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Lipid Modification to Reduce Cardiovascular Risk in Secondary Prevention Patients with Special Emphasis on PCSK9 Inhibitor Requirement: An Analysis Based on Delphi Panel Approach

Sekonder Önlem Hastalarında Kardiyovasküler Riski Azaltmada PCSK9 İnhibitör Gereksinimine Özel Vurgu ile Lipit Modifikasyonu: Delphi Panel Yaklaşımına Dayalı Bir Analiz

ORIGINAL ARTICLE
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ABSTRACT

Objective: The aim of this study is to analyze the low-density lipoprotein cholesterol-lowering therapies in secondary prevention patients by analyzing their plasma low-density lipoprotein cholesterol levels, current treatment, considering their inadequate response to medications (as defined in current guidelines), and the requirement for a protein convertase subtilisin/kexin type 9 inhibitor.

Methods: Delphi panel is used to seek expert consensus of experienced 12 cardiologists. A questionnaire consisting of 6 main questions is used to reflect the opinion of the expert panelists on the practices of low-density lipoprotein cholesterol-lowering therapies of patients with high and very high cardiovascular risk. Patients with atherosclerotic cardiovascular disease are covered in this present analysis.

Results: According to expert opinion data, 18.6% of the patient population with atherosclerotic cardiovascular disease is estimated to have experienced recurrent vascular events. The current treatment of the patient population is 39.7% on high dose, 36.9% on low/moderate dose of statin, 13.1% on maximum tolerated dose statin + ezetimibe, and 1.2% on maximum tolerated dose statin + ezetimibe + protein convertase subtilisin/kexin type 9 inhibitor. The percentage of atherosclerotic cardiovascular disease patients with inadequate treatment response is estimated to be 20.2% in those using "maximum tolerated dose statin + ezetimibe." The proportion of patients who will need to be treated with a protein convertase subtilisin/kexin type 9 inhibitor increases as their low-density lipoprotein cholesterol levels rises from 9.1% in 70-99 mg/dL to 50.8% in ≥160 mg/dL for these patients.

Conclusion: According to expert opinion, although a substantial proportion of patients with secondary prevention have not achieved low-density lipoprotein cholesterol goals, the use of protein convertase subtilisin/kexin type 9 inhibitors is very low. Since the questionnaire subject to panel discussion did not include any question elaborating the issue, the discrepancy between the recommendation of the related guidelines and Turkish practice needs further studies for the explanation.

Keywords: Cardiovascular risk factors, Delphi, LDL-cholesterol, PCSK9 inhibitor, Turkey

ÖZET

Amaç: Sekonder koruma hastalarının düşük yoğunluklu lipoprotein kolesterol (LDL-K) düşürücü tedavilerini, plazma LDL-K düzeylerini, mevcut tedavilerini, ilaçlara yanıtlarının yetersizliğini (mevcut rehberlerde açıklandığı şekilde) ve protein konvertaz subtilisin/keksin tip 9 (PCSK9) inhibitörlerine ihtiyaçlarını dikkate alarak analiz etmek.

Yöntemler: Delphi panel yaklaşımı kullanıldı. Panelde, deneyimli 12 kardiyolog yer aldı. Uzman panelistlerin yüksek ve çok yüksek KV riski olan hastaların tedavi uygulamaları ve bunların sonuçları ile ilgili ortak görüşlerini yansıtacak şekilde altı ana soru içeren bir anket hazırlandı. Bu çalışma aterosklerotik kardiyovasküler hastalığı (ASKVH) olan hastaların analizlerini kapsamaktadır.

Bulgular: Uzman görüşü verilerine göre, ASKVH olanların %18,4'inde tekrarlayan vasküler olayların görüldüğü tahmin edilmektedir. Bu hastaların %39,7'si yüksek, %36,9'u düşük/orta doz statin, %13,1 "maksimum tolere edilen doz (MTD) statin + ezetimib ve %1,2 MTD

statin + ezetimib + PCSK9 inhibitörü ile tedavi edilmektedir. MTD statin + ezetimib" ile tedavi edilen hastaların %20.2'sinde tedavi yanıtının yetersiz olduğu tahmin edilmektedir. PCSK9 inhibitörü ile tedavi edilmesi gereken hastaların oranı, LDL-K seviyeleri yükseldikçe artmaktadır. Tekrarlayan vasküler olayı olan LDL-K düzeyleri 70-99 mg/dL aralığında olan hastalarda %9,1 iken LDL-K düzeyleri ≥160 mg/dL olanlarda %50,8 olduğu tahmin edilmektedir.

