Ticagrelor does not mediate its early beneficial effects in ST-elevation myocardial infarction by improving coronary microvascular dysfunction – the TIMES double-blind randomised controlled trial

Background: Ticagrelor inhibits red cell adenosine re-uptake which may improve coronary microvascular dysfunction (CMD) and contribute to early benefits seen in patients with ST-elevation myocardial infarction (STEMI).

Methods: In a single-centre, double blind randomised controlled adaptive designed trial, 62 patients with STEMI and loaded with clopidogrel 600mg were randomised to ticagrelor reloading and maintenance vs. placebo reloading with clopidogrel maintenance, prior to primary Percutaneous Coronary Intervention (PCI). The primary endpoint was PressureWire X derived index of microcirculatory resistance (IMR) at completion of PCI with secondary endpoints including basal microvascular resistance (BMR), optical coherence tomography (OCT) percentage clot burden, cardiac troponin I (cTnI) and creatinine kinase (CK-MB), cardiac magnetic resonance (CMR) microvascular obstruction (MVO) and infarct size (IS) at 24-48hrs, ADP-platelet reactivity, ticagrelor and adenosine levels. The trial was stopped early after the first interim analysis.

Results: The groups were well matched. Plasma ticagrelor was detectable: 335 (494) vs 0 (0)ng/mL, $p<0.0001$ and platelet reactivity was more inhibited: 33.3 (24.6) vs 51.7 (33.1)U, $p<0.05$, at the time of primary endpoint and 24-48hrs later: 672 (359) vs 0 (0)ng/mL, $p<0.0001$ and 11.2 (9,9) vs 20.7(13.7)U, $p<0.01$, respectively, compared to clopidogrel. Plasma adenosine levels were no different at either timepoint. There was no difference in the median (IQR) IMR: 32.5 (54.1) vs. 31.4 (62.4), $p=0.68$ or BMR: 77.8 (104.2) vs. 50.6 (90.7), $p=0.89$, between the 2 groups. There was a trend to reduced clot burden in the ticagrelor arm: 1.7 (2.6) vs 3.6 (6.8)%, $p=0.16$ and reduced IS at 12hrs measured by cardiac biomarkers: cTnI: 29184 (13848) vs. 33805 (12179)ng/mL, $p=0.19$; CK-MB: 191 (161) vs 371 (348)IU, $p=0.03$. However, MVO and IS by CMR was not significantly different.

Conclusion: Ticagrelor is bioavailable by the end of primary PCI and significantly inhibits platelet reactivity compared to clopidogrel. However, circulating adenosine levels and measures of CMD were no different, possibly indicating that early ticagrelor benefits are not mediated by improving CMD.