



# High Doses of Clopidogrel Overcome the Atorvastatin-Clopidogrel Drug-Drug Interaction in Known Clopidogrel Responders

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## INTRODUCTION

We have previously demonstrated that the platelet anti-aggregatory effect of clopidogrel (300 mg loading dose, 75 mg/day maintenance dose) is attenuated in a dose-dependent fashion by atorvastatin in variable clopidogrel response patients undergoing percutaneous coronary intervention measured by ex vivo point-of-care platelet aggregometry.<sup>1</sup> Others report no drug-drug interaction with clopidogrel 600 mg loading dose.<sup>2</sup> This study examined whether the anti-aggregatory effect of 3 different loading doses of clopidogrel is attenuated by the co-administration of atorvastatin 40 mg in known clopidogrel responders and correlates point-of-care and light transmission aggregometry measurements.

## METHODS

This was a prospective randomized study in 48 healthy human volunteers who were clopidogrel responders, defined by mean inhibitory platelet aggregation (IPA) = (baseline platelet aggregation - post-treatment platelet aggregation/baseline platelet aggregation x 100) > 30% at 0, 2, 4, 6, and 8 hours after a loading dose of clopidogrel 450 mg. Measurements were made by light transmission aggregometry (Chronolog, Haverton, PA) and point-of-care Plateletworks platform (Helena Laboratories, Beaumont, TX) using 20 μM ADP agonist. Volunteers with IPA ≤ 30% (n = 16) were excluded. Atorvastatin 40 mg was administered for 28 days during the clopidogrel washout period. Then subjects were randomized into 4 groups: Group 1, clopidogrel 300 mg (n = 12); Group 2 clopidogrel 300 mg + atorvastatin (n = 12); Group 3, clopidogrel 450 mg + atorvastatin (n = 12); Group 4, clopidogrel 600 mg + atorvastatin (n = 12). Platelet aggregation was measured before and after clopidogrel at 0, 2, 4, 6, and 8 hours.

## RESULTS

Figure 1. Inhibitory Platelet Aggregation measured by Light Transmission Aggregometry

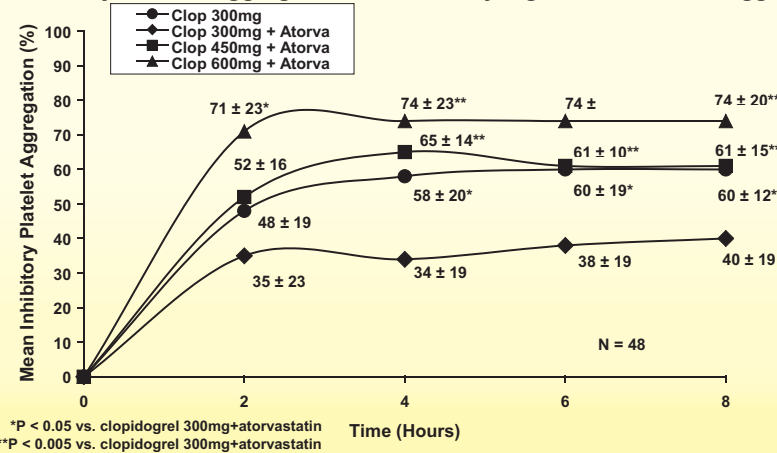


Figure 2. Inhibitory Platelet Aggregation measured by Platelet Works Aggregometry

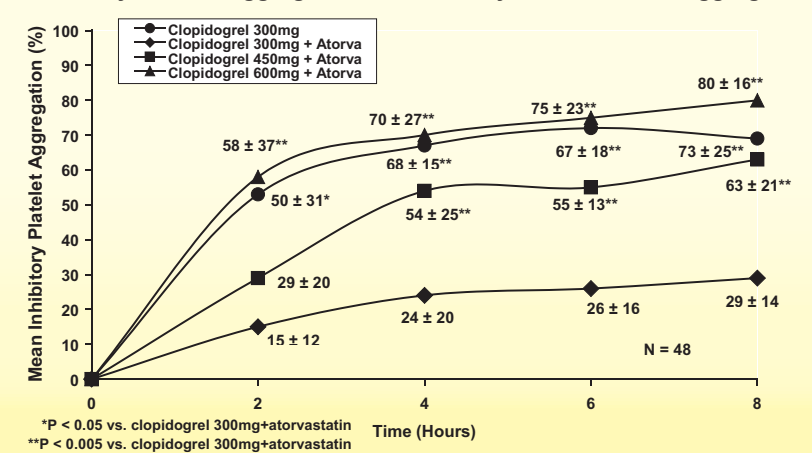
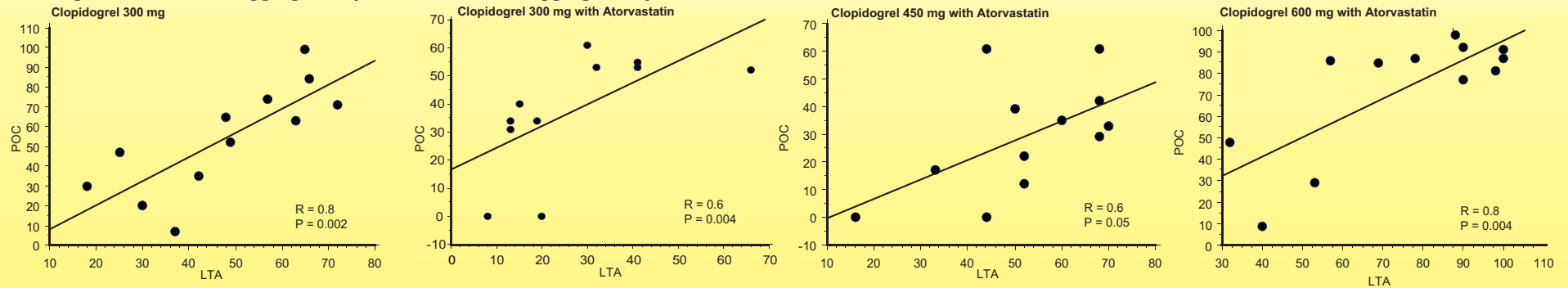


Figure 3. Light Transmission Aggregometry vs. Point of Care Aggregometry at 4 Hour



## DISCUSSION

- Atorvastatin attenuated the anti-aggregatory effect of a 300 mg loading dose of clopidogrel.
- Clopidogrel 600 mg overcomes the attenuation of the anti-aggregatory effect demonstrated with 300 and 450 mg during atorvastatin co-administration.
- There was a significant correlation between light transmission and point-of-care aggregometry at 4 hours after clopidogrel administration.

## REFERENCES

1. Lau WC, et. al. Circulation. 2003; 107:32-7.
2. Muller I, et. al. Circulation. 2003; 108: 2195-7.