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Homocysteine Reduction and Vascular–Metabolic Changes During PCSK9 Inhibition in Familial Hypercholesterolemia:A Prospective Cohort Study

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Research Article

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Abstract

Background

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors reduce low-density lipoprotein cholesterol (LDL-C) and cardiovascular risk, but their effects on homocysteine (Hcy) and broader vascular–metabolic pathways remain poorly characterized.

Objective

To evaluate changes in plasma Hcy and related vascular–metabolic biomarkers during PCSK9 inhibitor treatment in patients with familial hypercholesterolemia (FH).

Methods

In this prospective, single-center observational cohort study, 50 patients with FH initiating a PCSK9 inhibitor were evaluated at baseline and after 12 weeks. The primary endpoint was the within-subject change in plasma Hcy. Paired assessments included lipid parameters, urinary oxidative stress markers, biomarkers of the arginine–nitric oxide pathway, and ancillary untargeted metabolomic profiling.

Results

Mean Hcy decreased from 12.6 ± 6.7 to 8.9 ± 2.4 μmol/L, a 29% reduction, while median Hcy decreased from 10.7 μmol/L (IQR, 9.0–13.4) to 9.1 μmol/L (IQR, 7.0–10.5), a 15% reduction ($P < 0.001$). Hyperhomocysteinemia (> 15 μmol/L) resolved in all 10 affected patients ($P = 0.002$). Total cholesterol, corrected LDL-C, and lipoprotein(a) decreased by 37.9%, 34.1%, and 35.2%, respectively. Urinary F_2-isoprostanes, DH-isoprostanes, and dinor-isoprostane metabolites also decreased significantly, whereas arginine–nitric oxide pathway biomarkers did not. Multivariable analysis identified coordinated associations between ΔHcy and methylmalonic acid, arginine–nitric oxide metabolites, LDL-C reduction, and lipoprotein(a). Metabolomics showed sterol and phospholipid remodeling, lower choline abundance, and a higher putative betaine-related signal.

Conclusion

PCSK9 inhibition was associated with reduced Hcy, marked lipid remodeling, and lower oxidative stress in FH, supporting further investigation of Hcy as a treatment-responsive biomarker of broader vascular–metabolic remodeling. This response may help characterize vascular biology during intensive lipid-lowering therapy in high-risk FH.

Introduction

Familial hypercholesterolemia (FH) is characterized by lifelong exposure to elevated low-density lipoprotein cholesterol (LDL-C), resulting in accelerated atherosclerosis and a markedly increased risk of premature atherosclerotic cardiovascular disease. The introduction of intensive lipid-lowering strategies, including high-intensity statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, has substantially improved lipid control and reduced cardiovascular event rates in this high-risk population. Nevertheless, a considerable burden of residual cardiovascular risk persists even in patients receiving optimized LDL-C-lowering therapy, indicating that vascular risk in FH is not exclusively determined by circulating LDL-C concentrations. Additional contributors may include lipoprotein(a) [Lp(a)], oxidative stress, inflammation, endothelial dysfunction, and the cumulative effects of lifelong arterial exposure to atherogenic lipoproteins [1–4].

Although randomized trials of Hcy-lowering strategies based on folic acid and B-vitamin supplementation have not consistently reduced cardiovascular events, hyperhomocysteinemia has been associated with endothelial dysfunction, oxidative stress, impaired nitric oxide bioavailability, and atherothrombotic events [5–10], supporting its potential value as an integrated marker of vascular and metabolic dysregulation. Experimental evidence suggests a biological interaction between Hcy metabolism and PCSK9-related pathways. In a murine model of hyperhomocysteinemia, elevated Hcy increased PCSK9 expression, impaired macrophage cholesterol efflux, and promoted atherosclerotic lesion development; pharmacological PCSK9 inhibition attenuated these abnormalities and was accompanied by lower circulating Hcy concentrations [15]. Human observational data have likewise identified associations between circulating PCSK9 and Hcy levels [16]. These findings are consistent with broader vascular effects attributed to PCSK9 inhibition, including modulation of oxidative stress, inflammation, endothelial homeostasis, and coronary plaque characteristics [11–14].

Despite this biological rationale, clinical data on changes in circulating Hcy during PCSK9 inhibitor treatment remain limited, particularly in patients with FH. We therefore evaluated the within-subject change in plasma Hcy after 12 weeks of treatment with a PCSK9 inhibitor. Secondary and ancillary analyses assessed whether Hcy variation was accompanied by changes in lipid parameters, urinary oxidative stress biomarkers, components of the arginine–nitric oxide pathway, and metabolomic features related to lipid remodeling and one-carbon metabolism.

