ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

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Aterosklerotik Kardiyovasküler Hastalıktan Birincil Korunma için 2019 ve 2016 Avrupa Kardiyoloji Cemiyeti/Avrupa Ateroskleroz Derneği Dislipidemi Kılavuzlarının Karşılaştırılması

Comparison of 2019 and 2016 ESC/EAS Dyslipidemia Guidelines for Primary Prevention of Atherosclerotic Cardiovascular Disease

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ÖZ

Giriş: Güncellenen Avrupa Kardiyoloji Cemiyeti/Avrupa Ateroskleroz Derneği (AKC/AAD) dislipidemi kılavuzu birincil korumada statin tedavisi konusunda yeni öneriler içermektedir, ancak dislipidemi yönetiminde kılavuz güncellemelerinin etkisi konusunda az sayıda araştırma mevcuttur. Çalışmamızın amacı 2016 ve 2019 AKC/AAD dislipidemi tedavisi kılavuzlarını karşılaştırarak, kılavuz güncellemesinin birincil koruma olarak statin tedavisi almaya uygun bireyleri belirleme konusundaki etkisini araştırmaktı.

Yöntem: 2014-2020 yılları arasında ilk akut koroner sendrom (AKS) tanısıyla başvuran ardışık hastalar çalışmaya dahil edildi. Kardiyovasküler riskler, 2016 ve 2019 dislipidemi kılavuzlarındaki SCORE çizelgelerine ve 2021 koruyucu kardiyoloji kılavuzundaki SCORE2 ve SCORE-OP çizelgelerine göre hesaplandı. Hastaların statin tedavisi endikasyonları 2016 ve güncellenmiş 2019 AKC/AAD dislipidemi kılavuzlarına göre belirlendi. 10 yıllık kardiyovasküler risk tahmini için tüm hastaların verileri 'HeartScore' yüksek riskli ülke tablosuna girildi.

Bulgular: Çalışmaya toplam 920 hasta dahil edildi. Hastaların ortalama yaşı 57±13 idi (erkekler için 56 ± 12; kadınlar için 63 ± 15, p <0.001). SCORE2 hesaplaması ile, 2016 ve 2019 SCORE hesaplamalarına kıyasla, çok yüksek riskli hastaların oranı anlamlı derecede yüksekti (sırasıyla; %15,3, %28,3, %58,7; p<0.001). 'Beraberinde statin tedavisi' önerileri 2019 kılavuzuna göre hastaların %57'si (n: 522) için, 2016 kılavuzuna göre ise %47'si (n: 433) için uygundu. 'Toplam statin tedavisi' önerileri oranı 2019 güncellemesi ile %86,2'den %88,6'ya yükselmişti. 2019 AKC/AAD kılavuzu statin tedavisi önerisi için yaş aralığını 40-75 yaşa çıkararak genişletti. Ancak çalışmamızın sonuçları hastaların %15,5'inin bu yaş aralığı dışında ilk AKS atağını geçirdiğini gösterdi.

Sonuç: 2019 güncellemesi, kılavuzun çok yüksek riskli hastaları belirleyebilme başarısını ve bu hastalara statin tedavisi öneri kapsamını artırmıştır. SCORE 2' ye uyarlanan dislipidemi kılavuzları, popülasyondaki çok yüksek riskli bireylerin belirlenerek statin tedavisi alma şansı sunulmasına katkı sağlayabilir.

Anahtar Kelimeler: birincil korunma, dislipidemi, ESC kılavuzları, SCORE riski, statin tedavisi

ABSTRACT

Objective: The aim of the current study was to investigate the impact of guideline updates for the management of dyslipidemias by comparing the performance of 2019 and 2016 ESC/EAS guidelines in determining individuals who are eligible for statin as a primary prevention therapy.

Method: We enrolled consecutive patients diagnosed with first episode of acute coronary syndrome (ACS) between 2014 and 2020. Statin treatment indications of the patients were calculated based on 2016 and updated 2019 ESC/EAS Dyslipidemia Guidelines.

Results: A total of 920 patients were included in the study. 83% of the patients were male. The mean age was 57 ± 13 years (56 ± 12 years for men; 63 ± 15 years for women, p <0.001). The Concomitant statin therapy (CST) recommendations was appropriate for 57 % (n: 522) of the patients according to the 2019 guideline, while this rate was 47% according to the 2016 guideline (n: 433). The overall statin therapy (OST) recommendations rate increased from 86.2% to 88.6% with the 2019 update.

The 2019 ESC / EAS Guidelines have extended the age range to recommend statin up to 75 years. However, the study shows that 15.5% of the patients had their first ACS attack outside this age range.

Conclusion: The 2019 guideline update has increased the success of the guideline to classify very high-risk patients in this risk group, and the scope of statin therapy recommendations has also increased in these patients. Lipid treatment guidelines need to be improved, especially in individuals calculated in the intermediate cardiovascular (CV) risk group.

