CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Risk of Cardiovascular Events in Patients With Type 2 Diabetes and Metabolic Dyslipidemia Without Prevalent Atherosclerotic Cardiovascular Disease

Jamal S. Rana, MD, PhD,[a,b,c] Jennifer Y. Liu, MPH,[c] Howard H. Moffet, MPH,[c] Robert J. Sanchez, PhD,[d] Irfan Khan, PhD,[e] Andrew J. Karter, PhD[c]

[a]Division of Cardiology, Kaiser Permanente Northern California, Oakland, Calif; [b]Department of Medicine, University of California, San Francisco; [c]Division of Research, Kaiser Permanente Northern California, Oakland, Calif; [d]Health Economics and Outcomes Research, Medical Affairs, Regeneron Pharmaceuticals, Inc., Tarrytown, NY; [e]Real-World Evidence and Clinical Outcomes, Sanofi, Bridgewater, NJ.

ABSTRACT

BACKGROUND: The relationship between achieved low-density lipoprotein cholesterol (LDL-C) levels and risk of incident atherosclerotic cardiovascular disease events among patients with diabetes and metabolic dyslipidemia has not been well described.

METHODS: We conducted an observational cohort study of statin-treated adults (ages 21−90 years) with type 2 diabetes without established atherosclerotic cardiovascular disease (as of January 1, 2006) who had metabolic dyslipidemia (elevated triglycerides ≥150 mg/dL and low high-density lipoprotein cholesterol, <50 mg/dL [women] and <40 mg/dL [men]). All subjects were members of Kaiser Permanente Northern California, an integrated health care delivery system. Adjusted multivariable Cox models were specified to estimate hazard ratios (HRs) for incident atherosclerotic cardiovascular disease events by achieved LDL-C levels (<50, 50-<70, 70-<100, and ≥100 mg/dL). Incident atherosclerotic cardiovascular disease events were defined as a composite of nonfatal myocardial infarction, ischemic stroke, or coronary heart disease death through December 31, 2013.

RESULTS: A total of 19,095 individuals met the selection criteria. Mean age was 63.4 years, 53.5% were women, and the mean follow-up was 5.9 years. Unadjusted rates of atherosclerotic cardiovascular disease events were not significantly different across specified LDL-C categories. In models adjusted for demographics and clinical characteristics, the risk was significantly lower with decreasing achieved LDL-C levels (P <0.0001 for trend). Relative to achieved LDL-C ≥100 mg/dL, LDL-C <50 mg/dL had an hazard ratio of 0.66 (95% confidence interval [CI] 0.52-0.82).

CONCLUSION: In a large, contemporary cohort of statin-treated patients with type 2 diabetes and metabolic dyslipidemia without established atherosclerotic cardiovascular disease, lower achieved LDL-C levels were associated with a monotonically lower risk of incident atherosclerotic cardiovascular disease events. The benefits of achieving very-low LDL-C (<50 mg/dL) in this population requires further evaluation in prospective interventional studies.

 • The American Journal of Medicine (2020) 133:200−206

KEYWORDS: Atherosclerotic cardiovascular disease; Diabetes; Metabolic dyslipidemia

Funding: This work was supported by a contractual agreement between Kaiser Permanente Northern California and Regeneron Pharmaceuticals, Inc. and Sanofi U.S. Funders were involved in the analysis and interpretation of data; in writing the report; and in the decision to submit the article for publication.

Conflicts of Interest: AK, none. JSR, JYL, and HHM have received institutional research funding from Regeneron Pharmaceuticals, Inc. and Sanofi. RJS is an employee of Regeneron Pharmaceuticals, Inc. IK is an employee of Sanofi.

Authorship: All authors had access to the data and a role in writing this manuscript.

Requests for reprints should be addressed to Jamal S. Rana, MD, PhD, 3600 Broadway, Division of Cardiology, Kaiser Permanent Oakland Medical Center, Oakland, California, 94611.

