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New options for lowering cholesterol

- ***What can we hope these deliver?***

Elevated low-density lipoprotein (LDL) cholesterol is one of the most important modifiable risk factors for heart disease. While statins are effective and represent the current mainstay of treatment, it is clear that we need new options, particularly in high-risk patients who rarely achieve guideline-recommended targets.

Who are these high-risk groups?

Clearly, patients who have already had a heart attack are at high risk. However, the latest data from EUROASPIRE IV, a survey of clinical management of secondary prevention patients, show that while most are prescribed a statin, LDL cholesterol goal achievement falls short. Overall findings from 24 countries show that only 21% reached an LDL cholesterol target of <1.8 mmol/L (70mg/dL).¹

Another important group of patients who often fail to achieve LDL cholesterol target are patients with familial hypercholesterolaemia (FH). Underdiagnosis and undertreatment of these patients is a particular issue, as highlighted by the recent EAS Consensus Statement on FH.² Less than 5% of FH patients achieve the recommended LDL cholesterol goal.² Importantly, in most patients who are not optimally treated, the risk of a heart disease can be up to 13-fold higher compared with those who achieve LDL cholesterol targets.³ Novel options are particularly needed for these patients.

'FH is a common genetic condition. For example, in Italy, it is estimated that up to 300,000 patients may have FH; worldwide up to 37 million people may be affected. Yet most of these patients are not diagnosed. Even if FH is detected, the majority of patients are undertreated.

– Professor Alberto Corsini, University of Milan, Italy

Additionally, current options for managing high-risk patients who are unable to tolerate statins are limited. This group of patients represents an important unmet need; in a recent study of a lipid-lowering therapy in this group of patients, the mean LDL cholesterol level was about 5 mmol/L (193 mg/dL), despite current options.⁴

What novel treatments may help address these unmet needs?

Several strategies under investigation, or recently approved, that offer promise. These include treatments targeting proprotein convertase subtilisin/kexin type 9 (PCSK9); cholesteryl ester transfer protein (CETP) inhibitors; as well as antisense oligonucleotide inhibitors (such as mipomersen), and the microsomal triglyceride transport protein (MTP) inhibitor lomitapide, both of which have been recently approved as adjunctive therapy for homozygous FH.

- PCSK9 inhibitors have attracted much attention. PCSK9 plays a key role in LDL metabolism, mainly by enhancing degradation of LDL receptors in the liver. The development of monoclonal antibodies to PCSK9 is supported by a strong genetic rationale. Gain-of-function mutations in the PCSK9 gene have been linked to FH, whereas mutations in which there is loss of function have been associated with decreased LDL cholesterol concentration and decreased risk of heart disease.⁵

'PCSK9 monoclonal antibody therapy is a hot topic. These treatments have been shown to provide consistent LDL cholesterol lowering by more than 50% on top of statin therapy across the spectrum of high-risk patients including FH patients and patients with statin intolerance.⁶⁻⁹ At this EAS Congress, impressive results in homozygous FH patients with defective LDL receptor function were presented in a late breaking session.¹⁰ – Prof. Alberto Corsini

- CETP plays a key role in the transfer of triglyceride and cholesteryl ester between lipoproteins; inhibiting this pathway can increase the concentration of high-density lipoprotein (HDL) cholesterol substantially. The two CETP inhibitors in advanced development not only lower LDL by 35-40%, but also substantially raise (HDL) cholesterol by more than 100%.¹¹⁻¹³ These agents may offer a novel approach in the management of high risk patients with low HDL cholesterol together with elevated LDL cholesterol.

An exciting time ahead

'Initial results from some of these outcomes studies with the PCSK9 inhibitors and CETP inhibitors are expected in the future. Only then we will learn if additional LDL cholesterol reduction with these novel agents translates to improved clinical benefit for our patients at high risk of heart disease'

- Prof. Alberto Corsini

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