Hemostasis Basics: Figures and Facts

1

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Introduction

In order to understand hemostatic system easily, visualization is usually more effective than text. While the details of each system are found in other chapters of this textbook, Figs. 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, and 1.9 give a general overview of the hemostatic system. Explanations for each figure are included in the legend. The tables list characteristics of individual coagulation factors and von Willebrand factor. The half-life of each factor, minimum requirement for hemostasis, and choice of blood components or hemostatic drugs may be clinically useful (Figs. 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, and 1.9; Tables 1.1, 1.2, and 1.3).

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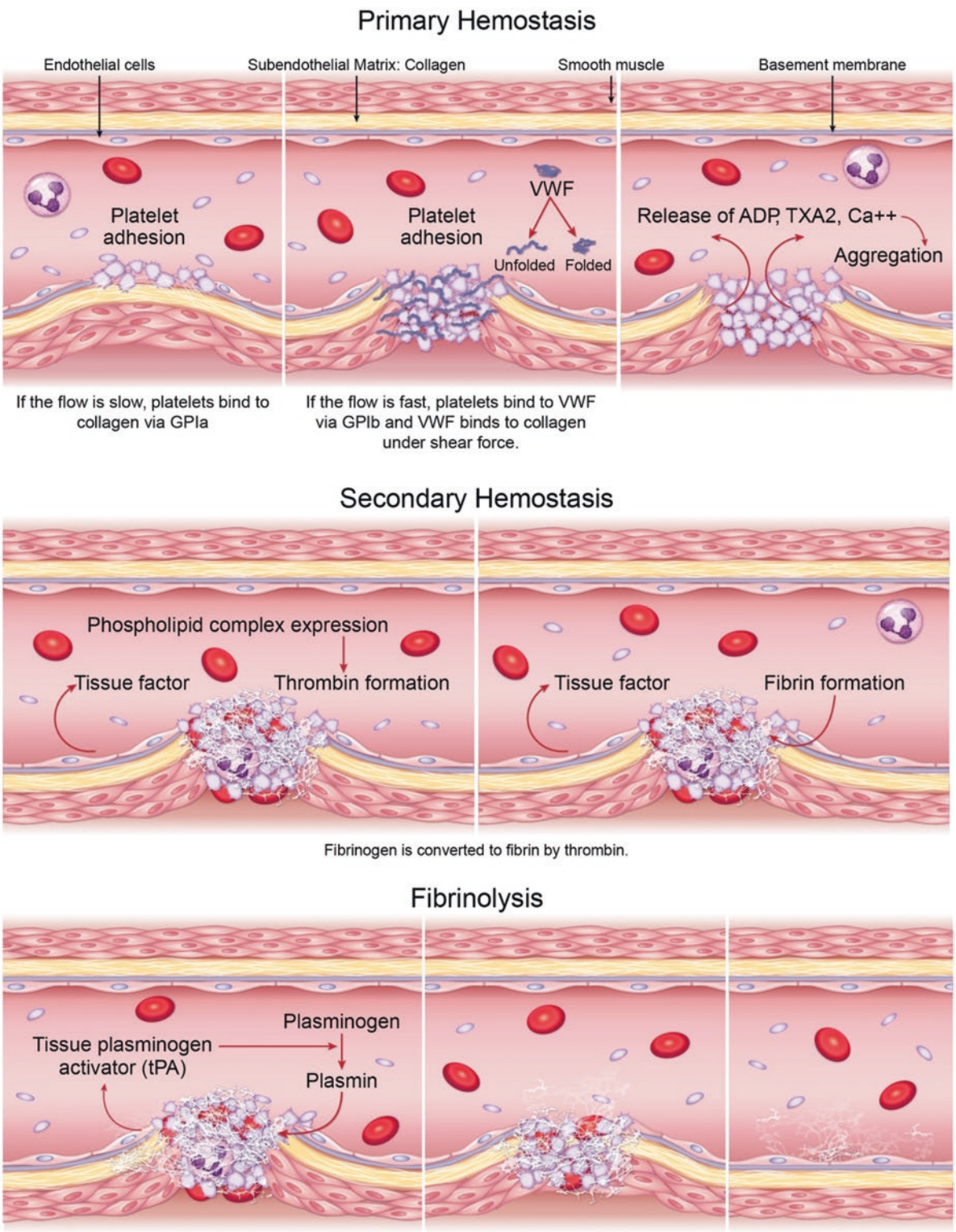