E-mail address: jamal.s.rana@kp.org

https://doi.org/10.1016/j.amjmed.2019.07.003

INTRODUCTION

Patients with type 2 diabetes are considered to be at a high risk for incident and recurrent atherosclerotic cardiovascular disease events compared to those without diabetes.[1] Among patients with diabetes, those with metabolic dyslipidemia (high triglycerides and low high-density cholesterol [HDL-C] levels) are at even higher risk.[2,3] Statin therapy remains the mainstay to reduce the risk of atherosclerotic cardiovascular disease events among patients with diabetes; however, whether to use low-density lipoprotein cholesterol (LDL-C) goals for reducing the risk of atherosclerotic cardiovascular disease events has been a source of some controversy in past guidelines.[4] With regard to patients with diabetes, the 2017 focused update of the 2016 American College of Cardiology Expert Consensus Decision Pathway for nonstatin therapies for LDL-C lowering recommended that among patients with diabetes without established atherosclerotic cardiovascular disease, an LDL-C goal of <100 mg/dL should be considered for initiation of nonstatin therapy.[5] The 2018 cholesterol clinical practice guidelines recommend that for adults with diabetes without established atherosclerotic cardiovascular disease but with multiple atherosclerotic cardiovascular disease risk factors, it may be reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more; for those with diabetes without established atherosclerotic cardiovascular disease and a 10-year atherosclerotic cardiovascular disease risk of 20% or higher, it may be reasonable to add ezetimibe to maximally tolerated statin therapy to achieve this goal.[6]

The benefits of further LDL-C lowering in a diabetes primary prevention population receiving statin therapy has not been well described. We evaluated the association between achieved LDL-C levels and the risk of incident atherosclerotic cardiovascular disease events in a large and contemporary cohort of patients with type 2 diabetes with metabolic dyslipidemia without established atherosclerotic cardiovascular disease receiving statin therapy.

CLINICAL SIGNIFICANCE

- In patients with type 2 diabetes and metabolic dyslipidemia without established atherosclerotic cardiovascular disease who are already receiving statin therapy, a lower achieved low-density lipoprotein-cholesterol (LDL-C) level was associated with a lower risk of incident atherosclerotic cardiovascular disease events.
- Achieving very-low LDL-C levels (<50 mg/dL) could be of potential benefit in this population. Confirming this benefit requires evaluation in prospective randomized studies.

METHODS

The current investigation was an observational cohort study of a population with diabetes and metabolic dyslipidemia without atherosclerotic cardiovascular disease receiving statins. The study population represented members of Kaiser Permanente Northern California (KPNC), a large, integrated health care delivery system caring for ~4.2 million people. Specifically, we used the KPNC Diabetes Registry (N ~346,000) which was established in 1994. The registry is based on a well-validated algorithm, benefits from long follow-up, and excellent representation across age, sex, and race and ethnicity, with extensive capture of end points, pharmacotherapy, and clinical characteristics facilitated by comprehensive electronic medical records (EMRs).[7–9]

In the KPNC Diabetes Registry, we selected individuals with diabetes and metabolic dyslipidemia (elevated triglycerides ≥150 mg/dL and low HDL-C <50 mg/dL [women], <40 mg/dL [men]), ages 21−90 years, receiving statins, and without established atherosclerotic cardiovascular disease (based on up to 10 years of EMR data) as of January 1, 2006 (index date). Further eligibility criteria included continuous health plan membership during the 2 years baseline (2004-2005) prior to the index date, last baseline lipid measures (LDL-C, total cholesterol, triglycerides, HDL-C, and non-HDL-C), and maintenance on statins (≥2 dispensings per year through the end of individual follow-up; evaluated in those with at least 1 year of follow-up prior to censoring or outcome event to mitigate potential for immortal time bias). There were 41,085 patients with diabetes and metabolic dyslipidemia without established atherosclerotic cardiovascular disease at baseline. We excluded 12,649 who were not on statins at baseline. Among the remaining cohort of 28,436, an additional 9,341 (~33%) were excluded because they failed to maintain at least 2 statins dispensings annually during follow-up. Follow-up for atherosclerotic cardiovascular disease events ended on December 31, 2013, or censoring as a result of death, atherosclerotic cardiovascular disease event, or loss of health plan coverage.

