

Triglyceride concentrations and non-high-density lipoprotein cholesterol goal attainment in the ODYSSEY phase 3 trials with alirocumab

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Abstract

Aims: Guidelines recommend targeting non-high-density lipoprotein cholesterol to reduce cardiovascular risk. We assessed the impact of baseline triglycerides on non-high-density lipoprotein cholesterol goal attainment in 10 phase 3 trials with alirocumab versus control ($n = 4983$).

Methods: Trials were grouped into four pools based on alirocumab dose (75–150 mg every 2 weeks), control (placebo/ezetimibe) and statin use. Baseline triglyceride quintiles were built within each pool. Non-high-density lipoprotein cholesterol goal attainment (very high risk: <100 mg/dl; moderate/high risk: <130 mg/dl), low-density lipoprotein cholesterol goal attainment (very high risk: <70 mg/dl; moderate/high risk: <100 mg/dl) and changes from baseline in lipid parameters were assessed at Week 24 among baseline triglyceride quintiles.

Results: Higher baseline triglycerides were associated with a worse cardiovascular risk profile. Low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol increased with higher triglycerides, but the magnitude in non-high-density lipoprotein cholesterol was three- to four-fold higher compared with the increase in low-density lipoprotein cholesterol. Non-high-density lipoprotein cholesterol and low-density lipoprotein cholesterol percentage reductions from baseline with alirocumab were similar regardless of baseline triglycerides. A greater proportion of alirocumab-treated patients attained non-high-density lipoprotein cholesterol and low-density lipoprotein cholesterol goals compared with placebo or ezetimibe. Unlike low-density lipoprotein cholesterol goal attainment, non-high-density lipoprotein cholesterol goal attainment significantly declined with increasing baseline triglycerides ($p < 0.05$ for trend tests). A single standard deviation increase in baseline log(triglycerides) was significantly associated with lower odds ratios of attaining non-high-density lipoprotein cholesterol goals in the different pools and treatment (alirocumab/placebo/ezetimibe) groups, unlike low-density lipoprotein cholesterol goal attainment.

Conclusion: Individuals with increased triglycerides have higher non-high-density lipoprotein cholesterol levels and lower rates of non-high-density lipoprotein cholesterol goal attainment (unlike low-density lipoprotein cholesterol goal attainment). Alirocumab improves non-high-density lipoprotein cholesterol goal attainment in this population. These results highlight the impact of triglycerides on non-high-density lipoprotein cholesterol and the need for novel therapies targeting triglyceride-related pathways.

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Introduction

Non-high-density lipoprotein cholesterol (non-HDL-C) comprises the cholesterol carried by pro-atherogenic, apolipoprotein B (apoB)-containing particles, including low-density lipoprotein cholesterol (LDL-C), intermediate-density lipoprotein cholesterol and very low-density lipoprotein cholesterol and their remnants, chylomicron particles and lipoprotein(a).¹ Non-HDL-C levels have been more strongly associated with risk of cardiovascular events and atherosclerosis than LDL-C.^{1,2} Hence, although LDL-C remains the main target for lipid-lowering therapy (LLT), guidelines also recommend non-HDL-C as a secondary target in an attempt to further reduce cardiovascular (residual) risk, especially among patients with diabetes, obesity or metabolic syndrome, where a phenotype consisting of increased levels of non-HDL-C and triglycerides (TGs) and low high-density lipoprotein cholesterol (HDL-C) levels is frequently described.^{3–5} The portion of non-HDL-C that does not include LDL-C is represented by the cholesterol in triglyceride-rich lipoprotein cholesterol (TRL-C), which has been proposed to contribute to increased atherogenic risk and correlate with TG levels.⁶

Attainment of non-HDL-C targets among individuals with diabetes receiving statins was previously shown to be inversely correlated with TG levels,⁷ suggesting that additional LLTs may be required for high-risk patients with elevated TG levels to further clear atherogenic particles and reduce their residual cardiovascular risk. In the present study, we sought to determine whether alirocumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, would be more effective than statins alone or statins plus ezetimibe at attaining non-HDL-C goals among individuals with the highest levels of baseline TGs who were collectively studied in 10 phase 3 ODYSSEY clinical trials.

Methods

This analysis is based on pooled data from 10 randomised, double-blind, phase 3 ODYSSEY trials with alirocumab versus control (placebo or ezetimibe).^{8–16} Patients with TG levels >4.52 mmol/l (400 mg/dl) were excluded; further patient details are provided in the Supplementary Material. Trials were grouped into four pools based on alirocumab dose, control and

whether patients were receiving background statin therapy, as shown in Figure 1.

Quintiles of baseline TG levels (Q1–Q5) were built within each of the four pools. We assessed the percentage of patients in each pool who achieved cardiovascular risk-based non-HDL-C and/or LDL-C goals after 24 weeks of treatment, per quintiles of baseline TG levels. Goals were defined as non-HDL-C <3.36 mmol/l (130 mg/dl) and LDL-C <2.59 mmol/l (100 mg/dl) in patients with moderate/high cardiovascular risk, and non-HDL-C <2.59 mmol/l (100 mg/dl) and LDL-C <1.81 mmol/l (70 mg/dl) in patients with very high cardiovascular risk, according to guideline recommendations at the time of conducting the trials.⁴ By way of comparison, we also explored the percentage of patients achieving goals by quintiles of baseline TRL-C levels, since TGs and TRL-C levels correlate strongly between them (Supplementary Material Table 1).^{6,17}

