A Clinical Risk Score for Prediction of Stent Thrombosis

Kenneth W. Baran, MD[a,*], John M. Lasala, MD, PhD[b], David A. Cox, MD[c], Aijun Song, MS[d], Mahesh C. Deshpande, MS, MBA[d], Mary V. Jacoski, MS[d], and Stephen R. Mascioli, MD[d], for the ARRIVE Investigators

The aim was to develop a clinically useful patient risk score predictive for stent thrombosis (ST). Using readily available baseline clinical and angiographic characteristics, a Cox proportional hazards multivariate model was used to identify significant ($p < 0.10$) predictors of ST through 1 year in 2,487 patients receiving a TAXUS Express (Boston Scientific Corp., Natick, Massachusetts) drug-eluting stent (DES) in the ARRIVE 1 registry. Hazard ratios of significant predictors were rounded to an integer value ranging from 2 to 5. These values were summed for a maximum possible score of 24. The model was validated using 1-year data from a similar DES data set (ARRIVE 2, n = 4,820 patients). The 8 significant predictors found were thienopyridine therapy discontinuation before 6 months, insulin-requiring diabetes, smoker at baseline, left main stent placement, multiple stent placement, lesion length >28 mm, moderate to severe lesion calcification, and reference vessel diameter <3 mm. Model discrimination was high, indicated by an area under the receiver-operator characteristic curve of 0.819. Stratification of patients into low-, medium-, and high-risk groups showed that ST developed in 0.8% of patients with a score <6, 3.6% of patients with a score of 7 to 13, and 12.6% of patients with a score ≥14. In conclusion, using 8 readily available clinical and angiographic characteristics, we defined an ST risk score for patients receiving a DES during the first year. Analysis of patients from ARRIVE 1 and 2 showed that most (73%) were in the lowest risk category, with 25% in the moderate risk category. Less than 2% were at highest risk of developing ST. **(Am J Cardiol 2008;102:541–545)**

The use of risk stratification scores is very useful in assisting clinicians in determining optimal treatment strategies. The Gottschall risk score used preangiographic characteristics to determine the risk of target-vessel revascularization rates with bare-metal stents through 1 year.[1] The Mayo score identified 8 clinical and angiographic variables to create a simple integer risk score for prediction of major in-hospital complications after percutaneous coronary intervention (PCI).[2] However, patient stratification based on risk of developing early or late stent thrombosis (ST) was often difficult because of the low event rates and small populations studied. Determination of risk was often based on anecdotal data obtained from a combination of physician experience and literature case reviews. Several studies have identified predictors of ST,[3–5] but none has identified a useful or validated score for this purpose.

The TAXUS Peri-Approval Registry: A Multi-center Safety Surveillance (ARRIVE) registry of patients receiving the paclitaxel-eluting TAXUS Express[2] stent (Boston Scientific Corp., Natick, Massachusetts) in real-world clinical settings has provided a large patient group from which to evaluate ST data. Data were available for >7,000 patients in the ARRIVE 1 and 2 registries combined, with all ST cases adjudicated by an independent committee. We set out to develop a readily applied, clinically useful risk score predictive of future ST using baseline and 1-year follow-up data from the ARRIVE 1 registry and validate the score using the ARRIVE 2 registry.

Methods

The goal of this study was to use statistical modeling to develop a simple risk score for ST after drug-eluting stent (DES) implantation. The primary end point of the analysis was ST defined using the Academic Research Consortium (ARC) criteria.[6] Real-world registry data from the ARRIVE program were used as the source to develop and validate the risk score model. The ARRIVE program consisted of 2 registries of patients from the United States who received a paclitaxel-eluting stent. The ARRIVE 1 registry, a Food and Drug Administration–mandated peri-approval registry consisting of 2,487 patients, was used to develop the risk score model. ARRIVE 2, a post-approval DES registry consisting of 4,820 patients, was used to validate the risk score model derived from ARRIVE 1. Thus, data from >7,000 patients were used in this risk score model development and validation. Very late STs (>1 year) were excluded from this analysis because the very low frequency of these events provided an inadequate sample size for modeling purposes. All analyses were conducted using statistical software SAS, version 8.2 (SAS Institute, Cary, North Carolina).

