CV Care: Lipid-modifying Agents--From Statins to PCSK9 inhibitors

Brief title: LDL-C lowering agents and their effects

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Abstract
Mendelian randomization studies and randomized trials have conclusively demonstrated that lower LDL-cholesterol results in fewer cardiovascular events. This review describes key stages in the evolution of LDL-cholesterol lowering treatment. Data from over 25 cardiovascular outcome trials confirm that, within a few years, statins lower the relative risk of major atherosclerotic events by about 22% per 38.7 mg/dL (1 mmol/L) reduction in LDL-cholesterol, with similar benefit across patient subgroups. Meta-analyses of these trials have established the safety of statins with regard to non-vascular mortality and cancer. Other agents available for prescription include ezetimibe and PCSK9 inhibitors, which both reduce major atherosclerotic events in proportion to their effects on LDL-cholesterol and have good safety profiles, though PCSK9 inhibitors remain costly. Investigational LDL-cholesterol-lowering agents currently being tested in cardiovascular outcome studies are bempedoic acid, an ATP-citrate lyase inhibitor that reduces cholesterol synthesis, and inclisiran, a double-stranded small interfering RNA, that inhibits PCSK9 synthesis.

Condensed abstract
Randomized trials of statins, ezetimibe and PCSK9 inhibitors have proved that lowering LDL-cholesterol reduces the risk of atherosclerotic cardiovascular events. Beneficial effects of these treatments on cardiovascular outcomes, including myocardial infarction, ischemic stroke and arterial revascularization procedures, are proportional to the absolute reduction in LDL-cholesterol. Statins are the most widely prescribed LDL-cholesterol lowering agents, and among the most commonly used medicines worldwide.

Bempedoic acid, an ATP-citrate lyase inhibitor that reduces cholesterol synthesis, and inclisiran, a double-stranded small interfering RNA, that inhibits PCSK9 synthesis, are newer LDL-cholesterol-lowering agents with different mechanisms of action currently being tested in cardiovascular outcome studies.

Key words: LDL-cholesterol, cardiovascular, statin, PCSK9, ezetimibe, Mendelian randomization

Abbreviations

LDL	low-density lipoprotein
PCSK9	proprotein convertase subtilisin/kexin type 9
HDL	high-density lipoprotein
ULN	upper limit of normal
NPC1L1	Niemann-Pick C1-Like 1
VLDL	very-low-density lipoprotein
RNA	ribonucleic acid
RCT	randomized controlled trial

Lipoprotein particles carrying apolipoprotein B, most notably low-density lipoprotein (LDL), initiate atherosclerosis by entering the subendothelial space and triggering a local inflammatory response. The central role of the LDL particle in this process was recognized over 30 years ago (1) and is indisputable (2), in large part because of a very consistent body of evidence from randomized controlled trials (RCTs). These show that lowering LDL-cholesterol and apolipoprotein B (markers of LDL particle volume and number, respectively) by treatment with statins, ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors reduces the risk of major atherosclerotic vascular events (3-5), with concordant results from Mendelian randomization studies (2,6,7). There is no reliable evidence for a threshold below which lowering LDL-cholesterol is dangerous or serves no therapeutic purpose (8,9); PCSK9 inhibitors added to maximal statin therapy can safely bring LDL-cholesterol down to a median level of 30 mg/dL (5). This is very low relative to Western adult averages, but comparable to the concentration of LDL-cholesterol in human newborns and many adult mammals (2).

Although other lipids and lipoproteins, in particular triglycerides, HDL-cholesterol and lipoprotein(a), are risk factors for atherosclerotic disease, there is currently no clear evidence that pharmacological interventions to increase HDL-cholesterol or lower lipoprotein(a) or triglycerides yield meaningful clinical benefit. Therefore, the focus of this review is the principal pharmacological treatments that primarily lower LDL-cholesterol and are available for prescription or in late-stage clinical development.

THE CURRENT THERAPEUTIC ARMAMENTARIUM

STATINS

Statins are universally recognized as the bedrock of pharmacological treatment to lower LDL-cholesterol. Statins are inhibitors of HMG-CoA reductase, the enzyme controlling the rate-

limiting step in the cholesterol biosynthesis pathway, leading to reduced hepatic cholesterol and up-regulation of hepatic LDL receptors (10) (Figure 1). The first marketed statin, lovastatin, was approved for prescription in 1987 (11), and six other statins are currently available: simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin and pitavastatin. Apart from pitavastatin, these are available as affordable generic products and are widely prescribed worldwide.

Landmark placebo-controlled cardiovascular outcomes trials

At the dawn of the statin era, there was considerable doubt about both the validity of LDL-cholesterol as a therapeutic target and the safety of statins, in particular concerns that lowering LDL-cholesterol might increase the risk of cancer and/or non-vascular mortality (11). These doubts were resolved by large RCTs, including the landmark Scandinavian Simvastatin Survival Study (4S) (12), the West of Scotland Coronary Prevention Study (WOSCOPS) (13) and the Heart Protection Study (HPS) (14) (Table 1). In brief, 4S and HPS showed beyond doubt that simvastatin treatment reduced cardiovascular morbidity and mortality in patients with pre-existing atherosclerotic vascular disease (and in HPS, also in patients with diabetes) while WOSCOPS demonstrated that pravastatin reduced non-fatal atherosclerotic events in a high-risk primary prevention population with elevated LDL-cholesterol levels.

Collectively, these three studies randomized approximately 30,000 participants and followed them for about 5 years, providing substantial evidence of safety in addition to the very clear reductions in cardiovascular risk. These landmark studies were followed by numerous further large-scale RCTs involving all statins (Figure 2). The study populations were diverse, including middle aged and elderly participants with diabetes, end-stage renal disease, heart failure, and a history of stroke. The results of these studies, involving more than 170,000

patients, have been the subject of a series of meta-analyses by the Cholesterol Treatment Trialists' (CTT) Collaboration (www.cttcollaboration.org).

