PCSK9 Inhibitors: Research and new perspectives in clinical practice

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Abstract

Statins are the cornerstone of hypolipidemic treatment. However, there are cases with no satisfactory results, as when statin intolerance occurs or LDL target is very low. PCSK9 inhibitors are a new drug category, promising to cover this treatment gap. They are monoclonal antibodies which get attached to PCSK9 protein and prevent its binding to LDL receptors on the hepatocyte surface. Consequently, LDL receptors are free to withdraw LDL cholesterol from blood. Evolocumab and alirocumab are the two drugs approved by FDA and EMA for patients with familial hypercholesterolemia or patients with very high cardiovascular risk on statin treatment who haven't reached LDL target. PCSK9 inhibitors can lower LDL cholesterol up to levels of 20 mg/dL or 10 mg/dL. This is not an unusual or extreme effect, as normal LDL cholesterol values less than 50 mg/dL have been found in some native human population groups and wild mammals. On-going trials achieving LDL cholesterol levels less than 20 mg/dL have already shown very important cardiovascular benefit in post-hoc analysis. Safety of new drugs compared to placebo seems acceptable but final conclusions will be drawn when studies are completed.

Key words: evolocumab; alirocumab; PCSK9; hyperlipidemia

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1. Introduction

Optimal cholesterol levels are very important in preventing atherosclerosis and cardiovascular events, which are the first cause of death worldwide. The current therapeutic arsenal is based on statins with effective LDL cholesterol decrease, but often statins are not sufficient or well tolerated by patients.

Monoclonal antibodies against proprotein convertase subtilisin/kexin type 9 (PCSK9) are a promising new approach in hypolipidemic treatment, especially in patients with familial hypercholesterolemia and in cases where further cholesterol decrease is required.

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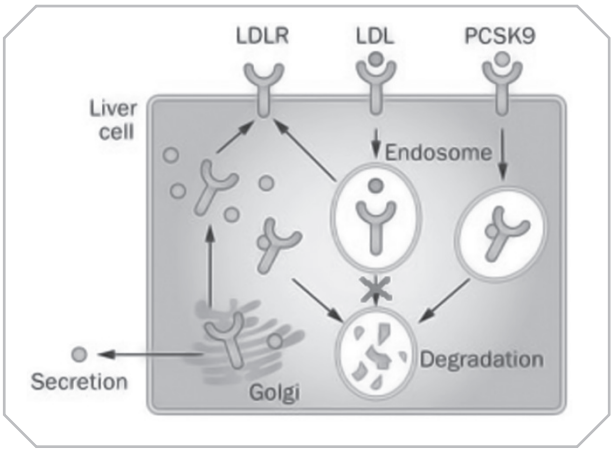

Figure 1. Mechanism of action of PCSK9 protein.[31]

Currently, statins remain the lipid lowering treatment of choice,as PCSK9 inhibitors have not been proven yet to reduce cardiovascular risk and the cost is significantly higher.[1]

Specifically, treatment costs are estimated at about 5,000-12,000 dollars a year per patient. Complicated production procedures of monoclonal antibodies augment the cost, while generic production that could reduce the cost in the future is not yet possible. Therefore, there is need for careful selection of patients suitable to receive this treatment.[2] On the other hand, reducing cardiovascular events in both primary and secondary prevention, if documented in clinical trials, will also reduce cost of treatment for cardiovascular events. Consequently, PCSK9 inhibitors could become cost effective in the near future.[3]

2. Function and utility of PCSK9 inhibitors - data from the ARIC study

PCSK9 inhibitors are human monoclonal antibodies, binding with high affinity to PCSK9, a 692 amino-acid protein. This protein gets attached to the LDL receptor (LDL-R).[2]

