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FULL RESEARCH PAPER
Lipids & atherosclerosis

Effect of angiopoietin-like protein 3 inhibitors on lipid profile and other biomarkers: a meta-analysis of randomized controlled trials

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Aims Inhibition of angiopoietin-like protein 3 (ANGPTL3) has been proposed as a promising approach to reduce residual cardiovascular risk. We conducted a meta-analysis of randomized controlled trials (RCTs) to provide a comprehensive evaluation of the metabolic effects of ANGPTL3 inhibitors.

Methods Databases (PubMed, EMBASE, Web of Science, CENTRAL, ClinicalTrials.gov) were searched from inception to July 2025. Eligible studies were RCTs comparing ANGPTL3 inhibitors against placebo. Outcomes included triglycerides (TG), LDL-C, apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), very-low-density lipoprotein cholesterol (VLDL-C), apolipoprotein A1 (ApoA1), apolipoprotein C3 (ApoC3), lipoprotein(a) (Lp(a)), remnant cholesterol (RC), ANGPTL3 and C-reactive protein (CRP). Pooled estimates of percentage change from baseline were obtained using fixed- and random-effects models. Subgroup analysis was performed based on the mechanism of action: monoclonal antibodies (mAbs, evinacumab), antisense oligonucleotides (ASOs, vupanorsen), and small interfering RNAs (siRNA, zodasiran and solbinsiran).

Results Nine RCTs (1254 participants) were included. ANGPTL3 inhibition significantly reduced TG (−47.1%), LDL-C (−21.6%), ApoB (−19.9%), non-HDL-C (−31.5%), TC (−32.8%), VLDL-C (−40.6%), and RC (−72.7%). Modest but consistent reductions were also observed in Lp(a) (−11.5%), ApoA1 (−18.3%), and ApoE (−16.4%). ANGPTL3 inhibitors markedly reduced circulating ANGPTL3 protein (−70.7%), with no significant effect on high-sensitivity CRP. Subgroup analyses demonstrated greater reductions in LDL-C, ApoB, non-HDL-C, and TC with evinacumab compared to the other groups, whereas small interfering RNAs produced more pronounced VLDL-C lowering compared with vupanorsen.

Conclusion ANGPTL3 inhibition offers broad lipid-lowering benefits, with particularly marked reductions in TG-rich lipoproteins.

Lay Summary This meta-analysis shows that ANGPTL3 inhibitors consistently improve multiple lipid parameters, offering a promising therapeutic option for patients with dyslipidaemia who respond poorly to conventional lipid-lowering treatments, although their impact on cardiovascular outcomes remains to be established.

- ANGPTL3 inhibitors produce significant and consistent reductions in triglycerides and moderate but clinically meaningful decreases in LDL-C through an LDL receptor–independent mechanism, confirming their broad lipid-modifying effects.

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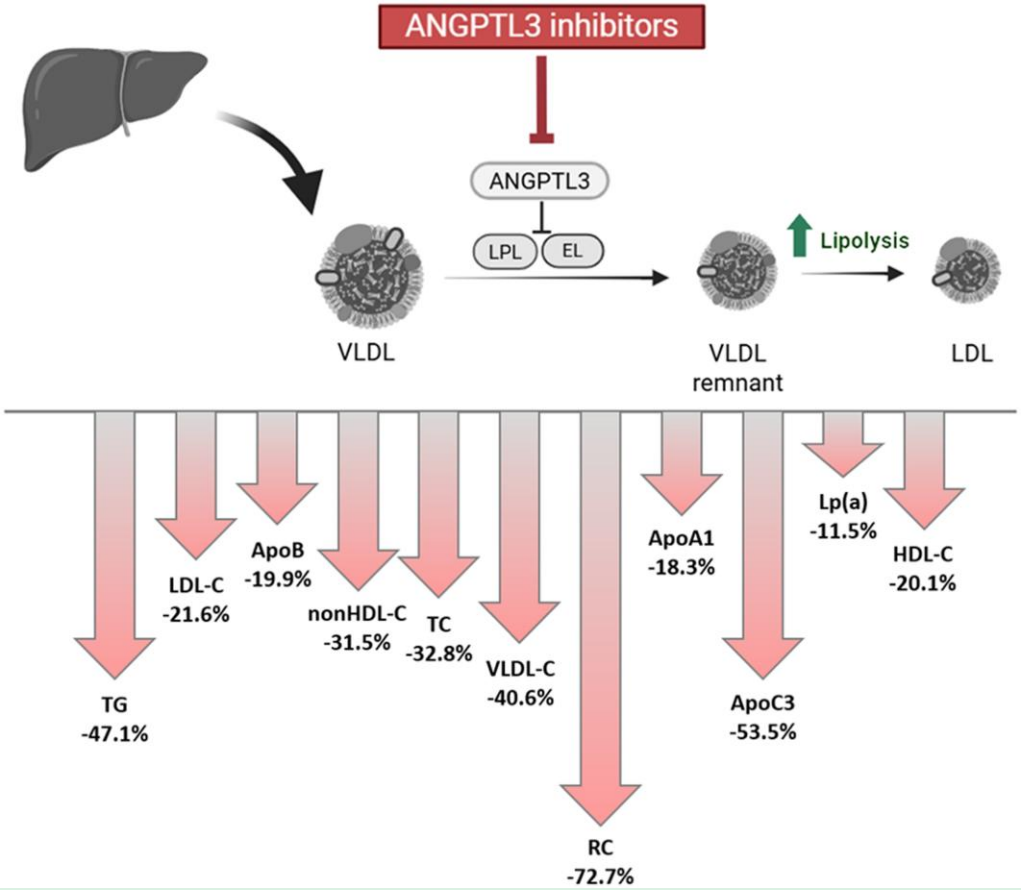
- These lipid improvements are particularly relevant for high-risk populations such as patients with familial hypercholesterolaemia or severe hypertriglyceridaemia, but evidence from large, long-term cardiovascular outcome trials is still needed to confirm clinical benefit.

