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Effect of Infusion of High-Density Lipoprotein Mimetic Containing Recombinant Apolipoprotein A-I Milano on Coronary Disease in Patients With an Acute Coronary Syndrome in the MILANO-PILOT Trial
A Randomized Clinical Trial

Stephen J. Nicholls, MBBS, PhD; Rishi Puri, MBBS, PhD; Christie M. Ballantyne, MD; J. Wouter Jukema, MD, PhD; John J. P. Kastelein, MD, PhD; Wolfgang Koenig, MD; R. Scott Wright, MD; David Kallend, MBBS; Peter Wijngaard, PhD; Marilyn Borgman, RN, BSN; Kathy Wolski, MPH; Steven E. Nissen, MD

IMPORTANCE Infusing a high-density lipoprotein mimetic containing apolipoprotein A-I Milano demonstrated potential atheroma regression in patients following an acute coronary syndrome. To our knowledge, the effect of infusing a new mimetic preparation (MDCO-216) with contemporary statin therapy is unknown.

OBJECTIVE To determine the effect of infusing MDCO-216 on coronary atherosclerosis progression.

DESIGN, SETTING, AND PARTICIPANTS This double-blind, randomized clinical trial conducted in 22 hospitals in Canada and Europe compared the effects of 5 weekly intravenous infusions of MDCO-216 at a dose of 20 mg/kg weekly (n = 59) with placebo (n = 67) in statin-treated patients with an acute coronary syndrome.

MAIN OUTCOMES AND MEASURES The primary efficacy measure was the nominal change in percent atheroma volume (PAV) from baseline to day 36 as measured by serial intravascular ultrasonography. The secondary efficacy measures were the nominal changes in normalized total atheroma volume (TAV), atheroma volume in the most diseased 10-mm segment, and the percentage of patients who demonstrated plaque regression. Safety and tolerability were also evaluated.

RESULTS Among 122 randomized patients (mean [SD] age, 61.8 [10.4] years; 93 men [76.2%]; 61 [50.0%] with prior statin use; and a mean [SD] low-density lipoprotein cholesterol [LDL-C] level of 87.6 [40.5] mg/dL [to convert to millimoles per liter, multiply by 0.0259]), 113 (92.6%) had evaluable imaging results at follow-up. The receiving-treatment LDL-C levels were comparable with the placebo and MDCO-216 (68.6 vs 70.5 mg/dL; difference, −2.5 mg/dL; 95% CI, −10.1 to 5.0; $P = .51$). A reduction in high-density lipoprotein cholesterol levels was observed in MDCO, but not placebo patients (−3.3 vs 3.0 mg/dL [to convert to millimoles per liter, multiply by 0.0259]; difference, −6.3 mg/dL; 95% CI, −8.5 to −4.1; $P < .001$). Percent atheroma volume, which was adjusted for baseline values, decreased 0.94% with the placebo and 0.21% with MDCO-216 (difference, 0.73%; 95% CI, −0.07 to 1.52; $P = .07$). Normalized TAV decreased 7.9 mm^3 with the placebo and 6.4 mm^3 with MDCO-216 (difference, 1.6 mm^3; 95% CI, −5.6 to 8.7; $P = .67$), and atheroma volume in the most diseased segment decreased 1.8 mm^3 with the placebo and 2.2 mm^3 with MDCO-216 (difference 0.4 mm^3; 95% CI, −4.4 to 3.5; $P = .83$). A similar percentage of patients demonstrated a regression of PAV (67.2% vs 55.8%; $P = .21$) and TAV (68.9% vs 71.2%; $P = .79$) in the placebo and MDCO-216 groups, respectively.

CONCLUSIONS AND RELEVANCE Among patients with an acute coronary syndrome, infusing MDCO-216 did not produce an incremental plaque regression in the setting of contemporary statin therapy.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Stephen J. Nicholls, MBBS, PhD, South Australian Health and Medical Research Institute, PO Box 11060, Adelaide, SA 5001, Australia (stephen.nicholls@sahmri.com).

The substantial residual clinical risk that persists despite widespread use of statin therapy[1] motivates ongoing efforts to identify novel therapeutic approaches to the treatment of atherosclerotic cardiovascular disease. High-density lipoproteins (HDLs) have received considerable attention as a therapeutic target based on epidemiology[2,3] and animal[4-6] studies that suggest a potential protective role for this lipoprotein. Several recent clinical trials of HDL cholesterol-raising therapies have failed to demonstrate a favorable effect on cardiovascular events in the setting of statin treatment.[7-12] Recently, attention has turned to strategies that may enhance the functional properties of HDL.

