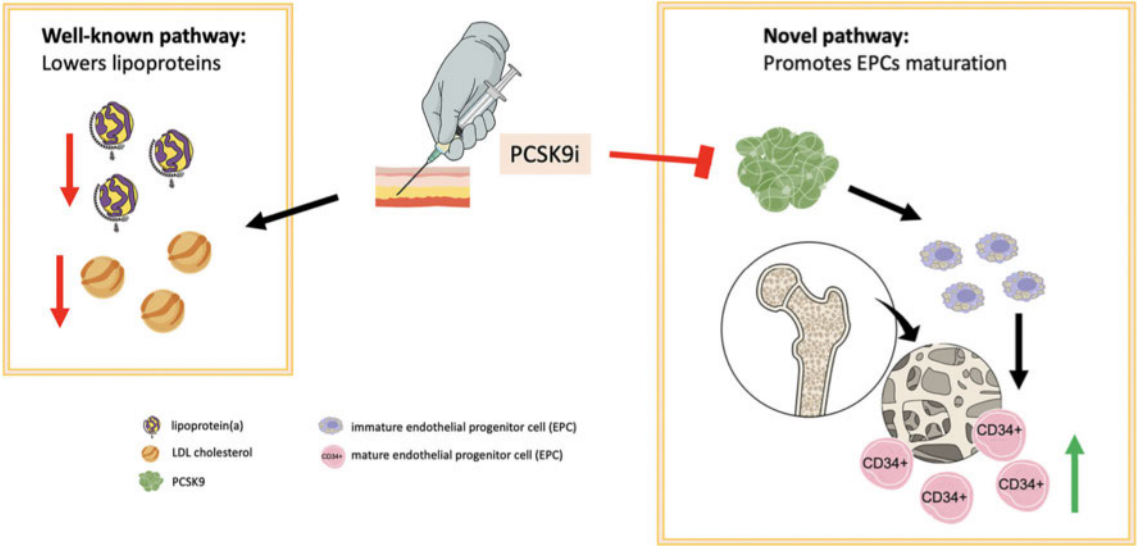
Accepted Manuscript online: 2026-06-24 Article published online: 2026-07-09

Original Article

PCSK9 Inhibitors Increase CD34+ But Not Other Endothelial Progenitor Cells in Patients with Chronic Coronary Disease and Increased Lp(a) Values

Sabina Ugovšek[1], Andreja Rehberger Likozar[2], Tina Levstek[3,4], Katarina Trebušak Podkrajšek[3,4], Janja Zupan[5], Frieda Marka[6], Tamara Trimmel[6], Mira Brekalo[6], Walter S. Speidl[6], Philipp J. Hohensinner[7,8], Patrick Haider[6], Miran Šebeštjen[1,2,3,9]
Affiliation addresses are listed at the end of the article.

GRAPHICAL ABSTRACT



ABSTRACT

Background Endothelial dysfunction is an independent predictor of cardiovascular events in patients with established atherosclerosis, while the circulating levels of endothelial progenitor cells (EPCs) reflect active endothelial function in heart failure patients. Although protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (PCSK9i) lower lipid concentration and reduce cardiovascular events, their impact on endothelial function remains poorly understood.

Purpose We aimed to examine the effect of PCSK9i on the levels of EPCs in the peripheral blood of patients with chronic coronary disease and significantly elevated lipoprotein(a) (Lp(a)) concentrations.

Methods In this randomized, double-blind, placebo-controlled trial, we included 100 statin-treated patients at least 6 months post-myocardial infarction with elevated Lp(a) values. The patients received PCSK9i or a placebo every 2 weeks for 6 months. Biochemical and flow cytometric analyses of peripheral blood mononuclear cells were performed at baseline and after 6 months.

Results Treatment with PCSK9i increased the levels of mature EPCs ($CD34^+$) compared with placebo ($p = 0.003$). In contrast, no significant effects were observed on early EPC subtypes ($CD34^+CD309^+$, $CD34^+CD133^+$, $CD133^+CD309^+$, and $CD133^+$; $p = 0.611$, $p = 0.451$, $p = 0.739$, and $p = 0.161$, respectively). The increase in mature EPCs ($CD34^+$) levels did not correlate with changes in PCSK9 concentration. No associations were detected between changes in PCSK9 concentration and changes in levels of EPC subtypes predominantly expressing CD309, nor between changes in levels of any EPCs and lipoprotein concentration variations at baseline or at the end of the study.

© 2026. The Author(s).

Conclusion In patients with chronic coronary disease, treatment with PCSK9i increases circulating levels of mature CD34$^+$ EPCs, without affecting other EPC subtypes.

Keywords endothelial function, endothelial progenitor cells, CD34$^+$, lipoprotein(a), proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (PCSK9i), myocardial infarction

received March 01, 2026 | **accepted after revision** June 23, 2026 | **accepted manuscript online** June 24, 2026 | **article published online** 2026

Bibliography TH Open 2026; 10: a29012564 **DOI** 10.1055/a-2901-2564 **Art ID** THOpen-26-03-0017
© 2026. The Author(s). Georg Thieme Verlag KG, Oswald-Hesse-Straße 50, 70469 Stuttgart, Germany

Correspondence Sabina Ugovšek, MD, Faculty of Medicine, University of Ljubljana, Vrazov trg 2, 1000 Ljubljana, Ljubljana, Slovenia, Email: ugovsek.sabina@gmail.com

Introduction

Atherosclerosis, along with its clinical consequences such as acute coronary syndrome, cerebrovascular complications, and peripheral vascular disease, remains one of the most common causes of both morbidity and mortality in the world.[1] It is a chronic inflammatory disease that begins with endothelial cell damage, progressing from endothelial dysfunction, which is the earliest detectable functional stage of atherosclerosis, to overt morphological changes. Endothelial dysfunction has been identified as an independent predictor for future cardiovascular events in patients with established atherosclerosis.[2] In one of our previous studies, blood levels of endothelial progenitor cells (EPCs) were shown to be an independent predictor of active endothelial function in heart failure patients, regardless of ischemic or non-ischemic etiology.[3] Furthermore, patients who experienced late-stent thrombosis had significantly lower circulating levels of EPCs compared with those without this complication,[4] suggesting that EPC depletion may impair endothelial regeneration and exacerbate arterial thrombosis risk.[5,6] This observation is consistent with findings by Werner et al.,[6] who demonstrated that reduced peripheral blood counts of EPCs were associated with higher rates of cardiovascular events and mortality even after adjustment for other risk factors. The levels of EPC are influenced by the presence of risk factors, including arterial hypertension,[7] smoking,[8] and lipoprotein levels.[9] Increased concentrations of oxidized forms of lipoproteins, especially oxidized low-density lipoprotein (oxLDL) cholesterol, promote EPC apoptosis and impair their differentiation into functional endothelial cells, further compromising their vascular repair capacity.[10] EPC populations are commonly classified based on the presence of surface markers. Cells expressing CD34 are generally considered mature EPCs, whereas cells expressing CD133 are regarded as immature EPCs.[11] The former exhibit greater biological activity, including the ability to differentiate into endothelial cells and thus contribute to neovascularization and endothelial regeneration.[12]

Lipoprotein(a) (Lp(a)) is a complex plasma protein that consists of LDL-cholesterol (LDL-C) and apolipoprotein B-100 (apoB) linked to the plasminogen-like apolipoprotein(a) (apo(a)) via a disulfide bond. Oxidized phospholipids bound to apo(a) drive Lp(a)-induced inflammation.[13] Despite the relatively high similarity between Lp(a) and LDL-C, Lp(a) is a risk factor that, independent of LDL-C concentration, increases the risk of acute cardiovascular events. There are no clinical data on the relationship between Lp(a) concentration and the number or activity of EPCs, but in vitro studies have shown that exposure of EPCs to increased concentrations of Lp(a) causes their increased apoptosis, and reduced proliferation, migration, adhesion, and angiogenesis.[14] Patients who have experienced a myocardial infarction (MI) remain at increased risk of recurrent events, particularly in the first few years following the primary MI.[15] In our group of patients, this risk is likely further amplified by suboptimal controlled LDL-C levels, despite maximally tolerated lipolytic therapy, as well as markedly elevated Lp(a) levels.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (PCSK9i) are the first class of drugs shown to significantly reduce both LDL-C and Lp(a) concentrations, and have also proven efficacy in preventing cardiovascular events.[16,17] The aim of our study was to examine the effect of PCSK9i on circulating levels of EPCs in peripheral blood in our group of patients.

