Coronary calcium measurement improves prediction of cardiovascular events in asymptomatic patients with Type 2 diabetes: the PREDICT Study

Robert S Elkeles (1,2), Ian F Godsland (1), Michael D Feher (3), Michael B Rubens (4), Michael Roughton (5), Fiona Nugara (6), Steve E. Humphries (7), William Richmond (2), Marcus D Flather (5,6) for the PREDICT (PRospective Evaluation of Diabetic Ischaemia by Computed Tomography) Study Group

Endocrinology and Metabolic Medicine, Imperial College London (1) and Imperial College NHS Trust (2); Beta Cell Unit, Chelsea and Westminster Hospital (3); CT Scanning Unit, Royal Brompton Hospital (4); National Heart and Lung Institute, Imperial College London (5); Clinical Trials and Evaluation Unit, Royal Brompton Hospital (6); The Rayne Institute, Royal Free and University College Medical School (7); London, U.K.

address for correspondence and reprint requests:
Robert S. Elkeles.
Unit for Metabolic Medicine, St. Mary's Hospital,
Praed Street, London, W2 1NY. U.K.
tel: *44 (0) 20 7886 1209, fax *44 (0) 20 7886 1790
email:robert.elkeles@imperial.nhs.uk
total word count: 5590

ABSTRACT

Aims: The PREDICT Study is a prospective cohort study designed to evaluate coronary artery calcification score (CACS) as a predictor of cardiovascular events in Type 2 diabetes (T2DM).

Methods and Results: 589 patients with no history of cardiovascular disease and with established T2DM had CACS measured, as well as risk factors, including plasma lipoprotein, apolipoprotein, homocysteine and C-reactive protein concentrations, homeostasis model assessment insulin resistance (HOMA-IR) and urine albumin creatinine ratio. Participants were followed for a median of 4 years and first coronary heart disease (CHD) and stroke events were identified as primary endpoints. There were 66 first cardiovascular events (including 10 strokes). CACS was a highly significant, independent predictor of events ($p<0.001$), with a doubling in CACS being associated with a 32% increase in risk of events (29% after adjustment). Hazard ratios relative to CACS in the range 0-10 Agatston units (AU) were: CACS 11-100AU, 5.4 ($p=0.02$); 101-400AU 10.5 ($p=0.001$); 401-1000AU, 11.9 ($p=0.001$) and >1000AU, 19.8 ($p<0.001$). Only HOMA-IR predicted primary endpoints independently of CACS ($p=0.01$). The areas under the ROC curve for UKPDS risk engine primary endpoint risk and for UKPDS risk plus CACS were 0.63 and 0.73, respectively ($p=0.03$). .

Conclusion: Measurement of CACS is a powerful predictor of cardiovascular events in asymptomatic patients with type 2 diabetes and can further enhance prediction provided by established risk models.

Key words:

Coronary calcification; Type 2 diabetes; coronary events; stroke

Cardiovascular disease (CVD), especially coronary heart disease (CHD), is the most common complication and the principal cause of death in Type 2 diabetes (T2DM). The risk of CHD is 2-5 times greater in patients with T2DM than in those free of the disease [1] and there is evidence that its incidence can be reduced by control of hyperglycaemia, hypertension and dyslipidaemia [2]. Methods are established for assignment of individual risk based on the major risk factors: age, gender, family history, smoking history, blood pressure, diabetes and lipid profile [3, 4].

Diabetes is now considered a CHD equivalent and patients with T2DM are offered cardiovascular risk reduction. There may, nevertheless, be undetected subgroups at relatively low risk that should not be over-treated, while others may be at high risk and in need of more intensive risk modification. Furthermore, despite current treatments there is still an excess cardiovascular mortality in T2DM.

Electron beam computed tomography (EBCT) enables high resolution, quantitative images of coronary artery calcification to be rapidly acquired. Coronary artery calcium is well-established as an index of atherosclerosis [5]. Coronary artery calcium score (CACS) predicts CHD in non-diabetic groups [6] but there is uncertainty over whether it is equally effective in patients with diabetes and more information in this area is needed [7, 8]. The primary aim of the Prospective Evaluation of Diabetic Ischaemic Disease by Computed Tomography (PREDICT) Study was to assess the role of the EBCT-derived coronary calcium score (CACS) in predicting CHD and stroke in patients with T2DM without existing clinical CVD. A secondary aim was to compare the ability of CACS and both conventional and novel risk factors and risk models to predict cardiovascular endpoints.

METHODS

The study was designed specifically to evaluate CACS as a predictor of first cardiovascular events in patients with T2DM free of clinical CVD and its protocol was published at the outset [9]. In summary, 589 patients with T2DM, recruited from outpatient diabetes clinics in Central and West London, U.K had coronary artery calcification measured. Recruitment started in November 2000, and finished in November 2003. Participants' clinical status was reviewed annually up to November 2006. The median follow up time was 4 years, as per our original protocol [9]. Ethics committee approval for the study was obtained from each of the participating centres. All participants gave written, informed consent.

Participants

Participants had T2DM diagnosed by standard criteria and were on standard diabetic therapy, including diet, tablets or insulin. They were of either sex, aged 50 to 75 years and were Caucasian or Asian. Those of Black African origin were excluded because of their known low event rate for CHD in the U.K. at the time the study was planned [10]. Other exclusion criteria were: known coronary artery disease or other cardiac disease; congestive heart failure; uncontrolled hypertension (baseline systolic BP >160 mmHg or diastolic BP >95 mmHg, with or without anti-hypertensive treatment); pregnancy; inability to provide informed consent; or other medical conditions likely to limit life expectancy or requiring extensive medical treatment.

Electron beam computed tomography

As previously described [9], EBCT was carried out on an Imatron C-150 electron beam computed tomography scanner (Imatron Inc., San Francisco, CA, USA), which uses the

high resolution, single slice mode without contrast agent. The scan time was 100 ms with 3 mm slices, electrocardiographic triggering and holding of breath by subjects. Total procedure time was 15 min with a radiation dose of 0.5– 0.9 mSv (cf U.K. annual background radiation of 2.5– 7.5mSv). Quantification of CACS was in Agatston units (AU)[11].

