Non-invasive assessment of coronary artery disease in diabetes

Nico R Van de Veire, Roxana Djaberi, Joanne D Schuijf, et al.

Heart 2010 96: 560-572
doi: 10.1136/hrt.2007.122788

NON-INVASIVE IMAGING

Non-invasive assessment of coronary artery disease in diabetes

Nico R Van de Veire, Roxana Djaberi, Joanne D Schuijf, Jeroen J Bax

▸ Supplementary references are published online only at http://hrt.bmj.com/content/vol96/issue7

Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands

Correspondence to
Professor Jeroen J Bax, Leiden University Medical Center, Department of Cardiology (C5-P), PO BOX 9600, Leiden, 2300 RC, The Netherlands; j.j.bax@lumc.nl

More than 150 million subjects have diabetes mellitus (DM) worldwide and the number is expected to increase further.[w1] Many cases, however, are undiagnosed and do not receive appropriate treatment. The risk of coronary artery disease (CAD) for patients with overt DM is increased by two to three times for men and three to five times for women compared to individuals without DM.[1] CAD accounts for 75% of all deaths in DM patients while 30% of patients presenting with acute coronary syndromes have DM.[w1] International guidelines consider DM as an equivalent of CAD requiring aggressive anti-atherosclerotic treatment. In the general population, the most typical clinical manifestation of myocardial ischaemia is the occurrence of chest pain. In DM patients, however, myocardial ischaemia is often expressed by angina equivalents: dyspnoea, arrhythmias and (pre-) syncope rather than typical angina. The outcome of CAD events may be three times worse in DM patients who have shortness of breath as a primary symptom. Diabetic patients have a high incidence of occult CAD, reflected by an increased incidence of silent myocardial infarction and ischaemia. The available evidence suggests that occult CAD is a common finding among asymptomatic DM patients, ranging from 20% in healthier subjects to >50% in patients with more complicated DM.[w2] This poses the challenge of how to efficiently identify CAD in DM, for diagnosis, referral for invasive coronary angiography, and risk stratification. Various non-invasive methods are available and their diagnostic and prognostic value will be discussed.

RESTING ECG

Although a resting 12 lead ECG should be recorded in every DM patient to detect signs of CAD, one should realise that its diagnostic value is limited for several reasons. The ECG is normal in approximately 50% of patients with CAD and often abnormalities are not sufficiently specific for the diagnosis of CAD. Pathologic Q waves, negative symmetric T waves and ST segment depression strongly suggest CAD. Importantly, during an episode of angina, the ECG becomes abnormal in over 50% of patients with normal resting ECG.[w3]

SURROGATE MARKERS FOR CORONARY ARTERY DISEASE

Surrogate markers provide indirect evidence for the presence of CAD. Although most of these markers are still experimental tools, they could be useful in identifying high risk groups among asymptomatic diabetic patients that might benefit from intensified screening for CAD.

Inflammatory markers: high sensitivity C reactive protein (hsCRP)

Detection of CAD using hsCRP

During the recent decade, research has established the role of the inflammatory process as an important contributor to atherosclerosis. Serum C reactive protein (CRP) is the most extensively studied inflammatory biomarker in cardiovascular disease. High sensitivity methods (hs-CRP) which detect low concentrations are necessary for cardiovascular risk stratification. The 2003 Centers for Disease Control and Prevention/America Heart Association (CDC/AHA) statement has defined CRP concentrations <1 mg/l as low risk, 1–3 mg/l as average risk, and >3 mg/l as high risk.[2] Serum CRP is significantly associated with age, smoking, hypertension, body mass index, metabolic syndrome, type 2 DM, reduced exercise frequency, and serum concentrations of homocysteine and lipoprotein.[w4 w5] Hs-CRP values are elevated in DM.[w4] In 590 middle-aged individuals from the Atherosclerosis Risk in Community Study (ARIC), the number of subjects with DM increased from 2.2% in the lowest CRP quintile (<0.83 mg/l) to 14.2% in the highest CRP quintile (>6.9 mg/l).[w4] It is suspected that chronic subclinical inflammation may be associated with insulin resistance and precede the development of clinically overt type 2 DM.[w6]

Prognostic value of hsCRP

In the INVADE study, 882 DM patients were followed for 2 years. Serum hsCRP was identified as an independent predictor of carotid atherosclerosis and its progression, assessed by carotid artery intima media thickness.[w7] Schulze and colleagues have studied the predictive value of CRP for cardiovascular events defined as myocardial infarction, revascularisation and stroke, in 746 men with type 2 DM. High plasma values of CRP were associated with an increased risk of incident cardiovascular events, independent of currently established lifestyle risk factors, blood lipids, and glycaemic control.[w8] However, in the prospective Honolulu Heart Program the associations between CRP and risk of thromboembolic stroke or myocardial infarction were generally weaker and not significant in diabetic versus non-diabetic subjects.[w9 w10] Accordingly, the role of CRP as

Heart 2010;96:560–572. doi:10.1136/hrt.2007.122788

a prognostic marker in DM needs to be further analysed.

Intima–media thickness

Intima–media thickness (IMT) of the carotid artery (CIMT) is increasingly used as a surrogate for atherosclerosis in clinical research and can be assessed by B mode ultrasound (figure 1). A recent consensus by the American Society of Echocardiography has recommended measurements of the *mean* CIMT along a length of at least 1 cm, on the far wall of the common carotid arteries, at minimum three angles.[3] For this purpose, manual reading techniques or validated semi-automated edge detecting programmes can be used. Not all intima–media thickening is attributable to atherosclerosis and CIMT is shown to increase with age as an adaptive response to flow and wall tension.[w11] Accordingly, normal CIMT values range from 0.4 mm in healthy young adults to 0.9 mm at the age of 90 years.[3] Specific CIMT values therefore correspond with different cardiovascular risk levels depending on patient's age, sex and carotid artery (right or left). The consensus has recognised the presence of CIMT >75th centile for patient's age and sex to be indicative of increased cardiovascular risk in the general population.[3]

Detection of CAD with CIMT

Mean CIMT increases with cardiovascular risk factors and correlates with atherosclerosis assessed on coronary angiography.[w12 w13] In the ARIC study, mean CIMT was shown to be on average 0.07 mm thicker for each age and gender category in diabetic patients as compared to non-diabetic controls, after adjustment for other cardiovascular risk factors.[w14] In DM, prevalent CAD is associated with higher CIMT.[w15 w16] However, CIMT values indicative of CAD vary in accordance with the age and characteristics of the study population as well as with the definition of CIMT (mean or maximum). In the Insulin Resistance Atherosclerosis Study of older middle aged adults, *maximum* CIMT was 0.9 mm in diabetic patients with confirmed CAD as compared to 0.86 mm in diabetic patients with no history of CAD.[w17] A sub-analysis of the ARIC study, in diabetic patients aged 45–64 years, revealed *mean* CIMT to be significantly higher in patients with a prior myocardial infarction (0.83 mm) than in those without (0.78 mm).[w18] Limited data are available on CIMT values associated with CAD in asymptomatic diabetic patients. However, in a recent study of relatively young middle aged asymptomatic diabetic patients (mean age 50 years), a *mean* CIMT cut-off value of 0.67 mm showed a sensitivity and specificity of respectively 85% and 72% for predicting obstructive CAD on multislice computed tomography (MSCT) angiography.[w19]

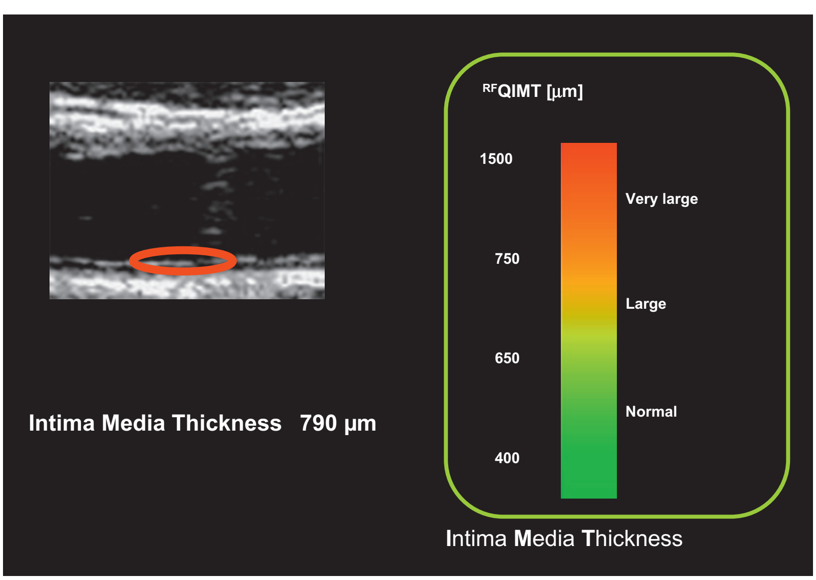

Figure 1 A 55-year-old male patient is referred to the outpatient clinic because of dyspnoea. Besides diabetes, his coronary risk factors include arterial hypertension, hypercholesterolaemia and smoking. The resting ECG shows an old inferolateral infarction. The left panel shows the patients' carotid intima media thickness (CIMT). The right panel provides reference values for this measurement.

