N eointimal proliferation after stent implantation remains a concern even if local delivery of various antimitotic drugs has led to a significant reduction in smooth cell proliferation and a subsequent reduction in the rate of target vessel revascularization. The prevention of arterial restenosis in those treated by percutaneous coronary intervention using such new-generation stents fails in approximately 10% of patients, contributing to recurrent ischemic events and new revascularization procedures. Thus far, the systemic approach with statins, pioglitazone, angiotensin-converting enzyme inhibitors, and various antiproliferative drugs has not been successful in further reducing in-stent stenosis, raising the question of whether the aim included the right targets.

**Key Role of Platelets in the Natural History of In-Stent Restenosis**

Histopathologic studies in humans have demonstrated that after coronary stent placement, thrombus formation and acute inflammation are followed by vascular smooth cell proliferation, resulting in neointimal growth and leading to restenosis.1,2 Platelets play a key role in early thrombus generation and in the late neointima formation that results from arterial injury, such as after percutaneous coronary intervention or as a consequence of vessel wall inflammation, as occurs with atherosclerosis. Indeed, once recruited to or in the proximity of the vessel wall and exposed to thrombin, collagen, or thromboxane A2, platelets may release or express a plethora of growth factors (eg, platelet-derived growth factor) and proinflammatory molecules, of which adenosine nucleotides are present in high concentrations.3 Two G-protein–coupled receptors, P2Y1, and P2Y12, mediate the effects of ADP on platelets, a central mediator of platelet activation in the physiological process of hemostasis and the development and extension of arterial thrombosis. ADP acting on P2Y12 receptors also stimulates vasoconstriction, but its pathophysiological significance regarding vessel response to injury is uncertain.

**P2Y12 Receptor: A Dual Pathway?**

Numerous studies established the role of this receptor in the amplification of platelet activation, the stabilization of platelet aggregation, and thrombosis.3 New evidence suggests that the platelet receptor P2Y12 is also expressed by vascular smooth muscle cells4 and might be involved in arterial inflammatory response after injury. However, the substantial role of P2Y12 in promoting neo-intima formation appears to be specifically related to the receptors on platelets that mediate this response. This latter finding has suggested that more effectively targeting the platelet P2Y12 receptor before percutaneous coronary intervention might prove effective in reducing restenosis and could have a beneficial inhibitory effect on atherogenesis during long-term administration of P2Y12 antagonists.5

**Platelet Blockade to Prevent Restenosis: Is It Still Relevant?**

A reduction of neointimal formation models has been observed in different experimental models using various antiplatelet agents, including aspirin and clopidogrel, with an effect proportional to the extent of platelet inhibition (Figure). However, despite promising experimental observations, clinical investigations that have attempted to demonstrate a significant diminution of restenosis by using antiplatelet agents (eg, aspirin or clopidogrel) were disappointing and confusing. A more profound inhibition of platelet function did not lead to better results, especially with abciximab, a specific and potent inhibitor of the α2bß3 integrin, which blocks the final pathway of platelet aggregation.6 On the other hand, the phosphodiesterase III inhibitor cilostazol, whose ability to inhibit platelet aggregation is relatively weak compared with aspirin or clopidogrel, displays a specific antiproliferative effect and reduces smooth muscle proliferation. Different randomized studies showed consistent evidence toward a reduction in clinical restenosis after both bare metal and drug-eluting stent implantation.7 Altogether, these data do not support platelet inhibition and P2Y12 receptor blockade in particular as relevant targets to prevent restenosis after stent implantation.

**Ticagrelor and Restenosis: Is It Platelet Aggregation or Beyond?**

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Patil et al8 provide evidence that inhibition of P2Y12 receptor by ticagrelor can be beneficial in the prevention of the pathological vessel wall response to injury. Ticagrelor is a new reversible P2Y12 inhibitor that provides more consistent platelet inhibition than clopidogrel. Ticagrelor, as opposed to clopidogrel, has shown that stronger P2Y12 inhibition led to a significant 16% relative risk reduction of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke; a 1.1% absolute reduction of cardiovascular...
death; and a significant 27% excess of thrombolysis in myocardial infarction major bleeding not related to coronary artery bypass grafting.9,10 The benefit of ticagrelor may be even larger in patients at high risk of vascular complications and restenosis, such as those experiencing renal failure.11,12

The researchers first demonstrated that ticagrelor effectively inhibits reversible platelet aggregation and P-selectin expression in mice. By using a laser injury cremaster model, P2Y12 inhibition by ticagrelor led to a reduction in thrombus formation to a similar extent as in P2Y12-deficient mice without additional effect of ticagrelor in deficient mice. This further finding suggests that this is a platelet-driven effect. By using a specific model of endothelium oxidative damage by application of iron chloride, a significant reduction of neointimal formation was observed in mice treated with ticagrelor. The researchers demonstrated that P2Y12 inhibition must be started before vessel injury and continued as an infusion for a few hours after injury to be efficient.

We commend the researchers for having conducted such a complex experimental study. The design was carefully chosen to respond to all the potential explanations of such a mechanistic hypothesis. A real effect of ticagrelor on restenosis is consistent with the benefit of ticagrelor growing slowly, but constantly, over the entire follow-up of the Platelet Inhibition and Patient Outcomes (PLATO) trial as it is observed in the natural history of restenosis.

The remaining question is whether this effect is specifically driven by P2Y12 inhibition or whether adenosinergic effects beyond pure P2Y12 receptor inhibition are involved. Indeed, the vascular outcome benefit of ticagrelor cannot be explained by faster and more potent platelet inhibition alone when compared with clopidogrel or prasugrel (indirect comparison). Although the antiplatelet potency of ticagrelor in the Platelet Inhibition and Patient Outcomes trial closely matches that of prasugrel in Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON), the magnitude and timing of outcome patterns are entirely different for a variety of reasons.

An optical coherence tomographic investigation in patients randomized in the different trials comparing clopidogrel with new P2Y12 inhibitors could be an elegant retrospective approach to verify this hypothesis in humans. However, a prospective evaluation remains mandatory in a specifically designed trial.

Disclosures
None.

References

**Figure.** Schematic representation of the different approaches used to prevent restenosis after stent placement.

### Strategies for prevention of restenosis:

- **Systemic drugs studied to prevent restenosis**

<table>
<thead>
<tr>
<th>Thrombus formation</th>
<th>Inflammation</th>
<th>Vascular cell proliferation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet agents: P2Y12 inhibitors?</td>
<td>Corticosteroids</td>
<td>Antiproliferative agents</td>
</tr>
</tbody>
</table>

- **Local delivery of drugs: drug eluting stent**

**Antiproliferative agents (Sirolimus, Everolimus, Zotarolimus, Paclitaxel)**

![Schematic representation of the different approaches used to prevent restenosis after stent placement.](http://atvb.ahajournals.org/Downloaded from)


Key Words: platelet receptor blockers ■ restenosis ■ stent
Ticagrelor to Prevent Restenosis: New Drug for an Old Hypothesis?
Guillaume Cayla, Gilles Montalescot and Jean-Philippe Collet

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