Predictors of coronary heart disease in Japanese patients with type 2 diabetes: Screening for coronary artery stenosis using multidetector computed tomography

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ABSTRACT

Aims/Introduction: Multidetector computed tomography (MDCT) coronary angiography has been applied as a tool for non-invasive evaluation of the coronary arteries. The purpose of the present study was to evaluate the effectiveness of MDCT in screening for coronary artery disease (CAD), and to identify the indications for screening in diabetes patients with CAD.

Materials and Methods: The study population consisted of 52 Japanese type 2 diabetes patients who underwent examination with a 64-slice MDCT scanner, electrocardiogram (ECG), echocardiography and ultrasonographic scanning of the carotid arteries. Regression analysis was carried out to assess the correlation between MDCT results and CAD risk factors.

Results: Stenosis of the coronary artery was detected in 19/52 patients. Of the 19 patients, 7 patients had no symptoms, including chest pain, and no ischemic changes in ECG. Significant differences between patients with stenosis and those without stenosis were detected by mean IMT (1.21 vs 0.95 mm), and duration of diabetes (20 vs 13 years). Two-tailed χ^2-test showed that a duration of diabetes of more than 20 years (odds ratio 6.222) and more than 1.1 mm of mean-IMT (odds ratio 4.600) significantly correlated with the stenosis.

Conclusions: It was shown that MDCT is useful in detecting coronary artery stenosis in diabetic patients without symptoms of CAD or ECG abnormality, and the predictors of CAD are mean IMT and duration of diabetes. It is recommended that patients with more than 1.1 mm mean IMT at the carotid artery and/or more than 20 years duration of diabetes should be screened for CAD by carrying out MDCT. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2009.00003.x, 2010)

KEY WORDS: Cronary artery disease, Multidetector computed tomography, Silent myocardial ischemia

INTRODUCTION

In 2007, 246 million people had diabetes worldwide, and its prevalence is expected to continue increasing. A close relationship between type 2 diabetes and the development of atherosclerosis exists, and type 2 diabetes is associated with a two to fourfold increase in coronary artery disease (CAD)[1]. In fact, cardiovascular disease is the leading cause of death in this patient population. Myocardial ischemia in patients with diabetes is often asymptomatic and frequently in an advanced stage when it becomes clinically manifest. Once CAD is symptomatic in patients with diabetes, morbidity and mortality are high and significantly worse than those in patients without diabetes.

Therefore, early identification of CAD is of paramount importance in patients with diabetes[2–4].

Non-invasive tests, including electrocardiogram (ECG), echocardiography and myocardial perfusion scintigraphy, have been used to detect CAD in diabetic patients. Nonetheless, after normal findings of the tests, elevated event rates are still observed in diabetic patients compared with non-diabetic individuals. Furthermore, direct visualization of the coronary arteries is preferred because patients with diabetes frequently have diffuse, multivessel CAD. Although conventional angiography is carried out to evaluate the presence and extent of CAD, this is an invasive approach associated with a minimal but definitive risk of complications. Therefore, non-invasive techniques, which are capable of directly visualizing the coronary arteries, are required for further refinement of prognostication in diabetes patients[2].

Recently, contrast-enhanced multidetector computed tomography (MDCT) coronary angiography has been shown to be a

tool for non-invasive visualization of the coronary arteries. MDCT permits the detection of coronary lesions with high sensitivity and specificity, which could be valuable for preventing risk during examination[5–9]. Furthermore, MDCT is useful for the evaluation of coronary plaque characteristics[10]. The purpose of the present study was to evaluate the indication of MDCT for the screening of CAD, especially asymptomatic CAD, and to identify the predictors of CAD in Japanese patients with type 2 diabetes.

MATERIALS AND METHODS

Subjects
Between June 2006 and December 2007, 56 patients with type 2 diabetes were enrolled for the present study. The inclusion criteria were: (i) diabetes was diagnosed according to the American Diabetes Association criteria[11]; (ii) absence of a history of myocardial infarction; (iii) absence of renal failure (serum creatinine >1.5 mg/dL [114 mol/L]); and (iv) absence of an allergic history to iodinated contrast media. The enrolled patients satisfied all criteria ($n = 56$). Four patients were excluded because they manifested arrhythmia or tachycardia of more than 75 b.p.m. ($n = 3$), and severe calcification of coronary arteries that caused blooming artifacts and obscured over 75% of the entire vessel lumen in the proximal segment of the coronary artery ($n = 1$). Consequently, 52 patients were available for the assessment, they were 37 men and 15 women ranging in age from 34 to 81 years (mean 66.2 ± 11.8 years). The present study was approved by the ethical committee of Kumamoto University School of Medicine. Informed consent was obtained from each patient.