The outcomes of interest were incident atherosclerotic cardiovascular disease events defined by hospitalizations due to nonfatal myocardial infarction (International Classification of Diseases, 9th Edition [ICD-9] codes 410.xx or International Classification of Diseases, 10th Edition [ICD-10 codes] I21.xx, I22.xx in primary position), coronary heart disease death (ICD-9 codes 410.xx − 414.xx, 429.2x; or ICD-10 codes: I20.xx − I25.xx from California Mortality Files), or fatal or nonfatal ischemic stroke (ICD-9 codes 430.xx, 431.xx, 433.xx, 434.xx, 436.xx; or ICD-10 codes I60.xx, I61.xx, I63.xx, I64.xx in the primary position).

Unadjusted rates of incident atherosclerotic cardiovascular disease events based on the number of events per 1000 person-years were estimated by strata of achieved LDL-C levels (<50, 50-<70, 70-<100, and ≥100 mg/dL). Cox Proportional Hazard (Cox-PH) models were used to estimate

Table 1 Baseline Characteristics of Patients With Type 2 Diabetes and Metabolic Dyslipidemia With Ongoing Use of Statins, *Per* Achieved LDL-C Categories

	Achieved LDL categories (mg/dL)				*P* Value
	<50	50-<70	70-<100	≥100	
Number (%)	815 (4.3)	3267 (17.1)	9001 (47.1)	6012 (31.5)	
Age, mean (SD)	63.85 (10.9)	64.27 (11.0)	64.37 (10.9)	61.40 (11.5)	<0.0001
Male (%)	504 (61.8)	1810 (55.4)	4185 (46.5)	2377 (39.5)	<0.0001
Race					
White (%)	482 (59.1)	1,877 (57.5)	5,448 (60.5)	3553 (59.1)	<0.0001
Black (%)	32 (3.9)	130 (4.0)	353 (3.9)	372 (6.2)	—
Latino (%)	85 (10.4)	402 (12.3)	1,089 (12.1)	756 (12.6)	—
Asian (%)	155 (19.0)	546 (16.7)	1,288 (14.3)	718 (11.9)	—
Other/ unknown (%)	61 (7.5)	312 (9.6)	823 (9.1)	613 (10.2)	—
Hypertension (%)	780 (95.7)	3135 (96.0)	8521 (94.7)	5411 (90.0)	<0.0001
Smoking status					
Never (%)	431 (54.3)	1739 (54.9)	4979 (56.8)	3250 (56.0)	<0.0001
Past (%)	262 (33.0)	1071 (33.8)	2756 (31.5)	1685 (29.1)	—
Current (%)	101 (12.7)	355 (11.2)	1027 (11.7)	864 (14.9)	—
LDL-C (mg/dL) mean (SD)	40.5 (7.3)	61.2 (5.5)	84.7 (8.3)	123.3 (24.5)	<0.0001
DM duration, (years) mean (SD)	8.4 (6.8)	8.2 (6.8)	7.79 (6.7)	6.6 (6.3)	<0.0001
BMI (kg/m^2) mean (SD)	31.9 (6.1)	32.7 (6.5)	32.8 (6.6)	33.2 (6.7)	<0.0001
Follow-up (years) (SD)	5.9 (2.8)	5.9 (2.7)	6.0 (2.7)	5.7 (2.8)	*P* <0.0001
Charlson comorbidity score (SD)	2.3 (1.6)	2.1 (1.5)	2.0 (1.4)	1.9 (1.4)	*P* <0.0001
Prebaseline insulin use (%)	186 (22.8)	678 (20.8)	1,677 (18.6)	961 (16.0)	<0.0001
Prebaseline oral hyperglycemic agent use (%)	691 (84.8)	2,686 (82.2)	7,117 (79.1)	4,561 (75.9)	<0.0001

