

REVIEW ARTICLE

Coronary Stents, Hypersensitivity Reactions, and the Kounis Syndrome

NICHOLAS G. KOUNIS, M.D., PH.D., F.E.S.C., F.A.C.C.,¹ GEORGE HAHALIS, M.D., PH.D.,²
and THEOHARIS C. THEOHARIDES, B.A., M.S., M.PHIL., M.D., PH.D., F.A.A.A.I.³

From the ¹Department of Medical Sciences, School of Health Sciences, Patras Highest Institute of Education and Technology, Queen Olga Square, Patras, Greece; ²Catheterization Laboratory, Division of Cardiology, Department of Medicine, University of Patras Medical School, Rion, Patras, Greece; ³Departments of Pharmacology and Experimental Therapeutics, Internal Medicine and Biochemistry, Tufts University School of Medicine and Tufts-New England Medical Center, 136 Harrison Avenue, Boston, MA

The use of drug-eluting stents (DES) for the treatment of coronary stenosis has increased sharply and now accounts for more than 75% of all coronary stents utilized. However, concern has been increasing that DES could be associated with stent thrombosis, paradoxical coronary vasoconstriction, and hypersensitivity reactions. Components of currently used DES have been reported to induce, either separately or synergistically, hypersensitivity reactions and possibly lead to cardiac events. DES-activated intracoronary mast cells could release histamine, arachidonic acid metabolites, proteolytic enzymes, as well as a variety of cytokines, chemokines, and platelet-activating factor (PAF) leading to local inflammation and thrombosis. These events may be more common than suspected because it is hard to document them, unless they become systemic, in which case they manifest themselves as the "Kounis syndrome," characterized by the concurrence of acute coronary events with hypersensitivity reactions. Recognition of this problem may lead to better vigilance, as well as new DES with mast cell blocking molecules that may also be disease modifying. (J Interven Cardiol 2007;:1–11)*

Introduction

Stent thrombosis is an emerging serious clinical problem in patients treated with DES.¹ Recent data have shown that a small but increasing number of patients develop stent thrombosis after insertion of DES.² Stent thrombosis may lead to catastrophic consequences³ including myocardial infarction (MI) with estimated 30-day mortality ranging from 20 to 48%. Several meta-analyses of large trials have shown that the overall mortality from DES was increased by 2, 3, and 4 years in comparison with bare metal stents.⁴ Another study⁵ showed that the rate of cardiac death and nonfatal MI 7–18 months after DES insertion was

4.9%, and additional data⁶ showed that the rate of mortality and MI up to 3 years after sirolimus-eluting stent insertion increased to 6.3%. These studies have prompted a statement from the Food and Drug Administration (FDA) warning about the small but significant increase in the rate of death and MI from possible stent thrombosis that followed 18 months to 3 years after stent implantation.⁷ However, these rates have been challenged and three recent reports^{8–10} showed no significant differences in the rates of death, MI, and stent thrombosis between DES and bare metal stents. It has been suggested that large randomized trials are necessary^{11,12} in order to ascertain the long-term safety of DES.

Stent thrombosis has been classified as acute, occurring within 48 hours; subacute, occurring between the 2nd and the 30th day; late, occurring after the first 30 days to one year; and very late, occurring after one year of the implantation. Potential causes include delayed endothelialization, stent length, complex

Address for reprints: Nicholas G. Kounis M.D., Ph.D., F.E.S.C., F.A.C.C., Professor and Director, Department of Medical Sciences, Patras Highest Institute of Education and Technology, Queen Olga Square, Patras 26221, Greece. Fax: +30-2610-279579; e-mail: ngkounis@otenet.gr

lesions, suboptimal stent insertion, flow disturbances and changes in shear stress, withdrawal of clopidogrel and/or aspirin, brachytherapy for in-stent restenosis, patient characteristics, and hypersensitivity to stent components.¹³ The concurrence of acute coronary syndromes with hypersensitivity reactions has been long established,¹⁴ and the question which arises is whether hypersensitivity to DES components could be associated with acute coronary events.^{15,16} Since it is not known if stent thrombosis is a time-limited event, this might become a major clinical concern in patients who have already been treated with DES.

The Clinical Problem: Hypersensitivity to DES Components?

Data derived from the FDA's Manufacturer and User Device Experience Center (MAUDE)¹⁷ and the Research on Adverse Drug/Device events and Reports (RADAR)¹⁸ project have listed 262 cases of DES implantation associated with hypersensitivity reactions. The RADAR project mentioned 17 cases classified as probably or certainly caused by stent insertion; of these, 4 developed fatal in-stent thrombosis and died at 4, 5, 18, and 18 months after implantation, respectively.¹⁸ These reactions included rash, itching, hives, dyspnea, fever, atypical chest pain, high or low blood pressure, joint pain, joint swelling, and anaphylaxis. The cutaneous rash was associated with hives, desquamation, or blisters and covered the entire body in 21% of the cases. Based on MAUDE seriousness codes, 95% of these reactions were classified as serious, requiring hospitalization, emergency intervention, intravenous steroids, or cardiac catheterization, or resulted in permanent dis-

ability and even death. Laboratory findings associated with the above reactions included eosinophilia and elevated serum IgE titers. Clinical or laboratory findings did not abate with discontinuation of the concurrent antiplatelet medications. The MAUDE and RADAR project data may be biased because these are likely to underreport such events and because of lack of information on causality relationships. Hypersensitivity to DES is now regarded as real clinical entity¹⁹ and there is obvious risk of serious complications. It has been proposed that health professionals should be vigilant and should submit detailed adverse event reports to the manufacturer of DES or to the FDA.¹⁹ The proportion of 262 cases with allergic reactions in >5 million DES implantation is well below the 4% expected for allergy from drugs alone. However, coronary events associated with hypersensitivity reactions are not common and are dependent on allergen concentration, number of insulting allergens, route and rate of allergen entrance in the circulation, magnitude of the initial allergic response, area and localization of antibody-antigen reaction, patient's sensitivity, and patient's comorbidity.²⁰ A threshold level of inflammatory cell content, closely associated with the above conditions, has been suggested, above which smooth muscle contraction and plaque erosion or rupture may occur.²¹

Kounis Syndrome: The Hypersensitivity Coronary Syndrome

The concurrence of acute coronary syndromes with conditions associated with allergic or hypersensitivity and anaphylactic or anaphylactoid reactions constitutes the Kounis syndrome²⁰ (Table 1). It has been proposed