Its precursor is produced in hepatocytes and after separation in the endoplasmic reticulum, active PCSK9 is excreted to the plasma. Circulating PCSK9 binds to LDL-R, in a location different from that binding LDL cholesterol. When LDL-R-LDL cholesterol complex enters the cell, it merges with an endosome. LDL-c is then degradated, while the fate of LDL-R is highly determined by the presence of PCSK9 protein. In the presence of PCSK9 binded to LDL-R, both LDL cholesterol and LDL-R-PCSK9 complex are driven into the lysosomes for degradation LDL-R is thus quickly destroyed after having cleared only one LDL particle from the circulation. In contrast, in the absence of PCSK9, LDL particle gets also metabolized, but LDL-R escapes lysosomal degradation and is returned on hepatic surface, available to bind another LDL particle. One LDL-R, free from PCSK9 can be used multiple times to clear LDL cholesterol via recycling (**Figure 1**). This process reduces the number of LDL receptors and consequently LDL cholesterol clearance. As a result, plasma LDL cholesterol levels increase. Therefore, PCSK9 plays a key role in the regulation of LDL-c plasma levels, by affecting the LDL-R catabolism in the hepatocyte.[4,5]

Anti-PCSK9 monoclonal antibodies that have been released in the United States and Europe are evolocumab (Repatha) of Amgen company and alirocumab (Praluent) of Sanofi-Regeneron. Their administration is easy with subcutaneous injection of a prefilled pen every 2 or 4 weeks. FDA (Food and Drug Administration) in USA and EMA (European Medicines Agency) in Europe have approved clinical use of these two drugs in cases of familial hypercholesterolemia and very high cardiovascular risk patients who haven't reached LDL target with dietary measures and other hypolipidemic agents at the maximum tolerated doses. Many patients do not achieve LDL cholesterol target, despite receiving high intensity statin treatment. Data published three years ago shows that among patients receiving a statin, less than 50% have LDL levels of around 100 mg/dL and even fewer (10-15%) less than 70 mg/dL. Only 25% of very high risk patients achieve cholesterol level below 70 mg/dL, which indicates a failure in attaining treatment goals.[6]

Adding anti-PCSK9 monoclonal antibody in current optimal treatment results in an extra reduction of LDL cholesterol by 60%, leading even at levels below 50 mg/dL, which is far below the desirable target of 100 mg/dL or 70mg/dL according to patient's cardiovascular risk. With such hypolipidemic results, it is likely that cardiovascular events will be further reduced.

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It is indicative that people with loss of function mutations of PCSK9 gene present with lifelong extremely low LDL-c levels and lower incidence of cardiovascular events.[2] In contrast, gain of function mutations of PCSK9 account for 1-3% of cases with familial hypercholesterolemia, and are accompanied by early onset coronary heart disease.[2]

In ARIC study (The Atherosclerosis Risk in Communities Study), a multicenter prospective cohort epidemiological study which began in 1987 and is still ongoing, the etiology and natural history of atherosclerosis are being investigated. The study was also designed to analyze the variation of cardiovascular risk factors and disease by race, gender, location and date. According to findings, three genetic mutations related to PCSK9 (the Y142X and C979X in black and the C679X in white population) are related to reduced levels of LDL cholesterol and lower risk for coronary artery disease. Specifically, LDL cholesterol was decreased by 15% in white population and by 28% in black population, while the risk of coronary heart disease was reduced by 47% and 88% respectively.[7, 8]

The most important question concerning PCSK9 treatment is how low should we go. There is concrete evidence based on research that "the lower the better" applies in patients at high risk. Studies with statins have proved that lowering LDL cholesterol as low as possible results in significant risk reduction, compared to less aggressive targets.[9]

Looking at the nature, indigenous population groups in New Guinea and rural areas of China, newborns as well as some wild mammals, have LDL cholesterol levels of around 50 mg/dL. This phenomenon may reflect nutrition concepts that differ from the western world. Based on some theories, such low LDL cholesterol may represent humans' natural lipidemic profile rather than higher levels seen today.[10]

Evidence has shown that a decrease in LDL cholesterol by 40 mg/dL leads to 22% fewer cardiovascular events. In two of evolocumab clinical studies, patients with an average LDL cholesterol of 120 mg/dL presented with an absolute LDL reduction of 70 mg/dL. Assuming there is a linear relationship in LDL cholesterol and cardiovascular risk decrease, evolocumab could theoretically reduce cardiovascular risk by 38.5%.[3] Furthermore, additional LDL cholesterol reduction with a non statin treatment can be beneficial regarding cardiovascular risk reduction. Specifically, the IMPROVE-IT study showed additional benefit in reducing cardiovascular events when LDL was further reduced at levels below 70 mg/dL by adding ezetimibe to simvastatin, in patients already achieving strict hypolipidemic targets with simvastatin, after an acute coronary syndrome.

