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Association of Serum Cytokines, Human Growth Hormone, Insulin-Like Growth Factor (IGF)-I, IGF-II and IGF-Binding Protein (IGFBP)-3 with Coronary Artery Disease

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Abstract

The roles that serum cytokines, human growth hormone (h-GH), insulin-like growth factor (IGF)-I, IGF-II and IGF-binding protein (IGFBP)-3 play in coronary artery disease (CAD) are not completely clear. A total of 80 participants comprising 20 patients with stable angina (SA), 20 patients with unstable angina (UA), 20 patients with myocardial infarction (MI) and 20 healthy control subjects were recruited during the period January 2010 to August 2010. Blood samples were drawn from all participants on admission and one week later in MI patients undergoing percutaneous coronary intervention (PCI). We found that MI patients had significantly lower levels of IGF-I, IGF-II and IGFBP-3, and significantly higher levels of h-GH, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and IL-10 than controls. Furthermore, patients with SA or UA had higher levels of TNF-α and lower levels of IGF-II than control subjects. Moreover, h-GH, IGF-I, IGF-II, IGFBP-3 and IL-6 levels returned to within normal range in MI patients one week after PCI. Our preliminary findings suggest that TNF-α and IGF-II are potential biomarkers of early CAD. Furthermore, h-GH, IGF-I, IGF-II, IGFBP-3 and IL-6 might be predictors of and potential modifiable targets for MI.

Key Words: cytokines, insulin-like growth factor-I, insulin-like growth factor-II, insulin-like growth factor binding protein-3, myocardial infarction, percutaneous coronary intervention

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Introduction

Coronary artery disease (CAD) is mainly caused by obstruction of the vascular lumen by atherosclerotic plaques (6). Inflammation is critical in triggering acute cardiovascular events, namely unstable angina (UA) and acute myocardial infarction (MI) (19). The balance between pro- and anti-inflammatory cytokines might reflect the stability of atherosclerotic plaques (14, 19). Pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor-necrosis factor-α (TNF-α), are markedly increased in patients with MI. The roles that anti-inflammatory cytokines, specifically IL-10, play in the pathogenesis and development of atherosclerotic lesions remain controversial (2, 5, 21, 22, 29). Previous studies have shown that patients with MI typically have higher levels of human growth hormone (h-GH) and lower levels of insulin-like growth factor-I (IGF-I) (10, 12, 32). The correlation between IGF-binding protein (IGFBP)-3, which binds over 90% of IGF-I and modulates its bioactivity, and the development of atherosclerotic lesions is not completely clear (1, 23, 25). In addition, changes in h-GH, IGF-I, IGF-II and IGFBP-3 in MI patients who have undergone percutaneous coronary intervention (PCI) have not been well elucidated (1, 10, 12, 23, 25, 32). Thus, the purpose of this study was to investigate whether serum cytokine levels, as well as h-GH, IGF-I, IGF-II and IGFBP-3 levels, are associated with CAD. We also investigated the changes in serum cytokines as well as the IGF axis after PCI for MI.

Materials and Methods

Study Population

This prospective case-control study was conducted during the period January 2010 to August 2010 at the China Medical University Hospital. A total of 60 patients who presented with chest pain and who were subsequently shown to have MI (n = 20), UA (n = 20), or stable angina (SA) (n = 20) were enrolled in this study. MI was diagnosed based on the presence of chest pain and/or ECG change suggestive of infarction or ischemia with an increase in one or more cardiac enzymes to at least twice the upper limit of the normal range. UA was diagnosed based on the presence of chest pain lasting for at least 15 minutes within the 24-hour period prior to hospitalization, which was not relieved by nitroglycerin or rest, and without increase in cardiac biomarkers. SA was defined as typical ischemic chest pain brought on by exertion and relieved by rest or nitroglycerin without change in cardiac enzymes. Criteria for exclusion were active infection, rheumatologic disease and malignancy. PCI was performed in patients with MI according to current ACC/AHA guidelines (16, 18). Impatient medical treatment, such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, antiplatelet or anticoagulation therapy, beta-blockers, and statin therapy, was administered in patients without contraindications based upon current guidelines (3, 7, 11). An age- and gender-matched group of 20 patients with normal electrocardiograms, without history of chest pain and not currently taking anti-angina medications who had sought treatment at our hospital for dermatologic diseases was investigated as the control group. All participants gave written informed consent.