Biochemical measurements

After an overnight fast, blood samples were taken for baseline measurement of plasma glucose, glycosylated haemoglobin (HbA_{1c}), specific insulin, total and HDL cholesterol, triglycerides, apolipoproteins B (apoB) and AI (apoAI), LDL cholesterol (by Friedewald method), creatinine, fibrinogen, homocysteine and high sensitivity CRP and urine creatinine albumin ratio, as previously described[12, 13]. Those patients being treated with insulin had taken no insulin since the previous day.

Clinical endpoints

Clinical endpoints were selected to be comparable with other recent cardiovascular trials in diabetes [14] and included: death due to MI or other cardiovascular causes, non-fatal MI, unstable angina, other objective evidence of coronary artery disease or stroke. Diagnoses of death from cardiovascular causes were obtained from the results of post-mortem examination. Non-fatal MI was determined from review of hospital case notes and required two or more of: typical symptoms, diagnostic ECG changes, or diagnostic enzyme changes. Unstable angina was diagnosed on the basis of clinical features of an acute coronary syndrome without diagnostic enzyme changes or need for hospital

admission or both. Other objective evidence of coronary artery disease included diagnostic thallium stress testing, coronary arteriogram showing >50% stenosis or a clearly positive exercise stress test. Stroke was defined as rapid onset of focal, global or neurological deficit, either lasting more than 24 hours or leading to death, with clinical findings supplemented by neurological imaging. Study size was originally estimated on the basis of an anticipated 2:3 ratio in the number of patients with CACS ≥100AU and CACS <100AU and a 1.5% annual event rate in those with CACS <100AU. A risk ratio of 2.5 between patients with CACS>100AU and with CACS<100AU would then be detected as significant ($p<0.05$) at 86% power with 600 patients, and an anticipated 57 events over 3 years of follow-up. [9].

Follow-up

Clinical events were ascertained by direct contact with the patients and inspection of medical or other records. Relevant documentation of all reported events was reviewed by experienced clinicians not involved in the study to ensure that these fulfilled the protocol definitions. Subjects received usual therapy throughout and, as set out in the original study protocol [9]. Neither participants nor their physicians were informed of their CACS until their last follow-up visit, when they were given their scores on request.

Data Analysis

Insulin resistance was calculated from the fasting plasma glucose and insulin concentrations, according to the homeostasis model assessment (HOMA) formula [15]. Presence of the Metabolic Syndrome was determined according to International Diabetes Federation (IDF) criteria [16]. Ratios between apolipoprotein B and AI concentrations, and

between triglyceride and HDL cholesterol concentrations were calculated. In all analyses, CACS was evaluated in the 5 CACS categories: 0-10, 11-100, 101-400, 401-1000 and 1001-10000 AU as widely used[17, 18]. Statistical analysis was carried out using STATA 9.2 (StataCorp, Tx). Our analysis was designed to answer the following questions: 1) Is CACS a significant predictor of primary outcome events in the PREDICT cohort? 2) If CACS is a significant predictor, is this statistically independent of other, more readily measurable, risk factors? 3) If CACS is an independent predictor, can it improve risk prediction by the established Framingham and UKPDS risk models? To answer these questions, Cox proportional hazards modelling was used to predict time free of a first cardiovascular endpoint, with confirmation of the proportional hazards assumption for each model. The first question was addressed by entering CACS in the model as a continuous variable. CACS was also explored as a predictor in the categories 11-100, 101-400, 401-1000, >1000 AU relative to the category 0-10. The second question was addressed in a multivariable model with CACS as a categorical predictor plus the classical risk factors: age, sex, South Asian ethnicity, cigarette smoking, duration of diabetes, cholesterol, HDL cholesterol, systolic BP, diastolic BP, antihypertensive use, lipid-lowering agent use. The following variables were also entered in the model, but only if they were significant ($p<0.05$) univariate predictors of primary outcomes: alcohol intake, exercise habit, BMI, waist circumference, waist hip ratio, heart rate, fasting plasma glucose, HbA_1c, urine albumin/creatinine ratio, serum creatinine, total, LDL and HDL cholesterol, triglycerides, triglycerides/HDL cholesterol ratio, total cholesterol/HDL cholesterol ratio, apolipoproteins AI and B and the apoAI/apoB ratio, IDF metabolic syndrome, fasting plama insulin, HOMA-IR, fibrinogen, C-reactive protein and homocysteine . To answer the third question, the probability of a first CHD endpoint was estimated for each

PREDICT participant during their individual follow-up period using both the Framingham risk equations and the United Kingdom Prospective Diabetes Study (UKPDS) risk engine for CHD [3, 4] (version 3 of the UKPDS risk engine, kindly provided by Professor Rury Holman, was used in these analyses). CHD alone was considered since the Framingham equation for CVD includes peripheral vascular disease as an endpoint. The probability of a CVD primary endpoint was also estimated using the UKPDS risk engine (version 3 also provides risk estimates for CHD and stroke combined). To evaluate the ability of predictors to discriminate those who would experience an event, receiver operator characteristic (ROC) areas under the curve (AUC) were derived. Framingham and UKPDS CHD and UKPDS CVD risks were evaluated and, using predicted probabilities of a CHD or CVD event from Cox proportional hazards modelling, risks for each of these plus CACS as a continuous variable. The ROC AUCs for the Framingham or UKPDS risks alone were then compared with ROC AUC for the respective score plus CACS. A conventional significance cut-off of p=0.05 was adopted throughout.

