Systemic Atherosclerotic Inflammation Following Acute Myocardial Infarction: Myocardial Infarction Begets Myocardial Infarction

Nikhil V. Joshi, MD; Iqbal Toor, MD; Anoop S. V. Shah, MD; Kathryn Carruthers, MPhil; Alex T. Vesey, MD; Shirjel R. Alam, MD; Andrew Sills, MD; Teng Y. Hoo; Adam J. Melville, MD; Sarah P. Langlands, MD; William S. A. Jenkins, MD; Neal G. Uren, MD; Nicholas L. Mills, PhD; Alison M. Fletcher, PhD; Edwin J. R. van Beek, PhD; James H. F. Rudd, PhD; Keith A. A. Fox, MD; Marc R. Dweck, PhD;* David E. Newby, DSc;*

Background—Preclinical data suggest that an acute inflammatory response following myocardial infarction (MI) accelerates systemic atherosclerosis. Using combined positron emission and computed tomography, we investigated whether this phenomenon occurs in humans.

Methods and Results—Overall, 40 patients with MI and 40 with stable angina underwent thoracic 18F-fluorodeoxyglucose combined positron emission and computed tomography scan. Radiotracer uptake was measured in aortic atheroma and nonvascular tissue (paraspinal muscle). In 1003 patients enrolled in the Global Registry of Acute Coronary Events, we assessed whether infarct size predicted early (<30 days) and late (>30 days) recurrent coronary events. Compared with patients with stable angina, patients with MI had higher aortic 18F-fluorodeoxyglucose uptake (tissue-to-background ratio 2.15±0.30 versus 1.84±0.18, P<0.0001) and plasma C-reactive protein concentrations (6.50 [2.00 to 12.75] versus 2.00 [0.50 to 4.00] mg/dL, P=0.0005) despite having similar aortic (P=0.12) and less coronary (P=0.006) atherosclerotic burden and similar paraspinal muscular 18F-fluorodeoxyglucose uptake (P=0.52). Patients with ST-segment elevation MI had larger infarcts (peak plasma troponin 32 300 [10 200 to >50 000] versus 3800 [1000 to 9200] ng/L, P<0.0001) and greater aortic 18F-fluorodeoxyglucose uptake (2.24±0.32 versus 2.02±0.21, P=0.03) than those with non–ST-segment elevation MI. Peak plasma troponin concentrations correlated with aortic 18F-fluorodeoxyglucose uptake (r=0.43, P=0.01) and, on multivariate analysis, independently predicted early (tertile 3 versus tertile 1: relative risk 4.40 [95% CI 1.90 to 10.19], P=0.001), but not late, recurrent MI.

Conclusions—The presence and extent of MI is associated with increased aortic atherosclerotic inflammation and early recurrent MI. This finding supports the hypothesis that acute MI exacerbates systemic atherosclerotic inflammation and remote plaque destabilization: MI begets MI.

Clinical Trial Registration—URL: https://www.clinicaltrials.gov. Unique identifier: NCT01749254. (J Am Heart Assoc. 2015;4: e001956 doi: 10.1161/JAHA.115.001956)

Key Words: 18F-fluorodeoxyglucose positron emission and computed tomography • atherosclerosis • inflammation • vulnerable plaque

Despite recent advances, prognosis following acute myocardial infarction (MI) remains poor.1-3 Because of a considerable risk of recurrent infarction4 and ischemia,5 Such recurrent events are as likely to occur at the site of nonculprit plaques as at the site of the original culprit lesion.6 In postmortem studies of patients dying after acute MI, there is evidence of multiple plaque-related thrombotic events: on average, 2.4 per patient.7 Moreover, there is an increased


An accompanying Table S1 is available at http://jaha.ahajournals.org/content/4/9/e001956/suppl/DC1

*Dr Dweck and Dr Newby contributed equally as joint senior authors.

Correspondence to: Nikhil V. Joshi, MD, University/BHF Centre for Cardiovascular Science, SU 305, Chancellors Building, Little France Crescent, Edinburgh, United Kingdom. E-mail: nikhil.joshi@ed.ac.uk

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incidence of ischemic stroke following MI (not exclusively due to embolic events), suggesting systemic and localized desta-
bilization of remote atherosclerotic plaque.6,9

MI occurs predominantly as a result of acute atheroscle-
rotic plaque rupture,3,9–11 with inflammation believed to be a
key precipitant.10,11 Macrophages infiltrate high-risk plaque
and secrete matrix metalloproteinases that weaken the
fibrous cap and predispose the plaque to rupture.10,11 Recent
preclinical murine data have indicated that MI induced by
coronary artery ligation causes a systemic inflammatory
response that involves macrophage mobilization, a general-
ized increase in atherosclerotic inflammation, and accelerated
plaque progression12; however, this phenomenon has not
been observed directly in humans.

