Localized Hypersensitivity and Late Coronary Thrombosis Secondary to a Sirolimus-Eluting Stent
Should We Be Cautious?

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Background—The US Food and Drug Administration recently issued a warning of subacute thrombosis and hypersensitivity reactions to sirolimus-eluting stents (Cypher). The cause and incidence of these events have not been determined.

Methods and Results—We present findings of a 58-year-old man who died of late stent thrombosis 18 months after receiving 2 Cypher stents for unstable angina. Although angiographic and intravascular ultrasound results at 8 months demonstrated the absence of neointimal formation, vessel enlargement was present. An autopsy showed aneurysmal dilation of the stented arterial segments with a severe localized hypersensitivity reaction consisting predominantly of T lymphocytes and eosinophils.

Conclusions—The known pharmacokinetic elution profile of Cypher stents and the presence of polymer fragments surrounded by giant cells and eosinophils suggest that a reaction to the polymer may have caused late stent thrombosis. Careful long-term follow-up of patients with vessel enlargement after Cypher stent placement is recommended. (Circulation. 2004;109:701-705.)

Key Words: sirolimus ■ stents ■ thrombosis ■ death, sudden

The drug-eluting stent (DES) era was ushered in with the first published human study by Sousa et al in 2001 showing a nearly complete abolition of neointimal hyperplasia by use of the sirolimus-eluting stent (Cypher, Cordis Johnson & Johnson). Cypher stents are coated with a thin layer of a poly-n-butyl methacrylate and polyethylene–vinyl acetate copolymer containing 140 µg sirolimus (Wyeth-Ayers). Since the approval of Cypher stents in Europe and the United States, a total of 450,000 units have been distributed worldwide as of October 20, 2003, reflecting an increasing percentage of the >1.5 million individuals treated annually with coronary stents. The incidence of subacute and late stent thrombosis within the first 30 days in patients randomized to Cypher in clinical trials is reported to be no different from that with control bare metal stents. Long-term published follow-up data are available only up to 2 years in 45 patients in the “First in Man” study and up to 1 year in 120 patients enrolled in the Randomized Study with Sirolimus-Coated Bx Velocity Balloon-Expandable Stent (RAVEL) trial. The Food and Drug Administration, along with Cordis Johnson & Johnson, have posted adverse event information for physicians; there have been >290 reports of subacute thrombosis (of which 60 have been fatal) and 50 reports of possible hypersensitivity reactions. The rates and reasons of these adverse outcomes associated with Cypher stent use are unknown.

This report describes the first case of fatal acute myocardial infarction and cardiac rupture as a result of late thrombosis of a Cypher stent deployed 18 months previously. The patient, enrolled in the European Sirolimus Eluting Stent in De Novo Native Coronary Lesions (E-SIRIUS) trial, developed a hypersensitivity reaction limited to the coronary artery wall surrounding the stent.

Case Report
A 58-year-old man was first seen in December 2001 with unstable angina. The patient was a smoker, with hyperlipidemia, without a history of diabetes and hypertension. A
coronary angiogram showed a 20-mm-long 95% diameter stenosis extending from the proximal to mid left circumflex coronary artery (LCx) (Figure 1), a 70% diameter stenosis in the mid left anterior descending coronary artery (LAD), and a noncritical lesion in the proximal right coronary artery (RCA). The patient was enrolled in the E-SIRIUS trial and randomized to the sirolimus-eluting stent group.\textsuperscript{5} The LCx artery lesion was predilated with an undersized balloon (2.5 mm at 14 atm), and 2 sirolimus-eluting Cypher stents (3.0×18 mm and 2.5×18 mm) were implanted with a 1-mm overlap. The proximal stent was postdilated with a noncompliant balloon. Intravascular ultrasound (IVUS) imaging was performed at the end of the stent procedure, and quantitative angiographic and volumetric IVUS analyses were measured by independent core laboratories (Brigham and Women’s Hospital, Boston, Mass, and Cardialysis, BV, Rotterdam, the Netherlands). The reference laboratory determined a minimal reference lumen and stent diameter of 2.3 mm. The patient was discharged without in-hospital complications on ticlopidine, aspirin, simvastatin, and β-blocker.

Three weeks later, the patient presented to the clinic with a skin rash on the trunk, neck, ankle, and wrist with itching and irritation; there was no previous history of allergy. The reaction was interpreted as an allergic response to ticlopidine, which was discontinued and replaced by clopidogrel 75 mg/d for 2 months. At this time, the total leukocyte count was normal, without eosinophilia. The rash resolved within a few days.

