Meeting Impression

EBAC-Accredited Satellite symposium during ESC 2018 Congress
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PCSK9 inhibition: Science, outcomes & guidance

This EBAC-accredited symposium was held during ESC 2018 in Munich, Germany. Prof. Ference, prof. Robinson and prof. Kastelein discussed PCSK9 as validated therapeutic target in CVD and translation into clinical practice. Combined data on PCSK9 inhibitors and statins were presented by prof. Ference, showing biologically and therapeutically equivalent effects of these two drugs on CV risk reduction. The selection of eligible patients for PCSK9 inhibition therapy was presented by prof. Robinson, focusing on patients at risk and phenotypes. Prof. John Kastelein discussed issues surrounding prescription of PCSK9 inhibitors and future perspective, with focus on other lipid-lowering therapies in statin-intolerant patients.

TOPICS

PCSK9 as target for treatment: The genetic validation

Prof. Brian Ference, MD – *Cambridge, United Kingdom*

Prof. Brian Ference started his presentation by illustrating that PCSK9 is the prime example of how genomics can be used to guide drug discovery and development. Just 15 years ago, gain-of-function mutations in the *PCSK9* gene were discovered to be associated with markedly elevated plasma LDL cholesterol (LDL-c) levels in the phenotype of familial hypercholesterolemia (FH) [1]. Just a few years later, rare loss-of-function mutations in the *PCSK9* gene were shown to be associated with remarkably lower plasma LDL-c levels and lower risk of cardiovascular disease (CVD). Indeed, in African Americans rare loss-of-function mutations in the *PCSK9* gene were associated with a lifetime exposure to lower LDL and 88% lower lifetime risk of CVD, as shown in the Atherosclerotic Risk and Community (ARIC) Study and in the Dallas Heart Study. In European individuals, more common partial loss-of-function mutations were associated with lifetime exposure to intermediate LDL-c levels and a more modest, but still substantial 50% reduction in lifetime risk of CVD [2]. These data established PCSK9 as a genetically validated therapeutic target in reducing lifetime risk of CVD.

In the same period, the mechanism by which PCSK9 inhibition lowers plasma LDL-c levels was elucidated. Normally, expression of both the LDL receptor (LDL-R) on liver cells and PCSK9 is upregulated in response to decreased intracellular concentrations of cholesterol. Circulating PCSK9 protein binds to the LDL-R and marks the LDL-LDL-R complex for degradation in the lysosome. PCSK9 inhibition prevents this degradation, thereby allowing the receptor to be re-used. The resulting increased density of LDL-R on the hepatocytes leads to lower plasma LDL-c levels, and thereby reduced risk of CVD [3-6].

These data gave rise to the development of a number of different therapies directed against PCSK9, with the monoclonal antibodies against PCSK9 being the first therapy in clinical development. Several studies demonstrated that treatment with a monoclonal antibody directed against PCSK9 consistently reduces plasma LDL-c levels by 50-60% in numerous different patient populations, regardless of the background therapy. A meta-analysis on the cardiovascular (CV) outcomes of these initial studies suggested that 50% reduction in LDL-c could potentially translate into 50% reduction in lifetime risk of CVD [7,8]. The suggestion that 50% reduction in plasma LDL-c could result in 50% reduction in CV risk creates perhaps an irrational exuberance about what we might expect therapeutically from inhibition of PCSK9, as compared with the effect of a rare loss-of-function mutation in *PCSK9*.

To more precisely anticipate what we might expect from PCSK9 inhibition, a Mendelian randomization study, framed as a naturally randomized trial, was conducted, using a number of common variants in the *PCSK9* gene. The study demonstrated that lower LDL-c levels due to genetically lower PCSK9 levels was indeed causally associated with risk of CVD and that this effect appeared to be consistent across numerous different outcomes and composite outcomes. A dose-response between genetically reduced LDL-c due to PCSK9 polymorphisms and lower risk of CVD was observed [9].
The study also showed that the effect of lower LDL-c due to *PCSK9* polymorphisms appeared to be similar to the effect of lower LDL-c due to other genetic variants associated with risk of CVD. When each of these variants is plotted, a log-linear association between the absolute magnitude of LDL-c reduction and the corresponding reduction in lifetime risk of CVD appears. This log-linear association is similar to the log-linear association observed in statin trials between the absolute reduction in LDL-c and the corresponding proportional reduction in the risk of CV events. A difference of course lies in that long-term exposure to lower LDL-c is associated with a greater reduction in risk of CV events per unit change in LDL-c, as compared to short-term exposure to lower LDL-c levels as achieved in randomized trials [10,11]. This implies that LDL has both a causal and a cumulative effect on risk of CVD. Because of this cumulative effect, one can therefore not use genetics or Mendelian randomization to directly estimate the effect of therapeutic PCSK9 inhibition in a trial.

