Acute coronary syndromes (ACS) are thought to be the endstage of coronary atherosclerosis with silent progression and few clinical symptoms. The composition and vulnerability of plaque, rather than its volume or the severity of stenosis, have emerged as the most important determinants for the onset of ACS.

Rapid progression of coronary artery disease (CAD) has been demonstrated as a powerful predictor of cardiovascular events, attributable to complex lesions, increased plasma endothelin levels, micro-inflammations revealed by high-sensitivity C-reactive protein (hs-CRP), endothelial damage and macrophage activation. Indeed, Nakachi et al comprehensively demonstrated higher hs-CRP levels on admission and at 48 h after percutaneous coronary intervention, a higher level of low-density lipoprotein (LDL) cholesterol at follow-up, a higher rate of multiple complex lesions, and a lower frequency of statin use at follow-up in the patients with rapid progression of a non-culprit lesion than in the patients with non-progression of a non-culprit lesion and non-ST-segment elevation ACS.

On the top of these events, impaired glucose metabolism is reportedly a predictor of poor clinical outcome in patients with acute myocardial infarction. Recently, glycemic variability (GV), expressed as the mean amplitude of glycemic excursion (MAGE), was reported to negatively correlate with the myocardial salvage index, and positively correlate with left ventricular remodeling (LVR).

Furthermore, MAGE correlates with coronary plaque rupture in culprit lesions. However, is unclear whether MAGE correlates with the rapid progression of non-culprit lesions in patients with ACS.

### Table: Modalities for Identifying Rapid Progression of CAD

<table>
<thead>
<tr>
<th>Invasive</th>
<th>Noninvasive</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVUS</td>
<td>Glycemic variability (MAGE&lt;sub&gt;11&lt;/sub&gt;)</td>
</tr>
<tr>
<td>CAS</td>
<td>Inflammation (hs-CRP&lt;sub&gt;6,13&lt;/sub&gt;, IL-6&lt;sup&gt;13&lt;/sup&gt;, TNF-α&lt;sup&gt;13&lt;/sup&gt;, IL-18&lt;sup&gt;13&lt;/sup&gt;)</td>
</tr>
<tr>
<td>OCT</td>
<td>Macrophage activation (neopterin&lt;sup&gt;6&lt;/sup&gt;, MMP-9&lt;sup&gt;9&lt;/sup&gt;)</td>
</tr>
<tr>
<td>CAG</td>
<td>Endothelial activation (endothelin&lt;sup&gt;5&lt;/sup&gt;, sICAM-1&lt;sup&gt;9&lt;/sup&gt;)</td>
</tr>
<tr>
<td>MSCT</td>
<td>LDL cholesterol&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>MRI</td>
<td>FMD&lt;sup&gt;14&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; CAG, coronary angiography; CAS, coronary angiography; FMD, flow-mediated dilation; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; IVUS, intravascular ultrasound; LDL, low-density lipoprotein; MAGE, mean amplitude of glycemic excursion; MMP-9, matrix metalloproteinase-9; MRI, magnetic resonance imaging; MSCT, multislice computed tomography; OCT, optical coherence tomography; sICAM-1, soluble intercellular adhesion molecule-1; TNF-α, tumor necrosis factor-α.

Complex lesions were all higher in the progressor group than in the non-progressor group. Multivariate logistic regression analysis showed that MAGE levels and hs-CRP level 1 month after the onset of ACS were independent predictors of rapid progression. Using cutoff values for these parameters obtained by maximizing the sums of sensitivity and specificity, they divided the patients into 4 groups according to a cutoff of >0.1355 mg/dl for hs-CRP level 1 month after the onset of ACS and >44.035 mg/dl for MAGE level, and found that 58% of patients with higher levels of both parameters suffered from rapid progression of non-culprit lesions. In contrast, only 3% of patients with lower levels of both hs-CRP and MAGE suffered from rapid progression of non-culprit lesions. We assume that these parameters can form the basis for a protocol.
to predict patients who are vulnerable for ACS.

Because the ultimate goal of patient management for CAD is to prevent progression, or even facilitate regression of coronary lesions, we can follow-up such vulnerable patients using presented tactic. The most important merit of this study is that the protocol does not need invasive measurements, which enables its immediate clinical use. When the present parameters are combined with coronary stenosis morphology (complex lesions), increased levels of plasma endothelin and hs-CRP, endothelial damage and macrophage activation, the predictive accuracy would be further increased (Table).

Although this study demonstrated that GV as defined by MAGE is an independent predictor of rapid progression, unfortunately the mechanistic insights underlying these findings were not examined. Therefore, we would like to discuss this issue briefly. First of all, Monnier et al demonstrated that MAGE showed significant correlations with excretion of urinary 8-iso prostaglandin F2α, an oxidative stress marker, and acute glucose fluctuations exhibited a more specific effect on oxidative stress than chronic sustained hyperglycemia. Esposito et al showed that an intravenous bolus injection of glucose (0.33 g/kg) elevated plasma interleukin (IL)-6, tumor necrosis factor-α, and IL-18 levels in control subjects, but were more evident in the impaired glucose tolerance subjects; and inhibited the development of cardiovascular events in healthy adults without a history of cardiovascular disease. Because almost all patients with ACS in Japan are prescribed statins in accordance with treatment guidelines, the present results suggest that interventions to decrease GV may prevent rapid progression of CAD independent of statin use. This study examined only patients who were not receiving antidiabetic drugs, so an interventional study to test the present observation is truly desired.

COI Disclosures

M.K. reports no COI for this work, but personal fees from Takeda and Ono outside the submitted work and research grants from Mitsubishi-Tanabe and Novartis outside the submitted work.

References