

# A new coronary artery disease grading system correlates with numerous routine parameters that were associated with atherosclerosis: a grading system for coronary artery disease severity

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**Background:** Several scoring systems have tried to determine the severity of coronary artery disease (CAD) to investigate the connection between CAD severity and laboratory parameters.

**Methods:** In total, 189 male (mean age:  $61.86 \pm 10.77$  years) and 75 female CAD patients (mean age:  $67.84 \pm 7.70$  years) were recruited and underwent angiography, which determined stenosis grade, of 17 coronary segments: no points for each nonstenosed segment or only calcified segments, one point for each stenosis from  $<30\%$  to  $<50\%$ , two points for each stenosis from  $50\%$  to  $<70\%$ , and three points for each stenosis  $>70\%$ . The points were added and should represent the severity of patients' CAD.

**Results:** The coronary score correlated positively with systolic blood pressure, creatinine, blood urea nitrogen, lipase, glucose, glycated hemoglobin, triglycerides, C-reactive protein, fibrinogen Clauss, and leukocytes, and correlated negatively with  $\text{Cl}^-$ , iron, and high-density lipoprotein cholesterol. Stepwise multiple regression analysis with backward elimination revealed diabetes status, sex, and fibrinogen Clauss as significant predictors of coronary score.

**Conclusion:** The coronary score delivers a quite simple but very precise tool for the quantification of CAD severity. These results show plainly the connection between CAD severity and the lipid, glucose, coagulation, and immunologic status of CAD patients, and substantiate the importance of sufficient treatment in this group of patients – in particular, CAD patients suffering from type 2 diabetes mellitus. The coronary score would offer a suitable tool for the investigation of the connection between CAD and new biomarkers. Further studies are needed to investigate the correlation of the coronary score with outcome parameters (eg, death).

**Keywords:** coronary artery disease, grading system, angiography, diabetes mellitus, atherosclerosis

## Introduction

For scientists and clinicians who carry out research about the genesis of atherosclerosis, it has always been compelling to somehow quantify the grade of severity of coronary artery calcification and stenosis. Since the late 1960s, the severity of coronary stenosis was suspected to be a prognostic factor for patients with coronary artery disease (CAD),<sup>1–3</sup> and this hypothesis was proven in several clinical studies with long follow-up periods.<sup>4–7</sup> However, the quantification of CAD poses a problem due to the lack of consistent and universally valid scoring systems. For example, in one of their studies, Proudfit et al<sup>3</sup> concentrated on the number of severe stenoses and correlated them to clinical characteristics such as duration of the history of angina pectoris, distribution

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of pain, and serum cholesterol. In another study,<sup>1</sup> they used a more precise system by classifying the coronary vessels as non/slightly/moderately/severely/totally obstructed depending on the grade of obstruction in percental gradations from no to total stenosis, but they concentrated on the major arteries and branches. Parker et al<sup>2</sup> used a similar system. As basis for their quantification, they measured the remaining lumina in the right coronary artery, main left coronary artery and its anterior descending and circumflex branches. However, in case there were multiple lesions in a vessel, they counted the most severe. Humphries et al<sup>5</sup> used a scoring system that included the three major coronary arteries and determined the severity of CAD by measuring “narrowing(s)” in them. Further studies that used coronary scoring systems were performed by Reardon et al,<sup>8</sup> Jenkins et al,<sup>9</sup> Sullivan et al,<sup>10</sup> Brandt et al,<sup>11</sup> Leaman et al,<sup>12</sup> Sianos et al,<sup>13</sup> and Hamsten et al,<sup>14</sup> who all more or less concentrated on the grade of stenosis in different coronary arteries. A work by Neeland et al<sup>15</sup> in 2012 compared ten angiographic scoring systems in about 3,600 patients and found a strong correlation of the systems with each other and with atherosclerotic plaque burden.

