The gap between the current dyslipidemia guidelines and the physicians' treatment targets in patients with type 2 diabetes in Turkey

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Aim. **Lipid-lowering therapy (LLT) is a key factor in the prevention of cardiovascular mortality and morbidity in diabetic patients. Current guidelines have expanded the population of patients with diabetes for whom aggressive low-density lipoprotein cholesterol (LDL-C) lowering therapy should be considered. This study evaluated the management of dyslipidemia in patients with type 2 diabetes in real life.**

Methods. **Secondary care physicians in a tertiary center recruited 707 patients. The prevalence of statin use along with the achievement of cholesterol targets, predictors for receiving statin, and possible reasons for lack of therapy were investigated.**

Results. **Only 33% of the patients had received statin therapy, and this was significantly higher in those with cardiovascular disease (47% *versus* 27%; P<0.001). Most of the patients had LDL-C levels of >100 mg/dL (77%), with only 5% having LDL-C levels of <70 mg/dL. Forty-one percent of the patients had never been prescribed LLT previously while 26% had been prescribed this type of therapy in the past but had stopped using it. The most frequent reason for discontinuation of the statin therapy was a physician's advice to stop the medication. The patients taking statins had similar LDL-C levels as those who had never been prescribed statins and those who had discontinued their use of statins on the advice of a physician.**

Conclusion. **The majority of diabetic patients are undertreated with statins and minority of them achieve LDL-C target levels. Our findings suggest that there is a large discrepency between evidence-based recommendations and physicians' treatment attitudes.**

KEY WORDS: Lipids - Diabetes mellitus - Statins.

Cardiovascular disease (CVD) accounts for most of the morbidity and mortality of type 2 diabetes. Diabetic patients have at least twice the absolute risk of CVD compared to those without diabetes. Furthermore, beyond having an increased risk for coronary events, people with diabetes who develop coronary artery disease (CAD) have a relatively poor prognosis for recurrent coronary events and coronary death.[1-3] There is clear evidence that atherogenic dyslipidemia is an important modifiable cardiovascular risk factor in patients with type 2 diabetes.[3, 4] Statins have proven to provide significant clinical benefits with regard to cardiovascular events for diabetic patients. Statin therapy reduces the five-year incidence of major CVD events by ~20% per mmol/L reduction in low-density lipoprotein cholesterol (LDL-C), and this occurs regardless of the initial LDL-C levels or other baseline characteristics based on the Cholesterol Treatment

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Trialists' (CTT) Collaboration.[5] The current guidelines for the management of dyslipidemias classify most persons with type 2 diabetes as very high risk.[4] Recent European guidelines recommend lowering LDL-C to a target of <70 mg/dL in patients with type 2 diabetes and CVD or chronic kidney disease (CKD). Similar LDL reduction is also recommended for diabetic patients who are over 40 years of age with one or more CVD risk factors or markers of target organ damage. In accordance with these new recommendations, the target LDL-C level is <70 mg/dL for most diabetic patients, thus advocating more widespread prescription of statins.

Previous studies suggested that there is a large discrepancy between treatment targets and 'real life' practice. Damci et al. showed that the proportion of patients with type 2 diabetes in Turkey receiving a statin is low, with a rate of only 19.7%.[6] Similarly, reports from the United States and European countries have shown that lipid-lowering therapies are inadequately used in diabetic patients.[7-10]

The aim of this study was to evaluate the following: 1) the current lipid target achievement rates in type 2 diabetic patients attending endocrinology and cardiology clinics in a tertiary hospital; 2) the prevalence of statin use and its predictors; and 3) the prevalence of patients who discontinue statin therapy and the possible causes for this.

Materials and methods

This prospective cross-sectional study was conducted at the cardiology and endocrinology outpatient clinics in a tertiary hospital in Turkey. Consecutive type-2 diabetic patients were invited to participate in the study, and a total of 707 patients who were willing to provide informed consent were recruited. Physicians were instructed to perform a routine visit and compile a standard questionaire specifying the following: demographic data and lifestyle habits (cigarette smoking, ongoing dietary therapies, and regular physical activity ≥30 minutes at least three times a week), anthropometric data, diabetes duration, pharmacological therapies, laboratory data, history of hypertension, clinical history, and data on microvascular (retinopathy, nefropathy) and macrovascular (coronary, cerebral, and peripheral arterial disease) complications. Each patient's current lipid-lowering therapy, dosage, and side effects, if any, were recorded, and for those who had discontinued their therapy, the possible causes for this were investigated, including possible side effects, physician's advice, or noncompliance.

