Primary Prevention, Treatment, and Secondary Prevention of Late and Very Late Stent Thrombosis

Norman E. Lepor, MD, FACC, FAHA, FSCAI

The David Geffen School of Medicine at UCLA, Cedars-Sinai Medical Center, Los Angeles, CA

The occurrence of late and very late thrombotic complications in association with drug-eluting stents (DES) has recently garnered much attention, but these complications are also associated with bare-metal stents (BMS). Predisposing factors for BMS thrombosis, both early and late, include noncompliance with antiplatelet agents, an exercise-induced procoagulant state, brachytherapy, small stent size, underdeployment of the stent, depressed left ventricular ejection fraction, and impaired response to antiplatelet therapy. Independent predictors of DES thrombosis include premature interruption of antiplatelet therapy, primary stenting in acute myocardial infarction, total stent length, and renal failure. Prevention depends on applying an optimal stent deployment technique at the time of the index percutaneous coronary intervention (PCI), compliance with dual antiplatelet therapy, and extending antiplatelet therapy beyond current package insert recommendations. In patients who develop late stent thrombosis, efforts to achieve rapid normalization of coronary blood flow with PCI are mandatory.

[Rev Cardiovasc Med. *2007;8(suppl 1):S27-S33*]

Key words: Bare-metal stents • Drug-eluting stents • Late thrombosis • Very late thrombosis • Percutaneous coronary intervention

Coronary stents are accepted as effective treatment for acute vessel closure during percutaneous coronary intervention (PCI) and as an effective method for decreasing the rate of restenosis as compared with balloon angioplasty alone. Thrombotic complications following coronary stent placement have been appreciated since stents were commercialized in 1999. Nevertheless, these infrequent adverse events were an acceptable trade-off compared

with the 2% to 6% incidence of abrupt vessel closure that followed balloon angioplasty alone. The relatively high incidence (>6%) of late stent thrombosis (LST) following coronary artery brachytherapy for in-stent restenosis, particularly in patients receiving additional stents, focused attention on this important clinical issue.[1] The mechanism of brachytherapy-induced LST is believed to be secondary to delayed intimal healing and re-endothelialization. Understanding the similarities and differences of LST in bare-metal stents (BMS) and drug-eluting stents (DES) may allow refinement in the management strategies employed to prevent and treat this life-threatening complication of coronary artery stent placement.

Bare-Metal Stents

The occurrence of late and very late thrombotic complications in association with DES has recently garnered much attention and is recognized as a "hot button" clinical issue. However, the fact that this complication is also associated with BMS has largely been underappreciated.

Important observations by Farb and colleagues[2] provide us with key insights into the pathological mechanisms of LST in 13 bare-metal fatal stent thrombosis cases from a registry of human coronary stents. Twelve of the 13 cases demonstrated a failure to form a completely healed neointimal layer over the stent struts. Five cases were associated with stenting across the ostia of major side branches; 2 cases were associated with plaque disruption in the non-stented segment within 2 mm of the stent margin (zone of injury); 2 cases involved stenting of markedly necrotic, lipid-rich plaques with extensive plaque prolapse through the stent struts; and 1 case followed diffuse in-stent restenosis (Figure 1).

Based on these findings, Farb and colleagues[2] have proposed a variety of mechanisms of bare-metal LST, all of which involve delayed or impaired neointimal healing (Figure 2). Late-acquired stent malapposition was felt to be a possible underlying factor in LST and was observed in about 5% of patients following treatment with BMS. This phenomenon has not been associated with any major cardiac events during long-term follow-up.[3]

Wang and colleagues[4] reported a 0.76% incidence of late (bare-metal) stent thrombosis occurring between 31 days and 365 days following implantation. They demonstrated that the predisposing factors of subacute thrombosis differ from those of late thrombosis. Compared with patients who developed LST, patients who developed subacute thrombosis had smaller final balloon size and stent diameter. These authors have therefore suggested that, in contrast to subacute thrombosis, which is probably related to suboptimal stent deployment, LST is related to inadequate late re-endothelialization, residual thrombus, and/or persistent intimal tears adjacent to the stented segment.[4]

