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How Did the Updated 2019 European Society of Cardiology/European Atherosclerosis Society Risk Categorization for Patients with Diabetes Affect the Risk Perception and Lipid Goals? A Simulated Analysis of Real-life Data from EPHESUS Study

ABSTRACT

Background: The recent 2019 European Society of Cardiology/European Atherosclerosis Society practice guidelines introduced a new risk categorization for patients with diabetes. We aimed to compare the implications of the 2016 and 2019 European Society of Cardiology/European Atherosclerosis Society guidelines with regard to the lipid-lowering treatment use, low-density lipoprotein cholesterol goal attainment rates, and the estimated proportion of patients who would be at goal in an ideal setting.

Methods: Patients with diabetes were classified into 4 risk categories according to 2019 European Society of Cardiology/European Atherosclerosis Society dyslipidemia guidelines from the database of EPHESUS (cross-sectional, observational, countrywide registry of cardiology outpatient clinics) study. The use of lipid-lowering treatment and low-density lipoprotein cholesterol goal attainment rates were then compared according to previous and new guidelines.

Results: This analysis included a total of 873 diabetic adults. Half of the study population (53.8%) were on lipid-lowering treatment and almost one-fifth (19.1%) were on high-intensity statins. While low-density lipoprotein cholesterol goal was achieved in 19.5% and 7.5% of patients, 87.4% and 69.6% would be on target if their lipid-lowering treatment was intensified according to 2016 and 2019 European Society of Cardiology/European Atherosclerosis Society lipid guidelines, respectively. The new target <55 mg/dL could only be achieved in 2.2% and 8.1% of very high-risk primary prevention and secondary prevention patients, respectively.

Conclusion: The control of dyslipidemia was extremely poor among patients with diabetes. The use of lipid-lowering treatment was not at the desired level, and high-intensity lipid-lowering treatment use was even lower. Our simulation model showed that the high-dose statin plus ezetimibe therapy would improve goal attainment; however, it would not be possible to get goals with this treatment in more than one-third of the patients.

Keywords: Diabetes mellitus, dyslipidemia, atherosclerosis, lipid guidelines, low-density lipoprotein cholesterol, cardiovascular risk

INTRODUCTION

Diabetes mellitus (DM) is associated with an average 2-fold increased risk for cardiovascular disease (CVD).[1] However, the risk of having CVD is not uniform among DM patients and varies according to comorbidities and duration of the disease. The risk of CVD in a newly diagnosed DM patient is similar to a patient without DM. However, DM accelerates atherosclerosis and patients become CVD risk equivalent after 5-15 years of diagnosis.[2]

Patients with DM mostly have additional risk factors for CVD. The clustering of risk factors has a greater impact on cardiovascular outcomes than hyperglycemia alone.[3] Hence, every patient with DM should be screened for CVD risk factors.

ORIGINAL INVESTIGATION

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Apart from conventional risk factors, the presence of microvascular disease has also been associated with a higher CVD risk in DM patients.[4] Therefore, patients with target organ damage are considered at very high risk in the present European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines for the management of dyslipidemia.[5]

The new guidelines re-classified the CVD risk of patients with diabetes quite differently from the previous one. Accordingly, the treatment goals seem to be changed in most patients with diabetes. As it is essential to implement the guidelines into real-life practice, we wondered about the impact of the new CV risk classification introduced with the recent update of the ESC/EAS dyslipidemia guidelines on the risk classification of patients with DM in daily practice. We planned analysis of the patients with diabetes from the Evaluation of Perceptions, Knowledge and Compliance with tHE Guidelines for Secondary Prevention in Real-Life Practice: A survey on the Under-treatment of HypercholeSterolemia (EPHESUS) study database to assess the use of lipid-lowering treatment (LLT) and lipid target attainment comparing the recommendations of the ESC/EAS 2016 and 2019 guidelines'.[1,5] We also aimed to uncover to what extent LLT was effective and the required percent reductions of low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C) to get patients with diabetes to the treatment goals.

METHODS

Study Design and Setting

The methodology of EPHESUS trial (identifier no: NCT02608645, Clinical Trials.gov) has been published in detail elsewhere.[6] In brief, the EPHESUS trial was a cross-sectional, observational, countrywide registry which included consecutive 1868 patients admitted to cardiology outpatient clinics between 1 March 2016 and 1 January 2018. Patients < 18 years of age, current pregnancy or postpartum status of <6 months, a history of acute coronary syndrome within the last month, a history of liver or muscle disease, and chronic kidney disease with a creatinine level of >3 mg/dL were all excluded. The study covered both primary prevention (PP) and secondary prevention (SP) patients. The demographic and clinical characteristics of the patients were evaluated by a survey. Risk factors for CVD such as smoking, hypertension, and family history were noted. Current treatment for dyslipidemia, the use of LLT, and the dose of the drugs were recorded. Atorvastatin 40 and 80 mg/day, and rosuvastatin 20 and 40 mg/day were accepted as high-intensity statin treatment. The present analysis included only the patients with diabetes in the EPHESUS database. Patients with diabetes were recognized as self-report, had a previous diagnosis of diabetes in medical records, or being on antidiabetic agent, and both type 1 and type 2 patients with diabetes were included. Patients who have not had diabetes were not included in the present analysis.

Study Population

The PP group consisted of very high risk (DM with target organ damage or at least 3 major risk factors), high risk (patients with DM duration ≥ 10 years or another additional risk factor), and moderate risk (young patients (<50 years) with DM duration < 10 years, without additional risk factors) in line with the 2019 ESC/EAS dyslipidemia guidelines.[1] The former 2016 ESC/EAS guideline has categorized patients with diabetes into 3 risk

HIGHLIGHTS

- The control of dyslipidemia is poor among patients with diabetes.
- The updated target of <55 mg/dL could only be achieved in a minority of patients.
- High-dose statin plus ezetimibe therapy might not be good enough for high-risk patients.
- Non-high-density lipoprotein cholesterol goal attainment is also very poor in patients with diabetes.
- Knowledge and awareness of physicians giving care to diabetics should be increased urgently.

