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* Conflict of interest declarations of the authors who contributed to this special issue are available on TKD website (www.tkd.ogr.tr).

ABBREVIATIONS

ACS: Acute coronary syndrome	HDL-C: High-density lipoprotein cholesterol
ALT: Alanine aminotransferase	HeAH: Heterozygous familial hypercholesterolemia
Apo: Apolipoprotein	HF: Heart failure
BMI: Body mass index	HIV: Human immunodeficiency virus
BP: Blood pressure	HMG-CoA: Hydroxy-methyl-glutaryl-coenzyme A
CABG: Coronary artery bypass grafting	HoAH: Homozygous familial hypercholesterolemia
CAD: Coronary artery disease	ICD: Implantable cardioverter defibrillator
CETP: Cholesteryl ester transfer protein	L: Liver
CHD: Coronary heart disease	LDL-C: Low-density lipoprotein cholesterol
CK: Creatine kinase	LDLR: Low-density lipoprotein receptor
CKD: Chronic kidney disease	LLT: Lipid lowering treatment
CRP: C-reactive protein	Lp: Lipoprotein
CT: Computed tomography	LSM: Lifestyle modification
CV: Cardiovascular	MetS: Metabolic syndrome
CVD: Cardiovascular disease	MI: Myocardial infarction
CYP: Cytochrome P450	NO: Nitric oxide
DM: Diabetes mellitus	PAD: Peripheral arterial disease
DNA: Deoxyribonucleic acid	PCI: Percutaneous coronary intervention
EAS: European Atherosclerosis Society	PCSK9: Proprotein convertase subtilisin/kexin type 9
EMA: European Medicines Agency	RCT: Randomized controlled trial
ESC: European Society of Cardiology	SCORE: Systematic Coronary Risk Evaluation
FA: Fatty acid	TC: Total cholesterol
FDA: USA Food & Drug Administration	TG: Triglyceride
FH: Familial hypercholesterolemia	TIA: Transient ischemic attack
GFR: Glomerular filtration rate	TRL: Triglyceride-rich lipoprotein
HbA1c: Glycated hemoglobin	ULN: Upper limit of normal
HD: Hemodialysis	VLDL: Very low-density lipoprotein

Question 1 – What is the cholesterol hypothesis? Does it cause cardiovascular disease? What are the currently available evidence on this subject?

Dr. Mahmut Şahin

Ondokuz Mayıs University Faculty of Medicine, Cardiology Department, Samsun

Atherosclerosis is the most common cause of cardiovascular (CV) diseases and a progressive condition which starts in childhood with clinical signs that occur during middle-old age. The characteristic lesion of atherosclerosis is a fibrous capsule of smooth muscle cells and fibrous tissue covered by an endothelial layer and a fibrous plaque with a nucleus that contains a yellowish lipid. More than 45% of the lesion is composed of lipids, particularly cholesterol.

The cholesterol hypothesis claims that lowering the levels of cholesterol reduces clinical outcomes since lipids have an important role in the development of atherosclerosis and high levels of cholesterol cause atherosclerosis. With the abundant evidence available, cholesterol-atherosclerosis hypothesis is now a proven scientific fact rather than a hypothesis.

There is a large number of experimental and clinical studies demonstrating the role of lipids in the physio-pathology of atherosclerosis (Table 1). This hypothesis is confirmed by the fact that atherosclerotic plaques generated by a high-cholesterol diet show regression after normalization of the diet in animal studies and by the significant clinical benefits achieved with decreased LDL-cholesterol in secondary prevention and plaque regression studies carried out in humans given high doses of statins.

Table 1. Evidence supporting cholesterol-diet-heart hypothesis

I.	Atherosclerotic lesion studies
II.	Animal experiments
III.	Epidemiologic studies
IV.	Experimental studies in humans
V.	Genetic disorders of lipoprotein metabolism

In secondary prevention studies, the first striking result was obtained from the 4S study. In this study, a 34% reduction was achieved in major coronary events by reducing LDL-cholesterol by 35% in the group treated with simvastatin.^[1]

In REVERSAL,^[2] ASTEROID^[3] and SATURN^[4] plaque regression studies, plaque regression was achieved and major CV events were significantly reduced by lowering LDL-cholesterol through aggressive lipid lowering treatment.

The most dramatic indication of the association between high cholesterol levels and CV disease is familial hypercholesterolemia. LDL-cholesterol levels are very high in homozygous familial hypercholesterolemia and are associated with atherosclerosis and fatal clinical outcomes even during 2nd decade of life.^[5]

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Question 2 – What is total cholesterol burden?

Dr. Çetin Erol

Ankara University Faculty of Medicine, Cardiology Department, Ankara

New ideas have arisen in recent years suggesting reassessment of hypercholesterolemia after a thorough investigation of Familial Hypercholesterolemia (FH) and the structure of protease PCSK9 (Proprotein convertase subtilisin/kexin type 9)^[1,2]. The current practice includes a risk scoring determined by a single cholesterol test value in addition to other risk factors and starting treatment if necessary in accordance with the guidelines (e.g. SCORE, Framingham). Age is the most important contributing.

It is known that following birth humans have low levels of total cholesterol and LDL-cholesterol (LDL-C: 30-70 mg/dL) which rise rapidly with age and environmental factors, and this is thought to be a serious risk factor for cardiovascular disease, causing deposits in the arterial wall and resulting in atherosclerotic plaques. This condition is particularly seen much earlier in patients with FH and with PCSK9 mutation.^[3] Thus, the idea has been developed that the earlier a person at risk due to total lifetime exposure to cholesterol levels is diagnosed and treated, the more benefit may be achieved. This view is defined as ‘Total Cholesterol Burden’.

In line with this perception, it has been recommended that all youngsters between 9–11 years of age in the United States should be evaluated for hypercholesterolemia. Rate of reaching cardiovascular disease limit with monitored cholesterol levels and the benefits achieved by early treatment have been demonstrated (Figures 1, 2).^[2,4]

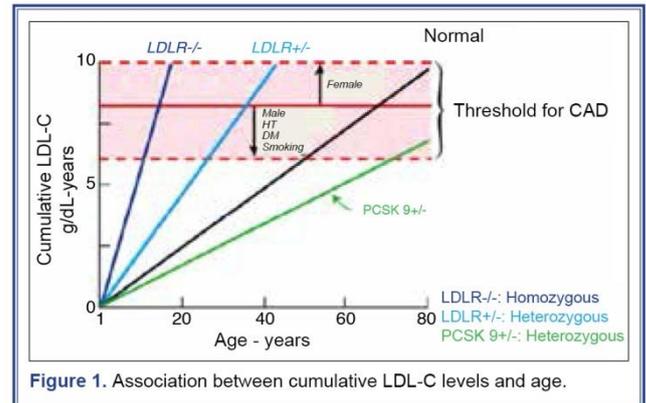


Figure 1. Association between cumulative LDL-C levels and age.

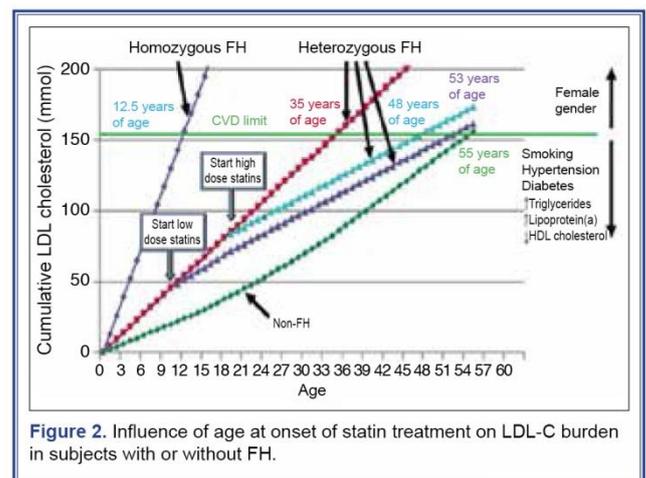


Figure 2. Influence of age at onset of statin treatment on LDL-C burden in subjects with or without FH.

The figure shows the time in years for various groups to reach a threshold determined for coronary artery disease. Therefore, the aim is to set this threshold to lower levels by initiating treatment with statins at a much earlier stage, particularly in patients with FH. The threshold level may also be brought to lower levels by the other risk factors.

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Question 3 – What are normal levels for total cholesterol and LDL cholesterol?

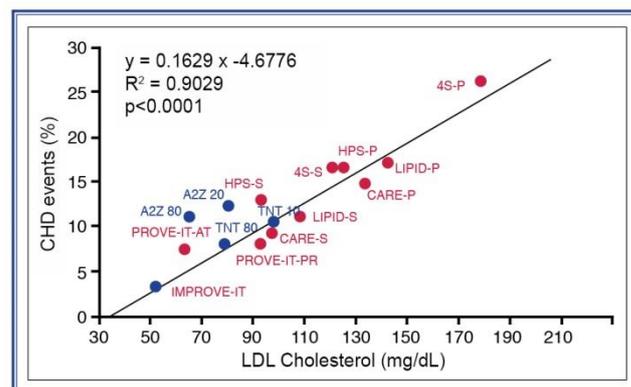
Dr. Nevrez Koylan

Anadolu Health Center, Department of Internal Medicine and Cardiology, İstanbul

The main methods used to determine the normal ranges of any biologic parameter may be identified by lower and upper limits where pathology begins or by ± 2 standard deviation from or as 95% confidence intervals of the average value in healthy individuals. Can this also be used for cholesterol and its fractions which are deemed as a risk factor rather than a clinical problem indicator?

When normal values are analyzed for cholesterol and cholesterol fractions, it can be seen that most of the mammals in the nature have a total plasma cholesterol value of 40 mg/dL or below. Similarly, total plasma cholesterol level in a newborn baby is around 40 mg/dL which increases by age, reaching usually over 200 mg/dL in adults. Genetic background and lifestyle also have important influences on these levels. In this regard, results of epidemiological and clinical studies investigating the association between the risk and levels of total cholesterol and LDL cholesterol (LDL-C) should be examined.

From an epidemiological point of view, the association between serum levels of total cholesterol and LDL-C and the frequency and mortality of coronary heart disease (CHD) appears to be linear.^[1,2] Results of various clinical studies carried out in a similar way also demonstrate a linear correlation between the reductions in total cholesterol and LDL-C levels by using statins and the decrease in CHD risk.^[3]



The question that arises is where this linear association ends, i.e. what the normal levels (not causing cardiovascular risk) of total and LDL cholesterol are. Providing the first significant evidence, the Heart Protection Study,^[4] demonstrated that the reduction in LDL-C levels are in parallel with the decrease in CHD frequency, regardless of the initial LDL-C levels. It was observed later in the PROVE IT- TIMI 22^[5] study that aggressive reduction of total cholesterol and LDL-C levels provide further risk reduction. Finally, the IMPROVE- IT^[6] study has shown that lowering LDL-C levels to 50 mg/dL results in continuation of the linear trend in risk reduction. If this linear trend is pursued in the same way, lowering LDL-C levels to 30 mg/dL may be predictive of zero risk for cardiovascular disease. In order to see the degree of applicability of this approach in a multifactorial setting such as atherosclerosis, outcomes of aggressive treatment studies using potent cholesterol lowering agents including PCSK9 inhibitors are to be awaited.

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Question 4 – What are the clinical findings of hypercholesterolemia?

Dr. Meral Kayıkçioğlu

Ege University Faculty of Medicine, Cardiology Department, İzmir

Hypercholesterolemia is usually asymptomatic and exhibits clinical symptoms only after resulting in serious atherosclerosis. These clinical findings can rarely be detected during physical examination. Extremely high levels of serum cholesterol may show symptoms by accumulating in the skin and tendons in genetic disorders of lipoprotein metabolism, particularly in familial hypercholesterolemia (FH). These deposits may be in the form of xanthelasma in the corneal arcus and eyelids or as xanthoma in the skin and/or tendons.^[1] In homozygous FH (HoFH), lipid deposits in the skin may have a very early onset in younger ages and are often the initial symptom of the disease. Therefore, these patients often initially refer to dermatologists or ophthalmologists.^[2]

Xanthelasma (Figure 1a, b) are yellowish painless and soft blisters on the skin around the periorbital area. They are seen most frequently in FH but may also be seen at normal cholesterol levels, although rarely.

Corneal arcus (Figure 1c) may be defined as a half or complete whitish ring in the cornea. The incidence of this finding is 30%. Developing corneal arcus before the age of 50 suggests FH.

Tendon xanthomas (Figure 1d, e) mostly affect extensor tendons and are most apparent in the elbows, Achilles tendon, hands and areas exposed to pressure.^[1] These need to be diagnosed not only by inspection but also by careful palpation of the lesions.^[3] Tendon xanthomas are actually pathognomonic for FH; however, they appear only in less than half of the cases.^[3] Xanthomas of the Achilles tendon develop due to tendonitis and are 6-fold more frequent compared to the normal population. In some patients with heterozygous FH, tuberous xanthomas develop as a result of precipitations rich in triglycerides.

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In addition, sitosterolemia may lead to tuberous and tendinous xanthomas.^[3] Xanthoma may not be seen in 20–30% of genetically confirmed HoFH cases.

There may also be yellowish-orange painless soft cholesterol deposits in the skin in individuals with HoFH (Figure 1e) with varying extensiveness and size which disappear within 1–2 years after achieving completely normal cholesterol levels with treatment.^[2]

Question 5 – How long should the fasting be prior to measuring lipid levels? Is non-fasting measurement appropriate? Which cut-off values should be accepted as normal?

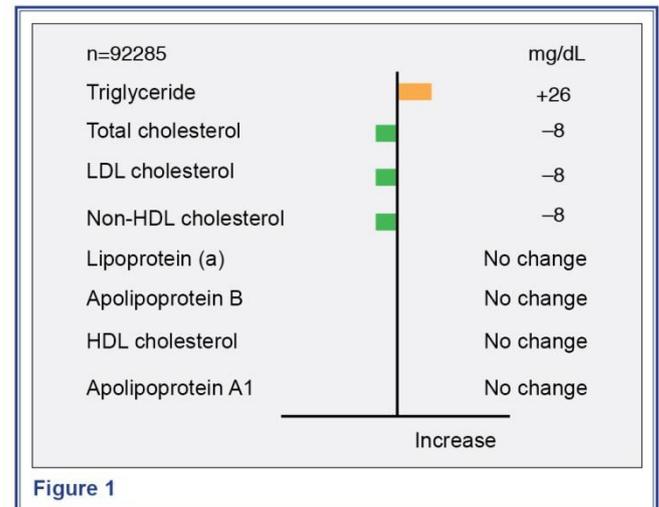
Dr. Mustafa Şan

Çukurova University Faculty of Medicine, Cardiology Department, Adana

When assessing the lipid panel, HDL (high-density lipoprotein) cholesterol and triglycerides can be measured directly while LDL (low-density lipoprotein) may be measured directly, or by using the Friedwald formula in those with triglyceride levels <400 mg/dL. LDL is required to be measured directly in people with triglyceride levels >400 mg/dL.^[1]

Today, most people have three square meals a day plus snacks. Thus, these people happen to be full (post-prandial) during daytime. In clinical practice, however, lipid panel is measured following 8–12 hours of fasting. Therefore, fasting plasma lipids may not properly reflect the risk of cardiovascular disease.^[2]

Mean triglyceride levels are increased by 26 mg/dL and total cholesterol and LDL cholesterol levels by 8 mg/dL, while no change is observed in HDL levels in a lipid panel within 1–6 hours of non-fasting compared to fasting conditions (Figure 1). These differences are clinically insignificant.^[2] According to the latest EAS (European Atherosclerosis Society) consensus report, fasting is not routinely required for the lipid panel assessment. However, lipid panel should be evaluated under fasting conditions in individuals with a post-prandial plasma triglyceride level >440 mg/dL.^[3]



The 2016 European Society of Cardiology Dyslipidemia Guidelines state that measurement may be performed both under fasting and non-fasting conditions since there is no extreme difference between pre- and post-prandial lipid levels, while it is recommended that monitoring should be conducted with fasting blood levels in hypertriglyceridemia.^[4]

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Question 6 – What is non-HDL cholesterol? Who should be tested for this parameter? Should it be a part of monitoring?

Dr. Öner Özdoğan

Izmir Tepecik Training and Research Hospital, Internal Diseases Department, Izmir

Non-HDL cholesterol (non-HDL-C) level is used to estimate the total quantity of atherogenic lipoproteins [very low-density lipoprotein (VLDL), VLDL remnants, chylomicron remnants, intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), lipoprotein(a)] and it is associated with apolipoprotein B levels.^[1] Non-HDL-C is easily calculated by extracting high-density lipoprotein (HDL) cholesterol from total cholesterol. Non-HDL-C targets are obtained by adding 30 mg/dL to LDL-C (Table 1).

The fact that non-HDL-C does not require fasting before the measurement offers an important advantage over LDL-C, which is often adopted as the primary treatment target in guidelines. Therefore, non-HDL-C is more appropriate as a screening test. Furthermore, the use of LDL-C is limited in hypertriglyceridemia regardless of whether it is measured directly or by means of the Friedewald formula [LDL-C=Total cholesterol - (HDL-C)-(TG/5)].^[2] While some guidelines³ define non-HDL-C as a better risk determinant than LDL-C, the commonly accepted notion is to use non-HDL-C as a secondary treatment target after achieving the LDL-C target.^[3,4] ESC/EAS 2016 Dyslipidemia guidelines specify non-HDL-C as a strong and standalone risk factor. This parameter is accepted as a risk predictor particularly in patients with high triglyceride (TG) levels and it is recommended to be calculated in hypertriglyceridemia with a class I, level of evidence C indication.^[4] The UK's NICE guidelines adopt non-HDL-C as the primary treatment target.^[2]

Table 1. LDL-C and non-HDL-C targets in different risk groups

Risk category	LDL-C target (mg/dL)	non-HDL-C level (mg/dL)
Very high risk	<70	<100
High risk	<100	<130
Moderate and low risk	<115	<145

C: Cholesterol.

However, these guidelines recommend a 40% reduction t 3 months compared to the baseline value rather than specifying a target level for non-HDL-C.

In certain clinical conditions, non-HDL-C may be high despite LDL-C target being within the normal range. For example, let's assume post-statin treatment levels in a high-risk primary prevention patient are as follows; total cholesterol: 185 mg/dL, LDL-C: 99 mg/dL, HDL-C: 30 mg/dL and TG: 280 mg/dL. Non-HDL-C level is approximately 155 mg/dL in this patient. Although LDL-C is <100 mg/dL, i.e. at the desired level in this patient, the non-HDL-C level indicating elevated atherogenic particles is >130 mg/dL, therefore requiring an additional treatment plan. Fibrates or omega 3 fatty acids should be planned as combination therapy for non-HDL-C in addition to lifestyle modifications and statin treatment.

In conclusion, non-HDL-C indicates atherogenic dyslipidemia and it is accepted as a risk marker, particularly in patients with elevated TG levels.

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Question 7 – At what age should LDL-cholesterol screening start? What should be the age for initial screening in groups at risk?

Dr. Barış İlerigelen

Istanbul University Cerrahpaşa Faculty of Medicine, Cardiology Department, İstanbul

Cardiovascular (CV) diseases are the major cause of morbidity and mortality despite the advances in treatment methods. Therefore, adopting preventive measures before the occurrence of clinical symptoms (primary prevention) constitutes critical importance. The current approach related to primary prevention is based on determining CV risk at population level and individual level and on the struggle against modifiable risk factors.

The most important reason of the decrease in CV mortality rates over the past thirty years is the interventions on CV risk factors, particularly the reduction in cholesterol levels, blood pressure and smoking rates.^[1] In order to obtain more favorable results, CV risks should be determined and the

struggle against risk factors should start as early as possible.

It is recommended to start LDL-cholesterol screening at 2 years of age in families with history of familial hypercholesterolemia and/or early-onset coronary artery disease.^[2] For young adults (20-35 years of age for males, 20-45 years of age for females), CV events are relatively less frequent in the absence of serious risk factors (excessive smoking, diabetes); however, the coronary atherosclerosis at an early stage may actually progress rapidly. Therefore, LDL-cholesterol levels should be monitored starting from the age of 20 years and if the results are within appropriate limits for the relevant age group, tests should be repeated every five years.^[3]

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Question 8 – What is lipoprotein(a)? Whom should we test for this parameter? Which drugs are effective on lipoprotein(a) levels?

Dr. Oben Döven

Mersin University Faculty of Medicine, Cardiology Department, Mersin

Lipoprotein a (Lp[a]) consists of a LDL particle bound to apolipoprotein a (apo[a]).^[1] Lp(a) has various isoforms depending on the different number of 'kringles' in Apo(a). Lp(a) concentrations are inversely proportional to the size of apo(a) isoform. In addition, apo(a) is thought to be responsible for the antifibrinolytic properties of Lp(a).^[1] Lp(a) may contribute to atherothrombosis by being involved in atherosclerotic lesions and by local effects through oxidized lipid pathways. Lp(a) has a similar structure to that of plasminogen and leads to predisposition for thrombosis by binding to its receptor. Studies have shown that increased Lp(a) is associated with the development of cardiovascular disease in individuals with normal levels of LDL cholesterol.^[2] In addition, genetic studies have also shown that Lp(a) plays a role in the development of aortic stenosis as well as atherosclerotic cardiovascular disease.

Lp(a) levels can be measured by various methods. However, commercial Lp(a) tests may reveal conflicting results with the use of techniques that are sensitive to the size of apo(a). Nevertheless, commercial tests measuring the level of Lp(a) independent from the size of apo(a) isoform are currently available in some reference laboratories. Lp(a) levels over 50 mg/dL are considered as high.^[3] A single measurement is sufficient in patients who are not receiving medication for Lp(a) since Lp(a) levels do not change with nutrition and lifestyle.

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Table 1. ESC 2016 Dyslipidemia Guideline recommendations on conditions that require Lipoprotein(a) measurement

- Early cardiovascular disease
- Familial hypercholesterolemia
- Presence of early cardiovascular disease and/or elevated Lp(a) in family history
- Recurrent cardiovascular disease despite optimal lipid-lowering treatment
- 10-year risk of fatal cardiovascular disease $\geq 5\%$ with SCORE risk estimation

2016 guidelines of European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) for Treatment of Dyslipidemia do not recommend plasma Lp(a) analyses in general population for risk scanning. Lp(a) test is recommended in selected high-risk patients and in those with a family history of early onset cardiovascular disease (Table 1).^[4]

There are limited number of studies on medicines that lower Lp(a) levels. Statin groups are known to be ineffective in lowering Lp(a). Nicotinic acid has a broad lipid-regulating activity. Nicotinic acid 2 g daily has been shown to lower the Lp(a) levels by 30%.^[5] Proprotein Convertase Subtilisin/Kexin type 9 (PCSK 9) inhibitors have been shown to lower Lp(a) by 25-30%.^[6]

Question 9 – Should we use other lipid fractions except total cholesterol, LDL, HDL and triglycerides for cardiovascular risk assessment?

Dr. Armağan Altun

Başkent University Faculty of Medicine, Cardiology Department, İstanbul Hospital, İstanbul

The routine use of other lipid parameters in addition to a standard lipid panel (total cholesterol, LDL, HDL and triglycerides) is not required for cardiovascular risk assessment in all patients.^[1] However, evaluating some of these are recommended under special conditions.

Apolipoprotein B (Apo-B) is the main apoprotein of atherogenic lipoproteins. It has often been assessed together with LDL-cholesterol in clinical outcome studies. Apo-B is a risk marker similar to LDL-cholesterol. Besides, less laboratory errors are likely to occur while determining Apo-B compared to LDL-cholesterol, particularly in patients with hypertriglyceridemia (>300 mg/dL). Based on available evidence, Apo-B is not a better risk marker than LDL-cholesterol and has no additional value in risk assessment. However, its measurement is recommended as an alternative risk marker in 2016 ESC Dyslipidemia guidelines in order to assess atherogenic particle burden in hypertriglyceridemia (Indication: IIa, Level of evidence: C).

Lipoprotein(a) (Lp[a]) is a low-density lipoprotein that binds to an additional protein known as apolipoprotein(a). High levels of Lp(a) are associated with risk of coronary heart disease and ischemic stroke. However, there are no randomized trials

showing that lowering Lp(a) levels may reduce the risk of cardiovascular disease. At present, there is no rationale for Lp(a) scanning in general population. However, Lp(a) assessment may be considered in patients with a family history of early onset cardiovascular disease or during the risk estimation of individuals at moderate risk. There is no evidence to suggest that considering Lp(a) levels as a target is reasonable approach.

Apolipoprotein B/Apolipoprotein A1 ratio; Apolipoprotein A1 (Apo-A1) is the basic apoprotein of HDL. There is no doubt that Apo-B/Apo-A1 ratio is one of the most powerful risk markers. However, employing this variable as a treatment goal is yet to be clarified. General use of apolipoprotein measurement is not recommended yet since its common use is not possible in Europe, due to its high cost compared to the currently used lipid variables and because it provides limited additional information. Its measurement is recommended as an alternative risk marker in 2016 ESC Dyslipidemia guidelines (Indication: IIb, Level of evidence: C). Similarly, non-HDL cholesterol/HDL-cholesterol ratio may be an alternative risk marker (Indication: IIb, Level of evidence: C). However, using HDL-cholesterol instead provides a better risk estimation in HeartScore.

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Question 10 – Should we assess lipid electrophoresis in every hypercholesterolemic patient?

Dr. Şevki Çetinkalp

Ege University Faculty of Medicine, Endocrinology Department, İzmir

Lipid electrophoresis is used to determine the distribution of lipoprotein subgroups. The patient should have no specific diet during the 2 weeks before the test. Alcohol should not be used within the last 24 hours. Blood samples should be drawn following at least 12 hours of fasting and without taking any lipid medicines. Information is obtained regarding the abnormal distribution of serum lipoproteins and relative concentrations; and no quantitation is made.

Phenotypes of Type I (Familial Lipoprotein Lipase Deficiency, Exogenous Hypertriglyceridemia), Type IIa (Familial Hypercholesterolemia, Hyperbetalipoproteinemia), Type IIb (Familial Combined Hyperlipidemia), Type III (Familial Dysbetalipoproteinemia, "Broad" Beta Disease), Type IV (Familial Hypertriglyceridemia, Endogeneous Lipemia, Hyperprebetalipoproteinemia) and Type V (Mixed Endogeneous and Exogeneous Hyperlipidemia) according to Fredrickson

classification are determined based on the ratios of lipoproteins detected with lipid electrophoresis (Table 1).

Reliability of lipid electrophoresis has diminished as it has been shown to demonstrate different phenotypes at different times in the same individual or different phenotypes in different individuals with the same familial disorder. In addition, differential diagnosis is possible using simple plasma lipid measurements according to increasing fractions (cholesterol, triglycerides or both). It is more important for prognosis to demonstrate primary (e.g. familial hypercholesterolemia) or secondary (e.g. hypothyroidism, nephrotic syndrome) hyperlipidemia for differential diagnosis. More importantly, lipid electrophoresis is not required to set up a treatment plan. Lipid electrophoresis is not recommended in the management of dyslipidemic patients in national or international lipid guidelines.

Table 1. Classification of Primary Hyperlipoproteinemias

Type	Highest plasma lipoprotein	Highest lipid fraction	Sample
I	Chylomicrons	Triglyceride	LPL deficiency
IIa	LDL	Cholesterol	Familial hypercholesterolemia
IIb	VLDL and LDL	Triglyceride Cholesterol	Familial Combined hyperlipidemia
III	Residues of IDL and VLDL	Triglyceride, Cholesterol	Type III hyperlipoproteinemia
IV	VLDL	Triglyceride	Familial hypertriglyceridemia
V	Chylomicrons, VLDL	Triglyceride, Cholesterol	Apo CII deficiency

Table 2. Laboratory test recommended in dyslipidemic patients

To determine lipoprotein levels	To investigate secondary causes
Total cholesterol	TSH
Triglyceride	Blood glucose, A1c, HOMA-IR(?)
LDL-cholesterol	Hematologic tests
HDL-cholesterol	Liver, renal functions
VLDL	ECG
Non-HDL cholesterol	Lipase
If applicable in addition to the above standard measurements; ApoA, ApoB, Lp(a)	Abdominal USG

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Question 11 – What are the criteria to initiate anti-lipid therapy?

Dr. Seçkin Pehlivanoglu

Başkent University Cardiology Department, İstanbul Hospital, İstanbul

Lipid-lowering therapy (LLT) is the most important component of key treatment strategies to prevent both the development of atherosclerosis and cardiovascular events resulting from atherosclerotic cardiovascular diseases (ASCVD).

The criteria to initiate LLT is based on current guidelines. The most important common aspect of both European and American guidelines is to firstly "determine total cardiovascular risk" in a patient with dyslipidemia and to initiate LLT according to this risk.^[1,2] Though both guidelines have several points in common, they also have seriously conflicting views on starting medication (and treatment targets) (Table 1).^[3]

Key patient groups for whom statin treatment is recommended

I) Individuals with ASCVD

There is a not serious difference of opinion in the two guidelines regarding secondary prevention patients. European guidelines consider these patients at very high risk and recommend starting LLT in patients with a baseline LDL level over 70 mg/dL, targeting LDL levels below 70 mg/dL or at least 50% LDL-C reduction for those with a baseline LDL-C level between 70 and 135 mg/dL. On the other hand, American guidelines recommend starting highly intensive treatment (e.g. atorvastatin 80-40 mg, rosuvastatin 40-20 mg) and lowering LDL by more than 50% regardless of baseline or target LDL levels.

II) Diabetic patients (without ASCVD)

Both guidelines recommend "statin treatment of moderate-high intensity" in these patients according to the level of accompanying risk. European guidelines recommend statin treatment according to the target LDL level; LDL levels below 70 mg/dL are targeted in high-risk patients (presence of other CVD risk factors or target organ damage) while the LDL target is <100 mg/dL in other patients with diabetes mellitus (DM). American guidelines recommend statin treatment of "moderate/high intensity" in high-risk patients with DM (10-year risk of ASCVD >7.5%) and of "moderate intensity" (e.g. atorvastatin 20-10 mg, rosuvastatin 10-5 mg) in other patients with DM (10-year risk of ASCVD %5-<7.5%)

III) LDL >190 mg/dL or familial hypercholesterolemia (without ASCVD or DM);

In American guidelines, high-intensity statin treatment is recommended in patients over 21 years of age with a LDL level >190 mg/dL. European guidelines target LDL <100 mg/dL in these patients

and recommend drugs other than statins if this level cannot be achieved.

IV) Other patients that cannot be classified in the aforementioned groups

In this group, the most important criterion to start treatment with statins is the estimated level of CVD risk. American guidelines recommend statin treatment of "moderate/high intensity" in patients with a 10-year ASCVD risk of >7.5% and of "moderate intensity" if the risk is between 5% and <7.5%. According to European guidelines, those with a "10-year risk of experiencing the first fatal atherosclerotic cardiovascular event (SCORE)" >10% are considered to have very high risk, while 5%-10% is deemed as high risk and 1%-5% as moderate risk. LDL target is determined as <70 mg/dL for very high risk, and as <100 mg/dL for high risk.

Do LDL levels (baseline or target) matter in terms of statin treatment?

In recent years, "the most important paradigm shift for the primary treatment goal has been to reduce the risk of CVD events instead of lowering lipid levels (target LDL level)". Lowering blood lipid levels should be considered as a concurrent effect due to the treatment given. In 2016 European guidelines, the risk degree is evaluated by combining LDL levels with the SCORE risk scale, while LDL level is not sought to initiate treatment with statins in 2013 American guidelines if the absolute risk for that patient is high enough, except for those with very high levels of LDL (>190 mg/dL). In American guidelines, LDL criteria specified for patients with or without diabetes is within a range as broad as 70-189 mg/dL which consequently excludes this parameter as a criterion to initiate treatment.

In our country, in accordance with the reimbursement regulations of the Ministry of Health, the European guidelines have been adopted to some extent which require considering initial LDL levels together with accompanying clinical risk factors to initiate statin treatment (Table 2).

In conclusion, the answer to the question "which factors should we consider when starting antilipid treatment? and is an elevated LDL level alone sufficient?" is clearly no. There is powerful evidence that the key efficacy/benefit of statins regardless of LDL levels in patients with and without ASCVD disease is due to their preventive/modulatory (pleiotropic) effects on multiple physiopathologies known to have a role in the development of atherosclerotic process and cardiovascular events.

Table 1. Target patient groups for lipid-lowering therapy according to guidelines

ACC/AHA (2013) lipid guidelines ¹		ESC/EAS (2016) lipid guidelines ²	
Clinical risk categories	Treatment	Clinical risk categories	Treatment
Individuals with clinical atherosclerotic cardiovascular disease (ASCVD)	High-intensity statin treatment. Combination of drugs may be considered if a reduction of 50% cannot be achieved.	Patients with cardiovascular disease.	LDL <70 mg/dL or at least 50% reduction after treatment in subjects with baseline LDL levels of 70-135 mg/dL
Patients with diabetes mellitus (DM) (type I or II) without ASCVD (LDL 70-189 mg/dL)	High-risk DM patients; high-intensity statin treatment.	Patients with target organ damage such as proteinuria together with DM or those with a major risk factor including smoking, hypertension, dyslipidemia.	LDL <70 mg/dL or at least 50% reduction after treatment in subjects with baseline LDL levels of 70-135 mg/dL
	Low-risk DM patients; moderate-intensity statin treatment.	DM patients other than those included in the high-risk group	LDL <100 mg/dL or at least 50% reduction after treatment in subjects with baseline LDL levels of 100-200 mg/dL
Patients >21 years of age with LDL >190	At least 50% reduction goal with high-intensity statin treatment.	Familial hypercholesterolemia	LDL 100 mg/dL or maximal LDL reduction using any possible drug combination or LDL apheresis
Patients with a 10-year ASCVD risk of 5-7.5% or above who cannot be classified into one of the aforementioned groups (LDL 70-189 mg/dL)	If ASCVD risk is >7.5%; moderate-intensity statin treatment.	Patients with a SCORE risk score >10% who cannot be classified into one of the aforementioned groups are classified as patients at very high risk,	Among patients at very high risk, treatment goal is LDL <70 mg/dL or at least 50% reduction after treatment if baseline LDL levels are 70-135 mg/dL
	If ASCVD risk is 5-7.5%; moderate-intensity statin treatment is more reasonable.	those between 5-10% are deemed as at high risk,	In high-risk patients, <100 mg/dL or at least 50% reduction after treatment if baseline LDL levels are 100-200 mg/dL
		an those between 1-5% are considered to have moderate risk.	LDL <115 mg/dL in patients at low and moderate risk.

*adapted from reference 3.

Table 2. Reimbursement regulations for lipid-lowering drugs (as per Healthcare Implementation Communiqué dated 28 July 2012)

LDL values	Additional risk factors*
Above 190 mg/dL	No risk factor is sought
Above 160 mg/dL	2 risk factors are required
Above 130 mg/dL	3 risk factors are required
Above 100 mg/dL	Treatment is initiated without considering risk factors in patients with diabetes mellitus, acute coronary syndrome, previous MI, previous stroke, coronary artery disease, abdominal aortic aneurysm or carotid artery disease.

*Additional risk factors: Hypertension, family history of early onset cardiovascular disease, patients 65 years of age and older.

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Question 12 – Which risk factors should be assessed to decide initiating treatment in a hypercholesterolemic patient?

Dr. N. Bülent Boyacı

Hacettepe University Faculty of Medicine, Cardiology Department, Ankara

Hypercholesterolemic patients have an important place in atherosclerotic cardiovascular (CV) disease process. In clinical practice and in guidelines on the prevention of CV diseases (primary and secondary prevention), it is emphasized that total CV disease risk should be estimated since the atherosclerotic process is accelerated with the presence of other risk factors accompanying hypercholesterolemia (e.g. age, gender, family history, hypertension, diabetes mellitus (DM) and smoking). For this purpose, different risk estimation systems are used in different guidelines. These systems include Framingham, SCORE, ASSIGN, Q-RISK2, PROCAM and the WHO system. These are mostly based on scoring systems like Framingham and SCORE. In our country, SCORE is used as the risk scoring system. In this system, risk charts determine the risk of CV events which may occur within 10 years in subjects who are healthy or show no clinical and/or preclinical signs of CV disease. Almost all of the aforementioned risk estimation systems include risk factors such as age, gender, family history (non-modifiable), hypertension, smoking (modifiable).^[1,2]

Risk assessment

Patients with known CV disease (previous myocardial infarction, acute coronary syndrome, coronary revascularization, transient ischemic attack, peripheral artery disease and presence of apparent plaque(s) in coronary angiography or carotid ultrasound), with target organ damage such as proteinuria together with diabetes or at least one major risk factor such as smoking, hypertension, hyperlipidemia, subjects with severe chronic renal failure (GFR <30 mL/min/1.73 m²) and those with an estimated 10-year risk of >10% as per the SCORE system are included in the group of very high or high total CV risk. Our country is among high-risk countries and it is more appropriate to employ a SCORE table adapted for our country (the relevant table is available online at TKD website).^[3]

High-risk group; patients with a total cholesterol level >310 mg/dL (e.g. familial hypercholesterolemia) or those with a single significant risk factor such as serious hypertension (blood pressure >180/110 mmHg), patients with diabetes other than those considered to be at high risk, moderate chronic renal disease (GFR: 30-59 mL/min/1.73 m²) and those with a 10-year SCORE risk between 5-10%.

Table 1. Risk markers used in risk estimation scales

ESC 2016 SCORE	ACC/AHA 2013	NICE 2014 QRISK2
Age	Age	Age
Gender	Gender	Gender
T. Cholesterol	Race	Height Body Weight
Systolic Blood Pressure	T. Cholesterol	Ethnic group
Smoking	HDL-Cholesterol	Cholesterol/HDL-cholesterol
	Systolic Blood Pressure	Systolic Blood Pressure
	Treatment for Blood Pressure	Treatment for Blood Pressure
	Diabetes mellitus	Diabetes mellitus
	Smoking	Chronic Renal Disease
	Atrial Fibrillation	
	Connective Tissue Disease	
	Smoking	
	Family history	

Moderate risk; covers those with a 10-year risk of 1-5%. In this group, presence of family history, abdominal obesity, sedentary lifestyle and HDL-cholesterol, triglycerides, high-sensitivity CRP and emerging risk factors such as lipoprotein(a), fibrinogen, homocysteine, apolipoprotein-B and social status contribute to an accurate risk assessment.

Low risk; conditions in which the 10-year risk is <1%.

In these risk estimation tables, assessment is made according to risk factors such as age, gender, blood pressure, total cholesterol, and smoking. Age is specified as 40-65 years in European guidelines. Risk is underestimated using this calculation method in younger patients. Therefore, relative risk charts are used in those with lower absolute risk.

The risk estimates CV mortality in European guidelines and CV events (fatal or non-fatal) in American and British guidelines. For this reason, a risk of >5% in SCORE is considered as high risk (as it indicates CV mortality). CV events are observed with an approximate rate of 15%, which is 3 times greater than this risk.^[1,2] In this system, <1% indicates low risk. A rate of 1-5% defines the moderate risk group.

In American guidelines, a calculation method is used to determine the total risk of ASCVD which includes age, gender, race, total cholesterol, HDL-cholesterol, systolic blood pressure or use of antihypertensive drugs, DM and smoking. Recently,

the predominating view is that long-term (15 years) or lifelong risk estimation may be more appropriate than 10-year risk estimation. The 10-year risk estimation can be calculated using these scales within the range of 40-79 years of age. Besides, 30-year long or lifelong risk estimation may also be assessed in the 20-59 year age group. A 10-year risk of >7.5% is considered as high risk. The risk should be calculated every 4-6 years in those between 20-79 years of age with a risk <7.5%. In patients with a risk <7.5%, 30-year long or lifelong risk calculation is assessed using the 10-year risk data from 40-79 year-age group.^[2]

QRISK2 calculation system employed in the British approach is a risk evaluation tool which may be used via internet for primary prevention in people up to 84 years of age. In this system, race, body mass index, family history and early atherosclerosis are also included in the calculation system in addition to the classic risk factors mentioned above. Primary prevention is indicated if the 10-year risk of CV events is >10% as determined by this system in people over forty years of age. Those over 85 years of age, with known CV disease, type 1 diabetes, chronic renal disease and familial hypercholesterolemia are directly considered as high-risk cases.^[5]

In all these risk calculation methods, a country-specific calculation method should be used to determine the total CV risk and the physician should define the risk precisely and start treatment after discussing it with the patient and having his/her consent.

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Question 13 – In which patients should we calculate total cardiovascular risk? What is the most appropriate risk scoring system for our country?

Dr. Dilek Ural

Koç University Faculty of Medicine, Cardiology Department, İstanbul

Cardiovascular (CV) risk scoring refers to calculating the likelihood of an individual to experience certain CV events (e.g. CV death, myocardial infarction, stroke etc.) in a certain period of time (e.g. 10 years, 30 years or lifelong). Several different risk calculation models have been developed for this purpose based on the data collected with long-term epidemiological studies and by means of different statistical analyses on relatively similar parameters. The total score obtained as a result of the calculation is classified according to the previously specified prediction values in the relevant model, and this is used to determine whether the individual falls into the low, medium or high risk group.

Risk scoring is not required for individuals with established CV disease or those directly high risk for different reasons.^[1] However, risk scoring is required for individuals who are seemingly healthy or determined to carry certain risk factors in order to increase their adherence to healthy lifestyle recommendations and to make a decision on initiating medical treatment for relevant risk factors. Cases where risk estimation is useful to determine the approach to the patient are presented in Table 1. As CV disease risk is closely linked with age and changes in key risk factors, calculation should be repeated at certain intervals. While risk calculation every 5 years is sufficient for individuals at low-medium risk, this period should be shorter for those closer to the high risk group.

Framingham risk scoring, 2013 ACC/AHA atherosclerotic CV disease risk index and SCORE are

the most frequently used risk calculation models. The former two are recommended for the United States and SCORE is recommended for European countries. While risk calculation models provide accurate results for the populations of the countries where they are developed as they reflect the data from epidemiological studies they are based on, the risk may be underestimated or overestimated in other countries with different CV mortality rates.^[2] Attempts to overcome this problem include preparing two different types of the SCORE model as the low-risk group and high-risk group for European countries. It is possible to calibrate the SCORE model in a country-specific manner according to the up-to-date CV mortality data of countries. This study was conducted for our country to prepare the SCORE-Turkey model (<http://file.tkd.org.tr/kilavuzlar/SCORETurkiye-160125.PDF?menu=52>). When we compare SCORE-Turkey with the models developed for low- and high-risk countries, it is highlighted that the CV mortality risk is higher in our country and the ratio of high-risk individuals has started increasing particularly in among women in their 50s (Figure 1). This observation also corresponds to epidemiological data which reveal that the risk among women in our country over the previous years has been higher compared to the women in Western countries.^[3] Although validity of SCORE-Turkey in real-life setting has yet to be verified with other studies conducted in our country, it is currently the most appropriate for the everyday practice.

Table 1. Individuals who require and do not require CV risk calculation*

Individuals who require CVRC	Individuals who may be subject to CVRC	Individuals who do not require CVRC
<ul style="list-style-type: none"> Family history of early onset CVD Family history of hyperlipidemia Presence of major CV risk factors (smoking, hypertension, hyperlipidemia) Conditions likely to increase the risk of CVD (rheumatoid arthritis etc.) 	<ul style="list-style-type: none"> Male and female patients aged >40 years without known CVD risk factors 	<ul style="list-style-type: none"> Documented CVD history Diabetes mellitus Renal impairment (GFR <60 mL/min/1.73 m²) Total cholesterol >310 mg/dL (e.g.: familial hypercholesterolemia) BP ≥ 180/110 mmHg

*Adopted from Source 1. BP: Blood pressure; CVD: CV disease; CVRC: CV risk calculation.

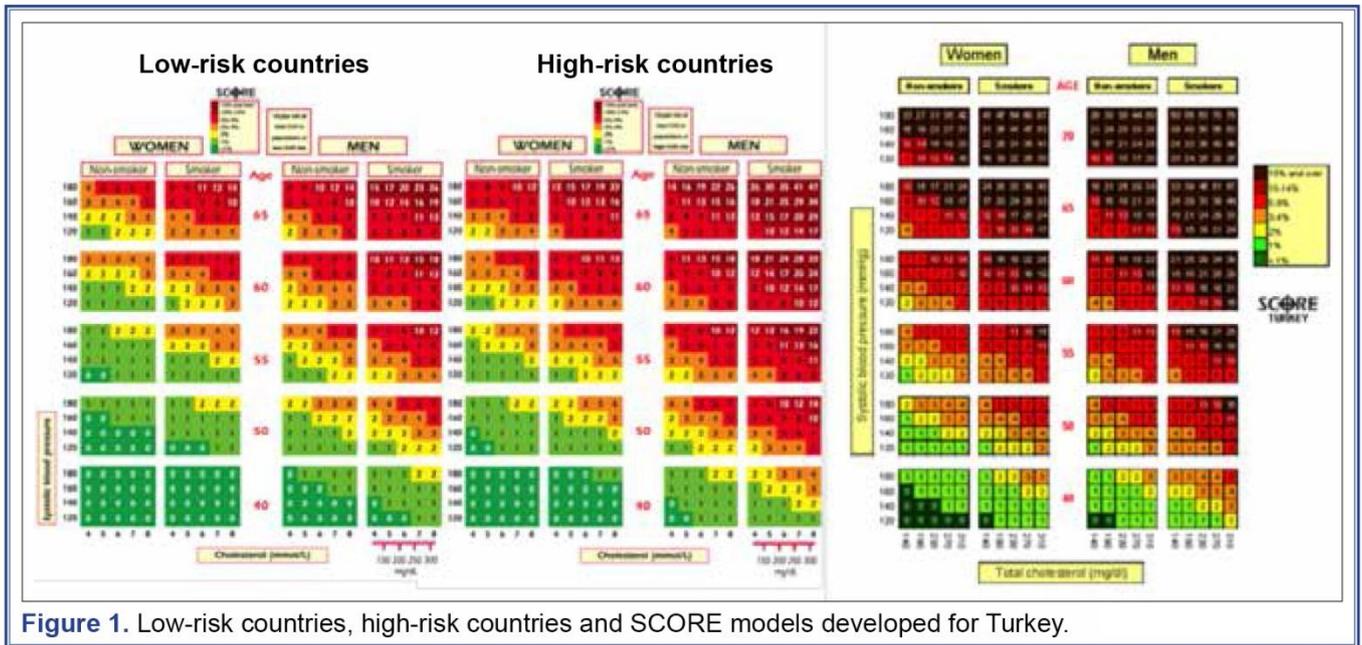


Figure 1. Low-risk countries, high-risk countries and SCORE models developed for Turkey.