Infusing lipid-poor HDL mimetics has been reported to exert favorable effects on lipid transport[13,14] and endothelial function,[15,16] with robust increases in HDL cholesterol levels. A preliminary proof-of-concept study demonstrated that 5 weekly intravenous infusions of an HDL mimetic containing a recombinant form of the naturally occurring variant apolipoprotein (apo) A-I Milano (ETC-216) resulted in a signal of potential rapid regression of coronary atherosclerosis on intravascular ultrasonography (IVUS) in patients with a recent acute coronary syndrome (ACS).[17] This finding stimulated considerable interest in the field of HDL therapy as a potential strategy for patients with established coronary disease.

Refining the manufacturing process has led to the production of large quantities of a purified form of the mimetic (MDCO-216), retaining the ability to promote cholesterol efflux[18,19] without any adverse effect on immune function.[20] However, to our knowledge, the effect of MDCO-216 on atherosclerotic plaques has not been established in a contemporary setting where patients with ACS receive intensive statin therapy. The MDCO-216 Infusions Leading to Changes in Atherosclerosis: a Novel Therapy in Development to Improve Cardiovascular Outcomes—Proof of Concept IVUS, Lipids, and Other Surrogate Biomarkers (MILANO-PILOT) trial was designed to assess whether infusions of MDCO-216 would reduce the burden of coronary atherosclerosis as measured by IVUS.

Key Points

Question Does the infusion of the high-density lipoprotein mimetic MDCO-216 modify coronary atherosclerosis disease progression?

Findings In this randomized clinical trial, 122 patients with an acute coronary syndrome were treated with weekly intravenous infusions of MDCO-216 or a placebo for 6 weeks and underwent serial intravascular ultrasonography determination of coronary atheroma volume. Infusing MDCO-216 did not promote the regression of coronary atherosclerosis compared with the placebo in statin-treated patients.

Meaning Adding the high-density lipoprotein mimetic MDCO-216 did not produce plaque regression in statin-treated patients following an acute coronary syndrome.

Methods

Study Design

The MILANO-PILOT trial was a randomized, multicenter, double-blind, placebo-controlled clinical trial. The randomization was stratified according to geographic region and statin use prior to the index ACS event. The trial was designed by the Cleveland Clinic Coordinating Center for Clinical Research (C5Research) in collaboration with the sponsor. Institutional review boards at each site approved the protocol and patients provided written informed consent.

Patients were eligible for inclusion if they were 18 years or older, had an ACS event within the prior 14 days that required a clinically indicated coronary angiogram, and target vessel deemed suitable for imaging, defined as a major epicardial coronary artery that contained a maximum lumen stenosis between 20% to 50% and not having undergone prior revascularization. Patients were excluded if they had uncontrolled diabetes or hypertension, a triglyceride level of more than 400 mg/dL (to convert to millimoles per liter, multiply by 0.0113) or heart failure, renal dysfunction, or liver disease. Patients were asked to identify race/ethnicity according to fixed categories that were determined by the study protocol to evaluate potential differences in concomitant treatment and atheroma burden.

Patients underwent randomization in a 1:1 allocation ratio using an interactive voice response system to treatment with MDCO-216 at a dose of 20 mg/kg or a saline placebo that were administered weekly on 5 occasions via intravenous infusion. During the treatment period, patients underwent clinic visits at the time of each study drug infusion and repeated IVUS imaging at day 36. An independent, unmasked data monitoring committee that was led by an academic cardiologist reviewed clinical trial safety during the study.

Acquisition and Analysis of Ultrasonography Images

Following coronary angiography, baseline IVUS was performed. The methods of image acquisition and analysis have been described previously.[17,21-29] Imaging was performed in a single artery and screened by a core laboratory. Patients who met prespecified requirements for image quality were eligible for randomization. At day 36, patients underwent a second ultrasonographic examination within the same artery. Using digitized images, personnel who were unaware of the treatment status of the participants measured the lumen and external elastic membrane in images within a matched artery segment. The measurement personnel were masked to the sequence of the imaging studies (baseline vs follow-up). The accuracy and reproducibility of this method have been reported previously.[17,21-28]

