Title:

Coronary artery calcification on routine CT has prognostic and treatment implications in all ages

Key words:

Coronary artery disease; Computed tomography.

Manuscript

Introduction

Cardiovascular disease (CVD) is the leading cause of death internationally, with coronary artery disease (CAD) the predominant contributor[1,2]. As such, both the 2019 NHS Long Term Plan and the 2021 NICE Impact Cardiovascular Disease Management report highlighted the optimisation of cardiovascular disease management as a key area for improvement to save lives over the next 10 years[3,4]. CAD is a progressive, inflammatory disorder[5] with calcification forming as plaque heals[6]. The presence of coronary artery calcification (CAC) is an imaging biomarker of CAD. The severity of CAC is both a marker of the overall burden of underlying CAD, as well as prognosis[6,7].

The early identification of asymptomatic CAD enables a review of modifiable cardiovascular risk factors and the initiation of optimal medical therapy (OMT)[8]. The presence of atherosclerotic CVD also intensifies treatment targets, further personalising the optimisation of an individual's cardiovascular risk profile[9].

Traditionally, CAC is formally assessed via a dedicated cardiac CT to measure the Agatston score, a well-validated prognostic marker[10,11]. This requires the proactive clinical decision to investigate a patient for CAC, typically as part of a cardiovascular screening process in patients without a current

indication for medical therapy for CAD at intermediate risk of future major adverse cardiovascular event (MACE)12. However, international guidelines now recommend the reporting of CAC on all non-contrast chest CT imaging where the heart is in the field of view13. Further, a 2020 consensus statement from the British Society of Cardiovascular Imaging/British Society of Cardiac Computer Tomography (BSCI/BSCCT) and British Society of Thoracic Imaging (BSTI) clarified, for the first time, that CAC should be reported regardless of the indication or acquisition protocol14.

This provided an important step forward in the recommended reporting of chest CT imaging with the potential for ~~clear~~ patient benefit. However, the routine reporting of incidental CAC is infrequently performed in routine clinical practice and its clinical relevance in all age groups has been debated15. Additionally, the presence and severity of CAC varies with age and, as such, the clinical impact of its reporting may also. The prognostic implications of CAC remain regardless of patient age. Lifetime risk is significantly higher in younger patients12,16. Equally, there is increasing evidence to support the beneficial effects of statins for primary prevention irrespective of age, including in older (>75 years) patients17,18.

This study aimed to (1) quantify the prevalence and severity of CAC across unselected patients in all age groups undergoing routine non-cardiac, non-gated CT chest imaging, (2) assess the potential impact of its reporting on clinical management, and (3) track its association with clinical outcomes.

Methods

Study design

All non-cardiac chest CT imaging performed in our institution (XXXXX) from January to December 2015 were reviewed to include 200 consecutive patients in each age group (<40, 40-49, 50-59, 60-69, 70-79, 80-89, and ≥90). Scans were excluded if repeat imaging in the same patient within the study period or evidence of prior coronary intervention.

Electronic records

Electronic patient records were screened for the presence of cardiovascular risk factors, statin prescription at the time of imaging, and subsequent outcomes including documented history of myocardial infarction (MI) and stroke. Although some patients may have had a statin indicated prior to CT according to their cardiovascular risk score, in real-world practice many are not prescribed. Therefore, the potential impact on clinical management was assessed against a patient's history of a statin prescription prior to the reporting of incidental CAC.

All-cause mortality data and date of death was obtained via NHS Spine (the digital central information point for local and national NHS systems) independently of other clinical or imaging data.

In patients under 50 years-old where presence of CAC constitutes premature atherosclerosis, records were additionally screened for a lipid profile where available within 6 months of CT imaging. Familial hypercholesterolaemia is a well-documented cause of premature CAD and is known to be underdiagnosed. For patients where CAC was identified, subsequent attendance at the lipid clinic and diagnosis were recorded if available.

