

# Risk stratification in uncomplicated type 2 diabetes: prospective evaluation of the combined use of coronary artery calcium imaging and selective myocardial perfusion scintigraphy

Dhakshinamurthy Vijay Anand<sup>1,2,3\*</sup>, Eric Lim<sup>1</sup>, David Hopkins<sup>4</sup>, Roger Corder<sup>2</sup>, Leslee J. Shaw<sup>5</sup>, Patrick Sharp<sup>6</sup>, David Lipkin<sup>1,3</sup>, and Avijit Lahiri<sup>1</sup>

<sup>1</sup> Cardiac Imaging and Research Centre, Wellington Hospital (South), Wellington Place, St John's Wood, London NW8 9LE, UK;

<sup>2</sup> William Harvey Research Institute, Barts and The London, Queen Mary's School of Medicine and Dentistry, London, UK;

<sup>3</sup> Department of Cardiology, Royal Free Hospital, London, UK; <sup>4</sup> Department of Endocrinology, Kings College Hospital, London, UK; <sup>5</sup> Departments of Imaging and Medicine, Cedars Sinai Medical Center, Los Angeles, CA, USA; and <sup>6</sup> Department of Endocrinology, Northwick Park Hospital, Harrow, UK

Received 3 July 2005; revised 3 December 2005; accepted 1 February 2006; online publish-ahead-of-print 23 February 2006

See page 631 for the editorial comment on this article (doi:10.1093/eurheartj/ehi612)

## KEYWORDS

Diabetes mellitus;  
Atherosclerosis;  
Coronary calcium;  
Ischaemia;  
Prognosis

**Aims** To determine the prevalence and clinical predictors of subclinical atherosclerosis and myocardial ischaemia in uncomplicated type 2 diabetes and assess their relationship to short-term outcome.

**Methods and results** Established risk factors and coronary artery calcium (CAC) scores were prospectively measured in 510 asymptomatic type 2 diabetic subjects (mean age  $53 \pm 8$  years, 61% males) without prior cardiovascular disease. Myocardial perfusion scintigraphy (MPS) was performed in all subjects with  $CAC > 100$  Agatston units (AU) ( $n = 127$ ), and a random sample of the remaining patients with  $CAC \leq 100$  AU ( $n = 53$ ). Significant CAC ( $>10$  AU) was found in 46.3%. Twenty events occurred (two coronary deaths, nine non-fatal myocardial infarctions, three acute coronary syndromes, three non-haemorrhagic strokes, and three late revascularisations) during a median follow-up of 2.2 years (25th–75th percentile = 1.9–2.5 years). The age, systolic blood pressure, the duration of diabetes, United Kingdom Prospective Diabetes Study risk score, CAC score, and extent of myocardial perfusion abnormality were significant predictors of time to cardiovascular events in a univariable Cox proportional hazard model. No cardiac events or perfusion abnormalities occurred in subjects with  $CAC \leq 10$  AU up until 2 years of follow-up. CAC and MPS findings were synergistic for the prediction of short-term cardiovascular events.

**Conclusion** Subclinical atherosclerosis, measured by CAC imaging, is superior to the established cardiovascular risk factors for predicting silent myocardial ischaemia and short-term outcome. Further studies evaluating the impact of CAC imaging on clinical outcomes and its cost effectiveness are warranted.

## Introduction

Type 2 diabetes is associated with accelerated atherothrombosis and high rates of cardiovascular morbidity and mortality.<sup>1</sup> Patients frequently have asymptomatic coronary artery disease (CAD),<sup>2–4</sup> and prognosis is substantially poorer compared with their non-diabetic counterparts.<sup>5,6</sup> Recently, there has been substantial interest in the use of imaging tests such as myocardial perfusion scintigraphy (MPS) and coronary artery calcium (CAC) imaging to detect

subclinical CAD and improve risk stratification in this population.

Although the National Institute of Clinical Excellence (NICE) in the UK<sup>7</sup> and the American Heart Association (AHA) support the use of MPS for the diagnostic and prognostic evaluation of patients with suspected CAD, it is not recommended for the routine evaluation of asymptomatic diabetic patients.<sup>8</sup> However, the risk profile of this group of patients is well documented to be very high,<sup>5,6</sup> and type 2 diabetes is considered to be a CAD 'risk equivalent'.<sup>8</sup> The prospectively conducted Detection of Ischaemia in Asymptomatic Diabetics (DIAD) trial recently showed that myocardial perfusion abnormalities were found in  $>1$  in five patients with uncomplicated type 2 diabetes; but

\*Corresponding author. Tel: +44 2074835062; fax: +44 2074835083.  
E-mail address: vdanand@hotmail.com

these individuals were not accurately identified by the established cardiovascular risk factors.<sup>3</sup>

Coronary calcium imaging is a simple, rapid, non-invasive technique that quantifies the extent and severity of CAC, a prominent feature of atherosclerosis.<sup>9</sup> Its incremental value over risk factors and prognostic power in the general population is established,<sup>10–13</sup> but unclear in diabetic subjects.<sup>14,15</sup> Although CAC imaging provides an assessment of the coronary atherosclerotic plaque burden, it does not identify the severity of coronary luminal narrowing. Therefore, the primary objective of our study was to prospectively evaluate the prevalence of CAC in asymptomatic uncomplicated type 2 diabetic patients and to determine its relationship to myocardial perfusion abnormalities. The primary hypothesis tested was whether the CAC score was superior to the established cardiovascular risk factors for identifying subjects with silent myocardial ischaemia. A secondary objective was to determine the relationship between CAC, abnormal myocardial perfusion, and short-term cardiovascular events.

## Methods

### Patients

Asymptomatic patients with uncomplicated type 2 diabetes were prospectively recruited from four diabetes clinics in secondary care (Northwick Park and Central Middlesex Hospitals, London, UK). Inclusion criteria were: type 2 diabetes >1-year duration and age between 30 and 65 years. Exclusion criteria were: documented CAD, typical angina, abnormal resting electrocardiogram (e.g. Q waves and LBBB), cerebrovascular or peripheral arterial disease (PAD), renal impairment (creatinine >140  $\mu\text{mol/L}$ ), or serious life-threatening illness. The study was approved by the local research ethics committees of participating institutions and the Administration of Radioactive Substances Advisory Committee, and all subjects gave informed consent.