Graphical Abstract



Keywords ANGPTL3 inhibitors • Lipid-lowering effect • Meta-analysis

Introduction

Hypercholesterolemia represents one of the most significant and well-established risk factors for the development of atherosclerotic cardiovascular disease.[1] Elevated levels of low-density lipoprotein cholesterol (LDL-C) play a central role in the initiation and progression of vascular injury, promoting plaque formation and subsequent cardiovascular events.[2] Over the past decades, substantial progress has been made in the development of pharmacological therapies aimed at reducing LDL-C concentrations, including statins, ezetimibe, and, more recently, PCSK9 inhibitors.[3] Nevertheless, despite these advances, a considerable residual risk of cardiovascular disease remains, particularly among patients who exhibit only partial or suboptimal responses to available treatments.[4] This therapeutic gap is even more pronounced in individuals affected by familial hypercholesterolemia (FH).[5] Standard lipid-lowering therapies often show reduced efficacy in this population, underscoring the urgent need for novel treatment strategies and more personalized approaches to lipid management.

Angiopoietin-like protein 3 (ANGPTL3) is a hepatically derived glycoprotein that plays a pivotal role in lipid metabolism by inhibiting both lipoprotein lipase (LPL) and endothelial lipase (EL), thereby regulating the catabolism of triglyceride-rich lipoproteins.[6] Genetic studies have demonstrated that individuals with loss-of-function variants in the *ANGPTL3* gene exhibit markedly reduced plasma concentrations of atherogenic lipoproteins and a significantly lower risk of atherosclerotic cardiovascular disease,[7] highlighting ANGPTL3 as a promising therapeutic target.

Pharmacological strategies to inhibit ANGPTL3 include monoclonal antibodies (mAbs, evinacumab), antisense oligonucleotides (ASOs, vupanorsen), and small interfering RNAs (siRNAs, zodasiran and solbinsiran), all of which aim to reduce ANGPTL3 expression or neutralize its activity.[8] Together, these agents represent complementary strategies to inhibit

ANGPTL3 activity and improve lipid profiles in patients with hypercholesterolemia.

Such therapies reduce both triglycerides (TG) and LDL-C, primarily by increasing the activity of LPL, leading to enhanced clearance of TG-rich lipoproteins and improved very-low-density lipoprotein (VLDL) composition, which reduces the pool of LDL precursors.[9] This unique mechanism provides a therapeutic advantage in populations with impaired LDL receptor (LDLR) function and may contribute to reducing residual cardiovascular risk beyond current standard-of-care treatments.[10] Given the variety of strategies that have been developed and evaluated in clinical trials to inhibit ANGPTL3, we conducted a meta-analysis of the currently available trials to summarize and synthesize the effects of these agents on different lipid parameters.

Materials and methods

We performed a meta-analysis according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[11] As our meta-analysis protocol has followed standard guidelines and is based on secondary data (already published), it does not require submission to the ethics committee.

Study selection and eligibility criteria

Inclusion criteria were: (1) randomized controlled trials (RCTs) in human; (2) English language and full-text available (abstracts were excluded); (3) comparing the effect of ANGPTL3 inhibitors (ANGPTL3i—evinacumab, vupanorsen, zodasiran, and solbinsiran) to placebo (addition of the same drug to both intervention and control group was acceptable); (4) reporting the effects on lipid levels (at least one among TG, LDL-C, apolipoprotein B [ApoB], non-high-density lipoprotein cholesterol [non-HDL-C], high-density lipoprotein cholesterol [HDL-C], total cholesterol [TC], VLDL-C, apolipoprotein A1 [ApoA1], apolipoprotein C3 [ApoC3], lipoprotein(a) [Lp(a)], remnant cholesterol [RC]) or other markers [ANGPTL3 and C-reactive protein (CRP)].

All selected articles and their supplementary materials were independently screened by two researchers (S.X. and F.G.), and any doubts were resolved by discussion with other members of the review group.

Search strategy and information sources

PubMed, EMBASE, Web of Science, CENTRAL, and ClinicalTrial.gov were searched from inception to July 2025. The following keywords were combined for literature searches: 'randomized controlled trials', 'ANGPTL3 inhibitors', 'evinacumab', 'vupanorsen', 'zodasiran', and 'solbinsiran' (searching strategies are shown in detail in the Supplementary File *S1*).

Data extraction and quality assessment

Data were extracted by using a predefined data collection form including the first author; year of publication; country; the number of participants and their main characteristics [e.g. sex, mean age; CV prevention (primary or secondary)]; intervention duration; treatment (active substance and dosage) and control; mean or median values and variance (standard deviation [SD], standard error [SE], interquartile range [IQR], 95% confidence interval [95%CI]) at baseline and follow-up, absolute change, or percentage change for lipid levels and other markers.

We evaluated the methodological quality of individual studies with the Cochrane risk of bias (RoB) tool.[12]

Data synthesis and statistical analysis

The between-group (treatment-placebo) percentage mean differences and their 95%CI were collected. We converted SE, IQR, and 95%CI to SD by using formulas recommended by Cochrane Handbook.[13] Multiple intervention groups were combined into a single intervention group when they were compared with a single control group in the trial (except those only reported placebo-controlled results). All data were presented as mean and SD.

