SUPPLEMENTAL MATERIAL

Table S1. Comparison of Founder Swine Blood Lipoproteins by Nuclear Magnetic Resonance.

	Particle Concentration (Mean Particle Size in nm)		
	HDL (µmol/l)	VLDL (nmol/l)	LDL (nmol/l)
Control *(N=2)*	25.9 ± 8.6 (8.7 ± 0.07)	8.75 ± 1.5 (58.7 ± 5.23)	541 ± 31 (19.9 ± 0.8)
Landrace *PCSK9* GOF *(N=2)*	10.5 ± 4 (10.25 ± 0.35)	128 ± 52 (33.05 ± 0.07)	1821 ± 409 (20.9 ± 0.14)
Ossabaw *PCSK9* GOF *(N=1)*	16.2 (9.8)	139 (32.9)	2280 (20.6)

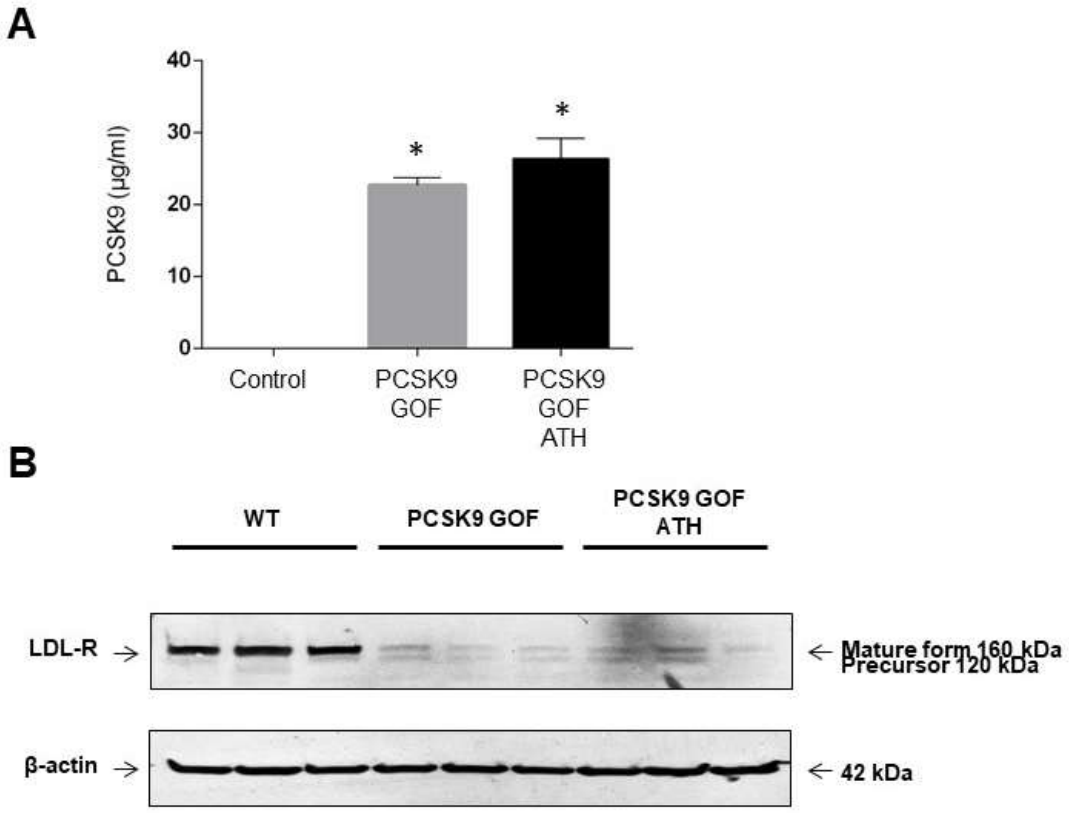
No statistics were done due to low number of founder animals for comparison

Table S2. Comparison of Cardiac Function.

