ORIGINAL ARTICLE

LDL-cholesterol goal attainment in light of the 2019 dyslipidemia guidelines

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Abstract: **Objective –** The purpose of our study was to evaluate LDL-cholesterol goal attainment in patients at very high-cardiovascular risk due to concurrent arterial hypertension, type 2 diabetes mellitus and ASCVD, in light of the recently updated dyslipidemia guidelines. **Methods –** Data from patients enrolled between January 2016 and December 2017 was collected in order to assess LDL cholesterol target attainment (≤70 mg/dL and <55 mg/dL) corresponding to 2016 and 2019 European Dyslipidemia Guidelines. **Results –** A total of 993 patients were included in the analysis. Only 31% of patients achieved LDL-c goals of ≤70 mg/dL, without gender differences, a percentage which further dropped to 15% after establishing the target below 55 mg/dL. Patients with concurrent atrial fibrillation (34.9% vs. 25.1%, p=0.006), heart failure (37.1% vs. 27.2%, p=0.047) and chronic kidney disease (36.3% vs. 28.2%, p=0.028) had better, though far from optimal lipid control per the 2016 guidelines. Two in three patients had controlled diabetes with HbA1c values below 7%. **Conclusion –** Our study shows that LDL-c targets were not met by very-high risk patients even with the lower 2016 threshold, with the new recommendations making lipid goals look more daunting.
Keywords: arterial hypertension; diabetes; dyslipidemia; LDL-cholesterol goals; very-high cardiovascular risk.

Rezumat: **Obiective –** Evaluarea atingerii ţintei LDL prin prisma noului ghid de tratament al dislipidemiei la pacienţii cu risc cardiovascular foarte înalt prin asocierea hipertensiunii arteriale, diabetului zaharat şi aterosclerozei. **Metode –** Au fost colectate date de la pacienţi internaţi în perioada ianuarie 2016 – decembrie 2017 şi s-a evaluat atingerea ţintelor LDL (≤70 mg/dl, respectiv <55 mg/dl) prevăzute în recomandările ghidului de tratament al dislipidemiei ediţia 2016, respectiv 2019. **Rezultate –** Au fost incluşi 993 de pacienţi, dintre care numai 31% au atins valori LDL ≤70 mg/dl, fără diferenţe între bărbaţi şi femei, număr care a scăzut până la 15% după stabilirea ţintei la 55 mg/dl. Pacienţii cu comorbidităţi precum fibrilaţia atrială (34,9% vs. 25,1%, p=0,006), insuficienţa cardiacă (37,1% vs. 27,2%, p=0,047) şi boala cronică de rinichi (36,3% vs. 28,2%, p=0,028) au un control mai bun, deşi insuficient al ţintelor lipidice stabilite în 2016. Doi din trei pacienţi au un control corect al diabetului zaharat, cu valori HbA1c sub 7%. **Concluzii –** Studiul prezent ilustrează cum pacienţii cu risc cardiovascular foarte înalt nu reuşeau să atingă ţintele de profil lipidic recomandate în 2016 şi sunt şi mai departe de acest deziderat cu noile praguri prevăzute de Ghidul de Dislipidemie, ediţia 2019.
Cuvinte-cheie: hipertensiune arterială, diabet, LDL-colesterol, risc cardiovascular înalt.

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INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality with an estimated 30% of deaths worldwide[1]. From an economic standpoint, CVD places a heavy burden which could potentially be limited by population-wide interventions, but should also be addressed in a patient-oriented approach, especially in patients who are at high or very-high cardiovascular risk[1,2].

The prevalence of arterial hypertension and type 2 diabetes mellitus, keystone factors of CVD, is high and likely to increase further due to „globalization" of dietary habits and urbanization[1,3]. These conditions potentiate one another in producing atherosclerotic cardiovascular disease (ASCVD) which may lead to stroke, myocardial infarction, chronic kidney disease and ultimately death.

Low-density lipoprotein cholesterol has been attested as a determinant of atherosclerotic cardiovascular disease. Recent studies have shown little risk associated with a drastic LDL-cholesterol decrease[4]. According to the 2019 ESC guidelines for the management of dyslipidemia, diabetic patients at very-high cardiovascular risk should aim for an LDL-c reduction ≥50% from baseline or an LDL-c goal <55 mg/dL[5] irrespective of primary or secondary prevention; this new goal aims for tighter lipid control than previously recommended in the 2016 version (≤70 mg/dL)[6]. However, real world data has shown time and again that lipid control is achieved in relatively few patients[7,8].