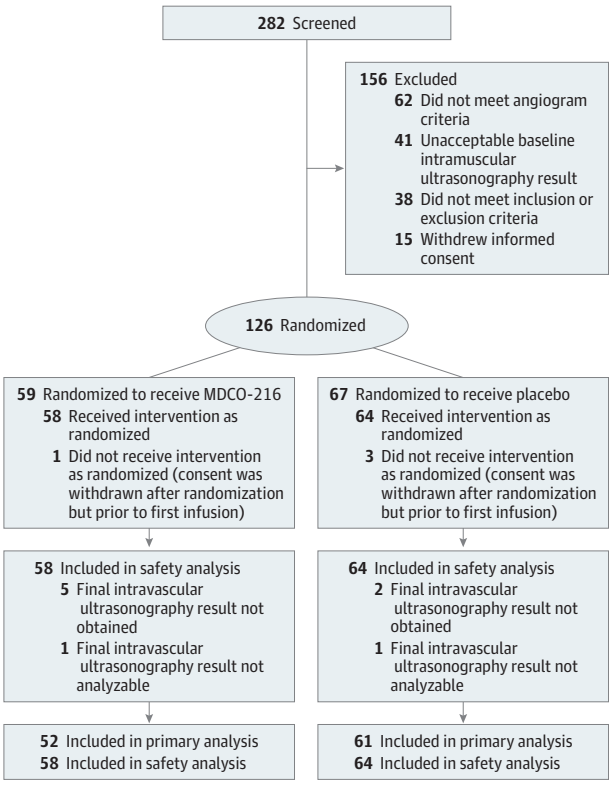
The primary efficacy measure, percent atheroma volume (PAV), was calculated as follows:

$$PAV = \frac{\sum(EEM_{area} - Lumen_{area})}{\sum EEM_{area}} \times 100$$

in which external elastic membrane area is the cross-sectional area of the external elastic membrane and $Lumen_{area}$ is the cross-sectional area of the lumen. The change in PAV was calculated as the PAV at day 36 minus the PAV at baseline. A secondary measure of efficacy, normalized total atheroma volume (TAV), was calculated as follows:

$$TAV_{Normalized} = \frac{\sum(EEM_{area} - Lumen_{area})}{\text{Number of Images in Pullback}} \times \text{Median number of images in cohort}$$

Figure. Flow Diagram of Patients Throughout the Trial



in which the average plaque area in each image was multiplied by the median number of images that were analyzed in the entire cohort to compensate for differences in segment length between patients. The change in normalized TAV was calculated as the TAV at day 36 minus the TAV at baseline. The change in atheroma volume was also determined in the 10-mm segment that contained the greatest atheroma volume at baseline. Regression was defined as any decrease in PAV or TAV from baseline.

Efficacy End Points

The primary efficacy end point was the nominal change in PAV from baseline to day 36 as described previously. The secondary efficacy end points included the nominal change in TAV throughout the entire vessel analyzed and within the 10-mm segment that contained the greatest atheroma volume from baseline to day 36 and the percentage of participants who demonstrated a regression of PAV and TAV, defined as any reduction in the parameter from baseline.

Statistical Analysis

The study protocol and statistical analysis plan are available in Supplements 1 and 2. All statistical analyses were performed using SAS, version 9.4 (SAS Institute). For normally distributed continuous variables, means and standard deviations are reported. For variables that are not normally distributed, medians and interquartile ranges are reported. A modified intent-to-treat analysis was applied that included all participants who received at least 1 dose of study drug with evaluable imaging results at both points. Self-reported race/ethnicity by participants was recorded. Intravascular ultrasonography efficacy parameters are reported as mean and standard deviation and median with distribution free 95% confidence intervals. Treatment groups were compared using analysis of covariance with adjustment for baseline value, previous statin use, and geographic region. Absolute and percentage changes in laboratory parameters were determined as the difference from baseline to average postbaseline values.

For the change in the primary efficacy parameter, PAV, a sample size of 50 patients in each treatment group provided 70% power at a 2-sided α of .05 to detect a nominal treatment difference of 1.5% assuming a 3.0% SD. The limited power reflected the pilot study design. Assuming a withdrawal rate of 20%, 120 randomized patients were required. All reported *P* values are 2-sided. $P < .05$ was considered statistically significant.

Table 1. Baseline Characteristics of 122 Patients in the Randomized Population Who Received the Study Drug[a]

Parameter	Placebo (n = 64)	MDCO-216 (n = 58)
Age, mean (SD), y	61.4 (10.3)	62.2 (10.6)
Men	48 (75.0)	45 (77.6)
White	63 (98.4)	56 (96.6)
BMI, mean (SD)	28.0 (4.2)	29.0 (13.9)
Hypertension	36/63 (57.1)	42/57 (73.7)
Previous PCI	10 (15.6)	6 (10.3)
Previous MI	5 (7.8)	7 (12.1)
Smoking	21 (32.8)	24 (41.4)
Diabetes	13/63 (20.6)	11/57 (19.3)
Baseline statin use	33 (51.6)	28 (48.3)
High intensity	11 (33.3)	15 (53.6)
Baseline medications		
Anti-platelet therapy	63 (98.4)	58 (100.0)
β-Blocker	50 (78.1)	50 (86.2)
ACE inhibitor	45 (70.3)	49 (84.5)
ARB	2 (3.1)	5 (8.6)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MI, myocardial infarction; PCI, percutaneous coronary intervention.

