Thrombosis and Drug-Eluting Stents
An Objective Appraisal

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Stent thrombosis (ST) after percutaneous coronary intervention has been the focus of intense interest because of its attendant morbidity and mortality. There is controversy about several facets of the problem. These include the frequency of ST with drug-eluting stents (DES) versus bare-metal stents (BMS), the timing of the event, clinical consequences, risk factors, adjunctive therapy, and new preventive approaches. Information has accrued rapidly from several sources, including randomized controlled clinical trials of DES versus BMS in carefully selected subsets of patients and registry experiences in larger patient groups, which provide a more universal real-world picture. The results from these different data sets are not completely concordant. However, several general conclusions can be made: 1) ST is an infrequent but very severe complication of both BMS and DES; 2) at the present time, during 4 years of follow-up from randomized controlled trials that compared DES and BMS, there is no apparent difference in overall ST frequency, although the time course for occurrence appears to differ, with a relative numeric excess of ST late after DES implant; 3) despite this relative imbalance, no differences in the end points of death or death and infarction between DES and BMS are observed; 4) longer-term follow-up of these patients as well as larger angiographic and clinical subsets of patients who receive this technology outside of randomized trials are required to fully study this issue; and 5) advances in stent platforms for drug elution as well as adjunctive pharmacologic therapy are being evaluated to enhance long-term safety.

Definitions of ST

Several definitions of ST have been used, clouding the issue of incidence as well as presentation. In angiographic series, the definition has required acute ischemic symptoms and angiographic documentation of Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 or 1 or the presence of a flow-limiting thrombus in the stented segment. This identifies a very select group of patients and might underestimate the true incidence.

“Clinically suspected ST” requires clinical presentation with an acute ischemic event and electrocardiographic changes in the distribution of the stented segment. While it is traditional to include sudden death within 30 days of the procedure in the definition of ST, broader definitions now in use include sudden unexplained death beyond 30 days. This definition of ST is the most liberal and may overestimate the incidence.

Definitions may also vary with regard to timing. Acute or subacute ST includes 1 of the previously mentioned
events (angiographic or clinical) occurring either during the index procedure (acute) or within 30 days (subacute). Late ST has been defined as occurring from 30 to 360 days after the index procedure. Very late ST has been defined variably as occurring either >6 months or >1 year later. Recently, a standardized definition has been proposed by the Academic Research Consortium (ARC) (10). Using this approach, some authors have suggested that definite or probable ST is the most accurate representation of the event (10).

**Clinical Consequences of ST**

The consequences of abrupt coronary closure after percutaneous coronary intervention have been well described. With conventional balloon angioplasty, acute or threatened closure was observed in 6% to 8% of patients. In the National Heart, Lung, and Blood Institute percutaneous transluminal coronary angioplasty (PTCA) registry 1985 to 1986 cohort, when occlusion occurred during the procedure, 40% of patients developed infarction (17); this was the most important predictor of in-hospital infarction and mortality (18). Although these data relate to conventional PTCA, they remain valid today for ST.

**Thrombosis With Different Stent Platforms**

**Bare-metal ST.** The majority of studies with bare-metal stents (BMS) reported ST only within the first 30 days. In a cumulative analysis of 8 clinical series involving almost 20,000 patients, an average incidence of ST of 1.2% (range 0.4% to 2.8%) was reported through 30 days of follow-up (19). Late ST with BMS has been incompletely studied. A recent publication by Ferrari et al. (20) is noteworthy because it documents 10 late or very late ST occurring with BMS after aspirin withdrawal. Those events occurred at 15 ± 6.5 months after stent implantation. When ST occurs, it is catastrophic. In one analysis of bare-metal ST, Cutlip et al. (6) found that the 30-day death or infarction rate was 64%. Mortality was 18.9% at 30 days and 20.8% at 6 months. Registry reports by Karillon et al. (21) and Moussa et al. (22) of stented patients document 30-day mortality of 26% and 24%, respectively, when thrombosis occurs. In the Orford et al. analysis (23), ST was observed in 0.51% of 4,509 patients who received BMS; with ST, 48% died and 39% had a nonfatal infarction.

