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Sepsis – it is all about the platelets

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Sepsis is accompanied by thrombocytopenia and the severity of the thrombocytopenia is associated with mortality. This thrombocytopenia is characteristic of disseminated intravascular coagulation (DIC), the sepsis-associated coagulopathy. Many of the pathogens, both bacterial and viral, that cause sepsis also directly activate platelets, which suggests that pathogen-induced platelet activation leads to systemic thrombosis and drives the multi-organ failure of DIC. In this paper we review the mechanisms of platelet activation by pathogens and the evidence for a role for anti-platelet agents in the management of sepsis.

KEYWORDS

platelets, sepsis, innate immunity, thrombosis, anti-platelet agents

Introduction

The development of a circulatory system was critical in the evolution of complex organisms. However, this also created the vulnerability that loss of blood due to injury could be fatal to the organism. Thus, it was essential that a system that could limit blood-loss was also developed. Furthermore, as blood is also a very fertile environment for the growth of bacteria, especially after a trauma, there was a need to develop a system to fight infection. In the case of primitive organisms such as the Horseshoe crab, a single cell – the haematocyte – fulfilled both these requirements. This cell could respond to bacteria and fight the infection. Once stimulated they also clumped together sealing any leak. Thus, the haematocyte mediated both the immune and haemostatic responses (1).

As organisms became more complex, so too did the regulatory systems. This simple haematocyte evolved into multiple specialised cells such as leucocytes and monocytes. One specific cell type – the megakaryocyte - became the sole cell type responsible for haemostasis. While not directly involved in haemostasis the megakaryocyte fragments into platelets, which are the key regulator and mediator of haemostasis.

Since megakaryocytes evolved from the haematocyte it is not surprising that not only did they acquire the haemostatic properties of haematocytes, they also retained some of the immune functions of the haematocyte. Thus, as well as being mediators of haemostasis platelets are also part of the innate immune system.

The immune and haemostatic response to injury were conventionally considered as distinct systems. However, recently it has become clear that the two are intimately linked. The role of platelets in mediating the innate immune response to infection is known as

immunothrombosis (2) and is a normal physiological response to infection. Thrombus formation is a complex process that also involves cells of the innate immune system and the role of the innate immune response in thrombus formation is known as thrombo-inflammation (3). Thus, infection activates the innate immune system and if this innate immune response persists (either because the pathogen is resistant or if it is an autoimmune response) it results in enhanced thrombus formation (4, 5). Platelets are the first responders to trauma (in part due to their high concentration in plasma) and their activation leads to recruitment of immune cells to the site of injury as well as the formation of a clot. Thus, platelet activation acts to both prevent blood-loss and to sterilize the site of injury.

Platelets and thrombosis

Platelets can be considered to have multiple distinct functions that are often, but not necessarily, connected. These are adhesion, aggregation, secretion, and platelet-leucocyte complex formation.

Platelets are highly responsive to many of the components found at the site of injury. Thus, they have receptors for collagen, fibrinogen and von Willebrand factor (vWF) all of which are to be found on the damaged blood vessel. The primary function of the interaction with these ligands is to immobilise the platelet to the damaged vessel under both low shear (venous) conditions (collagen and fibrinogen receptors) and high shear (arterial) conditions (vWF receptors) (6). Platelets can also bind to bacteria that have attached to a surface. Platelet adhesion mediated by these receptors usually results in platelet activation facilitating thrombus formation, while also ensuring that thrombus formation is restricted to the site of injury.

Platelets also express receptors for soluble ligands. These are all G-protein coupled receptors and respond to ligands such as ADP, adrenaline, and thrombin. Platelet activation by these ligands is important in recruiting platelets to the site of injury and growing the thrombus (7).

Once activated, platelets aggregate forming a thrombus, but they also secrete the content of their granules. Platelets contain multiple granule types including alpha- granules, dense granules, and lysosomes. This platelet secretome is rich in bioactive molecules including over 2,000 proteins (8), small molecules such as ADP and serotonin and polyphosphates (9). While the platelet secretome plays a role in thrombosis it is primarily involved in the non-thrombotic roles of platelets.

While platelet-platelet interactions are a critical property of platelets, activated platelets can also bind to leucocytes and endothelial cells. This interaction can modify the function of the target cell.

Platelets and the innate immune system

While platelets play a critical role in haemostasis it has become clear that they also play a role in the innate immune system. As there are many dedicated immune cell types any immune function of platelets is likely redundant. However, as platelets are the first responders to a cut (a primary cause of infection), they are perfectly placed to help sterilise the wound and to coordinate the immune response to the injury.

There is strong evidence to suggest that this happens clinically. Serious infections are associated with thrombocytopenia (10) and this thrombocytopenia is associated with outcome. Thus, in sepsis the extent of thrombocytopenia is associated with severity of disease and outcome (11–13). Furthermore, in severe viral infections (14) such as Dengue (15), COVID-19 (16), Hantavirus (17), Hepatitis B (18) and mononucleosis (19) the severity of the thrombocytopenia is associated with outcome.

The cause of this thrombocytopenia is unclear, and it has been proposed that it could be due to suppression of platelet production by the megakaryocytes as a result of infection. There is certainly evidence that megakaryocytes can be infected by viruses such as Dengue virus (DENV) and influenza virus (20). However, the result of this infection is complex. Megakaryocyte infection by DENV has been shown to reduce megakaryocyte levels which would lead to decreased platelet production (21). However, inflammation has also been shown to increase platelet function and an increase in platelet count has been seen in the initial response to COVID-19 (22) and increased levels of IL-1 and CCL5 increase platelet production by around 50% (23, 24). Ultimately, changes in platelet synthesis are unlikely to be relevant as the lifespan of a platelet is approximately 10 days and even if infection entirely shut down platelet production it would take 9 days for severe thrombocytopenia to occur, while in sepsis it occurs rapidly. Furthermore, while thrombocytopenia would create a risk of bleeding it is unlikely to be involved in the pathogenesis of the infection and would only be a biomarker of outcome.

Thus, it is likely that infection-associated thrombocytopenia is due to platelet activation as this is likely to be rapid in onset and the resultant large-scale thrombosis would have pathological consequences. This level of platelet activation will result in extensive thrombosis throughout the circulation. This is in fact what happens in a condition known as disseminated intravascular coagulation (DIC). DIC is a coagulopathy that is associated with severe infections such as sepsis and COVID-19 and is characterised by thrombocytopenia, platelet activation and systemic thrombosis (25). If this thrombosis occurs in the microvasculature of multiple organs, it will lead to ischemic damage. As this ischemic damage expands, this leads to the multi-organ failure of severe sepsis.

