Cardiol Ther (2019) 8:5–20
https://doi.org/10.1007/s40119-018-0123-0

REVIEW

Pharmacological Options in Atherosclerosis: A Review of the Existing Evidence

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Received: October 16, 2018 / Published online: December 12, 2018

ABSTRACT

Coronary heart disease (CHD) is the leading cause of mortality worldwide and high low-density lipoprotein (LDL) cholesterol levels have been shown to be key in the pathogenesis of this condition. Lipid control has therefore been the subject of decades of research and has led to many large and robust randomized controlled trials, as well as the highest grossing drug of all time—Lipitor (atorvastatin). Statin therapy has long been indicated for secondary and more recently primary prevention. However, despite the large-scale use of statins, CHD prevalence remains high, and some patients do not respond to statin therapy. There has been a large push to find and test alternative lipid-lowering agents, these include fibrates, cholesterol absorption inhibitors, and proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors. It is the aim of this review to assess the literature surrounding each of these groups of drugs.

Keywords: Cholesterol absorption inhibitor; Fibrates; Lipid; LDL; PCSK-9 inhibitor; Statin

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INTRODUCTION

Atherosclerosis is a chronic inflammatory process that leads to arterial lumen narrowing [1, 2]. Its pathophysiology is complex (Fig. 1), involving endothelial dysfunction, intimal thickening, and atheromatous plaque formation [3]. Plaque rupture forming a thrombus, or continued plaque growth leading to stenosis, can both occlude arteries leading to ischemia and infarction [4–7]. Heart disease (including coronary heart disease, hypertension, and stroke) remains the number one cause of death in the US. Coronary heart disease is the leading cause (43.8%) of deaths attributable to cardiovascular disease in the US, followed by stroke (16.8%), heart failure (9.0%), high blood pressure (9.4%), diseases of the arteries (3.1%), and other cardiovascular diseases (17.9%) [8].

Elevated low-density lipoprotein cholesterol (LDL-C) is a major risk factor for CHD [9]. This is because of its crucial role in the promotion, development, and progression of atherosclerosis [10]. Clinical evidence has shown a 10%

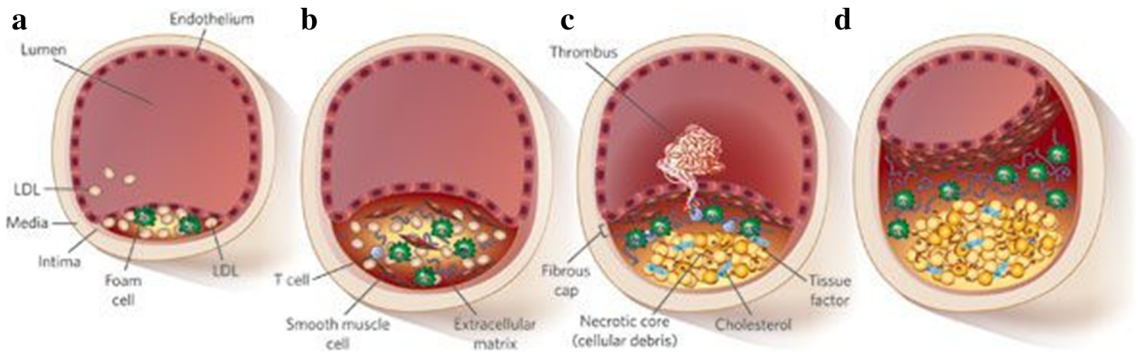


Fig. 1 **a** Atherogenic lipoproteins such as low-density lipoproteins (LDLs) entering the intima are modified, by oxidation or enzymatic activity, and aggregate within the extracellular intimal space. Unregulated uptake of these lipoproteins by macrophages generates foam cells and fatty streaks. These are usually asymptomatic. **b** Vascular smooth muscle cells secrete large amounts of extracellular-matrix components, such as collagen, which increase the retention and aggregation of atherogenic lipoproteins. The inflammatory state is potentiated by monocyte and leukocyte recruitment. As the plaque grows, compensatory remodeling (adaptive intimal thickening) occurs to preserve the lumen diameter. **c** Foam cells eventually die and release cellular debris, which forms a necrotic core. Smooth muscle cells form a fibrous cap beneath the endothelium, which walls off the plaque from the blood. **d** The advanced lesion can either rupture or continue to grow, eventually leading to clinically significant obstructive disease. Reproduced by permission from Springer Nature, Nature, Translating molecular discoveries into new therapies for atherosclerosis, Daniel J. Radar & Alan Daugherty (2008, Vol 451, 904-913)

