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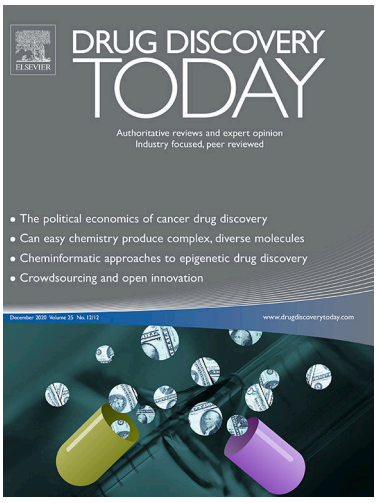

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Blocking platelet glycoprotein VI (GPVI) as a promising anti-thrombotic treatment

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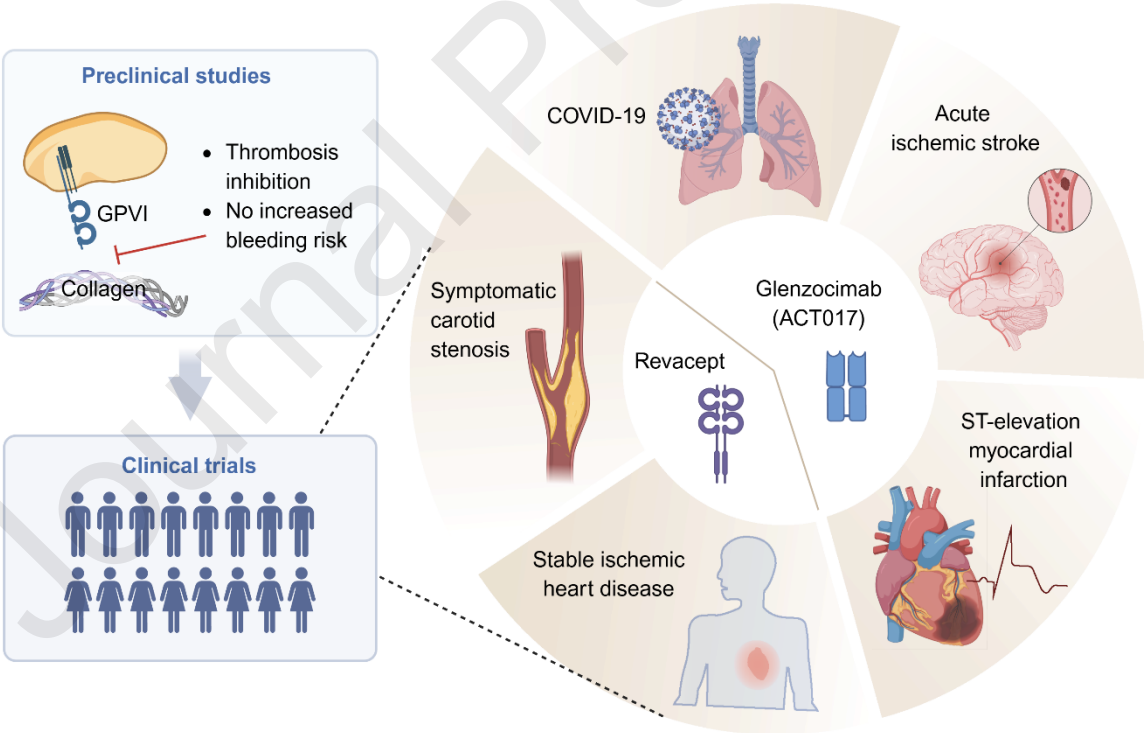

Glycoprotein VI (GPVI), a key platelet receptor, mediates collagen-induced platelet activation and interacts with fibrin to promote thrombus growth. Studies demonstrate the mechanisms of GPVI in thrombosis, showing its inhibition reduces thrombosis without impairing hemostasis, consistent with the mild bleeding phenotype in GPVI-deficient individuals. GPVI is also implicated in inflammation and cancer. This review introduces the mechanism of GPVI in thrombosis and highlights two investigational GPVI-targeting drugs (glenzocimab and Revacept), summarizing current evidence and future directions for this novel anti-thrombotic approach.

Therapeutic targeting of glycoprotein VI (GPVI) with inhibitors such as glenzocimab and Revacept. This graphic summarizes the transition from preclinical evidence, which established antithrombotic efficacy without increasing bleeding risk, to ongoing clinical evaluation across several conditions including acute ischemic stroke, myocardial infarction, COVID-19, and symptomatic carotid stenosis. The figure is created with BioRender.

Teaser

This review highlights the multifaceted roles of GPVI in thrombosis, inflammation, and cancer, while summarizing the latest advances in GPVI-targeted drug development, offering new insights for therapeutic intervention in related diseases.

Highlights

- Platelet glycoprotein VI (GPVI) serves as the coreceptor for collagen.
- Blocking GPVI effectively inhibits thrombosis without increasing the risk of bleeding.
- Two investigational drugs (glenzocimab, Revacept) show potential as novel anti-thrombotic agents.
- Blocking GPVI shows promise as a novel anti-thrombotic therapy.