Pooled estimates were assessed by using both the fixed-effects[14] and the random-effects[15] models. The generic inverse variance method was used to balance the heterogeneity between studies, and the restricted maximum likelihood estimator was used to estimate the between-study variance.[16] When significant heterogeneity was discovered (as determined by Cochrane's Q test and the I^2 statistic,[17] $P < 0.05$), the results from the random-effects model were presented.

An influence analysis was performed by omitting one study at a time, to determine how much a single study influenced the results.[18] Potential publication bias was visually assessed through funnel plot asymmetry,[19] also quantitatively evaluated by Begg's rank correlation[20] and Egger's weighted regression tests.[21]

Subgroup analysis was performed based on mechanism of action (mAbs, ASOs, siRNA). For evinacumab, an additional analysis was conducted according to administration route (IV: intravenous, SC: subcutaneous).

All tests were considered statistically significant for P-value less than 0.05. The analyses and the corresponding graphical visualization of forest and funnel plots were performed using R (version 4.3.2).

Results

Characteristics of included studies

The flow chart indicating the procedure of literature searching and study screening is shown in Supplementary material online, *Figure S1*. A total of 1254 subjects from 9 RCTs were included in our meta-analysis. The main characteristics of included studies are summarized in *Table 1*. Sample sizes of the included studies ranged from 12 to 281 participants. In terms of risk of bias, 5 (55.6%) trials were rated low risk, 4 (44.4%) unclear risk, and no high risk (see Supplementary material online, *Table S1*).

Meta-analysis results

As illustrated in *Figure 1*, ANGPTL3i significantly reduced TG by −47.10% (95%CI −54.73 to −39.46, data from 8 RCTs), LDL-C by −21.61% (95%CI −31.91 to −11.30, data from 9 RCTs), non-HDL-C by −31.45% (95%CI −38.24 to −24.67, data from 9 RCTs), and HDL-C by −20.08% (95%CI −22.98 to −17.19, data from 7 RCTs). For other lipids, TC was decreased by −32.83% (95%CI −40.89 to −24.77, data from 5 RCTs), VLDL-C by −40.61% (95%CI −50.39 to −30.83, data from 3

Table 1 Characteristics of the 9 trials included in the analysis

Trial	Year published	*n*	Enrolled subjects	Intervention group	Control group	Intervention duration	Mean age (years)	Sex (% Men)	FH (%)	LLTs (%)	Baseline LDL-C (mmol/L)	Baseline TG (mmol/L)
Harada-Shiba et al. (2020)[22]	2020	96	Healthy subjects	Evinacumab 5 or 15 mg/kg Q4W or Evinacumab 300 mg single-dose or QW	Placebo	8 weeks	38.8	58.3%	0.0%	0.0%	3.2	1.3
ELIPSE HoFH[23]	2020	65	Patients with homozygous familial hypercholesterolemia	Evinacumab 15 mg/kg Q4W	Placebo	24 weeks	41.7	46.2%	100.0% HoFH	Statins:94.0% PCSK9i: 77.0%	6.6	1.1
Rosenson et al. (2020)[24]	2020	266	Patients with refractory hypercholesterolemia	Evinacumab 5 or 15 mg/kg Q4W or Evinacumab 300 mg QW or Q2W or Evinacumab 450 mg QW	Placebo	16 weeks	54.2	40.2%	72.0% HeFH	Statins:62.0% PCSK9i: 100.0%	3.9	1.3
NCT03371355[25]	2021	105	Patients with hypertriglyceridemia	Vupanorsen 40 mg Q4W or Vupanorsen 80 mg Q4W or Vupanorsen 20 mg QW	Placebo	25–27 weeks	53.5	53.3%	0.0%	Statins: 45.7%	2.6	3.7
TRANSLATE-TIMI 70[26]	2022	281	Patients with hyperlipidaemia	Vupanorsen 80/120/160 mg Q4W or Vupanorsen 60/80/120/160 mg Q2W	Placebo	24 weeks	64.0	57.4%	0.0%	Statins: 50.7%	2.3	2.6
Fukuhara et al. (2023)[27]	2023	12	Patients with hypertriglyceridemia	Vupanorsen 80 or 160 mg single-dose	Placebo	15 days	50.0	100.0%	0.0%	0.0%	3.7	1.9
Rosenson et al. (2023)[28]	2023	51	Patients with severe hypertriglyceridemia	Evinacumab 15 mg/kg Q4W	Placebo	12 weeks	47.8	52.9%	0.0%	Statins: 51.0% Fibrates:65%	1.1	24.0
ARCHES-2[29]	2024	190	Patients with mixed hyperlipidaemia	Zodasiran 50 or 100 or 200 mg twice (day 1 and week 12)	Placebo	24 weeks	60.5	53.4%	0.0%	Statins: 96.1% PCSK9i: 1.0%	2.5	2.8
PROLONG-ANG3[30]	2025	204	Patients with mixed dyslipidaemia	Solbinsiran 100 or 400 or 800 mg twice (day 0 and day 90)	Placebo	180 days	57.0	45.9%	0.0%	Statins: 95.6%	3.2	2.6

HoFH, homozygous familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia.