BMI=body mass index; DM=diabetes mellitus; LDL-C=low-density lipoprotein-cholesterol; SD=standard deviation.

the adjusted hazard ratios (HRs) for incident atherosclerotic cardiovascular disease events by achieved LDL-C levels (reference: ≥100 mg/dL). The fully adjusted model included age, sex, race, smoking status, duration of diabetes, glycated hemoglobin (HbA1c) levels, hypertension, body mass index, and Charlson comorbidity score.[10]

Unadjusted nonparametric Kaplan−Meier (KM) curves and fully adjusted curves for incident atherosclerotic cardiovascular disease events were generated for participants classified by the 4 LDL-C exposure groups. We performed all statistical analyses using SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

A total of 19,095 individuals met the inclusion criteria. The mean age was 63.4 years and 53.5% were women, with mean duration of diabetes 7.5 years and a mean follow-up of 5.9 years (range: 0 to 8 years) (Table 1). At baseline, the overall cohort had mean LDL-C 91 mg/dL, with 31.5% having LDL-C ≥100 mg/dL. The unadjusted association between rates of incident atherosclerotic cardiovascular disease events per 1000 person-years and achieved LDL-C levels was not significant across LDL-C categories (Table 2). However, after multivariable adjustment for confounding factors, the risk of incident atherosclerotic cardiovascular disease events decreased with decreasing levels of achieved LDL-C relative to reference category of LDL ≥100 mg/dL (*P* <0.001 for trend; Table 2, Figure 1). Compared to the reference group (≥100 mg/dL), statistically significant adjusted HRs were observed for all LDL-C categories <100 mg/dL (*P* value for trend <0.001), with the lowest risk observed in individuals with LDL-C <50 mg/dL (HR 0.7; 95% confidence interval [CI]: 0.5-0.8). There were 6 fewer events per 1000 person-years among patients who had LDL<50 relative to those with LDL≥100 mg/dL (risk difference=−0.006; 95% CI: −0.009, 0.003). We repeated the analyses by using a modified Cox-PH model with death due to other causes as the competing risk.[11]The results were unchanged from previous findings as in Table 2.

Rates of incident atherosclerotic cardiovascular disease events over time during follow-up were estimated for study participants by LDL-C groups via KM curves. We performed both unadjusted and fully adjusted for age, race, smoking, duration of diabetes, HbA1C levels, HDL-cholesterol, hypertension, body mass index, and Charlson comorbidity score. Comparison of the unadjusted (Figure 2A) versus fully adjusted KM curves (Figure 2B) demonstrated a difference in atherosclerotic cardiovascular disease event rates after adjustment resulting in increased time to event among those in low LDL-C categories.

DISCUSSION

In a large, contemporary, statin-treated primary prevention cohort with diabetes and metabolic dyslipidemia, a monotonically lower risk of incident atherosclerotic cardiovascular disease events was observed with lower achieved LDL-C levels. The findings of our study, based on a large

Table 2 Rate and Risk of Future Atherosclerotic Cardiovascular Disease Events Among Patients with Type 2 Diabetes Mellitus and Metabolic Dyslipidemia with Ongoing Use of Statins, per Achieved LDL-C Categories

	Achieved LDL-C categories (mg/dL)				
Follow-up	<50	50- <70	70- <100	≥100	*P* Value
Crude atherosclerotic cardiovascular disease rate (per 1000 person-years)	20.0	22.4	21.0	19.8	
Incident events					
Atherosclerotic cardiovascular disease	96 (11.8)	434 (13.3)	1,130 (12.6)	674 (11.2)	0.017
Nonfatal MI	49 (6.0)	217 (6.6)	532 (5.9)	325 (5.4)	0.12
CHD (fatal)	12 (1.5)	62 (1.9)	165 (1.8)	95 (1.6)	0.54
Ischemic stroke (fatal/nonfatal)	35 (4.3)	155 (4.7)	433 (4.8)	254 (4.2)	0.37
Hazard ratios					Trend
Unadjusted	1.0 (0.8- 1.2	1.1 (1.0-1.3)	1.1 (1.0-1.2)	Reference	<0.0001
Age-gender-race	0.8 (0.7-1.0)	1.0 (0.8-1.1)	0.9 (0.8-1.0)	Reference	<0.0001
Multivariable adjusted model 2*	0.7 (0.5-0.8)	0.8 (0.7-1.0)	0.8 (0.8-0.9)	Reference	<0.0001
Model 2 + Charlson score	0.7 (0.5-0.8)	0.8 (0.7-1.0)	0.9 (0.8-1.0)	Reference	<0.0001

