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Clinician prescription of lipid-lowering drugs and achievement of treatment goals in patients with newly diagnosed type 2 diabetes mellitus

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ABSTRACT

Introduction Lipid control is essential in type 2 diabetes mellitus (T2DM). The aim of this study is to investigate factors associated with lipid therapy adherence and achievement of goals in real-life setting among patients with recently diagnosed T2DM.

Research design and methods This is a longitudinal analysis in a center of comprehensive care for patients with diabetes. We include patients with T2DM, <5 years of diagnosis, without disabling complications (eg, amputation, myocardial infarct, stroke, proliferative retinopathy, glomerular filtration rate <60 mL/min/m^2) and completed 2-year follow-up. The comprehensive diabetes care model includes 9 interventions in 4 initial visits and annual evaluations. Endocrinologists follow the clinic's guideline and adapt therapy to reach risk-based treatment goal. The main outcome measures were the proportion of patients meeting low-density lipoprotein cholesterol (c-LDL) (<100 mg/dL) and triglycerides (<150 mg/dL) and proportion of patients taking statin, fibrate or combination at baseline, 3 months and annual evaluations.

Results We included 288 consecutive patients (54±9 years, 53.8% women), time since T2DM diagnosis 1 (0–5) year. Baseline, 10.8% patients were receiving statin therapy (46.5% moderate-intensity therapy and 4.6% high-intensity therapy), 8.3% fibrates and 4.2% combined treatment. The proportion of patients with combined treatment increased to 41.6% at 3 months, decreased to 20.8% at 1 year and increased to 38.9% at 2 years of evaluation. Patients receiving treatment met LDL and triglycerides goals at 3 months (17% vs 59.7%, relative ratio (RR)=0.89, 95% CI 0.71 to 1.12), at 1 year (17% vs 26.7%, RR=0.62, 95% CI 0.41 to 0.95) and at 2 years (17% vs 29.9%, RR=0.63, 95% CI 0.43 to 0.93). Main reasons for medication suspension: patient considered treatment was not important (37.5%) and other physician suspended treatment (31.3%).

Conclusion 88.2% of patients with T2DM required lipid-lowering drugs. Education for patients and physicians is critical to achieve and maintain diabetes goals.

Trial registration number NCT02836808.

Significance of this study

What is already known about this subject?
► Lipid abnormalities are common in patients with type 2 diabetes mellitus.
► Medication adherence plays a major role in achieving lipid control.
► For patients with chronic conditions, adherence remains suboptimal causing significant costs.
► Discontinuation or non-compliance with lipid-lowering treatments, lack of adherence to guidelines, previous adverse effects, clinical inertia or preference for behavioral changes first are the main factors associated with uncontrolled lipid goals.

What are the new findings?
► On admission, 77% did not receive any lipid-lowering medication.
► This proportion changed after following established treatment algorithms.
► The main reasons for not receiving treatment were hypothyroidism without levothyroxine treatment, use of drugs that cause dyslipidemia or allergy reported to the substances.
► The most common dose of atorvastatin was 10 mg, to achieve low-density lipoprotein cholesterol goal.
► The main causes of suspended treatment were the same for statins and fibrates.
► The most common reasons were because patients considered it was not important for their control and because their treating physician changed the treatment.

How might these results change the focus of research or clinical practice?
► These results can help to establish strategies to improve drug therapy adherence to achieve and maintain metabolic goals.

INTRODUCTION

Lipid abnormalities such as elevated total cholesterol and triglycerides, low high-density lipoprotein cholesterol (HDL-C) cholesterol and a predominance of small, dense low-density lipoprotein cholesterol (LDL-C)

particles[1] are common in patients with type 2 diabetes mellitus (T2DM). Medication adherence, described as the extent to which patients take their medications as prescribed, plays a major role in achieving lipid control. Treating a symptomless disease such as diabetes and hyperlipidemia presents a remarkable challenge.[2] For patients with chronic conditions, adherence remains suboptimal causing significant costs,[3] and has been recognized as a public health problem.[4] Discontinuation or non-compliance with lipid-lowering treatments is likely to be a complex phenomenon in which the physician, the patient, various comorbidities and the characteristics of the prescribed medications may play a role.[5]

