Coronary Artery Stents: Part I. Evolution of Percutaneous Coronary Intervention

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The subspecialty of interventional cardiology has made significant progress in the management of coronary artery disease over the past three decades with the development of percutaneous coronary transluminal angioplasty, atherectomy, and bare-metal and drug-eluting stents (DES). Bare-metal stents (BMS) maintain vessel lumen diameter by acting as a scaffold and prevent collapse incurred by angioplasty. However, these devices cause neointimal hyperplasia leading to in-stent restenosis and requiring reintervention in more than 20% of patients by 6 mo. DES (sirolimus and paclitaxel) prevent restenosis by inhibiting neointimal hyperplasia. However, DESs also delay endothelialization, causing the stents to remain thrombogenic for an extended, yet unknown, period of time. Late stent thrombosis is associated with a 45% mortality rate. Premature discontinuation of antiplatelet therapy, particularly clopidogrel, is the strongest predictor of stent thrombosis. Sixty percent of patients receive stents for off-label (unapproved) indications, which also increases the frequency of stent thrombosis. Clopidogrel and aspirin are the cornerstone of therapy in the prevention of stent thrombosis in both BMS and DES. Recommendations pertaining to the optimal duration of dual-antiplatelet therapy have been debated. Both the Food and Drug Administration and the American Heart Association/American College of Cardiologists, in association with other major societies, have made recommendations to extend the duration of dual-antiplatelet therapy in patients with DES to 1 yr. The 6-wk duration of dual-antiplatelet therapy in patients with BMS remains unchanged. All patients with coronary stents must remain on life-long aspirin monotherapy. Since the introduction of percutaneous transluminal coronary angioplasty for the treatment of coronary atherosclerosis, the practice of percutaneous coronary intervention has undergone a dramatic transformation from simple balloon dilation catheters to sophisticated mechanical endoprostheses. These advancements have impacted the practice of perioperative medicine. In this series of two articles, in Part I we will review the evolution of percutaneous coronary intervention and discuss the issues associated with percutaneous transluminal coronary angioplasty and coronary stenting; in Part II we will discuss perioperative issues and management strategies of coronary stents during noncardiac surgery.
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THE BEGINNING OF INTERVENTIONAL CARDIOLOGY

Grüentzig and Myler performed the first coronary angioplasty during coronary artery bypass graft (CABG) surgery in San Francisco in May 1977.[1] Grüentzig later performed the first coronary angioplasty in an awake patient in Zurich, Switzerland in September 1977.[1] In a Letter to the Editor of *Lancet* in February 1978, he described the first series of percutaneous transluminal coronary angioplasty, performed successfully in five patients.[2] The technique involved advancement of a balloon-tipped catheter into a narrowed coronary artery, inflation of the balloon to cause plaque compression, and removal of the catheter after balloon deflation. However, in the first 50 patients who underwent percutanueous transluminal coronary angioplasty (PTCA), the primary success rate was only 64% and emergency CABG was required in 14%, with a periprocedural myocardial infarction (MI) rate of 6%.[3] As experience with PTCA grew, its success rate increased to approximately 90%.[4] Balloon dilation, by virtue of tissue injury/trauma, produces several morphological alterations, which occur individually or collectively.[5] These include (1) endothelial denudation with rapid accumulation of platelets and fibrin; (2) stretching, fracturing, fissuring, or disruption of the atheromatous plaque, causing intimal dissection, medial tearing, and aneurysmal dilation of the media and adventitia; (3) elastic recoil; and (4) post-injury arterial shrinkage (constrictive negative remodeling).[5–7]

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Successful PTCA thus induces a "controlled injury" of the diseased arterial segment that accounts for its two major limitations: acute vessel closure and restenosis.[7–10] Acute vessel closure occurs within the first 24 h in 6%–8% of cases.[8,11] Among patients with periprocedural vessel occlusion, 41% suffered a MI and 72% required CABG; the overall mortality rate was 4.9%. This rate remained constant in subsequent registries.[12] Despite improved equipment and experience with PTCA, the incidence of abrupt closure after balloon dilation in the late 1980s and early 1990s remained in the range of 4%–8% with more than 20% of patients requiring emergency CABG.[13,14] Although patients may experience ischemic complications (MI, CABG, death) due to intimal dissection not associated with acute vessel closure, this is an infrequent occurrence.[15,16]

Restenosis often occurs within the first 6 mo after PTCA.[8] This process appears to be an exaggerated response to the controlled injury induced by PTCA and involves mechanical, biochemical, and histological factors.[5,7,17,18] After initial elastic recoil, adventitial myofibroblasts form vascular scar tissue; this scar contracts, causing constrictive negative remodeling.[6,7,18] Endothelial injury triggers an inflammatory response.[18–20] Activated white blood cells and platelets migrate and release vasoconstrictors, cytokines, and growth factors.[18–20] Consequently, medial smooth muscle cells and adventitial myofibroblasts migrate toward the lumen, hyper-proliferate, and secrete elements to form the extracellular matrix.[18] Defined as a more than 50% reduction in postprocedural luminal diameter, restenosis rates have varied from 30% to 50%, with a higher incidence after saphenous vein graft angioplasty (68.2%) and left anterior descending angioplasty (45%).[17–22] Target lesion revascularization during 6-mo follow-up was performed in 20%–30% of cases.[22] Hirshfeld et al.[21] found that restenosis rates were inversely proportional to postprocedural luminal diameter (<2.9 mm, 44%; ≥2.9 mm, 34%; P = 0.036).

In the 1980s, devices specifically designed to remove atherosclerotic plaque were developed.[6,8] By reducing vessel wall trauma observed with PTCA, investigators envisaged ablative devices would diminish acute vessel closure and restenosis.[22] The clinical efficacies of excimer laser coronary angioplasty and rotational atherectomy were evaluated relative to PTCA in the Excimer Laser, Rotational Atherectomy, and Balloon Angioplasty Comparison study of 620 patients with high-risk angiographic lesion morphology.[23] Despite significantly improved procedural success with rotational atherectomy, restenosis rates increased in patients treated with laser angioplasty (46%) and rotational atherectomy (46%) compared with PTCA (35%) (P = 0.04). The Coronary Angioplasty Versus Excisional Atherectomy Trials and the Canadian Coronary Atherectomy Trial evaluated the efficacy of directional coronary atherectomy relative to PTCA.[24–26] None of these trials demonstrated this technique to be superior to PTCA in reducing restenosis; in fact, abrupt vessel closure and non-ST segment elevation myocardial infarction (non-STEMI) increased with atherectomy. Further, 1-yr follow-up revealed a significant excess mortality rate in the atherectomy group (2.2% vs 0.6%; P = 0.035).[27]

THE DEVELOPMENT OF BARE-METAL STENTS

The idea of using foreign bodies to maintain arterial luminal integrity was introduced by the Nobel laureate Alexis Carrel in 1912 when he described experiments in which paraffin-covered glass and metal tubes were implanted into canine thoracic aortae.[28] Dotter and Judkins reintroduced the concept of using an implantable prosthetic device to maintain the luminal diameter of diseased vessels in 1964; Dotter continued developing devices, such as self-expanding coils, over the following two decades.[29,30] Rousseau et al.[31] developed flexible, self-expanding, stainless-steel mesh tubes, which were implanted in canine coronary arteries. In 1985, Palmaz et al.[32] introduced the use of balloon-mounted stents in peripheral arteries. Interest in stent implantation in human coronary arteries intensified after Schatz et al.[33] reported the results of successful percutaneous implantation of Palmaz-type stents in canine coronary arteries. With the hope that acute occlusion and restenosis could be alleviated, Jacques Puel in Toulouse, France, and Ulrich Sigwart in Lausanne, Switzerland, deployed the first human coronary stents after PTCA in 1986.[34] Twenty-four self-expanding mesh devices were implanted in 19 patients (17 restenosis, 4 acute closure, and 3 venous bypass grafts).[34] Sigwart et al.[34] also first described the use of this stent for arterial dissection. The stent, acting as a scaffold, optimized lumen integrity by tacking down dissection flaps against the vessel wall, and providing mechanical support to offset elastic recoil during PTCA.[22,35] In 1993, bare-metal stents (BMS) were approved in the United States to treat acute and threatened vessel closure after failed PTCA.[20,36] Subsequent studies confirmed the efficacy of percutaneous coronary intervention (PCI), with stenting as an alternative to avoid emergency CABG surgery after failed PTCA.[37]

In 1993, two landmark trials, the Belgium Netherlands Stent Arterial Revascularization Therapies Study (BENESTENT) and the North American Stent Restenosis Study (STRESS), confirmed coronary stenting significantly improved angiographic and clinical outcomes, thus establishing elective coronary stent implantation as an accepted standard of care.[38,39] These studies also prompted the Food and Drug Administration (FDA) to approve BMS for elective use in the United States.[22] Restenosis decreased from 42% to 32% (P = 0.04) in the STRESS trial and from 32% to 22% (P = 0.02) in the BENESTENT trial.[38,39] The incidence of target-lesion revascularization decreased from 25% to 35% with PTCA alone to 10%–15% with

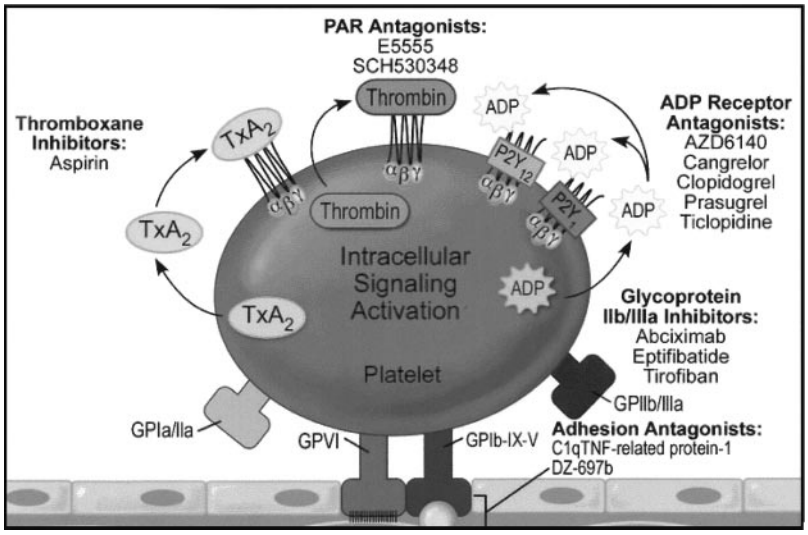

Figure 1. The activation of complex intracellular signaling processes causes the production and release of various stimuli, including thromboxane A_2 (TxA_2), thrombin, and adenosine diphosphate (ADP), which act by binding to their respective G protein-coupled receptors. Therapies targeted at inhibiting these receptors and also the integrins and proteins involved in platelet activation include the thromboxane inhibitors, the ADP receptor antagonists, the GPIIb/IIIa inhibitors, and the novel PAR antagonists and adhesion antagonists. (Reprinted from Meadows TA, Bhatt DL. Clinical aspects of platelet inhibitors and thrombus formation. Circ Res 2007;100:1261–75. Fig. 2, p 1263).

stenting.[38–40] By 1999, 84.2% of all interventions involved stent insertion.[5,41] Although BMS implantation effectively eliminated acute vessel closure, initial trials reported acute (<24 h) and subacute (24 h to 30 days) stent thrombosis rates of 16%–24%.[10,22,36,42] Thrombosis had long been recognized as a serious complication of stent implantation in both animal and early clinical studies; aggressive anticoagulation attempts were implemented to prevent this.[32–36]

The BENESTENT and STRESS studies reported subacute stent thrombosis rates of 3.5% and 3.4%, respectively, despite the use of a complex anticoagulation regimen consisting of dextran, aspirin, dipyridamole, heparin, and warfarin.[38,39] The incidences of stent thrombosis, MI and death were higher than with PTCA alone.[38,39] Thrombosis is the most devastating complication of stent placement and manifests itself as a STEMI in 90% of patients; 20% of patients die.[43,44] Moreover, extensive anticoagulation in these patients was associated with a 15%–18% bleeding incidence and extended hospital stays.[42,44–46] Two practices led to a dramatic reduction in the incidence of stent thrombosis in BMS: (1) the use of intravascular ultrasound and high balloon pressures to optimize apposition of the stent struts to the vessel wall, and (2) the replacement of anticoagulation with dual-antiplatelet therapy.[47,48] The combination of a thienopyridine with aspirin became the cornerstone of antithrombotic prophylaxis. Their combined effects resulted in superior antithrombotic activity when compared to conventional anticoagulation in initial studies.[46–49] Initially, ticlopidine was prescribed with aspirin. Clopidogrel later replaced ticlopidine owing to its better safety profile, including less frequent incidences of rash, neutropenia, and thrombotic thrombocytopenic purpura.[50] These advancements effectively reduced the incidence of BMS thrombosis to the current rate of 1.2%.[51–53]

The thienopyridines and aspirin selectively inhibit platelet activation by different mechanisms. The thienopyridines inhibit the adenosine diphosphate (ADP) pathway, whereas aspirin inhibits the arachidonate-thromboxane A_2 (TxA_2) pathway. The complementary mechanisms illustrate their importance in the amplification of platelet activation.

Ticlopidine and clopidogrel are prodrugs, which are oxidized to active metabolites via the hepatic cytochrome P450-dependent CYP3A4 pathway.[54] These active moieties are reactive thiol derivatives and are antagonists of the platelet $P2Y_{12}$ ADP receptor. The metabolites irreversibly inactivate the $P2Y_{12}$ receptor subtype by covalent binding (Fig. 1). The $P2Y_{12}$ receptor is negatively coupled to adenylyl cyclase through the Gi protein, and is expressed on the platelet membrane.[55] ADP-$P2Y_{12}$ downregulation of adenylyl cyclase causes (1) amplification of the response to ADP, thromboxane, thrombin, and collagen, and (2) enhanced platelet activation and aggregation.[56,57] $P2Y_{12}$ plays a central role in thrombus formation and stabilization.[57] Covalent binding of $P2Y_{12}$ by thienopyridines inhibits both mechanisms that are otherwise essential for platelet aggregation and stabilization[58]: (1) ADP-mediated activation of glycoproteins IIb/IIIa and Ia/IIa, and (2) binding of fibrinogen to glycoprotein IIb/IIIa.[58] Although the $t_{1/2}$ of clopidogrel is 4 h, its irreversible inhibition requires platelet regeneration to normalize platelet function (a 7–10 day process).

Aspirin affects the arachidonate-TxA_2 pathway by irreversibly binding the enzyme cyclooxygenase-1 (COX-1).[59] Aspirin acetylates a serine residue on the enzyme at position 530, thereby preventing the conversion of arachidonate to the unstable prostaglandin intermediate PGH_2, which is converted to TxA_2, a potent vasoconstrictor and platelet agonist (Fig. 1). A single dose of 160 mg completely eliminates platelet TxA_2 production (measured as its stable analog TxB_2).[59] The same effect can be progressively achieved with daily doses of 30–50 mg, or maintenance dose as low as 0.5 $mg \cdot kg^{-1} \cdot day^{-1}$ to provide more than 95% inhibition of TxA_2 synthesis during 24 h.[59,60] High

doses of aspirin may have antithrombotic effects independent of platelet COX-1 inhibition: increased fibrinolytic activity, depressed prothrombin synthesis, improved endothelial function, and antiinflammatory effects.[60–62]

CLINICAL EFFECTIVENESS OF DUAL-ANTIPLATELET THERAPY IN BMS

Multiple studies confirmed the clinical superiority of combined thienopyridine and aspirin therapy to prevent stent thrombosis in patients undergoing PCI. Schömig et al. performed the first randomized controlled study comparing the safety and efficacy of aspirin/ticlopidine with aspirin/warfarin in patients undergoing stent implantation. The Intracoronary Stenting and Antithrombotic Regimen Trial reported significantly lower incidences of death, MI, and target vessel revascularization with aspirin and ticlopidine at 1-mo (1.6% vs 6.2%).[49] Major vascular and/or bleeding complications were also reduced (0% vs 6.5%). Leon et al.[63] reported similar results, randomizing patients to receive (1) ticlopidine and aspirin, (2) aspirin alone, or (3) aspirin plus warfarin. The 30-day end point for the composite of death, target lesion revascularization, angiographic-evident stent thrombosis, and MI, in the ticlopidine/aspirin group reported a 0.5% event rate, as compared with aspirin alone (3.6%), and to aspirin/warfarin (2.7%) ($P = 0.001$). However, both ticlopidine/aspirin (5.5%) and warfarin/aspirin (6.2%) were associated with higher rates of bleeding and vascular complications than aspirin alone (1.8%) ($P < 0.001$). The Full Anticoagulation Versus Aspirin and Ticlopidine trial found patients undergoing elective or unplanned stenting had fewer adverse cardiac events (2.4% vs 9.9%; $P = 0.01$), a 41% reduction in bleeding complications, and significantly shorter hospital stays (4.3 ± 3.6 vs 6.4 ± 3.7 days; $P = 0.0001$) when receiving dual-antiplatelet therapy.[46]

Subsequent research delineated the most effective antiplatelet regimen. Moussa et al.[64] compared the combination of clopidogrel/aspirin with ticlopidine/aspirin in patients undergoing PCI. At 1-mo, both treatment regimens were equally effective, with similar rates of stent thrombosis (1.4% vs 1.5%; $P = 1.0$) and major adverse cardiac events (2.4% vs 3.1%, $P = 0.85$). However, the incidence of side effects was lower with clopidogrel (5.3% vs 10.6%; $P = 0.006$). Additional studies confirmed the efficacy of clopidogrel in the treatment of acute coronary syndrome with PCI. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial showed patients with unstable angina or non-STEMI who received clopidogrel/aspirin experienced 20% fewer cardiac complications (cardiac death, MI, and stroke) than patients treated with placebo after PCI.[65] Minor bleeding was significantly more frequent in the clopidogrel/aspirin group (5.1% vs 2.4%; $P < 0.001$). Significant bleeding complications were not observed. The PCI-CURE substudy reported death and MI decreased by 31% at 30 days in patients receiving long-term clopidogrel/aspirin after PCI with BMS versus aspirin/placebo ($P = 0.002$).[66] No difference in bleeding was observed. Additional studies suggest prolonged therapy with clopidogrel/aspirin improves long-term outcome. Data from the Clopidogrel for the Reduction of Events During Observation trial revealed treatment after PCI with clopidogrel/aspirin beyond 30 days reduces the combined risk of death, MI, and stroke by 26.9% at 1-yr as opposed to remaining on aspirin alone.[67] The Clopidogrel for High Atherosclerotic Risk and Ischemic Stabilization, Management, and Avoidance trial demonstrated combined clopidogrel and aspirin were beneficial in patients with established cardiovascular disease, although no benefit was derived in patients with risk factors for developing vascular disease.[68] The current antithrombotic regimen for BMS implantation involves an initial dose of clopidogrel 300–600 mg and aspirin 325 mg several hours before the procedure. Aspirin 75–325 mg and clopidogrel 75 mg are prescribed daily for 4–6 wks to allow stent endothelialization.[69,70] Aspirin is then continued for life as secondary prevention.[69,70]

BMS AND IN-STENT RESTENOSIS

Despite the advancements made with BMS implantation, restenosis continues to be the "Achilles heel" of this device (Fig. 2).[40] BMS are associated with a 20%–25% restenosis rate within 6 mo of implantation. Lesion complexities, comorbidities (diabetes, renal insufficiency) increase this incidence, and restenosis rates approaching 80% have been observed in these subgroups.[21,44,71–74] Repeat revascularization occurs in 60%–80% of restenotic lesions.[74] Although initial stent placement prevents acute recoil, the stent struts traumatize the vascular wall provoking an inflammatory reaction followed by an exaggerated proliferative response within the media and adventitia, which produces greater neointimal formation when compared with PTCA-induced restenosis.[8,20,21,74] In-stent restenosis incidence peaks at 3 mo, reaches a plateau between 3 and 6 mo, but can persist beyond 1 yr after stent deployment.[21] The presence of BMS worsened the incidence of restenosis by threefold when implanted in patients ineligible for the BENESTENT and STRESS trials.[75,76]

In-stent restenosis is not a benign event; approximately 35% of patients present with an acute coronary syndrome requiring reintervention in 12%–20% of patients.[77] In 2006, Chen et al.[77] reported morbidity and mortality rates of 9.5% and 0.7%, respectively. Reintervention attempts to prevent in-stent restenosis have included PTCA, atherectomy, repeat stenting, and brachytherapy (intracoronary delivery of a radioactive isotope).[78,79] Yokoi et al.[78] reported a recurrent

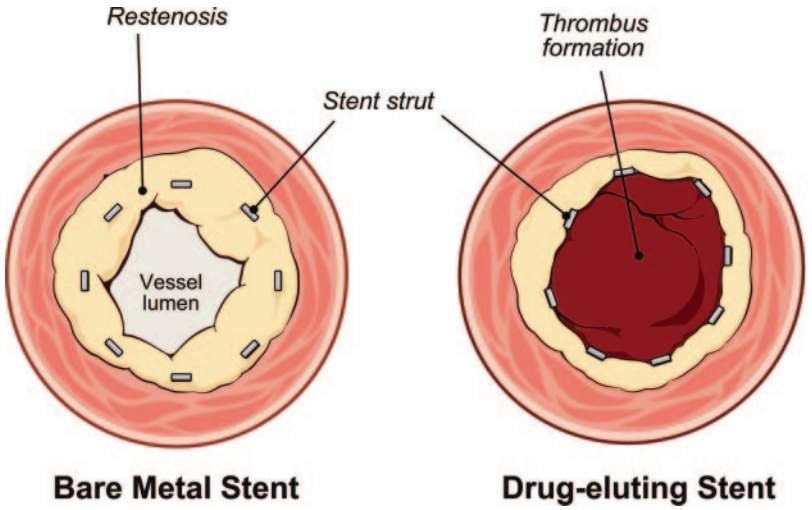

Figure 2. Illustration depicting complications of coronary artery stents: restenosis of bare metal stent (left) and acute stent thrombosis in drug eluting stent (right).

restenosis rate of 85% when in-stent restenosis is treated with PTCA. Brachytherapy increases stent margin restenosis and delays endothelialization, leading to a 15.6% stent thrombotic occlusion rate.[79–81] The overall failure rate is 30%.[80]

THE ADVENT OF DRUG-ELUTING STENTS

Drug-eluting stents (DES) were developed to prevent neointimal hyperplasia (medial hyperproliferation) and consequent restenosis while preserving vessel architecture compromised by PTCA.[82] By coating a BMS with a polymer containing antiproliferative material that inhibits neointimal hyperplasia, cardiologists hoped these devices would eliminate restenosis and the need for reintervention.[44,82,83] The first-generation DES locally release either sirolimus or paclitaxel from a nonresorbable polymer. Both agents effectively inhibit vascular smooth cell migration and proliferation, although by different intracellular mechanisms[79] (Table 1).

DES were approved for use in Europe in 2002. In the United States, the FDA granted expedited review of both DES, and approved sirolimus-eluting stents (Cypher®, Cordis Corporation) for use in April 2003 while paclitaxel-eluting stents (Taxus®, Boston Scientific) were approved in March 2004. Initial approval was based on the results of randomized controlled trials with carefully selected patient populations (Table 2).[84–93] These trials demonstrated the superior ability of both sirolimus-DES and paclitaxel-DES to reduce neointimal hyperplasia, restenosis, and reintervention at 6–12 mo when compared with BMS (Figs. 3D and 4D). At 2-yr follow-up using angiography and intravascular ultrasound, the clinical safety of DES was further established with minimal late lumen loss observed in both sirolimus-DES and paclitaxel-DES.[94,95] Both types of DES have shown continued efficacy in preventing restenosis (74% reduction) when studied 4 yrs after initial deployment (Figs. 3D and 4D).[96,97] Although a meta-analysis of randomized trials comparing paclitaxel-DES with sirolimus-DES revealed significantly higher restenosis rates with the former ($P = 0.001$), clinical outcomes (death and MI) were similar in both groups.[98] In 2005, at the height of clinical enthusiasm, 85% of all stents implanted in the United States and Europe were DES.[99]

DES AND STENT THROMBOSIS

Despite the effectiveness of DES in reducing restenosis, concerns about stent thrombosis plague these devices (Fig. 2). The overall risk of DES thrombosis is

Table 1. Comparison of Sirolimus vs Paclitaxel

	Sirolimus	Paclitaxel
Origin	Macrolide antibiotic produced by the fungus *Streptomyces hygroscopicus*	Antineoplastic drug derived from the Pacific yew tree, *Taxus brevifolia*
Type of agent	Antifungal and immuno-suppressive properties	Antineoplastic agent used in the treatment of breast and ovarian cancers
Cellular function	Cytostatic agent which possesses antimitotic properties[80]	Cytotoxic agent which alters intracellular microtubule function and impairs mitosis[41]
Mechanism of action	Binds with the intracellular receptor, FKBP12, inhibits down-regulation of the cyclin-dependent kinase inhibitor, p27K1P1, thus arresting the cell cycle in the G1/S phase[80]	Binds to the N-terminal 31 residues of the β-tubulin subunit, causing polymerization and disassembly of the microtubules, thus inhibiting cellular replication in the G0/G1 and G1/M phases[41]
Drug kinetics	100% of the drug elutes from the polymer over 4–6 wk[41]	10% of the drug elutes from the polymer in the initial 10–14 d; the remaining 90% remains sequestered indefinitely[41]

Table 2. Characteristics of the Study Trials Gaining Food and Drug Administration (FDA) Approval

Trial	No. patients	Geographic location	Months of clopidogrel	#Stents (mean)	6–12 mo restenosis rates (% vs BMS)	Study characteristics	6–12 mo target lesion revascularization
Sirolimus-eluting stents							
RAVEL[85]	238	Global	2	1	0% vs. 26% (<0.001)	Single lesions	0%–27% (<0.001)
SIRIUS[86]	1058	USA	3	1.4	3.2% vs. 35.4% (<0.001)	26% vs 20% diabetics; smaller and longer lesions	4.1%–16.6% (<0.001)
E-SIRIUS[87]	352	Europe	2	1.7	5.9% vs. 42.3% (<0.0001)	hx of MI; longer lesions	4%–20.9% (<0.0001)
C-SIRIUS[88]	100	Canada	2	1.5	2.3% vs. 52.3 (<0.001)	hx of MI; longer lesions	4%–18% (=0.05)
Paclitaxel-eluting stents							
TAXUS-I[89]	61	Germany	6	1	13.6% vs. 27.2% (=0.0006)	Single lesions	0%–10% (0.237)
TAXUS-II[90]	536	Global	6	1	2.3% vs. 17.9% (SR) 4.7% vs. 20.2% (MR) (<0.0001; <0.0002)	Single lesions	4.7%–12.9% 3.8%–16.0% (0.03; 0.002)
TAXUS-IV[91]	1314	USA	6	1.08	7.9% vs. 26.6% (<0.001)	31% vs 33% diabetics 23% vs 20% smokers	3.0%–11.3% (<0.001)
TAXUS-V[92]	1156	USA	6	1.4	13.7% vs. 31.9% (<0.001)	Longer lesions, Larger and smaller vessels	8.6%–15.7% (<0.001)
TAXUS-VI[93]	446	Europe	6	1.8	9.1% vs. 32.9% (<0.0001)	Longer lesions 17.8% vs 22% diabetics	6.8%–18.9% (<0.0001)

MR = moderate release; SR = slow release; MI = myocardial infarction; BMS = bare-metal stents.

