High Blood Pressure & Cardiovascular Prevention
https://doi.org/10.1007/s40292-025-00741-w

Online ISSN 1179-1985

ORIGINAL ARTICLE

Pulse Wave Velocity Progression Determinants: No Significant Association with Novel Lipids Parameter

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Received: 1 July 2025 / Accepted: 4 September 2025

Abstract

Introduction Whether novel lipid parameters are related to arterial stiffness (pulse wave velocity-PWV), changes during follow-up (i.e ΔPWV) has never been evaluated.

Aim To evaluate the relationship between standard and emerging lipid parameters (non-HDL/HDL, LDL/HDL, total cholesterol/HDL, TG/HDL, Log(TG)/HDL, Log(TG/HDL) and the triglyceride-glucose index [TyG]) and ΔPWV among hypertensive patients.

Methods We included 469 hypertensive patients enrolled from September 2006 to October 2010 from the Hypertension Unit of San Gerardo Hospital (Monza, Italy). PWV was measured at baseline and after a mean follow-up of 3.8 years (I-III quartiles 3.5–4.2 years) and the relative change (ΔPWV) was calculated.

Results The study cohort had a mean age of 53.6 ± 12.9 years and 58.4% were male. PWV significantly increased from baseline to follow-up (8.6 ± 2.1 vs. 9.2 ± 2.4 m/s; p=0.0001), with 51.6% of patients exhibiting a ΔPWV≥0.5 m/s. These patients had a significantly lower HDL cholesterol (51.5 ± 13.5 vs. 54.7 ± 13.3 mg/dL) with higher LDL/HDL ratio (2.5 ± 0.9 vs. 2.3 ± 0.9 p=0.049), non-HDL/HDL ratio (3.0 ± 1.1 vs. 2.8 ± 1.1), total cholesterol/HDL ratio (4.0 ± 1.1 vs. 3.8 ± 1.1), Log(TG)/HDL (0.043 ± 0.015 vs. 0.039 ± 0.014) and Log(TG/HDL) (0.351 ± 0.290 vs. 0.295 ± 0.278, p<0.05 for all comparison). A significant univariate association was found between ΔPWV and ΔPWV≥0.5 and Log(TG)/HDL (r = 0.121, $p = 0.009$ and r = 0.094, $p = 0.042$, respectively) but it didn't persist at multivariable analysis adjusted for age, sex, Δ systolic blood pressure, anti-hypertensive therapies and statins, diabetes, and glomerular filtration rate.

Conclusions Our study found no significant associations between emerging lipid parameters and PWV/ΔPWV. Age and blood pressure values remains the main determinants of PWV and its changes over time.

Keywords Pulse Wave Velocity · Pulse Wave Velocity progression · Novel lipid parameter · Arterial hypertension

1 Introduction

Arterial stiffness is a subclinical Hypertension-Mediated Organ Damage (HMOD) strongly associated with the development of future CardioVascular (CV) events [1]. Carotid-femoral Pulse Wave Velocity (PWV) is the gold standard for its evaluation and its use for CV risk reclassification has been suggested by the latest European society of cardiology guidelines for arterial hypertension management [2].

Age and Blood Pressure (BP) are the main PWV determinants [3] but also lipids have been significantly related [4–17]. However, the majority of data on the relationship between lipids and PWV comes from cross-sectional studies while only few studies evaluate PWV progression over time (i.e. ΔPWV) [3, 18–23]. Furthermore, only few of these take into account novel lipid parameters.

Over classic lipid parameter (total, High Density Lipoptotein—HDL, Low Density Lipoprotein—LDL, non-HDL cholesterol and triglycerides—TG), novel ones have been described such as non-HDL/HDL, LDL/HDL, total

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Published online: 22 September 2025

cholesterol/HDL, TG/HDL, Log(TG)/HDL, Log(TG/HDL) and TG-glucose index (TyG). These indices seem to perform better than classic one in predicting CV risk and in identifying early atherosclerosis [9, 24].

So, in our study, we aimed to evaluate the correlation between standard and emerging lipid parameters with changes in PWV (ΔPWV) in a population of hypertensive subjects. PWV was assessed at baseline and after a median follow-up of 3.8 (I-III quartiles 3.5–4.2) years.

2 Methods

2.1 Study Population

From September 2006 to October 2010, we enrolled 1,179 consecutive essential hypertensive outpatients aged 18 to 80 years followed by the Hypertension Unit of San Gerardo Hospital (Monza, Italy).

Inclusion criterion was the presence of hypertension defined as a Systolic BP (SBP) of at least 140 mmHg and/or a diastolic BP (DBP) of at least 90 mmHg or as the reported use of any antihypertensive drug. When no hypertensive therapies were takes the diagnosis of hypertension was confirmed with an office BP evaluation in a second occasion or with a home BP or 24h-Ambulatory BP monitoring average BP values higher than 135/85 mmHg.

When anti-hypertensive therapies were taken this need to be stable for at least 3 months.

A history of CV events (myocardial infarction, angina pectoris, heart failure, stroke, transient ischemic attacks and claudication) and all the diseases that would modify the reliability of the PWV evaluation (atrial fibrillation, very frequent ventricular or supraventricular extrasystoles and previous stent placement at carotid, aortic or femoral levels) were exclusion criteria as well as the presence of secondary hypertension (investigated by biochemical and instrumental assessment appropriated to the patients' presentation and conditions). Further exclusion criteria were: pregnancy, atrial fibrillation, chronic pulmonary disease, substance abuse, and active cancer.