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groups; very high risk: patients with target organ damage or 1 major risk factor, high risk: patients with diabetes without risk factors or moderate risk criteria, moderate risk: some young people with type I diabetes.[5] Major risk factors were recognized as hypertension, dyslipidemia, smoking, and obesity. Hypertension was defined as having systolic blood pressure > 140 mm Hg, or diastolic blood pressure > 90 mm Hg, or taking antihypertensive medication. Dyslipidemia was defined as fasting total cholesterol > 240 mg/dL, or LDL > 160 mg/dL, or being on LLT. Hypertriglyceridemia was defined as serum triglycerides ≥ 150 mg/dL or being on LLT. Smoking status was recorded based on the patient's self-report. A body mass index > 30 kg/m^2 was accepted as obesity. Patient's body weight and height were measured during their outpatient clinic visit with the equipment available in the clinic or simply recording the value if they knew them. The SP group was composed of patients with coronary artery disease including post-myocardial infarction patients or patients who had undergone percutaneous coronary intervention or coronary bypass surgery, patients with peripheral artery disease, or patients with documented atherosclerotic cerebrovascular disease. The study population was divided into 4 groups according to the aforementioned risk levels (moderate, high, very high-risk, and SP) and the target attainment of those groups was then compared according to the 2016 and 2019 ESC/EAS guidelines.[1,5]

Laboratory Analysis and Definition of Targets

Fasting blood glucose, total cholesterol (TC), HDL-C, triglycerides, and creatinine levels were measured according to standardized biochemical tests. Friedewald's formula was used to estimate LDL-C levels, and for patients whose triglyceride was >400 mg/dL, direct LDL-C levels were used.

Non-HDL-C was calculated by subtracting HDL-C from TC. All blood tests were performed within 1 month before enrollment of the subjects, and levels of LDL-C before the initiation of LLT were obtained from patient records.

The target LDL-C levels for PP patients with very high, high, and moderate risk groups were <55, <70, and <100 mg/dL and non HDL-C levels were <85, <100, and <130 mg/dL, respectively, according to 2019 ESC/EAS guidelines, while <70, <100, and <115 mg/dL for LDL-C and <100, <130, and <145 mg/dL for non-HDL-C levels according to the 2016 ESC/EAS guidelines, respectively. In accordance with the 2019 ESC/EAS guidelines, the same target values were used for both the SP and very high-risk PP groups.

Simulation Model

A simulation model was created to estimate what percentage of patients would be at goal and the hypothetical decrease in LDL-C in an ideal setting using intensified doses of statins and ezetimibe. The 2019 ESC/EAS lipid guidelines recommendations were used to calculate additional lipid-lowering effects of statins and ezetimibe.[1] For patients who were not on LLT, a decrease in LDL-C of 65% was estimated, simulating the effect of high-dose statin plus ezetimibe. For patients who were on moderate-intensity statin, a decrease in LDL-C of 50% was estimated, simulating the effect of high-dose statin plus ezetimibe. For patients who were on high-dose statin, a decrease in LDL-C of 15% was estimated, simulating the effect of ezetimibe.

Ethical Considerations

The study was approved by the Local Ethics Committee on January 26, 2016 with number: 80558721/11, and all the participants gave written informed consent. The study was conducted in compliance with the Declaration of Helsinki following the current legal regulations and medical research recommendations suggested by the good clinical practice guidelines.

Statistical Analysis

Continuous variables were expressed as median and interquartile range. The normality of the variables was tested using Shapiro–Wilk test. Non-normally distributed variables were analyzed with the Kruskal–Wallis test, and Dunnet's multiple comparison test was used in post hoc analysis. Categorical variables were given as frequency and percentage. The chi-square or Fisher exact test was used for the analysis of categorical variables. Data obtained in this study were statistically analyzed with the IBM Statistical Package for Social Sciences Statistics for Windows, Version 22.0. (IBM Corp., Armonk, NY, USA). A *P* value of <.05 was considered significant.

RESULTS

A total of 873 consecutive patients with diabetes (mean age 61.74 ± 10.55, 48.7% female) were included in the present analysis. Of those, 571 (65.4%) were in SP and 302 (34.6%) in PP groups. Of the PP subjects, about one-third (29.8%) were at very high, more than half (62.2%) were at high, and 7.9% were at moderate CVD risk according to 2019 dyslipidemia guidelines. However, 2016 guidelines have classified 90% of PP patients as very high, 3% as high, and 7% as moderate risk groups. The distribution of patients in accordance with 2016 and 2019 ESC/EAS guidelines and risk groups is shown in Figure 1. Demographic characteristics and the comorbidities of the study population are presented in Table 1. As expected, the median age was increasing significantly with the escalation of the risk categories. The number of females was also rising with the increasing risk levels among the patients

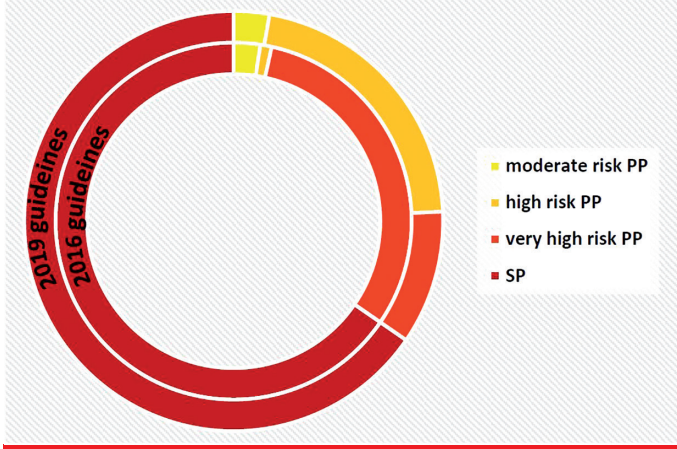

Figure 1. Distribution of our study population according to risk groups.

Table 1. Demographic Characteristics of the Diabetic Patient Population with Regard to Risk Levels