In JUPITER study, patients receiving rosuvastatin with LDL cholesterol below 130 mg/dL were randomized into three groups according to LDL cholesterol levels, one with LDL-c below 50 mg/dL, one with LDL-c higher than 50 mg/dL and one control (placebo) group. In patients with very low cholesterol levels (<50 mg/dL), further decrease in cardiovascular risk was observed, while safety of such low LDL cholesterol levels was established. In details, no difference in the incidence of muscle pain, liver associated adverse events, neurological events, cataract and cancer was found among the three groups.[11] The effect of very low cholesterol LDL cholesterol levels (<50 mg/dL) on the atherosclerotic plaque is evaluated via intravascular coronary ultrasound in a large clinical trial, the results of which are awaited in the future.[12]

Until now it has been proven that even a small LDL cholesterol decrease can suspend the development of the atherosclerotic plaque (measured with coronary vascular ultrasound). In addition, atherosclerosis can be reversed when LDL cholesterol levels remain lower than 65 mg/dL while 18-24 months of intensive hypolipidemic treatment achieving LDL cholesterol <65 mg/dL the volume of the coronary atherosclerotic plaque has decreased .[13]

3. Efficacy of anti-PCSK9 antibodies in various hypercholesterolemic populations

Approved anti-PCSK9 monoclonal antibodies, evolocumab and alirocumab, have specific indications for patients clearly failing to attain LDL cholesterol targets while already on maximum tolerated hypolipidemic treatment. Patients having these criteria are: a) patients with heterozygous familial hypercholesterolemia, b) patients with homozygous familial hypercholesterolemia having a minimum LDL-R function

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preserved, c) patients with very high cardiovascular risk (especially with established cardiovascular disease) who fail to reach LDL cholesterol target with optimal current treatment. In addition, statin intolerant patients, mainly suffering from muscle associated adverse events, could also be included in populations suitable to receive anti-PCSK9 antibodies.

PCSK9 inhibitors hve been studied studied in different groups of patients including those with pure hypercholesterolemia, mixed dyslipidemia, heterozygous and homozygous familial hypercholesterolemia and patients intolerant to statins. These groups included predominantly patients who were at very high risk for cardiovascular events but also patients at high and moderate risk.

3.1 Patients with pure hypercholesterolemia or mixed dyslipidemia

In LAPLACE 2 study clinical trial, 1889 patients with primary hypercholesterolemia or mixed dyslipidemia receiving high or moderate intensity statin treatment were randomized to receive either evolocumab (every two or four weeks) or placebo (every two or four weeks). After 12 weeks of treatment, evolocumab reduced LDL cholesterol by 66%-75% (every two weeks) and by 63%-75% (every month) compared to placebo. In addition, mean LDL cholesterol level in the evolocumab group was well under 50 mg/dL. [14]

DESCARTES-2 study included patients with hypercholesterolemia (LDL cholesterol >75 mg/dL and triglycerides <400 mg/dL) and randomized them to receive evolocumab or placebo on top of lipid lowering treatment with a statin +/- ezetimibe. After 52 weeks of treatment, evolocumab reduced LDL cholesterol by 50%. A high percent of patients receiving evolocumab reached the most strict target of LDL cholesterol of 70 mg/dL. [15]

Alirocumab was administered to patients with hypercholesterolemia, who were at very high risk for cardiovascular events along with their current lipid-lowering treatment. Studies with alirocumab are:

The ODYSSEY LONG TERM trial, including 2431 patients with LDL cholesterol >70 mg/dL despite maximum tolerated statin dose +/- other lipid lowering treatment, reduced LDL cholesterol by 62% by week 24. Furthermore, in 76% of the patients receiving alirocumab LDL cholesterol reduced at least in half from baseline.[2]

In ODYSSEY COMBO I trial, alirocumab was administered in very high cardiovascular risk patients, already receiving adequate hypolipidemic treatment. Alirocumab reduced LDL cholesterol by 48%, while 75% of the patients attained their LDL cholesterol target of 70 mg/dL.[16]