In an analysis of 6058 patients who were followed after BMS implantation between 1995 and 2003, 25% of patients who developed stent thrombosis did so more than 30 days following the stent procedure.[5] The development of LST resulted in myocardial necrosis (measured by the release of creatinine kinase in 81% of patients) and a reduction of left ventricular ejection fraction from 0.54 before LST to 0.48 following LST. Emergency PCI was successful in 91% of these patients and was complicated by death in only 2%. However, these patients remained at high risk for subsequent adverse events, with 6-month rates of mortality, reinfarction, and recurrent stent thrombosis of 11%, 16%, and 12%, respectively. BMS thrombosis occurred an average of 8 days after the index procedure and ranged from 0 days to 639 days post–stent deployment (Figure 3).

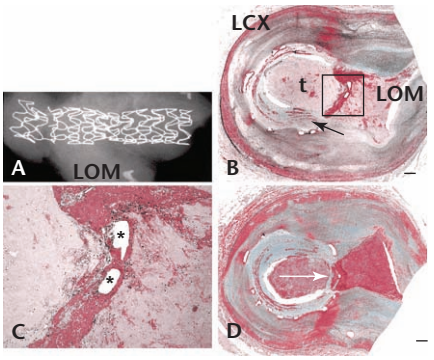

Figure 1. *Postmortem radiography* **(A)** *shows a MULTI-LINK® stent crossing the ostium of the LOM branch. An occlusive, platelet-rich thrombus (indicated by t) at the ostium of the LOM is shown in a low-power view* **(B)** *and a high-power view* **(C;** *box in* **B).** *Stent struts across the ostium* **(C,** *indicated by *) are not covered by neointima. Struts in contact with the LCX plaque are covered with alternating layers of neointima and fibrin* **(B,** *indicated by black arrow). A deeper section* **(D)** *demonstrates in-stent restenosis, a neointima with layered fibrin overlying the LOM ostium (indicated by white arrow), and an occlusive luminal thrombus. (B, C, and D images are shown in Movat pentachrome; scale bars are 0.36 mm in B and D, and 0.18 mm in C). LOM, left obtuse marginal; LCX, left circumflex artery. Reprinted with permission from Farb A et al.*[2] www.medreviews.com

Overall, 70% of patients received both aspirin and a thienopyridine at the time of stent thrombosis. The study does not comment specifically on the dose of aspirin and the type of thienopyridine used for those patients who developed LST and very late stent thrombosis (VLST). Multivariate analysis demonstrated that the achievement of Thrombolysis In Myocardial Infarction (TIMI) 3 flow and of a diameter stenosis less than 50% following treatment for stent thrombosis were associated with decreased mortality. In this same multivariate analysis, only the use of adjunctive periprocedural abciximab was associated with a decreased risk of recurrent stent thrombosis.