Introduction

In 1987, Tateo Sugiyama *et al*. reported a patient with steroid-responsive immune thrombocytopenic purpura who exhibited deficient collagen-induced platelet function, marking the first description of glycoprotein VI (GPVI).[1] GPVI is primarily expressed on platelets and megakaryocytes and belongs to the immunoglobulin (Ig) superfamily.[2] As a transmembrane protein with an apparent molecular weight of approximately 62 kDa, its

structure consists of three domains.[3] The extracellular domain contains two Ig-C2-like loops (D1 and D2) for ligand binding. The transmembrane domain functions by interacting with the Fc receptor γ (FcRγ) chain and its immunoreceptor tyrosine-based activation motif (ITAM). The cytoplasmic tail features a proline-rich region that binds to Src homology 3 (SH3) domains of nonreceptor tyrosine kinases.[4] GPVI is the core receptor for collagen and is activated via the ITAM-based signaling complex. The binding of collagen to platelet GPVI triggers phosphorylation of ITAM on the FcRγ chain by Src family kinases (SFKs). This enables the binding and activation of spleen tyrosine kinase (Syk), initiating a downstream signaling cascade. The signaling cascade involves key adaptor proteins including linker for activation of T cells (LAT), Src homology 2 domain-containing leukocyte protein of 76 kDa (SLP-76), and Grb2-related adaptor downstream of Shc (Gads), along with kinases such as Bruton's tyrosine kinase (Btk) and phosphatidylinositol 3-kinase (PI3K). These components collectively activate phospholipase Cγ2 (PLCγ2), which in turn generates inositol trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 mediates calcium release, whereas DAG activates PKC. Calcium and DAG work synergistically to promote platelet granule secretion and integrin activation, leading to platelet aggregation and thrombosis (Figure 1).[5] A recent study revealed the GPVI-induced protein phosphorylation sites critical for platelet activation signaling: phosphorylation of Syk Y352 and Btk Y551 is essential for their respective activation, whereas PLCγ2 activation is mediated through dual phosphorylation at Y759 and Y1217.[6] These findings provide novel insights into GPVI downstream signaling and potential therapeutic targets for antiplatelet interventions.

Collagen serves as the primary ligand for GPVI, though controversy persists regarding whether GPVI binds collagen in its monomeric or dimeric form. Although early studies proposed that GPVI dimerization was essential for collagen binding,[7] recent research indicates that both monomeric and dimeric forms of GPVI can bind collagen.[8] As summarized in Figure 1, monomers are capable of forming dimers through affinity-driven interactions, and although dimers might enhance activation by increasing avidity, they are not the specific conformation for collagen binding.[8] Evidence supporting the capability of monomeric GPVI to bind collagen and initiate activation includes steric hindrance between GPVI molecules and the preservation of the extracellular domain conformation during dimerization.[9,10] Furthermore, advanced biophysical techniques have consistently demonstrated that GPVI predominantly exists in monomeric form and that although the D2 domain mediates dimerization, this domain is not essential for collagen-induced activation, demonstrating that monomeric GPVI is sufficient to mediate signaling.[8] In humans, GPVI also bound to both fibrinogen and fibrin, promoting thrombus growth and thrombin generation. Notably, this interaction was species-specific; mouse GPVI did not function as a receptor for fibrinogen, although it could be activated by fibrin.[11–13] The reasons underlying the species differences in fibrinogen-mediated activation of GPVI remained unclear. Additionally, GPVI interacted with other ligands including matrix proteins (laminin),[14] the monocyte surface receptor extracellular matrix metalloproteinase inducer {EMMPRIN [cluster of differentiation (CD)147]; basigin in mice},[15] and additional molecules.

An ideal novel anti-thrombotic target should effectively inhibit thrombosis without increasing

bleeding risk. Studies of patients with GPVI deficiency and mouse models with antibody-induced GPVI depletion collectively demonstrate that GPVI deficiency results in severely impaired collagen-induced platelet aggregation while causing only minimal or no bleeding, highlighting its therapeutic potential.[16,17] Extensive research has demonstrated the multifunctional role of GPVI in platelet adhesion, aggregation, and thrombus formation, as well as its emerging involvement in inflammation and cancer progression. In this review, we first summarize the mechanism of GPVI in thrombus formation, then analyze its association with inflammation and cancer progression. Finally, we synthesize recent advances from clinical trials targeting GPVI, evaluating their translational potential for thrombosis treatment.

Mechanisms of GPVI in thrombosis

It has been demonstrated that GPVI activity is regulated through two mechanisms to efficiently activate platelets: dimerization and receptor clustering.[18] Platelets express multiple collagen receptors. Following vascular injury under flow conditions, the interactions of GPIbα–von Willebrand factor (VWF), integrin α2β1–collagen, and GPVI–collagen cooperatively mediate platelet adhesion. Among these, GPIbα–VWF plays a critical role in the initial platelet capture under high shear stress (>1000 s^{-1}).[19] Although not essential, integrin α2β1 stabilizes collagen binding and promotes GPVI dimerization and clustering, thereby amplifying GPVI activation and synergistically supporting platelet aggregation and thrombus formation.[18,20] As the central receptor for collagen, GPVI activates the FcRγ chain-dependent pathway, triggering calcium fluxes and integrin αIIbβ3 activation to promote platelet firm adhesion and thrombosis.[20] Furthermore, under extremely high shear stress (>2000 s^{-1}), the interaction between GPVI and fibrin contributes significantly to thrombus stability.[19]

GPVI plays a dual role in thrombosis by promoting both platelet aggregation and coagulation. GPVI participates in coagulation mainly via the following mechanisms. First, collagen-stimulated platelets exhibit procoagulant activity, with collagen exposure leading to phosphatidylserine (PS) externalization and factor V release from platelet α-granules, thereby enhancing thrombin and fibrin generation.[21,22] The rate and intensity of this procoagulant response correlate with GPVI expression levels.[23] Additionally, tissue factor and fibrin can activate platelets through GPVI-dependent pathways.[13,21] Recent studies have further demonstrated that coagulation factor FXIIIa potentiates platelet activity via GPVI.[24] Interestingly, high concentrations of FVIII (>50 nM) inhibit GPVI-dependent activation, suggesting a potential negative feedback mechanism.[25] Furthermore, pharmacological inhibition of GPVI signaling (using Btk inhibitors) alters clot architecture and function, as evidenced by increased clot porosity and reduced contractility.[26] GPVI has also been shown to contribute to platelet-mediated clot contraction in thromboelastography (TEG) studies.[27]