**Drug-eluting ST.** Subacute ST with drug-eluting stents (DES) remains equally serious (3–5,10–16,24–30), with associated fatality rates of 40% to 50% and the composite of death or infarction in 50% to 70% of patients. The specific incidence of events varies depending on whether the definition was "angiographic subacute thrombosis" or "presumed clinical subacute thrombosis." In one small series, Ong et al. (28) found that after "angiographic subacute thrombosis," the 30-day mortality was 15% and nonfatal infarction occurred in 65% of patients. After "presumed clinical subacute thrombosis," mortality was 75% and nonfatal infarction was 25%.

Selection bias as well as the limits and assumptions about timing of ST events and their outcomes makes categorization and understanding difficult. Although most cases occur during the first 6 months, sporadic cases continue to be reported in much later time frames (4,27–29). Because observational reports usually include only patients who present with acute syndromes, the question is raised of whether stents may thrombose and go undetected more frequently when associated with less dramatic clinical presentations.

The relative frequency of ST with different stent platforms is of great interest. Given the unique differences between DES in terms of specific drug, polymer, and metal backbone, there may be differences in ST. Comparisons have been hampered by the fact that the overall event rate is small, and the duration of follow-up has been limited. No randomized trials to date have been adequately powered to evaluate ST as a primary end point. Given the low event rate, sample sizes for such a trial would be very large. The results of the analyses to date have documented either no appreciable or only a slight difference (31–33).

**Thrombosis in BMS versus DES.** Evaluation of the frequency of ST with DES versus BMS has been difficult (9,27,28,31,33). Ideally, one would like to compare the frequency of ST in comparable patients treated with DES versus BMS. Such a comparison would have to overcome the complexities of whether patients and adjunctive therapies as well as definitions and surveillance programs were similar enough for such analyses. A major confounding factor is that in randomized trials, which offer the best opportunity for comparable patient and lesion demographics, mostly lower-risk patients are studied and the actual incidence of ST may be underestimated relative to "real world" post-market patient populations (15). Conversely, owing to the lower restenosis rate, it is also clear that more complex lesions are being treated with DES than was the case with BMS.

In a pooled analysis of 10 randomized trials of DES versus BMS and sirolimus-eluting stents (SES) as well as paclitaxel-eluting stents (PES) with data on 5,030 patients, ST out to 9 months occurred in 0.6% of 2,602 DES patients and 0.5% of 2,428 BMS patients (9). This incidence is similar to nonrandomized trial data previously published with BMS (6,23). In another meta-analysis confined to PES, 8 trials involving 3,817 patients were analyzed (31). The hazard ratio (HR) for ST within the first year was 1.06 (95% confidence interval [CI] 0.55 to 2.04), indicating no significant difference between PES and BMS. A more recent analysis of pooled data from the TAXUS (Taxus Paclitaxel-Eluting Stent)-II, -IV, -V, and -VI trials dem-
onstrated that between 6 months and 3 years of follow-up, a slight but statistically significant increase in ST was observed after Taxus versus BMS deployment ($p = 0.019$) (34).

More recently, the results of several pooled analyses have become available based on pooled patient-level data (10,12–14). These studies have considerable overlap because the central component of each is the inclusion of many of the same randomized trials of DES versus BMS that were used for Food and Drug Administration approval. The definition of ST included both the protocol as well as the ARC definitions. The primary end points of each of these pooled analyses varied.

