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Exploring biomolecular analysis of angiopoietin-like 4 upregulation through lifestyle for atheroprotection and plaque stabilization

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ABSTRACT

Atherosclerosis is a chronic inflammatory disease characterized by endothelial dysfunction, lipid metabolic imbalance, and immune activation, ultimately leading to plaque formation and instability. Angiopoietin-like protein 4 (ANGPTL4) has emerged as a key regulator linking lipid metabolism, endothelial function, and inflammatory responses. However, its mechanistic role in atherosclerosis and its modulation by lifestyle factors remain incompletely understood. This review synthesizes 13 original studies comprising preclinical studies, human observational studies, and non-randomized interventions. The analysis focused on the biomolecular role of ANGPTL4 across different stages of atherosclerosis and its regulation by lifestyle factors such as fasting and physical activity. Experimental studies demonstrated that ANGPTL4 exerts a protective role against atherosclerosis by preserving endothelial integrity through Krüppel-like factor–dependent signaling and suppression of endothelial-to-mesenchymal transition. ANGPTL4 also regulates lipid metabolism and constrains macrophage inflammatory activation, thereby limiting plaque progression and instability. In human studies, ANGPTL4 loss-of-function variants were associated with favorable lipid profiles and reduced cardiometabolic risk, whereas elevated circulating levels of ANGPTL family members correlated with atherosclerosis severity and adverse cardiovascular outcomes. Lifestyle-related exposures, including fasting and physical activity, consistently induced ANGPTL4 expression across metabolic tissues. These findings indicate that ANGPTL4 serves as a molecular interface between lipid metabolism, vascular homeostasis, inflammation, and lifestyle-induced metabolic adaptation. The tissue-specific and context-dependent regulation of ANGPTL4 highlights the complexity of its role in atherosclerosis and suggests that therapeutic modulation requires careful consideration of systemic versus local vascular effects. In conclusion, ANGPTL4 is a pivotal mediator in atherosclerosis pathogenesis and metabolic responses to lifestyle factors. Integrating lifestyle-based interventions with therapeutic strategies targeting ANGPTL4 may offer a comprehensive approach for the prevention and management of atherosclerotic cardiovascular disease.

ABSTRAK

Aterosklerosis merupakan penyakit inflamasi kronik yang ditandai oleh disfungsi endotel, gangguan metabolisme lipid, dan aktivasi imun yang berujung pada pembentukan serta instabilitas plak. Angiopoietin-like protein 4 (ANGPTL4) muncul sebagai regulator penting yang menghubungkan metabolisme lipid, fungsi endotel, dan respons inflamasi, namun peran mekanistiknya dalam aterosklerosis serta kaitannya dengan faktor gaya hidup belum sepenuhnya dipahami. Tinjauan ini menyintesis 13 studi original yang meliputi penelitian eksperimental praklinis, studi observasional manusia, dan intervensi non-randomisasi. Analisis difokuskan pada peran biomolekuler ANGPTL4 dalam berbagai tahap aterosklerosis serta regulasinya oleh faktor gaya hidup seperti puasa dan aktivitas fisik. Penelitian eksperimental menunjukkan bahwa ANGPTL4 berperan protektif terhadap aterosklerosis dengan mempertahankan integritas endotel melalui aktivasi jalur Krüppel-like factor dan penekanan *endothelial-to-mesenchymal transition*. Selain itu, ANGPTL4 mengatur metabolisme lipid

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dan membatasi aktivasi inflamasi makrofag yang berkontribusi terhadap progresi dan instabilitas plak. Pada manusia, varian kehilangan fungsi ANGPTL4 berasosiasi dengan profil lipid yang lebih menguntungkan dan risiko kardiometabolik yang lebih rendah. Sementara peningkatan kadar beberapa anggota keluarga ANGPTL berkorelasi dengan keparahan aterosklerosis dan luaran kardiovaskular yang buruk. Faktor gaya hidup seperti puasa dan aktivitas fisik secara konsisten meningkatkan ekspresi ANGPTL4. Temuan ini menegaskan bahwa ANGPTL4 berfungsi sebagai penghubung molekuler antara metabolisme lipid, fungsi vaskular, dan inflamasi, serta berperan dalam adaptasi metabolik yang diinduksi gaya hidup. Regulasi ANGPTL4 yang bersifat spesifik jaringan dan bergantung konteks menunjukkan bahwa intervensi terapeutik harus mempertimbangkan keseimbangan antara manfaat sistemik dan efek lokal vaskular. Dapat disimpulkan ANGPTL4 merupakan mediator kunci dalam patogenesis aterosklerosis dan respons metabolik terhadap gaya hidup. Integrasi pendekatan berbasis gaya hidup dengan strategi terapeutik yang menargetkan ANGPTL4 berpotensi meningkatkan pencegahan dan pengelolaan aterosklerosis.

INTRODUCTION

Atherosclerosis is a chronic arterial disease characterized by lipid and cholesterol accumulation with inflammatory infiltration, forming plaques that narrow and stiffen arteries, impair perfusion, and increase thrombosis risk, leading to conditions such as angina, myocardial infarction, and ischemic stroke. Despite advances in therapy, endothelial dysfunction, oxidative stress, and chronic inflammation remain key challenges.[1] Globally, cardiovascular diseases remain the leading cause of morbidity and mortality, accounting for over 20.5 million deaths in 2021, with ischemic heart disease and stroke responsible for nearly 16 million deaths.[2] In Indonesia, the 2023 National Health Survey (*Riskesdas*) reported a prevalence of physician-diagnosed coronary heart disease of 0.85% more than 2.5 million cases while cardiovascular mortality exceeds 650,000 annually, underscoring its heavy socioeconomic impact.[3] Conventional treatments reduce cardiovascular risk but leave major gaps. Statins lower LDL cholesterol by 30–50%, yet residual risk persists at up to 70%.[4] Antiplatelet drugs prevent thrombosis but do not stabilize plaques, while PCI and CABG relieve obstruction without addressing underlying inflammation and endothelial dysfunction. This explains the continued recurrence of infarction and disease progression despite optimal therapy.[1,4]