CT Acquisition

All imaging was obtained using routine acquisition parameters on either a Siemens Definition Edge or Drive scanner (Siemens Healthineers, Erlangen, Germany) with suspended respiration from lung apices to bases. ~~Specific CT protocols are in the supplemental materials.~~ Acquisition protocols for CT thorax, CT pulmonary angiogram (CTPA) and high-resolution CT chest (HRCT) studies are listed below, with the CT thorax protocol used in CT chest and abdomen and CT chest, abdomen and pelvis scans:

CT Thorax: 120kV with kV modulation. Automated tube current mA modulation with 66 quality reference mAs. Pitch 0.6 and rotation time 0.5s on the Definition Edge and 0.28s on the Drive. Acquisition matrix 128x0.6mm. 60mls Omnipaque 350 at 3mls/sec (if a contrast acquisition).

CTPA: 120kV with kV modulation. Automated tube current mA modulation with 66 quality reference mAs. Pitch 1 and rotation time 0.5s on the Definition Edge and 0.28s on the Drive. Acquisition matrix 128x0.6mm. 60mls Omnipaque 350 at 5mls/sec with bolus tracking and threshold trigger at 100HU.

HRCT: 120kV with kV modulation. Automated tube current mA modulation with 66 quality reference mAs. Pitch 0.6 and rotation time 0.5s on the Definition Edge and 0.28s on the Drive. Acquisition matrix 128x0.6mm.

Coronary artery calcification

All CT scans were re-reviewed for the presence or absence of CAC by two Radiologists with at least 4 years' experience each in radiology, and then visually graded semi-quantitatively using an ordinal scale on axial images of the chest, which is a previously described reproducible method19,20. The four major epicardial coronary vessels (left main stem [LMS], left anterior descending [LAD], left circumflex [LCx], and right coronary artery [RCA]) were assigned a score of 0 (none), 1 (mild), 2 (moderate) or 3 (severe) related to the degree of calcification present. Individual vessel results were summed to give a total CAC score, which was then classified as none (0), mild (1 - 3), moderate (4 - 8) or severe (9 - 12).

Statistical analysis

Statistical analysis was performed using SPSS v.21 (Armonk, NY, USA: IBM Corp). Data were assessed for normality, with continuous parametric data presented as mean (± standard deviation) and analysed with student t-test or analysis of variance (ANOVA) as appropriate. For non-parametric data, categorical data are presented as frequency (percentage) and assessed with chi-squared test

and continuous data presented as median (interquartile range [IQR]) and assessed with the Kruskal-Wallis test.

Inter- and intra-observer reliability for the assessment of CAC presence and severity was assessed in 40 scans with Cohen's κ. This was measured against pre-defined levels of agreement, with values ≤0 indicating no agreement, 0.01–0.20 as none to slight, 0.21–0.40 as fair, 0.41– 0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement21. For intra-observer analysis scans were re-reviewed >2 weeks after initial assessment by the same two Radiologists, blinded to baseline grading.

A 'number needed to report' outcome was designed to track the potential clinical impact of CAC reporting, matching the premise of the number needed to treat (NNT) assessment. An 'event' was defined as the absence of a statin prescription when there is CT evidence of CAC. This enabled an assessment of the number of patients where CAC would need to be reported to identify 1 patient with CT evidence of CAC not currently prescribed a statin. Patients with missing statin prescription data were excluded from this analysis, which was performed on a whole cohort and per age group basis.

Individual outcome analysis for MI, stroke and all-cause mortality is presented with Kaplan-Meier assessment and differences between curves evaluated with the log-rank test. Patient follow-up was defined from date of CT to either event of interest or censored on 13th Dec 2021. As all potential confounders showed association with the exposure of interest (CAC), variables were considered significant confounders if they showed an association with the outcome of interest (death, MI and stroke). This was assessed using multivariate logistic regression. Current age was adjusted for within the Cox regression model of the main associations of interest. Age-stratified results are also presented in Supplementary Table S1, which use a Lexis expansion to obtain strata for current age rather than age at entry. Significance was defined as two-tailed $p<0.05$.