[a]St. Paul Heart Clinic, St. Paul, Minnesota; [b]Washington University School of Medicine, St. Louis, Missouri; [c]Lehigh Valley Heart Specialists, Allentown, Pennsylvania; and [d]Boston Scientific Corp., Natick, Massachusetts. Manuscript received February 29, 2008; revised manuscript received and accepted April 23, 2008.

This work was supported by Boston Scientific Corp., Natick, Massachusetts.

*Corresponding author: Tel: 651-292-0616; Fax: 651-726-7258.

E-mail address: kbaran@stphc.com (K.W. Baran).

0002-9149/08/$ – see front matter
doi:10.1016/j.amjcard.2008.04.068

Table 1
Baseline characteristics

Insulin Dependent Diabetic	In-stent Restenosis	Multiple Stenting per patient
Diabetes, not requiring insulin	Renal Disease	Failed Brachytherapy
Thienopyridine discontinued before 6 months	Previous coronary artery bypass grafting	Multivessel Stenting
Age > 70 years	Previous percutaneous coronary intervention	Lesion Calcification (Moderate and Severe)
Gender	Cardiogenic Shock	Lesion Type B2/C
Smoker at Baseline	Congestive Heart Failure	Pre-procedure TIMI = 0
Hypercholesterolemia	Acute Myocardial Infarction	Reference Vessel Diameter < 3 mm
Hypertension	Left Main Stenting	Left Anterior Decending Artery as Target Vessel
Prior Myocardial Infarction	Chronic Total Occlusion	Lesion length longer than 28 mm
Previous Stroke	Bifurcated Lesion	
Known Multi-vessel disease	Ostial Lesion	

Table 2
TAXUS ARRIVE Program (N = 7307)[§]

36% Simple Use	64% Expanded Use	
	Complex Patients*	Patients with Complex Lesions*
Single vessel	Acute myocardial infarction (12.5%)	Calcification (mod/severe) (19.6%)
Single stent	Congestive heart (6.9%)	Multivessel stenting (15.7%)
	Left main disease (4.8%)	Long lesion (>28 mm) (10.0%)
	Renal dysfunction (2.5%)	Ostial lesion (8.7%)
	Cardiogenic shock (0.4%)	Bifurcated lesion (7.6%)
		In-stent restenosis (6.5%)
		Graft stenting (6.3%)
		Severe tortuosity (3.8%)
		Small vessel (3.4%) (reference vessel diameter <2.5 mm)
		Chronic total occlusion (2.2%)
		Left main stenting (2.2%)
		Failed brachytherapy (0.4%)

* A patient may belong to >1 expanded use group.
[§] Patients with and without Diabetes Mellitus were in both simple and expanded use groups. Please note the total patient number in the ARRIVE program used in this analysis included the total patients for which data were available at the time.

The ARRIVE registry was described in detail elsewhere.[7] Briefly, the ARRIVE program was a 2-part prospective real-world registry program undertaken in conjunction with the Food and Drug Administration to study use patterns and long-term outcomes of the TAXUS Express[2] stent in the United States. All cardiac events including ST were adjudicated by an independent external clinical events committee. Patients were followed up at 1, 6, 12, and 24 months. Data quality was ensured using independent audits of 100% of cardiac events and random audits of 20% of ARRIVE 1 and 10% of ARRIVE 2 patients.

Significant baseline characteristics predictive of ST were identified using Cox univariate regression analysis. Thirty-one candidate variables were considered based on statistical significance and clinical relevance (Table 1). A Cox multivariate model was then used to identify significant baseline predictors of 1-year ST. Backward selection was used with a threshold to stay in the model set at 0.1. The resulting model yielded 8 independent variables predictive of ST. Hazard ratios of these risk factors were rounded to the nearest integer, then summed to yield a maximum possible ST score of 24. To evaluate goodness of fit of the model, we report the C statistic (area under the receiver-operator characteristic curve) and Hosmer-Lemeshow goodness-of-fit statistic (high probability value corresponds to good fit).