Data Collection

Baseline clinical parameters and a plasma samples for cytokine and biochemical analysis were obtained from each participant at the time of admission. Clinical variables included gender, age (years), body height (cm), body weight (kg), heart rate (beats per minute), and systolic and diastolic blood pressure (mmHg). Age and gender were self-reported. Body height and weight were measured with the participants wearing light clothing without shoes. Height was recorded to the nearest 0.5 cm and weight to the nearest 0.2 kg. Blood pressure was measured with a sphygmomanometer and determined as the mean of two measurements taken on the left arm. Diastolic blood pressure (DBP) was determined by the fifth Korotkoff phase. A venous blood sample was drawn on admission from each participant and one week later from MI patients who underwent PCI. The measured biochemical parameters and cytokines included triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TC), lactate dehydrogenase (LDH), creatinine phospho-kinase (CPK), IL-6, TNF-α, IL-10, h-GH, IGF-I, IGF-II and IGFBP-3. The biochemical parameters were measured by the analytical unit of the biochemistry department of the institution using standard methods.

ELISA for IL-6, TNF-α and IL-10

IL-6, TNF-α and IL-10 levels were measured from frozen stored plasma samples. Cytokine levels were determined using enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. The ELISA kits had a lower limit of detection of 0.7 pg/ml for IL-6, 2.5 pg/ml for TNF-α and 0.5 pg/ml for IL-10. All cytokines were standardized by inclusion of a titration of the appropriate purified recombinant cytokines of known concentration. The absorbance of the samples was determined on a microplate reader (Model: RS01, Kansin instruments, CO, LTD,

Table 1. Basic characteristics of the controls (group 1) and of patients with stable angina (group 2), unstable angina (group 3) or myocardial infarction before (group 4a) or one week after percutaneous coronary intervention (group 4b)

Variables	Group 1 (n = 20)	Group 2 (n = 20)	Group 3 (n = 20)	Group 4a (n = 20)	Group 4b (n = 20)
Sex (M/F)	11/9	11/9	11/9	11/9	11/9
Age at study (years)	62.3 ± 12.8	64.5 ± 10.8	63.7 ± 8.9	65.6 ± 13.9	65.6 ± 13.9
Body height (cm)	162.2 ± 9.7	160.2 ± 7.4	158.9 ± 6.3	162.6 ± 7.2	161.4 ± 6.8
Body weight (kg)	71.8 ± 12.5	62.3 ± 8.2*	62.8 ± 9.8*	69.7 ± 12.6	69.3 ± 11.8
Heart rate (beats/min)	74.1 ± 8.1	75.4 ± 8.2	84.1 ± 17.4	81.2 ± 11.4	82.7 ± 13.6
SBP (mmHg)	140.7 ± 15.9	130.3 ± 21.4*	127.7 ± 23.7*	114.8 ± 13.6*	123.5 ± 15.1
DBP (mmHg)	84.9 ± 12.0	71.8 ± 13.2*	67.9 ± 10.8*	62.8 ± 10.9*	73.7 ± 11.8
TG (mg/dl)	170 ± 160.5	194.6 ± 185.7	217.3 ± 193.7	196.9 ± 132.3	177.3 ± 71.4
HDL (mg/dl)	38 ± 11.6	35.4 ± 11.6	29.8 ± 10.1	38.2 ± 9.9	38.2 ± 11.1
LDL (mg/dl)	104 ± 32.2	109.8 ± 33.1	112.1 ± 44.2	126.1 ± 43.1*	107.9 ± 43.9**
TC (mg/dl)	161 ± 43.1	183.9 ± 38.5	185.3 ± 56.3	192.9 ± 47.6*	186 ± 39.8
LDH (IU/l)	280 ± 160.5	286.9 ± 108.3	351.9 ± 148.8	629.6 ± 50.2*	492.3 ± 19.7**
CPK (IU/l)	65 ± 50.5	72.4 ± 55.5	59.8 ± 44.3	388.4 ± 54.3*	258.7 ± 43.6**

Data are expressed as means ± SEM. CPK, creatinine phosphokinase; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride. *$P < 0.05$ compared with group 1. **$P < 0.05$ compared with group 4a.