Fasting lipid levels were measured in the present trials. LDL-C was calculated using the Friedewald equation unless TG levels were >4.52 mmol/l (400 mg/dl) (in such cases, LDL-C was determined using beta-quantification; however, such values were not included in this calculated LDL-C analysis). In the majority of ODYSSEY trials (except HIGH FH and MONO trials) LDL-C was also assessed directly by beta-quantification at Weeks 0 and 24 (termed ‘directly measured LDL-C’ in this report). By way of comparison, sensitivity analyses using these directly measured LDL-C levels were conducted as well. Non-HDL-C levels were calculated as total cholesterol minus HDL-C. TRL-C levels were derived by non-HDL-C minus LDL-C, and by way of comparison, ‘directly measured TRL-C’ levels were derived by non-HDL-C minus directly measured LDL-C as previously described.¹⁸

Statistical analyses

Efficacy data were analysed in the intention-to-treat population. Percentage/absolute changes in lipids were analysed using a mixed-effect model with repeated measures (MMRM) to account for missing data, except for TRL-C levels which were analysed using multiple imputation followed by robust regression. For analysis of goal achievement across baseline TG quintiles, *p*-values were computed using the Cochran-Armitage test for trend. The Breslow and Day test was used to

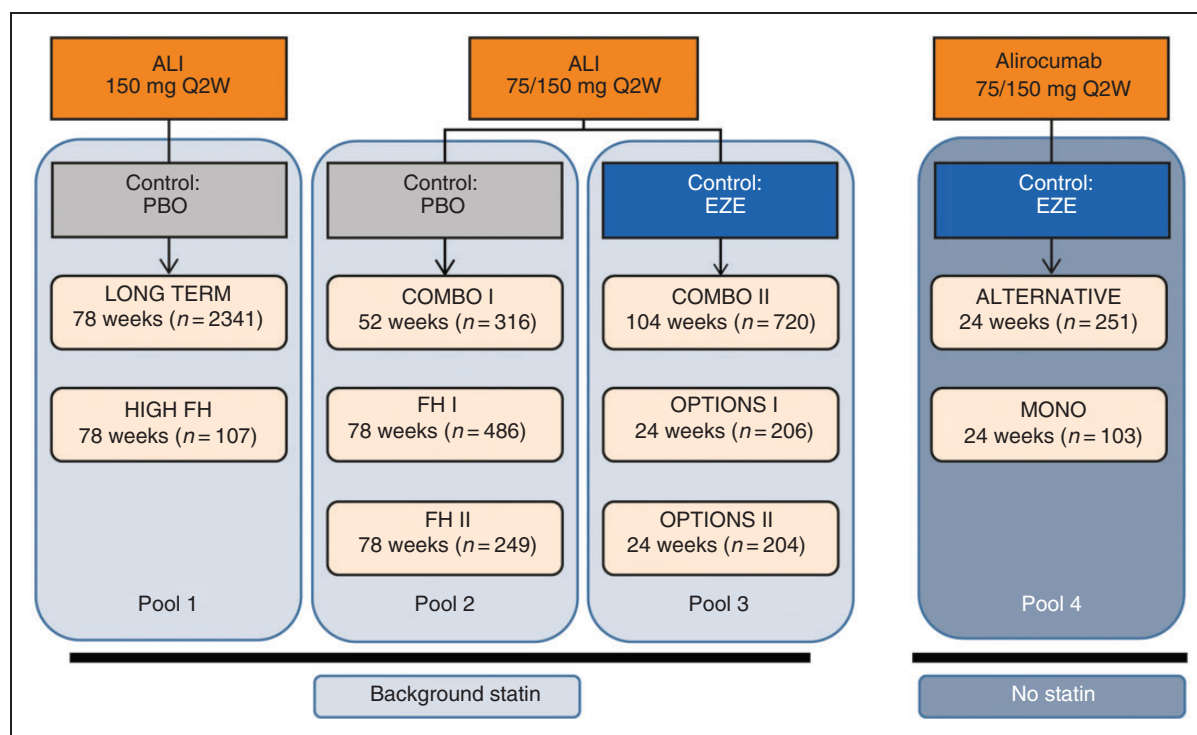


Figure 1. Overview of ODYSSEY trials included in this analysis.

Pool 1 ($n = 2448$) included two studies comparing alirocumab 150 mg every two weeks (Q2W) versus placebo, on background statin therapy. Pools 2–4 used a dose-increase strategy whereby the alirocumab starting dose of 75 mg Q2W was increased to 150 mg Q2W at study Week 12, based on achievement of prespecified low-density lipoprotein cholesterol (LDL-C) levels at Week 8 (denoted as 75/150 mg). Pool 2 ($n = 1051$) included three studies comparing alirocumab (ALI) 75/150 mg Q2W versus placebo (PBO) on background statins; pool 3 ($n = 1130$) included three studies comparing ALI 75/150 mg Q2W versus ezetimibe (EZE) on background statins; pool 4 ($n = 354$) included two studies comparing ALI 75/150 mg versus EZE with no background statins. Further details are described in the Supplementary Material Methods. ALI 75/150 denotes that the dose could be increased from 75 to 150 mg at Week 12 depending on Week 8 LDL-C levels.

test homogeneity of the odds ratios (ORs), measuring the association between goal attainment and treatment (alirocumab versus control) across the quintiles. ORs for LDL-C and non-HDL-C goal attainment associated with a one standard deviation (SD) increase of $\log(\text{TG})$ at baseline were derived by treatment arm from a logistic regression model analysis. For the analysis of change from baseline in lipids at Week 24, least-squares means and standard errors (SEs) were taken from an MMRM analysis as previously described¹⁵ (except for TRL-C, where adjusted means and SEs were obtained by combining adjusted means and SEs from robust regression model analyses of the different imputed data sets). Further details on the statistical analysis are described in the Supplementary Material.