Methods

Study design and participants

This prospective, single-center cohort study was conducted at the Lipid Clinic of the Department of Clinical Medicine and Surgery, University of Naples Federico II, and is reported in accordance with the STROBE statement [17]. Consecutive adults with a clinical phenotype compatible with autosomal-dominant FH who were considered for initiation of a PCSK9 inhibitor between 2023 and 2024 were

assessed for eligibility. FH was defined by a Dutch Lipid Clinic Network score > 6, LDL-C above the age- and sex-specific 95th percentile, normal triglyceride levels, and a compatible family history [18]. Genetic data for LDLR, APOB, and PCSK9 were retrieved when available using previously reported LIPIGEN procedures [22].

Participants met the Italian Medicines Agency reimbursement criteria applicable during enrollment: LDL-C ≥ 70 mg/dL (1.81 mmol/L) in patients with established cardiovascular disease or ≥ 130 mg/dL (3.35 mmol/L) in those without cardiovascular disease, documented on 3 determinations despite maximally tolerated lipid-lowering therapy. Exclusion criteria were age < 18 years; inability to provide consent; aminotransferase levels > 3 times the upper limit of normal; triglycerides > 250 mg/dL; estimated glomerular filtration rate < 30 mL/min/1.73 m²; active or recent malignancy; previous exposure to a PCSK9 inhibitor; secondary hypercholesterolemia; a phenotype suggestive of familial combined hyperlipidemia; or current folic acid or vitamin B12 supplementation. Initiation of either supplement was not permitted during the 12-week study period. Background lipid-lowering therapy remained unchanged. Evolocumab 140 mg or alirocumab 150 mg was administered subcutaneously every 2 weeks.

Clinical and laboratory assessment

After written informed consent was obtained, a comprehensive medical history was collected at enrollment. Clinical characteristics, cardiovascular risk factors, comorbidities, medications, height, weight, and body mass index were recorded at baseline. Dietary habits were assessed by clinical interview at baseline and at 12 weeks. Participants were instructed to maintain their habitual diet throughout follow-up, and no clinically relevant dietary changes were reported. Fasting blood samples were obtained immediately before PCSK9 inhibitor initiation (T0) and after 12 weeks (T12). Routine analyses included total cholesterol, LDL-C, HDL-C, triglycerides, creatinine, alanine aminotransferase, aspartate aminotransferase, and creatine phosphokinase.

Plasma total Hcy was quantified on the ACL TOP 550 system (Werfen, Barcelona, Spain) using an automated competitive enzymatic immunoassay based on conversion of Hcy to S-adenosyl-L-homocysteine. Hyperhomocysteinemia was defined as Hcy > 15 µmol/L [19]. ADMA, SDMA, arginine, ornithine, and citrulline were quantified by liquid chromatography–tandem mass spectrometry [20]. The arginine bioavailability index was calculated as arginine/(ornithine+citrulline).

Morning urine samples were collected at T0 and T12 and stored at − 80°C. F_2-isoprostanes, DH-isoprostanes, and dinor-isoprostane metabolites were quantified using validated mass-spectrometric methods [21]. Untargeted plasma metabolomics was performed using the previously reported workflow [23]; annotations were considered putative unless confirmed against authentic standards, and metabolomic p values were adjusted for multiple testing [23, 24].

Study endpoints

The primary endpoint was the within-subject change in plasma Hcy from T0 to T12. Secondary endpoints were changes in the lipid profile, urinary oxidative stress markers, and biomarkers of the arginine–nitric oxide pathway. Metabolomic changes and associations between ΔHcy and other biomarkers were analyzed as ancillary, hypothesis-generating outcomes. Δ was defined as T12 minus T0.

Statistical analysis

Continuous variables are reported as mean±standard deviation or median (IQR), according to their distribution as assessed by the Shapiro–Wilk test. Categorical variables are reported as n (%). Paired Student t tests or Wilcoxon signed-rank tests were used for continuous outcomes, and the exact McNemar test was used for paired hyperhomocysteinemia status. Pearson or Spearman correlation coefficients were used according to variable distribution. Metabolomic findings are reported with multiplicity-adjusted P values. An ancillary multivariable linear regression model was fitted with ΔHcy as the dependent variable. Changes in methylmalonic acid, arginine, citrulline, ornithine, asymmetric dimethylarginine (ADMA), symmetric dimethylarginine (SDMA), the arginine bioavailability index, LDL score, lipoprotein(a) (Lp(a)), and LDL-C reduction were entered simultaneously using the enter method on the basis of their biological relevance to homocysteine metabolism, lipid remodeling, and vascular homeostasis. A complete-case analysis was used. Model performance was summarized by R^2, adjusted R^2, and the overall F statistic. Standardized regression coefficients and corresponding P values are reported. All tests were 2-sided, with $P < 0.05$ considered statistically significant. Analyses were performed using R and IBM SPSS Statistics version 29.0.

