

Supp Fig. A. WAY-362450 selectivity. Activity of WAY-362450 on a panel of twenty-two human nuclear hormone receptors was determined using LanthaScreen time resolved fluorescence resonance energy transfer (TR-FRET) nuclear receptor coregulator interaction assay kits essentially as described by the manufacturer (Invitrogen). WAY-362450 was tested up to a maximal concentration of 50 μ M. Activity is plotted as percent agonism, with 100% agonism established using appropriate concentrations of reference ligand for each receptor. The EC₅₀ of WAY-362450 was 5 nM for FXR, and was estimated to be >50 μ M for ERR α or PXR. No other nuclear receptor showed agonist activity with WAY-362450.

Supp Fig. B. WAY-362450 regulates genes involved in lipolysis. Hepatic expression of apoCII, apoCIII, apoAV and LPL from male western-diet fed LDLR $-/-$ mice as described in Fig. 2 and chow fed KK-Ay mice as described in Fig. 3 were determined by real time RT-PCR and normalized to GAPDH. * p<0.01 versus western diet fed vehicle treated LDLR $-/-$ mice or KK-Ay vehicle treated mice.

Supp Fig. C. WAY-362450 regulates genes involved in TG synthesis and secretion. Hepatic expression of MTP-1, SREBP-1c, SCD-1 from male western-diet fed LDLR $-/-$ mice as described in Fig. 2 and chow fed KK-Ay mice as described in Fig. 3 were determined by real time RT-PCR and normalized to GAPDH. * p<0.01 versus western diet fed vehicle treated LDLR $-/-$ mice or KK-Ay vehicle treated mice.

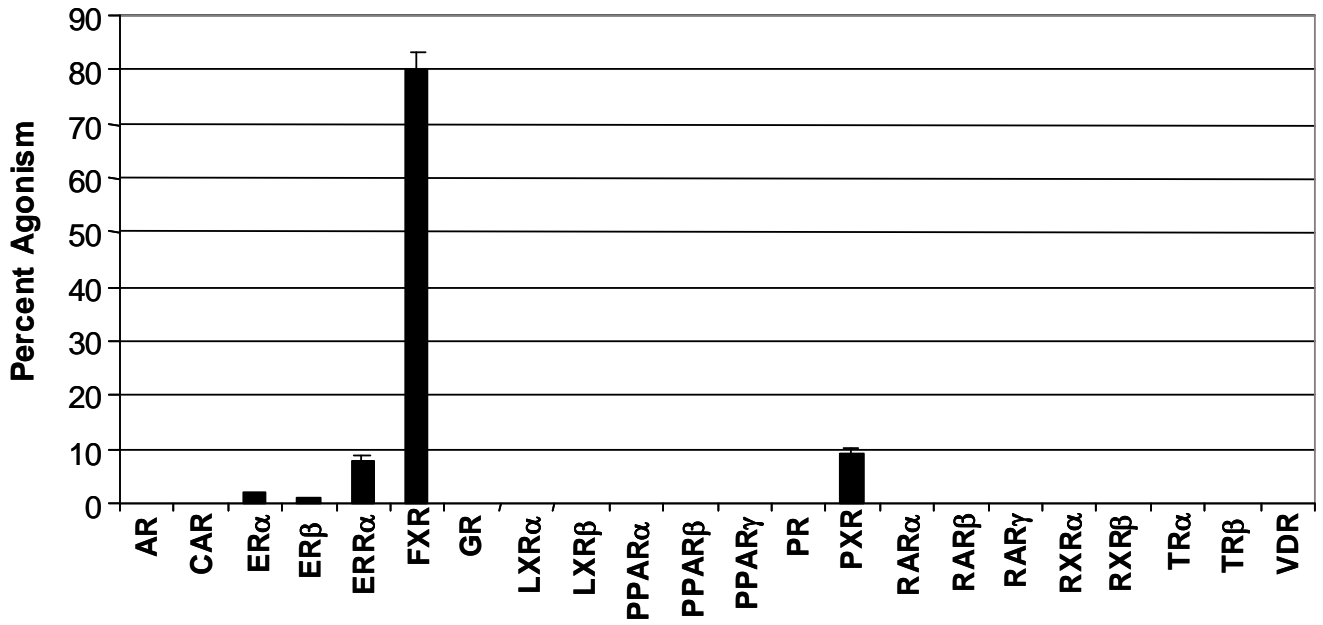
Supp Fig. D. WAY-362450 regulation of genes involved in LDL clearance. Hepatic expression of LDLR and PCSK9 from male KK-Ay and db/db mice as described in Fig. 4 were determined by real time RT-PCR and normalized to GAPDH. * p<0.01 versus vehicle treated mice.