Patients and Methods

Patients

The current study was performed using a patient cohort as published previously.[18] We included patients aged 18–65 years with chronic coronary disease, defined as at least 6 months after MI. Eligible patients were those who had experienced an MI before the age of 55 years and had serum Lp(a) levels ≥1,000 mg/L irrespective of LDL-C levels, or serum Lp(a) levels >600 mg/L in combination with LDL-C >2.6 mmol/L. The main exclusion criteria were liver transaminase levels exceeding three times the upper limit of normal, severe renal impairment, and serum creatinine >200 μmol/L, or a history of acute illness within the preceding 6 weeks. Patients were randomized to receive a PCSK9i (alirocumab 150 mg or evolocumab 140 mg subcutaneously every 2 weeks) or placebo for 6 months. At least 8 weeks prior to enrolment, all patients were receiving maximally tolerated statin therapy, with the addition of ezetimibe where indicated, as well as standard cardiovascular medications, including β-blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers, and antiplatelet drugs. Concomitant therapy remained unchanged throughout the study.

Approval for this study was obtained from the National Medical Ethics Committee of the Republic of Slovenia (reference number: KME 0120-357/2018/8). All patients signed written informed consent prior to inclusion in the study.

Peripheral Blood Mononuclear Cell Isolation

Peripheral blood mononuclear cells (PBMCs) were isolated from EDTA-anticoagulated blood using density gradient centrifugation with Ficoll-Paque PLUS based on a previously validated protocol.[19] The mixture was placed into a CoolCell freezing container (Corning, Corning, NY, United States) and initially stored at −80°C before being moved to liquid nitrogen for extended storage. Briefly, approximately 2 mL of 1× phosphate-buffered saline (PBS) was added to a 15-mL conical tube, and the buffy coat fraction was carefully transferred into the PBS. In a separate 15-mL conical tube, 3 mL of Ficoll-Paque PLUS was added. The diluted cell suspension was then gently layered onto the density gradient at an angle to minimize mixing of the phases. Samples were centrifuged at 400 × *g* for 40 min at 20 °C with the brake turned off.

Following centrifugation, the PBMC layer at the plasma–Ficoll interface was carefully collected using a pipette with a widened tip and transferred to a new tube. Cells were washed with PBS and centrifuged at 200 × *g* for 10 min at room temperature. The supernatant was discarded, and the cell pellet was resuspended in 2 mL of fresh PBS. This washing step was repeated once under the same conditions.

For cryopreservation and consecutive thawing for analysis, the handling was performed according to previously published data on cryopreservation of individual leukocyte subsets.[19] In detail, freezing medium consisting of fetal bovine serum (FBS Gold Seraglob, Schaffhausen, Switzerland) supplemented with 10% high-purity dimethyl sulfoxide (DMSO, >99.9%, Sigma–Aldrich, St. Louis, United States) was prepared. After the final wash, residual PBS was completely removed, and the cell pellet was gently resuspended in 1.3 mL of freezing medium. The cell suspension was transferred to cryovials and placed in CoolCell (Corning, Corning, NY, United States) freezing container to achieve an approximate cooling rate of −1°C/min before storage at −80°C for a maximum of 24 months. Thawing was performed by putting the cells at room temperature until a liquid layer formed. The cells were then transferred to ice-cold full PBMC medium and washed once using medium to get rid of DMSO.

Biochemical Analysis

Blood for laboratory analysis was drawn in the morning after 12 hours of fasting. Samples were collected from the antecubital vein into 5 mL vacuum-sealed tubes containing clot activator (Vacutube; LT Burnik, Skaručna, Slovenia). Blood was centrifuged at 2000 × *g* for 15 min to separate the serum. In fresh serum samples, we measured total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), apolipoprotein A1 (apoA1), and apoB by standard colorimetric or immunologic assays. We used an automated biochemical analyzer (Fusion 5.1; QuidelOrtho, Raritan, NJ, United States). The same biochemical analyzer was used to determine Lp(a) with the Denka reagent (Randox, Crumlin, United Kingdom). Because of the apo(a)-isoform-insensitive antibodies used in the reagent, the bias associated with apo(a) size is minimal. The Friedewald equation[20] was used to calculate LDL-C.

Total PCSK9 was measured in serum samples using a sandwich enzyme-linked immunosorbent assay (ELISA; Human Proprotein Convertase 9/PCSK9 Quantikine ELISA Kit, R&D Systems, Minneapolis, MN, United States) on a Sunrise microplate reader and Magellan software (Tecan, Männedorf, Switzerland) as instructed by the manufacturer. Sensitivity and assay range provided by the manufacturer were 0.219 and 0.6–40 ng/mL, respectively. Samples were diluted 1:20 with calibrator diluent. Samples exceeding the upper limit were diluted 1:40 and reanalyzed. The assay used measured total PCSK9 in serum, so it was not possible to distinguish between bound and unbound PCSK9.

Flow Cytometric Analysis of Peripheral Blood Mononuclear Cells

Flow cytometry was used to analyze PBMCs that had been cryopreserved for subsequent follow-up analysis (**Fig. 1**).

On the day of analysis, frozen PBMCs were rapidly thawed in 25 mL of cold PBS (Sigma–Aldrich, St. Louis, United States) and centrifuged at 500 × *g* for 5 min. The supernatant was removed, and the cell pellet was resuspended in 1 mL of PBS. A 70-µL aliquot was used to determine total cell count and population distribution using a Sysmex hematology analyzer set to the whole blood differential count mode. The cells were then washed once more and diluted to a final concentration of 2×10^7 cells/mL in PBS.

To label cell surface markers, 5 µL of a premixed antibody solution and 5 µL of the cell suspension were added to each well of a 96-well U-bottom plate. All samples were prepared in duplicate. EPCs were identified using fluorescently labeled antibodies against CD34 (PE/Cy7, BD Biosciences), CD309 (AlexaFluor488, BioLegend), and CD133 (BrilliantViolet421, BioLegend). Each antibody was used at 0.2 µL per well. Cells were incubated with the antibody mixture for 15 minutes in the dark at room temperature. After staining, cells were fixed by adding 220 µL of 1% paraformaldehyde in PBS. The samples were analyzed on the same day using a three-laser Attune flow cytometer (Thermo Fisher, Waltham, MA, United States). Data analysis was performed using Attune Cytometric Software v.5.3.1.

Statistical Analysis

For descriptive statistical analysis, we analyzed the normality of the distribution of continuous variables with the Shapiro–Wilk test. Continuous variables are presented as median with interquartile range (IQR) or as mean with standard deviation (SD), as appropriate. Frequencies were used to describe the distribution of the categorical variables. The chi-square test was used to compare the distribution of the categorical variables between different groups, whereas the *t* test or Mann–Whitney U test was used for the continuous variables. The Wilcoxon signed-rank test was used to assess within-group changes during the placebo and treatment periods. Correlations between continuous variables were calculated using Spearman's rank correlation coefficient (ρ). All statistical tests were two-sided. We used 0.05 as the level of statistical significance. To control for the risk of type I error due to multiple testing, the Bonferroni correction was applied, and the adjusted level of significance was set to 0.01. IBM SPSS Statistics version 27.0 (IBM Corporation, Armonk, NY, United States) was used to perform the statistical analyses. Figures were generated using GraphPad Prism 9 (San Diego, CA, United States). GPower was used to perform the power of the study calculations.[21]

© 2026. The Author(s).

