

Supplemental Figures

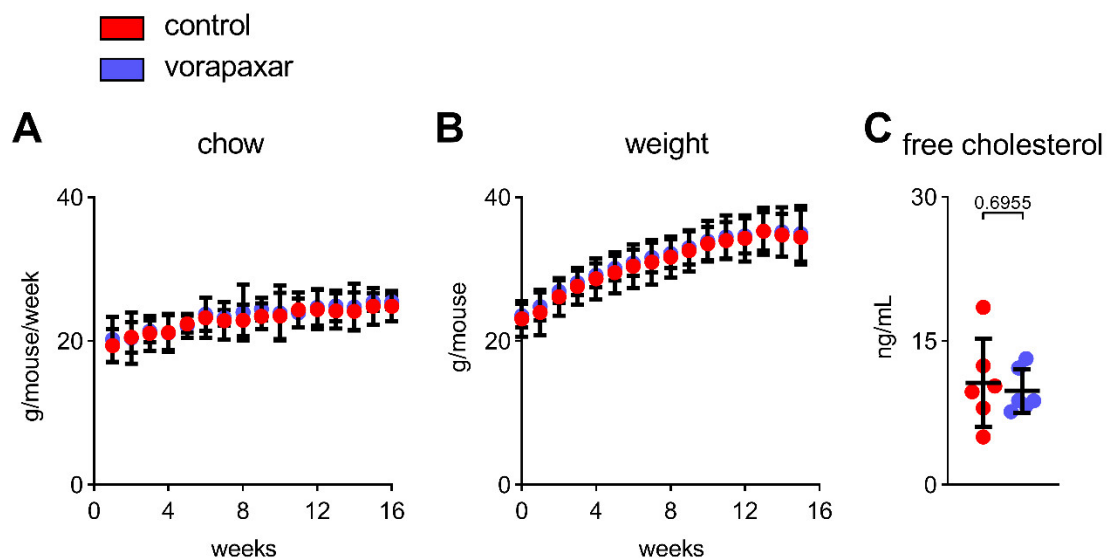


Figure S1. Vorapaxar does not alter food intake, weight gain, or circulating cholesterol. Monitoring of (A) food intake (g/mouse/week) and (B) weight gain (g/mouse). (C) Plasma concentration of free cholesterol after 16 weeks on diet, $n = 6$. Results are expressed as mean with SD (A,B) or as single values ($n = 6$), mean with SD (C).

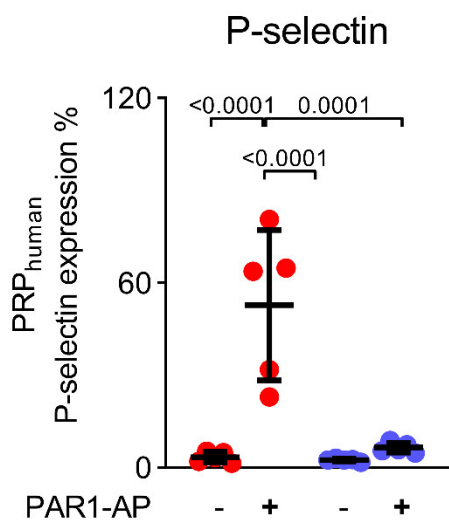


Figure S2. Vorapaxar maintains its PAR1-inhibiting capacity in blood after oral uptake in mice. Pooled human platelets (PRP) were resuspended in isolated plasma (PPP) from mice that received WD \pm vorapaxar ($n = 5$) for 7 days and stimulated with the PAR1-activating peptide (PAR1-AP). The expression of P-selectin in platelets was measured by flow cytometry.

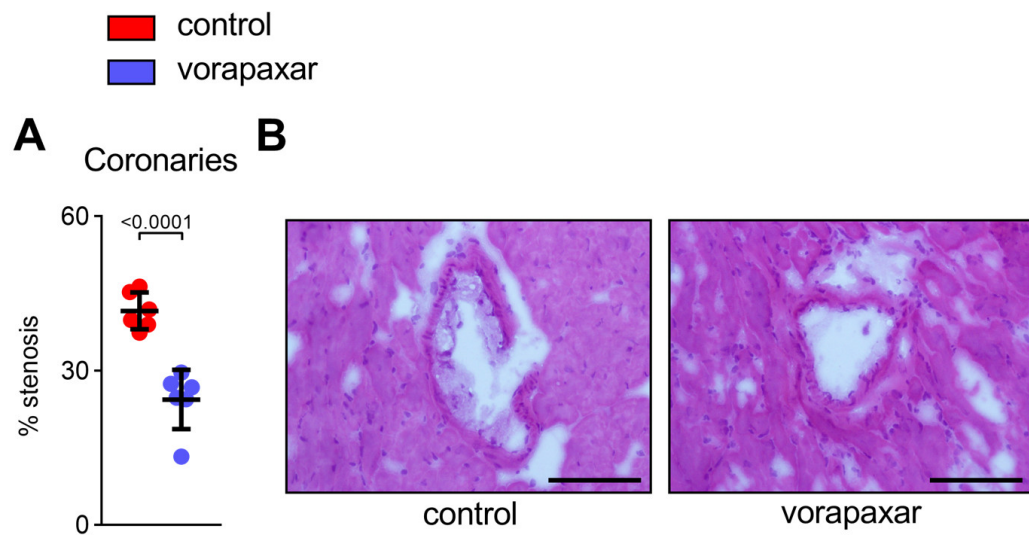


Figure S3. Vorapaxar reduces de-novo atherosclerosis in ApoEko mice fed an atherogenic diet. (A) Coronary artery stenosis (% lumen reduction). Representative images, scale bars 80 μ m (B). Results are expressed as single values ($n = 6$), mean with SD.

