Hellenic Journal of Atherosclerosis 6(3):155–159

Ελληνική Επιθεώρηση Αθηροσκλήρωσης 6(3):155–159

Europe to US
Re-establish specific low density lipoprotein cholesterol targets because we all need them

Ευρώπη προς ΗΠΑ
Επαναφέρατε τους συγκεκριμένους θεραπευτικούς στόχους της LDL χοληστερόλης, επειδή όλοι τους χρειαζόμαστε

V.G. Athyros,[1] K. Tziomalos,[2] A. Karagiannis[1]

[1]2nd Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, "Hippocration" General Hospital, Thessaloniki, [2]1st Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA Hospital, Thessaloniki, Greece

Β.Γ. Άθυρος,[1] Κ. Τζιόμαλος,[2] Α. Καραγιάννης[1]

[1]Β΄ Προπαιδευτική Παθολογική Κλινική, Ιατρική Σχολή, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης, «Ιπποκράτειο» Γενικό Νοσοκομείο, Θεσσαλονίκη [2]Α΄ Προπαιδευτική Παθολογική Κλινική, Ιατρική Σχολή, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης, Νοσοκομείο ΑΧΕΠΑ, Θεσσαλονίκη

ABSTRACT: The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines do not recommend specific low density lipoprotein cholesterol (LDL-C) targets in contrast to all other previous guidelines for the management of dyslipidemia. Instead, they recommend a ≥50% reduction in LDL-C in high risk patients and a 30–50% reduction in moderate risk patients with the administration of either high- or moderate-intensity statin therapy depending on the cardiovascular risk. These guidelines had several practical problems but the most important was the lack of specific LDL-C targets. The dogma "shoot and forget" is not applicable to everyone. In several cases of high risk patients, we need to know if LDL-C during treatment has reached a specific and desired level, so that we can add ezetimibe and/or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

ΠΕΡΙΛΗΨΗ: Οι οδηγίες του 2013 του Αμερικανικού Κολεγίου Καρδιολογίας και της Αμερικανικής Καρδιολογικής Εταιρείας (ACC/AHA) δεν πρότειναν συγκεκριμένους θεραπευτικούς στόχους για τη χαμηλής πυκνότητας χοληστερόλη (LDL-C), σε αντίθεση με όλες τις προηγούμενες κατευθυντήριες οδηγίες για τη διαχείριση της δυσλιπιδαιμίας. Αντίθετα, πρότειναν μείωση ≥50% στην LDL-C σε ασθενείς υψηλού κινδύνου και μείωση 30–50% σε άτομα μέτριου κινδύνου με τη χορήγηση υψηλής ή μέτριας έντασης θεραπείας με στατίνες, ανάλογα με τον καρδιαγγειακό κίνδυνο. Αυτές οι κατευθυντήριες οδηγίες είχαν πολλά πρακτικά προβλήματα, αλλά το πιο σημαντικό ήταν η έλλειψη συγκεκριμένων θεραπευτικών στόχων για την LDL-C. Σε αρκετές περιπτώσεις ασθενών υψηλού κινδύνου θα πρέπει να γνωρίζουμε αν η LDL-C κατά τη διάρκεια της θεραπείας έχει φτάσει σε ένα συγκεκριμένο και επιθυ-

Vasilios G. Athyros, MD, FESC, FRSPH, FASA, FACS
2nd Propedeutic Department of Internal Medicine, "Hippocration" General Hospital, 15 Marmara street, GR-551 32 Thessaloniki, Greece
Tel. (+30) 2310-892 606, Fax: (+30) 2310-835 955
e-mail: vathyros@gmail.com