Sample size

In the absence of previous clinical studies specifically evaluating changes in plasma homocysteine during PCSK9 inhibitor treatment, assumptions for the primary-endpoint sample-size calculation were based on published data from intensive lipid-lowering therapy in patients with hypercholesterolemia. In a previous study, high-dose simvastatin (80 mg/day) reduced plasma homocysteine from 13.0 ± 4.0 to 10.6 ± 3.5 μmol/L, corresponding to an expected mean within-subject difference of 2.4 μmol/L [25]. Because the standard deviation of the paired differences was not reported, it was conservatively estimated from the baseline and follow-up standard deviations assuming no within-subject correlation, yielding an estimated standard deviation of 5.32 μmol/L. With a 2-sided α of 0.05 and 80% power, 41 evaluable participants were required. Allowing for approximately 15% incomplete or nonevaluable paired assessments, the target sample size was 49 participants.

Results

Participant characteristics

Between 2023 and 2024, 61 consecutive patients with FH were screened for eligibility within project PNRR-MAD-2022-12375721. Fifty met all eligibility criteria, initiated a PCSK9 inhibitor, completed the 12-week assessment, and were included in the paired analyses (**Supplementary Fig. 1**). The cohort had a mean age of 52 ± 15 years and included 26 men (52%). Hypertension was present in 24 patients (48%), previous cardiovascular events in 14 (28%), diabetes in 4 (8%), and current smoking in 4 (8%). The mean Dutch Lipid Clinic Network score was 8.5 ± 2.9. Thirty-eight patients (76%) received a statin and 44 (88%) received ezetimibe; 12 (24%) were classified as statin intolerant. All participants completed treatment, with no reported treatment-related adverse events and no significant changes in liver or muscle enzyme levels (Table 1).

Changes in homocysteine

Mean Hcy decreased from 12.6 ± 6.7 to 8.9 ± 2.4 μmol/L, corresponding to a 29% reduction; the mean within-subject change was − 3.7 ± 5.6 μmol/L. Median Hcy decreased from 10.7 μmol/L (IQR: 9.0–13.4) at T0 to 9.1 μmol/L (IQR: 7.0–10.5) at T12 ($P < 0.001$), corresponding to a 15.0% reduction based on median values (Fig. 1A).

Hyperhomocysteinemia was present in 10 of 50 patients (20.0%) at T0 and in none at T12. All 10 patients crossed below the prespecified threshold of 15 μmol/L, and no participant crossed in the opposite direction (exact McNemar $P = 0.002$; Fig. 1B).

Changes in lipid profile

Total cholesterol decreased from 7.05 mmol/L (IQR: 5.59–8.41) to 4.38 mmol/L (IQR: 3.56–5.38), a 37.9% reduction ($P < 0.001$). Corrected LDL-C decreased from 5.11 mmol/L (IQR: 3.94–6.27) to 3.37 mmol/L (IQR: 2.53–4.63), a 34.1% reduction ($P = 0.001$), and Lp(a) decreased from 64.4 mg/dL (IQR: 19.8–83.4) to 41.7 mg/dL (IQR: 15.6–80.6), a 35.2% reduction ($P < 0.001$). HDL-C increased from 1.27 to 1.40 mmol/L ($P = 0.065$), whereas triglycerides were unchanged (1.24 vs 1.25 mmol/L; $P = 0.607$) (Fig. 2).

Oxidative stress, endothelial biomarkers, and metabolomics

Urinary F_2-isoprostanes decreased by 23.1% ($P = 0.001$), DH-isoprostanes by 17.8% ($P = 0.044$), and dinor-isoprostane metabolites by 27.7% ($P = 0.004$). By contrast, ADMA (+ 5.3%; $P = 0.370$), SDMA (− 9.1%; $P = 0.210$), and the arginine bioavailability index (− 8.2%; $P = 0.130$) did not change significantly (Fig. 3).

Ancillary metabolomic profiling showed lower abundance of a cholesterol-related feature (log fold change [logFC] − 0.362; adjusted $P < 0.001$), PA(20:4/2:0) (− 0.174; adjusted $P = 0.033$), PC(20:4/0:0) (− 0.166; adjusted $P = 0.041$), PC(0:0/18:0) (− 0.128; adjusted $P = 0.042$), platelet-activating factor C-16 (−

0.139; adjusted P = 0.041), and choline (− 0.113; adjusted P = 0.045), with an increase in a putative betaine-related feature (+ 0.233; adjusted P = 0.023) (**Supplementary Table 1**).

