Early short-term doxycycline therapy in patients with acute myocardial infarction and left ventricular dysfunction to prevent the ominous progression to adverse remodelling: the TIPTOP trial

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Aims
Experimental studies suggest that doxycycline attenuates post-infarction remodelling and exerts protective effects on myocardial ischaemia/reperfusion injury. However, the effects of the drug in the clinical setting are unknown. The aim of this study was to examine the effect of doxycycline on left ventricular (LV) remodelling in patients with acute ST-segment elevation myocardial infarction (STEMI) and LV dysfunction.

Methods and results
Open-label, randomized, phase II trial. Immediately after primary percutaneous coronary intervention, patients with STEMI and LV ejection fraction < 40% were randomly assigned to doxycycline (100 mg b.i.d. for 7 days) in addition to standard therapy, or to standard care. The echo LV end-diastolic volumes index (LVEDVi) was determined at baseline and 6 months. 99mTc-Sestamibi-single-photon emission computed tomography infarct size and severity were assessed at 6 months. We calculated a sample size of 110 patients, assuming that doxycycline may reduce the increase in the LVEDVi from baseline to 6 months 50% compared with the standard therapy (statistical power 80% with a type I error = 0.05). The 6-month changes in %LVEDVi were significant smaller in the doxycycline group than in the control group [0.4% (IQR: 2 to 16.0 to 14.2%) vs. 13.4% (IQR: 0 to 7.9 to 29.3%); P = 0.012], as well as infarct size [5.5% (IQR: 0 to 18.8%) vs. 10.4% (IQR: 0.3 to 29.9%); P = 0.052], and infarct severity [0.53 (IQR: 0.43–0.62) vs. 0.44 (IQR: 0.29–0.60), P = 0.014], respectively.

Conclusion
In patients with acute STEMI and LV dysfunction, doxycycline reduces the adverse LV remodelling for comparable definite myocardial infarct size (NCT00469261).

Keywords
Myocardial infarction • Remodelling • Echocardiography

Introduction
Post-myocardial infarction (MI) left ventricular (LV) remodelling is the leading cause of LV dysfunction and heart failure, and the degree of remodelling predicts morbidity and mortality.1 Left ventricular remodelling is observed in a substantial proportion of post-MI patients, especially when LV systolic dysfunction is present, despite successful mechanical reperfusion and current optimal medical therapy.2

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The extracellular collagen matrix (ECM) plays a major role in post-MI remodelling and increased matrix metalloproteinases (MMPs) activation is a well-accepted pathway leading to early ECM damage and LV remodelling. Experimental studies have shown that pharmacological MMPs inhibition attenuates post-MI remodelling. Matrix metalloproteinases activation can also occur intracellularly in hearts subjected to ischaemia/reperfusion, and it is responsible for the degradation of sarcomeric proteins, thus contributing to cardiomyocytes injury under oxidative stress. Accordingly, MMPs inhibitors can reduce reperfusion injury.

Therefore, MMPs inhibition could be a desirable pharmacological strategy in patients with acute ST-elevation myocardial infarction (STEMI) at a higher risk of LV remodelling, as those with LV dysfunction.

Doxycycline is the most potent MMPs inhibitor of the tetracycline class of antibiotics and exhibits MMPs inhibition in vivo at blood levels lower than those required for its antibacterial effect. It effectively crosses cell membranes, accumulates preferentially in cardiomyocytes, and inhibits mainly the MMP-9 and -2, which are largely up-regulated in the setting of animal and human remodelled hearts after MI. Accordingly, pre-clinical studies showed that timed treatment with doxycycline significantly attenuates post-infarct LV remodelling. Moreover, doxycycline shows a cardioprotective effect in isolated animals heart subjected to ischaemia/reperfusion injury. Given the clinical availability and well-recognized safety profile of tetracyclines, their use appears to represent an ideal starting point for clinical studies in patients with acute MI.

This study sought to determine the effects of doxycycline on LV remodelling in patients treated with primary percutaneous coronary intervention (PCI) for a first STEMI and LV dysfunction.

