Journal of the American College of Cardiology
© 2006 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 48, No. 1, 2006
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.03.042

EXPEDITED REVIEWS

Pathology of Drug-Eluting Stents in Humans

Delayed Healing and Late Thrombotic Risk

Michael Joner, MD,* Aloke V. Finn, MD,† Andrew Farb, MD,§ Erik K. Mont, MD,‡ Frank D. Kolodgie, PHD,* Elena Ladich, MD,* Robert Kutys, MS,* Kristi Skorija, BS,* Herman K. Gold, MD,† Renu Virmani, MD*

Gaithersburg and Rockville, Maryland; Boston, Massachusetts; and Miami, Florida

OBJECTIVES This study examined human drug-eluting stents (DES) to determine the long-term effects of these stents on coronary arterial healing and identified mechanisms underlying late stent thrombosis (LST).

BACKGROUND Although DES reduce the need for repeat revascularization compared with bare-metal stents (BMS), data suggest the window of thrombotic risk for Cypher (Cordis Corp., Miami Lakes, Florida) and Taxus (Boston Scientific Corp., Natick, Massachusetts) DES extends far beyond that for BMS.

METHODS From a registry of 40 autopsies of DES (68 stents), 23 DES cases of >30 days duration were compared with 25 matched autopsies of BMS implantation. Late stent thrombosis was defined as an acute thrombus within a stent >30 days old.

RESULTS Of 23 patients with DES >30 days old, 14 had evidence of LST. Cypher and Taxus DES showed greater delayed healing characterized by persistent fibrin deposition (fibrin score 2.3 ± 1.1 vs. 0.9 ± 0.8, p = 0.0001) and poorer endothelialization (55.8 ± 26.5%) compared with BMS (89.8 ± 20.9, p = 0.0001). Moreover, DES with LST showed more delayed healing compared with patent DES. In 5 of 14 patients suffering LST, antiplatelet therapy had been withdrawn. Additional procedural and pathologic risk factors for LST were: 1) local hypersensitivity reaction; 2) ostial and/or bifurcation stenting; 3) malapposition/incomplete apposition; 4) restenosis; and 5) strut penetration into a necrotic core.

CONCLUSIONS The Cypher and Taxus DES result in delayed arterial healing when compared with BMS of similar implant duration. The cause of DES LST is multifactorial with delayed healing in combination with other clinical and procedural risk factors playing a role. (J Am Coll Cardiol 2006;48:193–202) © 2006 by the American College of Cardiology Foundation

Stent thrombosis remains a major cause of death and morbidity after percutaneous coronary interventions (1–4). The pivotal clinical trials that formed the basis for approval of drug-eluting stents (DES) have not shown an increase in stent thrombosis compared with bare-metal stents (BMS) (5,6). However, recent publication of "real-world" patients

See page 203

receiving DES have suggested that the window of thrombotic risk at sites where these stents have been deployed extends far beyond that for BMS (7,8). Understanding the time course of healing in DES compared with BMS and the pathologic mechanisms underlying late stent thrombosis (LST) might more clearly delineate the time course of thrombotic risk and redefine the optimal duration of antiplatelet therapy.

Current polymer-based sirolimus-eluting (Cypher, Cordis Corp., Miami Lakes, Florida) and paclitaxel-eluting (Taxus, Boston Scientific Corp., Natick, Massachusetts) stents are the only DES approved by the U.S. Food and Drug Administration (FDA) for human use. Some published studies of animal models with similar DES implanted in normal arteries show a substantial impairment of arterial healing relative to BMS (9–13). To date, there has been no systematic published analysis of the long-term effects of DES on arterial healing in humans. We examined 40 consecutive autopsies of patients who died subsequent to DES implantation to determine the long-term effects of DES placement on coronary arterial healing and to identify pathologic mechanisms underlying LST.

MATERIALS AND METHODS

From a registry of 484 human coronary stents submitted for consultation, 40 consecutive cases with evidence of one or more DES were examined (3 have been previously reported) (14–16). Of these cases, 23 (32 stents) had DES implanted for >30 days and were included in the DES study group. Clinical histories and cardiac catheterization reports were reviewed when available. A total of 25 cases of BMS implantation (36 stents) of patients of similar age, gender, case duration, and

From *CVPath, International Registry of Pathology, Gaithersburg, Maryland; †Cardiac Unit, Department of Internal Medicine, Massachusetts General Hospital, Boston, Massachusetts; ‡Miami Dade County Medical Examiner Department, Heart Radiology, Miami, Florida; and the §Interventional Cardiology Devices Branch, U.S. Food and Drug Administration, Rockville, Maryland. Drs. Joner and Finn contributed equally to this work.

Manuscript received January 26, 2006; revised manuscript received March 10, 2006, accepted March 16, 2006.

Abbreviations and Acronyms
BMS = bare-metal stents
DES = drug-eluting stents
FDA = Food and Drug Administration
LST = late stent thrombosis

artery of implantation were blindly selected from our registry and formed the control BMS group. Cases with a history of prior brachytherapy were excluded.

Stented arteries had been fixed in 10% buffered formalin, dissected off the heart, examined via radiography, and submitted for plastic embedding. Arteries were sectioned 2 to 3 mm apart and stained with hematoxylin and eosin and Movat pentachrome as previously described (17). Cases with histologic evidence of an acute occlusive or nonocclusive mural thrombus within a coronary artery stent in place >30 days were defined as LST. Stented arteries with severe narrowing, defined as in-stent luminal cross-sectional area narrowing of ≥75% by neointimal growth, were defined as restenosis; and those <75% area narrowing were designated as patent stents.

Morphologic and morphometric measurements. Computer-guided morphometric measurements were performed using IPLab Spectrum software (Scanalytics Inc., Vienna, Virginia) on sections from stents implanted for >30 days. Digital images were captured (4× magnification), and area measurements included the internal elastic lamina, plaque burden, stent area, and lumen area; stent lengths were measured from radiographs. For calculation of in-stent neointimal growth, fibrin deposition, and surface endothelialization, stents with occlusive thrombi were excluded to overcome biased measurements. Ordinal data for fibrin were collected on each stent section using a scale of 0 to 3+ as previously reported (18). Inflammation was scored at each stent strut using a scale from 0 to 5 (with 0 for 0 to 25 surrounding inflammatory cells, 1 for 25 to 50, 2 for 50 to 100, 3 for 100 to 150, 4 for 150 to 200, and 5 for >200 surrounding inflammatory cells). The percentage of struts with surrounding fibrin and luminal surface endothelium was also recorded. Delayed arterial healing was defined as persistence of fibrin beyond 30 days. Total eosinophils were evaluated by counting the four most severely inflamed struts per section and reported as eosinophils per strut.

