Prevention of Premature Discontinuation of Dual Antiplatelet Therapy in Patients With Coronary Artery Stents: A Science Advisory From the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, With Representation From the American College of Physicians

Cindy L. Grines, Robert O. Bonow, Donald E. Casey, Jr, Timothy J. Gardner, Peter B. Lockhart, David J. Moliterno, Patrick O'Gara and Patrick Whitlow

Circulation 2007;115;813-818; originally published online Jan 15, 2007;
DOI: 10.1161/CIRCULATIONAHA.106.180944
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

AHA/ACC/SCAI/ACS/ADA Science Advisory

Prevention of Premature Discontinuation of Dual Antiplatelet Therapy in Patients With Coronary Artery Stents

A Science Advisory From the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, With Representation From the American College of Physicians*

Cindy L. Grines, MD, FACC; Robert O. Bonow, MD, FAHA, FACC; Donald E. Casey, Jr, MD, MPH, MBA, FACP; Timothy J. Gardner, MD, FAHA, FACC, FACS; Peter B. Lockhart, DDS, FDS RCSEd; David J. Moliterno, MD, FAHA, FSCAI, FACC; Patrick O'Gara, MD, FAHA, FACC; Patrick Whitlow, MD, FAHA, FACC

Abstract—Dual antiplatelet therapy with aspirin and a thienopyridine has been shown to reduce cardiac events after coronary stenting. However, many patients and healthcare providers prematurely discontinue dual antiplatelet therapy, which greatly increases the risk of stent thrombosis, myocardial infarction, and death. This advisory stresses the importance of 12 months of dual antiplatelet therapy after placement of a drug-eluting stent and educating the patient and healthcare providers about hazards of premature discontinuation. It also recommends postponing elective surgery for 1 year, and if surgery cannot be deferred, considering the continuation of aspirin during the perioperative period in high-risk patients with drug-eluting stents. (***Circulation*****. 2007;115:813-818.)**

Key Words: AHA Scientific Statements ■ thrombosis ■ myocardial infarction ■ stents ■ myocardial stunning

After placement of a bare-metal stent, thienopyridines (clopidogrel [Plavix, sanofi-aventis, Bridgewater, NJ] or ticlopidine [Ticlid, Hoffmann-La Roche Inc, Nutley, NJ]), in combination with aspirin therapy, have been shown to dramatically reduce the incidence of early major adverse cardiac events after stent placement compared with aspirin alone or in combination with warfarin (Table 1).[1] In addition, the use of thienopyridine therapy plus aspirin for up to 1 year after non–ST-segment–elevation acute coronary syndromes is known to decrease the incidence of ischemic cardiovascular events and is recommended in the American College of Cardiology/American Heart Association practice guidelines for the treatment of patients undergoing percutaneous coronary intervention and for the medical treatment of patients with non–ST-segment–elevation acute coronary syndromes.[2–4] Despite these benefits, antiplatelet therapy is sometimes prematurely discontinued within the first year after stent implantation, either by the patient or by a healthcare provider who may not realize these benefits or the potentially severe consequences of antiplatelet therapy cessation. The leading adverse event associated with early antiplatelet

*Representation does not imply endorsement by the American College of Physicians.

The American Heart Association, the American College of Cardiology, the Society for Cardiovascular Angiography and Interventions, the American College of Surgeons, and the American Dental Association make every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on December 21, 2006, by the American College of Cardiology on December 28, 2006, by the Society for Cardiovascular Angiography and Interventions on December 20, 2006, by the American College of Surgeons on December 16, 2006, and by the American Dental Association on December 17, 2006.

This article has been copublished with the American College of Cardiology and the Society for Cardiovascular Angiography and Interventions.

Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/CIRCULATIONAHA.106.180944**

TABLE 1. After Bare-Metal Stent Placement, Aspirin Plus Thienopyridine Reduces Cardiac Events Compared With Aspirin Alone or With Oral Antithrombins

			MACE, %*			
Study	No. of Pts Studied	No. of Pts Treated	ASA Thienopyridine	ASA Warfarin	ASA Alone	*P*
ISAR[32]	517	626	1.6	6.2	...	0.01
FANTASTIC[33]	473	485	5.7†	8.6†	...	0.37
STARS[34]	1653	1965	0.5	2.7	3.6	0.0001
MATTIS[35]	350	350	5.6	11.0	...	0.07
Hall et al[36]	226	358	0.8	...	3.9	0.1

MACE indicates major adverse cardiovascular events; Pts, patients; ASA, aspirin; ISAR, Intracoronary Stenting and Antithrombotic Regimen trial; FANTASTIC, Full ANTicoagulation versus ASpirin TIClopidine after stent implantation; STARS, STent Anticoagulation Regimen Study; and MATTIS, Multicenter Aspirin and Ticlopidine Trial after Intracoronary Stenting.

