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Review Article

Lipid-lowering Medications - Statins Versus PCSK9 Inhibitors

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Abstract

Elevated levels of low-density lipoprotein cholesterol (LDL-C) are a key risk factor for atherosclerosis and cardiovascular disease (CVD). Statins are the primary therapy recommended by the European Society of Cardiology for hyperlipidaemia. If LDL-C targets are not achieved with statins alone, additional treatments such as PCSK9 inhibitors (e.g. evolocumab and alirocumab) are considered. Statins reduce cholesterol synthesis by inhibiting HMG-CoA reductase, while PCSK9 inhibitors prevent LDL receptor degradation, thereby enhancing hepatic LDL-C clearance. Clinical trials and meta-analyses suggest that both drug classes are effective in reducing cardiovascular events, although statins have been shown to have a greater impact on all-cause and cardiovascular mortality. PCSK9 inhibitors are particularly beneficial for high-risk patients or those intolerant to statins. Emerging therapies such as inclisiran offer the advantage of reduced injection frequency. Both statins and PCSK9 inhibitors are generally well tolerated; the most common side effect of statins is muscle pain, while the most common side effect of PCSK9 inhibitors is an injection site reaction. No significant association with neurocognitive adverse effects has been found for either therapy. Overall, both statins and PCSK9 inhibitors play a crucial role in lipid management and cardiovascular disease prevention.

Kew Words: cardiovascular risk; atherosclerosis; hyperlipidemia; statins; pcsk9 inhibitors

Introduction

An elevated level of low-density lipoprotein cholesterol (LDL-C) is one of the most significant risk factors for atherosclerosis, a condition that leads to cardiovascular disease (CVD) and its associated complications. Treating hyperlipidaemia is essential to prevent mortality and morbidity among the millions of people worldwide who suffer from CVD. The European Society of Cardiology (ESC) and other societies have published guidelines for treating high cholesterol [1]. According to these guidelines, statins are the primary medication for treating hyperlipoproteinaemia. However, if the recommended treatment goals are not achieved, further treatment options must be considered; PCSK9 inhibitors are among the most effective of these (Table 1). This article aims to compare the efficacy of statins and PCSK9 inhibitors in reducing LDL-C and clinical events.

Treatment	Average LDL-C reduction
Moderate intensity statin	ca. 30%
High intensity statin	ca. 50%
High intensity statin plus ezetimibe	ca.65%
PCSK9 inhibitor	ca.60%
PCSK9 inhibitor plus high intensity statin	ca. 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	ca. 85%

Table 1: Efficacy of LDL-lowering agents and combinations (1)

The mechanism of action of statins and PCSK9 inhibitors

Statins work by inhibiting the enzyme HMG-CoA reductase, which converts HMG-CoA into mevalonic acid — a precursor to cholesterol synthesis. This reduces the concentration of cholesterol in cells, which increases the production of LDL receptors and the uptake of LDL cholesterol in liver cells, where it is broken down. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a protein that increases LDL-C levels by promoting the transport of LDL receptors from the cell surface to lysosomes for degradation [3]. Inhibiting PCSK9 results in more LDL receptors being recycled to the cell surface, leading to increased cholesterol uptake and breakdown by the liver.

Cardiovascular prevention

Zhao [5] conducted a meta-analysis that included 84 randomised controlled trials involving 246,706 patients. Most of these studies were

rated as having a low risk of bias. It was found that the probability of statins reducing the risk of cardiovascular events (CV) was 60.6%, compared to 37.1% for PCSK9 inhibitors. However, there was no significant difference in the effectiveness of the two agents in reducing CV events (odds ratio [OR] 0.98, 95% confidence interval [CI] 0.87–1.11). Statins were most effective in reducing all-cause mortality and mortality from cardiovascular diseases. Compared with a placebo, statins were associated with a reduced risk of death (OR: 0.90; 95% CI: 0.85–0.96) and cardiovascular death (OR: 0.83; 95% CI: 0.75–0.91), whereas PCSK9 inhibitors and ezetimibe were not. It should be noted that almost all studies involving PCSK9 inhibitors were based on maximally tolerated statin doses combined with a PCSK9 inhibitor.

