# GENDER DIFFERENCES AND PREDICTORS OF INCREASED CORONARY CALCIUM SCORE AND MYOCARDIAL ISCHEMIA IN DIABETES TYPE 2 PATIENTS

Mitevska Irena<sup>1</sup>, Zdravkovska M<sup>2</sup>, Stoilovska B<sup>2</sup>, Manevska N<sup>2</sup>, Mileva M<sup>2</sup>, Vavlukis M<sup>1</sup> <sup>1</sup>University Cardiology Clinic, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, R. of North Macedonia

<sup>2</sup>Institute for Pathophysiology and Nuclear Medicine, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, R. of North Macedonia

# Abstract

We wanted to assess prevalence, predictors and gender difference of coronary calcium score (CCS) and myocardial ischemia in diabetes type 2 patients.

We have evaluated 145 patients (58 male and 87 females, age 63+/-9), who underwent singlephoton emission computed tomography myocardial perfusion imaging computer tomography (SPECT/CT) for assessment of myocardial ischemia and coronary atherosclerosis burden. Forward logistic regression analysis was used to assess predictive parameters for myocardial ischemia and increased CAC.

Gender differences between myocardial perfusion and CCS findings were analyzed. SPECT results were normal in 102 patients (70%). Mild ischemia was noted in 16 patients (37%), moderate ischemia in 9 patients (20%), severe ischemia in 10 patients (23%), and fixed defects in 8 patients (18%). CCS >0 Agatston Units (AU) was found in 69 patients (62.7%), with average CAC 198+/-45 in male and 98+/33AU in female patients. 24 patients (34%) had moderate CCS (100–399 AU) and 19 patients (27.5%) had severe CCS (401–1000 AU). Multivariate regression analysis showed independent predictors for CCS (>0AU) age ( $\geq$ 65 years) (odds ratio (OR): 1.074, *p* = 0.028), smoking (OR: 1.81, *p* = 0.048) and male gender (OR: 1.43, *p* = 0.051).

We found stress-induced ECG changes, CCS>400AU and diabetes type 2 over 10 years to be independent predictors of myocardial ischemia in the model that included CCS.

CCS was increased predominantly in male and myocardial ischemia was more prevalent in female patients. SPECT/CT imaging enable assessment of anatomic and functional aspects of CAD and optimize treatment in diabetes type 2 patients.

*Keywords*: Myocardial perfusion imaging, coronary calcium score, type 2 diabetes, coronary artery disease

## Introduction

Diabetes mellitus is one of major health care problem with significantly increased prevalence. Cardiovascular complications are the leading cause of mortality in these patients. Vascular wall damage starts in the early stage of disease, with longer asymptomatic period. Although diabetes type 2 patients have high CV risk, certain heterogeneity of risk is reported even in this patient's population depending of the target organ damage and presence of coronary and extracoronary atherosclerosis [1].

Early identification of patients with diabetes and coronaryartery disease (CAD) is very important for intensive treatment, which may affect otherwise poor prognosis. There is increased interest in the use of coronary artery calcium (CCS) imaging to assess early subclinical atherosclerosis and total atherosclerosis burden in patients with intermediate cardiovascular risk, but also as prognostic parameter in diabetic patients[2].

Several scientific data have reported significant gender differences in the incidence and progression of atherosclerosis and myocardial ischemia. Gender differences in the symptoms, diagnosis, and prognosis of cardiovascular disease are present and lead to delayed CAD diagnosis in female population (3,4). In fact, while often neglected, cardiovascular disease are the leading cause of death in women, far beyond cancer and infectious causes.

Although diabetes type 2 is considered CAD equivalent, there have been dilemmas on the clinical significance of the information's obtained from coronary calcium score (CCS) as a marker of coronary atherosclerosis [4]. CCS results could lead to change of intensity of statin therapy and individual patient risk assessment. From other side detection of CAD in patients with diabetes is often challenging, because CAD is often without symptoms. In the DIAD Study, the overall prevalence of silentmyocardial ischemia according to single-photon emissioncomputed tomography (SPECT) was 22% [5].