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Question 14 – What is the distribution of LDL levels in Turkey and how is the lipid profile of our population?

Dr. Altan Onat

Istanbul University Cerrahpaşa Faculty of Medicine, Cardiology Department, İstanbul

I will answer these questions by including the most recent data collected with TARF study and summarize the impact of this lipid profile on general and coronary heart disease (CHD) mortality based on gender as critical information.

LDL-cholesterol levels

Adults aged between 30-70 years in our country (more than 3300 TARF participants) have an average LDL-cholesterol (LDL-C) level of (95% confidence interval) 111 (45; 176) mg/dL in men and 116 (44; 188) mg/dL in women.

Age is an boosting determinant for these levels only in women. One of the two factors with an impact apart from age is the status of glucose regulation status and the other is the area of residence. While (LDL-C) is relatively low for individuals with normoglycemia, it is high for patients diagnosed with diabetes, and pre-diabetes in particular. Moreover, the residents of Marmara and Central Anatolian regions exhibit approximately 10 mg/dL higher levels compared to the residents of Black Sea, Eastern and Southeastern Anatolian and Mediterranean regions.

While high (LDL-C) (>130 mg/dL) prevalence was 39% among male subjects in TARF 2011/14 cohort, was 46% among female subjects in a sample dominated by menopausal female subjects. When compared with German adults, while our (LDL-C) and apolipoprotein B concentrations are significantly lower (especially for our men), fasting triglyceride levels were found to be higher and HDL-cholesterol (HDL-C) levels were found to be lower.

Triglyceride and HDL-cholesterol levels

TARF participants were found to have average HDL-C levels (95% CI) of 38 (17; 60) mg/dL in men and 45.5 (22; 69) mg/dL in women. These levels tend to increase with age. In the 2013/14 cohort with the average age increased up to 60 years, median values were 44/52 mg/dL for men and women, respectively, with 44 (26; 70) mg/dL on average among men and 52 (32; 82) mg/dL among women.

The geometric mean of fasting triglyceride levels, which tends to increase over time was 152 mg/dL among men and 136 mg/dL among women. The atherogenic index which reflects the ratio of HDL-C levels to triglycerides is high in our population. High atherogenic index is considered an indicator of small

LDL particle size, and reflects obesity and hyperinsulinemia in men and proinflammatory status in women.

In terms of lipoprotein (a), when the GA genotype present in 3% of our population is not taken into consideration within the framework of LPA genotype rs10455872 (with AA genotype), Lp(a) levels are 8.72 *2.84 mg/dL in men and 11.3 *2.8 mg/dL (with 30% excess) in women for individuals with normoglycemia.

In conclusion, lipid profile of our population is significantly affected from the relatively small LDL particle size and it is characterized by low LDL-C and HDL-C and high triglycerides.

Lipids in predictions on overall and CHD mortality

In an algorithm study we conducted recently with 3300 participants, the 120-150 and >150 mg/dL categories were shown to not increase the risk of mortality for men and women compared to non-HDL-cholesterol levels <120 mg/dL, both for the general population and for individuals without CHD.

In our algorithm study conducted with regards to CHD mortality, the >150 mg/dL category predicted a slight CHD mortality risk in men but not in women compared to non-HDL-cholesterol levels <120 mg/dL. Compared to HDL-C levels <40 mg/dL, the 40-49 mg/dL range demonstrated slight protection among male subjects whereas there was no evidence of risk reduction at higher levels. Levels >50 mg/dL among women exhibited protection signs in terms of CHD mortality compared to lower levels. Taken together, the CHD mortality algorithm findings explained significant differences from the SCORE Turkey model. The presence of diabetes is the most important determinant for CHD mortality risk.

In summary, the lipid profile of our population compared to the Western lipid profile in terms of general mortality and fatal CHD risk exhibit important features which differentiate conventional risk factors from risk overlap. An important conclusion revealed by these findings is that the target recommendations of ACC/AHA guidelines should be applied moderately for individuals under 60 years of age and these should be disregarded to follow an individualized approach for adults older than sixty years of age.

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Question 15 – Is HDL-cholesterol actually low in Turkish population?

Dr. Mahmut Şahin

Ondokuz Mayıs University Faculty of Medicine, Cardiology Department, Samsun

Turkish Heart Study (THS, 1995) and the TARF study (1999) both asserted that HDL-cholesterol levels of the Turkish population are 10-15 mg/dL lower than the average values of Western European and American populations. According to TARF data, average HDL-cholesterol levels for the Turkish population are 37.2 mg/dL among men and 44.9 mg/dL among women. Investigators of both studies have linked the low HDL-cholesterol levels observed in the Turkish population to genetic and environmental factors. Hepatic lipase activity is 25-30% higher than normal among the Turkish population and this causes a reduction particularly in HDL2 levels. Compared to individuals with regular physical activity, HDL-cholesterol levels of those who live a sedentary life are 20% lower. Parallel to the duration and intensity of tobacco consumption, a significant drop is observed in HDL-cholesterol levels. Moreover, dietary habits rich in simple carbohydrates also increase blood triglyceride levels and decrease HDL significantly. High rates of smoking among men and being overweight among women, low levels of physical activity and dietary habits based on carbohydrates are the most important factors.^[1,2]

When the value of <40 mg/dL was taken as a threshold at the time, low HDL levels were reported

in 74% of the men and 53% of the women who participated in THS and 64% of men and 35.5% of women in the TARF 2001/2002 cohort.

The METSAR study conducted afterwards found average HDL-cholesterol levels of 46.3 mg/dL in men and 52 mg/dL in women in the Turkish population, which were significantly higher compared to the average values reported in the 2 former studies. Although low HDL threshold was considered as <40 mg/dL for men and <50 mg/dL for women, low HDL levels were determined among 44.1% (38.3% of men, 49.7% of women) of the Turkish population. When evaluated as a component of metabolic syndrome in this study with a frequency of 63.5%, there was no statistically significant difference between Turkish and American populations in terms of low HDL-cholesterol frequency. There are other studies which support this argument.^[3]

The statistically significant difference between these studies may stem from the HDL measurement technique. Previous studies have used the conventional precipitation technique, which results in lower HDL-cholesterol levels.

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Question 16 – Should hsCRP be used while calculating cardiovascular risk?

Dr. Cem Barçın

Sağlık Bilimleri University Gülhane Faculty of Medicine, Cardiology Department, Ankara

Almost all of the risk calculation methods currently used to estimate cardiovascular (CV) risk include classic risk factors (smoking, hypertension, hyperlipidemia and diabetes) in addition to age and gender. However, it is indicated that other biochemical markers or imaging methods may also be used in addition to classic risk factors, particularly for the individuals termed as the "medium-risk group". The most commonly investigated parameter among these markers is the high-sensitivity C-reactive protein (hs-CRP).

CRP increases as an acute phase reactant in the event of inflammation and infection. CRP levels are very low in healthy individuals and classic methods fail to measure the values at these levels. Therefore, hs-CRP values which are more sensitive are used during CV risk assessment.

One of the most important steps in CV risk management is distinguishing individuals at "high" and "low" risk. From this perspective, there are no net hs-CRP values which indicate "high" risk. However, in line with study results and the recommendations of American Heart Society, "asymptomatic individuals" are evaluated as low (hs-CRP <1 mg/dL), medium (hs-CRP 1-3 mg/dL) and high (hs-CRP >3 mg/dL) risk individuals.^[1] Along with this, it is recommended to take into account the mean of two values obtained with an interval of 2 weeks hs-CRP is not a constant but rather a "variable" parameter. Moreover, hs-CRP should not be used as a CV risk marker above >10 mg/dL and the presence of an inflammation/infection should be investigated.

Despite several studies, there is no consensus on the importance and necessity of hs-CRP measurement as part of daily clinical practice from an individual and population perspective. In a cohort study where nineteen thousand individuals were observed to have an average of 18, the "independent" effect of CRP was found to be low after adjustments for age, gender and other classic risk factors (odds rate 1.45). In another study, approximately 10% of the individuals who were classified in the "medium" risk group according to Framingham risk scoring were included in the "high" risk group based on their

hs-CRP values.^[2] However, based on this approach, the total number needed to treat ("number needed to treat") with a drug to prevent CV incidents in 1 patient would be 209.

In one of the most important studies in this field, namely the JUPITER study, approximately 18,000 individuals consisting of males above the age of 50 years and females above the age of 60 years with LDL-cholesterol levels below <130 mg/dL and hs-CRP values >2.0 were randomized to receive rosuvastatin 20 mg or placebo and the study was terminated approximately at 2 years due to the apparent benefit in the group treated with rosuvastatin.^[3] As a result of this study, some guidelines have recommended investigating hs-CRP values for individuals particularly with the aforementioned characteristics and administering statin treatment accordingly.^[4] Actually, JUPITER study revealed that the approach for the individuals in the "medium" risk group was "cost effective".^[5] However, this study did not include a comparison against patients with low hs-CRP values. A meta-analysis conducted with the American population included the investigation on the contribution of four different "non-classic" risk factors including hs-CRP on the predictive value of Framingham Risk Scoring, and this value was shown to be increased is only with calcium scoring.^[6]

When we examine the guidelines, we see that the recommendations regarding the use of hs-CRP in clinical practice are not that strong. Two different European guidelines published in 2016 (Dyslipidemia Guidelines and Guidelines for the Prevention of CV diseases) indicated that hs-CRP is a "risk predictor" but it has a "low" contribution to the classic risk scoring systems and therefore, recommendations to use hs-CRP in daily practice were not included.^[7,8] However, the guidelines on dyslipidemia management published in 2016 in Canada state that particularly the individuals classified in the "medium-risk" group according to Framingham score without any other strong indication for statin treatment "may be considered" as candidates for statin administration in addition to life style changes in the presence of hs-CRP >2 mg/L.^[4]

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Question 17 – Should tests such as C-reactive protein, carotid intima-media thickness, coronary artery calcification etc. be assessed while guiding cholesterol-lowering treatment?

Dr. Serdar Payzin

Ege University Faculty of Medicine, Cardiology Department, İzmir

Atherosclerotic plaque and rupture have been long known to have inflammatory properties. However, it remains unclear whether C-reactive protein (CRP), an acute phase reactant, is a non-specific marker or one of the direct causes of atherosclerosis progression. CRP, and high-sensitivity CRP (hs-CRP) in particular, can be used as marker to determine the risk level for recurrent ischemic events in acute coronary syndromes, acute infarction, following coronary bypass surgeries, and in individuals with established coronary artery disease (CAD). hs-CRP levels lower than 1 mg/L demonstrate low risk while hs-CRP levels of 10 mg/L and above indicate high risk. Statin treatment is known to allow significant decreases in CRP levels both in stable CAD and acute coronary syndrome. This effect may be considered as a result of reduced inflammation with statins. **Although there is no precise recommendation in the guidelines,^[1] it may be appropriate in practice to attempt to adjust hs-CRP levels above 1 mg/L together with achieving the best-fit LDL-cholesterol targets of the statin dose in high-risk CAD.**

Carotid intima media thickness (cIMT) measured with ultrasound is notable as a simple and repeatable non-invasive test used to show the presence of atherosclerotic disease, and to determine the risk level as well as drug effects. In the studies conducted, serial measurements were found to help estimating the cardiovascular (CV) risk in a clearer way; however, they do not offer any additional benefit in disease monitoring.^[2,3] ACC/AHA 2013 guidelines on risk-estimation in CV diseases do not recommend routine cIMT measurement. Drugs which have positive effects on carotid intima-media thickness include statins, metoprolol, amlodipine, certain antidiabetic agents (rosiglitazone, pioglitazone, glimepiride), folic acid, Vitamin E, and Vitamin B12.

Studies with statins and other lipid-lowering agents showed significantly decreased cIMT in patients receiving medication who had asymptomatic or atherosclerotic disease.^[4,5] On the other hand, when all studies are considered together, these positive developments about cIMT do not make a difference in endpoints such as death, myocardial infarction, and stroke. **In practice, it is not necessary to measure cIMT regularly in patients using statins or other lipid-lowering agents.**

The relationship between coronary artery calcification (CAC) and vascular disease has been long known. In studies, it was demonstrated that calcification in coronary arteries is a precise marker for atherosclerotic plaques. However, stenosis in coronary arteries is not associated with presence and intensity of calcifications. Agatston scoring is the most frequently used method for determining the presence and quantitatively measuring calcium in coronary arteries.^[6] In this scoring system, zero refers to "no disease", 0-99 refers to "mild disease", 100-399 refers to "moderate disease", and scores above 400 refer to "severe disease". CAC scoring is not recommended in patients who show low or high risk (10-year-risk <10% or >20%) in Framingham scoring as it does not offer any additional contribution to risk estimation. Also, there is an ongoing debate on the contribution of serial (annual) measurements. To date, no medical treatment has allowed eliminating or halting the progression of coronary calcification. Although the expected benefit was achieved in lipid levels in randomized trials with statins, there was no difference in the rate of CAC progression.^[7,8] **In practice, presence of CAC should be considered as evidence for the presence of atherosclerotic disease and plaques, but should not be considered as a method to guide hyperlipidemia treatment.**

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Question 18 – Should echocardiography be a part of cardiovascular risk calculation?

Dr. L. Elif Sade

Başkent University Faculty of Medicine, Cardiology Department, Ankara

Imaging methods are not a part of the global risk scoring for the estimation of cardiovascular (CV) risk. There is insufficient data to show that echocardiography (ECHO) and other imaging methods are cost-effective in predicting the global CV risk or to suggest that baseline ECHO findings and those observed after employing preventive measures may change the risk stratification. Imaging is more useful for determining risk modifiers. This is particularly important for adjudication in patients whose risk scores are in between two categories. Furthermore, demonstrating cardiac involvement offers prognostic value.^[1,2] In certain cases, particularly in the presence of conditions which put patients at the high risk group beyond scoring, ECHO may be necessary for screening purposes.

Diabetes (DM) puts patients directly at high risk; and detecting target organ damage is necessary to differentiate high risk from very high risk. However, cardiac imaging is not required at this stage. Ischemia screening is not recommended in patients with DM without any CV disease symptoms; because risk factor modification achieves a better event-free survival rate than revascularization.^[3] However, ECHO and/or other imaging modalities are appropriate for investigating the presence and extent of ischemia and left ventricular (LV) dysfunction in patients with ECG abnormalities and CV disease symptoms.^[4]

While ECHO is highlighted in 2013 ESC/ESH guidelines on CV risk assessment in hypertension,^[5] ECHO is only recommended in the presence of suspected hypertensive heart disease. LV

hypertrophy is a risk determinant independent from blood pressure. However, it should be noted that hypertensive heart disease involves LV systolic and diastolic dysfunction, local contraction disorder, and left atrium enlargement.^[6] When ischemic heart disease is suspected in patients with LV hypertrophy, it is appropriate to perform dobutamine stress echocardiogram rather than an exercise treadmill test. In such patients, despite a high risk of ischemic heart disease,^[5] ECHO for screening purposes is not recommended in the absence of symptoms.

Dyslipidemia is a major risk factor for CV diseases; however, ECHO for screening purposes is not required in asymptomatic patients with dyslipidemia. In advanced dyslipidemia cases (e.g. Homozygous Familial Hypercholesterolemia), stenosis may develop due to cholesterol accumulation in aortic valve and rarely in pulmonary valve. Regular ECHO monitoring is necessary following the initial diagnosis in such patients. Although aortic sclerosis without aortic stenosis is observed in heterozygous cases, there is no guideline recommendations regarding the importance of ECHO in risk estimation. Longitudinal strain may be useful to determine LV contraction abnormalities more precisely than ejection fraction before the onset of clinical symptoms; and it may be a part of clinical monitoring in cases with advanced dyslipidemia.^[6] With further improvement, imaging techniques, ECHO in particular, will likely be part of global risk stratification systems for the estimation of CV disease risk in the future.

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Question 19 - Should we prescribe statin for a primary prevention patient who has high LDL-cholesterol but no family history? How aggressive should we act?

Dr.Enver Atalar

Hacettepe University Faculty of Medicine, Cardiology Department, Ankara

Cardiovascular (CV) diseases are the most important cause of death worldwide. As treatment is associated with high costs after the diagnosis and does not result in the desired level of efficacy, primary prevention approaches become more and more significant every day. The presence of atherosclerotic disease in first degree relatives under the age of 55 years in women and under the age of 65 years in men is defined as a positive "family history". In terms of atherosclerotic disease, not only the CV system but also the other potential atherosclerotic organ involvements such as vascular dementia, peripheral artery disease, sudden death and falls should be investigated. The most important approaches to reduce the risk in patients with early-onset CV history in their families include screening for CV risk at an early age and implementing preventive lifestyle modifications based on the risk scores as well as initiating medical treatment when deemed necessary. European Society of Cardiology highlights in the SCORE risk scale it recommends that relative risk calculation and risk modification, if necessary, in the early period would reduce long-term exposure to risks and improve outcomes in patients who are at low risk due to their age but carry other risk factors except age and have early-onset CV disease in their family history. Additionally, care should be exercised for familial dyslipidemia and if necessary, frequent mutations should be investigated to assist the screening of family members; however, it should be taken into account that new mutations may also cause this condition in mutation-negative patients.

Currently, there are questions related to the therapeutic approach for young patients with high levels of LDL-cholesterol in the absence of early-onset atherosclerotic disease in their family, and this

group stands out as the patients with the least apparent benefit in several statin studies. At this point, the risk of these patients should be calculated in line with the risk scores recommended by guidelines. ACC/AHA 2013 Dyslipidemia guidelines recommend high efficacy statin treatment for patients aged 21 years and above with LDL-cholesterol levels higher than 190 mg/dL even in the absence of other risk factors, and it is recommended to calculate other risk factors according to "Pooled Cohort Estimation" for the patients with LDL-cholesterol levels between 70 and 189 mg/dL. ESC 2016 Dyslipidemia guidelines classify patients in low, medium, high and very high risk groups based on the SCORE risk scale, and while lifestyle modifications and medical treatment, if deemed necessary, are recommended for low-risk patients with LDL-cholesterol levels of 190 mg/dL and above, lifestyle modifications and medical treatment are recommended for medium-risk patients with LDL-cholesterol levels of 100 mg/dL and above. While it is considered reasonable to determine how aggressive the treatment will be based on the individual patient's risk factors and LDL levels, ACC/AHA recommendations suggest high efficacy statin for all patients if they can tolerate treatment rather than titrating the statin dose based on a target LDL value. ESC guidelines recommend determining the efficacy of statin treatment based on the patient's LDL value and the desired reduction rate according to the target LDL value, with dose titration if deemed necessary. The different approaches included in different guidelines should be evaluated taking into consideration certain factors such as the country and patients as well as social and environmental factors, and they should be employed taking into account these differences in each patient as a requirement of the medical profession.

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Question 20 – What are the causes of secondary dyslipidemia?

Dr. Gülay Sain Güven

Hacettepe University Faculty of Medicine, Internal Diseases Department, Ankara

Non-lipid factors may also lead to dyslipidemia. Investigating the presence of a secondary cause is essential in dyslipidemia:^[1]

- Similar to primary dyslipidemias, the secondary changes in lipid metabolism also increase the risk of cardiovascular (CV) events. Presence of dyslipidemia may increase the complications of the underlying disease.
- Treating the underlying disease may help improve lipid anomalies and avoid using unnecessary lipid-lowering treatment (LLT).
- The first clue for the underlying disease may be dyslipidemia and may help establishing the diagnosis.
- Causes of secondary dyslipidemia such as hypothyroidism or renal failure may increase the risk of LLT side effects.
- The treatment of choice may be changed due to potential drug interactions between LLT and the medicines used to treat the underlying disease.
- Leaving the underlying disease untreated may result in a treatment-resistant dyslipidemia.

Secondary causes of dyslipidemia

1. Smoking: Slightly decreases HDL-cholesterol (HDL-C) levels. Smoking interrupts the function of HDL by decreasing antioxidant and anti-inflammatory capacity and by inhibiting cellular cholesterol efflux. The unfavorable impacts on HDL resolve within a few months after smoking cessation.

2. Alcohol consumption: Moderate alcohol consumption (10-20 gr ethanol/day) has favorable effects on lipid profile while excessive consumption (≥ 30 gr ethanol/day) may increase triglyceride (TG) levels.

3. Hypothyroidism: The levels of total cholesterol, LDL-cholesterol (LDL-C) and TG increase in hypothyroidism, which should certainly be investigated as a secondary cause of dyslipidemia.

HDL-C levels may also be increased by decreased activities of hepatic lipase (HL) and cholesteryl ester transfer protein (CETP). Replacement therapy with L-thyroxine restores lipid metabolism anomalies within 4-6 weeks.

4. Hyperthyroidism: In hyperthyroidism, both the synthesis of cholesterol and the expression of the LDL-receptor gene responsible for the breakdown of LDL are increased. Levels of total cholesterol and LDL-C decrease as a result of the antagonistic effect of these two factors.^[3] While low HDL-C levels are seen, there is no change regarding TG levels.

5. Obesity: Although levels of total cholesterol, LDL-C, VLDL-C and TG are high while HDL-C is low, atherogenic dyslipidemia is predominant rather than hypercholesterolemia. Weight loss helps improve hypertriglyceridemia. Therefore, ideal body weight should be targeted through diet and exercise in patients with obesity and hyperlipidemia.

6. Type 2 Diabetes mellitus (DM): Atherogenic dyslipidemia (hypertriglyceridemia and low HDL-C) related to insulin resistance is frequent in Type 2 DM. VLDL particle size increases while LDL and HDL sizes decrease with increasing insulin resistance. In addition, the number of intermediate-density lipoproteins (IDL) and LDL particles increase while HDL concentration decreases.^[4]

7. Cholestatic Liver Diseases: In diseases like primary biliary cholangitis, hypercholesterolemia develops as a result of lipoprotein-X accumulation.

8. Nephrotic Syndrome (NS) and Chronic Kidney Disease (CKD): Lipoprotein lipase activity is low in NS. Hepatic lipoprotein production is increased with decreasing oncotic pressure. Serum total cholesterol, VLDL and LDL-C levels are high in NS due to decreased catabolism and increased production.

In CKD, levels of LDL-C are often low while TGs are high and HDL-C levels are low. Hypertriglyceridemia occurs in 30-50% of patients with CKD.^[5] Dyslipidemia due to CKD may also accelerate the disruption of renal function.

9. Rheumatic Diseases: Autoimmunity results in dyslipidemia and development of atherosclerotic plaques. It is important to clarify whether there is an underlying rheumatic disease in the presence of dyslipidemia. Using anti-inflammatory drugs results in a less atherogenic lipid profile.

- a. Rheumatoid Arthritis (RA): Dyslipidemia is frequent in RA (55-65%). It may be seen in both the early and late stages of the disease. Levels of total cholesterol, TG and apolipoprotein B (Apo-B) may be elevated and HDL-C may be decreased years before the diagnosis of RA. For the risk assessment of these patients, it is recommended to use ratios such as total cholesterol/HDL and LDL-C/HDL-C, which are less influenced by inflammatory fluctuations compared to lipid parameters alone.^[6]
- b. Systemic lupus erythematosus: Levels of total cholesterol, LDL-C, TG and Apo-B are increased and HDL-C is decreased. Systemic inflammation triggers proatherogenic modifications such as generation of oxidized LDL. Lp(a) levels may also be increased.
- c. Sjogren's syndrome: HDL-C levels are low.
- d. Systemic Sclerosis: Hypertriglyceridemia is present due to low lipoprotein lipase activity. Lp(a) level is high and oxidation of LDL is increased.

10. TG is elevated by the metabolic effect of human immunodeficiency virus (HIV). Anti-HIV medications also lead to insulin resistance and dyslipidemia.

11. Medications: Drugs may affect serum lipid levels directly or indirectly by their influences on body weight or glucose metabolism.^[1] Leading drugs which cause dyslipidemia include thiazide diuretics, beta-blockers, oral estrogens, anabolic or glucocorticoid steroids, oral retinoids, some atypical antipsychotic drugs (in particular olanzapine, clozapine), immunosuppressants and antiretroviral drugs (in particular protease inhibitors).

In conclusion, secondary causes should be excluded primarily by means of medical history, physical examination and very basic laboratory techniques (TSH, fasting plasma glucose, etc.) in the presence of dyslipidemia. Lifestyle modifications (including smoking cessation and achieving ideal body weight) should be consistently emphasized, all CV risk factors should be investigated and total CV risk should be estimated using risk models when a secondary cause is detected. CV disease risk score should influence the decision to start LLT. Fighting against the secondary cause should not delay starting LLT.

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Question 21 – How should we approach hypercholesterolemia in subclinical hypothyroidism?

Dr. A. Gökhan Özgen

Ege University Faculty of Medicine, Endocrinology Department, Izmir

Subclinical hypothyroidism (SCH) is defined as elevated levels of thyroid stimulant hormone (TSH) despite normal levels of serum thyroid hormones. This condition is more frequent among elderly people and women. Hypercholesterolemia, left ventricular diastolic function disorder, changes in endothelial functions, increased CRP levels and increased risk of atherosclerosis have been reported in SCH.^[1]

Thyroid hormone (TH), hepatic expression of HMG-CoA reductase and eventually cholesterol synthesis increase in this condition. Hepatic cholesterol synthesis is decreased in apparent hypothyroidism but TH also increases the expression of LDL receptors on the cell surface of fibroblasts, in the liver and other tissues. LDL receptor levels are regulated by negative feedback in the presence of high intracellular cholesterol levels. This regulation is likely to be mediated by "sterol regulatory element-binding protein-2" (SREBP-2). The SREBP-2 gene is directly regulated by T3. The decrease in LDL receptors reduces LDL-cholesterol (LDL-C) clearance from the circulation. Intestinal absorption of cholesterol is also increased in hypothyroidism due to the effects of TH on the "Niemann-Pick C1-like 1" protein in the bowel. Although hepatic synthesis of cholesterol is decreased in hypothyroidism, the net outcome is increased LDL-C because of the effects on LDL receptor expression and cholesterol absorption. Concentration of plasma cholesterol ester transfer protein (CETP) also decreases in hypothyroidism, leading to a change in HDL levels. TH also has effects on hepatic lipase, which effects HDL subfractions. Additionally, TH stimulates cholesterol efflux from macrophages through ABCA1 transporters. TH also increases the activity of lipoprotein lipase. Low activity of this enzyme in hypothyroidism results in elevated triglyceride levels. TH also has a role in the production of bile acids. Therefore, thyroid hormone exerts its functions in cholesterol removal by increasing cholesterol utilization in the production of bile acids.^[2]

SCH is seen in approximately 4-10% of the adult population, with a 2-5% annual rate of progression to apparent hypothyroidism. The prevalence of SCH among patients with dyslipidemia is 1.4%-11.2%.

In many patients with SCH, serum lipid concentrations remain within normal ranges. Although some publications indicate that there is a positive correlation between TSH levels and high levels of cholesterol and LDL-C and that all patients with SCH are dyslipidemic, it has also been reported that the most frequent form of dyslipidemia is low HDL while atherogenic lipid profile is observed in those with a TSH level >10 mIU/L.^[3]

Although there is a consensus that replacement therapy has positive effects on serum lipid profile and cardiovascular risk in apparent hypothyroidism, there is no such consensus for SCH treatment with regard to similar benefits. This is related to the fact that the degree of disruption in lipid profile is not clearly known in SCH, and there is no definite evidence whether treating this condition has positive effects on morbidity and mortality. Some clinical studies have demonstrated positive effects of TSH replacement therapy on lipid parameters.^[4] Other studies have shown no positive effects on lipid profile while some others suggest that its positive effects on lipids has no benefits on cardiovascular morbidity and survival. These results have led to a conflict on whether all patients with SCH may benefit from LT4 replacement. In the event of dyslipidemia in cases with SCH, the first intervention should be lifestyle modifications. T4 replacement therapy is appropriate for the elderly, smokers, anti TPO Ab (+) patients with TSH levels >10 mIU/L, and those with high baseline cholesterol levels. Lipid profile should be checked again after achieving euthyroidism.

Specific lipid-lowering treatment should be administered together with T4 treatment and even without T4 in the presence of elevated LDL-C levels requiring treatment in SCH.

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Question 22 – What should be the goal of anti-lipid therapy? How should we assess treatment success?

Dr. Mustafa Kemal Erol

Kemerburgaz University Faculty of Medicine, Cardiology Department, İstanbul

The aim of lipid lowering therapy (LLT) is to reduce atherosclerotic cardiovascular (CV) risk. Therefore, risk factors warrant a global (integrated) approach. Total CV risk should be evaluated for the individual patient and medical treatment should be planned accordingly. A more aggressive approach is required in patients with high CV risk and multiple risk factors while the approach should be rather modest in those at lower risk. It should be noted that LLT does not refer to medical treatment alone but also includes lifestyle modifications aiming to improve other risk factors which increase CV risks as the mainstay of the treatment. In this context, a proper diet, smoking cessation, weight loss in overweighted individuals, avoiding inactivity, adjustment of blood sugar in diabetics, and treating high blood pressure should also be considered along with LLT.

Several studies have demonstrated the associated between high LDL-cholesterol (LDL-C) and atherosclerotic CV diseases including coronary artery disease, stroke, and peripheral artery disease. Similarly, it has clearly been defined in randomized clinical studies that lowering LDL-C with statins lowers the risk of CV events in the following 4 patient groups: 1. Patients with clinical atherosclerotic heart disease, 2. Subjects with LDL-C levels >190 mg/dL, 3. Diabetics between 40-75 years of age with LDL-C levels between 70-189 mg/dL, and 4. Non-diabetics with estimated 10-year atherosclerotic CV risk over 7.5% who are in the age groups of 40-70 years.

American guidelines recommend starting low-intensity (to decrease LDL-C by <30%), moderate-intensity (to decrease LDL-C by 30-50%) or high-intensity (to decrease LDL-C by more than 50%) statins and continuing with the same dose without a specific LDL-C target after determining the CV risk. This guideline recommends high-intensity treatment in patients under 75 years of age and moderate-intensity treatment for those older than 75 years, and starting high-intensity statins for those with LDL-C >190 mg/dL in primary prevention, high-intensity treatment for diabetics with a calculated 10-year atherosclerotic CV risk >7.5%, and moderate-intensity statin treatment for the others. In primary prevention, starting moderate-intensity statin

treatment is recommended for non-diabetic individuals with LDL-C <190 mg/dL and a calculated 10-year atherosclerotic CV risk >7.5%.^[1]

On the contrary, European guidelines continue recommend LDL-C level as the primary goal in lipid-lowering treatment. This guideline recommends a LDL-C target of <70 mg/dL or at least 50% LDL-C reduction if baseline LDL-C is 70 to 135 mg/dL in patients with very high CV risk [people with established CV disease, organ damage such as proteinuria or smoking, diabetics with major risk factors such as hypertension or dyslipidemia, severe chronic renal disease (GFR <30 mL/min/1.73 m²) and a 10-year fatal CV disease risk calculated as ≥ 10% according to the SCORE scale]. A LDL-C target below 100 mg/dL or at least 50% LDL-C reduction is recommended if baseline LDL-C is 100 to 200 mg/dL in patients with high CV risk [those with a significant increase in a single risk factor (for instance, familial dyslipidemias and serious hypertension), diabetics other than those at very high risk, moderate chronic renal disease (GFR 30-59 mL/min/1.73 m²) and a SCORE level 5-10%]. In patients with moderate CV risk (SCORE value between 1-5), the LDL-C target is adopted as 115 mg/dL.^[2]

The British NICE guidelines has a rather different approach which suggests the use of non-HDL cholesterol which does not require fasting blood tests instead of LDL-C. Atorvastatin 20 mg/day is recommended for primary prevention in individuals with a 10-year CV disease risk of 10%; for type 1 diabetics over 40 years of age, those with nephropathy and other CV risk factors and those who are diabetic for more than 10 years; for those with type 2 diabetes and a 10-year CV risk of 10% or above; and for those with chronic renal failure. Atorvastatin 80 mg/day is recommended for secondary prevention of people with established CV disease. In this guideline, 40% or more reduction in non-HDL cholesterol at three months compared to baseline has been recognized as the treatment goal. Similar to American guidelines, no specific LDL-C level is specified in this guideline but the target is specified as the percentage reduction in non-HDL cholesterol compared to baseline.^[3]

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Question 23 – What is the position of statins in primary prevention? Who should receive statins and what should be the dose?

Dr. Hakan Kültürsay

Ege University Faculty of Medicine, Medical Biology Department, İzmir

The role of statin treatment in secondary prevention is beyond dispute. Primary prevention consists of precautions to reduce CV risk in asymptomatic individuals in whom no cardiovascular (CV) disease has yet clinically developed. Statin use in this group has long been a matter of debate, particularly in low risk people. In daily practice, cost-effectiveness of statin use is still a subject of debate despite the availability of generic statin preparations. It is suggested that the cost of statin treatment may be balanced by the risk reduction achieved by strict adherence to treatment.^[1]

In guidelines related to CV prevention, statin use is regulated according to the risk level and levels of LDL-cholesterol (LDL-C).^[2,3] Since all drug treatments are associated with trade-off to some extent, the future risk should be properly evaluated. It should be kept in mind that several calculation scales used for risk assessment overestimate the actual risk.

There are many clinical randomized trials as well as numerous meta-analyses on statin use in primary prevention. Studies on primary prevention include earlier trials from 1990's such as WOSCOPS, AFCAPS/TexCAPS and the recent JUPITER trial carried out in 2000's^[4] (Table 1). Finally, 20th year results of the WOSCOPS study announced in 2014 reported a 27% reduction in mortality associated with coronary heart disease and 13% reduction in all-cause mortality in patients receiving treatment with a statin (pravastatin 40). Moreover, cancer rates in patients

taking statins were the same as placebo after 20 years.^[5]

The role of statins in guidelines on primary prevention

American guidelines (ACC/AHA) (2013): Statin treatment is divided into 3 groups as high-, moderate- and low-intensity. Statin treatment for primary prevention is recommended in cases with no atherosclerotic CV disease in the following individuals: 1) ≥ 21 years old with a LDL-C ≥ 190 mg/dL, 2) subjects aged 40-75 years with diabetes and LDL-C: 70-189 mg/dL, and 3) non-diabetics with LDL-C: 70-189 mg/dL and a 10-year risk of $\geq 7.5\%$. High-intensity, moderate-intensity and high-intensity statin treatment, are recommended in these cases, respectively. For cases not classified in the aforementioned groups in whom statins are considered for primary prevention, the decision of treatment should be individualized based on potential benefit, side effects, drug-drug interactions and patient preferences.

A sample of high-intensity treatment: Atorvastatin 40-80 mg, Rosuvastatin 20-40 mg

A sample of moderate-intensity treatment: Atorvastatin 10-20 mg, Rosuvastatin 10 mg, Pravastatin 40 mg

A sample of low-intensity treatment: Simvastatin 10 mg Pravastatin 10-20 mg

Table 1.

Study	Follow-up period	Endpoint	Result
WOSCOPS	4.9 years	MI, CV death	33% risk ↓
AFCAPS/TexCAPS	5.2 years	ACS	32-40% risk ↓
ALLHAT-LLT	3.3 years	Death, CV event	No difference
ASCOT-LLA	4.8 years	MI, CV death	36% risk ↓
CARDS	4 years	ACS, intervention, stroke	37% risk ↓
ASPEN	2.4 years	CV death, MI	8% risk ↓ (NS)
MEGA	5.3 years	CAD	33% risk ↓
JUPITER	1.9 years	Major CV event	44-54% risk ↓

MI: Myocardial infarction; ACS: Acute coronary syndrome; CV: Cardiovascular; CAD: Coronary artery disease; NS: Not significant.

European Society of Cardiology (ESC) (Prevention guidelines 2016): The 10-year risk calculation is recommended as the first step for primary prevention. The SCORE risk calculation system may be used for this purpose. Determining the LDL-C target should follow the risk calculation (i.e. low-moderate, high or very high group) of the individual. These targets are: <115 mg/dL, 100 mg/dL and <70 mg/dL, respectively. Statins are the first drug group recommended for this for this approach.

Cases of familial hypercholesterolemia are considered as high-risk in all guidelines in the context of primary prevention owing to exposure to high cholesterol levels from birth, and statin treatment is recommended for such patients.

Result: Pleiotropic effects (improving endothelial function, anti-inflammatory effects, etc.) of statins also play a favorable role in prevention from CV events in addition to their lipid-lowering effects. Therefore, statins should be used in primary prevention particularly in high-risk cases.

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Question 24 – Which patient groups should receive high-dose statins for secondary prevention?

Dr. Oktay Ergene

Atatürk Training and Research Hospital, Cardiology Clinic, İzmir

Among large randomized controlled trials comparing high-dose statin treatment (or high-intensity treatment) with standard dose statin treatment, the PROVE IT-TIMI-22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction-22) and TNT (Treating to New Targets) studies have shown that high-dose statin treatment is more effective in reducing cardiovascular (CV) events compared to standard dose treatment. However, there was an insignificant trend towards the benefit of high-dose statin treatment on primary endpoints in the A-to-Z (Aggrastat to Zocor) and IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) studies. In the meta-analysis of these four studies, high-dose statin was found to be beneficial particularly for the prevention of non-fatal CV events compared to standard dose treatment.^[1]

In 2013 ACC/AHA guidelines on reducing atherosclerotic CV risk with cholesterol lowering treatment in adults, clinical atherosclerotic CV disease (ASCVD) diagnosis consisted of acute coronary syndrome, history of myocardial infarction, stable and unstable angina, coronary and other arterial revascularization, stroke, transient ischemic attack, and peripheral arterial disease considered as of atherosclerotic origin which were gathered under the title of secondary prevention.

No LDL-cholesterol (LDL-C) limit has been specified to start treatment. Statin treatment has been classified as high-, moderate- and low-intensity (Table 1). According to this guideline, high-intensity

statin treatment should be initiated and continued in men and women with ASCVD younger than 75 years of age as long as there is no contraindication (Class I, evidence level A). For patients with clinical ASCVD who require high-intensity statin treatment, statin treatment of moderate intensity should be administered in the presence of contraindications or characteristics leading to predisposition to side effects of statins (Class I, evidence level A). It is recommended that the benefits achieved by reducing the risk of ASCVD should be evaluated together with drug-related side effects and drug interactions, and patient preferences should be considered when starting statin treatment of moderate-high intensity in individuals over 75 years of age with clinical ASCVD, which should be continued in patients who can tolerate the treatment (Class 2A, evidence level B).^[2]

It has been stated in 2016 ESC dyslipidemia guidelines that LDL-C <70 mg/dL or at least 50% reduction should be the target if baseline LDL-C level is between 70 to 135 mg/dL for secondary prevention in CV disease demonstrated by means of interventional or non-interventional tests (coronary angiography, nuclear imaging, stress echocardiography, carotid plaque shown by ultrasound), previous myocardial infarction, acute coronary syndrome, coronary revascularization (percutaneous coronary intervention, coronary artery bypass grafting), history of other arterial revascularizations, ischemic stroke or peripheral arterial diseases. (Class I, evidence level A)

Table 1. High-, moderate-, and low- intensity statin treatment

High-intensity statin treatment	Moderate-intensity statin treatment	Low- intensity statin treatment
Daily dose decreases LDL cholesterol by approximately $\geq 50\%$	Daily dose decreases LDL cholesterol by 30-50%	Daily dose decreases LDL cholesterol by $<30\%$
Atorvastatin 40–80 mg	Atorvastatin 10 (20) mg	Simvastatin 10 mg
Rosuvastatin 20 (40) mg	Rosuvastatin (5) 10 mg	Pravastatin 10–20 mg
	Simvastatin 20–40 mg	Lovastatin 20 mg
	Pravastatin 40 (80) mg	Fluvastatin 20–40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg bid	
	Pitavastatin 2–4 mg	

The highest tolerated dose of statins have been recommended to achieve target levels (Class I, evidence level A). It was recommended that drug treatment should be considered in LDL-C values <70 mg/dL and that treatment should be started with statins in patients with acute coronary syndrome regardless of LDL-C levels.^[2]

Secondary prevention recommendations in 2016 ESC CV disease prevention guidelines as well as patient groups that require secondary prevention and LDL-C goals are similar to those in 2016 ESC/EAS dyslipidemia guidelines. Statins have been reported

to reduce CV mortality and morbidity in addition to decreasing the need for coronary artery interventions by reducing LDL-C, and the effective statin dose to reduce LDL-C by at least 50% halts the progression of coronary atherosclerosis and may contribute to plaque regression, and it is therefore recommended as the first choice of drug in hypercholesterolemia. According to this guideline, the LDL-C target should be <70 mg/dL or at least a 50% reduction compared to baseline in secondary prevention. Statin treatment should also be considered in secondary prevention even if LDL-C is <70 mg/dL, and should be started between LDL-C levels of 70-130 mg/dL.^[4]

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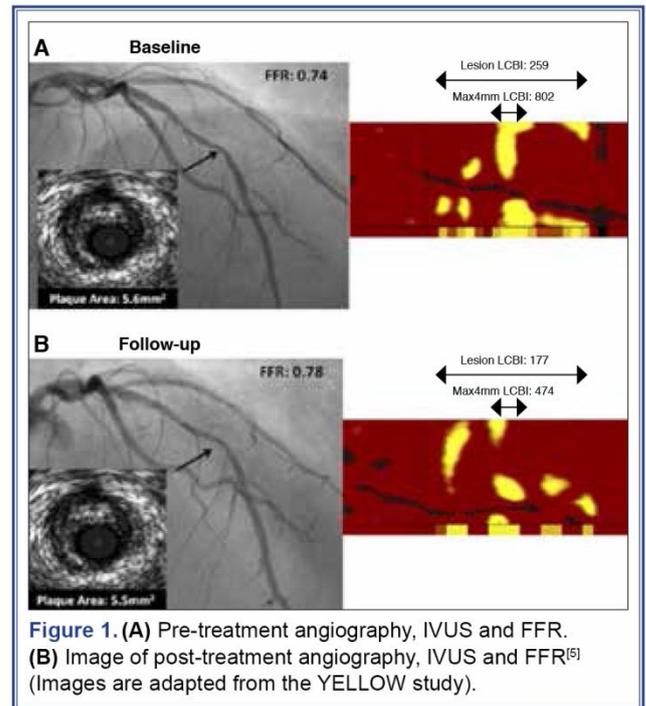
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Question 25 – Does anti-lipid therapy actually regress plaques?

Dr. Ömer Göktekin

Bezmialem Vakıf University Faculty of Medicine, Department of Cardiology, İstanbul

Atheromatous plaque rupture and the associated thrombosis are the major causes of acute myocardial infarction and sudden cardiac death. The most recent European Guidelines on prevention of cardiovascular disease in clinical practice recommend maintaining high-density lipoprotein (LDL)-cholesterol (LDL-C) levels <70 mg/dL as a class 1, level of evidence B recommendation; and to lower LDL-C to below 50% of the baseline level as a class 1, level of evidence B recommendation.^[1] The same guidelines also highlight that decreased LDL-C levels reduce cardiovascular morbidity and mortality as well as providing decreased need for invasive coronary interventions. Furthermore, in the ASTEROID study, lowering LDL-C levels to below 50% of the baseline level was shown to slow down and even stop the progression of coronary atherosclerosis.^[2] Statins may regress atherosclerotic plaques by decreasing their lipid content, vascular inflammation and oxidative stress. MIRACL studies have shown that statin treatment may improve plaque stability, reduce the incidence of acute coronary syndromes and decrease recurrent coronary ischemia.^[3,4] Plaque instability is associated with the thin fibrous cap and high macrophage content. Decreasing lipid content in the formation of coronary plaques increases plaque stability. The YELLOW study has shown decreased lipid content in the plaques by means of intravascular ultrasound (IVUS) in patients receiving intensive anti-lipid therapy (Figure 1).^[5] Statins enhance plaque stability by reducing the macrophage accumulation and cholesteryl ester content in the atheromatous plaque as well as increasing the collagen content volume.



By using optical coherence tomography (OCT), the reduction in LDL-C levels with optimal lipid-lowering treatment after drug-eluting stent implantation has been shown to provide prevention against increased neointimal thickness.^[6] As seen in OCT and IVUS studies, anti-lipid therapy plays an important role in the regression of plaque formation as well as prevention against the major mechanisms involved in atherosclerosis development.

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Question 26 – How should we monitor anti-lipid therapy? How frequently should lipid levels be assessed? Which parameters should we monitor?

