9

Detection of Silent Ischemia in Patients with Type 2 Diabetes

Babes Elena Emilia and Babes Victor Vlad
University Oradea, Faculty of Medicine and Pharmacy
Romania

1. Introduction

The prevalence of diabetes mellitus has reached epidemic proportions and constitutes a major public health problem. Diabetes mellitus affects an estimated 171 million people worldwide in 2000 and this number is projected to double to 366 million by 2030 (Wild et al., 2004). Silent myocardial ischemia is common in diabetic patients and may delay or mask the diagnosis of coronary artery disease, particularly in its early stages.

2. Diabetes, a coronary artery disease risk equivalent

Coronary artery disease is the leading cause of morbidity and mortality in individuals with type 2 diabetes mellitus. Coronary artery disease is more severe, more prevalent and occurs at younger age in patients with type 2 diabetes mellitus. Using a range of diagnostic methods, the overall prevalence of coronary artery disease is reported to be as high as 55% in patients with diabetes, compared with 2% to 4% in the general population (Hammoud et al., 2000). In an asymptomatic and uncomplicated cohort of type 2 diabetic patients, 46, 3% had evidence of coronary calcification indicative of coronary atherosclerosis (Anand et al., 2006). In an autopsy study of diabetic patients the prevalence of anatomic coronary artery disease was 50% to 81% (Goraya et al., 2002).
An estimated 80% of diabetic patients die from cardiovascular disease, 75% of which is attributed to coronary artery disease (American Diabetes Association, 1998). In general diabetic patients have more extensive atherosclerosis with a higher prevalence of multivessel coronary artery disease, frequent silent myocardial ischemia and infarction with a higher cardiac event rate when compared with non-diabetic patients (Goraya et. al, 2002; Nesto et al., 1998; Stamler et al., 1993). Patients with diabetes without previous myocardial infarction or cardiovascular disease have been shown to have a similar prognosis as persons without diabetes but with prior myocardial infarction or cardiovascular disease (Haffner et al., 1998). Based on these data, diabetes is considered a coronary artery disease risk-equivalent according to current Framingham Risk Score Adult Treatment Program III guidelines and secondary prevention of coronary artery disease is recommended for all adult diabetic patients (http://www.nhlbi.nih.gov/giudelines/cholesterol/atp3_rpt.htm).

3. Silent ischemia - prevalence and prognosis in diabetic patients

Silent ischemia is a common, under-recognized condition that is associated with an adverse prognosis. It is a marker of a significant underlying coronary artery disease and therefore of future cardiovascular events. Myocardial ischemia is often asymptomatic in patients with diabetes mellitus and coronary artery disease is frequently in an advanced stage when it becomes clinically manifest.

A number of studies have confirmed the presence of silent ischemia in diabetic patients. The reported prevalence of myocardial ischemia varied between studies from 6% to 59% (MiSAD group, 1997; Miller et al, 2004; Rajagopalan et al., 2005; Zellweger et al., 2004; Wackers et al., 2004; Scognamiglio et al., 2006). This variation is probably related to differences in patient selection, stress methodology and imaging techniques. Autopsy studies have identified a high prevalence of coronary atherosclerosis in patients with diabetes, even among those without clinical coronary heart disease. Almost 75% of diabetic decedents without clinical coronary artery disease have high grade coronary atherosclerosis (Goraya et al., 2002).

The importance of identifying silent ischemia is highlighted by the poor outcomes associated with silent ischemia in patients with type 2 diabetes. Silent ischemia was significantly related to future coronary events in asymptomatic diabetic patients after 2, 8 years (risk ratio: 21) (Rutter et al., 1999). Similarly, 5-year follow-up of the MISAD (Milan Study on Atherosclerosis and Diabetes) cohort showed that abnormal baseline scintigraphy was associated with fivefold increase in fatal and nonfatal cardiac events (risk ratio: 5,47) (Faglia et al., 2002). Diabetic patients with inducible ischemia on stress myocardial perfusion imaging using single-photon emission computed tomography (SPECT) have a significantly higher annual cardiac death or myocardial infarction rate than nondiabetic patients with ischemia (10% vs. 8%)(Shaw & Iskandrian, 2004). In one study of female diabetic patients with high-risk stress SPECT perfusion scan characterized by a multivessel disease pattern only 60% survived without infarction in the next 3 years. For male diabetic patients with high-risk scan this value was 79% (Giri et al., 2002). Similarly diabetic patients with abnormal stress echocardiography have a worse prognosis that non-diabetic patients (Cortigiani et al., 2006). Diabetic patients with coronary atherosclerosis as determined by computed tomography calcium scanning have a worse outcome regarding cardiac death and nonfatal infarction that non-diabetic patients with the same coronary artery calcium score (Raggi et al., 2004). Compared with nondiabetic patients diabetic patients with zero coronary artery calcium score had a similar annual mortality rate of 0, 36%. It seems that 48% of diabetic patients had coronary artery calcium score compatible with significant coronary artery disease (Khaleeli et al., 2001).

The exact reason for the poor prognosis associate with silent ischemia is unclear. Silent ischemia confirms the presence of significant coronary artery disease and therefore this population is more at risk for future coronary events. Also repeat episodes of silent ischemia could lead to progressive fibrosis which can progress to left ventricular systolic dysfunction or life threatening arrhythmias. Myocardial biopsies from hypokinetic territories supplied by stenosed coronary arteries have shown areas of fibrosis and myocite death in the absence of infarction (Schaper, 1988).

4. Diagnostic of silent ischemia, which test should be used in which diabetic patient

There are numerous non-invasive test available for myocardial ischemia detection: exercise stress test, Holter ECG monitoring, stress myocardial perfusion imaging, stress echocardiography and other non-invasive techniques can detect the atherosclerotic disease: as carotid-intimae-media thickness evaluation via high resolution ultrasound or coronary artery calcium scoring via computed tomography or computed tomography coronary angiography. It is unclear if for screening the detection of early markers of coronary artery disease is preferred over the actual visualisation of myocardial ischemia.

4.1 Exercise stress test

Exercise stress test is the most widely available, inexpensive and commonly used test used to detect coronary artery disease. It has been well validated in the general population and it can be used as the first diagnostic test for patients with an intermediate risk of having coronary artery disease. Given the differences in presentation of coronary artery disease within the diabetic population and the high incidence of silent myocardial ischemia, various groups have attempted to evaluate whether exercise ECG has similar accuracy in a diabetic population. Few data exist regarding the relationship between exercise ECG test results and coronary artery disease risk in persons with type 2 diabetes mellitus and most studies have involved small samples.

In a prospective study (Blandine et al., 1999) 203 diabetic patients without angina and with normal resting ECG were screened with exercise ECG test (stress nuclear imaging was used if exercise ECG was contraindicate or inconclusive). Sixteen percent had abnormal stress test whereas 9% had silent coronary artery disease as defined by angiography. In a study (Bacci et al., 2002) which evaluated 206 higher risk asymptomatic type 2 diabetes patients with peripheral arterial disease and at least 2 cardiovascular risk factors, 19% had an abnormal test and the positive predictive accuracy of the exercise ECG was 79%. These studies collectively support the notion that among higher-risk cohorts of asymptomatic patients with type 2 diabetes nearly 1/3 may have unrecognized coronary artery disease and exercise ECG may be useful in identifying these patients. In an evaluation of the correlation between the ECG exercise stress test and coronary angiography in 59 diabetic patients the sensitivity and specificity were 75% and 77% (Paillole et al., 1995). The mean positive predictive value of exercise ECG for predicting angiographic coronary disease varies between 70 and 90% (Bacci et al., 2002; Blandine et al., 1999).

Regarding the prognostic value of exercise stress test a study on 68 asymptomatic male veterans (Rubler et al., 1987) with diabetes mellitus found that exercise ECG testing had 50% sensitivity and 83% specificity for predicting subsequent cardiac events over an average of 41 months of follow-up. In the Milan study on Atherosclerosis and Diabetes (Faglia et al., 2002) 735 asymptomatic diabetic patients were screened for coronary artery disease and followed-up for 5 years. In all patients exercise ECG was performed with a positive test prompting stress nuclear testing. Among the subjects with normal exercise ECG test the incidence of cardiac events was significantly lower compared to those with abnormal stress testing ($p<0, 0001$). These data suggest that asymptomatic patients with uncomplicated type 2 diabetes who have a negative exercise ECG test have a lower cardiac event rate and relatively favourable prognosis.

In diabetic patients the value of exercise ECG testing is limited because its low sensitivity requires a workload that is difficult to achieve owing to comorbidities such as peripheral neuropathy, peripheral arterial diseases, poor physical fitness and obesity. The specificity of exercise testing is limited and false positive results are common in patients without angina. Furthermore the specificity is lower in diabetes because of the presence of microvascular disease (Bacci et al., 2002). Exercise ECG has moderate sensitivity and specificity for detection of coronary artery disease. During intermediate follow up exercise ECG has been shown to have a good predictive value for coronary events. It can identify a subgroup of asymptomatic diabetic patients who have significant coronary artery disease as defined by angiography and in lower risk diabetic cohorts it may offer short term prognostic reassurance to those asymptomatic patients with negative test. Parameters including exercise capacity and heart rate recovery offer significant information particularly in diabetic patients who may not experience angina during exercise and who may have increased autonomic dysfunction (Albers et al., 2006). Application of exercise ECG as a screening tool in type 2 diabetes is limited as the test is often inconclusive (Djaberi et al., 2008).

4.2 Holter ECG monitoring

The prevalence of silent myocardial ischemia as assessed by Holter ECG monitoring varies between 35% and 58% (Chiariello et al., 1985; Aronow et al., 1992). Comparison between diabetic patients and nondiabetic individuals in Asymptomatic Cardiac Ischemia Pilot (ACIP) study showed that despite more extensive and diffuse coronary disease, diabetic ACIP patients tended to have less measurable ischemia during the 48-hour ambulatory ECG (Caracciolo et al, 1996). Comparing exercise ECG and ambulatory ECG for detection of silent ischemia in diabetes a study revealed that ambulatory ECG identified ischemia only in diabetics with three vessel disease but exercise ECG also revealed ischemia in one or two vessel disease (Ahluwalia et al., 1995). Regarding the prognostic value, in one study patients with silent ischemia detected on ambulatory ECG had a higher incidence of new coronary events (87%) than those without silent ischemia (51%) during 40 month follow-up period (Aronow et al., 1992). Further studies are necessary to evaluate the prognostic value of silent ischemia detected by ambulatory ECG.

In conclusion the diagnostic value of ambulatory ECG for coronary heart disease is poor. The predictive value of ischemia detected by ambulatory ECG has not been extensively evaluated (Djaberi et al., 2008).