Supp Fig E. Hepatic regulation of EL is FXR-dependent. The regulation of hepatic EL gene expression by real time RT-PCR was determined in (A) WT and FXR $-/-$ mice after 7 day oral administration of 30 mpk WAY-362450 or vehicle. * p<0.05 versus vehicle treatment.

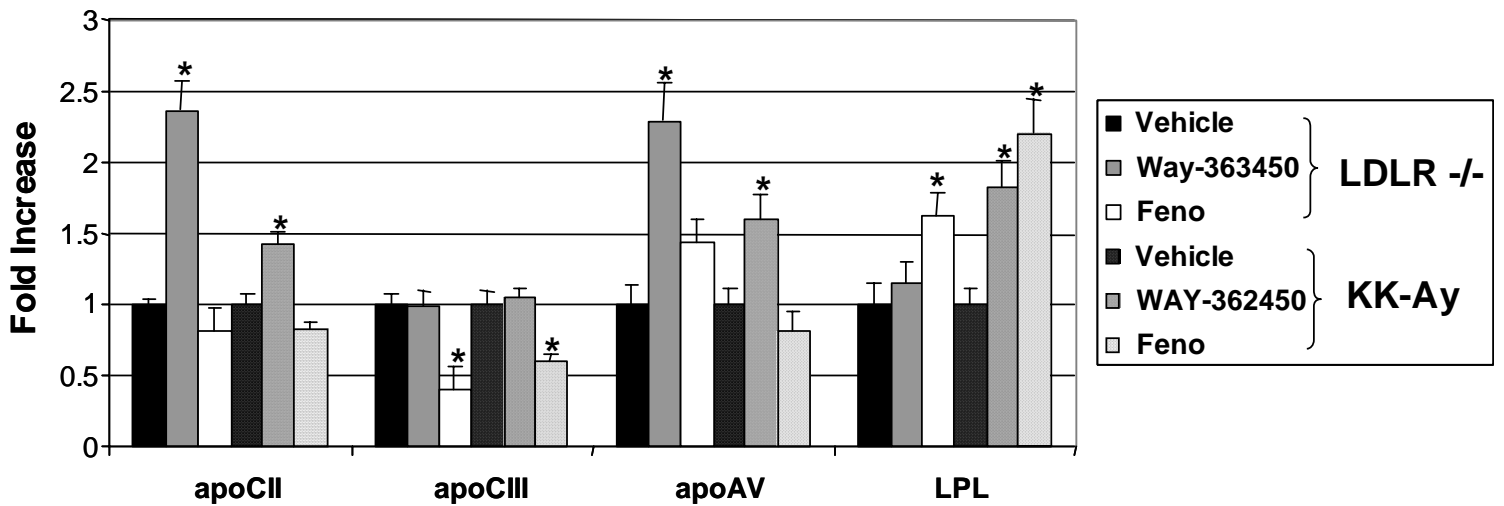
Supp Fig. F. WAY-362450 regulates genes involved in cholesterol biliary secretion. Hepatic expression of ABCG5, ABCG8, BSEP and MDR-2 from male western-diet fed LDLR $-/-$ mice as described in Fig. 2 were determined by real time RT-PCR and normalized to GAPDH. * p<0.01 versus western diet fed vehicle treated LDLR $-/-$ mice.

Supp Fig. G. The regulation of ABCG5 and ABCG8 in primary human hepatocytes. Primary human hepatocytes were treated for 24 hr with increasing concentrations of WAY-362450. Gene regulation of ABCG5, ABCG8, BSEP and MDR-2 were determined by real time RT-PCR and normalized with GAPDH. The data is the average of 3 different donors.

