Brief Review

Factor XII as a Therapeutic Target in Thromboembolic and Inflammatory Diseases

Katrin F. Nickel, Andy T. Long, Tobias A. Fuchs, Lynn M. Butler, Thomas Renné

Abstract—Coagulation factor XII (FXII, Hageman factor) is a plasma protease that in its active form (FXIIa) initiates the procoagulant and proinflammatory contact system. This name arises from FXII’s unique mechanism of activation that is induced by binding (contact) to negatively charged surfaces. Various substances have the capacity to trigger FXII contact-activation in vivo including mast cell–derived heparin, misfolded protein aggregates, collagen, nucleic acids, and polyphosphate. FXII deficiency is not associated with bleeding, and for decades, the factor was considered to be dispensable for coagulation in vivo. However, despite the fact that humans and animals with deficiency in FXII have a normal hemostatic capacity, animal models revealed a critical role of FXIIa-driven coagulation in thromboembolic diseases. In addition to its role in thrombosis, FXIIa contributes to inflammation through the activation of the inflammatory bradykinin-producing kallikrein-kinin system. Pharmacological inhibition of FXII/FXIIa interferes with thrombosis and inflammation in animal models. Thus, targeting the FXIIa-driven contact system seems to be a promising and safe therapeutic anticoagulation treatment strategy, with additional anti-inflammatory effects. Here, we discuss novel functions of FXIIa in cardiovascular thrombotic and inflammatory disorders. (Arterioscler Thromb Vasc Biol. 2017;37:13-20. DOI: 10.1161/ATVBHA.116.308595.)

Key Words: blood coagulation ■ factor XII ■ inflammation ■ reperfusion injury ■ therapy ■ thrombosis

Factor XII–Driven Contact System

The factor XII (FXII)–driven plasma contact system is a procoagulant and proinflammatory protease cascade. The system consists of the serine protease zymogens FXII, plasma prekallikrein (PPK), the nonenzymatic cofactor high molecular weight kininogen, and the serpin C1 esterase inhibitor (C1INH), the major inhibitor of both activated FXII (FXIIa) and plasma kallikrein.1–3 In addition, the FXIIa substrate FXI, although not a classical contact factor, structurally and functionally belongs to the system.4 FXII binding to negatively charged surfaces induces a conformational change in the presence of zinc ions. Minute amounts of formed FXIIa activate PPK to plasma kallikrein by limited proteolysis. PPK then reciprocally activates further FXII and also cleaves high molecular weight kininogen to release the proinflammatory peptide hormone bradykinin (kallikrein-kinin system).1–3

Binding of bradykinin and its metabolite desArg9-bradykinin to their G-protein–coupled kinin B2 and B1 receptors, respectively, initiates a variety of signaling pathways culminating in pain, reduced blood pressure, vascular leakage, and neutrophil chemotaxis.5,6 In addition to the kallikrein-kinin system, contact-activated FXII triggers the intrinsic pathway of coagulation via FXI (Figure 1).

A role of FXII for fibrin formation has been established for decades. FXII contact activation is used to initiate plasma clotting in the diagnostic coagulation assay activated partial thromboplastin time. Although deficiency in any of the contact factors, with the exception of C1INH, prolongs the activated partial thromboplastin time, contact factor deficiency is not associated with hemostatic abnormalities in humans or in mice.6 In contrast to FXII, FXI deficiency is associated with trauma-induced bleeding in humans (hemophilia C), possibly because of FXII-independent activation by the thrombin-driven feedback loop.7 In contrast to FXI-deficient humans, FXI-deficient mice do not bleed excessively, suggesting species-specific functions of the protein in hemostasis.8 Normal bleeding in FXI-deficient individuals led to the premise that the factor has no function for coagulation in vivo. This hypothesis was challenged by the discovery that thrombosis was defective in FXII-deficient mice, despite the fact that the animals have a normal hemostatic capacity.9 FXII-driven coagulation specifically contributes to thrombosis but not to hemostasis, indicating that these 2 processes principally differ in mechanism.5 The critical role of FXII in thrombosis has sparked renewed interest in the contact system pathway in the past decade and several FXII-in vivo contact activators, such as platelet polyphosphate,10 nucleic acids (RNA11 and DNA12), collagen,13 misfolded protein aggregates,14 and mast cell–released heparin15,16 have been identified. Furthermore, FXII can be directly activated through proteolytic activation...
independent of plasma kallikrein by plasmin or bacterial proteases.18

