PROGNOSTIC VALUE OF NORMAL MYOCARDIAL PERFUSION IMAGING IN ASYMPTOMATIC DIABETIC PATIENTS WITH MODERATE AND HIGH CALCIUM SCORES

Irena Peovska Mitevska, Jelka Daceva Pavlovska, Maja Zdravkovska, Marina Zdravkovska
University Cardiology Clinic, Institute for Pathophysiology and Nuclear Medicine, Skopje, Macedonia, 1000 Skopje, Macedonia

PROGNOSTIČKI ZNAČAJ RADIO-TOMOGRAFSKOG ISPITIVANJA PERFUZIJE MIOKARDA KOD PACIJENATA SA ASIMPTOMATSKIM DIJABETISOM I UMERENIM DO VISOKIM VREDNOSTIMA KALCIJUM SKORA

Irena Peovska Mitevska, Jelka Dačeva Pavlovska, Maja Zdravkovska, Marina Zdravkovska
Univerzitetska kardiološka klinika, Institut za patofiziologiju i nuklearnu medicinu, Skopje, Makedonija, 1000 Skopje, Makedonija

Received / Priljubljen: 20. 10. 2014.

Accepted / Prihvaćen: 26. 11. 2014.

ABSTRACT

The purpose of this study was to evaluate the intermediate prognostic value of normal myocardial perfusion imaging (MPI) in asymptomatic diabetic patients with intermediate and high coronary artery calcium (CAC) scores. Methods: A total of 115 asymptomatic diabetic patients with no known coronary artery disease (CAD) underwent MPI after multi-slice computed tomography CAC assessment for the detection of suspected CAD. The study included 75 patients with normal MPI results. A 17-segment model for myocardial perfusion and function analysis was used. Patients were divided into three groups: I gr-20 patients with a diabetes duration between 1-5 years; II gr-24 patients with a diabetes duration 5-10 years; and III gr-31 patients with a diabetes duration >10 years. End points (cardiac death, non-fatal myocardial infarction, heart failure, new angina, revascularization) were assessed at 6, 12 and 24 months.

All patients had normal resting left ventricular function and normal myocardial perfusion scans. Forty patients had moderate coronary artery calcification with an average CAC of 290 ± 95 . Thirty-five patients had severe coronary calcification with an average CAC of 568 ± 67 . A correlation was found between diabetes duration and CAC severity ($r=0.62$ for diabetes duration over 10 years). Three cardiac events were identified at 24-month follow-up (new angina with percutaneous coronary intervention-PCI). Hard events (cardiac death, nonfatal myocardial infarction) were observed at a rate of 0% in group I, 4.2% in group II and 6.4% in group III. The overall event rate at 24-month follow-up was 4.0%.

MPI and CAC are valuable techniques for the preclinical assessment of CAD in asymptomatic diabetic patients. This could guide decision-making to result in optimal treatment and prognosis. Even diabetic patients with normal MPI are at increased intermediate risk for CV events.

Key words: myocardial imaging, coronary calcium score, coronary artery disease, prognosis

SAŽETAK

Cilj ovog istraživanja je da utvrdi prognostički značaj radio-tomografskog ispitivanja perfuzije miokarda (eng. MPI) kod pacijenata sa asimptomatskim dijabetesom i umerenim do visokim vrednostima kalcijum skora.

115 asimptomatskih dijabetičnih pacijenata je bilo podvrgnuto radio-tomografskom ispitivanju perfuzije miokarda nakon tomografskog ispitivanja koronarnog kalcijuma skora (eng. CAC) radi dijagnoze koronarne arterijske bolesti (KAB). Studija je obuhvatila 75 pacijenata sa normalnim rezultatima MPI-ja. Korišćen je 17-osegmentni model MPI-ja. Pacijenti su bili podeljeni u tri grupe: I grupa – 20 pacijenata sa istorijom dijabetesa od 1-5 godina, II grupa – 24 pacijenta sa istorijom dijabetesa od 5-10 godina, III – 31 pacijent sa istorijom dijabetesa od >10 godina. Krajnje tačke (srčani zastoj, ne-fatalni infarkt miokarda, srčana insuficijencija, nova epizoda angine, revaskularizacija) su ispitivane u šestom, dvanaestom i dvadesetčetvrtom mesecu.

