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GPVI inhibition by glenzocimab synergistically inhibits atherosclerotic plaque-induced platelet activation when combined with conventional dual antiplatelet therapy

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Introduction

- Platelet GPVI receptors are activated by collagen, which is exposed following atherosclerotic plaque rupture during acute coronary syndromes (ACS). GPVI has also recently been identified as a receptor for fibrin.
- Aspirin and a $P2Y_{12}$ inhibitor are routine treatments for myocardial infarction (MI). However, these drugs are not always sufficient for heavy coronary thrombus burden during ST-elevation MI (STEMI).
- More potent antiplatelet drugs (GPIIb/IIIa-inhibitors) may help in this setting, but are limited by excessive bleeding.

AIM

- Since GPVI has major roles in thrombosis but is much less important than GPIIb/IIIa for haemostasis, we aimed to investigate whether a novel platelet GPVI inhibitor, glenzocimab (Acticor Biotech), provides additional antithrombotic effects when combined with aspirin and ticagrelor.

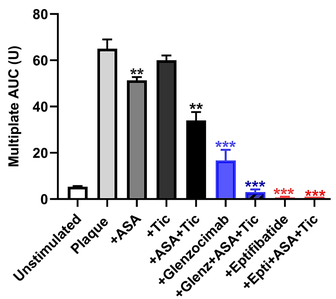
METHODS

- Investigated the antithrombotic effects of adding glenzocimab (previously known as ACT017) to blood from healthy donors and 22 patients with ACS treated with aspirin and ticagrelor.
- Compared the effect of glenzocimab with the GPIIb/IIIa inhibitor eptifibatide *ex-vivo*.
- Investigated the effect on platelet aggregation, signalling, adhesion, thrombin generation, thrombus formation and clot stability *ex vivo*.
- Platelets stimulated with collagen and atherosclerotic plaque material.
- Intravital microscopy in a murine model of ST-elevation myocardial infarction and ischaemia-reperfusion injury to investigate microvascular thrombosis.

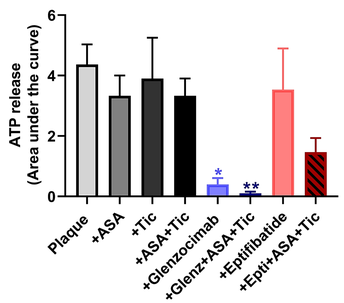
RESULTS

Glenzocimab inhibited plaque-induced responses

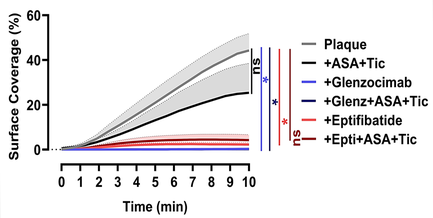
Platelet aggregation



ATP secretion

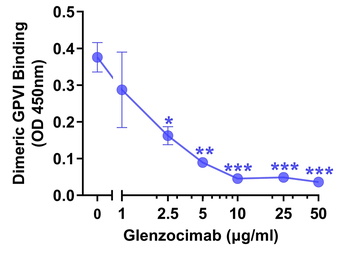


Platelet adhesion and P-selectin expression

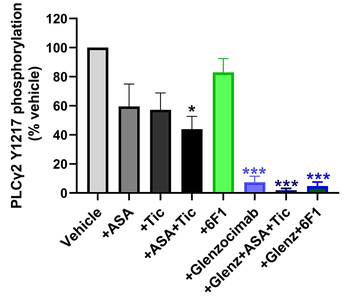


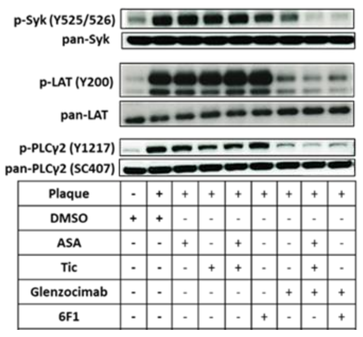
Glenzocimab inhibited GPVI and abolished GPVI signalling in response to atherosclerotic plaque

