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Impact of periprocedural myonecrosis on clinical events after implantation of drug-eluting stents

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Abstract

Background: High level of creatine kinase myocardial band isoenzyme (CK-MB) elevation has been associated with late mortality after coronary intervention. We sought to evaluate the impact of periprocedural myonecrosis on clinical events in patients undergoing drug-eluting stents (DES) implantation.
Methods: A total of 1807 patients (2550 lesions) with successful DES implantation were followed for mean duration of 13±7 months. Patients with acute myocardial infarction and those with elevated CK-MB at baseline were excluded. Based on the CK-MB levels after stenting, patients were classified into three groups: group I: normal CK-MB (n=1429, 79.1%), group II: 1 to 5 times normal CK-MB (n=263, 14.6%), and group III: >5 times normal CK-MB (n=115, 6.4%). Major adverse cardiac events (MACE) were defined as cardiac death, myocardial infarction, and target lesion revascularization.
Results: With increasing levels of periprocedural CK-MB, there was an increased incidence of MACE (5.0% in group I vs. 6.1% in group II vs. 10.4% in group III, p=0.010) and cardiac death (0.5% in group I vs. 1.1% in group II vs. 2.6% in group III, p=0.016). By multivariate analysis, periprocedural peak CK-MB level was independent predictor of MACE (hazard ratio 1.01, 95% confidence interval 1.00 to 1.03; p=0.044).
Conclusions: Periprocedural myonecrosis was significantly associated with subsequent adverse clinical events after DES implantation.

Keywords: Creatine kinase; Coronary artery disease; Stent

1. Introduction

Myonecrosis occurs in up to 30% of patients after percutaneous coronary intervention (PCI) in spite of major advance in technology and pharmacotherapy [1–4]. Several studies have reported that PCI leading to creatine kinase myocardial band isoenzyme (CK-MB) elevation was associated with an adverse long-term clinical outcomes, including death [4–6]. However, some reports have shown that CK-MB elevation of modest degree after PCI has not been related with clinical consequences [7,8]. Thus, we sought to evaluate the clinical consequence of periprocedural CK-MB elevation in a large cohort of patients undergoing planned implantation of drug-eluting stents (DES), and to define whether it is an independent predictor of poor clinical outcomes in DES era.

2. Methods

2.1. Study population

A total of 1807 patients (2550 lesions) who underwent successful DES implantation between September 2003 and March 2005 were followed for mean duration of 13±7 months. Stents used in this study included sirolimus-eluting stents (Cypher, Cordis Corp., Johnson & Johnson, Miami, Florida) in 1276 patients with 1725 lesions and paclitaxel-eluting stents (Taxus, Boston Scientific Corp., Natick, Massachusetts) in 531 patients with 825 lesions. Exclusion criteria were acute myocardial infarction and elevated CK-MB at baseline, and

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Table 1
Baseline clinical characteristics by CK-MB level

Characteristics	Group I (n=1429)	Group II (n=263)	Group III (n=115)	p-value
Age	62.6±9.8	63.0±9.6	63.3±9.6	0.547
Male sex	993 (69.5)	170 (64.6)	78 (67.8)	0.267
Smoking	407 (28.5)	62 (23.6)	35 (30.4)	0.614
Hypertension	834 (58.7)	162 (62.3)	68 (59.1)	0.275
Diabetes mellitus	432 (30.4)	75 (28.8)	30 (26.1)	0.321
Hypercholesterolemia	138 (20.9)	20 (18.9)	12 (26.1)	0.693
Previous PCI	347 (24.3)	65 (24.7)	26 (22.6)	0.848
Previous CABG	40 (2.8)	9 (3.4)	0	0.312
Clinical presentation				0.078
Stable angina	866 (60.6)	134 (51.0)	68 (59.1)	
Unstable angina	563 (39.4)	129 (49.0)	47 (40.9)	
Multivessel disease	718 (50.3)	184 (70.0)†	94 (81.7)†	<0.001
Use of Gp IIb/IIIa inhibitor	16 (1.1)	9 (3.5)	10 (9.2)†	<0.001
Use of statin	87 (13.2)	12 (11.3)	8 (17.4)	0.217
LV ejection fraction, %	58.4	59.4	59.8	0.324

Data shown as number (%) or mean±SD. †p-value <0.05 vs. group I. CABG = coronary artery bypass graft surgery; LV = left ventricular; Gp = glycoprotein; PCI = percutaneous coronary intervention.

contraindication to antiplatelet agents. All patients gave written informed consent to the procedure.

