Early validation study of 64-slice multidetector computed tomography for the assessment of myocardial viability and the prediction of left ventricular remodelling after acute myocardial infarction

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Aims
We aim to validate the ability of multidetector computed tomography (MDCT) for assessing myocardial viability and predicting left ventricular (LV) remodelling after acute myocardial infarction (AMI).

Methods and results
In 52 consecutive patients with first AMI, 64-slice MDCT without iodine re-injection was performed immediately following coronary stenting. Electrocardiogram-gated thallium-201 single-photon emission tomography was performed using QGS programs within 5 days and 6 months after onset. Among the 52 patients, 18 patients (Group A) showed transmural contrast-delayed enhancement on MDCT images, 20 patients (Group B) showed subendocardial contrast-delayed enhancement, and 14 patients (Group C) had no contrast-delayed enhancement. In the acute phase, peak creatine kinase-MB [497 (189–744), 182 (90–358), 85 (40–204) IU/mL, respectively, \( P = 0.0004 \)] was significantly higher in Group A, while the incidence of myocardial blush grade 3 (22, 67, 75%, respectively, \( P = 0.001 \)) and LV ejection fraction (41 ± 7, 53 ± 12, 62 ± 11%, respectively, \( P < 0.0001 \)) were significantly lower in Group A. During the 6-month period, LV remodelling (\( P = 0.001 \)) and the number of rehospitalization for heart failure (\( P = 0.0017 \)) were more significantly observed in Group A.

Conclusion
Myocardial contrast-delayed enhancement patterns provide promising information regarding myocardial viability, LV remodelling, and prognosis in AMI.

Keywords
MDCT • Perfusion • Myocardial infarction • Remodelling

Introduction
Primary percutaneous coronary intervention (PCI) has improved the prognosis of patients with acute myocardial infarction (AMI), however, left ventricular (LV) remodelling occurs in an appreciable proportion of patients with AMI that has been treated with primary PCI, despite the sustained restoration of epicardial blood flow in the infarct-related artery. LV remodelling following AMI is a major predictor of morbidity and mortality for overt congestive heart failure and life-threatening arrhythmias.

Myocardial contrast echocardiography (MCE), positron emission tomography, and contrast-enhanced magnetic resonance (CE-MR) imaging are considered effective methods for assessing microvascular integrity. Furthermore, delayed CE-MR imaging enables
identification of both viable and non-viable myocardium and prediction of the functional recovery and prognosis after AMI. In contrast, angiographic myocardial blush (MB) grade and resolution of ST-segment elevation on 12-lead electrocardiogram (ECG) have been considered simple and useful tools for assessing microvascular reperfusion of the infarct area and for predicting LV remodelling in patients with AMI.

The recent advent of multidetector computed tomography (MDCT) with retrospective ECG-gating has enabled the detection of AMI, while delayed enhancement MDCT imaging demonstrates accurate measurement of infarct size in AMI, analogous to hyperenhancement CE-MR imaging in animals and humans. The preliminary study recently demonstrated that transmural contrast enhancement on MDCT without iodine re-injection immediately after coronary angiography for AMI was correlated with non-viable myocardium. Therefore, in the present study we attempt to investigate the clinical value of 64-slice MDCT in assessing myocardial viability and predicting LV remodelling and prognosis after primary PCI in patients with AMI.

Methods

Study population

Between June 2005 and January 2006, 58 consecutive patients with first AMI were initially assessed for inclusion into the study. The inclusion criteria for AMI patients were as follows: (1) chest pain >30 min in duration with presentation within 12 h after the onset of symptoms; (2) ST-segment elevation >0.1 mV within two contiguous electrocardiograph leads; (3) elevated creatine kinase-MB (CK-MB) isoenzymes within 12 h of chest pain; and (4) successful primary coronary intervention (defined as thrombolysis in myocardial infarction (TIMI) flow grade >2 and residual diameter stenosis <30%). In one patient cardiogenic shock caused death, three patients refused to give their informed consent, and two patients were lost to follow-up. The remaining 52 patients (42 males and 10 females, mean age, 63 ± 10 years) represent the population of this study.

