ORIGINAL ARTICLE

THE INFLUENCE OF PERINDOPRIL ON PTX3 PLASMA LEVELS IN HYPERTENSIVE PATIENTS WITH ENDOTHELIAL DYSFUNCTION

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Abstract

Long pentraxin 3 (PTX3) is a new multimeric inflammatory biomarker, from the family of pentraxins, as well as C-reactive protein (CRP). PTX3 is produced at the sites of inflammation like vascular endothelial cells and leukocytes, while CRP is produced by hepatocytes. Having as a starting point the link between hypertension, inflammation and endothelial dysfunction, we aimed to compare the influence of perindopril *versus* other antihypertensive drugs on these biomarkers, in hypertensive patients with endothelial dysfunction. Our results showed that hypertensive patients treated with perindopril have lower levels of PTX3, suggesting the fact that the vascular inflammation is better controlled by perindopril than by other classes of antihypertensive drugs, like beta blockers, calcium channel blockers, or diuretics.

Rezumat

Pentraxin 3 (PTX3) este un nou marker inflamator, din familia pentraxinelor, la fel ca şi binecunoscuta proteină C reactivă (CRP). PTX3 este produs local, de către celulele endoteliale vasculare şi leucocite, iar CRP este produsă de către hepatocite. Având ca şi punct de plecare legătura dintre hipertensiune, inflamaţie şi disfuncţia endotelială, ne-am propus să comparăm influenţa perindoprilului faţă de alte medicamente antihipertensive asupra acestor biomarkeri, la pacienţi hipertensivi cu disfuncţie endotelială. Rezultatele acestui studiu arată faptul că pacienţii hipertensivi sub tratament cu perindopril au nivele mai mici de PTX3, sugerând faptul că inflamaţia la nivel vascular este mult mai bine controlată de perindopril, comparativ cu alte medicamente antihipertensive, cum ar fi betablocantele adrenergice, blocantele canalelor de calciu, sau diureticele.

Keywords: perindopril, pentraxin 3, hypertension, endothelial dysfunction, CRP

Introduction

Under basal conditions, the endothelium, the single layer of cells of the vessels that comes in direct contact with the blood, acts as a homeostatic balance between thrombosis and anticoagulation. Being one of the largest organs in the body (in a 70 kg male, it covers approximately 3 m^2, weights over 1 kg and contains up to trillion cells), it regulates the vascular tone (favouring dilatation over constriction) and it is involved in the regulation of angiogenesis, fibrosis, inflammation, smooth muscle cell proliferation, wound healing etc. Hypertension, hyperlipidaemia, obesity, age, tobacco smoking use, physical inactivity alter the normal function of the endothelium, having as a result an imbalance between the NO, nitric oxide (produced by the endothelium from L-arginine) production and consumption. This pathologic state, endothelial dysfunction (ED), contributes to the activation and adhesion of platelets and leukocytes to the arterial wall. Also, it contributes to the activation of cytokines which will increase the permeability of the vessel wall to inflammation mediators and oxidized lipoproteins, having as a result the damage of the structure of the vessel wall, smooth muscle cell proliferation and the formation of the atherosclerotic plaque [3, 29].

Several studies confirmed that ED is characteristic for patients with essential arterial hypertension and it consists in a functional and reversible alteration of endothelial cells (ECs) which induce an altered production of vasodilating and vasoconstricting factors, the most important factors being NO and angiotensin II. Angiotensin II (Ang II), a powerful vasoconstrictor substance, is one of the main responsible substances for the development of ED, because through its stimulation of AT1 receptors, it increases: arterial pressure, oxidative stress, NO depletion and endothelial cells' senescence [3, 4, 25, 29].

Perindopril, an ACE (angiotensin converting enzyme) inhibitor, through its mechanism of action, not only decreases the blood pressure by blocking the formation of angiotensin (Ang) II, but it also plays an important role in reversing ED. It blocks the converting enzyme that, firstly, transforms Ang I in Ang II and secondly, transforms the bradykinins in inactive peptides. In these ways, it inhibits the formation of Ang II and increases the concentrations of bradykinins, which are responsible for the cardio-protective properties. The bradykinins exercise favourable vascular effects through their B2 receptor, inducing vasodilatation, stimulation the synthesis nitric oxide (NO), prostaglandin PGI_2 and endothelium-derived hyperpolarizing factor (EDHF). NO, produced from L-arginine under the action of eNOS (endothelial nitric oxide synthetase), diffuses from the endothelium in the smooth muscle cells, where it activates the guanylate cyclase. The other mediator, prostacyclin PGI_2, will later stimulate the production of cyclic adenosine monophosphate (AMP) in the smooth muscle cells [3, 5, 9, 27].

