Original article

Potential of the novel START index in assessing arterial stiffness in patients with coronary artery disease

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Abstract: *Background* — Recently, a novel method for assessing arterial stiffness was developed under the name of START (*STiffness of ARTeries*), which, unlike the conventional stiffness parameter β, is calculated based on other physical principles. Our study aimed to investigate the possibility of using the new START index in patients with coronary artery disease (CAD).
Methods — The study included 353 patients with CAD: 277 men and 76 women. Their median age was 57.0 (53.0; 64.0) years. The arterial stiffness was assessed in all subjects using VaSera VS-1000 sphygmomanometer. The novel arterial stiffness index (START) was analyzed retrospectively. We assessed the correlation of cardio-ankle vascular index (CAVI) and START index, as well as each of these indices with risk factors in the entire cohort of those examined, and also separately for men and women.
Results — In examined CAD patients, the median value of the CAVI was within the borderline values (8.0-9.0) [5]: 8.3 (7.6; 9.2) on the right side and 8.3 (7.6; 9.2) on the left side. A median value of the START index was 8.3 (7.1; 9.8) on the right and 8.1 (7.0; 9.6) on the left. A strong relationship between CAVI and START was revealed in the total sample (r=0.879, p<0.001). Women exhibited a more pronounced association (r=0.982, p<0.001) than men (r=0.805, p<0.001). For the total sample, we revealed a strong dependence of the indices on age (r=0.4, p<0.001 for CAVI; r=0.36, p<0.001 for the START index). Both stiffness indices exhibited a weak but significant correlation with glomerular filtration rate (GFR) in the entire sample of study subjects (r=-0.168, p=0.003 for CAVI; r=-0.0159, p=0.004 for START).
Conclusion — In patients with CAD, the START index was strongly associated with the CAVI throughout the entire cohort, albeit the correlation in women was slightly stronger than in men. Also, these indices had similar associations with clinical factors and age. Strong correlation between these indices is important for the subsequent practical application of the START index. The possibility of using START index in similar clinical situations as the CAVI requires confirmation in further studies.

Keywords: coronary artery disease, arterial stiffness, cardio-ankle vascular index, START index.

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Introduction

The vascular wall condition is an important factor underlying the risk of development and progression of cardiovascular diseases (CVD). This does not come as a surprise since all other CVD risk factors largely realize their impact through effects on the vascular system and increased vascular stiffness [1]. Therefore, it seems reasonable to use some index of vascular stiffness as an integral indicator of the CVD risks. Such indicator would accumulate the impact of various risk factors on the cardiovascular system throughout life. Accordingly, arterial stiffness is not only an important component of vascular aging [2], but also a powerful predictor of CVD risks; and as such, it becomes an appropriate therapeutic target [1,3].

It is recognized that despite recent technological advances in measuring vascular stiffness in clinical practice, unmet needs continue to include the following: complexity of use and heterogeneity of approaches, lack of validation in clinical settings, fragmentation of experience, lack of research on treatment, and direct comparisons between different methods. In clinical practice, the most widely used methods for assessing vascular wall stiffness employ the determination of the pulse wave velocity (PWV) propagation through the vessels of the carotid-femoral arterial bed. However, the method for assessing carotid-femoral PWV depends on the blood pressure. Certain limitations of this method are associated with the technique of recording pulse waves in the carotid and femoral arteries, requiring an involvement of a highly qualified specialist and being operator dependent [4].

The proposed cardio-ankle vascular index (CAVI) eliminates the effect of blood pressure on PWV [5]. However, the velocity underlying the CAVI formula is determined in a non-standard part of the arterial bed. Consequently, a number of researchers [6,7] question the clinical significance of this indicator. However, studies conducted predominantly in Asian populations showed that the CAVI directly correlated not only with CVD risk factors and the severity of coronary atherosclerosis [8], but also with prognosis [8-10]; hence, CAVI was proposed as an important predictor in patients at high cardiovascular risk.