Sonuç: Uzman görüşüne göre, sekonder koruma hastalarının önemli bir kısmı hedef LDL-K seviyelerinde olmasa da PCSK9 inhibitörlerinin kullanımı çok düşüktür. Panel tartışmasına konu olan ankette bu konuyu detaylandıran herhangi bir soru bulunmadığından, ilgili kılavuzların tavsiyesi ile Türkiye uygulaması arasındaki çelişkinin açıklanması için daha fazla araştırma yapılması gerekmektedir.

Anahtar Kelimeler: Delphi, kardiyovasküler risk, LDL-kolesterol, PCSK9 inhibitor, Türkiye

Cardiovascular (CV) disease is the leading cause of worldwide deaths. An estimated 17.9 million people died from CV diseases in 2019, representing 32% of all global deaths. Turkish Statistical Institute reported that 36.8% of deaths in 2019 were due to CV disease.[1] Systematic review and meta-analysis of 7 studies, including lipid data, demonstrated that dyslipidemia constitutes Turkey's significant public health problem. In the adult population, almost 3 of 10 have hypercholesterolemia, 1 of 2 has a low high-density lipoprotein (HDL)-cholesterol, and 1 of 3 has high triglycerides levels.[2] A multicenter observational study conducted in Turkey revealed that only 18% of the secondary prevention and 10.6% of the primary prevention patients had low-density lipoprotein (LDL)-C level at the recommended level of <70 mg/dL.[3]

A recent study conducted in 452 centers, including Turkey, revealed that the achievement of LDL-C goals in patients is suboptimal with the currently used lipid-lowering therapies.[4] This report is in line with the previous report of Sözmen et al.[5] According to these data, despite the relatively high population awareness rates of high LDL-C in Turkey, 49% of the population with high LDL-C levels is not being treated to the recommended levels.

In the present study, hypothetical patient populations with atherosclerotic cardiovascular disease (ASCVD) were constructed by an expert panel and their (a) plasma LDL-C levels, (b) current treatment practices, (c) inadequate response to current treatment, and (d) requirement for a protein convertase subtilisin/kexin type 9 (PCSK9) inhibitor were analyzed.

Methods

This study used the Delphi panel approach to seek expert consensus. Of note, the Delphi panel is a structured process that invites experts to complete a series of "rounds" to gather and refine information on the study questions until expert consensus is reached.[6] In the present study, the panel included 12 cardiologists with a minimum of 20 years of experience, clinical practice in cardiology, leader in dyslipidemia and CV risk, and currently working at university hospitals or training and research hospitals.

The questionnaire was prepared by an experienced medical statistician and Delphi panel experts. Thus, it is unique and original. The questionnaire consisted of 6 main questions, which were structured considering the management of patients with high and very high CV risk. For this purpose, literature data related to the subject and the guidelines (i.e., from Turkish Society of Cardiology, European Society of Cardiology, and American Heart Association) were examined thoroughly.

1. "CV risk categories in patients,"
2. "Medications that the patients are currently receiving,"
3. "LDL-C levels of the patients,"
4. "The patients with inadequate response to current treatment,"
5. "New medication approach to the patients with inadequate response to current treatment," and
6. "PCSK9 inhibitor requirement of the patients" (with/without restriction to reimbursement on PCSK9 inhibitors)

In the first round, the questionnaire form was sent to the expert panelists via e-mail. The questions were requested to be answered by considering the general practice in Turkey, not according to the panelists' own practice or institution. The panelists were asked to send back the filled forms within 10 days for the first round. In the second round, an online expert meeting was organized to review the answers given at the first round. The second-round meeting included items to reflect the opinion of the expert panelists on the treatment practices of secondary prevention patients and their outcomes. Finally, in the third round, the answers (revised and fine-tuned during the second round) were re-evaluated by the panelists, and the results were finalized.