Table 1. Historical Background of Kounis Syndrome

Pfister CW, et al. Acute myocardial infarction during a prolonged allergic reaction to penicillin. <i>Am Heart J</i> 1950;40:945.
Kounis NG, et al. Histamine-induced coronary artery spasm: The syndrome of allergic angina. <i>Br J Clin Pract</i> 1991;45:121.
Constantinides P. Allergic reactions can promote plaque disruption. <i>Circulation</i> 1995;92:1083.
Kounis NG, et al. Allergic angina and allergic myocardial infarction. <i>Circulation</i> 1996;94:1789.
Braunwald E. Allergic reactions with mediators such as histamine or leukotrienes acting on coronary smooth muscle can induce vasospastic angina. <i>Circulation</i> 1998;98:2219.
Zavras GM, et al. Kounis syndrome secondary to allergic reaction. <i>Int J Clin Pract</i> 2003;57:62.
Kounis NG. Kounis syndrome. <i>Int J Cardiol</i> 2006;119:7.
Kounis NG, et al. Hypersensitivity to DES: A manifestation of Kounis syndrome? <i>J Am Coll Cardiol</i> 2006;48:592.
Rana JS, Sheikh J. Serum sickness-like reactions after placement of sirolimus-eluting stents. <i>Ann Allergy Asthma Immunol</i> 2007;98:201.

CORONARY STENTS

that this syndrome represents nature's own experiment and important natural paradigm that might have profound clinical and therapeutic implications.²² Two variants of this syndrome have been described.²³ The type I variant includes patients with normal coronary arteries without predisposing factors for coronary artery disease in whom hypersensitivity reactions induce either coronary artery spasm with normal cardiac enzymes and troponins or coronary artery spasm progressing to acute coronary thrombosis with increased cardiac enzymes and troponins. This variant might represent a manifestation of endothelial dysfunction or microvascular angina. The type II variant includes patients with active or quiescent preexisting atheromatous disease in whom acute hypersensitivity reactions can induce plaque erosion or rupture culminating in acute coronary thrombosis.

Causes of Kounis syndrome include^{20,24} environmental exposure, various drugs and substances such as latex, nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, analgesics, contrast media, intravenous anesthetics, skin disinfectants, and cancer chemotherapeutic agents. All DES components, including the metal and the polymer coating, can induce hypersensitivity reactions either separately or synergistically. The two main impregnated drugs of DES are the antineoplastic agent paclitaxel for the TAXUS brand and the antiproliferative agent rapamycin for the CYPHER brand.

Allergic inflammation is initiated by allergens cross-bridging their corresponding, receptor-bound, immunoglobulin IgE or IgG antibodies on the surface of the mast cells.²⁵⁻²⁷ Clinical studies indicate that allergic patients simultaneously exposed to several allergens have more symptoms than mono-sensitized individuals.²⁸ A recent study also showed that IgE antibodies with different specificities can have an additive effect with even small amounts of corresponding allergens able to trigger mediator release when the patient is simultaneously exposed to them.²⁹ Intracoronary mast cells are increased in atherosclerosis and especially in areas of plaque rupture.³⁰⁻⁴³ Vasoconstricting and collagen-degrading compounds are released locally and in the peripheral circulation during hypersensitivity reactions from activated mast cells. These compounds include (Table 2) preformed mediators such as, histamines, neutral proteases (tryptase, chymase), neuropeptides, and proteoglycans, as well as newly synthesized mediators such as arachidonic acid products,

Table 2. Inflammatory Mediators Released from Mast Cells

Preformed mediators
<i>Biogenic amines</i>
-histamine
-serotonin
Chemokines
-IL-8, MCP-1, MCP-3, MCP-4, RANTES
<i>Enzymes</i>
-arylsulfatases
-carboxypeptidase A
-chymase
-kinogenases
-phospholipases
-tryptase
<i>Peptides</i>
-bradykinin
-corticotropin-releasing hormone
-endorphins
-endothelin
-renin
-substance P
-vasoactive intestinal peptide
-urocortin
-vascular endothelial growth factor
-vasoactive intestinal peptide
<i>Proteoglycans</i>
-chondroitin sulphate
-heparin
-hyaluronic acid
Newly synthesized mediators
<i>Cytokines</i>
-interleukins (IL)-1,2,3,4,5,6,9,10,13,16,32
-macrophage inflammatory factor
-tumor necrosis factor- α
<i>Growth factors</i>
-granulocyte monocyte—colony stimulating factor
-fibroblast growth factor
-nerve growth factor
-stem cell factor
-vascular endothelial growth factor
<i>Arachidonic acid products</i>
-leukotrienes
-platelet-activating factor
-prostaglandins
-thromboxanes

an array of cytokines and chemokines, and platelet-activating factor.

It should be noted that mast cells can release many of these mediators *selectively*, especially to nonallergic triggers such corticotropin-releasing hormone (CRH), IL-1, LPS, stem cell factor (SCF), and thrombin,⁴⁴ thus originally contributing to coronary inflammation without full-blown anaphylaxis that may occur only in rare instances. These mediators have been implicated,

in many clinical and experimental studies as inducing coronary artery spasm and/or acute MI.³⁰⁻⁴³ The same mediators released during hypersensitivity reactions have been found to be increased in blood or urine of patients suffering from acute coronary syndromes of nonhypersensitivity etiology. In particular, histamine is elevated in the coronary circulation of patients with variant angina,⁴⁵ can be released under acute stress,⁴⁶ and induces tissue factor expression.⁴⁷ Tryptase has implicated in acute coronary syndromes^{48,49} and can degrade HDL.⁵⁰ Mast cells also contain renin,⁵¹ which can convert angiotensinogen to angiotensin, while mast cell chymase has been shown to convert angiotensin I to angiotensin II⁵² and also remove cholesterol from HDL.⁵³ Mast cell proteases also participate in plaque rupture.⁵⁴ IL-6 has been shown to be released in the coronary sinus of patients with acute coronary syndromes^{55,56} from a cardiac source,⁵⁷ and is also released exclusively from mast cells during acute stress in mice.⁵⁸ Serum IL-6 was also shown to be increased in ischemia-reperfusion in mice, but not in mast cell-deficient mice,⁵⁹ again stressing the importance of mast cells in coronary inflammation and pathology.

