

# Minor Myocardial Damage During Percutaneous Coronary Intervention Does Not Affect Long-Term Prognosis

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**Introduction and objectives.** To determine whether long-term prognosis is affected by myocardial damage taking place during percutaneous coronary intervention (PCI).

**Methods.** The study included consecutive patients undergoing PCI. Those with elevated baseline cardiac marker levels were excluded. Cardiac markers were evaluated and an ECG was recorded before and 12 and 24 hours after PCI. Patients were divided into 3 groups after PCI according to their cardiac marker levels: no myocardial damage (ie, normal troponin and creatine kinase MB fraction [CK-MB]), minor damage (elevated troponin with normal CK-MB), and myonecrosis (elevated troponin and CK-MB). The occurrence of death, myocardial infarction, or repeat revascularization during follow-up was recorded.

**Results.** Minor myocardial damage associated with PCI was observed in 127 (16.8%) of the 757 patients included in the study and myonecrosis, in 46 (6.1%). During a follow-up of 45 (14) months, cardiac events occurred in 151 (19.1%) patients. Mortality during follow-up was significantly higher in patients with myonecrosis (13%) than in the other 2 groups (4.8% and 3.9%; log rank, 6.83;  $P=.032$ ). No difference was observed in the rate of myocardial infarction or repeat revascularization during follow-up.

**Conclusions.** Minor myocardial damage during PCI had no effect on long-term prognosis. In contrast, myonecrosis was associated with increased mortality. Consequently, the CK-MB level should be measured after all PCIs because of its prognostic implications, and strategies for reducing the risk of myonecrosis developing should be implemented.

**Key words:** Coronary angioplasty. Myocardial infarction. Creatine kinase. Troponin. Prognosis.

**El daño miocárdico mínimo durante el intervencionismo coronario percutáneo no influye en el pronóstico a largo plazo**

**Introducción y objetivos.** Evaluar el pronóstico a largo plazo del daño miocárdico producido durante el intervencionismo coronario percutáneo (ICP).

**Métodos.** Incluimos una serie de pacientes consecutivos a quienes se practicó ICP, excluyendo a los que ya presentaban basalmente elevación de marcadores cardíacos. El ECG y los marcadores de daño miocárdico se evaluaron antes y a las 12 y 24 h tras el procedimiento. Según el valor de dichos marcadores, se clasificó a los pacientes en tres grupos: ausencia de daño miocárdico (troponina y CK-MB normal), daño miocárdico mínimo (elevación del valor de troponina, con CK-MB normal) y mionecrosis (elevación de troponina I y CK-MB). Muerte, infarto de miocardio y nueva revascularización fueron evaluados durante el seguimiento.

**Resultados.** De 757 pacientes incluidos, en 127 (16,8%) se detectó daño miocárdico mínimo asociado al procedimiento y en 46 (6,1%) mionecrosis. Durante un seguimiento de  $45 \pm 14$  meses, 151 (19,1%) pacientes sufrieron eventos cardíacos. Los pacientes que presentaron mionecrosis tuvieron un significativo incremento de la mortalidad durante el seguimiento (13%) respecto a los otros dos grupos (el 4,8 y el 3,9%; *log rank test*, 6,83;  $p = 0,032$ ). No se detectaron diferencias en la tasa de IAM o nueva revascularización en el seguimiento.

**Conclusiones.** El daño miocárdico mínimo durante el intervencionismo no influye en el pronóstico a largo plazo. Por contra, la mionecrosis se asocia a un incremento de mortalidad. Este hecho implica la necesidad de determinar la CK-MB tras todo ICP debido a su implicación pronóstica y la aplicación de estrategias que disminuyan la aparición de mionecrosis.