Platelet surface GPVI undergoes ectodomain shedding, releasing a soluble 55-kDa fragment (sGPVI). Elevated sGPVI levels were observed in patients with coronary artery disease (CAD),[28] and higher sGPVI correlated with increased atherosclerotic plaque burden in

coronary arteries.[29] However, another study found that patients with chronic coronary syndrome with elevated sGPVI levels showed no increased risk of ischemic events after percutaneous coronary intervention, but rather demonstrated higher bleeding risk.[30] In patients with ischemic stroke treated with endovascular thrombectomy alone, sGPVI levels (both pre- and post-procedure) were negatively associated with short-term stroke severity.[31] This observation demonstrates that retained platelet surface GPVI might be preferentially recruited for vascular wall repair following thrombectomy, thereby limiting sGPVI release. These findings collectively suggest that elevated sGPVI reflects both enhanced platelet activation and potential platelet surface GPVI receptor downregulation, which could attenuate platelet responsiveness to vascular collagen while simultaneously increasing hemorrhagic risk.

Associations of GPVI with inflammation and cancer

Platelet GPVI contributes to inflammatory processes through interactions with neutrophils, monocytes, and macrophages. Five distinct inflammation models demonstrate the role of GPVI in platelet–neutrophil interactions. In immune complex (IC)-induced glomerulonephritis, GPVI mediated initial platelet recruitment to glomerular capillaries, followed by integrin αIIbβ3 activation. Subsequent P-selectin release from platelets facilitated neutrophil binding, driving glomerulonephritis development.[32] In IC-mediated dermatitis models, GPVI deficiency did not affect neutrophil recruitment but significantly impaired their cytotoxic activity.[33] In lipopolysaccharide (LPS)-induced acute lung injury, GPVI deficiency reduced neutrophil infiltration, myeloperoxidase activity, and blood lactate levels, demonstrating its role in neutrophil aggregation and adhesion, stable platelet–neutrophil complex formation, and neutrophil extracellular trap (NET) formation.[34] In an imiquimod-induced psoriasis model, the antimicrobial peptide Cathelicidin-HG specifically inhibits GPVI-mediated platelet activation, effectively reduces the formation of platelet–neutrophil complexes, and suppresses neutrophil activation and inflammatory cytokine release, thereby alleviating psoriasis symptoms.[35] In abdominal aortic aneurysm, GPVI deficiency reduced platelet–neutrophil interactions, NET formation, and inflammatory cytokine release, while improving vascular remodeling and attenuating disease progression.[36] Regarding monocyte interactions, studies revealed that platelet–monocyte adhesion depends on GPVI–EMMPRIN binding, with blockade of either molecule inhibiting firm adhesion.[15] Moreover, in a folic acid-induced acute kidney injury model, galectin-3 derived from renal tubular epithelial cells activated platelet GPVI receptors, induced platelet granule release, promoted the formation of monocyte–platelet aggregates in circulation, and drove monocyte differentiation into pro-inflammatory M1-type macrophages, thereby exacerbating renal inflammatory responses and tissue damage.[37] GPVI also modulates macrophage polarization: in zymosan-induced inflammation, GPVI-deficient mice showed increased anti-inflammatory macrophage markers and decreased proinflammatory mediators [prostaglandin E2 and interleukin (IL)6] in inflamed paws, resulting in reduced mechanical allodynia.[38] In addition to interacting with inflammatory cells, the activation of platelet GPVI also promoted microvascular thrombosis, thereby exacerbating multiple organ dysfunction and inflammation in sepsis.[39] Studies have revealed that enhanced GPVI activation was

associated with an increased risk of requiring (non)invasive ventilation and/or mortality in patients with COVID-19, as well as in those with sepsis-related acute respiratory distress syndrome (ARDS).[40,41] Collectively, these findings unveil the multifaceted biological functions of GPVI in thrombo-inflammatory regulation.

The pro-metastatic effects of GPVI are mediated through multiple molecular pathways. Its interaction with galectin-3 on tumor cell surfaces activated platelets and enhanced platelet–tumor cell adhesion, while also upregulating the expression of cyclooxygenase-2 and prostaglandin E_2 in tumor cells. The upregulated molecules promoted tumor cell invasiveness by modulating cell cycle-related proteins (downregulation of $p21^{WAF1/CIP1}$ and upregulation of cyclin B1) and activating the epithelial–mesenchymal transition program.[42] Additionally, GPVI–galectin-3 interaction activates the nuclear factor (NF)-κB and transforming growth factor (TGF)β/suppressor of mothers against decapentaplegic (SMAD) pathways.[43] A recent study revealed that GPVI selectively promoted metastatic growth in specific tumor types (e.g. B16F10 melanoma) by promoting an immunosuppressive tumor microenvironment (upregulation of pro-tumorigenic genes associated with melanoma progression, immune checkpoint proteins, and cell cycle activation) while sustaining platelet infiltration in metastatic niches.[44] The platelet extracellular vesicles generated via activation of the platelet receptor GPVI also promoted tumor proliferation, invasion, and metastasis.[45] These mechanisms collectively enhance tumor cell invasiveness, proliferative capacity, and metastatic potential. The platelet receptor GPVI also played a critical role in maintaining tumor vascular integrity. GPVI inhibition induced intratumor bleeding and necrosis while improving the accumulation and efficacy of co-administered chemotherapeutic agents.[46] With regard to the inhibition of tumor progression by GPVI, GPVI activated immune responses and suppressed tumor proliferation, and was associated with favorable patient prognosis.[47] In summary, GPVI exhibits dual regulatory roles in tumor progression: on the one hand, it promotes tumor metastasis through platelet–tumor cell interactions and induction of an immunosuppressive microenvironment; on the other hand, under specific tumor microenvironment conditions, it might suppress tumor progression by activating anti-tumor immune responses. This functional duality positions GPVI as a therapeutic target with complex regulatory mechanisms, and future studies need to elucidate its differential mechanisms of action across various tumor types to guide the development of GPVI-targeted therapeutic strategies.