Prognostic value of CIMT

In prospective studies, CIMT has proven to be a consistent and independent predictor for cardiovascular events (table 1). In two prospective studies including diabetic patients, baseline CIMT was shown to be an independent predictor of cardiovascular events (table 1).[w25 w26] However, in a cohort of 1500 diabetic subjects, the baseline CIMT showed limited incremental value on top of a basic clinical risk score in a risk prediction model for incident CAD during 10 years follow up.[w27] Herein, the area under the curve (AUC) increased only modestly from 0.71 to 0.72 in women, and from 0.68 to 0.70 in men. Nevertheless, the gain in AUC from adding CIMT above the basic risk score was more substantial than the observed gain for other studied markers (ankle–brachial index, baseline ECG, and presence of left ventricular hypertrophy).

Vascular stiffness

Applanation tonometry can be used to assess the pressure wave form and to calculate pulse wave velocity (PWV), which enables estimation of vascular stiffness (figure 2). PWV is the velocity of a pulse pressure wave as it travels between two sites. PWV increases with increasing vascular stiffness, whereas arterial stiffness increases with age due to structural changes. Furthermore, a correlation between increased PWV and atherosclerotic risk factors, including elevated systolic blood pressure, insulin resistance, body mass index (BMI) and smoking, as well as the presence of coronary atherosclerosis itself has been demonstrated.[w28 w29] In addition, increased arterial stiffness has been demonstrated in the presence of DM.[w29] Deposition of advanced glycation end products on aortic extracellular matrices is suspected to underlie premature stiffness of the central arteries in DM.[w30] Consequently, in diabetic patients aortic PWV is increased in all age groups and shows

Table 1 Prognostic value of carotid intima–media thickness (IMT): general population versus diabetic patients

Study	Site of measure	No of subjects	Age (years)	Gender	Follow-up (years)	Increase in IMT	Outcome	Hazard ratio (95% confidence interval)
General population								
Salonen and Salonen[w20]	CCA	1288	42–60	Male (100%)	1–2.5	≥1mm	MI	2.2 (0.7 to 6.7)
Chambless *et al*[w21]	Mean maximum 6 sites	5552	45–64	Male (100%)	4–7	≥1 mm	Cardiac death or MI	1.9 (1.3 to 2.7)*
		7289	45–64	Female (100%)	4–7	≥1mm	Cardiac death or MI	5.1 (3.1 to 8.4)*
O'Leary *et al*[w22]	CCA	4464	≥ 65	Male (39%)	6	Per 0.2 mm	MI, stroke	1.3 (1.2 to 1.4)†
van der Meer *et al*[w23]	CCA	5116	≥ 55	Male (38%)	7–10	Per 0.21 mm	MI	1.3 (1.1 to 1.4)†
Lorenz *et al*[w24]	CCA	5052	19–90	Male (49%)	4	Per 0.16 mm	MI	1.2 (1.1 to 1.3)†
Diabetes								
Yamasaki *et al*[w25]	Mean 3 sites	287	38–84	Male (43%)	3	–	Angina/non-fatal MI	OR: 4.9 (1.7 to 14.1)
Bernard *et al*[w26]	CCA	229	35–75	Male (65%)	5	Per 0.13 mm	CVE	1.6 (1.0 to 2.6)†

*Corrected for age, gender and race.
†Corrected for age, gender, race and other cardiovascular risk factors.
CCA, common carotid artery; CVE, cardiovascular events defined as cardiovascular death, non-fatal myocardial infarction, unstable angina, stable angina and ischaemic stroke; F, female; M, male; MI, myocardial infarction.

a steeper increase with age.[w31] In a study by Taniwaki *et al*, a higher mean aortic PWV was observed in young diabetic patients in the age category <40 years (7.0±0.7 m/s) versus non-diabetic controls (6.2±0.6 m/s) (p<0.05). Of note, the gap in mean aortic PWV was further increased in older patients ≥60 years, wherein a mean value of 10.7±2.1 was observed in DM as compared to 7.9±1.2 in non-diabetic controls.[w32]

Detection of CAD using PWV

To date, limited studies have evaluated the relation between PWV and presence of CAD in DM. Hatsuda and colleagues assessed the aortic PWV in 70 diabetic patients with CAD versus 525 diabetic patients without known CAD. Higher aortic PWV was associated with the presence of CAD, and each 1 m/s increase in PWV was thereby associated with a 14.5% increase in risk of prevalent CAD.[w33] In another study, arterial stiffness of lower extremities was shown to correlate with the presence and extent of coronary calcium, as detected by electron beam computed tomography.[w34]

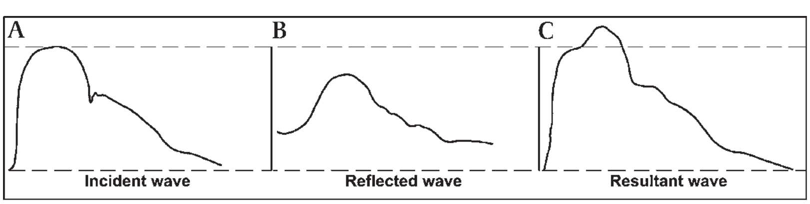

Figure 2 During applanation tonometry, the pulse pressure wave is recorded by using a micromanometer tipped probe. The artery is compressed between the sensor and underlying structures and the intra-arterial pressure is transmitted to the sensor. The pressure wave form is then digitalised so that it can be viewed on a screen. (A) Incident wave generated by the left ventricle (ascending aorta). (B) Waves reflected back from the peripheral vascular bed (ascending aorta). (C) Resultant wave (ascending aorta) which is a combination of A and B. Both the form (pulse wave analysis) and the speed (pulse wave velocity) of the resultant pulse wave can be studied to assess functional vascular properties, such as vascular stiffness. The pulse wave velocity is recognised as the most validated measure of vascular stiffness and increases with stiffness due to reduced distensibility. Diabetes is mainly associated with an increase in pulse wave velocity of the central arteries.

Prognostic value of PWV

The prognostic value of arterial stiffness in DM has been evaluated by Cruishank *et al* in 397 diabetic patients. During a 10 year follow-up period PWV independently predicted all cause and cardiovascular mortality mortality (hazard ratio (HR) 1.08, 95% confidence interval (CI) 1.03 to 1.14, for each 1 m/s PWV increase).[4]

NON-INVASIVE STRESS TESTING TO DETECT CAD

Non-invasive stress testing can provide indispensable information to establish the diagnosis of CAD in DM. However, it is important to realise that the predictive value of these tests is not only defined by their sensitivity and specificity but also by the prevalence of disease in the investigated population. The incremental value of non-invasive stress testing is largest when the pre-test likelihood is intermediate because the test result is likely to have the largest effect on the post-test probability of CAD and hence on clinical decision making. Some authors have proposed the use of clinical scoring in DM to select patients with intermediate risk for further testing.[w35] Another important issue is that sensitivities and specificities reported in studies evaluating stress testing modalities suffer from verification or referral bias. Patients with normal stress test results are rarely referred for cardiac catheterisation. On the one hand, this yields a somewhat inflated value for sensitivity.[w36] On the other hand, because of the referral bias, patients with angiographically normal coronary arteries are likely to have abnormal stress test results.[w36] Consequently, the specificity of the technique appears inappropriately low. Therefore, the true specificity of non-invasive stress tests cannot be assessed in referred patients who have angiographically normal coronary arteries. Because of referral bias, the 'normalcy rate' (ie, the percentage of normal subjects with normal images) should be tested in patients with a low probability of CAD, as a surrogate for specificity.

Heart 2010;96:560–572. doi:10.1136/hrt.2007.122788

Exercise ECG

Treadmill or bicycle exercise testing is a widely accepted and well validated non-invasive stress test to detect ischaemia. According to the American Heart Association/American College of Cardiology (AHA/ACC) guidelines, patients with an intermediate pre-test probability of CAD based on age, gender and symptoms should undergo exercise ECG testing.[5]

Detection of CAD with exercise ECG

In patients with DM, the proportion at intermediate risk is probably high because of associated risk factors. The large majority of studies have focused on asymptomatic or silent ischaemia among diabetic patients. Few studies have been published evaluating the utility of exercise ECG in diabetic patients suspected of having CAD. Lee *et al* retrospectively analysed standard exercise ECG results in 1282 male patients without myocardial infarction who had undergone coronary angiography.[6] In patients with DM, the sensitivity was 47% while the specificity was 81%. In patients without DM, the sensitivity and specificity were 52% and 80%, respectively. These data demonstrated that standard exercise ECG has similar diagnostic accuracy in diabetic compared to non-diabetic patients. In these symptomatic patients who had a positive exercise ECG and evidence of CAD on angiography, ischaemia was without symptoms (silent) in 37% of diabetic and 40% of non-diabetic patients. It should be emphasised that the presence of silent myocardial ischaemia is not only a prelude to symptomatic ischaemia, but also to hard (fatal) cardiac events.[w37]

As part of the initial workup for chest pain, AHA/ACC guidelines recommend the exercise ECG.[5] Of note, the choice of initial stress testing modality should be based on the patient's ability to perform exercise and evaluation of the patient's resting ECG. Those with baseline ST depression (≥1 mm), left bundle branch block and intraventricular conduction delay (QRS >120 ms) or paced rhythm should preferably be tested with an imaging modality rather than with exercise ECG.[5] Importantly, if the patient fails to achieve 85% of the maximal predicted heart rate response to stress, the predictive value of the test is considerably reduced and additional testing should be considered.