Βασίλειος Γ. Άθυρος, MD, FESC, FRSPH, FASA, FACS
Β΄ Προπαιδευτική Παθολογική Κλινική, «Ιπποκράτειο» Γενικό Νοσοκομείο, Μαρμαρά 15, 551 32 Θεσσαλονίκη
Τηλ: 2310-892 606, Fax: 2310-835 955
e-mail: vathyros@gmail.com

if they have not reached that level. In patients with heterozygous familial hypercholesterolaemia (HeFH), who have very high baseline LDL-C levels, the 50% reduction is not enough to reach an acceptable level. In addition, in statin intolerant patients and in those high risk patients who do not adequately respond to combined treatment (statin plus ezetimibe) we need to add PCSK9 inhibitors that can further reduce LDL-C by 50–60% with a different mechanism of action than statins. Thus, there is a pressing need for a change in 2013 ACC/AHA guidelines towards adopting specific LDL-C goals so that rules are established for the administration of the expensive PCSK9 inhibitors only in those who need them. Otherwise, healthcare systems will not approve the use of PCSK9 inhibitors and that will cost a lot of lives.

Key words: Dyslipidemia, LDL-C targets, statins, PCSK9 inhibitors.

μητό επίπεδο, έτσι ώστε να μπορούμε να προσθέσουμε εζετιμίμπη και/ή αναστολείς της PCSK9, αν δεν έχουν φτάσει σε αυτό το επίπεδο. Σε ασθενείς με ετερόζυγη οικογενή υπερχοληστερολαιμία (HeFH) που έχουν πολύ υψηλά αρχικά επίπεδα LDL-C, η μείωση κατά 50% δεν είναι αρκετή για να επιτευχθεί ένα αποδεκτό επίπεδο. Επίσης, σε ασθενείς με δυσανεξία στη στατίνη και σε ασθενείς υψηλού καρδιαγγειακού κινδύνου που δεν ανταποκρίνονται επαρκώς σε συνδυασμένη θεραπεία (στατίνη συν εζετιμίμπη) πρέπει να προσθέσουμε αναστολείς PCSK9 που μπορούν να μειώσουν περαιτέρω την LDL-C κατά 50–60% με διαφορετικό μηχανισμό από τις στατίνες. Έτσι, υπάρχει μια πιεστική ανάγκη για αλλαγή των κατευθυντήριων γραμμών των ACC/AHA προς την κατεύθυνση της υιοθέτησης συγκεκριμένων θεραπευτικών στόχων της LDL-C, ώστε να καθορίζονται κανόνες για τη διαχείριση των ακριβών αναστολέων της PCSK9 και τη χορήγησή του μόνο σε εκείνους που τους έχουν ανάγκη. Διαφορετικά, τα συστήματα υγειονομικής περίθαλψης δεν θα εγκρίνουν τη χρήση των αναστολέων της PCSK9 και αυτό θα κοστίσει πολλές ανθρώπινες ζωές.

Λέξεις ευρετηρίου: Δυσλιπιδαιμία, στόχοι LDL χοληστερόλης, στατίνες, αναστολείς PCSK9.

1. Introduction

The management of dyslipidaemias is a major component of primary and secondary cardiovascular disease (CVD) prevention strategies. In this context, several medical organizations have formulated guidelines for the management of dyslipidaemias. Nearly two years ago, the joint American guidelines for the treatment of dyslipidaemias were issued by an expert panel consisting of members of the American Heart Association (AHA), the American College of Cardiology (ACC) and the My.American.Heart.org, under the auspices of the US National Heart Lung and Blood Institute.[1] In contrast to all other previous guidelines for the management of dyslipidemia, the 2013 ACC/AHA guidelines do not recommend specific low density lipoprotein cholesterol (LDL-C) targets. Instead, they propose a ≥50% reduction in LDL-C in high risk patients and a 30–50% reduction in moderate risk patients with the administration of high- or moderate-intensity statin therapy depending on the CVD risk. High-intensity statin therapy includes atorvastatin 40–80 mg/day and rosuvastatin 20–40 mg/day whereas moderate-intensity statin therapy includes lower doses of atorvastatin and rosuvastatin, simvastatin 20–40 mg/day, pravastatin 40–80 mg/day, fluvastatin 40–80 mg/day and pitavastatin 2–4 mg/day. The risk of developing CVD in the next decade was estimated by a new risk calculator. Since treating to specific LDL-C targets was no longer recommended, clinicians should focus on assessing patients' risk of atherosclerotic CVD and whether they fall into one of four high-risk patient groups, for which moderate- or high-intensity statin therapy is recommended: (a) patients with clinical atherosclerotic CVD, (b) patients with LDL-C levels ≥190 mg/dL, (c) patients with type 2 diabetes mellitus (T2DM) aged 40–75 years with LDL-C levels of 70–189 mg/dL but without clinical ASCVD and (d) patients without clinical ASCVD or diabetes but with LDL-C levels of 70–189 mg/dL and estimated 10-year CVD risk ≥7.5%.

