Persistent Changes in lipoprotein lipids after a Single Infusion of Ascending Doses of MDCO-216 (ApoA-IMilano/POPC) in Healthy Volunteers and Stable Coronary Artery Disease Patients

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Running title: MDCO-216 infusion in healthy volunteers and CAD patients

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Abbreviations: CAD, coronary artery disease; CE, esterified cholesterol; CER, cholesterol esterification rate; FC, free cholesterol; PL, phospholipids; TC, total cholesterol.

Abstract

Background. Effects of single ascending doses of MDCO-216 on plasma lipid and lipoprotein levels were assessed in human healthy volunteers and in patients with stable coronary artery disease (CAD).

Methods. MDCO-216 was infused at a single dose of 5, 10, 20, 30 or 40 mg/kg over 2h and blood was collected at 2, 4, 8, 24, 48, 168 and 720 h after start of infusion (ASOI). Lipoprotein lipids were assessed by FLPC and by 1H-NMR.

Results. Plasma concentrations of free cholesterol (FC) displayed a rapid and dose-dependent rise peaking at 8 h but remaining above baseline until 48 h ASOI, whereas levels of esterified cholesterol (CE) increased at lower doses but not at higher doses, and even decreased below baseline at the highest dose. Plasma cholesterol esterification rate (CER) decreased with a first nadir between 4 and 8 h and a second nadir at 48 h ASOI. Taken over all subjects receiving MDCO-216 the increase in FC at 8 h correlated inversely with the drop in CER at 4 h but positively with the increase in basal and SR-BI-mediated cholesterol efflux capacities at 2 h ASOI.

Upon FPLC analysis FC was found to increase first in HDL and VLDL and later (at 48 or 168 h ASOI) in LDL. CE initially decreased in LDL and HDL but after 24 h started to increase in VLDL and LDL whereas HDL-CE was still below baseline at 48 h. PL showed the same pattern as FC. TG also rose rapidly, most prominently in VLDL, but also in LDL and HDL. Apo-E in VLDL increased at 4-8 h but returned to baseline at 24 h ASOI.

1H-NMR analysis showed a rapid and dose-dependent increase in HDL particle size, peaking at 2 h and returning to baseline at 24h, and a small increase in HDL particle concentration. After infusion of the 40 mg/kg dose LDL and VLDL-particles also increased in number and size.

Conclusion: a single administration of MDCO-216 caused rapid changes in lipid levels and lipoprotein composition, some of which persisted for at least 7 days.

Keywords: Clinical Trials; Drug therapy; Lipoproteins; Lipids; Atherosclerosis; HDL.

Supplementary keywords: apoA-IMilano; synthetic HDL; Coronary artery disease.

INTRODUCTION

Intravenous infusion of various apoA-I -phospholipid complexes ("reconstituted HDL", rec-HDL) has been under investigation since the mid-1990ties as an approach to reduce atherosclerotic plaque burden (reviewed in 1).

Based on the observation that carriers of the apolipoprotein A-I Milano (apoA-IM) variant have a reduced incidence of atherosclerosis and cardiovascular events (reviewed in 2) rec-HDL containing apoA-IM has been developed and was shown to reduce plaque burden in several animal studies (3-7). More than 10 years ago repeated infusion of rec-HDL containing apoA-IM (at the time named ETC-216) was shown to cause rapid regression of atherosclerotic plaque burden in patients with acute coronary syndromes, as measured by intravascular ultrasound (8). More recently the same product manufactured by an improved process, called MDCO-216, was shown by us to be safe in a multiple ascending dose toxicity study in cynomolgus monkeys (9). This study also demonstrated strongly elevated free cholesterol (FC) levels and enhanced ABCA1-mediated cholesterol efflux capacity of serum after drug infusion, accompanied by a shift of apoE from HDL toward VLDL and LDL (9).

Most recently we assessed the safety and pharmacodynamics of single ascending doses of MDCO-216 in healthy volunteers and in patients with stable coronary artery disease (CAD). We recently reported time- and dose-dependent changes in plasma lipids, apolipoproteins and serum cholesterol efflux capacities (10). Somewhat surprisingly we found only minimal changes in total plasma cholesterol (10). Other groups infusing other rec-HDL products in humans have described strong increases in plasma cholesterol after infusion of CER-001 (11) or CSL-112 (12), initially in the form of a rise in FC in HDL. The goal of the present paper was therefore to assess the effects of MDCO-216 on levels of FC, esterified cholesterol (CE) and other lipids in total plasma and in individual lipoproteins HDL, LDL and VLDL. We found that

MDCO-216 causes rapid and sustained dose-dependent increase of plasma FC, first within HDL and VLDL and later in LDL. At the highest dose HDL-CE was decreased for at least 48 h, while VLDL-and LDL-CE increased. The initial increase in FC correlated with the rise in basal or SRB1-mediated cholesterol efflux capacity and inversely with the drop in endogenous cholesterol esterification rate.

MATERIALS AND METHODS

Drug Product

MDCO-216 is a complex of highly purified dimeric recombinant apoA-IM and palmitoyl-oleoyl-phosphatidylcholine (POPC). Complexation with POPC was performed using a high-pressure homogenization procedure. The final product contained 13 mg/ml protein, 14 mg/ml POPC, 1.3 mg/ml di-sodium hydrogen phosphate heptahydrate, 0.178 mg/ml sodium dihydrogen phosphate dehydrate, 62 mg/ml sucrose, 8.2 mg/ml mannitol. Physicochemical properties of the complex were described in detail before (9) and its concentration is expressed as protein content.