Baseline Demographics	Primary Prevention n=302 (34.6%) Moderate Risk n=24 (2.7%)	High Risk n=188 (21.5%)	Very High-Risk n=90 (10.3%)	Secondary Prevention n=571 (65.4%)	*P*
Age (years)	51 (45-55)	57 (50-63)	66 (59-71)	64 (56-76)	<.001
BMI (kg/m^2)	29 (26-31)	30 (27-34)	32 (29-37)	29 (26-32)	<.001
Female (%)	10 (41.7)	127 (67.6)	67 (74.4)	221 (38.7)	<.001
Place of residence (rural) (%)	1 (4.3)	31 (16.5)	29 (32.2)	152 (26.7)	.001
Education (primary or illiterate) (%)	12 (52.2)	118 (62.8)	66 (73.3)	403 (70.6)	.05
Diabetes duration (months)	24 (9-54)	60 (28-120)	84 (41-120)	84 (39-120)	<.001
Risk factors for CVD					
Smoking (%)	4 (16.7)	37 (19.7)	30 (33.3)	124 (21.7)	.055
Hypertension (%)	6 (25.0)	136 (72.3)	86 (95.6)	446 (78.1)	<.001
Family history of CVD (%)	9 (37.5)	70 (37.4)	28 (31.5)	241 (42.7)	.172
Dyslipidemia (%)	4 (16.7)	62 (33.0)	70 (77.8)	185 (32.4)	<.001
Hypertriglyceridemia (%)	7 (29.2)	69 (36.7)	38 (42.2)	163 (28.5)	.024
Concomitant diseases					
Chronic kidney disease (%)	1 (4.2)	8 (4.3)	11 (12.2)	61 (10.7)	.034
Atrial fibrillation (%)	1 (4.2)	13 (6.9)	14 (15.6)	38 (6.7)	.024
Heart failure (%)	0 (0)	10 (5.3)	8 (8.9)	109 (19.3)	<.001
COPD (%)	3 (12.5)	28 (14.9)	17 (18.9)	120 (21.0)	.245

Categorical variables were given as frequency and percentage n (%). Not normally distributed data are presented as median and interquartile range.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease.

with diabetes in the PP category. Detailed post hoc analysis of the variables is given in Supplementary Table 1.

Comorbidities were more common in patients with higher risks (Table 1). Almost all patients (95.6%) in the very high-risk group had hypertension, whereas only 25.0% of the moderate-risk group were hypertensive ($P < .001$). Dyslipidemia was also very common in the very high-risk group compared to lower risk groups (77.8% vs. 16.7%, 33.0%, and 32.4% for moderate-risk, high-risk, and SP groups, respectively, $P < .001$).

More than half of the study population (55.5%, n=485) was on LLT and about one-fifth (19.1%, n=159) was on high-intensity LLT. The use of LLT was comparable with aspirin in PP patients 34.1% vs. 33.8% and lower than aspirin among SP patients 68.1% vs. 84.4%, respectively. None of the patients were on ezetimibe. Almost all patients were receiving oral antidiabetic agents (Table 2).

The laboratory data are shown in Table 3. Briefly, fasting blood sugar level was not different according to the risk

Table 2. MedicationsThat Diabetic Patients Were Receiving During the Survey

n (%)	Primary Prevention Moderate Risk n=24 (2.7)	High Risk n=188 (21.5)	Very High-Risk n=90 (10.3)	Secondary Prevention n=571 (65.4)	*P*
Statins (%)	3 (12.5)	52 (27.7)	37 (41.1)	378 (66.2)	<.001
High-intensity statins (%)	0 (0)	8 (15.4)	11 (30.6)	140 (36.4)	.013
Fibrates (%)	2 (8.3)	7 (3.7)	5 (5.6)	25 (4.4)	.719
LLT (%)	5 (20.8)	56 (29.8)	42 (46.7)	389 (68.1)	<.001
Aspirin (%)	3 (12.5)	56 (29.8)	43 (47.8)	482 (84.4)	<.001
P2Y12 (%)	0 (0)	5 (2.7)	2 (2.2)	251 (44.0)	<.001
OAC (%)	1 (4.2)	8 (4.3)	8 (8.9)	32 (5.6)	.462
OAD (%)	20 (83.3)	172 (91.5)	80 (88.9)	455 (79.7)	.001
Insulin (%)	3 (12.5)	51 (27.1)	28 (31.1)	226 (39.6)	.001
Beta-blockers (%)	4 (16.7)	56 (29.8)	38 (42.2)	437 (76.5)	<.001
ACE/ARB (%)	3 (12.5)	110 (58.5)	62 (68.9)	570 (65.3)	<.001
CCB (%)	3 (12.5)	33 (17.6)	27 (30.0)	115 (20.1)	.072
Digoxin (%)	0 (0)	2 (1.1)	5 (5.6)	10 (1.8)	.058

ACE/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blocker; OAC, oral anticoagulant; OAD, oral antidiabetic; P2Y12, platelet purinoceptor.

Table 3. Laboratory Data of the Diabetic Patients with Regard to Risk Categories

Biochemistry	Primary Prevention			Secondary Prevention	*P*
	Moderate Risk n = 24 (2.7)	High Risk n = 188 (21.5)	Very High-Risk n = 90 (10.3)	n = 571 (65.4)	
Glucose (mg/dL)	146 (125-195)	142 (116-193)	145 (117-206)	151 (121-200)	.657
Creatinine (mg/dL)	0.8 (0.7-0.9)	0.8 (0.6-0.9)	0.9 (0.7-1.0)	0.9 (0.8-1.1)	<.001
eGFR (mL/min)	125 (78-179)	108 (82-137)	82 (63-117)	89 (67-112)	<.001
AST (U/L)	19 (15-25)	20 (16-28)	21 (16-31)	20 (15-26)	.372
ALT (U/L)	29 (17-36)	22 (16-35)	22 (15-31)	20 (15-29)	.017
CK (U/L)	58 (46-81)	78 (48-121)	55 (44-93)	77 (47-132)	.043
Lipid parameters					
Total-C (mg/dL)	205 (191-225)	211 (182-239)	233 (198-268)	185 (149-221)	<.001
HDL-C (mg/dL)	45 (35-47)	45 (38-52)	45 (39-51)	41 (35-49)	<.001
Triglycerides(mg/dL)	153 (126-250)	172 (125-226)	184 (131-243)	157 (119-216)	.045
Non-HDL-C(mg/dL)	161 (148-181)	164 (133-189)	190 (158-225)	142 (107-178)	<.001
LDL-C (mg/dL)					
Before treatment	127 (113-151)	147 (125-178)	175 (162-199)	144 (120-169)	<.001
On treatment	125 (108-151)	128 (101-148)	151 (118-175)	105 (78-138)	<.001
LDL-C change	0 (0-5)	9 (0-36)	20 (0-56)	27 (0-64)	<.001
%LDL-C change	0 (0-4)	6 (0-23)	11 (0-29)	19 (0-42)	<.001
Goal attainment rates					
-LDL-C goal					
2019	5 (20.8)	13 (6.9)	2 (2.2)	46 (8.1)	.018
2016	8 (33.3)	46 (24.5)	9 (10.0)	108 (18.9)	.011
Non-HDL-C goal					
2019	4 (16.7)	12 (6.4)	5 (5.6)	52 (9.1)	.216
2016	5 (20.8)	44 (23.4)	5 (5.6)	114 (20.0)	.004
Goal attainment rates among high-dose LLT					
LDL-C Goal					
2019	-	2 (25.0)	0	17 (12.7)	.276
2016	-	3 (37.5)	1 (10.0)	38 (28.4)	.372
Non-HDL-C goal					
2019	-	1 (12.5)	1 (10.0)	20 (14.9)	.901
2016	-	4 (50.0)	1 (10.0)	42 (31.3)	.181