The critical question is how the platelet activation arises. One possibility is that platelets are innocent bystanders. Infection leads to a highly pro-inflammatory environment that in turn could lead to platelet activation. Evidence for this is that platelets can be activated by some cytokines including IL-6 and IL-8 (26). Dengue virus has been shown to induce IL-1β production which in turn induces iNOS in platelets (27). Another possibility is that platelets may interact with inflammed/infected endothelial cells leading to their activation (28). It is important to note that not all platelet activation is the same. Platelets have been shown to undergo a form of activation known as pyroptosis (29), which can be considered to be a cross between apoptosis (membrane blebbing and caspase activation) and necrosis (cell swelling and lysis) (30). This is a pro-

inflammatory response that involves inflammasome formation. Pyroptosis is induced in platlelets by circulating S100A8/A9 (29).

Infection can lead to thrombin generation either through activation of the contact system or generation of tissue factor. As well as causing the formation of fibrin clots this thrombin will also activate platelets. However, this is unlikely to be clinically relevant and activated protein C (aPC) is a thrombin inhibitor and was introduced for the treatment of sepsis (31), however, it was ultimately removed from the market due to the lack of benefit (32). Furthermore, while the use of anti-thrombins have some benefit in both sepsis (33) and COVID-19 (34) their use has been disappointing as DIC continues to be a major problem. This suggests that while thrombin generation may occur during inflammation/infection it is not the major driver of DIC in humans not withstanding the benefit of these agents in animal models of DIC.

Both thrombosis and inflammation are closely intertwined and this connection is bi-directional, with inflammation leading to increased thrombosis and vice-versa, and is known as immunothrombosis (35). While the production of pro-inflammatory cytokines or thrombin generation may play a minor role in DIC it is clear that platelet activation in response to infection is unikely to be incidental and is more likely to be a direct response to infection.

Pathogen interaction with platelet haemostasis receptors

Considering that platelets are the first responders to injury it is reasonable that they would respond directly to any infecting pathogen. It is no conicidence that nearly all of the bacteria that are associated with sepsis have been shown to induce platelet aggregation when added to platelet-rich plasma (PRP) which presumably represents a direct interaction between pathogen and platelets. Furthermore, bacteria such as *S. aureus* have multiple different interactions with platelets (36).

There are two families of receptors on platelets that are involved in the interaction with pathogens – receptors involved in haemostasis such as GPIIb/IIIa and GPIb and immune receptors. The known interactions of bacteria are summarised in Figure 1 and Table 1.

Glycoprotein IIb/IIIa

GPIIb/IIIa is the fibrinogen receptor that is unique to platelets. It is the dominant protein on the platelet surface and plays a critical role in platelet aggregation. It is a member of the integrin family of cell adhesion molecules and binds many proteins in an RGD-dependent manner. It also binds a fibrinogen-specific domain (γ-chain dodecapeptide). Binding of soluble ligands requires activation of GPIIb/IIIa although resting GPIIb/IIIa can bind to immobilised ligands (75).

GPIIb/IIIa mediates platelet adhesion to the sub-endothelial matrix and to other platelets and it is the fibrinogen-mediated binding to other platelets that results in thrombus formation. However, GPIIb/IIIa is also involved in platelet activation. GPIIb/IIIa binding to the NGR sequence in immobilised fibrinogen results in platelet activation and spreading (76). Furthermore, small molecule GPIIb/IIIa antagonists have been shown to activate platelets and the development of this class of drug was discontinued due to increased platelet activation leading to increased cardiovascular events (77).

GPIIb/IIIa is a key receptor for interacting with pathogens. *Staphylococcus aureus* expresses multiple fibrinogen-binding proteins including clumping factors A and B and fibronectin-binding protein. Fibrinogen-coated *S. aureus* binds to platelet GPIIb/IIIa and induces platelet activation (37). Similarly, strains of *Streptococcus pyogenes* that express fibrinogen-binding M proteins (M1, M3 and M5) can also induce platelet aggregation in a GPIIb/IIIa-dependent manner (48). Other fibrinogen-binding proteins that mediate platelet aggregation include Sdr G (*Staphylococcus epidermidis*) (43), SpsL (*Staphylococcus pseudintermedius*) (44, 55), and FOG (Group G streptococci) (55). On the other hand *S. aureus* secretes extracellular fibrinogen binding protein (Efb) which acts to inhibit platelet aggregation (41).

While GPIIb/IIIa is primarily the fibrinogen receptor and mediates that FOG interaction via the γ-chain dodecapeptide, it is also an RGD-binding integrin and is capable of binding many RGD-containing proteins. For instance GPIIb/IIIa is capable of binding fibronectin via its RGD-binding site. *S. aureus* expresses a fibronectin-binding protein (Fnbp) and binding of fibronectin to this protein mediates an interaction with GPIIb/IIIa and triggering platelet activation in a manner similar to fibrinogen-bound bacteria (37). *S. epidermidis* Sdr G (43), *S. aureus* Isd protein (78) and *S. gordonii* PadA (45) can bind directly to GPII/IIIa. DENV has been shown to directly bind to GPIIb/IIIa (61). The RGD-binding ability of GPIIb/IIIa creates another possibility. RGD-is a common peptide motif found in matrix proteins and supports cell adhesion via one of the many RGD-dependent integrins. Pathogens often express the RGD motif and use it as a virulence factor as it allows them to attach to and subsequently infect host cells. Examples of pathogens that use an RGD-containing protein to mediate adhesion to host cells include *Bordetella pertussis* (filamentous hemagglutinin) (79), *Streptococcus agalactiae* (*scpB*) (53), *Mycobacterium tuberculosis* (Peptidyl Prolyl Isomerase A) (58), *Borrelia burgdorferi* (BBB07) (59), *Helicobacter pylori* (CagL) (80). *Candida albicans* (Sap6) (81), SARS-CoV-2 (82), Coxsackievirus A9 (VP1) (83) and HIV-1 (Tat protein) (70) also express RGD-containing proteins. As GPIIb/IIIa is capable of binding many RGD-containing proteins it is likely that it can also bind RGD-containing pathogen proteins. Figure 1A illustrates GPIIb/IIIa-mediated platelet activation by fibrinogen-binding pathogens)

