Several studies have demonstrated effective reduction of intimal hyperplasia within a drug-eluting stent (DES) when compared with a bare metal stent (BMS), thereby resulting in a lower incidence of target lesion revascularization.\(^1\)\(^-\)\(^3\) Restenosis at the stent edges, however, is not appreciably reduced by DES. Thus, to understand stent edge effect in DES, it is important to improve the efficacy of this technology. The concern that stent edge effects alter intimal hyperplasia in the stent but not at the edges has existed for many years, and often is described as the “candy wrapper phenomenon.” This phenomenon was first described in radioactive stents\(^4\)\(^-\)\(^5\) and is due to local inhibition of intimal growth and endothelial healing\(^6\) only within the stent. Many DES trials, therefore, sought to better understand the edge effect using intravascular ultrasound (IVUS) to assess the vessel response post stent implantation.

Many studies have documented DES edge effect in older- and newer-generation DES. One challenge facing IVUS studies that assess DES edge effect is a high degree of patient-to-patient variability, along with potential variability among the different DES types. Because of these variables and the relatively small size of most sequential IVUS studies, there is no general consensus regarding stent edge effect in DES. We therefore reviewed the literature to find common findings and tendency. This review focused on 4 DES types approved by the United States Food and Drug Administration: the Cypher sirolimus-eluting stent (SES) (Cordis), the Taxus paclitaxel-eluting stent (PES) (Boston Scientific), the Endeavor zotarolimus-eluting stent (ZES) (Medtronic CardioVascular Inc.), and the XIENCE V everolimus-eluting stent (EES) (Abbott Vascular).

Mechanical Edge Effect Post Stent Implantation

Edge stenosis can occur from several different mechanisms: a vascular response from peri-stent vascular injury, plaque shift, and thrombus or hematoma formation post stent implantation. Before discussing DES and the impact of adding a drug to a stent platform, it is helpful to fully understand the edge effect from BMS implantation.

In a comprehensive study of BMS,\(^7\) the major changes at the edge were plaque and media (P&M) increase and lumen area decrease observed within the first 1 to 2 mm from the stent edge. The degree of P&M increase within the first 2 mm of the stent edge was correlated with the degree of intimal hyperplasia within the stent. This relationship did not hold true beyond 2 mm of the stent edge. The impact of a BMS on the edge segment progressively decreases at greater distances from the stent edge.\(^7\)\(^-\)\(^9\) These findings are consistent with the results of the BMS arm (as a control group) in several DES studies. Thus, it is generally recognized that lumen loss in close proximity to the stent was mostly caused by P&M increase (or intimal hyperplasia spread beyond the stent edges) in BMS.

Edge Effect of DES

Previous reports written in English were searched comprehensively in PubMed on November 1, 2010. The following terms were used to search: intravascular ultrasound, stent, and coronary. Additionally, the following terms were searched separately: sirolimus, paclitaxel, zotarolimus, and everolimus. A total of 275 articles were identified at first search. Sixty-one articles were excluded because of their nature: review, case report, letter communication, or animal study. Nineteen studies that treated restenosis or saphenous vein graft lesions were excluded. Twenty-eight studies with different platforms, such as self-expandable stents, bioabsorbable stents, biodegradable polymers, different drugs, or oral rapamycin were excluded.

In DES, drug and polymer effects have the potential to further influence the mechanical edge effect from the BMS, and the physical effects from the stent implantation. Most studies define stent “edge” as the peri-stent segments within 5 mm of the stent edge. From the BMS literature we know that edge effects vary depending on the distance from the edge (changes that occur within the first 1 to 2 mm from the stent edge are not synonymous with changes that occur 4 to 5 mm from the stent edge).\(^9\) This review will discuss edge effect using specific millimeter by millimeter assessments from the stent edge if available.
Paclitaxel-Eluting Stents
The TAXUS II trial\textsuperscript{10} studied the vessel response of the slow- and moderate-release formulation of PES compared with BMS. In this trial, there was an increase in vessel area and P&M area for the segments closest to the edge of the PES 6 months after implantation. The luminal area at the distal edge of PES was significantly greater than that of BMS at follow up owing to the occurrence of positive vessel remodeling in volume analysis. Within the PES cohorts, there was greater decrease in lumen area at the proximal compared with the distal edges both in moderate- ($P=0.01$) and slow-release groups ($P=0.03$).

