

Use of drug-eluting stents for patients with coronary heart disease

Proper patient selection is important, but which patients are good candidates for drug-eluting stents, and how do we ensure the best long-term outcome?

Jessica Justice, MHS, PA-C; Christian Yacono, MHS, PA-C

Coronary atherosclerotic disease remains the leading cause of mortality in the industrialized world. One American dies from coronary heart disease (CHD) every minute, with an estimated 1.2 million MIs occurring annually in the United States.¹ With the epidemic of obesity in this country and Americans' increasingly sedentary lifestyle, more patients are at risk of developing CHD than ever before. Additionally, more patients are developing abnormal lipid profiles at younger ages, including elevated LDL and decreased HDL cholesterol levels. Abnormal lipid profiles are a well-documented risk factor for the development of

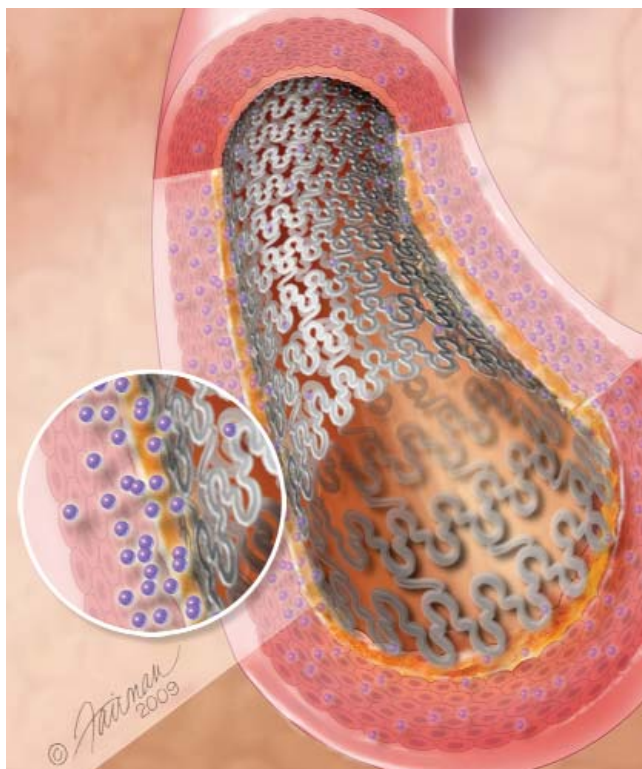
atherosclerosis. The coupling of abnormal lipid profiles with vascular injury promotes atherosclerosis, causing symptomatic CHD, including angina pectoris and MI. When symptoms can no longer be medically managed, more invasive options, including percutaneous intervention (PCI) and coronary artery bypass grafting (CABG), may be advised. This article reviews the factors leading to development of CHD and the evolution of PCI technology, discusses how to identify which patients are the best candidates for drug-eluting stent (DES) implantation, and explains how to maintain patient safety after PCI.

HOW ATHEROSCLEROSIS DEVELOPS

CHD results when neointimal injury occurs in one of the coronary arteries. Increased blood flow to this area of injury launches an inflammatory process, causing the migration of lipid-laden macrophages. Those macrophages preferentially incorporate LDL into their cells as they form a subendothelial "fatty streak." Macrophages work in a pro-inflammatory manner by recruiting smooth-muscle cells from the tunica media, thus attracting and stimulating more macrophages. Numerous chemical mediators, including cytokines and adhesion molecules, are produced, attracting smooth muscle, connective tissue, and more lipids. The result of this inflammatory process is the formation of a fibrous plaque. This lesion grows with time until the lumen narrows, producing symptomatic CHD. When complete lumen occlusion occurs, ischemia of the myocardium results. At this point in the process, we, as practitioners, have failed to prevent morbidity from our patients' cardiovascular disease and must consider more invasive options than medical management, including PCI with stent (PCI-S) placement.

TREATMENT APPROACHES

Treatment of patients with CHD starts with risk factor identification and modification. Risk factors for CHD include positive family history, male gender, blood lipid abnormalities, diabetes mellitus, hypertension, physical inactivity, obesity, and cigarette smoking. Most MIs are attributable to eight modifiable risk factors: abnormal lipids, smoking, hypertension, diabetes mellitus, abdominal obesity, psychosocial factors, consumption of too few fruits and vegetables and too much alcohol, and lack of regular physical activity.²



© Fairman Studios, LLC.