2.2. Definitions

CK-MB was measured at baseline before the procedure and at 6 h after the procedure. If the CK-MB level was elevated after the procedure, it was monitored every 6 h until it came back to normal values. In patients with normal post-PCI CK-MB level, additional measurement was done if there were symptoms or signs of ongoing ischemia. Absolute CK-MB levels were determined by sandwich immunoassay (normal <5 ng/ml) (Bayer corporation, Tarrytown, NY). Patients were classified according to the peak CK-MB values into three groups: group I: no CK-MB elevation following the procedure, group II: 1 to 5 times normal CK-MB (5 to 25 ng/ml), and group III: >5 times normal CK-MB (>25 ng/ml).

Cardiac death, nonfatal myocardial infarction, and target lesion revascularization (TLR) were considered as major adverse cardiac events (MACE). TLR was defined as any repeat PCI or coronary artery bypass graft surgery of the target lesion.

2.3. Stenting procedure and adjunctive pharmacotherapy

Stenting procedure was performed using a standard femoral approach, and guide wires were usually used to cross the lesion. After predilation, the stents were deployed by inflating the stent delivery balloon at nominal pressure and, if necessary, adjunct high-pressure balloon dilation was performed to achieve angiographic optimization (residual diameter stenosis <30%). Premedication consisted of aspirin (200 mg/day) and clopidogrel (300 mg loading) before PCI. A bolus of 8000 U heparin was administered after sheath insertion with a repeat bolus to keep an activated clotting time ≥250 s. After the intervention, the patients received aspirin (200 mg/day) indefinitely and clopidogrel (75 mg/day) for at least 6 months. The use of glycoprotein IIb/IIIa inhibitors was left to the operator's discretion.

2.4. Angiographic analysis

For quantitative analysis, the angiograms taken just before and after the procedure were selected for each patient. All measurements were performed in two orthogonal views after intra-coronary injection of 0.2 mg of nitroglycerin. An end-diastolic frame in the projection best showing the lesion severity was selected. Quantitative coronary angiographic (QCA) analysis was performed by on-line analysis system (CAAS QCA V2.0.1, Pie Medical Imaging B.V., Netherlands).

2.5. Statistical analysis

Categorical variables are presented as absolute numbers and percent values. Continuous variables are expressed as mean±standard deviation (SD). Multiple group comparisons for categorical variables were performed using Pearson's chi-square test. One-way analysis of variance was used to determine differences of continuous variables in the three groups. Post hoc comparison was performed using Turkey's honestly significant differences test. Predictors of MACE and cardiac death were obtained using Cox's proportional hazard model and expressed as hazard ratios (HR) and 95% confidence intervals (CI). A p-value of <0.05 was considered statistically significant. All calculations were done with SPSS for Windows (SPSS version 12.0 Inc., Chicago, Illinois).

3. Results

3.1. Baseline patient and lesion characteristics

We studied 1807 patients who underwent successful implantation of DES (2550 lesions). Two hundred sixty-three

Table 2
Angiographic lesion characteristics by CK-MB level

Characteristics	Group I (1941 lesions)	Group II (420 lesions)	Group III (189 lesions)	p-value
Target coronary vessel				0.372
Left anterior descending	967 (50.7)	197 (47.6)	83 (45.6)	
Left circumflex	285 (14.9)	70 (16.9)	39 (21.4)	
Right	503 (26.4)	118 (28.5)	42 (23.1)	
Left main	142 (7.4)	25 (6.0)	17 (9.3)	
Graft	10 (0.5)	4 (1.0)	1 (0.5)	
ACC/AHA type B2/C lesion	1330 (68.5)	336 (80.0)†	151 (79.9)†	<0.001
Lesion length	25.0±14.2	30.8±16.0†	30.5±16.1†	<0.001
Chronic total occlusion	114 (6.1)	16 (3.9)	12(6.7)	0.517
In-stent restenosis	220 (11.8)	35 (8.6)	16 (8.8)	0.315
Ostial	158 (8.5)	31 (7.6)	12 (6.7)	0.329
Bifurcation	330 (17.7)	68 (16.6)	30 (16.6)	0.584

Data shown as numbers (%) or mean±SD. †p-value <0.05 vs. group I. ACC/AHA = American College of Cardiology/American Heart Association.