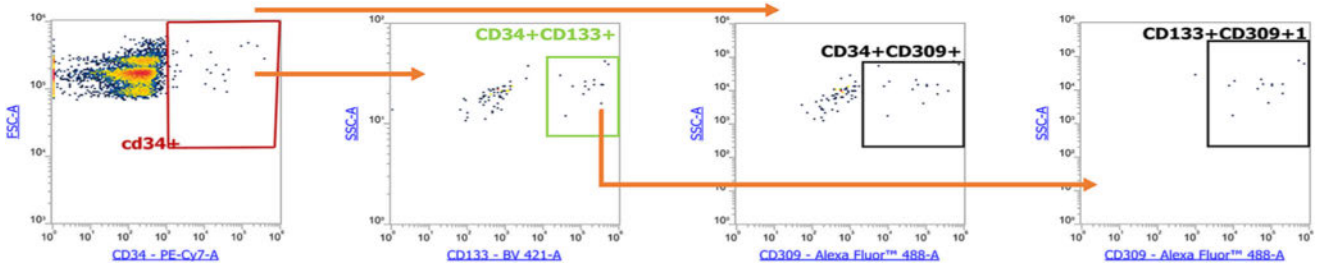


Fig. 1 Gating strategy for identification of CD34$^+$ endothelial progenitor cell (EPC) subsets in peripheral blood. Peripheral blood mononuclear cells were first visualized by forward scatter (FSC-A) versus side scatter (SSC-A), and CD34$^+$ cells were identified by gating on CD34-positive events. Within the CD34$^+$ population, co-expression of CD133 was used to define the CD34$^+$CD133$^+$ progenitor compartment. Other endothelial progenitor subsets were further characterized based on expression of CD309, identifying CD34$^+$CD309$^+$ and CD34$^+$CD133$^+$CD309$^+$ positive cells. Source: Created using GraphPad Prism 11.0.0.84.

The required sample size as determined using the apriori analysis (with the 0.80 power of the study, 0.15 effect size, and 0.05 α error) was 29 subjects per group.

Results

Patients' Characteristics

Since no significant differences were observed between the groups receiving alirocumab or evolocumab, either at baseline or after treatment, these two groups were combined to enhance the statistical power. The baseline characteristics of the study participants are summarized in **Table 1**. Clinical parameters, lipid indicators, and inflammatory parameters were comparable between groups. A total of 69 patients were enrolled in the active treatment group (34 treated with alirocumab and 35 with evolocumab), while there were 31 subjects in the placebo group. There were no significant differences between groups in age (50.7 ± 7.2 years in the treatment group vs. 47.6 ± 9.5 years in the placebo group; $p = 0.350$), body mass index (BMI, 28.4 ± 3.5 kg/m^2 vs. 28.6 ± 3.8 kg/m^2; $p = 0.863$), or sex distribution ($p = 0.753$). Additionally, the prevalence of diabetes ($p = 0.190$) and current smoking ($p = 0.547$) did not differ between the groups.

Effect of PCSK9i on Biochemical Characteristics

In the control group, 6 months of placebo treatment had no significant effect on lipoprotein fractions, except for HDL-C, which showed a statistically significant increase in concentration ($p = 0.010$). By contrast, treatment with PCSK9i led to significant changes in all lipoprotein fractions ($p < 0.001$ for all). Notably, high-sensitivity C-reactive protein (hs-CRP) concentrations—already below 1 mg/L at baseline—remained unchanged in both groups following treatment with either placebo or PCSK9i. Similarly, leukocyte counts did not change in any of the groups (**Fig. 2**).

Effect of PCSK9i on Endothelial Progenitor Cells

Treatment with PCSK9i significantly increased levels of all studied EPC populations. Interestingly, the placebo group also demonstrated significant increases in the majority of the EPC subsets, with the exception of CD34$^+$ and CD34$^+$CD309$^+$ cells (**Table 2**).

Interrelationship between Lipoprotein and Endothelial Progenitor Cell Levels and Their Changes

In the group treated with PCSK9i, changes in EPC levels were independent of lipoprotein changes (**Table 3**).

Table 1 The baseline patients' biochemical characteristics.

Parameter	Placebo group, *N* = 31	Active treatment group, *N* = 69	*p*-Value
Leukocytes (10^9/L)	7.1 ± 1.9	7.1 ± 1.7	0.935
Blood glucose (mmol/L)	6.7 ± 3.4	6.2 ± 1.7	0.375
TC (mmol/L)	4.3 ± 1.0	4.2 ± 0.8	0.812
LDL-C (mmol/L)	2.4 ± 0.9	2.3 ± 0.7	0.871
HDL-C (mmol/L)	1.1 ± 0.2	1.2 ± 0.3	0.227
TG (mmol/L)	1.6 (1.0–2.0)	1.7 (1.0–2.1)	0.840
Lp(a) (mg/L)	15.552 (1.185–1.739)	1.416 (1.201–1.781)	0.915
PCSK9 (ng/L)	240.3 (195.1–364.4)	285.7 (210.0–401.3)	0.265
hs-CRP (mg/L)	0.8 (0.4–2.2)	0.9 (0.4–1.9)	0.592

Abbreviations: HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); PCSK9, proprotein convertase subtilisin/kexin type 9; TC, total cholesterol; TG, triglyceride.

© 2026. The Author(s).

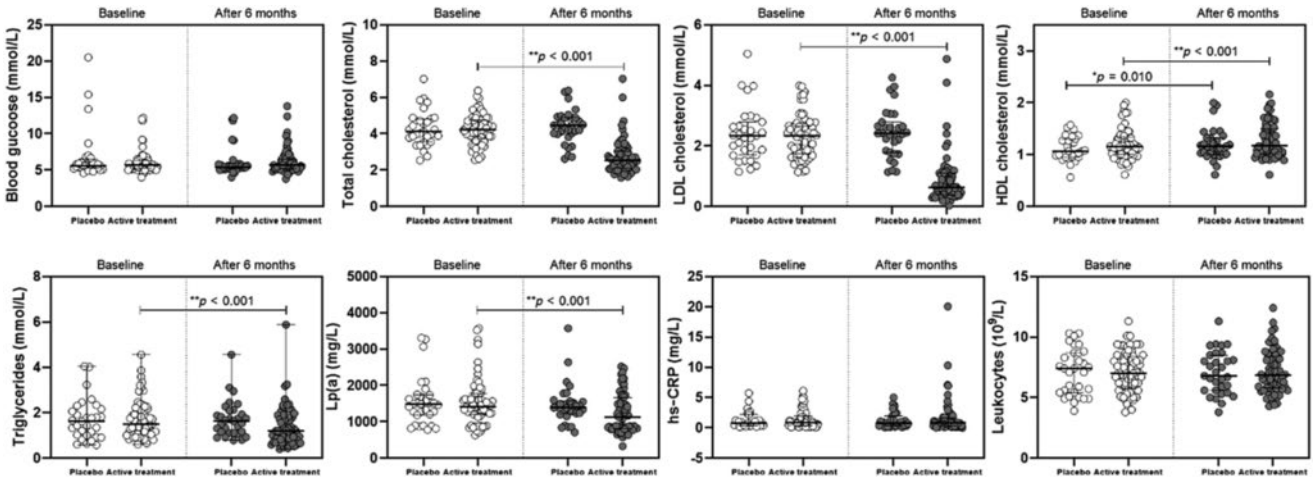


Fig. 2 The comparison of lipid and biochemical profiles at the beginning and at the end of the study. The significant changes in all lipoprotein fractions after treatment with PCSK9i were observed, while hs-CRP concentrations and leukocyte counts remained unchanged. There were no changes in the control group, except for the increase in HDL-C. The difference between parameters at baseline and after 6 months of treatment within each group was calculated using the Wilcoxon matched-pairs signed-rank test. $^{**}p < 0.001$ is shown as statistically significant. HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; TC, total cholesterol; TG, triglyceride.

Table 2 The populations of endothelial progenitor cells at baseline and after 6 months.