Physical examinations were carried, and blood and urine samples were obtained from patients for laboratory testing. A resting 12-lead ECG was recorded, and we determined Q-wave myocardial infarction, ischemic ST-segment change (horizontal and downsloping ST-segment depression of over 0.3 mV or ST-segment elevations of more than 0.1 mV) or T-wave change were determined to be 'ischemic change positive'. Ankle-brachial blood pressure index (ABI) and pulse wave velocity (PWV) were measured using an automatic waveform analyzer (BP-203RPEII, Colin, Komaki, Japan). Ultrasonographic scanning of the carotid arteries was carried out using an echotomographic system (SDU-2200, Shimadzu, Kyoto, Japan) and carotid intima-media thickness (IMT) was measured as described previously[12]. Echocardiography (Vivid-7, GE-Vingmed, Milwaukee, WI, USA and SSA-770A, Toshiba Medical Systems, Tokyo, Japan) was also carried out. Wall motion was analyzed using the 17-segment model and evaluated by a four-point scale according to the guideline[13].

MDCT Data Acquisition and Analysis
Each patient received an additional oral beta-blocker (metoprolol, 20 mg, single dose) 2–3 h before examination and 0.3 mg of nitroglycerin (Nitropen, Nippon Kayaku, Tokyo, Japan) sublingually 5 min before scanning. All patients were scanned in the supine position during a single breath-hold with inspiration during scanning on a 64-detector computed tomography (CT) scanner (Brilliance-64, Philips Medical Systems, Cleveland, OH, USA). In all patients, Iohexol-350 (Omnipaque-350, Daiichi-Sankyo, Tokyo, Japan) was delivered through a 20-gauge catheter inserted into an antecubital vein and a power injector (Autoenhance A-250, Nemoto Kyorindo, Tokyo, Japan).

We used the test-bolus technique to synchronize the arrival of contrast media (CM). This technique is based on the intravenous injection of a small amount (10 mL) of contrast material during the acquisition of a series of dynamic low-dose (120 kV, 20 mAs) monitoring scans at the level of the ascending aorta. The time interval between each monitoring scan acquisition was 1 s. Acquisition of the dynamic monitoring scans started 5 s after the beginning of the injection of intravenous contrast material (10 mL of CM injected at 5 mL/s). A region of interest (ROI) was drawn inside the ascending aorta to generate an enhancement curve (generated by Test Injection Bolus Timing Application, Philips Medical Systems), which showed the time needed to reach the peak of maximum enhancement for the test-bolus. We selected the delay applied for angiographic scanning as 3 s after the time of peak enhancement at the test-bolus in the ascending aorta. Our contrast injection protocol was a patient bodyweight (BW)-tailored small contrast dose protocol, 0.7 mL/kg BW of CM at a fixed injection duration of 9 s.

The scan parameters were as follows: detector collimation 64×0.625 mm, 11.9 mm/s table feed, 0.20 helical pitch (beam pitch), 420 msec tube rotation time, 120 kV tube voltage, 900 mAs tube current time-product. Depending on the cardiac dimensions, the scanning time varied from 6 to 8 s. Image reconstruction was in a 16.5–20.0-cm display field-of-view depending on the patient's physique. All scans started at the upper end of the coronary sinus in a craniocaudal direction. We reconstructed axial images with a section thickness of 0.67 mm, a section interval of 0.33 mm, and a 16.5–20.0-cm display field-of-view depending on the patient's physique using a medium cardiac kernel (XCB) with ECG gating. Initially, a single data set was reconstructed during the mid-diastolic phase (75% of the R-wave to R-wave interval). In cases with unsatisfactory image quality, image reconstruction of the raw data was carried out at 0, 10, 20, 30, 40, 50, 60, 70, 80 and 90% of the R-wave to R-wave interval to improve the image quality of all available coronary segments.