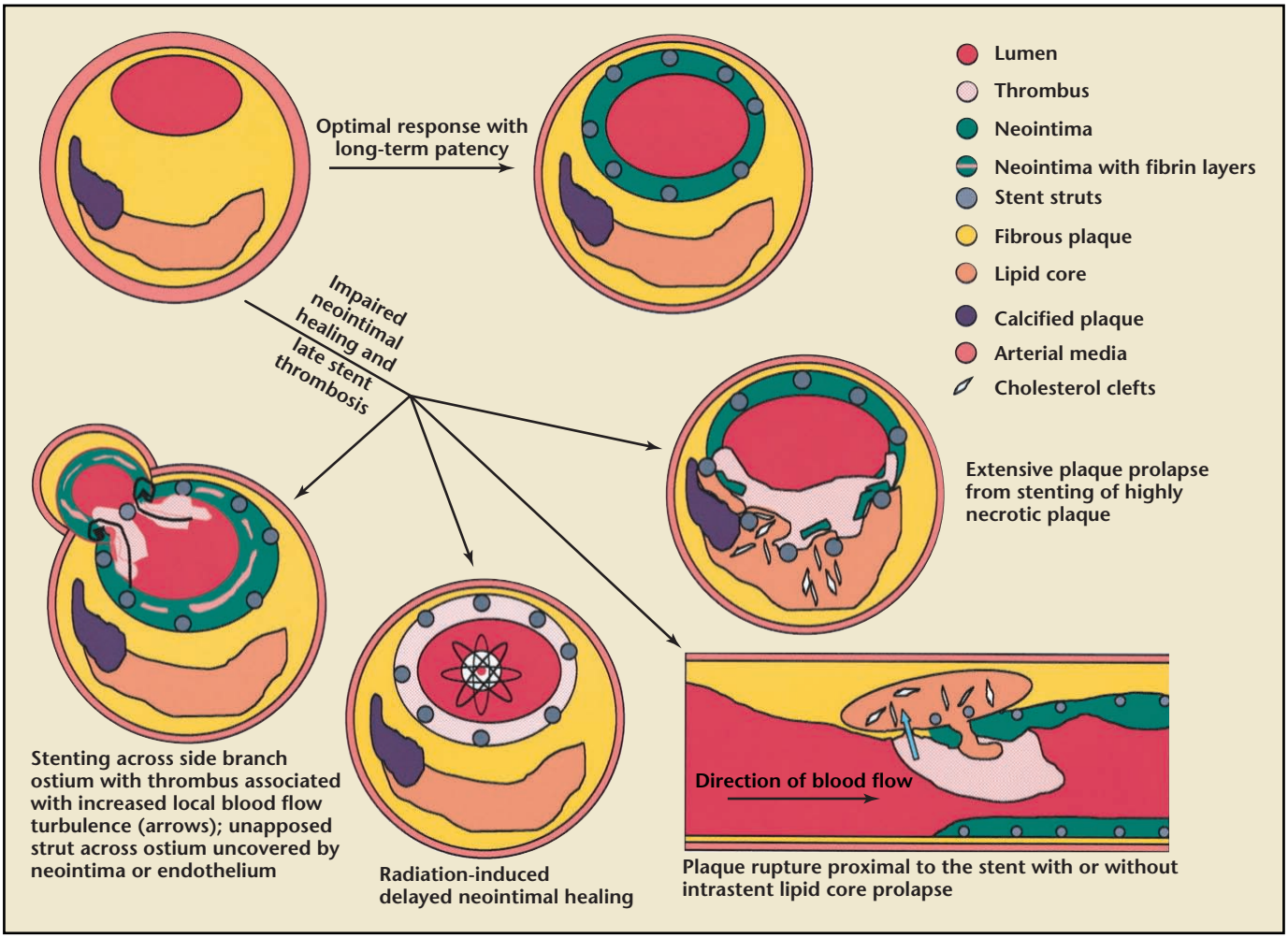

Figure 2. *Diagram depicting a postulated pathological mechanism of late stent thrombosis: the association of bare-metal stents with impaired neointimal healing. Reprinted with permission from Farb A et al.*[2] www.medreviews.com

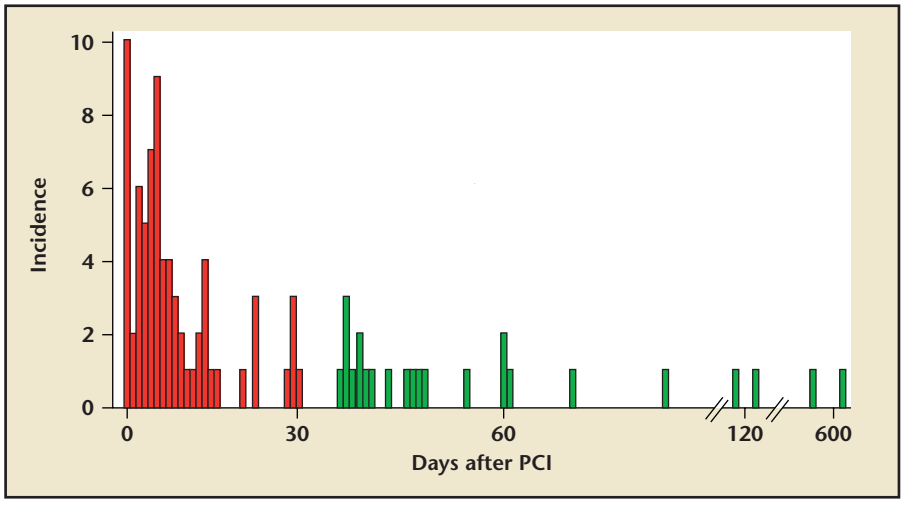

Figure 3. *Incidence of bare-metal stent thrombosis after percutaneous coronary intervention (PCI) occurring within 30 days (red) and after 30 days (green). Reprinted with permission from Wenaweser P et al.*[5] www.medreviews.com