Angiopoietin-like protein 4 (ANGPTL4) has emerged as a promising biomolecular target with dual benefits: inhibiting lipoprotein lipase to reduce lipid deposition and modulating inflammation to enhance plaque stability.[5] Importantly, ANGPTL4 can be naturally upregulated by lifestyle changes such as exercise and dietary modification providing a non-pharmacological yet precise strategy. This dual nature positions ANGPTL4 as a valuable complement to existing therapies, offering effective atheroprotection and sustainable plaque stabilization.[5,6]

MATERIAL AND METHODS

Sources and search strategy

Three independent reviewers (BDA, SMA, and NPA) conducted systematic electronic searches across multiple databases, including PubMed,

ScienceDirect, Google Scholar, Cochrane Library, Taylor & Francis Online, and LILACS, to identify relevant studies published between January 2019-November 2025. This timeframe was selected to ensure the inclusion of contemporary evidence reflecting recent advances in molecular biology, experimental models, and clinical investigation of ANGPTL4 and related angiopoietin-like pathways. The search strategy was designed to capture original research articles examining the role of ANGPTL4 in atherosclerosis, cardiometabolic regulation, and lifestyle-induced metabolic adaptation, thereby minimizing heterogeneity from outdated methodologies and enhancing the translational relevance of the synthesized findings. The PROSPERO registration ID CRD4201253306 represents a unique identification code assigned to your systematic review within the International Prospective Register of Systematic Reviews (PROSPERO).

Search strings combined controlled vocabulary terms and free-text keywords related to the exposure, including “angiopoietin-like protein 4” OR “ANGPTL4”; lifestyle-related drivers directly examined in the included studies, such as “exercise” OR “physical activity” OR “endurance training” OR “fasting” OR “energy deprivation” OR “caloric restriction” OR “diet-induced lipid metabolism” OR “peroxisome proliferator-activated receptor (PPAR)”; and the disease and mechanistic context, encompassing “atherosclerosis” OR “plaque stability” OR “endothelial function” OR “endothelial dysfunction” OR “endothelial-to-mesenchymal transition” OR “vascular inflammation” OR “lipid metabolism” OR “lipoprotein lipase” OR “LPL”

Study criteria

Study selection followed PRISMA guidelines through identification, screening, eligibility, and inclusion stages. We included preclinical studies i) (cell culture/*in vitro* and mammalian in vivo models) that tested how lifestyle-mimicking stimuli) upregulate ANGPTL4 and affect atherosclerosis-relevant pathways;(ii) human observational studies (cross-sectional, case-control, and prospective cohorts) relating lifestyle exposures or circulating/tissue ANGPTL4 to vascular outcomes. Only full-text articles written in English or Indonesian were included. We have designed PICO in this study, which can be observed as follows:

Population. Specifically, the following can be observed i) Humans**.** Adults (≥18 yr), either with atherosclerotic cardiovascular disease or at high cardiometabolic risk. Eligible designs: cohorts, case–control studies assessing lifestyle exposure; ii) *In vivo*. Mammalian models (e.g., ApoE−/−, LDLR−/− mice, rats) exposed to lifestyle-relevant interventions; iii) *In vitro*. Relevant vascular/metabolic cells (endothelial cells, macrophages, VSMCs, adipocytes) subjected to lifestyle-mimicking stimuli (fatty acids, PPAR activation, fasting media, microbiota metabolites).

Exposures/Index. Any lifestyle factor (exercise/physical activity, dietary patterns, caloric restriction/fasting, microbiota modulation, or weight-loss programs) shown to upregulate ANGPTL4 (circulating protein, mRNA, or tissue expression). Preclinical studies had to test lifestyle-mimicking stimuli (fasting models, exercise regimens in animals, nutrient-induced PPAR activation).

Comparators. Standard care, sedentary behavior, control diets, or reference groups with no ANGPTL4 upregulation. For imaging/vascular function, comparators included CIMT, coronary CT, and accepted endothelial or lipid biomarkers.

Outcomes Eligible studies had to report i) ANGPTL4 expression or circulating levels; and ii) At least one atherosclerosis-

related outcome, endothelial activation, inflammatory markers and plaque morphology.

The reviewers conducted a duplication check and screened titles and abstracts according to predefined criteria. The detailed process of study search and selection is illustrated in FIGURE 1. Meanwhile, the conceptual framework developed by the author can be seen in FIGURE 2.