To translate genetic effects into an expected therapeutic benefit in a short-term trial, one has to compare *PCSK9* variants with a reference standard, which is the HMG-CoA reductase (*HMGCR*) gene coding for the target of statins. Lower LDL-c due to *HMGCR* gene variants that mimic the effect of statins are clearly associated with a lower risk of CVD, which is consistent across multiple different composite CV outcomes and in all subgroups studied, similar to treatment with a statin in randomized trials [10,12]. The effects of *PCSK9* and *HMGCR* variants appear to be nearly identical on the risk of CVD per unit change in LDL-c. This implies that lower LDL-c due to PCSK9 inhibition and HMG-CoA reductase inhibition have biologically equivalent effects on the risk of CVD. It is therefore reasonable to anticipate that treatment with a PCSK9 inhibitor and statins should have therapeutically equivalent effects on the risk of CV events, implicating that roughly a 20% reduction in LDL-c per mmol/L, which is seen with statins, should be expected with a PCSK9 inhibitor, rather than a 50% reduction [9].

PCSK9 inhibitors and statins appear to have therapeutically equivalent effects on the risk of CVD per unit change in LDL-c, precisely as anticipated by the genetic studies.

When examining the results of three major PCSK9 inhibition trials (FOURIER, ODYSSEY and SPIRE-2) and plotting the results on the Cholesterol Treatment Trialists (CTT) regression line, it appears that PCSK9 inhibition may result in a smaller reduction in the risk of CVD per unit change in LDL-c, as compared to statins [12,13]. However, it should be noted that the CTT regression line represents the average expected benefit after five years of treatment with a statin. Importantly, treatment with a statin only lowers LDL-c by about 10% during the first year and ~20% during each subsequent year of treatment [12]. The CTT regression line was calculated as a simple meta-analysis of effects of statins per mmol/L reduction in LDL-c each year of therapy. But we can now calculate a CCT regression line for any duration of therapy. Doing that shows that statins should lower CVD risk by ~10% after one year of therapy, ~15% after two years of therapy, ~18% after three years of therapy and only after four of five years an LDL-c reduction of 20-22% per mmol/L is seen. When plotting the effect of PCSK9 inhibition in the ODYSSEY, FOURIER and SPIRE-2 trials on CTT lines based on duration of therapy, the effect was nearly exactly what one would have anticipated from the observed absolute reduction in LDL-c and the duration of therapy. Combination of all PCSK9 inhibition trials, including >54,700 participants with >5,000 events, resulted in a 15% relative risk reduction after a median follow-up of 2.5 years of therapy. This is precisely what would have been anticipated from the same absolute magnitude of LDL-c reduction and the same duration of statin therapy. Indeed, PCSK9 inhibitors and statins appear to have equivalent effects on CV outcomes during each year of therapy. During the first year both PCSK9 inhibitors and statins reduced the risk of CVD by ~10% per mmol/L reduction and ~20% during the second year, demonstrating that PCSK9 inhibitors and statins do have therapeutically equivalent effects on the risk of CVD per unit change in LDL-c, precisely as anticipated by the genetic studies [14].

Ference repeated that PCSK9 is the prime example of how we can use genomics to guide drug discovery and development. Rare gain-of-function mutations are associated with markedly elevated plasma LDL-c levels, while loss-of-function mutations are associated with remarkably lower plasma LDL-c levels and correspondingly lower risk of CVD. Mendelian randomization studies suggested that lower LDL-c due to PCSK9 inhibition and HMG-CoA reductase inhibition have biologically equivalent effects on the risk of CVD. Randomization trial evidence suggests that PCSK9 inhibitors and statins have therapeutically equivalent effects on the risk of CVD.

