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EXPEDITED REVIEW

Hypersensitivity Cases Associated With Drug-Eluting Coronary Stents

A Review of Available Cases From the Research on Adverse Drug Events and Reports (RADAR) Project

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OBJECTIVES We undertook the review of all available cases of hypersensitivity reactions after placement of a drug-eluting stent (DES) and classified potential causes.

BACKGROUND Six months after the approval of the first DES, the Food and Drug Administration (FDA) reported 50 hypersensitivity reactions after stent placement but later concluded these were due to concomitantly prescribed medications such as clopidogrel. Nevertheless, the FDA continued to receive reports of hypersensitivity.

METHODS Reports available from April 2003 through December 2004 for hypersensitivity-like reactions associated with the sirolimus-eluting stent (CYPHER, Cordis Corp., Miami Lakes, Florida) and paclitaxel-eluting stent (TAXUS, Boston Scientific Corp., Natick, Massachusetts) were reviewed. Sources of reports included the FDA's adverse-device-event database, the published literature, and investigators from the Research on Adverse Drug/Device events And Reports (RADAR) project. Causality was assessed using standardized World Health Organization criteria.

RESULTS Of 5,783 reports identified for the DES in the FDA database, 262 unique events included hypersensitivity symptoms. Of these reports, 2 were certainly and 39 unlikely caused by clopidogrel and 1 was certainly, 9 probably, and 13 unlikely caused by the DES. From all sources, we identified 17 distinct cases that were probably or certainly caused by the stent, of which 9 had symptoms that lasted longer than four weeks. Four autopsies confirmed intrastent eosinophilic inflammation, thrombosis, and lack of intimal healing.

CONCLUSIONS The FDA reports and autopsy findings suggest that DES may be a cause of systemic and intrastent hypersensitivity reactions that, in some cases, have been associated with late thrombosis and death. (J Am Coll Cardiol 2006;47:xxx) © 2006 by the American College of Cardiology Foundation

Since being approved by the Food and Drug Administration (FDA), drug-eluting stents (DES) have reduced the occurrence of major cardiac events from 16.4% with bare-metal stents to 7.8% with DES (1). The stainless steel struts of the stent are coated with polymers impregnated with a drug that inhibits local intimal hyperplasia. The sirolimus-eluting stent (SES) (CYPHER, Cordis Corp., Miami Lakes, Florida), approved by the FDA in May 2003, is impregnated with an anti-inflammatory agent. The paclitaxel-eluting stent (PES) (TAXUS, Boston Scientific Corp., Natick, Massachusetts), approved in March 2004, is impregnated with a chemotherapeutic agent. More than two million DES have been implanted, now accounting for 75% of all coronary artery stents utilized (2,3).

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In October 2003, an FDA advisory described 50 hypersensitivity cases after CYPHER stent implantation (4). Symptoms included rash, dyspnea, hives, itching, and fe-

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Abbreviations and Acronyms

DES = drug-eluting stent
FDA = Food and Drug Administration
MAUDE = Manufacturer and User Device Experience
PES = paclitaxel-eluting stent
RADAR = Research on Adverse Drug/Device events And Reports
SES = sirolimus-eluting stent
WHO = World Health Organization

vers. In November 2003, a follow-up advisory indicated that almost all of the hypersensitivity reactions were caused by standard drug therapy associated with stent implantation (5). Nevertheless, components of DES and closely related compounds have caused hypersensitivity reactions in other settings, suggesting that components of the stent itself may be causative factors in some cases (6–8). Moreover, there has been no public verification of the FDA case-based findings through epidemiologic analysis of clinical trial data; hypersensitivity data is not presented in the package insert or in publications of the clinical trials (9,10).

The recently initiated Research on Adverse Drug/Device events And Reports (RADAR) project reviews in detail adverse event reports gathered from diverse sources, including the FDA, in order to evaluate causal associations between therapeutic agents and potentially fatal adverse events (11). Herein, RADAR investigators assessed all available cases to date for the possibility that DES may be a cause of hypersensitivity reactions, including cases identified independent from the FDA database.