Methods

Study design and patients

The Early Short-term Doxycycline Therapy In Patients with Acute Myocardial Infarction and Left Ventricular Dysfunction to Prevent The Ominous Progression to Adverse Remodeling: the TIPTOP trial is a prospective, phase-2, single-centre, randomized, open-label controlled trial. All the patients older than 18 years with acute STEMI and LV ejection fraction (LVEF) < 40%, as calculated by the on-site operator at the first echo examination in the coronary care unit immediately after PCI, were considered eligible for the study. The diagnosis of acute STEMI was based on chest pain persisting > 30 min and < 12 h, and ST-segment elevation > 1 mm in at least two contiguous leads or presumably new left bundle branch block. Criteria for exclusion were cardiogenic shock, a previous MI or another disease potentially responsible for LV dysfunction or abnormal collagen turnover, life-limiting non-cardiac disease, allergy to tetracyclines.

Consenting, eligible patients were randomly assigned in a 1:1 ratio to receive doxycycline or standard care. All the patients were treated with primary PCI, including bare-metal stenting of the infarct-related artery (IRA), and received medical therapy for STEMI and LV dysfunction in accordance with standard and recommended practice. Doxycycline (Bassado; Pfizer Italia S.r.l.) was administered at 100 mg oral dose immediately after primary PCI and then every 12 h for 7 days. The antimicrobial dose we used ensures plasma levels of doxycycline similar to those obtained with higher doses used in the experimental model where the doxycycline has proved effective in inhibiting MMPs and preventing abdominal aortic aneurysm and post-infarction LV remodelling.

The therapeutic time window has been planned on the basis of an experimental work which showed a favourable effect of doxycycline treatment in the first 7 days after MI on 6-week LV remodelling.

A 12-lead ECG was recorded just before and at the end of the procedure. To evaluate the remodelling process two-dimensional echocardiographic (2D Echo) studies were performed at baseline (immediately after primary PCI) and at 6 months, DICOM standardized images were recorded and stored on a digital media, and sent to an independent blind off-site Core Laboratory (Core-Lab) for analysis. 99mTc-sestamibi-gated single-photon emission computed tomography (SPECT) was performed and analysed by two experts who were unaware of the treatment group assignments, to evaluate the final infarct size at 6-month follow-up.

Furthermore, a coronary angiography was repeated at 6 months for the evaluation of persistence of IRA patency. Blood samples for enzymatic evaluation (troponin I, creatine kinase, and creatine kinase-MB) were taken immediately after primary PCI and after 3, 6, 12, and 24 h.

The primary endpoint of the study was the percentage change from baseline to 6 months (% Δ) in echocardiographic LV end-diastolic volume index (LVEDVi). Secondarily, we evaluated the infarct size and infarct severity as assessed by 6-month 99mTc-sestamibi SPECT.

Randomization was performed with the use of a computer-generated randomization sequence. Treatment allocations were concealed until patients were enrolled.

The study protocol was approved by local ethical committee. Doxycycline was provided directly from the local hospital, and the manufacturer had no role in the study.

Procedures

Electrocardiographic analysis

The ST-segment elevation was measured at the J point with magnified calipers to the nearest 0.05 mV. For anterior STEMI, the Δ ST-segment elevation was measured from leads I, aVL, and V1-V6, and for non-anterior STEMI in leads II, III, aVF, V5, and V6. The Δ of ST-segment elevation immediately before primary PCI was considered as a surrogate of the area at risk.

Echocardiographic analysis

Ultrasound examination was performed with commercially available imaging systems (Philips IE-33, Amsterdam, The Netherlands). Two-dimensional echo and Doppler studies were performed to obtain measurements of LV volumes, ejection fraction, mitral inflow E- and A-wave velocity, lateral mitral annulus E‘- and A‘-wave velocity, and LV flow propagation velocity. The Core-Lab analysis was performed with a workstation-based system for 2D Echo visualization and image processing (Philips Xcelera R3.1L1, Amsterdam, The Netherlands). Details about the modality of acquisition and analysis of echocardiographic data have been reported elsewhere. The mean Core-Lab inter-reader variability value for LV volumes analysis was 6.1% (ICC 0.90 with standard error 6.3 mL) and intra-reader variability was 4.1% (ICC 0.93 with standard error 3.8 mL).

