Prognostic significance of arterial stiffness and osteoprotegerin in patients with stable coronary artery disease

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Abstract
Background: Arterial stiffness and vascular calcification significantly contribute to coronary atherosclerosis progression. The prognostic value of increased arterial stiffness and vascular calcification in subjects with stable coronary artery disease (CAD) after percutaneous coronary intervention (PCI) is currently under question.

Materials and Methods: We randomly enrolled 262 patients with stable CAD 1 month after successful PCI. Carotid-femoral pulse wave velocity (PWV) was measured as a well-established index of central aortic stiffness. Osteoprotegerin (OPG) plasma levels were measured as a biomarker of vascular calcification. Patients were followed up prospectively up to 52 months. The primary endpoint was the composite of death from cardiovascular causes, myocardial infarction, stroke or hospitalization for cardiovascular causes.

Results: During the follow-up period, 48 patients presented the primary composite endpoint. Subjects who presented the primary endpoint, compared to subjects free of cardiovascular events, had significantly increased PWV (9.45 ± 2.19 m/s vs 8.73 ± 2.07 m/s, P = .04) and OPG levels (4.21 ± 2.19 pmol/L vs 3.18 ± 1.74 pmol/L, P = .003). Survival analysis indicated that PWV predicted adverse cardiac events MACE (Hazard ratio = 1.29 95%CI: 1.07-1.57, P = .008) independently from confounders such as age, sex, smoking habits, ejection fraction, extent of coronary artery disease, hypertension and diabetes mellitus. Interestingly, for every increase in pulse wave velocity by 1 m/s, there is an anticipated increase in the risk of major adverse cardiovascular event (MACE) by 29%.

Conclusions: These findings extend the current knowledge concerning the role of arterial stiffness as powerful biomarkers in cardiovascular disease. Measurement of PWV might have a role in ascertaining prognosis and managing treatment in patients with stable CAD after PCI.

Keywords: arterial stiffness, atherosclerosis, coronary artery disease, osteoprotegerin, prognosis, vascular calcification
INTRODUCTION

Coronary artery disease (CAD) is a major cause of death in the Western societies. Coronary atherosclerosis, which is the pathophysiologic mechanism of CAD, is a chronic process which continues throughout life.\(^1\) Several established cardiovascular (CV) risk factors, such as diabetes, hypertension, dyslipidemia, have been recognized as significant determinants for the progression of coronary atherosclerosis, affecting the prognosis of cardiovascular events. During the last decade, several studies have demonstrated that novel parameters associated with vascular function and architecture are related to coronary atherosclerosis and its clinical manifestations.\(^4\)\(^,\)\(^6\) In addition, several biomarkers have been associated with the progression of atherosclerosis and estimation of future cardiovascular complications.

Arterial stiffness, as non-invasively estimated by pulse wave velocity (PWV), is associated with the presence of CV risk factors and the severity of CAD.\(^7\)\(^,\)\(^8\) Moreover, the measurement of arterial stiffness by PWV is a powerful prognostic marker for future cardiovascular events in subjects with CV risk factors.\(^9\)\(^,\)\(^10\)

Vascular calcification is a commonplace feature of the atherosclerotic plaques while the acuteness and length of mineralization reflect the burden of the atherosclerotic plaque.\(^3\)\(^,\)\(^11\) Calcium (Ca\(^{2+}\)) deposit in coronary arteries may also affect plaque stability, leading to plaque rupture which causes myocardial infarction.\(^12\) Recently, osteoprotegerin (OPG), a novel biomarker of the tumour necrosis factor alpha receptor family, showed an association with the development of atherosclerosis linking vascular calcification with atherosclerosis progression.\(^3\)\(^,\)\(^13\) Moreover, previous studies indicated that OPG levels are related to the manifestation, existence and the severity of CAD.\(^13\)\(^,\)\(^14\)

In conclusion, none of the studies so far have evaluated the prognostic significance of both PWV and OPG in patients with stable CAD who underwent a successful PCI. The purpose of our study was to depict the prognostic significance of arterial stiffness, measured by PWV, and serum OPG levels, in patients with stable CAD who were treated with a successful PCI.

