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STATE-OF-THE-ART PAPER

Drug-Eluting Stent Thrombosis

The Kounis Hypersensitivity-Associated Acute Coronary Syndrome Revisited

Jack P. Chen, MD,* Dongming Hou, MD, PhD,* Lakshmana Pendyala, MD,*
John A. Goudevenos, MD, PhD,† Nicholas G. Kounis, MD, PhD‡

Atlanta, Georgia; and Ioannina and Patras, Greece

The advent of drug-eluting stents (DES) has revolutionized the field of interventional cardiology. Their dramatic and persistent restenotic and target lesion revascularization advantages are unquestioned. However, concerns over the rare but potentially catastrophic risk of stent thrombosis (ST) have tempered universal acceptance of these devices. Although the precise mechanism of DES ST is undoubtedly multifactorial and as yet not fully elucidated, delayed or incomplete endothelial healing clearly plays a pivotal role. Detailed histopathological data have implicated a contributory allergic or hypersensitivity component, as verified by the Food and Drug Administration's Manufacturer and User Device Experience Center and the Research on Adverse Drug/device events And Reports (RADAR) project. These findings thus suggest a potential connection with the Kounis syndrome, the concurrence of acute coronary events with allergic, hypersensitivity, anaphylactic, or anaphylactoid reactions. Potential culprits responsible for this phenomenon include: arachidonic acid metabolites such as leukotrienes and thromboxane, proteolytic enzymes such as chymase and tryptase, histamine, cytokines, and chemokines. Additionally, inflammatory cells such as macrophages, T-lymphocytes, and mast cells are probably also contributory. Autopsy-confirmed infiltrates of various inflammatory cells including lymphocytes, plasma cells, macrophages, and eosinophils have been reported in all 3 vascular wall layers and are reminiscent of those associated with the Kounis syndrome. Although the concurrence of acute coronary syndromes with hypersensitivity reactions has been long established, the specific association with DES ST remains unproven. Potential incorporation of hypersensitivity suppressive agents might represent a promising paradigm shift from efficacy to safety in future DES designs. (J Am Coll Cardiol Intv 2009;2:583–93) © 2009 by the American College of Cardiology Foundation

The advent of drug-eluting stents (DES) has witnessed dramatic reductions in clinical restenosis and the need for target lesion revascularization (TLR) over prior bare-metal counterparts (1,2). Initial enthusiasm, however, has been tempered by growing concerns surrounding risks of late stent thrombosis (ST) and very late ST. In his address to the 2006 European Society of Cardiology, Camenzind (3) reported a significantly higher 6.3% combined death/myocardial infarction (MI) rate of DES over the 3.9% observed for bare-metal stents (BMS). This announcement amplified brewing concerns raised by previous isolated reports of DES late/very late ST. The Academic Research Consortium (ARC) has further subclassified ST according to the timing and relative certainty of the diagnosis (Table 1) (4).

From the *Saint Joseph's Translational Research Institute, Saint Joseph's Heart and Vascular Institute, Atlanta, Georgia; †Cardiology Department, Ioannina University Medical School, Ioannina, Greece; and ‡Medical Sciences, Patras Highest Institute of Education and Technology, Patras, Greece. Sotirios Tsimikas, MD, served as Guest Editor for this paper.

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DES ST

Studies have differed in conclusions regarding overall DES and BMS thrombosis rates, however. Specifically, the RESEARCH (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology

Hospital) registry reported a 0.4% DES ST rate compared with 1.6% for BMS ($p = 0.10$). All events occurred within 30 days of implantation (5). The meta-analysis of 4 of the TAXUS (Boston Scientific, Natick, Massachusetts) randomized trials by Ellis et al. (6) reported similar 3-year cumulative ST rates for DES and BMS patients of 1.28 ± 0.31% and 0.76 ± 0.23%, respectively ($p = 0.26$). Thrombosis rates from 6 months to 3 years, however, were higher for DES versus BMS (hazard ratio [HR]: 0.19 vs. 0.02, $p = 0.05$). Of note, no patients with DES were receiving clopidogrel at the time of ST.

The much-publicized BASKET-LATE (Basel Stent Kosten Effiktivitats Trial-Late Thrombotic Events) followed 544 DES and 281 BMS patients for 18 months after implantation. The investigators found that DES patients experienced higher major adverse cardiovascular event (MACE) rates from 6 to 18 months. In particular, there were absolute excesses in late mortality of 1.2% (1.2% vs. 0%, $p = 0.09$) and nonfatal MI of 2.7% (4.1% vs. 1.3%, $p = 0.04$), compared with BMS. Nonetheless, no difference in cumulative MACE was observed, owing to the early (<6-month) benefit conferred by DES. Two noteworthy issues should be mentioned. First, dual antiplatelet therapy (DAT) with clopidogrel/acetylsalicylic acid (ASA) was continued for only 6 months in these patients. Additionally, only those patients free of events during the initial 6 months were included in the late follow-up. As expected, a higher percentage of BMS patients were thus excluded, introducing a potential bias (7). These findings further underscore the importance of adherence to prolonged DAT.