Correlates of homocysteine variation and multivariate analysis

ΔHcy correlated inversely with baseline Hcy (r = − 0.643; P < 0.001), consistent with larger absolute decreases among participants with higher baseline values. ΔHcy correlated positively with Δmethylmalonic acid (r = 0.527; P < 0.001) and ΔLDL-C (r = 0.308; P = 0.033) (**Supplementary Table 2**).

In multivariable analysis, Δmethylmalonic acid was positively associated with ΔHcy (standardized β = 1.014; P < 0.001). Positive associations were also observed for Δarginine (β = 0.792; P = 0.005) and Δsymmetric dimethylarginine (β = 0.506; P < 0.001). Inverse associations were observed for Δornithine (β=−1.163; P < 0.001), Δasymmetric dimethylarginine (β=−0.335; P < 0.001), Δcitrulline (β=−0.217; P = 0.046), the Δarginine bioavailability index (β=−1.418; P = 0.002), Δlipoprotein(a) (β=−0.262; P = 0.013), and LDL-C reduction (β=−0.311; P = 0.002) (**Supplementary Fig. 2; Supplementary Table 3**).

Discussion

In this prospective cohort of patients with FH, 12 weeks of PCSK9 inhibitor treatment was associated with a significant reduction in plasma Hcy, together with substantial lipid lowering and decreases in urinary oxidative stress biomarkers. All participants with hyperhomocysteinemia at baseline had Hcy concentrations below the prespecified threshold at follow-up. By contrast, biomarkers of the arginine–nitric oxide pathway did not change significantly. These findings indicate that the change in circulating Hcy occurred within a broader biochemical response characterized predominantly by lipid remodeling and attenuation of oxidative stress rather than by uniform modification of all vascular biomarker pathways.

The present observations extend the biological framework of PCSK9 inhibition beyond its established effects on LDL-C and Lp(a). Although the cardiovascular benefit of PCSK9 inhibitors is primarily attributable to the marked reduction in atherogenic lipoproteins, increasing evidence suggests that PCSK9-related pathways may also interact with oxidative, inflammatory, endothelial, and metabolic processes involved in atherosclerosis progression [11–14]. Within this context, Hcy is of particular interest because it lies at the intersection of one-carbon metabolism, redox homeostasis, endothelial function, and atherothrombotic risk. Elevated Hcy concentrations have been associated with increased reactive oxygen species generation, reduced nitric oxide bioavailability, endothelial activation, and promotion of prothrombotic signaling [7–10]. The observed reduction in Hcy during PCSK9 inhibitor treatment therefore provides a clinically relevant signal supporting the hypothesis that PCSK9 inhibition may be accompanied by metabolic adaptations extending beyond conventional lipid parameters.

A mechanistic interaction between Hcy and PCSK9 has previously been suggested by experimental evidence. In a murine model of hyperhomocysteinemia, elevated Hcy increased PCSK9 expression,

impaired macrophage cholesterol efflux through downregulation of ABCA1- and ABCG1-mediated pathways and promoted atherosclerotic lesion development. Conversely, pharmacological inhibition of PCSK9 attenuated these abnormalities and was associated with a reduction in circulating Hcy concentrations in murine models [15]. Human observational studies have also reported associations between plasma PCSK9 and Hcy levels [16]. Although the present study was not designed to establish the directionality or molecular basis of this interaction, the reduction in Hcy observed after PCSK9 inhibitor initiation is consistent with the existence of a reciprocal relationship between lipid regulatory pathways, oxidative stress, and one-carbon metabolism.

The concomitant decrease in urinary F_2-isoprostanes, DH-isoprostanes, and dinor-isoprostane metabolites further supports the biological coherence of the findings. Isoprostanes are established indices of lipid peroxidation and systemic oxidative stress, and their reduction suggests attenuation of oxidative injury during treatment. This observation is particularly relevant because oxidative stress represents one of the principal mechanisms through which Hcy may adversely affect vascular homeostasis. Increased Hcy concentrations can promote oxidative inactivation of nitric oxide, endothelial nitric oxide synthase uncoupling, and amplification of vascular inflammatory signaling [7–10, 24]. The parallel reduction in Hcy and oxidative stress biomarkers may therefore reflect interconnected metabolic and redox adaptations occurring during PCSK9 inhibition. Importantly, however, ADMA, SDMA, and the arginine bioavailability index remained unchanged. These findings indicate that the biochemical response was not uniformly expressed across all pathways related to endothelial function and suggest that the principal short-term changes involved lipid metabolism and oxidative balance.