Predisposing factors for BMS thrombosis, both early and late, include noncompliance with antiplatelet agents,[6] an exercise-induced procoagulant state,[7] brachytherapy,[8] small stent size, underdeployment of the stent,[9] depressed left ventricular ejection fraction, and impaired response to antiplatelet therapy.[10,11]

In summary, factors that contribute to bare-metal stent thrombosis can be placed into 3 categories: stent thrombogenicity, patient/lesion-related factors, and procedure-related factors (Figure 4). Characteristics of stents that may affect thrombogenicity include the type of alloy, the design, and the surface coatings.

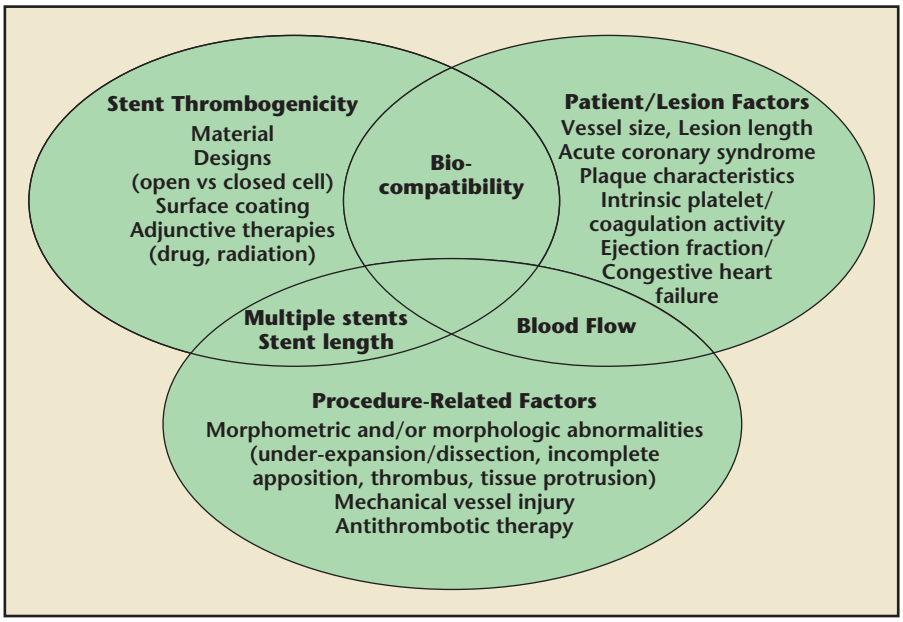

Figure 4. *Factors contributing to stent thrombosis: bare-metal stent era. Adapted with permission from Honda Y and Fitzgerald PJ,[25] and Kereiakes DJ et al.[12]* www.medreviews.com

Patient/lesion characteristics include the acuity of clinical presentation, vessel diameter and length, plaque characteristics, level of systemic coagulation activity, and ejection fraction. Procedure-related characteristics include the presence of dissection, especially at the edges of the stent, stent apposition to the vessel wall, and presence of thrombus and tissue protrusion through the stent struts.[12]

Drug-Eluting Stents

In an important study examining healing and late thrombotic risk associated with DES and BMS, Joner and colleagues[13] found that both sirolimus-eluting stents and paclitaxel-eluting stents were associated with delayed healing characterized by persistent fibrin deposition and reduced re-endothelialization compared with BMS (Figure 5). Follow-up to more than 40 months following PCI demonstrated a marked reduction in the index of endothelialization with DES compared with BMS.

In addition, the DES-treated patients who suffered LST had evidence of more delayed healing compared with DES patients with patent stents. Risk factors for LST included the presence of local inflammation or hypersensitivity reaction, ostial and bifurcation stenting, stent strut malapposition/incomplete apposition, restenosis, and strut penetration into a necrotic core. It would appear then that the pathophysiology of late (31 days to 360 days following DES placement) and very late (361 days to 1440 days following placement) DES thrombosis is related to incomplete neointimal formation on the deployed stent, which has direct implications for recommendations regarding the duration of dual antiplatelet therapy.