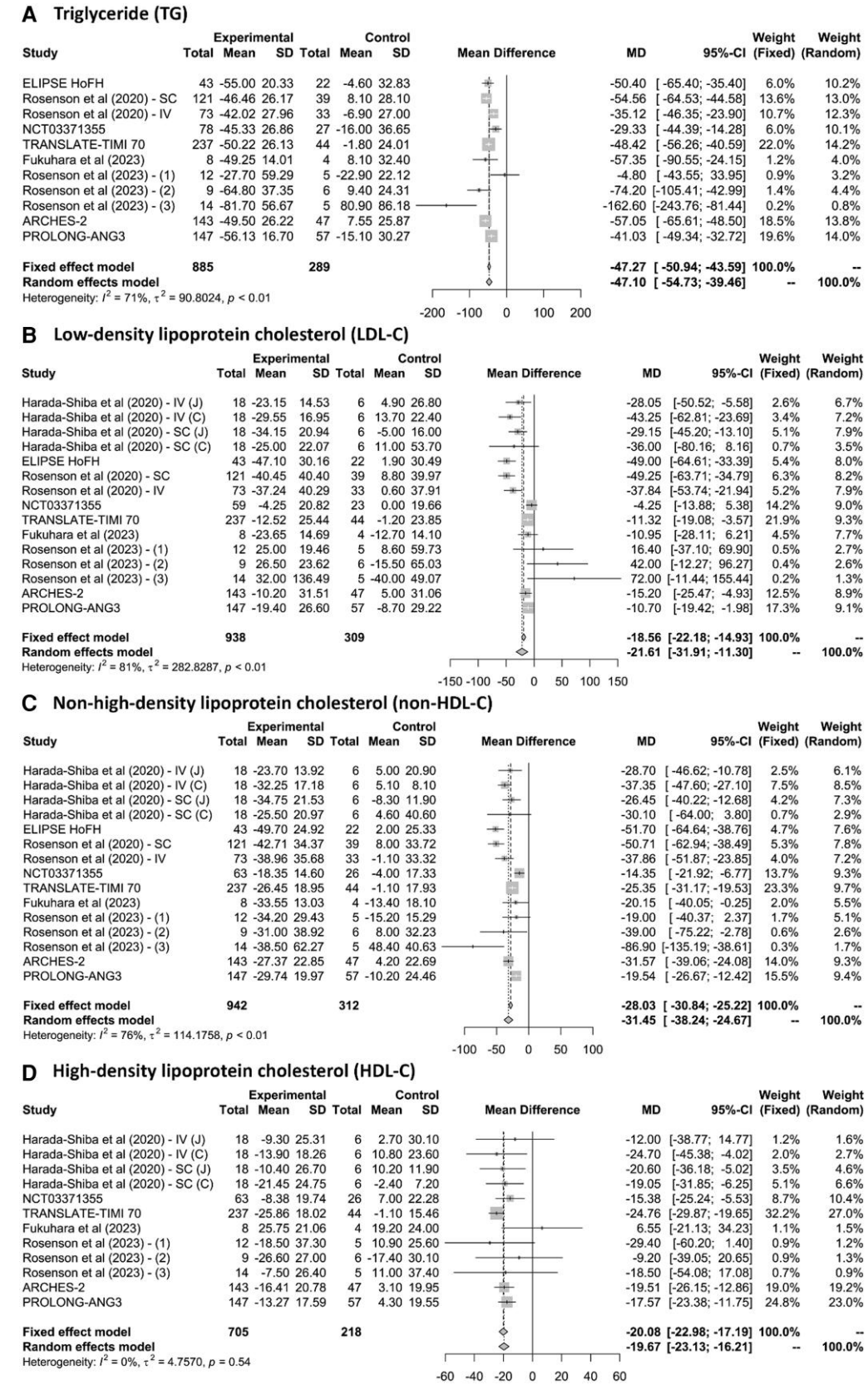


Figure 1 Effect of angiopoietin-like protein 3 (ANGPTL3) inhibitors on lipid levels. Forest plots indicate the impact of ANGPTL3 inhibitors on TG (*A*), LDL-C (*B*), non-HDL-C (*C*), and HDL-C (*D*) levels. The trials are sorted by published year. The pooled estimate and 95% confidence intervals were represented by the centre line and lateral tips of the diamond and shown in percentage mean differences (%). CI: confidence interval; MD: mean difference; SD: standard deviation.

RCTs), RC by −72.67% (95%CI −98.71 to −46.63, data from 2 RCTs), and Lp(a) by −11.48% (95%CI −15.09 to −7.87, data from 5 RCTs), as shown in *Figure 2*. They also reduced ApoB by −19.90% (95%CI −25.68 to −14.12, data from 9 RCTs), ApoA1 by −18.30% (95%CI −23.76 to −12.85, data from 5 RCTs) and ApoC3 by −53.49% (95%CI −64.90 to −42.08, data from 6 RCTs) (*Figure 3*). ANGPTL3 was reduced by −70.71% (95%CI −80.49 to −60.92, data from 5 RCTs). No significant effect on CRP levels was observed [−7.87% (95%CI −27.18 to 11.44), data from 2 RCTs] (*Figure 4*).

No publication bias was found when evaluating funnel plot asymmetry through quantitative analysis (Begg's rank correlation and Egger's linear regression tests) for all outcomes (see Supplementary material online, *Figure S2* and Supplementary material online, *Table S2*).

Influence analyses illustrated that no appreciable impact on pooled estimates was observed omitting one study at a time for all outcomes, as shown in Supplementary material online, *Figure S3*.

Subgroup analysis

In the subgroup analysis by mechanism of action, patients treated with evinacumab experienced larger reductions in LDL-C, non-HDL-C, and ApoB compared with the other groups (−31.95% [95%CI −44.08 to −19.81], $P < 0.01$; −38.38% [95% CI −46.27 to −30.50], $P < 0.01$; and −27.74% [95%CI −32.34 to −23.14], $P < 0.01$, respectively). Larger VLDL-C decrease was observed in patients treated with siRNA than vupanorsen (−48.22% vs. 29.45%, $P < 0.01$). No differences regarding TG ($P = 0.76$), HDL-C ($P = 0.53$), RC ($P = 0.94$), Lp(a) [$P = 0.28$], ApoA1 ($P = 0.43$), ApoC3 ($P = 0.18$), ANGPTL3 ($P = 0.42$), and CRP ($P = 0.92$) levels. All the results are shown in Supplementary material online, *Figure S4*, Supplementary material online, *Figure S5*, Supplementary material online, *Figure S6* and Supplementary material online, *Figure S7*.

