The main adverse reactions to coronary stents are in-stent restenosis (ISR) and stent thrombosis. Along with procedural factors, individual susceptibility to these events plays an important role. In particular, inflammatory status, as assessed by C-reactive protein levels, predicts the risk of ISR after bare-metal stent implantation, although it does not predict the risk of stent thrombosis. Conversely, C-reactive protein levels fail to predict the risk of ISR after drug-eluting stent (DES) implantation, although they appear to predict the risk of stent thrombosis. Of note, DES have abated ISR rates occurring in the classical 1-year window, but new concern is emerging regarding late restenosis and thrombosis. The pathogenesis of these late events seems to be related to delayed healing and allergic reactions to polymers, a process in which eosinophils seem to play an important role by enhancing restenosis and thrombosis. The identification of high-risk individuals based on biomarker assessment may be important for the management of patients receiving stent implantation. In this report, we review the evolving role of inflammatory biomarkers in predicting the risk of ISR and stent thrombosis. (J Am Coll Cardiol 2010;56:1783–93) © 2010 by the American College of Cardiology Foundation

Stent implantation has substantially replaced plain old balloon angioplasty for the treatment of coronary stenosis because of better angiographic results and fewer complications. Unfortunately, in-stent restenosis (ISR) has largely limited the efficacy of bare-metal stents (BMS), because it occurs in up to 30% of patients treated with BMS. The introduction of drug-eluting stents (DES) significantly reduced the incidence of ISR as compared with BMS, although ISR still occurs (7% to 13%) depending on lesion and procedural features (1). Furthermore, new concerns are emerging with DES regarding late ISR and stent thrombosis (ST) (2–5).

Along with technical/mechanical factors, the individual response to stent implantation is another often underestimated important player in ISR and ST (Fig. 1). Interestingly, several experimental studies have demonstrated that local and systemic inflammation plays a pivotal role in the pathogenesis of ISR, promoting neointimal proliferation through the stent struts (6,7). Moreover, recent evidence suggests a role for inflammation in the pathogenesis of ST (4,8–10). In the clinical arena, a marker of systemic inflammation, C-reactive protein (CRP), has been shown to predict clinical and angiographic outcomes in patients undergoing BMS implantation or plain old balloon angioplasty (11,12). In contrast, the relation between systemic inflammation and DES restenosis remains controversial, whereas recent observations suggest an association of CRP levels with ST (10,13). Finally, allergic inflammation, largely mediated by eosinophils, has recently been involved in adverse reactions to DES (4,8). In this report, we review the evolving role of inflammatory biomarkers in predicting ISR and ST.

**ISR: An Old Problem Incompletely Solved by DES**

From a pathologic point of view, neointimal proliferation is the leading mechanism involved in the pathogenesis of ISR (6,7). After an acute inflammatory reaction, which occurs very early after stent implantation, the metal stent struts promote a “foreign-body” reaction, with migration into the intima and subsequent proliferation of vascular smooth muscle cells (VSMC) (14).

Drug-eluting stents were designed to obtain a site-specific delivery of drugs with antiproliferative and anti-inflammatory properties, able to counteract the mechanisms leading to ISR. In particular, each DES comprises 3 components: the stent platform, the active drug, and the drug carrier (usually a polymer). Of note, polymer-free DES have recently been introduced into clinical practice; in these DES, the drug is eluted directly from reservoirs inside the stent (15). First-generation DES were coated with either sirolimus (sirolimus-
eluting stent (SES) or paclitaxel (paclitaxel-eluting stent [PES]), able to block VSMC migration and proliferation. Despite exciting results being reported during the initial trials evaluating the safety and efficacy of first-generation DES, the real-world use of DES has clearly shown that ISR still occurs after DES implantation, the temporal window of ISR presentation being wider compared with that of BMS. Some studies indeed have raised the possibility of a late catch-up phenomenon (2,3,16,17), as if antiproliferative drugs might simply delay the occurrence of ISR; however, other studies have failed to demonstrate a significant occurrence of late restenosis after DES implantation (18,19), thus prompting further investigations.