Dr. Meral Kayıkçıoğlu

Ege University Faculty of Medicine, Cardiology Department, İzmir

The success of lipid-lowering treatment (LLT) is based on adequate monitoring. A good monitoring approach may minimize side effects and drug interactions, and may maximize treatment success as well. Adequate monitoring also facilitates treatment adherence and persistence. Current guidelines recommend performing the first follow-up assessment at 4-8 weeks after LLT initiation and to subsequently adjust monitoring intervals based on the clinical prognosis (response).^[1] However, one should bear in mind that treatment does not aim to decrease lipid levels alone but also aims to reduce all risk factors. Figure 1 illustrates the monitoring schedule employed in the lipid polyclinic of Ege University [adapted from ATP-II^[2]]. During the monitoring visits, lipid measurements should include full lipid profile, side effect assessment, query on lifestyle modifications and reminders regarding the diet.^[2] The lipid profile should consist of total cholesterol, LDL-C, triglycerides and HDL-C measurements. Non-HDL cholesterol should be evaluated in hypertriglyceridemia and lipoprotein(a) should be assessed in early atherosclerosis. Apolipoprotein-B may also be evaluated, if possible.^[1]

Monitoring Lipid Levels

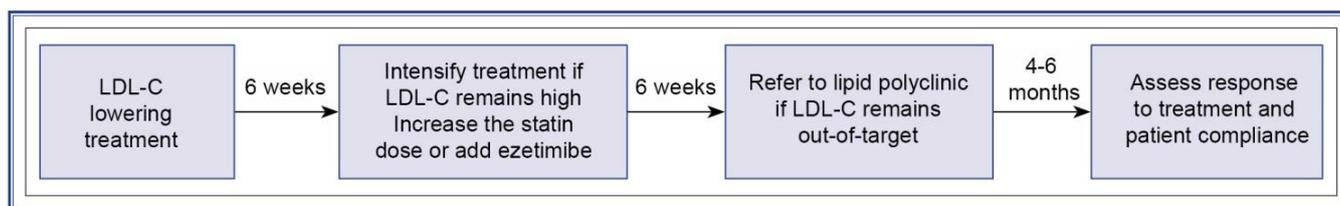
According to ESC 2016 guidelines, at least 2 measurements should be obtained with intervals of 1-12 weeks prior to starting LLT (2). This excludes patients at very high risk or conditions such as acute coronary syndrome which require concomitant drug treatment. The first measurement should be performed 8 (\pm 4) weeks after starting drug treatment. Then, measurements should be repeated with

intervals of 8 (\pm 4) weeks until target levels are achieved. Upon achieving target values, annual lipid measurement would be appropriate (it may be more frequent in the presence of problems with treatment adherence or any other specific reason). However, our experience at Ege University lipid polyclinic shows that annual measurement is not adequate in patients at high or very high risk and that infrequent monitoring may decrease treatment adherence. Therefore, we prefer more frequent (every 3-6 months) monitoring visits with short durations.

Monitoring Liver and Muscle Enzymes

Liver enzymes should be checked routinely before treatment initiation and then 8-12 weeks after starting the drug as well as after any dose increase in patients receiving LLT. Routine liver enzyme tests are not indicated during treatment for stable LLT monitoring.

Among muscle enzymes, creatine kinase (CK) should be measured at baseline and if the CK level exceeds the upper limit of normal by 4-fold, treatment should not be initiated and measurement should be repeated.^[1] Routine CK measurements are not indicated during the follow-up. However, patients should be informed about findings such as muscle pain, dark colored urine etc. at the time of treatment initiation. ESC guidelines recommend raising awareness on myopathy and elevated CK levels particularly in patients at risk such as the elderly, patients receiving concurrent medication which interact with LLT, those receiving multiple drugs, patients with hepatic or renal disease and athletes.



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Question 27 – Why do patients discontinue LDL-lowering treatment? How can we increase adherence?

Dr. Murat Biteker

Muğla Sıtkı Kocman University Faculty of Medicine, Department of Cardiology, Muğla

A number of large randomized studies demonstrated that decreasing low-density lipoprotein cholesterol (LDL-C) levels with statin treatment lowers the risk of major coronary events.^[1,2] Despite current guideline recommendations on effective cholesterol treatment, prescription rates and adherence to statin treatments remain low.^[3] Non-adherence to statin treatment in Turkey can be analyzed in 4 main categories:

1. Patient related factors: Such factors may include insufficient knowledge on health, a low level of disease awareness, prejudice against treatment efficiency, negative experiences with the previous medication, psychological problems, or cognitive disorders.

2. Physician related factors: Insufficient explanation about the disease or benefits and side effects of the treatment, and inconsistent information provided by different physicians may cause non-adherence to statin treatment.

3. Healthcare system related factors: Turkish healthcare system limits the time physicians allocate for their patients to a large extent. This may hinder informing patients about the drugs, assessing adherence to treatment, and encouraging patients to adhere to their statin treatment. Price difference paid by the patient may also affect adherence unfavorably.

4. Press related factors: In recent years, both visual and printed media have published articles against statins and claim that high cholesterol levels

are harmless. Such articles have negative effects on adherence to treatment.^[4]

In a recent national and observational study, 532 patients who discontinued statin use were assessed.^[5] This study showed that patients decided to discontinue statin treatment to a large extent based on their own decision stating the main reason of that as the negative news articles about statins on TV programs.

In the national multi-center EPHEBUS (Evaluation of Perceptions, Knowledge and Compliance with the Guidelines for Secondary Prevention in Real Life Practice: A Survey on the Under-treatment of hypercholesterolemia) study (NCT02608645) for which we have started enrolling patients last year, it is planned to determine the role of level of patient education and knowledge in secondary prevention to achieve target LDL-C levels. Preliminary results of the study have shown that the main factor in discontinuing statin treatment is the negative publications on statin use on both visual and printed press. Although there is no single way to increase long-term adherence to statin use, I think listening to patient concerns even if briefly, and exchanging opinions on possible side effects may create a big difference. The best way to increase patient adherence may be allowing the patients to have an active role in deciding the treatment to be administered.

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Question 28 – Do current guidelines on lipids differ in terms of statin use?

Dr. Murat Ersanli

Istanbul University Cardiology Institute, İstanbul

To briefly answer the question: No, not essentially -but they appear to have some differences from a detailed perspective.

Statins are the most widely studied drugs which are shown to significantly reduce cardiovascular (CV) morbidity and mortality in both primary and secondary prevention against CV diseases in increasingly larger scale studies.

The primary goal is LDL-C, for which each 1.0 mmol/L (\approx 40 mg/dL) reduction is associated with a 23% decrease in major coronary events and a 17% decrease in stroke risk.

Considering that the most important guidelines are ATP III 2002 Guidelines, ESC/EAS 2011 Guidelines and AHA/ACC 2013 Guidelines, which have been developed through the update of the former two,^[1] and ESC/EAS 2016 Guidelines^[2], we can summarize the considerations and differences of statin treatments as follows:

1. Updated versions of both guidelines have extended statin treatment in a broader age range with a more sensitive approach in CV risk calculation, recommending more intensive or moderate-intensive doses of statin treatment.

2. While AHA/ACC Guidelines are mainly based on randomized controlled trials (RCTs) and meta-analyses, ESC/EAS Guidelines also take into account post hoc analyses as well as observational, epidemiological, genetic and metabolic studies. In this regard, considering that large RCTs are conducted with statins, AHA/ACC Guidelines are more statin-centered and focused on LDL-C compared to ESC/EAS Guidelines.

3. The proportional change in lipid quantities rather than the lipid levels are important in AHA/ACC Guidelines whereas both are important in ESC/EAS Guidelines. While AHA/ACC Guidelines aim to reduce LDL-C level by 50% or more in a high-risk patient, ESC/EAS Guidelines aim a LDL-C

target of <70 mg/dL. ESC/EAS Guidelines also recommend 50% LDL-C reduction in high-risk patients with baseline LDL-C levels of 70 to 100 mg/dL.

4. The age range for treatment is indicated as 21-75 years in AHA/ACC Guidelines whereas it is 40-65 years in EAS/ESC Guidelines. Therefore, AHA/ACC Guidelines appear to encourage statin use in young age. Both guidelines find it favorable to use moderate-intensity statin treatment where necessary, particularly in the elderly.

5. Non-statin drugs and combination therapy with statins are discussed and included in EAS/ESC Guidelines to a greater extent.

6. While AHA/ACC Guidelines consider 500 mg/dL and higher levels for hypertriglyceridemia treatment; EAS/ESC Guidelines consider statin treatment primarily based on CV risk for the treatment of hypertriglyceridemia relative to LDL-C and non-HDL cholesterol, although they also include fibrates, nicotinic acid and n-3 fatty acids where necessary.

7. There are no recommendations on chronic kidney disease (CKD) in AHA/ACC Guidelines. ESC/EAS Guidelines recommend treatment with a statin or statin-ezetimibe combination as a class I indication particularly in patients with stage 3-5 CKD, taking into account the advanced atherosclerosis risk in these patients. These treatments should not be initiated in patients undergoing dialysis, however, treatment may be continued in patients already receiving these drugs.

8. ESC/EAS 2016 Guidelines have been issued more recently and include PCSK9 inhibitors, which provided favorable results in RCTs, as a class IIb indication in patients with statin intolerance and in patients with persistently high LDL-C levels who fail to achieve the target despite maximal treatment with a statin or statin-ezetimibe combination.

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Question 29 – Is statin use actually cost-effective?

Dr. Yücel Balbay

Turkey Higher Specialization Training and Research Hospital Cardiovascular Diseases Clinic, Economy Specialist, Ankara.

In essence, the cost-effectiveness of statin use for coronary artery disease depends on two main parameters. The first parameter is the absolute risk, and the second one is the price of statins. Statins are cost-effective at high absolute risk levels. However, there are uncertainties with low risk levels.^[1]

The cost-effectiveness of statins essentially depend on the absolute risk. Statin treatment is cost-effective at high absolute risk levels while there is some uncertainty regarding low risk levels. Statin treatment is a cost-effective intervention used to treat the members of the population with high cardiovascular risk levels (>4%/year); however, it is not cost-effective for treating individuals at low risk levels (<1%/year).^[1]

Compared to standard lipid-lowering therapies, early use of high doses and potent statins reduce mortality risk and major cardiovascular events in Acute Coronary Syndrome. Relatively high dose-

standard dose cost-effectiveness models also support the administration of high doses for acute coronary syndrome patients.^[2]

Administering statin treatment in large segments of the population is also thought to be susceptible to statin prices. In a study assuming only generic drug prices, it was foreseen that treating between 61% to 67% of the adult population would be cost-effective.^[3]

In a systemic analysis which included an economic assessment carried out under the sponsorship of the pharmaceutical industry, cost-effectiveness trends in primary cardiovascular prevention were shown mostly for their own products.^[4]

In conclusion, statins are highly cost-effective for patients diagnosed with coronary artery disease.^[5]

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Question 30 – What is the effect of dietary fats on cardiovascular events?

Dr. Murat Tuzcu

Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH, USA

Epidemiologic and clinical trial data support the relationship between foods rich in saturated fatty acids (SFA) and higher LDL cholesterol levels and cardiovascular disease (CVD) risk. There is evidence from nutritional studies supporting the practice of reduced SFA consumption. (1) Having said that, I should also note the complexity of these relationships. Curtailing the consumption of SFAs has a variable effect on lipid and risk profiles due to a number of factors, such as overall diet that SFAs are consumed with, heterogeneity of the SFAs, individual variability of the response due to genetic and other factors including insulin resistance and obesity and importantly choice of replacement macronutrient. (2)

The studies showing the deleterious effects of replacing SFA by refined carbohydrates are convincing but do not negate the role SFA in the development of CVD. Studies in which SFA were replaced by poly or monounsaturated fatty acids revealed significant improvements in lipid profile and reduction in CVD risk. (3) But are all the latter fats healthy? There are studies suggesting that some are not. For example there are data showing omega 6 fatty acids, unlike omega-3 fatty acids which are widely regarded as protective, do not reduce the CVD

risk. Similarly there are studies suggesting heterogeneity among the SFAs in regard to their impact on serum LDL levels and CVD risk and need for their replacement.

Replacing one macronutrient with another is an oversimplified solution that is not always appropriate. Accordingly many experts shifted their focus to the food groups and dietary patterns. This approach led to more consistent findings. For example dietary patterns such as Mediterranean diet containing healthy food groups improve lipid profile and reduce CVD risk. This and similar diets are rich in vegetables, legumes, fruits, nuts, fish, poultry, olive oil but limited in red meat, refined carbohydrates and SFAs. (4)

Adopting healthy dietary patterns early in life would minimize the risk of CVD as well as many other chronic health problems including, diabetes, hypertension and some cancers. Recent research findings clearly demonstrate that the impact of risk factors becomes more powerful as time goes on. Minimizing the time span that the vascular cells are exposed to high LDL cholesterol by replacing the excess SFAs in the food by PUFAs and MUFAs would lead to healthier blood vessels.

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Question 31 – What are the dietary considerations for a patient with high LDL-cholesterol levels?

Dr. Meral Kayıkçıoğlu

Ege University Faculty of Medicine, Cardiology Department, İzmir

Patients with high LDL-cholesterol (LDL-C) levels must follow a diet regardless of whether they receive medication or not. The diet to be followed by these patients does not have to restrict all types of fats, in other words a "balanced fatty" diet should be recommended instead of a completely fat-free diet.^[1-3]

Low fat diet regimens initially proposed in 1980s (limiting the amount of fat coming from the diet to 30% of the total calorie intake) and the fat-free diet proposed in 2005 (so that it does not exceed 20-35% of the total calorie intake) are no longer employed. The objective of restricting fats was to limit the consumption of saturated fats and cholesterol which are thought to elevate serum (LDL-C) levels and increase cardiovascular risk (CV).[2] At the same time, this is also important for obesity as fats contain twice as much calories compared to carbohydrates and protein. However, low-fat diet policy has not reduced CV mortality over the past 40-year period. The actual problem here was increasing carbohydrate intake in order to fulfill the energy requirements arising as a result of reduced fat consumption. Randomized controlled studies and meta-analyses have revealed that replacing unsaturated fats with carbohydrates would elevate serum triglyceride levels, reduce HDL-C and trigger diabetes and obesity in the long-term.^[3] Another inevitable negative result of restricting total fat intake is the reduction of consumption of fish, dry nuts and other vegetable unsaturated fats which are beneficial for health. While replacing saturated fats with unsaturated fats (particularly polyunsaturated in diet studies) reduced total cholesterol and LDL-C levels at a statistically significant rate, it was also shown to reduce CV disease risk and coronary mortality. Replacing the energy obtained from each 1% of

saturated fats with polyunsaturated fats reduces CV diseases by 2-3%. According to a 2012 meta-analysis, reducing and modifying saturated fats decrease CV events by 14%. This preventive effect results from the modification of the fats rather than the reduction of total amount of fats consumed, and it is especially apparent in long-term (2 years and above) studies.^[4]

In light of the available evidence, American Dietary Guidelines published in 2015 recommend 'balanced fat nutrition' with reduced saturated fats without restricting the total amount of fats instead of low-fat diets.^[1-3] The guidelines have maintained the recommendation that "the calorie intake from saturated fats should not exceed 10% of total energy". However, reduced saturated fat intake should be balanced with increased poly- or monounsaturated fat intake instead of by increasing the carbohydrate consumption.

2015 American Guidelines highlight that non-hydrogenated vegetable oils (soy, corn, olive and canola oils) should be preferred instead of animal fats and tropical oils (palm, coconut oil etc.) given that they contain higher levels of unsaturated fats and lower levels of saturated fats. Partially hydrogenated vegetable oils containing trans fats should be avoided at all costs as they increase the risk of CV disease risk.

In summary, fat-free diet strategy which reduces the total fat intake has been completely abandoned in light of scientific data. On the contrary, the focus has been directed on diets comprised of more fruits, vegetables, legumes and sea food with less meat (reduced saturated fats) and less sugar-sweetened food and beverages.

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Question 32 – Does genetic background affect absorption of dietary cholesterol? Is this clinically relevant?

Dr. Zeynep Tartan

Ataşehir Memorial Hospital, Cardiology Clinic, İstanbul

Dyslipidemia is a significant risk factor in the etiopathogenesis of atherosclerotic disease. Therefore, dietary recommendations have a crucial part in regulating serum lipid levels. However, when saturated fat and cholesterol are limited in diet, apparent decrease is observed in blood cholesterol levels of some individuals while no such difference is seen in others. Therefore, the fact that not everyone experiences the expected decrease suggests that there may be individual genetic differences.

In order to understand the genetic differences regarding the link between diet and blood cholesterol levels, various gene polymorphisms responsible for lipid metabolism have been investigated. The most frequent genetic differences that are investigated include apolipoprotein (Apo) E, Apo-B, Apo-CIII, Apo-A4, lipoprotein lipase, hepatic lipase, endothelial lipase, cholesteryl ester transfer protein (CETP), hepatic fatty acid binding protein (FABP), beta-3 adrenergic receptor, adiponin and peroxisome proliferator-activated receptor gamma, microsomal triglyceride transfer protein, and "scavenger" receptor class B type I. However, due to inconsistent results between studies and extensive individual differences, it is not clearly determined which genetic factor(s) play a role in the relevant mechanism. This suggests that other factors apart from the investigated polymorphisms of Apo, receptor, and enzymes may be effective in determining diet-blood-lipid levels. Diet content, life style, presence of other

physiological and pathological diseases other than genetic factors are known to be effective. For example, adding 1 egg per day to a vegetarian diet significantly affects blood cholesterol levels while adding even 2 eggs per day does not affect cholesterol levels in the American diet which is rich in cholesterol and saturated fat. Furthermore, ABCG5 and ABCG8 have a critical role in cholesterol absorption apart from the investigated polymorphisms, and the mutation prevalence of these two genes is frequent in the population. This result is significant as it is not highly surprising that the interactive diet-blood-lipid differences are more frequent than expected in terms of genetic explanation.

However, the question regarding its usefulness in our daily practice currently awaits a clear answer. "Nutrigenetics", in other words the science of "diet-gene interaction" is a currently developing field which promises future for treatment with nutrition recommendations personalized for genetic traits of individuals. Nevertheless, it is still early to recommend using these gene polymorphisms, which have been investigated in available studies, as biomarkers in patients with hyperlipidemia. It is pleasing that more effective personalized methods will be available for prevention from cardiovascular disease in the future with the advances in nutrigenomics.

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Question 33 – Do plant sterols and stanols play a role in lipid-lowering treatment?

Dr. Bengi Başer

Giresun University Faculty of Medicine, Cardiology Department, Giresun

Plant sterols (phytosterols) are naturally found in vegetable oils, oilseeds, plant seeds, cereals and grains. The most common sterols in plants are beta sitosterol (80%), stigmasterol, campesterol and ergosterol. Plant stanols are saturated forms of sterols, and are present in trace amounts in sources such as corn and wheat. Although there is common belief that consuming dietary phytosterols reduces blood cholesterol levels, thereby decreasing the risk of atherosclerotic cardiovascular disease (ASCVD), there is no scientific evidence on this subject. While the mechanism of action is not fully understood, plant sterols are claimed to lower the cholesterol content of micella, and therefore decrease the transport to intestinal brush border. Furthermore, their effect on the transport-mediated cholesterol uptake process is also known.^[1]

We need evidence based scientific studies in order to offer rational recommendations for the role of plant sterols and stanols in lipid-lowering treatment. European Society of Cardiology 2016 Guidelines on Prevention of Cardiovascular Diseases state that plant sterols and stanols lower LDL-cholesterol (LDL-C) levels by 10% on average when consumed 2 g/day.^[2] Furthermore, this is an additional effect observed following statin treatment and a diet containing low levels of fat. However, there is no long-term clinical study to date with a relevant clinical endpoint. Although American 2015 Dietary Guidelines do not have a particular emphasis on sterol and stanol consumption, they recommend increasing vegetable and fruit consumption.^[3] American Heart Association 2016 Consensus Report on the Use of Non-Statin Anti-lipid Agents for Management of ASCVD points out lifestyle modifications and encouragement of plant sterols consumption in patients who cannot receive the desired dose due to side effects or fail to achieve optimal response although a sufficient dose is used for secondary prevention.^[1] Furthermore, in

addition to moderate statin treatment, lifestyle modifications and using plant sterols are emphasized for the individuals between the ages of 40 and 75 years with diabetes and without high risk criteria whose LDL-C levels are between 70-189 mg/dL with a 10-year cardiovascular risk of <7.5%. Plant sterol use as a recommendation stands out in individuals between the ages of 40 and 75 years with ASCVD or with a 10-year cardiovascular risk above 7.5% without diabetes whose LDL-C levels are between 70-189 mg/dL under statin treatment for primary prevention. The same guidelines present as an FDA approved recommendation that twice daily consumption of nutrients containing 0.65 g plant sterol esters in a portion together with food is necessary in order to ensure minimum 1.3 g daily intake as part of a diet which is poor in saturated fat and cholesterol. A daily plant sterol intake of 2 g lowers LDL-C levels by 5-15%, but consumption above 3 g/day does not provide any additional benefit. However, there are studies advocating that further plant sterol consumption provides more reduction in cholesterol levels.^[4] Guidelines point out that there is no available data showing that plant sterols and stanols provide a moderate cholesterol lowering effect or that they are well-tolerated and have effects on cardiovascular morbidity and mortality. Furthermore, the literature also contains some studies demonstrating negative effects on endothelial function with oxidized beta sitosterol.^[5]

In conclusion, in light of the current guidelines, plant sterols and stanols should not be used instead of statin treatment; and they may be used as an additional treatment method together with intensified lifestyle modifications in patients with insufficient results, however, they do not offer any positive effects at higher amounts than recommended, and some scientific data indicate that there may even be potential negative effects in this setting.

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Question 34 – Does the consumption of natural omega 3, 6 and 9 sources play a role in cardiovascular prevention?

Dr. Cihan Örem

Karadeniz Technical University Faculty of Medicine, Cardiology Department, Trabzon

Omega-3 fatty acids (FA) are polyunsaturated FAs which are naturally found in seafood (oily fish such as salmon, trout, tuna, anchovy, sardine, mackerel, and thunnus), flaxseed, and walnuts. Among omega-3 FAs; eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are abundantly found in seafood, are especially important. Protective effect of seafood on cardiovascular (CV) diseases results from their omega-3 FA content. In CV prevention guidelines published in 2016 by European Society of Cardiology (ESC), consumption of fish 1-2 times a week, one being an oily fish, is considered as a trait of healthy diet.^[1] A meta-analysis of prospective cohort studies showed that consuming fish at least once a week lowers coronary artery disease (CAD) by 16% compared to less consumption.^[2] 2015 American Dietary Guidelines recommend moderate seafood consumption, and consuming approximately 230 g fish (250 mg/day EPA and DHA) is associated with reduced number of cardiac deaths in individuals with or without CV disease.^[3] In the CV disease: Risk Assessment and Reduction Guidelines, the National Institute for Health and Care Excellence (NICE) recommends consuming minimum 2 portions of fish a week, one being an oily fish, for patients at high risk or with CV disease.^[4]

Omega-6 FA (linolenic acid and gamma linolenic acid) is an unsaturated FA found in vegetable oils (canola oil, corn oil, soybean oil, and sunflower oil etc.), red meat, poultry, and eggs. Omega-9 FA (oleic acid) is a monounsaturated FA found in vegetable oils (canola oil, olive oil, hazelnut oil, and sunflower oil), avocado, several nuts, and also in animal fat in a

small amount. ESC CV prevention and American dietary guidelines recommend reducing the amount of saturated fat to quantify less than 10% of the total dietary energy intake and replacing these fats with oils containing polyunsaturated FAs such as omega-3 and 6.^[1,2] Increasing polyunsaturated FAs in the diet has been shown to reduce total cholesterol and LDL-cholesterol levels and it also lowers the CAD risk by 2-3%.^[1] In a meta-analysis, consuming unsaturated fat instead of saturated fat was found to lower CV events by 14%.^[5] Although there are a few literature studies on replacing saturated FA with carbohydrates and monounsaturated FA compared to polyunsaturated fat, beneficial results are not clearly shown in such studies.^[1,2] In guidelines, it is emphasized that vegetable oils (soy bean, maize, olive, and canola oils) should be preferred to animal derived fat as they are rich in unsaturated fat content and contain low amounts of saturated fat.^[1,2] Mediterranean die, which contains high amounts of fruits and vegetables, cereals and legume, fish and unsaturated FA, moderate alcohol with low amounts of red meat and saturated FA is one of the healthy diets recommended in American diet guidelines.^[2] In a meta-analysis of prospective cohort studies investigating the effects of this diet, the rate of CV disease or death was shown to be reduced by 10% and all-cause mortality by 8%.^[6]

In conclusion, it is recommended to reduce saturated fat intake and to increase consumption of natural sources of polyunsaturated fat such as omega-3 and 6 without reducing the amount of total fat for CV prevention.

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Question 35 – To what extent does lifestyle affect LDL-cholesterol levels?

Dr. Dilek Yeşilbursa

Bursa Uludağ University Faculty of Medicine, Cardiology Department, Bursa

Dietary treatment and lifestyle modifications (LM) have a major role at every stage of hyperlipidemia treatment. LM includes limiting foods which increase LDL-cholesterol (LDL-C), using food supplements containing soluble fibers and plant stanols/sterols, increasing physical activity, maintaining ideal weight, smoking cessation, and decreasing alcohol consumption.^[1]

As part of LM, saturated fat including trans fats in the diet is recommended to not exceed 10% (7% in patients with hypercholesterolemia) of the daily calorie intake. Each 1% reduction in saturated fats decreases serum cholesterol levels by 2%. In the DELTA study, amount of saturated fats in the diet was reduced from 15% to 6% of the total calorie intake, and LDL-C levels were shown to decrease by 11%.^[2] In a meta-analysis, Gordon et al. stated that decreasing saturated fat intake lowers serum cholesterol levels and decreases the risk of coronary artery disease by 24%.^[3] Similarly, a trend to coronary mortality reduced by 21% and total mortality decreased by 6% have also been observed.

Soluble fibers lower LDL-C levels by decreasing fat absorption from the intestines. Soluble fiber intake of 5-10 g in daily diet decreases LDL-C by 5% on average. Consuming 2 g plant stanols/sterols daily lowers LDL-C by 6-15%.

Although plant sterols are clearly demonstrated to lower LDL-C, there is no study investigating their effects on cardiovascular events. A meta-analysis by Robinson et al. showed that LDL-C lowering decreases cardiovascular events independent from the mechanism.^[4]

Weight loss affects LDL-C; however, to a small extent where LDL-C concentrations decrease by approximately 8 mg/dL with a weight loss of 10 kg in overweight individuals. As weight loss often improves cardiovascular risk factors in obese or overweight individuals, calorie intake must be decreased and energy consumption must be increased in such individuals.

Regular exercise results in a small decrease in LDL-C levels.

Table 1. Effects of lifestyle modifications on LDL-C

	Decrease in LDL-C%
Reducing saturated fat	8-10
Reducing dietary cholesterol	3-5
Weight loss (losing 5 kg)	5-8
Soluble fiber	3-5
Plant sterols & stanols	6-15
Cumulative	20-30

However, in order to benefit from exercise, it should be performed regularly for a certain period of time. In a meta-analysis of 52 exercise studies investigating exercise duration longer than twelve weeks in 4700 individuals, LDL-C levels were shown to decrease by 5%.^[5] In the “HERITAGE” trial, which is the largest controlled study on exercise to date, 675 normolipidemic individuals followed an exercise program for 5 months, and at the end of the study, LDL-C was observed to decrease by 0.8% in males, and by 0.6% in females.^[6] Moderate weight loss and regular moderate exercise are very effective in improving other cardiovascular disease risk factors; therefore at least 30 minutes daily physical exercise is recommended. Studies where exercise was performed together with a diet containing low saturated fatty acid, LDL-C levels were shown to be reduced by 7-15%. Patients who exercise and follow a diet containing plant sterols and soluble fibers have achieved 8-30% LDL-C reduction.^[7] Following a diet and exercise together creates an additive or at least a synergistic effect.

According to NCEP ATP III, approximate changes on LDL-C by LM are shown in Table 1. Decrease in LDL-C with LM is generally not sufficient to achieve target levels in high-risk patients and patients with cardiovascular disease. Medication is often required to achieve target LDL-C levels.

LDL-C levels may be re-evaluated during the second visit at 6 weeks after the initial recommendations, and if sufficient LDL-C levels are not achieved, the necessary advice should be given in order to encourage adherence to recommendations. LDL-C levels should be checked again in six weeks, and if sufficient control is still not achieved, medication should be started. Patient's adherence to LM should be evaluated again in 4 to 6 months.

In the first year, controls are conducted every 4-6 months, and then every 6-12 months in the following years. Lifestyle modifications are recommended to

continue for life as add-on to medication or as a single solution for suitable patients.

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Question 36 – Does obesity lead to hypercholesterolemia?

Dr. Füsün Saygılı

Ege University Faculty of Medicine, Endocrinology and Metabolism Diseases Department, İzmir

Obesity is one of the leading causes of secondary hyperlipidemia. All obese and overweight patients should be screened for dyslipidemia. Patients with dyslipidemia should be evaluated in terms of being overweight. In young adults who start to gain weight, dyslipidemia has been determined to be the first cardiovascular (CV) risk factor. In atherogenic dyslipidemia in obese individuals: 1) Triglycerides (TGs) and small low-density LDL-cholesterol (LDL-C) levels increase while HDL-cholesterol (HDL-C) decreases; 2) Post-prandial hyperlipidemia may occur with isolated HDL-C decrease or TG increase; 3) It may sometimes occur with increased LDL-C; lower LDL receptor expression is observed in these patients; 4) familial dyslipidemia may become severe.

Lipoprotein lipase (LPL) mRNA expression in adipose tissue and LPL activity in muscle tissue decrease in obese patients; and VLDL and chylomicrons compete for lipolysis. Lipolysis in lipoproteins rich in TG slows down. Hepatic lipase activation follows the cholesteryl ester transfer protein-mediated (CETP) change of TG in these remnants and cholesterol esters in HDL-C, resulting in small low-density LDL particles. Cholesterol content is reduced and TG content is increased in small low-density LDL, which occurs in hypertriglyceridemia. Small low-density LDL is metabolized slower than LDL, and its atherogenicity is higher. There is increased subendothelial retention as well as oxidation in small low-density LDL with high proteoglycan affinity.

Increased chylomicron remnants and VLDL levels are responsible for atherosclerosis in obesity. Direct relationship to coronary, cerebral, and peripheral arterial diseases have been demonstrated. The increase in TG-rich particles increase CETP activity. This allows the change of HDL cholesterol esters and TGs in VLDL and LDL. As HDL lipolysis rich in TG reduces Apolipoprotein (Apo) A1 affinity, Apo-A1 and HDL differentiate. Consequently, cholesterol

transfer is disrupted and lower HDL-C levels are seen.

The first step of treatment in obesity-associated dyslipidemia consists of lifestyle modifications (LM). LM means healthy eating and regular exercise. The amount of fat consumption and calorie intake are the predictors of obesity and post-prandial hyperlipidemia. LPL activity increases with weight loss due to limitation of calories. TG concentration, Apo-C3 level, and CETP activity decrease due to the increase in LPL activity. Weight reduction of 4-10 kg in obese individuals allows a 27% increase in LDL receptor mRNA and a 12% decrease in LDL-C levels. Exercise increases TG lipolysis by increasing LPL and hepatic lipase activity.

Dyslipidemic changes specific to obesity determine the goals of medical treatment. Treatment goals are LDL as well as Apo-B and non-HDL cholesterol. According to a meta-analysis, when these levels are targeted, 300-500 thousand CV events may be prevented in 10 years in the USA. Statins are among the drugs that lower LDL-C, non-HDL cholesterol, and Apo-B. However, as statins lower TG levels to a small extent, they are not sufficient to correct the characteristic dyslipidemia in obese patients. Fibrates have a primary indication in hypertriglyceridemia. They lower LDL-C levels by 8% and triglycerides by 30%; and increase HDL-C by 9%. Nicotinic acid reduces adipocyte lipolysis, free fatty acids and VLDL synthesis; and increase HDL-C levels. While TGs decrease by 15-35%, HDL-C increases by 10-25%. Omega 3 fatty acids reduce hepatic synthesis and deposition of TGs and decrease the plasma levels by 25-30%. Furthermore, they increase IDL formation from VLDL, and also increase VLDL, IDL, and LDL catabolism. Secondary dyslipidemia due to obesity also benefits from bariatric surgery. TGs are shown to decrease by 63%, while VLDL is reduced by 74% and LDL-C levels decrease by 31% following the RYGB (Roux en Y gastric bypass) type bariatric surgery.

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Question 37 – What is the mechanism of action of statins?

Dr. İnan Soydan

Retired Prof. Dr., Ege University Faculty of Medicine, Cardiology Department

Statins are also known as "HMG-CoA reductase inhibitors". This is because these agents exert their major effects, i.e. lowering total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) by inhibiting the HMG-CoA enzyme, which plays a vital role in cholesterol synthesis, through competitive inhibition and by means of a portion similar to mevalonic acid.

Statins lower blood cholesterol levels by inhibiting hepatic cholesterol synthesis and increasing LDL receptors. In response to the decreased free cholesterol extent in hepatocytes, the membrane-bound sterol regulatory element-binding proteins (SREBPs) are cleaved by a protease and transferred to the cellular nucleus. Subsequently, "transcription factors" bind by means of the LDL receptor gene element responsible for the sterol, enhancing "transcription" and thereby leading to increased LDL receptor synthesis. At the same time, breakdown of LDL receptors decreases as well. The increased number of LDL receptors on hepatocytes increase the amount of LDL clearance from the blood, resulting in lower LDL-C levels. Statins lower LDL-C levels by 20-55% depending on the statin type and the dose.

Furthermore, there are studies suggesting that statins may also lower LDL levels by reducing hepatic VLDL production and by enhancing blood clearance of LDL precursors such as very low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL). The statin-associated decrease in hepatic VLDL production is thought to be mediated by reduced synthesis of cholesterol, which is required for VLDL formation. This mechanism is likely to be also involved in the triglyceride (TG) reducing effects of statins. TG levels above 250 mg/dL decrease dramatically with statins and the rate of this reduction tends to be the same as that of LDL-C. Accordingly, a 35-45% decrease is seen in LDL-C levels of patients with hypertriglyceridemia receiving the highest doses of potent statins (e.g. daily simvastatin or atorvastatin 80 mg) and a similar reduction is observed in their fasting TG levels. In the event of pre-treatment TG levels below 250 mg/dL, the reduction in TG is unlikely to exceed 25% , regardless of the statin dose.

In the cholesterol synthesis pathway, intermediate molecules of dimethylallyl pyrophosphate are converted to geranyl pyrophosphate and finally to farnesyl pyrophosphate by prenyltransferase. This is the step before squalene formation. These mediators called geranylgeranyl and farnesyl are involved in protein prenylation, which refers to the covalent bonding between a lipid particle and a protein (which enhances the binding to cellular membranes and their biological effectiveness). GTP-binding proteins (Rho A, Rac and Ras) undergo this process. Indeed, statins may partially increase high-density lipoprotein cholesterol (HDL-C) by preventing the phosphorylation of "peroxisome proliferator-activated receptor (PPAR α)", a factor involved in the regulation of geranylgeranylation of Rho A and apolipoprotein A-I transcription.

Statins decrease cardiovascular events not only in patients with hypercholesterolemia but also in subjects with normal cholesterol levels. Clinical studies and observations have demonstrated that statins have other beneficial effects and that they are independent from lipid levels. These beneficial effects of statins which are independent from cholesterol (or, with a broader definition, from blood fats) are termed as "pleiotropic effects" and include improved or restored endothelial function, reduced oxidative stress and vascular inflammation, increased stability in atherosclerotic plaques and inhibition of thrombogenic response. Furthermore, some studies have shown beneficial extra-hepatic effects of statins on the immune system, central nervous system and bones. Statins may show pleiotropic effects by inhibiting conversion of HMG-CoA to L-mevalonic acid. This is because they inhibit the synthesis of major isoprenoids, which are the precursors of cholesterol synthesis as well as lipid junctions of intracellular signaling molecules. The statin-triggered inhibition of Rho GTPases on vascular wall cells enhances the proliferation of vascular smooth muscle cells and expression of genes that provide protection against atherosclerosis.

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Question 38 – Which statin and which dose should be used to initiate treatment?

Dr. İzzet Tandoğan

Sırtmapınarı Gözde Hospital, Cardiology Clinic, Malatya

Statins are among the most widely studied drugs in prevention of cardiovascular (CV) diseases and these agents decrease CV mortality in all populations they have been evaluated except for patients with heart failure and patients undergoing hemodialysis.

According to the data obtained from meta-analyses, clinical benefits of statin treatment depend on the reduction of low-density lipoprotein cholesterol (LDL-C) rather than the type of statin treatment.^[1] LDL-C reduction is primarily associated with the statin dose, and the type of statin is also a contributing factor (Table 1).^[2] There may be inter-individual differences in the efficacy obtained with statins. These differences may be explained with factors such as patient non-compliance and different genetic background.^[1]

Current guidelines recommend establishing the total CV risk and a LDL-C target based on this risk ratio in a patient planned to receive treatment. According to this target, it should be determined to what extent the LDL-C level will be lowered and which type and dose of statin is to be used.^[1] ESC 2016 Dyslipidemia Guidelines determine the proportional LDL-C lowering rate required to achieve the target LDL-C level based on baseline LDL-C value and the relevant risk level (Table 2), and recommend choosing a statin dose (Figure 1) which can provide the target reduction. In the event of failure to achieve the target, the recommendation is initial dose titration, followed by planning combination treatment.^[2]

These guideline recommendations are general recommendations and may gain meaning only with the physician's discretion. Factors such as the patient's clinical condition, concurrent medications and drug cost should also be taken into account while choosing the drug and the dose. Upon decision to use a statin, the factors to be considered are high efficacy and low cost criteria.

For primary prevention, it is a reasonable approach to initiate treatment with atorvastatin 20 mg in a patient whose 10-year CV disease risk is 10% or higher. It would also be reasonable to initiate treatment with atorvastatin 20 mg in patients > 40 years of age with type 1 diabetes or those with long-term diabetes, i.e. longer than 10 years, or in patients with nephropathy/other CV disease risk and in subjects with type 2 diabetes for whom the 10-year CV disease risk is 10% or higher.^[2]

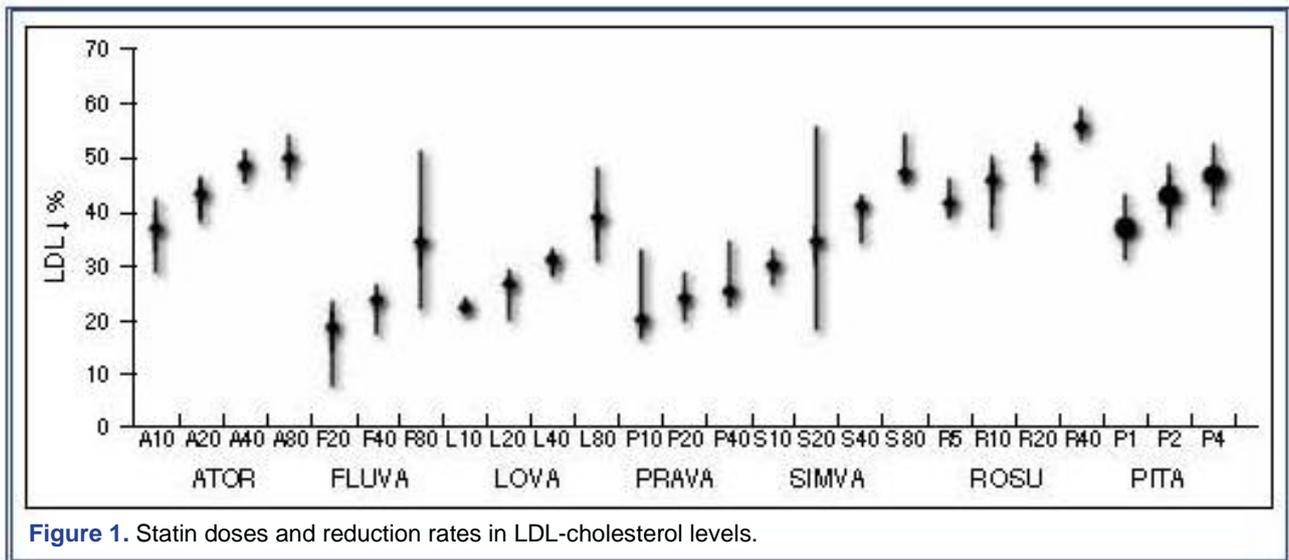
Table 1. Statin doses and reduction rates in LDL-cholesterol levels

Dose (mg/day)	Reduction in LDL-cholesterol level (%)				
	5	10	20	40	80
Fluvastatin	10	15	21	27	33
Pravastatin	15	20	24	29	33
Simvastatin	23	27	32	37	42
Atorvastatin	31	37	43	49	55
Rosuvastatin	38	43	48	53	58

Table 2. The desired reduction in LDL-C levels (%) to achieve the targets as a function of the baseline LDL-C value

Index (baseline) LDL-C level (mg/dL)	The LDL-C reduction (%) required to achieve the target LDL-C value		
	<70 mg/dL	<100 mg/dL	<115
> 240	> 70	> 60	> 55
200-240	65-70	50-60	40-55
170-200	60-65	40-50	30-45
150-170	55-60	35-40	25-30
130-150	45-55	25-35	10-35
110-130	35-45	10-25	<10
90-110	22-35	<10	-
70-90	<22	-	-

Treatment may be initiated with atorvastatin 80 mg for the secondary prevention of patients with established CV disease.^[2] While these data highlighting atorvastatin also reflect my personal approach, they are primarily based on NICE guidelines.^[2] Generally, the aim of hypercholesterolemia treatment is to achieve 50% reduction in LDL-C levels. Atorvastatin is highlighted in this paper due to the fact that it provides significantly increased efficacy in short dose intervals without any notable difference in the side effect profile.



This does not mean that other agents cannot be used. Although not data from guidelines, the subgroup analysis of the STELLAR study highlights that similar

results may also be obtained with rosuvastatin in all groups.^[3]

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Question 39 – What are the equivalent doses of different statins?

Dr. Mehmet Akbulut

Firat University Faculty of Medicine, Cardiology Department, Elazığ

Statins increase the expression of LDL receptors which allow low-density lipoprotein (LDL)-cholesterol (LDL-C) intake to hepatocytes via receptor-dependent endocytosis. Statins inhibit hepatic apolipoprotein B100 synthesis as well as reducing the synthesis and release of triglyceride-rich lipoproteins.^[1] Statins are the most potent LDL-C lowering agents among the available lipid-lowering drugs, providing 25-45% reduction in LDL-C, 5-15% increase in high-density lipoprotein (HDL)-cholesterol (HDL-C) and 7-30% reduction in triglyceride levels with standard doses.^[2]

Despite having similar mechanisms of action, statins may differ in terms of daily doses, excretion and solubility. While atorvastatin, serivastatin, fluvastatin, pravastatin and rosuvastatin are taken as

active drugs; lovastatin and simvastatin are prodrugs which are converted to their active form, i.e. hydroxy acid in the liver. Taken together, statins differ in terms of dose-dependent LDL-lowering efficacy; in other words, different statins have different LDL-C lowering capacities at their recommended doses. For example, the 10, 20, 40 and 80 mg/day doses of atorvastatin decrease LDL-C by 30-40%, 40-45%, 45-50% and 50-55% on average, respectively, while the equivalent doses of pravastatin at the same mg dosing (namely the 10, 20, 40 and 80 mg/day doses) reduce LDL-C by 10-20%, 20-30%, 30-40% and 40-45% on average, respectively^[3] (Table 1). Generally, doubling the dose during statin treatment provides an additional 7% reduction in LDL .^[4] On the other hand, the effects on HDL-cholesterol are not dose-dependent.

Table 1. Equivalent doses and pharmacological properties of statins

Equivalent doses						
Reduction in LDL cholesterol (%)	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
10-20	–	20 mg	10 mg	10 mg	–	5 mg
20-30	–	40 mg	20 mg	20 mg	–	10 mg
30-40	10 mg	80 mg	40 mg	40 mg	5 mg	20 mg
40-45	20 mg		80 mg	80 mg	50-10 mg	40 mg
46-50	40 mg				10-20 mg	80 mg ¹
50-55	80 mg				20 mg	–
56-60	–				40 mg	–
Pharmacological properties						
Starting dose	10-20 mg	20 mg	10-20 mg	40 mg	10 mg ²	20 mg
In patients with a higher LDL-lowering target	40 mg (>45%)	40 mg (>25%)	20 mg (>20%)	–	20 mg (LDL >190 mg/dL)	40 mg (>45%)
Renal clearance (%)	2	6	30	60	10	13
Half life (hours)	13-16	0.5-1	2-3	1-3	15-20	2-3
Solubility	Lipophilic	Hydrophilic	Lipophilic	Hydrophilic	Lipophilic	Lipophilic
Ideal timing	Anytime	Evening	Evening	Anytime	Anytime	Evening

¹ Long-term use of the 80 mg dose is not recommended due to the high risk of rhabdomyolysis.

² 5 mg in subjects over sixty-five years of age, in patients with hypothyroidism and in Asians.

However, the currently available evidence suggest that the clinical benefit is independent from the statin type while it depends on the extent of reduction in LDL-C levels. Therefore, the statin type preferred for treatment should reflect the required LDL-C reduction to achieve the LDL-C target in a given patient.^[5] For this reason, treatment targets for

LDL-C should be determined in different risk groups; followed by focusing on target LDL-C levels and using the appropriate type and dose of statin which may allow rapid achievement of the relevant target based on the baseline low-density lipoprotein cholesterol level (Table 2).

Table 2. High-, moderate-, and low- intensity statin treatment

High-intensity statin treatment	Moderate-intensity statin treatment	Low- intensity statin treatment
Average daily doses providing approximately $\geq 50\%$ LDL cholesterol reduction	Average daily doses providing approximately 30-50% LDL cholesterol reduction	Average daily doses providing approximately $<30\%$ LDL cholesterol reduction
Atorvastatin 40 (80) mg	Atorvastatin 10 (20) mg	Fluvastatin 20–40 mg
Rosuvastatin 20 (40) mg	Fluvastatin XL 80 mg	Lovastatin 20 mg
	Fluvastatin 40 mg bid	Pravastatin 10–20 mg
	Lovastatin 40 mg	Simvastatin 10 mg
	Pravastatin 40 (80) mg	Pitavastatin 1 mg
	Rosuvastatin 5 (10) mg	
	Simvastatin 20–40 mg	
	Pitavastatin 2–4 mg	

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Question 40 – What is statin resistance? Which pathologies should be considered?