ALT, alanine transaminase; AST, aspartate transaminase; CK, creatinine kinase; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

categories of the patients. However, lipid control was not at the desired level and the median LDL-C values were higher than the target recommended levels. The median LDL-C change after LLT was not good enough to get the goals (Figure 2). Overall, 19.5% and 7.5% of the study population have attained the LDL-C goals, and only 14.8% and 4.9% have reached both the LDL-C and non-HDL-C targets according to the 2016 and 2019 ESC/EAS guidelines, respectively. Of those patients who were on high dose LLT, 26.4% (n = 42) and 11.9% (n = 19) attained 2016 and 2019 ESC/EAS guidelines LDL-C targets, respectively. Detailed post- hoc analysis of the variables is given in Supplementary Table 2. A comparison of 2016 and 2019 guidelines according to goal attainment rates is presented in Figure 3.

The additional LDL-C and non-HDL-C reductions required to reach the guidelines recommended goals are presented in Table 4. The median LDL-C decreases required to reach 2019 and 2016 guidelines' targets were 55 and 36 mg/dL, respectively, and non-HDL-C reductions were 63 and 43 mg/dL respectively, for the whole diabetic population. Of the patients who were on LDL-C target, 60.2% and 34.8% were not on non-HDL-C target according to 2016 and 2019 ESC/EAS guidelines respectively. Detailed post hoc analysis of the variables is given in Supplementary Table 3.

The simulation model that assumed every patient was on ideal LLT showed 763 (87.4%) and 608 (69.6%) patients would be at LDL-C goal as per 2016 and 2019 ESC/EAS lipid guidelines, respectively. The number of patients who would be at LDL-C goal according to 2016 and 2019 guidelines is depicted in Figure 4.

DISCUSSION

The main findings of the present analysis of EPHESUS study are: (a) guidelines recommended goal attainment is poor

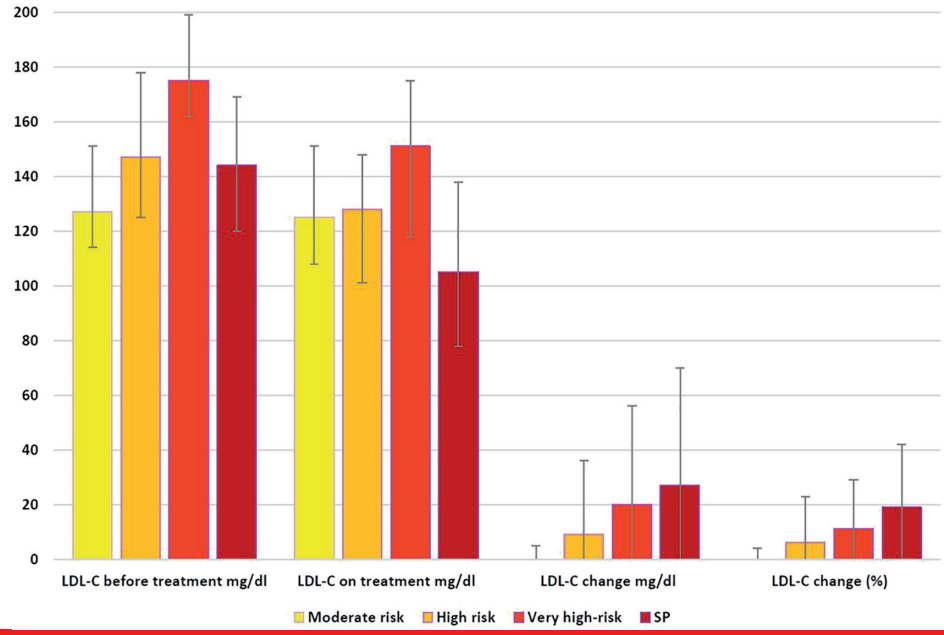

Figure 2. Effect of LLT on LDL-C. LDL-C before treatment, after treatment, absolute change in LDL-C, and percent change in LDL-C were shown respectively. LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering treatment.

(20%) according to 2016 ESC/EAS guidelines and even worse (8%) as per new 2019 ESC/EAS guidelines recommendations in the patients with DM followed in cardiology outpatient clinics; (b) the updated LDL-C target of <55 mg/dL could only be achieved in a minority of both SP (8%) and very high-risk PP (2%) patients with DM; and (c) high-dose statin plus ezetimibe therapy might not be good enough for high-risk patients with diabetes according to our simulation model. Moreover, two-thirds and one-third of the patients who have achieved LDL-C target are not on non-HDL-C target according to 2016 and 2019 ESC/EAS guidelines, respectively.

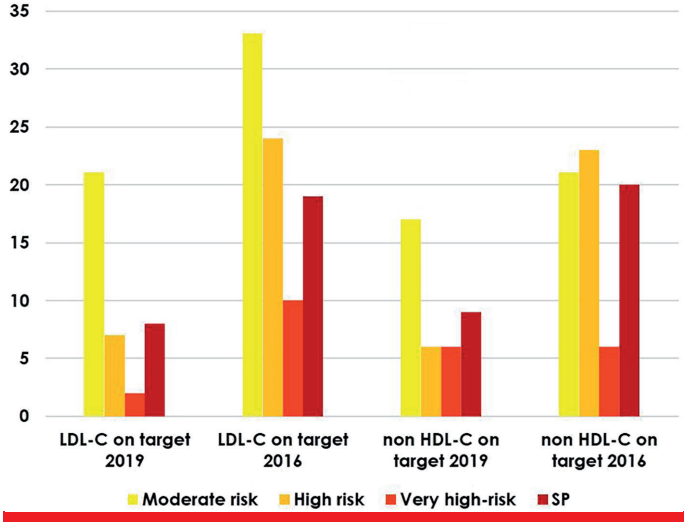

Figure 3. Goal attainment rates according to 2019 and 2016 ESC/EAS guidelines for LDL-C and non-HDL-C. ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol;

Interestingly, aspirin use is higher than expected and is comparable with LLT use in PP patients.