**ST: An Expanding Concern With DES**

A near-complete re-endothelialization of stent struts has been demonstrated to occur 3 to 4 months after coronary BMS stent implantation (7). In contrast, after DES implantation, the eluted drug, besides affecting neointima formation, has been shown to affect arterial healing with delayed re-endothelialization, resulting in a prothrombotic environment and the need for prolonged dual antiplatelet therapy (20). Furthermore, hypersensitivity reactions against the polymer have been associated with thrombotic complications probably mediated by persistent inflammation and late malapposition (4,20). Finally, enhanced tissue factor expression induced by both sirolimus and paclitaxel, as well as persistent endothelial dysfunction, may contribute to the pathophysiology of DES-associated ST (21–23).

**DES Versus BMS Adverse Reactions: The Case for a Distinction**

Whereas the occurrence of early adverse reactions to coronary stents seems to be mainly related to procedural and

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### Abbreviations and Acronyms

- **BMS** = bare-metal stent(s)
- **CRP** = C-reactive protein
- **DES** = drug-eluting stent(s)
- **ECP** = eosinophil cationic protein
- **ISR** = in-stent restenosis
- **MACE** = major adverse cardiac event(s)
- **MI** = myocardial infarction
- **PCI** = percutaneous coronary intervention
- **PES** = paclitaxel-eluting stent(s)
- **SES** = sirolimus-eluting stent(s)
- **ST** = stent thrombosis
- **TLR** = target lesion revascularization

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**Figure 1** Mechanisms Involved in Adverse Reaction to Stents

Multiple interacting mechanisms including stent characteristics, procedural factors, individual susceptibility, and inflammation may lead to adverse reaction to stents. *Factor involved mainly or exclusively in drug-eluting stent (DES) restenosis. CTO = chronic total occlusion; SVG = saphenous vein graft.

- **Classical** inflammation
  - Mainly mediated by neutrophils, monocytes and Th1 lymphocytes

- **Allergic** inflammation *
  - Mainly mediated by eosinophils and Th2 lymphocytes

**Inflammation**

**Mechanical factors**

- Lesion characteristics
  - lesion length
  - complex lesions (bifurcations, SVG, CTO, restenosis)
  - vessel diameter (pre- and post-procedural diameter)

- Procedural factors
  - stent under/over expansion
  - stent fracture
  - stent malapposition
  - non-uniform strut distribution

**Stent characteristics**

- Metal platform
  - foreign body reaction
- Polymer *
  - hypersensitivity reaction
  - non-uniform drug release
- Drug *
  - drug resistance
  - time course of elution

**Genetic predisposition**

- inflammation-related genes
  - cell-cycle regulating genes

**Clinical factors**

- acute coronary syndrome
- diabetes
- renal failure
technical factors for both DES and BMS (24), a growing body of evidence suggests that late adverse reactions to DES and BMS are different in relation to pathogenesis, histopathologic features, and clinical presentation (Fig. 2).

Pathologic examinations of specimens derived from human coronary atherectomy revealed that DES restenosis was associated with a larger amount of old thrombus and fibrinoid compared with BMS, possibly as a consequence of the delayed tissue healing induced by the eluted drug (25). Indeed, incomplete endothelialization and the presence of thrombus were more frequently found at angioscopy up to 2 years after percutaneous coronary intervention (PCI) for patients with DES but not BMS (26). Otherwise, the increased thrombotic burden in DES-treated patients might also be related to hypersensitivity reaction to stent polymer (4). Furthermore, a recent study showed different smooth muscle cell phenotypes in specimens of restenotic tissue obtained from BMS or DES ISR (27). Optical coherence tomography (OCT) studies confirmed that DES restenosis may be composed of different tissues, showing the presence of neointimal components with different optical properties (28). In contrast, neointimal hyperplasia after BMS implantation is recognized by OCT as homogeneous tissue (29). Of interest, coronary segments treated with DES showed the angioscopic evidence of yellow neointima coverage at 10-month follow-up, suggesting nouveau atherosclerosis, which is associated with increased thrombotic burden (30). Similar findings have been obtained by using OCT (31) and

Figure 2 ISR of BMS or DES: Role of Biomarkers and Potential Therapy Targeting Inflammation

The evolving role of biomarkers in risk assessment after bare-metal stent (BMS) or drug-eluting stent (DES) implantation, along with potential therapies targeting inflammation, are shown. The contribution of specific cell types is also shown in the different phases of response of the vessel wall against the stent. Of note, late thrombotic events may complicate the healing process after DES implantation. Figure illustration by Craig Skaggs. (+++) = useful for risk assessment with much evidence from published reports. (+) = probably useful in risk assessment but little evidence from published reports. (+/−) = not useful in risk assessment. (?) = data are lacking about use in risk assessment. CRP = C-reactive protein; ECP = eosinophil cationic protein; ISR = in-stent restenosis.
may be related to increased lipid deposition within the arterial wall, leading to an accelerated atherosclerosis with a higher thrombogenic potential. Accordingly, clinical presentation of symptomatic ISR was observed with myocardial infarction (MI) more often with DES than with BMS (32).