The high prevalence of dyslipidemia and low rate of its control in Mexico is a challenge.[6] The National Health Survey from Mexico (2006) reported that only 28.6% of patients with diabetes had LDL levels <100 mg/dL.[7] Another National Health Survey from Mexico (2016) reported that 44.5% of patients measured blood cholesterol levels once in their lives, and only 28% received a previous diagnosis of dyslipidemia.[8] Lowering cholesterol levels in recent years are attributable to greater use of cholesterol-lowering drugs rather than dietary changes. Statins are the first-line treatment for elevated LDL-C levels and fibrates are first-line therapy for hypertriglyceridemia.[9 10] Poor statin adherence has been reported in up to 50% of patients, discontinuation rates are around 15% and changing to lower potency statin therapy has been noted in up to 42% of patients.[11–13] Many factors have been linked to poor adherence, such as lack of information about the potential benefits of therapy, denial, adverse effects, impaired memory, discontinuation, dose reduction, statin switching and non-acceptance to therapy.[2 14] Reasons for not prescribing lipid-lowering medications include lack of adherence to guidelines, previous adverse effects, clinical inertia or preference for behavioral changes first.[15] There is a lack of information about adherence to lipid-lowering therapy in newly diagnosed diabetes in a real-life setting. Here, we investigate the association between lipid-lowering drug prescription and adherence with lipid control among patients with recently diagnosed diabetes.

MATERIALS AND METHODS
CAIPaDi program
Details about the CAIPaDi model have been published elsewhere.[15 16] Briefly, CAIPaDi is a comprehensive diabetes care model that consists of two phases. The first phase comprises a baseline visit followed by 3 monthly visits where patients are attended by nine different specialists (endocrinologists, diabetes educator, nutritionist, psychologist, dentist, psychiatrist, ophthalmologist, physical therapist and foot care expert). After this 3-month phase, patients continue their treatment with their treating physician. For the second phase, patients return to CAIPaDi annually. In each visit, each healthcare professional treats patients following specific protocols

for each intervention. Endocrinologists assess maintenance of metabolic control and adjust drug treatment following a treatment algorithm[15–18] for glucose, lipids and blood pressure control. The algorithm makes treatment recommendations considering economic resources of the patient. During these visits, information about the importance of metabolic control and treatment adherence for a long-term is also provided to patients. The CAIPaDi model was approved by the Institutional Ethics and Research Committees (Ref 1198) and registered in ClinicalTrials.gov (NCT02836808). All patients signed an informed consent form.

Study design and sample
This was a longitudinal study of data collected in the CAIPaDi program. CAIPaDi patients with T2DM, with <5 years of diagnosis, body mass index ≤45 kg/m^2, non-smokers, without disabling chronic complications (amputations, myocardial infarction, stroke, glomerular filtration rate <60 mL/min/m^2) were included. In this analysis we included all patients who finished their 2 years evaluation.

Measures
Fasting concentrations of cholesterol, triglycerides and HDL-C (Bio-Rad Variant II Turbo Hemoglobin A1c Kit 2, with high-pressure liquid chromatography method) were assessed in each visit. The laboratory is certified by ISO 90001:2015 and the College of American Pathologist.

The cholesterol goal was LDL <100 mg/dL consistent with primary prevention in the American College of Cardiology/American Heart Association 2013 guidelines[19] to achieve a 30%–50% reduction in LDL levels. The triglyceride goal was <150 mg/dL, based on American Diabetes Association Standards of Care.[20]

We also estimated the proportion of patients taking a statin (St), fibrate (Fib) or combinations (St+Fib). All measures are conducted at baseline (V0), the first visit (V1), at 3 months (V4), at 1 year (V5) and at 2 years (V6). Statins indicated were moderate intensity to achieve a 30%–50% reduction.

Statistical analysis
Results were reported as means (±SD) if they followed a normal distribution or medians and IQRs (25–75) if they did not have a normal distribution, according to Kolmogorov-Smirnov test. Percentages were used for discrete values. Changes in the percentages of patients were compared using McNemar test. Analysis by protocol was performed and included T-test for related samples. Analysis included T-test or Mann-Whitney U test for related samples when appropriate to analyze changes in lipid parameters between visits. SPSS Statistics V.21 was used for data analysis and point differences with 95% CIs are reported for all comparisons between variables.