ODYSSEY COMBO II trial compared alirocumab with ezetimibe in high cardiovascular risk patients receiving statins. In the alirocumab group LDL cholesterol decreased by 50% and 77% of the patients reached LDL cholesterol target. On the other hand, in the ezetimibe receiving group, LDL cholesterol reduced by 20% and only 45% of the patients reached their target. [17]

In ODYSSEY CHOICE I study, alirocumab reduced LDL cholesterol by 58%.[18]

3.2 Patients intolerant to statins

Statin intolerant patients were enrolled in GAUSS-2 study and randomized in 4 groups, 2 receiving evolocumab 140 mg/dL or 420 mg/4 weeks and placebo (p.os.) every day and 2 receiving placebo s.c. every 2 or 4 weeks and 10 mg ezetimibe (p.os.) daily. After 12 weeks, the 2 groups receiving evolocumab had 53-56% lower LDL cholesterol (compared with baseline), which stands for an additional 37-39% reduction compared with ezetimibe monotherapy.[19]

In the Odyssey Choice I study alirocumab was administered to patients intolerant to statins who are at very high cardiovascular risk. LDL was lowered by 52%.[18]

3.3 Patients with heterozygous familial hypercholesterolemia

The RUTHERFORD-2 study included patients meeting the criteria of heterozygous familial hypercholesterolemia who had not reached their LDL cholesterol target of 100 mg/dL, while on treatment with statin +/- ezetimibe. After addition of evolocumab, LDL cholesterol decrease by up to 61%.[20]

3.4 Patients with homozygous familial hypercholesterolemia

In TESLA-2 study, patients with homozygous famil-

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ial hypercholesterolemia were treated with evolocumab 420 mg every 4 weeks. Patients receiving the drug achieved a LDL reduction of 31%. Patients with partial deficiency of LDL receptors had a higher decrease, whereas no decrease was observed in patients with complete loss of LDL-R function.[21]

OSLER-1 and OSLER-2 studies included patients who participated at the parental phase II and III studies, including LAPLACE[14], MENDEL[22, 23], GAUSS[19] and RUTHERFORD[20] study. These studies showed maintenance of hypolipidemic effect of evolocumab when it was continued, while the discontinuation of the drug returned LDL cholesterol to initial levels.

4. Safety of antibodies against PCSK9 up to now

Results from studies with alirocumab and evolocumab have not revealed significant difference in the incidence of adverse events when compared with placebo or current hypolipidemic treatment. Safety analysis on alirocumab was based on data from the ODYSSEY program and the ODYSSEY Long Term Trial. In total 5234 patients were included, of which 3340 were treated with alirocumab, while 1894 participated in the placebo group. Approximately 24% of patients reached very low levels of LDL cholesterol (<25 mg/dL), while a small percent of 9% had such LDL cholesterol levels as 15 mg/dL or less. The safety of such low LDL cholesterol levels has always been a subject of controversy but clinical trials seem to have the answer. There was no increase in adverse events in patients receiving the drug compared to placebo. Specifically, there was no significant increase in muscle pain, neurological side effects or new-onset diabetes.[24]

However, in one study (ODYSSEY LONG TERM) local reaction at the site of injection, muscle pain, neurocognitive and ophthalmological adverse events appeared at a higher rate in patients receiving alirocumab.[25] On the contrary, statistical analysis showed that cardiovascular events (death from coronary disease, acute myocardial infarction, ischemic stroke or unstable angina) were fewer in patients treated with alirocumab (1,7% *vs* 3,3%, P=0,02).[25]

Safety analysis on evolocumab was based on studies of phase 2 and 3 (Proficio program), involving over 10000 patients. The incidence of adverse effects were similar in both the treatment and placebo arms, while antibodies against the drug were not detected.[26] In two other double-blind trials (OSLER-1 and OSLER-2), 4465 patients with hypercholesterolemia already under statin treatment received an injection of 140mg of evolocumab twice monthly. Effects of evolocumab were not limited on LDL cholesterol alone, as the whole lipid profile was beneficially altered with reduction in non-HDL cholesterol (-52%), apoprotein B (-47.3%), total cholesterol (-36%), triglycerides (-12.6%) and lipoprotein (a) (-25%), while HDL cholesterol was increased by 7% and apoprotein A1 by 4.2%. Regarding adverse events, evolocumab did not increase the incidence of all kind of adverse events compared with placebo.[27]