In a study of 1911 consecutive patients undergoing DES deployment (sirolimus-eluting in 1545 patients and paclitaxel-eluting in 366 patients) who were followed for a mean of 19.4 months, the observed incidence of late thrombosis was 0.6%, a rate similar to prior observations of BMS.[14] Independent predictors of DES thrombosis in this study included premature interruption of antiplatelet therapy, primary stenting in acute myocardial infarction, total stent length, and renal failure (Table 1).

In the Sirolimus-Eluting Stent in de Novo Native Coronary Lesions

Figure 5. *Comparison of healing timeline by percentage of endothelialization: drug-eluting stents (DES) versus bare-metal stents (BMS). Reprinted with permission from Joner M et al.[13]* www.medreviews.com

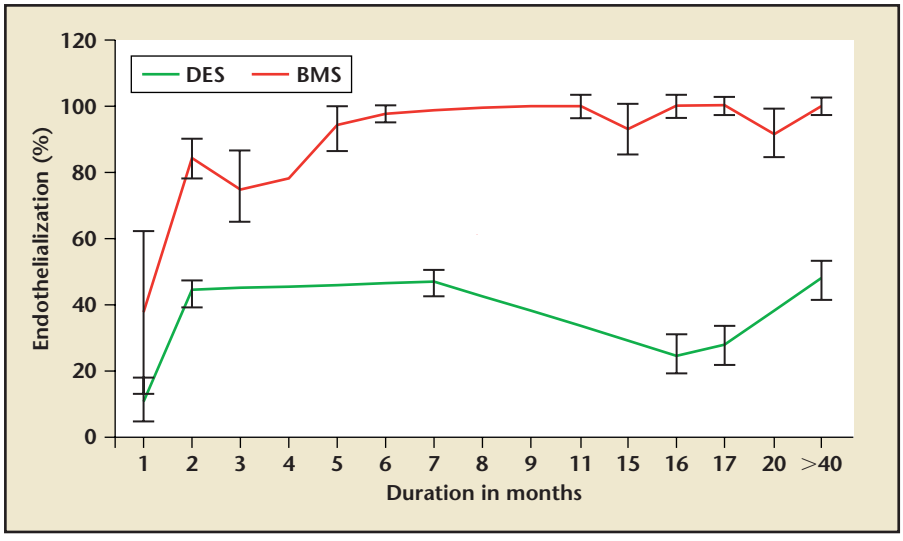

Table 1
Independent Predictors of Stent Thrombosis

Variable	Hazard Ratio	95% Confidence Interval	*P* Value
Total ST			
Premature interruption of antiplatelet therapy	19.21	5.63-65.51	<.001
Primary stenting in acute MI	12.24	1.67-89.71	.014
Total stent length (mm)	1.02	1.001-1.04	.037
Acute/subacute stent thrombosis			
Primary stenting in acute MI	74.22	5.89-861.45	.001
Total stent length (mm)	1.04	1.01-1.08	.048
Late stent thrombosis			
Premature interruption of antiplatelet therapy	24.79	7.51-81.84	<.001
Renal failure	8.40	1.81-39.09	.007

MI, myocardial infarction. Reprinted with permission from Park DW et al.[14]

(SIRIUS) trial, no differences in mortality or myocardial infarction were observed between sirolimus-eluting stents and BMS within the first 1 to 2 years following PCI.[15] In a "real world" registry experience of DES (including "off-label" use of DES), the overall rate of stent thrombosis was higher compared with that of clinical trial experience.[16] Although premature antiplatelet therapy discontinuation, renal failure, bifurcation lesions, diabetes, left ventricular dysfunction, and stent length were independent predictors of subacute stent thrombosis on univariate analysis, only premature discontinuation of antiplatelet therapy, bifurcation lesion treatment, and left ventricular dysfunction remained independent predictors of LST on multivariate analysis. "Crush" bifurcation stenting was also predictive of LST, with rates approaching 5%. An additional concern raised by this study was a 4-fold increase in the incidence of LST in patients treated with multiple paclitaxel-eluting stents (4.0%) versus sirolimus-eluting stents (0.9%) for bifurcation disease, although this difference did not achieve statistical significance ($P = .39$).

