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DECODING DYSLIPIDEMIA

Human Genetic Studies of Drug Targets in Atherosclerotic Vascular Disease

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Akademisk avhandling

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Abstract

Despite significant advancements in prevention and treatment, atherosclerotic cardiovascular disease remains a leading cause of mortality and morbidity. Atherosclerosis develops from the accumulation of lipoprotein debris in arterial walls, resulting in plaque buildup that causes arterial narrowing, thickening, or softening and may ultimately trigger thrombosis. Current therapies effectively lower low-density lipoprotein (LDL) levels while insufficiently addressing other atherogenic lipids like very-low-density lipoproteins (VLDL) and chylomicron remnants. Furthermore, the optimal timing for initiating lipid-lowering interventions is debated. Conventional cardiovascular prevention approaches, which base treatment on ten-year risk calculations, may underestimate the cumulative impact of lifelong lipid exposure.

This thesis uses human genetics to explore the lifelong impact of inhibiting specific lipid-lowering drug candidate targets. We examine two key approaches in lipoprotein lowering: activating the rate-limiting enzyme in intravascular triglyceride hydrolysis, lipoprotein lipase (LPL), focusing on its activation through inhibiting the angiotensin-like protein (ANGPTL) family of regulators; and the reverse cholesterol transport system, reevaluating cholesteryl ester transfer protein (CETP) as a drug target.

Through genetic association studies, Mendelian randomization, genetic mimicry analyses, and meta-analyses of clinical trials, we demonstrate that targeting these proteins may offer protection against atherosclerotic cardiovascular disease. Our findings support the ongoing clinical development of ANGPTL3, ANGPTL4, and CETP inhibitors for cardiovascular prevention while emphasizing the value of human genetics in drug discovery. Lastly, this work improves our understanding of lipid management throughout the lifespan and highlights the potential benefits of early intervention.

Keywords

Atherosclerosis, Cardiovascular disease, Lipoproteins, LDL, VLDL, Lipoprotein lipase (LPL) Angiotensin-like proteins (ANGPTL), ANGPTL3, ANGPTL4, Cholesteryl ester transfer protein (CETP), Cardiovascular prevention

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