The ancillary metabolomic analyses provide additional insight into the metabolic context of Hcy variation. As expected, PCSK9 inhibitor treatment was associated with changes in sterol- and phospholipid-related features, consistent with extensive lipoprotein remodeling. More notably, changes were also observed in metabolites related to one-carbon metabolism, including a reduction in choline and an increase in a putative betaine-related signal. Choline oxidation represents a major source of betaine, which acts as a methyl donor in the betaine–homocysteine methyltransferase-mediated remethylation of Hcy to methionine [27]. The observed metabolic pattern is therefore compatible with modulation of pathways involved in Hcy homeostasis. The association between ΔHcy and Δmethylmalonic acid further supports the involvement of interconnected vitamin B12-dependent and one-carbon metabolic processes [28].

The multivariable analysis was consistent with a coordinated metabolic response. Changes in methylmalonic acid, selected metabolites of the arginine–nitric oxide pathway, LDL-C, and Lp(a) were associated with Hcy variation when considered jointly. Given the limited sample size, number of covariates, and exploratory nature of the analysis, these associations should be interpreted as hypothesis-generating and not as evidence of independent mechanistic effects.

From a clinical perspective, these findings may be relevant to the characterization of residual cardiovascular risk in FH. Despite intensive lipid-lowering therapy, patients with FH remain exposed to

risk determinants beyond LDL-C, including elevated Lp(a), oxidative stress, endothelial dysfunction, inflammation, and the cumulative consequences of lifelong arterial exposure to atherogenic lipoproteins. In this setting, Hcy may represent an integrated biomarker reflecting the interaction between metabolic and vascular pathways during treatment. Its potential value should not be interpreted in terms of an independent therapeutic target. Randomized trials of folic acid and B-vitamin supplementation have not consistently demonstrated cardiovascular benefit despite lowering Hcy concentrations [29, 30]. Rather, the present results suggest that Hcy may serve as a treatment-responsive indicator of broader vascular–metabolic remodeling during PCSK9 inhibition.

Whether changes in Hcy provide incremental prognostic information beyond established lipid parameters remains to be determined. The clinical relevance of the present findings lies primarily in the identification of a previously insufficiently characterized biochemical response to PCSK9 inhibitor and in the generation of a mechanistic framework linking lipid lowering, oxidative stress, and one-carbon metabolism. Future studies should investigate whether the magnitude of Hcy reduction is associated with changes in vascular function, plaque phenotype, or cardiovascular outcomes and whether it identifies specific metabolic phenotypes among patients receiving PCSK9 inhibitors.

The study has several strengths. Its prospective design enabled standardized paired assessment before and after treatment. Complete follow-up and simultaneous evaluation of lipid, oxidative stress, endothelial, and metabolomic biomarkers allowed a multidimensional characterization of the biological response to PCSK9 inhibition. The concordance between the primary Hcy finding, reductions in oxidative stress markers, and metabolomic signals related to one-carbon metabolism supports the internal coherence of the observations.

Several limitations should be acknowledged. The single-center, uncontrolled design precludes attributing the observed changes exclusively to PCSK9 inhibitor; however, the prospective within-subject design, standardized timing of assessments, unchanged background lipid-lowering therapy, and complete follow-up reduced interindividual variability and potential treatment-related confounding. The relatively limited sample size restricts the precision and generalizability of ancillary analyses, which were therefore prespecified as exploratory and interpreted as hypothesis-generating. The 12-week follow-up does not establish the long-term persistence or clinical significance of the observed biochemical changes. Untargeted metabolomic profiling does not provide definitive metabolite identification or information on metabolic flux; accordingly, annotations were considered putative, multiple-testing correction was applied, and the betaine-related feature will require validation using targeted quantitative methods. Finally, although folic acid and vitamin B12 supplementation were excluded by protocol and participants were instructed to maintain their habitual diet, circulating folate and vitamin B12 concentrations were not measured.

In conclusion, PCSK9 inhibitor treatment was associated with a significant reduction in plasma Hcy in patients with FH, together with marked lipid remodeling and attenuation of systemic oxidative stress. Ancillary biomarker and metabolomic analyses suggest that this change may be part of a coordinated

vascular–metabolic response involving lipid, redox, and one-carbon pathways. These findings provide a rationale for prospective mechanistic studies incorporating targeted metabolomics, nutritional and renal covariates, vascular phenotyping, and longer-term follow-up to determine the biological and potential prognostic significance of Hcy modulation during PCSK9 inhibition.

Declarations

Ethics approval and consent to participate: The study was conducted in accordance with the Declaration of Helsinki and was approved by the “Federico II-Cardarelli” Ethics Committee (protocol no. 2023/221). Written informed consent was obtained from all participants.