Table 3
Procedural characteristics by CK-MB level

Characteristics	Group I (1941 lesions)	Group II (420 lesions)	Group III (189 lesions)	*p*-value
Balloon/artery ratio	1.23±0.16	1.25±0.18	1.26±0.16	0.152
Maximal inflation pressure (atm)	15.9±3.9	15.8±3.8	15.7±3.9	0.589
Stents per lesion	1.3±0.6	1.6±0.8†	1.5±0.7†	<0.001
Stent length per lesion (mm)	31.3±17.9	37.6±20.5†	38.6±9.0†	<0.001
Type of stent				0.247
Use of cypher stent	1285 (66.2)	309 (73.6)	131 (69.3)	
Use of taxus stent	656 (33.8)	111 (26.4)	58 (30.7)	

Data shown as numbers (%) or mean±SD. †*p*-value <0.05 vs. group I.

patients (14.6%) had an intermediate postprocedural CK-MB elevation (1 to 5 times normal) and 115 (6.4%) patients sustained a CK-MB elevation >5 times normal. Baseline clinical characteristics are presented in Table 1. Patients in group I had lesser multivessel coronary involvement ($p<0.001$) compared with patients in group II or III. Patients in group III received glycoprotein IIb/IIIa inhibitor more frequently than in group I ($p<0.001$). Use of statin or cilostazol was not different between the three groups (p=NS). Angiographic lesion characteristics are shown in Table 2. Patients in group II and III had more American College of Cardiology/American Heart Association B2/C lesions ($p<0.001$) and longer lesion length ($p<0.001$) than patients in group I.

3.2. Procedural variables and QCA analysis

Procedural variables and QCA data are presented in Tables 3 and 4. The ratio of balloon to artery and maximal inflation pressure were not different in all groups. Patients in group II and III had more number of stents ($p<0.001$) and longer stent length per lesion ($p<0.001$) than patients in group I. Type of stents used was not different in three groups ($p=0.247$). Patients in group III had smaller reference vessel size than patients in group I ($p=0.001$) and patients in group I had a larger post-intervention minimal luminal diameter than patients in group III ($p=0.001$).

Table 4
Quantitative coronary angiography analysis

Variables	Group I (1941 lesions)	Group II (420 lesions)	Group III (189 lesions)	*p*-value
Reference vessel, mm	2.90±0.50	2.86±0.48	2.74±0.44†	0.001
Preintervention				
MLD, mm	0.98±0.56	0.91±0.50	0.97±0.52	0.122
Diameter stenosis, %	66.5±16.7	68.0±15.1	65.3±17.4	0.147
Postintervention				
MLD, mm	2.83±0.48	2.78±0.49	2.71±0.45†	0.001
Diameter stenosis, %	2.1±13.3	2.7±14.9	0.8±12.5	0.470

Data shown as mean±SD. †*p*-value <0.05 vs. group I. MLD = minimal luminal diameter.

Table 5
In-hospital and long-term clinical outcome by CK-MB levels

	Group I (n=1429)	Group II (n=263)	Group III (n=115)	*p*-value
In-hospital				
Total death	0	1(0.4)	0	NS
Q-wave myocardial infarction	0	0	0	NS
Target lesion revascularization	0	1(0.4)	0	NS
Follow up				
Total death	9 (0.6)	4 (1.5)	4 (3.5)†	0.005
Cardiac death	7(0.5)	3(1.1)	3(2.6)†	0.016
Non-cardiac death	1(0.1)	1(0.4)	1(0.9)	0.063
Q-wave myocardial infarction	5 (0.3)	1 (0.4)	0	0.757
Target lesion revascularization	59 (4.1)	12 (4.6)	9 (7.8)	0.108
Repeat coronary intervention	51	11	9	
Bypass surgery	8	1	0	
Major adverse cardiac events	71 (5.0)	16 (6.1)	12 (10.4)†	0.010

Data shown as numbers (%). †*p*-value <0.05 vs. group I. NS = not significant.

