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1 **Title:**

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

3

4 **Key words:**

5 Coronary artery disease; Computed tomography.

6

7 **Manuscript**

8 **Introduction**

9 Cardiovascular disease (CVD) is the leading cause of death internationally, with coronary artery
10 disease (CAD) the predominant contributor^{1,2}. As such, both the 2019 NHS Long Term Plan and the
11 2021 NICE Impact Cardiovascular Disease Management report highlighted the optimisation of
12 cardiovascular disease management as a key area for improvement to save lives over the next 10
13 years^{3,4}. CAD is a progressive, inflammatory disorder⁵ with calcification forming as plaque heals⁶.
14 The presence of coronary artery calcification (CAC) is an imaging biomarker of CAD. The severity of
15 CAC is both a marker of the overall burden of underlying CAD, as well as prognosis^{6,7}.

16 The early identification of asymptomatic CAD enables a review of modifiable cardiovascular risk
17 factors and the initiation of optimal medical therapy (OMT)⁸. The presence of atherosclerotic CVD
18 also intensifies treatment targets, further personalising the optimisation of an individual's
19 cardiovascular risk profile⁹.

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

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

29 This provided an important step forward in the recommended reporting of chest CT imaging with the
30 potential for clear patient benefit. However, the routine reporting of incidental CAC is infrequently
31 performed in routine clinical practice and its clinical relevance in all age groups has been debated¹⁵.
32 Additionally, the presence and severity of CAC varies with age and, as such, the clinical impact of its
33 reporting may also. The prognostic implications of CAC remain regardless of patient age. Lifetime risk
34 is significantly higher in younger patients^{12,16}. Equally, there is increasing evidence to support the
35 beneficial effects of statins for primary prevention irrespective of age, including in older (>75 years)
36 patients^{17,18}.

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

40

41 **Methods**

42 **Study design**

43 All non-cardiac chest CT imaging performed in our institution (XXXXX) from January to December
44 2015 were reviewed to include 200 consecutive patients in each age group (<40, 40-49, 50-59, 60-
45 69, 70-79, 80-89, and ≥90). Scans were excluded if repeat imaging in the same patient within the
46 study period or evidence of prior coronary intervention.

47 **Electronic records**

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

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

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

62 **CT Acquisition**

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

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

72 *CTPA*: 120kV with kV modulation. Automated tube current mA modulation with 66 quality reference
73 mAs. Pitch 1 and rotation time 0.5s on the Definition Edge and 0.28s on the Drive. Acquisition matrix
74 128x0.6mm. 60mls Omnipaque 350 at 5mls/sec with bolus tracking and threshold trigger at 100HU.

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

78 **Coronary artery calcification**

79 All CT scans were re-reviewed for the presence or absence of CAC by two Radiologists with at least 4
80 years' experience each in radiology, and then visually graded semi-quantitatively using an ordinal scale
81 on axial images of the chest, which is a previously described reproducible method^{19,20}. The four
82 major epicardial coronary vessels (left main stem [LMS], left anterior descending [LAD], left circumflex
83 [LCx], and right coronary artery [RCA]) were assigned a score of 0 (none), 1 (mild), 2 (moderate) or 3
84 (severe) related to the degree of calcification present. Individual vessel results were summed to give
85 a total CAC score, which was then classified as none (0), mild (1 - 3), moderate (4 - 8) or severe (9 -
86 12).

87 **Statistical analysis**

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

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

94 Inter- and intra-observer reliability for the assessment of CAC presence and severity was assessed in
95 40 scans with Cohen's κ . This was measured against pre-defined levels of agreement, with values ≤ 0
96 indicating no agreement, 0.01–0.20 as none to slight, 0.21–0.40 as fair, 0.41–0.60 as moderate,
97 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement²¹. For intra-observer analysis
98 scans were re-reviewed >2 weeks after initial assessment by the same two Radiologists, blinded to
99 baseline grading.

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

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

116 **Ethical approval**

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

122

123 **Results**

124 **Demographics**

125 1,343 patients (mean age 63 ± 20 , 590 [44%] male) were included in the analysis. Exclusions included
126 10 (0.6%) for incomplete chest imaging and 47 (3%) for CT evidence of prior cardiac intervention
127 (Figure 1). Demographics, cardiovascular risk factors present at time of CT and scan acquisition type
128 are presented in Table 1.

129 **CAC prevalence and severity**

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

136 **CAC reporting variability**

137 Both inter- and intra-observer variability for presence of CAC were graded as almost perfect (κ 0.89,
138 $p < 0.001$, and κ 0.90, $p < 0.001$). Additionally, the inter- and intra-observer variability for categorising
139 CAC severity when present was substantial (κ 0.68, $p < 0.001$) and almost perfect (κ 0.91, $p < 0.001$)
140 respectively.

