

# Is endocan a biochemical marker for asymptomatic target organ damage in hypertensive patients?

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## ABSTRACT

**Objective:** Identification of the asymptomatic target organ damage (AOD) helps to stratify the overall risk of cardiovascular (CV) diseases and guides a treatment decision in hypertensive patients without a symptomatic CV or renal disease. The endothelial-cell-specific molecule 1 (endocan) is regarded as a novel marker of endothelial dysfunction. Its release is increased in hypertensive patients, especially those with symptomatic CV and renal disease. In the present study, we aimed to evaluate the endocan levels in asymptomatic hypertensive patients with or without AOD.

**Methods:** The study included 132 asymptomatic hypertensive patients, and 101 of who had at least one AOD.

**Results:** Serum endocan levels did not differ between patients with and without AOD ( $3.81 \pm 0.78$  vs.  $3.83 \pm 0.63$  ng/mL,  $p=0.88$ ). An analysis according to the presence of any specific AOD did not show any difference between groups. No significant correlation was found between serum endocan levels and any of the continuous variables related to AOD, such as the pulse pressure, carotid intima-media thickness, cardio-ankle vascular index, ankle-brachial index, left ventricular mass index, Sokolow–Lyon index, Cornell voltage-duration product, and estimated glomerular filtration rate.

**Conclusion:** Endocan may not serve as a useful biomarker at asymptomatic vascular stages of hypertension, despite its role in indicating disease severity and inflammatory activation in advanced symptomatic CV and renal disease. (*Anatol J Cardiol* 2018; 20: 00-00)

**Keywords:** endocan, asymptomatic target organ damage, hypertension

## Introduction

Hypertension is a serious public health problem that affects almost all organs in the body and is associated with significant morbidity and mortality. It is an important accompanying risk factor in majority of patients with chronic kidney disease (CKD) and cardiovascular diseases (CVD), such as ischemic heart disease, cerebrovascular disease, and peripheral vascular disease (1). However, in a significant proportion of patients with hypertension, especially those at early stages, no obvious signs or symptoms of CV or renal disease are observed. Those patients might be truly asymptomatic despite the presence of occult organ damage such as micro albuminuria, left ventricular hypertrophy, and carotid intima thickening (2). The asymptomatic target organ damage (AOD) may actually represent an intermediate stage between hypertension and vascular disease. Identification of an

AOD helps to stratify the overall CVD risk and guides a treatment decision in hypertensive patients (3, 4). It was hypothesized that, along with other factors, endothelial dysfunction may present as a proceeding factor in the pathogenesis of hypertension. However, endothelial dysfunction may serve as a link between hypertension and AOD (5, 6).

The endothelial-cell-specific molecule-1 (ESM-1), or endocan, is a soluble proteoglycan (50 kDa), secreted by human vascular endothelial cells and is involved in the regulation of major endothelial processes such as cell adhesion, migration, proliferation, and neovascularization (7). Its secretion is increased in a variety of endothelium-dependent pathological states, such as inflammation, cancer, infections, and atherosclerosis. Growing evidence suggests that endocan is a potential endothelial cell marker representing the immuno-inflammatory activation of endothelium (8). Celik et al. (9) have shown that the serum endocan level is increased in drug-naive hypertensive patients, which in

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turn decreased by the antihypertensive treatment. It was demonstrated that hypertensive patients with coronary artery disease (CAD) had a significantly higher serum endocan level than those without CAD and that it was correlated with the presence and severity of CAD (10).

Elevated levels of serum endocan have repeatedly been shown in hypertensive patients, especially those with symptomatic CVD (11) or CKD (12). However, there is paucity of data on the endocan levels in the asymptomatic vascular stages of hypertension. Thus, in the present study, we aimed to investigate the endocan levels in hypertensive patients without symptomatic CVD or CKD. In addition, we sought the relationship between the endocan levels and the presence and extent of AOD in hypertensive patients.

## Methods

The present study was carried out at the Sakarya University Training and Research Hospital, Cardiology Clinic from June 2016 to October 2017. The study was performed in accordance with the Declaration of Helsinki, and the study protocol was approved by the Medical Research Ethics Committee of Sakarya University, Faculty of Medicine. All the patients provided written informed consent to participate in the study.