Validation of this model was carried out in an independent data set, the ARRIVE 2 registry, which had collected the same DES patient-level data using the same protocol and event definitions as ARRIVE 1. The goodness-of-fit statistic was computed along with the C statistic. A bootstrap method was used as a second validation tool to assess the model stability.

Each of the 7,000 patients in the combined ARRIVE data set was scored, then stratified into 1 of the 3 risk categories for ST of low (0 to 6), moderate (7 to 13), and high risk (14 to 24). ST rates were calculated for each risk category.

Table 3
Integer assignment of risk factors

Clinical Factors	HR	Weight
thienopyridine discontinuation <6 months	5.28	5
insulin-treated diabetes	4.74	5
left main stenting	2.73	3
smoking status	2.63	3
lesion length >28 mm	2.35	2
multiple stenting	2.25	2
moderate to severe lesion calcification	1.77	2
reference vessel diameter <3 mm	1.72	2
Total Possible Score		24

HR = hazard ratio.

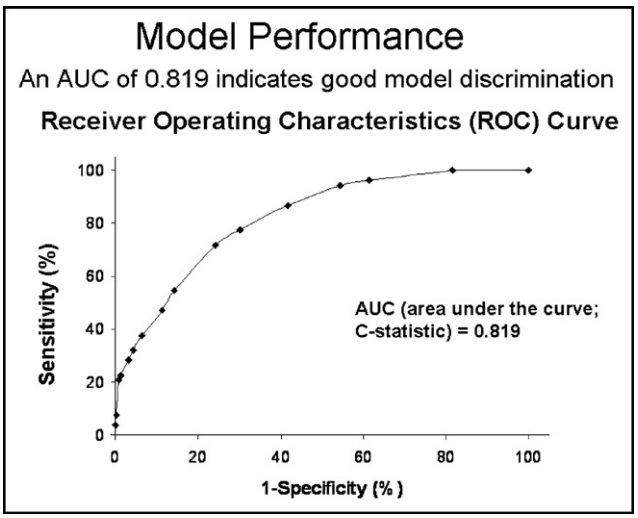

Figure 1. Model performance assessed using examination of the receiver-operator characteristics curve.

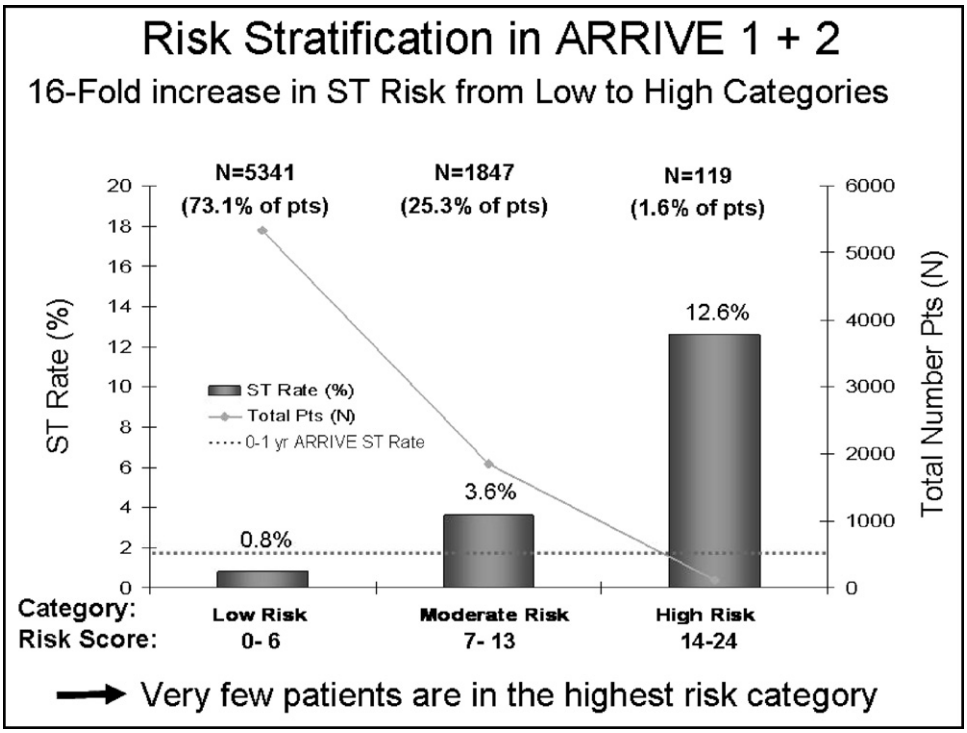

Figure 2. Risk stratification of patients (pts) in ARRIVE showed very few patients in the highest risk category for developing ST at 1 year.