Fig. 1.1 When there is a defective vessel wall, von Willebrand factor (VWF) binds to the subendothelial matrix (composed of collagen) via the A1 and A3 domains of VWF under shear force. Platelets bind to the A1 domain of VWF via glycoprotein Ib. Platelets bound to the subendothelial matrix are activated. These activated platelets undergo shape change and degranulation, resulting in further platelet activation and the formation of platelet aggregates. This process is called primary hemostasis or platelet hemostasis. The coagulation cascade is activated by negatively charged surface and tissue factor and ultimately results in the formation of fibrin which is crosslinked via factor XIIIa. Together, crosslinked fibrin and platelet aggregates form a strong clot. This process is known as secondary hemostasis or coagulation hemostasis. Finally, once the defective vessel wall is healed, the clot is removed by the action of plasmin in a process called fibrinolysis. GPIa glycoprotein Ia, GPIb glycoprotein Ib, TXA2 thromboxane A2.

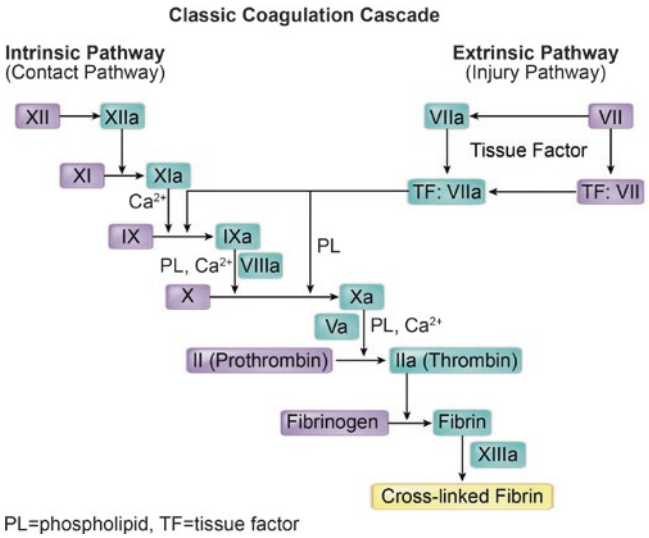

Fig. 1.2 The coagulation process was initially called "waterfall sequence for intrinsic blood clotting" in order to explain fibrin clot formation (Davie EW, Ratnoff OD. Waterfall sequence for intrinsic blood clotting. Science. 1964;145:1310–12.). Then, it was called "coagulation cascade." Now it is known that coagulation is not a one-way process. Thrombin provides positive feedback to activate various coagulation factors. See Fig. 1.3. © 2019, Texas Children's Hospital. Reproduced/used with permission

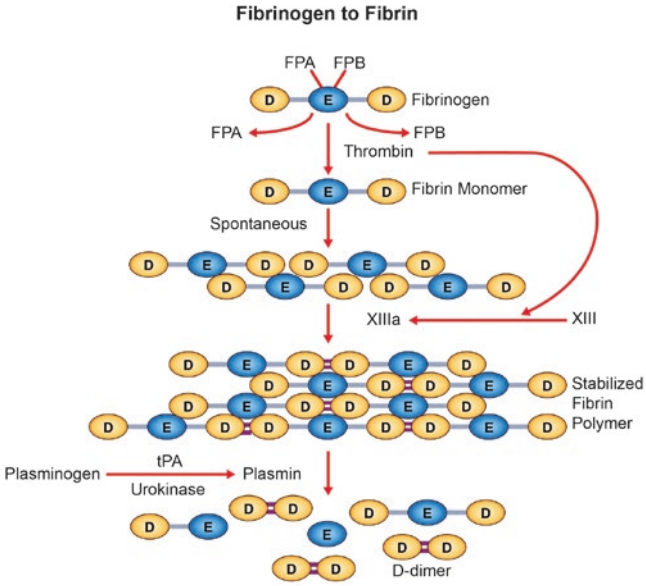

Fig. 1.4 The interaction of thrombin with fibrinogen results in the release of fibrinopeptide A (FPA) and fibrinopeptide B (FPB). A fibrin monomer is formed after releasing FPA and FPB. The fibrin monomers polymerize spontaneously. Thrombin also activates factor XIII to factor XIIIa, which crosslinks fibrin. Eventually, crosslinked fibrin will be degraded to D-dimer by plasmin. © 2019, Texas Children's Hospital. Reproduced/used with permission