4.3 Stress echocardiography

Stress echocardiography imaging provides improved sensitivity and specificity compared with exercise ECG testing. There are limited data regarding the utility of stress echocardiography in patients with diabetes particularly in those who are asymptomatic. In a study, 52 patients with diabetes were referred for cardiac assessment using dobutamine stress echocardiography (Hennessy et al., 1997). Sensitivity, specificity and positive and negative predictive values of dobutamine stress echocardiography for coronary artery disease detection were 82%, 54%, 84% and 50% respectively. Although the study was limited by the small size of the cohort it demonstrated similar diagnostic accuracy for dobutamine stress echocardiography in a diabetic population as in the general population. In another study on 55 diabetics who underwent dobutamine stress echocardiography and angiography the sensitivity and specificity of stress echocardiography were 81% and 85% (Elhendy et al., 1998). The efficacy of dobutamine stress echocardiography was compared to exercise ECG testing and SPECT nuclear perfusion imaging in 56 asymptomatic diabetic patients with three additional cardiovascular risk factors but normal resting ECG. Participants underwent all forms of noninvasive stress testing but coronary angiography was only performed if at least one test was abnormal (47%), which precluded the measurement of diagnostic sensitivity and specificity. Positive predictive value was 69% for dobutamine stress echocardiography, 60% for exercise ECG and 75% for thallium SPECT (Penfornis et al., 2001).

A study was performed on 1899 asymptomatic diabetic patients which underwent dipyridamole myocardial contrast echocardiography and in those with myocardial perfusion defects the anatomy of coronary vessels was analyzed by coronary angiography (Scognamiglio et al., 2006). Patients were divided in two groups according to the number of risk factors for coronary artery disease. In the two study groups the prevalence of abnormal myocardial contrast echocardiography (59 vs. 60%) and of significant coronary artery disease (64, 6% vs. 65, 5%) was similar irrespective of risk profile. The criteria of ≥ 2 risk factors did not help to identify asymptomatic patients with a higher prevalence of coronary artery disease and is only related to a more severe coronary artery disease with unfavourable coronary anatomy. The findings of this study suggest that a substantial number of asymptomatic diabetic patients have myocardial perfusion defects and significant coronary artery disease independent of risk factor profile. As a consequence a large number of asymptomatic diabetic patients with few risk factors might have occult coronary artery disease and might be missed on the basis of 1998 American diabetes association guidelines (ADA, 1998).

Several studies have evaluated the prognostic value of stress echocardiography among diabetic patients. In a prospective study stress echocardiography plus an exercise ECG were used to screen 71 diabetic patients with unknown asymptomatic cardiac disease and two or more cardiovascular risk factors. Those who obtained an abnormal result in one test underwent coronary angiography and if necessary revascularization. Compared with patients randomised to the control arm (n=70) coronary events were significantly reduced in the screening arm during follow-up (Faglia et al, 2005). The preclinical diagnosis of coronary artery disease by stress echocardiography may therefore be effective. However more studies are needed to determine the prognostic role of stress echocardiography in screening for cardiac disease in asymptomatic diabetic patients.

Stress echocardiographic imaging provides improved sensitivity and specificity compared with exercise ECG testing. Increasing data are available to support both its diagnostic accuracy and its prognostic role. The presence of resting left ventricular systolic dysfunction and stress induced wall motion abnormalities provides incremental prognostic information to clinical and exercise parameters in multiple studies. Patients referred for pharmacological stress echocardiography demonstrate a higher risk for cardiovascular events than those referred for exercise testing which likely reflects more severe underlying cardiovascular disease and comorbidities. Diabetic patients with normal stress echocardiography appear to have a greater risk for subsequent cardiovascular events than non-diabetic patients, particularly beyond 2 years. The sensitivity and specificity of stress echocardiography for diagnosing extensive coronary artery disease are satisfactory. However the predictive value of a positive test in type 2 diabetes needs to be further analysed (Djaberi et al., 2008).

4.4 Nuclear single photon emission computed tomography (SPECT) myocardial perfusion imaging

Nuclear SPECT myocardial perfusion imaging has been employed in several series to test the prevalence of silent ischemia or to analyse the prognostic impact of perfusion abnormalities in diabetes. It is known that perfusion abnormalities precede abnormalities in systolic function in the ischaemic cascade (Nesto & Kowalchuk, 1987). Accordingly comparisons between myocardial perfusion imaging and stress echocardiography have shown a higher sensitivity for myocardial perfusion imaging for the detection of multi-vessel and single-vessel coronary artery disease (Schinkel et al., 2003).

In asymptomatic diabetic patients the rate of silent myocardial ischemia diagnosed by stress myocardial perfusion imaging ranges from 6 to 59% (Zellweger et al., 2004; Faglia et al., 2002; , De Lorenzo et al., 2002; Wackers et al., 2004; Rajagapolan et al., 2005; Vanzetto et al., 1999; Cosson et al., 2004). This wide range in the prevalence of silent ischemia is related to differences in patient selection, stress methodology and imaging techniques. In retrospective data base analyses of patients with diabetes referred for stress testing a high prevalence (41-58%) of abnormal stress myocardial perfusion imaging and a high cardiac event rate were found (Giri et al., 2002; Kang et al., 1999; Rajagapolan et al., 2005). A retrospective analysis performed by on 1427 diabetic patients referred for myocardial perfusion imaging reported an abnormal in 58% and high risk scan in 18% of subjects (Rajagopalan et al., 2005). Sixty-one percent of patients with high risk results had angiographically high risk coronary artery disease. According to SPECT imaging scans patients were categorized as being at high, intermediate or low risk with significant difference regarding annual mortality rate($p<0,001$) between groups. It is likely that these patients were referred for stress testing because of typical or atypical symptoms and/or perceived clinical high risk.

The retrospective database analyses of known asymptomatic patients with diabetes referred for stress testing showed a lower prevalence of abnormal stress myocardial perfusion imaging and cardiac event rate (Zellweger et al., 2004; Miller et al., 2004; De Lorenzo et al., 2002, Prior et al., 2005). These patients may not be representative of asymptomatic patients with diabetes in the larger population because they were referred for stress myocardial perfusion imaging for example before noncardiac surgery. The mean prevalence of ischemia ranged from 26-39% although Miller et al. reported abnormal myocardial perfusion imaging in 59% asymptomatic patients. But in the study performed by Miller et al. higher risk population was studied including patients with antianginal medication and ECG abnormalities (Q waves, ST-T changes). Because of the retrospective nature of these two types of studies the true prevalence of silent ischemia is uncertain. In general a higher percentage of perfusion defects have been detected in retrospective studies.

Several prospective studies showed lower prevalence of silent coronary artery disease ranging from 6 to 22%. There were important differences in design and stress testing methodology. In the Milan study on Atherosclerosis and Diabetes (MiSAD) asymptomatic patients with diabetes were first screened with exercise stress test and only if this test was abnormal stress myocardial perfusion imaging was performed. It is possible that because the low sensitivity of exercise ECG the overall observed prevalence of silent coronary artery disease was low 6% (Faglia et al., 2002). In DIAD (Detection of Ischemia in Asymptomatic Diabetics) a large prospective study, 1124 type 2 diabetic asymptomatic patients were enrolled. Half of the patients were randomized to an adenosine Tc 99 m sestamibi myocardial perfusion imaging and half were not. In the imaging cohort 22% of the individuals showed abnormal myocardial perfusion imaging and 1 in every 18 subjects (5, 5%) showed moderate to severe perfusion defects indicative of a poor prognosis. Coronary artery disease would remain undetected in as many as 41% of type 2 diabetic patients if 1998 American Diabetes Association recommendations for coronary artery disease screening were strictly followed. Although the study could not demonstrate benefit from routine screening stress myocardial perfusion imaging allowed a good stratification of risk. The 12% participants with moderate or large perfusion defects had higher event rates (2, 4% per year) compared with participants with small or no defects that had low event rates (0, 4% per year) (Wackers et al., 2004). In a study, 510 asymptomatic patients with diabetes had pre-screening performed using electron-beam computed tomography. If the coronary artery calcification score was 100 Agatston units or greater stress myocardial perfusion imaging was performed (Anand et al., 2006). The prevalence of silent coronary artery disease in this study was 13% and established cardiovascular risk factors failed to predict silent ischemia. These two recent prospective studies indicated that the prevalence of silent coronary artery disease in asymptomatic patients is considerably lower than was suggested by retrospective database analyses. Regarding the prognostic role of myocardial perfusion imaging, in pooled studies including both diabetic and non-diabetic patients and symptomatic as well as asymptomatic patients a normal stress myocardial perfusion imaging has been associated with a cardiac event rate of < 1% per year (Iskander & Iskandrian, 1998). With abnormal stress myocardial perfusion imaging studies the extent and severity of myocardial ischemia strongly predicts short and long term risks of coronary events (Hachamovitch et al., 1998). A study was performed on 180 asymptomatic adult-onset diabetic patients referred to exercise myocardial perfusion imaging to detect asymptomatic obstructive coronary artery disease (De Lorenzo et al., 2002). In this study a short-term follow-up was conducted to correlate the imaging findings with patients outcome. A positive test result was reported in 26% of all subjects and clinical variables were not associated with the type of defect or subsequent events. During follow-up two percent of hard events and 5% of total events occurred in patients with normal SPECT. These numbers increased to 9% of hard events and 38% of total events in those with an abnormal SPECT. Male sex and perfusion abnormalities were independent predictors of cardiac events. The presence of an abnormal SPECT in asymptomatic patients seemed to provide added prognostic value over clinical predictors alone. In a multicenter cohort consisting of 370 asymptomatic patients with diabetes with at least two additional cardiovascular risk factors silent ischemia was identified in 35% of patients using stress SPECT imaging as well as ECG stress testing (Valensi et al., 2005). During follow-up there was a significant association between positive stress test results and subsequent cardiac events only in patients > 60 years.

Myocardial perfusion imaging showed good sensitivity but poor specificity (possibly because microvascular disease) for diagnosing coronary artery disease in diabetes. Intermediate follow-up has shown good predictive value of myocardial perfusion imaging for coronary events in type 2 diabetes (Djaberi et al., 2008).