One hypothesis suggests that aspirin resistance and persistent adenosine diphosphate–induced platelet aggregation may be related to the occurrence of late thrombotic events in patients undergoing stent implantation. In the prospective Platelet Reactivity in Patients And Recurrent Events Post-Stenting (PREPARE POST-STENTING) study, 192 consecutive patients underwent elective stenting with 6-month follow-up. Gurbel and colleagues[17] demonstrated a higher rate of recurrent ischemia in patients within the highest quartile of adenosine diphosphate–induced platelet aggregation as compared with patients within the lowest quartile. Higher loading doses of clopidogrel have reduced, though not eliminated, the incidence of platelet resistance, and marked interindividual variability in clopidogrel response persists.

Incomplete neointimal formation following DES implantation may be responsible for the late thrombotic events observed in the Basel Stent Kosten-Effektivitats Trial-Late Thrombotic Events (BASKET-LATE) experience.[18] Pfisterer and colleagues continued to follow 746 patients from the original BASKET trial who underwent stent placement (DES or BMS) and were free from major cardiac events at 6 months after stent deployment (and in whom clopidogrel treatment was discontinued). The aim of BASKET-LATE was to define the incidence of clinical events related to stent thrombosis—and the timing of these events over 18-month follow-up—in patients treated with either a BMS or a DES. Patients treated with sirolimus-eluting stents or paclitaxel-eluting stents were combined into a single DES treatment group for comparisons. The initial benefit—a relative reduction in death/non-fatal myocardial infarction observed with DES compared with BMS—was lost by 16 months post-PCI (Figure 6).

This "catch up" phenomenon for event rates was related to an increased incidence of cardiac death and nonfatal myocardial infarction in the DES cohort following the cessation of clopidogrel therapy at 6 months post-PCI (Table 2). These results are consistent with delayed re-endothelialization and would indicate the need to consider more prolonged dual antiplatelet therapy in high-risk patients.

The initial benefit—a relative reduction in death/non-fatal myocardial infarction observed with drug-eluting stents compared with bare-metal stents—was lost by 16 months post-percutaneous coronary intervention.

Efforts to prevent LST include optimization of the mechanical delivery

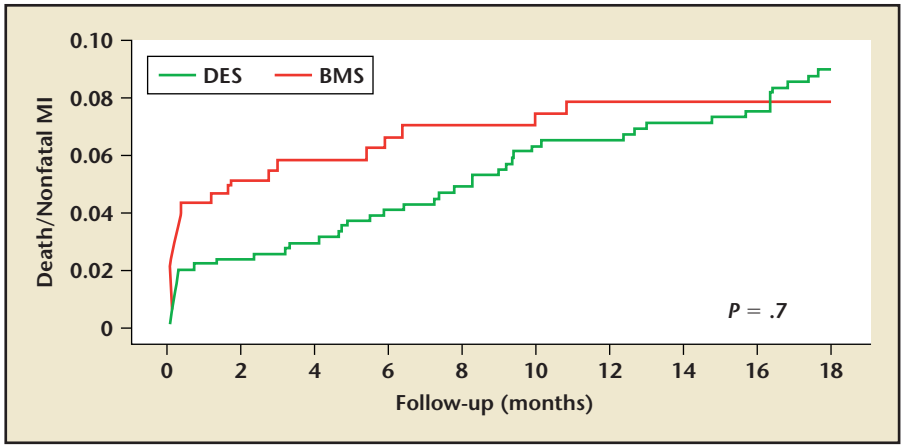

Figure 6. *Death and nonfatal myocardial infarction (MI) in patients undergoing placement of drug-eluting stents (DES) versus bare-metal stents (BMS). Reprinted with permission from Pfisterer M et al.*[18] www.medreviews.com

of the stent and the adjunctive pharmacologic management. In an analysis of 11 patients with LST, stent expansion was less and incomplete stent strut apposition was more common in patients with LST (55% vs 12%; $P < .0001$ compared with those patients who did not have LST).[19] Stent expansion should be dictated by the vessel size rather than by the arbitrary measure of the minimum stent cross-sectional area of 5.0 mm^2 to 5.5 mm^2.[20]