FIGURE 1. A drug-eluting stent consists of a backbone, a drug, and a polymer coating that controls the drug's release.

Reducing patient risk for CHD is a necessity in clinical practice, but despite our best efforts at lowering risk, some patients will require pharmacologic therapy, including metformin and sulfonylureas for improved glycemic control, beta-blockers and calcium channel blockers for BP control, and statins and fibrates for patients with abnormal lipid profiles. Even then, a number of patients will become the next victims of CHD. Thus, PCI is still a much-needed and much-valued therapeutic modality.

PERCUTANEOUS INTERVENTION

When pharmacologic measures fail to control patients' CHD, PCI is the next treatment option. In the 1970s, percutaneous coronary angioplasty (PTCA) with an inflatable balloon became the newest modality for restoring luminal diameter to stenotic coronary arteries. In 1986, PTCA started losing popularity and bare-metal stent (BMS) use exploded. Initially PCI-S was heralded because it reduced the incidence of death and MI in patients presenting with acute coronary syndromes.³ BMS improved stenotic coronary artery diameter by more than 41% and routinely decreased clinical angina.⁴ This trend of using BMS to reduce stenosis and restore coronary blood flow to ischemic areas continued into the 1990s. However, restenosis became the Achilles' heel of BMS, occurring in 15% to 50% of all cases.² Restenosis of BMS, which results from vascular injury, underlying atherosclerosis, and inflammation, is furthered by neointimal hyperplasia after stent deployment. This can lead to acute or gradual loss of lumen diameter. The addition of pharmacologic antiplatelet and anti-inflammatory treatment after BMS implantation reduced this side effect, but the cardiology community continued its investigation into other PCI modalities with improved efficacy. As a result of BMS restenosis, target-vessel and target-lesion revascularization became necessary in 30% to 50% of patients, dictating the need for a more effective intervention.⁵

The 1990s marked the arrival of the DES. The basic design includes three principal components: a stent backbone, the pharmacologic agent to reduce neointimal hyperplasia, and a polymer responsible for the slow release of the pharmacologic agent (Figure 1). As the metal stent itself is inherently thrombogenic, therapeutic agents have been investigated to limit this particular property. Paclitaxel, a chemotherapeutic agent, and

“The data indicate that the annual incidence of stent thrombosis in DES increases over time, reaching a 2.9% incidence in 3 years.”

sirolimus, an immunosuppressant, are the leading pharmacologic agents for DES. Paclitaxel and sirolimus have reduced rates of restenosis to 2.1% and 7%, respectively.^{6,7} The use of DES yields similar long-term survival benefits with less morbidity in patients with severe left ventricular dysfunction when compared with CABG.⁶ Patients receiving DES also have lower rates of subsequent revascularization and angina.³

In light of these dramatic improvements in patient outcomes, DES became the default PCI of choice from the late 1990s into the 21st century—until a literal fatal flaw was discovered. One of the main improvements of DES over BMS was the addition of powerful antirestenotic agents that decreased the hyperplasia seen with BMS. According to an FDA Circulatory System Devices Advisory Panel meeting in December 2006, on-label use of DES reduces the need for repeated revascularizations for 3 or more years during which time no increase in mortality rates or MIs was seen.⁸ However, thrombosis occurred more frequently in DES patients compared with BMS patients, 1% to 2% versus 0.4%, respectively. Although rare, thrombosis is associated with increased morbidity, including acute MI, and mortality.

Thrombosis occurs when the inherently thrombogenic metal DES does not achieve full endothelialization. This failure results in vascular injury, which initiates the clotting cascade, platelet activation, and platelet aggregation and leads to acute thrombosis of the entire lumen. The rate of thrombosis occurrence is low in the first 6 weeks after DES implantation, but an increasing number of studies document thrombus formation as late as 24 months after the procedure.^{7,9} In fact, data indicate that the annual incidence of stent thrombosis in DES, initially 0.6%, steadily increases over time, with a documented 2.9% incidence in 3 years.⁹ This trend has caused a decline in DES use from 80% in 2004 to less than 50% at present.