The ideal solution seems to be the development of a device capable of measuring the carotid-femoral PWV using the conventional method and leveling off the effect of blood pressure vis some analogue of the CAVI. Bakholdin et al. [11] developed a novel method for estimating arterial stiffness, START (*STiffness of ARTeries*). Unlike the standard stiffness parameter β, it is calculated based on different physical principles. The calculation formula uses the law of conservation of mass and momentum, a standard method for deriving conditions at a discontinuity where the pulse wave front is modeled as a discontinuity. The formula also takes into account nonlinear effects affecting the velocity of a large amplitude wave. Until now, only a few studies have evaluated the novel START index [11,12]. For instance, a fairly strong correlation was shown between the START and β indices, along with a certain deviation of both indices from CAVI (starting from the CAVI value of approximately 8.9) [11]. In a previous study, we examined the START index in healthy people [12]; however, the possibility of its use in heart diseases remains unexplored. There is a need for further research in this field. The fastest solution to accumulate information on this indicator is conducting a retrospective study with a revision of the results of previous studies, but taking into account a new parameter. Previously, our research group assessed the prognostic impact of the CAVI in patients undergoing coronary artery bypass graft (CABG) surgery [9,10]. Accordingly, *the objective* of this study was to examine the feasibility of using the novel START index in patients with CAD.

Material and Methods

Study population

The analysis included data on a cohort of patients with chronic coronary syndrome who were examined before CABG in the Department of Cardiology of the Research Institute for Complex Problems of Cardiovascular Diseases from March 2011 through March 2012. Detailed criteria for inclusion and exclusion from the study were presented in our previous publications [9,10]. Because we compared the new arterial stiffness index with the CAVI, we did not include patients with diseases that could affect the CAVI values in our analysis. Consequently, patients with recent acute coronary syndrome, valvular heart disease, low left ventricular ejection fraction, low ankle-brachial index (ABI) (≤0.9), presence of atrial fibrillation, or implanted pacemaker were excluded. The study protocol was approved by the Ethics Committee of the Research Institute for Complex Problems of Cardiovascular Diseases (protocol #20110216). All patients signed informed consent prior to their inclusion in the study (*Figure 1*).

Data collection

Baseline patient data were obtained from the electronic registry database of the institute. For each patient, the following data were collected: anthropometric indicators, clinical characteristics (severity of angina pectoris and heart failure, number of affected coronary arteries), anamnestic characteristics (previous myocardial infarction and coronary interventions, operations on peripheral arteries, history of stroke), risk factors, concomitant diseases and laboratory data. The condition of peripheral arteries was also assessed in patients using duplex ultrasound. Arterial stiffness was assessed using CAVI, and the START index was calculated based on data obtained from volumetric sphygmography.

Measuring CAVI

Stiffness of peripheral arteries was assessed by the CAVI using the VaSera VS-1000 sphygmomanometer (Fukuda Denshi, Japan) according to a previously described protocol [13]. CAVI is measured using cuffs on all four limbs in combination with a microphone on the chest. This provides several logistical advantages useful for clinical use: the CAVI is operator independent; it does not require groin exposure and constitutes a highly reliable measurement; finally, it is automated for better ease of use and reproducibility [14]. In addition to including the peripheral arteries of the legs, CAVI measurements represent the entire aorta, especially the ascending aorta, where the earliest changes associated with aging are visible (the CAVI pulse travels from the aortic valve to the ankle). This index is calculated automatically by the device on the right and left (R-CAVI and L-CAVI) and originates from the so-called stiffness parameter β in combination with the modified Bramwell-Hill equation: CAVI=a{(2p/ΔP)·ln(Ps/Pd)PWV2}+β. This equation evaluates the relationship between the PWV propagation and the elasticity of the vascular wall. For CAVI, the measurement uses the mean brachial artery blood pressure. In addition, when assessing CAVI, the stiffness parameter β is taken into account, which is defined as the ratio of the natural logarithm of pressure (ln [Ps/Pd]) to the degree of change in the inner diameter (D/ΔD) of the blood vessel. It is known that this parameter does not depend on internal pressure, and the higher β, the lower the extensibility and the greater the vascular stiffness.