Study Design

The study design and protocol were described in detail before (10). Briefly, the study protocol was developed by the Sponsor, The Medicines Company, and organized and executed by the Centre for Human Drug Research (CHDR) in Leiden, Netherlands, in compliance with the Declaration of Helsinki. The protocol was approved by accredited local (BEBO, Assen, The Netherlands) and national (CCMO, The Hague, The Netherlands) independent medical ethics committees. After signing informed consent and meeting all inclusion and exclusion criteria, 24 healthy volunteers and 24 patients with stable CAD were randomized between February and October 2013 and received a two hour infusion of MDCO-216 or placebo.

Concomitant treatment

Subjects were excluded from the trial if there was a recent or current history of investigational drug products. Stable CAD patents were allowed to remain on all current medications, including those for hypercholesterolemia, hypertension and diabetes.

Drug administration, randomization

After overnight fasting healthy volunteers received single doses of 5, 10, 20, 30 or 40 mg (based on protein)kg and stable CAD patients received doses of 10, 20, 30 or 40 mg (based on protein)/kg. Subjects were assigned in a 2:1 ratio to MDCO-216 or matching placebo to maintain blinding. Dose escalation was only permitted after approval from a Safety Review Committee consisting of specialists in Cardiology, Vascular Medicine, the Principal Investigator and Medical Director from the sponsor following the review of safety data to day 7. In the first two cohorts of healthy volunteers (5 mg/kg and 10 mg/kg) 2 subjects received MDCO-216 and 1 subject received placebo. In the remaining cohorts of both healthy volunteers and CAD patients 4 subjects received MDCO-216 and 2 received placebo. Altogether, therefore, 8 healthy volunteers and 8 CAD patients received placebo.

Laboratory analyses

Plasma levels of free and esterified cholesterol, of cholesterol esterification rate (CER) and of lipoprotein lipids and apolipoproteins after separation by FPLC were measured using methods described in detail before (9). In the healthy volunteers only the 20 mg/kg and 40 mg/kg dose groups were analyzed, while in the CAD patients all 4 dose groups except placebo were analyzed. For the 10, 20 and 30 mg/kg doses only the 0 h, 4 or 8 h and 24 h time points were analyzed, while for the 40 mg/kg dose the 48 h and 168 h time points were also assessed. After FPLC separation total cholesterol (TC), free cholesterol (FC), triglycerides

(TG) and phospholipids (PL) were measured in the 30 fractions eluted from the column. Esterified cholesterol (CE) was calculated as TC minus FC.

For CER, which estimates the ability of LCAT to esterify cholesterol within endogenous lipoproteins, FC was measured in plasma samples before and after 1h incubation at 37°C by a standard enzymatic assay. Reaction was stopped by adding 0.15 mol/L sodium iodoacetate as LCAT inhibitor. Results are expressed as nmoles of esterified cholesterol generated.

Basal and ABCA1-mediated cholesterol efflux capacities in control or cAMP-pretreated J774 cells, SR-BI-mediated cholesterol efflux from Fu5AH cells and ABCG-1 mediated efflux from transfected BHK cells were determined as described in the previous paper (10).

Lipoprotein particle concentrations and sizes were assessed by *NMR LipoProfile*® analysis at LipoScience (now LabCorp), Raleigh, NC, as described before (14). Particle concentrations and mean sizes are reported for HDL (diameter between 7.3 and 14 nm), LDL plus IDL (diameter between 18-29 nm) and VLDL plus chylomicrons (diameter above 29 nm).

Results are presented as means and SEM according to dose and time after start of infusion. For each subject and measured parameter the delta (value at time point x – value at baseline just prior to start of infusion) was calculated. Student t-test for paired observations was done within each dose group to see if a mean value at t=x significantly differed from baseline value of that dose group. Student t-test for unpaired observations was performed to see whether a mean delta in a drug-treated group for a given time point differed significantly from the mean delta in the placebo-treated subjects for that time point. *P* values <0.05 were considered statistically significant.

RESULTS

Effects on plasma free cholesterol, esterified cholesterol and cholesterol esterification rate

Plasma levels of FC remained stable over time in the subjects receiving placebo and increased in those receiving MDCO-216 reaching peak at 8 h with a second peak at 48 h in CAD patients. In healthy volunteers these increases were significant at doses >= 20 mg/kg while in CAD patients the increase was significant at all doses as compared to baseline and placebo (Fig. 1 top panels). As shown in Data Supplement Fig. I the effect on FC was not dose-linear: the amount of FC increase at 8 h was small at lower doses but at doses >= 30 mg/kg the rise was stronger and in CAD patients more pronounced than in healthy subjects. In contrast CE levels did not clearly increase (as compared to placebo values which tended to rise over time), and after the 40 mg/kg dose CE levels were even below placebo at 24 and 48 h after infusion (Fig. 1 bottom panels).