At 8 months after stenting, per protocol, the patient underwent follow-up angiography and IVUS. Angiographic quantitative coronary arteriography and IVUS imaging demonstrated an absence of in-stent restenosis or neointimal proliferation (Figures 1 and 2). Laboratory blood tests were normal, including a total eosinophil count of 140 μL. The patient remained asymptomatic at 1-year clinical follow-up, with a negative isotope stress test.

Eighteen months after stenting, the patient developed an episode of epigastric and retrosternal chest pain with syncope followed by prompt recovery. Over the next few days, the individual experienced recurrent episodes of intermittent chest pain and was admitted to the coronary care unit with a diagnosis of a recent non-Q-wave myocardial infarction.

**Figure 1.** Baseline angiogram (A, right anterior oblique projection) showing 95% narrowing of mid LCx (arrow). Two overlapping Cypher stents (3×18 and 2.5×18 mm) (arrow) were placed (postdeployment angiogram, B). Stents (arrow) were widely patent 8 months after deployment (C) and similar to angiogram in B. At 18 months (D), there was total occlusion at site of proximal Cypher stent (arrow).

coronary angiogram showed a >20-mm-long 95% diameter stenosis extending from the proximal to mid left circumflex coronary artery (LCx) (Figure 1), a 70% diameter stenosis in the mid left anterior descending coronary artery (LAD), and a noncritical lesion in the proximal right coronary artery (RCA). The patient was enrolled in the E-SIRIUS trial and randomized to the sirolimus-eluting stent group.\textsuperscript{5} The LCx artery lesion was predilated with an undersized balloon (2.5 mm at 14 atm), and 2 sirolimus-eluting Cypher stents (3.0×18 mm and 2.5×18 mm) were implanted with a 1-mm overlap. The proximal stent was postdilated with a noncompliant balloon. Intravascular ultrasound (IVUS) imaging was performed at the end of the stent procedure, and quantitative angiographic and volumetric IVUS analyses were measured by independent core laboratories (Brigham and Women’s Hospital, Boston, Mass, and Cardialysis, BV, Rotterdam, the Netherlands). The reference laboratory determined a minimal reference lumen and stent diameter of 2.3 mm. The patient was discharged without in-hospital complications on ticlopidine, aspirin, simvastatin, and β-blocker.

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**Figure 2.** Longitudinal reconstruction of IVUS of stented LCx (top image, immediately after stent deployment; bottom image, 8-month follow-up) illustrating borders of artery wall (green line), stent (blue line), and lumen (red line). Note increased plaque volume and vessel size (indicative of positive remodeling, arrowheads) at 8 months, with nearly absent neointimal thickening.

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<th>Baseline</th>
<th>8 Months</th>
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<tr>
<td>Vessel Volume (mm$^3$)</td>
<td>407</td>
<td>462</td>
</tr>
<tr>
<td>Stent Volume (mm$^3$)</td>
<td>187</td>
<td>194</td>
</tr>
<tr>
<td>Plaque behind stent (mm$^3$)</td>
<td>221</td>
<td>269</td>
</tr>
<tr>
<td>Neointimal Volume (mm$^3$)</td>
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<td>0.7</td>
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<tr>
<td>% Stent Volume Obstruction (mm$^3$)</td>
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The patient was now asymptomatic and was treated with heparin, β-blockers, aspirin, and intravenous nitroglycerin. There was no fever, and the leukocyte count was normal, without evidence of eosinophilia. Coronary angiography 8 days after the onset of chest pain showed occlusion of the LCx at the entrance of the proximal Cypher stent, with TIMI grade 1 flow. In addition, there was progressive stenosis of lesions in the mid LAD and proximal RCA. A careful attempt to cross the LCx stenosis with a floppy guidewire was unsuccessful (Figure 1). Soon thereafter, the patient experienced a sudden profound hypotension immediately followed by cardiorespiratory arrest and pulseless electrical activity; resuscitation attempts were unsuccessful.

An autopsy limited to the heart and brain was performed. A 300-mL hemorrhagic pericardial effusion was present associated with a ruptured acute transmural basal lateral myocardial infarction. The coronary arteries were dissected free from the heart and radiographed (Figure 3, A and B). The 2 sequential Cypher stents were observed in close apposition but without overlap (Figure 3B). The adventitial surface of the LCx artery in the region of the distal stent was hemorrhagic, and the proximal stented segment was dilated. The stented region of the LCx was processed for methylmethacrylate embedding and sectioned at 3-mm intervals for a total of 12 sections. The remainder of the epicardial coronary arteries were sectioned at 3- to 4-mm intervals and embedded in paraffin.