Role of FXII in Experimental Thrombotic Disease
FXII deficiency impairs contact-driven plasma clotting; however, defective in vitro clotting is not associated with bleeding abnormalities. This apparent discrepancy motivated us to produce FXII-deficient (F12−/−) mice and to phenotype the animals in a variety of thrombosis models. FXII deficiency provided potent thromboprotection and infusion of human FXII restored thrombus formation in F12−/− mice.9 Deficiency in FXII interfered with ferric chloride–induced thrombus formation in F12−/− mice.9 Deficiency in FXII interfered with ferric chloride–induced thrombus formation in the carotid artery19,20 and mesenteric arteriols.9 Thromboprotection seen in F12−/− mice was not restricted to chemical vessel injury. Thrombosis was also defective in mechanically9 or Rose Bengal laser-injured19 carotid arteries. Carotid arteries are prone for atherosclerosis. FXII and the proteins of the contact system are enriched in early and unstable human atherosclerotic plaques suggesting a role of FXII in atherothrombosis.21 In a mouse model of atherosclerosis (ApoE−/− mice fed with Western-type diet) targeting FXIIa with corn trypsin inhibitor interfered with vessel occlusive clot formation on ultrasound-driven ruptured atherosclerotic plaques in carotid arteries.22 Similarly, knockdown of FXI expression by an antisense nucleotide–approach reduced thrombus size in the same model.23 FXIIa was localized in human thrombi removed during carotid endarterectomy24 and tissue homogenates prepared from human atherosclerotic plaques showed FXII activity.21 Deficiency in FXII or FXI, or combined deficiencies, similarly reduced thrombus formation on immobilized plaque material in a laminar flow chamber system, indicating that FXIIa operates via FXI in plaque-driven coagulation.23 Intravital microscopy studies revealed the mechanism of defective vessel occlusive thrombus formation associated with FXII deficiency.9,23 Initially, thrombi similarly develop in wild-type and FXII-targeted mice, consistent with the hypothesis that tissue factor mostly, if not exclusively, drives coagulation at vascular injury sites. However, subsequently thrombus propagation is defective in the absence of FXII. Both FXII-deficient and FXIIa-targeted mice have impaired thrombus propagation and exposed to arterial shear the developing thrombus sheds microemboli. In contrast, inhibition of tissue factor–driven coagulation reduced early thrombus size without increased embolization.23 Together, the data show that FXII-driven coagulation contributes to thrombus propagation by producing fibrin within the developing clot, leading to increased thrombus stability. Vice versa, deficiency in FXII does not allow for intrinsic pathway-driven fibrin production, impairs thrombus growth, and protects from vessel occlusive clot formation. Consistently, mechanical clot stability (assessed by thromboelastography) is largely reduced in

![Figure 1. Factor XII (FXII)–driven contact system and its roles in diseases. Polyphosphate (polyP), mast cell–derived heparin, collagen, nucleic acids (DNA and RNA), and misfolded protein aggregates such as amyloid β-protein (Aβ) induce FXII contact-activation in vivo. Activated FXII (FXIIa) triggers fibrin formation through the factor XI (FXI)–mediated intrinsic coagulation pathway, contributing to atherothrombosis, ischemic stroke, venous thromboembolism (VTE) such as deep vein thrombosis (DVT), pulmonary embolism (PE), and cancer-driven VTE. FXIIa also activates prekallikrein (PPK) leading to release of bradykinin (BK) by plasma kallikrein (PK)–mediated cleavage of high molecular weight kininogen (HK). Both FXI and PPK are bound indirectly to cells via HK. BK activates kinin B2 receptors (B2R), whereas the BK metabolite des-Arg9 BK binds to kinin B1 receptor (B1R), both of which activate proinflammatory signaling cascades that contribute to increased vascular leak in hereditary and angiotensin-converting enzyme (ACE) inhibitor–induced angioedema (AE), allergic and anaphylactic reactions, and vascular dysfunction in patients with Alzheimer’s disease. Serpin C1 esterase inhibitor (C1INH) is the major inhibitor of both activated FXII and PK.](https://arch.ahajournals.org/content/62/1/14)
Nickel et al  Factor XII as a Therapeutic Target  15