4.5 Coronary artery calcium scores

The presence of coronary calcium is indicative of coronary atherosclerosis. Coronary calcification can be detected noninvasively be electron beam computed tomography and more recently multislice computed tomography. Diabetic patients without manifest

coronary artery disease have a higher coronary artery calcium score that non-diabetic independent of classical risk factors (Hoff et al., 2003; Schurgin et al., 2001, Reaven & Sacks, 2005). Also coronary artery calcium scores show significantly more progression over time in patients with diabetes that in nondiabetics (Raggi et al., 2005).
A substantial body of evidence has established that coronary artery calcium measurement provides potent risk stratification for asymptomatic diabetics. In a cohort of 10.377 asymptomatic individuals which included 903 diabetics the mean coronary artery calcium score was significantly higher in subjects with diabetes than in those without diabetes and for every increase in coronary artery calcium score there was a greater increase in mortality for diabetic patients than for nondiabetic patients (Raggi et al., 2004).
In the presence of multiple cardiac risk factors, the prevalence of coronary artery calcium is increased. In asymptomatic patients with three or more cardiac risk factors the prevalence of coronary artery calcium was significantly increased (Moser et al., 2003). An Agatston score greater than 400 is a threshold for further testing with myocardial perfusion imaging (Moser et al., 2003). These data suggest that coronary artery calcium scoring may have value as an approach to enrich target population of asymptomatic patients with diabetes for screening.
Currently only limited data are available on the relative values of coronary artery calcium and myocardial perfusion imaging for detection silent coronary artery disease and prognostic evaluation. Wong et al. studied 1043 patients without known coronary artery disease (140 patients with diabetes) with coronary artery calcium scoring and stress myocardial perfusion imaging (Wong et al., 2005). A coronary artery calcium score lower than 100 was associated with absence of stress induced ischemia on myocardial perfusion imaging. The likelihood of stress-inducible ischemia increased in parallel with increasing coronary artery calcium score and was greater in diabetics. A recent study explored the combined use of coronary artery calcium assessment and myocardial perfusion imaging in asymptomatic patients with diabetes (Anand et al., 2006). The study evaluated 510 asymptomatic patients with type 2 diabetes using initially electron beam computed tomography to assess coronary artery calcium. If coronary artery calcium score was greater than 100 (25%) stress myocardial perfusion imaging was performed. For comparison, 53 randomly selected patients with a coronary artery calcium score of 100 or less also underwent stress myocardial perfusion imaging. Patients with coronary artery calcium score of 10 or less had no abnormalities on myocardial perfusion imaging. The prevalence of abnormal myocardial perfusion imaging studies increased at higher coronary artery calcium scores. From patients with a coronary artery calcium score between 101 and 400, 23% had abnormal myocardial perfusion imaging and this number increased to 71, 4% of patients with a coronary artery calcium score greater than 1000. Sequential use of electron beam computed tomography and myocardial perfusion imaging may optimize screening of asymptomatic diabetic patients. During a mean follow-up of 18±5 months, no events occurred in patients with coronary artery calcium score of 10 or less; as compared with 82% of events occurring in patients with a coronary artery calcium score greater than 400. The coronary artery calcium score and the extent of myocardial perfusion imaging abnormalities were the only predictors of future cardiac events (Anand et al., 2006). The calcium score was demonstrated to be superior to the established risk factors in predicting silent ischemia and cardiac events. Other studies (He et al., 2000; Berman et al., 2004) found also that the prevalence of stress-induced ischemia on myocardial perfusion was very low if the coronary

artery calcium score was lower than 100 Agatston units and increased in parallel to the coronary artery calcium score. Of patients with coronary artery calcium score 400 or greater, 46% had demonstrable stress-induced myocardial ischemia on myocardial perfusion imaging (He et al., 2000). The decision to perform coronary artery calcium scoring should be based on clinical judgment, only if the results have the potential to change the management of the patient (Bax et al., 2007).

4.6 Multislice computed tomography coronary angiography

In type 2 diabetes multislice computed tomography angiography has demonstrated a higher percentage of noncalcified and calcified plaques and a relatively lower percentage of mixed plaques in diabetes (Pundziute et al., 2007) which can be explained by the rapid progression of atherosclerosis. The sensitivity and specificity is 81% and 82% respectively for detection of coronary stenosis (Schuijf et al., 2004). The diagnostic accuracy of multislice computed tomography angiography is similar in diabetic and nondiabetic individuals (Schuijf et al., 2005). Importantly negative predictive value of multislice computed tomography angiography in diabetes was to be found 98% - 100 %(Berman et al., 2004). The prevalence of coronary heart disease has been assessed by multislice computed tomography angiography in 70 asymptomatic patients with type 2 diabetes. The majority of the patients (80%) had atherosclerosis: obstructive coronary artery disease in 26% and nonobstructive coronary heart disease in 54% of patients (Wong et al., 2005).

Thus, results on the use of noninvasive multislice computed tomography angiography for coronary heart disease screening and as a prognostic indicator in the diabetic population appear promising but further studies in larger population groups are needed.

Multislice computed tomography angiography has good sensitivity, specificity and negative predictive value for identification of coronary heart disease in diabetic patients. However assessment of coronary heart disease by multislice computed tomography in asymptomatic type 2 diabetic patients should be limited to patients at high-risk because of exposure to high radiation and contrast as well as cost factors (Djaberi et al., 2008).

4.7 Carotid intimae-media thickness in type 2 diabetes

Mean common carotid intimae-media thickness in middle aged individuals is higher in diabetic patients versus controls. In diabetics without a history of myocardial infarction carotid intimae-media thickness is similar to that in non-diabetic with a history of myocardial infarction (Lee et al., 2004). Progression of maximal carotid intimae-media thickness in the Insulin Resistance Atherosclerosis Study was twice as high in person with diabetes versus controls (Wagenknecht et al., 2003) but other studies report lower rates (van der Meer et al., 2003). In type 2 diabetes prevalent cardiovascular disease is associated with a higher carotid intimae-media thickness (Lee et al., 2004). Carotid intimae-media thickness was shown to be an independent predictor of cardiovascular events (Bernard et al., 2005). Folsom and colleagues analysed carotid intimae-media thickness in a large cohort that included 1500 diabetic participants and they found that carotid intimae-media thickness has predictive value for future coronary events only in combination with other novel risk factors (Folsom et al., 2003). Carotid intimae media thickness is increased in type 2 diabetic patients with cardiovascular disease and is an independent predictor of coronary events. However the magnitude of its predictive value when added to other risk factors is questionable (Djaberi et al., 2008).

4.8 Arterial stiffness in type 2 diabetes

Diabetic patients have increased arterial stiffness (Weber et al., 2004, Cruickshank et al., 2002). Compromised carotid distensibility and pulse wave velocity have been demonstrated even before the onset of diabetes, in patients with impaired glucose tolerance. Arterial stiffness in diabetes is related to prevalent cardiovascular disease (Fukui et al., 2003) and has shown to be an independent predictor of coronary heart disease (Hatsuda et al., 2006). Pulse wave velocity does seem to have a reasonable value for mortality prediction in patients with impaired glucose tolerance and type 2 diabetes (Cruickshank et al., 2002). Vascular stiffness is increased in type 2 diabetic patients with cardiovascular disease and has been shown to predict cardiovascular mortality (Djaberi et al., 2008)

4.9 Flow mediated dilation in type 2 diabetes

Type 2 diabetes is associated with endothelial dysfunction. Insulin-mediated dilation being at least in part nitric-oxid dependent, insulin resistance may cause endothelial dysfunction. Clustering of risk factors such as dyslipidemia, hypertension and obesity in the metabolic syndrome play an additional role. The predictive value of endothelial dysfunction in epicardial coronary arteries of diabetic patients has been established for long-term coronary events (Nitenberg et al., 2005). Flow mediated dilation is a marker of endothelial dysfunction. The potential of flow mediated dilation for the identification of type 2 diabetic patients at risk for cardiovascular disease is unknown.

Surrogate markers of atherosclerosis: carotid intimae media thickness, arterial stiffness and flow mediated dilation are abnormal long time before the onset of diabetes. These measurements can be useful for the identification of at risk patients during early stages of atherosclerosis. Further studies are necessary to evaluate whether these measurements will provide any additional prognostic value in combination with risk scores (Djaberi et al., 2008).

4.10 Coronary angiography

Coronarography is an invasive diagnostic tool, the gold standard for identifying obstructive lesions and will be considered in the presence of ischemia revealed by noninvasive screening tests.

4.11 Cardiovascular magnetic resonance imaging

Cardiovascular magnetic resonance imaging studies can provide information regarding coronary stenoses and flow, evaluation of myocardial perfusion and metabolism, wall motion during stress and evidence of infarction. There are limited data to support the use of cardiovascular magnetic resonance in asymptomatic patients.

4.12 Biomarkers

A simple, inexpensive blood test for B type natriuretic peptide (BNP) or N terminal prohormone B type natriuretic peptide (NT-proBNP) is a candidate for screening tool of silent myocardial ischemia. BNP is of value in predicting silent ischemia at exercise testing in type 2 diabetic patients (Rana et al., 2006). Hamano et al. showed in a recent study that NT-proBNP has a very high negative predictive value which enables to focus on patients with silent ischemia independent of microalbuminuria (Hamano et al., 2010). Cosson et al. conclude that NT-proBNP helps to better define diabetic patients with silent ischemia independently of cardiac structure and function (Cosson et al., 2009).

5. Deciding who to investigate? Which are the patients with diabetes at high risk that should be screened?

Population screening is not feasible but diabetic patients with high risk of silent ischemia should be identified and investigated further. It still remains under debate what would be the best strategy for proper patient selection to screening and if screening will alter patient outcome when added to primary preventive measures. Several studies of asymptomatic patients with type 2 diabetes have specifically examined whether risk factor burden is predictive of silent ischemia (determined by myocardial perfusion imaging) and these studies have not supported the recommendation of the 1998 ADA consensus panel for screening asymptomatic patients with two or more risk factors (Rajagopalan et al., 2005; Scognamiglio et al., 2006). In asymptomatic patients with diabetes mellitus clinical features that help to identify the patient with increased risk for myocardial infarction or cardiac death include: evidence of other atherosclerotic disease, microalbuminuria and chronic renal disease, abnormal resting ECG, diabetes complications including autonomic neuropathy, rethinopathy, age, sex, unexplained dyspnoea and multiple both traditional and novel risk factors (Bax et al., 2007).

Atherosclerotic disease involving lower extremity, cerebral, renal or mesenteric arteries identifies a patient with diabetes who is at increased risk for adverse cardiovascular outcomes and might have advanced coronary atherosclerosis (Golomb et al., 2006). Other atherosclerotic location is of bad prognosis in asymptomatic diabetic patients leading to increased silent myocardial ischemia and cardiovascular event rates (Criqui et al., 1992). A diminished ankle-brachial index is sensitive indicator of increased risk for future cardiovascular events (Doobay & Anand, 2005). In patients with claudication or asymptomatic peripheral arterial disease, 90% of deaths are attributable to coronary artery disease (Mann et al., 2001).

Microalbuminuria predicts increased risk for vascular disease complications (Schuijf et al., 2006, Anand et al., 2006, Gerstein et al., 2001) as well as for the progression to overt nephropathy in patients with diabetes. Microalbuminuria has been a predictor of inducible ischemia in some (Rutter et al., 1999) but not all (Wackers et al., 2004) studies of asymptomatic patients with diabetes. An increased microalbuminuria predicts a high cardiovascular event rate with a two-time earlier mortality rate (Dinneen & Gerstein, 1997).

Asymptomatic patients with type 2 diabetes occasionally have evidence of previously unrecognized myocardial infarction on resting ECG, including abnormal Q waves or deep T-wave inversions or left bundle branch block. These findings should trigger evaluation for coronary artery disease and inducible ischemia. In a retrospective study of 1427 asymptomatic patients who were referred to the Mayo Clinic for stress testing, Rajagopalan and colleagues aimed to define the variables that would characterize which asymptomatic diabetic patients are most suitable for screening with stress myocardial perfusion imaging. They conducted multivariate analysis and found that high-risk scans were most strongly associated with seven independent variables, the most notable being electrocardiographic Q waves and peripheral arterial disease. Although this was a retrospective study and many have been influenced by verification bias, it provides additional support for identifying high-risk asymptomatic diabetic patients with electrocardiographic abnormalities, peripheral arterial disease, among other clinical variable. Nonspecific ST-T wave changes also are a strong predictor of inducible ischemia in asymptomatic diabetic patients (Rajagopalan et al., 2005).

Cardiovascular autonomic neuropathy is associated with poor overall prognosis in patients with type 2 diabetes (Vinik et al., 2003). That is probably due to impairment in ischemia awareness delaying the diagnosis of coronary artery disease or hemodynamic lability due to blunted parasympathetic activation. Autonomic neuropathy might also be a parallel consequence of cardiac risk factors including hyperglycaemia, dyslipidemia and renal disease. Several studies have implicated autonomic neuropathy as a contributing factor in the mechanism of silent ischemia (Marchant et al, 1993; O'Sullivan et al., 1991). Autonomic neuropathy was a major predictor of inducible ischemia in DIAD (Detection of Ischemia in Asymptomatic Diabetics) (Wackers et al., 2004) and has been associated with abnormal cardiac test findings in other (Valensi et al., 2001) but not all (MiSAD Group, 1997) studies. Cardiac autonomic neuropathy should be considered in the presence of unexplained tachycardia, orthostatic hypotension and other autonomic or peripheral neuropathies.

Diabetic retinopathy is a manifestation of microvascular disease but is also an indicator of risk for coronary artery disease. In clinical studies retinopathy has been associated with inducible ischemia in some (Akasaka et al., 1997) but not all screening studies. In a recent study that assessed the prevalence and risk factors predictors of true silent myocardial ischemia in asymptomatic type 2 diabetic patients, the prevalence of silent ischemia was 21, 9% and male gender and the presence of diabetic retinopathy were the risk factors related to its development (Hernandez et. al, 2011). Hyperglycaemia is a stronger predictor of microvascular disease than atherosclerotic macrovascular disease in people with diabetes (Laakso, 1999).

Although diabetes increases relative cardiovascular risk more in women than in men the absolute risk for cardiovascular events is still higher in men than in women (Abbott et al., 1988). Male sex and duration of diabetes were also strong predictors of silent ischemia in DIAD, but traditional risk factors, novel biomarkers (hs C reactive protein, homocysteine, lipid subtractions, and plasminogen activator inhibitor-10) and the number of risk factors were not predictive of abnormal myocardial perfusion (Wackers et al., 2004). Age is an important determinant of cardiovascular risk and the prevalence of inducible ischemia is significantly higher in patients with type 2 diabetes >65 years (Chaowalit et al., 2006). Patients with exertional symptoms as shortness of breath, generalized fatigue should be screened for ischemia. It is difficult to attribute these symptoms to myocardial ischemia (an angina equivalent) or to obesity and deconditioning. But however patients who are unable to exercise are at increased cardiac risk. The incidence of inducible ischemia is increased in these patients and when present is associated with poor prognosis (Vanzetto et al., 1999).

Patients with type 2 diabetes often have multiple cardiac risk factors including hypertension, dyslipidemia, inactivity, smoking and abdominal obesity. Multiple risk factors in the same patient substantially increase the overall cardiovascular risk (Multiple Risk Factor Intervention Trial, 1996). Also intervention directed at multiple risk factors significantly improves cardiovascular prognosis (Gaede et al., 2003). A prospective smaller study performed on 120 truly asymptomatic diabetic patients with one or more risk factors for coronary artery disease revealed that 33% had an abnormal myocardial perfusion stress study. Smoking, duration of diabetes and cholesterol/HDL ratio were identified as independent predictors of an abnormal stress myocardial perfusion imaging (Scholte et al., 2009).

Some recent prospective studies in type 2 diabetes have been unable to link the number of risk factors to inducible ischemia on perfusion imaging (Wackers et al., 2004). That is probably due to the fact that these studies did not account for the severity, duration, and effect of treatment of dyslipidemia and hypertension in patients with long-standing type 2 diabetes. It is important to improve the ability to identify based on clinical data those patients at highest risk for cardiovascular events. While simple categorical risk factor burden has not proven to effectively discriminate which asymptomatic diabetic patients will or will not have ischemia on stress testing it is possible that risk factor burden might predict risk of cardiovascular events in individual patients (Bax et al., 2007). Efforts have been made using data from Framingham, which included fewer than 400 diabetic subjects, the UKPDS (United Kingdom Prospective Diabetes Study) which included only newly diagnosed diabetic subjects and excluded patients with significant comorbidities and other populations (Guzder et al., 2005) to develop models that identify individuals at higher risk for cardiovascular events (Bax et al., 2007). It is necessary to define a subgroup of high risk asymptomatic patients that will benefit from silent ischemia screening.

A substantial body of evidence has established that coronary artery calcium measurement provides potent risk stratification for asymptomatic diabetics. Diabetic patients with a low coronary artery calcium score have a very favourable prognosis. Among diabetics with a CAC score <10, the 5 year all cause mortality rate was extremely low and was similar to rates for those without diabetes and similar coronary artery calcium score. For any category of coronary artery calcium over zero, there a stepwise increased mortality risk in individual with diabetes compared to those without diabetes (Raggi et al., 2004).

The study PREDICT (PRospective Evaluation of Diabetic Ischemic heart disease by Computed Tomography) a prospective cohort study on 589 asymptomatic type 2 diabetic patients showed that coronary artery calcium score was a highly significant independent predictor of cardiovascular events. A doubling in coronary artery calcium was associated with a 29% increase in risk of events (Elkeles et al., 2008). Coronary artery calcium provided greater predictive value for cardiac events than Framingham risk score and UKPDS risk scores, and than conventional and novel risk factors. In asymptomatic diabetic patients, the prevalence of stress induced ischemia increases the higher the coronary artery calcium score is on computed tomography scanning. From asymptomatic diabetic patients with coronary artery calcium score between 100 and 400, 23% had a positive stress SPECT scan, and 48% from those with coronary artery calcium score >400. This number increased to 71, 4% for asymptomatic diabetic patients with coronary artery calcium score >1000. The greater the extent of ischemia, the worse the clinical outcome and coronary artery calcium score was superior to established risk factors for predicting silent ischemia and cardiac events (Anand et al., 2006).

It is now possible to test a new paradigm for screening asymptomatic diabetic patients (Berman et al., 2004). This consist of using coronary artery calcium scanning rather than cardiac stress testing as the first line screening test. Above coronary artery calcium threshold (400 or 100) SPECT-myocardial perfusion imaging could be selectively used for identifying high-risk silent ischemia. In the presence of high-risk ischemia coronary angiography should be performed, this being the group that could benefit from revascularization (He et al., 2000). It is expected that approximately one-third of such patients would have no detectable coronary artery calcium and many others would have coronary artery calcium scores at levels which obviate the need for SPECT-myocardial perfusion imaging. The inclusion of various clinical parameters as suggested by Bax et al. could alter the threshold criteria used to guide referral to stress testing respectively selective use of a lower coronary artery calcium score threshold among those with high-risk clinical features. In patients with < 10% ischemia, repeat myocardial perfusion imaging might be appropriate in 3 years (Qu et al., 2003).

There are continuing controversies regarding the screening for coronary artery disease in asymptomatic diabetic patients. Given the growing threat posed by increasing prevalence of diabetes, testing of algorithms which cost-effectively select for the identification of high-risk asymptomatic individuals with diabetes is urgently warranted.

6. What are the implications of an early diagnosis of coronary atherosclerosis or ischemia? The detection of silent ischemia in diabetic patients impacts upon their treatment and outcome?

Several recent prospective studies have addressed the value of screening for coronary artery disease in asymptomatic diabetic patients. The DIAD (Detection of Ischemia in Asymptomatic Diabetics) study is a randomized controlled trial in which 1123 patients with type 2 diabetes and no symptoms of coronary artery disease were randomly assigned to be screened with adenosine-stress radionuclide myocardial perfusion imaging or not to be screened. The aim of the study was to test that systematic screening would identify higher-risk individuals and beneficially affect their risk of myocardial infarction or cardiac death. In DIAD although type 2 diabetes is considered to be a coronary artery disease equivalent patients had a low cardiac event rate (0, 6%/year) and the identification of patients with abnormal screening did not serve to eliminate their risk over 5 years of follow-up. The cardiac event rate is 3-4 folds lower than that reported in previous retrospective studies on asymptomatic diabetic patients referred to nuclear cardiology laboratories. But these patients had a higher incidence of peripheral arterial disease, renal insufficiency and many were referred to preoperative evaluation (Rajagopalan et al., 2005; Zellweger et al., 2004). The favourable outcomes of patients in DIAD likely reflect in part the impact of aggressive, guideline-driven management of cardiac risk factors. One of the surprises of the DIAD was that there was no evidence for more inducible ischemia in screened patients when myocardial perfusion imaging was repeated after 3 years. Rather than greater prevalence of abnormal myocardial perfusion there was significantly less inducible ischemia at repeated imaging: 12% vs. 20%. A remarkable 79% of participants with initially abnormal stress myocardial perfusion at recruitment had resolution of ischemia. This improvement was not restricted to small perfusion defects but rather occurred regardless of the initial magnitude of perfusion defect. Only 10% of participants with initially normal screening myocardial perfusion imaging developed new inducible ischemia after 3 years. This resolution of ischemia was unanticipated but can be explained after the review of the medical regimens of participants. In the course of three years there was a significant increase in the treatment of patients with aspirin, statins and angiotensin converting enzyme inhibitors. The observed resolution of inducible ischemia was also a harbinger of the low cardiac events that subsequently emerged (Young et al., 2009). Routine screening for inducibile ischemia in asymptomatic patients with type 2 diabetes is not recommended because: the yield of detecting inducible ischemia is relatively low (Wackers et al., 2004); the overall cardiac event rate is low, even in patients with moderate or large defects and the highest event rate are conventionally assigned to an intermediate risk category; routine screening does not appear to affect overall outcome and routine screening of millions of asymptomatic diabetic patients is prohibitively expensive. Although screening had no impact on outcomes in

DIAD it is noteworthy that stress myocardial perfusion imaging did effectively stratify patients into higher risk (moderate-large defects and ischemic ECG) and low-risk (small defects or normal myocardial perfusion imaging) subsets. On the other hand there were adverse cardiac events in both screened and unscreened patients. Thus DIAD results do not exclude the possibility that strategies to better identify patients at higher risk coupled with more effective treatment strategies might prove effective for screening in the future. A selective evaluation of asymptomatic diabetic patients will be a better approach for screening.

The COURAGE (Clinical Outcomes Utlizing Revascularization and Aggresive Drug Evaluation) (Boden et al., 2006) reported among 2.287 patients with stable angina, overall event rates nearly 5%/year indicating a significant residual risk in intensively medically treated patients as well as those undergoing percutaneous interventions. These findings seem to highlight the need for improved methods to stratify residual risk within populations undergoing intensive medical management. Many of these patients had multivessel or proximal left anterior descending coronary artery disease and intensive medical treatment was as effective as percutaneous intervention combined with intensive medical treatment in preventing overall mortality or myocardial infarction. Results were similar in the approximate one-third of the subjects with diabetes. It may be not appropriate to extrapolate the results of this trial in symptomatic patients (in which the event rate for diabetic subjects approached 5% per year) to somewhat lower-risk asymptomatic patients. In the treatment arm of the CARDS (Collaborative Atorvastatin Diabetes Study) trial (Colhoun et al., 2004) which included individuals with type 2 diabetes and no history of cardiovascular disease even after risk factor modification in the active treatment group in whom LDL cholesterol was lowered, still the cardiovascular mortality of diabetic patients remains high; 1, 54/100 person-years. These findings suggest that type 2 diabetic patients being treated according to intensive treatment guidelines likely have a residual, intermediate risk (1-2% per year) for cardiac events. This high mortality will be due in part to silent, prognostically important coronary artery disease (left main, proximal left anterior descending, three vessel disease). Detection and revascularization of this disease will improve this poor prognosis (Sorajja et al., 2005, The BARI Investigators, 1997). This is an important argument for screening high risk diabetic patients for silent ischemia. In diabetic patients autopsy studies observed a greater prevalence of severe multivessel coronary artery disease among patients with diabetes compared with nondiabetic patients even in the absence of prior symptoms or clinical evidence of disease (Goraya et al., 2002). Thus the presumed benefit of evaluation of the presence and extent of myocardial ischemia is to identify those patients with left main or severe multivessel disease with a large area of myocardium at risk and who would have a benefit from coronary revascularization. Diabetic patients have a significant risk for atherosclerotic vascular disease and aggressive treatment of risk factors is recommended in the absence of symptomatic or known coronary artery disease. The role of coronary imaging is not to document the presence of atherosclerosis but to identify those with more extensive disease. Patients with myocardial ischemia involving a large segment of left ventricular myocardium are candidates for coronary angiography and subsequent revascularization. Available data (Hachamovitch et al., 2003, Sorajja et al., 2005) suggests that patients with ischemia involving 10% or more of the left ventricle have a better outcome after myocardial revascularization compared with the results of medical therapy alone.

The hypothesis that asymptomatic patients with severe ischemia benefit from revascularization above aggressive medical was subject of several prospective randomized trials some specifically targeted to the diabetic population. The BARI (Bypass Angioplasty Revascularization Investigation) trial evaluated the effectiveness of percutaneous coronary intervention versus coronary artery bypass grafting in over 1800 patients with symptomatic multivessel coronary artery disease (The BARI Investigators, 2007). The primary outcome of survival was similar in both groups. In a subgroup of patients with diabetes and multivessel disease coronary artery bypass grafting conferred higher survival rates (57,8%) versus percutaneous coronary intervention (45,5%) (p=0,025). The BARI 2D study Group (A Randomized Trial of Therapies for Type 2 Diabetes and Coronary Artery Disease) (The BARI 2D Study Group, 2009) randomly assigned 2368 patients with type 2 diabetes and stable ischemic heart disease to undergo either prompt revascularization with intensive medical therapy or intensive medical therapy alone. Overall there was no significant difference in rates of death and major cardiovascular events between patients undergoing prompt revascularization and those undergoing medical therapy. Prompt revascularization significantly reduced cardiovascular events as compared to medical therapy among patients who were selected to undergo coronary artery bypass grafting but not among those who were selected to undergo percutaneous coronary intervention. The study suggest that patients with diabetes, evidence of myocardial ischemia and extensive multivessel disease would benefit from prompt surgical revascularization mainly because of a lower rate of nonfatal myocardial infarction. Accurate and early diagnosis of coronary artery disease is likely of benefit in those patients with severe anatomic disease, where revascularization has particular benefits. It is not recommended extensive and expensive diagnostic testing to define the presence of coronary artery disease before implementing medical therapy for established risk factors in diabetic patients. Negative screening tests in patients with diabetes do not uniformly confer a benign prognosis. Tests that detect inducible ischemia or assess atherosclerotic burden do not always identify patients at risk for plaque rupture and thrombosis which leads to acute coronary events. Further research focusing on the biological properties of the vessel wall and characterization of plaque structure and stability are warranted. Eventually, we will need better imaging techniques that can assess both plaque burden (soft and calcified) and the extent of vulnerable plaques. These techniques will require molecular imaging that permit delineation of plaque macrophage density and inflammatory markers, the thickness of the fibrous cap, the extent of the lipid-laden necrotic core, fibrin deposition, and the presence of neovessels (Davies et al., 2004; Jaffer et al., 2006; Waxman et al., 2006). If total plaque burden and some index of "vulnerability" could be detected noninvasively, at a reasonable cost, then this approach may be preferable to plaque coronary artery calcium imaging, which is merely reflective of the presence of atherosclerosis. Soft plaques, as previously mentioned, are missed, and no information on vulnerability to rupture is obtained (Beller, 2007).

7. Conclusion

Although the coronary artery disease asymptomatic patient with diabetes is by definition at least at intermediate risk for cardiovascular events it is difficult to support routine screening for these patients. As previous recommendations for stratifying diabetic patients based upon the number of risk factors have not proven effective the question remains whether there are individuals with diabetes in whom coronary artery imaging would seem particularly appropriate. The motivation of such testing would be the clinical suspicion that the individual is at high risk for having a coronary artery disease event in the short term. What would be the best strategy for identifying at-risk individuals is still under debate. In patients evaluated clinically to be at high risk coronary artery calcium scoring may be reasonable first test with subsequent functional imaging performed if the calcium scoring indicates a substantial atherosclerotic burden. The concept of screening asymptomatic subjects is heavily debated and the controversy can only be resolved by gathering evidence for or against screening, which requires data from a randomized clinical trial.

8. References

Abbott, RD., Donahue, RP., Kannel, WB., & Wilson, PW. (1988). The impact of diabetes on survival following myocardial infarction in men vs. women: the Framingham Study. *JAMA*, Vol. 260, No.23, (December 1988), pp. 3456–3460, ISSN 0098-7484.

Ahluwalia, G., Jain, P., Chugh, SK., Wasir, HS., & Kaul, U. (1995) Silent myocardial ischemia in diabetics with normal autonomic function. *Int J Cardiol*, Vol. 48, No.2, (February 1995) pp.147–153, ISSN: 0167-5273.

Albers, AR., Krichavsky, MZ., & Balady, GJ. (2006). Stress testing in patients with diabetes mellitus: Diagnostic and Prognostic value *Circulation*, Vol.113, No.4, (January 2006), pp.583-592, ISSN 1524-4539.

Akasaka, T., Yoshida, K., Hozumi, T., Takagi, T., Kaji, S., Kawamoto, T., Morioka, S., & Yoshikawa, J. (1997). Retinopathy identifies marked restriction of coronary flow reserve in patients with diabetes mellitus. *J Am Coll Cardiol*, Vol. 30, No.4, (October 1997), pp. 935–941, ISSN 0735-1097.

American Diabetes Association (1998). Consensus development conference on the diagnosis of coronary heart disease in people with diabetes. *Diabetes Care*, Vol.21, No.9, (September 1998), pp.1551-1559, ISSN 1935-5548.

Anand, DV., Lim, E., Hopkins, D., Corder, R., Shaw, LJ., Sharp, P., Lipkin, D., & Lahiri A, (2006). Risk stratification in uncomplicated type 2 diabetes: prospective evaluation of the combined use of coronary artery calcium imaging and selective myocardial perfusion scintigraphy. Eur Heart J, Vol.27, No. 6, (March 2006), pp.713-721, ISSN1522-9645.

Anand, DV., Lim, E., Lahiri ,A., & Bax, JJ. (2006). The role of non-invasive imaging in the risk stratification of asymptomatic diabetic subjects (review). *Eur Heart J*, Vol.27, No.8, (April 2006), pp. 905–12, ISSN 1522-9645.

Aronow, WS., Mercando, AD.,& Epstein, S. (1992). Prevalence of silent myocardial ischemia detected by 24-hour ambulatory electrocardiography, and its association with new coronary events at 40-month follow-up in elderly diabetic and nondiabetic patients with coronary artery disease. *Am J Cardiol*, vol.69, No.5, (February 1992), pp.555–556, ISSN 0002-9149.

Bacci, S., Villela, M., Villela, A., Langialonga, T., Grilli, M., Rauseo, A., Mastroianno, S., De Cosmo, S., Fannelli, R., & Trischitta, V. (2002). Screening for silent myocardial ischemia in type 2 diabetic patients with additional atherogenic risk factors: applicability and accuracy of the exercise stress test. *Eur J Endocrinol*, Vol. 147, No.5, (July 2002), pp. 649–654, ISSN 0804-4643.

Bax, JJ., Young, LH., Frye, RL., Bonow, RO., Steinberg, HO., & Barrett, EJ. (2007). Screening for coronary artery disease in patients with diabetes *Diabetes Care*, Vol.30, No.10, (October 2007), pp. 2729-2736, ISSN 1935-5548.

Beller, GA. Noninvasive screening for coronary atherosclerosis and silent ischemia in asymptomatic type 2 diabetic patients. Is it appropriate and cost-effective?. *J Am Coll Cardiol*, Vol.49, No.19, (May 2007), pp.1918-1923, ISSN 0735-1097.

Berman, DS., Wong, ND., Gransar, H.,Miranda-Peats, R., Dahlbeck, J., Hayes, SW., Friedman, JD., Kang, X., Polk, D., Hachamovitch, R., Shaw, L., & Rozanski, A. (2004). Relationship between stress-induced myocardial ischemia and atherosclerosis measured by coronary calcium tomography. *J Am Coll Cardiol*, Vol. 44, No. 4, (August 2004), pp.923-930, ISSN 0735-1097.

Bernard, S., Sérusclat, A., Targe, F., Charriere, S., Roth, O., Beaune, J., Berthezene, F., & Moulin, P. (2005) Incremental predictive value of carotid ultrasonography in the assessment of coronary risk in a cohort of asymptomatic type 2 diabetic subjects. *Diabetes Care*, Vol. 28, No.5, (May 2005), pp.1158–1162, ISSN 1935-5548.

Blandine, JD., Bernard, S., Habib, G., Bory, M., Vague, P., & Lassman-Vague, V. (1999). Silent myocardial ischemia in patients with diabetes: who to screen. *Diabetes Care*, Vol. 22, No. 9, (September 1999), pp. 1396–1400, ISSN 1935-5548.

Boden, WE., O'Rourke, RA., Teo, KK., Hartigan, PM., Maro, DJ., Kostuk, W., Knudtson,M., Dada, M., Casperson, P., Harris, CL., Spertus, JA., Shaw, L., Chaitman, BR., Mancini, GB., Berman, DS., & Weintraub, WS. (2006). Design and rationale of the Clinical Outcomes Utilizing Revascularization and Aggressive DruG Evaluation (COURAGE) trial Veterans Affairs Cooperative Studies Program no. 424. *Am Heart J*, Vol. 151, No.6, (June 2006), pp.1173–1179, ISSN 0002-8703.

Caracciolo, EA., Chaitman, BR., & Forman, SA. (1996) Diabetics with coronary disease have a prevalence of asymptomatic ischemia during exercise treadmill testing and ambulatory ischemia monitoring similar to that of nondiabetic patients. An ACIP database study. ACIP Investigators. Asymptomatic Cardiac Ischemia Pilot Investigators. *Circulation*, Vol.93, No.12, (June 1996), pp. 2097–2105. ISSN 1524-4539.

Chaowalit, N., Arruda, AL., McCully, RB., Bailey KR., & Pellikka, PA. (2006). Dobutamine stress echocardiography in patients with diabetes mellitus: enhanced prognostic prediction using a simple risk score. *J Am Coll Cardiol*, Vol. 47, No.5, (March 2006), pp.1029–1036, ISSN 0735-1097.

Chiariello, M., Indolfi, C., Cotecchia, MR., Sifola, C., Romano, M., & Condorelli, M. (1985) Asymptomatic transient ST changes during ambulatory ECG monitoring in diabetic patients. *Am Heart J*, Vol.110, No.3, (September 1985) pp.529–534, ISSN 0002-8703.

Colhoun, HM., Betteridge, DJ., Durrington, PN., Hitman, GA., Neil, AW., Livingstone, SJ., Thomason, MJ., Mackness, MI., Charlton-Menys, V. & Fuller, JH. CARDS investigators. (2004). Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet*, Vol. 364, No.9435, (August 2004), pp. 685-696, ISSN 0140-6736.

Cortigiani, L., Bigi, R., Sicari, R., Landi, P., Bovenzi, F., & Picano, E. (2006). Prognostic value of pharmacological stress echocardiography in diabetic and nondiabetic patients with known or suspected coronary artery disease. *J Am Coll Cardiol* ,Vol. 47, No. 3, (February 2006), pp. 605–610, ISSN 1558-3597.

Cosson, E., Paycha, F., Paries, J. Cattan, S., Ramadan, A., Meddah, D., Attali, J-R., & Valensi, P. (2004) Detecting silent coronary stenoses and stratifying cardiac risk in patients with diabetes: ECG stress test or exercise myocardial scintigraphy? *Diabet Med*, Vol.21, No.4, (April 2004), pp. 342–348, ISSN 1464-5491.

Cosson, E., Nguyen, MT., Pham, I., Pontet, M., Nitenberg, A. & Valensi, P. (2009). N-terminal pro-B-type natriuretic peptide: an independent marker for coronary artery disease in asymptomatic diabetic patients. *Diabetic Medicine,* Vol.26, No.9, (September 2009), pp. 872-879, ISSN 1464-5491.

Criqui, MH., Langer, RD., Fronek, A., Feigelson, HS., Klauber, MR., Mc Cann, TJ., & Browner D. (1992). Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med*, Vol. 326, No.6, (February 1992), pp. 381-386, ISSN 0028-4793.

Cruickshank, K., Riste, L., Anderson, SG., Wright, JS., Dunn, G., & Gosling, RG, (2002) Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function*? Circulation*, Vol.106, No.16, (October 2002), pp.2085–2090, ISSN 1524-4539.

Davies, JR., Rudd, JH., & Weissberg, PL. (2004). Molecular and metabolic imaging of atherosclerosis (review). *J Nucl Med*, Vol.45, No.11, (November 2004), pp.1898 – 1907, ISSN 1071-3581.

De Lorenzo, A., Lima, RS., Siquiera-Filho, AG., & Pantoja, MR. Prevalence and prognostic value of perfusion defects detected by stress technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography in asymptomatic patients with diabetes mellitus and no known coronary artery disease. *Am J Cardiol.*, Vol.90, No.8, (October 2002), pp.827-832, ISSN 0002-9149.

Dinneen, SF. & Gerstein, HC. (1997). The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus. A systematic overview of the literature. *Arch Intern Med*, Vol. 157, No.13, (July 1997), pp.1413-1418, ISSN 1538-3679.

Djaberi, R., Beishuizen, ED., Pereira, AM., Rabelink, TJ., Smit, JW., Tamsma, JT., Huisman, MV., & Jukema, JW. (2008). Non-invasive cardiac imaging techniques and vascular tools for the assessment of cardiovascular disease in type 2 diabetes mellitus *Diabetologia*, Vol. 51, No.9, (September 2008), pp.1581–1593, ISSN1432-0428.

Doobay, AV., & Anand, SS. (2005). Sensitivity and specificity of the ankle-brachial index to predict future cardiovascular outcomes: a systematic review. *Arterioscler Thromb Vasc Biol*, Vol.25, No.7, (July 2005), pp. 1463–1469, ISSN: 1524-4636.

Elhendy, A., van Domburg, RT., Poldermans, D., Bax, JJ., Nierop, PR., Geleijnse, ML., & Roelandt, JR. (1998) Safety and feasibility of dobutamine-atropine stress echocardiography for the diagnosis of coronary artery disease in diabetic patients unable to perform an exercise stress test. *Diabetes Care*, Vol.21, No.11, (November 1998), pp. 1797–1802, ISSN 1935-5548.

Elkeles, RS., Godsland, IF., Feher, MD., Rubens, MB., Roughton, M., Nugara, F., Humphries, SE., Richmond, W., & Flather, MD., (2008). Coronary calcium measurement improves prediction of cardiovascular events in asymptomatic patients with type 2 diabetes: the PREDICT study. *Eur Heart J*, Vol. 29, No. 18, (September 2008), pp.2244-2251, ISSN1522-9645.

Faglia, E., Favales, F., Calia, P., Paleari, F., Segalini, G., Gamba, PL., Rocca, A., Musacchio, N., Mastropasquq, A., Testori, G., Rampini, P., Moratti, F., Braga, A., & Morabito, A. (2002). Cardiac Events in 735 Type 2 Diabetic Patients Who Underwent Screening for Unknown Asymptomatic Coronary Heart Disease: 5-year follow-up report from the Milan Study on Atherosclerosis and Diabetes (MiSAD). *Diabetes Care* ,Vol. 25, No. 11, (November 2002), pp. 2032-2036, ISSN 1935-5548.

Faglia, E., Manuela, M., Antonella, Q., Michela, G., Vincenzo, C., Maurizio, C., Roberto, M., & Alberto, M. (2005) Risk reduction of cardiac events by screening of unknown asymptomatic coronary artery disease in subjects with type 2 diabetes mellitus at high cardiovascular risk: an open-label randomized pilot study. *Am Heart J*, Vol. 149, No.2, (February 2005), pp.e1–6, ISSN 0002-8703.

Folsom AR, Chambless LE, Duncan BB, Gilbert AC,& Pankow JS, Atherosclerosis Risk in Communities Study Investigators (2003) Prediction of coronary heart disease in middle-aged adults with diabetes. *Diabetes Care*, Vol, 26, No.10. (October 2003), pp. 2777–2784, ISSN 1935-5548.

Fukui, M., Kitagawa, Y., Nakamura, N.,Mogami, S., Ohnishi, M., Hirata, C., Ichio, N., Wada, K., Kamuchi, K., Shigeta, M., Sawada, M., Hasegawa, G., & Yoshikawa, T. (2003) Augmentation of central arterial pressure as a marker of atherosclerosis in patients with type 2 diabetes. *Diabetes Res Clin Pract* (February 2003), Vol.59, No.2, (February 2003), pp.153–161, ISSN 0168-8227.

Gaede, P., Vedel, P., Larsen, N., Jensen, GV., Parving, HH., & Pedersen, O. (2003). Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*, Vol.348, No.5, (January 2003, pp.383–393, ISSN 0028-4793.

Gerstein, HC., Mann, JF., Yi, Q., Zinman, B., Dinneen, SF., Hoogwerf, B., Halle, JP., Young, J., Rashkow, A., Joyce, C., Nawaz, S., & Yusuf, S. (2001). Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA*, Vol.286, No.4, (July 2001), pp. 421–426, ISSN 0098-7484.

Giri, S., Shaw, LJ., Murthy, DR., Travin, MI., Miller, DD., Hachamovitch, R., Borges-Neto, S., Berman, DS, Waters, DD., & Heller, GV. (2002). 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*, Vol. 105, No.1, (January 2002), pp. 32– 40, ISSN 1524-4539.

Golomb, BA., Dang, TT., & Criqui, MH. (2006). Peripheral arterial disease: morbidity and mortality implications. *Circulation*, Vol.114, No.7, (August 2006), pp. 688–699, ISSN 1524-4539.

Goraya, T., Leibson, CL., Palumbo, PJ., Weston, SA., Killian, JM., Pfeifer, EA., Jacobsen, SJ., Frye, RL., & Roger, V, (2002). Coronary atherosclerosis in diabetes mellitus: A population based autopsy study. J Am Coll Cardiol, Vol. 40, No.5, (September 2002), pp. 946-953, ISSN 1558-3597.

Grundy, SM., Cleeman, JI., Merz, CN., Brewer, HB Jr., Clark LT., Hunninghake, DB., Pasternak, RC., Smith, SC., & Stone, NJ. for the Coordinating Committee of the National Cholesterol Education Program Endorsed by the National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association (2004). Implications of recent clinical trials for the National Cholesterol

Education Program Adult Treatment Panel III guidelines (review). *Circulation*, Vol.110, No. 2, (July 2004), pp. 227–239, ISSN 1524-4539.

Guzder, RN., Gatling, W., Mullee, MA., Mehta, RL., & Byrne, CD. (2005). Prognostic value of the Framingham cardiovascular risk equation and the UKPDS risk engine for coronary heart disease in newly diagnosed type 2 diabetes: results from a United Kingdom study. *Diabet Med*, Vol.22, No.5, (May 2005), pp. 554–562, ISSN 1464-5491.

Hachamovitch, R., Berman, DS., Shaw, LJ., Kiat, H., Cohen, I., Cabico, AJ., Friedman, J., & Diamond, GA. (1998). Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. *Circulation*, Vol.97, No.6, (February 1998), pp.535–543, ISSN 1524-4539.

Hachamovitch, R., Hayes, SW., Friedman, JD., Cohen, I., & Berman, DS. (2003). Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation*, Vol.107, No.23, (July 2003), pp. 2900–2907, ISSN 1524-4539.

Haffner, SM., Lehto, S., Ronnemaa, T., Pyorala, K., & Laakso, M, (1998). 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*, Vol. 339, No.4 , (July 1998), pp. 229-234, ISSN 1533-4406.

Hamano, K., Abe, M., Komi, R., & Kobayasi, S. (2010). N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) for predicting silent myocardial ischaemia in type 2 diabetes mellitus independent of microalbuminuria. *Diabetes/Metabolism Research and Reviews*, Vol. 26, No.7, (October 2010), pp. 534-539.ISSN 1520-7560.

Hammoud, T., Tanguay, J-F., & Bourassa, MG, (2000). Management of coronary artery disease: therapeutic options in patients with diabetes. *J Am Coll Cardiol*, Vol. 36, No. 2, (August 2000), pp. 355–365, ISSN 1558-3597.

Hatsuda, S., Shoji, T., Shinohara, K., Kimoto, E., Mori, K., Fukumoto, S., Koyama, H., Masanori, E., & Nishizava, Y. (2006). Regional arterial stiffness associated with ischemic heart disease in type 2 diabetes mellitus. *J Atheroscler Thromb*, Vol.13, No.2, (May 2006), pp.114–121, ISSN 1340-3478.

He, ZX., Hedrick, TD., Pratt, CM., (2000). Severity of coronary artery calcification by electron beam computed tomography predicts silent myocardial ischemia. *Circulation*, Vol. 101, No.3, (January 2000), pp.244-251, ISSN 1524-4539.

Hennessy, TG., Codd, MB., Kane, G., McCarthy, C,. McCann, HA., & Sugrue, DD. (1997). Evaluation of patients with diabetes mellitus for coronary artery disease using dobutamine stress echocardiography. *Coron Artery Dis.*, Vol. 8, No.3-4, (March-April 1997), pp. 171–174, ISSN 1473-5830.

Hernandez, C., Candell-Riera, J., Ciudin, A., Francisco, G., Aguade-Bruix, S. & Simo, R. (2011). Prevalence and risk factors accounting for true silent myocardial ischemia: a pilot case-control study comparing type 2 diabetic with non-diabetic control subjects. *Cardiovascular Diabetology* 10:9 doi:10.1186/1475-2840-10-9, (January 2011), ISSN 1475-2840.

Hoff, JA., Quinn, L.,& Sevrukov, A., (2003) The prevalence of coronary artery calcium among diabetic individuals without known coronary artery disease. *J Am Coll Cardiol*, Vol. 41, No.6, (March 2003), pp. 1008–1012, ISSN 0735-1097.

http://www.nhlbi.nih.gov/giudelines/cholesterol/atp3_rpt.htm.

Iskander, S., & Iskandrian, AE. Risk assessment using single-photon emission computed tomographic technetium-99 m sestamibi imaging. *J Am Coll Cardiol*, Vol. 32, No.1, (July 1998), pp.57–62, ISSN 0735-1097.

Jaffer, FA., Libby, P., & Weissleder, R. (2006). Molecular and cellular imaging of atherosclerosis: emerging applications (review). *J Am Coll Cardiol*, Vol. 47, No.7, (April 2006), pp. 1328 –38. ISSN 0735-1097.

Khaleeli, E., Peters, SR., Bobrowsky, K., Oudiz, RJ., Ko, JY., & Budoff, MJ. (2001). Diabetes and the associated incidence of subclinical atherosclerosis and coronary artery disease: implications for management. *Am Heart J*, Vol.141, No. 4, (April 2001), pp. 637– 644, ISSN 0002-8703.

Laakso, M. (1999) Hyperglycemia and cardiovascular disease in type 2 diabetes. *Diabetes*, Vol.48, No.1, (January 1999), pp.937–942, ISSN: 1939-327X.

Lee CD, Folsom AR, Pankow JS, & Brancati FL, For the Atherosclerosis Risk in Communities (ARIC) Study Investigators (2004). Cardiovascular events in diabetic and nondiabetic adults with or without history of myocardial infarction. *Circulation*, Vol.109, No.7, (February 2004), pp.855–860, ISSN 1524-4539.

Mann, JF., Gerstein, HC., Pogue, J., Bosch, J., & Yusuf, S. (2001). Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. *Ann Intern Med*, Vol.134, No.8, (April 2001), pp. 629–636, ISSN 1539-3704.

Marchant, B., Umachandran, V., Stevenson, R., Kopelman, PG., & Timmis, AD. (1993). Silent myocardial ischemia: role of subclinical neuropathy in patients with and without diabetes. *J Am Coll Cardiol*, Vol.22, No.5, (November 1993), pp.1433-1437, ISSN 0735-1097.

Milan Study on Atherosclerosis and Diabetes (MiSAD) Group. (1997). Prevalence of unrecognized silent myocardial ischemia and its association with atherosclerotic risk factors in noninsulin-dependent diabetes mellitus. *Am. J. Cardiol.*, Vol.79, No.2, (January 1997), pp.134-139, ISSN 0002-9149.

Miller, TD., Rajagopalan, N., Hodge, DO., Frye, RL., & Gibbons, RJ. (2004). Yield of stress single-photon emission computed tomography in asymptomatic patients with diabetes. *Am Heart J*, Vol.147, No.5, (May 2004), pp.890-896, ISSN 0002-8703.

Miller, TD., Redberg, RF., & Wackers, FJ.(2006). Screening asymptomatic diabetic patients for coronary artery disease: why not? *J Am Coll Cardiol*, Vol.48, No. 4, (September 2006), pp.761– 764, ISSN1558-3597.

Mortality after 16 years for participants randomized to the Multiple Risk Factor Intervention Trial. *Circulation,* Vol.94, No.5, (September 1996), pp.946–951, ISSN 1524-4539.

Moser, KW., O`Keefe, JH., Jr, Baterman, TM., & McGhie, IA. (2003). Coronary calcium screening in asymptomatic patients as a guide to risk factor modification and stress myocardial perfusion imaging. *J Nucl Cardiol*, Vol. 10, No.6, (November 2003), pp.590-598, ISSN 1071-3581.

Nesto, RW., & Kowalchuk, GJ. (1987). The ischemic cascade: temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia. *Am J Cardiol*., Vol.59, No.7, (March 1987), pp.23C–30C, ISSN 0002-9149.

Nesto, RW., Philips, RT., Kett, KG., Hill, T., Perper, E., Young, E., & Leland, OS Jr, (1988). Angina and exertional myocardial ischemia in diabetic and nondiabetic patients:

assessment by exercise thallium scintigraphy. *Ann Intern Med*, Vol.108, No. 1, (February 1998), pp. 170-175, ISSN 1539-3704.

Nitenberg, A., Pham, I., Antony, I., Valensi, P., Attali, JR., & Chemla, D. (2005) Cardiovascular outcome of patients with abnormal coronary vasomotion and normal coronary arteriography is worse in type 2 diabetes mellitus than in arterial hypertension: a 10 year follow-up study. *Atherosclerosis*, Vol.183, No.1, (November 2005), pp.113–120, ISSN 0021-9150.

O' Sullivan, JJ., Conroy, RM., MacDonald, K., Mc Kenna, TJ., & Maurer, Bj. (1991). Silent ischemia in diabetic men with autonomic neuropathy. *Br Health J,* Vol.66, No.4, (October 1991), pp.313-315, ISSN1687-5958.

Paillole, C., Ruiz, J., Juliard, JM., Leblanc, H., Gourgon, R., & Passa, P. (1995). Detection of coronary artery disease in diabetic patients. *Diabetologia*, Vol. 38, No.6, (June 1995), pp. 726–731, ISSN: 1432-0428.

Penfornis, A., Zimmerman, C., Boumal, D., Sabbah, A., Meneveau, N., Gaulteir-Bourgeois, S., Bassand, JP., & Bernard, Y. (2001). Use of dobutamine stress echocardiography in detecting silent myocardial ischaemia in asymptomatic diabetic patients: a comparison with thallium scintigraphy and exercise testing. *Diabet Med.*, Vol. 18, No.11, (November 2001), pp. 900–905, ISSN 1464-5491.

Prevalence of unrecognized silent myocardial ischemia and its association with atherosclerotic risk factors in noninsulindependent diabetes mellitus: Milan Study on Atherosclerosis and Diabetes (MiSAD) Group. *Am J Cardiol*, Vol.79, No.2, (January 1997), pp.134 –139, ISSN 0002-9149.

Prior, JO., Monbaron, D., Koehli, M., Calcagni, ML., Ruiz, J., & Bischof, DA. (2005). Prevalence of symptomatic and silent stress-induced perfusion defects in diabetic patients with suspected coronary artery disease referred for myocardial perfusion scintigraphy. *Eur J Nucl Med Mol Imaging*, Vol. 32, No. 1, (January 2005), pp.60-69, ISSN 1619-7070.

Pundziute, G., Schuijf, JD., Jukema, JW,. Boersma, E., Scholte, AJHA., Kroft, LJM., van der Wall, EE., & Bax, JJ. (2007). Noninvasive assessment of plaque characteristics with multislice computed tomography coronary angiography in symptomatic diabetic patients. *Diabetes Care*, Vol.30, No.5, (May 2007), pp.1113–1119, ISSN 1935-5548.

Qu, W., Le, TT., Azen, SP., Xiang, M., Wong, ND., Doherty, TM., & Detrano, RC. (2003).Value of coronary artery calcium scanning by computed tomography for predicting coronary heart disease in diabetic subjects. *Diabetes Care*, Vol. 26, No.3, (March 2003), pp.905-910, ISSN 1935-5548.

Raggi, P., Shaw, LJ., Berman, DS., & Callister, TQ. (2004). Prognostic value of coronary artery calcium screening in subjects with and without diabetes. *J Am Coll Cardiol*, Vol. 43, No. 9, (May 2004), pp. 1663–1669, ISSN 1558-3597.

Raggi, P., Cooil, B., Ratti, C., Callister, TQ., & Budoff, M. (2005). Progression of coronary artery calcium and occurrence of myocardial infarction in patients with and without diabetes mellitus. *Hypertension*, Vol.46, No.1, (July 2005), pp.238–243, ISSN: 1524-4563.

Rajagopalan, N., Miller, TD., Hodge, DO., Frye, RL., & Gibbons, RJ. (2005). Identifying high-risk asymptomatic diabetic patients who are candidates for screening stress single-photon emission computed tomography imaging. *J Am Coll Cardiol*, Vol. 45, No.1, (January 2005), pp.43-49, ISSN 1558-3597.

Rana,BS., Davies, JI, Band, MM., Pringle, SD., Morris, A., & Struthers, AD. (2006). B-type natriuretic peptide can detect silent myocardial ischaemia in asymptomatic type 2 diabetes *Heart*, Vol. 92, No.7, (July 2006), pp.916-920, ISSN 1355-6037.

Reaven, PD.,& Sacks, J., Investigators for the VADT (2005). Coronary artery and abdominal aortic calcification are associated with cardiovascular disease in type 2 diabetes. *Diabetologia*, Vol. 48, No.2, (February 2005), pp. 379–385, ISSN 1432-0428.

Rubler, S., Gerber, D., Reitano, J., Chokshi, V., & Fisher, VJ. (1987). Predictive value of clinical and exercise variables for detection of coronary artery disease in men with diabetes mellitus. *Am J Cardiol.* Vol. 59, No.15, (June 1987), pp 1310–1313, ISSN 0002-9149.

Rutter, MK., McComb, JM., Brady, S., & Marshall, SM. (1999). Silent myocardial ischemia and microalbuminuria in asymptomatic subjects with non-insulin-dependent diabetes mellitus. *Am J Cardiol*, Vol.83, No.1, (January 1999), pp.27–31, ISSN 0002-9149.

Rutter, MK., Wahid, ST., McComb, JM., & Marshall, SM. (2002). Significance of silent ischemia and microalbuminuria in predicting coronary events in asymptomatic patients with type 2 diabetes. *J. Am. Coll. Cardiol.* (July 2002), Vol.40, No.1, pp. 56-61, ISSN 1558-3597.

Schaper, J. (1988). Effects of multiple ischemic events on human myocardium: an ultrastructural study. *Eur Heart J*, Vol. 9, No suppl. A, (January 1988), pp. 141-149, ISSN1522-9645.

Schinkel, AFL., Bax, JJ., Geleijnse, ML., Boersma, E., Elhendy, A, Roelandt, JRTC., & Poldermans, D. (2003). Non-invasive evaluation of ischemic heart disease: myocardial perfusion imaging or stress echocardiography. Eur Heart J, Vol.24, No.9, (May 2003) pp.789–800.

Scholte, AHJA., Bax, JJ., Wackers, FJTh. (2006). Screening of asymptomatic patients with type 2 diabetes mellitus for silent coronary artery disease. Combined use of stress myocardial perfusion imaging and coronary calcium scoring *J Nucl Cardiol*, Vol.13, No.1, (January 2006), pp. 11-18, ISSN 1071-3581.

Scholte, AJHA., Schuijf, JD., Kharagjitsingh, AV., Dibbets-Schneider, P., Stokkel, MP., van der Wall, EE.,& Bax, JJ. (2009). Prevalence and predictors of an abnormal stress myocardial perfusion study in asymptomatic patients with type 2 diabetes mellitus. *Eur J Nucl Med Mol Imaging*, Vol.36, No.4, (April 2009), pp.567–575, ISSN 1619-7070.

Schuijf, JD., Bax, JJ., Jukema, JW., Lamb, HJ., Vliegen, HW., Salm, LP., de Ross, A., & van der Wall, EE. (2004). Noninvasive angiography and assessment of left ventricular function using multislice computed tomography in patients with type 2 diabetes. *Diabetes Care*, Vol.27, No.12, (December 2004), pp.2905–2910, ISSN 1935-5548.

Schuijf, JD., Pundziute, G., Jukema, JW., Lamb, HJ., van der Hoeven, BL., de Roos, A., van der Wall, EE., & Bax, JJ. (2006). Diagnostic accuracy of 64-slice multislice computed tomography in the noninvasive evaluation of significant coronary artery disease. *Am J Cardiol*, Vol.98, No.2, (July 2006), pp.145–148, ISSN 0002-9149.

Schuijf, JD., Bax, JJ., Jukema, JW., der Wall, EE., Lamb, HJ., de Roos, A., Mollet, NR., Cademartiri, F., & Feyter, PJ. (2006). Do risk factors influence the diagnostic accuracy of noninvasive coronary angiography with multislice computed tomography? *J Nucl Cardiol*, Vol.13, No.5, (September 2006), pp.635–641, ISSN 1071-3581.

Schurgin, S., Rich, S., & Mazzone, T. (2001). Increased prevalence of significant coronary artery calcification in patients with diabetes. *Diabetes Care*, Vol. 24, No.2, (February 2001), pp. 335–338, ISSN 1935-5548.

Scognamiglio, R., Negut, Christian., Ramondo, A., Tiengo, A., & Avogaro, A. (2006). Detection of coronary artery disease in asymptomatic patients with type 2 diabetes mellitus. *J Am Coll Cardiol*, Vol. 47, No.1, (January 2006), pp.65-71, ISSN 0735-1097.

Shaw, LJ., & Iskandrian, AE, (2004). Prognostic value of gated myocardial perfusion SPECT (review). *J Nucl Cardiol*, Vol. 11, No. 2, (March 2004), pp. 171– 185, ISSN: 1532-6551.

Sorajja, P., Chareonthaitawee, P., Rajagopalan, N., Miller, TD., Frye, RL., Hodge, DO., & Gibbons, RJ. (2005). Improved survival in asymptomatic diabetic patients with high-risk SPECT imaging treated with coronary artery bypass grafting. *Circulation,* Vol.112, No.9, (August 2005), Suppl. 1 pp. I-311–316, ISSN: 1524-4539.

Stamler, J., Vaccaro, O., Neaton, JD., & Wentworth, D, (1993). Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care*, Vol. 16, No.2, (February 1993), pp. 434-444, ISSN 1935-5548.

The BARI Investigators. Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease: the Bypass Angioplasty Revascularization Investigation. *Circulation*, Vol. 96, No.6, (September 1997), pp.1761-1769, ISSN 1524-4539.

The BARI Investigators: The Final 10 Year Follow-Up Results From the BARI Randomized Trial. *J Am Coll of Cardiol*, Vol. 49, No.15, (April 2007), pp. 1600-1606, ISSN 0735-1097.

The BARI 2D Study Group (2009). A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med*, Vol. 360, No. 24, (June 2009), pp. 503-2514, ISSN 0028-4793.

Valensi, P., Sachs, R-N., Harfouche, B., Lormeau, B., Paries, J., Cosson, E., Paycha, F., Leutenegger, M., & Attali, J-R. (2001). Predictive value of cardiac autonomic neuropathy in diabetic patients with or without silent myocardial ischemia. *Diabetes Care*, Vol.24, No.2, (February 2001), pp. 339–343, ISSN 1935-5548.

Valensi, P., Paries, J., Brulport-Cerisier, V., Torremocha, F., Sachs, RN., Vanzetto, G., Cosson, E., Lormeau, B., Attali, JR., Marechaud, R, Estour, B, & Halimi, S. (2005). Predictive value of silent myocardial ischemia for cardiac events in diabetic patients: influence of age in a French multicenter study. *Diabetes Care*, Vol. 28, No.11, (November 2005), pp.2722–2727, ISSN 1935-5548.

van der Meer, IM., Iglesias del Sol, A, Hak, AE, Bots, ML., Hofman, A., & Witteman, JC. (2003). Risk factors for progression of atherosclerosis measured at multiple sites in the arterial tree: the Rotterdam Study. *Stroke*, Vol.34, No.10, (October 2003), pp.2374–2379, ISSN 0039-2499.

Vanzetto, G., Halimi, S., & Hammoud, T. Prediction of cardiovascular events in clinically selected high-risk NIDDM patients. Prognostic value of exercise stress test and thallium-201 single-photon emission computed tomography. *Diabetes Care*, Vol.22, No.1, (January 1999), pp.19-26, ISSN 1935-5548.

Vinik, AI., Maser, RE., Mitchell, BD., & Freeman, R. (2003). Diabetic autonomic neuropathy. *Diabetes Care*, Vol.26, No.5, (May 2003), pp.1553–1579, ISSN 1935-5548.

Wackers, FJ., Young, LH., Inzzuchi, SE., Chuyn, DA., Davey, JA., Barrett EJ., Taillefer, R., Wittlin, SD., Heller, GV., Filipchuck, N., Engel, S., Ratner, RE., & Iskandrian, AE. . For The Detection of Ischemia in Asymptomatic Diabetics Investigators (2004). Detection of silent myocardial ischemia in asymptomatic diabetic subjects; the DIAD study. *Diabetes Care*, Vol. 27, No.8, (August 2004), pp.1954-1961, ISSN 1935-5548.

Wagenknecht, LE., Zaccaro, D., Espeland, MA., Karter, AJ., O'Leary, DH., & Haffner, SM. (2003). Diabetes and progression of carotid atherosclerosis: the insulin resistance atherosclerosis study. *Arterioscler Thromb Vasc Biol*, Vol. 23, No.6, (June 2003), pp.1035–1041, ISSN: 1524-4636.

Waxman, S., Ishibashi, F., & Muller, JE. (2006). Detection and treatment of vulnerable plaques and vulnerable patients: novel approaches to prevention of coronary events (review). *Circulation*, Vol.114, No.28, (November 2006), pp. 2390–411, ISSN 1524-4539.

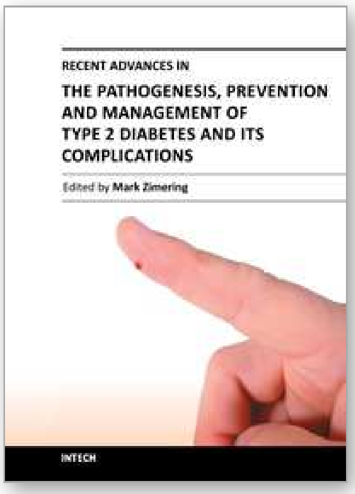
Weber, T., Auer, J., O'Rourke, MF., Kvas, E., Lassing, E., Berent, R., & Eber, B. (2004). Arterial stiffness, wave reflections, and the risk of coronary artery disease. *Circulation*, Vol.109, No.2, (January 2004), pp.184–189, ISSN 1524-4539.

Wild, S., Roglic, G., Green, A., Sicree, R., & King, H, (2004). Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. *Diabetes Care*, Vol. 27, No. 5, (May 2004), pp. 1047–1053, ISSN 1935-5548.

Wong, ND., Rozanski, A., Gransar, H., Miranda-Peats, R., Kang, X., Hayes, S., Shaw, L., Friedman, J., Polk, D., & Berman, DS. (2005). Metabolic syndrome and diabetes are associated with an increased likelihood of inducible ischemia among patients with subclinical atherosclerosis. *Diabetes Care*, Vol.28, No. 6, (June 2005), pp.1445-1450, ISSN 1935-5548.

Young, LH., Wackers, FJT., Chyun, DA., Davey, JA., Barrett, EJ., Taillefer, R., Heller, GV., Iskandrian, AE., Wittlin, SD., Filipchuk, N., Ratner, RE.,& Inzucchi, SE., for the DIAD Investigators (2009). Cardiac Outcomes After Screening for Asymptomatic Coronary Artery Disease in Patients With Type 2 Diabetes .The DIAD Study: A Randomized Controlled Trial. (Reprinted with Corrections) *JAMA*, Vol. 301, No. 15, (April 2009), pp.1547-1555, ISSN 0098-7484.

Zellweger, MJ., Hachamovitch, R., Kang, X., Hayes, SW., Friedman, JD., Germano, G., Pfisterer, ME., & Berman DS. (2004). Prognostic relevance of symptoms versus objective evidence of coronary artery disease in diabetic patients. *Eur Heart J*, Vol. 25, No.7, (April 2004), pp. 543-550, ISSN1522-9645.



Recent Advances in the Pathogenesis, Prevention and Management of Type 2 Diabetes and its Complications
Edited by Prof. Mark Zimering

ISBN 978-953-307-597-6
Hard cover, 442 pages
Publisher InTech
Published online 29, August, 2011
Published in print edition August, 2011