increase in LDL-C to increase CHD risk by 20% [11]. A large multi-center trial [12] in 52 countries found that dyslipidemia accounted for nearly 50% of risk for developing myocardial infarction (MI). Furthermore, the Cholesterol Treatment Trialists' (CTT) Collaboration confirmed that lowering LDL-C reduces cardiovascular disease (CVD) in a dose-dependent relationship [13].

Therefore, multiple guidelines [14–16] identify lipid management targets, specifically LDL-C, as the focus for reducing cardiovascular risk [17]. Patients with a higher cardiovascular (CV) risk require greater reductions in their LDL-C or lower absolute LDL-C targets compared to those with a lower overall CV risk [14]. Additionally, a recent review [10] found that nine guidelines out of 12 recognized LDL-C as the primary target for reducing CHD risk.

This review will evaluate the current evidence for the treatment options in atherosclerosis by comparing statins with other lipid-lowering drugs. These are fibrates, cholesterol absorption inhibitors, and proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

STATINS

Currently, statins are the first-line treatment in primary and secondary prevention of cardiovascular disease [18]. They work by inhibiting the rate-limiting enzyme in cholesterol biosynthesis—3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase [19]. The body responds to this by upregulating the hepatocyte LDL receptors (LDL-R). This increases hepatic uptake of LDL-C from the circulation [19].

Secondary Prevention

Many clinical trials have been conducted to show the efficacy of statins in different patient CHD risk groups. For example, the 4S group [20] randomized 4444 high-risk patients (i.e., with a history of CHD and elevated LDL-C) into an

intervention or placebo group. Over 5.4 years, the statin group had lower total cholesterol and LDL-C levels. Long-term simvastatin therapy was concluded to reduce coronary mortality and major coronary events in high-risk CHD patients. The advantages of this study are the large sample size, long-term follow-up (importantly with no loss-to follow up), and the clinically relevant primary end point. However, the low percentage (19%) of women enrolled makes a positive conclusion hard to extrapolate to the female sub-group.

Other studies examined statin effects in lower-risk groups. The LIPID trial [21] demonstrated pravastatin to reduce CHD mortality, all-cause mortality, and cardiovascular events in patients with broad baseline cholesterol levels (Fig. 2). The CARE trial [22] showed the efficacy of statins in reducing coronary events and stroke in patients with average cholesterol levels. However, the trial was based in the USA and Canada and underrepresented ethnic groups. Therefore, caution must be applied when generalizing conclusions to other populations, as other factors such as diet and ethnicity are known to be confounders for CHD [23].

Sub-group analysis from both trials [24, 25] demonstrated that statins reduce the frequency of cardiovascular events in diabetics and non-diabetics with impaired fasting glucose. The LIPID analysis also showed a reduction in absolute risk of stroke [24]. It is likely, however, that in both studies, the incidence of other co-morbidities, such as obesity and hypertension, was higher in the diabetic group than the placebo. These are known risk factors for CHD [26], which are hard to control. Better steps could be taken to match these baseline characteristics in both groups, as was done in the 4S trial [20].