Continued on page 32

KEY POINTS

- Proper patient selection decreases risk of in-stent thrombosis.
- The most appropriate patients to receive a drug-eluting stent (DES) are those with symptomatic coronary heart disease who have de novo coronary lesions of a relatively small size (shorter than 28 mm) in a coronary artery with a minimum diameter of 2.5 mm.
- To prevent restenosis after implantation of a drug-eluting stent, dual antiplatelet therapy (DAT), consisting of aspirin (ASA) and a thienopyridine (clopidogrel or ticlopidine), is the standard of care. Such therapy may be required for life.
- DES patients who may be exempt from lifelong DAT include those at risk for GI bleeding, those on oral anticoagulation regimens prior to receiving a DES, and patients with prosthetic heart valves.
- Patients allergic to ASA or clopidogrel should be desensitized prior to DES implantation.
- Patients who are scheduled for surgery in the next 12 months should receive a bare-metal stent rather than a DES.

WHO SHOULD RECEIVE A DES?

While the absolute percentage of persons affected by in-stent thrombosis is small, increased risk in any patient mandates a discussion on which patients should be selected for DES. The CYPHER sirolimus-eluting stent is indicated for use in de novo lesions 30 mm or shorter in native coronary arteries 2.50 to 3.50 mm in diameter.¹⁰ The TAXUS paclitaxel-eluting stent is indicated for use in de novo lesions 28 mm or shorter in native coronary arteries with a diameter of 2.25 to 4.00 mm.¹¹ Thus the most appropriate patients to receive DES are those with symptomatic CHD who have de novo coronary lesions of a relatively small size (shorter than 28 mm) in a coronary artery with a minimum diameter of 2.5 mm. Patients should not have undergone previous CABG or PCI-S or have a bifurcation lesion or a lesion of the left anterior descending artery.

Despite specific on-label indications, patients have received DES for countless off-label indications, increasing the risk for adverse outcomes.¹² More than 60% of patients receive their DES for an off-label indication, which increases their risk of complications, including in-stent thrombosis.^{6,7}

Clearly, proper patient selection is essential in order to decrease the risk of in-stent thrombosis. As the FDA Circulatory System Devices Advisory Panel concluded in 2006, off-label use of DES is associated with an increased risk of death and MI compared with on-label use.⁸ Other research has established hypertension and smoking as independent predictors of early stent thrombosis.⁹ Additionally, lack of a high school education, being unmarried, avoid-

“Antiplatelet therapy, consisting of aspirin and a thienopyridine, has reduced in-stent thrombosis to 0.5% to 0.9% of patients.”

ance of health care because of cost, preexisting cardiovascular disease (CVD), and anemia all correlated with an increased risk of thrombosis.¹³ Other modifiable means of preventing thrombosis include beta-blocker and statin therapy. The absence of these two drug classes correlated with increased mortality in patients with DES.⁶

THE ROLE OF DUAL ANTIPLATELET THERAPY

Pharmacologic agents have been routinely prescribed following PCI for more than 20 years in an attempt to reduce the risk of adverse cardiac events. Since the development of DES, restenosis has dramatically decreased, but further pharmacologic approaches to prevent restenosis and in-stent thrombosis have been aggressively pursued. The resultant dual antiplatelet therapy (DAT), consisting of aspirin (ASA) and a thienopyridine (clopidogrel or ticlopidine), is the standard of care and has reduced in-stent thrombosis to 0.5% to 0.9% of patients.¹²

The number of studies and trials dedicated to finding the most efficacious and safe DAT regimen is extensive.¹³⁻¹⁵ These studies have additionally investigated varying durations of treatment, the use of a third antiplatelet agent, and the substitution of a glycoprotein (GP) IIb/IIIa inhibitor for a thienopyridine. The variety of antiplatelet therapy regimens may overwhelm and confuse practitioners who do not closely follow the literature, so a brief review is in order.