From June 2010 to June 2012, we performed the follow-up examination with a median follow-up time of 3.8 (I-III quartiles 3.5–4.2) years on 583 patients. Since a second evaluation was not planned at the time of enrolment, only 49.4% of the patients agreed to come to the follow-up visit. The present analysis focuses on the 469 subjects participating at the follow-up visit for whom baseline lipid profiles were available. Figure 1 shows the flow chart of the enrolment process.

At baseline, participants underwent a comprehensive medical history review and physical examination. Furthermore, classes of antihypertensive drugs and statins use were recorded. Then, BP was measured twice with an oscillometric sphygmomanometer (OMRON M3, OMRON Healthcare Europe, Hoofddorp, The Netherlands) after the patient had been seated for at least five minutes, and the average of the two readings was used for the analysis. Body Mass Index (BMI) was calculated from height and weight, and overweight was defined as a value between 25 and 29.9 Kg/m^2 while obesity as a value higher than 30 Kg/m^2. Finally, Glomerular Filtration Rate (GFR) was estimated by the Cockcroft-Gault equation.

At the follow-up, we repeated the physical examinations and medical history collection, with BP and PWV recorded using the same techniques. ΔPWV represent the difference between PWV at the two times (calculated as value at follow-up minus value at baseline).

The study protocol complies with the Helsinki Declaration and was approved by the San Gerardo Hospital Ethics Committee (approval number 638-2006), and all participants provided informed written consent.

2.2 Lipid Parameter

Biochemical analyses were conducted using an automated Modular Analytics SWA system (Roche Diagnostics), employing enzymatic colorimetric assays for glucose (GOD-PAP method), total cholesterol (CHOD-PAP method), HDL cholesterol (third-generation enzymatic colorimetric method) and triglycerides (GPO-PAP method).

Starting from these data LDL cholesterol (Friedewald equation), non-HDL, non-HDL /HDL, LDL/HDL, total cholesterol/HDL, TG/HDL, Log(TG)/HDL, Log(TG/HDL) and TyG were calculated. The latest was calculated through the following formula: Ln [fasting triglycerides (mg/dL) × fasting plasma glucose (mg/dL)/2] [25].

2.3 Pulse Wave Velocity

Arterial stiffness was assessed as carotid-femoral PWV using an automatic device (Complior, Colson; Alam Medical, Paris, France). Pressure pulse waveforms were simultaneously obtained on the two arterial sites on the same side of the patients and transit time was automatically calculated as the time differences between the point of maximal upstroke of the pressure wave.

The distance between the arterial sites was calculated with a rigid ruler with sliding vertical extension has been used in order to overcome problem with obese patients. Vertical extensions have been placed on the carotid and femoral point of evaluation so that the distance can be measured without the encumbrance of the patient's belly or breast. The values were corrected by a 0.8 factor accordingly to