Results

Baseline characteristics

A total of 4983 patients with elevated LDL-C were randomised across the 10 studies and analysed in four

pooled groups according to study design (Figure 1). Baseline characteristics for each pool are shown in Table 1 (further details are shown in the Supplementary Material). Baseline characteristics stratified by baseline TG quintiles are shown in Supplementary Material Table 2 and Figure 2(a) (lipids). Briefly, within each pool, increasing quintiles of baseline TGs were associated with a higher prevalence of hypertension ($p \leq 0.002$) and a more adverse metabolic profile consisting of higher body mass index (BMI; $p < 0.0001$), higher levels of fasting glucose, glycated haemoglobin (HbA1c) and prevalence of diabetes ($p \leq 0.0007$), increased LDL-C ($p < 0.04$) and non-HDL-C, TRL-C and apoB ($p < 0.0001$), and decreased levels of HDL-C and apoA1 ($p \leq 0.005$). Further details are described in the Supplementary Material.

Changes in lipid parameters

At Week 24, overall percentage reductions with alirocumab versus control in LDL-C, non-HDL-C and

Table 1. Patient baseline characteristics and lipid levels.

| | Pool 1 LONG TERM + HIGH FH (ALI 150 vs PBO with statin) n = 2448 | Pool 2 COMBO I + FH I/II (ALI 75/150 vs PBO with statin) n = 1051 | Pool 3 COMBO II + OPTIONS I/II (ALI 75/150 vs EZE with statin) n = 1130 | Pool 4 ALTERNATIVE + MONO (ALI 75/150 vs EZE no statin) n = 354 |
|--|---|--|--|--|
| Age, years, mean (SD) | 60.1 (10.7) | 55.6 (12.8) | 61.9 (9.7) | 62.5 (8.6) |
| Males, n (%) | 1514 (61.8) | 613 (58.3) | 777 (68.8) | 192 (54.2) |
| Race, white, n (%) | 2265 (92.5) | 946 (90.0) | 967 (85.6) | 326 (92.1) |
| Body mass index, kg/m ² , mean (SD) | 30.2 (5.6) | 30.0 (5.7) | 30.5 (5.8) | 29.0 (6.0) |
| Hypertension, n (%) | 1822 (74.4) | 571 (54.3) | 887 (78.5) | 194 (54.6) |
| Type 2 diabetes, n (%) | 827 (33.8) | 203 (19.3) | 405 (35.8) | 64 (18.0) |
| Smoking, n (%) | 506 (20.7) | 178 (16.9) | 237 (21.0) | 27 (7.6) |
| Heterozygous familial hypercholesterolaemia, n (%) | 522 (21.3) | 735 (69.9) | 44 (3.9) | 39 (11.0) |
| Baseline lipids, mmol/l | | | | |
| Calculated LDL-C (Friedewald equation), mean (SD) | 3.26 (1.18) | 3.35 (1.21) | 2.79 (0.93) | 4.58 (1.72) |
| Directly measured LDL-C (beta-quantification), mean (SD) | 3.02 (1.00) | 3.29 (1.18) | 2.68 (0.90) | 4.75 (1.86) |
| Apolipoprotein B, mean (SD) | 103.4 (28.8) | 105.9 (28.8) | 93.5 (23.2) | 129.8 (37.6) |
| Non-HDL-C, mean (SD) | 4.03 (1.27) | 4.03 (1.28) | 3.57 (1.05) | 5.47 (1.97) |
| HDL-C, mean (SD) | 1.29 (0.32) | 1.30 (0.39) | 1.25 (0.34) | 1.34 (0.42) |
| Triglycerides, median | 1.50 | 1.26 | 1.48 | 1.55 |
| Triglyceride quintiles | | | | |
| Q1 | ≥0.35–<0.98 | ≥0.40–<0.89 | ≥0.52–<1.02 | ≥0.41–1.00 |
| Q2 | 0.98–≤1.33 | ≥0.89–<1.15 | ≥1.02–<1.33 | ≥1.00–<1.37 |
| Q3 | 1.33–≤1.70 | ≥1.15–<1.45 | ≥1.33–<1.67 | ≥1.37–<1.78 |
| Q4 | >1.70–≤2.30 | ≥1.45–<1.98 | ≥1.67–<2.27 | ≥1.78–<2.57 |
| Q5 | >2.30–≤16.05 | ≥1.98–<11.28 | ≥2.27–<6.37 | ≥2.57–<8.21 |

ALI: alirocumab; EZE: ezetimibe; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; PBO: placebo; SD: standard deviation.

To convert cholesterol and triglycerides to mg/dl, multiply by 0.02586 and 0.01129, respectively. Values in each column are combined data for patients randomised to alirocumab and control. ALI 75/150 denotes that the dose could be increased from 75 to 150 mg at Week 12 depending on Week 8 LDL-C levels.

apoB were significant in all study pools (all $p < 0.0001$; Supplementary Material Table 3). For HDL-C, percentage increases were significant in all study pools (all $p < 0.0001$) except in pool 4. Percentage reductions in TGs and TRL-C were significant in the alirocumab versus placebo pools (all $p < 0.0001$) but not in the alirocumab versus ezetimibe pools.

Absolute changes from baseline at Week 24 in LDL-C, non-HDL-C, HDL-C and TRL-C by baseline TG quintiles are shown in Figure 2(b) (and for apoB in Supplementary Material Figure 1). Significant reductions in LDL-C, non-HDL-C and apoB were observed with alirocumab treatment compared with controls across all TG quintiles, with no systematic trend towards

higher or lower magnitude of changes with increasing TG quintiles overall (except for pool 4 where a larger mean reduction from baseline was observed for LDL-C and non-HDL-C with increasing TG quintiles with alirocumab versus control). Percentage changes in LDL-C, non-HDL-C, HDL-C, TRL-C and apoB were similar across baseline TG quintiles (Supplementary Material Figure 2(a) and (b), respectively).