Calculating a novel index of vascular stiffness (START)

Considering the shortcomings of the methods for calculating the standard parameter β and the CAVI index based on it, it was proposed to take into account the nonlinear effects on the velocity of waves at large amplitudes. This method for assessing stiffness is based on the research by Bakholdin I.B. [15,16] who investigated waves in pipes with elastic walls using a complete membrane and plate model for the walls, along with approximation for hydraulic conductivity inside the pipe. The resulting novel parameter of stiffness, in contrast to the standard stiffness parameter β, was therefore based on the law of conservation of mass and momentum The latter is the standard method for deriving conditions at a discontinuity where the pulse wave front is modeled as a discontinuity, it and takes into account nonlinear effects on the wave velocity at its large amplitude. Consequently, this coefficient better describes the elastic walls of the vessel with a large difference between systolic (SBP) and diastolic blood pressure (DBP) values [11].

The START index was calculated by us using the following formula:

$$START = \frac{-\ln\left(\frac{P_S}{P_d}\right)(v_S - U) + \sqrt{\left[\ln\left(\frac{P_S}{P_d}\right)(v_S - U)\right]^2 - v_S(v_S - U)\ln^2\left(\frac{P_S}{P_d}\right)(1-\alpha)}}{(1-\alpha)v_S} \quad [11], (1)$$

where V_S is the maximum systolic blood flow velocity; V_d is the end-diastolic velocity; ρ *is* the density of blood; α represents the ratio of V_d to V_S; U is the discontinuity velocity coinciding with the previously measured PWV; P_s is SBP; P_d is DBP.

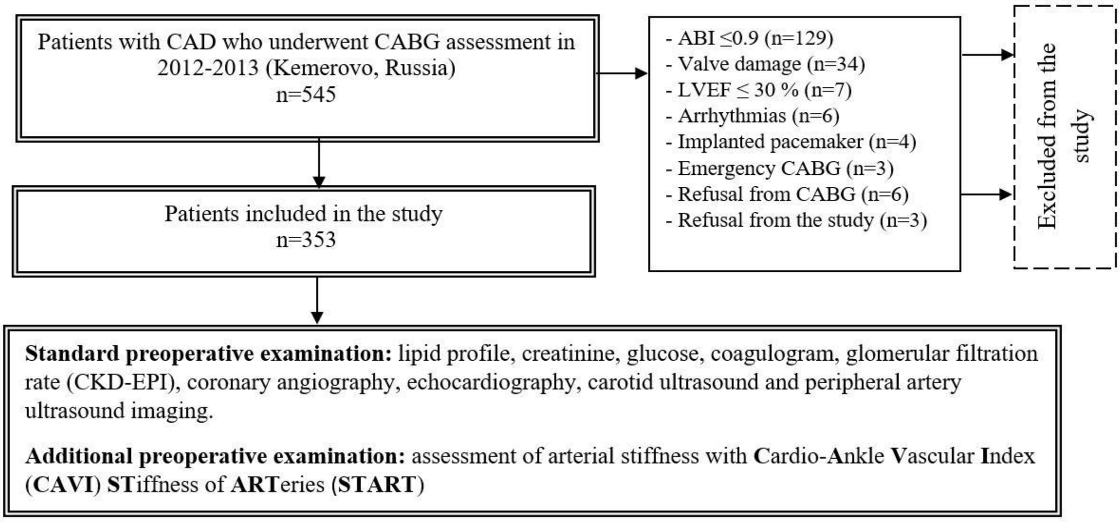

Figure 1. Flowchart of patient selection. CABG, coronary artery bypass grafting; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ABI, ankle-brachial index; LVEF, left ventricular ejection fraction.

Because the blood flow velocity is small compared to the PWV, it is usually advisable to assume the value of α equal to zero. We calculated PWV in the area from the heart valve to the ankle using the formula proposed by the VaSera VS-1000 Fukuda Denshi manufacturer:

$$caPWV=L/T, \quad (2)$$

where the distance is $L=L1+L2+L3$, and the time is $T=tb+tba$.

As a result, we obtained the START index, which reflected stiffness in the cardio-ankle arterial bed (caSTART), since this is the area in which the VaSera device allows calculating the vascular stiffness index. The calculation of the novel START index was carried out using the online calculator (https://stelari-start.com) by applying values from the research protocol of the VaSera-1000 device (Ps, Pd and PWV).