Additionally, there are many important interactions among mast cells, T cells, and macrophages. For instance, mast cells can enhance T cell activation,⁶⁰ T cells can mediate mast cell proliferation and activation,⁶¹ inducible macrophage protein-1 α can activate mast cells,⁶² mast cells can activate macrophages,⁶³ and T cells can regulate macrophage activity.⁶⁴ These effects can lead to coronary inflammation, as well as epithelial and endothelial cell proliferation, fibrosis, and stenosis. Hypersensitivity reactions that do not involve IgE appear to involve activation of the complement (C) system and are sometimes called "C activation-related pseudoallergy" (CARPA).⁶⁵ Drugs and agents causing CARPA include radiocontrast media, liposomal drugs, and micellar solvents containing amphiphilic lipids (e.g., Cremophor EL, the vehicle of Taxol).

Paclitaxel

Paclitaxel and docetaxel belong to a distinct type of antineoplastic drugs which in micromolar concentrations, easily achieved in patients, inhibit microtubule assembly (M-phase of the cell cycle) resulting in dissolution of the mitotic spindle structure, thereby inhibiting proliferation of human endothelial cells.⁶⁶ Antineoplastic drugs capable to induce acute coro-

Table 3. Cardiac Hypersensitivity Reactions to Stent Components

Reactions	Latex	Nickel	Paclitaxel	Sirolimus
- Atrioventricular block			±	
- Kounis syndrome	±	±	±	±
- Left bundle branch block			±	
- Paradoxical coronary vasoconstriction			±	±
- Pericarditis		±		
- Coronary thrombosis			±	±
- Ventricular tachycardia			±	

nary syndromes include⁶⁷ the antimicrotubule paclitaxel (Taxol). Recent *in vitro* studies⁶⁸ have shown that paclitaxel enhances tissue factor expression and activity in endothelial cells in concentrations comparable with those achieved locally after paclitaxel stent insertion.⁶⁹

There are several reported instances of hypersensitivity reactions to antineoplastic drugs.⁷⁰ Severe and lethal reactions have also occurred.^{71,72} Apart from neutropenia, thrombocytopenia, paralytic ileus, alopecia, gastrointestinal upset, and peripheral neuropathy, hypersensitivity reactions are quite common with the use of paclitaxel (Table 3) with 90% of these occurring after the first or second dose.⁷³ According to a recent report,⁷⁴ up to 42% of patients receiving systemic paclitaxel for treatment of various types of cancer experienced a hypersensitivity reaction and up to 2% developed serious allergic reactions. So far, there are several reports associating type I and type II variants of Kounis syndrome with paclitaxel systemic administration.⁷⁵⁻⁸⁶ In another report,⁸⁷ a patient experienced anaphylactic reaction during a Taxus stent implantation; this patient developed erythematous rash and hypotension immediately after the stent insertion, as well as coronary spasm and thrombus formation. Delayed severe multivessel coronary artery spasm and aborted sudden death has also been observed after systemic Taxus stent implantation.⁸⁸ In another study⁸⁹ involving 23 patients with recurrent ovarian cancer, combination chemotherapy with carboplatin and paclitaxel induced hypersensitivity reactions in 5 patients. One of these patients exhibited severe allergic reaction compatible with Kounis syndrome; the rest of the patients developed eruptions, hypotension, and tachycardia. It must be pointed out that all hypersensitivity reactions occurred immediately after carboplatin administration and not during paclitaxel administration. Perhaps, in this occasion, paclitaxel had acted as hapten. Low-molecular-weight

Table 4. Noncardiac Hypersensitivity Reactions to Stent Components

Reactions	Latex	Nickel	Paclitaxel	Sirolimus
- Angioedema	±		±	±
- Anaphylaxis				
- Acrocyanosis				±
- Asthma			±	
- Baboo syndrome		±		
- Bronchospasm			±	
- Conjunctivitis	±			
- Contact dermatitis		±		
- Diaphoresis			±	
- Eczematiform eruption				±
- Erythema		±		
- Fever			±	
- Flushing			±	±
- Interstitial pneumonitis				±
- Pruritus				±
- Purpura				±
- Rhinitis	±	±		
- Rosacea		±		±
- Schonlein-Henoch purpura				±
- Stomatitis	±			
- Urticaria	±		±	
- Vasculitis				±

antineoplastics that have haptenic properties have been proposed.⁹⁰

Sirolimus

Sirolimus (rapamycin, Rapamune®) is a macrolide antibiotic derived from actinomycete streptomyces hygroscopicus, which for many years has been used as an immunosuppressive and antiproliferative agent in the treatment of organ rejection in transplant recipients. Unlike cyclosporine and tacrolimus, sirolimus does not inhibit the calcineurin pathway, but inhibits the mammalian target of rapamycin (mTOR), a multifunctional serine-threonine kinase that acts on IL-2-mediated signal transduction pathways, which is the central regulator of cell growth proliferation and apoptosis.⁹¹ These properties have also been utilized in coronary stents in order to reduce neointimal formation and restenosis. Rapamycin can increase thrombin and tumor necrosis factor- α -induced endothelial tissue factor expression and activity at concentrations that are encountered in vivo.⁹²

Apart from the well-known adverse effects associated with sirolimus use such as hyperlipidemia, hypercholesterolemia, and thrombocytopenia, some se-

rious hypersensitivity reactions have been observed with its use (Table 4). Generalized, pruritic, ulcerating maculopapular rash necessitating cessation of sirolimus have been observed in a liver transplant patient.⁹³ A variety of cutaneous effects have also been reported in renal transplantation patients.⁹⁴ Sirolimus can induce allergic angioedema with diffuse swelling of eyelids, epiglottid edema, and edema of floor of the mouth, tongue, and soft palate.⁹⁵ Despite vigorous therapy of these patients with angioedema complete resolution of this effect may occur only after withdrawal of sirolimus. Furthermore, sirolimus-induced pulmonary hypersensitivity has been reported.^{96,97} Acneiform eruption,⁹⁸ leucocytoclastic vasculitis,^{99,100} even cardiac tamponade,¹⁰¹ are some additional but rare side effects (Table 4).

In an experimental study,¹⁰² the side effects of rapamycin on treated rats were evaluated by histopathological examination of heart, kidney, and eyes. Rapamycin administration at doses of 1.5 and 1.0 mg/kg/day resulted in focal MI in 60% and 9% of rats, respectively. In addition, animal experiments indicate a propensity for thrombus formation in a rat model with synthetic vascular grafts treated by systemic or local administration of rapamycin.¹⁰³ Although no evidence of hypersensitivity was noted in this experiment, thrombus formation was largest in animals that received high doses of rapamycin either orally or intraperitoneally, when compared with the control group.

