Ticagrelor induces ischaemic preconditioning in coronary artery disease

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Ticagrelor is a reversibly P2Y12 antagonist used in patient undergoing coronary interventions, able to block adenosine re-uptake through inhibition of ENT-1 cotransporter. The increased levels of adenosine are responsible for some of its side effects (dyspnea, bradycardia), but adenosine bioavailability increase could also provide beneficial effects. We sought to investigate whether ticagrelor, as compared to clopidogrel, could enhance ischemic preconditioning in patients with stable CAD undergoing PCI.

Methods and results: The "Ticagrelor and preconditioning in patients with stable coronary artery disease (TAPER-S)" trial was a prospective, randomized 1:1, blinded end-point trial enrolling stable patients with CAD requiring fractional flow reserve (FFR)-guided PCI. Ischemic preconditioning was assessed by measuring the ST-segment elevation at intracoronary ECG during a two-step sequential coronary balloon inflation (2 minutes each, with a 5-minute interval) in the reference vessel.

The primary endpoint of the study was the comparison of the delta (difference in millimeters) of ST-segment elevation extent at first and second coronary balloon inflations between ticagrelor and clopidogrel arms. Secondary endpoints were: 1) changes in coronary flow reserve (CFR), index of microvascular resistance (IMR), and FFR measured in the index vessel before and at the end of PCI; 2) difference in anginal pain (measured with VAS) during inflations. Also, lab tests with assessment of adenosine serum concentration and ENT-1 expression were conducted at baseline and after index procedure.

The study was stopped by the DSMB after two thirds (n=53) of the patients qualifying for the primary endpoint were enrolled. Indeed, an independent statistical report evaluating the blinded results at a pre-specified interim analysis found a statistically significant difference in primary endpoint between the groups.

The primary endpoint was significantly higher with ticagrelor as compared to clopidogrel (p < 0.0001). Ticagrelor group was also associated with lower extent of chest pain during coronary balloon inflations (p=0.04), whereas no difference was observed in the delta between pre and post PCI values of FFR (p=0.70), CFR (p=0.72) or IMR (p=0.72). Among lab tests, ticagrelor administration promoted a statistically significant increase in adenosine serum concentration when compared with clopidogrel group, while ENT-1 expression was not different.

Conclusions: Ticagrelor induces ischemic preconditioning among patients with stable CAD undergoing PCI and reduces intraprocedural anginal pain. Adenosine bioavailability was confirmed to be increased in ticagrelor-treated patients. However, since ENT-1 expression was proved not to be different between groups and all patients in this study underwent adenosine infusion during pre-PCI FFR, our results suggest ticagrelor can further induce ischemic preconditioning via non-adenosine mediated mechanisms.