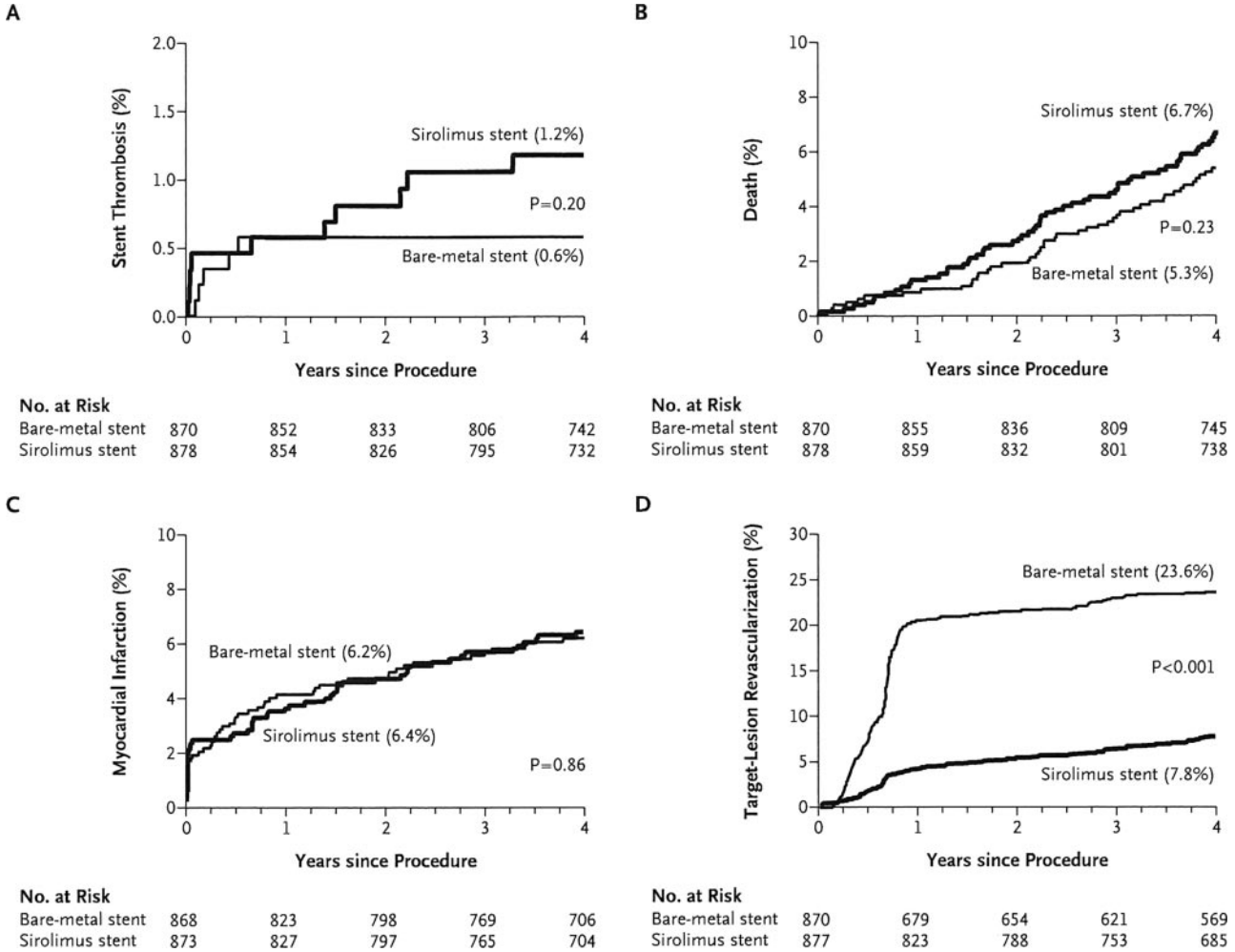

Figure 3. Comparison of sirolimus-eluting stents to bare-metal stents in randomized clinical trials. (Reprinted from Stone GW, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, Colombo A, Schampaert E, Grube E, Kirtane AJ, Cutlip DE, Fahy M, Pocock SJ, Mehran R, Leon MB. Safety and efficacy of sirolimus-and paclitaxel-eluting coronary stents. N Engl J Med 2007;356:998–1008. Fig. 1, p 1004).

between 0.5% and 3.1%.[100,101] When stent thrombosis occurs, it is catastrophic. Fatality and MI rates associated with stent thrombosis have ranged from 45% to 75% and 25% to 65%, respectively.[102–106] Of the 1% angiographic incidence of late stent thrombosis observed by Ong et al.,[104] 75% of these patients presented with a MI, and

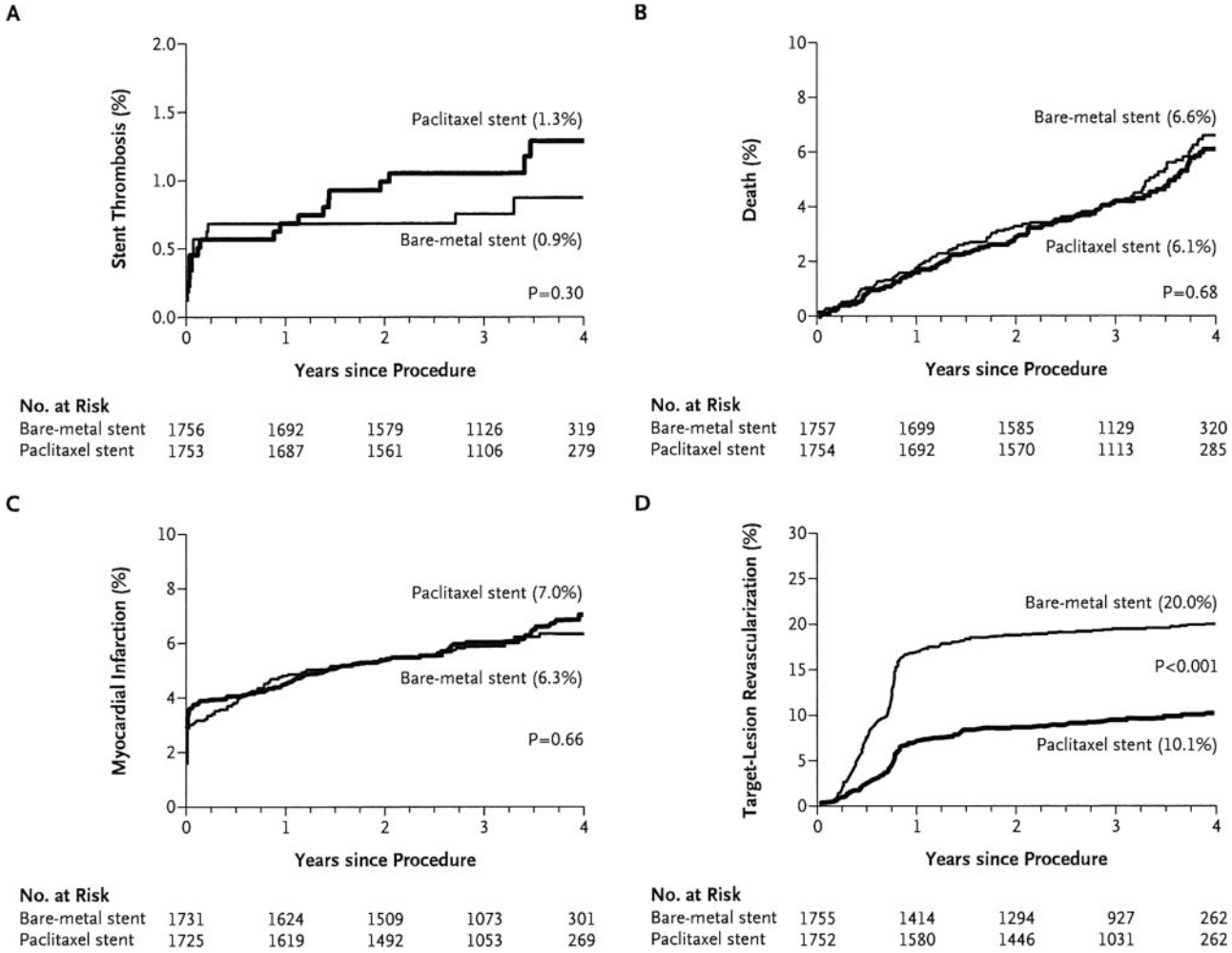

Figure 4. Comparison of paclitaxel-eluting stents to bare-metal stents in randomized clinical trials. (Reprinted from Stone GW, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, Colombo A, Schampaert E, Grube E, Kirtane AJ, Cutlip DE, Fahy M, Pocock SJ, Mehran R, Leon MB. Safety and efficacy of sirolimus-and paclitaxel-eluting coronary stents. N Engl J Med 2007;356:998–1008. Fig. 2, p 1005).

12% died. The pivotal clinical trials reported similar early (acute and subacute) stent thrombosis rates for DES and BMS (≤1%) and attributed this complication to mechanical factors.[97,107–109] Late (30 days to 12 mo) and very late (beyond 1 yr) stent thrombosis also occur with BMS and DES, but the pathophysiology differs between these devices.[110] In DES, late stent thrombosis presents as primary thrombosis.[111] It is affected by the degree of endothelial coverage and the intensity of antiplatelet therapy.[111–113] In contrast, BMS thrombosis is related to target lesion revascularization, and carries a 0.4%–0.8% incidence.[110] However, Ferrari et al.[114] reported 10 cases of late or very late stent thrombosis occurring with BMS after aspirin withdrawal. Those events occurred 15 ± 6.5 mo after stent implantation.

Although the initial randomized controlled trials did not reveal an increased incidence of stent thrombosis, case reports and longer follow-up studies were published suggesting otherwise. In 2003, more than 290 cases of subacute stent thrombosis occurring after sirolimus-DES implantation were reported to the FDA; a 20% mortality rate was also reported.[107] Cases of premature discontinuation of clopidogrel were associated with subacute stent thrombosis.[115] Jeremias et al.[116] reported a 1.1% incidence of subacute stent thrombosis at a mean of 7 days postsirolimus-DES implantation. All patients had prematurely stopped clopidogrel, increasing the risk of stent thrombosis by 30-fold. The first case of late stent thrombosis in a sirolimus-DES was published in 2003.[117] Clopidogrel was discontinued after 4 wks of dual-antiplatelet therapy; late stent thrombosis and a nonfatal MI occurred 2 wks later. McFadden et al.[118] reported the first case series of late stent thrombosis in 2004. Late stent thrombosis and MI occurred in four patients with DES (two sirolimus-DES; two paclitaxel-DES) after discontinuation (4–14 days earlier) of antiplatelet therapy. In all four cases, the DES had been implanted longer than a year. One patient with a sirolimus-DES stopped both clopidogrel and aspirin; the remaining patients were taking aspirin only. Of interest, three of the four patients were undergoing noncardiac surgery. Karvouni et al.[119] reported a case of very late stent thrombosis in a diabetic patient 17 mo after

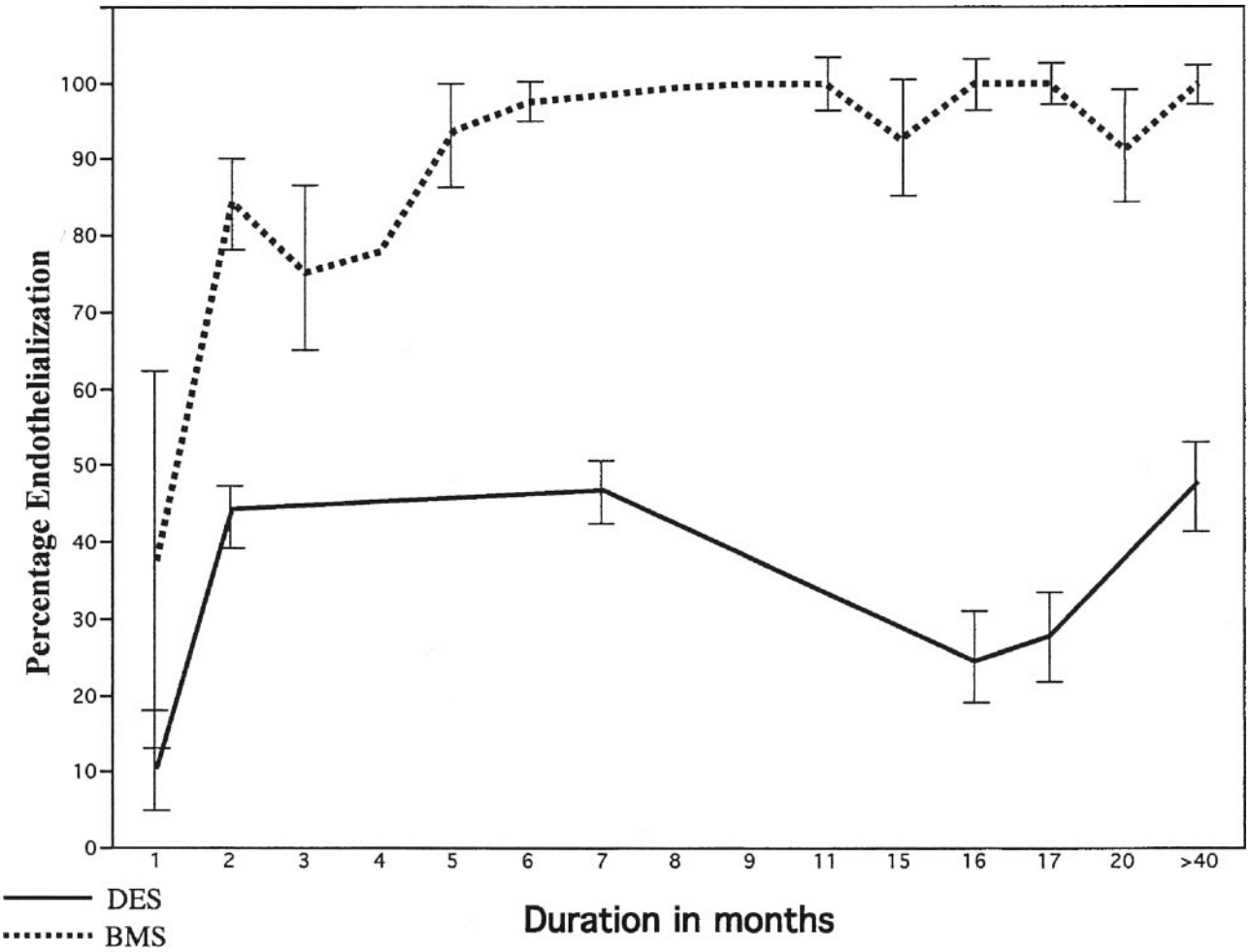

Figure 5. Line chart comparing the percentage of endothelialization in drug-eluting stents (DES) versus bare-metal stents (BMS) as a function of time. Note that DES (solid line) consistently show less endothelialization compared with BMS (dashed line) regardless of time point. Even beyond 40 mo DES are not fully endothelialized, whereas BMS are completely covered by 6 to 7 mo. (Reprinted from Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193–202. Fig. 2, p 195).

sirolimus-DES implantation; he had taken clopidogrel for 9 mo and remained on aspirin monotherapy. Waters et al.[120] published a case of late stent thrombosis in a left circumflex-sirolimus-DES after a 6-mo course of dual-antiplatelet therapy and life-long aspirin therapy. These serendipitous findings created an intense debate, questioning the safety of DES.

Research continues to elucidate the pathophysiology of stent thrombosis. Experimental models of BMS demonstrated complete endothelialization at 28 days, whereas at 6 mo, DES uniformly revealed incomplete healing, fibrin deposition, and inflammatory cells, indicating a hypersensitivity reaction.[100,121–123] In late 2003, the FDA notified physicians of possible hypersensitivity reactions to sirolimus-DES associated with stent thrombosis.[124] In autopsy studies of DES implanted 1–4 yrs, Virmani et al. found eosinophilic inflammation, thrombus, impaired vessel healing, persistent fibrin deposition and poor endothelialization in 45% of the stents (Fig. 5).[115,125–130] Sirolimus and paclitaxel impair endothelial function both within the stent and in the distal coronary artery, leading to delayed arterial healing of the stent itself, as well as enhancing the risk for distal arterial ischemia and coronary occlusion.[111] Both antiproliferative agents enhance the expression of endothelial cell tissue factor, creating a prothrombogenic environment.[111,131] Sirolimus has also been shown to directly activate platelets, induce local platelet aggregation, and contribute to local thrombus formation at the stent site.[131,132] The most powerful histological predictor of stent thrombosis has been incomplete endothelial coverage ($P < 0.00005$).[113] Kotani et al.[127] performed angioscopy in sirolimus-DES and BMS 3 to 6 mo after implantation, and compared the extent of neointimal coverage. All of the BMS were completely endothelialized, whereas 86.7% of the sirolimus-DES were not; 50% of these contained thrombi. Investigators analyzed the histology of restenosis retrieved from paclitaxel-DES, sirolimus-DES, and BMS of patients presenting for reintervention.[128] DES showed incomplete neointimal healing with fibrinoid deposition

Table 3A. Off-Label (Non-Food and Drug Administration [FDA] Approved) Uses of Drug-Eluting Stents (DES)/Predictors of Drug-Eluting Stent Thrombosis

Advanced age	Long stent length
Acute coronary syndrome	Multiple lesions
Diabetes	Overlapping stents
Low ejection fraction	Ostial or bifurcation lesions
Prior brachytherapy	Small vessels
Renal failure	Suboptimal stent results
Resistance to aspirin/clopidogrel	Stent mal-apposition
Premature discontinuation of antiplatelet therapy	Persistent dissection
Saphenous vein graft stenting (strut penetration into a necrotic core)	Stent underexpansion/ overexpansion
Left main coronary artery stenting (discontinuation of standard antiplatelet therapy)	Multivessel stenting
Lesion with chronic total occlusion	Vessels with in-stent restenosis

3B. On-label (FDA-approved) use of drug-eluting stents
Single de novo lesion in a native coronary artery in patients with stable coronary artery disease
Cypher® (sirolimus) 2.5–3.5 mm reference vessel diameter, ≤30 mm long
Taxus® (paclitaxel) 2.5–3.75 mm reference vessel diameter, ≤28 mm long

two yrs after implantation. Patients with paclitaxel-DES restenosis presented more frequently with unstable angina and showed more pronounced signs of delayed healing than sirolimus-DES. Additional predictors for late stent thrombosis are included in Table 3.[115,133–137]

Several studies and registries have identified predictors of DES thrombosis. Of these, acute coronary syndrome, left ventricular ejection fraction ≤30%, bifurcation treatment, renal insufficiency, diabetes, and premature or standard discontinuation of antiplatelet therapy were the strongest predictors of cumulative stent thrombosis.[106,130,133,134,138–148] Premature discontinuation of clopidogrel remains the strongest independent predictor of stent thrombosis in multivariate analysis.[106,138–148] Iakovou et al.[106] found a more frequent prevalence of diabetes, multivessel disease, small reference-vessel diameter, and complex lesions in 2229 nonrandomized patients who prospectively received DES. Again, the strongest independent predictor of stent thrombosis remained premature clopidogrel discontinuation ($P < 0.001$). Park et al.[139] reported a 7.8% stent thrombosis rate in patients who prematurely stopped clopidogrel, aspirin, or both. An analysis from the Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER) Registry, which studied 500 patients with acute MI treated with DES, reported a 7.5% mortality rate among patients who had prematurely discontinued thienopyridine therapy; patients who remained on clopidogrel and aspirin experienced a 0.7% mortality rate ($P < 0.0001$).[140] Ellis et al.[141] recently performed a meta-analysis of the Taxus II–VI trials to determine the incidence of late and very late stent thrombosis in patients followed 3 yrs after paclitaxel-DES implantation. In the initial 6 mo, an incidence of 0.8% was observed with both paclitaxel-DES and BMS. Beyond 6 mo, there was a 0.4% absolute increased risk of stent thrombosis in patients with paclitaxel-DES, and all patients who were diagnosed with late or very late stent thrombosis had discontinued clopidogrel. Time from clopidogrel termination to stent thrombosis ranged from 42 to 800 days. One case of very late stent thrombosis occurred when aspirin and clopidogrel were discontinued 5 days before surgery.

Kuchulakanti et al.[142] evaluated the correlates of angiographically proven stent thrombosis from a cohort of 2974 consecutive patients treated with DES. In this prospective registry with 12-mo follow-up, the mean duration to late stent thrombosis was 152.7 ± 100.4 days. The incidence of late stent thrombosis was higher in patients who discontinued clopidogrel therapy than in patients who continued clopidogrel (36.8% vs 10.7%; $P < 0.0001$). The 6-mo mortality rate in patients with late stent thrombosis was 31% ($P < 0.001$). In addition to clopidogrel discontinuation, independent predictors of stent thrombosis included renal failure, bifurcation lesions, and increased degree of restenosis. The authors concluded that strict adherence to clopidogrel compliance is paramount in patients with increased risk factors for stent thrombosis after DES implantation. Eisenstein et al.[143] observed continued clopidogrel use at 6, 12, and 24 mo was associated with a significantly lower rate of cardiac death and MI as compared with patients who had discontinued clopidogrel at 6 or 12 mo (Fig. 6).

Resistance to antiplatelet therapy has been cited as a risk factor for developing stent thrombosis.[149] Four percent to 30% of patients respond inadequately to clopidogrel on *in vitro* testing, and 4%–45% respond inadequately to aspirin.[150,151] Evidence suggests patients with stent thrombosis have abnormally high rates of excessive platelet activity.[152,153] Wenaweser et al.[149] reported 48% of patients with stent thrombosis had impaired *in vitro* responses to aspirin compared with 32% of patients without stent thrombosis ($P = 0.01$). Although clopidogrel resistance was similar between patients with stent thrombosis and patient controls, combined aspirin/clopidogrel resistance was significantly higher in patients with stent thrombosis (52%, $P < 0.05$).[149]

Most cases of aspirin and clopidogrel resistance result from patient noncompliance and improper physician dosing.[151,154] Alternatively, compliant patients may have poor intestinal absorption or decreased receptor binding secondary to drug interactions.[151,155–160]

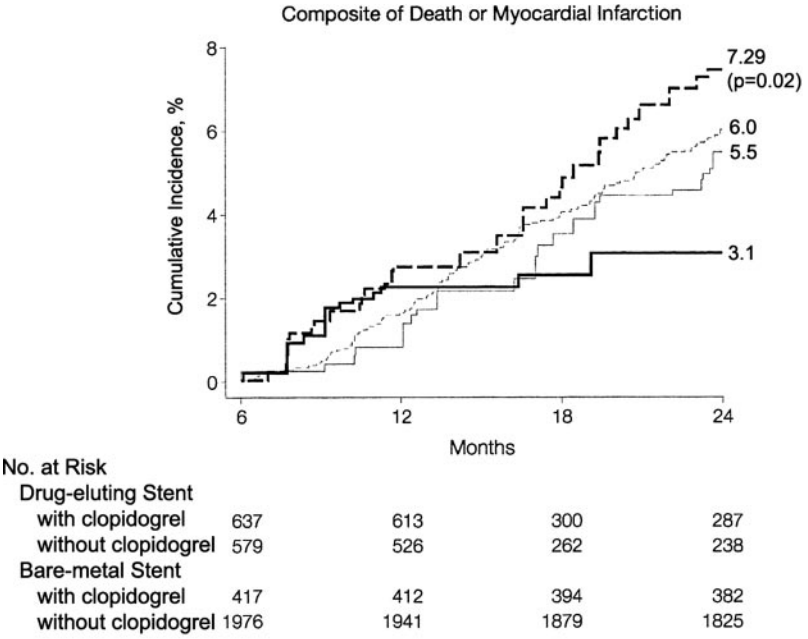

Figure 6. Six-month landmark analysis of patients who discontinued clopidogrel use at 6 and 12 mo versus continuing to 24 months. Drug-eluting stents (DES) 7.2 vs 3.1, $P = 0.02$; bare-metal stents (BMS) 6.0 vs 5.5, $P = 0.70$ (Reprinted from Eisenstein EL, Anstrom KJ, Kong DF, Shaw LK, Tuttle RH, Mark DB, Kramer JM, Harrington RA, Matchar DB, Kandzari DE, Peterson ED, Schulman KA, Califf RM. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. JAMA 2007;297:159–68. Fig. 2, p 164).

Studies suggest response variability to clopidogrel may be dose-dependent.[153,161] Multiple cellular etiologies have been described.[55,150,162] Increased levels of urinary 11-dehydro TxB_2 (a marker of thromboxane generation) have been associated with heightened risk of MI and cardiac death.[156] Genetic etiologies include polymorphisms of COX-1, $P2Y_{12}$, and CYP3A4.[150,155,163–165] However, there is no universally accepted test for antiplatelet resistance, and consequently its prevalence varies among studies.[155] Moreover, there is no consensus as to the role antiplatelet resistance may play in late stent thrombosis.[166]

THE CONTROVERSY INTENSIFIES

The current firestorm regarding DES was ignited by the findings of two meta-analyses presented at the American College of Cardiology's 55th Annual Scientific Session in March 2006 and the European Society of Cardiology/World Congress of Cardiology meeting in September 2006.[144] These studies confirmed that late stent thrombosis occurs more frequently than reported in randomized controlled trials. The Basel Stent Kosten Effektivitäts Trial-Late Thrombotic Events (BASKET-LATE) study presented in March 2006 sought to determine the true incidence of late stent thrombosis, MI, and death in 746 patients randomized to receive DES or BMS who had remained on dual-antiplatelet therapy for 6 mo. The patients had not experienced an adverse cardiac event during that period.[147] At 6 mo, clopidogrel was stopped and patients were followed an additional 12 mo. In addition to a 19% mortality rate and an 88% composite rate of death or MI, the researchers found the following: (1) late stent thrombosis-related events (death and MI) occurred two to three times more frequently in patients with DES than those with BMS (Fig. 7); (2) late stent thrombosis carried a four times higher risk of cardiac death/MI ($P < 0.0001$, Fig. 8); and (3) late stent thrombosis and its complications occurred up to 1 yr after clopidogrel discontinuation. The authors concluded that while DES use in 100 patients avoids five target lesion revascularization events at 6 mo, it unfortunately leads to 3.3 late deaths or MI. Camenzind et al. presented in September 2006 a meta-analysis of all company-supported randomized trials (RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS, and TAXUS I-VI) comparing sirolimus-DES and paclitaxel-DES with BMS controls for an average 3-yr follow-up.[145,146] Sirolimus-DES were associated with a 60% relative increase in death or MI ($P = 0.03$), whereas paclitaxel-DES demonstrated a statistically insignificant 15% increase. The authors concluded late stent thrombosis and discontinuation of antiplatelet therapy caused the higher rates of death and MI.

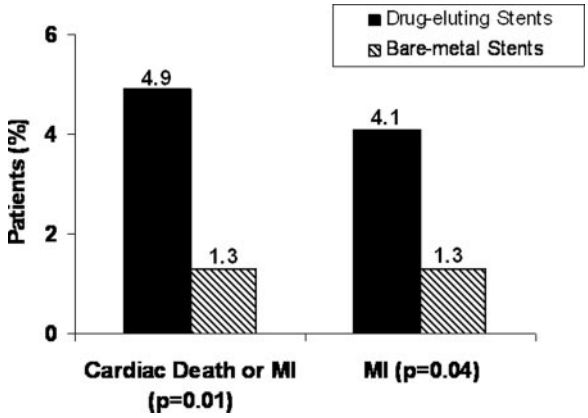

Figure 7. Outcomes related to late stent thrombosis. MI = myocardial infarction. (Reprinted from Gruberg L. BASKET-LATE: Late clinical events related to late stent thrombosis after stopping clopidogrel: drug-eluting vs bare-metal stenting. Available at: http://www.medscape.com/viewarticle/529648. Accessed June 12, 2007. Fig. 3).

