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Pleiotropic effects of ticagrelor: a physiopathological advantage over clopidogrel?

Reiner MF, Akhmedov A, Stivala S, Keller S, Gaul DS, Bonetti NR, et al. Ticagrelor, but not clopidogrel, reduces arterial thrombosis via endothelial tissue factor suppression. **Cardiovasc Res. 2017;113:61-9. http://doi.org/f9vmxs**

The activation of the coagulation and platelet aggregation cascade plays a key role in arterial thrombotic complications, as myocardial infarction and ischemic stroke. Therefore, use of antiplatelet therapy with P2Y12 receptor inhibitors, as clopidogrel or ticagrelor, in combination with acetylsalicylic acid is the treatment of choice for patients with acute coronary syndrome and for the secondary prevention of vascular occlusions after endovascular prostheses, as stent implantation or coronary artery bypass grafting.

For years, clopidogrel has been one of the main cornerstones for the management of coronary artery disease patients, with indisputable clinical usefulness. However, its slow mechanism of action, its unpredictable intensity of action and prolonged effects, induced the search of new options among this group of drugs. Ticagrelor thus appears in the field of research, with a faster and more potent mechanism of action, more predictable effects, and a less prolonged action due to its reversible effects. The first clinical trials comparing clopidogrel with ticagrelor were so favorable to the latter that it led to a modification in the levels of indication for the treatment of patients with acute coronary syndrome. As a result, patients receiving ticagrelor exhibited a significant reduction in the rates of overall and cardiovascular mortality, myocardial infarction or coronary stent thrombosis. Although further clinical trials will probably be necessary to confirm some aspects associated to its use in patients, the indication of ticagrelor has significantly increased. However, there is as yet no convincing physiopathological explanation of the mechanisms involved in this apparent significant reduction of ischemic events and mortality in patients, without increasing hemorrhagic complications.

In this interesting work, Reiner et al. demonstrate antithrombotic effects of ticagrelor which are independent of its already known antiplatelet action. Human aortic endothelial cells, stimulated with tumor necrosis factor-alpha (TNF-a), were treated with ticagrelor or clopidogrel active metabolite (CAM). It was seen that ticagrelor but not CAM reduced procoagulant tissue factor (TF) expression and activity via proteosomal degradation, independently of the P2Y12 receptor. It should be recalled that TF is a membrane glycoprotein which is essential to activate the extrinsic pathway of the coagulation cascade that can lead to thrombus formation. Moreover, to test the physiological relevance of these in vitro findings, photochemical endothelial injury was induced in mice previously treated with CAM or ticagrelor for 2 weeks. Mice receiving ticagrelor evidenced a significant longer time to develop occlusive thrombus in the carotid arteries compared with those receiving CAM. In agreement with in vitro findings, ticagrelor reduced endothelial TF expression in mice, without changes in the plasmatic levels of thrombin and the systemic TF activity, suggesting a local antithrombotic effect. Given the similar chemical structure between ticagrelor and adenosine, with known vascular effects, it could be presumed that some beneficial effects could be due to a pharmacologic interaction at the level of membrane receptors. Ruling out this hypothesis, the administration of selective adenosine receptor antagonists did not block the positive effects of ticagrelor.

There are some important pharmacokinetic and pharmacodynamic differences between ticagrelor and clopidogrel. Although more potent antiplatelet effects are attributed to ticagrelor, the pleiotropic effects which are independent of its platelet P2Y12 receptor antagonism but have endothelial-dependent local antithrombotic action, might explain the lower incidence of thrombotic events in patients receiving ticagrelor in clinical trials. Despite more basic research and clinical trials are required to confirm these findings, the dual antiplatelet and antithrombotic properties of ticagrelor indicate that it is an interesting option for patients requiring both interventions.