Medical device-induced thrombosis: what causes it and how can we prevent it?

I. H. JAFFER,* † J. C. FREDENBURGH,* ‡ J. HIRSH* ‡ and J. I. WEITZ* ‡ §

*Thrombosis and Atherosclerosis Research Institute, McMaster University; †Department of Surgery, McMaster University; ‡Department of Medicine, McMaster University; and §Department of Biochemistry and Biomedical Sciences, McMaster University, Hamilton, ON, Canada

Summary. Blood-contacting medical devices, such as vascular grafts, stents, heart valves, and catheters, are often used to treat cardiovascular diseases. Thrombus formation is a common cause of failure of these devices. This study (i) examines the interface between devices and blood, (ii) reviews the pathogenesis of clotting on blood-contacting medical devices, (iii) describes contemporary methods to prevent thrombosis on blood-contacting medical devices, (iv) explains why some anticoagulants are better than others for prevention of thrombosis on medical devices, and (v) identifies future directions in biomaterial research for prevention of thrombosis on blood-contacting medical devices.

Keywords: catheters; factor XI; factor XII; medical devices; thrombosis.

Introduction

Blood-contacting medical devices, such as vascular grafts, stents, and heart valves, are widely used to treat cardiovascular diseases. In addition, indwelling central venous catheters and ports are a mainstay for venous access and drug delivery in patients with cancer, including hematological malignancies. Thrombus formation is a common cause of failure of these devices. Thrombi that form on blood-contacting medical devices are composed of platelet aggregates and fibrin, so it is not surprising that antiplatelet agents and/or anticoagulants are often used to prevent or treat such clotting. Consequently, it is important for hematologists to understand how blood-contacting medical devices initiate clotting so as to know how best to manage it. The purpose of this study was to (i) examine the interface between devices and blood, (ii) review the pathogenesis of clotting on blood-contacting medical devices with a focus on the role of the intrinsic pathway of coagulation, (iii) describe contemporary methods to prevent thrombosis on blood-contacting medical devices, which include surface modifications to render biomaterials less thrombogenic and/or administration of systemic antithrombotic agents, (iv) explain why some anticoagulants are better than others for prevention of thrombosis on medical devices, and (v) identify future directions in biomaterial research for prevention of thrombosis on blood-contacting medical devices.

Pathogenesis of blood-contacting medical device-induced clotting

In contrast to the healthy endothelium, which actively resists thrombosis, artificial surfaces promote clotting through a complex series of interconnected processes that include protein adsorption, adhesion of platelets, leukocytes, and red blood cells, thrombin generation, and complement activation (Fig. 1). Each of these processes will briefly be described.

Protein adsorption

Blood is a complex mixture of plasma and cells. Proteins are a major constituent of plasma, and plasma contains about 300 distinct proteins, which range in concentration from 35 to 50 mg mL⁻¹ for albumin to less than 5 pg mL⁻¹ for interleukin-6 [1]. Rapid adsorption of plasma proteins onto artificial surfaces is thought to be the initiating event in thrombus formation because the protein layer modulates subsequent reactions. The dynamics of protein adsorption are related to the chemical and physical properties of the surface and the proteins. Thus, adsorption involves interactions between charged groups at the protein–surface interface and/or conformational changes in protein structure. Adsorbed proteins can form a surface monolayer with a thickness of 2–10 nm, and the concentrations of proteins on the surface can be 1000-fold higher.
than those in plasma [2]. Surface adsorption is a reversible process, and the composition of absorbed proteins changes over time, a phenomenon known as the Vroman effect. This dynamic change in protein monolayer composition is particularly evident on negatively charged hydrophilic surfaces [3] and appears to be independent of flow [4]. Thus, hydrophilicity is a key determinant of the protein adsorption process, and more proteins adsorb to hydrophobic surfaces than to hydrophilic surfaces [2]. Protein and surface charge also are important determinants [5]. Conformational changes in protein structure can be an important driver of protein adsorption, particularly in the absence of hydrophobic interactions or electrostatic attraction. In addition, conformational changes in protein structure induced by surface adsorption may alter their biological activity [2].