Statistical data processing

To identify the type of distribution, we employed the Shapiro–Wilk test. For non-normal distributions of variables, data are presented as median and interquartile range (Me [Q25; Q75]). Spearman's rank correlation coefficient was used to assess the correlation of CAVI and START indices, as well as each of those with risk factors (both in the entire cohort of patients, and separately for men and women). The level of critical significance (p) in regression analysis was taken equal to 0.05.

Results

Clinical and anamnestic characteristics of patients with CAD are presented in *Table 1*. In the investigated sample, there were more men (78.5%) than women. Median age of study subjects was 57.0 (53.0; 64.0) years. We revealed a higher body mass index in study participants, with a median value of 28.3 (25.3; 31.2) years. The proportion of smokers was 31.7%. The median content of total cholesterol (4.95 mmol/L) and low-density lipoprotein cholesterol (2.94 mmol/L) exceeded the upper limit of assumed normal values for this category of patients. According to clinical data, 146 (41.4%) patients had angina pectoris of the functional class III. Symptoms of chronic heart failure (CHF) were observed in 95.5% of cases, with stage I CHF prevailing. Study subject had a history of myocardial infarction in 227 cases (64.3%), stroke in their anamneses in 21 (5.9%) cases, while 58 (16.4%) patients suffered from type 2 diabetes mellitus. When analyzing the results of coronary angiography in patients with CAD, a more frequent detection of three-vessel lesions was characteristic in 161 (45.7%) cases. Instrumental examination demonstrated that changes in extracranial arteries and/or arteries of the lower limbs occurred in 140 (39.7%) cases.

Analysis of volumetric sphygmography parameters (*Table 2*) in examined CAD patients showed that a median value of the CAVI was within the borderline values (8.0-9.0) [5]: 8.3 (7.6; 9.2) on the right and 8.3 (7.6; 9.2) on the left. The median START index was 8.3 (7.1; 9.8) on the right and 8.1 (7.0; 9.6) on the left. Median values of blood pressure indicators were within their normal range.

The comparison of two vascular stiffness indicators (CAVI and START) in patients with CAD (*Figure 2*) yielded their strong relationship in the total sample (r=0.879, p<0.001). It is worth noting that a more pronounced dependence was found in women (r=0.982, p<0.001) vs. in men (r=0.805, p<0.001).

When conducting a correlation analysis aimed at studying the effect of risk factors on vascular stiffness (*Table 3*, *Figure 3*), a significant dependence of the indices on age in the total sample was detected (for CAVI: r=0.4; p < 0.001; for START index: r=0.36; p < 0.001). Women exhibited a more pronounced direct relationship between age and indices (CAVI: r=0.531, p<0.001; START: r=0.509, p<0.001) vs. men (CAVI: r=0.423, p<0.001; START r=0.336, p<0.001). Both stiffness measures showed weak albeit significant (p<0.05) correlations with GFR in the total sample (for CAVI: r=-0.168, p=0.003; for START: r=-0.0159, p=0.004). In women, a weak but highly significant relationship was established between GFR and two indices (CAVI: r=-0.331, p=0.004; START: r=-0.382 p=0.001), whereas in men, a significant relationship was found solely with the CAVI (CAVI: r=-0.134, p=0.028; START: r=-0.104, p=0.099).