Drug targeting GPVI

Anti-GPVI Fab

In a mouse model of myocardial ischemia–reperfusion injury, JAQ1 (anti-mouse GPVI antibody) significantly reduced infarct size, with its protective mechanism potentially related to decreased leukocyte infiltration in reperfused myocardium following GPVI inhibition.[48] Similarly, in a transient middle cerebral artery occlusion model, JAQ1 pretreatment not only reduced cerebral infarct volume on day 1 but also improved neurological scores, without increasing the risk of recombinant tissue plasminogen activator (rt-PA) thrombolysis-

associated intracerebral hemorrhage.[49] However, it should be noted that in both studies JAQ1 was administered prior to model induction (exerting its protective effect through GPVI depletion).

Glenzocimab (formerly ACT017) is a humanized Fab fragment designed from the murine monoclonal antibody 9O12. *In vitro* studies using human platelets demonstrated its potent inhibition of collagen-induced platelet aggregation, with mean IC_{50} values of 3.2 ± 2.5 μg/ml (intensity) and 2 ± 0.7 μg/ml (velocity).[50] In addition to inhibiting the generation of thrombus, glenzocimab also promoted platelet thrombi disaggregating in a shear-dependent manner, suggesting the interaction of GPVI with fibrin and the role of GPVI in maintaining the stability of thrombus.[51] At the molecular level, glenzocimab binds to the C–C′ loop region of the D2 domain, leading to structural modifications and steric hindrance and thus inhibiting collagen binding and receptor dimerization.[52] Pharmacological studies in cynomolgus monkeys demonstrated reversible inhibition of collagen-induced platelet aggregation at doses of 2–8 mg/kg, without prolonging bleeding time or adverse effects, demonstrating its preliminary safety and efficacy.[50] Study using reverse passive Arthus reaction (rpA)-induced skin inflammation and skin tumor models in huGPVI mice demonstrated that glenzocimab does not impact inflammatory hemostasis or tumor-related bleeding.[53] Notably, unlike GPVI-depleted mice, glenzocimab neither reduces platelet count nor downregulates GPVI expression. This distinction is crucial for explaining their differential bleeding phenotypes in rpA-inflamed skin models. Additionally, under physiological conditions related to hemostasis, glenzocimab did not critically affect platelet adhesion, which was likely another key reason for its lack of interference with normal hemostasis.[19] A recent study used two murine models to assess glenzocimab: primary intracranial hemorrhage and hyperglycemia-induced hemorrhagic transformation after cerebral ischemia–reperfusion injury. Results from both models demonstrated that the treatment does not impact bleeding severity.[54] Therefore the use of glenzocimab appears to be safe in patients with stroke without prior hemorrhagic risk assessment. An efficacy study revealed that glenzocimab strongly inhibited platelet aggregation induced by human atherosclerotic plaques. When glenzocimab was added *ex vivo* to blood samples from patients with acute coronary syndrome (ACS) treated with aspirin and ticagrelor, it demonstrated additional antithrombotic effect.[55]

A Phase I clinical trial of glenzocimab provided data on its safety, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity, demonstrating its potential as an antiplatelet drug. Administration of doses from 62.5 to 2000 mg to healthy subjects showed no serious adverse events or bleeding time prolongation. AUC and C_{max} demonstrated linear PK over the tested dose range. Glenzocimab exhibited dose-dependent inhibition of platelet aggregation during infusion at 125–500 mg (60–80% reduction; maximal inhibitory effect lasting 6–8 h), whereas 1000/2000-mg doses achieved maximal 90% inhibition with prolonged duration (18 h), demonstrating the requirement for a high dose to compensate for its short half-life and significant antibody displacement. Consistent with preclinical findings, glenzocimab administration did not impact the platelet count and GPVI expression.[56]

In patients with acute ischemic stroke receiving alteplase treatment, a Phase Ib clinical trial

demonstrated good tolerability of glenzocimab 1000 mg, establishing it as the recommended dose for the phase IIa study. The phase IIa study showed that the use of glenzocimab 1000 mg as add-on therapy to alteplase within 4.5 h of the onset of stroke symptoms might reduce intracranial hemorrhage and all-cause mortality. Primary analysis [with a modified Rankin Scale (mRS) score of 0–2 defined as favorable outcome] showed no differences between groups. Exploratory analysis (with mRS score 4–6 defined as poor outcome) suggested potential improvement in 90-day outcome with glenzocimab, and further *post hoc* analysis revealed this effect to be particularly pronounced in patients undergoing mechanical thrombectomy.[57] However, because of limitations including *post hoc* analyses, small sample size, baseline imbalance, and unappropriated time of imaging to evaluate ischemic lesion volume, the safety and efficacy of glenzocimab in acute ischemic stroke require further investigation. Hence, two Phase IIb trials have been initiated in the target population. In the ACTISAVE study, glenzocimab did not affect the primary endpoint (poor 90-day outcome, mRS score 4–6) or secondary endpoint (good 90-day outcome, mRS score 0–2), potentially because of baseline imbalances (higher National Institutes of Health Stroke Scale scores, higher proportion of diabetes, and later treatment in the glenzocimab group). Adjusted analyses suggested potential benefits for functional improvement (mRS score 0–1), and a better outcome was also found in the glenzocimab group in patients with concomitant antithrombotic or full recanalization after mechanical thrombectomy, or a high severity score at inclusion.[58] The GREEN study, evaluating glenzocimab combined with endovascular therapy, was terminated early because of futility (based on an interim analysis of the first 78 patients).[59] These findings suggest a possible benefit of glenzocimab in a more restricted population, though further validation is required. Following these three trials, the Phase II–III GALICE study was registered to evaluate the efficacy and safety of glenzocimab in patients with large ischemic core eligible for endovascular therapy.[60] In addition, the GARDEN trial, a Phase II clinical study evaluating the safety and efficacy of glenzocimab in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-associated ARDS, found that glenzocimab did not significantly prevent clinical progression of ARDS in patients with COVID-19 but demonstrated favorable safety, without increasing bleeding risk.[61] The other registered Phase II clinical trial, the LIBERATE trial, aimed to evaluate whether glenzocimab could reduce myocardial infarct size in patients with ST-elevation myocardial infarction, but was prematurely stopped in April 2025 because of insufficient funding.[62]