*Cardiac death, acute MI, or repeat target-vessel revascularization at 30 days (except for the FANTASTIC study).

†Death, MI, or stent occlusion at 6 weeks.

Adapted from ten Berg et al.[1]

discontinuation is stent thrombosis, and the majority of these events lead to acute myocardial infarction (MI) or death. Therefore, the American Heart Association, working with the American College of Cardiology, the Society for Cardiovascular Angiography and Interventions, the American College of Physicians, the American College of Surgeons, and the American Dental Association, commissioned this advisory to emphasize the potential complications of premature discontinuation of thienopyridine therapy and to address potential strategies to minimize this occurrence.

Dual Antiplatelet Therapy for Prevention of Ischemic Cardiovascular Events and Stent Thrombosis

Current American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions recommendations for the prevention of stent thrombosis after coronary stent implantation state that, at a minimum, patients should be treated with clopidogrel 75 mg and aspirin 325 mg for 1 month after bare-metal stent implantation, 3 months after sirolimus drug-eluting stent (DES) implantation, 6 months after paclitaxel DES implantation, and ideally, up to 12 months if they are not at high risk for bleeding.[3] These recommendations were based on the antiplatelet regimen used in trials that were conducted to obtain US Food and Drug Administration approval (low-risk lesions in low-risk patients) and the anticipated time it takes for the metal stent struts to become adequately endothelialized to reduce the risk of stent thrombosis. However, DESs are now being used in high-risk lesions, and reports have suggested that they may be associated with delayed (or absent) endothelialization,[5,6] localized hypersensitivity reactions,[7,8] and late stent thrombosis.

Stent thrombosis most commonly occurs in the first month after stent implantation, and in this interval, it is referred to as "subacute stent thrombosis." However, numerous cases of "late" stent thrombosis, particularly in patients who have been treated with DES, have been described as occurring months or even years after stent implantation.[9–21] In the majority of cases, stent thrombosis is a catastrophic event, resulting in life-threatening complications. In a pooled analysis of 6 trials and registries from the 1990s, the incidence of death or MI associated with angiographically documented stent thrombosis was found to be 64.4%.[14] Mortality rates due to presumed or documented stent thrombosis range from 20% to 45%.[19–21]

In the current era of dual antiplatelet therapy, the average reported occurrence of subacute stent thrombosis is 1%.[16–22] The timing of thrombosis appears to be delayed in DES. Late (1 to 12 months) stent thrombosis was not readily apparent with bare-metal stents yet was reported to occur in 0.19% of patients in a large DES registry.[18] Predictors of late stent thrombosis have included stenting of small vessels, multiple lesions, long stents, overlapping stents, ostial or bifurcation lesions, prior brachytherapy, suboptimal stent result (underexpansion, malapposition, or residual dissection), low ejection fraction, advanced age, diabetes mellitus, renal failure, acute coronary syndrome, and premature discontinuation of antiplatelet agents (Table 2).[9,13,18–21]

On December 7–8, 2006, the US Food and Drug Administration convened an advisory panel meeting to discuss stent thrombosis and the overall safety of DES.[23] They concluded that there appears to be a numerical excess of late stent thrombosis with DES, but the magnitude is uncertain; and the off-label use of DES, as with bare-metal stents, is associated with increased risk when compared with on-label use. The panel also agreed that, in the future, new DES studies should have longer follow-up, enroll greater numbers of patients, and include stent thrombosis as a study end point. The advisory panel concurred with the joint clinical practice guideline recommendation[3] for 12 months of dual antiplatelet therapy after placement of a drug-eluting stent in patients who are not at high risk of bleeding. However, they agreed that a large randomized trial looking specifically at appropriate duration of dual antiplatelet therapy is needed.

