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Effect of add-on PCSK9 inhibitors on endocan and arterial stiffness in heterozygous familial hypercholesterolemia: a two-lipid center real-world study

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ABSTRACT

Background and aims: Endothelial dysfunction (ED) represents an early key event in atherogenesis. Our aim was to evaluate the efficacy of six months add-on PCSK9 monoclonal antibodies (mAbs) on endothelial function assessed by endocan plasma levels and PWV in a cohort of HeFH subjects; furthermore, we investigated the association of endocan lowering and PWV variation.

Methods and results: In this prospective observational study, we evaluated 30 FH subjects on high-intensity statins plus ezetimibe and with an off-target LDL-C. All patients received PCSK9 mAbs therapy and obtained biochemical analysis as well as endocan measurement and PWV evaluation at baseline and after six months of PCSK9 mAbs. After six months of add-on PCSK9 mAbs therapy, a significant reduction of TC, LDL-C, Non-HDL-C, TG, Lp(a) and ApoB was observed; moreover, both PWV and endocan significantly improved after six months of treatment. Finally, univariate linear regression analysis showed that ΔPWV was significantly associated with ΔEndocan (p value < 0.001).

Conclusions: PCSK9 inhibition was associated with significant improved endocan levels and PWV in a cohort of HeFH subjects. ΔEndocan was significantly associated with ΔPWV. Our exploratory findings demonstrate endothelial benefits of PCSK9 mAbs in addition to LDL-C lowering and support endocan and PWV as complementary markers of vascular response in FH.

1. Introduction

Heterozygous familial hypercholesterolemia (HeFH) is the most common form of monogenic hypercholesterolemia affecting roughly 1 in every 250 individuals [1]. Accelerated atherosclerosis and premature cardiovascular (CV) events in FH are due to lifetime exposure to very high LDL-cholesterol (LDL-C) levels [2]. Endothelial dysfunction (ED) represents an early key event in atherogenesis, driving plaque formation, inflammation, and thrombosis [3]. Growing interest is directed toward circulating biomarkers that can detect early ED, improve CV stratification and minimize the risk of atherosclerotic cardiovascular disease (ASCVD). One such candidate is endocan, a soluble 50 kDa dermartan sulfate proteoglycan, that can be readily measured in the circulation [4]. Endocan is secreted by vascular endothelium, especially in inflammatory states [5], and participates in various biological activities including cell adhesion, proliferation, migration and neovascularization [6]. Endocan is emerging as a CV biomarker [7], and its association with ED markers supports its role in vascular health [4]. However, no studies are available on the effect of lipid-lowering therapies (LLTs) on endocan plasma levels in subjects with FH. Pulse wave velocity (PWV) is a non-invasive and well-established measure of arterial stiffness, widely recognized as an independent predictor of CV

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outcomes and often used to assess vascular health [8,9]. Recent studies have shown that LDL-C reduction achieved through LLTs leads to improvement in PWV, thereby helping to mitigate CV risk in individuals with FH [10,11].

In this study we aimed to evaluate the efficacy of six months add-on PCSK9 monoclonal antibodies (mAbs) on endothelial function assessed by endocan plasma levels and PWV in a cohort of FH subjects; furthermore, we investigated the association of endocan lowering and PWV variation.