Nine hundred potentially eligible type 2 diabetic subjects were invited to participate in the study either during their clinic visit or by postal invitation. Two hundred and ninety-eight patients did not respond to the invitation and 37 patients were not interested in taking part in the study. The remaining 565 patients were willing to participate in the study. Of these, seven patients were found to be subsequently ineligible; 48 patients agreed to participate in the study, but did not attend their appointment for baseline blood tests or CAC imaging; 510 subjects fulfilled the eligibility criteria, provided informed consent and participated in the study. There was no significant age difference between the responders and non-responders ( $53 \pm 8$  vs.  $53 \pm 6$  years,  $P = \text{NS}$ ).

Medical history including cardiovascular risk factors, duration of diabetes, microvascular complications, treatment history, and the predicted 10-year absolute coronary heart disease risk based on the Framingham risk function and United Kingdom Prospective Diabetes Study (UKPDS) risk engine<sup>16</sup> were recorded at baseline. Height, weight, body mass index (BMI), waist-to-hip ratio, and blood pressure were recorded and a 12-lead electrocardiogram was obtained. Fasting blood and urine samples were obtained for Diabetes Control and Complications Trial-aligned HbA<sub>1c</sub>, lipid profile, urea, creatinine, and urine albumin/creatinine ratio.

### Coronary calcium imaging

CAC imaging was performed using an electron beam computed tomography (EBCT) scanner (GE Imatron C-150, San Francisco, CA, USA) equipped with high-resolution detectors. Forty contiguous 3-mm slices were obtained during a single breath-hold starting at

the carina and proceeding to the level of the diaphragm. Scan time was 100-ms per slice, synchronized to 40% of the R-R interval.

A single experienced investigator blinded to the clinical data calculated all CAC scores on an Aquarius workstation (TeraRecon, Inc., San Mateo, USA). CAC scores were classified into five categories, based on cut-offs that have been widely used in the literature:  $\leq 10$  (minimal or insignificant CAC), 11–100 (mild CAC), 101–400 (moderate CAC), 401–1000 (severe CAC), and >1000 AU (extensive CAC).<sup>12</sup>

### Myocardial perfusion scintigraphy

On the basis of the previous data from predominantly non-diabetic populations,<sup>17,18</sup> we selected all patients with a CAC score >100 AU for gated MPS. From the remainder, i.e. subjects with CAC scores <100 AU, 53 individuals were randomly selected by computer for MPS (Figure 1). A 2-day stress rest <sup>99m</sup>Tc sestamibi protocol was used. Symptom-limited treadmill exercise (Bruce protocol) was combined with vasodilator stress (0.56 mg/kg dipyrimidole infused intravenously over 4 min). SPECT images were acquired 60–120 min after injection of 600 MBq of <sup>99m</sup>Tc sestamibi using a large field of view, dual-headed gamma camera equipped with a high-resolution collimator (SMV DSTi, GE Medical Systems). Thirty-two projections (40 s/projection) were acquired over a 180° arc, from 45° right anterior oblique to 45° left posterior oblique positions. Strict quality control and motion artefact correction were employed.

### Interpretation of MPS

Semi-quantitative visual analysis was performed using a 17-segment model<sup>19</sup> recommended by the American College of Cardiology/AHA/American Society of Nuclear Cardiology. Segments were scored by consensus of two experienced observers who were blinded to the CAC and risk factor data using a 5-point score (0 = normal, 1 = equivocal, 2 = moderately reduced, 3 = severely reduced radioisotope uptake, and 4 = absence of tracer uptake). Total ischaemic burden was estimated using summed stress, rest, and difference scores (SSS, SRS, and SDS). SSS and SRS were determined by the sum of scores of each segment from the stress and rest images, respectively. An SSS  $\geq 4$  was considered to be abnormal. SDS was determined by the sum of the difference between the SSS and the SRS. The SDS was converted to percent myocardium ischaemic by dividing the SDS by 68—the maximum potential score ( $4 \times 17$ )—and multiplying by 100.<sup>17</sup> The extent of reversible

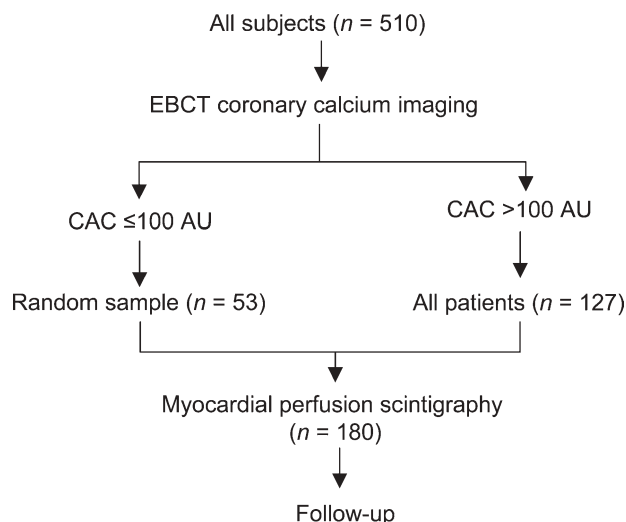


Figure 1 The study design.

myocardial ischaemia was categorized as mild ( $\leq 5\%$ ), moderate ( $> 5$  and  $\leq 10\%$ ), or large ( $> 10\%$ ).<sup>20</sup>

## Patient management and follow-up

Attending physicians were informed of study results; management was left to their discretion. All subjects were followed for the occurrence of major cardiovascular events. Procedures for follow-up were defined *a priori*. Follow-up was conducted at 12 and 18 months after enrolment of the last study participant. Telephone interviews and review of medical notes were used to determine the occurrence of cardiovascular events [cardiac death, myocardial infarction (MI), acute coronary syndrome (defined by ECG changes and/or troponin levels), late coronary revascularization ( $> 60$  days after MPS), or non-haemorrhagic stroke]. Subjects who underwent revascularization within 60 days after MPS were excluded from survival analysis to eliminate events driven by MPS findings. In cases in which a study participant experienced more than one endpoint, only the first endpoint was counted.

## Statistical analysis

Analyses were carried out using Stata V7 (Statacorp LP, TX, USA) or SPSS version 12.0 (Chicago, IL, USA). Continuous variables were summarized as mean  $\pm$  SD or median, 25th–75th percentile. Comparisons were performed using *t*-tests, Wilcoxon's rank-sum, Kruskal Wallis or  $\chi^2$  tests, as appropriate. A *P*-value of  $< 0.05$  (two-sided) was considered statistically significant. Comparison of the extent of CAC with the Framingham and UKPDS risk scores was performed using Spearman correlation.