TABLE 2. Predictors of DES Thrombosis: Considerations for Prolonged Dual Antiplatelet Therapy

Clinical	Angiographic
Advanced age	Long stents
Acute coronary syndrome	Multiple lesions
Diabetes	Overlapping stents
Low ejection fraction	Ostial or bifurcation lesions
Prior brachytherapy	Small vessels
Renal failure	Suboptimal stent results

Premature Thienopyridine Discontinuation and Stent Thrombosis

The premature discontinuation of thienopyridine therapy is associated with a marked increase in the risk of stent thrombosis and is the leading independent predictor for stent thrombosis in multivariate analyses. Although the number of actual stent thromboses reported in individual studies is modest, the findings are noteworthy.

In a large observational cohort study of patients treated with DES, stent thrombosis occurred in a striking 29% of patients in whom antiplatelet therapy was discontinued prematurely.[9] This discontinuation of antiplatelet therapy was associated with a hazard ratio of 161 (95% confidence interval 26 to 998) for the occurrence of subacute stent thrombosis and a hazard ratio of 57 (95% confidence interval 15 to 220) for the occurrence of late (>30 days) stent thrombosis.

In a single-site study of 652 patients treated with sirolimus DES, premature discontinuation of clopidogrel was associated with an ≈30-fold greater risk of stent thrombosis, with >25% of patients who discontinued clopidogrel therapy within the first month suffering stent thrombosis.[17] Park et al[13] reported on 1911 consecutive patients with DES followed up for a median of 19.4 months. Five (7.8%) of 64 patients with premature interruption of aspirin, clopidogrel, or both experienced stent thrombosis.

Spertus and colleagues[19] published an analysis from the PREMIER (Prospective Registry Evaluating Myocardial Infarction: Events and Recovery) registry of 500 patients with acute MI treated with DES. The mortality rate over the next 11 months of those who stopped thienopyridine therapy was 7.5% compared with 0.7% in those who had not stopped therapy (hazard ratio 9.0, $P<0.0001$). Although the rates of stent thrombosis were not reported, it is reasonable to presume that many of the deaths were related to coronary artery disease.

Pfisterer et al[20] randomized 746 patients (1133 lesions) to DES versus bare-metal stents. All patients received dual antiplatelet therapy for 6 months, after which aspirin alone was continued. At 30 days, rates of death or nonfatal MI were lower in the DES group (2.0% versus 4.69%, $P=0.05$); however, after discontinuation of clopidogrel at 6 months, late stent thrombosis (2.6% versus 1.3%) and death or nonfatal MI (4.9% versus 1.3%) occurred more frequently in the DES group.

Similarly, Eisenstein et al[21] reported an observational study in 4666 patients with follow-up at 6, 12, and 24 months after stenting. In patients treated with bare-metal stents, continued use of clopidogrel did not influence death or MI rates between 6 and 24 months. Conversely, in DES patients, extended use of clopidogrel at 6, 12, and 24 months was associated with reduced death or death/MI rates at all time intervals.

Stent Thrombosis After Noncardiac Surgery

Several reports have specifically described incidents of stent thrombosis that occurred after the discontinuation of antiplatelet therapy for noncardiac surgery among patients recently treated with coronary stents.[24–26] Kaluza et al[25] reported on 40 patients treated with bare-metal stents who underwent noncardiac surgery within 6 weeks of stent implantation. Seven patients had an MI, of which 6 were fatal. Stent thrombosis was presumed to be the cause of all MIs. In 5 of 7 cases, thienopyridine therapy (ticlopidine) had been withheld before surgery. In a similar analysis of 47 patients who underwent noncardiac surgery within 90 days of bare-metal stent implantation, 6 of the 7 patients in whom thienopyridine therapy was discontinued died "in a manner suggestive of stent thrombosis."[26]

Factors Related to Premature Cessation of Thienopyridine Therapy

Premature cessation of thienopyridine may occur for several different reasons. The cost of clopidogrel (approximately $4 daily) has been cited as one reason patients discontinue (or do not renew) their therapy.[27] It is unclear whether the introduction of modestly lower-cost generic clopidogrel will significantly affect this issue. In an analysis from the PREMIER registry,[19] factors identified with premature discontinuation of thienopyridine therapy included older age, not having completed high school, not being married, not receiving discharge instructions for medication use, not being referred for cardiac rehabilitation, greater likelihood of having preexistent cardiovascular disease or anemia, and not seeking health care because of cost. The study authors concluded that "additional patient education about the rationale for and importance of continuing thienopyridine treatment may be needed—particularly for patients with less formal education."

