Coronary Artery Aneurysms After Drug-Eluting Stent Implantation

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Drug-eluting stents (DES), which locally elute antiproliferative drugs, can dramatically inhibit neointimal growth. However, several pathological studies have indicated that DES may delay healing after vascular injury, and DES implantation may be theoretically associated with a risk of coronary artery aneurysm formation. Coronary aneurysms have been reported from 3 days to up to 4 years after DES implantation procedures, with varying clinical presentations. The incidence of coronary artery aneurysms after DES implantation is low within the first 9 months, with a reported incidence of 0.2% to 2.3%, a rate similar to that reported after bare-metal stent (BMS) implantation (0.3% to 3.9%) in the DES versus BMS randomized trials. However, the true incidence of coronary aneurysms in an unselected patient population is still largely unknown. This article reviews the published literature on coronary artery aneurysms specifically relating to DES. (J Am Coll Cardiol Intv 2008;1:14–21) © 2008 by the American College of Cardiology Foundation

Diagnosis of Coronary Artery Aneurysms After Stent Implantation

Coronary artery aneurysms after coronary intervention are rare, with a reported incidence of 0.3% to 6.0%, and most “aneurysms” are in fact pseudoaneurysms rather than true aneurysms (1–4). Residual dissection and deep arterial wall injury (rupture or resection of the vessel media) caused by oversized balloons or stents, high-pressure balloon inflations, atherectomy, and laser angioplasty have all been associated with coronary artery aneurysms after coronary intervention (1–3). Drug-eluting stents (DES), which locally elute antiproliferative drugs, can dramatically inhibit neointimal growth, thereby suppressing restenosis (5,6), but at the same time potentially causing coronary aneurysms due to other mechanisms, such as delayed re-endothelialization, inflammatory changes of the medial wall, and hypersensitivity reactions (7–10). These findings may be due to delayed healing secondary to the antiproliferative action of the eluted drug, cell necrosis and/or apoptosis from the antimetabolite effect of the drug, and hypersensitivity reactions to the drug/polymer mixture on the DES (7–9). Given these findings as well as the described association of coronary artery aneurysm formation with systemic administration of anti-inflammatory agents (glucocorticoids and colchicine) after bare-metal stent (BMS) implantation (11), DES implantation may be associated with a greater risk of aneurysm formation. However, the true incidence, clinical course, and treatment of coronary artery aneurysms after DES implantation remain largely unknown. Therefore, in this review, it is our goal to summarize the current status of coronary artery aneurysms after DES implantation from the published medical literature.
Pathophysiology of Aneurysm Formation After DES Implantation

In addition to the mechanical risk factors for aneurysm formation that are observed with both BMS and DES, there are other potential mechanisms that may be specific to DES. Inflammatory reactions in response to implanted DES have been postulated as 1 such factor. Although inflammatory and allergic reactions to nickel and molybdenum have been reported after BMS implantation (23), the triggers for inflammatory and allergic reactions after DES implantation are more complex because DES consist of 3 components: the antirestenotic drug, the drug carrier vehicle (polymer), and the stent platform. In particular, the polymer carrier has been shown to provoke eosinophilic/heterophilic infiltration and induce a marked inflammatory reaction of the arterial wall (8,24,25). Several histological studies have shown extensive inflammation consisting primarily of eosinophils and lymphocytes with a focal giant cell reaction around the stent struts and surrounding the polymer after DES implantation (8,9). Among these reports, Virmani et al. (8) presented an autopsy case with aneurysmal dilation of the stented arterial segments with a severe localized hypersensitivity reaction consisting predominantly of T lymphocytes and eosinophils through all layers of the vessel wall.

In addition, delayed healing reactions in response to DES, such as incomplete endothelialization over DES struts, have been detected by invasive approaches (angiography and optical coherence tomography) as well as in autopsy studies (9,26–28). Whether the presence of incomplete endothelialization is a precursor of aneurysm formation or just a sign of vessel injury is unknown, but this phenomenon has not been described after BMS implantation. An additional phenomenon that has been observed after DES implantation is late acquired incomplete stent apposition, which is observed in 8% to 10% of patients (29,30). Although it may be a precursor of aneurysm formation, the exact nature of the relationship between these 2 findings remains to be determined. In short, the combination of physical trauma induced by stent implantation and specific biological reactions after DES implantation might together contribute to coronary aneurysm formation after DES implantation.