EMA601 is a recently reported humanized anti-GPVI Fab fragment that demonstrates potent inhibitory effects by targeting the membrane-proximal epitope of GPVI. In an *in vitro* study, EMA601 completely inhibited GPVI-dependent platelet activation with high affinity (KD = 0.195 nM), exhibiting over 50-fold higher potency than glenzocimab. At a concentration of 1 μg/ml, EMA601 blocked collagen-induced platelet aggregation, whereas glenzocimab failed to achieve complete inhibition even at 50 μg/ml.[63] This significant potency difference has been debated: Mangin and Jandrot-Perrus have questioned the bioequivalence between commercially available ACT017 and glenzocimab, citing studies demonstrating complete platelet aggregation inhibition by glenzocimab at 2 μg/ml.[64] However, Nieswandt *et al*. maintained that their findings were valid, suggesting methodological variations (including the use of washed platelets versus platelet-rich plasma, and differences in collagen stimulation

intensity) might account for these differences, while also highlighting that even in human clinical trials, glenzocimab showed residual platelet aggregation (~10%) at high doses (>50 μg/ml plasma concentration).[65] Enhanced GPVI inhibitory activity of EMA601 was consistently observed in both *in vitro* aggregation assays under arterial shear rates (1000 s^{-1}) and *in vivo* studies using GPVI-humanized mice. The precursor of EMA601, Emf6.1^{Fab} (4 mg/kg), demonstrated antithrombotic efficacy by effectively preventing arterial thrombosis in models of mechanical abdominal aorta injury and ferric chloride ($FeCl_3$)-induced carotid artery thrombosis, while also reducing cerebral infarct volume at 24 h following transient middle cerebral artery occlusion. Notably, Emf6.1^{Fab} treatment did not prolong tail bleeding time, even when co-administered with aspirin and rt-PA, which is attributable to its preservation of partial platelet adhesive function.[63] Although both Fabs exhibit rapid urinary clearance, the superior affinity and unique binding capability to the GPVI dimerization domain of EMA601 could provide more sustained inhibitory effects. These findings highlight EMA601 as a highly promising antithrombotic agent, offering a novel therapeutic strategy for arterial thrombosis and ischemic stroke, though further PK/PD studies are needed to evaluate its clinical potential compared with glenzocimab.

Soluble dimeric GPVI-Fc fusion protein (Revacept)

The soluble GPVI-Fc was generated by fusing the extracellular domain of human GPVI to the human Fc domain, forming a 150-kDa homodimer with a specific hinge region. GPVI-Fc exhibited half-maximal collagen binding at a concentration of 6.0 μg/ml. *In vitro* studies revealed that GPVI-Fc effectively inhibited platelet adhesion to immobilized collagen and thrombus formation. In a murine carotid artery injury model, administration of GPVI-Fc at doses of 1–2 mg/kg reduced firm platelet adhesion and aggregation.[66] Mechanistic investigations showed that, in addition to directly binding to exposed collagen at injured endothelial sites, GPVI-Fc competitively interacted with fibronectin on activated endothelial cell surfaces and type III collagen in the core regions of atherosclerotic plaques. Long-term administration experiments demonstrated that GPVI-Fc suppressed atherosclerotic plaque formation in apolipoprotein E (ApoE)-deficient mice and ameliorated endothelial dysfunction while attenuating disease progression in atherosclerotic rabbits.[67,68] As for the risk of bleeding, GPVI-Fc induced moderate prolongation of tail bleeding time and absolute bleeding time in mice.[66] These findings demonstrate that GPVI-Fc represents a promising therapeutic strategy for targeting both thrombotic and atherosclerotic pathologies.

In a Phase I clinical trial, researchers evaluated the safety, tolerability, and PK/PD of Revacept (the GPVI-Fc fusion protein) in 30 healthy male subjects. Across the tested dose range (infusion of 10, 20, 40, 80, and 160 mg), Revacept exhibited dose-dependent PK properties, with a long half-life (67.7–136.6 h), and demonstrated a dose-dependent inhibitory effect on collagen-induced platelet aggregation. The safety assessment showed that Revacept did not significantly prolong bleeding time, and had no impact on platelet counts or coagulation parameters, and no anti-drug antibodies were detected. Furthermore, no serious adverse events were observed during the study period.[69]

