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### Ticagrelor to Reduce Myocardial Injury in Patients With High-Risk Coronary Artery Plaque

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2

3 **Ticagrelor to reduce myocardial injury in patients with**

4 **high-risk coronary artery plaque**

5

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33

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35 DEN has received honoraria for consultancy and lectures from AstraZeneca. All other authors have  
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37

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## 42 **Structured Abstract**

### 43 **Background**

44 High-risk coronary atherosclerotic plaque is associated with higher plasma troponin  
45 concentrations suggesting ongoing myocardial injury that may be a target for dual antiplatelet  
46 therapy.

### 47 **Objectives**

48 To determine whether ticagrelor reduces high-sensitivity troponin I concentrations in patients  
49 with established coronary artery disease and high-risk coronary plaque.

### 50 **Methods**

51 In a randomized double-blind placebo-controlled trial, patients with multivessel coronary  
52 artery disease underwent coronary 18F-fluoride positron emission tomography-computed  
53 tomography and measurement of high-sensitivity cardiac troponin I and were randomized  
54 (1:1) to ticagrelor 90 mg twice daily or matched placebo. The primary endpoint was troponin  
55 I concentration at 30 days in patients with increased coronary 18F-fluoride uptake.

### 56 **Results**

57 In total, 202 patients were randomized and 191 met the pre-specified criteria for inclusion in  
58 the primary analysis. In patients with increased coronary 18F-fluoride uptake (n=120/191)  
59 there was no evidence that ticagrelor had an effect on plasma troponin concentrations at 30  
60 days (ratio of geometric means for ticagrelor *versus* placebo, 1.11, [95% confidence interval  
61 0.90 to 1.36], p=0.32). Over 1 year, ticagrelor had no effect on troponin concentrations in  
62 patients with increased coronary 18F-fluoride uptake (ratio of geometric means, 0.86, 95%  
63 confidence interval 0.63 to 1.17, p=0.33).

### 64 **Conclusions**

65 Dual antiplatelet therapy with ticagrelor does not reduce plasma troponin concentrations in  
66 patients with high-risk coronary plaque, suggesting that subclinical plaque thrombosis does  
67 not contribute to ongoing myocardial injury in this setting.

68

69 **Clinical Trials.gov Study ID: NCT02110303**

70

71 **Keywords**

72 Myocardial infarction, Troponin, 18F-fluoride

## 73 **Condensed Abstract**

74 In a double-blind randomized placebo-controlled trial, 191 patients with multivessel coronary  
75 artery disease underwent 18F-fluoride positron emission tomography and computed  
76 tomography coronary angiography. In patients with high-risk plaque defined by 18F-fluoride  
77 uptake in at least one coronary plaque (n=120/191), there was no evidence that dual  
78 antiplatelet therapy with ticagrelor affected 30-day plasma troponin concentrations (ratio of  
79 geometric means 1.11 [95% confidence interval 0.90-1.36], p=0.32). This suggests that  
80 subclinical plaque thrombosis does not contribute to ongoing myocardial injury in patients  
81 with multivessel coronary artery disease and higher risk plaque.

82

## 83 **List of Abbreviations**

84 ECG – Electrocardiogram

85 MBq - Megabecquerel

86 PET-CCTA – Positron emission tomography – Coronary computed tomography angiography

87 PLATO – PLATelet inhibition and patients Outcomes Trial

88  $SUV_{MAX}$  – maximum standardized uptake value

89 TBR – Tissue to background ratio

## 90 **Introduction**

91 Coronary plaque rupture is the commonest cause of acute coronary thrombosis and  
92 myocardial infarction (1). Patients who have an increased risk of recurrent plaque rupture  
93 events may benefit from intensification of secondary prevention therapy (2). In this regard,  
94 the addition of a P2Y<sub>12</sub> receptor antagonist to low-dose aspirin reduces the risk of  
95 cardiovascular death, myocardial infarction and stroke in patients with recent (3) or prior (4)  
96 myocardial infarction. Ticagrelor is an oral reversible antagonist of the platelet adenosine  
97 diphosphate P2Y<sub>12</sub> receptor. It provides faster, more potent and more consistent P2Y<sub>12</sub>  
98 inhibition than clopidogrel (5). In the PLATelet inhibition and patients Outcomes (PLATO)  
99 trial of 18,624 patients presenting with acute coronary syndrome, ticagrelor was superior to  
100 clopidogrel for the prevention of cardiovascular events and death (3). Moreover, the  
101 prolonged use of dual antiplatelet therapy following myocardial infarction continues to  
102 reduce cardiovascular events, albeit at the expense of increased rates of major bleeding (4).  
103 Thus, there is a clinical need to improve the risk stratification of patients to enable physicians  
104 to better select ‘vulnerable’ patients who may benefit from extended duration of dual  
105 antiplatelet therapy.

106

107 A novel approach for assessing patients at high-risk of coronary plaque rupture is using  
108 positron emission tomography and coronary computed tomography angiography (PET-  
109 CCTA). This technique uses the radiotracer 18F-fluoride to identify regions of increased  
110 disease activity in coronary artery plaques. Previous studies have demonstrated that coronary  
111 18F-fluoride uptake correlates with a high-risk cardiovascular profile and identifies ruptured  
112 coronary plaques in patients with recent myocardial infarction (6, 7). Importantly, we have  
113 previously reported an association between increased coronary 18F-fluoride uptake and  
114 higher plasma high-sensitivity cardiac troponin I concentrations in patients with stable

115 coronary artery disease (7). Silent plaque rupture is common and subclinical plaque thrombus  
116 formation is a frequent incidental post-mortem finding in patients with multivessel coronary  
117 artery disease who have died from non-cardiovascular causes (8). This suggests that coronary  
118 <sup>18</sup>F-fluoride uptake may identify high-risk plaque that is associated with thrombus formation  
119 and subclinical myocardial injury from microemboli. If correct, this would potentially be  
120 modifiable with intensive dual antiplatelet therapy.