2. Acceptability and implementation of 2013 ACC/AHA guidelines

The ACC/AHA guidelines were considered impractical and were not adopted by any other scientific organization. The Task Force of the European Atherosclerosis Society/European Society of Cardiology, the National Lipid Association smaller Societies from South America or Asia declined to endorse these new cholesterol (statin) guidelines and suggest sticking with previous guidelines.

In Greece, we continue to use the 2011 European guidelines,[2] and especially the Hellenic guidelines adapted to the data of the Greek population,[3] recently validated.[4]

2.1. This happens for various reasons

1. The 2013 Risk Equation was based solely in epidemiological data and the ACC/AHA guidelines on prospective, randomized, controlled, survival trials. We are long past from defining CVD main risk factors; at present we face difficulties in implementing previous simpler treatment guidelines.
2. The studies used for the formulating the CVD risk estimation equation were conducted in the US only. Thus, this equation might be applicable in US but not elsewhere (Europe, Asia, Africa and South America).
3. The guidelines suggest only statin treatment and practically ignore all other hypolipidaemic agents; thus, these are statin- and not lipid guidelines.
4. The algorithms used to define the choice of treatment are very complex and could not be understood by all physicians that have to implement a number of algorithms for various diseases within their specialty.
5. There is no mention about coronary heart disease (CHD) equivalents, such as T2DM and chronic kidney disease as well as their combination (diabetic nephropathy has an annual mortality rate of 20%, similar to that of cancer, and is ignored by these guidelines). This occurs in an era when other panels are considering to expand the concept of CHD equivalents and to include rheumatoid arthritis, non-alcoholic fatty disease or its advanced form of non-alcoholic steatohepatitis, and others.
6. On the other hand, the CVD risk estimation equation overestimates CVD risk in subjects without overt CVD or T2DM and may increase by up to 150% the number of subjects that require statin treatment. Patients on statins are at present 31.5 million in US and their number is estimated to rise to more than 70 million. It has also been projected that the application of the ACC/AHA guidelines will render eligible for statin treatment more than 1 billion subjects worldwide. It appears that these guidelines panel aim to prevent an increase in CVD mortality in the US due to the ever increasing prevalence of obesity, with cheep (generic atorvastatin costs 5$ a month, and 10$ for a 3 month "refill") statins for everybody. Obesity, hypertension, dyslipidemia, T2DM and metabolic syndrome (MetS) are driving the CVD risk in US. Despite the fact that 70% of US adults are overweight or obese, still diet quality continues to deteriorate, leading to the fact that at present time more than half of US adults have dyslipidemia. However, statin for everybody without weighting the risk/benefit ratio is dangerous. Statins are known to cause new onset diabetes from 1% up to 33%[5] of people that take them, especially in obese people, those with MetS and those with prediabetes. Thus, this policy will probably cause a boost in the prevalence of T2DM and at a second stage of CVD.
7. The lack of specific LDL-C targets is probably the greatest problem with these guidelines. It is not rare to see a patient with heterozygous familial hypercholesterolemia (HeFH) (approximately 1 million cases in the US) with LDL-C levels of 300–400 mg/dl. According to the ACC/AHA guidelines, a 50% reduction in these levels is enough. However, does anybody believe that an LDL-C concentration of 150–200 mg/dL is within the normal range? Therefore, if the ACC/AHA guidelines are adopted, many patients who need intensive hypolipidaemic (mainly combination) treatment will be deprived of it, while others who do not need it are considered eligible to receive it.
8. These guidelines will be an immense barrier that will at least delay the use of novel hypolipidaemic drugs, such as antibodies against proprotein convertase subtilisin/kexin type