In humans, paradoxical coronary vasoconstriction¹⁰⁴ and life-threatening coronary spasm¹⁰⁵ following sirolimus-eluting stent deployment has also been reported and was attributed to severe endothelial dysfunction¹⁰⁶ as in type I variant of Kounis syndrome. For example, localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent has been reported in a 58-year-old man who died 18 months after stent implantation.^{107,108}

Polymers and Latex

Synthetic biodegradable polymers are commonly used in drug-eluting stents as a vehicle for local drug delivery; the impregnated drugs are released by diffusion through and/or breakdown of the base polymer. Cypher stents are coated with a thin layer of poly-n-butyl methacrylate and polyethylene-vinyl acetate copolymer. In sirolimus-eluting stents, about 80%

of the rapamycin is eluted by 30 days, leaving a polymer-coated metal stent with small drug amounts. In Taxus stents, about 10% of paclitaxel is eluted by 10 days and the rest remains in the polymer for a longer period.¹⁰⁹

Hypersensitivity reactions have been reported with the use of polymers (Table 4) like those in latex and vinyl gloves, as well as with polyurethane and methyl-methacrylate in dentistry.^{110,111} The latter has induced labial edema and allergic stomatitis confirmed by patch tests in orthodontic patients.^{112,113} Chronic urticaria,¹¹⁴ stomatitis venenata,¹¹⁵ and allergic erythema of the hard palate¹¹⁶ have also been reported due to exposure to auto-polymerized acrylic resin. These allergic reactions are usually type IV reactions caused by compounds of low molecular weight that are acting as haptens. For acrylic resins these would be formaldehyde, benzyl peroxide, methyl-methacrylate, and plasticizers such as dibutyl phthalate.¹¹⁷

Nonbioerodable polymers such as polyurethane polydimethyl siloxane (silicone) and polyethylene terephthalate (Dacron) can promote inflammation when implanted in swine coronary arteries.¹¹⁸⁻¹²⁰ 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 Cypher stents.¹²¹ Furthermore, the polyethylene-vinyl acetate compound of the Cypher copolymer induces inflammatory reaction in 25% of rabbits when used as an antigen delivery matrix.¹²² Cases of immediate and delayed allergic reactions to anionic cellulose polymers carboxymethyl-cellulose and methyl hydroxyethylcellulose have also been reported.¹²³

Latex can cross-react with the hevimine in fruits and cause an immediate hypersensitivity reaction.¹²⁴

Hypersensitivity to Metals

The majority of intracoronary stents are made from 316L stainless steel, which contains nickel, chromium, and molybdenum. Ions from the above metals are eluted through the action of blood, saline, proteins, and mechanical stress. It has been already seen that allergy and inflammatory reactions have occurred in patients with prosthetic valves and other endovascular prostheses.¹²⁵ Allergic reactions to metallic implants have been implicated in postoperative complications such as loosening or formation of new tissue around

the metals.^{126,127} In a patient with aseptic loosening of an orthopedic chromium/cobalt alloy and positive patch tests to potassium dichromate, peri-implantar tissue examination showed oligoclonal T-cell infiltration with Th1-type cytokine expression.¹²⁸

Hypersensitivity reactions to nickel occur in up to 17.2% of the population and are the most frequent cause of allergic contact dermatitis.¹²⁹ In patients undergoing percutaneous atrial septal defect and patent foramen ovale closure, nickel allergy can be the cause of systemic effects such as chest discomfort, palpitation, and migraine headache with or without aura.¹³⁰ It is postulated that local allergic reaction to the implanted device could result in formation of platelet adhesions that could embolize in heart and brain.¹³¹ Local nickel allergy from intracardiac devices and subsequent systemic allergic reactions confirmed by patch tests as an allergy to nitinol (nickel-titanium alloy) have necessitated the removal of these devices.^{132,133}

Reports concerning hypersensitivity reactions to various metals used in orthodontics have also been published.¹³⁴ Nickel is the metal which can provoke the most severe responses.¹³⁵ Delayed hypersensitivity reactions to nickel and molybdenum might be part of inflammatory process and one of the triggering factors for development of in-stent restenosis.¹³⁶ The rate of nickel allergy following initial stent implantation has been estimated¹³⁷ to be 9.2%. Skin clips containing nickel, chromium, molybdenum, cobalt, and titanium can induce allergic reactions and may be the cause of delayed wound healing.¹³⁸ Hypersensitivity to molybdenum has been implicated to induce a syndrome resembling systemic lupus erythematosus.¹³⁹ Contact allergy to gold has been associated with increased incidence of restenosis when patients are stented with gold-plated stents and these stents have been abandoned.¹⁴⁰ On the other hand, the titan stent, which is a stainless steel stent coated with titanium-nitride oxide (TINOX) can prevent discharge of nickel, chromium, and molybdenum and it seems promising in eliminating local allergy and inflammation.¹⁴¹

Conclusions and Future Directions

At present, as stated by the FDA, coronary DES remain safe and effective when used in patients according to approved indications. However, as DES are used in most cases, it seems likely that cases of intracoronary and even systemic hypersensitivity reactions to DES

might go unreported. Apart from the risk of thrombosis, physicians should be aware also of the reports of life-threatening paradoxical coronary vasoconstriction associated with DES implantation.^{88,104–106} Such cases may be more likely to occur in atopic patients, those with food allergy, or those who have already experienced a first Kounis syndrome and are going to have DES implantation. A series of 13 patients who developed severe life-threatening coronary artery spasm after DES implantation has been recently published.¹⁴² Two patients did not respond to vasodilators and died. The postmortem examination in one patient showed scattered mast cells infiltrating the adventitia of the left anterior coronary artery suggesting a hypersensitivity reaction to the stent.¹⁴³ Simultaneous multivessel acute drug-eluting stent thrombosis has been recently reported suggesting hypersensitivity reaction involving multiple vessels as a possible cause.¹⁴⁴

New DES, combining drugs with antiallergic and antiinflammatory actions that may also be disease modifying, might be the solution to the problem. For instance, mast cell stabilizers may be used since the latter have abrogated late thrombotic events experimentally.¹⁴⁵

Disclosure

US patents No. 6,689,748; 6,984,667; 10/811,525 and EPO 136577 (awarded to TCT) cover the use of antiallergic/antiinflammatory methods and compositions, including coated medical devices.