121

122 In this study, we assessed whether coronary <sup>18</sup>F-fluoride activity identifies patients with  
123 stable multivessel coronary artery disease who respond favorably to ticagrelor as assessed by  
124 a reduction in high-sensitivity cardiac troponin I concentrations.

125



## 126 **Methods**

127

### 128 *Study Design*

129 This was an investigator-initiated double-blind randomized parallel-group placebo-controlled  
130 trial conducted at a single centre in Edinburgh, UK. The study was approved by the local  
131 institutional review board, the Scottish Research Ethics Committee (REC reference:  
132 14/SS/0089), Medicines and Healthcare products Regulatory Agency, and the United  
133 Kingdom (UK) Administration of Radiation Substances Advisory Committee. It was  
134 performed in accordance with the Declaration of Helsinki. All patients provided written  
135 informed consent prior to any study procedures.

136

### 137 *Study Population*

138 Patients were recruited between March 2015 and March 2017. Patients were included if they  
139 met the following criteria: age  $\geq 40$  years and already receiving aspirin therapy with  
140 angiographically proven multivessel coronary artery disease defined as at least two major  
141 epicardial vessels with any combination of either (a)  $>50\%$  luminal stenosis, or (b) previous  
142 revascularization (percutaneous coronary intervention or coronary artery bypass graft  
143 surgery). Patients were excluded if they had any of the following criteria: an acute coronary  
144 syndrome within the last 12 months, any ongoing indication for dual anti-platelet therapy, or  
145 concurrent thienopyridine (clopidogrel or prasugrel) or oral anticoagulant therapy, or  
146 percutaneous coronary intervention or coronary artery bypass graft surgery within the last 3  
147 months. Full eligibility criteria are provided in the *Supplementary Table 1*.

148

149 *Trial Intervention and Randomization*

150 Patients were randomly assigned 1:1 to either ticagrelor 90 mg twice daily or matched  
151 placebo tablets (AstraZeneca, UK). Randomization was performed using a web-based system  
152 that ensured allocation concealment, with treatment allocation incorporating minimization  
153 based on age (<65, ≥65 years old), sex, baseline plasma high-sensitivity troponin I  
154 concentration (≤5.1, >5.1 ng/L) and the presence or absence of coronary 18F-fluoride uptake.  
155 A random element was included with a 1 in 10 chance of the determined treatment allocation  
156 being switched to the other treatment arm.

157

158 *Study Procedures*

159 All patients underwent a baseline assessment to confirm eligibility and measurement of  
160 plasma high-sensitivity cardiac troponin I concentration and platelet-monocyte aggregates.  
161 An electrocardiogram (ECG) gated 18F-fluoride PET-CTCA was performed after patients  
162 had received 50-100 mg of oral metoprolol if their resting heart rate was >65 beats/min prior  
163 to the intravenous administration of 250 MBq 18F-fluoride. After 60 min, patients were  
164 imaged with a hybrid PET-CT scanner (64-multidetector Biograph mCT, Siemens Medical  
165 Systems, Erlangen, Germany). Attenuation correction CT scans were performed prior to the  
166 acquisition of ECG-gated list-mode PET data using a single 30-min bed position centred on  
167 the heart. Finally, an ECG-gated CCTA was performed in mid-diastole during held expiration  
168 following sublingual glyceryl trinitrate.

169

170 *Image Analysis*

171 Positron emission tomography images were reconstructed in diastole (50-75% of the R-R  
172 interval, 2 iterations, 21 subsets Siemens Ultra-HD algorithm) and fused with contrast  
173 enhanced CCTA. Analysis of the CT images was performed using dedicated software (Vitrea

174 Advanced, Toshiba Systems) with multi-planar reformatting for plaque analysis as required.  
175 Coronary arteries with a diameter  $\geq 2$  mm were assessed according to the 18-segment Society  
176 of Cardiac Computed Tomography model. Qualitative and semi-quantitative analysis of the  
177 PET images was performed by trained observers using an OsiriX workstation (OsiriX version  
178 3.5.1 64-bit; OsiriX Imaging Software, Geneva, Switzerland). The analysis of coronary 18F-  
179 fluoride activity has been described previously (6, 7). In brief, visual assessment for  
180 increased coronary 18F-fluoride activity was performed on both a per-patient level and per-  
181 segment basis. For a signal to be co-localised to the coronary artery, an atherosclerotic plaque  
182 had to be present on the CCTA and the increased pattern of radiotracer had to arise from the  
183 coronary artery and follow its course over  $>5$  mm in three dimensions on orthogonal views.  
184 Semi-quantitative PET analysis was undertaken for all proximal coronary segments in  
185 addition to any atherosclerotic segment with focal 18F-fluoride activity as described above.  
186 Maximum standardized uptake values ( $SUV_{MAX}$ ) were measured within regions of interest.  
187 Correction was made for uptake in a referent proximal coronary plaque with no evidence of  
188 increased 18F-fluoride activity. To calculate coronary target to background ratios (TBR),  
189 coronary  $SUV_{MAX}$  was divided by these background measures providing  $TBR_{MAX}$ . Coronary  
190 18F-fluoride activity with  $TBR_{MAX} > 1.25$  was classified a high-risk plaque.

191

#### 192 *High-sensitivity cardiac troponin I*

193 Plasma high-sensitivity cardiac troponin I concentrations were measured using the  
194 ARCHITECT<sub>STAT</sub> assay (Abbott Laboratories, Abbott Park, Illinois). The limit of detection is  
195 1.0 ng/L with an inter-assay co-efficient of variation  $<10\%$  at 4.7 ng/L (9). The upper  
196 reference limit (99<sup>th</sup> centile) based on 4,590 samples from healthy men and women is 34 ng/L  
197 for men and 16 ng/L for women (10). Samples were collected at baseline, 30 days and 3, 6, 9

198 and 12 months. A value of 0.5 ng/L was imputed for troponin values below the limit of  
199 detection.

