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A Retrospective Study: The Effectiveness of Lipid-Lowering Medications in Individuals at High Risk for Cardiovascular Disease

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Abstract

Objective: The effective administration of lipid-lowering treatment is of utmost importance in mitigating cardiovascular (CV) risk in patients who are undergoing secondary prevention.

High-dose statins, ezetimibe, and the relatively newer PCSK9 inhibitors (PCSK9i) have shown effectiveness in achieving low density lipoprotein cholesterol(LDL-C) treatment targets for these patients.

However, despite substantial evidence supporting their efficacy, these interventions remain significantly underutilized, primarily due to poor levels of patient adherence.

Moreover, there is limited data available on the overall effectiveness of cholesterol-lowering treatment and the proportion of secondary prevention patients who have achieved a well-regulated lipid profile.

In light of these factors, the principal aim of this investigation was to evaluate the present status of lipid-lowering medication within this specific group of individuals.

Methods: The study was conducted at Mardin Artuklu University, Mardin Training and Research Hospital between April 2021 and March 2023, focusing on patients with a history of secondary prevention of CVD. The study investigated prescribed cholesterol-lowering drugs, factors contributing to statin underuse, and lipid profile disclosure.

Results**:** 872 patients were included. 86.8% received statins, 5.2% ezetimibe, and 3.4% fibrates, while 13.2% received no lipid-lowering therapy. 64% of those on statins were on high doses. LDL-C values were assessed in 452 patients, with only 30% below the recommended cutoff of 70 mg/dL.

Conclusion: In this investigation involving secondary prevention patients, slightly over half of the participants received high-dose statins, while a negligible proportion received ezetimibe treatment.

Alarmingly, over two-thirds of the patients demonstrated LDL-C values that deviated significantly from the therapeutic range, indicating a considerable gap between their lipid profiles and the recommendations set forth by clinical guidelines.

Keywords: Statins, PCKS-9i, Ezetimibe, Low-density lipoprotein cholesterol (LDL-C), Secondary prevention

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Kardiyovasküler Hastalık Yüksek Riskine Sahip Bireylerde Lipit Düşürücü İlaçların Etkinliği

Öz

Amaç: Lipid düşürücü tedavinin optimal yönetimi, ikincil koruma altındaki hastalarda kardiyovasküler (KV) riskin azaltılmasında kritik bir rol oynamaktadır. Yüksek doz statinler, ezetimib ve nispeten yeni PCSK9 inhibitörleri (PCSK9i), bu hastalarda LDL kolesterol (LDL-K) tedavi hedeflerine ulaşmada etkinlik göstermiştir. Ancak, etkinliklerini destekleyen önemli kanıtlara rağmen, bu müdahaleler özellikle düşük hasta uyum düzeyleri nedeniyle önemli ölçüde yeterince kullanılmamaktadır. Dahası, kolesterol düşürücü tedavinin genel etkinliği ve ikincil koruma hastalarının düzenli bir lipid profili elde etme oranı hakkında sınırlı veri bulunmaktadır. Bu nedenle bu çalışmanın temel amacı, bu hasta grubundaki lipid düşürücü tedavi durumunu değerlendirmekti.

Yöntemler: Çalışma, kardiyovasküler hastalık ikincil koruma geçmişi olan hastalara odaklanarak, Nisan 2021 ile Mart 2023 tarihleri arasında Mardin Artuklu Üniversitesi, Mardin Eğitim ve Araştırma Hastanesi'nde yapıldı. Çalışmada, reçetelenen kolesterol düşürücü ilaçlar, statin kullanımının yetersizliğine katkıda bulunan faktörler ve lipid profilinin açıklanması incelendi.

Bulgular: 872 hasta çalışmaya dahil edildi. Hastaların %86,8'i statin (statin ile birlikte %5,2'si ezetimib ve %3,4'ü fibrat) kullanırken, %13,2'si herhangi bir lipid düşürücü tedavi almadı. Statin kullananların %64'ü yüksek dozda ilaç alıyordu. LDL-K değerleri 452 hastada değerlendirildi ve sadece %30'u önerilen 70 mg/dL altında bulunmaktaydı.