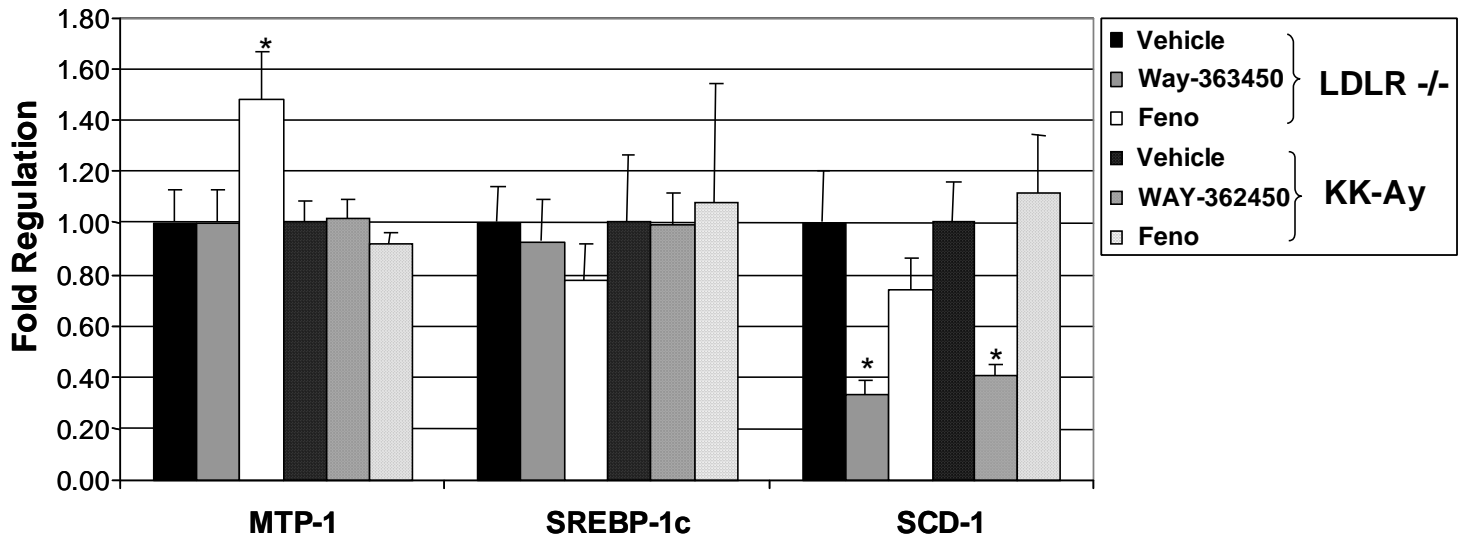
Supp Fig A.



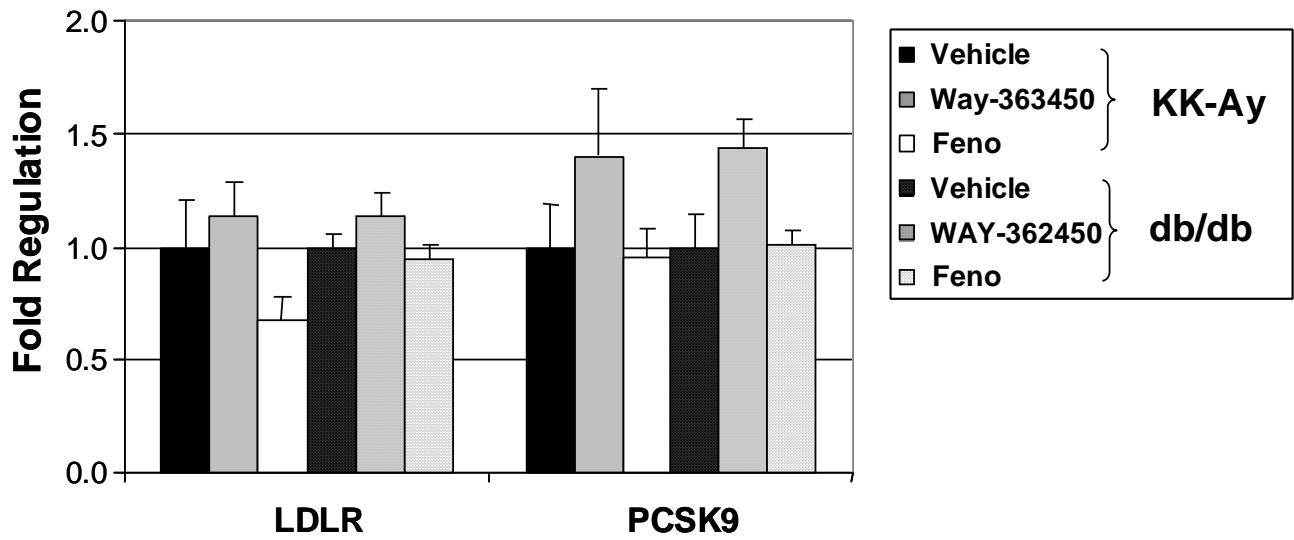
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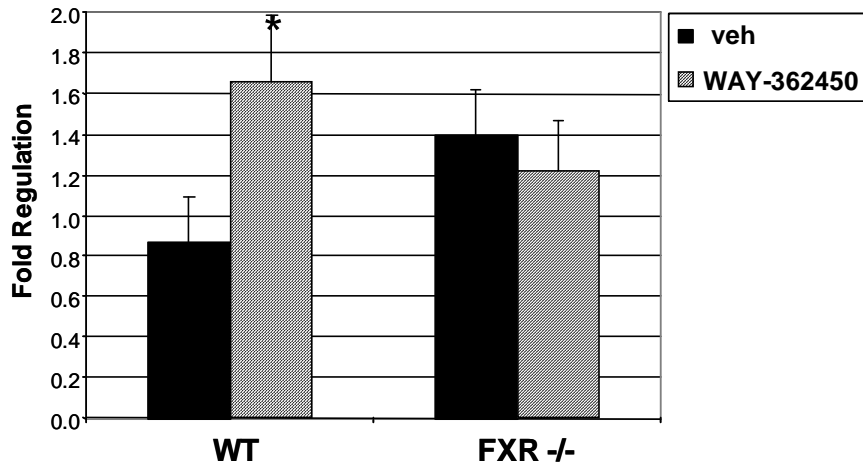
Supp Fig C