Hybrid SPECT/CT imaging technique enable assessment of physiological and anatomical aspects of coronary artery disease. However, the debate still persist wether assessment of CCS will change patient's prognosis in the era of intensive medical treatment. ISCHEMIA trial showed that there was no significant prognostic differences in the invasive management of patients with moderate and severe ischemia comparing to optimal medical therapy even in diabetic patients [6].

The retrospective observational study was designed to evaluate the prevalence and gender differences of coronary atheroscleros is and myocardial ischemia and their interrelationship in the are of modern intensive medical therapy.

#### Methods

### Study design and data source

The study is an observational cohort study which included 145 consecutive patients with type 2 diabetes (58 male,87 female; age range: 63  $\pm$  9 years), without previously known or established CAD. Physical examination and clinical symptoms were evaluated in all patients. Chest pain was assessed based on Diamond and Forested classification. Screening for myocardial ischaemia and coronary calcifications was performed using myocardial SPECT/CT imaging.CCS scores wereperformed and data evaluated using Agatston units (AU).Distribution fstudy subjects is presented in Figure 1.

All patients underwent a physical examination and included blood pressure measurements, weight, height, body mass index (BMI) and risk factoranalysis. Full blood examination with high-densitylipoprotein (HDL), low-density lipoprotein (LDL), non-HDL and triglyceride levels, fasting glucose levels, % glycated haemoglobin (HbA1c) and blood creatinine levels were performed within a maximum of 4 weeks prior toMPI.

Medical history was evaluated and corrected according to target risk factor goals based on latest EuropeanSociety of Cardiology (ESC) recommendations for cardiovascular prevention, and diabetes and heart disease. Clinical and laboratory data are shownin Table 1.

The following **inclusion criteria** were used:patients with type 2 diabetes, not known od established previous CAD. **Exclusion criteria** were as follows: typical stableangina pectoris, previously known or established CAD (history of myocardial infarction, acute coronary syndromes (ACS), previous percutaneous intervention or coronaryartery bypass surgery), LVEF <50% at rest, severevalvular disease, atrial fibrillation, left bundle branchblock, presence of pace maker and severe chronic pulmonarydisease.

#### Definition of study variables

Risk factor definitions were made according to the mostrecent ESC guidelines on dyslipidemia and diabetes and heart disease: arterial hypertension (systolic blood pressure (SBP) >140 bpm or diastolicblood pressure >90 bpm], dyslipidaemia (LDL >1.4 mmol/L in very high risk patients, >1,8mmol/l in high risk patients; HDL <1.1 and 1.0 mmol/L for females andmales, respectively, and triglycerides >1.7 mmol/L), familyhistory of myocardial infarction or sudden cardiacdeath in an immediate male relative <55 years or female<65 years and smoker (current smoker or those who quitin the past 6 months). BMI  $\geq$ 30 kg/m2 was used to defineobese patients. Type 2 diabetes mellitus was defined asestablished disease in patients treated with oral anti-diabetic medication or insulin following initial treatment withoral anti-diabetic therapy. Newly diagnosed diabetes was defined as having either one of the following criteria, based on the ESC guidelines on pre-diabetes and diabetes: fasting glucose of 7.0 mmol/L or non-fasting glucose 11.0 mmol/L in two separate samples, HbA1c >6.5% or pathologicoral glucose tolerance test in patients with fastingglucose over 6.5 without previously known or treated diabetes.

