What is the long-term safety with extremely low LDL levels (<100 mg/dL) in patients treated with PCSK9 inhibitors?

Background

Elevated low-density lipoprotein cholesterol (LDL-C) remains a major risk factor for developing atherosclerotic cardiovascular disease (ASCVD).[1] Despite the prevalent use of lipid-lowering therapy (LLT), it is estimated that 69% of adults in the United States (US) have LDL-C >100 mg/dL. The American Association of Clinical Endocrinologists and the American College of Endocrinology (AACE/ACE) guidelines recommend a target LDL-C level less than 100 mg/dL for individuals with 2 or more risk factors for ASCVD events; ASCVD risk factors include LDL-C ≥160 mg/dL, family history of premature ASCVD, high-sensitivity C-reactive protein level ≥2 mg/L, coronary artery calcium score ≥300 Agatston units, and ankle-brachial index <0.9.[2] Lower LDL-C levels are recommended for patients with very high risk and extreme risk for ASCVD. Very high risk is defined as presence of heterozygous familial hyperlipidemia (HeFH), diabetes or chronic kidney disease with at least 1 risk factor, or established ASCVD or recent hospitalization for an ASCVD incident. Extreme risk is defined as established clinical cardiovascular disease, a premature history of ASCVD, or progressive ASCVD despite LDL-C <70 mg/dL. The target levels for patients at very high risk and extreme risk are LDL-C <70 mg/dL and LDL-C <55 mg/dL, respectively.

The current guideline recommendations support the use of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in addition to a statin to achieve a desired LDL-C level.[2] The AACE/ACE guidelines recommend the use of PCSK9 inhibitors in combination with statin therapy for patients with familial hypercholesterolemia (FH) and for patients with clinical cardiovascular disease unable to reach a target LDL-C level despite maximally tolerated statin therapy. They recommend against PCSK9 inhibitor monotherapy unless a patient is unable to tolerate statin therapy. The newly released American College of Cardiology and American Heart Association (ACC/AHA) guidelines are consistent with the AACE/ACE recommendations.[3] The ACC/AHA guidelines, however, consider the cost associated with PCSK9 inhibitor therapy. The cost-effectiveness ratio for evolocumab and alirocumab ranges from $141,700 to $450,000 per quality-adjusted-life-year (QALY). In order to maintain cost-effectiveness, ACC/AHA recommends use of PCSK9 inhibitors in patients with clinical ASCVD at very high risk who are receiving a maximally tolerated dose of a statin with or without ezetimibe. They further suggest modifying the LDL-C threshold when initiating a PCSK9 inhibitor. The ACC/AHA also assert that improvement in cost-effectiveness can be achieved if PCSK9 inhibitors are reserved for individuals on a maximal statin therapy with higher LDL-C levels. Clinical judgment is recommended for patients receiving a PCSK9 inhibitor with 2 consecutive LDL-C levels <25 mg/dL. De-intensification of the LLT may be warranted based on the prohibitive cost of therapy and the unknown long-term effects of low LDL-C levels.

PCSK9 inhibitors, evolocumab (Repatha®) and alirocumab (Praluent®), are novel lipid-lowering agents that have proven effective in reducing LDL-C levels beyond target goals.[4] Their mechanism of action entails the reduction of circulating LDL-C by preventing PCSK9-modulated lysosomal uptake and degradation of low-density-lipoprotein receptors (LDL-R). These agents were approved by the Food and Drug Administration (FDA) in 2015. Alirocumab is indicated as adjunct therapy to diet or LLT (e.g., statin, ezetimibe) for adults with HeFH or as secondary prevention for individuals requiring additional LDL-lowering therapy.[5] Evolocumab

is indicated as adjunct therapy to diet or LLT (e.g., statin, ezetimibe) or as monotherapy for adults with primary hyperlipidemia including HeFH.[6] Evolocumab is also approved for the treatment of adults with homozygous familial hyperlipidemia (HoFH) who require additional LDL-C lowering. When added to statin therapy, PCSK9 inhibitors resulted in a 43% to 64% decrease in LDL-C levels.[3]

Although referred to as "bad-cholesterol," LDL-C plays an integral role in hormone secretion (e.g., cortisol) and rapidly dividing cells (e.g., liver).[7] The current guideline recommendations are not explicit regarding the recommended minimum LDL-C level for patients receiving LLT.[2,3] LDL-C levels as low as a median of 30 mg/dL have been reported in a clinical trial.[8] In patients with PCSK9 nonsense mutations, LDL-C levels <20 mg/dL have been reported.[9] As of this writing, low LDL-C levels achieved by patients receiving PCSK9 inhibitors remain controversial. This review will examine the medical literature to assess the clinical implications and potential long-term effects of low LDL levels. Additionally, given the recent approval of PCSK9 inhibitors, this review will focus on the effects of low LDL-C levels associated with other LLT.