Keywords: dyslipidemia, ESC guidelines, primary prevention, statin therapy, SCORE risk

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INTRODUCTION

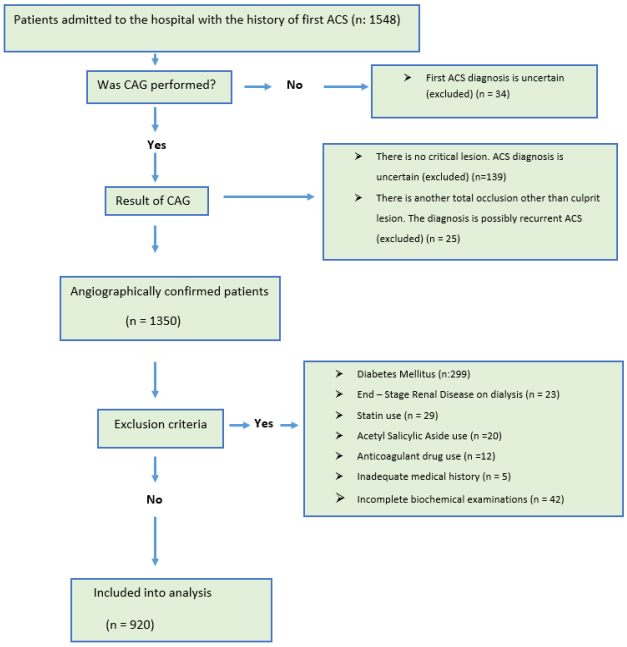
Increasing evidence has showed a strong relationship of plasma low-density lipoprotein cholesterol (LDL-C) with the risk of coronary artery disease (CAD) and the effectiveness of lipid-lowering therapy in reducing cardiovascular events in primary and secondary prevention. As a result, target LDL-C value was introduced into the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) dyslipidemia guidelines published in 1994 (1). With these guidelines, statin therapy, which has strong evidence of LDL-C reduction, has started to be recommended to individuals whose LDL-C values are above the targets. Over time, new drugs have been developed in addition to statins in lipid-lowering therapy. Recent placebo-controlled studies have shown that proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors or ezetimibe treatment given in addition to statin therapy further reduces the risk of cardiovascular events (2-4). A linear correlation was found between risk reduction and decrease in LDL-C level (5). In these studies, much lower LDL-C levels were achieved, and the decrease in LDL-C level was shown to continue its relationship with the reduction in cardiovascular events. It is determined that there is no J curve relationship. In view of these compelling results, practice guidelines have endorsed the "treat-to-target" strategy. At the same time, recent articles have been published discussing the adequacy of the SCORE risk calculation system and ESC/EAS dyslipidemia guidelines for primary prevention. As a result, ESC/EAS dyslipidemia guidelines have been updated in 2019 (6).

ESC/EAS 2019 guideline update contains three important differences in primary protection. First, the upper age limit was increased to 75 years in primary protection. Second, the SCORE risk chart was updated. Finally, the LDL-C target values were changed. Adding statin therapy is included in people with low cardiovascular risk with an LDL cholesterol level of ≥ 116 mg/dl. In addition, concomitant statin therapy was included in intermediate and low-risk individuals with LDL-C levels of ≥ 190 mg/dl (6) (Supplementary Table 1).

The aim of the current study was to investigate the impact of guideline updates for the management of dyslipidemias by comparing the performance of 2019 and 2016 ESC/EAS guidelines in determining individuals who are eligible for statin as a primary prevention therapy.

MATERIALS AND METHODS

This cross-sectional observational study enrolled consecutive adult patients (>18 years) who were diagnosed with ACS for the first time and admitted to the intensive coronary care unit of the xxx Training and Research Hospital between 2014 and 2020. During the hospitalization period, face-to-face interviews and physical examinations were performed, and laboratory findings and CV risk factors were determined. The exclusion criteria were as follows: CVD; Diabetes Mellitus (DM), chronic renal disease; chronic obstructive pulmonary disease; malignancy; regular use of statins, antiplatelets, or anticoagulants; situations where oral communication with the patient is impossible; situations where coronary angiography could not be performed. Patients with findings that might be related to previous MI on electrocardiography or echocardiography and total occlusion other than "culprit" lesion and no critical stenosis on coronary angiography were also excluded (Supplementary Fig. 1). Our study conformed to the principles of the Declaration of Helsinki and was approved by the ethics committee of xxx Training and Research Hospital, University of Health Sciences (2014-097) (Clinical trial number: NCT04578964). Written informed consent was obtained from all participants.



Supplementary Fig. 1. Patient flow through inclusion/exclusion procedure.

The diagnosis of ACS included ST-elevated MI (STEMI), non–ST-elevated MI (NSTEMI), and unstable angina pectoris (USAP). MI was defined according to the fourth universal MI definition of the 2018 ESC (7). Our study included type 1 (spontaneous) MI. Acute MI was classified as either STEMI or NSTEMI according to the presence or absence of ≥1 mm of ST-segment elevation in two or more contiguous leads on initial electrocardiography. USAP referred to admitted patients with typical chest pain lasting more than 20 min without increased cardiac markers and ST-segment elevation.

The medical history was obtained on the second day of hospitalization. Fasting (>10 h) venous blood samples were taken in the first 24 h of MI to measure blood cholesterol levels. Low-density lipoprotein cholesterol (LDL-C) values were calculated using the Friedewald method (8). For triglyceride levels > 400 mg/dl, "direct LDL-C" measurements were used.

Blood pressure was measured before any treatment that can affect blood pressure levels. In this study, a resting systolic blood pressure >140 mm Hg or diastolic blood pressure > 90 mm Hg or treatment with anti-hypertensive medications defined hypertension (HTN). DM was defined as having an established diagnosis of DM or using insulin or oral hypoglycemic drugs. Furthermore, hyperlipidemia (HLD) was defined as having an established diagnosis or treatment with a lipid-lowering agent. A smoker for >1 year consuming at least 1 pack per year was considered as a "current smoker."