Two of these studies were restricted to trials of SES versus BMS. Spaulding et al. (14) evaluated 1,748 patients for 4 trials, using as a primary safety end point 4-year survival, and found no difference between the 2 groups: 93.3% survival rate for SES and 94.6% for BMS (HR for death 1.24, 95% CI 0.84 to 1.83; $p = 0.28$). The incidence of death or any infarction was also not different: 11.6% for SES versus 10.5% for BMS ($p = 0.48$). Finally, ST rates were not different; using the ARC definition (10), any ST occurred in 30 of 878 SES patients (3.6%) versus 28 of 870 BMS patients (3.3%). In a larger analysis of 14 trials and 4,958 patients, Kastrati et al. (12) also evaluated a primary end point of all-cause mortality during a mean follow-up of 12.1 to 58.9 months. They also found no difference in the incidence of death or the combined end point of death or infarction (Fig. 1). In addition, using the combined end point of death, infarction, or reintervention, SES was associated with marked improvement in outcomes (HR 0.43, 95% CI 0.34 to 0.54). An important finding in this study was that although the overall risk of ST was not different between SES and BMS, there was “evidence of a slight increase in ST with SES after the first year” (12).

The outcomes with SES, PES, and BMS were evaluated by Stone et al. (13) and Mauri et al. (10). Stone et al. (13) evaluated the same 4 SES trials as Spaulding et al. (14) and then included 5 additional trials of 3,513 patients randomly assigned to PES or BMS (Fig. 2). The primary end point of the analysis was 4-year safety and efficacy. The 4-year target vessel revascularization rates were markedly reduced irrespective of whether SES or PES was used. In addition, the rate of death or infarction was not different between SES and BMS. Of interest was the finding that although overall ST through 4 years was not different with DES versus BMS, beginning after 1 year ST was more frequent after DES. No differences in death or myocardial infarction were observed. In the final study, Mauri et al. (10) specifically evaluated ST in randomized trials of both SES and PES versus BMS using both the original protocol definitions and the ARC definitions. In these randomized trials with carefully selected patients and lesions, depending upon the definition used the absolute frequency of ST varied and was highest with the most inclusive definition. The authors concluded that using the ARC definition of definite or probable ST provided the best approximation of the true incidence of the phenomenon. With this definition, no significant differences between DES and BMS were observed.

In nonrandomized registry experiences, particularly those including longer-term follow-up, the incidence of ST has been variable but appears to be slightly higher than observed in randomized controlled trials. In a 2-center registry with 9-month follow-up, Iakovou et al. (3) observed a 1.3% incidence, whereas in the RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) and T-SEARCH (Taxus Stent Evaluated at Rotterdam Cardiology Hospital) registries the incidence was 1.0% (28). In the Cypher (Cypher Sirolimus-Eluting Stent) post-market surveillance study on an “all comers” registry of 15,000 patients (35), the ST rate at 1 year was 0.87%. In the integrated TAXUS program involving over 3,400 patients, the total rate of ST to 3 years was 1.2% with PES versus 0.7% with BMS. After Taxus stent deployment, 50% of ST were observed within 30 days; the remainder occurred between 30 and 180 days (36). Given the fact that ST may present as sudden death, cause of death was studied in 4
randomized Cypher stent trials involving 1,748 patients (37). In that analysis, total mortality was slightly increased in patients who received the SES (vs. BMS), but that was the result of an increase in noncardiac mortality in the 2 smallest studies (RAVEL [Randomized Comparison of a Sirolimus Eluting Stent With a Standard Stent for Coronary Revascularization] and e-SIRIUS [Sirolimus-Eluting Stent in Coronary Lesions]) (Fig. 3). When cardiac deaths alone were analyzed, no difference in frequency was seen in patients treated with DES or BMS.