References

- Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005;293:2126–2213.
- Joner M, Finn AV, Farb A, Mont EK, et al. Pathology to drug-eluting stents in humans. Delayed healing and late thrombotic risk. *J Am Coll Cardiol* 2006;48:193–202.
- Cutlip DE, Baim DS, Ho KK, et al. Stent thrombosis in the modern era: A pooled analysis of multicenter coronary stent trials. *Circulation* 2001;103:1967–1971.
- Nordmann AJ, Briel M, Bucher HC. Mortality in randomized controlled trials comparing drug-eluting vs. metal stents in coronary artery disease: A meta-analysis. *Eur Heart J* 2006;27:2784–2814.
- Pfisterer ME, Brunner-La Rocca HP, Buser PT, et al., for BASKET-LATE Investigators. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents. An observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol* 2006;48:2584–2591.
- Camenzind E, Steng PG, Wijns W. A meta-analysis of first generation drug eluting stent programs. Presented at Hotline Session I, World Congress of Cardiology 2006, Barcelona, September 2–5, 2006. (Abstract)
- FDA Statement on Coronary Drug-Eluting Stents. <http://www.fda.gov/cdrh/news/010407.html>
- Spaulding C, Daemen J, Boersma E, et al. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007;356:989–997.
- Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting stents. *N Engl J Med* 2007;356:998–1008.
- Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007;356:1030–1039.
- Lagerqvist B, James SK, Stenestrand U, et al. Long-term outcomes with drug-eluting stents versus bare-metal stents. *N Engl J Med* 2007;356:1009–1019.
- Luscher TF, Steffel J, Eberli FR, et al. Drug-eluting stent and coronary thrombosis. Biological mechanisms and clinical implications. *Circulation* 2007;115:1051–1058.
- Farb A, Burke AP, Kolodgie FD, et al. Pathological mechanisms of fatal late coronary stent thrombosis in humans. *Circulation* 2003;108:1701–1706.
- Kounis NG, Zavras GM. Histamine-induced coronary artery spasm: The concept of allergic angina. *Br J Clin Pract* 1991;45:121–128.
- Kounis NG, Kounis GN, Kouni SN. Coronary-artery stents. *N Engl J Med* 2006;354:2076–2077.
- Kounis NG, Kounis GN, Kouni SN, et al. Allergic reactions following implantation of drug-eluting stents: A manifestation of Kounis syndrome? *J Am Coll Cardiol* 2006;48:592–593.
- Bennett CL, Nebeker JR, Lyons EA, et al. The research on adverse drug events and reports (RADAR) project. *JAMA* 2005;293:2131–2140.
- Nebeker JR, Virmani R, Bennet CL, et al. Hypersensitivity cases associated with drug-eluting stents. A review of available cases from the research on adverse drug events and reports (RADAR) project. *J Am Coll Cardiol* 2006;47:175–181.
- Azarbal B, Currier JW. Allergic reactions after the implantation of drug-eluting stents. *J Am Coll Cardiol* 2006;47:182–183.
- Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): A natural paradigm? *Int J Cardiol* 2006;110:7–14.
- Kounis NG, Zavras GM. Allergic angina and allergic myocardial infarction. *Circulation* 1996;94:1789.
- Kounis NG, Grapsas ND, Goudevenos JA. Unstable angina, allergic angina, and allergic myocardial infarction. *Circulation* 1999;100:e156.
- Nikolaidis LA, Kounis NG, Grandman AH. Allergic angina and allergic myocardial infarction: A new twist on an old syndrome. *Can J Cardiol* 2002;18:508–511.
- Zavras GM, Papadaki PJ, Kokkinis CE, et al. Kounis syndrome secondary to allergic reaction following shellfish ingestion. *Int J Clin Pract* 2003;57:622–624.
- Wickman M. When allergies complicate allergies. *Allergy* 2005;60:14–18.
- Galli SJ, Nakae S, Tsai M. Mast cells in the development of adaptive immune responses. *Nat Immunol* 2005;6:135–142.
- Theoharides TC, Kalogeromitros D. The critical role of mast cells in allergy and inflammation. *Ann NY Acad Sci* 2006;1088:78–99.