Abbreviations and Acronyms

ARC = Academic Research Consortium
ASA = acetylsalicylic acid
BMS = bare-metal stent(s)
DAT = dual antiplatelet therapy
DES = drug-eluting stent(s)
FDA = Food and Drug Administration
HR = hazard ratio
Ig = immunoglobulin
MACE = major adverse cardiovascular events
MI = myocardial infarction
PCI = percutaneous coronary intervention
ST = stent thrombosis
TLR = target lesion revascularization

More recent large-scale trials and meta-analyses, however, have reaffirmed the overall MACE equivalency of BMS and DES during long-term follow-up. From 2002 to 2005, the Western Denmark Heart Registry reported percutaneous coronary intervention (PCI) data from 12,395 patients who underwent 17,152 stent implantations. A total of 5,422 and 11,730 lesions received DES and BMS, respectively. Over the mean follow-up duration of 15 months, ARC-defined ST was observed in 1.80% and 2.15% of BMS and DES patients, respectively. Definite thrombosis rates were similar between groups, but late ST beyond 12 months occurred more frequently in the DES cohort (HR: 10.93). Furthermore, the risk of MI after 12 months was higher in the DES patients (HR: 4.00). Nonetheless, importantly, overall mortality was similar; and TLR was reduced by 43% in the DES group (HR: 0.57) (8).

Additionally, in a recent meta-analysis, Mauri et al. (9) pooled and analyzed 4-year data from 2,278 DES and 2,267 BMS patients, according to ARC criteria. No significant intergroup differences were found for overall ST or definite/probable ST. Specifically, the occurrences of definite/probable ST from 1 to 4 years were similar.

Although current data demonstrate that overall MI, ST, mortality, and MACE rates are similar for BMS and DES, that of late/very late ST seems slightly higher for DES (0.2% to 0.6%/year beyond the first year). This is counterbalanced, however, by a 10% to 15% absolute reduction in TLR seen with DES, conferring equivalent or even slightly superior MACE rates in most trials and series (10,11). The present evidence overwhelmingly supports prolonged DAT. Accordingly, the current U.S. Food and Drug Administration's (FDA) recommendations for DAT are a minimum of 1 year for DES or 1 month for BMS (4). Tables 2 and 3 summarize the ST rates in recently published randomized controlled DES trials and registries.

Pathophysiology of Late ST

The pathophysiology of ST has not been fully elucidated. A combination of factors might be involved, including procedure-related variables, patient-related issues, and lesion characteristics (12–14) (Table 4). In one prospective observational study, premature clopidogrel discontinuation predicted risk of subacute and late ST within 6 months of deployment but not beyond (14).

Late/very late ST and prevention of in-stent restenosis likely represent 2 sides of the double-edged sword of DES neointimal inhibition. Platelets, when exposed to non-endothelialized stent struts, are the key mechanistic trigger for thrombosis. Initial platelet adhesion results from binding of von Willebrand's factor, glycoprotein Ib and Ia/IIa, and collagen. Next, activation occurs via release of vasoactive factors including thrombin, adenosine diphosphate, thromboxane A2, and serotonin. Subsequently, activated platelets are linked into an aggregate meshwork by glycoprotein IIb/IIIa, serotonin, and fibrinogen. The resultant platelet plug might acutely progress to thrombotic stent occlusion (15–17). Additionally, experimental models suggest that inhibition of proliferation and differentiation of human endothelial progenitor cells might further impede delayed or absent vascular endothelial healing in DES patients. Moreover, animal DES data have demonstrated significant intramural thrombus formation within the stent lumen as well as endothelial dysfunction at both proximal and distal adjacent nonstented segments (18,19) (Figs. 1 and 2).

Table 1. Reported Rates of ST in Randomized Controlled Trials and Meta-Analyses

Study (Ref. #)	n	Study Design	Stent Type	Antiplatelet Medication and Duration	Follow-Up Duration (Months)	ST Definition	ST Rate
Moreno et al.*	5,030	Meta-analysis:	BMS (48%) SES (17%) PES (34%)	ASA+TP (1–6 months)	6–12	Unspecified	SAT: 0.35% (BMS = DES) LST: 0.23% (BMS = DES)
Bavry et al. (71)	3,817	Meta-analysis: RCT of BMS vs. PES	BMS (48%) PES (52%)	ASA+TP (0–6 months)	6–12	ACS+angio	SAT+LST: 0.6% (PES = BMS)
Kastrati et al.†	3,669	Meta-analysis: RCT of SES vs. PES	SES (50%) PES (50%)	ASA+TP (2–12 months)	6–13	ACS+angio, unexplained SCD, MI in stented territory	SAT+LST: 1.0% (PES = SES)
Mauri et al. (9)	4,545	Meta-analysis: RCT of BMS vs. DES	BMS (50%) SES (19%) PES (31%)	ASA+TP (2–6 months)	48	ARC: definite+probable	SES vs. BMS SAT 0.5% vs. 0.3% LST 0.1% vs. 1% VLST 0.9% vs. 0.4% PES vs. BMS SAT 0.5% vs. 0.5% LST 0.4% vs. 0.3% VLST 0.9% vs. 0.6%
Pfisterer et al. (BASKET-LATE) (7)	746	RCT of BMS vs. DES	BMS (38%) SES (34%) PES (38%)	ASA	18	Definite: ACS+angio Possible: all SCD and MI attributable to the target vessel	Definite: DES 1.4% vs. BMS 0.8% Definite+possible: DES 2.6% vs. 1.3%
Ellis et al. (6)	3,445	Meta-analysis: RCT of BMS vs. PES	PES (50%) BMS (50%)	ASA+TP (6 months)	14–41	ACS+angio, MI in stented territory	SAT: PES 0.5% vs. BMS 0.5% LST+VLST: PES 0.5% vs. BMS 0.06%
Stone et al. (2)	5,261	Meta-analysis: RCT of BMS vs. DES	BMS (50%) SES (17%) PES (33%)	ASA+TP (2–6 months)	48	According to definitions in individual trial protocols	SES vs. BMS SAT 0.5% vs. 0.1% LST 0.5% vs. 0.1% VLST 0.6% vs. 0% PES vs. BMS SAT 0.5% vs. 0.6% LST 0.2% vs. 0.1% VLST 0.7% vs. 0.2%
Bavry et al. (10)	6,675	Meta-analysis: VLST in RCT of BMS vs. DES	BMS (50%) SES (24%) PES (26%)	ASA	12–36	ACS+angio	DES vs. BMS 0.5% vs. 0% SES vs. BMS 0.36% vs. 0% PES vs. BMS 0.59% vs. 0%