2. Methods

2.1. Study design and population

This was a prospective observational study involving patients with a FH diagnosis previously confirmed by genetic analysis [1], who were enrolled from two tertiary centers for the screening, diagnosis and management of familial dyslipidemias (Lipid Center University Hospital of Messina and the University Hospital of Catania, Italy), between September 2019 to May 2021. According to the Italian reimbursement criteria of PCSK9i, 3 FH subjects started alirocumab 75 mg, 9 started alirocumab 150 mg and 18 started evolocumab 140 mg. All subjects were aged between 18 and 70 years and were off LDL-C target despite high-intensity statin therapy (atorvastatin 40-80 mg, rosuvastatin 20-40 mg) plus ezetimibe for at least six months at the time of enrollment. Moreover, all subjects were free of hematopoietic disorders, malignancies and/or treatment with chemotherapy, acute infections, chronic inflammatory status and glucocorticoid therapy within the past three months. Individuals with hypertension, diabetes mellitus and active treatment with PCSK9 mAbs at the time of enrolment were also excluded. After a 12 h fast biochemical analyses, endocan measurement and PWV evaluation were performed at baseline (T0) and after six months (T1) of PCSK9 mAbs treatment. Body mass index, statin therapy and smoking habits were defined as previously reported [12]. LDL-C target was set according to the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines 2019 [13]. ASCVD was defined as established coronary, cerebral or peripheral arterial injuries. PWV was estimated as previously reported [10]. Endocan concentrations were determined in 30 paired aliquots (60 samples in total) collected at T0 and T1 (processed within 2 h and stored at −80 °C); the T1 blood draw was scheduled at week 25 to minimize potential variability in mAbs plasma levels.

In total, 127 subjects with FH were evaluated; of these 30 subjects with HeFH fulfilling the inclusion criteria and were selected for this study. The study protocol was approved by the local ethics committee (protocol no. 46/19). Informed consent was obtained from each subject enrolled in the study.

2.2. Endocan measurement

Endocan was measured using a commercially available ELISA kit (Cohesion Bioscences, London, UK). The determinations were carried out once in duplicate following the manufacturer's instructions. The intra-essay variability was evaluated (CV 1.53%).

2.3. Pulse wave velocity evaluation

The SphygmoCor CVMS (AtCor Medical, Sydney, Australia) system was used for the determination of the PWV. This system uses a tonometer and 2 different pressure waves obtained at the common carotid artery (proximal recording site) and at the femoral artery (distal recording site). The distance between the recording sites and the suprasternal notch was measured using a tape measure. An electrocardiogram was used to determine the start of the pulse wave. The PWV was determined as the difference in interval time of the pulse wave between the 2 different recording sites and the suprasternal notch, divided by the travel distance of the pulse waveform. The PWV was calculated on the mean of 10 consecutive pressure waveforms to cover a complete respiratory cycle.

2.4. Statistical analysis

The distributional characteristics of each variable were assessed by the Kolmogorov-Smirnov test. Data are reported as mean ± standard deviation (SD) for continuous parametric and median (interquartile range-IQR) for continuous nonparametric variables and as frequency (percentage) for categorical variables. The $\chi 2$ test was used for categorical variables. Changes from baseline (T0) to the follow-up time point (T1 vs T0) were evaluated as delta (Δ), calculated according to the following formula: [(T1-T0)/T0)*100] and expressed as percentage change. To compare time-dependent differences (T1 vs T0) the paired *t*-test was used for normally distributed variables, whereas the Wilcoxon signed-rank test was used for non-normally distributed variables. Linear regression analysis was performed to assess the relation of ΔEndocan with ΔPWV and the relation of ΔLDL-C with ΔEndocan. Regression coefficients are reported as unstandardized coefficients (B) with their corresponding standard errors and 95% confidence intervals. All statistical analyses were performed using IBM SPSS Statistics for Windows version 23. For all tests, $p < 0.05$ was considered significant.

3. Results

The baseline characteristics of the study population are shown in Table 1. After six months of add-on PCSK9 mAbs therapy, 46.6% of the study population achieved LDL-C targets. As expected, TC, LDL-C and ApoB plasma levels significantly decreased from baseline (TC: - 38.1%, $p < 0.001$; LDL-C: - 52.2%, $p < 0.001$; ApoB: - 41.2%, $p < 0.001$); moreover, a significant reduction was also found in non-HDL-C (-48.3%, $p < 0.001$), TG (-31.6%, $p < 0.01$) and Lp(a) (−26%, $p < 0.05$). Concerning glucose and inflammatory profiles, no significant changes were observed in FPG and hs-CRP, respectively, after the add-on of PCSK9 mAbs. Both PWV and Endocan significantly improved after six months of PCSK9 mAbs therapy (PWV: 10.4 ± 1.16 vs 8.6 ± 1.12 m/s [Δ - 17.3%], $p < 0.001$; Endocan: 229.6 (179.6 - 281.2) vs 191.6 (150.7 - 243.0) ng/mL [Δ - 16.5%], $p < 0.01$) (Table 2). Moreover, patients achieving LDL-C targets showed a significantly greater reduction in both ΔPWV and ΔEndocan compared to those not achieving targets (Fig. 1). Multivariate linear regression analysis showed that ΔPWV was