All patients underwent 64-slice MDCT without any additional contrast media administration immediately following the final angiogram of primary PCI. An MDCT room is next to the catheterization laboratory in our hospital. The amount of contrast media of coronary injection and time delay between last injection of PCI and MDCT scanning were measured. All patients underwent follow-up coronary angiography at 6 months later. Written informed consent was obtained from all patients, and the study protocol was approved by our institutional review board.

64-slice multidetector computed tomography scanning procedure

Scanning was performed using a 64-slice MDCT scanner (Aquilion 64; Toshiba Medical Systems Corporation, Otawara, Japan), which is a 64 x 0.5 mm collimation scanner with a gantry rotation speed of 400 ms/rotation. Scanning was performed at 120 kV and 400 mAs, and the table feed was 6.4 mm/gantry rotation with a beam pitch of 0.2. The computed tomography dose index volume and dose-length product of the 64-slice MDCT using this scan protocol were 75.2 mGy and 1.10 Gy cm corresponding to an approximate mean radiation dose of 20 mSv. Acquisition of CT data and an ECG trace were automatically started during a 7–9 s breath-hold.

Reconstruction and image analysis of 64-slice multidetector computed tomography

Analysis of the scans was performed using a ZIOSTATION workstation (ZIOSOFT Inc., Tokyo, Japan). The original axial CT images and multplanar reformations were used for analysis of the myocardium. The images used for interpretation and for quantitative analysis were reconstructed at a slice thickness of 1 mm and an increment of 0.5 mm in the diastolic phase (75%) of the RR interval. When the images were blurred by motion artifacts due to high heart rate (>90 b.p.m.), systolic reconstructions were performed. Images were analysed using a 17-segment model. Hyperenhancement extent was judged as transmural if ≥75% of LV wall thickness in each segment of axial, short-axis and long-axis multi-planar images was visually involved, and subendocardial if <75%. The myocardial contrast delayed enhancement patterns were divided into three groups according to the following scheme (Figure 1): Group A=transmural contrast-delayed enhancement (whenever two or more segments exhibited transmural hyperenhancement); Group B=subendocardial contrast-delayed enhancement; Group C=no contrast-delayed enhancement. Infarct size was expressed as an infarct size index (percent LV involvement) obtained by adding the percentages of delayed enhancement of every segment divided by 17 (number of LV segments). The absolute value of myocardial contrast-staining tissue was computed using Simpson’s method: areas of contrast-delayed enhancement, defined as regions of increased signal intensity (SI) compared with normal myocardium, were visually traced on consecutive slices by the two observers. The extent of hyperenhanced regions was computed in absolute terms (grams).

ECG-gated thallium-201 single-photon emission tomography imaging

ECG-gated myocardial single-photon emission tomography (SPECT) by thallium-201 was serially performed within 5 days and at 6 months after onset. Imaging was performed at rest in the supine position 30 min after intravenous injection of 111 MBq of thallium-201 (Nihon Mediphysics Ltd, Osaka, Japan) as a radiotracer, using a double-detector SPECT system (PICKER PRISM 2000 XP; Shimadzu Corporation, Kyoto, Japan) equipped with a low-energy high-resolution collimator. Sixty projection data were obtained with a 64 x 64 matrix over 360°. Data were acquired for 60 s for each projection; the total acquisition time was ~33.4 min. The energy window was set at the 67 keV photo peak of thallium-201 with a 15% window. No attenuation or scatter correction was used. SPECT images were assessed using a 17-segment model and a semiquantitative visual score on a 5-point scale (0=normal uptake, 1=mildly decreased uptake, 2=moderately decreased uptake, 3=severely decreased uptake, 4=no uptake) in a blinded method by the consensus of two nuclear physicians. The defect score (DS) of thallium-201 was calculated as the summation of each of the scores. Images were gated at 16 frames per cardiac cycle, with an R-wave trigger and standard parameters similar to the LV ejection fraction (LVEF), LV end-diastolic volume (EDV), and LV end-systolic volume (ESV), which were provided using commercially available software.

