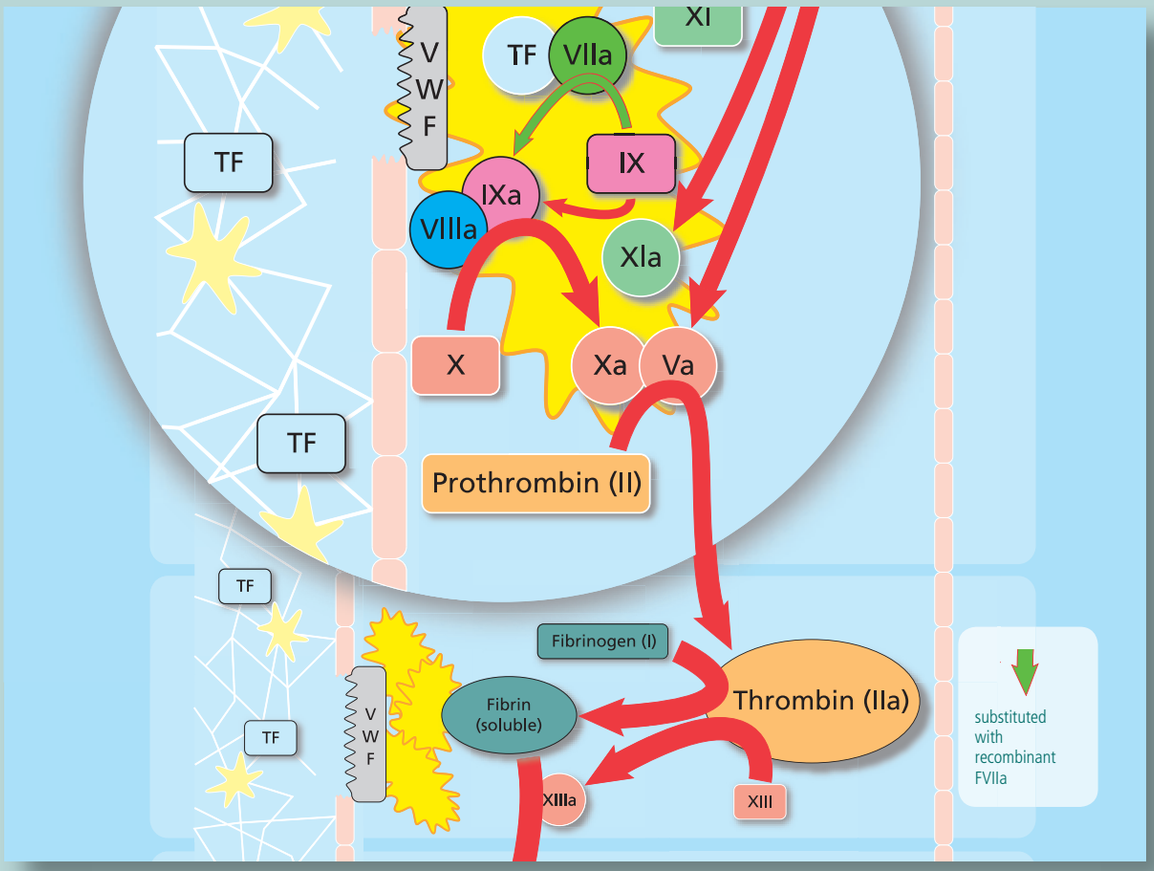

Treatment approaches for Factor VII deficiency 2/2

Recombinant FVIIa (rFVIIa) is used and licensed in FVII deficiency, haemophilia A and B, when the development of inhibitors causes severe bleeding or poses patients at an increased bleeding risk. In addition, rFVIIa has been approved in Glanzmann disease. Although positive reports exist for rFVIIa in acquired bleeding conditions, e.g., trauma or intracranial haemorrhage, efficacy of rFVIIa has not yet been established in indications other than haemophilia or Glanzmann disease.

Antifibrinolytics, including aminocaproic acid and tranexamic acid, interfere with the lysis of newly formed clots by saturating the binding sites on plasminogen, thereby preventing its attachment to fibrin and making plasminogen unavailable within the forming clot. They can be used for prophylaxis in minor surgical (e.g., dental) procedures in usually asymptomatic patients.

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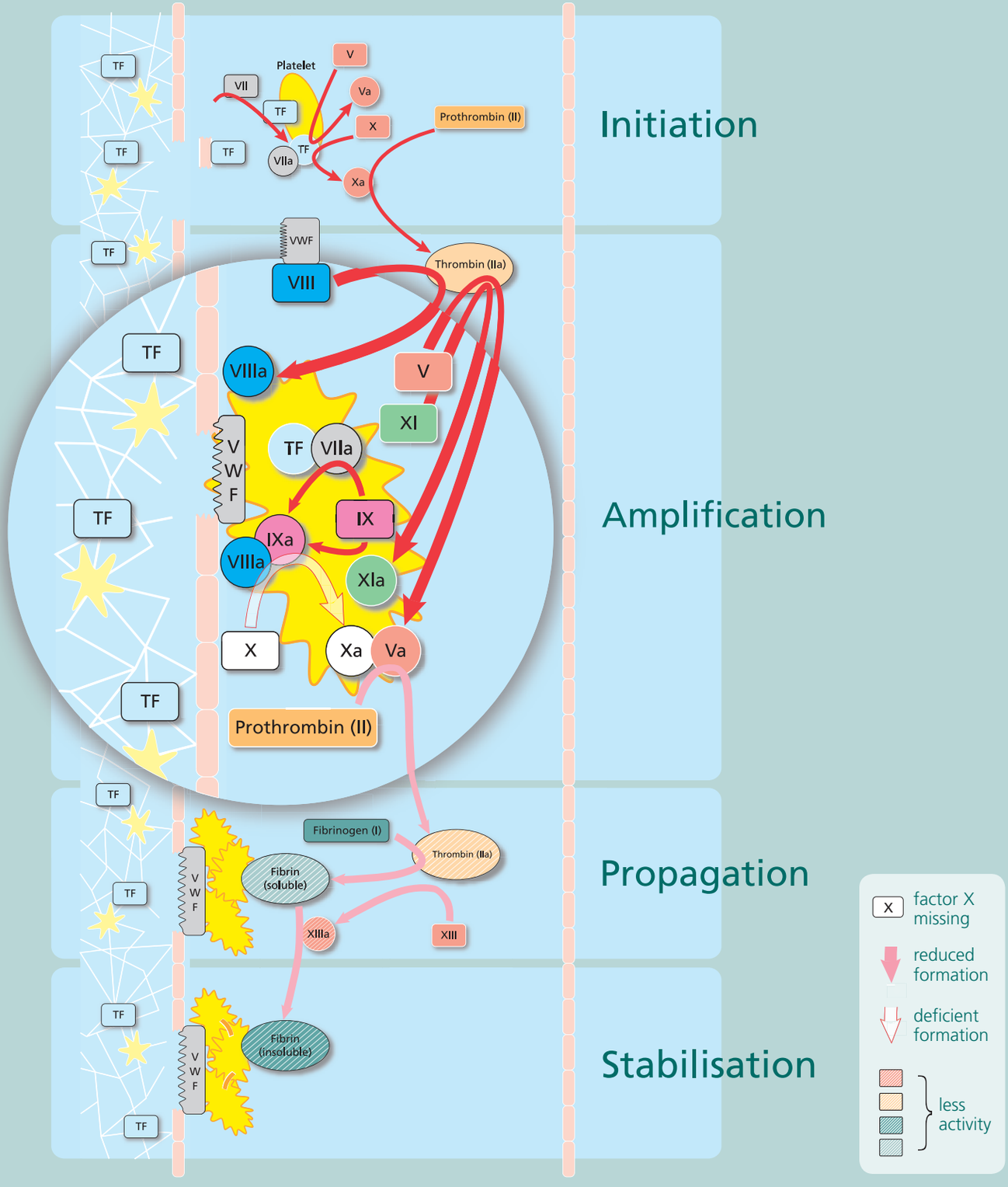
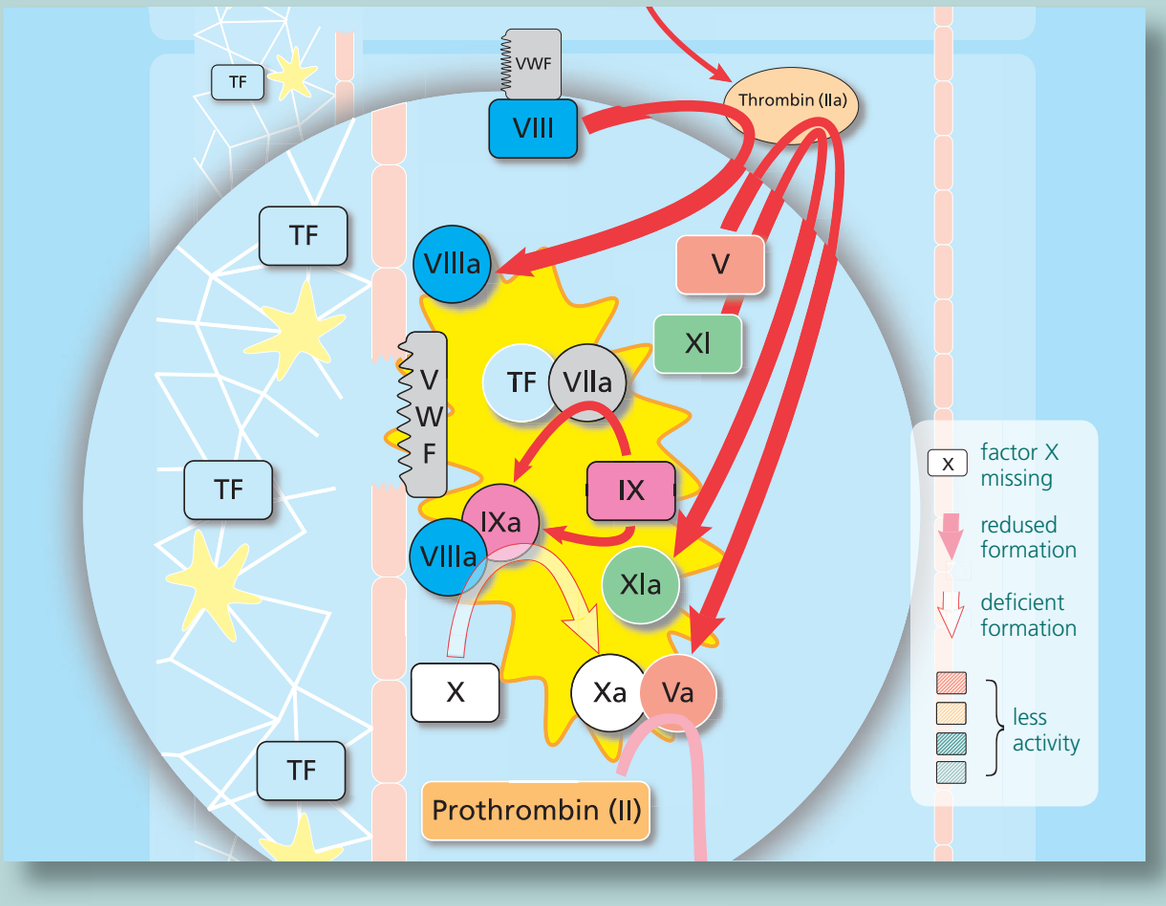
Factor X deficiency

Disorders, treatment approaches, and CSL Behring products





Physiology of Factor X

Factor X (FX) is one of the vitamin K-dependent coagulation factors produced by the liver that occupies a central role in the coagulation cascade. FX is activated either by the tissue factor/factor VIIa (TF/FVIIa) complex in the initiation phase of blood coagulation or by factor IXa (FIXa), together with factor VIIIa (FVIIIa) as an accelerator in the amplification/production phase.
Activated FX (FXa) in association with activated FV (FVa), which also acts as an accelerator, form the prothrombinase complex, leading to conversion of prothrombin to thrombin. Thrombin then promotes thrombus formation by activating platelets and converting fibrinogen to fibrin.

