VOLUME 8 | ISSUE 4 | OCTOBER - DECEMBER 201

Low-density lipoprotein cholesterol targets: Lowest is best

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Abstract

Data from both observational studies and from large randomized controlled trials (RCT) with statins, as well as emerging data from RCTs with other lipid-lowering agents, show that achieving low-density lipoprotein cholesterol (LDL-C) levels considerably lower than the currently recommended is both safe and also results in further reductions in cardiovascular events. In fact, until now, a threshold of LDL-C levels where safety concerns arise and cardiovascular risk reduction disappears has not been identified. Therefore, current LDL-C targets might have to be further reduced, particularly in very high risk patients.

Key words: low-density lipoprotein cholesterol; targets; statins

SUBMISSION: 18/02/2018 | ACCEPTANCE: 24/02/2018

Elevated low-density lipoprotein cholesterol (LDL-C) levels represent a major modifiable risk factor for cardiovascular disease, particularly coronary heart disease [1]. Accordingly, current guidelines state that LDL-C is the primary target in the management of dyslipidemias [2]. Moreover, LDL-C targets depend on cardiovascular risk; the higher the cardiovascular risk, the lower the LDL-C target [2]. This recommendation is based on the finding of randomized controlled trials (RCT) that showed that more aggressive lipid-lowering treatment, particularly with statins, reduces cardiovascular morbidity more than less aggressive treatment [3].

In recent years, accumulating data suggest that lowest is best for LDL-C levels in terms of reductions in cardiovascular events. Indeed, hunter-gatherer societies have very low total cholesterol (TC) levels

Citation

Papagianni M, Papagiannis A, Tziomalos K. Low-density lipoprotein cholesterol targets: Lowest is best. *Hell J Atheroscler* 2017; 8: 95-98

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(mean levels < 100-140 mg/dl) and also exhibit very low cardiovascular morbidity [4]. In a meta-analysis of 61 prospective studies in the general population (*n*= 892.237), subjects with TC levels of 220 mg/dl had 50% higher risk of dying from CHD than subjects with TC levels of 200 mg/dl [1].

Data from interventional studies with statins also show that lowest is best for LDL-C levels. In a meta-analysis of 26 RCT (*n*= 169.138), cardiovascular risk reduction for every reduction in LDL-C levels by 39 mg/dl was the same in patients with baseline LDL-C levels < 78 mg/dl and for those with higher LDL-C levels [3]. In another meta-analysis of 8 RCT (*n*= 64.323), patients who achieved LDL-C levels < 50 mg/dl during treatment with statins had lower rates of cardiovascular events than patients who achieved higher LDL-C levels [5]. Importantly, these levels do not appear to be associated with higher risk for adverse events. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 (PROVE IT-TIMI 22) trial, patients with a recent acute coronary syndrome (ACS) (*n*= 4.162) who achieved LDL-C levels < 40 mg/dl during treatment with atorvastatin 80 mg/day had similar rates of adverse events compared with patients who had higher LDL-C levels [6]. In the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), patients without established CVD or type 2 diabetes mellitus (*n*= 17.802) who had LDL-C levels < 30 mg/dl during treatment with rosuvastatin also had similar rates of adverse events compared with patients who had higher LDL-C levels except for a higher incidence of insomnia (1.5% *vs.* 1.2%) and hematuria (1.9% *vs.* 1.1%) in the former [7].

Emerging data from interventional studies with other LDL-C-lowering agents also support the benefit of very low LDL-C levels. In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), patients with a recent ACS (*n*= 18.144) and mean LDL-C levels 94 mg/dl were randomized to receive simvastatin 40 mg/day in combination with either ezetimibe or placebo [8]. The former achieved mean LDL-C levels 54 mg/dl and had 6.4% lower risk for cardiovascular events than the former, who achieved mean LDL-C levels of 69 mg/dl [8]. Importantly, rates of adverse events were similar in the 2 groups [8]. More recently, in the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial, 27,564 patients with established CVD were randomized to receive evolocumab, an inhibitor of proprotein convertase subtilisin–kexin type 9, or placebo [9]. Mean LDL-C levels at baseline were 92 mg/dl and all patients were receiving a statin (70% were on atorvastatin 40-80 mg/day or rosuvastatin 20-40 mg/day)[9]. Treatment with evolocumab reduced LDL-C levels to a median of 30 mg/dl and also reduced cardiovascular events by 15% [9]. Moreover, patients who had LDL-C levels at baseline < 80 mg/dl experienced similar reductions in cardiovascular morbidity with patients who had higher baseline LDL-C levels [9]. Furthermore, patients who achieved LDL-C levels < 20 mg/dl during treatment with evolocumab had lower rates of cardiovascular events than patients who achieved higher LDL-C levels [10]. Again, rates of adverse events did not differ between patients who reached LDL-C levels < 20 mg/dl and those with higher levels [10]. In the ODYSSEY LONG-TERM trial, 2.345 high cardiovascular risk patients were randomized to receive alirocumab or placebo for 52 weeks [11]. The former achieved mean LDL-C levels of 58 mg/dl and had 48% lower risk for cardiovascular events than the latter in a preliminary analysis [11]. In addition, rates of adverse events did not differ between patients who achieved LDL-C levels < 25 mg/dl and those who achieved higher LDL-C levels [11]. Very recently, in the Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification (REVEAL) trial, 30,449 patients with established CVD and mean baseline LDL-C levels of 61 mg/dl were randomized to receive anacetrapib, a cholesteryl-ester transfer protein inhibitor, or placebo [12]. Treatment with anacetrapib further reduced LDL-C by 17% and also reduced major coronary events by 9% [12]. Rates of adverse events were similar in the anacetrapib and placebo group except for a marginal increase in blood pressure and decrease in glomerular filtration rate in the former [12].

In conclusion, data from both observational studies and from large RCTs with statins, as well as emerging data from RCTs with other lipid-lowering agents, show that achieving LDL-C levels considerably lower than the currently recommended is both safe and also results in further reductions in cardiovascular events. In fact, until now, a threshold of LDL-C levels where safety concerns arise and cardiovascular risk reduction disappears has not been identified. Therefore, current LDL-C targets might have to be further reduced, particularly in very high risk patients.

Conflict of Interest

All authors declare no conflict of interest.

Περίληψη

Στόχοι της LDL χοληστερόλης: τα ελάχιστα επίπεδα είναι τα καλύτερα

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Δεδομένα τόσο από μελέτες παρατήρησης όσο και από μεγάλες τυχαιοποιημένες μελέτες με στατίνες, καθώς και αναδυόμενα στοιχεία από τυχαιοποιημένες μελέτες με άλλα υπολιπιδαιμικά φάρμακα, δείχνουν ότι η επίτευξη επιπέδων LDL χοληστερόλης σημαντικά χαμηλότερων από τις τρέχουσες συστάσεις είναι ασφαλής και συνεπάγεται περαιτέρω ελάττωση των καρδιαγγειακών συμβαμάτων. Πράγματι, μέχρι σήμερα δεν έχουν βρεθούν επίπεδα LDL χοληστερόλης κάτω από τα οποία αυξάνονται οι ανεπιθύμητες ενέργειες ή παύει η ελάττωση του καρδιαγγειακού κινδύνου. Συνεπώς, οι τρέχοντες στόχοι της LDL χοληστερόλης θα πρέπει ενδεχομένως να μειωθούν περαιτέρω, ιδιαίτερα στους πολύ ψηλού κινδύνου ασθενείς.

Λέξεις ευρετηρίου: LDL χοληστερόλη, στόχοι, στατίνες

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