Sunnyvale, CA, USA) with 450 nm as the wavelength.

ELISA for IGF-I, IGF-II, IGFBP-3 and h-GH

Serum concentration of IGF-I, IGF-II and IGFBP-3 were measured by a commercially available non-extraction ELISA kit (Diagnostic Systems Laboratories, Inc., Webster, TX, USA) with a monoclonal antibody according to the manufacturer's instructions (DSL-10-2800, DSL-10-2600, DSL-10-6600, Texas , USA). The target proteins were immunoadsorbed using an enzyme-conjugated antibody before adding the corresponding substrates for color development. Protein contents were determined by comparing the relative absorbance of the samples to that of known amounts of standard using a microplate reader (Model: RS01, Kansin instruments). Serum h-GH was determined using another ELISA kit (Biosource, Europe, SA and American Diagnostica, Inc., Greenwich, CT, USA) according to the manufacturer's instructions (IBL-MG-59121, ELISA KIT Product No. 860).

Statistical Analysis

Results are expressed as means ± SEM. Differences among the groups were determined by one-way analysis of variance (ANOVA). Fisher's least significant difference test was used to determine differences. A P value < 0.05 was considered to represent statistical significance.

Results

Basic Characteristics

The 3 groups of study subjects and the control group were compared with regard to basic characteristics (Table 1). Because of matching, the distribution of the gender was identical in each group (11 males and 9 females). The mean age was 62.3 ± 12.8 years in the control group (group 1), 64.5 ± 10.8 years in the group of patients with SA (group 2), 63.7 ± 8.9 years in the group of patients with UA (group 3), and 65.6 ± 13.9 years in the group of patients with MI (group 4). The mean body weight of individuals with UA or SA (62.8 ± 9.8 kg and 62.3 ± 8.2 kg, respectively) was lower than that of the control subjects (71.8 ± 12.5 kg). Mean systolic and diastolic blood pressure were both significantly lower in CAD patients than in the controls. There was no significant difference in TG and HDL levels among the 4 groups. Patients with MI had significantly higher baseline levels of LDL (126.1 ± 43.1 *vs*. 104 ± 32.2 mg/dl), TC (192.9 ± 47.6 *vs*. 161 ± 43.1 mg/dl), LDH (629.6 ± 50.2 *vs*. 280 ± 160.5 IU/l) and CPK (388.4 ± 54.3 *vs*. 65 ± 50.5 IU/l) than the controls. In the secondary analysis of MI patients, we found a significant reduction in the levels of LDL (126.1 ± 43.1 *vs*. 107.9 ± 43.9 mg/dl), LDH (629.6 ± 50.2 *vs*. 492.3 ± 19.7 IU/l) and CPK (388.4 ± 54.3 *vs*. 258.7 ± 43.6 IU/l) one week after PCI. A decline in TC was also found; however, the difference was not significant (192.9 ± 47.6 *vs*. 186 ± 39.8 mg/dl, $P > 0.05$).