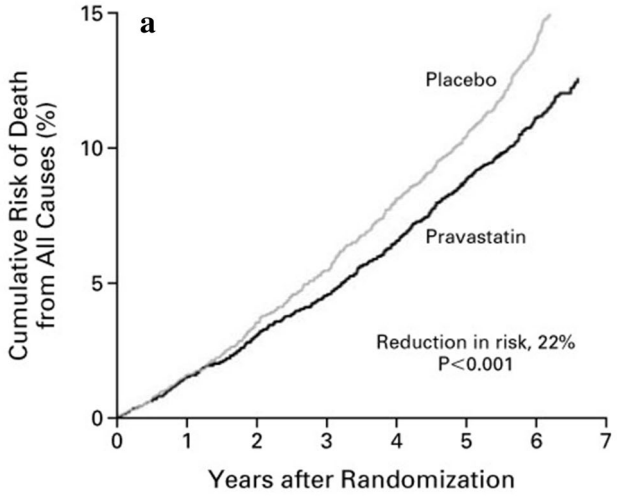
The Heart Protection studies (HPS) [27, 28] backed up these results. Simvastatin significantly reduced rates of MI, stroke, and revascularization in high-risk and diabetic groups irrespective of their initial cholesterol levels. The size of the benefit was dependent on their overall risk of major vascular events rather than their blood lipid concentrations. They therefore advocated for statin use to be considered for patients at risk of any vascular, not just cardiovascular, events. The US Food and Drug Administration (FDA) changed simvastatin indications to those at high-risk of vascular events rather than just for those with high cholesterol following this publication [29].

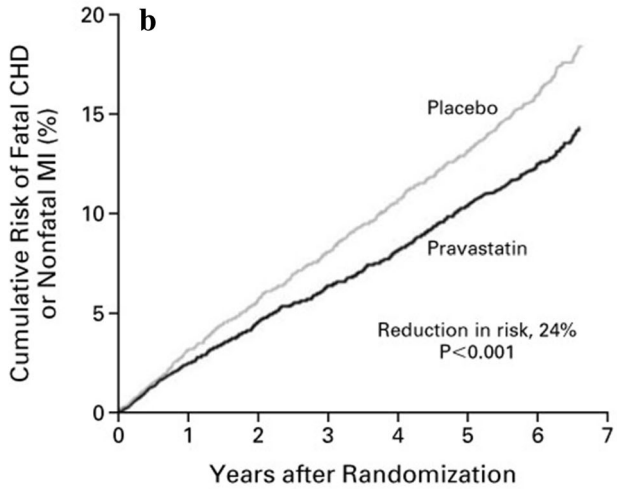
Primary Prevention

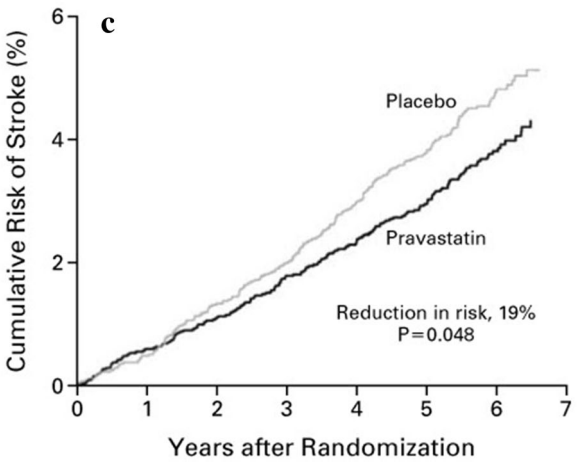
Statin efficacy was taken a step further and shown to be beneficial even in primary prevention. The WOSCOP [30] found that pravastatin reduced the relative risk of coronary events, and deaths from all cardiovascular causes in addition to lowering LDL-C by 26%. The study was robust in the sense that sub-group analysis demonstrated the effect to be independent of age, smoking status, and other vascular risk factors. An important study limitation, however, is the inclusion of only males with severe hypercholesterolemia.

More recently, a 20-year WOSCOPS follow-up [31] showed that 5-year statin treatment reduced cardiovascular disease outcomes over two decades. This observation may be due to the relatively young age of patients receiving the initial treatment (mean age, 55 years). Nevertheless, the results show a clear benefit with statins throughout the "lifetime period for risk of cardiovascular morbidity and mortality", and therefore show their advantage in primary prevention.