To determine whether the increase in FC could be attributed to a decreased LCAT activity we determined the endogenous plasma CER before and after infusion of MDCO-216. As shown in Fig. 2 infusion of MDCO-216 caused a time and dose-dependent decrease in CER in both healthy volunteers and patients, with the first drop between 2 and 8 h, the second at 48 h after start of infusion. As shown in Fig. 3 (A), the increase in FC at 8 h was significantly inversely correlated with the decrease in CER at 4 h ($r = -0.43$, $p = 0.03$).

Since this correlation was not very strong we explored whether the increase in FC could also be related to the changes in cholesterol efflux capacities described in our previous paper (10). We found that delta FC at 8 h correlated strongly and positively with the increase of basal (Fig. 3B) and SR-BI-mediated (Fig. 3C) efflux capacities at 2 h ($r = 0.74$ and 0.76 respectively, $p<0.001$), but not significantly with the increase of ABCA1-mediated efflux at 2 h ($r=0.36$, $p=0.15$), nor with the increase in ABCG1-mediated efflux at 2 h ($r=0.27$, $p=0.19$).

Thus, the increase of plasma FC is mainly the result of MDCO-216-induced increase of SR-BI-mediated cholesterol efflux with a minor contribution of a decrease of CER.

Effects on the composition of lipoprotein fractions isolated by FPLC

Complete results of the FPLC analyses are provided in Supplementary Tables II and III for the healthy volunteers and CAD patients, respectively. The changes in lipoprotein lipids induced by the 40 mg/kg dose are depicted in detail in Fig. 4. There was an early increase in HDL-PL likely reflecting the POPC infused as constituent of MDCO-216, accompanied by a parallel rise in HDL-FC. These lipids rapidly left the HDL region, and then increased in the VLDL and thereafter in the LDL fraction, where they were still significantly above baseline at 2 or 7 days after infusion. CE in HDL decreased below baseline whereas CE in VLDL and later in LDL rose above baseline.

We showed before (10) that MDCO-216 infusion caused a rapid and considerable increase in total plasma TG; here we report that this increase occurs in all three lipoprotein fractions, although most pronounced in VLDL. Effects on TG were more marked in CAD patients than in healthy volunteers in all lipoprotein fractions.

Plasma apoC-III levels showed changes over time after MDCO-216 infusion but these were not significantly different from those of placebo-treated subjects at all time-points (Data Supplement Figure II).

Changes in plasma levels of apoA-I (total and apoA-IMilano), apoB and apoE were reported before (10, 16). The distribution of apoA-I, apoA-I Milano and apoE over lipoproteins was determined by Western blotting after FPLC separation. ApoA-I and apoA-IMilano (detected with the 17F3 Mab) were recovered for over 90% in the HDL fraction prior to and at all times after infusion of all doses (not shown). As shown in Fig. 5 apoE showed a small but significant

increase in the VLDL fraction at 8 h after start of infusion of MDCO-216 parallel with a decrease in the LDL fraction and no change in the HDL fraction.

Lipoprotein particle concentrations and sizes measured by NMR

HDL

MDCO-216 caused an increase in HDL particle concentration between 2 and 8 h after start of infusion at 10 mg/kg in the healthy volunteers and at all doses in the CAD patients. At the 40 mg/kg dose HDL particle concentration decreased below baseline at 2h and in healthy volunteers also at 48 h after start of infusion (Fig. 6 and Supplementary Table III).
MDCO-216 at doses of 20, 30 and 40 mg/kg caused the HDL particle size to increase during the first 8 h in both groups, the increase being larger in healthy volunteers than in CAD patients. In the healthy volunteers receiving 20 or 30 mg/kg HDL size decreased significantly below baseline between 24 and 168 h after infusion (Fig. 6 and Supplementary Table III).

LDL

MDCO-216 at 40 mg/kg caused a rapid and long lasting increase in LDL particle number in healthy volunteers and more pronounced in CAD patients. Peak values were reached at 48 h in both groups. At 20 mg/kg the increases were smaller (Supplementary Table IV).
LDL size increased slightly after infusion of 40 mg/kg in healthy volunteers between 4 and 24 h, but not at lower doses, while in CAD patients there was no significant changes in LDL size at any dose or timepoint (Supplementary Table IV).

VLDL

VLDL particle number increased in both healthy volunteers and CAD patients at 4 and 8 h after infusion of the 10 and 20 mg/kg doses and also at 24 and 48 h at the 30 g/kg doses (Supplementary Table V). VLDL size was increased above baseline between 4 and 168 h in healthy volunteers after the 30 and 40 mg/kg dose. In CAD patients VLDL size increased to a smaller extent and only at 4 and 8 h after infusion. Lower doses had no or little effect on either particle number or size (Supplementary Table V).

DISCUSSION

Effects on free and esterified cholesterol; relation with CER and cholesterol efflux capacity

Infusion of MDCO-216 caused rapid increases in plasma FC which was more pronounced and sustained in CAD patients. The increase in FC could in theory be the result of (i) increased efflux of cholesterol from tissues into plasma, (ii) hampered esterification of FC by LCAT, (iii) a decreased delivery from plasma to tissues, or (iiii) an increased secretion of FC as new lipoproteins by the liver and small intestine. The first mechanism is clearly plausible in view of the strong increases in serum efflux capacities as reported in the previous paper (10), and is actually supported by the high positive correlations between the delta FC at 8 h and the delta's for basal and SR-BI-mediated efflux capacities at 2 h (Fig. 3 B and C). This relation is also in agreement with the finding, reported recently elsewhere (16), that infusion of MDCO-216 leads to a prompt increase of larger (alpha-1 and alpha-2) HDL which are known to be a functional cholesterol acceptor via the SR-BI carrier in liver cells (17).