Over the past decades, many methodological approaches for measuring the pathophysiological function of the endothelium were developed. The most commonly used techniques are the non-invasive methods like the measurement of carotid intima-media thickness (C-IMT), the brachial arterial flow-mediated vasodilatation (FMD) and the aortic stiffening measured as carotid-femoral pulse wave velocity (cf PWV). Although these methods are widely used in the research field, their use as a clinical tool in the daily practice routine hasn't been yet established, nor has any of these methods been recommended in clinical guidelines for the assessment of primary and secondary prevention of the vascular disease [1, 2, 18, 21, 29, 30].

PTX3 is a novel biomarker that has been associated by several studies in the last decade, to inflammation, the key point of ED. PTX3 (also called $TSG\text{-}1_4$) is a marker of vascular damage that was firstly identified in the early '90s in the endothelial cells and in the fibroblasts. It is a multimeric glycoprotein present in the acute phase of inflammation, belonging to the same superfamily as the CRP- the superfamily of pentraxins. CRP is a well-known and studied short pentraxin, produced in the liver, by the hepatocytes, secondary to systemic inflammation. PTX3 is one of the long pentraxins which is synthesized by the local vascular cells (endothelial cells, smooth muscle cells and fibroblasts), as well as by innate immune cells, at the inflammatory sites. Pentraxin-3 has been found to play a very important role in the regulation of cell proliferation and angiogenesis, it is highly expressed in the cardiac monocytes and in the atherosclerotic plaques [8, 12, 13, 15-17, 20, 22, 23].

There are few studies on the impact of PTX3 in hypertension and ED, in comparison with CRP, but no study showed the influence of different classes of antihypertensive drugs on these inflammatory biomarkers. So, this study aims to investigate the influence of perindopril on these biomarkers, and to compare this effect in other classes of anti-hypertensive drugs [12 - 15, 17].

In this study, we aimed to evaluate the endothelial function by measuring the alterations in the arterial structure (IMT evaluation) and function (FMD determination), as well as by testing some inflammatory biomarkers, such as pentraxin-3 (PTX3) and C-reactive protein (CRP).

Materials and Methods

This cross-sectional prospective, comparative study was conducted in the Cardiology Clinic of Timisoara Hospital, Romania, from January 2014 to March 2015. We examined 144 hypertensive patients from which 66 patients were under treatment with perindopril (group C), 78 patients were under treatment with other antihypertensive drugs (group B) and 54 normotensive subjects/ healthy controls (group A), all of them of matched age and sex.

Patient selection

All the patients recruited in this study completed the informed consent form and participated voluntary in the study. The study was approved by the ethical committee of the hospital.

The hypertensive patients underwent a screening including medical history, physical examination, duration of hypertension and associated medical conditions. The criteria for the inclusion of the subjects were: age over 18 years, diagnosis of essential arterial hypertension (for at least 1 year at values over 140/90 mmHg). We excluded subjects with pathologies like coronary artery disease and other atherosclerotic diseases (carotid and peripheral), diabetes, chronic heart failure, chronic kidney disease, asthma, acute or chronic inflammatory diseases and chronic hepatic disease. The hypertensive patients were divided into 2 groups: group C that included patients treated with perindopril 5-10 mg daily and group B that included patients treated with other classes of antihypertensive drugs except angiotensin

converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs): beta blockers, calcium channel blockers, and diuretics.

The normotensive patients had been initially examined with the suspicion of hypertension (HTN), but the 24 h ambulatory blood pressure monitoring device, Holter, did not confirm the diagnosis. They were included in the control group A.