RESULTS

Study population

Clinic records and interview identified 661 eligible patients of whom 39 declined participation in the study, 31 declined EBCT either because they did not wish to proceed in the study or were unable to attend for EBCT and 2 did not have CACS measured for technical reasons. The remaining 589 had CACS measured by EBCT. Their median (IQR) follow-up duration was 4.0 (3.0, 4.2) years, representing 2,256 person-years. Their clinical and biochemical characteristics on recruitment are given in Table 1 and their risk factor characteristics in successive categories of CACS in Table 2. Among the 33 recruits who did not proceed to EBCT, there were significantly fewer who were Caucasian, had metabolic syndrome or were being treated with antihypertensive drugs (Chi Square test, $p<0.05$). Un-scanned patients also tended to be younger (Mann Whitney U test, $p=0.02$). Results below relate exclusively to the 589 participants who underwent EBCT.

Study endpoints

During follow-up, 66 (11.2%) participants experienced a primary endpoint. The incidence rate overall was 31 per 10^3 person years. Figure 1 shows proportions of primary endpoints according to follow-up time. Non-fatal primary endpoints comprised 36 coronary artery disease, 7 MI, 1 revascularisation, 5 unstable angina and 8 strokes. Fatal primary endpoints comprised 7 coronary events and 2 strokes. Overall, during the entire follow-up period, there were 19 non-cardiovascular deaths and 123 cardiovascular events recorded, including 13 cardiovascular deaths and 29 ‘hard’ endpoints comprising

non-fatal MI, stroke or cardiovascular death. During follow-up, 7.4% of women had a primary outcome event in contrast to 13.4% of men and 10.0% of South Asians had an event compared with 11.5% of non-South Asians.

Is CACS a significant predictor of primary outcome events in the PREDICT cohort?

Incidence rates and numbers of primary outcome events in each CACS category are shown in Table 2. The highest proportions of fatal, stroke and CHD primary endpoints were in the category CACS>1000AU (results not shown). In Cox proportional hazards modeling, CACS was entered in the model as base 2 log(CACS+1). Logarithmic transformation rendered the relationship between CACS and primary outcome event rate approximately linear up to a calcification score of 1000 (Figure 2) and markedly improved model prediction (likelihood ratio: untransformed 20.2; transformed 37.2). Use of base 2 log enabled the effect of a doubling in CACS to be determined. CACS was significantly related to endpoint-free survival time (Table 3) and a doubling of CACS was associated with a 32% increase in risk of a primary outcome event. With a doubling of CACS, there was a 31% increase in risk for the 56 CHD endpoints alone ($p<0.001$) and a 33% increase in risk for the 29 hard endpoints alone ($p<0.001$). Successive CACS categories were highly significantly related to endpoint-free follow-up time (Table 3). The proportions of primary endpoints according to follow-up time in each CACS category are shown in Figure 3. Only 9% of patients had a CACS score of >1000, but this group accounted for 25% of all patients experiencing first endpoints (unadjusted HR 19. 8 95% CI (4.6, 86.0)).

Does CACS predict events independently of other, more readily measurable, risk factors?

Among the classical risk factors only age (p=0.006), male gender (p=0.01) and increased levels of SBP (0.04) were significant univariate predictors of endpoint-free follow-up time. Among the other risk factors only serum creatinine (p=0.01) and HOMA-IR (p=0.02) were significant predictors. There was little evidence for significant interactions between CACS and other risk factors, including age, duration of diabetes and HbA1c level. In multivariable analysis, with entry of classical risk factors plus serum creatinine and HOMA-IR, CACS remained a highly significant predictor of primary endpoints with a doubling in CACS being associated with a 29% increase in risk (Table 3). In multivariable analysis with entry of CACS categories, prediction by the category 11-100 AU was reduced to borderline significance (p=0.07), but the three higher CACS categories remained significantly predictive. In the fully-adjusted model, with entry of CACS either as a continuous or categorical variable, the only other significant predictor was HOMA-IR (p=0.01).

Does CACS add to risk prediction provided by the established Framingham and UKPDS risk models?

Framingham CHD risk was a significant predictor of CHD-free survival time (p=0.002). With inclusion of CACS in the model, the significance of Framingham CHD risk was markedly reduced (p=0.05) and CACS remained significant (p<0.001). In identifying those who would experience a CHD event, inclusion of CACS with Framingham risk increased the ROC AUC from 0.63 to 0.73 (p=0.01, Table 4). UKPDS CHD risk was a significant predictor of CHD-free survival time (p<0.001). With inclusion of CACS in the model, the significance of UKPDS CHD risk was markedly reduced (p=0.02) and

CACS remained significant ($p<0.001$). In identifying those who would experience a CHD event, inclusion of CACS with UKPDS CHD risk increased the ROC AUC from 0.67 to 0.75 ($p=0.07$, Table 4). UKPDS CVD primary end-point risk was a significant predictor of CVD-free survival time ($p=0.007$). With inclusion of CACS in the model, UKPDS CVD risk ceased to be significant ($p=0.3$) and CACS remained significant ($p<0.001$). In identifying those who would experience a CVD event, inclusion of CACS with UKPDS CVD risk increased the ROC AUC from 0.63 to 0.73 ($p=0.03$, Table 4).

DISCUSSION

We have shown that CACS is highly predictive of cardiovascular endpoints in patients with T2DM with no history of CVD in a prospective study specifically designed to test this possibility. The risk of sustaining an endpoint increased with increasing category of CACS. Furthermore CACS had greater predictive value for endpoints than a broad range of conventional and novel risk factors, and added to the predictive power of the Framingham or UKPDS risk scores. Our study differs from most previously reported in that it included only patients with T2DM and without known or suspected CVD, who were recruited from routine diabetic clinics. Moreover all measurements were systematically made at baseline.

Apart from insulin resistance, no other conventional or novel risk factor (including high sensitivity CRP, homocysteine, HBA1c, lipids and lipoproteins and albumin creatinine ratio) independently predicted cardiovascular endpoints. In the UKPDS [19], as in PREDICT, blood pressure was a strong independent predictor of CVD in patients with T2DM. However, in the UKPDS, LDL and HDL cholesterol also emerged as important predictors [19]. On recruitment, PREDICT participants had already been diagnosed with diabetes for a mean of 7 years. They will, therefore have been receiving treatment and may also have been at a different stage in diabetes-related atherosclerosis from the UKPDS participants. The UKPDS risk equation did, nevertheless, provide for significant prediction of both CHD and CVD risk in the PREDICT cohort, as did the Framingham

equation for CHD. Inclusion of CACS clearly enhanced Framingham CHD risk estimation and also enhanced UKPDS CHD risk estimation at borderline significance. Importantly CACS enhanced UKPDS risk estimation for PREDICT CVD primary endpoints.