Positron emission tomography (PET) combined with com-
puted tomography (CT) allows the in vivo assessment of
atherosclerotic disease in humans. Glucose analogue 18F-
fluorodeoxyglucose (18F-FDG) is taken up by cells with high
metabolic requirements. It has become a widely used as a
measure of acute vascular inflammation correlating with
atherosclerotic macrophage burden, response to drug ther-
apy, and symptomatic status.13–16 Its generalized uptake
within large arteries is a powerful predictor of subsequent
adverse cardiovascular events.17

In this prospective clinical trial, we determined whether
systemic atherosclerotic plaque metabolism is increased in
patients with MI compared with those with stable coronary
disease and whether this increase is more marked in those
with larger infarctions. Furthermore, we explored whether this
increase might be of clinical relevance and whether infarct
size could predict recurrent early MI.

Methods
The study comprised 2 cohorts of patients: an imaging cohort,
consisting of subjects with stable angina and MI, and an
outcome cohort, comprising patients enrolled in the Global
Registry of Acute Coronary Events (GRACE).18

Imaging Cohort

Subjects
Consecutive patients with acute ST-segment elevation MI
(STEMI), non-STEMI,19 and stable angina pectoris scheduled
for invasive coronary angiography were recruited from the
Royal Infirmary of Edinburgh, as described previously.20
Patients with MI fulfilled the criteria for type 1 MI according
to the Universal Definition of MI.19 STEMI was defined as new
ST-segment elevation at the J point in 2 contiguous leads with
the following cut points: ≥0.1 mV in all leads except V2 to V3,
for which the thresholds were ≥0.2 mV for men and
≥0.25 mV for women. Consecutive patients with stable
angina pectoris were recruited if they had typical symptoms
of exertional anginal chest pain, had previously documented
coronary artery disease (>70% stenosis of at least 1 major
epicardial coronary artery), and were scheduled for invasive
coronary angiography. Patients were excluded if they had
suffered an acute coronary syndrome within the previous
3 months.

Other exclusion criteria were age <50 years, insulin-
dependent diabetes mellitus, women of childbearing age not
taking contraception, severe renal failure (serum creatinine
>250 μmol/L), known contrast allergy, and inability to
provide informed consent. Studies were performed with the
approval of the local research ethics committee, in accord-
cance with the Declaration of Helsinki, and with the written
informed consent of each participant.

All patients underwent a comprehensive baseline clinical
assessment including evaluation of their cardiovascular risk
factor profile. Blood was drawn from all participants for
evaluation of plasma C-reactive protein (CRP) concentra-
tions, which were measured using the Multigent CRP Vario assay
(Archi-Tech cSystems Assay; Abbott Laboratories).

PET-CT imaging
All patients underwent PET-CT imaging of the thorax with a
hybrid scanner (Biograph mCT; Siemens Medical Systems)
using 18F-FDG as well as coronary calcium scoring and CT
angiography of the aorta and coronary arteries.20–22 Subjects
were administered a target dose of 200 MBq 18F-FDG
intravenously and subsequently rested in a quiet environment
for 90 minutes. A low-dose attenuation-correction CT scan
(50 mAs, 120 keV with CARE Dose 4D) was then performed,
followed by PET imaging of the thorax, covering 1 PET bed for
20 minutes. Patients were asked to observe a low-carbohy-
drate, high-protein, and high-fat diet and to refrain from
alcohol intake for at least 24 hours prior to the 18F-FDG scan
to minimize cardiac uptake.

Following acquisition of the PET data, an electrocardio-
gram-gated breath-hold CT scan (non–contrast enhanced,
40 mAs/rotation, 120 kV; Siemens Medical Systems) was
performed for calcium scoring. CT angiography was per-
formed immediately afterward per the standardized scanning
protocol.

