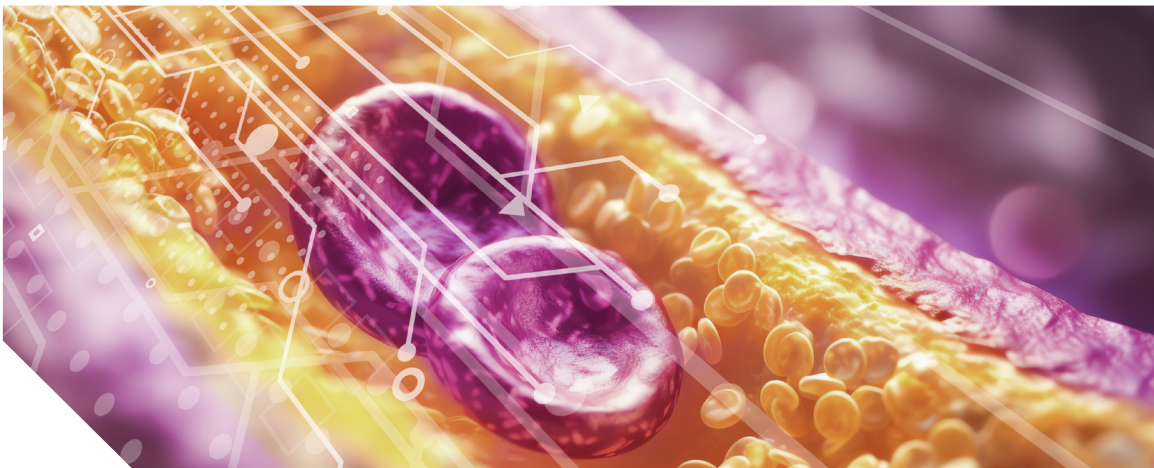


# LDL-C goals in international guidelines and how to achieve them

Across major guidelines, low-density lipoprotein cholesterol (LDL-C) remains the primary target for atherosclerotic cardiovascular disease (ASCVD) prevention, although other guidelines (e.g. United Kingdom) propose non-high-density lipoprotein cholesterol (non-HDL-C) as the main metric for monitoring ASCVD. The primary aim of LDL-C management is to achieve the lowest possible levels through appropriate treatment intensification, while tailoring it to the patient's cardiovascular risk category, with particular attention to those at high or very high risk.<sup>1</sup>



## What do international guidelines say?

**European guidelines** set explicit risk-based goals and reflect outcome data showing proportional risk reductions with each incremental LDL-C drop. The last proposal is a stepwise approach to treatment goals that resembles clinical practice, where treatment intensification is considered based on cardiovascular risk (SCORE2 or SCORE2-OP) benefit, side effects and patient preferences. The ultimate lipid goals are LDL-C <1.4 mmol/L (55 mg/dL) in patients with established ASCVD. For very-high risk patients without ASCVD, a target of <55 mg/dL (1.4 mmol/L) with  $\geq 50\%$  reduction from baseline values is recommended while for high-risk patients target is set at <70 mg/dL (1.8 mmol/L) with  $\geq 50\%$  reduction. Goals of <100 mg/dL (<2.6 mmol/L) should be considered for moderate

risk cases and <116 mg/dL (3.0 mmol/L) may be planned for low-risk patients.<sup>2,3</sup>

**North American guidance** also recommends the use of a validated tool or calculator to predict future risk of ASCVD events and emphasizes threshold-based initiation of statin therapy rather than fixed numeric goals but converges on similar intensification points. In primary prevention, a  $\geq 30\%$  reduction in LDL-C is recommended for patients at intermediate risk. For all patients with clinical ASCVD or at increased risk for ASCVD, a  $\geq 50\%$  reduction in LDL-C levels is recommended and if LDL-C remains  $\geq 70$  mg/dL (1.8 mmol/L) despite maximally tolerated statin therapy a complementary non-statin therapy should be considered.<sup>4,5</sup>

# How are these goals achieved?

All main international guidelines coincide on the importance of a healthy lifestyle for controlling LDL-C levels.<sup>2,4</sup> This includes behavioural approaches implying changes in diet, physical activity, as well as in smoking and alcohol consumption patterns, among others. When these approaches are not sufficient to maintain or improve blood lipid profiles, pharmacotherapy should be considered.<sup>2,4,5</sup> This concurrent initiation of lifestyle and pharmacological therapy should not give patients the impression that lifestyle changes are of lesser importance, and the patient should be counselled that these lifestyle changes may allow subsequent discontinuation or down-titration of medication. The main pharmacological approaches can be classified into the following categories:

- **Statins.** By inhibiting the HMG-CoA reductase, they reduce the synthesis of cholesterol in the liver. A reduction in intracellular cholesterol, increases the expression of the LDL receptor (LDLR) at the surface of liver cells and promotes uptake of LDL-C from the blood.<sup>3</sup>
- **Cholesterol absorption inhibitors (such as ezetimibe).** Intestinal absorption of cholesterol is inhibited, decreasing cholesterol levels in the liver. This promotes LDLR expression in hepatocytes and increases uptake of plasma LDL-C.<sup>3</sup>

- **Cholesterol synthesis inhibitors:** Bempedoic acid acts by inhibiting adenosine triphosphate-citrate lyase (ACL) and consequently cholesterol biosynthesis, leading to increased expression of LDL receptors and increasing LDL-C plasma clearance.<sup>6</sup>

- **Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9 inhibitors).** PCSK9 promotes a reduction of LDLR levels through lysosomal catabolism leading to an increase in LDL levels. By lowering the function or concentration of PCSK9 in plasma, PCSK9 inhibitors increase LDLR expression, reducing LDL-C levels.<sup>3</sup>

Statins remain the golden standard in lipid management. High-intensity statins can lower LDL-C by  $\geq 50\%$ , while moderate-intensity statins achieve 30-49% reductions. Treatment intensity is selected according to the magnitude of LDL-C reduction required and the patient's cardiovascular risk. When LDL-C targets are not achieved with maximally tolerated statin therapy, guidelines recommend stepwise combination therapy.<sup>2,5</sup> Dual therapy with statins and ezetimibe can achieve reductions of up to 65%, whereas triple therapy (statin+ezetimibe+PCSK9 inhibitor) can lower LDL-C levels up to 85%.<sup>2</sup> Bempedoic acid is an alternative to PCSK9 inhibitors or to patients with statin intolerance.<sup>7</sup>

## Conclusion

Achieving LDL-C goals is not a mere numerical objective but a cornerstone of cardiovascular risk reduction. International guidelines converge on the principle that “lower is better” and underscore the importance of timely escalation from lifestyle interventions to combination with pharmacologic approaches. Effective LDL-C management ultimately translates into a reduced incidence of cardiovascular events and improves long-term clinical outcomes.

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