ORIGINAL RESEARCH

How Low Is Too Low? A Retrospective Analysis of Very Low LDL-C Levels in Veterans

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Background: Low-density lipoprotein cholesterol (LDL-C) can build up on the walls of blood vessels, leading to coronary heart disease. Medications used to lower LDL-C levels have demonstrated decreased risks of atherosclerotic cardiovascular disease, but currently, there is no consensus on how to define very low LDL-C levels. It is necessary for the body to have LDL-C to maintain proper brain function; however, the safety and effects of prolonged very low LDL-C levels are unknown. The current study sought to gather information to determine the risks of very low LDL-C levels in a veteran population.

Methods: A retrospective chart review was conducted at a US Department of Veterans Affairs medical center. Patients with hyperlipidemia/dyslipidemia treated with HMG-CoA reductase inhibitors or proprotein convertase subtilisin/kexin type 9 (PCSK9) therapy and LDL-C levels < 40 mg/dL between January 1, 2010, and September 1, 2020, were included. The primary outcome was the rate of intracranial hemorrhage that could be caused by an LDL-C level < 40 mg/dL. The secondary outcomes included actions taken by clinicians, adverse drug reactions (ADRs), duration of therapy, and medication adherence.

Results: This study included 3027 patients. Of the included patients, 8 had an intracranial hemorrhage within 1 year from a documented LDL-C level < 40 mg/dL (0.26%). Thirty-two patients with an LDL-C level < 40 mg/dL did not have a documented ADR with the studied medications. Of the 32 charts, 26 had a clinician address the LDL-C level < 40 mg/dL with either documentation and/or modification of the medication prescribed. The most common ADRs among the studied medications were muscle and joint pain, rash, and cramps. Adherence to the medications was consistently similar for all studied medications.

Conclusions: Of the patient population included in this study, 0.26% of patients had an intracranial hemorrhage within 1 year of having an LDL-C level < 40 mg/dL. The rate of ADRs related to the medications analyzed in this study shows no statistical significance ($P > .05$). When compared with low- and moderate-intensity statin medications, high-intensity statin medications were statistically significant in resulting in an LDL-C level < 40 mg/dL ($P < .001$). LDL-C levels < 40 mg/mL were not routinely documented as being addressed in the chart by the clinician.

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According to the Centers for Disease Control and Prevention (CDC), approximately 795,000 strokes occur in the United States yearly and are the fifth leading cause of death.[1] The CDC also states that about 43 million Americans who could benefit from cholesterol medication are currently taking them.[2] As of 2019, West Virginia, Ohio, and Kentucky are 3 states with the highest rates of heart disease mortality.[3]

Low-density lipoprotein cholesterol (LDL-C) accumulates on the walls of blood vessels, which can lead to coronary heart disease. However, some LDL-C is necessary to maintain proper brain function. Guidelines from the American College of Cardiology (ACC) and American Heart Association (AHA) recommend LDL-C goal levels < 70 mg/dL.[4] Yet, there is no consensus on how low LDL-C levels should be. According to clinical practice guidelines for dyslipidemia, developed by the US Department of Veterans Affairs (VA) and US Department of Defense, statin medications are first-line agents for lowering LDL-C. The intensity of the statin medication is based on primary or secondary prevention, atherosclerotic cardiovascular disease (ASCVD) risk, and current LDL-C levels prior to treatment.[5]

Statin medications are used for primary and secondary prevention of ASCVD. In addition, statin medications decrease total cholesterol, LDL-C, and triglycerides while causing a mild increase in high-density lipoprotein cholesterol. Although statin medications are first-line therapy for LDL-C lowering, other medications can be used to assist in decreasing LDL-C. Ezetimibe, fenofibrates, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors can also be used.[5] Statin medications do pose a risk of severe adverse drug reactions (ADRs), such as rhabdomyolysis and myopathy.[6]

One prospective cohort study looked at 27,937 women and analyzed total cholesterol, LDL-C, high-density lipoprotein cholesterol, triglycerides, and strokes. The study noted a mean 19.3-year follow-up and within that follow-up, 137 hemorrhagic strokes occurred. Based on the study's results, LDL-C levels < 70 mg/dL had 2.17 times the risk of experiencing a hemorrhagic stroke.[7] A meta-analysis of prospective studies analyzed 476,173 patients

and 7487 hemorrhagic stroke cases. This review concluded that a 10 mg/dL increase in LDL-C was associated with a 3% lower risk of hemorrhagic stroke.[8]