Statin treatment indications of the patients were calculated based on 2016 and updated 2019 ESC/EAS Dyslipidemia Guidelines. For the estimation of 10-year cardiovascular risk, data for each individual patient were entered into charts of "HeartScore" high-risk country. "Lifestyle intervention and concomitant drug intervention" ESC recommendations were called concomitant statin therapy (CST). "Lifestyle intervention, consider adding drug if uncontrolled" ESC recommendation was called "adding statin therapy" (AST). Both the AST and CST recommendations were named the "overall statin treatment" (OST) recommendation.

Statistical Analysis: For continuous variables arithmetic mean ± standard deviation, and for categorical variables frequencies and percentages were used. For the evaluation of normality assumption, Shapiro Wilk test was used. Within-group comparison in terms of categorical variables was tested by McNemar test. Comparison of continuous variables among three or more independent groups was evaluated by using One-way analysis of variance. When the p-value from the One-way analysis of variance test statistics is statistically significant, Tukey HSD test was used to know which groups differ from which others. Degree of association between continuous variables were calculated by Pearson's correlation coefficient. All statistical data were analyzed by R version 3.4.4. P value less than 0.05 was considered statistically significant.

RESULTS

A total of 920 patients were included in the study. 83% of the patients were male. The mean age was 57 ± 13 years (56 ± 12 years for men; 63 ± 15 years for women, p <0.001). Total and LDL cholesterol levels are similar between genders (men: 209 ± 51 mg/dl, female 206 ± 47 mg/dl, p = 0.500; male 138 ± 40 mg/dl, female 134 ± 40 mg/dl, p = 0.272, respectively), HDL-C level was significantly higher in women (48 ± 11 mg/dl, 42 ± 11 mg/dl, p = <0.001). The median cardiovascular risk was 5% in all patients and 4% in the 40-65 age group. The general characteristics of the patients are given in Table 1.

Concomitant statin therapy (CST) recommendations: Among all patients included in the study, the CST recommendation was appropriate for 57% (n: 522) of the patients according to the 2019 guideline, while this rate was 47% according to the 2016 guideline (n: 433). With the guideline update, the CST recommendation increased by 9%. With the 2019 update, 89 new patients (9.7%) were included in the CST recommendation. Three (0.3%) patients covered by CST in the 2016 guideline were not included in the CST recommendation by the 2019 guideline (Figure 1). When 40-65 age group patients (n: 648) were examined, 320 patients according to the 2019 guideline and 291 patients according to the 2016 guideline were within the scope of CST. The guideline update increased CST coverage by 29 patients (4%) in this age group.

Compared by sex, men were covered at a higher rate of CST in the 2019 guideline as in the 2016 guideline. However, in the 65-75 age group, the CST recommendation for women in the 2019 guideline increased by approximately four times compared to the 2016 guideline and reached 84%. In the 40-65 age group, CST coverage in the female gender increased by 3.5% with the guideline update (Figure 2). In all age groups, the rate of suggestions for CST in women increased from 20.3% to 40.1%. In men, it increased from 52.7% to 56.6%.

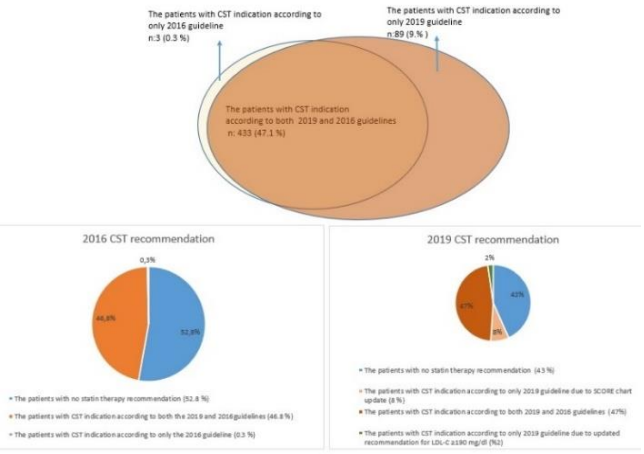


Figure 1. Comparison of CST recommendations in 2016 and 2019 ESC/EAS dyslipidemia guidelines (CST: Concomitant statin therapy ESC/EAS: European Society of Cardiology/European Atherosclerosis Society)

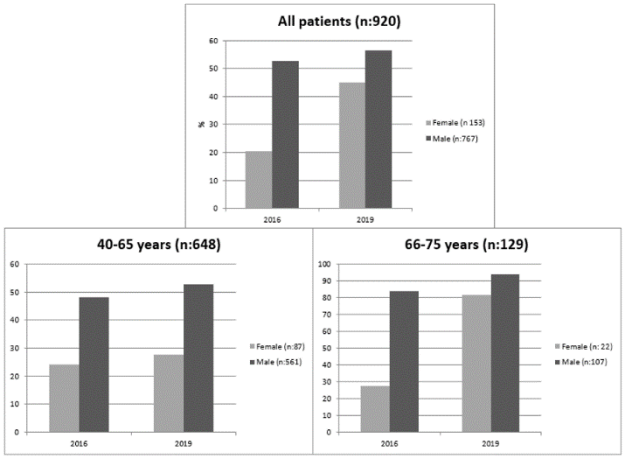


Figure 2. Comparison of CST recommendations by gender (CST: Concomitant statin therapy)