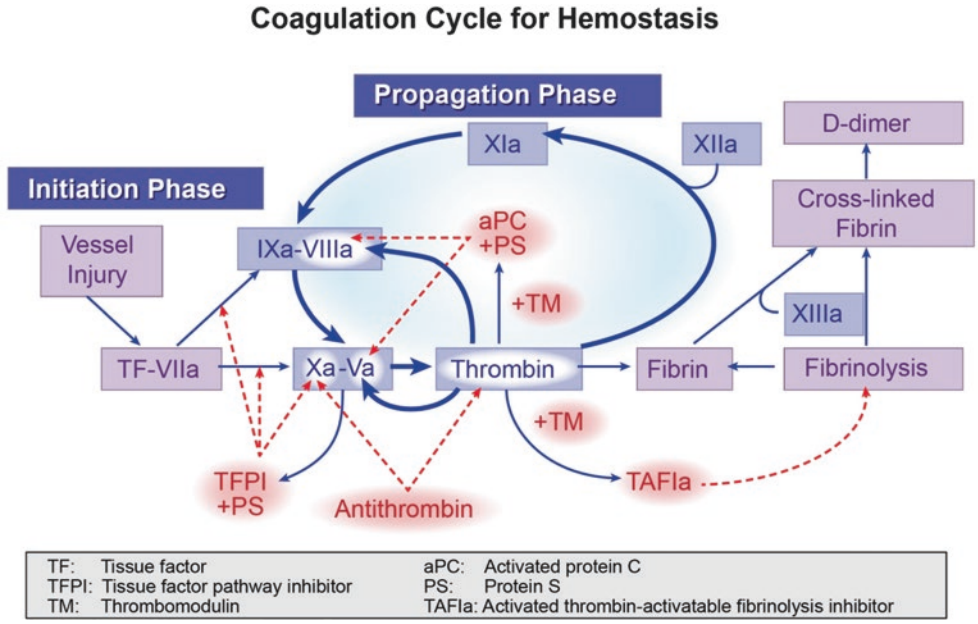

Fig. 1.3 When a vessel is injured, the factor VIIa (a small amount of activated form is circulating) and tissue factor complex activates factor IX and factor X to factor IXa and factor Xa, respectively. Tissue factor pathway inhibitor (TFPI) inhibits the activation of factor IX and factor X. Factor Xa together with factor Va, called prothrombinase, activates prothrombin to thrombin. Thrombin activates factor XI, factor VIII, factor V, and factor XIII and converts fibrinogen to fibrin. Thrombin also forms a complex with thrombomodulin on the endothelial cells. This complex then activates protein C to activated protein C and thrombin-activatable fibrinolysis inhibitor (TAFI) to TAFIa. Thrombin continues activating these factors until the process is completely inhibited by antithrombin and activated protein C. Of note, thrombin formation occurs without involvement of factor XII, which is why hemostasis is maintained in patients with factor XII deficiency. However, when factor XII is activated to factor XIIa, thrombin is formed. © 2019, Texas Children's Hospital. Reproduced/used with permission