Table 1 Changes in metabolic parameters at basal, 3 months and 1 year and treatment indicated

	Basal parameters (V0)	Lipids at 3 months (V4)	Lipids at 1-year follow-up (V5)	Lipids at 2-year follow-up (V6)
Triglycerides† (mg/dL)	169 (122–248)	111 (86–147)	141 (103–195)	138 (105–188)
Total cholesterol† (mg/dL)	194±43.6	151±30.1	173±39.2	171±36.5
LDL cholesterol† (mg/dL)	115±38	85±24	109±33	106±31
LDL cholesterol† (mg/dL)				
<50 years old	105.5±34.4	83.11±20.2	108.8±31.8	106.8±31.3
≥50 years old	118.5±38.7	85.9±25.9	109.1±33.2	105.8±31.3

	Basal	Treatment indicated in the first visit	Treatment indicated in visit 4 (3 months) (%)	How patients arrive at 1-year follow-up (%)	Treatment indicated in the first annual visit (%)	How patients arrive at 2 years (%)	Treatment indicated in the second annual visit (%)
Patients without treatment (%)	76.7	20.1*	11.8*	48.3	16.7	47.6	17.7
Only statins (%)	10.8	35.8*	34.4*	19.8‡	35.1	22.6	36.1
Only fibrates (%)	8.3	13.9	12.2	11.1	7.6	9.7	7.3
Statin±fibrate (%)	4.2	30.2*	41.6*	20.8‡	40.6	20.1‡	38.9

*P<0.001 comparing with basal evaluation (V0).
†Analysis of variance for lipid control parameters p<0.001.
‡P<0.001 compared with previous visit.
LDL, low-density lipoprotein.

RESULTS

In this report, we included 288 patients who finished their second annual evaluation of the CAIPaDi program. The mean age was 54±9 years, 53.8% were women, with a median time since diagnosis of 1 year. The percentage of patients treated with lipid-lowering agents and lipid concentrations are shown in table 1. At baseline, 10.8% patients were receiving statin therapy (46.5% moderate-intensity therapy/4.6% high-intensity therapy), 8.3% fibrates and 4.2% combined treatment. The most frequent lipid-lowering drugs used were atorvastatin (10 mg (10–20 mg)) and bezafibrate (200 mg (200–400 mg)).

On admission, 76.7% did not receive any lipid-lowering medication. This proportion changed to 11.8% at 3 months because they were in good control (low-density lipoprotein cholesterol (LDL-C) 85±24 mg/dL and triglycerides 111 mg/dL (84–147 mg/dL)). At visit 4 (3 months), around 40% received combined treatment (St+Fib). At 1 and 2 years, 60 and 75% of the patients requires treatment with ST and St+Fib. The median of triglycerides in the studied population remained in the control goal.

We divided the patients in four groups for triglyceride and LDL-C control: 1) patients that do not require treatment, 2) on LDL-C target taking drugs, 3) above LDL-C target despite taking drugs, and 4) bad control without treatment. The fourth group show the percentage of patients in control and bad control with or without lipid lowering treatment in each visit.

The main reasons for not receiving treatment were hypothyroidism without levothyroxine treatment, use of drugs that cause dyslipidemia or allergy to statins. The proportion of patients who continued statin treatment at 3 months was 76%. When they were evaluated at 1 year, this percentage decreased to 40.6%. These percentages were similar for the 2-year evaluation (42.7% continued taking statins and was indicated in 75% at the end of the visit). Tables 2 and 3 show the percentage of patients in control and bad control with or without lipid lowering treatment in each visit.

Table 4 shows the distribution of lipid-lowering drugs in patients aged <50 and >50 years. The proportion of patients treated with only Fib is constant. Almost half of the patients having suspended lipid-lowering treatment attend annual check-ups. This was similar in patients over and under 50 years of age. In around half of the patients, statins were prescribed in 78% at 1 year.