Laboratory analysis

Venous blood samples were collected from all the subjects after 20 minutes of rest and overnight fast (minimum 10 hours from the last intake of food). The standard biochemical screening was performed, including determination of serum glucose, total cholesterol, creatinine, triglycerides, and transaminases, by routine laboratory methods. hs-CRP was measured through a highly sensitive immuno-turbidimetric method, using a CRP Ultra Kit, produced by Abbott Diagnostics. The plasma long PTX3 levels were estimated using the quantitative sandwich enzyme immunoassay technique, using a kit provided by R&D Systems. A streptavidin-coated plate was incubated with a biotinylated monoclonal antibody specific for human PTX3. Then, the plates were washed and pre-treated standards and the samples were added to the wells. Any PTX3 present was bounded by the immobilized biotinylated antibody. An enzyme-linked conjugate specific for human PTX3 was added to the wells, after washing away any unbound substances. After another wash to remove any unbound conjugate, a substrate solution was added to the wells and colour developed in proportion to the amount of PTX3 bound. Afterward, the development of the colour had stopped and it was measured the intensity of the colour. For each set of samples assayed, a standard curve was obtained.

Arterial pressure, FMD and IMT

The patients were examined in a fasting state and in a temperature controlled room. The blood pressure was measured after 20 minutes of rest, in a supine position, at the right brachial artery, and expressed as the mean value of 3 measurements. We calculated the mean arterial blood pressure as follows:

$$(2 \text{ diastolic pressure} + \text{systolic pressure}) / 3.$$

FMD was determined by a high-resolution ultra-sound of the brachial artery, based on the literature data [7]. Brachial arterial diameter was measured with a 7.5 MHz transducer. All the measurements were performed after at least 20 minutes of resting in a supine position, in a quiet air- conditioned room and after at least 10 hours from the last intake of food, caffeine, smoking or any vasoactive drugs. Longitudinal scans of the brachial artery, approximately 5 cm proximal of the antecubital fossa, were performed. The transmit focus zone was set at the depth of the anterior wall and then, an image of 5 cm longitudinal section of the brachial artery was recorded on S-VHS for 30 sec.

Measurements were done at the baseline, before and during the peak (5 min) reactive hyperaemia, induced by deflation of a blood pressure cuff, previously inflated to 50 mmHg above the subject's systolic blood pressure point. FMD was calculated from the diameters as:

$$\text{FMD \%} = (\text{reactive hyperaemia} - \text{baseline}) / \text{baseline} \times 100.$$

We considered FMD to be "normal" when the response of brachial artery was a vasodilatation $\geq 20\%$, and "impaired" when it was $< 20\%$.

Carotid-IMT of the common carotid artery (CCA) was determined, as agreed in Mannheim Consensus [26], at baseline, in both carotid arteries, with a General Electric medical system VIVID S6, a high-resolution ultrasonography system, equipped with a 9 MHz linear array transducer. The subjects were examined in the same supine position and IMT was calculated online by the built-in software of the ultrasound system. The mean IMT was calculated after 3 measurements in each patient, for the left and right carotid, 1cm before the bifurcation. We considered 0.9 - 1.1 mm as normal values of IMT, and IMT > 1.2 mm as presence of atherosclerotic plaque. All the FMD and IMT measurements were performed by the same experienced doctor.

Statistical analyses

Numerical data were presented as mean (± SD) and median (25^{th} - 75^{th}). Categorical data were presented as frequency (%). Differences among the groups were detected using ANOVA analysis of variance and Kruskal-Wallis tests. Correlations between different variables were detected using Spearman's correlation. The statistical software used was SPSS v. 17. Statistical significance was considered at a p value < 0.05.

Results and Discussion

Characteristics of the study groups and controls

Table I shows the characteristics of the studied patients (n = 198). The two hypertensive groups B and C were homogenous in terms of age, sex and duration of HTN. No significant difference was found in sex distribution among the patients in all the three groups and also no significant difference was found between the duration of HTN in the two groups (B and C), although the duration of hypertension was higher in the group of patients treated with perindopril. The heart rate was significantly lower in group C when compared with group B.