Fibrinogen is one of the first plasma proteins to deposit on artificial surfaces. Other adhesive proteins, including fibronectin and von Willebrand factor (vWF), also adsorb to the surface and together with fibrinogen mediate platelet adhesion. Adsorbed fibrinogen is soon replaced with components of the contact system, including factor (f) XII, high molecular weight kininogen (HK), prekallikrein, and fXI [3]. Activation of bound fXII not only triggers thrombin generation via the intrinsic pathway of coagulation, but also induces complement activation. With cross talk between the complement and coagulation pathways, complement activation amplifies thrombin generation. Therefore, the protein monolayer serves as a dynamic modulator of thrombosis on artificial surfaces [6].

**Cell adhesion**

Adsorbed proteins mediate the attachment of platelets, leukocytes, and red blood cells to artificial surfaces.

Fibrinogen is the major protein responsible for platelet adhesion, and the platelet–fibrinogen interaction is mediated by \(\alpha IIb\beta3\) [7], the most abundant integrin on the platelet surface. Whereas \(\alpha IIb\beta3\) on the surface of circulating platelets must be conformationally activated via inside-out signaling before it is capable of binding fibrinogen, even in its quiescent state, \(\alpha IIb\beta3\) is capable of binding fibrinogen adsorbed to artificial surfaces [7]. This is a high-affinity interaction, and adsorbed fibrinogen densities as low as 7 ng cm\(^{-2}\) are capable of mediating platelet adhesion [8]. Although adsorbed fibronectin and vWF also bind platelets, they are less important mediators of platelet adhesion on artificial surfaces than fibrinogen [8,9]. The adsorption and retention of fibrinogen is greater on hydrophobic surfaces than on hydrophilic surfaces [10], which likely explains why platelets adhere readily to hydrophobic surfaces [11]. Platelets adherent to artificial surfaces become activated and release thromboxane A\(_2\), ADP, and other agonists. By activating platelets, these substances amplify adhesion, activation, and aggregation on the artificial surface. This leads to platelet thrombus formation, and the circulating platelet count may decrease with prolonged exposure of thrombogenic materials to blood.

Leukocytes, particularly neutrophils, also adhere to adsorbed fibrinogen via CD11b/CD18 [12,13]. Adherent platelets promote leukocyte adhesion via an interaction between P-selectin on the surface of activated platelets and leukocyte P-selectin glycoprotein ligand-1 [14], as do activated complement components [15]. In addition to generating superoxide and other free radicals, adherent leukocytes may degranulate and release substances such as platelet activating factor, interleukins, and tumor necrosis factor, which enhance local platelet activation and induce tissue factor expression by ambient monocytes.
In contrast to receptor-mediated adherence of platelets and leukocytes to the protein monolayer, red blood cell adhesion is passive [16]. Adherent red cells can release ADP, which activates platelets, and under high shear conditions, erythrocyte hemolysis may occur. Therefore, protein adsorption onto artificial surfaces promotes platelet and leukocyte adhesion, and red blood cell adhesion follows.

**Activation of the contact system**

Components of the contact system adsorb to artificial surfaces, thereby facilitating activation of the intrinsic pathway of coagulation. Adsorbed fXII undergoes autoactivation to become the enzyme fXIIa, which then activates PK and fXI. Because HK serves as a cofactor in these reactions and binds to artificial surfaces, further activation of fXII and the contact pathway occurs. PK activation results in the generation of kallikrein, which activates more fXII in a reciprocal fashion. Activation of fXII initiates a series of proteolytic reactions that culminate in thrombin generation. Thrombin not only converts fibrinogen to fibrin monomers, but also serves as a potent platelet agonist, thereby promoting local platelet aggregation. The fibrin monomers polymerize and the fibrin strands stabilize the platelet aggregates thus creating a platelet–fibrin thrombus. This thrombus fouls the device and can cause it to fail. Furthermore, parts of the thrombus can detach from the surface, travel through the circulation, and lodge in vessels supplying blood to critical organs. Therefore, thrombus formation on artificial surfaces is the result of both platelet activation and aggregation and fXIIa-induced thrombin generation, and thrombosis on these devices can have local or systemic consequences.

We have done studies that highlight the importance of the contact system and intrinsic pathway in the initiation of clotting on blood-contacting medical devices. Thus, we showed that the clotting time of recalcified plasma was 3-fold shorter in the presence of catheter segments than in their absence [17]. The prothrombotic activity of the catheters was mediated via the intrinsic pathway because it was blocked with corn trypsin inhibitor (CTI) [18], a potent and specific inhibitor of fXIIa, and it was attenuated in plasma depleted of fXII or fXI [17]. In contrast, catheter segments had no effect on the clotting time of fVII-depleted plasma [17]. As shown with other artificial surfaces, we demonstrated that catheter segments bind fXII, induce fXII autoactivation, and promote fXII-mediated activation of fXI [18]. Therefore, catheters promote clotting *in vitro* via the intrinsic pathway of coagulation.