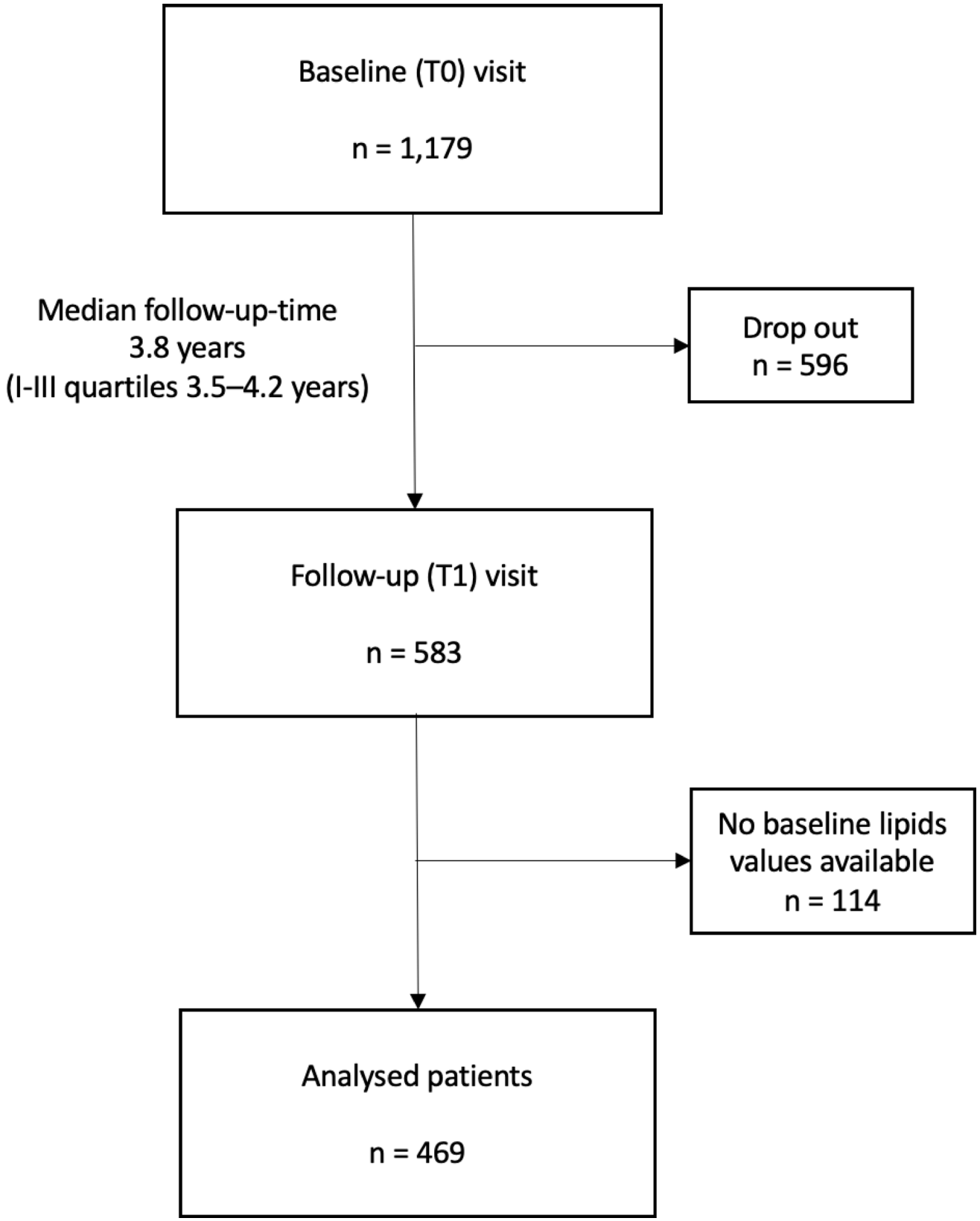

Fig. 1 Flow chart of included and excluded patients.

the PWV measurement methods consensus documents. This correction factor has been introduced in order to correct for the contemporary travel of the pulse wave to the carotid artery and to the femoral artery through the aortic arch. In fact, measuring the direct distance between the two points lead to an overestimation of the real path length traveled by the pulse wave. So, the formula used for PWV calculation [26] was:

$$\text{PWV} = (\text{carotid} - \text{femoral distance/transit time}) \text{ x } 0.8\,[\text{m/s}]$$

Two measurements were obtained in each patient and the mean value was used for the analysis. In our laboratory the intra-session within- and between-operator Coefficient of Variation (CV) of PWV measurements were 2% and 4% respectively, the corresponding value for the inter-session between-operator CV was 4%. PWV HMOD was defined as a value ≥ 10 m/s [26].

Table 1 Whole population's characteristics.

Variable	Baseline (n = 469)	Follow-up (n = 469)	*p*-value
Anamnestic data			
Age (years)	53.6 ± 12.9	–	–
Sex (men), n (%)	274 (58.4)	–	–
Cardiovascular risk factors			
Non smokers, n (%)	282 (60.4)	–	–
Diabetes Mellitus, n (%)	31 (6.6)	–	–
BMI (kg/m^2)	26.8 ± 3.9	26.9 ± 4.0	0.353
Overweight, n (%)	46.9	45.6	0.235
Obesity, n (%)	20.0	20.6	0.837
SBP (mmHg)	141.8 ± 18.0	132.9 ± 17.3	<0.001
DBP (mmHg)	86.9 ± 10.6	79.3 ± 10.6	<0.001
HR (bpm)	66.0 ± 10.3	74.7 ± 11.9	<0.001
Biochemical variables			
Glycemia (mg/dL)	89.1 ± 21.3	–	–
Creatinine (mg/dL)	0.87 ± 0.20	–	–
GFR (mL/min/1,73 m^2)	91.9 ± 19.8	–	–
Lipids parameters			
Total Cholesterol (mg/dL)	198.0 ± 34.7	–	–
HDL Cholesterol (mg/dL)	53.0 ± 13.6	–	–
LDL Cholesterol (mg/dL)	120.2 ± 31.5	–	–
Triglycerides (mg/dL)	123.4 ± 72.6	–	–
Non-HDL (mg/dL)	145.0 ± 34.5	–	–
Non-HDL/HDL	2.9 ± 1.1	–	–
LDL/HDL	2.4 ± 0.8	–	–
Total Cholesterol/HDL	3.9 ± 1.1	–	–
TG/HDL	2.7 ± 2.3		
Log(TG)/HDL	0.040 ± 0.010	–	–
Log(TG/HDL)	0.324 ± 0.286		
TyG	4.0 ± 0.5	–	–
Arterial stiffness			
PWV (m/s)	8.6 ± 2.1	9.2 ± 2.4	<0.001
PWV HMOD, n (%)	81 (17.3)	129 (27.6)	<0.001
ΔPWV>0,5 (m/s) n (%)	242 (51.6)	–	–
Cardiovascular drugs			
ARB or ACEi, n (%)	277 (59.1)	366 (78.0)	<0.001
β-Blockers, n (%)	105 (22.4)	136 (29.0)	0.012
CCB, n (%)	148 (31.6)	177 (37.7)	0.027
α-Blockers, n (%)	54 (11.4)	65 (13.9)	0.163
Diuretics, n (%)	147 (31.3)	172 (36.7)	0.049
Statins, n (%)	52 (11.1)	100 (21.3)	<0.001

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; GFR, glomerular filtration index; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglycerides; TyG, triglyceride and glucose index; PWV, pulse wave velocity; HMOD, hypertension mediated organ damage; ARB, angiotensin receptor blockers; ACE-I, angiotensin converting enzime – inhibitors; CCB, calcium channel blockers.

