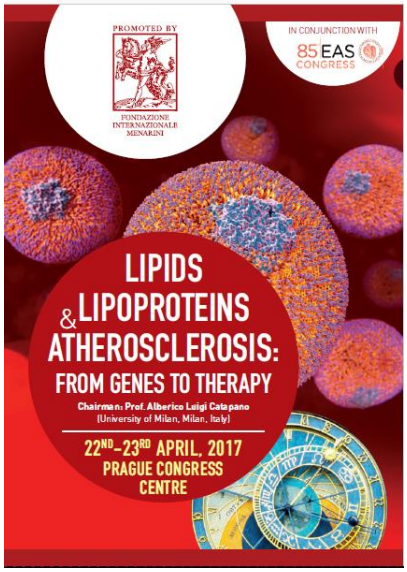
LIPIDS
LIPOPROTEINS
&
ATHEROSCLEROSIS:
FROM GENES TO THERAPY

Highlights

Prague (Czechia), April 22 2017

Introduction



This symposium directed by Prof. Catapano from Milan (IT) was characterized by a very high scientific level. It was focused on Atherosclerosis, Genetic dyslipidemia, new Guidelines Recommendations and new Therapeutic options under the patronage of the European Atherosclerosis Society. Many top researchers in Atherosclerosis and Familial dyslipidemias, coming from all the world attended this symposium. This congress represented a very unique occasion for a full update on Atherosclerosis, Genetic Dyslipidemia, Therapy and Precision Medicine in lipids disorders.

To follow the presentations of this congress, click on the link below:
http://www.fondazione-menarini.it/Home/Eventi/Fondazione-Internazionale-Menarini-Pre-Symposium-of-the-85-EAS-Congress-Lipids-lipoproteins-and-atherosclerosis-From-genes-to-therapy/Video-Slide
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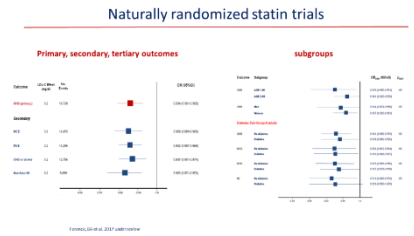
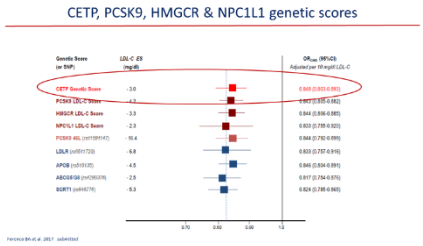
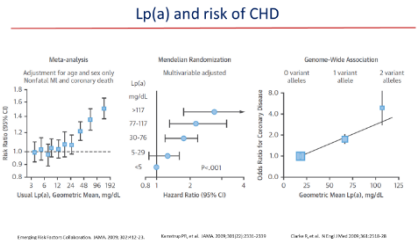
The lessons learned from genetics



The lessons learned from genetics, was the topic discussed by Prof. Ference in his opening lecture. The speaker, coming from Detroit (USA), at the beginning of his lecture spoke about the concept of mendelian randomization and naturally randomized trials, by highlighting that mendelian randomization is at a last analysis, a merely randomization scheme. Going deeper in his talk, Prof. Ference presented very interesting data comparing the effect of the mendelian randomization applied to the results of the RCTs, by highlighting that the mendelian randomization leads to an overestimation of the results of these trials. In the main part of his presentation, the speaker talked about how naturally randomized trials can be used to inform the design of RCTs, to improve drug discovery and the development of new lipid lowering therapies. More in particular, Prof. Ference presented very impressive data given by naturally randomized trials on the biological effects of the PCSK9 inhibitors compared to statins, showing that they have a biological equivalent effect on the cardiovascular risk reduction per unit change of LDL, with the consequence that they have also a therapeutic equivalent effect on the risk of cardiovascular events. The speaker presented also other very interesting data on the application of the naturally randomized trials to all the methods used for lowering the LDL-C, with the result that the biological effect is basically the same. In his lecture Prof. Ference spoke also about naturally randomized trials applied to triglycerides, by highlighting that, based on these studies, triglycerides lowering therapies lead to the reduction of the cardiovascular events. In the last part of his lecture, the speaker presented very interesting data on the relationship between Lp(a) reduction and the risk of CHD, by highlighting that, based on the data of the mendelian randomization studies, the effect on CHD is proportional to the absolute difference in Lp(a) levels. Finally, Prof. Ference talked about the relationship between mendelian randomization studies and Personalized Medicine, by highlighting the role played by genomics from a predictive and a prescriptive point of view, in order to predict the risk and to prevent the disease itself. In conclusion, the speaker, pointed out that, thanks to the naturally randomized trials, the causal effect of LDL on the risk of CVDs appears to be due to the circulating concentration of the LDL particles (apoB) rather than the cholesterol content carried by those particles (LDL-C).