At the initial visit, a low percentage of patients do not require treatment, which increases at the end of the 3-month period. For triglyceride control, 43.1% of patients do not require treatment in the 3-month evaluation, but for the annual visits, this percentage stays steady. For LDL-C where 43.1% of patients do not require treatment in the 3-month evaluation and stays

Table 2 Percentage of patients in control and bad control of triglycerides with or without fibrate treatment in each visit

	Basal (before intervention)	With treatment indicated in the first visit	Evaluation at 3 months visit (%)	Evaluation at 1-year follow-up (%)	Evaluation at 2-year follow-up (%)
Treatment and control	5.6	5.6	32.6	15.6	14.9
Treatment and bad control	0	6.9	21.2	16.3	14.6
Without treatment and control	36.1	36.1	43.1	41	43.4
Without treatment and bad control	58.3	51.4	3.1	27.1	27.1
OR (95% CI)	1.15 (1.07–1.23)	0.89 (0.48–1.65)	2.02 (1.69–2.4)	1.35 (0.97–1.90)	1.36 (0.95–1.95)
P vaue	<0.001	<0.001	<0.001	<0.001	<0.001

constant for annual visits. On the other hand, patients with bad control and requiring treatment changes drastically in annual visits. For triglycerides, only 3.1% of patients still have levels >150 mg/dL and are without treatment (mostly because of borderline results), but changes to 27.1% of patients uncontrolled and without treatment in the annual evaluations. In the CAIPaDi visit, treatment is adjusted and only 9.4% and 10.4% of patients are without treatment in 1 and 2-year visits, respectively.

For LDL-C we observed something similar, where only 3.1% of patients are still with bad control and not taking statin, but the percentage increases to 27.1% in annual evaluations (figure 1).

The most common dose of atorvastatin was 10 mg. The percentage of patients receiving this dose were 54% at the beginning, which increased to 62% in that initial visit depending on LDL-C results, and 41% of the patients were taking 10 mg at the end of the 3-month period. For annual evaluations, 50.8% arrived with that dosage, and changed to 53% of patients. For the 2-year evaluation, 52% were under atorvastatin 10 mgs treatment and changed to 54% of the patients (p=0.53).

Characteristics of patients who abandoned treatment

The patients who abandoned treatment with fibrates for the first annual evaluation were 54±8.7 years of age compared with the patients who did not abandon treatment (53±9.7, p=0.57; OR −0.43; 95% −2.5 to 1.6).

The time of diagnosis of diabetes was 1 (0–3) years. For the second annual evaluation, the age of patients who did not abandon fibrates was 54.7±8.7 years of age vs 52±9.4 years for those who abandoned treatment (p=0.03). The time of diagnosis of diabetes was 1 (0–3) years for both groups. The patients who abandoned treatment with statins for the first annual evaluation were 54±9 years of age compared with the patients who did not abandon treatment who were 53±9 (p=0.51). The time of diagnosis of diabetes was 1 (0–3) years. For the second annual evaluation, the age of patients who did not abandon statins was 53±9 years of age vs 54±8.9 years for those who abandoned treatment (p=0.42). The time of diagnosis of diabetes was 1 (0–3) years for those who did not abandon statins and 1 (0–4) for those who abandoned.

The main causes of suspended treatment were the same for statins and fibrates. The most common reasons being because they considered it was not important for their

Table 3 Percentage of patients in control and bad control of LDL-C with or without statin treatment in each visit

	Basal (before intervention)	With treatment indicated in the first visit	Evaluation at 3 months visit (%)	Evaluation at 1-year follow-up (%)	Evaluation at 2-year follow-up (%)
Treatment and control	7.7	16 (5.6)	94 (32.6%)	45 (15.6%)	43 (14.9%)
Treatment and bad control	0	20 (6.9%)	61 (21.2%)	47 (16.3%)	42 (14.6%)
Without treatment and control	29.3	104 (36.1%)	124 (43.1%)	118 (41.0%)	125 (43.4%)
Without treatment and bad control	63.1	148 (51.4%)	9 (3.1%)	78 (27.1%)	78 (27.1%)
OR (95% CI)	1.26 (1.14–1.39)	0.89 (0.48–1.65)	2.02 (1.69–2.4)	1.35 (0.97–1.90)	1.36 (0.95–1.95)
P value	<0.001	<0.001	<0.001	<0.001	<0.001

LDL-C, low-density lipoprotein cholesterol.