2.4 Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as percentages. The population was then divided in two groups based on the best predictive values for CV outcomes for change in PWV (ΔPWV) from baseline to follow-up (that was 0.5 m/s) [27]. The Student t-test and χ^2 test were used for continuous and categorical variables, respectively for between-group comparison.

Univariate analysis was used to assess correlation between ΔPWV and ΔPWV ≥ 0.5 m/s and lipids parameter. Multivariate regression analyses were then performed to assess the association between ΔPWV (as a continuous variable, linear regression model) or ΔPWV ≥ 0.5 (categorical variable, logistic regression model) with lipids parameter with age, sex, ΔSBP, anti-hypertensive therapies and statins use, diabetes mellitus and GFR as covariates. Statistical analyses were conducted using SPSS 13.0 (IBM, United States), with significance set at $p < 0.05$.

3 Results

3.1 Population Characteristics

Table 1 shows the clinical characteristics of the whole population enrolled in the study. The majority of patients were male (58.4%) with a mean age of 53.6 ± 12.9 years. Non-smokers were 60.4% of the patients and 6% were diabetic. Both SBP and DBP improved significantly from baseline to follow-up (from 141.8 ± 18.0 mmHg to 132.9 ± 17.3 mmHg, and from 86.9 ± 10.6 mmHg to 79.3 ± 10.6 mmHg, respectively; p<0.001 for both comparison) while heart rate significantly increased (from 66.0 ± 10.3 to 74.7 ± 11.9 bpm; $p = 0.0001$).

BMI doesn't change between baseline and follow-up (26.8 ± 3.9 vs. 26.9 ± 4.0, $p = 0.353$) as well as the

prevalence of overweight and obese patients (46.9 vs. 45.6, $p = 0.235$; 20.0 vs. 20.6, $p = 0.837$, respectively).

Baseline values for fasting glucose, total cholesterol, HDL, LDL, and triglycerides were 89.1 ± 21.3 mg/dL, 198.0 ± 34.7 mg/dL, 53.0 ± 13.6 mg/dL, 120.2 ± 31.5 mg/dL, and 123.4 ± 72.6 mg/dL, respectively. Derivate lipid parameters included non-HDL cholesterol (145.0 ± 34.5 mg/dL), non-HDL/HDL ratio (2.9 ± 1.1), LDL/HDL ratio (2.4 ± 0.8), total cholesterol/HDL ratio (3.9 ± 1.1), TG/HDL (2.7±2.3), Log(TG)/HDL (0.040 ± 0.010), Log(TG/HDL) (0.324±0.286) and TyG index (4.0 ± 0.5).

Table 2 Comparison between the baseline characteristics of the enrolled subjects when divided accordingly to ΔPWV≥0,5

Variables	ΔPWV≥0,5 ($n=242$)	ΔPWV<0,5 ($n=227$)	p-value
Anamnestic data			
Age (years)	54.7±12.7	52.5±13.0	0.072
Sex (male), n (%)	140 (57.8)	134 (59.0)	0.434
Cardiovascular risk factors			
Non smokers, n (%)	140 (58.0)	142 (63.0)	0.165
Diabetes Mellitus, n (%)	20 (8.3)	11 (4.8)	0.096
BMI (kg/m^2)	27.1±4.0	26.5±3.8	0.164
Overweight, n (%)	43.4	50.6	0.115
Obesity, n (%)	22.7	17.1	0.134
SBP (mmHg)	139.8±18.3	143.9±17.4	0.013
ΔSBP (mmHg)	-4.9±18.9	-13.6±19.1	<0.001
DBP (mmHg)	85.2±10.2	88.7±10.8	<0.001
ΔDBP (mmHg)	-5.4±11.0	-10.6±13.0	<0.001
HR (bpm)	65.0±10.4	67.1±10.4	0.033
Biochemical variables			
Glycemia (mg/dL)	90.8±24.3	87.3±17.5	0.086
Creatinine (mg/dL)	0.90±0.20	0.90±0.20	0.321
GFR (mL/min/1,73 m^2),	90.4±19.7	93.3±19.8	0.124
Lipids parameters			
Total Cholesterol (mg/dL)	197.5±35.7	198.5±33.5	0.743
HDL Cholesterol (mg/dL)	51.5±13.5	54.7±13.3	0.011
LDL Cholesterol (mg/dL)	120.6±32.1	119.9±30.8	0.797
Triglycerides (mg/dL)	127.3±67.9	119.4±77.2	0.239
Non-HDL (mg/dL)	146.0±34.8	143.9±34.2	0.504
Non-HDL/HDL	3.0±1.1	2.8±1.1	0.038
LDL/HDL	2.5±0.9	2.3±0.9	0.049
Total Cholesterol/HDL	4.0±1.1	3.8±1.1	0.038
TG/HDL	2.8±2.1	2.5±2.5	0.149
Log(TG)/HDL	0.043±0.015	0.040±0.138	0.009
Log(TG/HDL)	0.351±0.290	0.295±0.278	0.031
TyG	4.0±0.5	4.0±0.5	0.711
Arterial stiffness			
PWV (m/s)	8.0±1.6	9.3±2.3	<0.001
PWV HMOD, n (%)	9.9	25.1	<0.001
Cardiovascular drugs			
ARB or ACEi, n (%)	155 (64.0)	122 (53.7)	0.015
β-Blockers, n (%)	61 (25.2)	44 (19.4)	0.080
CCB, n (%)	82 (33.9)	66 (29.1)	0.154
α-Blockers, n (%)	34 (14.0)	20 (8.8)	0.051
Diuretics, n (%)	90 (37.2)	57 (25.1)	0.003
Statins, n (%)	32 (13.2)	20 (8.8)	0.084