Ordered logistic regression analysis was applied to identify clinical predictors of subclinical atherosclerosis (CAC). The distribution of CAC scores was highly skewed and could not be transformed back to normality. Hence, they were evaluated as a categorical variable as previously described, i.e. CAC  $\leq 10$ , 11–100, 101–400, 401–1000, and  $> 1000$  AU, respectively. A similar analysis was conducted to identify clinical predictors of myocardial perfusion abnormality. The summed stress scores were compared using a categorical variable, i.e. SSS  $\leq 4$ , 5–8, and  $> 8$ , respectively. For this analysis and the subsequent Cox proportional hazards model, it was necessary to split CAC scores into four categories, i.e. CAC  $\leq 100$ , 101–400, 401–1000, and  $> 1000$  AU, respectively. A backward selection procedure was applied to identify candidate variables for the multivariable model in both instances. Only those variables with  $P < 0.05$  were retained.

A univariable and multivariable Cox proportional hazards model was devised to estimate time to cardiovascular events. Clinical variables were initially identified, largely based upon individual components of varying global risk scores, including age, gender, systolic, and diastolic blood pressure, duration of diabetes, and total cholesterol values. These variables were identified *a priori* based upon prior evidence and included evaluating global risk scores and their components (i.e. traditional risk factors). Variables that were not normally distributed were transformed including examining log transformation and, in the case of coronary calcium, the logarithm of  $(1 + \text{CAC})$ . Although the transformed values and their univariable associations were evaluated, for ease of clinical interpretation, the untransformed variables are presented. In each case, the presented analysis does not differ from the results using the transformed variables.

Event-free survival curves were calculated for MPS and CAC variables. Extent of ischaemia was defined as 0, 1–5, and  $> 5\%$  of the myocardium. A first-order interaction was tested using MPS categories of 0, 1–5, and  $> 5\%$  ischaemic myocardium by CAC categories of  $\leq 100$ , 101–400, 401–1000, and  $> 1000$  AU. Additionally, a receiver operating characteristics (ROC) curve was plotted for the CAC, UKPDS, and Framingham risk score with the endpoint of cardiovascular events; thus, evaluating the ability of each variable to classify the primary endpoint of cardiovascular outcomes. The area under

the curve and 95% confidence intervals were calculated for this ROC curve. The prognostic models of CAC were internally validated by bootstrapping. Random subset sampling (with re-sampling) of 100 patients was performed.

## Sample size estimation

Previous studies indicate a substantial prevalence of significant CAC ( $\sim 25\%$ ) in the asymptomatic diabetic population.<sup>21</sup> Therefore, a sample size of 510 subjects is expected to provide 125 patients with significant CAC. Allowing 10–15 patients per variable, this enables the predictive value of 8–12 variables to be evaluated. We also performed a *post hoc* sample size calculation of the rate of abnormal MPS. One goal of the proposed study is to test the null hypothesis that the proportion of cases with MPS abnormalities is identical for all calcium score patient subsets. The criterion for significance ( $\alpha$ ) was set at 0.05 (two-tailed). Using the results put forth in Figure 2, this corresponds to an effect size ( $w$ ) of 0.532. Equivalently, it corresponds to a contingency coefficient (*C*) of 0.470 and a Cramer's  $\phi$  coefficient of 0.532. Thus, with a sample size of 180, the study has 99.9% power to yield a statistically significant result. Furthermore, when calculating the projected statistical power for risk stratification by CAC subsets, a criterion for significance ( $\alpha$ ) was set at 0.05 (two-tailed). For the overall sample of low- to high-risk CAC scores, the study will have power of 89.4% to yield a statistically significant result (Figure 3). Similar results yielding sufficient prognostic power were noted for the SPECT imaging results.

## Results

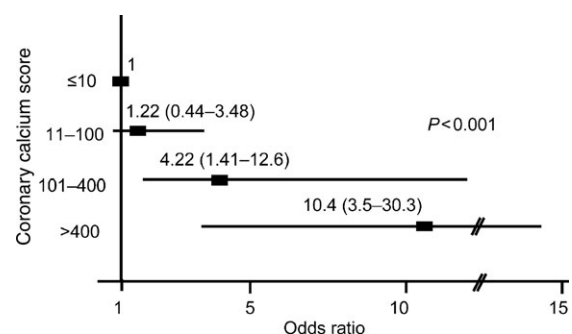
Baseline characteristics of the study population are listed in Table 1.

### Distribution of CAC

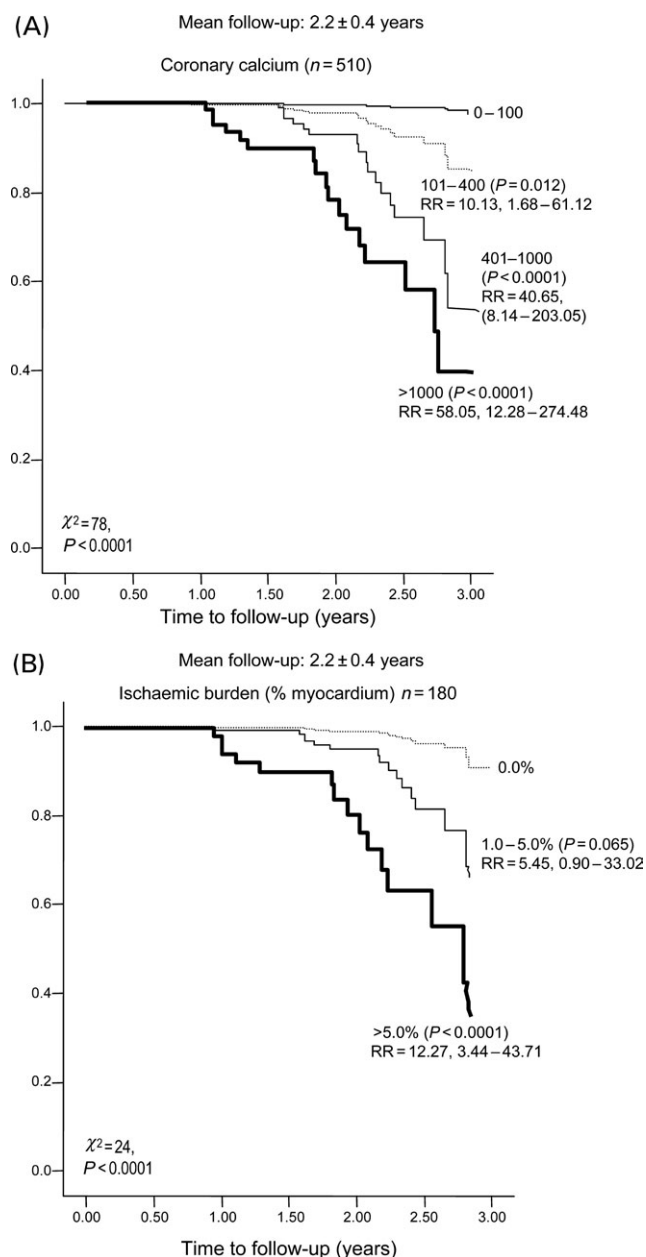
The extent of CAC was minimal ( $< 10$  AU) in 274 (53.7%), mild (11–100 AU) in 100 (19.6%), moderate (101–400 AU) in 77 (15.1%), severe (401–1000 AU) in 31 (6.1%), and extensive ( $> 1000$  AU) in 28 patients (5.5%). Image quality was poor in one patient due to respiratory movement artefacts.