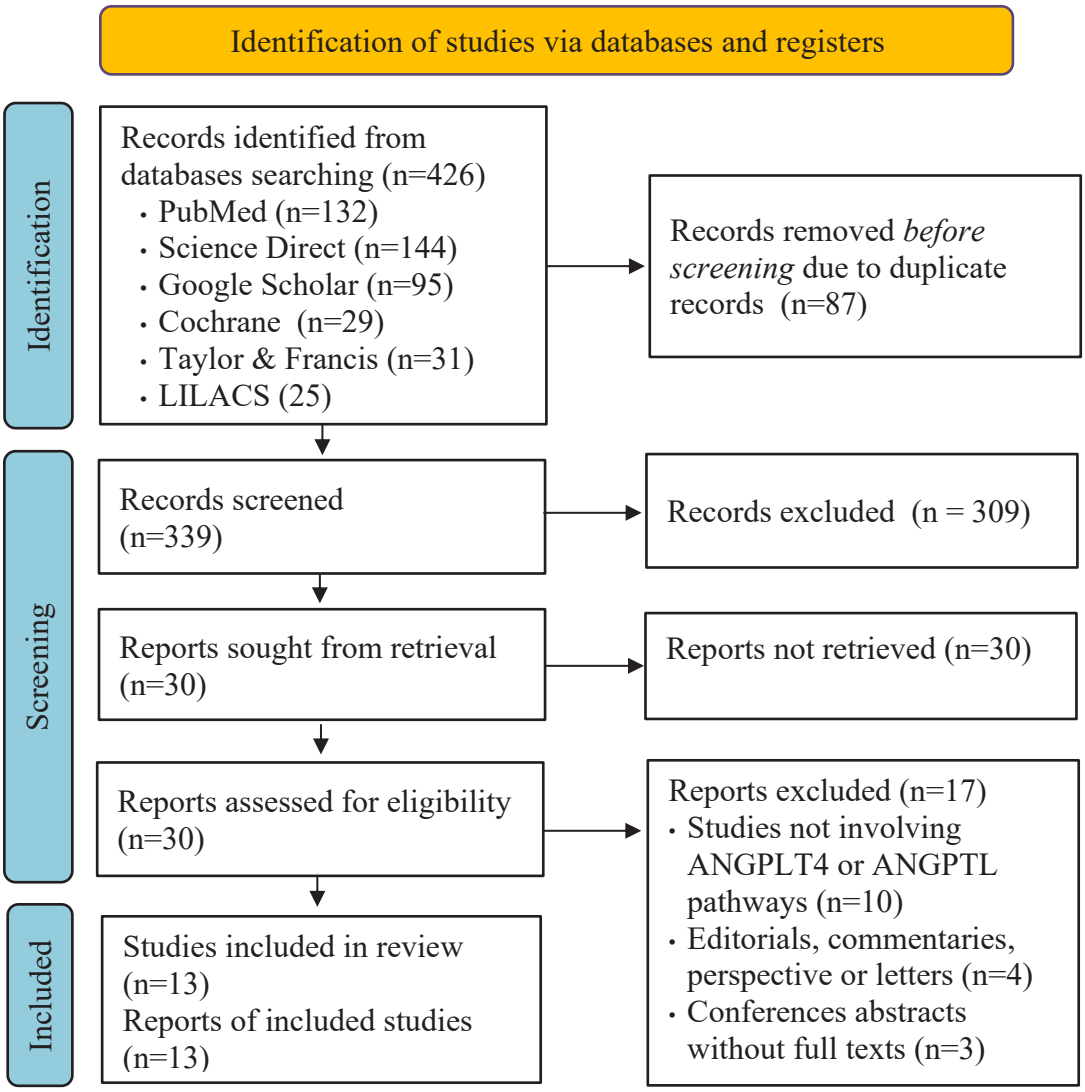

FIGURE 1. Literature search flow.

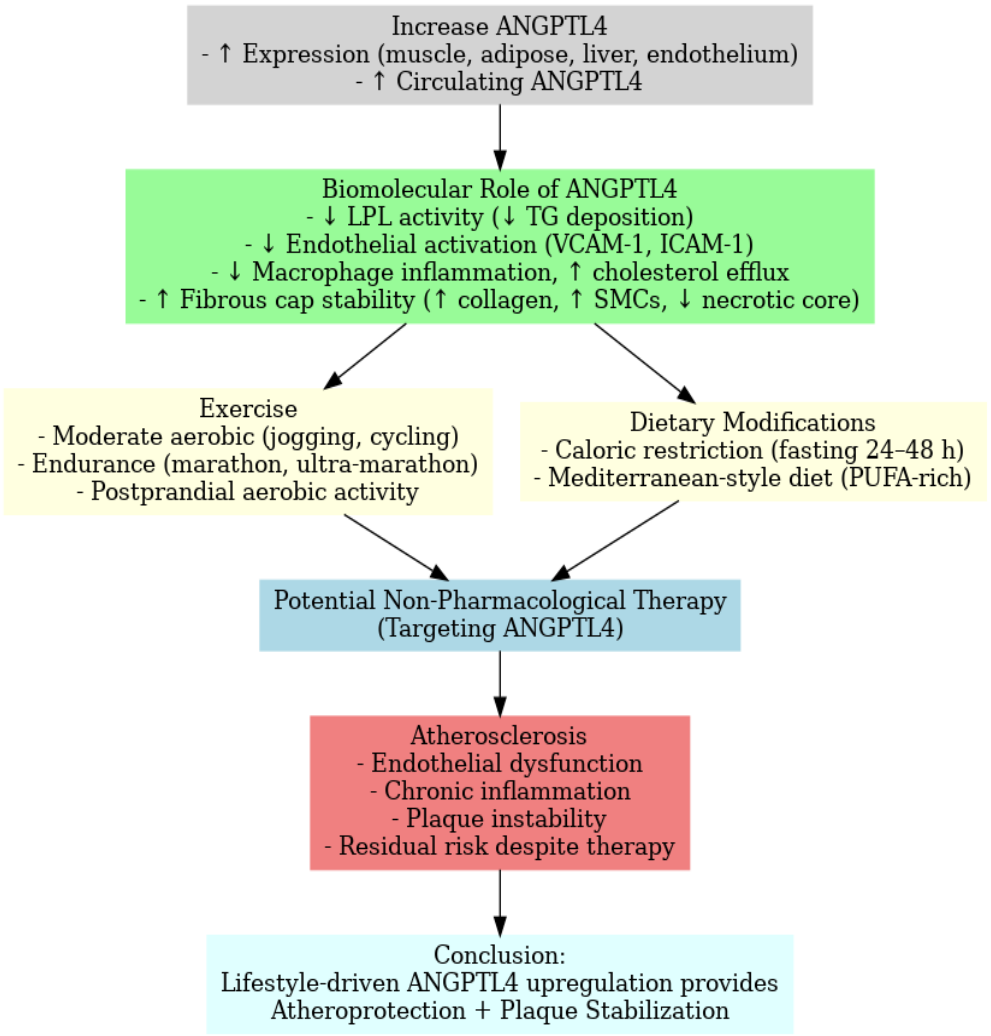

FIGURE 2. Conceptual framework

Data extraction & risk of bias

The data extraction was performed by the reviewer and included details such as the author and year of publication, country of origin, study design, sample characteristics, research focus, intervention type, and study duration. Each article was then assessed for quality using the appropriate tool according to the study design: SYRCLE RoB tool for animal studies and Newcastle–Ottawa Scale (NOS) for observational studies. Risk of bias can be observed in the TABLE 1.

TABLE 1. Results of risk of bias

1. Animal Studies (SYRCLE RoB)

Author	Sequence generation	Baseline balance	Allocation concealment	Random housing	Blinding caregivers	Random outcome assessment	Blinding outcome assessor	Incomplete outcome data	Selective reporting	Other bias	Overall
Cho *et al.*,[7]	Low risk	Low risk	Some concerns	Low risk	Some concerns	Low risk	Some concerns	Low risk	Low risk	Low risk	Low risk
Cho *et al.*,[13]	Low risk	Low risk	Some concerns	Low risk	Some concerns	Low risk	Some concerns	Low risk	Low risk	Low risk	Low risk
Sweet *et al.*,[12]	Low risk	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns	Low risk	Low risk	Low risk	Low risk
Ding *et al.*,[19]	Some concerns	Low risk	Some concerns	Some concerns	High risk	Some concerns	High risk	Low risk	Low risk	Some concerns	Some concerns