Prognostic value of exercise ECG

In the Milan Study on Atherosclerosis and Diabetes, 735 asymptomatic diabetic patients were prospectively screened for CAD, using exercise ECG, and followed for cardiac events during 5 years.[w38] The incidence of cardiac events (death, myocardial infarction or angina) among the 638 (87%) patients with a normal exercise ECG was 0.97/100 person-years (95% CI 0.66 to 1.38) compared to 3.85/100 person-years in those with an abnormal exercise ECG ($p<0.0001$). These data, although biased (the study excluded patients with nephropathy, retinopathy, peripheral vascular disease and cerebrovascular disease), suggest that asymptomatic patients with uncomplicated DM who have a negative exercise ECG test have a lower cardiac event rate.

Myocardial perfusion imaging/nuclear imaging

Stress perfusion imaging with thallium-201 or technetium-99m sestamibi detects heterogeneous flow distribution due to decreased coronary flow reserve during exercise or pharmacological vasodilatation. In patients with suspected or known chronic stable CAD, the largest accumulated experience in myocardial perfusion imaging has been with the tracer thallium-201, but the newer tracers technetium-99m-sestamibi and technetium-99m-tetrofosmin yield similar diagnostic accuracy. Current state of the art is ECG gated single photon emission computed tomography (SPECT), allowing both quantitative evaluation of perfusion and cardiac function (figure 3).[w39] Perfusion imaging is combined with exercise testing or with pharmacological stressors such as adenosine, dipyridamole and dobutamine. Pharmacological stress is preferred over physical exercise in patients unable to perform adequate exercise because of peripheral vascular disease. In addition, patients with resting left bundle branch block on the ECG and patients with ventricular pacing preferentially undergo pharmacological stress testing because of the potential induction of perfusion defects related to the abnormal depolarisation pattern.[7] Adenosine has a shorter half-life than dipyridamole; in case of significant side effects, termination of adenosine infusion alone may suffice whereas with dipyridamole, reversal of drug action with aminophylline is often required. Many patients undergoing vasodilator stress testing perform simultaneous low intensity exercise, which is safe, reduces vasodilator side effects, and improves overall imaging quality. Dobutamine perfusion imaging is potentially indicated in patients with contraindications to dipyridamole and adenosine (obstructive pulmonary disease, heart block). In general, patients are instructed to fast after midnight. To simplify management of diabetic patients, their testing is routinely scheduled for early morning appointments, and they are instructed to take their oral DM medication on a regular schedule and to withhold morning doses of insulin.[w39]

Detection of CAD using gated SPECT

Stress testing combined with nuclear imaging has a sensitivity of 86% and a specificity of 74% to detect obstructive CAD (≥50% stenosis) in the general population (based on pooled analysis of 79 studies, 8964 patients), and has a similar diagnostic accuracy among diabetics.[7] Sensitivity and specificity of vasodilator stress SPECT for detecting CAD—without correction for referral bias—are 89% and 75%, respectively.[7] Kang *et al* have shown that technetium-99m-sestamibi myocardial perfusion SPECT has comparable sensitivity, specificity and normalcy rate for the diagnosis of obstructive CAD in diabetic and non-diabetic patients with

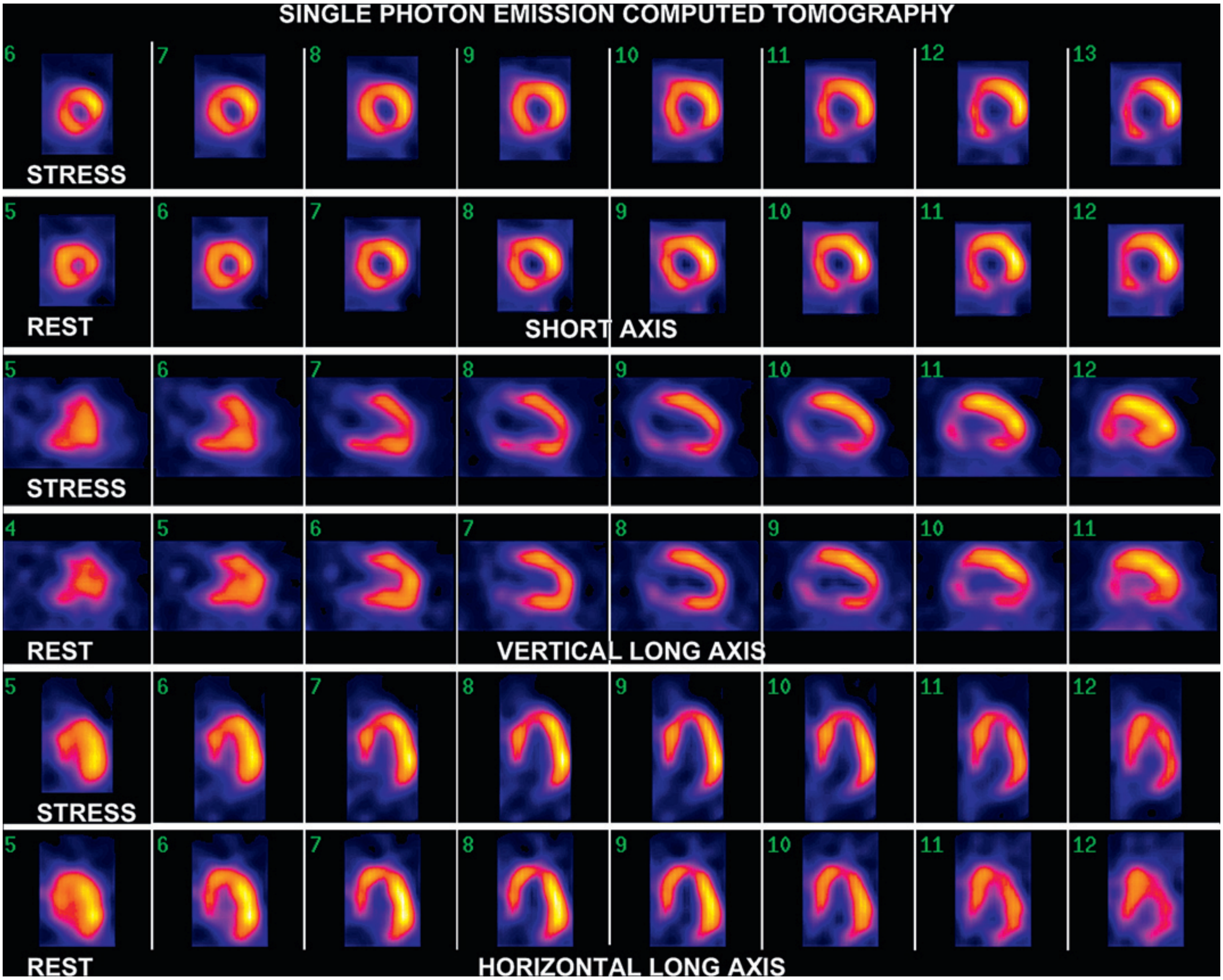

Figure 3 The patient discussed in figure 1 undergoes myocardial perfusion using gated single photon emission computed tomography (SPECT) at rest and following bicycle exercise testing. Both resting images and stress images in the short axis, horizontal and vertical long axis are depicted. A persistent perfusion defect is observed in the inferior and inferolateral region confirming the ECG findings. Reversible ischaemia is demonstrated in the anteroseptal region.

suspected CAD (figure 4).[w40] Available nuclear cardiology studies in asymptomatic diabetic patients reveal a high incidence of patients with silent ischaemia. In the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study, for instance, half of the 1123 patients with type 2 DM were randomly assigned to stress testing by adenosine technetium-99m sestamibi SPECT and 5 year clinical follow-up, while the other half of the population was assigned to follow-up only.[8] Twenty-two per cent of patients exhibited evidence of silent myocardial ischaemia on SPECT. Importantly, 41% of all abnormal nuclear studies occurred in diabetic patients with fewer than two risk factors, suggesting limited value of baseline risk factors for risk stratification in DM patients.