Lipid control is poor in DM patients in real-life studies.[7] Our study showed that 68% of SP patients with diabetes were on LLT (36% were on high-intensity statins) in a real-world analysis of a large multicenter countrywide data. The rate of LLT use was higher in SP patients of registries from Western populations. Euroaspire V study which aimed to provide an objective assessment of the clinical implementation of European guidelines on the management of dyslipidemias in coronary patients reported that 84% of SP patients were on LLT whereas 31% of them were on high-intensity LLT.[8] However, Euroaspire V was performed in 27 countries without real-world representation of their population (national coordinators identified one to three geographical areas within their country) and enrolled patients non-consecutively which might cause a selection bias. Another study from the UK conducted on SP patients (30% diabetic) reported that 79% of subjects were on statins and 31% were using high-intensity statin therapy. A total of 31% of the patients were reported to attain the LDL-C goal of <70 mg/dL.[9] Retrospective design and availability of patient information in the database were the limitations of the study. The SURF (The SUrvey of Risk Factors) study intended to simplify the recording and control of CVD risk factors of patients with established coronary heart disease from European, Asian, and the Middle East countries. The SURF study showed that 80% of the SP patients were on statins and 30% of them were at the LDL-C target of <70 mg/dL.[10] The SURF study was conducted in centers those willing to participate which might cause a selection bias. Lipoprotein-Associated phospholipasE A2 in stable coronary aRTEry diSease (LAERTES) study examined very high-risk patients and reported a higher proportion of LLT

Table 4. Additional Median Absolute (mg/dL) and Percent (%) Decrease Required to Reach the Goals in Diabetic Patients According to 2019 and 2016 Guidelines

		Primary Prevention				
		Moderate Risk n = 24 (2.7%)	High Risk n = 188 (21.5%)	Very High-Risk n=90 (10.3%)	Secondary Prevention n = 571 (65.4%)	*P*
2019 Guidelines	LDL-C, mg/dL	25 (8-51)	58 (31-78)	96 (64-120)	50 (23-83)	<.001
	LDL-C, %	20 (8-34)	45 (31-53)	63 (53-68)	48 (29-60)	<.001
	Non-HDL-C, mg/dL	31 (18-51)	64 (33-89)	105 (73-140)	57 (22-93)	<.001
	Non-HDL-C, %	19 (12-28)	39 (25-47)	55 (46-62)	40 (21-52)	<.001
2016 Guidelines	LDL-C, mg/dL	10 (0-37)	28 (1-48)	81 (49-105)	35 (8-68)	<.001
	LDL-C, %	8 (0-24)	21 (1-32)	54 (41-60)	33 (10-49)	<.001
	Non-HDL-C, mg/dL	16 (3-36)	34 (3-59)	90 (58-125)	42 (7-78)	<.001
	Non-HDL-C, %	9 (2-20)	21 (2-31)	47 (38-56)	29 (6-44)	<.001

LDL-C: low-density lipoprotein cholesterol, non-HDL-C: non-high-density lipoprotein cholesterol.

use (87%). Of those, 20% were at LDL-C level of <70 mg/dL and 5% were at LDL-C level of <55 mg/dL.[11] LAERTES was a prospective hospital-based study conducted in Greece which did not represent a wide population. Unlike these studies, we included all consecutive patients admitted to cardiology outpatient clinics with a real-world representation of the countrywide population.

Household and regional income and also the availability of the drug are the determinants of SP drug use for CVD prevention. The PURE (The Prospective Urban Rural Epidemiology) study aimed to investigate the use of proven effective secondary preventive drugs including statins in individuals with a history of coronary heart disease or stroke in high-, upper-middle-, lower-middle-, or low-income countries.[12] Use of statins was highest in high-income countries (66.5%), lowest in low-income countries (3.3%), and decreased in line with the reduction of the country's economic status [*P* (trend) < .0001]. Turkey was classified as an upper-middle income country in the PURE study. However, the Turkish health system has some unique features that differentiate it from other upper-middle-income countries. First, statins, ezetimibe, and fibrates are fully reimbursed by the social security system of Turkey which covers almost all the citizens. Second, generic statins are cheap and widely available, and third, it is very easy to make an appointment for a specialist visit with the help of e-health technologies. Despite these advantages, LLT use is far from the ideal level. Therefore, we might speculate lower rate of LLT use could not only be associated with economic problems while physician- and patient-related factors might even play a greater role. Medical inertia is also common in patients with diabetes.[13] We have shown physician-related factors play a major role in the discontinuation of statin therapy.[14,15] Another study from our country has shown statin discontinuation was at the patient's discretion in 74% of cases emphasizing the importance of patient-related factors.[16] Hence, educational activities regarding atherosclerosis treatment