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; GFR, glomerular filtration index; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglycerides; TyG, triglyceride and glucose index; PWV, pulse wave velocity; HMOD, hypertension mediated organ damage; ARB, angiotensin receptor blockers; ACE-I, angiotensin converting enzime – inhibitors; CCB, calcium channel blockers

Use of ACE inhibitors/ARBs increased significantly over time (from 59.1 to 78.0%, p<0.001), as did the use of diuretics and β-blockers (from 31.3 to 36.7%, $p = 0.049$; from 22.4 to 29.0%, $p = 0.012$) as well as statins use (from 11.1 to 21.3%, p<0.001).

Despite improvement in BP control and anti-hypertensive and statins therapies, PWV increased significantly from baseline to follow-up (8.6 ± 2.1 m/s to 9.2 ± 2.4 m/s; $p = 0.0001$), with 51.6% of patients showing ΔPWV ≥ 0.5. PWV HMOD prevalence also increase from 17.3 to 27.6% (p<0.001).

3.2 Comparison Between Progressors (ΔPWV ≥ 0.5) and Stable/Regressors (ΔPWV < 0.5)

Patients with ΔPWV ≥ 0.5 had significantly lower baseline SBP and DBP (139.8 ± 18.3 vs. 143.9 ± 17.4 mmHg, $p = 0.013$; and 85.2 ± 10.2 vs. 88.7 ± 10.8 mmHg, p<0.001, respectively) but with lower reduction during the follow-up (ΔSBP: −4.9±18.9 vs. −13.6±19.1 mmHg; ΔDBP: −5.4±11.0 vs. −10.6±13.0 mmHg; p<0.001 for both comparison) (Table 2).

They also present a significantly lower baseline PWV (8.0 ± 1.6 vs. 9.3 ± 2.3; p<0.001) with lower prevalence of the relative HMOD (9.9 vs. 25.1%, p<0.001). Furthermore, progressors had higher use of ACE inhibitors/ARBs and diuretics (64.0 vs. 53.7%, $p = 0.015$; and 37.2 vs. 25.1%, $p = 0.003$, respectively).

Significant differences in lipid parameters were found for HDL cholesterol (51.5 ± 13.5 vs. 54.7 ± 13.3, $p = 0.011$), LDL/HDL ratio (2.5 ± 0.9 vs. 2.3 ± 0.9 $p = 0.049$, figure 2, panel A), non-HDL/HDL ratio (3.0 ± 1.1 vs. 2.8 ± 1.1, $p = 0.038$, figure 2, panel B) total cholesterol/HDL ratio (4.0 ± 1.1 vs. 3.8 ± 1.1, $p = 0.038$, figure 2, panel C) and Log(TG)/HDL (0.043 ± 0.015 vs. 0.040 ± 0.014, $p = 0.009$, figure 2, panel D) and Log(TG/HDL) (0.351 ± 0.290 vs. 0.295 ± 0.278, $p = 0.031$).

3.3 Univariate and Multivariate Association Analysis

No significant univariate association were seen between none of the lipid parameter evaluated and baseline PWV values nor as a continuous variable and nor as dichotomous one (PWV HMOD).