Ethical approval

This was a retrospective observational study in patients who had undergone clinical scans, so written informed consent and ethical committee approval were not obtained in line with the Health Research Authority decision tool22. The Trust audit department approved the project as a service evaluation waiving the need for formal written consent. Patients and the public were not involved in the design, conduct, reporting or dissemination plans of our research.

Results

Demographics

1,343 patients (mean age 63 ± 20, 590 [44%] male) were included in the analysis. Exclusions included 10 (0.6%) for incomplete chest imaging and 47 (3%) for CT evidence of prior cardiac intervention (Figure 1). Demographics, cardiovascular risk factors present at time of CT and scan acquisition type are presented in Table 1.

CAC prevalence and severity

CAC of any degree was present in 729/1343 (54%) of patients. CAC was present more frequently in males (61% vs 49%, $p<0.001$) and older age, varying from 3% in those <40 up to 94% in those ≥90 ($p<0.001$), as demonstrated in Figure 2. CAC severity increased with age ($p<0.001$). CAC identified a high proportion of patients in all age groups without a pre-existing diagnosis of CAD at the time of their scan (Figure 2). The anatomical spread of CAC across the coronary tree is presented in Figure 2 (panel C). The LAD was the most commonly affected vessel.

CAC reporting variability

Both inter- and intra-observer variability for presence of CAC were graded as almost perfect (κ 0.89, p<0.001, and κ 0.90, p<0.001). Additionally, the inter- and intra-observer variability for categorising CAC severity when present was substantial (κ 0.68, p<0.001) and almost perfect (κ 0.91, p<0.001) respectively.

Potential impact on clinical management

Reporting CAC would have identified patients who would potentially benefit from a change in clinical management (statin prescription) in all age groups.

When CAC is reported on all scans regardless of whether it is present or not, the number needed to report to potentially impact management across all age groups is 4. This ranged from 40 for those aged <40 to 3 for patients aged ≥70 (Supplementary Table S2). If CAC is only reported in patients with CAC the number needed to report is 2, ranging from 1 for patients aged <40, to 3 for those aged 80-89. Figure 3 provides a visual breakdown of CAC presence per age category, sub-divided by the presence of a statin prescription.

Of patients aged under 50 with CT evidence of CAC, 3/30 (10%) had a lipid profile checked within 6 months of their CT and 0/30 (0%) had been reviewed in the lipid clinic.

Outcomes

Of the 1343 patients included, 689 (51%) had died after a median follow-up of 74 months (IQR 15–82). Over the same period there were 101 (8%) patients who had suffered an MI and 124 (9%) a stroke. Across the whole cohort, CAC presence was associated with increased all-cause mortality (p<0.001; Figure 4), as was increasing severity of CAC (p<0.001; Figure 4).

After adjusting for confounders (current age, gender, dyslipidaemia and IHD), CAC presence was associated with an increased risk of MI (hazard ratio [HR] 4.0 [1.9, 8.8], p<0.001). After adjusting for confounders (current age, gender, diabetes, dyslipidaemia and AF), CAC presence was associated

with an increased risk of stroke (HR 3.6 [1.7, 7.5], p=0.001; Table 2). After adjusting for confounders (current age, gender, diabetes, dyslipidaemia and AF), CAC presence did not meet the threshold for significance in association with all-cause mortality (HR 1.2 [1.0, 1.5], p=0.06; Table 2).

Additionally, after adjusting for confounders (current age, gender, dyslipidaemia and IHD), rising CAC severity was associated with a 2.9-fold increased risk of MI (Table 3). After adjusting for confounders (current age, gender, hypertension, dyslipidaemia and AF) rising CAC severity was associated with a 3.7-fold increased risk of stroke. After adjusting for confounders (current age, gender, diabetes, dyslipidaemia and AF), rising CAC severity was associated with a 1.8-fold increased risk of all-cause mortality.