99mTc-sestamibi single-photon emission computed tomography analysis

Scintigraphic acquisition began 60 min after 99mTc-sestamibi injection (740 MBq), by the use of double-head gamma-camera equipped with high-resolution collimator, with a 180° rotation arc, 32 projection, 60 s per projection, 8 frames per heart cycle, and 64 × 64 matrices. Details about the modality of acquisition and analysis of scintigraphic data have been reported elsewhere.

Infarct severity, as a measure of infarct transmurality, was defined as the lowest ratio of minimal to maximal counts in the short-axis slices evaluated for infarct size; therefore, the lower the severity index the greater the infarct transmurality.
Statistical analysis
The sample size calculation was based on the following assumptions: (i) in myocardial infarction experimentally induced, doxycycline treatment (2–7 days post-MI) reduces LV dilatation at 6 weeks by 65% compared with control;18 (ii) in our previous study on patients with AMI successfully treated with primary PCI, those with LV dysfunction (LVEF < 40%) showed an average increase in the LVEDVi of 14 ± 16 mL/m² at 6-month follow-up.22 We hypothesized that treatment with doxycycline for the first 7 days after primary PCI would reduce the increase in the LVEDVi from baseline to 6-month >50% compared with that observed with the standard therapy in the control group. An estimated sample size of 110 patients (55 per group) would be needed to detect the difference with a statistical power >80% and a probability type I error of 0.05, considering an attrition rate of 10–15%.

Discrete data were summarized as frequencies, whereas continuous data were summarized as mean ± SD or median and interquartile range (IQR) when appropriate. The χ² test or Fisher’s exact test was used for comparison of categorical variables, and the unpaired and paired 2-tailed Student t test or Mann-Whitney-Wilcoxon rank-sum test were used to detect differences among continuous variables.

ANCOVA was used to test for equality the slopes of regression of % Δ LVEDVi on the 6-month 99mTc-sestamibi SPECT infarct size in the doxycycline and control groups. All tests were two-sided, and a P value < 0.05 was considered statistically significant. Analyses were performed with SPSS software, version 19 (IBM Corp, Somers, NY).

Results
Study patients
From May 2007 to February 2011, a total of 429 patients with STEMI were treated with primary PCI. We randomly assigned 110 of these patients to doxycycline treatment (55 patients) or control (55 patients). Figure 1 shows the flow chart of the study. The study groups were well matched in all baseline characteristics (Table 1).

Echocardiographic findings
From baseline to 6-month follow-up LVEDVi remained substantially unchanged in the doxycycline group, while it was significantly increased in the control group (0.3 ± 12.5 and 8.7 ± 15.5 mL, respectively, P = 0.004). Left ventricular end-systolic volume index (LVEDVi) slightly increased in the control group while was reduced in the doxycycline group (1.3 ± 13.3 and −4.5 ± 10.7 mL, respectively, P = 0.02). Consequently, the increase from baseline to the 6-month follow-up of LVEF was higher in the doxycycline group than in the control group (12.1 ± 11.7 and 7.5 ± 10.2%, respectively, P = 0.04) (Figure 2).

The primary endpoint (% Δ LVEDVi) was significantly lower in the doxycycline group than in the control group [0.4 (IQR: −16.0 to 14.2) and 13.4 (IQR: −7.9 to 29.3), respectively, P = 0.012] (Figure 3).

99mTc-sestamibi-gated single-photon emission computed tomography findings
Six-month 99mTc-sestamibi SPECT was performed in 46 patients (84%) of the doxycycline group and 45 patients (82%) of the control group; the final infarct size and infarct severity resulted smaller in the doxycycline group than in the control group (infarct size: 5.5% (IQR: 0 to 18.8%) vs. 10.4% (IQR: 0.3 to 29.9%), P = 0.052; infarct severity: 0.53 (IQR: 0.43 to 0.62) vs. 0.44 (IQR: 0.29 to 0.60), P = 0.014).

Angiographic findings
The 6-month angiographic follow-up rate was 85%. The IRA patency was observed in all patients of the doxycycline group and in all but one in the control group, and there was no difference in binary restenosis >50% between groups [12 of 46 (26%) patients in the doxycycline group and 11 of 42 (26%) patients in the control group].