FXa is the most important activator of prothrombin. In addition, it has some power to cleave FV and FVIII to produce FVa and FVIIIa. To regulate the activity of FXa, antithrombin forms a stable inactive complex with FXa which is then removed from the circulation by the liver. Another inhibitor for FXa in the initiation phase of blood coagulation is the tissue factor pathway inhibitor that also serves as inhibitor for FVIIa, as well as the protein Z/protein Z inhibitor complex.

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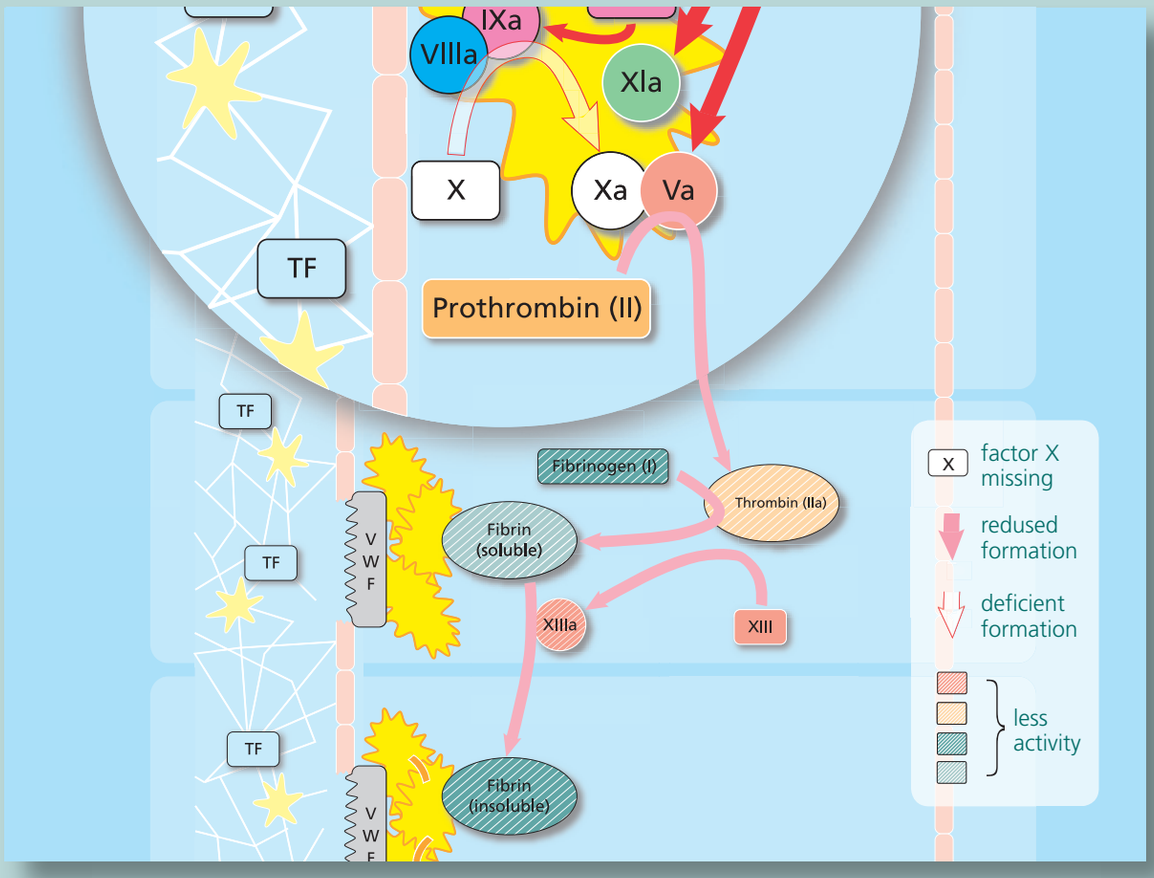

Factor X deficiency 1/3

Determination of the functional levels of FX can be performed by the following assays: prothrombin time (PT) and activated partial thromboplastin time (aPTT), Russell viper venom assay, and chromogenic assays. Due to the heterogeneous nature of congenital FX deficiencies, all assays are required for detailed protein characterisation.

Congenital factor X deficiency

Congenital FX deficiency is a rare haemorrhagic condition, characterised by autosomal recessive inheritance and variable severity. The incidence of homozygotes in the general population is 1:1,000,000. Heterozygous deficiency manifests with an incidence of approximately 1:500, but is usually clinically asymptomatic. Even so, some heterozygotes do have a significant bleeding tendency.

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Factor X deficiency 2/3

Most individuals affected by congenital FX deficiency have low but measurable levels of FX activity. However, clinical phenotype correlates poorly with laboratory phenotype, and FX coagulation activity cannot be used to classify clinical severity.

Patients with FX deficiency may present with any symptom also observed in less rare coagulation disorders, such as haemophilia A or B. Bleeding can occur at any age with, for example, perinatal intracranial haemorrhage, umbilical stump bleeding, joint and muscle bleeding, or severe postoperative haemorrhage. Patients who are only mildly affected may experience easy bruising or menorrhagia.

Factor X deficiency 3/3

Acquired factor X deficiency
Conditions which can cause an acquired FX deficiency, leading to an increased frequency of bleeding, include:

- Liver disease/vitamin K deficiency – Since FX is produced by the liver as a vitamin K-dependent coagulation factor, deficiency of vitamin K and hepatocellular damage can cause a deficiency of FX. In both cases, the situation is usually accompanied by deficiencies of other coagulation factors.
- Amyloidosis – A deficiency of FX can occur in primary amyloidosis. FX adsorbs onto amyloid fibrils and thus has a shortened half-life in plasma. Therapeutic options, such as substitution of the missing factor, are often ineffective due to rapid removal of FX from the circulation.
- Tumours – Some tumours have been reported to be associated with FX deficiency, e.g., gastric carcinoma, renal/adrenal carcinoma, and acute non-lymphoblastic leukaemia.

Other causes of acquired FX deficiency can be infections, myeloma, and certain drugs.

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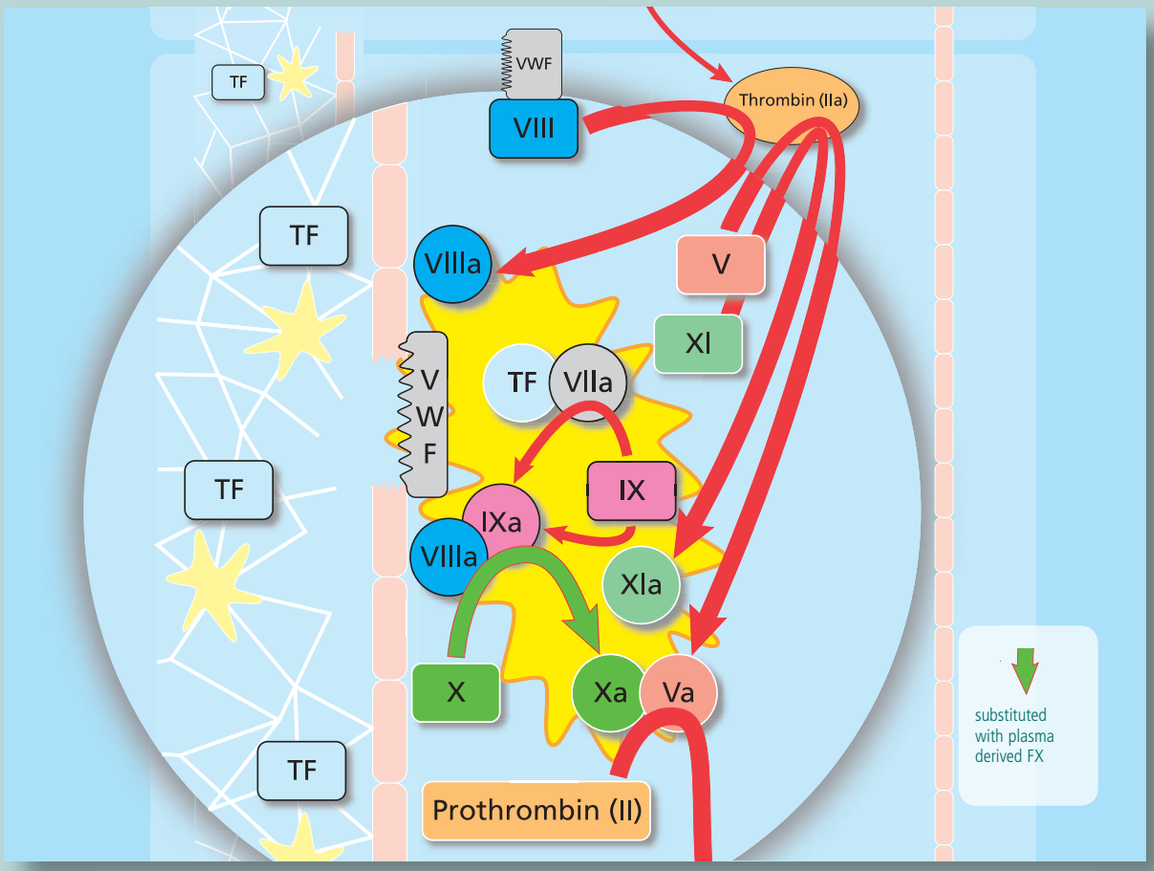

Treatment approaches for Factor X deficiency

Treatment approaches for patients with FX deficiency include administration of fresh-frozen plasma (FFP), or of prothrombin complex concentrates (PCC) that contain and therefore replace FX. However, these treatments are associated with the risk of volume overload or viral transmission in the case of FFP, a non-standardised range of FX content, and potentially with thromboembolism due to the substitution of other (activated) coagulation factors of which the patient has normal levels. The alternative to FFP and PCC is replacement of deficient FX with FX concentrate.