All mentioned methods, although some of them are nearly half a century old, are mostly simple and reasonable, and their application provided an enormous increase in knowledge concerning the connection between the severity of CAD and clinical and prognostic correlations. A further method to investigate the genesis of atherosclerosis in CAD is the determination of coronary calcification by means of electron beam computed tomography and multidetector computed tomography. The scoring system used (Agaston Score) has again provided important information about the development of atherosclerosis.<sup>16,17</sup>

In the present explorative study, we investigated the connection between a new score grading severity of stenosis (“coronary score”) determining the severity of CAD in 17 segments and anamnestic and clinical circumstances, as well as routine laboratory parameters in patients with CAD.

## Materials and methods

In total, 189 male (mean age:  $61.86 \pm 10.77$  years) and 75 female (mean age:  $67.84 \pm 7.70$  years) CAD patients were recruited, whereby 45.3% had never had an ischemic cardiac event before and 54.7% had had at least one ischemic event (ST-segment elevation myocardial infarction [STEMI], non-ST-segment elevation myocardial infarction [NSTEMI], or acute coronary syndrome [ACS]) before. Patients with

thrombotic occlusions were excluded from the study. They underwent a coronary angiography for diagnostic and/or therapeutic reasons on grounds of their underlying disease. The coronary artery system was divided into 17 segments, and stenosis grade for each segment was measured. The coronary arteries were divided into the following 17 segments – left main, proximal/medial/distal left anterior descending, intermediate branch, first and second marginal branch, posterolateral branch, first and second diagonal branch, proximal/medial/distal left circumflex, proximal/medial/distal right coronary artery, and ramus interventricularis posterior – and stenosis grade for each segment was measured. A simple three-point grading per stenosis was used to develop a score considering both frequency and severity of CAD stenoses: no points for each nonstenosed segment or only calcified segments, one point for each stenosis from  $<30\%$  to  $<50\%$ , two points for each stenosis from  $50\%$  to  $<70\%$ , and three points for each stenosis  $>70\%$ . The points were added over all stenoses per patient and should represent the severity of patients’ CAD (score).

Anthropometric and anamnestic data, including age, body mass index (BMI), systolic and diastolic blood pressure, heart rate, risk factor assessment (type 2 diabetes mellitus [T2DM] status, hypertension, hypercholesterolemia, family history, smoking, physical activity), and routine laboratory parameters were gathered. Blood samples for determination of routine laboratory parameters were taken before or at least 48 hours after invasive therapies/acute events (eg, angiography/STEMI, NSTEMI) to avoid a strong distortion. Statistical analysis was done with SPSS 20.0 (IBM Corporation, Armonk, NY, USA). Continuous and normally distributed data are described by mean  $\pm$  standard deviation. Ordinal data or continuous data with skew distribution or outliers are described by median and first and third quartiles. Simple associations of the coronary score with continuous variables were assessed by Spearman’s correlation coefficient, and point biserial correlation coefficients were calculated for dichotomous variables. Those variables that correlated significantly with the coronary score were then entered in a stepwise multiple regression analysis with backward elimination to assess the variables that predict the coronary score best. Simple tests were performed two-sided, and  $P$ -values  $\leq 0.05$  were considered significant. To adjust for multiple testing, only parameters correlating with  $P < 0.01$  were used for the multiple regression analysis. The study protocol, which is in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, was approved by the Ethical Commission of the