Each patient had fasting plasma glucose and lipid profile, hemoglobin A1c (HbA1c), serum creatinine and spot urinanalysis for proteinuria no more than 3 months prior to interview as well as an eye examination by an ophthalmologist.

Hypertension was defined by the presence of antihypertensive therapy or a blood pressure reading of ≥140/90 mmHg. Body mass index (BMI) was calculated as kg/m^2. Microalbuminuria was defined as albumin excretion in urine of ≥30 mg/L assessed by spot urinanalysis, and creatinine clearance was estimated by the Cockcroft-Gault formula.

The patients were classified as having coronary artery disease (CAD) if there was a history of previous myocardial infarction, angiographically documented coronary stenosis of ≥50%, percutaneous coronary intervention or coronary bypass surgery. The patients were classified as having peripheral arterial disease (PAD) if there was a history of previous peripheral bypass or percutaneous intervention, amputation, angiographically documented peripheral vascular stenosis of ≥50%. Patients were identified as having cerebrovascular disease if they had suffered from a neurological dysfunction associated either with temporrary or permanent brain injury.

The study was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

Continuous variables were presented as mean±standard deviation or median as appropriate, and categorical variables were presented as percentages. Distributions of continuous variables were determined by

the Kolmogorov-Smirnov test. Group differences for continuous variables were examined by an unpaired Student's *t*-test or by either the Mann–Whitney U or Kruskal-Wallis test. In case of categorical variables, comparisons between groups were made with a Chi-square (χ^2) or Fisher's exact test.

Multivariate logistic regression analysis was used to identify demograhic, anthropometric, and clinical characteristics associated with the achievement of statin therapy. Initially, univariate analysis with a χ^2 test was performed to assess the possible association between the outcome of variable statin usage and all demograhic, anthropometric, and clinical variables. Subsequently, multiple forward stepwise logistic regression analysis was performed to determine the independent predictors for statin usage. All statistical comparisons were two-tailed, and p values of <0.05 were considered to be statistically significant.

Results

A total of 707 type 2 diabetic patients were included in the study. The physicians who cared for the study population were most commonly endocrinology specialists (71%) while the remainder were cardiologists. The mean age of the patients was 58±11.04 years, and 40% were male. Table I shows the demographic and clinical characteristics of the patients in the entire cohort and the

TABLE I.—*Demographic and clinical characteristics of the study population along with data related to the presence of cardiovascular disease.*

	Total (N.=707)	With CVD (N.=225)	Without CVD (N.=482)	P value
Men (%)	40.3%	53.3%	34.2%	<0.001
Age (years)	58±11.04	62.9± 9.6	56.9±11.2	<0.001
Diabetes duration (years)*	6	8	5	<0.001
Body mass index (kg/m²)	30.45±5.8	30.57±6.1	30.42±5.7	0.880
Current smoker (%)	15%	12.4%	16.4%	0.179
Hypertension (%)	70.6%	89.3%	61.8%	<0.001
Nephropathy (%)	19%	29.3%	14.3%	<0.001
Retinopathy (%)	22.5%	32.4%	17.8%	<0.001
Coronary artery disease (%)	26%	81.3%	0%	
Cerebrovascular disease (%)	8.8%	27.6%	0%	
Peripheral artery disease (%)	4.5%	14.2%	0%	
Fasting plasma glucose (mg/dL)	159.6±68.3	171.6±75.2	151.3±61.3	0.002
HbA1c (%)	7.6±1.8	7.7±1.8	7.4±1.7	0.107
Total cholesterol (mg/dL)	206±46	197.7±44.8	207.2±43.5	0.004
LDL-C (mg/dL)	128±38	121.2±37.8	131.3±38.2	0.001
<70 mg/dL	5.4%	7.3 %	4.5%	0.042
≥70 and <100 mg/dL	17.3%	21.1%	15.5%	
≥100 and < 130 mg/dL	33.3%	35.3%	32.3%	
≥130 and <160	24.3%	21.1%	25.9%	
≥160 mg/dL	19.6%	15.1%	21.8%	
HDL-C (mg/dL)	45±12	42.8±10.5	47.0±12.5	<0.001
<40 (M) or <50 (F)	54%	58.2%	52.1%	0.145
≥40 (M) or ≥50 (F)	46%	41.8%	47.9%	
Triglycerides (mg/dL)	177±118	166.9±73.8	158.3±69.4	0.277
<150 mg/dL	48.1%	43.6%	50.2%	
≥150-400 mg/dL	48.4%	52.9%	46.3%	
≥400 mg/dL	3.5%	3.6%	3.5%	
Creatinine clearance (mL/min)	106±38	93.2±35	113±38.5	<0.001
Microalbumiuria (%)	17.5%	28.1%	12.7%	<0.001
Statin (%)	33.4%	47%	27%	<0.001
Fibrate (%)	6.2%	7.6%	5.6%	0.320
Physical activity (%)	21%	16.4%	23.4%	0.038
Diet (%)	47%	40.9%	50.6%	0.019