**Palabras clave:** Angioplastia coronaria. Infarto de miocardio. Creatinina. Troponina. Pronóstico.

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## ABBREVIATIONS

AMI: acute myocardial infarction  
 CK-MB: creatine kinase MB fraction  
 MACE: major adverse cardiac events  
 MMD: minor myocardial damage  
 PCI: percutaneous coronary intervention

## INTRODUCTION

One of the most serious complications following percutaneous coronary intervention (PCI) is acute myocardial infarction (AMI). Traditionally, it has been defined in terms of creatine kinase (CK) and creatine kinase MB fraction (CK-MB) elevation 3 times greater than normal, with or without the appearance of new Q waves after PCI. This elevation is of clinical importance as it is associated with reduced survival during follow-up<sup>1-7</sup> and can be detected as a structural cardiac lesion by magnetic resonance imaging.<sup>8</sup>

More recently, in the detection of myocardial damage, elevation of cardiac troponin (I or T isoforms) has proved a more sensitive marker than CK both spontaneously and after PCI.<sup>9-11</sup> Several studies have demonstrated that troponin elevation in patients with acute coronary syndrome is associated with worse prognosis.<sup>12-14</sup> However, current data on prognostic implications of post-PCI troponin elevation are controversial.<sup>15-24</sup> A document jointly edited by the European Society of Cardiology and the American Society of Cardiology define troponin elevation >3 times the 99 percentile value as procedure-related myocardial infarction.<sup>25</sup>

The objective of our study was to determine the prognostic implications of isolated post-PCI troponin elevation with normal CK-MB, in comparison with patients with no myocardial damage, and patients with CK-MB elevation.

## METHODS

### Selection of Patients

We included all consecutive patients with significant coronary stenosis who had undergone PCI. We excluded those with cardiac marker elevation (troponin or CK-MB) immediately before PCI, and those in the acute phase of myocardial infarction with persistent ST-segment elevation (primary or emergency PCI). All patients underwent coronary angiography at >24 h following the last episode of angina.

## Percutaneous Coronary Intervention

All patients were pretreated with oral aspirin and a thienopyridine (ticlopidine or clopidogrel) in accordance with the established protocol: 250 mg acetylsalicylic acid (ASA), 500 mg ticlopidine, or 300 mg clopidogrel, at 2-6 h prior to the procedure. All percutaneous revascularization procedures were performed using femoral access. Prior to balloon dilatation, an intravenous bolus of 250 mg ASA, an intravenous bolus of 100 IU/kg weight unfractionated heparin, and an intracoronary bolus of 200 µg nitroglycerin were administered. Postprocedure, no additional heparin was administered. Patients received intravenous nitroglycerin for 6 h until catheter introducer sheaths were withdrawn. Oral aspirin was recommended indefinitely and the same thienopyridine that had been administered prior to the procedure was continued for 1 month if a bare metal stent had been deployed. Angiographic success was defined as coronary artery residual stenosis <50% after balloon angioplasty or <20% after stent implantation, with normal TIMI 3 coronary flow.

### Electrocardiogram

To rule out Q wave AMI during the procedure, a 12-lead ECG was performed before and at 24 h postprocedure. Additional ECGs were conducted in patients with postprocedural chest pain.

### Biochemical Markers

Pre-PCI blood samples were taken to analyze baseline myocardial damage marker values as this was an exclusion criterion. We measured 2 cardiac markers, CK-MB and troponin I, before and at 12 h and 24 h postprocedure. Troponin I was determined using the RxL Dimension analyzer (Dade Behring). We defined troponin I elevation as >3 times our laboratory's upper limit for normal (normal, <0.2 µg/L), following the universal definition of AMI. We defined CK-MB elevation as 3 times our laboratory's upper limit for normal (normal, <0.42 µkat/L), following European Society of Cardiology recommendations.

### Definition of Myocardial Damage Groups

We used postprocedural troponin I and CK-MB results to define 3 patient groups: no myocardial damage (normal troponin I and CK-MB); minor myocardial damage (MMD) (elevated troponin I and normal CK-MB); and myonecrosis (simultaneous elevation of troponin I and CK-MB).

## Clinical Follow-up

Prospectively, patients were attended at our outpatient clinic or they, or close family, were contacted by telephone. When events occurred during follow-up, we reviewed clinical records. Major adverse cardiac events (MACE) recorded for analysis were: death, myocardial infarction, and the need for repeat revascularization (new PCI or coronary revascularization surgery).