To determine whether our *in vitro* findings also apply *in vivo*, we selectively knocked down the levels of fXII, fXI, HK, or fVII in rabbits using antisense oligonucleotides (ASOs) [19]. Using a chronic model of catheter thrombosis, the effect of clotting factor knockdown on the time to occlusion of catheters implanted into the jugular vein was then determined up to a maximum of 35 days. Compared with the time to occlusion in control rabbits given saline, fXII and fXI knockdown prolonged the time to catheter occlusion by 2.2- and 2.3-fold, respectively [19]. In contrast, neither HK nor fVII knockdown had any effect on the time to catheter occlusion, nor did dual treatment with the fVII and fXI ASO prolong the time to occlusion more than treatment with the fXI ASO alone [19]. Although involvement of HK and fVII cannot be totally excluded because knockdown was incomplete, our data suggest that catheter-induced clotting *in vitro* and *in vivo* is mainly mediated via the intrinsic pathway.

Recent studies suggest that clotting on extracorporeal circuits and vascular grafts also is mediated via the intrinsic pathway. Thus, a fXIa inhibitory antibody attenuates thrombosis in a rabbit extracorporeal membrane oxygenation (ECMO) model [20] and reduced platelet and fibrin deposition on vascular grafts in a baboon arterio-venous shunt model [21]. Similar results were obtained with fXI inhibition. Thus, ASO-mediated knockdown of fXII or administration of a fXI-directed antibody reduced clotting on vascular grafts in this model [22,23]. Therefore, fXII and fXI have emerged as promising targets for prevention of thrombosis on blood-contacting devices and extracorporeal circuits.

**Complement activation**

Complement activation occurs during cardiopulmonary bypass, hemodialysis, and ECMO when blood comes into contact with the extracorporeal circuitry and the membrane oxygenator or dialysis membrane [24]. Complement activation also occurs with catheters and vascular grafts [25]. The complement cascade is initiated by three distinct pathways; the classical, alternative, and lectin pathways. Artificial surfaces trigger complement activation via the classical and alternative pathways. Kallikrein generated on artificial surfaces cleaves fXIIa to generate β-FXIIa, which by activating the first component of complement initiates the classical pathway. C3 and C5 deposit on artificial surfaces, particularly extracorporeal circuits. Kallikrein activates C3 and C5, and fIxa, fXa, and thrombin activate C5 [26,27]. The resultant C3a and C5a serve as potent chemoattractants for leukocytes and promote their adhesion to the surface and their subsequent activation. Therefore, the coagulation and complement systems are intimately linked, and both systems are activated on artificial surfaces.

**Methods to prevent thrombosis on blood-contacting medical devices**

Efforts to prevent thrombosis on blood-contacting medical devices have focused on methods to render artificial
surfaces less thrombogenic and/or administration of systemic antithrombotic agents, or both to attenuate device-induced thrombosis. As outlined above, protein adsorption and cell deposition initiate thrombus formation on artificial surfaces. Consequently, efforts have focused on surface modifications designed to resist adsorption of blood proteins. Even with currently available biomaterials, however, thrombosis remains a concern, a problem that necessitates administration of antithrombotic agents and/or anticoagulants to patients with devices such as coronary stents, mechanical heart valves, or left ventricular assist devices. Despite these approaches, even with the most advanced ventricular assist devices, for example, failure rates due to thrombosis of up to 6% have been reported [28]. The results of recent clinical trials suggest that some anticoagulants may be better than others for prevention of thrombosis on blood-contacting medical devices. The following sections describe the approaches to synthesizing less thrombogenic biomaterials and explain why some anticoagulants are better than others for prevention of biomaterial-induced clotting.

Synthesis of less thrombogenic biomaterials
Methods to render artificial surfaces less thrombogenic have focused on inhibition of protein and cell absorption, inhibition of thrombin generation and fibrin formation, and/or inhibition of platelet activation. Each approach will be briefly discussed in turn.