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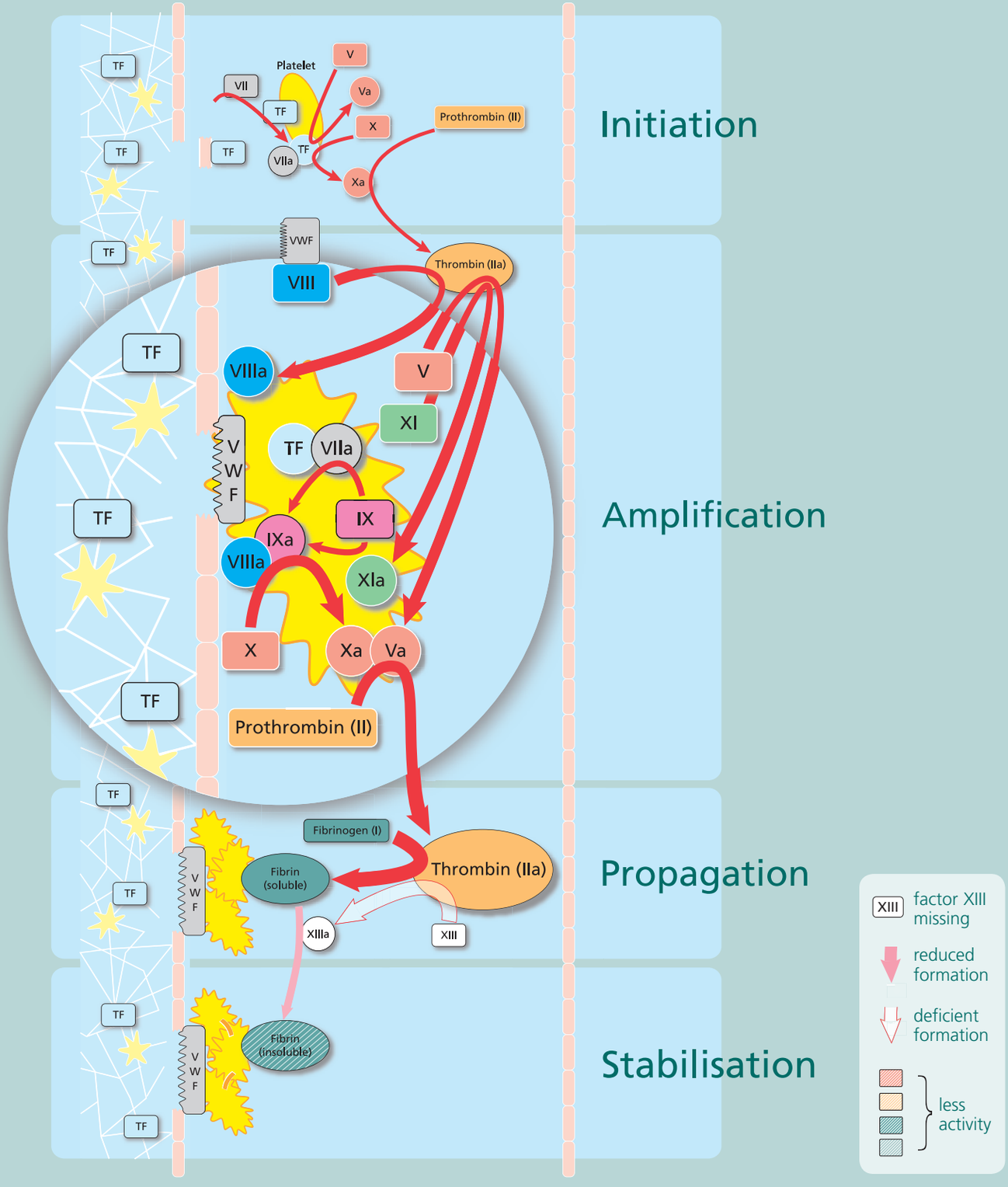
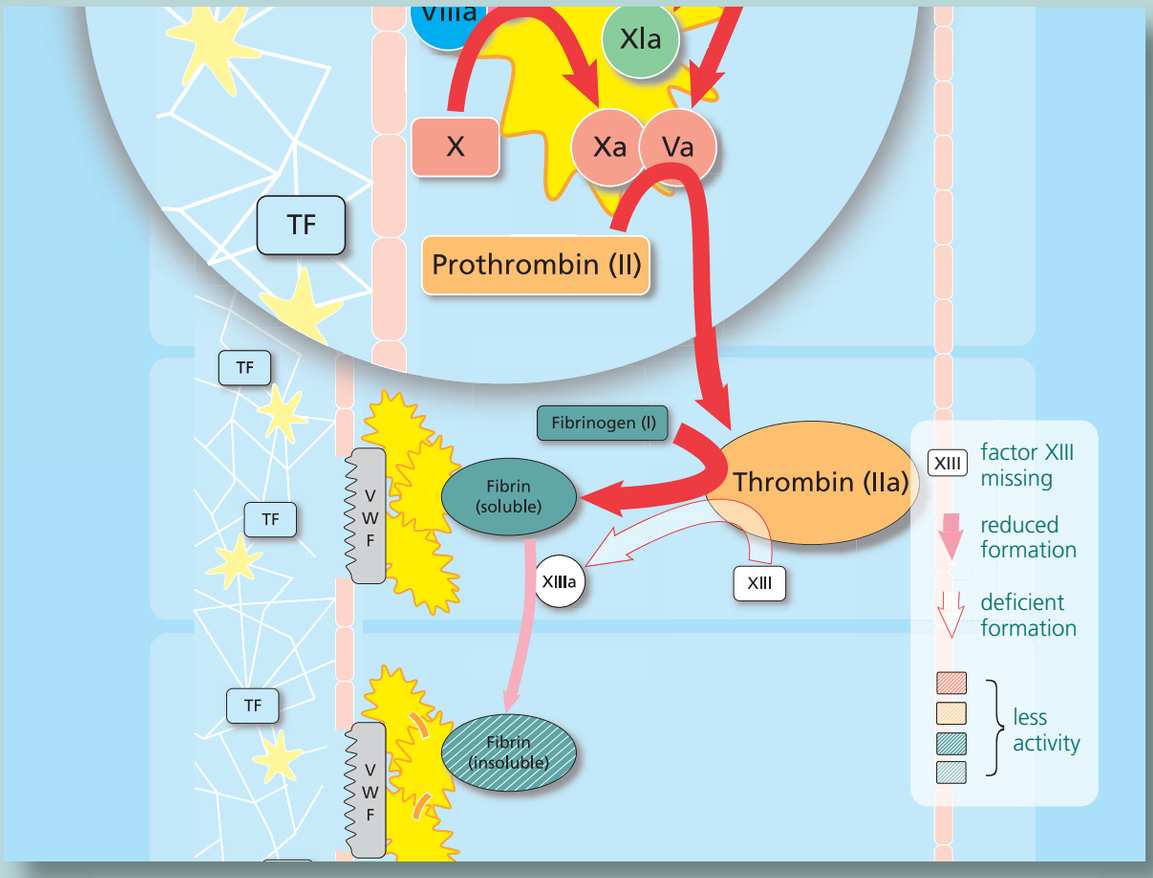
Factor XIII deficiency

Disorders, treatment approaches, and CSL Behring products





Physiology of Factor XIII

Coagulation factor XIII (FXIII), otherwise known as fibrin stabilising factor, plays an important role in haemostasis and wound healing. As a transglutaminase, it stabilises fibrin, incorporates α2-antiplasmin into fibrin, and thereby reduces initial fibrinolytic activity. FXIII also stimulates proliferation of fibroblasts, their adhesion to the fibrin threads, and their migration into the fibrin clot as well as prevents edema formation and stabilizes wound healing.

Activation of FXIII (to FXIIIa) requires proteolytic modification by thrombin, and conformational alteration by calcium ions. FXIIIa is an α-lysine transferase containing an α-chain synthesised in megakaryocytes, and a β-chain synthesised in the liver.

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Congenital factor XIII deficiency

The rare congenital FXIII deficiency is inherited as an autosomal recessive disorder. Approximately 200 cases have been documented worldwide since the first report of congenital FXIII deficiency appeared in 1960, corresponding to an incidence of approximately one in 3–5 million people. Haemorrhagic states are encountered mainly in homozygotes; heterozygotes usually have sufficient FXIII activity to ensure haemostasis under normal conditions. In line with the identification of more than 60 FXIII gene mutations, clinical presentation of congenital FXIII deficiency is highly heterogeneous. Clinical manifestations include:

- umbilical cord haemorrhage in the first 2 weeks of life
- haematomas, bruises and ecchymoses after trauma
- intracranial haemorrhage – may be prominent in childhood
- abnormal scar formation and defective wound healing
- habitual abortion
- intra-abdominal haemorrhage from the corpus luteum
- postoperative haemorrhage
- poor wound healing.

In individuals unaffected by coagulation disorders, FXIII activity is normally found in the range of 50–220%. It has been shown that plasma levels between 5–30% are sufficient to prevent spontaneous bleeding.

Diagnosis based on standard coagulation profile testing is difficult, as parameters such as prothrombin time (PT), activated partial thromboplastin time (aPTT), and platelet count are usually normal. However, abnormal clot solubility of 1% or less appears to correlate well with the characteristic umbilical bleeding seen after birth.

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Acquired factor XIII deficiency
One or more of the following components may be involved in the pathogenesis of an acquired FXIII deficiency:

- impaired synthesis of FXIII, e.g., due to liver failure
- loss by excessive bleeding or dilution, due to massive transfusion
- enhanced utilisation and depletion (consumption) by intra- or extravasal processes involving cross-linking of coagulation and matrix proteins
- enhanced unspecific proteolysis by enzymes such as elastase released from neutrophil granulocytes due to inflammatory processes.

Disorders of Factor XIII 2/3

An acquired reduction of plasma FXIII has been found in diseases of quite different aetiology including:

- leukaemia
- severe liver disease
- disseminated intravascular coagulation (DIC)
- inflammatory bowel disease
- connective tissue diseases.

The FXIII deficiency in such conditions is usually caused by an autoantibody which binds to, and interferes with, the normal function of the FXIII. Such inhibitors can also develop in response to certain medications, including penicillin. Presentation tends to be in middle-aged to elderly patients with spontaneous or post-traumatic deep haematomas.

Disorders of Factor XIII 3/3

Acute phases of leukaemia are frequently associated with haemorrhagic episodes. It has been found that elastase-like granulocytic proteases induce degradation of isolated coagulation factors, including FXIII. FXIII seems to be particularly susceptible to proteolysis, and plasma FXIII levels in leukaemic patients tend to fall below 50%. More than half of patients with acute leukaemia suffer from a decrease of FXIII. This leads to defective fibrin stabilisation and to an increase of fibrin split products which is not related to plasmin-induced fibrinolytic activity. Fibrinogen levels, however, appear to be within the normal range, or even elevated.