In the subgroup analysis by administration route for evinacumab, no differences were found for all the outcomes, as illustrated in Supplementary material online, *Figure S8*.

Discussion

Our meta-analysis provides a comprehensive synthesis of currently available clinical evidence regarding the efficacy of ANGPTL3 inhibition on lipid parameters in patients with dyslipidaemia. Our findings confirm that pharmacological strategies targeting ANGPTL3, regardless of the molecular approach employed, are consistently associated with significant improvements in the lipid profile. Specifically, ANGPTL3i demonstrated robust reductions in plasma TG concentrations, moderate decreases in LDL-C, and variable effects on other lipid fractions. These results highlight the therapeutic potential of this novel drug class, particularly in populations with limited responses to conventional lipid-lowering therapies.

Triglyceride lowering: comparison with existing therapies

We confirmed the pronounced effect of ANGPTL3 inhibition on TG levels, with an overall reduction of −47.10%, with no significant differences across diverse ANGPTL3 inhibition approaches. Our pooled estimates are consistent with the findings reported by Jin et al. in their meta-analysis focusing exclusively on evinacumab.[31] The ability of evinacumab to reduce triglyceride levels has been confirmed across trials, despite the heterogeneity in baseline TG values, and our leave-one-out sensitivity analysis reinforces the robustness of our meta-analysis results. Elevated TG concentrations have emerged as an independent risk factor for atherosclerotic cardiovascular disease.[32,33] ANGPTL3 inhibition represents a promising alternative, as the magnitude of TG reduction observed across the analysed trials in comparable to that typically achieved with fibrates,[33,34] and it occurs independently of LDLR activity. Moreover, the dual inhibition of LPL and EL by ANGPTL3 blockade suggests a broader metabolic impact that may extend beyond TG lowering, potentially contributing to an improved cardiometabolic profile.

LDL-C lowering and LDLR-independent mechanism

Although the reduction in LDL-C achieved with ANGPTL3i is not as pronounced as that obtained with statins or PCSK9 inhibitors, our results demonstrate a consistent and clinically relevant lowering of LDL-C levels, more pronounced for evinacumab compared with the other ANGPTL3i. Importantly, this effect occurs through an LDLR-independent pathway, which distinguishes ANGPTL3ifrom the majority of currently available lipid-lowering drugs. This feature is particularly relevant in patients with FH, where LDLR function is impaired and therapeutic options remain limited.[35] In these high-risk populations, even modest LDL-C reductions can translate into meaningful reductions in cardiovascular risk, especially when combined with therapies acting via LDLR-dependent mechanisms.[36] One population that could particularly benefit from this approach is patients with FH. Two included trials specifically enrolled FH patients: one in homozygous FH,[23] and another in a mixed population with ∼75% heterozygous FH.[24] In the former trial,[23] the mean baseline LDL-C was ∼255 mg/dL despite intensive lipid-lowering therapy, and at 24 weeks evinacumab yielded a mean relative LDL-C reduction of 47.1% (vs. +1.9% with placebo), corresponding to an absolute difference of about −132.1 mg/dL. In the latter,[24] at week 16 the reductions with evinacumab across various doses ranged from −38.5% to −56.0% vs. placebo, depending on route and dose. These results support that ANGPTL3 inhibition is effective also in FH subjects.

Broader lipid effects

Beyond TG and LDL-C, ANGPTL3 inhibition clearly showed reductions in VLDL-C and ApoB, and a mild although significant reduction in Lp(a). Collectively, these shifts suggest a global improvement in the atherogenic lipid profile, which may contribute to cardiovascular benefit.[37] However, further investigation are warranted to unravel the precise metabolic consequences of ANGPTL3 blockade.[38] By blocking ANGPTL3, either with mAbs, ASOs, or siRNAs, LPL activity is preserved, resulting in enhanced hydrolysis of TG, accelerated clearance of VLDL and chylomicrons, and a subsequent reduction in plasma TG, LDL-C, and non-HDL-C.

The pharmacological inhibition of ANGPTL3 needs to be interpreted in the context of its functional interaction with