METHODS

2.1 Study population

A number of 262 patients with stable CAD who underwent a successful PCI with stenting at least a month ago were consecutively selected for the purposes of this study. All patients received the optimal treatment for afterwards PCI (dual antiplatelet treatment with aspirin 100 mg and P2Y12 ADP receptor inhibitor, statins, β-blockers, angiotensin-converting enzyme inhibitors). All measurements were taken by at least two observers who were unaware of the disease status or the treatment of the patients. Subjects with decreased left ventricular ejection fraction (LVEF) <40% (estimated by echocardiography), significant valvular heart disease, myocardial infarction or acute coronary syndrome within the last 1 month, patients further planned for a second PCI or cardiovascular surgery at a later date, atrial fibrillation, chronic kidney disease or other comorbidities were excluded from the study. All subjects were enrolled between June 2010 and December 2013.

The patient’s demographical parameters including age, medical history and cigarette use were determined with the use of certain questionnaires prior to physical examination. In addition, it was also performed a measurement of blood pressure as well as a haematological and biochemical control. The presence of diabetes, hypertension or hyperlipidemia was defined according to guidelines. Kidney function and glomerular filtration rate were estimated with MDRD formula.\(^15\)

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was a priori approved by the institution’s human research committee. Furthermore, each subject has given a written informed consent.

2.2 Evaluation of arterial stiffness

Arterial stiffness was evaluated in all patients by the measurement of PWV using a well-validated non-invasive device (SphygmoCor; AtCor Medical) as previously described.\(^9\)\(^,\)\(^16\)\(^-\)\(^18\)

2.3 Biochemical analyses

Venous blood samples, obtained from all participants in the study, were centrifuged at 3000 rotations/min, and serum/plasma was collected and stored at −80°C until assayed. Serum levels of osteoprotegerin were measured by commercially available ELISA kits (R&D Systems, Minneapolis, MN, respectively). The sensitivity for osteoprotegerin was 0.13 pmol/L with an intra- and interassay CV of <4% and <6%, respectively. ELISA kits used to measure intercellular adhesion molecule-1 (sICAM-1) in serum as an inflammatory marker.

2.4 Evaluation of angiographic coronary atherosclerosis severity with Gensini score

Coronary angiographies were interpreted by at least two experienced cardiologists. The severity of coronary artery disease was evaluated by Gensini score as previously described.\(^19\)
2.5 | Cardiovascular events monitoring

The primary endpoint was the incidence of a major adverse cardiovascular event (MACE) including death from cardiovascular causes, cardiac arrest, myocardial infarction, stroke, nonfatal stroke or other arterial thrombotic events and hospitalization for cardiovascular conditions such as unstable or progressive angina. The follow-up time interval (months) was estimated from the index PCI till the last hospital outpatient or inpatient record or telephone interview before May 2016. The event time was counted (months) from the index PCI till the 1st MACE occurred. Follow-up in the study population has been performed by three postdoctoral fellows who were unaware of the baseline measurements of the participants and the study protocol.

2.6 | Statistical analysis

All variables were tested for normal distribution by plotting P-P plots. Continuous variables with normal distribution were presented as mean ± standard deviation or otherwise as median with interquartile range. Categorical variables were presented as valid percentages. To test for intergroup differences (between subjects who presented the primary endpoint and those free of events), independent samples t test and Mann–Whitney test were used for continuous variables and chi-squared test for categorical variables. In addition, receiver operating characteristics (ROC) curve analysis was used to confirm the predicting ability of the variables that significantly differed between patients who presented the primary endpoint and those free of events. Subsequently, Cox proportional hazards models were used to examine the association between variables of interest (including OPG and PWV) and the main endpoint of our study after adjustment for confounders revealed significant by the univariate analysis (Gensini score, LVEF) as well as known confounders (age, gender, smoking habits, history of hypertension, diabetes mellitus, dyslipidemia and creatinine clearance); data were censored at the time of the last visit. Associations are presented as hazard ratio (HR) with 95% confidence intervals (CI). To address the small number of events (n = 48) and to avoid overfitting of our final multivariable Cox models, resampling techniques were implemented (i.e. bootstrapping with 1000 replications).

Finally, we calculated the continuous net reclassification index (cNRI), according to Pencina et al., a category-free version of the NRI, to evaluate the additive clinical significance of PWV. As previously described, bootstrapping with 1000 replications was performed to derive bias-corrected standard error of the cNRI.

P-values of <.05 were considered to indicate statistical significance. In terms of survival analysis, the final sample size of 218 subjects with survival follow-up data provided over 80% power to establish two-fold alteration in HR (two-sided) for Cox proportional hazards models towards primary endpoint. Statistical analysis and power calculations were performed with Stata version 11, College Station TX 77845, USA.