CHD=coronary heart disease; LDL-C=low-density lipoprotein-cholesterol; MI=myocardial infarction.
*Age, sex, race, smoking, duration of diabetes, HbA1C levels, high-density lipoprotein (HDL), hypertension, obesity (body mass index).

contemporary cohort, lend support to practice guidelines and treatment strategies based on LDL-C thresholds for atherosclerotic cardiovascular disease risk reduction in this high-risk population.

In a previous investigation of statin-treated patients with diabetes and without atherosclerotic cardiovascular disease, we found that a lower risk of incident atherosclerotic cardiovascular disease events was associated with lower achieved lipid levels.[12] The current study specifically focused on the higher risk subset of those patients with diabetes and with metabolic dyslipidemia,[2,3] in whom prevention of atherosclerotic cardiovascular disease events despite receiving statins remains a clinical challenge. Traditional nonstatin medications to lower triglycerides such as fibrates (eg, gemfibrozil) and niacin; as well as the more recent studies evaluating agents that increase HDL-C such as the cholesteryl ester transfer protein inhibitors, have shown disappointing results when used in combination with statins.[13] A randomized trial assessing icosapent ethyl, a triglyceride-lowering agent, among patients (50% of whom had diabetes) with elevated triglyceride levels showed that, despite the use of statins, the risk of ischemic events, including cardiovascular death, was significantly lower among those who received treatment.[14] Recently, randomized trials of non-statins (ezetimibe and proprotein convertase subtilisin/kexin 9 [PCSK9] inhibitors) that further lower LDL-C in patients with established atherosclerotic cardiovascular disease (with or without diabetes) reported lower atherosclerotic cardiovascular disease event risk with these agents.[15–17] Interestingly, the absolute benefit of the PCSK9 inhibitor alirocumab with respect to the composite primary end point was greater among patients who had a baseline LDL-C level of ≥100 mg/dL than among patients who had a lower baseline level.[17]

In the population with diabetes without atherosclerotic cardiovascular disease receiving maximally tolerated statins, the 2017 Focused Update of the American College of Cardiology Expert Consensus Decision Pathway recommends considering adding ezetimibe in patients unable to achieve a >50% LDL-C reduction with statin or who have

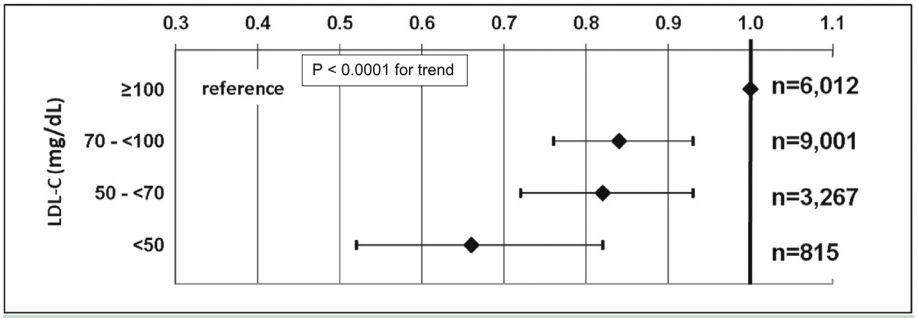

Figure 1 Risk of future atherosclerotic cardiovascular disease events among 19,095 patients with type 2 diabetes mellitus and metabolic dyslipidemia with ongoing use of statins, per achieved low-density lipoprotein-cholesterol (LDL-C) categories.
Adjusted for age, sex, race, smoking, duration of diabetes, HbA1C levels, high-density lipoprotein (HDL), hypertension, obesity (body mass index) and Charlson comorbidity score.