28. MacGlashan Jr. DW, Brochner BS, Adelman DC, et al. Down-regulation of FcRI expression in human basophils during in vivo treatment of atopic patients with anti-IgE antibody. *J Immunol* 1997;158:1438–1445.
29. Nopp A, Johansson SGO, Lundberg M, et al. Simultaneous exposure of several allergens has an additive effect on multi-sensitized basophils. *Allergy* 2006;61:1366–1368.
30. Laine P, Kaartinen M, Penttila A, et al. Association between myocardial infarction and the mast cells in the adventitia of the infarct-related coronary artery. *Circulation* 1999;99:361–369.
31. Kaartinen M, van der wal AC, Van Der Loos CM, et al. Mast cell infiltration in acute coronary syndromes: Implications for plaque rupture. *J Am Coll Cardiol* 1998;32:606–612.
32. Kaartinen M, Penttila A, Kovanen PT. Mast cells in rupture-prone areas of human coronary atheromas produce and store TNF-alpha. *Circulation* 1996;94:2787–2792.
33. Kaartinen M, Penttila A, Kovanen PT. Mast cells accompany microvessels in human coronary atheromas: Implications for intimal neovascularization and hemorrhage. *Atherosclerosis* 1996;123:123–131.
34. Kovanen PT, Kaartinen M, Paavonen T. Infiltrates of activated mast cells at the site of coronary atheromatous erosion or rupture in myocardial infarction. *Circulation* 1995;92:1084–1088.
35. Kaartinen M, Penttila A, Kovanen PT. Accumulation of activated mast cells in the shoulder region of human coronary atheroma, the predilection site of atheromatous rupture. *Circulation* 1994;90:1669–1678.
36. Kovanen PT. Chymase-containing mast cells in human arterial intima: Implications for atherosclerotic disease. *Heart Vessels* 1997;12(Suppl.):125–127.
37. Kaartinen M, Penttila A, Kovanen PT. Mast cells in rupture-prone areas of human coronary atheromas produce and store TNF-alpha. *Circulation* 1996;94:2787–2792.
38. Kovanen PT. Mast cells in human fatty streaks and atheromas: Implications for intimal lipid accumulation. *Curr Opin Lipidol* 1996;7:281–286.
39. Sun J, Sukhova GK, Wolters PJ, et al. Mast cells promote atherosclerosis by releasing proinflammatory cytokines. *Nat Medicine* 2007;13:719–724.
40. Ma H, Kovanen PT. Inhibition of mast cell-dependent conversion of cultured macrophages into foam cells with antiallergic drugs. *Arterioscler Thromb Vasc Biol* 2000;20:E134–E142.
41. Bot I, de Jager SCA, Zerneck A, et al. Perivascular mast cells promote atherogenesis and induce plaque destabilization in apolipoprotein E-deficient mice. *Circulation* 2007;115:2516–2525.
42. Mayranpaa MI, Heikkila HM, Lindstedt KA, et al. Desquamation of human coronary artery endothelium by human mast cell proteases: Implications for plaque erosion. *Coron Artery Dis* 2006;17:611–621.
43. Lappalainen H, Laine P, Pentikainen MO, et al. Mast cells in neovascularized human coronary plaques store and secrete basic fibroblast growth factor, a potent angiogenic mediator. *Arterioscler Thromb Vasc Biol* 2004;24:1880–1885.
44. Theoharides TC, Kempuraj D, Tagen M, et al. Differential release of mast cell mediators and the pathogenesis of inflammation. *Immunol Rev* 2007;217:65–78.
45. Sakata Y, Komamura K, Hirayama A, et al. Elevation of the plasma histamine concentration in the coronary circulation in patients with variant angina. *Am J Cardiol* 1996;77:1121–1126.
46. Huang M, Pang X, Letourneau R, et al. Acute stress induces cardiac mast cell activation and histamine release, effects that are increased in Apolipoprotein E knockout mice. *Cardiovasc Res* 2002;55:150–160.
47. Steffel J, Akhmedov A, Greutert H, et al. Histamine induces tissue factor expression. Implications for acute coronary syndromes. *Circulation* 2005;112:341–349.
48. Deliargyris EN, Upadhyya B, Sane DC, et al. Mast cell tryptase: A new biomarker in patients with stable coronary artery disease. *Atherosclerosis* 2005;178:381–386.
49. Kervinen H, Kaartinen M, Makynen H, et al. Serum tryptase levels in acute coronary syndromes. *Int J Cardiol* 2005;104:138–143.
50. Lee M, Sommerhoff CP, von Eckardstein A, et al. Mast cell tryptase degrades HDL and blocks its function as an acceptor of cellular cholesterol. *Arterioscler Thromb Vasc Biol* 2002;22:2086–2091.
51. Reid AC, Silver RB, Levi R. Renin: At the heart of the mast cell. *Immunol Rev* 2007;217:123–140.
52. Lee M, Calabresi L, Chiesa G, et al. Mast cell chymase degrades apoE and apoA-II in apoA-I-knockout mouse plasma and reduces its ability to promote cellular cholesterol efflux. *Arterioscler Thromb Vasc Biol* 2002;22:1475–1481.
53. Bacani C, Frishman WH. Chymase: A new pharmacologic target in cardiovascular disease. *Cardiol Rev* 2006;14:187–193.
54. Lee-Rueckert M, Kovanen PT. Mast cell proteases: Physiological tools to study functional significance of high density lipoproteins in the initiation of reverse cholesterol transport. *Atherosclerosis* 2006;189:8–18.
55. Raymond RJ, Dehmer GJ, Theoharides TC, et al. Elevated interleukin-6 levels in patients with asymptomatic left ventricular systolic dysfunction. *Am Heart J* 2001;141:435–438.
56. Deliargyris EN, Raymond RJ, Theoharides TC, et al. Sites of interleukin-6 release in patients with acute coronary syndromes and in patients with congestive heart failure. *Am J Cardiol* 2000;86:913–918.
57. Huang M, Pang X, Karalis K, Theoharides TC. Stress-induced interleukin-6 release in mice is mast cell-dependent and more pronounced in Apolipoprotein E knockout mice. *Cardiovasc Res* 2003;59:241–249.
58. Shu J, Ren N, Du JB, et al. Increased levels of interleukin-6 and matrix metalloproteinase-9 are of cardiac origin in acute coronary syndrome. *Scand Cardiovasc J* 2007;41:149–154.
59. Bhattacharya K, Farwell K, Huang M, et al. Mast cell deficient W/W^v mice have lower serum IL-6 and less cardiac tissue necrosis than their normal littermates following myocardial ischemia-reperfusion. *Int J Immunopathol Pharmacol* 2007;20:69–74.
60. Nakae S, Suto H, Likura M, et al. Mast cells enhance T cell activation: Importance of mast cell costimulatory molecules and secreted TNF. *J Immunol* 2006;176:2238–2248.
61. Mekori YA, Metcalfe DD. Mast cell-T cell interactions. *J Allergy Clin Immunol* 1999;104:517–523.
62. Miyazaki D, Nakamura T, Toda M, et al. Macrophage inflammatory protein-1 α as a costimulatory signal for mast cell-mediated immediate hypersensitivity reactions. *J Clin Invest* 2005;115:434–442.
63. Salari H, Chan-Yeung M. Mast cell mediators stimulate synthesis of arachidonic acid metabolites in macrophages. *J Immunol* 1989;142:2821–2827.
64. Doherty TM. T cell regulation of macrophage function. *Curr Opin Immunol* 1995;7:400–404.
65. Szebeni J. Complement activation-related pseudoallergy: a new class of drug-induced acute immune toxicity. *Toxicology* 2005;216:106–121.