Dual antiplatelet therapy is not without risk. Like all antithrombotic agents, both aspirin and clopidogrel increase the risk of bleeding compared with placebo. When compared with aspirin, clopidogrel may be associated with lower risk of GI bleeding.[28] However, when clopidogrel was combined with aspirin and administered for prolonged duration (up to 28 months), randomized trials demonstrated an absolute increase (ranging from 0.4% to 1.0%) in major bleeding, compared with aspirin alone.[28]

Antiplatelet therapy may be stopped at the instruction of physicians, dentists, and other healthcare providers who are to perform an invasive or surgical procedure on the patient because of misguided concerns about excessive procedure-related bleeding. Unfortunately, many patients are routinely instructed to stop "blood thinners" before such procedures without a thorough evaluation of the rationale for such therapy and without distinction between warfarin and antiplatelet agents. Many of these procedures (eg, minor surgery, teeth cleaning, and tooth extraction) can likely be performed at no or only minor risk of bleeding or could be delayed until the prescribed antiplatelet regimen is completed. Although there is a longstanding concern on the part of dental practitioners about the possibility of prolonged bleeding during and after invasive dental procedures on patients receiving antiplatelet drugs, a recent prospective study of single tooth extractions on patients randomized to aspirin versus a placebo failed to show a statistically significant difference in postoperative bleeding.[29] Although there are no prospective studies of invasive dental procedures on patients taking a thienopyridine alone or in combination with aspirin, there are also no well-documented cases of clinically significant bleeding after dental procedures, including multiple dental extractions. Given the relative ease with which the incidence and severity of oral bleeding can be reduced with local measures during surgery (eg, absorbable gelatin sponge and sutures) and the unlikely occurrence of bleeding once an initial clot has formed, there is little or no indication to interrupt antiplatelet drugs for dental procedures.[30]

The likelihood of increased bleeding and/or an increased requirement for blood transfusion in patients undergoing major noncardiac surgery can be inferred from reports of increased bleeding when

cardiac surgery (including off-pump coronary bypass grafting) is undertaken in patients taking a thienopyridine drug. Independent documentation of the scope of this risk of increased bleeding during noncardiac surgery, however, is not available. If one must discontinue the thienopyridine drug before major surgery to reduce the risk of excessive bleeding, consideration should be given to continuing aspirin for its antiplatelet action to mitigate the risk of late stent thrombosis and to restarting the thienopyridine as soon as possible. Although some have attempted "bridging" stent patients with antithrombin agents, there is no evidence of a benefit of warfarin (Table 1) or other antithrombins, and there is an increased risk of bleeding.[31] Similarly, there are no data to support the use of "bridging" glycoprotein IIb/IIIa agents.

Summary and Recommendations

Thienopyridine therapy in combination with aspirin has become the mainstay antiplatelet treatment strategy for the prevention of stent thrombosis. Premature discontinuation of antiplatelet therapy markedly increases the risk of stent thrombosis, a catastrophic event that frequently leads to MI and/or death. Factors contributing to premature cessation of thienopyridine therapy include drug cost, physician/dentist instructions to patients to discontinue therapy before procedures, and inadequate patient education and understanding about the importance of continuing therapy.

To eliminate premature discontinuation of thienopyridine therapy, this advisory group gives the following recommendations.