"P values" refers to comparisons of the variables between patients with and without CVD. *Median; other values are mean±standard deviation. CVD: cardiovascular disease; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol.

TABLE II.—*Demographic and clinical characteristics of patients with and without statin therapy.*

Characteristics	With statin therapy (N.=236)	No statin therapy (N.=471)	P value
Gender			
Men (%)	35%	65%	0.569
Women (%)	32.5%	67.5%	
Age (years)	59.7±9.8	58.3±11.5	0.112
≤40	4	30	0.015
40-50	29	79	
51-60	101	161	
61-70	65	129	
>70	37	72	
Diabetes duration (years)*	7	5	0.04
Body mass index (kg/m²)	30.6±5.9	30.4±5.8	0.980
Current smoker (%)			
Yes	33%	67%	0.912
No	33.5%	66.5%	
Hypertension (%)			
Yes	40%	60%	<0.001
No	18%	82%	
Nephropathy (%)			
Yes	34.1%	65.9%	0.840
No	33%	67%	
Retinopathy (%)			
Yes	46.5%	53.5%	<0.001
No	30%	70%	
Coronary artery disease (%)			
Yes	47%	53%	<0.001
No	28.6%	71.4%	
Cerebrovascular disease (%)			
Yes	40.3%	59.7%	0.259
No	32.7%	67.3%	
Peripheral artery disease (%)			
Yes	62.5%	37.5%	0.001
No	32%	68%	
HbA1c (%)	7.7±1.6	7.4±1.8	0.005
Total cholesterol (mg/dL)	198.5±48.0	206.9±41.9	0.011
LDL-C (mg/dL)	122.8±41.6	130.7±36.4	0.008
<70 mg/dL	9.7%	3.3%	0.001
≥70 and <100 mg/dL	21.1%	15.4%	
≥100 and <130 mg/dL	28.2%	35.8%	
≥130 and <160	20.7%	26.2%	
≥160 mg/dL	20.3%	19.3%	
HDL-C (mg/dL)	45.0±12.5	46.0±11.8	0.173
Triglycerides (mg/dL)	163.6±70.6	159.7±71.1	0.350

*Median; other values are median±standard deviation. LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

data regarding the presence of CVD. There were 499 patients (71%) who had hypertension (HT), 19% had nephropathy, and 23% had diabetic retinopathy. There were 225 patients (32%) with established CVD, and 81% of these had CAD, 27% had cerebrovascular disease, and 14% had PAD. The patients with CVD were older and had a higher prevalence of HT, nephropathy, and retinopathy as well as a longer duration of diabetes than the patients without CVD.

In our study, the mean LDL-C level was 128±38 mg/dL, and 77% of the patients had LDL-C levels of ≥100 mg/dL. Only 5.4% of patients had LDL-C levels of <70 mg/dL. The patients with CVD had lower LDL-C levels than the patients without CVD, but only 7% of these reached the LDL-C target levels of <70 mg/dL. Nearly half of the patients had low levels of high-density lipoprotein cholesterol (HDL-C) and raised triglyceride (TG) levels (Table I).