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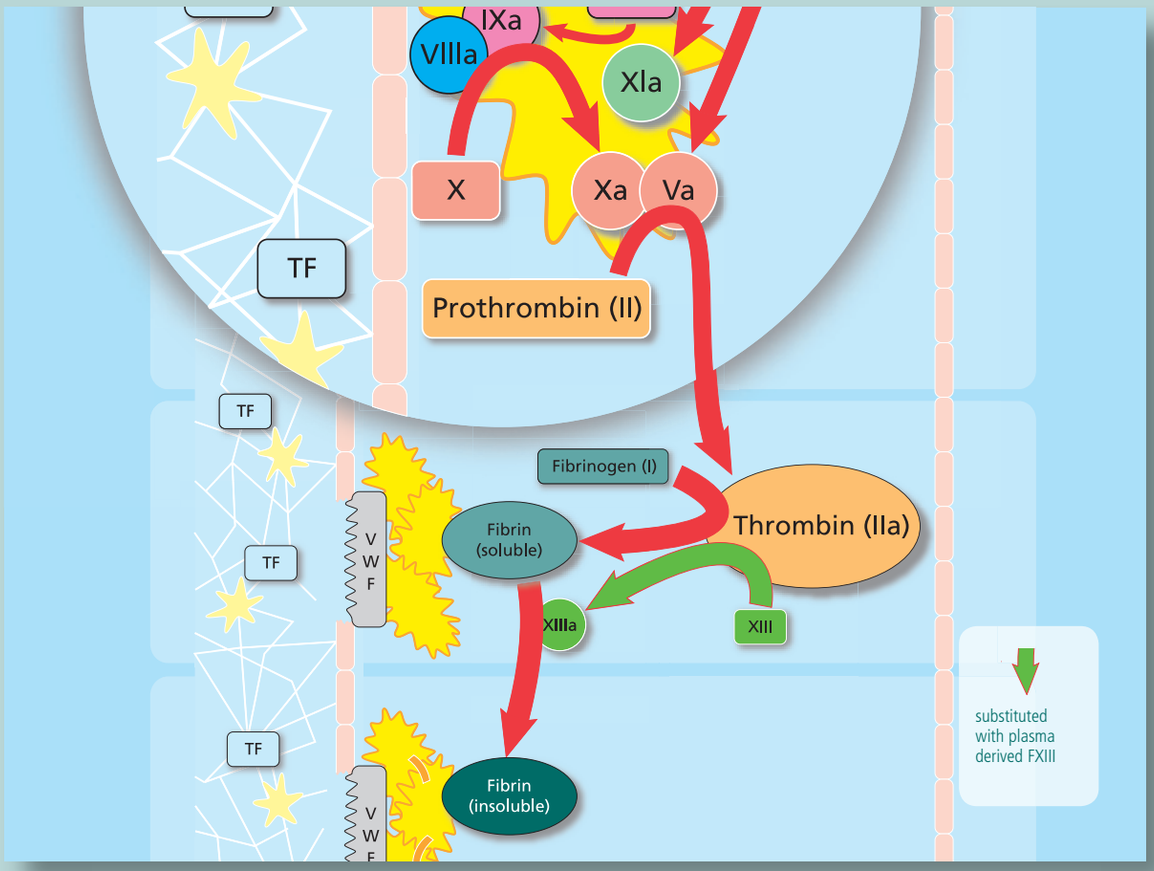

Treatment approaches for Factor XIII deficiency

Ideally, any therapy used in the prophylaxis and treatment of bleeding in FXIII deficiency will restore FXIII activity levels to normal or near-normal. Traditionally, fresh frozen plasma (FFP) and cryoprecipitate have been used for the treatment of FXIII deficiency. Due to the long half-life of FXIII (5–11 days), it is possible to administer prophylactic FFP once every 4–6 weeks, or prophylactic cryoprecipitate once every 3–4 weeks. FFP and cryoprecipitate can also be used as on-demand therapy for acute and recurrent bleeding.

More recently, use of plasma-derived FXIII (pdFXIII) concentrate has become increasingly available worldwide, and the majority of FXIII-deficient patients in the US are treated with this product. The heterogeneity of patient characteristics means that doses and treatment regimens need to be similarly diverse, with most programmes based on individual patient pharmacokinetics. The half-life of pdFXIII is the same as endogenous FXIII, therefore it can be administered for prophylaxis once every 4–6 weeks.

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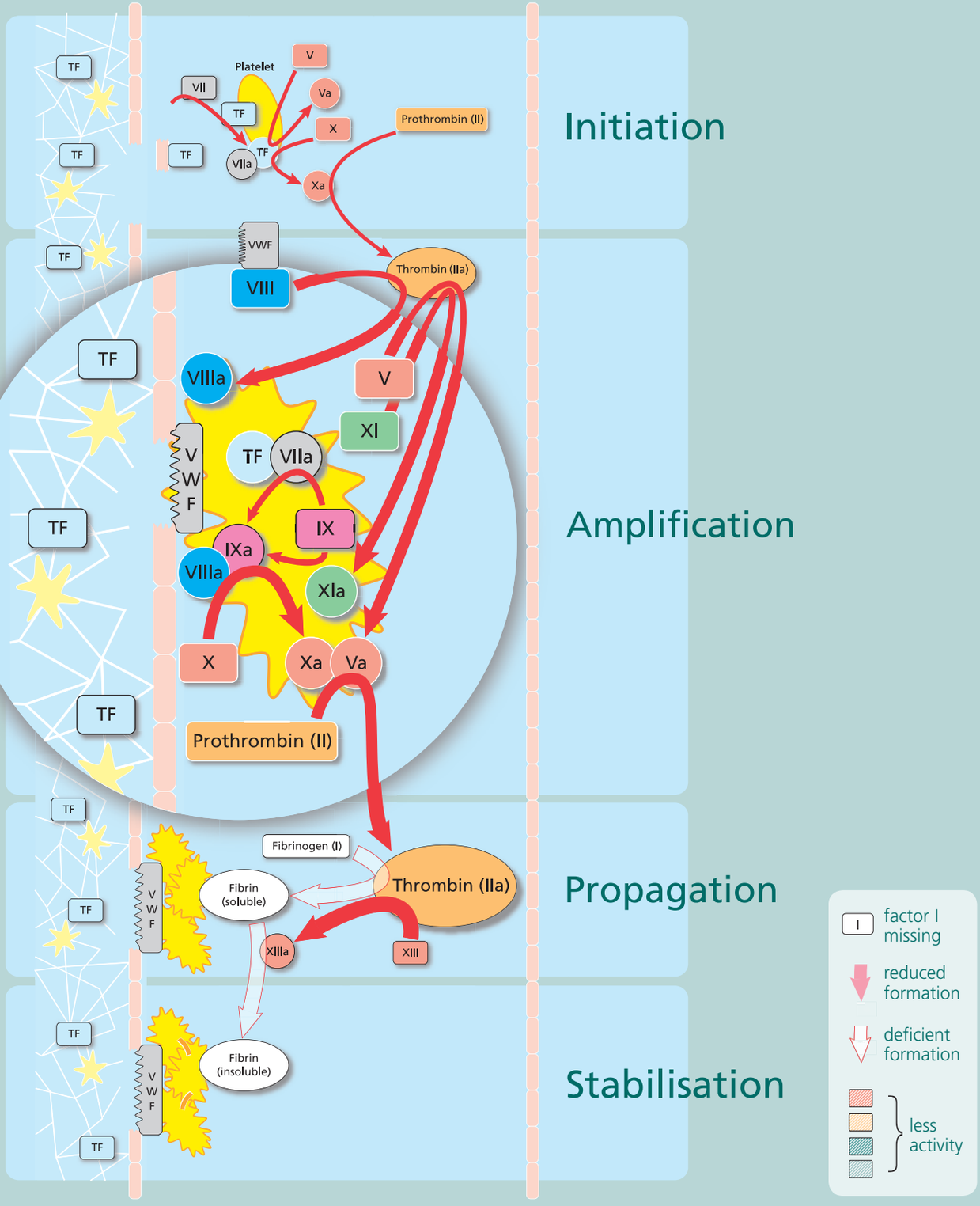
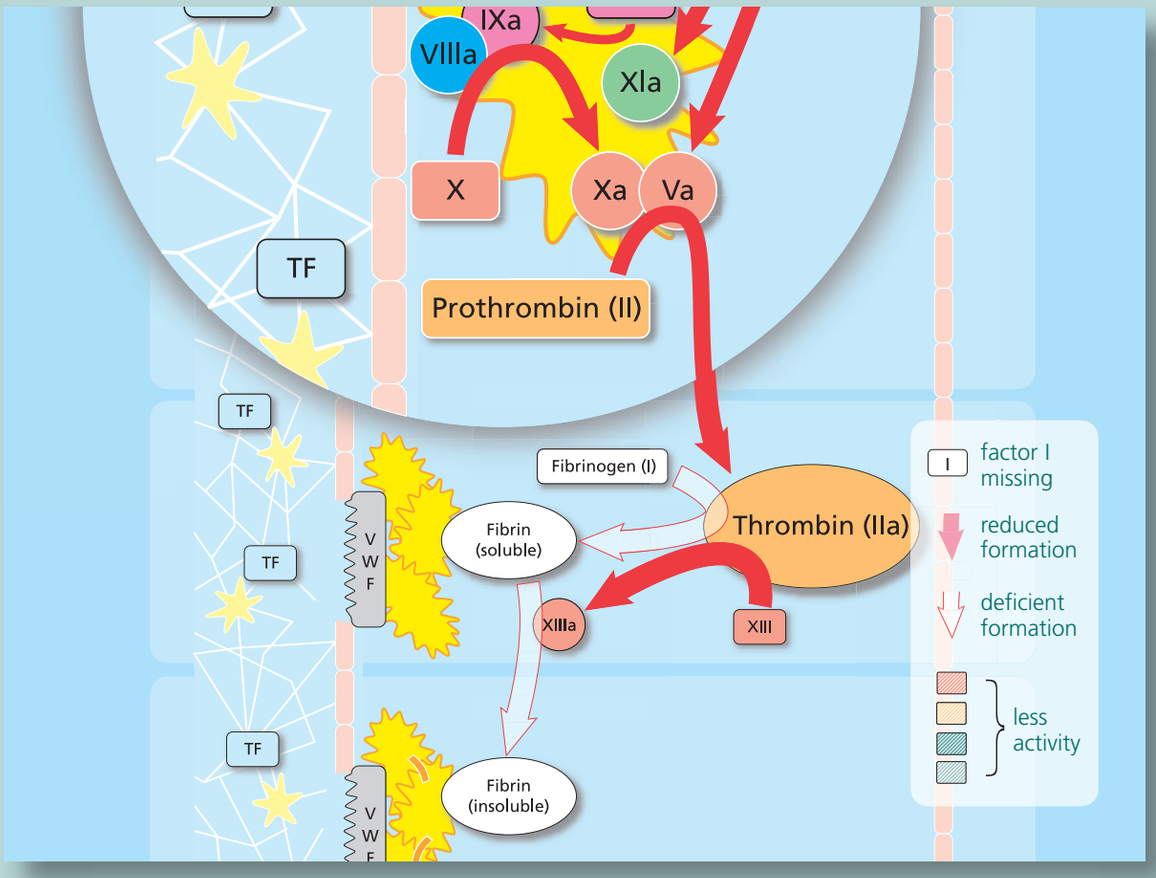
Fibrinogen (factor I) deficiency

Disorders, treatment approaches, and CSL Behring products





Physiology of fibrinogen

The high plasma concentration of fibrinogen (factor I) is indicative for its unique position in the coagulation system. In the first phase of haemostasis, fibrinogen binds to activated platelets and mediates platelet aggregation via fibrinogen receptors (glycoprotein IIb/IIIa complex). Subsequently, during blood coagulation, fibrinogen is converted to fibrin through proteolytic activation by thrombin, and fibrin forms a polymerized protein network that stabilizes the entire clot. In addition, fibrinogen is also regarded as acute phase reactant. Diagnosis of fibrinogen deficiency is performed by means of a specific fibrinogen assay.