200

### 201 *Platelet function analysis*

202 Platelet and monocyte activation in response to adenosine diphosphate (ADP) was  
203 determined by flow cytometry, as described previously (11). These analyses were performed  
204 by a single technician blinded to study allocation with the results of these investigations  
205 withheld from the study team until after trial database lock. Briefly, peripheral venous blood  
206 was obtained from all participants at the baseline and 1-month visits. Blood was drawn by  
207 clean venepuncture of a large antecubital vein using a 19-gauge needle, and care was taken to  
208 ensure a smooth blood draw without venous stasis. Blood was collected into tubes containing  
209 the direct thrombin inhibitor, D-Phenylalanine-L-prolyl-L-arginine chloromethyl ketone  
210 (PPACK, Cambridge Biosciences). Tubes were gently inverted to ensure mixing of whole  
211 blood with anticoagulant.

212

213 Immunolabelling and flow cytometry were performed in whole blood to avoid centrifugation  
214 and washing steps which can lead to artefactual platelet activation. All chemicals were  
215 obtained from BD Biosciences. (Oxford, UK). Aliquots of whole blood (50  $\mu$ L) were  
216 incubated with anti-CD14-Allophycocyanin (APC), anti-CD42a-fluorescein isothiocyanate  
217 (FITC), anti-CD11b-PE-Cyanine(Cy)7, anti-CD62p-Phycoerythrin (PE) and isotype matched  
218 controls for 20 min at room temperature in Eppendorfs with and without ADP (at final  
219 concentration of 20  $\mu$ mol/L). Thereafter, samples were fixed with 1% paraformaldehyde (p-  
220 selectin) or FACS-Lyse (platelet-monocyte aggregates). All samples were analysed within 24  
221 hours using a FACSCalibur flow cytometer (Becton-Dickinson). Data analysis was  
222 performed using FlowJo v10 (Treestar, Oregon, USA). A medium flow setting was used to

223 minimize leukocyte-platelet coincident events. Monocytes were identified based on their  
224 forward and side scatter characteristics and then by triggering on FL-4 to identify CD14-PE  
225 positive monocytes and exclude large granular lymphocytes. For each measurement a  
226 minimum of 2,500 monocytes were collected. Platelet-monocyte aggregates were defined as  
227 monocytes positive for CD42a. All results are expressed as geometric mean of fluorescence.  
228 P-selectin expression was defined as CD42a-FITC positive platelets that were also positive  
229 for CD62p-PE.

230

### 231 *Study Endpoints*

232 The pre-specified primary endpoint was high-sensitivity cardiac troponin I concentrations at  
233 30 days in patients with increased coronary 18F-fluoride activity. Secondary endpoints were  
234 plasma high-sensitivity cardiac troponin I concentration at 30 days in patients without  
235 coronary 18F-fluoride activity, and plasma high-sensitivity troponin I concentration over 1  
236 year. Adverse events were recorded in all patients who received a single dose of study  
237 medication and included bleeding events categorized according to PLATO criteria as major  
238 life-threatening, other major, minor or minimal bleeding (3).

239

### 240 *Sample Size*

241 In patients with increased coronary 18F-fluoride uptake, we previously reported that mean  
242 troponin concentrations were more than double those in patients without increased coronary  
243 18F-fluoride uptake (7.9 [SD 9.3] vs. 3.1 [SD 1.9] ng/L,  $p=0.047$ ) (7). It was estimated that  
244 ticagrelor would reduce troponin concentration by half. Forty-eight patients per treatment  
245 arm were required to achieve 80% power at two-sided  $p<0.05$ . After allowing for 15% drop-  
246 out, we estimated that fifty-five patients will be required per treatment arm. Previous studies  
247 had found that 45% of patients with advanced but stable coronary artery disease

248 demonstrated increased coronary 18F-fluoride uptake, so a total sample size of 250 patients  
249 was estimated to be required to identify 110 patients with increased coronary 18F-fluoride  
250 activity. Termination of further recruitment could be authorized by the trial steering  
251 committee once a per-protocol population of 110 patients with increased coronary 18F-  
252 fluoride activity had been randomized and completed the primary endpoint at 30 days.

253

#### 254 *Statistical Analysis*

255 Categorical data are presented using counts and percentages, whilst continuous variables are  
256 presented using mean, standard deviation (SD), median, interquartile range, minimum,  
257 maximum, and number of patients. Participants were removed from formal statistical analysis  
258 where data were missing for that outcome variable. All (except safety) analyses were  
259 performed on a per-protocol population that excluded participants without a blood sample, or  
260 whose compliance was <80% for the study medication, at the 30-day visit. For the primary  
261 analysis, the change in troponin I concentration from baseline to 30 days was compared  
262 between the two treatment groups (ticagrelor and placebo) using linear regression, adjusting  
263 for the minimisation variables in patients with increased coronary 18F-fluoride uptake. Prior  
264 to analysis, tests for normality were undertaken and, where data were skewed, logarithmic  
265 transformation was performed. Central estimates and 95% confidence intervals (CI) were  
266 calculated. Similar analyses were performed for secondary outcomes. In post-hoc testing, we  
267 compared baseline troponin concentrations between patients with and without evidence of  
268 coronary 18F-fluoride activity and also confirmed treatment efficacy by comparison of ADP-  
269 stimulated platelet activation between the two trial intervention groups (ticagrelor *versus*  
270 placebo). For 1-year evaluation of changes in cardiac troponin I concentrations, an adjusted  
271 linear regression model (adjusted for the minimisation variables) was generated and  
272 descriptive statistics were presented for the area under the curve. Where there were missing

273 values, the value was imputed linearly from adjacent measurements. Adjustment for age was  
274 performed as a linear term. To determine whether there was efficacy of ticagrelor using a  
275 baseline troponin I concentration  $\geq 5$  ng/L, a post-hoc comparison was made between groups  
276 using the method described in the primary analysis. For all analyses, a two-sided  $p < 0.05$  was  
277 taken as statistically significant. Statistical analysis was performed using SAS (Software 9.4,  
278 North Carolina) with the primary analysis validated by a second statistician in Edinburgh  
279 Clinical Trials Unit. Post-hoc analyses were performed separately from the primary statistical  
280 analysis plan using R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria)  
281 by PDA.