In previously-published, cross-sectional analyses of baseline relationships, we found relatively few associations between other risk factors and CACS; only age, waist hip ratio, duration of diabetes and male gender were independently related [12, 13]. In the present analysis, age and male gender predicted primary endpoints, but not independently of CACS and neither waist hip ratio nor duration of diabetes were predictive, either in univariate or multivariable analysis. Correlates of CACS were therefore relatively weak as predictors of cardiovascular endpoints compared with CACS *per se*.

In non-diabetic subjects, several studies have shown that CACS predicts cardiac events in symptomatic and asymptomatic individuals [5, 6, 18]. Recently investigators from the Multi-Ethnic Study of Atherosclerosis (MESA) have reported on the predictive power for coronary events of CACS in an ethnically-weighted population sample of 6722 men and women [20]. They found that a doubling in CACS was associated with a 26% increase in risk of CHD. This high risk compares with our finding of a 31% increase in risk in patients with T2DM, as did their finding that CACS added significantly to prediction by conventional risk factors. There is less information about the predictive value of CACS in those with diabetes. CACS predicted all cause mortality in the 8.7 percent of diabetic participants in a large observational study (n=10,377) and added to the predictive power

of the Framingham score [17]. Moreover for those patients with undetectable coronary artery calcification, mortality was similar to that of non-diabetic individuals. However, risk factors were not measured systematically at baseline and participants had been referred for risk assessment and may, therefore, have not been representative of a more general diabetic population. In another study in patients with T2DM, CACS was found to be superior to established risk factors in identifying subjects with silent myocardial ischaemia, assessed by perfusion scintigraphy [21]. First coronary heart disease and stroke events were also analysed in the 510 participants, but there were only 2.2 years of follow-up and 20 events. CACS was, nevertheless, a stronger predictor of events than conventional risk factors or scores.

Our study has limitations. Although risk of cardiovascular events increased monotonically in successive categories of CACS, confidence intervals overlapped between categories, reflecting the relatively small numbers of events in each of the categories we analysed. There was an unexpected lack of association between established risk factors and the primary outcomes, which could relate to the treatments PREDICT participants were taking, particularly the prevalent use (46%) of lipid modifying drugs. Whether treating to achieve lower lipid and blood pressure targets in patients with high CACS will be of value remains to be established. Also further studies will be needed to ascertain whether CACS is equally predictive of cardiovascular events among people of Black African origin with T2DM.

Our study identified a group with low CACS (≤10 AU), comprising 23 percent of our sample, who appear at relatively low risk for cardiovascular events and in whom use of statins, for example, may not be necessary. This could be an important consideration in the light of a recent meta-analysis of trials of cholesterol-lowering by statins which found an inverse relationship between achieved levels of LDL cholesterol and potential side effects [22]. Conversely, we have identified high risk groups in whom more intensive preventive therapy and investigation may be warranted.

The measurement of CACS will become more readily available with the use of multi-detector computed tomography (MDCT), and levels of calcification that can be reliably distinguished by this technique and EBCT (CACS >10 AU) are highly comparable [23]. Our findings indicate that measurement of coronary artery calcification in patients with established T2DM without evidence of CVD is a powerful tool for evaluating future risk of cardiovascular events that can enhance risk evaluation in these patients beyond that provided by current methods. Whether it becomes a routine procedure will depend on consideration of cost benefit relative to measurement of conventional risk factors.

Funding

Financial support for the PREDICT Study was provided by the Tompkins Foundation and the British Heart Foundation (grant no PG/03/112/16033). The study was also supported by the North West London Diabetes Local Research Network. IFG is supported by the Heart Disease and Diabetes Research Trust.

Acknowledgements

The contribution of other members of the PREDICT Study group is gratefully acknowledged: Alex Dunlop; Anna Widdowson, Nicola Delahunty and Krishna Suppiah. Victor Anyaoku and Jackie Donovan kindly provided insulin and homocysteine measurements. Drs. Hugh Mather and Anne Dornhorst kindly allowed us to study their patients. We thank Professor Rury Holman for making available to us the UKPDS Risk Engine version 3 prior to publication.

Conflict of interest:

None declared

REFERENCES

1. Pyörälä K, Laakso M. Macrovascular disease in diabetes. In: Mann J, Pyörälä K, Teuscher A, editors. Diabetes in Epidemiological Perspective: Churchill Livingstone; 1983. p. 183-247.

2. Gaede P, Vedel P, Larsen N, Jensen GVH, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with Type 2 diabetes. *N Engl J Med* 2003;**348**:383-393.

3. Anderson KM, Odell PM, Wilson PWF, Kannel W. Cardiovascular disease risk profiles. *Am Heart J* 1990;**121**:293-298.

4. Stevens RJ, Kothari V, Adler AI, Stratton IM, Holman RR. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). *Clin Sci* 2001;**101**:671-679.

5. Ardehali R, Nasir K, Kolandaivelu A, Budoff M, Blumenthal RS. Screening patients for subclinical atherosclerosis with non-contrast cardiac CT. *Atherosclerosis* 2007;**192**:235-242.

6. 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**:158-65.

7. 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.

8. Bax JJ, Inzucchi SE, Bonow RO, Schuijf JD, Freeman MR, Barrett EJ for the Global Dialogue Group for theEvaluation of Cardiovascular Risk in Patients with

Diabetes. Cardiac imaging for risk stratification in diabetes. Cardiac imaging for risk stratification in diabetes. *Diab Care* 2007;**30**:1295-1304.

9. Elkeles RS, Flather M, Feher MD, Godsland I, Richmond W, Humphries SE, Rubens MB, Underwood SR. Prospective evaluation of diabetic ischaemic heart disease by computed tomography: the PREDICT study. *Br J Diabetes Vasc Dis* 2002;**2**:69-72.