the absence of FXII in human and mouse blood. How is FXII activated in thrombosis? Platelets store an inorganic polymer, polyphosphate, in their dense granules that is released on activation.25 Platelet-size synthetic polyphosphate activates FXII and initiate coagulation in an FXII-dependent manner in human plasma.26 Using thrombosis and inflammation models in mice, as well as a human disease model, our laboratory has shown that polyphosphate-mediated FXII activation drives platelet-driven thrombosis and inflammation in vivo.10 Targeting polyphosphate with recombinant exopolyphosphatase mutants ablates thrombus formation in ferric chloride–challenged carotid arteries without increasing bleeding risk reproducing the thromboprotective phenotype of F12−/− mice in this model.27 Neutralizing polyphosphate interferes with carotid artery thrombosis by increasing the embolization rate, confirming a central role of the platelet polyphosphate/FXII pathway for arterial thrombosis. In sum, the data support a model of tissue factor–initiated and polyphosphate/FXII–propagated coagulation in atherothrombosis (Figure 2).

FXII also contributes to cerebrovascular thrombosis. F12−/− mice are protected from cerebral ischemia in a model of ischemic stroke (transient middle cerebral occlusion [tMCAO] induced by an inert filament).28 Brain damage and vessel occlusive fibrin formation were similarly reduced in FXI-deficient mice, indicating that FXII contributes to ischemic stroke through the intrinsic coagulation pathway. In contrast, FXII deficiency was not protective in a model of permanent occlusion of the middle cerebral artery.29 The underlying mechanisms are not clear, but may relate to thrombus stability. Similar to atherothrombosis, unstable thrombi are formed in cerebral vessels occluded by the inserted filament in the absence of FXII. In the reperfusion phase that occurs in the tMCAO, but not in the permanent occlusion of the middle cerebral artery model, these thrombi are cleared more easily facilitating restoration of blood flow. FXII functions in cerebral thrombosis are not limited to ischemia/reperfusion injury. Targeting FXII interferes with trauma-induced thrombosis in microvessels and reduces brain injury.30

Importance of FXII is not restricted to arterial thrombosis and contributes to venous thromboembolism. Mouse models have shown a critical role of FXII in deep vein thrombosis. Stasis-driven deep vein thrombosis in the inferior vena cava (IVC ligation model) is reduced in F12−/− mice.31 Embolization of venous thrombi can cause pulmonary embolism (PE). F12−/− mice are protected from PE triggered by the infusion of collagen/epinephrine or synthetic and platelet-derived polyphosphate into the vena cava.10 Furthermore, malignant disease is a major and well-established risk factor for venous thromboembolism. Mouse PE models and cancer patient materials showed that the polyphosphate/FXII pathway drives coagulation in cancer-associated venous thromboembolism.32 Prostate cancer cells and cancer cell–derived microvesicles exposed polyphosphate on their plasma membrane, activating FXII and induced FXIIa-driven clotting in patient plasma and PE in mice.32 The polyphosphate/FXII pathway operates independently of tissue factor–driven coagulation33 and

Figure 2. Model of atherothrombosis after atherosclerotic plaque rupture. A, After plaque rupture, tissue factor (TF) is exposed to blood and triggers fibrin formation. B, Platelets rapidly bind to formed fibrin, become activated, and secrete polyphosphate (polyP) and TF pathway inhibitor (TFPI) that terminates TF activity. C, PolyP activates factor XII (FXII)–driven coagulation driving fibrin formation within the forming thrombus that is critical for thrombosis.
interference with this pathway allows for safe anticoagulation. Collectively, these data show that the FXII-driven contact system drives arterial and venous thrombosis in mice.

**Role of FXII in Human Thrombotic Disease**

Despite accumulating evidence that FXII critically contributes to thrombosis in experimental mouse and baboon models, a role of FXII for human thrombotic disease has remained controversial.36 Anecdotal reports suggesting that FXII deficiency independently of FXII deficiency.36 In addition, antiphospholipid antibodies, although a thrombotic risk factor, cause a prolonged clotting time in an activated partial thromboplastin time–based assay and may suggest false-positive results (pseudo-FXII deficiency). Indeed, controlled clinical studies failed to find an association of FXII deficiency with increased risk of thromboembolic disease.37 Because there is still a lack of clinical data analyzing for potential thromboprotection in FXII-deficient individuals, we have initiated a registry on FXII-deficient humans (www.factor12.net) and invite readers to include individuals with inherited severe FXII deficiency.