MATERIAL AND METHODS

We performed a retrospective, unicentric, cohort study on consecutive patients admitted to the Department of Internal Medicine and Cardiology between January 2016 and December 2017. All patients were over 18 years of age and signed an informed consent; all had arterial hypertension, diabetes mellitus and AS-CVD diagnosed prior to enrollment. Data regarding demographics (gender, age) was collected along with laboratory assay results including lipid profile (serum cholesterol, triglycerides, LDL-cholesterol, HDL-cholesterol), glycated hemoglobin and renal function (serum urea, creatinine, uric acid). All patients were undergoing statin treatment, though data was not acquired as to the specific type or dose.

LDL-c goal attainment categorical variables were created in accordance with the ESC Guideline for the management of dyslipidemias as all patients were considered to be at very-high cardiovascular risk due to association of arterial hypertension, type 2 diabetes mellitus, age (≥40 years for men, ≥50 years for women) and diagnosed ASCVD (in the form of stable angina, prior myocardial infarction or coronary revascularization). Thus, treatment targets were LDL-cholesterol ≤70 mg/dL and <55 mg/dl, respectively, according to the 2016 and 2019 editions of the guideline.

Statistical analysis was performed using IBM® SPSS for Windows version 20. Descriptive statistics – means ± SD and proportions – were used to define patient demographics and lipid profile goal attainment. Computations included the χ^2 test to compare proportions and analysis of variance to compare differences between continuous variables. A p-value below 0.05 was considered statistically significant.

RESULTS

We enrolled a total of 993 patients with a slight predominance of the female gender (59.9%) and a mean age of 69.2 ± 9.7 years. Women were slightly older than men (70.4 ± 9.6 years vs. 67.3 ± 9.6, p<0.001). Two in three patients had controlled diabetes, with glycated hemoglobin values below the 7% target (Table 1).

In accordance with the 2016 ESC dyslipidemia targets (LDL-cholesterol ≤70 mg/dL), only about a third of patients had LDL-c levels within the desired range (31.6%, mean LDL-c: 91.7 ± 38.3 mg/dL). Taken further, with the 2019 ESC dyslipidemia targets applied (patients at very-high cardiovascular risk should aim for an LDL-c goal <55 mg/dL), the number of patients dropped by half (15.8%).

Patients who attained lipid goals were slightly older when considering LDL-c target ≤70 mg/dL (70.3 ± 9.3 vs. 68.0 ± 9.9, p=0.004) but not <55 mg/dL (p=0.064). There was no difference between LDL-c values of male or female patients (89.9 ± 38.6 mg/dL vs. 92.8 ± 38.7 mg/dL, p=0.341) and, thus, no gender specific differences between LDL-c target achievement in terms of 2016 goals, though there seems to be a trend when evaluating by 2019 recommendations (2016: 30.9% vs. 32.1%, p=0.410; 2019: 18.5% vs. 14.1%, p=0.078).

The most prevalent comorbidity was heart failure (82.5%), followed by chronic kidney disease and atrial fibrillation in up to a third of patients (31.5% and 30.5%). As expected, patients with heart failure were older (71.8 ± 9.0 vs. 62.8 ± 8.6, p<0.001), as were those with atrial fibrillation (73.2 ± 8.7 vs. 67.4 ± 9.6, p<0.001) or chronic kidney disease (73.9 ± 8.4 vs. 66.9 ± 9.6, p<0.001). In the HF and AF groups, there was no gender difference (84.1% vs. 80.2%, p=0.116 and 31.4% vs. 29.1%, p=0.244 respectively), though

more women had CKD than men (36.1% vs. 24.5%, p<0.001).

It is apparent that the subgroup of patients with atrial fibrillation had better control of lipid profile parameters (81.1 ± 30.5 mg/dL vs. 95.9 ± 40.7 mg/dL, p<0.001). In other words, more AF patients reached the 2016 LDL-c goal (34.9% vs. 25.1%, p=0.006); however, when considering the 2019 goals, as the percentages drop to 18.5% and 14.8%, there is also a loss of statistical significance (p=0.140).