An observational study conducted in Asia of Chinese adults found that 22% of all strokes were hemorrhagic. The incidence of the hemorrhagic strokes was higher for patients who had an LDL-C < 1.8 mmol/L than those who had an LDL-C between 1.8 and 2.6 mmol/L. This study also showed that if hypertension was inadequately treated, the risk of hemorrhagic stroke increased. This study concluded that the benefit of reducing ASCVD outweighs the small risk of hemorrhagic strokes.[9]

Another prospective cohort study included 96,043 stroke-free participants and analyzed LDL-C concentrations and incidence of intracranial hemorrhage. The average LDL-C concentrations were calculated from data collected in 4 separate reporting years, and incidence of intracranial hemorrhage was confirmed through review of medication records. Over a 9-year follow-up period, the study concluded that participants with an LDL-C level of < 70 mg/dL had a significantly higher risk of developing intracranial hemorrhage than participants with LDL-C levels 70 to 99 mg/dL.[10]

The safety and effects of prolonged very low LDL-C levels are currently unknown. The current study sought to gather information to determine the risks of very low LDL-C levels in a veteran population.

METHODS

A retrospective chart review was conducted on patients aged 18 to 90 years receiving care at the Hershel "Woody" Williams Veterans Affairs Medical Center (HWW VAMC) in Huntington, West Virginia, between January 1, 2010, and September 1, 2020. Approval of the current study was obtained through the Marshall University Institutional Review Board, HWW VAMC Research and Development Committee, and Veterans Health Administration (VHA) DATA Access Request Tracker (DART)/VA Informatic and Computing Infrastructure (VINCI). Data were obtained via the VHA Corporate Data Warehouse (CDW) for the HWW VAMC using Microsoft Structured Query Language (SQL) server available in VINCI. Analysis of the data was conducted using STATA v. 15.

Patients were included if they had a diagnosis of hyperlipidemia/dyslipidemia, received treatment with HMG-CoA reductase inhibitors or PCSK9 medications, and had an LDL-C level ≤ 40 mg/dL. The primary outcome was the rate of intracranial hemorrhage that could be caused by very low LDL-C levels. The secondary outcomes included actions taken by clinicians to address LDL-C level < 40 mg/dL, ADRs, duration of therapy, and medication adherence. Patients were excluded if they were aged < 18 or > 90 years, were pregnant during the study period, had hypothyroidism, received chronic anticoagulation medications, or had a triglyceride level > 300 mg/dL.

TABLE 1 Statin Intensity and Low LDL-C Levels

Statin intensity	Low LDL-C (< 40 mg/dL), %
Low	11.43
Moderate	51.27
High	37.30[a]

Abbreviation: LDL-C, low-density lipoprotein cholesterol.
[a]$P < .001$.

RESULTS

The study included 3027 patients. Of those patients, 78 patients were female while 2949 were male, and the mean (SD) age was 68.3 (9.4) years. A subsample of 32 patients was analyzed to determine whether an ADR was noted or low LDL-C level was addressed in the chart. The subsample size was determined through chart review and included patients who had a documented intracranial hemorrhage. None of the 32 patients had an ADR documented, and 6 (19%) had the low LDL-C level addressed in the chart by monitoring levels, reducing statin doses, or discontinuing the medication. Of the total population analyzed, 8 patients (0.3%) had a documented intracranial hemorrhage within 1 year following the low LDL-C level.

We also analyzed the intensity of statin related to the low LDL-C level (Table 1). The intensity of statin was broken into low, moderate, and high intensity according to ACC/AHA guidelines. There was a statistically significant difference between patients who had an LDL-C level < 40 mg/dL on a high-intensity statin compared with patients on a moderate- or low-intensity statin ($P < .001$). There was no statistically significant difference between moderate- and low-intensity statins ($P > .05$).

The most common ADRs were muscle, joint, and leg pain, rash, and cramps (Table

TABLE 2 Medication Therapies

Criteria	Alirocumab	Atorvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
Duration, mean, y	1.1	3.1	1.5	3.9	2.6	4.2
Adherence, %	85.6	85.5	91.2	85.6	86.9	85.9
Adverse reaction, No. (%)	0	187 (7.3)	2 (3.1)	187 (7.7)	54 (4.7)	89 (1.0)
Cramps		13	0	12	2	3
Joint pain		23	0	17	3	4
Leg pain		12	0	18	4	3
Muscle pain		127	2	123	41	76
Rash		12	0	17	4	3

2). Of the patients included in this study, the most common medications with ADRs documented were atorvastatin and pravastatin. Of the patients taking atorvastatin and pravastatin, 7.3% and 7.7%, respectively, had a documented ADR; however, this was not statistically significant. The medications with the least ADRs documented were lovastatin and simvastatin, with 3.1% and 1%, respectively ($P > .05$).

