Angiotensin-Converting Enzyme Inhibition Is Associated With Reduced Troponin Release in Non–ST-Elevation Acute Coronary Syndromes

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OBJECTIVES
This study was done to determine the effects of angiotensin-converting enzyme (ACE) inhibition and other clinical factors on troponin release in non–ST-elevation acute coronary syndrome (ACS).

BACKGROUND
Troponin is now widely used as a marker of risk in ACS, but determinants of its release have not been defined.

METHODS
This was a prospective cohort study of 301 consecutive patients admitted with non–ST-elevation ACS. Baseline clinical data were recorded, ACE gene polymorphism was determined and serial blood samples were obtained for troponin-I assay.

RESULTS
Significant troponin-I release (>0.1 μg/l) was detected in 93 (31%) patients. Pretreatment with ACE inhibitors, recorded in 53 patients (17.6%), independently reduced the odds of troponin-I release (odds ratio 0.25; 95% confidence intervals 0.10 to 0.64) and was associated with lower maximum troponin-I concentrations (median [interquartile range]) compared with patients not pretreated with ACE inhibitors (0.44 μg/l [0.19 to 2.65 μg/l] vs. 4.18 μg/l [0.91 to 12.41 μg/l], p = 0.01). Pretreatment with aspirin, recorded in 173 patients (57.5%), did not significantly reduce the odds of troponin-I release after adjustment but was associated with lower maximum troponin-I concentrations compared with patients not pretreated with aspirin (2.31 μg/l [0.72 to 8.02 μg/l] vs. 5.85 μg/l [1.19 to 12.79 μg/l], p = 0.05). The ACE genotyping (n = 268) showed 81 patients (30%) DD homozygous and 77 (29%) II homozygous. There was no association between ACE genotype and troponin release.

CONCLUSIONS
We conclude that ACE inhibition reduces troponin release in non–ST-elevation ACS. This is likely to be mediated by the beneficial effects of treatment on vascular reactivity and the coagulation system. (J Am Coll Cardiol 2001;38:724–8) © 2001 by the American College of Cardiology

Troponin release occurs in about a third of all patients with unstable angina and is widely used for risk stratification, being associated with a 20% rate of death and myocardial infarction (MI) in the first six months compared with a 2% rate in troponin-negative cases (1). It reflects ischemic myocardial injury, probably caused by transient thrombotic occlusion at the site of plaque rupture or thrombotic embolization into the distal arterial bed (2). Thus, both troponin release and prognosis in unstable angina are likely to be determined, at least in part, by the thrombotic burden, which in turn is influenced by factors affecting the degree of plaque disruption and the coagulability of the blood (3,4). Identification of these factors may have important implications for risk reduction in unstable angina, yet to date there have been no studies in which determinants of troponin release have been clearly documented.

The renin-angiotensin system is a potential determinant of troponin release through its ability to regulate coronary endothelial function and influence vascular reactivity, endogenous thrombolytic activity and platelet activation (5–9). This may have important clinical implications because the renin-angiotensin system is amenable to therapeutic modification, and the benefits of angiotensin-converting enzyme (ACE) inhibition for risk reduction in cardiovascular disease have already been demonstrated (10). In the present study, therefore, we have prospectively analyzed troponin-I concentrations in an unselected cohort of patients with non-ST-elevation acute coronary syndromes (ACS) to determine whether pretreatment with ACE inhibitors and the ACE gene polymorphism influence troponin release.

METHODS
Patients. Consecutive patients with non–ST-elevation ACS were recruited if they fulfilled criteria for Braunwald
class 3B unstable angina (11). Electrocardiographic (ECG) changes (ST depression, T-wave inversion) were not required for inclusion, but patients who developed Q-waves were excluded as were patients with MI in the previous 21 days. Other exclusion criteria included percutaneous coronary intervention in the previous six months and cardiac failure (New York Heart Association class III or IV). The study protocol was approved by the East London and the City Research Ethics Committee, and all patients gave written informed consent.

**Data collection.** **CLINICAL DATA.** Baseline characteristics including demographic, clinical and biochemical data as well as details of the presenting ECG were collected prospectively and stored electronically. Medication being taken prior to admission was documented.

