Meeting Impression

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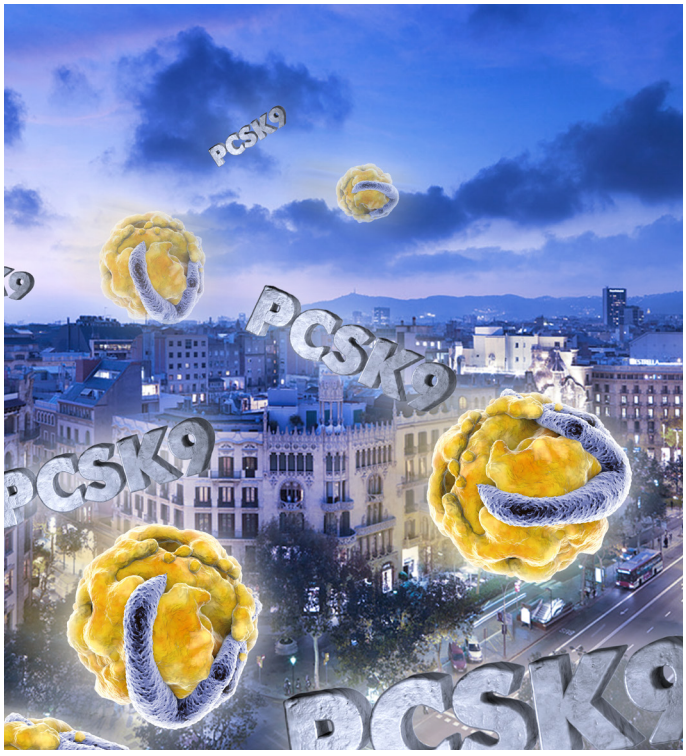
PCSK9 inhibition & Cardiovascular Outcomes: Review of lipid targets and treatment strategies

The role of PCSK9 inhibitors as a novel strategy to reduce LDL-c was addressed in this educational program chaired by Wolfgang Koenig and Michel Farnier at the ESC Congress 2017 in Barcelona, Spain. John Chapman, Kees Hovingh, and Peter Sever discussed the need for additional LDL-c lowering therapies in patients with familial hypercholesterolemia (FH) and the mechanisms and potential applications of therapies, including PCSK9-based therapies, to lower LDL-c in combination with statins or without in statin-intolerant patients. Moreover, evidence from recent trials of novel agents, the need for outcomes data from clinical trials, and the implications of new therapies for future management were presented.

TOPICS



Understanding new PCSK9 outcome data: From the LDL-c hypothesis to LDL-c causality

Prof. John Chapman, PhD – *Paris, France*

Two monoclonal antibodies directed against PCSK9 have been evaluated in CV outcome trials; evolocumab in the FOURIER trial[1] and alirocumab in the ODYSSEY OUTCOMES trial.[2] Different patient populations were studied in these trials; the FOURIER trial primarily enrolled patients with a history of myocardial infarction (MI), with peripheral arterial disease (PAD) and a history of stroke, whereas the ODYSSEY OUTCOMES trial focuses on patients with a recent MI (< 1 year). The FOURIER trial showed a decrease of 15% in the composite endpoint (CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization) and CV benefit across all patients subgroups.[3] One of the key features of this trial was the addition of evolocumab on top of intensive statin therapy compared to placebo, standard care and statin therapy. Moreover, this trial was the first that attained an on-treatment LDL-c level less than the ESC target of 70 mg/dL in secondary prevention patients; the target level attained had a median of 30 mg/dL (0.75 mmol/L).

Foam cells play a key role in the development of plaques and plaque vulnerability by driving inflammation through their secretory profile.

The FOURIER trial raised the question of the relationship between highly efficacious lowering of LDL-c and event reduction. The missing link here is the pathophysiology of atherosclerotic CVD (ASCVD), in other words the disease process. Thus, more importantly, what is the impact of LDL-c lowering on this missing link? By focusing on the pathophysiology of atherosclerosis, we can perhaps better understand the impact of the very low levels of LDL-c obtained in the FOURIER trial.