Literature Review

A meta-analysis conducted by Sabatine et al evaluated the clinical efficacy and safety of lowering LDL-C levels <70 mg/dL.[10] The analysis included the Cholesterol Treatment Trialists Collaboration (CTTC) meta-analysis evaluating statin therapy, and 3 trials: the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk (FOURIER) trial and the Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification (REVEAL) trial, evaluating ezetimibe, evolocumab and anacetrapib, respectively.[8,11-13] Alirocumab was not included in the analysis since no trials met the study's LDL-C inclusion threshold.[10] The authors performed a Medline search for randomized, double-blinded trials with reported clinical outcomes of adding LLT to statin therapy in patients with a mean or median LDL-C <70 mg/dL. The primary endpoint of the analysis was overall major vascular events. Major vascular events included coronary heart death, myocardial infarction, ischemic stroke, and coronary revascularization. The authors reported risk ratios per 1 mmol/L (38.7 mg/dL) reduction in LDL-C level for each trial. The safety outcomes investigated were serious adverse events, myalgias, myositis, elevated aminotransferase levels, new onset diabetes, hemorrhagic stroke, and cancer. The reported risk ratios were derived from raw data and a fixed effects inverse weighting model.

The median follow-up periods for CTTC, IMPROVE-IT, FOURIER, and REVEAL were 4.9, 6, 2.1 and 4.1 years, respectively.[10] The mean baseline LDL-C level in the statin group was 65.7 mg/dL; the median LDL-C in the non-statin trials ranged from 63 mg/dL to 70 mg/dL. Non-statin therapy led to reductions in LDL-C levels of 11-45 mg/dL. The median LDL-C levels achieved were <58 mg/dL in IMPROVE-IT and REVEAL and <21 mg/dL in FOURIER.

With regard to efficacy, the risk ratios per 1 mmol/L LDL-C reduction of overall major vascular events were 0.78 (95% confidence interval [CI] 0.65-0.94) and 0.79 (95% CI 0.70-0.88) for statin and non-statin trials, respectively.[10] In non-statin trials, myocardial infarction and coronary revascularization were significantly reduced, with the respective risk ratios of 0.64 (95% CI 0.53-0.77) and 0.79 (95% CI 0.68-0.92). Coronary heart deaths and ischemic stroke were not significantly reduced in the non-statin trials. In the FOURIER trial, evolocumab therapy resulted in profound LDL-C reduction with a mean level <21 mg/dL. The FOURIER trial did not provide a significant risk reduction for overall major vascular events; the reported risk ratio was 0.80 (95% CI 0.61-1.04). With regard to safety, LDL-C lowering was not associated with a significant increase in adverse events. This finding was consistent across the different treatment interventions.

The authors concluded that persistent clinical benefits with no observed adverse effects in patients with LDL-C levels as low as 21 mg/dL supports lowering LDL-C levels below guideline-recommended levels.[10] Still, when looking at the FOURIER trial, evolocumab was the only drug that resulted in LDL-C levels as low as 21 mg/dL, and also the only intervention not associated with significant risk reduction for overall major vascular events. Hence, further investigation is needed to ascertain the efficacy and safety of LDL-C levels <21 mg/dL.

In a prospective analysis of pooled data, Robinson et al evaluated the safety of very low LDL-C levels with alirocumab.[14] The analysis consisted of 4 phase 2 trials (DFI11565, CL-1003, DFI12361, DFI11566) and 10 phase 3 trials from the ODYSSEY program (LONG TERM, HIGH FH, FH I + FH II, COMBO I, COMBO II, OPTIONS I + II, MONO, ALTERNATIVE). The duration for the phase 3 trials ranged from 24 to 104 weeks, while the phase 2 trials ranged from 8 to 12 weeks. With the exception of MONO and ALTERNATIVE, all trials evaluated alirocumab in patients receiving LLT (statin with or without ezetimibe). The study population was comprised of 3,340 patients receiving alirocumab 75 mg or 150 mg every 2 weeks and 1,894 patients in the control group receiving either a statin with or without ezetimibe or ezetimibe only. The primary outcome was the incidence of treatment emergent adverse effects (TEAEs) in patients with at least 2 consecutive LDL-C levels <25 mg/dL and <15 mg/dL obtained at least 21 days apart. The adverse events of interest were neurological events, neurocognitive disorders, musculoskeletal events, ophthalmologic TEAEs, and hepatic disorders. The authors performed a propensity analysis to account for the differences in baseline characteristics and a correlation analysis to compare calculated and measured LDL-C levels. The median follow-up of this study was 18 months.