Image analysis
Anonymized PET-CT data sets were presented in a random
order on an OsiriX workstation (64 bit; version 5.5.1; OsiriX
Imaging Software) to trained observers (N.V.J., A.S.) who were
blinded to the patients’ clinical status.18 To aid image analysis,
PET images were fused with the CT angiograms, and regions of interest were drawn around the thoracic aorta.
on serial 3-mm axial slices. Within these regions, mean and maximum tracer activities were measured using standard uptake values and corrected for blood-pool activity in the superior vena cava to provide tissue-to-background ratios (TBRs). The ascending aorta was defined as the segment of the aorta from the lower level of the right pulmonary artery up to the last slice at which the aorta maintained its circular cross-sectional appearance. The descending aorta was defined similarly as the region extending up from the tip of the diaphragm to the last circular slice. The aortic arch was defined as the region of aorta connecting the ascending and descending aortas (Figure 1). Aortic radiotracer uptake was quantified using the method of Fayad et al. In brief, the following measures of uptake were measured on axial slices across the aorta as a whole and within each region: TBRmax, the average of the maximum TBR values measured on each axial slice; TBRmean, the average of the mean TBR values measured on each slice; max TBR, the maximum uptake TBR value in any axial section; and TBRMD50, the most diseased segment, defined as the highest maximal TBR value averaged over 3 consecutive slices. Thirty patients were selected randomly to test the repeatability of 18F-FDG measurements in the aorta. Fifteen patients from each cohort were selected, and 2 trained readers (N.V.J., S.P.L.) quantified aortic activity independently. Activity within nonvascular tissue was assessed using oval-shaped regions of interest drawn within paraspinal muscle (area ≈7 cm²) on 5 consecutive axial slices.

CT analysis was performed on a dedicated cardiovascular workstation (Vitrea; Vital Images). Vessel-specific and total Agatston calcium scores were calculated, as described previously, for the coronary arteries, the aorta, and its different regions using a threshold of 130 Hounsfield units.

**Outcome Cohort**

Full details of the GRACE methods have been published previously. The Edinburgh cohort of the prospectively maintained GRACE database was used to identify 1003 patients admitted with an acute coronary syndrome between January 20, 2003, and June 9, 2009. To be eligible, patients (aged >18 years) had to be admitted with an acute coronary syndrome as a presumptive diagnosis and had to have at least 1 of the following conditions: electrocardiographic changes consistent with acute coronary syndrome, serial increases in biomarkers of cardiac necrosis, or documented coronary artery disease. For consistency, only patients who had plasma troponin I concentrations quantified (Abbott Laboratories) in a standardized accredited laboratory were included. Exclusion criteria were secondary myocardial injury precipitated or accompanied by a significant comorbidity, trauma, or surgery. Information regarding patient demographic characteristics, medical history, timing and occurrence of acute coronary symptoms, clinical characteristics, electrocardiographic findings, treatment approaches, and in-hospital outcomes was collected through completion of a standardized proforma.

The baseline and peak troponin I concentrations during admission were recorded, and patients were placed in tertiles based on their peak troponin I to reflect the degree of myocardial injury and the size of their infarct. The primary end point of the analysis was early recurrent MI following the index admission, defined as recurrent type 1 MI within 30 days of index admission. To avoid confounding with the index presentation, only those patients having recurrent MI beyond the first 24 hours after presentation were analyzed, as described previously. We also examined the factors associated with late recurrent MI as an exploratory end point, defined as a recurrent type 1 MI >30 days following index admission.

**Statistical Analysis**

As a prespecified end point of our previously reported trial (ClinicalTrials.gov identifier NCT01749254), we explored 18F-FDG uptake in remote aortic atheroma of patients with recent MI or stable coronary heart disease. Continuous data were tested for normality with the Agostino and Pearson criteria were secondary myocardial injury precipitated or accompanied by a significant comorbidity, trauma, or surgery. Information regarding patient demographic characteristics, medical history, timing and occurrence of acute coronary symptoms, clinical characteristics, electrocardiographic findings, treatment approaches, and in-hospital outcomes was collected through completion of a standardized proforma. The baseline and peak troponin I concentrations during admission were recorded, and patients were placed in tertiles based on their peak troponin I to reflect the degree of myocardial injury and the size of their infarct. The primary end point of the analysis was early recurrent MI following the index admission, defined as recurrent type 1 MI within 30 days of index admission. To avoid confounding with the index presentation, only those patients having recurrent MI beyond the first 24 hours after presentation were analyzed, as described previously. We also examined the factors associated with late recurrent MI as an exploratory end point, defined as a recurrent type 1 MI >30 days following index admission.