*Moreno R, Fernandez C, Hernandez R, et al. Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. J Am Coll Cardiol 2005;45:954–9. †Kastrati A, Dibra A, Eberle S, et al. Sirolimus-eluting stents vs paclitaxel-eluting stents in patients with coronary artery disease: meta-analysis of randomized trials. JAMA 2005;294:819–25.

ACS = acute coronary syndrome; angio = angiography; ARC = Academic Research Consortium; ASA = acetylsalicylic acid; bifurc = bifurcation; BASKET-LATE = Basel Stent Kosten Effiktivitats Trial-Late Thrombotic Events; BMS = bare-metal stent(s); DES = drug-eluting stent(s); LST = late stent thrombosis; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent(s); RCT = randomized controlled trial; SAT = subacute stent thrombosis; SCD = sudden cardiac death; SES = sirolimus-eluting stent(s); ST = stent thrombosis; TP = thienopyridines; VLST = very late stent thrombosis.

Human autopsy series have suggested that DES late/very late ST is partly attributable to impairment of arterial healing characterized by incomplete re-endothelialization, persistent fibrin deposition, and macrophage infiltration when compared with BMS. In a recent necropsy comparison of 23 DES with 25 BMS cases, delayed healing manifested by persistent fibrin deposition and incomplete re-endothelialization emerged as an important discriminator between BMS and DES. In cases of late/very late ST, compared with those of patent DES or BMS, re-endothelialization was reduced (27 ± 26% vs. 66 ± 25% vs. 90 ± 21%), whereas fibrin scores were increased (3.0 ± 0.9 vs. 1.9 ± 1.1 vs. 0.9 ± 0.8). Endothelial coverage was nearly complete in BMS specimens examined beyond 6 months, whereas incomplete re-endothelialization in DES specimens persisted beyond 40 months. Fourteen of 21 DES patients suffered late/very late ST, which was related to delayed healing in all cases (20). The results of this analysis, however, might have been confounded by selection bias, because DES patients were more likely to undergo autopsy for suspected ST, whereas those with BMS were likely referred for other reasons.

Mounting reports of DES late/very late ST beyond 1 year, often in association with cessation of DAT, suggest

Table 2. Reported Rates of ST: Patient Registries

Study (Ref. #)	n	Stent Type	Antiplatelet Medication and Duration	Follow-Up Duration (Months)	ST Definition	ST Rate
Ong et al.*	2,512	BMS (20%) SES (40%) PES (40%)	ASA+TP (≥1 month)	1	Definite: angio Possible: SCD or MI attributable to the target vessel	Definite: BMS 0.8%, SES 1%, PES 1% Possible: BMS 1.4%, SES, 1.5%, PES 1.6%
Lemos et al. (5)	958	BMS (53%) SES (47%)	ASA+TP (≥1 month)	12	ST: angio	SES 0.4% vs. BMS 1.6%
Jensen et al. (8)	12,395	DES (27%) SES (73%)	ASA+TP (3–12 months)	5	ARC: definite+probable+possible	Overall ST: 1.8% DES, 2.15% BMS
Iakovou et al.†	2,229	SES (48%) PES (52%)	ASA+TP (2–6 months)	9	ACS+angio, SCD or MI after successful PCI not due to another coronary lesion	SAT: 0.6% LST: 0.7%
Williams et al.‡	6,906	BMS (6%) SES (56%) PES (38%)	ASA+TP	12	Definite: angio Possible: SCD or MI attributable to the target vessel	Definite+probable: BMS 0.8%, SES 0.5%, PES 0.8%
Ong et al.§	2,006	SES (51%) PES (49%)	ASA+TP (2–6 months)	12 ± 6	ACS+angio	LST: 0.25% VLST: 0.15%
Kuchulakanti et al. (21)	2,974	SES (72%) PES (28%)	ASA+TP (≥6 month)	12	Autopsy or angio (+ACS if >30 days after PCI)	SAT: 0.84% LST: 0.27%
Daemen et al. (11)	8,146	SES (47%) PES (53%)	ASA+TP (2–6 months)	20	ACS+angio	SAT: 1.1% LST: 0.3% VLST: 0.4%

*Ong AT, Hoye A, Aoki J, et al. Thirty-day incidence and six-month clinical outcome of thrombotic stent occlusion after bare-metal, sirolimus, or paclitaxel stent implantation. J Am Coll Cardiol 2005;45:947–53. †Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293:2126–30. ‡Williams D, Abbott J, Kip K. Outcomes of 6906 patients undergoing percutaneous coronary intervention in the era of drug-eluting stents. Report of the DEScover Registry. Circulation 2006;114:2154–62. §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.
Abbreviations as in Table 1.

perhaps that even further prolongation of treatment might be appropriate (21–24). Additionally, there is compelling evidence for clopidogrel or ASA resistance as strong predictors for DES as well as BMS thrombosis (20). Buonamici et al. (15) investigated clopidogrel-induced platelet inhibition in patients after DES implantation. The incidence of subacute and late ST among nonresponders was 8.6%, compared with 2.3% among responders (HR: 3.08, p = 0.009). Although higher clopidogrel dosing (150 mg daily) might have theoretical advantages in these situations, the risk-to-benefit ratio of this treatment strategy is unknown (24). Triple antiplatelet therapy with ASA, a thienopyridine, and cilostazol has been associated with a reduced rate of subacute BMS thrombosis compared with ASA/thienopyridine (25), although the regimen's role in the DES era is undetermined.