## Statistical Analysis

Discrete variables are given as numbers and percentages, and continuous variables as mean (SD). Statistical analysis was with SPSS-PC 12.0. We compared discrete variables with  $\chi^2$  or the Fisher exact test, if necessary, and continuous variables with the Student *t* test. We constructed Kaplan-Meier survival curves to analyze possible differences between groups using the log rank test. To determine possible independent factors related to prognosis during follow-up, we conducted Cox logistic regression analysis. In all instances,  $P < .05$  was considered statistically significant.

## RESULTS

From 2001 thru 2003, 769 PCIs that met our inclusion criteria were performed. Twelve patients were lost to follow-up (8 with no myocardial damage, 3 with MMD, and 1 with myonecrosis), leaving 757 patients in the study group. Patients' baseline clinical, angiographic and procedural characteristics are in Table 1. Mean age was 63 (10) years, 74.8% were men, and 32% had diabetes. Overall ventricular function was conserved even though 29% presented previous AMI. Forty-eight percent presented significant lesions in  $>1$  epicardial coronary artery. We performed PCI on 1014 lesions (1.3 lesions/procedure) with stent implantation in 91.3% of procedures. Angiographic success was achieved in 95.3% of patients.

Postprocedure, we found MMD in 127 (16.8%) patients and myonecrosis in 46 (6.1%), with no myocardial damage marker elevation in the remaining 584 (77.1%). Table 2 presents myocardial damage marker data for each group. Table 3 presents differences in myocardial damage marker values between the 3 groups. We detected greater incidence of pre-PCI kidney failure in patients with myocardial damage (both MMD and myonecrosis groups). We found no differences in patients' baseline angiographic characteristics. However, we found a series of differences in procedural characteristics between patients with MMD and patients with myonecrosis. Furthermore, we found

**TABLE 1. Baseline Clinical, Angiographic and, Procedural Characteristics of 757 Patients Included**

Clinical variables	
Age, mean (SD), y	63 (10)
Men	567 (74.9)
Smokers	451 (59.6)
High blood pressure	421 (55.6)
Diabetes mellitus	243 (32.1)
Peripheral vascular disease	80 (10.6)
Hypercholesterolemia	518 (68.4)
Kidney failure	36 (4.8)
Previous AMI	221 (29.2)
Previous PCI	165 (21.8)
Previous coronary surgery	43 (5.7)
Acute coronary syndrome	490 (64.7)
Angiographic variables	
Native coronary artery	745 (98.4)
Type B2-C lesion	498 (65.8)
Vessels with $>50\%$ lesions, mean (SD)	1.7 (0.7)
Ejection fraction, mean (SD), %	60 (12)
Procedural variables	
Procedure time, mean (SD), min	49 (23)
Side branch occlusion	47 (6.2)
No-reflow phenomenon	8 (1.1)
Preprocedural anti-GPIIb/IIIa	36 (4.8)
Final angiographic success	722 (95.4)

AMI indicates acute myocardial infarction; anti-GPIIb/IIIa, glycoprotein IIb/IIIa inhibitors; PCI, percutaneous coronary intervention. Data are given as n (%) or mean (SD).

a higher percentage of complications during the procedure in patients with MMD and in patients with myonecrosis. Side branch occlusion (RR=4.3 [1.4-12.7]) and the no-reflow phenomenon (RR=15.5 [2.7-88.9]) were the only variables that independently associated with myonecrosis.

We found no major events in patients during hospitalization.

During a mean follow-up of 45 (14) months, 151 (19.9%) patients experienced MACE. Thirty-seven patients (4.9%) died, 33 (4.4%) presented AMI, and 100 (13.2%) were clinically indicated for repeat revascularization: 79 (10.6%) underwent another PCI and 21 (2.6%), coronary artery by pass graft. Mortality was due to cardiovascular causes in 34 (91.8%) patients. Long-term follow-up analysis with Kaplan-Meier survival curves is presented in Figure 1. In patients with myonecrosis during PCI, the survival rate (86%) was significantly lower than in patients with MMD (96.1%) or patients with no damage (95.2%; log rank test, 6.83;  $P=.032$ ). The difference in survival between patients with MMD and those with no myocardial damage was not statistically significant. We observed no differences between other components of MACE (AMI or repeat revascularization) during follow-up (Figure 2).