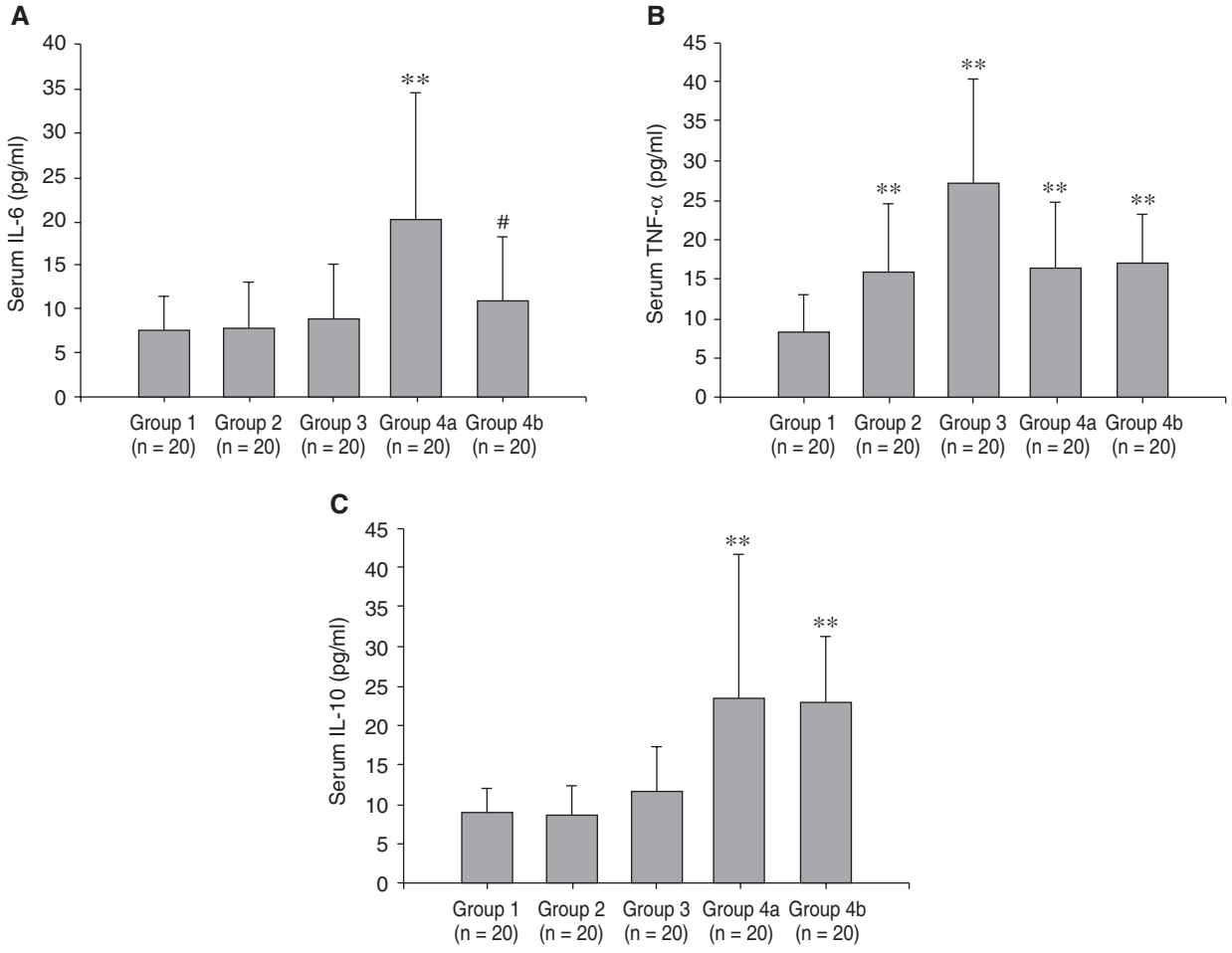

Fig. 1. Enzyme-linked immunosorbent assays (ELISA) of serum (A) interleukin-6 (IL-6), (B) tumor necrosis factor-α (TNF-α) and (C) IL-10. Data are expressed as means ± SEM. Differences in concentration compared with group 1 (the control group): $^{**}P < 0.05$. Differences in concentration compared with group 4a: $^{\#}P < 0.05$.

Serum levels of IL-6, TNF-α and IL-10

The serum concentrations of (A) IL-6, (B) TNF-α and (C) IL-10 are shown in Fig. 1. MI patients had higher levels of IL-6, TNF-α and IL-10 than the control subjects. Serum levels of TNF-α were significantly higher in groups 2, 3 and 4. Serum IL-6 was significantly higher in the group of MI patients than in the other groups but returned to within normal range after PCI. There were no significant differences in the serum levels of TNF-α and IL-10 before and after PCI.