3 | RESULTS

3.1 | Characteristics of the study population

We randomly enrolled 262 patients with stable CAD 1 month after successful PCI, and the final study population consisted of 218 subjects due to loss of forty-four (44) patients during the follow-up period including 4 patients who withdrew consent to participate. The final study population was observed for a median time of 36 months (range 5-52). The baseline characteristics of the patients are demonstrated in Table 1. Furthermore, there were no differences in the baseline demographical characteristics (age, gender, EF, creatine clearance etc.; P > .05 for all) between the subjects who finally included in the analysis and the forty-four lost to follow-up subjects (Table S1).

3.2 | Cardiovascular events

During the follow-up period of 52 months, MACE occurred in 48 patients (22% of patients presented the composite primary and point). Most events were rehospitalization for unstable or progressive angina (30 patients, 14%), followed by revascularization (27 patients) or sole pharmaceutical therapy (3 patients). Death from cardiovascular causes, cardiac arrest or myocardial infarction occurred in 13 patients (6%). Five patients (2%) were hospitalized due to other cardiovascular causes.

3.3 | Characteristics of the study population according to the presence of cardiovascular events

The characteristics of the study population according to the presence of MACE are shown in Table 2. Patients with MACE had lower left ventricular ejection fraction, increased burden of coronary artery atherosclerosis as estimated by Gensini score, increased PWV and OPG levels, while there was no difference concerning treatment for diabetes, hypertension and lipids. Furthermore, there was no difference concerning levels of ICAM-1.

3.4 | Time to event analysis

Kaplan–Meier estimates were compared between patients with lower binary PWV (<8.56 m/s) vs upper binary
we further sought to assess their reclassification dynamics for CV risk. PWV significantly reclassified subjects for adverse CV events on top of Gensini score (NRI = 44.7 ± 19.7%, P = .01; Table 4). Moreover, PWV correctly and significantly reclassified patients from lower to higher risk and vice versa over the combination of our best predictive model and Gensini score (NRI = 66.3 ± 24.2%, P = .006; Table 4).

4 | DISCUSSION

Our findings underline the prognostic importance of the estimation of baseline arterial stiffness in patients with stable CAD undergoing a successful PCI. We found that beyond the established risk factors and predictive models, increased arterial stiffness depicted by PWV is a significant predictor of major adverse cardiovascular events in patients with stable CAD after PCI.

4.1 | PWV and cardiovascular prognosis

Several studies have examined the prognostic importance of increased arterial stiffness for CV events such as MI, revascularization, stroke and cardiovascular mortality in certain populations. More specifically, arterial stiffness, evaluated by PWV, has a significant prognostic value in patients with hypertension, ACS, heart failure, renal disease, diabetes, the elderly as well as in the general population.

In hypertensive patients, PWV is strongly associated with all-cause and cardiovascular mortality, independently of age or previous cardiovascular diseases. Moreover, in patients with impaired glucose tolerance, aortic PWV is a powerful indicator of the causal pathway of the arterial disease and can be utilized as an integrated index of vascular status and thus cardiovascular risk in these patients. Also, Framingham Heart Study revealed that increased aortic stiffness, estimated by PWV, is associated with increased risk of a first cardiovascular event and the assessment of PWV assists in the prediction of CV risk when added to standard risk factors. Therefore, PWV may be used as potent indicator of CV risk in the general population. Contrary to the previous studies, Meguro et al revealed that patients with HF and PWV values above 17.5 m/s had a lower event-free survival rate for the primary and secondary endpoints, in contrast to patients with HF and PWV values below 17.5 m/s.

In the present study, we investigated the potential prognostic usefulness of PWV in patients with stable CAD who underwent a successful PCI. Our results showed an incidence of almost 22% of the primary endpoint which is similar to other studies in patients after myocardial infarction.

### TABLE 1 Baseline characteristics of the study population

| Age (y) | 62 ± 10 |
|---------|---------|
| Male gender (%) | 90 |
| Systolic blood pressure (mmHg) | 127 ± 19 |
| Diastolic blood pressure (mmHg) | 76 ± 9 |
| Body mass index (Kg/m²) | 27.93 ± 3.41 |
| Left ventricular ejection fraction (%) | 50 (45-59) |
| Arterial hypertension (%) | 85 |
| Diabetes mellitus (%) | 23 |
| Dyslipidemia (%) | 80 |
| Active smokers (%) | 19 |
| Creatinine Clearance (mL/min/1.73 m²) | 81 ± 19 |
| Severity of coronary artery disease | |
| One-vessel disease (%) | 41 |
| Two-vessels disease (%) | 38 |
| Three-vessels disease (%) | 21 |
| Gensini score | 33.59 (18.75-51.25) |
| Pulse wave velocity (m/s) | 8.95 ± 2.21 |
| Osteoprotegerin (pmol/L) | 3.49 ± 1.94 |

(≥8.56 m/s; P = .04), lower binary LVEF (≤50%) vs upper binary LVEF (>50%; P = .01), lower binary Gensini score (<33.5) vs upper binary (≥33.5; P = .04) and lower binary OPG levels (<3.26 pmol/L) vs upper binary (≥3.26 pmol/L; P = 0.04). For all 4 variables, subjects distributed in the upper binary had significantly increased probability to experience a MACE during our follow-up (Figure 1, panels A, B, C, D).

