KANSAS JOURNAL of MEDICINE

Brief Report

Descriptive Evaluation in Outpatient Follow-Up of Direct LDL-C in Patients with Elevated Triglycerides and Diabetes

Monica Bennett, Pharm.D., BCACP[1], Lyndsey N. Buzzard, Pharm.D., BCACP, CDCES[2], Erica N. Presnell, Pharm.D., BCCCP[3], Samuel Ofei-Dodoo, Ph.D., MPA, M.A., CPH[4], Bradley J. Newell, Pharm.D., BCACP, BCGP, BC-ADM, FASCP[5]

[1]Muscogee Creek Nation Department of Health, Okmulgee, Oklahoma

[2]Ascension Medical Group Via Christi, P.A., Wichita, Kansas

[3]Ascension Via Christi Hospitals, Wichita, Kansas

[4]The University of Kansas School of Medicine-Wichita, Wichita, Kansas

[5]The University of Kansas School of Pharmacy-Wichita, Wichita, Kansas

Received May 1, 2024; Accepted for publication Aug. 22, 2024; Published online Nov. 15, 2024
Kans J Med 2024 Nov-Dec; 17:136-138. https://doi.org/10.17161/kjm.vol17.22327

ABSTRACT

Introduction. An annual fasting lipid panel (FLP) is recommended for patients with diabetes, with more frequent testing advised during the escalation of cholesterol-lowering therapy. However, the calculated low-density lipoprotein cholesterol (LDL-C) using the Friedewald equation becomes unreliable when triglycerides are ≥400 mg/dL. In such cases, providers must order a separate direct LDL-C assay to obtain accurate results. Failing to do so may lead to missed opportunities for therapy intensification. This study examined an institution's current practices for following up on invalid LDL-C results, especially considering the stringent LDL-C targets outlined in recent guidelines and consensus statements.

Methods. The authors conducted a retrospective chart review across 13 outpatient clinics within a single health system over five years. The study included patients aged 40-75 with diabetes who had at least one invalid LDL-C result. They assessed the frequency of ordering a direct LDL-C assay within seven days of an invalid LDL-C result.

Results. Out of 1,364 unique invalid FLPs, 97 (7.1%) met the criteria for the primary outcome. The rate of therapy escalation was not numerically affected by whether a direct LDL-C was ordered or the provider type. However, patients without a direct LDL-C ordered within seven days showed a trend towards more frequent therapy escalation (16.2%, n = 25/154) compared to those with a direct LDL-C (14.9%, n = 23/154).

Conclusions. The current practice at this institution of manually ordering a direct LDL-C assay to verify invalid LDL-C results poses a risk of missing necessary guideline-directed therapeutic intensification. This process may be improved by implementing a reflex direct LDL-C assay.

INTRODUCTION

Diabetes mellitus is a major risk factor for the development of atherosclerotic cardiovascular disease (ASCVD), the leading cause of mortality and morbidity in patients with diabetes.[1,2] ASCVD also significantly increases the costs and demands of diabetes care.[3,4] A fasting lipid panel (FLP) is essential for assessing clinical ASCVD risk, with low-density lipoprotein cholesterol (LDL-C) identified as the primary contributor to atherogenic risk.[5] However, FLPs do not directly measure LDL-C; instead, the Friedewald equation is used to calculate its value. When triglycerides (TG) exceed 400 mg/dL, the Friedewald equation yields an "invalid" LDL-C value, rendering it clinically useless.[6] In such cases, a direct LDL-C assay, which measures LDL-C independently, provides a more accurate estimation of ASCVD risk. While a direct LDL-C is generally more reliable than other formulas, most comparison studies in patients with diabetes have excluded those with elevated TG.[7-13]

In this health system, the standard outpatient practice relies on the Friedewald equation to calculate LDL-C from a patient's FLP. However, there is no automated reflex order for a direct LDL-C assay when an "invalid" LDL-C is reported. Providers must manually review FLP results and determine whether a direct LDL-C assay is necessary. Given that recent guidelines and consensus statements have set increasingly stringent LDL-C goals, appropriate monitoring and pharmacotherapy are crucial for effective care.[1,14,15] Adjusting medications to achieve LDL-C targets has been associated with a reduction in major vascular events.[16,17] However, limited information is available on the clinical consequences of relying on manual ordering of direct LDL-C assays rather than automating the process for elevated TG.[18-20]

The authors of this retrospective study examined the institution's current practices in following up on "invalid" LDL-C results to identify opportunities for improving patient care and reducing ASCVD risk.