Results

In ARRIVE 1, a total of 53 patients (2.2%) had ST in the first year of follow-up. In ARRIVE 2, a total of 70 patients (1.5%) had ST in the first year. Although the ARRIVE registries enrolled a large number of complex patients or lesions (Table 2), with most patients receiving a DES in an off-label indication, the rate of ST was low in contrast to data reported by Win et al[8] and the Evaluation of Drug Eluting Stents and Ischemic Events (EVENT) Registry Investigators, which showed that off-label use of DESs was associated with higher rates of ST. In ARRIVE 1, variables found to be predictive of ST included thienopyridine therapy discontinuation before 6 months, insulin-requiring diabetes, smoker at baseline, multiple stent placement, lesion length >28 mm, left main stent placement, moderate to severe lesion calcification, and reference vessel diameter <3 mm. Integer values of 2 to 5 corresponding to each factor's hazard ratio were assigned, yielding a maximum possible score of 24 (Table 3). The area under the curve or C statistic, a measure of discrimination of the model, was 0.819, indicating high discrimination between patients with versus without ST (Figure 1). The goodness of fit using Hosmer Lemeshow χ^2 statistic showed a good fit ($p = 0.79$). The strongest predictors were thienopyridine therapy discontinuation before 6 months and insulin-requiring diabetes.

Validation of the model was performed using the ARRIVE 2 registry and calculating risk scores using the 8 predictors identified in the model from ARRIVE 1. Cox regression was performed between the risk score and 1-year ST events in ARRIVE 2. The validation model had a C statistic of 0.74, an indication of good discriminatory ability, and a Hosmer Lemeshow χ^2 goodness-of-fit test with a p-value of 0.79, indicating utility of the model.

Finally, all ARRIVE registry patients were combined and divided into 3 groups of risk using the risk score. Most patients (73%) were in the low-risk group (0 to 6 points), with an ST rate of 0.8% (Figure 2). Twenty-five percent of patients were in the moderate-risk group (7 to 13 points), with an ST rate of 3.6%. Finally, 1.6% of patients were in the high-risk group (14 to 24 points), with an ST rate of 12.6%.

The following example illustrates the practical utility of the score. A 60-year-old nonsmoking man with a medical history of hypercholesterolemia and arthritis presented with chest pain. He underwent PCI with the placement of 2 DESs to the left circumflex artery to cover a nontortuous, highly calcified, approximately 32-mm lesion. At 4 months after PCI, his primary care physician and orthopedic surgeon would like to discontinue clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi Aventis Pharmaceuticals Partnership, Bridgewater, New Jersey) to schedule a total knee replacement. Applying the ST risk score yielded the factors of a long lesion >28 mm (2 points), multiple stents (2 points), and a highly calcified lesion (2 points), for a total score of 6 points, which put his risk of developing ST at 0.8%. However, discontinuing clopidogrel therapy before 6 months added another 5 points, which increased his score to 11 points and his overall risk to 3.6%. In a nonurgent setting, his care team may want to consider delaying knee replacement surgery until the patient is at least beyond 6 months of post-PCI clopidogrel treatment.

Discussion

We were able to define an ST clinical risk assessment tool for patients undergoing DES implantation in the ARRIVE 1 registry using 8 readily available clinical and angiographic variables. Excellent predictive ability of the model was

indicated when validated using data from ARRIVE 2. Most patients (73%) were classified into the lowest risk category, whereas 25% were in the moderate-risk category (Figure 2). Less than 2% of patients were in the high-risk group. Use by clinicians of this simple scoring system, which is based on readily available baseline clinical and angiographic measures, may provide guidance in DES patient management, particularly when dual-antiplatelet medication interruption is being considered. This score may help identify patients likely to be at higher risk, and therefore appropriate periprocedural and postdischarge care can be determined.