## 282 **Results**

283

### 284 *Study Population*

285 A total of 361 patients were screened and 202 patients were randomized following the  
286 baseline coronary 18F-fluoride PET-CCTA (**Figure 1**). Eleven patients discontinued the  
287 study early due to withdrawal of consent (n=1), a new diagnosis of malignancy on baseline  
288 PET-CCTA (n=1), <80% compliance with study medication at 30 days (n=8), and a sudden  
289 unexpected death prior to receiving study medication (n=1). The randomized groups were  
290 well matched for the presence of cardiovascular risk factors and represented a high-risk  
291 cohort with 70% having a history of acute coronary syndrome (median 2.25 years prior to  
292 study enrolment) (**Table 1**). A per-protocol population of 191 patients (mean age 65.9, SD  
293 8.3 years, 80% male) had both blood sampling at 30 days and  $\geq 80\%$  compliance with the  
294 study medication, comprising 94 patients in the ticagrelor group and 97 patients in the  
295 placebo group. One hundred and twenty (62.8%) patients had evidence of coronary 18F-  
296 fluoride activity in at least one epicardial vessel (**Table 2, Figure 2**).

297

298 The geometric mean troponin I concentration at baseline was 3.8 (Geometric SD 2.9) ng/L in  
299 patients with increased coronary 18F-fluoride activity compared with 2.5 (Geometric SD 2.6)  
300 ng/L in those without uptake ( $p=0.004$ ; **Table 2**) from a post-hoc analysis.

301

### 302 *Effect of ticagrelor on platelet function*

303 Baseline platelet and monocyte reactivities were well balanced between treatment arms.  
304 Consistent with its known pharmacological action, ticagrelor markedly inhibited platelet P-  
305 selectin expression and reduced the formation of platelet-monocyte aggregates following *ex*  
306 *vivo* stimulation with ADP (**Figure 3**,  $p<0.001$  for all). Ticagrelor had no effect on 30-day



307 unstimulated platelet activation ( $p>0.05$  for all). These results were derived from post-hoc  
308 analysis.

309

#### 310 *Effect of ticagrelor on high-sensitivity troponin I at 30 days*

311 For the primary endpoint, there was no effect of ticagrelor on troponin I at 30 days in patients  
312 who had increased coronary  $^{18}\text{F}$ -fluoride activity (ratio of geometric means ticagrelor *versus*  
313 placebo 1.11, 95% CI 0.90 to 1.36;  $p=0.32$ ) (**Table 3**). Similarly, amongst the 71 (37.2%)  
314 patients without discernible coronary  $^{18}\text{F}$ -fluoride activity, there was no difference in the 30-  
315 day troponin I concentration between ticagrelor and placebo (ratio of geometric means 1.02,  
316 95% CI 0.80 to 1.31;  $p=0.87$ ) (**Table 3**).

317

318 We explored whether a reduction in cardiac troponin I could be demonstrated over twelve  
319 months. Twelve-month troponin I concentrations were measured in 183 (95.8%) patients,  
320 comprising of 91 (96.8%) patients in the ticagrelor group and 92 (94.8%) patients in the  
321 placebo group. There was no difference in area under the concentration curve of troponin I  
322 over twelve months between the ticagrelor and placebo groups (ratio of geometric means  
323 0.92, 95% CI 0.74 to 1.13;  $p=0.42$ ) (**Figure 4**) (**Table 4**). Post-hoc analysis of the subset of  
324 patients with a baseline troponin I concentration  $\geq 5$  ng/L (ticagrelor  $n=34$ , baseline geometric  
325 mean 10.3 ng/L; placebo  $n=33$ , baseline geometric mean 8.7 ng/L), found there was no  
326 change in troponin I concentration at 30 days ( $p=0.89$ ) or twelve months ( $p=0.86$ ).  
327 (**Supplementary Figure 1, Supplementary Table 2**).

328

#### 329 *Safety outcomes*

330 There were no suspected unexpected serious adverse reactions over the course of this study.  
331 Serious adverse events occurred in 7/100 (7%) patients who received at least one single dose

332 of ticagrelor and 15/101 (11.9%) patients who were administered placebo (*Supplementary*  
333 *Table 3*). There were no reported major life-threatening or other major bleeding events over  
334 the course of this study. Minimal bleeding events (bruising) were reported in 64 (64.0%)  
335 patients in the ticagrelor group and 12 (11.9%) patients in the placebo group (*Supplementary*  
336 *Table 4*). Dyspnea episodes occurred in 24 (24%) patients in the ticagrelor group compared  
337 with 8 (7.9%) patients in the placebo group at one year.

## 338 **Discussion**

339

340 In this randomized placebo-controlled trial, we found no evidence that ticagrelor 90 mg twice  
341 daily reduces plasma high-sensitivity cardiac troponin I concentrations in patients with high-  
342 risk plaque and established multivessel coronary artery disease. This suggests that, in patients  
343 with high-risk coronary plaque, plasma cardiac troponin I concentrations are not attributable  
344 to subclinical myocardial injury from thrombotic microembolic injury.

345

346 Our study has several important strengths. This is the first trial to use PET-CCTA imaging  
347 with 18F-fluoride to identify patients with high-risk coronary plaque who may be at  
348 heightened risk of future coronary events and thereby have the most to gain from potent dual  
349 antiplatelet therapies. It is also the largest trial to date employing coronary plaque PET  
350 imaging. Whilst previous PET studies have used 18F-fluorodeoxyglucose to visualise  
351 inflammation within the carotid arteries as a surrogate to guide intensification of  
352 atherosclerotic therapy (12, 13), the coronary and cerebral vascular beds differ both with  
353 respect to their underlying molecular pathophysiology and also in response to the treatment  
354 effect using ticagrelor (3, 14). Second, our unique study design enabled high-risk patients  
355 with multivessel coronary disease and *in vivo* evidence of disease activity to be precisely  
356 phenotyped prior to randomization in a manner that can seldom be achieved in larger clinical  
357 outcome trials (3, 15). Finally, this is the first prospective randomized controlled trial to use  
358 high-sensitivity cardiac troponin I concentrations as a surrogate outcome measure for  
359 assessing future cardiovascular risk.