Dr. Öner Özdoğan

İzmir Tepecik Training and Research Hospital, Internal Diseases Department, İzmir

Some patients who fail to achieve the target LDL-cholesterol (LDL-C) level despite the most appropriate treatment, which often means the maximum tolerated statin dose, are accepted as statin-resistant patients. According to the EURO-ASPIRE-4 study, many patients fail to achieve their LDL-C targets. In our country, LDL-C levels are lowered to less than 70 mg/dL with statin treatment only in 10% of the patients. In other words, there are serious inter-individual differences in dyslipidemia treatment with statins. Although the response to treatment is more prominent in the elderly, significant drug interactions may alter the response. Response to statin treatment is observed to be poor in women compared to men. Statin resistance is usually associated with drug absorption and transport, hepatic drug metabolism, drug metabolism in other organs and excretion pathways of the drug. Apart from failure to achieve LDL-C targets, failure to achieve improvement in ADMA-associated endothelium-dependent vasodilation during statin treatment may also be defined as statin resistance.

Several different factors contribute to statin resistance. Smaller LDL-C reductions with statin treatment are observed in smokers compared to non-smokers^[1] and in subjects with hypertension compared to non-hypertensive subjects. Inflammatory cytokines, particularly interleukin-1 β may cause statin resistance by disrupting the "feedback" regulation of the LDL receptor. Therefore, high statin concentrations are required for adequate LDL-C lowering in conditions with increased inflammation.^[2] Smaller LDL-C reductions with statin treatment are also seen in HIV (+) patients.^[3] During the concurrent

use of statin and amiodarone, statin resistance may occur as both amiodarone treatment and amiodarone-associated hypothyroidism affect the synthesis of LDL receptors.^[4]

Genetic polymorphisms of the genes and proteins involved in the synthesis, absorption and transport of cholesterol contribute to the response to statin treatment. The pharmacodynamic and pharmacokinetic genetic variations commonly associated with statin resistance are as follows; 3-P-glycoprotein (Pg-P/ABCB1), breast cancer resistance protein (BCRP/ABCG2), multidrug resistance-associated proteins (MRP1/ABCC1 and MRP2/ABCC2), organic anion transporter polypeptides (OATP), RHOA, Nieman-Pick C1-like-1 protein, farnesoid X receptor, cholesterol 7 α -hydroxylase (CYP7A1), apolipoprotein E, proprotein convertase subtilisin/kexin type 9 (PCSK9), LDL receptor (LDLR), lipoprotein(a), cholesteryl ester transfer protein and tumor necrosis factor- α .^[5] However, the currently available evidence are not sufficient to require pharmacogenetic tests prior to initiating statin treatment.^[6]

In conclusion, several metabolites in various pathways with or without direct relation to cholesterol metabolism may affect the response to statin treatment. On the other hand, it should be noted that the main cause of inadequate LDL-C response to statin treatment may be the pseudo-resistance resulting from irregular drug use in real world setting.

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Question 41 – How should be the therapeutic approach in patients who fail to achieve target values with statin treatment?

Dr. Adnan Abaci

Gazi University Faculty of Medicine, Cardiology Department, Ankara

Lipid levels should be evaluated 4-12 weeks after initiating statin treatment. In patients who achieve their lipid targets, lipid levels should be evaluated every 3-12 months based on the clinical condition. In patients who fail to achieve target lipid levels; adherence to statin treatment should be evaluated, lifestyle modifications should be intensified, dose should be increased unless the patient is already receiving high-dose statin, and other risk factors should be managed. Adding other drugs to statin treatment should be considered in patients who fail to achieve their lipid targets despite the aforementioned interventions.

The Improve-IT study found it beneficial to add ezetimibe to statin treatment. On the other hand, adding PCSK9 inhibitors to statin treatment has provided additional low-density lipoprotein (LDL)-cholesterol (LDL-C) reduction up to 50%. Although there is no large clinical study published to date which shows prevention of clinical events with PCSK9 inhibitors, studies with evolocumab and alirocumab suggest that these agents may reduce clinical events. Therefore, both of these drugs have been granted FDA approval. Upon this approval, ACC has published a consensus report on the use of non-statin drugs for lipid management. The consensus report recommendations on using non-statin drugs are summarized below.

- If the LDL-C reduction is <50% (or LDL-C \geq 100 mg/dL) despite the maximum tolerated statin dose in stable atherosclerotic cardiovascular disease (ASCVD) without comorbidities, adding ezetimibe to treatment may be considered as a primary intervention [bile acid sequestrants in the event of ezetimibe intolerance or if triglyceride (TG) level is <300 mg]. If the target cannot be achieved by adding ezetimibe to treatment, replacing or adding PCSK9 to ezetimibe may be considered as a secondary intervention.

- In ASCVD cases with comorbidities, defined comorbidities include diabetes, ASCVD event within the last three months, ASCVD event while receiving statin, other inadequately controlled risk factors for ASCVD, elevated lipoprotein(a) levels or non-hemolysis chronic kidney disease. The recommendations for such patients are identical to those recommended for stable ASCVD patients. However, the LDL-C cut-off value is <50% (or LDL-C \geq 70 mg/dL or non-HDL cholesterol \geq 100 mg/dL) for these patients.

- If LDL-C reduction is not \geq 50% (or LDL-C <70 mg/dL) despite the maximum statin dose in stable ASCVD patients with baseline LDL-C levels \geq 190 mg/dL, adding ezetimibe to treatment may be considered as a primary intervention. Bile acid sequestrants may be considered as an alternative to ezetimibe if TG level is <300 mg. However, the guidelines committee recommend choosing PCSK9 inhibitors as the primary intervention in these patients instead of ezetimibe or bile acid sequestrants as they offer a greater reduction in LDL-C levels. If the target cannot be achieved despite adding non-statin drugs to treatment, a second non-statin agent may be added. Such patients may require mipomersen, lomitapide or LDL apheresis for LDL-C management.

- If LDL-C reduction is <50% (or LDL-C \geq 100 mg/dL, or non-HDL cholesterol \geq 130 mg/dL in diabetic patients) despite the maximum tolerated statin dose given for primary prevention in subjects with baseline LDL-C \geq 190 mg/dL, adding ezetimibe or PCSK9 inhibitors to treatment by discussing with the patient may be considered depending on the desired additional LDL-C reduction. Bile acid sequestrants may be given as an alternative to ezetimibe if TG level is <300 mg. If the patient cannot tolerate treatment after adding ezetimibe, it is reasonable to administer PCSK9 inhibitors rather than bile acid sequestrants. The guidelines committee consider it an acceptable outcome which does not require increasing treatment when LDL-C reduction is \geq 50% and LDL-C is <130 mg/dL in the absence of comorbidities or other risk factors in a patient with baseline LDL-C \geq 190 mg/dL. Patients with LDL-C \geq 190 mg/dL may require specific treatments such as mipomersen, lomitapide or LDL apheresis.

- Combination treatment may be considered if LDL-C reduction is <50% (LDL-C \geq 100 mg/dL or non-HDL cholesterol \geq 130 mg/dL) despite maximum statin treatment in diabetic patients initiated on a statin for primary prevention. In such cases, the first choice is ezetimibe. Bile acid sequestrants have mild hypoglycemic effects and this may be beneficial in patients with TG <300 mg. Bile acid sequestrants may also be considered in patients who demonstrate inadequate response or are intolerant to ezetimibe. The role of PCSK9 inhibitors for primary prevention in diabetic patients is currently unclear.

- Adding non-statin drugs to treatment may be considered in non-diabetic patients with a $\geq 7.5\%$ risk of ASCVD receiving statin treatment for primary prevention in the presence of high risk predictors. The predictors established by the committee are as follows: A 10-year ASCVD risk of $\geq 20\%$, baseline LDL-C ≥ 160 mg/dL, other inadequately controlled major CV risk factors, family history of premature ASCVD with or without elevated lipoprotein(a) levels, evidence of accelerated subclinical atherosclerosis (such as coronary artery calcification), increased hs-CRP and chronic kidney disease, HIV or chronic inflammatory disease.

Lowering LDL by 30-50% (LDL-c <100 mg/dL) is accepted adequate in patients without predictors of high risk. Ezetimibe may be considered if $\geq 50\%$ LDL reduction (LDL-C <100 mg/dL) cannot be achieved with high-dose statin treatment in subjects with high risk predictors (or bile acid sequestrants as the second choice). Bile acid sequestrants should be considered only in ezetimibe-intolerant patients and in the presence of multiple risk factors for ASCVD. PCSK9 inhibitors should not be used in these patients due to lack of relevant data.

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Question 42: When should we discontinue statin treatment? Could it be harmful to discontinue statins?

Dr. Levent Hürkan Can

Ege University Faculty of Medicine, Cardiology Department, İzmir

While discontinuing statin treatment has always been controversial, the clearest answer to this question is that the treatment should be discontinued if hypercholesterolemia disappears following treatment of the secondary cause in a patient with secondary hypercholesterolemia. For example; if the LDL-cholesterol levels are normal prior to hypothyroidism in a patient who becomes euthyroid with thyroid replacement treatment, statin treatment may be discontinued.

Considering that hypercholesterolemia is actually a metabolism disorder and that statins and similar drugs inhibit the cholesterol synthesis only as long as they are used, we would conclude that the treatment should be life-long. In addition, the treatment should also be continued in order to achieve continuance of favorable effects of statins, including pleiotropic effects and primarily endothelial effects as well as LDL cholesterol-lowering efficacy.

Studies performed in patients in whom statin treatment has been discontinued, particularly during

treatment for acute coronary syndrome, showed increased mortality and cardiovascular events even at early stages in patients who discontinue treatment compared to those who continue treatment^[1, 2].

Here, the problematic points are the patients who develop side effects and those who end up with extremely low LDL-cholesterol levels. In patients with side effects, the first intervention should preferably be reducing the dose or the patient should be switched to another statin. If the target cannot be achieved with this approach, combination of low-dose statin and ezetimibe etc. should be used. For patients with very low LDL-cholesterol levels, the 2013 American Guidelines indicate that the treatment decision should be at the physician's discretion in patients with LDL levels < 40 mg/dL since there is no evidence below the threshold of 40 mg/dL^[3].

In conclusion, discontinuing statin treatment in patients who have achieved their LDL-cholesterol level is harmful. Treatment should definitely be continued.

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Question 43: How should we approach a patient who achieves the LDL-cholesterol target with anti-lipid therapy? Should we discontinue the drug? Should we reduce the dose? Or should we continue without any changes?**Dr. Ersel Onrat**

Afyon Kocatepe University Faculty of Medicine, Cardiology Department, Afyonkarahisar

There are differences between guidelines with respect to LDL-cholesterol targets in anti-lipid treatment. However, as a general opinion, it is recommended to continue the treatment at the same dose upon achieving the target LDL-cholesterol level in patients on anti-lipid treatment. Recurrence of dyslipidemia was observed in 79% of type 2 diabetes mellitus patients who achieved their target LDL-cholesterol levels on statin treatment and then interrupted statin treatment for a short duration. Thus, discontinuation or interruption of treatment is not recommended^[1]. In high-risk patients, the reduction in major cardiovascular and cerebrovascular events was maintained without an increase in side effects even below the target LDL-cholesterol value of 50 mg/dL^[2]. In these patients, even if the LDL-cholesterol level is below 70 mg/dL, the treatment

dose that is beneficial should be maintained. Recent publications have shown increased cardiovascular mortality and morbidity with inter-visit LDL-cholesterol fluctuations^[3]. In other words, interruption or irregular use of statins also has an unfavorable effect.

The guidelines do not include the concept of a limit value for LDL-C lowering. Only the 2013 ACC/AHA Guidelines indicate that the statin dose may be reduced in case of two consecutive LDL-cholesterol values < 40 mg/dL (recommendation: IIb, level of evidence: C). However, this results not from an increase in side effects but from the fact that this value was adopted as a limit value in 2 randomized controlled studies^[4].

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Question 44 - What is the maximum lowering that can be achieved for LDL-cholesterol levels? Could very low levels be harmful?

Dr. Aylin Yıldırım

Başkent University Faculty of Medicine, Cardiology Department, Ankara

Since the correlation between low-density lipoprotein cholesterol (LDL-C) and cardiovascular (CV) disorders has been defined clearly, lowering LDL-C has been the main target of lipid-lowering treatment. Primary and secondary prevention studies show that the CV risk is significantly reduced with lowering LDL-C levels and that further CV risk reduction is achieved with greater reduction in LDL-C values. Thus, the conclusion is: “the lower the better”. CV risk reduction is related to the absolute reduction in LDL-C value rather than the percentage reduction. Therefore, while individuals with high baseline LDL-C values benefit more from the treatment, longer follow-up and larger sample sizes are warranted for studies in patients with lower baseline LDL-C levels. To what level could the LDL-C value be reduced, is there an established lower limit? Could the very low levels be harmful?

While seeking answers to these questions, we need to first discuss what the normal value of LDL-C is. The LDL-C level is approximately 40 mg/dL in the healthy newborn. It is known that the LDL-C values are between 50 and 75 mg/dL in primitive populations that live on hunting and that these individuals are protected against CV diseases. Individuals with LDL-C values <20 mg/dL as a result of the mutation leading to loss of function in the PCSK9 gene were found to be very healthy and protected against CV diseases. In light of all these data, LDL-C values around 40-50 mg/dL may be considered ideal. Thus, the essential question that should be answered is not whether these LDL-C levels are safe but whether it is safe to reach these levels with medication.

Since the rates of reaching the LDL-C targets defined in guidelines are much lower than the expected rates in real-life data, this question is addressed by primary and secondary prevention studies. Using high-dose statin, addition of ezetimibe to statin or using PCSK9 inhibitors have allowed achieving LDL-C values much lower than the targets and have also provided data on the outcomes of reaching very low LDL-C values with medication.

In the IMPROVE-IT (IMproved Reduction of Outcomes: Vytorin Efficacy International Trial) study, >18,000 patients with acute coronary syndrome and mean LDL-C levels of 95 mg/dL were randomized to either the simvastatin 40 mg/day group or the simvastatin 40 mg/day+ ezetimibe 10

mg/day group; and the LDL-C difference of 16 mg/dL between the study groups (69 mg/dL vs 53 mg/dL) provided a 2% absolute risk reduction in CV clinical endpoints^[1]. Follow-up of patients for a mean duration of 6 years with an average LDL-C value of 62 mg/dL provided very important data on the long-term efficacy and safety of very low LDL-C values. When the patients included in the IMPROVE-IT study were stratified into 4 groups based on the LDL-C values in the first month as <30 mg/dL (n=975), 30-<50 mg/dL (n=4603), 50-<70 mg/dL (n=5552), and \geq 70 mg/dL (n=4016), similar rates were observed in terms of side effects leading to treatment discontinuation including creatine kinase-increasing myalgia, hemorrhagic stroke, high transaminase levels, neurocognitive functions, gallbladder disorders, cancer, cardiac failure and CV mortality. Thus, it was concluded that very low LDL-C did not result in safety issues while reducing the CV risk. In the PROVE-IT TIMI 22 study (Pravastatin or Atorvastatin Evaluation and Infection Therapy- Thrombolysis in Myocardial Infarction 22), the two-year-long follow-up of patients reaching LDL-C levels < and \geq 40 mg/dL (n=193) revealed no difference with respect to rhabdomyolysis, cerebral hemorrhage and other safety profile parameters^[2]. On the other hand, in the subgroup analysis of the JUPITER trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) which included more than 16,000 patients, increased incidence was reported for diabetes, hematuria, hepatobiliary disease and insomnia in patients with LDL-C levels reduced to < 30 mg/dL with 20 mg rosuvastatin treatment (n=767) compared to patients with LDL-C levels > 30 mg/dL^[3].

In studies performed with statins, patients reaching very low levels of LDL-C represent a small portion of the study population. However, in studies where PCSK9 inhibitors are added to statins, the ratio of patients reaching very low LDL-C levels increases markedly. In the OSLER program, while the median LDL-C values decreased from 120 mg/dL to 48 mg/dL (61% reduction) in 4465 patients, CV events were significantly reduced in one year (2.18% vs 0.95%, p=0.003)^[4]. While the incidence of serious side effects was similar between the groups; arthralgia, headache, leg pain, fatigue and neurocognitive events were numerically more common in the evolocumab arm. Overall, 4.3% of the patients receiving evolocumab developed injection

site-related side effects but only 0.2% of them discontinued treatment for this reason. Although rare (<1%), the higher incidence of neurocognitive events in the evolocumab group should be considered as a warning (0.9% vs 0.3%). However, subgroup analyses revealed no difference in side effects between the groups of patients in whom LDL-C was reduced to < 25 mg/dL or < 40 mg/dL or patients with LDL-C levels > 25 mg/dL or > 40 mg/dL. Thus, these side effects do not appear to be related to achieving very low LDL-C values. In the recently published OSYSSEY LONG TERM study with a follow-up period of 78-months, patients with LDL-C levels > 70 mg/dL and a high CV event risk despite using maximum tolerated statin were randomized to alirocumab or placebo^[5]. In patients using alirocumab, the 62% reduction in LDL-C provided a significant decrease in CV endpoints (1.7% vs 3.3%, $p=0.02$); however, neurocognitive issues, primarily

memory, injection site related problems, myalgia and ophthalmological side effects were numerically more common. The subgroup analysis of the study showed similar findings between the patients with LDL-C values < 25 mg/dL and > 25 mg/dL. In other words, this study also supports the notion that the increase in side effects is related to the drug itself rather than the low LDL-C levels.

All these data show us that there is no lower limit for lowering LDL-C and support “the lower the better” view on LDL-C reduction. There is a statistically insignificant impairment in neurocognitive functions with PCSK9 treatment, and this should not be ignored. The results from neurocognitive tests and neurologic side effect assessments in the ongoing FOURIER study are expected to shed some light on the topic.

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Question 45 – Which side effects may occur in a patient initiating statin treatment?

Dr. Meral Kayıkçoğlu

Ege University Faculty of Medicine, Cardiology Department, İzmir

Overall, statins are safe drugs with mild side effects. Table 1 presents the side effects related to statin treatment with their incidences. The rate of treatment discontinuation due to side effects is reported to be 1.0-4.8%. However, side effects gain importance due to common and high-dose use.

In the clinical setting, the most common side effect is the increase in liver transaminases which occurs in 0.5-2% of the patients. This side effect is dose-dependent, reversible and commonly asymptomatic. It usually occurs at the start of treatment or at the time of dose adjustment. It may be considered a class effect, and it does not indicate liver damage. In the literature, severe liver failure secondary to statin treatment is very rare and limited to case reports only. Hepatotoxicity findings include jaundice, lethargy, indirect bilirubin increase, hepatomegaly and prolonged thrombin time. Attention should be exercised in case of transaminase levels exceeding the upper limit of normal (ULN) by 3-fold. This occurs in <1% of the patients using statins. Generally, the condition is benign and does not show any difference relative to placebo in clinical trials. The incidence is 2-3% at high doses. It is usually transient. Unless there is increased bilirubin or prolonged prothrombin time, isolated high transaminase levels do not indicate hepatic injury or dysfunction.

The mostly feared side effect of statins is myopathy, which may potentially progress to renal failure. Generally, it manifests as myositis. The incidence of muscular pain ranges between 1 to 7% while the incidence of myopathy with severely elevated creatine kinase is 0.5%.

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Table 1: Side effects reported with statins and their incidences

	percentage (%)
Dyspepsia	7.9
Diarrhea	4.9
Abdominal pain	4.9
Nausea	3.2
Bloating	2.6
Insomnia	2.7
Headache	8.9
Accident/trauma	5.1
Flu-like etc.	5.1
Fatigue	2.7
Allergy	2.3
Urinary system infection	1.6
Sinusitis	2.6
Bronchitis	1.8

The manifestations of myopathy include extensive, flu-like bodily pain; the pain usually starts in the origin muscles (arm and thigh) and extends to the whole body. CK is used to monitor muscle breakdown. Muscular pain may be observed without CK increase in 5-10% of the patients. Tolerable myopathy is defined as an increase in CK levels to an extent that is less than 5-fold of ULN. Patients should be advised to urgently refer to a hospital if they have severe muscular pain and darkening of urine color (myoglobinuria). Development of myopathy is irrespective of the dose. Other side effects reported with statins do not affect the clinical use (proteinuria, diabetes development).

Question 46 - Which patients have a high tendency to statin intolerance? What kind of precautions may be taken for such patients when starting treatment?

Dr. Meral Kayıkçoğlu

Ege University Faculty of Medicine, Cardiology Department, İzmir

Factors involved in development of statin-associated side effects can be classified under three titles ^[1].

1. Patient characteristics:

Advanced age, female gender, low body mass index, Asian origin, intensive physical activity, unexplainable cramps, joint/ tendon pain, history of myopathy while using other lipid-lowering drugs, history of statin-associated familial myopathy, neuromuscular disease, alcohol consumption, use of antipsychotics

2. Other concomitant systemic diseases

Neuromuscular disease, renal failure, acute/decompensated liver failure, hypothyroidism, diabetes mellitus, major surgery, presence of infection, hypertension/heart failure (due to renal effects)

3. Genetics

Cytochrome P450 isoenzyme and drug transport gene polymorphisms (e.g. the SLCO1B1 gene)

Table 1 summarizes the conditions leading to predisposition to statin-related side effects ^[2]. Patients with previous history of myopathy represent the group with the highest risk. However; female gender, low body mass index and advanced age also represent risk in a patient to start statin treatment for the first time,. If present, hypothyroidism should definitely be treated prior to statin treatment. In addition, one should keep in mind that even the mild muscular involvement related to statin use could represent an issue in athletes and sportsmen.

In these patients, the approach should include initiation of treatment at a low dose followed by adjustment according to the response. The interactions between statins or the differences between statins in terms of side effects remain unknown. Particularly in patients at risk, statin preference should be based on the effects of cytochrome P450 if there is associated drug use. Table 2 summarizes the effects of statins on cytochrome P450 ^[2]. In this regard, while the LDL-C lowering effect of pravastatin is weak, it may be preferred in these patients since it is not metabolized by the liver. In addition, fluvastatin also has a reliable side effect profile.

Table 1: Risk conditions for statin toxicity

Endogenous risks
advanced age (above 65 years of age)
low body mass index
multi-system diseases
renal dysfunction
liver diseases
thyroid dysfunction, particularly hypothyroidism
Metabolic muscular diseases
carnitine palmitoyltransferase II deficiency
McArdle disease (myophosphorylase deficiency)
Myoadenylate deaminase deficiency
muscular symptoms and high creatinine kinase levels
Exogenous risks:
Alcohol consumption
Heavy exercise

Table 2: Hepatic cythochrome P450-related elimination of statins

Statin	Cytochrome p450
Atorvastatin	CYP2C9
Fluvastatin	CYP2C9, CYP3A4 (minor)
Lovastatin	CYP3A4
Pravastatin	–
Rosuvastatin	CYP2c, CYP2C19 (minor)
Simvastatin	CYP3A4, CYP3A5, CYP2D6

As a matter of fact, it has been very well tolerated in patients with previous myopathy in the PRIMO study ^[3]. Examples of drug interactions include:

- Cytochrome P450 3A4 and 2C9 inhibitors (e.g. macrolide antibiotics, antifungals, cyclosporine, HIV-protease inhibitors) may increase statin concentrations and lead to toxicity.
- As for barbiturates, carbamazepine, rifampicin and phenytoin, they may reduce statin levels by inducing P450 CYP3A4 and CYP2A9.

- CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem may cause severe myopathies in combination with high doses of CYP3A4 inhibitors, particularly with simvastatin.
- Grapefruit juice may lead to an increase especially in simvastatin levels.
- Combination with CYP3A4 inhibitors should be avoided at high doses of atorvastatin.
- Erythromycin should be avoided during rosuvastatin use due to its relation to CYP3A4.
- While fluconazole causes CYP2C9 and CYP3A4 inhibition, ketoconazole inhibits CYP2A6 and CYP3A4.
- Simvastatin, atorvastatin, rosuvastatin and fluvastatin may enhance the effect of warfarin.
- If fluvastatin is used in combination with phenytoin, oral anticoagulants, ibuprofen, naproxen and diclofenac, the serum concentrations of these drugs are increased.
- The risk of myositis with statins is increased upon use with other antilipidemics, macrolide antibiotics and cyclosporine.
- Fenofibrate should be preferred for combination treatments with fibrates. If gemfibrozil is to be used, fluvastatin or pravastatin should be preferred.
- Pravastatin is preferred in patients using cyclosporine.

In summary, the alternatives that can be employed in high-risk patients while starting statin treatment are as follows:

Pravastatin does not have such an effect.

- Simvastatin and atorvastatin may increase digoxin levels.

1. Statin may be started at a low dose
2. Statin may be used at a low dose and combined with ezetimibe.
3. Statins with a low risk of side effects such as pravastatin or fluvastatin may be preferred.

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Question 47 – Do statins differ in terms of side effects?

Dr. Öykü Gülmez

Başkent University, İstanbul Healthcare Practice and Research Center, Cardiology Clinic, İstanbul

Statins have been proven to be effective for the primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD); however, these drugs are associated with muscle-related, metabolic, neurological and other side effects. Because majority of patients are able to tolerate lower doses of statins, the term, 'statin intolerance' has been currently replaced with statin-associated symptoms (SAS). The rate of true statin intolerance (complete intolerance = intolerance to any statin at any dose) is reported to be 5-6%.^[1]

While all statins lower cholesterol levels by inhibiting hydroxy-methyl-glutaryl-coenzyme A reductase, they differ in terms of pharmacokinetics. Lipophilic statins (atorvastatin, lovastatin, simvastatin) are highly exposed to first-pass by cytochrome P450 (CYP 450) enzymes in the liver and gastrointestinal tract. Hydrophilic statins (pravastatin and rosuvastatin) are not considerably affected by the first-pass mechanism but they are subject to rapid uptake by the active transport proteins in hepatocytes.^[2] The fact that 75% of the drugs on the market are metabolized by the CYP system, half of which are metabolized with the 3A4 isoenzyme, may explain the drug-drug interactions and side effects associated with various statins. Fluvastatin, pitavastatin and rosuvastatin are less likely to cause drug interactions as they are primarily metabolized by the CYP2C9 enzyme.^[1] Pravastatin on the other hand, is not metabolized by the CYP450 system and is therefore considerably unlikely to result in drug interactions and side effects. Furthermore, consuming fruit juices containing CYP3A inhibitors such as grapefruit juice also increases systemic statin concentrations (600 mL/day grapefruit juice increases simvastatin levels by 16-

fold, lovastatin levels by 15-fold and atorvastatin levels by 2.5-fold).^[2] Drug interactions by statin type and recommended statin doses are presented in Table 1.

The absolute indication for statin treatment, patient's knowledge level on statin use, possible drug-drug interactions or concomitant conditions, baseline and target levels of low-density lipoprotein (LDL) cholesterol levels should be evaluated in patients who develop statin-associated side effects. The most commonly encountered side effects in clinical practice are muscle-related complaints and elevated transaminase levels. Transaminase monitoring is not necessary if the elevation is less than 3-fold of normal while changing the dose or type of statin treatment. New onset diabetes associated with statin treatment is often seen in patients with risk factors for diabetes treated with potent and high-dose statins. Furthermore using potent and high-dose statins also has unfavorable effects on blood sugar regulation in diabetic patients. The risk of new onset diabetes is not a factor to consider while planning statin treatment as it provides greater reduction regarding the risk of ASCVD events in the benefit-harm curve. Statin therapy should be discontinued and expert opinion should be sought for differential diagnosis in the case of cognitive changes during treatment, and treatment should be continued with another type of statin after improvement of symptoms.^[3]

In conclusion, accurate diagnosis of SAS is important in statin treatment. Statins differ in terms of side effects. In the event of SAS occurrence, it would be an important precaution to discontinue statin treatment and switch to another statin.

Table 1. Statin-drug interaction

Statin	Interacting Drug	Note – Recommended dose
Atorvastatin	Azole antifungals, amlodipine, macrolide antibiotics, fenofibrate, gemfibrozil	Myopathy risk, dose: ≤ 20 mg
	Cyclosporine	Myopathy risk, dose: ≤ 10 mg
	Antiviral agents	Myopathy risk, dose: required minimal dose
	Digoxin	Digoxin levels increase
	OCS	Increased OCS levels
Rosuvastatin	Antacids	Decreased rosuvastatin levels, statin should be taken at least 2 hours later
	Antiviral agents, gemfibrozil	Myopathy risk, dose: ≤ 10 mg
	Cyclosporine	Myopathy risk, dose: ≤ 5 mg
	Warfarin	Increased INR
	OCS	Increased OCS levels, myopathy risk, dose: ≤ 10 mg
Pravastatin	Fenofibrate, gemfibrozil	Myopathy risk
	Cyclosporine	Myopathy risk, dose ≤ 20 mg
	Macrolide antibiotics	Myopathy risk, dose ≤ 40 mg
Fluvastatin	Cyclosporine, azole antifungals	Dose ≤ 20 mg
	Warfarin	Increased INR
Simvastatin	Amiodarone, verapamil	Dose ≤ 20 mg
	Cyclosporine, gemfibrozil	Dose ≤ 10 mg
	Digoxin	Increased digoxin levels
	Azole antifungals, macrolide antibiotics, protease inhibitors	Increased myopathy risk, no simvastatin should be given during treatment
	Warfarin	Increased INR
Lovastatin	Amiodarone, verapamil	Myopathy risk, dose ≤ 40 mg
	Azole antifungals, macrolide antibiotics, protease inhibitors	Increased myopathy risk, no lovastatin should be given during treatment
	Cyclosporine, fenofibrate, gemfibrozil	
		Myopathy risk, dose ≤ 20 mg
Pitavastatin	Macrolide antibiotics	Myopathy risk, dose ≤ 1 mg
	Rifampicin	Dose ≤ 2 mg

OCS: Oral contraceptives; INR: International normalization ratio.

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Question 48 – When should we take elevated LFT results seriously in patients receiving statin treatment? Should we wait until an increase of 3x upper limit of normal?

Dr. Merih Baykan

Karadeniz Technical University Faculty of Medicine, Cardiology Department, Trabzon

Hepatic transaminase (ALT/AST) levels may be elevated up to more than 3-fold of upper limit of normal (ULN) without any associated symptoms in 0.5-2% of patients receiving statin treatment. This is a class effect of statins, and occurs with high-doses of statin treatment. It is often transient and may resolve even with continued statin treatment at the same dose in 70% of the cases. Statin-related hospitalization, death or clinically significant liver damage requiring liver transplantation is considerably rare and the existing cases are in the form of case reports. The AST/ALT elevations seen during statin treatment have been shown to be not accompanied by histological liver damage. In fact, asymptomatic ALT increases without elevated bilirubin (particularly direct bilirubin) levels indicate the release of enzymes from hepatocytes and this does not always refer to liver toxicity. Furthermore, it also does not mean that acute liver failure will develop following the increase in ALT levels.

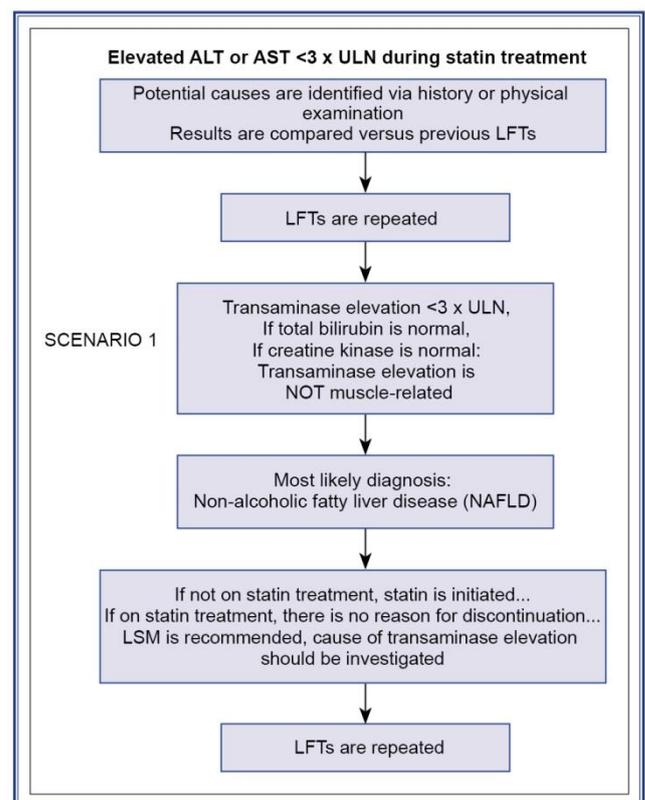
Several mechanisms have been suggested for the statin-related increases in hepatic transaminase levels. These mechanisms include reduced cholesterol and coenzymeQ10 in hepatocytes, induced caspase activity, autoimmune mechanisms in subjects with genetic disposition, apoptosis and free radical formation.^[1,2]

Guideline recommendations on monitoring liver functions in patients receiving statin treatment are as follows:

ATP IV recommends checking ALT levels prior to statin initiation and to re-evaluate ALT levels in the event of findings indicative of liver damage such as jaundice, unexplained fatigue, loss of appetite, abdominal pain, yellow coloration in the skin and sclera and dark colored urine. In other words, ATP IV does not recommend routine monitoring of transaminase levels. There is also no FDA recommendation on routine monitoring when baseline hepatic transaminase levels are normal.

The ATP IV approach is based on the fact that randomized controlled trials have shown no difference in ALT levels between statin users and those receiving placebo. Furthermore, it should be noted that routine ALT monitoring may lead to unnecessary statin discontinuation.^[3]

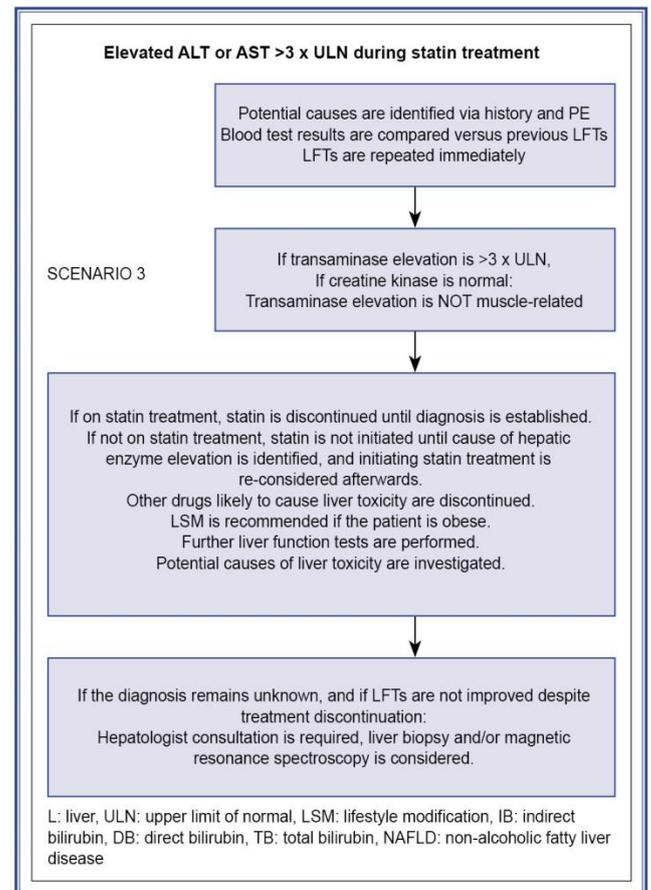
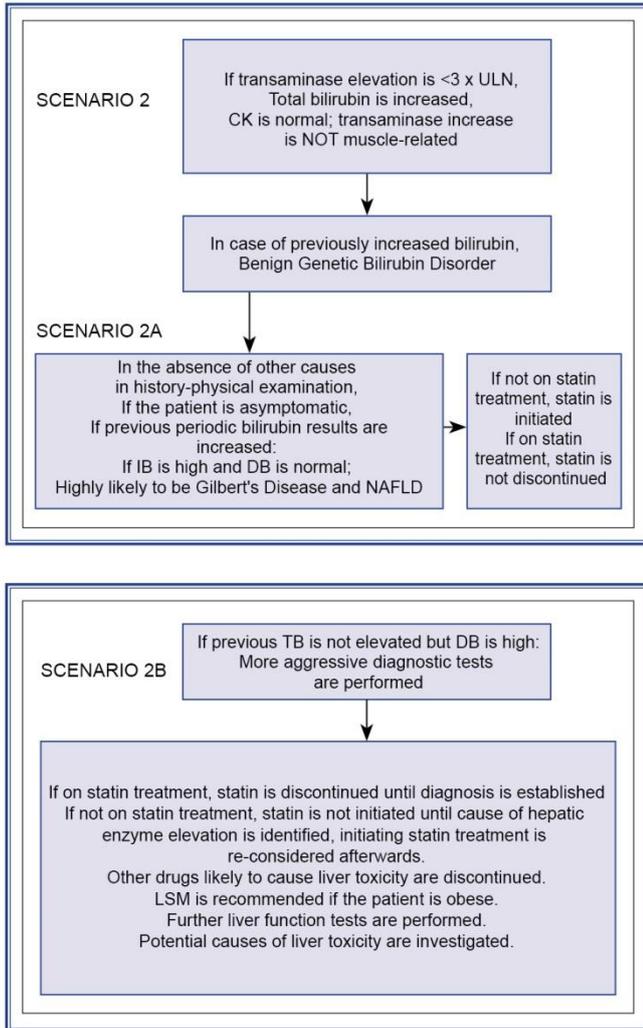
EAS/ESC Dyslipidemia Guidelines on the other hand, adopt a more conservative approach in this regard. They recommend evaluating ALT levels before and 8 weeks after treatment initiation or any dose escalation, and performing routine annual follow-up in the event of ALT levels <3x ULN. According to the recent 2016 EAS/ESC Dyslipidemia Guidelines, liver enzymes should be checked routinely before treatment initiation and then 8-12 weeks after starting the drug any dose increase. Afterwards, routine ALT monitoring is not required during the course of lipid-lowering treatment. It is recommended to continue statin treatment if the ALT increase is <3 x ULN, and to re-evaluate ALT levels at 4-6 weeks.



According to the same guidelines, if the ALT increase is $\geq 3 \times$ ULN, statins should be discontinued or the dose should be reduced and liver enzymes should be re-evaluated 4-6 weeks later, and it may be considered to resume statin treatment after liver enzymes return to normal.^[4]

NICE Guidelines also state that statins may be used unless hepatic transaminase levels are $>3 \times$ ULN.^[5]

In conclusion, in line with the recommendations in all these guidelines, it may be concluded that statins may be used as long as asymptomatic hepatic transaminase levels are not $>3 \times$ ULN. However, symptoms and signs indicative of clinical liver damage should be carefully evaluated at the time of initiating statin treatment.



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Question 49 – What should be the pathway for elevated liver enzymes during statin treatment?

Dr. Atiye Çengel

Gazi University Faculty of Medicine, Cardiology Department, Ankara

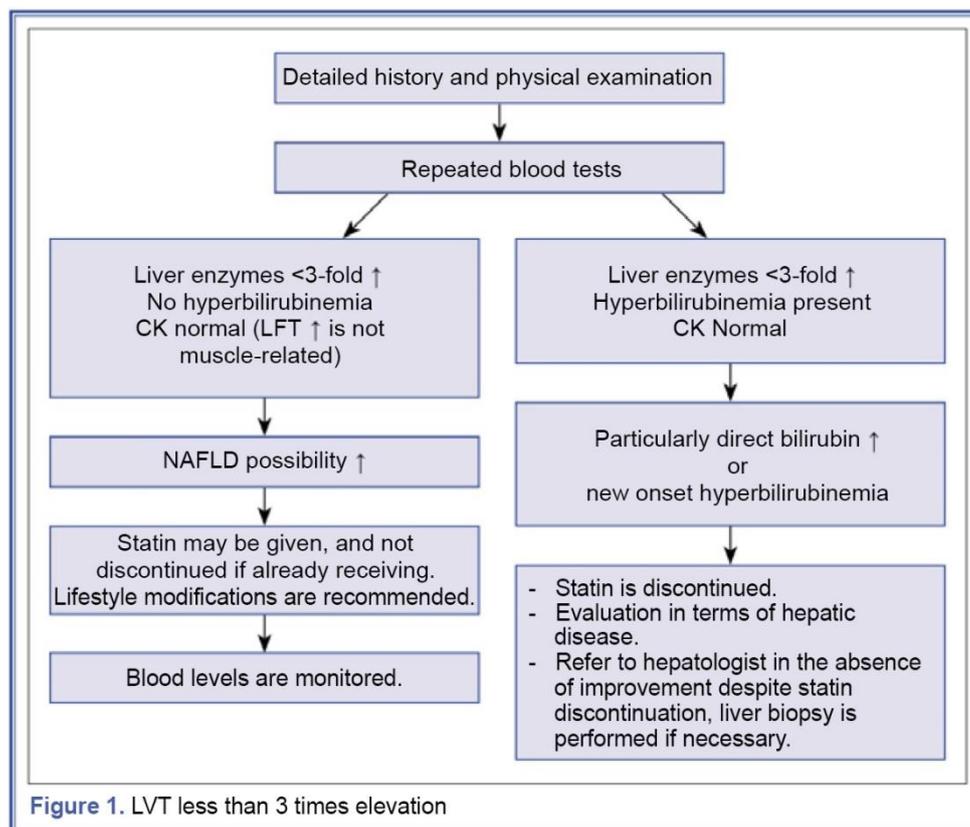
Elevation of transaminases in the liver (transaminitis) is commonly seen during statin treatment (incidence: 1-3%). The general opinion regarding the related mechanism is hepatic enzyme leakage associated with increased permeability resulting from the altered lipid content in hepatocyte membranes. This is a class effect and may even occur with non-statin lipid-lowering agents. Female gender, high-dose administration, advanced age and presence of comorbidities increase the incidence of transaminitis. Transaminitis is most frequently reported with atorvastatin and simvastatin.

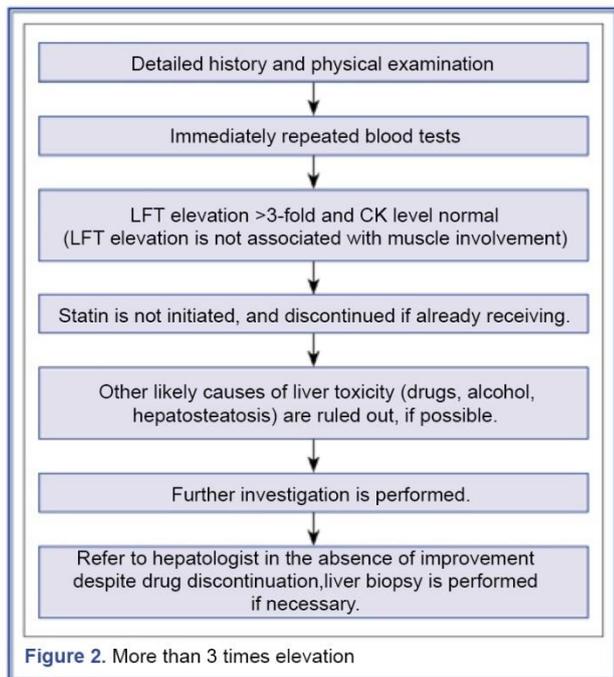
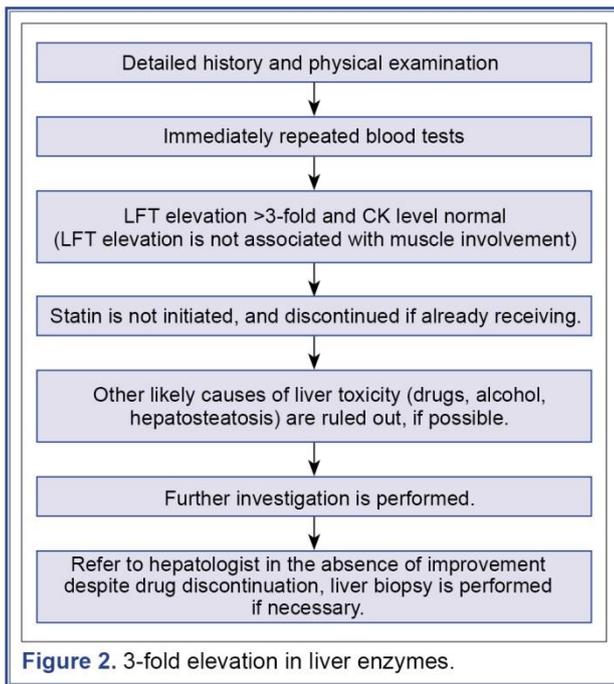
The currently available guidelines recommend evaluating hepatic enzymes prior to initiating statin treatment. This recommendation aims to recognize non-alcoholic fatty liver disease (NAFLD) and baseline values. However, taking into account both the cost and the fact that statins are highly unlikely to cause serious liver damage, and also because it is deemed to provide no benefit in terms of preventing serious liver damage, periodic enzyme monitoring is

not recommended; however, it is recommended to repeat LFTs (Liver Function Tests) in the presence of symptoms such as extreme asthenia, nausea or jaundice.

Despite the guideline recommendations, periodic LFT monitoring in patients receiving statin treatment is a common practice among physicians and also appears to be the expected approach among patients. In this regard, the recommended scheme for monitoring is divided into 2 categories (Figure 1 and 2).

Statin-associated hepatic enzyme elevations resolve in 70% of the cases, even with continued treatment. However, apart from transaminitis, there is also a risk of idiosyncratic serious liver damage, even if very low (1 in 100 thousand to 1 in a million). This occurs approximately 3-4 months after treatment, although there have been cases reported from Day 34 to 10 years. It may develop in the hepatocellular, cholestatic or mixed form.





Should Statin Treatment Be Re-initiated If Enzymes Are Improved?

There is no consensus regarding this question. The dominant opinion is to try a different statin at a lower dose in the absence of idiosyncratic serious liver damage.

However, it is recommended to not re-initiate statin treatment in cases who develop serious liver damage and improve afterwards.

Nevertheless, there are 4 case reports in the literature describing treatment with a different statin without any problems in patients with the aforementioned characteristics.