Nearly half of the patients reported that they had received dietary advice and were compliant with the recommendations, and one-fifth reported that they did regular physical activity. Only 33% of the diabetic patients had received statins, and significantly more patients with CVD were prescribed this medication than those without CVD (47% versus 27%; P<0.001). Only 6% of the patients were on fibrate therapy. Ten percent of the patients undergoing statin therapy had LDL-C levels of <70 mg/dL, and 31% had levels <100 mg/dL (Table II). The most frequently prescribed statin was atorvastatin. The type of statins prescribed and the dosage information are presented in Table III. As shown in Table II, the patients with HT, retinopathy, CAD, PAD and those with longer diabetes duration and worse glycemic control were more likely to be prescribed statins. The variables that were found to be associated with statin therapy in univariate analysis were further validated in multivariate logistic regression analysis. Having HT and PAD more than doubled the likelihood of statin treatment (Table IV). Having retinopathy, CAD, doing regular physical exercise, and being in the fifth decade of life were predictors for statin treatment.

TABLE III.—*Statin doses of the patients.*

Statin type and dosage	All (N.=236)
Atorvastatin 10 mg	35.1%
Atorvastatin 20 mg	35.6%
Atorvastatin 40 mg	5.9%
Rosuvastatin 5 mg	2.5%
Rosuvastatin 10 mg	11.4%
Rosuvastatin 20 mg	7.6%
Fluvastatin 80 mg	0.4%
Simvastatin 40 mg	1.2%

Among the patients who were not on statin threrapy, 288 (61%) had never been prescribed lipid- lowering therapy previously, and 183 patients (39%) had used statins in the past but discontinued their use. The patients who had never been prescribed statin were younger and had a lower prevalence of HT and diabetic microvascular and macrovascular complications than those who were using statins or who had discontinued this therapy at some point in the past (Table V). The total cholesterol, LDL-C, and high-density lipoprotein cholesterol (HDL-C) levels were similar in patients receiving statins and those who had never been prescribed statin therapy. The patients who had stopped statin therapy had significantly higher total cholesterol, LDL-C, and triglyceride levels than the two other groups.

The discontinuation of the therapy was due to drug side effects in 7% of the patients, physician's advice in 58%, and patient noncompliance in 34%. The patients who had quit using statins on the advice of a physician had significanty lower total cholesterol and LDL-C levels than those who had stopped taking statins due to side effects or non-compliance (Table VI). Furthermore, the LDL-C levels were similar in patients who had discontinued statin therapy on the advice of a physician and in those who were already using these type of therapy (129.0±33.1 mg/dL *versus* 123±41.4 mg/dL; P=0.116).

Discussion

Our results demonstrate that the majority of diabetic patients do not receive lipid-low-

TABLE IV.—*Predictors of statin therapy at multivariate logistic regression analysis.*

	Odds ratio	95% Confidence interval	P value
Hypertension	2.54	1.63-3.95	<0.001
Coronary artery disease	1.51	1.02-2.26	0.039
Peripheral artery disease	2.63	1.19-5.84	0.017
Diabetic retinopathy	1.80	1.20-2.70	0.004
Physical activity	1.69	1.11-2.57	0.013
Age (years)			
≤40	0.50	0.15-1.65	0.260
40-50	1.13	0.59-2.16	0.707
51-60	1.70	1.01-2.85	0.043
61-70	1.10	0.64-1.90	0.712

TABLE V.—*Characteristics of patients according to current or past statin therapy.*