Group	Control		PCSK9 GOF		PCSK9 GOF ATH Diet	
Age	6 months	9 months	6 months	9 months	6 months	9 months
Heart Rate^{SED} Heart Rate^{AMB} (beats/min)	70.7 ± 21.5 67.0 ± 14.9	60.7 ± 17.5 64.4 ± 14.3	73.6 ± 13.9 71.3 ± 10.6	65.9 ± 6.5 58.9 ± 5.0	75.6 ± 9.0 69.7 ± 16.0	82.3 ± 13.4‡† 61.0 ± 10.4
Mean Arterial Pressure* (mmHg)	117.6 ± 13.5	118.4 ± 18.7	120.6 ± 9.3	120.6 ± 9.7	113.9 ± 13.1	117.4 ± 7.5
EDV	81.2 ± 5.4	87.1 ± 11.3	66.6 ± 9.8‡	81.0 ± 15.6†	63.8 ± 5.0‡	73.9 ± 7.2†
ESV	34.2 ± 3.5	42.0 ± 11.2	25.8 ± 4.8‡	24.8 ± 4.8‡	25.8 ± 2.9‡	27.6 ± 4.0‡
LVM (g)	67.2 ± 7.6	68.3 ± 6.4	60.1 ± 4.5	77.7 ± 9.6†‖	57.2 ± 3.7‡†	66.7 ± 4.0†
Ejection Fraction (%)	57.7 ± 3.1	52.1 ± 11.3	61.3 ± 3.2	69.2 ± 2.8†‡	59.6 ± 3.4	62.7 ± 3.9
Cardiac Output (l/min)	3.3 ± 1.0	2.7 ± 0.8	3.0 ± 0.7	3.7 ± 0.9	2.9 ± 0.3	3.8 ± 0.7†
Myocardial Perfusion (ml/min/g)	1.1 ± 0.2	1.0 ± 0.4	1.3 ± 0.4	1.2 ± 0.2	1.4 ± 0.4	1.4 ± 0.3
Pericardial Fat (%)	0.06 ± 0.01	0.07 ± 0.02	0.05 ± 0.01	0.06 ± 0.01	0.06 ± 0.01	0.07 ± 0.01
Glucose (mg/dL)	116 ± 7.6	135 ± 41.1	139 ± 52.5	159 ± 27.0	163 ± 48.6‡	141 ± 17.6
Insulin (mmol/L)	0.23 ± 0.13	0.38 ± 0.22	0.20 ± 0.1	0.18 ± 0.09‡	0.36 ± 0.25	0.21 ± 0.08‡

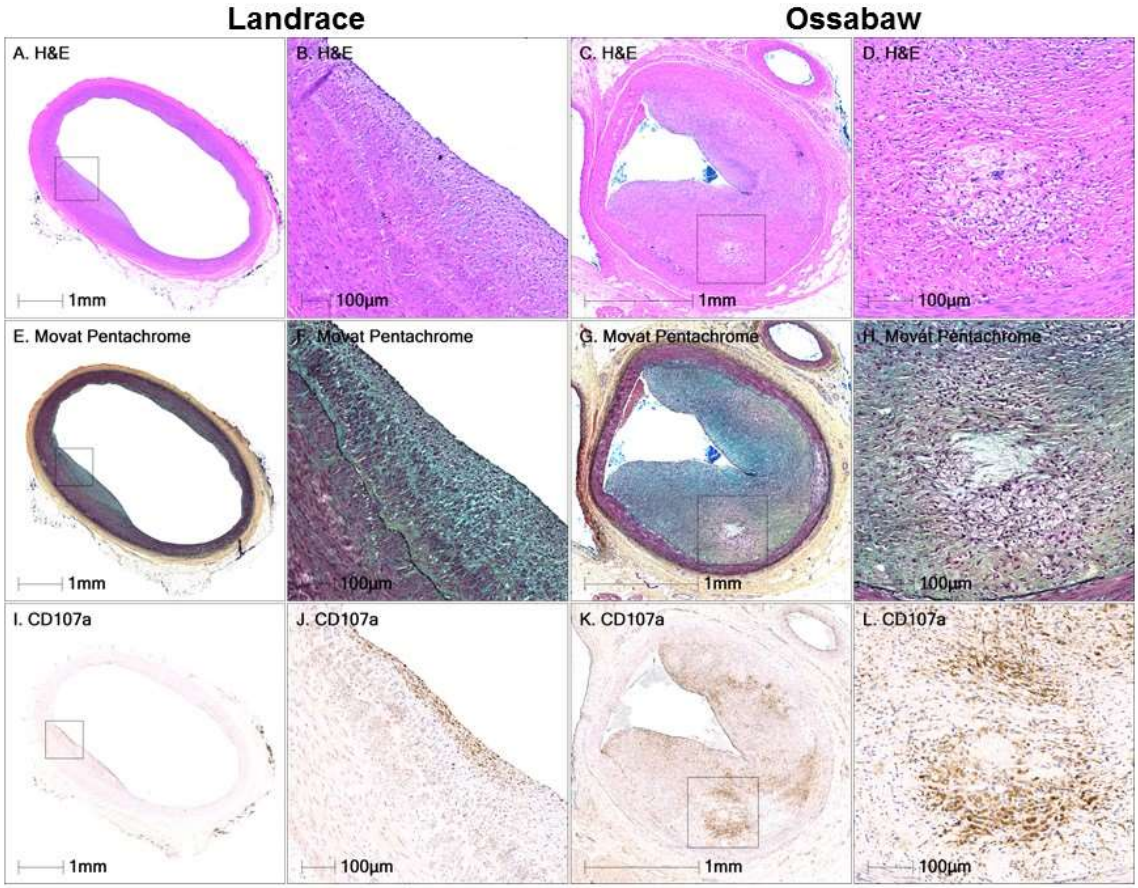
Mean ± SD shown for each. Mean arterial pressure was recorded in ambulatory animals. † $p<0.05$ vs. same group at 6 months of age; ‡ $p<0.05$ vs. control at same age; § $p<0.05$ vs. all other groups; ‖ $p<0.05$ vs. PCSK9 GOF ATH Diet at same age. Variance of means between study groups were analyzed by one way ANOVA, and where significant, all pairs comparison of means using Tukey-Kramer HSD method. Mean difference within groups determined by matched pairs repeated measures analysis followed by two-tailed t-testing.
LVM: left ventricular mass; ESV: End systolic volume; EDV: End diastolic volumes; AMB: ambulatory; SED: sedated.