Novel PCSK9 outcomes in perspective: Lessons from FOURIER & ODYSSEY

Prof. Jennifer Robinson, MD – *Iowa, USA*

To start her presentation, prof. Jennifer Robinson showed the classic CTT regression line. She noted that the ODYSSEY and FOURIER trial findings did not quite fall on the CTT regression line. This was surprising, because earlier trials with only 1-1.5 years of follow-up had shown 50% relative risk reduction. The explanation may lie in that little risk reduction was seen in the first year of FOURIER. In the second year this was more, showing 25% relative risk reduction of atherosclerotic CVD (ASCVD), which is lower than the anticipated 35% risk reduction based on 1.6 mmol/L decrease in LDL-c on the CTT regression line [15].
Robinson presented another CTT analysis of high versus low statin trials, showing an identical 28% reduction in the relative risk of CVD each year [16]. This risk reduction emerged in the first year. Even if the trial had lasted longer, we would not have expected a 50-percent reduction in FOURIER.
When comparing the PCSK9 inhibitor trials, the ODYSSEY trial showed 15% relative risk reduction in major CV events after a median follow-up of 2.8 years [15], which is equivalent to the risk reduction observed in the FOURIER trial after a median follow-up of 2.2 years [17]. In the SPIRE-2 trial another PCSK9 inhibitor, bococizumab, showed a much higher relative risk reduction of 21 % after a median follow-up of only one year [18]. However, bococizumab did not move forward in development, because of allergenic potential due to mouse antigen.

The greatest benefit of PCSK9 antibodies can be obtained at higher LDL-c levels, as seen in high-risk populations.

The big difference in risk reduction can be explained by baseline LDL-c level, which was 134 mg/dL (3.5 mmol/L) in the SPIRE-2 trial versus 87 mg/dL (2.25 mmol/L) and 92 mg/dL (2.4 mmol/L) in the ODYSSEY and FOURIER trial, respectively.

The importance of baseline LDL-c levels is demonstrated in the ODYSSEY trial with only benefit of all outcomes emerging in those patients whose LDL-c levels were over 100 mg/dL (2.6 mmol/L) at baseline [18,19]. Moreover, a meta-analysis demonstrated that baseline LDL-c drives all endpoints for CV risk reduction. There was no total mortality benefit with statins, PCSK9 inhibitors and ezetimibe when LDL-c levels <100 mg/dL (2.6 mmol/L) [20]. With LDL-c levels >100 mg/dL (2.6 mmol/L) a ~10-14% reduction was seen in total mortality for each additional mmol reduction in LDL-c, indicating that the full effect of PCSK9 inhibitors is only observed at higher LDL-c levels. The reduction in total mortality was due to reduction in CV mortality.

Robinson showed a plot in which all studies came together, which demonstrates a clear log-linear relationship between LDL lowering and absolute CV reduction in patients with coronary heart disease and diabetes. This relationship is attenuated at lower LDL-c levels as seen in ODYSSEY and FOURIER [18,21,22]. Thus, the greatest benefit of PCSK9 antibodies can be obtained at higher LDL-c levels, as seen in high-risk populations.

Other evidence comes from the IVUS trial [23], in which lower achieved LDL-c reduction was associated with greater regression of plaque atheroma. Interestingly, the benefit seems to appear around LDL-c level of 100 mg/dL (2.6 mmol/L) [23-25]. The best value for money is probably when LDL-c levels are ≥100 mg/dL (2.6 mmol/L) and this may reflect the underlying pathophysiology. With very low LDL-c levels due to chronic statin therapy, it is more likely to observe regression in plaques, indicating stable plaques. However, patients with long-term statin therapy still suffer from events and the plaque does not disappear completely. More recent pathophysiologic evidence suggests that it is plaque erosion on these stable plaques that causes acute coronary syndromes. On the other hand, patients with LDL-c levels >100 mg/dL (2.6 mmol/L) show active plaques that are less likely to be stable, increasing the chance of large occlusive thrombi, STEMIs and even events like ASCVD that can be fatal. These results again show a big difference in response to LDL-c lowering therapies depending on baseline LDL-c levels.

Next, Robinson set out to translate these insights into clinical guidance. PCSK9 inhibitors are quite expensive and it is therefore not affordable to give those drugs to all patients with LDL-c levels >70 mg/dL (1.8 mmol/L). The benefit and net benefit from adding therapy can be quantified by calculating the number needed to treat to prevent one event (NNT) [26]. If the absolute risk is high and the relative risk is reduced by ~22%, the absolute risk reduction is actually 1 divided by the NNT. Someone with lower risk but higher LDL-c levels and a greater relative risk reduction may have a very similar NNT to somebody whose risk is higher, even though LDL-c levels are lower.