Current recommendations The first month after PCI poses the greatest risk for adverse cardiac events if patients are not on DAT. Thus the initiation and continued prescribing of DAT is of the utmost importance. According to DES manufacturers, the DAT regimen should consist of 3 to 6 months of a thienopyridine and 12 months or longer of ASA. However, this duration seems inadequate given results of more recent studies documenting adverse cardiac events with such short duration of DAT.^{13,16} Rates of death and cardiac rehospitalizations are almost twice as high in the ensuing 11 months when patients discontinue thienopyridine therapy.¹³

Numerous studies suggest that longer-term DAT, including lifetime ASA and clopidogrel, may be beneficial, but no studies have found the most efficacious regimen to date. However, the American College of Cardiology, the American Heart Association, and the Society for Cardiovascular Angiography and Interventions (ACC/AHA/SCAI) have provided recommendations regarding DAT, including the utilization of a 325-mg dose of ASA at least 2 hours prior to DES deployment followed by 325 mg daily for a minimum of 12 months. Lifetime ASA therapy is preferred, if tolerated, because such therapy will prevent late stent thrombosis in both BMS and DES patients.¹⁶ The ACC/AHA/SCAI recommendations prefer clopidogrel to ticlopidine because clopidogrel has a lower risk of side effects, including hematologic complications. Clopidogrel 75 mg daily should be continued for 12 months in patients with a low risk for bleeding and can be discontinued after 12 months if cost or adverse events are prohibitive. Factors that put patients at higher risk for bleeding include advanced age, history of peptic ulcer disease (PUD), concurrent use of an NSAID, underlying liver disease, and the presence of thrombocytopenia.

A number of studies have established that DAT is more efficacious than a thienopyridine alone and that DAT is vital in improving outcomes for both BMS and DES patients.^{6,9,15} Specifically, a Washington Hospital Center registry of 2,769 DES patients who received clopidogrel monotherapy after stent implantation were found to have an incidence of definite/probable stent thrombosis of 6.8% at 2-year follow-up. Reportedly 78.7% of the patients on the registry were still taking clopidogrel.⁸ This finding suggests that clopidogrel alone is insufficient to prevent in-stent thrombosis. Despite other studies that have delved into the utilization of GP IIb/IIIa inhibitors in lieu of a thienopyridine or in conjunction with DAT, there is insufficient evidence to support the routine use of GP IIb/IIIa inhibitors.

The case for continuing DAT Compelling evidence abounds for the continuation of DAT after DES placement. Several

studies have identified premature discontinuation of DAT as the most potent predictor of stent thrombosis.^{7,9,13,15} Stent thrombosis occurs more frequently in patients who discontinue DAT sooner than 6 months post implantation compared with patients who continue DAT for a longer duration. This underscores the need for patients to have a firm understanding of the importance of long-term and uninterrupted DAT prior to DES implantation.

Many patients undergo DES implantation on an elective basis, and much of the research has been directed toward this cohort. However, patients who receive emergent revascularization via DES (an off-label indication) are at increased risk of thrombosis because they have not been educated about the need for lifelong DAT or screened for willingness or ability to comply with the necessary regimen. Studies show that those who do not take DAT as recommended suffer serious consequences. In one study, patients who discontinued thienopyridine therapy within 30 days of their MI had a significantly higher likelihood of dying in the first year.¹³ The same study also showed that by 12 months after MI, all-cause mortality was 7.5% for patients who discontinued DAT within 30 days compared with 0.7% for those who continued DAT.¹³ Cardiac rehospitalization rates between 30 days and 1 year were also higher in the noncompliant group. Despite the well-established importance of thienopyridine therapy after DES implantation, approximately one in seven DES-treated patients was noncompliant with DAT 30 days after an MI and DES implantation. This is an important factor to consider when recommending DES in an emergent setting, as patients may be unwilling or unable to adhere to DAT. As previously noted, patient education level, marital status, avoidance of health care because of cost, preexisting CVD, and anemia all tend to be associated with premature discontinuation of DAT.¹³

SPECIAL CONSIDERATIONS

Risk of GI bleeding Patients who may be considered for shorter durations of DAT include those with a history of GI bleeding. Aggressive antithrombotic therapy can lead to rebleeding of the GI tract. GI bleeds occur in up to 2.3% of DAT patients. Risk factors include age older than 70 years, history of PUD, concurrent use of an NSAID, underlying liver disease, thrombocytopenia, or need for prolonged critical care due to MI complications. The occurrence of GI bleeds in DES patients increases length of hospital stay, in-hospital mortality, and 6-month mortality.¹⁷ Unless bleeding becomes life-threatening, every effort should be made to continue DAT in DES patients.¹⁷ When hemodynamic instability does occur, urgent GI consultation with potential therapeutic intervention is recommended. Patients with a known history of PUD or gastroesophageal reflux and those deemed to be at high risk for GI bleeds should receive prophylaxis utilizing a proton pump inhibitor.