Biochemical analysis

Serum CK-MB levels were analysed by enzymatic means, and plasma B-type natriuretic peptide (BNP) concentrations were measured with a specific immunoradiometric commercial assay using a commercial kit (Shionogi Inc., Japan). Serum levels of tenasin-C (TN-C) with the large subunit containing the C domain of FNIII repeats were determined using an ELISA kit with two monoclonal antibodies, 4F10TT and...
Blood samples for plasma BNP on Day 28 and serum TN-C on Day 5 after admission were obtained from all patients.

**Electrocardiographic analysis**

ST-segment resolution was defined as the percentage reduction in summed ST-segment elevation score between ECG prior to PCI and within 1 h post-PCI. The sum of ST-segment elevation was measured 20 ms after the end of the QRS complex in leads V1–6, I, and aVL for anterior infarction, and in leads II, III, aVF, V5, and V6 for non-anterior infarction.

**Angiographic myocardial blush analysis and collateral flow grade**

MB grade from the final angiograms after PCI was defined according to the following method: 0, no contrast density or persistent contrast staining; 1, minimal contrast density; 2, moderate contrast density, but less than that obtained during angiography of a non-infarct-related artery; and 3, normal contrast density, comparable with that obtained during angiography of a non-infarct-related artery. Good collateral flow was defined as grade 2 or 3 according to Rentrop et al.

**Definition of left ventricular remodelling and cardiac events**

LV remodelling was defined as an increase in LVEDV of ≥20% at 6 months after infarction compared with that based on measurements in individual patients, as described by Bolognese et al.

Major cardiac adverse events, defined as cardiac death, non-fatal AMI, and hospitalization for worsening heart failure, were the primary outcomes for the present analysis. After hospital discharge, all patients on medication were monitored at our outpatient clinic for up to 6 months.

**Statistical analysis**

All data are expressed as the mean ± SD or median and interquartile range. Comparisons of categorical variables between groups were performed by the χ² test or two-sided Cochran–Armitage trend test. Comparisons of continuous variables were analysed by one-way analysis of variance, Kruskal–Wallis test or Jonckheere–Terpstra trend test. The mean differences of LV functional parameters between acute and 6 months were calculated using the paired Student’s test. Due to the exploratory nature of the study, no adjustment was made to the significance level for the multiplicity of testing. All probability values are considered significant when <0.05.

**Results**

**Patient characteristics**

Among the 52 patients, 18 patients (Group A) showed transmural contrast-delayed enhancement on MDCT imaging (Figure 2), 20 patients (Group B) showed subendocardial contrast-delayed enhancement (Figure 3), and 14 patients (Group C) had no contrast-delayed enhancement. The clinical characteristics of the patients are shown in Table 1. The time delay between last injection of contrast media and MDCT scanning was 13 ± 3 min (range 8–18 min). Heart rate during scanning was 76 ± 14 b.p.m.
Iodine volume injected during PCI was 198 ± 22 mL (range 161–250 mL). There were no differences in iodine volume among the three groups (206 ± 5, 197 ± 8, 186 ± 6 mL, respectively, P = 0.1221). The body mass index of the patients was 23.7 kg/m². There are no restenosis of the culprit coronary arteries at 6 months later.

Biochemical markers, angiographic characteristics, and ST-segment resolution

Peak serum CK-MB, plasma BNP levels on Day 28 and serum TN-C levels on Day 5 were significantly higher in Group A than in the other groups (Table 2). The incidence of Pre-TIMI flow 1 and MB grade 3, and recovery of ST-segment resolution were significantly lower in Group A than in the other groups.

Infarct size, transmurality, and signal intensity on multidetector computed tomography

Group A showed a significantly larger contrast-delayed enhancement, infarct size index, and number of LV segments with transmurality than that of the other groups (Table 3). The contrast-delayed enhancement region of infarcted myocardium in Groups A and B demonstrated significantly higher SI than the remote myocardium and LV cavity, while the infarcted region in Group C did not show higher SI than the remote myocardium. There were no differences in SI of the remote myocardium and LV cavity among the three groups.