### Study population

Patients who were admitted to our outpatient cardiology clinic and diagnosed with systemic hypertension were prospectively enrolled to present study according to prespecified inclusion and exclusion criteria. The inclusion criterion was the presence of systemic arterial hypertension in subjects older than 18 years. The following patients were excluded from the study: those with secondary hypertension, diabetes mellitus, chronic kidney disease stage  $\geq 3$ , symptomatic CVD (those who had documented coronary artery disease, cardiac failure, valvular heart disease, peripheral arterial disease, and cerebrovascular disease). Patients who had suggestive symptoms or signs of CVD and needed further evaluation were also excluded from the study. After exclusion, a total of 132 eligible patients met the criteria and were consecutively enrolled to the study.

### Clinical variables and definitions

We carried out a complete clinical history and CV examination in all participants with particular emphasis on personal CV risk factors. Clinical variables included age, smoking status, a family history of CAD, presence of hypercholesterolemia, body mass index (BMI), waist circumference, and systolic and diastolic blood pressures. Hypertension was defined as a systolic BP (SBP) of  $>140$  mm Hg and/or a diastolic BP (DBP) of  $>90$  mm Hg (the mean of 3 measurements at  $\geq 2$  visits) or current use of an antihypertensive medication. Likewise, hypercholesterolemia was defined as the presence of total serum cholesterol levels greater than 200 mg/dL or the use of lipid-lowering agents.

The following six parameters were studied and considered to be the indicators of AOD (4): a) the pulse pressure  $\geq 60$  mm Hg; b) electrocardiographic left ventricular hypertrophy (LVH) (Sokolow–Lyon index  $>3.5$  mV;  $RaVL >1.1$  mV; Cornell voltage duration product  $>244$  mV\*ms) or echocardiographic LVH (left ventricular mass index: men  $>115$  g/m<sup>2</sup>, women  $>95$  g/m<sup>2</sup>); c) carotid wall thickening [intima-media thickness (CIMT)  $>0.9$  mm] or plaque; d) the ankle-brachial index (ABI)  $<0.9$ ; e) arterial stiffness indicated by the cardio-ankle vascular index (CAVI)  $>8$ ; f) CKD with estimated glomerular filtration rate (eGFR) 30–60 mL/min/1.73 m<sup>2</sup>.

### Biochemical measurements

Blood samples were collected in the morning following a 12-hour fasting. Samples for routine biochemical tests such as the fasting blood glucose, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglycerides were studied in the Central Biochemistry Laboratory of Sakarya University Training and Research Hospital, using standard laboratory techniques. For endocan measurement, a 10 mL blood sample was immediately centrifuged for 10 minutes to separate the plasma and serum, and serum was stored at  $-80^{\circ}\text{C}$  until analyzed. The endocan levels were measured using an enzyme-linked immunosorbent assay (Abbkin Scientific Co., Ltd. Bldg 1, No.35, Optical Valley Ave, California, USA), in accordance with the manufacturers' instructions.

### Assessment of asymptomatic target organ damage

The pulse pressure was calculated by subtracting the systolic arterial pressure from diastolic arterial pressure. A value  $\geq 60$  mm Hg was considered abnormal, indicating loss of the elasticity in aorta. The arterial stiffness and ABI measurements were obtained in a quiet, temperature-controlled room after 10 min at rest with patient in the supine position, according to the recommendations. CAVI and ABI were measured with a VeSera VS-2000 instrument (Fukuda Denshi Co. Ltd., Tokyo, Japan) by the methods previously described (13). Briefly, a cuff was applied to bilateral upper arms and ankles with subject in the supine position and head held in the mid-line position. Then, the phonocardiography microphone and electrocardiography (ECG) electrodes were placed. After resting for 10 min, the VeSera VS-2000 measured extremity blood pressures and calculated the CAVI and ABI automatically. A CAVI value  $\geq 8$  was used to define abnormal level of arterial stiffness (13). An ABI value  $<0.9$  was considered abnormal and an indicator for asymptomatic peripheral arterial disease.