Past observations have indicated that the peak rate of BMS restenosis occurs at 6 to 9 months, and this time frame was used to evaluate DES efficacy. However, data about the time course of DES restenosis are more limited. A recent study by Byrne et al. (16) investigated the notion of late catch-up restenosis, evaluating the time course of ISR following implantation of DES, with an angiographic follow-up at 6 to 8 months and at 2 years. Interestingly, DES showed an increasing late luminal loss beyond 6 to 8 months, which was less pronounced for polymer-free DES compared with permanent-polymer DES, suggesting a critical role of polymer-induced inflammation in determining late DES restenosis.

Similarly, the temporal course of ST after BMS implantation is quite different compared with that observed after DES implantation. Although acute, subacute, and late ST (<1 year) rates are similar for BMS and DES, concerns have been raised about a higher occurrence of very late ST after DES implantation (5,33), particularly following cessation of double antiplatelet therapy (24,34). Whereas acute, subacute, and late ST appear to share common procedure-related mechanisms for both BMS and DES, very late ST seems to be a consequence of an abnormal reaction of the vessel wall against the polymer, as suggested by postmortem observations that showed eosinophilic inflammation, delayed healing, and strut malapposition of thrombosed stents (4,20). The occurrence of coronary aneurysms observed following DES implantation is also probably related to late stent malapposition (4,35). Finally, local immunosuppression induced by the eluted drug has been suggested as a favoring factor for stent-related infections with DES (36), which may be complicated with mycotic aneurysms.

Although cessation of dual antiplatelet therapy has been associated with ST, it is worth noting that ST may occur in patients on double antiplatelet therapy, thus suggesting that other mechanisms may be involved. In particular, many biologic observations suggest a close link between inflammation and platelet reactivity or blood thrombogenicity (37), although recent observations suggest beneficial effects of antiplatelet drugs being mediated in part by antiinflammatory effects (38). Interestingly, acute infection-inflammation has been linked in an observational study with ST, especially in those patients with a low-risk profile for ST based on known risk factors (39).

Taken together, these findings suggest that after a first phase when the eluted drug is able to counteract the inflammatory reaction following stent implantation, a second window of inflammation, perhaps enhanced by the presence of the stent polymer, may contribute to delayed ISR by favoring late neointimal proliferation and ST. This second window of inflammation is reminiscent of the late phase reaction, also called type IV allergic reaction or delayed-type hypersensitivity with infiltration of T helper 2 lymphocytes and eosinophils (40).

**Mechanical and Patient-Related Predictors of ISR and ST**

Many studies have assessed predictors of ISR or ST after BMS or DES implantation. Lesion-related (type C lesion, vessel size, and lesion severity) and procedure-related (number of stents implanted and angiographic, intravascular ultrasound [IVUS], or pressure-derived indexes of stent expansion at stent level) factors have been associated with ISR after BMS implantation, and most of them have been confirmed to play a role also after DES implantation (41,42). Among patient-related factors, diabetes and renal failure increase ISR rates after both BMS and DES implantation (41,43).

Stent thrombosis shares most of the previously described predictors of ISR (44). It is worth noting, however, that most BMS-related ST occurs early (<30 days) and is mainly associated with procedural factors (stent underexpansion, stent length, dissection, and residual disease at the stent edges), but late, and particularly very late, DES-related ST has been mainly associated with patient-related factors (poor response to antiplatelet drug, premature discontinuation of antiplatelet therapy, diabetes, malignancy, renal failure, and acute coronary syndrome at presentation) (45).