Prognostic value of gated SPECT

Extensive data on the prognostic significance of perfusion imaging in the general population have been published.[w41] With a normal scan, the annual death rate or myocardial infarction event rate is 0.7% for exercise and 1.2% for pharmacological stress.[w41] In patients with an abnormal exercise stress scan, the cardiac event rate is 5.6%, increasing to 8.3% for an abnormal pharmacological stress study.[w42] Kang *et al* demonstrated that a normal scan was similarly predictive of low cardiac event rates in 1271 diabetics and in 5862 subjects without DM (1.2% vs 0.7%, p=NS).[w43] Nonetheless, risk adjusted event-free survival in patients with moderately to severely abnormal scans was considerably worse in patients with DM than in non-diabetics (87% vs 91%, p=0.01).[w43] Giri *et al* demonstrated that the presence and extent of perfusion abnormalities on gated SPECT was an independent predictor of cardiac death alone or cardiac death and myocardial infarction in patients with and without DM.[w44] Risk stratification by stress and SPECT was shown to be incremental to

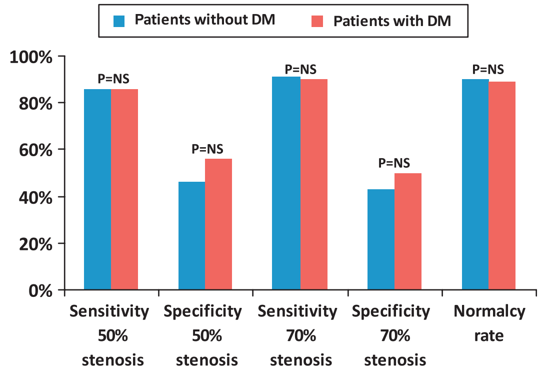

Figure 4 Diagnostic accuracy of myocardial perfusion single photon emission computed tomography (SPECT) to detect coronary artery disease in patients with and without diabetes mellitus (DM). Sensitivity and specificity to detect a 50% or 70% coronary lesion are reported separately. Modified, with permission, from Kang *et al*.[w40]

baseline clinical risk assessment (figure 5). During the first 2 years of follow-up, survival in patients with normal SPECT results was similar between DM patients and patients without DM. After this warranty period of 2 years, however, the mortality rates increased in patients with DM but not in subjects without DM. Based on these observations, the investigators suggested that re-testing of patients with normal studies should occur earlier in diabetic patients than in the general population.[w44]

Image quality can be suboptimal in obese (diabetic) patients when SPECT is used.[w45] As compared to SPECT, positron emission tomography (PET) offers several advantages. The high energy gamma photons produced by positron emitting radionuclides, combined with attenuation correction in PET cameras, makes assessment of myocardial perfusion with PET a good option in obese patients. The short half-lives of N-13, O-15 and Rb-2 decrease the amount of time required to complete rest and stress studies. SPECT imaging only provides information about relative flow heterogeneity but does not offer information on absolute flow, therefore balanced ischaemia in the setting of multivessel CAD may be missed. This problem may be surpassed with the use of PET. In a recent review, nine studies, representing a total of 877 studies, were summarised, and a weighted sensitivity of 90% and specificity of 89% for detection of CAD were observed.[9] In a head-to-head comparison, Rb-82 PET had a higher sensitivity (93% vs 76%) and accuracy (90% vs 77%) with a similar specificity (78% vs 80%) as thallium-201 SPECT.[w46]

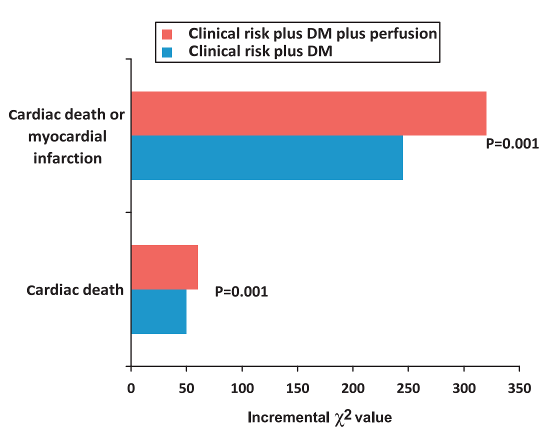

Figure 5 Incremental value of nuclear imaging (expressed as the difference in the model likelihood ratio χ^2 statistic from the overall model with and without nuclear variables) to predict cardiac death or cardiac death/myocardial infarction in diabetes mellitus (DM) patients. Based on data published in Giri *et al*.[w44]

Stress echocardiography

Detection of CAD using transthoracic echocardiography is based on regional wall motion analysis during exercise or pharmacologic stress. Most echocardiography facilities are experienced with dobutamine stress echocardiography (DSE). During DSE, myocardial contractility and heart rate are stimulated by infusion of dobutamine up to 40 μg/kg/min until 85% of maximum predicted heart rate response is achieved. Wall segments are divided into 17 segments as recommended by the AHA and ACC.[w47] A four point scoring system is used (1: normal, 2: hypokinetic, 3: akinetic, 4: dyskinetic). Ischaemia is identified when a deterioration of ≥1 score occurs during stress testing or a hypokinetic segment at rest fails to improve contractility.

Detection of CAD with DSE

In the general population stress echocardiography has a sensitivity ranging between 71–84% and a specificity ranging between 82–93%. Unfortunately, there are only limited data available on the diagnostic value of DSE in diabetic patients. One small study evaluated the diagnostic accuracy of DSE to detect significant CAD in 52 diabetics and reported a sensitivity of 82% and a specificity of 54%.[w48] Another small study compared several forms of non-invasive stress testing in 56 asymptomatic diabetic patients, demonstrating a positive predictive value of 60% for exercise ECG, 69% for DSE, and 75% for myocardial perfusion imaging.[w49]

Prognostic value of DSE

The prognostic value of DSE in the general population has been well studied. A recent meta-analysis of 13 studies including more than 32 000 patients reported an event rate (death or myocardial infarction) of 1.7% for patients with a normal DSE, whereas those with an abnormal study had an event rate of 4.8%.[w50] Moreover, the prognostic accuracy of stress echocardiography is comparable to that of nuclear imaging. The prognostic value of stress echocardiography among diabetic patients has been evaluated in several larger studies. Either pharmacological or exercise echocardiography was applied in diabetic patients with cardiac symptoms. The prevalence of abnormal studies ranged from 40–60%.[10] Diabetics with an abnormal study had a significantly higher event rate as compared to diabetics with normal studies. Marwick *et al* performed exercise echocardiography in 333 diabetics and DSE in 604 diabetics.[w51] An abnormal test result was an independent predictor of mortality (HR 1.77). Patients referred for pharmacological stress testing had a four times higher risk than patients undergoing exercise echocardiography. The largest study thus far has been performed at the Mayo Clinics and included 2349 patients with DM who underwent DSE and were followed for 5.4±2.2 years.[11] Mortality and cardiovascular morbidity were significantly higher in patients with abnormal or ischaemic test results (figure 6). Similar to that observed with nuclear techniques, normal stress echocardiograms have a limited warranty period. Elhendy *et al* followed 563 diabetics who underwent exercise echocardiography for 5 years.[w52] The 1 year event rate was 0% but the 5 year event rate 7.6%. A normal stress test was found in 40%. Among patients with an abnormal stress echocardiogram, the event rate was higher in those with multivessel wall motion abnormalities. Considering an event rate <1% indicative for a low risk group, the warranty period of a normal stress echo in diabetics is 2 years. Karmalesh *et al* also report late event rates among diabetic patients with normal stress imaging results.[w53] This observation has led to the suggestion that diabetics might need a reassessment of potential ischaemia after 2 years. Cortigiani *et al* prospectively followed 5456 patients (749 diabetics) undergoing dobutamine or dipyridamole stress echocardiography for the occurrence of hard events during a median time of 31 months.[w54] A normal test was associated with a greater than twofold annual event rate in diabetic patients as compared with diabetics who were either younger (2.6% vs 1.0%) or older (5.5% vs 2.2%) than 65 years of age.

Myocardial contrast echocardiography

With recent developments in echocardiographic equipment and microbubble contrast agents, real-time perfusion imaging is now feasible.[w55] The infused microbubbles remain in the vascular space until they dissolve, reflecting the microvascular circulation. Resting perfusion defects suggest infarcted myocardium, whereas stress induced perfusion defects indicate ischaemia (figure 7). In the general population, based on pooled analysis of seven studies (245 patients), the sensitivity and specificity of contrast echocardiography for the detection of CAD are 89% and 63%, respectively, as compared with invasive angiography.[12] One study has specifically addressed the value of contrast echocardiography in the detection of CAD in patients with DM. Elhendy *et al* evaluated 128 patients with contrast echocardiography; in 101 (79%) patients, invasive angiography detected CAD.[13] The sensitivity and specificity were 89% and 52%, respectively. In a retrospective analysis including 788 patients with suspected or known CAD, dobutamine stress myocardial contrast echocardiography provided independent information for predicting mortality and non-fatal myocardial infarction.[w56] No studies have addressed the prognostic value of dobutamine stress myocardial contrast perfusion echocardiography in a specific DM population.