Statistical analysis. Continuous variables are presented as the mean ± SD and categorical variables either as mean ± SD or frequency (%). Continuous variables were first checked for normal distribution using Shapiro-Wilk goodness-of-fit test and compared by Student *t* test for normally distributed or a Wilcoxon rank-sum test for non-normally distributed variables. For comparison of rates of LST between the DES group and the control BMS group, a Fisher exact test was used. A p value ≤0.05 was considered significant. The percentage of struts covered by endothelial cells was plotted against the duration of implant to derive a slope, intercept, and correlation coefficient to determine relationships.

RESULTS

Patient characteristics. Thirty-two DES were examined from 23 individuals and compared with 36 matched BMS from 25 individuals. In patients with DES, indications for stenting were unstable angina or acute myocardial infarction (n = 5 patients for Cypher, n = 7 for Taxus), stable angina (n = 5 for Cypher, n = 5 for Taxus), or restenosis (n = 1 for Cypher). The location of the stents was: left anterior descending/left diagonal (Cypher, n = 10 stents; Taxus, n = 6; BMS, n = 13); right coronary artery/posterior descending artery (Cypher, n = 4; Taxus, n = 5; BMS, n = 12); and left circumflex/left obtuse marginal (Cypher, n = 3; Taxus, n = 4; BMS, n = 11).

Procedural outcome. At the time of coronary intervention, all patients had angiographically successful stent deployment with one DES placed in 15 patients, two DES in 7 patients, and three DES in 1 patient. Mean stent length for DES was 32.1 ± 17.3 mm (range 8 to 76 mm; median 25 mm, 75% <35 mm). Ostial/bifurcation stenting was performed in three cases (left circumflex/obtuse marginal bi-

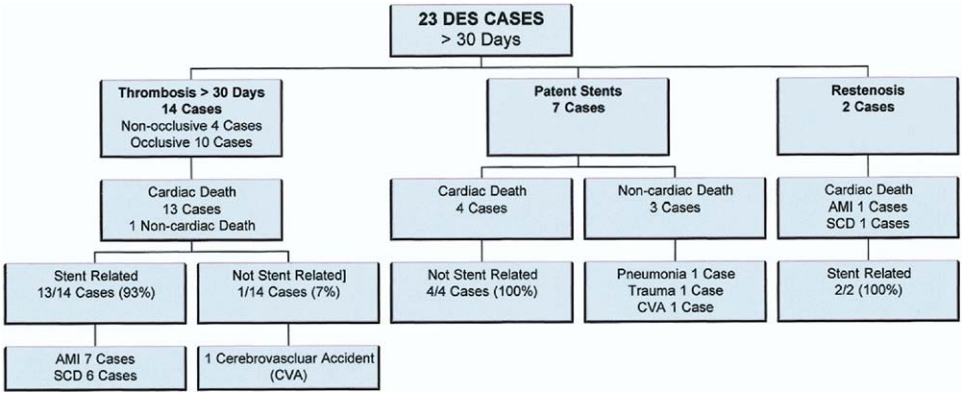

Figure 1. Flow diagram illustrating cause of death in drug-eluting stents (DES) patients with stents in place >30 days. These cases are divided into three major categories depending on whether stents showed evidence of late thrombosis, were patent, or were restenotic. AMI = acute myocardial infarction; SCD = sudden cardiac death.

Table 1. Morphometric Characteristics of DES Versus BMS >30 Days

Group	Mean Duration (days)	IEL Area (mm^2)	Plaque Area (mm^2)	Stent Length (mm)	Stent Area (mm^2)	Neointimal Area† (mm^2)	% Stenosis†
DES (n = 32)	223 ± 253	12.9 ± 5.3	8.1 ± 4.2	32.1 ± 17.3	6.7 ± 2.7	2.8 ± 1.1	51.4 ± 22.4
BMS (n = 36)	299 ± 360	12.5 ± 5.1	6.3 ± 3.3	20.2 ± 11.9	7.7 ± 3.5	4.9 ± 3.0	66.5 ± 22.0
p Value	ns*	ns*	ns	0.01*	ns*	0.0003>*	0.01*

Group	Inflammation Score	No. of Eosinophils/Strut†	Fibrin Score†	% Struts With Fibrin†	% Struts Endothelialized†
DES (n = 32)	1.7 ± 1.5	5.6 ± 11.1	2.3 ± 1.1	49.3 ± 30.8	55.8 ± 26.5
BMS (n = 36)	1.3 ± 0.8	0.6 ± 2.3	0.9 ± 0.8	22.3 ± 17.8	89.8 ± 20.9
p Value	ns*	0.01*	0.0001>*	0.0005*	0.0001*

*Chi-square; †stents with occlusive thrombi were excluded for neointimal area measurements (n = 11 excluded for DES, 0 for BMS).
BMS = bare-metal stent; DES = drug-eluting stent; IEL = internal elastic lumen.

furcation stenting, crush technique; left anterior descending/diagonal ostial stenting; and left anterior descending at the take-off of left circumflex [ostial stenting]), and all three cases showed occlusive thrombi.

Thirty-six BMS were examined from 25 individuals (mean age 61 ± 9 years) with one BMS placed in 18 patients, two BMS in 4 patients, three BMS in 2 patients, and four BMS in 1 patient. Mean stent length for BMS was 20.2 ± 11.9 mm (range 8 to 42 mm; median 18 mm, 75% <33 mm). Ostial/bifurcation stenting was performed in two cases (left anterior descending/diagonal bifurcation stenting, V-stenting technique; and left circumflex/obtuse marginal ostial stenting), and both died secondary to restenosis without evidence of thrombosis.

Antiplatelet therapy. During catheterization procedures, aspirin and clopidogrel were administered to all patients; 17 of 23 patients were being continued on an antiplatelet regimen at the time of death. In five cases, it was confirmed that patients were not receiving clopidogrel or aspirin at the time of death. In one case the antiplatelet therapy was unknown at the time of death. Of the 17 patients who could be confirmed to be on antiplatelet therapy, 14 were maintained on dual antiplatelet therapy with aspirin and clopidogrel. An additional two patients were receiving clopidogrel monotherapy, and one patient was on aspirin only.