### Ethnic variation in CAC

There was a high proportion of South Asians compared with White Caucasians and Black African/Caribbeans (Table 1), due to the geographic location of the study population and the high prevalence of type 2 diabetes in South Asians. Median and interquartile ranges of CAC scores in order of severity in Black African/Caribbeans, South Asians, and



**Figure 2** The multivariable predictors of myocardial perfusion abnormality. Black squares denote odds ratios and the horizontal lines represent 95% confidence intervals.



**Figure 3** Event-free survival during an average follow-up of  $2.2 \pm 0.4$  years by Cox proportional Hazards model. Survival curves according to the extent of coronary calcification (A) and myocardial perfusion abnormalities (B) are shown. Relative risk ratios (RR), confidence intervals, and P-values are provided for each CAC/MPS category.

Caucasians were 0 (0–42.5), 7.2 (0–124.3), and 18.8 (0–268.4) AU, respectively ( $P < 0.001$ ).

### Predictors of CAC

Table 2 shows the univariable predictors of CAC. However, in the multivariable logistic regression model, the predictors of CAC were: age, male gender, ethnicity, hypertension, duration of diabetes, statin use, and the UKPDS risk score. There was a weak but statistically significant correlation between the CAC score and the estimated UKPDS risk score ( $r = 0.46$ ;  $P < 0.0001$ ), Framingham risk score ( $r = 0.28$ ;  $P < 0.0001$ ).

**Table 1** Patient characteristics

Variable	Number	Percentage
Male	309	60.6
Ethnicity		
Caucasian	110	21.6
South Asian	273	53.5
Black	115	22.5
Other	12	2.4
Blood pressure > 140/90 or antihypertensive R <sub>x</sub>	380	74.5
Treated with BP < 140/90	104	20.4
Treated with BP > 140/90	140	27.4
Untreated (BP > 140/90)	136	26.7
Hyperlipidaemia or lipid lowering R <sub>x</sub>	318	62.4
Treated with total cholesterol < 5 mmol/L	133	26.1
Treated with total cholesterol > 5 mmol/L	64	12.6
Untreated (total cholesterol > 5 mmol/L)	121	23.7
Family history of premature CAD	158	31
Smoking		
Past	110	21.6
Current	97	19
Insulin only	57	11.2
Insulin + oral agent	51	10
Oral agent	434	85.1
Diet only	19	3.7
Microalbuminuria	74	14.5
Proteinuria	40	7.8
Peripheral neuropathy	90	17.6
Retinopathy	116	22.7
	Mean	SD
Age (years)	52.7	8.4
Duration of diabetes (years)	8	6
BMI	28.54	5.04
Waist-to-hip ratio	0.94	0.08
CAC score	6.2 <sup>a</sup>	0–115.8 <sup>a</sup> ; 0–5725 <sup>b</sup>
DCCT-aligned HbA <sub>1c</sub> (%)	8.2	1.7
Total cholesterol (mmol/L)	4.8	0.93
LDL cholesterol (mmol/L)	2.73	0.8
HDL cholesterol (mmol/L)	1.28	0.42
Triglyceride (mmol/L)	1.88	1.2

<sup>a</sup>Median values and interquartile ranges of CAC score.

<sup>b</sup>Overall range of CAC score.

### Relationship between CAC and myocardial perfusion

One hundred and thirty-six patients had a CAC score of >100 AU and were scheduled for MPS. Of these, nine failed to attend. The remaining 127 underwent MPS in addition to a randomly selected cohort of patients ( $n = 53$ ) with  $CAC \leq 100$  AU. One study was uninterpretable due to significant movement artefacts.

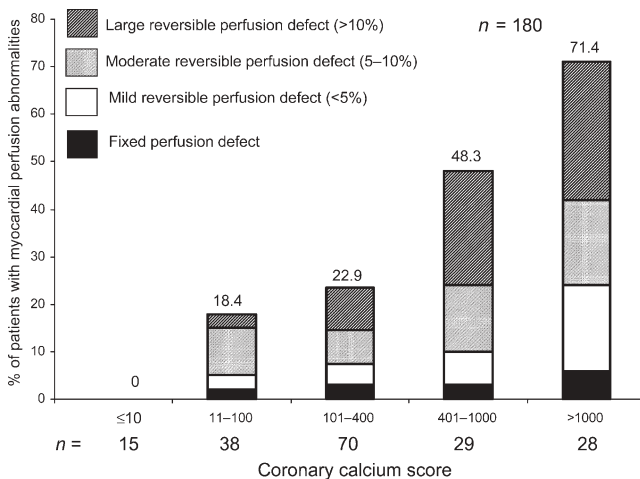
Myocardial perfusion abnormalities were seen in 57 patients (31.7%). Majority of the perfusion abnormalities were reversible (89%). The relationship between the extent of CAC and the prevalence/severity of myocardial perfusion abnormality is illustrated in Figure 4. None of the patients with  $CAC \leq 10$  AU had perfusion defects. In