METHODS

The FDA's Manufacturer and User Device Experience center (MAUDE) receives adverse event reports from device monitoring programs worldwide (12). All MAUDE reports regarding the CYPHER and TAXUS stents received from April 2003 through December 2004 were reviewed. The case definition included DES placement and hypersensitivity findings including rash, dyspnea, hives, anaphylaxis, thrombocytopenia, itching, arthralgia, joint swelling, myalgia, or fevers. Reports were reviewed for similar dates, location, and clinical findings to minimize double counting of events. Other instances of DES-associated hypersensitivity reactions were identified by review of electronic databases (medical subject headings terms of DES, hypersensitivity) and/or from the clinical practice of study co-investigators.

Fields in the MAUDE database used for analysis and classification included the event identification, report identification, date received, seriousness of outcome according to FDA criteria (death, life-threatening, hospitalization, emergency intervention), source of report (manufacturer or other), and free text descriptions. Reviewers were blinded to all data except the event identification, report identification, and free text descriptions of the case. Reviewers coded the time from implantation to onset of symptoms ("immediately afterwards" classified as one day, and "soon after" classified as five days), duration of symptoms (no time stated but one physician visit with subsequent telephone follow-up classified as four weeks), rash type, rash distribution, other symptoms, allergy history, reported attribution of cause to stent, reported attribution of cause to concomitant medication, treatments (for each: drug/intervention, duration, effect), concomitant medication (for each: physician attribution of cause for symptoms, started more than seven days before stent, previous continuous exposure without reaction).

Causal association grades for clopidogrel, aspirin, and the DES were assigned according to World Health Organization (WHO) criteria (13). These criteria classify causal associations as certain, probable, possible, or unlikely based on timing, pathophysiology, de-challenge (agent withdrawal), re-challenge (agent re-exposure), and competing explanations (Table 1).

The crude odds ratio was used as the measure of association between the source of the report and the presence of a causal attribution statement. The kappa statistic was used to measure agreement between the reported cause of the reaction and the WHO-criteria-based classification dichotomized between probable and possible scores. All statistical analyses were conducted using Stata 8.2 (StataCorp., College Station, Texas).

RESULTS

Since DES have been marketed, we identified 5,781 MAUDE reports received by the FDA (3,695 for

Table 1. Application of World Health Organization Criteria to Potential Causal Agents

Agent	Classification Criteria*
Anti-platelet agents	Certain if the hypersensitivity findings resolved on dechallenge and recurred on re-challenge. Probable if the reaction resolved after dechallenge. Unlikely if there was prior, continuous exposure without hypersensitivity findings or no change in hypersensitivity findings in response to dechallenge or re-challenge.
Intravenous agents used at implantation	Certain if the hypersensitivity findings resolved on dechallenge and recurred on re-challenge. Probable if the reaction began the day of implantation and resolved within two days. Unlikely if the reaction began more than 2 days after use of these agents.
Drug-eluting stents	Certain if there was histological evidence of eosinophilic reaction confined to the area of the stent at autopsy. Probable if all other potential causes were scored as unlikely (all medications we discontinued) and there was evidence of a persistent allergic response for at least two weeks' duration. Unlikely if another agent was identified as a probable or certain cause.

*If no cause was otherwise classifiable, it was classified as possible. Some cases required referral to the original World Health Organization criteria for final classification.

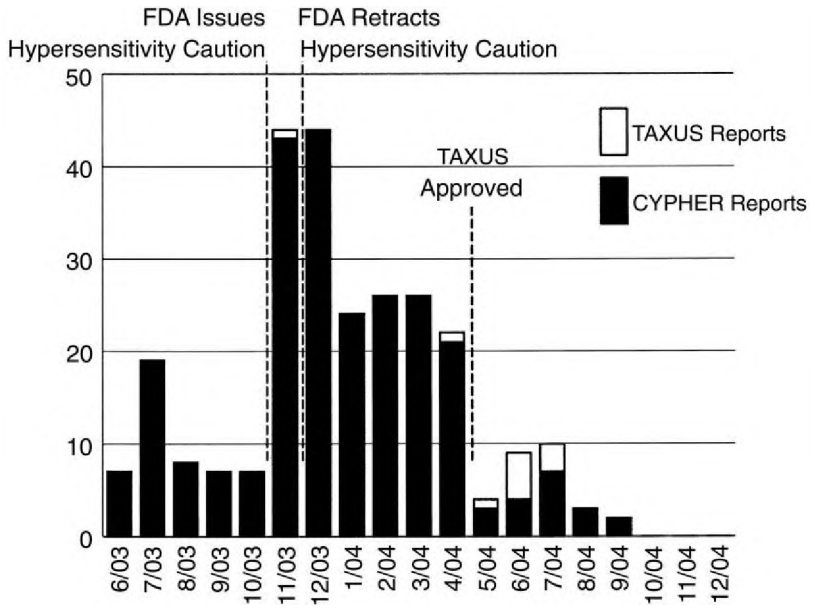

Figure 1. Reports received by the Food and Drug Administration for hypersensitivity-like symptoms associated with drug-eluting coronary stents.

