

Aterotrombosi e Tromboembolismo arterioso:
aspetti di laboratorio

METABOLOMIC AND LIPOPROTEOMIC MODULATION FOLLOWING INCLISIRAN TREATMENT IN DYSLIPIDEMIC PATIENTS

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Background and Aims. Inclisiran is a subcutaneously administrated synthetic small interfering RNA directed against proprotein convertase subtilisin–kexin type 9, leading to sustained low-density lipoprotein cholesterol (LDL-C) reduction with a twice-yearly dosing regimen. While its lipid-lowering efficacy is well established, its broader metabolic effects remain incompletely characterized. Metabolomics refers to the comprehensive analysis of small-molecule metabolites reflecting systemic biochemical activity, whereas lipoproteomics focuses on the detailed characterization of lipoprotein particles and their subclasses, providing deeper insight into lipid transport and cardiovascular risk. This study aimed to comprehensively evaluate serum metabolomic and lipoproteomic changes in patients with dyslipidemia before and after inclisiran treatment using an integrated nuclear magnetic resonance (NMR)-based approach.

Methods. This observational single-center study included 69 patients with dyslipidemia treated with inclisiran in routine clinical practice. Fasting serum samples were collected at baseline and three months after treatment initiation. A total of 30 metabolites and 112 lipoprotein-related parameters were quantified using NMR spectroscopy. Paired comparisons between time points were performed using the Wilcoxon signed-rank test with false discovery rate correction. Clustering based on lipoprotein changes was conducted using the KODAMA algorithm to identify distinct response patterns.

Results. Inclisiran treatment was associated with extensive and coherent reductions in lipoprotein-related parameters. Seventy-four lipoprotein variables showed significant changes. Reductions were observed across LDL, IDL, and VLDL subclasses, while some HDL-related parameters were increased. In contrast, the global metabolomic profile remained largely unchanged; trimethylamine-N-oxide (TMAO) was the only metabolite significantly increased at follow-up. KODAMA clustering identified three patient groups with heterogeneous responses. Two groups demonstrated marked lipoprotein reductions, particularly those with higher baseline LDL-related parameters, whereas one group exhibited minimal changes. Baseline TMAO levels were lower in the group with the most pronounced lipid response and increased at follow-up, potentially reflecting changes in concomitant lipid-lowering therapy rather than a direct effect of inclisiran.

Conclusions. Inclisiran induces a broad and consistent improvement in lipoprotein profiles, extending beyond LDL-C reduction, while exerting only minimal effects on the global metabolomic landscape. These findings reinforce the highly specific lipid-lowering mechanism of inclisiran and underscore inter-individual variability in treatment response, particularly in the context of concomitant lipid-lowering therapies.

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