Serum levels of h-GH, IGF-I, IGF-II and IGFBP-3

The serum concentrations of (A) h-GH, (B) IGF-I, (C) IGF-II and (D) IGFBP-3 are shown in Fig. 2. MI patients had the highest concentration of h-GH and the lowest concentrations of IGF-I, IGF-II and IGFBP-3. Serum levels of IGF-II were also found to be significantly lower in groups 2, 3 and 4. The levels of h-GH, IGF-I, IGF-II and IGFBP-3 returned to normal range after PCI in MI patients.

Discussion

The present study demonstrates that MI patients had significantly lower levels of IGF-I, IGF-II and IGFBP-3, and significantly higher levels of h-GH, IL-6, TNF-α, and IL-10 than the control subjects. Raised levels of TNF-α as well as reduced levels of IGF-II were also detected in patients with SA and in patients with UA. Furthermore, h-GH, IGF-I, IGF-II, IGFBP-3 and IL-6 levels returned to normal in MI patients one week after PCI.

Previous studies have shown that circulating levels of IL-6 and TNF-α are increased in MI patients (2, 4, 17, 20, 21, 26, 27); our data revealed similar findings. In addition, we detected that TNF-α levels were higher in patients with SA and in those with UA than in the healthy controls. TNF-α, therefore, is a potential biomarker of early CAD. Previous studies

