EX-VIVO PHARMACODYNAMIC EFFECTS OF ESCALATING CANGRELOR CONCENTRATIONS AND CANGRELOR-MORPHINE INTERACTION IN PATIENTS UNDERGOING PCI

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INTRODUCTION

Inhibition of platelet aggregation (IPA) mitigates the ischemic risk in patients with chronic (CCS) or acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). Cangrelor is an intravenous and reversible $P2Y_{12}$ receptor inhibitor, which was associated with lower than expected IPA in ACS patients. Whether higher cangrelor doses allow greater IPA and at what extent its effects are affected by concomitant morphine administration remains unknown.

METHODS

Single-center study, including 15 PCI patients (n=6 CCS, n=9 ACS) and investigating the *ex-vivo* pharmacodynamic effects of escalating cangrelor concentrations (0, 250, 1000 and 2500 nmol/l) with and without morphine spiking at baseline and at 30±5 minutes after *in-vivo* cangrelor administration. Platelet aggregation (PA) was evaluated by Light Transmittance Aggregometry (LTA using ADP 5 umol/L as agonist) and Multiplate.

RESULTS

Baseline and procedural patient characteristics are shown in **Table 1**. At 30 minutes after *in-vivo* drug administration, cangrelor resulted in a near-complete IPA at Multiplate (89.8%, interquartile range 72-91.8%), but not at peak-LTA (51.6%, interquartile range:43.5-57.8%) (**Figure 1**). Escalating cangrelor doses did not further enhance IPA at Multiplate. At LTA, *ex-vivo* incremental cangrelor concentrations only marginally affected IPAs, which remain far from profound inhibition throughout (**Figure 2**). *Ex-vivo* morphine spiking did not affect cangrelor-induced PA at Multiplate or LTA (**Figure 2**). Results remained consistent irrespective of patient clinical presentation (ACS or CCS, **Figure 3)**.

Table 1. Baseline characteristics. Values are mean ± standard deviation or n (%).

	N=15
Baseline characteristics	
Age, yrs	65 ± 10
Female sex	7 (47%)
Arterial hypertension	5 (33%)
Dyslipidemia	9 (60%)
Diabetes	6 (40%)
Current smoker	3 (20%)
Prior MI/PCI	4 (27%)
PAD	0 (0%)
CKD	2 (13%)
Procedural characteristics	
Clinical presentation	
CCS	6 (40%)
STEACS	7 (47%)
NSTEACS	2 (13%)
Vessel treated	
LAD	11 (73%)
LCx	3 (20%)
RCA	1 (7%)
>2 stents	0 (0%)

Abbreviations: CCS, chronic coronary syndrome; CKD, chronic kidney disease; LAD, left anterior descending artery; LCx, left circumflex; MI, myocardial infarction; NSTEACS, non-ST segment elevation acute coronary syndrome; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEACS, ST-segment elevation acute coronary syndrome.

Figure 1. Multiplate and LTA platelet aggregation at escalating doses of Cangrelor.