Table 4 Distribution of lipid-lowering drugs in patients aged <50 and >50 years

	Basal	Treatment indicated in the first visit	Treatment indicated in visit 4 (3 months) (%)	How patients arrive at 1-year follow-up (%)	Treatment indicated in the first annual visit (%)	How patients arrive at 2 years (%)	Treatment indicated in the second annual visit (%)
<50 years old (n=80)							
Without treatment (%)	82.5	31.3	17.5	51.2	21.3	48.8	22.5
Only statins (%)	3.8	22.5	25	13.8	20	15	22.5
Only fibrates (%)	11.3	16.3	17.5	11.3	8.8	12.5	11.3
Statin±fibrate (%)	2.5	30	40	23.8	50	23.8	43.8
>50 years old (n=208)							
Without treatment (%)	74.5	15.9	9.6	47.1	14.9	47.6	15.9
Only statins (%)	13.5	40.9	38	22.1	40.9	25.5	41.3
Only fibrates (%)	7.2	13	10.1	11.1	7.2	8.2	5.8
Statin±fibrate (%)	4.8	30.3	42.3	19.7	37	18.8	37

control and because their treating physician changed the treatment. The main reasons are shown in figure 2.

DISCUSSION

We found at the beginning of the study that 76.7% of the patients did not have lipid-lowering treatment, being that the average LDL-C was 115±38 mg/dL. This parameter improved at the end of the first phase of the CAIPaDi program. Lipid-lowering therapy has long been an underused therapy to lower cardiovascular risk despite compelling evidence of the effectiveness of this therapy.[21] The National Multicenter Population Health Examination Survey in Poland showed that only 3% of patients with hypercholesterolemia achieved the recommended cholesterol levels.[22] A Spanish study reported that 86.7% of the patients had an initial out-of-target LDL-C. The

percentage of patients with a LDL-C within the objective evolved from 13.3% at the initial time to 27.5% at the end of the follow-up (p<0.001).[23]

Although lipid control reduces the risk of coronary heart disease, statin therapy is commonly abandoned. In a study done by Yang et al,[5] statin treatment was associated with more treatment continuations when the patients were under many other drug treatments. Different to our study, we found that half of the patients who have prescribed a scheme with St and those with St+Fib discontinued their lipid-lowering treatment. The most frequent lipid-lowering drugs were atorvastatin and bezafibrate since these are economically accessible and potent drugs.