The AFCAP study [32] analyzed statin use in primary prevention in patients with average cholesterol levels. It concluded that lovastatin "reduces the risk for the first major coronary event in men and women". However, there was a lack of explanation on their method of randomization, which is concerning considering such a large sample size. These results were reproduced by a 2008 meta-analysis [33] and a 2013 systematic review [34]. Another meta-analysis specifically assessing primary prevention in the elderly also found a reduction in vascular events but no significant effect on all-cause or cardiovascular mortality [35]. However, in addition to vascular event benefits, an 11-year follow-up of the ASCOT-LLA trial [36, 37] showed a reduction in all-cause mortality.


a
Cumulative Risk of Death from All Causes (%)
Placebo
Pravastatin
Reduction in risk, 22%
P<0.001
Years after Randomization


b
Cumulative Risk of Fatal CHD or Nonfatal MI (%)
Placebo
Pravastatin
Reduction in risk, 24%
P<0.001
Years after Randomization


c
Cumulative Risk of Stroke (%)
Placebo
Pravastatin
Reduction in risk, 19%
P=0.048
Years after Randomization

◀**Fig. 2** Kaplan–Meier estimates of the incidence of major secondary outcomes in the pravastatin and placebo groups. **a** Mortality from all causes. **b** Death due to coronary heart disease (CHD) or nonfatal myocardial infarction (MI). **c** Stroke of any type. The graphs show a reduction in risk in the pravastatin group for all-cause mortality, cardiovascular events, and stroke. For every 1000 patients in the pravastatin group, the analysis showed that death from any cause was avoided in 30 patients, death due to CHD or nonfatal MI in 35 patients, and stroke in eight patients. Reproduced by permission from Elsevier, NEJM, Prevention of Cardiovascular Events and Death with Pravastatin in Patients with Coronary Heart Disease and a Broad Range of Initial Cholesterol Levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group 1998;Vol 339(19):1349–1357

Adverse Effects

As with all drugs, statins are not free from adverse effects (AEs). In 2013, 17% of 100,000 patients taking statins reported AEs and 10% discontinued therapy [38]. However, the study used secondary retrospective data, which may have resulted in misinterpretation and incomplete documentation. When patients who discontinued were rechallenged, it was found that many (92.2%) could eventually tolerate statins long-term. This was supported by a meta-analysis, which found AEs to be 'uncommon', and discontinuation rates to be no higher than placebo [39]. One possible explanation for the discrepancy in AEs reported in RCTs and real-world observations is that RCTs use a run-in period, which excludes those who are intolerant to statins from the randomization process, thereby artificially decreasing the AE rate. However, a meta-analysis comparing trials with and without a run-in phase found a similar adherence rate discrediting this theory [40]. This pattern of conflicting evidence is preserved throughout trials monitoring statin AEs, making it difficult to establish their true risk.

Myopathies are the most common reported AE [41], ranging from myalgia to rhabdomyolysis. Again, the reported incidence of myalgia is variable, ranging from 1 to 20% [42–44]. The FDA [45] cautioned against high simvastatin doses in 2012 due to large studies reporting increased myopathy risks [46].

Previous epidemiological studies have suggested lowering total cholesterol levels and cancer are correlated. Studies have detected an increased risk of specific cancers in specific populations such as the elderly [47, 48] or in

Table 1 Summary of the effects of statins on LDL-C and vascular events and mortality Modified by permission from Elsevier: American Journal of Cardiology. Review of Primary and Secondary Prevention Trials with Lovastatin, Pravastatin, and Simvastatin, Antonio M. Gotto Jr (2005, Volume 96(5)S:34–38)

	Trial	LDL-C post-treatment (% reduction)	Placebo event* rate (%)	Statin event* rate (%)	RRR (%)	ARR (%)	NNT
High baseline CHD risk ↓ Low CHD risk	4S	35	28.0	19.4	31	8.6	12
	HPS	29	25.4	19.9	22	5.5	18
	LIPID	25	15.9	12.3	23	3.6	28
	CARE	32	13.2	10.2	23	3.0	34
	WOSCOPS	26	7.5	5.3	29	2.2	46
	AFCAPS	25	5.5	3.5	36	2.0	50

Major trials are arranged in order of descending levels of baseline population CHD risk