Incidence of Coronary Artery Aneurysms in BMS Versus DES Randomized Trials

In the pivotal DES versus BMS randomized trials, routine angiographic follow-up was performed in a large subset of patients at 6 to 9 months after the initial procedure (5,6,31–33). In these trials, the definition of coronary artery aneurysms was vessel distension of 20% or more in diameter compared with the reference vessel at follow-up, a stricter definition compared with the definition used in the BMS era (vessel distension of ≥50%). Figure 3 depicts odds ratios and respective 95% confidence intervals for coronary artery aneurysms in association with DES and BMS derived from a fixed-effects meta-analytic model. In this analysis, the incidence of coronary aneurysms was similar overall with DES compared with BMS (1.1% [18 of 1,615] with DES and 0.8% [12 of 1,587] with BMS [odds ratio 1.326, 95% confidence interval 0.571 to 3.078; p = 0.512]).

There are several notable caveats to these crude frequency estimates. First, these data are derived from the pivotal randomized trials of DES versus BMS, which enrolled patients with simple, de novo coronary lesions who met strict entry criteria. In addition, the relative rarity of overall events (reflected in the wide confidence intervals of the summary estimate) makes it difficult to definitively rule out a treatment effect upon aneurysm formation. Additionally, these data are derived from early angiographic follow-up of patients enrolled in these trials and, at this point, it remains unclear whether late aneurysm formation occurs more frequently in 1 treatment group compared with another. For example, a case report of acquired incomplete stent apposition after DES implantation described late aneurysm formation 18 months after the initial procedure (22). Furthermore, it is currently unknown whether DES or BMS...
predispose to different types of aneurysm formation (such as pseudo vs. true aneurysms, and saccular vs. nonsaccular).

**Coronary Artery Aneurysms After DES or BMS Implantation Outside of Randomized Trials**

An estimate of the actual incidence of coronary artery aneurysm formation after BMS or DES implantation outside of randomized trials has been reported in only 2 abstracts. Kachru et al. (34) reported an incidence of 0.2% (4 of 2,408) per DES without routine angiographic follow-up and Rha et al. (35) reported an incidence of 1.7% (5 of 296) per patient at 6-month routine angiographic follow-up. However, the overall incidence of coronary artery aneurysms after DES in the “real world” is unclear due to the limited data.

There have been several case reports of coronary aneurysms occurring after DES or BMS implantation (Tables 1 and 2) (36–70). Similar to the case reports of aneurysm formation after BMS implantation, the clinical course of patients with coronary artery aneurysms after DES implantation is variable. Moreover, these published reports demonstrate that in some cases, aneurysms may naturally resolve (46). Overall, coronary aneurysms were detected from 3 days to up to 4 years after the initial procedure for DES and 6 days to up to 9 years for BMS, and patients had variable clinical presentations.

**Proposed Classification of Coronary Artery Aneurysms**

On the basis of a review of the published literature, 3 different types of aneurysms after DES or BMS implantation have been described. Although there are no data regarding the prognostic import of differing aneurysm types, a system of aneurysm classification may be useful to guide therapies because some coronary aneurysms are fatal without prompt and appropriate treatment (39,71,72), and some coronary aneurysms are not life-threatening events and need only careful observation without treatment (41,45,46,51).