The present analysis covered only the Delphi Panel's opinion on the management of patients with ASCVD. The ASCVD was defined as documented atherosclerotic cardiovascular disease (ASCVD), either clinical or unequivocal on imaging (documented ASCVD includes previous acute coronary syndrome [myocardial infarction or unstable angina], stable angina, coronary revascularization [percutaneous coronary intervention, coronary artery bypass graft surgery, and other arterial revascularization

ABBREVIATIONS

ASCVD	Atherosclerotic cardiovascular disease
CT	Computed tomography
CV	Cardiovascular
DESCARTES	Durable Effect of PCSK9 Antibody Compared with Placebo Study
EAS	European Atherosclerosis Society
ESC	European Society of Cardiology
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
MTD	Maximum tolerated dose
PCSK9	Protein convertase subtilisin/kexin type 9

procedures], stroke and transient ischemic attack, and peripheral arterial disease). Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or computed tomography scan (a multivessel coronary disease with 2 major epicardial arteries having >50% stenosis) or on carotid ultrasound.

Recurrent vascular events are defined as experiencing at least 2 vascular events within 2 years while using maximum tolerated dose (MTD; the highest dose of a drug that does not cause overt toxicity or unacceptable adverse effects within a specified time) of statins.

Statistical Analysis

Data related to the answers of 12 expert panelists were analyzed using descriptive statistics. At the first and second rounds, the answers' average values and median, minimum, and maximum values were reviewed. The answers were accepted as final as they were given by the experts when minimum and maximum values were not much apart and average and median values were close to each other. When, however, the range of the answers was too wide and/or average and median values were not close, the experts who had answered with extreme values were contacted again and were asked if they wished to revise their answers, considering the average and range of the answers. Again, their decisions were accepted as final, whether they revised their answers or not. These final values were considered to connect the related questions and calculate the combined proportions.

Results

As demonstrated in Table 1, 18.4% of the patient population with ASCVD is estimated to have experienced recurrent vascular events. In the remaining patient population with no recurrent vascular event, 46.7% is assumed to have experienced coronary revascularization, 41.3% acute coronary syndrome, and 36.7% stable angina pectoris.

Secondary Prevention Patients with Recurrent Vascular Events

Evaluation of the current treatment practices in these patients revealed that 39.7% are being treated with a high dose of statin, 36.9% low/moderate dose of statin, 13.1% MTD statin + ezetimibe, and 1.2% MTD statin + ezetimibe + PCSK9 inhibitor. The remaining 9.2% is not on any pharmacologic treatment (Figure 1). The distribution of regularly treated patients into LDL-C level categories is presented in Table 2.

Table 1. Underlying Cardiovascular Events/Disorders in Secondary Prevention Patients

Underlying Cardiovascular Events/Disorders	Patients (%)
Secondary prevention patients	
Recurrent vascular events	18.4
No recurrent vascular events	81.6
Coronary revascularization	46.7
Previous acute coronary syndrome (*myocardial infarction or unstable angina pectoris*)	41.3
Stable angina pectoris	36.7
Documented significant plaque (*on coronary angiography or CT scan (multivessel coronary disease with 2 major epicardial arteries having >50% stenosis), or on carotid ultrasound*)	32.9
Peripheral arterial disease	14.0
Stroke or transient ischemic attack	10.2

CT, computed tomography.

According to the expert opinion, response to treatment will be inadequate in an estimated 24.8% of all the patients receiving a high dose of statin (Table 3). Therefore, it is assumed that the treatment in 77.5% of these patients will be upgraded to MTD statin + ezetimibe, and 1.67% will be further prescribed PCSK9 inhibitor in addition to MTD statin + ezetimibe (Table 4).

On the other hand, the percentage of the patients with inadequate treatment response is estimated to be 20.2% in those using MTD statin + ezetimibe (Table 3). Among these patients, 89.1% will continue with the same treatment, and a PCSK9 inhibitor will be added to MTD statin + ezetimibe in the remaining 10.9% (Table 4).