[a] Four patients did not receive study drug.

Results

Participants Characteristics

The demographic characteristics of patients who were enrolled in the study are described in the **Figure**. From December 14, 2015, to August 28, 2016, at 22 centers 126 patients were randomized and 122 (96.8) received study the drug (64 [52.5%] were randomized to the placebo group and 58 [47.5%] to the MDCO-216 treatment group). A total of 113 patients (89.7%) had evaluable IVUS imaging results at both baseline and follow-up. Of these patients, 61 (54.0%) were in the placebo group and 52 (46.0%) were in the MDCO-216 group. The mean (SD) number of infusions administered was 4.7 (1.9), with 106 (87%) receiving all 5 infusions of study drug. **Table 1** reports the

baseline characteristics of randomized patients who received study drug. Patients (mean [SD] age, 61.8 [10.4] years; 93 men [76.2%]; 119 [97.5%] white) presented with an ACS and had a high prevalence of atherosclerotic risk factors (hypertension, 78 [65%]; diabetes, 24 [20%]; smoking, 45 [36.9%]; prior myocardial infarction, 12 [9.8%]; prior coronary revascularization, 16 [13.1%]). Prior to the index ACS event, 63 patients (50%) had been previously treated with a statin, of whom 26 (42.6%) were receiving high-intensity statins (atorvastatin ≥ 40 mg or rosuvastatin ≥ 20 mg). During the course of the study, all patients were treated with a statin (54 [44.3%] receiving high-intensity statins).

Biochemical Measurements

Table 2 summarizes the baseline and receiving-treatment laboratory values for the 122 patients who received study drug. The time-weighted average of all postbaseline measurements demonstrated that the mean (SD) low-density lipoprotein cholesterol (LDL-C) levels were 68.6 (31.0) mg/dL (to convert to millimoles per liter, multiply by 0.0259) in the placebo group and 70.5 (21.9) mg/dL in the MDCO-216 group, representing a decrease in both groups from baseline (between-groups difference, −2.5 mg/dL; 95% CI, −10.1 to 5.0; $P = .51$). In contrast to the placebo group, MDCO-216–treated patients demonstrated reductions in HDL cholesterol (HDL-C) levels (−3.3 vs 3.0 mg/dL [to convert to millimoles per liter, multiply by 0.0259]; between-groups difference, 6.3 mg/dL; 95% CI, −8.5 to −4.1; $P < .001$) and apoA-I (−5.4 vs 8.0 mg/dL [to convert to grams per liter, multiply by 0.01]; between-groups difference, −13.4 mg/dL; 95% CI, 20.6 to −6.2; $P < .001$). During the course of the study in the 2 hours following the study drug infusion, a progressive reduction in HDL-C levels (−2.0 vs 0.8 mg/dL; between-groups difference, −2.8 mg/dL; 95% CI, −5.0 to −0.58; $P = .01$) and an increase in apoA-I (23.1 vs 1.8 mg/dL; between-groups difference, 21.4 mg/dL; 95% CI, 14.1-28.6; $P < .001$) were observed in the MDCO-216 treatment group, consistent with prior observations of this mimetic (eFigure 1 in Supplement 3). Time-weighted median high-sensitivity C-reactive protein levels from baseline to day 36 were 1.9 mg/L (interquartile range, 0.9-5.0) in the placebo group and 3.0 mg/L (interquartile range, 1.7-6.1) in the MDCO-216 group ($P = .09$), having been 7.2 and 7.5 mg/L at baseline, respectively.