The Kounis Syndrome: Role in Late/Very Late ST?

The Kounis, or hypersensitivity-associated acute coronary, syndrome (26) was first described 18 years ago as the concurrence of acute coronary syndrome with allergic, hypersensitivity, anaphylactic, or anaphylactoid reactions. Potential culprits responsible for this phenomenon include: arachidonic acid metabolites such as leukotrienes and thromboxane, proteolytic enzymes such as chymase and tryptase, histamine, cytokines, and chemokines. Additionally, inflammatory cells such as macrophages, T-lymphocytes, and mast cells are also contributory. Mast cells usually exist within the atherosclerotic lesion and release massive quantities of inflammation mediators such as cytokines and chemokines, leading to platelet activation. Platelets play a critical role in the inflammatory pathways. Two variants of the Kounis syndrome have been described recently. Type I includes patients with normal coronary arteries and represents a manifestation of endothelial dysfunction, whereas the Type II variant describes individuals with quiescent preexisting atheromatous disease (27).

Hypersensitivity might be an under-recognized component of ST, especially in delayed cases. All 3 components of DES can potentially elicit hypersensitivity responses involved in the Kounis syndrome (28). Patients with positive allergic patch-test reactions to the metallic strut components nickel and molybdenum seem to have increased rates of in-stent thrombosis (29). Autopsy-confirmed inflammatory cell infiltrates—namely lymphocytes, plasma cells, macrophages, and eosinophils—permeate all 3 vascular wall layers; comprising a histopathological landscape reminiscent of that observed in the Kounis syndrome (20).

Virmani et al. (30) described a case of local hypersensitivity reaction in a patient suffering DES very late ST 18 months after DES implantation. Autopsy findings revealed extensive vasculitis of the intima, media, and adventitia, consisting predominantly of lymphocytes and eosinophils. Aneurysmal coronary dilation was observed within the

Table 3. Potential Risk Factors for Drug-Eluting Stent Thrombosis

Patient factors
Diabetes mellitus
Chronic renal insufficiency
Low left ventricular ejection fraction
Acute myocardial infarction
Hypersensitivity to metal
Low or nonresponder to dual antiplatelet therapy
Early discontinuation of dual antiplatelet therapy
Lesion factors
Necrotic core lesion
Ostial lesion
Bifurcation lesion
Long lesion
Small vessel lesion
Device factors
Durable polymer
Uneven drug distribution
Incomplete drug release
Drug cytotoxicity
Uneven expansion
Foreign body
Incomplete strut coverage
Procedure factors
Overlapping stents
Multiple stents
Crush stenting
Stent malapposition or underexpansion
In-stent restenosis
Untreated residual dissection/thrombus

stented segment, with evidence of stent malapposition and thick fibrin thrombus between the stent and arterial wall. The polymer matrix was thus postulated to be the allergenic culprit, because sirolimus is nondetectable beyond 60 days.

Data derived from the FDA's Manufacturer And User Device Experience (MAUDE) Center (31) and the Research on Adverse Drug/device events And Reports (RADAR) (31,32) project have registered several hundred cases of hypersensitivity reactions in conjunction with DES implantation. They designated 17 cases as probably or definitely DES-related; of these, 4 developed fatal ST at 4, 5, 18, and 18 months after implantation, respectively. These reactions included rash, itching, hives, dyspnea, fever, atypical chest pain, hypertension, hypotension, arthralgia, joint swelling, and anaphylaxis.

Although MAUDE and RADAR data might be skewed by under-reporting, hypersensitivity to DES is now regarded as a true clinical entity with obvious serious implications. Health care providers are encouraged to submit detailed adverse event reports to the manufacturer as well as the FDA (33). The proportion of allergic reactions in the over 5 million DES implantations is well below the expected 4% for allergy from drugs alone. However, coronary events associated with hypersensitivity reactions are not common and are dependent on allergen concentration, route and rate of allergen entrance into the circulation, and magnitude of the initial allergic response. Moreover, the area and localization of antibody–antigen reaction as well as the patient's sensitivity tolerance and pre-existent comorbidities are further determinants of ultimate clinical manifestations (34). As determined by the aforementioned conditions, patient-specific threshold inflammatory cell burdens likely exist, above which smooth muscle contraction and plaque erosion or rupture might occur (35).

Several reports have implicated antineoplastic agents, such as those incorporated into DES, in hypersensitivity reactions (36–41). In 1 recent series (36), up to 42% of patients receiving systemic paclitaxel chemotherapy experienced some form of hypersensitivity reaction; and up to 2% developed serious allergic sequelae. Studies have linked this compound in both Types I and II variants of the Kounis syndrome (37–39). In another report (40), a patient experienced anaphylactic reaction during DES implantation. Upon DES deployment, the patient developed an erythematous rash, accompanied by hypotension, coronary spasm, and thrombosis. Delayed severe multivessel coronary arterial spasm and aborted sudden death have also been observed after DES implantation (41).