There are still in progress multiple phase 3 studies on evolocumab and alirocumab such as FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk), THOMAS-1 and THOMAS-2 trials. Their aim is to prove both additional reduction in cardiovascular events and long term safety of anti PCSK9 antibodies and are expected to be completed in the couple of years to come.[28]

5. Cardiovascular benefit: PCSK9 antibodies seem to decrease cardiovascular events

ODYSSEY LONG TERM study compared alirocumab (150 mg every two weeks) to placebo in 2338 high cardiovascular risk patients already receiving statins at the maximum tolerated dose with or without other hypolipidemic therapy.[2] The primary endpoint was the reduction of LDL cholesterol. The incidence of cardiovascular events was studied by means of post hoc analysis comparing the groups receiving alirocumab or placebo in addition to current hypolipidemic treatment. The analysis took as combined endpoint any of the following: death from coronary heart disease, nonfatal myocardial infarction, fatal or non-fatal ischemic stroke and hospitalization for unstable angina. The same combined endpoint is also used in ODYSSEY OUTCOMES trial, analyzing the effect of alirocumab within a year after an acute coronary syndrome. The trial is expected to be completed in 2018.[29] The ODYSSEY LONG TERM study includ-

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ed 2338 patients of which 1550 received alirocumab and 788 placebo.[2] Among the participants, 69% had a history of coronary heart disease, 17% had heterozygous familial hypercholesterolemia, all patients (except two) were receiving statin and 28% were receiving another lipid-lowering treatment. Mean LDL cholesterol level at the beginning of the study was 122 mg/dL. The average follow-up period was 70 weeks. The study revealed a reduction of LDL cholesterol by 58% with alirocumab compared with an increase by 0.8% in the placebo group. Major cardiovascular events were observed in 4.6% of the patients in the alirocumab group vs 5.1% in the placebo group. By examining the combined endpoint, the incidence of cardiovascular events was 1.7% and 3.3% respectively and hazard ratio was 0.52. If these results repeat in ongoing studies, it will mean that for the first time after statin treatment was introduced, a single drug will dramatically decrease cardiovascular risk by half. The study limitations are its relatively short duration and the limited overall number of cardiovascular events observed.

The studies OSLER 1 and 2 included patients from the parental phase II and III studies including LAPLACE[14], MENDEL[22, 23], GAUSS[19] and RUTHERFORD studies.[4, 20] Patients of the phase II studies were enrolled in OSLER-1 and patients of the phase III studies enrolled in OSLER-2.[4] The addition of evolocumab to the current lipid-lowering therapy was assessed against placebo. The primary endpoint was apart from LDL cholesterol reduction, the incidence of adverse events including increased creatine phosphokinase or liver enzymes and the development of neutralizing antibodies against evolocumab. No difference in the incidence of adverse events was observed between groups, except for myalgia which was more frequent in patients receiving evolocumab. Among other frequently adverse events reported were: rhinopharyngitis, upper respiratory infections, flu, headache, low back pain, urinary tract infection, diarrhea, vomiting but with no higher incidence in the evolocumab group. Major side effects such as pulmonary embolism, need for hip replacement surgery and death occurred in individual patients but they were attributed to other cause. Low-level antibodies against PCSK9 inhibitors were infrequently found and were without clinical significance. A predefined analysis method was used to assess the difference in the incidence of the following cardiovascular events: Cardiovascular and non-cardiovascular death, nonfatal myocardial infarction, hospitalization for unstable angina, reperfusion therapy after myocardial infarction, stroke and transient ischemic attack and hospitalization for heart failure. During a one-year period, it was found that the incidence of cardiovascular events was 1.7% in the treated group and 3.3% in OSLER 1 trial in the placebo group. The limitations of this study were the relatively short duration and the small overall number of cardiovascular events observed.

6. Prospective, randomized, placebo controlled survival trial program for both evolocumab and alirocumab

The FOURIER study is expected to be completed by 2018 and is a prospective, double-blind, randomized, placebo-controlled, multicenter study, with a 5-year duration including 27,564 patients male and female, aged 40-85 years with a history of cardiovascular disease, at high risk for new cardiovascular event, having LDL-c>70 mg/dL and triglycerides<400 mg/dL.[30] The study hypothesis is that further LDL cholesterol reduction with evolocumab added on the current lipid-lowering therapy reduces the risk of cardiovascular events in patients with established cardiovascular disease. Primary endpoints include: cardiovascular death, myocardial infarction, stroke and time until their occurence. Secondary endpoints include: death from any cause, myocardial revascularization and hospitalization for heart failure.