The randomised, controlled, phase III MENDEL-2 clinical trial compared evolocumab with a placebo and oral ezetimibe [6]. In the largest monotherapy trial to date using a PCSK9 inhibitor, evolocumab produced significant reductions in LDL-C of between 55% and 57% compared to the placebo group and between 38% and 40% compared to the ezetimibe group (p = 0.001 for all comparisons) in patients with hypercholesterolemia. Evolocumab was well tolerated by these patients. Statins are used in the primary and secondary prevention of cardiovascular disease (CVD).

A systematic Cochrane review found that statins reduce overall mortality and lead to a reduction in major cardiovascular events without increasing the risk of adverse events [7]. I

The CTT Collaboration has shown that lowering LDL C using statin therapy reduces the risk of major vascular events (heart attacks, stroke or coronary revascularisation procedures) by about one fifth for each 1 mmol/L reduction in LDL cholesterol achieved. These benefits are achieved in a wide range of people at risk of cardiovascular disease, irrespective of pre-existing cardiovascular disease or diabetes, and regardless of age, sex and other factors [8].

	Odds Ratio (95% CI)	
Cardiovascular Events	Pairwise Meta-Analysis	Network Meta-Analysis
Statins vs. Placebo	0.80 (0.76, 0.85)	0.80 (0.76,0.85
PCSK9 inhibitor vs. Placebo	0.79 (0.68, 0.92)	0.82 (0.74, 0.92
Statins vs. PCSK9 inhibitor	N/A	0.98 (0.87, 1.11)
Cardiovascular Mortality		
Statins vs. Placebo	0.83 (0.75, 0.92)	0.83 (0.75, 0.91)
PCSK9 inhibitor vs Placebo	0.99 (0.87, 1.13)	0.94 (0.76, 1.17)
Statins vs. PCSK9 inhibitor	N/A	0.88 (0.69, 1.11)
All-cause mortality		
Statins vs. Placebo	0.91 (0.86, 0.96)	0.90, (0.85, 0.90
PCSK9-inhibitor v. Placebo	0.99 (0.87, 1.13)	0.90 (0.79, 1.04
Statins vs. PCSK9 inhibitor	N/A	1.00 (0.87, 1.18)

Table 2 : Comparison of statins and PCSK9 inhibitors with respect to clinical outcomes (all-cause mortality, cardiovascular events and cardiovascular mortality) (modified according to (7)).

PCSK9 inhibitors in cardiovascular prevention

A 2020 Cochrane review rated the evidence for the clinical endpoint effects of the PCSK9 inhibitors alirocumab and evolocumab as high [9]. There is strong evidence to support prescribing PCSK9 inhibitors to individuals who are not suitable for other lipid-lowering therapies or who do not achieve their lipid targets with conventional therapy. This was the primary patient group in the available studies. However, most of these studies included individuals with established cardiovascular disease or a high risk of developing it, and there is minimal evidence regarding low-to-moderate risk situations.

Alirocumabcompred to placebo		
Outcome	relative effect (OR, 95% CI))	Certainty of evidence (grade)
CVD	0.87 (0.80,0.94)	high
All-cause mortality	0.83 (0.72, 0.96)	high
MI	0.86 (0.79, 0.94)	high
Any stroke	0.73 (0.58, 0.91)	high
Evolocumab		
CVD	0.84 (0.78, 0.91)	high
All-cause mortality	1.04 (0.91, 1.19)	high
MI	0.72 (0.64, 0.82)	high
Any stroke	0.79 (0.65, 0.94)	high

Table 3: PCSK9 inhibitors and clinical outcomes (modified according to (9))

Evolocumab and cardiovascular prevention

In the FOURIER OLE study, long-term LDL-C lowering with evolocumab was associated with persist ently low rates of adverse events over a period of more than eight years. These rates did not exceed those observed in the original placebo group. Patients had a 20% lower risk of cardiovascular death, myocardial infarction or stroke, and a 23% lower risk of cardiovascular death.