Table I

Caracteristics of thecontrol and study groups

	Group A control (n = 54)	Group B (n = 78)	Group C - perindopril (n = 66)	p
Age (years)	55.87 ± 14.56	62.79 ± 12.05 (1)	62.72 ± 14.96 (1)	0.008
Men (n%)	30 (54)	33 (78)	36 (66)	1
Women (n%)	24 (54)	45 (78)	30 (66)	
HTN duration in months	-----	95.07 ± 73.30	113.59 ± 82.06	0.155
SBP (mmHg)	124.53 ± 16.74	140.68 ± 21.21 (1)	138.68 ± 14.90 (1)	0.0001
DBP (mmHg)	77.18 ± 8.90	82.38 ± 13.19 (1)	81.87 ± 10.77 (1)	0.024
Heart rate (beats/min)	71.35 ± 6.66	73.98 ± 10.6 (2)	69.51 ± 5.25 (2)	0.004

Data are represented as mean ± SD. SBP - systolic blood pressure, DBP - diastolic blood pressure, HTN – hypertension. Statistical significance was considered at a p value less than 0.05. (1) Significant difference when compared with the control group. (2) Significant difference between both hypertensive groups.

Biochemical data for the patients in the study groups

The levels of erythrocyte sedimentation rate (ESR), blood urea nitrogen (BUN), alanine amino transferase (ALAT), aspartate amino transferase (ASAT), cholesterol, creatinine and potassium were significantly higher in group C, compared with group B, but in the normal range. No significant difference was found regarding the triglycerides levels between the groups (Table II).

Table I

Biochemical data among the patients in the study groups

	Group A - control (n = 54)	Group B (n = 78)	Group C - perindopril (n = 66)	p
ALAT (U/L)	37.87 ± 12.56	39.80 ± 11.55 (2)	47.40 ± 16.49 (2)	0.0002
ASAT (U/T)	23.88 ± 8.00	22.76 ± 6.92 (2)	27.28 ± 11.24 (2)	0.008
Cholesterol (mg/dL)	184.44 ± 44.93	209.27 ± 52.18 (2)	223.32 ± 51.17 (2)	0.0001
Triglicerides (mg/mL)	131.96 ± 32.48	121.69 ± 50.20	129.65 ± 48.09	0.38
Glucose (mg/dL)	98.20 ± 17.35	106.59 ± 30.73 (1)	109.35 ± 15.40 (1)	0.027
Creatinine (mg/dL)	0.826 ± 0.27	0.80 ± 0.20 (2)	0.97 ± 0.36 (2)	0.0009
Potassium (mmol/L)	4.38 ± 0.39	4.19 ± 0.50 (2)	4.42 ± 0.48 (2)	0.011
INR	1.19 ± 0.41	1.00 ± 0.09	1.14 ± 0.32	**0.00049**
ESR (mm/h)	7.98 ± 5.57	13.59 ± 8.30 (2)	15.63 ± 9.01 (2)	0.0001
Fibrinogen (mg/dL)	298.06 ± 66.09	320.05 ± 54.10 (2)	296.97 ± 59.68 (2)	0.0347
BUN (mg/dL)	20.63 ± 7.48	16.76 ± 6.44 (2)	20.01 ± 5.90 (2)	0.001

Data are represented as mean ± SD. (1) Sign difference when compared with the control group. (2) Sign difference between both hypertensive groups. ALAT - alanine amino transferase (GTP), ASAT - aspartate amino transferase (GOT), INR - international normalised ratio, ESR - erythrocyte sedimentation rate, BUN - blood urea nitrogen

hs-CRP, PTX3 , FMD, IMT values in different study groups

Table III shows that in group C, although the levels of hs-CRP were higher (probably due to the presence of a systemic inflammation), the local, vascular inflammation, assessed by PTX3 and FMD, was less important than in group B. The IMT values were close in all groups, although lower levels were found in the control group A, due to the lack of cardiovascular risk factors in this group.

Table III

hs-CRP, PTX3 , FMD, IMT values in different study groups

	Group A - control (n = 54)	Group B (n = 78)	Group C - perindopril (n = 66)	p
hs-CRP (mg/dL)	0.1657 ± 0.22	0.2013 ± 0.22	0.2632 ± 0.36	0.149
PTX3 (ng/mL)	1.26 ± 1.70	0.98 ± 1.07	0.59 ± 0.31	0.005
FMD (%)	20 ± 0.3	10.63 ± 0.3	13.93 ± 0.3	0.00001
CC IMT (mm)	0.850 ± 0.164	0.949 ± 0.166	0.9395 ± 0.183	0.004

Data are represented as mean ± SD. FMD - flow mediated vasodilatation. CC IMT - commune carotid intima-media thickness. hs-CRP high sensitive C- reactive protein. PTX - pentraxin. CC IMT - common carotid intima- media thickness.