Hypersensitivity reactions have likewise been reported with polymers; these allergic responses are predominately type-IV reactions, involving low molecular weight haptens. Macrophages, giant cells, tissue damage, and fibrosis are seen during subcutaneous implantation of poly-n-butylmethacrylate, which is a component of bone cement and the polymer coating of sirolimus-eluting stents (42). Furthermore, the polyethylene-vinyl acetate component of the co-polymer induces inflammatory reaction in 25% of rabbits when used as an antigen delivery matrix (43).

The majority of intracoronary stents are constructed from 316L stainless steel, which contains nickel, chromium, and molybdenum. Nickel hypersensitivity occurs in up to 17.2%

Table 4. Academic Research Consortium Definition of ST

Timing of ST after stent implantation (combined acute and subacute are also considered early ST)
Acute: between 0 and 24 h
Subacute: between 24 h and 30 days
Late: between 30 days and 1 year
Very late: after 1 year
Definite ST
Angiographic confirmation: intrastent thrombus (or within 5 mm of stent edge)
Target vessel occlusion
Probable ST
Acute MI in the target vessel territory
Possible ST
Any unexplained death in a patient with prior DES implantation

Abbreviations as in Table 1.

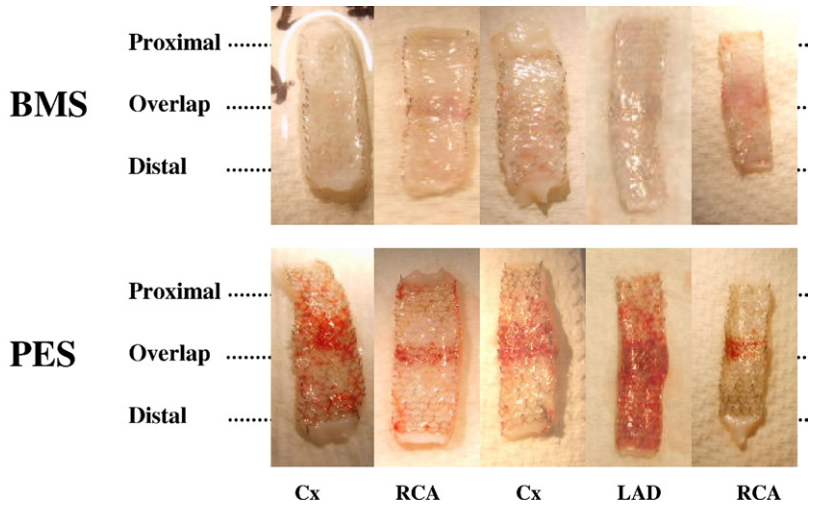

Figure 1. Macroscopic Images of Porcine Coronary Luminal Surfaces After Overlapping DES and BMS Implantation

All drug-eluting stent (DES) segments revealed mild-to-severe mural thrombi and transparently visible stent struts, consistent with absent to sparse neointima. These features are particularly prominent in the central segments of DES overlap. Conversely, bare-metal stent (BMS)-treated vessels developed robust, white neointima, with virtual strut non-visualization. Reprinted, with permission, from Pendyala et al. (19). Cx = circumflex coronary artery; LAD = left anterior descending artery; RCA = right coronary artery; PES = paclitaxel-eluting stent(s).

of the population and is the most frequent cause of allergic contact dermatitis (44). In patients undergoing percutaneous atrial septal defect and patent foramen ovale closure, nickel allergy can result in a cadre of systemic symptomatology including chest discomfort, palpitations, and migraine headache with or without aura (45). It is postulated that local allergic reaction to the implanted device could elicit platelet adhesion and activation, resulting in coronary or cerebrovascular thromboembolism (46). When nickel allergy is confirmed by patch testing, systemic allergic reactions to nitinol have necessitated the removal of these intracardiac devices (47,48). Delayed hypersensitivity reactions to nickel and molybdenum have been implicated as triggers for initiation of ST (29); the incidence of nickel allergy after initial stent deployment has been estimated at 9.2% (49). Presently, there is insufficient evidence for recommendation of widespread screening for nickel allergy for all potential DES patients. Nonetheless, given the prevalence of this metallic hypersensitivity, future research is needed to address the potential necessity for assessment of this and other component hypersensitivities before contemplation of stent implantation.

Contact allergy to gold has been associated with restenosis of gold-plated stents; these devices have since been abandoned (50). In contrast, the Titan stent (Hexacath Corporation, Pune, India), a stainless steel stent coated with titanium-nitride oxide (TINOX) can prevent discharge of nickel, chromium, and molybdenum and seems promising in the reduction of local allergy and inflammation (51). Although the concurrence of acute coronary syndrome with hypersensitivity reactions has been long-established (26), the specific association with hypersensitivity to DES components is unproven (52–54).

Furthermore, both ASA and clopidogrel, crucial therapy for DES patients, are themselves known antigenic substances (55). ASA hypersensitivity has been well-described, and prior published data have substantiated successful desensitization as a safe and beneficial strategy in the appropriate individual (56). The incidence of clopidogrel hypersensitivity is estimated at 4% (57). As with many other allergens, the spectrum of clinical manifestations ranges from mild rash to potentially fatal anaphylaxis. Presently, no serologic assay for clopidogrel allergy is available; hence, diagnosis can only be made clinically, after exposure. Although alternative therapy with ticlopidine can be considered in such cases, this drug's associated side-effects, especially hematologic, make it a less-attractive agent.