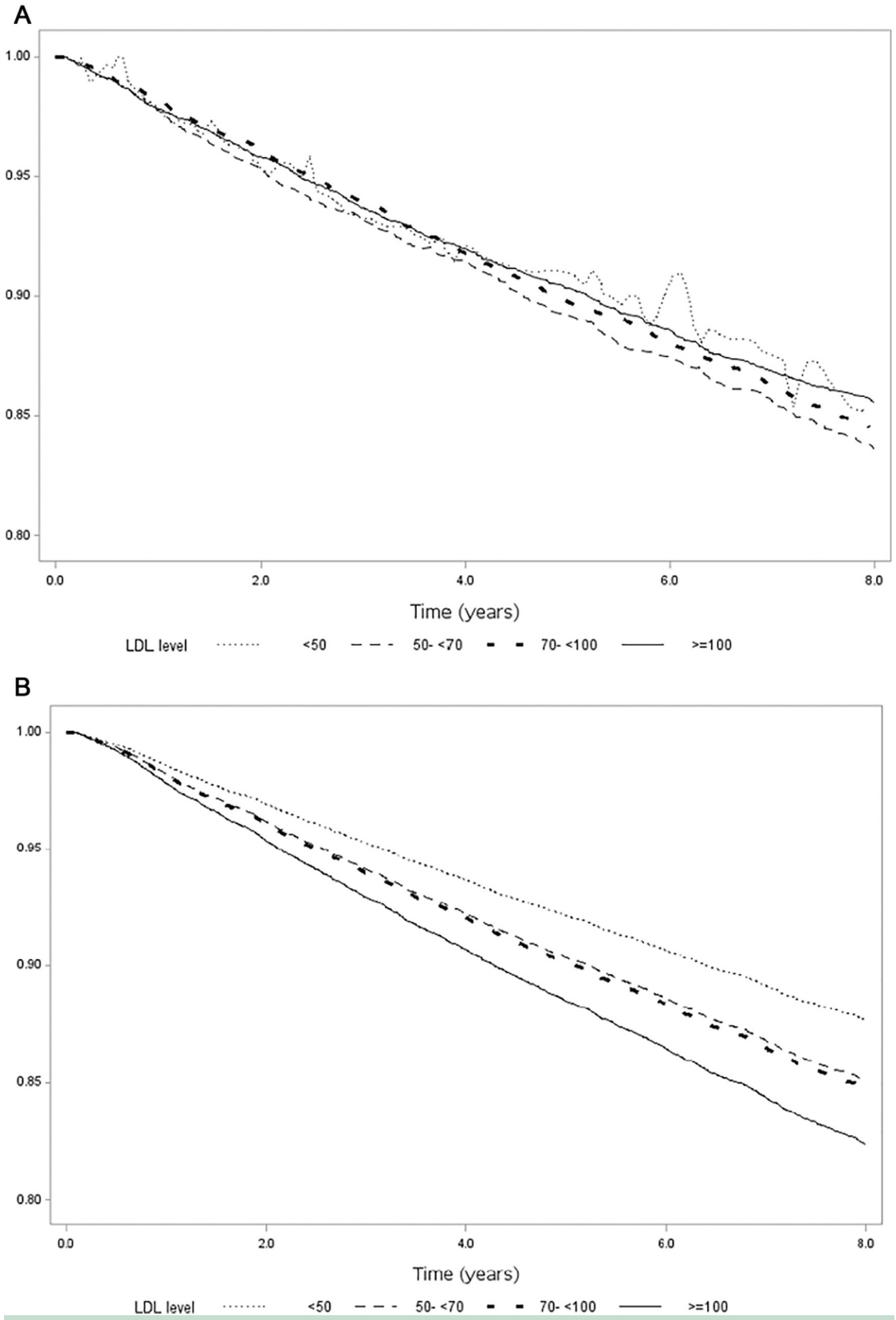

Figure 2 **(A)** Unadjusted Kaplan-Meier curves for incident atherosclerotic cardiovascular events by low-density lipoprotein-cholesterol (LDL-C) categories.
(B) Fully adjusted Kaplan-Meier curves for incident atherosclerotic cardiovascular events by low-density lipoprotein-cholesterol (LDL-C) categories.