**Prognostic Value of Inflammatory Biomarkers With BMS**

Several inflammatory biomarkers have been investigated in the setting of coronary stenting to stratify the risk of both angiographic and clinical outcomes. CRP is the most widely studied biomarker in patients undergoing PCI and represents a sensitive marker of systemic inflammation. CRP is an acute-phase protein produced mainly by hepatocytes in response to stimulation by inflammatory cytokines, primarily interleukin (IL)-6 (46). CRP has been shown to predict future cardiac events in both primary and secondary prevention studies (47,48). Interestingly, CRP has also been demonstrated to be an excellent marker of post-stenting inflammatory status. Indeed, the levels of CRP increase after PCI in a time-dependent manner, peaking at 48 h, and the magnitude of CRP change after the procedure has been shown to predict ISR in patients undergoing BMS deployment (49).

Notably, a few studies only evaluated serum levels of CRP after stent implantation over time, by serial assessment. CRP protein levels have been shown to be persistently higher at 6 months in those patients with ISR in some studies (50) but not in others (51), thus suggesting that baseline or post-procedural levels of CRP may help in prediction of ISR more than that at follow-up.
A recently published meta-analysis of 9 studies involving 2,747 patients undergoing BMS implantation showed that higher baseline CRP serum levels were a significantly predictor of angiographic restenosis (odds ratio: 1.59, 95% confidence interval: 1.21 to 2.07; p = 0.01) (52) (Fig. 3). Of interest, Hoshida et al. (50) demonstrated that in patients with stable angina, increased pre-procedural CRP levels were an important risk factor for ISR only among patients who were not receiving statins, but not among treated patients. Accordingly, Walter et al. (53) showed an interaction among admission CRP levels, statin therapy, and rate of restenosis in patients undergoing BMS implantation. Finally, Hong et al. (54) showed that plaque morphology is another factor modulating the link between inflammation and ISR, concluding that the combination of soft plaque detected by IVUS and elevated CRP levels was the most significant independent predictor of ISR.

The association between CRP and BMS-related ISR is probably accounted for by the fact that acute-phase proteins represent a marker of hyper-responsiveness to inflammatory stimuli, thus suggesting that pre-procedural activation of inflammatory cells may play a role in the modulation of the vessel wall response to injuries derived from stent deployment (11). The association between CRP and ISR might also be explained by the direct proinflammatory effects of CRP on endothelial cells (55). However, mendelian trials evaluating patients with genetically elevated CRP levels failed to demonstrate a pathogenetic role for CRP in cardiovascular diseases (56). Accordingly, a study by Zee et al. (57) found no association between CRP polymorphisms and restenosis after balloon angioplasty.

Importantly, both baseline and post-procedural peak levels of CRP have been associated with the overall rate of major cardiovascular events (MACE) after BMS implantation (53,58), although no large study has specifically assessed the association of CRP levels with ST after BMS. In studies without systematic angiographic follow-up, it is obviously impossible to determine whether the association with MACE is due to stent-related events or to atherosclerosis progression in native coronary arteries.

Other inflammatory biomarkers have been investigated for risk prediction after BMS implantation. In particular, matrix metalloproteinase (MMP)-2, MMP-9, and pregnancy-associated plasma protein A, involved in extracellular matrix degradation and VSMC migration following vascular injury, have been associated with angiographic ISR (59–61).

### Figure 3 Forest Plot of Studies Assessing Relation Between Pre-Procedural CRP Levels and BMS Restenosis

Overall and each study estimate of the odds ratio (OR) of the angiographic restenosis associated with high versus low levels of pre-procedural CRP. **Boxes = OR; horizontal lines = 95% confidence intervals (CIs).** High CRP levels mean that the level of CRP was greater than the cut-off value specified in each study. The cut-off value ranged from 0.3 to 1.0 mg/dl according to the study. Modified from Ferrante et al. (52). Abbreviations as in Figure 2.
Furthermore, platelet and neutrophil activation as assessed by sCD40L and glycosylphosphatidylinositol-80 levels, respectively, was associated with ISR after BMS implantation (62,63). Finally, fibrinogen and plasminogen activator inhibitor (PAI)-1 activity, proteins involved in the coagulation system that are usually considered inflammatory biomarkers, have been associated with ISR after BMS implantation (64,65). Overall, the results are less robust than that observed with CRP. This may be related to their short half-lives, which increase measurement variability. In contrast, the long half-life of CRP (approximately 19 h) makes the measurements more reproducible (66).