The second mechanism, inhibition of cholesterol esterification, is supported by the temporary drop in CER with a nadir at 4 h (Fig. 2) which correlated inversely with the increase in FC at 8 h (Fig. 3 A). It also is consistent with decreased LCAT activity in carriers of the apoA-IMilano mutation reported before (15). However, the size of the CER drop (15 nmoles/ml/h in the period between 2 and 8 h) would predict an increase of 8*15 = 120 nmoles at 8h, much below the actually observed increase in plasma free cholesterol (800 nmoles/ml at 8 h after start of infusion in CAD patients). It seems therefore that the increase in FC is mainly driven by enhanced cholesterol efflux capacity, at least during the initial 8 h. The third or fourth mechanism may play a role in the increased FC seen at later time points, which remains to be assessed in future studies.

In contrast to studies with CSL-112 (12) no significant increase or even a decrease in plasma CE occurred as compared to placebo. The reason for the drop in CE at the higher doses is discussed in the next section.

Rise of FC not only in HDL but also in VLDL and LDL

Lipoprotein separation by FPLC demonstrated that the increase in free cholesterol occurred not only in HDL but also in VLDL and LDL (Fig. 4, Supplementary Tables II and III). The appearance of FC and PL in the VLDL and LDL regions has been observed before after infusion of ETC-216 in rabbits (5) or monkeys (9) or of reconstituted human HDL containing wild-type apoA-I in mice (18). Increased amounts of FC in the VLDL region and LDL regions was also observed in humans receiving ETC-216 (19) or reconstituted HDL containing wild-type apoA-I (20). This may be attributed to relative lack of activation of LCAT by apoA-I Milano accompanied by formation of FC/PL rich particles containing apoE (9), as discussed in more detail below.

Drop of CE in HDL and rise in LDL

Fig. 4 also showed that the reduced plasma CE level at 24 and 48 h was the result of a drop in both HDL-CE and LDL-CE. Whereas the drop in HDL-CE was sustained up to 168 h after infusion, LDL-CE started to rise above baseline between 24 and 48 h and then remained elevated until 168 h. This suggests that the FC extracted from tissues was esterified by LCAT initially on HDL, followed by CETP-mediated transfer to VLDL and LDL in exchange for TG. This HDL-TG then may have been subsequently hydrolyzed by hepatic lipase.

In line with this hypothesis the drop of HDL-CE below baseline at 24 and 48 h after the higher doses was accompanied by a smaller sized HDL (Fig. 6), indicating net loss of HDL core lipids.

LDL-TG showed peaks at 8 and 48 h, whereas LDL-CE initially decreased but then increased from 48h onwards. The pronounced increase in all LDL-lipids at 48 h in the CAD patients is in good agreement with the increase in LDL particle concentration observed by 1H-NMR at that time point, and also with the increase in LDL-cholesterol and apoB as reported in the previous paper (10).

Increase in VLDL-lipids and apoE

Increases in TG, PL and FC in VLDL were observed between 4 and 48 h after infusion of the 40 mg/kg dose (Fig. 4). In line with this, 1H-NMR detected prominent increases in VLDL particle size occurred at these time points. Whether these rises in VLDL lipids are due to decreased VLDL clearance or increased VLDL production is as yet unclear. Interestingly, it was recently shown that apoA-IMilano triggers lipolysis in primary adipose cells (21). In case this would have occurred in our study in vivo, it remains to be investigated whether the liberated FFA are directed to the liver for TG and VLDL synthesis and thereby affect VLDL levels. Another cause for increased VLDL production may be enhanced delivery of cholesterol from the plasma compartment into the liver, as observed in older studies (22).

Alternatively, decreased VLDL clearance could have been resulted from inhibition of lipoprotein lipase by MDCO-216 or by an increase of apoC-III levels. Plasma apoC-III indeed rose to some extent at 8 h after infusion of the 40 mg/kg dose but also after infusion of saline (Fig. II Data Supplement), excluding apoC-III changes as explanation of the rise in TG. Further studies are needed to address this question.

In our previous cynomolgus study (9) infusion of 100 mg/kg of MDCO-216 resulted in a drastic shift of apoE away from HDL towards the VLDL and LDL fractions in parallel with a several-fold increase of FC and PL in these fractions, suggesting the formation of new FC-PL-apoE-rich particles with low density. In the present study infusion of 40 mg/kg caused a

doubling of FC and PL in VLDL at 8 h (Data Supplement Table III) but only a minor increase increase of apoE in the VLDL region and a decrease of apoE in the LDL region, not suggestive of formation of such new particles.

General conclusions

As reported in our previous paper (10) infusion of MDCO-216 caused clear increases in plasma PL and TG but non-significant changes in TC. We now report that the infusion causes rapid increases of FC but unchanged or at higher doses even decreased CE. The FC rise was non-linear with respect to dose, suggesting that the capacity to handle the influx of FC from tissues to plasma is saturating a doses of doses of >= 30 mg/kg.