CYPHER over 18 months and 2,086 for TAXUS over 8 months). Of these, 251 reports for CYPHER and 11 reports for TAXUS described hypersensitivity symptoms. Figure 1 demonstrates an increase from a monthly mean of 10 to 44 after the release of the FDA caution. The four months after the FDA retraction of the hypersensitivity caution, a mean of 25 reports were received. The number of reports received by the FDA decreased to zero thereafter.

Among MAUDE hypersensitivity reports with symptom onset information (n = 185), symptoms began within 1 day of stent implantation (20%), 2 to 7 days (46%), 8 to 14 days (19%), and >2 weeks (15%) after stent implantation (mean 11.5 days). Among the 115 cases for which symptom duration information was available, symptoms persisted for ≤1 week for 15% of cases and <30 days for 50%. Presenting symptoms included rash (78%), itching (27%), hives (23%), dyspnea (16%), fever (13%), atypical chest pain (8%), high or low blood pressure (8%), joint pain or swelling (8%), and anaphylaxis (6%). Among hypersensitivity reports with descriptions of rash (n = 204), 26% involved hives, 3% involved desquamation or blisters, 21% covered the entire body, 11% were focal eruptions, and 57% lacked characterizing information. Based on MAUDE seriousness codes (n = 242) and additional classifications from case descriptions (n = 8), 95% of hypersensitivity reactions were classified as serious including events that required emergency interventions (34%) (e.g., intravenous steroids and cardiac catheterization) or hospitalization (18%), or resulted in permanent disability (5%), or may have contributed to death (2%). At least one antiplatelet drug was discontinued at the onset of hypersensitivity in 19% of cases.

Potential causative factors—concomitant medications versus the DES—were evaluated using WHO criteria (Tables 1 and 2). Lack of key information resulted in simultaneous classifications of "possible" for the three major causes of hypersensitivity (clopidogrel, aspirin, and the DES) in 80% of reports. Over one-fifth of all MAUDE hypersensitivity reactions, of which three were fatal, persisted more than 30 days but could not be scored above "possible" for any cause because of lacking information.

From the MAUDE database, cases seen by RADAR co-investigators (14), and published cases (15), 17 cases (14 CYPHER and 3 TAXUS) of probable or certain DES-induced hypersensitivity syndromes were identified (Table 3). Four patients died of coronary thrombosis that extended into the stent. Histological examination demonstrated intrastent eosinophilic infiltrates and poor intimal healing as late as 18 months after implantation (Fig. 2). In one of these

Table 2. World Health Organization Causation Assessment Categories for Associated Hypersensitivity Identified in the MAUDE Database

Putative Causative Agent	Certain	Probable	Possible	Unlikely
Clopidogrel	2 (1%)	0	221 (84%)	39 (15%)
Aspirin	0	0	240 (92%)	22 (8%)
Agents administered during implantation	0	3 (1%)	13 (5%)	246 (93%)
CYPHER stent	1 (<1%)	7 (3%)	230 (92%)	13 (5%)
TAXUS stent	0	2 (18%)	9 (82%)	0

For percent values, each agent is denominated by the number of cases in which the agent was used.