Other registry experiences have also become available. Williams et al. (38) reported on 6,906 patients undergoing PCI at 140 medical centers from January to June 2005. Bare-metal stents were used in 397, SES in 3,873, and PES in 2,636 patients. They found that although the unadjusted 1-year rates of death and myocardial infarction were higher with BMS than DES, after adjustment the rates were not significantly different. Stent thrombosis occurred with 0.8% of BMS, 0.5% of SES, and 0.8% of PES.
Recently, the results of the Swedish Coronary Angiography and Angioplasty Registry have been published and included 6,033 patients with DES and 13,738 patients with BMS (15). The primary outcome analysis was death and infarction. During 3 years of follow-up, there was no difference in the composite of death and infarction between the 2 groups. There was a bimodal distribution of events: at 6 months, the event rate was lower with DES. After 6 months, however, patients with DES had higher events. After 6 months, patients with DES experienced death and/or infarction at a rate of 0.5% to 1.0% higher per year. Of interest, the marked improvement in need for new revascularization procedures seen with other studies of DES was not seen: of patients with DES, 14.7% underwent new percutaneous coronary interventions compared with 14.5% of BMS patients. The basis for the differences between this study and the DEScover (Drug-Eluting Stent Versus Bare Stent in Acute Myocardial Infarction) Registry (38) of 6,906 patients is unclear but may relate to length of follow-up available or other factors.

In higher-risk patient/lesion subsets, the incidence of ST may be increased. This may relate to the specific drug as well as to differences in drug diffusion that depend on the presence and amount of organized thrombus (39). The TYPHOON (Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated With Angioplasty) study (40) randomized 700 patients with acute infarction to either SES or BMS. The overall incidence of ST was 3.4% for SES and 3.6% for BMS. In a similar randomized study of 423 patients with acute infarction, the SESAMI (Sirolimus Stent Versus Bare Stent in Acute Myocardial Infarction) investigators observed ST in 3.1% of SES versus 3.7% of BMS (41). Although it makes intuitive sense that higher-risk patients would have more frequent ST, the data are not all concordant. For example, the PASSION (Paclitaxel-Eluting Versus Uncoated Stents in Primary Percutaneous Coronary Intervention) trial reported 619 patients with ST-segment elevation myocardial infarction randomized to either PES or BMS (42). Acute ST occurred in only 1 patient (0.3%) in the PES group. Subacute ST (1 to 30 days after the procedure) occurred in 1 patient (0.3%) in the PES group and 3 patients (1.0%) in the BMS group. Late ST (after 30 days) occurred in 1 patient in the PES group and none in the BMS group. The reasons for apparent discordance in the incidence of ST (for both BMS and DES) between the PASSION and the TYPHOON or SESAMI trials are unclear but may in part be related to differences in definition and/or requirement for angiographic documentation.

An overriding concern regarding ST is not so much the early incidence, which has been reasonably well studied, but the potential long-term continuing risk that patients may face, especially after DES deployment. The BASKET-LATE (Basel Stent Kosten Effektivitats Trial-Late) study evaluated this issue in 826 patients randomized in a 2:1 fashion to receive DES or BMS (43). Discontinuation of Plavix (clopidogrel bisulfate) at 6 months was not specified by protocol, and the study was not designed primarily to detect differences in ST. Between 7 and 18 months of follow-up, the rates of nonfatal infarction and death were increased in the DES group (Fig. 4) although the absolute frequency was low. In addition, there was an imbalance in ST and thrombus-related events.

It is now clear from a few limited series with long-term follow-up that late and even very late ST may occur with both BMS and DES. As already mentioned, recent patient pooled analyses (12) document some evidence of a numeric excess in ST after 1 year with DES. The focus now is to minimize the risk of this occurrence with either BMS or DES. Should the incidence of late ST be found to be small but continuous after DES, the challenge will be to mitigate this risk given the known benefits of these devices in terms of their efficacy in reducing clinical and angiographic restenosis (44,45).
Pathology of ST

There is limited information about the histopathology underlying ST (5–8,24,46). A recent autopsy study (8) identified several important observations, including: 1) DES were characterized by persistent fibrin deposition (indicative of delayed healing) as well as reduced endothelialization compared with BMS ($p < 0.0001$); and 2) other factors associated with late ST included local tissue hypersensitivity reaction, placement of the stent in ostial and/or bifurcation stenoses, incomplete stent apposition (malapposition), in-stent restenosis, and stent penetration of the necrotic core of the underlying plaque.

