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2013 American College of Cardiology/American Heart Association guidelines for the management of dyslipidemias

Are they relevant for Greece?

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ABSTRACT: The recently published American College of Cardiology/American Heart Association guidelines for the management of dyslipidemias have already sparked intense debate. Even though these guidelines appear to simplify treatment by recommending specific doses of specific statins instead of pursuing low-density lipoprotein cholesterol targets, several issues might limit their applicability outside US. Indeed, their implementation might lead to undertreatment of high-risk patients (e.g. many patients with type 2 diabetes melitus (T2DM), chronic kidney disease or atherogenic dyslipidemia) or the overtreatment of moderate- to low-risk patients (e.g. many patients without either T2DM or established cardiovascular disease). Therefore, the use of the European Society of Cardiology/European Atherosclerosis Society guidelines appears more appropriate for Europe.

Key words: Dyslipidemia, guidelines, statins, type 2 diabetes mellitus, primary prevention, chronic kidney disease, atherogenic dyslipidemia.

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Κατευθυντήριες οδηγίες των American College of Cardiology/American Heart Association για την αντιμετώπιση των δυσλιπιδαιμιών

Είναι εφαρμόσιμες στην Ελλάδα;

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ΠΕΡΙΛΗΨΗ: Οι πρόσφατα δημοσιευμένες κατευθυντήριες οδηγίες των American College of Cardiology/American Heart Association για την αντιμετώπιση των δυσλιπιδαιμιών αποτελούν ήδη αντικείμενο διχογνωμίας. Αν και οι εν λόγω κατευθυντήριες οδηγίες φαίνεται να απλοποιούν την υπολιπιδαιμική αγωγή συνιστώντας συγκεκριμένες δόσεις συγκεκριμένων στατινών αντί να προτείνουν στόχους για την LDL χοληστερόλη, αρκετά στοιχεία τους φαίνεται ότι περιορίζουν την εφαρμογή τους εκτός των ΗΠΑ. Πράγματι, η εφαρμογή των οδηγιών αυτών θα μπορούσε να οδηγήσει σε υποθεραπεία ασθενών υψηλού κινδύνου (π.χ. αρκετοί ασθενείς με σακχαρώδη διαβήτη, χρόνια νεφρική νόσο ή αθηρογόνο δυσλιπιδαιμία) ή σε δυσανάλογα επιθετική θεραπεία ασθενών μέτριου ή χαμηλού κινδύνου (π.χ. αρκετοί ασθενείς χωρίς σακχαρώδη διαβήτη ή καρδιαγγειακή νόσο). Συνεπώς, οι κατευθυντήριες οδηγίες των European Society of Cardiology/European Atherosclerosis Society φαίνεται να είναι πιο κατάλληλες για την Ευρώπη.

Λέξεις ευρετηρίου: Δυσλιπιδαιμία, κατευθυντήριες οδηγίες, στατίνες, σακχαρώδης διαβήτης, πρωτογενής πρόληψη, χρόνια νεφρική νόσος, αθηρογόνος δυσλιπιδαιμία.

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1. Introduction

Elevated serum low-density lipoprotein cholesterol (LDL-C) levels are a major risk factor for cardiovascular disease (CVD).[1] Reduced levels of high-density lipoprotein cholesterol (HDL-C) are also related to increased CVD morbidity and mortality.[2] The association between elevated triglyceride levels and CVD events is more controversial, but they also appear to play a role in the pathogenesis of atherosclerosis.[3] Accordingly, the management of dyslipidemias is a major component of primary and secondary CVD prevention strategies.[4–7] In this context, several medical organizations have formulated guidelines for the management of dyslipidemias.[4–7] Despite the rigorous methodology applied in the process of drafting of these guidelines, important differences exist between them, stimulating controversy.[4–7] The recently published American College of Cardiology/American Heart Association (ACC/AHA) "Guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults"[7] have already sparked intense debate.[8–10]

In the present editorial, we summarize the key characteristics of the ACC/AHA guidelines and discuss some potential issues that might limit their applicability outside US.

2. 2013 ACC/AHA guidelines for the management of dyslipidemias: Key points

In contrast to all other guidelines for the management of dyslipidemia, the 2013 ACC/AHA guidelines do not recommend specific LDL-C targets.[7] Instead, they propose administering high- or moderate-intensity statin therapy depending on the CVD risk.[7] High-intensity statin therapy includes atorvastatin 40–80 mg/day and rosuvastatin 20–40 mg/day. Moderate-intensity statin therapy includes atorvastatin 10–20 mg/day, rosuvastatin 5–10 mg/day, simvastatin 20–40 mg/day, pravastatin 40–80 mg/day, fluvastatin 40–80 mg/day, and pitavastatin 2–4 mg/day. According to the ACC/AHA guidelines, patients aged ≤75 years with established CVD (coronary heart disease (CHD), stroke or peripheral arterial disease) and subjects with LDL-C levels>190 mg/dL should be treated with high-intensity statin therapy.[7] Patients aged 40–75 years with type 2 diabetes mellitus (T2DM) and LDL-C 70–189 mg/dL but without CVD should be treated with high-intensity statin therapy if their estimated 10-year risk for CVD (including CHD death, nonfatal myocardial infarction, fatal and nonfatal stroke) is ≥7.5% and with moderate-intensity statin therapy if their estimated 10-year CVD risk is <7.5%.[7] Finally, patients aged 40–75 years with LDL-C 70–189 mg/dL but without T2DM or CVD should be treated with high- to moderate-intensity statin therapy if their estimated 10-year CVD risk is ≥7.5%, whereas it is reasonable to administer moderate-intensity statin therapy if their estimated 10-year CVD risk is 5% to <7.5%.[7] In other patient groups (i.e. those older than 75 years with or without CVD or T2DM and those without CVD or T2DM and with 10-year CVD risk <5%), the use of statins should be individualized based on perceived benefits and risks of statin treatment, potential for drug-drug interactions, and patient's preferences.[7] To estimate 10-year CVD risk, a new equation is proposed, the Pooled Cohort Equation, derived from data from 5 large epidemiological studies (n=24,626) conducted in the US (Atherosclerosis Risk in Communities, Cardiovascular Health Study, Coronary Artery Risk Development in Young Adults, and the Framingham and Framingham Offspring studies).[7]