Currently, two clinical trials of Revacept have been completed and published their results. One Phase II clinical trial evaluated the safety and efficacy of Revacept in patients with symptomatic internal carotid artery stenosis. Treatment of patients with Revacept 120 mg showed a trend toward reducing both the primary efficacy endpoint [number of new diffusion-weighted magnetic resonance imaging (MRI) lesions] and the composite clinical endpoint of ischemic events and bleeding complications. However, these findings were not consistently significant across all prespecified analyses (including negative binomial regression for lesion number and logistic regression for the composite endpoint), highlighting the need for further confirmation in larger trials. Treatment of patients with Revacept 40 mg did not demonstrate significant differences. No significant differences in bleeding events or adverse events were observed among the three groups (placebo, Revacept 40 mg, and Revacept 120 mg), indicating favorable safety.[70] However, we should not ignore several factors leading to potential bias, including the small number of participants, different intergroup treatment modalities, and the need to modify the end point of microembolic signals during the study. These findings suggest that Revacept might provide a safe and effective adjunctive treatment option for patients with symptomatic carotid artery stenosis, though Phase III clinical trials with larger populations and standardized protocols are warranted to further validate its safety and efficacy in the target population. The other study was a Phase II clinical trial evaluating the safety and efficacy of Revacept in patients with stable ischemic heart disease (SIHD) undergoing elective percutaneous coronary intervention. The results showed no statistical difference among the three groups (placebo, Revacept 80 mg, and Revacept 160 mg) in the primary endpoint of a composite of death or myocardial injury, defined as an increase in the high-sensitivity cardiac troponin T (hsTnT) value to at least five times the upper limit of normal within 48 h of randomization. The safety endpoint included 30-day bleeding events [Bleeding Academic Research Consortium (BARC) type 2–5], which also showed no significant difference between groups. The authors mentioned two explanations for the lack of increase in clinical efficacy: one was the fivefold increase in hsTnT, a surrogate endpoint of myocardial injury with little prognostic value, and the other was that Revacept did not have an effect on plaque shifting or distal plaque material embolization, which is a key trigger of type 4a myocardial infarction.[71] Subsequent analysis of this clinical trial population demonstrated that Revacept treatment induced dose-dependent alterations in the chemokine profile. Although the changes in MIG (monokine induced by gamma interferon) levels did not reach statistical significance, the upward trend following Revacept administration suggested the drug might exert a dual mechanism of action: mitigating atherosclerotic progression while maintaining hemostasis.[72] These findings demonstrated that Revacept did not show a clinical benefit in patients with SIHD but exhibited favorable safety. Further validation in a high-risk population for ischemic events (e.g. ACS) is warranted to assess its potential. Clinical trials targeting GPVI are summarized in Table 1. Figure 2 illustrates the pharmacological effects of glenzocimab and Revacept, highlighting the more critical role of GPVI in thrombosis than in hemostasis.

Other drugs

Other drugs include inhibitors of signal molecules, GPVI small molecule antagonists, *cis*-

acting platelet receptor inhibitors (CAPRIs), and some natural products. The Btk inhibitor ibrutinib was primarily used in the treatment of chronic lymphocytic leukemia, and bleeding events in patients treated with ibrutinib prompted researchers to explore the effect of Btk inhibitors on platelet reactivity. Inhibition of Btk significantly reduced GPVI-mediated platelet activation, spreading, and aggregation *in vitro*. Subsequent studies found that Btk inhibitors not only inhibited plaque-induced platelet activation, but also inhibited platelet procoagulant activity and thrombin generation, and that the highly selective Btk inhibitor AB-95-LH34 did not have the off-target inhibitory effect of ibrutinib on Src, which did not lead to an increased risk of bleeding, suggesting that the selective Btk inhibitor has promising efficacy and safety as an antithrombotic drug.[73]

Small molecule antagonists that have been extensively studied include losartan and its active metabolite EXP3179. In the study by Grothusen *et al*, EXP3179 dose-dependently inhibited collagen type I-induced aggregation and activation of human platelets, with significant effects seen at 500 μmol/l, and the inhibition could be prevented by the selective GPVI-activating antibody 4C9. In a mouse model of carotid injury, EXP3179 significantly reduced platelet adhesion to the site of injury.[74] Subsequent study showed that the interaction between hydrophobic residues in GPVI and the phenyl group in losartan was key to the binding.[75] A study has demonstrated that losartan is a small molecule antagonist of GPVI inhibiting GPVI-mediated platelet aggregation *in vitro*.[76] A further study measured platelet aggregation, P-selectin exposure, and GPVI dimerization levels in patients with Marfan syndrome treated with losartan, and there were no statistical differences in any of these parameters compared with patients treated with placebo. The authors suggested that losartan had no effect on platelet reactivity in patients with normal blood pressure.[77] In conclusion, the antiplatelet effect of losartan as a small molecule GPVI antagonist remains to be verified. APX-115, a pan-NADPH oxidase (NOX) inhibitor, exerted antithrombotic effects by suppressing NOX-mediated reactive oxygen species (ROS) generation, thereby alleviating ROS-induced oxidative inactivation of protein tyrosine phosphatases (PTPs) and restoring PTPs activity. The reactivated PTPs dephosphorylate key signaling molecules (e.g. PLCγ2) in the GPVI pathway, leading to inhibition of platelet activation. In a $FeCl_3$-induced carotid artery occlusion model, APX-115 significantly prolonged occlusion time without affecting tail bleeding time, suggesting its potential as an antithrombotic agent.[78]

The development of bispecific single-chain variable fragments, termed CAPRIs, represents a novel therapeutic strategy. These agents are engineered by fusing the variable regions of an anti-G6b-B antibody to those of an anti-GPVI antibody, creating a molecule that mediates hetero-clustering between the two receptors. As an immunoreceptor tyrosine-based inhibition motif-containing receptor, G6b-B acts as a native inhibitor of ITAM signaling receptors like GPVI. This proximity modulates the signaling of the inhibitory receptor G6b-B, thereby potently inhibiting the GPVI activation pathway and suppressing thrombus formation. Although CAPRIs might achieve more precise modulation of platelet function by targeting physiological co-inhibitory receptors (G6b-B), they still carry the potential risk of mediating trans-receptor interactions between platelets, which could induce platelet agglutination. Therefore this novel therapeutic approach requires further validation.[79]