Withdrawal of thienopyridine therapy before 6 months was the strongest predictor in the model. Frequency distributions of patients with this predictor within each of the subsets of low, medium, and high risk were 5%, 47%, and 88%, indicating, as expected, that the strongest predictor was almost always found in the highest risk group. The model could also be used to assess risk of ST with DESs with or without assurance of clopidogrel compliance. Early clopidogrel therapy withdrawal added 5 points, so if the baseline risk score was $\leq$9, clopidogrel therapy withdrawal would put the patient into only a moderate risk category. However, if the baseline risk score was already $\geq$10, that would put the patient at high risk of thrombosis.

Other groups have identified similar variables as highly predictive of ST. Iakovou et al[3] identified several independent predictors of either subacute or late ST through 9 months, including premature discontinuation of thienopyridine therapy, diabetes, and stent length. In the Registry Experience at the Washington Hospital Center with Drug Eluting Stents (REWARDS) Registry, univariate and multivariate independent predictors of ST at 1 year included total number of stents implanted, age, male gender, and sirolimus-eluting stents (SES).[4] In the The CYPHER U.S. Post Market Surveillance (eCYPHER) Registry study, predictors of ST included insulin-dependent diabetes and moderate to heavy calcifications.[5] No study identified smoking as a risk factor. However, a possible mechanism of the contribution of smoking to ST could be through induction of a prothrombotic state through platelet-dependent increases in thrombin generation.[9]

We did not find renal disease as a predictor of ST in the first year, which was found to be predictive by some investigators,[3,10] but not others.[5] This may be caused in part by the low number of patients with known acute or chronic renal disease in the ARRIVE 1 study (60 of 2,487; 2.4%). Also, Park et al[11] found that renal disease was predictive of late ST, but not early events,[11] and our model was limited to prediction of ST events in the first year.

Recent data indicated that continuation of clopidogrel therapy beyond 6 months resulted in a lower incidence of death or myocardial infarction (MI),[12] confirming earlier data from the Basel Stent Kosten-Effektivitats Trial-Late Thrombotic Events (BASKET-LATE) trial, which also found an increased risk of death and MI after discontinuation of clopidogrel therapy, which the investigators suggested may be caused by a higher rate of late thrombosis-related events.[13] Also, earlier data from the Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER) registry found that patients with MI who stopped thienopyridine therapy by 30 days after DES implantation were significantly more likely to die during the next 11 months.[14] The Late Angiographic Stent Thrombosis (LAST) Study investigators specifically reported that no case of late ST was observed in patients on dual-antiplatelet therapy.[15] The latest American College of Cardiology/American Heart Association guideline released for the management of patients after PCI recommended extending dual-antiplatelet therapy (aspirin and thienopyridine) to $\geq$1 year after DES placement in patients not at increased bleeding risk.[16] However, the benefits of extending clopidogrel therapy in patient after stent placement need to be validated in a large randomized clinical trial.

Limitations of the present risk score included the relatively small number of events, which limited the discriminatory ability of the model. Although data used in creation of this score were from a real-world registry of >2,400 patients, the number of patients with ST was still relatively small (n = 53). Although the final data yielded statistical significance, their clinical impact has not yet been measured. This was not a model intended to aid in the decision of how to treat patients in the catheterization laboratory; patients should be treated using the clinician's judgment and the best tools available. Rather, this model was designed to assist in the management of patients after DES placement. Also, care should be used in extrapolating these data to a risk beyond 1 year because only data through 1 year were used to both generate and validate this score. Preliminary analysis of the pooled ARRIVE data set suggested that additional predictive factors may be in operation in patients with very late ST.[17] Additionally, although thienopyridine therapy discontinuation at 6 months was used in the multivariate modeling, there were few data available beyond 6 months to determine the ideal length of thienopyridine administration in patients after DES placement. Finally, the score needs to be validated in additional independent data sets and with other types of DESs, although no clear inter-DES differences in ST have been shown for similar lesion types.