10. Wild S, Mckeigue P. Cross sectional analysis of mortality by country of birth in England and Wales, 1970-92. *Br Med J* 1997;**314**:705-10.

11. Agatston AS, Janowitz WR, Hilner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;**15**:827-832.

12. 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 (The PREDICT Study). *Diab Med* 2004;**21**:1129-1134.

13. Godsland IF, Elkeles RS, Feher MD, Nugara F, Rubens MB, Richmond W, Khan M, Donovan J, Anyaoku V, Flather MD. Coronary calcification, homocysteine, C-reactive protein and the Metabolic Syndrome in type 2 diabetes: the PREDICT Study. *Diab Med* 2006;**23**:1192-1200.

14. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:7-22.

15. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and ß-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;**28**:412-19.

16. Alberti KG, Zimmet P, Shaw J for the IDF Epidemiology Task Force Consensus Group. The metabolic syndrome--a new worldwide definition. *Lancet* 2005;**366**:1059-62.

17. 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.

18. Budoff MJ, Shaw LJ, Liu ST, Weinstein SR, Mosler TP, Tseng PH, Flores FR, Callister TQ, Raggi P, Berman DS. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. *J Am Coll Cardiol* 2007;**49**:1860-1870.

19. Turner RC, Milns H, Neil HW, Stratton IM, Manley SE, Matthews DR, Holman RR, for the United Kingdom Prospective Diabetes Study Group. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus United Kingdom prospective diabetes study (UKPDS 23). *Br Med J* 1998;**316**:823-828.

20. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, Liu K, Shea S, Szklo M, Bluemke DA, O'Leary DH, Tracy R, Watson K, Wong ND, Kronmal, RA. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* 2008;**358**(1336-1345)

21. Anand DV, Lim E, Hopkins D, Corder R, Shaw LJ, Sharp P, Lipkin D,

Lahiri A. Risk stratification in uncomplicated type 2 diabetes: prospective evaluation of the combined use of coronary artery calcium imaging and selective myocardial perfusion scintigraphy. *Eur Heart J* 2006;**27**:713-721.

22. Alsheikh-Ali AA, Maddukuri PV, Han H, Karas RM. Effect of of the magnitude of lipid lowering on risk of elevated liver enzymes, rhabdomyolysis and cancer. Insights from large randomized statin trials. *J Am Coll Cardiol* 2007;**50**:409-418.

23. Stanford W, Thompson BH, Burns TL, Heery SDE, Burr MC. Coronary artery calcium quantification at multi-detector row helical CT versus electron beam CT. *Radiology* 2004;**230**:397-402.

Table 1: Group characteristics

For the 589 PREDICT study patients who had coronary artery calcification score (CACS) measured, numbers and percentages for categorical variables in each category are given and for continuous variables, medians and interquartile ranges.

	N (%)
Coronary artery calcification (AU)	
CACS 0-10	138 (23.4)
CACS 11-100	150 (25.5)
CACS 101-400	151 (25.6)
CACS 401-1000	89 (15.1)
CACS 1001-10000	61 (10.4)
Male	373 (63.3)
Caucasian	419 (71.1)
Asian Indian	120 (20.4)
Non-smoker	261 (44.3)
Ex-smoker	239 (40.6)
Current cigarette smoker	89 (15.1)
Other current smoker	34 (5.8)
Alcohol (>28 units/wk)	35 (5.9)
Exercise (regular or aerobic)	466 (79.1)
Oral hypoglycaemic therapy	475 (80.6)
Insulin therapy	147 (25.0)
Statin therapy	225 (38.2)
Fibrate therapy	49 (8.3)
BP-lowering therapy	373 (63.3)
Metabolic syndrome (IDF)	440 (74.7)
	Median (IQR)
Age (yr)	63.1 (56.8, 68.5)
Duration of diabetes (years)	7 (3, 13)
BMI (kg/m^2)	28.7 (25.5, 32.2)
Waist circumference (cm)	99 (90.5, 108)
Waist hip ratio (x100)	96.6 (90, 102.1)
Systolic BP (mmHg)	131 (121, 142)
Diastolic BP (mmHg)	78 (72, 84)
Heart rate (per min)	74 (66, 81)
HbA1c (%)	7.7 (6.9, 9.2)
Fasting plasma glucose (mmol/l)	8.9 (7.3, 11.5)
Urine albumin creatinine ratio	1.2 (0.7, 3.3)

Serum creatinine (μmol/l)	98 (90, 109)
Total cholesterol (mmol/l)	4.7 (4.1, 5.4)
LDL cholesterol (mmol/l)	2.7 (2.2-3.3)
HDL cholesterol (mmol/l)	1.1 (0.9, 1.3)
Triglycerides (mmol/l)	1.5 (1.2, 2.3)
Triglycerides HDL cholesterol ratio	1.4 (0.9, 2.2)
Total / HDL cholesterol ratio	4.1 (3.4, 5)
Fasting plasma insulin (pmol/l)	0.9 (0.4, 2.3)
HOMA-IR	0.3 (0.2, 1)
Apolipoprotein AI (mg/dl)	141.9 (125.4, 162.4)
Apolipoprotein B (mg/dl)	95.9 (81.5, 109.6)
ApoAI / ApoB ratio	1.5 (1.2, 1.8)
Fibrinogen (g/l)	3.3 (2.7, 3.9)
C-reactive protein (mg/dl)	0.3 (0.1, 0.5)
Homocysteine (μmol/l)	10.3 (8.3, 12.7)

Table 2. Primary endpoint and risk factor characteristics by CACS category

Medians and interquartile ranges are shown, except where indicated. Significant differences across categories were present ($p<0.05$) for all variables except HbA1c, total cholesterol, HDL cholesterol, Triglycerides and HOMA-IR.