## Myocardial perfusion SPECT imaging

MPI SPECT/CT imaging was performed using 1-day reststress protocol with radiotracer technetium (Tc-99m) sestamibi, using 15 mCi for the rest and 25 mCi for the stressstudy. We used dual head gamma camera Siemens Symbia Truepoint SPECT/CT. Patientswere instructed to refrain from caffeine-containing beverages for at least 12 h, nitrates for 24 h and beta-blockers for 48 h before the study. All patients underwent pharmacological stressing with dipyridamole. We used the 17-segment model for quantitative Bull's eye analysis of regional perfusion and function. Myocardial perfusionwas assessed by 5-point score system (0: normal radiotraceruptake; 1: mild; 2: moderate; 3: severe hypo perfusion;4: absent uptake).

Semi-quantitative analysis of regional perfusion at rest and stress was performed using summed stress score (SSS), summed rest score (SRS) and summed differential score (SDS), aimed to assess the presence and extent of myocardial ischemia. Scan abnormalities were defined as follows: SSS <4 normal perfusion,4–8 mild, 9–13 moderate and >13 severely abnormalscan; SDS <6 mild (<10% of left ventricle (LV), SDS7–10 moderate (10%–15% of LV) and SDS >10 severe ischemia (>15% of LV). Fixed defects were defined asSRS >4. Any perfusion abnormality was defined as SDS>4 and/or SRS >4. LV volumes, LVEF at rest and stress, presence of transit ischemic LV dilation (TID), visualization of right ventricle and lung uptake were also analyzed. Regional wall motion analysis was assessed by a 6-pointscoring system at rest and stress (0: normal wall motion; 1:mild; 2: moderate; 3: severe hypokinesia; 4: akinesia; 5:dyskinesia) using wall motion score index.

Results considered normal were those that showed ahomogeneous distribution of the radiotracer throughoutthe LV myocardium at the stress and rest images with normal systolic movement and thickening and preserved LV function. The fixedperfusion defects, present in both images and with a segmental contractile deficit and systolic thickening were interpreted as fibrosis. Transient perfusion defects, presentat the stress phase and absent at the resting phase, withnormal range of movement and thickening, were considered to be ischemia. When the recovery of these defectswas only partial, with a contractile deficit, it configured the simultaneous existence of fibrosis and ischemia.

#### Coronary calcium score (CCS) imaging

For CCS imaging, a non-enhanced, prospectively ECG gated scan was obtained after the rest MPI study by the use of SPECT/CT camera described in the previous section. The estimated effective radiation dose for this protocolwas bellow 1 mSv. Image reconstruction was performed at55% of the R-R interval with prospective gating usage. The total calcium burden in the coronary arteries wasmeasured according to the scoring algorithm of Agatston. On the basis of the total calcium score expressed in AU, patients were placed into five categories, as previouslyreported: CCS 0 (no evidence of atherosclerosis), 1–10AU (minimal or insignificant CCS), 11–100 (mild CCS), 101–400 (moderate CCS) and 401–1000 (severe CCS. Total CCS score and CAC score in each coronary arterywas evaluated. The average heart rate during the study was 72±9 bpm.

#### Medical therapy and lifestyle advice

Medical therapy was reviewed in in all patients. Therapy was additionally corrected after SPECT/CT results. All patients received recommendations for lifestyle andrisk factor control. Therapeutic targets were based on the latestESC guidelines for cardiovascular prevention and diabetes and heart disease.

### Statistical analysis

Statistical analysis was performed with the use of the SPSSstatistical package (version 18.0). Categorical variableswere compared using chi-square test and continuous variablesusing unpaired Student's *t* test. Normality of variablesdistribution was performed. Categorical values wereexpressed in percentages, continued as mean value ±standard deviation (SD). Linear regression analysis wasused to determine whether there was a correlation betweenthe CCS score and perfusion abnormalities on SPECT. Multivariate forward stepwise logistic regression analysiswas built in order to identify factors associated independently with the presence of myocardial ischemia. The analysis includes age, gender hypertension, hyperlipidaemia, smoking, obesity, diabetesduration, myocardial perfusion imaging (MPS) perfusionscores, ECG ST segment depression during pharmacologicalstress and CCS. The criterion for entrance into themodel was a univariate probability value of p < 0.05 and p > 0.10 for removal from the model. p < 0.05 was considered to be statistically significant for all statistical tests.