Disorders of Fibrinogen 1/2

Congenital fibrinogen deficiency
Congenital fibrinogen deficiency is a very rare disease, affecting an estimated one person per million. Depending on the causative genetic alteration, it can be divided into three subgroups:

- afibrinogenaemia – fibrinogen activity levels <0.5 g/l
- hypofibrinogenaemia – fibrinogen activity levels 0.5–1.17 g/l
- dysfibrinogenaemia – normal or low plasma concentrations of qualitatively abnormal fibrinogen.

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Disorders of Fibrinogen 2/2

The clinical presentation of patients with congenital fibrinogen deficiency is heterogenous. Congenital fibrinogen deficiency syndromes include silent forms with almost no symptoms over a long period of time, forms involving moderate bleeding (e.g., increased tendency for epistaxis), and forms involving life-threatening events such as intracerebral bleeding. Female patients with afibrinogenaemia tend to have a high incidence of miscarriages. In rare cases, spontaneous thromboses and thromboembolic events have been reported during replacement therapy.

Acquired fibrinogen deficiency
Acquired fibrinogen deficiencies may occur due to impaired synthesis of fibrinogen, massive blood loss, or coagulopathy (defect in the blood clotting mechanism) due to other causes. Plasma fibrinogen levels below 1.0 g/l are regarded as an indicator for coagulopathy.

Conditions in which fibrinogen deficiencies occur, and their pathophysiological origins, include:

- massive blood loss – loss of fibrinogen
- disseminated intravascular coagulation – excessive utilisation and depletion of fibrinogen
- impaired liver function – impaired fibrinogen synthesis
- surgery or injury of organs with profibrinolytic potential (e.g., liver, prostate) – hyperfibrinolysis (solubilisation of fibrin in blood clots).

The origin may be complex, e.g., obstetric bleeding caused by a combination of utilisation/depletion, blood loss, and hyperfibrinolysis.

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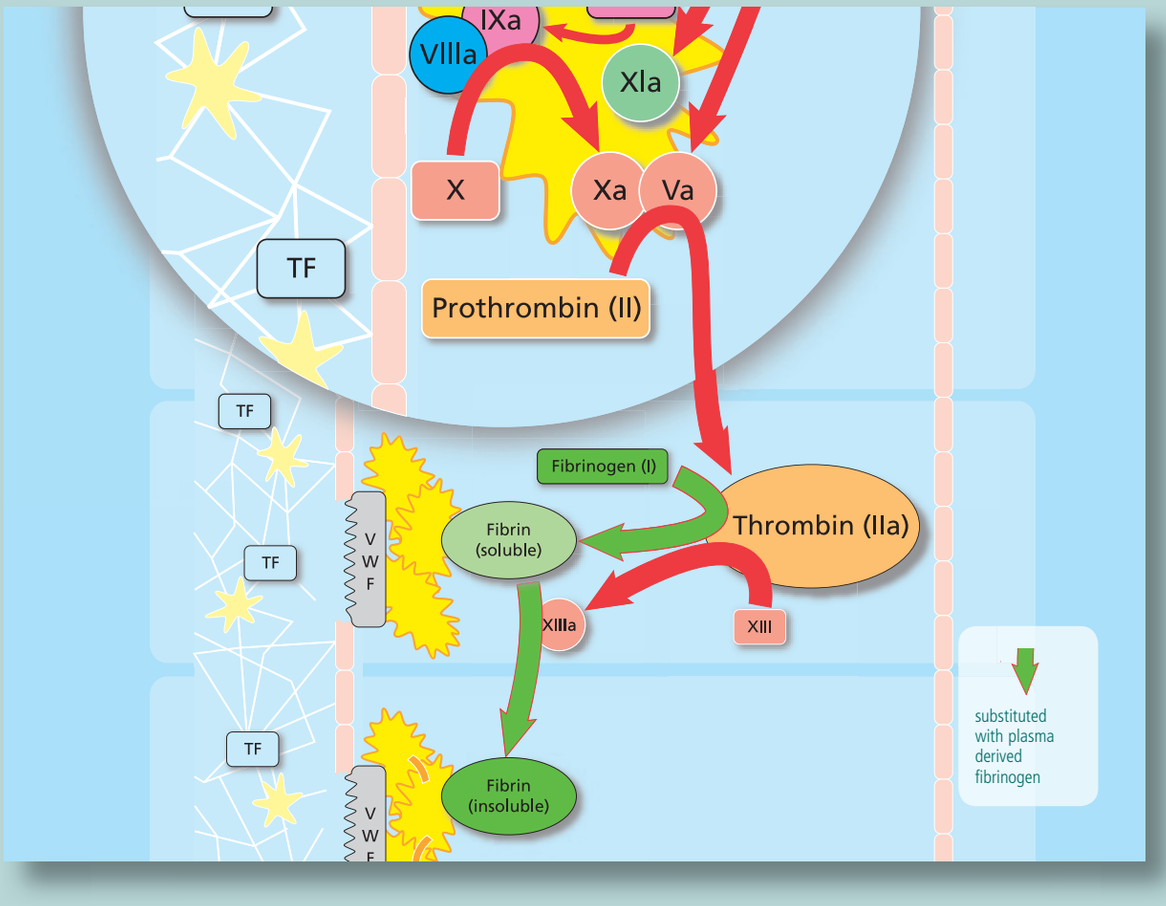

Treatment approaches for Fibrinogen deficiency 1/2

Treatment is required in fibrinogen (factor I) deficiency for the acute management and prophylaxis of bleeding episodes. Replacement of fibrinogen to a level of 0.8 g/l is advised for maintenance of haemostasis (>1.0 g/l for CNS haemorrhage). In severe bleeding episodes, some guidelines even recommend higher plasma levels. Treatment options include fibrinogen concentrates, cryoprecipitate, and antifibrinolytics. In addition, anticoagulant therapy may be required if thrombosis occurs spontaneously, or as a result of fibrinogen replacement.

Fibrinogen concentrates
Fibrinogen concentrates are derived from human plasma and replace fibrinogen. These products are virus-inactivated for improved safety. Fibrinogen concentrate products include the CSL Behring-marketed Haemocomplettan® P, or Riastap™.

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Treatment approaches for Fibrinogen deficieny 2/2

Cryoprecipitate
Cryoprecipitate contains mainly factor VIII, factor XIII, fibrinogen, von Willebrand factor, and fibronectin, and is also derived from human plasma. It is the precipitate formed when fresh frozen plasma is slowly thawed. Indications for cryoprecipitate include supplementation of fibrinogen and factor VIII. The variability of fibrinogen content as well as the amount of other proteins are further disadvantages of cryoprecipitate.

Fibrinogen concentrates are favoured in clinical practice as first-line treatment for therapy and prophylaxis of haemorrhagic events arising from fibrinogen deficiencies, as cryoprecipitate is normally not virus-inactivated. Cryoprecipitate is used if fibrinogen concentrates are unavailable.

Antifibrinolytics
Antifibrinolytics inhibit local fibrinolysis, thereby maintaining clot stability and decreasing rebleeding. These agents are often given as an adjunct to fibrinogen replacement in bleeding involving mucosal surfaces, and include aminocaproic acid and tranexamic acid.