Liver diseases in which statin treatment is contraindicated

- Active Acute Hepatitis
- Decompensated Cirrhosis
- Acute Liver Failure

Liver diseases requiring caution with statin treatment

- Chronic Hepatitis
- Chronic Liver Disease
- Compensated Cirrhosis
- Liver Transplant Patients

LFTs should be monitored 2 weeks after treatment initiation and every 3 months afterwards.

Liver disease thought to benefit from statin treatment

- Non-Alcoholic Fatty Liver Disease (NAFLD)

This condition does not constitute a contraindication for statin treatment, and statins have also been shown to reduce cardiovascular endpoints and improve enzyme levels in this group.

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Question 50 – Does every muscle pain that occurs while receiving statin treatment mean statin-associated myopathy?

Dr. Ceyhun Ceyhan

Adnan Menderes University Faculty of Medicine, Cardiology Department, Aydın

While there is no universal definition for statin intolerance, it is described as a clinical syndrome associated with the inability to tolerate at least two statins (one of them at the lowest daily initial dose, the other at any dose).^[1] The most common form of statin intolerance is related to muscles and referred to as myopathy. The mean incidence is 15%. For the diagnosis, the objective symptoms or abnormal laboratory values should be clearly linked with statin treatment, i.e., the complaints should improve upon discontinuation of statin treatment and recur with re-initiated treatment. Conditions such as hypothyroidism, drug interactions, concomitant diseases, intensive physical activity or exercise and blood disorders should be ruled out.^[2]

Major muscle groups are involved in statin-associated myopathy. Symmetrical and proximal muscle involvement is more common. Creatine kinase (CK) elevation may be accompanied by pain, weakness, rigidity and cramps in muscles. Muscle-related symptoms often develop within the first 4-6 weeks of statin treatment. Other muscle enzymes and measurements (such as EMG, biopsy) are not routinely used for diagnosis. The classification of and approach to muscle symptoms and CK levels have been established in the Consensus Report of European Atherosclerosis Society (Table 1).

Table 1.

Muscle symptoms	Creatine kinase	Interpretation
Yes	Normal	Should be often defined as myalgia and it may be statin-associated; however, statin should not be discontinued.
Yes	<4- fold or >4-fold and <10-fold	Intensive exercise should be considered. May be related to an underlying muscle disease.
Yes	>10-fold	Often defined as myositis or 'myopathy' Biopsy is not required. Associated with statin or muscle disease.
Yes	>40-fold	Rhabdomyolysis may co-exist, renal failure and myoglobinuria should be investigated, statin should be discontinued immediately.
None	<4-fold	Often detected incidentally. Statin treatment should be continued. Re-testing CK is recommended. Secondary causes such as increased exercise or hypothyroidism should be evaluated.
None	>4-fold	Asymptomatic clinical relevance is known. However, CK should be re-tested and statin treatment should be continued. CK monitoring is recommended.

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Question 51 – What should be done in the event of true statin intolerance (myopathy)?

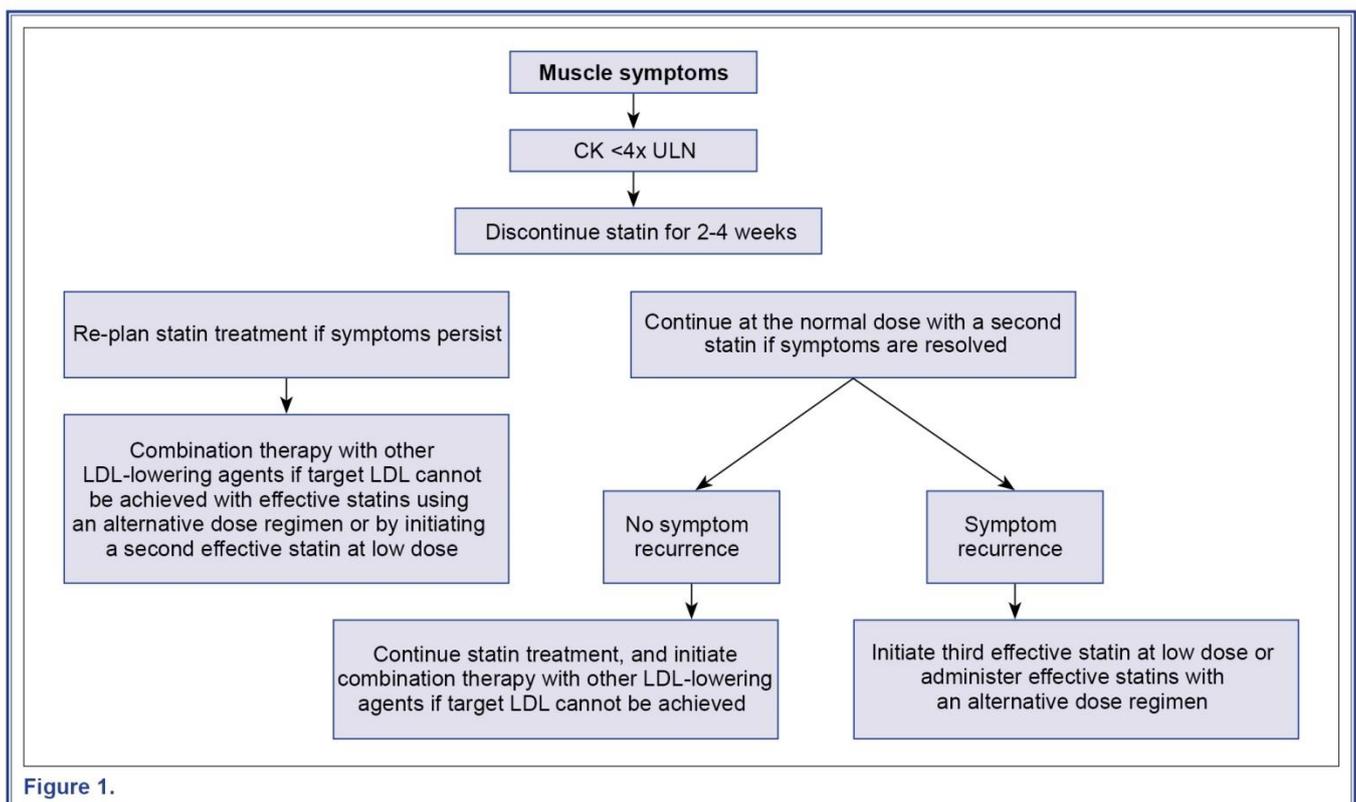
Dr. Sinan Aydoğdu

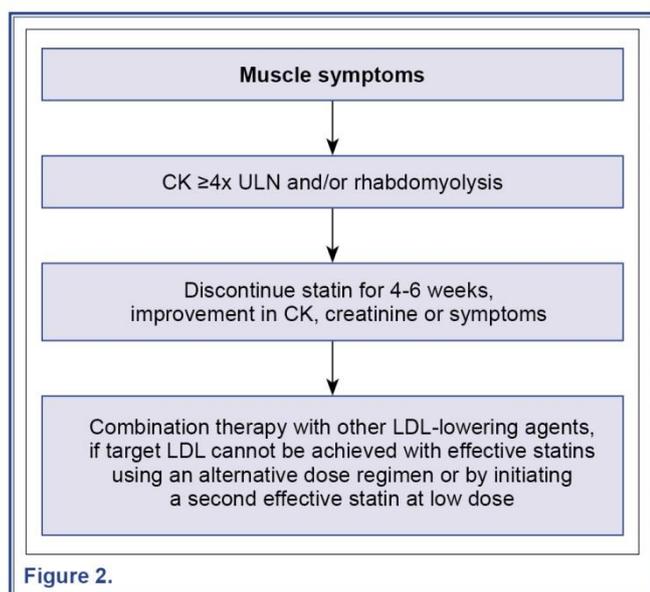
Turkey Higher Specialty Hospital, Cardiology Clinic, Ankara

While statins are well-tolerated, the most common reason of treatment discontinuation is the occurrence of statin-related muscle symptoms. Muscle symptoms with normal or mildly elevated creatine kinase (CK) levels are reported with a rate of 7-29%.^[1] However, the incidence of true myopathy is 0.01-0.001% with standard doses of statin treatment. It is important to distinguish true myopathy from muscle-related symptoms in patients receiving statin treatment. The European Atherosclerosis Society Consensus Report^[2] defines myopathy as CK levels $>10 \times$ upper limit of normal (ULN) accompanied by muscle symptoms (weakness, pain, rigidity etc.).

The number of patients presenting with muscle symptoms has increased due to the widespread use of statins. However, it is very important to distinguish whether these are related to true statin-associated myopathy. The dyslipidemia treatment guidelines issued by the European Society of Cardiology (ESC) in 2016 recommend a similar approach algorithm regarding statin-associated myopathy compared to the EAS consensus report. The approach recommended by EAS for patients with elevated CK levels who present with muscle symptoms is summarized in Figures 1 and 2.

While true myopathy often occurs within the first 4-6 weeks in patients receiving statin treatment, it may also develop in later stages with dose escalation or in the event of drug interactions. Predisposing risk factors (treatment with agents affecting the cytochrome P450 system or renal impairment etc.) should be investigated in patients receiving statin treatment who present with true myopathy, potential secondary causes of myopathy (hypothyroidism, polymyalgia etc.) should be ruled out and statin indication should be re-evaluated. Creatinine and myoglobinuria should be evaluated to rule out rhabdomyolysis. In the event of concurrent rhabdomyolysis, treatment should be scheduled for urine alkalization and intravenous hydration. Statin treatment should be discontinued for 6 weeks in the presence of statin-associated myopathy and CK should be measured with 2-week intervals. Until symptoms and CK return to normal, the patient's statin indication should be re-evaluated and low-dose statin should be initiated if the patient needs statin treatment, then the dose should be increased to the maximum tolerable dose with ongoing CK monitoring.





Alternatively, statin treatment every other day or two days a week, or statin treatment in divided doses may also be considered. Treatment with the alternative dose has been shown to provide similar LDL reduction compared to routine doses of potent statins, i.e. atorvastatin or rosuvastatin.^[3]

Generally, it is an acceptable option to use low doses of a potent statin with long half-life.

Majority of patients who develop statin-associated myopathy are known to show good tolerance without myopathy recurrence when switched to a different statin. Thus, the goal should be achieving target LDL by starting with alternative dose schemes of different statins. If target LDL levels cannot be achieved with the maximum tolerated statin dose, it is appropriate to combine the statin with other LDL-lowering agents. In this context, the first choice should be ezetimibe as per EAS recommendations. Combination treatment with ezetimibe and statin is well-tolerated and achieves target LDL levels. If target LDL levels still cannot be achieved, the second choice should be a fibrate or bile acid resins. These agents may be combined with statin and ezetimibe. Niacin is known to lower LDL; however, it is not recommended for treatment as it has been shown to not reduce cardiovascular events. Similarly, agents such as vitamin D and co-enzyme Q, which are thought to increase statin tolerance are also not recommended as their efficacy has not been shown with studies. The introduction of PCSK-9 inhibitors in clinical practice is a notably important step in anti-lipid treatment. ESC 2016 guidelines on dyslipidemia state that these agents may be considered as an alternative in patients who develop myopathy.

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Question 52 – Is vitamin D deficiency relevant in terms of statin intolerance?

Dr. Alper Sönmez

Sağlık Bilimleri University Gülhane Faculty of Medicine, Internal Diseases Department, Ankara

Myalgia is one of the most common side effects seen in patients receiving statin treatment. The pathogenesis of statin-related myalgia and general statin-associated myopathy is poorly understood. Statin-associated myopathy is characterized by muscle weakness and pain which often affect major proximal muscle groups. The complaints disappear upon treatment discontinuation and usually recur within 2-3 days after re-initiating the drug. Vitamin D deficiency may be one of the factors related to statin-associated myopathy. However, there is no robust evidence on this notion. Vitamin D receptors are found in skeletal muscle and varying degrees of myopathy may develop in vitamin D deficiency. Myopathy due to vitamin D deficiency is a rare condition, and may manifest with proximal muscular weakness, gait disorder and skeletal muscle pain. There are some case reports and cross-sectional studies suggesting that vitamin D deficiency may lead to statin-associated myopathy in patients receiving statin treatment. However, because myalgia is a subjective complaint and owing to the lack of randomized placebo-controlled studies, it is difficult to establish causality between vitamin D deficiency and statin-associated myopathy.^[1]

While improvement in muscle-related symptoms have been reported upon resolved vitamin D deficiency in some patients with statin-associated myopathy, data on this subject appear to be inconsistent. It is not possible to conclude whether vitamin D replacement is beneficial in statin-associated myopathy as there are no randomized, placebo-controlled, prospective studies on this treatment.^[1,2]

Current guidelines include similar recommendations on investigating vitamin D deficiency in patients with statin-associated myopathy and on vitamin D replacement for prophylaxis or treatment. American College of Cardiology and American Heart Association (ACC/AHA) recommend investigating other causes which may lead to myopathy (vitamin D deficiency,

hypothyroidism, hepatic or renal disease, polymyalgia rheumatica, primary muscle diseases, drug interactions, history of heavy exercise etc.) in patients who develop muscle related symptoms while receiving statin treatment.^[3] European Atherosclerosis Society and Canada Consensus Group Guidelines do not recommend vitamin D prophylaxis in patients receiving treatment with statin.^[2,4] The same guidelines also do not recommend vitamin D replacement for statin-associated myopathy owing to the limited data on this treatment.^[2,4]

Taking into account the available information and guideline recommendations on vitamin D, the most appropriate approach for patients who develop myopathy during statin treatment may be summarized as follows: Firstly, the link between symptoms and statin treatment should be confirmed. There is no universally adopted definition for statin-associated myopathy. Irrelevant pain and complaints may be mistaken for statin-associated myopathy. Therefore, clinicians should be careful to obtain an accurate anamnesis and should carefully evaluate the symptoms. Other conditions or history of heavy exercise etc. which may cause muscle pain and weakness should be interrogated. In the absence of other relevant causes, it would be a reasonable approach to assess vitamin D levels and re-initiate statin treatment after the deficiency is resolved, if any.^[5] The elderly constitute the group with the highest risk in terms of vitamin D deficiency, and these patients are also the ones with the highest rate of statin use in the population. Therefore, it may be recommended to be extra cautious regarding vitamin D deficiency in the elderly. Avoiding vitamin D deficiency in this population would be beneficial not only in terms of preventing statin-associated myopathy but also to prevent several other problems such as cognitive disorders, osteomalacia and the risk of falls.

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Question 53 – Do statins cause diabetes? Is this clinically important?

Dr. Bülent O.Yıldız

Hacettepe University Faculty of Medicine, Department of Endocrinology and Metabolism Diseases, Ankara

Statins are the drugs of first choice for primary and secondary cardiovascular (CV) prevention in individuals with dyslipidemia. In 2008, the JUPITER trial showed a small but statistically significant increase in new onset diabetes with rosuvastatin compared to placebo.^[1] Other randomized controlled trials (RCTs), observational studies and meta-analyses of these studies have also supported this finding which is why product information of all statins since 2012 have included wording that statin use may increase fasting glucose and HbA1c levels.

The JUPITER trial included healthy subjects with low-density lipoprotein (LDL) cholesterol levels below 130 mg/dL and C-reactive protein (CRP) values of 2.0 mg/dL, and 8901 subjects received rosuvastatin 20 mg while 8901 subjects received placebo for a follow-up period of 1.9 years. The number of subjects with new onset diabetes was 270 (3%) in the rosuvastatin group and 216 (2.4%) in the placebo group ($p=0.01$).^[1] In this study, 4 risk factors were investigated in terms of diabetes development (metabolic syndrome, impaired fasting glucose, body mass index >30 kg/m² and HbA1c $>6\%$) and the risk of diabetes occurrence was 28% increased in those with at least one risk factor (95% CI: 1.07-1.54) while rosuvastatin, similar to placebo, had no effect on diabetes development in subjects without risk factors for diabetes. Study results demonstrated 39% risk reduction regarding the primary CV endpoint with rosuvastatin in subjects with at least one risk factor for diabetes and 52% risk reduction in those with no risk factors for diabetes.^[1]

Meta-analyses of RCTs show a statistically significant increase of 10-12% in new onset diabetes with statin treatment, with higher risk in patients receiving high-dose statin and in the presence of risk factors for type 2 diabetes.^[2,3] A meta-analysis demonstrated one extra case of new onset diabetes with 4 years of statin use in 255 patients.^[2] On the other hand, statin use and intensified statin treatment

are known to prevent several other major CV events.^[2,3]

While studies on the increased risk of diabetes with statin use conducted with cell cultures and animal models indicate some cellular mechanisms, there is no sufficient clinical data to explain the effects of statins on insulin secretion from pancreatic beta cells or the peripheral or hepatic insulin resistance in humans.^[4] Similarly, starting statin treatment may mildly increase blood glucose levels in patients with previously existing diabetes; however, this increase can be readily managed by adjusting the antihyperglycemic treatment.^[4] Currently there is no sufficient evidence to show the clinical significance of unfavorable effects of statins on glycemic control in diabetic patients.

In conclusion:^[5]

Statin use leads to a mildly increased risk of new onset diabetes and the increased risk is more prominent with high-dose statin treatment and in subjects with risk factors for diabetes.

CV benefits of statin treatment outweigh the potential risk of diabetes development.

It is very important to emphasize lifestyle modifications in patients planned to receive statin treatment in order to reduce the CV risk as well as the risk of diabetes occurrence.

Before initiating statin treatment, patients should be evaluated in terms of risk factors for diabetes and fasting plasma glucose and HbA1c should be assessed or standard 75 g oral glucose tolerance test should be performed regarding the risk of pre-diabetes or diabetes. It is recommended to repeat these evaluations at one year after starting statin treatment and with intervals of no longer than three years afterwards.

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Question 54 – Do statins cause erectile dysfunction or gonadal dysfunction?

Dr. Zeki Öngen

Istanbul University Cerrahpaşa Faculty of Medicine, Cardiology Department, İstanbul

Erectile dysfunction (ED) and gonadal dysfunction are not among the side effects associated with treatment or found different compared to placebo in an article investigating which side effects thought to be associated with statins are actually related to the drug.^[1] So, why do we encounter this question? Erectile dysfunction is most commonly seen in individuals with metabolic syndrome, diabetes and cardiovascular disease. The fact that statins are most commonly prescribed for the same patients raises the question, is this a coincidental co-existence rather than a cause-and-effect relation?

In terms of erectile dysfunction, some findings indicate no unfavorable effects or even suggest favorable effects with statins. A retrospective cohort study found no difference in terms of ED between subjects receiving statin for one year and non-users.^[2] A similar cohort study conducted in Taiwan demonstrated significant improvement of 25% in ED incidence with statin treatment.^[3] Because endothelial dysfunction is the common component of the conditions listed in the first paragraph which most commonly co-exist with ED, and because statins

improve endothelial dysfunction, statins have also been employed in the treatment of ED. A meta-analysis on studies in this subject matter has shown notable improvements in ED with statins.^[4]

The cholesterol in low-density lipoprotein (LDL) particles is used for the synthesis of several gonadal hormones. Therefore, it has been a subject of interest whether lowering LDL cholesterol levels with statin treatment leads to reduced gonadal hormone production. A meta-analysis conducted with 11 studies evaluating this question revealed a moderate but statistically significant decrease in testosterone levels.^[5] The same study also reported a similar decrease in testosterone levels among women with polycystic ovaries. In a cohort study investigating testis functions and frequency of infertility among males receiving statin treatment, no difference was observed compared to non-users.^[2]

To answer the question with a single sentence, one may conclude that statin treatment does not result in ED or infertility despite causing a moderate decrease in testosterone levels.

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Question 55 – Do statins cause cancer?

Dr. Aytül Belgi Yıldırım

Akdeniz University Faculty of Medicine, Cardiology Department, Antalya

Studies on the safety of statins have demonstrated the safety of these drugs with high benefit/risk ratios. While statins are generally considered as well-tolerated drugs with mild side effects, there have been claims regarding cancer occurrence associated with statin use. Some observational cohort studies have indicated co-existence with increased risk of cancer. Analysis of cancer cases in randomized statin studies would allow a non-biased evaluation of the association between cancer and statin treatment. Some observational studies have demonstrated results indicating a link between low LDL-C levels and increased risk of cancer. The mechanism of the inverse correlation between cholesterol levels and cancer remains unclear. In some meta-analyses, no increase was observed regarding cancer risk with statins (upon an evaluation with follow-up periods of 4-5 years in relevant studies). However, these analyses have not been clarified regarding the concerns of a potential increase in certain cancer types with LDL-C lowering. Safety concerns related to increased occurrence have been reported for gastrointestinal cancers in the PROSPER study and for breast cancer in the CARE study. Because the PROSPER study included subjects ≥ 70 years of age, the increase in cancers was thought to be age-related. The CTT analysis found no correlation between statin treatment and the risk or mortality of cancer. An analysis on 27 statin studies including studies on intensified treatment (175,000 patients and 10,000

cancer cases) demonstrated no increase in cancer risk with LDL-C lowering, even in the elderly. The most recent data on this subject matter comes from the follow-up data of approximately 20 years published in 2016 by the WOSCOPS study (West of Scotland Coronary Prevention Study; primary prevention study with a duration of 5 years). The results have indicated maintained protective effect of statins on all-cause mortality and CV mortality as well as safety in terms of cancer occurrence.

The study conducted by Nielsen and colleagues in the Dutch population tested whether LDL-C lowering may prevent cancerous cell proliferation, which is required for cancer growth and metastasis. Findings obtained from 18,721 patients receiving statin treatment before cancer diagnosis were compared with findings from 277,204 non-users and reduction was observed in terms of cancer-related mortality.

In conclusion, the LDL-C lowering achieved with statin treatment results in encouraging outcomes regarding the prevention of CV disease and CV events. Some data on the safety of statins have raised concerns regarding an increased risk of cancer. However, subsequent meta-analyses and long-term follow-up data obtained from statin studies have resolved these concerns and encouraged us regarding the safety of statins.

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Question 56 – Do statins lead to cognitive dysfunction?

Dr. Fatih Sinan Ertuş

Ankara University Faculty of Medicine, Cardiology Department, Ankara

On 28 February 2012, USA Food & Drug Administration (FDA) issued a warning stating that "statins may cause short-term memory loss and confusion, this is often not a serious effect which improves upon treatment discontinuation". Before this warning, statins were known to prevent dementia and reduce the brain damage associated with atherosclerosis.

Experts suggesting that statins may have unfavorable effects advocate that cholesterol is vital for human brain and that statin treatment reduces cholesterol production in the brain, leading to unfavorable outcomes. Indeed, 25% of the cholesterol in human body is found in the brain. Because the intact blood-brain barrier has very limited permeability for lipoproteins, the cholesterol required for neuronal structure in the brain is stored in astrocytes. The synthesized cholesterol is utilized in the cell membrane structure. In the brain, it plays a very critical role in the formation of interneural synapses which are vital for rapid thinking, immediate reaction, memory and learning. From this point of view, can we say that statins inhibit cholesterol production and thereby reduce the amount of cholesterol that is required for brain functions? This question may be answered only by means of clinical studies and by observing the side effects in statin users. The warnings which form the basis of FDA sources are based on case reports and these reports are not based on objective cognitive assessments. The notifications based on case reports show that statin-associated cognitive problems are rare and there is no direct cause-and-effect relation in these cases. The reported incidence of cognitive side effects is not different than that reported with other cardiovascular drugs (e.g. losartan). Furthermore, there is no evidence indicating increased incidence of dementia or Alzheimer's disease among patients receiving statin treatment in observational studies. On the contrary, there is data suggesting favorable effects in this regard. No difference was seen between subjects receiving statin or placebo in comparative studies evaluating brain functions such as cognition, comparison, memory, attention and response rate. Several recent meta-analyses have clearly demonstrated there is no increased risk.

The claims on prevention from Alzheimer's with statins are based on 2 observations: The first observation comes from experimental studies in

animals and in patients with Alzheimer's showing that statins protect interneural synapses, prevent inflammation and reduce the toxic beta amyloid protein, which is thought to play an important role in Alzheimer's pathology or even cause this condition. Despite the favorable results observed in initial studies, further studies demonstrated that statins do not prevent dementia or mental breakdown. The second observation is the fact that brain autopsies of patients with Alzheimer's often show atherosclerotic alterations as well as senile plaques and neurofibrillary tangles, which are the main components of Alzheimer's pathophysiology. Atherosclerosis is seen as a co-existing problem with Alzheimer's, and also as a pathology aggravating the condition. On the other hand, while Alzheimer's disease accounts for approximately 75-80% of all dementia cases, the second most common type is vascular dementia resulting from occlusive vascular disease. Co-existence of these two conditions is the most commonly seen presentation in dementia and termed as "mixed dementia". Despite intensive investigations, the causal role of high cholesterol levels in excessive beta amyloid production has not been proven in Alzheimer's disease. The increasingly adopted notion in this subject matter is that cholesterol does not have a direct role in Alzheimer's pathology. However, it is a fact beyond dispute that cholesterol is a standalone risk factor for atherosclerosis and associated cerebrovascular events. Therefore, the suggested protective role of statins in Alzheimer's is likely to be related to neuroprotective and anti-atherosclerotic effects rather than a direct effect on Alzheimer's pathology. On the other hand, evidence clearly shows that statins do not cause Alzheimer's or any other type of dementia. This is because Alzheimer's is a irreversible progressive condition. However, the aforementioned side effects associated with statins rapidly resolve upon treatment discontinuation.

In conclusion, the benefits of statins outweigh their risks in terms of cognitive functions. In the event of mental disorders where no other cause is considered to be likely, treatment should be discontinued, and the patient may be readily switched to another statin if the cardiovascular risk is high, provided that the complaints are resolved. The fact that statins prevent stroke should be strongly emphasized for patients with such side effects.

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Question 57 – Do statins interact with oral anticoagulants and antithrombotic agents?

Dr. Murat Özdemir

Gazi University Faculty of Medicine, Cardiology Department, Ankara

Statin – Oral Anticoagulant Interaction

Statins and Warfarin: Atorvastatin and simvastatin are metabolized by the cytochrome P450 (CYP) 3A4 system while rosuvastatin, pitavastatin and fluvastatin are metabolized by means of CYP2C9. The CYP2C9 system is also associated with warfarin, which is the main reason of statin-warfarin interaction. Atorvastatin has been reported to be not interacting with warfarin;^[1] however, increased efficacy of warfarin and bleeding cases have been reported with simvastatin and fluvastatin. The CYP2C9-substrate statins may be thought to be increasing the anticoagulant efficacy of warfarin by reducing warfarin degradation when co-administered; however, a recently published study on rosuvastatin and pitavastatin, both of which are CYP2C9 substrates, has shown significantly increased INR with rosuvastatin 40 mg added to stable warfarin treatment whereas no such effect was demonstrated with pitavastatin 4 mg.^[2] Pravastatin is not a CYP substrate and appears to be the safest statin in terms of interaction with warfarin. Indeed, a recent

publication has reported the highest frequency of gastrointestinal bleeding with rosuvastatin and the lowest frequency with pravastatin among patients receiving statin and warfarin concurrently.^[3] Despite the population based studies suggesting a counter-argument^[4] and although the mechanism of interaction remains unclear, it would be a reasonable approach to take into account the potential INR increase and intensify monitoring when adding statin to the treatment of a patient on warfarin.

Statins and novel oral anticoagulants: Dabigatran has been reported to increase serum atorvastatin levels by 18% in healthy subjects, which has no clinical significance and dose adjustment is therefore not recommended when using these two agents together.

There is no data on apixaban – statin interaction.

No interaction has been observed between atorvastatin and rivaroxaban or edoxaban in healthy subjects.

Table 1. Interaction of statins with oral anticoagulants and antithrombotic agents

Drug	Statin	Mechanism	Effect/Recommendation
Warfarin	Atorvastatin	–	–
	Simvastatin	?	Increased INR/close INR monitoring
	Fluvastatin	?	Increased INR/close INR monitoring
	Pravastatin	–	–
	Pitavastatin	–	–
	Rosuvastatin	CYP2C9	Increased INR/close INR monitoring
Dabigatran	Atorvastatin	P-glycoprotein, CYP3A4	Increased atorv. levels by 18%/-
Apixaban	–	–	–
Rivaroxaban	Atorvastatin	–	–
Edoxaban	Atorvastatin	–	–
Aspirin	–	–	–
Clopidogrel	Atorvastatin	CYP3A4	No response to clopidogrel?/-
	Rosuvastatin	?	No response to clopidogrel?/-
Ticagrelor	Atorvastatin	–	–
	Simvastatin	CYP3A4	Increased simva. levels/max 40 mg/d
	Rosuvastatin	–	–
Prasugrel	Atorvastatin	–	–

Statin – Antithrombotic Agent Interaction

There is no significant interaction between statins and aspirin.

Statins – clopidogrel: In 2003, Lau et al.^[5] demonstrated inhibited antithrombotic efficacy of clopidogrel with atorvastatin in a dose-dependent manner by means of laboratory methods while no such effect was shown with pravastatin. The potential mechanism was explained as the atorvastatin-related inhibition of CYP3A4, which is required for the conversion of clopidogrel to its active form. Since then, several publications have been published regarding this matter; most of which supported no such interaction, suggesting that it would be of no clinical relevance even if such an interaction did exist. Therefore, current guidelines do not have any recommendations with regards to molecule or dose selection for the concurrent use of statins with clopidogrel. A relatively recent analysis has demonstrated increased no-response to clopidogrel with rosuvastatin compared to atorvastatin^[6] while a very recent publication reported increased unresponsiveness to clopidogrel with rosuvastatin

while no such effect was seen with atorvastatin in patients receiving dual antiplatelet therapy (aspirin + clopidogrel or ticagrelor) and it was also shown that rosuvastatin had no influence on the antithrombotic effect of aspirin or ticagrelor.^[7] It remains unknown to what extent these new findings on rosuvastatin will reflect in clinical practice before prospective evidence is obtained on this subject.

Statins – ticagrelor: A study investigating the interaction of ticagrelor with atorvastatin and simvastatin in healthy subjects reported no effects on ticagrelor pharmacokinetics with these 2 statins while ticagrelor significantly increased simvastatin levels, indicating that simvastatin dose should be limited to 40 mg/day in the event of co-administration.^[8] Unlike clopidogrel, ticagrelor may increase the efficacy of statins metabolized by the CYP3A4 system and this may be one of the reasons related to the superiority it demonstrated versus clopidogrel in the PLATO study.

Statins – prasugrel: The antithrombotic effect seen after the loading dose or maintenance doses of prasugrel is not affected by atorvastatin.^[10]

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Question 58 – Which drugs do statins interact with? Do statins differ in terms of drug interactions? What can we do to avoid this problem?

Dr. Alev Arat Özkan

Istanbul University Cardiology Institute, Cardiology Department, İstanbul

Statins are considerably safe drugs; however, they may cause side effects varying from mild hepatic enzyme elevations to rhabdomyolysis, although rare. The undesired effects may develop not only because of the dose but may also occur due to increased statin concentrations in circulation owing to drug interactions. Because statins differ in terms of pharmacokinetic properties, their potentials for drug interactions and the clinical outcomes of these interactions are also different.

Pharmacokinetic properties and interaction mechanisms: All statins except lovastatin and simvastatin are active molecules. Atorvastatin and rosuvastatin have active metabolites. All statins except pravastatin are associated with high rates of plasma protein binding. Their affinity for plasma proteins may lead to increased free forms and circulatory concentrations of other drugs, e.g. those that bind to albumin. All statins except pravastatin

and pitavastatin are metabolized in the liver via the cytochrome P450 (CYP) enzyme system (most commonly by CYP3A followed by CYP2C8, 9, 19, CYP2D6) and excreted mainly through the biliary tract. Various transport proteins [such as the multidrug-resistant protein (MDR), organic anion transport protein (OATP1B), breast cancer-resistant protein (BCRP) and P-glycoprotein] are involved in entry to and exit from the cells during the several stages of statin metabolism including their absorption, entry to circulation and transport from circulation to the liver and finally excretion to bile. Statin-drug interactions occur through the inhibition/induction of CYP enzymes by other pharmacological substrates and by means of the common transport proteins. CYP-inducing drugs decrease the efficacy of statins while enzyme inhibitors increase the plasma concentrations and thereby the dose-dependent risk of side effects.

Table 1. Statin-drug interactions

Factor	Mechanism	Precaution
Digoxin	Membrane transport proteins	Interacts with all statins, avoid high-dose statin, monitor plasma digoxin levels
Fibrate	Gemfibrozil ↓ statin elimination	Maintain low-dose statin or combine with pravastatin/fluvastatin; preferably use fenofibrate
Niacin	Non-CYP mechanisms (?)	Do not exceed 1 g/day except fluvastatin/pitavastatin
Warfarin	Plasma proteins	Decrease warfarin dose if close monitoring is required for prolonged PT
Calcium channel b.	CYP enzyme inhibition	Use verapamil/diltiazem only with low-dose statin, prefer amlodipine
Amiodarone	CYP enzyme inhibition	Use low-dose simvastatin/lovastatin
Cyclosporines	CYP enzyme inhibition/transport proteins	Safe only with low-doses of statins
Antifungals (azole derivatives)	CYP enzyme inhibition	Do not use with lovastatin and simvastatin, combine with low-dose atorvastatin/rosuvastatin
Antiretrovirals	CYP enzyme inhibition	Do not use with simvastatin, close monitoring with low-dose atorvastatin/rosuvastatin
Macrolide antibiotics	CYP enzyme inhibition	Do not use with atorvastatin (>20 mg), lovastatin and simvastatin
Oral contraceptives	CYP enzyme inhibition	Plasma levels ↑ with atorvastatin/rosuvastatin, combine with low doses of these statins.

While not all pharmacokinetic drug interactions result in clinically significant outcomes, dose-dependent side effects are more common with combination treatments; therefore, statin doses have been limited in co-administration with CYP inhibitors. Drug interactions with statins may change not only the plasma statin levels but also the circulatory concentration of concomitant medications, which is why treatment should be scheduled taking into account the potential interactions in patients receiving treatment with multiple drugs.

Interactions and precautions with commonly used drugs: The drugs statins commonly interact with and relevant precautions are provided in the table. Generally rosuvastatin, pravastatin, pitavastatin and fluvastatin exhibit lower interaction potentials. Genetic factors, life style and comorbidities also play an important role in drug interactions. Grapefruit and other citrus juices should be limited to 60 mL/day. Allowing at least 4 hours between citrus juices and the statin dose reduces the interaction. Because alcohol is also metabolized in the liver, statin users are recommended to not exceed 2 standard alcoholic beverages per day. The elderly are the group at highest risk in terms of drug interactions and undesirable effects due to age-related polypharmacy, age-related functional changes and low muscle mass, and these patients should be monitored closely.

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Statins should be used with caution in heavy alcohol consumers or in patients with hepatic impairment, and statin treatment should be discontinued in the event of active disease or new onset and persistent elevation in transaminase levels. It should be noted that dose adjustment is required in patients with chronic renal impairment (particularly with creatinine clearance <30 mL/min). Fluvastatin, pitavastatin and in some cases pravastatin should be preferred in patients with HIV on antiretroviral therapy, and statins which are not metabolized by CYP3A4 should be used with antiviral agents in patients with hepatitis C.

The recommendation for the clinicians in clinical practice is to be closely familiar with the statins they use and also be knowledgeable regarding their interactions with commonly used drugs, and to refer to interaction tables when necessary. Benefit-risk assessment should be performed in patients receiving treatment with multiple drugs. The best solution in statin-drug interaction is to replace the statin or the other drug with an equivalent agent (preferably with one that is metabolized by a different pathway). If the combination cannot be changed in moderate interactions, the statin dose should be reduced to the lowest recommended level. In all cases, patients should be monitored closely in terms of side effects, symptoms and signs.

Question 59 – In which patients can we use bile resins for lipid-lowering treatment? What are the relevant considerations?

Dr. Fahri Bayram

Erciyes University Faculty of Medicine, Endocrinology and Metabolism Diseases Department, Kayseri

Bile acid binding resins (sequestrants) are indigestible substances which bind to bile acids to form insoluble compounds in the intestines and are excreted via feces. This binding reduces the enterohepatic cycle of bile acids, leading to disappearance of the "negative feedback" effect on the conversion of cholesterol to bile acids. Correspondingly, the decreased cholesterol content in hepatocytes lead to increased expression of low-density lipoprotein (LDL) receptors and result in elevated serum LDL-C levels. The main resins used in clinical practice are cholestyramine and colestipol, followed by colesevelam and colestimide. Cholestyramine preparations are available in our country.

Cholestyramine and colestipol are commonly used for the treatment of cholestasis-associated pruritus which may occur particularly in primary sclerosing cholangitis. Additionally, recent studies show that resins may also be used in diabetes treatment owing to their favorable effects on insulin resistance.

Although these agents are inexpensive and safe, they are associated with high rates (30-50%) of non-adherence to treatment due to common gastrointestinal side effects such as constipation, abdominal pain, nausea and bloating. These side effects are more frequently seen with high doses (16-20 g/day). Because these agents may increase triglyceride (TG) levels, they are not recommended in patients with TG levels >400 mg/dL. While they may be used safely in patients with triglyceride levels <200 mg/dL, they should be used with caution in

patients with TG levels 200-400 mg/dL. Furthermore, drugs in this group may decrease the intestinal absorption of several drugs (warfarin, tetracycline, furosemide, penicillin G, hydrochlorothiazide, propranolol, digoxin, gemfibrozil) and vitamins (vitamin A, D, E and K). Colesevelam, the recent member of the group, is thought to cause less gastrointestinal side effects with doses of 2.6-3.8 g/day as well as reducing the absorption of concomitant drugs to a lesser extent.

As monotherapy, cholestyramine 8-10 g/day or colestipol 10-12.5 g/day decrease LDL-C levels by 15-25% and increase HDL-C by 3-5%. These agents have been demonstrated to show more potent effects when used with statins or ezetimibe. Cholestyramine and other bile acid binding resins are used as monotherapy in the absence of hypertriglyceridemia for moderately elevated LDL-C levels, in patients who do not respond to diet and exercise, and in second or third line treatment. They may also be used in combination therapy with statins or ezetimibe in cases with resistance to medical treatment. These agents, colesevelam in particular, are more safe compared to other antilipemic drugs and may therefore be considered for monotherapy when medical treatment is required in young individuals and in women of child-bearing potential who wish to become pregnant. Bile acid resins are considered as a good alternative in cases with mandatory medical treatment and in dyslipidemic patients intolerant to statins (patients with hepatic or renal impairment).

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Question 60 – Is niacin still considered within the context of anti-lipid therapy?

Dr. Zerrin Yiğit

Istanbul University Cardiology Institute, Cardiology Department, İstanbul

Niacin (Nicotinic acid = vitamin B3 = vitamin PP) is a pyrimidine derivative. It plays the co-factor role for several dehydrogenase enzymes. Therefore, it has vasodilator and antilipemic effects at high doses. It activates the hormone-sensitive lipase in adipose tissue. It reduces the fatty acid mobilization from adipocytes. Niacin decreases the release of very low-density lipoprotein (VLDL) particles by inhibiting the diacylglycerol acyltransferase-2 enzyme in the liver. This reduces the intermediate (IDL) and low-density lipoprotein (LDL) particles. Niacin increases apolipoprotein (apo)-A1 and high-density lipoprotein cholesterol (HDL-C) levels by inducing apo-A1 production in the liver.^[1] As a result, plasma HDL-cholesterol increases while LDL-C and triglyceride levels are decreased. Niacin increases HDL-C by 15-35% in a dose-dependent manner and reduces LDL-C by 15-18%, TG by 20-40%, and lipoprotein [Lp(a)] levels by 30% with a dose of 2 g/day. It is the only agent to provide Lp(a) reduction. The favorable effects of this agent have been shown in "HDL-Atherosclerosis Treatment Study (HATS)" and "Familial Atherosclerosis Treatment Study (FATS)", which was based on angiographic measurements.^[2]

The major side effects of niacin include redness on the face and neck (flushing), pruritus and urticaria, peptic ulcer flare-up, hyperglycemia and hyperuricemia, and cholestatic jaundice and hepatitis. It may cause orthostatic hypotension by lowering blood pressure due to the vasodilation effect. Flushing and orthostatic hypotension often occur during chronic use and in a dose-dependent manner as a secondary effect to prostaglandin synthesis. Niacin use is contraindicated during pregnancy.

Considering all of these favorable effects of niacin, two large, randomized outcome studies have been planned. "Atherothrombosis Intervention in

Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH)" study included 3414 patients who received simvastatin 40 or 80 mg with the necessary ezetimibe addition. The patients were randomized to ER-niacin 1500-2000 mg/day (1718 patients) and placebo (1696 patients) groups. At two years, niacin was observed to increase HDL-C significantly (from 35 mg/dL to 42 mg/dL) and decrease TGs from 164 mg/dL to 122 mg/dL with LDL-C reduction from 74 mg/dL to 62 mg/dL. However, no significant difference was seen in primary endpoints.^[3]

A total of 25673 patients were randomized to the "Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE)" study. Simvastatin at moderate-high dose was given to all patients. Laropiprant 40 mg was administered with ER-nicotinic acid 2 g in order to reduce the side effects of niacin, and comparison was performed versus placebo. During the 3.9-year long follow-up, niacin was observed to lower LDL-C by 10 mg and increase HDL-C by 6 mg on average; however, no difference was seen between the two groups in terms of cardiovascular events (13.2% vs. 13.7%). Serious problems were encountered in the niacin group in terms of diabetes control and a significantly greater number of side effects were observed in this group.^[4]

These two large-scale studies did not show any favorable effects of niacin on cardiovascular events. Therefore, European Medicines Agency (EMA) has removed niacin from treatment options for hyperlipidemia in Europe.^[5] While 2013 ACC/AHA lipid guidelines recommend niacin as add-on to statin or as a single agent in individuals with statin intolerance, it is not included in the reports issued in 2014 and 2016.^[6]

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Question 61 – Does fish oil have LDL-cholesterol lowering effects?

Dr. Tahir Durmaz

Ankara Yıldırım Beyazıt University Faculty of Medicine, Cardiology Department, Ankara

Omega 3 (n-3, ω3) fatty acids [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] are components of fish oil and Mediterranean diet. Omega-3 polyunsaturated fatty acids are known as "fish oil" as they are abundantly found in oily fish. While the underlying mechanism of action remains poorly understood; the related effect is thought to be associated partially with the ability to interact with PPARs and partially with the reduced apolipoprotein (apo)-B release.

Omega-3 fatty acids do not have low-density (LDL) cholesterol-lowering effects. On the contrary, pharmacological doses (2-4 g/day) of omega-3 fatty acids reduce triglycerides by 30% at while higher doses may cause mild increases in LDL-cholesterol levels. Omega-3 fatty acids exert their main effect on triglyceride levels without significant effects on other lipoproteins. Some studies have shown mild (<5%) increases in high-density lipoprotein (HDL) cholesterol with these fatty acids while other studies did not demonstrate such an effect. Studies with high doses including EPA have shown reduction up to 45% in triglyceride levels in a dose-dependent manner. Food and Drug Administration (FDA) has approved prescribing n-3 fatty acids in addition to diet in the event of dietary triglyceride levels exceeding 496 mg/dL. It should be noted that pharmacological doses provide reduction particularly in very low-density lipoprotein (VLDL) levels. Alpha-linoleic acid (medium-chain n-3 fatty acid found in chestnuts, some vegetables and seed oils) has smaller effects on triglyceride levels.

2016 European Dyslipidemia guidelines include a Class IIa recommendation to add n-3 fatty acids as combination therapy when triglyceride levels cannot be managed with statins and fibrates and a Class IIb recommendation to add 1 g/day to treatment in patients with heart failure. However, clinicians

should take into account the gastrointestinal side effects when initiating treatment with these preparations.

While 2016 European guidelines include recommendations suggesting that cardiovascular (CV) events and stroke risk may be reduced in primary prevention by consuming fish twice a week and using low doses of medium-chain n-3 fatty acid supplements based on observational studies, fatty acids have been shown to have no major effects on plasma lipoprotein metabolism. A Japanese study conducted in patients with hypercholesterolemia reported a 19% reduction in CV endpoints; however, these findings are not deemed convincing and the efficacy appears to be associated with non-lipid effects. National Institute for Health and Care Excellence (NICE) guidelines do not recommend the use of omega-3 fatty acid alone or in combination therapy in patients with type 1 diabetes, those with type 2 diabetes and subjects with chronic renal impairment or in other patients considered for primary or secondary CV prevention as there is limited evidence on this approach. Two recent randomized controlled studies, namely "REDUCE-IT (Reduction of Cardiovascular Events with EPA-Intervention Trial)" and "STRENGTH (Outcomes Study to Assess STatin Residual Risk Reduction with EpaNova in HiGh CV Risk PatienTs with Hypertriglyceridemia)" currently investigate the potential benefits of EPA on cardiovascular endpoints in patients with elevated triglyceride levels. Both being large-scale studies, it is planned to enroll approximately 8,000 patients in the REDUCE-IT study and approximately 13,000 patients in the STRENGTH study. The results of these currently ongoing studies are expected to guide the use of omega-3 fatty acids in CV prevention.

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Question 62 – What is the mechanism of action of ezetimibe? How much LDL-cholesterol lowering can it provide? Could it be used alone?

Dr. Murat Sezer

Istanbul University Istanbul Faculty of Medicine, Cardiology Department, Istanbul

Ezetimibe inhibits the absorption of dietary and biliary cholesterol by interfering with the cholesterol transport on intestinal wall. The effect of this agent is highly specific and does not alter the absorption of triglycerides, fatty acids or fat-soluble vitamins.

