Supplemental Table I. PECAM-1 does not affect the concentration of plasma lipids. Plasma lipids of 23-week-old *Apoe*$^{-/-}$ (left) and *Pecam1*$^{-/-}$*Apoe*$^{-/-}$ (right) mice on western diet for 13 weeks demonstrate no significant differences in total cholesterol (TC), low density lipoprotein (LDL), or triglycerides (TG). Data are presented as mean±SEM in mg/dL.

Supplemental Figure I. Analysis of atherosclerotic lesion was performed in a region-specific manner. Harvested and oil red O-stained vessels were microdissected as shown, and pinned to reveal the luminal surface. The whole aorta, aortic arch (aortic root to descending thoracic aorta), lesser curvature, thoracic aorta (descending thoracic aorta to the superior mesenteric artery), and abdominal aorta (superior mesenteric artery to the common iliac arteries) were analyzed for each mouse (23 weeks old, 13-week western diet). See Figure 1 and supplemental Figure II for data using this method.

Supplemental Figure II. Endothelial PECAM-1 is responsible for lesion formation in regions of disturbed flow. Lesion size after 16-week western diet in male *Pecam1*$^{-/-}$*Apoe*$^{-/-}$ mice receiving female *Apoe*$^{-/-}$ bone marrow (black, n=3) demonstrated a 129% increase in atherosclerotic lesion in the abdominal aorta compared to male *Pecam1*$^{-/-}$*Apoe*$^{-/-}$ mice receiving female *Pecam1*$^{-/-}$*Apoe*$^{-/-}$ bone marrow (white, n=3, p<0.05). No differences were observed in the aortic arch.

Supplemental Figure III. siRNA-based knockdown of PECAM-1 decreases VCAM-1 expression in endothelial cells exposed to atheroprone flow. Ad-NF-κB-Luc-transfected

endothelial cells co-transfected with control siRNA (siControl) or siRNA to PECAM-1 (siPECAM-1) were exposed to static conditions, atheroprone ("prone") flow, and atheroprotective ("protective") flow. VCAM-1 expression was quantified from western blot in Figure 3A via densitometry and normalized to total α-tubulin (* = $p<0.001$ compared to atheroprone siControl, $n=5$).

Supplemental Figure IV. Complex lesions are absent in PECAM-1-deficient aortic arches. **(A)** Movat-stained aortic cross sections from 23-week-old *Apoe*$^{-/-}$ (left) and *Pecam1*$^{-/-}$*Apoe*$^{-/-}$ (right) mice on 13-week western diet demonstrate much reduced lesion size in *Pecam1*$^{-/-}$*Apoe*$^{-/-}$ mice (sections 3 and 5), except at the aortic root (section 1). The greater and lesser curvatures are on the left and right, respectively, of each image. Numbers correspond to sections as described in Figure 4A. See Figure 4B for more sections.

Supplemental Figure V. Absence of PECAM-1 reduces macrophage accumulation but not ICAM-1 or P-selectin expression in the aortic wall. Aortic cross-sections proximal to (left, corresponding to location 2 in Figure 4A), between (middle, corresponding to location 4) or distal to (right, corresponding to location 6) the aortic arch branches were stained for **(A)** Mac2 to detect macrophages **(B)** ICAM-1 and **(C)** P-selectin. Images depict the lesser curvature of representative histological sections.