Table 3. Findings for 17 Individuals With Hypersensitivity Symptoms Classified as Certainly or Probably Due to a Drug-Eluting Stent

Patient Number	Data Source	Stent	Days From Implantation to First Symptom	Duration of Symptoms (weeks)	Hospitalization	Non-Urticarial Rash	Urticaria	Dyspnea
Cases with focal hypersensitivity on autopsy scored as certainly caused by the stent								
1	RADAR	T	150	0	−	−	−	−
2	RADAR	C	30	12	+	−	−	+
3	MAUDE*	C	78	NA	−	−	−	−
4	RADAR (14)	C	21	3	−	+	−	−
Cases with generalized hypersensitivity scored as probably caused by the stent								
5	MAUDE	C	3	>4	−	+	−	−
6	MAUDE	C	4	2	+	+	−	+
7	MAUDE	C	1	>4	−	−	+	
8	MAUDE	C	2	>8	−	+	−	−
9	MAUDE	C	0.25	>4	+	+	−	−
10	MAUDE	C	4	>4	+	−	+	−
11	MAUDE	C	NA	>4	−	−	+	−
12	MAUDE	T	10	>2	+	−	+	+
13	MAUDE	T	9	>1	−	−	+	−
14	RADAR	C	21	>40	−	+	−	+
15	RADAR	C	4	40	−	+	+	+
16	RADAR	C	14	>4	+	+	−	+
17	Case report (15)	C	210	>16	−	−	−	−

Duration indicated by ">" was approximate time through the end of follow up. Peripheral eosinophilia and IgE elevation was determined after anti-platelet drugs were discontinued. *Case 3 and 4 had similar timing and findings but different coronary anatomy and were reported from different regions.

A = attenuated (symptoms persisted at low level or returned after prednisone holiday); BMS = bare-metal stent; C = CYPHER; DES = drug-eluting stent; NA = not available; R = resolved (symptoms completely resolved after course of prednisone); T = TAXUS.

patients, concomitantly placed bare-metal stents were not associated with these hypersensitivity findings. For all 17 cases, clinical manifestations included non-urticarial rash (n = 8), hives (n = 5), dyspnea (n = 6), myalgia/arthralgia (n = 3), itching (n = 2), and blisters (n = 1). All urticarial eruptions began within 10 days of implantation. Laboratory findings included eosinophilia and elevated IgE titers over five times normal for three patients. Clinical or laboratory findings did not abate with discontinuation of antiplatelet medications.

We also evaluated the MAUDE dataset for completeness and potential bias. Many MAUDE reports did not include information on time to symptom onset (30%), time of symptom duration (55%), concomitant drugs (40%), and de-challenge response to concomitant drugs (81%). In comparison to reports submitted from sources other than the manufacturer, manufacturer reports were 3.4-fold (95% confidence interval 1.0 to 17.7) more likely to include a statement that the DES was not the cause of the hypersensitivity symptoms and 3.1-fold (95% confidence interval 1.1 to 12.6) more likely to include text indicating that clopidogrel was the most likely cause of the hypersensitivity symptoms. Agreement was low between the likelihood that clopidogrel was the most probable cause of the hypersensitivity findings included in the MAUDE database versus our review (kappa = 0.05).

Table 3. Continued

Elevated IgE or Eosinophilia	Other Symptoms	Other Findings	Medications Started at Implantation	Discontinued Medications	Response to Prednisone
NA	In-stent thrombosis and death at 5 months	Eosinophilic infiltrates within DES but not within 3 BMS, of which two were placed 2 months earlier and one simultaneously	None	None	—
NA	In-stent thrombosis and death at 4 months	Eosinophilic infiltrates at site of stent on autopsy (Fig. 2)	Aspirin, clopidogrel	None	—
NA	In-stent thrombosis and death at 18 months	Eosinophilic infiltrates at site of stent on autopsy	NA	NA	
NA	In-stent thrombosis and death at 18 months	Eosinophilic infiltrates at site of stent on autopsy	Ticlopidine, aspirin, simvastatin, beta-blocker	Ticlopidine	—
NA	Painful, swollen joints, fever, itching	Bare-metal stent the previous year	None	None	A
+	Anaphylaxis	NA	Aspirin, clopidogrel	Aspirin, clopidogrel	R
NA	Headache, intermittent hypertension	NA	NA	Aspirin, clopidogrel	—
NA	Itching	NA	Clopidogrel	Clopidogrel	A
NA	Hypertension	NA	None	None	A
NA	Urticaria worsened after second CYPHER™ stent	NA	NA	Clopidogrel	—
NA	NA	NA	Clopidogrel	Clopidogrel	A
NA	Dysphagia, joint pain, aches	History of allergy to vascular catheters	NA	Clopidogrel	A
NA	Dysphagia	NA	None	None	A
+	Itching, blisters on hands	Previously tolerated intermittent aspirin	Aspirin, clopidogrel	Clopidogrel	—
+	Hypertension	Skin biopsy consistent with drug reaction while off all drugs, gallium-67 uptake in carinal node	Clopidogrel	Aspirin, clopidogrel	A
+	Weakness, cough, fever	Broncoscopy proven eosinophilic pneumonitis. Rechallenge to clopidogrel without hypersensitivity response.	Clopidogrel	Clopidogrel	R
NA	Myalgia	Gallium-67 uptake at site of stent	NA	NA	—