Furthermore, several polymorphisms of inflammation-related genes have been associated with an increased risk of restenosis (67–69). In particular, a single-nucleotide polymorphism of the cyclin-dependent kinase inhibitor p27kip1, a key regulator of VSMC and leukocyte proliferation, has been found to be associated with ISR rate (67), as well as a polymorphism of toll-like receptor 2, a molecule involved in the interaction between the immune system and infective pathogens (68).

Taken together, studies performed in the setting of BMS implantation have strengthened the role of inflammatory biomarkers in risk prediction of ISR. Because of its prolonged half-life, as compared with that of other inflammatory biomarkers, CRP has been the most investigated. Although inflammatory biomarkers do not specifically predict ISR because they may also predict progression and destabilization of atherosclerosis in native coronary arteries, data coming from angiographic studies clearly show that both baseline and post-procedural CRP levels are useful for the identification of patients at higher risk of restenosis after BMS. Whether CRP levels are associated with ST cannot be extrapolated by published studies.

### Prognostic Value of Inflammatory Biomarkers With DES

Recent studies evaluated the association between CRP or other inflammatory biomarkers and angiographic and clinical outcomes after DES deployment (Table 1). In contrast with findings of studies on BMS, pre-procedural serum CRP levels do not appear to predict ISR in this setting. Park et al. (70) failed to show increased ISR and late loss among tertiles of baseline CRP on 1,650 consecutive patients undergoing successful DES implantation. The prognostic value of the magnitude of CRP changes after DES implantation has also been investigated. Gaspardone et al. (58) prospectively enrolled 160 consecutive patients with stable single-vessel disease undergoing BMS, SES, PES, or dexamethasone-eluting stent (DEX) implantation and assessed serum CRP changes at 48 h compared with baseline. Pre-procedural CRP levels were similar among all groups of patients, and CRP levels significantly increased after coronary stenting without any difference across the 4 groups. Interestingly, the incidence of angiographic binary restenosis at 12 months was significantly lower in the SES and PES groups compared with that of BMS and DEX, suggesting that the lower rate of ISR observed after DES deployment was unlikely to be related to a reduced acute systemic inflammatory response but rather to a local blunted inflammatory response. Dibra et al. (71), enrolling 301 stable or unstable patients treated with BMS or SES implantation, showed that a higher CRP change after the procedure was a predictor of ISR in the BMS group but not in the SES group. Moreover, a study by Kang et al. (72) failed to demonstrate an association between changes in CRP or IL-6 levels and neointima hyperplasia evaluated by IVUS, following SES or PES deployment.

Serum levels of MMP, PAI-1, and complement components C3a and C5a have also been evaluated for risk prediction after DES implantation. Katsaros et al. (73) demonstrated that baseline MMP-9 and post-procedural (after 24 h) MMP-9 and MMP-2 levels were significantly higher in patients with ISR at the 6- to 8-month angiographic follow-up compared with those in patients without ISR. Moreover, plasma levels of PAI-1 before and 24 h after PCI were associated with the occurrence of angiographic ISR (74). Finally, Speidl et al. (75) found that serum levels