Absolute reductions in directly measured LDL-C and TRL-C are shown in Supplementary Material Figure 3 and S4, respectively. In general, unlike calculated TRL-C, the magnitude of the reductions in directly measured TRL-C declined as baseline TG levels increased.

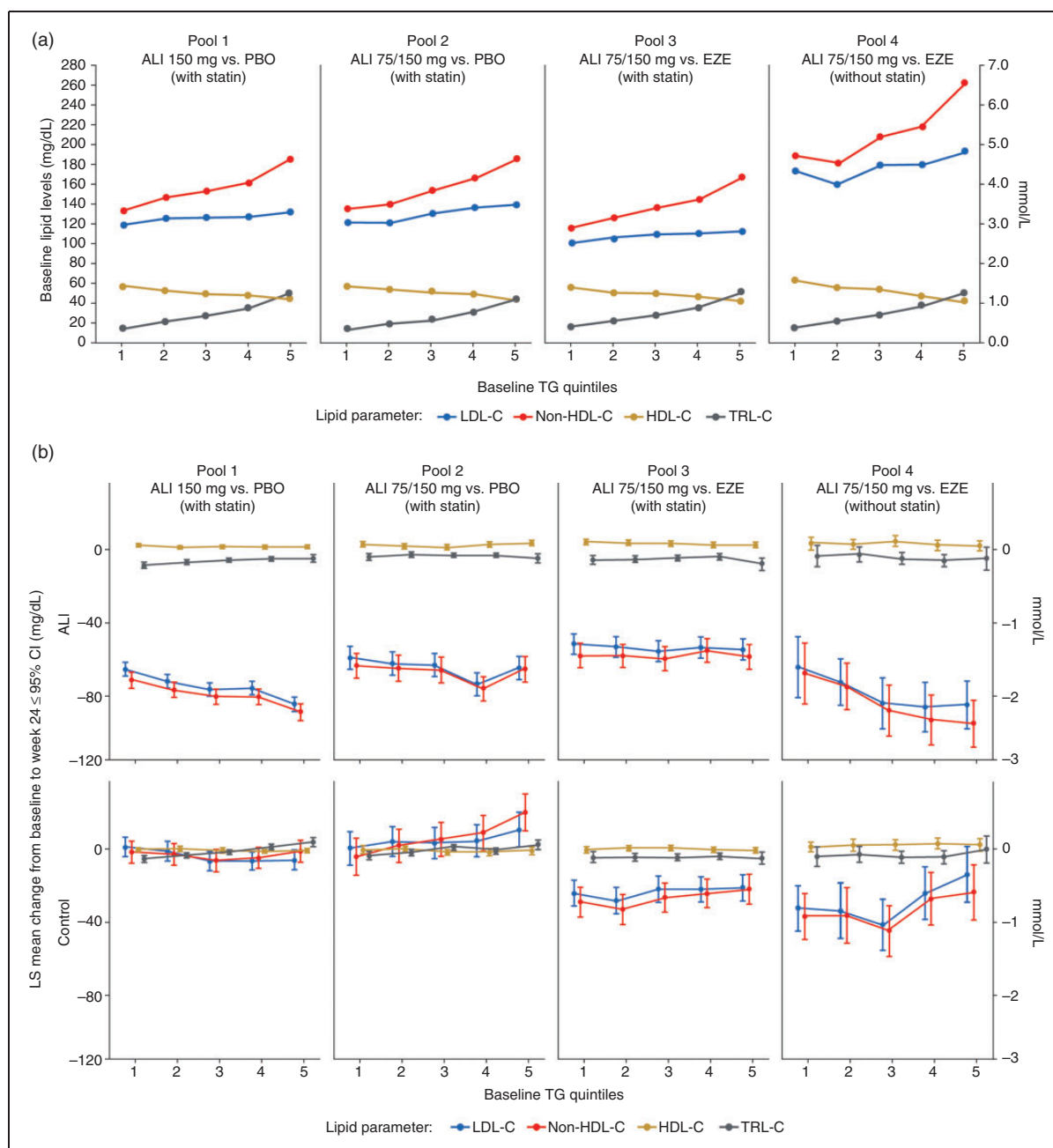


Figure 2. (a) Baseline mean levels of non-high-density lipoprotein cholesterol (non-HDL-C), calculated low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) and median of calculated triglyceride-rich lipoprotein cholesterol (TRL-C), and (b) mean absolute change from baseline at Week 24 in these lipid parameters per quintile of baseline triglyceride (TG) levels for each.

Alirocumab (ALI) 75/150 denotes that the dose could be increased from 75 to 150 mg at Week 12 depending on Week 8 LDL-C levels. CI: confidence interval; EZE: ezetimibe; LS: least squares; PBO: placebo.

Relationship between baseline TG levels, LDL-C and non-HDL-C goal attainment

Overall, treatment with alirocumab had significantly greater proportions of patients achieving LDL-C and non-HDL-C goals compared with control, particularly when compared with placebo (pools 1–2),

but also when ezetimibe was the comparator (pools 3–4).