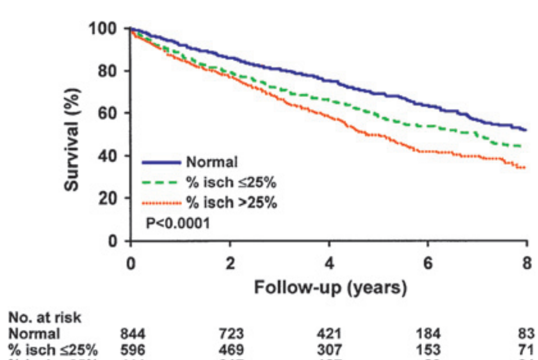

Figure 6 Prognostic value of dobutamine stress echocardiography in patients with diabetes. Kaplan–Meier survival curves for patients with diabetes according to the test result and extent of inducible ischaemia. % isch, the percentage of ischaemic segments. Reproduced, with permission, from Chaowalit *et al*.[11]

Magnetic resonance imaging

MRI combines superb image quality and the advantage of conducting myocardial perfusion and wall motion measurements at rest and under stress conditions during a single session examination.[w57] For perfusion imaging with MRI, adenosine is the first choice agent. For the detection of wall motion abnormalities both adenosine and dobutamine can be administered as a stressor. In various studies, combined dobutamine/atropine stress MRI protocols have a sensitivity of 80–90% and specificity of 80–86% for detecting inducible ischaemia.[w57] Paetsch and colleagues compared dobutamine stress MRI, adenosine stress MRI, and adenosine stress MRI perfusion in 79 consecutive patients (24% DM) with suspected or known CAD (no history of myocardial infarction) scheduled for cardiac catheterisation (figure 8).[w58] The authors concluded that dobutamine stress MRI is superior (89% sensitivity and 80% specificity) to adenosine stress for the induction of wall motion abnormalities in patients with significant CAD. Visual assessment of adenosine stress perfusion is sensitive (91%) with a low specificity (62%), whereas adenosine stress MR wall motion is highly specific (96% specificity, 40% sensitivity) because it identifies only patients with high grade perfusion deficits. Jahnke and coworkers studied 461 patients with known or suspected CAD, prior coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI) with a combined adenosine stress MRI perfusion and dobutamine stress examination, and followed them for a median period of 2.3 years.[w59] DM was present in 20% of patients. Ischaemia by MRI was an independent predictor of cardiac events. The 3 year event-free survival was 99.2% for patients with normal stress and perfusion MRI and 83.5% for those with abnormal test results. At present no specific MRI studies have addressed the diagnostic and prognostic value of cardiac MRI stress testing in a DM population.

ANATOMICAL IMAGING

Coronary artery calcium scoring

Detection of CAD using coronary artery calcium (CAC) scoring

A promising modality to identify high risk patients with DM is coronary calcium scoring with

 Heart 2010;96:560–572. doi:10.1136/hrt.2007.122788

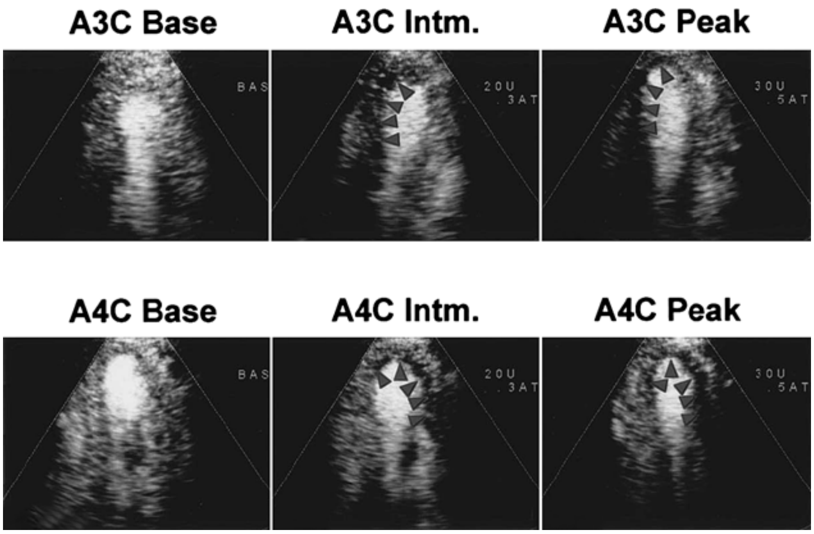

Figure 7 Myocardial contrast echocardiographic images from the apical four chamber and three chamber views, at rest, intermediate stage (Intm.), and peak stage of dobutamine stress in a patient with left anterior descending and left circumflex coronary artery disease. Perfusion abnormalities were evident in the lateral, posterior, and apical segments at intermediate phase with extension of these abnormalities at peak stress (arrows). The patient had inducible wall motion abnormalities confined to the apex at peak stress. Reproduced, with permission, from Elhendy *et al*.[w55]

computed tomography (CT) techniques. Since the presence of calcium is related to the presence of atherosclerosis, coronary calcifications serve as a direct marker for CAD. During a non-contrast scan, performed by either MSCT or electron beam CT (EBCT), the heart is imaged from base to apex allowing the identification of coronary calcifications (figure 9). The extent of calcium is expressed using the Agatston score, which is based on the plaque size and density.[w60] In general, a calcium score of 0 is considered to rule out CAD, whereas calcium scores >400 represent extensive calcifications and as a consequence extensive CAD. The majority of data with this technique have been obtained using EBCT, which in comparison to MSCT may be slightly more reproducible as well as associated with a lower radiation dose. Studies exploring the presence and extent of calcium between patients with and without DM showed considerably higher calcium scores in patients with DM as compared to their non-diabetic counterparts.[w61 w62] Moreover, Khaleeli and colleagues demonstrated that asymptomatic patients with DM presented with similar extent of coronary artery calcium (CAC) as compared to symptomatic patients without DM.[w63] Accordingly, coronary calcium may be used to identify CAD non-invasively in patients with DM. However, it is important to realise that although calcium strongly correlates with total atherosclerotic burden, it is not directly related to the degree of stenosis.[14] Also, the technique is not site-specific and high grade lesions may be observed at sites with limited calcium, whereas extensive calcium can occur in the absence of significant stenosis. Accordingly, the presence of obstructive CAD cannot be diagnosed with this technique, and the strength in calcium scoring mainly lies in risk stratification based on the evaluation of total atherosclerotic burden.

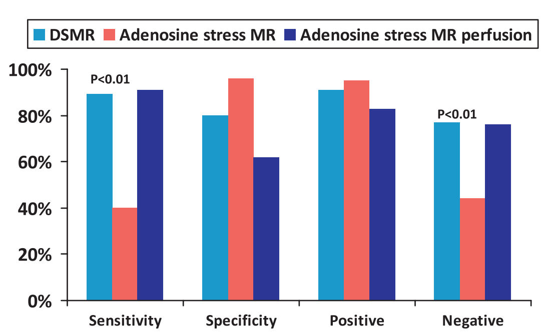

Figure 8 Diagnostic performance of dobutamine stress magnetic resonance (DSMR), adenosine stress magnetic resonance (MR), and adenosine stress MR perfusion ($p<0.01$ for dobutamine versus adenosine stress magnetic resonance). Figure based on results published in Tsutsui *et al*.[w56]

Prognostic value of CAC scoring

Indeed, in the general population coronary calcium score has been demonstrated as a strong predictor for coronary events.[15] Recently, observations from a large registry of 25253 asymptomatic patients followed for all cause mortality after EBCT calcium scoring were published confirming the predictive value of calcium scoring, independently for baseline characteristics.[w64] Relative risk ratios (as compared to zero calcium) rose from 2.2-fold for a calcium score of 11–100 to 12.5-fold for a calcium score exceeding 1000. In line with these findings, 10 year survival (adjusted for clinical characteristics) decreased from 99.4% for absence of calcium to 87.8% for scores >1000 ($p<0.0001$). Data on prognostification with calcium scoring obtained in studies restricted to patients with DM are presently less available. Raggi *et al* reported their findings in 10 377 individuals, including 903 diabetic patients.[16] An average follow-up of 5 years revealed coronary calcium scoring as the best predictor of all cause mortality in both diabetic and non-diabetic individuals. Interestingly, the authors revealed a strong association between the presence of DM and calcium. For every higher calcium score, a greater increase in mortality rate was observed in diabetic patients as compared to non-diabetics, whereas survival was similar in the absence of calcium. Similar observations were reported more recently by Anand *et al*, who studied 510 asymptomatic patients with type 2 DM.[w65] In line with the observations of Raggi *et al*, calcium scores were demonstrated to be superior to baseline risk factors in predicting short term outcome. Accordingly, calcium scoring may be used to improve risk stratification, thereby allowing initiation of more appropriate and targeted preventive treatment strategies. However, considering the fact that patients with DM are generally considered to represent coronary risk equivalents as well as the high prevalence of calcifications in this population (~60%), cost effectiveness of strategies incorporating calcium scoring need to be determined and