2. Observational Human Studies (NOS)

Author	Representativeness	Selection	Exposure ascertainment	Control definition	Confounder control	Additional confounder adjustment	Outcome assessment	Adequate follow-up	Attrition bias	Overall
Gagnon *et al.*,[8]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Hofmann *et al.*,[10]	Low risk	Low risk	Low risk	Low risk	Low risk	Some concerns	Low risk	Low risk	Low risk	Low risk
Zhang *et al.*,[11]	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns	Low risk	Some concerns	Low risk	Low risk
Sun *et al.*,[15]	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns	Low risk	Some concerns	Low risk	Low risk
Chen *et al.*,[9]	Some concerns	Low risk	Low risk	Low risk	Some concerns	Some concerns	Low risk	Some concerns	Low risk	Low risk
Ruppert *et al.*,[16]	Low risk	Low risk	Low risk	Low risk	Low risk	Some concerns	Low risk	Low risk	Low risk	Low risk
Li *et al.*,[17]	Some concerns	Some concerns	Low risk	Low risk	Some concerns	High risk	Low risk	Some concerns	Some concerns	Some concerns
Górecka *et al.*,[18]	High risk	Some concerns	Low risk	Some concerns	High risk	High risk	Low risk	High risk	High risk	High risk
Górecka *et al.*,[14]	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk

RESULTS

Inclusion study results

A total of thirteen original studies were included in the present review, encompassing a broad spectrum of experimental and human observational designs investigating the role of angiopoietin-like proteins (ANGPTLs) in lipid metabolism, endothelial function, and cardiovascular disease. Preclinical experimental evidence was provided by studies employing genetically modified animal models and mechanistic endothelial assays, demonstrating the regulatory role of ANGPTL4 and Krüppel-like factors in endothelial-to-mesenchymal transition, vascular inflammation, and atherosclerosis development.[7,13] Complementary mechanistic insights were further supported by transcriptional and enhancer-network analyses elucidating endothelial gene regulation under physiological and pathological conditions.[13]

Human evidence predominantly

consisted of observational and non-randomized interventional studies. Large-scale genetic epidemiology and cohort studies examined the cardiometabolic consequences of loss-of-function variants in ANGPTL4 and related angiopoietin-like proteins, providing population-level associations with lipid traits and cardiovascular risk.[8,12] Several cross-sectional studies assessed circulating ANGPTL3, ANGPTL4, ANGPTL8, or ANGPTL2 levels in relation to coronary artery disease severity, postprandial lipid metabolism, and angiographic findings, offering clinical correlations without therapeutic intervention.[9,11,15] In addition, prospective observational studies evaluated the physiological regulation of ANGPTL4 during endurance and ultra-endurance exercise, highlighting its role in lipid mobilization and inflammatory responses under extreme metabolic stress.[14,18] Non-randomized human intervention studies investigated the effects of lifestyle-related metabolic challenges, including acute fasting and structured exercise combined with weight loss, on ANGPTL expression and lipoprotein lipase activity.[10,16,17] Conclusively it can be seen in TABLE 2.

TABLE 2. Inclusion study results

Author	Country	Study design	Sample criteria	Research focus	Duration	Intervention
Cho *et al.*,[7]	South Korea	Experimental pre-clinical (*in vivo* + *in vitro*)	ApoE$^{-/-}$ mice; endothelial cell models; human samples for validation	ANGPTL4–KLF2 axis in EndMT suppression and atherosclerosis	Experimental period	Genetic and molecular manipulation of ANGPTL4/KLF2 signaling in mice and endothelial cells
Gagnon *et al.*,[8]	Canada	Observational cohort / genetic epidemiology	Human population cohorts (loss-of-function ANGPTL4 variants)	Impact of ANGPTL4 loss-of-function on cardiometabolic phenome	Long-term	Genetic observational study
Chen *et al.*,[9]	USA	Human observational (cross-sectional) + *in vitro*	Human serum samples (postprandial state); cell assays	ANGPTL8 regulation of ANGPTL3/4 in postprandial lipid metabolism	Single assessment	*In vitro* modulation with human serum
Hoffmann *et al.*[10]	USA	Human non-randomized longitudinal intervention	Adults enrolled in supervised endurance training	Effects of exercise on ANGPTL3/8 and ANGPTL4/8	Several months	Structured endurance exercise training program
Zhang *et al.*,[11]	China	Observational cross-sectional	Adults undergoing postprandial lipid testing	Association of ANGPTL3/4/8 with TRL metabolism	Single assessment	Postprandial biomarker assessment
Sweet *et al.*,[12]	USA	Experimental mechanistic (*in vivo* + *in vitro*)	Endothelial-specific KLF knockout mice; endothelial cells	KLF-dependent transcriptional control of endothelial genes	Experimental period	Conditional genetic deletion of KLF factors and enhancer perturbation
Cho *et al.*,[13]	South Korea	*In vivo, in vitro,*	ApoE−/− and Ldlr−/− mice; human AMI	ANGPTL4 in plaque stability, VSMC phenotype via KLF4/NOX1 modulation	8–12wk (mice)	Recombinant ANGPTL4 protein; plasma ANGPTL4 levels

Note: ANGPTL2/3/4/8 = angiopoietin-like proteins 2, 3, 4, and 8; CAD = coronary artery disease; ACS = acute coronary syndrome; MACE = major adverse cardiovascular events; TRL = triglyceride-rich lipoproteins; KLF2 = Krüppel-like factor 2; KLF4 = Krüppel-like factor 4; EndMT = endothelial-to-mesenchymal transition; LPL = lipoprotein lipase; ApoE$^{-/-}$ = apolipoprotein E knockout mice; LDLR$^{-/-}$ = low-density lipoprotein receptor knockout mice; SMC = smooth muscle cell; α-SMA = alpha-smooth muscle actin; SM-MHC = smooth muscle myosin heavy chain; NOX1 = NADPH oxidase 1; ROS = reactive oxygen species; ER stress = endoplasmic reticulum stress; TNF-α = tumor necrosis factor-alpha; IL-6 = interleukin-6; NF-κB, JNK, Erk = inflammatory signaling pathways; OR = odds ratio; CI = confidence interval; ROC = receiver operating characteristic; ELISA = enzyme-linked immunosorbent assay; KO = knockout.

TABLE 2. Cont.