Figure S1. Ectopic *Pt*PCSK9^{D374Y} expression reduces hepatic expression of LDLR.



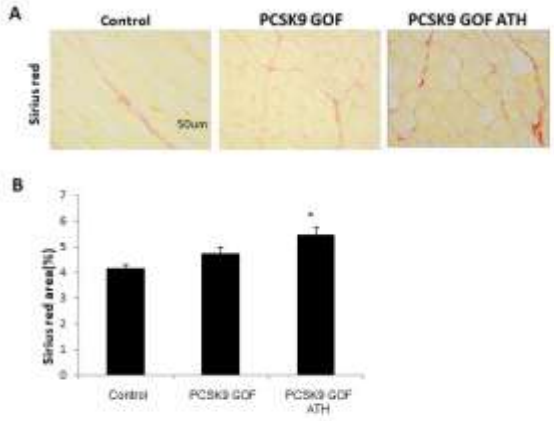
A, Serum PCSK9 levels, *p<0.05 compared to Control using ANOVA followed by t-tests. **B,** Western blot shows decreased LDLR detection in liver extracts in GOF groups.

Figure S2. Representative Lesions from LCX Artery of PCSK9 GOF Founders.



A-L, Left circumflex artery (LCX); Landrace founder at 14 months of age; Ossabaw founder at 15 months of age; Histologic coronary staining: hematoxylin & eosin (H&E) (**A-D**), modified Movat's Pentachrome (**E-H**), Immunohistochemistry staining for CD107a highlighting inflammation (**I-L**).

Figure S3. Myocardial fibrosis in PCKS9 GOF animals.



A, Representative Sirius Red stating in left ventricle myocardial tissue. **B,** Quantification of Sirius Red staining in each group was analyzed using ANOVA followed by t-tests. *p<0.05 compared to Control.

Figure S4. Coronary artery lesion measurements by quantitative coronary angiography (CT images) in Ossabaw pigs at 9 months of age.