The formation of atherosclerotic plaques in the arterial tree, primarily in the coronary tree, takes place at sites of predilection. Endothelial dysfunction is involved and is a consequence of a number of risk factors. One of them is LDL-c, a major driver of plaque formation. Sites of endothelial dysfunction show enhanced permeability and as a result, LDL-c penetrates the intima more efficiently. This higher influx of LDL-c results in accumulation of cholesterol derived from LDL. LDL undergoes modification, which may involve oxidation. In addition, monocytes adhere and penetrate at sites of plaque predilection, and subsequently transform into macrophages. The uptake of modified LDL in those macrophages of the M1 (proinflammatory) phenotype results in formation of macrophage foam cells, which give rise to the earliest lesions of ASCVD, also called fatty streaks.

Then, intraplaque formation starts as a result of growth factors and proinflammatory cytokines secreted by monocytes/macrophages. These cells also attract regulatory T cells and T helper cells. These T cell subtypes, growth factors and cytokines cause migration of smooth muscle cells from the media into the intima, giving rise to the production of the extracellular matrix (ECM). Interaction between these cells amplifies intraplaque formation.

Foam cells play a key role in the development of plaques and plaque vulnerability by driving inflammation through their secretory profile. More specifically, they drive plaque progression by production of proinflammatory cytokines, an excess of matrix degradation due to the production of matrix metalloproteinases, an excess of oxidative stress due to the production of reactive oxidative species, production of tissue factor (TF) and finally apoptosis and necrosis. The latter two result in formation of the necrotic core in the plaque.

Cholesterol crystals are a feature of mature plaques and they can induce plaque rupture through several mechanisms. Analysis of ruptured plaques showed that these have a marked accumulation of cholesterol, both free cholesterol and cholesterol esters,[4] almost exclusively located in macrophage foam cells.[5] Focusing on the site of a ruptured plaque shows that the content of the plaque may have come into contact with circulating elements in plasma and blood cells, a major coagulation reaction may be triggered because TF is present, resulting in thrombus formation, either partially or completely occlusive.[6]

The GLAGOV trial was the first intervention trial with a PCSK9 inhibitor that focused on the potential impact on plaque progression or regression.

Intravascular ultrasound (IVUS) in prevention trials showed that plaque progression can be stopped to a large degree by statin treatment that lowered LDL-c to the critical goal of 70 mg/dL (1.7 mmol/L) In some patients, a small degree of plaque regression is observed, as shown by Nicholls.[7] A Japanese study using optical coherence tomography showed plaque volume and lipid content decrease upon lowering of LDL-c by statins, and fibrous volume (the thickness of the fibrous cap) increased. Together, these factors favor plaque stability.[8]

The GLAGOV trial was the first trial with a PCSK9 inhibitor that focused on the potential impact on plaque progression or regression.[9] Evolocumab on a background of optimized statin treatment was compared to placebo on top of statin treatment. IVUS was performed at baseline and 78 weeks.[10] Treatment with evolocumab reduced LDL-c to 36.6 mg/dL (60% decrease) and gave a change in total atheroma volume of 6 mm^3 compared to 0.9 mm^3 in the control group, indicating a significant degree of regression with evolocumab. A significant reduction of 80% in atheroma volume was observed in individuals on evolocumab who had a baseline LDL-c <70 mg/dL.

Several mechanisms in response to highly efficacious LDL-c lowering may contribute to plaque regression and plaque remodeling and ultimately to plaque stabilization and reduction in CV events. Arterial accumulation of LDL-c and apoB-lipoproteins is reduced. Animal studies suggest an efflux of cholesterol and toxic oxidized lipids from the plaque, perhaps mediated by HDL. Marked reduction of intracellular and extracellular lipid content in the plaque has been shown in response to LDL-c lowering, as well as a reduction in plaque inflammation with an increase in ECM, thereby favoring plaque stabilization. Also, animal models have shown an influx of phagocytes, removal of necrotic debris and efferocytosis of macrophages.