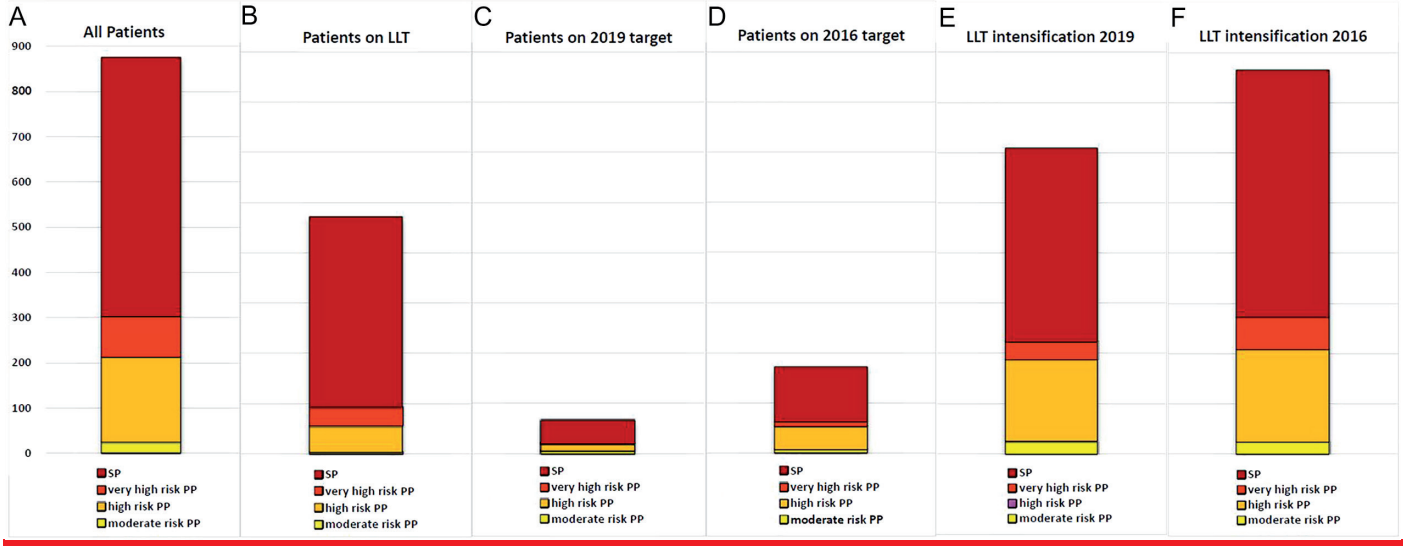

Figure 4. A: All patients. B: Patients on LLT. C: Patients on 2016 ESC/EAS guidelines target. D: Patients on 2019 ESC/EAS guidelines target. E: Patients who would be on 2019 ESC/EAS guidelines target if they were on ideal LLT. F: Patients who would be on 2016 ESC/EAS guidelines target if they were on ideal LLT. ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; LLT, lipid-lowering treatment; PP, primary prevention; SP, secondary prevention.

options both for physicians and patients might be a part of the solution.

A number of studies have shown that increased cholesterol levels lead to higher rates of CVD in patients with diabetes.[17-20] Our work showed that 30% of PP patients were on LLT, while 21% and 7% of them have attained the 2016 and 2019 guidelines targets, respectively. Similarly, the TEMD (Türkiye Endokrinoloji ve Metabolizma Derneği - Turkey Endocrinology and Metabolism Society) dyslipidemia study which included patients with diabetes from Turkish endocrinology outpatient clinics showed that 40% of the subjects were on LLT and 21% of them were on target of LDL-C.[21] In contrast, the PALM (Patient and Provider Assessment of Lipid Management Registry) registry from the US showed that 70% of PP patients with DM were on LLT and 16% of them were on guideline-recommended intensity statin therapy.[22] Our study showed utilization and the intensity of LLT are lower in PP patients compared to SP patients. The 2019 ESC/EAS guidelines lowered the thresholds for LDL-C targets and there was also a change in the risk categorization of patients with diabetes. Particularly, very high-risk patients should have at least 3 major risk factors according to new guidelines which was 1 major risk factor in previous guidelines. Hence, the number of patients in the very high-risk category decreased, but a better categorization has been introduced. Our study showed only 2% of very high-risk patients with diabetes were on target LDL-C levels. Masson et al[23] included very high-risk PP and SP patients with diabetes in their analysis and showed that 16.4% of them attained LDL-C target. However, they did not perform a subgroup analysis for PP patients.

Only 8% of patients attained LDL-C goal according to 2019 ESC/EAS guidelines in our study. While 55% of those patients were on statin therapy, none of them were using ezetimibe for CVD risk reduction. Ezetimibe is an inhibitor of intestinal cholesterol absorption and is recommended as an add-on therapy for patients who are not at guidelines recommended LDL-C goals.[24] Furthermore, it also seems to improve renal function, insulin resistance, and inflammatory markers.[25] These additional mechanisms might also contribute to CVD risk lowering in patients with diabetes. Therefore, it is important to follow DM patients for lipid goal attainment, and if those targets were not met, LLT should be intensified.

Our study showed widely available oral LLT might not be good enough for patients with DM who were at high or very high CVD risk. Although 87% of the patients would attain their lipid targets according to 2016 ESC/EAS guidelines with the intensification of LLT, only 69% would get goals when 2019 ESC/EAS guidelines recommendations were considered. Similarly, a multicenter study from Argentina showed that 52% and 73% of patients with diabetes with high or very high CVD risk would be on 2019 ESC/EAS guidelines LDL-C target, respectively.[23] We also showed less than half of SP group patients would be at LDL-C goal with maximum tolerated statin plus ezetimibe combination. Similarly, a large, nationwide simulation study from Sweden has shown that about 50% of patients with MI (myocardial infarction) would be eligible for proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors even with optimal use of high-dose statin plus ezetimibe according to 2019 ESC/EAS guidelines.[26] Yet there is a need for novel oral and/or parenteral LLT to reach guidelines recommendations to eliminate residual cholesterol risk in this very high-risk population. The use of currently available PCSK9 inhibitors is very restricted in our country because of the high cost and lack of reimbursement. Cost-effectiveness of these drugs has been studied and clinical practice guidelines have recommended higher thresholds for initiation of PCSK9 inhibitors according to these studies.[1,18,24] However, country-specific cost-effectivity analyses are not available for many countries to support the use of PCSK9 inhibitors in each country. Balbay et al[27] have recently shown that reducing LDL-C to a target of <100 mg/dL would lead to US$8.8 billion cost saving in very high-risk patients over the next 20 years for Turkey; however, the cost of the drug was not taken into account in their analysis.

Diabetic dyslipidemia is characterized by high non-HDL-C, high triglycerides, and high levels of small dense LDL-C.[28] The calculation of non-HDL is important and is a secondary target in the management of dyslipidemia, especially in DM patients. The non-HDL is easy to calculate and is a good surrogate of atherogenic lipoproteins. Elevated non-HDL-C increases CVD risk and maybe a stronger predictor of CVD risk in patients with diabetes.[29] Kayıkçıoğlu et al[30] have recently shown cumulative non-HDL-C is a predictor of CVD and development of DM in long-term follow-up hypertriglyceridemic patients. Our study showed more than one-third and about two-thirds of the patients who have attained LDL-C goal were not at non-HDL-C goal as per 2016 and 2019 ESC/EAS lipid guidelines. Hence, secondary lipid targets should be taken into consideration in patients with DM. The role of antiplatelet therapy in PP of CVD is controversial as the benefit of aspirin might be attenuated by the risk of hemorrhage. Both US and European guidelines state that aspirin might be considered in selected high/very high-risk patients with diabetes who are at low bleeding risk.[31,32] Our study showed aspirin use was comparable to LLT use in PP patients with diabetes. Aspirin is probably more harmful and less effective than LLT for the prevention of CVD. The ASCEND (A Study of Cardiovascular Events in Diabetes) trial randomized 15 480 patients with diabetes without CVD to receive aspirin or placebo and showed aspirin was effective in preventing serious vascular events, and also caused more major bleeding events.[33] However, large-scale evidence from randomized controlled trials has shown that LLT would prevent 500-1000 vascular events if 10 000 patients were treated for 5 years and symptomatic adverse events would occur in up to 50-100 patients.[17] Therefore, there is a need for a paradigm shift in the management of CVD risk in PP patients with diabetes.