Causes of death. Thirteen of the 14 DES cases of LST died of cardiac causes (Fig. 1). The cause of death was either total thrombotic occlusion of the stent or subtotal occlusion with distal embolization leading to acute myocardial infarction or sudden cardiac death. Seven DES cases had patent stents, and none died of stent-related complications. Two DES cases had in-stent restenosis and died of acute myocardial infarction or sudden cardiac death. Two of the 25 BMS patients died of LST. Eighteen BMS cases had patent stents, and no patients died of stent-related complications (15 patients had a cardiac cause of death and 3 had a noncardiac cause of death). Five patients with BMS implants had in-stent restenosis and died secondary to stent

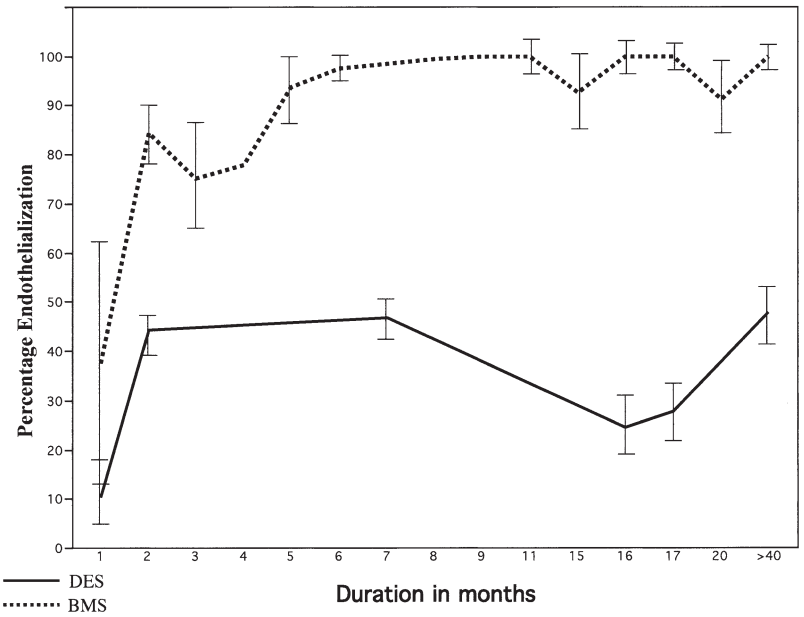

Figure 2. Line chart comparing the percentage of endothelialization in drug-eluting stents (DES) versus bare-metal stents (BMS) as a function of time. Note that DES **(solid line)** consistently show less endothelialization compared with BMS **(dashed line)** regardless of time point. Even beyond 40 months DES are not fully endothelialized, whereas BMS are completely covered by 6 to 7 months.

Table 2. Morphometric Characteristics of DES With Late (>30 Days) Thrombosis Versus Patent Stents (No Thrombosis)

Group	Mean Duration (days)	IEL Area (mm^2)	Plaque Area (mm^2)	Stent Length (mm)	Mean No. of Stents/ Patient	Stent Area (mm^2)	Fibrin Score	% Struts Endothelialized
Thrombosis (n = 20)	197 ± 139	13.1 ± 4.6	9.6 ± 4.0	38.8 ± 18.1	1.74 ± 0.86	6.9 ± 2.5	3.0 ± 0.9	27.1 ± 25.9
No thrombosis (n = 12)	181 ± 135	11.0 ± 5.8	5.8 ± 3.5	23.6 ± 12.2	1.25 ± 0.70	6.1 ± 3.0	1.9 ± 1.1	66.1 ± 25.4
p Value	ns*	ns	0.008	0.009*	0.04*	ns	0.03*	0.001

*Chi-square.
Abbreviations as in Table 1.

related acute myocardial infarction (three cases) or sudden cardiac death (two cases).

LST (≥30 days). Of 23 DES cases, 14 (61%) had stent thrombosis, and of the 25 cases of BMS included as controls, 2 (8%) had LST (p = 0.0001). Both cases of BMS LST also had evidence of in-stent restenosis. The rate of LST in the control BMS group is similar to that previously reported from our registry of BMS (19).

Comparison of DES and BMS implants. Stent length in DES was greater than in BMS (32.1 ± 17.3 vs. 20.2 ± 11.9, p = 0.01) (Table 1). The DES had significantly less in-stent neointimal growth compared with BMS (neointimal area 2.9 ± 1.1 mm^2 vs. 4.9 ± 3.0 mm^2, p = 0.005; % stenosis 54.4 ± 23.6% vs. 66.5 ± 22.0%, p = 0.05). Although the extent of overall inflammation was not significantly different in the two groups, eosinophils surrounding struts were more frequent in DES compared with BMS (5.6 ± 11.1 vs. 0.6 ± 2.3 per strut, p = 0.01). The DES also showed significantly higher fibrin scores (2.3 ± 1.1 vs. 0.9 ± 0.8, p = 0.0001) and percentage of struts surrounded by fibrin (49.3 ± 30.8% vs. 22.3 ± 17.8%, p = 0.0005). The percentage of endothelialized stent struts was significantly higher in BMS compared with DES (89.8 ± 20.9% vs. 55.8 ± 26.5%, p = 0.0001). Regardless of implant duration, BMS stents showed significantly greater endothelialization than DES (Fig. 2).

Morphometric characteristics of DES with LST versus patent DES. Implant duration in DES with LST was no different from patent DES (197 ± 139 days vs. 181 ± 135 days, respectively, p = ns) (Table 2). The internal elastic lamina and stent area were also similar among groups, whereas plaque area was significantly larger in cases with LST (9.6 ± 4.0 mm^2 vs. 5.8 ± 3.5 mm^2, p = 0.008). The mean number of stents per patient was significantly higher in patients with LST versus those with patent stents (1.74 ± 0.86 vs. 1.25 ± 0.70, p = 0.04), as was stent length (38.8 ± 18.1 mm vs. 23.6 ± 12.2 mm, p = 0.009). Signs of delayed healing were also significantly greater in thrombosed DES with increased fibrin score (3.0 ± 0.9% vs. 1.9 ± 1.1%, p = 0.03) and less

Table 3. Pathological Mechanisms of Stent Thrombosis >30 Days Other Than Delayed Stent Healing

Age (yrs), Gender	PCI Indication	Artery Stented	Stents	No. of Stents	Stent Length (mm)	Time to ST (days)	Presentation/ Cause of Death	Thrombosis
ST Associated With Delayed Healing + Chronic Inflammation (Hypersensitivity)								
45, M	Angina	LAD	Taxus	3	76	200	SCD	Occlusive
58, M	UA	LCX	Cypher	2	27	504	AMI/rupture	Occlusive*
61, M	Angina	PDA	Cypher	1	18	112	SCD	Nonocclusive
ST Associated With Delayed Healing + Penetration of Necrotic Core								
47, F	Angina	LAD	Taxus	1	56	40	AMI	Occlusive
ST Associated With Delayed Healing + Ostial and/or Bifurcation Stenting								
77, M†	AMI	LAD, LCX	Cypher	1	36	450	SCD	Occlusive
68, F‡	Angina	LOM	Cypher, Taxus	2	25, 20	172	AMI	Occlusive
42, M§	AMI	LAD	Taxus	1	32	278	SCD	Occlusive
ST Associated With Delayed Healing + Malapposition/Incomplete Apposition¶								
62, M	Angina	RCA	Cypher	2	40	130	SCD	Nonocclusive
38, F‖¶	Angina	LAD	Taxus	1	32	278	SCD	Occlusive
ST Associated With Delayed Healing + Restenosis								
75, M	AMI	RCA	Cypher	1	18	120	AMI	Nonocclusive
70, F	AMI	LAD	Taxus	2	47	112	SCD	Nonocclusive