GPIb

After GPIIb/IIIa, the most highly expressed protein on the platelet surface is GPIb which exists as a complex with GPIX and GPV. GPIb is a receptor for von Willebrand Factor (vWF) and this interaction mediates platelet adhesion to matrix-associated

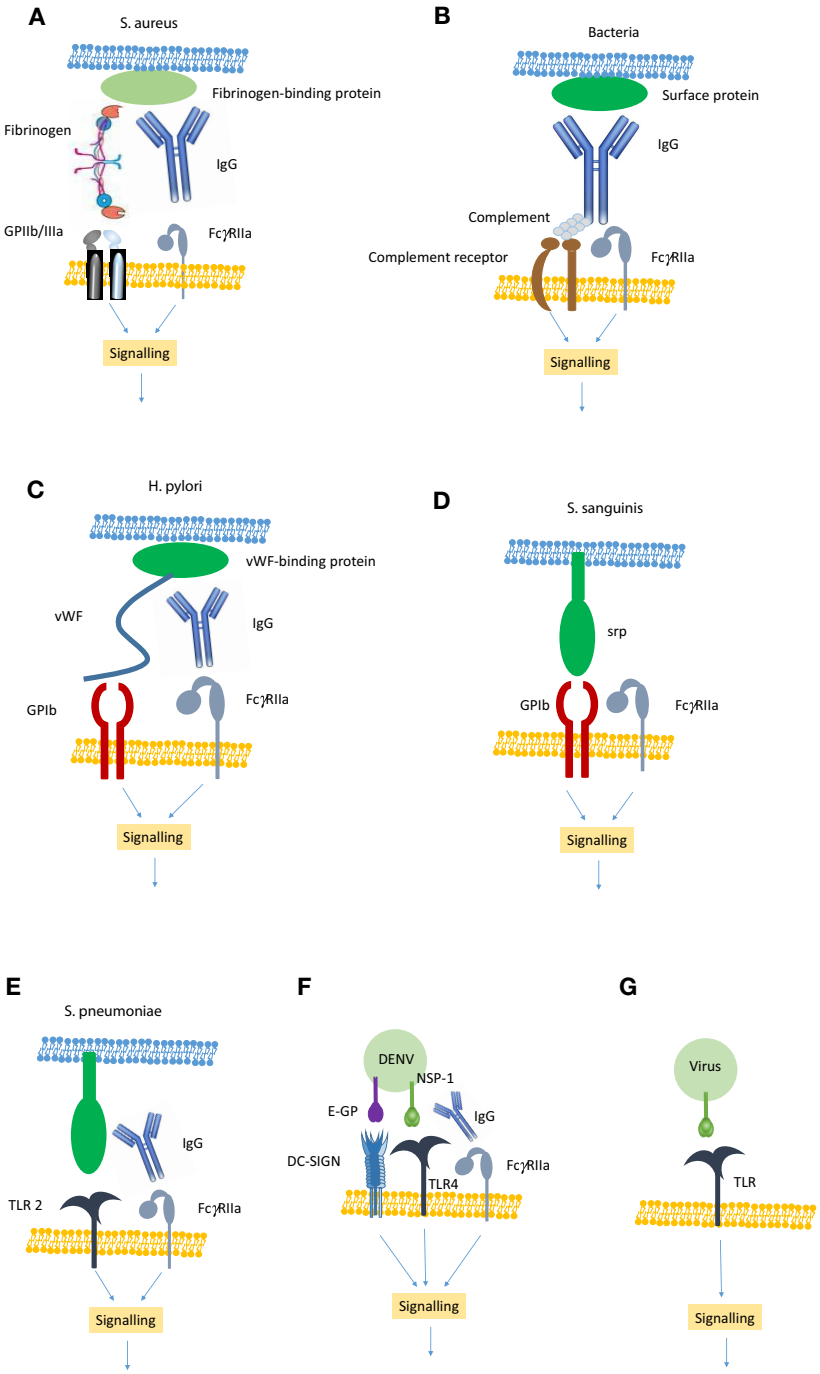

FIGURE 1
Showing the main mechanisms of pathogen-induced platelet activation. **(A)** Bacteria such as *S. aureus* express proteins that bind fibrinogen which in turn binds to GPIIb/IIIa. Simultaneously, IgG binds to the bacteria and also to FcγRIIa generating an activation signal. **(B)** Any bacteria can bind IgG which in turn leads to the assembly of complement. The IgG binds to FcγRIIa and the complement to a complement receptor to generate an activation signal. **(C)** Bacteria such as *H. pylori* express a protein that binds vWF, which in turn binds GPIb. IgG also binds to the bacteria and also to FcγRIIa generating an activation signal. **(D)** Bacteria such as *S. sanguinis* express proteins (e.g. serine-repeat protein; srp) that can directly bind GPIb. This generates an FcγRIIa-dependent activation signal. **(E)** Bacteria such as *S. pneumonia* express a protein that binds to Toll-like receptor (TLR) 2. In conjunction with IgG engagement of FcγRIIa they can generate an activation signal. **(F)** DENV E-glycoprotein can bind directly to DC-SIGN and non-structural protein (NSP)-1 can bind to TLR4. In conjunction with IgG binding to FcγRIIa this leads to the generation of an activation signal. **(G)** Some viruses express proteins that bind to TLR (e.g TLR 2, 4 &7) leading to a platelet activation signal.

vWF but only under high shear conditions. This interaction leads to platelet spreading and activation (84). Pathogens also use GPIb to facilitate an interaction with platelets. One way to do this is by the expression of vWF-binding proteins on the bacteria surface. *H. pylori* binds vWF and induces platelet aggregation in a GPIb-dependent manner (56). This is unusual as high shear is not necessary for this interaction. Thus, it is likely that when bound to the surface of *H. pylori* vWF-undergoes a conformational

TABLE 1 Summary of the known pathogen proteins that interact with platelets either through a direct interaction or via a bridging protein.