Sonuç: İkincil korunma hastalarının yer aldığı bu araştırmada, katılımcıların yarısından biraz fazlası yüksek doz statin alırken, ihmal edilebilir bir oran ezetimib tedavisi almıştır. Endişe verici bir şekilde, hastaların üçte ikisinden fazlası, LDL-K değerleri terapötik aralıktan önemli ölçüde sapma gösterdi ve bu durum, lipid profilleri ile klinik kılavuzlar tarafından önerilen değerler arasında önemli bir boşluk olduğunu göstermektedir.

Anahtar kelimeler: Statinler, PCKS-9i, Ezetimib, Düşük Dansiteli Lipoprotein Kolesterol(LDL), İkincil Koruma.

INTRODUCTION

Individuals undergoing secondary prevention for CV events have a greater than 10% risk of experiencing a new event in ten years[1]. Among the markers of increased risk, we know that high low density lipoprotein cholesterol (LDL-C) levels directly increase it and represent one of the main therapeutic targets[2].

HMG-CoA reductase inhibitors, often referred to as statins, are one of the most potent lipid-lowering medications for the secondary prevention of CV disease[3]. In addition, therapy with statins of high potency is even more successful in reducing the occurrence of events[4]. PCSK9 inhibitors (PCSK9i) have recently led to a seismic shift in lipid-reducing medication by lowering LDL-C levels in statin-treated patients to an average of 30 mg/dL[5]. American College of Cardiology and American Heart Association (ACC/AHA) and European Society of Cardiology and the European Atherosclerosis Association (ESC/EAS) clinical practice recommendations urge using of high-intensity statins in patients undergoing secondary prevention, establish therapeutic goals, and stress that the higher the LDL-C decrease, the higher the reduction in CV risk[6].

The primary aim of this research was to assess the status of lipid-lowering therapy, adherence to therapeutic goals, and potential indication for treatment with PCSK9i in patients at high CV risk.

METHODS

Study design

This cross-sectional research was conducted between April 2021 and March 2023 at Gazi Yaşargil Training and ResearchHospital.

The study enrolled patients aged 18 years and above with various cardiovascular conditions, including acute coronary syndrome, stable chronic angina with functional test (SPECT, ergometry, stress echo), previous percutaneous coronary angioplasty, myocardial revascularization surgery, significant non-

revascularized plaques observed in coronary angiography or non-invasive study (CT or MRI), ischemic stroke/TIA, symptomatic peripheral vascular disease of the lower limbs due to intermittent claudication or revascularization, and carotid stenosis greater than 70% or previous carotid artery revascularization (percutaneous or surgical).

Participants for whom data were unavailable or whose laboratory test analysis was inconclusive were excluded from the study.

The Ethics Commission of Gazi Yaşargil Training and Research Hospital authorized the study and waived the necessity for informed consent (No: 2023-301 Date: January 13th, 2022) The present manuscript was conducted in line with the provisions of the Declaration of Helsinki (2013).

The research was conducted in compliance with the ethical criteria for human testing outlined in the Helsinki Declaration (Date: 13/01/2023) (2013).

Study protocol

Source of the patients and data collection: the inclusion of patients was recruited by personal meeting or completion of a self-administered questionnaire, either while hospitalized or in an outpatient clinic. Data loading was done online through a custom-designed electronic form with password-protected access. Automatically and immediately, the data was merged into the central server. LDL-C objectives: compliance with LDL-C treatment plans were based on patients who underwent a laboratory test in the last 6 months with measurement of LDL-C, HDL-C, and triglycerides.