Table 1. Characteristics of examined patients with coronary artery disease

Variables		*(n=353)*
Male sex (n, %)		277 (78.5)
Age, years		57.0 [53.0; 64.0]
Current smoking (n, %)		112 (31.7)
Duration of smoking, years		30.0 [20.0; 40.0]
Anthropometric indicators		
Height, cm		170.0 [164.0; 176.0]
Weight, kg		80.0 [71.0; 89.0]
BMI, kg/m2		28.3 [25.3; 31.2]
Laboratory data		
Total cholesterol, mmol/L		4.95 [4.2; 6.0]
HDL cholesterol, mmol/L		0.99 [0.83; 1.2]
LDL cholesterol, mmol/L		2.94 [2.24; 3.66]
Triglycerides, mmol/L		1.76 [1.28; 2.33]
Creatinine, µmol/L		84.0 [69.0; 100.0]
Glucose, Me (LQ; UQ) mmol/L		5.5 [5.0; 6.2]
Uric acid, µmol/L		5.6 [5.1; 7.1]
CKD-EPI GFR, mL/min/1.73 m2		82.4 [66.3; 103.5]
Clinical characteristics		
Functional class of angina pectoris	0 (n, %)	69 (19.5)
	I (n, %)	11 (3.2)
	II (n, %)	118 (33.4)
	III (n, %)	146 (41.4)
	IV (n, %)	9 (2.5)
Heart failure grade *sensu* NYHA	0 (n, %)	16 (4.6)
	I (n, %)	212 (60.1)
	II (n, %)	117 (33.1)
	III (n, %)	8 (2.3)
Anamnestic characteristics		
History of myocardial infarction (n, %)		227 (64.3)
Arterial hypertension (n, %)		306 (86.7)
History of stroke (n, %)		21 (5.9)
Diabetes mellitus (n, %)		58 (16.4)
Previous PCI (n, %)		33 (9.3)
Previous CABG (n, %)		2 (0.6)
Carotid endarterectomy (n, %)		7 (2.0)
Coronary angiography		
One-vessel CAD (n, %)		82 (23.2)
Two-vessel CAD (n, %)		110 (31.1)
Three-vessel CAD (n, %)		16 (45.7)
Left coronary artery ≥ 50% (n, %)		67 (19.0)
Atherosclerosis of arterial bed		
Carotid artery stenoses ≥ 50% (n, %)		49 (13.9)
Stenoses of the lower limb arteries ≥ 50% (n, %)		20 (5.7)
Multifocal atherosclerosis ≥ 50% (n, %)		61 (17.3)

Data are presented as a median and interquartile range (25th-75th percentiles) or a number [%], as indicated. BMI, body mass index; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; HDL, high-density lipoproteins; LDL, low-density lipoproteins; GFR, glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

Discussion

Our study established a strong correlation of the new START index with the previously proposed measure of arterial stiffness, the CAVI, in patients with CAD. This finding is vital for the subsequent practical application of the START index. In addition, there was a statistically significant correlation of the START index with various clinical parameters (glomerular filtration rat, previous myocardial infarction) and age.

In previous studies, a strong correlation between the CAVI and the START index was noted in a nonselective population (healthy individuals and patients with cardiovascular diseases) [11], in apparently healthy individuals, and also in patients with arterial hypertension (Sumin, *in press*). The revealed fairly complete coincidence of age-related changes and the correlation between CAVI and the START index were not predetermined. For example, the relatively recently developed CAVI0 [6], intended to level off the dependence on blood pressure, turned out to be less concordant with the CAVI, particularly, in patients with arterial hypertension [17], even though initially, supporters of the CAVI0 showed in their mathematical calculations that this index was more accurate and less dependent on blood pressure levels [6]. However, the CAVI exhibited a greater accuracy in clinical situations. On the contrary, the CAVI0, when examining healthy individuals and patients with arterial hypertension in a population sample, was a less accurate measure of arterial stiffness vs. the CAVI [17]. Also, it possessed better prognostic significance, compared with both the CAVI0 and another indicator of arterial stiffness, ankle-brachial PWV [17]. Additionally, the authors of a recent review doubted that CAVI0 was a reliable and sensitive indicator of arterial stiffness independent of blood pressure because it had inconsistency in its formula [18]. Therefore, a fairly strong correlation of the START index with CAVI allows the use of the former in similar clinical situations as the CAVI. The latter is already well studied, albeit mainly in Asian countries.