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assessed using the Pearson correlation coefficient, and the Spearman rank correlation was used for nonparametric data.

Patients in the registry cohort were placed in tertiles according to their peak troponin concentration. Kaplan–Meier curves were used to estimate the distribution of early recurrent MI across the tertiles. Univariate analysis was undertaken to identify associations with early (<30 days) and late (≥30 days) recurrent MI that were then entered into the multivariate logistic regression model based on a univariate association of \( P < 0.1 \). In addition, age and sex were included in the model. Statistical analysis was performed with GraphPad Prism version 6 (GraphPad Software Inc) and SPSS 19.0 (IBM Corp), as appropriate. Unless stated, a 2-sided \( P < 0.05 \) was considered statistically significant.

## Results

### Imaging Cohort

Overall, 40 patients with stable angina and 40 with MI underwent 18F-FDG PET imaging. The median time between hospitalization and 18F-FDG PET imaging was 11 days (IQR 8 to 17 days) in patients with MI. Compared with patients with stable angina, patients with MI were younger, had less extensive coronary artery disease (Table 1), and had lower coronary artery calcium scores (coronary artery calcium score: stable angina 599 Agatston units [AU; IQR 60 to 1302 AU]; MI 159 AU [IQR 42 to 456 AU]; \( P = 0.006 \) (Tables 1 and 2). Although apparently higher aortic calcium scores were noted in patients with stable angina, this difference did not reach statistical significance (aortic calcium scores; stable angina 538 AU [IQR 4 to 1870 AU]; MI 135 AU [IQR 0 to 805 AU]; \( P = 0.12 \) (Table 2).

### Positron emission tomography

The reproducibility of TBR measurements in the aorta for tracer activity was excellent, with no fixed or proportional biases and with narrow limits of agreement (Table S1). In contrast to the calcium scores, 18F-FDG uptake was 20% higher in the aortas of patients with recent MI than those with stable coronary artery disease (Table 2 and Figure 2). This finding was consistent in all regions of the aorta assessed (entire thoracic aorta, ascending aorta, aortic arch, descending aorta; all \( P < 0.0001 \)) and with all measures of tracer activity (mean TBR\(_{\text{max}} \), mean TBR\(_{\text{mean}} \), max TBR, TBR\(_{\text{MDS}} \), all \( P < 0.001 \)). Furthermore, 18F-FDG activity was higher in patients with STEMI compared with those with non-STEMI (TBR\(_{\text{max}} \), 2.24±0.32 versus 2.02±0.21, respectively; \( P = 0.03 \) (Table 2), consistent with the former having sustained larger MIs (peak plasma troponin concentration 32 300 ng/L [IQR 10 200 to >50 000 ng/L] versus 3800 ng/L [IQR 1000 to 9200 ng/L]; \( P < 0.001 \)). Indeed, aortic 18F-FDG activity correlated with peak plasma troponin I concentrations \( (r=0.43, P = 0.01) \).

In patients with stable angina and those with MI, paraspinal uptake of 18F-FDG (mean TBR\(_{\text{max}} \) 0.79±0.25 versus 0.75±0.21, respectively; \( P = 0.52 \) was similar.

### C-reactive protein

Compared with patients with stable angina, patients with MI had higher plasma CRP concentrations (6.50 mg/dL [IQR 2.00 to 12.75 mg/dL] versus 2.00 mg/dL [IQR 0.50 to 4.00 mg/dL], \( P = 0.0005 \)). Among patients with MI, patients with STEMI appeared to have higher plasma CRP concentrations (7.50 mg/dL [IQR 2.00 to 13.75 mg/dL] versus 2.50 mg/dL [IQR 1.75 to 9.50 mg/dL], but this difference did not reach statistical significance \( (P = 0.22) \). There was a modest correlation between peak troponin I concentrations and CRP \( (r=0.35, P = 0.03) \).

### Outcome Cohort

A total of 1003 patients enrolled in the GRACE database were followed for a median follow-up period of 34 months (IQR 18 to 50 months). Early recurrent MI occurred in 54 patients following index admission, whereas late recurrent MI occurred in 89 patients.