**BLOOD SAMPLING AND BIOCHEMICAL ANALYSIS.** In addition to samples taken for routine laboratory analysis according to hospital protocols, samples were also taken on admission (before antithrombotic therapy) for troponin-I assay and ACE genotyping and at 12, 24 and 48 h after admission for troponin-I assays only. Whole blood and, after separation, serum samples were stored at −80°C for analysis in batches. Troponin-I concentrations were measured using a one-step sandwich immunoassay with magnetic separation (Bayer Immuno 1 Analyzer, Bayer Plc, Newbury, United Kingdom). The coefficient of variation was 3.2% at 2.5 μg/l and 10% at 0.3 μg/l (manufacturer’s data sheet). As recommended by the manufacturer, the cutoff point used was 0.1 μg/l.

**DETERMINATION OF ACE GENOTYPES.** Genomic deoxyribonucleic acid was extracted from 200 μl of whole blood with a QIAmp (96 wells per plate) blood kit (QIAGEN, Crawley, United Kingdom). The ACE genotype was determined as previously described (12) and recently modified (13). Briefly, amplification by polymerase chain reaction using previously described specific primers flanking the polymorphic region in intron 16 of the ACE gene yielded a 480 bp amplicon (I allele) and/or a 191 bp amplicon (D allele), which were analyzed on a 3% agarose gel. Because there is preferential amplification of the D allele in heterozygotes, all ACE DD individuals were verified by reamplification with primers specific for the 287 deleted alu repeat region as previously described (14).

**Statistical analysis.** Results for continuous variables are presented as means and SD. Two sample t tests were used to compare those with and without peak troponin concentrations >0.1 μg/l. Variables not normally distributed are presented as medians and interquartile ranges and compared using the Mann-Whitney U-test. Categorical variables are presented as numbers and percentages and compared using either the chi-square test or the Fisher exact test. Variables significant (p ≤ 0.05) on univariate analysis were selected for testing in a stepwise multiple logistic regression model. The criterion for entry at each stage was significance at the 5% level. We then looked at the effect of adding variables insignificant on univariate analysis to test whether any of these became important after adjustment. Results from the logistic regression were expressed as the odds of having a peak troponin-I > 0.1 μg/l relative to a reference category for categorical variables and as the relative odds associated with a 1 SD increase in continuous variables. The Pearson χ² test was used to compare the ACE genotype in those with and without peak troponin concentrations >0.1 μg/l.

**RESULTS**

A total of 304 patients were recruited, but troponin data were unavailable in three patients because of insufficient sample size and sample wastage. The remaining 301 patients comprised the study group in whom troponin positivity (>0.1 μg/l) was recorded in 93 patients (31%).

**Univariate predictors of troponin positivity.** In patients who were troponin positive, pretreatment with ACE inhibitors and aspirin was recorded significantly less frequently than in patients who were troponin negative (Table 1). Troponin-positive patients were older but less likely to report a previous history of ACS or coronary revascularization. Admission blood concentrations of creatinine and glucose were higher in troponin-positive patients, and cholesterol showed a similar trend. Ischemic ECG changes were more common in troponin-positive patients, and peak creatine kinase concentrations were strongly associated with troponin release.

**Multivariate predictors of troponin positivity.** Logistic regression analysis showed that pretreatment with ACE inhibitors independently reduced the odds of troponin release by 75%. Troponin release was also less likely in those who had previously presented with unstable angina, but pretreatment with aspirin had no independent effect. Ischemic ECG changes, however, more than doubled the odds of troponin release, which also increased by 70% for every 1 SD increase in admission serum glucose concentration, and by 25% for every five-year increase in age (Table 2).

**The magnitude of troponin release.** Detectable troponin release occurred in 98 (33%) of the 301 patients recruited. Peak troponin concentrations in these patients were unrelated to many of the variables associated with troponin positivity, including previous ACS and coronary revascularization. Pretreatment with aspirin and ACE inhibitors, however, was associated with a 61% (p = 0.05) and 89% (p = 0.01) decrease in peak troponin concentrations, respectively (Table 3).

**The ACE gene polymorphism.** The ACE genotype data were available in 268 patients, of whom 81 (30%) were DD
**Table 1.** Baseline Characteristics According to Troponin Status