Parameter	Group	Baseline	After 6 months	*p*-Value
$CD34^+CD309^+$ (%)	Placebo	0.0850 (0.0550–0.1360)	0.1275 (0.0880–0.1785)	0.023
	Active treatment	**0.0960 (0.0640–0.1680)**	**0.1563 (0.1106–0.2698)**	**<0.001**[a]
	p-value	0.144	**0.009**[b]	0.611
$CD34^+CD133^+$ (%)	Placebo	**0.1270 (0.0705–0.1555)**	**0.2615 (0.1590–0.3355)**	**<0.001**[a]
	Active treatment	**0.1595 (0.0998–0.2708)**	**0.3190 (0.1816–0.4540)**	**<0.001**[a]
	p-value	**0.010**[b]	0.078	0.451
$CD34^+$ (%)	Placebo	0.4565 (0.3855–0.6385)	0.4330 (0.3330–0.5745)	0.537
	Active treatment	**0.4775 (0.3328–0.5833)**	**0.6475 (0.4458–0.8743)**	**0.001**[b]
	p-value	0.952	**0.002**[b]	**0.003**[b]
$CD133^+CD309^+$ (%)	Placebo	**0.0455 (0.0325–0.790)**	**0.0805 (0.0625–0.1320)**	**<0.001**[a]
	Active treatment	**0.0645 (0.0392–0.1123)**	**0.1235 (0.0709–0.2099)**	**<0.001**[a]
	p-value	0.041	**0.020**[b]	0.739
$CD133^+$ (%)	Placebo	**0.2885 (0.2025–0.3990)**	**0.5110 (0.3580–0.7675)**	**<0.001**[a]
	Active treatment	**0.3890 (0.2340–0.6110)**	**0.6090 (0.3800–0.7759)**	**<0.001**[a]
	p-value	0.016	0.374	0.161

Note: Data are medians (lower–upper quartile). The differences between placebo and active treatment at baseline and after treatment were calculated with the Mann–Whitney *U* test. The difference between parameters at baseline and after 6 months of treatment within each group was calculated using the Wilcoxon matched-pairs signed-rank test. The Δ values were calculated using the following equation: (Value at 6 months − Value at baseline)/Value at baseline. The differences in Δ values between the placebo and active treatment group were compared using the Mann–Whitney *U* test. The bold numerical values denote those results that are statistically significant ($p < 0.01$).
[a]$p < 0.001$ and [b]$p \leq 0.01$ are considered statistically significant.

At baseline, the levels of some EPCs ($CD34^+CD133^+$, $CD34^+$, and $CD133^+$) were associated only with total PCSK9 concentration (**Fig. 3**). However, we found no correlation between the levels of the studied EPCs and any measured lipoprotein fractions.

After treatment, no significant associations were found between EPC and lipoprotein levels (**Table 4**).

The distribution of EPC populations stratified by median PCSK9 values before and after treatment with PCSK9i is shown in **Fig. 4**. Briefly, prior to PCSK9i treatment, only $CD34^+CD133^+$ ($p = 0.011$) and $CD133^+$ ($p = 0.007$) populations differed significantly across the median PCSK9 value, whereas no significant differences were observed for $CD34^+CD309^+$, $CD34^+$, or

© 2026. The Author(s).

Table 3 The interrelationship between changes in lipoprotein or PCSK9 concentrations and endothelial progenitor cell concentrations.

Parameter	ΔTC	ΔLDL-C	ΔHDL-C	ΔTG	ΔLp(a)	ΔApoA1	ΔApo B	ΔPCSK9
ΔCD34 CD309$^+$	ρ = 0.042	ρ = 0.136	ρ = −0.173	ρ = −0.112	ρ = 0.064	ρ = 0.033	ρ = 0.018	ρ = −0.205
	p = 0.740	*p* = 0.285	*p* = 0.172	*p* = 0.376	*p* = 0.623	*p* = 0.803	*p* = 0.890	*p* = 0.120
ΔCD34 CD133$^+$	ρ = −0.081	ρ = 0.058	ρ = −0.192	ρ = −0.092	ρ = 0.031	ρ = −0.091	ρ = −0.168	ρ = 0.008
	p = 0.525	*p* = 0.651	*p* = 0.129	*p* = 0.469	*p* = 0.812	*p* = 0.485	*p* = 0.195	*p* = 0.950
ΔCD34$^+$	ρ = −0.036	ρ = 0.090	ρ = −0.227	ρ = −0.014	ρ = 0.110	ρ = 0.053	ρ = −0.054	ρ = −0.262
	p = 0.779	*p* = 0.479	*p* = 0.072	*p* = 0.912	*p* = 0.394	*p* = 0.684	*p* = 0.680	*p* = 0.045
ΔCD133 CD309$^+$	ρ = 0.047	ρ = 0.111	ρ = −0.083	ρ = −0.092	ρ = 0.066	ρ = 0.068	ρ = −0.033	ρ = −0.128
	p = 0.710	*p* = 0.382	*p* = 0.512	*p* = 0.468	*p* = 0.610	*p* = 0.601	*p* = 0.799	*p* = 0.334
ΔCD133$^+$	ρ = −0.196	ρ = −0.105	ρ = 0.074	ρ = −0.134	ρ = −0.082	ρ = −0.025	ρ = −0.265	ρ = 0.098
	p = 0.123	*p* = 0.412	*p* = 0.566	*p* = 0.297	*p* = 0.527	*p* = 0.851	*p* = 0.041	*p* = 0.462

Abbreviations: ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); PCSK9, proprotein convertase subtilisin/kexin type 9; TC, total cholesterol; TG, triglyceride.
Note: Spearman's correlation analysis was used to determine the statistically significant correlations (ρ, rho coefficient, $p < 0.01$). Δ was calculated using the following equation: (Value at 6 months − Value at baseline)/Value at baseline.

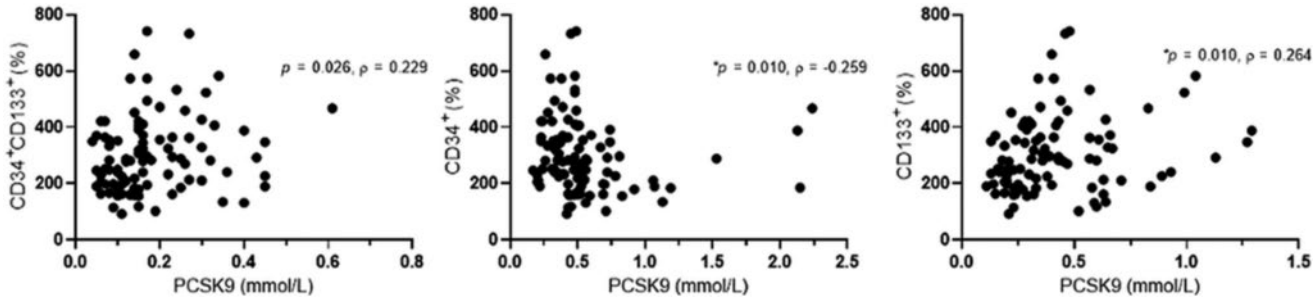


Fig. 3 **The significant correlations between PCSK9 concentration and CD34$^+$CD133$^+$ (A), CD34$^+$ (B), and CD133$^+$ (C) in 100 patients before treatment with PCSK9i. *$p \leq 0.01$ is shown as statistically significant. PCSK9, proprotein convertase subtilisin/kexin type 9.**

Table 4 The correlations between lipoproteins or PCSK9 and endothelial progenitor cells after PCSK9i treatment.

Parameter	TC (mmol/L)	LDL-C (mmol/L)	HDL-C (mmol/L)	TG (mmol/L)	Lp(a) (mg/L)	ApoA1 (g/L)	ApoB (g/L)	PCSK9 (ng/L)
CD34$^+$ CD309$^+$ (%)	ρ = −0.028	ρ = −0.090	ρ = −0.143	ρ = 0.012	ρ = −0.093	ρ = −0.012	ρ = 0.050	ρ = 0.033
	p = 0.826	*p* = 0.478	*p* = 0.259	*p* = 0.924	*p* = 0.469	*p* = 0.924	*p* = 0.699	*p* = 0.804
CD34$^+$ CD133$^+$ (%)	ρ = −0.053	ρ = 0.037	ρ = −0.163	ρ = 0.007	ρ = −0.093	ρ = −0.064	ρ = −0.025	ρ = 0.031
	p = 0.676	*p* = 0.772	*p* = 0.197	*p* = 0.958	*p* = 0.469	*p* = 0.622	*p* = 0.850	*p* = 0.816
CD34$^+$ (%)	ρ = −0.046	ρ = 0.110	ρ = −0.262	ρ = 0.046	ρ = −0.147	ρ = −0.113	ρ = 0.084	ρ = 0.099
	p = 0.716	*p* = 0.385	*p* = 0.037	*p* = 0.712	*p* = 0.251	*p* = 0.382	*p* = 0.517	*p* = 0.454
CD133$^+$ CD309$^+$ (%)	ρ = −0.016	ρ = 0.093	ρ = −0.149	ρ = 0.025	ρ = −0.106	ρ = −0.014	ρ = 0.064	ρ = 0.028
	p = 0.903	*p* = 0.467	*p* = 0.241	*p* = 0.846	*p* = 0.408	*p* = 0.913	*p* = 0.622	*p* = 0.831
CD133$^+$ (%)	ρ = −0.111	ρ = −0.034	ρ = −0.099	ρ = −0.082	ρ = −0.067	ρ = −0.055	ρ = −0.157	ρ = 0.102
	p = 0.384	*p* = 0.789	*p* = 0.436	*p* = 0.519	*p* = 0.604	*p* = 0.673	*p* = 0.224	*p* = 0.441

Abbreviations: ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); PCSK9, proprotein convertase subtilisin/kexin type 9; TC, total cholesterol; TG, triglyceride.
Note: Spearman's correlation analysis was used to determine the statistically significant correlations (ρ, rho coefficient).