**4S* nonfatal MI or coronary death, *LIPID, CARE, WOSCOPS* nonfatal MI or coronary artery disease death, *HPS* major vascular events (total CHD, total stroke, and revascularizations), *AFCAPS* nonfatal or fatal MI, unstable angina or sudden cardiac death, *RRR* relative risk reduction, *ARR* absolute risk reduction, *NNT* number-needed to treat

patients with a positive history of breast or prostate cancer [22, 49]. However, this risk has been refuted, with more recent studies finding no increased risk of any cancer type with any statin [50–53]. In fact, recent evidence suggests that statins may be chemoprotective for certain cancers, such as esophageal [54], hepatocellular [55], and colorectal [56].

Summary of Effect

The major trials are summarized in Table 1. This shows the relative risk reduction (RRR) of event rates is fairly consistent between trials in primary and secondary prevention, and between high and low CHD risk groups (24–37%). Therefore, the greater the baseline CHD risk, the greater the statin benefit. This is shown in Table 1, as the absolute risk reduction increases with increasing CHD risk.

ALTERNATIVE PHARMACOLOGICAL AGENTS

While statins are largely effective, studies have shown some patients to still have CVD risk following statin therapy, despite achieving LDL-C targets [57–59]. This may be due to other CVD risk factors such as triglycerides and high-density lipoprotein cholesterol (HDL-C). Therefore, alternative therapies to statins may be useful in modifying these metabolic markers and therefore helping reduce this residual CVD risk.

Fibrates

Fibrates alter lipid metabolism by activating peroxisome proliferator-activated receptor-alpha (PPARα) [60, 61]. They reduce plasma triglycerides by inducing fatty-acid β-oxidation [62] and lipoprotein lipase activity [63]. Additionally, fibrates increase HDL-C by promoting apolipoprotein A I and II synthesis [64] and reducing cholesterol ester transfer protein activity [65].

Randomized controlled clinical trials have shown fibrate monotherapy to increase HDL-C by 10–50% [66, 67] and decrease triglycerides by 20–50% [68]. Compared to statins, these HDL-C and triglyceride effects are much greater. Because statins mainly work by altering LDL-C, the results of this comparison are not surprising.

Secondary Prevention

A trial assessed the effects of gemfibrozil in secondary prevention in 2531 men [69]. The fibrate group exhibited an overall increase in HDL-C and reduction in triglycerides with no change in LDL-C compared with placebo. This manifested as a significant risk reduction in major cardiovascular events (similar to the reduction seen in the LIPID and CARE statin trials). There was no significant reduction in all-cause mortality as statins demonstrate. However, the study cannot be fully compared to statin trials, as men with low LDL-C were recruited. Therefore, the clinical outcome measures are achieved through changes in HDL-C rather than LDL-C with statin therapy. It is therefore unreasonable to extrapolate these conclusions to the atherosclerotic population who generally have elevated LDL-C. Furthermore, such an efficacious result was not seen in the similar BIP study [70], which found only a 9.4% reduction in major CHD (compared to 22%) that was restricted to nonfatal events. A possible explanation for this is due to the higher baseline LDL-C levels. Although the study produced a more favorable reduction in all lipid parameters, it did not manifest via a reduction of coronary events. Therefore, there is debate about whether fibrates result in an improved clinical end-point or just have beneficial metabolic effects.

A Cochrane review [71] found that fibrate therapy did not prevent composite outcomes such as non-fatal stroke, non-fatal MI, or vascular death in patients with CHD. However, they were significant in preventing MI. Most trials studied in this review compared fibrate to placebo therapy. More research needs to be conducted exploring the addition of fibrates to established statin therapy to investigate additional benefit.

Primary Prevention

In the FIELD trial [72], fenofibrate did not significantly reduce the risk of major coronary events in diabetic patients. This may have been due to a larger proportion of patients in the placebo group taking statins compared to the intervention group. Another study found contradicting results [73], however direct comparisons are limited due to different baseline patient characteristics and lipid profiles. When analyzing statin effects, this was not a problem, as statins consistently demonstrated significant efficacy across all patient risk-groups in both primary and secondary prevention.