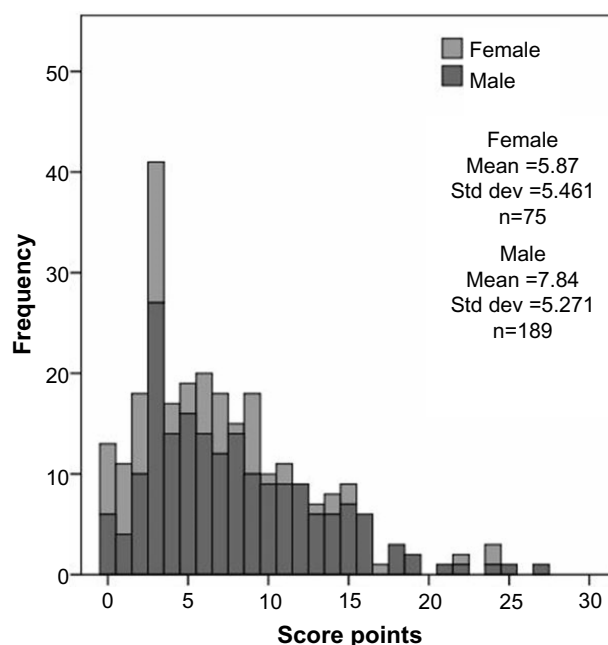
Medical University of Vienna, Vienna, Austria, and informed consent was obtained from patients.

## Results

The present study aimed to investigate the connection between the severity of CAD determined by the coronary score (as described in the “Materials and methods” section) and routine laboratory parameters, as well as CAD risk factors such as T2DM or physical activity in 264 CAD patients. The distribution of score points is shown in Figure 1. Table 1 shows anthropometric and hemodynamic data of the population, and Table 2 shows median levels (first and third quartile) of routine laboratory parameters, correlation coefficient (Spearman’s correlation), and *P*-value of the correlation with the coronary score.

The score points correlated positively with systolic blood pressure ( $P=0.018$ ), creatinine, blood urea nitrogen (BUN), lipase, glucose, glycated hemoglobin ( $HbA_{1c}$ ), triglycerides (TGs), C-reactive protein (CRP), fibrinogen Clauss, and leukocytes, and correlated negatively with  $Cl^-$ , iron, and high-density lipoprotein (HDL) cholesterol.

The score points independent of CAD risk factors are shown in Table 3. The coronary score correlated significantly only with sex ( $P<0.01$ ) and T2DM status ( $P<0.01$ ). There was no difference between T2DM with and without insulin therapy and patients without T2DM. Consequently, sex, T2DM status (yes/no), creatinine,  $HbA_{1c}$ , HDL cholesterol,



**Figure 1** Distribution of the score points within the study population.  
**Abbreviation:** Std dev, standard deviation.

**Table 1** Anthropometric and hemodynamic data and score points within the population

Age (years)	63.55±10.34
Height (cm)	171.78±9.34
Weight (kg)	83.41±18.57
Body mass index (kg/m <sup>2</sup> )	28.14±5.26
Systolic blood pressure (mmHg)	130.56±16.24
Diastolic blood pressure (mmHg)	76.02±10.95
Heart rate (bpm)	70.02±13.35
Score points	7.28 (3.00–10.00)

**Note:** Data are given as mean ± standard deviation or median (first and third quartile), respectively.

TGs, and fibrinogen Clauss were used for multiple regression analysis. As can be seen in Table 4, only T2DM, sex, and fibrinogen Clauss were significant but moderate predictors of the coronary score ( $r^2_{adj}=0.14$ ;  $F=13.59$ ;  $P<0.01$ ). The presence or absence of the other risk factors (BMI, hypertension/statin therapy, ex-smoking status, positive family anamnesis, physical inactivity) did not have a significant impact on the height of the coronary score.

## Discussion

It was the aim of the present study to test the connection between the severity of CAD represented by the coronary score, which is described in the “Materials and methods” section, and routine laboratory parameters, as well as cardiovascular risk factors. Considering data of 264 female and male CAD patients, this score showed a significant positive correlation with creatinine, BUN, lipase, glucose,  $HbA_{1c}$ , TGs, CRP, fibrinogen Clauss, and leukocytes, and a negative correlation with  $Cl^-$ , iron, and HDL cholesterol. The major part of the aforementioned factors has already been connected to CAD. It was shown that ferritin and transferring saturation levels were not associated with an increased extent of CAD.<sup>18</sup> Our results confirm these findings, but we found a negative correlation between iron and CAD severity. Serum creatinine was shown to be an independent predictor of coronary heart disease mortality in normotensive and normal-weighted survivors of a myocardial infarction but with pre-existing renal disease or heart failure.<sup>19</sup> In patients with chest pain undergoing angiography, creatinine correlated with the extent of CAD.<sup>20</sup> Consequently, the tested score seems to confirm data from other study groups concerning creatinine.