Svi pacijenti su imali normalne vrednosti funkcije leve komore u mirovanju i normalne miokardne perfuzione skenere. 40 pacijenata je imalo srednje vrednosti CAC-a koje su iznosile 290 ± 95 . Tridesetpet pacijenata je imalo visoke vrednosti CAC-a, u proseku 568 ± 67 . Pronadjena je korelacija između dužine trajanja dijabetesa i težine CAC-a ($r=0.62$ za trajanje dijabetesa >10 godina). Tri srčane smetnje su identifikovane tokom 24-voromesečnog perioda praćenja (nova epizoda angine, sa perkutanom koronarnom intervencijom - PCI). Teži srčani poremećaji (srčani zastoj, ne-fatalni infarkt miokarda) su zabeleženi u grupi I sa stopom od 0%, u grupi II sa stopom od 4.2% i u grupi III sa stopom od 6.4%. Ukupna stopa srčanih poremećaja tokom 24-voromesečnog perioda praćenja je iznosila 4.0%.

MPI i CAC su korisne tehnike za preklinička ispitivanja KAB kod pacijenata sa asimptomatskim dijabetesom. To može olakšati donošenje odluka o izboru adekvatne terapije i imati prognostičku vrednost. Čak i dijabetični pacijenti sa normalnim rezultatima MPI-ja imaju povećan rizik za nastanak neželjenog kardiovaskularnog događaja.

Ključne reči: radio-tomografija miokarda, koronarni kalcijum skor, koronarna arterijska bolest, prognoza

UDK: 616.379-008.64-06-056.24; 616.132.2 / Ser J Exp Clin Res 2015; 16 (2): 109-114

DOI: 10.1515/SJECR-2015-0014

Corresponding author: I Peovska Mitevska, University Cardiology Clinic, Ul. Vodnjanska 17, 1000 Skopje, Macedonia,
Tel: +389 75 491 216, E-mail: peovskai@yahoo.com

ABBREVIATIONS

MPI - myocardial perfusion imaging	SPECT - single photon emission computed tomography
CAC - coronary calcium score	LVEF - left ventricular ejection fraction
CAD - coronary artery disease	BMI - body mass index
PCI - percutaneous coronary intervention	CV - cardiovascular

INTRODUCTION

Coronary artery disease (CAD) is a leading cause of morbidity and mortality and is associated with high medical costs in the management of high-risk patients. Because of the lack of sufficient CAD screening, asymptomatic patients' first clinical presentation is often in the form of acute myocardial infarction or sudden cardiac death. On-going debate exists over the best diagnostic and therapeutic approaches for asymptomatic diabetic patients at high risk for CAD. There is also controversy regarding whether non-invasive imaging-based risk stratification improves patient management and prognosis when compared with traditional risk factor-based stratification. Strategies that can identify asymptomatic patients who are at high risk of future cardiac events may favourably affect CAD risk and outcomes in this population. MPI with gated SPECT is a well-established test for the diagnostic and prognostic evaluation of patients with known or suspected CAD (1, 2). A normal myocardial perfusion study is associated with low cardiac risk, while increasing coronary calcium scores are associated with increased risk. There has been increased interest in the use of coronary artery calcium (CAC) imaging to diagnose early subclinical atherosclerosis and to improve risk stratification in asymptomatic individuals (3–5). Our study aimed to evaluate the intermediate prognostic value of normal myocardial scintigraphic results with moderate and high calcium scores in diabetic patients without known coronary artery disease.

MATERIALS AND METHODS

Study Population

Seventy-five consecutive asymptomatic diabetic patients (41 male, 34 female; age range 63 ± 15 years) with high CV risk based on the European Society of Cardiology SCORE risk stratification system ($>5\%$ risk for fatal cardiovascular event in the next 10 years) and without previously known or established CAD were included in the study. All patients completed the World Health Organization (WHO) Rose Angina Questionnaire for confirmation of their asymptomatic status.