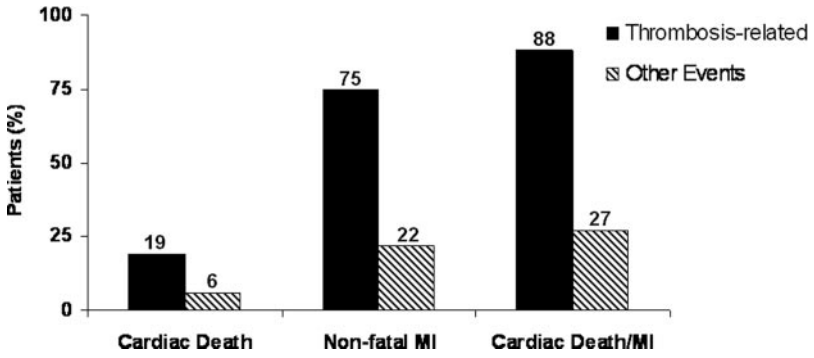

Figure 8. Incidences of death/myocardial infarction and composite of death and myocardial infarction related to stent thrombosis in patients with drug-eluting stents. (Reprinted from Gruberg L. BASKET-LATE: Late clinical events related to late stent thrombosis after stopping clopidogrel: drug-eluting vs bare-metal stenting. Available at: http://www.medscape.com/viewarticle/529648. Accessed June 12, 2007.)

In response, several investigators performed 4-yr follow-up analyses of the initial pivotal trials to support the safety and efficacy of these devices[95,167] (Figs. 3 and 4). Further, as the definition of thrombosis varies among studies, adding to the confusion and disagreement among investigators, the Academic Research Consortium (ARC) recently proposed standardized definitions in an effort to develop uniformity and improve sensitivity for the diagnosis of stent thrombosis.[109,168] These subsequent meta-analyses were performed using these definitions. In their examination of the data from the RAVEL, SIRIUS, and TAXUS trials, Mauri et al.[109] reported no statistical difference in the cumulative incidence of stent thrombosis (paclitaxel-DES 1.3% vs BMS 0.8%, $P = 0.24$; sirolimus-DES 1.2% vs BMS 0.6%, $P = 0.20$), although the power to detect such differences was limited. When compared with BMS, Stone et al.[97] detected a small, but significant increase in the incidence of late stent thrombosis for both sirolimus-DES (0.6% vs 0%; $P = 0.025$) and paclitaxel-DES (0.7% vs 0.2%; $P = 0.028$) 1 to 4 yrs after implantation. No differences in death or MI were initially observed. However, a reanalysis of the data demonstrated a threefold increase in the composite of death and MI after 1 yr ($P = 0.05$); the 3-yr incidence was 1.2% with paclitaxel-DES versus 0.7% with BMS.[169,170] Although Kastrati et al.[171] found an increased rate of very late stent thrombosis with sirolimus-DES compared with BMS (0.6% vs 0.05%; $P = 0.02$), there was no difference in 5-yr mortality. Spaulding et al.[169] also did not detect any difference in the incidence of MI or stent thrombosis after a 4-yr follow-up, but the survival rate for diabetics with BMS was significantly higher than in diabetics with sirolimus-DES (95.6% vs 87.8%, $P = 0.008$). Babapulle et al.[170] performed a meta-analysis of 11 trials, showing DES were effective at decreasing rates of death and MI (DES 7.8% vs BMS 16.4%) by reducing rates of target vessel revascularization.

Nonrandomized registries more representative of clinical practice and additional meta-analyses of pivotal trial data have challenged these findings, particularly when the ARC definitions are not applied. The ARC definitions may introduce bias in favor of DES and are not universally accepted. Iakovou et al.[106] observed a 1.3% incidence of stent thrombosis with a 45% mortality rate. In 2005, Bavry et al.[108,172] performed a meta-analysis of eight randomized clinical trials, finding no difference in stent thrombosis between DES and BMS; the investigators performed a subsequent meta-analysis of 14 randomized clinical trials in 2006 and found DES increased the risk for late stent thrombosis by four- to fivefold. The median thrombosis time was 15.5–18 mo; a greater incidence of late stent thrombosis was seen with paclitaxel-DES. In 2007, Lagerqvist et al.[105] performed a 3-yr outcomes analysis comparing 6033 patients treated with DES versus 13,738 treated with BMS through the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). DES implantation was associated with a 32% relative increase in death from 6 mo to 3 yrs. The absolute risk of death increased 0.5%–1.0% per yr. The authors noted a higher frequency of comorbidities and procedural complexities associated with DES use and hypothesized stent thrombosis caused the increased mortality. Further, the incidence of reintervention was the same for DES and BMS (14.7% vs 14.5%), questioning the benefit of DES. However, when the authors studied data from 2005 (yr 4), they found no difference in the relative risk for death and MI (RR = 1.01 for both groups). The authors attributed this improvement in outcome to better technique and longer duration of clopidogrel therapy. Daemen et al.[173] evaluated the incidence of late stent thrombosis in unrestricted use of DES in routine clinical practice. Between 2002 and 2005, a persistent excess stent thrombosis risk of 0.6% per year was found compared with historical control subjects who received BMS. The Evaluation of Active Stent (EVASTENT) study evaluated sirolimus-DES in diabetics and nondiabetics.[174] At 1 yr, the stent thrombosis and mortality rates were 1.8-times and 3.1-times higher, respectively, in diabetics ($P < 0.001$).

The disparity among the various studies has generated both confusion and controversy. Those who dispute the safety of DES question the validity of the pivotal trial data, which excluded the highest risk patients: the population who are currently receiving DES. The prospective, randomized controlled trials are considered not to have adequate power to reliably detect late stent thrombosis or to evaluate clinically relevant end points (death or MI).[175] Moreover, these pivotal trials and their analyses were based on the

original indications for which the FDA approved the use of DES, which were defined by the inclusion and exclusion criteria of the original trials themselves.[167] Use within these well-defined criteria is termed "on-label."[176] Currently, 40% of DES are implanted for on-label indications (Table 3).[167,176] The remaining 60% of use is "off-label," currently unapproved by the FDA, occurring in patients with comorbidities or with complex coronary lesions (Table 3).[138,148,176] This population more accurately reflects those patients represented in nonrandomized trials, registries, and clinical practice. Unfortunately, these same comorbidities and lesion complexities are also predictors of stent thrombosis, suggesting serious complications are higher in off-label populations compared with their less-complex, on-label counterparts (Table 3).[148] The Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) registry of nonrandomized unrestricted paclitaxel-DES use comparing off- and on-label use found off-label use was associated with higher rates of death (6.5% vs 4.6%; $P = 0.08$), MI (3.6% vs 2.1%; $P < 0.0001$), and stent thrombosis (3.0% vs 1.4%; $P < 0.0001$) at 2 yrs.[177] Win et al.[138] recently published data from a prospective registry of patients receiving DES for on- and off-label use. At 1-yr, the composite of death and MI occurred more frequently with off-label use (17.5% vs 8.9%, $P < 0.001$). Similar results have been confirmed in other studies and registries.[138–148]

Along with the stent thrombosis issue, the subject of the appropriate duration of dual-antiplatelet therapy came under scrutiny. The initial recommendations made for both sirolimus-DES and paclitaxel-DES were completely arbitrary, and the FDA, American Heart Association/American College of Cardiology/Society for Cardiovascular Angiography Interventions (AHA/ACC/SCAI) and the stent manufacturers advised patients to remain on clopidogrel and aspirin for 3 (sirolimus-DES) and 6 (paclitaxel-DES) mo followed by life-long aspirin therapy without validation by scientific arguments (Table 2).[128,178–181] However, data from several studies suggest a longer duration of antiplatelet therapy than is currently included in the product labeling may be beneficial.[138–148] In 2005, the European Society of Cardiology and the AHA/ACC/SCAI extended the recommended duration of therapy, ideally for up to 12 mo, in patients at low risk of bleeding.[182,183] As publications continued questioning the safety of DES, the FDA convened in December 2006 to review then-current data relevant to stent thrombosis, and to address the appropriate duration of dual-antiplatelet therapy in both on- and off-label use of DES. The FDA concluded that (1) when DES are used for their approved, or on-label, indications, the risk of thrombosis does not outweigh their advantages over BMS in reducing the rate of revascularization; and (2) off-label use is associated with a higher rate of stent thrombosis, MI and death.[94,115,148] With respect to dual-antiplatelet therapy, the panel concluded there was sufficient data to suggest a prolonged course of clopidogrel was beneficial, but the ideal duration was unknown.[148] "Premature discontinuation, however, of dual-antiplatelet therapy after DES implantation does appear to be associated with an increased risk of stent thrombosis, death, and MI. These risks may even be higher in the off-label compared with the on-label use of DES.[148]" After the FDA deliberations, a scientific advisory endorsed by five major professional societies was published in January 2007.[183] This advisory, written by the ACC/AHA/SCAI, the American College of Surgeons and the American Dental Association, emphasized the importance of 12-mo dual-antiplatelet therapy and life-long aspirin therapy after DES implantation. However, the ideal duration of dual-antiplatelet therapy is not yet known, and may need to be extended beyond one-year in patients with additional risk factors for stent thrombosis.[184–187] The National Heart, Lung, and Blood Institute also convened a panel of representatives from academia, industry, and the FDA in January 2007 to readdress the issues raised during the FDA panel, and emphasized the importance of evidence-based medicine to resolve these continuing controversies.[144]

CONCLUSION

The progress of interventional cardiology over the last three decades has revolutionized the treatment of coronary artery disease. However, the enthusiasm for each advance has been fraught with unforeseen complications, which subsequently limit its use. This is of benefit, as clinicians must decide the most appropriate procedure for their patients; DES may not be the panacea once thought. In fact, the data accumulated over the last 5 yrs have caused cardiologists to carefully deliberate the most appropriate stent(s) to implant in a patient, with a decline in DES use from 90% to the current rate of 70%. Research is focused on developing more biocompatible absorbable coatings and newer drugs with biological targets other than smooth muscle proliferation.[110] Development of more biocompatible and bioabsorbable stents facilitating adequate endothelialization is expected in the near future.[110] Second-generation DES, containing everolimus or zotarolimus, are undergoing clinical trials to assess their ability to resolve the issues discovered with the first generation of DES. Virmani[188] has demonstrated complete endothelialization in animal models, suggesting a better safety profile with these stents. Despite these new technologies, there must still be focus on the stents already implanted to ensure patient safety and improve outcomes.

REFERENCES

1. Mueller RL, Sanborn TA. The history of interventional cardiology: cardiac catheterization, angioplasty, and related interventions. Am Heart J 1995;129:146–72
2. Gruntzig A. Transluminal dilatation of coronary-artery stenosis. Lancet 1978;1:263
3. Gruntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. N Engl J Med 1979;301:61–8

4. Bentivoglio LG. Immediate and long-term results of percutaneous transluminal coronary angioplasty. Comparison of the National Heart, Lung and Blood Institute Registry experience with current experience. Herz 1985;10:275–80
5. McBride W, Lange RA, Hillis LD. Restenosis after successful coronary angioplasty. Pathophysiology and prevention. N Engl J Med 1988;318:1734–7
6. Castaneda-Zuniga WR, Formanek A, Tadavarthy M, Vlodaver Z, Edwards JE, Zollikofer C, Amplatz K. The mechanism of balloon angioplasty. Radiology 1980;135:565–71
7. Serruys PW, Kutryk MJ, Ong AT. Coronary-artery stents. N Engl J Med 2006;354:483–95
8. Narins CR, Holmes DR Jr, Topol EJ. A call for provisional stenting: the balloon is back! Circulation 1998;97:1298–305
9. Grech ED. ABC of interventional cardiology: percutaneous coronary intervention. I. History and development. BMJ 2003;326:1080–2
10. Coolong A, Mauri L. Clopidogrel treatment surrounding percutaneous coronary intervention: when should it be started and stopped? Curr Cardiol Rep 2006;8:267–71
11. Cowley MJ, Dorros G, Kelsey SF, Van Raden M, Detre KM. Acute coronary events associated with percutaneous transluminal coronary angioplasty. Am J Cardiol 1984;53:12C–6C
12. Holmes DR Jr, Holubkov R, Vlietstra RE, Kelsey SF, Reeder GS, Dorros G, Williams DO, Cowley MJ, Faxon DP, Kent KM, Bentivoglio LG, Detre K, the Coinvestigators of the National Heart, Lung and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. Comparison of complications during percutaneous transluminal coronary angioplasty from 1977 to 1981 and from 1985 to 1986: the National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. J Am Coll Cardiol 1988;12:1149–55
13. Lincoff AM, Popma JJ, Ellis SG, Hacker JA, Topol EJ. Abrupt vessel closure complicating coronary angioplasty: clinical, angiographic and therapeutic profile. J Am Coll Cardiol 1992;19:926–35
14. Kuntz RE, Piana R, Pomerantz RM, Carrozza J, Fishman R, Mansour M, Safian RD, Baim DS. Changing incidence and management of abrupt closure following coronary intervention in the new device era. Cathet Cardiovasc Diagn 1992;27:183–90
15. Ischinger T, Gruentzig AR, Meier B, Galan K. Coronary dissection and total coronary occlusion associated with percutaneous transluminal coronary angioplasty: significance of initial angiographic morphology of coronary stenoses. Circulation 1986;74:1371–8
16. Black AJ, Namay DL, Niederman AL, Lembo NJ, Roubin GS, Douglas JS Jr, King SB III. Tear or dissection after coronary angioplasty. Morphologic correlates of an ischemic complication. Circulation 1989;79:1035–42
17. Hillegass W, Ohman O, Califf R. Restenosis: the clinical issues. In: Topol EJ, ed. Textbook of interventional cardiology. Vol. 2. Philadelphia, PA: W.B. Saunders, 1994:415–35
18. Birkenhauer P, Yang Z, Gander B. Preventing restenosis in early drug-eluting stent era: recent developments and future perspectives. J Pharm Pharmacol 2004;56:1339–56
19. Ross R, Glomset JA. The pathogenesis of atherosclerosis (first of two parts). N Engl J Med 1976;295:369–77
20. Sousa JE, Serruys PW, Costa MA. New frontiers in cardiology: drug-eluting stents: Part I. Circulation 2003;107:2274–9
21. Hirshfeld JW Jr, Schwartz JS, Jugo R, MacDonald RG, Goldberg S, Savage MP, Bass TA, Vetrovec G, Cowley M, Taussig AS, Whitworth HB, Margolis JR, Hill JA, Pepine CJ, The M-Heart Investigators. Restenosis after coronary angioplasty: a multivariate statistical model to relate lesion and procedure variables to restenosis. The M-Heart Investigators. J Am Coll Cardiol 1991;18:647–56
22. King SB III. The development of interventional cardiology. J Am Coll Cardiol 1998;31(4 suppl B):64B–88B
23. Reifart N, Vandormael M, Krajcar M, Gohring S, Preusler W, Schwarz F, Storger H, Hofmann M, Klopper J, Muller S, Haase J. Randomized comparison of angioplasty of complex coronary lesions at a single center. Excimer Laser, Rotational Atherectomy, and Balloon Angioplasty Comparison (ERBAC) study. Circulation 1997;96:91–8
24. Topol EJ, Leya F, Pinkerton CA, Whitlow PL, Hofling B, Simonton CA, Masden RR, Serruys PW, Leon MB, Williams DO, King SB, Mark DB, Isner JM, Holmes DR, Ellis SG, Lee KL, Keeler GP, Berdan LG, Hinohara T, Califf RM, for the CAVEAT Study Group. A comparison of directional atherectomy with coronary angioplasty in patients with coronary artery disease. The CAVEAT study group. N Engl J Med 1993;329:221–7
25. Holmes DR Jr, Topol EJ, Califf RM, Berdan LG, Leya F, Berger PB, Whitlow PL, Safian RD, Adelman AG, Kellett MA Jr, Talley JD III, Shani J, Gottlieb RS, Pinkerton CA, Lee KL, Keeler GP, Ellis SG; the CAVEAT-II Investigators. A multicenter, randomized trial of coronary angioplasty versus directional atherectomy for patients with saphenous vein bypass graft lesions. CAVEAT-II Investigators. Circulation 1995;91:1966–74
26. Adelman AG, Cohen EA, Kimball BP, Bonan R, Ricci DR, Webb JG, Laramee L, Barbeau G, Traboulsi M, Corbett BN, Schwartz L, Logan AG. A comparison of directional atherectomy with balloon angioplasty for lesions of the left anterior descending coronary artery. N Engl J Med 1993;329:228–33
27. Elliott JM, Berdan LG, Holmes DR, Isner JM, King SB, Keeler GP, Kearney M, Califf RM, Topol EJ. One-year follow-up in the coronary angioplasty versus excisional atherectomy trial (CAVEAT I). Circulation 1995;91:2158–66
28. Nobel's Lectures. Physiology or Medicine 1901–1921. Amsterdam: Elsevier Publishing Company, 1967
29. Dotter CT, Judkins MP. Transluminal treatment of arteriosclerotic obstruction. Description of a new technic and a preliminary report of its application. Circulation 1964;30:654–70
30. Dotter CT, Buschmann RW, McKinney MK, Rosch J. Transluminal expandable nitinol coil stent grafting: preliminary report. Radiology 1983;147:259–60
31. Rousseau H, Puel J, Joffre F, Sigwart U, Duboucher C, Imbert C, Knight C, Kropf L, Wallsten H. Self-expanding endovascular prosthesis: an experimental study. Radiology 1987;164:709–14
32. Palmaz JC, Sibbitt RR, Reuter SR, Tio FO, Rice WJ. Expandable intraluminal graft: a preliminary study. Work in progress. Radiology 1985;156:73–7
33. Schatz RA, Palmaz JC, Tio FO, Garcia F, Garcia O, Reuter SR. Balloon-expandable intracoronary stents in the adult dog. Circulation 1987;76:450–7
34. Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med 1987;316:701–6
35. de Feyter PJ, de Jaegere PP, Serruys PW. Incidence, predictors, and management of acute coronary occlusion after coronary angioplasty. Am Heart J 1994;127:643–51
36. Ruygrok PN, Serruys PW. Intracoronary stenting. From concept to custom. Circulation 1996;94:882–90
37. Roubin GS, Cannon AD, Agrawal SK, Macander PJ, Dean LS, Baxley WA, Breland J. Intracoronary stenting for acute and threatened closure complicating percutaneous transluminal coronary angioplasty. Circulation 1992;85:916–27
38. Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, Emanuelsson H, Marco J, Legrand V, Materne P, Belardi J, Sigwart U, Colombo A, Goy JJ, van den Heuvel P, Delcan J, Morel M-a, for The Benestent Study Group. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent study group. N Engl J Med 1994;331:489–95
39. Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, Detre K, Veltri L, Ricci D, Nobuyoshi M, Cleman M, Heuser R, Almond D, Teirstein PS, Fish RD, Colombo A, Brinker J, Moses J, Shaknovich A, Hirschfeld J, Bailey S, Ellis S, Rake R, Goldberg S, for the Stent Restenosis Study Investigators. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. N Engl J Med 1994;331:496–501
40. Moliterno DJ. Healing achilles–sirolimus versus paclitaxel. N Engl J Med 2005;353:724–7
41. Versaci F, Gaspardone A, Tomai F, Crea F, Chiariello L, Gioffre PA. A comparison of coronary-artery stenting with angioplasty for isolated stenosis of the proximal left anterior descending coronary artery. N Engl J Med 1997;336:817–22

42. Serruys PW, Strauss BH, Beatt KJ, Bertrand ME, Puel J, Rickards AF, Meier B, Goy JJ, Vogt P, Kappenberger L, Sigwart U. Angiographic follow-up after placement of a self-expanding coronary-artery stent. N Engl J Med 1991;324:13–7
43. Holmes DR Jr, Savage M, LaBlanche JM, Grip L, Serruys PW, Fitzgerald P, Fischman D, Goldberg S, Brinker JA, Zeiher AM, Shapiro LM, Willerson J, Davis BR, Ferguson JJ, Popma J, King SB III, Lincoff AM, Tcheng JE, Chan R, Granett JR, Poland M. Results of Prevention of REStenosis with Tranilast and its Outcomes (PRESTO) trial. Circulation 2002;106:1243–50
44. Arjomand H, Turi ZG, McCormick D, Goldberg S. Percutaneous coronary intervention: historical perspectives, current status, and future directions. Am Heart J 2003;146:787–96
45. Cutlip DE, Baim DS, Ho KK, Popma JJ, Lansky AJ, Cohen DJ, Carrozza JP Jr, Chauhan MS, Rodriguez O, Kuntz RE. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. Circulation 2001;103:1967–71
46. Bertrand ME, Legrand V, Boland J, Fleck E, Bonnier J, Emmanuelson H, Vrolix M, Missault L, Chierchia S, Casaccia M, Niccoli L, Oto A, White C, Webb-Peploe M, Van Belle E, McFadden EP. Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting. The full anticoagulation versus aspirin and ticlopidine (fantastic) study. Circulation 1998;98:1597–603
47. Colombo A, Hall P, Nakamura S, Almagor Y, Maiello L, Martini G, Gaglione A, Goldberg SL, Tobis JM. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. Circulation 1995;91:1676–88
48. Barragan P, Sainsous J, Silvestri M, Bouvier JL, Comet B, Simeoni JB, Charmasson C, Bremondy M. Ticlopidine and subcutaneous heparin as an alternative regimen following coronary stenting. Cathet Cardiovasc Diagn 1994;32:133–8
49. Schomig A, Neumann FJ, Kastrati A, Schuhlen H, Blasini R, Hadamitzky M, Walter H, Zitzmann-Roth EM, Richardt G, Alt E, Schmitt C, Ulm K. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med 1996;334:1084–9
50. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH, CLASSICS Investigators. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS). Circulation 2000;102:624–9
51. Topol EJ, Serruys PW. Frontiers in interventional cardiology. Circulation 1998;98:1802–20
52. Wenaweser P, Rey C, Eberli FR, Togni M, Tuller D, Locher S, Remondino A, Seiler C, Hess OM, Meier B, Windecker S. Stent thrombosis following bare-metal stent implantation: success of emergency percutaneous coronary intervention and predictors of adverse outcome. Eur Heart J 2005;26:1180–7
53. Kereiakes DJ, Choo JK, Young JJ, Broderick TM. Thrombosis and drug-eluting stents: a critical appraisal. Rev Cardiovasc Med 2004;5:9–15
54. Savi P, Herbert JM. Clopidogrel and ticlopidine: P2Y12 adenosine diphosphate-receptor antagonists for the prevention of atherothrombosis. Semin Thromb Hemost 2005;31:174–83
55. Cattaneo M. Aspirin and clopidogrel: efficacy, safety, and the issue of drug resistance. Arterioscler Thromb Vasc Biol 2004;24:1980–7
56. Cattaneo M. Platelet P2 receptors: old and new targets for antithrombotic drugs. Expert Rev Cardiovasc Ther 2007; 5:45–55
57. Gachet C. The platelet P2 receptors as molecular targets for old and new antiplatelet drugs. Pharmacol Ther 2005;108:180–92
58. Rozalski M, Nocun M, Watala C. Adenosine diphosphate receptors on blood platelets—potential new targets for antiplatelet therapy. Acta Biochim Pol 2005;52:411–5
59. Patrono C. Aspirin as an antiplatelet drug. N Engl J Med 1994;330:1287–94
60. Buczko W, Mogielnicki A, Kramkowski K, Chabielska E. Aspirin and the fibrinolytic response. Thromb Res 2003; 110:331–4
61. Cattaneo M, D'Angelo A, Canciani MT, Asti D, Vigano-D'Angelo S, Tripodi A, Mannucci PM. Effect of oral aspirin on plasma levels of vitamin K-dependent clotting factors—studies in healthy volunteers. Thromb Haemost 1988;59:540
62. Husain S, Andrews NP, Mulcahy D, Panza JA, Quyyumi AA. Aspirin improves endothelial dysfunction in atherosclerosis. Circulation 1998;97:716–20
63. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, Giambartolomei A, Diver DJ, Lasorda DM, Williams DO, Pocock SJ, Kuntz RE. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. N Engl J Med 1998;339:1665–71
64. Moussa I, Oetgen M, Roubin G, Colombo A, Wang X, Iyer S, Maida R, Collins M, Kreps E, Moses JW. Effectiveness of clopidogrel and aspirin versus ticlopidine and aspirin in preventing stent thrombosis after coronary stent implantation. Circulation 1999;99:2364–6
65. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494–502
66. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I, Fox KA, Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527–33
67. Steinhubl SR, Berger PB, Mann JT 3rd, Fry ET, DeLago A, Wilmer C, Topol EJ, CREDO Investigators. Clopidogrel for the reduction of events during observation. early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288:2411–20
68. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Brennan DM, Fabry-Ribaudo L, Booth J, Topol EJ, CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006;354:1706–17
69. Tamberella MR, Furman MI. The role of platelet inhibition in the drug-eluting stent era. Coron Artery Dis 2004;15:327–9
70. Stone GW, Aronow HD. Long-term care after percutaneous coronary intervention: focus on the role of antiplatelet therapy. Mayo Clin Proc 2006;81:641–52
71. Elezi S, Kastrati A, Pache J, Wehinger A, Hadamitzky M, Dirschinger J, Neumann FJ, Schomig A. Diabetes mellitus and the clinical and angiographic outcome after coronary stent placement. J Am Coll Cardiol 1998;32:1866–73
72. de Feyter PJ, Vos J, Rensing BJ. Anti-restenosis trials. Curr Interv Cardiol Rep 2000;2:326–31
73. Kobayashi Y, De Gregorio J, Kobayashi N, Akiyama T, Reimers B, Finci L, Di Mario C, Colombo A. Stented segment length as an independent predictor of restenosis. J Am Coll Cardiol 1999;34:651–9
74. Hoffmann R, Mintz GS. Coronary in-stent restenosis - predictors, treatment and prevention. Eur Heart J 2000;21:1739–49
75. Wilson JM. Stents or surgery: the case for stents. Tex Heart Inst J 2005;32:331–8
76. Sawada Y, Nokasa H, Kimura T. Initial and six months outcome of Palmaz-Schatz stent implantations: STRESS/BENESTENT equivalent vs non-equivalent lesions. J Am Coll Cardiol 1996;27(suppl A):252A
77. Chen MS, John JM, Chew DP, Lee DS, Ellis SG, Bhatt DL. Bare metal stent restenosis is not a benign clinical entity. Am Heart J 2006;151:1260–4
78. Yokoi H, Kimura T, Nakagawa Y. Long-term clinical and quantitative angiographic follow-up after the Palmaz-Schatz stent restenosis. J Am Coll Cardiol 1995;27(suppl A):224A
79. Woods TC, Marks AR. Drug-eluting stents. Annu Rev Med 2004;55:169–78
80. Lemos PA, Serruys PW, Sousa JE. Drug-eluting stents: cost versus clinical benefit. Circulation 2003;107:3003–7
81. Drenth DJ, Veeger NJ, Winter JB, Grandjean JG, Mariani MA, Boven van AJ, Boonstra PW. A prospective randomized trial comparing stenting with off-pump coronary surgery for high-grade stenosis in the proximal left anterior descending coronary artery: three-year follow-up. J Am Coll Cardiol 2002;40:1955–60