**Table 2** Univariable predictors of increased coronary calcification: logistic regression analysis

Variable	Category	Odds ratio (95% CI)	P-value
Age <sup>a</sup>	—	2.18 (1.76, 2.69)	<0.001
Sex	Female	1	
	Male	2.64 (1.88, 3.71)	<0.001
Ethnicity	White	1	
	Asian	0.67 (0.45, 1.01)	0.001
	Black	0.37 (0.22, 0.60)	
BMI	—	0.96 (0.70, 1.32)	0.80
Waist-hip ratio <sup>b</sup>	—	1.67 (1.34, 2.07)	<0.001
Systolic BP	—	1.20 (1.09, 1.32)	<0.001
Diastolic BP	—	1.18 (1.04, 1.35)	0.01
Hyperlipidaemia	Yes	1.71 (1.21, 2.41)	0.002
Family history of premature CAD	Yes	1.19 (0.84, 1.67)	0.33
Smoking (pack years)	None	1	
	1–10 years	1.23 (0.71, 1.82)	0.001
	> 10 years	2.23 (1.45, 3.44)	
Duration of diabetes <sup>a</sup>	—	1.79 (1.38, 2.32)	<0.001
Microalbuminuria	Yes	1.04 (0.67, 1.62)	0.84
Retinopathy	Yes	1.47 (1.01, 2.15)	0.04
Peripheral neuropathy	Yes	1.43 (0.95, 2.15)	0.08
HbA <sub>1c</sub>	—	1.00 (0.91, 1.10)	0.96
Statin therapy	Yes	1.72 (1.25, 2.38)	0.001
Framingham risk score <sup>a</sup>	—	1.30 (1.10, 1.61)	<0.001
UKPDS risk score <sup>a</sup>	—	1.60 (1.35, 1.9)	<0.001

<sup>a</sup>Odds ratios are given for a 10-unit increase in the explanatory variable.

<sup>b</sup>Odds ratios are given for a 0.1-unit increase in the explanatory variable.



**Figure 4** The relationship between the extent of coronary calcification and the prevalence/severity of myocardial perfusion abnormality. *n* denotes the number of patients in each CAC category who underwent MPS.

contrast, seven of 38 patients with mild CAC (18.4%), 16 of 70 patients with moderate CAC (22.9%), 14 of 29 patients with severe CAC (48.3%), and 20 of 28 patients with extensive CAC (71.4%) had abnormal perfusion. Moderate-to-large perfusion abnormalities occurred in 18.4% of patients with mild CAC and 31.5% of patients with CAC >100 AU. Despite normal perfusion, 21 additional patients (11.7%) had other significant test abnormalities including 16 patients with stress-induced ST segment depression, five patients with transient ischaemic left ventricular (LV) dilatation (TID) and two patients with LV dysfunction at stress. At least one of these abnormalities

was also present in 34 patients (59.7%) with myocardial perfusion defects.

### Predictors of silent myocardial ischaemia

CAC and male gender were univariable predictors of abnormal myocardial perfusion. Multivariable logistic regression analysis showed that CAC score was the only predictor of myocardial perfusion abnormality ( $P < 0.001$ ) (Figure 2).

### Follow-up

Follow-up was completed in 99.8% of patients (median follow-up = 2.2 years; 25th–75th percentile = 1.9–2.5 years). Twenty events occurred (two cardiac deaths, nine non-fatal MIs, three acute coronary syndromes, three non-haemorrhagic strokes, and three late revascularizations). MPS data were available in 18 patients. Myocardial perfusion was abnormal in 16 patients; the remaining two had a normal MPS, but significant CAC (110 and 1442 AU, respectively). No cardiovascular events occurred in subjects with a CAC < 10 AU up until 2 years of follow-up; overall 3-year event-free survival was 98.8%. The majority of events ( $n = 15$ ) occurred in subjects with severe CAC (>400 AU). The CAC score predicted events more accurately than the UKPDS and Framingham risk scores [area under the curves were 0.92, 0.74, and 0.60 for CAC, UKPDS, and Framingham risk scores, respectively ( $P < 0.0001$ ); Figure 5].

The age, systolic blood pressure, the duration of diabetes, UKPDS risk score, CAC score, and extent of myocardial perfusion abnormality were significant predictors of time to cardiovascular events in a univariable Cox proportional hazard model (Table 3). In the multivariable model, the

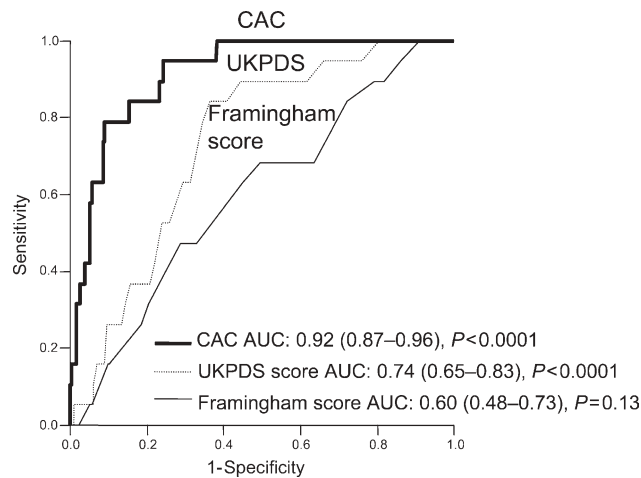
CAC score and extent of myocardial ischaemia were the only independent predictors of outcome (Figure 3). Analysis of the prognostic value of CAC in estimating time to cardiovascular events in random samples (with re-sampling) of 100 patients revealed a  $P < 0.05$  in each of these models.

To further explore the relationship between CAC and MPS, a first-order interaction term was evaluated in the survival model. This interaction term was highly significant ( $P = 0.003$ ) and revealed CAC and MPS were synergistic for predicting survival (Table 4); for example, in patients with

CAC scores  $> 400$ , event-free survival was lowest in those with  $> 5\%$  myocardium ischaemia.

We also compared the incidence of hard cardiac events (death and MI only) according to CAC ( $\leq 100$ , 101–400, 401–1000, and  $> 1000$  AU) and MPS categories (0, 1–5, and  $> 5\%$  myocardial ischaemic burden) using  $\chi^2$  test. This revealed that the overall rate of death or MI by CAC categories was 0 ( $n = 0$ ), 2.6 ( $n = 2$ ), 13.3 ( $n = 4$ ), and 17.9% ( $n = 5$ ), respectively ( $P < 0.0001$ ). Death or MI rates based on MPS categories were 0.8 ( $n = 1$ ), 18.2 ( $n = 2$ ), and 20% ( $n = 8$ ), respectively ( $P < 0.0001$ ).

Finally, we examined the predictive value of additional gated SPECT variables in a combined model incorporating the extent of myocardial ischaemia. This revealed that TID ( $P = 0.018$ ), stress left ventricular ejection fraction ( $P = 0.038$ ), and stress end-systolic volume ( $P = 0.018$ ) were also significant predictors of event-free survival.