Primary goals

The aim of this study is to assess the utilization of statins, including dosing patterns, among patients at high cardiovascular risk under a secondary prevention strategy. Additionally, the study seeks to identify candidates who would potentially benefit from PCSK9 inhibitors (PCSK9i). Furthermore, the research aims to investigate the reasons behind the lack of lipid-lowering drug treatment or inadequate treatment in this patient population. Lastly, the study will evaluate the proportion of patients who achieve the LDL-C therapeutic goals outlined in the 2019 ACC/AHA lipid guidelines and the 2019 ESC/EAS dyslipidemia guidelines.

Endpoints

We investigated the frequency of lipid-lowering medication treatments and their dosages. LDL-C threshold was determined according to the ESC/EAS (55 mg/dL, 2nd vascular incident in 2 years 40 mg/dL) and ACC/AHA (70 mg/dL)[7].

Insufficient therapy was defined as the patient not receiving high-dose statins for secondary prevention (atorvastatin 40 mg or 80 mg, or rosuvastatin 20 mg or 40 mg).

LDL-C greater than 100 mg/dL notwithstanding therapy with high-intensity statins at maximal dosages, or unable to get appropriate doses of statins owing to tolerability, in line with the 2019 ESC/EAS guideline, is the indication for PCSK9i[8].

Laboratory Analysis

A total of 6 mL of venous blood samples were collected from the patients while they were in the fasting state.

Following this, the blood samples were subjected to centrifugation at a force of 2500-3000 times the acceleration due to gravity (xg) for a duration of 10 minutes. The resulting serum samples were then divided into smaller portions and preserved at a temperature of -70 °C until they were ready for analysis. The measurement of triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) was conducted using an enzymatic Hitachi Auto Analyzer (Tokyo, Japan)

Statistics

The statistical study was performed with IBM SPSS software, specifically version 24.0. Initial continuous variables were represented using descriptive statistics, including measures such as mean, standard deviation, and median with interquartile range. The assessment of the normality of variable distributions was conducted using the Kolmogorov-Smirnov and Shapiro-Wilk tests, in conjunction with graphical tools.

The categorical data were analyzed by presenting frequencies and percentages, and the chi-square test was employed to examine the associations.

During the initial phase of the study's design, a sample size of 872 patients was chosen in order to achieve 95% confidence intervals (95% CI) that are acceptably small. A significance level of 0.05 was established for all statistical tests.

RESULTS

The study involved a sample size of 872 individuals, comprising 371 females (42.6%) and 501 males (57.4%). The participants had an average age of 68.2 ± 9.6 years. Within the cohort under investigation, arterial hypertension was shown to be the most prevalent comorbidity, affecting 65.6% of the study population. This was followed by dyslipidemia, which was present in 55.6% of individuals, and diabetes, which affected 38.6% of the cohort (Table 1). A notable percentage of the individuals involved in the study received revascularization interventions (49.1%), such as percutaneous coronary intervention (PTCA) or coronary artery bypass grafting (CABG). The prevalence of patients diagnosed with unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) exhibited comparable proportions, with rates of 21.7%, 21.5%, and 21.7% respectively.

Table I: Clinical characteristics of patients

PARAMETERS	n, %
Age	68.2 ± 9.6
Sex, female	371 (42.6)
Hypertension	572 (65.6)
Diabetesmellitus	337 (38.6)
Dyslipidemia	485 (55.6)
BMI >25kg/m^2	457 (52.4)
Smoking	527 (60.4)
Sedentary life	561 (64.3)
STEMI	189 (21.7)
Non-STEMI	187 (21.5)
Unstableanginapectoris	189 (21.7)
Stableanginapectoris	71 (8.1)
Revascularization	428 (49.1)
Ischemicstroke/TIA	94 (10.8)
Peripheralvasculardisease	141 (16.2)
Carotiddisease	42 (4.8)

BMI: Body-mass ındex. STEMI: ST-segment elevation myocardial infarction. TIA: Trans-ischemic attack