*Associated with aneurysm and malapposition; †ostial stenting LAD/LCX; ‡bifurcation stenting LCX/LOM; §ostial stenting LAD/left diagonal; ‖ostial stenting LAD/left diagonal; ¶incomplete apposition.
AMI = acute myocardial infarction; LAD = left anterior descending artery; LCX = left circumflex artery; LOM = left obtuse marginal; PDA = posterior descending artery; RCA = right coronary artery; SCD = sudden cardiac death; ST = stent thrombosis.

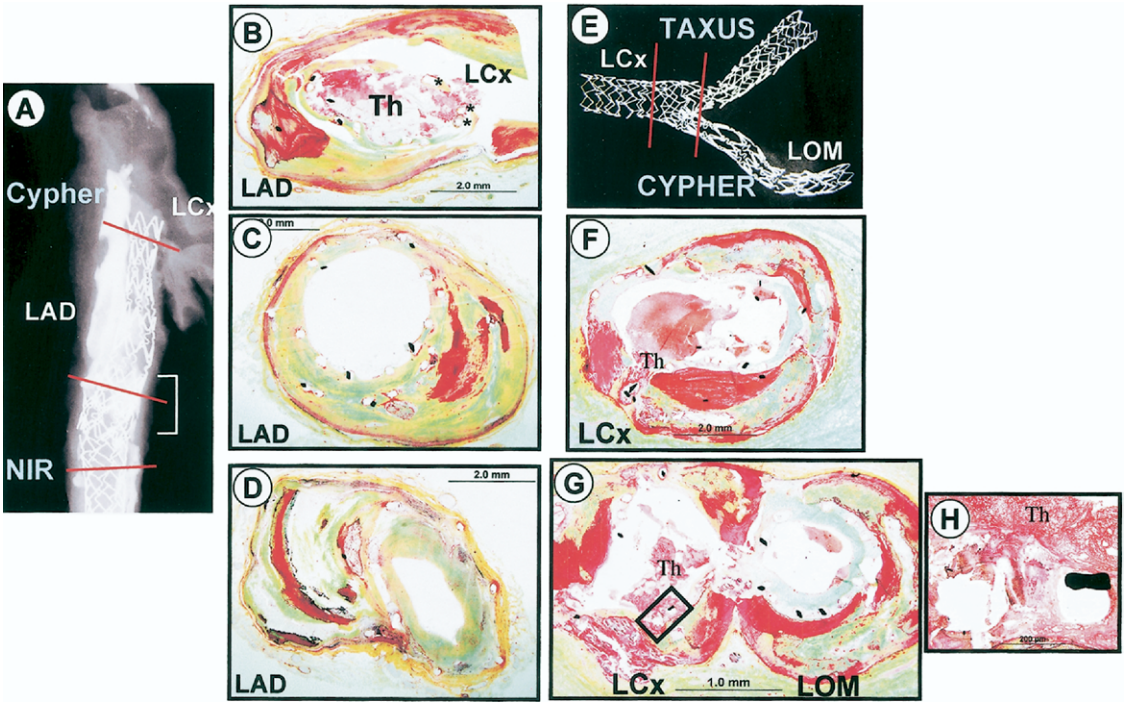

Figure 3. Mechanisms of late stent thrombosis in ostial and bifurcation stenting. **(A to D)** Radiograph and histologic sections (Movat pentachrome) from a 77-year-old man who had two stents placed in the native left anterior descending coronary artery (LAD) for stable angina 450 days before sudden cardiac death. **(A)** Radiograph of the LAD with two stents in place, a proximal Cypher and a distal bare-metal stent (NIR). The Cypher stent struts **(*)** protrude into the ostium of the left circumflex artery (LCx). **(B)** Section taken from the proximal Cypher stent, which is totally occluded by a platelet-rich thrombus while distally it is patent **(C)** with minimal neointimal tissue. The NIR stent **(D)** in the distal LAD demonstrates 50% in-stent area stenosis consisting of neointimal tissue composed of smooth muscle cells in a proteoglycan/collagen matrix with absence of fibrin. **(E to H)** Radiographs and histologic sections (Movat pentachrome) from a 68-year-old black woman with a history of stenting of the LCx and left obtuse marginal (LOM) using the crush technique (Taxus to LCx and Cypher to LOM) 172 days before death. She presented 2 days before her death with acute myocardial infarction and was taken to the catheterization laboratory, where 90% occlusion of the LCx near the LOM take-off was found. The LCx artery was opened with balloon angioplasty, but the patient died of complications shortly thereafter. **(E)** Cypher struts within LOM and fracture of the Taxus stent after the LOM take-off. Histologic sections taken proximal to the bifurcation **(F)** and at the LCx/LOM bifurcation **(G)** show thrombus (Th) in the LCx (Taxus), whereas the Cypher stent is covered by neointimal growth. Two struts with overlying thrombus are shown at high power in **H**. Note the absence of neointimal coverage of the Taxus struts with overlying thrombus.

endothelial coverage of stent struts (27.1 ± 25.9% vs. 66.1 ± 25.4%, p = 0.001).

Antiplatelet therapy in cases of late DES thrombosis. Of the 14 patients with LST, maintenance on dual antiplatelet therapy (i.e., aspirin and clopidogrel) could be confirmed in 7 patients. An additional 2 patients were either on aspirin or clopidogrel monotherapy. Five of 14 patients with evidence of LST were not receiving any antiplatelet therapy at the time of death. In the two cases of LST after BMS implantation, dual antiplatelet therapy was administered for only 1 month and patients were on aspirin monotherapy at the time point of death.

Pathologic mechanisms of DES LST. In all 14 patients with LST delayed arterial healing was found as a cardinal risk factor and was the only pathologic risk factor in 3 (21%) patients. Additional pathologic risk factors for LST were found in 11 of the 14 patients (Table 3). They were grouped into five major categories: 1) chronic inflammation characterized by lymphocytes, macrophages, and extensive eosinophilic infiltration of the intima and media (hypersensitivity) (n = 3); 2) stenting along major side branches using the crush technique and/or stenting over major branch points (n = 3) (Fig. 3); 3) malapposition refers to arterial wall expansion (positive remodeling) late after stent deployment (>6 months) or incomplete apposition caused by suboptimal stent deployment (n = 2) (Fig. 4); 4) in-stent restenosis (n = 2) with superimposed thrombosis; and 5) struts penetration of necrotic core (n = 1). In comparison, in the 2 patients with BMS the cause of LST was in-stent restenosis.