When the patients using MTD statin + ezetibime + PCSK9 inhibitor are evaluated in terms of their LDL-C levels, the

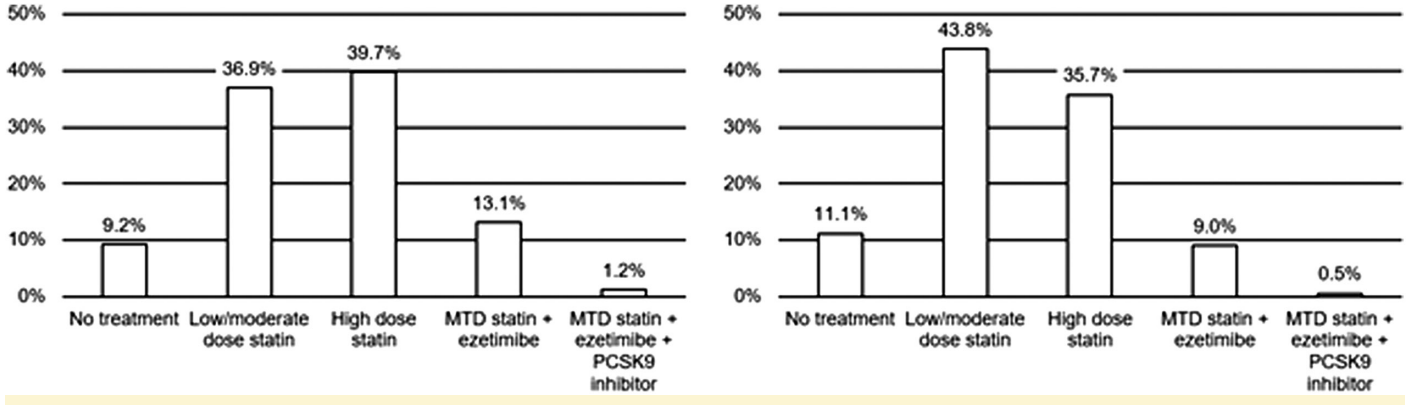

Figure 1. Current treatment practices in secondary prevention patients. Left panel: Secondary prevention patients with recurrent vascular events. Right panel: Secondary prevention patients without recurrent vascular events. LDL-C, low-density lipoprotein cholesterol; MTD, maximum tolerated dose; PCSK9, proprotein convertase subtilisin/kexin type 9.

Table 2. Distribution of Patients into LDL-C-Level Categories, when on Regular Treatment

	LDL-C Level (mg/dL)				
	<100	100-129	130-159	≥160	Total
Secondary prevention patients					
With recurrent vascular events					
On high-dose statin	72.0%	16.9%	8.5%	2.6%	100%
On MTD statin + ezetimibe	69.8%	19.2%	8.7%	2.4%	100%
On MTD statin + ezetimibe + PCSK9 inhibitor	93.1%	4.9%	1.3%	0.7%	100%
Without recurrent vascular events					
On high-dose statin	71.5%	17.3%	8.8%	2.4%	100%
On MTD statin + ezetimibe	65.8%	20.3%	10.5%	3.3%	100%
On MTD statin + ezetimibe + PCSK9 inhibitor	89.4%	7.3%	2.8%	0.6%	100%

LDL-C, low-density lipoprotein cholesterol; MTD, maximum tolerated dose; PCSK9, proprotein convertase subtilisin/kexin type 9.

Table 3. Proportion of Patients with Inadequate Response to Current Treatment, Split by LDL-C-Level Category

	LDL-C Level (mg/dL)				
	<100	100-129	130-159	≥160	Overall*
Secondary prevention patients					
With recurrent vascular events					
On high-dose statin	13.6%	46.7%	60.8%	78.5%	24.8%
On MTD statin + ezetimibe	8.8%	41.2%	52.4%	70.3%	20.2%
Without recurrent vascular events					
On high-dose statin	5.2%	42.1%	58.7%	80.0%	18.1%
On MTD statin + ezetimibe	3.6%	47.5%	62.9%	85.9%	21.5%

*The values are weighted considering the distribution of patients among different LDL-C categories.
LDL-C, low-density lipoprotein cholesterol; MTD, maximum tolerated dose; PCSK9, proprotein convertase subtilisin/kexin type 9.