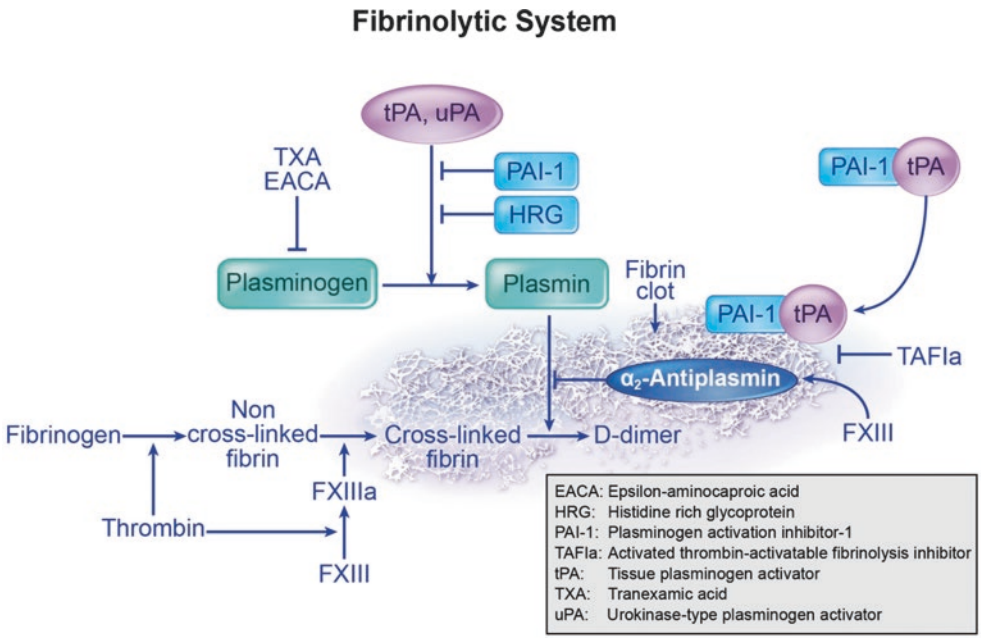

Fig. 1.5 Plasminogen is converted to plasmin by the actions of tissue plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA). Plasmin cleaves fibrinogen, fibrin, fibronectin, thrombospondin, laminin, and von Willebrand factor. Plasmin is inactivated by α_2-antiplasmin and α_2-macroglobulin. Plasminogen activator inhibitor 1 (PAI-1) and histidine-rich glycoprotein inhibit the actions of tPA and uPA. © 2019, Texas Children's Hospital. Reproduced/used with permission

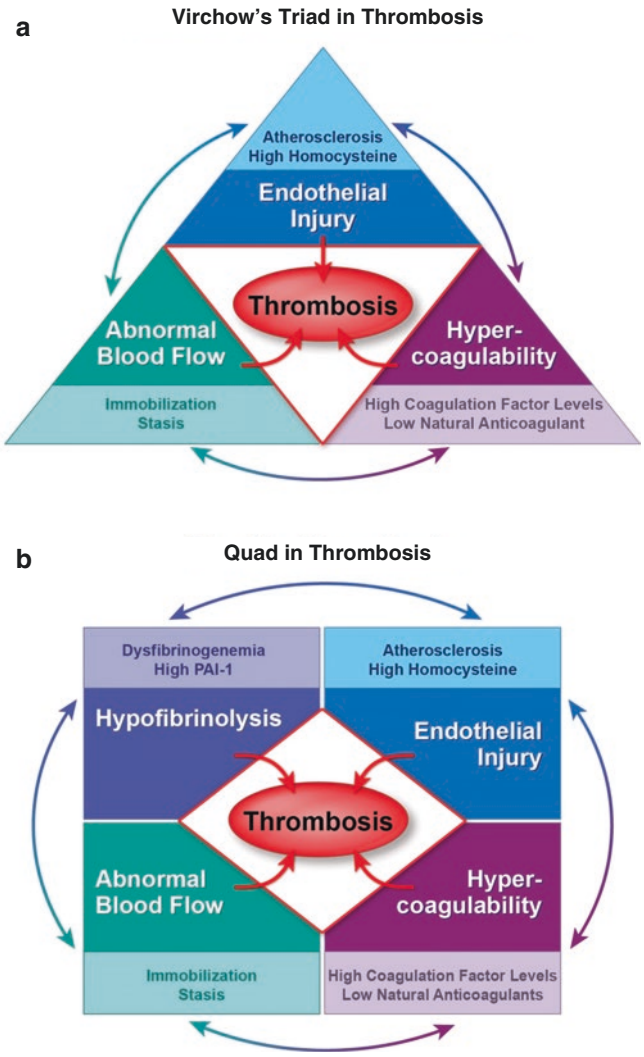

Fig. 1.6 Virchow proposed three key elements in the development of thrombosis (**a**). Hypofibrinolysis may be added to the triad (**b**). PAI-1 plasminogen activator inhibitor 1. © 2019, Texas Children's Hospital. Reproduced/used with permission