Discussion

This is one of the first, and largest, studies to report the prevalence of CAC in an unselected population referred for non-gated, non-cardiac CT chest imaging, and first across a comprehensive age population. We found that the detection and grading of CAC presence and severity was reproducible and had both prognostic and potential treatment implications across all age groups.

The prevalence and severity of CAC for patients in our study is similar to other studies analysing CAC via formal Agatston scoring. The presence of any CAC in patients aged <50 in our cohort was 7.5%, compared to 10.2% in the 2017 CARDIA study of asymptomatic patients aged 32 - 46 years23. The presence and burden of CAC in patients aged >50 was also similar to the formal measurement of CAC in asymptomatic populations using dedicated Agatston score severity categories24,25. There is limited data on the prevalence of CAC graded in the ordinal fashion recommended by BSCI/BSTI, but there was a slightly lower burden of CAC in the 55-69 years old patients in our study versus those in a recent lung cancer screening study (41% with no CAC in ours vs 35%, 40% mild CAC in ours vs 32%, 17% moderate in ours vs 26% and 2% severe in ours vs 8%)26. This is likely to reflect the differences in baseline characteristics between the two study cohorts, particularly given all patients in the ITALUNG study had a ≥20 pack-year smoking history26.

As expected, CAC presence and severity increased significantly with age. However, even after allowing for confounders (which, importantly, included age), both presence and severity of CAC was significantly associated with important clinical outcomes. This included a 2.9-fold increased risk of MI, 3.7-fold increased risk of stroke and 1.8-fold risk of all-cause mortality with severe CAC. This matches well with several previous studies that have demonstrated the association of CAC presence and rising severity (assessed via the visual ordinal scale used here) with outcomes19,20,26,27. Further, this aligns well with the large volume of data on the association of CAC measured via the Agatston score with outcomes when used in a primary prevention screening23,28. The identification

of asymptomatic CAC via this visual ordinal scale demonstrably identifies patients at increased cardiovascular risk.

Importantly, CAC presence retained its potential impact on clinical management regardless of age group. The 'number needed to report' for the presence of CAC to change clinical management remained low across all age groups (supplementary Table S2). This is relevant as although prevalence is lower in younger patients, lifetime cardiovascular risk is significantly heightened in this sub-group23. Equally, many patients in older age groups have cardiovascular risk scores that meet the threshold for statin therapy regardless of CAC presence on CT yet are not currently prescribed one, as demonstrated in our study. Indeed, a recent US study found that only 59% of diabetic patients with proven atherosclerotic CVD were prescribed a lipid-lowering therapy, with only a quarter prescribed a guideline-recommended dose29. Similar findings have been seen in lung cancer screening studies30. Identifying CAC in asymptomatic patients may change clinician behaviours, triggering a dialogue with the patient on the importance of cardiovascular risk optimisation in a personalised fashioned for individuals at heightened risk, which may include the prescription of a statin as part of this. CAC presence was recently shown to reclassify statin eligibility, increase use of preventive medications, and improve cardiovascular risk factors, with very low rates of invasive downstream testing31. The same may also be true of patient behaviour. Indeed, the improvement in clinical outcomes seen in the SCOT-HEART study has been partly attributed to increased prescription of medical therapy and patient willingness to both consider lifestyle change and adhere to recommended treatments32.

There is increasing evidence supporting the beneficial effects of statins for primary prevention in patients >75 years old, particularly when there is evidence of atherosclerosis17,18. Whilst it does add to the workload of the reporter, the visual ordinal semi-quantitative assessment of CAC presence and severity is quick, was highly reproducible in our study, and has a demonstrably clear potential to impact patient care. Treatments are generally inexpensive and its reporting may be a cost-effective approach to improving CVD outcomes, which is a national priority3, though a health economic

assessment was outside the scope of this study. Whether the benefits of statins in patients with proven atherosclerotic CVD translates into this cohort of patients identified via non-gated thoracic CT was beyond the scope of this study and warrants a future randomised controlled trial.