Table 1
Baseline characteristics of the Study Population.

Demographic Characteristics	
N	30
Age, years	50.6 ± 12.0
Men, n (%)	18 (60)
BMI, kg/m^2	25.4 ± 4.3
ASCVD, n (%)	15 (50)
FH Genotype	
LDLR, n (%)	28 (93.3)
- *LDLR defective, n (%)*	19 (63.3)
- *LDLR null, n (%)*	11 (36.6)
ApoB, n (%)	2 (6.7)
FH Phenotype	
Heterozygous, n (%)	30 (100)
Risk factors	
Systolic BP, mmHg	123.5 ± 12.4
Diastolic BP, mmHg	75.2 ± 11.5
Smoking, n (%)	7 (23.3)
Treatment	
Lipid lowering therapy, n (%)	30 (100)
- *High-intensity statin plus ezetimibe, n (%)*	30 (100)

Data are presented as mean ± standard deviation, percentages, or median (interquartile range). BMI = body mass index, ASCVD = atherosclerotic cardiovascular disease, FH = familial hypercholesterolemia, LDLR = low-density lipoprotein receptor, ApoB = apolipoprotein B, BP = blood pressure.

Table 2
Metabolic and vascular profile of the Study Population at baseline and after six months of add on PCSK9 mAbs.

Study parameter	FH subjects (n = 30)	FH subjects (n = 30)	Δ	*p* value between two groups[a]
	Baseline	6-months add-on PCSK9 mAb		
Lipid profile				
TC, mg/dL	255.2 ± 15.8	157.9 ± 16.6	−38.1%	<0.001
HDL-C, mg/dL	53.4 ± 14.1	53.7 ± 12.5	-	0.8
Triglycerides, mg/dL	117.0 (74.0 - 150.0)	80.0 (65.0 - 114.0)	−31.6%	<0.01
LDL-C, mg/dL	178.2 ± 15.4	85.2 ± 16.3	−52.2%	<0.001
LDL-C target, n (%)	-	14 (46.6)	-	-
Non-HDL-C, mg/dL	201.8 ± 15.2	104.3 ± 15.5	−48.3%	<0.001
ApoB, mg/dL	125.5 ± 10.5	73.8 ± 11.3	−41.2%	<0.001
ApoAI, mg/dL	144.1 ± 10.6	136.6 ± 11.9	−5.2%	0.3
Lp(a), mg/dL	30.0 (12.9 - 56.3)	22.2 (9.7 - 43.1)	−26.0%	<0.05
Glucose profile				
FPG, mg/dL	93.6 ± 9.9	96.1 ± 8.4	2.7%	0.4
Inflammatory profile				
hs-CRP, mg/dL	0.1 (0.05 - 0.30)	0.1 (0.05 - 0.20)	-	0.2
Vascular profile				
Endocan, ng/mL	229.6 (179.6 - 281.2)	191.6 (150.7 - 243.0)	−16.5%	<0.01
PWV, m/s	10.4 ± 1.16	8.6 ± 1.12	−17.3%	<0.001