© 2026. The Author(s).

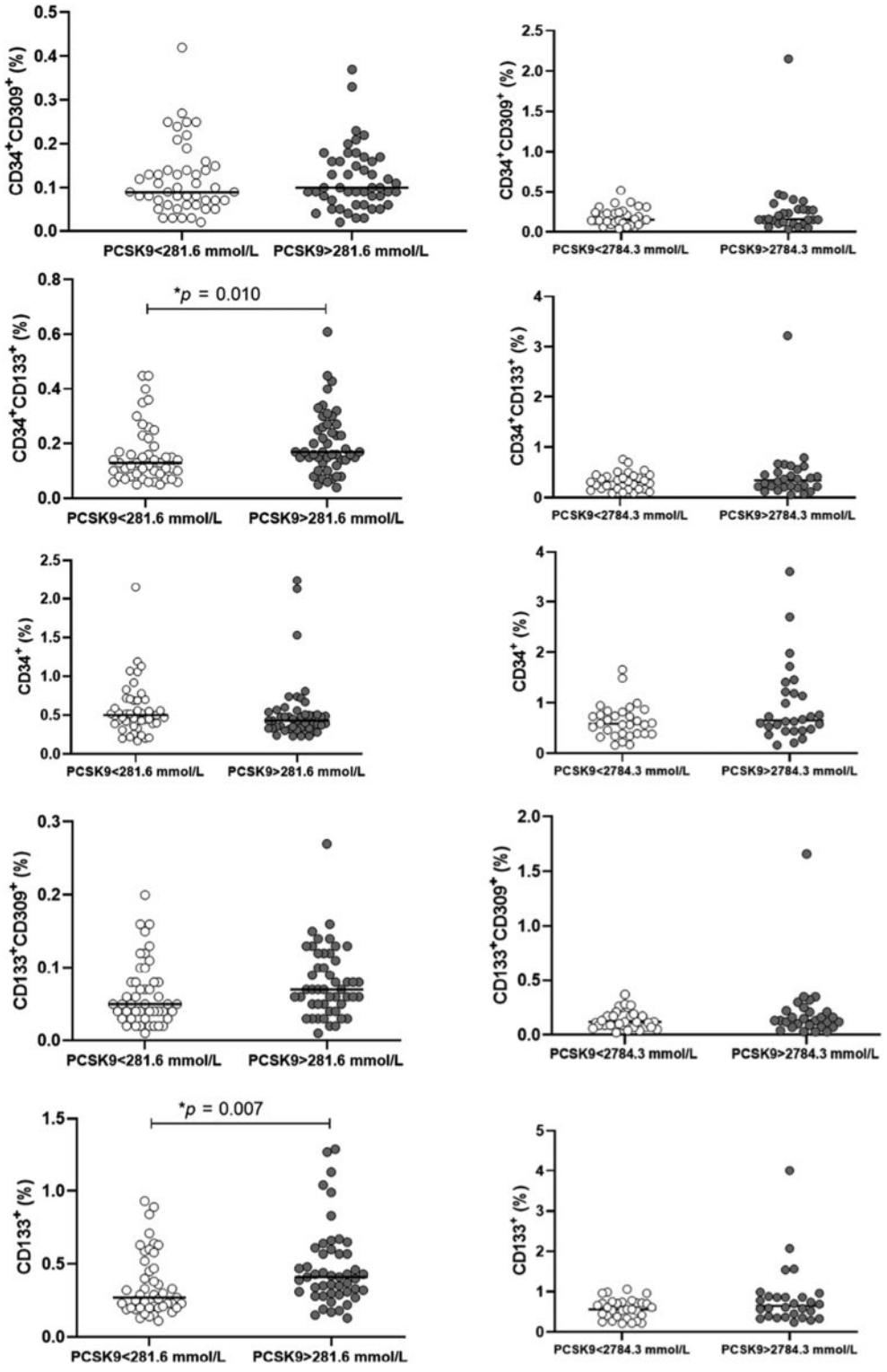


Fig. 4 The distribution of EPC populations stratified by median PCSK9 values before (left panel) and after (right panel) treatment with PCSK9i. $^{*}p \leq 0.01$ is statistically significant. EPC, endothelial progenitor cell; PCSK9, proprotein convertase subtilisin/kexin type 9.

© 2026. The Author(s).

$CD133^+CD309^+$ populations. After treatment, none of the EPC populations differed significantly across median PCSK9 values in the PCSK9i group.

Discussion

To the best of our knowledge, this is the first study to investigate the effects of PCSK9i on EPC subtypes in post-MI patients with persistently elevated LDL-C and Lp(a) levels despite optimal medical therapy. The primary finding of our study is that treatment with PCSK9i significantly increases the levels of mature EPCs ($CD34^+$) compared with placebo, while no significant effects were observed on early EPC subtypes ($CD34^+CD309^+$, $CD34^+CD133^+$, $CD133^+CD309^+$, and $CD133^+$).

We included patients who, despite receiving maximum tolerated statin therapy and adjunctive ezetimibe where indicated, failed to achieve guideline-recommended LDL-C targets,[22] and at the same time exhibited markedly elevated Lp(a) levels. The magnitude of lipoprotein reduction in our study was comparable to that reported in major clinical trials evaluating alirocumab[17] and evolocumab,[16] which demonstrated reductions in both lipid parameters and major adverse cardiovascular events. Owing to the inclusion of patients with severely elevated Lp(a) concentrations, levels remained within a highly atherogenic range despite significant reductions following treatment,[23] consistent with results from these landmark studies.

EPCs are typically defined as cells co-expressing hematopoietic stem cell markers, such as CD34, together with endothelial markers, including CD309 (also known as vascular endothelial growth factor receptor-2, VEGFR-2). More immature EPC subsets additionally express CD133 (prominin-1), although the precise biological role of this marker remains poorly understood.[12] At first glance, our results appear to suggest that treatment with PCSK9i increases the levels of both immature and mature EPC populations. However, a more detailed analysis reveals an important differential effect. Specifically, the proportion of immature EPCs increased in both the PCSK9i-treated and the placebo groups, whereas the increase in mature EPCs was observed exclusively in the PCSK9i-treated group. The observed rise in immature EPCs within the placebo group cannot be fully explained. One possible contributing factor could be seasonal variation; however, this is unlikely, as randomization procedures were designed to minimize the impact of such confounding variables.

To date, only one previous study has investigated the effects of PCSK9i on EPCs in statin-treated patients,[24] later expanded to a larger cohort without detecting differences between alirocumab and evolocumab.[25] However, several key methodological differences limit direct comparison with our findings. First, our study was a randomized, double-blind, placebo-controlled study, whereas the aforementioned studies were non-randomized, prospective studies lacking a control group. Second, although both studies reported increases in immature EPC populations following treatment with PCSK9i, the prior work focused exclusively on immature EPCs, whereas our analysis evaluated both mature and immature populations. Third, only approximately one-third of patients in their cohort were receiving statin therapy prior to the study, in contrast to our cohort, in which all patients were treated with maximally tolerated statin doses. Finally, our patients were characterized by markedly elevated Lp(a) levels, a parameter not reported in the previous studies. Evidence regarding the effects of statins on EPCs are limited, but available data suggest that atorvastatin therapy (40 mg daily) increases circulating $CD34^+$ EPC levels within 4 weeks, after which a plateau is reached.[26] Given that all patients in our study had been receiving stable, high-intensity statin therapy (atorvastatin ≥40 mg or rosuvastatin ≥20 mg) for at least 6 weeks prior to enrollment, it is unlikely that statins contributed to the observed changes. We, therefore, attribute the observed effects on EPC populations primarily to PCSK9i treatment. These differential effects on EPC subtypes suggest that PCSK9i may promote the differentiation of immature EPCs into more mature forms. However, our data do not allow us to definitively conclude that they accelerate the mobilization or migration of immature EPCs. Nevertheless, the higher levels of immature EPCs observed in the PCSK9i group, compared with placebo, may be consistent with this possibility.