In younger patients (<50 years old), CAC highlights individuals with premature CAD where an underlying genetic predisposition, such as FH, may be present. This is relevant given the widely reported under-diagnosis of FH, with many such patients not receiving crucial lipid-modifying therapies and in whom their first presentation may be with a cardiac event4. In our study only 3/30 (10%) patients aged <50 with CT evidence of CAC had a lipid profile checked within 6 months of their CT and no patients were referred to the lipid clinic. The routine reporting of CAC would have provided an additional, opportunistic approach to identifying this important patient group and highlighted the need for a cardiovascular risk review, including a lipid profile. In such cases, not only does this enable the opportunity to discuss these findings and institute treatment for the patient in question, it also enables consideration for cascade screening of relatives.

The identification of CAC in the sub-clinical phase enables simple and effective interventions that can be personalised to the individual patent's risk. However, the real-world reporting of CAC in all patients across all age groups regardless of comorbidities, e.g. a terminal malignancy or severe frailty, will include patients where it may not be appropriate to act on the finding. A proportion of patients in all age groups undergo imaging due to other life-limiting pathology, as evidenced by the high mortality rate observed across all age groups referred for thoracic CT in this study (supplementary Table S1). Additionally, our results are only applicable to patients having non-gated CTs for clinically indicated reasons and further study would be required to test the role of ordinal CAC scoring on non-cardiac CT in a screening setting. Nevertheless, the routine reporting of CAC for patients who are undergoing a thoracic CT enables the clinician to make personalised decision-making in collaboration with the patient with a simple tool that improves cardiovascular risk stratification.

This study is limited by its single centre nature, with geographical variations in ethnicity and socio-economic status potentially also influencing results elsewhere, though the prevalence matches well with available comparative data. Additionally, its retrospective nature, missing data and use of a single institution electronic patient records for most data-points leaves the potential for underestimation of comorbidities, outcomes (MI and stroke), and statin prescription. This enables an estimation rather than a definitive assessment of the potential impact of reporting CAC on clinical management. However, even when adjusting for confounders, CAC presence and severity was associated with all important clinical outcomes, whilst, importantly, all-cause mortality was recorded via the centralised NHS Spine. The impact of CAC on outcomes became more apparent with age, which may partly reflect the increased lifetime risk of MACE associated with atherosclerotic CVD16. Whilst calculators for bespoke percentile assessment per age group exist for Agatston scores, ordinal visual CAC grading cannot provide as refined assessment. Furthermore, it is well recognised that assessment of CAC does not include the detection of non-calcific plaque and individuals with no CAC may still be at risk33, though CAC acts as a surrogate of total plaque burden (calcific and non-calcific)34. Additionally, the study period selected included CTs acquired 7 years ago and modern scanners may now provide enhanced sensitivity for the detection of CAC, whilst as CT technology improves it may be possible for a more complete coronary assessment on non-gated contrast-enhanced CT.

Conclusion

This study demonstrates that the reporting of CAC on non-cardiac chest CT provides a reliable, reproducible and opportunistic screening tool to identify patients with asymptomatic CAD at enhanced risk of future major adverse cardiovascular events. Importantly, the association with clinical outcomes and identification of individuals who may benefit from cardiovascular risk optimisation held regardless of age.

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Figure Legends:

Figure 1. Study flowchart, with patients excluded if there was absent or incomplete chest imaging or if there was CT evidence of prior cardiac or coronary intervention (i.e. coronary artery bypass grafts, percutaneous coronary intervention or valve surgery).