Data are presented as mean ± standard deviation, percentages, or median (interquartile range). FH = familial hypercholesterolemia, PCSK9 mAbs = Proprotein Convertase Subtilisin/Kexin type 9 monoclonal antibodies, TC = total cholesterol, LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, Non-HDL-C = non-HDL cholesterol, ApoB = apolipoprotein B, ApoAI = apolipoprotein AI, Lp(a) = lipoprotein (a), FPG = fasting plasma glucose, hs-CRP = high sensitivity C-reactive protein, PWV = pulse wave velocity.
Δ, Δ-change with respect to baseline and its significance.
"-" indicates not applicable (no delta calculated).
[a] Significance level for the Paired-Sample T Test or the Wilcoxon signed-rank test, baseline and after 6-month add-on PCSK9 mAbs groups.

significantly associated with ΔEndocan ($p < 0.001$) after adjustment for potential confounders (Table 3). Moreover, simple linear regression analyses showed that ΔLDL-C was significantly associated with ΔEndocan ($p < 0.001$) (Table 4).

4. Discussion

ED represents a key early stage in atherogenesis, and the identification of biomarkers that can reliably reflect endothelial activation is of growing clinical relevance. Among these, endocan has emerged as a promising indicator of endothelial inflammation and vascular health in individuals at high CV risk [4].

In this study, we evaluated the effect of add-on PCSK9 mAbs on endocan plasma levels in HeFH patients already treated with high-intensity statin plus ezetimibe and explored the relationship between biochemical changes and vascular stiffness, assessed through PWV. To the best of our knowledge, this is the first study exploring the effect of PCSK9 mAbs on both circulating endocan levels and PWV in a cohort of FH subjects.

In our study we demonstrated that PCSK9 mAbs provide a significant LDL-C reduction (52.2%) and a 26% decrease in Lp(a) after six months, consistent with results from the ODYSSEY FH I-II and the RUTHERFORD-2 studies [14,15]. At T1, a significant reduction in PWV was observed, with values decreasing from above to below the commonly recommended 10 m/s carotid-femoral PWV threshold, indicating a clinically meaningful improvement [16]. The magnitude of change (~17%) is in line with previous findings in both FH and non-FH populations treated with PCSK9 inhibitors [17,18]. Concerning the ED, we found that endocan levels significantly improved after six months of add-on PCSK9 mAbs; moreover, we observed a significant improvement in arterial stiffness, in line with previous studies [10,11]. Importantly, univariate linear regression analysis showed that ΔEndocan was significantly associated with ΔPWV after 6 months of PCSK9 mAbs therapy, enhancing the concept of a parallel biochemical and functional vascular impairment. This finding supports the evidence that endothelial effects of PCSK9 mAbs do not depend on LDL-C reduction alone [19,20]; in line with our results, PCSK9 mAbs could improve endothelial function across multiple vascular beds [21,22], often without changes in hs-CRP. This reinforces the concept that hsCRP, although recognized as