<table>
<thead>
<tr>
<th>Troponin Status</th>
<th>No TnI (n = 208)</th>
<th>≥ TnI (n = 93)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>58.8 (10.9)</td>
<td>64.5 (10.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male gender</td>
<td>150 (72.1)</td>
<td>75 (80.7)</td>
<td>0.12</td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>53 (25.5)</td>
<td>21 (22.6)</td>
<td>0.59</td>
</tr>
<tr>
<td>Diabetic</td>
<td>43 (20.7)</td>
<td>24 (25.8)</td>
<td>0.32</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>94 (45.2)</td>
<td>41 (44.1)</td>
<td>0.86</td>
</tr>
<tr>
<td>Smoker</td>
<td>62 (29.8)</td>
<td>34 (36.6)</td>
<td>0.25</td>
</tr>
<tr>
<td>Family history</td>
<td>112 (53.9)</td>
<td>37 (39.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cardiac history</td>
<td>56 (26.9)</td>
<td>10 (10.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>89 (42.8)</td>
<td>27 (29.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Revascularization</td>
<td>46 (22.1)</td>
<td>10 (10.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Creatinine</td>
<td>102.3 (22.4)</td>
<td>12 (12.9)</td>
<td>0.24</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>77 (37.2)</td>
<td>35 (37.6)</td>
<td>0.94</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>5.61 (1.14)</td>
<td>5.85 (1.15)</td>
<td>0.09</td>
</tr>
<tr>
<td>Glucose</td>
<td>6.3 (5.7–7.6)</td>
<td>7 (6–11.7)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Creatinine</td>
<td>102.3 (22.4)</td>
<td>12 (12.9)</td>
<td>0.24</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>77 (37.2)</td>
<td>35 (37.6)</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Data are medians (interquartile range). ACE = angiotensin-converting enzyme; ECG = electrocardiography; TnI = troponin-I.

**DISCUSSION**

**ACE inhibition and troponin release.** This prospective study of non–ST-elevation ACS has shown that troponin release is influenced importantly by ACE inhibition, an observation that has not previously been reported. Thus, in patients pretreated with ACE inhibitors, the odds of troponin positivity were reduced by 65%, and maximum troponin concentrations were almost 90% lower than in patients not pretreated with ACE inhibitors. This cardioprotective effect may account, at least in part, for the benefits of these drugs in patients at high risk of cardiac events reported by the Heart Outcomes Prevention Evaluation (HOPE) study investigators (10). This hypothesis is strengthened by the well-documented effects of ACE inhibition on endothelial function and the coagulation system, which provide potential mechanisms whereby pretreatment might reduce myocardial injury. ACE inhibition restores endothelium-dependent vasodilator responses in patients with coronary artery disease (CAD), helping to preserve coronary flow when luminal patency is threatened by thrombosis (5). Moreover, ACE inhibition may also modify the thrombotic burden by enhancing the endogenous fibrinolytic system through reductions in endothelial production of plasminogen-activator inhibitor-1 (6,7). Reductions in platelet aggregability have also been reported (8,9). The combination of improved coronary vasodilator activity, enhanced endogenous fibrinolysis and reduced platelet aggregability would provide an environment more conducive to coronary patency during plaque events, readily accounting for the beneficial effects that pretreatment with ACE inhibitors had on troponin release in this study of non-ST-elevation ACS.

**The ACE genotype.** Similar mechanisms have been proposed to explain the protection against coronary events seen in patients pretreated with ACE inhibitors. This protective effect may account, at least in part, for the benefits of these drugs in patients at high risk of cardiac events reported by the Heart Outcomes Prevention Evaluation (HOPE) study investigators (10). This hypothesis is strengthened by the well-documented effects of ACE inhibition on endothelial function and the coagulation system, which provide potential mechanisms whereby pretreatment might reduce myocardial injury. ACE inhibition restores endothelium-dependent vasodilator responses in patients with coronary artery disease (CAD), helping to preserve coronary flow when luminal patency is threatened by thrombosis (5). Moreover, ACE inhibition may also modify the thrombotic burden by enhancing the endogenous fibrinolytic system through reductions in endothelial production of plasminogen-activator inhibitor-1 (6,7). Reductions in platelet aggregability have also been reported (8,9). The combination of improved coronary vasodilator activity, enhanced endogenous fibrinolysis and reduced platelet aggregability would provide an environment more conducive to coronary patency during plaque events, readily accounting for the beneficial effects that pretreatment with ACE inhibitors had on troponin release in this study of non-ST-elevation ACS.

**Table 2.** Multivariate Predictors of Troponin-I Positivity

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-wave inversion</td>
<td>2.73 (1.45–5.17)</td>
<td>0.002</td>
</tr>
<tr>
<td>ST depression</td>
<td>2.44 (1.29–4.63)</td>
<td>0.006</td>
</tr>
<tr>
<td>Glucose*</td>
<td>1.70 (1.27–2.30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age*</td>
<td>1.25 (1.08–1.45)</td>
<td>0.002</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>0.36 (0.15–0.87)</td>
<td>0.02</td>
</tr>
<tr>
<td>ACE inhibitors*</td>
<td>0.25 (0.10–0.64)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Odds ratios are for a five-year increase in age and a 1 SD increase in glucose. *Odds ratios represent odds of maximum troponin-I concentrations being >0.1 µg/l.