Together, two board-certified radiologists (TN and KA) with 5 and 7 years of experience interpreting cardiac CT analyzed the generated images on the same workstation (ZAIO. M900®, ZAIO Software, Tokyo, Japan). Both were blinded to the patients' clinical information. Coronary arteries were divided into 17 segments according to the modified American Heart Association classification[14]. The presence of coronary lesions was evaluated visually using a volume rendering view, angiographic view, curved multiplanar reconstructions and a cross-sectional image. Plaques were classified as stenosis and no stenosis using a 75% threshold of luminal narrowing, and one coronary plaque was

assigned per coronary segment. Interobserver disagreement was solved by consensus of the two radiologists.

Statistical Analysis

Continuous variables are described as means and standard error. Categorical data are presented with absolute frequencies and percentages. Unpaired *t*-tests were carried out to evaluate differences between patient groups or samples. Values of $P < 0.05$ were considered to show statistically relevant differences.

A forward stepwise logistic-regression procedure was then carried out to adjust CAD risk factors with the use of covariates that were found to be significant predictors of MDCT detecting stenosis. Furthermore, to identify the threshold value of each significant predictor, two-tailed χ^2-test was used for each variable and the odds ratios were calculated by cross-tabulation. We carried out further receiver operating characteristics (ROC) curve analyses to evaluate the sensitivity and specificity of IMT and the duration of diabetes on MDCT detecting stenosis. Statistical analyses were carried out using computer software (SigmaStat for Windows version 3.5, Systat Software, Chicago, IL, USA).

RESULTS

The patient characteristics are summarized in Table 1. The study group consisted of 52 patients with type 2 diabetes (age 66.2 ± 11.8 years; 37 men; BMI 24.7 ± 4.2; glycated hemoglobin [HbA1c] 7.9 ± 1.7%). The average duration of diabetes was 15.9 ± 10.8 years at the time of MDCT. A total of 36 patients received oral hypoglycemic medication and 17 patients received insulin.

In MDCT, stenosis of coronary arteries was detected in 19/52 patients (36.5%). Of the 19 patients, one-vessel disease was identified in 12 patients, two-vessel disease in four patients, and three-vessel disease in three patients. Accidents during MDCT or side-effects as a result of contrast material were not detected in the present study.

Table 1 | Patient characteristics

Age (years)	66.2 ± 11.8
Male/female	37/15
Body mass index (kg/m^2)	24.7 ± 4.2
Duration of diabetes (years)	15.9 ± 10.8
Smoking (+/−)	26/26
Diabetes therapy (insulin/oral agents)	17/36
Glycated hemoglobin (%)	7.9 ± 1.7
Systolic blood pressure (mmHg)	132 ± 21
Diastolic blood pressure (mmHg)	72 ± 12
LDL-cholesterol (mg/dL)	124 ± 39
HDL-cholesterol (mg/dL)	52 ± 15
Triglyceride (mg/dL)	133 ± 94
Oral agents for hypertension (+/−)	34/18
Statins (+/−)	19/33

Data are mean ± SE or *n*.
HDL, high density lipoprotein; LDL, low density lipoprotein.

Table 2 | Correlation between multidetector computed tomography results and electrocardiogram or echocardiography

	n	Echocardiography LV dysfunction (+) (*n* = 3)		Echocardiography LV dysfunction (−) (*n* = 49)	
		ECG positive (*n* = 2)	ECG negative (*n* = 1)	ECG positive (*n* = 19)	ECG negative (*n* = 30)
MDCT stenosis	19	2	1	8	8
MDCT No stenosis	33	0	0	11	22

ECG, electrocardiogram; LV, left ventricular; MDCT, multidetector computed tomography results.

The correlation between MDCT and symptoms, ECG, and echocardiography are provided in Tables 2 and 3. Of the 19 patients who had stenosis detected by MDCT, eight patients (42%) were identified with neither a positive ischemic change in ECG nor a wall motion abnormality in echocardiography (Table 2). Thirteen patients (25% of 52 patients) who had no symptoms of ischemic heart disease (IHD) had coronary artery stenosis detected by MDCT, indicating the presence of silent myocardial ischemia. More importantly, of the 19 patients with stenosis, seven patients (37%) had no symptoms, including chest pain, nor ischemic changes in ECG (Table 3). These data indicate the high prevalence of asymptomatic ischemia in diabetes patients and the usefulness of MDCT for the screening of silent ischemic heart disease in diabetes patients.