Relationship between left ventricular remodelling and infarct size
In the control group, there was a significant correlation between % Δ LVEDVi and 99mTc-sestamibi SPECT (r = 0.65, P < 0.001), with a smaller slope of the regression line for the doxycycline group than for the control group (P = 0.01 by analysis of covariance) (Figure 4).

Clinical follow-up
The length of hospital stay was 6.1 ± 3.2 and 6.3 ± 3.4 days for the doxycycline group and the control group, respectively (P = 0.75). All the patients assigned to the doxycycline treatment received the drug and the adherence to therapy was fully respected. No side-effects secondary to doxycycline treatment were observed. The 6-month clinical follow-up rate was 100%. The seven patients who were missing for echocardiographic primary endpoint analysis were uneventful and the baseline characteristics were similar to the other analysed patients. Overall, 6 months mortality was 4.6% (5 of 110 patients), 1 patient (1.8%) in the doxycycline group and 4 patients (7.3%) in the control group. Four patients died of acute heart failure during the first month after index MI, and one patient died of ischaemic stroke at 5 months after MI. One patient in the control group had a non-fatal recurrent MI, and this patient was excluded from echocardiographic and scintigraphic evaluation. One patient (1.8%) in the doxycycline group and two patients (3.6%) in the control group had an ischaemic stroke; 4 of 54 patients in the doxycycline group (7.4%) and 7 of 51 patients in the control group (13.7%) had a worsening NYHA class III–IV and/or hospital readmission for congestive heart failure. Overall, the rate of composite of death, MI, congestive heart failure and stroke was higher in the control group than in the doxycycline group (25.5 vs. 10.9%, P = 0.04).

Discussion
This study shows that in patients with a first STEMI and LV dysfunction treated with primary PCI a timely short-term treatment with doxycycline significantly reduces LV remodelling.

Contrary to pre-clinical studies performed with broad-spectrum MMPs inhibitors,4–7 the only phase II clinical trial in patients with AMI, the Prevention of Myocardial Infarction Early Remodeling (PREMIER) trial,25 failed to show a treatment benefit of a selective MMPs inhibitor (PG11680) in remodelling process. However, this disappointing finding may be the result of important concerns of the study. In the PREMIER trial, the clinical dose of PG11680 was approximately four-fold lower than that reported to be effective for achieving a LV anti-remodelling effect observed in the pre-clinical studies.26 Moreover, MMPs inhibition was instituted too late
(54.4 ± 14.0 h post-MI) to counteract the infarct expansion, which is a major determinant of remodelling process, and was too much prolonged (90 days post-MI) and therefore potentially responsible for an adverse effect on LV remodelling process. The rationale for evaluating the ability of doxycycline to reduce post-MI remodelling was based on experimental evidences indicating that doxycycline is able to inhibit members of the MMPs family of endopeptidases, preferentially MMP-9 and -2, which are largely up-regulated in the setting of animal and human remodelled hearts after MI. In addition to inhibiting MMPs directly, tetracyclines also inhibit MMPs synthesis by modulating cytokine cascade, which plays an essential role in the post-infarct remodelling process. Emerging experimental evidences suggest that IL-1 blockade and deletion of the IL-1 type 1 receptor could favourably affect LV remodelling.

A time-dependent effect on modifying myocardial MMPs activity exists within the post-MI period with respect to LV remodelling, because an early short-term MMPs inhibition after experimental myocardial infarction confers a beneficial effect, while a prolonged MMPs inhibition is associated with an adverse LV remodelling. Results of pre-clinical studies, taken together, imply that the use of doxycycline in the first 7 days post-MI may yield improved LV remodelling, and this favourable effect is accompanied by the lack of suppression of inflammation.