Acknowledgment: The authors thank Kevin Najarian, MS, for contributions to the statistical design and analysis, and Ruth Starzyk, PhD, for valuable editorial assistance.

1. Gottschall CAM, Quadros AS, Sarmento-Leite R. Acute coronary syndromes: predictive score for target vessel revascularization after bare metal coronary stenting. *J Invasive Cardiol* 2006;18:22–26.
2. Singh M, Lennon RJ, Holmes DR, Bell MR, Rihal CS. Correlates of procedural complications and a simple integer risk score for percutaneous coronary intervention. *J Am Coll Cardiol* 2002;40:387–393.
3. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005;293:2126–2130.
4. Waksman R, Buch AN, Torguson R, Xue Z, Smith K, Javaid A, Chu WW, Satler LF, Kent KM, Pichard AO. Long-term clinical outcomes and thrombosis rates of sirolimus-eluting versus paclitaxel-eluting stents in an unselected population with coronary artery disease (REWARDS registry). *Am J Cardiol* 2007;100:45–51.
5. Urban P, Gershlick AH, Guagliumi G, Guyon P, Lotan C, Schofer J, Seth A, Sousa JE, Wijns W, Berge C, Deme M, Stoll H-P. Safety of coronary sirolimus-eluting stents in daily clinical practice: one-year follow-up of the e-Cypher Registry. *Circulation* 2006;113:1434–1441.

6. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es G-A, Steg PG, Morel M-A, Mauri L, Vranckx P, et al; for the Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;115:2344–2351.
7. Lasala JM, Cox DA, Dobies D, Muhlestein JB, Katopodis JN, Revtyak G, Baim DS; for the ARRIVE 1 Participating Physicians. Usage patterns and 2-year outcomes with the Taxus Express stent: results of the U.S. ARRIVE 1 registry. *Catheter Cardiovasc Interv*. Epub ahead of print, April 21, 2008. doi:10.1002/ccd.21618.
8. Win HK, Caldera AE, Maresh K, Lopez J, Rihal CS, Parikh MA, Granada JF, Marulkar S, Nassif D, Cohen DJ, Kleiman NS; for the EVENT Registry Investigators. Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. *JAMA* 2007;297: 2001–2009.
9. Hioki Y, Aoki N, Kawano K, Homori M, Hasumura Y, Yasumura T, Maki A, Yoshino H, Yanagisawa A, Ishikawa K. Acute effects of cigarette smoking on platelet-dependent thrombin generation. *Eur Heart J* 2001;22:56–61.
10. Machecourt J, Danchin N, Lablanche JM, Fauvel JM, Bonnet JL, Marliere S, Foote A, Quesada JL, Eltchaninoff H, Vanzetto G; for the EVASTENT Investigators. Risk factors for stent thrombosis after implantation of sirolimus-eluting stents in diabetic and nondiabetic patients; the EVASTENT matched-cohort registry. *J Am Coll Cardiol* 2007;50:501–508.
11. Park D-W, Park S-W, Park K-H, Lee B-K, Kim Y-H, Lee CW, Hong M-K, Kim J-J, Park S-J. 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.
12. Eisenstein EL, Anstrom KJ, Kong DF, Shaw LK, Tuttle RH, Mark DB, Kramer JM, Harrington RA, Matchar DB, Kandzari DE, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA* 2007;297:159–168.
13. Pfisterer M, Brunner-La Rocca 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: an observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol* 2006;48:2584–2591.
14. 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.
15. 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.
16. King SB, Smith SC, Hirshfeld JW, Jacobs AK, Morrison DA, Williams DO. 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.. *Circulation* 2008;117:261–295.
17. Lasala JM, Cox DA, Mascioli SR, Baim DS; for the ARRIVE Participating Physicians. Predictors for stent thrombosis in real-world use of the Taxus Express2 paclitaxel-eluting stent: insights from the 7000-patient ARRIVE program. Presented at Transcatheter Cardiovascular Therapeutics. Washington, DC, October 22, 2007. Available at http://www.aievolution.com/tct0701/index.cfm?do=abs.pubSearchOptions TCT no. 536. Accessed June 6, 2008.