1. Before implantation of a stent, the physician should discuss the need for dual antiplatelet therapy. In patients not expected to comply with 12 months of thienopyridine therapy, whether for economic or other reasons, strong consideration should be given to avoiding a DES.
2. In patients who are undergoing preparation for percutaneous coronary intervention and are likely to require invasive or surgical procedures within the next 12 months, consideration should be given to implantation of a bare-metal stent or performance of balloon angioplasty with provisional stent implantation instead of the routine use of a DES.
3. A greater effort by healthcare professionals must be made before patient discharge to ensure patients are properly and thoroughly educated about the reasons they are prescribed thienopyridines and the significant risks associated with prematurely discontinuing such therapy.
4. Patients should be specifically instructed before hospital discharge to contact their treating cardiologist before stopping any antiplatelet therapy, even if instructed to stop such therapy by another healthcare provider.
5. Healthcare providers who perform invasive or surgical procedures and are concerned about periprocedural and postprocedural bleeding must be made aware of the potentially catastrophic risks of premature discontinuation of thienopyridine therapy. Such professionals who perform these procedures should contact the patient's cardiologist if issues regarding the patient's antiplatelet therapy are unclear, to discuss optimal patient management strategy.
6. Elective procedures for which there is significant risk of perioperative or postoperative bleeding should be deferred until patients have completed an appropriate course of thienopyridine therapy (12 months after DES implantation if they are not at high risk of bleeding and a minimum of 1 month for bare-metal stent implantation).
7. For patients treated with DES who are to undergo subsequent procedures that mandate discontinuation of thienopyridine therapy, aspirin should be continued if at all possible and the thienopyridine restarted as soon as possible after the procedure because of concerns about late-stent thrombosis.
8. The healthcare industry, insurers, the US Congress, and the pharmaceutical industry should ensure that issues such as drug cost do not cause patients to prematurely discontinue thienopyridine therapy and to thus incur catastrophic cardiovascular complications.

Disclosures

Writing Group Disclosures

Writing Group Member	Organization Represented	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Ownership Interest	Consultant/ Advisory Board	Other
Cindy L. Grines	AHA Representative	William Beaumont Hospital	None	None	None	None	None	None
Robert O. Bonow	AHA Representative	Northwestern University	None	None	None	None	None	None
Donald E. Casey, Jr	ACP Representative	Atlantic Health	None	None	None	None	None	None
Timothy J. Gardner	ACS Representative	Christiana Care Health System	None	None	None	None	None	None
Peter B. Lockhart	ADA Representative	Carolinas Medical Center	None	None	None	None	None	None
David J. Moliterno	SCAI Representative	University of Kentucky	None	None	None	None	None	None
Patrick O'Gara	ACC Representative	Brigham and Women's Hospital	None	None	None	None	None	None
Patrick Whitlow	ACC Representative	Cleveland Clinic	None	None	None	None	ICON Interventional Systems,* Medlogics*	None

AHA indicates American Heart Association; ACP, American College of Physicians; ACS, American College of Surgeons; ADA, American Dental Association; SCAI, Society for Cardiovascular Angiography and Interventions; and ACC, American College of Cardiology.

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives $10 000 or more during any 12-month period or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Elliott M. Antman	Brigham and Women's Hospital	Eli Lilly*	None	None	None	None	None	None
Gregory J. Dehmer	Texas A&M University College of Medicine and Scott & White Clinic	None	None	None	None	None	None	None
T. Bruce Ferguson	East Carolina University	None	None	None	None	None	None	None
Raymond J. Gibbons	Mayo Clinic	Radiant Medical,† KAI Pharmaceuticals,† TargeGen,† TherOx†	None	None	None	None	Hawaii Biotech,* TIMI 37A*	None
Arthur H. Jeske	University of Texas Health Science Center, Houston	None	None	None	None	None	None	None
Vincenza Snow	American College of Physicians	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives $10 000 or more during any 12-month period or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