Table 1. General Characteristics

	All	2019 statin eligible	2016 statin eligible	Only 2019 statin eligible
All patients n % Individuals n (%)	920 (100)	522 (56.7)	433 (47.1)	89 (9.7)
Male gender (%)	83	90	90	85
Age (years)	56 (48-65)	61 (53-69)	62(54-69)	47 (41-50)
Systolic blood pressure (mmHg)	134 (124-140)	137 (128-144)	137 (128-145)	134 (128-140)
Diastolic blood pressure (mmHg)	80 (75-85)	81 (76-87)	81 (76-89)	81 (78-91)
Total Cholesterol(mg/dl)	204 (176-236)	216(189-252)	213 (187-245)	270(263-280)
LDL cholesterol (mg/dl)	132 (111-156)	145 (124-174)	142 (122-170)	200 (194-213)
HDL cholesterol (mg/dl)	42 (36-49)	43 (37-49)	43(37-49)	43(38-53)
Non-HDL cholesterol (mg/dl)	159 (133-189)	172 (147-203)	169 (146-197)	227(223-242)
Triglyceride (mg/dl)	120 (84-182)	114(81-172)	118 (84-182)	134(74-194)
SCORE 10-year fatal ASCVD (%)	5 (2-7)	7 (5-10)	7 (5-10)	2(2-4)
Current smoke (%)	59	55	62	24
Age 40-65 years Individuals n %	648 (100)	320 (49)	291 (45)	29 (4)
Male gender (%)	87	93	94	84
Age (years)	53 (47- 59)	57 (52-61)	57(52-61)	48 (42-50)
Systolic blood pressure (mmHg)	134 (126-140)	137 (128-144)	137 (128-145)	134 (124-140)
Diastolic blood pressure (mmHg)	81 (75-85)	81(77-90)	81 (77-90)	81 (76-92)
Total Cholesterol(mg/dl)	206(179-240)	220 (193-261)	215 (191-251)	270 (257-287)
LDL cholesterol (mg/dl)	134 (111-163)	148 (127-185)	144 (125-174)	200 (194-212)
HDL cholesterol (mg/dl)	41(35-48)	41 (36-48)	41 (36-48)	43 (39-53)
Non-HDL cholesterol (mg/dl)	161 (134-193)	175 (150-208)	171 (148-204)	226 (222-239)
Triglyceride (mg/dl)	126 (85-192)	129 (89-193)	126 (89-194)	132 (68-172)
SCORE 10-year fatal ASCVD (%)	4(2-7)	7 (5-9)	7 (5-9)	3 (2-4)
Current smoke (%)	67	71	74	41
Age 66-75 years n % Individuals n %	129 (100)	122 (94.6)	97 (75.2)	25 (19.4)
Male gender (%)	107 (83)	104 (86)	91 (94)	13 (52)
Age (years)	70 (68- 73)	70 (68-73)	69 (67-72)	70 (69-73)
Systolic blood pressure (mmHg)	136 (120-148)	136 (120-148)	137 (126-157)	125 (109-138)
Diastolic blood pressure (mmHg)	80 (74-85)	80 (73-85)	81 (75-89)	77 (60-82)
Total Cholesterol(mg/dl)	200 (172-221)	202 (174-224)	206 (181-234)	171 (144-217)
LDL cholesterol (mg/dl)	128 (113-158)	129 (114-158)	133 (119-160)	113 (88-142)
HDL cholesterol (mg/dl)	44 (38-50)	44 (39-50)	45 (39-51)	43 (39-53)
Non-HDL cholesterol (mg/dl)	151 (125-176)	154 (1132-178)	158 (1136-186)	128 (103-164)
Triglyceride (mg/dl)	98 (71-147)	99 (71-155)	105 (74-158)	81 (64-129)
SCORE 10-year fatal ASCVD (%)	8 (6-12)	8 (6-13))	7 (5-9)	5 (4-7)
Current smoke (%)	35	37	43	12

CST: Concomitant statin therapy HDL: High-density lipoproteins, LDL: Low-density lipoproteins, Note: Three patients were CST recommendation group only according to 2016 guidelines. These patients' risk levels were calculated 6 % with the 2016 chart and 4 % with the 2019 chart. LDL cholesterol levels were 171 -179 mg/dl.

The 2019 ESC / EAS Guidelines have extended the age range to recommend statin up to 75 years. Thus, the age range has become 40-75 years. However, our study shows that 15.5% of the patients had their first ACS attack outside this age range. 6.2% of the patients who presented with ACS for the first time were <40 years old, 9.3% were> 75 years old. When the patients in the study were examined in terms of age distribution, the highest rate was in the 40-65 age group (70.4%) (Figure 3).

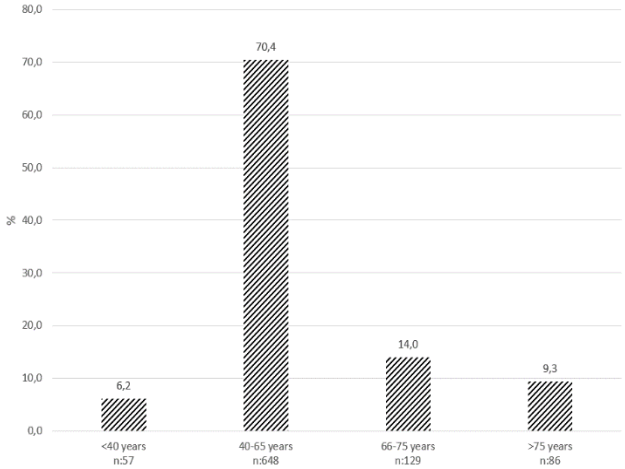


Figure 3. Distribution of the first ACS patients by age groups (ACS: Acute coronary syndrome)

With the 2019 update, the inclusion of 66-75 years of age within the scope of statin treatment increased the total coverage of the guideline by 14%. The fact that the SCORE calculation system can be applied up to the age of 75 has significantly increased the rate of concomitant statin treatment in people aged 66-75. The 2016 guideline does not recommend lipid-lowering therapy for people over 65 years of age in primary prevention. When we calculated these people as 65 years old, CST was not recommended for 24.8% of the people in this age range, according to the 2016 guide. In 2019, this rate had dropped to 5.4% (Figure 4).