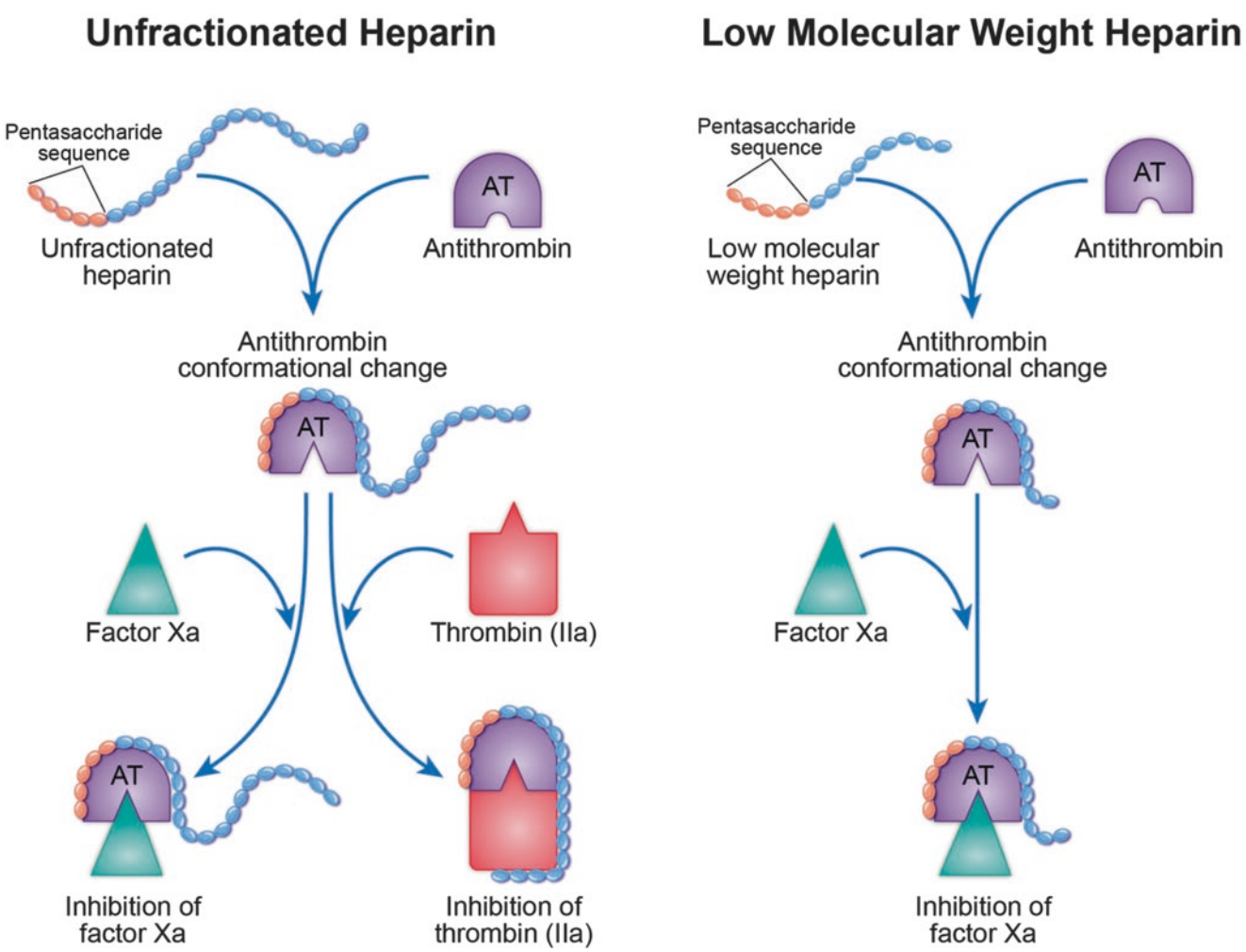

Fig. 1.7 Without heparin or heparinoids, antithrombin (AT) slowly inhibits factor Xa and thrombin. This is the "progressive form" of AT. AT also inhibits factor VIIa, factor IXa, and, to lesser extent, factor XIa. Unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) forms a complex with AT resulting in a confirmational change in AT and accelerating its anticoagulant action. This is called the "immediate form" of AT. The AT and UFH complex inhibits thrombin and factor Xa immediately. Alternatively, the AT and LMWH complex inhibits primarily factor Xa immediately. Heparin also binds heparin cofactor II which inhibits only thrombin. Heparin additionally functions as an anticoagulant by causing the release of tissue factor pathway inhibitor (TFPI) from endothelial cells.