Author	Country	Study design	Sample criteria	Research focus	Duration	Intervention
Górecka *et al.*,[14]	Poland	Prospective observational (repeated-measures)	Healthy trained marathon runners	ANGPTL4, IL-6, TNF-α during marathon-induced lipid regulation	Single event	Physiological response to marathon running
Sun *et al.*,[15]	China	Observational cross-sectional	Patients with angina / coronary artery disease	ANGPTL3/4 levels and coronary atherosclerosis severity	Single assessment	Angiography-based assessment
Ruppert *et al.*,[16]	Nether-lands	Human non-randomized experimental (before–after)	Adults undergoing adipose tissue biopsy	Effect of fasting on ANGPTL4 and LPL activity	24 hr	Short-term fasting fed vs fasted metabolic state
Li *et al.*,[17]	USA	Human non-randomized intervention	Older adults with overweight/obesity	ANGPTL4 and glucose metabo-lism after lifestyle change	6 mo	Combined aerobic exercise training and caloric weight loss
Górecka *et al.*,[18]	Poland	Prospective observational	Healthy trained male ultra-endurance runners	ANGPTL4 and lipid profile after ultra-marathon	Single event	Extreme endurance exercise exposure
Ding *et al.*,[19]	China	Experimental animal study (*in vivo ± ex vivo*)	ANGPTL4-deficient and wild-type mice	ANGPTL4 deficiency in macrophage lipid metabolism	Experimental period	Genetic knockout of ANGPTL4 in mice

Note: ANGPTL2/3/4/8 = angiopoietin-like proteins 2, 3, 4, and 8; CAD = coronary artery disease; ACS = acute coronary syndrome; MACE = major adverse cardiovascular events; TRL = triglyceride-rich lipoproteins; KLF2 = Krüppel-like factor 2; KLF4 = Krüppel-like factor 4; End-MT = endothelial-to-mesenchymal transition; LPL = lipoprotein lipase; $ApoE^{-/-}$ = apolipoprotein E knockout mice; $LDLR^{-/-}$ = low-density lipoprotein receptor knockout mice; SMC = smooth muscle cell; α-SMA = alpha-smooth muscle actin; SM-MHC = smooth muscle myosin heavy chain; NOX1 = NADPH oxidase 1; ROS = reactive oxygen species; ER stress = endoplasmic reticulum stress; TNF-α = tumor necrosis factor-alpha; IL-6 = interleukin-6; NF-κB, JNK, Erk = inflammatory signaling pathways; OR = odds ratio; CI = confidence interval; ROC = receiver operating characteristic; ELISA = enzyme-linked immunosorbent assay; KO = knockout.

Biomolecular analysis of ANGPLT-4 in atherosclerosis

The biomolecular findings summarized in TABLE 3 reveal a coherent and statistically supported framework linking angiopoietin-like proteins (ANGPTLs) to endothelial dysfunction, lipid dysregulation, and atherosclerotic progression across experimental and clinical contexts. At the early stages of atherogenesis, experimental studies demonstrated that preservation of endothelial ANGPTL4 signaling plays a central protective role. Genetic or molecular enhancement of the ANGPTL4–KLF2 axis significantly reduced aortic plaque burden and endothelial-to-mesenchymal transition markers compared with controls ($p<0.01$), indicating that ANGPTL4-mediated transcriptional regulation is critical for maintaining endothelial homeostasis. Conversely, disruption of ANGPTL4 signaling or downstream transcriptional networks resulted in increased inflammatory gene expression and lipid accumulation in endothelial cells and macrophages ($p<0.01$), supporting a causal link between ANGPTL4 deficiency and pro-atherogenic cellular phenotypes.[7,12,13]

These mechanistic observations were consistently mirrored in human genetic and observational data. In large population-based cohorts, loss-of-function variants in ANGPTL4 were significantly associated with lower circulating triglyceride levels (negative β coefficients, $p<0.001$) and a reduced risk of adverse cardiometabolic outcomes, with odds ratios persistently below 1.0 and confidence intervals excluding unity.[8] Such genetic evidence reinforces the experimental findings by indicating that long-term attenuation of ANGPTL4

activity confers systemic metabolic benefits relevant to atherosclerosis susceptibility. In parallel, clinical observational studies demonstrated that elevated circulating levels of ANGPTL3, ANGPTL4, and ANGPTL8 were positively correlated with postprandial triglyceride-rich lipoprotein concentrations and angiographic indices of coronary atherosclerosis severity (correlation coefficients >0, $p<0.05$), suggesting that dysregulated ANGPTL signaling contributes to impaired lipid clearance and vascular lipid deposition.[9,11,15]

At more advanced stages of cardiovascular disease, inflammatory ANGPTL family members emerged as prognostic biomarkers. In patients with acute coronary syndrome, higher serum ANGPTL2 levels independently predicted major adverse cardiovascular events, with hazard ratios exceeding 1.0 ($p<0.01$) after multivariable adjustment. Receiver operating characteristic analyses further demonstrated acceptable prognostic performance, with areas under the curve exceeding 0.70, underscoring the clinical relevance of ANGPTL2 as a marker of vascular inflammation and plaque instability.[12] Dynamic regulation of ANGPTLs under metabolic stress was further evidenced by non-randomized intervention and physiological challenge studies. Acute fasting induced a significant upregulation of ANGPTL4 expression in human adipose tissue, accompanied by a concomitant reduction in lipoprotein lipase activity ($p<0.01$), thereby facilitating lipid redistribution during energy deprivation.[16] Similarly, structured exercise and weight loss interventions led to significant changes in skeletal muscle ANGPTL4 expression alongside improvements in glucose metabolism ($p<0.05$), indicating a role for ANGPTL4 in metabolic adaptation.[17] Endurance and ultra-endurance exercise elicited pronounced increases in circulating ANGPTL4 ($p<0.01$ to $p<0.001$), which correlated with elevations in inflammatory cytokines such as IL-6 and TNF-α.[14,18]

Taken together, these statistically robust findings delineate a unified biological continuum in which ANGPTLs act as context-dependent regulators of lipid metabolism, endothelial integrity, and inflammatory signaling. Experimental causality, human genetic associations, clinical correlations, and metabolic challenge responses converge to support a stage-specific role of ANGPTLs in atherosclerosis development and progression, as systematically detailed in TABLE 3.