Patients were classified into tertiles according to their peak plasma troponin I concentrations measured during the index admission (tertile 1, ≤220 ng/L; tertile 2, 230 to 6130 ng/L; and tertile 3, ≥6140 ng/L) (Table 3). On univariate analysis, the risk of early recurrent infarction (≤30 days) was >4-fold higher among patients in the highest troponin tertile compared with the lowest, whereas risk was doubled in the middle tertile compared with the lowest (Table 4 and Figure 3). The variables with univariate association of \( P < 0.1 \) were Killip score ≥2, ST-segment deviation, multivessel disease, and troponin I concentrations. On multivariate analysis, troponin emerged as an independent predictor of early MI after adjustment for other relevant variables (tertile 3 versus 1: relative risk 4.40 [95% CI 1.90 to 10.19], \( P = 0.001 \); tertile 2 versus 1: relative risk 2.63 [95% CI 1.08 to 6.38], \( P = 0.03 \)). The only other independent predictor was Killip class 2 (1.86 [95% CI 1.06 to 3.24], \( P = 0.03 \)).

In contrast, recurrent late MI was not associated with troponin tertiles on univariate analysis (tertile 2 versus 1: relative risk 1.07 [95% CI 0.64 to 1.79], \( P = 0.79 \); tertile 3 versus 1: relative risk 0.80 [95% CI 0.46 to 1.39], \( P = 0.43 \) but rather was more closely related to traditional predictors of MI (Table 4).
Discussion

Using 18F-FDG PET imaging, in patients with recent MI, we demonstrated increased metabolic activity in remote aortic atherosclerotic plaques that correlated with the degree of myocardial necrosis and exceeded that observed in patients with stable coronary disease who had a greater atherosclerotic burden. Using the GRACE registry, we explored the...
clinical relevance of these findings to assess whether infarct size and the associated increase in atherosclerotic inflammation could predict recurrent coronary atherothrombotic events in everyday clinical practice. Intriguingly, patients with the largest infarcts had a >4-fold increase in the risk of early recurrent MI, with baseline tertiles of plasma troponin concentration emerging as an independent predictor of these events. Consequently, we provided clinical data to support the hypothesis that MI exacerbates systemic atherosclerotic inflammation, destabilizes remote atheromatous plaque, and causes an increase in early recurrent atherothrombotic events.

Preclinical data have indicated that MI induces a macrophage-driven proinflammatory state\textsuperscript{31} that directly increases inflammation in remote atheroma and induces further atherosclerosis.\textsuperscript{12,32,33} In a mouse model, MI induced by coronary artery ligation increased splenic monocyte motility,\textsuperscript{12} with these cells exiting the spleen en masse and migrating both to the injured myocardium and, crucially, to remote atherosclerotic plaque.\textsuperscript{34} In addition, sympathetic stimulation following infarction increased the production and liberation of hematopoietic stem and progenitor cells from the bone marrow, resulting in further increases in circulating monocytes and the accumulation of macrophages within regions of remote atheroma.\textsuperscript{12} The net result was a marked accumulation of macrophages in remote atherosclerotic plaque following MI that resulted in acceleration of the disease process in these areas. The first aim of the current study was to examine whether baseline plasma troponin concentration is associated with early recurrent MI in patients with a first MI. Towards this goal, we assessed the clinical relevance of these findings to assess whether infarct size and the associated increase in atherosclerotic inflammation could predict recurrent coronary atherothrombotic events in everyday clinical practice. Intriguingly, patients with the largest infarcts had a >4-fold increase in the risk of early recurrent MI, with baseline tertiles of plasma troponin concentration emerging as an independent predictor of these events. Consequently, we provided clinical data to support the hypothesis that MI exacerbates systemic atherosclerotic inflammation, destabilizes remote atheromatous plaque, and causes an increase in early recurrent atherothrombotic events.

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study was to test whether this proinflammatory phenomenon also occurred in humans, using 18F-FDG as a marker of vascular macrophage inflammatory activity. Because we could not measure 18F-FDG uptake before and after MI, we prospectively compared uptake between patients with stable coronary heart disease and those with recent MI. Despite a comparable or lower overall aortic and coronary plaque burden, aortic 18F-FDG uptake was 20% higher in patients who had sustained a recent MI. Indeed, the aortic 18F-FDG uptake was consistently increased across all regions of the thoracic aorta. In contrast, paraspinal muscle uptake was similar between the cohorts, indicating a specific vascular and atherosclerotic response rather than generalized nonspecific inflammation across all tissues. Based on clinical factors and peak plasma troponin concentration, patients with STEMI had larger infarcts and demonstrated greater increases in aortic plaque burden.