### Table 1 CRP Levels and Adverse Reaction to Stent in Patients Undergoing DES Implantation

<table>
<thead>
<tr>
<th>First Author (Ref. #)</th>
<th>Year</th>
<th>Stent</th>
<th># of Patients With DES</th>
<th>Clinical Presentation</th>
<th>Predicted Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CRP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dibra et al. (71)</td>
<td>2005</td>
<td>SES</td>
<td>149</td>
<td>SA</td>
<td>ISR not predicted</td>
</tr>
<tr>
<td>Park et al. (70)</td>
<td>2007</td>
<td>SES/PES</td>
<td>1,650</td>
<td>ACS or SA</td>
<td>ISR not predicted</td>
</tr>
<tr>
<td>Niccoli et al. (83)</td>
<td>2009</td>
<td>SES/PES</td>
<td>200</td>
<td>ACS or SA</td>
<td>TVR not predicted</td>
</tr>
<tr>
<td>Park et al. (10)</td>
<td>2009</td>
<td>SES/PES</td>
<td>2,691</td>
<td>UA or SA</td>
<td>TVR not predicted, ST predicted</td>
</tr>
<tr>
<td>Choi et al. (76)</td>
<td>2010</td>
<td>SES/PES</td>
<td>1,859</td>
<td>ACS or SA</td>
<td>TVR not predicted, ST predicted</td>
</tr>
<tr>
<td>Delhaye et al. (77)</td>
<td>2010</td>
<td>SES/PES</td>
<td>936</td>
<td>UA or SA</td>
<td>TVR not predicted</td>
</tr>
<tr>
<td>Post-procedural CRP changes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dibra et al. (71)</td>
<td>2005</td>
<td>SES</td>
<td>149</td>
<td>SA</td>
<td>ISR not predicted</td>
</tr>
<tr>
<td>Gaspardone et al. (58)</td>
<td>2006</td>
<td>SES/PES/DEX</td>
<td>121</td>
<td>SA</td>
<td>ISR predicted</td>
</tr>
<tr>
<td>Kang et al. (72)</td>
<td>2009</td>
<td>SES/PES</td>
<td>79</td>
<td>SA</td>
<td>ISR not predicted</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome; CRP = C-reactive protein; DES = drug-eluting stent(s); DEX = dexamethasone-eluting stent(s); ISR = in-stent restenosis; PES = paclitaxel-eluting stent(s); SA = stable angina; SES = sirolimus-eluting stent(s); ST = stent thrombosis; TVR = target vessel revascularization; UA = unstable angina.
of C3a before and 24 h after PCI, as well as baseline C5a levels, were significantly higher in patients developing ISR at the 6- to 8-month angiographic follow up.

CRP levels have recently been associated with the risk of MACE (10,76,77). Park et al. (10) conducted a study on a large patient population (n = 2,691) with a median follow-up of 3.9 years; baseline CRP levels were associated with an increased risk of death, MI, and ST, with CRP levels improving the predictive value above that of clinical, angiographic, and procedural factors. Interestingly, this large study failed to show an association of baseline CRP levels with target vessel revascularization.

Taken together, available information suggests that the predictive role of inflammation for adverse reactions to stent, as assessed by CRP levels, seems to shift from restenosis as observed with BMS to thrombotic complications, including ST with DES. This apparent paradox may be explained by the following observations. After DES implantation, the eluted drug is able to halt the inflammatory reaction leading to restenosis also in patients with enhanced inflammatory response as revealed by high CRP levels. In contrast, very late thrombosis occurs when the drug effect is over; in this setting, an enhanced inflammatory response as revealed by high serum CRP levels, perhaps triggered by the polymer, may predispose patients to thrombus formation. With BMS, the lack of drug elution leaves unopposed the inflammatory reaction, leading to restenosis, especially in patients with an enhanced inflammatory response. In contrast, very late thrombosis is rare, perhaps because of the lack of polymer, and therefore difficult to predict.

Allergic Reaction to Stent Implantation: A New Player

As noted previously, recent evidence supports the notion that a localized hypersensitivity reaction to stent components may be involved in the inflammatory process following stent implantation. Eosinophil infiltrates surrounding stent struts have been described in ISR tissue of patients treated with BMS but rarely in post-balloon restenotic tissue (78,79). Notably, histopathologic studies showed that eosinophils are observed among inflammatory cells more with DES than with BMS, suggesting that allergy-mediated inflammation plays a greater role with DES than with BMS-related ISR (80).

Although DES can promote eosinophil recruitment through different mechanisms, available pathologic evidence supports the notion that hypersensitivity to the polymer is the most likely mechanism. In fact, polymers have been shown to produce hypersensitivity reactions in humans and to promote inflammation when implanted in swine coronary arteries (81). On the other hand, the hypersensitivity reaction is unlikely to be caused by the eluted drug because pharmacokinetic studies performed in dogs and rabbits show that the drug is no longer present in the arterial wall after 60 days and because of its anti-inflammatory properties that would suppress accumulation of such inflammatory cells (82).

Accordingly, we have recently shown for the first time that enhanced eosinophilic activation at baseline, as assessed by pre-procedural serum eosinophil cationic protein (ECP) levels, predicts the clinical outcome after implantation of first-generation DES (83). Because the target lesion revascularization (TLR) rate was highly prevalent in the composite end point when compared with death or MI, our findings should mainly be applied to TLR.