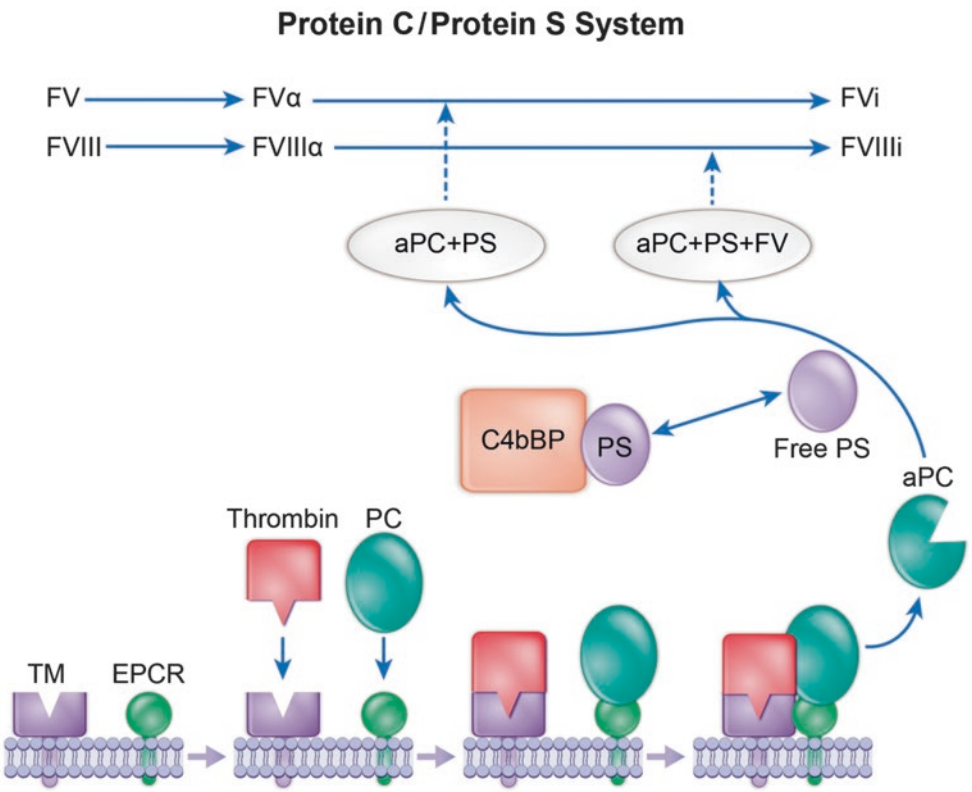

Fig. 1.8 Protein C binds to the endothelial protein C receptor (EPCR), and thrombin makes a complex with thrombomodulin (TM) on the endothelial cell surface. The thrombin thrombomodulin complex activates protein C which is bound to EPCR. Activated protein C (aPC) makes a complex with free protein S and inactivates factor Va. The aPC and protein S complex binds to factor V and inactivates factor VIIIa. This pathway inhibits procoagulant activity resulting in the prevention of excessive clot formation. C4bBP C4b binding protein, PS protein S, FV factor V, FVa activated factor V, FVi inactivated factor V, FVIII factor VIII, FVIIIa activated factor VIII, FVIIIi inactivated factor VIII, APC activated protein C, PC protein C. © 2019, Texas Children's Hospital. Reproduced/used with permission