The LVH was assessed using ECG and echocardiography. The following ECG criteria were used to detect LVH: the Sokolow–Lyon index (S wave in V1+R wave V5  $>3.5$  mV), the modified Sokolow–Lyon index (largest S-wave+largest R-wave  $>3.5$  mV), R wave in aVL  $>1.1$  mV, or Cornell voltage QRS duration product  $>244$  mV\*ms. The Cornell voltage QRS duration product is calculated by multiplying the Cornell voltage sum (R wave in aVL+S wave in V1) by the duration of the QRS complex. Echocardiogra-

phy was performed by an investigator blinded to each patient's clinical status, using a commercial echocardiography machine (Philips IE33, Andover, MA, USA) equipped with a 2.5 MHz phased array transducer. Complete 2D, color, pulsed, and continuous-wave Doppler examinations were performed according to standard techniques. The calculation of the LVMI was performed according to the American Society of Echocardiography formula (14). Thresholds of 95 g/m<sup>2</sup> for women and 115 g/m<sup>2</sup> (body surface area) for men were used for estimates of clear-cut LVH.

Carotid ultrasonography was performed with an Aplio MX unit (Toshiba Medical Systems Co, Ltd, Tokyo, Japan) equipped with a 7.5 MHz linear array imaging probe. The right common carotid artery (CCA) was examined with the patient lying in the supine position, the head directed away from the side of interest and the neck extended slightly. The transducer was manipulated so that the near and far walls of the CCA were parallel to the transducer footprint, and the lumen diameter was maximized in the longitudinal plane. A region 1 cm proximal to the carotid bifurcation was identified, and the CIMT of the far wall was evaluated as the distance between the lumen-intimae interface and the media-adventitia interface. The CIMT measurement was obtained from four contiguous sites at 1 mm intervals, and the average of the four measurements was used for analyses. All measurements were performed by the same investigator (Y.G.) without the knowledge of clinical data and study protocol.

The glomerular filtration rate (GFR) was estimated and indexed according to the MDRD formula (15). An estimated GFR value of 30–60 mL/min/1.73 m<sup>2</sup> was considered to be an indicator of asymptomatic kidney damage.

### Statistical analysis

Data are expressed as mean±standard deviation (SD) for normally distributed continuous variables, as median and interquartile ranges for skew-distributed continuous variables, and as frequencies for categorical variables. Participants were dichotomized according to having at least one AOD marker. Comparisons

were performed in the AOD (+) and AOD (–) groups. The Pearson chi-squared test was used to compare categorical variables. The means for normally distributed continuous variables were compared by independent-samples t-test. Skew-distributed continuous variables were compared using a Mann–Whitney U-test. Likewise, serum endocan levels were compared for any independent AOD marker. The correlation between the serum endocan level and pulse pressure, CIMT, ABI, CAVI, LVMI, Sokolow-Lyon index, Cornell voltage QRS duration product, and eGFR were assessed using Pearson's or Spearman's correlation coefficient.

It was hypothesized that the serum endocan level would be higher in the AOD (+) group. Careful review of literature revealed no referent values for endocan in asymptomatic hypertensive patients, specifically evaluating the levels at pre-AOD and post-AOD stages. Thus, it was not possible to gauge the effect size based on previous reports. With the assumption of the medium effect size of 0.5 and a Type I error of 5%, the study required approximately 102 patients to yield a statistical power of 80%. Statistical analyses were performed with the SPSS software (version 15.0 for Windows; SPSS Inc., Chicago, IL, USA). The power and sample size analysis was performed with the G\*Power software (version 3.1.9.2 for Windows; The G\*Power Team: Axel Buchner, Edgar Erdfelder, Franz Faul, Albert-Georg Lang, Heinrich Heine University Dusseldorf, Germany).

### Results

The study included 132 patients. The majority of patients were women (82 female, 50 male), and the mean age was 50±9 years. The number of patients in different hypertension stages were as follows: 20 patients (15%) were at Stage 1, 79 patients (60%) were at Stage 2, and 33 patients (25%) were at Stage 3. The number of patients who were receiving an antihypertensive medication was 114 (86%). The frequency of patients with different AOD markers is presented in Table 1.

**Table 1. Frequency of patients with different asymptomatic target organ damage markers**

	Asymptomatic target organ damage	n	%
1	Pulse pressure ≥60 mm Hg	38	28.8
2	Electrocardiographic LVH (Sokolow–Lyon index >3.5 mV; RaVL >1.1 mV; Cornell voltage duration product >244 mV*ms) or Echocardiographic LVH (LVM index: men >115 g/m <sup>2</sup> ; women >95 g/m <sup>2</sup> [BSA])	58 63	43.9 47.7
3	Carotid wall thickening (CIMT >0.9 mm) or plaque	32	24.2
4	Ankle-brachial index <0.9	5	3.8
5	Cardio-ankle vascular index (CAVI) >8	51	38.6
6	CKD with eGFR 30-60 mL/min/1.73 m <sup>2</sup>	0	0