At baseline, the reported mean LDL-C levels were 125 mg/dL and 126.3 mg/dL for the treatment and control groups, respectively; during treatment, the reported mean LDL-C levels were 58.8 mg/dL and 117 mg/dL, respectively.[14] Eight hundred thirty-nine patients on alirocumab (25% of the treatment group) achieved 2 consecutive LDL-C levels <25 mg/dL, while 314 patients (9.4% of the treatment group) achieved 2 consecutive LDL-C levels <15 mg/dL. Baseline LDL-C level and alirocumab dose were significant prognostic factors of achieving 2 consecutive LDL-C levels <25 mg/dL and <15 mg/dL. Background statin therapy consisted of high-intensity statin therapy or a maximally tolerated dose of a statin. The reported proportions of high-intensity statin use were 52.8%, 55.9%, 53.0%, and 49.5% for placebo, LDL-C ≥25 mg/dL, LDL-C <25 mg/dL, and LDL-C <15 mg/dL, respectively. High-intensity statin was defined as atorvastatin 40 to 80 mg daily, rosuvastatin 20 to 40 mg daily, or simvastatin 80 mg daily. One patient in the control group achieved an LDL-C <25 mg/dL. The median exposure time was 78 weeks, the median time to first consecutive LDL-C level <25 mg/dL was 6.1 weeks, and the median period for LDL-C levels <25 mg/dL was 43.3 weeks.

Overall rates of TEAEs, serious TEAEs, deaths, and discontinuations were similar across LDL groups (LDL-C ≥25 mg/dL, LDL-C <25 mg/dL, LDL-C <15 mg/dL, and the control group [no alirocumab]).[14] Ophthalmologic TEAEs, such as cataract events, were significantly higher with LDL-C <25 mg/dL when compared to LDL-C ≥25 mg/dL (hazard ratio [HR] 3.4, 95% CI 1.58-7.35, p=0.0018). There was no significant difference in the number of cataract events between the control and overall treatment groups. The incidence of cataracts reported with the LDL-C <15 mg/dL group was not statistically significantly different when compared to the LDL-C ≥25 mg/dL group. The authors found no significant differences among the study groups for other TEAEs. The laboratory analysis also showed no clinically meaningful differences in cortisol levels or gonadal hormones among the groups.

The authors found cataracts to be a potential side effect attributable to LDL-C levels <25 mg/dL.[14] Their finding was not consistent in patients with LDL-C levels <15 mg/dL. The small sample size of patients that achieved LDL-C <15 mg/dL may have contributed to the lack of significant results. As a potent lipid-lowering agent, statins are a possible confounding factor that may have led to overestimation of cataract events. The implications of low-cholesterol levels achieved with statin therapy and cataracts remains controversial.[15,16] While evaluating treatment groups, the authors did not account for the intensity of the statin or lack of statin therapy. It is possible that neurocognitive disorders may have been underestimated in this analysis. The time for onset of neurological effects and the standardization of symptom assessment are variables not addressed by this study. Lastly, the authors were unable to ascertain cardiovascular benefit given the small number of individuals with LDL-C <25 mg/dL.

In addition to the above studies, there is a study in which Everett et al evaluated the safety of low LDL-C levels with rosuvastatin.[17] The authors performed an analysis of data from the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial. JUPITER was a randomized, double-blinded placebo controlled trial in male patients ≥50 years of age and female patients ≥60 years of age with LDL-C <130 mg/dL and C-reactive protein ≥2 mg/dL. Patients with diabetes or cardiovascular disease were excluded. The following groups were studied: a placebo-allocated group and 2 groups that received rosuvastatin (20 mg daily) with either an LDL-C <30 mg/dL or a ≥70% LDL-C reduction from baseline. The outcomes investigated were any adverse effect, musculoskeletal disorders, hepatobiliary disorders, nervous system disorders, psychiatric disorders, diabetes, cancer, and renal/urinary disorders.