Pre-DES oral anticoagulation Other patients worthy of special consideration are those who are on an oral anticoagulation (OAC) regimen prior to DES implantation. The typical OAC regimen is daily warfarin, although heparin is often

used until therapeutic levels of warfarin are achieved. Patients receive OAC most commonly for venous thromboembolism, cerebrovascular accident (CVA), prosthetic valve replacement, and atrial fibrillation. OAC decreases those patients' risk for everyday thrombotic events, including transient ischemic attack, CVA, and MI.

Previously, OAC and ASA were utilized as the post-PCI-S antithrombotic regimen of choice. However, numerous studies established the increased efficacy and safety of DAT over OAC and ASA,^{18,19} even in patients with a prior indication for OAC. The Stent Antithrombotic Regimen Study in 1998 established that patients receiving DAT after DES had significantly fewer events that correlate with thrombosis (death, emergency CABG, Q-wave MI, angiographically evident thrombosis) versus patients receiving only ASA or ASA and

“After a stent, patients who have mechanical prosthetic heart valves are urged to continue with oral anticoagulation rather than DAT.”

warfarin. A more recent meta-analysis established the increased safety and efficacy of DAT over OAC and ASA with regard to adverse cardiac events and hemorrhagic/vascular complications after PCI-S.¹⁸ Investigators reported a 50% decrease in nonfatal MI and a 71% reduction in need for repeat revascularization in the DAT patients. Cardiac death was also decreased by 27% in DAT patients.

Patients receiving OAC for reasons other than valve replacement should receive DAT in the post-stent implantation period to avoid an increased risk of nonfatal MI and need for repeat revascularization.¹⁸ Note that continuation of OAC in the post-stent implantation period is efficacious, but patients may experience increased cardiac outcomes, including in-stent thrombosis. If you, as the treating PA prefer, OAC may be restarted with ASA, but the patient's international normalized ratio should be kept at the lower end of the therapeutic range.

Prosthetic heart valves Patients with mechanical prosthetic heart valves are the only subset of patients previously on OAC who are urged to continue this treatment regimen rather than DAT, as these patients were not adequately protected by antiplatelet agents alone.

Surgical candidates In patients who are scheduled for invasive procedures or surgeries in the next 12 months, BMS is recommended over DES per ACC/AHA/SCAI recommendations.¹⁶ Use of a BMS may avoid the need for antithrombotic therapy altogether.

Drug hypersensitivity Be aware that patients with a hypersensitivity to ASA or clopidogrel should undergo desensitization therapy prior to PCI, as no other agents have been deemed as efficacious and safe as this combination.

Continued on page 34

“Patients receiving triple therapy had less restenosis, reduced target-lesion revascularization, and fewer major adverse cardiac events.”

Third antiplatelet agent Additional studies have focused on use of a third antiplatelet agent following DES implantation. Patients receiving triple therapy have demonstrated a 33.2% decrease in late luminal loss at 6-month angiographic follow-up.²⁰ These patients had less restenosis, reduced target-lesion revascularization, and fewer major adverse cardiac events. However, at present, the addition of a third agent is not routinely recommended.

SUMMARY

Although DES effectively reduces restenosis, a small but significant number of patients suffer complications of in-stent thrombosis. Thus, each patient’s health history should be determined before recommending DES. Patients must understand the importance of post-implantation DAT and the need for continued DAT, potentially for life, in order to reduce complications. Current recommendations advocate at least 12 months of uninterrupted clopidogrel and ASA (lifelong ASA if tolerated). With each new generation of stents, patients experience fewer adverse outcomes and improved quality of life. For the present, DES remains a strong therapeutic option for patients with symptomatic CHD. **JAAPA**

Jessica Justice is a PA with Aria Health-Torresdale in Philadelphia, Pennsylvania. **Christian Yacono** works at Cardiology Consultants of Philadelphia, PC, also in Philadelphia. The authors have indicated no relationships to disclose relating to the content of this article.