Primary and Secondary IVUS End Points

The changes in IVUS measures of plaque burden are summarized in **Table 3**. The primary efficacy measure, PAV, decreased by 0.94% in the placebo group ($P = .02$ compared with the baseline) and 0.21% in the MDCO-216 group ($P = .58$ compared with the baseline; between-groups difference, 0.73%; 95% CI, −0.07 to 1.52; $P = .07$). The secondary efficacy measure, TAV, decreased by 7.9 mm^3 in the placebo group ($P = .02$ compared with the baseline) and by 6.4 mm^3 in the MDCO-216 group ($P = .07$ compared with the baseline; between-groups difference, 1.6%; 95% CI, −5.6 to 8.7; $P = .67$). Atheroma volume in the 10-mm segment containing the greatest plaque burden at baseline decreased by 1.8 mm^3 in the placebo group ($P = .35$ compared with the baseline) and by 2.2 mm^3 in the MDCO-216 group ($P = .22$ compared with the baseline; between-groups difference, −0.4%; 95% CI, −4.4 to 3.5; $P = .83$). A similar percentage of patients demonstrated a regression in PAV (67.2% vs 55.8%; $P = .21$) and TAV (68.9% vs 71.2%; $P = .79$) in the placebo and MDCO-216 treatment groups, respectively. For all prespecified subgroups, there was no statistical evidence of interaction with regard to treatment effects (eFigure 2 in Supplement 3). An exploratory analysis demonstrated greater reductions in PAV with placebo compared with MDCO-216 (−1.39% vs −0.22%; $P = .03$) in patients treated with a statin before the index ACS event, although the numbers are small (n = 57) and caution should be applied to interpreting this finding (eTable 1 in Supplement 3).

Cholesterol Efflux Capacity

Acute thrombocytopenic purpura binding cassette subfamily A member 1 (ABCA1)–mediated cholesterol efflux was measured from a limited number of serum samples at study visits on days 1 and 29 immediately before the study drug infusion and at 2 and 4 hours following infusions, as previously described (eFigure 3 in Supplement 3). Compared with samples obtained before infusions, ABCA1-mediated efflux increased by 80.4% ($P < .001$ compared with the baseline) at 2 hours and by 41.6% ($P < .001$ compared with the baseline) at 4 hours on day 1. At the day 29 visit, ABCA 1 efflux increased by 90% ($P < .001$ compared with the baseline) at 2 hours and by 60.3% ($P < .001$ compared with the baseline) at 4 hours. No significant differences were observed between the 2 visits at any point. No significant correlation was observed between cholesterol efflux and plaque burden at the baseline or their change (eTable 2 in Supplement 3).

Laboratory and Clinical Adverse Events

Table 4 describes clinical adverse events, laboratory abnormalities, and the reasons for study discontinuation. In general, infusions were well tolerated in both groups, with no increased incidence of infusion reactions or biochemical abnormalities observed with the infusion of MDCO-216.

Discussion

A small preliminary study of infusions of an HDL mimetic containing apoA-I Milano (ETC-216) demonstrated a rapid regression of coronary atherosclerosis in patients following an ACS.[17] After refinements in the manufacturing process to enable the production of safe and large quantities of the HDL mimetic for clinical use (MDCO-216), we aimed to demonstrate a similar effect on coronary atherosclerosis. However, in the setting of patients who were treated with intense and established therapies for managing an ACS, we observed no incremental benefit of infusing MDCO-216 in patients with coronary disease. This suggests that infusing HDL that contains apoA-I Milano is unlikely to modulate the residual cardiovascular risk observed in patients treated with contemporary therapies following an ACS.

The preliminary observation that ETC-216 infusions promoted plaque regression in 2003[17] provided support for developing therapies targeting HDL function. This benefit

Table 2. Baseline and On-Treatment Biochemical Measures and Blood Pressure in the Randomized Population Who Received the Study Drug