Notably, eosinophils might play a role not only in ISR but also in ST. Indeed, eosinophilic infiltrates may affect vessel remodeling, leading to secondary stent malapposition and local thrombosis (4). Moreover, eosinophils can directly stimulate the coagulation pathway and promote platelet activation (84). Virmani et al. (4) initially documented a localized hypersensitivity reaction associated with late inti-stent thrombosis in a patient implanted with an SES. Moreover, Joner et al. (20) reported post-mortem findings from a series of 40 patients who died after DES implantation, showing local hypersensitivity reaction as a risk factor for late ST. Additional data on hypersensitivity reactions after DES deployment were shown by the RADAR (Research on Adverse Drug Events and Reports) project, which concluded that DES may be a cause of systemic and intrastent hypersensitivity reactions that, in some cases, have been associated with late thrombosis and death, confirming the association among local hypersensitivity reaction, thrombosis, and lack of intimal healing (9). Finally, a recent study by Cook et al. (8) showed that eosinophilic infiltrates are more common in thrombi harvested from very late DES thrombosis as compared with those harvested from other causes of MI.

The role of eosinophil activation, as assessed by ECP serum levels, needs to be evaluated more extensively in the setting of coronary stenting with BMS. Indeed, eosinophil infiltrates have been demonstrated around stent struts of restenotic BMS (78), and positive patch test to metal allergy has been associated with restenosis of BMS (85).

The Evolving Role of Biomarkers in Risk Assessment After Stent Implantation

Based on the different mechanisms of ISR and ST between DES and BMS, the use of inflammatory biomarkers after DES needs to be reappraised. Both choice of biomarkers and timing of measurements need careful reassessment (Fig. 2). Indeed, CRP measurement before DES implantation may be useful in the identification of a nonspecific inflammatory hyper-reactivity that may lead to an increased rate of ST (10). CRP may also predict a worse clinical outcome not related to stent-related events but rather to the progression and destabilization of coronary atherosclerosis, as previously observed in subjects without or with pre-existing coronary artery disease. The role of new biomarkers such as MMP-9,
C3a, and C5a to predict the risk of ISR after DES implantation should be further investigated.

More importantly, biomarkers of hypersensitivity, like ECP, may be useful for the identification of patients at increased risk to develop an allergic response to the stent polymer (83). Further studies are warranted to evaluate the prognostic value of biomarkers of allergy not only at baseline but also at other time points (for instance, when drug elution is over) to better detect potential allergic reactions to polymer or even to metal. Furthermore, other biomarkers (e.g., IL-5, leukotrienes) or diagnostic tests of allergy (e.g., intradermal or patch tests) need to be investigated. Interestingly, patients with allergic patch-test reactions to nickel and molybdenum appear to have a higher rate of ISR following BMS implantation (85).

**Therapeutic Implications**

Both traditional and allergic inflammation may become a therapeutic target in patients undergoing stent implantation. Administration of statins or steroids has been suggested to reduce the risk of MACE after BMS. Statins exhibit well-known anti-inflammatory properties (86); their beneficial effects in patients undergoing stent deployment have been documented in many clinical studies, although the studies are limited by small sample sizes (87–89). The ARMYDA (Atorvastatin for the Reduction of Myocardial Damage During Angioplasty) studies demonstrated that patients treated with atorvastatin 40 mg/day either before or at the time of PCI have a smaller increase in CRP levels compared with placebo (87). These acute effects are more likely explained by anti-inflammatory rather than lipid-lowering effects. Moreover, a small study with angiographic follow-up confirmed a reduced risk for the occurrence of ISR after BMS implantation in patients receiving statin therapy (90). Accordingly, the LIPS (Lescol Intervention Prevention Study) showed that treatment with fluvastatin 80 mg/day in patients undergoing first PCI, with or without BMS implantation, resulted in a 5.3% absolute reduction and 22% relative reduction in the risk of MACE during 4 years of follow-up compared with placebo (89).