82. Serruys PW. Fourth annual American college of cardiology international lecture: a journey in the interventional field. J Am Coll Cardiol 2006;47:1754–68
83. Sousa JE, Serruys PW, Costa MA. New frontiers in cardiology: drug-eluting stents: Part II. Circulation 2003;107:2383–9
84. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME, TAXUS-IV Investigators. One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. Circulation 2004;109:1942–7
85. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R; RAVEL Study Group. Randomized study with the sirolimus-coated bx velocity balloon-expandable stent in the treatment of patients with de novo native coronary artery lesions. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773–80
86. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE, SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–23
87. Schofer J, Schluter M, Gershlick AH, Wijns W, Garcia E, Schampaert E, Breithardt G, E-SIRIUS Investigators. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). Lancet 2003;362:1093–9
88. Schampaert E, Cohen EA, Schluter M, Reeves F, Traboulsi M, Title LM, Kuntz RE, Popma JJ, C-SIRIUS Investigators. 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
89. Grube E, Silber S, Hauptmann KE, Mueller R, Buellesfeld L, Gerckens U, Russell ME. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. Circulation 2003;107:38–42
90. Colombo A, Drzewiecki J, Banning A, Grube E, Hauptmann K, Silber S, Dudek D, Fort S, Schiele F, Zmudka K, Guagliumi G, Russell ME, TAXUS II Study Group. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. Circulation 2003;108:788–94
91. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME, TAXUS-IV Investigators. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221–31
92. Stone GW, Ellis SG, Cannon L, Mann JT, Greenberg JD, Spriggs D, O'Shaughnessy CD, DeMaio S, Hall P, Popma JJ, Koglin J, Russell ME, TAXUS V Investigators. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. JAMA 2005;294:1215–23
93. Dawkins KD, Grube E, Guagliumi G, Banning AP, Zmudka K, Colombo A, Thuesen L, Hauptman K, Marco J, Wijns W, Popma JJ, Koglin J, Russell ME, TAXUS VI Investigators. Clinical efficacy of polymer-based paclitaxel-eluting stents in the treatment of complex, long coronary artery lesions from a multicenter, randomized trial: support for the use of drug-eluting stents in contemporary clinical practice. Circulation 2005;112:3306–13
94. Grube E, Buellesfeld L. Paclitaxel-eluting stents: current clinical experience. Am J Cardiovasc Drugs 2004;4:355–60
95. Sousa JE, Costa MA, Sousa AG, Abizaid AC, Seixas AC, Abizaid AS, Feres F, Mattos LA, Falotico R, Jaeger J, Popma JJ, Serruys PW. Two-year angiographic and intravascular ultrasound follow-up after implantation of sirolimus-eluting stents in human coronary arteries. Circulation 2003;107:381–3
96. Hill RA, Dundar Y, Bakhai A, Dickson R, Walley T. Drug-eluting stents: an early systematic review to inform policy. Eur Heart J 2004;25:902–19
97. Stone GW, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, Colombo A, Schampaert E, Grube E, Kirtane AJ, Cutlip DE, Fahy M, Pocock SJ, Mehran R, Leon MB. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. N Engl J Med 2007;356:998–1008
98. Kastrati A, Dibra A, Eberle S, Mehilli J, Suarez de Lezo J, Goy JJ, Ulm K, Schomig A. Sirolimus-eluting stents vs paclitaxel-eluting stents in patients with coronary artery disease: meta-analysis of randomized trials. JAMA 2005;294:819–25
99. Kandzari DE, Kandzari DE, Roe MT, Ohman EM, Milford-Beland S, Chen AY, Lytle BL, Cohen DJ, Smith SC, Harrington RA, Gibler WB, Peterson ED. Frequency, predictors, and outcomes of drug-eluting stent utilization in patients with high-risk non-ST-segment elevation acute coronary syndromes. Am J Cardiol 2005;96:750–5
100. Tsimikas S. Drug-eluting stents and late adverse clinical outcomes lessons learned, lessons awaited. J Am Coll Cardiol 2006;47:2112–5
101. Rodriguez AE, Mieres J, Fernandez-Pereira C, Vigo CF, Rodriguez-Alemparte M, Berrocal D, Grinfeld L, Palacios I. Coronary stent thrombosis in the current drug-eluting stent era: insights from the ERACI III trial. J Am Coll Cardiol 2006;47:205–7
102. Ong AT, Serruys PW. Drug-eluting stents: current issues. Tex Heart Inst J 2005;32:372–7
103. Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, Mihalcsik L, Tespili M, Valsecchi O, Kolodgie FD. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? Circulation 2004;109:701–5
104. Ong AT, Hoye A, Aoki J, van Mieghem CA, Rodriguez Granillo GA, Sonnenschein K, Regar E, McFadden EP, Sianos G, van der Giessen WJ, de Jaegere PP, de Feyter P, van Domburg RT, Serruys PW. 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
105. Lagerqvist B, James SK, Stenestrand U, Lindback J, Nilsson T, Wallentin L, SCAAR Study Group. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. N Engl J Med 2007;356:1009–19
106. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293:2126–30
107. FDA Public Health Web Notification: final update of information for physicians on sub-acute thromboses (SAT) and hypersensitivity reactions with use of the cordis CYPHER™ sirolimus-eluting coronary stent. U.S. Food and Drug Administration. October 18, 2004. Available at: http://www.fda.gov/cdrh/safety/cypher3.html. Accessed January 12, 2008
108. Bavry AA, Kumbhani DJ, Helton TJ, Bhatt DL. What is the risk of stent thrombosis associated with the use of paclitaxel-eluting stents for percutaneous coronary intervention: a meta-analysis. J Am Coll Cardiol 2005;45:941–6
109. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl J Med 2007;356:1020–9
110. Serruys PW, Daemen J. Are drug-eluting stents associated with a higher rate of late thrombosis than bare metal stents? Late stent thrombosis: a nuisance in both bare metal and drug-eluting stents. Circulation 2007;115:1433–9
111. Luscher TF, Steffel J, Eberli FR, Joner M, Nakazawa G, Tanner FC, Virmani R. Drug-eluting stent and coronary thrombosis: biological mechanisms and clinical implications. Circulation 2007;115:1051–8
112. Jaffe R, Strauss BH. Late and very late thrombosis of drug-eluting stents: evolving concepts and perspectives. J Am Coll Cardiol 2007;50:119–27
113. Finn AV, Joner M, Nakazawa G, Kolodgie F, Newell J, John MC, Gold HK, Virmani R. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation 2007;115:2435–41
114. Ferrari E, Benhamou M, Cerboni P, Marcel B. Coronary syndromes following aspirin withdrawal: a special risk for late stent thrombosis. J Am Coll Cardiol 2005;45:456–9
115. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193–202

116. Jeremias A, Sylvia B, Bridges J, Kirtane AJ, Bigelow B, Pinto DS, Ho KK, Cohen DJ, Garcia LA, Cutlip DE, Carrozza JP Jr. Stent thrombosis after successful sirolimus-eluting stent implantation. Circulation 2004;109:1930–2
117. Kerner A, Gruberg L, Kapeliovich M, Grenadier E. Late stent thrombosis after implantation of a sirolimus-eluting stent. Catheter Cardiovasc Interv 2003;60:505–8
118. McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, Suddath WO, Weissman NJ, Torguson R, Kent KM, Pichard AD, Satler LF, Waksman R, Serruys PW. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet 2004;364:1519–21
119. Karvouni E, Korovesis S, Katritsis DG. Very late thrombosis after implantation of sirolimus eluting stent. Heart 2005;91:e45
120. Waters RE, Kandzari DE, Phillips HR, Crawford LE, Sketch MH Jr. Late thrombosis following treatment of in-stent restenosis with drug-eluting stents after discontinuation of antiplatelet therapy. Catheter Cardiovasc Interv 2005;65:520–4
121. Kornowski R, Hong MK, Virmani R, Jones R, Vodovotz Y, Leon MB. Granulomatous 'foreign body reactions' contribute to exaggerated in-stent restenosis. Coron Artery Dis 1999;10:9–14
122. Farb A, Burke AP, Kolodgie FD, Virmani R. Pathological mechanisms of fatal late coronary stent thrombosis in humans. Circulation 2003;108:1701–6
123. 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
124. FDA Talk Paper. FDA advises physicians of adverse events associated with cordis cypher coronary stents. U.S. Food and Drug Administration. October 29, 2003. T03–T71. Available at: http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01257.html. Accessed January 12, 2008
125. ESC Congress 2006, Rapid News Summaries: pathology of drug-eluting stents (Virmani R). Available at: http://www.cardiosource.com/rapidnewssummaries/index.asp?EID=23&DoW=Mon&SumID=180. Accessed January 12, 2008
126. Virmani R, Farb A, Guagliumi G, Kolodgie FD. Drug-eluting stents: caution and concerns for long-term outcome. Coron Artery Dis 2004;15:313–8
127. Kotani J, Awata M, Nanto S, Uematsu M, Oshima F, Minamiguchi H, Mintz GS, Nagata S. Incomplete neointimal coverage of sirolimus-eluting stents: angioscopic findings. J Am Coll Cardiol 2006;47:2108–11
128. van Beusekom HM, Saia F, Zindler JD, Lemos PA, Swager-Ten Hoor SL, van Leeuwen MA, de Feijter PJ, Serruys PW, van der Giessen WJ. Drug-eluting stents show delayed healing: paclitaxel more pronounced than sirolimus. Eur Heart J 2007;28:974–9
129. Nebeker JR, Virmani R, Bennett CL, Hoffman JM, Samore MH, Alvarez J, Davidson CJ, McKoy JM, Raisch DW, Whisenant BK, Yarnold PR, Belknap SM, West DP, Gage JE, Morse RE, Gligoric G, Davidson L, Feldman MD. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. J Am Coll Cardiol 2006;47:175–81
130. 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
131. Gurbel PA, DiChiara J, Tantry US. Antiplatelet therapy after implantation of drug-eluting stents: duration, resistance, alternatives, and management of surgical patients. Am J Cardiol 2007;100:18M–25M
132. Babinska A, Markell MS, Salifu MO, Akoad M, Ehrlich YH, Kornecki E. Enhancement of human platelet aggregation and secretion induced by rapamycin. Nephrol Dial Transplant 1998;13:3153–9
133. Gurbel PA, Kandzari DE. Stent thrombosis associated with first-generation drug-eluting stents: issues with antiplatelet therapy. Neth Heart J 2007;15:148–50
134. Beohar N, Davidson CJ, Kip KE, Goodreau L, Vlachos HA, Meyers SN, Benzuly KH, Flaherty JD, Ricciardi MJ, Bennett CL, Williams DO. Outcomes and complications associated with off-label and untested use of drug-eluting stents. JAMA 2007;297:1992–2000
135. Fujii K, Carlier SG, Mintz GS, Yang YM, Moussa I, Weisz G, Dangas G, Mehran R, Lansky AJ, Kreps EM, Collins M, Stone GW, Moses JW, Leon MB. 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
136. Vermeersch P, Agostoni P, Verheye S, Van den Heuvel P, Convens C, Van den Branden F, Van Langenhove G, DELAYED RRISC (Death and Events at Long-term follow-up AnalYsis: Extended Duration of the Reduction of Restenosis In Saphenous vein grafts with Cypher stent) Investigators. Increased late mortality after sirolimus-eluting stents versus bare-metal stents in diseased saphenous vein grafts: results from the randomized DELAYED RRISC trial. J Am Coll Cardiol 2007;50:261–7
137. Dixon SR, Grines CL, O'Neill WW. The year in interventional cardiology. J Am Coll Cardiol 2007;50:270–85
138. Win HK, Caldera AE, Maresh K, Lopez J, Rihal CS, Parikh MA, Granada JF, Marulkar S, Nassif D, Cohen DJ, Kleiman NS, EVENT Registry Investigators. Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. JAMA 2007;297:2001–9
139. Park DW, Park SW, Park KH, Lee BK, Kim YH, Lee CW, Hong MK, Kim JJ, Park SJ. Frequency of and risk factors for stent thrombosis after drug-eluting stent implantation during long-term follow-up. Am J Cardiol 2006;98:352–6
140. 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;113:2803–9
141. Ellis SG, Colombo A, Grube E, Popma J, Koglin J, Dawkins KD, Stone GW. Incidence, timing, and correlates of stent thrombosis with the polymeric paclitaxel drug-eluting stent: a TAXUS II, IV, V, and VI meta-analysis of 3,445 patients followed for up to 3 years. J Am Coll Cardiol 2007;49:1043–51
142. Kuchulakanti PK, Chu WW, Torguson R, Ohlmann P, Rha SW, Clavijo LC, Kim SW, Bui A, Gevorkian N, Xue Z, Smith K, Fournadjieva J, Suddath WO, Satler LF, Pichard AD, Kent KM, Waksman R. Correlates and long-term outcomes of angiographically proven stent thrombosis with sirolimus- and paclitaxel-eluting stents. Circulation 2006;113:1108–13
143. Eisenstein EL, Anstrom KJ, Kong DF, Shaw LK, Tuttle RH, Mark DB, Kramer JM, Harrington RA, Matchar DB, Kandzari DE, Peterson ED, Schulman KA, Califf RM. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. JAMA 2007;297:159–68
144. Kaul S, Shah PK, Diamond GA. As time goes by: current status and future directions in the controversy over stenting. J Am Coll Cardiol 2007;50:128–37
145. Nordmann AJ. Safety of drug-eluting stents: insights from meta-analysis. Hotline and clinical trial updates. European Society of Cardiology. Available at: http://www.escardio.org/knowledge/congresses/CongressReports/hotlinesandctus/707009_Camenzind.htm. Accessed January 12, 2008
146. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. Circulation 2007;115:1440–55
147. Pfisterer M, Brunner-La Rocca HP, Buser PT, Rickenbacher P, Hunziker P, Mueller C, Jeger R, Bader F, Osswald S, Kaiser C, 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;48:2584–91
148. Laskey WK, Yancy CW, Maisel WH. Thrombosis in coronary drug-eluting stents: report from the meeting of the circulatory system medical devices advisory panel of the food and drug administration center for devices and radiologic health, December 7–8, 2006. Circulation 2007;115:2352–7
149. Wenaweser P, Dorffler-Melly J, Imboden K, Windecker S, Togni M, Meier B, Haeberli A, Hess OM. Stent thrombosis is associated with an impaired response to antiplatelet therapy. J Am Coll Cardiol 2005;45:1748–52
150. Nguyen TA, Diodati JG, Pharand C. Resistance to clopidogrel: a review of the evidence. J Am Coll Cardiol 2005;45:1157–64

151. Gum PA, Kottke-Marchant K, Welsh PA, White J, Topol EJ. A prospective, blinded determination of the natural history of aspirin resistance among stable patients with cardiovascular disease. J Am Coll Cardiol 2003;41:961–5
152. Ajzenberg N, Aubry P, Huisse MG, Cachier A, El Amara W, Feldman LJ, Himbert D, Baruch D, Guillin MC, Steg PG. Enhanced shear-induced platelet aggregation in patients who experience subacute stent thrombosis: a case-control study. J Am Coll Cardiol 2005;45:1753–6
153. Gurbel PA, Bliden KP, Hayes KM, Yoho JA, Herzog WR, Tantry US. The relation of dosing to clopidogrel responsiveness and the incidence of high post-treatment platelet aggregation in patients undergoing coronary stenting. J Am Coll Cardiol 2005;45:1392–6
154. Cotter G, Shemesh E, Zehavi M, Dinur I, Rudnick A, Milo O, Vered Z, Krakover R, Kaluski E, Kornberg A. Lack of aspirin effect: aspirin resistance or resistance to taking aspirin? Am Heart J 2004;147:293–300
155. Wang TH, Bhatt DL, Topol EJ. Aspirin and clopidogrel resistance: an emerging clinical entity. Eur Heart J 2006;27:647–54
156. Eikelboom JW, Hirsh J, Weitz JI, Johnston M, Yi Q, Yusuf S. Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events. Circulation 2002;105:1650–5
157. Taubert D, Kastrati A, Harlfinger S, Gorchakova O, Lazar A, von Beckerath N, Schomig A, Schomig E. Pharmacokinetics of clopidogrel after administration of a high loading dose. Thromb Haemost 2004;92:311–6
158. Bates ER, Lau WC, Bleske BE. Loading, pretreatment, and interindividual variability issues with clopidogrel dosing. Circulation 2005;111:2557–9
159. Bailey DG, Dresser GK. Interactions between grapefruit juice and cardiovascular drugs. Am J Cardiovasc Drugs 2004;4:281–97
160. Saw J, Steinhubl SR, Berger PB, Kereiakes DJ, Serebruany VL, Brennan D, Topol EJ, Clopidogrel for the Reduction of Events During Observation Investigators. Lack of adverse clopidogrel-atorvastatin clinical interaction from secondary analysis of a randomized, placebo-controlled clopidogrel trial. Circulation 2003;108:921–4
161. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation 2003;107:2908–13
162. Hankey GJ, Eikelboom JW. Aspirin resistance. Lancet 2006;367:606–17
163. Faraday N, Yanek LR, Mathias R, Herrera-Galeano JE, Vaidya D, Moy TF, Fallin MD, Wilson AF, Bray PF, Becker LC, Becker DM. Heritability of platelet responsiveness to aspirin in activation pathways directly and indirectly related to cyclooxygenase-1. Circulation 2007;115:2490–6
164. Lamba JK, Lin YS, Schuetz EG, Thummel KE. Genetic contribution to variable human CYP3A-mediated metabolism. Adv Drug Deliv Rev 2002;54:1271–94
165. Lau WC, Gurbel PA, Watkins PB, Neer CJ, Hopp AS, Carville DG, Guyer KE, Tait AR, Bates ER. Contribution of hepatic cytochrome P450 3A4 metabolic activity to the phenomenon of clopidogrel resistance. Circulation 2004;109:166–71
166. Rabbat MG, Bavry AA, Bhatt DL, Ellis SG. Understanding and minimizing late thrombosis of drug-eluting stents. Cleve Clin J Med 2007;74:129–36
167. Farb A, Boam AB. Stent thrombosis redux—the FDA perspective. N Engl J Med 2007;356:984–7
168. Holmes DR Jr, Kereiakes DJ, Laskey WK, Colombo A, Ellis SG, Henry TD, Popma JJ, Serruys PW, Kimura T, Williams DO, Windecker S, Krucoff MW. Thrombosis and drug-eluting stents: an objective appraisal. J Am Coll Cardiol 2007;50:109–18
169. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:989–97
170. Babapulle MN, Joseph L, Belisle P, Brophy JM, Eisenberg MJ. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents. Lancet 2004;364:583–91
171. Kastrati A, Mehilli J, Pache J, Kaiser C, Valgimigli M, Kelbaek H, Menichelli M, Sabate M, Suttorp MJ, Baumgart D, Seyfarth M, Pfisterer ME, Schomig A. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:1030–9
172. Bavry AA, Kumbhani DJ, Helton TJ, Borek PP, Mood GR, Bhatt DL. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. Am J Med 2006;119:1056–61
173. Daemen J, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, Kukreja N, Juni P, Sianos G, Hellige G, van Domburg RT, Hess OM, Boersma E, Meier B, Windecker S, Serruys PW. 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;369:667–78
174. Machecourt J, Danchin N, Lablanche JM, Fauvel JM, Bonnet JL, Marliere S, Foote A, Quesada JL, Eltchaninoff H, Vanzetto G, 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;50:501–8
175. Carrozza JP Jr. Duration of clopidogrel therapy with drug-eluting stents. J Interv Cardiol 2006;19(suppl):S40–S6
176. Maisel WH. Unanswered questions—drug-eluting stents and the risk of late thrombosis. N Engl J Med 2007;356:981–4
177. Baim DS. Real-world use of the TAXUS Drug-eluting stent system. Available at: http://www.taxus-stent.com/usa/hcp_fda_info.html. Accessed January 28, 2007
178. Popma JJ, Weiner B, Cowley MJ, Simonton C, McCormick D, Feldman T. FDA advisory panel on the safety and efficacy of drug eluting stents: summary of findings and recommendations. Available at: http://www.theheart.org/documents/satellite_programs/cybersessions/760859/FDA_Advisory_Panel.pdf. Accessed on January 12, 2008
179. Popma JJ, Berger P, Ohman EM, Harrington RA, Grines C, Weitz JI. Antithrombotic therapy during percutaneous coronary intervention: the seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 2004;126(3 suppl):576S–99S
180. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC Jr, American College of Cardiology, American Heart Association, Canadian Cardiovascular Society. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary. A report of the American college of cardiology/American heart association task force on practice guidelines (Writing Committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). J Am Coll Cardiol 2004;44:671–719
181. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, Jacobs AK, Kern MJ, King SB III, Morrison DA, O'neill WW, Schaff HV, Whitlow PL, Williams DO, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B, American College of Cardiology/American Heart Association Task Force on Practice Guidelines, ACC/AHA/SCAI writing committee to update the 2001 Guidelines for Percutaneous Coronary Intervention. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention-Summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). J Am Coll Cardiol 2006;47:216–35
182. Silber S, Albertsson P, Aviles FF, Camici PG, Colombo A, Hamm C, Jorgensen E, Marco J, Nordrehaug JE, Ruzyllo W, Urban P, Stone GW, Wijns W, Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Guidelines for percutaneous coronary interventions. The task force for percutaneous coronary interventions of the European Society of Cardiology. Eur Heart J 2005;26:804–47
183. Grines CL, Bonow RO, Casey DE Jr, Gardner TJ, Lockhart PB, Moliterno DJ, O'Gara P, Whitlow P, American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, American Dental Association, American College of Physicians. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. Circulation 2007;115:813–8

184. Devereaux PJ, Goldman L, Yusuf S, Gilbert K, Leslie K, Guyatt GH. Surveillance and prevention of major perioperative ischemic cardiac events in patients undergoing noncardiac surgery: a review. CMAJ 2005;173:779–88
185. Hutter AM Jr, Lincoff M, Grines C, Bhatt D. ACC conversations with experts: preventing late thrombosis of drug-eluting stents. Available at: http://conversations.acc.org/modules/conv/acc/0607c/main.asp?bhcp=1. Accessed January 12, 2008
186. Rabbat MG, Bavry AA, Bhatt DL, Ellis SG. Understanding and minimizing late thrombosis of drug-eluting stents. Cleve Clin J Med 2007;74:129–36
187. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleishmann KE, Freeman WK, Froehlich JB, Kasper E, Kersten JR, Riegel B, Robb JF. ACC/AHA 2007 Guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Circulation 2007;116:1971–96
188. Virmani R. Next generation technologies—preclinical phase (TCTMD lecture)

CME Coronary Artery Stents: II. Perioperative Considerations and Management

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The management of patients with coronary artery stents during the perioperative period is one of the most important patient safety issues clinicians confront. Perioperative stent thrombosis is a life-threatening complication for patients with either bare-metal or drug-eluting stents. Noncardiac surgery appears to increase the risk of stent thrombosis, myocardial infarction, and death, particularly when patients undergo surgery early after stent implantation. The incidence of complications is further increased when dual-antiplatelet therapy is discontinued preoperatively. It is generally agreed that aspirin must be continued throughout the perioperative period, except in circumstances when the risk of bleeding significantly outweighs the benefit of continued anticoagulation, such as procedures performed in a closed space. We present considerations for regional anesthesia, as well as postoperative recommendations as the occurrence of perioperative stent thrombosis appears to be greatest during this period. Immediate percutaneous coronary intervention is the definitive treatment for perioperative stent thrombosis, and 24-h access to an interventional cardiology suite should be readily available. Algorithms for perioperative management of patients with bare-metal and drug-eluting stents are proposed.
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Nearly 23 yr after the first percutaneous coronary interventions (PCIs) were performed, reports of deleterious outcomes in patients undergoing noncardiac surgery who had previously undergone PCI appeared in the literature.[1] Of the more than 2 million patients undergoing PCI annually, more than 90% will receive one or more intracoronary stents.[2] Approximately 5% of patients in this group will undergo noncardiac surgery within the first year after stenting, and an increasing number will continue to present for surgery thereafter.[3] Because success of the stents requires long-term antiplatelet therapy, management of patients with these devices poses a dilemma to the anesthesiologist. This is Part II in a series that reviews perioperative issues and management related to coronary artery stents relevant to the anesthesiologist.

CORONARY ARTERY STENTS AND NONCARDIAC SURGERY

Discontinuation of antiplatelet therapy relatively soon after PCI with stenting confers significant morbidity and mortality during noncardiac surgery (Tables 1 and 2). Because stent endothelialization may not yet be complete at the time of surgery, abrupt discontinuation of clopidogrel and aspirin combined with the prothrombotic state induced by surgery increases the risk of acute perioperative stent thrombosis and abrupt vessel closure, leading to significant morbidity and mortality (Fig. 1). Kaluza et al. reported 7 myocardial infarctions (MIs) and 8 major bleeding episodes in patients who underwent elective noncardiac surgery <14 days after PCI with bare-metal stenting (BMS)[1] (Table 1). Mortality occurred in six of the patients who suffered postoperative MIs and in two of the patients who developed major postoperative bleeding. Moreover, patients who stopped all or part of their antiplatelet regimen preoperatively died. In two patients who underwent immediate cardiac catheterization, stent thrombosis was confirmed angiographically, and was presumed to occur in the remaining patients who suffered MIs diagnosed by electrocardiographic criteria. Despite the 2002 American Heart Association/American College of Cardiology (AHA/ACC) guidelines, which recommended a 4–6 wk interval between BMS and noncardiac surgery "to allow 4 full weeks of dual-antiplatelet therapy and re-endothelialization of the stent to be completed, or nearly so," reports of perioperative morbidity and mortality continued to be published[4–9] (Table 1). Sharma et al. reported an 85.7% mortality rate among patients who stopped thienopyridine therapy and underwent surgery within 3 wk of BMS implantation.[6] Wilson et al. reported 4% morbidity and 3% mortality rates among patients who stopped dual-antiplatelet therapy preoperatively and underwent surgery within 6 wk of BMS placement.[7] The authors

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Table 1. Percutaneous Coronary Intervention with Bare-Metal Stenting and Noncardiac Surgery

Study author	Type of study	No. of patient/ date	Type of PCI	Time from PCI to surgery	Surgical procedures	Antiplatelet therapy	Perioperative management of dual antiplatelet therapy	Outcome and time to adverse cardiac event
Kaluza et al. 2000[1]	CS	40 (1996–98)	BMS	1–39 d average 13 d	General 10% Cardiac 2.5% Thoracic 5% Vascular 75% Urologic 7.5%	100% patients received >1 dose of ticlopidine after PCI 100% patients were receiving ASA before PCI Dual APT was continued for variable period of time after PCI 9 patients received abciximab during PCI	Management for patients with MI/death (n = 9) 8/9: ASA withheld 0–2 d preop 6/9 ticlopidine discontinued 0–2 d preop 1/9 dual APT continued 31/40 most had dual-APT discontinued 0–1 day preop & restarted 0–1 day postop	Death (n = 8, 20%); MI (n = 7, 18%, 6 fatal, 1 nonfatal); 4/7 MI occurred within 24 hr postop 11 major bleeding episodes (28%, 6 in patients who died) All deaths, MI, 8/11 bleeding episodes occurred in patients who underwent surgery within 14 d of PCI; death/MI occurred within 6 d of PCI
Vicenzi et al. 2001[5]	CR	1 (2000)	BMS	32 d	Urologic	Aspirin only	ASA stopped 5 d preop and LMWH administered	MI 2 hr postop; PCI performed with successful recanalization of stent
Wilson et al. 2003[7]	R	207 (1990–2000)	BMS	1–60 d	Vascular 57.8% Orthopedic 7.8% Genitourinary 5.8% General 8.3% Thoracic 7.3% Head/neck 4.4% Breast 2.4% Other 5.8%	All patients started on ASA/heparin prior to procedure 1995: ticlopidine started before PCI and continued with ASA 2–4 post-PCI 1998: clopidogrel substituted and continued with ASA for 2–4 wks	At time of surgery: ASA/thieno 27% (n = 54) ASA continued/ thieno stopped <10 d before surgery 14% (n = 29) ASA/Warfarin 2% (n = 4) ASA alone 51% (n = 104) No APT/ACT for >10 d 6% (n = 13)	Death/MI/stent thrombosis 4% (n = 8) All adverse cardiac events occurred in patients who underwent surgery within 6 wks of PCI No adverse cardiac events in patients who underwent surgery 7–9 wks after PCI 2 patients with excessive bleeding (1 ASA only; 1 ASA/Thieno) 43% (n = 23) patients on ASA/thieno received transfusion – all related to PCI complications 7/8 adverse events – on thieno/ASA
Marcucci et al. 2004[8]	CR	1 (2003)	BMS (1-LAD; 1 LCx)	6 wk	Thoracic	Dual APT with ASA/ clopidogrel for 4 wk	Clopidogrel stopped 2 wk preop; ASA continued	MI secondary to LAD stent thrombosis 1 hour postop; PCI performed with successful recanalization patient died of cardiogenic chock 4 d later
Sharma et al. 2004[6]	R	47 (1995–2000)	BMS	All patients: <90 d– 27 pts <3 wk 20 pts >3 wk	Vascular GI Urologic Cancer Ortho No difference between groups (<3 wk vs >3 wk)	Dual APT 2–4 wk 1995–98: ASA/ticlopidine 1998–2000: ASA/ clopidogrel	<3 wk: 7/27 patients stopped thieno 5+ d preop >3 wk: 6/20 patients stopped thieno 5+ d preop	<3 wk: 6/7 patients off thieno died (85.7% mortality); 1 patient died while on dual APT >3 wk: 1/6 patients off thieno died (16.6% mortality); 2 patients suffered non-STEMI (no thieno); all deaths occurred early postop (<17 d) No difference in bleeding between patients on/off thieno

(*Continued*)

Table 1. Continued

Study author	Type of study	No. of patient/ date	Type of PCI	Time from PCI to surgery	Surgical procedures	Antiplatelet therapy	Perioperative management of dual antiplatelet therapy	Outcome and time to adverse cardiac event
Reddy et al. 2005[9]	R	56 (1993–2004)	BMS	0–14 d: 8 pts 15–42 d: 8 pts >42 d: 40 pts	Vascular 20% Abdominal 18% Ortho 13% Ophtho 11% GYN/GU 11% ENT 7% Neuro 7% Transplant 5%	21%-GPIIb/IIIa inhibitors 14%-heparin 98%-on ASA after PCI 96%-on clopidogrel after PCI	79% taking ASA; 32% clopidogrel Time to discontinuation of ASA/ clopidogrel not reported	0–14 d: 2 MI, 1 death, 1 major bleeding 15–42 d: 4 MI, 3 deaths, 2 major bleeding >42 d: no adverse events of patients with MI/death 60% taking ASA and 60 taking clopidogrel (patients no specified)
Vicenzi et al. 2006[3]	P/O	103 (2001–2004)	25 BMS 5 DES 79 cases: stent type not reported	Within 1 yr Vascular 25.2% ENT 2.9% Orthopedic 6.8% Reconstructive 7.8% Neurologic 3.9% Thoracic 1.9% Other 11.7%	General 26.2% Urologic 13.6%	ASA plus clopidogrel	ASA plus clopidogrel either continued throughout periop period or stopped <3 d preop 100% patients received either UFH or LMWH in therapeutic doses	Cardiac complications 44%; death 5%; MI 13%; myocardial cell injury 22%; bleeding 4% All cardiac complications occurred within 60 d of PCI 2.11-fold risk of suffering cardiac event <25 d after PCI v >90 d after PCI
Brichon et al. 2006[34]	R	32 (1999–2004)	32 pts–all BMS	<30 d 22% 30–60 d 53% 61–90 d 25%	Lobectomy 84% Pneumonectomy 16%	ASA plus clopidogrel	Periop heparin 34% (ASA discontinued) Periop heparin/ ASA 66% Clopidogrel stopped in all pts 7–10 d before surgery	1 pt: postop MI (31 d after BMS)–no PCI 1 pt: postop MI (90 d after BMS)–no PCI 1 pt: postop MI (44 d after BMS)–PCI, then MI and death

CS = case series; CR = case report; R = retrospective study; P/O = prospective/observational study; L = letter.