METHODS

Study Design and Setting. The authors conducted a retrospective chart review across 13 outpatient clinics within a single health system, from January 1, 2016 to December 31, 2021. This study was reviewed and approved by the local Institutional Review Board (IRB). The clinics are part of Ascension Medical Group Via Christi, which provides both primary and specialty care to patients in south-central Kansas.

Study Population. The authors included patients diagnosed with Type 1 or Type 2 diabetes, aged 40-75 years, who had at least one "invalid" LDL-C result due to TG ≥400 mg/dL during the study period. The lipid panels were ordered by affiliated outpatient providers practicing in primary care, cardiology, or endocrinology. Patients with familial hypercholesterolemia or those who were pregnant at the time of the baseline lipid panel were excluded.

Data Collection. Clinical and demographic data were collected from the health system's electronic health record (EHR). Patient characteristics included age, biological sex, diabetes diagnosis (Type 1 or Type 2), race, ethnicity, and primary insurance payer. The active medication list for each patient was reviewed at the time of the baseline "invalid" LDL-C and again two weeks later. Data were collected on documented prescriptions and any escalation of cholesterol-lowering therapy, including the use of statins, fibric acid derivatives, ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors, bile acid sequestrants, prescription omega-3 fatty acids, niacin, and bempedoic acid. The ordering provider type for the baseline FLP and

any follow-up labs also was noted, distinguishing between physicians (M.D. or D.O.), physician associates (P.A.), and advanced practice registered nurses (APRN). The first FLP with an invalid LDL-C during the study period was defined as the "baseline FLP," though this may not have been the first FLP recorded in the EHR. All subsequent FLPs and direct LDL-C results following the baseline event were collected until the end of the study period. Lab results from outside the health system or during inpatient admissions were excluded.

Primary Outcome. The primary outcome was the frequency of direct LDL-C assays ordered within seven days of an "invalid" LDL-C result. The health system retains blood samples for up to seven days, allowing for additional analysis without requiring a repeat blood draw. Each FLP with an invalid LDL-C result was treated as a new encounter, meaning that a single patient could have multiple FLPs included in this study.

Secondary Outcomes. Secondary outcomes were analyzed in encounters where a repeat FLP was available within 18 months of the baseline event or before the study period ended, whichever came first. These outcomes included the time from the baseline FLP to the direct LDL-C order and/or repeat FLP, as well as the frequency of direct LDL-C inclusion in subsequent lipid panels. The frequency of cholesterol-lowering therapy escalation within two weeks of the baseline lipid panel also was examined. Therapy escalation was defined as an increase in dose, the addition of a cholesterol-lowering medication, or a change in statin use from a lower to a higher intensity dose. Rates of therapy escalation were compared based on provider type and whether a direct LDL-C had been ordered within seven days. Additionally, the frequency of direct LDL-C orders within seven days of the baseline FLP, stratified by provider type, was compared.

Statistical Analysis. Descriptive statistics were used to analyze the data. The secondary outcome analysis was restricted to baseline FLPs. IBM SPSS (Statistical Package for the Social Sciences; Armonk, NY), version 26, was used for the analysis.

RESULTS

A total of 1,392 diabetic patients were identified as having at least one "invalid" LDL-C result during the study period. These patients collectively had 1,806 unique FLPs with an "invalid" LDL-C result. After applying the inclusion criteria, 442 baseline FLPs were excluded, leaving 1,364 FLPs for analysis. Of these, 97 (7.1%) had a direct LDL-C assay ordered within seven days of the "invalid" LDL-C result. The characteristics of the entire patient population are detailed in Table 1.

Table 1. Patients' characteristics.

Clinical Variables	Total FLP Assays (N = 1364)
Biological sex at birth, no. (%)	
Male	792 (58.1)
Female	572 (41.9)
Age, mean years (SD)	57 (8.8)
Diabetes diagnosis, no. (%)	
Type 2	1,340 (98.2)
Type 1	24 (1.8)
Race, no. (%)	
White or Caucasian	1,257 (92.1)
Black or African American	53 (3.9)
Asian	16 (1.2)
American Indian or Alaska Native	8 (0.6)
Decline to specify	30 (2.2)
Ethnicity, no. (%)	
Not Hispanic or Latino	1,249 (91.6)
Hispanic or Latino	92 (6.7)
Decline to specify	23 (1.7)
Primary insurance, no. (%)	
Commercial	806 (59.1)
Medicare	373 (27.3)
Medicaid	39 (2.9)
Tricare	11 (0.8)
Self-pay	52 (3.8)
Charity	3 (0.2)
Not reported	80 (5.9)

FLP, fasting lipid panel; SD, standard deviation.