Among patients on background statins (pools 1–3), either treated with alirocumab or controls, the proportion of patients achieving non-HDL-C goals was significantly lower with increasing baseline TG quintiles ($p < 0.05$ for trend-tests), particularly among those in

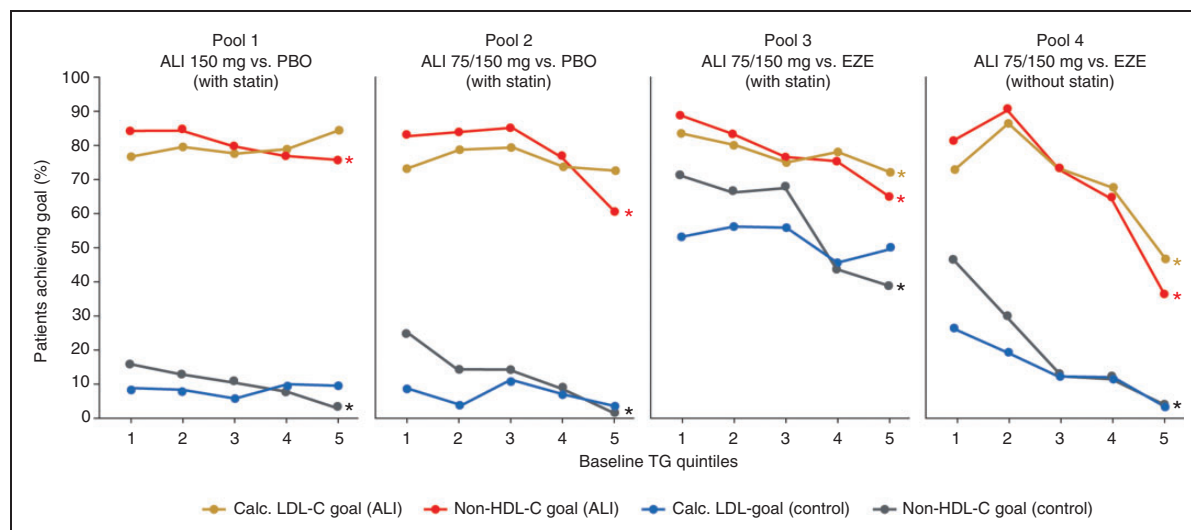


Figure 3. Proportion of patients achieving goals at Week 24 for non-high-density lipoprotein cholesterol (non-HDL-C) and calculated low-density lipoprotein cholesterol (LDL-C) by baseline triglyceride (TG) quintiles.

Goals are LDL-C < 100 mg/dl and non-HDL-C < 130 mg/dl in patients with moderate or high cardiovascular risk, and LDL-C < 70 mg/dl and non-HDL-C < 100 mg/dl in patients with very high cardiovascular risk. Quintiles of baseline TGs computed from the randomised population (see Table 1). Calculated LDL-C was determined by the Friedewald equation. * $p < 0.05$ for trend-test. Alirocumab (ALI) 75/150 denotes that the dose could be increased from 75 to 150 mg at Week 12 depending on Week 8 LDL-C levels. EZE: ezetimibe; PBO: placebo.

TG quintiles Q4–Q5 (Figure 3). By contrast, the proportions of patients achieving LDL-C goals were not significantly different across TG quintiles, whether treated with alirocumab or control. The only exception was patients on alirocumab in pool 3. Among patients not receiving statins as background therapy (pool 4), higher TG levels were associated with significantly lower proportions of patients achieving LDL-C and non-HDL-C goals ($p < 0.05$ for trend-tests), both in the alirocumab and ezetimibe groups (Figure 3).

Sensitivity analyses using directly measured LDL-C (Supplementary Material Figure 5 and 6) demonstrated similar results to calculated LDL-C for LDL-C goal achievement among those on background statins; among those not receiving statins, however, the proportion of patients achieving LDL-C goals was not significantly different across TG quintiles, unlike that which was observed with calculated LDL-C.

ORs for achieving non-HDL-C goals were significantly greater with alirocumab compared with control (either placebo or ezetimibe) in all pools and for any TG quintile within each pool (Figure 4(a)). The magnitude of this association was similar across baseline TG quintiles within each pool (p -value for homogeneity of ORs across TG quintiles in each pool: all $p > 0.22$; Figure 5(a)). Results were similar for achievement of both LDL-C and non-HDL-C goals combined (Figure 5(b)). To further assess the impact of baseline TG levels on the likelihood of achieving LDL-C and non-HDL-C goals, we calculated the OR for a single

SD increase in baseline log(TG) within each pool and treatment group. Calculated and directly measured LDL-C goal attainment was not associated with a single SD increment in baseline log(TG) in any group (Figure 4). In contrast, non-HDL-C goal attainment was inversely associated with a single SD increment in baseline log(TG) in all but one group (Figure 4(a)).

Discussion

Despite optimal LDL-C-lowering therapy with high-intensity statins, a significant residual risk remains, which can be accounted for by non-HDL-C.^{19–21} This seems to be particularly relevant in patients where TG levels are elevated.^{3,4,22,23} Some reports have indicated that attainment of non-HDL-C goals correlates inversely with TG levels,^{7,23} suggesting that additional lipid-lowering may be needed among these patients. This issue has not been studied among patients receiving PCSK9 inhibitors, who attain lower levels of on-treatment LDL-C.