## Results

Mean age of patients was  $63\pm$ -9 years. 82 patients were male (56.5%) and 63 female patients (43.4%). Demographic characteristics, risk factors and medical therapy are presented in Table 1. All patients had on average two risk factors. The risk factors for the cardiovascular disease were distributed as follows: 79.0% of systemic arterial hypertension, 53.2% of dyslipidemia, 12.4% of cigarette-smoking, 13.0% with obesity and 41.3% of family history for CAD. Average duration of diabetes was  $6 \pm 5$  years. A total of 49 patients (34%) used insulin therapy. Chest pain in the form of stable angina was found in 45 patients, chest pain of non cardiac origin was present in 23 patients and 77 patients were asymptomatic.

#### *Myocardial SPECT findings*

One day rest/stress SPECT/CT study was performed in all patients using dipyridamole pharmacological stress. A total of 2465 segments were analyzed. 112 patients showed normal rest left ventricular function with EF > 50.0% and 33 patients had mildly reduced LV function (LVEF 40-49%) assessed by gated SPECT. A total of 102 patients (73.4%) had normal MPI results. The scintigraphy results were abnormal in 43 patients (29.6%). Stress-inducible ischemia was found in 35 patients (24.1%). Ischemia and fixed perfusion defects were found in 5 patients and fixed defects only in 3 patients. Mild ischemia was found in 16 patients – summed difference score (SDS) < 4, moderate ischemia (SDS 7–10) in 9 and severe ischemia (SDS > 10) in 10 patients (Figures 2 and 3). Patients with severe ischemia had a drop of LVEF during stress study by >5.0% and TID. There was a correlation with hypertension and smoking with the presence of myocardial ischemia (r = 0.52 and r = 0.59, respectively).

Table 1. Clinical characteristics of the patients

Variables	Patients n=145					
Age	65+/-9					
Gender	58m; 87 f					
Chest pain	45					
Hypertension	113 (78%)					
Hyperlipidemia	74 (51%)					
Obesity	26 (18%)					
HbA1C %	7.9+/-0.6					
Ejection fraction (%)	61+/-10%					
Fam history CAD	46 (32%)					
Active smoker	16 (11%)					
HDL (mmol/l)	0.8+/-0.4					
LDL (mmol/l)	3.6+/-0.7					
TGL (mmol/l)	2.4+/-0.6					
Non-HDL						
Mean risk factors per patient	2+/-1					

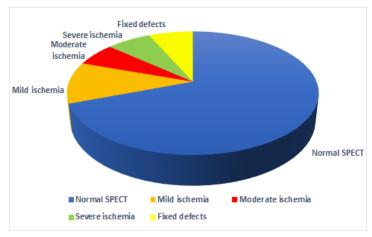


Figure 1. Myocardial SPECT results

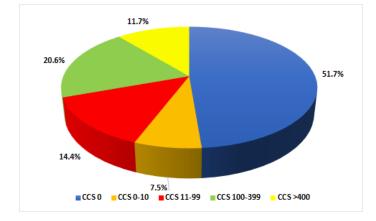


Figure 2. Coronary calcium score values and distribution

Table 2. Gender characteristics of myocardial SPECT and coronary calcium score results

	Male patients (n=82)	Female patients (n=63)	p values
Normal SPECT	44	58	< 0.0013
Mild ischemia	6	10	< 0.0011
Moderate ischemia	5	4	< 0.052
Severe ischemia	6	4	< 0.041
Average CCS	198+/-45	98+/-33	< 0.0017
CCS LMN	211+/-33	151+/-36	< 0.0023
CCS LAD	239+/-51	159+/-39	< 0.0010
CCS LCx	143+/-22	89+/-25	< 0.0036
CCS RCA	165+/-42	67+/-21	< 0.0014