Furthermore, lipid profile discrepancies among the subgroups of patients with and without heart failure or chronic kidney disease were noted (see Table 2); as such, patients with heart failure had better LDL-c goal attainment when compared to the 2016 but not the newer guidelines (37.1% vs. 27.2%, p=0.047 and 17.6% vs. 12.0%, p=0.125), while CKD patients maintained the differences irrespective of LDL-c goal (36.3% vs. 28.2%, p=0.028 and 18.9% vs. 13.0%, p=0.037).

DISCUSSION

Our study is the first to assess LDL-c goal attainment in a Romanian population through the lens of the newly published dyslipidemia guidelines and shows that while results were unsatisfactory before, even in very-high risk patients the new threshold only makes the task more daunting.

Out of all the very-high risk patients enrolled, only a third managed to reach LDL-c values below 70 mg/dL, a figure which dropped to under 1 in 5 patients when considering the 55 mg/dL target. Our findings are in accordance with literature data showing that despite publication of guidelines with clear treatment goals and availability of lipid-lowering therapies (LLTs), only few patients actually reach the desired level of control

in terms of cholesterol and triglycerides[9,10]. The EU-ROASPIRE IV study evaluated cholesterol goal achievement in European patients and included a subgroup of Romanian patients; little under half had LDL-c values below 100 mg/dL and only a fifth managed to reach the LDL-c goal (≤70 mg/dL) despite lipid-lowering therapy (LLTs) with high-intensity statin[11].

In a large German cohort, only 19.5% of patient with preexisting cardiovascular disease were able to reach the desired LDL-c goal ≤70 mg/dL, with only a marginally better target achievement in diabetic patients (33.5%) despite moderate- to high-intensity statin use[10].

Studies have shown that patients are more likely to attain lipid goals with increasing age[12,13], as did the patients in our cohort. However, it has also been reported that gender differences are relevant in terms of lipid goal achievement with diabetic men having lower LDL-c values under treatment.[14,15] In our study population, no gender specific differences were registered in terms of LDL-c values or LDL goal achievement irrespective of target (≤70 mg/dL or <55 mg/dL). Furthermore, there were no significant gender differences in triglyceride levels, despite total cholesterol being higher in women, and the LDL to HDL ratio higher in men (see Table 1, Figure 1).

Failure to attain cholesterol goals draws attention to the physician, on the one hand, who may be reluctant to up-titrate LLT regiments due to safety concerns and the patient, on the other, who may not be adherent to lifestyle and medication recommendations. It is somewhat alarming that only 1% of moderate-intensity statin patients undergo up-titration of treatment regimens and up to a quarter of patients on high-intensity statin discontinue treatment[10]. With

Table 1. Gender differences in lipid profile parameters (expressed as mean ± standard deviation) and goal attainment of cholesterol and glycated hemoglobin targets

|	Men	Women	p-value
Age (years)	67.3 ± 9.6	70.4 ± 9.6	<0.001
Total cholesterol (mg/dL)	166.3 ± 48.1	174.7 ± 48.9	0.013
LDL-cholesterol (mg/dL)	89.9 ± 38.6	92.8 ± 38.7	NS
HDL-cholesterol (mg/dL)	43.0 ± 14.0	49.6 ± 15.0	<0.001
Non-HDL-cholesterol (mg/dL)	123.8 ± 46.3	126.7 ± 46.2	NS
Triglycerides (mg/dL)	173.9 ± 144.6	161.6 ± 90.2	NS
LDL/HDL (mg/dL)	2.3 ± 1.1	2.0 ± 0.9	0.005
LDL-c ≤70 mg/dL (%)	30.9	32.1	NS
LDL-c <55 mg/dL (%)	18.5	14.1	NS
Triglycerides <150 mg/dl (%)	27.4	24.9	NS
HbA1c	7.17 ± 1.5	7.3 ± 1.6	NS
HbA1c <7% (%)	68.8	67.0	NS