CORONARY STENTS

66. Blagosklonny MV, Darzyziewicz Z, Halicka HD, et al. Paclitaxel induces primary and postmitotic G1 arrest in human arterial muscle cells. *Cell Cycle* 2004;3:1050–1056.
67. Yeh ETH, Tong AT, Lenihan DJ, et al. Cardiovascular complications of cancer therapy. Diagnosis, pathogenesis, and management. *Circulation* 2004;109:3122–3131.
68. Finn AV, Kolodgie FD, Hamek J, et al. Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. *Circulation* 2005;112:270–278.
69. Stahl BE, Camici GG, Steffel J, et al. Paclitaxel enhances thrombin-induced endothelial tissue factor expression via c-jun terminal NH2 kinase activation. *Circ Res* 2006;99:149–155.
70. Zanutti KM, Markman M. Prevention and management of antineoplastic-induced hypersensitivity reactions. *Drug Saf* 2001;24:767–777.
71. Weiss RB, Donchover RC, Wiernik PH, et al. Hypersensitivity reactions from taxol. *J Clin Oncol* 1990;8:1263–1268.
72. Rowinsky EK, McGuire WP, Guarnieri T, et al. Cardiac disturbances during the administration of taxol. *J Clin Oncol* 1991;9:1704–1712.
73. Rowinsky EK, Eisenhauer EA, Chaudhry V, et al. Clinical toxicities encountered with paclitaxel (Taxol). *Semin Oncol* 1993;20(Suppl. 3):S1–S15.
74. Zanutti KM, Markman M. Prevention and management of antineoplastic-induced hypersensitivity reactions. *Drug Saf* 2001;24:767–777.
75. Sevela P, Mayerhofer K, Obermair A, et al. Thrombosis with paclitaxel. *Lancet* 1994;343:727.
76. Hekmat E. Fatal myocardial infarction potentially induced by paclitaxel. *Ann Pharmacother* 1996;30:1110–1112.
77. Laher S, Karp SJ. Acute myocardial infarction following paclitaxel administration for ovarian carcinoma. *Clin Oncol (R Coll Radiol)* 1997;9:124–126.
78. Pai VB, Nahata MC. Cardiotoxicity of chemotherapeutic agents: Incidence, treatment and prevention. *Drug Saf* 2000;22:263–302.
79. Mersin N, Boulbair F, Davani S, et al. Myocardial infarction after paclitaxel use. *Therapie* 2003;58:467–469.
80. Nguyen-Ho P, Keiman NS, Verani MS. Acute myocardial infarction and cardiac arrest in a patient receiving paclitaxel. *Can J Cardiol* 2003;19:300–302.
81. Kloover JS, den Bakker MA, van Meerbeeck JP, et al. Fatal outcome of a hypersensitivity reaction to paclitaxel: A critical review of premedication regimens. *Br J Cancer* 2004;90:304–305.
82. Schrader C, Keussen C, Bewig B, et al. Symptoms and signs of acute myocardial ischemia caused by chemotherapy with paclitaxel (Taxol) in a patient with metastatic ovarian carcinoma. *Eur J Med Res* 2005;10:498–501.
83. Ruiz-Casado A, Calzas J, Garcia J, et al. Life-threatening adverse drug reaction to paclitaxel. Postmarketing surveillance. *Clin Transl Oncol* 2006;8:60–62.
84. Turkoglu S, Simsek V, Abasi A. Possible anaphylactic reaction to Taxus stent: A case report. *Catheter Cardiovasc Interv* 2005;66:554–556.
85. Kim JW, Park CG, Seo HS, et al. Delayed severe multivessel spasm and aborted sudden death after Taxus stent implantation. *Heart* 2005;91:e15.
86. Vial T, de Saint Hilaire PJ, Descotes J. Paclitaxel hypersensitivity reactions: Assessment of the utility of a test-dose program. *Cancer J* 2006;12:237–245.
87. Henry A, Charpiat B, Perol M, et al. Possible anaphylactic reaction to Taxus stent: A case report. *Catheter Cardiovasc Interv* 2005;66:554–556.
88. Kim JW, Park CG, Seo HS, et al. Delayed severe multivessel spasm and aborted sudden death after Taxus stent implantation. *Heart* 2005;91:e15.
89. Watanabe Y, Nakai H, Ueda H, et al. Carboplatin hypersensitivity induced by low-dose paclitaxel/carboplatin in multiple platinum-treated patients with recurrent ovarian cancer. *Int J Gynecol Cancer* 2005;15:224–227.
90. Soufras GD, Ginopoulos PV, Papadaki PJ, et al. Penicillin allergy in cancer patients manifesting as Kounis syndrome. *Heart Vessels* 2005;20:159–163.
91. Vasquez EM. Sirolimus: A new agent for prevention of renal allograft rejection. *Am J Health Syst Pharm* 2000;57:437–448.
92. Steffel J, Latini RA, Akhmedov A, et al. Rapamycin, but not FK-506, increases endothelial tissue factor expression: Implications for drug-eluting stent design. *Circulation* 2005;112:2002–2011.
93. Tracey C, Hawley C, Griffin AD, et al. Generalized, pruritic, ulcerating maculopapular rash necessitating cessation of sirolimus in a liver transplantation patient. *Liver Transpl* 2005;11:987–989.
94. Warino L, Libecco J. Cutaneous effects of sirolimus in renal transplant recipients. *J Drugs Dermatol* 2006;5:273–274.
95. Wadei H, Gruber SA, El-Amm JM, et al. Sirolimus-induced angioedema. *Am J Transplant* 2004;4:1002–1005.
96. Mingos MA, Kane GC. Sirolimus-induced interstitial pneumonitis in a renal transplant patient. *Respir Care* 2005;50:1659–1661.
97. Howard L, Gopalan D, Griffiths M, et al. Sirolimus-induced pulmonary hypersensitivity with a CD4 T-cell infiltrate. *Chest* 2006;129:1718–1721.
98. Kunzle N, Venetz JP, Pascual M, et al. Sirolimus-induced acneiform eruption. *Dermatology* 2005;211:305–306.
99. Hardinger KL, Cornelius LA, Trulock EP 3rd, et al. Sirolimus-induced leukocytoclastic vasculitis. *Transplantation* 2002;74:739–743.
100. Pasqualotto AC, Bianco PD, Sukiennik TC, et al. Sirolimus-induced leukocytoclastic vasculitis: The second case reported. *Am J Transplant* 2004;4:1549–1551.
101. Truong U, Moon-Grady AJ, Butani L. Cardiac tamponade in a pediatric renal transplant recipient on sirolimus therapy. *Pediatr Transplant* 2005;9:541–544.
102. Walpoth BH, Hess OM. Late coronary thrombosis secondary to a sirolimus-eluting stent. *Circulation* 2004;110:e309.
103. Walpoth BH, Pavlicek M, Celik B, et al. Prevention of neointimal proliferation by immunosuppression in synthetic vascular grafts. *Eur J Cardiothorac Surg* 2001;19:487–492.
104. Togni M, Winddecker S, Cocchia R, et al. Sirolimus-eluting stents associated with paradoxical coronary vasoconstriction. *J Am Coll Cardiol* 2005;46:231–236.
105. Wheatcroft SW, Byrne J, Thomas M, et al. Life-threatening coronary artery spasm following sirolimus-eluting stent deployment. *J Am Coll Cardiol* 2006;47:1911–1912.
106. Maekawa K, Kawamoto K, Fuke S, et al. Severe endothelial dysfunction after sirolimus-eluting stent implantation. *Circulation* 2006;113:e850–e851.
107. Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus stent. Should we be cautious? *Circulation* 2004;109:701–705.
108. Virmani R, Farb A, Kolodgie FD, et al. Late coronary thrombosis secondary to a sirolimus-eluting stent. *Circulation* 2004;110:e309.
109. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 2004;364:1519–1521.