DISCUSSION

This study is the first comprehensive assessment of hypersensitivity-like reactions that occurred after placement of DES. Only 2 of 262 cases of hypersensitivity cases reported to the FDA could be attributed to clopidogrel despite the widespread perception that this antiplatelet agent is the major culprit for hypersensitivity reactions. For 17 cases, the stent itself appears to be the most probable cause of hypersensitivity findings. Pathology findings from four autopsies present the strongest evidence that DES cause hypersensitivity reactions.

Medications initiated after DES implantation are a possible source of hypersensitivity-like symptoms. About 4% of persons who receive intravenous iodinated contrast agents develop rashes or itching, with symptoms usually beginning within minutes of contrast administration (16). For ticlopidine, clopidogrel, and aspirin, rash is reported in 5.1%, 4.2%, and 3.5% of recipients, respectively (16). In a prospective study of 130 patients who received ticlopidine and aspirin after a bare-metal stent, the mean onset of hypersensitivity symptoms was 10 days, and mean duration was 5 days; no case lasted longer than 30 days (17). Although FDA officials concluded that most of the CYPHER stent-associated hypersensitivity reactions could be attributed to concomitant drugs, particularly antiplatelets, our analysis suggests that, in all but two cases, clopidogrel would be classified as a possible or an unlikely cause of the clinical findings. Moreover, the duration of symptoms in the MAUDE dataset, in which 50% of cases lasted more than a month, is not congruent with the shorter duration of symptoms in patients receiving ticlopidine after bare-metal stents (17). It is particularly important not to misattribute