LDL-C ≥100 mg/dL.[5] The 2018 Cholesterol Clinical Practice Guidelines similarly recommend adding nonstatin treatment to maximally tolerated statin therapy for adults with diabetes with a high estimated 10-year atherosclerotic cardiovascular disease risk with an aim to reduce LDL-C levels by 50% or more.[6] The American Diabetes Association 2018 Standards for Medical Care guidelines for patients with diabetes and established atherosclerotic cardiovascular disease recommend considering the addition of nonstatin therapies (such as ezetimibe and PCSK9 inhibitors) in patients on maximally tolerated statin dose with LDL-C ≥70 mg/dL; however, no specific LDL-C goal is suggested for patients with diabetes without atherosclerotic cardiovascular disease.[1] The European Society of Cardiology and European Atherosclerosis Society Task Force provide more inclusive recommendations regarding PCSK9 inhibitors, such that PCSK9 inhibitors might be considered in patients with diabetes with, or at high risk for, target organ damage even if they do not have a history of atherosclerotic cardiovascular disease and are not able to meet LDL-C goals through statin and ezetimibe use.[18] Our study provides support for such an LDL-C goals-based approach, although we do not offer evidence of the benefit of any particular pharmacological strategy to achieve those goals. These and other strategies required to achieve treatment goals need to be further assessed in randomized studies for a primary prevention population with diabetes and metabolic dyslipidemia.

The strengths of our study include a large, representative, and diverse population of patients with diabetes and metabolic dyslipidemia in a usual care setting, with comprehensive and a relatively accurate ascertainment of the risk factors and end points of interest. The nature of data source used also helped ascertain the included population was receiving statins throughout the study follow up period. Several limitations of our study should also be noted. Although we controlled for the duration of diabetes and HbA1c in our models, historical control of other risk factors such as hypertension and past duration of statin use may further confound the results. In addition, the study did not account for potential changes in LDL-C levels during follow-up. Though the study was limited to patients who had ≥2 statin dispensing during each year of follow-up, it did not account for baseline level of the intensity of statin treatment and potential changes in statin dosing during follow-up; however, restricting the analyses to ongoing statin users helped ensure that background therapeutic effect of statins was incorporated across various levels of achieved LDL-C. We did not evaluate secondary adherence (ie, refill timing and gaps in day's supply), though we did ensure from the refill history that the patient continued to be dispensed statins throughout the follow-up period. Finally, although the study was restricted to well-defined end points of myocardial infarction, ischemic stroke, and coronary heart disease death, the progression or incidence of atherosclerotic cardiovascular disease in this population may manifest in absence of these hard events (eg, as stable angina or percutaneous coronary interventions).

We studied how incidence of atherosclerotic cardiovascular disease events was related to achieved LDL-C, but had no data on the LDL-C goal that was targeted by the provider. Although our data are suggestive, we cannot directly infer whether altering lipid targets or lipid-lowering therapy will change the incidence of atherosclerotic cardiovascular disease events in the study population. Moreover, unlike a clinical trial with a specific intervention, we did not study how patients achieved their LDL-C levels and, thus, cannot address the impact of different treatment strategies on atherosclerotic cardiovascular disease event risk. Because of the adopted study design, we also cannot rule out the possibility of whether the observed reduction in risk for atherosclerotic cardiovascular disease event was influenced by variations in statin adherence, duration, and intensity measures as opposed to variation on achieved LDL-C while being on stable therapy.