Several kinds of evidence support LDL-c as a causal factor in ASCVD, including data from animal models, epidemiology, PCSK9 genetics, trials with statins, cholesterol absorption inhibitors or the first PCSK9 inhibitor. Lowering of LDL-c induces plaque regression, and this results in remodeling of plaque composition and impacts plaque stabilization, thereby reducing CV events. Prof. Chapman concluded by saying that LDL-c is clearly a privileged target and lowering does not only lead to regression and plaque stabilization, but above all reduces CV outcomes.

PCSK9 inhibition across a wide spectrum of patients: One size fits all?

Prof. Kees Hovingh, MD, PhD, MBA – *Amsterdam, the Netherlands*

Prof. Hovingh started by emphasizing that PCSK9 is a new step on the roadmap towards complete acceptance of the LDL-c hypothesis. Anitschkow first formulated the

hypothesis in 1913 and several important findings since then have bolstered the hypothesis that LDL-c plays a causal role in CV events. One of the main steps in the last two decades is the finding by Abifadel who identified PCSK9 as a culprit gene in LDL-c metabolism. Hovingh believes that this century is going to be a new LDL century, as we are facing huge changes in the coming years.
One of the reasons why patients do not reach their LDL-c target level is the lack of potency of LDL-c lowering therapy. Also, LDL-c target levels tend to decrease with subsequent guidelines[11] and patients do not always tolerate the lipid-lowering therapies they are prescribed.[12]

Once the PCSK9 inhibitor evolocumab was injected, the level of PCSK9 decreased directly and basically dropped to zero in a phase Ib trial of 57 hyperlipidemic adults on stable statin therapy.[13] As a result, LDL-c level decreased dramatically as well for 2 weeks, after which levels rose again. Consequently, in the clinical setting PCSK9 inhibitors are injected every 2 weeks. Robinson *et al.* reported a similar 60% decrease in LDL-c levels in patients with hypercholesterolemia randomized to evolocumab while on moderate to high statin therapy.[14] Treatment with alirocumab, another monoclonal antibody against PCSK9, showed a very similar decrease in LDL-c levels (~60% decrease) in patients at high risk for CV events.[15]

Both evolocumab and alirocumab treatment result in stable LDL-c lowering over time

Some patients start with very high levels, making it difficult to meet the LDL-c target, such as patients with FH, a genetic disorder that is characterized by extremely high LDL-c levels and a high CV risk. Data by Pijlman *et al.* in 2009[16] and also more recent studies demonstrated that the majority of FH patients did not reach the LDL-c target level. When 2.5 mmol/L LDL-c was considered as the target level, only 20% of patients reached that goal, as shown in an S-shaped curve of LDL-c target level against the percentage attainment of target. Treatment with evolocumab in a population of heterozygous FH in the RUTHERFORD trial showed a 60% decrease in LDL-c levels after 12 weeks.[17] Prolonged LDL-c lowering was also observed with treatment of alirocumab after 78 weeks of follow-up.[18] Both evolocumab and alirocumab treatment result in stable LDL-c lowering over time. The TAUSSIG trial enrolled >100 patients with homozygous FH on apheresis or not on apheresis who were randomized to evolocumab.[19] As expected, patients had high baseline LDL-c levels, regardless of apheresis. After 12 and 48 weeks, reductions of 20.6% and 23.3%, respectively, were observed when all patients were grouped together, with a smaller change in patients on apheresis. Considering that these patients have 2 dysfunctional LDL-receptors, a reduction of 26.7% in the non-apheresis group is quite striking.