Since our study is the first clinical study that evaluated the effects of doxycycline in post-infarction remodelling, on the basis of the above-mentioned
### Table 1  Baseline and procedural characteristics

<table>
<thead>
<tr>
<th></th>
<th>Doxycycline group (n = 55)</th>
<th>Control group (n = 55)</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69 ± 11</td>
<td>69 ± 12</td>
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<tr>
<td>Male sex</td>
<td>73</td>
<td>66</td>
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<tr>
<td>Hypertension</td>
<td>29</td>
<td>18</td>
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<tr>
<td>Diabetes</td>
<td>15</td>
<td>27</td>
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<tr>
<td>Dyslipidaemia</td>
<td>16</td>
<td>10</td>
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<tr>
<td>Heart rate (b.p.m.)</td>
<td>77 ± 15</td>
<td>81 ± 14</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>130 ± 31</td>
<td>128 ± 26</td>
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<tr>
<td>Killip class</td>
<td>1.91 ± 0.2</td>
<td>1.85 ± 0.2</td>
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<tr>
<td>Anterior myocardial infarction</td>
<td>95</td>
<td>89</td>
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<tr>
<td><strong>ST-elevation pre-PCI (mm)</strong></td>
<td></td>
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</tr>
<tr>
<td>Mean</td>
<td>16.8 ± 10.6</td>
<td>14.9 ± 8.8</td>
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<tr>
<td>Median</td>
<td>14 (8.9–12.1)</td>
<td>13.2 (6.9–18.8)</td>
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<tr>
<td><strong>ST-elevation post-PCI (mm)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>6.1 ± 5.1</td>
<td>5.9 ± 4.3</td>
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<tr>
<td>Median</td>
<td>4.8 (2–8.6)</td>
<td>4.4 (2.7–7.8)</td>
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<tr>
<td>LVEDVi (mL/m²)</td>
<td>48.4 ± 12.2</td>
<td>48.8 ± 14.1</td>
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<tr>
<td>Median</td>
<td>47 (40–56)</td>
<td>47 (38–61)</td>
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<tr>
<td>LVESVi (mL/m²)</td>
<td>30.5 ± 9.1</td>
<td>31.8 ± 11.4</td>
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<tr>
<td>Median</td>
<td>30 (24–35)</td>
<td>31 (23–37)</td>
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<tr>
<td>LVEF (%)</td>
<td>37.2 ± 7.5</td>
<td>35.6 ± 7.2</td>
</tr>
<tr>
<td>Median</td>
<td>38 (32–42)</td>
<td>35 (31–42)</td>
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<td>Left anterior descending artery</td>
<td>95</td>
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<td>Infarct-related artery TIMI flow grade 0–1</td>
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<td>Multi-vessel disease</td>
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<td>Procedural success</td>
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<tr>
<td>Multiple stenting</td>
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<tr>
<td>Number of stents</td>
<td>1.4 ± 0.6</td>
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<td>Stent length (mm)</td>
<td>24 ± 11</td>
<td>22 ± 11</td>
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<tr>
<td>Abciximab use</td>
<td>94</td>
<td>93</td>
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<tr>
<td>IRA TIMI flow grade 3 after PCI</td>
<td>100</td>
<td>100</td>
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<tr>
<td>Symptoms to door time (min)</td>
<td>223 ± 177</td>
<td>225 ± 228</td>
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<tr>
<td>Door to balloon time (min)</td>
<td>17 ± 15</td>
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<tr>
<td>Procedural time (min)</td>
<td>32 ± 16</td>
<td>32 ± 19</td>
</tr>
<tr>
<td>Ischaemia time (min)</td>
<td>273 ± 178</td>
<td>276 ± 237</td>
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<tr>
<td>Troponine I peak (ng/mL)</td>
<td>224 ± 214</td>
<td>255 ± 184</td>
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<tr>
<td>AUC of Troponin I (ng/mL)</td>
<td>3400 ± 3229</td>
<td>3957 ± 2611</td>
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<tr>
<td>Creatine kinase MB peak (IU/L)</td>
<td>278 ± 225</td>
<td>309 ± 219</td>
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<tr>
<td>AUC of creatine kinase MB (IU/L)</td>
<td>3920 ± 2904</td>
<td>4493 ± 3143</td>
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<tr>
<td>Aspirin</td>
<td>98</td>
<td>96</td>
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<td>ACE inhibitor/ARB antagonist</td>
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<td>Loop diuretics</td>
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Σ denotes sum. PCI, primary percutaneous coronary intervention; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; TIMI, thrombolysis in myocardial infarction; IRA, infarct related artery; AUC, area under curve; ACE, angiotensin-converting-enzyme; ARB, angiotensin II receptor blockers. Values are expressed as mean ± SD, or median [IQ range] or numbers (%).
experimental studies, we decided to plan a therapeutic time window of 7 days post-MI to allow doxycycline to counteract the early damage of the ECM while still allowing later processes, such as inflammation and wound healing, to proceed normally.