To evaluate which of the factors can predict MACE independently from other covariates and risk factors, we conduct a Cox regression analysis. In the model, we included significant factors from the univariate analysis such as Gensini score, LVEF, OPG levels, PWV and known confounders such as age, gender, smoking habits, history of hypertension, diabetes mellitus, dyslipidemia and creatinine clearance. This model reveals that both Gensini score and PWV were significant determinants of the occurrence of MACE independently of age, gender and known traditional risk factors (Table 3). Indeed for every increase in PWV by 1 m/s, there is an anticipated increase in the risk of MACE by 29%, and for every increase in Gensini score by 10 units, there is an anticipated increase in the risk of MACE by 16% after adjusting for the aforementioned confounders.
and can be explained by the average follow-up period of 36 months in a population of PCI patients mainly after myocardial infarction. Furthermore, among the study population, patients who presented the primary endpoint had significantly increased PWV values than those who did not present any MACE. More importantly, a Cox regression model revealed that the primary endpoint was strongly associated with increased PWV values. Therefore, the additive clinical utility of PWV in these settings is important as it provides a non-invasive, easy to apply and reproducible index which can be used on top of the well-known cardiovascular risk factors (Gensini score, age, gender, smoking habits, hypertension, diabetes mellitus, dyslipidemia, creatinine clearance and LVEF) to reclassify subjects in a lower or higher risk cohort. These findings are in accordance with a recent publication of our study group which demonstrated that increased aortic stiffness, evaluated by aortic PWV, can predict future CV events, especially in patients with a deteriorated CV risk profile.10

In this context, the European Society of Hypertension/European Society of Cardiology suggested the measurement of aortic PWV, which is a well-established indicator of aortic stiffness, as a valuable marker for the assessment of subclinical target organ damage.30,31

4.2 | OPG and cardiovascular prognosis

Osteoprotegerin was initially thought to be a molecule involved in the inhibition of bone absorption whose action is regulated by a variety of hormones and cytokines.32,33 Current published data suggest that OPG also holds a pivotal role in vascular remodelling, atherogenesis,
inflammation and vascular calcification\textsuperscript{3,34-36} and is associated with increased cardiovascular risk\textsuperscript{13,14,37-40}. Several clinical studies have investigated the prognostic significance of serum OPG levels in general population,\textsuperscript{35,37,41,42} in patients with ACS,\textsuperscript{43} ischaemic HF\textsuperscript{44-46} and in patients with stable angina pectoris.\textsuperscript{47}

Population-based cohort studies which enrolled both men and women of the general population associated serum OPG levels with cardiovascular outcomes. All of them concluded that increased OPG levels are independently associated with the risk of MI, ischaemic stroke and cardiovascular mortality.\textsuperscript{35,37,41,42} Interestingly, data from the 4th Copenhagen City Heart Study revealed that plasma OPG and hsCRP levels, when combined, provide higher prognostic value than the independent effect of each one biomarker.\textsuperscript{42} Furthermore, Omland et al\textsuperscript{43} found that serum OPG levels may predict long-term mortality, the development of HF as well as the events of hospitalization in patients with ACS independently of established markers such as CRP and troponin. Moreover, Yang et al\textsuperscript{48} suggested that OPG levels can be useful for the risk assessment in patients with intermediate coronary stenosis and for the recognition of the subgroups which could benefit from aggressive intervention.