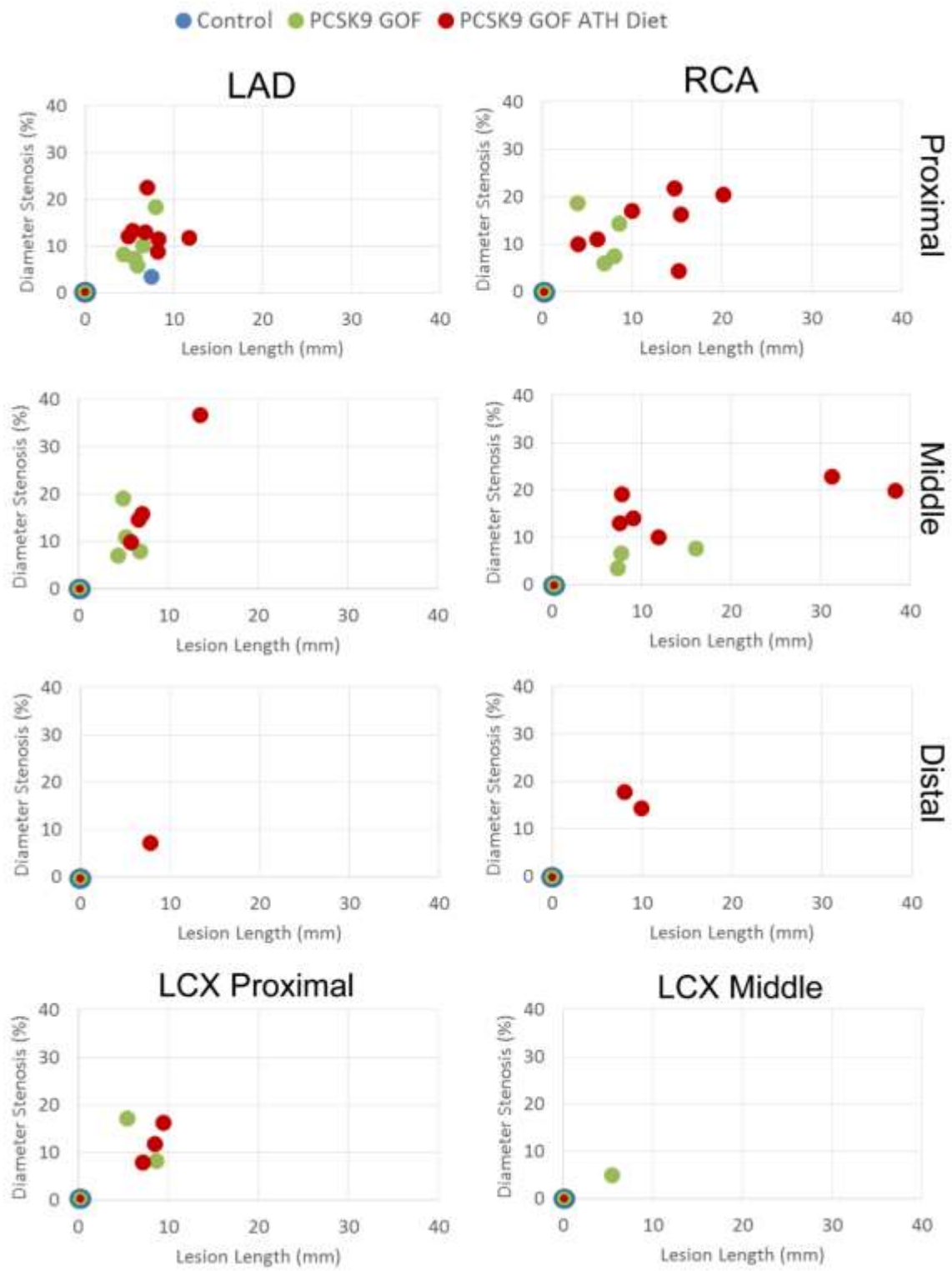
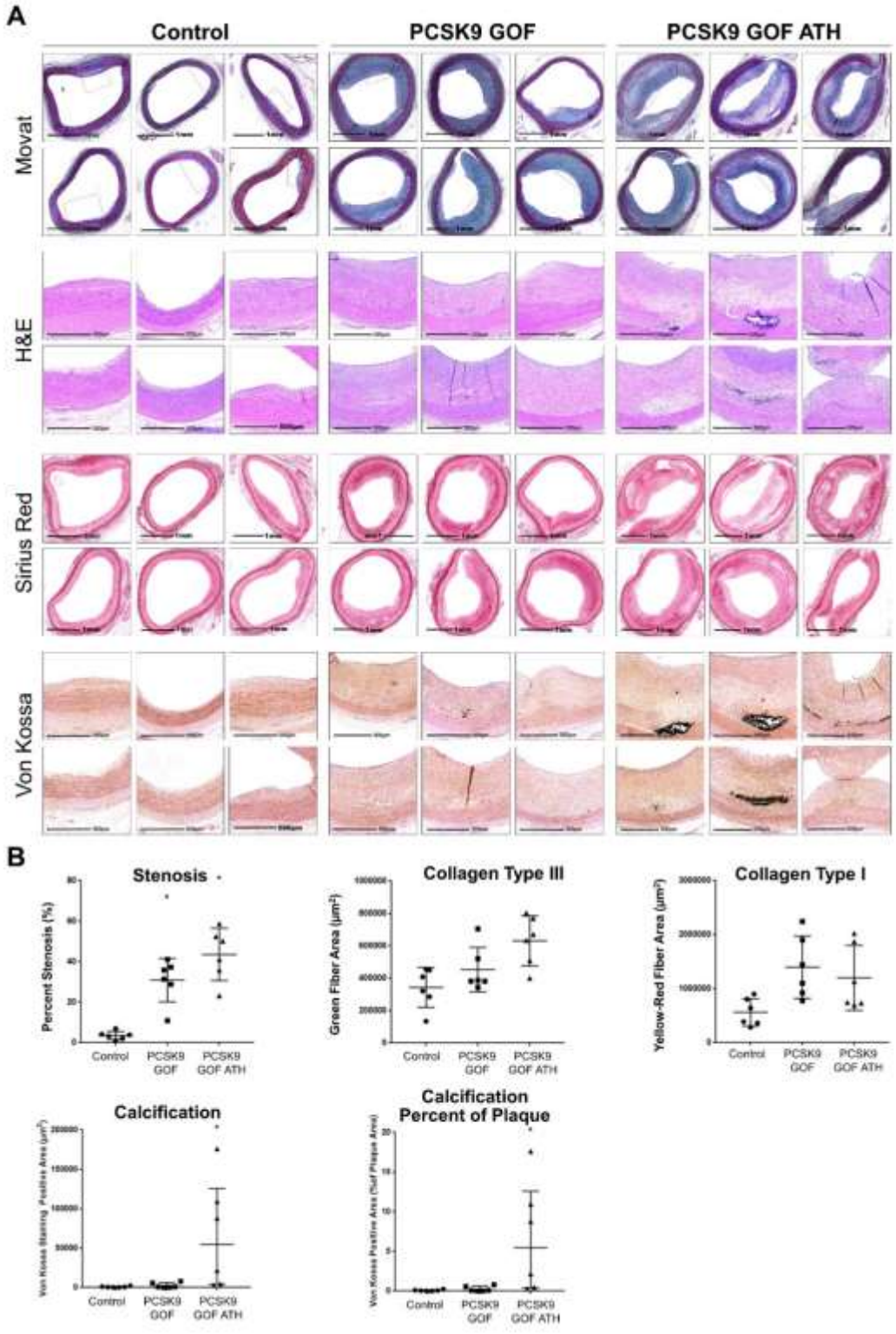
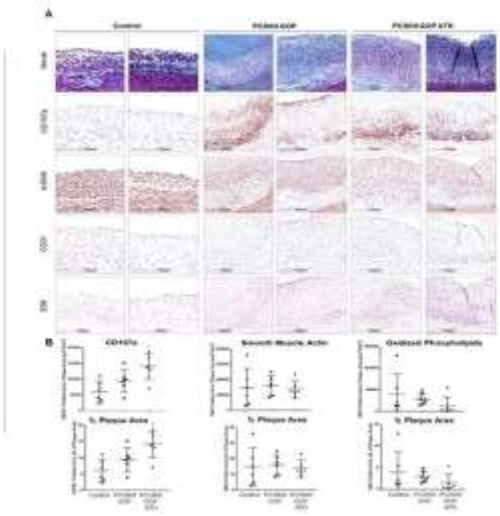