Variable	0-10 AU	11-100 AU	101-400 AU	401-1000 AU	1001-10000 AU
Number in CACS category (%)	138 (23)	150 (26)	151 (26)	89 (15)	61 (10)
Primary endpoint event rate, incidence per 10^3 person years (n)	4 (2)	21 (12)	40 (22)	45 (14)	75 (16)
Male n (%)	63 (46)	96 (64)	97 (64)	67 (75)	50 (82)
Statin therapy n (%)	43 (31)	51 (34)	70 (46)	43 (48)	18 (30)
Age (yr)	59 (54, 65)	62 (56, 67)	64 (59, 70)	65 (60, 70)	68 (60, 71)
Duration of diabetes (years)	6 (2, 11)	7 (3, 12)	8 (3, 14)	9 (5, 13)	10 (4, 15)
Waist/Hip ratio (x100)	92 (86, 100)	97 (90, 103)	97 (91, 103)	98 (93, 103)	98 (94, 104)
Systolic BP (mmHg)	127 (116, 135)	130 (120, 142)	134 (123, 145)	135 (124, 146)	134 (124, 142)
HbA1c (%)	7.9 (7, 8.9)	7.6 (6.8, 9.2)	7.7 (6.9, 9.3)	7.4 (7, 9.1)	7.8 (6.9, 9.7)
Urine albumin creatinine ratio	0.95 (0.6, 2.1)	1.3 (0.7, 4)	1.3 (0.75, 3.8)	1.3 (0.7, 3.3)	1.3 (0.7, 3.8)
Total cholesterol (mmol/l)	4.9 (4.2, 5.4)	4.7 (4.2, 5.4)	4.7 (4.1, 5.4)	4.6 (4.1, 5.5)	4.6 (4.1, 5.2)
LDL cholesterol (mmol/l)	2.7 (2.2, 3.3)	2.7 (2.3, 3.3)	2.7 (2.2-3.3)	2.7 (2.1, 3.3)	2.6 (2.2, 3.2)
HDL Cholesterol (mmol/l)	1.2 (1, 1.4)	1.1 (0.93, 1.4)	1.1 (0.94, 1.3)	1.1 (0.95, 1.4)	1 (0.91, 1.3)
Triglycerides (mmol/l)	1.5 (1.2, 2.2)	1.5 (1.1, 2.1)	1.5 (1.2, 2.3)	1.7 (1.2, 2.3)	1.6 (1.1, 2.3)
HOMA-IR	0.3 (0.13, 0.86)	0.35 (0.16, 1)	0.34 (0.15, 0.98)	0.47 (0.16, 1)	0.45 (0.17, 1)

Table 3: Prediction of first cardiovascular events (n=66) by coronary artery calcium category in the PREDICT cohort

Hazard ratios and 95% confidence intervals (HR, 95% CI, respectively) for Cox proportional hazards model are shown. In the fully-adjusted model the classical risk factors, age, sex, South Asian ethnicity, cigarette smoking, duration of diabetes, cholesterol, HDL cholesterol, systolic BP, diastolic BP, antihypertensive use, lipid-lowering use plus the significant univariate predictors serum creatinine and HOMA-IR were entered stepwise.

	Unadjusted model (n=589)*		Fully-adjusted model (n=556)*	
Coronary artery calcification (CACS)	HR (95% CI)	significance	HR (95% CI)	significance
Continuous				
$\log_2$ (CACS+1)	1.320 (1.195, 1.459)	<0.001	1.292 (1.156, 1.443)	<0.001
Categorical				
CACS 0-10	1.000 (Reference)		1.000 Reference	
CACS 11-100	5.409 (1.210, 24.169)	0.02	4.001 (0.867, 18.465)	0.07
CACS 101-400	10.491 (2.467, 44.622)	0.001	7.090 (1.604, 31.330)	0.01
CACS 401-1000	11.915 (2.707, 52.442)	0.001	8.391 (1.843, 38.209)	0.006
CACS 1001-10000	19.770 (4.545, 85.998)	<0.001	13.793 (3.067, 62.041)	0.008

* Likelihood ratios for the unadjusted and fully-adjusted models with CACS entered as a continuous variable were 37.1 and 44.6, respectively, both $p<0.001$

Table 4: Framingham and UKPDS Risk Engine estimates of coronary heart disease risk and UKPDS cardiovascular disease risk as predictors of case status without and with CACS