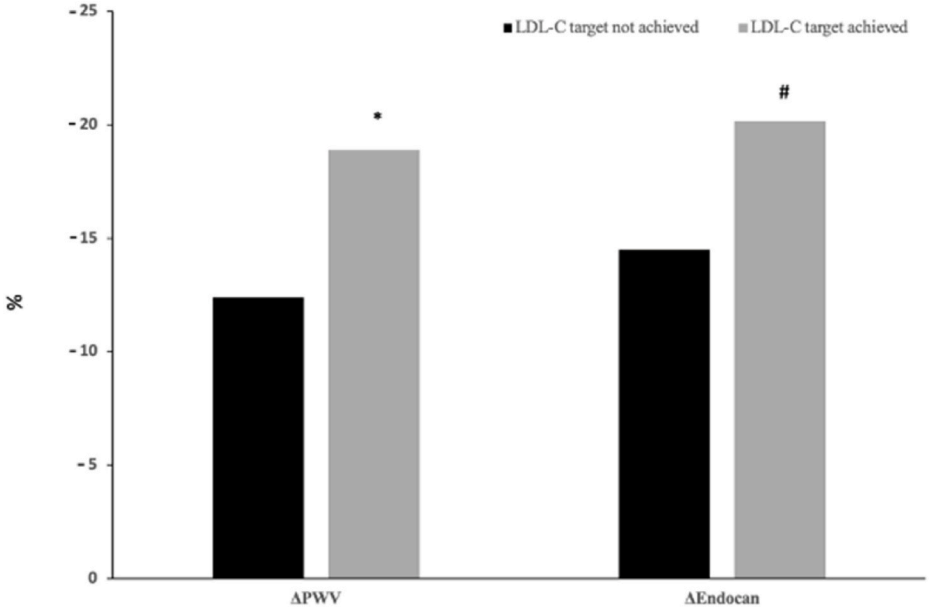

Fig. 1. Changes in ΔPWV and ΔEndocan according to LDL-C target achievement. PWV = pulse wave velocity, LDL-C = low-density-lipoprotein cholesterol.
*$p < 0.001$.
#$p < 0.05$.

Table 3
Multivariate Linear Regression analysis of ΔPWV in the Study Population.

Dependent Variable	ΔPWV					
	Univariate			Multivariate		
Independent Variables	B (SE)	95% CI	*p* Value	B (SE)	95% CI	*p* Value
ΔEndocan, %	0.27 (0.03)	0.21 - 0.33	<0.001	0.19 (0.03)	0.13 - 0.25	<0.001
ΔLDL-C, %				0.24 (0.02)	0.20 - 0.28	<0.001
Age, years				0.16 (0.06)	0.04 - 0.28	<0.05
PWV T0, m/s				1.72 (0.21)	1.31 - 2.13	<0.001

PWV = pulse wave velocity, LDL-C = low-density lipoprotein cholesterol, B = unstandardized coefficient B, SE = standard error, CI = confidence interval.

Table 4
Univariate Linear Regression analysis of ΔEndocan in the Study Population.

Dependent Variables	ΔEndocan		
Independent Variable	B (SE)	95% CI	*p* Value
ΔLDL-C, %	0.26 (0.05)	0.16 - 0.36	<0.001

LDL-C = low-density lipoprotein cholesterol, B = unstandardized coefficient B, SE = standard error, CI = confidence interval.

a CV risk modifier [23], does not necessarily mirror endothelial changes. Conversely, endocan may be considered as a marker more closely related to endothelial activation than systemic inflammatory markers. In combination with PWV, it may reflect vascular response to the marked LDL-C reduction by PCSK9 inhibition, in line with experimental evidence suggesting that both PCSK9 and endocan are involved in endothelial inflammatory pathways [4]. However, as these molecular mechanisms were not investigated in the present study, their clinical relevance remains to be fully elucidated.

There are several limitations to our study. First, its prospective, observational and non-randomized design introduces the possibility of residual confounding, as treatment strategy was based on clinical decision-making and national reimbursement rules, which may have influenced both patient selection and the observed outcomes. Moreover, the absence of a control group limits the ability to establish a causal relationship between PCKS9 inhibition and the observed changes, particularly as endocan levels could be influenced by several physiological and pathological factors, and its intra-individual variability is not fully established. The relatively small sample size, mainly driven by the stringent inclusion criteria, may limit the generalizability of our findings. However, the significant improvement in endocan levels and PWV as well as a significant association of ΔEndocan and ΔPWV supports the internal coherence of the results. Information on lifestyle changes during follow-up (diet, physical activity, weight variation) was not systematically collected and their potential influence cannot be excluded, although the relatively short follow-up may have limited their impact. Overall, these findings should be considered hypothesis-generating and warrant confirmation in a larger, controlled studies.

In conclusion, PCSK9 inhibition significantly improved endocan levels and PWV in a cohort of HeFH subjects. Moreover, ΔEndocan was significantly associated with ΔPWV. While the improvement in arterial stiffness is consistent with previous evidence [10], our findings demonstrate endothelial benefits of PCSK9 mAbs in addition to LDL-C lowering and support endocan and PWV as complementary markers of vascular response in FH. As molecular mechanisms were not directly assessed in our study, the findings should be interpreted with caution and no mechanistic conclusions can be inferred.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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