Based on a systematic review and updated with subgroup information of the FOURIER trials, three different absolute ASCVD risk categories were identified: extremely high risk (CVD++; ≥45% 10-years ASCVD risk), very high risk (CVD+ risk factors/FH+ risk factors; 30-40% 10-years ASCVD risk) and high risk (CVD or FH, no risk factors; ~20% 10-years ASCVD risk [26,27].
A next step is to phenotype patients. Those with extremely high risk have a poorly controlled cardio-metabolic milieu and an extensive burden of atherosclerosis, and these patients will benefit greatly from further LDL-c lowering. The very high-risk patients still have an adverse cardio-metabolic milieu, with a less extensive burden of active plaque. Finally, high-risk patients have quite well-controlled risk factors and are maybe younger of age with single vessel coronary disease; this may represent primary prevention of FH [28].
When the phenotype of the patient is known, NNT can be estimated, showing cost-effectiveness at NNT of 20-25 with more acceptable cost-effectiveness at greater discounting [26,29].
To illustrate the selection of patients who benefit from expensive PCSK9 inhibition therapy, Robinson showed an extremely high-risk CVD FH patient with LDL-c levels of 100 mg/dL (2.6 mmol/L). Treatment with ezetimibe will likely give a ~20% reduction in LDL-c levels. The NNT is 39 and LDL-c levels may go down to ~70-80 mg/dL (1.8-2.1 mmol/L). It makes sense to add a PCSK9 inhibitor, because the NNTs are still quite reasonable. On the other hand, a PCSK9 inhibitor could have been added directly, because the NNT is in the cost-effectiveness range. When LDL-c levels are >100 mg/dL (2.6 mmol/L), the NNTs for adding ezetimibe are not very good, whereas PCSK9 inhibitors are still in the range of cost-effectiveness with these LDL-c levels [26].

In conclusion, prof. Robinson suggests to add LDL thresholds to various risk phenotypes, at which it is reasonable to add a PCSK9 inhibitor. For instance, treatment starts to approach cost-effectiveness when LDL-c levels >70 mg/dL (1.8 mmol/L) in extremely high-risk patients and >100 mg/dL (2.6 mmol/L) in very high-risk patients. In the high-risk patients with LDL-c levels ≥130 mg/dL (3.4 mmol/L), particularly primary prevention of FH is cost-effective. Obviously, PCSK9 inhibitors would likely be used more widely if they were much less expensive, but the model based on NNT can be used as a rule of thumb to select the right patients for use of these monoclonal antibodies.

Targeting PCSK9 in clinical practice: Guidance & future

Prof. John JP Kastelein, MD – *Amsterdam, The Netherlands*

Prof. John Kastelein discussed targeting PCSK9 in clinical practice, focusing on issues surrounding prescription of PCSK9 monoclonal antibodies and looked into the future on what's next. He started with a short introduction on ASCVD, which is not only a major cause of death and disease, but also of health care costs [30].

In his opinion we may have become a bit complacent over the last decade, with people thinking that we do not need new drugs to lower LDL-c. However, when looking at recent literature, he thinks the numbers are very disappointing. Only 80% of patients with ASCVD show LDL <70 mg/dL (1.8 mmol/L), despite optimal therapy [31-33]. There are so many perceived or real side effects of therapy that the adherence in ASCVD is suboptimal and there are some registry data that suggest that only 30% of people who should receive high intensity statins, in fact do. And then interestingly, most of the discussion on the PCSK9 monoclonal antibodies has focused on costs, while theoretically with these drugs it should be possible that more than 99% of all ASCVD patients will achieve LDL <70 mg/dL (1.8 mmol/L) [31-33]. Thus, Kastelein concludes that we have somewhat of a dissociate between what is possible, and what in fact is currently done.

Another issue is that recent scientific evidence has taught us in the last five years that it is cumulative LDL-c exposure that matters: lifetime exposure. The consequence of that observation is that the real important thing is to start at a younger age. And we have also learned from the FOURIER data that we can basically go as low with LDL-c as we want. These two lessons are still very far from being realized in clinical practice.

The PCSK9 monoclonal antibodies can address this unmet need. We know that the only available alternative, ezetimibe, is not potent enough. The question is who should receive them. In theory everyone would benefit, but currently eligible patients are only those with ASCVD and high LDL-c, those with heterozygous or homozygous FH and some patients with statin intolerance. Some people think that statin intolerance would be a major market for PCSK9 monoclonal antibodies, but so far, Kastelein perceives that the regulators and the payers have really resisted this idea.