The comparison of the patient characteristics and clinical variables between MDCT stenosis detection and no MDCT stenosis detection are presented in Table 4. Interestingly, there were no significant differences in age (69 ± 8 years in stenosis *vs* 64 ± 13 years in no stenosis, $P = 0.061$), blood pressure (131 ± 22/72 ± 13 mmHg *vs* 133 ± 20/72 ± 11 mmHg), serum low density lipoprotein (LDL)-cholesterol (123 ± 44 mg/dL *vs*

Table 3 | Correlation between multidetector computed tomography results and electrocardiogram or presence of symptoms

	n	Symptomatic (*n* = 11)		Asymptomatic (*n* = 41)	
		ECG positive (*n* = 6)	ECG negative (*n* = 5)	ECG positive (*n* = 15)	ECG negative (*n* = 26)
MDCT stenosis	19	4	2	6	7
MDCT No stenosis	33	2	3	9	19

ECG, electrocardiogram; MDCT, multidetector computed tomography.

Table 4 | Comparisons between patients with multidetector computed tomography detected stenosis and those without stenosis

	MDCT stenosis	MDCT no stenosis	P-value
n	19	34	–
Age (years)	69 ± 8	64 ± 13	0.061
Duration of diabetes (years)	20 ± 11	13 ± 10	0.008*
Glycated hemoglobin (%)	8.1 ± 1.8	7.7 ± 1.7	0.240
Blood glucose (2 h, mg/dL)	257 ± 89	256 ± 108	0.482
eGFR (mL/min/1.73 m^2)	64.9 ± 25.3	74.8 ± 20.6	0.066
Systolic blood pressure (mmHg)	131 ± 22	133 ± 20	0.379
Diastolic blood pressure (mmHg)	72 ± 13	72 ± 11	0.483
LDL-cholesterol (mg/dL)	123 ± 44	126 ± 37	0.388
HDL-cholesterol (mg/dL)	55 ± 14	51 ± 15	0.195
Triglyceride (mg/dL)	115 ± 63	144 ± 109	0.144
Urinary albumin excretion (mg/gCre)	80.7 ± 149.6	83.1 ± 167.2	0.481
ABI	1.10 ± 0.15	1.12 ± 0.10	0.311
PWV (cm/s)	1917 ± 323	1899 ± 433	0.411
Mean IMT (mm)	1.21 ± 0.44	0.95 ± 0.26	0.007*

Data are mean ± SE and n. * $P < 0.05$ by unpaired t-test and Mann–Whitney U-test.
ABI, ankle brachial index; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; IMT, intima-media thickness; LDL, low density lipoprotein; MDCT, multidetector computed tomography; PWV, pulse wave velocity.

126 ± 37 mg/dL, $P = 0.388$), serum high density lipoprotein (HDL)-cholesterol (55 ± 14 mg/dL vs 51 ± 15 mg/dL, $P = 0.195$), urinary albumin excretion (80.7 ± 149.6 mg/g creatinin vs 83.1 ± 167.2 mg/g creatinin, $P = 0.481$), estimated glomerular filtration rate (eGFR) (64.9 ± 25.3 mL/min/1.73m^2 vs 74.8 ± 20.6 mL/min/1.73m^2, $P = 0.066$) and PWV (1917 ± 323 cm/s vs 1899 ± 433 cm/s, $P = 0.411$) between the patients with stenosis and those with no stenosis. Significant differences were detected in mean IMT (1.21 ± 0.44 mm in stenosis vs 0.95 ± 0.26 mm in no stenosis, $P = 0.007$) and duration of diabetes (20 ± 11 years vs 13 ± 10 years, $P = 0.008$).

To identify the correlation between the presence of stenosis of coronary arteries on MDCT and CAD risk factors, we carried out forward stepwise logistic regression analysis (Table 5).

Table 5 | Independent predictors of coronary artery stenosis by multiple logistic regression analysis

	Odds ratio	95% CI	P-value
Duration of diabetes (per year)	1.157	1.034–1.294	0.011
Statin (yes vs no)	9.867	1.655–58.882	0.012
Mean IMT (per 0.1 mm)	1.359	1.018–1.814	0.038

IMT, intima-media thickness.