Previous studies have reported guideline adherence among patients with diabetes mellitus as varying between 24% and 80%.[15] In primary prevention, drugs were
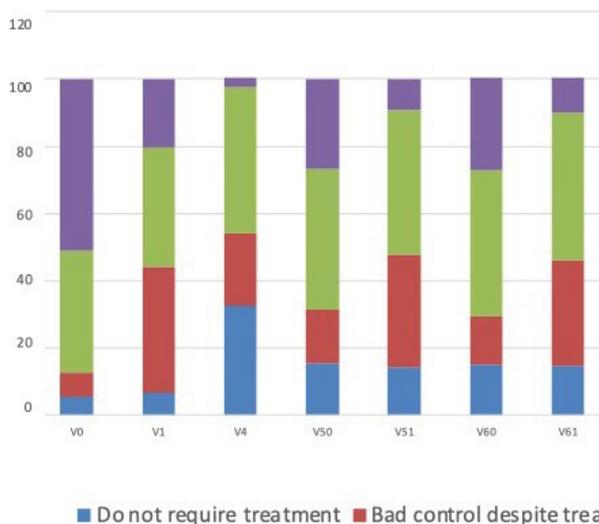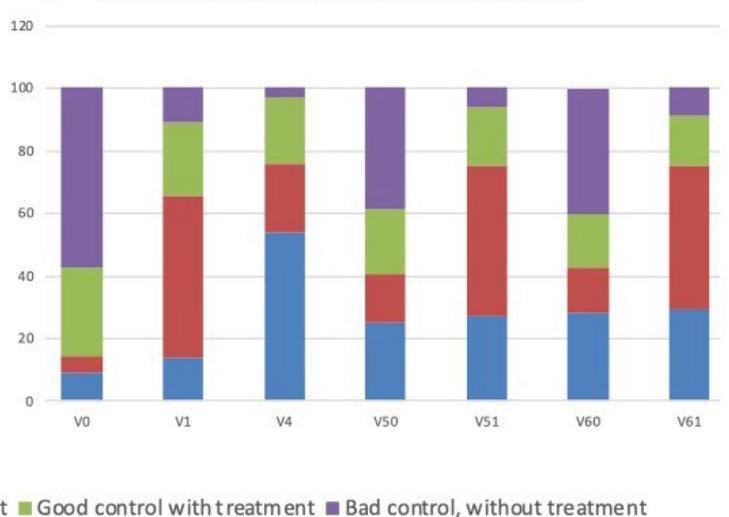
Figure 1 Percentage of patients in control/without control and treatment/without treatment. (A) Control and treatment for triglycerides. (B) Control and treatment for low-density lipoprotein cholesterol (LDL-C).
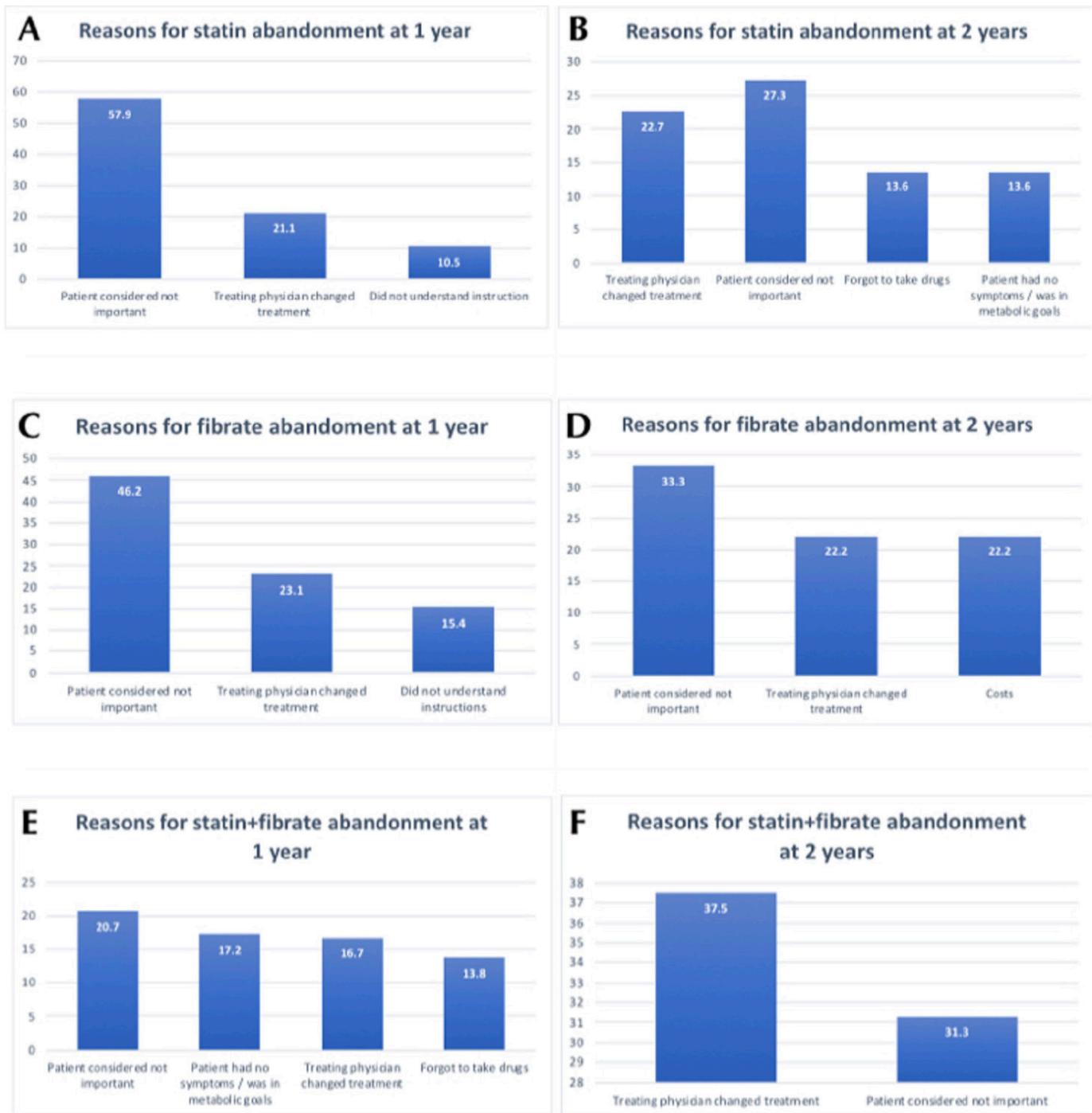
Figure 2 Main reasons for treatment suspension at 1 and 2 years of follow-up. (A) Statin suspension at 1 year; (B) statin suspension at 2 years; (C) fibrate suspension at 1 year; (D) fibrate suspension at 2 years; (E) combination of lipid-lowering drugs suspension at 2 years; (F) combination of lipid-lowering drugs suspension at 2 years.