MDCO-216 infusion caused complex changes in plasma and lipoprotein lipids, with some of the responses still visible at 168 h after infusion. These late effects cannot be explained by the increased cholesterol efflux capacities reported in our previous paper (10), because these had returned to baseline by 24 h after infusion.

Changes in lipid content in the HDL, LDL and VLDL fractions seen by FPLC are generally consistent with the effects on particle concentrations and/or sizes assessed by 1H-NMR.

The changes in lipoprotein lipids after the 30 and 40 mg/kg doses were in the direction of a more “atherogenic” profile (increase in LDL-cholesterol, apoB and LDL particle number, increase in plasma and VLDL-TG, decrease in HDL-cholesterol and HDL-particle number) and were sustained over a considerable length of time. However, similar lipoprotein profiles are observed in carriers of the apoA-IMilano mutation, which do not seem to have more manifest heart disease than related subjects not carrying the mutation (2). We emphasize that these changes are much less prominent at doses below 30 mg/kg, whereas the 3-4 fold

increases in total and ABCA1-mediated cholesterol efflux capacities are already close to maximum at the 20 mg/kg dose (10).

Potential conflicts of interest**:**

H.J. Kempen, D.G. Kallend. S. Bellibas, PLJ Wijngaard: at the time of this work employed at The Medicines Company. E. Jeyarajah, J. Otvos: employed at LipoScience (now Labcorp).

Acknowledgements

Joannes Reijers and Jacobus Burggraaf are acknowledged for their contributions to the meticulous design and execution of the Phase I study at CHDR Leiden, The Netherlands.

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FIGURE LEGENDS

Fig. 1: Effect of increasing doses of MDCO-216 on plasma free cholesterol (top panels) and esterified cholesterol (bottom panels) in healthy volunteers (left panels) and CAD patients (right panels), expressed as absolute change from baseline. Error bars are SEM for n=4. Absolute baseline values for free cholesterol were between 1.01 and 1.18 mM in healthy volunteers and between 0.94 and 1.24 mM in CAD patients. For esterified cholesterol they were between 3.04 and 3.48 mM in healthy volunteers and between 2.65 and 3.77 mM in CAD patient. **P*<0.05 vs 0h (baseline), # P<0.05 vs placebo at the same time-point.

Fig. 2. Effect of increasing doses of MDCO-216 on endogenous plasma cholesterol esterification rates in healthy volunteers (left panel) and CAD patients (right panel), expressed as absolute change from baseline. Error bars are SEM. Baseline values are between 29 and 36 nmoles/ml/h for healthy volunteers and between 35 and 48 nmoles/ml/h for CAD patients. **P*<0.05 vs 0h (baseline).

Fig. 3. Scatterplots showing the relation between the increase of plasma free cholesterol at 8 h and (A) change in endogenous cholesterol esterification rate at 4 h, (B) change in basal efflux from J774 cells at 2 h, and (C) change in SR-B1 mediated efflux from Fu5AH cells at 2 h.

Fig.4. Changes in PL, FC, CE and TG levels in VLDL, LDL and HDL separated by FPLC after infusion of 40 mg/kg MDCO-216 in healthy volunteers (left panels) and CAD patients (right panels). Error bars represent SEM. **P*<0.05 vs 0h (baseline). Absolute values are provided in Supplementary Tables II and III.

Fig. 5. Distribution of apoE among VLDL, LDL and HDL before and 8 and 24 h after infusion of 40 mg/kg MDCO-216. Bars represent means + SEM for 8 subjects (4 healthy volunteers and 4 CAD patients). *: significantly different ($p<0.05$) from baseline.

Fig. 6. Effect of increasing doses of MDCO-216 on HDL particle concentration and HDL size in healthy volunteers (left panels) and CAD patients (right panels), expressed as absolute change from baseline. Error bars are SEM. *: significantly different ($P<0.05$) from zero; #: significantly different ($p<0.05$) from placebo at the same time point.