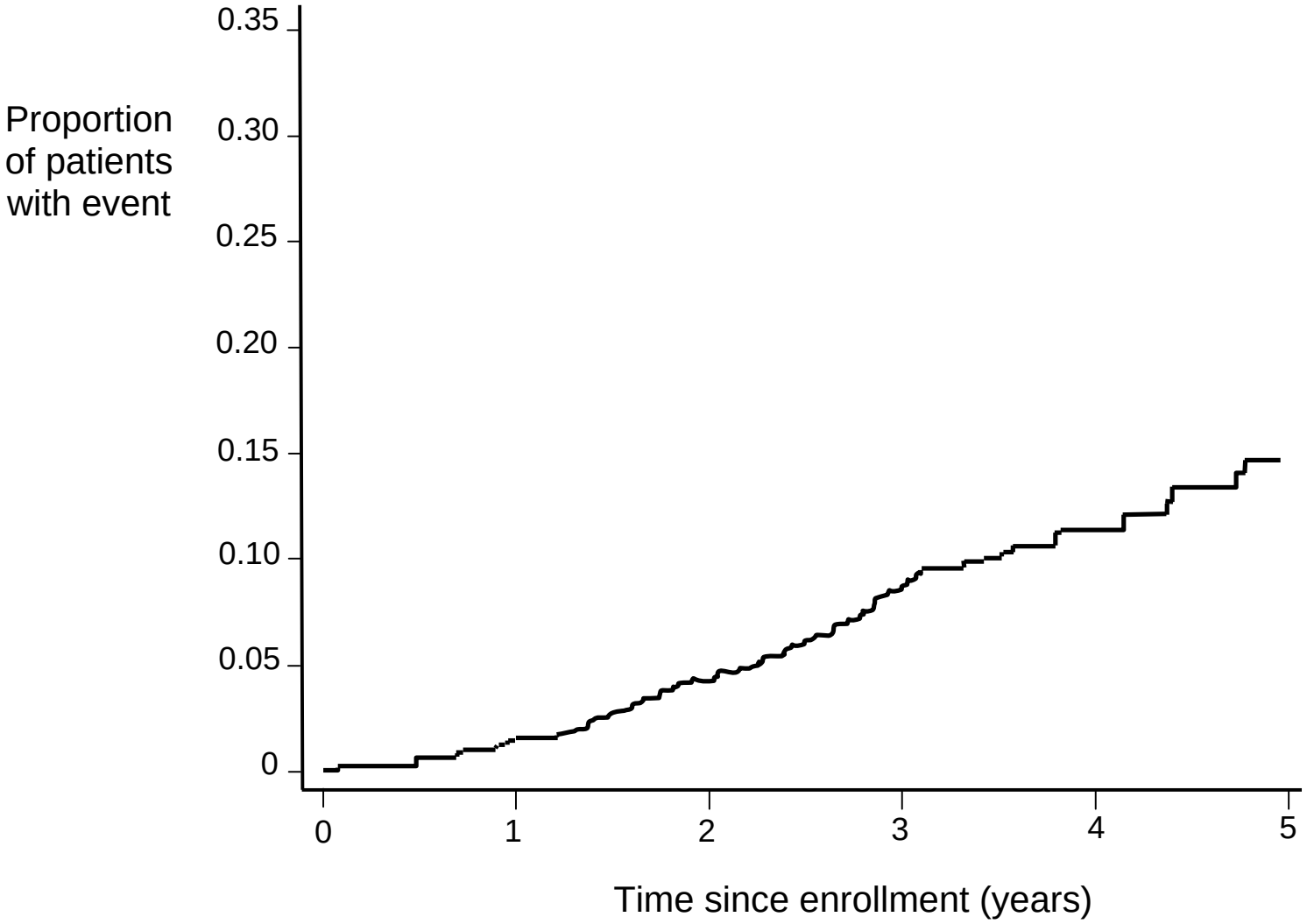
Areas under the receiver operator characteristic curves and 95% confidence intervals (AUC ROC, 95% CI, respectively) are shown for each risk score as a predictor of whether a PREDICT participant would experience a CHD event (n=56) or CVD event (n=66). Significances for the differences between AUC ROC without and with inclusion of CACS in the model are shown.

		Risk score alone	Risk score + CACS	
	n	AUC ROC (95% CI)	AUC ROC (95% CI)	p
Framingham CHD risk	572	0.63 (0.55, 0.71)	0.74 (0.67, 0.80)	0.01
UKPDS CHD risk	566	0.67 (0.60, 0.75)	0.75 (0.68, 0.81)	0.07
UKPDS CVD risk*	576	0.63 (0.56, 0.71)	0.73 (0.67, 0.79)	0.03

* Framingham CVD risk was not analysed because this includes peripheral vascular disease (PVD) as an endpoint. This was not a PREDICT endpoint and in a diabetic cohort PVD adds substantially to the number of endpoints predicted by the Framingham CVD equation.