To date, the scientific data which examine the prognostic significance of serum OPG levels in general population,\textsuperscript{35,37,41,42} in patients with ACS,\textsuperscript{43} ischaemic HF\textsuperscript{44-46} and in patients with stable angina pectoris.\textsuperscript{47}

| TABLE 3 | Cox regression analysis for the risk of cardiovascular events |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | Hazard ratio    | 95% confidence intervals | P-value |
| Age (y)        | 0.97            | 0.92                     | 1.03               | .47              |
| Gender (female)| 1.92            | 0.47                     | 7.85               | .36              |
| Smoking        | 1.11            | 0.31                     | 3.94               | .87              |
| Dyslipidemia   | 0.18            | 0.02                     | 1.94               | .11              |
| Diabetes mellitus | 0.94         | 0.30                     | 2.92               | .92              |
| Hypertension   | 1.08            | 0.22                     | 5.27               | .92              |
| Creatinine clearance (mL/min/m\textsuperscript{2}) | 1.01            | 0.98                     | 1.03               | .34              |
| LVEF (%)       | 0.97            | 0.91                     | 1.03               | .41              |
| Osteoprotegerin (pmol/L) | 1.09            | 0.87                     | 1.35               | .47              |
| Gensini score  | 1.01            | 1.00*                    | 1.03*              | .009             |
| PWV (m/sec)    | 1.29            | 1.07*                    | 1.57*              | .008             |

In categorical variables as reference, category was set male gender, active smokers, and the presence of dyslipidemia, diabetes mellitus, hypertension. LVEF, Left ventricular ejection fraction; PWV, Pulse wave velocity. *95% CIs are provided under 1000 bootstrap replications.

$\text{FIGURE 1}$ Kaplan–Meier estimates curves for: Panel A: Higher PWV levels ($>8.56$ m/s) vs lower PWV values ($\leq8.56$ m/s). Panel B: Lower LVEF ($\leq50\%$) vs higher LVEF ($>50\%$). Panel C: Higher Gensini score values ($>33.5$) vs lower Gensini score values ($\leq33.5$). Panel D: Higher osteoprotegerin levels ($>3.26$ pmol/L) vs lower osteoprotegerin levels ($\leq3.26$ pmol/L). PWV, Pulse wave velocity; LVEF, Left ventricular ejection fraction; OPG, Osteoprotegerin.
PCI. Moreover, all subjects received the optimal medication for PCI (aspirin 100 mg, P2Y12 ADP receptor inhibitor, statins, β-blockers, ACE inhibitors).

In the current study, we demonstrated that patients with CAD after PCI under dual antiplatelet treatment patients who had serum OPG values ≥ 3.26 pmol/L, depicted significantly increased risk of a MACE during the following 4 years. Although in the Cox regression analysis, only Gensini score and PWV were significant determinants of the occurrence of MACE.

5 | CLINICAL IMPLICATIONS

This study extends the current knowledge concerning the role of PWV measurement and OPG serum levels as potent biomarkers for the prognosis and monitoring in patients with CAD after PCI. Interestingly, for every increase in PWV by 1 m/s, there is an anticipated increase in the risk of major adverse cardiovascular event (MACE) by 29%. Therefore, the additive clinical utility of PWV in these settings is important as it provides a non-invasive, easy to apply and reproducible index which can be used on top of the well-known cardiovascular risk factors (Gensini score, age, gender, smoking habits, hypertension, diabetes mellitus, dyslipidemia, creatinine clearance and LVEF) to reclassify subjects in a lower or higher risk cohort. Although to date our results cannot generalized and used in the daily practice, we believe that the introduction of a new risk score incorporating the measurement of PWV may be applicable in the near future for the management of the PCI population.

6 | LIMITATIONS

Vascular calcification is a consequence of tightly regulated processes that culminate in organized extracellular matrix deposition by osteoblast-like cells. These cells may be derived from stem cells (circulating or within the vessel wall) or differentiation of existing cells, such as smooth muscle cells (SMCs) or pericytes. Although OPG cannot replace vascular calcification, several studies demonstrated the significant association of OPG serum levels with vascular calcification. Moreover, our purpose was to determine the association of PWV and serum OPG levels with cardiovascular prognosis; therefore, imaging modalities to detect the vascular calcification were not performed in the current study. Finally, a high proportion of men were included in the study population.

7 | CONCLUSIONS

Increased arterial stiffness is significant determinant of major adverse cardiovascular events in patients with stable CAD who undergo a successful PCI. These findings extend the current knowledge concerning the role of PWV values and OPG serum levels as potent biomarkers in stable CAD and suggest that the measurement of PWV may be a helpful indicator for the risk assessment and the optimal treatment in subjects with stable CAD undergoing PCI.

DISCLOSURES

Gerasimos Siasos received a scholarship from “The Behrakis Foundation.” The remaining authors have nothing to disclose.

CONFLICT OF INTEREST

None.

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**SUPPORTING INFORMATION**

Additional Supporting Information may be found online in the supporting information tab for this article.

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