Physical examination, including blood pressure, weight, height, waist circumference, and body mass index (BMI), was performed on all patients; we also performed

risk factor analysis and documented the duration of diabetes. Full blood laboratory analyses, including lipid status, fasting glucose levels, HbA1C in diabetic patients, and creatinine levels, were performed on all patients. Urine testing for evidence of albuminuria (30–300 mg/l) was conducted on patients with diabetes and hypertension. Patients were divided into three groups: I gr- 20 patients with a diabetes duration between 1–5 years; II gr- 24 patients with a diabetes duration 5–10 y; and III gr- 31 patients with a diabetes duration >10 y. The clinical and laboratory characteristics of the patients are presented in Tables 1 and 2.

Exclusion criteria were the following: typical stable angina pectoris, previously known or established CAD (history of myocardial infarction, acute coronary syndromes, previous percutaneous intervention or coronary artery bypass surgery), LVEF $<50\%$ at rest, severe valvular disease, atrial fibrillation, left bundle branch block, presence of pacemaker, and severe chronic pulmonary disease.

Patients were treated with optimal medical therapy and risk factor control based on the latest European Society of Cardiology guidelines on cardiovascular disease prevention in diabetes and heart disease.

All patients signed a written informed consent form before study enrolment. The study was approved by all authors and the local ethical committee.

Study protocol

Patients who met the inclusion criteria underwent ECG and resting transthoracic 2D echocardiography for the assessment of left ventricular systolic and diastolic function. All patients had preserved resting systolic LV function and left ventricular ejection fraction (LVEF $>55\%$) and then underwent myocardial perfusion Single Photon Emission Computed Tomography (SPECT) imaging for the detection of silent myocardial ischaemia or silent myocardial infarction. The coronary artery calcium (CAC) score was calculated, and the results were evaluated using Agatston units.

Myocardial perfusion SPECT imaging (MPI)

MPI SPECT imaging was performed using a one-day rest-stress protocol with a Tc-99 m sestamibi radiotracer, using 15 mCi for the rest and 25 mCi for the stress study.

We used a single-head gamma camera with a commercially available quantitative gated and perfusion SPECT software package (4DM-SPECT). Patients were instructed to abstain from caffeine-containing beverages for at least 12 h, nitrates for 24 h, and beta-blockers for 48 h before the study. All patients were subjected to a pharmacological stress with Dipyridamole. We used a 17-segment model for a quantitative bulls-eye analysis of regional myocardial perfusion and function. Myocardial perfusion was assessed by a 5-point scoring system (0-normal radiotracer uptake, 1-mild, 2-moderate; 3-severe hypo perfusion; 4-absent uptake). Semi -quantitative analyses of regional perfusion at rest and stress were performed using the summed stress score (SSS), summed rest score (SRS) and summed differential score (SDS) to assess the presence and extent of myocardial ischaemia. Scan abnormalities were defined as follows for SSS: SSS <4, normal perfusion; 4-8, mild; 9-13, moderate; and >13, severely abnormal perfusion scan. Abnormalities for SDS were broken down categorized as follows: SDS <6, mild (<10% of LV); SDS 7-10, moderate (10-15% of LV); and SDS >10, severe ischemia ischaemia (>15% of LV). In addition, LV volumes, LVEF at rest and stress, presence of transit ischaemic LV dilation (TID), visualization of the right ventricle and lung uptake were also analysed. Regional wall motion was assessed by a 6-point scoring system at rest and stress (0-normal wall motion, 1-mild, 2- moderate; 3-severe hypokinesia, 4- akinesia, 5- dyskinesia) using a wall motion score index.

Coronary Artery Calcium (CAC) Score Imaging

For CAC imaging, a non-enhanced retrospectively ECG-gated scan was obtained with a 128-slice CT scanner (Siemens Somatom Definition 128). The estimated effective radiation dose for this protocol was below 1 mSv. Patients with a heart rate greater than 65 beats per minute received metoprolol 5–10 mg IV before the CT scan. Image reconstruction was performed at 55% of the R-R interval. The total calcium burden in the coronary arteries was measured according to the scoring algorithm of Agatston. On the basis of the total Agatston score, only patients with CAC scores 101–400 (moderate CAC) and 401–1,000 (severe CAC) were included in the study and were referred for MPI. The total CAC score and the CAC score in the each coronary artery was evaluated.

Medical therapy and lifestyle advice

Medical therapy was reviewed, and all patients were put on optimal medical treatment with lifestyle advice based on the latest ESC guidelines for CV prevention and the management of stable CAD.

Statistical analysis

We used the SPSS statistical package (version 18.0). Categorical values were expressed in percentages, while

continuous variables were expressed as the mean value $\pm$ SD. We used the Pearson method for correlation assessment. Multivariable regression analysis was built to identify factors independently associated with cardiovascular events. Statistical significance was defined at $p < 0.05$ for all statistical tests.

RESULTS

The prevalence of metabolic risk factors, laboratory findings and medical therapy are presented in Tables 1 and 2. All patients had, on average, 2 risk factors.

The risk factor distribution among the groups was as follows: Calcium Score of 100-400 ($n=40$): hypertension ($n=32$, 80, 1%), hypercholesterolemia ($n=18$, 44.5%), smoking $n=12$, 30.0%), obesity ($n=3$, 7.5%), family history of heart disease ($n=13$, 32.5%), average HbA1C 7, 6%; Calcium Score >400 ($n=35$): hypertension ($n=27$, 77, 0%), hypercholesterolemia ($n=37$, 61.6%), smoking ($n=13$, 37.1%), obesity ($n=4$, 11, 4%), family history of heart disease ($n=7$, 20.0%), average HbA1C 7, 9+/-1, 1%.

Table 1. Clinical characteristics of the study population

Variables	Patients n=75
Age	65+/-9
Gender	45 m; 30 f
Hypertension	52 (69.5%)
Dislipidaemia	45 (59, 8%)
Obesity	7 (9.2%)
Peripheral artery disease	6 (8.0%)
Smoking	26 (34.6%)
Family history	20 (26.6%)
HbA1C % in diabetic patients	7.9+/-1.1
Ejection fraction (%)	58+/-6%
Microalbuminuria	33 (44.0%)
Mean risk factors per patient	2+/-1

Table 2. Therapeutic characteristics of the study population

Variables	Values
ACE/ARB	75 (82.6%)
Ca antagonist	47 (62.6%)
Thiazide diuretic	45 (60.0%)
Beta blocker	6 (8.0%)
Statins	69 (92.0%)
Oral therapy for diabetes	49/75 (65.3%)
Insulin therapy	26/75 (34.6%)

ACE-angiotensin receptor inhibitors, ARB-Angiotensin receptor inhibitors

Myocardial SPECT findings

A total of 1275 segments were analysed. All patients had normal resting left ventricular function with EF >50% assessed by Gated SPECT. All patients had normal MPI findings, with SDS 2+/-1. Five patients had transient ischaemic dilation all of them had hypertension. All patients had normal wall motion.

Coronary Artery Calcium Score findings

Forty patients had moderate calcification of the coronary arteries with average CAC 290+/-95. Thirty-five patients had severe coronary calcification with average CAC 568+/-67. A correlation was seen observed between diabetes duration and CAC severity (r=0,62 for diabetes duration over 10 years). No patients had extensive CAC >1000. Calcium was present in the left main artery in 8 patients (10%), in the left anterior descending coronary artery (LAD) in 22 patients (29%), in the left circumflex artery (LCX) in 13 patients (17%), and in the right coronary artery (RCA) in 16 patients (21%). The average calcium score in the LAD (289+/-72) was significantly higher than in the LCX (115 +/-56) or in the RCA (192+/-68).

Cardiac events

Only 3 cardiac events were noted at the 24-month follow up in the II and III groups (new angina with percutaneous coronary (PCI) revascularization). The rate of hard events (cardiac death or nonfatal myocardial infarction STEMI/NSTEMI) was 0% in gr I, 4.2% in gr II and 6.4% in gr III. The overall rate of CV events at the 24-month follow up was 4.0%. Two patients required PCI to the RCA and one patient underwent PCI to the LAD.

DISCUSSION

Patients with diabetes mellitus are a special population at with increased CV risk that has been the focus of a robust amount of prognostic literature. The prevalence of diabetes is increasing dramatically. Globally, it is estimated that 382 million people suffer from diabetes with a prevalence of 8.3%; this number is expected exceed 380 million within the next 20 years. European guidelines on CV prevention and the treatment of stable CAD and American guidelines on screening for CAD in asymptomatic adults suggest that the imaging of atherosclerosis and functional imaging of CAD can be applied in this population (4, 9). On-going debate continues regarding the best screening approach in asymptomatic diabetic patients, as well as the period of usefulness for normal MPI scan results in these patients. Screening for silent CAD in high-risk patients aims to be performed to detect the disease in an early stage and initiate appropriate treatment, mindful of the fact that, in up to 60% of males and 42% of females, the

initial presentation of CAD is acute myocardial infarction; in approximately 40% of patients, the initial presentation of CAD is sudden cardiac death (1, 2). Consequently, there is a strong argument for using atherosclerosis and myocardial ischaemia imaging to evaluate the risk of subsequent CAD and guide treatment decisions (3).

Diabetes is considered to be a CAD equivalent, and diabetic patients are considered to be at high -risk of CAD (5). The European and American guidelines recommend screening of asymptomatic high-risk patients; these include diabetic patients with evidence of peripheral or carotid occlusive arterial disease, microvascular disease (proliferative retinopathy, nephropathy), or at least two cardiovascular risk factors (diabetic dyslipidaemia, hypertension, smoking, family history of premature CAD) (4, 9). Risk stratification by normal stress MPS may identify patients with and without CAD who do not require further intervention. It has also been demonstrated that the incremental prognostic value of MPS is greater in diabetic patients than in those without diabetes (6-10). Although the presence of a normal scan should indicate a good prognosis, a normal MPS in diabetic patients may be less encouraging than in non-diabetic subjects. Giri et al. showed that diabetic men have a 13.8% risk of death or MI at 3 years (11). Despite the prognostic benefit of SPECT MPI, the rate of cardiac events is unacceptably high in diabetic patients with normal myocardial perfusion (12, 13). Our study results found hard events (cardiac death, nonfatal myocardial infarction STEMI/NSTEMI) to occur at 0% in gr I, 4.2% in gr II and 6.4% in Gr III. The overall rate of CV events at the 24-month follow-up was 4.0%. This high rate is likely secondary to both false-negative studies for significant CAD by SPECT MPI and to the increased prevalence of mild stenosis with a higher risk of plaque rupture, indicating that non-invasive techniques, such as PET MPI, should be improved to more accurately diagnose CAD and that more aggressive medical therapy should be pursued (13).

Several studies have shown that the duration of the low-risk status after a normal stress MPS depends on several factors that may influence the natural progression of CAD (14). Kang and colleagues (11) reported a 1.9% annual event rate in 440 patients with diabetes mellitus who had normal results on dual isotope SPECT examinations (15). These studies have shown that abnormal stress perfusion study results enable the identification of subjects with diabetes mellitus who are at high risk. However, normal scan results in patients with diabetes mellitus have not been as accurate in identifying subjects who are at low risk, such as patients without diabetes mellitus. Negative stress MPS reliably predicts an excellent outcome, as less than 1% of patients with a normal study will experience hard cardiac events such as cardiac death or nonfatal myocardial infarction. The results of these studies also suggest that a normal stress imaging study predicts a relatively good short-term prognosis, but the predictive value of the test declines steadily after 2 years. However, it appears that the expected event rate is driven not only by MPS findings but also

by the underlying risk factors and comorbidity burden as well as the extent of atherosclerosis and rest and stress left ventricular function. The diagnostic and prognostic value of MPI SPECT is well established, although there are less data for asymptomatic high-risk patients. A meta-analysis involving patients with normal MPI SPECT demonstrated that the annual rate of cardiac death or non-fatal myocardial infarction is much smaller in non-diabetic patients (0.6%) than in diabetic populations, in whom published rates have ranged from 1.6 to 3.3% (16, 17). In particular, combining perfusion and functional data, patients with normal perfusion and LV function had a higher annualized event rate compared with those with discordant perfusion and LV function. The highest probability of cardiac death or nonfatal myocardial infarction and the major risk acceleration was observed in patients with diabetes and abnormal post-stress LVEF.

The decision to undertake coronary artery calcium screening should be based on clinical judgement, and the test should be performed only if the results have the potential to change patient management. If coronary calcium testing is performed, it appears reasonable to proceed with further testing in diabetic patients with calcium scores >400, considering factors such as age and renal function (18). In higher risk groups, a higher prevalence of CAC has been shown to impart a high short-term risk of CV events. In an 8-year follow up study of 716 asymptomatic diabetic patients, it was shown that those with higher CAC scores (>400) had a significantly higher prevalence of annual cardiac events compared with those with lower scores (5.6% versus 0.7%, $P<0.01$) (18). There are fewer studies assessing the value of normal SPECT scans in patients with moderate and high CAC values.

Our study results confirm the literature data on the increased intermediate risk for CV events in diabetic patients, even with normal myocardial SPECT scan results. The difficulty in identifying diabetic patients at low risk for CV events on the basis of negative cardiac imaging stress test results has major clinical implications. In our study, all patients with CV events had evidence of transient ischaemic left ventricular dilatation, reduced stress LV function and a diabetes duration of over 10 years. From a therapeutic standpoint, the threshold for proceeding to angiography should be lower in diabetic patients. Additionally, measures of risk factor control should be no less aggressive in patients with normal versus abnormal non-invasive imaging results. Recently, Simonsen and colleagues evaluated long-term temporal risk variations in patients with suspected or known CAD and suggested a warranty period of 5 years following a normal MPS. However, these authors did not stratify according to LVEF (20). Our results indicate that an increased CAC score is not always related to haemodynamically significant CAD. It is well known that most unstable plaques causing acute coronary events are angiographically non-significant. Combining anatomic with functional data provides complementary information due to the evaluation of different

pathophysiologic aspects of CAD. However, the presence of atherosclerosis does not necessarily result in perfusion abnormalities, nor does a normal perfusion SPECT finding exclude obstructive CAD. Berman and colleagues found that patients with normal SPECT results frequently have extensive atherosclerosis on the basis of CAC criteria, which is perceived as subclinical CAD (21). Even in patients with normal MPI results, a high CAC score is a marker of increased long-term risk. Several studies indicate that patients' knowledge of increased CAC scores improved their compliance with medical therapy and led to intensified medical treatment (19-21).

CONCLUSION

Coronary calcium score and SPECT MPI are valuable methods for the preclinical assessment of atherosclerosis and haemodynamically-significant CAD. CAC imaging is useful for identifying patients with extensive atherosclerosis, without haemodynamically significant CAD, and who may be referred for risk factor modification and aggressive medical treatment. Diabetic patients, even those with normal MPI, have an increased intermediate risk for CV events. Among patients with a normal study, the calcium score may represent an additional risk factor for future cardiac events.

CONFLICTS OF INTEREST: none declared.

REFERENCES

1. Fuster V, Mearns BM. The CVD paradox: mortality vs prevalence. *Nat Rev Cardiol* 2009; 6: 669-670.
2. Shah PK. Screening asymptomatic subjects for subclinical atherosclerosis: can we, does it matter, and should we? *J Am Coll Cardiol* 2010; 56: 98-105. <http://www.ncbi.nlm.nih.gov/pubmed/20620724>
3. Chillarón JJ, Roux JA, Benaiges D, Pedro-Botet J. Subclinical cardiovascular disease in type 2 diabetes mellitus: To screen or not to screen. *World J Clin Cases*. 2014 Sep 16;2(9):415-21. <http://www.ncbi.nlm.nih.gov/pubmed/25232543>
4. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2010; 56: e50-103 <http://www.ncbi.nlm.nih.gov/pubmed/21144964>
5. Detrano RC, Doherty TM, Davies MJ, Sary HC: Predicting coronary events with coronary calcium: pathophysiologic and clinical problems. *Curr Probl Cardiol* 25:374-402, 2000. <http://www.ncbi.nlm.nih.gov/pubmed/10849509>

6. Carli MF, Hachamovitch R. Should we screen for occult coronary artery disease among asymptomatic patients with diabetes? *J Am Coll Cardiol*. 2005;45:50–53. <http://www.ncbi.nlm.nih.gov/pubmed/15629372>
7. Rajagopalan N, Miller TD, Hodge DO, Frye RL, Gibbons RJ. Identifying high-risk asymptomatic diabetic patients who are candidates for screening stress single-photon emission computed tomography imaging. *J Am Coll Cardiol* 2005;45:43–49. <http://www.ncbi.nlm.nih.gov/pubmed/15629371>
8. Miller TD, Rajagopalan N, Hodge DO, Frye RL, Gibbons RJ. Yield of stress single-photon emission computed tomography in asymptomatic patients with diabetes. *Am Heart J* 2004;147:890–6. <http://www.ncbi.nlm.nih.gov/pubmed/15131547>
9. European Guidelines on cardiovascular disease prevention in clinical practice. The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice *Eur Heart J* 2012; 33: 1635–1701. <http://www.ncbi.nlm.nih.gov/pubmed/22698795>
10. Kang X, Berman DS, Howard CL et al. Incremental prognostic value of myocardial perfusion single photon emission computed tomography in patients with diabetes mellitus. *Am Heart J*. 1999;138:1025–32. <http://www.ncbi.nlm.nih.gov/pubmed/10577431>
11. Giri S, Shaw LJ, Murthy DR, Travin MI, et. all. Impact of diabetes on the risk stratification using stress single-photon emission computed tomography myocardial perfusion imaging in patients with symptoms suggestive of coronary artery disease. *Circulation*. 2002 Jan 1;105(1):32–40. <http://www.ncbi.nlm.nih.gov/pubmed/11772873>
12. Hachamovitch R, Hayes S, Friedman JD, et al. Determinants of risk and its temporal variation in patients with normal stress myocardial perfusion scans: what is the warranty period of a normal scan? *J Am Coll Cardiol* 2003; 41:1329–40. <http://www.ncbi.nlm.nih.gov/pubmed/12706929>
13. Bateman TM, Heller GV, McGhie AI, et al. Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: comparison with ECGgated Tc-99 m sestamibi SPECT. *J Nucl Cardiol* 2006;13:24–33. <http://www.ncbi.nlm.nih.gov/pubmed/16464714>
14. Shaw LJ, Iskandrian AE. Prognostic value of gated myocardial perfusion SPECT. *J Nucl Cardiol*. 2004;11:171–185. <http://www.ncbi.nlm.nih.gov/pubmed/15052249>
15. Kang X, Berman DS, Lewin H, et al. Comparative ability of myocardial perfusion single-photon emission computed tomography to detect coronary artery disease in patients with and without diabetes mellitus. *Am Heart J*. 1999;137:949– 957. <http://www.ncbi.nlm.nih.gov/pubmed/10220646>
16. Bourque JM, Beller GA. Stress myocardial perfusion imaging for assessing prognosis: an update. *JACC Cardiovasc Imaging*. 2011 Dec;4(12):1305–19. <http://www.ncbi.nlm.nih.gov/pubmed/22172788>
17. Kamalesh M, Feigenbaum H, Sawada S. Challenge of identifying patients with diabetes mellitus who are at low risk for coronary events by use of cardiac stress imaging. *Am Heart J*; 2004; 147(4): 561–563. <http://www.ncbi.nlm.nih.gov/pubmed/15077067>
18. Qu W, Le TT, Azen SP, et al. Value of coronary artery calcium scanning by computed tomography for predicting coronary heart disease in diabetic subjects. *Diabetes Care*. 2003 Mar; 26(3):905–10. <http://www.ncbi.nlm.nih.gov/pubmed/12610057>
19. Doherty TM, Detrano RC, Mautner SL, Mautner GC, Shavelle R: Coronary calcium: the good, the bad, and the uncertain. *Am Heart J* 137:806–814, 1999. <http://www.ncbi.nlm.nih.gov/pubmed/10220628>
20. Simonsen JA, Gerke O, Rask CK et al. Prognosis in patients with suspected or known ischaemic heart disease and normal myocardial perfusion: Long-term outcome and temporal risk variations. *J Nucl Cardiol*. 2013 Jun;20(3):347–57 <http://www.ncbi.nlm.nih.gov/pubmed/23456830>
21. Berman DS, Wong ND, Gransar H, et al. Relationship between stress-induced myocardial ischaemia and atherosclerosis measured by coronary calcium tomography. *J Am Coll Cardiol*. 2004;44(4):923–930. <http://www.ncbi.nlm.nih.gov/pubmed/15312881>