	On statin therapy	Never used statin	Used statin in the past but quit	P value
Number (%)	236 (33%)	288 (41%)	183 (26%)	0.001
Age (years)	59.9±9.8	57.0±11.7	60.1±11.0	0.001
Male (%)	41.9%	39.0%	39.3%	0.820
Current smoker (%)	14.8%	18.4%	10.3%	0.060
Hypertension (%)	83.9%	56.9%	74.9%	<0.001
Nepropathy (%)	19.1%	14.2%	26.8%	0.003
Retinopathy (%)	31.4%	14.9%	23%	<0.001
Coronary artery disease (%)	36.4%	17.0%	26.2%	<0.001
Cerebrovascular disease (%)	10.6%	5.9%	10.9%	0.082
Peripheral artery disesae (%)	8.5%	3.1%	1.6%	0.001
Total cholesterol (mg/dL)	198.8±47.7	198.7±37.0	219.8±45.4	<0.001
LDL-C (mg/dL)	123.0±41.4	125.1±33.2	139.6±39.1	<0.001
<70 mg/dL	9.7%	4.7%	1.1%	<0.001
≥70 and <100 mg/dL	21.1%	17.6%	11.9%	
≥100 and < 130 mg/dL	28.2%	38.8%	31.1%	
≥130 and <160	20.7%	23.7%	29.9%	
≥160 mg/dL	20.3%	15.1%	26.0%	
HDL-C (mg/dL)	45.1±12.5	46.3±11.9	45.2±11.5	0.209
Triglycerides (mg/dL)	163.0±70.4	146.9±63.5	180.9±76.6	<0.001
On diet (%)	52.1%	48.6 %	39.9%	0.041
Physical activity (%)	23.3%	20.8%	19.1%	0.571

LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

TABLE VI.—*Lipid profiles of patients who discontinued statin therapy in the past due to drug side effects, physician's advice or non-compliance.*

	Side effect (N.=13)	Physician's advice (N.=107)	Non-compliance (N.=63)	P value
Total cholesterol (mg/dL)	241.0±52.6	209.6±38.9	233.1±49.9	0.001
LDL-C (mg/dL)	156.0±30.1	129.0±33.1	154.5±44.2	<0.001
HDL-C (mg/dL)	52.8±15.7	44.7±11.7	44.7±9.9	0.320
Triglycerides (mg/dL)	207.4±96.6	179.7±78.6	177.8±68.8	0.565

Data is expressed as mean±standard deviation. LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

ering therapy, and LDL-C levels, which are the primary target in diabetic dyslipidemia, are much higher than the recommended target levels, even in patients on statin therapy. Several trials have assessed the benefits of statin therapy in diabetic patients.[11-13] In a meta-analysis of 14 statin trials, this type of therapy reduced the five-year incidence of major vascular events in diabetic patients by about one-fifth per mmol/L reduction in LDL-C.[13] The proportional reduction in major vascular events per mmol/L reduction in LDL-C was similar, irrespective of a previous history of CVD, gender, age, HT, BMI, smoking history, or estimated glomerular filtration rate. Recent European guidelines on dyslipidemia recommend lowering the LDL-C to a target of <70 mg/dL in patients with type 2 diabetes who have concurrent CVD or CKD or who are over 40 years of age with CVD risk factors or markers of target organ damage. In our study, 80% of the patients met these criteria, but only 7% of patients with CVD and 5% of patients without CVD had LDL-C levels of <70 mg/dL. The proportion of patients receiving statin in these groups was 47% and 30%, respectively. In the entire cohort, only 33% of patients were on statin therapy and majority of patients had LDL-C levels of ≥100 mg/dL. Accordingly, statins not only were underprescribed, but they were also prescribed at inadequate doses.

An Italian study in 2007 revealed that only 20% of the diabetic patients attending an urban network of community-based diabetes care clinics received statins, and only one in four were meeting their treatment targets.[14] Berthold *et al.* demonstrated that statin prescription rates in diabetic patients in Germany were 18.5% and 38% in primary and secondary prevention, respectively, and only 12.6% of the patients in primary prevention and 16.3% of the patients in secondary prevention had LDL-C levels of <100 mg/dL.[15] In 2004, Damci *et al.* showed that statin usage in Turkey for type 2 diabetic patients was 19.7%.[6] Turkish data from the EUROASPIRE III study showed that only 65% of the patients with coronary artery disease 33% of whom had concurrent diabetes were under statin therapy.[16] Accordingly, despite the increasing evidence in favor of agressive lipid lowering therapy in diabetic patients and statement of new guidelines on managemet of dyslipidemia, the rate of statin usage and achievement of target levels do not seem to be increased in parellel with these. Ninety-eight percent of the patients included in our study had social insurance, and social insurance institude in Turkey affords statins in diabetic patients when the LDL-C level is >100 mg/dL. In our study, 81% of patients who were not on statin therapy were at this level; therefore, the lack of achievement of LDL-C levels in diabetic patients does not seem to be due to financial causes but can be attributed to underprescription by the treating physicians or patient-related factors.