Mechanism: Ezetimibe is localized in the enterocytes in brush border of the small intestine and specifically inhibits the uptake and absorption of cholesterol by binding the "Niemann-Pick like 1 protein" (NPL-1) sterol transporter in enterocytes.^[1] Additionally, ezetimibe has been shown to inhibit the uptake of oxidized low-density lipoprotein (LDL) in macrophages. This finding suggests effects of ezetimibe also beyond the interstitial epithelium. The inhibitory effect on the transport of dietary and biliary cholesterol from the intestines to the liver decrease the hepatic cholesterol reservoir, thereby leading to up-regulation in HMG-CoA reductase activity. Therefore, this agent inhibits cholesterol absorption and induces cholesterol synthesis at the same time. For this reason, it is recommended to be used as a complementary agent in combination with statin treatment to reduce plasma total cholesterol levels. The synergistic effect occurs with the combination of cholesterol synthesis-reducing effect of statins and the cholesterol absorption-inhibiting effect of ezetimibe.

Pharmacokinetics: After oral ingestion, ezetimibe is rapidly glucuronidated in the small intestine and enters enterohepatic recirculation, affecting only the region of impact (brush border of the small intestine) without any systemic effects. It has a long half-life (approximately 22 hours) owing to enterohepatic recirculation, and a once-daily dose is therefore sufficient. It does not interfere with food and other drugs.

Efficacy: In monotherapy, ezetimibe 10 mg daily decreased LDL-cholesterol (LDL-C) by 17-20% while increasing high-density lipoprotein (HDL)

cholesterol by 2%.^[2] The use of ezetimibe together with atorvastatin 10 mg provides a LDL-C reduction (54%) equal to the reduction achieved with atorvastatin 80 mg alone (53%).^[3] The comparison of these ratios are comparable across other statin combinations as well.^[4] Providing a different and complementary effect, the addition of ezetimibe may be useful to meet treatment goals in patients who fail to achieve targets with statin treatment, particularly in patients with familial hypercholesterolemia. During treatment, the reduction in LDL-C levels start at 2 weeks.^[2]

Side effects: In combination therapy with statins, the safety profile is generally no different than that of statin monotherapy. AST and ALT elevations of more than 3-fold have been observed only in less than 1% of patients receiving ezetimibe. The incidences of myopathy and myositis are also very low (incidence of 10-fold increase in creatine kinase: <1%) and comparable to the incidences seen with statins. Because this agent is not metabolized by cytochrome P450, it does not interfere with the plasma concentrations of other concomitant drugs.

In summary, ezetimibe monotherapy may provide significant LDL-C reduction (17-20%) in patients with mild to moderate hypercholesterolemia, it is more appropriate to use this agent in combination therapy with statins in clinical practice owing to the complementary synergistic effects. The combination of ezetimibe with a statin allows achieving target LDL-C levels in a greater number of patients with a decreased need for dose titration, and does not constitute an additional risk in terms of the side effect profile. Ezetimibe combination should be considered taking into account the high tolerance profile, particularly in patients for whom it is deemed inappropriate to use the maximum dose of statin treatment.

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Question 63 – Does ezetimibe provide any benefits in cardiovascular prevention?

Dr. Sema Güneri

Dokuz Eylül University Faculty of Medicine, Cardiology Department, İzmir

Currently, it is a universally accepted fact that statins play an important role in the primary and secondary prevention of cardiovascular (CV) disease by significantly decreasing total cholesterol and low-density lipoprotein (LDL) levels as well as reducing triglyceride levels, although to a lesser extent. However, 1-3% of patients are unable to receive statin treatment due to contraindications or gastrointestinal side effects or myalgia. Furthermore, some patients fail to achieve the target levels with the use of statins. Therefore, non-statin treatments have become important. In this context, bile acid sequestrants and nicotinic acid are effective; however, these agents are not widely used owing to poor tolerability and side effects.

The meta-analysis of 8 randomized placebo-controlled studies conducted with ezetimibe has shown 18.6% reduction in LDL-cholesterol at the end of 12 weeks in 2722 patients ($p < 0.00001$). Total cholesterol was observed to be decreased by 13.5% with 8.1% reduction in triglyceride levels and 3.0% increase in high-density lipoprotein (HDL) cholesterol values ($p < 0.00001$). Ezetimibe has been shown to be well-tolerated with a side effect profile comparable to that of placebo.^[1]

The SANDS study has investigated atherosclerosis regression in carotid artery by monitoring 499 patients with type 2 diabetes for 36 months. The reduction in carotid intima-media thickness has been found to be similar in both groups receiving statin monotherapy or statin+ezetimibe combination.^[2]

On the other hand, the SHARP study included 9270 patients with chronic renal impairment. Among these, 3023 were receiving dialysis and had no history of myocardial infarction or previous coronary

revascularization. These patients were divided into two groups in a placebo-controlled randomized manner where the treatment arm received simvastatin 20 mg +ezetimibe 10 mg. At the end of a mean follow-up of 4.9 years, simvastatin+ezetimibe was associated with a significant reduction of 17% in major atherosclerotic events compared placebo ($p = 0.0021$).^[3]

IMPROVE-IT is another recent, randomized, double-blind study investigating the effect of adding ezetimibe to statins on CV events in patients with Acute Coronary Syndrome (ACS). The study included 18,144 patients hospitalized with ACS within the last 10 days. The baseline values of these patients were LDL-cholesterol 50-100 mg/dL during lipid-lowering treatment and LDL-cholesterol 50-125 mg/dL without lipid-lowering treatment. Half of the patients were given simvastatin 40 mg+placebo while the other half was given simvastatin 40+ezetimibe 10 mg. The primary endpoint evaluated with long-term follow-up (avg. 6 years) included CV death, non-fatal myocardial infarction, hospitalization due to unstable angina, coronary revascularization or non-fatal stroke. At the end of the study, LDL-cholesterol levels were 69.5 mg/dL in the simvastatin monotherapy group versus 53.7 mg/dL in the simvastatin +ezetimibe group ($p < 0.001$). Primary endpoints were observed in 32.7% of the simvastatin +ezetimibe group compared to 34.7% in the simvastatin monotherapy group ($p = 0.016$). There were no differences between the two groups in terms of muscle pain or hepatic side effects. Cancer occurrence was also similar between the two groups. This study showed significantly reduced LDL-cholesterol and CV events in ACS patients with the addition of ezetimibe to statins in long-term.^[4]

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Question 64 – Which patients should receive ezetimibe?

Dr. Hakan Karpuz

Istanbul University Cerrahpaşa Faculty of Medicine, Cardiology Department, İstanbul

The role of dyslipidemia in cardiovascular disease is a well-established notion in current cardiology practices. We have strong weapons against this important risk factor and the importance of statins in this context is uncontroversial; however, other alternative agents to be used with or instead of statins have been a subject of interest as statin treatment may be inappropriate or insufficient in some cases. Ezetimibe is the leading drug among the alternative agents. Recent studies have clarified our insight on this agent and have led it to be included in current guidelines.

European Society of Cardiology (ESC) 2015 guidelines indicate ezetimibe as a treatment option stating that "further LDL-C lowering with a non-statin agent should be considered in patients with low-density lipoprotein cholesterol (LDL-C) levels >70 mg/dL after non-ST elevation acute coronary syndrome despite receiving statin treatment with the maximum tolerable dose"^[1] (Table 1). The 2015 National Lipid Association (NLA) guidelines also recommend ezetimibe in combination treatment with

first-line statin as "a controlled clinical study has shown decreased atherosclerotic cardiovascular disease events with the addition of this agent to statin treatment".^[2] American Diabetes Association (ADA) recommends "moderate-dose statin + ezetimibe in ACS patients aged 40 years or older who have LDL-C levels above 50 mg/dL and cannot tolerate high-dose statins" in their 2016 guidelines.^[3] Similarly, British NICE guidelines stated this year that "ezetimibe may be an appropriate option for the treatment of primary hypercholesterolemia when adequate control cannot be achieved regarding serum total cholesterol or LDL-C concentrations in adults who start receiving statin treatment".^[4] The 2016 version of American College of Cardiology (ACC) guidelines also demonstrated their approach to position this agent in treatment stating that "ezetimibe is recommended as the first choice instead of adding a PCSK9 inhibitor to treatment or continuing the treatment with a PCSK9 inhibitor in patients who fail to achieve 50% or further reduction in their LDL-C levels despite receiving statin treatment with the maximum tolerable dose".^[5]

Table 1. The Position of Ezetimibe in Current Guidelines

Guidelines	Year	Recommendations
ESC	2015	Further LDL-C lowering with a non-statin agent should be considered in patients with LDL-C levels >70 mg/dL NSTEMI-ACS despite receiving statin treatment with the maximum tolerable dose ^[1]
NLA	2015	Ezetimibe is recommended in combination treatment with first-line statin as a controlled clinical study has shown decreased ASCVD events with the addition of this agent to statin treatment. ^[2]
ADA	2016	Moderate-dose statin + ezetimibe is recommended in ACS patients aged > 40 years who have LDL-C levels > 50 mg/dL and cannot tolerate high-dose statins ^[3]
NICE	2016	Ezetimibe is recommended as option for the treatment of Primary Hypercholesterolemia when adequate control cannot be achieved regarding serum total cholesterol or LDL-C concentrations in adults who start receiving statin treatment ^[4]
ACC	2016	Ezetimibe is recommended as the first choice instead of adding a PCSK9 inhibitor to treatment or continuing the treatment with a PCSK9 inhibitor in patients who fail to achieve 50% or further reduction in their LDL-C levels despite receiving statin treatment with the maximum tolerable dose ^[5]
ESC	2016	Statin + ezetimibe is the only combination with evidence on providing clinical benefit in the treatment of dyslipidemia ^[6]
ESC-EAS	2016	The benefits of LDL-C lowering are not specific for statin treatment. Statin + ezetimibe combination should be considered in post-ACS patients if LDL-C targets cannot be achieved with the highest tolerable dose of statin treatment ^[7]

Finally, the ESC 2016 update;^[6] emphasized that "statin + ezetimibe is the only combination with evidence on providing clinical benefit in the treatment of dyslipidemia. Taken together, ezetimibe

should be the first-choice treatment with the available strong evidence when statins cannot be used or sufficient to achieve treatment targets in dyslipidemia treatment.

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Question 65 – Should we administer combination treatment in patients who achieve the LDL-cholesterol target with persistently high triglyceride levels? Which combination treatment should we use?

Dr. Ertan Ural

Kocaeli University Faculty of Medicine, Department of Cardiology, Kocaeli

Low-density lipoprotein cholesterol (LDL-C) is the main molecule involved in the increased cardiovascular risk in atherogenic dyslipidemia. While LDL-C has the predominant role in atherogenesis, epidemiological data suggest that triglycerides may also be a risk factor for CV disease.^[1] LDL-C levels is adopted as the primary target in the approach to atherosclerosis in all guidelines.^[2] Triglycerides (TG) on the other hand, are commonly recommended as the primary target of treatment in patients with TG levels >500-1000 mg/dL as these levels are associated with an increased risk of pancreatitis.^[2] However, the approach in patients with elevated TG levels (>150-200 mg/dL – <500 mg/dL) when LDL-C targets are achieved remains a subject of debate.

Studies on Fibrate-Statin Combination

In the ACCORD study,^[3] patients with diabetes were randomized to receive fenofibrate or placebo following simvastatin treatment for one month. While LDL-C levels were decreased from 100 mg/dL to 81 mg/dL in both groups, TG levels were reduced from 164 to 122 mg/dL in the fenofibrate group versus a reduction from 160 to 144 mg/dL in the placebo group. However, a mean follow-up of 4.7 years showed no difference between the groups in the composite endpoint [non-fatal myocardial infarction (MI), non-fatal stroke or CV death] ($p=0.32$). This study has shown no additional benefits with fibrate (low-dose) directly added to statin treatment in patients with diabetes.

Studies on Niacin-Statin Combination

The AIM HIGH and HPS2 THRIVE studies investigating niacin-statin combination also revealed discouraging results.^[4,5] AIM HIGH showed that niacin effectively decreased TG levels in patients aged >45 years with CV disease and LDL-C levels lowered to 70 mg/dL with simvastatin -plus ezetimibe when required- who had elevated TG (>150–400 mg/dL) and low HDL (<40 mg/dL for men, <50 mg/dL for women) values at baseline although there was no benefit in the composite primary endpoint consisting of coronary-related death, non-fatal MI, ischemic stroke, acute coronary syndrome and revascularization ($p=0.79$). In fact, the rate of ischemic stroke was unexpectedly higher in those receiving niacin. The HPS2 THRIVE study

randomized secondary prevention patients of 50-80 years of age to receive niacin 2 g/laropiprant 40 mg or placebo following simvastatin 40 mg plus ezetimibe 10 mg, if required (mean LDL-C achieved 64 mg/dL). The four-year long follow-up no differences between the two groups in terms of the first major vascular event, which was evaluated as the primary endpoint (non-fatal MI or coronary-related death, any stroke and revascularization). Furthermore, while using niacin made it more difficult to control blood sugar levels in patients with diabetes, an increase was observed regarding patients newly diagnosed with diabetes. Moreover, gastrointestinal ulcer, myopathy, skin rash, bleeding and infections were also more common in the niacin group.

Based on these two clinical studies and the previously conducted ACCORD study, which revealed no clinical benefits, the Food and Drug Administration (FDA) has withdrawn the previously granted approval for the co-administration of statins with niacin or fibrates.

Studies on Omega-3 and Statin Combination

The JELIS study investigating the combination of eicosapentaenoic acid (EPA) with a statin is completely irrelevant in terms of providing an answer to the question in this context.^[6] In the JELIS study, patients with total cholesterol levels >250 mg/dL who were completely different in terms of CV risk (primary prevention and secondary prevention) were grouped together and were randomized to receive EPA-statin combination or statin alone without considering baseline TG levels. Subsequently, the groups were compared based on the frequency of coronary artery disease which occurred during the follow-up by observing whether they had achieved LDL and non-HDL-cholesterol targets. However, one of the findings of this study showed 38% reduction in major coronary events in patients receiving combination therapy compared to those receiving statin alone among subjects who failed to achieve their LDL and/or non-HDL cholesterol targets.

In summary, there is insufficient evidence on the benefits of combination treatment in patients with persistently high TG values despite adequately lowered LDL levels based on the currently available information.

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Question 66 – When should we add fibrates to statin treatment?

Dr. Kubilay Karşıdağ

Istanbul University Istanbul Faculty of Medicine, Internal Diseases Department, Endocrinology and Metabolism Division, Istanbul

Hypercholesterolemia is one of the important actors in the etiopathogenesis of atherosclerotic cardiovascular (CV) disease. However the "Atherogenic Lipoprotein Phenotype" consisting of hypertriglyceridemia, low HDL-cholesterol levels and increased small-density LDL-cholesterol is much more atherogenic in terms of atherosclerotic disease development compared to hypercholesterolemia.

The commonly accepted notion in all guidelines developed for the treatment of atherosclerotic CV diseases is to lower LDL as the primary target of treatment. Statins are the first-choice treatment for this purpose. While fibrates show favorable effects on lipid profile when used for the treatment of hypertriglyceridemia, the favorable effects of this group of drugs on CV endpoints is different than that of statins. Studies on primary and secondary prevention have revealed no effects or insignificant effects on all-cause mortality and cardiac mortality. The exception of this controversial subject is the patients with metabolic syndrome and borderline-increased triglyceride levels with low HDL-C values (<40 mg/dL) accompanied by triglyceridemia >200 mg/dL indicating an insulin-resistant lipid profile.

Insulin resistance and the resulting type 2 diabetes is the most important cause of atherosclerosis. The two major problems regarding the physiopathology of insulin resistance and type 2 diabetes are glucotoxicity (hyperglycemia) and lipotoxicity (hypertriglyceridemia). Hypertriglyceridemia disrupts not only the insulin consumption in peripheral tissues but also the functions of beta cells. Increased plasma free fatty acids have other effects as well: disrupts glucose consumption, interrupts the normal cell signal transduction cascade, causes mitochondrial damage via increased ROS, and activates cellular

stress response. The change in cytokine secretion alters islet response to nutrients.

In summary, hyperglyceridemia worsens insulin resistance and type 2 diabetes as does hyperglycemia, consequently leading to an atherogenic lipid profile.

Because this physiopathological mechanism is specific to metabolic syndrome and type 2 diabetes, treatment of hypertriglyceridemia in these two conditions translates into treatment of macrovascular disease, thereby treatment of hyperglycemia. This mechanism may explain the difference regarding the effect of treating triglycerides on prognosis in hypercholesterolemic patients without metabolic syndrome and diabetes.

Hypertriglyceridemia is also one of the factors involved in the etiopathology of acute pancreatitis. There is an increased risk of pancreatitis in diabetes, even in the absence of hypertriglyceridemia. Pancreatitis eventually accelerates beta cell damage, which worsens hyperglycemia.

In practice, the approach to combination treatment with statin + fibrate may be as follows: If triglyceride levels are higher than 500 mg/dL, fibrate therapy must be initiated regardless of receiving statin treatment. Exercise, alcohol restriction and diet play a very important role in providing the appropriate regulation during hypertriglyceridemia treatment. Once the non-medication factors are managed, fibrate should be added to treatment particularly in patients with insulin resistance- based conditions whose triglyceride levels are higher than 200 mg/dL. Micronized fibrates should be preferred in combination treatment in order to minimize muscle damage.

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Question 67 – What is PCSK9 and why is it so popular?

Dr. Abdullah Tunçez

Selçuk University Faculty of Medicine, Cardiology Department, Konya

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease containing 692 amino acids. It was initially described in central nervous system and was referred to as "neural apoptosis regulated convertase 1".^[1] In 2003, Abifadel et al. identified a mutation in the PCSK9 region of chromosome 1 in two families with autosomal dominant familial hypercholesterolemia.^[2] In 2006, Zhao et al. reported two patients with Low-density lipoprotein cholesterol (LDL-C) levels of 15 mg/dL in whom blood PCSK9 were undetectable.^[3] These two excellent studies inspired all the studies in these field.

The key function of PCSK9 in lipid metabolism is the breakdown of LDL-R on the surface of hepatocytes. Investigators have shown increased LDL-C levels in the presence of gain-of-function mutations in PCSK9 whereas loss-of-function mutations of PCSK9 have been associated with reduced LDL-C levels. Increased PCSK9 levels and decreased LDL-R result in elevated LDL-C levels.

The currently available guidelines report very low rates of achieving target LDL-C levels, i.e. approximately 53% in patients receiving statin treatment. On the other hand, statin intolerance affects 10-20% of patients treated with statins. Other anti-lipid drugs such as ezetimibe and niacin provide mild reductions in LDL-C levels and there are controversial data regarding the effects of these

agents on cardiovascular mortality.^[4] Therefore, there is an unmet need of more potent drugs to achieve lower LDL-C levels, particularly in patients at high risk (e.g. coronary artery disease) and in familial hypercholesterolemia.

Investigators have focused on PCSK9 inhibition to reduce LDL-C levels. For this purpose, monoclonal antibodies such as evolocumab (AMG-145), alirocumab (REGN-727) and bococizumab (RN-316) have been developed. These monoclonal PCSK9 antibodies are completely specific to PCSK9. The reason of the popularity of these novel agents is the fact that they have been shown to provide 60-75% reduction in LDL-C levels. Phase 3 clinical studies have also demonstrated 60% additional reduction in LDL-C with the use of these agents in addition to standard of care (treatment with statins or other drugs). Preliminary results of the studies have suggested tendency to decreased rates of cardiovascular events as well.^[5]

Several large-scale, randomized studies on these agents are currently ongoing and we expect that we will soon meet a novel and encouraging drug group following statins for the treatment of hypercholesterolemia. We believe that these drugs will be introduced to clinical practice in the near future to be used particularly in patients with familial hypercholesterolemia and in patients with high cardiovascular risk.

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Question 68 – In which patients can we use PCSK9 inhibitors and for whom should we use it?

Dr. Sadi Güleç

Ankara University Faculty of Medicine, Cardiology Department, Ankara

PCSK9 Inhibitors (Alirocumab and Evolocumab) in ESC/EAS 2016 Guidelines on Dyslipidemia

1. The indication group is Class 2b in patients at very high risk who cannot tolerate statins or fail to achieve the target despite treatment with the highest tolerable doses of statin and ezetimibe (Translates into that they may be used in these patients; however, not using would not be incorrect, either).

2. PCSK9 inhibitors have a Class 2a indication in patients with familial hypercholesterolemia in the presence of concomitant cardiovascular disease or multiple risk factors or in the presence of statin intolerance (Because the risk is very high and treatment options are limited in patients with familial hypercholesterolemia, it is thought that PCSK9 inhibitors* proven to effectively lower LDL would be beneficial in these patients).

* While both molecules are indicated in heterozygous patients, only evolocumab is indicated in patients with homozygous disease.

ACC 2016 Consensus Report: The Use of Non-Statins LDL-Cholesterol Lowering Drugs

1- It is recommended to decide using additional drugs after discussing the potential benefits and risks with the patient if targets cannot be achieved with the highest tolerable doses of statin treatment in patients with atherosclerotic cardiovascular disease. In the event that the patient refuses additional drugs, treatment should be continued with statin alone, and

if the patient accepts additional treatment, ezetimibe should be the first choice followed by an PCSK9 inhibitor.

2- It is recommended to inform the patient on potential benefits and risks of adjunct therapy in patients with LDL-cholesterol ≥ 190 mg/dL (potential familial hypercholesterolemia patients) regardless of the presence of concomitant atherosclerotic disease. When the decision is in favor of add-on therapy, PCSK9 may be considered before trying ezetimibe (due to very high levels of LDL-cholesterol and the limited LDL-lowering effect of ezetimibe).

Personal Opinion

In the absence of robust evidence, it is inevitable to make decisions on clinical judgment. I would consider using PCSK9 inhibitors in 2 patient groups:

The first group is the patients who present with acute coronary syndrome despite statin treatment. In terms of LDL-cholesterol values, I would prefer patients with levels greater than 100 mg/dL.

The second group is the patients with familial hypercholesterolemia, in the name of providing an opportunity for these subjects unfortunate from birth. In this group, I would select patients with LDL levels higher than 160 mg/dL despite treatment with a statin and ezetimibe. I hope that we will soon have evidence and personal judgments will be left behind...

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Question 69 – How should we use the PCSK9 inhibitor? Which side effects should be considered while monitoring?

Dr. Meral Kayıkçıoğlu

Ege University Faculty of Medicine, Cardiology Department, İzmir

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have started a new period in anti-lipid treatment with monoclonal antibody technology, and the most important difference regarding these agents is the fact that they are periodically administered via subcutaneous injection.

Administration, dosage: Among the monoclonal antibodies developed against PCSK9, those that are most likely to be introduced to clinical practice are presented in Table 1.^[1,2] Among these, alirocumab is administered as a single dose every 2 weeks, and it may provide an advantage in terms of offering different doses of 75/150 mg for dose titration. Bococizumab is available as 150 mg only, administered as a single dose every 15 days. Evolocumab is available as a single dose treatment; however, it has the advantage of being administered every 2 weeks (140 mg) or once a month (420 mg). While the monthly administration is advantageous, it differs from the other dose by requiring 3 injections on 3 different extremities.^[2]

Anti-lipid efficacy: The agents are similar in terms of efficacy on lipid levels. They provide reductions up to 50% - 60 mg in LDL-C levels (reduction compared to placebo is 39-62% with alirocumab and 47-56% with evolocumab). The LDL-C values achieved with these agents are the

lowest levels achieved to date. LDL-C levels reduced to less than 25 mg/dL in two consecutive measurements have been reported with 37% of patients receiving evolocumab and in 24% of those receiving alirocumab.^[3] Furthermore, the anti-lipid efficacy occurs with the initial dose (within the first 15 days). Therefore, the initial dose allows understanding whether it is likely to provide any benefit.

Side effects: Currently, there are no serious side effects reported to be associated with PCSK9 inhibition. There is also no clinical report on the development of neutralizing antibodies. The frequency of injection site reactions is also low. Theoretically, some potential side effects have been suggested. These include: 1 possibility of increased viral infections as LDL receptors also have a viral entry function,^[4] effects on sugar metabolism as insulin resistance and glucose intolerance have been reported in subjects with R46L-PCSK9 loss-of-function mutation^[5] and increased visceral fat and decreased free fatty acid clearance due to effects on apolipoprotein B.^[6] Furthermore, monitoring continues for potential neurological complications as PCSK9 expression has also been detected in central nervous system.^[1]

Table 1. PCSK9 inhibitors

Agent	Alirocumab	Evolocumab	Bococizumab
Dose and frequency of administration	75 mg, 1 administration every 2 weeks 150 mg, 1 administration every 2 weeks	140 mg, 1 administration every 2 weeks 420 mg, 1 administration every 4 weeks	150 mg, 1 administration every 2 weeks
Company	Sanofi	Amgen	Pfizer

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Question 70 – Do PCSK9 inhibitors provide cardiovascular prevention?

Dr. Lale Tokgözoğlu

Hacettepe University Faculty of Medicine, Cardiology Department, Ankara

Reducing low-density lipoprotein cholesterol (LDL-C) levels provides plaque stabilization and significant reduction in coronary events. While guidelines recommend lowering LDL-C to certain target levels, this may not always be possible with the currently available treatments. The highly increased lowering achieved with emerging PCSK9 inhibitors has led to great expectation and hope regarding treatment. These agents also reduce apolipoprotein B, total cholesterol, triglyceride, non-HDL cholesterol and lipoprotein(a) levels while increasing HDL and apolipoprotein A1 levels.

Studies have shown that PCSK9 inhibitors provide effective LDL-C reduction both as monotherapy and in combination therapy with a statin and/or ezetimibe. These agents decrease LDL-C by approximately 50-60% (~~39-62% with alirocumab and 47-56% with evolocumab~~). Similar significant reduction have been observed in patients not receiving statin treatment, in those receiving moderate- or high-dose statin, and in patients receiving treatment with ezetimibe. Age, gender, diabetes and risk levels also affect the outcomes. Results up to one year have been found similar to those seen at 12 weeks.

The main expectation with PCSK9 inhibitors is whether they affect cardiovascular (CV) endpoints. There 4 currently ongoing phase III placebo-controlled studies expected to provide clinical data from >70,000 patients.

The ODYSSEY outcome study^[1] compares alirocumab versus placebo in 18,000 patients who experienced acute coronary syndrome within the last 2-12 months undergoing maximum dose treatment with atorvastatin or rosuvastatin. The ey inclusion criterion is LDL-C levels >70 mg/dL in this study. Repeated measurements in patients receiving 75 mg alirocumab showing LDL-C levels <15 mg/dL is considered as the criterion to discontinue the study. The dose is increased to 150 mg in patients with LDL-C >50 mg/dL. Patient enrollment has been

completed in this study and it will demonstrate whether it is beneficial to lower LDL-C levels to <50 mg/dL with PCSK9 inhibition in secondary prevention patients who recently experienced acute coronary syndrome.

The FOURIER study^[2] evaluates 27,500 patients with stable CV disease receiving statin treatment with the optimal dose. Inclusion criterion for this study is LDL-C >70 mg/dL or non-HDL cholesterol >100 mg/dL. The patients receive evolocumab 140 mg every 2 weeks or 420 mg every 4 weeks. Dose titration is not employed in this study. Patient enrollment has been completed in this study which will clarify the effect of adding evolocumab to statin treatment on CV events in stable patients with coronary artery diseases for secondary prevention.

The 2 placebo-controlled phase III studies conducted with bococizumab^[3] are currently enrolling patients. In these studies, subjects at very high risk of CV events will receive bococizumab 150 mg every 2 weeks. Among these, it is planned to enroll 17,000 patients with LDL-C levels of 70 to 100 mg/dL in the SPIRE-1 study and to enroll 9,000 patients with LDL-C levels >100 mg/dL in the SPIRE-2 study. These studies are expected to clarify the effect of PCSK9 inhibitors on CV event development in patients without CV disease who are at high risk and included in primary prevention.

In conclusion, PCSK9 inhibitors are novel, effective and encouraging agents which reduce apolipoprotein B and lipoprotein(a) levels as well as LDL-C in patients with familial or non-familial hypercholesterolemia receiving or not receiving statin or ezetimibe.^[1] This LDL reduction is expected to reflect in CV events. The GLAGOV study, which will be announced this year, will report the effect of evolocumab on coronary arteries investigated with intravascular ultrasonography. The currently ongoing studies with these agents are expected to determine the main position of their position in the treatment of dyslipidemia.

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Question 71 – Could genetics be a determinant for anti-lipid therapy?

Dr. Bahadır Kırılmaz

Çanakkale Onsekiz Mart University Faculty of Medicine, Cardiology Department, Çanakkale

Genetic analyses have associated several single nucleotide polymorphisms with low-density lipoprotein (LDL) cholesterol levels and cardiovascular (CV) risk.^[1] Therefore, the role of genetics on anti-lipid therapy has become an important subject matter. Current European and American guidelines on dyslipidemia pay particular attention on familial dyslipidemia. In the current practice, available anti-lipid therapies and diet options re observed to be often insufficient to meet target LDL-cholesterol values. This is particularly more important in people with familial dyslipidemia and studies are ongoing to develop individualized treatment options.

Familial combined hyperlipidemia is the most common form (1/100) of familial dyslipidemias. It is characterized by elevated triglyceride and LDL-cholesterol levels. Another commonly seen form of familial dyslipidemia is familial hypercholesterolemia (FH) (1/200-500).^[1] Some centers perform genotyping for these patients and other forms in order to estimate the CV risk. Genotyping is an encouraging method; however, it is currently associated with high costs. Furthermore, genetic diagnosis is no mandatory in FH as the diagnosis can be established with clinical findings.

The most commonly encountered mutations in genetic investigations on FH are the LDL-receptor and apolipoprotein B mutations.^[2] The finding of mutations related to favorable lipid profiles and low LDL-cholesterol levels in genetic studies have increased the hope to develop novel anti-lipid agents. An example of this may be the association between proprotein convertase subtilisin/kexin type 9 (PCSK9) levels and LDL-cholesterol levels. Genetic studies have shown that gain-of-function mutations in PCSK9 cause hypercholesterolemia whereas loss-of-

function mutations are associated with low LDL-cholesterol levels and reduced risk of CV disease. The finding that deletion of PCSK9 gene had no unfavorable effects on vital functions in animal experiments have led to studies on the inhibition of this enzyme.^[3] Anti-PCSK9 monoclonal antibodies have created a novel therapeutic approach by providing LDL-cholesterol reductions up to 70%. These studies led to the development of PCSK9 inhibitors such as alirocumab, evolocumab and bococizumab.^[2] While these agents have been shown to provide significant reduction in LDL-cholesterol in the short-term, their long-terms effects are evaluated in currently ongoing studies. With these anti-lipid agents, new and robust evidence have been demonstrated regarding the determining role of genetics in dyslipidemia treatment. The 2014 consensus report issued by European Atherosclerosis Society has recommended using PCSK9 inhibitors in the treatment algorithm of homozygous FH cases.^[1] The 2016 ESC guidelines on dyslipidemia treatment recommend these agents as an option in the event of no response to treatment with statins in FH patients with very high risk.^[4]

The significant effect of genetic background on cholesterol metabolism, which plays a role in the development of CV diseases, is clearly seen in FH. Related evidence show that genetic characteristics is a determinant of treatment planning and treatment success as well as CV risk estimation. It appears to be an appropriate strategy to determine genetic factors prior to anti-lipid therapy in subjects at high CV risk with elevated LDL-cholesterol levels and to plan their treatment according to these factors. However, there are currently several issues regarding genetic-based treatment such as high cost and questions on the side effects and long-term effects of LDL-cholesterol reduction on CV mortality.

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Question 72 – What is LDL apheresis? For whom should it be performed? At what age should apheresis be started?

Dr. Ahmet Temizhan

Turkey Higher Specialty Hospital, Cardiology Clinic, Ankara

What is LDL apheresis?

This method refers to selectively removing low-density lipoprotein (LDL) from the blood and returning the remaining blood components with the aim of extracorporeal treatment. A single apheresis application reduces LDL-cholesterol levels by 65-70% and decreases the expression of adhesion molecules. Because LDL-cholesterol levels increase within 1-2 weeks, apheresis should be repeated with intervals of 1-2 weeks.

Currently, there are 6 main systems in use.^[1]

Immunoabsorption: Uses columns containing anti-lipoprotein (apo)-B antibodies.

Dextran sulphate columns: Removes apo-B lipoproteins from the plasma by means of electrostatic interaction.

Heparin extracorporeal LDL precipitation (HELP): Precipitation of apo-B with heparin in low-pH setting.

Direct absorption of lipoproteins by means of hemoperfusion: Removal of apo-B lipoproteins from whole blood by means of electrostatic interaction using polyacrylate-covered polyacrylamide beds.

Dextran sulphate cellulose columns: The same method as the second method above; however, this method uses whole blood.

Membrane differential filtration: LDL is filtered from the plasma.

The cholesterol-lowering effects and side effects are similar with all of these methods. Recently, Food & Drug Administration (FDA) have withdrawn dextran sulphate plasma adsorption and HELP systems.

For whom should it be performed?

According to the National and American Apheresis Association guidelines on therapeutic apheresis application in clinical practice, LDL apheresis is recommended for patients with homozygous (HoFH) and heterozygous familial hypercholesterolemia (HeFH). Both guidelines

emphasize the indication criteria for LDL apheresis from three countries.^[1-3]

FDA

Functional HoFH patients with LDL-cholesterol >500 mg/dL

Functional HeFH patients with no known history of coronary heart disease (CHD) and LDL-cholesterol >300 mg/dL

Functional HeFH patients with CHD history and LDL-cholesterol >200 mg/dL

Germany

In HoFH patients,

Patients with severe hypercholesterolemia whose LDL-cholesterol cannot be adequately reduced with maximum diet and documented medical treatment for a period of longer than 12 months.

Patients with cardiovascular disease (CHD, peripheral arterial occlusive disease, cerebrovascular disease) accompanied by isolated lipoprotein(a) level >60 mg/dL and borderline LDL-cholesterol levels documented with clinical and imaging methods.

International FH Management Panel (Spain)

Lipid apheresis is recommended as the standard of care for HoFH patients.

It is recommended to be used in HeFH patients with symptomatic CHD whose LDL-cholesterol is reduced less than 40% or remain >160 mg/dL despite maximal treatment.

The recently issued European Atherosclerosis Society consensus report on FH states that lipoprotein apheresis may be considered without any specific criteria in patients with HoFH.^[4]

What is the ideal age to initiate apheresis?

Apheresis provides more benefits in parallel with early initiation. Ideally, it should be started before 5 years of age and no later than 8 years of age. While skin deposits regress in patients for whom apheresis is initiated later, particularly the progression of aortic valve stenosis cannot be halted and the risk of mortality and morbidity cannot be lowered as intended.^[5]

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Question 73 – What are the considerations for patients undergoing LDL-apheresis?

Dr. Meral Kayıkçioğlu

Ege University Faculty of Medicine, Cardiology Department, İzmir

Lipid apheresis (LA) remains as the most effective treatment method for patients with homozygous familial hypercholesterolemia (HoFH).^[1-4] However, continuous LDL-C lowering is required in order to achieve the true life-saving effect of this approach. The fact that apheresis needs to be performed periodically makes this difficult. LDL-C levels tend to increase rapidly after the procedure and return to previous values within a few days although it may

vary from patient to patient. The anti-lipid drugs the patient receives also affect this process. Therefore, weekly LA treatment is recommended in HoFH.^[4-6] Frequency of the procedure and the duration of each procedure should be determined taking into account the patient adherence, severity of disease (clinically and in terms of lab values) and the status of progressive cardiovascular (CV) disease.

Table 1. Monitoring and scanning scheduled employed for homozygous familial hypercholesterolemia at the Lipid Polyclinic of Ege University Faculty of Medicine Cardiology Department

	At the time of diagnosis	During follow-up	Remarks
History Physical examination	+	+	Repeated physical examination every 3 months
Family history (premature CV event, xanthoma, xanthelasma, consanguineous marriage etc.)	+	-	After obtaining family history, all family members are evaluated for lipid profile and clinical assessment, if possible (family scanning).
Lipid profile [total cholesterol, LDL, HDL, triglycerides, lipoprotein(a)]	±	±	While full lipid panel is monitored every 3 months, T. cholesterol and LDL-C checked before and after each apheresis session in patients with no abnormalities except LDL
Biochemistry analyses	+	+	CRP, LFT, RFT, Albumin, BS, Electrolytes, TSH, Hemogram at baseline. All except TSH are repeated every 3 months during follow-up. Pre- and post-apheresis Ca ⁺² , Hemogram, Albumin control.
Scanning for CV risk factors and patient education (including the family)	+	+	Every 3 months during follow-up
ECG	+	+	Every 3 months during follow-up
Echocardiography	+	+	Every 6-12 months depending on valve involvement
Carotid Doppler USG	+	+	Annually
Renal artery Doppler USG	+	±	Annually (every 2 years in non-problematic patients)
Eye fundus examination	+	+	Annually
Exertion test	+	±	Every 6 months in the absence of symptoms
Measurement of Achilles tendon thickness (ultrasonography or X-ray)	+	±	Annually
Coronary CT angiography	±	±	Not routinely, varies based on clinical status of the patient
Coronary angiography	-	-	Not routinely, varies based on clinical status of the patient
Cardiac MR imaging	±	±	Routinely performed at baseline in the presence of valve involvement, repeating decided based on clinical status of the patient

CRP: C-reactive protein; LFT: Liver function tests, RFT: Renal function tests, BS: Blood sugar; TSH: Thyroid-stimulating hormone; CT: Computed tomography, MR: Magnetic resonance.

Progression or recurrence of CV disease is reported in 25% of the patients even with regular LA treatment.^[7] Therefore, LDL-C reduction in the acute period should be approximately 60% in order to deem LA treatment as successful (Table 1).^[4-6]

However, measuring pre- and post-apheresis LDL-C alone is not sufficient to assess treatment efficacy as LDL-C levels tend to increase within a short period of time. For this reason, several formulas have been developed to show the time-LDL change.^[4] The current National Therapeutic Apheresis Guidelines state the treatment goal as "reducing LDL-C by 40-60% and temporally averaged cholesterol level by 45-55%".^[4] It is recommended to continue treatment indefinitely and adjust the procedure frequency (usually every 1-2 weeks) to maintain target levels after reduction to specified temporally averaged cholesterol levels and LDL-C levels.^[1-6] It should be noted that the LDL-C levels recommended for primary and secondary prevention is 100 and 70 mg/dL in these patients, respectively.^[6]

LA is not commonly used as it is a costly, not easily accessible, time-consuming and invasive method. Apheresis-related side effects include hypotension during the procedure, abdominal pain, nausea, hypocalcemia, iron deficiency anemia and allergic reactions.^[2,3] Therefore, patients should be

closely monitored during the procedure. ACE inhibitors should not be used on the day of the apheresis procedure. Syncope and decreased output is more common in these patients. The duration of procedure should be longer and apheresis rate should be slower in order to prevent this, particularly in patients with aortic stenosis. Albumin, hemoglobin etc. are removed from the blood to some extent during the LA procedure. These levels should also be monitored. Discomforting symptoms and hypocalcemia may occur in some patients owing to the use of citrate in some apheresis methods. Post-session Ca²⁺ levels should be measured.

LA treatment is associated with high rates of treatment rejection and discontinuation. The rate of treatment persistence was reported as 60% in an adult apheresis series at Ege University.^[2] Patients end up weary and non-compliant due to the invasive nature of the procedure as well as being a chronic and time-consuming method. The unfavorable effect on family, school and work may also increase non-adherence. Because the condition is chronic and as apheresis is associated with unpopular characteristics, depressive mood may develop and reduce adherence to treatment. Therefore, LA centers must provide psychological consultancy services as well. Another way of increased treatment adherence is to educate the patient and their family on FH.

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Question 74 – What is familial hypercholesterolemia? How is the diagnosis established? Is genetic diagnosis essential for treatment?

Dr. Meral Kayıkçıoğlu

Ege University Faculty of Medicine, Cardiology Department, İzmir

Familial hypercholesterolemia (FH) is metabolic disorder resulting from the genetic absence of low-density lipoprotein (LDL) receptors in the liver.^[1-4] This condition shows autosomal dominant inheritance and is characterized by extremely high serum cholesterol levels with associated cholesterol deposition on the skin, tendons and arterial wall together with premature, severe cardiovascular (CV) events. The cholesterol deposition, particularly accumulating in proximal regions of the vessels, lead to severe ostial stenosis in coronary arteries and aortic stenosis in homozygous individuals. Blood cholesterol levels are 250-500 mg/dL in heterozygous subjects, with CV events occurring in the age groups of 30-50 years in men and 40-60 years in women.^[3] Blood cholesterol levels are much higher (500-1000 mg/dL) in homozygous FH (HoFH) and severe atherosclerosis starts from early childhood in these patients.^[1-3]

In recent years, FH has been acknowledged as the most common genetic disorder. While FH incidence in Turkey remains unknown, a rough estimation may be 1/100 to 1/200 for carriers.^[4]

FH develops as a result of mutations in the genes encoding LDL-receptors, apolipoprotein B (apo B) and proprotein convertase subtilisin/kexin type 9 (PCSK9) or LDL-R adapter protein 1 (LDLRAP 1) proteins, although rarely.^[1,3,4] The most common

cause of this condition appears to be LDL-receptor defects. Therefore, response to statin treatment is often inadequate.

Although a genetic disorder, FH does not require analysis for diagnosis. The diagnosis is notably simple as it is based on the history of CV events, blood LDL-C levels and physical examination findings. While there are several scales developed for diagnosis, we recommend using the "Dutch Lipid Clinic Network" criteria in our country.^[1-4] In this scale, LDL-C >190 mg/dL accompanied by history of early-onset (<55 years of age in men, <60 years of age in women) CV disease is sufficient for diagnosis. However, suspicion should arise starting from LDL-C 160 mg/dL. LDL-C cut-off values are lower in children and young adults.

Early diagnosis is very important in FH, which is a major cause of premature heart attacks. In the event of achieving lipid reduction with early diagnosis, these patients may live a completely normal life. Therefore, scanning appears to be increasingly important for this condition. Current guidelines emphasize that CV risk estimation is not required in these patients owing to exposure to elevated cholesterol levels from birth and that they should be considered at high risk in any age group.^[3] LDL-C levels are <70 mg/dL for those with CV event history, and <100 mg/dL for primary prevention.

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Question 75 – What should be the treatment algorithm in heterozygous familial hypercholesterolemia?

Dr. Vedat Sansoy

Istanbul University Cardiology Institute, Cardiology Department, İstanbul

Heterozygous familial hypercholesterolemia (HeFH) requires cholesterol-lowering lifestyle modifications and medical treatment immediately from the time of diagnosis. Because cardiovascular (CV) risk is high in these patients, low-density lipoprotein cholesterol (LDL-C) levels should be <100 mg/dL for primary prevention and <70 mg/dL in the presence of CV event history.^[1-2]

Treatment requires effective management of risk factors starting from early age. Most of the patient require high-dose treatment with potent statins such as atorvastatin or rosuvastatin. In the event of inadequate effect with high-dose statins and intolerance, cholesterol absorption inhibitors, bile acid binders, niacin or stanol esters may be used as combination therapy; however, the benefit of these agents are known to be limited. Among the alternative drugs, ezetimibe is the most appropriate agent to be used with a statin, providing additional LDL-C reduction by 15-20%. It is indicated for use in individuals older than 10 years of age in US and Europe.^[1-2]

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are among the novel agents currently unavailable in our country and they have been granted approval in US and Europe to be used in FH treatment as they lower LDL-C levels by preventing the breakdown of LDL-receptors. These agents provide LDL-C reduction up to 60% when they are used as monotherapy or in combination treatment with statins. Therefore, using these agents should be considered in the event of LDL-C levels which remain much higher despite treatment with a statin or ezetimibe and in the presence of CV disease or family history of premature CV disease in HeFH. They may also be used in patients who cannot tolerate statins or those with high lipoprotein(a) levels. As a matter of fact, the 2016 European Society of Cardiology guidelines state that treatment with PCSK9 inhibitors may be considered in the presence of CV disease in HeFH or in subjects at very high risk of CV diseases [other CV risk factors, family

history, elevated lipoprotein(a) levels] and in the event of statin intolerance.^[3]

While there are no placebo-controlled studies on HeFH conducted in children, observational studies show improved endothelial functions, decelerated atherosclerosis development and reduced CV outcomes with statin treatment initiated in early years of life. Cardiovascular-protective diet and statin treatment may be initiated at 8-10 years of age. Statin treatment should be started with a low-dose and increased until achieving the target. Target LDL-C levels are <155 mg/dL in children ages 8-10 years, and <135 mg/dL in those older than 10 years of age (all statins have been granted approval for use in those older 10 years of age, and pravastatin indicated for use from 8 years of age in USA). Once treatment is initiated; lipid levels, body weight, physical and sexual development and liver enzymes should be monitored. Women should be warned as statins are contraindicated during pregnancy and lactation. Early onset treatment in FH may reduce CV disease risk to near-normal levels. Despite being a relatively less potent statin, pravastatin may be preferred in children as it is not associated with the cytochrome P450 system in the liver, hence less likely to interact with other drugs.

LDL apheresis is indicated in patients who cannot achieve adequate LDL-C reduction despite medical treatment.^[4,5] FDA approves LDL apheresis in patients with HeFH if LDL-C levels persist higher than 300 mg/dL in subjects without CV disease and higher than 200 mg/dL in patients with CV disease despite appropriate diet and maximally tolerated combination treatment for 6 months. The National Lipid Association Expert Panel on Familial Hypercholesterolemia (NFHAP) recommends apheresis as adjunct therapy in HeFH patients with symptomatic CAD whose LDL-C remain >160 mg/dL or reduce by less than 40% despite maximal treatment. The recent National Therapeutic Apheresis Guidelines issued by the Republic of Turkey Ministry of Health state that LDL apheresis indication may be based on one of the several inclusion criteria employed globally.^[5]

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Question 76 – How should we approach the patient with homozygous familial hypercholesterolemia?