110. Leggat PA, Ketjarune U. Toxicity of methyl methacrylate in dentistry. *Int Dent J* 2003;53:126–131.
111. Ahmed DD, Sobczak SC, Yunginger JW. Occupational allergies caused by latex. *Immunol Allergy Clin North Am* 2003;23:205–219.
112. Ruiz-Genao DP, Moreno De Vega MJ, Sanchez Perez J, et al. Labial edema due to an acrylic dental prosthesis. *Contact Dermatitis* 2003;48:273–274.
113. Giunta J, Zablotsky N. Allergic stomatitis caused by self-polymerizing resin. *Oral Surg Med Oral Pathol* 1976;41:631–637.
114. Lunder T, Rogl-Butina M. Chronic urticaria from an acrylic dental prosthesis. *Contact Dermatitis* 2000;43:222–223.
115. Nealey ET, Del Rio CE. Stomatitis venenata: Reaction of a patient to acrylic resin. *J Prosthet Dent* 1969;21:480–484.
116. Concalves TS, Morganti MA, Campos LC, et al. Allergy to auto-polymerized acrylic resin in an orthodontic patient. *Am J Orthod Dentofacial Orthop* 2006;129:431–435.
117. Devlin H, Watts DC. Acrylic “allergy”? *Br Dent J* 1984;157:272–275.
118. van Beusekom HM, Schwartz RS, van der Giessen WJ. Synthetic polymers. *Semin Interv Cardiol* 1998;3:145–148.
119. Van Der Giessen WJ, Lincoff AM, Schwartz RS, et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. *Circulation* 1996;94:1690–1697.
120. van Beusekom HM, Serruys PW, van der Giessen WJ. Coronary stent coatings. *Coron Artery Dis* 1994;5:590–596.
121. Revell PA, Braden M, Freeman MA. Review of the biological response to a novel bone cement containing poly(ethyl methacrylate) and n-butyl methacrylate. *Biomaterials* 1998;19:1579–1586.
122. Niemi SM, Fox JG, Brown LR, et al. Evaluation of ethylene-vinyl acetate copolymer as a non-inflammatory alternative to Freund’s complete adjuvant in rabbits. *Lab Anim Sci* 1985;35:609–612.
123. Moreau L, Alomer G, Dube N, et al. Contact urticaria from carboxymethylcellulose in white chalk. *Dermatitis* 2006;17:29–31.
124. Ownby DR. Mechanisms in adverse reactions to food: The whole body. *Allergy* 1995; 50(20 Suppl.):26–30.
125. Lyell A, Bain WH, Thomson RM. Repeated failure of nickel-containing prosthetic valves in a patient allergic to nickel. *Lancet* 1978;2:657–659.
126. Kanerva L, Sipilainen-Malm T, Estlander T, et al. Nickel rease from metals, and a case of allergic contact dermatitis from stainless steel. *Contact Dermat* 1994;31:299–303.
127. Hillen U, Haude M, Erbel R, et al. Evaluation of metal allergies in patients with coronary stents. *Contact Dermat* 2002;47:353–356.
128. Thomas P, Summer B, Sander CA, et al. Intolerance of osteosynthesis material: Evidence of dichromate contact allergy with concomitant oligoclonal T-cell infiltrate and TH1-type cytokine expression in the peri-inplantar tissue. *Allergy* 2000;55:969–972.
129. Oppei T, Schnuch A. The most frequent allergens in allergic contact dermatitis. *Dtsch Med Wochenschr* 2006;131:1584–1589.
130. Wertman B, Azarbal B, Riedl M, et al. Adverse events associated with nickel allergy in patients undergoing percutaneous atrial septal defect or patent foramen ovale closure. *J Am Coll Cardiol* 2006;47:1226–1227.
131. Fukahara K, Minami K, Reiss N, et al. Systemic allergic reactions to the percutaneous patent foramen ovale closure. *J Thoracic Cardiovasc Surg* 2003;125:213–214.
132. Dasika UK, Kanter KR, Vincent R. Nickel allergy to percutaneous patent foramen ovale occluder and subsequent systemic nickel allergy. *J Thoracic Cardiovasc Surg* 2003;125:2112–2113.
133. Sharifi M, Burks J. Efficacy of clopidogrel in the treatment of post-ASD closure migraines. *Catheter Cardiovasc Inter* 2004;63:255.
134. Menezes LM, Campos LC, Quintao CC, et al. Hypersensitivity to metals in orthodontics. *Am J Orthod Dentofacial Orthop* 2004;126:58–64.
135. Koster R, Vieluf D, Kiehn M, et al. Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis. *Lancet* 2000;356:1895–1897.
136. Kawano H, Koide Y, Baba T, et al. Granulation tissue with eosinophil infiltration in the restenotic lesion after coronary stent implantation. *Circ J* 2004;68:722–723.
137. Iijima R, Ikari Y, Amiya E, et al. The impact of metallic allergy on stent implantation. Metal allergy and recurrence of in-stent thrombosis. *Int J Cardiol* 2005;104:319–325.
138. Lhotka CG, Szekeres T, Fritzer-Szekeres M, et al. Are allergic reactions to skin clips associated with delayed wound healing? *Am J Surg* 1998;176:320–323.
139. Federmann M, Morell B, Graetz G, et al. Hypersensitivity to molybdenum as a possible trigger of ANA-negative systemic lupus erythematosus. *Ann Rheum Dis* 1994;53:403–405.
140. Svedman C, Tillman C, Gustavsson CG, et al. Contact allergy to gold in patients with gold-plated intracoronary stents. *Contact Dermatitis* 2005;52:192–196.
141. Mosseri M, Tamari I, Plich M, et al. Short- and long-term outcomes of the titanium-NO stent registry. *Cardiovasc Revasc Med* 2005;6:2–6.
142. Brott BC, Anayiotos A, Chapman G, et al. Severe, diffuse coronary artery spasm after drug-eluting stent placement. *J Invasive Cardiol* 2006;18:584–592.
143. Togni M, Eberli FR. Vasoconstriction and coronary artery spasm after drug-eluting stent placement. *J Invasive Cardiol* 2006;18:593.
144. Garcia JA, Hansgen A, Casserly IP. Simultaneous multi-vessel acute drug-eluting stent thrombosis. *Int J Cardiol* 2006;113:E11–E15.
145. Nemmar A, Hoet PHM, Vermylen J, et al. Pharmacological stabilization of mast cells abrogates late thrombotic events induced by diesel exhaust particles in hamsters. *Circulation* 2004;110:1670–1677.