Risk Factors for ST

Any study of ST is complicated by the fact that there are multiple risk factors, including patient-, lesion-, and procedure/device-related variables as well as compliance with, or resistance to, antiplatelet agents (5,7–9,46–55). Multiple angiographic, procedural, and patient demographic factors associated with BMS thrombosis have been identified (47). Thrombosis after DES deployment has been associated with the presence of renal insufficiency, diabetes, and depressed left ventricular function as well as stent length, bifurcation target stenosis, and stent overlap. Intravascular ultrasound (IVUS) evaluation (51,52,56) has identified other factors (lower minimum stent cross-sectional area, reduced stent expansion, and residual significant stenosis) related to DES thrombosis. In addition, interruption or discontinuation of dual antiplatelet therapy has been associated with thrombosis of DES, even late after deployment.

An early report of 4 patients (4) documented angiographic ST which occurred “soon after antiplatelet therapy was interrupted” between 335 and 442 days after stent deployment (2 Taxus and 2 Cypher stents). Each of these 4 patients experienced an acute ST myocardial infarction related to the ST. A subsequent report from the same centers suggested that the incidence of late angiographic ST after DES deployment was approximately 0.35% (27). In the large, 2-center experience published by Iakovou et al. (3), late ST (30 days to 9 months) was observed in 0.5% of Cypher- and 0.8% of Taxus-treated patients, and premature discontinuation of antiplatelet therapy was the most significant single factor implicated in the occurrence of either subacute or late ST. In the recent analysis by Mauri et al. (10) of SES, 2 of 9 patients with sirolimus-eluting ST and 6 of 12 patients with bare-metal ST after 30 days were receiving dual antiplatelet therapy.

It must be remembered that late ST is a rare event. An important missing piece of information relates to the number of patients who discontinue dual antiplatelets after 3 or 6 months after DES implantation but do not develop ST. Irrespective of that, the recurrent theme of antiplatelet therapy discontinuation raises important issues. Although the current instructions for use of the 2 approved DES recommend dual (aspirin + thienopyridine) antiplatelet therapy for 3 months (Cypher) or 6 months (Taxus), the more protracted persistent risk for ST raises the question of whether combination antiplatelet therapies should be continued indefinitely (57). Indeed, a recent report suggested that early ($≤30$ days) discontinuation of thienopyridine therapy is associated with a highly significant ($p < 0.001$) increase in mortality to 1 year after DES deployment for ST-segment elevation myocardial infarction (58). Although the benefit of extended clopidogrel (dual) antiplatelet therapy beyond 6 months has been debated (43,59), recent data suggest that extension of dual therapy beyond 6 months and even 1 year is associated with significant clinical benefit (43,60). Indeed, in a nonrandomized clinical experience with follow-up to 2 years after stent deployment, treatment with a DES with continued aspirin and clopidogrel therapy beyond 1 year was associated with a survival advantage as
well as survival free of death and myocardial infarction at 24 months (60). These data argue for longer duration clopidogrel therapy in patients treated with DES (57,61,62). In this context, a recent American Heart Association Science Advisory (57) has recommended continuation of dual antiplatelet therapy for “at least 1 year” and deferral of elective surgical procedures for this time frame as well. Despite these data, the optimal duration of dual antiplatelet therapy will only be determined by large-scale scientifically controlled studies.

Dual antiplatelet therapy may also be associated with economic challenges as well as bleeding risk compared with aspirin alone. Thus, continuation of dual antiplatelet therapy in patients at low risk for ST is problematic because it might be associated with increased bleeding. Accordingly, any incremental risk of bleeding must be weighed against the incidence of ST, both of which are very infrequent (57).