Prof. Hovingh then asked the question how many individuals with heterozygous FH in the S-shaped curve[16] who had not reached their LDL-c target level, would theoretically have reached it if they were given a high dose of statin, ezetimibe and evolocumab or alirocumab. To answer this question, a Dutch database of adults with heterozygous FH was used, comprising data of 10.000 individuals. Assuming full adherence to medication, 50% of patients would reach the LDL-c target level with high dose statin and ezetimibe. Addition of a PCSK9 inhibitor would result in a sharp increase in the number of individuals reaching their target (>90%). This would shift the S-shaped curve dramatically. However, adherence to medication might be different in real life, and therefore real life data is needed to see what the effect of PCSK9 inhibition is in clinical settings. In this study, consistent LDL-c lowering was observed, as shown by waterfall plots with an LDL-c reduction >25% in the majority of patients (Hartgers *et al.*, submitted).

He showed the full clinical trial program of three monoclonal antibodies against PCSK9; alirocumab, evolocumab, and bococizumab. Development of the latter was stopped because of the development of neutralizing antibodies in the large SPIRE outcome trials.[20] The first two drugs have been tested in all kinds of patient populations, among which statin-intolerant patients. In the ODYSSEY Alternative Study, patients were randomized to alirocumab, ezetimibe, or atorvastatin, and the primary outcome was LDL-c reduction at 24 weeks. As expected, a 45-55% reduction in LDL-c levels was observed in those randomized to alirocumab compared to a reduction of 15-17% in the ezetimibe group.[21] More importantly, fewer skeletal muscle adverse events were seen in the alirocumab-treated patients compared to the atorvastatin group.
PCSK9 inhibition in diabetes patients was recently examined in the ODYSSEY trials. Type 2 diabetes patients were randomized to 75 mg alirocumab or standard care in a 2:1 ratio.[22] The primary endpoint was the reduction in non-HDL-c levels, the prime driver of outcomes, at 24 weeks. A reduction of 37.3% was observed in the alirocumab group compared to a 4.7% reduction with standard care. Ongoing studies examine patients with renal impairment and those with HIV. We are also waiting for the study results of specific patient categories who are at high risk for CV endpoints.

Patients with FH, statin intolerance, and diabetes all seem to respond similarly to PCSK9 inhibition in terms of LDL-c lowering.

In addition to monoclonal antibodies to PCSK9, also adnectins, vaccines, small interfering (si)RNA and small molecules are being developed. The ORION-1 trial evaluated treatment with inclisiran, a 3rd generation siRNA specifically targeting PCSK9, in 500 individuals with high CVD risk.[23] Patients were treated with either one or two starting dose

regimens of siRNA, resulting in a very large reduction in LDL-c levels. Injection site reactions were observed in some patients, but not considered serious. A sharp decrease in PCSK9 level (> 60% reduction) resulted in large reductions of LDL-c level (50%) after only 2 injections of siRNA. The waterfall plots showed that all individuals responded with lowering of LDL-c levels.
Many roads may lead to PCSK9 inhibition, for example using the CRISPR approach or vaccines. Treatment with antibodies is ahead of the game, but data from the ORION trial suggest similar results with a different approach. Prof. Hovingh concluded that he believes that in case of PCSK9 inhibition one size fits all; patients with FH, statin intolerance, and diabetes all seem to respond similarly to PCSK9 inhibition in terms of LDL-c lowering.

PCSK9 inhibition & CV events: Review of recent and upcoming hard endpoint outcome trials

Prof. Peter Sever, MD – *London, UK*

Antibodies against PCSK9 have been tested in three major CV outcome trials; the FOURIER trial[3], the ODYSSEY trial, and SPIRE 1 and 2, of which the SPIRE trials were prematurely stopped in 2016. In SPIRE, treatment with bococizumab was compared to placebo in high risk prevention or secondary prevention patients. The trial was stopped due to antibody development against the drug, which attenuated in the therapeutic effect.[24]
In the ODYSSEY trial,[1,2] dose titration of the drug was possible with up-titration to reach the prevailing LDL-c target level or down-titration when the achieved LDL-c level was ≤ 25 mg/dL. For patients who achieved extremely low levels (≤ 15 mg/dL) the intake of drug was stopped. There was no dose titration in the FOURIER trial. Prof. Sever speculated that although the baseline risk of the patient populations in these 2 trials was different, similar baseline lipid profiles and in all probability, similar percentage reduction in CV events for similar baseline LDL-c levels, similar reduction in LDL-c and similar duration of follow-up will be seen in these trials. The FOURIER outcomes were compatible with those in a meta-analysis of statin trials produced by the Cholesterol Treatment Trialists Collaboration (CTTC), and Sever thinks the same results will be observed in ODYSSEY.