Table 4. Treatment Practices Following Inadequate Response to Current Treatment

	Next Therapeutic Approach				
	Low/Moderate-Dose Statin	High-Dose Statin	MTD Statin + Ezetimibe	MTD Statin + Ezetimibe + PCSK9 Inhibitor	Total
Secondary prevention patients					
With recurrent vascular events					
On high-dose statin	-	20.8%	77.5%	1.67%	100%
On MTD statin + ezetimibe	-	-	89.1%	10.9%	100%
All patients on any treatment	5.8%	16.0%	14.3%	0.45%	36.5%
Without recurrent vascular events					
On high-dose statin	-	29.6%	68.6%	1.83%	100%
On MTD statin + ezetimibe	-	-	90.3%	9.8%	100%
All patients on any treatment	4.9%	18.6%	9.5%	0.31%	33.4%

LDL-C, low-density lipoprotein cholesterol; MTD, maximum tolerated dose; PCSK9, proprotein convertase subtilisin/kexin type 9.

expert opinion estimated the proportions of patients as 93.1%, 4.9%, 1.3%, and 0.7%, in LDL-C levels <100 mg/dL, 100-129 mg/dL, 130-159 mg/dL, and ≥160 mg/dL, respectively (Table 2).

As seen in Table 5, the proportion of patients who will be treated with a PCSK9 inhibitor when response to MTD statin + ezetimibe is inadequate increases as their LDL-C levels rises (9.1% in LDL-C 70-99 mg/dL, 21.l9% in 100-129 mg/dL,

Table 5. Proportion of Patients Who Will Be Treated with PCSK9 Inhibitor (In Case There Is No Restriction for Reimbursement), When Response to MTD Statin + Ezetimibe is Inadequate, Split by LDL-C Level Category

	LDL-C level (mg/dL)					
	<70	70-99	100-129	130-159	≥160	Overall*
Secondary prevention patients						
With recurrent vascular events	0.9%	9.1%	21.9%	36.3%	50.8%	1.56%
Without recurrent vascular events	0.1%	6.1%	18.3%	29.9%	48.8%	0.95%

*The values are weighted considering the distribution of patients among different LDL-cholesterol categories.
LDL-C, low-density lipoprotein cholesterol; MTD, maximum tolerated dose; PCSK9, proprotein convertase subtilisin/kexin type 9.

36.3% in 130-159 mg/dL, and 50.8% in those with LDL-C ≥160 mg/dL).

Secondary Prevention Patients without Recurrent Vascular Events

Evaluation of the current treatment practices on the secondary prevention patients not having experienced recurrent vascular events revealed that of these patients, 43.8% were on a low/moderate dose of statin, 35.7% on a high dose of statin, 9.0% on MTD statin + ezetimibe, and 0.5% on MTD statin + ezetimibe + PCSK9 inhibitor (Figure 1).

Of those using a high-dose statin, 18.1% will not respond inadequately to the current treatment (Table 3). The expert opinion estimated that the treatment would shift to MTD statin + ezetimibe in 68.6% and to MTD statin + ezetimibe + PCSK9 inhibitor in 1.83% (Table 4).

21.5% of the patients currently using MTD statin + ezetimibe are estimated as having inadequate treatment response (Table 3). The experts suggest that 90.3% of these patients will continue with the same treatment and that 9.8% are expected to use a PCSK9 inhibitor added to MTD statin + ezetimibe (Table 4).

Among those using MTD statin + ezetimibe + PCSK9 inhibitor, the estimated proportion of patients are 89.4%, 7.3%, 2.8% and 0.6%, in LDL-C levels <100 mg/dL, 100-129 mg/dL, 130-159 mg/dL, and ≥160 mg/dL, respectively (Table 2).

The proportion of patients who will be treated with a PCSK9 inhibitor when response to MTD statin + ezetimibe is inadequate seems to rise as their LDL-C levels rises (6.1% in LDL-C 70-99 mg/dL, 18.3% in 100-129 mg/dL, 29.9% in 130-159 mg/dL, and 48.8% in those with LDL-C ≥160 mg/dL) (Table 5).

Discussion

In this study, the analysis of the experts' opinions demonstrated the status of the secondary prevention patients in terms of their inadequate response to current medications and treatment options to reach target LDL-C values.