For the secondary outcome analysis, 955 FLPs with an eligible follow-up FLP were included. Among these, 71 (7.4%) had a direct LDL-C obtained within seven days. The majority of baseline FLPs were ordered by physicians (839), followed by P.A.s (67) and APRNs (49). When a direct LDL-C was measured, it was typically obtained a mean of 115 days after the baseline "invalid" LDL-C result. The follow-up FLP was drawn a median of five months after the baseline FLP, with a direct LDL-C being measured during follow-up in 2.6% (n = 25) of cases.

Of the 955 FLPs included in the secondary outcome analysis, 154 (16.1%) were associated with an increase in cholesterol-lowering therapy within two weeks of the FLP. Although overall rates were low, patients without a direct LDL-C ordered within seven days showed a slight trend toward more frequent therapy escalation (16.2%, n = 25/154) compared to those who had a direct LDL-C ordered (14.9%, n = 23/154).

DISCUSSION

Findings of this study highlighted that direct LDL-C values are infrequently obtained in patients with "invalid" LDL-C results due to elevated triglycerides. The clinics involved may not be achieving timely cholesterol monitoring, which could hinder optimal, evidence-based patient care. Identifying these potential gaps in current practice may support the development of new procedures to enhance patient outcomes.

The findings also indicated that the rate of follow-up using a direct

LDL-C assay within seven days of an "invalid" LDL-C result is low, with the direct assay most ordered on the same day as the baseline lab. Instead, providers often opted for a repeat FLP, which typically occurred five to six months after the initial event. This delay may suggest difficulties providers face in making guideline-directed medical therapy adjustments. The data across different provider types suggested that these monitoring trends are consistent throughout the institution.

Within this health system, it was estimated that a direct LDL-C assay costs approximately 50% less than an FLP. Despite this, the study showed that providers tend to favor repeating an FLP over ordering a direct LDL-C, resulting in a 100% increase in monitoring costs. Implementing a reflex direct LDL-C assay could potentially reduce lab monitoring costs by about 25%, not accounting for the additional time health care personnel spend collecting, analyzing, and interpreting labs. Previous literature has found that using direct LDL-C assays can lead to a 33% cost savings compared to FLP monitoring.[21]

Limitations. This study had several limitations, primarily due to its retrospective design. The rationale behind dose escalation decisions, or the lack thereof, could not be determined without insight into the treatment decision-making process. The accuracy of the medication lists relied on the practices of individual providers, and there was a possibility of incomplete lab records. Additionally, only the provider's degree was analyzed, leaving the influence of the provider's specialty on lab monitoring preferences unknown.

CONCLUSIONS

Through this study, the authors found that the lack of LDL information, due to the limitations of the standard FLP, can increase the risk of patients receiving insufficient therapeutic intensification. This, in turn, may impede the achievement of guideline-based goals for optimal cholesterol-lowering therapy and ASCVD risk reduction. Implementing a reflex direct LDL-C assay with FLP orders, coupled with provider education, could enhance adherence to guideline-recommended therapy while reducing healthcare costs.