3.3. In-hospital and long-term clinical outcome

In-hospital and long-term clinical events are presented in Table 5. During the hospitalization, there were one total death due to ventricular fibrillation preceded by severe left ventricular dysfunction and one TLR caused by stent thrombosis which was treated with repeat stenting in group II. During the long-term follow-up, patients in group III had an increased incidence of cardiac death compared with patients in group I ($p=0.016$) and showed a trend toward more TLR ($p=0.108$). There were three non-cardiac deaths, including two malignancy and one septic shock complicated by ischemic colitis, and there was no statistical significance ($p=0.063$). Overall MACE were more common in patients with group III compared with those in group I ($p=0.010$). Variables used in Cox analysis for death and MACE are age, left ventricular ejection fraction, smoking, presence of diabetes, prior history of PCI and CABG, presence of stent overlapping, cutting angioplasty, ACC/AHA B2/C lesions, type of stent used, use of any glycoprotein IIb/IIIa antagonists, reference vessel size, pre-and post-PCI minimal lumen diameter, number of stents, and lesion length, and so on. A Cox's proportional hazard model showed that the predictor of cardiac death was number of stents per lesion (HR 2.41, 95% CI 1.32–4.42, $p=0.004$). Although CK-MB level (HR 1.02, 95% CI 0.99–1.05, $p=0.065$) was not an independent predictor of cardiac death, it was a predictor of

Table 6
Cox proportional hazards model cardiac death and MACE

Variables	Hazard ratio	95% confidence interval	*p*-value
Cardiac death			
Peak CK-MB level	1.02	0.99–1.05	0.065
Stents per lesion	2.41	1.32–4.42	0.004
Major adverse cardiac events			
Peak CK-MB level	1.01	1.00–1.03	0.044
Stents per lesion	2.01	1.25–3.41	0.004
In-stent restenosis lesion	3.57	1.38–9.22	0.009

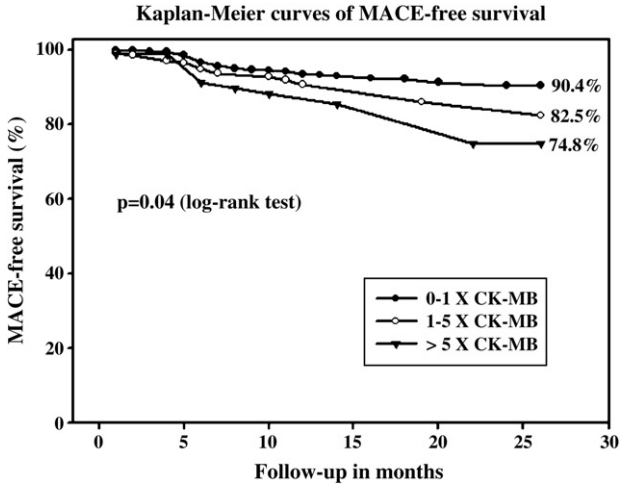

Fig. 1. Kaplan–Meier curves of major adverse cardiac events (MACE)-free survival after implantation of drug-eluting stents (DES), for increments of periprocedural creatine kinase myocardial band isoenzyme (CK-MB) elevation as a multiple of the upper limit of normal.

MACE (HR 1.01, 95% CI 1.00–1.03, $p=0.044$) in addition to number of stents per lesion and in-stent restenosis lesion (Table 6). Kaplan–Meier estimates of MACE-free survival for groups I to III (Fig. 1) were 90.4% versus 82.5% versus 74.8%, respectively ($p=0.04$). The incidence of MACE in group I was nearly parallel for the long-term period. For the patients with group II and III, the risk of MACE was higher from 3 to 10 months after implantation of DES.

4. Discussion

In the analysis of 1807 patients who underwent successful PCI, we found that there is a close relationship between periprocedural myonecrosis and long-term outcome in patients undergoing DES implantation. This study complements the previous studies on myonecrosis following PCI because it pertains specifically to the most commonly used method of coronary revascularization, namely DES implantation. The major findings of the present study suggested that despite development in technology and adjunctive pharmacology, periprocedural myonecrosis frequently occurs and there remains significant MACE associated with periprocedural CK-MB elevation after implantation of DES.

Although there were significant decreases in acute major complications of abrupt vessel closure and emergency coronary bypass graft surgery, a paradoxical increase in the rate of periprocedural CK-MB elevation has been reported after implantation of coronary stent as compared with balloon angioplasty to a degree of atherectomy procedures [6]. Distal embolization of platelet aggregates is considered as the most common cause of periprocedural cardiac enzyme elevation after stenting in contrast to balloon PTCA and atherectomy procedures, in which recognized angiographic complications such as acute vessel closure and persistent dissections are thought to be causes of periprocedural CK-MB elevation [8–11].