Analysing the correlations of PTX3 plasma levels with other parameters, we found positive correlations ($r > 0.3$) with age, duration of HTN and common carotid (CC) IMT value, in groups B and C (Tables IV and V). These findings suggest that patients treated with antihypertensive drugs other than angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) have a higher degree of inflammation when compared to patients treated with perindopril.

Table IV

Correlation of long PTX3 levels with all data in Group C

	PTX3	Correlation
Age	----	r = 0.017, p = 0.014
Duration of HTN (months)	----	r = 0.025, p = 0.00001
SBP (mmHg)	----	r = 0.032, p = 0.848
DBP (mmHg)	----	r = 0.08, p = 0.779
Cholesterol (mg/dL)	----	r = 0.025, p = 0.0001
Triglicerides (mg/dL)	----	r = 0.262, p = 0.0905
Creatinine (mg/dL)	----	r = 0.1202, p = 0.0045
Glucose (mg/dL)	----	r = 0.1527, p = 0.3056
Potasium (mmol/L)	----	r = 0.013, p = 0.4548
Heart rate (beats/min)	----	r = 0.110, p = 0.1191
hs-CRP (mg/dL)	----	r = 0.034, p = 0.0001
FMD (%)	----	r = 0.004, p = 0.014
CC IMT (mm)	----	r = 0.0219, p = 0.00003

HTN- hypertension, SBP-systolic blood pressure, DBP- diastolic blood pressure, hs-CRP- high sensitive C reactive, FMD- flow mediated dilatation, CC IMT- common carotid intima media thickness

Table V

Correlation of long PTX3 levels with all data in Group B

	PTX3	Correlation
Age	positive	**r = 0.3903, p = 0.0001**
Duration of HTN (months)	positive	**r = 0.4054, p = 0.5393**
SBP (mmHg)	----	r = 0.0341, p = 0.0059
DBP (mmHg)	----	r = 0.1838 , p = 0.00001
Cholesterol (mg/dL)	----	r = 0.0313 , p = 0.0008
Triglicerides (mg/dL)	----	r = 0.0985 , p = 0.00001
Creatinine (mg/dL)	----	r = 0.1135, p = 0.3331
Glucose (mg/dL)	----	r = 0.0006, p = 0.0492
Potasium (mmol/L)	----	r = 0.0950 , p = 0.0766
Heart rate (beats/min)	----	r = 0.0721 , p = 0.0005
hs-CRP (mg/dL)	----	r = 0.0240 , p = 0.00001
FMD (%)	----	r = 0.0269, p = 0.0229
CC IMT (mm)	positive	**r = 0.3052, p = 0.0001**

HTN- hypertension, SBP-systolic blood pressure, DBP- diastolic blood pressure, hs-CRP- high sensitive C reactive, FMD- flow mediated dilatation, CC IMT- common carotid intima media thickness

Figure 1 shows the variation of pentraxin-3 plasma levels in different classes of antihypertensive drugs. It can be noticed that for perindopril, the PTX3 plasma levels are the lowest, compared with other classes of drugs.

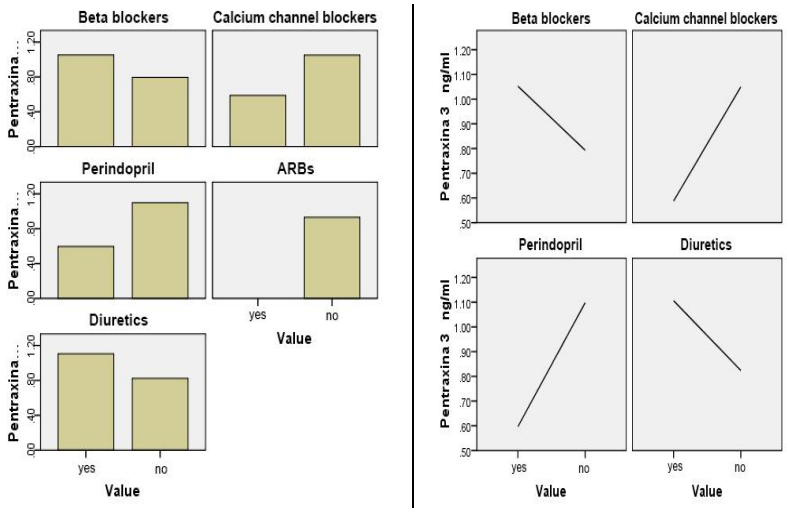

Figure 1.