Inhibition of protein and cell adsorption
Approaches to reduce protein and cell adsorption are guided by the concepts that protein adsorption to the surface is favored by electrostatic and hydrophobic interactions between the adsorbed protein and the artificial surface, and by the local increase in entropy that occurs with displacement of water molecules and counter ions from the protein layer on the surface [29]. Synthetic and natural materials have been investigated in an attempt to modulate these processes. These include poly(ethylene oxide), pyrolytic carbon, albumin, phosphorylcholine, and elastin-inspired protein polymers.

Poly(ethylene oxide) (PEO)
Hydrophilic ether oxygen in the structural repeat unit of PEO, that is, \((\text{CH}_2-\text{CH}_2-\text{O})_n\), leads to a water-solvated structure that forms a liquidlike surface with highly mobile molecular chains with no particular molecular order. This property is thought to explain why PEO exhibits lower levels of protein and cellular adsorption than other polymers [30]. Several methods have been used to modify artificial surfaces with PEO, including bulk modification, covalent grafting, and physical adsorption. Although most PEO-modified surfaces demonstrate resistance to protein and cell binding in vitro, results in vivo have been inconsistent and studies in humans are lacking [30].

Albumin-coated surfaces
Compared with plasma proteins such as fibrinogen and \(\gamma\)-globulin, albumin induces less platelet adhesion [31,32]. This finding prompted its use as an inert thromboresistant coating. Albumin has been covalently grafted onto surfaces [33]. Alternatively, surfaces have been modified with long aliphatic chains to promote binding of endogenous albumin, or warfarin, which binds albumin with high affinity [34,35]. Such surfaces exhibit reduced platelet and leukocyte adhesion in vitro [36], but when a glutaraldehyde-cross-linked albumin coating was applied to Dacron grafts, studies in animals and humans failed to improve performance characteristics compared with uncoated grafts [37–39].

Pyrolytic carbon-coated surfaces
Mechanical heart valves, stents, and vascular grafts have been coated with pyrolytic carbon. Pyrolytic carbon films are produced by chemical vapor deposition. Although there is less platelet adhesion and spreading on carbon-coated surfaces than on uncoated surfaces in vitro and in animals, long-term patency rates of carbon-coated vascular grafts and coronary stents in humans were similar to uncoated grafts [40–42]. Furthermore, despite pyrolytic carbon coating of contemporary bileaflet mechanical heart valve components, patients with mechanical valves continue to require lifelong anticoagulation with vitamin K antagonists to prevent thromboembolic complications.

Phosphorylcholine surfaces
Phosphatidylcholine, the predominant lipid on the outer surface of non-activated cell membranes, resists protein and cell adhesion likely because its zwitterionic polar head group is electrically neutral at physiological pH. Polymethacrylate and polyurethane-based polymers that incorporate the phosphorylcholine head group within the polymer backbone have been synthesized. Alternatively, the phosphatidylcholine head group has been chemically grafted onto metal or polymer surfaces [43,44] or a polymerized membrane-mimetic film has been coated onto the inner surface of vascular grafts [45]. Although all of these surfaces exhibit reduced platelet adhesion in vitro and in some animal models [46], phosphorylcholine polymer-coated stents had no advantages over uncoated stents in porcine or rabbit angioplasty models [47] and initial results in humans have been disappointing [48].
Elastin-inspired polymers

The rationale for elastin-based coatings stems from the observation that there is minimal platelet adhesion and aggregation on elastin, an integral component of the vessel wall. Although original coatings used elastin derived from bovine or porcine tissues, elastin is difficult to isolate and purify from these sources because of its inherent insolubility. This problem was circumvented by the identification of an elastin consensus sequence that formed the basis for the synthesis of elastin-inspired protein polymers [49–51]. When soluble and cross-linked poly(Val-Pro-Gly-Val-Gly) was photochemically linked to silicone through amino-terminal lysine residues, the surface exhibited decreased fibrinogen and immunoglobulin adsorption and induced less proinflammatory cytokine release from monocytes [52]. Passive absorption of a recombinant elastin polypeptide onto synthetic surfaces resulted in decreased platelet deposition in vitro and delayed catheter occlusion in animals [53]. Elastin-mimetic protein polymer films also have been synthesized, and when coated on the inner surface of vascular grafts, these films reduced thrombogenicity in a baboon arterio-venous shunt model [54]. Therefore, elastin-inspired polymers are promising new biomaterials, although most of the current efforts are focused on their applications for targeted therapeutic drug delivery [55].

