Marked Differences in the Pharmacokinetic and Pharmacodynamic Profiles of Ticagrelor in Patients Undergoing Treatment For ST Elevation and Non ST Elevation Myocardial Infarction (STEMI and NSTEMI)

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Key words: ticagrelor, platelet function, ACS

Introduction
Ticagelor, an orally administered, direct acting, reversible inhibitor of the P2Y12 inhibitor, provides faster onset and greater levels of platelet inhibition when compared to clopidogrel. Current data indicates a reduced antiplatelet effect in STEMI. We sought to investigate the early pharmacokinetic (PK) and pharmacodynamic (PD) effect of ticagrelor loading doses administered to patients undergoing percutaneous coronary intervention (PCI) for STEMI and NSTEMI.

Methods
This is a single centre non-randomised study. P2Y12 naïve patients presenting with STEMI/NSTEMI were considered for inclusion. All patients gave informed consent. Enrolled patients were administered a loading dose of aspirin 300mg and ticagrelor 180mg prior to PCI. Blood was sampled at 20 minutes, coronary balloon time, 1 hour and 4 hours after loading.

PD results are expressed as P2Y12 reaction units (PRU) and were assessed using VerifyNow. A PRU > 208 indicates a sub-optimal antiplatelet response.

PK properties we assessed by measuring the plasma concentration of the parent compound and active metabolite of Ticagrelor using liquid chromatography in tandem with mass spectrometry. The lower limits of quantification of ticagrelor parent compound (T-PC) and its active metabolite, AR-C124910XX (T-AM) are 1.0ng/ml and 2.5ng/ml respectively.

PRU and plasma concentrations over time were tested between groups using 2-way ANOVA. $P < 0.05$ was considered significant.

Results
30 patients (15 STEMI/15 NSTEMI) were recruited. Baseline characteristics are described in Table 1.

PD analysis: In STEMI patients high residual platelet reactivity is seen at 20 minutes following administration of ticagrelor 180mg (256 ± 13.1) an attenuated antiplatelet effect is also observed at 4 hours. However, in our NSTEMI patients, a marked and rapid antiplatelet effect is seen at all time points (figure 1).

PK analysis: Low plasma concentrations of T-PC are observed in STEMI vs NSTEMI patients; 9.0 ± 4.1 vs 22.8 ± 10.3, p = 0.225 and this trend continues until 4 hours. A similar trend is also noted for T-AM concentrations as shown in figure 2.

Conclusion
Ticagrelor, in STEMI does not provide adequate P2Y12 inhibition at the point of reperfusion. In contrast platelet inhibition is significantly more rapid in patients with NSTEMI.

Although a directly acting P2Y12 inhibitor that can exert an antiplatelet effect independent of metabolic biotransformation, ticagrelor is still reliant upon absorption via the gastrointestinal (GI) tract. The sub-therapeutic PRU and plasma concentrations of both T-PC and T-AM indicate that GI absorption is an important determinant of the onset of action and clinical efficacy of ticagelor during the acute phase of a STEMI.

Modification of formulation e.g. administration of chewed/orodispersible tablets or an intravenous agent (cangrelor) could help to overcome delayed GI absorption and provide adequate levels of platelet inhibition during the acute phase of presentation in STEMI patients.

Table 1: Baseline patient characteristics

Characteristic	STEMI (n =15)	NSTEMI (n =15)	*P-value*
Age (yrs)	63.7 ± 11.6	62 ±13.9	0.714
Female	4 (27)	2 (13)	0.651
Diabetes Mellitus	2 (13)	4 (27)	0.651
Hypertension	7 (47)	7 (47)	1.000
Current Smoker	4 (27)	3 (20)	1.000
Ex Smoker	4 (27)	6 (40)	0.700
Hyperlipidaemia	3 (20)	12 (80)	0.003
Familial History of CAD	8 (53)	8 (53)	1.000
Patient therapy on admission			
Analgesia	13 (87)	3 (20)	0.001
Comprising of:-			
Morphine	13	0	<0.001
GTN	0	3	0.224

(CAD = coronary artery disease, GTN = glyceryl trinitrate)

Figure 1: Mean VerifyNow PRUs (and standard error) after administration of a 180mg ticagrelor loading dose in STEMI vs NSTEMI patients.
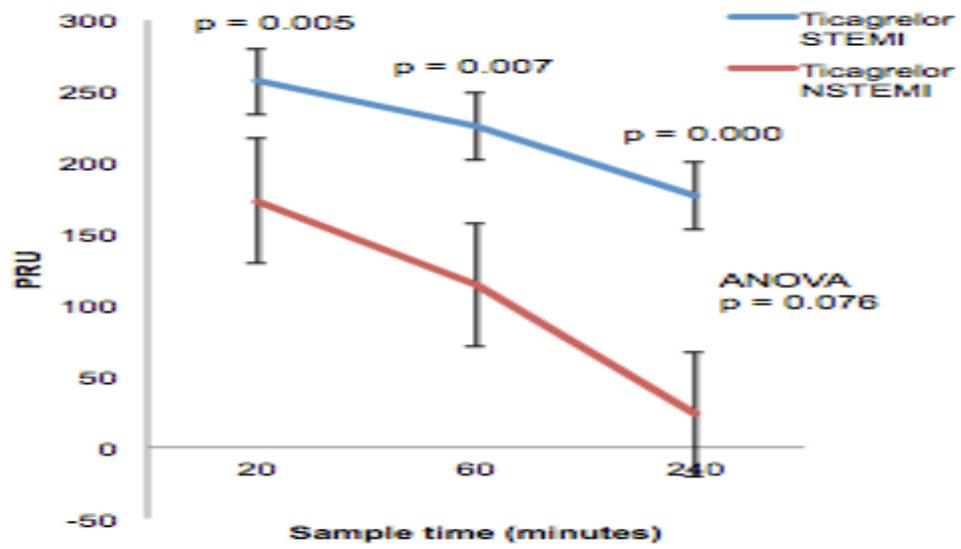
Figure 2: Plasma concentration of T-PC and T-AM (ng/ml) expressed as mean ± standard error following administration of a loading dose in STEMI vs NSTEMI patients