**Figure 5** ROC analysis comparing the value of Framingham risk function, UKPDS risk engine, and the CAC score for predicting cardiovascular vents. AUC denotes area under the curve.

## Discussion

### Principal findings

In a representative, asymptomatic, and uncomplicated cohort of type 2 diabetic subjects from Northwest London, 46.3% had evidence of coronary calcification, a reliable marker of coronary atherosclerosis. The established cardiovascular risk factors predicted CAC but not abnormal myocardial perfusion. The extent of CAC was superior to established risk factors for predicting silent myocardial ischaemia and short-term cardiovascular events. There

**Table 3** Univariable predictors of cardiovascular event-free survival—Cox proportional hazards model

Variable	Category	Relative risk (95% CI)	P-value
Age (years)	—	1.09 (1.02, 1.17)	0.011
Sex	Female	1	
	Male	2.32 (0.77, 6.99)	0.12
Waist-hip ratio <sup>a</sup>	—	34.72 (0.14, >100)	0.21
Systolic BP (mmHg)	—	1.03 (1.004, 1.06)	0.023
Cholesterol	Total	0.74 (0.44, 1.25)	0.26
	LDL	0.72 (0.39, 1.31)	0.28
	HDL	0.47 (0.10, 2.26)	0.36
Triglycerides	1.10 (0.78, 1.56)	0.59	
History of premature CAD	Yes	1.25 (0.49, 3.19)	0.64
Smoking (pack years)	—	0.98 (0.92, 1.05)	0.62
Duration of diabetes (yrs)	—	1.07 (1.01, 1.13)	0.02
Microalbuminuria	Yes	0.84 (0.24, 2.95)	0.79
Retinopathy	Yes	2.31 (0.89, 5.96)	0.076
Peripheral neuropathy	Yes	1.42 (0.46, 4.36)	0.54
HbA <sub>1c</sub>	—	0.94 (0.70, 1.26)	0.68
Framingham risk score <sup>b</sup>	—	1.03 (0.98, 1.08)	0.22
UKPDS risk score <sup>b</sup>	—	38.61 (3.84, >100)	0.002
Coronary calcium score	$\leq 100$	1	
	100–400	10.13 (1.68, 61.12)	0.012
	400–1000	40.65 (8.14, >100)	<0.0001
	$> 1000$	58.05 (12.28, >100)	<0.0001
Extent of MPS Abnormality	0%	1	
	1–5%	5.45 (0.90, 33.02)	0.065
	$> 5\%$	12.27 (3.44, 43.71)	<0.0001

<sup>a</sup>Relative risks are given for a 0.1-unit increase in the explanatory variable.

<sup>b</sup>Relative risks are given for a 10-unit increase in the explanatory variable.

**Table 4** Interaction between CAC scores and the extent of myocardial perfusion abnormality for prediction of event-free survival ( $P = 0.003$ )

% Myocardium	CAC 0–100	CAC 101–400	CAC 401–1000	CAC >1000
0%	100%	98%	96%	90%
1–5%	100%	92%	83%	77%, RR = 9.20 (1.48, 57.19), $P = 0.017$
>5%	100%	80%, RR = 8.30 (1.35, 50.99), $P = 0.022$	64%, RR = 12.64 (2.97, 53.84), $P = 0.001$	48%, RR = 24.43 (5.59, >100), $P < 0.0001$

Interaction  $P = 0.003$  (unadjusted) and  $<0.0001$  (adjusted for UKPDS risk score). Event-free survival estimates are from a stratified Cox model.

was a synergistic relationship between CAC and MPS findings for the prediction of events.

#### Relationship between established cardiovascular risk factors, CAC score, and myocardial perfusion in diabetic subjects

It is paradoxical that although established cardiovascular risk factors predict CAC, they are not predictive of abnormal myocardial perfusion, yet CAC predicts myocardial ischaemia. These findings are supported by other studies: the St Francis Heart Study<sup>10</sup> and the PREDICT Study<sup>22</sup> showed that many of the established risk factors predict CAC, and the recently published DIAD Study<sup>3</sup> showed that the established risk factors do not predict abnormal MPS. Both these studies were conducted in asymptomatic type 2 diabetic subjects, similar to the present study. Given that MPS has been extensively validated as a prognostic tool, these findings suggest that CAC is a more reliable indicator of CAD risk than the established cardiovascular risk factors, probably because measuring atherosclerotic plaque burden takes into account risk factors (both known and unknown) and their possible interactions. Consistent with previous data,<sup>23</sup> we have also demonstrated a close association between features of the metabolic syndrome (intra-abdominal obesity and systolic blood pressure) and CAC.

It is also worth noting that the likelihood of abnormal MPS for any given CAC score is higher in our study than has previously been reported by studies in predominantly non-diabetic subjects.<sup>17,18</sup> Our data are however consistent with Wong *et al.*,<sup>23</sup> who have recently reported a similar increased prevalence of inducible myocardial ischaemia in diabetic/metabolic syndrome patients with subclinical atherosclerosis. A possible explanation is that diabetes could be responsible, causing microvascular dysfunction and by affecting arterial remodeling/plaque morphology so that total atherosclerotic burden is underestimated by CAC imaging.

#### Prognostic value of CAC in diabetic subjects

In support of the view that CAC is a more reliable indicator of CAD risk than the established cardiovascular risk factors, the survival analysis shows that CAC was the strongest predictor of short-term cardiovascular events. As this study was only powered to detect strong risk associations, it does not negate the prognostic value of established cardiovascular risk factors. It merely shows that CAC is a significantly better predictor of CAD risk in this patient group. We also found that the diabetes-specific UKPDS risk engine,<sup>18</sup> which incorporates additional variables such as

glycaemic control, duration of diabetes, and ethnicity, was superior to the Framingham risk function for predicting short-term cardiovascular risk.