Figure 2. Burden of CAC sub-divided by age and (A) whether patients with CAC had a pre-existing diagnosis of CAD ("Known CAD" versus "Not known CAD"), (B) breakdown of CAD severity (all vessels), and (C) vessel involvement (LMS = left main stem; LAD = left anterior descending; LCx = left circumflex; RCA = right coronary artery).

Figure 3. Clinical impact of identifying CAC in each age group, highlighting patients prescribed a statin at the time of their CT scan versus those not.

Figure 4. Kaplan-Meier curves demonstrating risk of composite outcome of all-cause mortality, MI and stroke against (A) CAC presence, and (B) CAC severity.

Table 1. Study population demographics and scan acquisition sub-divided by age group and coronary artery calcification (CAC) presence. (N = number; s.d. = standard deviation; Dyslipid. = dyslipidaemia; IHD = ischaemic heart disease; AF = atrial fibrillation, CTPA = CT pulmonary angiography; CT C/A/P (c) = CT chest/abdomen/pelvis with contrast; CT C/A/P (nc) = CT chest/abdomen/pelvis without contrast; CT C/A = CT chest/abdomen; HRCT = high-resolution CT).

Variable (% [n])				**Age Group**													
	All	**All**		**<40 (n=199)**		**40-49 (n=199)**		**50-59 (n=191)**		**60-69 (n=190)**		**70-79 (n=187)**		**80-89 (n=187)**		**≥90 (n=190)**	
		CAC+	**CAC-**	**CAC+**	**CAC-**	**CAC+**	**CAC-**	**CAC+**	**CAC-**	**CAC+**	**CAC-**	**CAC+**	**CAC-**	**CAC+**	**CAC-**	**CAC+**	**CAC-**
N	1343	54 [729]	46 [614]	3 [5]	97 [194]	13 [25]	87 [174]	45 [85]	55 [106]	64 [121]	36 [69]	78 [146]	22 [41]	90 [169]	10 [18]	94 [178]	6 [12]
Demographics																	
Age (years) mean±s.d.	63±20	76±14	48±17	34±6	31±6	47±2	46±3	55±3	54±3	65±3	64±3	75±3	74±3	83±2	82±2	92±2	92±2
Sex (male) %[n]	44 [585]	50 [362]	36 [223]	50 [2]	48 [94]	60 [15]	36 [63]	55 [47]	33 [35]	55 [66]	38 [26]	55 [80]	17 [7]	47 [80]	22 [4]	42 [74]	0 [0]
Diabetes %[n]	10 [140]	15 [106]	5 [33]	0 [0]	2 [4]	8 [2]	4 [7]	11 [9]	8 [8]	16 [19]	7 [5]	18 [26]	17 [7]	17 [28]	11 [2]	12 [22]	8 [1]
Hypertension %[n]	35 [472]	52 [378]	15 [94]	0 [0]	5 [9]	20 [5]	16 [27]	20 [17]	10 [11]	39 [47]	25 [17]	62 [90]	37 [15]	64 [108]	44 [8]	62 [111]	58 [7]
Smoking History %[n]																	
Current	8 [106]	8 [62]	7 [44]	20 [1]	4 [8]	8 [2]	7 [13]	18 [15]	13 [14]	12 [15]	10 [7]	14 [20]	7 [3]	4 [6]	0 [0]	2 [3]	0 [0]
Ex	19 [259]	21 [153]	17 [106]	0 [0]	17 [33]	16 [4]	18 [31]	22 [19]	19 [20]	22 [26]	18 [12]	25 [36]	17 [7]	20 [34]	17 [3]	19 [34]	0 [0]
Never	17 [226]	17 [123]	17 [103]	0 [0]	16 [30]	8 [2]	14 [24]	14 [12]	9 [10]	10 [12]	14 [10]	33 [49]	47 [19]	20 [34]	33 [6]	8 [14]	33 [4]
Missing data	56 [752]	54 [391]	59 [361]	80 [4]	63 [123]	68 [17]	61 [106]	46 [39]	59 [62]	56 [68]	58 [40]	28 [41]	29 [12]	56 [95]	50 [9]	71 [127]	67 [8]
Obesity %[n]	18 [182]	9 [89]	9 [93]	1 [1]	24 [26]	4 [4]	37 [38]	11 [18]	9 [14]	6 [11]	3 [6]	12 [20]	4 [7]	16 [24]	1 [2]	7 [11]	1 [1]
Dyslipid. %[n]	8 [110]	13 [92]	3 [18]	0 [0]	1 [2]	4 [1]	2 [4]	9 [8]	4 [4]	11 [13]	4 [3]	22 [32]	5 [2]	14 [23]	6 [1]	8 [15]	17 [2]