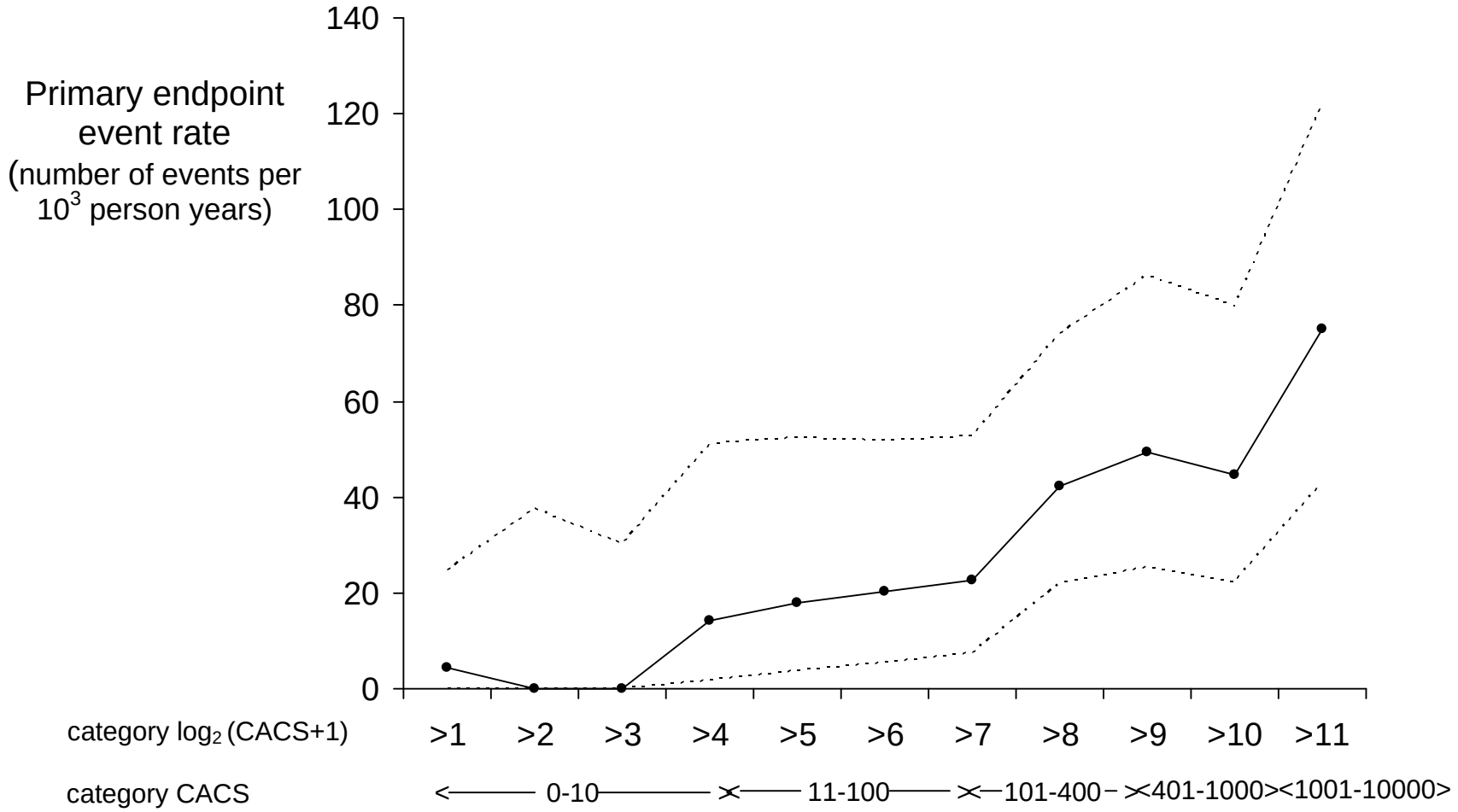
Legend to Figure 1

Proportions of patients with an event with increasing time since recruitment into the PREDICT study


Proportion of patients with event
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0
1
2
3
4
5
Time since enrollment (years)

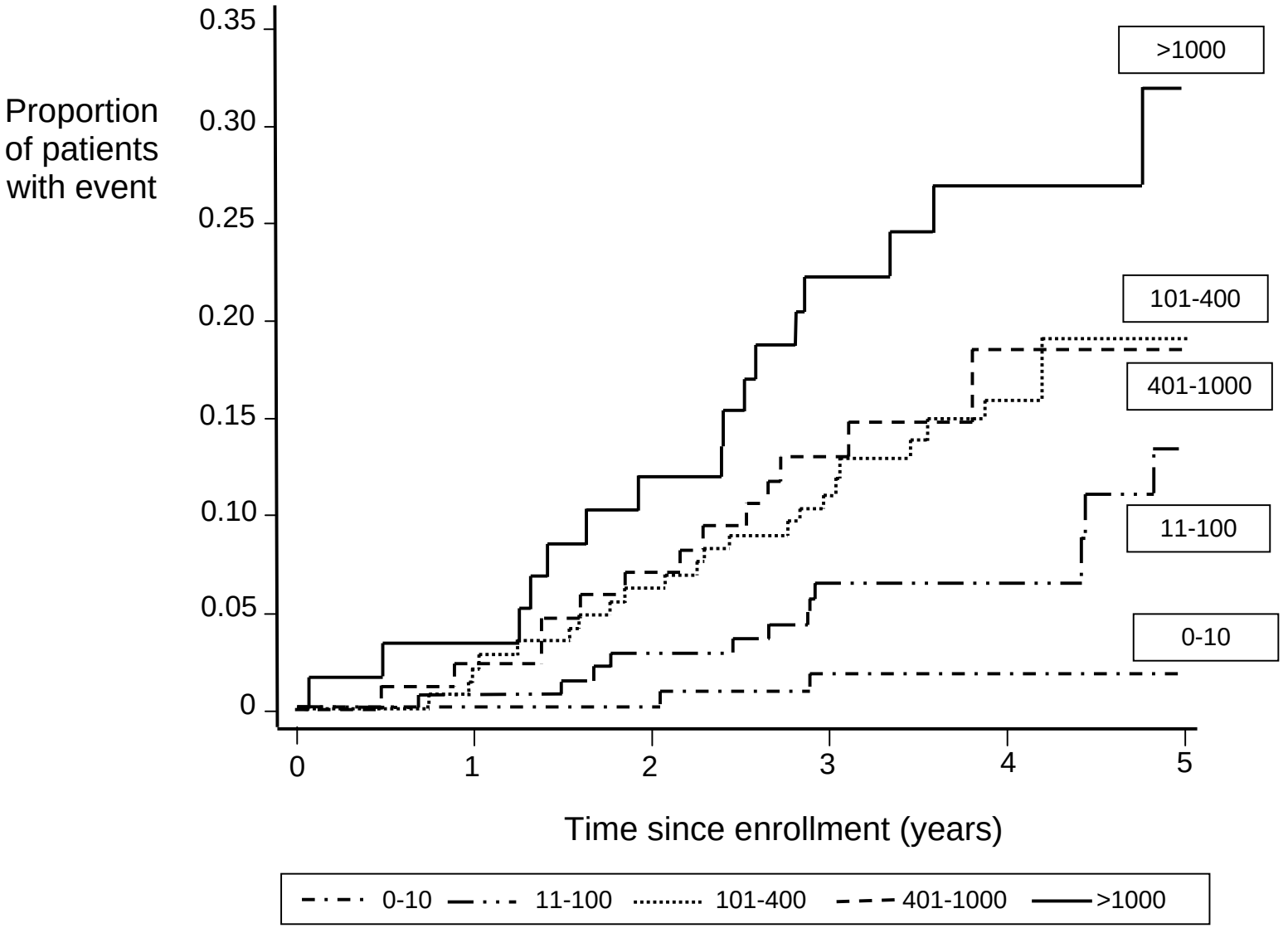
Legend to Figure 2

Primary endpoint event rates in successive categories of coronary artery calcification score. Each unit increase in $\log_2$ (CACS+1) represents a doubling in CACS. The calcification score categories 0-10, 11-100, 101-400, 401-1000 and 1001-10000 include log-transformed CACS categories 1-4, 4-7, 7-9, 9-10 and 11 respectively. Dotted lines show 95% confidence intervals.


Primary endpoint event rate
(number of events per 10^3 person years)
140
120
100
80
60
40
20
0
category $\log_2$ (CACS+1)
>1
>2
>3
>4
>5
>6
>7
>8
>9
>10
>11
category CACS
0-10
11-100
101-400
401-1000
1001-10000

Legend to Figure 3

Proportions of patients with an event with increasing time since recruitment into the PREDICT study in successive coronary artery calcification score categories (Agatston Units).


Proportion of patients with event
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0
1
2
3
4
5
Time since enrollment (years)
>1000
101-400
401-1000
11-100
0-10
0-10
11-100
101-400
401-1000
>1000