References

1. ten Berg JM, Plokker H, Verheugt F. Antiplatelet and anticoagulant therapy in elective percutaneous coronary intervention. *Curr Control Trials Cardiovasc Med*. 2001;2:129–140.
2. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D, Kupersmith J, Levin TN, Pepine CJ, Schaeffer JW, Smith EE III, Steward DE, Theroux P, Gibbons RJ, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Smith SC Jr. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *J Am Coll Cardiol*. 2002;40:1366–1374.
3. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, Jacobs AK, Kern MJ, King SB III, Morrison DA, O'Neill WW, Schaff HV, Whitlow PL, Williams DO. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force of Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). 2005. Available at: http://www.americanheart.org/presenter.jhtml?identifier=3035436. Accessed November 2006.
4. Smith SC Jr, Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, Grundy SM, Hiratzka L, Jones D, Krumholz HM, Mosca L, Pasternak RC, Pearson T, Pfeffer MA, Taubert KA. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute [published correction appears in *Circulation*. 2006;113:e847]. *Circulation*. 2006;113:2363–2372.
5. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol*. 2006;48:193–202.
6. Kotani J, Nanto S, Morozumi T, et al. Angioscopic findings of the neo-intimal coverage over the sirolimus-eluting stent: nine months follow-up study. *J Am Coll Cardiol*. 2006;47(suppl B):27B.
7. Nebeker JR, Virmani R, Bennett CL, Hoffman JM, Samore MH, Alvarez J, Davidson CJ, McKoy JM, Raisch DW, Whisenant BK, Yarnold PR, Belknap SM, West DP, Gage JE, Morse RE, Gligoric G, Davidson L, Feldman MD. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *J Am Coll Cardiol*. 2006;47:175–181.
8. Virmani R, Guagliumi G, Farb A, Musumeci G, Greico N, Motta T, Mihalcsik L, Tespili M, Valsecchi O, Kolodgie FD. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation*. 2004;109:701–705.
9. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briquori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA*. 2005;293:2126–2130.
10. Levine GN, Kern MJ, Berger PB, Brown DL, Klein LW, Kereiakes DJ, Sanborn TA, Jacobs AK. Management of patients undergoing percutaneous coronary revascularization. *Ann Intern Med*. 2003;139:123–136.
11. McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, Suddath WO, Weissman NJ, Torguson R, Kent KM, Pichard AD, Satler LF, Waksman R, Serruys PW. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet*. 2004;364:1519–1521.
12. Ong AT, McFadden EP, Regar E, de Jaegere PP, van Domburg RT, Serruys PW. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. *J Am Coll Cardiol*. 2005;45:2088–2092.
13. Park DW, Park SW, Park KH, Lee BK, Kim YH, Lee CW, Hong MK, Kim JJ, Park SJ. Frequency of and risk factors for stent thrombosis after drug-eluting stent implantation during long-term follow-up. *Am J Cardiol*. 2006;98:352–356.
14. Cutlip DE, Baim DS, Ho KK, Popma JJ, Lansky AJ, Cohen DJ, Carrozza JP Jr, Chauhan MS, Rodriguez O, Kuntz RE. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. *Circulation*. 2001;103:1967–1971.
15. Moussa I, Di Mario C, Reimers B, Akiyama T, Tobis J, Colombo A. Subacute stent thrombosis in the era of intravascular ultrasound-guided coronary stenting without anticoagulation: frequency, predictors and clinical outcome. *J Am Coll Cardiol*. 1997;29:6–12.
16. Karrillon GJ, Morice MC, Benveniste E, Bunouf P, Aubry P, Cattan S, Chevalier B, Commeau P, Cribier A, Eiferman C, Grollier G, Guerin Y, Henry M, Lefevre T, Livarek B, Louvard Y, Marco J, Makowski S, Monassier JP, Pernes JM, Rioux P, Spaulding C, Zemour G. Intracoronary stent implantation without ultrasound guidance and with replacement of conventional anticoagulation by antiplatelet therapy: 30-day clinical outcome of the French Multicenter Registry. *Circulation*. 1996;94:1519–1527.
17. Jeremias A, Sylvia B, Bridges J, Kirtane AJ, Bigelow B, Pinto DS, Ho KK, Cohen DJ, Garcia LA, Cutlip DE, Carrozza JP Jr. Stent thrombosis after successful sirolimus-eluting stent implantation. *Circulation*. 2004;109:1930–1932.