Among the patients, 86.8% were on lipid-lowering therapy, with 3.4% receiving fibrates and 5.2% receiving ezetimibe, while 13.2% were not receiving any treatment. Among those under statin treatment, 64% (n=484) received high-dose statins (55.5% of all statin-treated patients), with atorvastatin doses of 40-80 mg/d being the most common (Table 2). In the last six months, LDL-C samples were available for analysis from 452 individuals, with an average LDL-C value of 95.4 (91.7-99.1) mg/dL, HDL-C at 42.6 (41.7-43.5) mg/dL, and triglycerides at 153.4 (144.9-161.8) mg/dL (Figure 1). Among the patients, 30% had LDL-C values below the cutoff of 70 mg/dL, while 14% had values below 55 mg/dL. Additionally, 37% of the patients had LDL-C levels exceeding 100 mg/dL.The most commonly prescribed statin among these individuals was atorvastatin.

Table II: Statin doses used by patients

	5 mg	10 mg	20 mg	40 mg	80 mg
Simvastatin (n=20)	4.2%	47.5%	39.5%	8.8%	_
Rosuvastatin (n=324)	6.8%	23.8%	37.8%	31.6%	_
Atorvastatin (n=413)	2.4%	9.7%	24.9%	53%	10%

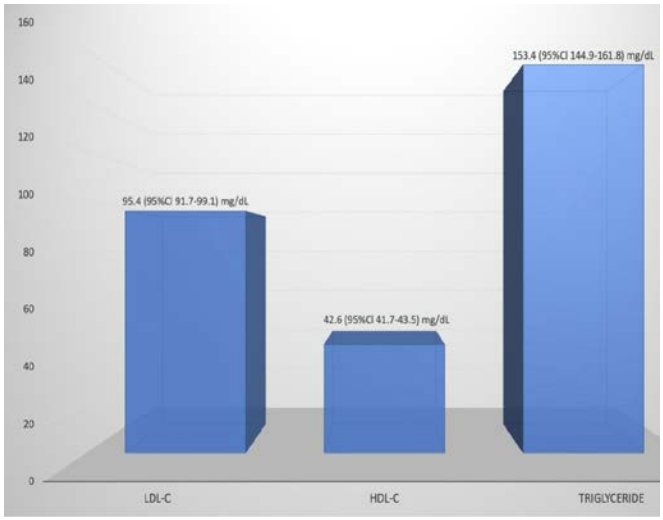

Figure 1. Average lipid values of the participants (n = 452)

Lipid profile information, including LDL-C targets, was available for 51.8% of the participants (n=452). In terms of general compliance with LDL-C goals, 30% of the participants met the ACC/AHA guidelines, while 14% met the ESC/EAS guidelines (Figure 2). The proportion of patients receiving high-dose statins versus not receiving high-dose statins was 41.4% vs. 23.5% ($p < 0.001$) based on the ACC/AHA guidelines, and for ESC/EAS targets, it was 22.3% vs. 13.1% ($p = 0.04$). No statistically significant differences were found in compliance with the clinical guidelines of the ACC/AHA or ESC/EAS based on the diagnosis, whether it was the type of acute coronary syndrome (ACS) or other vascular disease diagnoses ($p > 0.05$).

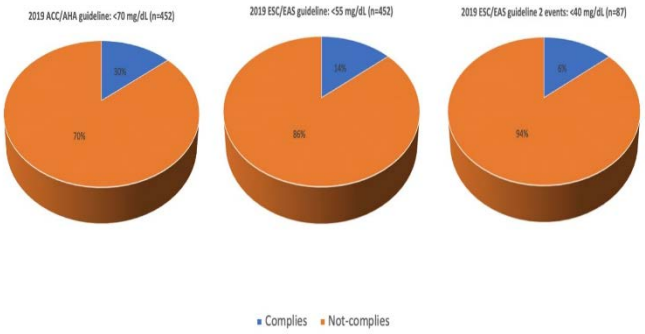

Figure 2. Compliance with therapeutic goals according to guidelines

Among the 87 patients with two or more cardiovascular events in the previous two years, only 6% fulfilled the ESC/EAS objective of the LDL-C levels were observed to be below 40 mg/dL. Regarding the potential indication for PCSK9 inhibitors (PCSK9i), 37% of the patients had LDL-C levels greater than 100 mg/dL. Within the group with a potential indication for PCSK9i, 38% were on high-dose statins, and 3% were also receiving ezetimibe in combination with statin therapy. Based on the ACC/AHA criteria for PCSK9i use, only 3% of the examined individuals would qualify for receiving PCSK9i.