Arterial healing Cypher versus Taxus versus BMS. Histologic sections from patent DES and BMS were evaluated at corresponding time points to assess the different patterns of arterial healing (Figs. 5 and 6). The Cypher stents showed greater inflammatory reaction including eosinophils and giant cells at 60 days, whereas Taxus stents predominantly showed greater fibrin deposition and fewer inflammatory cells at a similar time point. At 120 days there was focal fibrin deposition and giant cell reaction around Cypher stents, whereas Taxus stents showed greater inflammation consisting of lymphocytes, eosinophils, and macrophages at this time point. Fibrin deposition persisted in both Taxus and Cypher stents. In comparison, at 60 days BMS did not show fibrin deposition, but relatively greater neointimal

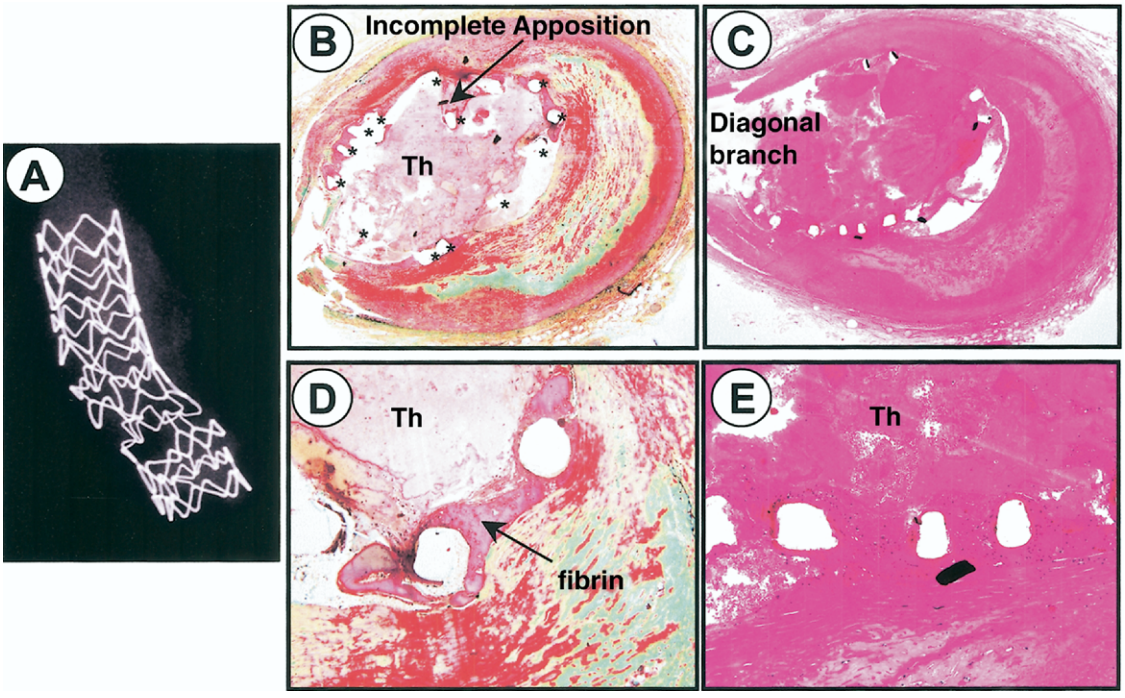

Figure 4. Histologic sections of the stented artery from a 38-year-old woman who had undergone stenting of the proximal left anterior descending coronary artery (LAD) with a 3.0 × 12-mm Taxus stent 6 months before death. The patient had been taking clopidogrel and aspirin, but presented to a local emergency room with severe chest pain and shortly thereafter went into ventricular fibrillation and died. **(A)** Radiograph of the stented LAD. **(B and C)** Proximal and middle sections of the stented LAD stained with Movat pentachrome and hematoxylin and eosin (HE), respectively. There is total occlusion of the lumen by platelet-rich thrombus (Th) with absence of healing of the stent strut regions, which are surrounded by fibrin. The stent is placed across the orifice of the diagonal branch. High-power view of the stent struts in **D** (Movat) and **E** (HE) show peristrut fibrin with absence of smooth muscle, endothelial, and inflammatory cells.

coverage of stent struts was seen. Giant cell reaction and inflammation was substantially less in the BMS examined. The 120-day BMS showed circumferential neointimal growth with complete coverage of stent struts. Chronic inflammatory cells (mostly lymphocytes, macrophages, and giant cells) are commonly seen in BMS at this time point but without evidence of eosinophilic infiltrate.

DISCUSSION

The pathologic findings of our study underscore the causal relationship between the two currently FDA-approved DES and delayed arterial healing. The persistence of fibrin and incomplete endothelialization far beyond 30 days from the time of stenting form the critical pathologic substrate underlying the phenomenon of LST. These partially endothelialized, fibrin-rich sites remain a potent thrombogenic stimulus. In high-risk clinical situations such as bifurcation stenting, excessive stent length, or cessation of antiplatelet therapy, these sites may develop thrombosis, leading to death or other serious consequences.

Histologic findings ≥30 days. In patients suffering from LST after DES placement, the major pathologic finding distinguishing thrombosed from patent DES was evidence of significantly greater delay in arterial healing as manifested by persistent peristrut fibrin deposition and poor endothelialization. In contrast, the control group of BMS implants showed greater neointimal healing with very little peristrut fibrin and near complete endothelialization consistent with earlier pathologic studies of BMS, which have suggested near-complete endothelialization by 3 to 4 months (19,20). Throughout a wide range of time points examined, BMS consistently showed evidence of greater healing when compared with DES.

Mechanisms of delayed arterial healing. The mechanisms by which DES cause a prolongation of arterial healing in humans are poorly understood. Although sirolimus or paclitaxel reduce neointimal formation by impeding smooth muscle cell proliferation and migration, these drugs also impair the normal healing processes of the injured arterial wall (21–23). Animal studies using healthy pigs have shown persistence of fibrin at 28 days, however, endothelialization was similar between DES and BMS (9). Also, it is well known that in pig coronary arteries endothelialization after BMS implantation may be >80% by 7 days and that healing takes longer in humans as compared with normal animal coronary arteries (24). Moreover, rates of endothelialization after stent implantation seem to vary among currently used animal models. Although experience from porcine coronary implants suggests complete endothelialization 28 days after stent deployment (11), our own data of rabbit iliac implants indicate a clear delay of endothelialization in sirolimus- and paclitaxel-eluting stents (13).