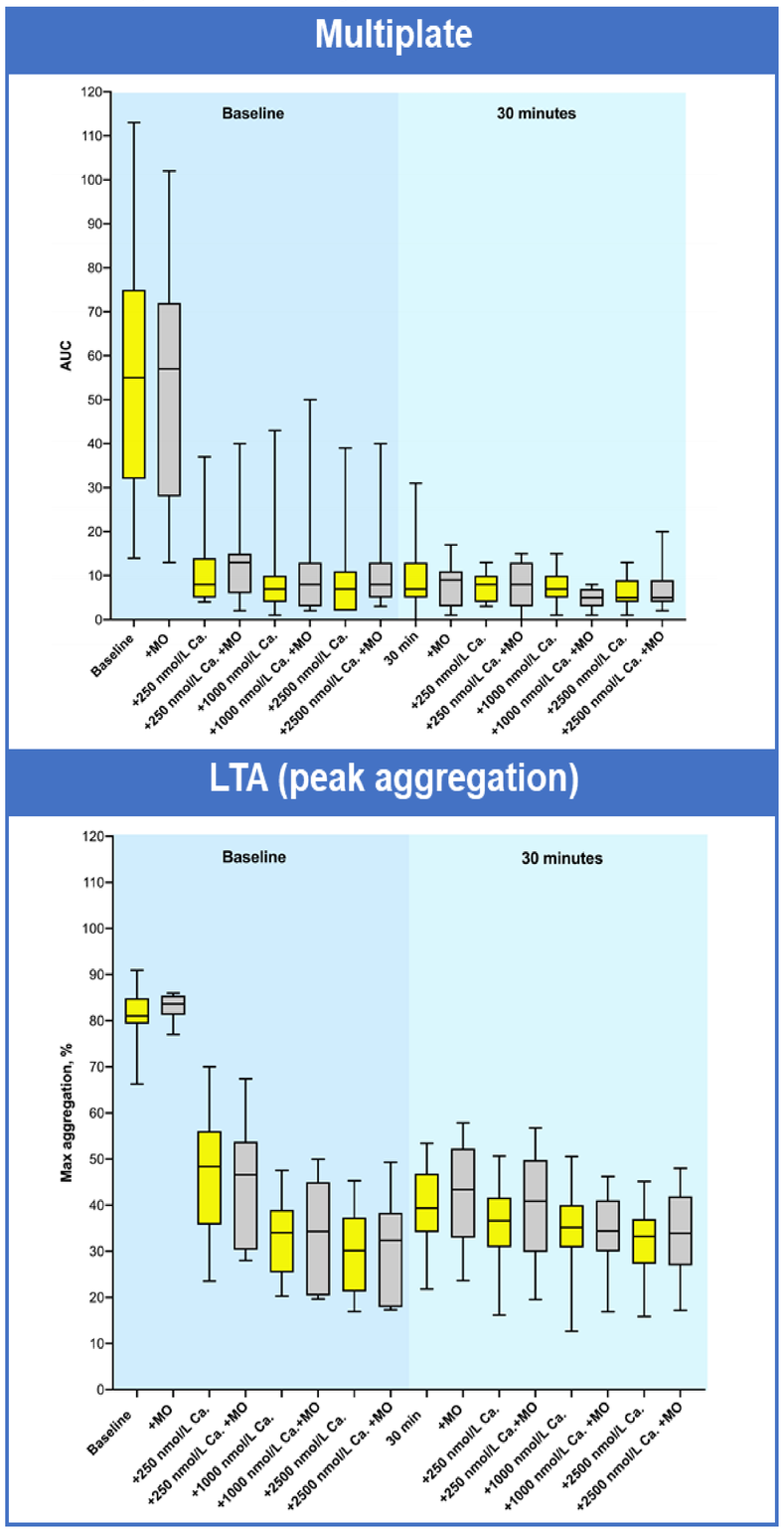


Figure 2. IPA values at LTA platelet aggregation.

