Percutaneous coronary intervention (PCI) with stent implantation is a mainstay in the management of severe coronary artery atherosclerotic disease. Indeed, PCI currently outperforms coronary artery bypass grafting, and the use of interventional procedures is projected to increase even more with the adoption of new-generation drug-eluting stents (1). Even when performed by the best operators and with the most recent technologies, however, PCI may be fraught by significant short- and long-term risks of adverse events (1).

Two major processes are involved in adverse events following PCI: (a) coronary restenosis, and (b) progression of disease on the same vessel or in another vessel (2). The latter is central to the understanding of ischemic heart disease and to its primary and secondary prevention, and has been addressed in numerous studies. On the other hand, the long-term outlook after PCI can be affected by neo-intimal proliferation at the site of PCI, leading to in-stent restenosis, recurrent angina, and ultimately, target-lesion revascularization (3). In this issue, Rittersma et al. (4) address specifically the issue of in-stent restenosis. Although restenosis is a decreasing problem with the use of drug-eluting stents, the cost of these devices is high, and in most European countries only a minority of stents are drug-eluting, making prediction of restenosis a still-hot clinical and biological problem.

To accurately stratify patients according to their risk of future adverse events, a quest for risk predictors is ongoing worldwide, but only a few powerful and independent predictors of early and late major adverse cardiovascular events have been found. These include traditional risk factors, such as acute coronary instability, diabetes mellitus, reference vessel diameter, and lesion and/or stent length (1, 5, 6). Nonetheless, risk assessment is still incomplete if based only on such “traditional” prognostic variables (6). For this reason, since the last decade, biochemical markers have been carefully investigated; among these, several have been related to the risk of death, myocardial infarction, or restenosis after PCI, but only C-reactive protein (CRP) has been consistently shown to significantly and independently confer an adverse prognosis in patients with coronary artery disease, including those undergoing PCI (7–12). This is probably because of its relatively long half-life and chemical stability as well as the limited costs and logistic hurdles faced by clinicians willing to measure it (12).

The prognostic role of CRP in the risk of in-stent restenosis, and the consequent occurrence of coronary target-lesion revascularization, is less well established than the relation of CRP to overall prognosis (13). The inflammatory process leading to plaque growth, rupture, or activation is different from the healing inflammatory process after angioplasty and stent implantation, and the latter may also induce a strong inflammatory response by itself, with confounding effects on the role of preprocedural inflammatory markers such as CRP (3, 13).

An early report by Buffon et al. (14) suggested that CRP could predict clinical restenosis as well as death or myocardial infarction after PCI, but this 121-patient study was limited by the lack of coronary stenting. A significant and independent prognostic role of CRP on both major adverse events and angiographic restenosis was later shown in 276 patients undergoing intracoronary stenting (P = 0.002) (15). Similarly, CRP was found to predict at long-term follow-up a composite end-point of death, myocardial infarction, or repeat revascularization among 62 patients with acute coronary syndromes (P < 0.001), but no disaggregated data on restenosis were reported (16). Angioi et al. (17) reported from a 55-patient study an increased risk for angiographic in-stent restenosis for those with increased CRP (P = 0.003). Similar data were also reported by Jeong et al. (18) in a 272-patient study and by Rahel et al. (19) in a 600-patient study.

Conversely, the 483-patient GENERATION study found no association between increased preprocedural CRP and in-stent restenosis, but angiographic follow-up was largely incomplete (67%) (2). Similar findings on the lack of association between CRP and angiographic restenosis have also been reported in 75 patients treated with directional coronary atherectomy (20), in a report from Dibra et al. (21) on 1152 stable patients undergoing PCI, and in another cohort of 1458 patients undergoing both balloon angioplasty and stenting (22). Despite such conflicting reports, the potential contribution of CRP to restenosis was intriguingly demonstrated by Ishikawa et al. (23), showing a significant correlation between restenosis after directional coronary atherectomy and degree of CRP immunoreactivity in the excised coronary plaques. In the current issue of this journal, Rittersma et al. (4) add their original contribution to the scientific appraisal of the prognostic role of CRP after PCI. They report on 345 patients undergoing nonurgent percutaneous coronary stent implantation who underwent clinical and angiographic follow-up to ascertain prognostic variables for target-lesion revascularization and angiographic restenosis. The strong points of the study are the preprocedural measurement of high-sensitivity CRP and the thorough analysis of its predictive role as well as the 100% angio-
graphic follow-up at 6–10 months. In this study, the authors could not find any association or trend between CRP concentrations and angiographic restenosis or target-lesion revascularization. This result appears in line with findings from Zairis et al. (2) and Zhou et al. (20), even if in conflict with other reports. Nonetheless, the patients enrolled by Rittersma et al. (4) were at very low risk: only 9% were diabetics and only 3% had undergone previous coronary artery bypass surgery. Indeed, the low risk was confirmed by the low rate of death or myocardial infarction 12 months after stenting, which was only 1.7% in the overall cohort. Moreover, the statistical power of this patient cohort to recognize predictive variables for restenosis may have been suboptimal, as evidenced by the surprising fact that a well-recognized and independent predictor of restenosis, such as diabetes mellitus (5), was not associated with either restenosis or target lesion revascularization in this study (4). The more immediate implication of this study is thus that CRP might not be a major or independent predictor of in-stent restenosis in low-risk patients undergoing elective PCI with stent implantation. These results, however, can be applied only to a low-risk population undergoing single-vessel stenting (a population in which the risk-benefit and cost-benefit ratios of PCI are still debated) and not to the entire population of patients with ischemic heart disease. It should be also stressed that angiographic evaluation of restenosis is accurate in describing the biological events, but not necessarily their clinical impact, and that target-vessel revascularization may also be affected by physician choices. The specific prognostic role of CRP in predicting restenosis in patients with acute coronary syndromes, who supposedly have more inflamed and unstable plaques and arteries, was not assessed in this study. However, the same group has recently published a large study confirming the predictive role of CRP on the risk of death and myocardial infarction after PCI (22), and their current study (4), notwithstanding the low-risk population and relatively small number of patients, has shown a trend in this direction. Because the data in favor of the predictive role of CRP for death and myocardial infarction are very consistent, patients undergoing PCI should not be denied a CRP measurement. Moreover, current evidence on the systemic and pancoronary nature of inflammatory mechanism in atherothrombosis strongly reminds us that we are treating vulnerable patients and not simply vulnerable coronary lesions or atherosclerotic plaques (24).

In relation to the major question raised by Rittersma et al. (4), the available data are insufficient to support the intriguing hypothesis that CRP can be used to guide decisions about bare-metal vs drug-eluting stenting. The problem of stenting or not stenting, and of which stent to use, is not a small one clinically or, indeed, economically in an era of cost containment in many countries. This underscores the need for large, prospective, randomized studies to explore this issue and provides the basis for systematic and comprehensive risk stratification.

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