In the present analyses we have observed, firstly, that higher baseline levels of TGs were associated with a higher prevalence of cardiovascular and metabolic risk factors. Secondly, LDL-C and non-HDL-C levels both increased along with higher TG levels, but the magnitude of the increase in non-HDL-C levels was approximately three- to four-fold higher (Q1–Q5 of TGs) compared with the increase in LDL-C. Thirdly, similar absolute and percentage reductions of

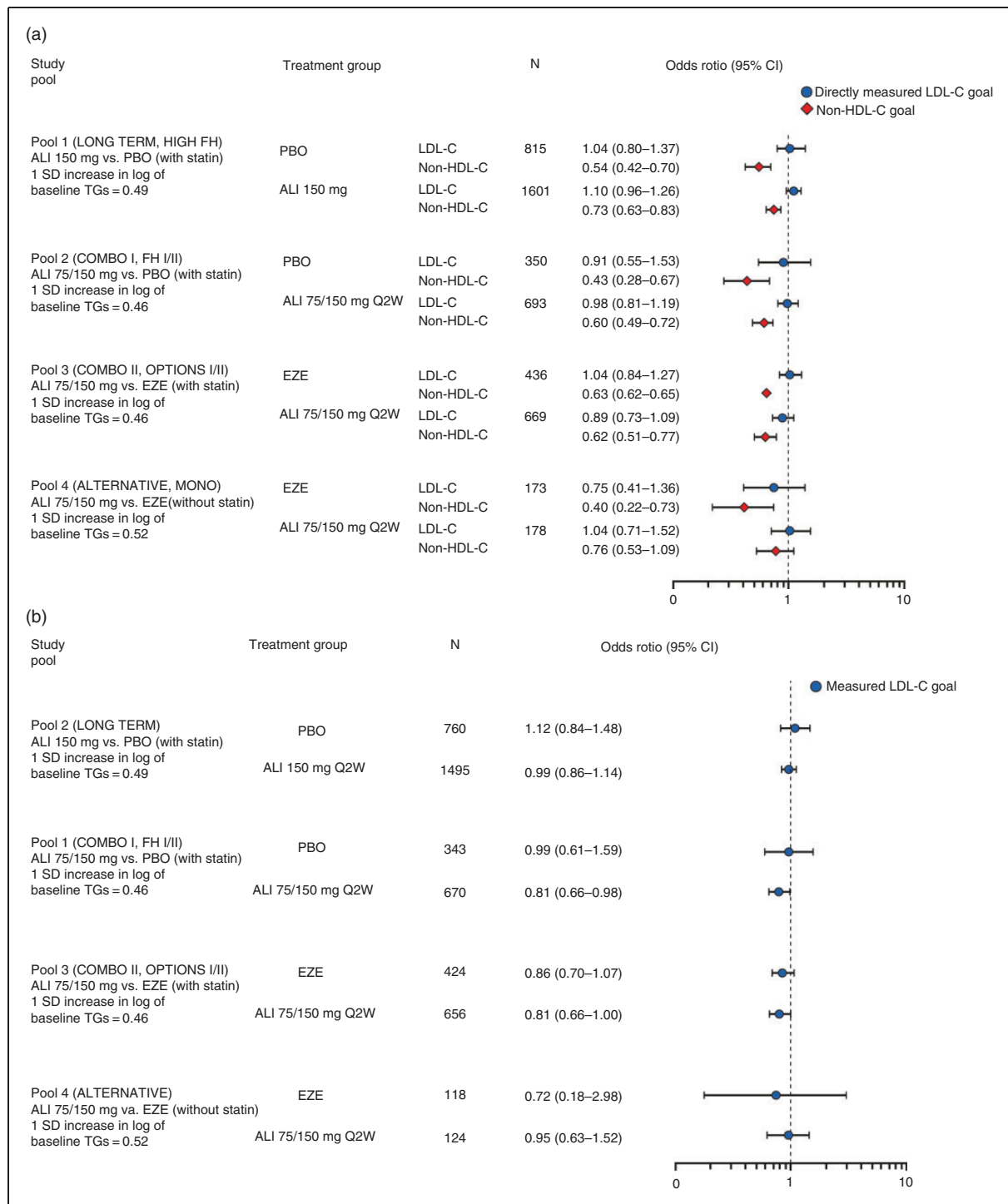


Figure 4. Odds ratios for risk-based non-high-density lipoprotein cholesterol (non-HDL-C) and (a) calculated or (b) measured low-density lipoprotein cholesterol (LDL-C) goal attainment at Week 24 associated with baseline log(triglyceride(TG)) increase of one standard deviation (SD).

LDL-C and non-HDL-C goal achievement per one SD increase in baseline log(TG). Calculated LDL-C: determined by the Friedewald equation; directly measured LDL-C: determined by beta-quantification (not available for the MONO and HIGH FH studies). ALI 75/150 denotes that the dose could be increased from 75 to 150 mg at Week 12 depending on Week 8 LDL-C levels. ALI: alirocumab; CI: confidence interval; EZE: ezetimibe; PBO: placebo; Q2W: every 2 weeks; SD: standard deviation.