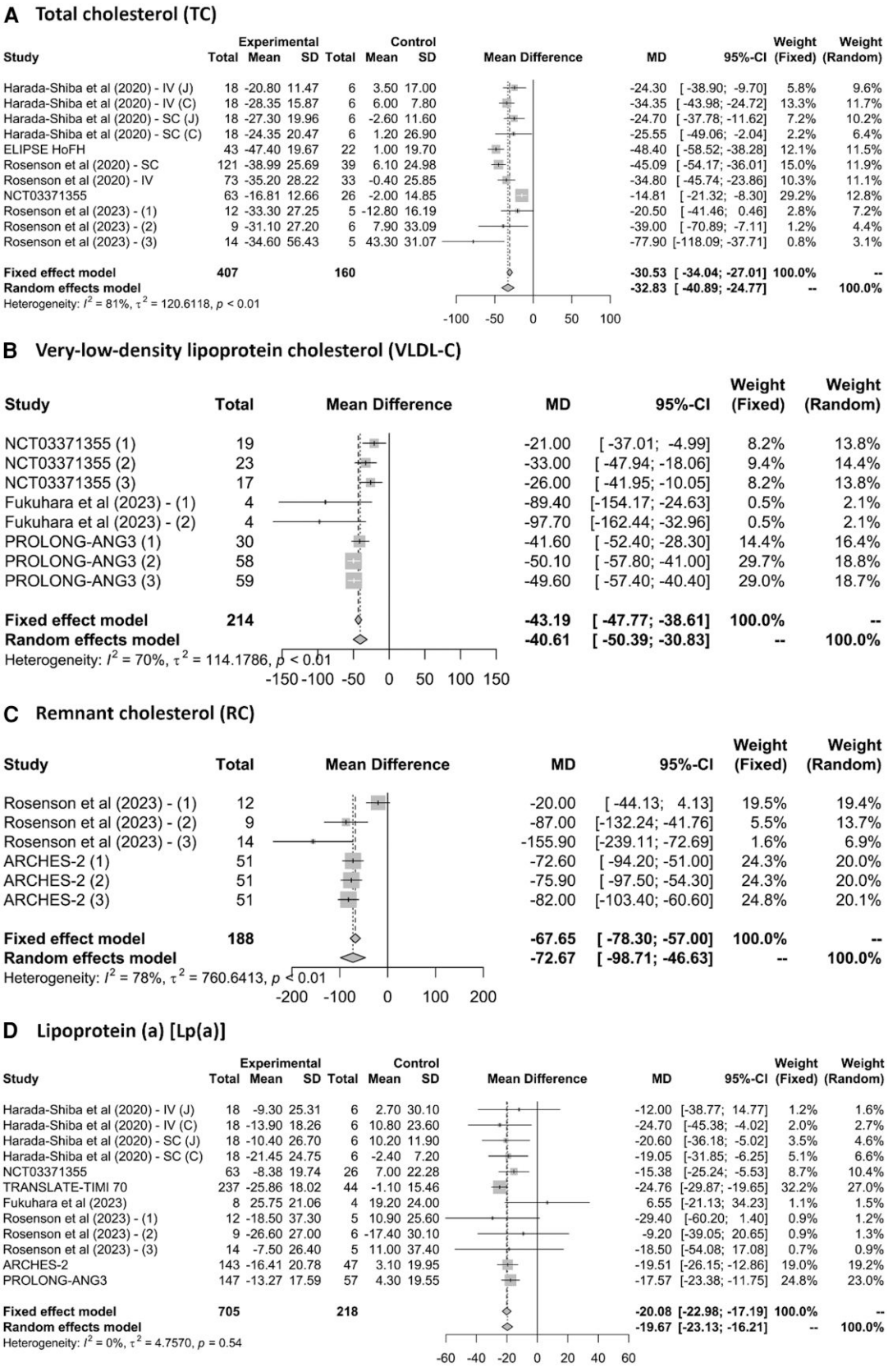


Figure 2 Effect of angiopoietin-like protein 3 (ANGPTL3) inhibitors on other lipid levels. Forest plots indicate the impact of ANGPTL3 inhibitors on TC (*A*), VLDL-C (*B*), RC (*C*), and Lp(a) (*D*) levels. The trials are sorted by published year. The pooled estimate and 95% confidence intervals were represented by the centre line and lateral tips of the diamond and shown in percentage mean differences (%). CI: confidence interval; MD: mean difference; SD: standard deviation.