Comparison of myocardial contrast-delayed enhancement patterns and electrocardiogram-gated thallium-201 single-photon emission tomography

The defect scores of thallium-201 in the acute phase and at 6 months were significantly higher in Group A than in the other groups (Table 3). The thallium-201 defect scores in the acute phase were significantly reduced at 6 months in Groups B and C, but not in Group A (Figure 4).

LVEDV and LVESV in the acute phase and at 6 months were significantly higher in Group A than in the other groups. LVEF in the acute phase and at 6 months was significantly lower in Group A than in the other groups. During the 6-month period, LVEDV significantly increased in Group A, but there was no significant increase in Group B or C (Figure 5).
Figure 3 Result for a 62-year-old man with anterior acute myocardial infarction. (A) Multidetector computed tomography images show sub-endocardial contrast-delayed enhancement on (a) axial, (b) short-axis, and (c) long-axis multi-planar reconstructions. (B) Myocardial thallium-201 single-photon emission tomography shows reduced uptake in the anteroseptal, anterior, and apical walls in the acute phase (left) and 6 month later (right). (C) Quantitative gated single-photon emission tomography shows improvement in wall motion after 6 months. Left ventricular end-diastolic volume decreased from 122 to 95 mL, while left ventricular ejection fraction improved from 39 to 50%.

Table 1 Clinical characteristics in 52 patients with first acute myocardial infarction according to myocardial contrast-delayed enhancement patterns

<table>
<thead>
<tr>
<th></th>
<th>Transmural (n = 18)</th>
<th>Subendocardial (n = 20)</th>
<th>No enhancement (n = 14)</th>
<th>P-value</th>
</tr>
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<tr>
<td>Age (years)</td>
<td>61 ± 11</td>
<td>64 ± 11</td>
<td>62 ± 9</td>
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<tr>
<td>Male (%)</td>
<td>16 (89)</td>
<td>16 (80)</td>
<td>10 (71)</td>
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<td>Diabetes mellitus (%)</td>
<td>6 (33)</td>
<td>7 (35)</td>
<td>7 (50)</td>
<td>0.3629</td>
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<td>Hypertension (%)</td>
<td>6 (33)</td>
<td>7 (35)</td>
<td>4 (28)</td>
<td>0.8013</td>
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<td>Hyperlipidaemia (%)</td>
<td>15 (83)</td>
<td>15 (75)</td>
<td>7 (50)</td>
<td>0.0458</td>
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<td>Smoker (%)</td>
<td>10 (56)</td>
<td>10 (50)</td>
<td>7 (50)</td>
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<td>Time to reperfusion (h)</td>
<td>4.4 ± 2.6</td>
<td>4.3 ± 2.2</td>
<td>4.3 ± 2.4</td>
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<td>Killip class &gt;1 (%)</td>
<td>4 (22)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.0121</td>
</tr>
<tr>
<td>Infarct-related artery LAD/RCA/LCX (%)</td>
<td>16/2/0 (89/11/0)</td>
<td>9/5/6 (45/25/30)</td>
<td>5/7/2 (35/50/15)</td>
<td>0.0015</td>
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<tr>
<td>Medical therapy (%)</td>
<td></td>
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</tr>
<tr>
<td>ACE-inhibitor/ARB</td>
<td>15 (83)</td>
<td>15 (75)</td>
<td>9 (64)</td>
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<td>Beta-blockers</td>
<td>7 (39)</td>
<td>4 (20)</td>
<td>4 (28)</td>
<td>0.4473</td>
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<td>Diuretics</td>
<td>8 (44)</td>
<td>5 (25)</td>
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<tr>
<td>Calcium antagonists</td>
<td>3 (17)</td>
<td>5 (25)</td>
<td>5 (35)</td>
<td>0.22</td>
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</table>