AOD - asymptomatic target organ damage; BSA - body surface area; CAVI - cardio-ankle vascular index; CIMT - carotid intima-media thickness; CKD - chronic kidney disease; LVH - left ventricular hypertrophy; LVM - left ventricular mass

**Table 2. Frequency of patients according to asymptomatic target organ damage load**

Asymptomatic target organ damage load	n	%
0	31	23.5
1	45	34.1
2	28	21.2
3	24	18.2
4	4	3.0
5	0	0
6	0	0
Total	132	100

**Table 3. Clinical and laboratory characteristics of patients with and without asymptomatic target organ damage**

	AOD + (n=101)	AOD – (n=31)	P value
Gender (Male/Female)	45/56	5/26	<b>0.005</b>
Age, years	51.2±9.5	48.2±8.1	0.11
BMI, kg/m <sup>2</sup>	30.0±4.6	30.4±4.4	0.64
Waist circumference, cm	99.4±11.4	96.1±11.2	0.16
Family history for CAD, n (%)	11 (10.9)	3 (9.7)	0.84
Current smokers, n (%)	30 (29.7)	6 (19.4)	0.26
Antihypertensive drug use (%)	89 (88.1)	25 (80.6)	0.29
Systolic blood pressure, mm Hg	145±12	132±8	<b>&lt;0.0001</b>
Diastolic blood pressure, mm Hg	86±8	80±8	<b>&lt;0.0001</b>
Pulse pressure*, mm Hg	52/57/63	49/50/54	<b>&lt;0.0001</b>
ECG parameters			
Skolow–Lyon index, mV	3.8±2	2.2±1.1	<b>&lt;0.0001</b>
RaVL*, mV	0.3/0.5/0.6	0.3/0.4/0.7	0.92
Cornell voltage duration product, mV*msn	116±56	96±45	0.07
Echocardiographic parameters			
LVEF, %	60.7±4.0	62.2±3.6	0.06
E wave, cm/sec	69.0±16.3	75.7±15.6	<b>0.04</b>
A wave, cm/sec	76.4±20.1	70.3±19.2	0.14
E/A*	0.68/0.83/1.21	0.81/1.23/1.41	<b>0.01</b>
Septal e' wave, cm/sec	6.7±1.6	7.8±1.6	<b>0.002</b>
E/e' *	8.7/10.1/11.5	8.4/9.9/11.2	0.45
GLS, %	18.9±4.1	22.5±3.3	<b>&lt;0.0001</b>
LVMI, gr/m <sup>2</sup>	81±18	67±13	<b>&lt;0.0001</b>

**Table 3. Cont.**

	AOD + (n=101)	AOD – (n=31)	P value
Biochemical parameters			
Fasting blood glucose, mg/dL	101±12	99±12	0.57
Creatinine, mg/dL	0.76±0.16	0.66±0.13	<b>0.001</b>
eGFR*, mL/min/1.73 m <sup>2</sup>	93/98/101	97/100/108	<b>0.007</b>
ALT*, u/L	17/23/32	14/18/32	0.06
AST*, u/L	19/21/27	16/19/22	<b>0.05</b>
Total cholesterol, mg/dL	206±38	211±44	0.52
Triglyceride*, mg/dL	93/145/188	102/146/245	0.51
HDL, mg/dL	46±14	47±12	0.62
LDL, mg/dL	137±32	142±42	0.45
Endocan, ng/mL	3.81±0.78	3.83±0.63	0.88
CIMT*, mm	0.5/0.8/1	0.4/0.6/0.7	<b>&lt;0.0001</b>
ABI	1.03±0.09	1.02±0.08	0.45
CAVI	7.8±1.3	7.0±0.8	<b>0.001</b>

\*Skew-distributed continuous variables were expressed as 25<sup>th</sup>, median and 75<sup>th</sup> percentiles.