Epidemiological studies have found an association between plasma FXII/FXIIa levels and arterial thrombosis. Plasma FXIIa, measured by FXIIa-specific antibody-based ELISA, was elevated in a large cohort (>2400) of middle-aged men with high risk of coronary heart disease. FXIIa was independent and positively associated with risk factors for coronary heart disease, such as cholesterol and triglycerides, blood pressure, body mass index, fibrinogen concentration, tobacco smoking, and alcohol intake.38 Thus, the contact system of coagulation seems to be activated when coronary heart disease risk is increased. Circulating levels of FXIIa are increased in patients with ischemic heart disease, compared with control subjects.39 Using the same assay, FXIIa was elevated in a large cohort of 870 patients with acute coronary syndrome at the time of admission and predicted long-term all-cause and cardiac mortality.40 Elevated FXIIa plasma level also predicted recurrent cardiovascular events after acute myocardial infarction.41 Free FXIIa is unstable as the protease binds to inhibitors in plasma and inhibitor binding mask the anti-FXIIa antibody epitope that was used in the aforementioned studies. To overcome these preanalytical challenges, later studies assessed that FXIIa bound to its endogenous inhibitors C1INH or antithrombin as a biomarker for contact activation. FXIIa/C1INH or FXIIa/antithrombin levels were elevated in plasma of patients with myocardial infarction at admission.42 Similarly, the Dutch RATIO study involving >200 young women with myocardial infarction found levels of activated contact system proteins associated with arterial thrombosis. Although elevated kallikrein/C1INH complexes strongly indicated risk of myocardial infarction, FXIIa/C1INH was elevated in patients with a history of ischemic stroke.43 In the same cohort, however, FXII zymogen levels were not associated with the incidence for myocardial infarction or ischemic stroke.44 In contrast, a Dutch study found FXII clotting activity associated with decreased risk of myocardial infarction.45 Consistently, low FXIIa/C1INH and kallikrein/C1INH complexes were associated with increased risk for coronary heart disease and ischemic stroke.46 Other studies failed to find an association between FXII activity and myocardial infarction47 or ischemic stroke.48 Possible explanation for the discrepant results may reflect the use of different nonstandardized biomarkers, the short half-life of free FXIIa in plasma, rapid clearance of FXIIa/C1INH complexes, different study designs and patient cohorts. In summary, the wealth of the data has remained somehow uncertain indicating a need for novel clinical studies and better biomarkers.

Data from a large Austrian registry reported an inverted U-shape association of FXII plasma levels (assessed by an activated partial thromboplastin time–based clotting assay) and mortality.49 Mortality in patients with severe FXII deficiency (<10%) was similar to those with FXII level in the normal range (100%) and elevated for all reduced levels. The underlying mechanism remains unclear; however, it may reflect a delicate interplay of thromboprotection and increased risk of embolization in individuals with reduced FXII levels.

**FXII and Inflammation**

Activated FXII triggers the kallikrein-kinin system leading to release of bradykinin.5 Bradykinin activates kinin B2 receptor–mediated signaling cascades that lead to increased intracellular calcium, formation of nitric oxide and eicosanoids, and release of tissue-type plasminogen activator. B2 receptors are constitutively expressed throughout healthy tissues, whereas B1 is selectively expressed. Bradykinin induces increase in microvascular permeability, nitric oxide–mediated vasodilation, hypotension, and inflammatory reactions such as swelling, hyperperfusion, and pain.50 Furthermore, bradykinin stimulates macrophages to release neutrophil, monocyte, and eosinophil chemotactic substances51 and directly stimulates migration of neutrophils.52 Bradykinin is rapidly degraded by kinin-degrading enzymes (kininases) such as angiotensin-converting enzyme or carboxypeptidases N and M resulting in a short plasma half-life (second-range) of bradykinin in vivo (Figure 1).