The Cholesterol Treatment Trialists meta-analysis demonstrated a 37% risk reduction in major vascular events in patients with LDL-C levels of 70 mg/dL while on statin treatment.[7] On the other hand, the meta-analysis of 8 statin trials reported the percentages of patients who failed to reach LDL-C levels of <100 mg/dL and <70 mg/dL while being treated with high-dose statin as 13% and 40%, respectively.[8] High baseline LDL-C levels, inadequate drug doses, poor adherence, and/or poor tolerability are the major reasons for the lack of achieving target LDL-C levels in patients on statin treatment. EPHESUS registry (a national, observational, and multicenter study) including hypercholesterolemia patients in cardiology outpatient clinics in Turkey reported that only 18% of the secondary prevention patients were below the target LDL-C levels (70 mg/dL).[9] The same study also revealed that media reports (31.4%) and physician recommendations to stop the lipid-lowering therapy (13.2%) were major reasons for discontinuing statin therapy. Additionally, the diabetic patients are also far below the recommended LDL-C treatment goals (15% for overall high or very high-risk diabetics and 17.5% for people with diabetes in secondary prevention) in real-life cardiology practice.[10]

Many patients need a combination treatment if they have very high CV risk or very high LDL-C levels. For these patients, 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines recommend the addition of ezetimibe and, if still not at goal, the addition of a PCSK9 inhibitor.[11] In our study, 25% of the secondary prevention patients with recurrent vascular events have an inadequate response to high-dose statin (18% in those without recurrent vascular events). These items are 20% and 22% in those under MTD + ezetimibe therapy, respectively. On the other hand, among the patients receiving "MTD statin + ezetimibe + PCSK9 inhibitor," those having LDL-C <100 mg/dL are in the range of 89%-93%. These expert opinion data demonstrate that a substantial proportion of patients with ASCVD cannot achieve optimal LDL-C levels with high-dose statin or MTD statin + ezetimibe therapies and that the addition of a PCSK9 inhibitor is an effective strategy to reach the goal.

The use of monoclonal antibodies directed against PCSK9 seems to be an effective therapeutic strategy for hyperlipidemia management. Inhibition of PCSK9 improves LDL receptor recycling, increases the availability of LDL receptors on hepatocyte cell surfaces, increases LDL-C plasma clearance, and thus, reduces plasma LDL-C levels. Recent clinical studies showed that treatment with PCSK9 inhibitors-alirocumab, or evolocumab (the 2 human monoclonal PCSK9 antibodies) in combination with MTD statin reduced LDL-C levels by 46% to 73% more than placebo and by 30% more than ezetimibe. These PCSK9 inhibitors also effectively lower LDL-C levels in patients with high CV risk.[12,13]

As reported in the multicenter, double-blind FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition on Subjects with Elevated Risk) trial, the treatment with

evolocumab reduced the risk of the primary endpoint (a composite of CV death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization) by 15% in 27 564 patients with atherosclerotic CV disease, LDL-C levels of ≥70 mg/dL, and on statin treatment.[14] In addition, the multicenter, double-blind, randomized control trial, ODYSSEY (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) conducted on 18 924 patients (LDL-C ≥70 mg/dL, hospitalized for acute myocardial infarction/unstable angina, and treated with statins) demonstrated a 15% reduction in premature CV outcomes.[15] Furthermore, OSLER-1, OSLER-2, and ODYSSEY LONG TERM trials evaluating the CV outcomes of PCSK9 inhibitors found a reduction in major CV events with evolocumab and alirocumab added to standard treatment in comparison to standard treatment alone.[16,17]

Although the European guideline recommends the addition of ezetimibe (a cholesterol absorption inhibitor) in patients who are far below the lipid targets, only one-fifth of patients with diabetes mellitus who were on statin therapy reach the LDL-C target levels in real-life practice in Turkey. As observed in the EPHESUS trial, one-fifth of diabetic patients on statin therapy were receiving MTD statins, and less than 25% of those attained LDL-C targets, and none of them were using ezetimibe.[9] In our study, the expert opinion assumed that ezetimibe is added to current treatment in the majority of secondary prevention patients with inadequate response to "high-dose statin" (78% in those with recurrent vascular events and 69% in those without recurrent vascular events). However, the secondary prevention patients with inadequate response to "MTD statin + ezetimibe" continue with the current medications in the majority. Therefore, it was expected that in only 11% of those with recurrent vascular events and 10% of those without recurrent vascular events, a PCSK9 inhibitor would be used as an add-on-treatment. On the other hand, among the patients on "MTD statin + ezetimibe" therapy, the proportion of those expected to receive a PCSK9 inhibitor increases as their LDL-C levels rise. In patients with recurrent vascular events and inadequate response to "MTD statin + ezetimibe" therapy, the need for a PCSK9 inhibitor is in 9.1% of those with LDL-C of 70-99 mg/dL and 50.8% in those with LDL-C of >160 mg/dL. There is a similar trend in those without recurrent vascular events and inadequate response to "MTD statin + ezetimibe" therapy.