Inhibition of thrombin generation and fibrin formation

Endothelial cells have anticoagulant properties that render them non-thrombogenic. Approaches to mimic these properties include seeding prothrombotic surfaces with endothelial cells and grafting antithrombotic substances onto the biomaterial surface. Endothelial cell seeding is challenging because of problems with cell sourcing, stability, viability, and function. Biologically inspired biomaterials have been generated by introducing bioactive molecules such as CTI, heparin, direct thrombin inhibitors such as hirudin, bivalirudin, or argatroban, or thrombomodulin onto their surface.

CTI

Because protein adsorption and fXII activation on biomaterial surfaces are the root cause of thrombin generation and fibrin formation, we set out to develop blood-contacting surfaces that not only resist protein deposition, but also inhibit fXIIa. This was accomplished by coating surfaces with a polyethylene glycol (PEG)-CTI conjugate starting with either a preformed conjugate or by sequential attachment of PEG followed by CTI [56–58]. PEG attachment to the surface reduced fibrinogen adsorption from buffer or plasma, properties that were retained when PEG-CTI was attached. However, in contrast to PEG coating alone, PEG-CTI coating also inhibited fXII autoactivation on the biomaterial surface, attenuated fXIIa-mediated activation of fXI, reduced thrombin generation, and prolonged the clotting time of calcified plasma [56–58]. Furthermore, when implanted into the jugular veins of rabbits, PEG-CTI-coated catheters remained patent 2.5-fold longer than uncoated catheters, catheters coated only with PEG, and catheters coated with a PEG-albumin conjugate [18]. Therefore, by attenuating protein deposition and inhibiting fXIIa, PEG-CTI coating has the potential to block the root causes of clotting on blood-contacting medical devices.

Heparin

Heparin or covalent heparin–antithrombin complexes have been immobilized on the surface of biomaterials [59]. Methods to immobilize heparin have included electrostatic self-assembly via the charged sulfate groups of heparin, covalent grafting often using a spacer, endpoint immobilization, integration into hydrogel networks, and loading into bulk polymers for controlled release. Although preclinical data and results in animal models were promising, in randomized clinical trials, angiographic and clinical endpoints were similar with heparin-coated and bare metal coronary stents [60,61]. Likewise, although they appeared to attenuate some aspects of the inflammatory response, neither covalent nor ionic-bonded heparin-coated cardiopulmonary bypass circuits reduced thrombin generation, altered platelet consumption, or decreased postoperative transfusion requirements compared with uncoated circuits [62]. Therefore, the utility of heparin-coated biomaterials has been questioned. Current efforts include binding heparin-polyl-L-lysine nanoparticles onto dopamine-coated surfaces [63], coating multilayer films of heparin-mimicking polyanions and polycations synthesized from β-cyclodextrin onto membrane surfaces [64], or covalently immobilizing alginate–heparin composites onto the surface of polyvinyl chloride components of extracorporeal circuits [65].

Direct thrombin inhibitors

Agents such as hirudin, bivalirudin, or argatroban have been grafted on surfaces to inhibit thrombin [66–68]. In contrast to heparin, which, by activating antithrombin, inhibits thrombin, fXa and other clotting enzymes in a catalytic fashion, hirudin, bivalirudin, and argatroban are stoichiometric inhibitors that bind thrombin in a 1 : 1 fashion. Direct thrombin inhibitors have been cross-linked to poly(D,L-lactide-co-glycolide) or have been grafted onto a cross-linked-modified albumin basecoat. In vivo data with such surfaces are limited, and their durability is questionable.

Thrombomodulin

By binding thrombin, thrombomodulin promotes the activation of protein C. Activated protein C limits coagulation
by inactivating fVIIIa and fVa, important cofactors for fXa and thrombin generation, respectively. Recombinant thrombomodulin has been conjugated to aminated and carboxylated surfaces, including poly(vinyl amine) polyurethane, poly(acrylic acid) surface-grafted polyurethane, and surface-hydrolyzed poly(ether urethaneurea) [69,70]. Because attachment occurs via any functional group on the protein, including those involved in thrombin binding, the bioactivity of attached thrombomodulin is reduced. Nonetheless, thrombomodulin-coated surfaces exhibit attenuated thrombin generation under static and flow conditions [71]. However, data in animals are limited.