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Data availability: De-identified data may be made available by the corresponding author upon reasonable request and subject to ethics and institutional requirements.

Conflict of interest: The authors declare that they have no conflict of interest related to this work.

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Tables

Table 1

Baseline characteristics of the study cohort

Variable	Study cohort (n = 50)
Age, years	52 ± 15
Male sex	26 (52%)
Hypertension	24 (48%)
Previous cardiovascular events	14 (28%)
Obesity	26 (52%)
Diabetes mellitus	4 (8%)
Current smoking	4 (8%)
Body mass index, kg/m²	26 ± 5
Dutch Lipid Clinic Network score	8.5 ± 2.9
ALT, IU/L	24 (21–26)
AST, IU/L	27 (21.3–38.8)
Creatine phosphokinase, IU/L	110 (90–171)
Total cholesterol, mg/dL	279.6 ± 69.2
Triglycerides, mg/dL	107.5 (81.8–130.8)
HDL-C, mg/dL	52.5 ± 12.8
LDL-C, mg/dL	201.0 ± 68.8
Lp(a), mg/dL	69.3 (22.3–83.4)
Homocysteine, µmol/L	10.7 (9.0–13.4)
Hyperhomocysteinemia (> 15 µmol/L)	10 (20%)
Statin therapy	38 (76%)
Ezetimibe therapy	44 (88%)
Statin intolerance	12 (24%)
Antiplatelet therapy	18 (36%)

Data are mean ± standard deviation, median (interquartile range), or n (%). ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a).

