**In vitro aspirin has little additional anti-platelet effect in the presence of prasugrel active metabolite**

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Dual anti-platelet therapy is commonly used to protect against secondary thrombotic risk with the idea that platelet activation dependent upon thromboxane A₂ (TXA₂) will be blocked by aspirin and that activation dependent upon P2Y₁₂ receptors will be blocked by thienopyridines. However, blockade of platelet P2Y₁₂ receptors also blocks TXA₂–dependent aggregation and platelet production of TXA₂. These latter observations have led us to the hypothesis that aspirin may have only little or no additional anti-aggregatory effects in the presence of strong P2Y₁₂ receptor blockade. We have investigated this idea in vitro using combinations of prasugrel-active metabolite (PAM) and aspirin.

Platelet-rich plasma was prepared from citrated whole blood and incubated for 30 minutes at 37°C with vehicle, PAM, aspirin or PAM+aspirin in combination. Incubates were used to determine platelet reactivity by 96-well light transmission aggregometry, ATP+ADP release and platelet TXA₂ production in response to a range of agonists (n=4-6 for all).

PAM (3µM) inhibited (p<0.05) the platelet production of TXA₂ induced by arachidonic acid (AUC: control, 187±41; PAM, 58±18), collagen (control, 171±29; PAM, 91±18) and epinephrine (control, 13±2; PAM, 6±2) and the ATP+ADP release in response to U46619 (control, 0.98±0.11; PAM, 0.20±0.04), TRAP-6 amide (control, 0.95±0.11; PAM, 0.66±0.08) and collagen (control, 0.56±0.15; PAM, 0.30±0.07). Addition of aspirin further reduced the production of TXA₂ but not the release of ATP+ADP. In full agonist concentration response curves, PAM inhibited platelet aggregation induced by all agonists with no extra inhibition following from addition of aspirin (30µM), with the exception of collagen for which a weak additional effect was noted (AUC: control, 143±3; PAM, 48±4; PAM+aspirin, 38±2).

We have shown in vitro that PAM alone inhibits P2Y₁₂ and TXA₂-driven platelet aggregation and secondary mediator release with little additional effect of aspirin. Given the increased risk of bleeding events associated with aspirin, its overall benefit as an additional anti-platelet therapy to potent thienopyridines warrants further investigation through appropriate clinical studies.