Parameter	Baseline			Receiving-Treatment[a]			Absolute Change[b]		
	Placebo (n = 64)	MDCO-216 (n = 58)	*P* Value[c]	Placebo (n = 64)	MDCO-216 (n = 58)	*P* Value[c]	Placebo (n = 64)	MDCO-216 (n = 58)	*P* Value[c]
Cholesterol, mean (SD), mg/dL									
Total cholesterol	152.0 (41.9)	162.0 (49.0)	.24	138.4 (37.6)	133.7 (27.1)	.45	−16.1 (−22.6 to −9.6)	−25.6 (−32.4 to −18.8)	.05
LDL cholesterol	84.1 (37.7)	93.8 (44.2)	.21	68.6 (31.0)	70.5 (21.9)	.71	−18.0 (−23.2 to −12.8)	−20.5 (−26.0 to −15.1)	.51
HDL cholesterol	43.5 (10.8)	43.3 (9.7)	.94	46.4 (12.3)	40.0 (11.4)	.005	3.0 (1.4 to 4.5)	−3.3 (−4.9 to −1.7)	<.001
Triglycerides, median (IQR), mg/dL[d]	104.5 (85.0 to 141.5)	108.0 (92.0 to 146.0)	.47	103.0 (76.0 to 148.9)	114.2 (82.4 to 104.4)	.58	−4.6 (−12.9 to 3.7)	−8.3 (−17.0 to 0.4)	.54
Non-HDL cholesterol, mean (SD), mg/dL	108.5 (41.1)	118.7 (49.0)	.23	92.0 (34.1)	93.7 (25.4)	.76	−19.2 (−25.1 to −13.3)	−22.1 (−28.2 to −16.0)	.50
Free cholesterol, mean (SD), mg/dL	42.0 (12.2)	44.2 (15.1)	.37	37.7 (10.1)	37.2 (7.4)	.76	−4.9 (−6.7 to −3.1)	−6.4 (−8.2 to −4.5)	.25
Apolipoprotein, mean (SD), mg/dL									
ApoB	78.8 (25.9)	85.0 (31.6)	.25	66.8 (20.0)	68.6 (17.1)	.62	−13.6 (−17.2 to −10.0)	−14.7 (−18.4 to −10.9)	.69
ApoA-I	123.2 (19.5)	123.1 (17.8)	.99	131.2 (21.8)	117.7 (26.4)	.003	8.0 (3.0 to 13.0)	−5.4 (−10.6 to −0.2)	<.001
ApoB/A-I	0.65 (0.2)	0.70 (0.3)	.30	0.52 (0.2)	0.62 (0.2)	.005	−0.15 (−0.18 to −0.11)	−0.07 (−0.10 to −0.03)	.004
hsCRP level, median (IQR), mg/L[d]	7.2 (2.1 to 14.4)	7.5 (3.2 to 14.9)	.41	1.9 (0.9 to 5.0)	3.0 (1.7 to 6.1)	.09	−7.5 (−9.0 to −5.9)	−8.1 (−9.7 to −6.5)	.58
Glucose level, mean (SD), mg/dL	115.1 (39.4)	109.5 (41.6)	.46	114.1 (27.8)	112.4 (44.2)	.81	−0.35 (−5.2 to 4.5)	2.2 (−2.9 to 7.2)	.48
Systolic BP, mean (SD), mm Hg	127.0 (19.7)	126.6 (18.4)	.91	126.8 (15.9)	129.3 (12.1)	.33	−0.4 (−2.9 to 2.1)	2.7 (0.1 to 5.4)	.10
Diastolic BP, mean (SD), mm Hg	73.7 (11.1)	74.5 (9.1)	.64	74.4 (8.2)	76.3 (6.0)	.17	0.4 (−1.2 to 1.9)	1.9 (0.3 to 3.5)	.18

Abbreviations: Apo, apolipoprotein; BP, blood pressure; CRP, C-reactive protein; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL, low-density lipoprotein.

SI conversion factors: To convert apolipoprotein to grams per liter, multiply by 0.01; for cholesterol, HDL, and LDL to millimoles per liter, multiply by 0.0259; for glucose to millimoles per liter, multiply by 0.0555; for triglycerides to millimoles per liter, multiply by 0.0113.

[a] Receiving-treatment laboratory parameters are the time-weighted mean (SD) of all postbaseline values.

[b] Absolute changes are presented as least square means (95% CI) derived from an analysis of covariance model with the baseline value as a covariate and treatment group, previous statin use, and country as factors.

[c] *P* value for between-treatment group comparison.

[d] Median and interquartile range are presented for nonnormally distributed parameters and tested using the Wilcoxon rank sum test.

was observed in the absence of any demonstrable change in traditional HDL cholesterol measures and suggested that promoting HDL function may represent a novel approach in reducing cardiovascular risk. This observation motivated not only the development of HDL infusions, but also a range of additional therapeutic strategies that target HDL. The mechanisms underlying the lack of benefit in this study remain uncertain. While the manufacturing process was refined to produce MDCO-216, biochemical and functional studies suggested that the mimetic exerted predictable changes in HDL metabolism and cholesterol efflux capacity. This was evidenced by reproducible reductions in both HDL-C and apoA-I levels, which is likely to reflect an altered metabolism of endogenous apoA-I with infusions of apoA-I Milano. However, background medical therapies for patients following an ACS have changed dramatically since 2003, specifically involving a more frequent use of higher-intensity statin therapy with rapid reductions in LDL-C and inflammatory markers. In fact, not all patients in the 2003 study received background statin therapy. This may have influenced the ability of HDL mimetics to modulate coronary atherosclerosis. It is also possible that the original report reflected a false-positive finding.