Figures

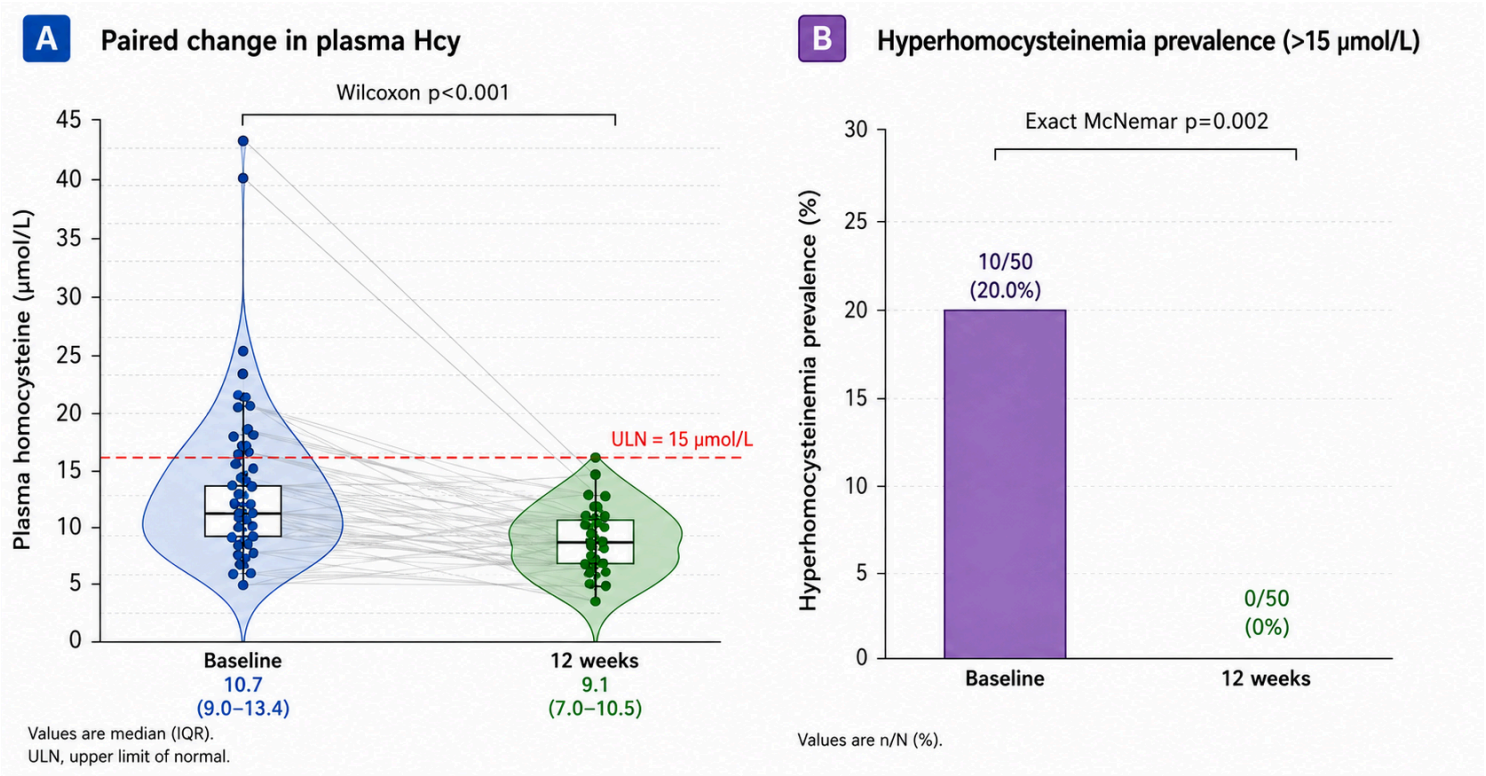


Figure 1

Changes in plasma homocysteine concentrations and prevalence of hyperhomocysteinemia during PCSK9 inhibitor treatment.

Panel A shows paired Hcy concentrations at baseline and 12 weeks. Violin and box plots summarize the *distributions*, and*individual observations are connected. The dashed line indicates* the threshold for hyperhomocysteinemia (*>15 µmol/L*). *Panel B shows* the *prevalence* of hyperhomocysteinemia; *paired categorical* data were compared using the *exact McNemar* test.

Abbreviations: Hcy, homocysteine; IQR, interquartile range; ULN, upper limit of normal.

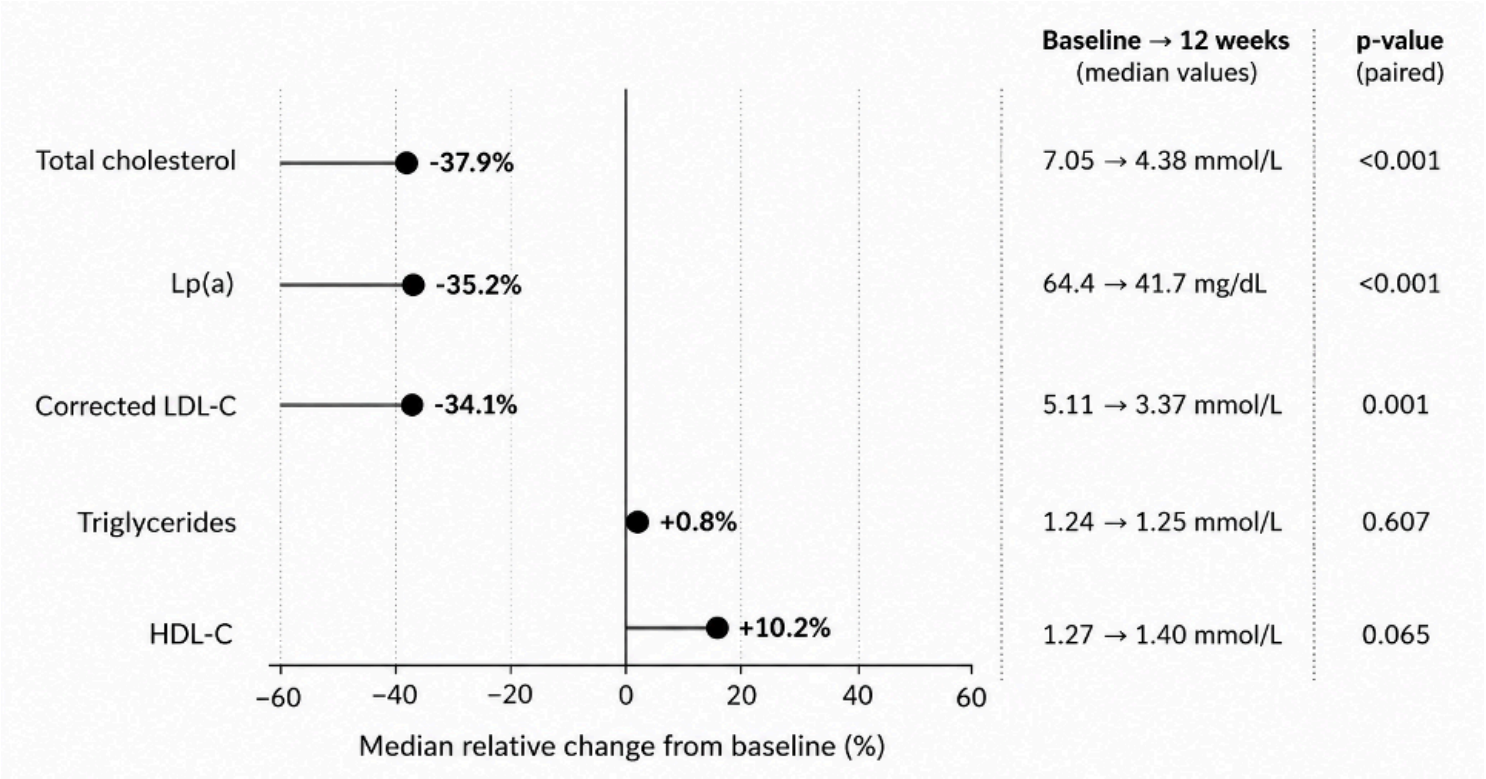


Figure 2

Changes in lipid parameters during 12 weeks of PCSK9 inhibitor treatment.