Concerning BUN, Kirtane et al<sup>21</sup> showed that it is associated with an increased mortality in patients with unstable coronary syndromes, and Saygitov et al<sup>22</sup> even found BUN to be a more significant risk factor for ACS outcome compared with creatinine. However, available literature is rare.

**Table 2** Routine laboratory parameters within the study population

	Median (first and third quartiles)	Correlation coefficient	P-value
Na <sup>+</sup> (mmol/L)	139 (137–141)	−0.090	0.144
K <sup>+</sup> (mmol/L)	4.07 (3.80–4.30)	0.043	0.486
Cl <sup>−</sup> (mmol/L)	104 (102–106)	−0.143	0.020
Ca <sup>++</sup> (mmol/L)	2.39 (2.28–2.47)	−0.012	0.853
Mg <sup>++</sup> (mmol/L)	0.85 (0.79–0.90)	−0.031	0.618
Inorganic phosphate (mmol/L)	0.98 (0.86–1.11)	0.070	0.257
Iron (μg/dL)	65 (44–90)	−0.138	0.044
Creatinine (mg/dL)	1.02 (0.89–1.19)	0.189	0.002
Blood urea nitrogen (mg/dL)	17.30 (13.40–23.20)	0.156	0.011
Uric acid (mg/dL)	6.30 (5.15–7.60)	0.113	0.071
Alkaline phosphatase (kU/L)	76 (61–94)	−0.004	0.950
ASAT (GOT, U/L)	30 (24–45)	−0.032	0.604
ALAT (GPT, U/L)	29 (20–43)	−0.032	0.609
Gamma-GT (U/L)	36 (23–63)	0.038	0.543
LDH (U/L)	231 (194–313)	−0.005	0.933
Alpha-amylase (U/L)	58 (42–73)	0.098	0.115
Lipase (U/L)	27 (18–40)	0.135	0.030
Cholinesterase (U/L)	7.49–8.61	0.027	0.665
Glucose (mg/dL)	107 (93–133)	0.138	0.026
Glycated hemoglobin (relative%)	6.0 (5.5–6.5)	0.224	0.001
Cholesterol (mg/dL)	168 (140–202)	−0.105	0.091
High-density lipoprotein cholesterol (mg/dL)	44 (37–54)	−0.208	0.002
Low-density lipoprotein cholesterol (mg/dL)	99 (74–126)	−0.092	0.177
Triglycerides (mg/dL)	130 (95–199)	0.176	0.005
TSH (μU/mL)	1.65 (0.97–2.49)	−0.008	0.905
C-reactive protein (mg/dL)	0.48 (0.15–1.66)	0.142	0.023
Transferrin (mg/dL)	250 (221–291)	0.142	0.531
Ferritin (μg/L)	131 (61–216)	−0.075	0.234
Combined prothrombin time (%)	101 (85–116)	0.140	0.712
aPTT (sec)	34.2 (31.6–37.8)	0.024	0.880
Fibrinogen Clauss (mg/dL)	395 (340–478)	0.252	<0.001
Erythrocytes (Terra/liter)	4.5 (4.2–4.9)	0.028	0.657
Hemoglobin (g/dL)	13.3 (12.0–14.4)	−0.058	0.353
Hematocrit (%)	39.9 (36.2–42.7)	−0.059	0.347
Thrombocytes (Giga/liter)	7.17 (5.95–8.80)	0.011	0.859

**Note:** Data are given as median (first and third quartiles), correlation coefficient of Spearman correlation, and P-value.