These data are derived from a regional-based integrated health care delivery system, and the distribution of LDL-C levels and atherosclerotic cardiovascular disease events may not be representative of other regions or health care settings in the United States or other regions. However our findings concerning purely the associative relationships between LDL-C and atherosclerotic cardiovascular disease event risk should be generalizable across health care systems. This study was based on point treatment models limited to individuals that maintain statin treatment throughout follow-up. Given these constraints, we consider the findings can generate many hypothesis, but acknowledge that in addition to randomized controlled trials, other observational cohort studies are needed that better address the effects of changes in LDL-C, statin utilization, dose, and intensity (eg, including those that were excluded because of discontinued statin use) during follow-up.

CONCLUSION

In a large cohort of statin-treated patients with diabetes and metabolic dyslipidemia without atherosclerotic cardiovascular disease, we observed a lower risk of incident atherosclerotic cardiovascular disease events with lower levels of achieved LDL-C levels. Compared to the reference category of those with LDL-C ≥100 mg/dL, the HR for incident atherosclerotic cardiovascular disease events was lowest for patients achieving a very-low LDL-C level of <50 mg/dL. The benefits of achieving this very-low level of LDL-C in this population, especially in those who have elevated LDL-C despite statin therapy, as well as strategies to achieve these LDL-C targets, requires further evaluation in prospective interventional studies.

References

1. American Diabetes Association. Cardiovascular Disease And Risk Management: Standards Of Medical Care In Diabetes-2018. *Diabetes Care* 2018;41:S86–S104.
2. Rana JS, Liu JY, Moffet HH, et al. Metabolic dyslipidemia and risk of coronary heart disease in 28,318 adults with diabetes mellitus and

low-density lipoprotein cholesterol <100 mg/dl. *Am J Cardiol* 2015;116:1700–4.
3. Lee JS, Chang PY, Zhang Y, Kizer JR, Best LG, Howard BV. Triglyceride and HDL-C dyslipidemia and risks of coronary heart disease and ischemic stroke by glycemic dysregulation status: the strong heart study. *Diabetes Care* 2017;40:529–37.
4. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:2889–934.
5. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2017 focused update of the 2016 ACC Expert Consensus Decision Pathway on the Role of non-statin therapies for ldl-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: A report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol* 2017;70:1785–822.
6. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [epub ahead of print]. *J Am Coll Cardiol* 2019;73(24):e285–350. https://doi.org/10.1016/j.jacc.2018.11.002.
7. Karter AJ, Ferrara A, Liu JY, Moffet HH, Ackerson LM, Selby JV. Ethnic disparities in diabetic complications in an insured population. *JAMA* 2002;287:2519–27.
8. Karter AJ, Schillinger D, Adams AS, et al. Elevated rates of diabetes in Pacific Islanders and Asian subgroups: The Diabetes Study of Northern California (DISTANCE). *Diabetes Care* 2013;36:574–9.
9. McEwen LN, Karter AJ, Waitzfelder BE, et al. Predictors of mortality over 8 years in type 2 diabetic patients: Translating Research Into Action for Diabetes (TRIAD). *Diabetes Care* 2012;35:1301–9.
10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* 1987;40:373–83.
11. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509.
12. Rana JS, Liu JY, Moffet HH, Boklage SH, Khan I, Karter AJ. Risk of incident atherosclerotic cardiovascular disease events by achieved atherogenic lipid levels among 62,428 statin-treated individuals with diabetes mellitus. *Am J Cardiol* 2018;122(5):762–7.
13. Warraich HJ, Wong ND, Rana JS. Role for combination therapy in diabetic dyslipidemia. *Curr Cardiol Rep* 2015;17:32.
14. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med* 2019;380(1):11–22.
15. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;372:2387–97.
16. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;376:1713–22.
17. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018;379(22):2097–107. https://doi.org/10.1056/NEJMoa1801174.
18. Landmesser U, Chapman MJ, Farnier M, et al. European Society of Cardiology/European Atherosclerosis Society Task Force consensus statement on proprotein convertase subtilisin/kexin type 9 inhibitors: practical guidance for use in patients at very high cardiovascular risk. *Eur Heart J* 2017;38:2245–55.