### Table 3. Baseline Characteristics of Patients From the GRACE Cohort

<table>
<thead>
<tr>
<th></th>
<th>Tertile 1 (n=332)</th>
<th>Tertile 2 (n=336)</th>
<th>Tertile 3 (n=335)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak troponin I, range</td>
<td>≤220</td>
<td>230 to 6130</td>
<td>≥6140</td>
<td>—</td>
</tr>
<tr>
<td>Age, y</td>
<td>65±12</td>
<td>66±12</td>
<td>63±13</td>
<td>0.02</td>
</tr>
<tr>
<td>GRACE score</td>
<td>124±47</td>
<td>197±49</td>
<td>218±41</td>
<td>&gt;0.0001</td>
</tr>
<tr>
<td>Male sex</td>
<td>212 (63.9)</td>
<td>226 (67.3)</td>
<td>254 (75.8)</td>
<td>0.003</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>214 (64.5)</td>
<td>243 (72.3)</td>
<td>235 (70.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>Previous MI</td>
<td>149 (44.9)</td>
<td>91 (27.1)</td>
<td>51 (15.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Killip score ≥2</td>
<td>82 (24.7)</td>
<td>114 (33.9)</td>
<td>98 (29.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>61 (18.4)</td>
<td>25 (7.4)</td>
<td>12 (3.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Previous heart failure</td>
<td>26 (7.8)</td>
<td>25 (7.4)</td>
<td>13 (3.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>Diabetes</td>
<td>53 (16.0)</td>
<td>47 (14.0)</td>
<td>47 (14.0)</td>
<td>0.71</td>
</tr>
<tr>
<td>ST-segment deviation</td>
<td>77 (23.2)</td>
<td>142 (42.3)</td>
<td>275 (82.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>92 (27.7)</td>
<td>141 (42.0)</td>
<td>125 (37.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Recurrent MI ≤30 days</td>
<td>7 (2.1)</td>
<td>18 (5.4)</td>
<td>29 (8.7)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are shown as mean±SD or number (percentage). CABG, coronary artery bypass grafting; GRACE, Global Registry of Acute Coronary Events; MI, myocardial infarction.

### Table 4. Univariate Predictors of Early (≤30 Day) and Late (>30 Day) Recurrent MI

<table>
<thead>
<tr>
<th></th>
<th>Early (≤30 Day) Recurrent MI</th>
<th>P Value</th>
<th>Late (&gt;30 Day) Recurrent MI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>1.02 (0.99 to 1.04)</td>
<td>0.14</td>
<td>1.04 (1.02 to 1.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.30 (0.70 to 2.43)</td>
<td>0.45</td>
<td>0.89 (0.56 to 1.41)</td>
<td>0.63</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.82 (0.46 to 1.46)</td>
<td>0.55</td>
<td>1.04 (0.65 to 1.67)</td>
<td>0.91</td>
</tr>
<tr>
<td>Previous MI</td>
<td>0.69 (0.36 to 1.32)</td>
<td>0.28</td>
<td>3.81 (2.43 to 5.95)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Killip score ≥2</td>
<td>1.86 (1.06 to 3.24)</td>
<td>0.03</td>
<td>1.79 (1.14 to 2.82)</td>
<td>0.01</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>0.94 (0.37 to 2.42)</td>
<td>0.99</td>
<td>2.91 (1.66 to 5.10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Previous heart failure</td>
<td>0.86 (0.26 to 2.82)</td>
<td>0.99</td>
<td>2.77 (1.40 to 5.45)</td>
<td>0.008</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.72 (0.30 to 1.71)</td>
<td>0.56</td>
<td>1.41 (0.80 to 2.48)</td>
<td>0.27</td>
</tr>
<tr>
<td>ST-segment deviation</td>
<td>1.81 (1.03 to 3.19)</td>
<td>0.05</td>
<td>1.18 (0.76 to 1.82)</td>
<td>0.50</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>1.73 (0.99 to 2.99)</td>
<td>0.06</td>
<td>1.57 (1.01 to 2.44)</td>
<td>0.05</td>
</tr>
<tr>
<td>Troponin tertiles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertile 2 vs tertile 1</td>
<td>2.63 (1.08 to 6.38)</td>
<td>0.03</td>
<td>1.07 (0.64 to 1.79)</td>
<td>0.79</td>
</tr>
<tr>
<td>Tertile 3 vs tertile 1</td>
<td>4.40 (1.90 to 10.19)</td>
<td>0.001</td>
<td>0.80 (0.46 to 1.39)</td>
<td>0.43</td>
</tr>
<tr>
<td>Linear trend across tertiles</td>
<td>—</td>
<td>&lt;0.0001</td>
<td>—</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Data are shown as relative risk (95% CI). CABG, coronary artery bypass grafting; MI, myocardial infarction.