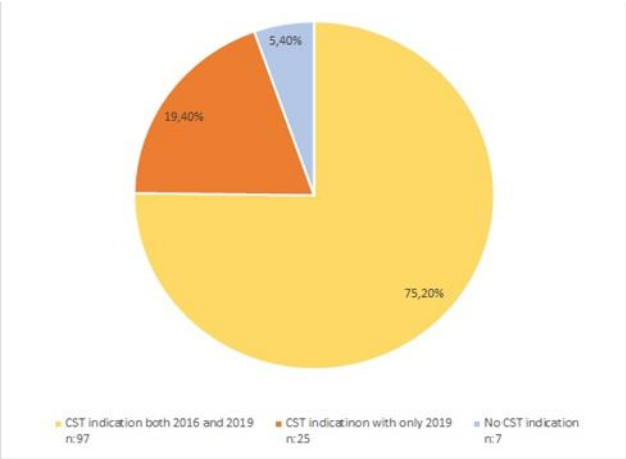


Figure 4. Comparison of 2016 and 2019 ESC/EAS dyslipidemia guidelines for CST recommendations in people aged 65-75 years (CST: Concomitant statin therapy ESC/EAS: European Society of Cardiology/European Atherosclerosis Society)

When we analyzed the 5-year age range, it was found that the CST rates of both guidelines in the 50-60 age range were close, but the 2019 guideline's CST rates were higher except for these age ranges. CST rates of the 2019 guidelines were higher, especially in people over 60 years (Figure 5).

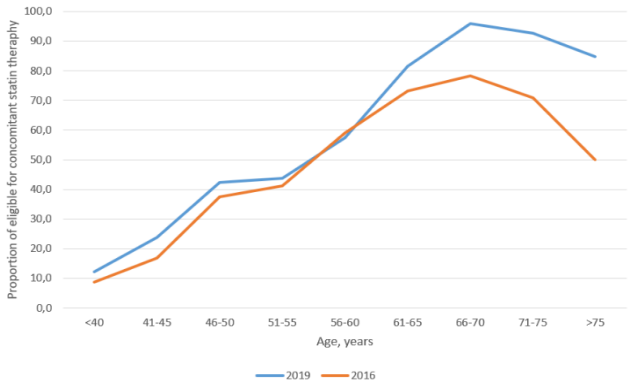


Figure 5. According to 5 years age groups proportion for eligibility of statin therapy

With the 2019 guideline, including low- and moderate-risk patients with LDL ≥ 190 mg/dl within the scope of CST enabled 26 (2.06%) new patients to be included in the scope of indication. The LDL-C value of 86 (9%) of the patients was ≥ 190 mg/dl. However, since most of them were in the medium- and high-risk groups, it was also within the scope of CST in 2016.

When examining the role of the factors that increase the scope of 2019 in terms of the CST recommendations, the strongest effect was the increase in the age limits. The second strongest effect was the updated SCORE chart. Treatment recommendation ≥ 190 mg/dl had the least effect at moderate and low CV risk (Figure 6).

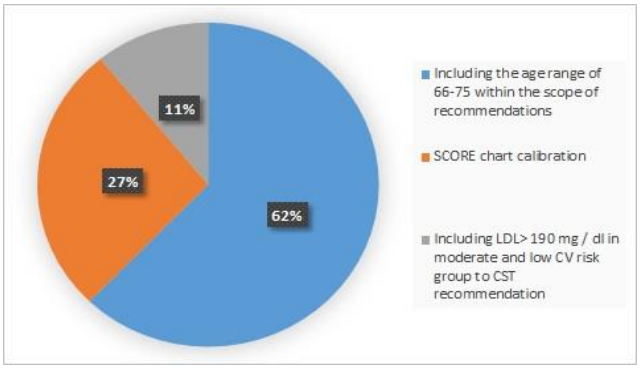


Figure 6. Factors contributing to the increase in CST recommendations in the 2019 guideline

Overall statin therapy (OST) recommendations: 86.2% of the patients were in the common OST indication group according to both guidelines. The 2019 guideline completely covered the 2016 guideline in terms of OST. In addition, we found that 22 patients (2.4%) were eligible for OST in the 2019 guideline. Thus, it was determined that the OST rate increased to 88.6% with the 2019 update (Figure 7).

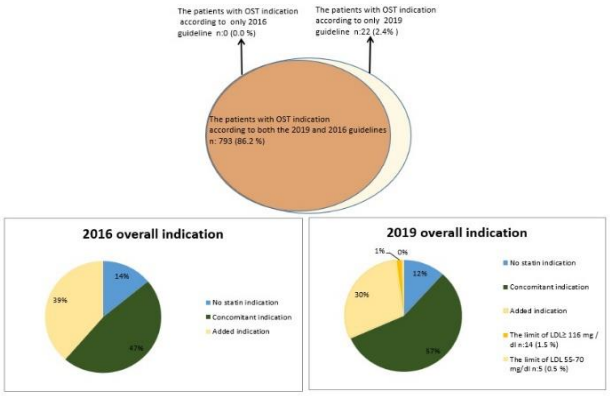


Figure 7. Comparison of 2016 and 2019 ECS dyslipidemia guidelines for OST recommendations

With the 2019 update, it was found that the AST recommendation increased the OST recommendation by 1.5% in people with low cardiovascular risk with LDL ≥ 116 mg/dl. In the very high-risk patient group with LDL 55-70 mg/dl, the AST recommendation increased the 2019 OST indication by 0.4%. In the 2016 guideline, it was observed that the difference in coverage between the guidelines was narrowed in terms of OST, as most patients not in CST were included in the AST.