It is essential to implement guidelines in real-life practice. However, there are certain barriers to optimal guidelines implementation. A recent paper has evaluated these factors and grouped them into 5 aspects; guidelines-related, patient-related, healthcare personnel, organizational, and external barriers.[7] The recommendations of new guidelines are clear and easy to adapt to daily clinical practice with

user-friendly illustrations. However, patient- and physician-related factors remain as the main barrier to LLT use. It is hard to convince a patient to use a medicine for a disease with no recognizable symptoms and with probable side effects. Also, negative press coverage regarding statins leads to the discontinuation of LLT. Clinical inertia is another obstacle to the implementation of guidelines. Physicians often tend to be more conservative than guideline recommendations. Fear of side effects, fear of very low cholesterol levels, and negative beliefs of clinicians might influence their decision-making. Our study showed that LLT use was not at a desired level both in PP and SP patients with diabetes. Therefore, we propose that the awareness of dyslipidemia and CVD risk reduction should be improved among patients with diabetes and physicians. Also, health policy-makers, health educators, and patient organizations should be involved to get optimal results. There is a need for multifaceted cooperation between all stakeholders.

Study Limitations

This is an observational registry conducted in outpatient cardiology clinics. Therefore, it is limited to cardiology clinics and has all limitations of an observational study. However, it has a good representation of the population with broad participation of secondary and tertiary hospitals. We also do not have follow-up data of the patients; however, we used patient records for retrospective analysis. There might be some missed data which were not recorded in patient records. The study might not well represent the whole PP patient spectrum as a small number of moderate-risk patients were included. Our exclusion of low CVD risk patients may also have decreased the generalizability of our results to low-risk groups. However, our aim was to explore the real-life approach in cardiology clinics for high and very high-risk patients.

CONCLUSION

The control of dyslipidemia is poor in high and very high-risk patients with diabetes due to the low rate use of both statin and non-statin LLTs. Combination therapy is used only in a few patients and ezetimibe is ignored in the treatment of patients with diabetes even in a country with full reimbursement conditions, denoting the major obstacles as the low level of both patient and physician awareness. Attainment of non-HDL-C goals is extremely low implicating again the insufficient awareness of physicians. There is an urgent need for better implementation of guidelines in terms of using intensive doses of statins and also non-statin therapies in patients with DM. Therefore, patients with diabetes should be educated regarding the benefits of LLT and the knowledge and awareness of physicians giving care to diabetics should also be questioned on the CVD prevention and treatment goals. A good-constructed postgraduate education program for cardiologists might be an effective solution.

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Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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Supplementary Table 1. Demographic Characteristics of the Diabetic Patient Population with Regard to Risk Levels

	Primary Prevention n = 302 (34.6%)			Secondary Prevention n = 571 (65.4%)	
Baseline Demographics	**Moderate Risk n = 24 (2.7%)**	**High Risk n = 188 (21.5%)**	**Very High-Risk n = 90 (10.3%)**		***P***
Age (years)*	51 (45-55)	57 (50-63)	66 (59-71)	64 (56-76)	<.001
BMI (kg/m^2)**	29 (26-31)	30 (27-34)	32 (29-37)	29 (26-32)	<.001
Female (%)	10 (41.7)	127 (67.6)	67 (74.4)	221 (38.7)	<.001
Place of residence (rural) (%)	1 (4.3)	31 (16.5)	29 (32.2)	152 (26.7)	.001
Education (primary or illiterate) (%)	12 (52.2)	118 (62.8)	66 (73.3)	403 (70.6)	.05
Diabetes duration(months)***	24 (9-54)	60 (28-120)	84 (41-120)	84 (39-120)	<.001
Risk factors for CVD					
Smoking (%)	4 (16.7)	37 (19.7)	30 (33.3)	124 (21.7)	.055
Hypertension (%)	6 (25.0)	136 (72.3)	86 (95.6)	446 (78.1)	<.001
Family history of CVD (%)	9 (37.5)	70 (37.4)	28 (31.5)	241 (42.7)	.172
Dyslipidemia (%)	4 (16.7)	62 (33.0)	70 (77.8)	185 (32.4)	<.001
Hypertriglyceridemia (%)	7 (29.2)	69 (36.7)	38 (42.2)	163 (28.5)	.024
Concomitant diseases					
Chronic kidney disease (%)	1 (4.2)	8 (4.3)	11 (12.2)	61 (10.7)	.034
Atrial fibrillation (%)	1 (4.2)	13 (6.9)	14 (15.6)	38 (6.7)	.024
Heart failure (%)	0 (0)	10 (5.3)	8 (8.9)	109 (19.3)	<.001
COPD (%)	3 (12.5)	28 (14.9)	17 (18.9)	120 (21.0)	.245

Categorical variables were given as frequency and percentage n (%). Not normally distributed data are presented as median and interquartile range. *P* values according to Dunnet's multiple comparison test.

*Age: $P > .05$ when high and very high-risk groups were compared. All other post hoc comparisons had a $P < .05$.

**BMI: $P > .05$ when moderate risk group compared to other risk groups. Only very high-risk group had a $P < .05$ when high-risk group compared to other risk groups. High-risk group had a $P < .05$ when compared to other risk groups except for moderate risk group.

***Diabetes duration: $P > .05$ when high and very high-risk groups were compared. All other post hoc comparisons had a $P < .05$.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease.