Dr. Öner Özdoğan

Tepecik Training and Research Hospital, Cardiology Department, İzmir

Early diagnosis and treatment are critical to prevent cardiovascular (CV) mortality in homozygous familial hypercholesterolemia (HoFH).^[1,3] HoFH often presents with premature CV events in 2nd decade of life and/or very high cholesterol levels or cholesterol deposits on the skin (Table 1).^[1,3] Conventional risk factor assessment is not meaningful in these patients owing to exposure to high cholesterol levels from birth.^[2]

Diet is recommended due to its other CV benefits although it may not be considerably effective in HoFH patients who are negative for low-density lipoprotein (LDL) receptor (LDL-R). The management of CV risk factors should be maintained effectively. The goal of HoFH treatment is to chronically lower LDL-C levels to <70 mg/dL for primary prevention and to <100 mg/dL for secondary prevention.^[4] To achieve this, statins (high-intensity), ezetimibe, resins and apheresis in the event of no response should be used in this order (Figure 1).^[3] While anti-lipid therapy (statins) may not be sufficient to lower LDL-C levels to target values, statin treatment should be initiated at the maximum

tolerated dose immediately after diagnosis owing to the effect of preventing/delaying CV events.

Table 1. Diagnostic criteria in homozygous FH

1. Confirmation of alterations in 2 mutant alleles associated with FH with genetics tests or
2. LDL-C \geq 500 mg/dL in those not receiving treatment and/or LDL-C \geq 300 mg/dL* during treatment together with:
 - Presence of skin or tendon xanthomas before 10 years of age or
 - LDL-C values suggesting untreated heterozygous FH in both parents*

*These LDL-C levels are only descriptive. Lower LDL-C values do not rule out homozygous FH, particularly in children or in adults receiving treatment. FH: Familial hypercholesterolemia.

The second step in treatment is to add ezetimibe (10 mg/day), which provides additional LDL-C reduction by 15%. Acetylsalicylic acid should be used for CV protection, even in asymptomatic patients.^[1]

LDL apheresis should be regularly performed once or twice a week in HoFH cases.

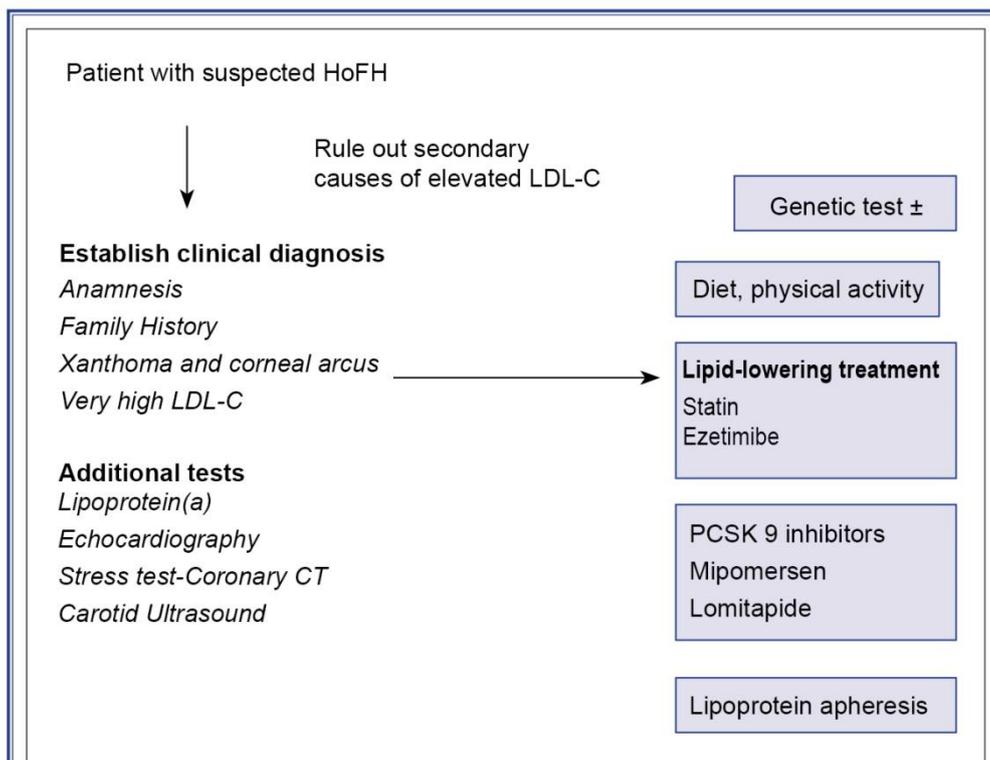


Figure 1. Approach to patients with homozygous familial hypercholesterolemia.

Treatment should be preferably initiated before 6-7 years of age.^[1-5] Although a life-saving treatment in HoFH, it is a difficult approach in real-life setting with low rates of adherence. In fact, new treatments are sought to provide more chronic and effective lipid reduction and more readily accessible options. There are 3 drug groups which have moved from clinical development to clinical use for this purpose. These agents are proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors which prevent LDL-R breakdown, anti-sense oligonucleotides which

prevent apolipoprotein (apo)-B synthesis (mipomersen) and lomitapide, the microsomal triglyceride transfer protein (MTTP) inhibitor which prevents transfer to very low-density lipoprotein and chylomicrons. FDA has approved the use of mipomersen and lomitapide in HoFH in 2012. PCSK9 inhibitors may be effective in HoFH patients with residual LDL receptor activity. Among these agents, evolocumab has been granted approval for patients with HoFH.

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Question 77 – What is mipomersen? Who may use it?

Dr. Mehmet Birhan Yilmaz

Cumhuriyet University Faculty of Medicine, Cardiology Department, Sivas

Mipomersen is a second-generation anti-sense oligonucleotide containing 20 amino acids which targets human messenger RNA related to apo-B-100, the apolipoprotein (apo) pf low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL).^[1] The hybridization of mipomersen and sister RNA causes in RNase-mediated mRNA degradation, leading inhibited translation of the expected protein product, i.e. apo-B-100.^[1] A dose of 200 mg/dL administered via subcutaneous route once a week provides a mean reduction of 25% in LDL cholesterol per injection.^[2] However, LDL-cholesterol reduction of 70% have also been reported in some cases. The most common adverse events seen during mipomersen treatment include injection site reactions (rates up to 84% with 5% of injection site reactions leading to treatment discontinuation), flu-like symptoms and serum transaminase elevations (particularly ALT, with rates up to 17%.^[2] This agent causes essentially fatty liver; however, this is a class effect seen in all anti-apo-B agents due to preventing apo-B formation rather than a side effect. While clinical relevance is unknown, Food & Drug

Administration (FDA) has initiated monitoring for this consideration.

Mipomersen has been recommended as an add-on therapy to lipid-lowering agents and diet to provide further LDL-cholesterol reduction in patients with homozygous familial hypercholesterolemia (HoFH)^[3] (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologyandMetabolicDrugsAdvisoryCommittee/UCM323927.pdf>).

SIS 301012-CS5 (HoFH), MIPO3500108 (severe hypercholesterolemia), ISIS301012-CS7 (HeFH), ISIS301012-CS12 (high risk as per the NCEP ATP III guidelines) are the major studies of the mipomersen development program. There is limited data on the safety and efficacy of mipomersen in patient groups except HoFH patients (e.g. heterozygous FH or patients with high cardiovascular risk).^[4,5] Furthermore, currently there is no clinical study on cardiovascular outcomes.

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Question 78 – Do cholesteryl ester transfer protein inhibitors play a role in dyslipidemia treatment?

Dr. Mehmet Birhan Yılmaz

Cumhuriyet University Faculty of Medicine, Cardiology Department, Sivas

Cholesteryl ester transfer protein (CETP) is responsible for the transfer of cholesteryl esters from high-density lipoprotein cholesterol (HDL-C) to low-density lipoprotein (LDL) and to very low-density lipoprotein (VLDL). It is a HDL-dependent hydrophobic glycoprotein mainly released from Kupffer cells in the liver.^[1] Therefore, CETP inhibition is expected to increase HDL-C levels and decrease LDL-C. Because there is a strong inverse correlation between HDL-C levels and the risk of cardiovascular (CV) events, hypothetically, increasing HDL-C levels with CETP inhibition has the potential to improve CV outcomes. There are at least five different CETP inhibitors which have been defined and completed phase II programs until date (Table 1): torcetrapib,^[2] dalcetrapib,^[3] anacetrapib,^[4]

evacetrapib,^[5] TA-8995.^[6] Among these, the programs for torcetrapib, evacetrapib and dalcetrapib are currently ongoing. There are several potential explanations of the unsuccessful results obtained in clinical studies with these agents including hyperaldosteronism, disrupted endothelial function, reduced endothelial nitric oxide, increased endothelin production and elevated CRP levels.^[7,8] However, a more recent analysis of the Dal-Outcome study showed that the effect of dalcetrapib on CV outcomes was determined by polymorphisms in the ADCY9 gene and that the appropriate genetic profile was detected in approximately one in every five patients, leading to significant protection against CV disease; however the exact translational mechanism has not been understood.^[9]

Table 1. Comparison of CETP inhibitors

Company	Drug	HDL ↑	Status
Dal-Cor Pharmaceuticals	Dalcetrapib	40%	15.871 patients Dal-Outcomes is an event-driven study (acute coronary syndrome within the 4-12 weeks prior to enrollment) which has been terminated upon demonstrating in expediency during the second interim analysis. 5,000 patients Dal-GenE is an event-driven study initiated in 2016 and planned to be completed 2020.
Merck Research Laboratories	Anacetrapib	138.1%*	30.000 patients REVEAL is an event-driven study for which the results are expected to be announced in 2017
Eli Lilly & Company	Evacetrapib	86%*	12,000 patients ACCELERATE is an event-driven study which was terminated in 2015 upon demonstrating in expediency.
Pfizer Inc.	Torcetrapib	72.1%	15,067 patients The ILLUMINATE study was terminated early, in 2006, due to increased mortality associated with the use of torcetrapib
Dezima Pharma	TA-8995	179.1%*	A multi-center randomized phase 2 double-blind placebo-controlled parallel group study with monotherapy or combination treatment with a statin in patients with mild dyslipidemia (TULIP study)

*In line with the Phase II program

Therefore, the Dal-GenE study which is based on individualized treatment has been initiated. It appears to be a reasonable approach to try a CETP inhibitor

without potential hazardous pleiotropic effects in patients with low HDL-C levels and high CV risk.

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Question 79 – What is lomitapide? Who should use it? Is there a specific considerations for monitoring?

Dr. Levent Hürkan Can

Ege University Faculty of Medicine, Cardiology Department, İzmir

Lomitapide is a microsomal triglyceride transfer protein (MTP) inhibitor. This agent inhibits MTP in the intestine and liver, preventing the transfer of triglycerides and phospholipids to very low-density lipoprotein (VLDL) and chylomicrons.^[1,2] Inhibiting the formation of VLDL, the precursor of LDL is expected to lower LDL-C levels. MTP inhibition reduces not only LDL-C but also all atherogenic lipoproteins that contain apolipoprotein (apo) B. Therefore, lomitapide would provide benefit in hypertriglyceridemia considered as residual risk and in mixed lipid disorders.^[2,3] However, because the LDL-C-lowering effect of this drug is highly prominent, it is used only in homozygous familial hypercholesterolemia (HoFH).

Lomitapide for oral use has been shown to reduce LDL-C and apo-B levels by 50% and lipoprotein (a) levels by 15% in addition to standard of care during 26 weeks of treatment in HoFH patients.^[3] Furthermore, adding lomitapide to treatment in patients undergoing LDL apheresis was also shown to eliminate the need for apheresis or allow decreasing the apheresis frequency in 34% of the patients during the 26 weeks.

Lomitapide was granted FDA approval in 2012 owing to its LDL-C, apo-B and non-HDL cholesterol

lowering effects as an adjunct therapy with maximal treatment (\pm apheresis) in HoFH patients.^[2,3] As expected with orphan drugs and rare diseases, there was a limited number of clinical studies, which raised concerns; however, it was approved without waiting for the results of further studies as it indicated an encouraging treatment option in HoFH, which is a condition associated with high mortality rates. EMA, the European authority approved lomitapide in 2013. Lomitapide received EMA approval to be used alone or with LDL apheresis in addition to other lipid-lowering treatments and low-fat diet for the treatment of adult patients with HoFH.

Lomitapide may cause severe diarrhea and flatulence as side effects owing to being effective in the intestines. In order to avoid these side effects, patients should adhere to a very strict, low-fat diet (with $<20\%$ of the total energy derived from fat).^[1-3] Lipid-soluble vitamin supplements should be used in addition to medical treatment. An expected side effect of this agent is fat deposition in the liver. Studies have shown 9% increase in liver fat in 26 weeks and 8% increase in 78 weeks.^[2,3] Lomitapide-associated fatty liver is related to chronic use and appears to be reversible side effect. In fact, this is an expected effect of all novel anti-lipid agents which reduce apo-B levels.^[1-3]

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Question 80 – What should we do in patients at high or very high risk with baseline LDL values under target levels, should we use statins?

Dr. M. Akif Düzenli

Selçuk University Meram Faculty of Medicine, Cardiology Department, Konya

To date, efficacy and safety of statin treatment have not been evaluated in patients at high and very high cardiovascular (CV) risk with low density lipoprotein cholesterol (LDL-C) values below target levels. Currently, only limited and indirect data from observational studies or subgroup analyses of some large studies are available on this subject.

In a subgroup analysis of the TNT study comparing low- and high-dose atorvastatin treatment in patients with stable angina pectoris; less clinical events developed without any increased risk in patients whose mean baseline LDL-C values were 84 mg/dL which dropped below 64 mg/dL with both treatment regimens. The greatest clinical benefit was obtained in patients with baseline LDL-C values of 72 mg/dL which decreased below 40 mg/dL with treatment.^[1] In an observational study in patients with stable angina pectoris with unknown baseline LDL-C values, less CV events were observed among patients with LDL-C levels of 70-100 mg/dL compared to those with values between 100-130 mg/dL after statin treatment while reducing LDL-C below 70 mg/dL showed no additional benefit.^[2] However, the larger number of patients with heart failure in the group in which LDL-C was reduced below 70 mg/dL as well as different types and doses of statins and the study design make it difficult to interpret these findings.

In the PROVE-IT TIMI 22 study, less CV events were observed in patients whose LDL-C levels decreased to <40 mg/dL and 40-60 mg/dL with statin

treatment among patients with acute coronary syndrome.^[3]

Low LDL-C is considered as an indicator of poor health status and is associated with increased mortality in the elderly and in disabled individuals, those with malnutrition, advanced heart failure and multiple comorbidities. This is known as the lipid paradox.^[4]

ACC-AHA 2013 guidelines recommend statins regardless of LDL-C values in patients with atherosclerotic CV disease. In ESC-EAS 2016 guidelines, high dose statin is recommended in all patients with acute coronary syndrome while medical treatment may be considered in patients at very high or high risk with LDL-C values below target levels. In light of the available evidence, starting statin treatment at doses based on the age and clinical characteristics of the patient appears to be a reasonable approach in patients with acute coronary syndrome whose LDL-C levels are below the target. As for patients at high or very high risk with baseline LDL-C values below the target, personalized treatment would be more appropriate. Avoiding statin treatment and advising lifestyle modifications would be more rational for patients previously described as those for whom low LDL-C levels indicate increased mortality, for those with very low LDL-C levels (30-40 mg/dL) and those receiving several drugs. Low-dose statin treatment may be considered in apparently healthy patients for whom statin treatment is considered to be harmless.

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Question 81 – What is the normal range for LDL-cholesterol in children and young adults? Does family history of early atherosclerosis change cut-off values for hypercholesterolemia in children?

Dr. Sema Kalkan Uçar

Ege University Faculty of Medicine Pediatrics Department, Division of Pediatric Metabolism and Nutrition, İzmir

Unlike the homozygous form, heterozygous familial hypercholesterolemia (FH) in children and young adults does not manifest itself by physical examination findings such as tendon xanthomas. Since the patient remains asymptomatic during this period, family history and lipid levels constitute the basis for their assessments.^[1] Evaluation of lipid levels are predominantly made through LDL-cholesterol (LDL-C). Normal LDL-C values recognized by international sources are shown in Table 1.^[2] However, there are conflicts regarding the "cut-off values" of this condition. There are various definitions based on "normal", "borderline" and "definite" values for disease. According to the consensus decrees of experts from 2011 American National Health Heart, Lung and Blood Pressure Institute for children and adolescents, LDL-C <110 mg/dL is considered as normal, 110-129 mg/dL as borderline, and ≥ 130 mg/dL as high.^[3] According to Simon Broome scale of United Kingdom, a LDL-C level <155 mg/dL is normal for children <16 years; and LDL >155 mg/dL plus presence of one of the two following conditions a) total cholesterol >290 mg/dL or coronary artery disease in adult relatives [<50 years in 2nd degree relative (e.g. grandfather, grandmother, uncle) or <60 years in a 1st degree relative (mother, father, sibling)] or b) total cholesterol >260 mg/dL in 1st degree relatives younger than 16 years makes the individual a "potential" heterozygous FH patient.^[1] For definitive diagnosis, LDL >155 mg/dL is required in addition to presence of tendon xanthomas in the patient him/herself or in 1st or 2nd degree relatives. Detection of LDL-receptor, Apo-100, PCSK9 mutations refers to "definite" disease.^[1] In the scale system of the Netherlands, a LDL-C level <159 mg/dL is considered normal. Presence of early (<55 years for males and <60 for females) cardiovascular (CV) events in family history, a LDL-C level above 95th percentile in 1st degree relatives and/or tendon xanthomas are meaningful for the relevant individual.^[4]

Table 1. Lower and upper limits for LDL-cholesterol in children and young adults

Age groups	LDL-Cholesterol (mg/dL)	
	Male	Female
Cord blood	10/-50	10/-50
1-9 years	60/-140	60/-150
10-19 years	50/-170	50/-170
20-29 years	60/-175	60/-160

Double screening is recommended during childhood as per a call in 2011 since high LDL-C has a "silent" course in children and young adults: the first screening between 9-11 years of age followed by the second screening between 17-21 years of age. In addition, presence of CV risk factors (hypertension, type I and II diabetes mellitus, overweight or obesity) is also a "selective" cause for screening.^[5]

In conclusion, many centers and diagnostic scaling declarations agree to: considering a LDL-C value of 160 mg/dL (measured at least twice) as the cut-off value in children. Values above 160 mg/dL are considered "meaningful" in case of early CV event in the relevant individual. Values above 190 mg/dL are considered as diagnostic for heterozygous FH regardless of familial CV disease, high cholesterol and apparent unfavorable personal lifestyle (such as immobility, smoking, nutritional habits and obesity). This approach is also important in practice since these values influence the decision to start pharmacotherapy.^[4]

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Question 82 – What is the appropriate age and dose to initiate statin treatment in children?

Dr. Mahmut Çoker

Ege University Faculty of Medicine Pediatrics Department, Division of Pediatric Metabolism and Nutrition, İzmir

In the treatment of hypercholesterolemia, a "step by step" treatment approach is preferred particularly in heterozygous familial hypercholesterolemia (FH).^[1] Therefore, lifestyle modifications (exercise, diet, smoking cessation for adolescents) for at least 3-6 months is desired before starting pharmacotherapy in the follow-up of a child with hypercholesterolemia. A diet known as CHILD-2 (saturated fatty acids should not exceed 7% of total calories and cholesterol consumption should be below 200 mg/day) is recommended. For children older than five years of age, herbal steroids or stanols may be considered.^[2] Although sports activities have no moderate effect directly on LDL-cholesterol (LDL-C), enhancing daily physical activities is desired based on the concept that it may have an indirect benefit by increasing HDL-cholesterol and insulin sensitivity.^[3]

Statins may be started as the leading pharmacotherapy in FH between 8-10 years of age. Pravastatin is approved by FDA and EMA starting from 8 years of age and simvastatin, lovastatin, atorvastatin, fluvastatin and rosuvastatin over 10 years of age.^[2] In recent articles, pitavastatin has been found to be effective and safe between 6-17 years of age.^[4] Basic principles of statin treatment are: presence of at least 2 separate measurements showing high LDL-C; choosing the initial dose as low as possible, and establishing the titration based on LDL-C decline rates and patient tolerability (Table 1).^[1] Statins are recommended if LDL-C is ≥ 190 mg/dL in children without family history and if LDL-C is ≥ 160 mg/dL in children with a family history of early atherosclerotic disease. The goal is usually reducing LDL-C to <130 mg/dL or a drop $\geq 50\%$; however, based on age: LDL-C values are defined as <155 mg/dL for 8-10 years of age and 135 mg/dL for >10 years of age.^[2] In Cochrane analysis reports, LDL-C decline is reported to be 32% (21-39%) depending on the type and dose of statins.^[3]

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Table 1. Standard treatment doses for anti-lipid agents

	Adults	Children and adolescents
Simvastatin	10-80 mg/day	10-40 mg/day
Atorvastatin	10-80 mg/day	10-40 mg/day
Pravastatin	20-80 mg/day	20-40 mg/day
Fluvastatin	20-80 mg/day	20-40 mg/day
Rosuvastatin	10-40 mg/day	10-20 mg/day
Cholestyramine	12 g/day	6 g/day
Ezetimibe	10 mg/day	5 mg/day

Despite infrequent side effects with statins in children, care should be taken with regard to muscle cramps, gastrointestinal complaints, elevations in hepatic function tests and rhabdomyolysis. Growth, pubertal development and lipid profile as well as liver and muscle enzymes should be monitored in children before and during treatment with statins. Besides, treating physicians should be knowledgeable particularly on drug interactions.^[2]

A reduction of approximately 15% in LDL-C levels has been reported in children using resins. Because of their gastrointestinal side effects, these agents are rather preferred in troublesome cases for statin safety in daily practice (for instance, in small children). Ezetimibe is generally used together with statins in patients with severe phenotype who are poorly controlled with statins.^[1]

In the Netherlands, achieving LDL-C target levels was reported in only 21% of children.^[5] Agents including PCSK9 inhibitors, Lomitapide and Mipomersen are continued to be investigated for more effective treatment in order to meet this need.^[2]

Question 83 – Can we position statin use during percutaneous coronary intervention (PCI)? Should statin loading be performed prior to PCI?

Dr. Oğuz Yavuzgil

Ege University Faculty of Medicine, Cardiology Department, İzmir

Percutaneous coronary intervention (PCI) is an important component of the treatment in many clinical presentations of coronary artery disease when used together with optimal pharmacological therapy. However, myocardial damage during PCI has negative impacts on prognosis both in the short and long-term. Even short-term use of statins before PCI has been shown to have clinical benefits and reduce myocardial damage during the procedure. Although the mechanism is unknown, statins may have a similar mechanism to stabilization of atherosclerotic plaques, prevention of coronary slow flow, reduction of restenosis and reduction of contrast-induced nephropathy risk.^[1] Vascular and myocardial protective effects during PCI are thought to originate from the "pleiotropic effects" in acute phase independent of their lipid-lowering effects. This is basically detailed into antioxidant, anti-inflammatory and anti-thrombotic effects.^[1] Statins have been shown to result in a rapid increase in the biopresence of nitric oxide and improved endothelial response even as early as 3 hours after administration.

There is increasing evidence supporting this view from observational, single-center studies, meta-analyses of these studies and randomized multi-center controlled trials. The meta-analyses by Patti et al. evaluated 3341 subjects from 13 prospective and randomized studies which were performed between 1996-2010 and met certain standards.^[2] All of these studies except ARMYDA-RECAPTURE were performed in patients not using statins and had similar antithrombotic treatment protocols. Significantly favorable effects were seen in both myocardial damage due to the procedure and in 30-day clinical outcomes, particularly in groups receiving high-dose statins (Table 1). Data from 9 studies which measured high-sensitivity CRP also demonstrated that statin treatment reduces CRP alterations due to the procedure.^[2]

In ACCF/AHA/SCAI 2011 guidelines on PCIs, administration of high-dose statins before coronary intervention/stent implantation to prevent procedure-related myocardial infarction was recognized as a class IIa recommendation with evidence level A in statin-naïve patients and evidence level B for those on maintenance therapy.^[3]

Table 1. Differences during the procedure and in 30-day clinical outcomes

All trials gathered	Premedication with high-dose statins	Odds ratio (95% confidence interval)	p
MI due to procedure	118	0.56 (0.44-0.71)	<0.00001
Myocardial damage due to procedure			
Post-PCI troponin >x1 ULN	572	0.57 (0.49-0.67)	<0.00001
Post-PCI CK-MB >x1 ULN	380	0.61 (0.52-0.71)	0.00001
Post-PCI troponin >x3 ULN	289	0.57 (0.48-0.68)	<0.00001
Clinical events within 30 days			
Death	3	0.42 (0.11-1.64)	0.2
Spontaneous MI	3	1.49 (0.25-8.92)	0.66
MACE			
Death/all MI/TVR	125	0.56 (0.44-0.71)	<0.00001
Death/all MI/TVR/ST	126	0.56 (0.44-0.71)	<0.00001
Death/spontaneous MI/TVR	8	0.44 (0.19-1.01)	0.05

MI: Myocardial infarction; ULN: Upper limit of normal; CK-MB: Creatine kinase myocardial band; MACE: Major adverse cardiac event; TVR: Target vessel revascularization; ST: Stent thrombosis.

Although not stated in ESC guidelines for myocardial revascularization, using atorvastatin (80 mg), rosuvastatin (20-40 mg) or simvastatin (80 mg) is recommended as a class IIa, recommendation with evidence level A to avoid contrast-induced nephropathy during angiographic examinations of patients with moderate to severe renal failure.^[4] ESC 2016 dyslipidemia guidelines recommend routine use of high-dose statin treatment as short-term preloading before elective PCI (along with background chronic treatment) (IIa, evidence-A).

In conclusion, statins should be given in all cases undergoing PCI in order to prevent myocardial damage during procedure, to preserve coronary flow and perfusion, to reduce the risk of contrast-induced nephropathy and to obtain favorable effects in 30-day clinical outcomes. Although most of the data comes from atorvastatin and rosuvastatin^[5], the general recommendation is to use a high-dose, potent agent. It should be given at least 24 hours before the procedure and the treatment should be continued in the long term. This practice poses no problems as well with regard to side effects and costs.

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Question 84 – Statin use in acute coronary syndromes: Which dose, and when?

Dr. Ömer Kozan

Dokuz Eylül University Faculty of Medicine, Cardiology Department, İzmir

Using high-dose statins in acute coronary syndromes (ACS) reduces recurrent ischemic events and the possibility of revascularization (1-5). However, its impact on solid outcomes is controversial. Despite no impact on mortality in short-term (<4 months), it was observed to reduce mortality during long-term (>24 months) use. Guidelines recommend starting high-dose statins before discharge from hospital for ACS regardless of lipid levels (class 1-A recommendation). However, there is no consensus on optimal timing and dose. Since inflammatory response is in the forefront in terms of pathophysiology in ACS, statins are given early (<24 hours) and at high-dose taking into consideration their pleiotropic effects (reducing inflammation, improving endothelial functions and stabilizing plaques - Figure 1).^[1-5]

The later statin treatment is started following ACS, the later favorable cardiovascular (CV) effects occur. For instance, benefit was seen within 1-2 years in CARE and 4S studies in which statin treatment was started from 6th month while CV benefits were obtained at 16 weeks and 30 days in MIRACL where statins were started at the time of hospitalization and PROVE-IT TIMI22 in which statins were immediately started, respectively. The A-to-Z trial showed no significance within 4 months; however, the results reached significance at a later stage.

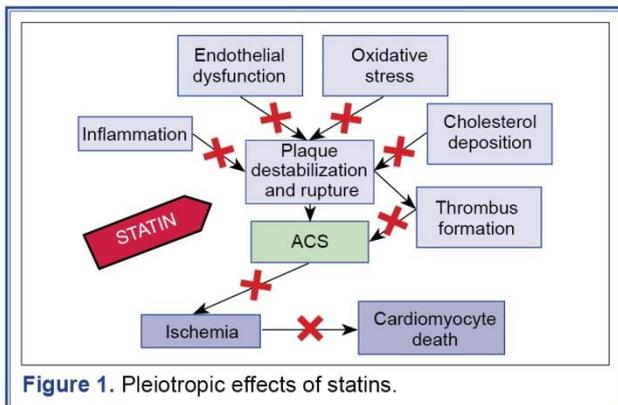


Figure 1. Pleiotropic effects of statins.

A-to-Z and PROVE-IT TIMI22 trials demonstrated that using high-dose statins is beneficial. According to the most recent studies, benefit from high-dose statins in ACS is maintained for 5 years (Table 1).

In 2016 European Society of Cardiology (ESC) guidelines on dyslipidemia, it is recommended as Class IA indication to start early after admission or continue giving high-dose statin treatment in all patients with ACS without history of contraindication or intolerance regardless of baseline LDL-C values. In case LDL-C targets cannot be achieved using the maximum tolerated statin dose, combination with ezetimibe should be considered in the period following ACS (Class IIa-B). PCSK9 inhibitors may be given if statins cannot be tolerated or are not sufficient (Class IIb-C). According to this guideline, lipids should be measured 4-6 weeks after ACS to determine whether the goal of 50% has been achieved or whether there has been a safety issue if LDL-C is <70 mg/dL or the baseline level is 70 to 135 mg/dL, and the treatment dose should be adjusted accordingly.^[5]

Table 1. Intensive statin treatment in ACS

	A to Z	MIRACL	PROVE IT
Number of patients	4497	3086	4162
LDL-C target (mg/dL)			
Early	62	63	33
Late	15	–	28
C-reactive protein %	17	34	38
Reduction in events %			
Early	0	16	18
Late	11	–	16
Myopathy	9	0	0

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Question 85 – When should we initiate statin treatment in a coronary bypass patient, and what should be the starting dose? Would initiating or discontinuing statin treatment cause any harm for these patients?

Dr. Tahir Yağdı

Ege University Faculty of Medicine, Cardiovascular Surgery Department, İzmir

Coronary artery by-pass grafting (CABG) is the recognized surgical treatment of coronary atherosclerosis. Unfortunately, this surgical method does not prevent the progression of atherosclerosis; therefore, negative changes continue in native vessels through atherosclerosis after CABG. Thrombosis and intimal hyperplasia observed in the early phase particularly in saphenous vein grafts (SVG) have negative impacts on survival in addition to chronic atherosclerosis process in patients undergoing CABG. Factors such as endothelial damage and inflammation in SVGs produced by the traumatic preparation process, smooth muscle cell proliferation, and insufficient synthesis of endothelial nitric oxide also decrease patency rates in the long term.

One of the most important determinants of early and long-term success after surgery is continuous precaution against atherosclerosis. The first study to angiographically show that lipid-lowering treatment (LLT) is effective in decelerating the atherosclerotic process following CABG is the CLAS trial published in 1987.^[1] Post-CABG^[2] is another very important study to show the benefits of aggressive LLT which demonstrated a 50% reduction in new lesions and occlusions by maintaining low-density lipoprotein cholesterol (LDL-C) values below 100 mg/dL. Studies in recent years have shown that statins improve endothelial functions, increase the activity of nitric oxide, have antioxidant properties, decrease inflammatory response and stabilize atherosclerotic plaques as a result of their pleiotropic effects in addition to anti-lipid properties. Statins also have preventive effects for vasoconstriction, thrombosis and platelet aggregation which contribute to decreasing the rates of post-operative non-fatal myocardial infarction, atrial fibrillation, neurological dysfunction, renal impairment, infection and death when given during the preoperative phase. Upon these

data, American Heart Association recommended using statins at a level of class 1 in patients undergoing CABG unless there is any contraindication.^[3] European Societies support these recommendations as well.^[4]

Vast majority of patients undergoing coronary by-pass surgery already receive antiplatelet drugs, beta-blockers, ACE inhibitors and statins. Statins should be started or if already started, should not be discontinued until surgery. Some evidence show that statins have a preventive effect in cases where coronary blood flow is disrupted. It has been demonstrated that post-operative rates of fatal arrhythmia, unstable angina, myocardial infarction and death would be higher if statin treatment is not initiated in the preoperative phase. Dose adjustment is as important as administering statins. The recommended initial and maximum doses of statins are 40-80 mg for pravastatin, 20-80 mg for simvastatin, 40-80 mg for fluvastatin, 10-80 mg for atorvastatin and 10-40 mg for rosuvastatin, respectively. Target LDL-C level is specified as <70 mg/dL in CABG patients.^[5] Studies show that high-intensity treatment (the dose to reduce LDL-C levels by $\geq 50\%$; e.g. atorvastatin 80 mg/day or rosuvastatin 40 mg/day) is more effective to decelerate the development or even for the regression of atherosclerotic lesions.

LLT is known to reduce the development of atherosclerosis after CABG and is strongly recommended in guidelines although it is not just about prescribing the drug at an appropriate dose. In order to achieve success, it is essential for the patient to believe in this lifetime treatment together with the doctor and diet expert, and be ready to implement dramatic modifications in terms of lifestyle and habits.

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Question 86 – Should we administer anti-lipid therapy in patients above 70 years of age? What are the indications, targets and doses for anti-lipid therapy in the elderly?

Dr. Filiz Özerkan

Ege University Faculty of Medicine, Cardiology Department, İzmir

There is an increasing population rate of individuals over 65 years of age. Additionally, the incidence of cardiovascular (CV) disease is known to increase with advanced age as well. People over 65 years of age are associated with higher incidences of smoking, hypertension, diabetes and hyperlipidemia. Furthermore, CV disease is the leading cause of death in the population aged >65 years. In this group, 25% of males and 42% of females have total cholesterol levels >240 mg/dL.^[1]

Statins are used in the elderly as well as the younger population to prevent disease and prolong life expectancy. The PROSPER (The Prospective Study of Pravastatin in the Elderly at Risk) study included a total 5,804 male and female patients in the age group of 70-82 years who had CV disease or CV risk factors. After three years of monitoring, low-density lipoprotein cholesterol (LDL-C) levels were 34% lower in patients receiving pravastatin compared to those receiving placebo, and while there was no difference in terms of total mortality; 15% reduction was seen in the risk of CV death, non-fatal myocardial infarction and stroke among patients receiving pravastatin.^[1,2] In this study, statin treatment did not show any unfavorable effects on cognitive functions in the elderly. The SAGE (Results of the Study Assessing Goals in the Elderly) study evaluated the effects of intensive or moderate anti-lipid therapy in the elderly and included 893

patients with coronary heart disease in the age group of 65-85 years who had LDL-C levels of 100-250 mg/dL and >1 episode longer than 3 minutes in 48-hour long Holter ECG. Patients were randomized to 2 groups to receive atorvastatin 80 mg/day (intensive treatment arm) or pravastatin 40 mg/day (moderate treatment arm).^[3] Twelve-month long monitoring revealed similar efficacy for both statin regimens in terms of frequency and duration of myocardial ischemia. High-intensity atorvastatin treatment was more effective than moderate-intensity pravastatin in terms of lipids and reducing all-cause mortality. The study concluded that high-intensity statin treatment may be routinely recommended in the elderly at high CV risk.

Possible drug interactions may raise concern in older patients due to the increased frequency of concomitant diseases, polypharmacy and altered drug metabolism. Therefore, statin treatment should be initiated with a low dose in order to avoid side effects and the dose should be up-titrated until optimal LDL-C is achieved. 2013 American Lipid Guidelines recommend moderate-intensity statin treatment for those aged >75 years, even in the presence of increased CV risk. The recommendations on dyslipidemia treatment in the elderly from ESC 2016 Dyslipidemia Guidelines are summarized in Table 1.^[1]

Table 1.

Recommendations	Class	Evidence
Statin treatment is recommended in the elderly with established CV disease.	I	A
Owing to the presence of concomitant diseases and altered pharmacokinetic mechanisms in the elderly, it is recommended to initiate lipid-lowering treatment with a low dose and carefully up-titrate the dose until achieving the lipid levels set as target in younger patients.	IIa	C
Statin treatment should be considered in the elderly without established CV disease in the presence of at least one additional risk factor (hypertension, smoking, diabetes and dyslipidemia) apart from old age.	IIa	B

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Question 87 – Are there differences in terms of anti-lipid therapy between males and females?

Dr. Saide Aytekin

Istanbul Florence Nightingale Hospital, Cardiology Clinic, Istanbul

Several studies have demonstrated reduced cardiovascular (CV) events and mortality with statin treatment. However, it remains a matter of debate whether there are differences between males and females in terms of treatment benefits. The major reason of obtaining contradicting results in relevant studies is the fact that women encounter CV events at a later stage in life compared to men and advanced age population is often excluded from studies.^[1] A meta-analysis conducted in 2010 concluded that statin treatment is less effective in women than men among individuals without known CV disease.^[2] Another meta-analysis in 2012, which included patients receiving statin treatment mostly for primary prevention demonstrated non-inferiority for statins between the two genders.^[3]

Recently, "The Cholesterol Treatment Trialists (CTT) Collaboration" issued a meta-analysis which included 22 studies comparing standard statin treatment versus a control group and 5 studies comparing intensive statin treatment versus treatment with lower doses.^[1] All 27 studies were shown to reveal significantly reduced major vascular events with statin treatment in both males and females. The reduction was considerably high in both gender groups although significance was mildly lower in

women than men in the 22 studies comparing standard statin treatment versus a control group. The analysis of the 5 studies comparing intensive statin treatment versus treatment with lower doses showed similar reductions in male and female patients. Furthermore, the decrease in major coronary events, coronary revascularization and all-cause mortality was observed to be similar in women and men.

The recent dyslipidemia guidelines do not provide different recommendations for the treatment of male and female patients. However, the Framingham risk scoring^[4] used for risk assessment provides a higher CV risk for women compared to men with the same risk factors. The 2013 Guidelines on hyperlipidemia treatment to reduce atherosclerotic CV risk in adults issued by "American Heart Association" (AHA) and "American College of Cardiology" (ACC) recommend classifying male patients with diabetes mellitus (DM) who are over 40 years of age, male patients with other risk factors or those over 50 years of age, female patients with DM who are over 45 years of age, and female patients with other risk factors or those over 55 years of age in the same risk group as the patients with known coronary artery disease.^[5]

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Question 88 – What should be the approach for pregnant women with high LDL-cholesterol levels?

Dr. Necla Özer

Hacettepe University Faculty of Medicine, Cardiology Department, Ankara

Until recent years, gestational dyslipidemia used to be considered as a physiological condition without clinical relevance. However, the finding of fatty streaks in aorta in 6-month old fetuses of hypercholesterolemic pregnant women and demonstrating similar findings in animal models have led gestational dyslipidemia to become a subject of interest.

Cholesterol is important for fetal development. While the fetus can synthesize its own cholesterol, maternal cholesterol may also enter fetal circulation through the placenta. Maternal cholesterol levels have been shown to be directly associated with the development of fatty streaks in the fetus.

There are no universally adopted threshold values to define normal lipid or lipoprotein levels during pregnancy. While lipid levels decrease during the first 6 weeks of pregnancy, they tend to progressively increase with each trimester. Low-density lipoprotein cholesterol (LDL-C) levels increase by 42% at 36 weeks of pregnancy. Lipoprotein(a) and high-density lipoprotein cholesterol (HDL-C) also increase during pregnancy. Triglycerides (TGs) start increasing from 14 weeks on and reach roughly a three-fold increase at 36 weeks but often remain under 300 mg/dL.

The increase in lipid levels may reach extreme values in pregnant women with genetic dyslipidemia. During pregnancy, TGs increase more than expected and severely in Fredrickson type-I and type-V hyperlipidemia, while the increase is moderate in type-III and type-IV. TGs exceeding >1000 mg/dL poses a risk for acute pancreatitis. Although acute pancreatitis is rarely seen during pregnancy, it is associated with increased maternal and fetal mortality. Elevated TG levels during pregnancy are associated with problems such as gestational hypertension, preeclampsia, preterm labor and larger fetus for the relevant gestational age.

Conditions such as hypothyroidism, alcohol consumption, glucocorticoid use, cocaine use, kidney disease and lipodystrophy should be evaluated in hyperlipidemic pregnant women. The target for

elevated TG levels is to lower TGs to <400 mg/dL in order to reduce the risk of pancreatitis. Fat consumption should be limited with 15-20% of daily calorie intake in severe hypertriglyceridemia. If TG levels are >500 mg/dL, omega-3 fatty acids may be recommended as they may provide moderate TG reduction. Although gemfibrozil and fenofibrate are agents with pregnancy category-C, they may be employed in some cases. Plasmapheresis can be successfully performed in pregnant women at risk of acute pancreatitis.

Caution should be exercised during pregnancy, particularly in subjects with familial hypercholesterolemia (FH). Lipid profile should be checked before pregnancy and in each trimester in these patients. Pregnancy cannot be tolerated in homozygous FH. Mortality is increased during pregnancy in such patients due to acute coronary syndromes. Fetal growth failure and accelerated fetal atherosclerosis are the important issues in addition to the increased risk of coronary events in hypercholesterolemic mothers. Lifestyle modification and bile acid sequestrants, mainly colestevlam, may be used in pregnant women with elevated cholesterol levels. The sequestrants are safe as they do not enter systemic circulation. Statins are teratogenic and therefore not recommended during pregnancy. Statins should be discontinued before planning pregnancy and should not be resumed until the end of breastfeeding period. Mipomersen (Class B) and LDL-apheresis may be necessary in some cases. LDL-apheresis can be safely performed in homozygous FH and heterozygous FH accompanied by coronary artery disease. There are no specific guidelines on the practice during pregnancy.

While statin use is category-X during pregnancy; fibrate, ezetimibe, niacin, cholestyramine and omega-3 are classified as category-C, and the pregnancy category is B for colestevlam and mipomersen. It is recommended to discontinue all lipid-lowering treatments except sequestrants and omega-3 fatty acids before planning pregnancy or as soon as pregnancy is recognized.

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Question 89 – Do lipids play a role in aortic stenosis development? What should be the therapeutic approach for lipids in patients with aortic stenosis?

Dr. Engin Bozkurt

Ankara Yıldırım Beyazıt University Faculty of Medicine, Cardiology Department, Ankara

Age-related calcific stenosis of the congenital bicuspid or normal tricuspid aortic valve is the most frequently seen cause of aortic stenosis (AS) in adults. A population based echocardiographic study revealed apparent calcific AS in 2% of the group >65 years of age while 29% had age-related aortic valve sclerosis (AVScl) without stenosis. AVScl is detected on echocardiography as the irregular thickening of aortic valve without occlusion. The risk factors for degenerative aortic valve disease are largely similar to cardiovascular risk factors. While historically the mechanical stress on the valve was thought to cause disruption, the new opinion is that the degenerative process represents a form of bone formation similar to vascular calcification (however, not the same condition) resulting from inflammatory and proliferative changes such as lipid deposition, elevated angiotensin converting enzyme (ACE), increased oxidative stress and infiltration of macrophages and T-lymphocytes. Risk factors involved in calcific AS development and calcification of bioprosthetic valves are similar to those involved in vascular atherosclerosis and include increased low-density lipoprotein cholesterol (LDL-C) and lipoprotein (a) [LP(a)] levels, diabetes, smoking and hypertension. Calcific AS has also been suggested to be associated with inflammatory markers and metabolic syndrome components. Although rarely, AS may also be a result of severe atherosclerosis of

the aorta and aortic valve; and this type of AS is often seen in patients with severe hypercholesterolemia and in children with homozygous familial hypercholesterolemia.

Owing to the mechanisms of stenosis formation, statins are technically thought to prevent lipid deposition and inflammation in aortic valve. Early uncontrolled observational studies have shown decelerated AS progression with aggressive lipid-lowering treatment. However, randomized controlled studies such as "Scottish Aortic Stenosis and Lipid Lowering Trial Impact on Regression (SALTIRE; 155 patients, atorvastatin 80 mg and placebo)", "SEAS (1873 patients, simvastatin 40 mg + ezetimibe 10 mg and placebo)" and "Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin (ASTRONOMER; 269 patients, rosuvastatin 40 mg and placebo)" did not show decelerated AS progression with high-dose statin treatment.^[1] Furthermore, the "post-hoc" analyses of "Incremental Decrease In Endpoints Through Aggressive Lipid-lowering Trial (IDEAL)" and "Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)" did not demonstrate reduced AS incidence with high-dose or routine-dose statin treatment versus placebo in patients without AS.^[2]

Table 1. Lipid-lowering studies in aortic sclerosis and aortic stenosis

Study	Year	Number	Patient characteristics	Follow-up (years)	Outcome of statin treatment
Pohle et al.	2001	104	Coronary and AVC	Retrospective	Related to decelerated AVC progression with low LDL-C
Aronow et al.	2001	180	Patients with mild AS	Retrospective	Decelerated AS progression
Novaro et al.	2001	174	Mild-moderate AS	Retrospective	Decelerated AS progression
Shavelle et al.	2002	65	AVC (with tomography)	Retrospective	Decelerated AVC progression
Bellamy et al.	2002	156	AS with avg. gradient 10 mmHg and AS area of 2.0 cm ²	Retrospective	Decelerated AS progression
Rosenhek et al.	2004	211	Aortic velocity >2.5 m/sec and normal EF	Retrospective	Decelerated AS progression, independent from LDL-C
Antoni-Canterin et al.	2005	1257	Aortic sclerosis with mild or moderate AS	Retrospective	No change in AS progression; however, aortic sclerosis velocity is reduced

Table 1. Lipid-lowering studies in aortic sclerosis and aortic stenosis (continued)

Study	Year	Number	Patient characteristics	Follow-up (years)	Outcome of statin treatment
Ardehali et al.	2012	1689	Aortic sclerosis	Retrospective	Reduced CV mortality
SALTIRE	2005	151	AS with aortic velocity >2.5 m/sec without statin indication	2.1	No change in AS progression after atorvastatin treatment
RAAVE	2007	121	Moderate-severe AS with AVA of 1.0-1.5 cm ² as recommended by guidelines	1.5	Decelerated AS progression and lower LDL-C levels with rosuvastatin
SEAS	2008	1873	Asymptomatic mild-moderate AS with aortic velocity 2.5-4.0 m/sec	4.4	No difference in AS-related CV outcomes with simvastatin and ezetimibe treatment
ASTRONOMER	2010	269	Mild-moderate AS with aortic velocity 2.5-4.0 m/sec	3.5	No difference in AS progression with rosuvastatin
Panahi et al.	2013	75	Patients with mild-moderate AS	1	Lower gradient with atorvastatin without any change in AS progression

AS: Aortic stenosis; AV: Aortic valve; AVA: Aortic valve area; AVC: Aortic valve calcification; CV: Cardiovascular.

