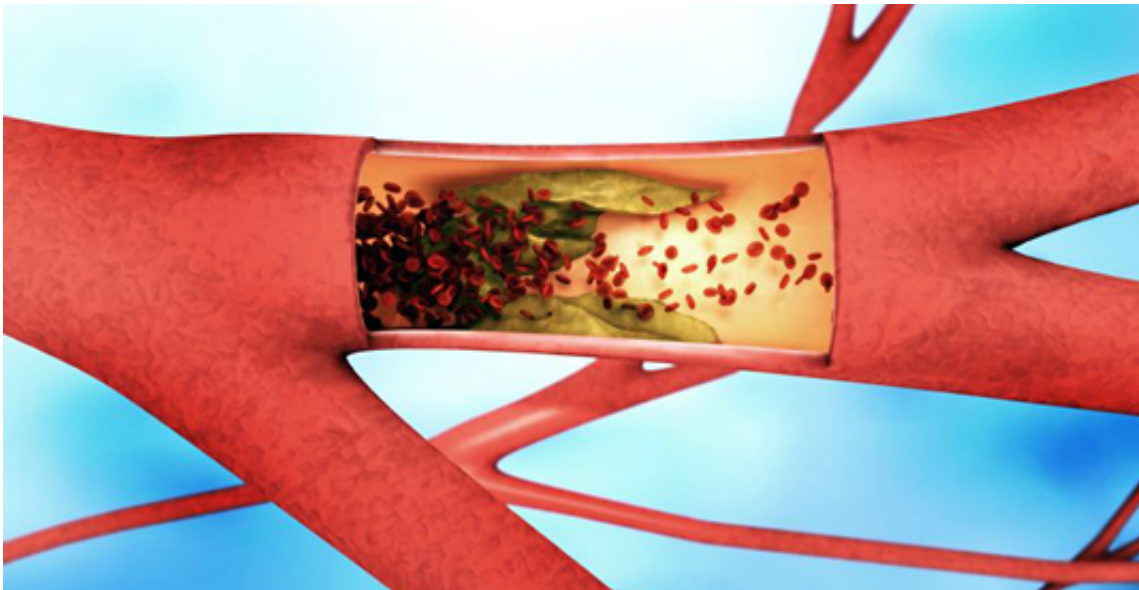


Arterial thrombosis: Cloaking of collagen frees up the flow

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Blood clots often form when lipid-rich plaques on the inner surface of arteries rupture and platelets aggregate at the site of injury. Cardiologists from Ludwig-Maximilians-Universitaet (LMU) in Munich have now compared the effects of two new platelet aggregation inhibitors.

Blood clots that form in arteries – so-called arterial thrombosis – are among the most common causes of heart attack and stroke. They are particularly prone to develop when '[atherosclerotic plaques](#)', fatty deposits that build up within the inner lining of major arteries, fracture

and break. Circulating thrombocytes (also known as platelets) then stick to the site of injury, and emit signals that initiate thrombus formation. Consequently, pharmacological agents that inhibit platelets, such as aspirin, reduce the risk of thrombus formation, albeit to a limited extent. Moreover, since such compounds act on platelets throughout the circulation, they increase the risk of bleeding. "Our goal is to develop antithrombotic drugs that are more effective and have fewer side-effects than those we now have," says Professor Wolfgang Siess. He and his research team at LMU's Institute for Prophylaxis and Epidemiology of Cardiovascular Diseases have compared the impact of two novel ways of inhibiting atherosclerotic plaque-induced platelet activation. Their findings appear in the *Journal of the American College of Cardiology (JACC)*.

Rupture of atherosclerotic plaques promotes the arterial thrombus formation because it brings extracellular fibrous proteins, such as collagen, that serve to hold the plaques together into contact with cells that circulate in the bloodstream. Collagen is a structural protein found in connective tissue, and it is also a potent activator of thrombocytes. When these cells bind to collagen, they release signal molecules that recruit more platelets to the site. "The [platelets](#) stick to one another and ultimately form a thrombus, which in extreme cases may obstruct [blood flow](#) completely," says Siess.

Blocking platelet binding to plaque collagen

Strikingly, while thrombocyte binding to 'normal' collagens requires a second surface receptor, platelet aggregation onto the collagen found in plaques occurs exclusively via the so-called glycoprotein VI (GPVI), which is found only on the cell membranes of thrombocytes. "We have taken advantage of this difference to test inhibitors that are specific for GPVI, because this should allow us to selectively inhibit the activation of thrombocytes by plaque collagen without simultaneously increasing the

risk of bleeding at other sites of injury in the vasculature," Siess explains.

To achieve this goal, two basic strategies were compared. "One can mask the GPVI on the thrombocyte surface directly with antibodies that are specific for the receptor," says Siess. "Alternatively, one can block the sites on plaque collagen that are recognized by the thrombocytes, using a synthetically produced, soluble form of GPVI that has been fused to a so-called Fc antibody fragment." In an international collaboration with academic researchers, and in cooperation with advanceCOR GmbH, the LMU team has applied both strategies and compared their respective impacts on arterial thrombus formation.

High flow rates make GPVI-Fc more effective

The study found that the antibody approach very effectively inhibited GPVI-mediated activation of thrombocytes by atherosclerotic plaques irrespective of the rate of blood flow. The GPVI-Fc strategy was comparatively less effective. "However, to our surprise, the degree of inhibition by GPVI-Fc was dependent on the flow rate. The higher the rate of blood flow, the greater the inhibition," Siess explains. "At low arterial flow rates some thrombocytes are despite of GPVI-Fc able to bind to collagen in niches downstream of plaque fragments, and secrete mediators that promote there the formation of platelet aggregates. When flow rates are higher, these mediators are rapidly diluted out, so that aggregation occurs relatively rarely, and the clumps tend to be smaller." Since the risk of plaque rupture is increased at stenotic sites of arteries, where flow is particularly high, it is possible that GPVI-Fc can be used specifically to block thrombus formation at those plaques that are most likely to rupture.

Overall, the results indicate that the new GPVI inhibitors more effectively prevent the formation of arterial [blood clots](#), and have fewer

side-effects, than the current standard of care, which combines aspirin with so-called P2Y12 antagonists. "And since the effects of GPVI-Fc are more localized, it is probably the better option. Even though the GPVI antibodies are intrinsically more potent, they inhibit thrombocyte activation systemically, and might therefore be more likely to cause bleeding," says Siess. "These factors should be taken into account in the design of clinical studies on patients with cardiovascular disease."

More information: "Differential inhibition of human atherosclerotic plaque-induced platelet activation by dimeric GPVI-Fc and anti-GPVI antibodies: functional and imaging studies." *JACC* 2015 [DOI: 10.1016/j.jacc.2015.03.573](https://doi.org/10.1016/j.jacc.2015.03.573)

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