Among the remaining 62%, 14% were undermedicated due to reported adverse effects, primarily myopathies, and in the remaining 48%, the absence of physician indication, medication refusal, concerns about the side effects of statins, and failure to obtain prescription renewals were the reasons for inadequate treatment compliance.

DISCUSSION

In this study, just over half of the 872 patients undergoing secondary prevention of cardiovascular (CV) events were prescribed high-dose statins, while a negligible proportion received ezetimibe treatment. Among the subset of individuals for whom data was available, the average LDL-C level exceeded any treatment target specified by clinical guidelines. Consequently, only 30% of the patients met the ACC/AHA recommendations of LDL-C < 70

mg/dL, and merely 14% achieved the ESC/EAS treatment target of LDL-C < 55 mg/dL. Furthermore, 37% of the individuals had LDL-C levels greater than 100 mg/dL, even though a few were receiving the maximum dosage of statins and ezetimibe. As a result, this subset of patients would be potential candidates for PCSK9i treatment to effectively lower LDL-C levels.

Cardiovascular (CV) disease has been a leading cause of mortality worldwide[9]. Although there was a 31% decline in CV deaths from 2001 to 2011, despite this, they still represented one-third of all mortality in the USA[10]. Extensive research has consistently shown a direct association between high cholesterol levels and cardiovascular mortality, particularly in the development of coronary disease, with evidence indicating that reducing LDL-C levels can lower the risk[11].

Notable studies have provided further evidence of the benefits of lipid-lowering interventions. The 4S research, with a 5-year follow-up, demonstrated a 30% reduction in mortality for individuals with acute myocardial infarction (AMI) or coronary disease who were administered simvastatin compared to a placebo[12]. Likewise, the CARE trial observed a noteworthy 24% decrease in the primary endpoint of cardiac mortality or recurrent AMI (acute myocardial infarction) among AMI patients treated with 40 mg of pravastatin over a two-year period[13].

Additionally, the IMPROVE-IT study demonstrated that adding ezetimibe to simvastatin 40 mg in post-AMI individuals resulted in a further decrease in LDL-C levels and subsequently reduced the likelihood of cardiovascular events[14]. Meta-analyses conducted by the CTT group revealed that for each 38.6 mg/dL decline in LDL-C levels, there was a 22% reduction in the risk of major CV events, 23% reduction in coronary events, 20% reduction in coronary-related deaths, and 10% reduction in total mortality[15].

Additional studies, such as PROVE-IT, the study showed that using atorvastatin 80 mg resulted in a 16% reduction in the risk of major cardiovascular events compared to atorvastatin 40 mg while the TNT study showed a 22% risk reduction when atorvastatin 80 mg was compared to atorvastatin 10 mg[16]. A meta-analysis of the RACING trial further supported the use of high-intensity statins, showing a 15% reduction in major cardiovascular events compared to lower-intensity statin use[17].

The advancement of PCSK9 inhibitors (PCSK9i) has further emphasized the idea that larger reductions in LDL-C result in greater risk reductions[18]. In patients receiving maximally tolerated doses of statins, studies have demonstrated that PCSK9 inhibitors (PCSK9i) lead to a reduction in LDL-C levels by 45 to 75 percent more than placebo and 35 percent more than ezetimibe[19]. Additionally, there is compelling evidence supporting the role of PCSK9i in reducing the incidence of cardiovascular (CV) events[20].