Because of the small number of stents examined, it is impossible to make definitive comparative conclusions

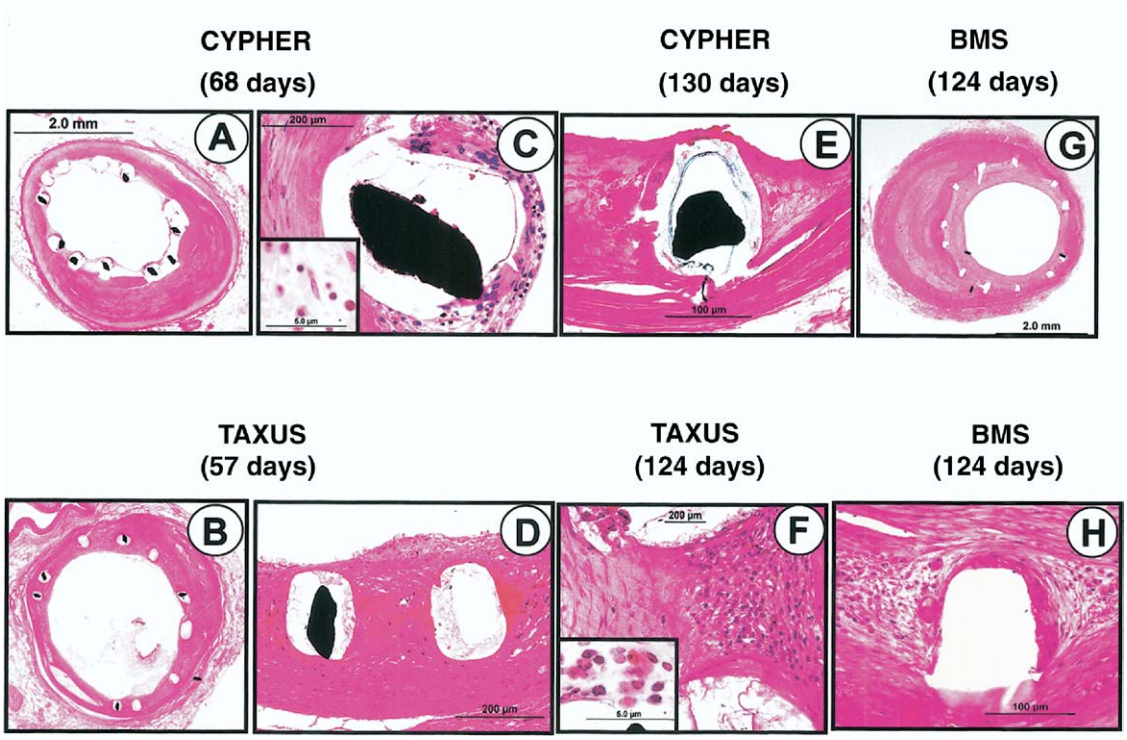

Figure 5. Histologic sections stained with hematoxylin and eosin (HE) from patent drug-eluting stents (DES) and bare-metal stents (BMS) from various time points. Coronary arteries with Cypher **(A)** and Taxus **(B)** stents at 68 and 57 days, respectively. High-power views showing inflammatory infiltrate around Cypher struts **(C)** including eosinophils (**inset** Luna stain), whereas around the Taxus stent struts **(D)** there is a predominance of fibrin. At 130 and 124 days, respectively, there is focal fibrin deposition and giant cell reaction seen around the Cypher stent **(E)**, whereas in the Taxus stent **(F)** there is greater inflammation including eosinophils (**inset** Luna stain). A BMS at 124 days is shown in **G and H**.

about the selective effects of each type of drug/stent combination on arterial wall healing in humans. Coronary segments implanted with either type of DES showed delayed healing when compared with BMS.

Both the Cypher and Taxus stents allow the selective release and binding of drug that significantly influences arterial wall concentration and distribution responsible for local pharmacologic effects (25). For example, Cypher stents elute nearly all of the loaded sirolimus by 30 days from a polyethylene-co-vinyl acetate and poly n-butyl methacrylate non-erodable polymer (10,26). In contrast, Taxus stents release paclitaxel as a initial burst from poly(styrene-b-isobutylene-b-styrene) polymer followed by a constant slow release up to 90 days (R. Virmani, unpublished data, April 2005).

The thrombus as well as lipid within the stented atherosclerotic plaque may also influence drug distribution and retention (27). Previous data regarding drug levels of sirolimus and paclitaxel delivered on stents have been generated in normal animals (10,26), and given the hydrophobic nature of both compounds it is unclear whether atherosclerosis prolongs tissue retention leading to long-term biological effects.

Pathologic correlates: late thrombosis is likely multifactorial in causality. Although the degree of arterial healing was significantly less in thrombosed DES sections, stent length was significantly greater. A governing principle in the deployment of DES has been to effectively treat the entire lesion (28,29). This dictum has led to the use of longer stents.

The findings of this study support prior clinical observations that the risk of stent thrombosis after DES placements is related to stent length (29,30). As stent length increases, it may be more difficult to ensure complete deployment (30,31), causing a predispositon toward thrombosis by creating abnormal shear stress (32,33) at malapposed or incompletely apposed stent struts. Malapposition/incomplete apposition was observed in 2 of 14 cases and thus represents an additional risk factor for LST. This is consistent with intravascular ultrasound studies that have shown that stent malapposition and underexpansion are significantly associated with stent thrombosis (34).

Other additional risk factors that predispose toward late thrombosis include local arterial hypersensitivity reactions as evidenced by eosinophils, which may be secondary to polymer (15). Further, penetration of a necrotic core by stent struts, crossing branch points, or bifurcation stenting are additional risk factors for late DES thrombosis as occurs with BMS (19,35). Breaching a necrotic core may lead to the exposure of thrombogenic lipid content to flowing blood. Arterial branch points may also predispose towards thrombosis by inducing flow disturbances and changes in shear stress (35,36). Withdrawal of aspirin and/or clopidogrel therapy has previously been reported to be a very significant risk factor for LST with DES. It is not surprising