Another representative drug is colchicine; 174 patients with a history (>6 months) of ACS treated with colchicine showed a decrease in serum GPVI.[80] Subsequent studies found that colchicine did not affect platelet GPVI expression, but reduced GPVI-mediated ROS production, although it was not clear which component of ROS production colchicine acted on.[81] Other drugs mentioned as having potential inhibitory effects on GPVI include ginsenoside Rg5[82] and sulforaphane.[83]

Concluding remarks

Targeting GPVI, a central collagen receptor that plays a crucial role in thrombus formation following endothelial injury or atherosclerotic plaque rupture, represents a promising antithrombotic strategy with a favorable safety profile, primarily because it effectively inhibits collagen-induced thrombosis without significantly compromising hemostasis. Among the emerging antiplatelet agents targeting GPVI, glenzocimab and Revacept represent the most advanced candidates in clinical development. Although glenzocimab demonstrates potential in reducing intracranial hemorrhage and all-cause mortality, and improving functional outcomes, in patients with stroke, these findings are derived from exploratory analyses and remain insufficient to confirm efficacy, necessitating further validation in well-defined high-risk populations. Regarding Revacept, the effect of the 120-mg dose in patients with symptomatic carotid artery stenosis still requires further validation, as the findings are based on exploratory analyses and were inconsistent across different statistical methods. Another Phase II trial showed no significant protective effect against myocardial injury. Collectively, although clinical evidence to date indicates that GPVI-targeted therapies maintain a favorable safety profile without increasing bleeding risk, there is still insufficient evidence to confirm their efficacy. Moreover, a recent study revealed that glenzocimab induces thrombus fragmentation under pathological shear stress, a phenomenon that raises new concerns regarding its safety profile. Emerging agents such as EMA601, with superior affinity and inhibitory potency, show potential for GPVI inhibition. Additionally, novel CAPRIs offer alternative mechanisms for modulating GPVI signaling. Overall, GPVI inhibition holds therapeutic potential for arterial thrombosis and ischemic events, but further investigation is required to establish its long-term safety and to better define which patient subgroups would derive the greatest clinical benefit from this therapeutic approach.

CRediT authorship contribution statement

R. L.: Writing – review & editing, Writing – original draft, Visualization, Investigation. **Z. Q.:** Writing – review & editing, Writing – original draft, Visualization. **Y. C.:** Writing – review & editing, Project administration. **Q. X.:** Writing – review & editing, Project administration.

Data availability

No data were used for the research described in the article.

Declarations of interest

No interests are declared.

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FIGURE 1

Signal and conformation of glycoprotein VI (GPVI). Btk, Bruton's tyrosine kinase; Ca^{2+}, calcium ion; DAG, diacylglycerol; ER, endoplasmic reticulum; FcRγ, Fc receptor γ; Gads, Grb2-related adaptor downstream of Shc; IP3, inositol trisphosphate; ITAM, immunoreceptor tyrosine-based activation motif; LAT, linker for activation of T cells; P, phosphorylation; PI3K, phosphatidylinositol 3-kinase; PIP2, phosphatidylinositol-4,5-bisphosphate; PKC, protein kinase C; PLCγ2, phospholipase Cγ2; SFK, Src family kinase; SLP-76, Src homology 2 domain-containing leukocyte protein of 76 kDa; Syk, spleen tyrosine kinase. Figure created with BioRender.

FIGURE 2

The role of glycoprotein VI (GPVI) in thrombosis and hemostasis, and the pharmacological effects of glenzocimab and Revacept. Figure created with BioRender.

TABLE 1

Summary of clinical trials targeting glycoprotein VI (GPVI).

Drug	Phase	Condition	Study ID	Trial name	Note
Glenzocimab	I	Healthy volunteers	EUCTR2017-003047-38-NL	ACT-CS-001 (CS0278)	The study provided information on the safety, pharmacokinetics, pharmacodynamics, and immunogenicity of glenzocimab.[56]
	I/II	Acute ischemic stroke	NCT03803007	ACTIMIS	Glenzocimab 1000 mg might reduce hemorrhage and mortality.[57]
	II	COVID-19	NCT04659109	GARDEN	Glenzocimab failed to prevent ARDS progression in patients with COVID-19.[61]
	II	ST-elevation myocardial infarction	ISRCTN15443962	LIBERATE	The study was prematurely stopped because of insufficient funding.[62]
	II/III	Acute ischemic stroke	NCT05070260	ACTISAVE	The primary and secondary endpoints were not achieved.[58]

	II/III	Acute ischemic stroke	NCT05559398	GREEN	The study was terminated early because of futility.[59]
	II/III	Acute ischemic stroke	NCT06437431	GALICE	The study was incomplete (it assessed the efficacy of glenzocimab in patients with large ischemic core acute ischemic stroke).[60]
Revacept	I	Healthy volunteers	NCT01042964	PR-15/01	The study provided information on safety, tolerability, and pharmacokinetics.[69]
	II	Symptomatic carotid stenosis	NCT01645306	RevaceptCS02	Revacept 120 mg might reduce both the number of new ischemic lesions and the incidence of composite ischemic/bleeding events.[70]
	II	Stable coronary artery disease	NCT03312855	ISAR-PLASTER	The primary endpoint and safety endpoint were not achieved.[71]