18. Urban P, Gershlick AH, Guagliumi G, Guyon P, Lotan C, Schofer J, Seth A, Sousa JE, Wijns W, Berge C, Deme M, Stoll HP; e-Cypher Investigators. Safety of coronary sirolimus-eluting stents in daily clinical practice: one-year follow-up of the e-Cypher registry. *Circulation*. 2006; 113:1434–1441.
19. Spertus JA, Kettelkamp R, Vance C, Decker C, Jones PG, Rumsfeld JS, Messenger JC, Khanal S, Peterson ED, Bach RG, Krumholz HM, Cohen DJ. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. *Circulation*. 2006;113:2803–2809.
20. Pfisterer M, Brunner-LaRocca HP, Buser PT, Rickenbacher P, Hunziker P, Mueller C, Jeger R, Bader F, Osswald S, Kaiser C; for the BASKET-LATE Investigators. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents. *J Am Coll Cardiol*. 2006;48:2584–2591.
21. Eisenstein EL, Anstrom KJ, Kong DF, Shaw LK, Tuttle RH, Mark DB, Kramer JM, Harrington RA, Matchar DB, Kandzari DE, Peterson ED, Schulman KA, Califf RM. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA*. 2006 Dec 5:E1–E10 [Epub ahead of print].
22. Bhatt DL, Bertrand ME, Berger PB, L'Allier PL, Moussa I, Moses JW, Dangas G, Taniuchi M, Lasala JM, Holmes DR, Ellis SG, Topol EJ. Meta-analysis of randomized and registry comparisons of ticlopidine with clopidogrel after stenting. *J Am Coll Cardiol*. 2002;39:9–14.
23. US Food and Drug Administration. Circulatory System Devices Panel. Available at http://www.fda.gov/ohrms/dockets/ac/cdrh06.html#circulatory. Accessed December 21, 2006.
24. Nasser M, Kapeliovich M, Markiewicz W. Late thrombosis of sirolimus-eluting stents following noncardiac surgery. *Catheter Cardiovasc Interv*. 2005;65:516–519.
25. Kaluza GL, Joseph J, Lee JR, Raizner ME, Raizner AE. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. *J Am Coll Cardiol*. 2000;35:1288–1294.
26. Sharma AK, Ajani AE, Hamwi SM, Maniar P, Lakhani SV, Waksman R, Lindsay J. Major noncardiac surgery following coronary stenting: when is it safe to operate? *Catheter Cardiovasc Interv*. 2004;63: 141–145.
27. Mixed thoughts on how generic clopidogrel might impact patients, providers. HeartWire; August 11, 2006. Available at: http://www.theheart.org/article/729929.do. Accessed November 2006.
28. Eikelboom JW, Hirsh J. Bleeding and management of bleeding. *Eur Heart J*. 2006;8[suppl]:G38–G45.
29. Valerin MA, Brennan MT, Noll JL, Napenas JJ, Kent ML, Fox PC, Lockhart PB. Relationship between aspirin use and postoperative bleeding from dental extractions in a healthy population. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2006;102:326.
30. Lockhart PB, Gibson J, Pond SH, Leitch J. Dental management considerations for the patient with an acquired coagulopathy: part II: coagulopathies from drugs. *Br Dent J*. 2003;195:495–501.
31. McDonald SB, Renna M, Spitznagel EL, Avidan M, Hogue CW Jr, Moon MR, Barzilai B, Saleem R, McDonald JM, Despotis GJ. Preoperative use of enoxaparin increases the risk of postoperative bleeding and re-exploration in cardiac surgery patients. *J Cardiothorac Vasc Anesth*. 2005;19:4–10.
32. Schömig A, Neumann F-J, Kastrati A, Schühlen H, Blasini R, Hadamitzky M, Walter H, Zitzmann-Roth E-M, Richardt G, Alt E, Schmitt C, Ulm K. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med*. 1996;334:1084–1089.
33. Bertrand ME, Legrand V, Boland J, Fleck E, Bonnier J, Emmanuelson H, Vrolix M, Missault L, Chierchia S, Casaccia M, Niccoli L, Oto A, White C, Webb-Peploe M, Van Belle E, McFadden EP. Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting: the full anticoagulation versus aspirin and ticlopidine (FANTASTIC) study. *Circulation*. 1998;98: 1597–1603.
34. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KKL, Giambartolomei A, Diver DJ, Lasorda DM, Williams DO, Pocock SJ, Kuntz RE, for the Stent Anticoagulation Restenosis Study Investigators. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. *N Engl J Med*. 1998;339:1665–1671.
35. Urban P, Macaya C, Rupprecht H-J, Kiemeneij F, Emanuelsson H, Fontanelli A, Pieper M, Wesseling T, Sagnard L, for the MATTIS Investigators. Randomized evaluation of anticoagulant versus antiplatelet therapy after coronary stent implantation in high-risk patients: the multicenter aspirin and ticlopidine trial after coronary stenting (MATTIS). *Circulation*. 1998;98:2126–2132.
36. Hall P, Nakamura S, Maiello L, Itoh A, Blengino S, Martini G, Ferraro M, Colombo A. A randomized comparison of combined ticlopidine and aspirin therapy versus aspirin therapy alone after successful intravascular ultrasound-guided stent implantation. *Circulation*. 1996;93:215–222.