Dual antiplatelet therapy may be discontinued for the performance of noncardiac surgical procedures or for cost considerations in addition to bleeding. The required duration of antiplatelet therapy has become a significant factor in undertaking percutaneous coronary intervention in patients with substantial and complex comorbidities who are likely to need subsequent medical attention over the ensuing years. In those patients, estimation of ST risk is crucial, particularly >1 year after initial implantation.

Although antiplatelet therapy discontinuation has been a common theme in most clinical series of DES, this single factor does not completely explain the phenomenon (57). In almost one-half of reported ST cases, antiplatelet therapy discontinuation does not appear to be implicated, and other factors (renal failure, treatment of bifurcation lesions, diabetes mellitus, decreased ejection fraction, increasing stent length, and clopidogrel nonresponsiveness) appear to be operative (8,9,50).

Patient and lesion complexity are also important considerations. In the RAVEL study (63) of patients with relatively simple lesions in a single vessel, ST rate after 5 years was 0 in both the SES and BMS arms of the study (P.W. Serruys, personal communication, 2006). In the ARTS (Arterial Revascularization Therapies Study) I multivessel stenting study using BMS, the thrombosis rate at 30 days was 2.8%, whereas in the more recent ARTS II study using SES it was only 0.8% (64). Short-term studies of new devices in noncomplex lesions are, therefore, unlikely to reflect the true risk of ST.

**Preventive Strategies**

Because the etiology of ST is multifactorial, strategies aimed at its prevention should be multimodal as well. To be effective, such strategies should include:

1. **Optimizing stent implantation.** Selection of the appropriate diameter and length of stent to both optimally cover the target lesion and appropriately expand the reference vessel is crucial. Placement of excessively long DES (“overstenting” relative to target lesion) should be avoided. Residual stent marginal dissections or significant stenoses proximal or distal to the target lesion should be treated. Suboptimal under- or overdeployment of stent diameter, which has been associated with increased risk for ST, should be avoided. Intravascular ultrasound may be useful in optimizing deployment results. Indeed, IVUS analyses have demonstrated that both Cypher and Taxus stents achieve only 75% ± 10% of predicted minimal stent diameter and 66% ± 17% of predicted minimum stent area (65,66). Approximately 25% of both stent types implanted into 3.0-mm vessels do not achieve a minimum stent area >5.0 mm² using manufacturer-supplied compliance charts to target final stent dimensions based on stent size and inflation pressure (65,66). Subsequent ST has been associated with both stent underexpansion and a lower minimum stent area. Some specific techniques may be associated with higher rates of ST (67). It is important to remember that the need for a specific technique, e.g., “stent crush,” may just be a marker for a stenosis at high risk for subsequent ST or other adverse events. It is also possible that different DES are associated with different risk for subacute closure (68).

2. **Adjunctive therapy.** Dual antiplatelet therapy (aspirin plus thienopyridine) after DES implantation is crucial. Recently, the recommendation has been to extend this therapy for up to 12 months in patients at low risk for bleeding events (57). Whether or not longer durations of dual antiplatelet therapy will be of actual benefit is unclear, although clinical practice patterns have shifted toward this direction, particularly in patients felt to be at low risk of bleeding. The length of this extended therapy remains the subject of considerable debate and concern. There has been considerable interest in identifying the specific smaller group of patients at increased risk of ST. Preliminary data suggest that “triple” antiplatelet therapy (adding 100 mg cilostazol orally twice daily to aspirin plus thienopyridine) may be associated with a reduction in major adverse cardiovascular events, including ST, and may be a therapeutic option for patients at high risk for ST (69). Similarly, the administration of 150 mg clopidogrel daily may be considered for patients at high risk for ST or those who are clopidogrel hyporesponsive (<50% platelet inhibition). This treatment option has been incorporated into the American College of Cardiology/American Heart Association clinical practice guideline recommendations (class IIa recommendation) (70). In patients who either will not (noncompliance, cost considerations) or cannot take extended dual antiplatelet therapy, BMS deployment should be used preferentially, particularly where the magnitude of benefit from DES compared with BMS is small (e.g., large vessel diameter with short stent length).
The treatment of patients who must discontinue dual antiplatelet therapy prematurely within 3 to 6 months of DES implantation is difficult. Interruption of antiplatelet therapy is usually prompted by the requirement for a noncardiac surgical procedure or, less commonly, by a clinically significant bleeding event. In cases where surgery is required, the surgeon should be consulted to determine the absolute necessity for discontinuing dual antiplatelet therapy. If at all possible, temporary interruption of clopidogrel therapy (stop 5 days before and restart ≤48 h after surgery) perioperatively without discontinuation of daily aspirin therapy (81 mg) should be attempted. There are no data to support interim perioperative therapies such as low-molecular-weight heparin or platelet glycoprotein IIb/IIIa receptor inhibitors to reduce the risk of ST during discontinuation of oral antiplatelet therapies. If a gradient for continued risk of very late thrombosis with DES is documented, this will significantly affect patient care. Finally, much less is known regarding late thrombotic risk after deployment of newly available DES platforms outside of the U.S. (71). The risk of thrombosis as well as optimal duration of dual antiplatelet therapy should optimally be assessed on an individual basis for each device.