Von Tiehl et al. (58) assessed the safety and efficacy of clopidogrel desensitization in 24 consecutive patients. Titration was gradually escalated until the targeted daily dose of 75 mg was achieved. Most (n = 20) were performed in the outpatient setting, and follow-up evaluations were conducted at 2 to 4 weeks and 6 months after initiation. They observed persistent pruritis in 1 patient, whereas the rest remained asymptomatic. The authors thus concluded that clopidogrel desensitization is safe, effective, and sustained and recommend consideration of this strategy in appropriate patients. It should be noted, however, that patients with severe allergic reactions to clopidogrel, including toxic epidermal necrolysis, Stevens-Johnson syndrome,

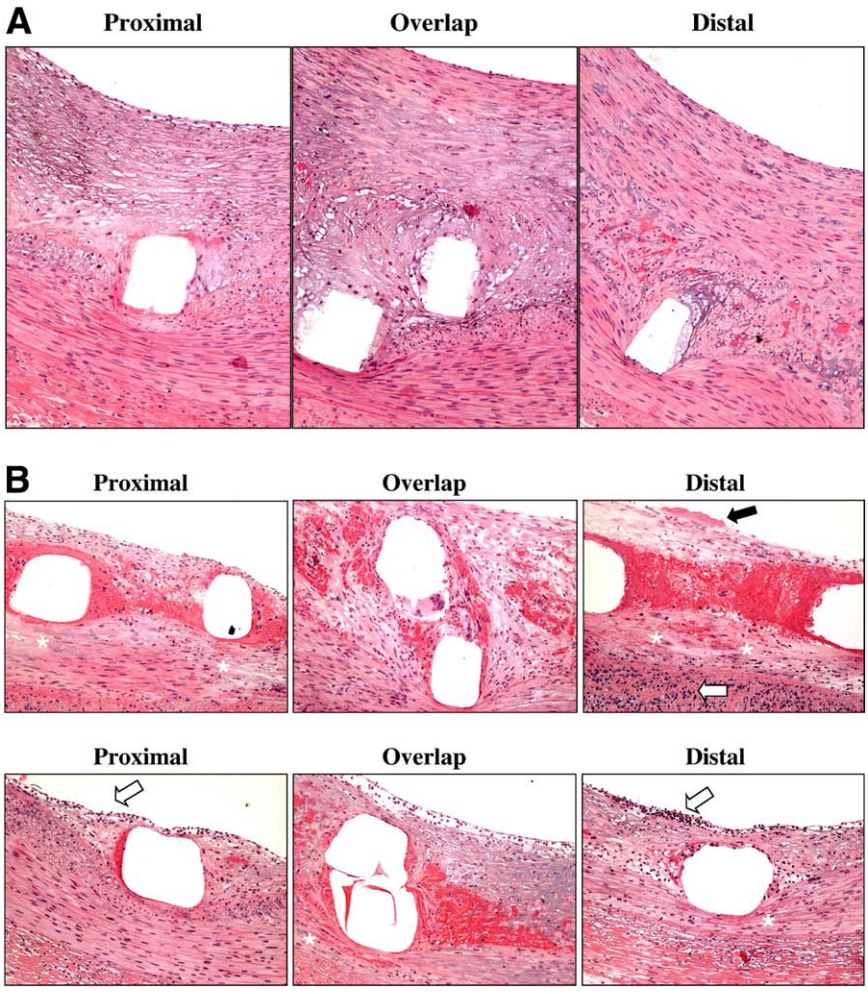

Figure 2. High Magnification (200×) Microscopic Images of Hematoxylin-Eosin Stained Porcine Coronary Sections

(A) Bare-metal stent (BMS) segments exhibited well-healed, thick fibrocellular neointima, completely covered with endothelial-like cells. For **(B)** drug-eluting stent (DES) (designated PES for paclitaxel-eluting stent), the neointima is attenuated, with thrombus and fibrinoid deposits juxtaposed to stent struts. Several large round mononuclear cells (inflammatory white blood cells; **white arrows**) as well as thrombus **(black arrows)** formations were observed. The media was necrotic and hemorrhagic in appearance **(*)**, and inflammatory cell infiltrations **(white arrows)** were present in DES segments. As in Figure 1, the inflammatory changes were markedly amplified in the DES overlap segments. Reprinted, with permission, from Pendyala et al. (19).

anaphylaxis, and respiratory compromise, were excluded from this study. Thus, the applicability of their findings to such a high-risk subgroup remains unknown.

The course of hypersensitivity is divided into 2 phases: immediate (either early or acute) and late. The immediate reaction occurs within 1 h after antigenic exposure and is driven by cross-linking of antigen-specific immunoglobulin E (IgE) bound to the surface of resident mast cells. Acute ST occurs within the same time frame as immediate hypersensitivity (within 24 h). Additionally, both pathophysiologic processes demonstrate similar patterns of inflammatory cell infiltration (55).