LAD, left anterior descending artery; RCA, right coronary artery; LCX, left circumflex artery; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers.
Left ventricular remodelling and cardiac events according to myocardial contrast-delayed enhancement patterns

Among the 52 patients, 10 patients (19.2%) showed LV remodelling at 6 months. A one-sided Cochran–Armitage trend test revealed that LV remodelling was significantly more observed in Group A (eight patients) than in Groups B (two patients) and C (no patients) \( (P = 0.001) \). There were no cardiac deaths or non-fatal AMI in any group during the 6-month period; six rehospitalizations for worsening heart failure were observed in Group A, but none in Group B or C \( (P = 0.0017) \).

Discussion

The important findings of the present study are as follows. The three types of myocardial contrast-delayed enhancement patterns on MDCT were observed immediately following primary PCI in the AMI patients. In patients with transmural contrast-delayed enhancement, the recovery in global LV function was significantly poorer and LV remodelling was more significantly observed than in patients with the other groups. These observations demonstrate that angiographically successful coronary reflow does not necessarily indicate adequate myocardial perfusion. Thus, myocardial contrast-delayed enhancement patterns may be reliably useful in predicting functional recovery of the post-ischaemic myocardium and LV remodelling in patients with AMI.

Myocardial contrast-delayed enhancement patterns on multidetector computed tomography

Previous studies demonstrated that contrast-enhanced MDCT can identify infarcted myocardium using a large volume of intravenous...
contrast injection in occlusion/reperfusion animal models.\textsuperscript{12,13} Habis\textit{et al.}\textsuperscript{14} recently demonstrated that 64-slice CT without iodine re-injection immediately after coronary angiography for AMI is a promising method of very early viability assessment. The present study is in agreement with those data and are complementary that it underlines the feasibility of using MDCT in the next minutes after coronary angiography.

In AMI, contrast wash-in and wash-out kinetics may play a role along with altered myocyte and sarcolemmal membrane integrity.\textsuperscript{22} Because iodinated contrast agents have similar kinetics to Gd-DTPA with Gd in infarcted and non-infarcted myocardium, the underlying mechanisms for contrast enhancement of infarcts are similar to those for CE-MR.\textsuperscript{14} The causes of reduced microcirculatory perfusion after reperfusion therapy are multifactorial and include distal thrombo-emboli, vasoconstriction, interstitial oedema, capillary leak syndrome, and possible reperfusion injury, among others.\textsuperscript{23} Under conditions of normal myocyte function, sarcolemmal membranes exclude iodine from the intracellular space; therefore, no contrast-delayed enhancement was observed on MDCT in non-infarcted myocardium. When myocyte necrosis and membrane dysfunction occur and iodine molecules penetrate the cell, this results in contrast-delayed enhancement. The possible

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4}
\caption{Comparison of the defect scores of thallium-201 between the acute phase and at 6 months according to myocardial contrast-delayed enhancement patterns. Values are expressed as mean ± SD. (A) Transmural enhancement, (B) subendocardial enhancement, and (C) no enhancement.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5}
\caption{Changes in left ventricular functional parameters from the acute phase to those at 6 months according to myocardial contrast-delayed enhancement patterns. Values are expressed as mean ± SD. (A) Left ventricular end-diastolic volume, (B) Left ventricular end-systolic volume, and (C) Left ventricular ejection fraction. Solid circles indicate transmural enhancement, open circles indicate subendocardial enhancement, and open squares indicate no enhancement. Asterisks are overall significance between three groups calculated by Jonckheere–Terpstra trend test. \textsuperscript{*}P < 0.0001, \textsuperscript{**}P < 0.0005}
iodine contrast interaction with infarct and peri-infarct regions immediately after reperfusion is not fully understood. Indeed, this present study showed that the infarct size evaluated by thallium defect was significantly larger in patients with transmural enhancement than those without enhancement. But, some patients without enhancement had slightly reduced uptake of thallium in the infarct territories. Although its discrepancy still remains unclear, it might be postulated that myocardial damages such as oedema in cases of small size of infarction are too little to enhance the myocardium. In addition, localized attenuation by overlying soft tissue or partial volume effect may create artifacts that mimic true perfusion abnormalities.

