



LDL-Cholesterol Background

Cardiovascular events and deaths continue to increase worldwide

Cardiovascular disease (CVD) is the number one cause of death globally: more people die annually from CVD than from any other cause.¹ An estimated 17.3 million people died from CVD in 2008, representing 30% of all global deaths, and by 2030 almost 23.6 million people will die from CVD.¹ In addition to the global health burden, CVD also has a significant economic impact, estimated at €169 billion in the EU and \$297 billion in the United States for direct and indirect annual costs.^{2,3} While a large proportion of CVD is preventable, it continues to rise mainly because preventive measures are inadequate.¹

LDL-C is a major risk factor for CVD

A high blood cholesterol level, or hypercholesterolemia, is a major risk factor for the development of CVD.² There are many types of cholesterol – the three most commonly referenced ones are:⁴

- Total cholesterol – all cholesterol levels combined
- High density lipoprotein cholesterol (HDL-C) – often called "good" cholesterol
- Low density lipoprotein cholesterol (LDL-C) – often called "bad" cholesterol

High LDL-C remains a leading cause of morbidity and mortality across the world. It is estimated that there are approximately 71 million people at least 20 years old in the US who have high LDL-C.⁵

Cholesterol management guidelines continue to evolve

Reducing LDL-C remains the primary goal when managing hypercholesterolemia and has been proven to be one of the most effective means of reducing the risk of CVD.^{6,7,8} A large number of randomized, controlled clinical trials, as well as the most recent Cholesterol Treatment Trialists' Collaboration (CTT) meta-analysis involving >170,000 patients, have documented that lowering LDL-C levels can reduce the risk for major coronary events.⁹

To help better manage CVD, all current guidelines strongly recommend selecting LDL goals according to the level of the total CV risk. Therefore, the higher the risk, the lower the LDL level should be. These patients are usually classified based on having known CVD (e.g. previous heart attack, acute coronary syndrome) or high risk for CVD (e.g. ischemic stroke, peripheral artery disease, or diabetes and target organ damage).

- In Europe, the recent 2011 European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) guidelines have set a new goal of <70mg/dL (<1.81 mmol/L) for the very high-risk population⁶
 - For patients with high to moderate CV risk, the LDL goal is <100 mg/dL (<2.59 mmol/L) and <115 mg/dL (<2.97 mmol/L) respectively⁶
- In the United States, the U.S. National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) IV guidelines will be updated in 2012. In a 2004 update, the goal of <70 mg/dL (<1.81 mmol/L) was optional¹⁰
 - For patients with moderately high or less CV risk, the LDL goal is <130 mg/dL (<3.36 mmol/L) and <160 mg/dL (<4.14 mmol/L), respectively¹⁰
- In Canada, the 2009 Canadian Cardiovascular Society/Canadian guidelines recommend a target LDL-C goal of <77 mg/dL (<1.99 mmol/L) for patients at both high and moderate risk¹¹

Current treatment and goal attainment

Statins are well established therapies which have significantly modified the management of patients with high cholesterol. Today they are first-line therapy in both primary and secondary prevention. They have not only been shown to decrease LDL-C, but also to reduce CV events.¹²

Despite the availability of statins, many hypercholesterolemic patients are not reaching their recommended LDL-C goals and remain in need of additional lipid-lowering to reduce cardiovascular risk:

- A cross-sectional survey of over 15,000 patients receiving lipid-lowering drugs in eight European countries found that 45% were not at goal (<2.5 or <3.0 mmol/L [<97 or <116 mg/dL], based on patient risk category)¹³
- A study of over 20,000 veterans with coronary heart disease in the U.S. found that 59% of very high-risk patients were not at goal (<70 mg/dL or <1.81 mmol/L)¹⁴
- A cross-sectional study of over 22,000 statin-treated outpatients in Canada and 11 European countries found that 52% of non-diabetic/non-metabolic syndrome patients were not at goal (<2.5 or <3.0 mmol/L [<97 or <116 mg/dL], based on patient risk category)¹⁵

In addition, many patients cannot tolerate statin-related side effects, such as muscle pain, particularly at the higher doses required to achieve LDL goal. It is estimated that around 5-10% of patients treated with statins cannot tolerate the treatment.¹⁶ An estimated 24 million people in the U.S. and 16 million in Europe are currently taking statins.^{17,18,19}

Some people have particular difficulty achieving optimal LDL-C levels

People with high, uncontrolled levels of cholesterol are described as having primary hypercholesterolemia. An important subgroup of these patients are those with heterozygous familial hypercholesterolemia (heFH), an inherited disorder of lipoprotein metabolism. It is estimated that no fewer than 1 in 500 people in most populations have this condition, which is clinically characterized by elevated levels of LDL-C and total cholesterol in the circulation, deposits of cholesterol in peripheral tissues, and premature or accelerated atherosclerosis.²⁰

heFH is caused primarily by a loss-of-function mutation in the LDL receptor gene; to date, over 1,000 unique such mutations have been identified. All of these abnormalities result in a reduced ability to clear LDL-C from the circulation, exposing patients to significantly increased LDL cholesterol (LDL-C) from birth; LDL-C levels of 200-400 mg/dL (5.17-10.34 mmol/L) are common.²¹

Due to the severe elevations in LDL-C, a large majority of patients with heFH are not achieving treatment goals with existing therapies.²¹ For example, one recent analysis specifically in 1,249 heFH patients found that only 21% were able to achieve a treatment goal of <2.5 mmol/L (<97 mg/dL).²² This patient population has a clear need for additional medication that can help further reduce LDL-C when added to existing therapies since, untreated, the majority of affected men and women will have symptomatic coronary disease by the time they are 60, and half of the men and 15% of the women will have died.²¹ A retrospective review of 327 heFH patients over a period of 34 years found that – even on aggressive therapy – the interval between symptomatic cardiovascular events was 7.4 ± 6.7 years, a non-significant difference from that observed before the initiation of treatment.²³

Need for additional new treatment options to reach LDL-C goal and reduce CV risk

As guidelines are evolving and LDL-C goals are shifting, there is a need for additional, significant lipid-lowering medications to achieve goal. Beyond statins the therapeutic options are limited, providing only small incremental LDL-C reductions. New treatment options which can provide significant LDL-C reduction beyond the statin effect are needed for patients who are not at goal.

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