The late phase reaction is, in many respects, a consequence of the initial mast cell-driven events and occurs 12 to 24 h after index antigenic exposure (55). The pathophysiology is characterized by recruitment of inflammatory cells including eosinophils, basophils, T-lymphocytes, neutrophils, and macrophages to the site of hypersensitivity and inflammation. The process is facilitated by chemokines such as eotaxins-1 and -2, and RANTES (regulation upon activation normal T-cell expressed and secreted). Additionally, monocyte chemoattractant proteins-3 and -4 as well as macrophage inflammatory protein 1α further contribute to augmentation of the cascade. These agents synergistically promote the expression of adhesion molecules on the vascular endothelial surface and provide a chemotactic gradient for cells recruited in the late-phase reaction (59). The acute-phase reaction, therefore, is additionally essential

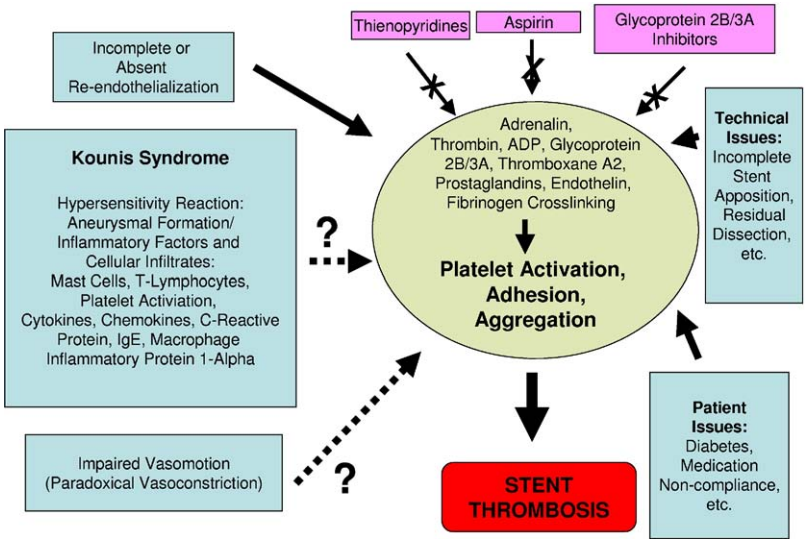

Figure 3. Pathophysiology of Drug-Eluting Stent Thrombosis

Many factors, including impaired neointimal formation, technical issues, possible hypersensitivity to drug-eluting stent components (Kounis-associated), impaired vasomotion, patient characteristics, and adjunct pharmacology, all potentially contribute to and modify platelet activity, the major determinant of stent thrombosis. **Solid arrows** = promotional factors. **Dashed arrows with question marks** = possible promotional factors. **Crossed arrows** = inhibitory factors. ADP = adenosine diphosphate; Ig = immunoglobulin.

for the development and propagation of the late-phase reaction as well as the subsequent chronic hypersensitivity inflammation (55).

Thus, potential antigens for the susceptible DES patient can include the stent metal, polymer, antiproliferative drug coating, ASA, or clopidogrel. Hypersensitivity and inflammation can be initiated by cross-bridging of culprit antigen with corresponding receptor-bound IgE antibodies on the basophil or mast cell surface. Of the total 500,000 to 1,000,000 immunoglobulin (Ig)E antibodies on the cell surface, a threshold number of bridged IgEs (usually >2,000) is required for cellular degranulation and mediator release (60). For the DES patient, the critical number of bridges is potentially achievable by more than 1 non–cross-reactive antigen and its corresponding IgE antibody (61).

Clinical data indicate that patients simultaneously exposed to several antigens experience more symptoms than mono-sensitized individuals (61). A recent study revealed that IgE antibodies with different specificities can elicit an additive effect; likewise, simultaneous exposure to subthreshold quantities of multiple antigens can synergistically trigger mediator release (62). This finding suggests that consideration for desensitization in the DES patient might necessitate inclusion of all DES components as well as ASA and clopidogrel.

Platelets play a significant role in the development of thrombosis and inflammation through cytokine secretion and subsequent interaction with leukocytes and endothelial cells. Antiplatelet agents such as ASA and clopidogrel (a specific antagonist of the platelet P2Y12 ADP-receptor) reduce the levels of the transcription factor nuclear factor kappaB (NF-kappaB), C-reactive protein, and soluble CD40 ligand. Furthermore, these agents also attenuate P-selectin concentrations and platelet-leukocyte aggregation (63). The pathophysiologic mechanism of DES ST, with postulated contribution from the Kounis syndrome, is outlined in Figure 3.

Mast cells are almost ubiquitous within the atherosclerotic lesion. Kounis syndrome is associated with mast cell activation, involving interrelated and interacting inflammatory cells including macrophages and T-lymphocytes; platelet activation and release of various inflammatory mediators such as cytokines and chemokines are also critical components of the phenomenon. Therefore, the crucial benefits of DAT after DES cannot be overemphasized; these agents decrease not only the propensity for thrombosis but likely also the Kounis-associated inflammatory response (64).

Chronic Allergic Inflammation

Drug release kinetics from DES polymers is a complex phenomenon dependent upon multiple factors. The rate varies with the type of polymer, layering, and drug/polymer formulation ratio. The rapidity of dissipation is further influenced by the overcoat dose and total load densities (63). Important determinants for tissue drug accumulation include drug physicochemical properties, distribution of drug in the arterial wall, rate and duration of release, endothelial

function, as well as overall health of the arterial wall (63). The DES drug release is characterized by an initial rapid phase followed by sustained slow dissipation (64). Lipophilic drugs are released slowly, allowing for higher concentrations in the intima (65). Conversely, hydrophilic drugs demonstrate faster elution into the circulation and require greater amounts with shorter durations of delivery to achieve optimal local levels (66). However, in human atherosclerotic intima, drug release characteristics have demonstrated considerable variability.