IHD %[n]	11 [153]	19 [135]	3 [18]	0 [0]	2 [4]	4 [1]	3 [6]	14 [12]	1 [1]	9 [11]	4 [3]	23 [33]	2 [1]	21 [35]	11 [2]	24 [43]	8 [1]
AF %[n]	14 [182]	22 [164]	3 [18]	0 [0]	2 [2]	4 [1]	1 [2]	4 [3]	1 [1]	11 [13]	3 [2]	19 [28]	10 [4]	28 [47]	28 [5]	40 [72]	17 [2]
Scan Acquisition %[n]																	
CTPA	21 [277]			25 [50]		20 [40]		19 [37]		16 [30]		17 [32]		20 [37]		27 [51]	
CT C/A/P (c)	33 [446]			26 [52]		39 [77]		36 [68]		40 [76]		40 [75]		31 [58]		21 [40]	
CT C/A/P (nc)	10 [139]			11 [21]		6 [11]		7 [14]		4 [8]		9 [17]		11 [21]		25 [47]	
CT C/A (c)	4 [53]			2 [3]		3 [6]		6 [11]		6 [12]		4 [8]		3 [6]		4 [7]	
CT chest (c)	26 [350]			26 [52]		24 [48]		27 [51]		28 [54]		25 [47]		30 [57]		22 [41]	
HRCT	6 [78]			11 [21]		9 [17]		5 [10]		5 [10]		4 [8]		4 [8]		2 [4]	

Table 2. Univariate (u) and multivariate (m) Cox regression analysis of MI, stroke and all-cause mortality. (AF = atrial fibrillation; CAC = coronary artery calcification; IHD = ischaemic heart disease).

Variable	MI (u)	MI (m)	Stroke (u)	Stroke (m)	Mortality (u)	Mortality (m)
Current age	1.06 [1.04, 1.07]	1.04 [1.03, 1.06]	1.08 [1.06, 1.09]	1.07 [1.05, 1.09]	1.04 [1.03, 1.04]	1.04 [1.03, 1.04]
	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01
Male sex	1.5 [1.0, 2.3]	1.7 [1.1, 2.5]	1.04 [0.7, 1.5]	1.4 [1.0, 2.0]	1.1 [1.0, 1.3]	1.3 [1.1, 1.6]
	p=0.03	p=0.01	p=0.81	p= 0.06	p=0.11	p <0.01
Diabetes	1.7 [1.0, 3.0]	1.05 [0.6, 1.8]	2.3 [1.5, 3.6]	1.7 [1.1, 2.7]	1.6 [1.3, 2.0]	1.4 [1.1, 1.8]
	p=0.04	p=0.86	p<0.01	p=0.03	p<0.01	p<0.01
Hypertension	2.8 [1.9, 4.2]	0.9 [0.6, 1.4]	4.1 [2.8, 5.9]	1.3 [0.9, 1.9]	1.9 [1.6, 2.2]	1.0 [0.9, 1.2]
	p<0.01	p=0.70	p<0.01	p=0.21	p<0.01	p =0.66
Dyslipidaemia	1.2 [0.6, 2.2]	0.4 [0.2, 0.7]	2.6 [1.7, 4.0]	1.6 [1.06, 2.6]	1.0 [0.8, 1.3]	0.63 [0.5, 0.8]
	p=0.60	p<0.01	p<0.01	p=0.03	p=0.92	p<0.01
AF	5.6 [3.7, 8.5]	1.1 [0.7, 1.8]	4.6 [3.2, 6.7]	1.5 [1.0, 2.2]	2.5 [2.1, 3.0]	1.3 [1.1, 1.6]
	p<0.01	p=0.59	p<0.01	p=0.06	p<0.01	p=0.01
CAC$^{\Delta}$	8.6 [4.6, 16.2]	1.4 [0.7, 3.1]	13.7 [6.9, 27.1]	2.5 [1.2, 5.0]	2.9 [2.5, 3.5]	1.3 [1.0, 1.6]
	p<0.01	p=0.36$^{\delta}$	p<0.01	p=0.01†	p<0.01	p=0.03*
IHD	18.0 [11.9, 27.0]	12.5 [8.0, 19.5]	3.0 [1.9, 4.5]	1.1 [0.7, 1.8]	1.8 [1.4, 2.2]	1.2 [1.0, 1.5]
	P<0.01	p<0.01	p<0.01	p=0.61	p<0.01	p=0.12