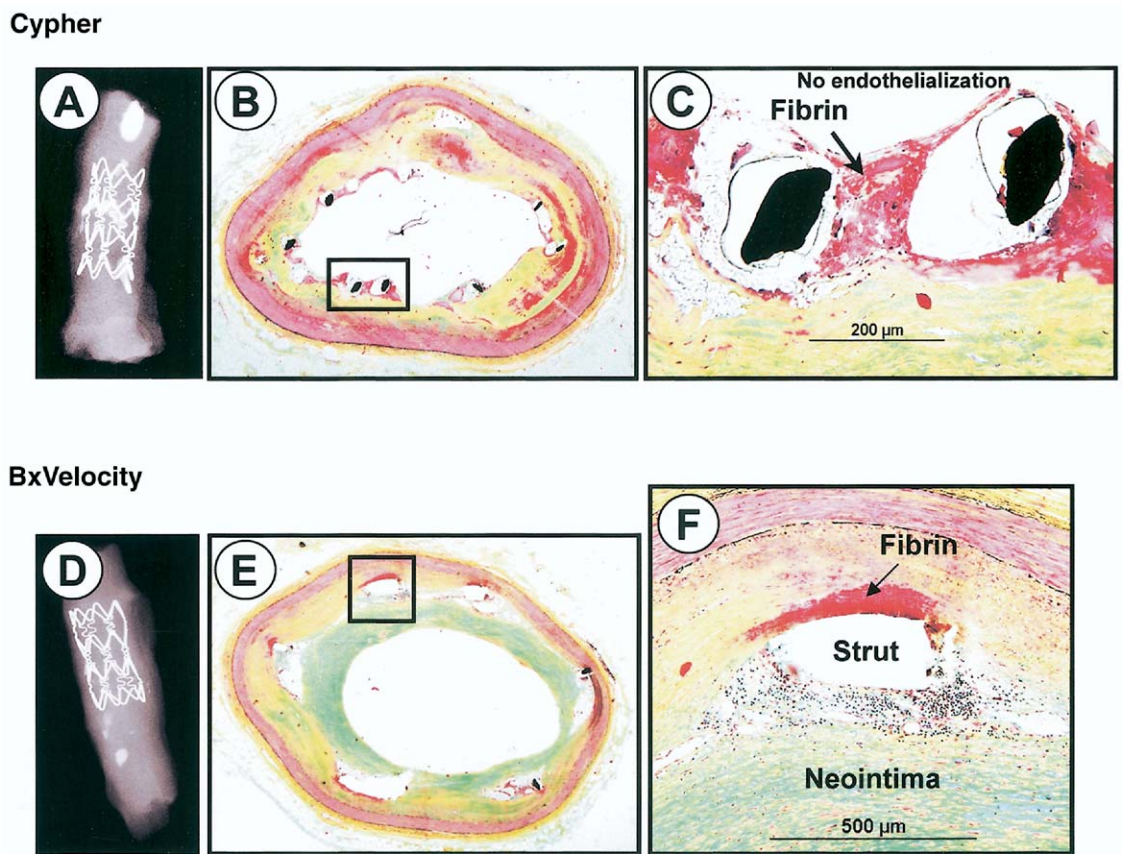

Figure 6. A 65-year-old man suffered traumatic injury to the head resulting in death. This patient had received two stents in the left anterior descending coronary artery (LAD), a proximal Cypher and a distal Bx Velocity 15 months before death, which were found to be patent at autopsy. **A** (Cypher) and **D** (Bx Velocity) are radiographs of the stented LAD segment. All sections shown have been stained with Movat pentachrome. **(B)** Histologic section of the Cypher stented artery showing minimal coverage of the struts by fibrin. **(C)** High-power magnification showing peristrut fibrin with rare endothelial cells but no luminal thrombus, whereas inflammation and smooth muscle cells are only rarely observed. **(E)** Section of the Bx Velocity stent. There is abundant neointimal tissue consisting of smooth muscle cells in a proteoglycan collagen matrix and an overlying endothelium. **(F)** High-power section of the boxed area in **E**. Lymphocytes are present around the stent strut with minimal fibrin underneath the strut. The luminal surface of the stent is covered by smooth muscle cells in a proteoglycan/collagen rich matrix.

that poorly healed sites of DES placement pose a significant risk for complete thrombosis when antiplatelet therapy is abruptly discontinued.

Late thrombosis: clinical correlates. The true incidence of DES LST is unknown. The reported rates of LST vary from 0.23% to 0.7% (7,29,37). Complicating the interpretation of these data are the differing definitions of LST (clinical vs. angiographic), the differing duration of antiplatelet therapy, the types of lesions stented, and duration of follow-up. The increasing use of DES for a wide variety of clinical and anatomic situations such as bifurcation stenting, overlapping stent deployment, or acute myocardial infarction, most of which have not been evaluated in randomized studies, means that the reported incidence of DES LST in these trials may not reflect the real-world incidence.

It is difficult to compare the incidence of DES LST with that from the BMS era because of the complicating issues of restenosis with superimposed thrombosis, prior brachytherapy treatment, and differing duration and type of antiplatelet therapy used. The reported incidence of late thrombosis for BMS varies from 0.6% to 0.8% (19,38,39). However, BMS do not cause the same degree of delay in arterial healing seen with the two currently FDA-approved DES.

Regardless of the true incidence, the consequences of DES LST are dire. Iakovou et al. (7) reported a 45% rate of death for patients suffering DES LST, with the majority of others suffering nonfatal myocardial infarction. This lethality is substantially higher than the reported 16.7% to 20.8% fatality rate for BMS LST, and in part may reflect the tendency to perform more complex multiterritory revascularization in the DES era (30,38). This study shows that even 6 to 7 months after implantation of Cypher and Taxus DES, these sites are not completely endothelialized in the patients studied in this report. Therefore, it remains uncertain at what time point after stenting the patients can safely be taken off of antiplatelet therapy.

Study limitations. Because this is an autopsy study, the results presented may not be representative of persons who receive DES and survive. Also, a large number of patients in this study received DES stents for non–FDA-approved indications such as acute myocardial infarction, and so may not reflect the arterial pathologic changes that occur when

these stents are placed only for approved uses. In the present study, however, a large number of stents were analyzed in individuals who did and did not suffer stent-associated morbidity, and it is likely that the results reported here are applicable to patients receiving DES.

Conclusions. This is the first published study to examine systematically the effects of the two currently FDA-approved DES on human coronary pathology. Both DES caused a significant delay in arterial healing characterized by persistent fibrin deposition and delayed re-endothelialization when compared with sites of BMS implantation. The cause of DES LST is likely multifactorial, with delayed healing in combination with other clinical and/or procedural risk factors such as withdrawal of antiplatelet therapy, malapposition/incomplete apposition, and bifurcation stenting playing an important role. Because the time course of arterial healing after Cypher or Taxus DES placement may vary from patient to patient, all patients at high risk for late thrombosis should receive dual antiplatelet therapy with aspirin and clopidogrel for prolonged periods of time.