One of the mechanisms through which EPCs contribute to the reduction of cardiovascular risk is endothelial regeneration.[27] While previous studies demonstrated that PCSK9i increases both EPC levels and their functional capacity—with comparable effects in statin-naïve and statin-treated patients[24]—it remains unclear whether baseline EPC parameters were equivalent between these subgroups. However, mature EPCs exhibit greater regenerative potential compared with immature forms of EPCs.[28] Although the precise mechanism by which PCSK9i contributes to endothelial repair remains incompletely understood, increased ability to form colonies and secrete growth factors could certainly contribute to this effect.[24]

In our study, as noted above, all patients were previously treated with statins. Statins are known to increase EPC levels in both individuals without[29] and in patients with ischemic heart disease,[30] although the results in the latter population remain inconsistent.[31]

Prior to initiation of PCSK9i therapy, we found no correlation between EPCs and lipoprotein levels. This observation appears somewhat surprising, as several studies have reported an inverse correlation between LDL-C concentration and both the quantity and functional capacity of EPCs in apparently healthy individuals[32] and in patients with ischemic heart disease.[33] However, this discrepancy may be attributable to the unique characteristics of our study population. Notably, all participants were receiving combination treatment with statins and either ACE inhibitors or angiotensin receptor blockers, both of which are known to independently increase EPC levels,[34,35] potentially confounding the relationship between EPCs and LDL-C levels.

The direct effects of Lp(a) on the counts and functional capabilities of EPCs remain poorly explored. In a murine model of ischemic limb, EPC transplantation significantly improved tissue perfusion; however, this beneficial effect was abolished when EPCs were pretreated with Lp(a). This impairment in angiogenesis was correlated with reduced density of $CD31^+$ capillaries and appeared to be mediated by Lp(a)-induced acceleration of EPC senescence and increased production of reactive oxygen species (ROS).[36] Notably, these findings may be connected to an emerging understanding of the interplay between ROS and PCSK9.

© 2026. The Author(s).

Current evidence suggests a reciprocal relationship, whereby elevated ROS levels increase PCSK9 expression, while higher PCSK9 levels upregulate the expression of lectin-like oxidized LDL receptor-1 (LOX-1), thereby promoting LDL-C oxidation.[37]

Associations were observed only between PCSK9 concentration and specific EPC subtypes ($CD34^+CD133^+$, $CD34^+$, and $CD133^+$). Importantly, these relationships likely reflect, at least in part, the effects of prior statin therapy, which is known both to increase levels of EPCs[30] and to increase PCSK9 concentrations, regardless of statin type or dose.[38] Very similar results were reported by Tripaldi et al.,[39] who demonstrated associations between endogenous PCSK9 concentrations and both early and late EPC populations in statin-treated type 2 diabetes mellitus (T2DM) patients, whereas no such associations were found in statin-naïve T2DM patients.

Overall, these results suggest that increased PCSK9 concentrations may impair both the mobilization of early EPCs from the bone marrow and their subsequent maturation into late EPCs. These findings are further supported by the previously mentioned study by Tripaldi et al.,[39] in which statin-treated T2DM patients exhibited the highest PCSK9 levels alongside the lowest concentrations of both early and late EPC subtypes.

Further evidence supporting this mechanism is provided by Chao et al.,[40] who found that in patients with peripheral artery disease (PAD)—a condition sharing key pathophysiological features with coronary artery disease patients—elevated PCSK9 levels were correlated not only with reduced EPC levels, but also with increased EPC apoptosis.

Changes in EPC levels were independent of variations in lipoprotein levels. However, a significant relationship was observed between the increase in $CD34^+$ cells—representing mature endothelial cells, and the change in the concentration of PCSK9. This inverse relationship may initially appear counterintuitive, given that total circulating PCSK9 levels increased during anti-PCSK9 monoclonal antibody treatment. However, this apparent paradox likely reflects the measurement of total rather than free PCSK9, as free PCSK9 levels are known to decrease during treatment with PCSK9i. Assessment of free PCSK9 might, therefore, have revealed a more intuitive relationship. Statins have been shown to promote EPC differentiation and upregulate EPC numbers both in vitro and in vivo via activation of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway.[41] Similarly, PCSK9i treatment has been reported to influence EPC number and differentiation through the same mechanisms. Given that all patients in our study were previously treated with statins, it is plausible that the observed effects reflect complementary or additive mechanism.[42]

These findings support two key observations. First, changes in EPC levels appear to be more closely associated with variations in measured PCSK9 concentrations per se than with lipoprotein changes, as evidenced by the complete disappearance of correlations between EPC subtypes and PCSK9 concentrations following treatment. Second, changes in PCSK9 concentrations were associated not only with changes in mature EPCs ($CD34^+$), but also with immature or early EPC subtypes ($CD34^+CD133^+$ and $CD133^+$). Notably, prior studies investigating the effects of PCSK9i on EPCs did not simultaneously measure total and free PCSK9 concentrations,[25,43] leaving these relationships largely unexplored. However, an important limitation of our study is that we measured total rather than free PCSK9, which more directly reflects its primary biological activity. Free PCSK9 represents the unbound fraction capable of interacting with the LDL receptor, whereas total PCSK9 includes both free and PCSK9i-bound (inactive) forms. Currently, data on the relationship between free and total PCSK9 concentrations—particularly in the absence of PCSK9i therapy—remain limited. Therefore, our findings allow us to establish correlations between total PCSK9 concentrations and some EPC subtypes, but not to draw definitive conclusions regarding the causality or underlying biological mechanisms. It is well-established that the concentrations of free PCSK9 decline rapidly following PCSK9i administration, whereas total PCSK9 levels increase and reach a steady state within a few days.[44] Given that free PCSK9 becomes difficult to quantify during treatment, analyses are typically restricted to total PCSK9, which remains measurable and stable even after repeated dosing.[45]

Interestingly, no correlation was detected between changes in PCSK9 concentrations and changes in EPC populations expressing CD309. This finding is consistent with the absence of differences in $CD309^+$ EPC levels when stratified according to median baseline PCSK9 values.

Furthermore, our study revealed no significant correlation between Lp(a) and either early or late EPC population levels, both at baseline and at the end of the study. Similarly, changes in Lp(a) concentrations were not associated with changes in EPC levels over the study period. These findings are somewhat unexpected, given the well-established role of Lp(a) as an independent cardiovascular risk factor, distinct from other lipoproteins evaluated in our study.[46] However, it is important to consider that baseline Lp(a) levels in our cohort were more than threefold higher than the threshold currently considered atherogenic.[23] Such extremely elevated concentrations may have obscured potential correlations that might be detectable at lower Lp(a) concentrations.

Despite significant reductions in Lp(a) following treatment with PCSK9i, absolute concentrations remained within a highly atherogenic range. Several factors may account for these findings. First, the relationship between Lp(a) concentration and pathogenesis of atherosclerosis remains unclear—specifically, whether risk increases in a linear, dose-dependent manner or whether a threshold effect exists beyond which additional increases confer limited incremental harm. Second, there is a notable lack of studies examining the relationship between Lp(a) concentration and quantity or function of EPCs.

The study by Schnitzler et al.[47] represents one of the few to investigate the influence of Lp(a) on bone marrow function in atherosclerosis. Their results demonstrated that Lp(a) can stimulate hematopoietic stem and progenitor cells (HSPCs) to produce proinflammatory monocytes. However, this effect was transient compared with the sustained impact of LDL-C, which the authors attributed to the relatively low Lp(a) concentrations used for bone marrow preconditioning. Importantly, these results derived from transgenic mouse models cannot be directly extrapolated to clinical settings, where numerous confounding factors may influence outcomes. Moreover, the effects of Lp(a) on bone

© 2026. The Author(s).

marrow stimulation and HSPC-driven monocyte production may not necessarily reflect its potential impact on EPCs.