**Inhibition of platelet aggregation**

Antiplatelet agents, such as aspirin and clopidogrel, are a mainstay for the prevention of stent thrombosis and recurrent ischemia in patients undergoing PCI for acute coronary syndrome (ACS), thereby highlighting the role of platelets in these processes. To mimic their effect, antiplatelet agents, such as prostacyclin or prostaglandin E2, have been immobilized on albuminized surfaces, or biomaterials that release or generate nitric oxide have been synthesized.

**Systemic administration of antiplatelet agents and/or anticoagulants**

Failure of medical devices is often due to corruption by thrombi. This results from a combination of flow disturbance and surface biocompatibility. Advancements in device hemodynamics offer the potential to reduce platelet activation due to flow disruption [28]. Similar efforts are directed at improvements in biomaterials; nonetheless, patients with coronary stents, mechanical heart valves, and left ventricular assist devices still require short- or long-term treatment with antiplatelet drugs and/or anticoagulants to prevent thrombosis. Likewise, patients undergoing cardiopulmonary bypass, hemodialysis, or ECMO also require anticoagulants to prevent clotting in the extracorporeal circuits and on the membrane oxygenators or dialysis membranes.

The results of clinical trials with fondaparinux, a synthetic pentasaccharide that inhibits fXa in an antithrombin-dependent fashion, and dabigatran, an oral thrombin inhibitor, support the concept that failure to block medical device-induced activation of the contact system can lead to adverse clinical outcomes. Thus, when fondaparinux was compared with LMWH in patients with non-ST-segment elevation ACS, there was a higher risk of catheter thrombosis in fondaparinux-treated patients undergoing PCI [72]. A similar phenomenon was observed when fondaparinux was compared with heparin in patients with ST-segment elevation ACS who underwent urgent PCI [73]. Likewise, when dabigatran was compared with warfarin in patients with mechanical heart valves, there was a trend for more ischemic strokes and bleeding with dabigatran, a finding that prompted early termination of the study [74].

Our *in vitro* and rabbit studies highlight the limited capacity of fondaparinux and dabigatran to inhibit catheter-induced clotting [17,75]. Whereas heparin inhibits catheter-induced thrombin generation and subsequent clot formation *in vitro* in a concentration-dependent fashion, fondaparinux has no effect on this process even with doses much higher than those used clinically. At concentrations with equivalent anti-Xa activity, the effect of enoxaparin on catheter-induced clotting is intermediate between that of heparin and fondaparinux [17], a finding that indicates that longer heparin chains inhibit catheter-induced clotting to a greater extent than shorter ones. This is not surprising because by simultaneously binding antithrombin and fIX, fXI, or fXII, longer heparin chains promote the formation of stable enzyme–inhibitor complexes. In contrast, fondaparinux, which only binds antithrombin, is unable to perform this bridging function. Without inhibition of these upstream enzymes, catheters induce the generation of fXa in concentrations that overwhelm fondaparinux. Supporting this concept is the observation that concomitant administration of low doses of fondaparinux and heparin to rabbits prolongs the time to catheter occlusion in a more than additive fashion [17]. Therefore, in addition to thrombin inhibition, effective prevention of catheter-induced clotting requires inhibition of coagulation enzymes above the level of fXa.

Enoxaparin has a greater effect on catheter-induced clotting than fondaparinux because some low molecular weight heparin chains are of sufficient length for bridging. This explains why in ACS patients undergoing PCI, there was less catheter thrombosis in patients randomized to enoxaparin than in those given fondaparinux [73]. Nonetheless, heparin is better than enoxaparin at preventing catheter-induced clotting *in vitro* and in rabbits [17]. If mechanical heart valves trigger clotting in the same fashion as catheters, this finding provides a potential explanation why in a small clinical trial, heparin was better than enoxaparin for prevention of valve thrombosis in pregnant women with mechanical heart valves and why there are case reports of valve thrombosis in enoxaparin-treated patients [76,77].