The stented LCx showed an occlusive luminal thrombus, starting at the mouth of the proximal stent and partially obstructing the distal stent (Figure 3, C through F). The wall of the stented artery was aneurysmally dilated with an extensive inflammatory infiltrate involving the intima, media, and adventitia consisting of lymphocytes, plasma cells, macrophages, and eosinophils. The luminal surface of the proximal stent was surrounded by fibrin-rich thrombus with sparse smooth muscle cells, whereas the distal stent showed an extensive inflammatory infiltrate consisting predominantly of lymphocytes and eosinophils and occasional giant cells (Figure 3, G through J). The abluminal surfaces of the proximal and distal stent were focally malapposed, with thick layers of fibrin thrombus separating the stent from the...
underlying plaque and arterial wall (Figure 3, D and F). The proximal stented artery also showed focal giant cell reaction surrounding a few polymer remnants that had become separated from the stent struts (Figure 3K). Although no medial necrosis or neutrophil infiltrates were observed in any of the sections, the inflammatory cells diffusely infiltrated the media, causing medial disruption and destruction.

Immunostains for inflammatory cells in the intima, media, and adventitia revealed dominant T-lymphocyte infiltration (CD45Ro) with scattered B lymphocytes (CD20) and less numerous macrophages (CD68) (Figure 3, M through O). Luna stains showed an extensive eosinophilic infiltration, especially prominent in the distal stent in the adventitia, media, and intima around stent struts (Figure 3, K and L). Stains for bacteria and fungi were negative. Collectively, these pathological changes are consistent with a localized hypersensitivity reaction.

Severe arterial stenoses were found in the nonstented lesions of the LAD and RCA; however, no significant inflammation or eosinophilic infiltrates were present.

**Discussion**

This is the first case of a localized hypersensitivity vasculitis in response to a Cypher coronary stent resulting in an acute myocardial infarction secondary to late in-stent thrombosis at 18 months. The hypersensitivity reaction could be caused by the metallic stent, polymer, or sirolimus. Available pathological evidence, however, supports the hypothesis that hypersensitivity to the polymer is the most likely mechanism.

Hypersensitivity to metals such as molybdenum, nickel, and chromium has been reported in 10% of patients undergoing stenting. To the best of our knowledge, hypersensitivity to bare stainless steel stents has been associated with restenosis and not thrombosis, and a late eosinophil-rich infiltrate has not been reported in human stented arteries. We have examined >400 stainless steel stents placed in human coronary arteries, and of these, ≈150 have been in place for >3 months; to date, none of the latter group show an eosinophilic reaction near the stent. In bare metal stents, inflammation around stent struts typically consists of macrophages and T lymphocytes, with a few B lymphocytes and giant cells. Moreover, the extent of inflammation correlates with the presence of restenosis, whereas in the present case, there was little to no underlying neointima. Remarkably, adventitial eosinophilic infiltrates are found primarily in patients with spontaneous coronary dissection. It is usually an acute phenomenon occurring soon after dissection of the artery; healed spontaneous dissections typically do not show inflammation.

We recently reported pathological findings of late stent thrombosis ≥30 days with bare metal stents. The mechanism of late thrombosis was stenting across a major branch ostium with either single or bifurcating stents, brachytherapy, plaque rupture just proximal or distal to the stent, extensive necrotic core prolapse, and in-stent restenosis with thrombosis. In these cases, there was no evidence of excessive inflammation of the arterial wall or infiltration of eosinophils. Incomplete neointimal healing was present in 12 of 13 cases with late thrombosis. In the present case, the marked hypersensitivity reaction clearly prevented arterial healing and was probably not exaggerated during the interval after the onset of chest pain and death, because this is not observed in the arterial wall in fatal cases of plaque rupture.

The hypersensitivity in the present patient was unlikely to have been caused by sirolimus, because pharmacokinetic studies performed in dogs and rabbits show that the drug is undetectable in the arterial wall by 60 days. Despite widespread use of oral sirolimus for transplant rejection (kidney and heart), we know of only 1 case report of leukoclastic vasculitis to sirolimus. Conversely, sirolimus has been shown to suppress eosinophilic infiltration in an animal model of bronchial hypersensitivity. Adverse side effects to sirolimus are limited primarily to bone marrow suppression and hypercholesterolemia and hypertriglyceridemia. Other reported side effects include hypokalemia, hyperglycemia, diarrhea, and abnormal liver function.