What we have termed a type I aneurysm is a type of aneurysm that demonstrates rapid early growth with pseudoaneurysm formation detected within 4 weeks (36,38,58). This type is typically complicated by clinical pericarditis. Given the rapid time course of aneurysm formation, it is likely that arterial injury related to the procedure is the likely contributor to aneurysm formation in these cases rather than the chronic arterial response to the stent, polymer, and drug. The second kind of aneurysm described in the literature is that with a “subacute to chronic” presentation (type II) and is typically detected incidentally during angiography for recurrent symptoms or as part of protocol mandated follow-up (usually detected ≥6 months after the procedure) (15,40–47,49–55,59,60,62–70). These aneurysms appear to have the most varied clinical presentations; some patients are asymptomatic, but some have complaints of angina. It
seems more likely in this scenario that a chronic arterial response to a metal stent, polymer, and/or drug, may be the basis for aneurysm formation in this subtype.

The final reported subtype in the published literature is mycotic or infectious in etiology (type III) (37,39, 48,56,57,61). Large mycotic aneurysms infected with Staphylococcus aureus after DES or BMS implantation have been reported. In these rare cases, patients typically present with systemic manifestations and fever as the result of bacteremia. Whether the local immunosuppressive effects of eluted drugs from stents tend to increase the incidence of these rare infectious aneurysms is unknown.

Proposed Treatment of Coronary Artery Aneurysms

A single study has reported similar 5-year mortality of patients with chronic native coronary aneurysms compared with patients without coronary aneurysms (73). However, the applicability of these data to intervention-associated aneurysms may not be appropriate. Iatrogenic dissections and deep arterial injury caused by the interventional procedures are the potential foundations of pseudoaneurysms, which may lead to rupture. In addition, turbulent and sluggish flow in the vicinity of the aneurysm that contains a metallic stent might be associated with stent thrombosis or distal embolism (53,74). Nevertheless, given the rarity of overall events as well as the lack of published data on the management of coronary artery aneurysms secondary to stent implantation and the absence of natural history data of untreated coronary aneurysms after stents, treatment strategies remain controversial and somewhat based on case-by-case “best clinical judgment” decisions. What complicates the clinical decision-making process further is the fact that complete resolution of these aneurysms has been observed in

<table>
<thead>
<tr>
<th>Study</th>
<th>DES n/N</th>
<th>BMS n/N</th>
<th>Odds ratio</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRIUS (5)</td>
<td>2/350</td>
<td>4/351</td>
<td>0.499</td>
<td>(0.091, 2.740)</td>
</tr>
<tr>
<td>TAXUS II SR (31)</td>
<td>3/131</td>
<td>1/136</td>
<td>3.164</td>
<td>(0.325, 30.812)</td>
</tr>
<tr>
<td>TAXUS II MR (31)</td>
<td>3/134</td>
<td>3/134</td>
<td>0.326</td>
<td>(0.033, 3.173)</td>
</tr>
<tr>
<td>TAXUS IV (5)</td>
<td>2/262</td>
<td>2/267</td>
<td>0.914</td>
<td>(0.128, 6.533)</td>
</tr>
<tr>
<td>TAXUS V (32)</td>
<td>7/498</td>
<td>1/492</td>
<td>7.000</td>
<td>(0.858, 57.107)</td>
</tr>
<tr>
<td>TAXUS VI (33)</td>
<td>3/209</td>
<td>1/207</td>
<td>3.000</td>
<td>(0.310, 29.079)</td>
</tr>
<tr>
<td>Total</td>
<td>18/1615</td>
<td>12/1597</td>
<td>1.326</td>
<td>(0.571, 3.078)</td>
</tr>
</tbody>
</table>

Test for heterogeneity
X²=6.335 (d.f.=5), P=0.275
Test for over all effect
Z=0.656, P=0.512

Favors DES  Favors BMS

The odds ratios are shown on a logarithmic scale. The size of the square is proportional to the weight of the individual studies, measured as the inverse of the variance in the study by the Mantel-Haenszel procedure. BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; MR = moderate release; SIRIUS = SIRollUS-coated 8x Velocity balloon expandable stent in the treatment of patients with de novo coronary artery lesions; SR = slow release.
some cases without treatment in contrast to the possibility of rupture if the aneurysm is left untreated. We propose that treatment of coronary aneurysms be "individualized" using a combination of aneurysm size, expansion history, pathophysiology, and symptoms to decide when and if to apply therapy alternatives (Fig. 4). It is also important to consider that therapy options for coronary aneurysms are somewhat controversial as well, because there are few data with interventional modalities (stent grafts or coils), and surgery may be problematic depending upon the aneurysm location and the clinical state of the patient. Concerns relating to stent graft treatment of coronary aneurysms include closure of contiguous side branches arising next to the aneurysm site, stent thrombosis, and recurrent restenosis. Placing coronary coils behind stents to thrombose the aneurysm sac can also be challenging and requires considerable expertise.