Figure S5. Histopathological features of plaques in the LAD.



A, Representative histopathological features of the most stenotic section of the proximal left anterior descending (LAD) from different individual animals at 9 months of age. The higher power magnifications (H&E and von Kossa stains) represent regions corresponding to the red box in the low power Movat's Pentachrome stain. Histologic coronary staining top to bottom: modified Movat's Pentachrome; hematoxylin & eosin (H&E), picrosirius red; and von Kossa (highlighting calcium). Scale Bar: low power image=1mm; higher power=500μm. **B**, Sirius Red staining images taken on BX51 Olympus microscope under polarized light were used for collagen quantification; the percentage of stenosis were also quantified in the displayed images. Values displayed are means and standard deviations. Calcification area in plaque and percent of plaque area was quantified from the displayed von Kossa stained images with median ± interquartile values displayed. **p*<0.05 compared to Control; † p<0.05 compared to PCSK9 GOF on standard diet using one-way ANOVA, multiple comparison analysis. Calcification data was analyzed by Kruskal-Wallis testing followed by Dunn's multiple comparison.

Figure S6. Immunohistochemical analysis of plaques in the LAD.



A, Immunohistochemistry staining for CD107a, smooth muscle actin (SMA), CD31, and E06 highlights inflammation, neointimal hyperplasia, endothelial cells, and oxidized phospholipids respectively, predominantly in GOF groups. **B**, CD107a, SMA immunostaining areas were quantified on HALO platform (Indica Labs, Corrales, NM), and results were presented as total CD107a or SMA positive area and the percentage of plaque area. Mean and standard deviation is displayed. Analysis was performed using one way ANOVA, multiple comparison analysis. **p*<0.05 compared to Control; † p<0.05 compared to PCSK9 GOF on standard diet.