In the present study, delayed enhancement on MDCT could be acquired with short-time delay between last injection of contrast media and MDCT scanning because MDCT room is next to the catheterization laboratory. It has been shown that hyperenhanced regions reach peak of SI only 5 min after contrast injection with a progressively reduced SI over time in animal study.13 Habis et al.14 could allow infarct size assessment during mean time delay, which was 24 ± 11 min. This aspects are potentially limiting reproducibility of the protocol in centres where MDCT and catheterization laboratory facilities are not enough close.

**Myocardial contrast-delayed enhancement patterns as a marker for left ventricular remodelling and cardiac events**

The present study demonstrates for the first time that transmural contrast-delayed enhancement on MDCT reveals larger infarct size and LV remodelling in the chronic phase, followed by a greater incidence of hospitalization for worsening heart failure, indicating the clinical usefulness of myocardial contrast-delayed enhancement patterns.

It has been reported that infarct size, anterior infarct location, perfusion status, and congestive heart failure on admission are major predictors of LV dilation.7 In the present study, patients with transmural contrast-delayed enhancement had higher peak CK-MB, plasma BNP, and serum TN-C levels; these are useful biomarkers of LV remodelling.9,24 These patients had a higher incidence of anterior myocardial infarction and poorer ST-segment resolution, a lower incidence of MB grade 3, and more often presented in Killip class 2 or higher on admission.

The number of LV segments with transmural delayed enhancement (infarct size) has been shown as a major factor for the prediction of remodelling.17 However, multivariable logistic regression analysis revealed that this parameter lost its predictive power because of the small number of patients in the current study. Therefore, we could not conclude which factors (transmurality or number of segment involved) are more important for LV remodelling and prognosis.

**Clinical limitations**

The current study has some limitations. First, dose radiation levels are high (~20 mSv). If only end-diastolic images were used for data analysis, the use of an ECG-pulsing technique could have provided a significant dose reduction. Post-infarction delayed enhancement has been successfully performed at low-kilovolt settings (80 kV), reducing drastically radiation dose and improving contrast visualization at the same time.11,14

Second, the sample size was relatively small. The prognosis of our patients receiving primary PCI was good, and there were no cardiac deaths out of 52 patients during the 6-month period. Therefore, the ability to predict cardiac events could be limited.

Third, we utilized ECG-gated thallium-201 SPECT in the present study. Since the photon energy of thallium-201 is considerably low, several attenuations such as breast, diaphragmatic attenuation are found in thallium-201 SPECT; however, gated SPECT with thallium-201 has been shown to provide high accuracy with regard to LV function and is applicable in clinical use.25 CE-MR imaging is superior to SPECT in detecting myocardial necrosis after reperfused AMI.26 A comparison with CE-MR would be more appropriate than thallium-201 scintigraphy, especially for evaluation of the subendocardial infarction.

Fourth, the definition of hyperenhancement was not standardized, and so there were limitations due to a global classification, in particular for patients with both transmural and subendocardial hyperenhancement.

Finally, MDCT could not exactly detect the areas of microvascular obstruction using direct acquisition of late phase in the present study.

**Clinical implications**

CE-MR is well established for assessment of myocardial viability without ionizing radiation and nephrotoxic contrast material. However, the facts that MDCT can be performed in short examination times and generally available with ease of application are considered important advantages in comparison with CE-MR. Furthermore, myocardial contrast-delayed enhancement patterns might be a very early predictive marker for future ventricular remodelling and clinical events.

**Conclusions**

The present study demonstrates that transmural contrast-delayed enhancement on MDCT showed larger infarct size and higher incidence of LV remodelling and hospitalizations for worsening heart failure when compared with the other groups in the chronic stage. We consider that myocardial contrast-delayed enhancement patterns on MDCT images immediately after primary PCI may provide promising information regarding myocardial viability, LV remodelling, and prognosis in AMI patients.

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