Variation of PTX3 plasma levels in different hypotensive classes of drugs

We chose perindopril for this study, because, compared to other ACE inhibitors, it was proved to have a higher duration of action (24 h control over the blood pressure), a more powerful ACE tissue binding due to its lipophilicity, a higher selectivity for the binding site of ACE. Perindopril also induces a local inhibition of renin-angiotensin-aldosterone system in the brain, heart, blood vessels, kidneys, and adrenal glands. Its capacity on restoring the endothelial function has been proven by several studies, which demonstrated an improvement of FMD and IMT with perindopril treatment [3, 9, 10, 11, 27].

To our knowledge, this is the first study that showed the action of perindopril on PTX3 plasma levels. In our study, perindopril decreased the PTX3 plasma levels in a more powerful manner than anti-hypertensive drugs, other than ACE-inhibitors and ARBs. Both ACE-inhibitors and ARBs are known to reverse endothelial dysfunction. Because of the fact that PTX3 is secreted by the vascular endothelial cells, it could be a better biomarker than CRP to evaluate the local inflammation. CRP is less specific for endothelial inflammation, as it is produced by hepatocytes secondary to a systemic inflammation. Perindopril had a better influence on restoring ED in hypertensive patients when compared to beta blockers, blockers of calcium channels and diuretics.

Concerning other studies that have been performed on PTX3, Parlak *et al.* showed that PTX3 levels are higher in newly diagnosed hypertensive subjects compared to healthy individuals and that increased PTX3 levels cause an increase in systolic and diastolic blood pressure [19]. Tamura *et al.* proposed PTX3 as a novel marker for the diagnosis of pulmonary hypertension [24]. Unlu *et al.* showed that valsartan and amlodipine decrease the PTX3 and CRP plasma levels in newly diagnosed hypertensive patients when compared to the baseline levels [28]. Carrizzo *et al.* showed a direct role of PTX3 in the vascular function and control of blood pressure, suggesting that PTX3, P-selectin and MMP-1 could be novel biomarkers that can early predict the vascular dysfunction in hypertensive patients [6]. PTX3 has also been reported to be associated with cardiac events in patients with heart failure and acute myocardial infarction [12, 14, 15]. Elevated PTX3 levels have been found in many cardiovascular diseases, like acute coronary syndrome, congestive heart failure, heart failure with normal ejection fraction etc. [12, 14, 15, 17].

It seems to be agreed that PTX3 levels increase with the age. This positive correlation was also found in our study. Other correlations, such as with hs-CRP, cholesterol, triglycerides, body mass index-were found to be contradictory in many other studies [12 - 15, 17]. Yasunaga *et al.* also reported that plasma PTX3 is a more potent predictor of endothelial dysfunction than hs-CRP in patients with coronary artery disease [32]. Our study confirmed this finding in hypertensive patients with endothelial dysfunction.

In this study, as well as in the study performed by Yano *et al.* PTX3 correlated positively with IMT, especially in elderly hypertensive patients [31]. Yilmaz *et al.* showed that combined treatment with valsartan and amlodipine in hypertensive patients with type 2 diabetes and proteinuria, improved FMD, normalized proteinuria and also the PTX3 levels [33].

Our study has several limitations, the most important ones being the limited number of patients and the short observation period. Being the first study to examine the PTX3 plasma levels in hypertensive patients with ED under perindopril treatment, the present findings should be confirmed in future studies with broader spectrum and a greater number of patients. Another limitation is the fact that our cross-sectional prospective and comparative study does not explain the molecular mechanisms by which perindopril decreases PTX3 plasma levels in hypertensive patients with endothelial dysfunction.

Conclusions

Pentraxin 3 could be a better inflammatory biomarker than hs-CRP in order to assess endothelial dysfunction, because of the local synthesis (endothelial cells and not hepatocytes). In the future, it might be used routinely as a screening biomarker.

Perindopril, an extensively used ACE inhibitor, decreases more powerful PTX3 plasma levels when compared to beta blockers, calcium channel blockers and diuretics. It was shown to decrease vascular inflammation, the key point of endothelial dysfunction. Apart from the antihypertensive effect, perindopril owns favourable vascular (pleiotropic) effects that were once again proven by the present study.

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