BMS = bare-metal stent; DES = drug-eluting stent; LAD = left anterior descending artery; LCx = left circumflex artery.

PCI = percutaneous coronary intervention; ASA = aspirin; APT = antiplatelet therapy; LMWH = low molecular weight heparin; ACT = anticoagulation therapy; MI = myocardial infarction; Thieno = thienopyridine; SES = sirolimus-eluting stent; PES = paclitaxel-eluting stent; UFH = unfractionated heparin; RCA = right coronary artery; OM = obtuse marginal artery; ENT = ear, nose, throat; GYN = gynecological; GU = genitourinary; GI = gastrointestinal.

recommended a 6-wk course of dual-antiplatelet therapy, presuming that BMS endothelialization would be completed during this time, thereby preventing perioperative stent thrombosis and its sequelae. The most powerful predictor of acute stent thrombosis in BMS is a time delay of <14 days between implantation and interruption of dual-antiplatelet therapy.[10] The current 2007 ACC/AHA Perioperative Guidelines state BMS thrombosis is exceedingly rare more than 4 wk after insertion.[11–13] However, Doyle et al. suggest otherwise.[14] In their retrospective study of 4503 patients, the investigators found a 2% cumulative incidence in BMS thrombosis at 10 yr, which was increased among patients considered "off-label" for drug-eluting stent (DES) use ($P = 0.024$). Very late (>12 mo) BMS thrombosis was also associated with increased risk of death ($P < 0.001$). However, the authors did not mention whether any of these cases occurred perioperatively.

Numerous publications of perioperative morbidity and mortality in patients with DES, coupled with clinical and pathology reports of incomplete stent endothelialization, suggest that acute stent thrombosis, MI, and death may be more prevalent than previously thought with these devices, particularly when dual-antiplatelet therapy is interrupted perioperatively[15–43] (Table 2). Currently, there are no available diagnostic tests to determine whether adequate stent endothelialization has occurred. Cook et al. performed intravascular ultrasound in 13 patients with very late (>1 yr) DES thrombosis, and found a high prevalence of incomplete stent apposition in these devices ($P < 0.001$).[44] The authors suggested that this finding may play a role in delaying endothelialization and causing thrombus formation. Of interest, three patients who developed perioperative stent thrombosis after discontinuation of dual-antiplatelet therapy were included in this study. Perioperative stent thrombosis can occur as late as 4 yr after DES insertion, despite prolonged periods of dual-antiplatelet therapy.[41] Artang and Dieter reviewed 36 cases of late stent thrombosis in patients receiving DES and found a strong association between late stent thrombosis (>30 days after deployment) and cessation of dual-antiplatelet therapy[45] (Fig. 2). The median time from stent deployment to an adverse clinical event (MI, death) was 242 days (range, 39–927 days). Overall, 55% of patients discontinued both clopidogrel and aspirin treatment, and 86.3% of patients

Table 2. Percutaneous Coronary Intervention with Drug-Eluting Stents and Noncardiac Surgery

Study author	Type of study	No. of patient/ date	Type of PCI	Time from PCI to surgery	Surgical procedures	Antiplatelet therapy	Perioperative management of dual antiplatelet therapy	Outcome and time to adverse cardiac event
Fleron et al. 2003[25]	CR	1 (2003)	2-SES	3 mo	Mastectomy	Dual APT with ASA/ clopidogrel for 3 mo–course completed	Clopidogrel/ ASA stopped 9 d prior to procedure	MI and cardiogenic shock postop
Auer et al. 2004[26]	CR	1 (2003)	1 BMS (RCA)	12 wk	Orthopedic	6-mo course ASA/ clopidogrel	Dual APT discontinued after 3 mo of therapy (length of cessation not reported)	MI occurred 2 hours postop–PCI performed: both PES occluded and recanalized; BMS patient–no therapy needed
McFadden et al. 2004[27]*	CS	4 (2004)	2 pts: 1 SES 2 ptt: 1 PES	331–442 d	Urologic General GI endoscopy	ASA plus clopidogrel	1 patient with SES: stopped dual APT other 3 patients stopped clopidogrel, taking ASA only	Stent thrombosis and MI occurred in all 4 patients 4–14 d after discontinuation of ASA/ clopidogrel (4–5 d postop) PCI performed with successful recanalization in all 4 cases 1 patient also had BMS which was patent
Nassar et al. 2005[28]	CR	2 (2004)	1 pt: 2 SES (RCA) 1 pt: 1 SES (LAD)	4 mo 21 mo	Excisional biopsy supraclavicular node Total hip replacement	Clopidogrel 1 mo; lifetime ASA Not reported	ASA stopped 10 d prior ASA stopped, but time not reported	2 hours postop: cardiogenic chock–emergent PCI, recanalized occluded RCA-SES, patient died 4 d later 11 d postop: cardiogenic shock, PCI performed with canalization to LAD-SES
Herbstreit et al. 2005[31]	CR	114 (2004–2006)	Not specified	1 mo	Vascular	ASA plus clopidogrel	Platelet transfusion (2 pooled concentrates) prior to neuraxial block	No complications
Charbuchinska et al. 2006[32]	CS	15 (18 procedures) 2006	7 pts: PES 7 pts: SES	1–12 mo 1 pt: 2 PES + 1 SES 3 pts: not reported	Vascular	All taking ASA preop; 14 taking clopidogrel preop	ASA stopped before 3 procedures (7–10 d) Clopidogrel stopped before 10 procedures (3–28 d) LMWH begun 5 d before 14 procedures	Death due to sepsis with peak troponi n = 11.53 mcg/L (SES implanted for 6 mo; ASA only continued) Two pts with troponin leaks, but no other abnormalities No complications in 11/15 pts, no excess bleeding

(*Continued*)

Table 2. Continued

Study author	Type of study	No. of patient/ date	Type of PCI	Time from PCI to surgery	Surgical procedures	Antiplatelet therapy	Perioperative management of dual antiplatelet therapy	Outcome and time to adverse cardiac event
Broad et al. 2007[143]	CS	3 (2006)	1 pt: PES (1st Dx), BMS (LAD)	49 d	Parathyroidectomy	ASA plus clopidogrel	Clopidogrel stopped 5 d preop	No complications in any patient
			1 pt: PES (LAD)	1 yr	Microlaryngoscopy/ vocal cord biopsy	ASA plus clopidogrel	Tirofiban (GPIIb/IIa inhibitor) started 3 d preop 6 h preop: tirofiban/ heparin discontinued ASA continued periop Postop day 1: clopidogrel loading dose, followed by maintenance dose thereafter	Patient 3 previously presented for subacromial decompression 18 mo after DES–clopidogrel was stopped, and the patient suffered a preop MI 7 d after clopidogrel stopped
			1 pt: PES (RCA)	33 mo	ENT/GU/Ortho	ASA plus clopidogrel		
de Souza 2007[40]	CR	1 (2006)	2 PES (1 LCx, 1 LAD)	29 mo	Nephroureterectomy	ASA plus clopidogrel for 1 yr, then ASA	ASA stopped 10 d preop	70 min in PACU: ventricular tachycardia, then ST changes indicating posterior MI, then cardiogenic shock PCI recanalized thrombosed LCx stent
Head et al. 2007[33]	CR	2 (2006)	1 pt: PES (2-RCA, 1-OM)	8 mo	Renal transplant	ASA plus clopidogrel	ASA plus clopidogrel stopped 7 d preop	MI 1 hr postop–PCI recanalized, thrombosed RCA stents
			1 pt: 2 DES-RCA, 2DES-LCx, 1 BMS-PDA	6 mo	Kidney–pancreas transplant	Lifelong ASA/ clopidogrel therapy	ASA plus clopidogrel stopped 1 day preop, ASA resumed POD1, clopidogrel resume POD2	No cardiac complications; patient suffered significant postoperative bleeding
Chung et al. 2007[35]	L		1 DES (LAD)	6 mo	Cervical medianoscopy	ASA plus clopidogrel	ASA plus clopidogrel stopped 7 d preop	Postop: emergent PCI for LAD thrombosis with unsuccessful canalization–death ensued
Bakhru et al. 2006[36]	R	114 (2004–2006)	DES	11.4%: 90 d 30.7%: 180 d 1 pt: 33 d 1 pt: 287 d	Not specified	ASA plus clopidogrel	ASA plus clopidogrel discontinued at 10 d in 77%	2 MI in 2 pts: thrombosis not seen by catheterization
Compton et al. 2006[37]	R	38 (2003–2006)	57% SES 43% PES	10% 0–30 d 26% 30–180 d 34% 180–365 d 30% >365 d	28 pts: 34% abdominal, 22% vascular, 17% urological, 27% other 10 pts: minor procedures	ASA plus clopidogrel	78% major cases: ASA continued 41% major cases: clopidogrel continued 94% minor cases: ASA continued 39% minor cases: ASA continued	No thrombotic or bleeding complications

(*Continued*)

Table 2. Continued

Study author	Type of study	No. of patient/ date	Type of PCI	Time from PCI to surgery	Surgical procedures	Antiplatelet therapy	Perioperative management of dual antiplatelet therapy	Outcome and time to adverse cardiac event
Vichova et al. 2007[38]	PRegist	215 (2003–2007)	175 BMS 156 DES	DES 6–12 mo BMS 4 mo–16 yr s	Not reported	ASA plus clopidogrel	6 ± 4 d preop: ASA stopped in 26% and clopidogrel stopped in 24%	3.25% (7 pts) developed stent thrombosis and MI, death occurred in 5 of these patients; ST occurred in both types of stents 4.65% (10 pts) died within 60 d after surgery
Varani et al. 2007[41]	CR	1 (2006)	1 PES (LAD)	47 mo	Right hip arthroplasty	ASA plus ticlopidine	Ticlopidine stopped 5 d preop	Anterior MI–PCI recanalized thrombosed LAD stent; BMS in OM branch patent
Schouten et al. 2007[42]	PRegist	192 (1999–2005)	48% BMS 52% DES	Within 2 yr of PCI	Abdominal 16% Vascular 16% Ophtho 12% Urologic 13% Ortho 12% Other 31%	ASA plus clopidogrel	30 (16%): early surgery = occurring before dual APT completed 162 (84%): late surgery = occurring after dual APT completed	Early surgery group: 13.3% had MI or death (all had APT = 30.7% event rate) Late surgery group: 0.6% had MI or death

CS = case series; CR = case report; R = retrospective study; P/O = prospective/observational study; L = letter; P Regist = prospective registry; BMS = bare-metal stent; DES = drug-eluting stent; LAD = left anterior descending artery; LCx = left circumflex artery; PCI = percutaneous coronary intervention; ASA = aspirin; APT = antiplatelet therapy; LMWH = low molecular weight heparin; ACT = anticoagulation therapy; MI = myocardial infarction; Thieno = thienopyridine; SES = sirolimus-eluting stent; PES = paclitaxel-eluting stent; UFH = unfractionated heparin; RCA = right coronary artery; OM = obtuse marginal artery; DX = diagonal; PDA = posterior descending artery; GU = genitourinary; POD = postoperative day; PACU = postanesthesia care unit.

stopped clopidogrel after the recommended duration for dual-antiplatelet therapy (3 mo for sirolimus-eluting stents; 6 mo for paclitaxel-eluting stents). When clopidogrel alone was discontinued, the median time to an adverse clinical event was 30 days (range, 14–690 days). In comparison, if both aspirin and clopidogrel were stopped, the median time to an adverse clinical event was 7 days (3–150 days, $P < 0.0001$). Forty-two percent of events occurred in relation to a surgical procedure in which dual-antiplatelet therapy or clopidogrel alone were discontinued. The morbidity and mortality rates were 92% and 8%, respectively. There was no difference in occurrence between sirolimus- and paclitaxel-eluting stents. The authors recommended the perioperative continuation of aspirin.

THE PERIOPERATIVE DILEMMA

Patients with coronary stents, particularly DES, who subsequently present for noncardiac surgery, pose a particular challenge during the perioperative period. Clinicians must balance the risks of discontinuing antiplatelet drugs and increasing the possibility of perioperative stent thrombosis, MI, and cardiac death against continuing clopidogrel and aspirin, thus increasing the potential for surgical bleeding, which in certain cases may be life-threatening. Patients who discontinue dual-antiplatelet therapy prematurely have higher rates of rehospitalization and mortality when compared with those who continue therapy.[46] Surgery performed early after DES implantation is associated with a significantly increased incidence of perioperative MI and death, regardless of whether clopidogrel and aspirin are continued.[47,48] Moreover, a patient may complete the recommended 12-mo duration of antiplatelet therapy yet still be at risk for perioperative stent thrombosis, MI, and death. Some institutions treat patients with dual-antiplatelet therapy for 12–24 mo, and in cases where there are additional stent complexities and comorbidities (Table 3), clopidogrel and aspirin are continued indefinitely.[4,47,49] This complicates management since 60%–70% of patients are receiving DES for "off-label" or unapproved use (Table 3), which further increases the risk of catastrophic stent thrombosis, MI, and death.[33,50–54] Chassot et al. contend, based on the currently available data, that the risks of withdrawing patients from antiplatelet drugs are greater than continuing them, imposing a perioperative cardiac death rate that is increased 5- to 10-times.[55]

Surgical intervention creates a prothrombotic and proinflammatory state conducive to development of perioperative stent thrombosis. The stress response to surgery includes sympathetic activation and cytokine

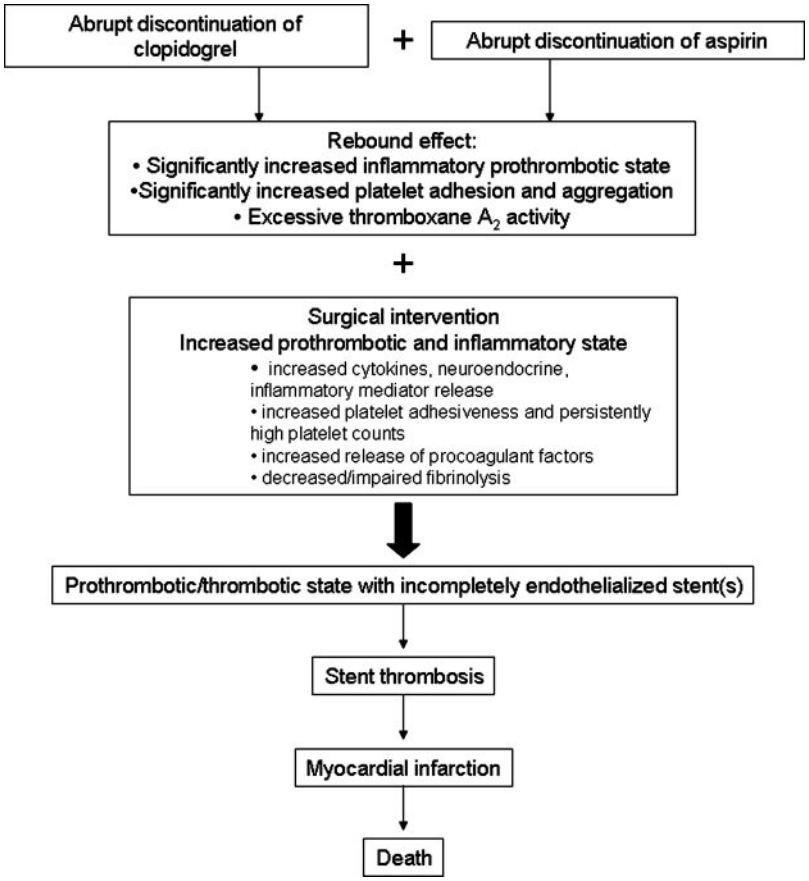

Figure 1. Diagram of the pathophysiology of acute perioperative stent thrombosis.

release that promote shear stress on arterial plaques, enhanced vascular reactivity conducive to vasospasm, reduced fibrinolytic activity, increased platelet activation, and hypercoagulability.[56,57] Significant increases in platelet counts may still be observed a week postoperatively.[58] While procoagulant clotting factors increase, fibrinolysis is impaired, producing a hypercoagulable state, which persists for several days postoperatively.[8,59] This environment far exceeds the prothrombotic state observed in acute coronary syndromes (ACS) in the absence of any surgical stimulation.[60] Inflammatory activation from endothelial damage, during both PCI and surgery, exacerbates the prothrombotic state, worsening the susceptibility for thromboembolic events. Autopsy results have shown this mechanism is responsible for at least half of all perioperative MIs.[48,61] Despite this milieu, surgeons often stop all antiplatelet drugs preoperatively, regardless of their patients' comorbidities, to minimize intraoperative bleeding.

Withdrawal of oral antiplatelet drugs is an independent predictor of mortality in patients with ACS and those at risk for coronary artery disease (CAD).[62,63] Abrupt cessation of aspirin results in a rebound phenomenon, whereby both cyclooxygenase-1 and thromboxane B_2 (the product of thromboxane A_2 [TxA_2] hydrolysis) levels increase rapidly, not returning to baseline for 3–4 days.[64] Complete recovery of platelet function occurs in half of patients by day 3, and 80% of patients by day 4.[65] These patients subsequently generate increased levels of thrombin and decrease fibrinolysis, further enhancing platelet aggregation and worsening the risk for perioperative stent thrombosis, MI, and death. Collet et al. prospectively studied 1358 patients admitted with ACS and found a two-fold increase in both death and death/MI among recent withdrawers compared with chronic users and nonusers.[66] Recent withdrawers comprised 5% of the patients who presented with ACS, having interrupted aspirin monotherapy <3 wk of admission. Of this group, 57.5% had known CAD, and 64% had discontinued aspirin for scheduled surgery. Multivariate analysis found aspirin withdrawal to be a strong independent predictor (OR = 2.02, $P = 0.003$) of mortality and death/MI at 30 days. Aspirin interruption was also found to be an independent predictor for bleeding events (OR = 2.6, $P < 0.01$). Ferrari et al. found, in 383 patients with established CAD hospitalized with recurrent ACS, 13.3% of events occurred 10.9 ± 1.9 days (range, 4–17 days) after abrupt aspirin withdrawal.[67] Ten (20%) patients developed thrombosis of a BMS implanted 15.5 ± 6.5 mo earlier, which accounted for 50% of the ST-segment elevation MIs (STEMIs) diagnosed. Aspirin was interrupted in 20 patients (40%) for minor surgery or dental treatment. Biondi-Zoccai et al. performed a meta-analysis of 50,279 patients at risk for CAD and found aspirin nonadherence/withdrawal was associated with a three-fold increase in the risk of death and MI (OR = 3.14, $P = 0.0001$).[63] The risk was significantly higher in patients with intracoronary stents (OR = 89.78, $P < 0.001$). Although the data from these

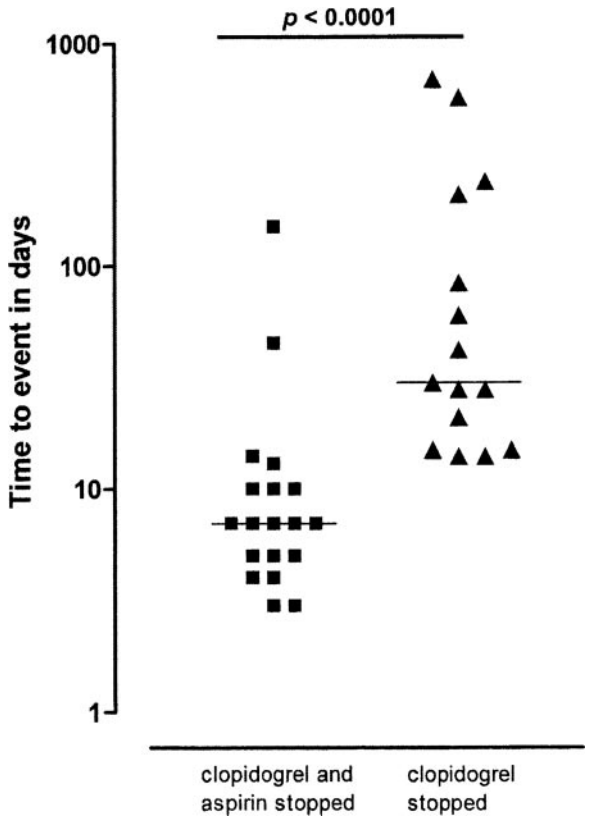

Figure 2. Time from discontinuation of clopidogrel (triangles) and of clopidogrel and aspirin (squares) to an adverse clinical event [death, myocardial infarction (MI)]. The time axis is in logarithmic scale. Bars = medians. Reproduced from Artang R, Dieter RS. Analysis of 36 reported cases of late thrombosis in drug-eluting stents placed in coronary arteries. (Reprinted with permission from Elsevier Limited. Am J Cardiol 2007;99:1039–43; Fig. 1, page 1041.)

Table 3. Risk Factors for Perioperative Stent Thrombosis with Drug-Eluting Stents

Stent(s) implanted in the left main coronary artery
Stent(s) implanted in bifurcations or crossing arterial branch points
Greater total stent length (multiple stents and/or overlapping stents)
Heightened platelet activity (surgery, malignancies, diabetes)
In-stent restenosis
Left ventricular dysfunction
Localized hypersensitivity vasculitis (possibly to the stent polymer or antiproliferative drug)
Penetration by stent into necrotic core
Plaque disruption into non-stented segment
Renal failure/insufficiency
Diabetes
Resistance to antiplatelet medications
Inappropriate discontinuation of antiplatelet drug therapy

studies are not specifically from perioperative patients, it is likely applicable. The loss of aspirin's protective effect during the hypercoagulable perioperative state confers an increased risk of stent thrombosis not fully appreciated by clinicians.

Recent studies suggest that clopidogrel may provide antiinflammatory protection, further attenuating the thrombotic process.[68] Abrupt withdrawal may result in a proinflammatory and prothrombotic state.[69] After 12 mo of dual-antiplatelet therapy in diabetics with DES, significant increases in platelet aggregation ($P < 0.0001$) and inflammatory biomarkers ($P < 0.05$ for C-reactive protein, $P < 0.001$ for P-selectin) were measured 1 mo after clopidogrel withdrawal.[70] This may have serious perioperative implications, particularly for surgical patients with additional risk factors for stent thrombosis.

IMPACT OF ASPIRIN AND CLOPIDOGREL ON PERIOPERATIVE BLEEDING

The impact of aspirin on surgical bleeding has been primarily studied in cardiac and vascular surgery.[71–77] Although preoperative aspirin may increase chest tube drainage and re-exploration rates in cardiac surgery, these clinical end-points were observed with larger doses (≥325 mg), prolonged duration of cardiopulmonary bypass, lack of antifibrinolytic use, and emergent/urgent surgery without a difference in operative mortality rates.[78–80] Tuman et al. evaluated the influence of preoperative aspirin versus placebo on patients undergoing reoperative coronary artery bypass graft (CABG).[81] No significant difference was found in mediastinal drainage, re-exploration, or blood-component transfusion between the two groups. Further, the timing of the most recent aspirin ingestion did not impact blood loss. In patients undergoing "off-pump" CABG, there was no difference in blood loss between aspirin users and nonusers.[82] Others advocate using 75–150 mg of aspirin, since these smaller doses reduce morbidity and mortality and have less risk of perioperative bleeding.[80,83,84]

The peri- and postoperative protective effects of aspirin have been well documented in vascular surgery.[74–77] Perioperative aspirin significantly improves long-term peripheral bypass graft patency.[74,75] Low-dose aspirin (75 mg/d) started preoperatively appears to have a protective effect against transient ischemic attacks and stroke in patients undergoing carotid endarterectomy.[76] Burger et al. performed a review and meta-analysis of the surgical and interventional literature to determine the risks of low-dose aspirin withdrawal versus the bleeding risks associated with aspirin continuation.[77] Aspirin withdrawal preceded 10.2% of acute cardiovascular syndromes (MI, stroke, peripheral arterial occlusion, cardiac death). Although aspirin increased the incidence of bleeding by a factor of 1.5, it did not increase the severity or perioperative morbidity/mortality, except in intracranial surgery and, possibly, transurethral prostatectomy, where increased bleeding may be life-threatening. The authors recommended discontinuing aspirin only if the risk of bleeding complications exceeds the cardiovascular risks of aspirin withdrawal. Whether aspirin increases blood loss in noncardiovascular surgery is not well

studied, and the data are conflicting, with increased bleeding observed only in specific procedures.[85–90] In their review, Merritt and Bhatt concluded aspirin monotherapy should be continued in elective noncardiac surgery.[91]

The likelihood of increased bleeding and/or an increased requirement for blood transfusion in patients undergoing major noncardiac surgery while taking clopidogrel has largely been inferred from the cardiac surgical literature, which contains conflicting data.[92] Patients who remain on clopidogrel and aspirin while undergoing CABG, particularly within days of the scheduled procedure, have a significantly higher incidence of perioperative bleeding, reexploration, blood-component transfusion, and extended intensive care/hospital stays.[83,93–100] Although Yende et al. reported a higher incidence of reexploration for bleeding in patients receiving clopidogrel preoperatively (9.8% vs 1.6%, $P = 0.01$), no significant difference in bleeding, transfusion requirements, and perioperative mortality was found among patients receiving clopidogrel/aspirin/heparin versus aspirin/heparin alone.[93,96,101,102] Of the 2072 patients who underwent CABG in the Clopidogrel in Unstable Angina to Prevent Recurrent Events study, there was an overall 1% excess of severe bleeding.[103] Patients who stopped clopidogrel >5 days before CABG did not have significant bleeding, but a trend towards increased postoperative bleeding was observed among patients who stopped clopidogrel within 5 days of CABG (9.6% vs 6.3% in the placebo group, relative risk = 1.53). Additional studies of on- and off-pump CABG report significantly increased blood component-transfusion rates without increased morbidity/mortality in patients receiving clopidogrel.[94,95,104] However, other studies of blood product transfusion have found transfusion itself to confer a significant long-term survival disadvantage. Koch et al. reported significant reductions in both early and long-term survival in patients receiving a perioperative blood transfusion with CABG.[105,106] The 10-yr survival rate among patients transfused with 1 U of red blood cells was 63% versus 80% in nontransfused patients ($P < 0.0001$). One may extrapolate that each additional unit of transfused blood products further decreases long-term survival.