A Cochrane review [74] found that fibrate in addition to statin therapy did not result in reduction of CVD death, non-fatal MI/stroke compared to statin therapy alone. It also found only a moderate reduction in these outcome measures when comparing fibrates to placebo. Given the low baseline risk of the patients studied in the primary prevention trials, the number needed to treat to prevent one CVD event in 5 years was calculated to be 125.

Adverse Effects

Generally, studies have demonstrated a good tolerability with fibrates [75]. Common reported AEs include mild musculoskeletal and gastrointestinal symptoms [67, 77]. Rhabdomyolysis was reported in three patients in the FIELD study [72], which is fewer than in statin trials.

Another AE found with fibrates is their effect on glomerular filtration rate (GFR). A double-blind placebo-controlled trial showed finofibrate reduced GFR by 20% [76]. Other studies have shown this effect to reverse following drug discontinuation [77]. On the other hand, statins have shown to have renal protective properties especially in patients at high cardiovascular risk [78].

Cholesterol Absorption Inhibitors

The main cholesterol absorption inhibitor used is ezetimibe, which inhibits intestinal brush-border absorption of dietary and biliary cholesterol. The liver responds to this by upregulating LDL receptors to increase LDL clearance from the blood [14].

Ezetimibe has been shown to significantly reduce serum LDL-C levels [79]. A meta-analysis demonstrated an 18.6% reduction [80]. However, this analysis pooled data from patients with familial and non-familial hypercholesterolemia, which may have lead to statistical heterogeneity. Furthermore, two large trials [81, 82] made up a large proportion (63%) of the patients analyzed. Since these trials found a positive correlation, they may have skewed the final result. Statins generally reduced LDL-C more (by 25–35%) (Table 1).

Combination Therapy

Due to the efficacy of statins in improving clinically relevant end-points, there are a limited number of trials comparing ezetimibe monotherapy with statin monotherapy. One such study [83] failed to demonstrate a significant improvement with ezetimibe in vascular events and all-cause mortality. The majority of trials therefore focus on adding ezetimibe to a statin in combination therapy.

Ezetimibe overcomes the statin "rule-of-six" [84], which dictates that doubling the statin dose only achieves an additional 6% reduction in LDL-C. In patients with primary hypercholesterolemia, LDL-C lowering was 21% greater when given stain + ezetimibe combination therapy compared to statin + placebo [84]. These results were backed up by a large meta-analysis, showing a significant LDL-C reduction with statin-ezetimibe combination therapy enabled more patients to achieve their LDL-C ATP III treatment targets [85].

Earlier trials demonstrating the clinical efficacy of combination therapy were ambiguous. The ENHANCE study [86] failed to show a significant difference in the surrogate end-point, carotid-artery-intima-media thickness (CIMT), in subjects with familial hypercholesterolemia, despite lowering LDL-C. This was contradicted by another similar trial, which reported a regression of CIMT with combination therapy versus statin alone [87].

However, the baseline and overall CIMT change was significantly lower in the ENHANCE study compared to the other trial, despite

similar LDL-C effects. This suggests that more of the ENHANCE population were subject to previous statin treatment, which is common in patients with familial hypercholesterolemia.

Therefore, their carotid arteries may have been devoid of lipid resulting in reduced treatment responsiveness. The measurable incremental changes in carotid atherosclerosis are limited by the low baseline CIMT. Furthermore, the use of CIMT as a marker of atherosclerosis has been questioned, as two meta-analyses have found no significant relationship between CIMT progression and future vascular events or all-cause mortality [88, 89].

Two randomized controlled clinical trials (SEAS [90] and SHARP [91]) have shown a benefit in reducing cardiovascular events with combination therapy versus placebo. This was in proportion to the degree of LDL-C reduction. The reduction in event rate was similar to that seen in the CTT meta-analysis of 14 statin trials [92].