Polymers like those in latex and vinyl gloves, methylmethacrylate in dentistry, and polyurethane, among others, have been shown to produce hypersensitivity reactions in some individuals. However, many nonbioerodable polymers [polyurethane, poly(dimethyl)siloxane (silicone), and polyethylene terephthalate (Dacron)] are known to promote inflammation when implanted in swine coronary arteries. Most inflammatory reactions to polymers involve macrophages and multinucleated giant cells and lymphocytes without eosinophils. In studies unrelated to stents, poly-n-butyl methacrylate, a component of bone cement and the same polymer coating as used in Cypher stents, when implanted subcutaneously promotes a macrophage and giant cell reaction accompanied by tissue damage and fibrosis. Polymers like those in latex and vinyl gloves, methylmethacrylate in dentistry, and polyurethane, among others, have been shown to produce hypersensitivity reactions in some individuals. However, many nonbioerodable polymers [polyurethane, poly(dimethyl)siloxane (silicone), and polyethylene terephthalate (Dacron)] are known to promote inflammation when implanted in swine coronary arteries. Most inflammatory reactions to polymers involve macrophages and multinucleated giant cells and lymphocytes without eosinophils. In studies unrelated to stents, poly-n-butyl methacrylate, a component of bone cement and the same polymer coating as used in Cypher stents, when implanted subcutaneously promotes a macrophage and giant cell reaction accompanied by tissue damage and fibrosis. In addition, the polyethylene–vinyl acetate component of the Cypher copolymer, when used as an antigen-delivery matrix, has been shown to elicit inflammation in 25% of rabbits.

Although there are no reports of excessive inflammation with Cypher stents in animals, our laboratory has observed inflammatory reactions in the arterial walls of pig coronary arteries with 28- and 90-day stainless steel and DESs (including Cypher, R.V., unpublished data, October 2003). Granulomas occur in 10% to 20% of implanted porcine coronary stents and involve either a few or multiple stent struts. Inflammatory infiltrates typically consist of lymphocytes, macrophages, giant cells, neutrophils, and eosinophils. In stainless steel stents, inflammation is usually much less pronounced at 90 days than at 28 days, whereas the reciprocal effect is found in DESs with nonerodable polymers. In DESs, there are often greater numbers of eosinophils, localized primarily to stent struts, which may extend into the lumen and adjoining media and adventitia. The inflammation is usually accompanied by excessive neointimal thickening, and thrombosis is infrequent.

The hypersensitivity to the Cypher stents was most likely present at 8 months after deployment, because significant vessel enlargement and persistent positive remodeling was found by IVUS. Furthermore, there was progressive enlargement of the artery, with aneurysm formation between 8 and 18 months. The significant malapposition noted in both proximal and distal stents probably occurred in the last 10 months of life; only focal late malapposition was observed at 8 months. In the RAVEL trial, late stent malapposition was
found in 21% of Cypher stent implants, compared with 4% in control BX Velocity stents; 1 patient with a Cypher stent developed an aneurysm. Lower rates of malapposition were reported in the SIRIUS trial (9% in Cypher versus 0% in bare metal stents) without any clinical events present at 18 months. A regional increase in external elastic membrane remodeling may represent the main cause of late stent malapposition. Although the precise mechanism(s) of late stent malapposition and thrombosis in our case are unknown, inflammatory destruction of the medial wall may have caused further dilatation accompanied by the accumulation of fibrin between stent struts and native plaque, suggesting a relationship between malapposition, inflammation, and thrombosis.

In October of 2003, a US Food and Drug Administration Public Health Web alert notified physicians of possible generalized hypersensitivity reactions in 50 patients receiving Cypher stents. The symptoms included pain, rash, respiratory alterations, hives, itching, fever, and blood pressure changes. None of these findings were documented in our patient at the time of death, and the hypersensitivity reaction was localized to the stented arterial segment at 18 months, when the drug is completely eluted off the stent. In this case, the polymer may serve as an antigenic stimulus resulting in a T-lymphocyte and/or foreign body response accompanied by eosinophils. Activated T lymphocytes, specifically CD4 helper cells, may secrete interleukins 4 and 13, causing an allergic response with eosinophil infiltration.

There is a likely spectrum of allergic responses to DESs in sensitive patients, varying from benign reactions to excessive inflammation with medial destruction, stent malapposition, and aneurysm formation with late in-stent thrombosis. The enhanced surveillance of patients with DES for late complications along with the development of tests to prescreen individuals with potential reactions to polymers may help avoid some of the late-term complications with DES. Continued efforts to improve polymer biocompatibility are warranted.

References

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