While our study represents, to our knowledge, the largest investigation of effects of PCSK9i on EPCs and the only randomized, double-blind, placebo-controlled trial conducted to date, several limitations should be acknowledged.

First, the relatively modest sample size—resulting from stringent inclusion criteria requiring markedly elevated Lp(a) levels—may limit the generalizability of our findings. This selective enrolment precludes assessment of potential concentration-dependent relationships between Lp(a) and EPCs across the full spectrum of Lp(a) concentrations observed in the general population, ranging from very low to extremely high levels. Second, the inability to measure free PCSK9 concentrations following treatment, due to the limited specificity of the ELISA used, represents an important technical limitation. As free PCSK9 more directly reflects biological activity, its absence restricts the interpretation of mechanistic relationships between PCSK9 and EPC dynamics.

Finally, although current evidence supports an association between EPC levels and cardiovascular risk in patients with chronic coronary disease, our study was not designed to assess whether the observed pharmacologically induced increases in EPC levels translate into clinically meaningful outcomes.

Conclusion

In this first randomized, double-blind, placebo-controlled trial examining the effects of PCSK9i on EPCs in patients with chronic coronary disease and elevated Lp(a) levels, we demonstrate that PCSK9i treatment significantly increases circulating $CD34^+$ EPCs levels, while no significant effects were observed in other EPC subpopulations. However, our study was limited to the quantification of EPC levels and did not include their functional capacity assessment, which represents an important consideration when interpreting the biological and clinical relevance of these findings.

Notably, despite PCSK9i treatment, patients maintained persistently elevated Lp(a) levels well above the atherogenic threshold. This observation raises intriguing questions about whether emerging Lp(a)-targeted therapies might exert distinct effects not only on EPC quantity but also on their functional capacity.

What is Known on This Topic?

- The concentration and function of EPCs reflect endothelial integrity and are associated with cardiovascular risk. Mature EPCs have greater regenerative potential.
- PCSK9i is known to significantly lower LDL-C and Lp(a), reducing major adverse cardiovascular events, but its effect on endothelial function and EPC biology is poorly understood.
- Statin therapy is known to increase EPC concentrations, which may complicate the assessment of additional therapies in statin-treated patients.

What Does This Paper Add?

- In statin-treated patients with stable coronary disease and high lipoprotein(a), PCSK9i specifically increases the concentration of mature EPCs (CD34+), but not early EPC subtypes, suggesting a role in promoting EPC maturation.
- The increase in mature EPCs is a lipid-independent effect of PCSK9i, as changes in EPC concentrations showed no association with variations in lipoprotein levels.
- This provides a novel, non-lipid mechanism for the cardiovascular benefit of PCSK9i, specifically enhancing endothelial repair capacity. It also highlights the need for future research to assess if this increase translates to improved EPC function and clinical outcomes.

Author Affiliations

1 Faculty of Medicine, University of Ljubljana, Ljubljana, Ljubljana, Slovenia
2 Department of Vascular Diseases, University Medical Centre Ljubljana, Ljubljana, Ljubljana, Slovenia
3 Laboratory for Translational Medical Biochemistry, Institute of Biochemistry and Molecular Genetics, Faculty of Medicine, University of Ljubljana, Ljubljana, Ljubljana, Slovenia
4 Clinical Institute for Special Laboratory Diagnostics, University Children's Hospital, University Medical Centre Ljubljana, Ljubljana, Ljubljana, Slovenia
5 Faculty of Pharmacy, University of Ljubljana, Ljubljana, Ljubljana, Slovenia
6 Department of Internal Medicine II, Medical University of Vienna, Vienna, Vienna, Austria
7 Ludwig Boltzmann Cluster for Cardiovascular Research, Vienna, Vienna, Austria
8 Center for Biomedical Research and Translational Surgery, Cardiovascular Institute, Medical University of Vienna, Vienna, Vienna, Austria
9 Department of Cardiology, University Medical Centre Ljubljana, Ljubljana, Ljubljana, Slovenia

Statements and Additional Information

Conflict of Interest The authors declare that they have no conflict of interest.

Contributors' Statement S.U.: Conceptualization, data curation, investigation, methodology, visualization, writing–original draft. A.R.L.: Conceptualization, investigation, methodology, writing–review and editing. T.L.: Data curation, writing–review and editing. K.T.P.: Data curation, resources, writing–review and editing. J.Z.: Data curation, visualization, writing–review and editing. F.M.: Data curation, writing–review and editing. T.T.: Data curation, writing–review and editing. M.B.: Data curation, writing–review and editing. W.S.S.: Data curation, writing–review and editing. P.J.H.: Data curation, resources, supervision, writing–review and editing. P.H.: Data curation, visualization, writing–review and editing. M.S.: Conceptualization, data curation, funding acquisition, investigation, methodology, project administration, resources, supervision, writing–original draft.

© 2026. The Author(s) This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (https://creativecommons.org/licenses/by-nc-nd/4.0/).

Acknowledgement We are thankful to the staff of the Laboratory for Haemostasis and Atherothrombosis in the Clinical Department of Angiology, University Clinical Centre Ljubljana (Slovenia) for serum biomarker measurements and technical assistance.

Funding Information This work was supported by the University Medical Centre Ljubljana (20240051 and 20250023), Amgen, Sanofi, Medizinische Universität Wien, and the Slovenian Research and Innovation Agency (programs P3-0308 and P1-0170, P1-0420).

References

1 GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. Lancet 2020;396(10258):1204–1222 Erratum in: Lancet 2020;396(10262):1562. 10.1016/S0140-6736 (20)32226-1

2 Matsuzawa Y, Sugiyama S, Sumida H, et al. Peripheral endothelial function and cardiovascular events in high-risk patients. J Am Heart Assoc 2013;2(06): e000426

3 Ugovšek S, Rehberger Likozar A, Finderle S, et al. TNF-α predicts endothelial function and number of $CD34^+$ cells after stimulation with G-CSF in patients with advanced heart failure. J Cardiovasc Dev Dis 2022;9(08):281

4 Lev EI, Leshem-Lev D, Mager A, et al. Circulating endothelial progenitor cell levels and function in patients who experienced late coronary stent thrombosis. Eur Heart J 2010;31(21):2625–2632

5 Crea F, Libby P. Acute coronary syndromes: the way forward from mechanisms to precision treatment. Circulation 2017;136(12):1155–1166

6 Werner N, Kosiol S, Schiegl T, et al. Circulating endothelial progenitor cells and cardiovascular outcomes. N Engl J Med 2005;353(10):999–1007

7 Matsuura K, Hagiwara N. The pleiotropic effects of ARB in vascular endothelial progenitor cells. Curr Vasc Pharmacol 2011;9(02):153–157

8 Di Stefano R, Barsotti MC, Felice F, et al. Smoking and endothelial progenitor cells: a revision of literature. Curr Pharm Des 2010;16(23):2559–2566

9 Pirro M, Schillaci G, Paltriccia R, et al. Increased ratio of CD31+/CD42- microparticles to endothelial progenitors as a novel marker of atherosclerosis in hypercholesterolemia. Arterioscler Thromb Vasc Biol 2006;26(11):2530–2535

10 Ma FX, Zhou B, Chen Z, et al. Oxidized low density lipoprotein impairs endothelial progenitor cells by regulation of endothelial nitric oxide synthase. J Lipid Res 2006;47(06):1227–1237

11 Medina RJ, Barber CL, Sabatier F, et al. Endothelial progenitors: a consensus statement on nomenclature. Stem Cells Transl Med 2017;6(05):1316–1320

12 Urbich C, Dimmeler S. Endothelial progenitor cells: characterization and role in vascular biology. Circ Res 2004;95(04):343–353

13 Ugovšek S, Šebeštjen M. Lipoprotein (a)-the crossroads of atherosclerosis, atherothrombosis and inflammation. Biomolecules 2021;12(01):26