- What are the main characteristics of the naturally randomized trials from the speaker point of view?
- Can we anticipate the results of the RCTs using the mendelian randomization trials?
- What are the main results of the naturally randomized statin trials?
- What's about the comparison between the PCSK9 effects and the HMGCR variants, based on the data presented by the speaker?
- How much do we have to lower Lp(a) to reduce the CVD risk?

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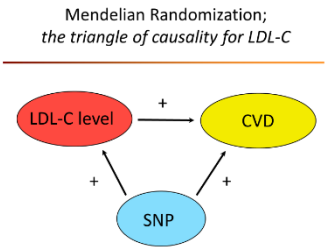
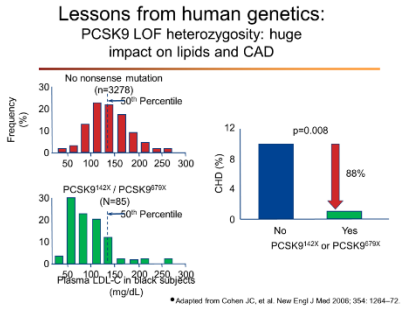
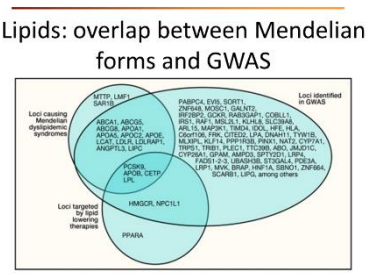
Genetic dyslipidaemias: are these rare diseases helping in identifying viable targets for therapy?



Prof. Hovingh from Amsterdam (the Netherland), spoke about Genetic dyslipidaemias as an help for identifying viable targets for therapy. The speaker went deeper in his talk, by presenting a list of novel agents, by highlighting that the drug development takes time and money and that genetics can help in replanning the projects. Going deeper in his lecture Prof. Hovingh presented a huge amount of data on the power of genetics for drug development starting from the novel target identification. The speaker talked about the processes linked with the discovery of new pathways leading to the onset of CVDs, based on SNP analyses and about the extreme genetics in dyslipidemia. He also presented very impressive data given by mendelian randomization studies running in patients affected by extreme familial dyslipidemias, like familial hypo/hypercholesterolemia, familial hypo/hyper-alphalipoproteinemia and familial hypo/hypertriglyceridemia. More in particular Prof. Hovingh spoke about the effects of PCSK9 inhibitors. Talking about the novel LDL-C lowering agents, the speaker presented very impressive data based on mendelian randomization studies able to predict the outcomes. More in particular he spoke about NPC1L, the cholesterol absorption inhibitors like Ezetimibe, the CEPT inhibitors, the apoC3 antisense and the ANGPTL3 inhibitors. In conclusion, the speaker pointed out that extreme genetics is a very useful tool for the drug development.





- What's about extreme HDL-C dyslipidemia, based on the data presented by the speaker?
- What's about the LCAT therapy from the speaker point of view?
- Will PCSK9 inhibitors reduce CVDs based on the data presented by the speaker?
- What is the role of the CETP inhibitors from the speaker point of view?
- What's about the role of the ANGPTL3 blockade from the speaker point of view?
- What are the genetic variants linked with the main adverse events in clinical trials presented by the speaker?
- What are the key points of the residual risk from the speaker point of view?