Although a significant correlation was not found between MDCT detecting stenosis and age, BMI, HbA1c, eGFR, diastolic blood pressure, serum LDL- and HDL- cholesterol concentrations, triglyceride, urine-microalbumine, ABI or PWV, the correlation of MDCT detecting stenosis and duration of diabetes, medication of statin and mean-IMT of carotid artery remained statistically significant after correction for baseline characteristics. The dependent variable of MDCT detecting stenosis can be predicted from a linear combination of the independent variables as follows: (i) duration of diabetes ($P = 0.004$), (ii) treatment with statin ($P = 0.029$); and (iii) mean IMT ($P = 0.023$). The odds ratio of these predictors were 1.157 (95% CI 1.034–1.294, $P = 0.011$) in duration of diabetes (per year), 9.867 (95% CI 1.655–58.882, $P = 0.012$) in treatment with statin, 1.359 (95% CI 1.018–1.814, $P = 0.038$) in mean IMT (per 0.1 mm) by multiple logistic regression analysis.

DISCUSSION

In the present study, it was shown that symptomatic or asymptomatic CAD in type 2 diabetes patients can be diagnosed noninvasively by the use of MDCT. The population of the present study group was considered to be representative of Japanese diabetic patients,[15] although the BMI had a tendency to be lower compared with other studies of Caucasian patients[3,16]. The patients in the present study were receiving contemporary medical treatment and were under almost reasonable metabolic control (blood pressure 132 ± 21/72 ± 12 mmHg, LDL-cholesterol 124 ± 39 mg/dL, HDL-cholesterol 52 ± 15 mg/dL, triglyceride 133 ± 94 mg/dL), although HbA1c (7.9 ± 1.7%) was considered to be higher.

Previous studies reported that both sensitivity and specificity of MDCT were high enough for the diagnosis of coronary artery stenosis to be made[5,7,8]. Continuous modification of hardware, scan protocol and renewing scanner generation has led to a significant stabilization and improvement of image quality[17]. Recently, studies using 64-slice scanners have been reported, showing a more accurate assessment for the diagnosis of CAD and characteristics of plaque[10,18,19]. However, several general limitations of MDCT, including the administration of an iodinated contrast agent and elevated radiation dose, should be mentioned. In the present study, we generated a protocol to carry out MDCT with less iodinated agent and lower radiation exposure.

In the present study group, 13 patients (25.0% of 52 patients) who had no symptoms of IHD had coronary artery stenosis detected by MDCT. Wackers et al. indicated that 133/522 patients with diabetes (25.5%) were diagnosed with silent myocardial ischemia using adenosine technetium-99m sestamibi single photon emission-computed tomography myocardial perfusion imaging[3]. The prevalence of MDCT detecting stenosis detection without IHD symptoms in the present study was similar to those of previous reports, suggesting that MDCT is useful in screening for silent ischemia in patients with diabetes. Furthermore, of 19 patients who had coronary artery stenosis

detected by MDCT, seven patients had neither positive ischemic change in rest ECG nor symptoms of IHD. For diagnosis of CAD, exercise ECG is the most commonly applied non-invasive test. However, Dewey *et al.* reported that both sensitivity and specificity of MDCT were significantly higher than those of exerciseECG[8]. It was also reported that exercise ECG had a certain risk, the most relevant being myocardial infarction or death which have been confirmed in multiple surveys to occur in approximately 10/10 000 tests[20]. Taken together, it is suggested that the MDCT is effective for the screening of CAD, especially silent myocardial ischemia.

It was reported that the incidences of coronary heart disease (CHD), per 1000 patients per year, among Japanese diabetes patients were 9.8 in men and 5.5 in women,[21] although that of CHD among Caucasian diabetes patients was 17.4[22]. The prevalence of CAD in type 2 diabetes in the Caucasian population has been reported to be 30–40%[4,10]. In the present study, even the incidence of CHD in Japanese type 2 diabetes patients was much lower than that of Caucasian patients, as 19/52 patients (36.5%) had coronary artery stenosis detected by MDCT. Therefore, it is thought that MDCT might detect more CAD in type 2 diabetes patients in the Caucasian population.