Pathogen	Pathogen protein	Binding protein	Platelet receptor	Reference
Staphylococcus aureus	Clumping factor (Clf) A&B	Fibrinogen	GPIIb/IIIa	(36)
	Fibronectin binding protein (Fnbp)	Fibronectin	GPIIb/IIIa	(37)
	serine-aspartate repeat protein (SdrE)	-	?	(36)
	Protein A	vWf	GPIb	(38)
	IsdB	––	GPIIb/IIIa	(39)
	Peptidoglycan		TLR-2	(40)
	Extra cellular fibrinogen binding protein (Efb)*	Fibrinogen	Inhibits aggregation	(41)
	SraP	–––	?	(42)
Staphylococcus epidermidis	serine-aspartate repeat protein (SdrG)	Fibrinogen ––	GPIIb/IIIa GPIIb/IIIa	(43)
Staphylococcus pseudintermedius	SpsL	Fibrinogen	GPIIb/IIIa	(44)
Streptococcus gordonii	Pad A	––––	GPIIb/IIIa	(45)
	Hsa	––––	GPIb	(46)
	GspB	––	GPIb	(47)
Streptococcus pyogenes	M proteins	Fibrinogen	GPIIb/IIIa	(48)
Streptococcus sanguinis	serine-rich protein (srp)	––	GPIb	(49)
Streptococcus oralis	Hsa	––	GPIb	(50)
Streptococcus pneumoniae	?	?	TLR2	(51)
Streptococcus agalactiae	?	?	TLR2	(52)
	scpB-1	RGD-containing protein	GPIIb/IIIa??	(53)
	FbsA	Fibrinogen	GPIIb/IIIa	(54)
Group G streptococci	FOG	Fibrinogen	GPIIb/IIIa	(55)
Helicobacter pylori	?	vWf	GPIb	(56)
	CagL	RGD-containing protein	GPIIb/IIIa??	(57)
Mycobacterium tuberculosis	Peptidyl Prolyl Isomerase A	RGD-containing protein	GPIIb/IIIa??	(58)
Borrelia burgdorferi	BBB07	RGD-containing protein	GPIIb/IIIa??	(59)
Leptospira interrogans	vwa-I&II	–––	GPIb Inhibition of aggregation	(60)
DENV	?	–––	GPIIb/IIIa	(61)
	?	–––	GPIb	(62)
	E-glycoprotein	–––	DC-SIGN	(63)
	Non-structural protein 1	–––	TLR4	(64)
SARS-CoV	Spike protein	–––	DC-SIGN	(65)
SARS-CoV-2	Spike protein	–––	ACE2	
	Spike protein	–––	TLR4	
	Spike protein		DC-SIGN	

(Continued)

TABLE 1 Continued

Pathogen	Pathogen protein	Binding protein	Platelet receptor	Reference
	Spike protein	RGD-containing protein	GPIIb/IIIa?	
Severe fever with thrombocytopenia syndrome (SFTS) virus	?	----	GPVI	(66)
Cytomegalovirus	?	?	TLR2	(67)
Encephalomyocarditis virus	?	?	TLR7	(68)
HIV	Gp120	----	DC-SIGN	(69)
			Clec-2	
	Tat	RGD-containing protein	GPIIb/IIIa??	(70)
Ebola virus	Ebola glycoprotein	---	DC-SIGN	(71)
Hepatitis C virus	Envelope protein	----	DC-SIGN	(72)
Influenza	Hemagglutinin Protein	----	DC-SIGN	(73)
All pathogens	?	IgG	FcγRIIa	(74)
	?	Complement	Complement receptor	

Direct interactions are indicated by the absence of a binding protein (-). ? indicates that the identity of the receptor is unknown.
* indicates a secreted product.

change that allows it to interact with GPIb without the need for shear.

Pathogens also express proteins that can directly bind to GPIb. Examples of GPIb-binding proteins include serine-rich protein (srp) A on *Streptococcus sanguinis* (49) and Hsa on *Streptococcus gordonii* (46) and *Streptococcus oralis* (50). On the other hand *Leptospira interrogans* secretes a vWF-like proteins (vwa-I&II) that bind to GPIb and play a role in the haemorrhagic shock by blocking the GPIb-vWF interaction (60). Dengue virus appears to interact with GPIb although the mechanism is unknown (62). Figures 1C, D illustrate GPIb-dependent pathogen-induced platelet aggregation.

Other receptors

ACE2 has been found to be expressed on platelets and mediates SARS-CoV-2 binding (85). Severe fever with thrombocytopenia syndrome (SFTS) virus (SFTSV) binds to platelet GPVI and induces platelet activation. Furthermore, SFTSV can enter platelets and replicate (66).

Pathogen interactions with platelet immune receptors

As innate immune cells, platelets express multiple immune receptors such as FcγRIIa and Toll-Like receptors (TLRs). While these are not involved in haemostasis they do play a role in platelet activation by pathogens. Many pathogens bind to GPIIb/IIIa or GPIb which is critical in the activation of platelets, however, these interactions are insufficient to induce platelet activation. In all case platelet activation and subsequent aggregation is FcγRIIa-dependent (74).

Aside from the haemostasis resceptors that mediate the unique haemostasis functions of platelets, platelets also express multiple receptors that are usually associated with immune function. These include FcγRIIa, Toll-like receptors (TLR) and Clec-2. The immune receptors are also involved in pathogen-mediated platelet activation.

FcγRIIa

It is clear that many pathogens can bind to, and activate, platelets by interacting with the major platelet surface receptors, however, while these interactions are necessary for platelet activaton they are not sufficient, as signalling through FcγRIIa was also essential in all cases. In haemostasis, direct activation of a platelet receptor is sufficient to induce thrombus formation. However, in immunology co-stimulation is the norm with multiple signals being required for immune cell activation.

Fc receptors are a super-family of receptors that bind the Fc portion of antibody. Each antibody class has its own Fc family (IgA/FcαR, IgG/FcγR and IgE/FcεR) that mediates immune cell activation by immune complexes. While the best known reaction is that of IgE complexes with FcεR on basophils leading to histamine release and anaphylaxis, by far the most widely expressed FcR is the FcγR family (86, 87).