**ACE Genotype**

<table>
<thead>
<tr>
<th>Troponin Status</th>
<th>DD</th>
<th>ID</th>
<th>II</th>
</tr>
</thead>
<tbody>
<tr>
<td>TnI ≤ 0.1 µg/l</td>
<td>60 (74.1)</td>
<td>69 (62.7)</td>
<td>53 (68.8)</td>
</tr>
<tr>
<td>TnI &gt; 0.1 µg/l</td>
<td>21 (25.9)</td>
<td>41 (37.3)</td>
<td>24 (31.2)</td>
</tr>
</tbody>
</table>

Data are medians (interquartile range). ACE = angiotensin-converting enzyme; TnI = troponin-I.
in individuals homozygous for the insertion polymorphism of the ACE gene in whom endogenous converting enzyme activity is lower than in individuals homozygous for the deletion polymorphism (15–17). However, this has not been a consistent finding (14), and in the present study troponin release was not influenced by ACE genotype. This may reflect the rather modest 40% relative reduction in ACE activity associated with the II polymorphism (15,16), which is considerably less than the 90% reduction in ACE activity produced by therapeutic doses of ACE inhibitors (16,18).

**Aspirin and troponin release.** Among patients pretreated with aspirin, troponin positivity was less common, and peak troponin levels were 60% lower than in patients not taking aspirin. Although these are new findings, they require cautious interpretation as a significant independent relation between pretreatment with aspirin and troponin release did not emerge from the multivariate analysis. Interestingly, in the Thrombolysis In Myocardial Infarction trial risk score for unstable angina/non–ST-elevation MI, use of aspirin in the seven days prior to presentation was an independent predictor of adverse prognosis (19). This remains unexplained and, in view of the demonstrable efficacy of aspirin as a secondary preventative measure (20), counterintuitive. Protection against troponin release would be a predictable response to the antiplatelet effects of aspirin, reductions in thrombosis helping to preserve coronary patency and reduce distal embolization and myocardial injury during plaque events. In this respect the effects of aspirin were analogous to those demonstrated in our previous studies of ACS in which pretreatment has been associated with less severe modes of presentation (21,22).

**Other factors influencing troponin release.** The strong independent effect of increasing age on troponin release is likely to reflect age-related changes in vascular endothelial function and thrombogenicity. Thus, advanced age has been shown to impair endothelium-dependent coronary vasodilatation and is also associated with increases in circulating fibrinogen and factor VII levels compared with younger individuals (23–25). These changes in vascular reactivity and thrombogenicity in the elderly would predispose to exaggerated thrombotic responses to plaque events, increasing the propensity to coronary occlusion and distal embolization, which are thought to account for ischemic myocardial injury and troponin release in non–ST-segment/ elevation coronary syndromes. Changes in thrombogenicity may also have contributed to the relation between glyceria and troponin release in the present study, blood glucose being an independent predictor of platelet-dependent thrombosis in patients with CAD (26). Nevertheless, glyceria—a well-recognized response to increased sympathetic-adrenal activation—is commonly taken to reflect the severity of ACS and, like ischemic ECG changes, therefore, associations with troponin release may have been casual rather than causal. The association between previous admissions with unstable angina and troponin release may relate to the protective effect of myocardial collateralization (27,28) and preconditioning (29,30).

**Study limitations.** The study was not powered to detect small differences in troponin status associated with ACE gene polymorphisms, and the possibility of a type II error cannot be ruled out. This contrasts with our observations concerning drug use and troponin status where differences were large and statistically significant despite the relatively small sample size. Nevertheless, it remains possible that with larger numbers an effect of statins would also have been detected and that statin treatment may have contributed more to the multivariate model.

**Conclusions.** This study has shown that pretreatment with ACE inhibitors is associated with reductions in troponin release in patients with non–ST-elevation ACS. Although causality has not been proven in this study, the association is likely to be mediated by the beneficial effects of treatment on vascular reactivity and the coagulation system. Because reductions in troponin release are associated with parallel reductions in risk, our observations provide a plausible new mechanism whereby ACE inhibition might contribute to secondary prevention in patients with CAD.

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**REFERENCES**