**Abbreviations:** LDH, lactate dehydrogenase; TSH, thyroid-stimulating hormone; GOT, glutamic oxaloacetic transaminase; ASAT, aspartate aminotransferases; aPTT, activated partial thromboplastin time.

A correlation of BUN with severity of CAD has never been shown before, and the same holds true for lipase.

To the contrary, much is known about glucose metabolism and CAD. Results from the Framingham Heart Study (>1,045 people)<sup>23</sup> showed a significant association between coronary heart disease, stroke, and ischemic attack with HbA<sub>1c</sub> in women but not in men. These findings were consistent with results of former analysis of the Framingham Heart Study population<sup>24,25</sup> indicating a stronger influence of diabetes and hyperglycemia on women compared with men. However, a recently published study by Pai et al<sup>26</sup> using data from the Nurses' Health Study and the Health Professionals Follow-Up Study, including 468 women and

454 men, suggested an association of HbA<sub>1c</sub> and coronary heart disease risk in apparently healthy nondiabetic men and women. A systematic search by Liu et al<sup>27</sup> found HbA<sub>1c</sub> to be an independent risk factor for mortality in CAD patients without diabetes but not with established diabetes. However, another study showed that diabetes – in particular, in combination with albuminuria – is a powerful risk factor of CAD,<sup>28</sup> and HbA<sub>1c</sub> was also correlated with severity of CAD,<sup>29</sup> which can be confirmed by our results, because both HbA<sub>1c</sub> and blood glucose correlated positively with the coronary score. Within our study group, the 191 CAD patients who did not suffer from T2DM had a median coronary score of 5 compared with the CAD patient suffering from DM who had a

**Table 3** Coronary score (points) dependent on cardiovascular risk factors

Type 2 diabetes mellitus	
No diabetes (n=191)	5 (3–9)
Type 2 diabetes mellitus (n=73)	9 (3–13.5)
Sex	
Male	7 (3.5–11)
Female	4 (2–9)
Physical inactivity	
No (n=183)	6 (3–9)
Yes (n=81)	7 (3–12.50)
Smoking	
Never smoking (n=99)	7 (3–11)
Ex-smoking (n=165)	6 (3–10)
Hypertension therapy	
No (n=20)	5 (3–10)
Yes (n=264)	6 (3–10)
Statin therapy	
No (n=24)	4 (3–11.75)
Yes (n=264)	6 (3–10)
Coronary artery disease family anamnesis	
No (n=116)	7 (3–11.75)
Yes (n=148)	6 (3–9)
Body mass index <24.99 kg/m <sup>2</sup> (n=78)	5 (2.75–9)
Body mass index 25.00–29.99 kg/m <sup>2</sup> (n=107)	6 (3–10)
Body mass index >30.00 kg/m <sup>2</sup> (n=79)	6 (3–12)

score of 9. These results show plainly worse coronary status in diabetic CAD patients.

Apart from glucose metabolism, lipid metabolism plays a distractive role in the genesis of coronary atherosclerosis. TGs were shown to be a clinical marker of CAD to a greater extent in hypertensive patients<sup>30</sup> and postmenopausal women;<sup>31</sup> however, in the last mentioned study, patients were divided into only three groups (nonobstructive, one vessel stenosis, or multivessel stenosis), which is a quite common but also vague method of CAD severity quantification. A recently published study<sup>32</sup> in which patients were again divided into three groups (single branch/double branch/multiple branch stenosis) showed that the TG/HDL cholesterol ratio is predictive for the severity of CHD. The connection between lipid profile and CAD severity was also observed and published for a Chinese population using a

four-step grading system of CAD severity (single/double/triple/multiple vessel stenosis).<sup>33</sup>

Contrary to TGs, high HDL cholesterol levels have a protective effect on the cardiovascular system. A large study including about 5,600 individuals showed that those without CAD had higher levels of HDL cholesterol compared with those with CAD.<sup>34</sup> Low levels of HDL cholesterol were shown to predict CHD mortality and the occurrence of new CHD events in persons aged >70 years. Interestingly, in the course of the same study, total cholesterol was not associated with CHD mortality in elderly men but was suggested as a CHD risk factor for elderly women.<sup>35</sup> Concerning the present study, the CAD severity correlated positively with TGs and the TG/HDL cholesterol ratio (but not with total or low-density lipoprotein [LDL] cholesterol) and negatively with HDL cholesterol. Regarding our results and the results of the aforementioned studies, TG and HDL levels seem to be of greater relevance for the genesis of coronary artery stenosis compared with total or LDL cholesterol.