141 **Potential impact on clinical management**

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

144 When CAC is reported on all scans regardless of whether it is present or not, the number needed to
145 report to potentially impact management across all age groups is 4. This ranged from 40 for those
146 aged < 40 to 3 for patients aged ≥ 70 (Supplementary Table S2). If CAC is only reported in patients
147 with CAC the number needed to report is 2, ranging from 1 for patients aged < 40 , to 3 for those aged
148 80-89. Figure 3 provides a visual breakdown of CAC presence per age category, sub-divided by the
149 presence of a statin prescription.

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

152 **Outcomes**

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

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

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

163 Additionally, after adjusting for confounders (current age, gender, dyslipidaemia and IHD), rising CAC
164 severity was associated with a 2.9-fold increased risk of MI (Table 3). After adjusting for confounders
165 (current age, gender, hypertension, dyslipidaemia and AF) rising CAC severity was associated with a
166 3.7-fold increased risk of stroke. After adjusting for confounders (current age, gender, diabetes,
167 dyslipidaemia and AF), rising CAC severity was associated with a 1.8-fold increased risk of all-cause
168 mortality.

169 **Discussion**

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

174 The prevalence and severity of CAC for patients in our study is similar to other studies analysing CAC
175 via formal Agatston scoring. The presence of any CAC in patients aged <50 in our cohort was 7.5%,
176 compared to 10.2% in the 2017 CARDIA study of asymptomatic patients aged 32 - 46 years²³. The
177 presence and burden of CAC in patients aged >50 was also similar to the formal measurement of
178 CAC in asymptomatic populations using dedicated Agatston score severity categories^{24,25}. There is
179 limited data on the prevalence of CAC graded in the ordinal fashion recommended by BSCI/BSTI, but
180 there was a slightly lower burden of CAC in the 55-69 years old patients in our study versus those in
181 a recent lung cancer screening study (41% with no CAC in ours vs 35%, 40% mild CAC in ours vs 32%,
182 17% moderate in ours vs 26% and 2% severe in ours vs 8%)²⁶. This is likely to reflect the differences
183 in baseline characteristics between the two study cohorts, particularly given all patients in the
184 ITALUNG study had a ≥ 20 pack-year smoking history²⁶.

185 As expected, CAC presence and severity increased significantly with age. However, even after
186 allowing for confounders (which, importantly, included age), both presence and severity of CAC was
187 significantly associated with important clinical outcomes. This included a 2.9-fold increased risk of
188 MI, 3.7-fold increased risk of stroke and 1.8-fold risk of all-cause mortality with severe CAC. This
189 matches well with several previous studies that have demonstrated the association of CAC presence
190 and rising severity (assessed via the visual ordinal scale used here) with outcomes^{19,20,26,27}.

191 Further, this aligns well with the large volume of data on the association of CAC measured via the
192 Agatston score with outcomes when used in a primary prevention screening^{23,28}. The identification

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

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

212 There is increasing evidence supporting the beneficial effects of statins for primary prevention in
213 patients >75 years old, particularly when there is evidence of atherosclerosis^{17,18}. Whilst it does add
214 to the workload of the reporter, the visual ordinal semi-quantitative assessment of CAC presence and
215 severity is quick, was highly reproducible in our study, and has a demonstrably clear potential to
216 impact patient care. Treatments are generally inexpensive and its reporting may be a cost-effective
217 approach to improving CVD outcomes, which is a national priority³, though a health economic

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

221 In younger patients (<50 years old), CAC highlights individuals with premature CAD where an
222 underlying genetic predisposition, such as FH, may be present. This is relevant given the widely
223 reported under-diagnosis of FH, with many such patients not receiving crucial lipid-modifying
224 therapies and in whom their first presentation may be with a cardiac event⁴. In our study only 3/30
225 (10%) patients aged <50 with CT evidence of CAC had a lipid profile checked within 6 months of their
226 CT and no patients were referred to the lipid clinic. The routine reporting of CAC would have provided
227 an additional, opportunistic approach to identifying this important patient group and highlighted the
228 need for a cardiovascular risk review, including a lipid profile. In such cases, not only does this enable
229 the opportunity to discuss these findings and institute treatment for the patient in question, it also
230 enables consideration for cascade screening of relatives.