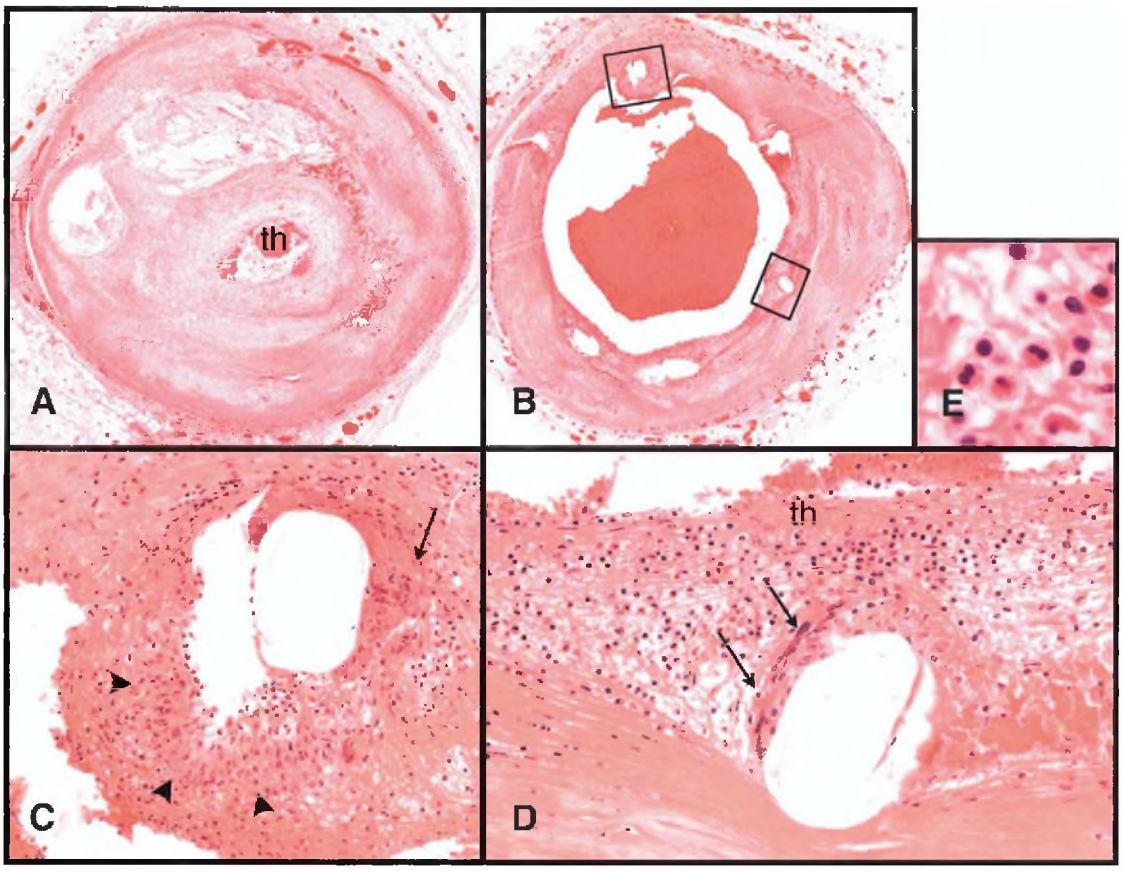

Figure 2. Photomicrograph of the non-stented coronary artery of Patient #2 just proximal to the stent showing severe stenosis and non-occlusive luminal thrombus (th) **(A)**. In **B** is shown the proximal stented artery with marked inflammatory reaction around stent struts; high-power magnification of the boxed areas in **B** is shown in **C and D**, note that there is severe granulomatous reaction consisting of macrophages **(arrowheads)** and giant cells **(arrows)**. In between the stent struts, there is severe eosinophilic and T-cell infiltration **(high-power E)** with only rare spindle-shaped cells seen close to the lumen. There is absence of endothelium in **D**; instead there is a surface thrombus.

the cause of hypersensitivity to antiplatelet medications, as premature discontinuation of these drugs increases the hazard of stent thrombosis 90-fold (18).

Drugs impregnated in the stent may also be a source of hypersensitivity. Sirolimus is an unlikely cause of hypersensitivity because it typically reduces eosinophilic infiltration and histamine release and has been associated with low rates of hypersensitivity (16). The incidence of hypersensitivity to paclitaxel itself is not known because large, published studies have used a castor-oil-derived vehicle known to have high rates of non-immune-mediated hypersensitivity reactions (19).

Non-drug components of the DES are potential causes of hypersensitivity. The polymer coating can fragment and expose metal struts (14), raising concern that nickel and molybdenum in the stainless steel may cause hypersensitivity (6). However, bare-metal stents have not been demonstrated to cause hypereosinophilic, IgE-mediated reactions in a human autopsy series of over 400 stents (14). The polymers coating the DES are a more likely cause of late, persistent hypersensitivity. Studies of related polymers have demonstrated local and systemic hypersensitivity responses to intravascular and locally applied polymers (7). In animal studies of DES, eosinophilic infiltrates developed in 25% of pigs receiving DES, and these infiltrates were more prominent at 90 days versus 28 days (14).

The limitations of our study should be acknowledged. First, hypersensitivity events in DES clinical trials are likely to be underreported, as some trials (9,10) solicited events that were judged by the treating clinician to be attributable to the stent instead of all hypersensitivity events. Moreover, the proportion of 262 cases in over two million insertions is well below the 4% expected for hypersensitivity from drugs alone. Second, MAUDE reports frequently lacked information necessary for causality attribution. Third, because of underreporting and missing case information, it is not appropriate to draw inferences that hypersensitivity reactions are more frequently caused by the stent than concomitant drugs or by one brand of stent than another. As with most of the reports from the RADAR project (11), incidence rate estimates are not possible to derive from spontaneous reports. However, because clinical trials with thousands of patients have not reported increased mortality with DES compared to bare-metal stents (9,10), the incidence

of fatal hypersensitivity events due to DES is likely to be low.

In conclusion, our findings suggest that local and systemic hypersensitivity manifestations can develop in response to implantation of DES in coronary arteries. These events may cause prolonged hypersensitivity symptoms and occasionally result in death. Further study is warranted to characterize the incidence and course of these events, to develop tests that predict or confirm the development of stent-associated hypersensitivity, and to determine whether stent-sensitive patients warrant prolonged antiplatelet therapy. Health professionals should be vigilant for hypersensitivity symptoms among persons receiving a DES and should submit detailed adverse event reports to the manufacturer or the FDA.

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