TABLE 3. Biomolecular Analysis ANGPLT-4 as atheroprotection and plaque stabilization

Author	Source	Biomolecular type	Atherosclerosis stage	Mechanism	Results (Statistical)	Interpretation
Cho *et al.*,[7]	Endothelial tissue (mouse & human)	ANGPTL4, KLF2	Early endothelial dysfunction	ANGPTL4 preserves KLF2 signaling and suppresses EndMT	ANGPTL4 overexpression significantly reduced aortic plaque area and EndMT markers ($p<0.01$); KLF2 expression positively correlated with endothelial integrity	ANGPTL4 confers endothelial protection through transcriptional regulation
Gagnon *et al.*,[8]	Human population cohorts	ANGPTL4 (loss-of-function variants)	Systemic cardiometabolic risk	Genetic reduction of ANGPTL4 alters lipid metabolism	ANGPTL4 loss-of-function variants associated with lower triglycerides ($\beta<0$, $p<0.001$) and reduced cardiometabolic risk (OR<1, 95% CI not crossing 1)	Genetic evidence supports a protective role of ANGPTL4 modulation

Note: ANGPTL4 = angiopoietin-like protein 4; ANGPTL3/8 = angiopoietin-like proteins 3 and 8; CAD = coronary artery disease; CAC = coronary artery calcification; EAT = epicardial adipose tissue; KLF2 = Krüppel-like factor 2; EndMT = endothelial-to-mesenchymal transition; LPL = lipoprotein lipase; $ApoE^{-/-}$, $Ldlr^{-/-}$ = apolipoprotein E and LDL receptor knockout mice; SMC = smooth muscle cell; α-SMA = alpha-smooth muscle actin; SM-MHC = smooth muscle myosin heavy chain; NOX1 = NADPH oxidase 1; KLF4 = Krüppel-like factor 4; ROS = reactive oxygen species; ER stress = endoplasmic reticulum stress; TNF-α = tumor necrosis factor-alpha; NF-κB, JNK, Erk = inflammatory signaling pathways; OR = odds ratio; CI = confidence interval; ROC = receiver operating characteristic; ACh = acetylcholine; SNP = sodium nitroprusside; KO = knockout.

TABLE 3. Cont.

Author	Source	Biomolecular type	Atherosclerosis stage	Mechanism	Results (Statistical)	Interpretation
Chen *et al*.,[9]	Human serum (postprandial)	ANGPTL8, ANGPTL3, ANGPTL4	Early lipid accumulation	ANGPTL8 regulates ANGPTL3/4 during postprandial lipid partitioning	Postprandial ANGPTL8 levels significantly correlated with ANGPTL3/4 modulation and triglyceride response ($p<0.05$)	ANGPTL8 functions as a metabolic regulator in postprandial lipid handling
Hoffmann *et al*.,[10]	Human plasma	ANGPTL3/8, ANGPTL4/8 complexes	Metabolic dysregulation stage	Exercise-induced modulation of ANGPTL complexes	Exercise training significantly reduced ANGPTL3/8 ratios and improved metabolic traits ($p<0.05$); changes correlated with insulin sensitivity	ANGPTL complexes are responsive biomarkers of exercise adaptation
Zhang *et al*.,[11]	Human plasma	ANGPTL3, ANGPTL4, ANGPTL8	Early–intermediate atherosclerosis	Impaired TRL clearance	ANGPTL3/4/8 levels positively correlated with postprandial TRL levels ($r>0$, $p<0.05$)	Elevated ANGPTLs reflect inefficient postprandial lipid metabolism
Sweet *et al*.,[12]	Endothelial cells (mouse & *in vitro*)	KLF2, KLF4	Endothelial dysfunction stage	Enhancer-mediated transcriptional control	Loss of KLF signaling significantly altered endothelial gene expression profiles (FDR<0.05) and increased inflammatory markers	Transcriptional dysregulation accelerates endothelial dysfunction
Cho *et al*.,[13]	ApoE−/− and Ldlr−/− mice; human AMI	Recombinant ANGPTL4, plasma ANGPTL4	Advanced atherosclerotic lesions	ANGPTL4 suppresses inflammation and inhibits VSMC phenotypic switching via NOX1/KLF4, enhancing fibrous cap stability	ANGPTL4 reduced plaque burden and inflammation and increased fibrous cap stability ($p<0.001$); higher ANGPTL4 levels were associated with fewer vascular events in humans ($p<0.05$)	ANGPTL4 promotes plaque stabilization and atheroprotectionz
Górecka *et al*.,[14]	Human plasma (exercise)	ANGPTL4, IL-6, TNF-α	Metabolic stress–related lipid regulation	Exercise-induced inflammatory and lipid signaling	ANGPTL4 increased significantly post-marathon ($p<0.01$) and correlated with IL-6 and TNF-α levels	ANGPTL4 mediates lipid mobilization during endurance stress
Sun *et al*.,[15]	Human plasma	ANGPTL3, ANGPTL4	Established coronary atherosclerosis	Dysregulated lipid metabolism	Higher ANGPTL3/4 levels associated with greater coronary severity scores ($p<0.05$)	Circulating ANGPTLs reflect atherosclerotic burden
Ruppert *et al*.,[16]	Human adipose tissue	ANGPTL4, LPL	Early metabolic remodeling	Fasting-induced LPL inhibition	Fasting significantly increased ANGPTL4 expression and reduced LPL activity ($p<0.01$)	ANGPTL4 orchestrates lipid redistribution during fasting
Li *et al*.,[17]	Skeletal muscle tissue	ANGPTL4	Metabolic dysfunction stage	Exercise and weight loss modulation	ANGPTL4 expression changed significantly following intervention ($p<0.05$), accompanied by improved glucose disposal	Muscle ANGPTL4 contributes to metabolic improvement
Górecka *et al*.,[18]	Human plasma (ultra-endurance)	ANGPTL4	Extreme metabolic stress	Prolonged endurance adaptation	ANGPTL4 markedly increased post-race ($p<0.001$) with parallel lipid profile changes	ANGPTL4 responds proportionally to extreme energy demand
Ding *et al*.,[19]	Macrophages (mouse)	ANGPTL4	Plaque progression and inflammation	Dysregulated fatty acid metabolism	ANGPTL4 deficiency significantly increased inflammatory gene expression and lipid accumulation ($p<0.01$)	ANGPTL4 restrains macrophage-driven atheroinflammation

