Supplementary Material

# Supplementary Figures and Tables

**Table 1: Risk factors contributing to CV risk and their causality, including the treatment effect on the particular risk factor and the treatment effect on MACE**.

| Risk factor / marker | Causal for CVD? | Treatment | Treatment mechanism | Treatment effect on risk factor/ marker | Treatment effect on MACE | Ref |
| --- | --- | --- | --- | --- | --- | --- |
| Study population | Effect size | Study population | Effect size |
| LDL-c | Yes | Statins | HMG-CoA reductase inhibitor | Hypercholesterolemic, mean baseline LDL-C 3.39-4.91 mmol/L | -50% | Hypercholesterolemic, mean baseline LDL-C 3.39-4.91 mmol/L | -20-35% | 1-9 |
| Alirocumab | mAb against PCSK9 | ACS, baseline LDL-C ≥1.80 mmol/L, on lipid-lowering therapy | -62-66% | ACS, baseline LDL-C ≥1.80 mmol/L, on lipid-lowering therapy | -1.6% (ARR) | 2, 10 |
| Ezetimibe | cholesterol-absorption inhibitor | Hypercholesterolemic, mean baseline LDL-C 1.29-3.17 mmol/L, statin-treated | -20-25% | Hypercholesterolemic, mean baseline LDL-C 1.29-3.17 mmol/L, statin-treated | -7-13% | 11, 12 |
| Inclisiran | siRNA targeting PCSK9 | ASCVD or at high CV risk with elevated LDL-C serum levels, mean baseline LDL-C 2.68-3.92 mmol/L, on lipid-lowering therapy | -51% | Hypercholesterolemic, mean baseline LDL-C 2.68-3.92 mmol/L, on lipid-lowering therapy | -24% | 12, 13 |
| Bempedoic acid | ACC and ATP-citrate lyase inhibitor | ASCVD and/or heFH, mean baseline LDL-C 2.68 mmol/L in statin-treatedHypercholesterolemic, mean baseline LDL-C 3.59 mmol/L, ezetimibe-treated and statin-intolerant | -17%-29% | Hypercholesterolemic, mean baseline LDL-C 3.59 mmol/L, ezetimibe-treated and statin-intolerant  | -13-23% | 11, 12, 14-17 |
| Mipomersen | ASO directed at apoB-100 | Mild dyslipidemic, mean baseline LDL-C 3.31 mmol/LheFH, mean baseline LDL-C 4.50 mmol/L, on lipid-lowering therapy | -35%-21-34% | - | Unknown | 2, 18, 19 |
| Lomitapide | MTP inhibitor | hoFH mean baseline LDL-C 8.69 mmol/L, on lipid-lowering therapy | -38-50% | - | Unknown | 2, 20 |
| Evinacumab | mAb against ANGPTL3 | HTG, mean baseline LDL-C 3.17-3.75 mmol/LhoFH, mean baseline LDL-C 8.32 mmol/L, on lipid-lowering therapy | -23%-47% | - | Unknown | 21-23 |
| ApoB | Potentially (CHD) | Mipomersen | ASO directed at apoB-100 | Mild dyslipidemic, mean baseline LDL-C 2.61-2.92 mmol/LSevere-hypercholesterolemic, mean baseline apoB 1.8 mmol/L, on lipid-lowering therapyheFH, mean baseline ApoB 1.52 g/L, on lipid-lowering therapy | -50%-36%-23-33% | - | Unknown | 2, 18, 19, 24, 25 |
| Lomitapide | MTP inhibitor | hoFH, mean baseline ApoB 2.6 g/L, on lipid-lowering therapy | -49% | - | Unknown | 20, 26 |
| Alirocumab | mAb against PCSK9 | ACS, baseline ApoB <0.75, 0.75–<0.90, ≥0.90 g/L, on lipid-lowering therapy | -42-54% | ACS, baseline ApoB <0.75, 0.75–<0.90, ≥0.90 g/L, on lipid-lowering therapy | -1.6%(ARR) | 10 |
| Bempedoic acid | ACC and ATP-citrate lyase inhibitor | ASCVD and/or heFH, mean baseline ApoB 0.87 g/L, statin-treated | -13% | Statin-intolerant  | -13-23% | 14, 15 |
| Fibrates | PPAR-α activator | Hypercholesterolemic | -10% | With and without known history of CVD | -22% | 12, 27, 28 |
| Saroglitazar | PPARα/γ agonist | Diabetic dyslipidemic, mean baseline ApoB 1.01 g/L, statin-treated | -32% | - | Unknown | 29 |