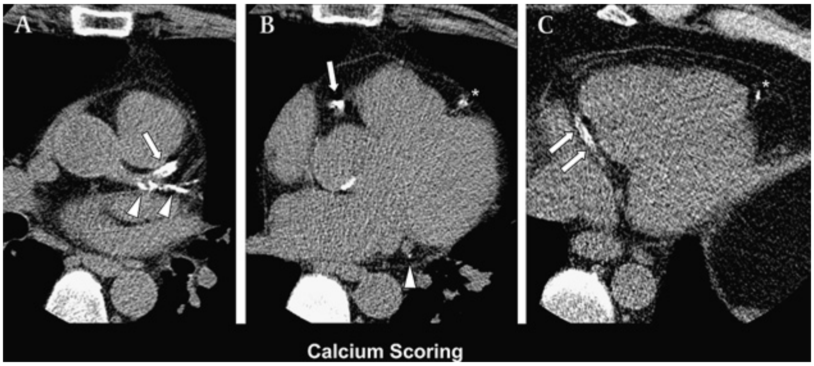

Figure 9 A 55-year-old man was referred for cardiac evaluation due to the presence of diabetes (type 1, duration 26 years), hypertension and hypercholesterolaemia in combination with occasional complaints of dyspnoea during exercise. Coronary calcium scoring revealed extensive coronary calcifications, as reflected by a coronary calcium score >1000. In panel A, dense calcium can be observed in the proximal left anterior descending artery (arrow), as well as in the proximal left circumflex artery (arrowheads). Panel B shows a section obtained at mid level, again showing the presence of calcium in the left anterior descending artery (asterix) and left circumflex artery (arrowhead) as well as in the proximal right coronary artery (arrow). Also in the more distal segments the presence of calcium was observed (panel C, asterix and arrows).

evaluation of advanced obstructive CAD resulting in ischaemia may be more relevant.[17]

Non-invasive evaluation of coronary arteries with MSCT

Detection of CAD with MSCT angiography

More recently, direct non-invasive visualisation of the coronary arteries has become possible with the introduction of MSCT. During a single breath hold of currently <10 s, the heart is imaged from base to apex during the administration of contrast. The accuracy of this technique to detect significant (≥50%) stenosis as compared to conventional coronary angiography has been evaluated in numerous studies. While older generations still frequently suffered from reduced image quality, more consistent results are obtained with 64 slice MSCT. With this generation of scanners, average weighted sensitivity and specificity (obtained in the general population) to detect significant stenosis are 92% and 96%, respectively.[w66] At present only two studies dedicated to patients with DM are available. Burgstahler and colleagues compared 16 slice MSCT to conventional coronary angiography in 22 patients with type 2 DM and 94 non-diabetic patients.[w67] In patients with DM, a sensitivity and specificity of 85% and 98% were observed, comparable to patients without DM, suggesting no major influence of the presence of DM. Reliable evaluation of CAD with MSCT in DM has also been described by Schuijf *et al*.[w68] In this study, using both 4 slice and 16 slice MSCT, a total of 220 of 256 coronary artery segments (86%) were interpretable on MSCT with a sensitivity and specificity for detection of coronary artery stenoses of both 95%. An interesting feature of MSCT is the fact that not only is the coronary lumen visualised but also the vessel wall. As a result, the technique allows imaging of subclinical atherosclerosis, albeit with significantly lower resolution as compared to invasive plaque imaging techniques.[w69]

Recently Pundziute *et al* compared MSCT plaque variables between DM (n=80) and non-diabetes (n=135).[w70] Increased plaque burden was observed in patients with DM, which was mainly attributable to an increased number of non-obstructive lesions. In addition, relatively more non-calcified (28% vs 19%), calcified (49% vs 43%) and less mixed (23% vs 38%) plaques were observed in patients with DM ($p<0.001$). Accordingly the authors concluded that DM appears to be associated with more extensive, diffuse CAD on MSCT. These observations were confirmed in a smaller population undergoing invasive evaluation using virtual histology intravascular ultrasound (VH IVUS) in addition to MSCT.[w71] Importantly, the relative increase in both non-calcified lesions and calcified lesions may suggest a relative underestimation of the extent of CAD based on calcium scoring in this population. Indeed, Scholte *et al*, who studied 80 asymptomatic diabetic patients with 64 slice MSCT, showed a high prevalence of CAD even in lower calcium categories with evidence of CAD in 55% of patients with minimal calcium.[w72] Accordingly, MSCT coronary angiography may be an attractive tool for non-invasive evaluation of the presence and extent of (subclinical) CAD in patients with DM. Particular strengths include the high negative predictive value, allowing CAD to be excluded with high diagnostic certainty. On the other hand, the technique is unlikely to miss severe CAD such as left main stenosis or three vessel disease (figure 10). However, the technique has several disadvantages, which include exposure to radiation, current inability to quantify accurately the degree of stenosis, and the fact that no information on the presence of ischaemia is derived.

Prognostic value of MSCT angiography

As the technique is relatively new, data on the prognostic value of MSCT are currently emerging. Although several studies have addressed this topic in the general population, data in patients with DM are still scarce. In a small preliminary study, Cademartiri *et al* evaluated event rates following MSCT coronary angiography in 49 patients with DM and 49 patients without DM.[w73] During a mean follow-up of 20 months, the presence of significant stenosis on MSCT was shown to be closely correlated with increased event rates both in the presence and absence of DM. Evidently, larger prospective studies addressing cost effectiveness as well as outcome are warranted before use of MSCT coronary angiography in patients with DM can be supported.

MRI coronary angiography

The first results on non-invasive coronary imaging with MRI were reported in 1993.[w74] In the general population the sensitivity and specificity of MRI for detection of CAD compared to invasive angiography are 72% and 86% (28 studies, 903

Heart 2010;**96**:560–572. doi:10.1136/hrt.2007.122788

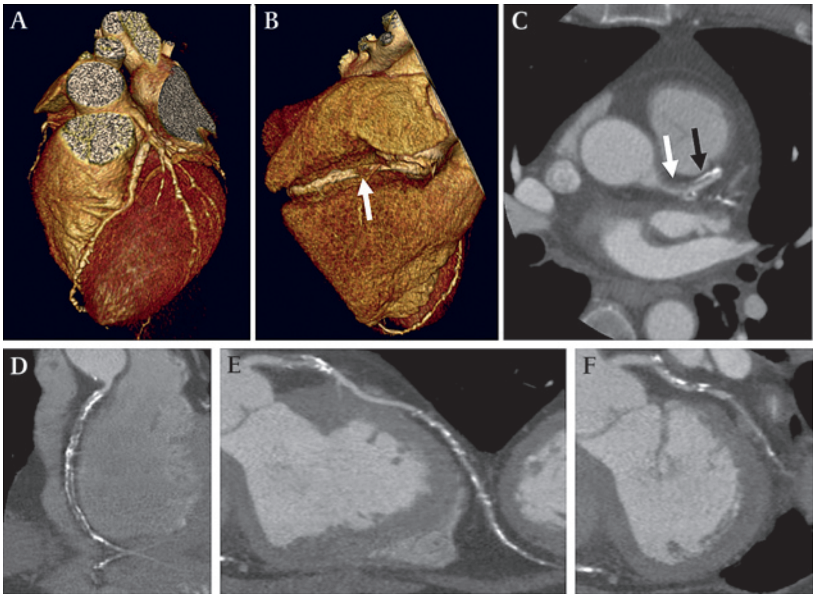

Figure 10 The 55-year-old patient discussed in figure 9 underwent 64 slice multislice computed tomography. In panels A and B, three dimensional volume rendered reconstructions are provided, showing extensive atherosclerosis, as well as an indication of a high grade lesion in the right coronary artery (panel B, arrow). In panel C, an axial image, which is used for evaluation, is shown. In the left main, non-calcified plaque can be observed, resulting in significant stenosis (white arrow). In the proximal left anterior descending artery, extensive calcifications are visible (black arrow). The presence of extensive atherosclerosis, resulting in multiple significant lesions, can also be observed on the curved multiplanar reconstructions of respectively the right coronary artery (panel D), left anterior descending artery (panel E), and left circumflex artery (panel F). Findings were confirmed during conventional coronary angiography and the patient subsequently underwent coronary bypass grafting.

patients).[12] Currently, despite recent developments such as free breathing and navigator techniques, the performance of MSCT coronary angiography is considered to be better than that of coronary MR. Diagnostic accuracy of MRI is expected to improve by the introduction of higher field magnets of 3 T and newer contrast agents. No studies dedicated to diabetic patients have been published using coronary MRI.