Although AVScl seems to be a more appropriate target for statin treatment, there is insufficient data on this subject. AVScl studies show that AS progression may be reduced or remain unchanged with statin treatment.^[1] Randomized studies on AVScl are warranted.

In light of these data, the recent European Society of Cardiology Guidelines on dyslipidemia do not recommend cholesterol-lowering treatment in patients with AS in the absence of coronary artery disease or other indications.^[1] Similarly, the recent American College of Cardiology Guidelines on valvular disease do not recommend statin treatment

to prevent hemodynamic progression of the valve in mild-moderate aortic valve disease.^[3] However, recent studies on Lp(a) indicate that Lp(a) is a genetic-based common risk factor for calcific AS. A mechanical link has been detected between AS development and the proinflammatory and procalcific content and oxidized phospholipid (OxPL) of Lp(a). Elevated Lp(a) and OxPL-apoB levels accelerate AS progression and increase the need for aortic valve replacement. In contrast to statin studies on LDL-C, the molecule to strongly reduce Lp(a) currently being evaluated in a phase I study provides new hope for AS treatment.^[4]

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Question 90 – Does hypercholesterolemia play a role in aortic aneurysm development? Which statin and which dose should be used for treatment?

Dr. Anil Z. Apaydin

Ege University Faculty of Medicine, Cardiovascular Surgery Department, İzmir

Aortic aneurysm is a condition thought to have a complex genetic basis for which the etiology and pathogenesis remain unclear. It most commonly occurs in ascending and abdominal aorta. Aneurysms of these two regions differ in certain aspects. Ascending aortic aneurysms are aneurysms with primary connective tissue weakness often seen in younger patients and may develop due to valvular disease and dissection. Abdominal aortic aneurysm (AAA) is usually seen in older males and traditionally, atherosclerosis is thought to be the primary factor in the etiology of this condition. However, the notion which is increasingly more adopted is that lumen-occluding atherosclerotic disease and mechanisms leading to lumen dilatation result from different vascular wall pathologies. Atherosclerosis may be present in aneurysm wall. The possible effect of atherosclerosis in AAA development may be the degenerative ischemic changes resulting from vasa vasorum occlusion, accompanied by the mechanical weakness associated with the loss of aortic wall flexibility. Inflammatory events are thought to be the essential factors in aneurysm development where mechanical forces may also be contributing factors. While there is no AAA development in majority of patients with advanced atherosclerosis, some patients with AAA show no findings of atherosclerosis. The association between AAA and atherosclerosis is likely to be a secondary contribution of atherosclerosis to the vascular wall damage caused by various factors rather than being a cause-and-effect relation.

AAA is most commonly seen in men over 65 years of age. Other risk factors include smoking, hypertension and family history. Hypercholesterolemia has been shown to be a weak risk factor in some studies^[1] while some others did not report it as a risk factor.^[2] Blanchard and colleagues found no association between AAA and cholesterol levels, and reported that AAA risk factors are different than those of atherosclerosis.^[2] Currently, there is no evidence to support an effect of hypercholesterolemia on aortic aneurysm development. Although there is no evidence on decelerated aneurysm development with possible pleiotropic effects of statin treatment apart from a few statistically weak, retrospective clinical studies and despite stating this clearly, European Society of Cardiology 2016 Lipid Guidelines recommend statin treatment to prevent aneurysm progression as a Class IIa recommendation with evidence level B.^[3-5] This is likely to be due to the fact that atherosclerosis is a systemic disease which affects the entire vascular bed at the same time. The treatment goal for LDL-C is <70 mg/dL in these patients.

Because there is no robust evidence supporting the role of hypercholesterolemia in aortic aneurysm development, I believe it would not be effective to administer statins only with an attempt to prevent the formation, growth or rupture of an aneurysm.

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Question 91 – Would anti-lipid therapy be beneficial in retinal vascular disorders?

Dr. Özcan Kayıkçoğlu

Celal Bayar University Faculty of Medicine, Ophthalmology Department, Manisa

Retinal vein-artery occlusions, diabetic retinopathy and ischemic optic neuropathy are the leading conditions among the retinal vascular diseases with currently increasing frequency. In addition to retinal artery and venous occlusions, atherosclerotic changes in retinal vessels may also affect optic nerve supply and lead to ischemic optic neuropathy. Age-related macular degeneration seen in patients with advanced age is a condition which significantly decreases visual acuity by disrupting central vision. The culprit factor for this presentation is macular ischemia resulting from the insufficiency in retinal and choroidal vessels. For several years, hyperlipidemia has been known as an important risk factor for the development of all retinal vascular disorders.^[1-5]

Although not directly, the presence of hyperlipidemia may contribute to the disruption in vasculature of diabetic patients, posing a risk for development of proliferative diabetic retinopathy. On the other hand, macular edema and exudation are associated with hyperlipidemia in diabetic maculopathy. While there are study results indicating that fibrates may decelerate diabetic retinopathy progression, the use of fenofibrate for this purpose has yet not been widely adopted in clinical practice.^[1]

Retinal vessel occlusions are the second most common group of vascular retinal diseases after diabetes. Retinal artery occlusions require immediate treatment in terms of ophthalmology as they cause sudden vision loss, and permanent damage occurs in retinal tissues unless the vascular occlusion is not regressed within the first 24 hours. On the other hand, retinal venous occlusions cause

vision loss but do not require emergency interventions. Atherosclerotic changes are involved in the mechanism of these disorders. Particularly the changes on arterial wall may cause compression on retinal veins located in the same adventitial sheath, thereby resulting in occlusion. In our practice, we recommend investigating the underlying etiology in patients under 50 years of age who experience retinal vascular problems. Hypercholesterolemia is involved in this etiology by creating an atherosclerotic environment.^[2] The changes in vascular system may disrupt optic nerve supply within the context of ischemic optic neuropathy by affecting posterior ciliary vessels.^[3]

With an increasing frequency and severity in aging populations, the pathogenesis of age-related macular degeneration is associated with vascular insufficiency and ischemic mechanisms as well as senile alterations in retinal tissues while atherosclerotic changes and hyperlipidemia also play a role in this condition. The lipid deposits referred to as "drusen" accumulate in the tissue and show similarity with the atheroma plaques that accumulate on vascular walls. In fact, statins were evaluated for the treatment of this condition; however, this approach has not been supported by large studies.^[4,5]

It should be noted that performing a fundus examination to any patient who will be evaluated for internal diseases is the most simple and most practical imaging method which provides insight not only about retinal vessels but also about the general status of the entire vasculature systemically.

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Question 92 – Is statin treatment indicated in patients with previous stroke? Could it be harmful?

Dr. Hadiye Şirin

Ege University Faculty of Medicine, Neurology Department, İzmir

Although the advances in early treatment of acute ischemic stroke have reduced mortality, the associated disability remains a significant problem. New treatment strategies are needed to improve the prognosis of stroke. While there are strong evidence on the benefits of statin use in acute myocardial ischemia and cardiovascular (CV) risk reduction, there is insufficient data regarding the effect on brain tissue and the contribution to stroke prognosis, and relevant studies are ongoing.^[1,2]

Hypercholesterolemia is accepted as a serious standalone risk factor in lacunar infarcts and in ischemic stroke secondary to atherosclerosis. Benefit has been shown only with statin treatment for the secondary prevention of stroke. High-dose statin treatment, i.e. atorvastatin 40- 80 mg or rosuvastatin 20-40 mg decreases baseline low-density lipoprotein cholesterol (LDL-C) level by 50% while moderate statin treatment provides a reduction of 30-50%. Liver enzyme levels should be checked before treatment, and if the results are normal, there is no need to routinely check these enzymes in the absence of clinical hepatitis findings.^[1]

Stroke and Transient Ischemic Attack (TIA) cases have been evaluated in two large studies, namely "The Heart Protection Study (HPS)" and "Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCLE)". In the HPS study, simvastatin (40 mg) group showed 39 mg/dL reduction in LDL-C levels compared to placebo with major vascular events decreased by 20% while stroke risk was reduced by 25% and ischemic stroke reduction was 38%. The SPARCLE study evaluated patients with

previous stroke or TIA within 1-6 months who were receiving high-dose statin (atorvastatin 80 mg) through a 5-year long period and results revealed 56 mg/dL (43%) reduction in LDL-C levels compared to placebo. Mean LDL-C level in this study was 73 mg/dL with non-fatal and fatal stroke decreased by 16%, and 20% reduction in major CV events. However, while hemorrhagic stroke incidence was high in the group receiving atorvastatin 80 mg (55/2365 vs. 33/2366 in the placebo group), fatal stroke rate was observed to be low (hazard ratio 0.57, 95% CI: 0.32-0.95, p=0.03). Experimental studies have shown possible favorable contributions to neurological prognosis with the initiation of acute statin treatment after stroke. The improvement achieved in neurological function by reducing the infarct area is thought to be associated with a direct mechanism providing antithrombotic, antioxidant, anti-apoptotic or neuroprotective effects. Statin use creates collateral circulation in humans, improving cerebrovascular reactions and thereby resulting in a smaller infarct area. Statin treatment exerts its indirect effect by reducing recurrent stroke, coronary events and infections.^[1,3]

In conclusion, patients with previous ischemic stroke are at risk of CV disease as well. Statin treatment shows strong efficacy in these patients in terms of decreasing CV risk along with lifestyle modifications, blood pressure control and antiaggregant therapy. It is recommended to initiate statin treatment in the acute period using high-moderate doses and to continue long-term treatment with appropriate monitoring.

Table 1. Recommendations on lipid-lowering drugs used for primary and secondary prevention from stroke

Recommendations	Class ^a	Level ^b
Statin treatment is recommended to achieve specified treatment targets for primary prevention from stroke in patients with high or very high CV risk.	I	A
Lipid-lowering treatment is recommended for primary prevention from stroke in patients with other presentations of CVD.	I	A
Intensive statin treatment is recommended for secondary prevention from stroke in patients with previous non-cardioembolic ischemic stroke or TIA.	I	A

CVD: Cardiovascular disease; TIA: Transient ischemic attack ^aRecommendation class. ^bLevel of evidence.

High-dose statin treatment may be used in subjects under 75 years of age without contraindications or intracerebral bleeding. However, moderate-dose statin treatment should be used in subjects over 75 years of age. Treatment should be scheduled

according to the etiology in non-atherosclerotic stroke.^[1,4] Table 1 shows the recommendations from ESC 2016 Dyslipidemia Guidelines on lipid-lowering drugs used for CV prevention in stroke.^[5]

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Question 93 – Can statins be part of the treatment in a patient with erectile dysfunction?

Dr. Giray Kabakçı

Memorial Ankara Hospital, Cardiology Clinic, Ankara

Erectile dysfunction (ED) is a common problem among men with an incidence reported to vary from 3% to 70% according to age. ED has a multifactorial pathophysiology for which the relevant part for the subject matter herein is detailed in Table 1.^[1] Except for the presence of particular reasons, the commonly adopted notion today is that ED is a result of general vascular disruption which starts with endothelial dysfunction. The decreased nitric oxide (NO) production in dysfunctional endothelium reduces cyclic guanosine monophosphate (cGMP) synthesis, leading to arterial and corporal vasodilation in corpus cavernosum.

Phosphodiesterase type 5 enzyme inhibitors (PDE5i) are the first-choice treatment in ED and by inhibiting the PDE5 enzyme, they prevent the breakdown of cGMP, regulate smooth muscle relaxation, increase arterial blood flow and lead to subtunical venous plexus compression, resulting in penile erection. However, many patients do not respond to PDE5i treatment. The major cause of this is thought to be the fact that these agents do not restore endothelial dysfunction.

Statins prevent mevalonate production by inhibiting 3-hydroxy-methylglutaryl-CoA reductase, decrease cholesterol synthesis, reduce oxidized LDL generation and its unfavorable effects on endothelial cells and therefore result in increased NO activity. Studies have demonstrated that statins show favorable effects on endothelial function before improving the lipid profile.^[2] However, there are some non-controlled studies suggesting that statin treatment may decrease testosterone levels, although there is no data indicating clinical relevance of this notion.^[3]

In light of the pathophysiological information, there are contradicting results regarding the use of statin treatment in patients with ED. While some studies and reviews suggest that statin treatment may

cause ED; larger prospective studies, reviews and meta-analyses indicate that statin treatment has beneficial effects in terms of ED with more prominent effects seen particularly in patients who receive and show inadequate response to PDE5i treatment.^[4-5]

Table 1. Pathophysiology of erectile dysfunction

Vasculogenic
Cardiovascular diseases (hypertension, coronary artery disease, peripheral vasculopathy, etc.)
Diabetes mellitus
Hyperlipidemia
Smoking
Major pelvic surgery or radiotherapy
Neurogenic
Central causes
Peripheral causes
Anatomic or structural
Hormonal
Drug effects
Antihypertensive
Antidepressants
Antipsychotic
Antiandrogen
Pleasure-inducing substances (alcohol, heroin, cocaine etc.)
Psychogenic
Trauma

Statins are not included among the drugs causing erectile dysfunction (ED) in the European Association of Urology guidelines on ED updated on March 2015 (Table 1).

In conclusion, there is no reason to not use statins in patients with ED. However, it would be appropriate to assess and monitor patients individually considering the different results in the literature. Large randomized clinical studies are warranted in this field.

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Question 94 – Should anti-lipid therapy be considered in heart failure?

Dr. Yüksel Çavuşoğlu

Eskişehir Osmangazi University Faculty of Medicine, Cardiology Department, Eskişehir

When anti-lipid treatment is indicated in heart failure (HF), there are two HF groups to be taken into account. The first group consists of patients with established HF (Stage C and D), and the other group includes those with HF risk factors or asymptomatic left ventricular (LV) dysfunction (Stage A and B).

There is no benefit of statin treatment in terms of improving HF in stage C and D patients who have already developed symptomatic heart failure. Two large randomized studies with rosuvastatin revealed a completely neutral effect of statin treatment in HF patients with low ejection fraction (EF). The Controlled Rosuvastatin Multinational Trial in Heart Failure (CO- RONA) study^[1] included 5011 cases with ischemic HF, NYHA II-IV and EF \leq 40% for whom anti-lipid therapy was not clinically indicated, and these patients were randomized to receive rosuvastatin or placebo, resulting in no difference regarding the primary endpoint consisting of cardiovascular (CV) death, myocardial infarction (MI) and stroke with a monitoring period of 32 months. The Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto miocardico-heart failure (GISSI-HF) study^[2] included 4574 symptomatic (NYH II-IV) patients with heart failure of ischemic or non-ischemic origin and low EF (\leq 40%) who were randomized to receive rosuvastatin or placebo, and no reduction was observed in the primary endpoint consisting of all-cause mortality and CV hospitalization with rosuvastatin over a monitoring period of 3.9 years. However, statin treatment was also not associated with an increased risk of adverse events in either of these 2 studies. Therefore,

guidelines do not recommend statins solely for the treatment of HF in Stage C or D heart failure in the absence of other indications requiring statin treatment.^[3-5] However, they do recommend using statins and continuing treatment in patients already on statins in HF cases with statin indication due to coronary artery disease (CAD) and hyperlipidemia.

Guidelines strongly recommend statin treatment when indicated to prevent or delay the development of apparent HF in patients with Stage A and B HF who have risk factors for heart failure (CAD, MI, diabetes, hypertension, etc.) or asymptomatic LV dysfunction (Class IA). Atherosclerotic heart disease is known to be a very important and common risk factor for the development of HF. Aggressive treatment of hyperlipidemia with statins has been shown to reduce or delay HF development in patients at high risk. 2016 ESC guidelines^[3] recommend statin treatment as a Class IA indication to prevent or delay the development of HF in patients with established CAD or at high risk for CAD regardless of LV systolic dysfunction. Similarly, 2013 ACC/AHA KY guidelines^[4] recommend statin treatment as a Class IA indication to prevent HF development in patients with previous MI.

In light of the available information, it may be concluded that statin treatment plays an important role to prevent or delay HF development in patients at Stage A and B with risk factors for HF or asymptomatic LV dysfunction while there is no value of statin treatment in patients with Stage C and D heart failure in the absence of obligatory indications.

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Question 95 – How should we approach LDL-cholesterol levels in transplant patients? Which anti-lipid agent and which dose should we prefer in transplant patients?

Dr. Sanem Nalbantgil

Ege University Faculty of Medicine, Cardiology Department, İzmir

Lipid disorders are common in individuals with solid organ transplants and play an important role in the development of atherosclerotic conditions as well as arterial transplant vasculopathy. Following heart transplantation, acute rejection and chronic allograft vasculopathy (chronic rejection) are the most significant causes of mortality and morbidity in the early period and in long-term, respectively. The first randomized study with statins demonstrated reduced rejection episodes and favorable effects on survival with pravastatin.^[1] The 10-year long follow-up with the same molecule also showed the effect of statins on survival with a significant difference compared to those not receiving statin treatment.^[2] Favorable effects on allograft vasculopathy have also been reported in studies.^[3] It is recommended to initiate statin treatment in each patient after transplantation regardless of lipid levels. Greater favorable effects have been reported with early initiation of statin treatment in these patients.

Hyperlipidemia occurs in 60-80% of post-transplant patients. Immunosuppressive agents have unfavorable effects on lipid metabolism. While corticosteroids increase total cholesterol, VLDL and TG levels; calcineurin inhibitors, cyclosporine in particular, decrease the clearance of atherogenic lipoproteins. Statin treatment provides regulatory effects on immunomodulation in addition to lipid-lowering effects. The favorable effects of statins are thought to be associated with inhibited natural killer cell activation through the influence on interferon gamma related to MHC-II expression. Other predicted mechanisms of action include inhibition of beta-2 integrin and leukocyte function antigen-1 (LFA-1), inhibition of intimal proliferation, and weakened antibody-associated responses.

Co-administration of statins with calcineurin inhibitors may elevate serum statin levels and increase immunomodulatory effects.

Table 1. Recommended doses and side effects

Drug	Dose (mg)	Side effect
Pravastatin	20-40	Low risk of myositis
Simvastatin	5-20 (>20 mg not recommended)	High risk of myositis
Atorvastatin	10-20	High risk of myositis
Fluvastatin	40-80	Low risk of myositis
Rosuvastatin	5-20	Myositis risk

The most common side effect of statins in these patients is myositis complicated with rhabdomyolysis and renal impairment. The risk is higher with lipophilic statins. It is recommended to exercise caution for high serum statin levels related to treatment with calcineurin inhibitors.

The ISHLT guidelines recommend initiating statin treatment at 1-2 weeks after surgery in all adult patients with a heart transplant. The starting dose should be low owing to the interactions with calcineurin inhibitors. Target lipid levels have not been established in these patients.^[4] Also, net superiority of using high-dose statins versus low-dose has not been demonstrated, either. Concomitant conditions should be taken into account while scheduling treatment and establishing target lipid levels in these patients. The ESC guidelines published this year recommend statins as the first-choice drug group for the treatment of hyperlipidemia (recommendation level IIa, level of evidence B). It is also emphasized that the dose should be gradually increased. Ezetimibe or fibrates may be considered in patients who do not respond to this treatment (recommendation level IIb, level of evidence C). Statin and fibrate combination should be avoided due to the side effect of myopathy.^[5]

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Question 96 – Does statin treatment provide additional benefits in a patient with intracardiac defibrillator (ICD)?

Dr. Cengiz Ermiş

Akdeniz University Faculty of Medicine, Cardiology Department, Antalya

The answer to this question would also address the question "does statin treatment affect ventricular arrhythmia burden?" and the brief answer for that would be "yes." A meta-analysis which included 29 statin studies and approximately 114 thousand patients demonstrated 10% reduction in sudden cardiac death and a 22% reduction in non-sudden cardiac death with statin treatment.^[1] Similarly, some intracardiac defibrillator (ICD) studies have also shown favorable effects of statin treatment on the incidence and duration of ventricular arrhythmia; however, these studies mostly evaluated patients with coronary artery disease.^[2,3] Therefore, it remains unclear whether this favorable effect of statins should be associated with ischemic-reducing effects, thereby decreased ischemic ventricular arrhythmias or with a true anti-arrhythmic effect.

For this reason, studies conducted in patients with non-ischemic cardiomyopathy are required to more subjectively demonstrate the effects of statins on ventricular arrhythmias. In this context, the MADIT-CRT is a major study evaluating patients with non-ischemic cardiomyopathy and ICD who receive cardiac resynchronization therapy as well as statin treatment.^[4] Including a total of 821 patients and a follow-up period of 4 years, this study has demonstrated a 77% reduction in death or fatal

arrhythmias such as accelerated ventricular tachycardia/ventricular fibrillation with a standalone effect of statin treatment. This finding shows that statins decrease ventricular arrhythmias independently from anti-ischemic effects, and to answer the main question here, they do provide additional benefit in patients with ICD by reducing the therapeutic need for anti-tachycardia "pacing" cardioversion or defibrillation.

The anti-arrhythmic influence of statins may be explained with pleiotropic effects. Statins primarily decrease inflammation, which plays an important role in the pathogenesis of sudden cardiac death and ventricular arrhythmias. Inflammation alters the autonomic tone measured by the variability of heart rate.^[5] Some other studies have demonstrated improved heart rate variability with statins as they affect autonomic activation^[6] and furthermore, desensitization of cardiomyocytes against beta-adrenergic stimulation has been shown in mice.^[7]

In conclusion, statins provide additional benefit by reducing ventricular arrhythmias and the need for associated treatment in patients with ICD in the presence of any structural heart disease, particularly coronary artery disease.

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Question 97 – What should be the cholesterol-lowering treatment algorithm in patients with high calcium scores?

Dr. Muzaffer Değertekin

Yeditepe University Faculty of Medicine, Cardiology Department, İstanbul

Coronary calcium scoring is an imaging method which has been in use since 1990s and it is based on determining atherosclerosis-related calcium burden in coronary arteries by means of multi-slice computed tomography. The most commonly used method is the measurement method suggested by Agatston and colleagues. High coronary calcium scores have been associated with significantly increased long-term cardiovascular (CV) event frequency.^[1]

Total CV risk is a concept describing the likelihood of experiencing a CV event for an individual at a given period. Estimating this risk helps preventing CV events in healthy subjects as well as allowing primary and secondary precautions as appropriate according to the risk group of the individual.

Coronary calcium scoring is particularly important for the net determination of an individual's risk group to specify primary prevention strategies in asymptomatic subjects. The parameters included in current scoring systems (age, gender, blood pressure, etc.) may overestimate or underestimate an individual's actual risk. The composite effect of calcium scoring method and clinical or subclinical risk factors may allow a more accurate risk estimation. Furthermore, a coronary calcium score of zero provides a high negative predictive value.

According to 2016 European Society of Cardiology Guidelines on Prevention of CV Disease in Clinical Practice, coronary calcium scoring is a risk modulating method which may be used for subjects with a 10-year risk score close to threshold values such as 5% or 10% according to the SCORE scale.^[2]

On the other hand, 2016 European Society of Cardiology and European Atherosclerosis Society Guidelines on Dyslipidemia^[3] suggest that coronary calcium scoring may be used for individuals in the moderate-risk group and that an increased risk may be estimated if Agatston score is >400.

In light of the available information, total CV risk score should be estimated for primary prevention from CV disease particularly in asymptomatic subjects. Coronary calcium scoring may be used for individuals included in the moderate-risk group or for those whose risk group cannot be clearly determined. Calcium scoring should be used to estimate whether the risk for an individual is higher or lower than that of the relevant risk group, and corresponding cholesterol levels should be the target of lifestyle modifications and drug treatment, if necessary. For instance, in the event that Agatston score is >400 in a subject for whom total CV risk is estimated as 4%, it would be more appropriate to classify such an individual in the high-risk category rather than the moderate-risk group and to determine the targets of cholesterol treatment accordingly.

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Question 98 – How should we approach high cholesterol levels in hypertensive patients?

Dr. Alparslan Birdane

Eskişehir Osmangazi University Faculty of Medicine, Cardiology Department, Eskişehir

Majority of hypertensive patients are known to have an additional cardiovascular (CV) risk or disease. Lowering blood pressure (BP) and low-density lipoprotein cholesterol (LDL-C) together is more effective than lowering either parameter alone to reduce CV events.

The ASCOT study published in 2003^[1] evaluated the efficacy of atorvastatin 10 mg in primary prevention from coronary heart disease (CHD) among hypertensive patients with at least three risk factors for CV disease without CHD whose total cholesterol levels were ≤ 250 mg/dL. The study was terminated 3.3 years early upon demonstrating the significant reduction in CV endpoints with atorvastatin. The 11-year long outcomes of the lipid-lowering arm from the ASCOT study were published in 2011.^[2] Significant reductions were observed in all-cause mortality and non-CV mortality in the atorvastatin group.

The recently published HOPE-3 study^[3] evaluated individuals at moderate risk without CV disease (mean annual major CV event risk: 1%) in 4 groups. The first group received candesartan hydrochlorothiazide (cande-HTZ) and rosuvastatin, the second group was given rosuvastatin and placebo, the third group received cande-HTZ and placebo, and

the fourth group was given placebo only. Mean baseline systolic BP level was 138 mmHg and mean LDL-C level was 128 mg/dL among the subjects included in the study. Reductions in CV events were observed with a follow-up of 5.6 years in the group receiving statin and cande-HTZ combination versus placebo. The favorable effects of rosuvastatin were found to be independent from BP and lipid levels in HOPE-3. Therefore, the study concluded that it would be more appropriate to use combination therapy in patients with elevated BP and administer statin treatment alone in those with normal BP. The HOPE-3 study has shown reduced CV events with fixed rosuvastatin and dual antihypertensive medication in subjects at moderate risk without CV disease.

Guidelines provide important information and algorithms for clinical practice. Thus, treatment and follow-up of patients should be based on guidelines. Recent guidelines recommend total CV risk assessment with the SCORE model in asymptomatic hypertensive patients without CV disease, chronic kidney disease and diabetes.^[4] The approach to lipid-lowering therapy should be decided based on the value calculated with the SCORE model in hypertensive patients.

Table 1. Total CV risk assessment and treatment strategies according to LDL-C levels^[5]

Total CV risk score (SCORE) %	LDL <70 mg/dL	LDL 70-100 mg/dL	LDL 100-155 mg/dL	LDL 155-190 mg/dL	LDL ≥ 190 mg/dL
<1	Lipid treatment is not indicated	Lipid treatment is not indicated	Lipid treatment is not indicated	Lipid treatment is not indicated	Firstly LSM; if not successful, drug treatment should be considered
≥ 1 -<5	Lipid treatment is not indicated	Lipid treatment is not indicated	Firstly LSM; if not successful, drug treatment should be considered	Firstly LSM; if not successful, drug treatment should be considered	Firstly LSM; if not successful, drug treatment should be considered
≥ 5 -<10 or at high risk	Lipid treatment is not indicated	Firstly LSM; if not successful, drug treatment should be considered	LSM and drug treatment	LSM and drug treatment	LSM and drug treatment
≥ 10 or at very high risk	LSM; if not successful, drug treatment should be considered	LSM and drug treatment	LSM and drug treatment	LSM and drug treatment	LSM and drug treatment

LSM: Lifestyle modification; CV: Cardiovascular; LDL-C: Low-density lipoprotein cholesterol.

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Question 99 – What are the targets of LDL-cholesterol-lowering treatment in a non-diabetic patient with metabolic syndrome?

Dr. Aytekin Oğuz

Istanbul Medeniyet University Faculty of Medicine, Internal Diseases Department, İstanbul

Metabolic syndrome (MetS) is a group of atherometabolic risk factors characterized by abdominal obesity, hyperglycemia, hypertriglyceridemia, hypertension and low HDL-cholesterol levels resulting from both genetic and environmental effects. There is a 5-fold increased risk of type 2 diabetes in patients with MetS. The risk of cardiovascular (CV) events is also increased by 2-fold in patients with MetS, independent from diabetes. The dyslipidemia in MetS is atherogenic dyslipidemia associated with insulin resistance. Atherogenic lipid triad includes elevated triglycerides, low HDL-cholesterol levels and presence of small dense LDL-cholesterol in blood. Elevated triglycerides and small dense LDL-cholesterol are also involved in the increased risk among MetS patients in addition to classic CV risk factors, namely obesity, hyperglycemia, hypertension and low HDL-cholesterol levels.

The primary goal of dyslipidemia treatment in MetS is LDL-cholesterol, which is not a component of metabolic syndrome but a major lipid risk factor. The secondary goal is non-HDL cholesterol or apolipoprotein (apo)-B levels. The target value is <100 mg/dL for LDL-cholesterol and apo-B, and <130 mg/dL for non-HDL cholesterol. LDL-cholesterol target is <70 mg/dL in patients at very high risk.^[1]

Evidence on favorable effects of LDL-cholesterol-lowering treatment in MetS are based on statin studies. While statins provide net CV risk reduction, these agents have the disadvantage of increasing risk of diabetes. No correlation is observed between statin treatment and development of diabetes in subjects

with no major risk factors for diabetes; however, the risk of developing diabetes has been observed to reach 28% in people with one or more major risk factors for diabetes. Nevertheless, CV benefits of statin treatment has been demonstrated in this group with the 39% risk reduction shown in the primary outcomes set consisting of CV events and CV death.^[2]

Considering the fact that MetS includes multiple risk factors for diabetes, the risk of developing diabetes with statin treatment would obviously be at least 28% or even higher in these patients. Although the highest risk of developing diabetes was reported with rosuvastatin, there is no consensus or high-level evidence to conclude which statin is more diabetogenic than others. The generally accepted notion is a probable association between the dose and potency of the statin and the risk of diabetes development.^[3]

It is critically important to strongly emphasize and implement lifestyle modifications in order to decrease diabetes risk in MetS where abdominal obesity is the underlying basis. The improvement in abdominal obesity would improve all MetS parameters and provide a dramatic risk reduction in terms of developing diabetes with statin treatment.

Effective treatment for prevention should be employed for multiple risk factors owing to the increased CV risk in MetS. The role of statin treatment in this aspect is particularly important in patients at high-risk, so much that it may justify ignoring the potential diabetogenic effect.

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Question 100 – How should anti-lipid therapy be in diabetic patients? Are the targets, drugs and preferences different?

Dr. Abdurrahman Çömlekçi

Dokuz Eylül University Faculty of Medicine, Endocrinology Department, İzmir

The fact that cardiovascular (CV) risk is increased in diabetic patients and even that diabetes is an equivalent of CV disease has been known for several years.^[1]

The UKPDS study has shown that low-density lipoprotein cholesterol (LDL-C) lowering treatment as well as blood sugar regulation is a leading factor to reduce mortality in diabetic individuals.^[2] The primary prevention study in diabetic patients, i.e. the CARDS study revealed a CV risk-reducing effect of moderate LDL-C reduction with atorvastatin 10 mg/day not only in subjects with high LDL-C levels but also in patients with near-normal LDL-C values.^[3]

Current guidelines (Table 1) recommend high-dose statin treatment in addition to lifestyle modifications in all diabetic patients with atherosclerotic CV disease (ACVD). Patients under the age of forty years with ACVD risk factors should receive moderate- or high-dose statin treatment. Moderate-dose statin treatment should be employed in patients aged 40-75 years without ACVD risk factors. Patients aged 40-75 years with additional risk factors for ACVD should receive high-dose statin treatment. Moderate-dose statin treatment should be employed in patients older than seventy five years of

age without additional CV risk factors. Patients older than seventy five years of age with additional risk factors for ACVD should receive moderate- or high-dose statin treatment. In clinical practice, the physician should adjust the statin dose based on the individual response (side effects, tolerability, LDL-C levels).^[4,5]

In patients with type 2 diabetes, precautions should be exercised for the increased risk of pancreatitis in subjects with triglycerides >500 mg/dL. Secondary causes should be reviewed and the fibrate group should be preferred for medical treatment. The primary target should be LDL in other patients.^[4-6]

Combination therapy with ezetimibe and statin has been shown to provide additional benefit compared to moderate statin treatment, and should be used in patients with recent acute coronary syndrome and LDL-C levels >50 mg/dL or in subjects who cannot tolerate high-dose statin treatment. Benefit on CV outcomes has not been demonstrated for additional fibrate combination with statin treatment. However, it may be considered in male patients with triglycerides >204 mg/dL and HDL-C <34 mg/dL. No benefits have been shown with statin-niacin combination. It is not recommended.^[5]

Table 1. Recommendations on statin and combination treatment in diabetic patients

Age range	Risk factors	Statin treatment
<40 years	None Risk factors for atherosclerotic cardiovascular disease* Atherosclerotic cardiovascular disease	None Moderate or high High
40-75 years	None Risk factors for atherosclerotic cardiovascular disease* Atherosclerotic cardiovascular disease Patients with high-dose statin intolerance or acute coronary syndrome and LDL >50 mg/dL	Moderate High High Moderate + ezetimibe
>75 years	None Risk factors for atherosclerotic cardiovascular disease* Atherosclerotic cardiovascular disease Patients with high-dose statin intolerance or acute coronary syndrome and LDL >50 mg/dL	Moderate Moderate or high High Moderate + ezetimibe

*Atherosclerotic cardiovascular risk factors. LDL cholesterol >100 mg/dL, high blood pressure, smoking, obesity, family history of premature cardiovascular disease.

Table 2. High-dose and moderate-dose statin treatment

High-dose statin treatment	Moderate-dose statin treatment
Lowers LDL cholesterol by >50%	Lowers LDL cholesterol by >30-50%
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg
	Simvastatin 20-40 mg
	Pravastatin 40-80 mg
	Fluvastatin XL 80 mg
	Pitavastatin 2–4 mg

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Question 101 – What is the position of lipid-lowering treatment in patients with chronic kidney disease? Who should receive treatment, and when?

Dr. Mustafa Arıcı

Hacettepe University Faculty of Medicine, Internal Diseases Department, Division of Nephrology Ankara

Chronic kidney disease (CKD) is defined as structural or functional kidney impairment of clinical relevance lasting longer than 3 months. CKD diagnosis and staging are based on glomerular filtration rate (GFR). CKD is grouped in 5 main stages according to the GFR value (Table 1). Decreasing GFR increases the risk of CKD progression as well as the cardiovascular (CV) risk. CV risk increases particularly from Stage 3 on, with severely increased risk in Stage 4 and 5. Therefore, CKD cases should be included in the high-risk category without necessarily using CV risk scores.

The changes in lipoprotein metabolism in CKD lead to an atherogenic lipid profile. Decreased GFR and increased urinary albuminuria may be seen with elevated triglycerides, low HDL-C values and high LDL-C levels. However, owing to the concomitant inflammation and malnutrition in CKD, LDL-C should not be used as a marker of coronary risk as is the case in the general population. It should be noted that the risk increases in parallel with CKD stage in CKD, regardless of LDL-C values.

Meta-analyses evaluating several studies on lipid-lowering therapy in CKD have shown significantly reduced mortality and CV events with statin treatment in CKD patients who do not undergo

dialysis. Mostly neutral results have been obtained in studies with patients undergoing dialysis. In light of the available data, Table 2 summarizes the recommendations on lipid-lowering treatment in CKD patients according to the "KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease" guidelines published in 2013 and the recently published "2016 ESC/EAS Guidelines for the Management of Dyslipidemias" guidelines.

Guidelines indicate that the safety of statin treatment should also be considered in CKD patients, emphasizing the importance of dose adjustment, particularly in patients with advanced CKD. Low-doses supported by relevant studies are recommended in patients with advanced CKD due to potential toxic effects of high doses (Table 3). There is no evidence supporting that side effects of statin treatment were different in patients with CKD than normal population.

In summary, both KDIGO and ESC/EAS guidelines highlight that CKD patients are in the high or very risk group in terms of CV risk and recommend using statin treatment or statin/ezetimibe combination in a significant portion of these patients regardless of LDL-C levels.

Table 1. Stages of chronic kidney disease

Stage	Description	GFR (mL/min/1.73 m ²)
1	Kidney injury with normal or high GFR	≥ 90
2	Kidney injury with mildly decreased GFR	89-60
3A	Mildly-moderately decreased GFR	59-45
3B	Moderately-severely decreased GFR	44-30
4	Severely decreased GFR	29-15
5	Renal failure	<15

GFR: Glomerular filtration rate.

Table 2. Major recommendations on lipid-lowering treatment in patients with chronic kidney disease as per KDIGO 2013 and ESC/EAS 2016 guidelines

KDIGO 2013 GUIDELINE		ESC/EAS 2018 GUIDELINE	
Recommendation	Level of evidence	Recommendation	Level of evidence
<ul style="list-style-type: none"> Statin or statin/ezetimibe combination treatment is recommended in CKD Stage 3A-5 patients aged ≥ 50 years with GFR < 60 mL/min/1.73 m² (in the absence of dialysis or kidney transplantation). 	1A	It should be noted that patients with CKD Stage 3-5 are in high or very high risk group in terms of CV risk.	IA
<ul style="list-style-type: none"> Statin treatment is recommended in CKD Stage 1-2 patients aged ≥ 50 years with GFR ≥ 60 mL/min/1.73 m². 	1B	Statin or statin/ezetimibe combination treatment is indicated in CKD patients who do not undergo dialysis.	IA
<ul style="list-style-type: none"> Statin treatment is recommended in the presence of one or more of the following conditions in CKD patients aged 18-49 years in the absence of dialysis or kidney transplantation: <ul style="list-style-type: none"> – Known coronary disease (myocardial infarction or coronary revascularization) – Diabetes – Ischemic stroke history – Estimated 10-year risk of coronary death or myocardial infarction $> 10\%$ 	2A		
<ul style="list-style-type: none"> It is not recommended to initiate statin or statin/ezetimibe combination in CKD patients undergoing dialysis. 	2A	Statin treatment should not be initiated in CKD patients with atherosclerotic CV disease undergoing dialysis.	IIA
<ul style="list-style-type: none"> It is recommended to continue treatment in patients already receiving statin or statin/ezetimibe combination at the time of initiating dialysis treatment. 	2C	Treatment should be continued in patients, particularly those with CV disease already receiving statin or statin/ezetimibe combination at the time of initiating dialysis treatment.	Ila C
<ul style="list-style-type: none"> Statin treatment is recommended in kidney transplant patients. 	2B	Statin treatment should be considered in kidney transplant patients.	IIBc

CKD: Chronic kidney disease; GFR: Glomerular filtration rate; CV: Cardiovascular.

Table 3. Statin doses recommended for patients with advanced (Stage 3A-5) chronic kidney disease

Statin	CKD Stage 3A-5
Fluvastatin	80
Atorvastatin	20
Rosuvastatin	10
Simvastatin/Ezetimibe	20/10
Pravastatin	40
Simvastatin	40

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Question 102 – What should be the LDL target in hemodialysis patients? Should we administer statins?

Dr. Gülay Aşçı

Ege University Faculty of Medicine, Internal Medicine Department, Division of Nephrology, İzmir

The survival of 2/3 of approximately three million individuals with end-stage renal disease across the globe depend on hemodialysis (HD). On the other hand, there is a 7-fold increased risk of mortality in HD patients compared to the general age-matched population. Being the most important cause of mortality, cardiovascular (CV) disease is also very frequent among these patients; and the CV disease risk of a 30-year old HD patient is similar to that of a 70-year old individual from the overall population. CV mortality is 8.1-fold greater in this group compared to general population. The presence of chronic renal impairment is accepted as equivalent to CV disease. CV mortality mostly occurs as a result of coronary artery disease, heart failure or arrhythmias. While the rate of cardiac mortality has decreased through the years in the overall population, such a decrease is not observed in the dialysis population.

A direct and strong association has been demonstrated between LDL-C levels and CV mortality in the general population. Dyslipidemia is also common in HD patients and is thought to be a risk factor for CV disease. However, a negative correlation has been shown between serum total cholesterol or LDL-C levels and the presence of CV disease. In a study, serum LDL-C levels under 70 mg/dL were found to be associated with increased all-cause mortality. This paradoxical risk increase was deemed as related to inflammation and malnutrition. However, some observational studies have suggested a U-shaped association between serum cholesterol levels and mortality. LDL-C levels do not determine the risk of CV events in HD patients.

Coronary artery disease and associated mortality have been shown to decrease with the reduction in total cholesterol and LDL-C levels obtained with HMG-CoA reductase inhibitors (statins) in the

general population. Conversely, randomized studies in HD patients (4D, AURORA and SHARP) and relevant meta-analyses did not demonstrate decreased CV mortality with statin treatment (with or without ezetimibe).

Together with elevated triglycerides and low HDL-C levels, majority of HD patients have normal or low LDL levels. The main causes of hypertriglyceridemia are increased apolipoprotein-B production and the reduced VLDL metabolism. Elevated levels are also seen for the atherogenic chylomicron remnant particles. Statin treatment shows no effect on these changes.

The approach to dyslipidemia is different in HD patients compared to the general population. KDIGO clinical practice guidelines recommend statin treatment in patients with chronic renal impairment over the age of 50 years who do not undergo dialysis (Class 1B). Initiating routine statin treatment is not recommended in patients undergoing hemodialysis or peritoneal dialysis.

One of the reasons of inadequate response to statin treatment in patients with chronic renal impairment may be the CV disease pathogenesis, which is different than the general population. While the primary cause of CV disease is atherosclerosis in the overall population, HD patients have additional factors such as hypervolemia, increased and accelerated medial vascular calcification, arterial stiffness, left ventricular hypertrophy, diastolic dysfunction, heart failure and arrhythmia-related sudden cardiac death.

In conclusion, it is well known that statins reduce mortality and the development of CV events in the general population. However, statins have no effect on the development of myocardial infarction and stroke in HD patients.

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Question 103 – Should anti-lipid therapy be considered in peripheral arterial disease?

Dr. Tanzer Çalkavur

Ege University Faculty of Medicine, Cardiovascular Surgery Department, İzmir

Peripheral artery disease (PAD) is an important clinical manifestation of systemic atherosclerosis; however, the medical treatment for this condition has been neglected until recently compared to atherosclerosis syndromes. RE-ACH Registry has shown increased vascular mortality in PAD compared coronary artery disease (CAD) and carotid artery disease at 3 years.^[1] The underlying reason of this finding may be the inadequate medical treatment of PAD. Guidelines recommend antithrombotic agents and statins as standard medical treatment for PAD; however, these drugs are used at very low doses compared to CAD.^[2]

There are two main treatment targets in PAD: reducing the patient's symptomatology (intermittent claudication) and preventing cardiovascular complications. Statins are effective in achieving these two main targets in PAD. Several studies have shown favorable effects of statin treatment on physical activities in patients with intermittent claudication.^[3-6] A Cochrane analysis of published series has demonstrated improved painless walking distance in

patients with intermittent claudication receiving statin treatment.^[7] While there is no clear explanation of how statins improve the painless walking distance, it is thought to be independent from the LDL-lowering effect and associated with pleiotropic effects which improve endothelial function, stabilize atherosclerotic plaques and reduce vascular inflammation.^[8]

The PAD subgroup analysis of the Heart Protection study revealed a 24% reduction in cardiovascular events in patients receiving statin treatment compared to the control group.^[9] Although limited in numbers with a series of 68 patients, studies in patient groups with isolated PAD have shown reduced rates of myocardial infarction, stroke and vascular death with aggressive statin treatment as well as decreased risk of extremity amputation.^[10]

Statins are an important weapon of our routine treatment as they are effective on both treatment targets in PAD.

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Question 104 – Does cholesterol-lowering treatment provide additional benefit in atrial fibrillation? Are there differences in therapeutic targets and doses?

Dr. Kudret Aytemir

Hacettepe University Faculty of Medicine, Cardiology Department, Ankara

The main mechanisms responsible for the onset and continuation of atrial fibrillation (AF) are the electrical and structural remodeling processes in the atrium.^[1] Inflammation, oxidative stress and finally atrial fibrosis are the main factors for the development of these pathophysiological processes.^[2] Statins are among the drug groups commonly used both for primary and secondary prevention from ischemic heart diseases and stroke owing to their lipid-lowering effects.^[3] Statins have anti-inflammatory and antioxidant effects which may be effective in preventing AF development in addition to their lipid-lowering effects.^[4] Meta analyses have shown a reduced risk of AF development with statin use in patients with sinus rhythm.^[5] While animal studies report decreased electrical and structural remodeling in the atrium,^[6] it remains unclear which mechanisms are involved in the prevention of AF development with statins. The aim of "upstream treatment" in AF patients is to modify the atrial substrate in order to prevent predisposition or the continuation of AF.^[7] Therefore, the agents included in the statin group are evaluated under the "upstream treatment" title in line with the literature evidence. According to current American and European guidelines on the diagnosis and treatment of AF, statin treatment is not indicated for the primary prevention of AF in patients without cardiovascular

disease (Class III, Level of evidence: B).^[7] These guidelines recommend initiating statin treatment as it may be beneficial for the prevention of post-operative new onset AF in patients undergoing coronary bypass grafting surgery (Class IIb, Level of evidence: A). While atorvastatin is the treatment of choice as the statin subgroup in most of the small scale studies providing evidence for the guidelines, drug doses vary across the studies. Guidelines do not specify which subgroup of statins should be used and when or at which dose prior to bypass grafting surgery; however, the available studies recommend initiating high-dose statin treatment at least 1 week before surgery in order to prevent post-operative AF. Additionally, results of STICS, a recently published randomized controlled study^[8] contradict with previous evidence by showing that treatment with 20 mg/day rosuvastatin does not prevent post-operative AF development following bypass surgery; and these results are likely to change the current clinical practice regarding statin treatment for the prevention of "post-operative AF following bypass surgery" which already is associated with a low recommendation class. The guidelines emphasize that statin treatment provides no additional clinical benefit to prevent AF and therefore is not indicated for this purpose except for prevention of post-operative AF following bypass surgery.

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