14 Zhang X, Wang S, Qin Y, Guo H. Downregulation of microRNA-221-3p promotes angiogenesis of lipoprotein (a)-injured endothelial progenitor cells by targeting silent information regulator 1 to activate the RAF/MEK/ERK signaling pathway. Mol Med Rep 2024;30(06):223

15 Nair R, Johnson M, Kravitz K, et al. Characteristics and outcomes of early recurrent myocardial infarction after acute myocardial infarction. J Am Heart Assoc 2021;10(16):e019270

16 Sabatine MS, Giugliano RP, Keech AC, et al. FOURIER steering committee and investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376(18):1713–1722

17 Schwartz GG, Steg PG, Szarek M, et al. ODYSSEY OUTCOMES committees and investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379(22):2097–2107

18 Rehberger Likozar A, Ugovšek S, Šebeštjen M. Effects of proprotein convertase subtilisin-kexin type 9 inhibitors on inflammatory and hemostatic parameters in post myocardial infarction patients. Eur J Pharmacol 2024;963:176232

19 Haider P, Hoberstorfer T, Salzmann M, et al. Quantitative and functional assessment of the influence of routinely used cryopreservation media on mononuclear leukocytes for medical research. Int J Mol Sci 2022;23(03):1881

20 Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18(06):499–502

21 Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*power 3.1: tests for correlation and regression analyses. Behav Res Methods 2009; 41(04):1149–1160

22 Vrints C, Andreotti F, Koskinas KC, et al. ESC scientific document group. 2024 ESC guidelines for the management of chronic coronary syndromes. Eur Heart J 2024; 45(36):3415–3537 Erratum in: Eur Heart J 2025, 21:ehaf079. 10.1093/eurheartj/ehaf079

23 Mach F, Baigent C, Catapano AL, et al. ESC scientific document group. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41(01):111–188, Erratum in: Eur Heart J 2020;41(44):4255. 10.1093/eurheartj/ehz826

24 Itzhaki Ben Zadok O, Mager A, Leshem-Lev D, Lev E, Kornowski R, Eisen A. The effect of proprotein convertase subtilisin kexin type 9 inhibitors on circulating endothelial progenitor cells in patients with cardiovascular disease. Cardiovasc Drugs Ther 2022;36(01):85–92

25 Gurevitz C, Zadok OIB, Leshem-Lev D, et al. Circulating endothelial progenitor cells in patients with established cardiovascular disease treated with PCSK9 monoclonal antibodies. Am J Prev Cardiol 2024;20:100896

26 Vasa M, Fichtlscherer S, Adler K, et al. Increase in circulating endothelial progenitor cells by statin therapy in patients with stable coronary artery disease. Circulation 2001;103(24):2885–2890

27 Peichev M, Naiyer AJ, Pereira D, et al. Expression of VEGFR-2 and AC133 by circulating human CD34 (+) cells identifies a population of functional endothelial precursors. Blood 2000;95(03):952–958

28 Yoder MC, Mead LE, Prater D, et al. Redefining endothelial progenitor cells via clonal analysis and hematopoietic stem/progenitor cell principals. Blood 2007; 109(05):1801–1809

29 Chantzichristos VG, Agouridis AP, Moutzouri E, Stellos K, Elisaf MS, Tselepis AD. Effect of rosuvastatin or its combination with omega-3 fatty acids on circulating CD34 (+) progenitor cells and on endothelial colony formation in patients with mixed dyslipidaemia. Atherosclerosis 2016;251:240–247

30 Ansheles AA, Rvacheva AV, Sergienko IV. Effect of atorvastatin therapy on the level of $CD34^+CD133^+CD309^+$ endothelial progenitor cells in patients with coronary heart disease. Bull Exp Biol Med 2017;163(01):133–136

31 Pesaro AE, Serrano CV Jr, Katz M, et al. Increasing doses of simvastatin versus combined ezetimibe/simvastatin: effect on circulating endothelial progenitor cells. J Cardiovasc Pharmacol Ther 2013;18(05):447–452

32 Hill JM, Zalos G, Halcox JP, et al. Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. N Engl J Med 2003;348(07):593–600

33 Heeschen C, Lehmann R, Honold J, et al. Profoundly reduced neovascularization capacity of bone marrow mononuclear cells derived from patients with chronic ischemic heart disease. Circulation 2004;109(13):1615–1622

34 Cacciatore F, Bruzzese G, Vitale DF, et al. Effects of ACE inhibition on circulating endothelial progenitor cells, vascular damage, and oxidative stress in hypertensive patients. Eur J Clin Pharmacol 2011;67(09):877–883

35 Pelliccia F, Pasceri V, Cianfrocca C, et al. Angiotensin II receptor antagonism with telmisartan increases number of endothelial progenitor cells in normotensive patients with coronary artery disease: a randomized, double-blind, placebo-controlled study. Atherosclerosis 2010;210(02):510–515

36 Iwabayashi M, Taniyama Y, Sanada F, et al. Inhibition of Lp (a)-induced functional impairment of endothelial cells and endothelial progenitor cells by hepatocyte growth factor. Biochem Biophys Res Commun 2012;423(01):79–84

37 Ding Z, Liu S, Wang X, et al. Cross-talk between LOX-1 and PCSK9 in vascular tissues. Cardiovasc Res 2015;107(04):556–567

38 Brusq JM, Ancellin N, Grondin P, et al. Inhibition of lipid synthesis through activation of AMP kinase: an additional mechanism for the hypolipidemic effects of berberine. J Lipid Res 2006;47(06):1281–1288

39 Tripaldi R, Lanuti P, Simeone PG, et al. Endogenous PCSK9 may influence circulating $CD45^{neg}/CD34^{bright}$ and $CD45^{neg}/CD34^{bright}/CD146^{neg}$ cells in patients with type 2 diabetes mellitus. Sci Rep 2021;11(01):9659

40 Chao TH, Chen IC, Li YH, Lee PT, Tseng SY. Plasma levels of proprotein convertase Subtilisin/Kexin type 9 are elevated in patients with peripheral artery disease and associated with metabolic disorders and dysfunction in circulating progenitor cells. J Am Heart Assoc 2016;5(05):e003497; Erratum in: J Am Heart Assoc 2016; 5(7):e002090. 10.1161/JAHA.116.002090

41 Dimmeler S, Aicher A, Vasa M, et al. HMG-CoA reductase inhibitors (statins) increase endothelial progenitor cells via the PI 3-kinase/Akt pathway. J Clin Invest 2001;108(03):391–397

42 Peng C, Liu GJ, Li J, et al. Evolocumab alleviates atherogenesis by inhibiting inflammation-mediated endothelial cell activation via the PI3K/AKT/NF-κB pathway. Eur J Pharmacol 2026;1020:178777

43 Scicali R, Mandraffino G, Scuruchi M, et al. Effects of lipid lowering therapy optimization by PCSK9 inhibitors on circulating CD34+ cells and pulse wave velocity in familial hypercholesterolemia subjects without atherosclerotic cardiovascular disease: real-world data from two lipid units. Biomedicine 2022;10(07):1715

44 Li H, Wei Y, Yang Z, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of alirocumab in healthy Chinese subjects: a randomized, double-blind, placebo-controlled, ascending single-dose study. Am J Cardiovasc Drugs 2020;20(05):489–503

© 2026. The Author(s).

45 Rey J, Poitiers F, Paehler T, et al. Relationship between low-density lipoprotein cholesterol, free proprotein convertase subtilisin/kexin type 9, and alirocumab levels after different lipid-lowering strategies. J Am Heart Assoc 2016;5(06): e003323

46 Reyes-Soffer G, Ginsberg HN, Berglund L, et al. American Heart Association Council on arteriosclerosis, thrombosis and vascular biology; council on cardiovascular radiology and intervention; and council on peripheral vascular disease. Lipoprotein (a): a genetically determined, causal, and prevalent risk factor for atherosclerotic cardiovascular disease: a scientific statement from the American Heart Association. Arterioscler Thromb Vasc Biol 2022;42(01):e48–e60

47 Schnitzler JG, Poels K, Stiekema LCA, et al. Short-term regulation of hematopoiesis by lipoprotein (a) results in the production of pro-inflammatory monocytes. Int J Cardiol 2020;315:81–85

© 2026. The Author(s).