Cyclooxygenase (COX) enzymes produce the pro-thrombotic mediator thromboxane A2 and the anti-thrombotic mediator prostacyclin, and in the form of Aspirin have been a target for thrombotic modulation for many years. However, COX-2 selective drugs are contraindicated in patients with underlying cardiovascular problems, due to evidence that they increase the risk of thrombotic events. The underlying cause of this is yet to be fully established so we contrasted the effects of Naproxen, a non selective COX-1 and COX-2 inhibitor, and nimesulide, a selective COX-2 inhibitor, by monitoring the effects of these compounds on the in vivo aggregation response of radiolabelled platelets to collagen in real-time in the anaesthetised mouse. Naproxen produced an anti-thrombotic effect shown as a decrease in the platelet aggregation response in vivo, whereas nimesulide did not affect the thrombotic response. The haemodynamic consequences of the thrombotic response were also measured by invasive cannulation, and supported the conclusion that Naproxen has anti-thrombotic effects (measured as a lower impairment of contractile function). This data opposes the suggestion that the pro-thrombotic effects of COX-2 selective drugs are due to inhibition of constitutive COX-2 production of prostacyclin in the endothelium and subsequent enhancement of platelet responsiveness and provide a platform for investigating the consequences and mechanisms of COX-2 inhibition in models of inflammation or atherosclerosis, where the role of COX-2 may be altered.