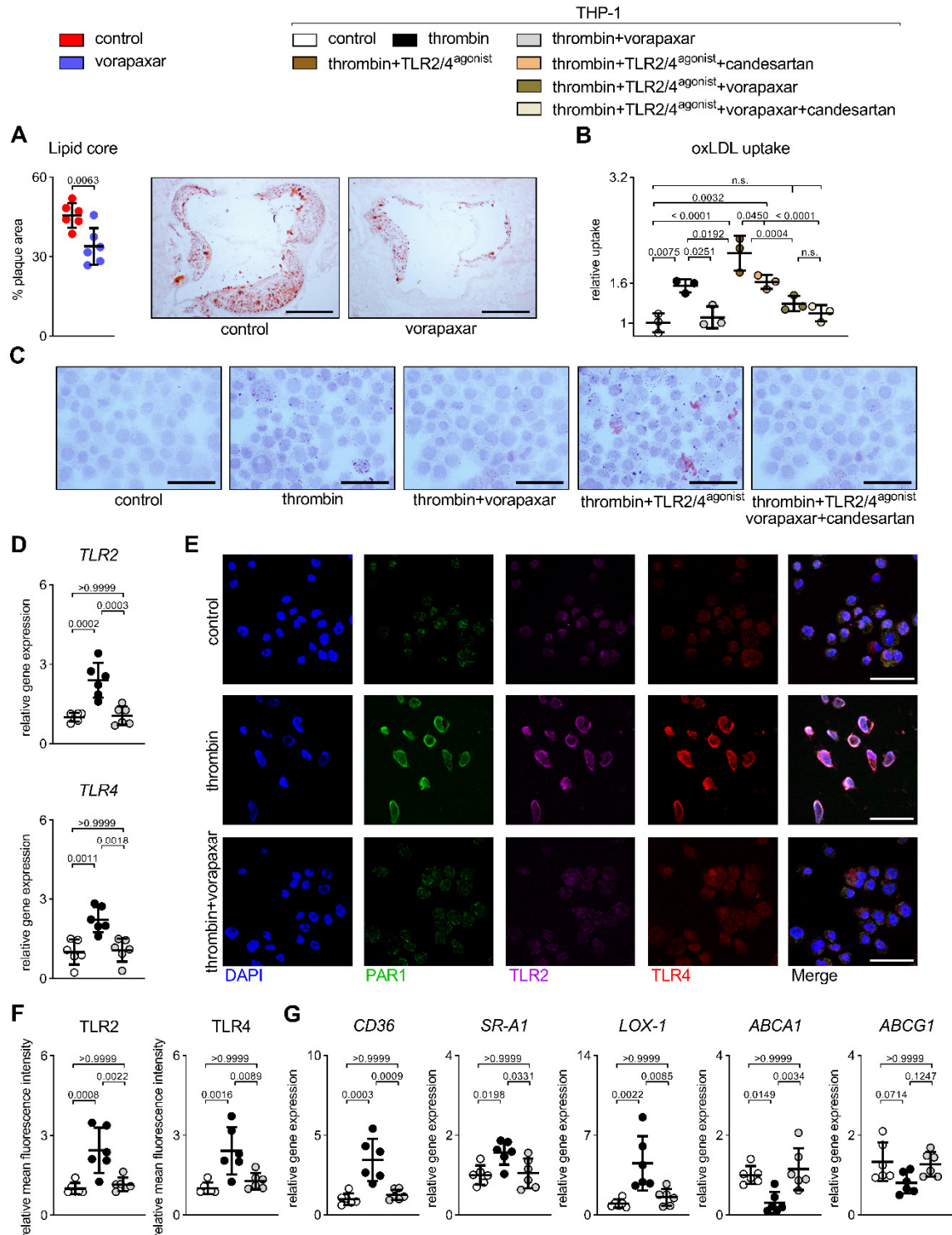


Figure S4. PAR1 inhibition with vorapaxar impairs foam-cell formation. (A) Treatment with vorapaxar is associated with reduction in plaque lipid content. The % Oil red O-positive area within aortic sinus of ApoEko mice. (B,C) Activation of PAR1, TLR2, and TLR4-activation increases oxLDL uptake (% Oil red O-positive intracellular area relative to control) in THP-1 cells. Cells were pretreated with thrombin, thrombin + vorapaxar, thrombin + TLR2/4-agonists, or a combination of thrombin + TLR2/4-agonists + vorapaxar + candesartan (combined TLR2/4-antagonist). (D) Effect of PAR1 activation on transcription of *TLR2* and *TLR4* in THP-1 cells. (E) Increased surface expression and colocalization of PAR1 with TLR2 and TLR4 under thrombin stimulation. (F) Effect of PAR1 activation on expression (relative mean fluorescence intensity) of TLR2 and TLR4 in THP-1 cells. (G) Thrombin-stimulated PAR1 is involved in

regulation of receptors that are involved in cellular lipid metabolism (*CD36*, *SR-A1*, *LOX-1*, *ABCA1*, *ABCG1*). Representative images, scale bars 400 μm (**A**), 50 μm (**C,E**). Results are expressed as single values (mice $n = 6$, THP-1 cells $n = 3-6$), mean with SD. n.s. = not significant.