**TABLE 2. Myocardial Damage Marker Levels Pre- and Post Procedure**

	No Damage (n=584)	MMD (n=127)	Myonecrosis (n=46)
Troponin I (µg/L)			
Baseline	0.1 (0-0.2)	0.1 (0-0.2)	0.1 (0-0.2)
At 12 h	0.2 (0-0.5)	1.4 (0.3-10.4)	16.4 (0.3-268)
At 24 h	0.2 (0-0.5)	1.8 (0.7-10.8)	19 (0.4-294)
CK-MB (µkat/L)			
Baseline	0.2 (0.1-0.4)	0.2 (0.1-0.4)	0.2 (0.1-0.4)
At 12 h	0.3 (0.1-0.6)	0.3 (0.1-0.7)	2.1 (1.2-18.6)
At 24 h	0.3 (0.1-0.6)	0.3 (0.1-0.7)	2.7 (1.2-18.9)

CK-MB indicates creatine kinase MB fraction; MMD, minor myocardial damage.  
Values are given as mean (range).

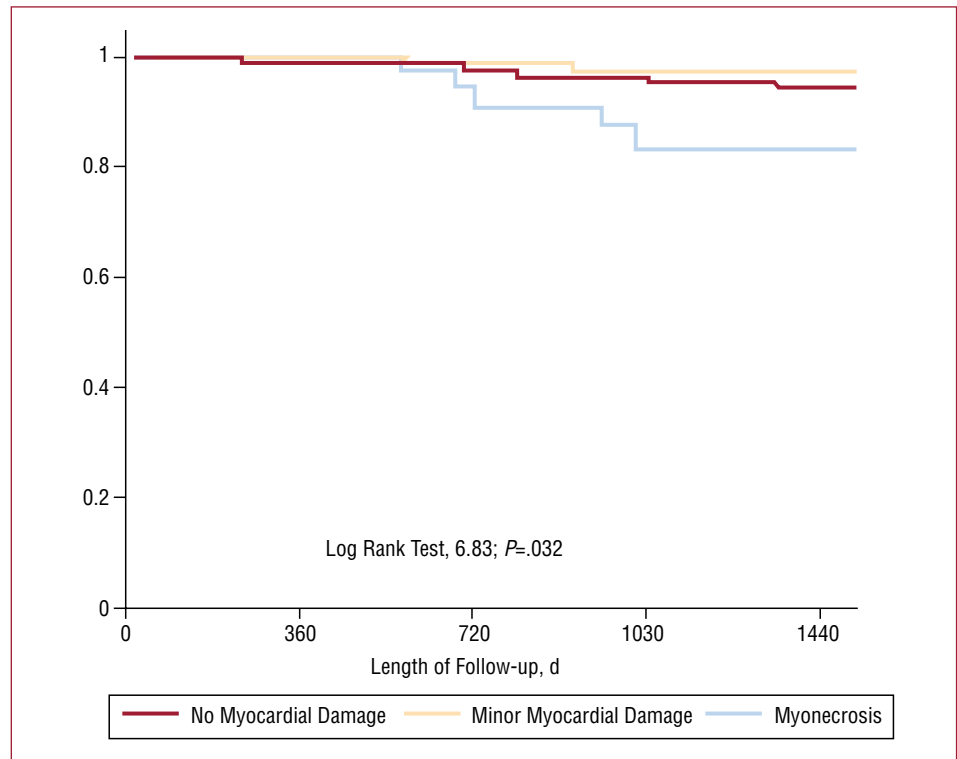
**TABLE 3. Differences in Clinical, Angiographic, and Procedural Characteristics Between the 3 Patient Groups With Respect to Degree of Myocardial Damage**