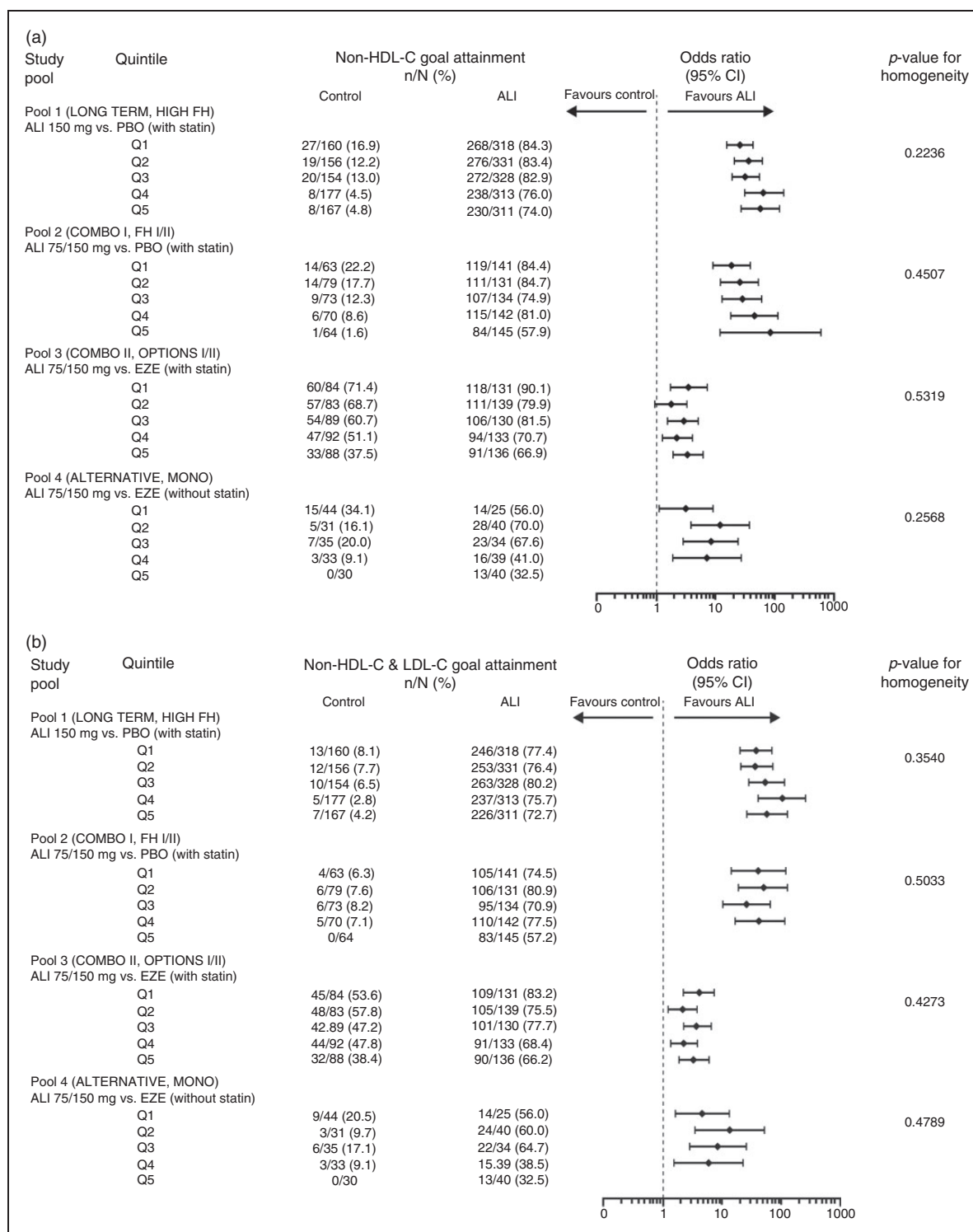


Figure 5. Association between treatment (alirocumab (ALI) versus control) and achievement of (a) non-high-density lipoprotein cholesterol (non-HDL-C) goals or (b) both calculated low-density lipoprotein cholesterol (LDL-C) and non-HDL-C goals at Week 24 per baseline triglyceride (TG) quintiles.

Targets are non-HDL-C < 130 mg/dl in patients with moderate or high cardiovascular risk, and non-HDL-C < 100 mg/dl in patients with very-high cardiovascular risk. Log-scale for odds ratio. ALI 75/150 denotes that the dose could be increased from 75 to 150 mg at Week 12 depending on Week 8 LDL-C levels. CI: confidence interval; EZE: ezetimibe; PBO: placebo.

non-HDL-C with alirocumab (versus control) were observed within each TG quintile (similar to LDL-C reductions) and, regardless of baseline TG levels, a greater proportion of alirocumab-treated patients attained non-HDL-C (and LDL-C) goals compared with placebo or ezetimibe. Consistent with this, alirocumab was shown to be a significant predictor for non-HDL-C goal attainment. Fourthly, attainment of non-HDL-C goals significantly declined with increasing baseline TG levels, with a similar impact in both alirocumab and controls, whereas this was not evident for LDL-C goal attainment except in the subgroup not receiving background statins (pool 4), in which LDL-C goal attainment significantly declined with increasing TG levels. Lastly, a single SD increase in baseline $\log(\text{TG})$ at baseline was associated with a lower likelihood (lower OR) of attaining non-HDL-C goals, unlike LDL-C goal attainment, in which no association with one SD increase in baseline $\log(\text{TG})$ was observed. Sensitivity analyses using directly measured LDL-C levels instead of calculated LDL-C levels did not meaningfully affect these results.

Treatment with alirocumab results in substantial reductions in LDL-C, non-HDL-C and apoB. However, only moderate reductions in TGs and TRL-C have been observed, consistent with previous studies and the mode of action of PCSK9 inhibitors (i.e. primarily clearing low-density lipoprotein particles from the circulation via increased number of low-density lipoprotein receptors in the liver). In the present study, treatment with alirocumab, compared with control, was observed to be a significant predictor for attaining non-HDL-C and LDL-C goals, regardless of TG quintiles at baseline. Interestingly, however, increasing levels of TGs at baseline, either in alirocumab or control groups, were correlated with lower rates and lower likelihood (OR per one SD increase in $\log[\text{TG}]$) of non-HDL-C goal attainment, unlike LDL-C goal attainment. This association was not so evident (at least among those on background statins) and the odds were neutral in all groups. This is consistent with previous observations in statin-treated patients with diabetes, in whom attainment of non-HDL-C goals was reported to decline with increasing TG levels and be more strongly associated with TG levels in comparison with LDL-C goal attainment.⁷