| Evinacumab | mAb against ANGPTL3 | hoFH, on lipid-lowering therapy | -46% | - | Unknown | 21 |
| Lp(a) | Yes(CVD, aortic valve stenosis) | Lipoprotein apheresis | intervention | Mean baseline LDL-C of 2.07 mmol/L and Lp(a) of 138 mg/dL on lipid-lowering therapy | -63% | Lp(a) > 60 mg/dL, normal LDL-C, and CVD | >70% | 30-33 |
| Alirocumab | mAb against PCSK9 | ACS, baseline LDL-C ≥1.80 mmol/L, on lipid-lowering therapy | -23% | ACS, baseline LDL-C ≥1.80 mmol/L, on lipid-lowering therapy | -1.6% (ARR) | 10, 34 |
| Pelacarsen | ASO directed at apo(a) | CVD, on lipid-lowering therapyHealthy | -35-80%-90% | CVD, on lipid-lowering therapy | Results expected in 2025 | 35-37 |
| Mipomersen | ASO directed at apoB-100 | heFH and CHD, on lipid-lowering therapyFH, on lipid lowering therapy | -21%-31% | - | Unknown | 34, 38 |
| Lomitapide | MTP inhibitor | hoFH, on lipid-lowering therapy | -13% | - | Unknown | 26, 34 |
| Evolocumab | mAb against PCSK9 | ASCVD, on lipid-lowering therapy | -27% | ASCVD, on lipid-lowering therapy | -16% | 11, 39 |
| Olpasiran | siRNA against apo(a) | ASCVD, on lipid-lowering therapy | -71-100% | ASCVD and elevated Lp(a) | Results expected in 2027 | 40 |
| HDL-C | No (CHD, MI, IHD) | Aerobic exercise | lifestyle intervention | Sedentary lifestyle without CVD | +5-10% | General population | ≤-50% | 41-44 |
| Smoking cessation | lifestyle intervention | Cigarette smokers | +0.1 mmol/L | Acute ischemic stroke | -14% | 44, 45 |
| Apabetalone (RVX-208) | apoA-I mimetics | Stable CAD, statin-treatedSymptomatic CAD with low HDL-C levels, statin-treated | +3-8%No effect | - | Unknown | 26 |
| ApoA-I | Likely not (CAD)  | CSL112 | apoA-I mimetics | MI, statin-treated | +123% | - | Unknown | 46, 47 |
| Apabetalone(RVX-208) | apoA-I mimetics | Stable CAD, statin-treatedSymptomatic CAD with low HDL-C levels, statin-treated | +5.6-10%No effect | - | Unknown | 26, 48 |
| TG | Yes (CHD) | Nicotinic acid(niacin) | Reduces hepatic TG synthesis | CHD with HDL-C <1.16 mmol/L, statin-treated | -13% | HDL-C <1.81 mmol/L or at high CV risk, statin-treated | No effect | 49-51 |
| Fibrates | PPAR-α activator,inhibits ApoC-III expression, inhibits VLDL synthesis and secretion, stimulates LPL expression | IIB phenotype of Fredrickson classificationHypercholesterolemic | -30-50%≤-30% | CAD | -24% | 27, 28 |
| Fenofibrate | PPAR-α activator,reduces ApoC-III,LPL activator | T2DM, statin-treated | -22% | T2DM, statin-treated TG≥ 2.31 mmol/L and HDL-C≤0.88 mmol/L, statin-treated  | No effect-31% | 27 |
| Pemafibrate(K-877) | SPPARMα modulator | DyslipidemicT2DM, mild-to-moderate HTG, and HDL-C <1.03 mmol/L, on lipid-lowering therapy and statin-intolerant | -42.7%-26.2% | T2DM, mild-to-moderate HTG, and HDL-C <1.03 mmol/L, on lipid-lowering therapy and statin-intolerant | No effect | 12, 52 |
| Saroglitazar | PPARα/γ agonist | Diabetic dyslipidemic, statin-treated | -45% | - | Unknown | 29 |
| EPA | ω3-fatty acid | Hypercholesterolemic, statin-treated | -9% | Hypercholesterolemic, statin-treated | -19% | 53-55 |
| EPA+DHA | ω3-fatty acid | MI, preventive treatmentsHTG, statin-treated | -3%-19% | MI, preventive treatmentsDM without CVDHTG, statin-treated | -30% No effectNo effect  | 55, 56 |
| Icosapent ethyl(IPE) | stable ethyl ester of EPA | Hypercholesterolemic, statin-treatedHigh CV risk and elevated TG, statin-treated | -9%-17% | HTG, statin-treated  | -25%  | 56 |