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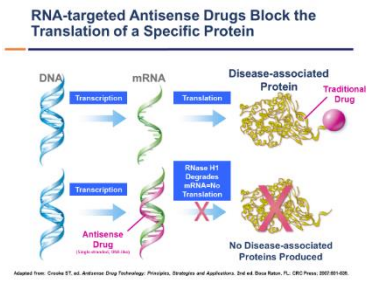
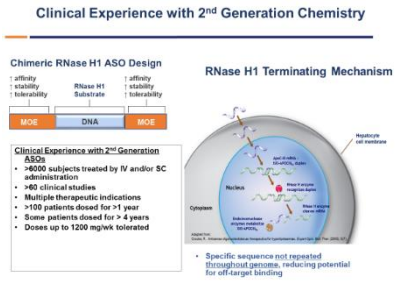
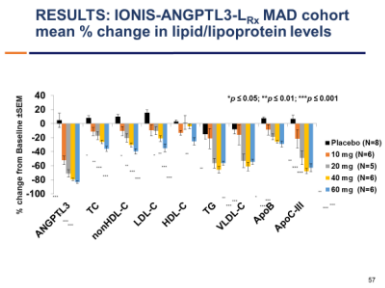
Interfering with gene expression: the present and the future in dyslipidaemias



Interfering with gene expression: the present and the future in dyslipidaemias was the topic discussed by Prof. Tsimikas. At the beginning of his talk the speaker, coming from San Diego (USA) presented very interesting data on RNA-based technologies and therapeutics. Going deeper in his lecture, Prof. Tsimikas spoke about the RNA-targeted antisense drugs and their effects on the protein synthesis process. More in particular, the speaker talked about the clinical experience with the second drugs generation and presented very interesting data on the lipoprotein targets in preventing and treating the cardiovascular diseases. In the main part of his talk, Prof. Tsimikas spoke about the data given by clinical studies comparing these drugs to placebo in dyslipidemic patients in reducing apoB, LDL-C, PCSK9, ApoC3, Triglycerides and Lp(a). In the last part of his lecture, the speaker presented a huge amount of data given by preclinical and phase I studies on the effects of an ANGPTL3 inhibitor on the lipoprotein metabolism and more in particular, on the reduction of triglycerides and LDL-C.





- How many drugs have been approved in these last 15 years by FDA for RNA therapeutics?
- What's about the technologies behind the RNA therapeutics presented by the speaker?
- What is the mechanism of action of these RNA-targeted antisense drugs, based on the data presented by the speaker?
- What's about the dosages per week of the 2nd generation of these new drugs, based on the data presented by the speaker?
- What's about the effect on triglycerides and LDL-C of the new ANGPTL3 inhibitors, presented by the speaker?

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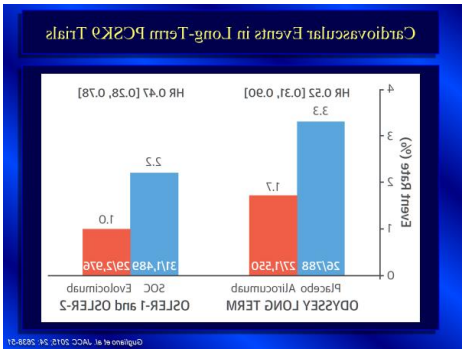
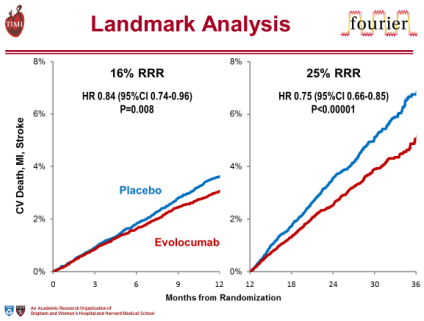
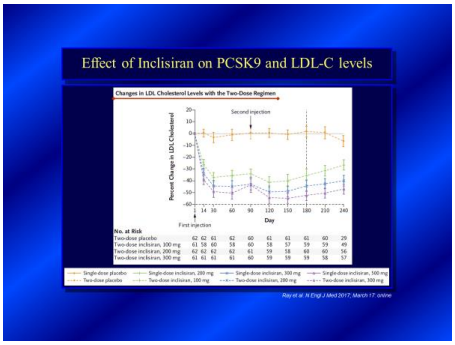
The use of monoclonal antibodies in controlling dyslipidaemias



The use of monoclonal antibodies in controlling dyslipidaemias was the topic discussed by Prof. Catapano. The speaker, chairman of the congress, introduced his talk by highlighting that the PCSK9 mutation is very rare, because the majority of the familial hypercolesterolemic patients present mutation in the receptor for LDL, but despite this rare condition, this mutation opened the way for the discovery of new drugs. Going deeper in his lecture, Prof. Catapano presented very interesting data given by the main clinical trials running in familial hypercolesterolemic patients treated with the PCSK9 inhibitors. More in particular, the speaker talked about the results of Alirocumab and Evolocumab on the cumulative incidence of CV events and on the LDL-C reduction compared to placebo. Prof. Catapano presented a huge amount of data comparing also the effects of these new drugs on the major cardiovascular events to those ones obtained with statins, by highlighting that the long-term benefits obtained with the PCSK9 inhibitors are consistent with those ones obtained with statins.