Future

Future objectives for reducing risk of ST and/or the requirement for extended (indefinite) dual antiplatelet therapy include evolutionary improvements in both drug-eluting stent platforms and adjunctive pharmacotherapies.

Efforts to reduce risk of ST have focused on the development of more biocompatible or biodegradable polymers for drug elution. New platforms with reduced polymer surface area (reservoirs) are in clinical testing. Whether a smaller amount of polymer or a bioabsorbable polymer will result in less ST will require the study of many more patients with more complex lesions and longer-term follow-up. Other strategies have been aimed at enhanced healing (72), incorporating antithrombotic medications into the polymer coating, and complete elimination of the persistent metal alloy prosthesis with biodegradable stent platforms (73). Long-term follow-up will be necessary to fully assess safety as well as efficacy.

New Adjunctive Pharmacotherapies

The issue of hyporesponsiveness or resistance of platelets to pharmacologic treatment has received considerable attention (74–79). It must be remembered that the extension from “in vitro hyporesponsiveness” to “clinical hyporesponsiveness” is a long leap, particularly because the incidence of in vitro hyporesponsiveness is much higher than the very low rate of ST. Clopidogrel (76–78) hyporesponsiveness has been correlated with adverse ischemic events, including ST. Although an increase in the oral loading dose of clopidogrel from 300 to 600 mg can reduce the prevalence of hyporesponsiveness as well as accelerate the time course and enhance the magnitude of platelet inhibition achieved, marked variability in individual patient response persists (80).

Novel thienopyridine derivatives (81,82) which bind the platelet P2Y12 receptor are in development specifically to address the limitations of clopidogrel.

Conclusions

Stent thrombosis is an infrequent but very severe complication of both BMS and DES. Acute ST may be the result of technical factors; the solution for this requires optimal deployment strategies. Late ST appears to be multifactorial in its etiology and thus requires a multifaceted solution. Although infrequent in occurrence, the consequences of late ST are frequently catastrophic and are just cause for concern. Specific patient- and target lesion-related as well as procedural factors which predispose to drug-eluting ST have been identified and must be kept in mind. Similarly, vigilance in maintenance of dual antiplatelet therapy is mandatory. More data are required to determine the optimal duration of dual antiplatelet therapy, which may ultimately be determined to be individual patient specific. Although there may be a difference in the time frame of ST between BMS and DES, at 4 years of follow-up in carefully selected patients, there is no difference in the hard end point of death and myocardial infarction. Longer-term studies of 5 years or even longer of DES in unselected patient populations are required to fully study the issues of this complex problem. Finally, advances in stent platforms for drug elution as well as adjunctive pharmacotherapies may be promising ways to enhance the long-term safety of DES.

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