FcγR is a family of receptors whose primary function is to mediate phagocytosis and thus their expression on phagocytic cells, although surprisingly, they are also expressed on platelets. There are three sub-families of FcγR – FcγRI, FcγRII and FcγRIII and these differ in their affinities for the different IgG isotypes. The most

important FcγR sub-family is FcγRII and it is compsoed of FcγRIIa and FcγRIIb. Aside from cellular distribution, these 2 receptors differ in their signalling. FcγRIIa, like other FcγR signals through an immunoreceptor tyrosine-based activation motif (ITAM). ITAM is characterised by a tyrosine residue separated from a leucine or isoleucine by 2 amino acids (YxxL/I). ITAMs contain 2 of these domains separated by 6-8 amino acids. Receptor activation leads to phosphorylation of the tyrosines in ITAM by Src family kinases. These phosphtyrosines then recruit the tyrosine kinase Syk, which commences the signalling cascade. FcγRIIb, however, contains an immunoreceptor tyrosine-based inhibitory motif (ITIM) that recruits phosphatases and thus is an inhibitory receptor (88).

FcγRII all have an ITAM/ITIM domain as part of the cytoplasmic tail of the receptor. Other FcRs such as FcγRI interact with an ITAM-containing adapter protein known as FcRγ (89). FcRγ also mediates signalling by the collagen receptor GPVI on platelets (90).

FcγRIIa is the only FcR on platelets where it plays a key role as a co-stimmulatory receptor for pathogen-induced aggregation (91). Its primary function is to bind pathogen-bound IgG. Extensive work with *S. aureus* showed that while binding to GPIIb/IIIa was critical in its interaction with platelets, activation only occurs in the presence of anti-*S. aureus* IgG which engages with FcγRIIa (92). As *S. aureus* is a commensal, nearly everbody has significant titres of anti-*S. aureus* IgG. In the case of *H. pylori*, which is not a commensal, platelet activation only occurs with platelets from *H. pylori*-positive individuals (56). *Streptococcus bovis/Spreptococcus equinus* complex also induce platelet aggregation in a FcγRIIa-dependent manner (93). Peptidoglycan from *Bacillus anthracis* can also induce platleet activation in an FcγRIIa- and IgG-dependent manner (94). Viruses can also cause platelet activation in an FcγRIIa-dependent manner. DENV triggers platelet activation in an IgG and FcγRIIa-dependent manner (95). These anti-DENV antibodies arise from a prior DENV infection with a different serotype. Influenza H1N1 (96) and some Bunyaviruses such as Crimea-Congo Haemorrhagic fever (97), also induce platelet activation via FcγRIIa. Antibodies to Spike protein have been found to lead to platelet activation in COVID-19 patients that was FcγRIIa-dependent (98). Blocking FcγRIIa has been found to prevent platelet activation by COVID-19 plasma *in vitro* (99, 100). In all cases blockade of FcγRIIa with an antibody or depletion of specific IgG inhibits platelet activation, confirming the role of the IgG- FcγRIIa interaction in platelet activation.

Platelet FcγRIIa is not only involved in pathogen-induced platelet activation but it is also involved in immune thrombocytopenia (ITP), where antibodies to platelet antigens trigger the immune destruction of platelets (101). This depletion of platelets in ITP is not the just the usual immune destruction, as these antibodies trigger platelet activation in an FcγRIIa-dependent manner. This is also found in heparin-induced thrombocytopenia (HIT) where heparin binds to PF4 on the platelet surface and in some individuals this complex can become antigenic. Antibodies bind to the complex and also engage FcγRIIa leading to platelet activation and consumption which presents as a severe thrombocytopenia.

While FcγRIIa is critical in platelet activation by pathogens the same is not true of IgG. *Streptococcus sanguinis* mediates platelet activation by engaging GPIb and the aggregation is inhibited by antibodies that block FcγRIIa, however, this aggregation occurs in the absence of IgG (102). This suggests that in this context, FcγRIIa is acting as a co-receptor for GPIb. This may be explained by evidence of co-localisation of GPIb with FcγRIIa (103).

A major challenge in investigating the role of FcγRIIa in thrombosis is its restricted expression. FcγRIIa is not expressed in mice and these are the primary animal model for both thrombotic and infectious disease. Thus, pathogen-induced platelet activation in mice occurs in an FcγRIIa-independent manner and is likely to be quite different to that in humans. This is supported by evidence of differences in gene expression between mice and humans in sepsis and trauma. This species difference has clinical consequences with activated protein C (APC) being approved for the treatment of sepsis based on animal studies (31) and yet had to be withdrawn from the market due to a lack of efficacy (32).

Toll-like receptors

TLRs are also expressed on platelet surface and these have been shown to be involved in pathogen interaction with platelets (40, 104). Most of the attention was focused on TLR2 and TLR4 as they are the most widely expressed TLRs. There are conflicting data regarding the functionality of these TLR in platelet function (105, 106). Lipopolysaccharide (LPS) is a TLR4 agonist and LPS from *E. coli* O157 fails to induce platelet aggregation even though *E. coli* O157 can induce aggregation, which suggests that TLR4 is not functional (39). The conflicting data appear to relate to the end point of any study. Thus, studies that use aggreation as the end point see no role for TLR4 while those that look at other markers of platelet activation do see a role. In contrast, the TLR2 agonist Pam3Csk4 can induce platelet aggregation (39), *Streptococcus pneumoniae* (51), *Streptococcus agalactiae* (52) and cytomegalovirus (67, 107) induce platelet aggregation in a TLR2-dependent manner. SARS-CoV-2 envelope protein has been shown to interact with TLR-2 (108). Encephalomyocarditis virus has been shown to bind to and activate platelets in a TLR7-dependent manner (68). SARS-CoV-2 has been shown to bind to TLR-4 thereby activating platelets (109). A key role for pathogen-binding to platelet TLR is to facilitate the platelet-leucocyte interaction (110, 111) and it may play a role in endocytosis of virions by platelets (112). TLR-4 has also been shown to induce platelet pyroptosis in a TLR-4-dependent manner (29). Figures 1D, G illustrate the role of TLRs in pathogen-induced platelet activation.

Lectins

Lectins are a family of receptors that recognise carbohydrates but can also bind to proteins. C-type lectins are calcium-dependent lectins that act as pathogen-recognition receptors (113). C-type lectins such as DC-SIGN (Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin) and CLEC (C-type lectin-like receptor) 2 are expressed on platelets. Clec-2 signalling is

similar to FcγRIIa (90) although it only has a single YxxL/I domain known as a hemITAM (114). DC-SIGN binds HIV (69), DENV (63, 115, 116), Ebola virus (71), Hepatitis virus (72), and influenza H1N1 (117) and H5N1 (73), SARS-CoV (118) and SARS-CoV-2 (119, 120) and this binding is implicated in platelet activation. CLEC-2 and 5A are also important in binding to viruses (121) such as HIV (69).