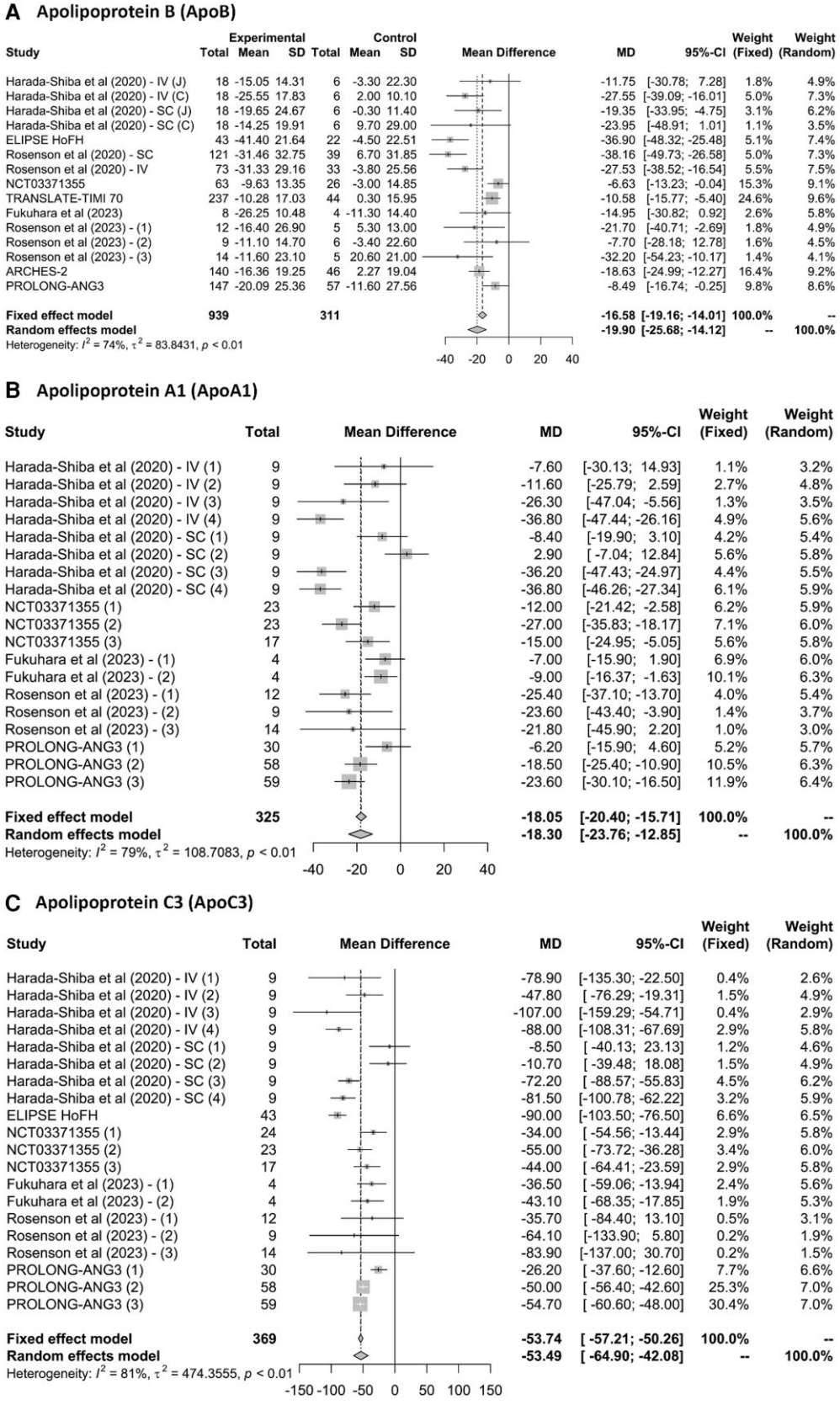


Figure 3 Effect of angiopoietin-like protein 3 (ANGPTL3) inhibitors on apolipoprotein levels. Forest plots indicate the impact of ANGPTL3 inhibitors on ApoB (*A*), ApoA1 (*B*), and ApoC3 (*C*) levels. The trials are sorted by published year. The pooled estimate and 95% confidence intervals were represented by the centre line and lateral tips of the diamond and shown in percentage mean differences (%). CI: confidence interval; MD: mean difference; SD: standard deviation.

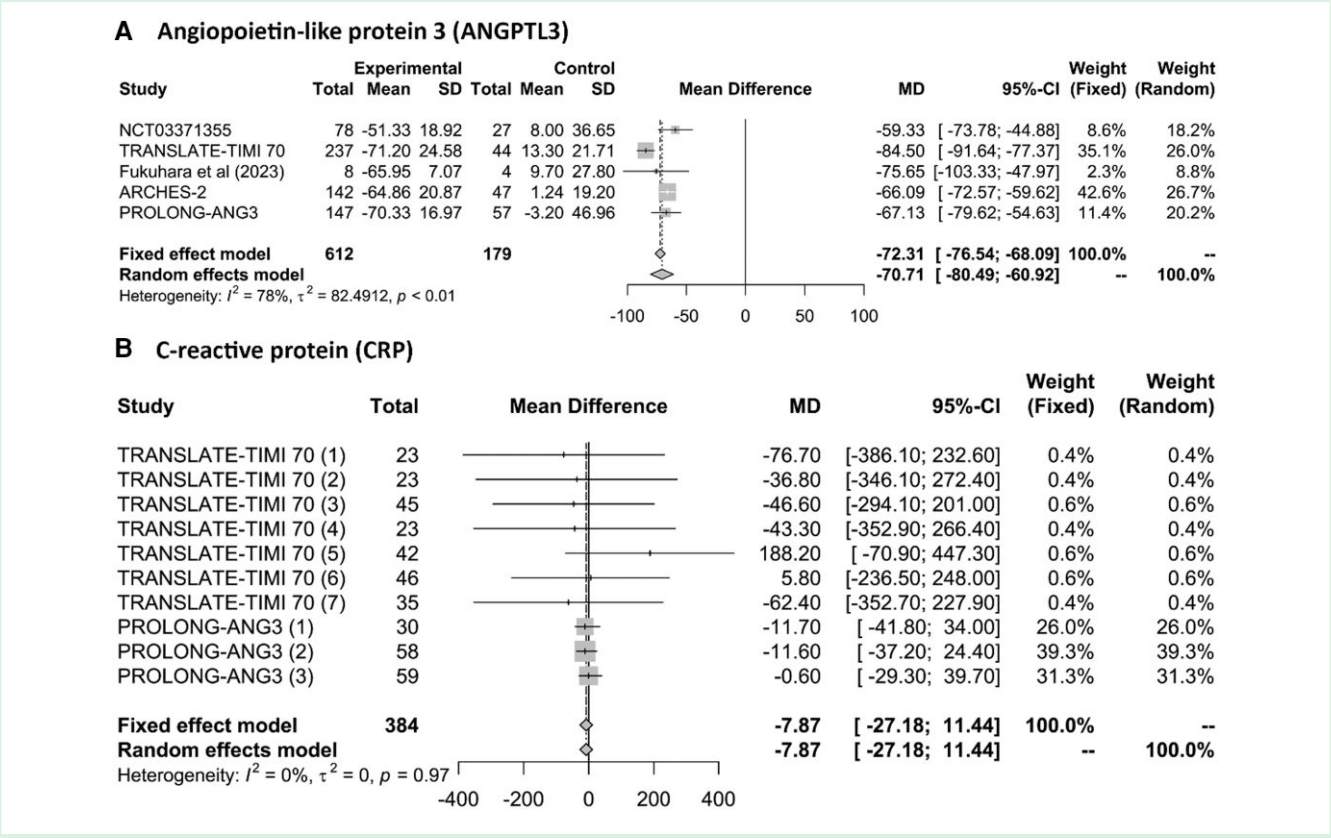


Figure 4 Effect of angiopoietin-like protein 3 (ANGPTL3) inhibitors on other markers. Forest plots indicate the impact of ANGPTL3 inhibitors on ANGPTL3 (*A*) and CRP (*B*) levels. The trials are sorted by published year. The pooled estimate and 95% confidence intervals were represented by the centre line and lateral tips of the diamond and shown in percentage mean differences (%). CI: confidence interval; MD: mean difference; SD: standard deviation.