The Cholesterol Treatment Trialists' Collaboration

The CTT Collaboration was established in the early 1990s prior to release of the 4S results, The CTT Collaboration conducts periodic meta-analyses of large-scale (≥1000 participants), long-term (≥2 years scheduled treatment duration) unconfounded RCTs of lipid intervention therapies, and has largely focussed on statin therapy to date. The resulting analyses (3,15), based on individual participant data have shown clearly that statin therapy proportionally reduces the risk of major atherosclerotic vascular events by about one fifth per 38.7 mg/dL (1 mmol/L) absolute reduction in LDL-cholesterol, largely irrespective of baseline cholesterol concentration (even when LDL-cholesterol is already less than 77 mg/dL [2 mmol/L]) (Table 2). Absolute benefit relates mainly to an individual's absolute risk of cardiovascular events and to the absolute reduction in LDL-cholesterol achieved (3) as shown in Figure 3, so that further reductions in LDL-cholesterol with more intensive statin regimens yield further reductions in risk (15) (Figure 3). In addition, CTT analyses have confirmed that statins are effective in a wide range of patients including those with diabetes, different levels of risk, mild-to-moderate chronic kidney disease, both women and men, and those aged over 75 (16).

Atherosclerotic lesions develop over decades but, in RCTs, LDL-cholesterol lowering treatments are given for only a few years. The implication is that starting treatment early and continuing it indefinitely may reduce risk even more (2,17,18). For logistical and cost reasons, however, the maximum feasible duration of pharmacological treatment in RCTs is about 6 years. Nonetheless, results from RCTs show that benefit for a given reduction in LDL-cholesterol is greater in longer trials (Figure 3). Mendelian randomization studies further support this

hypothesis (2,7), indicating that a genotype-driven lifelong 38.7 mg/dL reduction in LDL-cholesterol more than halves the risk of a major atherosclerotic event.

Statin safety

Statin safety has been the subject of three recent detailed large group reviews (16,19,20). All concluded that the benefits of statins far outweigh the few risks, summarized below. Nevertheless, misinformation is widespread, especially in social media (21), and a group of over 20 chief editors of cardiovascular journals have called for a stop to the distribution of misleading information (22).

Statins occasionally cause serious muscle injury, specifically myopathy (defined as unexplained muscle pain or weakness accompanied by a creatine kinase level exceeding 10X ULN), but the incidence is less than 0.1%. Myopathy can take the more extreme form of rhabdomyolysis, which can precipitate acute kidney injury. Treatment must be stopped promptly and is usually followed by recovery. Some statins, particularly simvastatin and lovastatin, are susceptible to drug interactions that increase the risk of myopathy (20). Statins can produce small increases in transaminases, but hepatitis caused by a statin is very rare (0.001%) (20). A more common adverse effect is new-onset diabetes occurring in about 0.2% of patients. A probable adverse effect, although evidence is not conclusive, is an increase in hemorrhagic stroke in patients with a history of cerebrovascular disease (15). Adverse events attributed to statins, but for which there is no good evidence, include supposed increased risks of cancer (unsupported by a CTT meta-analysis (23)), cognitive impairment, sleep disturbance, peripheral neuropathy, cataracts, erectile dysfunction, interstitial lung disease and tendonitis (16,19,20). Statins are contraindicated in women who are or may become pregnant. This stems from theoretical concerns about the need of the developing fetus for cholesterol coupled with skeletal

abnormalities in the offspring of rats given lovastatin (but not other statins) at a very high dose. This was later shown to be the result of maternal toxicity, not a direct effect on the fetus. Further detail is available in recent reviews (20,24). Limited outcome data from unintended pregnancies provide no evidence for a hazard, but cannot rule it out (20,24). Statins are used to treat familial hypercholesterolemia in children and adolescents with no evidence of any particular safety risk (20). The CTT Collaboration is currently extending its dataset to encompass all recorded adverse events (25).

Statin tolerability

A good measure of overall drug tolerability is the difference between active drug and placebo in the percentage of patients in double-blind RCTs stopping study treatment because of adverse events (20). For statins, there is no detectable difference (26), even when the analysis is confined to eight cardiovascular outcome trials in participants with substantial comorbidity (27): withdrawal due to adverse events across the eight studies was 8.0% (1814/22,714) and 8.1% (1843/22,715) in patients allocated to statin and placebo respectively (27).

Despite an excellent safety and tolerability profile in RCTs, as well as low cost, patient resistance may occur and long-term adherence to statin treatment is often problematic in clinical practice (28) and this remains a key challenge for clinicians. Part of the reason for the difficulty with adherence is the widespread perception (among both patients and some clinicians) that statins are not well tolerated, most commonly due to muscle symptoms without significant increases in creatine kinase. However, data from large double-blind statin RCTs show that statins cause muscle symptoms in at most 1% of treated patients (16,20). The best explanation for the much higher incidence in some clinical settings (29) is patient expectations of harm, i.e. the

nocebo effect (16,20,21,30,31). Recently published guidance provides useful strategies to encourage adherence to statin therapy (32).

EZETIMIBE

Ezetimibe and its active glucuronide localize at the brush border of the small intestinal villi where it inhibits the sterol transporter NPC1L1 (33), which mediates intestinal uptake of cholesterol (34) (Figure 1). NPC1L1 inhibition limits the absorption of cholesterol, which reduces delivery of chylomicron cholesterol to the liver, lowering hepatic cholesterol stores; this increases expression of the LDL receptor (as do statins and PCSK9 inhibitors) and thus increases hepatic LDL uptake, lowering plasma LDL-cholesterol.

Ezetimibe at the recommended 10 mg daily dose produces a mean reduction in LDL-cholesterol (net of placebo) of 19% as monotherapy and 23% from the on-statin baseline when added to statin treatment (35). Several large long-term cardiovascular outcome studies (4,36,37), as well as earlier studies, demonstrated a safety and tolerability profile not detectably different from placebo (38). Specifically, muscle injury (myopathy, or its more severe form, rhabdomyolysis) does not appear to be an adverse effect of ezetimibe: there has been no excess over placebo of cases in large RCTs, and most cases reported during post-marketing surveillance have been in patients also treated with a statin. As with statins, increases in transaminases to >3X ULN occur in about 1% of patients, but clinically apparent hepatotoxicity is extremely rare (if it occurs at all).

Cardiovascular outcome trials

Ezetimibe treatment has been included in three cardiovascular outcome trials; two of these compared concomitant simvastatin/ezetimibe vs. placebo, one (SEAS) (36) in patients with aortic stenosis, and the other in chronic kidney disease (SHARP) (37). The third and most recent

trial (IMPROVE-IT) (4) compared ezetimibe vs. placebo in 18,144 patients with acute coronary syndrome treated with simvastatin and followed for a median of 6 years. In SEAS, there was no effect on the primary endpoint, combined aortic valve events and ischemic events in patients with aortic stenosis. However, simvastatin/ezetimibe did reduce the incidence of ischemic cardiovascular events by 22% compared to placebo. In 9270 patients with chronic kidney disease randomly allocated to simvastatin/ezetimibe or placebo in SHARP, of whom about a third were on dialysis, there was a 17% reduction in the primary endpoint, major atherosclerotic events. Unlike SEAS and SHARP, IMPROVE-IT measured the effect of ezetimibe specifically, by adding ezetimibe or placebo to background simvastatin therapy. The risk of a major atherosclerotic event was reduced by 6% by ezetimibe compared to placebo (2572/9067 first events vs. 2742/9077 first events, hazard ratio 0.94, 95% CI 0.89-0.99, p=0.016). This modest effect reflects the small time-weighted difference between trial arms in LDL-cholesterol of 16mg/dL (4).

In SEAS, more cancers occurred in the simvastatin/ezetimibe group compared to placebo (105 vs. 70, p=0.01). There is no evidence that statins increase the risk of cancer (23), but this study caused concern that ezetimibe might do so (39). However, the absence of any such effect in the much larger SHARP (438 simvastatin/ezetimibe vs. 439 placebo cancers) and IMPROVE-IT (748 simvastatin/ezetimibe vs. 732 simvastatin/placebo cancers) studies alleviated this concern. There was no significant difference in the IMPROVE-IT trial regarding numbers stopping study treatment due to adverse events, 10.6% allocated to ezetimibe and 10.1% allocated to placebo, confirming the drug's excellent tolerability.

Ezetimibe is now available in generic form and is recommended as the first drug to add to statin treatment if further LDL-cholesterol lowering is required (40), for example in children and

adults with familial hypercholesterolemia, who typically require large reductions of LDL-cholesterol to reach guideline recommended levels. It can also be given as monotherapy in patients who decline or stop statin treatment.

PCSK9 INHIBITORS

PCSK9, a circulating enzyme produced in the liver, which plays a key role in hepatocyte expression of the LDL receptor, belongs to the proprotein convertase family of proteases. In 2003, Abifadel and colleagues reported a very severe form of familial hypercholesterolemia due to gain-of-function mutations in the PCSK9 gene in two kindreds with premature cardiovascular disease and marked elevations in LDL-cholesterol (41). Complementary data emerged from another study of individuals with loss-of-function PCSK9 mutations, low PCSK9 activity, low LDL-cholesterol levels and a substantially lower prevalence of coronary events compared to controls (42). These and multiple subsequent studies laid the foundation for the development of various strategies to reduce circulating PCSK9 levels (Figure 1), including monoclonal antibodies to PCSK9. Evolocumab and alirocumab are fully humanized antibodies given by subcutaneous injection every 2 or 4 weeks. Bococizumab is partially humanized and a considerable proportion of study participants developed neutralizing antibodies to the drug, progressively reducing its LDL-cholesterol lowering effectiveness (43) and eventually causing discontinuation of development of bococizumab and premature stopping of the associated SPIRE trials. Large phase 3 trials showed that both evolocumab and alirocumab produce mean reductions in LDL-cholesterol of approximately 60% when added to standard statin treatment or when given alone, with a good safety profile (44,45). Both evolocumab and alirocumab became available for prescription in 2015, an impressive achievement considering that PCSK9 had been identified as an important player in lipid metabolism only 12 years earlier (41).

Cardiovascular outcome trials

Cardiovascular outcome RCTs with PCSK9 inhibitors are summarized in Table 3 (5,46,47). The trials all recruited participants with or at high risk of cardiovascular disease. Follow-up durations were relatively short at <3 years. Both FOURIER and ODYSSEY Outcomes provided robust data proving that inhibition of PCSK9 reduces cardiovascular events. The primary endpoint of each of these two trials was reduced by 15% over 2.2 and 2.8 years respectively. The beneficial effect of statins on cardiovascular outcomes is limited in the first year and greater in subsequent years (15). The cardiovascular outcome benefit in years 1 and 2 of FOURIER and ODYSSEY Outcomes was almost identical to that observed in CTT analyses per 38.7 mg/dL reduction in LDL-cholesterol over the same period of time (15).

No adverse safety outcomes emerged, with detailed testing confirming no effect on cognition in the EBBINGHAUS sub-study (conducted within FOURIER) (45) though it is important to highlight the relatively short duration of the relevant trials. However, monoclonal antibodies are expensive to produce, and although list prices have fallen from over $14,000 annually at launch in 2015, the use of PCSK9 inhibitors is still constrained by cost-effectiveness considerations (40,48).

OTHER AGENTS

Bile acid sequestrants (cholestyramine, colestipol and colesevelam), often referred to as resins, are seldom used outside specialist lipid clinics because they commonly cause gastrointestinal symptoms and the dose is inconveniently high at several grams a day. Lomitapide is an orally administered inhibitor of microsomal transfer protein which leads to reduced hepatic production of VLDL and thereby lower circulating VLDL and LDL. Mipomersen is an antisense oligonucleotide, given by subcutaneous injection, which acts by hybridizing to apo B100

messenger RNA thereby reducing VLDL assembly and reducing circulating VLDL and LDL. Lomitapide and mipomersen are only used in the treatment of homozygous familial hypercholesterolemia under expert supervision.

INVESTGATIONAL LDL-CHOLESTEROL LOWERING DRUGS CURRENTLY IN CARDIOVASCULAR OUTCOME TRIALS

BEMPEDOIC ACID

Bempedoic acid is a prodrug, converted in the liver to its CoA conjugate, an inhibitor of ATP-citrate lyase. This enzyme acts at an earlier step than HMG-CoA reductase (which is inhibited by statins) in the cholesterol biosynthesis pathway (Figure 1). Bempedoic acid is in late stage clinical development with a cardiovascular outcome study in progress. When given as monotherapy, the mean reduction in LDL-cholesterol at 12 weeks is 22% (net of placebo) (49).

The largest trial to date, the CLEAR Harmony Trial (50), included 2230 patients on statin therapy and allocated 1488 to bempedoic acid 180mg daily and 742 to placebo. Bempedoic acid produced a mean reduction in LDL-cholesterol of 18% (net of placebo) from the on-statin baseline level at 12 weeks. CLEAR Harmony showed that bempedoic acid probably has at least one important adverse effect. Gout occurred in 18 patients (1.2%) in the bempedoic acid group and 2 patients (0.3%) in the placebo group (p=0.03). As is generally appropriate for a drug safety analysis, the reported P-value was not corrected for the multiplicity of comparisons; nevertheless this is likely to be a real difference because there was also a highly significant increase in plasma uric acid in patients allocated to bempedoic acid compared with those on placebo (+0.73mg/dL vs. -0.06mg/dL, P<0.001). This has been attributed to inhibition of renal transport mechanisms by the glucuronide metabolite of bempedoic acid (50). In addition, muscle symptoms occurred in 195 patients (13.1%) allocated to bempedoic acid and 75 (10.1%) to placebo (p=0.05). New-

onset or worsening diabetes occurred less frequently in the bempedoic acid group than in the placebo group (3.3% versus 5.4%, p=0.02). These differences in muscle symptoms and diabetes may represent chance findings and should be regarded as hypothesis-generating. There was a notable difference in the percentage of patients discontinuing study treatment due to adverse events: 10.9% in the bempedoic acid group vs. 7.1% in the placebo group (p=0.005), not driven by any particular adverse event. In the much smaller CLEAR Serenity trial (49), a similar but nonsignificant pattern was observed: 18.4% vs. 11.7%, respectively.

The ongoing CLEAR Outcomes RCT, which will include an estimated 13,000 patients followed for about 4 years, is testing the effect of bempedoic acid on cardiovascular outcomes in patients with a history of statin intolerance. This trial may also clarify the bempedoic acid intolerance observed in CLEAR Harmony, and the possible muscle adverse effect and possible diabetes protective effect noted above.

PCSK9 SYNTHESIS INHIBITION

An alternative therapeutic approach to clearing PCSK9 from the bloodstream (discussed above) is to reduce its production by the hepatocyte. The double-stranded small interfering RNA (siRNA), inclisiran, inhibits PCSK9 synthesis by degrading the relevant mRNA and thereby preventing its translation into the PCSK9 protein (Figure 1). Advantages of inclisiran include its prolonged effect on PCSK9 levels and LDL-cholesterol, allowing it to be administered once every 6 months by subcutaneous injection, plus its stability at room temperature (monoclonal antibodies require refrigeration).

Inclisiran is currently being evaluated in the ORION program of RCTs. The ORION-1 trial was a placebo-controlled dose-ranging study, conducted in 501 patients at high risk for cardiovascular disease and elevated LDL-cholesterol, testing the effect of one injection (at

baseline) or two injections (at baseline and 3 months) of inclisiran over 6 months (51). A single 300 mg injection reduced LDL-cholesterol levels by 40.5% at 6 months while the two-injection approach reduced LDL-cholesterol by 54.4% compared to placebo.

Data regarding safety and effects on lipids of inclisiran 300 mg in three detailed phase 3 placebo-controlled trials, each with 18 months' follow up duration, will emerge over the next year, namely ORION-9 (conducted in ~500 participants with heterozygous familial hypercholesterolemia), ORION-10 (conducted in the US in ~1500 patients with established cardiovascular disease and elevated LDL-cholesterol) and ORION-11 (conducted in Europe and South Africa in ~1500 patients with cardiovascular disease and elevated LDL-cholesterol). ORION-4 is a placebo-controlled cardiovascular outcomes trial designed to evaluate the effect of treatment with inclisiran (added to standard care) on cardiovascular outcomes over about 5 years. The trial is being conducted in the UK and US, and recruitment began in late 2018.

FUTURE PERSPECTIVES

Statin therapy is low cost and safely reduces atherosclerotic cardiovascular events Absolute benefit is directly related to the absolute reduction achieved in LDL-cholesterol and the patient's risk of events. Combination with ezetimibe yields modest further reductions in LDL-cholesterol and cardiovascular risk, while combination with PCSK9 inhibitors lowers LDL-cholesterol to a greater extent and yields moderate cardiovascular risk reduction. Demonstration of cardiovascular benefit with bempedoic acid and the siRNA inclisiran in ongoing trials will further broaden the therapeutic armamentarium if they are safe and well tolerated. Other agents in earlier stages of development, also targeting PCSK9, include *PCSK9* gene editing and vaccination-like approaches (52,53). New lipid-modifying agents with novel mechanisms of action that target other lipids and may not substantially reduce LDL-cholesterol are being

explored (54). Examples include triglyceride-lowering agents which target regulators of lipoprotein lipase activity such as antisense oligonucleotide and siRNA inhibitors of apolipoprotein C3, and antisense oligonucleotides, monoclonal antibodies and siRNA to angiopoietin-like 3. Genetic studies suggest such approaches may be fruitful if sufficient reductions in apolipoprotein B levels can be achieved (55).

Given the very low LDL-cholesterol levels which can be achieved with combinations of currently available medicines in most patients, new LDL-cholesterol lowering agents will need to demonstrate cost-effectiveness as well as cardiovascular outcome benefit to have a major role in clinical care. Indeed, developers of new agents for atherosclerotic disease face challenges that are at least as much economic as scientific (56).

Bullet points

- Genetic studies and randomized trials demonstrate that lower LDL-cholesterol leads to reductions in atherosclerotic vascular events
- The cardiovascular benefit of lowering LDL-cholesterol is related to duration of treatment and the absolute reduction in LDL-cholesterol
- Monoclonal antibodies to PCSK9 reduce LDL-cholesterol by approximately 50% and recent trials confirm reductions in cardiovascular disease
- Ongoing trials of bempedoic acid and inclisiran will establish the position of these novel agents in the therapeutic armamentarium

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Figure Legends

Figure 1 (and CENTRAL ILLUSTRATION).

Schematic diagram of the mechanisms of action of statins, PCSK9 inhibitors, PCSK9 synthesis inhibitors and bempedoic acid

Targets of LDL-cholesterol lowering agents represented in the Figure are shown in orange text. Bempedoic acid (1) and statins both inhibit steps in the synthesis of cholesterol in the hepatocyte, reducing available cholesterol; ezetimibe (3) inhibits the action of the transporter NPC1L1, reducing intestinal absorption of dietary and biliary cholesterol which reduces the delivery of chylomicron cholesterol to the hepatocyte via the portal circulation; monoclonal antibodies to PCSK9 (4) bind to PCSK9 within the circulation while inclisiran (5) targets messenger RNA for PCSK9 within the hepatocyte and both strategies lower circulating PCSK9, reducing lysosomal degradation of LDL receptors. All strategies ultimately lead to upregulation of LDL receptor expression by the hepatocyte.

Figure 2.

Timeline of completed and ongoing LDL-cholesterol lowering cardiovascular outcome trials

The figure plots major cardiovascular outcome trials of statins, ezetimibe and PCSK9 inhibitors completed since 1994, along with ongoing trials of statins, bempedoic acid and PCSK9 synthesis inhibition.

Figure 3.

The effect of lowering LDL-cholesterol on major cardiovascular events, stratified by the duration of treatment

The figure plots results for statin, PCSK9 inhibitor and ezetimibe outcome trials conducted in primary and secondary prevention populations according to their effects on cardiovascular outcomes and the difference in LDL-cholesterol at 1 year (grouped according to duration of follow up [less than (in red) or greater than (in black) 4 years]). The position and area of boxes represent effect estimates and weight of trial results respectively, while vertical lines represent 95% confidence intervals. For each group of trials, the regression lines shown are forced to have zero intercept with the slope equal to the inverse-variance-weighted average of the standardised trial results.

Table 1. Results from three landmark placebo-controlled cardiovascular outcome trials of statin therapy

Trial (intervention)	**N**	**Description of participants**	**y**	**LDL-C reduction at 1 year**	**Outcome**	**n statin**	**n placebo**	**Result (95% CI)**
4S (12) (simvastatin 20-40mg daily)	4444	Angina or previous MI, hypercholesterolemia	5.4 years	68 mg/dL	All cause death*	182	256	Rel R 0.70 (0.58-0.85)
					Major CHD events†	431	622	Rel R 0.66 (0.59-0.75)
WOSCOPS (13) (pravastatin 40mg daily)	6595	Men, hypercholesterolemia	4.9 years	41 mg/dL	CHD death or non-fatal MI*	174	248	HR 0.69 (0.57-0.83)
					Non-fatal MI†	143	204	HR 0.69 (0.55-0.85)
HPS (14) (simvastatin 40mg daily)	20,536	CHD, other occlusive arterial disease, or diabetes	5.0 years	50 mg/dL	All cause death*	1328	1507	RR 0.87 (0.81-0.94)
					CHD death*	587	707	RR 0.82 (0.74-0.92)
					Major CHD events†	898	1212	RR 0.73 (0.67-0.79)
					Major vascular events†	2033	2585	RR 0.76 (0.72-0.81)

4S is the Scandinavian Simvastatin Survival Study; WOSCOPS is the West of Scotland Coronary Prevention Study; HPS is the Heart Protection Study.

N = total randomized patients, n = patients with outcome events in each group, y = average duration of follow-up in years. LDL-C = LDL-cholesterol. CHD = coronary heart disease. MI = myocardial infarction. Rel R = relative risk. HR = hazard ratio. RR = rate ratio. CI = confidence interval

*primary outcome, †secondary outcome

Table 2. The effect of statin therapy on major cardiovascular outcomes – data from 170,000 participants in 26 trials

Outcome	**n statin / intensive statin**	**n control / moderate intensity statin**	**Unweighted RR**	**RR per 38.7 mg/dL lower LDL-C**
STATIN vs. CONTROL (n=129,526 in 21 trials, achieved difference in LDL-cholesterol 41.4 mg/dL) (15)				
Non-fatal MI	2310	3213	0.71 (99% CI 0.66-0.76)	0.74 (99% CI 0.69-0.78)
CHD death	1242	1587	0.78 (99% CI 0.71-0.86)	0.80 (99% CI 0.73-0.86)
Coronary revascularization	3103	4066	0.75 (95% CI 0.72-0.79)	0.76 (95% CI 0.73-0.80)
Ischemic stroke	987	1225	0.80 (99% CI 0.72-0.89)	0.80 (99% CI 0.73-0.88)
HIGH INTENSITY STATIN vs. MODERATE INTENSITY STATIN (n=39,612 in 5 trials, achieved difference in LDL-cholesterol 19.7 mg/dL) (15)				
Non-fatal MI	1175	1380	0.85 (99% CI 0.76-0.94)	0.71 (99% CI 0.58-0.87)
CHD death	645	694	0.93 (99% CI 0.81-1.07)	0.85 (99% CI 0.63-1.15)
Coronary revascularization	2250	2741	0.81 (95% CI 0.76-0.85)	0.66 (95% CI 0.60-0.73)

Ischemic stroke	440	526	0.84 (99% CI 0.71-0.99)	0.69 (99% CI 0.50-0.95)

n = number of patients in each group with outcome events

LDL-C = LDL-cholesterol. CHD = coronary heart disease. MI = myocardial infarction. RR = rate ratio. CI = confidence interval

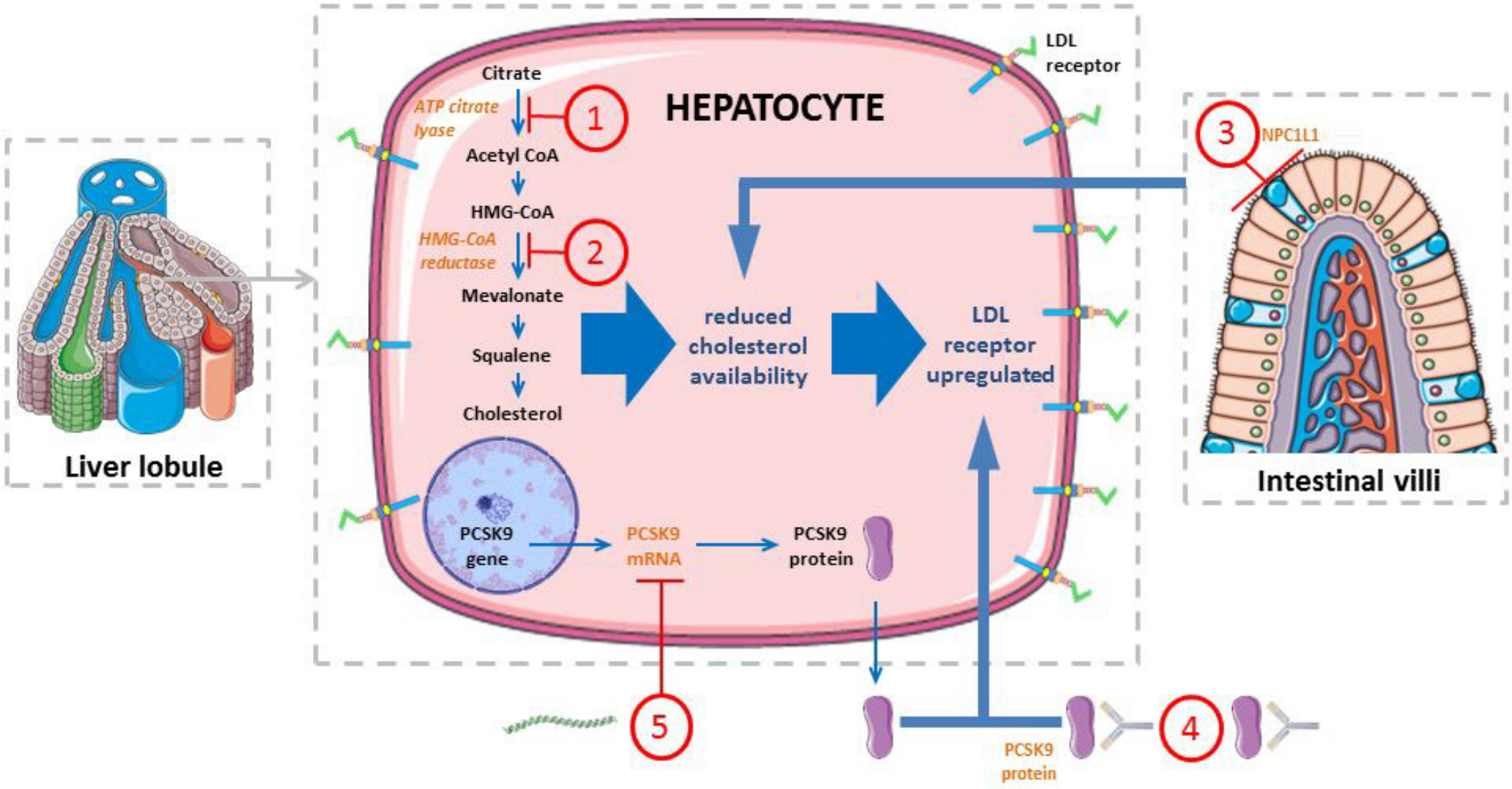
Table 3. Results from placebo-controlled cardiovascular outcome trials of PCSK9 inhibitor treatment

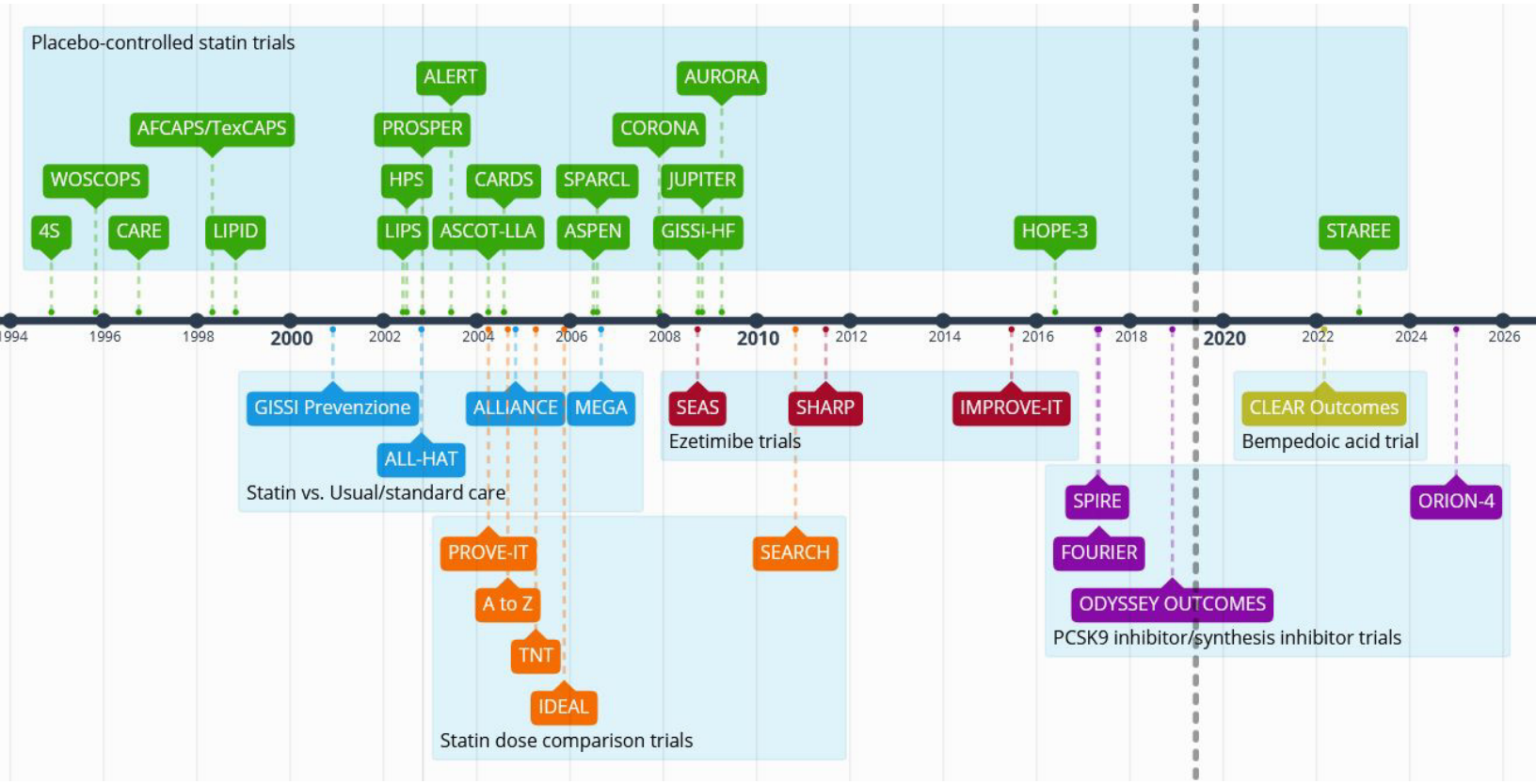
Trial (intervention)	N	Description of participants	y	LDL-C reduction	Outcome	n PCSK9i	n placebo	Result (95% CI)
FOURIER (5) (evolocumab 140mg every 2 weeks or 420mg monthly)	27,564	CVD, elevated LDL-C	2.2 years	56 mg/dL (at 52 weeks)	CVD death, MI, stroke, hospitalization for UA, or coronary revascularization*	1344	1563	HR 0.85 (0.79-0.92)
					CVD death, MI, or stroke†	816	1013	HR 0.80 (0.73-0.88)
ODYSSEY Outcomes (47) (alirocumab 75mg every 2 weeks)	18,924	Recent ACS, elevated LDL-C, non HDL-C or apo B	2.8 years	48 mg/dL (at 52 weeks)	CHD death, nonfatal MI, ischemic stroke, or hospitalization for UA*	903	1052	HR 0.85 (0.78-0.93)
					Major CHD event†	793	899	HR 0.88 (0.80-0.96)
					Any CVD event†	1301	1474	HR 0.87 (0.81-0.94)
SPIRE-1 and SPIRE-2 (46) (bococizumab 150mg every 2 weeks)	27,438	CVD or high risk	10 months	51 mg/dL (at 52 weeks)	nonfatal MI, nonfatal stroke, hospitalization for UA requiring urgent revascularization, or CVD death*	352	397	HR 0.88 (0.76-1.02)

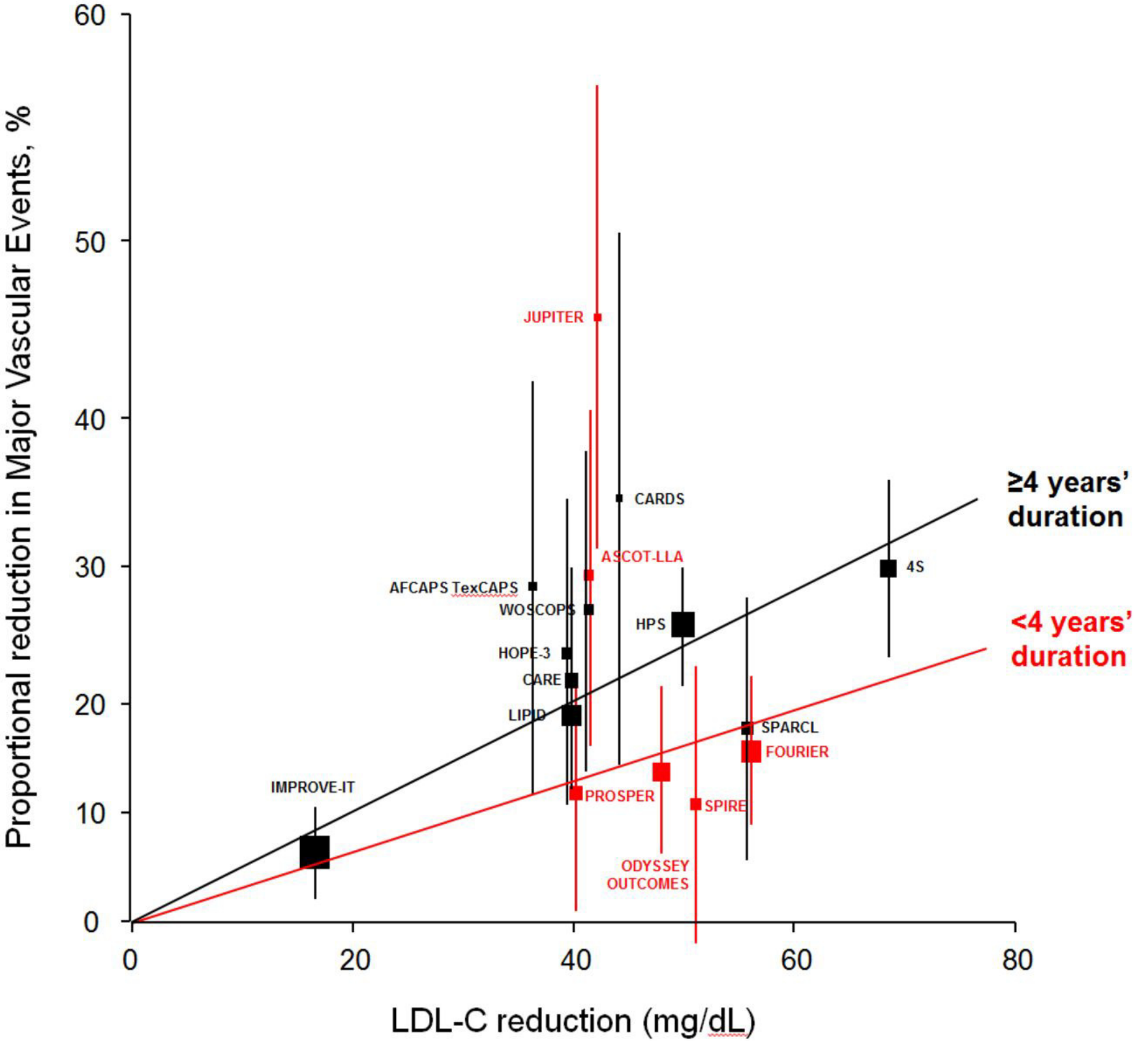
N = total randomized patients, n = patients with outcome events in each group, y = average duration of follow-up in years.

LDL-C = LDL cholesterol. Non HDL-C = non HDL cholesterol. Apo B = apolipoprotein B. ACS = acute coronary syndrome. MI = myocardial infarction. CVD = cardiovascular disease. CHD = coronary heart disease. HR = hazard ratio. CI = confidence interval. UA = unstable angina.

*primary outcome, †secondary outcome


Liver lobule
HEPATOCYTE
Citrate
ATP citrate lyase
1
Acetyl CoA
HMG-CoA
HMG-CoA reductase
2
Mevalonate
Squalene
Cholesterol
reduced cholesterol availability
LDL receptor upregulated
LDL receptor
PCSK9 gene
PCSK9 mRNA
PCSK9 protein
5
4
PCSK9 protein
3
NPC1L1
Intestinal villi


Placebo-controlled statin trials
4S
WOSCOPS
CARE
AFCAPS/TexCAPS
LIPID
ALERT
PROSPER
HPS
LIPS
CARDS
ASCOT-LLA
SPARCL
ASPEN
AURORA
CORONA
JUPITER
GISSI-HF
HOPE-3
STAREE
1994
1996
1998
2000
2002
2004
2006
2008
2010
2012
2014
2016
2018
2020
2022
2024
2026
GISSI Prevenzione
ALL-HAT
ALLIANCE
MEGA
Statin vs. Usual/standard care
SEAS
SHARP
IMPROVE-IT
Ezetimibe trials
CLEAR Outcomes
Bempedoic acid trial
SPIRE
FOURIER
ODYSSEY OUTCOMES
ORION-4
PCSK9 inhibitor/synthesis inhibitor trials
PROVE-IT
A to Z
TNT
IDEAL
SEARCH
Statin dose comparison trials


Proportional reduction in Major Vascular Events, %
LDL-C reduction (mg/dL)
0
10
20
30
40
50
60
0
20
40
60
80
JUPITER
CARDS
ASCOT-LLA
4S
AFCAPS TexCAPS
WOSCOPS
HPS
HOPE-3
CARE
LIPID
SPARCL
FOURIER
IMPROVE-IT
PROSPER
SPIRE
ODYSSEY OUTCOMES
≥4 years' duration
<4 years' duration