Adverse Effects

Trials with ezetimibe generally show it to induce fewer complications than statins. Life-threatening liver failure has been rarely documented [93–95] and a meta-analysis with 14,471 subjects showed no statistically significant elevation in liver enzymes with combination therapy versus placebo [85]. Ezetimibe is also not associated with an increased risk of myositis compared with statin monotherapy or placebo [96]. An analysis of three trials suggested there could potentially be a weak link between ezetimibe and cancer [97], however the authors concluded that there was no credible evidence to suggest this. A meta-analysis assessing the safety of ezetimibe also concluded there was no significant effect on the risk of cancer [98].

PCSK9 (Proprotein Convertase Subtilisin/Kexin Type 9) Inhibitors

The role of the pro-protein convertase PCSK9 in lipid metabolism was first characterized in 2003, following genetic studies in three families with autosomal dominant familial hypercholesterolemia [99]. In this population, gain-of-function mutations were identified in the PCSK9 gene, leading to higher plasma LDL-C and a higher risk of cardiovascular events [99]. Additional research found that rarer loss-of-function mutations were associated with reduced plasma LDL-C levels. It was therefore extrapolated that inhibition of PCSK9 may provide a useful therapeutic target for LDL-C reduction [100, 102].

PCSK9 is mainly secreted by liver hepatocytes where its action is to bind to LDL-receptors at the cell surface, promoting their internalization and degradation. As a result, fewer LDL-receptors are expressed and plasma LDL-C concentrations increase [99, 101–104]. Inhibition of PCSK9's action will therefore lead to a greater expression of LDL-R's and an increase in plasma LDL-C clearance [105].

Efficacy

The most well studied of the PCSK9 inhibitor is evolocumab, which is a complete human monoclonal antibody. Given the established efficacy of statin therapy, almost all clinical trials focus on using evolocumab as part of combination therapy rather than monotherapy.

The Laplace 2 trial was a randomized, placebo-controlled, and ezetimibe-controlled trial. It showed that the addition of evolocumab to both low- and high-dose statin groups led to a further reduction of LDL-C of 63–75% when given as a monthly dose. It also reported that the additional LDL-C reduction with evolocumab (up to 66%) was significantly greater than that achieved with ezetimibe (up to 24%) [106]. It must be noted that this study was limited by its duration of only 12 weeks and small sample group sizes [106].

Blom et al. corroborated the findings from Laplace 2. Patients were initially started on a range of treatments (from diet control to high-dose statin) based on their ATP-III defined cardiovascular risk. After a run-in period of 4–-12 weeks, evolocumab was added to each treatment arm [107]. In all groups, LDL-C was significantly reduced. This included those who were already on a high-dose statin and 10 mg ezetimibe where a further 49% reduction in LDL-C was shown over 52 weeks. The ability of

PCSK-9 inhibitors to reduce LDL-C has also been replicated in other large randomized controlled trials [108]. However, due to the short follow-up periods and variability/lack of patients in the trial arms, clinically relevant end-points were either not the aim of these trials or were difficult to determine.

The largest trial of its kind to assess the effect of PCSK-9 inhibitors on cardiovascular end points was the FOURIER trial [109]. This trial confirmed the findings of several previous trials with regard to evolocumab's LDL-C potential [106–108]. They showed a mean reduction of 59% in LDL-C when compared to placebo controls. This reduction was sustained over a mean period of 2.2 years. The main outcomes of this study were to determine the effect of PCSK9 inhibitors on cardiovascular outcomes. They were able to show a significant reduction of 15% in the primary efficacy end point of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina or coronary revascularization. They also reported a 20% reduction in their key secondary end-point of cardiovascular death, myocardial infarction, or stroke. These results suggest that the combination of the LDL-C lowering potential of evolocumab and statin work synergistically to reduce the risk of cardiovascular events. Despite this, the 2.2-year follow-up raises questions as to whether the longer-term benefits demonstrated with other lipid-lowering agents will be likewise sustained with PCSK-9 inhibitors [109].