The ODYSSEY OUTCOMES study is expected to be completed by 2018 and is a prospective, randomized, double-blind, placebo-controlled multicenter study, with a 5-year duration including 18,600 patients. Its aim is to the effect of alirocumab on cardiovascular events (combined endpoint: coronary death, nonfatal myocardial infarction, fatal and non-fatal ischemic stroke, hospitalization for unstable angina) in patients presenting with acute coronary syndrome 4-52 weeks before admission to the study and are currently receiv-

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ing high intensity statin treatment +/- ezetimibe and dietary treatment for dyslipidemia.

7. Conclusions

PCSK9 inhibitors are a revolutionary and promising lipid-lowering therapy, which has been approved for specific groups of patients. Many clinical trials are currently in progress evaluating the effect on cardiovascular events. Unanswered issues concerning the safety of long term treatment still remain and are investigated by ongoing large clinical trials. Hopefully, in the near future we will witness the broad clinical use of a modern, highly effective and safe drug in our endless effort to further reduce cardiovascular events and mortality.

Conflict of interest: All authors declare no conflict of interest.

Περίληψη

Αναστολείς PCSK9 Έρευνα και νέες προοπτικές στην κλινική πράξη

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Οι στατίνες αποτελούν τον ακρογωνιαίο λίθο στον οποίο στηρίζεται η φαρμακευτική αντιμετώπιση της υπερχοληστερολαιμίας. Υπάρχουν όμως περιπτώσεις στις οποίες δεν έχουμε το επιθυμητό αποτέλεσμα, όπως όταν υπάρχει δυσανεξία στις στατίνες ή όταν απαιτούνται πολύ μεγάλες μειώσεις της LDL-c. Μία νέα κατηγορία φαρμάκων, οι αναστολείς της πρωτεΐνης PCSK-9 υπόσχονται να καλύψουν αυτό το κενό. Πρόκειται για μονοκλωνικά αντισώματα, τα οποία δεσμεύουν την πρωτεΐνη PCSK9 και εμποδίζουν τη σύνδεσή της με τους υποδοχείς LDL στην επιφάνεια του ηπατοκυττάρου. Επομένως, οι υποδοχείς LDL μπορούν να αποσύρουν την LDL-c από την κυκλοφορία. Οι evolocumab και alirocumab είναι οι δύο ουσίες που έχουν πάρει ένδειξη από τον FDA και τον EMA για ασθενείς με οικογενή υπερχοληστερολαιμία και για ασθενείς πολύ υψηλού καρδιαγγειακού κινδύνου οι οποίοι δεν επιτυγχάνουν τον στόχο της LDL υπό αγωγή με στατίνες. Οι αναστολείς PCSK9 μειώνουν την LDL-c σε χαμηλά επίπεδα της τάξης των 20 mg/dl ή 10 mg/dl. Το αποτέλεσμα αυτό δεν είναι ακραίο ή αφύσικο, καθώς μελέτες σε ιθαγενείς πληθυσμούς ανθρώπων και σε άγρια θηλαστικά δείχνουν ότι τα φυσιολογικά επίπεδα της LDL-c αυτών δεν ξεπερνούν τα 50 mg/dl. Οι έρευνες που βρίσκονται σε εξέλιξη αγγίζοντας επίπεδα LDL-c μικρότερα του 20 mg/dl δείχνουν ήδη μεγάλη μείωση του καρδιαγγειακού κινδύνου σε post hoc αναλύσεις των πρόδρομων αποτελεσμάτων. Η ασφάλεια των νέων φαρμάκων συγκριτικά με αγωγή placebo εμφανίζεται ικανοποιητική, αλλά τα τελικά συμπεράσματα θα εξαχθούν μετά την ολοκλήρωση των μελετών.

Λέξεις ευρετηρίου: evolocumab, alirocumab, PCSK9, υπερλιπιδαιμία χοληστερόλης

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