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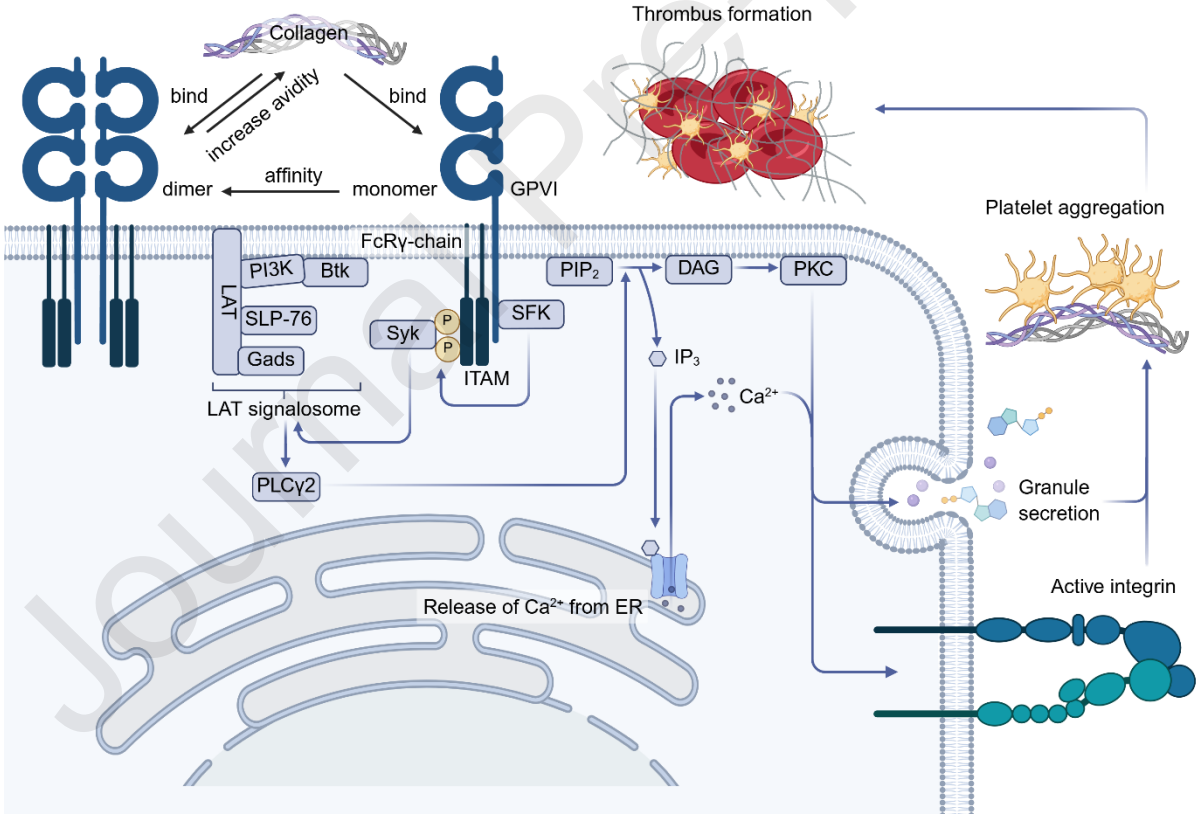

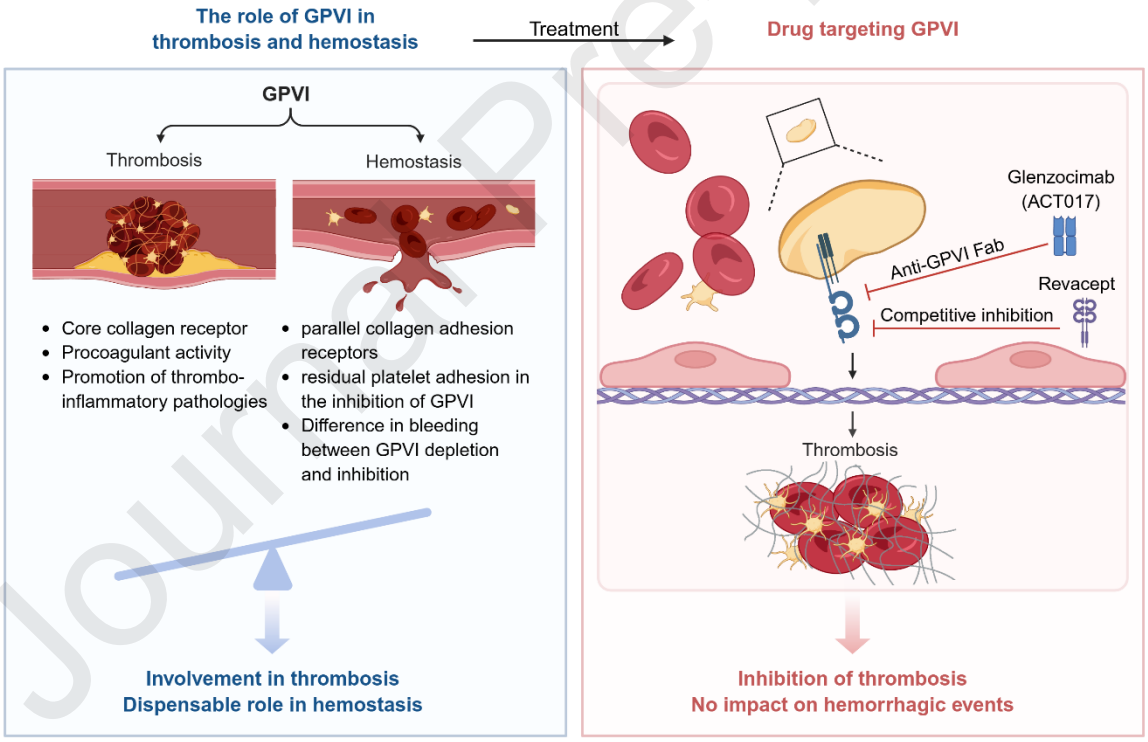

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: