Chapter 2

# 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

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# Abstract

Diabetes mellitus and coronary artery disease constitute an ominous clinical combination. Rates of morbidity and mortality as a result of cardiovascular complications are high in patients with type 2 diabetes mellitus. Screening for silent coronary artery disease, to detect the disease in an early stage and to be able to initiate early appropriate treatment, has recently become an important focus of clinical investigation. Recent prospective studies have shown that the overall prevalence of silent coronary artery disease in truly asymptomatic individuals with diabetes is about 20% to 25%. It is of practical and clinical importance to explore ways to "enrich" the target screening population. In this editorial point of view the relative roles of stress radionuclide myocardial perfusion imaging and coronary calcium scoring are examined. The two methodologies appear to have complementary values for the screening of asymptomatic individuals with diabetes mellitus. A screening algorithm involving sequential use of coronary calcium scoring and subsequent stress radionuclide myocardial perfusion imaging is proposed.

# Introduction

The prevalence of diabetes mellitus has reached epidemic proportions and constitutes a major public health problem. Worldwide, it affects almost 200 million individuals, and this number is expected to increase exponentionally as the population ages and obesity and sedentary life style become increasingly ubiquitous. In the United States almost 1.3 million individuals are diagnosed with diabetes each year.[16]

Cardiovascular complications, including coronary artery disease (CAD), are the leading causes of morbidity and mortality in individuals with type 2 diabetes mellitus.[6] The overall prevalence of CAD has been reported to be as high as 60% in patients with diabetes referred for stress testing.[17] The 10-year mortality rate in patients with known CAD and diabetes exceeds 70%.[7] Some studies suggest that the risk for future cardiac deaths in patients with diabetes without known CAD is similar to that in non-diabetic patients with overt clinical CAD.[7] In addition, early and late outcomes of diabetic patients with acute coronary syndrome are worse than those of their nondiabetic patient counterparts.

To compound the problem, myocardial ischemia is often asymptomatic in patients with diabetes mellitus, and CAD is frequently in an advanced state when it becomes clinically manifest.[8, 9] Coronary artery bypass grafting in patients with diabetes has been shown to improve the survival rate and may be superior to percutaneous coronary intervention, possibly due to the presence of more diffuse atherosclerosis.[9] Moreover, the need for repeated percutaneous coronary intervention or coronary artery bypass grafting is significantly greater in patients with diabetes as compared to nondiabetic patients.[18]

The previously described adverse clinical outcomes in patients with diabetes underscore the need to develop practical approaches for detecting CAD in an early stage before clinical complications have occurred. A number of noninvasive tests are available to detect myocardial ischemia: exercise electrocardiography, stress myocardial perfusion imaging (MPI), and stress echocardiography. Other noninvasive techniques may be able to detect the generalized process of atherosclerotic disease, such as imaging of the vessel wall of carotid arteries via high-resolution ultrasound or coronary artery calcium (CAC) scoring via computed tomography (CT). It is currently unclear whether, for the purpose of screening, detection of these early markers of CAD is preferred over the actual visualization of myocardial ischemia. In this editorial point of view we will focus on the potential roles of stress MPI and CT CAC scoring as two complementary approaches for screening asymptomatic patients with diabetes. In addition, on the basis of the available evidence in the literature, we propose a potential algorithm for this purpose.

**MPI in symptomatic patients with diabetes mellitus**

Although the role of stress MPI for risk stratification is well established in the general population, similar data are relatively scarce in patients with diabetes mellitus. Several studies in the literature suggest a high prevalence of abnormal MPI studies in diabetic patients (Table 1). Zellweger et al noted that this high prevalence was dependent of the clinical presentation: i.e. angina or shortness of breath. Patients with diabetes who presented with shortness of breath had a significantly higher incidence (51%) of abnormal MPI than patients who complained of angina (44%).[19] Symptomatic patients with diabetes in addition had a significantly higher hard and total cardiac event rate than patients without diabetes. Giri et al observed that the cardiac events rate in diabetic patients was 8.6%, as compared to 4.5% in non-diabetic patients.[20] As in the general population, stress MPI is able to stratify patients with diabetes in high- and low-risk prognostic groups (Table 1). The cardiac event rate for any given MPI abnormality was higher in diabetic patients than in nondiabetic patients, ranging from 3.6 % to 13.2, and diabetic women had the worst outcome. Moreover, patients with diabetes and normal MPI had a higher cardiac event rate than non diabetic patients, ranging from 0.7 % to 3.6 %. Not only is the outcome of patients with diabetes and normal MPI not as favourable as in patients without diabetes (< 1%), the "warrantee" period of normal MPI appears also to be shorter than 2 years.[20] It is conceivable that his may be attributed to accelerated progression of atherosclerosis in the diabetic state.

**MPI in asymptomatic patients with diabetes mellitus**

Nesto et al reported in 1990 that 57% of asymptomatic patients with diabetes mellitus and peripheral vascular disease had evidence of silent CAD on stress MPI.[26] A number of subsequent studies have confirmed the presence of silent ischemia in asymptomatic patients with diabetes. [19, 25-38] The reported prevalence of silent ischemia, however, varied markedly between studies, from 6% to 59%.[19, 30, 34, 36, 38-40] This wide range in the prevalence of silent ischemia is most likely related to differences in patient selection, stress methodology, imaging techniques and interpretive definitions.

Reviewing the available literature on stress testing in asymptomatic patients with diabetes, one can distinguish 3 types of studies (Table 2): (A) retrospective database analyses of patients referred for stress testing who had diabetes, (B) retrospective database analyses of known asymptomatic patients with diabetes referred for stress testing, and (C) prospective studies in truly asymptomatic patients with diabetes. Because of selection

**Table 1.** MPI in symptomatic patients with diabetes

| Year | Author (ref) | Nr Pts | Tracer | Stressor | Abnormal MPI (%) | Mean F/U (m) | HE in abnormal MPI (%/yr) | HE in normal MPI (%/yr) |
|---|---|---|---|---|---|---|---|---|
| 1987 | Felsher[21] | 123 | $^{201}$TL | Exercise | 56 | 36 | 4.8 | 1.3 |
| 1999 | Kang[22] | 1271 | $^{201}$TL,MIBI | Exercise, Adenosine | 41 | 24±8 | 3.9-7.9 | 1.2 |
| 2002 | Schinkel[23] | 207 | MIBI | Dobutamine | 64 | 49±29 | 6.6* | 0.7* |
| 2002 | Giri[20] | 929 | $^{201}$TL,MIBI | Exercise, Adenosine | 48 | 36±18 | 5.0-6.4 | 3.6-3.9 |
| 2003 | Berman[24] | 5333 | $^{201}$TL,MIBI | Adenosine | 37-62 | 27±9 | 4.7-9.0* | 1.8-2.5 |
| 2004 | Zellweger[19] | 911 | $^{201}$TL,MIBI | Exercise, Adenosine | 44-51 | 24 | 5.6-13.2 | 2.0-3.3 |
| 2004 | Miller[25] | 2998 | $^{201}$TL,MIBI | Exercise, Adenosine, Dipyridamole, Dobutamine | 60 | 70±42 | 3.6-5.9 | NA |

F/U, follow-up; HE, hard events (cardiac death or non-fatal myocardial infarction); MIBI, technetium-99m sestamibi; MPI, myocardial perfusion imaging; NA, not available; $^{201}$TL, thallium-201 chloride. *= only cardiac death.

bias, the first type of study in the literature (section A, Table 2) typically showed a high prevalence (41%-58%) of abnormal stress MPI results and a high cardiac event rate.[20, 22, 38] It is likely these patients were referred for stress testing because of typical or atypical symptoms and/or perceived clinical high risk. No details with regards to the type of diabetes mellitus or its treatment, duration, or comorbidity were generally available. The second type of studies in the literature (section B, Table 2) showed a lower prevalence of abnormal stress MPI and cardiac event rate.[19, 25, 34, 37] Nevertheless, these patients may not be representative of asymptomatic patients with diabetes in the larger population, because they were referred for stress MPI, for example, before noncardiac surgery. The mean prevalence of silent ischemia ranged from 26%-39%, although Miller et al reported abnormal MPI in 59% of presumably asymptomatic patients.[25] Because of the retrospective nature of these two types of studies, there remains uncertainty about the true prevalence of silent ischemia in asymptomatic patients with diabetes.

**Prospective studies in asymptomatic patients with diabetes mellitus**

Several prospective studies have been performed in truly asymptomatic patients with diabetes mellitus (section C, Table 2).[30, 31, 36, 40-42] In general, these studies showed a lower prevalence of silent CAD, ranging from 6% to 22%. However, there were important differences in design and stress testing methodology. These methodological differences

**Table 2.** Prevalence of abnormal MPI and cardiac events in retrospective data base analyses and prospective studies in patients with type 2 diabetes mellitus.

| Year | Author (ref) | Nr Pts | Mean F/U (m) | Tracer | Stressor | Abnormal MPI (%) | HE with abnormal MPI (%/yr) | HE with normal MPI (%/yr) |
|---|---|---|---|---|---|---|---|---|
| *A: Retrospective database analysis in patients with diabetes* | | | | | | | | |
| 1999 | Kang[22] | 1271 | 24±8 | $^{201}$TL,MIBI | Exercise, Adenosine | 41 | 3.9-7.9 | 1.2 |
| 2002 | Giri[20] | 929 | 36±18 | $^{201}$TL,MIBI | Exercise, Adenosine | 48 | 5.0-6.4 | 3.6-3.9 |
| 2005 | Rajagopalan[38] | 1427 | 70±42 | $^{201}$TL,MIBI | Exercise, Adenosine, Dipyridamole, Dobutamine | 58 | 5.9-3.6 | 1.6 |
| *B: Retrospective database analysis in asymptomatic patients with diabetes* | | | | | | | | |
| 2002 | De Lorenzo[34] | 180 | 36±18 | MIBI | Exercise, Dipyridamole | 26 | 9 | 2 |
| 2004 | Zellweger[19] | 826 | 12-102 | $^{201}$TL,MIBI | Exercise, Adenosine | 39 | 3.4 | 1.6 |
| 2004 | Miller[25] | 1738 | 70±42 | $^{201}$TL,MIBI | Exercise, Adenosine, Dipyridamole, Dobutamine, | 59 | NA | NA |
| 2005 | Prior[37] | 133 | | $^{201}$TL,MIBI | Exercise, Dipyridamole | 37 | NA | NA |
| *C: Prospective studies in asymptomatic patients with diabetes* | | | | | | | | |
| 1999 | Janand[31] | 203 | - | $^{201}$TL | Exercise, Dipyridamole | 19 | NA | NA |
| 2001 | Penfornis[41] | 56 | - | $^{201}$TL | Exercise, Dipyridamole | 21 | NA | NA |
| 2002 | Faglia[30] | 925 | 60 | $^{201}$TL | Exercise | 6 | 3.9# | 0.44# |
| 2004 | Cossson[40] | 262 | 42±24 | $^{201}$TL | Exercise, Dipyridamole | 16 | 0.75 | 3.4 |
| 2004 | Wackers[36] | 1123 | 60 | MIBI | Adenosine | 22 | Results expected in 2007 | |
| 2005 | Anand[42] | 510 | 18±5 | MIBI | Exercise, Dipyridamole | 13 | NA | NA |

F/U, follow-up; HE, hard events: cardiac death, nonfatal myocardial infarction, **#=** HE included resting and effort angina; MIBI, technetium-99m sestamibi; MPI, myocardial perfusion imaging; $^{201}$TL, thallium-201 chloride.

may explain the variation in observed prevalence of silent CAD. For example, in the Milan Study on Atherosclerosis and Diabetes (MiSAD) asymptomatic patients with diabetes had exercise electrocardiography as the first diagnostic test.[30] Only if this test was abnormal, stress MPI was performed. It is possible that, because of the insensitivity of exercise electrocardiography, the overall observed prevalence of observed silent CAD was low (6%). Moreover, fatal cardiac event rate was low as well. Janand-Delenne et al and Cosson et al performed either exercise electrocardiography or thallium-201 imaging, whereas Penfornis et al used exercise electrocardiography, stress MPI or stress echocardiography.[31, 40, 41] Currently, 2 prospective studies in asymptomatic patients with diabetes are still ongoing. Only in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study was the same stress test (adenosine Tc-99m Sestamibi MPI) consistently performed in all 522 randomized patients.[36] In the DIAD study 22% of patients had abnormal MPI results. In the study by Anand et al, 510 asymptomatic patients with diabetes had pre-screening performed using electron-beam CT (EBCT). If the EBCT CAC score was 100 Agatston units or greater, stress MPI was performed.[43] The imputed prevalence of silent CAD in their study was 13%. These 2 recent prospective studies indicated that the prevalence of silent CAD in truly asymptomatic patients is considerably lower than was suggested by retrospective database analyses. Thus, in order for screening to be cost-effective, one should find ways to "enrich" the target population of asymptomatic patients with diabetes.

**Value of CAC scoring in patients with diabetes mellitus**

CT techniques (EBCT, multislice CT) allow for noninvasive detection and quantification of CAC, an early marker of CAD.[44] Various studies have recently demonstrated the prognostic significance of CAC scores in the general population.[45-48] Because of the previously mentioned ominous association between CAD and diabetes mellitus, the prevalence of CAC has been explored in patients with diabetes without known CAD.[49] In a cohort study of 30,904 asymptomatic individuals, including 1,075 diabetics, the median CAC score was in general higher in patients with diabetes than in patients without diabetes. In addition, the likelihood of having a CAC score in the highest age/gender quartile was 70% greater for patients with diabetes. Raggi et al investigated the prognostic value of CAC in subjects with and without diabetes mellitus.[50] In a cohort of 10,377 asymptomatic individuals, which included 903 diabetics, the mean CAC score and death rate were significantly higher in subjects with diabetes than in those without diabetes. Moreover, for every increase in CAC score, there was a greater increase in mortality for diabetic

patients than for patients without diabetes. In contrast, patients with diabetes and no evidence of CAC had a similar survival compared to that of individuals without diabetes and no detectable CAC. Qu et al noted that subjects with diabetes and low CAC score had a four-fold increase in hard cardiac event rate compared with nondiabetic subjects with a low CAC score.[51] On the other hand, the prognostic value of CAC as a continuum was weaker in patients with diabetes than in patients without diabetes.

Elkeles et al found a close relationship between waist-hip ratios, systolic blood pressure and CAC score.[52] Thus, CAC scoring may be linked to the metabolic syndrome in type 2 diabetics. In asymptomatic individuals, Moser et al noted that the prevalence of CAC was significantly increased when more than 3 cardiac risk factors were present.[53] Thus, the presence of multiple cardiac risk factors could be used as a justification for CAC screening. Furthermore, an Agatston score of 400 or greater appeared to be a logical threshold for initiating further testing with stress MPI.[53] These data suggest that CAC scoring may have value as an approach to enrich target population of asymptomatic patients with diabetes for screening.

**Relative values of CAC score and ischemia on MPI for detecting CAD**

Currently, only limited data are available on the relative values of CAC and MPI for detection silent CAD and prognostication. He et al prospectively examined 3,895 asymptomatic subjects with EBCT; 411 of these underwent stress MPI.[54] Only 6.8% of these subjects had known diabetes mellitus. The likelihood of stress-induced myocardial ischemia on MPI increased in parallel to the CAC score, in particular at CAC scores of 400 or greater. Of patients with CAC score 400 or greater, 46% had demonstrable stress-induced myocardial ischemia on MPI.

Berman et al evaluated 1,195 patients without known CAD, including 51% asymptomatic individuals and 11.6 % patients with diabetes.[55] The authors noted that the likelihood of stress-induced myocardial ischemia on MPI was very low (<2%) if the CAC score was lower than 100 Agatston units. However, when the CAC score exceeded 400 Agatston units, a relatively high percentage of patients had abnormal MPI studies. These data suggested a role for CAC scoring as a gatekeeper for patients who may benefit from further risk stratification with stress MPI. Alternatively, 56% of patients with normal MPI had CAC scores of 100 and greater, indicating that absence of stress-induced myocardial ischemia does not exclude preclinical presence of atherosclerosis.

Wong et al similarly explored the interaction between CAC scoring and stress MPI in

1,043 patients without known CAD.[56] Of the patients, 313 had metabolic abnormalities, including 140 patients with diabetes mellitus and 173 patients with metabolic syndrome. Again, a CAC score lower than 100, which occurred in approximately 2 % of patients, was associated with absence of stress-induced ischemia on MPI. The likelihood of stress-inducible ischemia increased in parallel with increasing CAC score. It was noted that the presence of diabetes mellitus or metabolic syndrome significantly increased the likelihood of abnormal MPI. For instance, of patients with CAC score of 400 and greater, 13.6% of patients without metabolic abnormalities had stress induced ischemia, whereas this occurred in 23.4% of those with metabolic abnormalities.

As mentioned previously, one recent study explored the combined use of CAC assessment with EBCT and MPI in patients with asymptomatic diabetes.[43] Anand et al evaluated 510 asymptomatic patients with type 2 diabetes using EBCT to assess CAC. Stress MPI was performed in 127 (25%) patients with a CAC score greater than 100 Agatston units. For comparison, 53 randomly selected patients with a CAC score of 100 or less also underwent stress MPI. None of the patients with CAC score of 10 or less had abnormalities on MPI. An increasing prevalence of abnormal MPI studies was noted in patients with higher CAC score. Specifically, 18.4% of patients with a CAC score between 11 and 100 had ischemia, whereas 71.4% of patients with a CAC score greater than 1000 had ischemia. It should be noted that the incidences of abnormal MPI again are higher than those observed in the nondiabetic cohorts.[55] These observations suggest that sequential use of EBCT and MPI may optimize screening of asymptomatic diabetic patients and that EBCT may be used as gatekeeper for stress MPI. The clinical relevance of these findings is further underlined by the prognostic data in the study by Anand et al. During a mean follow-up of 18±5 months, no events occurred in patients with a CAC score of 10 or less; as compared with 82% of events occurring in patients with a CAC score greater than 400. Of note, the CAC score and the extent of abnormalities on MPI were the only predictors of future cardiac events.

# Conclusion

Stress-induced abnormalities on MPI and positive CAC scores represent two different aspects of CAD. The first one reflects the pathophysiologic consequences of luminal obstructive CAD, whereas the second one indicates the presence of the atherosclerotic process with calcium deposition in the vessel wall.

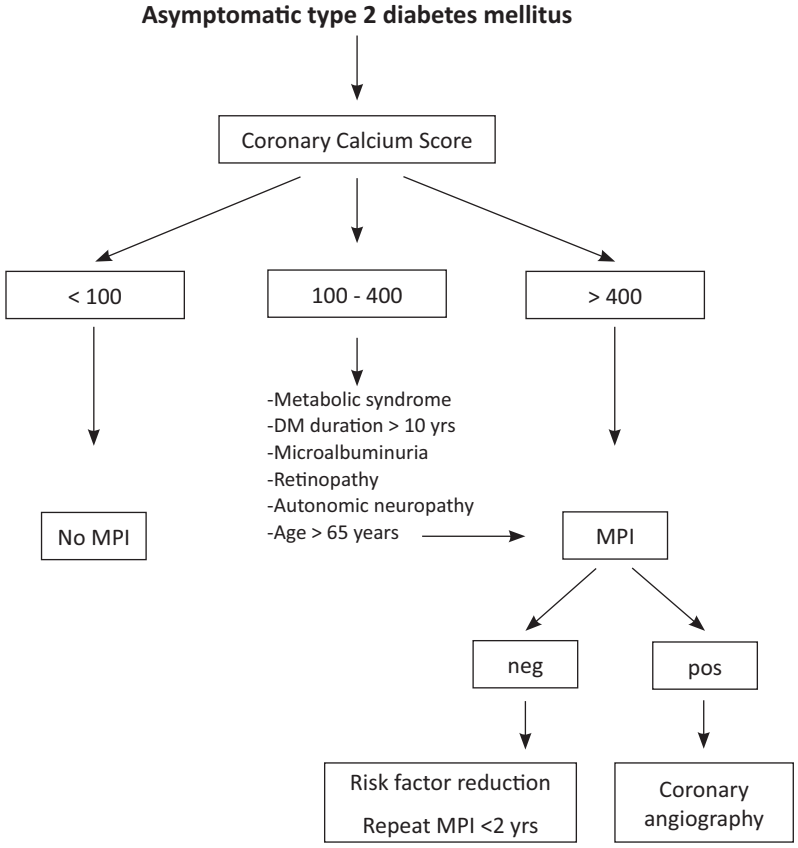
The recent findings of truly prospective studies in asymptomatic patients with diabetes mellitus, suggest a relatively low prevalence of silent CAD as evidenced by abnormal MPI. Although in most patients the MPI abnormalities were relatively modest, a significant number of patients had markedly abnormal test results.

CAC may occur in patients with and without abnormal MPI, but with increasing severity of CAC scores, the prevalence and severity of stress-induced MPI abnormalities increase. The screening of populations predisposed to CAD is performed to rule out (presumably indicating good prognosis) as well as to rule in (and treat) disease. At this time, it is not entirely clear, although presumed, that early detection of silent CAD and its treatment improves long-term outcome of asymptomatic individuals. Because of the relatively low overall prevalence of silent CAD (approximately 22%) it appears that screening all asymptomatic patients with diabetes mellitus by stress MPI may not be cost effective. Moreover, only a small number of patients may have severe MPI abnormalities. Thus it is important to device ways to enrich the target population. It has been suggested that conventional cardiac risk factors, duration of diabetes, macro and microvasculopathy, circulating markers such as C-reactive protein or plasminogen activator inhibitor-1 might be helpful to construct a “high-risk profile” for asymptomatic patients with diabetes mellitus. In the DIAD study none of these variables was associated with MPI abnormalities. Only male gender, body-mass-index and marked cardiac autonomic dysfunction were statistically associated with markedly abnormal MPI. The study by Anand et al suggests that CAC scoring might be an approach to identify an “enriched” asymptomatic patient population.

We propose an algorithm for the screening of asymptomatic diabetics (Figure 1). The first step of screening consists assessment of the CAC score by CT scanning. If the Agatston score is lower than 100, the yield of stress MPI is likely to be low and may not be indicated. If the Agatston score is between 100 and 400 and any of the following is present: metabolic syndrome, age greater than 65 years, duration of diabetes greater than 10 years, microalbuminuria, retinopathy, autonomic cardiac neuropathy, stress MPI appears justified. If the Agatston score is greater than 400, stress MPI is definitely indicated. If stress MPI shows evidence of myocardial ischemia, coronary angiography is indicated. If stress MPI is normal, aggressive medical treatment should be instituted and stress MPI has to be repeated within two years.

Prospective studies may be conducted to evaluate the effectiveness of such a screening approach and answer the following questions: Does the stepwise approach outlined in the algorithm yield higher prevalence of silent CAD? Is the outcome in patients with

**Figure 1.** Algorithm for screening of asymptomatic patients with diabetes mellitus.




MPI, myocardial perfusion imaging; DM, diabetes mellitus

low CAC score indeed favourable? Whether screening and early detection of disease ultimately result in improve outcome can only be evaluated in a large randomized treatment trial. It is conceivable that the BARI-2 trial will provide a partial answer to this pertinent question.