$^{\delta}$ Adjusting for confounders (current age, gender, dyslipidaemia, IHD), † Adjusting for confounders (current age, gender, diabetes, dyslipidaemia, AF), *Adjusting for confounders (current age, gender, diabetes, dyslipidaemia, AF), $^{\Delta}$ Measured as presence of CAC as a dichotomous variable rather than as a continuous variable based on the CAC score

Table 3. Univariate and multivariate Cox regression analysis of MI, stroke and all-cause mortality by CAC severity. (HR = hazard ratio; IHD = ischaemic heart disease; AF = atrial fibrillation).

Variable	MI			Stroke			All-cause mortality		
	Rate per 100 patient years	Uni- HR	Multi- HR [δ]	Rate per 100 patient years	Uni- HR	Multi- HR [†]	Rate per 100 patient years	Uni HR	Multi- HR*
None	0.3	1	1	0.3	1	1	6.1	1	1
	[0.2, 0.6]			[0.2, 0.5]			[5.3, 7.0]		
Mild	1.3	1.5	1.0	2.6	2.8	1.9	14.2	1.2	1.1
	[0.8, 2.0]	[0.6, 3.4]	[0.4, 2.4]	[1.9, 3.6]	[1.4, 5.7]	[0.9, 4.0]	[12.5, 16.3]	[0.9, 1.5]	[0.9, 1.4]
		p=0.357	p=0.932		p=0.004	p=0.098		p=0.185	p=0.254
Moderate	5.5	4.5	2.1	6.9	3.4	3.0	24.7	1.5	1.4
	[4.1, 7.2]	[2.0, 10.0]	[0.9, 4.8]	[5.4, 8.9]	[1.6, 7.1]	[1.4, 6.3]	[21.7, 28.2]	[1.2, 1.9]	[1.1, 1.8]
		P<0.001	p<0.001		p=0.001	p=0.005		p=0.001	p=0.010
Severe	16.3	10.0	2.9	12.0	4.9	3.7	37.0	1.9	1.8
	[10.9, 24.6]	[4.2, 24.1]	[1.1, 7.6]	[7.6, 19.0]	[2.1, 11.5]	[1.5, 9.2]	[28.6, 48.0]	[1.4, 2.7]	[1.2, 2.5]
		P<0.001	p=0.029		p<0.001	p=0.004		p<0.001	p=0.002

[δ] Adjusting for confounders (current age, gender, dyslipidaemia, IHD), [†] Adjusting for confounders (current age, gender, hypertension, dyslipidaemia, AF), * Adjusting for confounders (current age, gender, diabetes, dyslipidaemia, AF)