Table 2. Indicators of volumetric sphygmography (VaSera VS-1000 sphygmomanometer)

Indicators	*(n=353)*
Systolic BP right, mm Hg	129.0 [118.0; 141.0]
Systolic BP left, mm Hg	132.0 [120.0; 144.0]
Diastolic BP right, mm Hg	79.0 [73.0; 86.0]
Diastolic BP left, mm Hg	81.0 [75.0; 88.0]
Pulse pressure – right, mm Hg	49.0 [43.0; 57.0]
Pulse pressure – left, mm Hg	50.0 [42.0; 58.0]
ABI, right	1.13 [1.05; 1.21]
ABI, left	1.1 [1.03; 1.2]
CAVI, right	8.3 [7.6; 9.2]
CAVI, left	8.3 [7.6; 9.2]
START, right	8.3 [7.1; 9.8]
START, left	8.1 [7.0; 9.6]
caPWV, right	7.84 [7.21; 8.51]
caPWV, left	7.82 [7.22; 8.5]
Heart rate, beats per minute	60.0 [54.0; 66.0]

Data are presented as a median and interquartile range (25th-75th percentiles) or a number [%], as indicated. BP, blood pressure; CAVI, cardio-ankle vascular index; START, arterial stiffness index; caPWV, cardio-ankle pulse wave velocity; ABI, ankle-brachial index.

Table 3. Correlation of CAVI and START indices with risk factors

Variable	*CAVI*		*START*	
	r	p	r	p
Age (years)	0.4	<0.001	0.36	<0.001
BMI, (kg/m2)	-0.046	0.414	-0.053	0.347
Current smoking (% of total)	-0.702	0.207	-0.065	0.241
Arterial hypertension (% of total)	0.106	0.056	0.109	0.051
History of myocardial infarction (% of total)	-0.098	0.068	-0.123	0.024
History of stroke (% of total)	0.047	0.395	0.041	0.452
Diabetes mellitus (% of total)	0.103	0.064	0.053	0.347
Total cholesterol (mmol/L)	-0.59	0.29	-0.26	0.643
HDL cholesterol (mmol/L)	0.03	0.604	0.039	0.508
LDL cholesterol (mmol/L)	-0.184	0.758	0.018	0.760
Triglycerides (mmol/L)	-0.810	0.321	-0.054	0.508
Creatinine (µmol/L)	0.113	0.544	0.109	0.55
CKD-EPI GFR	-0.237	0.003	-0.209	0.01

BMI, body mass index; HDL, high-density lipoproteins; LDL, low-density lipoproteins; GFR, glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

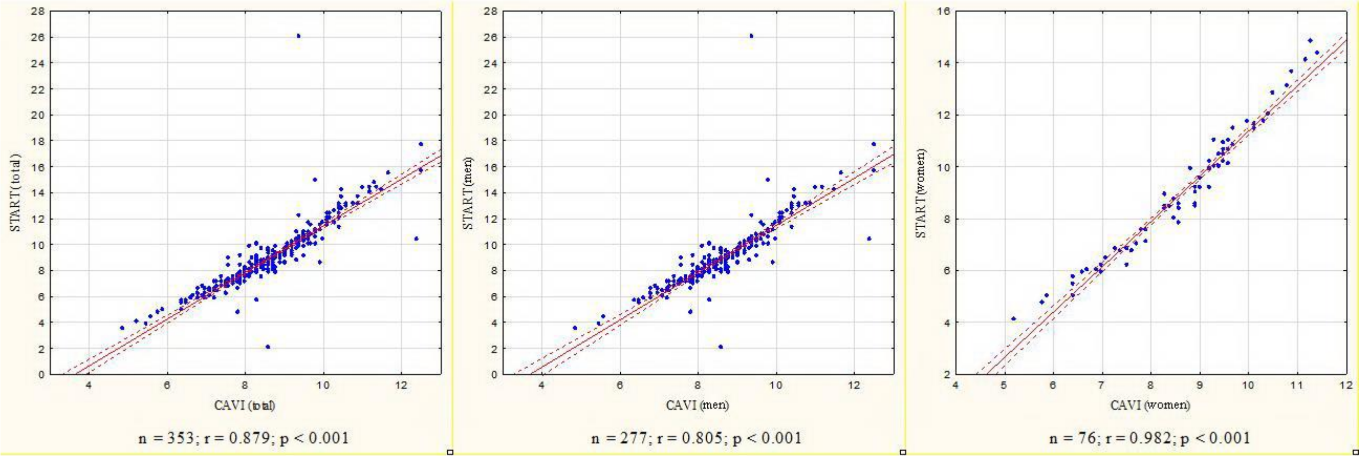

Figure 2. Correlation between CAVI and START in patients with coronary artery disease.