Acknowledgment

The authors thank Rosalind Mathew, Lila Adams, Hedwig Avallone, and Hazel M. Jenkins (CVPath) for their excellent technical assistance.

Reprint requests and correspondence: Dr. Renu Virmani, CVPath, International Registry of Pathology, 19 Firstfield Road, Gaithersburg, Maryland 20878. E-mail: rvirmani@cvpath.org.

REFERENCES

1. 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.
2. Schomig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med 1996;334:1084–9.
3. Ong AT, Hoye A, Aoki J, et al. Thirty-day incidence and six-month clinical outcome of thrombotic stent occlusion after bare-metal, sirolimus, or paclitaxel stent implantation. J Am Coll Cardiol 2005; 45:947–53.
4. Orford JL, Lennon R, Melby S, et al. Frequency and correlates of coronary stent thrombosis in the modern era: analysis of a single center registry. J Am Coll Cardiol 2002;40:1567–72.
5. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221–31.
6. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–23.
7. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293:2126–30.
8. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet 2004;364:1519–21.
9. Suzuki T, Kopia G, Hayashi S, et al. Stent-based delivery of sirolimus reduces neointimal formation in a porcine coronary model. Circulation 2001;104:1188–93.
10. Klugherz BD, Llanos G, Lieuallen W, et al. Twenty-eight-day efficacy and phamacokinetics of the sirolimus-eluting stent. Coron Artery Dis 2002;13:183–8.
11. Drachman DE, Edelman ER, Seifert P, et al. Neointimal thickening after stent delivery of paclitaxel: change in composition and arrest of growth over six months. J Am Coll Cardiol 2000;36:2325–32.
12. Farb A, Heller PF, Shroff S, et al. Pathological analysis of local delivery of paclitaxel via a polymer-coated stent. Circulation 2001;104: 473–9.
13. Finn AV, Kolodgie FD, Harnek J, et al. Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. Circulation 2005;112:270–8.
14. Guagliumi G, Farb A, Musumeci G, et al. Images in cardiovascular medicine. Sirolimus-eluting stent implanted in human coronary artery for 16 months: pathological findings. Circulation 2003;107:1340–1.
15. Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? Circulation 2004;109:701–5.
16. Sousa JE, Costa MA, Farb A, et al. Images in cardiovascular medicine. Vascular healing 4 years after the implantation of sirolimus-eluting stent in humans: a histopathological examination. Circulation 2004; 110:e5–6.
17. Farb A, Weber DK, Kolodgie FD, Burke AP, Virmani R. Morphological predictors of restenosis after coronary stenting in humans. Circulation 2002;105:2974–80.
18. Kolodgie FD, John M, Khurana C, et al. Sustained reduction of in-stent neointimal growth with the use of a novel systemic nanoparticle paclitaxel. Circulation 2002;106:1195–8.
19. Farb A, Burke AP, Kolodgie FD, Virmani R. Pathological mechanisms of fatal late coronary stent thrombosis in humans. Circulation 2003;108:1701–6.
20. Grewe PH, Deneke T, Machraoui A, Barmeyer J, Muller KM. Acute and chronic tissue response to coronary stent implantation: pathologic findings in human specimen. J Am Coll Cardiol 2000;35:157–63.
21. Marx SO, Jayaraman T, Go LO, Marks AR. Rapamycin-FKBP inhibits cell cycle regulators of proliferation in vascular smooth muscle cells. Circ Res 1995;76:412–7.
22. Poon M, Marx SO, Gallo R, Badimon JJ, Taubman MB, Marks AR. Rapamycin inhibits vascular smooth muscle cell migration. J Clin Invest 1996;98:2277–83.
23. Wiskirchen J, Schober W, Schart N, et al. The effects of paclitaxel on the three phases of restenosis: smooth muscle cell proliferation, migration, and matrix formation: an in vitro study. Invest Radiol 2004;39:565–71.
24. Virmani R, Kolodgie FD, Farb A, Lafont A. Drug eluting stents: are human and animal studies comparable? Heart 2003;89:133–8.
25. Levin AD, Vukmirovic N, Hwang CW, Edelman ER. Specific binding to intracellular proteins determines arterial transport properties for rapamycin and paclitaxel. Proc Natl Acad Sci U S A 2004;101:9463–7.
26. Ranade SV, Miller KM, Richard RE, Chan AK, Allen MJ, Helmus MN. Physical characterization of controlled release of paclitaxel from the TAXUS Express2 drug-eluting stent. J Biomed Mater Res A 2004;71:625–34.
27. Hwang CW, Levin AD, Jonas M, Li PH, Edelman ER. Thrombosis modulates arterial drug distribution for drug-eluting stents. Circulation 2005;111:1619–26.
28. Schampaert E, Cohen EA, Schluter M, et al. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). J Am Coll Cardiol 2004;43:1110–5.
29. Moreno R, Fernandez C, Hernandez R, et al. Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. J Am Coll Cardiol 2005;45:954–9.
30. Cutlip DE, Baim DS, Ho KK, et al. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. Circulation 2001;103:1967–71.
31. Cheneau E, Leborgne L, Mintz GS, et al. Predictors of subacute stent thrombosis: results of a systematic intravascular ultrasound study. Circulation 2003;108:43–7.
32. LaDisa JF, Jr., Olson LE, Guler I, et al. Stent design properties and deployment ratio influence indexes of wall shear stress: a three-dimensional computational fluid dynamics investigation within a normal artery. J Appl Physiol 2004;97:424–30; discussion, 16.
33. Fujii K, Carlier SG, Mintz GS, et al. Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after

sirolimus-eluting stent implantation: an intravascular ultrasound study. J Am Coll Cardiol 2005;45:995–8.
34. Alfonso F, Suarez A, Angiolillo DJ, et al. Findings of intravascular ultrasound during acute stent thrombosis. Heart 2004;90:1455–9.
35. Ge L, Airoldi F, Iakovou I, et al. Clinical and angiographic outcome after implantation of drug-eluting stents in bifurcation lesions with the crush stent technique: importance of final kissing balloon post-dilation. J Am Coll Cardiol 2005;46:613–20.
36. Goodall AH. Role of shear stress and turbulence on platelets in blood conduits and on endothelial cells in arterial conduits. In: Suigwart U, editor. Endoluminal Stenting. Philadelphia, PA: WB Saunders Co., 1996:52–9.
37. 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;45:2088–92.
38. Heller LI, Shemwell KC, Hug K. Late stent thrombosis in the absence of prior intracoronary brachytherapy. Catheter Cardiovasc Interv 2001;53:23–8.
39. Wang F, Stouffer GA, Waxman S, Uretsky BF. Late coronary stent thrombosis: early vs. late stent thrombosis in the stent era. Catheter Cardiovasc Interv 2002;55:142–7.