9 (PCSK9) (evolocumab and alirocumab) that are already commercially available and are expected to be very efficacious but also expensive. These have an indication to be used in very high CVD risk patients that cannot reach the <70 mg/dL LDL-C goal with available treatments. How can one use these drugs if there is no specific LDL-C goal above which PCSK9 inhibitors could be used?

10. Finally, the guidelines do suggest follow-up measurement of LDL-C levels to ensure compliance with statin treatment however, However, they recommend that a baseline measurement of transaminase (ALT) levels should be performed before initiation of statin therapy. There is no recommendation to monitor transaminase levels.

3. New problems with the ACC/AHA guidelines asking for reconsideration

Recently, the Consumer Value Stores (CVS) Health, a large pharmacy benefits manager with nearly 70 million clients in the US, requested ACC and AHA to return to goal-based LDL-C targets in order to reduce the massive costs of the new PCSK9 inhibitors.[6] In a recent publication in JAMA[7] authors discuss the costs of alirocumab (Praluent, Sanofi/Regeneron), which was approved by the Food and Drug Administration (FDA) in early August and is priced at $14,600 per year.[6,7] The FDA also approved Amgen's Repatha (evolocumab) for US marketing in late August 2015. Repatha is indicated for use in addition to diet and maximally-tolerated statin therapy in adult patients with HeFH, homozygous familial hypercholesterolemia (HoFH), or clinical atherosclerotic CVD, such as myocardial infarction or stroke, who require additional LDL-C lowering. Wholesale Acquisition Cost (WAC) of Repatha is $14,100 annually for the every two weeks subcutaneous administration. Actual costs to patients, payers and health systems are anticipated to be different in Europe; in UK it is estimated to have an annual cost of £6,000, based on pricing negotiations, insurance coverage or patient assistance programs.

The question is how many patients are going to use these medications. This will partly depend on the views of the cardiology community about how effective these medications are, and obviously these views partly depend on the current guidelines. Given the price of PCSK9 inhibitors, we know what they cost now, and we know how many patients are on statins, and when you put these two facts put together, the costs will likely be astounding.[6,7] It all depends of what part of people on statins will also be treated with PCSK9 inhibitors.[6] With more than 73 million adults in the US with elevated LDL-C levels, and with both alirocumab and evolocumab approved not as a cure but rather a lifelong treatment for managing hypercholesterolemia, specialists argue that if PCSK9 inhibitors are used broadly this would be the most costly treatment ever.[6] None of the health care providers in US has approved alirocumab or evolocumab waiting for whole sale deals with Sanofi and Amgen.

Express Scripts, the largest pharmacy benefit manager in the US, has also the same opinion and claimed that the cost of the PCSK9 inhibitors could "wreak financial havoc" on its business.[6] These huge Companies (7th and 10th largest Companies from all fields in US) covering more than 150 million people in US will not approve the use of PCSK9 inhibitors unless strict rules are adopted. For example patients with HeFH will be eligible for treatment with PCSK9 inhibitors, if not effectively controlled by statins or statin plus ezetimibe combinations. On the other hand, which is the exact definition of statin intolerance should be meticulously defined. Finally, high CVD risk patients not reaching LDL-C targets (i.e. a huge number of patients) should probably also be eligible for PCSK9 inhibitor therapy.[6,7] In all these cases, specific LDL-C goals have to be determined, so that only when these goals are not attained, during the implementation of a specific treatment algorithm, the patient would be a candidate for PCSK9 inhibitor treatment. Healthcare payers believe that it is a reasonable solution to return to a utilization-management strategy that relies on lipid goals.[7] The lipid goals, such as treating patients to an LDL-C target <100 mg/dL or <70 mg/dL in very high-risk patients would help support "rational decision making" regarding the use of PCSK9 inhibitors.[6] In any case, the revision of the ACC/AHA guidelines so that specific LDL-C targets are recommended is of paramount importance for the proper utilization of PCSK9 inhibitors. The high status of the organizations that issued the 2013 ACC/AHA guidelines is so great that affects physicians all over the world, despite the fact that these guidelines have not been adopted by local Scientific Organizations. Thus, the change of the ACC/AHA guidelines will have a global effect.