Recommendations to Prevent LST and VLST

Utilization of dual-antiplatelet therapy in patients undergoing placement of DES should be extended beyond the current package insert recommendations of 3 months (sirolimus-eluting stents) and 6 months (paclitaxel-eluting stents) for all patients who are at lower risk for hemorrhagic complications.[21,22] The 2005 American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions (ACC/AHA/SCAI) PCI guidelines recommend the use of dual antiplatelet therapy "ideally up to 12 months in patients who are not at high risk of bleeding."[23] It would be reasonable to continue dual antiplatelet therapy indefinitely in patients with high-risk characteristics who have no contraindications and a low risk of bleeding.

Patients who develop an acute coronary syndrome consistent with LST should undergo emergent coronary angiography to define the coronary anatomy and PCI to normalize coronary flow. Intravascular ultrasound (ACC/AHA Class IIA recommendation)[23] should be utilized to confirm full stent expansion and rule out malapposition as well as stent strut fracture. The ACC/AHA/SCAI 2005 PCI guidelines also give a Class IIA recommendation to the use of abciximab in patients presenting with ST-elevation myocardial infarction (STEMI) and to the use of any glycoprotein IIb/IIIa inhibitor in patients presenting with unstable angina/non-STEMI who will be undergoing PCI.[23] At the time of clinical presentation, patients with LST should also receive a loading dose of clopidogrel. Consideration could be given to evaluating these patients for the presence of platelet resistance to both thienopyridine and aspirin. Currently, however, no prospective data have demonstrated that assessment of platelet function (with subsequent adjustment in antiplatelet therapy) improves clinical outcomes, although ongoing studies are in progress to address this important issue. Fibrinolytic therapy has not demonstrated any benefit in the treatment of LST.

Summary

Prevention of LST and VLST depends on applying an optimal stent deployment technique at the time of the index PCI, compliance with dual antiplatelet therapy, and extending antiplatelet therapy beyond current package insert recommendations, especially in patients who are at higher risk of thrombosis and lower risk of bleeding. In patients who develop LST, efforts to achieve rapid normalization

Table 2
Major Cardiac Events Between 7 Months and 18 Months

Outcome	Bare-Metal Stent (%)	Drug-Eluting Stent (%)	*P* Value
Cardiac death	0	1.2	.09
Nonfatal MI	1.3	4.1	.04
Cardiac death/nonfatal MI	1.3	4.9	.01
Restenosis-related TVR	6.7	4.5	.21
MACE	7.9	9.3	.53

MI, myocardial infarction; TVR, target vessel revascularization; MACE, main adverse coronary event. Reprinted with permission from Pfisterer ME.[24]

of coronary blood flow (TIMI 3) with PCI are mandatory, and these patients should be approached with the same sense of urgency as patients presenting with ST-elevation myocardial infarction. Intravascular ultrasound can be useful to determine if there are any anatomic factors that predisposed the patient to the stent thrombosis and to help guide appropriate interventional strategies. ■