Horizontal lollipop plot showing *median relative changes. Negative values indicate reductions. P values refer to paired within-subject comparisons.*

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a).

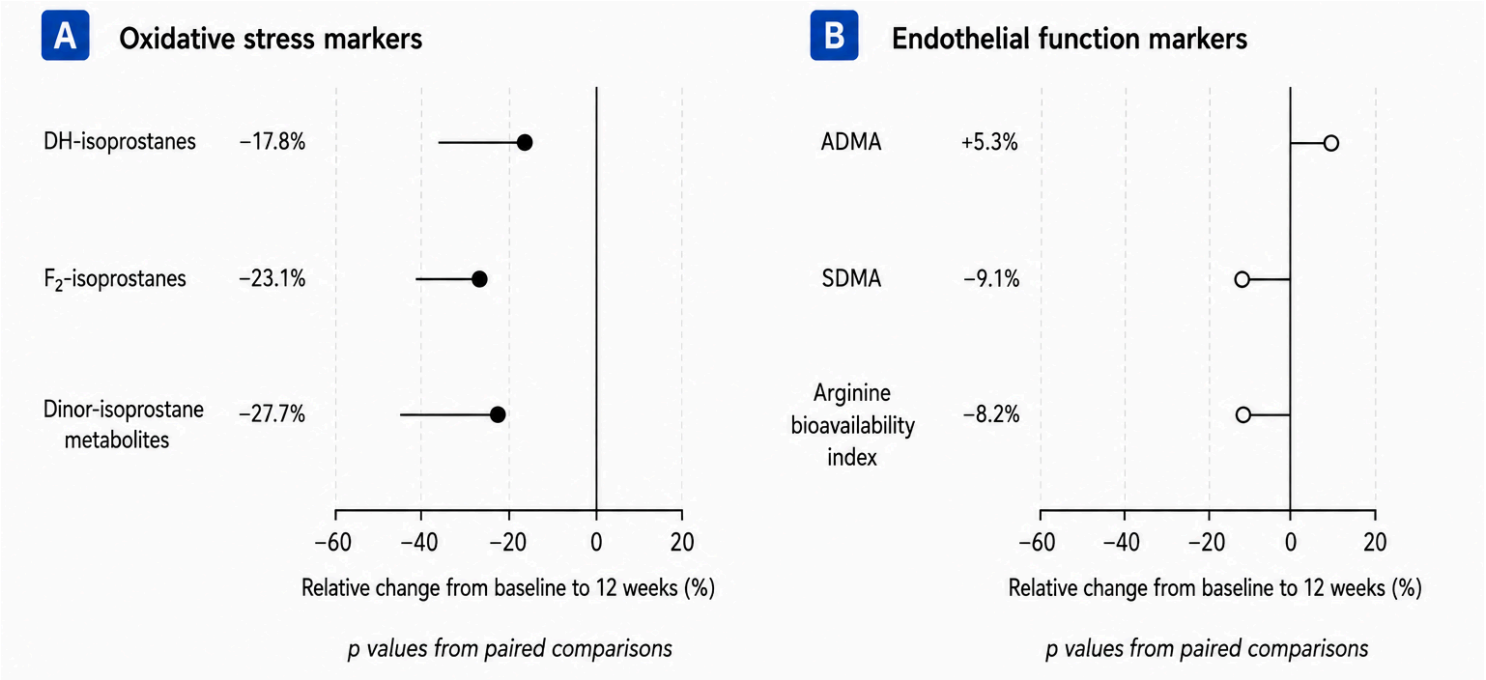


Figure 3

Changes in urinary oxidative stress markers and biomarkers of the arginine–nitric oxide pathway.

Panel A shows relative changes in urinary oxidative stress markers; Panel B shows changes in asymmetric dimethylarginine, symmetric dimethylarginine, and the arginine bioavailability index. Filled circles indicate P<0.05 and open circles indicate P≥0.05. P values are from unadjusted paired comparisons.

Abbreviations: ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine.

Supplementary Files

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- 004PCSK9HCysSupplementaryDEF.docx