There is little evidence to define the true impact of continuing thienopyridines on bleeding in noncardiac surgery, and the information available remains anecdotal and inconsistent.[91,107] When compared with aspirin alone, the combination of clopidogrel and aspirin increases the absolute risk of major bleeding by 0.4%–1.0%.[108–111] Chapman et al. described a case in which dual-antiplatelet therapy caused massive hemorrhage during elective abdominal aortic aneurysm repair.[112] Two other cases of severe bleeding during carotid endarterectomy have been reported.[113] Both patients were taking clopidogrel and aspirin. In a multicenter registry, Vichova et al. reported an 18.6% postoperative bleeding complication rate; aspirin and clopidogrel had been withheld in 26% and 24% of patients, respectively.[38] After transbronchial biopsy, Ernst et al. reported an 89% bleeding rate in patients taking clopidogrel versus 3.4% in patients not receiving antiplatelet therapy.[114] However, bleeding was controlled endoscopically and no transfusions were administered. A study conducted by Payne et al. in healthy volunteers found after 2 days of treatment with clopidogrel 75 mg and aspirin 150 mg that there was a significant 3.4-fold increase in bleeding time.[115] The authors suggested the combination of these drugs carried a significantly increased risk of surgical bleeding. In contrast, the same authors found that neither surgical bleeding nor transfusion rates increased during carotid endarterectomy in patients pretreated with clopidogrel and aspirin.[116] On the contrary, a beneficial and significant reduction in transcranial Doppler-determined incidence of emboli was demonstrated. If antiplatelet therapy is discontinued, the risk of bleeding decreases; however, if antiplatelet therapy is discontinued <10 days before surgery, there is still an increased risk, although this remains ill-defined.[1,7,9] Multiple case reports and series found similar bleeding and transfusion frequencies regardless of the dual-antiplatelet regimen administered.[3,6,7,42] Schouten et al. found transfusion was required in 24% of patients continuing and 20% of patients who discontinued antiplatelet therapy ($P = 0.50$).[47] Further, there was no difference in the number of units transfused between the two groups. In their review, Chassot et al. reported that perioperative clopidogrel use increased surgical bleeding and transfusion rates by 50% without concomitant increased morbidity and mortality, except in intracranial surgery.[55] Moreover, they report a complication rate of red blood cell transfusion of only 0.4%, and mortality due to massive surgical blood loss of ≤3%. In procedures where blood loss can be controlled easily, there may be no indication to stop antiplatelet drugs.[92,117]

Despite concerns regarding perioperative bleeding, data suggest postoperative clopidogrel confers a protective effect against MI, stroke, and death. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events trial indicates clopidogrel monotherapy was more effective than aspirin alone in reducing the combined risk of ischemic stroke, MI, and vascular death in high-risk patients with previous CABG (relative risk reduction 8.7%).[118,119] Fewer gastrointestinal side effects were observed with clopidogrel than with aspirin monotherapy.

CURRENT RECOMMENDATIONS FOR PERIOPERATIVE MANAGEMENT OF PATIENTS WITH CORONARY ARTERY STENTS

At present, there is no definitive standard of care for the management of surgical patients with coronary artery stents.[47] Evidence-based medicine currently

Table 4. Duration of Antiplatelet Therapy and Timing of Noncardiac Surgery

Dilatation without stenting: 2–4 wk of dual-antiplatelet therapy
Surgery postponed for 2–4 wk (vital surgery only)
PCI and BMS: 4–6 wk minimum of dual-antiplatelet therapy
Elective surgery postponed ≥6 wk, but not for more than 12 wk, when restenosis may begin to occur
PCI and DES: 12 mo of dual-antiplatelet therapy
Elective surgery postponed for ≥12 mo
In patients in whom coronary revascularization with PCI is appropriate for mitigation of cardiac symptoms and who need elective noncardiac surgery in the subsequent 12 mo, a strategy of balloon angioplasty or BMS placement followed by 4 to 6 wk of dual-antiplatelet therapy is probably indicated
Aspirin: lifelong therapy, whichever is the revascularization technique

(From 2007 AHA/ACC Science Advisory and Society of Cardiovascular Angiography DES Task Force Recommendations for Timing of Noncardiac Surgery after PCI and 2007 ACC/AHA Recommendations for Preoperative Coronary Revascularization and Chassot P-G, Delabays A, Spahn DR. Perioperative antiplatelet therapy: the case for continuing therapy in patients at risk of myocardial infarction. Br J Anaesth 2007;99:316–328).

PCI = percutaneous coronary intervention; BMS = bare-metal stent; DES = drug-eluting stent.

Table 5. Preoperative Evaluation in Patients with Coronary Artery Stents[4,78]

Determine the type of stent(s): BMS, SES, PES
When were stent(s) implanted?
Determine location of stent(s) in coronary circulation
How complicated was the revascularization (longer length, overlapping stents)
Were there any complications during the revascularization (i.e., malapposition)?
Is there a previous history of stent thrombosis?
What antiplatelet regimen is being followed?
Determine patient's comorbidities, if any, to further ascertain level of risk (ejection fraction, diabetes, renal insufficiency, see Table 3)
What is the recommended duration of dual-antiplatelet therapy for that specific patient?
Consultation with an interventional cardiologist, or preferably, patient's cardiologist to elucidate procedural complexities, review current antiplatelet management, and discuss optimal patient management strategy

BMS = bare-metal stent; DES = drug-eluting stent; PES = paclitaxel-eluting stent; SES = sirolumis-eluting stent.

fails to identify the optimum perioperative antiplatelet regimen in these patients, particularly those with DES. Ultimately, registries and prospectively studied protocols are critical to determine the safest management strategies and provide evidence-based recommendations. Education of surgeons and anesthesiologists, as well as development of well-publicized institutional policies and perioperative management guidelines, are paramount to understanding the perioperative risks associated with coronary stents and to preventing catastrophic stent thrombosis.[120,121] In a survey of anesthesiologists, 63% were unaware of recommendations regarding the appropriate length of time between stent placement and a subsequent surgical procedure.[120] Thirty-six percent of the respondents recommended no delay or a 1–2 wk interval between PCI and stenting, which is clearly insufficient regardless of the stent type implanted.

The 2007 AHA/ACC/Society for Cardiovascular Angiography and Interventions/American College of Surgeons/American Dental Association Science Advisory concluded that premature discontinuation of dual-antiplatelet therapy markedly increases the risk of catastrophic stent thrombosis, MI, and death.[11,92] They recommend postponing all elective procedures for which there is a significant risk of bleeding until dual-antiplatelet therapy is completed (Table 4).[92] However, if patients with DES are "*to undergo subsequent procedures that mandate discontinuation of thienopyridine therapy, aspirin should be continued if at all possible and the thienopyridine restarted as soon as possible after the procedure because of concerns about late stent thrombosis.*"[92] Aspirin should also be continued perioperatively in patients with BMS.[92] Additional guidelines for prophylactic PCI and stent implantation are included in Table 4.[11,92]

Similar recommendations have been published in multiple other publications, including the *ACC/AHA 2007 Perioperative Guidelines for Noncardiac Surgery*.[10,11,43,47,55,121–126] However, Chassot et al. and others contend dual-antiplatelet therapy is the cornerstone for stent thrombosis prevention, and the risk of discontinuing clopidogrel and aspirin preoperatively outweighs the benefit of reduced hemostasis, especially in patients with procedural complexities and comorbidities, which place them at higher risk for developing stent thrombosis (Table 3).[43,55,121] In their recent publication, the authors emphasized the importance of continuing aspirin throughout the perioperative period, except in instances when surgery is performed in a closed space (intracranial surgery, posterior chamber of the eye, spinal surgery in the medullary canal).[55] Chassot et al. also recommend postponing elective surgery for 3 mo in patients with BMS, whereas the 2007 ACC/AHA Guidelines state elective surgery should be performed between 6 and 12 wk after BMS, when restenosis begins to occur.[4,55]

Although case reports and series of perioperative management of patients with DES have been published, there are no universally accepted guidelines. The anesthesiologist, as perioperative physician, can play a pivotal role in ensuring patient safety. Early preoperative identification and use of a multidisciplinary team approach to guide perioperative management is essential.[11,54,92,121,126,127] Important aspects of the preoperative assessment are included in Table 5. Many advocate simply the perioperative continuation of clopidogrel and aspirin whenever possible.[50,127,128] In 2006, a French task force comprised of cardiologists, anesthesiologists, hematologists, and surgeons published perioperative management guidelines.[124] Although the task force emphasized total withdrawal of dual-antiplatelet therapy exposes patients to an undue risk of stent

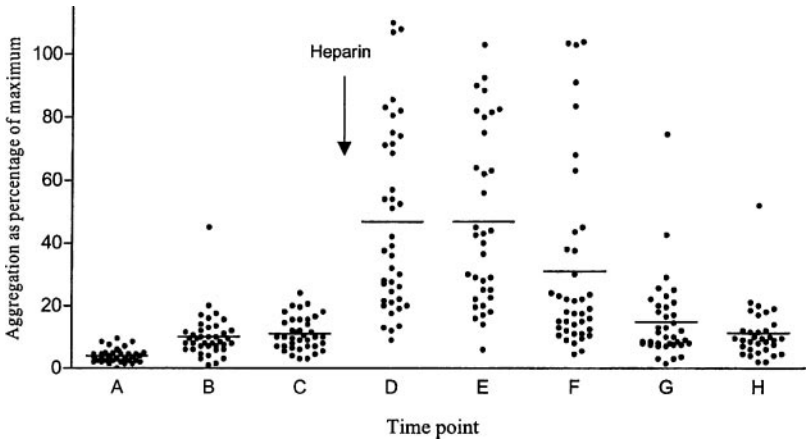

Figure 3. Platelet aggregation in response to arachidonic acid (5 mmol/L) in patients undergoing carotid endarterectomy at time points A, preoperative, at admission to hospital; B, after induction of anesthesia but before skin incision; C, after skin incision and soft tissue dissection but before heparinization; D, 3 min after heparin was administered, before insertion of shunt; E, 3 min after shunt opening; F, at the end of surgery, after flow restoration; G, 4 h postoperatively; and H, 24 h postoperatively but before the next dose of aspirin. Reproduced from Webster SE, Payne DA, Jones CI, Hayes PD, Bell PR, Goodall AH, Naylor AR. Antiplatelet effect of aspirin is substantially reduced after administration of heparin during carotid endarterectomy. J Vasc Surg 2004;40:463–8; Fig. 1, page 465.

thrombosis and advised the continuation of aspirin, they recommended the substitution of flurbiprofen, a reversible nonsteroidal antiinflammatory drug (NSAID), and low molecular weight heparin (LMWH) in surgical procedures with excessive hemorrhagic risk.[124,125] The substitution of nonselective NSAIDs and LMWH for dual-antiplatelet therapy is controversial and there is no scientific evidence to support their efficacies in preventing perioperative stent thrombosis, as ACS has been reported with this practice.[3,10,11,55,66,124,127,129] The concomitant use of nonselective NSAIDs and aspirin significantly increases cardiac morbidity and mortality in patients with CAD and the incidence may be even higher in patients with coronary stents.[130–132] Nonselective NSAIDs competitively inhibit aspirin binding to the serine residue at position 530 by binding to the catalytic site of cyclooxygenase-1.[132] Collet and Montalescot contend there are no good alternatives to clopidogrel and aspirin.[10]

Although heparin therapy is often used perioperatively for thromboembolic prophylaxis, it does not have antiplatelet properties and is not protective against stent thrombosis.[10,127] Further, "heparin rebound" occurs after abrupt cessation of an unfractionated heparin (UFH) infusion.[133] Vicenzi et al. described an association between perioperative heparin therapy and increased cardiac morbidity and mortality among patients with coronary stents.[3] During UFH infusion, increases in thrombin and platelet activity have been measured and persist for many hours after an infusion is discontinued, whereas any protective anticoagulant effect declines rapidly because of the short half-life of UFH.[134,135] Webster et al. found that the administration of UFH significantly and transiently increases platelet aggregation despite chronic aspirin therapy (150 mg/d) in patients undergoing carotid endarterectomy or lower extremity angioplasty, persisting into the immediate postoperative period[136] (Fig. 3). This effect may account for ischemic events observed when UFH is used to treat ACS.[135–137] Xiao et al. reported most ischemic cardiac events occur 9.5 h after stopping UFH.[135] However, when UFH was used in combination with aspirin and a glycoprotein (GP) IIb/IIIa platelet inhibitor in the treatment of ACS, Théroux et al. reported a lower incidence of death and MI at 7 days, 30 days, and 6 mo.[137] The authors reported major bleeding did not increase in patients receiving heparin alone or in combination therapy. McDonald et al. reported that preoperative LMWH was associated with significantly increased postoperative bleeding and reexploration in cardiac surgery.[138] However, the INTERACT (Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment) trial suggested enoxaparin, when compared with UFH, reduced perioperative blood loss during CABG and reduced the incidence of death and MI by 39% over a 2.5-yr period.[139,140] Di Nisio et al. found abrupt cessation of enoxaparin results in rapid increases in prothrombotic activity with maximum levels measured 12 and 24 h after discontinuation.[141] Xiao et al. found minor elevations in platelet activation associated with LMWH.[135]

Brilakis et al. recently summarized treatment options for patients with DES: (1) continue dual-antiplatelet therapy throughout the perioperative period for patients at low risk of bleeding; (2) implement "bridging therapy," in which a short-acting GP IIb/IIIa inhibitor (tirofiban or eptifibatide) or thrombin inhibitor, or both, is substituted for clopidogrel during the perioperative period; or (3) discontinue clopidogrel preoperatively, restarting it as soon as possible postoperatively.[121,142] Although empiric and without evidence-based data supporting its efficacy, multiple institutions use bridging therapy to prevent perioperative stent thrombosis.[46,55,92,126,127,143,144] GP IIb/IIIa inhibitors have been favored since this platelet receptor is the pivotal mediator for platelet aggregation and thrombus formation (Part I, Fig. 1).[145] Exposure to the vascular subendothelium activates the receptor, causing a marked affinity for fibrinogen and von Willebrand factor, the principal adhesive macromolecules responsible for crosslinking platelets by binding adjacent GP IIb/IIIa receptors.[146] This facilitates platelet aggregation, the final common pathway for platelet plug and thrombus formation. The development of GP IIb/IIIa inhibitors (abciximab, eptifibatide, and

tirofiban) was integral in preventing thrombus formation and improving outcome in patients with ACS, particularly patients with non-STEMI.[147] In addition to preventing platelet aggregation, these inhibitors (1) displace fibrinogen from GP IIb/IIIa receptors and (2) block signaling processes, which further prevents secretion, clot retraction, and prothrombotic activity.[148] GP IIb/IIIa inhibitors are more potent than the combination of aspirin and a thienopyridine.[149]

Broad et al. in 2007 published a series using bridging therapy in three patients undergoing elective noncardiac surgery 49 days to 33 mo after DES placement.[143] Aspirin was continued throughout the perioperative period. All three patients stopped clopidogrel therapy 5 days preoperatively and were admitted for bridging therapy with tirofiban and heparin 2 days later. Both infusions were continued for 3 days until midnight, the day before surgery. Each surgery proceeded uneventfully, and either clopidogrel (postoperative day 1) or tirofiban (4 h postoperatively) was resumed. There were no cardiac or bleeding complications reported. More recently published protocols, including from the Cleveland Clinic, recommend bridging therapy with GP IIb/IIIa inhibitors primarily (1) in patients who have not completed dual-antiplatelet therapy and (2) in patients whose stent complexities and comorbidities significantly increase their risk for developing catastrophic stent thrombosis and its sequelae[50,55,126,127,144] (Table 3). Tirofiban and eptifibatide are administered parenterally, have half-lives <2 h, and are eliminated by renal clearance.[146,150] The infusion rate is reduced by half in patients with reduced renal function (serum creatinine >2.0 mg/dL or creatinine clearance <50 mL/min). Platelet function returns to 60%–90% of normal after the infusion is stopped for 6–8 h.

Reversible $P2Y_{12}$ receptor antagonists are undergoing clinical trials, and may prove to be of value perioperatively (Part 1, Fig. 1).[151–157] Cangrelor is a parenteral, reversible direct $P2Y_{12}$ inhibitor whose half-life of 5–9 min allows 100% recovery of platelet function 1 h after the infusion is discontinued.[153,158] A $4\ \mu g \cdot kg^{-1} \cdot min^{-1}$ infusion achieves complete platelet inhibition when measured at 4 min.[152] Rabbat et al. suggest that cangrelor may play a role in bridging therapy.[50] AZD6140 is an oral, reversible direct $P2Y_{12}$ receptor antagonist. It provides more rapid and complete platelet inhibition than clopidogrel.[151,153,157] AZD6140 has a half-life of 12 h, making it effective in the perioperative setting.[157] Current trials have found similar rates of bleeding.[156] Phase III trials are currently evaluating the efficacy of AZD6140 versus clopidogrel in patients with non-STEMI or STEMI elevation ACS.[159]

Although success with bridging therapy has been reported, prospective studies are necessary to validate it as a viable management strategy. Opponents argue bridging therapy is (1) expensive, (2) logistically difficult, (3) exposes patients to risks associated with a prolonged hospitalization, and (4) confers no protection against intraoperative stent thrombosis.[121,127] Resuming clopidogrel or a GP IIb/IIIa inhibitor as soon as possible postoperatively is paramount to protecting against stent thrombosis when the risk is greatest.[121,127] Brilakis et al. recommend a postoperative 600 mg initial dose of clopidogrel, which reduces (1) the time to achieve maximal platelet inhibition (2 vs 6 h with a 300 mg initial dose), and (2) the frequency of hyporesponsiveness to clopidogrel, particularly in patients whose platelets are activated secondary to surgical intervention.[121,142,160–164] However, anesthetic drugs metabolized by CYP3A4 may irreversibly inhibit this isoenzyme and prevent the conversion of clopidogrel to its active state, modulating its antiplatelet effect.[165–169] Midazolam irreversibly inactivates CYP3A4 after metabolism to 1-hydroxymidazolam.[165–168] Midazolam also exerts antiplatelet activity, the mechanisms of which are not fully elucidated; whether this counteracts clopidogrel modulation is unknown.[170,171] Competitive (reversible) inhibitors, drugs that may not prevent clopidogrel activation, of CYP3A4 include fentanyl, alfentanil, and propofol.[172–174]

If a patient presents for surgery with aspirin and clopidogrel inadvertently stopped by their surgeon or another physician, some advocate administering 325 mg of nonenteric coated aspirin the day of surgery, and delaying the procedure until later that day.[144,175] Theoretically, the patient should have antiplatelet effects within 2 h secondary to the rapid absorption of aspirin.[144,175,176] A single dose of 160 mg has been shown to completely eliminate platelet TxA_2 production; however, this may not be the case in patients with aspirin resistance.[130–132,176–181] Others have suggested administering aspirin 325 mg for 3–5 days to achieve a steady-state, which may overcome issues with resistance.[144]

MANAGEMENT OF PATIENTS WITH CORONARY ARTERY STENT THROMBOSIS

When stent thrombosis occurs, it acutely manifests as a STEMI or a sudden malignant dysrhythmia, and must be treated with immediate reperfusion to avoid a transmural MI due to the abrupt interruption of coronary blood flow in a myocardial region that is neither collateralized nor preconditioned by recurrent chronic ischemia.[14,121,142] Thrombolytic therapy (IV or intracoronary) is significantly less effective than PCI in treating stent thrombosis and restoring myocardial perfusion.[120,182] Administration of thrombolytic therapy is often prohibitive in the perioperative period. Therefore, primary PCI is the definitive treatment for perioperative stent thrombosis and restoration of coronary stent patency.[55,121,144,183–186] Surgical procedures should be performed in institutions where 24-h interventional cardiology is available to provide immediate and emergent intervention.[55,121,144,183–186] PCI carries an increased risk of bleeding when performed early

after surgery because antiplatelet and antithrombin drugs must be administered during the procedure.[3,121] However, Brilakis et al. state that the only medications necessary for patients with an acute coronary stent occlusion who have an increased bleeding risk are aspirin and at least one dose of an antithrombin (heparin or bivalirudin).[121,142] Berger et al. performed a retrospective analysis of 48 patients with acute MI occurring within 1 wk postoperatively.[187] All patients received aspirin and heparin with immediate PCI. Despite the high frequency of cardiogenic shock and cardiac arrest in this study population, the survival rate was 65%. Only one patient developed significant bleeding at the operative site (patient with a knee replacement). Patients who had undergone craniotomies and thoracic surgery were included in this series.

Postoperative management should include admission to a higher-acuity unit with continued electrocardiogram monitoring and cardiology surveillance.[142,184] Routine monitoring of cardiac biomarkers would be useful in detecting myocardial injury, recurrent ischemia, and for risk stratification, and should be drawn before emergent transfer to the cardiac catheterization laboratory.[55] Elevated perioperative troponin levels are statistically significant independent predictors of morbidity and mortality 1 yr after surgery.[185] However, the occlusive nature of stent thrombosis, and continuing myocardial necrosis, may quickly lead to hemodynamic instability, ventricular arrhythmias, cardiogenic shock, or cardiac arrest, necessitating emergent PCI.[186]

CONSIDERATIONS FOR REGIONAL ANESTHESIA FOR PATIENTS WITH CORONARY ARTERY STENTS

In patients with coronary artery stents, particularly DES, the use of regional anesthesia (RA) must be carefully considered. RA, particularly neuraxial blockade, attenuates the hypercoagulable perioperative state by blunting the sympathetic response.[188–191] Systemic absorption of local anesthetics provides antiplatelet effects by blocking TxA_2 and decreasing platelet aggregation.[192–194] These benefits may be advantageous, and RA may seem the safest choice in certain situations.[31] However, the potential for stent thrombosis with discontinuation of antiplatelet drugs and potential coagulation abnormalities must be taken into account when considering RA, particularly in patients considered higher-risk[50,55] (Table 3).

It is generally interpreted from the 2003 American Society of Regional Anesthesia (ASRA) guidelines that the thienopyridines and dual-antiplatelet therapy are contraindications to neuraxial anesthesia or peripheral nerve blockade in noncompressible regions that cannot be observed for bleeding.[195] The actual risk of spinal hematoma is unknown in this population, although case reports of this unfortunate complication in the presence of antiplatelet and antithrombin drugs have been described.[195] Although the ASRA recommends discontinuing clopidogrel 7 days and ticlopidine 14 days before RA; they also state, "Variances from recommendations may be acceptable based on the judgment of the responsible anesthesiologist[195]." Following the guidelines confers no guarantee that neuraxial anesthesia will be free from bleeding complications.[195–199] In fact, only about one-third of patients who developed neuraxial hematoma in a large series of spinal and epidural anesthetics had any coagulation abnormality.[200] Aspirin alone does not appear to increase the risk of neuraxial hematoma, and does not appear to interfere with the performance of neuraxial blockade.[195,199,201] However, the concurrent use of UFH or LMWH increases the risks of bleeding and neuraxial hematoma in the presence of aspirin monotherapy.[195,202,203] In patients receiving LMWH prophylaxis alone, the current ASRA guidelines recommend delaying neuraxial blockade at least 10–12 h after the last LMWH dose. Patients receiving higher doses will require delays of at least 24 h to assure normal hemostasis at the time of needle placement.[195] Although there is small or very limited risk associated with neuraxial blockade in the presence of subcutaneous UFH treatment alone, ASRA does not consider this treatment a contraindication to neuraxial blockade or catheter placement.[195] However, in patients who have received UFH for >4 days, a platelet count should be obtained to exclude heparin-induced thrombocytopenia.[195] For patients receiving bridging therapy with eptifibatide or tirofiban, 8 h must elapse before a neuraxial blockade can be performed.[195,202,204]

Although perioperative platelet transfusions have been suggested in patients on dual-antiplatelet therapy when RA is considered safest, this practice cannot be justified.[31,144,184,205–207] Transfusions are not without risks.[207] An adequate platelet count does not reflect function, which may still be abnormal, precluding the performance of a regional anesthetic.[207] There are no clinically available tests, which accurately and reliably assess platelet function. Theoretically, apheresis platelets administered to patients with stents who then receive clopidogrel and aspirin may not develop antiplatelet effects to provide adequate protection from stent thrombosis for hours to days.[144] The administration of platelets should probably be avoided, except in instances of life-threatening bleeding.[14,144] If platelet administration is considered absolutely necessary, Doyle et al. recommend waiting for 12 h (3 half-lives) after the last dose of clopidogrel (half-life of clopidogrel is 4 h) when serum levels of the drug are no longer detectable to ensure normal platelet function.[14] However, Cornet et al. published a case series of three patients with gastrointestinal bleeding or who were scheduled for emergency surgery and who received platelet transfusions shortly after BMS insertion.[208] Dual-antiplatelet therapy was discontinued in one patient 14 h before transfusion, whereas the other