Although data with mechanical heart valves are lacking, dabigatran is less effective than heparin or warfarin at preventing catheter-induced thrombin generation *in vitro* [75]. We hypothesize that the same phenomenon occurs with mechanical heart valves. Therefore, we speculate that mechanical heart valves trigger clotting via the contact pathway and induce generation of thrombin in concentrations that exceed those of dabigatran, which inhibits thrombin in a 1:1 stoichiometric fashion. Supporting the limitations of dabigatran for prevention of thrombosis on medical devices, we demonstrated that...
dabigatran prevented catheter-induced thrombin generation in vitro, but only at concentrations greater than 100 ng mL⁻¹, levels similar to those found at peak in patients given the drug at a dose of 150 mg twice daily [75]. At concentrations around 50 ng mL⁻¹, levels similar to those measured at trough with the 150 mg twice daily dosing regimen, dabigatran had no effect on catheter-induced thrombin generation in vitro, nor did it prolong the time to catheter occlusion in rabbits [75]. If mechanical heart valves induce clotting in the same way as catheters, this phenomenon could explain why dabigatran was less effective than warfarin for stroke prevention in patients with mechanical heart valves in the RE-ALIGN trial [74]. In that study, the dabigatran dose was increased up to a maximum of 300 mg twice daily in an attempt to maintain trough levels above 50 ng mL⁻¹, an effort that was not always successful. In contrast, by lowering the functional levels of fVII, fIX, fX, and prothrombin, warfarin is a potent inhibitor of fXa and thrombin generation via the extrinsic and contact pathways. Therefore, if mechanical heart valves trigger clotting by activating fXII, inhibition of clotting enzymes upstream to fXa is likely to be a more effective strategy than inhibition of fXa or thrombin alone. Furthermore, the potential for bleeding is likely to be lower with agents that inhibit fXIIa or fXIa than with those that inhibit fXa or thrombin because fXII and fXI play little or no part in hemostasis.

Conclusions and future directions

The goal of biomaterial research is to synthesize blood-contacting surfaces that eliminate the risk of thrombus formation. Advances in materials science and an increased understanding of the processes involved in protein deposition and subsequent activation of platelets, coagulation, and complement on artificial surfaces have resulted in the synthesis of novel biomaterials that are more resistant to protein and cell deposition. Although biologically active coatings that inhibit platelet responses or coagulation reactions are promising, additional studies are needed to assess their utility with complex devices such as mechanical heart valves or left ventricular assist devices. Increasing recognition of the role of the intrinsic pathway of coagulation in the pathogenesis of thrombosis on blood-contacting surfaces offers new opportunities for local and/or systemic approaches to prevent this problem. Because protein adsorption and fXII activation are the root causes of device-induced thrombosis, synthesis of biomaterials that block these processes may prevent clotting; PEG-CTI-coated surfaces offer this potential. Moreover, the administration of heparin or fondaparinux in concentrations that have no effect on the potency of uncoated catheters prolongs the potency of PEG-CTI-coated catheters in a more than additive fashion. These findings highlight the potential for synergy between fXIIa inhibition on the device surface and systemic inhibition of downstream effectors in the coagulation pathway. Studies in humans are needed to test these concepts.

What is the future for blood-contacting medical devices? Advances in tissue engineering and stem cell technology may eventually lead to the development of valves and grafts that mimic their natural counterparts, thereby obviating the need for systemic antithrombotic therapy. In the interim, however, increasing use of implantable cardiovascular devices, such as transcatheter valves, mitral valve clips, ventricular assist devices, and left atrial appendage occlusion devices, will necessitate novel strategies to prevent thrombosis. To that end, emerging strategies for inhibition of components of the intrinsic pathway, including inhibitory antibodies against fXIIa or fXIa, small molecule inhibitors of fX1a, and fXII or fXI ASOs, have the potential to inhibit the root cause of device-associated thrombosis more safely than anticoagulants such as heparin or warfarin [78]. Thus, a fXIIa-directed inhibitory antibody reduced clotting to the same extent as heparin in a rabbit extracorporeal membrane oxygenation model without increasing bleeding [20]. Likewise, fXI knockdown and a fXI-directed antibody attenuated graft thrombosis in a baboon arteriovenous shunt model [21-23]. These studies identify fXII and fXI as potential targets for new strategies to prevent device-associated thrombosis.

Although studies to date have primarily been in animals, the importance of the intrinsic system in the pathogenesis of thrombosis in humans is highlighted by a recent study evaluating a fXI ASO in patients undergoing elective knee arthroplasty [79]. Reducing fXI levels below 20% of normal during and after surgery with the ASO resulted in a significantly lower rate of postoperative venous thromboembolism than was achieved with enoxaparin. Even though patients underwent surgery with low fXI levels, rates of bleeding with the ASO were numerically lower than those with enoxaparin. Together with the promising preclinical results in animals, these findings should stimulate investigation of strategies targeting fXI or fXII for prevention of clotting on blood-contacting biomedical devices.

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