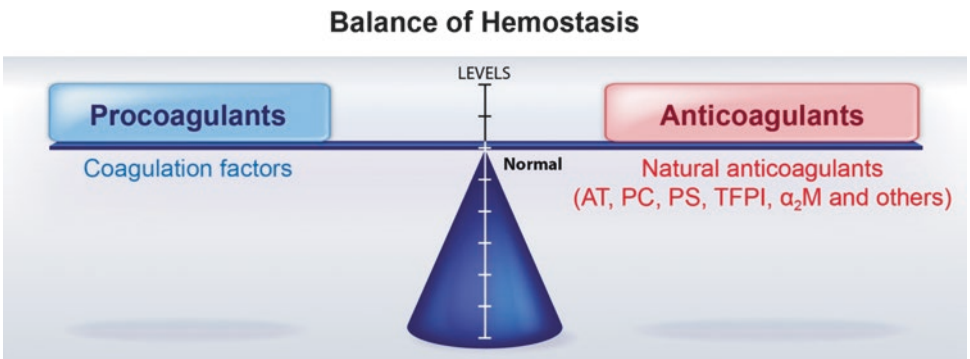

Fig. 1.9 In a normal state, procoagulants and anticoagulants are well balanced. AT antithrombin, PC protein C, PS protein S, TFPI tissue factor pathway inhibitor, α_2M α_2-macroglobulin. © 2019, Texas Children's Hospital. Reproduced/used with permission

Table 1.1 Characteristics of coagulation factors, contact factors, and von Willebrand factor

Factor	Common name	Molecular weight (Daltons) (activated form)	Concentration in 1 mL plasma	Concentration required for normal hemostasis
I	Fibrinogen	340,000 (330,000)	3 mg	100 mg/dL
II	Prothrombin	72,000 (38,000)	100 μg	20–40%
III	Tissue factor	45,000	0.02 μg	
IV	Calcium ions			
V	Proaccelerin	330,000	10 μg	>25%
VII	Proconvertin	50,000 (50,000)	0.5 μg	10–20%
VIII	Antihemophilic factor	280,000	0.1 μg	Minimum of 30% for major surgery; less for minor procedures
IX	Christmas factor	56,000 (46,000)	3–4 μg	25–30%
X	Stuart factor	55,000 (40,000)	6–8 μg	10–20%
XI	Plasma thromboplastin antecedent	160,000 (160,000)	7 μg	15–25%
XII	Hageman factor	80,000 (80,000)	30 μg	None required
XIII	Fibrin stabilizing factor	320,000 (320,000)	60 μg	>5%
	von Willebrand factor	1.2–5 million	7 μg	50%
	Prekallikrein	100,000	35–45 μg	None required
	High-molecular-weight kininogen	120,000	80 μg	None required

Table 1.2 Characteristics of coagulation factors and von Willebrand factor

Factor	In vivo half-life	Storage characteristics	Choice of components or hemostatic drug for replacement
I[a]	3–5 days	Stable in plasma at 4 °C	Cryoprecipitate, fibrinogen concentrate (RiaSTAP™, Fibryga™)
II	2–3 days	Stable in plasma at 4 °C	FFP, prothrombin complex concentrate (Kcentra™)
V	12 hours	Labile except when frozen	FFP
VII	3–6 hours	Stable in plasma at 4 °C	Recombinant activated factor VII (NovoSeven™), FFP, prothrombin complex concentrate (Kcentra™)
VIII[a]	8–12 hours	Labile except when frozen	Factor VIII concentrate, recombinant factor VIII
IX	18–24 hours	Stable in plasma at 4 °C	Factor IX concentrate, recombinant factor IX
X	30–40 hours	Stable in plasma at 4 °C	Prothrombin complex concentrate (Kcentra™, Coagadex™)
XI	52 hours	Stable in plasma at 4 °C	FFP, factor XI concentrate (not available in US)
XII	60 hours	Stable in plasma at 4 °C	Not necessary
XIII	9–10 days	Stable in plasma	Cryoprecipitate, factor XIII concentrate, recombinant factor XIII
VWF[a]	9–15 hours	Labile except when frozen	Humate-P™, Wilate™, Alphanate™, Vonvendi™ Cryoprecipitate[b]

FFP fresh frozen plasma, *VWF* von Willebrand factor
[a]Acute phase reactant
[b]If VWF concentrate or recombinant VWF is not available

Table 1.3 Natural anticoagulants

	Activation/mechanism of action	Inhibiting factors
Antithrombin	To immediate form by heparin and heparan sulfate	Thrombin, factor Xa
Protein C	Thrombin-thrombomodulin complex	Factor Va, factor VIIIa
Protein S	Cofactor of activated protein C	Factor Va, factor VIIIa
Tissue factor pathway inhibitor (TFPI)		Factor Xa, tissue factor, and factor VIIa complex
Heparin cofactor II	To immediate form by heparin and dermatan sulfate	Thrombin
α2-macroglobulin		Thrombin, factor Xa