Alirocumab and cardiovascular prevention

In the ODYSSEY OUTCOMES study [11], alirocumab reduced the risk of major adverse cardiac events (MACE) and death after acute coronary syndrome in 8,242 patients who were treated with the maximum tolerated statin. These patients were eligible for a three- to five-year placebo-controlled follow-up, during which no differences were observed in specific safety or overall side effects.

PCSK9 inhibitors and total mortality

PCSK9 inhibitors are effective in reducing cardiovascular mortality. Propensity score matching revealed that the use of PCSK9 inhibitors was linked to a 28.3% lower risk of all-cause mortality (adjusted hazard ratio (HR): 0.71; 95% confidence interval (CI): 0.673–0.763), despite a significant reduction in all-cause mortality being observed [12].

All-cause mortality was also significantly reduced in statin users (HR 0.72, 95% CI 0.65–0.76) and in non-CVD studies (HR 0.70, 95% CI 0.67–0.79) [12, 13]. (13).

Adverse effects of statins and PCSK9 inhibitors

Statins are generally well tolerated. The most common adverse effects are muscle pain and weakness [15]. They can also increase the risk of developing diabetes, particularly at high doses and in individuals who are predisposed to the condition. Inhibiting HMG-CoA reductase leads to the downregulation of mevalonate metabolism and an increase in LDL-C concentration in cells, which has a toxic effect on pancreatic beta cells. This results in impaired insulin secretion, ultimately leading to type 2 diabetes (16). (16). The risk of developing diabetes from statins is particularly high in individuals with prediabetes and other diabetes risk factors [17].

Furthermore, statin therapy has been shown to increase levels of both alanine aminotransferase (ALT) (OR 1.89, 95% CI 1.42–2.51) and creatine kinase (CK) (OR 1.45, 95% CI 1.09–1.93) [5].

Interactions with verapamil, diltiazem, cyclosporine, itraconazole and grapefruit juice should be anticipated for statins that are metabolised by CYP4503A4 [18]. Adverse side effects of PCSK9 inhibitors include colds or flu, reactions at the injection site, muscle pain, back pain, and diarrhoea [19]. Although none of the active ingredients caused adverse events (including neurocognitive events), statins were found to be more effective than PCSK9 inhibitors in reducing neurocognitive side effects.

Statins versus PCSK9 inhibitors: Neurocognitive Effects

A frequently discussed undesirable effect of statins and PCSK9 inhibitors is cognitive impairment caused by these treatments. Zhao et al. studied the comparative effectiveness and safety of the lipid-lowering medication in people with hypercholesterolemia. Neither PCSK9 inhibitors (OR 1.26, CI 0.80–2.00) nor statins (OR 0.97, CI 0.51–1.86) were associated with an increased risk of neurocognitive events compared to the placebo. Compared to PCSK9 inhibitors, statins were more effective at reducing neurocognitive side effects

Conclusions

A large body of research on lipid reduction indicates that statins and PCSK9 inhibitors are equally effective in reducing cardiovascular events in patients with high cholesterol.

Most studies compared statins with a placebo. PCSK9 inhibitors were administered alongside maximally tolerated statin therapy. However, the few studies that compared PCSK9 inhibitors with a placebo showed that both statins and PCSK9 inhibitors had similar effects in lowering LDL cholesterol. In terms of adverse effects, both medications have proven to be safe and well tolerated. Both medications have proven to be safe and well tolerated. The most frequent side effect of statins is muscle ache, while the most frequent adverse effect of PCSK9 inhibitors is infection at the injection site. This will be reduced to just two injections per year with inclisiran.

Conflicts of interest: The author did not declare any conflict of interest in the context of this article.

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