360

361 In trying to understand why P2Y<sub>12</sub> inhibition did not reduce cardiac troponin in this study, it  
362 is worth addressing some of the underlying assumptions in the trial design. Does coronary

363 18F-fluoride activity identify patients with high-risk plaque? Recent studies have found that  
364 18F-fluoride holds potential in identifying culprit plaques in the coronary circulation by  
365 classifying patients who have a high-risk cardiovascular phenotype and culprit plaque rupture  
366 following type 1 myocardial infarction (6, 7). Histological validation indicates that 18F-  
367 fluoride preferentially binds to microcalcification in regions of plaque mineralisation, a key  
368 component of high-risk plaque (16). Hydroxyapatite, the most common form of  
369 atherosclerotic microcalcification, is extruded from apoptotic macrophages, and accumulates  
370 within necrotic cores where it may destabilise the structural integrity of the fibrous cap (17,  
371 18). The identification of abnormal material composition of the arterial wall has clinical  
372 relevance, as these regions may lead to atherosclerotic plaque rupture manifesting as  
373 myocardial infarction, stroke or aneurysm rupture (7, 19, 20). In our cohort, the frequency of  
374 18F-fluoride activity (>60%) in stable coronary artery disease is similar to previous estimates  
375 in patients with a high burden of coronary artery disease and prior myocardial infarction (6).  
376 This work confirms the high prevalence of coronary 18F-fluoride activity in stable patients  
377 with multivessel coronary artery disease in whom intensification of antiplatelet therapy may  
378 be considered.

379

380 A key question is whether troponin measurement below the 99<sup>th</sup> centile reflects subclinical  
381 plaque rupture with accompanying distal microvascular embolisation as has previously been  
382 posited (21). In this regard, some therapies directed at reducing the risk of atherosclerotic  
383 plaque rupture, such as pravastatin, both modify troponin concentrations and reduce the risk  
384 of myocardial infarction (22, 23). In contrast, strategies that have failed to demonstrate a  
385 reduction in cardiovascular events in the context of stable coronary artery disease, such as  
386 coronary revascularisation, attenuation of plaque inflammation and inhaled therapies for  
387 respiratory disease, have not correlated with a reduction in serial troponin concentration (24,

388 25, 26). If subclinical plaque thrombosis is the dominant mechanism underlying detectable  
389 troponin I concentrations in patients with stable coronary artery disease, a reduction in  
390 troponin I concentration would be expected following the administration of potent antiplatelet  
391 therapy. The lack of response to ticagrelor in this study would suggest that other contributing  
392 mechanisms to myocardial injury should be considered. The emergence of newer therapies  
393 (such as sodium/glucose cotransporter 2 inhibition) that lower blood pressure may reduce  
394 troponin concentrations through an improvement in myocardial remodelling, further raising  
395 doubts over the subclinical plaque rupture hypothesis (27, 28). In this study, high-sensitivity  
396 cardiac troponin I concentrations were higher in patients with <sup>18</sup>F-fluoride activity, albeit the  
397 differences were small and below the established risk stratification threshold of 5 ng/L (9, 22,  
398 29). Therefore, it seems unlikely that troponin at these concentrations reflects subclinical  
399 plaque rupture and it is perhaps unsurprising that ticagrelor treatment did not result in an  
400 early or late reduction in troponin concentration.

401

402 Previous reports have suggested that there is a high incidence of subclinical intracoronary  
403 thrombus in patients with apparently stable coronary artery disease. Indeed, some have  
404 suggested that this occurs in as many as one in seven patients (8). If this is the case, it would  
405 appear that intracoronary thrombus does not track with troponin. This suggests we require  
406 better non-invasive markers of coronary thrombosis, such as novel PET tracers (30) or non-  
407 invasive imaging (31), to use as biomarkers of cardiovascular risk and anti-thrombotic  
408 therapeutic efficacy.

409

410 There are some study limitations that we should acknowledge. This study had a modest  
411 sample size to assess the impact of ticagrelor on a readily available plasma biomarker, and a  
412 larger study would be required to assess clinical outcomes of ticagrelor use in patients with

413 stable coronary artery disease and coronary 18F-fluoride activity. The low baseline troponin I  
414 concentrations observed in this study may have limited power to demonstrate the benefit of  
415 ticagrelor in this population. Enrichment of the population by selecting patients with higher  
416 troponin I concentrations prior to study entry may need to be considered for future trials. It  
417 should also be acknowledged that this study was undertaken in a single centre with expertise  
418 in coronary 18F-fluoride imaging and the methods for analysing coronary 18F-fluoride  
419 activity are subject to a number of operator and scan-dependent variables. Whilst recent  
420 reports have suggested that coronary 18F-fluoride activity may hold prognostic value in  
421 stratifying high-risk populations (32), larger prospective studies evaluating the prognostic  
422 utility of coronary 18F-fluoride activity in patients with cardiovascular disease are ongoing  
423 (NCT02278211).

424

#### 425 *Conclusions*

426 In patients with multivessel coronary artery disease and *in vivo* coronary 18F-fluoride activity,  
427 we found no evidence that intensification of antiplatelet therapy using ticagrelor 90 mg twice  
428 daily reduces plasma high-sensitivity cardiac troponin I concentration at 30 days or 1 year.  
429 These findings suggest that in this group of patients plasma high-sensitivity cardiac troponin I  
430 concentrations may not be a suitable marker to predict efficacy of P2Y<sub>12</sub> inhibition.

431

## 432 **Clinical Perspectives**

433

434 Competency in Medical Knowledge: High-risk coronary artery plaque and plasma high-  
435 sensitivity cardiac troponin I concentrations are associated with increased rates of  
436 cardiovascular events.

437

438 Competency in Patient Care: Patients with stable coronary artery disease and an increased  
439 risk of cardiovascular events may benefit from extended therapy with P2Y<sub>12</sub> inhibition.