Adherence to the medications and duration of therapy was also analyzed and was found to be similar among the various medications. Lovastatin had the highest percent adherence with 91.2% while atorvastatin had the lowest with 85.5%. It can be noted that lovastatin had a lower documented percentage of ADRs while atorvastatin had a higher documented percentage of ADRs, which can be clinically meaningful when prescribing these medications; however, these similar adherence rates are not influencing the primary outcome of the rate of intracranial hemorrhage due to LDL-C level < 40 mg/dL. Mean duration of therapy lasted between 1 year and > 4 years with 1.1 years for alirocumab and 4.2 for simvastatin. The duration of therapy could be influenced by formulary restrictions during the study time. Nonetheless, patients, regardless of formulary restrictions, have taken these medications for a duration long enough to affect LDL-C levels.

Eight patients of the total sample analyzed had an intracranial hemorrhage within 1 year of having a recorded LDL-C level < 40 mg/dL. Secondarily, 32 patients had clinicians address an LDL-C level < 40 mg/dL through documentation or modifying the medication therapy. The most common ADRs among all medications analyzed were leg and joint pain, rash, and cramps. Of all medications included in this study, the mean duration of therapy was > 1 year, which would allow them to affect LDL-C levels and have those levels monitored and recorded in patients' charts.

DISCUSSION

When comparing our primary outcome of risk of intracranial hemorrhage with previous literature, the results are consistent with previous outcomes. Previous literature had a smaller sample size but analyzed LDL-C levels < 50 mg/dL and had an outcome of 48 patients experiencing an intracranial hemorrhage within 1 year of an LDL-C level < 50 mg/dL. Due to this study having stricter parameters of LDL-C levels < 40 mg/dL, there were fewer patients with documented intracranial hemorrhages. With there being a risk of intracranial hemorrhage with low LDL-C levels, the results demonstrate the need to monitor and address LDL-C levels.

Limitations

There were several notable limitations to this study. The retrospective, single-center nature coupled with the predominately male study population may affect the generalizability of the study results to patients outside of the facility in which the study was performed. Additionally, the study only included statin medications and PCSK9 inhibitors. With future studies, all lipid-lowering medications could be analyzed. The study was largely reliant on the proper documentation of *International Statistical Classification of Diseases, Tenth Revision (ICD-10)* codes exclusive to the HWW VAMC, which may exclude patients who first present to outside facilities. Due to time restraints, the incidence of hemorrhage was only analyzed 1 year following an LDL-C level < 40 mg/dL. For considerations for future investigation, the length of time to analyze

incidence of hemorrhage could be expanded to be similar to previous studies, and the study could be expanded across the local Veterans Integrated Service Network or VA system. Additionally, the study could have analyzed the percentage of time a patient had an LDL-C level < 40 mg/dL in their lifetime.

CONCLUSIONS

These results show there is a risk that patients with an LDL-C level < 40 mg/dL may experience an intracranial hemorrhage. As seen by the results, there is a clinical need for practitioners to routinely monitor and address LDL-C levels. With various guidelines that recommend starting statin medication to reduce risk of ASCVD, it is necessary that practitioners routinely monitor cholesterol levels and adjust the medications according to laboratory results.[11]

Within 1 year of an LDL-C level < 40 mg/dL, 0.3% of patients had an intracranial hemorrhage. There was no statistical significance between the rate of ADRs among the medications analyzed. High-intensity statin medications were statistically significant in resulting in an LDL-C level < 40 mg/dL compared with moderate- and low-intensity statin medications. Of the 32 subsample of patients, LDL-C levels < 40 mg/mL are not routinely being addressed in the chart by the clinician.

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Ethics and consent

This study received approval from the Marshall University Institutional Review Board, Hershel "Woody" Williams Veterans Affairs Medical Center Research and Development Committee, and Veterans Health Administration DATA Access Request Tracker/Veterans Affairs Informatic and Computing Infrastructure.

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