Complement receptors

Complement formation in response to an infection is an important feature of the innate immune system. Platelets can become activated in response to complement. Furthermore, complement-bound immune complexes can bind to both FcγRIIa and complement receptors gC1q-R thereby triggereing platelet aggregation (122). Once platelet-binding proteins have been removed from both *S. sanguinis* (123) and *S. aureus* (92) they can induce platelet aggregation in a complement- and FcγRIIa-dependent manner. COVID-19 is associated with increased complement formation (124, 125) and complement fragments have been found in coronary micro-thrombi of COVID-19 patients after autopsy. SARS-CoV-2 can directly activate complement formation via the alternative pathway (126) and patients who died had higher levels of anti-N antibodies that fixed complement (127). The glycosylation profile of the anti-SARS-CoV-2 IgG also appears to be important with a low fucosylated form being more pro-inflammatory (128) and more pro-thrombotic (129). The role of complement in pathogen-induced platelet activation is illustrated in Figure 1B.

Interactions of secreted bacterial products with platelets

While direct interactions of bacteria with platelets are critical in the subsequent platelet activation, bacteria also secrete many products including toxins that have the potential to interact with platelets (130). *S. aureus* secretes a number of substances that have been shown to activate platelets including extracellular adherence protein Eap, chemotaxis inhibitory protein of *S. aureus* (CHIPS), formyl peptide receptor-like 1 inhibitory protein (FLIPr) and the autolysin Atl (131). *S. aureus* also secretes the prothrombin activating proteins staphylocoagulase and vWf-binding protein that can induce platelet activation through increased thrombin production (132). There is also a family of pore-forming toxins that act like the calcium ionophore (A23187) (133). These include pneumolysin (*S. pneumonia*), Streptolysin O (Group A streptococci) and α-toxin (*S. aureus*) (130). Shiga toxin is produced by some strains of *E. coli* and plays an important role in the pathogenesis of haemolytic uremic syndrome (HUS). Shiga toxin acts in conjunction with LPS to activate platelets leading to the generation of NETS (134). Staphylococcal superantigens and staphylococcal superantigen-like protein (SSL) also activate platelets. SSL5 has been shown to activate platelets by binding to GPIbα and GPVI (135). *S. aureus* toxic shock syndrome toxin-1 (TSST-1) mediates platelet activation and apoptosis, although the mechanism of TSST-1-mediated platelet activation is unknown (136). *Porphyromonas gingivalis* secretes gingipains that can mimic thrombin and activate platelets by cleaving protease-activated receptors (PAR) (137–139).

Platelet-infected cell interactions

While *in vitro*, pathogen interactions with platelets can easily be investigated, it is much more complex *in vivo* as multiple cell types, especially endothelial cells also play a role. Both bacteria and viruses can infect endothelial cells and platelets can play a role here. Typically, resting platelets and resting endothelial cells do not interact but activated platelets will bind to activated endothelial cells. Furthermore, activated platelets will enhance endothelial cell activation and vice versa (140, 141). *S. aureus* can bind to endothelial cells using multiple virulence factors and once bound they can attract platelets (142). Endothelial cells infected with Cytomegalovirus (CMV) induce platelet adhesion and aggregation that is vWF and GPIb-dependent (143). This immunothrombosis in response to endothelial cell infection may play a role in the increase in atherosclerosis and mortality post-infection (144).

Beyond thrombus formation

While the role of pathogen-platelet interactions in thrombus formation is well established these interactions also lead to activation of the immune system (145). The formation of neutrophil extracellular traps (NETs) – a mesh of neutrophil-derived chromatin fibres – plays an important role in trapping and killing pathogens (146). Full NET formation requires the formation of platelet-neutrophil complexes in a TLR4-dependent process (147). S100A8/A9 binding to TLR-4 induces platelet pyroptosis and these platelets are very potent at inducing NETosis, furthermore NETs release S100A8/A9 which increases platelet pyroptosis (29). Platelet-derived exosomes isolated from sepsis patients have been shown to induce NET formation (148). There is evidence that eosinophils (EET) and monocytes (MET) can also form extracellular traps (149). Platelet-eosinophil interactions are involved in EET formation (150, 151). Platelet-monocyte aggregate formation is also implicated in sepsis (152) and the have been shown to mediate killing of *Klebsiella pneumonia* (153). In severe COVID-19 (154) and Dengue (155) activated platelets activate monocytes and are implicated in disease severity.

Platelet activation by pathogens can also lead to release of granule contents that are rich in cytokines and can influence the immune response. DENV infection of platelets induces NO production and IL-1β release (27). SARS-CoV-2 (156) and DENV (157) have been shown to induce the release of multiple pro-inflammatory cytokines from platelets.

Pathogen-induced platelet activation: clinical implications

The innate immune role of platelets in responding to infection is not restricted to bacteria as they also play an important role in responding to viruses (158–161). The ability of pathogens to activate platelets has clinical implications. Infection is associated with platelet activation, and this is part of the pathogenesis of many infectious diseases. Platelet activation is associated with two types of infection – localised infection (infective endocarditis) and systemic infection (sepsis). Evidence for platelet activation being involved in the pathogenesis of infectious disease opens the possibility of anti-platelet agents in the treatment of some infectious diseases.

One of the best characterised interactions with viruses is the DENV-platelet interaction. There are 4 serotypes of DENV. Infection with any serotype leads to a minor infection with 'flu-like symptoms. The immune response soon clears the virus, and the patient is immune from future infection. However, if the patient is infected with a different DENV serotype there will be an immune response from the pre-existing anti-DENV antibodies, although these are not inhibitory antibodies for the new serotype. As a result, there are antibody-coated DENV virions in the circulation. These can interact with FcγRIIa on monocytes, leading to antibody-dependent enhancement (ADE) of the infectivity of DENV (95). The antibody-coated DENV virions can also bind to FcγRIIa on platelets which leads to platelet activation, DIC and Dengue haemorrhagic fever (DHF) (162, 163). Figure 1F illustrates DENV-induced platelet activation.

