Since stent thrombosis (ST) is one of the serious and mortal complications after percutaneous coronary intervention (PCI), especially drug-eluting stent (DES) implantation, we are eager that the means of predicting and preventing ST be established. Several studies have reported an association between inflammation and stent thrombogenicity. In a clinical setting, Hwang et al\(^1\) reported a positive association between elevated levels of interleukin (IL)-6, a marker of inflammation, and DES thrombosis. In their study, plasma levels of monocyte chemoattractant protein-1, tumor necrosis factor-\(\alpha\), and IL-6 were compared between ST patients and matched controls. The levels of these 3 cytokines were similar in the ST group, compared to the control group. When divided into quartiles, however, the patients with the highest quartile of IL-6 showed a significantly higher rate of ST, compared to the control group. In addition, the highest IL-6 quartile was an independent predictor of ST in the multivariate analysis. In that study, blood samples were collected when the patients in both groups were in a stable condition (ie, at least 3 months after the index procedure in the control group and at least 3 months after development of ST in the ST group) in order to avoid conditions that may interfere with baseline levels of biomarkers such as myocardial infarction, procedural issues, and medications used in the treatment of ST. Regarding the mechanism by which IL-6 but not other inflammatory markers was specifically associated with ST, they discuss promotion by IL-6 of tissue factor expression from endothelial cells and circulating monocytes, which is responsible for thrombogenicity. This study demonstrated that the trend in the relationship between IL-6 level and ST was more conspicuous in early ST patients than in late ST patients, and ST patients without clopidogrel treatment. Since the pathological and morphological mechanisms of late ST in DES patients are mainly attributed to lack of re-endothelialization as the vascular healing process, excessive fibrin deposition, acquired stent malapposition, and antiplatelet drug discontinuation,\(^2,3\) the predictive value of IL-6 for ST might be weak in late ST patients or ST patients without clopidogrel treatment. In the case of late ST, acquired stent malapposition, poor re-endothelialization and antiplatelet drug discontinuation would be rather better predictors.

We previously reported that the level of local inflammation early post-DES implantation was reduced compared to the baseline status before stenting.\(^4\) We subsequently demonstrated also that local inflammation thereafter relapsed and was prolonged because of impaired re-endothelialization and/or the polymer coating on the stent surface, resulting in a delayed wound healing response.\(^5\) Considering the DES-specific vascular response, patients’ underlying chronic inflammatory status, which as Hwang et al stated, seems never to mean the status before PCI but would be the status at late-stage after DES stenting. If so, their hypothesis that blood samples obtained at least 3 months after the procedure are able to represent the patient’s underlying chronic inflammatory status that predispose to ST seems likely. In other words, since inflammation would be reduced early post-DES implantation, a high IL-6 level leading to thrombogenesis might represent an underlying chronic inflammatory status at the late stage post-PCI. Chronic inflammation might be caused also by systemic atherosclerosis or other systemic diseases such as collagen diseases, malignancies or chronic infections.

Pretreatment with statins, which exert pleiotropic anti-inflammatory effects, appears to have a cardiovascular protective effect in patients undergoing PCI. The Atrovastatin for Reduction of Myocardial Damage During Angioplasty (ARMYDA-ACS) trial\(^6\) randomly assigned 171 patients with acute coronary syndrome (ACS) to pretreatment with a high dose of atorvastatin (80 mg, 12 h before PCI) or placebo. The patients in the atorvastatin arm had a significantly lower incidence of 30-day cardiac events, driven mostly by a lower incidence of ST within the first 24 h. Patti et al\(^6\) suggested that the anti-inflammatory effects of atorvastatin might be stronger in patients with an enhanced baseline inflammatory status. This evidence may indicate the association between inflammation and ST as demonstrated by the study of Hwang et al.

In the study by Hwang et al there are several issues to be further discussed. First, IL-6 may be a predictor of ST (early >late, on clopidogrel >without clopidogrel), but ST patients other than in the 4th quartile were 56%, and the 1st quartile especially, accounted for 27% of all the ST patients; therefore, other predictors in addition to IL-6 are required. It is common knowledge that the cause or mechanism of ST is multifactorial, so it is very difficult to pinpoint the potential for ST events with a single predictor. Yasuda et al\(^7\) have demonstrated in a pig model that Rho kinase, a downstream effector of the small GTP-binding protein Rho, played an important role in the pathogenesis of DES-induced coronary impairment, including coronary hyperconstriction and thrombus formation. Thus, some of the Rho-related markers would
be expected to be useful ST predictors. Taken together, a multiple biomarker strategy, including IL-6, could more powerfully predict ST. Next, we can now use several types of DES, and the vascular wound healing process may be somewhat different among each of these, so it is necessary to confirm the influence of the vascular response after each DES implantation with regard to the IL-6 level. Finally, Ikari et al reported that dialysis was the strongest predictor of target lesion revascularization, death or myocardial infarction in DES-implantation patients. In the study by Hwang et al renal insufficiency was also a strong predictor of ST, especially in early ST or ST in clopidogrel-treated patients. The message is that we need to learn whether or not the presence of chronic kidney disease can predict ST after DES implantation.

From the study by Hwang et al, we can envision that IL-6-guided PCI may be a useful strategy in the DES era. For example, in high IL-6 patients, we may have to use antiplatelet drugs strongly (ie, triple antiplatelet drugs therapy) post PCI. Based on the findings of previous large DES-related clinical trials, the science advisory committees of the ACC/AHA/SCAI/ACS/ADA summarized the factors relating to late ST, include stenting in small vessels, multiple lesions, long stents, overlapping stents, ostial or bifurcated lesions, prior brachytherapy, suboptimal stenting result, low ejection fraction, advanced age, diabetes, renal failure, ACS, and premature discontinuation of antiplatelet therapy. In addition to precautions against these factors, biomarker-guided PCI could be a standard PCI strategy to prevent ST in the near future.

References