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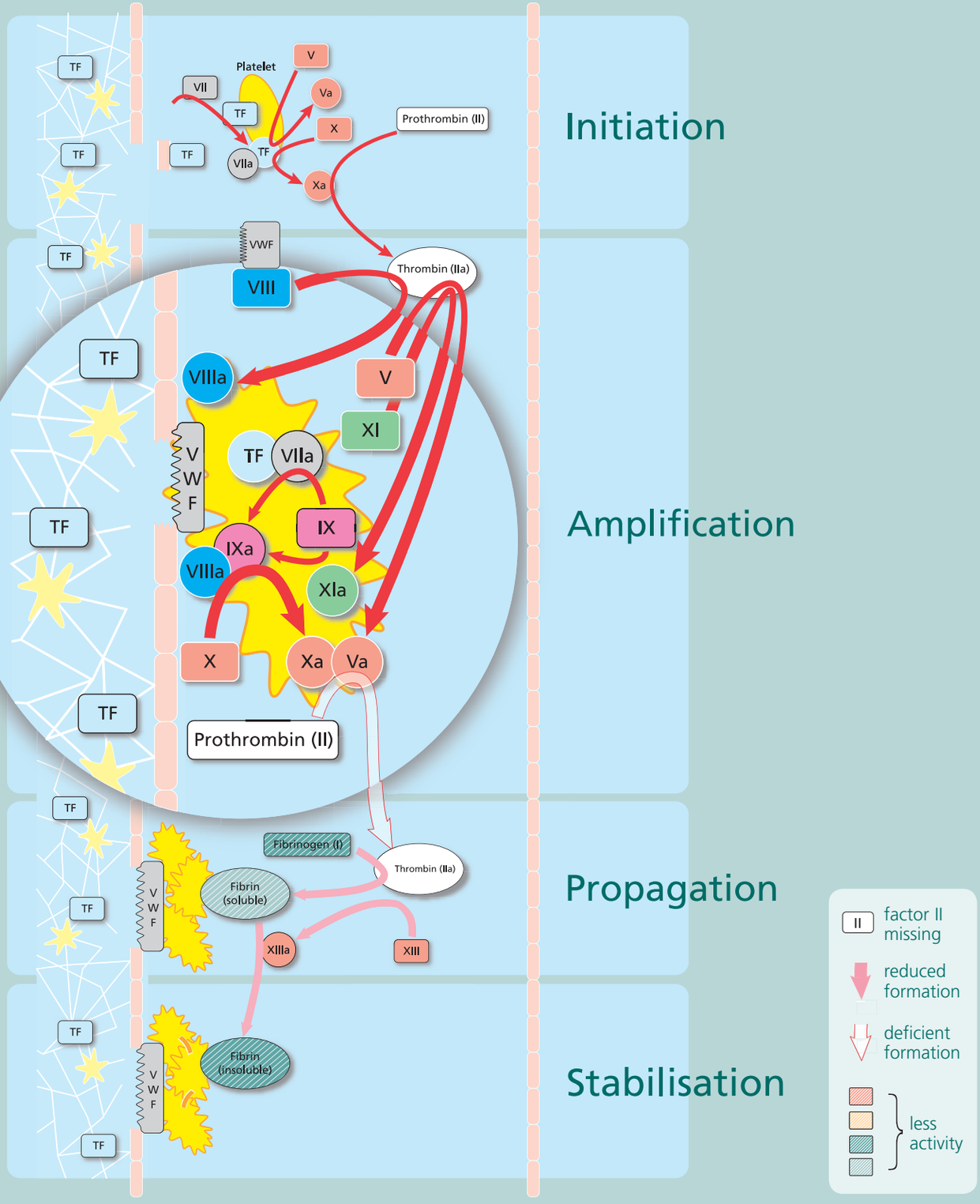
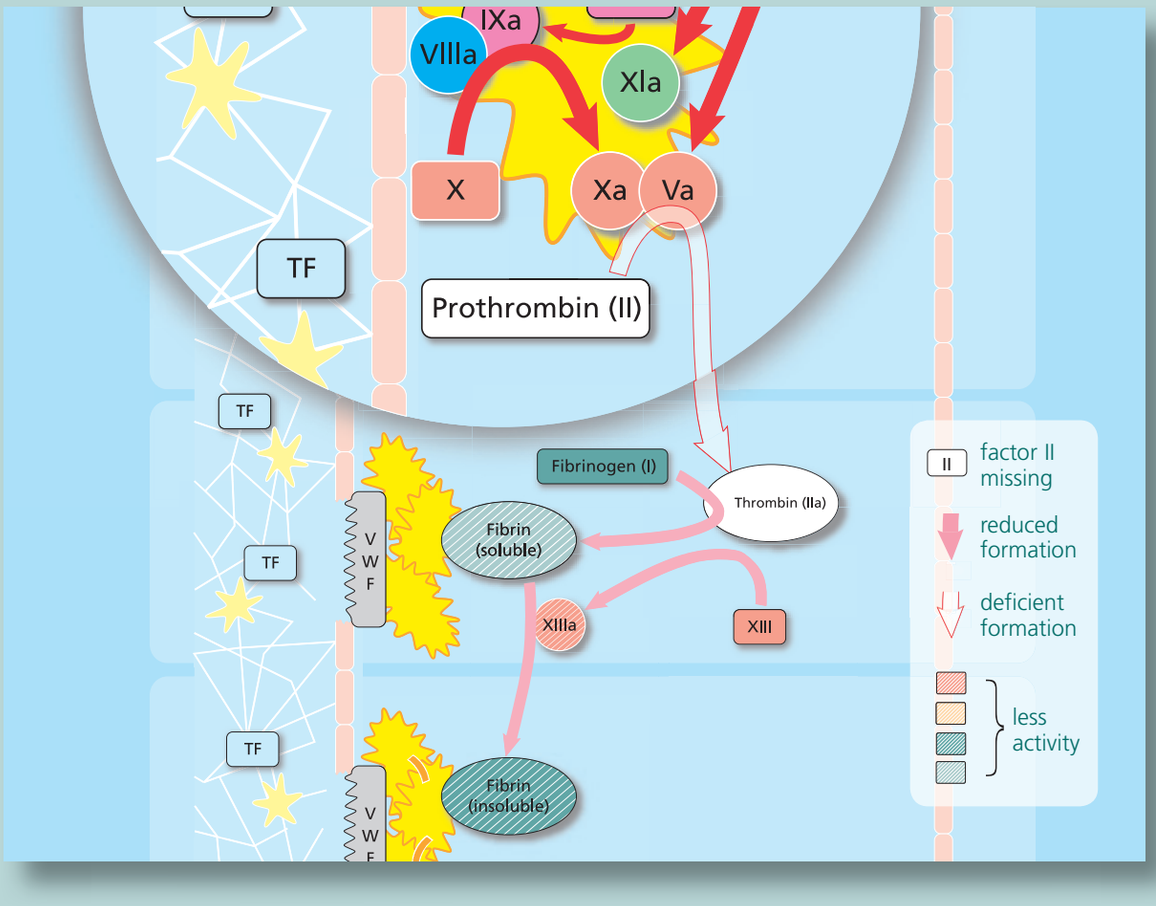
Prothrombin (factor II) deficiency

Disorders, treatment approaches, and CSL Behring products





Physiology of Prothrombin (Factor II)

Prothrombin, or factor II (FII), is one of the vitamin K-dependent coagulation factors, synthesised in the liver. It is the proenzyme to thrombin, which is otherwise known as activated FII (FIIa), and is a serine protease. Conversion of prothrombin to thrombin takes place via cleavage by activated factor X (FXa). Thrombin converts fibrinogen to fibrin, induces platelet aggregation, activates factors V and VIII into Va and VIIIa, and activates factor XIII (to FXIIIa) which stabilises fibrin. Therefore, prothrombin and thrombin are central components in the coagulation cascade. Moreover, by binding to its endothelial receptor thrombomodulin thrombin induces the formation of activated protein C that cleaves the cofactors VIIIa and Va and thereby limits further thrombin generation.

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Disorders of Prothrombin (Factor II)

Congenital prothrombin (factor II) deficiency

Congenital deficiency of prothrombin is extremely rare, with an incidence of approximately one in two million; this translates to only 26 cases documented worldwide. Inheritance is autosomal recessive. Manifestations of the deficiency are hypoprothrombinaemia, wherein synthesis of prothrombin is decreased, and dysprothrombinaemia, wherein the prothrombin synthesised is dysfunctional. When symptomatic, affected individuals present with easy bruising, mucocutaneous bleeding or intracerebral bleeding, rather than the joint bleeding typically seen in haemophilia.

Diagnostic laboratory testing reveals prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT).

Acquired prothrombin (factor II) deficiency

Acquired deficiency of prothrombin can occur following the use of coumarin oral anticoagulants (coumarins) such as warfarin, in the context of acquired deficiency of the other vitamin K-dependent coagulation factors (VII, IX and X).

Factors II, VII, IX, and X require carboxylation by vitamin K for their biological activity. Coumarins inhibit the vitamin K conversion cycle, and hence the synthesis of these coagulation factors.

Other causes of acquired prothrombin deficiency include severe liver disease, intestinal malabsorption (due to vitamin K deficiency), and some antibiotics.

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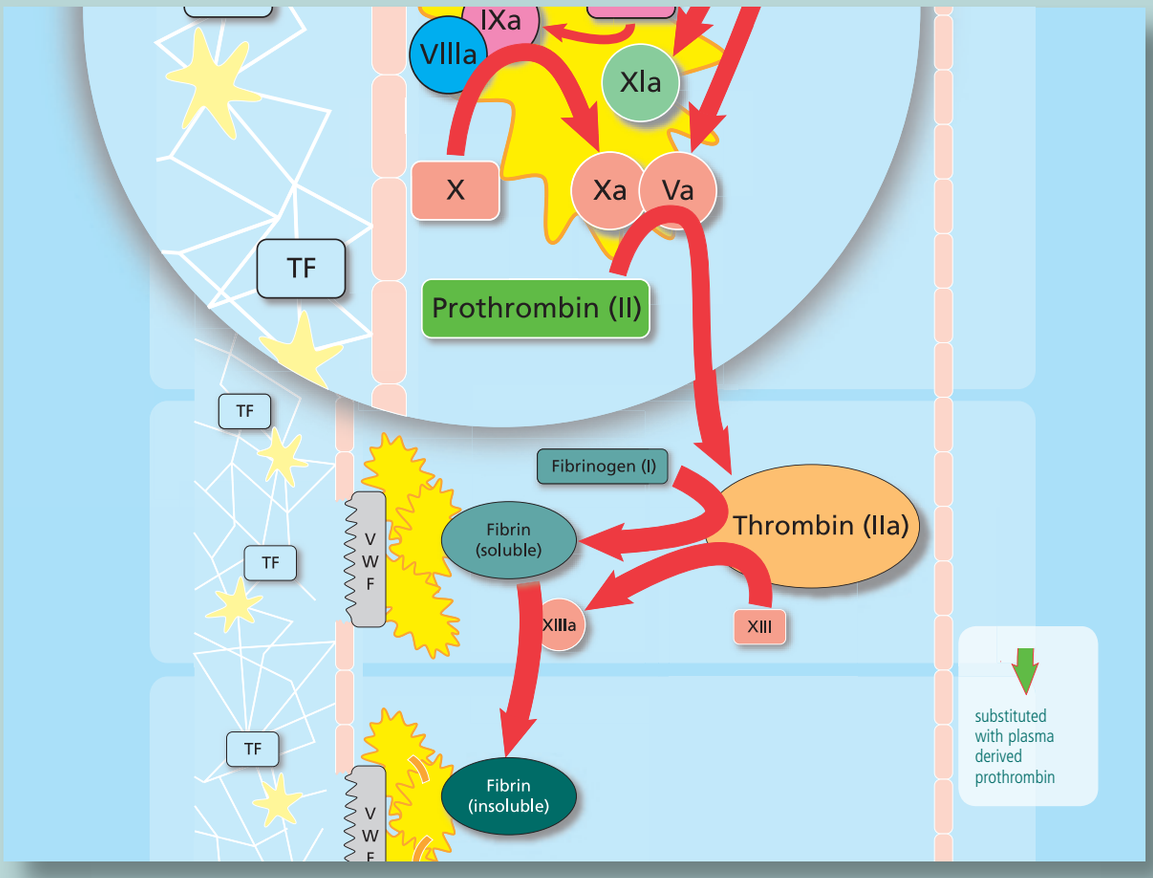

Treatment approaches for Prothrombin (Factor II) deficiency

Prothrombin (FII) deficiency is managed by substitution therapy. Fresh frozen plasma (FFP) is commonly used to treat acute bleeding. Prothrombin complex concentrates (PCC) may be used, particularly in the context of vitamin K-dependent coagulation factor deficiency (e.g., following coumarin anticoagulant administration). However, in cases of isolated prothrombin deficiency, caution should be exercised regarding thrombosis, as the coagulation factors that the patient is able to replenish will also be supplemented. Vitamin K supplementation may be effective in cases where prothrombin deficiency is the result of an inadequate vitamin K level.