Steroids are potent anti-inflammatory agents that may blunt cytokine-induced VSMC proliferation. The IMPRESS (Immunosuppressive Therapy for the Prevention of Restenosis After Coronary Artery Stent Implantation) study evaluated the administration of a systemic steroid therapy (oral prednisone 72 h after PCI, 1 mg/kg for the first 10 days, 0.5 mg/kg from day 11 to day 30, and 0.25 mg/kg from day 31 to day 45) in patients undergoing BMS implantation. Importantly, an inclusion criterion was the presence of persistently high CRP levels after the procedure (CRP >0.5 mg/dl at 72 h). This study showed a striking reduction in number of clinical events at 12 months (28% absolute reduction) and the angiographic restenosis rate at 6 months (7% vs. 33%) as compared with placebo. The use of systemic steroids after BMS should be further investigated because it may become an adjunctive therapy to prevent ISR after BMS implantation in patients at high risk for ISR who are not suitable for DES (e.g., patients with atrial fibrillation who need life-long anticoagulation). However, an important issue related to steroid administration is its applicability in the real-world population. In fact, side effects derived from systemic steroid therapy are well known and may preclude its use in patients with comorbid conditions, such as diabetes (a major cause of ISR), hypertension, and congestive heart failure. In the IMPRESS trial, 15% of patients among those referred for stent implantation fulfilled the enrollment criteria (91). Of note, no beneficial effect could be detected when the dose of prednisone was decreased by nearly one-half (91,92).

Stents releasing steroids, such as DEX, have been designed in the attempt to obtain a pharmacologic modulation of local inflammation. Yet evidence derived from clinical studies has not shown any clinical benefit (93,94). This might be due to suboptimal drug concentrations and/or to the fact that steroids are hydrophilic and therefore sink in blood rather than being absorbed by the lipophilic arterial wall (95).

The antidiabetic drug pioglitazone, ligand for peroxisome proliferator-activated receptors, is an anti-inflammatory drug. Several studies performed in patients with diabetes have demonstrated a reduced incidence of ISR and TLR after BMS deployment associated with peroxisome proliferator-activated receptor agonist administration (96–98). Accordingly, a recent study showed a lower ISR rate in patients with diabetes treated with DES when pioglitazone was added to standard treatment (96).

Antiplatelet drugs exhibit anti-inflammatory effects (38). Accordingly, a recent subanalysis of the CREDO (Clopidogrel for the Reduction of Events During Observation) trial in patients treated with nonurgent coronary stenting suggested that the clinical benefit of adding clopidogrel to aspirin was greater in those with higher levels of baseline CRP (99).

Besides treatment targeting “classical” inflammation, specific therapies for allergic reactions to stent polymer need to be investigated in the future. Of note, steroids have been shown to suppress eosinophil survival and activation, reducing the production of related cytokines. Thus, steroids might also be considered in patients with elevated baseline ECP levels. Moreover, recent evidence in animal models suggests that statins, besides their effects on classical inflammation, may affect hypersensitivity reactions by reducing eosinophilic activation (100). Antileukotriene drugs (leukotriene receptor antagonists or 5-lipoxygenase inhibitors) may represent another possible therapeutic approach to further reduce the allergic response toward the stent polymer because leukotrienes are involved in hypersensitivity reactions (101).

An allergen–specific desensitizing immunotherapy toward stent polymer or the introduction of bioabsorbable polymers or polymer-free stents represent other promising
therapeutic approaches to further reduce the risk of allergic reactions to DES (15,102). Bioabsorbable stents may become another possible tool to prevent ISR and ST (103,104).

Finally, important issues in the attempt to optimize anti-inflammatory treatment of stent-related adverse events are administration timing and patient selection. To prevent BMS-related ISR, anti-inflammatory drugs have to be given early. In contrast, the time course of DES-related ISR suggests that the best timing, for an antiallergic treatment, might be when the drug elution is over, leaving proinflammatory and proallergic effects of the polymer unopposed (Fig. 2). With regard to patient selection, it is critical to select patients with intense activation of inflammatory cells, as detected by systemic levels of inflammatory markers, who are likely to enjoy the highest benefit from an anti-inflammatory treatment. Surprisingly, in the past, only a few trials of anti-inflammatory treatment of stent-related adverse events have based patient enrollment on levels of inflammatory markers (91).

References


38. Kereiakes DJ. Adjunctive pharmacotherapy before percutaneous coro-


69. Hamann L, Gomma A, Schroder NW, et al. A frequent toll-like recep-


71. Park DW, Lee CW, Yun SC, et al. Prognostic impact of prepro-
cedural C-reactive protein levels on 6-month angiographic and 1-year clinical outcomes after drug-eluting stent implantation. Heart 2007;93:1087–92.


75. Choi DH, Park KW, Yang HM, et al. Renal dysfunction and high levels of hsCRP are additively associated with hard endpoints after percutaneous coronary intervention with drug eluting stents. Int J Cardiol 2010 Feb 4 [E-pub ahead of print].


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