Although defective FXII activity provides thromboprotection, excessive FXII activity results in hereditary angioedema (HAE), a rare life-threatening inherited disorder. HAE is caused by excessive bradykinin formation or signaling and characterized by recurrent episodes of acute swelling in multiple organs because of increased vascular permeability.53 HAE types I and II are characterized by deficiency or dysfunctionality of C1INH, respectively.54 Patients with a third HAE variant (HAE type III) have normal levels of a fully functional C1INH.55 This variant is associated with single-nucleotide polymorphisms in the F12 gene that cause missense mutations at position 309 (Thr309Arg and Thr309Lys) in FXII.56 The mutations lead to a loss of a single O-linked glycosylation that facilitates autoactivation of the zymogen. Mutant FXII presents a gain-of-function variant leading to excess bradykinin formation in patient plasma and edema in a humanized HAE type III mouse model.57 Mutated FXII zymogen also has increased sensitivity for enzymatic cleavage by plasmin.17 In sum, both
excess contact activation and proteolytic activation result in pathological mutant FXII activation culminating in excess bradykinin formation. Similar to increased bradykinin formation, reduced bradykinin metabolism mostly because of ACE inhibitor therapy provides a common cause of angioedema.50

A growing body of evidence suggests that the contact system contributes to Alzheimer’s disease (AD). AD is characterized by the accumulation of misfolded amyloid β-protein (Aβ) leading to neuroinflammation.36 Misfolded proteins have the capacity for activating FXII, and FXIIa levels are elevated in patients with systemic amyloidosis, a vascular disease marked by the accumulation and deposition of misfolded plasma proteins.14 Similarly, FXIIa is increased in plasma of AD mouse models and patients with AD.57 AD presents a prothrombotic state, and anticoagulation therapy has been shown to be beneficial in patients58 and mouse models.59 Indeed, the Aβ isoform Aβ42 promotes FXII-mediated thrombin generation through the intrinsic coagulation pathway48 and activates the kallikrein-kinin system.57 Thus, Aβ produced FXIIa may contribute to the procoagulant and inflammatory mechanisms in AD.

This cross talk of procoagulant and inflammatory mechanism, a concept described as thromboinflammation,61 also contributes to the pathophysiology of stroke. Previously, it was suggested that the kallikrein-kinin system plays an important role in the thromboinflammation process during cerebral ischemia. In addition to FXII, both PPK62 and high molecular weight kininogen63 contribute to microvascular thrombosis and blood–brain barrier leakage, edema formation, and inflammation after tMCAO. Significantly fewer macrophages/microglia and neutrophils were present in the brains of PPK- and high molecular weight kininogen–deficient mice when compared with wild-type mice. Consistently, infusion of C1INH protected mice and rats from intracerebral thrombosis and had antiedematous functions after tMCAO.64 Furthermore, genetic and pharmacological targeting of kinin B1 receptors, but not of B2 receptors, resulted in smaller infarct size, reduction of brain edema and reduced invasion of immune cells in the brain after tMCAO-induced ischemia/reperfusion injury.65 Furthermore, FXII was recently identified as a key regulator of adaptive immune responses in autoimmune diseases of the central nervous system such as multiple sclerosis via CD87-mediated modulation of dendritic cells.66

In sum, the dual role of FXII in thrombosis and inflammation makes it an attractive drug target.

Targeting FXII

Despite the increasing availability of anticoagulants, thrombotic disease treatment remains challenging. Currently available coagulation inhibitors target enzymes of the coagulation cascade that are important for fibrin formation and, therefore, bear an inherent risk for bleeding complications. Because of the selective importance of FXII in thrombus formation while being dispensable for hemostasis, the development of drugs targeting FXII(a) seems to be a promising approach. To date, several classes of FXII(a) inhibitors have been developed including recombinant proteins,67 synthetic peptides,28,68 small molecular weight FXIIa inhibitors,69 antibodies,20,34 and antisense oligonucleotides (ASO) that knockdown FXII expression.70 Most of these inhibitors have already been tested in vivo and demonstrated thromboprotective effects with additional anti-inflammatory properties.

The recombinant FXIIa inhibitor rHA-infestin-4 is based on the fourth domain of the nonclassic Kazal-type serine protease inhibitor from the midgut of the insect Triatoma infestans fused to human albumin to increase its stability.57 Intravenous infusion protected mice and rats from ferric chloride–induced arterial thrombosis and ischemic stroke. Furthermore, rHA-infestin-4–treated mice were protected from lethal PE, ischemic brain injury, thrombus formation on ruptured atherosclerotic plaques,77 hypotension during acute episodes of anaphylaxis,16 and experimental autoimmune encephalomyelitis.66 One of the drawbacks of using rHA-infestin-4 is that it modestly inhibits plasmin and FXa at high concentrations.71 Additionally, the insect-derived protein has immunogenic properties.