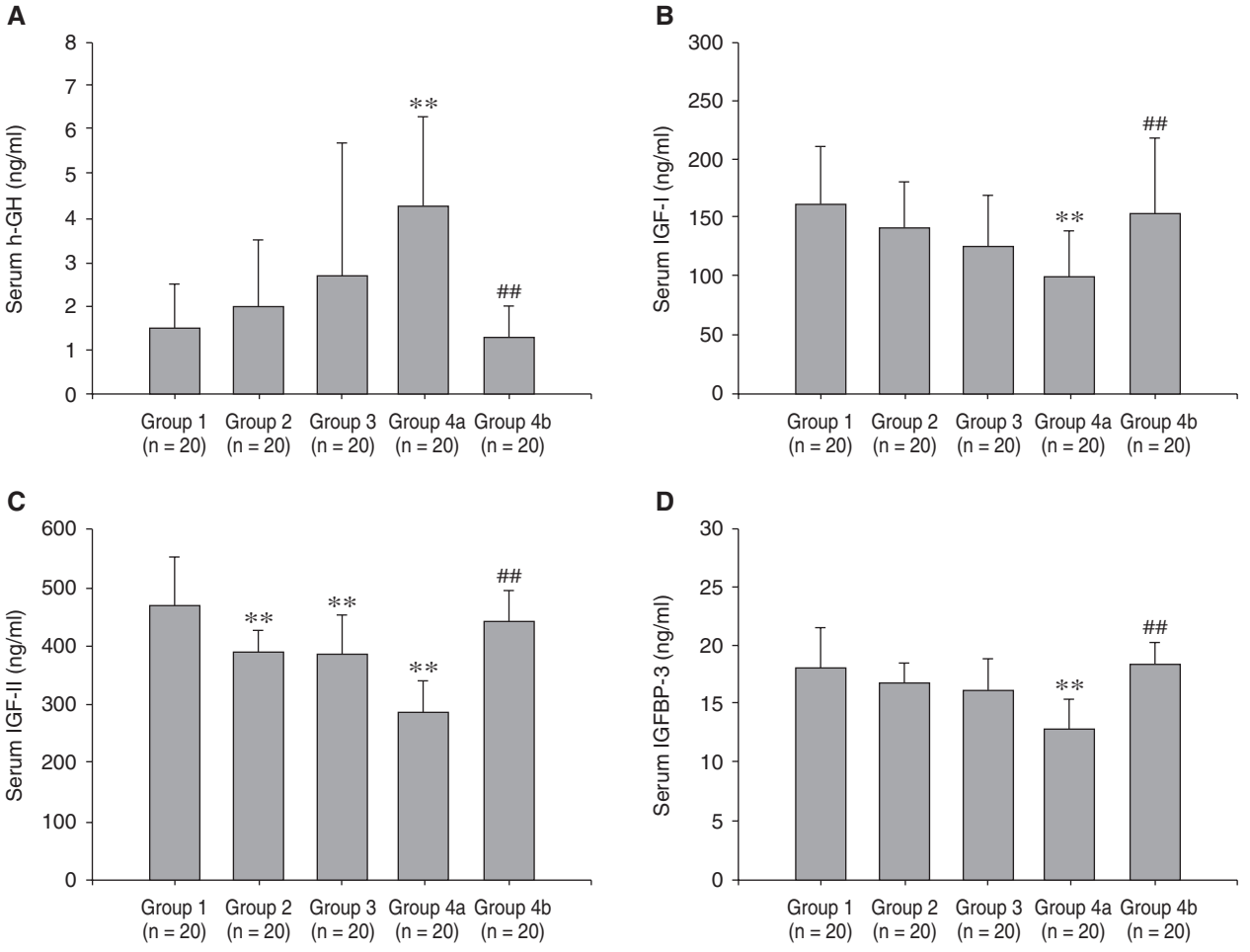

Fig. 2. Enzyme-linked immunosorbent assays (ELISA) of serum (A) human growth hormone (h-GH), (B) insulin-like growth factor (IGF)-I, (C) IGF-II and (D) IGF-binding protein (IGFBP)-3. Data are expressed as means ± SEM. Differences in concentration compared with group 1: $^{**}P < 0.05$. Differences in concentration compared with group 4a: $^{\#\#}P < 0.05$.

on the relationship between serum concentrations of IL-10 and MI have presented conflicting results (2, 5, 13, 21, 22, 26, 29-31, 33). We found that patients with MI had significant higher IL-10 levels than in the healthy controls, a finding that underscores the complexity of the inflammatory response in the development of atherosclerotic lesions. Further studies are needed to clarify the role of IL-10 plays as a prognostic marker in patients with MI. The present study is, to the best of our knowledge, the first to demonstrate that IL-6 levels in serum return to normal range in MI patients after PCI. IL-6 might, therefore, be a predictor of and a potential modifiable target for MI.

Friberg *et al*. reported detection of increased h-GH levels as well as decreased IGF-I levels in patients with acute MI (12). We found similar results indicating that the role of GH insensitivity or resistance is linked to the degree of the inflammatory reaction and stress elicited by the infarction. Few studies have found a correlation between IGF-II and the development of CAD (1, 24). In this study, we have shown that the level of IGF-II was significantly lower in individuals with CAD than in individuals without CAD. Our finding indicates that IGF-II is a potential biomarker of early CAD development.

Previous studies on the relationship between IGFBP-3 and the vulnerability of atherosclerotic plaque rupture have also presented conflicting results (1, 8, 9, 15, 23, 28). Some authors have suggested that IGFBP-3 promotes atherosclerotic plaque instability because IGFBP-3 is not only the major IGF carrier protein, but also traps IGFs, which restricts their extravascular transmission, thereby leading to a reduction in the bioactivity of IGF-I (9, 15, 23). We found that patients with MI had significantly lower levels of IGFBP-3 than the control subjects indicating that IGFBP-3 is part of an insulin resistance cluster (1, 8, 28). The present study is the first to demonstrate that serum levels of h-GH, IGF-I, IGF-II and IGFBP-3 in

MI patients returned to normal range after PCI. Our findings suggest that h-GH, IGF-I, IGF-II and IGFBP-3 might be predictors of as well as potential modifiable targets for MI.

Limitations of the present study include: firstly, only one anti-inflammatory and two pro-inflammatory cytokines were measured, leading to possible underestimation of multiple overlapping, synergic and antagonistic effects on cytokines. Secondly, because our baseline and follow-up blood samples were not obtained at a uniform time of day, our data might be limited by diurnal variations of cytokines and the IGF axis. Finally, there was a lack of long-term follow-up data in our study mostly due to the lack of patients' compliance. Despite these limitations, the present study is important as it is possibly the first such study to explore the associations between serum cytokines, the IGFs axis, and CAD as well as the first study to investigate changes in the serum cytokine levels and the IGF axis in patients with MI after PCI.

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