The findings provide further uncertainty regarding the therapeutic potential of targeting HDL functionality. While population studies consistently demonstrate an inverse relationship between HDL-C and cardiovascular events,[2,3] multiple clinical trials over the past decade have failed to demonstrate any benefit of infusing HDL or raising HDL-C levels on coronary atherosclerosis[25] or clinical events.[7-12] More recent studies have suggested the potential benefits of the cholesteryl ester transfer protein inhibitor anacetrapib; however, this agent has additional effects, such as reducing levels of apolipoprotein B that contains atherogenic lipoproteins, and its long-term safety is not established.[30] As a result, therapies that uniquely target HDL have yet to demonsrate any clinical benefit. Other strategies that target HDL with different protein and lipid composition than

Table 3. Primary and Secondary Study Intravascular Ultrasonography End Points

Parameter	Placebo (n = 61)	MDCO-216 (n = 52)	Mean Between Group Differences, (95% CI) (MDCO Minus Placebo)	*P* Value
Baseline				
Percent atheroma volume, %				
Mean (SD)	41.3 (7.8)	41.6 (7.2)	0.3 (−2.5 to 3.1)	.84
Median (95% CI)	41.2 (39.1 to 44.2)	41.0 (39.2 to 44.7)		
Total atheroma volume, mm^3				
Mean (SD)	207.9 (94.4)	195.9 (68.3)	−12.0 (−42.5 to 18.4)	.02
Median (95% CI)	190.5 (158.6 to 235.2)	184.4 (158.8 to 217.1)		
Most diseased 10-mm atheroma volume, mm^3				
Mean (SD)	54.9 (31.2)	66.0 (28.7)	11.1 (−1.9 to 24.2)	.09
Median (95% CI)	47.0 (37.6 to 62.3)	63.0 (52.7 to 77.2)		
Follow-up at day 36				
Percent atheroma volume, %				
Mean (SD)	40.2 (7.9)	41.2 (7.2)	1.0 (−1.8 to 3.9)	.48
Median (95% CI)	40.2 (37.8 to 42.5)	41.5 (38.3 to 43.2)		
Total atheroma volume, mm^3				
Mean (SD)	202.0 (94.8)	192.0 (64.7)	−10.0 (−40.0 to 20.0)	.51
Median (95% CI)	182.0 (143.0 to 236.2)	183.9 (149.7 to 219.4)		
Most diseased 10-mm atheroma volume, mm^3				
Mean (SD)	53.4 (32.7)	64.5 (29.4)	11.0 (−2.5 to 24.6)	.11
Median (95% CI)	42.8 (38.7 to 57.3)	59.5 (53.5 to 72.2)		
Change from baseline				Between-groups *P* Value[a]
Percent atheroma volume, %				
Least-square means (95% CI)	−0.94 (−1.7 to −0.18)	−0.21 (−0.98 to 0.55)	0.73 (−0.07 to 1.52)	.07
P value for change from baseline	.02	.58		
Total atheroma volume, mm^3				
Least-square means (95% CI)	−7.9 (−14.6 to −1.3)	−6.4 (−13.1 to 0.4)	1.6 (−5.6 to 8.7)	.67
P value for change from baseline	.02	.07		
Most diseased 10-mm atheroma volume, mm^3				
Least-square means (95% CI)	−1.8 (−5.6 to 1.4)	−2.2 (−5.8 to 1.4)	−0.4 (−4.4 to 3.5)	.83
P value for change from baseline	.35	.22		
Patients with regression of percent atheroma volume, % (95% CI)	67.2 (55.0 to 78.0)	55.8 (42.0 to 69.0)	NA	.21
Patients with regression of total atheroma volume, % (95% CI)	68.9 (57.0 to 80.0)	71.2 (58.0 to 83.0)	NA	.79

Abbreviation: NA, not applicable.

[a] The *P* values for comparison between treatments for change from baseline were generated from an analysis of covariance. Between differences are presented as least square means (95% CI).

MDCO-216 are continuing to undergo therapeutic evaluation.[14] Until such an agent is proven to be clinically effective, the HDL hypothesis remains an interesting scientific concept that lacks clinical validation.

The results of this study also raise questions regarding the utility of assessing the effect of medical therapies on cholesterol efflux. Promoting the removal of cholesterol from macrophages within atherosclerotic plaques has been postulated as a potential therapeutic approach for managing coronary artery disease. The development of standardized ex vivo assays of cholesterol efflux capacity has been considered useful in the early evaluation of novel HDL therapies. This is supported by reports that static measures of cholesterol efflux capacity are associated with cardiovascular risk.[31] While MDCO-216 infusions produced predictable increases in cholesterol efflux capacity,[18,19] this did not translate to favorable

Table 4. Clinical and Biochemical Adverse Events and Reasons for Discontinuation in the Safety Population

Parameter	No. (%)	
	Placebo (n = 64)	MDCO-216 (n = 58)
Clinically important adverse events		
Infusion site reaction	0	1 (1.7)
Cardiac disorders[a]	2 (3.1)	6 (10.3)
Acute hepatitis and cholethiasis	0	1 (1.7)
Abnormality in laboratory value		
Aspartate or alanine aminotransferase >2 × ULN	1 (1.6)	1 (1.7)
Total bilirubin >2 × ULN	0	1 (1.7)
Maximum creatinine kinase >3 × ULN	3 (4.7)	0
Discontinuation from treatment		
Patients, No.	2 (3.1)	5 (8.6)
Reason for discontinuation		
Preference of patient	2 (3.1)	3 (5.2)
Adverse event	0	0
Lost to follow-up	0	1 (1.7)
Other	0	1 (1.7)

Abbreviation: ULN, upper limit of normal.