Effective lipid lowering strategies in diabetic patients require the management of not only LDL-C but also HDL-C and TG levels as well.[4] Diabetic patients commonly present with atherogenic dyslipidemia characterized by low levels of HDL-C, increased levels of TG and small, dence LDL particles. Fibrates are associated with reduced cardiovascular risk in diabetic patients with atherogenic dyslipidemia.[17] In our study, about half of the patients had raised TG and low HDL-C levels and only 6% of them were on fibrate therapy. On the other aspect, about half of the patients were obese and 80% were physically inactive. All of these data demonstrate that lipid lowering therapies together with modification of unfavorable life style factors to improve cardiovascular risk in diabetic patients are not adequate for the majority of the affected patients.

Our study found that the presence of atherosclerotic disease, HT, and retinopathy are predictors for receiving statin therapy, and this suggests that these disease entities are being correctly perceived as predictors of higher cardiovascular risk. On the contrary, patients who had never been prescribed statins before had a lower prevelance of HT as well as microvascular and macrovascular complications. These findings are in line with previous studies. Berthold et al. found that prescription frequencies were higher in patients with CVD and that the presence of HT and albuminuria were associated with increased odds of statin prescription.[15] Likewise, Raum *et al.* found that the additional presence of HT and CAD increased the probability of receiving lipid-lowering therapy in diabetic patients.[7] We also found that pateints who are between 51 and 60 years old had a higher chance of being prescribed statins than those who were younger or older. This is in accordance with previous studies which demonstrated that the probability of receiving statin therapy decreased in the elderly.[18, 19] Several studies reported that younger and older age were significantly associated with decreased statin prescription, and an inverted U-shaped association between age and statin treatment was described.[15, 20] In our study, regular physical activity was found to be another predictor for receiving statin therapy. This may be because patients who exercise regularly are more likely to comply with the physician's advice in terms of lifestyle modifications and drug therapy.

Inappropriate underutilization of lipid-lowering therapy may be associated with factors related to the physicians, patients or setting.[7, 15, 16, 18-24] In this study, not only did we analyze the demographic, anthropometric, and clinical characteristics of the patients, which were predictors of statin prescription, but we also investigated the possible causes of not using cholesterol-

lowering therapy. An interesting finding in our study was that patients on statin therapy had LDL-C levels comparable with those who had never been prescribed statin and those who had discontinued their statin treatment due to advice from a physician. This implies that the physicians' perception of LDL-C targets are much higher than the target LDL-C levels recommended by the current guidelines. Hence, it seems that physician nonadherence with the current guidelines is an important factor for inappropriate statin therapy in type 2 diabetic patients. Further studies are needed to explore the possible reasons for this, but some possibilities are the underestimation of cardiovascular risk in patients with diabetes, the inability to keep up with the current guidelines, an insufficient amount of time because of caring for too many patients, or difficulty in understanding the long, complex guidelines. Educational interventions are needed for physicians to increase the awareness of cardiovascular risk in patients with diabetes and to improve physician adherence to treatment guidelines. Additionally, physicians should inform patients about their cardiovascular risk and lipid values to improve patients' compliance with the lipid lowering therapies.

Limitations of the study

This study is a single-center, cross-sectional, observational study, and the findings cannot be considered as fully representive of all Turkish diabetic patients. However, we believe that the number of patients included in our study was sufficient to conclude that the results are close to the overall patient profile in Turkey.

Additionally, the data regarding the possible reasons for lack of lipid-lowering therapy was obtained from interviews with the patients, and the reliability of their responses along with their reasons for discontinuing the therapy is another limitation. The small number of patients who did not respond to these questions were excluded from the study, and this may have caused selection bias.

Conclusions

Despite increasing scientific evidence in favor of aggresive treatment of dyslipidemia in patients with diabetes, the majority still do not achieve the targets set forth in the guidelines and are undertreated. This study shows that there is a large discrepancy between the physicians' perception of LDL-C targets and the targets established in these guidelines. This highlights the need for further studies to investigate the factors that prevent physicians from implementing these guideline recommendations into real-world practice.

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