References

1. Costa MA, Sabat M, Giessen WJ, et al. Late coronary occlusion after intracoronary brachytherapy. *Circulation*. 1999;100:789-792.
2. Farb A, Burke AP, Kolodgie F, et al. Pathological mechanisms of fatal late coronary stent thrombosis in humans. *Circulation*. 2003;108:1701-1706.
3. Hong MK, Mintz GS, Lee CW, et al. Incidence, mechanism, predictors and long-term prognosis of late stent malapposition after bare-metal stent implantation. *Circulation*. 2004;109:881-886.
4. Wang F, Stouffer GA, Waxman S, et al. Late coronary stent thrombosis: early vs. late stent thrombosis in the stent era. *Catheter Cardiovasc Interv*. 2002;55:142-147.
5. Wenaweser P, Rey C, Eberli FR, et al. Stent thrombosis following bare-metal stent placement: success of emergency percutaneous coronary intervention and predictors of adverse outcomes. *Eur Heart J*. 2005;26:1180-1187.
6. Bhargava B, Karthikeyan G, Yadav R, et al. Late stent thrombosis following antiplatelet withdrawal while fasting during holy months. *Indian Heart J*. 2004;56:685.
7. Parodi G, Antoniucci D. Late coronary stent thrombosis associated with exercise testing. *Catheter Cardiovasc Interv*. 2004;61:515-517.
8. Costa MA, Sabate M, van der Giessen WJ, et al. Late coronary occlusion after intracoronary brachytherapy. *Circulation*. 1999;100:789-792.
9. Celik T, Iyisoy A, Kursaklioglu H. A case of late stent thrombosis after exercise electrocardiography: exercise- or residual plaque–induced? *J Invasive Cardiol*. 2005;17:280-282.
10. Wenaweser P, Dörffler-Melly J, Imboden K, et al. Stent thrombosis is associated with an impaired response to antiplatelet therapy. *J Am Coll Cardiol*. 2005;45:1748-1752.
11. Barragan P, Bouvier JL, Roquebert PO, et al. Resistance to thienopyridines: clinical detection of coronary stent thrombosis by monitoring of vasodilator-stimulated phosphoprotein phosphorylation. *Catheter Cardiovasc Interv*. 2003; 59:29.
12. Kereiakes DJ, Choo JK, Young JJ, et al. Thrombosis and drug eluting stents: a critical appraisal. *Rev Cardiovasc Med*. 2004;5:9-15.
13. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans. Delayed healing and late thrombotic risk. *J Am Coll Cardiol*. 2006;48:193-202.
14. Park DW, Park SW, Park KH, et al. Frequency and risk factors for stent thrombosis after drug-eluting stent implantation during long-term follow-up. *Am J Cardiol*. 2006;98:352-356.
15. Weisz G, Leon M, Holmes D, et al. Two-year outcomes after sirolimus-eluting stent implantation. *J Am Coll Cardiol*. 2006;47:1350-1355.
16. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA*. 2005;293:2126-2130.
17. Gurbel PA, Bliden KP, Guyer K, et al. Platelet reactivity in patients and recurrent events post-stenting: results of the PREPARE POST-STENTING study. *J Am Coll Cardiol*. 2005;46: 1820-1826.
18. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al, BASKET-LATE Investigators. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol*. 2006;48:2584-2591.
19. Cook S, Wenaweser P, Togni M, et al. Intravascular ultrasound in very late DES-stent thrombosis [abstract]. *J Am Coll Cardiol*. 2006;47(suppl B):9B.
20. Serruys PW, Degertekin M, Tanabe K, et al. Intravascular ultrasound findings in the multicenter, randomized, double-blind RAVEL (Randomized study with the sirolimus-eluting Velocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) trial. *Circulation*. 2002;106:798-803.
21. Cypher [package insert]. Miami, FL: Cordis Corporation; 2006.
22. Taxus [package insert]. Natick, MA: Boston Scientific; 2006.
23. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). American Heart Association Web site. Available at: http://www.americanheart.org. Accessed December 8, 2006.
24. Pfisterer ME. Late clinical events related to late stent thrombosis after stopping clopidogrel: prospective randomized comparison between drug-eluting versus bare-metal stenting. Presented at: American College of Cardiology Scientific Sessions; March 14, 2006; Atlanta, GA.
25. Honda Y, Fitzgerald PJ. Stent thrombosis—an issue revisited in a changing world. *Circulation*. 2003;108:2-5.

Main Points

- In contrast to subacute thrombosis, which is probably related to suboptimal stent deployment, late stent thrombosis is related to inadequate late re-endothelialization, residual thrombus, and/or persistent intimal tears adjacent to the stented segment.
- In one trial, no differences in mortality or myocardial infarction were observed between sirolimus-eluting stents and bare-metal stents within the first 1 to 2 years following percutaneous coronary intervention (PCI).
- Patients who develop an acute coronary syndrome consistent with late stent thrombosis should undergo emergent coronary angiography to define the coronary anatomy and PCI to normalize coronary flow.
- Intravascular ultrasound can be useful to determine if there are any anatomic factors that predisposed the patient to the stent thrombosis and to help guide appropriate interventional strategies.
- Utilization of dual-antiplatelet therapy in patients undergoing placement of drug-eluting stents should be extended beyond the current package insert recommendations of 3 months (sirolimus-eluting stents) and 6 months (paclitaxel-eluting stents) for all patients who are at lower risk for hemorrhagic complications.