[a] A total of 8 patients (6.6%) had a cardiac disorder described as a serious adverse event. Events included unstable angina (1 [1.5%] in MDCO-216), atrial flutter (1 [1.5%] in MDCO-216), coronary artery disease (3 [4.5%] in MDCO-216 and 2 [3.1%] in the placebo group), and ventricular extrasystoles (1 [1.5%] in MDCO-216).

effects on coronary atherosclerosis. Furthermore, we observed no significant correlation between changes in cholesterol efflux and any measure of coronary plaque burden. This raises uncertainty regarding the use of cholesterol efflux capacity as a reliable approach to developing novel atheroprotective agents. Cholesterol efflux, like HDL, will therefore continue to require positive findings from cardiovascular clinical trials for ongoing validation.

Limitations

Several caveats should be noted. While the study was small, there was no evident trend toward the benefit of infusing MDCO-216 on any measure of coronary atherosclerosis. Nonetheless, this imaging study was larger than the original trial that was conducted in 2003. Whether HDL infusions would be more likely to be effective in the setting of stable coronary artery disease, in which the background therapy does not change and there are no major reductions in atherogenic lipoproteins and inflammatory markers, remains unknown. Preclinical studies suggest that HDL infusions may favorably modulate the cellular composition of atherosclerotic plaques before reducing atheroma size.[32,33] However, to our knowledge, there is currently no validated imaging modality that correlates with cardiovascular outcomes that could be used to demonstrate such effects. In contrast, changes in IVUS-derived plaque burden measures are associated with cardiovascular events,[34] and therapies that favorably affect coronary plaques have been demonstrated to reduce cardiovascular events.[29,35] Changes in vascular function may present an alternative approach for evaluation, although their correlation with outcomes is similarly limited. As a result, it would seem unlikely that an alternative approach to evaluating MDCO-216 would have provided a compelling reason to advance this mimetic in clinical development.

Conclusions

Infusing an HDL mimetic containing apoA-I Milano did not promote a rapid regression of coronary atherosclerosis in patients following an ACS. This provides further disappointing news for the clinical development of therapies that target HDL in the setting of contemporary medical treatment for patients with coronary disease. Until such an agent does prove to have a benefical effect on coronary atherosclerosis or clinical events, increasing interest will focus on alternative approaches to reducing residual cardiovascular risk.

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Author Affiliations: South Australian Health and Medical Research Institute, University of Adelaide, Adelaide, Australia (Nicholls); Department of Cardiovascular Medicine and Cleveland Clinic Coordinating Center for Clinical Research, Cleveland, Ohio (Nicholls, Puri, Borgman, Wolski, Nissen); Section of Cardiovascular Research, Baylor College of Medicine, Houston, Texas (Ballantyne); Methodist DeBakey Heart and Vascular Center, Houston, Texas (Ballantyne); Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands (Jukema); Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands (Kastelein); Deutsches Herzzentrum München, Technische Universität München, Munich, Germany (Koenig); Deutsches Zentrum für Herz-Kreislauf-Forschung E.V., partner site Munich Heart Alliance, Munich, Germany (Koenig); Department of Internal Medicine, University of Ulm Medical Center, Ulm, Germany (Koenig); Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota (Wright); The Medicines Company, Parsippany, New Jersey (Kallend, Wijngaard).

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Concept and design: Nicholls, Puri, Jukema, Kastelein, Kallend, Wijngaard, Borgman, Nissen.
Acquisition, analysis, or interpretation of data: Nicholls, Puri, Ballantyne, Jukema, Kastelein, Koenig, Wright, Kallend, Wijngaard, Wolski, Nissen.
Drafting of the manuscript: Nicholls, Borgman.
Critical revision of the manuscript for important intellectual content: Puri, Ballantyne, Jukema, Kastelein, Koenig, Wright, Kallend, Wijngaard, Wolski, Nissen.
Statistical analysis: Nicholls, Kallend, Wijngaard, Wolski.
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