Serum fibrinogen was shown in the course of the Scottish Health Study to be a predictor for fatal and nonfatal CAD in both middle-aged women and men,<sup>36</sup> and similar results were received for plasma levels of fibrinogen<sup>37</sup> whereby in the aforementioned study plasma levels of fibrinogen were shown to correlate with CAD severity (using a four-step grading system). Using the more precise coronary score of our study, we can confirm these results because serum fibrinogen levels correlated significantly with the score in both female and male patients.

Concerning the connection between the immunologic system and CAD severity, the parameters CRP and leukocytes are of special interest. Individuals without CAD show significantly lower levels of CRP compared with CAD patients.<sup>34</sup> A study by Auer et al<sup>38</sup> including 100 individuals (about 60 CAD patients) suggested an association of CRP with the presence but not with the severity of CAD (using a quite precise zero- to three-point grading system). However, a study by Liu et al<sup>39</sup> (including 418 patients with LDL cholesterol <3.37 mmol/L) and also our study, which included 264 CAD patients, found a significant correlation between CAD severity and CRP levels. Similar to CRP, the white blood cell count has earlier been associated with an increased risk for, and progression of, CHD, with a shorter survival time in CAD patients<sup>40</sup> and also with the extent of CAD severity,<sup>41</sup> which can be confirmed by our results and shows the importance of the immunological system in CAD. On the one hand, this score delivers interesting information on the connection between the severity of CAD and several routine laboratory parameters. On the other hand, further

**Table 4** Results from stepwise multiple regression analysis with backward elimination

	Beta	T	P-value	Change in r <sup>2</sup>
Constant	-2.11	-1.17	0.243	
Type 2 diabetes mellitus (0= no; 1= yes)	2.64	3.61	<0.01	0.06
Fibrinogen Clauss	0.01	3.63	<0.01	0.04
Sex (1= female; 2= male)	2.62	3.60	<0.01	0.05

studies (eg, in younger and elderly groups of CAD patients) should be performed to obtain further results.

A limiting factor was that some routine laboratory parameters such as CRP and glucose are influenced by numerous factors and circumstances. Although we tried to avoid strong distortions (eg, from invasive examinations such as the angiography) by taking blood samples with distance to invasive events, an influence of noncontrolled factors cannot be excluded. We included patients with chronic CAD (n=144) and patients who had just suffered their first event (n=120), which might have led to distortions because chronic CAD patients had already received stents in former times; however, most of the correlation was also present when analyzing just the patients who had never had a CAD event.

The coronary score delivers quite a simple tool for the quantification of CAD severity. In 264 CAD patients, the severity of CAD quantified by this score correlated positively with creatinine, BUN, lipase, glucose, HbA<sub>1c</sub>, TGs, TG/HDL cholesterol ratio, CRP, fibrinogen Clauss, and leukocytes, and correlated negatively with Cl<sup>-</sup>, iron, and HDL cholesterol. The results show plainly the connection between CAD severity and the lipid, glucose, coagulation, and immunologic status of CAD patients, and substantiate the importance of sufficient treatment in this group of patients – in particular, CAD patients suffering from T2DM. Furthermore, the coronary score would offer a suitable tool for the investigation of the connection between CAD and new biomarkers. Further studies are needed to investigate its correlation with clinical outcome parameters (eg, death).

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## Disclosure

The authors report no conflicts of interest in this work.

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