When the distribution of patients according to CV risk groups was examined, it was found that most of the patients were calculated in the medium-risk group in both guidelines. With the updated 2019 SCORE chart, it was observed that the rate of detection of patients in the very high-risk group increased. Especially in patients aged 65-75, the rate of detection in the very high-risk group increased significantly.

When the distribution of patients according to the traditional tables of ECS guidelines made according to SCORE risk and LDL values was examined, the group with the highest number of patients was the moderate CV risk group. The 2016 guideline defined 45.1% of the patients, and the 2019 guideline defined 37.1% in the intermediate-risk group. The LDL value range with the highest number of patients was 100- 155 mg/dl (n = 507, 55.1%) for 2016 and 116 - 190 mg/dl for 2019 (n = 555, 60.3%) (Figure 8).

Positive predictive results according to 2019 ESC / EAS Dyslipidemias Guidelines

Total CV risk (SCORE)	LDL – C levels (mg/dl)						Proportion eligible for statin therapy		
	n (%)	<55	55 to < 70 n (%)	70 to <100 n (%)	100 to <116 n (%)	116 to < 190 n (%)	≥190 n (%)	Concomitant n (%)	Added n (%)	Concomitant+Added n (%)
<1 %	32 (3.5)	0	1 (0.1)	9 (1.0)	7 (0.8)	14 (1.5)			14 (1.5)	15 (1.6)
COR / LOE			I/C	I/C	I/C	IIa/A	IIa/A			
Mean age (years) 43,1 ± 8.1				37	41 ± 6,3		39			
≥1 to <5	342 (37.2)	2 (0.2)	13 (1.4)	51 (5.5)	52 (5.7)	204 (22.2)			256 (27.8)	276 (30.0)
COR / LOE			I/C	IIa/A	IIa/A	IIa/A	IIa/A			
Mean age (years) 50.6 ±1.3			47.5 ± 6,5	52.6 ± 12.3	48.7 ± 10.8	49.7 ± 10.8	45.2 ± 6.9			
≥5 to <10	286 (31.1)	0	5 (0.5)	36 (4.22)					36 (3.9)	283 (30.8)
COR / LOE			IIa/A	IIa/A	IIa/A	I/A	I/A			
Mean age (years) 61.5 ±11.5			71 ± 21.4	65.1 ± 9.3	61.5 ± 9.5	57.9 ± 7.4	53.4 ± 4.6			
≥ 10	260 (28.3)	2 (0.2)	5 (0.5)						5 (0.5)	258 (28.0)
COR / LOE			IIa/A	IIa/A	/A	/A	/A			
Mean age (years) 66.4 ± 6.9				66.0 ± 4.6	65.7 ± 7.03	63.3 ± 4.8	61.5 ± 7.4			
Total	920 (100)	4 (0.4)	22 (2.4)	122 (13.3)	131 (14.2)	555 (60.3)	86 (9.3)		311 (33.8)	832 (90.4)

Positive predictive results according to 2016 ESC / EAS Dyslipidemias Guidelines

Total CV risk (SCORE)	LDL – C levels (mg/dl)						Proportion eligible for statin therapy		
	n (%)	< 70 n (%)	70 to <100 n (%)	100 to <155 n (%)	155 to < 190 n (%)	≥190 n (%)	Concomitant n (%)	Added n (%)	Concomitant+Added n (%)
<1 %	30 (3.3)	1 (0.1)	9 (1.0)	18 (2.0)	1 (0.1)	1 (0.1)	0	1 (0.11)	1 (0.1)
COR / LOE		I/C	I/C	I/C	I/C	IIa/A			
Mean age (years) 43,1 ± 8.1		1 (0.1)	37	41 ± 6,3	0	39			
≥1 to <5	415 (45.1)	17 (1.4)	71 (7.1)	233 (25.2)	75 (8.2)	20 (2.2)	0	327 (35.5)	327 (35.5)
COR / LOE		I/C	I/C	IIa/A	IIa/A	I/A			
Mean age (years) 50.6 ±1.3		47.5 ± 6,5	52.6 ± 12.3	48.7 ± 10.8	49.7 ± 10.8	45.2 ± 6.9			
≥5 to <10	334 (35.9)	6 (0.6)	30 (3.3)				298 (32.4)	30 (3.3)	328 (35.7)
COR / LOE		IIa/A	IIa/A	IIa/A	I/A	I/A			
Mean age (years) 61.5 ±11.5		71 ± 21.4	65.1 ± 9.3	61.5 ± 9.5	57.9 ± 7.4	53.4 ± 4.6			
≥ 10	141 (15.3)	2 (0.2)					139 (15.1)	2 (0.2)	141 (15.3)
COR / LOE		IIa/A	IIa/A	/A	/A	/A			
Mean age (years) 66.4 ± 6.9			66.0 ± 4.6	65.7 ± 7.03	63.3 ± 4.8	61.5 ± 7.4			
Total	920 (100)	26 (2.8)	122 (13.3)	507 (55.1)	179 (19.5)	86 (9.3)	437 (47.5)	360 (39.1)	797 (86.6)

Figure 8. Comparison of the statin indication tables of 2016 and 2019 dyslipidemia guidelines

DISCUSSION

The present study showed that the 2019 ESC/EAS guidelines on the use of statins for primary prevention of ASCVD have superior sensitivity compared to the 2016 guidelines. We have shown that the main role in sensitive increase is the update in the SCORE risk calculation system, and lowering the LDL cholesterol threshold contributes more limitedly. Particularly, the participation of the 65-75 age group in the SCORE calculation system and the inclusion of the statin recommendation led to a significant increase in the CST recommendation.