A recent systematic review and meta-analyses, which included 35 randomized control trials (45,539 patients), was performed to determine the efficacy of the PCSK9 inhibitors alirocumab and evolocumab. It demonstrated that although there is a statistically significant reduction in cardiovascular events such as stroke and MI, there is no statistically significant reduction in all-cause or cardiovascular mortality. The baseline LDL-C level for patients in these analyses was relatively normal at 106 mg/dl. However, meta-regression analysis showed that patients who had higher baseline LDL-C were more likely to benefit from PCSK9 treatment [110]. This could therefore explain the non-significant reduction in overall mortality. Nevertheless, a Cochrane review including 20 studies (67,237 patients) showed a decreased risk of cardiovascular events but had no significant effect on overall mortality compared to placebo [111].

It is clear from the evidence provided that PCSK-9 inhibitors have a profound biochemical effect on lipid parameters. The jury is still out as to whether this translates to a clinically valid endpoint in terms of cardiovascular and overall mortality. More trials are needed with a significantly longer follow-up period than any of the trials currently in the literature. A role for PCSK-9 inhibitors may exist in specific patient groups, for example patients who have refractory hypercholesterolemia despite maximum statin therapy or those with very high initial LDL-C levels. PCSK-9 therapy is unlikely to be the first-line therapy in the near future not only due to the lack of significant reduction in clinical events in the literature but also due to the cost of the drug, a recent cost-effectiveness study found that the addition of a PCSK-9 inhibitor to statin therapy would cost more than three times the accepted willingness-to-pay threshold [112].

Adverse Effects

The meta-analyses by Karatasakis et al. [110] showed that compared to placebo, there was no significant difference in rates of myalgia, liver function test dysfunction, or other serious adverse events. The Cochrane review found no difference vs. placebo in type 2 diabetes mellitus (T2DM), cancers, or neurocognitive events [111]. It is however difficult to comment on the long-term safety of the use of PCSK-9 inhibitors due to the short follow-up periods in the existing literature.

CONCLUSIONS AND LIMITATIONS

More trials comparing stand-alone effects of fibrates, ezetimibe, and PCSK-9 inhibitors against statin monotherapy are required to establish a true independent effect comparison. This also makes it difficult to directly compare other factors such as discontinuation rates. However, the ethical implications of withholding statins from patients with a risk of CHD means that this limitation is unlikely to be

overcome. Another limitation of the research is the different pathways targeted by different drug classes. This renders comparisons of the same lipid parameters like comparing apples and oranges. While fibrates and ezetimibe and PCSK-9 inhibitors may improve the overall lipid profile more than statins, this rarely manifests as a better clinical benefit.

Statin benefits far outweigh their risk. They have a role in reducing LDL-C, but more importantly they have a strong evidence base, which shows a reduction in vascular event rates and all-cause mortality in primary and secondary prevention. Comparatively, fibrates, ezetimibe, and PCSK-9 inhibitors do not exhibit such a consistent effect across all groups. On the basis of the evidence reviewed, statins still remain the best treatment choice for atherosclerosis. This is reflected in the recent lowering of clinical guidelines advising statin prescribing when there is a "10% (reduced from 20%) or more 10-year risk of developing CVD" [113]. Statins also show no significant treatment effects difference in terms of age, sex, and diabetes status [114]. At 50 years old, the majority of the population will exhibit some CHD risk and therefore would potentially benefit from statins [115]. Further cost–benefit analysis is required to assess the continued feasibility of such widespread statin use.

In certain patient groups, however, statin monotherapy is not enough. There remains populations of patients who are either unable to tolerate statins [41] or despite high-dose statin therapy continue to exhibit dyslipidemia and fail to meet recommended LDL-C levels [116]. In this population, the advent of alternative lipid-lowering therapies with or without statins may be vital to lower cardiovascular risk. This may be in the form of fibrates, cholesterol absorption inhibition, or PCSK-9 inhibitors. NICE has recently licensed the use of ezetimibe in familial hypercholesterolemia in those patients in whom statins are not tolerated or contra-indicated [117]. However, further large-scale trials encompassing all demographics are needed before non-statin cholesterol-lowering drugs are to receive the coveted reputation in cardiovascular risk control that statins have attained over decades of research.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Keshav Kumar Gupta, Shair Ali, and Ranjodh Singh Sanghera have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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