The FOURIER trial[3] was stopped prematurely after a follow-up of 2.2 years when the prespecified number of primary and secondary endpoints had been reached. 27564 patients were randomized at a 1:1 ratio to evolocumab or placebo in 49 countries. Importantly, there was a placebo run-in period in this trial during which statin therapy was optimized,[1] which was necessary for many patients. Safety assessment focused on the development of new-onset diabetes, since this had historically been an issue with statin treatment. All events in the trial were adjudicated independently by the TIMI Study Group (Boston, MA, USA). A small number of patients discontinued the drug, withdrew consent or were lost to follow-up. Baseline characteristics showed that ~80% of patients had MI, ~20% stroke, and 13% symptomatic PAD. About 2/3 of patients were on high intensity statin therapy at baseline, and 1/3 on moderate intensity in this high risk CV population.

Despite the observed reduction in the number of MI and stroke events with evolocumab, no reduction in CV death was seen.

The achieved baseline LDL-c levels were 92 mg/dL in both groups, and also other lipids levels were equally balanced. A 60% reduction in LDL-c levels was observed with treatment with evolocumab, which was maintained throughout the duration of the trial. The 3-year Kaplan Meier curve showed a relative risk reduction of 15% with evolocumab for the primary endpoint (HR 0.85) and a 2% absolute risk reduction. The number needed to treat (NNT) was 15 patients in 3 years. The relative risk reduction of the secondary endpoint was 20% (HR 0.80), a 2% absolute risk reduction, and the same NNT.
Despite the observed reduction in the number of MI and stroke events with evolocumab, no reduction in CV death was seen. In a number of early statin trials of secondary prevention, for example the 4S[25] and LIPID[26] trials, no divergence of the curves for the first two years following randomization was seen. This indicates that what we see in FOURIER may have been predicted based on earlier trials.
Prof. Sever warns for the dangers of subgroup analyses[3]; loss of randomization, smaller number of patients in each subgroup, and frequently inadequate power to detect drug effects in each subgroup. The only appropriate statistical test is the test of heterogeneity and he states that there does not appear to be a subgroup in the FOURIER trial that achieved a greater benefit from evolocumab than the whole trial population.
In view of the apparent delay in the development of the maximal protective CV effect, a landmark analysis was undertaken on the secondary endpoints CV death, MI and stroke, after PCSK9 inhibition at 1 year follow-up and 12-36 months follow-up; the event reduction after 1 year was substantially less than the reduction after 2 and 3 years. Landmark analysis for only MI and stroke showed again a substantially lower reduction in year 1 compared to year 2 and 3.

Focusing on the year-2 analyses of the trials when maximal benefits in terms of relative risk reduction were seen, there was little difference between the results of FOURIER and those predicted by the CTCC.[27] Therefore, the observed results of FOURIER were exactly what was predicted for the duration of the trial and the extent of LDL-c lowering.

Another important objective in FOURIER was to establish whether PCSK9 inhibition in those achieving extremely low levels of LDL-c was safe and whether the benefits of evolocumab were consistent across the whole achieved LDL-c range. There was a single and clear relationship with no attrition of benefit at the low end of the curve.[3] There were no safety issues among those achieving very low LDL-c levels and no difference in the number of adverse events between evolocumab and placebo groups.

Finally, although the trial was stopped, the SPIRE 2 trial also showed a relative risk reduction in CV events in patients taking bococizumab as compared to those randomized to placebo. Thus, two trials have demonstrated CV benefits of treatment with monoclonal antibodies directed against PCSK9.

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