CAC- Coronary calcium score, LMN-left main disease, LAD-left anterior coronary artery disease; LCx- circumphex coronary artery disease, RCA- right coronary artery disease

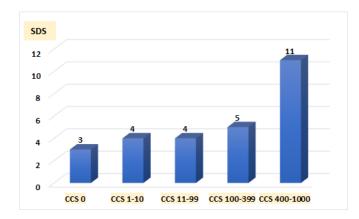


Figure 3 Coronary calcium score severity and corresponding SPECT summed differential score (SDS) values

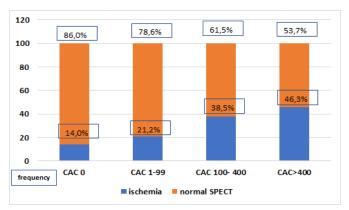


Figure 4. Bar graph illustrating the frequency of ischemic MPI by CAC score

#### Predictors of myocardial ischemia

Stepwise forward logistic regression analysis for prediction of ischemia in the model that included CCS showed OR 2.145 (95% CI: 1.105-4,512) for stress-induced ECG changes, OR 1.893 for CCS > 400 (95% CI: 0.932-3.241) and OR 2.911 for the presence of type 2 diabetes over 10 years (95% CI: 1.396-4.641). The second regression model which did not include CCS showed OR 2.421 (95% CI: 1.105-4.762) for male gender, OR 2.610 for non HDL cholesterol (95% CI: 0.941-5.241), shown in table 3.

	В	S.E.	Wald	df	Sign	OR	95% CI	
Model 1								
Stress ECG changes	1,242	0,561	4,729	1	0,000	2,145	1,105	4,512
CCS>400	1,058	0,428	5,831	1	0,001	1.893	0,932	3,241
DM >10y	1,62	1,564	7,497	1	0,002	2,911	1,396	4,641
Model 2.								
Male gender	1,352	0,961	5,139		0,000	2,421	1,105	4,762
Non-HDL cholesterol	1,081	0,648	5,431	1	0,001	2,610	0,941	5,241

Table 3 Multivariate Stepwise logistic regression analysis for predictors of stress induced ischemia

Abbreviations: HLP- hyperlipidemia; DM, type-2 diabetes mellitus; CAC, coronary calcium score *Coronary calcium score findings* 

CCS score was assessed in total 435 coronary arteries.CCS>0 was present in 69 patients (62.7%). 5 patients had CCS score1–10 AU, 21 patients had mild CAC score (11–99 AU), 24patients had moderate CCS (100–399 AU) and 19 patientshad severe CCS (401–1000 AU). No patients had extensive CCS > 1000 AU. Calcium was present in the left anteriordescending coronary artery (LAD) in 38 patients, in the leftcircumflex artery (LCX) in 18 patients and right coronaryartery (RCA) in 13 patients. The average calcium score was significantly higher in the LAD vascular region (211 ± 52) comparing to LCX region (112 ± 42) and in the RCA (135 ± 78).

Patients with moderate and severe ischemia had CCS score  $459 \pm 123$  AU. Patients with normal MPI scan had an average CCS score of  $45 \pm 34$ AU.

Independent predictors increased CCS (>0AU) were age ( $\geq 65$  years)(odds ratio (OR): 1.074, 95.0% confidence interval (CI):1.006–3.829, p = 0.000), smoking (OR: 1.812, 95% CI: 0.984–4.226, p = 0.000)

and male gender (OR: 1.43, 95% CI: 1.117–2.981, p = 0.003) in multivariate forward logistic regressionanalysis (table 4).