ANGPTL8. ANGPTL3, secreted primarily by the liver, plays a central role in lipid metabolism through the inhibition of LPL and EL. However, ANGPTL3 activity is markedly potentiated by its binding partner ANGPTL8, which is induced in the fed state and forms a functional complex with ANGPTL3 to inhibit LPL specifically in adipose tissue, promoting lipid partitioning toward storage. This interaction suggests that the metabolic consequences of ANGPTL3 inhibition may depend, at least in part, on the presence and regulation of ANGPTL8.[39] Indeed, experimental evidence indicates that ANGPTL3 inhibitors may have differential effects on TG metabolism depending on nutritional status or ANGPTL8 expression, raising the possibility that therapeutic outcomes could vary across patient populations.[8] Importantly, since ANGPTL8 does not act independently but requires ANGPTL3 to exert its LPL inhibitory function, targeting ANGPTL8 rather than ANGPTL3 may allow preservation of other potential ANGPTL3 functions unrelated to the ANGPTL3–ANGPTL8 complex, offering a more selective strategy. This concept is supported by the results of a phase 1 trial of the dual ANGPTL3/ANGPTL8 inhibitor LY3475766. Compared with placebo, LY3475766 dose-dependently reduced triglycerides (–70%), remnant cholesterol (–86%), LDL-C (–32%), non-HDL-C (–35%), and apolipoprotein B (–29%), while increasing HDL-C (+27%).[40] These lipid-lowering effects appear more pronounced than those observed in our meta-analysis of ANGPTL3 inhibitors alone. However, if compared with evinacumab, the lipid effects do not differ materially; yet, phase 1 data need to be confirmed at following stages of development. In addition to pharmacological inhibition, gene therapy-based approaches targeting ANGPTL3 are emerging as promising lipid-lowering strategies. Preclinical studies and early-phase clinical trials using gene editing and gene silencing technologies, including CRISPR-based approaches and siRNA therapies, have demonstrated substantial and sustained reductions in TG, LDL-C, and other atherogenic lipoproteins following a single administration.[41] These strategies may offer the potential for long-lasting lipid control and improved treatment adherence. However, their long-term efficacy and safety still need to be established in larger clinical studies.[42]

Clinical utility

From a clinical perspective, the introduction of ANGPTL3icould represent a valuable addition to the therapeutic armamentarium for dyslipidaemia, particularly in individuals who are either intolerant to existing therapies or who fail to achieve adequate lipid control despite maximal treatment.[43] Patients with homozygous or heterozygous FH may derive particular benefit given the LDLR-independent mechanism of action.[10] Furthermore, the substantial TG-lowering effect raises the possibility of

targeting populations with severe hypertriglyceridaemia, in whom pancreatitis risk is a major concern.[44] Nevertheless, the translation of lipid-lowering efficacy into cardiovascular outcome benefits still needs to be conclusively demonstrated in large, long-term studies. Regarding safety, adverse events were reported in all included RCTs according to standard clinical trial reporting. Although a formal quantitative analysis of adverse events was beyond the scope of the present meta-analysis, the individual trials did not identify major safety concerns or clinically relevant treatment discontinuation associated with ANGPTL3 inhibitors (see Supplementary material online, *Table S3*). Nevertheless, given the relatively small sample sizes and the short duration of follow-up in most studies, larger and longer-term trials will be necessary to better characterize the safety profile of these agents.

Strengths and limitations

This meta-analysis offers an updated and systematic assessment of the available evidence, pooling data across diverse trials and molecular approaches. A strength of our work lies in the inclusion of multiple ANGPTL3-targeting strategies, thereby providing a comprehensive overview of their shared and distinct effects. However, several limitations must be acknowledged. First, the number of clinical trials currently available is limited, with relatively small sample sizes and heterogeneous patient populations which might have contributed the differences among the different drugs evaluated. Moreover, the limited number of studies restricts our ability to perform meaningful subgroup analyses, for example by baseline lipid profile or underlying conditions such as familial hypercholesterolaemia. Therefore, while the results are encouraging, they should be considered exploratory, and conclusions remain to be confirmed. Second, the duration of follow-up in most studies was short, precluding conclusions on long-term efficacy and safety. Third, as for all meta-analyses, differences in trial design, background therapy, and endpoints introduce a degree of variability that may have influenced our pooled estimates.

In summary, the results of this meta-analysis demonstrate that ANGPTL3 inhibition produces substantial improvements in lipid parameters, with particularly marked reductions in TG and modest but clinically valuable decreases in LDL-C via an LDLR-independent pathway. These effects support the potential role of ANGPTL3-targeting therapies as an innovative option in the management of patients with dyslipidaemia, especially those with residual risk despite standard treatment or with genetic disorders affecting LDLR function. Future large-scale and long-term outcome trials are required to confirm the cardiovascular benefits and safety profile of this therapeutic approach.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Author contributions

Sining Xie (Conceptualization [lead], Data curation, Formal analysis, Writing—original draft [equal], Methodology [supporting]), Federica Galimberti [Data curation, Writing—review & editing (equal)], Elena Olmastroni (Formal analysis, Writing—review & editing [equal], Methodology [lead]), Alberico L Catapano (Supervision [lead], Writing—review & editing [equal]), and Manuela Casula (Supervision [supporting], Writing—original draft [equal]).

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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