	No Damage (n=584)	MMD (n=127)	Myonecrosis (n=46)	P
Clinical variables				
Age, mean (SD), y	63 (10)	62 (10)	63 (10)	NS
Men	431 (73.8)	96 (75.6)	39 (84.5)	NS
Smokers	344 (58.9)	79 (62.2)	28 (60.9)	NS
High blood pressure	323 (55.3)	76 (59.8)	21 (45.7)	NS
Diabetes mellitus	197 (33)	36 (28.6)	15 (32.6)	NS
Peripheral vascular disease	45 (9.7)	28 (11.2)	7 (15.2)	NS
Hypercholesterolemia	408 (69.9)	84 (66.1)	28 (60.9)	NS
Kidney failure	23 (3.9)	10 (7.9)	3 (6.5)	.02
Previous AMI	150 (25.7)	32 (25.2)	11 (23.9)	NS
Previous PCI	133 (22.8)	19 (15)	11 (23.9)	NS
Previous coronary surgery	33 (5.7)	6 (4.7)	4 (8.7)	NS
Acute coronary syndrome	376 (64.4)	90 (70.9)	25 (54.3)	NS
Angiographic variables				
Native vessel	574 (98.3)	125 (98.4)	45 (97.8)	NS
Presence of thrombus	61 (10.4)	15 (11.6)	7 (15.3)	NS
Ulcerated lesion	37 (8)	12 (4.9)	3 (6.5)	NS
Bifurcated lesion	138 (23.6)	24 (18.9)	10 (22.2)	NS
Vessels with lesions >50%	1.7 (0.7)	1.7 (0.8)	1.7 (0.8)	NS
Ejection fraction, %	60 (11)	60 (11)	57 (11)	NS
Procedural variables				
Procedure time, min	49 (22)	50 (21)	51 (27)	NS
Side branch occlusion	25 (4.3)	13 (10.2)	9 (19.6)	<.001
No-reflow phenomenon	2 (0.3)	2 (1.6)	4 (8.7)	.001
Preprocedural anti-GPIIb/IIIa	22 (3.8)	12 (9.4)	2 (4.3)	.005
Number of lesions treated	1.3 (0.5)	1.4 (0.6)	1.4 (0.6)	NS
Inflation time, s	67 (22)	68 (25)	66 (26)	NS
Length of stent implanted, mm	20 (10)	22 (11)	22 (8)	NS
Final angiographic success	553 (94.7)	125 (98.4)	43 (93.5)	NS

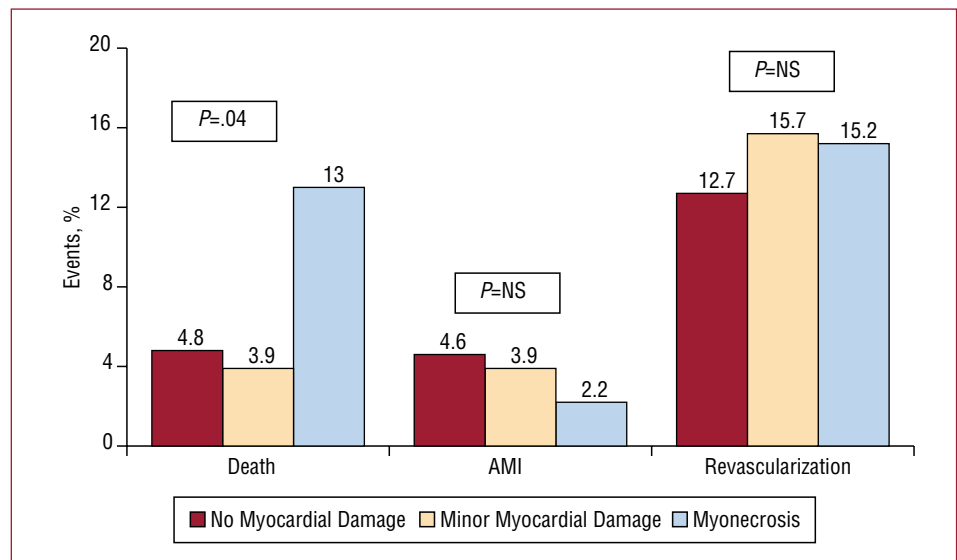
AMI indicates acute myocardial infarction; anti-GPIIb/IIIa, glycoprotein IIb/IIIa inhibitors; MMD, minor myocardial damage; PCI, percutaneous coronary intervention.  
Data are given as n (%) or mean (SD).