NS – non-significant
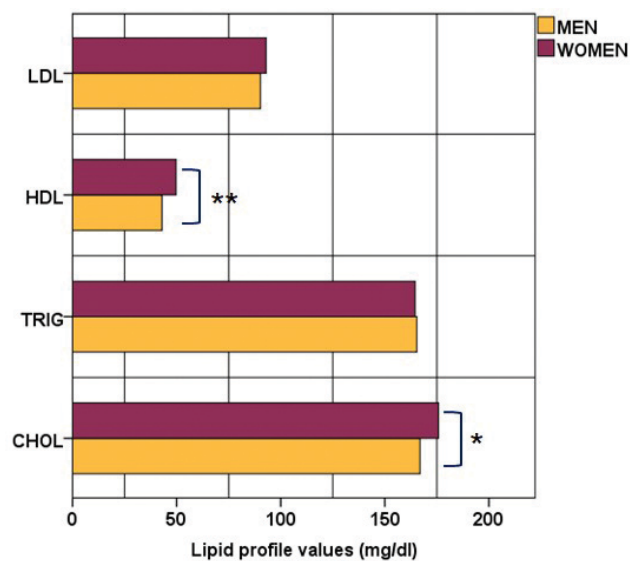
Figure 1. Mean values of lipid fractions shows no gender difference between mean LDL-cholesterol values, though slightly higher HDL-cholesterol in women and lower total cholesterol in men.
*statistically significant at a <0.05 level ; **statistically significant at a <0.001 level

the new targets in place we may expect an increase in the number of patients with recommendation for high-intensity statin and, potentially, an increase in the number of patients who discontinue treatment.

Several studies have tried to explain patient or physician reluctance to up-titrate statin dose through safety concerns.[16] However, it has been shown that there is no "J"-curve associated with low LDL-c values and muscle symptoms seem to occur with only a slight predominance, if any, in placebo-controlled randomized trials[4,5]. The newer guidelines recommend a stepwise approach to treatment: from maximal statin up-titration to addition of Ezetimibe and ultimately, PCSK9 inhibitors[5]. A comparison of LDL-c goal attainment spanning over a 6-year period in Europe and

the Middle East has shown that due to the advent of high-intensity statin and ezetimibe an improvement in target achievement has been possible, at least in term of very-high risk patients[7].

As polypharmacy is a known cause of treatment discontinuation, it is somehow surprising that in our cohort patients with various comorbidities such as atrial fibrillation, heart failure or chronic kidney disease, which in themselves require specific drugs, were more likely to attain lipid goals. It is our opinion that patients who develop such conditions undergo more frequent follow-ups which in turn lead to better adherence to treatment.

STUDY LIMITATIONS

Data regarding treatment regimens was not available and, as is the case of cross-sectional studies, patient follow-up could not be performed in order to assess the effect of LLT up-titration, nor provide information on treatment discontinuation. Finally, there was a lack of data on associated comorbidities, financial and health insurance status, which could potentially limit patients' adherence to treatment.

CONCLUSIONS

The gap between guideline recommendations and real world data has been made evident by a large number of studies to date, even considering previous LDL-c targets of ≤70 mg/dL. With the recently updated guidelines that lower the treatment threshold in very-high risk patients to a further <55 mg/dL, we expect to see even lower goal attainment, as is the case with our cohort of diabetic, hypertensive and ASCVD patients. Hence, primary care physicians and specialists must redouble their efforts to control risk factor in patients at very-high cardiovascular risk.

Table 2. LDL-cholesterol and glycated hemoglobin goal attainment in patients with atrial fibrillation, heart failure and chronic kidney disease

	2016 LDL goal		p-value	2019 LDL goal		p-value	HbaIC goal		p-value
	No	Yes		No	Yes		No	Yes	
AF	25.1	34.9	**0.006**	27.3	33.0	**NS**	17.9	32.3	**<0.001**
HF	77.4	84.4	**0.047**	78.7	85.3	**NS**	76.2	81.9	**NS**
CKD	28.1	36.1	**0.028**	29.1	39.1	**0.037**	27.1	31.2	**NS**
AF – atrial fibrillation; HF – heart failure; CKD – chronic kidney disease; HbA1c – glycated hemoglobin									

Conflict of interest: none declared.

List of abbreviations used
AF – atrial fibrillation
ASCVD – atherosclerotic cardiovascular disease
CKD – chronic kidney disease
CVD – cardiovascular disease
HbA1c – glycated hemoglobin
HDL-c – high-density lipoprotein cholesterol
HF – heart failure
LDL-c – low-density lipoprotein cholesterol
LLTs – lipid-lowering therapies

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