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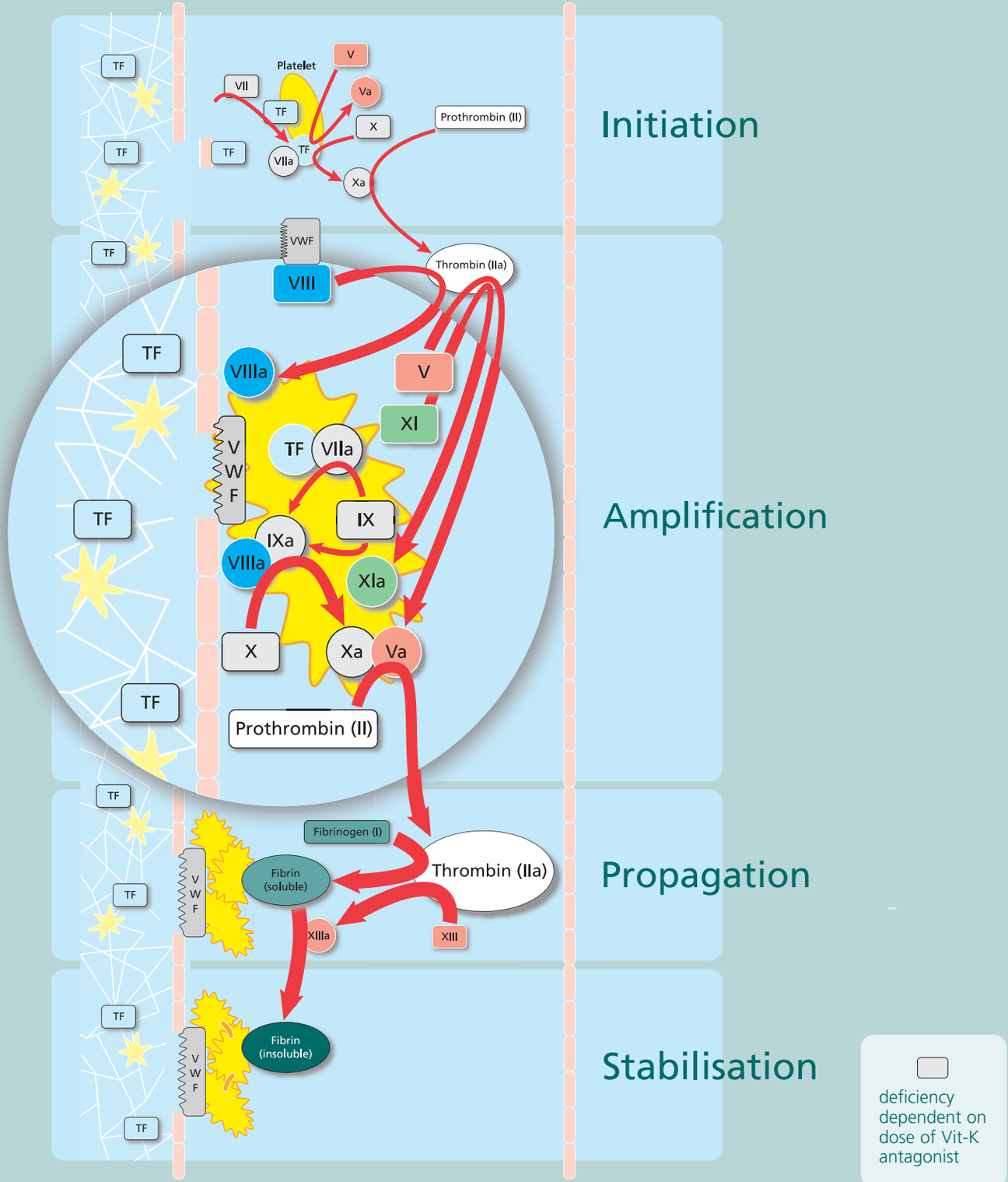
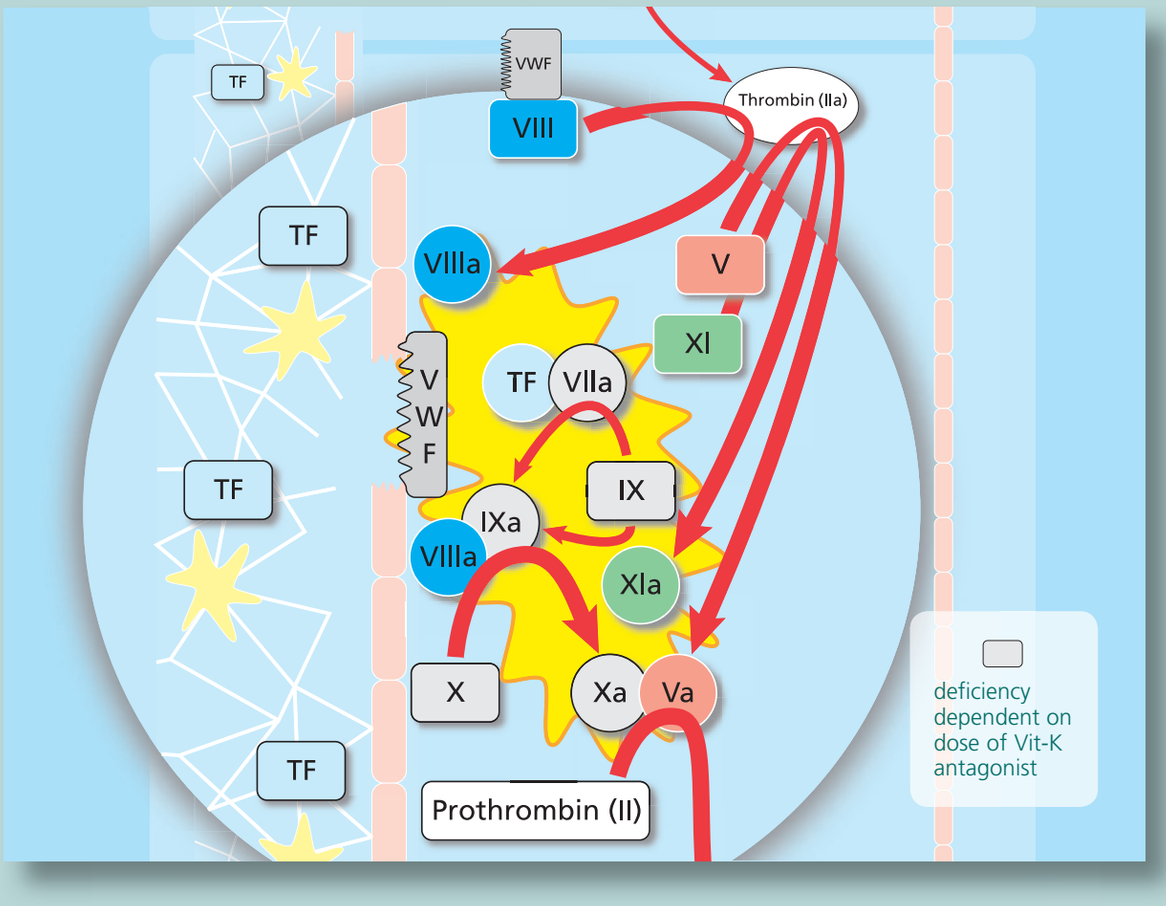
Deficiencies of Vitamin K factors

Disorders, treatment approaches, and CSL Behring products





Disorders of Vitamin K-dependent factors 1/2

Coumarins are highly effective, indirect anticoagulant agents, but have a narrow therapeutic window. Inter- and intra-individual dosage requirements vary widely. The primary complication of coumarin therapy is bleeding; the INR provides a good indication of haemorrhagic risk, with the risk increasing exponentially as the INR rises above 5.0. The annual risk of any bleeding due to coumarin use is estimated to be approximately 15%. Estimates for fatal or life-threatening bleeding risk associated with coumarin use range from 1–3%.

Congenital deficiency of vitamin K-dependent coagulation factors
Congenital deficiency of any, or all, of the prothrombin complex coagulation factors (factors II, VII, IX and X) is associated with disordered coagulation.

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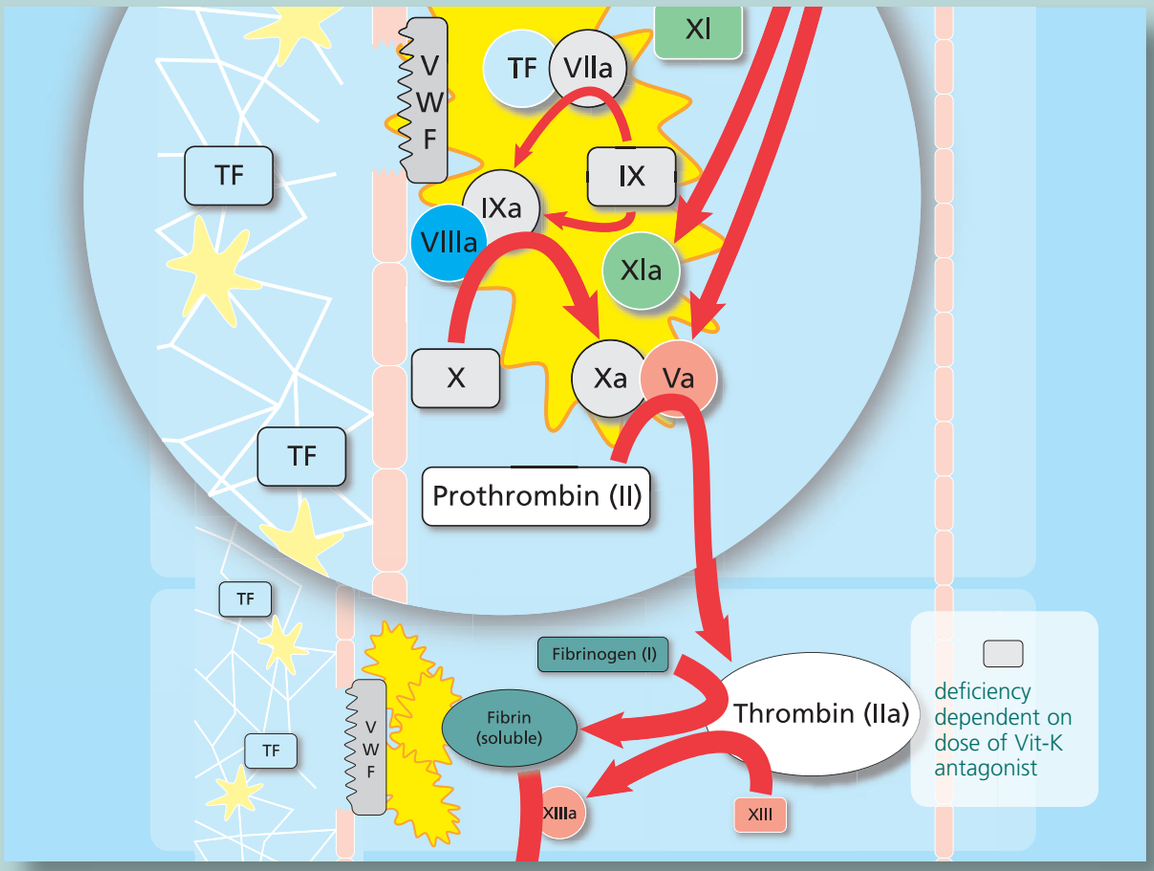