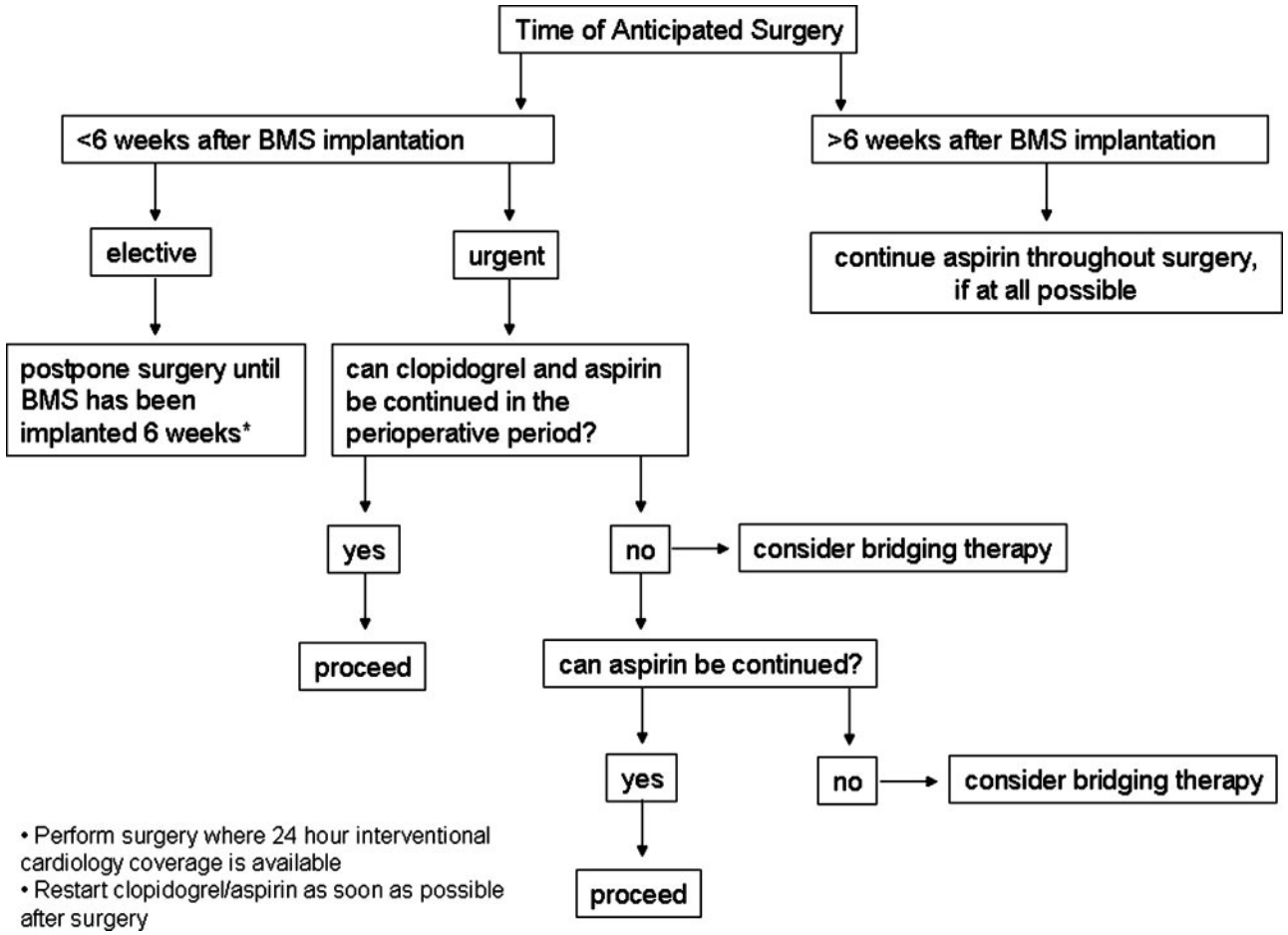

Figure 4. Proposed algorithm for perioperative management of patients with bare-metal stents based on current literature. *The 2007 ACC/AHA perioperative guidelines state, "it appears reasonable to delay elective noncardiac surgery for 4–6 wk to allow for at least partial endothelialization of the stent, but not for more than 12 wk, when restenosis may occur."

two patients remained on clopidogrel and aspirin. Stent occlusion was diagnosed 6–17 h after transfusion by electrocardiographic criteria in the two patients still receiving clopidogrel and aspirin, and by angiography in the patient whose antiplatelet therapy was discontinued. In this series, thrombus formation with donor platelets occurred in both the presence and absence of dual-antiplatelet therapy, suggesting that therapeutic serum levels of clopidogrel and aspirin may not affect transfused platelets. *Ex vivo* studies have shown that transfused platelets may not be inhibited by the presence of adequate serum levels of antiplatelet drugs.[209] Both MI and PCI can activate circulating platelets for at least 48 h, and their adhesive function may also increase.[210,211] Moreover, the thrombogenic surfaces of stents may attract and activate donor platelets to a even greater extent than endogenous platelets, further increasing the risk of stent thrombosis, MI, and death.[144,208]

The dilemma with RA, particularly neuraxial blockade, in patients with stents is that postoperative PCI, with concomitant administration of antithrombotic therapy plus GPIIb/IIIa inhibitors, cannot be delayed to allow for catheter removal and prevent spinal cord compromise. Performance of neuraxial instrumentation, whether a single-shot technique or involving catheter insertion, significantly increases the risk of a neuraxial hematoma in patients who must subsequently receive antithrombotic therapy with or without GP IIb/IIIa inhibitors during PCI for acute stent thrombosis.[203–205] The risk of spinal cord compromise in a patient who will receive antiplatelet and anticoagulant medication must be carefully balanced against the need for immediate coronary revascularization.[212] Indwelling catheters should not be removed in the presence of therapeutic anticoagulation.[195] If a surgical patient requires PCI, catheters should be removed before antithrombotic/antiplatelet/thrombolytic therapy, and PCI must be undertaken urgently. Popescu et al. recently described the postoperative management of an indwelling thoracic epidural catheter in a patient with postoperative right coronary artery DES thrombosis after aortic surgery.[212] After confirmation of a normal coagulation profile, the catheter was removed, and the decision was made to delay PCI 2 h to minimize the risk of an epidural hematoma. The patient received eptifibatide and bivalirudin with percutaneous transluminal coronary angioplasty,

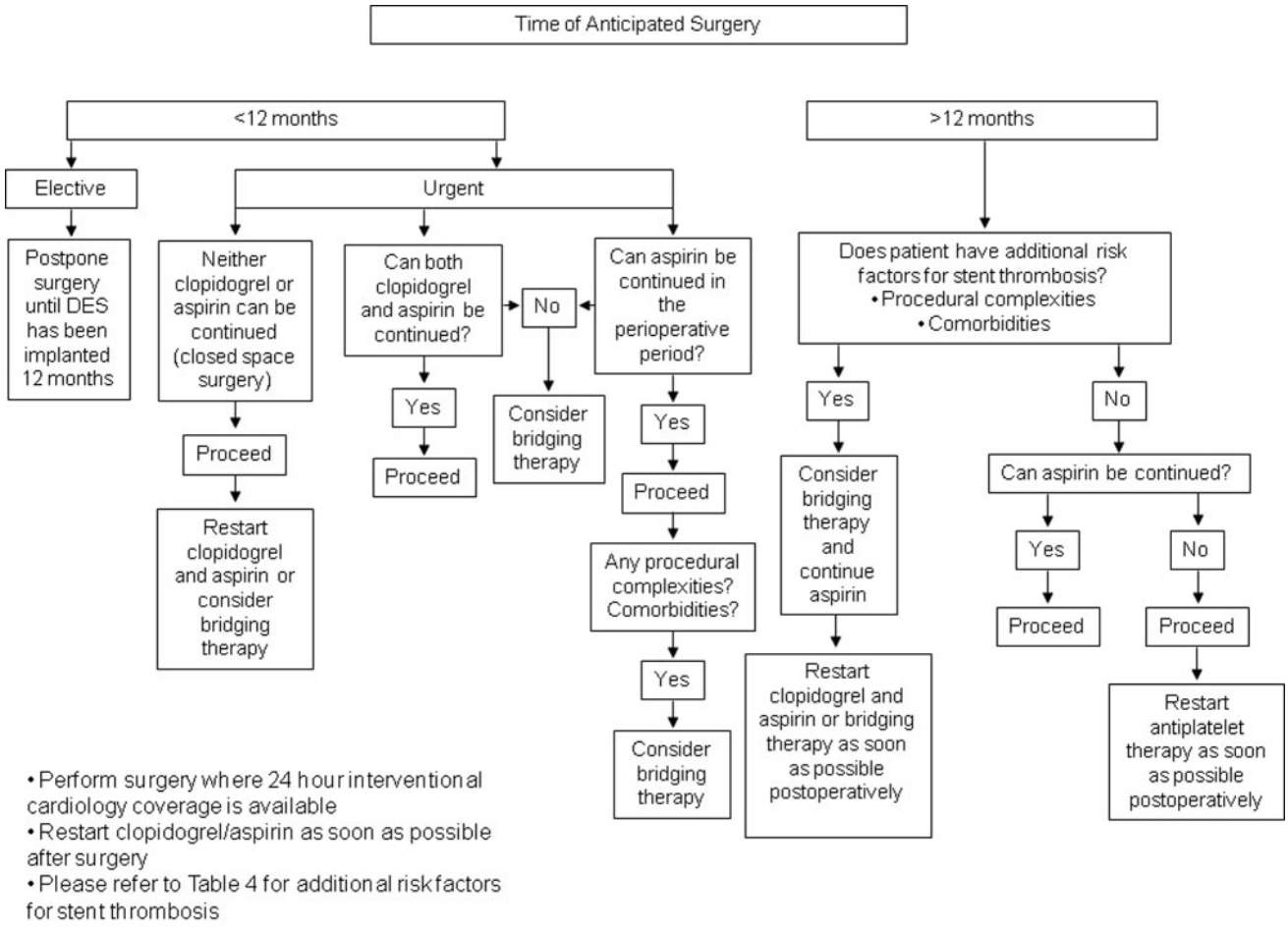

Figure 5. Proposed algorithm for perioperative management of patients with drug-eluting stents based on current literature.

and did not suffer any neurologic sequelae. Vigilant and intensive monitoring of sensorimotor function should be performed to detect any evidence of spinal cord compromise. In the case described by Popescu et al., neurologic examinations were continued for 48 h (every 2 h for the first day).[212] Current ASRA guidelines recommend removal of an epidural catheter 1 h before administration of UFH, and 2 h before LMWH.[195] The appropriate time delay between catheter removal and clopidogrel administration remains undefined. There are no guidelines for catheter removal preceding bivalirudin or GPIIb/IIIa inhibitor administration.[195,212] Douketis et al. recommend administering clopidogrel or GP IIb/IIIa inhibitors 2–3 h after epidural catheter removal. Although longer time delays have been suggested,[202,204,206] these increase the risk and complications of postoperative stent thrombosis if clopidogrel is withheld; this must be a mutual decision between the anesthesiologist and cardiologist. There are no guidelines regarding peripheral nerve blockade and catheters. Ultrasound-guided blockade, with and without catheter placement, may be safest in preventing potential bleeding complications, particularly in the setting of dual-antiplatelet therapy.[213] Based on the current information available, the decision to perform RA should be made case-by-case, with consideration given to all potential complications.[184,207]

CONCLUSION

The management of patients with coronary artery stents during the perioperative period is an important patient safety issue. Figures 4 and 5 present recommendations based on the currently available literature. Communication between the patient's cardiologist, surgeon, and anesthesiologist is essential to minimize the risk of catastrophic stent thrombosis, MI, and death. Elective surgery should be avoided until the appropriate course of dual-antiplatelet therapy is completed, as determined by the patient's cardiologist. Clinical judgment is of the utmost importance in balancing the risk/benefit ratio of dual-antiplatelet therapy interruption versus continuation. Aspirin should never be interrupted unless the risk of bleeding far outweighs the risk of stent thrombosis. Surgical procedures should be performed where 24-h interventional cardiology is available, as perioperative stent thrombosis acutely results in cardiogenic shock/arrest requiring emergent PCI. Although RA may provide some antithrombotic protection, the potential risk of bleeding complications must be carefully weighed

in these patients. Prospective studies to determine the safest perioperative management are of paramount importance.

REFERENCES

1. Kaluza GL, Joseph J, Lee JR, Raizner ME, Raizner AE. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. J Am Coll Cardiol 2000;35:1288–94
2. Steinhubl SR, Berger PB, Mann JT III, Fry ETA, DeLago A, Wilmer G, Topol RJ; for the CREDO Investigators. Clopidogrel for the reduction of events during observation. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288:2411–20
3. Vicenzi MN, Meislitzer T, Heitzinger B, Halaj M, Fleisher LA, Metzler H. Coronary artery stenting and non-cardiac surgery—a prospective outcome study. Br J Anaesth 2006;96:686–93
4. Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, Fleisher LA, Froehlich JB, Gusberg RJ, Leppo JA, Ryan T, Schlant RC, Winters WL Jr, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Jacobs AK, Hiratzka LF, Russell RO, Smith SC Jr. American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary. Circulation 2002;105:1257–67
5. Vicenzi MN, Ribitsch D, Luha O, Klein W, Metzler H. Coronary artery stenting before noncardiac surgery: more threat than safety? Anesthesiology 2001;94:367–8
6. Sharma AK, Ajani AE, Hamwi SM, Maniar P, Lakhani SV, Waksman R, Lindsay J. Major noncardiac surgery following coronary stenting. When is it safe to operate? Catheter Cardiovasc Interv 2004;63:141–5
7. Wilson SH, Fasseas P, Orford JL, Lennon RJ, Horlocker T, Charnoff NE, Melby S, Berger BP. Clinical outcome of patients undergoing non-cardiac surgery in the two months following coronary stenting. J Am Coll Cardiol 2003;42:234–40
8. Marcucci C, Chassot P-G, Gardaz J-P, Magnusson L, Ris HB, Delabays A, Spahn DR. Fatal myocardial infarction after lung resection in a patient with prophylactic preoperative coronary stenting. Br J Anaesth 2004;92:743–7
9. Reddy PR, Vaitkus PT. Risks of noncardiac surgery after coronary stenting. Am J Cardiol 2005;95:755–7
10. Collet JP, Montalescot G. Premature withdrawal and alternative therapies to dual oral antiplatelet therapy. Eur Heart J Suppl 2006;8(Suppl):G46–G52
11. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleishmann KE, Freeman WK, Froehlich JB, Kasper E, Kersten JR, Riegel B, Robb JF. ACC/AHA 2007 Guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Circulation 2007;116: e418–99
12. Wilson SH, Rihal CS, Bell MR, Velianou JL, Holmes DR Jr, Berger PB. Timing of coronary stent thrombosis in patients treated with ticlopidine and aspirin. Am J Cardiol 1999; 83:1006–11
13. Berger PB, Bell MR, Hasdai D, Grill DE, Melby S, Holmes DR Jr. Safety and efficacy of ticlopidine for only 2 weeks after successful intracoronary stent placement. Circulation 1999;99:248–53
14. Doyle B, Rihal CS, O'Sullivan CJ, Lennon RJ, Wiste HJ, Bell M, Bresnahan J, Holmes DR Jr. Outcomes of stent thrombosis and restenosis during extended follow-up of patients treated with bare-metal coronary stents. Circulation 2007;116:2391–8
15. Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, Mihalcsik L, Tespili M, Valsecchi O, Kolodgie FD. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? Circulation 2004;109:701–5
16. Ong AT, Hoye A, Aoki J, van Mieghem CA, Rodriguez Granillo GA, Sonnenschein K, Regar E, McFadden EP, Sianos G, van der Giessen WJ, de Jaegere PP, de Feyter P, van Domburg RT, Serruys PW. 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
17. FDA Public Health Web Notification*: Final Update of Information for Physicians on Sub-acute Thromboses (SAT) and Hypersensitivity Reactions with Use of the Cordis CYPHER™ Sirolimus-eluting Coronary Stent. U.S. Food and Drug Administration. October 18, 2004. Available at: http://www. fda.gov/cdrh/safety/cypher3.html. Accessed June 4, 2007
18. Luscher TF, Steffel J, Eberli FR, Joner M, Nakazawa G, Tanner FC, Virmani R. Drug-eluting stent and coronary thrombosis: biological mechanisms and clinical implications. Circulation 2007;115:1051–8
19. Finn AV, Joner M, Nakazawa G, Kolodgie F, Newell J, John MC, Gold HK, Virmani R. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation 2007;115:2435–41
20. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193–202
21. Kerner A, Gruberg L, Kapeliovich M, Grenadier E. Late stent thrombosis after implantation of a sirolimus-eluting stent. Catheter Cardiovasc Interv 2003;60:505–8
22. McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, Suddath WO, Weissman NJ, Torguson R, Kent KM, Pichard AD, Satler LF, Waksman R, Serruys PW. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet 2004;364:1519–21
23. Farb A, Burke AP, Kolodgie FD, Virmani R. Pathological mechanisms of fatal late coronary stent thrombosis in humans. Circulation 2003;108:1701–6
24. ESC Congress 2006, Rapid News Summaries: Pathology of drug-eluting stents (Virmani R). Available at: http://www. cardiosource.com/rapidnewssummaries/index.asp?EID=23&DoW=Mon&SumID=180. Accessed June 12, 2007
25. Fleron MH, Dupuis M, Mottet P, Le Feuvre C, Godet G. [Non cardiac surgery in patient with coronary stenting: think sirolumis now!]. Ann Fr Anesth Reanim 2003;22:733–5
26. Auer J, Berent R, Weber T, Eber B. Risk of noncardiac surgery in the months following placement of a drug-eluting coronary stent. J Am Coll Cardiol 2004;43:713
27. McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, Suddath WO, Weissman NJ, Torguson R, Kent KM, Pichard AD, Satler LF, Waksman R, Serruys PW. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet 2004;364:1519–1521
28. Nassar M, Kapeliovich M, Markiewicz W. Late thrombosis of sirolimus-eluting stents following noncardiac surgery. Catheter Cardiovasc Interv 2005;65:516–19
29. Cuthill JA, Young S, Greer IA, Oldroyd K. Anaesthetic considerations in a parturient with critical coronary artery disease and a drug-eluting stent presenting for caesarian section. Int J Obstet Anesth 2005;14:167–71
30. Murphy JT, Fahy BG. Thrombosis of sirolumis-eluting coronary stent in the postanesthesia care unit. Anesth Analg 2005;101:971–3
31. Herbstreit F, Peters J. Spinal anaesthesia despite combined clopidogrel and aspirin therapy in a patient awaiting lung transplantation: effects of platelet transfusion on clotting tests. Anaesthesia 2005;60:85–7
32. Charbucinska KN, Godet G, Itani O, Fleron NJ, Bertrand M, Rienzo M, Coriat P. Anticoagulation management for patients with drug-eluting stents undergoing vascular surgery. Anesth Analg 2006;103:261–3
33. Head DE, Sebranek JJ, Zahed C, Coursin DB, Prielipp RC. A tale of two stents: perioperative management of patients with drug-eluting stents. J Clin Anesth 2007;19:386–96
34. Brichon P-Y, Boitet P, Dujon A, Mouroux J, Peillon C, Riquet M, Velly JF, Ris HB. Perioperative in-stent thrombosis after lung resection performed within 3 months of coronary stenting. Eur J Cardiothorac Surg 2006;30:793–6
35. Chung D, Krysiak P. Post-mediastinoscopy mortality due to drug-eluting stent thrombosis. Eur J Cardiothorac Surg 2007;31:1149–50
36. Bakhru M, Saber W, Brotman D, Bhatt D, Angja A, Tillan-Martinez K, Jaffer A. Is discontinuation of antiplatelet therapy after 6 months safe in patients with drug-eluting stents undergoing noncardiac surgery? Cleve Clin J Med 2006;73(e-suppl 1):S23

37. Compton PA, Zankar AA, Adesanya AO, Banerjee S, Brilakis ES. Risk of noncardiac surgery after coronary drug-eluting stent implantation. Am J Cardiol 2006;98:1212–13
38. Vichova Z, Godet G, Attof Y, Cannesson M, Lehot JJ. Patients with coronary stents and non-cardiac surgery: preliminary results of POSTENT Study. Anesthesiology 2007;107(Suppl):A193
39. Brown MJ, Long TR, Brown DR, Wass CT. Acute coronary syndrome and myocardial infarction after orthopedic surgery in a patient with a recently placed drug-eluting stent. J Clin Anesth 2006;18:537–40
40. de Souza DG, Baum VC, Ballert NM. Late thrombosis of a drug-eluting stent presenting in the perioperative period. Anesthesiology 2007;106:1057–9
41. Varani E. Very late thrombosis of a paclitaxel-eluting stent. Available at: http://www.tctmd.com/csportal/appmanager/tctmd/descoe?_nfpb=true&_pageLabel=DESCenterContent&hdCon=740056&srcId=56&destId=4. Accessed October 25, 2007
42. Schouten O, van Domburg RT, Bax JJ, de Jaegere PJ, Dunkelgrun M, Feringa HH, Hoeks SE, Poldermans D. Noncardiac surgery after coronary stenting: early surgery and interruption of antiplatelet therapy are associated with an increase in major adverse cardiac events. J Am Coll Cardiol 2007;49:122–4
43. Spahn DR, Howell SJ, Delabays A, Chassot PG. Coronary stents and perioperative antiplatelet regimen: dilemma of bleeding and stent thrombosis. Br J Anaesth 2006;96:675–7
44. Cook S, Wenaweser P, Togni M, Billinger M, Morger C, Seiler C, Vogel R, Hess O, Meier B, Windecker S. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. Circulation 2007;115:2426–34
45. Artang R, Dieter RS. Analysis of 36 reported cases of late thrombosis in drug-eluting stents placed in coronary arteries. Am J Cardiol 2007;99:1039–43
46. Hodgson JM, Stone GW, Lincoff AM, Klein L, Walpole H, Bottner R, Weiner BH, Leon MB, Feldman T, Babb J, Dehmer GJ; Society of Cardiovascular Angiography and Interventions. Late stent thrombosis: considerations and practical advice for the use of drug-eluting stents: a report from the Society for Cardiovascular Angiography and Interventions Drug-eluting Stent Task Force. Catheteriz Cardiovasc Interv 2007;69:327–33
47. Schouten O, Bax JJ, Damen J, Poldermans D. Coronary artery stent placement immediately before noncardiac surgery: a potential risk? Anesthesiology 2007;106:1067–9
48. Poldermans D, Schouten O, Vidakovic R, Bax JJ, Thomson IR, Hoeks SE, Feringa HH, Dunkelgrun M, de Jaegere P, Maat A; DECREASE Study Group. A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery: the DECREASE-V Pilot Study. J Am Coll Cardiol 2007;49:1763–9
49. Carrozza JP Jr. Duration of clopidogrel therapy with drug-eluting stents. J Interven Cardiol 2006;19(Suppl):S40–S46
50. Rabbat MG, Bavry AA, Bhatt DL, Ellis SG. Understanding and minimizing late thrombosis of drug-eluting stents. Cleve Clin J Med 2007;74:129–36
51. Bavry AA, Kumbhani DJ, Helton TJ, Borek PP, Mood GR, Bhatt DL. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. Am J Med 2006;119:1056–61
52. Win HK, Caldera AE, Maresh K, Lopez J, Rihal CS, Parikh MA, Granada JF, Marulkar S, Nassif D, Cohen DJ, Kleiman NS; EVENT Registry Investigators. Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. JAMA 2007;297:2001–9
53. Pfisterer M, Brunner-La Rocca HP, Buser PT, Rickenbacher P, Hunziker P, Mueller C, Jeger R, Bader F, Osswald S, Kaiser C; 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;48:2584–91
54. Maisel WH. Unanswered questions—drug-eluting stents and the risk of late thrombosis. N Engl J Med 2007;356:981–4
55. Chassot P-G, Delabays A, Spahn DR. Perioperative antiplatelet therapy: the case for continuing therapy in patients at risk of myocardial infarction. Br J Anaesth 2007;99:316–28
56. Mangano DT. Perioperative cardiac morbidity. Anesthesiology 1990;72:153–84
57. Cohen MC, Aretz TH. Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. Cardiovasc Pathol 1999;8:133–9
58. Samama CM, Thiry D, Elalamy I, Diaby M, Guillosson JJ, Kieffer E, Coriat P. Perioperative activation of hemostasis in vascular surgery patients. Anesthesiology 2001;94:74–8
59. Lo B, Fijnheer R, Castigliego D, Borst C, Kalkman CJ, Nierich AP. Activation of hemostasis after coronary artery bypass grafting with or without cardiopulmonary bypass. Anesth Analg 2004;99:634–40
60. Neumann FJ, Ott I, Gawaz M, Puchner G Schomig A. Neutrophil and platelet activation at balloon-injured coronary artery plaque in patients undergoing angioplasty. J Am Coll Cardiol 1996;27:819–24
61. Dawood MM, Gupta DK, Southern J, Walia A, Atkinson JB, Eagle KA. Pathology of fatal perioperative myocardial infarction: implications regarding pathophysiology and prevention. Int J Cardiol 1996;57:37–44
62. Di Tano G, Mazzu A. Early reactivation of ischaemia after abrupt discontinuation of heparin in acute myocardial infarction. Br Heart J 1995;74:131–3
63. Biondi-Zoccai GGL, Lotrionte M, Agostoni P, Abbate A, Fusaro M, Burzotta F, Testa L, Shieban I, Sangiorgi G. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. Eur Heart J 2006;27:2667–74
64. Jimenez AH, Stubbs ME, Tofler GH, Winther K, Williams GH, Muller JE. Rapidity and duration of platelet suppression by enteric-coated aspirin in healthy young men. Am J Cardiol 1992;69:258–62
65. Beving H, Zhao C, Albage A, Invert T. Abnormally high platelet activity after discontinuation of acetylsalicylic acid treatment. Blood Coagul Fibrinolysis 1996;7:80–4
66. Collet JP, Montalescot G, Blanchet B, Tanguy ML, Golmard JL, Choussat R, Beygui F, Payot L, Vignolles N, Metzger JP, Thomas D. Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndromes. Circulation 2004;110:2361–7
67. Ferrari E, Benhamou M, Cerboni P, Marcel B. Coronary syndromes following aspirin withdrawal: a special risk for late stent thrombosis. J Am Coll Cardiol 2005;45:456–9
68. Xiao Z, Theroux P. Clopidogrel inhibits platelet-leukocyte interactions and thrombin receptor agonist peptide-induced platelet activation in patients with an acute coronary syndrome. J Am Coll Cardiol 2004;43:1982–8
69. McLachlan CS, Tay SK, Almsherqi Z, Chia SH. Atherothrombotic events and clopidogrel therapy. CMAJ 2007;176:349
70. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Ramirez C, Sabate M, Jimenez-Quevedo P, Hernandez R, Moreno R, Escaned J, Alfonso F, Banuelos C, Costa MA, Bass TA, Macaya C. Clopidogrel withdrawal is associated with proinflammatory and prothrombotic effects in patients with diabetes and coronary artery disease. Diabetes 2006;55:780–4
71. Eagle KA, Guyton RA, Davidoff R, Edwards FH, Ewy GA, Gardner TJ, Hart JC, Herrmann HC, Hillis LD, Hutter AM Jr, Lytle BW, Marlow RA, Nugent WC, Orszulak TA, Antman EM, Smith SC Jr, Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Ornato JP; for the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery, American Society for Thoracic Surgery, and Society of Thoracic Surgeons. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2004;44:e213–e310
72. Stein PD, Schunemann HJ, Dalen JE, Gutterman D. Antithrombotic therapy in patients with saphenous vein and internal mammary artery bypass grafts: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126(3 suppl):600S–608S
73. Mangano D; Multicenter Study of Perioperative Ischemia Research Group. Aspirin and mortality from coronary bypass surgery. N Engl J Med 2002;347:1309–17
74. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—II: maintenance of vascular graft or arterial patency by antiplatelet therapy. BMJ 1994;308:159–68
75. Jackson MR, Clagett GP. Antithrombotic therapy in peripheral arterial occlusive disease. Chest 2001;119 (1 Suppl):283S–299S