440

441 Translational Outlook 1: Although this study used an early biomarker (30-day plasma high-  
442 sensitivity cardiac troponin I concentration) to evaluate drug efficacy, coronary 18F-fluoride  
443 activity does not appear to be useful in identifying patients who may benefit from extended  
444 P2Y<sub>12</sub> inhibition.

445

446 Translational Outlook 2: A detailed phenotype of coronary plaque disease activity using  
447 positron emission tomography is both feasible and practical in the setting of a randomized  
448 placebo-controlled trial.

449

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469

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- 563

## **Tables**

### **Table 1.**

Baseline characteristics of the study population

	<b>Total Randomised Population (n=202)</b>	<b>Per Protocol population (n=191)</b>	<b>Ticagrelor (n=94)</b>	<b>Placebo (n=97)</b>	<b>P value (ticagrelor versus placebo)<sup>¶</sup></b>
<b>Age, years</b>	65.9±8.2	65.9±8.3	65.5±8.4	66.3±8.1	0.504
<b>Male</b>	162 (80)	152 (80)	74 (79)	78 (80)	0.912
<b>Body Mass Index, kg/m<sup>2</sup></b>	29.8±5.2	29.7±5.0	30.0±5.2	29.4±4.9	0.413
<b>Medical history</b>					
History of acute coronary syndrome	143 (71)	134 (70)	65 (69)	69 (71)	0.887
Days between ACS and randomisation*	821 (620, 1056)	821 (625, 1037)	800 (620, 970)	861 (646,1081)	
Percutaneous Coronary Intervention	163 (81)	154 (81)	75 (80)	79 (81)	0.915
Coronary Artery Bypass Grafting	40 (20)	38 (20)	18 (19)	20 (21)	0.942
Hypertension	113 (56)	105 (55)	52 (55)	53 (55)	1.000
Hypercholesterolaemia	195 (97)	185 (97)	93 (99)	92 (95)	0.228
Diabetes Mellitus	39 (19)	36 (19)	19 (20)	17 (18)	0.772
Prior Stroke/Transient Ischemic Attack	4 (2)	4 (2)	2 (2)	2 (2)	1.000

History of Atrial Fibrillation	5 (2)	5 (3)	4 (4)	1 (1)	0.346
Peripheral Vascular Disease	8 (4)	7 (4)	1 (1)	6 (6)	0.134
<b>Medications</b>					
Aspirin	202 (100)	191 (100)	94 (100)	97 (100)	NA
Statin	192 (95)	182 (95)	92 (98)	90 (93)	0.188
Beta-Blocker	138 (68)	130 (68)	66 (70)	64 (66)	0.637
Angiotensin Converting Enzyme Inhibitor/Angiotensin II Receptor Blocker	155 (77)	145 (76)	68 (72)	77 (79)	0.333
<b>Hemoglobin, g/dL</b>	14.0±1.3)	14.0±1.3	14.2±1.2	13.8±1.3	0.034
<b>Estimated Glomerular Filtration Rate, mL/min/1.73m<sup>2</sup></b>					0.547
31-60	23 (11)	22 (12)	9 (10)	13 (13)	
>60	179 (89)	169 (88)	85 (90)	84 (87)	
<b>Total Cholesterol, mg/dL</b>	162±39	162±39	162±39	162±35	0.852



<b>High density lipoprotein, mg/dL</b>	46±12	46±12	43±15	46±12	0.128
<b>Low density lipoprotein, mg/dL</b>	89 ±31	89±31	85±35	89±27	0.377
<b>Triglycerides, mg/dL</b>	159±97	151±97	159±106	151±80	0.556

Values are n (%) or mean±standard deviation

\* median (interquartile range)

¶ Post-hoc analysis

**Table 2.**

Plasma high-sensitivity cardiac troponin I concentration (ng/L) in the per-protocol population

	<b>Overall (n=191)</b>	<b>Ticagrelor (n=94)</b>	<b>Placebo (n=97)</b>	<b>p-value¶</b>
<b>Coronary 18F-Fluoride Uptake</b>				
<b>N</b>	120	59	61	
<b>Baseline</b>	3.8±2.9	4.2±2.9	3.5±3.0	0.197
<b>30 days</b>	3.6±2.7	4.1±2.5	3.2±2.9	0.072
<b>Ratio of 30 days to baseline</b>	0.95±1.87	0.97±2.13	0.93±1.59	0.907
<b>No Coronary 18F-Fluoride Uptake</b>				
<b>N</b>	71	35	36	
<b>Baseline</b>	2.5±2.6	2.5±2.8	2.4±2.4	0.872
<b>30 days</b>	2.4±2.7	2.4±2.8	2.3±2.6	0.877
<b>Ratio of 30 days to baseline</b>	0.97±1.68	0.97±1.77	0.96±1.59	

Geometric mean and geometric standard deviation, back transformed from log transformed values.

¶ Post-hoc analysis

**Table 3.**

Plasma high-sensitivity cardiac troponin I concentration (ng/L) at 30 days for the per-protocol population

	<b>Adjusted Geometric Mean</b>		<b>Ratio of Geometric Means</b>	
	<b>(GSE)</b>			
	<b>Ticagrelor</b>	<b>Placebo</b>	<b>(95% CI)</b>	<b>p-value</b>
Cardiac troponin I, ng/L <i>(18F-fluoride activity)</i>	3.8 (1.1)	3.4 (1.1)	1.11 (0.90 to 1.36)	0.32
Cardiac Troponin I, ng/L <i>(No 18F-fluoride activity)</i>	2.4 (1.1)	2.3 (1.1)	1.02 (0.80 to 1.31)	0.87

*Estimates are back transformed estimates from analysis of log transformed values at 30 days adjusting for age, sex and log transformed baseline troponin. Ratio of geometric means is Ticagrelor divided by Placebo. GSE, geometric standard error.*

**Table 4.**

Plasma high-sensitivity cardiac troponin I concentration over 1 year for participants in per protocol population