Guideline updates make significant changes to lipid-lowering therapy prescriptions. Examining the economic burden of treatment changing guidelines and analyzing their potential beneficial effect can be helpful in the development of guidelines. However, guideline evaluations have not yet taken a standard form. First, in 2014, Pencini et al. examined the patient burden created by the 2013 American College of Cardiology/ American Heart Association guideline change (9). Later, many studies examining the guidelines have been published. In 2020, Mortensen et al. published a study comparing the 2019 ESC/ EAS Dyslipidemia guideline with the 2016 guideline (10). To the best of our knowledge, this study is the first to evaluate the ESS dyslipidemia guideline with a sample from the Turkish population in terms of positive predictively.

Impact of updating the SCORE risk tables: The new updated SCORE risk charts are important features that distinguish the 2019 from the 2016 guidelines for primary prevention (6, 11). With this update, the rates of patients included in the very high CV risk group increased. In primary cardiovascular prevention, the benefit of prescribing treatment according to the risk level calculated by algorithms is not clear. Studies show that although very little benefit is obtained, too many lipid-lowering agents and antihypertensive drugs are prescribed. On the other hand, patients not calculated in the high or very high CV group constitute the majority of the first ACS patients. Primary prevention guidelines are faced with the dilemma of unnecessarily recommending medication and not being able to recommend medication when necessary (12-14). All of these create a renewal requirement for risk calculation systems. In the 2019 guide, revisions were made to the SCORE risk calculation system. The study showed that revisions in the 2019 guideline update increased predictively in identifying very high-risk patients.

The guideline recommends CST to a significant proportion of high and very high CV risk patients. However, our study shows that the pre-event risk levels of the majority of the first ACS patients are at the moderate CV risk level. This finding emphasizes the need for more detailed risk analysis in patients with a moderate CV risk level. In addition, these findings emphasize the importance of more stringent LDL-cholesterol target tracking in patients identified as moderate risk and initiation of treatment in cases where lifestyle changes are not successful. Identifying additional cardiovascular risk factors with prospective cohort studies in persons with moderate risk levels, identifying individuals requiring CST, or calculating appropriate lower LDL-C levels for cost-effectiveness may be beneficial in terms of cardiovascular risk prevention with lipid therapy.

The effect of increasing age limits: An important difference in the 2019 update is that the 66-75 age group is included in primary prevention.

The 2016 guidelines for individuals above age 65 suggested that statin therapy could be considered in the presence of other risk factors on a case by case basis (11). However, the 2019 ESC/EAS guidelines provide the same and strong risk-based Class I/A recommendations for statin therapy to individuals aged 66–75 as in those aged 40–65 (6). Strong evidence from randomized controlled trials showed that the beneficial effect of primary prevention with statin therapy in individuals aged > 65 years (15). Statin therapy reduces the risk for ASCVD irrespective of age. In a contemporary primary prevention cohort, people aged 70–100 years with elevated LDL cholesterol had the highest absolute risk of myocardial infarction and atherosclerotic cardiovascular disease and the lowest estimated NNT in 5 years to prevent one event (16).

It has been shown that 40–45% of all CVD events occur in individuals aged <65 years, even though the risk is much greater in individuals over age 65 than under. Mortensen et al. showed that the pattern is even more pronounced, with 60% of ASCVD events occurring in individuals < 65 years at baseline (10). In the current study, 65% of the patients who first presented with ACS were <65 years old. On the other hand, a quarter of the patients who had the first ACS were> 65 years old. Human life is prolonged worldwide. Increasing life expectancy between 2000 and 2016 is the biggest increase since the 1960s. According to world health organization data, the average age in Europe is 77.5 years. Evidence on the increased lifespan and the benefits of statin therapy in these age groups is supportive of the guidelines for increasing the age of recommendation in primary prevention. Increasing the age range with the guideline update was the change that increased the positive predictive value the most. The rate of CST for statin therapy reached the highest level in the 66-75 age range. There is a tendency for a decrease in statin treatment recommendations in older age. However, this downward trend is lower than the 2016 guideline calculations.

Effect of changing LDL cholesterol treatment recommendation levels: Recent studies showed a linear association between achieved low-density lipoprotein cholesterol (LDL-C) level and absolute coronary heart disease (CHD) event rate or progression of atherosclerosis. The effects of lipid-lowering therapies in secondary prevention are clear. However, data from primary prevention studies do not provide a clear idea that the decrease in LDL-C levels prevents cardiovascular events (17, 18). There are data available demonstrating the potential benefit of reducing the LDL burden (19, 20). However, the effort to reduce the LDL burden, which cannot be reduced by lifestyle changes, may lead the majority of society towards the initiation of statins. This study showed that the mean LDL-C during the first ACS episode was close to the population average. In the Turkish Heart Study, mean LDL-cholesterol concentrations were found as 136 mg/dl in men and 111 mg/dl in women (21). LDL-C values of the TEK-HARF study were 114.6 ± 34.7 mg/dl in men and 122.4 ± 38 mg/dl in women (22). These studies did not analyze according to age ranges. In a study comparing the lipid values of the US population between 1960 and 2002, LDL value was found as 136 mg/dl men (50-60 years) and 133 mg/dl in women (60-69) (23). In our study, considering that male or female age is 56, MI age is 62, it is seen that the mean LDL-C values we determined for the genders are close to the population average. With the 2019 guideline update, it was recommended that statin therapy should be initiated in people with low cardiovascular risk if the LDL-C level is> 116 mg/dl and the LDL level cannot be reduced with a change in lifestyle. It seems that this proposal will cover a very large part of the society. However, our study showed that the ratio of the first ACSs developing at this risk and cholesterol level to all ACSs is 1.5%. Statin therapy recommendation for lower LDL-C value in the low-risk patient increased the scope of the guideline as expected. However, it made a relatively small increase in positive predictively. The low LDL C target values guideline in the 2019 ESC /EAS guideline only increased the OST by 2% in terms of sensitivity. In the group with a SCORE risk level of <1%, this new regulation of the statin LDL level is a positive development as it gives some patients the chance of treatment. However, the fact that the majority of the society recommends statin therapy also creates a cost problem. Another important and uncertain situation is that the majority of the population is recommended to use statin therapy for life from the age of 40. This condition has a high potential to cause problems in terms of compliance with treatment. In this patient group, better risk calculation and better determination of statin therapy indication timing may be beneficial.