The FOURIER study, which included over 27,000 individuals with cardiovascular disease, LDL-C levels exceeding 70 mg/dL, and statin therapy, randomized participants to receive evolocumab (a PCSK9 inhibitor) or a placebo. The mean LDL-C level decreased from 92 mg/dL to 30 mg/dL, leading to a 15% reduction in the risk of cardiovascular events, including cardiovascular mortality, stroke, unstable angina, acute myocardial infarction (AMI), and revascularizations[21]. Similar risk reductions were observed in the ODYSSEY outcomes research, which investigated the use of alirocumab (another PCSK9 inhibitor) in patients with AMI or recent unstable angina, considering a combination of CV mortality, non-fatal myocardial infarction, stroke, and unstable angina[22].

In 2019, the American College of Cardiology (ACC) and American Heart Association (AHA) established an LDL-C target value of 70 mg/dL for patients in secondary prevention, while the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) advocated for a lower target of 55 mg/dL, and even lower, 40 mg/dL, for individuals with a history of two or more CV events in the preceding two years[23,24].

Despite the potential benefits of PCSK9i, the high cost of these medications prompted efforts to Identify a subgroup of high-risk individuals who would derive the greatest benefits, thus improving the cost-benefit balance[25]. As a result, patients in secondary prevention with an LDL-C value of more than 100 mg/dL, those on the highest tolerated doses of statins along with ezetimibe, or those with documented intolerance to statins are recommended for PCSK9i therapy[26]. Unfortunately, despite extensive research and stringent recommendations, the global utilization of lipid-lowering medications often falls short of meeting these criteria.

In a 2008 study involving 15,000 patients in the USA, the non-adherence rate to statin therapy was found to be 26%, and non-adherent individuals were found to have an increased risk of both total and cardiovascular (CV) mortality[27]. Following multivariate analysis, factors such as myalgia, lack of health insurance, and interestingly, patients' online searches and poor communication with prescribing physicians were identified as the most significant contributing factors to non-adherence[28].

The well-known "nocebo" effect, which involves the adverse effects of medications being heightened due to negative expectations, significantly influences statin adherence. The popularization of data suggesting that statins cause myalgias resulted in a sharp increase in the reporting of this adverse effect, reaching levels as high as 15% in some series. However, in randomized, double-blind trials like HOPE-3, the occurrence of myalgias barely exceeded 5%, and it was only 1% higher than in the placebo group[29].

Regarding PCSK9 inhibitors (PCSK9i), the EBBINGHAUS study, which utilized the CANTAB survey, did not find an increased incidence of neurocognitive events in individuals treated with PCSK9i. Similarly, a meta-analysis conducted by Cochrane revealed that there was no statistically significant disparity in the prevalence of neurocognitive events among individuals who had statin treatment[30].

In our opinion, although there have been large-scale studies previously conducted in countries such as the USA, considering the sociodemographic, cultural and economic differences of our country, larger-scale and multicenter studies should be conducted on the use of cholesterol-lowering drugs in our country.

Considering the positive effects of cholesterol-lowering treatment, it is important to raise awareness of patients and their relatives on this issue.

Limitations

In terms of the study's limitations, it's worth noting that only participants from the cardiology department were included, which might have introduced a potential bias in the data analysis. Although outpatients were also included, the fact that the majority of patients were in the coronary care unit could potentially compromise the external validity of the data.

CONCLUSION

Our results suggest that just over half of the patients undergoing secondary prevention were on intensive statin medication. However, adherence to therapy objectives was observed to be very poor, which directly impacts patients' cardiovascular (CV) risks. In this context,

appropriate lipid-lowering treatment with high-intensity statins has demonstrated effectiveness. However, beliefs concerning side effects and other barriers hinder the correct utilization of these drugs and adherence to planned therapeutic goals.

Therefore, we emphasize the importance of sustained administration of intensive statins and the promotion of strict LDL-C cholesterol management to improve patient outcomes in secondary prevention.

Ethics Committee Approval: The Ethics Commission of Gazi Yaşargil Training and Research Hospital authorized the study and waived the necessity for informed consent (No: 2023-301 Date: January 13th, 2022) The present manuscript was conducted in line with the provisions of the Declaration of Helsinki (2013).