	Adjusted Geometric Mean (GSE)		Ratio of Geometric Means	
	Ticagrelor	Placebo	(95% CI)	p-value
AUC from 30 days to 1 year ( <i>18F-fluoride activity</i> )	3.7 (1.1)	4.4 (1.1)	0.86 (0.63 to 1.17)	0.33
AUC from 30 days to 1 year ( <i>No 18F-fluoride activity</i> )	2.4 (1.1)	2.3 (1.1)	1.04 (0.84 to 1.28)	0.70

*Estimates are back transformed estimates from analysis of log transformed values area under curve from 30 days to 1 year adjusting for age, sex and log transformed baseline troponin. Ratio of geometric means is Ticagrelor divided by Placebo. AUC, area under curve, ng/L, GSE, geometric standard error.*

**Central Illustration.** [Using coronary 18F-fluoride to identify patients who may benefit from intensified dual antiplatelet therapy.](#)

Coronary 18F-fluoride positron emission tomography was used to identify high-risk coronary plaque in patients with stable multivessel coronary artery disease. Randomization to intensified dual antiplatelet therapy with ticagrelor did not reduce plasma high-sensitivity cardiac troponin I concentrations at 30-days in patients with high-risk plaque.

**Figure 1.** Consort Diagram.

[Flow diagram of the progress through the phases of the randomized trial between ticagrelor and placebo groups.](#)

**Figure 2.** Intracoronary thrombus and coronary 18F-fluoride activity.

A 72-year-old female with intracoronary thrombus in the left main stem (A, B arrow). Axial reconstructions demonstrate a non-obstructive intracoronary thrombus at 11 o'clock with coronary calcification at 2 o'clock and 7 o'clock (C and D, schematic). 18F-Fluoride activity was present in the coronary plaque (E and F, schematic).

**Figure 3.** Flow cytometry assessment of platelet activation at baseline and 30 days.

Unstimulated (upper panels) and adenosine diphosphate (20  $\mu$ mol/L) stimulated (lower panels) levels of (a) platelet activation (P-selectin expression) and (b) platelet-monocyte aggregates.

**Figure 4.** Plasma high-sensitivity cardiac troponin I concentration over 1 year.

Box-whisker plot of individual patient-level plasma high-sensitivity troponin I concentration (ng/L) in ticagrelor (blue) and placebo (red) groups at baseline, 1, 3, 6, 9 and 12 months. Median and interquartile range for each time point.

**Ticagrelor to reduce myocardial injury in patients  
with high-risk coronary artery plaque**

**Supplementary Appendix**

## Supplementary Table 1.

### Inclusion and Exclusion Criteria

<b>Inclusion Criteria</b>
For inclusion in the study subjects should fulfil the following criteria: <ol style="list-style-type: none"><li>1. Patients aged <math>\geq 40</math> years with angiographically proven multivessel coronary artery disease defined as at least two major epicardial vessels with any combination of either (a) <math>&gt;50\%</math> luminal stenosis, or (b) previous revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery).</li><li>2. Provision of informed consent prior to any study specific procedures</li><li>3. Receiving aspirin</li></ol>
<b>Exclusion Criteria</b>
Subjects should not enter the study if any of the following exclusion criteria are fulfilled: <ol style="list-style-type: none"><li>1. An acute coronary syndrome within the last 12 months</li><li>2. An indication for dual anti-platelet therapy, such as drug eluting stent</li><li>3. Receiving thienopyridine therapy such as clopidogrel or prasugrel</li><li>4. Percutaneous coronary intervention or coronary artery bypass graft surgery within the last 3 months</li><li>5. Inability or unwilling to give informed consent</li><li>6. Women who are pregnant, breastfeeding or of child-bearing potential (women who have experienced menarche, are pre-menopausal and have not been sterilised) will not be enrolled into the trial</li><li>7. Known hypersensitivity to ticagrelor or one of its excipients</li><li>8. Active pathological bleeding or bleeding diathesis</li><li>9. Significant thrombocytopenia: platelets <math>&lt;100 \times 10^9 /L</math></li><li>10. History of intracranial hemorrhage</li><li>11. Moderate to severe liver impairments (Child's Grade B or C)</li><li>12. Maintenance therapy with strong CYP3A4 inhibitors, such as ketoconazole, nefazodone, ritonavir, indinavir, atazanavir, or clarithromycin</li><li>13. Major intercurrent illness of life expectancy <math>&lt;1</math> year</li><li>14. Renal dysfunction (eGFR <math>\leq 30</math> mL/min/1.73m<sup>2</sup>)</li><li>15. Contraindication to iodinated contrast agents</li><li>16. Planned coronary revascularization or major non-cardiac surgery in the next 12 months</li><li>17. Maintenance therapy with simvastatin or lovastatin at doses greater than 40mg daily</li><li>18. Receiving oral anticoagulants including warfarin, rivaroxaban, dabigatran or apixaban</li></ol>



**Supplementary Table 2.**

Post-hoc analysis of efficacy of Ticagrelor in patients with troponin I concentration  $\geq 5$  ng/L

<b>PLACEBO</b>	Baseline 18F-fluoride uptake on PET-CT			
	Negative	Negative	Positive	Positive
	Baseline hs-cTnI <5 ng/L	Baseline hs-cTnI $\geq$ 5 ng/L	Baseline hs-cTnI <5 ng/L	Baseline hs-cTnI $\geq$ 5 ng/L
Baseline hs-cTnI, geometric mean (95% CI)	1.8 (1.4 to 2.3)	7.7 (5.9 to 10.1)	1.8 (1.4 to 2.3)	9.3 (7.2 to 12.1)
30 day hs-cTnI, geometric mean (95% CI)	1.7 (1.3 to 2.3)	7.1 (4.1 to 12.1)	1.8 (1.4 to 2.3)	8.3 (6.1 to 11.2)

<b>TICAGRELOR</b>	Baseline 18F-fluoride uptake on PET-CT			
	Negative	Negative	Positive	Positive
	Baseline hs-cTnI <5 ng/L	Baseline hs-cTnI >5 ng/L	Baseline hs-cTnI <5 ng/L	Baseline hs-cTnI >5 ng/L
Baseline hs-cTnI, geometric mean (95% CI)	1.8 (1.4 to 2.3)	8.7 (4.7 to 16.3)	2.3 (1.9 to 2.9)	10.3 (7.6 to 15.8)
30 day hs-cTnI, geometric mean (95% CI)	1.7 (1.3 to 2.2)	10.2 (5.2 to 20.1)	2.7 (2.1 to 3.4)	8.3 (6.1 to 11.2)