The results of the present study may be of particular interest for patients with a phenotype where increasing TG or TRL-C levels are frequently described, such as those with metabolic syndrome, insulin resistance or diabetes.^{3,24,25} In fact, in our study, higher TG levels were associated with greater proportions of patients with an adverse cardiometabolic profile, including higher BMI, glucose/HbA1c levels and prevalence of diabetes. In these groups of patients, it may be

particularly important to use non-HDL-C as a treatment target and LDL-C for reducing residual cardiovascular disease risk.^{3,26} Of note, the 2019 European Society of Cardiology and European Atherosclerosis Society guidelines recommend non-HDL-C levels $<2.2 \text{ mmol/l}$ ($<85 \text{ mg/dl}$), $<2.6 \text{ mmol/l}$ ($<100 \text{ mg/dl}$), and $<3.4 \text{ mmol/l}$ ($<130 \text{ mg/dl}$) in people at very high, high, and moderate cardiovascular risk, respectively.²⁷ Although previous studies have shown that PCSK9 inhibitors significantly increase the rates of non-HDL-C and LDL-C goal achievement compared with controls in populations with diabetes or diabetes with mixed dyslipidaemia,^{24,28} the present study still points towards the need to account for TG levels and the likelihood of goal attainment with different add-on therapies, considering that LLTs are required to achieve non-HDL-C targets.

Recent analyses from the TNT randomised trial⁶ observed that, among patients treated with atorvastatin 10 mg/day, those with higher TRL-C levels (Q5 versus Q1) had a higher risk of cardiovascular events. In addition, treatment with atorvastatin 80 mg, compared with atorvastatin 10 mg, led to significantly greater cardiovascular risk reductions among those patients with higher TRL-C levels, with consistent results using baseline TG or non-HDL-C levels. These data may suggest that patients with high TGs or TRL-C represent a group with a higher residual risk, where further LLTs principally aimed at apoB particle clearance may be needed. However, clinical trials have so far shown mixed results in this population in terms of cardiovascular risk reduction.^{29,30} Of interest, although both fibrates and n-3 fatty acids are effective TG-lowering drugs, they have shown variable effects in terms of apoB reduction (including increasing, reducing or null effects with n-3 fatty acids), which may potentially explain their variable effect in terms of cardiovascular risk reduction.^{29,31} A sub-analysis of the ACCORD study with fenofibrate suggested some evidence of benefit in patients with high baseline TG levels.³² Recently, a randomised controlled trial evaluating clinical outcomes with n-3 fatty acids (REDUCE-IT trial with icosapent ethyl)³³ in patients with hypertriglyceridaemia (and established cardiovascular disease or with diabetes plus other risk factors) reported a significant 25% relative reduction in risk of adverse cardiovascular events compared with placebo. However, these patients had only moderate hypertriglyceridaemia at baseline (median 2.44 mmol/l (216 mg/dl)) and these levels did not change appreciably with active treatment (39 mg/dl (0.44 mmol/l) reduction at one year). In addition, these results contrast with those from meta-analyses of n-3 fatty acid supplement trials, which did not find a significant consistent association with major vascular outcomes,³⁴ as has been reported individually with

two recent randomised controlled trials evaluating clinical outcomes (ASCEND, VITAL).^{33,35} Thus, the effectiveness of pharmacological lowering of TG levels requires further supportive evidence. Further research for novel TG-lowering therapies is underway and may provide additional information (e.g. the STRENGTH trial with omega-3 fatty acids³⁶ and the PROMINENT trial with pemafibrate).³⁷ The analyses from the present study add to the available evidence on the relationship between TG/TRL-C and non-HDL-C levels. For instance, among patients with optimal LDL-C in whom TG and non-HDL-C is high, non-HDL-C levels can be improved through the addition of a PCSK9 inhibitor to reduce their lipid related residual risk.

We must acknowledge some limitations to the present study. For instance, this was a post-hoc analysis with quintiles of TGs at baseline, although the analyses were adjusted for study and randomisation group, and data were pooled from 10 trials including different patient populations. Similarly, the number of patients for subgroup analysis was limited. In particular, this restriction did not allow us to further stratify the subgroups in those with and without diabetes. The study design excluded patients with TG > 4.52 mmol/L (>400 mg/dl), which limits generalisation of results to individuals with higher TG levels. In this analysis, TRL-C was calculated by non-HDL-C minus Friedewald-calculated LDL-C; this approach has been widely used, is convenient using routinely collected lipid parameters, and has been related to cardiovascular disease.^{6,7,17,38,39} Nevertheless, we conducted a sensitivity analysis using directly measured TRL-C (non-HDL-C minus beta-quantification-derived LDL-C), which showed similar results to those using calculated TRL-C.

In summary, individuals with increased TG levels and increased levels of atherogenic lipoproteins have lower rates of non-HDL-C goal attainment. Alirocumab improves non-HDL-C goal attainment compared with placebo in this population, although higher baseline TG levels were still associated with lower non-HDL-C goal attainment compared with lower TG levels at baseline. The present results highlight the impact of TGs and/or TRL-C on non-HDL-C levels, and the need for further research on novel therapies that target TG-related pathways.

Author contribution

AJVV, MBB, AL and KKR contributed to the conception or design of the work. AJVV, SDP, DMW, MBB, AL, JM, RS and KKR contributed to the analysis and interpretation of data for the work. LAL and MRT contributed to the acquisition, analysis, or interpretation of data for the work. AJVV and KKR drafted the manuscript. All critically revised the manuscript, gave final approval, and agree to be

accountable for all aspects of work ensuring integrity and accuracy.

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Declaration of conflicting interests

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