Figure 1

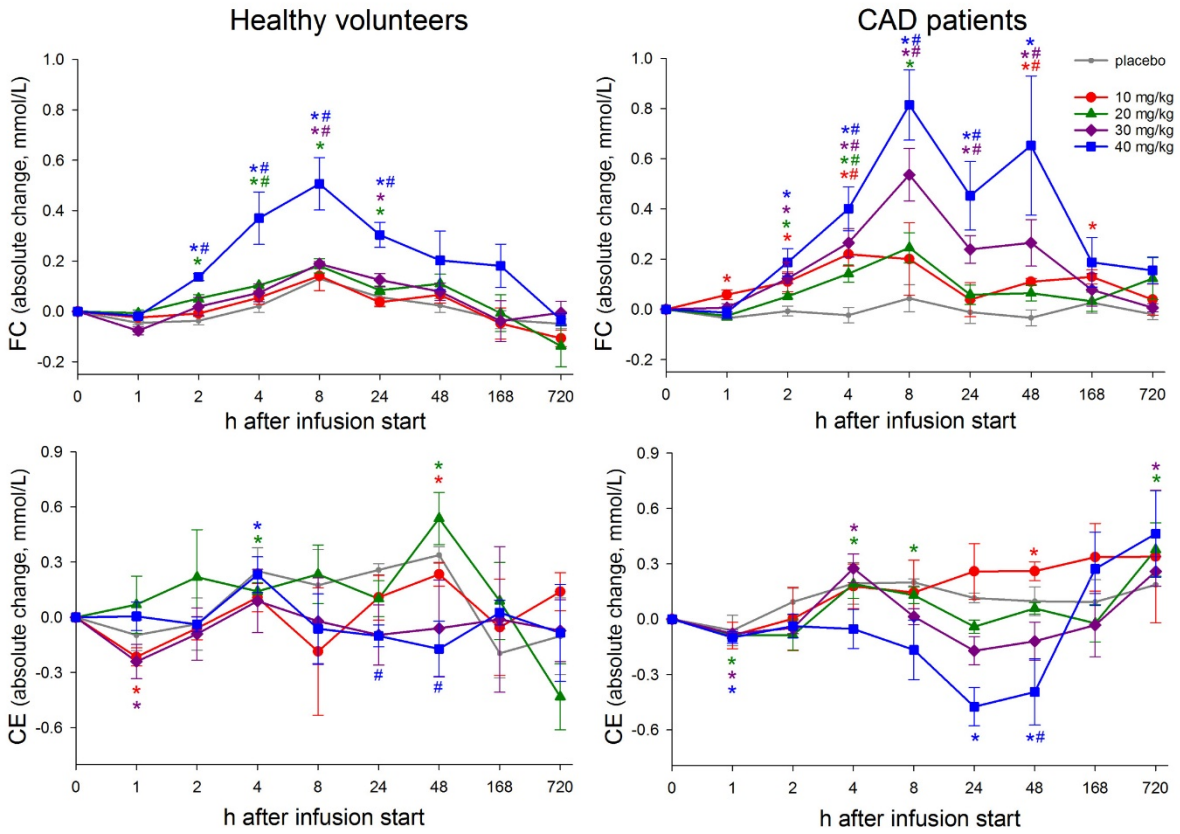


Figure 2

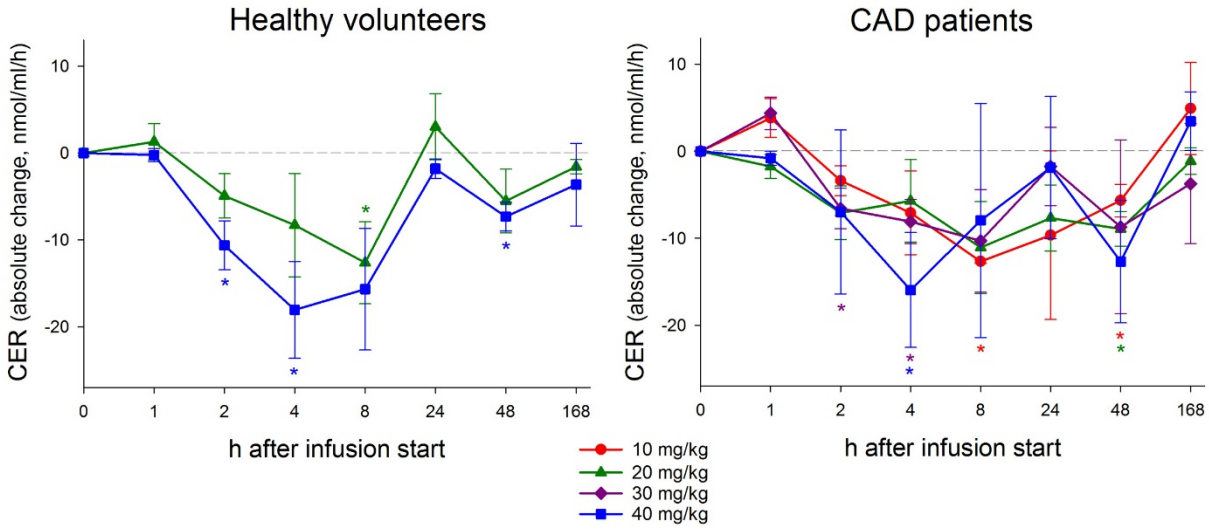


Figure 3

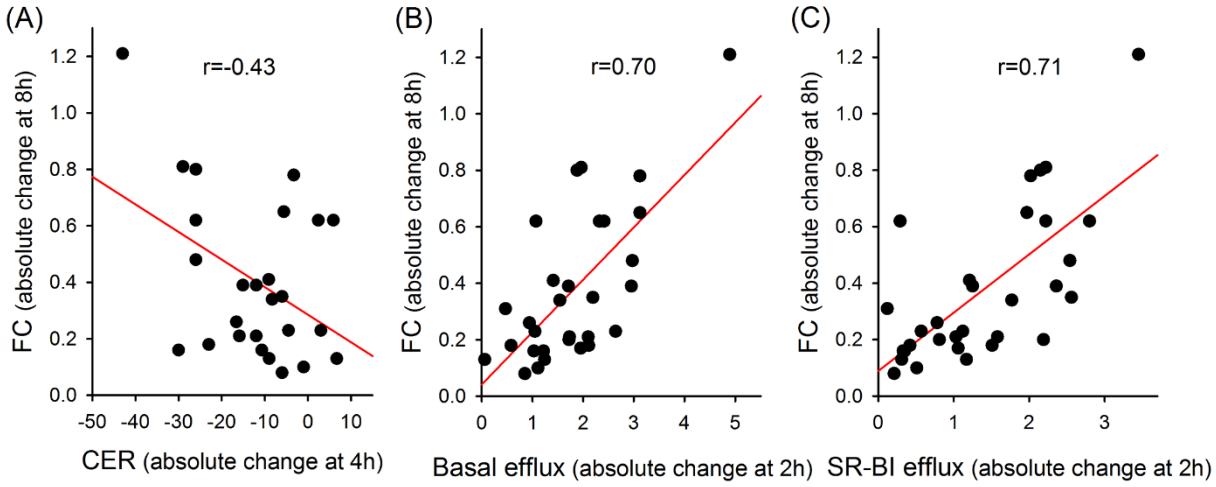

(A)
r=-0.43
FC (absolute change at 8h)
CER (absolute change at 4h)
(B)
r=0.70
FC (absolute change at 8h)
Basal efflux (absolute change at 2h)
(C)
r=0.71