Disorders of Vitamin K-dependent factors 2/2

Acquired deficiency of vitamin K-dependent coagulation factors
Acquired functional deficiency of vitamin K-dependent coagulation factors (factors II, VII, IX and X) occurs following the use of coumarin oral anticoagulants (coumarins), such as warfarin, or under conditions of vitamin K deficiency. Patients are carefully monitored by means of the International Normalised Ratio (INR), a standardised term of expressing the ratio between the patient´s prothrombin time (PT) in relation to the PT of a healthy individual not receiving any anticoagulant. Depending on the indication for anticoagulation, a target INR value of e.g. 2-3 will be specified for optimal efficacy/risk balance. Factors II, VII, IX, and X require carboxylation by vitamin K for their biological activity. Coumarins inhibit the vitamin K conversion cycle, and hence the functional outfit of these coagulation factors. The use of coumarins also results in a functional deficit of the natural anticoagulant proteins C and S.

Coumarins are used for the prevention of:

- venous thromboembolism
- systemic embolism in patients with prosthetic heart valves or atrial fibrillation
- acute myocardial infarction in patients with peripheral arterial disease
- stroke, or recurrent infarction, in patients with acute myocardial infarction (Hanley 2004; Ansell et al, 2004).

Makris M, Watson HG. The management of coumarin-induced over-anticoagulation Annotation. Br J Haematol 2001;114:271-280.
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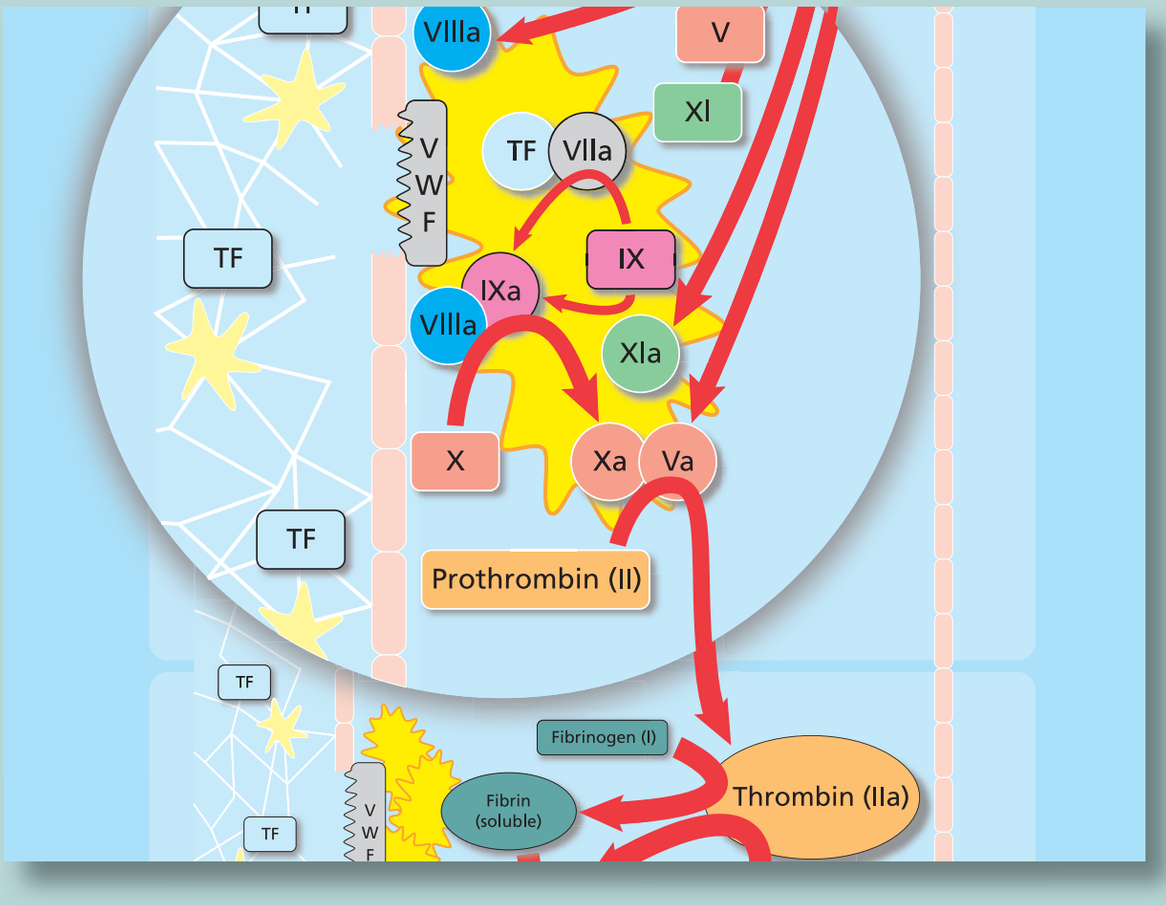

Treatment for deficiency of Vitamin K-dependent factors 1/2

Treatment is required in patients using coumarin anticoagulants when INR outside the desired reference range are encountered with, or without, obvious bleeding. Excessive anticoagulation is associated with increased risk of 60-day mortality, as well as stroke, myocardial infarction, hypotension, critical anaemia, and surgical or angiographic intervention at 30 days. Intracerebral haemorrhage is the most feared complication of warfarin therapy.

Speed of reversing the anticoagulant effect of coumarins is critical to halt haemorrhage and, therefore, stop haematoma growth. Therefore, clear strategies must be in place to swiftly and completely reverse oral anticoagulation in patients experiencing a serious bleed, requiring emergency invasive procedures, or with extremely elevated INR.

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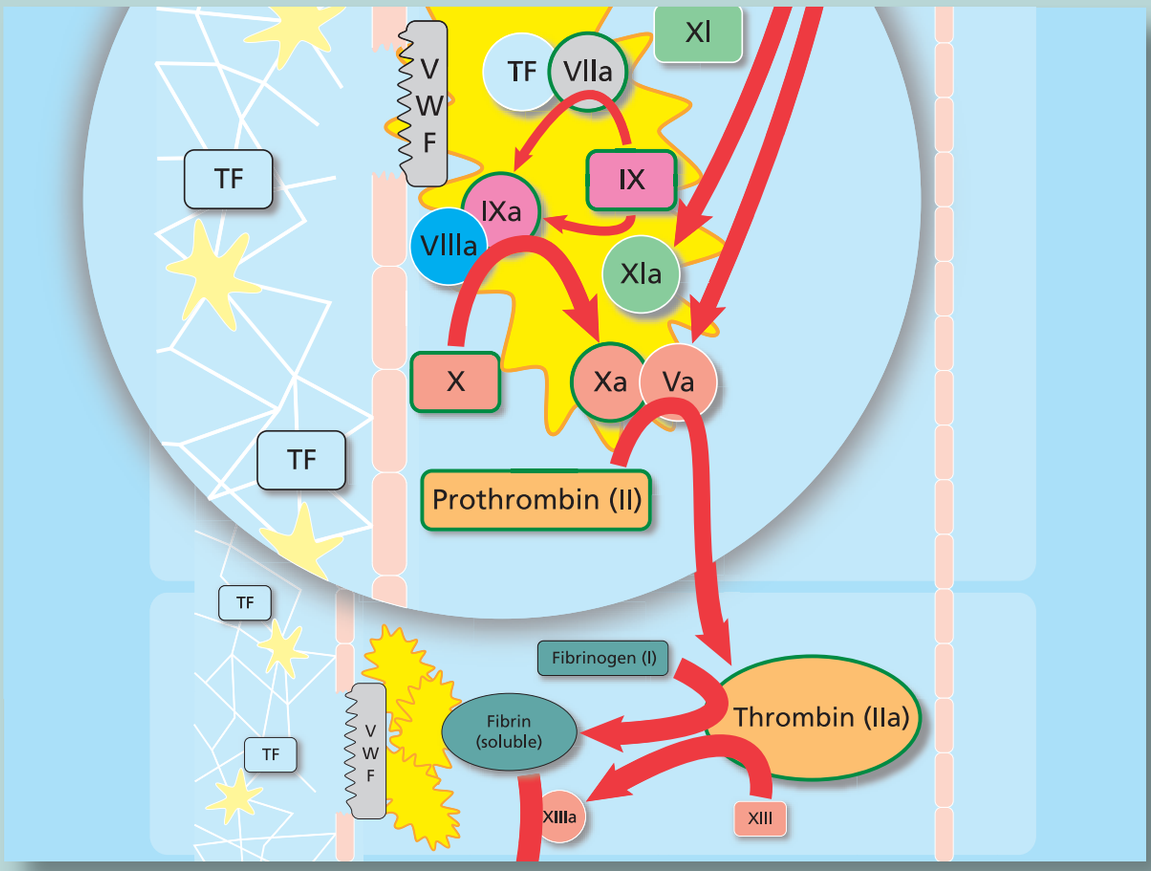

Treatment for deficiency of Vitamin K-dependent factors 2/2

Several options exist for the rapid reversal of coumarin anticoagulation, including:

- anticoagulant dose omission or withdrawal, to allow physiological restoration of INR to target level
- administration of vitamin K (oral or intravenous), to reverse the antagonistic effect of the anticoagulant
- plasma (fresh frozen plasma; solvent/detergent-treated plasma; or methylene blue-treated plasma), containing replacement coagulation factors in normal or near-normal concentrations
- prothrombin complex concentrates (PCC), most of which contain all four vitamin K-dependent coagulation factors in a highly concentrated form.

Plasma products have traditionally been the treatment of choice to restore adequate coagulation, but their effects are often incomplete, they are cumbersome to administer, and they carry a number of significant health risks. PCC are increasingly being recommended in guidelines as the optimal treatment for urgent restoration of normal coagulation. Rapid reversal of the elevated INR and clinically relevant response have been demonstrated in a pharmacokinetic investigation and a prospective, multinational clinical trial.

Baglin TP, Keeling DM, Watson HG; British Committee for Standards in Haematology. Guidelines on oral anticoagulation (warfarin): third edition, 2005 update. Br J Haematol 2006;132:277-285.
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