Despite increase in use since its introduction, little is known about the incidence and significance of cardiac enzyme elevation after implantation of DES. In fact, as most previous studies did not include patients undergoing DES implantation in their analyses, it is not relevant to adjust their findings to patients with DES implantation. We report an incidence of 14.5% intermediate CK-MB elevation (1 to 5 times normal) and 6.4% of high CK-MB elevation (>5 times normal) after DES implantation. However, this is somewhat lower than 8.5% CK-MB elevation >5 times normal reported following BMS implantation in Saucedo et al. study [6]. They also reported that 1-year mortality was significantly higher for patients with greater CK-MB elevation as compared with patients without CK-MB elevation (6.9% vs. 1.7%, $p=0.01$) showing greater incidence of total death compared with patients in our study (3.5% in group III). The precise mechanism of low mortality rate in group III patients of our study is difficult to be explained. Differences in techniques used in PCI, medications during hospitalization, and baseline characteristics of study population, such as a small number of patients with previous PCI or CABG, less presentation of unstable angina, and greater left ventricular ejection fraction might be responsible for the better clinical outcomes of patients in this study compared with previous BMS studies.

Although the degree of periprocedural myonecrosis seems to be associated with the risk of adverse clinical outcomes, the classification and clear definition of periprocedural myonecrosis has been debated [2,12,13]. Recent studies have suggested that only greater elevations of CK-MB (>5 to 10 times normal) independently correlates with mortality after elective PCI, whereas minor elevations did not [6,14,15]. Moreover, the association between peak CK-MB levels and mortality was not strong when peak CK-MB ratios were analyzed as distinct categories in the regression model, maybe due to small numbers of patients in this study. Results of the present study correspond with those of earlier studies which reported that CK-MB increases exceeding 5 times normal is associated with the adverse clinical outcomes [8,14]. However, such elevations of CK-MB are three times less frequent compared with elevations in the one- to five-fold. Hence, the influence of minor CK-MB elevations on increased mortality should not be overlooked. Further analyses are needed to clearly define a clinically useful threshold of CK-MB elevation for risk stratification of patients undergoing PCI.

We have documented an increasing long-term mortality risk with increasing levels of CK-MB elevation. It is not certain whether CK-MB elevation is associated with an adverse outcome in a cause-and-effect relationship or whether it simply represents a marker of the patient's worse underlying illness. The risk of CK-MB elevation should be weighted against the potential benefit of the PCI and it should not justify renunciation of PCI. However, postprocedural CK-MB rise should be prevented with possible modalities [16,17] and further investigations are needed for the aggressive secondary prevention strategies whether these improve the

long-term outcome of patients with periprocedural myonecrosis [14,18]. The Lescol Intervention Prevention Study (LIPS) [18], designed to investigate the effect of cholesterol lowering agent fluvastatin revealed that MACE-free survival time was significantly longer in the fluvastatin group ($p=0.01$). They also pointed out that there were no instances of CK elevations 10 or more times normal or rhabdomyolysis in the fluvastatin group. According to the recent study that compared the efficacy and safety of heparin with or without glycoprotein IIb/IIIa inhibitors and bivalirudin showed that patients who received bivalirudin had lower incidences of transfusion requiring bleeding (1.7% vs. 4.0%, $p<0.001$) and periprocedural myonecrosis (CK-MB >5 times normal 2.7% vs. 4.3%, $p=0.016$) following PCI compared with the former group [19].

This study was a single center, retrospective and non-randomized study. Also, there might be many confounding factors that could not be properly accounted for the analysis. Although CK-MB level was checked in all patients undergoing stent implantation, it is obscure to know whether the peak value was recorded, as some patients may have been discharged with no evidence of symptoms or signs of ongoing ischemia.

In conclusion, patients with greater CK-MB elevation (>5 times normal) after implantation of DES had higher mortality and increased MACE at long-term follow-up than patients without CK-MB elevation. However, routine measurement of CK-MB levels at baseline and serially after the PCI is mandatory in all patients and every possible efforts are warranted to reduce periprocedural myonecrosis, including intensive lipid lowering treatment, reduction of microembolization and procedure related myocardial damage with use of platelet glycoprotein IIb/IIIa inhibitors in high risk patients, and first of all, physician's effort to avoid unnecessary complex procedures in patients with poor clinical profiles.

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