ELISA



Protein Phosphorylation

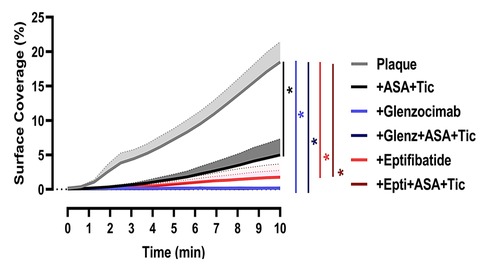




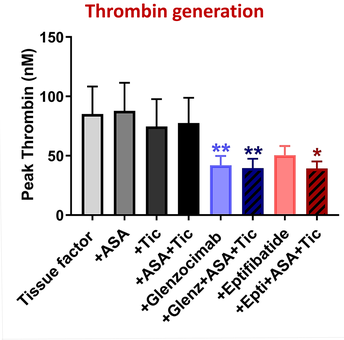
Plaque	-	+	+	+	+	+	+	+	+
DMSO	+	+	-	-	-	-	-	-	-
ASA	-	-	+	-	+	-	-	+	-
Tic	-	-	-	+	+	-	-	+	-
Glenzocimab	-	-	-	-	-	-	+	+	+
6F1	-	-	-	-	-	+	-	-	+

Glenzocimab inhibited procoagulant function of platelets

Phosphatidylserine exposure

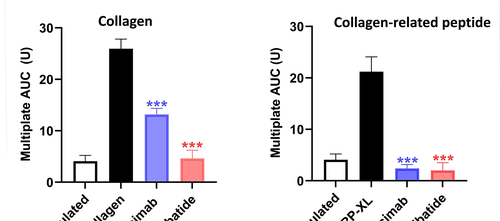


Thrombin generation

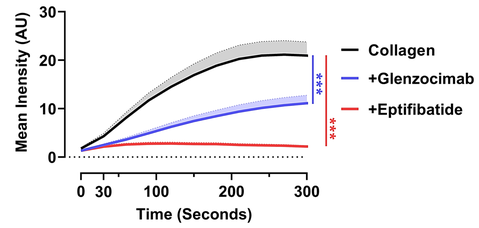


Glenzocimab provided synergistic effects when added to the blood of DAPT-treated ACS patients ex vivo

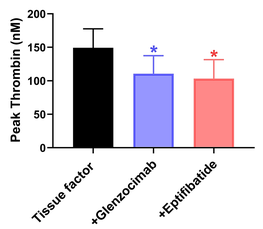
Platelet aggregation



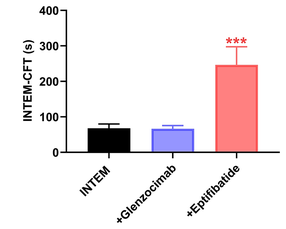
Thrombus formation on collagen



Thrombin generation

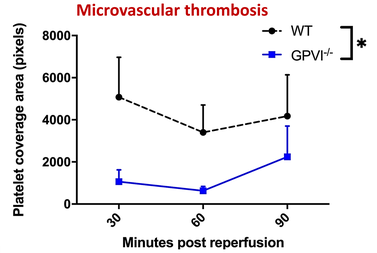


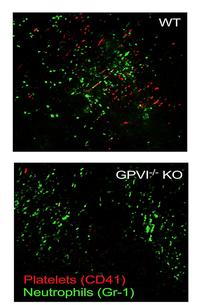
ROTEM (indicator of haemostasis)



GPVI depletion reduced microvascular thrombosis in an animal model of STEMI and ischaemia-reperfusion injury

Microvascular thrombosis





CONCLUSIONS

- Glenzocimab provided amplified antithrombotic effects when combined with DAPT
- Less effect on mechanisms of haemostasis compared to eptifibatide
- Appealing for further development for use in STEMI