76. Lindblad B, Persson NH, Takolander R, Bergqvist D. Does low-dose acetylsalicylic acid prevent stroke after carotid surgery? A double-blind, placebo-controlled randomized trial. Stroke 1993;24:1125–8
77. Burger W, Chemnitius JM, Kneissl GD, Rucker G. Low-dose aspirin for secondary cardiovascular prevention—cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation—review and meta-analysis. J Intern Med 2005;257:399–414
78. Ferraris VA, Ferraris SP, Lough FC, Berry WR. Preoperative aspirin ingestion increases operative blood loss after coronary artery bypass grafting. Ann Thorac Surg 1988;45:71–4
79. Bashein G, Nessly ML, Rice AL, Counts RB, Misbach GA. Preoperative aspirin therapy and reoperation for bleeding after coronary artery bypass surgery. Arch Intern Med 1991; 151:89–93
80. Sun JCJ, Crowther MA, Warkentin TE, Lamy A, Teoh KH. Should aspirin be discontinued before coronary artery bypass surgery? Circulation 2005;112:e85–e90
81. Tuman KJ, McCarthy RJ, O'Connor CJ, McCarthy WE, Ivankovich AD. Aspirin does not increase allogenic blood transfusion in reoperative coronary artery surgery. Anesth Analg 1996;83:1178–84
82. Srinivasan AK, Grayson AD, Pullan DM, Fabri BM, Dihmis WC. Effect of preoperative aspirin use in off-pump coronary artery bypass operations. Ann Thorac Surgery 2003;76:41–5
83. Ferraris VA, Ferraris SP, Moliterno DJ, Camp P, Walenga JM, Messmore HL, Jeske WP, Edwards FH, Royston D, Shahian DM, Peterson E, Bridges CR, Despotis G; Society of Thoracic Surgeons. The Society of Thoracic Surgeons practice guideline series: aspirin and other antiplatelet agents during operative coronary revascularization (executive summary). Ann Thorac Surg 2005;79:1454–61
84. Taggart DP, Siddiqui A, Wheatley DJ. Low-dose preoperative aspirin therapy, postoperative blood loss, and transfusion requirements. Ann Thorac Surg 1990;50:424–8
85. Kitchen L, Erichson RB, Sideropoulos H. Effect of drug-induced platelet dysfunction on surgical bleeding. Am J Surg 1982;143:215–17
86. Watson CJE, Deane AM, Doyle PT, Bullock KN. Identifiable factors in post-prostatectomy haemorrhage: the role of aspirin. Br J Urol 1990;66:85–7
87. Ferraris VA, Swanson E. Aspirin usage and perioperative blood loss in patients undergoing unexpected operations. Surg Gynecol Obstet 1983;156:439–42
88. Stage J, Jensen JH, Bonding P. Post-tonsillectomy haemorrhage and analgesics. A comparative study of acetylsalicylic acid and paracetamol. Clin Otolaryngol Allied Sci 1988;13:201–4
89. Thurston AV, Briant SL. Aspirin and post-prostatectomy haemorrhage. Br J Urol 1993;71:574–6
90. Palmer JD, Sparrow OC, Iannotti F. Postoperative hematoma: a 5-year survey and identification of avoidable risk factors. Neurosurgery 1994;35:1061–4
91. Merritt JC, Bhatt DL. The efficacy and safety of perioperative antiplatelet therapy. J Thromb Thrombolysis 2004;17:21–7
92. Grines CL, Bonow RO, Casey DE Jr, Gardner JT, Lockhart PB, Moliterno DJ, O'Gara P. Whitlow P. AHA/ACC/SCAI/ACS/ADA Science Advisory. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents. A science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. Circulation 2007;115: 813–18
93. Yende S, Wunderink RG. Effect of clopidogrel on bleeding after coronary artery bypass surgery. Crit Care Med 2001;29:2271–5
94. Ray JG, Deniz S, Olivieri A, Pollex E, Vermeulen MJ, Alexander KS, Cain DJ, Cybulsky I, Hamielec CM. Increased blood product use among coronary artery bypass patients prescribed preoperative aspirin and clopidogrel. BMC Cardiovasc Disord 2003;3:3
95. Chen L, Bracey AW, Radovancevic R, Cooper JR Jr, Collard CD, Vaughn WK, Nussmeier NA. Clopidogrel and bleeding in patients undergoing elective coronary artery bypass grafting. J Thorac Cardiovasc Surg 2004;128:425–31
96. Kapetanakis EI, Medlam DA, Boyce SW, Haile E, Hill PC, Dullum MK, Bafi AS, Petro KR, Corso PJ. Clopidogrel administration prior to coronary artery bypass grafting surgery: the cardiologist's panacea or the surgeon's headache? Eur Heart J 2005;26:576–83
97. Leong J-Y, Baker RA, Shah PJ, Cherian VK, Knight JL. Clopidogrel and bleeding after coronary artery bypass graft surgery. Ann Thorac Surg 2005;80:928–33
98. Purkayastha S, Athanasiou T, Malinovski V, Tekkis P, Foale R, Casula R, Glenville B, Darzi A. Does clopidogrel affect outcome after coronary artery bypass grafting? A meta-analysis. Heart 2006;92:531–2
99. Chu MWA, Wilson SR, Novick RJ, Stitt LW, Quantz MA. Does clopidogrel increase blood loss following coronary artery bypass surgery? Ann Thorac Surg 2004;78:1536–41
100. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kerpiakes D, Kupersmith J, Levin TN, Pepine Cj, Schaeffer JW, Smith EE III, Steward DE, Theroux P, Gibbons RJ, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Smith SC Jr. American College of Cardiology, American Heart Association. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). J Am Coll Cardiol 2002;40:1366–74
101. Grubitzsch H, Wollert HG, Eckel L. Emergency coronary artery bypass grafting: does excessive preoperative anticoagulation increase bleeding complications and transfusion requirements? Cardiovasc Surg 2001;9:510–16
102. Karabulut H, Toraman F, Evrenkaya S, Goksel O, Tarcan S, Alhan C. Clopidogrel does not increase bleeding and allogenic blood transfusion in coronary artery surgery. Eur J Cardiothorac Surg 2004;25:419–23
103. Fox KAA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ, Yusuf S; Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events Trials. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome. Circulation 2004;110:1202–8
104. Kapetanakis EI, Medlam DA, Petro KR, Haile E, Hill E, Hill PC, Dullum MK, Bafi AS, Boyce SW, Corso RJ. Effect of clopidogrel premedication in off-pump cardiac surgery: are we forfeiting the benefits of reduced hemorrhagic sequelae? Circulation 2006;113:1667–74
105. Koch CG, Li L, Duncan AI, Mihaljevic T, Cosgrove DM, Loop FD, Starr NJ, Blackstone EH. Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. Crit Care Med 2006;34:1608–16
106. Koch CG, Li L, Duncan AI, Mihaljevic T, Loop FD, Starr NJ, Blackstone EH. Transfusion in coronary artery bypass grafting is associated with reduced long-term survival. Ann Thorac Surg 2006;81:1650–7
107. Lecompte T, Hardy J-F. Antiplatelet agents and perioperative bleeding. Can J Anaesth 2006;53(6 Suppl):S103–112
108. Eikelboom JW, Hirsch J. Bleeding and management of bleeding. Eur Heart J Suppl 2006;8(Suppl):G38–45
109. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494–502
110. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71–86
111. Moore M, Power M. Perioperative hemorrhage and combined clopidogrel and aspirin therapy. Anesthesiology 2004;101:792–4
112. Chapman TW, Bowley DM, Lambert AW, Walker AJ, Ashley SA, Wilkins DC. Haemorrhage associated with combined clopidogrel and aspirin therapy. Eur J Vasc Endovasc Surg 2001;22:478–9

113. Beard JD, Mountney J, Wilkinson JM, Payne A, Dicks J, Mitton D. Prevention of postoperative wound haematomas and hyperperfusion following carotid endarterectomy. Eur J Vasc Endovasc Surg 2001;21:490–3
114. Ernst A, Eberhardt R, Wahidi M, Becker HD, Herth FJ. Effect of routine clopidogrel use on bleeding complications after transbronchial biopsy in humans. Chest 2006;129:734–7
115. Payne DA, Hayes PD, Jones CI, Balham P, Naylor AR, Goodall AH. Combined therapy with clopidogrel and aspirin significantly increases the bleeding time through a synergistic antiplatelet action. J Vasc Surg 2002;35:1204–9
116. Payne DA, Jones CI, Hayes PD, Thompson MM, London NJ, Bell PR, Goodall AH, Naylor AR. Beneficial effects of clopidogrel combined with aspirin in reducing cerebral emboli in patients undergoing carotid endarterectomy. Circulation 2004;109:1476–81
117. Lockhart PB, Gibson J, Pond SH, Leitch J. Dental management considerations for the patient with an acquired coagulopathy: Part II: coagulapathies from drugs. Br Dent J 2003;195:495–501
118. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996;348:1329–39
119. Bhatt DL, Chew DP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Superiority of clopidogrel versus aspirin in patients with prior cardiac surgery. Circulation 2001;103:363–8
120. Patterson L, Hunter D, Mann A. Appropriate waiting time for noncardiac surgery following coronary stent insertion: views of Canadian anesthesiologists. Can J Anesthesiol 2005;52:440–1
121. Brilakis ES, Banerjee S, Berger PB. Perioperative management of patients with coronary stents. J Am Coll Cardiol 2007;49:2145–50
122. Yan BP, Gurvitch R, Ajani AE. Double jeopardy: balance between bleeding and stent thrombosis with prolonged dual antiplatelet therapy after drug-eluting stent implantation. Cardiovasc Revasc Med 2006;7:155–8
123. Schouten O, Poldermans D. Coronary stent placement prior to non-cardiac surgery. Eur Cardiovasc Dis 2006;2:1–4
124. Albaladejo P, Marret E, Piriou V, Samama CM; French Society of Anesthesiology and Intensive Care. Perioperative management of antiplatelet agents in patients with coronary stents: recommendations of a French Task Force. Br J Anaesth 2006;97:580–2
125. Rodriguez AE, Mieres J, Fernandez-Pereira C, Vigo CF, Rodriguez-Alemparte M, Berrocal D, Grinfeld L, Palacios I. Coronary stent thrombosis in the current drug-eluting stent era: insights from the ERACI III trial. J Am Coll Cardiol 2006;47:205–7
126. Newsome LT, Kutcher MA, Gandhi SK, Prielipp RC, Royster RL. A protocol for the perioperative management of patients with intracoronary drug-eluting stents. APSF Newsletter 2007;21:81–2
127. Hutter AM Jr, Lincoff M, Grines C, Bhatt D. ACC Conversations with Experts: Preventing late thrombosis of drug-eluting stents. Available at: http://conversations.acc.org/modules/conv/acc/0607c/main.asp?bhcp=1. Accessed October 25, 2007
128. Park KW Tim. Drug & Innovation Update: Coronary Drug-Eluting Stents. Society of Cardiovascular Anesthesiologists Newsletter 2007;6(3). Available at: http://www.scahq.org/sca3/newsletters/2007jun/di_update.pdf. Accessed October 25, 2007
129. Patrono C, Bachmann F, Baigent C, Bode C, De Caterina R, Charbonnier B, Fitzgerald D, Hirsh J, Husted S, Kvasnicka J, Montalescot G, García Rodríguez LA, Verheugt F, Vermylen J, Wallentin L, Priori SG, Alonso Garcia MA, Blanc JJ, Budaj A, Cowie M, Dean V, Deckers J, Fernández Burgos E, Lekakis J, Lindahl B, Mazzotta G, Morais J, Oto A, Smiseth OA, Morais J, Deckers J, Ferreira R, Mazzotta G, Steg PG, Teixeira F, Wilcox R; European Society of Cardiology. Expert consensus document on the use of antiplatelet agents. The task force on the use of antiplatelet agents in patients with atherosclerotic cardiovascular disease of the European society of cardiology. Eur Heart J 2004;25:166–81
130. Kimmel SE, Berlin JA, Reilly M, Jaskowiak J, Kishel L, Chittams J, Strom BL. The effects of nonselective non-aspirin nonsteroidal anti-inflammatory medications on the risk of nonfatal myocardial infarction and their interaction with aspirin. J Am Coll Cardiol 2004;43:985–90
131. MacDonald TM, Wei L. Effect of ibuprofen on cardioprotective effect of aspirin. Lancet 2003;361:573–4
132. Catella-Lawson F, Reilly MP, Kapoor SC, Cucchiara AJ, DeMarco S, Tournier B, Vyas SN, FitzGerald GA. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. N Engl J Med 2001;345:1809–17
133. Théroux P, Waters D, Lam J, Juneau M, McCans J. Reactivation of unstable angina after the discontinuation of heparin. N Engl J Med 1992;327:141–5
134. Granger CB, Miller JM, Bovill EG, Gruber A, Tracy RP, Krucoff MW, Green C, Berrios E, Harrington RA, Ohman EM, Califf RM. Rebound increase in thrombin generation and activity after cessation of intravenous heparin in patients with acute coronary syndromes. Circulation 1995;91:1929–35
135. Xiao Z, Théroux P. Platelet activation with unfractionated heparin at therapeutic concentrations and comparisons with a low-molecular-weight heparin and with a direct thrombin inhibitor. Circulation 1998;97:251–6
136. Webster SE, Payne DA, Jones CI, Hayes PD, Bell PR, Goodall AH, Naylor AR. Antiplatelet effect of aspirin is substantially reduced after administration of heparin during carotid endarterectomy. J Vasc Surg 2004;40:463–8
137. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. N Engl J Med 1998;338:1488–97
138. McDonald SB, Renna M, Spitznagel EL, Avidan M, Hogue CW Jr, Moon MR, Barzilai B, Saleem R, McDonald JM, Despotis GJ. Preoperative use of enoxaparin increases the risk of postoperative bleeding and re-exploration in cardiac surgery patients. J Cardiothorac Vasc Anesth 2005;19:4–10
139. Fitchett DH, Langer A, Armstrong PW, Tan M, Mendelsohn A, Goodman SG; INTERACT Trial Long-Term Follow-up Investigators. Randomized evaluation of the efficacy of enoxaparin versus unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes receiving the glycoprotein IIb/IIIa inhibitor eptifibatide. Long-term results of the Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment (INTERACT) trial. Am Heart J 2006;151:373–9
140. Goodman S. Enoxaparin and glycoprotein IIb/IIIa inhibition in non-ST-elevation acute coronary syndrome: insights from the INTERACT trial. Am Heart J 2005;149(4 Suppl):S73–80
141. Di Nisio M, Bijsterveld NR, Meijers JC, Levi M, Buller HR, Peters RJ. Effects of clopidogrel on the rebound hypercoagulable state after heparin discontinuation in patients with acute coronary syndromes. J Am Coll Cardiol 2005;46:1582–3
142. Brilakis ES, Banerjee S, Berger PB. The risk of drug-eluting stent thrombosis with noncardiac surgery. Curr Cardiol Rep 2007;9:406–11
143. Broad L, Lee T, Conroy M, Bolsin S, Orford N, Black A, Birdsey G. Successful management of patients with a drug-eluting coronary stent presenting for elective, non-cardiac surgery. Br J Anaesth 2007;98:19–22
144. Newsome L, Royster R, Prielipp R. Cardiology experts share perspective on stents. Response to letter to the editor: antiplatelet therapy should not be stopped. Anesth Patient Safety Newslett 2007;22:32–3
145. Topol EJ, Byzova TV, Plow EF. Platelet GPIIb-IIIa blockers. Lancet 1999;353:227–31
146. Nurden AT, Poujol C, Durrieu-Jais C, Nurden P. Platelet glycoprotein IIb-IIIa inhibitors. Arterioscler Thromb Vasc Biol 1999;19:2835–6
147. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. N Engl J Med 1998;339:436–43
148. Shattil SJ, Kashiwagi H, Pampori N. Integrin signaling: the platelet paradigm. Blood 1998;91:2645–57
149. Meadows TA, Bhatt DL. Clinical aspects of platelet inhibitors and thrombus formation. Circ Res 2007;100:1261–75
150. Weant KA, Flynn JF, Akers WS. Management of antiplatelet therapy for minimization of bleeding risk before cardiac surgery. Pharmacotherapy 2006;26:1616–25
151. Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. Eur Heart J 2006;27:1038–47

152. Greenbaum AB, Grines CL, Bittl JA, Becker RC, Kereiakes DJ, Gilchrist IC, Clegg J, Stankowski JE, Grogan DG, Harrington RA, Emanuelsson H, Weaver WD. Initial experience with an intravenous P2Y12 platelet receptor antagonist in patients undergoing percutaneous coronary intervention: results from a 2-part, phase II, multicenter, randomized, placebo- and active-controlled trial. Am Heart J 2006;151:689.e1–689.e10
153. Cattaneo M. P2Y12receptor antagonists: a rapidly expanding group of antiplatelet agents. Eur Heart J 2006;27:1010–2
154. A Clinical Trial Comparing Cangrelor to Clopidogrel in Subjects Who Require Percutaneous Coronary Intervention. September 21, 2006. Available at: http://www.clinicaltrials.gov/ct/show/NCT00305162. Accessed October 25, 2007
155. A Clinical Trial Comparing Treatment with Cangrelor (in Combination With Usual Care) to Usual Care, in Subjects Who Require Percutaneous Coronary Intervention. October 5, 2006. Available at: http://www.clinicaltrials.gov/ct/show/NCT00385138. Accessed October 25, 2007
156. Cannon CP, Husted S, Harrington RA, Scirica BM, Emanuelsson H, Peters G, Storey RF, for the DISPERSE-2 Investigators. Safety, tolerability and initial efficacy of AZD6140, the first reversible, oral ADP receptor antagonist compared with clopidogrel in patients with non-ST elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. J Am Coll Cardiol 2007;50:1844–51
157. Husted S. New developments in oral antiplatelet therapy. Eur Heart J 2007;Suppl 9(Suppl D):D20–D27
158. Fugate SE, Cudd LA. Cangrelor for treatment of coronary thrombosis. Ann Pharmacother 2006;40:925–30
159. A Randomised, Double-Blind, Parallel Group, Phase 3, Efficacy and Safety Study of AZD6140 Compared With Clopidogrel for Prevention of Vascular Events in Patients With Non-ST or ST Elevation Acute Coronary Syndromes (ACS) [PLATO-a Study of PLATelet Inhibition and Patient Outcomes] October 27, 2006. Available at: http://www.clinicaltrials.gov/ct/show/NCT00391872
160. Cuisset T, Frere C, Quilici J, Morange PE, Nait-Saidi L, Carvajal J, Lehmann A, Lambert M, Bonnet JL, Alessi MC. Benefit of a 600-mg loading dose of clopidogrel on platelet reactivity and clinical outcomes in patients with non-ST-segment elevation acute coronary syndrome undergoing coronary stenting. J Am Coll Cardiol 2006;48:1339–45
161. Hochholzer W, Trenk D, Bestehorn HP, Fischer B, Valina CM, Ferenc M, Gick M, Caputo A, Buttner HJ, Neumann FJ. Impact of the degree of peri-interventional platelet inhibition after loading with clopidogrel on early clinical outcome of elective coronary stent placement. J Am Coll Cardiol 2006;48:1742–50
162. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Ramirez C, Sabate M, Banuelos C, Hernandez-Antolin R, Escaned J, Moreno R, Alfonso F, Macaya C. High clopidogrel loading dose during coronary stenting: effects on drug response and interindividual variability. Eur Heart J 2004;25:1903–10
163. Hochholzer W, Trenk D, Frundi D, Neumann FJ. Whole blood aggregometry for evaluation of the antiplatelet effects of clopidogrel. Thromb Res 2007;119:285–91
164. Muller I, Seyfarth M, Rudiger S, Wolf B, Pogatsa-Murray G, Schomig A, Gawaz M. Effect of a high loading dose of clopidogrel on platelet function in patients undergoing coronary stent placement. Heart 2001;85:92–3
165. Ohno Y, Hisaka A, Suzuki H. General framework for the quantitative prediction of CYP3A4-mediated oral drug interactions based on the AUC increase by coadministration of standard drugs. Clin Pharmacokinet 2007;46:681–96
166. Kanazawa H, Okada A, Igarashi E, Higaki M, Miyabe T, Sano T, Nishimura R. Determination of midazolam and its metabolite as a probe for cytochrome P450 3A4 phenotype by liquid chromatography-mass spectrometry. J Chromatogr A 2004;1031:213–8
167. Zhou S, Yung Chan S, Cher Goh B, Chan E, Duan W, Huang M, McLeod HL. Mechanism-based inhibition of cytochrome P450 3A4 by therapeutic drugs. Clin Pharmacokinet 2005;44:279–304
168. Zhou S, Chan E, Lim LY, Boelsterli UA, Li SC, Wang J, Zhang Q, Huang M, Xu A. Therapeutic drugs that behave as mechanism-based inhibitors of cytochrome P450 3A4. Curr Drug Metab 2004;5:415–42
169. Suh JW, Koo BK, Zhang SY, Park KW, Cho JY, Jang IJ, Lee DS, Sohn DW, Lee MM, Kim HS. Increased risk of atherothrombotic events associated with cytochrome P450 3A5 polymorphism in patients taking clopidogrel. CMAJ 2006;174:1715–22
170. Sheu JR, Hsiao G, Luk HN, Chen YW, Chen TL, Lee LW, Lin CH, Chou DS. Mechanisms involved in the antiplatelet activity of midazolam in human platelets. Anesthesiology 2002; 96:651–8
171. Hsiao G, Shen MY, Chou DS, Chang Y, Lee LW, Lin CH, Sheu JR. Mechanisms of antiplatelet and antithrombotic activity of midazolam in in vitro and in vivo studies. Eur J Pharmacol 2004;487:159–66
172. Oda Y, Mizutani K, Hase I, Nakamoto T, Hamaoka N, Asada A. Fentanyl inhibits metabolism of midazolam: competitive inhibition of CYP3A4 in vitro. Br J Anaesth 1999;82:900–3
173. Klees TM, Sheffels P, Dale O, Kharasch ED. Metabolism of alfentanil by cytochrome p4503a (cyp3a) enzymes. Drug Metab Dispos 2005;33:303–11
174. Leung BP, Miller E, Park GR. The effect of propofol on midazolam metabolism in human liver microsome suspension. Anaesthesia 1997;52:945–8
175. Rozalski M, Nocun M, Watala C. Adenosine diphosphate receptors on blood platelets - potential new targets for antiplatelet therapy. Acta Biochim Pol 2005;52:411–15
176. Cattaneo M. Aspirin and clopidogrel: efficacy, safety, and the issue of drug resistance. Arterioscler Thromb Vasc Biol 2004;24:1980–7
177. Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. BMJ 2005;330:1366
178. Graham DJ, Campen D, Hui R, Spence M, Cheetham C, Levy G, Shoor S, Ray WA. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. Lancet 2005;365:475–81
179. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. BMJ 2006;332:1302–8
180. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. JAMA 2006;296:1633–44
181. Wang TH, Bhatt DL, Topol EJ. Aspirin and clopidogrel resistance: an emerging clinical entity. Eur Heart J 2006;27:647–54
182. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13–20
183. Dupuis J-Y, Labinaz M. Noncardiac surgery in patients with coronary artery stent: what should the anesthesiologist know? Can J Anaesth 2005;52:356–61
184. Howard-Alpe GM, de Bono J, Hudsmith L, Orr WP, Foex P, Sear JW. Coronary artery stents and non-cardiac surgery. Br J Anaesth 2007;98:560–74
185. Devereaux PJ, Goldman L, Yusuf S, Gilbert K, Leslie K, Guyatt GH. Surveillance and prevention of major perioperative ischemic cardiac events in patients undergoing noncardiac surgery: a review. CMAJ 2005;173:779–88
186. Adesanya AO, de Lemos JA, Greilich NB, Whitten CW. Management of perioperative myocardial infarction in noncardiac surgical patients. Chest 2006;130:584–96
187. Berger PB, Bellot V, Bell MR, Horlocker TT, Rihal CS, Hallett JW, Dalzell C, Melby SJ, Charnoff NE, Holmes DR Jr. An immediate invasive strategy for the treatment of acute myocardial infarction early after noncardiac surgery. Am J Cardiol 2001;87:1100–2
188. Park WY, Thompson JS, Lee KK. Effect of epidural anesthesia and analgesia on perioperative outcome: a randomized, controlled Veterans Affairs cooperative study. Ann Surg 2001;234:560–71
189. Christopherson R, Beattie C, Frank SM, Norris EJ, Meinert CL, Gottlieb SO, Yates H, Rock P, Parker SD, Perler BA, Williams M. The Perioperative Ischemia Randomized Anesthesia Trial Study Group. Perioperative morbidity in patients randomized to epidural or general anesthesia for lower extremity vascular surgery. Perioperative Ischemia Randomized Anesthesia Trial Study Group. Anesthesiology 1993;79:422–34
190. Rodgers A, Walker N, Schug S, McKee A, Kehlet H, van Zundert A, Sage D, Futter M, Saville G, Clark T, MacMahon S. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. BMJ 2000;321:1493

191. Kehlet H, Holte K. Effect of postoperative analgesia on surgical outcome. Br J Anaesth 2001;87:62–72
192. Kohrs R, Hoenemann CW, Feirer N, Durieux ME. Bupivacaine inhibits whole blood coagulation in vitro. Reg Anesth Pain Med 1999;24:326–30
193. Borg T, Modig J. Potential anti-thrombotic effects of local anaesthetics due to their inhibition of platelet aggregation. Acta Anaesthesiol Scand 1985;29:739–42
194. Orr JE, Lowe GD, Nimmo WS, Watson R, Forbes CD. A haemorheological study of lignocaine. Br J Anaesth 1986;58:306–9
195. Horlocker TT, Wedel DJ, Benzon H, Brown DL, Enneking FK, Heit JA, Mulroy MF, Rosenquist RW, Rowlingson J, Tryloa M, Yuan CS. Regional anesthesia in the anticoagulated patient: defining the risks (the second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). Reg Anesth Pain Med 2003;28:172–97
196. Litz RJ, Gottschlich B, Stehr SN. Spinal epidural hematoma after spinal anesthesia in a patient treated with clopidogrel and enoxaparin. Anesthesiology 2004;101:1467–70
197. Tam NLK, Pac-Soo C, Pretorius PM. Epidural haematoma after a combined spinal-epidural anaesthetic in a patient treated with clopidogrel and dalteparin. Br J Anaesth 2006;96:262–5
198. Weller RS, Gerancher JC, Crews JC, Wade KL. Extensive retroperitoneal hematoma without neurologic deficit in two patients who underwent lumbar plexus block and were later anticoagulated. Anesthesiology 2003;98:581–5
199. Horlocker TT, Wedel DJ, Schroeder DR, Rose SH, Elliott BA, McGregor DG, Wong GY. Preoperative antiplatelet therapy does not increase the risk of spinal hematoma associated with regional anesthesia. Anesth Analg 1995;80:303–9
200. Moen V, Dahlgren N, Irestedt L. Severe neurological complications after central neuraxial blockades in Sweden 1990–1999. Anesthesiology 2004;101:950–9
201. CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group. CLASP: A randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. Lancet 1994;343:619–29
202. Douketis JD, Dentali F. Managing anticoagulant and antiplatelet drugs in patients who are receiving neuraxial anesthesia and epidural analgesia: a practical guide for clinicians. Techniques in Regional Anesthesia and Pain Management 2006;10:46–55
203. Vandermeulen EP, Van Aken H, Vermylen J. Anticoagulants and spinal-epidural anesthesia. Anesth Analg 1994;79:1165–77
204. Layton KF, Kallmes DF, Horlocker TT. Recommendations for anticoagulated patients undergoing image-guided spinal procedures. Am J Neuroradiol 2006;27:468–70
205. Allen DJ, Chae-Kim SH, Trousdale DM. Risks and complications of neuraxial anesthesia and the use of anticoagulation in the surgical patient. Proc (Bayl Univ Med Cent) 2002;15:369–73
206. Bengeri S. Coronary artery stents and non-cardiac surgery. Br J Anaesth 2007;99:299–300
207. Self RE, Howard-Alpe GM. Regional anesthesia in patients treated with aspirin and clopidogrel. Br J Anaesth 2007;99:594–96
208. Cornet AD, Klein LJ, Groeneveld AB. Coronary stent occlusion after platelet transfusion: a case series. J Invasive Cardiol 2007;19:E297–9
209. Vilahur G, Choi BG, Zafar MU, Viles-Gonzalez JF, Vorchheimer DA, Fuster V, Badimon JJ. Normalization of platelet reactivity in clopidogrel-treated subjects. J Thromb Haemost 2007;5:82–90
210. Gawaz M, Neumann FJ, Ott I, Schiessler A, Schömig A. Platelet function in acute myocardial infarction treated with direct angioplasty. Circulation 1996;93:229–37
211. Lev EI, Alviar CL, Arikan ME, Dave BP, Granada JF, DeLao T, Tellez A, Maresh K, Kleiman NS. Platelet reactivity in patients with subacute stent thrombosis compared with non-stent-related acute myocardial infarction. Am Heart J 2007;153:41.e1–6
212. Popescu WM, Gusberg RJ, Barash PG. Epidural catheters and drug-eluting stents: a challenging relationship. J Cardiothorac Vasc Anesth 2007;21:701–3
213. Hopkins PM. Ultrasound guidance as a gold standard in regional anesthesia. Br J Anaesth 2007;98:299–301