Another important finding of the present study is the assessment of the predictors of MDCT detecting stenosis in diabetes patients. In the guidelines for early detection of CHD in asymptomatic patients with diabetes from the American Diabetes Association (ADA), the presence of multiple cardiovascular risk factors including LDL-cholesterol, HDL-cholesterol, blood pressure, micro-/macroalbuminuria is mentioned[2]. In the analysis of risk factors that contribute to CHD risk in diabetic patients in the United Kingdom Prospective Diabetes Study, LDL-cholesterol, HDL-cholesterol, blood pressure and HbA1c were reported to be important[22,23]. However, in the present study, significant differences were not detected in blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, blood glucose, HbA1c, microalbuminuria, ABI or PWV between the MDCT detected stenosis and MDCT detecting no stenosis groups. The reason why there is no significant difference in these markers between MDCT detecting stenosis and MDCT detecting no stenosis groups might be a result of the limited number of subjects in our study group. With regard to blood pressure, it was also possible that aggressive blood pressure control using calcium channel blockers, angiotensin II receptor inhibitors, etc. in both MDCT detecting stenosis and MDCT detecting no stenosis groups led to no significant difference. We could not find a significant correlation between oral agents for hypertension and MDCT detecting stenosis. In addition, there was no significant difference in the presence/absence of diabetic retinopathy between the MDCT detecting stenosis and MDCT detecting no stenosis groups (data not shown). In contrast, significant differences were detected in mean IMT and duration of diabetes between MDCT detecting stenosis and MDCT no stenosis groups in the present study. The data of multiple logistic regression analysis indicated that the predictors of MDCT detecting stenosis were mean IMT, treatment with statin and duration of diabetes. This multiple regression analysis showed that the administration of statin is a predictor of MDCT detecting stenosis although the LDL-cholesterol is not. These results indicate that the subjects with diabetes and dyslipidemia, who were given statin and had relatively lower LDL-cholesterol levels, still were at risk of having coronary artery stenosis. Furthermore, to determine the threshold value of the duration of diabetes and mean IMT at the carotid artery for the prediction of MDCT detecting stenosis, two-tailed χ^2-test was used for each variable and the odds ratios were calculated by cross-tabulation, with a 95% CI. More than 20 years of duration of diabetes significantly correlated with the detection of stenosis of coronary arteries by MDCT (odds ratio 6.222 [95% CI 1.679–23.064, $P = 0.011$], sensitivity 0.474, specificity 0.805), and more than 1.1 mm of mean IMT in carotid arteries significantly correlated with MDCT detecting stenosis (odds ratio 4.600 [95% CI 1.207–17.525, $P = 0.047$], sensitivity 0.500, specificity 0.833). Recently, the American Heart Association reported that routine surveillance with MDCT in asymptomatic patients at low risk for IHD was not recommended[24]. The results of this study indicated that the type 2 diabetic patients with longer duration of diabetes or increased thickness of mean IMT in carotid arteries have a high risk of IHD. Thus, it is recommended that diabetic patients with more than 1.1 mm mean IMT in the carotid arteries and/or more than 20 years duration of diabetes should receive MDCT for screening of CAD even though they are in good control of blood pressure and lipid metabolism.

Several limitations of the present study should be mentioned. In the present study, 52 patients were included, and examinations were carried out at a single time-point and were not repeated over time. Prospective studies with larger patient cohorts are required.

In summary, it was shown that MDCT detects coronary artery stenosis in diabetic patients without symptoms of IHD or ECG abnormality. From the data of the present study, the predictors of CAD in Japanese type 2 diabetes patients were mean IMT and duration of diabetes. Thus, MDCT is a non-invasive, effective method to detect or rule out CAD, especially silent myocardial ischemia in patients with diabetes, and it is recommended that patients with more than 1.1 mm mean IMT at the carotid artery and/or more than 20 years duration of diabetes should be screened for CAD.

ACKNOWLEDGEMENTS

REFERENCES

1. Luscher TF, Creager MA, Beckman JA, *et al*. Diabetes and vascular disease: pathophysiology, clinical consequences,

and medical therapy: Part II. *Circulation* 2003; 108: 1655–1661.

2. American Diabetes Association. Consensus development conference on the diagnosis of coronary heart disease in people with diabetes: 10–11 February 1998, Miami, Florida. *Diabetes Care* 1998; 21: 1551–1559.