Our data are consistent with a recent large observational study by Raggi *et al.*<sup>15</sup> which demonstrated that CAC scores were the single best predictor of all-cause mortality in 903 diabetic and 9474 non-diabetic patients. We note that previous studies have raised some concern about the prognostic value of CAC in diabetic patients as factors specific to diabetes (such as autonomic dysfunction, increased predisposition for plaque erosion/rupture, and prothrombotic tendency) may also influence the likelihood of cardiovascular events, and thereby attenuate the relationship between calcified plaque burden and cardiovascular risk. Qu *et al.*<sup>14</sup> showed that although CAC scores were significantly greater in diabetic than in non-diabetic subjects, their prognostic value in diabetic subjects was lesser. As our study was conducted exclusively in type 2 diabetics, the relative prognostic value of CAC between non-diabetics and diabetics could not be evaluated. However, the strong relationship between CAC and short-term cardiovascular events observed in our study is in contrast to the findings observed by Qu *et al.*<sup>14</sup> Different patient selection criteria and the scanning protocols utilized may in part be responsible for these varying results. For example, Qu *et al.* studied a smaller cohort of mostly high-risk male diabetic subjects who were on average 13 years older and used a scanning protocol with a lower sensitivity for detection of CAC.<sup>24</sup>

#### Complementary value of CAC imaging and selective MPS

Previous studies using MPS confirm that, irrespective of the presence or absence of symptoms of CAD, objective evidence of myocardial ischaemia is an important determinant of cardiovascular risk in diabetic patients.<sup>25</sup> However, the recently published DIAD Trial<sup>3</sup> showed that although the overall prevalence of myocardial perfusion abnormalities in uncomplicated diabetic subjects was significant (15.9%), the prevalence of moderate-to-large defects was only 6.3%.

Our study shows that restricting MPS to those diabetic patients with a CAC score of >100 AU (26.7% of the overall study population) increased the proportion of MPS scans showing moderate-to-large perfusion abnormalities to 31.5% (8.4% of the overall study population). This selective strategy proved to be effective and allowed us to identify proportionately as many patients with moderate to large perfusion defects as the DIAD Study (6.3 vs. 8.4%), while performing only 25% as many MPS studies as DIAD.

This also implies that, in comparison to DIAD, this strategy will be less expensive provided the cost of CAC imaging is no more than 75% of the cost of MPS, and will also decrease the average radiation dose per patient by 65%,<sup>7,26</sup> thus resulting in cost-efficient patient care.

### Clinical implications

Currently, the American Diabetes Association consensus guidelines<sup>27</sup> recommend screening for CAD in diabetic patients with an abnormal resting ECG indicative of MI, carotid, or PAD and two or more risk factors using exercise stress testing. Recent investigations have demonstrated a high yield of stress SPECT in asymptomatic diabetic patients with an abnormal resting ECG or PAD<sup>28</sup> and those with dyspnoea,<sup>25</sup> supporting the appropriateness of testing in these circumstances. However, it is not clear if it is worthwhile screening for subclinical CAD in the larger asymptomatic diabetic population without symptoms or evidence of macrovascular disease. Nor is it clear whether screening will result in improved clinical outcomes.

Our study shows that high-risk but asymptomatic diabetic patients can be identified by a strategy of initial CAC imaging followed by selective MPS, which has the advantage of combining the high sensitivity of CAC imaging with the specificity of MPS for predicting angiographic stenosis.<sup>29</sup> Finally, such non-invasive testing strategies may guide further therapeutic decision-making. Although prospective studies conducted specifically in diabetic patients with silent myocardial ischaemia are lacking, previous observational studies have shown the benefit of revascularization in patients with moderate-to-large myocardial perfusion abnormalities.<sup>30</sup> In addition, the Asymptomatic Cardiac Ischaemia Pilot Study (ACIP) suggested that revascularization could also improve outcomes in asymptomatic patients with myocardial ischaemia.<sup>31</sup>

### Limitations

Attending physicians were informed of CAC results, which may bias treatment received and assessment of outcome. However, it was not felt ethical to withhold this information given the emerging data on its prognostic power in the general population. Although we only evaluated a subset of patients with CAC  $\leq$  100 AU (14.2%) by MPS, these subjects were selected randomly and the standard error of the mean for the summed stress score was small (0.50), indicating that this sample size was adequate to provide an estimate of the mean SSS in the entire group of patients with CAC  $\leq$  100 AU ( $n = 374$ ). Our findings may not apply to older patients with type 2 diabetes. Owing to the comparatively short follow-up period, both hard and soft endpoints were included in the analysis. Nevertheless, there were 11 hard cardiac events including two deaths and nine non-fatal MI's. Hence our findings should serve as a basis for a larger study.

### Conclusion

Conventional risk factors are of limited value in identifying type 2 diabetic patients with advanced but asymptomatic CAD. Coronary calcium imaging and MPS are superior methods of cardiovascular risk stratification that can accurately identify high-risk asymptomatic diabetic patients. The challenge now is to incorporate these tests into clinical practice in a way that will improve clinical outcomes.

### Acknowledgements

The study was supported by research grants from the Harrow Cardiovascular Research Trust, Michael Tabor Foundation, GE Healthcare Ltd, Bristol Myers Squibb Medical Imaging Inc., and the Derrick Smith Research Grant. We thankfully acknowledge the statistical help provided by Paul Bassett, Stats Consultancy, London. We are also grateful to Usha Raval and Kiran Nagar for technical assistance, Latif Firdoussi and Linda Pontello for study co-ordination.

**Conflict of interest:** L.J.S. has received grant support from Bristol Myers Squibb Medical Imaging. A.L. has received grant support from Bristol Myers Squibb Medical Imaging and GE Healthcare. None of the other authors have any conflicting interests.

### References

1. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *J Am Med Assoc* 2002;**287**:2570–2581.
2. Cabin HS, Roberts WC. Quantitative comparison of extent of coronary narrowing and size of healed myocardial infarct in 33 necropsy patients with clinically recognised and in 28 with clinically unrecognised ('silent') previous acute myocardial infarction. *Am J Cardiol* 1982; **50**:677–681.
3. Wackers FJ, Young LH, Inzucchi SE, Chyun DA, Davey JA, Barrett EJ, Taillefer R, Wittlin SD, Heller GV, Filipchuk N, Engel S, Ratner RE, Iskandrian AE, for the Detection of Ischaemia in Asymptomatic Diabetics Investigators. Detection of silent myocardial ischaemia in asymptomatic diabetic subjects. *Diabetes Care* 2004;**27**:1954–1961.
4. Miller TD, Rajagopalan N, Hodge DO, Frye RL, Gibbons RJ. Yield of stress single photon emission computed tomography in asymptomatic patients with diabetes. *Am Heart J* 2004;**147**:890–896.
5. Haffner SM, Lehto S, Ronnema T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in non-diabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998;**339**:229–234.
6. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993;**16**:434–444.
7. Underwood SR, Anagnostopoulos C, Cerqueira M, Ell PJ, Flint EJ, Harbinson M. Myocardial perfusion scintigraphy: the evidence. *Eur J Nucl Med Mol Imaging* 2004;**31**:261–291.
8. Grundy SM, Howard B, Smith S Jr, Eckel R, Redberg R, Bonow RO. Prevention Conference VI: Diabetes and Cardiovascular Disease: executive summary. Conference Proceedings for Healthcare Professionals from a special writing group of the American Heart Association. *Circulation* 2002;**105**:2231–2239.
9. Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron beam computed tomography and coronary atherosclerotic plaque area: a histopathologic correlative study. *Circulation* 1995;**92**:2157–2162.
10. Arad Y, Goodman KJ, Roth M, Newstein D, Guerci AD. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart study. *J Am Coll Cardiol* 2005;**46**:158–165.
11. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *J Am Med Assoc* 2004;**291**:210–215.
12. Shaw LJ, Raggi P, Schisterman E, Berman D, Callister TQ. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. *Radiology* 2003;**228**:826–833.