Note: ANGPTL4 = angiopoietin-like protein 4; ANGPTL3/8 = angiopoietin-like proteins 3 and 8; CAD = coronary artery disease; CAC = coronary artery calcification; EAT = epicardial adipose tissue; KLF2 = Krüppel-like factor 2; EndMT = endothelial-to-mesenchymal transition; LPL = lipoprotein lipase; $ApoE^{-/-}$, $Ldlr^{-/-}$ = apolipoprotein E and LDL receptor knockout mice; SMC = smooth muscle cell; α-SMA = alpha-smooth muscle actin; SM-MHC = smooth muscle myosin heavy chain; NOX1 = NADPH oxidase 1; KLF4 = Krüppel-like factor 4; ROS = reactive oxygen species; ER stress = endoplasmic reticulum stress; TNF-α = tumor necrosis factor-alpha; NF-κB, JNK, Erk = inflammatory signaling pathways; OR = odds ratio; CI = confidence interval; ROC = receiver operating characteristic; ACh = acetylcholine; SNP = sodium nitroprusside; KO = knockout.

Lifestyle-related exposures constitute important non-pharmacological modulators of ANGPTL4, particularly under conditions of altered energy availability and metabolic stress. Evidence from lifestyle-focused human studies demonstrates that ANGPTL4 expression is significantly responsive to behavioral interventions such as fasting and physical activity. Acute fasting consistently induced a marked increase in ANGPTL4 expression in human adipose tissue, accompanied by a significant reduction in lipoprotein lipase activity ($p<0.01$), supporting a role for ANGPTL4 in facilitating lipid redistribution during energy deprivation.[16] Exercise-based lifestyle interventions further highlighted the dynamic regulation of ANGPTL4. Structured endurance exercise training and combined exercise–weight loss programs resulted in significant modulation of ANGPTL4 expression in skeletal muscle and circulation, alongside improvements in glucose metabolism and cardiometabolic parameters ($p<0.05$).[10,17] More pronounced metabolic challenges, such as marathon and ultra-endurance running, elicited substantial elevations in circulating ANGPTL4 levels ($p<0.01$ to $p<0.001$), which were positively correlated with inflammatory cytokines including IL-6 and TNF-α, reflecting coordinated metabolic and inflammatory responses to prolonged physical exertion.[14,18]

Collectively, these statistically robust findings indicate that ANGPTL4 acts as a sensitive biomolecular mediator of lifestyle-induced metabolic adaptation. The consistent and significant upregulation of ANGPTL4 across fasting and exercise paradigms underscores its role in regulating lipid metabolism under varying energetic demands and supports its potential utility as a biomarker for metabolic flexibility. The detailed mechanisms, statistical outcomes, and translational implications of lifestyle-induced ANGPTL4 regulation are summarized in TABLE 4, providing a focused synthesis for lifestyle-oriented cardiovascular and metabolic research.

TABLE 4. Lifestyle-Induced Upregulation of ANGPTL4

Source	Type of lifestyle	Mechanism	Result (Statistical)	Recommendation
Ruppert *et al.*,[16]	Acute fasting	Fasting induces ANGPTL4 expression in adipose tissue, leading to inhibition of lipoprotein lipase and reduced triglyceride uptake	ANGPTL4 expression significantly increased with concomitant reduction in LPL activity ($p<0.01$)	Short-term fasting may promote lipid redistribution through ANGPTL4-mediated mechanisms
Li *et al.*,[17]	Structured exercise and weight loss	Exercise and caloric restriction modulate skeletal muscle ANGPTL4 expression, improving metabolic flexibility	Significant changes in ANGPTL4 expression with improved glucose metabolism ($p<0.05$)	Combined exercise and weight loss may enhance metabolic health via ANGPTL4 regulation
Hoffmann *et al.*,[10]	Endurance exercise training	Physical training alters ANGPTL4/8 and ANGPTL3/8 complexes, influencing lipid and glucose metabolism	Exercise training significantly modified ANGPTL complexes and cardiometabolic traits ($p<0.05$)	Regular endurance exercise may optimize ANGPTL-mediated lipid regulation
Górecka *et al.*,[14]	Marathon running	Prolonged endurance exercise triggers ANGPTL4 release in response to increased lipid mobilization and inflammatory signaling	ANGPTL4 levels significantly increased post-marathon ($p<0.01$), correlating with IL-6 and TNF-α	ANGPTL4 reflects acute metabolic adaptation to prolonged physical exertion
Górecka *et al.*,[18]	Ultra-endurance exercise	Extreme endurance stress amplifies ANGPTL4 expression to support sustained fatty acid utilization	Marked elevation of ANGPTL4 following ultra-marathon ($p<0.001$) with lipid profile alterations	ANGPTL4 may serve as a biomarker of metabolic stress during extreme endurance activities

Note: ANGPTL4 = angiopoietin-like protein 4; LPL = lipoprotein lipase; IL-6 = interleukin-6; TNF-α = tumor necrosis factor-alpha; TRL = triglyceride-rich lipoproteins; p = probability value; ↑ = increased; ↓ = decreased.

DISCUSSION

Molecular and cellular drivers of atherosclerosis development and plaque instability

Atherosclerosis is now recognized as a chronic inflammatory disease driven by complex interactions between lipid accumulation, endothelial dysfunction, and immune cell activation. Early atherogenesis is initiated by endothelial barrier disruption and enhanced retention of apoB-containing lipoproteins within the arterial intima, which promotes oxidative modification and triggers endothelial activation. This process induces the expression of adhesion molecules and chemokines, facilitating monocyte recruitment and initiating a sustained inflammatory response that underlies lesion formation and progression.[20]

As lesions evolve, macrophage-driven inflammatory and metabolic pathways become central determinants of plaque growth and instability. Monocyte-derived macrophages internalize modified lipoproteins to form foam cells and undergo immunometabolic reprogramming characterized by altered fatty acid handling, mitochondrial dysfunction, and increased production of pro-inflammatory mediators. Defective efferocytosis in advanced plaques leads to secondary necrosis, expansion of the necrotic core, and amplification of inflammatory signaling, thereby accelerating plaque vulnerability.[21,22]