REFERENCES

[1] ElSayed NA, Aleppo G, Aroda VR, et al. Cardiovascular disease and risk management: Standards of care in diabetes-2023. Diabetes Care 2023; 46(Suppl 1):S158-S190. Erratum in: Diabetes Care 2023. PMID: 36507632.
[2] Matheus AS, Tannus LR, Cobas RA, Palma CC, Negrato CA, Gomes MB. Impact of diabetes on cardiovascular disease: An update. Int J Hypertens 2013; 2013:653789. Epub 2013 Mar 4. PMID: 23533715.
[3] American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. Diabetes Care 2018; 41(5):917-928. Epub 2018 Mar 22. PMID: 29567642.
[4] Persson S, Nilsson K, Karlsdotter K, et al. Burden of established cardiovascular disease in people with type 2 diabetes and matched controls: Hospital-based care, days absent from work, costs and mortality. Diabetes Obes Metab 2023; 25(3):726-734. Epub 2022 Nov 28. PMID: 36371525.
[5] Correction. J Am Coll Cardiol 2019; 73(24):3234-3237. Erratum for: 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of Blood cholesterol: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019; 73(24):3168-3209. PMID: 31221268.
[6] Sung KC, Kwon CH, Lee MY, et al. Comparison of low-density lipoprotein cholesterol concentrations by direct measurement and by Friedewald calculation. Am J Cardiol 2020; 125(6):866-873. Epub 2019 Dec 26. PMID: 31928718.
[7] Sampson M, Ling C, Sun Q, et al. A new equation for calculation of low-density lipoprotein cholesterol in patients with normolipidemia and/or hypertriglyceridemia. JAMA Cardiol 2020; 5(5):540-548. Erratum in: JAMA Cardiol 2020; 5(5):613. PMID: 32101259.
[8] Ghayad JPE, Barakett-Hamadé VP. A tale of two approaches. Am J Clin Pathol 2022; 157(3):345-352. PMID: 34596224.
[9] Wolska A, Remaley AT. Measuring LDL-cholesterol: What is the best way to do it? Curr Opin Cardiol 2020; 35(4):405-411. PMID: 32412961.
[10] Ikezaki H, Fisher VA, Lim E, et al. Direct versus calculated LDL cholesterol and c-reactive protein in cardiovascular disease risk assessment in the Framingham Offspring study. Clin Chem 2019; 65(9):1102-1114. Epub 2019 Jun 25. PMID: 31239251.
[11] Mora S, Rifai N, Buring JE, Ridker PM. Comparison of LDL cholesterol concentrations by Friedewald calculation and direct measurement in relation to cardiovascular events in 27,331 women. Clin Chem 2009; 55(5):888-894. PMID: 19395440.
[12] Hirany S, Li D, Jialal I. A more valid measurement of low-density lipoprotein cholesterol in diabetic patients. Am J Med 1997; 102(1):48-53. PMID: 9209200.
[13] Sajja A, Park J, Sathiyakumar V, et al. Comparison of methods to estimate low-density lipoprotein cholesterol in patients with high triglyceride levels. JAMA Netw Open 2021; 4(10):e2128817. PMID: 34709388.
[14] Samson SL, Vellanki P, Blonde L, et al. American Association of Clinical Endocrinology Consensus Statement: Comprehensive Type 2 Diabetes Management Algorithm - 2023 Update. Endocr Pract 2023; 29(5):305-340. Erratum in: Endocr Pract 2023; 29(9):746. Erratum in: Endocr Pract 2023; 29(12):1025. PMID: 37150579.
[15] Writing Committee; Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2022 ACC Expert Consensus Decision Pathway on the role of nonstatin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: A report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2022; 80(14):1366-1418. Epub 2022 Aug 25. Erratum in: J Am Coll Cardiol 2023; 81(1):104. PMID: 36031461.
[16] Cholesterol Treatment Trialists' (CTT) Collaboration; Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010; 376(9753):1670-1681. Epub 2010 Nov 8. PMID: 21067804.
[17] Authors/Task Force Members; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Atherosclerosis. 2019; 290:140-205. Epub 2019 Aug 31. Erratum in: Atherosclerosis 2020; 292:160-162. Erratum in: Atherosclerosis 2020; 294:80-82. PMID: 31591002.
[18] Martin SS, Blaha MJ, Elshazly MB, et al. Friedewald-estimated versus directly measured low-density lipoprotein cholesterol and treatment implications. J Am Coll Cardiol 2013; 62(8):732-739. Epub 2013 Mar 21. PMID: 23524048.
[19] Evans SR, Fichtenbaum CJ, Aberg JA; A5087 Study Team. Comparison of direct and indirect measurement of LDL-C in HIV-infected individuals: ACTG 5087. HIV Clin Trials 2007; 8(1):45-52. PMID: 17434848.
[20] Fawwad A, Sabir R, Riaz M, Moin H, Basit A. Measured versus calculated LDL-cholesterol in subjects with type 2 diabetes. Pak J Med Sci 2016; 32(4):955-960. PMID: 27648047.
[21] Lane R, Agrawal K, Modir R. Cost-effectiveness of using LDL-direct versus lipid-panel as part of the inpatient stroke workup. J Stroke Cerebrovasc Dis 2021; 30(2):105417. Epub 2020 Dec 8. PMID: 33307290.

Keywords: ambulatory care, cardiovascular diseases, diabetes mellitus, hyperlipidemia, hypertriglyceridemia

Conflict Disclosure: Samuel Ofei-Dodoo, Ph.D., MPA, M.A., CPH, is the Editor-in-Chief of the *Kansas Journal of Medicine*.