For pseudoaneurysms detected by IVUS (type I) that are large at presentation (i.e., at least twice the reference vessel diameter) or show significant expansion over time, especially in the presence of symptoms, we propose interventional or surgical treatment. Our threshold for treatment is lower for pseudoaneurysms than for true aneurysms, because of the presumed greater likelihood for rupture. For large true aneurysms (type II), again more than twice as large as the reference vessel diameter,
especially with symptoms, we would also propose interventional or surgical treatment to avoid potential life-threatening complications, regardless of stent type (BMS or DES). We would have a somewhat lower threshold for treating DES aneurysms compared with BMS aneurysms. However, the true clinical course of type II

Table 2. Published Case Reports of Coronary Artery Aneurysm After BMS Implantation

<table>
<thead>
<tr>
<th>Authors (Ref. #)</th>
<th>Age (yrs)</th>
<th>Gender</th>
<th>Clinical Presentation at the Initial Treatment</th>
<th>Type of BMS</th>
<th>Vessel</th>
<th>Timing</th>
<th>Symptom</th>
<th>ISR</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouchart et al. (56)</td>
<td>38</td>
<td>M</td>
<td>ACS</td>
<td>Palmaz-Schatz</td>
<td>LCX</td>
<td>6 days</td>
<td>ACS</td>
<td>–</td>
<td>CABG Aneurysm repair</td>
</tr>
<tr>
<td>Liu et al. (57)</td>
<td>72</td>
<td>M</td>
<td>AMI</td>
<td>NIR</td>
<td>LAD</td>
<td>18 days</td>
<td>AP</td>
<td>–</td>
<td>CABG Aneurysm repair</td>
</tr>
<tr>
<td>Nohara et al. (58)</td>
<td>67</td>
<td>M</td>
<td>OMI</td>
<td>Wiktor</td>
<td>LAD</td>
<td>1 month</td>
<td>No symptom</td>
<td>+</td>
<td>CABG Aneurysm repair</td>
</tr>
<tr>
<td>Cafri et al. (59)</td>
<td>53</td>
<td>F</td>
<td>ACS</td>
<td>GFX</td>
<td>LAD</td>
<td>6 weeks</td>
<td>AP</td>
<td>+</td>
<td>N/A</td>
</tr>
<tr>
<td>Lubell et al. (60)</td>
<td>39</td>
<td>M</td>
<td>AMI</td>
<td>N/A</td>
<td>LAD</td>
<td>2 months</td>
<td>AP</td>
<td>–</td>
<td>N/A</td>
</tr>
<tr>
<td>Leroy et al. (61)</td>
<td>49</td>
<td>M</td>
<td>ACS</td>
<td>Palmaz-Schatz</td>
<td>LAD</td>
<td>10 weeks</td>
<td>CHF</td>
<td>–</td>
<td>CABG Aneurysm repair</td>
</tr>
<tr>
<td>Kishi et al. (62)</td>
<td>42</td>
<td>M</td>
<td>AP</td>
<td>S670</td>
<td>RCA</td>
<td>3 months</td>
<td>No symptom</td>
<td>–</td>
<td>Covered stent</td>
</tr>
<tr>
<td>Kitzis et al. (63)</td>
<td>43</td>
<td>M</td>
<td>AMI</td>
<td>Palmaz-Schatz</td>
<td>LCX</td>
<td>3 months</td>
<td>ACS</td>
<td>+</td>
<td>BMS</td>
</tr>
<tr>
<td>Berkalp et al. (64)</td>
<td>47</td>
<td>F</td>
<td>ACS</td>
<td>NIR</td>
<td>RCA</td>
<td>4 months</td>
<td>No symptom</td>
<td>–</td>
<td>Observation</td>
</tr>
<tr>
<td>Nisanci et al. (65)</td>
<td>36</td>
<td>M</td>
<td>ACS</td>
<td>AVE micro</td>
<td>LAD</td>
<td>6 months</td>
<td>No symptom</td>
<td>–</td>
<td>Observation</td>
</tr>
<tr>
<td>Regar et al. (66)</td>
<td>68</td>
<td>M</td>
<td>AP</td>
<td>Palmaz-Schatz</td>
<td>LAD</td>
<td>6 months</td>
<td>AP</td>
<td>+</td>
<td>CABG</td>
</tr>
<tr>
<td>Voigtlander et al. (67)</td>
<td>49</td>
<td>M</td>
<td>ACS</td>
<td>Palmaz-Schatz</td>
<td>LAD</td>
<td>6 months</td>
<td>No symptom</td>
<td>–</td>
<td>Observation</td>
</tr>
<tr>
<td>Noguchi et al. (68)</td>
<td>60</td>
<td>M</td>
<td>ACS</td>
<td>Palmaz-Schatz</td>
<td>LCX</td>
<td>6 months</td>
<td>No symptom</td>
<td>–</td>
<td>N/A</td>
</tr>
<tr>
<td>Oyama et al. (69)</td>
<td>53</td>
<td>M</td>
<td>Stress-induced ischemia</td>
<td>MultiLink</td>
<td>LAD</td>
<td>6 months</td>
<td>No symptom</td>
<td>–</td>
<td>Covered stent</td>
</tr>
<tr>
<td>Rubartelli et al. (70)</td>
<td>N/A</td>
<td>N/A</td>
<td>ACS</td>
<td>Palmaz-Schatz</td>
<td>LCX</td>
<td>1 yr</td>
<td>N/A</td>
<td>–</td>
<td>Covered stent</td>
</tr>
<tr>
<td>Porto et al. (15)</td>
<td>65</td>
<td>F</td>
<td>AMI</td>
<td>Palmaz-Schatz</td>
<td>RCA</td>
<td>9 yrs</td>
<td>AP</td>
<td>+</td>
<td>BMS</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