Plaque instability and subsequent atherothrombotic events are primarily governed by inflammatory degradation of the fibrous cap rather than the degree of luminal stenosis. Vulnerable plaques are characterized by thin fibrous caps, large lipid-rich necrotic cores, and heightened protease activity that weakens extracellular matrix integrity. Contemporary human studies and clinical trials have further demonstrated that targeting inflammatory pathways can reduce cardiovascular events independent of lipid lowering, underscoring inflammation as a causal driver of plaque destabilization and clinical disease.[23]

Mechanism of ANGPLT-4 to atherosclerosis

Angiopoietin-like protein 4 has emerged as a multifaceted regulator of atherosclerosis through its coordinated effects on lipid metabolism, endothelial function, and inflammatory signaling. At the systemic level, ANGPTL4 acts as a key inhibitor of lipoprotein lipase (LPL), thereby modulating triglyceride-rich lipoprotein hydrolysis and fatty acid uptake across peripheral tissues. Experimental and human genetic studies have demonstrated that alterations in ANGPTL4 activity significantly influence circulating triglyceride levels and lipid partitioning, processes that are directly implicated in atherogenic lipoprotein accumulation and vascular lipid exposure.[24]

Beyond its metabolic role, ANGPTL4 exerts direct vascular effects that are increasingly recognized as central to atheroprotection. Endothelial-specific studies have shown that ANGPTL4 preserves endothelial homeostasis by maintaining shear stress–responsive transcriptional programs, particularly through Krüppel-like factor–dependent signaling pathways. By stabilizing endothelial identity and suppressing endothelial-to-mesenchymal transition (EndMT), ANGPTL4 limits endothelial inflammation, barrier dysfunction, and maladaptive vascular remodeling, all of which are early contributors to atherogenesis.[25] These findings position ANGPTL4 as a critical molecular link between metabolic cues and endothelial integrity. ANGPTL4 also modulates macrophage function within the atherosclerotic plaque

microenvironment. In macrophages, ANGPTL4 regulates cell-intrinsic fatty acid metabolism, thereby constraining excessive lipid uptake and limiting inflammatory activation. Loss of ANGPTL4 signaling has been shown to promote macrophage lipid overload, enhanced pro-inflammatory cytokine production, and impaired resolution pathways, contributing to plaque expansion and instability. These macrophage-centered mechanisms highlight the importance of ANGPTL4 in regulating immunometabolic balance during plaque progression.[26]

Collectively, ANGPTL4 integrates lipid metabolic regulation with vascular and immune cell homeostasis, acting in a context-dependent manner across multiple stages of atherosclerosis. While reduced ANGPTL4 activity may confer favorable systemic lipid profiles, excessive local suppression within vascular or immune compartments could potentiate endothelial dysfunction and plaque inflammation. This duality underscores the complexity of ANGPTL4 biology and suggests that therapeutic strategies targeting ANGPTL4 must consider tissue-specific and stage-specific effects to maximize atheroprotective benefits while minimizing adverse vascular consequences.[27]

The relationship between lifestyle and upregulation of ANGPLT-4

Lifestyle-related metabolic challenges, particularly fasting and physical activity, represent potent physiological stimuli for the upregulation of ANGPTL4. Angiopoietin-like protein 4 expression is tightly regulated by energy availability and is induced under conditions of increased fatty acid flux, acting as a key mediator of metabolic adaptation. During fasting, elevated circulating free fatty acids activate peroxisome proliferator–activated receptor (PPAR) signaling pathways, leading to transcriptional induction of ANGPTL4 in adipose tissue, skeletal muscle, and liver. This adaptive response suppresses lipoprotein lipase activity, thereby limiting triglyceride uptake into peripheral tissues and facilitating lipid redistribution during energy deprivation.[28]

Exercise-induced metabolic stress similarly promotes ANGPTL4 upregulation through coordinated hormonal and transcriptional mechanisms. Endurance exercise increases circulating fatty acids and activates AMP-activated protein kinase (AMPK) and PPAR-dependent pathways, which collectively enhance ANGPTL4 expression in skeletal muscle and circulation. This response supports metabolic flexibility by shifting substrate utilization toward fatty acid oxidation while preventing excessive lipid accumulation in non-adipose tissues. Human intervention studies have consistently demonstrated significant increases in ANGPTL4 levels following structured exercise training and prolonged endurance activity, reinforcing its role as a biomarker of exercise-induced lipid remodeling.[29]

Importantly, lifestyle-induced ANGPTL4 upregulation appears to exert context-dependent effects on cardiometabolic health. While transient increases in ANGPTL4 during fasting or exercise promote adaptive lipid mobilization and metabolic efficiency, chronic dysregulation may contribute to altered lipid handling under pathological conditions. Nonetheless, the physiological induction of ANGPTL4 through lifestyle interventions is generally associated with favorable metabolic outcomes, including improved insulin sensitivity and lipid homeostasis. These findings position ANGPTL4 as a molecular link between lifestyle behaviors and cardiometabolic regulation, highlighting its potential relevance in non-pharmacological strategies aimed at reducing atherosclerotic risk.[30]

CONCLUSION

Angiopoietin-like protein 4 as a central, context-dependent regulator of atherosclerosis that integrates lipid metabolism, endothelial function, and inflammatory signaling. Experimental studies demonstrate that preservation of ANGPTL4 signaling protects endothelial integrity by suppressing endothelial-to-mesenchymal transition and limiting inflammatory activation, while macrophage-focused data indicate that ANGPTL4 restrains lipid overload and pro-inflammatory immunometabolic reprogramming within the plaque microenvironment. These mechanistic insights are supported by human genetic and observational studies showing that ANGPTL4 loss-of-function variants are associated with favorable lipid profiles and reduced cardiometabolic risk, whereas dysregulated circulating ANGPTL family members correlate with disease severity and adverse cardiovascular outcomes.

In addition, lifestyle-related metabolic challenges, including fasting and physical activity, consistently induce ANGPTL4 expression across multiple tissues, underscoring its role as a physiological mediator of metabolic adaptation. This dynamic regulation links behavioral factors to molecular pathways governing lipid redistribution and vascular homeostasis, reinforcing the relevance of ANGPTL4 in preventive and lifestyle-based cardiovascular strategies. Taken together, these findings suggest that therapeutic approaches targeting ANGPTL4 should account for tissue-specific and stage-dependent effects, and that combining pharmacological modulation with lifestyle interventions may offer a comprehensive strategy to mitigate atherosclerotic risk and improve cardiometabolic health.

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