Drug release kinetics, levels of insulting allergens, and presence of drug-reactive lymphocytes all likely contribute to the timing and type of hypersensitivity reactions; these can include: immediate (type I), antibody-mediated cytotoxic (type II), immune complex-mediated (type III), and delayed hypersensitivity (type IV) reactions (67). Atopic patients might experience recurrent reactions even after years of antigen avoidance (68), owing to high concentrations of drug-specific lymphocytes. Although the eluted drug and polymer components of DES dissolve over time, the stent itself presents a persistent antigenic stress to the susceptible patient. This possible mechanism is underscored by demonstration of immune cellular and extracellular matrix findings characteristic of chronic allergic inflammatory changes in both human and animal models of ST.

Recommendations for Prevention and Diagnosis of DES ST

The FDA has issued, on the basis of an expert panel testimony, guidelines for prevention of DES ST (4). Similar recommendations were echoed in the joint 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 (69). Although no strategy guarantees against ST, these measures likely enhance the safety profile of these devices.

Before stent deployment, patients should be thoroughly evaluated for risk of noncompliance or inability to comply with prolonged DAT. These include: upcoming surgeries, financial challenges to prolonged clopidogrel therapy, or poor compliance; DES should be avoided in these individuals. Consideration should be made for platelet inhibition assays to ASA and/or clopidogrel in appropriate stent implantation candidates.

Adherence to "on-label" indications for DES use can help to minimize the risks of ST; these indications include: use in native coronaries with diameters from 2.5 to 3.5 mm; avoidance of bifurcation stents, overlapping stents, multiple stents, or long stents. Consider intravascular ultrasound interrogation to optimize stent symmetry, apposition, and sizing. Providers need to thoroughly educate DES patients on the indications of DAT, in particular, strict adherence to FDA recommendations as well as the serious potential consequences of premature therapy termination.

Surgery or invasive procedures should be postponed until completion of the minimal recommended DAT duration. If such procedures are unavoidable during the first year after DES implantation, consideration should be given to DAT or at least ASA continuation, if at all possible. DAT should be resumed as promptly as deemed safe surgically. All proposed modifications to DAT should be fully discussed with the patient's cardiologist.

DES ST is usually quite dramatic and unambiguous in presentation, and all health care providers should be well-versed and vigilant in the diagnosis. For any stent patient presenting with acute coronary syndrome, especially MI, a low threshold for urgent coronary angiography/possible intervention should be exercised. Furthermore, elucidation of ST mechanism (e.g., incomplete stent expansion, residual dissection) with intravascular ultrasound interrogation is encouraged in most cases of DES thrombosis. Moreover, ST should be strongly considered in any unexplained death in a DES patient. These recommendations are summarized in Table 5.

Table 5. Suggestions for Prevention and Diagnosis of DES ST

Prevention
Avoid overlapping stents and other "off-label" indications.
Intravascular ultrasound assessment to ensure full and symmetric stent expansion and wall apposition as well as absence of thrombus or dissection.
Avoid DES in individuals at risk of noncompliance or inability to comply with prolonged dual antiplatelet therapy (e.g., upcoming invasive procedures, financial challenges, or history of medical noncompliance).
If invasive procedure or surgery is unavoidable within 1 year after DES implantation, consideration should be given to continuation of dual antiplatelet therapy; any antiplatelet alterations should be discussed with the patient's cardiologist.
For DES patients undergoing invasive or surgical procedures mandating thienopyridine discontinuation, ASA should be continued if at all feasible. Thienopyridine should be re-initiated as soon as possible after procedure.
Strict adherence to FDA antiplatelet therapy recommendations, with consideration for additional prolongation in high-risk anatomies and individuals.
Consideration in selected individuals for platelet function assays to assess for ASA or clopidogrel resistance.
Health care providers should more thoroughly educate patients regarding the indications of dual antiplatelet therapy as well as the risks of premature termination.
Diagnosis
Consider urgent coronary angiography/possible intervention for any stent patient presenting with acute coronary syndrome, especially MI.
Consider intravascular ultrasound interrogation in all cases of DES ST, to elucidate mechanism (e.g., incomplete stent expansion, residual dissection).
Suspect ST in any unexplained death in a DES patient.

Data is based on information in references 4 and 69.
Abbreviations as in Table 1.

Conclusions and Future Directions

With the ever-increasing prevalence of DES use, continued research into thorough understanding of the complex mechanisms of ST is paramount. Although hypersensitivity/allergic reactions are now recognized as key components of ST, the incidence, especially of subclinical cases, is likely under-reported. Before consideration for DES implantation, a thorough atopic history should be sought, with specific attention to previous Kounis syndrome or other allergic reactions. In appropriate patients, pre-PCI evaluation with patch-testing, antibody testing, macrophage and T-cell activation studies, with subsequent desensitization strategies might be considered. Post-procedural monitoring of inflammatory mediator levels as well as use of corticosteroids and mast cell stabilizers are potential topics for future investigations. Some of the aforementioned recommendations have recently been incorporated into current protocols (52).

In conclusion, the Kounis syndrome, as a possible manifestation of hypersensitivity to stent components or antiplatelet agents, might play a key role in the mechanism of DES thrombosis. Recent experimental data have reported attenuation of allergic and thrombotic events through treatment with corticosteroids and other mast cell stabilizing agents (70). Accordingly, we have proposed impregnation of such agents as a novel DES polymer matrix (71). Incorporation of anti-inflammatory, antiallergic, and/or antiplatelet agents might represent a promising paradigm shift from efficacy to safety in future DES designs.

Reprint requests and correspondence: Dr. Jack P. Chen, 5670 Peachtree Dunwoody Road, #880, Atlanta, Georgia 30342. E-mail: jchen@sjha.org.

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