Table 1. Comparison of genetic evidence supporting drug targets and results from clinical trials evaluating the drugs.

Drug target	Gene	Drug	Genetic evidence	Clinical trial evidence for drug
Peroxisome proliferator-activated receptor alpha	PPARA	Fibrates	rs4253772 [6]: Effect of 0.032 s.d. on total cholesterol Effect of 0.031 s.d. on LDL-c No genome-wide significant association with coronary heart disease in GWAS (smallest p-value in CARDIoGRAMplusC4D is 0.004 [121])	Fenofibrate (ACCORD) [36]: ↓ Total cholesterol ↓ Triglycerides ↑ HDL-c Meta-analysis of fibrates [37]: ↓ 10% major cardiovascular events but with marginal significance (p-value=0.048)
Niacin receptor 1 / GPR109A	HCAR2	Niacin	No GWAS association with blood lipids (smallest p-value in CARDIoGRAMplusC4D is 0.149 [121])	Niacin-laropiprant after mean follow-up of 3.9 years (HPS2-THRIVE) [47] ↓ LDL-c (10 mg/dl vs placebo) ↑ HDL-c (6 mg/dl vs placebo) No significant event reduction on background of statin therapy
HMG CoA Reductase	HMGCR	Statins	Gene-based score of 6 HMGCR variants [65]: ↓ LDL-c (3.2 mg/dl when score above median vs below median) ↓ Risk of myocardial infarction or death from coronary heart disease (OR 0.95, 95% CI 0.91 to 0.99)	Clinical trial of simvastatin vs. placebo in the secondary prevention setting (4S) [12]: ↓ Total cholesterol (25% over 5.4 years median follow-up) ↓ LDL-c (35%) ↑ HDL-c (8%) ↓ Coronary death (relative risk 0.58, 95% CI 0.46 to 0.73) In a systematic review of statins for the primary prevention of cardiovascular disease [122]: ↓ Fatal and non-fatal cardiovascular disease (relative risk for statin use 0.75, 95% CI 0.70 to 0.81)
Niemann-Pick C1-Like 1	NPC1L1	Ezetimibe	Gene-based score of 5 NPC1L1 variants [35]: ↓ LDL-c (2.3 mg/dl when score above median vs below median) ↓ Coronary heart disease (OR 0.956, 95% CI 0.930 to 0.983) Carriers of inactivating mutations identified by exome sequencing [123] ↓ LDL-c (12 mg/dl for heterozygous carriers vs noncarriers) ↓ Coronary heart disease (OR for carriers 0.47, 95% CI 0.25 to 0.87)	Clinical trial of ezetimibe vs placebo on a background of statin therapy and in patients hospitalized for an acute coronary syndrome (IMPROVE-IT) [32]: ↓ LDL-c (15.8 mg/dl difference in median between the statin monotherapy and statin+ezetimibe groups) ↓ Primary endpoint of cardiovascular events (HR 0.936, 95% CI 0.89 to 0.99)
Proprotein convertase subtilisin/kexin type 9	PCSK9	Alirocumab, evolocumab	Gene based score of 7 PCSK9 variants [65]: ↓ LDL-c (4.2 mg/dl when score above median vs below median) ↓ Triglycerides (5.3 mg/dl) ↑ HDL-c (0.5 mg/dl) ↓ Myocardial infarction or death from coronary heart disease (OR 0.92, 95% CI 0.88 to 0.95) PCSK9 nonsense mutation carriers [55]: ↓ 28% reduction in LDL-c ↓ Reduction in risk of coronary heart disease (HR 0.11, 95% CI 0.02 to 0.81)	Clinical trial of evolocumab vs placebo on a background of statin therapy in patients with atherosclerotic cardiovascular disease (FOURIER) [50]: ↓ LDL-c (56 mg/dl absolute difference between evolocumab and placebo at 48 weeks) ↓ Primary endpoint of cardiovascular events (HR 0.85, 95% CI 0.79 to 0.92)
Cholesteryl ester transfer protein	CETP	Anacetrapib, dalcetrapib	GWAS showed associations with [6]: ↓ Triglycerides ↓ LDL-c ↑ HDL-c (lead trait) ↓ Total cholesterol rs1800775 (-629C>A) in large exome-wide meta-analysis (the "A" allele is protective and HDL-c increasing) [75]: ↓ Coronary artery disease (OR 0.96, 95% CI 0.94 to 0.97)	Previous trials showed increases in HDL-c but no reduction in coronary events [77]. Clinical trial of anacetrapib vs placebo on background of statin therapy and in patients with atherosclerotic vascular disease (HPS3/TIMI55–REVEAL) [78]: ↑ HDL-c (43 mg/dl at trial midpoint) ↓ Non-HDL cholesterol (17 mg/dl) ↓ Primary endpoint of cardiovascular events (rate ratio 0.91, 95% CI 0.85 to 0.97)
Lp(a)	LPA	ISIS-Apo(a)Rx	rs10455872 [112] ↑ Lp(a) levels ↑ Coronary disease (OR 1.70, 95% CI 1.49 to 1.95) rs3798220 [112] ↑ Lp(a) levels ↑ Coronary disease (OR 1.92, 95% CI 1.48 to 2.49)	Phase I & II trials [113] ↓ Lp(a) (by 67-72%) Awaiting results from phase III trials
Angiopoietin-like 3	ANGPTL3	Evinacumab, IONIS-ANGPTL3-LRx	Loss-of-function ANGPTL3 mutations identified by sequencing [101] ↓ Triglycerides ↓ HDL-c ↓ LDL-c ↓ Coronary artery disease (OR 0.59, 95% CI 0.41 to 0.85)	Phase II trials [101,102] ↓ Triglycerides, VLDL-c, non-HDL cholesterol, total cholesterol Awaiting results from phase III trials
Apolipoprotein CIII	APOC3	Volanesorsen	Study of 4 functional APOC3 mutations [93] ↓ Triglycerides (39% reduction in carriers) ↓ Coronary heart disease (OR 0.60, 95% CI 0.47 to 0.75) Results published with consistent observations by another group [94]	Awaiting results from phase III trials