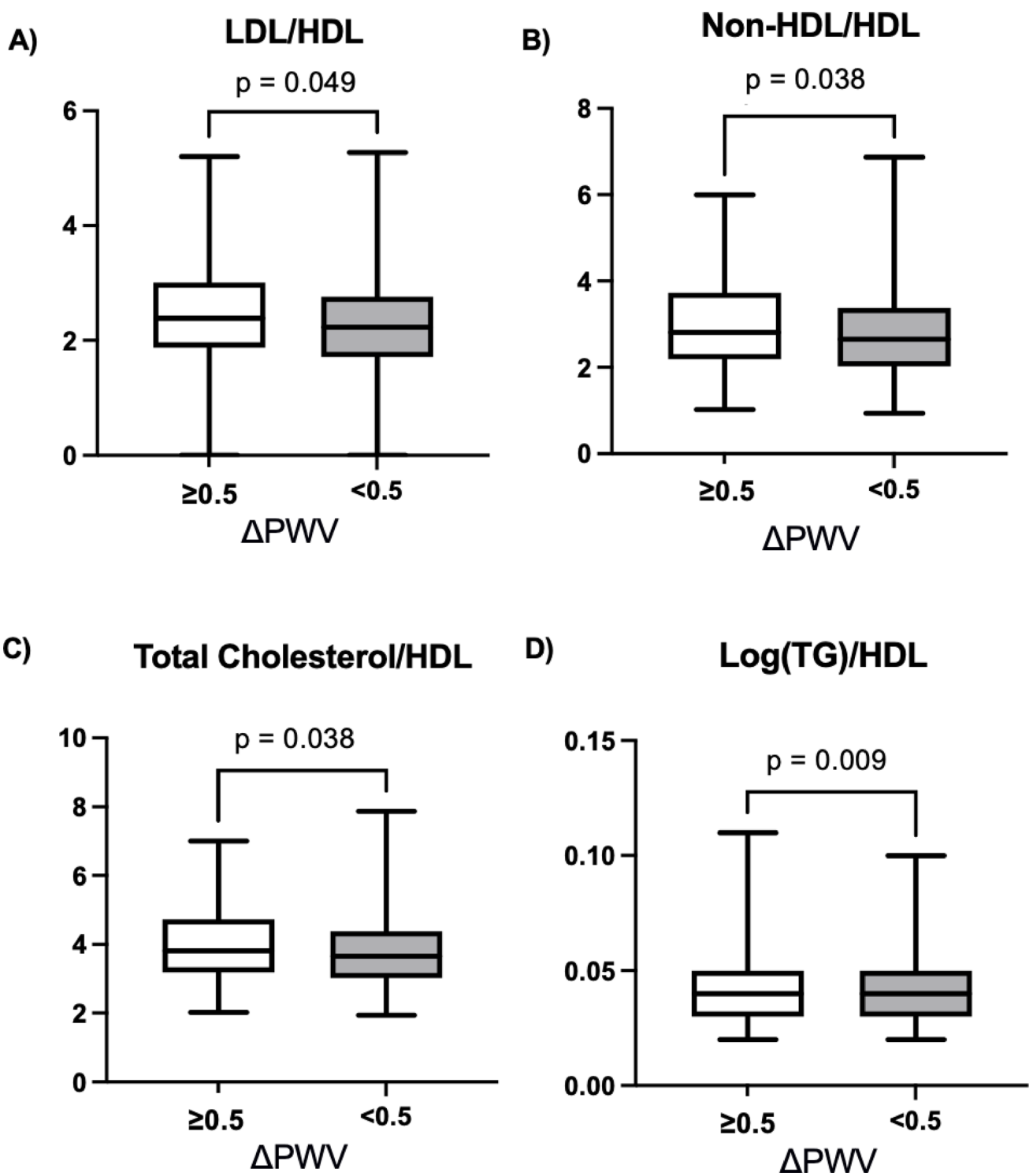

Fig. 2 Lipid parameters that significantly differ when patients were divided accordingly to ΔPWV≥ 0,5 m/s. LDL/HDL (panel A), non-HDL/HDL (panel B), total cholesterol/HDL (panel C), log(TG)/HDL (panel D).

Univariate association between ΔPWV and lipid parameter found significant correlation only with Log(TG)/HDL (r = 0.121, $p = 0.009$) and Log(TG/HDL) (r = 0.118, $p = 0.003$), both confirmed also for ΔPWV ≥ 0.5 (r = 0.094, $p = 0.042$ and r = 0.099, $p = 0.031$).

The significant associations found were then tested in multivariable models (Log(TG)/HDL—Table 3; Log(TG/HDL)—supplementary table 1) with age, sex, ΔSBP, antihypertensive therapies and statins use, diabetes mellitus and GFR as covariates. Nor the association between ΔPWV ≥

Table 3 Logistic multivariable regression analysis with ΔPVW≥0.5 as the dependent variable (A) and linear multivariable regression analysis with ΔPWV as the dependent variable (B). Covariates in the models: Log(TG)/HDL, sex, age, Δ systolic blood pressure, body mass index, diabetes mellitus, glomerular filtration rate and anti-hypertensive therapies and statins use

Variables	A: ΔPVW≥0.5			B: ΔPWV		
	HR	95% IC	p-value	B (crude)	95% IC	p-value
Sex (male)	1.322	(0.858; 2.044)	0.206	0.318	(−0.128; 0.764)	0.162
Age (per 1 year)	1.007	(0.987; 1.026)	0.495	0.015	(−0.004; 0.035)	0.125
ΔSBP (per 1 mmHg)	1.025	(1.014;1.037)	<0.001	0.030	(0.020; 0.040)	<0.001
BMI (per 1 Kg/m^2)	1.003	(0.948; 1.061)	0.914	0.030	(−0.028; 0.088)	0.311
ACEi/ARB (yes)	1.136	(0.712; 1.810)	0.590	−0.087	(−0.574; 0.399)	0.723
DM (yes)	1.311	(0.532; 3.348)	0.561	0.484	(−0.422; 1.392)	0.294
Statins (yes)	1.327	(0.645; 2.786)	0.445	0.701	(−0.039; 1.443)	0.063
β-Blockers (yes)	0.944	(0.566; 1.570)	0.824	−0.324	(−0.852; 0.204)	0.228
CCB (yes)	1.121	(0.725; 1.734)	0.606	0.178	(−0.273; 0.631	0.438
α-Blockers (yes)	1.551	(0.805; 3.046)	0.193	0.475	(−0.200; 1.151)	0.167
Diuretics (yes)	1.004	(0.600; 1.674)	0.989	−0.076	(−0.610; 0.457)	0.778
GFR (per 1 mL/min)	0.996	(0.985; 1.008)	0.578	−0.004	(−0.015; 0.007)	0.488
Log(TG)/HDL (per 1 unit)	1.472	(0.101; 1.525)	0.098	0.515	(−0.106; 0.209)	0.521

SBP, systolic blood pressure; BMI, body mass index; ACEi, angiotensin converting enzime – inhibitors; ARB, angiotensin receptor blockers; DM, diabetes mellitus; TG, triglycerides; HDL, high density lipoprotein; GFR, glomerular filtration index.