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REFERENCES

1. Presta V, Figliuzzi I, Miceli F, et al. Achievement of low density lipoprotein (LDL) cholesterol targets in primary and secondary prevention: Analysis of a large real practice database in Italy. Atherosclerosis. 2019;285:40-8. doi:10.1016/j.atherosclerosis.2019.03.017

2. Behbodikhah J, Ahmed S, Elyasi A, et al. Apolipoprotein B and Cardiovascular Disease: Biomarker and Potential Therapeutic Target. Metabolites. 2021;11(10):690. doi:10.3390/metabo11100690

3. Scott C, Lateef SS, Hong CG, et al. Inflammation, coronary plaque progression, and statin use: A secondary analysis of the Risk Stratification with Image Guidance of HMG CoA Reductase Inhibitor Therapy (RIGHT) study. Clin Cardiol. 2022;45(6):622-8. doi:10.1002/clc.23808

4. Westman EC. A review of decision aids to assess cardiovascular risk. Curr Opin Endocrinol Diabetes Obes. 2022;29(5):420-6. doi:10.1097/MED.0000000000000760

5. Sarsam S, Berry A, Degheim G, et al. Real-world use of PCSK9 inhibitors: A single-center experience. J Int Med Res. 2019;47(1):265-70. doi:10.1177/0300060518800595

6. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk [published correction appears in Eur Heart J. 2020 Nov 21;41(44):4255]. Eur Heart J. 2020;41(1):111-88. doi:10.1093/eurheartj/ehz455

7. Vallejo-Vaz AJ, Bray S, Villa G, et al. Implications of ACC/AHA Versus ESC/EAS LDL-C Recommendations for Residual Risk Reduction in ASCVD: A Simulation Study From DA VINCI [published online ahead of print, 2022 May 14]. Cardiovasc Drugs Ther. 2022;10.1007/s10557-022-07343-x. doi:10.1007/s10557-022-07343-x

8. Klug EQ, Raal FJ. New cholesterol targets for patients at high or very high cardiovascular risk and the indications for PCSK9 inhibitors. S Afr Med J. 2020;110(11):13126. doi:10.7196/SAMJ.2020.v110i11.15191

9. Mc Namara K, Alzubaidi H, Jackson JK. Cardiovascular disease as a leading cause of death: how are pharmacists getting involved? Integr Pharm Res Pract. 2019;8:1-11. doi:10.2147/IPRP.S133088

10. Murphy MJ, Grundy EMD. Slowdown in Mortality Improvement in the Past Decade: A US/UK Comparison. J Gerontol B Psychol Sci Soc Sci. 2022;77(Suppl_2):S138-S147. doi:10.1093/geronb/gbab220

11. Zhang Y, Pletcher MJ, Vittinghoff E, et al. Association Between Cumulative Low-Density Lipoprotein Cholesterol Exposure During Young Adulthood and Middle Age and Risk of Cardiovascular Events. JAMA Cardiol. 2021;6(12):1406-13. doi:10.1001/jamacardio.2021.3508

12. Pedersen TR. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344:1383-9. https://doi.org/10.1016/S0140-6736(94)90566-5

13. Sacks FM, Pfeffer MD, Moye LA, et al. The Effect of Pravastatin on Coronary Events after Myocardial Infarction in Patients with Average Cholesterol Levels. N Engl J Med. 1996;335:1001-9. https://doi.org/10.1056/ NEJM199610033351401

14. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387-97.https://doi.org/10.1056/ NEJMoa1410489

15. Cholesterol Treatment Trialists' (CTT) Collaboration. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of C-LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomized trials. Lancet. 2010; 376: 1670-81.https://doi.org/10.1016/S0140-6736(10)61350-5

16. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004; 350: 1495-504. https://doi.org/10.1056/NEJMoa040583