Previously, in healthy individuals, correlation of the START index with age, smoking experience, level of high-density lipoproteins, and GFR was noted. Interestingly, the increase in the START index with age was more pronounced than in the CAVI [12]. Our study did not reveal a clear correlation of the START and CAVI indices with risk factors (except for age). These findings are consistent with the results of studies on CAVI assessment in patients with clinical manifestations of atherosclerosis of a different localization [3].

It should be noted that, despite the high predicted clinical utility of assessing arterial wall stiffness, there is no consensus among experts on the most appropriate indicator for this purpose. Indeed, the proposed indicators differ both in the method of their assessment (PWV, CAVI, START) and in the assessed region of the vascular wall (carotid-femoral [cf], ankle-brachial [ab], cardio-ankle [ca]). For example, along with the cfPWV, the abPWV indicator developed in Japan was recently employed [19]. The latter is easier to register, and it is more convenient for patients. Consequently, it has become widespread in Asian countries [20]. But as later studies showed, the proposed modifications were unable to improve the diagnostic and prognostic value of the CAVI [8].

The developers of the START index proposed using it to assess the condition of various parts of the vascular bed, which corresponds to such indices as saSTART (shoulder-ankle), caSTART (cardio-ankle), cfSTART (carotid-femoral), etc. [11]. How useful this approach will be in the future remains to be seen. For example, the cfSTART index retains some of the disadvantages of the cfPWV index associated with its location of recording. Since the input data for calculating the caSTART index in this study were the same as for the CAVI, it was necessary to compare it first with the CAVI scores. We were able to show a strong correlation between the START indicator (or caSTART according to the developers) and CAVI in patients with CAD.

It is probably too early to talk about the clinical prospects of the START index. Further research is needed, the main directions of which can already be outlined. First of all, of the entire variety of START indices proposed by the developers, the most informative and convenient by definition should be chosen. Then, it is necessary to understand with what tools it can be assessed: whether this will be an analogue of the VaSera device (e.g., in the study by Rico Martin S. et al. [21]), or else an instrument assessing the PWV will be employed. For instance, abSTART, aoSTART, estSTART as indices that correct the effect of blood pressure of a specific type of PWV are promising in the context of study in combination with devices that record PWV in the corresponding sections of the arterial bed. Finally, it will also be necessary to define standards for various versions of the START index.

Such gradation may also allow some systematization of the modern ideas of researchers and practitioners about what type of pulse wave they record with one or another device, whether there are reference population values for different types of PWV, and whether it is logical to use cfPWV reference values for other regions of the vascular bed. Only after this, it is feasible to think about conducting further research on various diseases, as well as preventive examinations and rehabilitation programs. Such likely prospects for assessing vascular stiffness have already been discussed in relation to the CAVI [14]. Perhaps the new START index will allow approaching closer to solving this problem.

A limitation of our study is its retrospective nature, since the START index was calculated in patients with CAD who underwent arterial stiffness testing using the VaSera-1000 sphygmomanometer in order to assess the post-CABG prognostic value of the CAVI [9,10]. Nonetheless, this method is quite common in research: for example, a retrospective assessment of the results of three studies (PROMISE, CONFIRM and J. Reeh et al. [22-24]) can be used to develop a new scale for assessing the pretest probability of obstructive CAD [25].

Conclusion

In patients with coronary artery disease, the START index was strongly associated with the CAVI index throughout the entire cohort, albeit the correlation in women was slightly stronger than in men. In addition, these indices had similar associations with clinical factors and age. The strong association between these indices is important for the subsequent practical application of the START index. The possibility of using it in the same clinical situations as the CAVI index requires confirmation in further studies.