prescribed for 24% of patients with T2DM in Germany; among US veterans with diabetes mellitus (96% men) 40–75 years of age, lipid-lowering drugs were prescribed in 61% of primary prevention patients; and a total of 64% of patients with T2DM treated in primary care were prescribed lipid-lowering medicines in Australia.[15] We found at the beginning of the study that 35.8% were candidates for primary prevention with statins. The percentage of patients who need statins was maintained

with 35.1% and 36.1% at 1-year and 2-year evaluations for primary prevention.

Past studies have reported statin adherence rates from 25% to 40%.[24 25] Statin discontinuation (non-persistence) rates were based on real-world Dutch observational data.[26] After 1 year, treatment persistence was 61.5%; after 2 years, persistence was 47.7% for primary prevention patients and 57.7% for secondary prevention patients. After 1 year in the model, 38.5% of control patients

discontinued statin therapy compared with 19.0% in the intervention group; after 2 years, statin discontinuation was 47.7% vs 23.3%, respectively.[27] In our study, adherence was 54%–67% in annual visits. A major cause of non-adherence was an economic issue (52.04%). Among them, 46–55 years of age were highly adherent, males were more adherent to medication than females.[4]

A previous study from the National Diabetes Registry showed that lipid-lowering medications were prescribed for 70% of patients with T2DM with triglycerides >350 mg/dL.[28] In our study, 13.9% had fibrates indicated when triglycerides were >150 mg/dL. Our study found that patients who abandoned treatment with fibrates at 2 years were younger. For the other evaluations, there was no significant difference in age or time of diagnosis of diabetes. In other studies, patients who did not abandon treatment were older, more concurrent cardiovascular medications, more time with diabetes and more pre-existing or recently diagnosed cardiovascular diseases.[5]

The implementation of treatment guidelines in clinical practice is difficult. When a patient is diagnosed with T2DM, the guidelines recommend initiation of an extensive treatment regimen that includes several different medication classes. Patient perceptions of diabetes are influenced by the healthcare professionals they encounter. Clear communication between patient and provider is a predictor of good self-management, whereas poor communication is associated with poor treatment adherence.[15] Barriers to achieving lipid control are low recognition by the healthcare professionals that dyslipidemia requires long-term management and inadequate knowledge of algorithms. We found that blood pressure (BP) and LDL-C, as well as combined BP and LDL-C goal attainment rates were the lowest in endocrine but highest in other departments.[29] The use of statins and the lack of attention to LDL-C or adopting small doses for fear of side effects may be the reasons for the low LDL-C achievement rate. Most patients who should have received high-intensity therapy under the guidelines were treated appropriately (n=544, 72.2%). Adherence to the guideline recommendations among patients who received statin therapy was estimated as 72%, while 28% (n=208) were non-adherent. Of the non-adherent, 126 (16.7%) received less than the ideal therapy. We found that approximately one-third of patients received statin therapy at an inappropriate intensity according to the guideline recommendations. We observed underuse of appropriate statin therapy intensity based on the guideline recommendations, especially for primary prevention.[30]

One of the strengths of this study is the ability to include information on new diagnoses and treatment that occurred after initiation of lipid-lowering therapy. Some limitations of this study are that we did not have information on the reason for treatment discontinuation from all patients, we only included patients with <5 years of diagnosis of diabetes, and patients with high cardiovascular risk were not included.

CONCLUSION

To obtain control goals, almost 88.2% of patients require lipid-lowering agents. In the long term, half of the patients who were indicated an St and those with St+Fib discontinued their lipid-lowering treatment. It is necessary to establish strategies to convince about the benefits of starting and maintaining therapy, both for patients and healthcare professionals.

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