17. Lee YJ, Cho JY, You SC, et al. Moderate-intensity statin with ezetimibe vs. high-intensity statin in patients with diabetes and atherosclerotic cardiovascular disease in the RACING trial. Eur Heart J. 2023;44(11):972-83. doi:10.1093/eurheartj/ehac709

18. Warden BA, Fazio S, Shapiro MD. The PCSK9 revolution: Current status, controversies, and future directions. Trends Cardiovasc Med. 2020;30(3):179-85. doi:10.1016/j.tcm.2019.05.007

19. Gunta SP, O'Keefe JH, O'Keefe EL, et al. PCSK9 inhibitor, ezetimibe, and bempedoic acid: Evidence-based therapies for statin-intolerant patients [published online ahead of print, 2023 Mar 3]. Prog Cardiovasc Dis. 2023;S0033-0620(23)00013-0. doi:10.1016/j.pcad.2023.02.007

20. Giugliano RP, Keech A, Murphy SA, et al. Clinical Efficacy and Safety of Evolocumab in High-Risk Patients Receiving a Statin: Secondary Analysis of Patients With Low LDL Cholesterol Levels and in Those Already Receiving a Maximal-Potency Statin in a Randomized Clinical Trial. JAMA Cardiol. 2017;2(12):1385-91. doi:10.1001/jamacardio.2017.3944

21. Gencer B, Mach F, Guo J, et al. Cognition After Lowering LDL-Cholesterol With Evolocumab. J Am Coll Cardiol. 2020;75(18):2283-93. doi:10.1016/j.jacc.2020.03.039

22. Damask A, Steg PG, Schwartz GG, et al. Patients With High Genome-Wide Polygenic Risk Scores for Coronary Artery Disease May Receive Greater Clinical Benefit From Alirocumab Treatment in the ODYSSEY OUTCOMES Trial. Circulation. 2020;141(8):624-36. doi:10.1161/CIRCULATIONAHA.119.044434

23. Virani SS, Smith SC Jr, Stone NJ, et al. Secondary Prevention for Atherosclerotic Cardiovascular Disease: Comparing Recent US and European Guidelines on Dyslipidemia. Circulation. 2020;141(14):1121-3. doi:10.1161/CIRCULATIONAHA.119.044282

24. Sabouret P, Lemesle G, Bellemain-Appaix A, et al. Post-discharge and long-term follow-up after an acute coronary syndrome: International Collaborative Group of CNCF position paper. Arch Med Sci. 2022;18(4):839-54. doi:10.5114/aoms/150321

25. Pedretti RFE, Hansen D, Ambrosetti M, et al. How to optimize the adherence to a guideline-directed medical therapy in the secondary prevention of cardiovascular diseases: a clinical consensus statement from the European Association of Preventive Cardiology. Eur J Prev Cardiol. 2023;30(2):149-66. doi:10.1093/eurjpc/zwac204

26. Cosin-Sales J, Sidelnikov E, Villamayor S, et al. Identification of Secondary Prevention Patients Eligible for PCSK9 Inhibitors Therapy According to the Routine Clinical Practice in Spain [published online ahead of print, 2022 Dec 16]. Adv Ther.2022;10.1007/s12325-022-02384-y. doi:10.1007/s12325-022-02384-y

27. Ho PM, Magid DJ, Shetterly SM, et al. Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. Am Heart J. 2008; 155: 772-9. https://doi.org/10.1016/j.ahj.2007.12.011

28. Lin JL, Chen PS, Lin HW, et al. Real-World Analyses of the Safety Outcome among a General Population Treated with Statins: An Asian Population-Based Study. J Atheroscler Thromb.2022;29(8):1213-25. doi:10.5551/jat.63076

29. Tobert JA, Newman CB. The nocebo effect in the context of statin intolerance. J Clin Lipidol. 2016;10:739-47. https://doi.org/10.1016/j.jacl.2016.05.002

30. Giugliano RP, Mach F, Zavitz K, et al. Cognitive function in a randomized trial of evolocumab. N Engl J Med. 2017;377:633-43. https://doi.org/10.1056/NEJMoa1701131