0.5 (logistic model) nor the one with ΔPWV (linear model) were confirmed for Log(TG)/HDL and Log(TG/HDL).

4 Discussion

Our study demonstrates that neither novel nor traditional lipid parameters are significantly associated with changes in arterial stiffness over time (ΔPWV) in a hypertensive population. We observed significant differences in HDL cholesterol, LDL/HDL, non-HDL/HDL, total cholesterol/HDL, Log(TG)/HDL and Log(TG/HDL) ratios between progressors and stable/regressors patients. However, while these could suggest a potential role of these lipids' parameters in PWV progression, they were not confirmed in multivariable regression models.

The mechanisms that could underlying the relationship between lipid parameters and arterial stiffness involve insulin resistance, endothelial dysfunction, oxidative stress and chronic inflammation. In particular, insulin resistance reduces nitric oxide production from endothelial cells, impairing vasodilation and increasing arterial stiffness. Insulin resistance also activates the renin-angiotensin-aldosterone system, which promotes vasoconstriction and fibrosis in arterial walls. High triglycerides and LDL levels contribute to lipid deposition in arterial walls, that in a later phase of the disease, further reduce arterial elasticity [28, 29]. Lipids deposition boost oxidative stress, through the generation of reactive oxygen species, which triggers inflammation and macrophages activations, leading to vascular calcification and fibrosis [28].

Our results could appear unexpected since several previous studies have reported correlations between PWV and lipid parameters [5–14, 16–18, 20]. In these cross-sectional studies TG/HDL was found as the most related lipids ratio [6, 8–12] while also non-HDL [6, 8–13, 30], TC/HDL [8, 9], non–HDL/HDL [8, 9] and LDL/HDL [9] was found to be related with PWV. However, results are heterogeneous since some studies found negative results. In a systematic review on the relationship between PWV and lipids only 2 of 41 studies (5%) reported a significant association with total cholesterol, while LDL and HDL were significantly associated only in 5% and 11% of studies, respectively. Finally, only 3% of the studies found a significant association between TG and PWV [14].

Despite the numerous cross-sectional studies, only 3 published one have a longitudinal design with a second PWV evaluation, one with data on TG/HDL [31] and 2 with TyG evaluation [32, 33]. In the first study, TG/HDL ratio was significantly associated with baseline PWV and its progression [31]. This study had a higher number of patients (816) and a longer follow-up (5 years) than ours. However, they were younger (39.1 ± 7.8 vs. 53.6 ± 12.8 years) and hypertensive subjects were excluded (leading to lower BP values: 126.0/75.2 ± 9.4/7.1 vs. 141.7/86.9 ± 17.9/10.6 mmHg). These differences could partially explain the contrasting results and the peculiar characteristics of our population could be at the base of the absence of significant findings.

In fact, arterial hypertension is the main determinant of PWV and our patients were strongly exposed to this risk factor. Despite we observed a significant decrease in BP values, an increased proportion of well controlled hypertension, an increase in anti-hypertensive therapies and statins use during the follow-up, the damage of the artery cannot be further ameliorated. In fact, the higher the exposure (both in term of intensity and time) the higher the mechanical damage of the

artery and its stiffness. Furthermore, the higher the stiffness the less probable, or at least the longer the time needed, for its reduction.

This could be a reason of the absence of association, i.e. arterial hypertension could overshadow the damage determined by lipids and their ratio. It could be that lipids are able to act on arterial stiffness in a first phase of the process. When it progresses to a more advanced stage or other major risk factors (arterial hypertension in our case) are present their effects on arterial stiffness could be overshadowed limiting our possibility to find a significant association.

Furthermore, there could be also a statistical explanation. In fact, the multivariable models of the study of Li et al. [31] were not corrected for BP variation over time (ΔSBP), kidney function and lipid-lowering and antihypertensive therapies. Since these are all important factors related to PWV baseline values and its progression, their introduction in the multivariable model (as done in our study) could leads to negative results.

Regarding therapies, both statins [34] and anti-hypertensive therapies have been found to significantly act on PWV and its progression. Not all the anti-hypertensive drug classes had the same effects on PWV. In the SPARTE trial [35] (designed to compare a strategy of anti-hypertensive therapies up-titration based on PWV values versus a conventional one based on BP values) patients treated with a renin angiotensin system inhibitor and a calcium channel blockers combination shown a lower increase in PWV, confirming a protective effect of this combination on vascular aging, as also found in other trials [36, 37] and meta-analysis [38]. To mitigate the possible influences of these therapies on our results we have inserted them as covariates in our multivariable models.