Infective endocarditis

Infective endocarditis (IE) is due to infection of cardiac valves. This can be infection of healthy valves or compromised valves. One of the primary triggers for IE is rheumatic fever, which is an inflammatory disorder that arises from untreated streptococcal infection of the throat (164). One complication of rheumatic fever is damage to the cardiac valves which makes then susceptible to future infections. However, the use of antibiotics to manage streptococcal throat infections has greatly reduced the incidence of rheumatic fever. Another significant cause of IE is intravenous drug use which likely leads to damage to cardiac valves creating a susceptibility to infection. Finally, prosthetic cardiac valves are also risk factors for developing IE (165, 166).

While many bacteria can cause IE most cases are due to infection by staphylococci or streptococci, both of which are well known to induce platelet aggregation. As a result, when the valve becomes infected, platelets are attracted to the lesion, bind to the bacteria, and become activated. Once activated they recruit more platelets and form a thrombus. As the thrombus grows it can put a strain on the valve causing the valve to fail. The thrombus can become unstable due to the physical stress applied to it as the valve opens and closes. This can cause the thrombus to fracture and embolise which can lead to a stroke, myocardial infarction or pulmonary embolism depending on where the embolus becomes trapped (167). IE embolism has a high mortality rate.

Platelets are recruited to the infected valve to manage the infection. Once activated they secrete anti-microbial peptides to kill the bacteria and recruit immune cells. However, if these bacteria are resistant to the anti-microbial peptides they can continue to grow and, as the bacteria are surrounded by platelets, the immune cells cannot gain access to bacteria. Furthermore, by being surrounded by platelets antibiotics may not work as they also cannot gain access to the bacteria within the thrombus. Thus, if bacteria are resistant to platelet-derived anti-microbial peptides the ability to activate and recruit platelets is an effective survival mechanism.

The significant role for platelets in the development of infected thrombi suggests a role for anti-platelet agents in managing patients with IE (168, 169). However, the data have been mixed. Animal studies have shown reduced thrombus size, but clinical studies have been mixed with some showing benefit (170) and others no benefit. However, it is worth noting that these studies were small and no data on the causative agents or the role of antibiotics (169).

Sepsis

While IE is an example of a focal infection that triggers thrombus formation, sepsis is a systemic infection and thus there is no localised thrombus formation. However, platelets still interact with the bacteria and become activated while in the circulation. These activated platelets can clump together forming thrombi that can occlude the microvasculature. This results in ischemic damage to the surrounding tissue (this can be organs such as kidney, liver, and brain). As platelet activation spreads so too does the ischemic damage which, if it becomes extensive, can lead to organ failure.

Once bacteria gain access to the circulation, they interact with platelets leading to their activation and consumption. In response to this platelet consumption, there is an increase in platelet production and thus in early-stage sepsis it is common to see an increase in platelet count. However, soon the synthetic ability of the body is overcome as the rate of platelet consumption exceeds the rate of platelet production. At this point the patient begins to develop thrombocytopenia.

The occurrence of thrombocytopenia is well established in sepsis although its occurrence may simply be an association – a secondary event to increased inflammation during sepsis- rather than a causative factor in sepsis. However, there is a clear association between the extent of thrombocytopenia and outcome in sepsis. Furthermore, it is interesting to note that many cases of culture-positive sepsis are due to infection with Staphylococci, Streptococci and *E. coli* –all of which have been shown to directly activate platelets. Thus, direct activation of platelets by bacteria is a more likely cause of thrombocytopenia than secondary activation due to increased inflammation.

The role of platelets in infection is a double-edged sword. Platelet activation by bacteria leads to the release of anti-microbial peptides (171) and also enhances the ability of monocytes to kill *Klebsiella pneumoniae* (153) and thus platelets play an important role in preventing sepsis. Thrombus formation acts to trap bacteria and prevent dissemination of the bacteria (172) although there appears to be an organ-specific effect on the ability to trap *Salmonella*

Typhimurium (173). Thrombus formation occurred with *S. Typhimurium* infection of mice in a platelet Clec-2-dependent manner (174). However, specific deletion of platelet Clec-2 has been shown to enhance inflammation and organ damage in a caecal-ligation sepsis model (175). Depletion of GPVI but not Clec-2 has been shown to increase bacterial load and decrease inflammation in lungs after *K. pneumoniae* infection (176). There is also evidence that platelets can aid in dissemination of bacteria (*Streptococcus pyogenes*) (177). Thrombocytopenic mice have more severe sepsis (polymicrobial sepsis) (178) with impaired survival after *K. pneumoniae* (179) and *Streptococcus pneumoniae* (180) infection, although it lead to more severe sepsis with *S. aureus* infection (181). On the other hand, excessive platelet activation is critical to the pathogenesis of sepsis. As far back as 1981 aspirin was shown to reduce the impact of sepsis in mice (*Salmonella enteritidis*) (182, 183). It has been shown to protect mice from *S. aureus*-induced sepsis (184). Clopidogrel (185) and ticagrelor (186) were found to be protective in a polymicrobial model of sepsis although clopidogrel has also been shown to be of no benefit (187). In mouse studies of influenza-induced pneumonia the use of an anti-viral agent in conjunction with clopidogrel reduced mortality (188).

Thus, the above animal studies on sepsis have had contradictory results. Depletion of platelets prior to sepsis generally leads to worse outcome, although some studies have shown the opposite. Anti-platelet agents have been shown to be beneficial in sepsis although some studies found no effect. These conflicting studies make it difficult to understand the role of platelets in sepsis. Some of the differences can be due to the inducing agent – endotoxin versus live pathogen. Even with live pathogen there can be differences in whether a Gram-negative or Gram-positive pathogen is used, or whether it is a polymicrobial infection or a single pathogen. However, it does appear that the presence of platelets is important in protecting against sepsis due to their role in innate immunity. Sepsis only arises if the pathogen is resistant to the platelet anti-microbial peptides, or the dose of pathogen is so high that it overcomes the innate immune system. So not surprisingly platelet depletion can worsen sepsis outcomes possibly by inducing sepsis in animals that would normally clear the pathogen. However, if sepsis is established, the innate immune role of platelets has failed. At this point the platelet becomes part of the problem rather than the solution to the problem and thus, platelet inhibition is likely to be beneficial.