	В	S.E.	Wald	df	Sign	OR	95%	CI
Age >65	1,965	0,231	4,190	1	0,000	1,074	1,006	3,829
Smoking	1,052	0,478	5,769	1	0,000	1,812	0,984	4,226
Male	1,483	1,698	7,613	1	0,003	1,43	1,117	2.981

Table 4. Multivariate Stepwise logistic regression analysis for predictors of CAC >0AU

Abbreviations: DM, type-2 diabetes mellitus; CAC, coronary calcium score; ECG SSTD, electrocardiogram stress ST depression; OD, odds ratio; CI, confidence interval; S.E, standard error

### Relationship between coronary calcium score and gatedSPECT imaging results

The relationship between extent of CCS and severity ofmyocardial ischemiais shown in Figure 3. We have not found significant correlation between minimally, mild and moderately increased CCS and SPECT imaging. There was moderate correlation between severly increased CAC and myocardial ischemia (Pearson correlation coefficient, r -0.54). 23 patients with normal SPECTresults showed atherosclerosis with mild CCS and moderately increased CCS. 13 patients with moderate CAC and15patients with severe CCS had abnormal perfusion. Consistent with prior studies, we also observed a significantly higher frequency of abnormal scans among patients with CCS  $\geq$ 400AU (46,3%, *p*<0.001). However, patients with mild or no CAC had a relatively high frequency of ischemia (21,2% and14,0%; Figure 4).

#### Gender differences in coronary calcium score values and presence of myocardial ischemia

We found gender differences in the presence and severity of myocardial ischemia and CCS values. Female patients had more abnormal SPECT results with higher prevalence of mild ischemia (SDS <4) comparing to male patients (12 vs. 6, p<0.001). Moderate and severe ischemia (SDS >7) was more prevalent in male patients (14 vs 5, p<0.0001). Male gender was independent predictor for CCS >0, as shown in table 4.Increased BMI and hypertension were more prevalent in female patients with abnormal SPECT results. The mean CCS score was significantly higher in male patients with severe ischemia than in female patients (487 ± 122 vs 175 ± 38; p < 0.001). Patients with moderate and high CCS were older, predominantly male smokers.

#### Discussion

Diabetes has been evaluated as coronary heart disease risk equivalent, with similar prognosis in diabetic patients as in those with established CAD. Two thirds of all cause mortality in diabetic patients is caused by cardiovascular disease [7]. Diabetes is characterized by accelerated atherosclerosis, with increased amounts of connective tissue, glycoproteins, inflammation and calcified plaque in coronary vessels with diffuse distribution [8]. CCS evaluate the implication of risk factors and diabetes control on coronary vascular wall.Several studies have shown that diabetes type 2 patients have higher CCS score that predicts increased all-cause mortality [9]. Pencina et al. introduced the concept of net reclassification improvement (NRI), which measures the extent to which individuals with and without events are appropriately reclassified into higher or lower risk categories with the addition of a new marker [10].

Prospective Evaluation of Diabetic Ischemic Disease by Computed Tomography (PREDICT) study, assessed CCS as a predictor of CVD events in T2DM. The study showed that hazard ratios relative to CCS increased with increasing of the CAC from 5.4 (p=0.02) for CAC 11–100, 5.4 (P = 0.02) up to 19.8 (p<0.001) for CAC >1,000 [11]. Diabetic patients are heterogenous population, influenced by diabetes duration, diabetes control, risk factors, genetic factors and inflammatory activity. CCS identifies

a subgroup of patients with diabetes who are at lower risk for CVD mortality. This may have therapeutic implications leading to individualized therapies. Further, the CCS score provides an objective quantifiable measure of disease severity to both patient and physician and has the potential to modify behavior and improve treatment compliance [12].

CV disease are responsible for 49% of deaths in women in Europe. Along with the increasing focus on cardiovascular disease and their influence on morbidity and mortality in women, many randomized studies implicatesignificant differences in several aspects of cardiac disease between males and females [13].

There are several known causes causing gender differences in CAD manifestation and prognosis, such as smaller vessel size in women, hormone protection, traditional and non-traditional risk factors, psychological factors, comorbidities, endothelial function, coronary flow differences, pregnancy complications [14].

Our study included more female patients comparing to male patients, and we observed tendency of more women referred for SPECT MPI studies at our clinic comparing to male patients. We found several gender differences in our patients. Male patients have higher mean value of CCS comparing to female patients. Abnormal SPECT findings were more prevalent in women, with dominant mild and moderate myocardial ischemia. Severe ischemia was more prevalent in male patients. Female patients complained more often on atypical chest pain. Obesity, hypertension and psychologic problems were more prevalent in women, and dyslipidemia and smoking in male patients. There was no significant difference in average risk factors number. Risk factors control was poorer in male patients.

Multiple risk factors have been associated to the occurrence of CV events whichare evaluated through cardiovascular risk scores. However, this clinical scores have several limitations for prediction of CV events, when compared to risk prediction in addition of noninvasive methods.CCS start to increased even in the early stage of atherosclerosis. It has shown excellent accuracy in the prediction of future risk events and detection of early disease [15].

It is well established marker of atherosclerosis burden, which has been shown to add incremental prognostic value over traditional risk factors and reclassify patient risk. Calcium score has independent predictive values for cardiovascular risk comparing to carotid intimal-medial thickness, ankle-brachial index, and C-reactive protein, based on MESA study. Several studies have shown thateven minimal calcification presents an increased risk of 2 to 3 fold [16].

On the other hand, in CCS of zero, implicates small probability of disease even in symptomatic diabetic. However calcium score 0 does not exclude the presence of soft plaques, which means low risk for annual events, but it does not prevent us for all risk factors control to target values [17].

Myocardial perfusion scintigraphy (MPS) is the most robust technique for diagnostic and prognostic evaluation of these patients in clinical practice [18].

Based on the latest guidelines on myocardial revascularization and management of chronic ischemic heart disease, clinical presentation, patient's risk and presence of at least moderate ischemia is indication of invasivetreatment. Normal MPS study indicates good prognosis and annual risk for CV events below 1%. Results of latest ISCHEMIA trial put a new light on evidences we have so far.

The study referred absence of prognostic advantage of invasive treatment comparing to the medical therapy in patients with stable CAD, which also included patients with diabetes type 2. ISCHEMIA trial results validate the importance of optimal GDMT as well as the importance of shared decision making between the patient and the physician based on the overall clinical risk profile of each patient and the therapeutic goals for each patient.Information's provided by calcium score and MPS are complementary, which allows a joint approach [19]. CCS result potentially adds additional important information on patient coronary atherosclerosis, intensify patient's treatment, improve prognosis and patient compliance.

We did not find significant correlation between minimally, mild and moderately increased CCS and normal SPECT results as well as mild and moderate ischemia. However, we found significant correlation between severe ischemia and CCS over 400AU, indicating that as the extend of atherosclerosis increase, also increase the risk hemodynamically significant ischemia in both genders.

Additional information provided by the CCS result exert positive influence on the interpretation of MPS findings, improving accuracy and reducing the amount of equivocal results [20]. Several studies reported nonlinear correlation of CCS with MPS results. A high CCS in patients with normal MPI-SPECT reflects non-obstructive atherosclerosis, which is regarded as a preclinical state with strong predictive value for the development of CAD, were aggressive risk factor control should be recommended [21,22]. Those methods assess two different aspects of CAD, anatomical and functional repercussions of the disease.

# Conclusions

Our study found clear differences between males and females regarding total vessel calcium scores, presence and extend of myocardial ischemia. Males have higher average calcium scores in each coronary artery comparing to females with a greater tendency for multiple vessel involvement. In patients with normal scintigraphy results, calcium score indicates subclinical disease or it may exclude the presence of or significant atherosclerosis and CAD which implies the need of more intensive treatment measures.

# ABREVIATIONS

AU - Agatston units CCS - Coronary calcium score CAD - Coronary artery disease CV - Cardiovascular LMN - Left main disease LAD - Left anterior coronary artery disease LAD - Left anterior coronary artery disease RCA - Right coronary artery disease DM - Type-2 diabetes mellitus ECG - Electrocardiogram ST - ST segment HDL - High density cholesterol LDL - Low density cholesterol SPECT/CT - Single-photon emission computed tomography myocardial perfusion imaging computer tomography

# References

- 1. Cosentino F, Grant PJ, Aboyans V et al. ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020 Jan 7;41(2):255-323.
- 2. Mach F, Baigent C, Catapano AL et al. ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020 Jan 1;41(1):111-188.
- 3. Sarwar N, Gao P, Seshasai SR, et al. Emerging Risk Factors Collaboration Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010;375:2215–2222
- 4. Nakao YM, Miyamoto Y, Higashi M et al. Sex differences in impact of coronary artery calcification to predict coronary artery disease. Heart. 2018 Jul;104(13):1118-1124.

- 5. Wackers FJ, Young LH, Inzucchi SE et al. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. Detection of Ischemia in Asymptomatic Diabetics Investigators. Diabetes Care. 2004 Aug;27(8):1954-61.
- 6. ISCHEMIA Trial Research Group, Maron DJ, Hochman JS, O'Brien SM et al. International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial: Rationale and design. Am Heart J. 2018 Jul;201:124-135.
- 7. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. Cardiovasc Diabetol. 2018;17(1):83
- 8. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998;339:229–234.
- 9. Schurgin S, Rich S, Mazzone T. Increased prevalence of significant coronary artery calcification in patients with diabetes. Diabetes Care 2001;24:335–338
- Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157–172
- 11. Godsland IF, Elkeles RS, Feher MD et al. PREDICT Study Group. Coronary calcification, homocysteine, C-reactive protein and the metabolic syndrome in Type 2 diabetes: the Prospective Evaluation of Diabetic Ischaemic Heart Disease by Coronary Tomography (PREDICT) Study. Diabet Med. 2006 Nov;23(11):1192-200.
- Erbel R, Möhlenkamp S, Moebus S, et al. Heinz Nixdorf Recall Study Investigative Group Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. J Am Coll Cardiol 2010;56:1397–1406
- 13. Regitz-Zagrosek V, Kararigas G. Mechanistic Pathways of Sex Differences in Cardiovascular Disease. Physiol Rev. 2017 Jan;97(1):1-37.
- The EUGenMed, Cardiovascular Clinical Study Group, Vera Regitz-Zagrosek, Sabine Oertelt-Prigione, Eva Prescott et al. Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes. European Heart Journal, Volume 37, Issue 1, 1 January 2016, Pages 24–34
- 15. Greenland P, Bonow RO, Brundage BH, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) Circulation. 2007;115:402–426.
- Folsom AR, Kronmal RA, Detrano RC, et al. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). Arch Intern Med 2008;168:1333–1339
- 17. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med. 2008;358:1336–1345.
- 18. Schaap J, Kauling RM, Boekholdt SM, et al. Usefulness of coronary calcium scoring to myocardial perfusion SPECT in the diagnosis of coronary artery disease in a predominantly high risk population. Int J Cardiovasc Imaging. doi: 10.1007/s10554-012-0118-1
- 19. Arabi AR, Alqahtani A, Alsuwaidi J. After Ischemia Trial, What is the Role of Ischemia Detection on Noninvasive Testing?. Heart Views. 2020;21(1):31.
- 20. Rosman J, Shapiro M, Pandey A, VanTosh A, Bergmann SR. Lack of correlation between coronary artery calcium and myocardial perfusion imaging. J Nucl Cardiol. 2006;13:333–337.

- 21. Almoudi M, Sun ZH. A head-to-head comparison of the coronary calcium score by computed tomography with myocardial perfusion imaging in predicting coronary artery disease. J Geriatr Cardiol. 2012;9(4):349-354.
- 22. Greenland P, Labree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA. 2004;291:210–215.