Finally, there are three ways to evaluate the ratio between TG and HDL, also called atherogenic index of plasma: TG/HDL, Log(TG)/HDL and Log(TG/HDL). Although all the three ratios have been associated with CV events [39, 40] and there are no direct comparison studies published, the first report define it as the Log(TG/HDL) [41]. The Log transformation is needed to correct the skewed distribution of TG and so it could be better to be applied only to TG and not also to HDL. In our study we tested all the three formulae founding that the two Log transformed one were different between PWV progressor and regressor while this is not the case for TG/HDL. Although also the two Log transformed formulae lose their significance in multivariable models, studies are needed to compare them and found the best way to evaluate the ratio between TG and HDL.

Another point of our study deserved to be mentioned, i.e. the role of insulin resistance in arterial stiffness. The triglyceride-glucose (TyG) index has gained popularity as a superior insulin resistance marker compared to HOMA index, given its greater predictive power and simplicity of calculation [16, 42]. In fact, some studies suggest that the TyG index correlates more strongly with arterial stiffness than HOMA index [17, 43]. Numerous studies have explored the relationship between TyG index and arterial stiffness [15, 16, 43, 43], however, similarly to TG/HDL, most of them were cross-sectional. Only two of them were longitudinal [32, 33], both evaluating arterial stiffness trough brachial-ankle PWV and in less severely diseased patients in comparison to ours (50% [32] and 20% [33] of hypertensive patients [32], ten years younger than our patients [33]). While the second point have already been discussed we need to focus on the methodological issue regarding PWV evaluation. Several differences exist between brachial-ankle and carotid-femoral PWV being the latter the one suggested by guidelines [45]. The main differences regard the amount of non-aortic vessels included in the evaluation. Some non-aortic vessels (the carotid one) are also included in the carotid-femoral PWV evaluation, but they are significantly greater in brachial-ankle PWV evaluation where a large amount of medium sized and resistive arteries is included in the assessment. While some could claim that evaluating also these segments add useful information, it should be interpreted as a confounding factor. In fact, the stiffening process is mainly located at the aorta level (the main elastic vessel) while muscular arteries add resistance and could falsely increase evaluated stiffness. So, brachial-ankle and carotid-femoral PWV evaluations are not interchangeable and our study add a piece of information enlarging published results also to carotid-femoral PWV in which we didn't found a significant association with TyG.

Although not a focus of our study, another parameter of interest in its association with PWV and ΔPWV were obesity and adiposity indices. While studies with BMI found heterogeneous results [46–51], adiposity indices were more strongly related to PWV in cross-sectional studies [52–55]. However, the association with BMI was not found in any of the longitudinal studies [3, 20–23] and, to the best of our knowledge, no longitudinal studies have been published regarding the relationship with adiposity indices. Anyway, we have inserted BMI as a covariate in multivariable models to take into account previous findings.

Our study has some limitations. It was conducted in a single centre and only in hypertensive patients, which may limit generalizability to different context or populations. As already discussed, another limitation can be the relatively short follow-up duration, that might not have been long enough to fully capture long-term arterial stiffness progression and its relationship with lipid parameters.

Furthermore, the significant increase in the use of ACE inhibitors/ARBs, diuretics, β-blockers and statins over time could have influenced PWV progression and lipid profiles,

potentially masking or modifying the true relationship between them.

Also regarding therapies, statin type and dose were not registered doesn't permitting us to perform further subgroup analyses.

Moreover, while serial measurements of PWV could be an element of strength in the dynamic assessment of the arterial stiffness process, it could determine logistic and economic issue in large population. Regarding this, as in any study with serial measurements, we have to take into account the 'regression-to-the-mean' phenomenon and the related 'regression dilution bias'.

Finally, in the multifactorial context linking PWV and lipids it could be difficult to assess all parameters that can influence the relationship and it is possible that some of them have not been evaluated. For sure, factors such as diet, physical activity, smoking habits, and alcohol consumption were not deeply analysed, despite their possible impact on lipid metabolism and arterial stiffness.

5 Conclusions

While cross-sectional studies suggest a link between lipid parameters and arterial stiffness, longitudinal data remains limited. Our study doesn't find any significant role for traditional and novel lipids parameters in determine carotid-femoral PWV or its progression over time (i.e. ΔPWV). Given the growing evidence linking insulin resistance to arterial stiffness, markers like TyG index and TG/HDL ratio may provide better predictive value than traditional lipid measures. Further large-scale and longitudinal studies are needed to clarify this relationship and identify reliable biomarkers for early CV risk assessment.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40292-025-00741-w.

Acknowledgements the present study win the "Vincenzo Masini" grant of the Italian association of hospital cardiology (Associazione Nazionale Medici Cardiologi Ospedalieri – ANMCO).

Funding This work was funded by the: European Community Seventh Framework Programme (FP7/2007–2013) Grant Agreement n° 278249. Italian MUR Dipartimenti di Eccellenza 2023–2027 project (l. 232/2016, art. 1, commi 314–337). A. De Gasperis Cardiology and Cardiac Surgery Foundation.

Declarations

Competing interests The authors declare they have no conflict of interest.

Ethical Approval the study protocol complies with the Helsinki Declaration and was approved by the San Gerardo Hospital Ethics Committee (approval number 638–2006), and all participants provided informed written consent.

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