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

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

260

261 **Conclusion**

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

267

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270 not-for-profit sectors

271

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373 **Figure Legends:**

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

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

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

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

385 **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. =
386 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
387 chest/abdomen/pelvis without contrast; CT C/A = CT chest/abdomen; HRCT = high-resolution CT).

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389 Variable (% [n])	390 Age Group																
	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-	
392 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]
393 Demographics																	
394 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
395 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]
396 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]
397 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]
398 Smoking History %[n]																	
399 <i>Current</i>	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]
400 <i>Ex</i>	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]
401 <i>Never</i>	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]
402 <i>Missing data</i>	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]
403 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]
404 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]

405	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]
406	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]
407	Scan Acquisition %[n]																	
408	<i>CTPA</i>	21 [277]			25 [50]		20 [40]		19 [37]		16 [30]		17 [32]		20 [37]		27 [51]	
409	<i>CT C/A/P (c)</i>	33 [446]			26 [52]		39 [77]		36 [68]		40 [76]		40 [75]		31 [58]		21 [40]	
410	<i>CT C/A/P (nc)</i>	10 [139]			11 [21]		6 [11]		7 [14]		4 [8]		9 [17]		11 [21]		25 [47]	
411	<i>CT C/A (c)</i>	4 [53]			2 [3]		3 [6]		6 [11]		6 [12]		4 [8]		3 [6]		4 [7]	
412	<i>CT chest (c)</i>	26 [350]			26 [52]		24 [48]		27 [51]		28 [54]		25 [47]		30 [57]		22 [41]	
413	<i>HRCT</i>	6 [78]			11 [21]		9 [17]		5 [10]		5 [10]		4 [8]		4 [8]		2 [4]	

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422 **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 =
 423 ischaemic heart disease).

424 Variable	MI (u)	MI (m)	Stroke (u)	Stroke (m)	Mortality (u)	Mortality (m)
426 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]
427	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01
428 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]
429	p=0.03	p=0.01	p=0.81	p= 0.06	p=0.11	p <0.01
430 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]
431	p=0.04	p=0.86	p<0.01	p=0.03	p<0.01	p<0.01
432 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]
433	p<0.01	p=0.70	p<0.01	p=0.21	p<0.01	p =0.66
434 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]
435	p=0.60	p<0.01	p<0.01	p=0.03	p=0.92	p<0.01
436 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]
437	p<0.01	p=0.59	p<0.01	p=0.06	p<0.01	p=0.01
438 CAC ^Δ	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]
439	p<0.01	p=0.36 ^δ	p<0.01	p=0.01 [†]	p<0.01	p=0.03*
440 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]
441	P<0.01	p<0.01	p<0.01	p=0.61	p<0.01	p=0.12

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

444 dyslipidaemia, AF), ^Δ Measured as presence of CAC as a dichotomous variable rather than as a continuous variable based on the CAC score

445 **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 =
 446 atrial fibrillation).

447 Variable	448 MI			449 Stroke			450 All-cause mortality		
	451 Rate per 100 452 patient years	453 Uni- HR	454 Multi- HR ^δ	455 Rate per 100 456 patient years	457 Uni- HR	458 Multi- HR [†]	459 Rate per 100 460 patient years	461 Uni HR	462 Multi- HR*
463 None	0.3 [0.2, 0.6]	1	1	0.3 [0.2, 0.5]	1	1	6.1 [5.3, 7.0]	1	1
464 Mild	1.3 [0.8, 2.0]	1.5 [0.6, 3.4] p=0.357	1.0 [0.4, 2.4] p=0.932	2.6 [1.9, 3.6]	2.8 [1.4, 5.7] p=0.004	1.9 [0.9, 4.0] p=0.098	14.2 [12.5, 16.3]	1.2 [0.9, 1.5] p=0.185	1.1 [0.9, 1.4] p=0.254
465 Moderate	5.5 [4.1, 7.2]	4.5 [2.0, 10.0] P<0.001	2.1 [0.9, 4.8] p<0.001	6.9 [5.4, 8.9]	3.4 [1.6, 7.1] p=0.001	3.0 [1.4, 6.3] p=0.005	24.7 [21.7, 28.2]	1.5 [1.2, 1.9] p=0.001	1.4 [1.1, 1.8] p=0.010
466 Severe	16.3 [10.9, 24.6]	10.0 [4.2, 24.1] P<0.001	2.9 [1.1, 7.6] p=0.029	12.0 [7.6, 19.0]	4.9 [2.1, 11.5] p<0.001	3.7 [1.5, 9.2] p=0.004	37.0 [28.6, 48.0]	1.9 [1.4, 2.7] p<0.001	1.8 [1.2, 2.5] p=0.002

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

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