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

<table>
<thead>
<tr>
<th>Drug target</th>
<th>Gene</th>
<th>Drug</th>
<th>Genetic evidence</th>
<th>Clinical trial evidence for drug</th>
</tr>
</thead>
</table>
| 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 | 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 0.049 [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               | HMGR          | Statins        | Gene-based score of 6 HMGR 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 [45] [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 | Alirocumb, 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-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/IMI55–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 |
| Angiopoetin-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 |