3. 2013 ACC/AHA guidelines for the management of dyslipidemias: Potential issues

The management of patients without CVD or T2DM is perhaps the most controversial issue of the ACC/AHA guidelines. It has been suggested that the newly proposed Pooled Cohort Equation overestimates CVD risk.[8] It has also been projected that the application of the AHA/ACC guidelines will render eligible for statin treatment more than 1 billion subjects worldwide.[10] When applying the Pooled Cohort Equation outside US, it should be emphasized that it was derived by population studies performed exclusively in the US.[7] Its performance in non-US populations is unclear and it might over- or underestimate risk depending on the CVD risk profile of different countries.[8,11] Indeed, the European Society of Cardiology and European Atherosclerosis Society (ESC/EAS) guidelines recommend the use of different CVD risk prediction charts in countries at low or high CVD risk.[4] Given that there are country-specific prediction charts in many European countries (including Greece),[12] their use appears more reasonable for CVD risk estimation in Europe.

Another issue is that the ACC/AHA guidelines differentiate the intensity of statin treatment between patients with T2DM, i.e. high- and moderate-intensity

statin therapy is recommended for those with an estimated 10-year CVD risk ≥7.5% and <7.5%, respectively.[7] However, patients with T2DM have a similar CVD risk compared with patients with established CVD[13,14] and it can therefore be argued that they should managed as aggressively as the latter. Moreover, the greatest risk associated with the use of statins, i.e. development of T2DM,[15] obviously does not apply to patients with established T2DM. Accordingly, the ESC/EAS recommendations for aiming at LDL-C levels <70 mg/dL in all patients with T2DM appear sounder.[4]

The management of dyslipidemias in patients with chronic kidney disease (CKD) is another point that should be mentioned. Chronic kidney disease affects approximately 13% of the adult population in US and is associated with increased CVD risk.[16–18] Indeed, patients with CKD appear to have similar all-cause mortality rates with patients with established CHD.[18] Moreover, post-hoc analyses of studies in patients with or without CVD showed that statins yield similar or larger reductions in the relative risk of CVD events in patients with CKD and larger reductions in the absolute CVD risk compared with patients with normal kidney function.[20–22] Accordingly, the ESC/EAS guidelines recommend aiming at serum LDL-C levels <70 mg/dL in all patients with CKD.[4] The recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines also recommend treatment with statins in all patients aged >50 years with CKD but not treated with chronic dialysis or kidney transplantation.[23] In contrast, the ACC/AHA guidelines do not discuss the management of this population, possibly due to the lack of trials that evaluated statins in a population exclusively of patients with CKD.[7] However, it is uncertain whether it will be ethical to conduct such a trial given the overwhelming benefits of statins in this population in post-hoc analyses of large randomized control studies.[20–22]

The 2013 AHA/ACC guidelines also do not discuss the management of residual cardiovascular risk in patients who are treated with high-intensity statin therapy.[7] In this population, elevated non-high-density lipoprotein cholesterol levels (non-HDL-C) are associated with increased CVD risk.[2] Moreover, in patients with elevated triglyceride levels and low HDL-C levels with T2DM who were treated with simvastatin, the addition of fenofibrate was safe and reduced CVD events by 31% compared with simvastatin monotherapy.[24] The addition of omega-3 fatty acids might also be beneficial in these patients, particularly when CHD, heart failure or CKD are present.[25–27]

4. Conclusions

Even though the 2013 ACC/AHA guidelines for the management of dyslipidemias appear to simplify treatment by recommending specific doses of specific statins instead of pursuing LDL-C targets, several issues might limit their applicability outside US. Indeed, the implementation of these guidelines might lead to undertreatment of high-risk patients (e.g. many patients with T2DM, CKD or atherogenic dyslipidemia) or the overtreatment of moderate- to low-risk patients (e.g. many patients without either T2DM or established CVD). It is also possible that the lack of LDL-C targets will reduce adherence to statin treatment.4 Moreover, many very high-risk patients will not reach LDL-C levels <70 mg/dL, i.e. the concentration where several studies showed that regression of atherosclerosis occurs and the risk of CVD events further decreases.[28,29] Therefore, the use of the ESC/EAS guidelines appears more appropriate for Europe.[30]

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