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Myocardial Infarction Begets Myocardial Infarction  Joshi et al

stabilize once more. Our data are also consistent with later recurrent events after 30 days, by which time the only transitory, with no association between infarct size and clinical effects of this systemic inflammation such as CRP in our outcome cohort; however, given the unpredictable nature of these events, is extremely challenging in the clinical context. We also acknowledge that we did not directly measure MI size and used peak plasma troponin concentration as a surrogate measure; however, peak plasma troponin concentration has a strong correlation with infarct size (r=0.740, P<0.001) which also observed an increased early event rate in patients in the highest tertile of troponin concentration, with a trend for an increase in recurrent MI. Our findings are supported by recently reported studies. Patients with acute coronary syndromes have increased plaque vulnerability in nonculprit lesions, with increased incidence of thin-capped fibroatheromas and adherent thrombus. Furthermore, patients with STEMI have accelerated plaque progression in nonculprit lesions on follow-up angiography, whereas stenting of such lesions at the same time as culprit lesions reduces adverse cardiovascular events. Moreover, patients with unstable coronary disease have higher metabolic carotid plaque activity compared with patients with stable disease, suggesting a panvascular inflammatory process, as indicated by our study.

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18F-FDG uptake than those with non-STEMI. We observed good correlation between peak plasma troponin I concentrations and aortic 18F-FDG activity, suggesting that the association may be causal.

Next we investigated whether the observed increases in vascular inflammatory activity were of clinical importance in actual practice. Our imaging cohort was not large enough to address this question, so we turned to data from the well-established GRACE registry. In >1000 patients, we demonstrated that the size of the initial MI emerged as an independent predictor of early recurrent MI over and above traditional risk factors, with a 4-fold increase in these events among those with the biggest infarcts. This finding indicates that the increased vascular inflammation associated with MI translates into adverse clinical events, perhaps due to plaque destabilization and the associated increased risk of rupture. Interestingly, our data also suggest that the clinical effects of this systemic inflammatory response are only transitory, with no association between infarct size and later recurrent events after 30 days, by which time the inflammation will have subsided and plaques begun to stabilize once more. Our data are also consistent with those of the smaller (n=378) Evaluation of MCC-135 for Left Ventricular Salvage in Acute Myocardial Infarction (EVALVE) randomized controlled trial, which also observed an increased early event rate in patients in the highest tertile of troponin concentration, with a trend for an increase in recurrent MI. Our findings are supported by recently reported studies. Patients with acute coronary syndromes have increased plaque vulnerability in nonculprit lesions, with increased incidence of thin-capped fibroatheromas and adherent thrombus. Furthermore, patients with STEMI have accelerated plaque progression in nonculprit lesions on follow-up angiography, whereas stenting of such lesions at the same time as culprit lesions reduces adverse cardiovascular events. Moreover, patients with unstable coronary disease have higher metabolic carotid plaque activity compared with patients with stable disease, suggesting a panvascular inflammatory process, as indicated by our study.

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Acknowledgments
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Disclosures
None.

References


## SUPPLEMENTAL MATERIAL

### Supplementary Table S1. Inter-observer reproducibility of aortic tissue to background ratios

<table>
<thead>
<tr>
<th></th>
<th>Mean $TBR_{\text{mean}}$</th>
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<tbody>
<tr>
<td><strong>Ascending Aorta</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean bias±2SD</td>
<td>-0.03±0.07</td>
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<td>-0.05±0.12</td>
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<tr>
<td>ICC (95% CI)</td>
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<td>0.99</td>
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<td></td>
<td>(0.97-1.00)</td>
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Mean $TBR_{\text{mean}}$: Average of the maximum tissue to background ratios across all slices in the segment; mean $TBR_{\text{mean}}$: Average of the mean tissue to background ratios all slices in the segment; max TBR: highest value tissue to background ratios in any axial slice.

*Note: The table values are provided for aortic tissue to background ratios with mean bias±2SD, ICC, and (95% CI) as evaluated in the ascending, arch, descending, and overall thoracic aorta segments.*
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