The absolute increase in the LVEDVi observed in the control group of the present study is consistent with that reported in other studies on patients at a higher risk of post-infarction LV remodelling.22,31 – 33 The magnitude of the change in the LVEDVi obtained with doxycycline compared with the control group reflects the high-risk profile of our study patients, and confirms the principle that it is precisely in the higher risk patients that we can clearly detect a benefit from an additional therapy. Of note, the results of our study are in line with the encouraging early results of IL-1 inhibition with anakinra, a recombinant human IL-1 receptor antagonist, recently reported by Abbate et al.34 in patients with STEMI.

In agreement with experimental data,10,19,35 in our study the patients receiving doxycycline showed a slight, not significant reduction of myocardial enzymes, and a lesser99mTc-sestamibi SPECT infarct size. Although several properties of doxycycline related to its ability to act as reactive oxygen species scavenger, anti-apoptotic, and MMPs inhibitor13 can explain these beneficial effects, this hypothesis remains speculative, although intriguing given that the indirect measures of the area at risk (pre-PCI ST-segment elevation) and myocardial reperfusion effectiveness (post-PCI TIMI 3 flow and ST-segment elevation) were not different between the two treatment-groups. However, since the infarct size is one of the major factors that promote LV remodelling, we further investigated this relationship. Of note, ANCOVA revealed a significant downward shift in the regression relationship between %ΔLVEDVi (the primary study endpoint) with the99mTc-sestamibi SPECT infarct size for the doxycycline group compared with the control group. This indicates that a significant greater increase in LV volumes occurred in the control group than in the doxycycline group for any given of definite infarct size.

Finally, patients enrolled in this study reported no side-effects attributable to therapy with doxycycline. We believe that this is
largely due to the relatively small number of patients studied, the short duration of treatment (7 days), and the safety of the dosage used (100 mg twice daily). This result is even less surprising when one considers that ~47 million new doxycycline prescriptions were dispensed over 5 years in the late 1990s in the USA, with an event rate of 13 per million.36

Study limitations
The trial is an open-label study; however, the primary echocardiographic endpoint was evaluated by an off-site independent Core-Lab while the scintigraphic analyses were performed and analysed by two experts who were unaware of the treatment group assignments.

Moreover, without an assessment of infarct size by perfusion imaging at baseline, a selection bias favouring doxycycline therapy arm cannot be excluded. However, the indirect measures of the area at risk and myocardial reperfusion effectiveness did not differ between groups, and, anyway, the favourable effects of doxycycline were independent of the final scintigraphic infarct size.

The patients were treated with standard-of-care therapy for STEMI, accordingly to the current ESC guidelines,37 with the exception of the mineralocorticoid antagonists (MRA) which were used in one-fourth of the patients with the indication to that specific treatment; this was in part due to the temporal trend of study enrolment that started in early 2007, almost 2 years before the implementation of the use of MRA in the ESC guidelines for STEMI patient.38 It is therefore possible that the magnitude of the benefit we have observed with doxycycline might be reduced by treating with a MRA all the patients with such indication.

Finally, it must be acknowledged that delayed contrast enhancement magnetic resonance imaging is more accurate than $^{99m}$Tc-sestamibi SPECT for the assessment of small infarct and infarct transmurality. However, despite a lower spatial resolution, SPECT is a validated method for measurements of infarct size.39

Conclusions
In this study, a timely administration of doxycycline in patients with STEMI and LV dysfunction was associated with a reduction in LV remodelling. These results should be considered preliminary and require confirmation in a larger clinical study.

Conflict of interest: none declared

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18. Garcia RA, Go KV. Villarreal FJ. Effects of timed administration of doxycycline or methylprednisolone in myocardial infarction remodeling inflammation and left ventricular remodeling in the rat heart. Mol Cell Biochem 2007;300:159–169.