| Volanesorsen(ISIS-APOCIIIRx) | ASO directed at ApoC-III | FCS | -77% | - | Unknown | 21, 46, 57 |
| Olezarsen(AKCEA-APOCIII-LRx) | ASO directed at ApoC-III | Healthy, mildly elevated TG | -77% | - | Unknown | 57 |
| Evinacumab | mAb against ANGPTL3 | HTGhoFH, on lipid-lowering therapy | -76.9%-47% | - | Unknown | 21 |
| AKCEA-ANGPTL3-LRx | ASO directed at ANGPTL3 | Healthy | -49% | - | Unknown | 21, 26 |
| TGRLs | Yes (CHD and aortic valve stenosis) | Mipomersen | ASO directed at apoB-100 | hoFH, on lipid-lowering therapy | -17% VLDL-C | - | Unknown | 38, 58, 59 |
| Olezarsen | ASO directed at ApoC-III | Moderate HTG and at high CV risk, on lipid-lowering therapy | -58% VLDL-C | - | Unknown | 60 |
| Saroglitazar | PPARα/γ agonist | Diabetic dyslipidemic, statin-treated | -45% VLDL-C | - | Unknown | 29 |
| Pemafibrate(K-877) | SPPAR-α modulator | T2DM, mild-to-moderate HTG, and HDL-C <1.03 mmol/L, on lipid-lowering therapy and statin-intolerant | -26% VLDL-C | T2DM, mild-to-moderate HTG, and low HDL-C and LDL-C levels | No effect | 52 |
| Volanesorsen | ASO directed at ApoC-III | FCS | -58% VLDL-C | - | Unknown | 21 |
| Remnant-C | Yes (IHD, aortic valve stenosis) | Pemafibrate(K-877) | SPPAR-α modulator | T2DM, mild-to-moderate HTG, and HDL-C <1.03 mmol/L, on lipid-lowering therapy and statin-intolerant | -26%  | T2DM, mild-to-moderate HTG, and low HDL-C and LDL-C levels | No effect | 52, 58, 61, 62 |
| ApoC-III | Yes (CHD) | Volanesorsen | ASO directed at apoC-III | FCS | -84% | - | Unknown | 46, 57, 59, 63 |
| Olezarsen | ASO directed at apoC-III | Mildly elevated TGModerate HTG and at high CV risk lipid-lowering therapy | -92%-74% | - | Unknown | 57, 60 |
| Pemafibrate(K-877) | SPPAR-α modulator | T2DM, mild-to-moderate HTG, and HDL-C <1.03 mmol/L, on lipid-lowering therapy and statin-intolerant | -28% | T2DM, mild-to-moderate HTG, and HDL-C <1.03 mmol/L, on lipid-lowering therapy and statin-intolerant | No effect | 52 |
| ANGPTL3 | Yes (CVD) | Evinacumab | mAb against ANGPTL3 | - | Unknown | - | Unknown | 21, 64, 65 |
| AKCEA-ANGPTL3-LRx  | ASO directed at ANGPTL3 | Healthy | -47-82% | - | Unknown | 21, 26, 64 |
| ARO-ANG3 | siRNA targeting ANGPTL3 | Healthy | -55-83% | - | Unknown | 21, 64 |
| OxPL | Unknown | Pelacarsen | ASO directed at apo(a) | CVD, on lipid-lowering therapy | -30-90% |  | Results expected in 2025 | 36, 66 |
| PLA2 | No (CHD)  | Darapladib | Lp-PLA2i | CHD, statin-treated | -43-66% | ACS, on lipid-lowering therapyStable CHD, on lipid-lowering therapy | No effectNo effect | 67-70 |
|  | Varespladib | sPLA2i | - | Unknown | ACS <96 h prior | Increased risk | 71 |
| IL-6 | Indirectly, via IL-6 receptor for CHD, AF, and stroke | Darapladib | Lp-PLA2i | ACS, on lipid-lowering therapy | -12% | ACS, on lipid-lowering therapy | No effect | 71-75 |
| Methotrexate | folic acid antagonist | ASCVD | No effect | ASCVD | No effect | 76, 77 |
| Bempedoic acid | ACC and ATP-citrate lyase inhibitor | ASCVD and/or heFH, statin-treated | -4% | statin-intolerant | -13-23% | 14, 15 |
| Canakinumab | mAb against IL-1β receptor | Stable post-MI hsCRP levels>2mg/L, on lipid-lowering therapy | -20-40% | on-treatment hsCRP<2mg/L | -26% | 78 |
| IL-1 | Indirectly as part of IL-6 pathway | Methotrexate | folic acid antagonist | ASCVD | No effect | ASCVD | No effect | 76, 77 |