The next question is where we go from here. To answer this question, Kastelein continued with three subjects. The first being the advent of low-frequency injectables. Most monoclonal antibodies need to be injected at least 26 times a year. As monoclonal antibodies are made with biology,

not with chemistry, the costs are high. Secondly, there is the statin intolerance issue, which is important because in randomized trials there are not that many side effects, but in reality, it is very different. In lipid clinics, statin intolerance is now the most important reason for referral from both cardiologists and general practitioners. And finally, there are a number of other lipid targets that actually are not addressed by PCSK9 monoclonal antibodies, such as lipoprotein (a) (Lp(a)), apoC-III and triglycerides and AngPTL3.

The first low-frequency injectable that will come to market is inclisiran, an siRNA that is now being tested in a phase 3 program. It acts on the RISC complex in the nucleus and prevents synthesis of the PCSK9 protein, so there is no longer PCSK9 coming out of the liver. Exciting data published in the New England Journal last year showed that with a two-yearly injection of 300 mg, LDL-c levels can be reduced by about 80% for at least 12 months [34,35]. This offers hope that with less frequent dosing this drug could become an important adjunct to our armamentarium.

It is also very interesting that, when looking at the placebo arm in the ORION-1 trial, and comparing it to the treatment arm, it can be seen that injection of siRNA basically takes away the variability observed in patients who are just on statins. In the placebo arm, subjects were on a statin. However, people do not take their medication as they are supposed to; some people suddenly start taking their statin, and some people suddenly do not take it anymore. This is the reason for the immense variability in LDL-c levels. If you inject an siRNA you take that out, which is important because we know that LDL-c variability is associated with high risk of ASCVD [34].

Where are we with inclisiran now? More than 1,550 patient-years of safety data are available. Phase 3 is fully enrolled with 3,660 subjects. And the ORION-4 Cardiovascular Outcome Trial will recruit its first patient soon. Thus, the safety data, which are paramount in a program like this, are accumulating rapidly.

In the next ten years, there is a whole host of new drugs that we can add to our armamentarium.

Then statin intolerance, which has become a major issue in ASCVD. The total number of patients who are eligible for a statin across North America, Western Europe, and Japan, is about 350 million. But a number of large surveys show that 10.3% of patients cannot tolerate any statin [36-40]. Thus, this is not minor side issue and it is actually an extremely important reason for events. It is now estimated that in Europe 9% of all MACE events every year are due to the fact that patients are not taking statins at all, or are not taking adequate doses of statins. This is a major gap in therapeutic ASCVD prevention. There are several alternatives for statin-intolerant patients: PCSK9 inhibitors are very effective but costly; ezetimibe is safe and modestly effective; bempedoic acid is in development and is especially promising in combination with ezetimibe; CETP inhibition is still in development.

Bempedoic acid has been studied in four phase 3 lipid lowering studies. In combination with ezetimibe, up to 48% LDL-c reduction is shown. Especially the bempedoic acid/ezetimibe fixed dose combination may be a valuable option for statin-intolerant patients.

We now understand that the HDL-c increase with CETP inhibition is totally irrelevant and that it is the apoB reduction that matters. Lowering LDL-c apoB with a CETP inhibitor in statin-intolerant patients could become an important issue. This has come to light in the last year with publications by Brian Ference in JAMA [41], and also a post hoc in the REVEAL trial, in which patients on low doses of atorvastatin showed better MACE reduction than patients on high doses [42].

Other lipoproteins to pursue are Lp(a) which can be targeted by messenger RNA inhibitors, apoC-III, which can be targeted by siRNA inhibitors, and monoclonal antibodies for AngPTL3. The incredible reduction in Lp(a) levels achieved with the antisense oligonucleotide went up to 80% with a weekly dose [40,43]. The clinical potential of Lp(a) inhibition is great; however, Mendelian randomization data suggest that in order to get a 22% reduction in MACE, you need to reduce Lp(a) by 110mg/dL (2.8 mmol/L) [44,45]. This is a hefty assignment, which will mean that the baseline Lp(a) in the outcome trial will need to be really elevated.

Kastelein concluded that there is no reason for complacency. Statins are not enough for the majority of patients at very high ASCVD risk. Currently, the only answer is PCSK9 inhibition, but low-frequency injectables like inclisiran might even have a more profound impact on improving global ASCVD burden. It is important to mention that cumulative LDL-c exposure matters: start young, go low. A major clinical problem is statin intolerance, with the bempedoic acid/ezetimibe combination and the CETP inhibitor with great promise for the future. Improved understanding of Lp(a) apoC-III, and remnant lipoproteins is needed to open a multitude of new therapeutic avenues. Altogether, the future will not be boring in the next ten years. There is a whole host of new drugs that we can add to our armamentarium.

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