13. Taylor AJ, Bindeman J, Feuerstein I, Cao F, Brazaitis M, O'Malley PG. Coronary calcium independently predicts incident premature coronary heart disease over measured coronary disease risk factors. *J Am Coll Cardiol* 2005;**46**:807-814.
14. Qu W, Le TT, Azen SP, Xiang M, Wong ND, Doherty TM, Detrano RC. Value of coronary artery calcium scanning by computed tomography for predicting coronary heart disease in diabetic subjects. *Diabetes Care* 2003;**26**:905-910.
15. Raggi P, Shaw LJ, Berman DS, Callister TQ. Prognostic value of coronary artery calcium screening in subjects with and without diabetes. *J Am Coll Cardiol* 2004;**43**:1663-1669.
16. Stevens RJ, Kothari V, Adler AI, Stratton IM, Holman RR, on behalf of the United Kingdom Prospective Diabetes Study (UKPDS) Group. The UKPDS risk engine: a model for the risk of coronary heart disease in Type 2 diabetes (UKPDS 56). *Clin Sci* 2001;**101**:671-679.
17. Berman DS, Wong ND, Gransar H, Miranda-Peats R, Dahlbeck J, Hayes SW, Friedman JD, Kang X, Polk D, Hachamovitch R, Shaw L, Rozanski A. Relationship between stress-induced myocardial ischaemia and atherosclerosis measured by electron beam tomography. *J Am Coll Cardiol* 2004;**44**:923-930.
18. He ZX, Hedrick TD, Pratt CM, Verani MS, Aquino V, Roberts R, Mahmarian JJ. Severity of coronary artery calcification by electron beam computed tomography predicts silent myocardial ischaemia. *Circulation* 2000;**101**:244-251.
19. Anand DV, Lim E, Raval U, Lipkin D, Lahiri A. Prevalence of silent myocardial ischaemia in asymptomatic individuals with subclinical atherosclerosis detected by electron beam tomography. *J Nucl Cardiol* 2004;**11**:450-457.
20. Iskandrian AE. Risk assessment of stable patients (Panel II): proceedings of the 4th Invitational Wintergreen Conference Wintergreen panel summaries. *J Nucl Cardiol* 1999;**6**:93-155.
21. Schurgin S, Rich S, Mazzone T. Increased prevalence of significant coronary artery calcification in patients with diabetes. *Diabetes Care* 2001;**24**:335-338.
22. Elkeles RS, Feher MD, Flather MD, Godsland IF, Nugara F, Richmond W, Rubens MB, Wang D, for the PREDICT Study Group. The association of coronary calcium score and conventional cardiovascular risk factors in type 2 diabetic subjects asymptomatic for coronary heart disease. *Diabetes Med* 2004;**21**:1129-1134.
23. Wong ND, Rozanski A, Gransar H, Miranda-Peats R, Kang X, Hayes S, Shaw L, Friedman J, Polk D, Berman DS. Metabolic syndrome and diabetes are associated with an increased likelihood of inducible myocardial ischaemia among patients with subclinical atherosclerosis. *Diabetes Care* 2005;**28**:1445-1450.
24. Callister TQ, Janowitz W, Raggi P. Sensitivity of two electron beam tomography protocols for the detection and quantification of coronary calcium. *Am J Roentgenol* 2000;**175**:1743-1746.
25. Zellweger MJ, Hachamovitch R, Kang X, Hayes SW, Friedman JD, Germano G, Pfisterer ME, Berman DS. Prognostic relevance of symptoms vs. objective evidence of coronary artery disease in diabetic patients. *Eur Heart J* 2004;**25**:543-550.
26. Hunold P, Vogt FM, Schmermund A, Debatin JF, Kerkhoff G, Budde T, Erbel R, Ewen K, Barkhausen J. Radiation exposure during cardiac CT: effective doses at multi-detector row CT and electron beam CT. *Radiology* 2003;**226**:145-152.
27. Consensus Development Conference on the diagnosis of coronary heart disease in people with diabetes: February 1998, Miami, Florida. American Diabetes Association. *Diabetes Care* 1998;**21**:1551-1559.
28. Rajagopalan N, Miller TD, Hodge DO, Frye RL, Gibbons RJ. Identifying high-risk asymptomatic diabetic patients who are candidates for screening stress single-photon emission computed tomography imaging. *J Am Coll Cardiol* 2005;**45**:43-49.
29. Berman DS, Schisterman EF, Miranda R, Friedman JD, Hayes SW, Lewin HC, Germano G. Nuclear cardiology and electron-beam computed tomography: competitive or complementary? *Am J Cardiol* 2001;**88**(suppl.):51E-55E.
30. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman D. Comparison of the short-term survival benefit associated with revascularisation compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003;**107**:2899-2906.
31. Roger WJ, Bourassa MG, Andrews TC, Bertolet BD, Blumenthal RS, Chaitman BR, Forman SA, Geller NL, Goldberg AD, Habib GB, Masters RG, Moissa RB, Mueller H, Pearce DJ, Pepine CJ, Sopko G, Steingart RM, Stone PH, Knatterud GL, Conti CR, for the ACIP Investigators Asymptomatic Cardiac Ischaemia Pilot Study. Outcome at 1 year for patients with asymptomatic cardiac ischaemia randomised to medical therapy or revascularisation. *J Am Coll Cardiol* 1995;**26**:594-605.
32. Knez A, Becker C, Becker A, Leber A, White C, Reiser M, Steinbeck G. Determination of coronary calcium with multi-slice spiral computed tomography: a comparative study with electron beam CT. *Int J Cardiovasc Imaging* 2002;**18**:295-303.