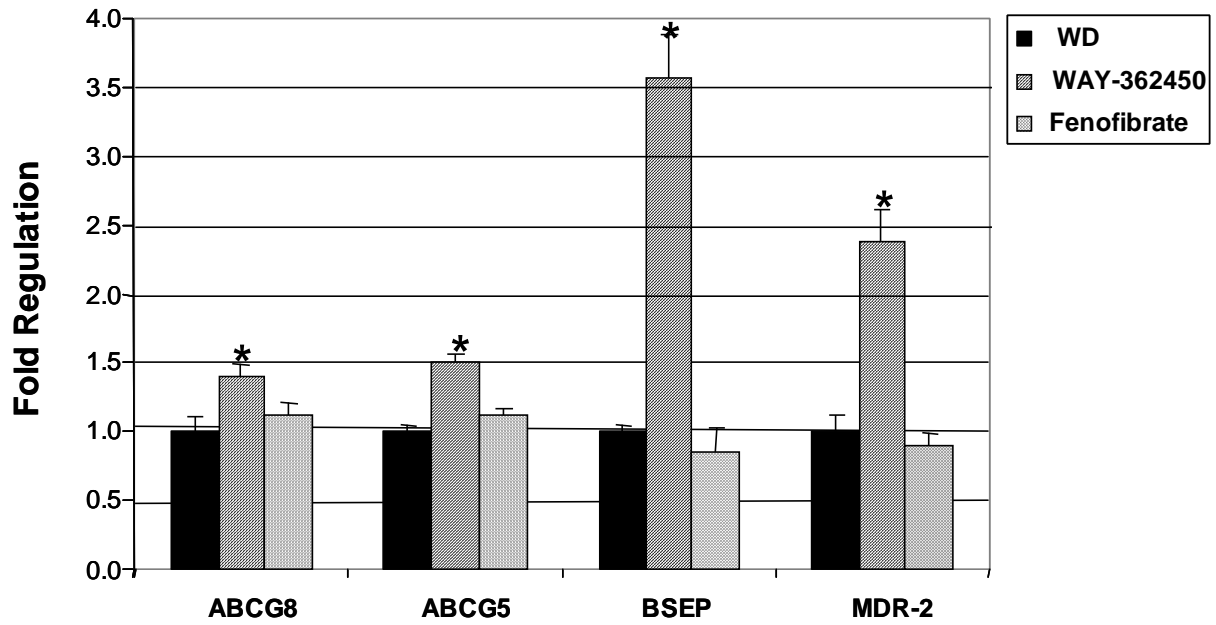
Supp Fig D



Supp Fig E



Supp Fig F



Supp Fig G