In the Durable Effect of PCSK9 Antibody Compared with Placebo Study (DESCARTES), the addition of evolocumab monthly resulted in an LDL-C reduction of 48% in 189 patients receiving atorvastatin 80 mg + ezetimibe 10 mg daily.[18] Trials on patients having heterozygous familial hypercholesterolemia including the Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD-2) trial demonstrated a reduction in LDL-C levels with evolocumab to a similar extent between patients receiving ezetimibe and those who were not.[19]

The United States 2018 guidelines define 2 patient populations for whom PCSK9 inhibitors are appropriate: those with a very high risk of CV events + LDL-C >70 mg/dL and those with primary hypercholesterolemia (LDL-C >100 mg/dL [baseline LDL-C ≥190 mg/dL] or >130 mg/dL [baseline ≥220 mg/dL]) when on MTD statin + ezetimibe treatment.[20] In the European 2019 guidelines, a combined treatment with a PCSK9 inhibitor is recommended in very high-risk patients who have not achieved the target LDL-C levels on MTD statin + ezetimibe treatment. In these guidelines, for very high-risk patients, either primary or secondary prevention, LDL-C reduction of ≥50% from the baseline, and LDL-C goal of <55 mg/dL are recommended.[11]

For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event), while taking maximally tolerated statin therapy, and LDL-C goal of <1.0 mmol/L (<40 mg/dL), a more intensive treatment might be considered.[11]

The PCSK9 inhibitors offer a comfortable dosing regimen in daily practice, requiring biweekly or monthly subcutaneous administrations. Prolonged dosing interval is an advantage of these drugs to enhance patient compliance and adherence to treatment. In addition, the safety profile of PCSK9 monoclonal antibodies is good as most of the reported adverse effects are mild (e.g., injection-site reactions). However, poor cost-effectiveness is the major limitation of the use of PCSK9 inhibitors. As their use could not be affordable for most healthcare systems, the patients may discontinue their treatment.[21] Thus, patients' adherence to PCSK9 inhibitors is significantly lower in real-world settings than in clinical studies. This may explain why the physicians seem unwilling to prescribe PCSK9 inhibitors for their patients, although they offer a safe and effective option for secondary prevention patients who are not at their LDL-C goals or intolerant to statins.

The study has several limitations that need to be mentioned. Some of these limitations are inherent to the methodology itself. First, the limited number of experts (being solely cardiologists) included in the study may not represent the general opinion; thus, this may cause a selection bias. On the other hand, cardiologists, in general, are highly experienced in managing high CV risk patients, which may strengthen our study. Secondly, judgment bias is an important limitation that is common for all consensus-based methods, including Delphi. And finally, this study did not aim to search the safety, tolerability, cost-effectiveness, duration, or any other aspects of the treatment with PCSK9 inhibitors, which would have shed light on the physicians' reluctance to prescribe them.

Conclusion

The present Delphi panel evaluation highlighted that in a substantial proportion of patients with ASCVD, response to the MTD statin + ezetimibe combination is inadequate, and the only minority of these patients (20%) are expected to be candidates for therapy with PCSK9 inhibitors. However, PCSK9 inhibitors are prescribed for only 1% of those suggested as candidates for anti-PCSK9 treatment. The major reason for this discrepancy between the physicians' attitudes and guidelines is probably the lack of reimbursement of these medications in Turkey. Studies to clarify other possible reasons are warranted to assist the physicians/patients toward achieving LDL-C goals with appropriate medications.

Ethics Committee Approval: N/A.

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