FC (absolute change at 8h)
SR-BI efflux (absolute change at 2h)

Figure 4

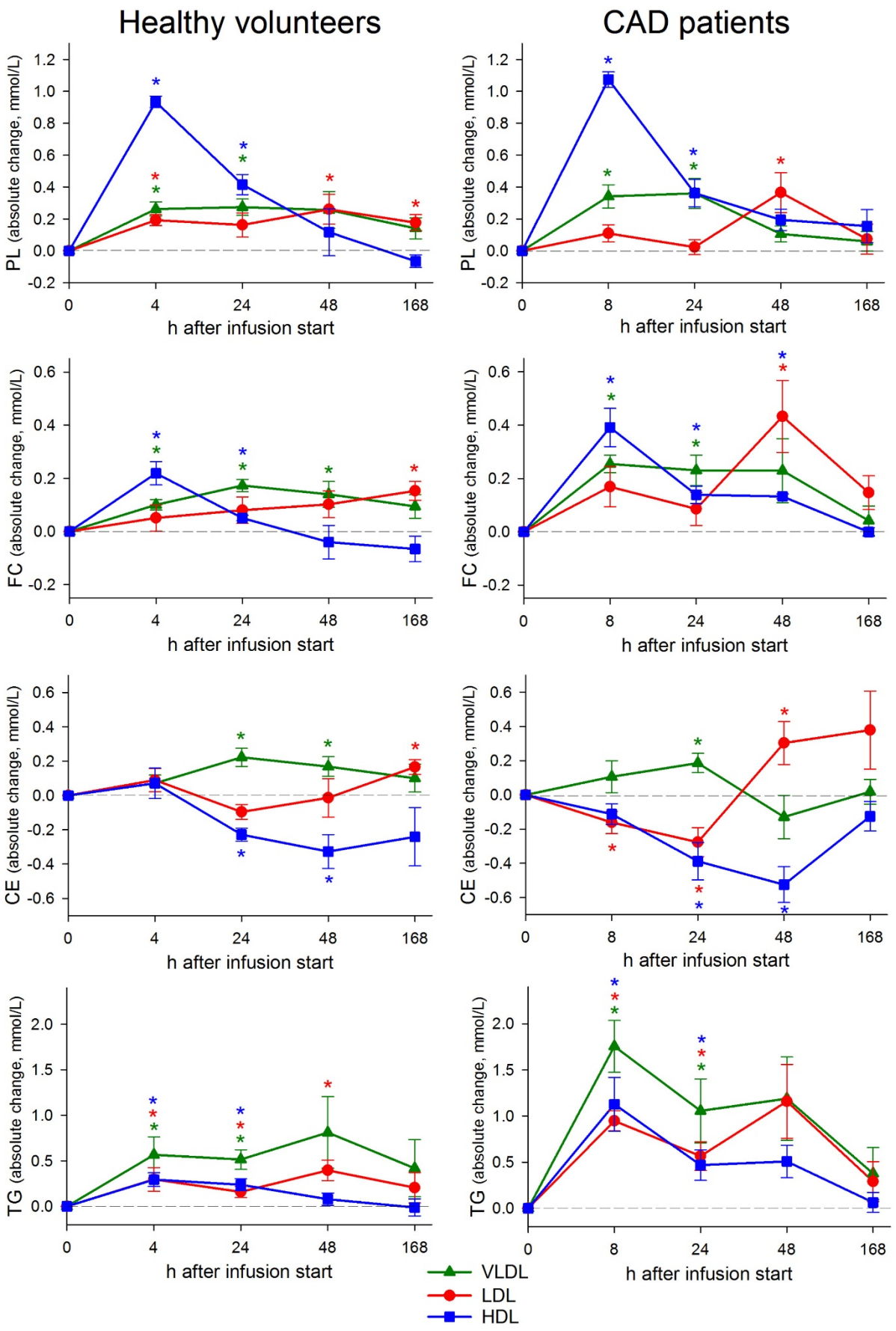

Healthy volunteers
CAD patients
PL (absolute change, mmol/L)
FC (absolute change, mmol/L)
CE (absolute change, mmol/L)
TG (absolute change, mmol/L)
h after infusion start
VLDL
LDL
HDL

Figure 5.