We also analyzed independent predictive factors associated with mortality during follow-up. In the model, we included baseline clinical characteristics (age, gender, cardiovascular risk factors, indication for revascularization), angiographic characteristics (number of diseased vessels, ejection fraction), and

periprocedural myocardial damage (myonecrosis, MMD, no myocardial damage). Isolated troponin elevation showed no association with mortality during follow-up so, adjusting for the previously mentioned factors, the risk of mortality in patients with MMD was 0.9 (95% confidence interval [CI],



**Figure 1.** Survival curves of the 3 patient groups differentiated by degree of myocardial damage during the percutaneous coronary intervention.



**Figure 2.** Cardiac events during follow-up in each of the 3 patient groups with respect to the degree of myocardial damage during percutaneous coronary intervention. AMI indicates acute myocardial infarction.

0.8-2.2). Results of multivariate analysis are in Table 4. These show that 3 of the factors associated with mortality during follow-up are clinical characteristics that patients presented prior to the procedure and which were not modifiable: ie, kidney failure, diabetes mellitus, and history of high blood pressure. In contrast, the only procedural factor related to long-term prognosis was simultaneous elevation of both myocardial damage markers.

## DISCUSSION

We present the results of a series of consecutive patients undergoing PCI at our center. To ensure that any postprocedural increase in cardiac markers was exclusively PCI-related, we only included patients with stable coronary disease or previously stabilized unstable coronary disease with normal cardiac markers before PCI.



**TABLE 4. Independent Predictors Associated With Long-Term Mortality**

	RR	95% CI
Kidney failure	6.3	2.6-15
Myonecrosis during PCI	3	1.2-7.7
Diabetes mellitus	1.8	1.1-3.6
High blood pressure	1.7	1.1-3.7

CI indicates confidence interval; PCI, percutaneous coronary intervention; RR, relative risk.

Our study differs from previously published work in that it is the first to combine both myocardial damage markers so as to facilitate the definition of 3 patient groups (no myocardial damage, MMD, and myonecrosis) on the basis of the results. Thus, we can clearly state that MMD was not associated with worse prognosis in patients with no myocardial damage post-PCI. In contrast, patients with myonecrosis during PCI showed a diminished survival rate at 3 years mean follow-up.

### Myonecrosis

All published data are consistent in considering that post-PCI CK-MB elevation is related to increased mortality during follow-up.<sup>1-5</sup> A linear relation between the degree of CK-MB elevation and mortality detected during follow-up has been reported.<sup>6,7</sup> Therefore, diagnosis of myocardial infarction defined as post-PCI CK-MB elevation has substantial prognostic implications. The magnitude of the increase that is considered the cutoff is arguable, but >3 times the upper limit for normal discriminates between patients with different long-term survival prospects.

### Minor Myocardial Damage

Troponin I is a more sensitive marker of myocardial damage than CK-MB,<sup>9,10</sup> and a clear relation exists between troponin elevation and prognosis in patients hospitalized for acute coronary syndrome.<sup>12-14</sup> In contrast, the prognostic implications of post-PCI troponin elevation are unclear. Large-scale studies, such as those reported by Fuchs et al<sup>15</sup> (n=1129), Cavallini et al<sup>16</sup> (n=3494) and Kini et al<sup>17</sup> (n=2873), showed that any increase in post-PCI troponin has no prognostic implications during mid- or long-term follow-up, which coincides with the findings of the present study. Nallamothu et al<sup>18</sup> (n=1157, with 960 patients in the follow-up) showed that only very substantial troponin elevation (>8 times the cutoff point) associates with reduced long-term survival. Small-scale studies have shown similar results with no prognostic implications for post-PCI survival.<sup>19-21</sup>

All these studies have analyzed the prognostic value of myocardial damage determined only by measuring post-PCI troponin. In this respect, they differ from our study because they include patients with very different degrees of myocardial damage in the same group. In our study, adding CK-MB values enables us to distinguish between 2 groups of patients: those with minimal damage and whose prognosis does not differ from that of patients with no myocardial damage observed during the procedure, and those with myonecrosis (major myocardial damage) and whose prospects for survival during follow-up are worse.