Comparison of the guidelines by gender: Since the Framingham Heart Study, male gender has been associated with an increased risk of cardiovascular events. A higher risk is calculated for the male gender in the risk algorithms. A man with the same risk factors in terms of primary prevention has a higher chance of being considered at higher risk than a woman and getting a recommendation to initiate statin therapy. In both of the guidelines, the positive predictive value was higher in male gender. However, in 2019, there was an increase in the positive predictive value in terms of female patients receiving CST. The update has improved treatment rates for female CST. However, there is still a shortage according to the male gender. New approaches should be developed for risk calculation in women.

Risk group with priority to focus on guideline development: Intermediate CV risk: Since all of the patients in our study had ACS, risk calculations before the event were expected to be classified in the very high-risk group with an ideal algorithm. However, in both 2016 and 2019 guidelines, the majority of patients are classified in the moderate-risk group. This rate decreased slightly in 2019, and the rate of classification of patients in the high and very high CV risk groups increased. In 2016, almost half of the patients were classified in the intermediate-risk group, and none were included in the CST group. In 2019, this ratio fell to one-third. It is clear that there are patients who can be calculated with the current SCORE algorithm at intermediate risk but need to be calculated at high risk. It should be a goal to develop guidelines and risk algorithms and identify patients who are calculated in the intermediate and low-risk groups, but actually have high cardiovascular risk. From the point of view of AST, it is seen that 76 percent of all patients calculated in this risk group of the guideline coverage are within the scope of AST. Therefore, in patients with AST recommendation calculated in the intermediate-risk group, if adequate lipid recovery cannot be achieved with follow-up and lifestyle changes, sufficient attention should be paid to guideline recommendations for initiation of statin therapy. Statin treatment compliance has been shown to reduce the risk of cardiovascular events in both primary and secondary prevention. However, it has been shown that treatment compliance is not sufficient and needs to be improved. In

the intermediate CV risk group, the only approach that will protect people from cardiovascular events in the process until the development of algorithm systems may be the implementation of AST recommendations.

Our study has some limitations. First of all, the working method allows only positive predictive value calculation. With the assumption of risk calculation just before the event in patients with ACS, pre-event cardiovascular risk is calculated in patients with ACS. Patients who did not have ACS were not included in the study. It does not provide information about the negative predictive value. However, studies conducted with a methodology similar to our study are associated with a lower cost and faster results in terms of positive predictivity compared to prospective cohort studies. Nevertheless, evaluating our findings with prospective cohort studies may be useful in terms of cost-effectiveness analysis.

Another limitation of our study is the single-center design; however, the characteristics of the patient group are compatible with the multicenter TURKMI study (24). The study was conducted in the center with the highest ACS patient burden in Antalya. Antalya is one of the cities in Turkey with the highest number of immigrants. When the data were analyzed according to the immigration status of the patients, it was observed that half of the participating patients were migrants from other provinces, and half of patients had emigrated from Turkey's 12 different geographical regions. Although our study was not planned as a multicenter study, patients from all geographical regions were included in the study.

In addition, the fact that the study covers a period of 5 years may cause limitations in terms of standardization of laboratory results. In the laboratory reviews included in the study within this time period, the kit or calculation methods remained the same.

An important difference between our study and other similar studies was that we included patients with culprit lesions in CAG, and excluded those without CAG. Moreover, patients diagnosed with Type 1 MI were included in the study, and other types of AMI were excluded. Thus, a more specific patient group was formed to calculate the age of the first ACS due to atherosclerotic plaque rupture. In addition, patients using drugs, such as statin and antiplatelet that affect the first ACS age, were excluded from the study. Hence, confusing factors were removed before calculating the first ACS age.

In conclusion, the 2019 dyslipidemia guideline update has increased the success of the guideline to classify very high-risk patients in this risk group, and the scope of statin therapy recommendations has also increased in these patients. Increasing the age range, updating the SCORE risk tables, and decreasing the LDL-C levels at the beginning of treatment contributed to this increase, respectively. Despite the new update, lipid treatment guidelines need to be improved, especially in individuals calculated in the intermediate CV risk group.

Ethics Committee Approval: The study was approved by the ethics committee of Antalya Training and Research Hospital (2014-097).

Authors' contributions: Concept: DD; Desigin: DD; Supervision: DD, DED; Resources: DD, Materials: DD; Data Collection and/or processing: DD, DED; Analysis and/or interpretation: DD, Literatur search: DD, DED; Writing manuscript: DD, DED; Critical review: DD, DED.

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