ABI - ankle-brachial index; ALT - alanine aminotransferase; AST - aspartate aminotransferase; AOD - asymptomatic target organ damage; BMI - body mass index; CAD - coronary artery disease; CAVI - cardio-ankle vascular index; CIMT - carotid intima-media thickness; eGFR - estimated glomerular filtration rate; GLS - global longitudinal strain; HDL - high-density lipoprotein; LDL - low-density lipoprotein; LVEF - left ventricular ejection fraction; LVMI - left ventricular mass index

Patients were rated according to the AOD load. With respect to studied parameters, it is theoretically possible that the AOD load could be rated 0 to 6. Thirty-one patients (23.5%) were AOD free; however, 101 patients had at least one AOD. In 4 patients, 4 different AOD markers were present at the same time. None of the patients had 5 or 6 AOD at the same time (Table 2).

Clinical and laboratory characteristics of subjects with and without AOD were summarized in Table 3. Male gender frequency (44.5% vs. 16%, p=0.005) was higher in patients with AOD. Due to close relation of some parameters with AOD, we found higher systolic, diastolic, and pulse pressures and higher CIMT and CAVI values in patients with AOD. Likewise, the Skolow–Lyon and LVM indices were higher in patients with AOD. Among other echocardiographic parameters, E wave, e' wave, E/A, and GLS were lower in the AOD group. There were no significant differences with respect to lipid parameters; however, creatinine and AST levels were higher in the AOD group. Interestingly, serum endocan levels did not differ between the groups (3.81±0.78 vs. 3.83±0.63 ng/mL, p=0.88).

Analyses of serum endocan levels, depending on the presence or absence of a specific AOD, showed no difference between groups (Table 4). The relationship between the serum endocan level and other continuous AOD variables was assessed by the correlation analysis. The serum endocan level did not significantly correlate with any of the variables such as pulse

**Table 4. Serum endocan level depending on presence or absence of specific asymptomatic target organ damage**

Asymptomatic target organ damage parameters	Endocan level, ng/mL		P value
	(+)	(-)	
Pulse pressure >60 mm Hg	3.8±0.8	3.8±0.7	0.72
Electrocardiographic LVH (Sokolow–Lyon index >3.5 mV; RaVL >1.1 mV; Cornell voltage duration product >244 mV*ms) or Echocardiographic LVH [LVM index: men >115 g/m <sup>2</sup> ; women >95 g/m <sup>2</sup> (BSA)]	3.7±0.8	3.9±0.7	0.07
Carotid wall thickening (CIMT >0.9 mm) or plaque	3.8±0.8	3.8±0.7	0.90
Ankle-brachial index <0.9	3.7±0.8	3.8±0.7	0.72
Cardio-ankle vascular index (CAVI) >8	3.8±0.8	3.8±0.7	0.69
CKD with eGFR 30–60 mL/min/1.73 m <sup>2</sup>	-	3.8±0.7	-

BSA - body surface area; CAVI - cardio-ankle vascular index; CIMT - carotid intima-media thickness; CKD - chronic kidney disease; LVH - left ventricular hypertrophy; LVM - left ventricular mass

pressure, the CIMT, CAVI, ABI, LVMI, Sokolow–Lyon index, Cornell voltage duration product, and eGFR.

A post-hoc power analysis revealed that the study achieved 78% power to demonstrate an effect size of 0.5, with a corresponding Type I error of 5%.

## Discussion

In our study, no significant difference in endocan levels was found in asymptomatic hypertensive patients with or without AOD. In addition, serum endocan levels did not correlate with any of the variables related to AOD. Our results suggest that endocan does not possess adequate usefulness as a surrogate biochemical marker for the presence of AOD in hypertensive individuals. To the best of our knowledge, this is the first study to evaluate the relationship of endocan with any specific AOD in hypertensive individuals without symptomatic CVD and CKD.

Hypertension is an important risk factor for several CV events such as stroke, myocardial infarction, sudden mortality, heart failure, peripheral arterial disease, as well as end-stage renal disease (1). The estimation of the total CV risk in a hypertensive individual is relatively easy in a particular subgroup of patients with established CVD, CKD or diabetes. In such patient subgroups, management is relatively straightforward, including intensive CV risk-reducing measures along with an antihypertensive medication (4). However, a large number of patients with hypertension are truly asymptomatic and do not belong to any of the above categories, yet may deserve specific therapeutic interventions. In such clinical scenario, identification of occult target organ damage helps clinician to stratify total CV risk appropriately (2, 3). AOD represents an intermediate stage between hypertension and vascular disease that requires additional tests for identification. Carotid ultrasound, ECG/echocardiography,

and applanation tonometry are some of laboratory tools for the identification of AOD, with specific thresholds for carotid intimal thickening, LV hypertrophy, and pulse velocity (3). Asymptomatic kidney damage can readily be identified with simple biochemical tests, such as eGFR and microalbuminuria.