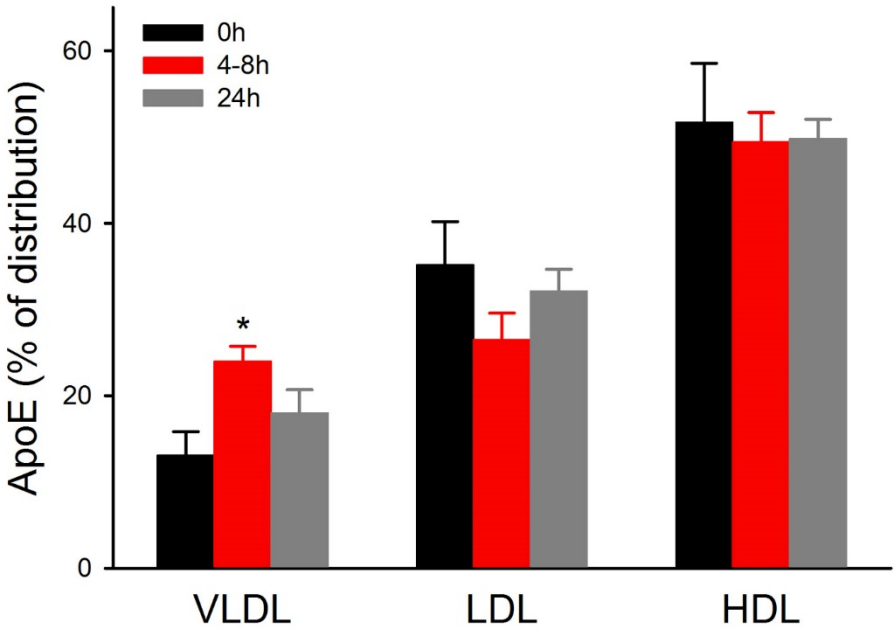
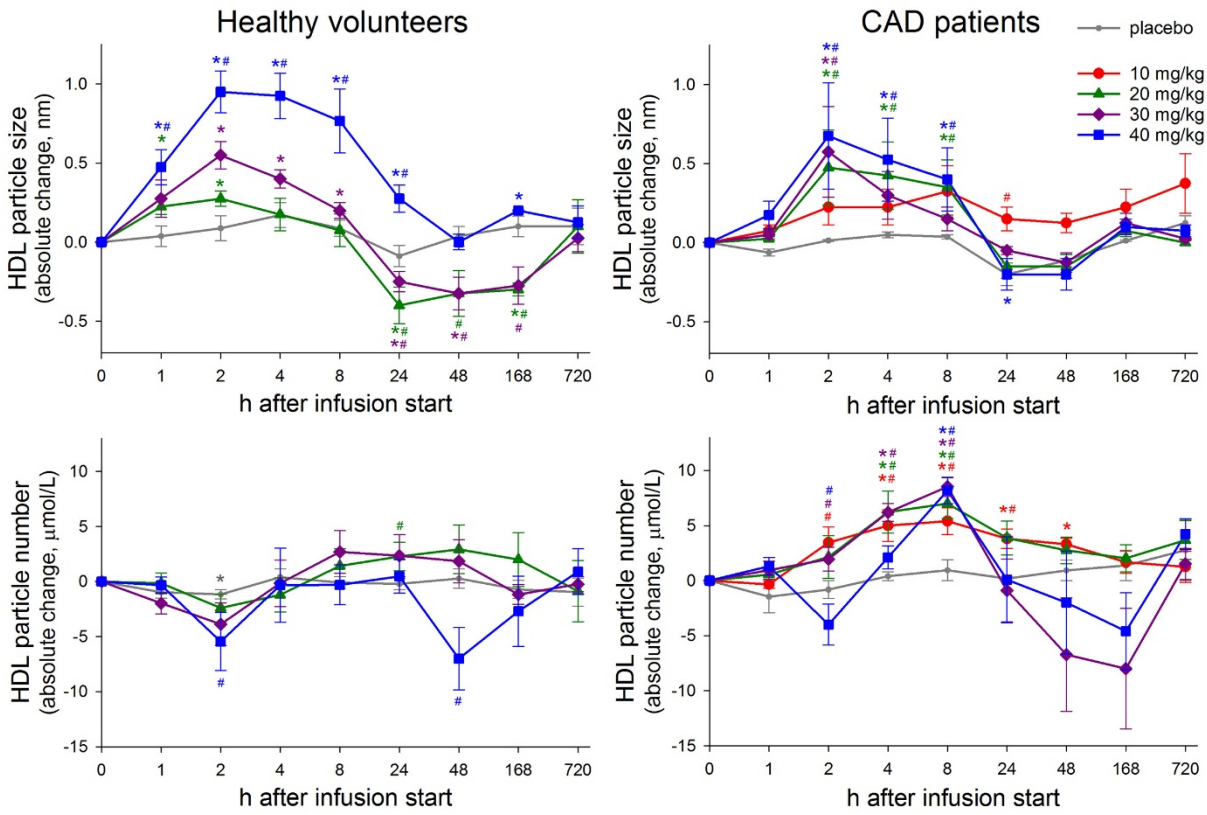


Figure 6.


Healthy volunteers
CAD patients
placebo
10 mg/kg
20 mg/kg
30 mg/kg
40 mg/kg
HDL particle size
(absolute change, nm)
HDL particle number
(absolute change, µmol/L)
h after infusion start
0
1
2
4
8
24
48
168
720