**Supplementary Table 3.**

Serious Adverse Events for safety population

		Ticagrelor n=100		Placebo n=101		Overall n=201	
		Number of Events	Number of Patients	Number of Events	Number of Patients	Number of Events	Number of Patients
<i>Any serious adverse event</i>		10	7 (7%)	15	12 (11.9%)	25	19 (9.5%)
<i>Outcome</i>	Resolved	10	7 (7%)	15	12 (11.9%)	25	19 (9.5%)
<i>Causality</i>	Unrelated to IMP & NIMP	9	7 (7%)	14	11 (10.9%)	23	18 (9%)
	Unrelated to IMP	1	1 (1%)	1	1 (1%)	2	2 (1%)
<i>Expectedness</i>	Expected	0	0 (0%)	0	0 (%)	0	0 (0%)
	Unexpected	10	7 (7%)	15	12 (11.9%)	25	19 (9.5%)
<i>Severity</i>	Mild	5	5 (5%)	5	4 (4%)	10	9 (4.5%)
	Moderate	5	3 (3%)	9	9 (8.9%)	14	12 (6%)
	Severe	0	0 (0%)	1	1 (1%)	1	1 (0.5%)

**Supplementary Table 4.**

Bleeding and Dyspnea events for safety population

		<b>Ticagrelor</b> <b>n=100</b>		<b>Placebo</b> <b>n=101</b>		<b>Overall</b> <b>n=201</b>	
		<b>Number of</b> <b>Events</b>	<b>Number of</b> <b>Patients</b>	<b>Number of</b> <b>Events</b>	<b>Number of</b> <b>Patients</b>	<b>Number of</b> <b>Events</b>	<b>Number of</b> <b>Patients</b>
<i>Any bleeding event</i>		88	64 (64%)	14	12 (11.9%)	102	76 (37.8%)
<i>PLATO</i> <i>classification</i>	Minimal	87	64 (64%)	14	12 (11.9%)	101	76 (37.8%)
	Minor	1	1 (1%)	0	0 (0%)	1	1 (0.5%)
	Major	0	0 (0%)	0	0 (0%)	0	0 (0%)
	Major life threatening	0	0 (0%)	0	0 (0%)	0	0 (0%)
<i>Dyspnea</i>	At 1 year	27	24 (24%)	8	8 (7.9%)	35	32 (15.9%)

**Supplementary Table 5.**

Post-hoc analysis of plasma high-sensitivity cardiac troponin I concentration (ng/L) in the intention to treat population who have measurement of troponin at 30 days

	<b>Overall (n=199)</b>	<b>Ticagrelor (n=98)</b>	<b>Placebo (n=101)</b>
<b>Coronary 18F-Fluoride Uptake</b>			
<b>N</b>	127	62	65
<b>Baseline</b>	3.8±2.9	4.2±2.9	3.5±2.9
<b>30 days</b>	3.7±2.7	4.2±2.5	3.3±2.9
<b>Ratio of 30 days to baseline</b>	0.97±1.86	1.00±2.12	0.95±1.59
<b>No Coronary 18F-Fluoride Uptake</b>			
<b>N</b>	72	36	36
<b>Baseline</b>	2.4±2.5	2.5±2.7	2.4±2.4
<b>30 days</b>	2.3±2.7	2.4±2.8	2.3±2.6
<b>Ratio of 30 days to baseline</b>	0.96±1.68	0.96±1.77	0.96±1.59

Geometric mean and geometric standard deviation, back transformed from log transformed values.

### Supplementary Table 6.

Post-hoc analysis of plasma high-sensitivity cardiac troponin I concentration (ng/L) at 30 days for the intention to treat population

	Adjusted Geometric Mean (GSE)		Ratio of Geometric Means	
	Ticagrelor	Placebo	(95% CI)	p-value
Cardiac troponin I, ng/L ( <i>18F-fluoride activity</i> )	3.9 (1.1)	3.5 (1.1)	1.12 (0.92 to 1.36)	0.26
Cardiac Troponin I, ng/L ( <i>No 18F-fluoride activity</i> )	2.3 (1.1)	2.3 (1.1)	1.00 (0.78 to 1.29)	0.98

*Estimates are back transformed estimates from analysis of log transformed values at 30 days adjusting for age, sex and log transformed baseline troponin. Ratio of geometric means is Ticagrelor divided by Placebo. GSE, geometric standard error.*

### Supplementary Table 7.

Post-hoc analysis of plasma high-sensitivity cardiac troponin I concentration over 1 year for participants in intention to treat population

	Adjusted Geometric Mean (GSE)		Ratio of Geometric Means	p-value
	Ticagrelor	Placebo	(95% CI)	
AUC from 30 days to 1 year ( <i>18F-fluoride activity</i> )	3.7 (1.1)	4.3 (1.1)	0.87 (0.64 to 1.17)	0.35
AUC from 30 days to 1 year ( <i>No 18F-fluoride activity</i> )	2.4 (1.1)	2.3 (1.1)	1.04 (0.84 to 1.28)	0.70

*Estimates are back transformed estimates from analysis of log transformed values area under curve from 30 days to 1 year adjusting for age, sex and log transformed baseline troponin. Ratio of geometric means is Ticagrelor divided by Placebo. AUC, area under curve, ng/L, GSE, geometric standard error.*

**Supplementary Figure 1.** Plasma high-sensitivity cardiac troponin I concentration (stratified population with troponin I >5ng/L at baseline) over 1 year.

Box-whisker plot of individual patient-level plasma high-sensitivity troponin I concentration (ng/L) in ticagrelor (blue) and placebo (red) groups at baseline, 1, 3, 6, 9 and 12 months ( $p=ns$  for all values). Median and interquartile range for each time point.