| hsCRP | No | Darapladib | Lp-PLA2i | CHD, statin-treatedACS, on lipid-lowering therapy | -20%-13% | ACS, on lipid-lowering therapyStable CHD, on lipid-lowering therapy | No effectNo effect | 71, 75 |
| Varespladib | sPLA2i | Stable CHD, statin-treated | -55.6% | ACS <96 h prior | Increased risk | 71 |
| Methotrexate | folic acid antagonist | ASCVD | No effect | ASCVD | No effect | 76, 77 |
| Bempedoic acid | ACC and ATP-citrate lyase inhibitor | ASCVD and/or heFH, statin-treated | -27% | Statin-intolerant | -13-23%  | 14, 15 |
| Colchicine | inhibits NLRP3 inflammasome activation | ACS, statin-treated | -37.3% | ACS, statin-treatedChronic coronary disease | -23% -30%  | 79-81 |
| Canakinumab | mAb against IL-1β receptor | Stable post-MI hsCRP levels>2mg/L, on lipid-lowering therapyT2DM | -20-40%-36-65% | Stable post-MI on-treatment hsCRP<2mg/L, on lipid-lowering therapy | -26%  | 71, 78 |
| Ziltivekimab | mAb against IL-6 | Elevated hsCRP and CKD | -77-92% | Unknown | - | 82 |
| Platelet-related |  | Rivaroxaban | Factor Xa inhibitor | - | - | ACS, in addition to standard therapyASCVD, aspirin-treatedPost-MI with stable CAD, aspirin-treated | -16%-24%-22% | 83, 84 |
| Clopidogrel | nhibits the binding of ADP | - | - | ASCVDPrior MI, ischemic stroke, or symptomatic PAD, aspirin-treated | -8.7%-17% | 85, 86 |
| Ticagrelor | P2Y12 inhibitor | - | - | ACS with stable CAD, aspirin-treated | -16% | 84 |
| Obesity | Controversial | Bariatric surgery | intervention | Adolescents | -30% BMI | Patients that underwent bariatric surgery | -27-42.1% | 43, 87 |
| Mediterranean diet | intervention | At high CV risk, without pre-existing CVD | Yes | Compared to low-fat diet in population at high CV risk, without pre-existing CVD | -30% | 88, 89 |
| Poor diet | Yes | Mediterranean diet | lifestyle intervention | At high CV risk, without pre-existing CVD | Yes | Compared to low-fat diet in population at high CV risk, without pre-existing CVD | -30% | 88, 89 |
| Inactivity | Controversial | Aerobic exercise | lifestyle intervention | Yes | Yes | General population | ≤-50% | 43 |
| Smoking | Yes(CVD) | Smoking cessation | lifestyle intervention | Yes | Yes | Acute ischemic stroke | -14% | 44, 45 |

ACS; acute coronary syndrome, AF; arterial fibrillation, ANGPTL; angiopoietin-like protein, Apo; apolipoprotein, mAb; monoclonal antibody, ASCVD; atherosclerotic cardiovascular disease, ASO; antisense oligonucleotide, ATP; adenosine triphosphate, CAD; coronary artery disease, CHD; coronary heart disease, CKD; chronic kidney disease, CVD; cardiovascular disease, FCS; familial chylomicronemia syndrome, FH; familial hypercholesterolemia, HDL; high-density lipoprotein, hsCRP; high sensitivity c-reactive protein, HTG; hypertriglyceridemia, IL; interleukin, LDL; low-density lipoprotein, Lp(a); lipoprotein (a), MI; myocardial infarction, MTP; mitochondrial triglyceride transfer protein, OxPL; oxidized phospholipids, siRNA; small interfering RNA, ACC; acetyl-CoA carboxylase, PCSK9; proprotein convertase subtilisin/kexin type 9, PLA2; phospholipase A2, PPAR; peroxisome proliferator-activated receptors, sPLA; secretory phospholipase A2, T2DM; type 2 diabetes mellitus, TG; triglycerides, TGRL; triglyceride-rich lipoprotein, VLDL; very low-density lipoprotein.

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