The synthetic peptide H-α-Pro-Phe-Arg-chloromethylketone irreversibly inhibits the amidolytic activity of FXIIa and plasma kallikrein-mediated activation of FXII. Mice pretreated with the inhibitor were resistant to cerebral infarction in the tMCAO model25 and were protected from polyphosphate-induced edema formation10 and hypotension during acute episodes of anaphylaxis.16

Targeting FXII/FXIIa by antibodies has been successfully used by various groups. Antibody 15H8 inhibited FXII activation and reduced platelet-rich thrombus formation in a collagen-coated vascular graft in baboons.14 The recombinant fully human FXIIa-neutralizing antibody 3F7 binds into the FXIIa enzymatic pocket of the protease with high affinity and interfered with FXIIa-mediated coagulation, abolished thrombus formation under flow, and blocked experimental thrombosis in mice and rabbits.20 3F7 provided thromboprotection as efficiently as heparin in an extracorporeal membrane oxygenation cardiopulmonary bypass system in rabbits. However, in contrast to heparin, 3F7 treatment did not impair hemostatic capacity or increase bleeding. 3F7 also protected mice from prostate cancer–induced lethal PE.32 In addition to its thromboprotective effects, 3F7 abolished bradykinin generation in HAE type III patient plasma and blunted edema in a humanized HAE type III mouse model.55 Humanized antibodies such as 3F7 have minimal immunogenic potential in humans and a long half-life in the circulation.

Another approach for FXIIa inhibition is based on ASO. Targeting FXII expression with ASO reduced arterial and venous thrombosis in mice72 and attenuated catheter-induced thrombosis in rabbits73 without increased therapy-associated bleeding. Furthermore, anti-FXII ASO treatment protected mice from C1INH deficiency–induced increased vascular permeability.74 Targeting FXII by ASO has a slow onset of action and requires multiple parenteral ASO applications. In contrast, small-molecule FXIIa inhibitors that can be taken orally are more suitable for long-term indications. These inhibitors are still under development.59

Taken together, pharmacological targeting of FXII has been identified as potent and safe strategy to interfere with thrombosis in mice, rats, rabbits, and baboons, and edema formation and hypotension in mice with possible implications for patients. The broad impact of FXII beyond thrombosis provides a promising treatment strategy, but future in-depth analysis is required to exclude potential limitations.
Conclusions and Future Directions

The FXII-driven contact system contributes to a variety of thrombotic and inflammatory life-threatening disease states (Figure 1). Genetic and pharmacological ablation of FXII interferes with arterial cardiovascular disease, venous thromboembolism, edema formation, and experimental autoimmune encephalomyelitis. Importantly, targeting FXII is not associated to an increased bleeding tendency. FXII is highly conserved between rodents and humans, underling the predictive value of animal models to study FXII in human disease states. Thus, targeting the FXII-driven contact system seems to be a promising and safe therapeutic treatment strategy for patients with thrombotic and inflammatory diseases that warrants further studies. In particular, FXII inhibitors would be useful for prophylactic treatment of all types of HAE and settings where blood comes in contact to nonphysiological surfaces such as catheters, heart lung machines, dialysis membranes, and ventricular assist devices with far reaching clinical implications.

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Disclosures

None.

References


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**Highlights**

- Coagulation factor XII activates the procoagulant intrinsic pathway of coagulation and the proinflammatory kallikrein-kinin system.
- Animal models have established a central role of factor XII in pathological thrombus formation. Despite its central function in thrombosis, deficiency in factor XII does not impair hemostasis in mice and humans.
- Factor XII contributes to several disease states. Although the factor XII–driven intrinsic coagulation pathway plays a role in atherothrombosis, ischemic stroke, and venous thromboembolism, the factor XII–driven kallikrein-kinin system contributes to hereditary and angiotensin-converting enzyme inhibitor–induced angioedema, allergic and anaphylactic reactions, and vascular dysfunction in patients with Alzheimer’s disease.
- Several classes of factor XII inhibitors are developed. Neutralizing factor XII provided safe thromboprotection with additional anti-inflammatory properties in animal models with possible implications for patients.
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