DRUGS MENTIONED

Aspirin	Paclitaxel
Clopidogrel (Plavix)	Sirolimus
Heparin	Ticlopidine (Ticlid, generics)
Metformin	Warfarin (Coumadin, generics)

REFERENCES

- Boyle AJ, Jaffe AS. Acute myocardial infarction. In: Crawford MH, ed. *Current Diagnosis and Treatment in Cardiology*. 3rd ed. New York, NY: McGraw-Hill; 2009:chap 5.
- Zahn R, Hamm CW, Schneider S, et al. Predictors of death or myocardial infarction during follow-up after coronary stenting with the sirolimus-eluting stent. Results from the prospective multicenter German Cypher Stent Registry. *Am Heart J*. 2006;52(6):1146-1152.
- Boden WE, O'Rourke RA, Teo KK, et al; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356(15):1503-1516.
- Radke PW, Friese K, Buhr A, et al. Comparison of coronary restenosis rates in matched patients with versus without diabetes mellitus. *Am J Cardiol*. 2006;98(9):1218-1222.
- Cutlip D. Drug-eluting intracoronary stents to prevent restenosis. UpToDate Web site. <http://www.uptodate.com/home/index.html>. January 31, 2008. Accessed July 2, 2008.
- Gioia G, Matthai W, Gillin K, et al. Revascularization in severe left ventricular dysfunction: Outcome comparison of drug-eluting stent implantation versus coronary artery by-pass grafting. *Catheter Cardiovasc Interv*. 2007(1);70:26-33.
- Sharifkazemi MB, Zamirian M, Aslani A. A current problem in cardiology: very late thrombosis after implantation of sirolimus eluting stent. *Cardiology*. 2007;108(4):273-274.
- Pinto Slottow TL, Waksman R. Overview of the 2006 Food and Drug Administration Circulatory System Devices Panel Meeting on drug-eluting stent thrombosis. *Catheter Cardiovasc Interv*. 2007;69(7):1064-1074.

- Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet*. 2007;369(9562):667-678.
- Cypher Sirolimus-eluting Coronary Stent on Raptor Over-the Wire Delivery System and Cypher Sirolimus-eluting Coronary Stent on Raptor Rapid Exchange Delivery System. [Instructions for use]. Bridgewater, NJ: Cordis Corp. http://www.cordislabeling.com/pdf/9578500_9.pdf. Updated June 18, 2009. Accessed July 2, 2009.
- TAXUS® Liberté® Atom™ Paclitaxel-Eluting Coronary Stent System. [Directions for use]. Natick, MA: Boston Scientific. http://www.bostonscientific.com/templatedata/imports/collateral/eDFU/taxusliberte_dfu_02_us.pdf. Accessed July 2, 2009.
- Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med*. 2007;356(10):998-1008.
- Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement; results from the PREMIER registry. *Circulation*. 2006;113(24):2803-2809.
- Schühlen H, Kastrati A, Mehilli J, et al. Abciximab and angiographic restenosis after coronary stent placement. Analysis of the angiographic substudy of ISAR-REACT—a double-blind, placebo-controlled, randomized trial evaluating abciximab in patients undergoing elective percutaneous coronary interventions after pretreatment with a high loading dose of clopidogrel. *Am Heart J*. 2006;151(6):1248-1254.
- Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med*. 2007;356(10):1030-1039.
- King SB III, Smith SC Jr, Hirschfeld JW, et al. 2007 Focused update of the 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. *Catheter Cardiovasc Interv*. 2007;71:E1-E40.
- Cutlip D, Levin T. Antithrombotic therapy for intracoronary stent implantation: recommendations. UpToDate Web site. <http://www.uptodate.com/home/index.html>. January 31, 2008. Accessed July 1, 2008.
- Rubboli A, Milandri M, Castelvetti C, Cosmi B. Meta-analysis of trials comparing oral anticoagulation and aspirin versus dual antiplatelet therapy after coronary stenting. Clues for the management of patients with an indication for long-term anticoagulation undergoing coronary stenting. *Cardiology*. 2005;104(2):101-106.
- Rubboli A, Brancaleoni R, Colletta M, et al. Contemporary antithrombotic treatment after coronary stenting in patients with indication for long-term anticoagulation. *Minerva Cardioangiologica*. 2006;54(5):687-693.
- Lee SW, Park SW, Kim YH, et al; DECLARE-Long Study Investigators. Comparison of triple versus dual antiplatelet therapy after drug-eluting stent implantation (from the DECLARE-Long Trial). *Am J Cardiol*. 2007;100(7):1103-1108.