Supplementary Table 2. Laboratory Data of the Diabetic Patients with Regard to Risk Categories

Biochemistry	Primary Prevention			Secondary Prevention	*P*
	Moderate Risk n = 24 (2.7)	High Risk n = 188 (21.5)	Very High-Risk n = 90 (10.3)	n = 571 (65.4)	
Glucose (mg/dL)	146 (125-195)	142 (116-193)	145 (117-206)	151 (121-200)	.657
Creatinine (mg/dL)*	0.8 (0.7-0.9)	0.8 (0.6-0.9)	0.9 (0.7-1.0)	0.9 (0.8-1.1)	<.001
eGFR (mL/min)**	125 (78-179)	108 (82-137)	82 (63-117)	89 (67-112)	<.001
AST (U/L)	19 (15-25)	20 (16-28)	21 (16-31)	20 (15-26)	.372
ALT (U/L)***	29 (17-36)	22 (16-35)	22 (15-31)	20 (15-29)	.017
CK (U/L)[#]	58 (46-81)	78 (48-121)	55 (44-93)	77 (47-132)	.043
Lipid parameters					
Total-C (mg/dL)[##]	205 (191-225)	211 (182-239)	233 (198-268)	185 (149-221)	<.001
HDL-C (mg/dL)[###]	45 (35-47)	45 (38-52)	45 (39-51)	41 (35-49)	<.001
Triglycerides(mg/dL)[&]	153 (126-250)	172 (125-226)	184 (131-243)	157 (119-216)	.045
Non-HDL-C (mg/dL)[&&]	161 (148-181)	164 (133-189)	190 (158-225)	142 (107-178)	<.001
LDL-C (mg/dL)					
Before treatment[&&&]	127 (113-151)	147 (125-178)	175 (162-199)	144 (120-169)	<.001
On treatment[˜]	125 (108-151)	128 (101-148)	151 (118-175)	105 (78-138)	<.001
LDL-C change[˜˜]	0 (0-5)	9 (0-36)	20 (0-56)	27 (0-64)	<.001
%LDL-C change[˜˜˜]	0 (0-4)	6 (0-23)	11 (0-29)	19 (0-42)	<.001
Goal attainment rates					
LDL-C goal					
2019	5 (20.8)	13 (6.9)	2 (2.2)	46 (8.1)	.018
2016	8 (33.3)	46 (24.5)	9 (10.0)	108 (18.9)	.011
Non-HDL-C goal					
2019	4 (16.7)	12 (6.4)	5 (5.6)	52 (9.1)	.216
2016	5 (20.8)	44 (23.4)	5 (5.6)	114 (20.0)	.004
Goal attainment rates among high-dose LLT					
LDL-C goal					
2019	-	2 (25.0)	0	17 (12.7)	.276
2016	-	3 (37.5)	1 (10.0)	38 (28.4)	.372
Non-HDL-C goal					
2019	-	1 (12.5)	1 (10.0)	20 (14.9)	.901
2016	-	4 (50.0)	1 (10.0)	42 (31.3)	.181

P values according to Dunnet's multiple comparison test.
*Creatinine: All *P* values were >.05 except for high-risk and secondary prevention groups.
**Creatinine clearance: All *P* values were >.05 except for high-risk, very high-risk, and high-risk secondary prevention groups.
***ALT: All *P* values were >.05 except for high-risk and secondary prevention groups.
[#]CK: *P* value was <.05 when moderate risk group was compared to very high-risk and secondary prevention groups. All other post hoc comparisons had a $P > .05$.
[##]Total-C: *P* value was >.05 when moderate risk group compared to high and very high-risk groups. All other post hoc comparisons had a $P < .05$.
[###]HDL-C: Only high-risk and secondary prevention groups had a $P < .05$. All other post hoc comparisons had a $P > .05$.
[&]Triglyceride: none of post hoc comparisons had a $P < .05$.
Non-HDL-C: Only moderate group had a $P > .05$ when compared to high and very high-risk groups. All other post hoc comparisons had a $P < .05$.
[&&&]LDL-C before treatment: Only very high-risk group had a $P < .05$ when compared to other groups. All other post hoc comparisons had a $P > .05$.
[˜]LDL-C on treatment: Only moderate group had a $P > .05$ when compared to high and very high-risk groups. All other post hoc comparisons had a $P < .05$.
[˜˜]LDL-C change: High-risk group and very high-risk group, very high-risk group and secondary prevention groups had a $P > .05$. All other post hoc comparisons had a $P < .05$.
[˜˜˜]% LDL-C change: High-risk group and very high-risk group, very high-risk group and secondary prevention groups had a $P > .05$. All other post hoc comparisons had a $P < .05$.
ALT, alanine transaminase; AST, aspartate transaminase; CK, creatinine kinase; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Supplementary Table 3. Additional Median Absolute (mg/dL) and Percent (%) Decrease Required to Reach the Goals in Diabetic Patients According to 2019 and 2016 Guidelines

		Primary Prevention			Secondary Prevention	
		Moderate Risk n = 24 (2.7%)	High Risk n = 188 (21.5%)	Very High-Risk n = 90 (10.3%)	n = 571 (65.4%)	*P*
2019 Guidelines	LDL-C, mg/dL*	25 (8-51)	58 (31-78)	96 (64-120)	50 (23-83)	<.001
	LDL-C, %**	20 (8-34)	45 (31-53)	63 (53-68)	48 (29-60)	<.001
	Non-HDL-C, mg/dL***	31 (18-51)	64 (33-89)	105 (73-140)	57 (22-93)	<.001
	Non-HDL-C, %#	19 (12-28)	39 (25-47)	55 (46-62)	40 (21-52)	<.001
2016 Guidelines	LDL-C, mg/dL##	10 (0-37)	28 (1-48)	81 (49-105)	35 (8-68)	<.001
	LDL-C, %###	8 (0-24)	21 (1-32)	54 (41-60)	33 (10-49)	<.001
	Non-HDL-C, mg/dL&	16 (3-36)	34 (3-59)	90 (58-125)	42 (7-78)	<.001
	Non-HDL-C, %&&	9 (2-20)	21 (2-31)	47 (38-56)	29 (6-44)	<.001

P values according to Dunnet's multiple comparison test.
*LDL-C: All *P* values were <.05 except for high-risk and secondary prevention groups.
**LDL-C %: All *P* values were <.05 except for high-risk and secondary prevention groups.
***Non-HDL-C: Secondary prevention group had a $P > .05$ when compared to moderate and high-risk goups. All other post hoc comparisons had a $P < .05$.
#Non-HDL-C %: Only secondary prevention group had a $P > .05$ when compared to high-risk group. All other post hoc comparisons had a $P < .05$.
##LDL-C: Only moderate risk group had a $P > .05$ when compared to high-risk group. All other post hoc comparisons had a $P < .05$.
###LDL-C %: Only moderate risk group had a $P > .05$ when compared to high-risk group. All other post hoc comparisons had a $P < .05$.
&Non-HDL-C: Only very high-risk group had a $P < 0.05$ when compared to other risk groups. All other post hoc comparisons had a $P > .05$.
&&Non-HDL-C %: Only moderate group had a $P > .05$ when compared to high-risk groups All other post hoc comparisons had a $P < .05$.
LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.