If direct platelet activation by bacteria plays a critical role in the development of multi-organ failure in sepsis, then anti-platelet agents should improve outcome in sepsis. While some clinical studies have found no evidence for reduced incidence of sepsis or subsequent mortality (189, 190) with the use of aspirin, other studies have shown benefit. Aspirin use prior to admission to ICU has been shown to reduce sepsis mortality (191, 192) and mortality from pneumococcal pneumonia (193). Lavie and co-workers (194) and Du and co-workers (195) used propensity matching to show that aspirin use reduced mortality in sepsis (hazard ratio approximately 0.7). Meta-analysis (196) have shown that prior aspirin and/or clopidogrel use was associated with a reduction in sepsis mortality of around 10%. The interesting thing about these studies is that patients with prior aspirin use are typically patients post myocardial infarction. Thus, patients with significant underlying health issues who are on aspirin do better than those with no underlying conditions.

The potential benefits of aspirin are not just restricted to preventing sepsis. A serious infection that requires hospitalisation (not sepsis) is associated with a significant increase in major cardiovascular events (MACE) - hazard ratio for MACE for the first month post-infection was 7.87 and for the following 19-years it was 1.41 (197). The increase in MACE was also seen in Dengue fever where the incidence rate ratio (IRR) of MACE in the 7-days post DENV infection was 17.9, post-influenza 15.76 and in the control group 0.91 (198). Risk factors for MACE post-infection were shown to be evidence of organ damage, atrial fibrillation and at least 2 risk factors of MACE (199). Similarly, the odds ratio for MACE in COVID-19 patients was 6 (200). These results are not surprising as MACE is due to platelet activation and subsequent thrombus formation. The last thing that a patient at risk of an MI needs is significant increase in platelet activation such as that which occurs when pathogens interact with platelets. Thus, the use of aspirin in patients with serious infection, especially in those with CVD risk factors has a role in preventing MACE following the infection.

One of the reasons for the diversity in outcomes may be due to timing of aspirin use. Just as in the animal studies, the presence of healthy, fully functional platelets is necessary to fight infection and thus instances of infection that may be resolved with the aid of platelets may progress to sepsis. The ideal time to administer aspirin would be when there is evidence that the infection has become established, i.e., at the point where there is evidence that the platelets have failed to contain the infection, but before there is significant thrombocytopenia as it is difficult to preserve platelet function if there are no platelets remaining.

However, there is a problem with using conventional anti-platelet agents in sepsis. As thrombocytopenia progresses so too does the bleeding risk. Anti-platelet agents also create a bleeding risk. Thus, the use of anti-platelet agents may preserve platelet number but increase the bleeding risk by impairing platelet function. An alternative strategy is to prevent the pathogen from activating the platelets. As FcγRIIa is the most significant platelet receptor mediating pathogen-induced platelet activation it would be the ideal drug target. It would prevent pathogen-induced platelet activation without any impact on platelet function. There is evidence to support this concept from studies using IVIg which is known to act by inhibiting FcγRIIa (201). High dose IVIg, if given early, improves outcome in severe COVID-19 infection (202). A network meta-analysis found that IVIg reduced mortality of sepsis in adults (odds ratio = 0.61) with an optimal dose of 1.5-2 g/kg (203). In contrast the use of IVIg in neonatal sepsis has shown no evidence of benefit (204, 205). However, it is worth noting that the doses used in the neonatal studies (500 mg/kg) are much lower than those found to be optimal in adults (1.5-2 g/kg). The American Heart Association guidelines (206) recommend 2 g/kg IVIg for children with Kawasaki Disease, noting that benefit is dose-dependent, which suggests there was a significant under-dosing in the neonatal sepsis studies. While IVIg is an FcγRIIa antagonist it has low affinity for the receptor and thus high concentrations are

required to get significant inhibition. Kawasaki disease is believed to be triggered by an infection, although the identities of the causative agents is unknown, and it is treated with a combination of aspirin and IVIg – a strategy that would protect platelets from direct activation of platelets by a pathogen (206). IVIg has been shown to be effective in Crimea-Congo Haemorrhagic fever (97), Influenza A (H1N1) (207) and COVID-19 (202, 208). A potential solution to the low affinity of IVIg is to discover high affinity small molecules. Small molecules have been discovered that have been shown to be effective in animal models of immune complex disease (209).

A key step in NETosis is the release of DNA which plays a role in trapping platelets (146). This has led to investigations on the use of DNase in sepsis although with mixed results that may be due to timing of DNase therapy (210–212). However, as platelet activation is critical in NETosis (147), anti-platelet agents may be more effective in regulating extracellular DNA.

Pandemic preparedness

COVID-19 has made the world realise that we are very vulnerable to a potential pandemic. While this may come from a known pathogen, the real threat comes from a novel pathogen – possible one that recently jumped species. While there is interest in discovering a pan-anti-viral inhibitor this seems unlikely as there are so many different viruses and existing agents are specific to a small number of viruses. An alternative approach is to target the host – all pathogens must interact with the host to cause illness and there is a much smaller repertoire of targets in the host.

With many pandemics, both bacterial and viral, death follows from disseminated intravascular coagulation and multi-organ failure. Covid-19 causes multi-organ failure and is a viral sepsis (65). Influenza A, both seasonal influenza and pandemic variants (H1N1 (1918 & 2009), H2N2 (1957) and H3N2 (1968)) can lead to multi-organ failure (213). Other viruses with the potential to become pandemics are the viral haemorrhagic fevers, including Marburg, Ebola and Dengue all of which cause DIC and multi-organ failure (214–216).

Just as anti-platelet agents have the potential to prevent DIC in bacterial sepsis and reduce mortality, their use in viral sepsis has the potential for similar benefit. The real advantage is that knowledge of the pathogen is not necessary to provide benefit.

Conclusions

Sepsis – both bacterial and viral – is associated with disseminated intravascular coagulation (DIC). This coagulopathy is characterised by extensive platelet activation that results in thrombus formation in the microvasculature leading to multi-organ failure. Ultimately it is this uncontrolled platelet activation that is the cause of mortality in sepsis. Preliminary data supports the idea of using anti-platelet agents to treat sepsis. These agents do not cure sepsis; however, they do stabilise the patient preventing progression to DIC. This buys time for the clinician to identify the cause of the sepsis and to select the appropriate antibiotic. Furthermore, it may prove beneficial in the 40% of sepsis cases that are culture-negative (217) where antibiotics have no role.

As anti-platelet agents create a risk of bleeding an alternative strategy is to discover agents that inhibit pathogen interaction with platelets. The two key receptors are FcγRIIa and DC-SIGN and inhibitors of these receptors have the potential to prevent pathogen-induced platelet activation without an increase in bleeding risk.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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