The speaker presented also data given by the clinical trials produced with Bococizumab, by highlighting that the hypocolesterolemic effect of this drug is significantly attenuated over time due to the development of anti-drug antibodies. Finally, Prof. Catapano spoke about Inclisiran, that is a synthetic si RNA PCSK9 inhibitor, by presenting the preliminary data of the Orion 1 clinical study, designed for the evaluation of the optimal dosing regimens in patients with elevated LDL-C and high CV risk.

- What's about the rate of responders to Inclisiran from the speaker point of view?
- What's about the Inclisiran safety data presented by the speaker?
- What's about Bococizumab and the cardiovascular outcomes, based on the data presented by the speaker?
- What are the main characteristics of Evolocumab, based on the data presented by the speaker?
- What is the cardiovascular event rate in the long-term PCSK9 inhibitors trials, based on the data presented by the speaker?

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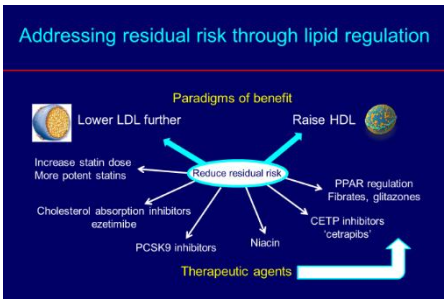
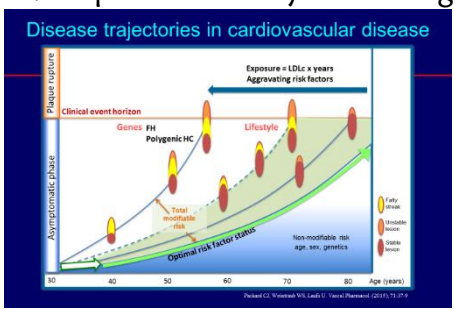
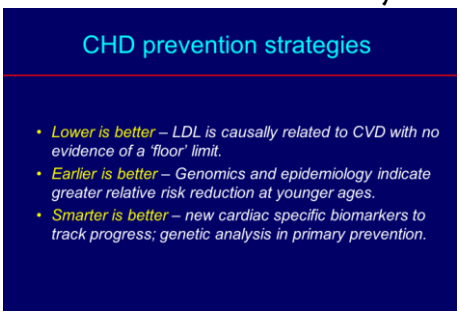
Lipid lowering therapy the present and immediate future



Lipid lowering therapy the present and immediate future was the topic of Prof. Packard presentation. The speaker, coming from Glasgow (UK), started his lecture, by highlighting that it is necessary to focus on the new therapeutic strategies that have to be developed, right at this moment and in the next two or three years. Going deeper in his talk, Prof. Packard presented very interesting data given by recent clinical trials in term of successes and failures, more in particular the speaker talked about the new strategies for reducing the residual risk, like the discovery of the CEPT inhibitors and the Cholesterol absorption inhibitors. In the main part of his lecture, Prof. Packard talked about the treatment strategies to be implemented in secondary prevention, by highlighting the role played by the combination therapy, mainly characterized by the association between statins and ezetimibe or PCSK9 inhibitors. In the last part of his talk, the speaker, presented very interesting data on the strategies to be implemented in primary prevention. More in particular, Prof. Packard talked about the long-term effects of the LDL lowering therapy, thanks to the data given by the WOSCOPS trial, where people, treated with statins were followed for more than 20 years after the end of the original trial. Finally, the speaker talked about the necessity to change the guidelines in order to stop to measure the CV risk level only based on age and to target people based on a gene score and presented very interesting data on Troponin as an index for cardiomyocyte damage or stress. In conclusion, Prof. Packard pointed out that the best prevention strategy should be based on three simple rules: the lower the better, the earlier the better, the smarter the better.





- What's about the advent of PCSK9 inhibitors from the speaker point of view?
- What's about the use of statins in primary prevention from the speaker point of view?
- What are the current, emerging and retreating treatment options in dyslipidemia, based on the data presented by the speaker?
- What's about an age-based plan for comprehensive primary CVD prevention, from the speaker point of view?