FUSION IMAGING

Because not all coronary stenoses detected by MSCT are flow limiting, stress myocardial perfusion data could complement the CT anatomic information by providing instant reading about the ischaemic burden of such stenoses. This could be achieved with emerging hybrid imaging technology such as SPECT-CT and PET-CT.[w75] Important limitations of hybrid technology, especially when screening asymptomatic diabetic patients, is the relatively high radiation dose and the issue of cost effectiveness. An alternative could be a combined or stepwise approach. Scholte *et al* submitted 100 asymptomatic patients with type 2 DM to SPECT, calcium scoring, and 64 slice MSCT coronary angiography to detect CAD.[17] Abnormal stress SPECT imaging consistent with inducible ischaemia was found in 23% of the patients, whereas 60% of the patients had positive calcium scoring and 70% had abnormal MSCT coronary angiography. Anatomic evidence of CAD (calcium scoring and MSCT angiography) occurred more frequently than functional evidence (SPECT). Clinically significant manifestations of CAD were observed in approximately 20–25% of patients by each modality, either separately or combined. Anand *et al* evaluated 510 asymptomatic patients with type 2 DM using EBCT, followed by nuclear myocardial perfusion in the 127 patients with a calcium score >100.[w65] The incidence of abnormal SPECT studies increased in parallel to the calcium score. During a mean follow-up of 18±5 months no events occurred in patients with a calcium score <10. Thus, EBCT could potentially be used as a gatekeeper for SPECT. Moreover, the calcium score and the extent of perfusion defects were the only predictors of future events. Based on this stepwise approach, patients with atherosclerosis on EBCT but without ischaemia could undergo aggressive medical treatment and monitoring, whereas patients with atherosclerosis and ischaemia could be referred for invasive treatment.

SCREENING FOR CAD IN ASYMPTOMATIC PATIENTS WITH DIABETES

The following criteria should be met before screening can be recommended. (1) The prevalence of CAD should be sufficiently high. Abnormal stress tests have been reported in 40–60% of patients in large retrospective series, and approximately 20% had high risk findings. However, the prospective DIAD trial reported much lower rates of abnormal myocardial perfusion tests (22%) and high risk findings (large defects in 5%).[8] (2) The screening test should accurately differentiate low and high risk patients. Normal stress tests seem to predict low risk for only 2 years (short warranty period). (3) Identification of patients at high risk should lead to treatment with better outcomes. However, DM patients are already considered high risk patients and receive secondary prevention treatment. (4) The screening strategy should be cost effective. Presently, there are no prospective data showing that screening asymptomatic DM patients is cost effective and that it will improve outcomes.

It remains unresolved whether patients with DM may benefit from screening. Available data thus far have been obtained with nuclear imaging. The 4.8 year follow-up results of the DIAD trial were recently published.[18] The cardiac event rates were low in this contemporary study population (figure 11) and were not significantly reduced by myocardial perfusion screening for CAD. The DIAD investigators concluded that routine screening for inducible ischaemia in asymptomatic patients with type 2 DM cannot be advocated. However, it is conceivable that selective evaluation may be preferred. Further investigation of strategies (possibly incorporating CAC scoring or carotid IMT) to redefine a high risk asymptomatic diabetic subgroup that will benefit from stress imaging for ischaemia, remain needed.

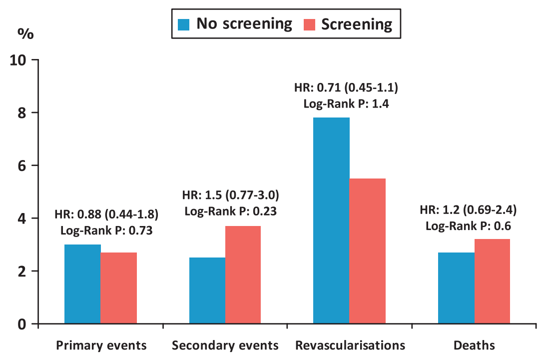

Figure 11 In the DIAD study 1123 participants with type 2 diabetes were randomly assigned to be screened with myocardial perfusion imaging or not to be screened. Participants were prospectively followed over 4.8 years. Bar graphs represent events according to randomisation group. Primary events include myocardial infarction and cardiac death. Secondary events include unstable angina, heart failure and stroke. Revascularisations: percutaneous coronary angioplasty, coronary artery bypass surgery. Death: all cause. Hazard ratios (HR, 95% CIs) represent the ratio of screening versus no screening participants from unadjusted Cox proportional hazards regression analysis. Log rank p values are derived from unadjusted actuarial survival analysis. Based on results from Young *et al*.[18]

GUIDELINES FROM THE SCIENTIFIC COMMUNITY

The general ACC/AHA guidelines on exercise testing recommend exercise ECG in patients with an intermediate pre-test probability of CAD on the basis of gender, age and symptoms.[5] These guidelines also recommend exercise ECG in asymptomatic persons with DM who plan to start vigorous exercise. In their statement on DM and cardiovascular disease, the AHA formulates some special considerations for exercise testing in diabetic patients: painless ST segment depression is common in diabetic patients, the diagnostic specificity of ST segment changes is often reduced due to previous silent myocardial infarction, conduction abnormalities and increases in LV mass.[w76] Exercise or pharmacological stress perfusion scintigraphy is a favourable alternative for exercise ECG in diabetic patients.[w76] The AHA/ACC and American Society of Nuclear Cardiology give a class I recommendation to exercise myocardial perfusion SPECT to identify the extent, severity and location of ischaemia in patients with an intermediate or high likelihood of CAD and/or who have ECG abnormalities that interfere with the interpretation of exercise induced ST segment changes.[7] In case of inability to perform exercise, left bundle branch block or ventricular pacing, adenosine or dipyridamole myocardial perfusion is recommended (class I recommendation). These guidelines recommend exercise myocardial perfusion SPECT or adenosine/dipyridamole myocardial perfusion SPECT in patients unable to exercise as the initial test in patients who are considered to be at high risk, including diabetics (class IIa recommendation).

The American Diabetes Association (ADA) Standard of Medical Care in Diabetes 2009 refers to a recently updated consensus statement.[10 19] The previous recommendation (ADA Consensus Development Conference 1998) that a risk factor approach should be used for the initial diagnostic evaluation has been abandoned.[w77] The screening of asymptomatic patients remains controversial, especially as intensive medical treatment indicated in diabetic patients at high risk for CAD has an increasing evidence base for providing equal outcomes to invasive revascularisation. In the Bypass Angioplasty Revascularization Investigation 2 Diabetes trial (BARI 2D), 2368 DM patients with heart disease were randomly assigned to either prompt revascularisation with intensive medical treatment or intensive medical treatment alone.[20] At 5 years, rates of survival did not differ significantly between the revascularisation group (88.3%) and the medical treatment group (87.8%, p=0.97). The rates of freedom from major cardiovascular events also did not differ significantly among the groups: 77.2% in the revascularisation group and 75.9% in the medical treatment group (p=0.70). Accordingly, testing for atherosclerosis or ischaemia should be reserved for those in whom medical treatment goals cannot be met and for selected individuals in whom there is strong clinical suspicion of very high risk CAD (table 2).[10] The 1998 ADA Consensus Development Conference recommended exercise ECG to screen patients. Imaging (myocardial perfusion imaging, DSE) was recommended as the initial strategy only in patients with abnormal resting ECGs. Since the prior consensus statement, newer imaging methods, such as CAC scoring and non-invasive angiography with MSCT have come into use. According to the updated consensus, it is reasonable to apply cardiac CT for detection of coronary artery calcification, using either EBCT or MSCT, as the first step.[60] If the calcium score exceeds 400, further testing could be performed using SPECT to assess myocardial perfusion or DSE to assess ischaemic wall motion

Table 2 Diabetic patients who should undergo screening for coronary artery disease according to the American Diabetes Association[10]

1. Typical or atypical cardiac symptoms
2. Clinically evident atherosclerotic disease involving lower extremity, cerebral, renal or mesenteric arteries
3. Microalbuminuria and chronic kidney disease
4. Abnormal resting ECG including abnormal Q waves or deep T wave inversions
5. Autonomic neuropathy (unexplained tachycardia, orthostatic hypertension and/or hypotension, peripheral neuropathy)
6. Retinopathy
7. Chronic undertreated hyperglycaemia
8. Patients with type 2 diabetes over the age of 65 years
9. Unexplained dyspnoea
10. Multiple cardiac risk factors including hypertension, dyslipidaemia, inactivity, smoking and abdominal obesity

Non-invasive assessment of coronary artery disease in diabetes: key points

- International guidelines consider diabetes mellitus (DM) as an equivalent of coronary artery disease (CAD) requiring aggressive anti-atherosclerotic treatment.
- Patients with DM and CAD often have no symptoms at all (silent ischaemia) or less typical symptoms such as dyspnoea.
- In DM, prevalent CAD is associated with higher carotid artery intima–media thickness.
- Standard exercise ECG testing has similar diagnostic characteristics for CAD in diabetic as in non-diabetic patients.
- Pharmacological stress testing is preferred over exercise testing in patients unable to perform adequate exercise because of peripheral obstructive artery disease, in patients with resting left bundle branch block, and patients with ventricular pacing.
- Diagnostic accuracy of myocardial perfusion SPECT and dobutamine stress echocardiography to detect CAD in diabetic patients is comparable with the diagnostic accuracy in the general population.
- Re-testing in diabetic patients with a normal myocardial perfusion study or normal stress echocardiography should occur earlier than in the general population.
- Coronary artery calcium scoring strongly correlates with total atherosclerotic burden.
- The screening of asymptomatic diabetic patients for CAD remains controversial.
- Testing for atherosclerosis or ischaemia should be reserved for those diabetic patients in whom there is strong clinical suspicion of very high risk CAD.

abnormalities. The timing of serial stress imaging studies in patients with initially normal stress test remains uncertain.