The recent experience with sofosbuvir, for the treatment of hepatitis C, showed that the healthcare system might be devastated by a single drug. Sofosbuvir is indicated for the treatment of 3 million people with hepatitis C in US for a specific period of time (12 weeks).[8] PCSK9 inhibitors will be probably used by a much higher number of patients and for life. This demonstrates that if rules are not utilized the healthcare providers will never approve PCSK9 inhibitors, not even for HeFH patients, because of the lack of a reliable HeFH registry. To have the most ever effective hypolipidaemic drug category at hand and not be able to use it because of lack of LDL-C targets or rules will be devastating. Therefore,

the appropriate use of PCSK9 inhibitors in specific patient categories should be facilitated, deriving the most benefit of these agents, without bankrupting the healthcare system.[6–8]

If the expert panel of the 2013 ACC/AHA guidelines decides to revise them, there will be a chance to report that hypolipidaemics other than statins, such as ezetimibe, can show a clinical benefit if used with a statin and induce a further LDL-C reduction and that in the case of LDL-C the lower the better, at least down to 52 mg/dl, as the IMPROVE-IT trial[9] showed. In this case, specific LDL-C targets are also necessary to decide in each patient if the use of ezetimibe is necessary.[9]

Disclosures

There is no conflict of interest.

References

1. Stone NJ, Robinson J, Lichtenstein AH et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014, 63:2889–2934
2. European Association for Cardiovascular Prevention & Rehabilitation, Reiner Z, Catapano AL, De Backer G et al. ESC Committee for Practice Guidelines (CPG) 2008–2010 and 2010–2012 Committees. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J* 2011, 32:1769–1818
3. Elisaf M, Pitsavos C, Liberopoulos E, Tziomalos K, Athyros VG. Guidelines of the Hellenic Society of Atherosclerosis for the diagnosis and treatment of dyslipidemia. *Hellenic J Atherosclerosis* 2014, 5:151–163
4. Panagiotakos DB, Georgousopoulou EN, Fitzgerald AP et al. Validation of the HellenicSCORE (a Calibration of the ESC SCORE Project) Regarding 10-Year Risk of Fatal Cardiovascular Disease in Greece. *Hellenic J Cardiol* 2015, 56:302–308
5. Cai R, Yuan Y, Zhou Y, Xia et al. Lower intensified target LDL-c level of statin therapy results in a higher risk of incident diabetes: a meta-analysis. *PLoS One* 2014, 9:e104922
6. O'Riordan M. Bring Back LDL Targets Back to Manage Cost and Use of PCSK9 Inhibitors, Says CVS Health. *Medscape 29 August* 2015
7. Shrank WH, Barlow JF, Brennan TA. New Therapies in the Treatment of High Cholesterol: an Argument to Return to Goal-Based Lipid Guidelines. *JAMA* 2015 Aug 10 (Epub ahead of print)
8. Brennan T, ShrankW. New expensive treatments for hepatitis C infection. *JAMA* 2014, 312:593–594
9. Cannon CP, Blazing MA, Giugliano RP et al, IMPROVE-IT Investigators. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med* 2015, 372:2387–2397

Submitted 08/09/2015
Accepted 21/09/2015