Out of the 16,304 study participants, 8,150 were in the placebo-allocated group; 767 achieved LDL-C <30 mg/dL, 718 achieved a 70% reduction of LDL-C level from baseline, and 469 achieved both LDL-C goals.[17] When comparing patients with LDL-C <30 mg/dL to those with LDL-C ≥30 mg/dL, the latter group had a lower incidence of adverse events; the adjusted relative risk (ARR) was 1.10 (95% CI 1.01-1.21, p<0.05). Significant adverse effects were hepatobiliary disorders, psychiatric disorders, insomnia, diabetes, renal/urinary disorders, and physician-reported hematuria. The reported ARRs for these effects were 1.77 (95% CI 1.15-2.73, p<0.01), 1.40 (95% CI 1.06-1.85, p<0.01), 1.59 (95% CI 1.03-2.48, p<0.05), 1.56 (95% CI 1.09-2.23, p<0.05), 1.56 (95% CI 1.09-2.23, p<0.001), and 2.10 (95% CI 1.39-3.19, p<0.001), respectively.

The median follow-up duration was 1.9 years.[17] When comparing the LDL-C <30 mg/dL and placebo groups, the incidences of any adverse event were not significantly different between the groups.[17] Besides psychiatric disorders, the incidences of hepatobiliary disorders, insomnia, diabetes, renal/urinary disorders, and physician-reported hematuria were again significantly greater in the LDL-C <30 mg/dL group. In addition, the data showed an increased risk for musculoskeletal disorders, cholelithiasis, and biliary disease when comparing the group with LDL-C <30 mg/dL to the placebo-allocated group. The respective ARRs were 1.14 (95% CI 1.00-1.29, p<0.05), 4.48 (95% CI 1.08-18.52, p<0.05), and 1.90 (95% CI 1.06-3.41, p<0.05).

When comparing the group with ≥70% LDL-C reduction and the placebo-allocated group, diabetes, physician-reported hematuria and hematuria were significantly greater in the group with ≥70% LDL-C reduction.[17] The reported ARRs were 1.55 (95% CI 1.11-2.19), 1.52 (95% CI 1.00-2.32), and 1.33 (95% CI 1.02-1.73, p<0.05), respectively. Everett et al concluded that although very low LDL-C levels were tolerated in patients receiving a statin, the low levels may be associated with an increased risk for physician-reported hematuria and the development of type 2 diabetes.

Although the study by Everett et al did not evaluate PCSK9 inhibitors, the findings should be considered since an association between low LDL-levels and adverse events was identified; these safety concerns were not reported in other trials.[17] The results of this study, however, should be interpreted with caution. The mean and median LDL-C levels achieved were not reported and the LDL-C level threshold was higher than the targets defined in the reviewed meta-analyses and guidelines.[3,10] Insomnia, diabetes, renal/urinary disorders, and physician-reported hematuria were significantly greater in the LDL-C <30 mg/dL group vs. the LDL-C ≥30 mg/dL and placebo groups.[17] Recent literature on PCSK9 inhibitors did not explore these side effects. Pending further investigation, patients on PCSK9 inhibitor therapy with a low LDL-C level should be monitored for insomnia, new onset of diabetes, hematuria, and renal/urinary disorders.

Summary

In summary, a meta-analysis and a pooled analysis exploring safety and efficacy of PCSK9 inhibitors found no evidence to support clinical benefit and safety for low LDL-C levels.[10,14] In the FOURIER trial, the LDL-C <21 mg/dL achieved with evolocumab did not show a significant decrease in major vascular events.[8] Lipid-lowering therapy resulting in LDL-C levels <25 mg/dL may result in the development of cataracts in patients treated with alirocumab; however, the current literature is insufficient to support the association between all PCSK9 inhibitors and cataracts.[14] Adverse effects reported with low LDL-C levels achieved with statin therapy have yet to be investigated with PCSK9 inhibitors.[17] Insomnia, new onset of diabetes, hematuria, and renal/urinary disorders were significant adverse effects observed in individuals taking rosuvastatin with LDL-C <30 mg/dL.

The current clinical guidelines recommend targets of LDL-C 100 mg/dL, 70 mg/dL, and 55 mg/dL for high risk, very high risk, and extreme risk patients, respectively.[2,3] The safety of low LDL-C levels remains controversial. The incidence of cataracts reported in some studies should be further investigated.[14] Until further data are available, providers should continuously monitor for adverse effects and re-assess the need for a PCSK9 inhibitor in patients with very low LDL-C levels. The guidelines recommend providers use clinical judgment in patients with 2 consecutive LDL-C levels <25 mg/dL while receiving a PCSK9 inhibitor.[3]

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