A range of data on prognostic implications of post-PCI troponin elevation has been reported. In the SYMPHONY study,<sup>22</sup> Cantor et al analyzed the evolution of 481 patients with acute coronary syndrome. Of these, only 151 had negative baseline troponin and they could be compared with the patients in our series. Patients with elevated post-PCI troponin presented greater incidence of death or myocardial infarction during short-term follow-up (90 days). Another important difference with our series was the type of patient analyzed: all patients included in the study had acute coronary syndrome and the follow-up was very short. An explanation for this difference in data can be found in Fuchs et al,<sup>15</sup> who showed that post-PCI troponin elevation increases the short-term risk of complications (intra-hospital complications), but does not increase mid-term (8 months follow-up) adverse clinical results.

Hermann et al<sup>23</sup> showed that after elective stent implantation, positive troponin T identified patients at risk of worse long-term results. Troponin T analysis was conducted quickly at the patient's bedside. With this test, post-PCI troponin T elevation was detected in 17.3% of patients, considerably fewer than in our patients with myocardial damage and in those reported elsewhere.<sup>16-19</sup> In a group of 1949 patients, Prasad et al<sup>24</sup> showed that troponin T elevation, which occurred in 19.6% of patients, had clear prognostic implications for mortality and incidence of myocardial infarction at 2 years follow-up. Moreover, troponin elevation was shown to be independently related to long-term mortality. These data indicate the lower sensitivity of troponin T versus troponin I in the detection of post-PCI myocardial damage, means that it detects greater degrees of myocardial damage and entails prognostic implications for death and AMI during follow-up.

Detection of troponin I post-PCI has high sensitivity, raising doubts as to whether a small increase in troponin I without concomitant post-PCI CK-MB elevation does imply worse prognosis. In our series, we found myonecrosis associates with substantial alterations in coronary circulation in a

specific territory such as the no-reflow phenomenon or side branch occlusion, causing structural damage in the myocardium that can be detected by magnetic resonance imaging, can cause some deterioration of cardiac function, and can affect patients' subsequent prognosis. On the other hand, isolated troponin elevation has not been associated with clinical phenomena, so its cause mechanism must differ and, therefore, reveal smaller myocardial lesions that would not alter long-term prognosis. Consequently, only substantial troponin elevation would affect long-term prognosis, as shown by Nallamothu et al.<sup>18</sup>

Myonecrosis is, then, the only procedure-related factor that independently associates with long-term prognosis. Therefore, we should apply all strategies aimed at reducing it, as demonstrated by pretreatment with beta blockers,<sup>26</sup> statins,<sup>27</sup> glycoprotein IIb/IIIa inhibitors,<sup>28</sup> or the preprocedural detection of aspirin-resistance.<sup>29</sup>

## Limitations

This is an observational study conducted between 2001 and 2003, when troponin I was used as a marker of myocardial damage. Most patients included in the study presented acute coronary syndrome, which was the clinical condition motivating their admission. Appropriate medical treatment and treatment strategies for these patients have since undergone substantial changes. This can particularly be seen in the decreasing use of glycoprotein IIb/IIIa inhibitors, and pretreatment with clopidogrel.

## CONCLUSIONS

In a group of patients with stable coronary disease or unstable coronary disease with negative myocardial damage markers prior to the procedure, troponin elevation without CK-MB elevation during PCI does not associate with adverse cardiac events during long-term follow-up, whereas simultaneous troponin I and CK-MB elevation does associate with increased mortality during follow-up. This indicates the need to determine CK-MB after all PCIs in order to determine its influence on the prognosis of PCI-related myocardial damage.

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