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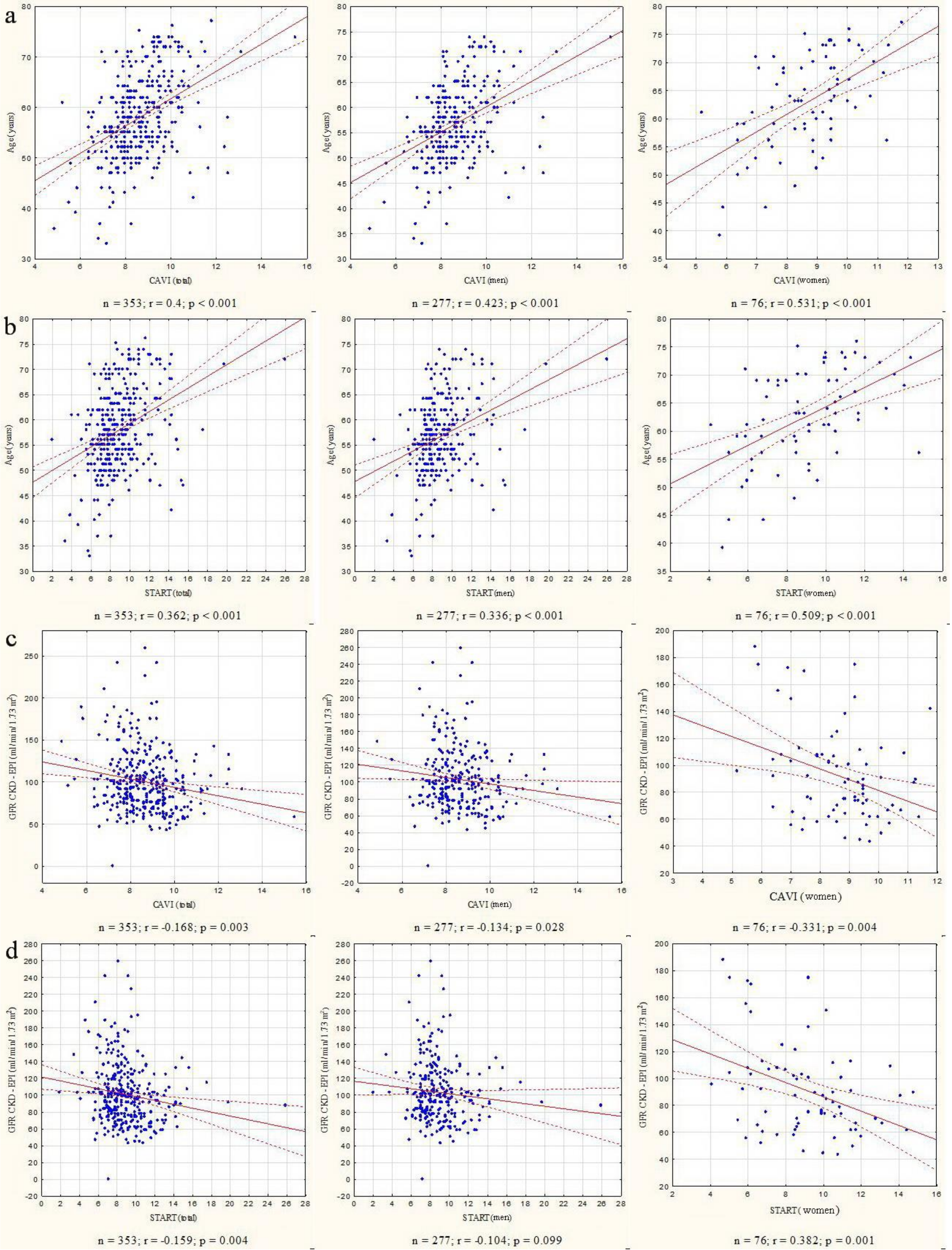

Figure 3. Correlation of CAVI and START with risk factors in patients with coronary artery disease. a – Correlation of CAVI with age; b – Correlation of START with age; c – Correlation of CAVI with CKD-EPI GFR; d – Correlation of START with CKD-EPI GFR.

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Institutional review board statement

The study was conducted in compliance with the guidelines of the Declaration of Helsinki, and was approved by the Ethics Committee of the Research Institute for Complex Problems of Cardiovascular Diseases (Protocol# 20110216).

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare no conflicts of interest. The funders had no role in the design of the study; when collecting, analyzing or interpreting data; when writing a manuscript or when deciding to publish the results.

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