Figure 4. Proposed Treatment Algorithm

Proposed algorithm for the treatment of coronary aneurysm after DES implantation. *More than and equal to twice as large as the reference vessel diameter; **Less than twice as large as the reference vessel diameter. CABG — coronary artery bypass grafting; CT — computed tomography; IVUS — intravascular ultrasound; other abbreviations as in Figure 3.
Aneurysms is not well defined. Some of these aneurysms, even large aneurysms, might be naturally resolved. We propose immediate surgical therapy for any confirmed infected aneurysm (type III). In addition, it must be taken into account that meticulous handling techniques (i.e., washing of gloves and hands, wearing a mask, and minimal handling of catheters and guidewires) and sterilization of the operating room may minimize the risk of bacterial contamination that results in infected aneurysms. Finally, long-term antithrombotic drug therapy, such as aspirin and clopidogrel, should be necessary to reduce the risk of stent thrombosis and distal embolism in patients with coronary artery aneurysms. Clearly, there is no consensus regarding the treatment algorithm and our proposal is not based on prospective data, underscoring the need for further study of this relatively infrequent phenomenon.

Conclusions

Coronary artery aneurysms after DES implantation are rare, with an incidence of 0.2% to 2.3% in the DES and BMS pivotal randomized trials. The clinical course of coronary artery aneurysms after DES implantation is variable. Some aneurysms naturally resolve, but some aneurysms can lead to life-threatening complications. Although the best treatment for coronary artery aneurysms after DES is controversial, we propose that a combination of aneurysm size, expansion history, pathophysiology, and symptoms be used to decide on treatment. Expanding pseudoaneurysms, infected aneurysms, and large, chronic (and expanding) aneurysms with symptoms should be treated. Further investigation is necessary to determine the pathophysiology, natural history, and best therapies for DES-associated aneurysms.

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