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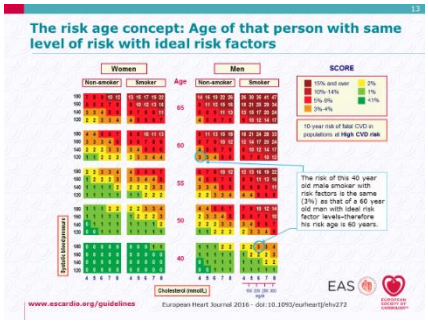
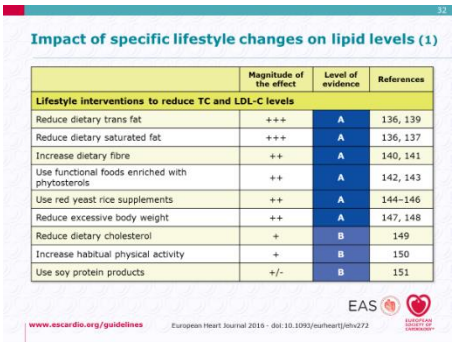
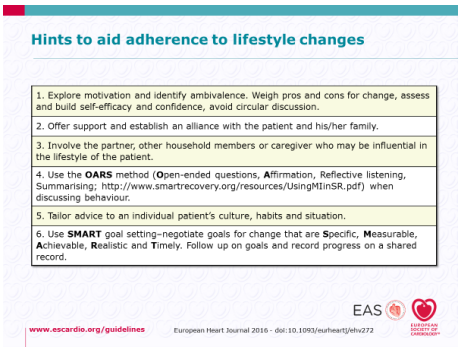
The ESC/EAS Guidelines for the diagnosis and therapy of dyslipidemias



The ESC/EAS Guidelines for the diagnosis and therapy of dyslipidemias was the topic of Prof. Tokgozoglu presentation. The speaker, coming from Ankara (Turkey), at the beginning of her lecture, addressed the audience by highlighting that these new guidelines take in account the results produced not only by the RCTs, but also by the epidemiological, and IVUS trials. Going deeper in her lecture, Prof. Tokgozoglu, pointed out that the main principles of these guidelines, are based on the determination of the risk of patient, on the plan for the treatment intensity according to the risk and finally on the target of the LDL-C level for treatment. Speaking about the score risk determination, Prof. Tokgozoglu highlighted that it is based on not only on age, but also on the risk level of any european country, divided into three categories of risk, high, medium and low. The speaker talked also about the risk age concept, characterized by the comparison of people at different age and with different exposure to the CV risk factors. These new guidelines take also in account the HDL-C levels for the determination of the risk level for men and women, the speaker pointed out. The treatment intensity is based on the CV risk level of any patient and LDL-C is causal and is the main target. Prof. Tokgozoglu, spoke also about the lifestyle modifications and their importance in these new guidelines, recommended with more emphasis than in the past. In conclusion, the speaker pointed out that, based on these new guidelines, three topics are very important: getting to goal, staying there and be adherent to the lifestyle modifications.





- What's about the risk age concept, based on the data presented by the speaker?
- What is the algorithm for the treatment of the muscular symptoms during the statin treatment?
- What's about the five dimensions of adherence, from the speaker point of view?
- What's about the treatment of dyslipidemia in patients affected by heart failure or valvular disease?
- What's about the treatment of dyslipidemia in diabetic patients?
- What's about the treatment of dyslipidemia in older adults?
- What are the main factors that modify the score risks, based on the data presented by the speaker?

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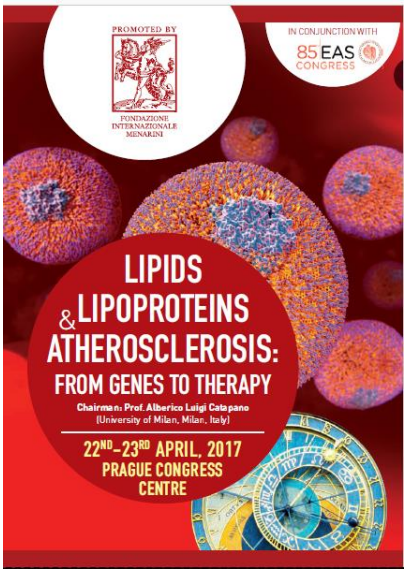

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