CONCLUSION

For the non-invasive assessment of CAD in DM patients, the clinician can choose from a variety of well established and validated techniques such as exercise ECG, DSE and gated SPECT combined with physiological or pharmacological stress. Novel emerging technologies such as CAC scoring and MSCT coronary angiography might provide an approach to more widespread coronary atherosclerosis screening. Since all DM patients receive secondary prevention treatment and recent data suggest no survival benefit between early revascularisation and intensive medical treatment, screening of asymptomatic diabetic patients remains controversial. Recent guidelines have identified clinical features of DM patients with a high suspicion for having a cardiovascular event in the short term. Screening for CAD should be performed in DM patients with symptoms, >65 years, multiple cardiac risk factors, and vascular, renal, retinal or neurological complications. A stepwise approach is recommended beginning with CAC scoring followed by DSE or myocardial perfusion imaging if the calcium score exceeds 400. The role of surrogate markers such as IMT, PWV and biomarkers is still under investigation, and is currently limited to the identification of high risk subgroups.

You can get CPD/CME credits for Education in Heart

Education in Heart articles are accredited by both the UK Royal College of Physicians (London) and the European Board for Accreditation in Cardiology—you need to answer the accompanying multiple choice questions (MCQs). To access the questions, click on **BMJ Learning: Take this module on BMJ Learning** from the content box at the top right and bottom left of the online article. For more information please go to: http://heart.bmj.com/misc/education.dtl

- **RCP credits:** Log your activity in your CPD diary online (http://www.rcplondon.ac.uk/members/CPDdiary/index.asp)—pass mark is 80%.
- **EBAC credits:** Print out and retain the BMJ Learning certificate once you have completed the MCQs—pass mark is 60%. EBAC/ EACCME Credits can now be converted to AMA PRA Category 1 CME Credits and are recognised by all National Accreditation Authorities in Europe (http://www.ebac-cme.org/newsite/?hit=men02).

Please note: The MCQs are hosted on BMJ Learning—the best available learning website for medical professionals from the BMJ Group. If prompted, subscribers must sign into *Heart* with their journal's username and password. All users must also complete a one-time registration on BMJ Learning and subsequently log in (with a BMJ Learning username and password) on every visit.

Supplementary references are published online only at http://hrt.bmj.com/content/vol96/issue7

Competing interests In compliance with EBAC/EACCME guidelines, all authors participating in Education in *Heart* have disclosed potential conflicts of interest that might cause a bias in the article. JJ Bax has research grants from Medtronic, Boston Scientific, BMS medical imaging, St Jude Medical, GE Healthcare, and Edwards Lifesciences.

Provenance and peer review Commissioned; not externally peer reviewed.

REFERENCES

1. **Ryden L,** Standl E, Bartnik M, *et al*. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2007;**28**:88–136.
   - **European Society of Cardiology clinical guidelines on diabetes and heart disease.**
2. **Pearson TA,** Mensah GA, Alexander RW, *et al*. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;**107**:499–511.
   - **American guidelines on inflammatory markers and heart disease.**
3. **Stein JH,** Korcarz CE, Hurst RT, *et al*. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr* 2008;**21**:93–111; quiz 89–90.
   - **American guidelines on the clinical use of carotid artery intima–media thickness.**
4. **Cruickshank K,** Riste L, Anderson SG, *et al*. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? *Circulation* 2002;**106**:2085–90.
   - **This clinical study relates vascular stiffness and outcome in diabetes patients.**
5. **Gibbons RJ,** Balady GJ, Bricker JT, *et al*. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to

Update the 1997 Exercise Testing Guidelines). *Circulation* 2002;**106**:1883–92.
- **American guidelines on exercise testing to detect coronary artery disease.**

6. **Lee DP,** Fearon WF, Froelicher VF. Clinical utility of the exercise ECG in patients with diabetes and chest pain. *Chest* 2001;**119**:1576–81.
- **This clinical study determined the characteristics of exercise treadmill testing in diabetic patients presenting with chest pain.**

7. **Klocke FJ,** Baird MG, Lorell BH, *et al*. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). *Circulation* 2003;**108**:1404–18.
- **American clinical guidelines on cardiac radionuclide imaging.**

8. **Wackers FJ,** Young LH, Inzucchi SE, *et al*. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. *Diabetes Care* 2004;**27**:1954–61.
- **This clinical study assessed the prevalence and clinical predictors of silent myocardial ischaemia in asymptomatic diabetes patients.**

9. **Bengel FM,** Higuchi T, Javadi MS, *et al*. Cardiac positron emission tomography. *J Am Coll Cardiol* 2009;**54**:1–15.
- **This state-of-the-art paper reviews current clinical cardiac applications of PET.**

10. **Bax JJ,** Inzucchi SE, Bonow RO, *et al*. Cardiac imaging for risk stratification in diabetes. *Diabetes Care* 2007;**30**:1295–304.
- **Consensus statement of the American Diabetes Association.**

11. **Chaowalit N,** Arruda AL, McCully RB, *et al*. Dobutamine stress echocardiography in patients with diabetes mellitus: enhanced prognostic prediction using a simple risk score. *J Am Coll Cardiol* 2006;**47**:1029–36.
- **This clinical study emphasises the prognostic value of stress echocardiography in diabetes patients.**

12. **Schuijf JD,** Shaw LJ, Wijns W, *et al*. Cardiac imaging in coronary artery disease: differing modalities. *Heart* 2005;**91**:1110–17.
- **This review paper discusses in depth various cardiac imaging modalities to detect coronary artery disease.**

13. **Elhendy A,** Tsutsui JM, O'Leary EL, *et al*. Noninvasive diagnosis of coronary artery disease in patients with diabetes by dobutamine stress real-time myocardial contrast perfusion imaging. *Diabetes Care* 2005;**28**:1662–7.
- **This clinical study investigated the role of contrast perfusion imaging to detect coronary artery disease in diabetes patients.**

14. **O'Rourke RA,** Brundage BH, Froelicher VF, *et al*. American College of Cardiology/American Heart Association Expert Consensus Document on electron-beam computed tomography for the diagnosis and prognosis of coronary artery disease. *J Am Coll Cardiol* 2000;**36**:326–40.
- **American consensus on the clinical use of multislice computed tomography.**

15. **Greenland P,** Bonow RO, Brundage BH, *et al*. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 2007;**49**:378–402.
- **American consensus on the clinical use of coronary artery calcium scoring.**

16. **Raggi P,** Shaw LJ, Berman DS, *et al*. Prognostic value of coronary artery calcium screening in subjects with and without diabetes. *J Am Coll Cardiol* 2004;**43**:1663–9.
- **This large trial provides data on prognosis and coronary artery calcium scoring.**

17. **Scholte AJ,** Schuijf JD, Kharagjitsingh AV, *et al*. Different manifestations of coronary artery disease by stress SPECT myocardial perfusion imaging, coronary calcium scoring, and multislice CT coronary angiography in asymptomatic patients with type 2 diabetes mellitus. *J Nucl Cardiol* 2008;**15**:503–9.
- **Clinical study emphasising anatomical and functional imaging to detect coronary artery disease in diabetes patients.**

18. **Young LH,** Wackers FJ, Chyun DA, *et al*. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. *JAMA* 2009;**301**:1547–55.
- **This clinical trial assessed whether routine screening for coronary artery disease identifies patients with type 2 diabetes as being at high risk and whether it affects their cardiac outcomes.**

19. **American Diabetes Association**. Standards of medical care in diabetes—2009. *Diabetes Care* 2009;**32**(Suppl 1):S13–61.
- **Position statement of the American Diabetes Association including screening, diagnostic, and therapeutic actions that are known or believed to favourably affect health outcomes of patients with diabetes.**

20. **Frye RL,** August P, Brooks MM, *et al*. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 2009;**360**:2503–15.
- **This trial compared outcome between diabetes patients undergoing prompt revascularisation and intensive medical treatment with intensive medical treatment.**