Endothelial dysfunction has been shown to be related to hypertension in a number of studies conducted on hypertensive patients and different animal models (5). Vascular alterations associated with hypertensive phenotype, such as vascular remodeling, increased peripheral vascular resistance, decreased synthesis of vasodilators, and inflammation, all share endothelial dysfunction as a common denominator (6). Vascular theory on the pathogenesis of hypertension has opened the way for the study of various biochemical markers related to endothelial functions. Among them, ESM-1 (endocan) has recently gained clinical attention. Balta et al. (16) have studied the endocan levels in hypertensive patients and reported higher endocan levels compared to healthy control group. Similarly, Celik et al. (9) have shown that the serum endocan level is higher in drug-naive hypertensive patients, which in turn decreased after the initiation of antihypertensive treatment. In the further researches, increased levels of serum endocan have consistently been shown in various disease states related to immuno-inflammatory activation of endothelium, such symptomatic CAD (10), CKD (12), psoriasis vulgaris (17), Behçet's disease (18), familial Mediterranean fever (19), SLE (20), and sarcoidosis (21). However, data, specifically evaluating the endocan levels in AOD stage of hypertension, are relatively scarce. In the present study, we systemically searched various AOD markers and analyzed endocan levels according to the presence and absence a specific AOD marker in patients belonging to the asymptomatic vascular stages of hypertension. We found no difference in endocan levels in patients with carotid intima-media thickening, which was one of our interests. Similarly, no significant correlation was found in serum endocan

levels and CIMT. The published data indicate positive correlations between serum endocan and CIMT in various disease states such as type 2 diabetes (22), CKD (12), psoriasis vulgaris (17), and SLE (20). The results of those studies are not comparable to the present study due to the inclusion of a different patient population. However, discordant to our results, Balta et al. (16) have found a positive correlation between the endocan level and CIMT in hypertensive patients without symptomatic CV disease.

Yilmaz et al. (12) studied the endocan levels in patients with CKD and its association with eGFR. They found a negative correlation between the endocan level and eGFR. In a study conducted in renal transplant recipient patients, higher endocan levels were demonstrated in more advanced CKD stages in a dose-dependent manner (23). In the present study, we could not demonstrate a significant correlation between the endocan level and eGFR. Of note, none of our patients had eGFR less than 60 mL/min/1.73 m<sup>2</sup>. This indicates a population with a relatively normal renal function, which might be the reason why we could not demonstrate a significant correlation between endocan levels and eGFR. Similar to the results in CIMT and eGFR, we could not demonstrate any significant correlation between the endocan levels and other continuous parameters related to AOD such as pulse pressure, LVMI, ABI, and CAVI. In addition, no difference in endocan levels was observed in case of the presence of any other AOD marker. Taking our consistent results and current literature into consideration, we propose that elevated endocan levels might be a characteristic of advanced endothelial damage, which coincides with symptomatic CVD and CKD.

### Study limitation

The main limitation of our study is a relatively small sample size. Since, we could not find published data on endocan levels in a study group similar to our patient population, our sample-size estimates might have been misleading due to a presumed effect size of 0.5. A small sample size might obscure the subtle difference in endocan levels in AOD positive and negative patients. Therefore, our results should be interpreted with caution. The actual effect size and corresponding power of the present study might be lower than reported. The second limitation of our study is the absence of a control group. The absence of other biomarkers related to endothelial dysfunction can be considered as another limitation.

### Conclusion

In conclusion, we suggest that endocan may not serve as a useful biomarker at asymptomatic vascular stages of hypertension, despite its role in indicating disease severity and inflammation activation in advanced symptomatic CVD and CKD.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

**Authorship contributions:** Concept – M.T.A., B.K., F.B.C.; Design – M.T.A., M.B.V.; Supervision – M.T.A., M.M.N.A., M.B.V.; Fundings – M.T.A., B.K., F.B.C.; Materials – F.B.C., Y.G.; Data collection &/or processing – M.T.A., B.K., M.M.N.A., Y.G.; Analysis &/or interpretation – M.T.A., B.K., Y.G.; Literature search – M.T.A., B.K.; Writing – M.T.A., B.K., F.B.C.; Critical review – M.T.A., B.K., M.M.N.A., F.B.C., M.B.V., Y.G.

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