3. Wackers FJ, Young LH, Inzucchi SE, *et al*. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. *Diabetes Care* 2004; 27: 1954–1961.

4. Kharlip J, Naglieri R, Mitchell BD, *et al*. Screening for silent coronary heart disease in type 2 diabetes: clinical application of American Diabetes Association guidelines. *Diabetes Care* 2006; 29: 692–694.

5. Bax JJ, Young LH, Frye RL, *et al*. Screening for coronary artery disease in patients with diabetes. *Diabetes Care* 2007; 30: 2729–2736.

6. Bax JJ, Inzucchi SE, Bonow RO, *et al*. Cardiac imaging for risk stratification in diabetes. *Diabetes Care* 2007; 30: 1295–1304.

7. Burgstahler C, Beck T, Reimann A, *et al*. Diagnostic accuracy of multislice computed tomography for the detection of coronary artery disease in diabetic patients. *J Diabetes Complications* 2007; 21: 69–74.

8. Dewey M, Dubel HP, Schink T, *et al*. Head-to-head comparison of multislice computed tomography and exercise electrocardiography for diagnosis of coronary artery disease. *Eur Heart J* 2007; 28: 2485–2490.

9. Raff GL, Gallagher MJ, O'Neill WW, *et al*. Diagnostic accuracy of noninvasive coronary angiography using 64-slice spiral computed tomography. *J Am Coll Cardiol* 2005; 46: 552–557.

10. Pundziute G, Schuijf JD, Jukema JW, *et al*. Noninvasive assessment of plaque characteristics with multislice computed tomography coronary angiography in symptomatic diabetic patients. *Diabetes Care* 2007; 30: 1113–1119.

11. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2004; 27: S5–S10.

12. Mitsuhashi N, Onuma T, Kubo S, *et al*. Coronary artery disease and carotid artery intima-media thickness in Japanese type 2 diabetic patients. *Diabetes Care* 2002; 25: 1308–1312.

13. Lang RM, Bierig M, Devereux RB, *et al*. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; 18: 1440–1463.

14. Austen WG, Edwards JE, Frye RL, *et al*. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation* 1975; 51: 5–40.

15. Sone H, Yoshimura Y, Tanaka S, *et al*. Cross-sectional association between BMI, glycemic control and energy intake in Japanese patients with type 2 diabetes. Analysis from the Japan Diabetes Complications Study. *Diabetes Res Clin Pract* 2007; 77: S23–S29.

16. Wong ND, Rozanski A, Gransar H, *et al*. Metabolic syndrome and diabetes are associated with an increased likelihood of inducible myocardial ischemia among patients with subclinical atherosclerosis. *Diabetes Care* 2005; 28: 1445–1450.

17. Nieman K, Cademartiri F, Lemos PA, *et al*. Reliable noninvasive coronary angiography with fast submillimeter multislice spiral computed tomography. *Circulation* 2002; 106: 2051–2054.

18. Leschka S, Alkadhi H, Plass A, *et al*. Accuracy of MSCT coronary angiography with 64-slice technology: first experience. *Eur Heart J* 2005; 26: 1482–1487.

19. Hacker M, Jakobs T, Hack N, *et al*. Sixty-four slice spiral CT angiography does not predict the functional relevance of coronary artery stenoses in patients with stable angina. *Eur J Nucl Med Mol Imaging* 2007; 34: 4–10.

20. Fletcher GF, Balady GJ, Amsterdam EA, *et al*. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. *Circulation* 2001; 104: 1694–1740.

21. Sone H, Mizuno S, Fujii H, *et al*. Is the diagnosis of metabolic syndrome useful for predicting cardiovascular disease in asian diabetic patients? Analysis from the Japan Diabetes Complications Study. *Diabetes Care* 2005; 28: 1463–1471.

22. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352: 837–853.

23. Turner RC, Millns H, Neil HA, *et al*. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). *BMJ* 1998; 316: 823–828.

24. Gerber TC, Carr JJ, Arai AE, *et al*. Ionizing radiation in cardiac imaging. A science advisory from the American Heart Association Committee on Cardiac Imaging of the Council on Clinical Cardiology and Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention. *Circulation* 2009; 119: 1056–1065.