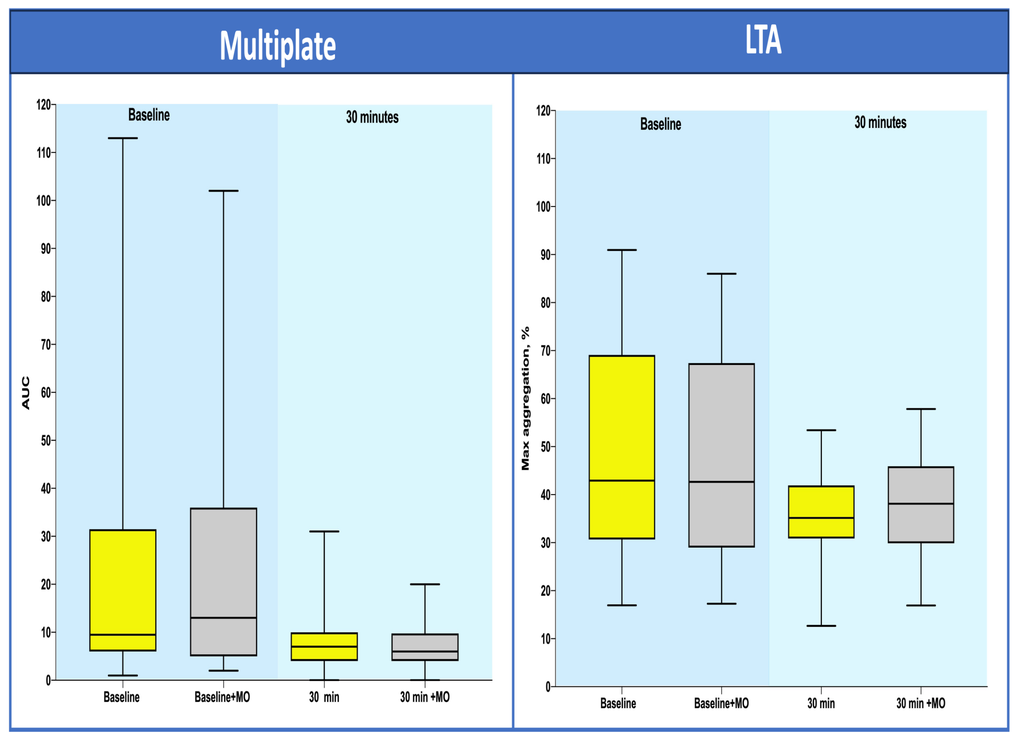
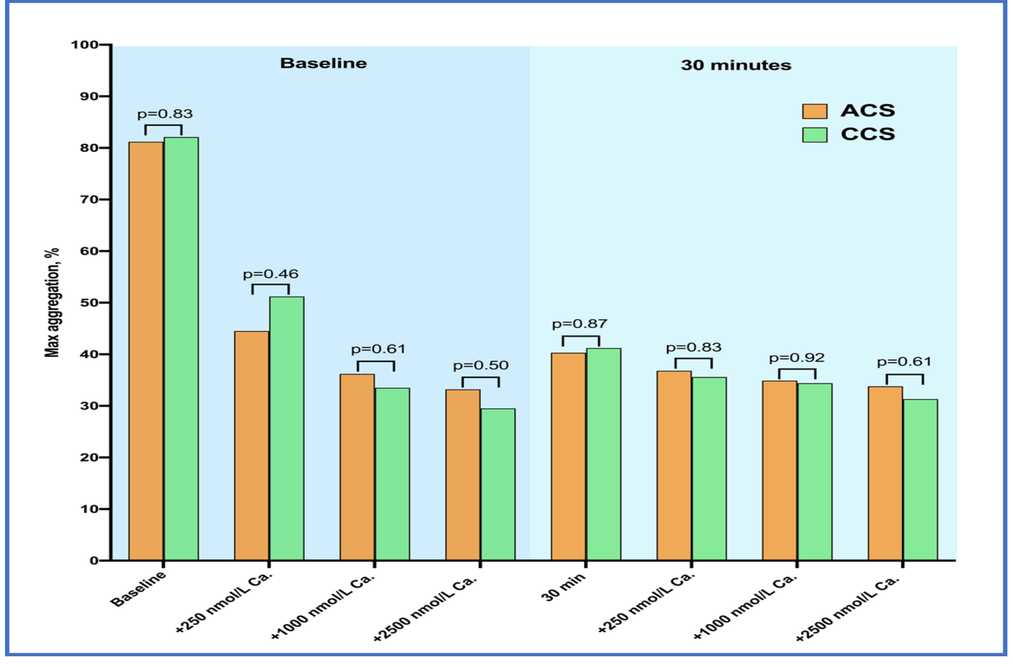


Figure 3. Maximum aggregation value between ACS and CCS group



CONCLUSION

The currently recommended cangrelor regimen is associated with far-from-complete IPA at LTA, but not at Multiplate testing, irrespective of clinical presentation and morphine supplementation. Escalating cangrelor doses yielded marginally greater IPA at LTA in a dose-dependent relationship. The inconsistent cangrelor-induced IPA values at Multiplate and LTA might reflect different whole blood *versus* platelet-rich plasma aggregation tests. Unlike oral P2Y12 inhibitors, morphine does not affect cangrelor effects on IPA.