The TAXUS IV, TAXUS V, and TAXUS VI trials\textsuperscript{11,12} were prospective, multicenter, randomized studies that compared the outcomes of PES versus BMS implantation in patients who underwent percutaneous coronary intervention. A prospective IVUS subgroup was prespecified in each trial. The TAXUS IV trial\textsuperscript{11} confirmed and expanded the results from TAXUS II, showing no aggravation of edge stenosis. Nonetheless, there were some differences between the 2 studies. In TAXUS IV there was a decrease in vessel area and lumen area at the distal edge of the PES, with a slight increase in P&M area. The luminal area at the distal edge nearest the PES was greater than that of the BMS at follow up, owing to the occurrence of less negative vascular remodeling in PES as compared with BMS. The integrated analysis of the IVUS subgroups from TAXUS IV, V, and VI trials\textsuperscript{12} provides detailed information of the stent edge effect with a relatively large sample size (PES: $n=287$; BMS: $n=260$). Less lumen reduction due to less negative remodeling was observed at the distal edge of PES compared with that of BMS, despite an almost similar amount of P&M. A comparable change was observed at the proximal edges of both the PES and BMS.

The beneficial effect of the PES was most notable in the area closest to its distal edge.

ASPECT (ASian Paclitaxel-Eluting Stent Clinical Trial)\textsuperscript{13} assessed the effectiveness of a polymer-free PES (high dose and low dose) compared with BMS. Lumen reduction appeared less in the segments immediately adjacent to the edge of the high-dose PES compared with the BMS or the low-dose PES, although formal statistical analysis was not reported.

The DiabeDES (Diabetes and Drug-Eluting Stent) trial\textsuperscript{14} assessed intimal hyperplasia after SES and PES implantation in diabetic patients. Lumen volume decreased at the proximal edge of the PES ($P=0.028$) because of plaque progression ($P=0.006$) during 8 months of follow up. At the PES distal edge there was an insignificant lumen volume decrease ($P=0.092$). A millimeter by millimeter analysis was performed along the length of the edge, which showed that the lumen reduction was due to plaque progression, most notably at the first millimeter immediately proximal and distal to the stent edge.

Vascular responses to PES in ST-segment elevation myocardial infarction were addressed in the IVUS substudy of the prospective, multicenter Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, randomization 3:1 to PES or BMS.\textsuperscript{15} At the proximal edge, lumen reduction (mean change in lumen cross sectional area: $-0.7$ in PES, $-0.6$ in BMS mm$^2$) due to negative remodeling was observed in both PES and BMS (mean change in external elastic membrane cross sectional area: $-0.5$, $-0.8$ mm$^2$). However, at the distal edge, less lumen reduction ($-0.2$ mm$^2$) with no remodeling (0 mm$^2$) was observed in PES, while lumen reduction ($-0.4$ mm$^2$) with negative remodeling ($-0.8$ mm$^2$) was observed in BMS.

Using IVUS, the BETAX (BESide TAXus) Study\textsuperscript{16} aimed to specifically assess the temporal changes occurring at the edges of PES. Lumen area with positive remodeling was observed at both proximal and distal edges. The pattern of vessel response in millimeter by millimeter analysis along the length of the stent edge was different from the other studies in many respects. These differences may be due to selection bias, a relatively small sample size, stent platform, or procedural differences, as suggested by Fitzgerald et al.\textsuperscript{17}

In summary, the consecutive serial IVUS studies from the TAXUS trials demonstrated no negative edge effects due to the paclitaxel in a PES compared with BMS. Release speed of paclitaxel does not seem to be related to the edge effect, but higher-dose paclitaxel seems to have an advantageous effect on the distal lumen. The beneficial effect of less lumen reduction with less negative vessel remodeling was observed at the PES distal edge when compared with BMS. However, it should be noted that despite the benefits of paclitaxel over a BMS for preservation of the distal lumen, the majority of studies indicated that lumen area at both the PES proximal and distal edges still demonstrated some decrease during the follow up period.

Sirolimus-Eluting Stents
The first-in-man registry\textsuperscript{18} of SES performed a serial volumetric IVUS analysis of the stent edges and compared the efficacy of SES for de novo coronary artery lesions ($n=43$) versus in-stent restenosis ($n=37$). In de novo lesions, lumen reduction due to both negative remodeling and P&M increase was found at the proximal stent edge, while lumen enlargement due to positive remodeling was found at the distal stent edge.

In the IVUS substudy of E-SIRIUS (European, multicenter, randomized, double blind trial of the sirolimus-coated Bx-Velocity stent in the treatment of patients with de novo coronary artery lesions),\textsuperscript{19} lumen reduction was observed at the proximal edge both in SES and BMS, while significantly less lumen reduction was observed at the distal edge of SES compared with BMS ($P=0.006$).

Degertekin et al\textsuperscript{20} addressed coronary remodeling after SES implantation compared with BMS. In this study, the lumen loss at the proximal edge was similar between SES and BMS, $-3.6\%$ versus $-2.8\%$ ($P=NS$). However, the mechanism for lumen loss at the proximal edge was different in the SES versus BMS. Plaque increase was observed in the SES at the proximal edge but not in the BMS (11.8\% versus $-4.5\%$, $P=0.054$), and vessel remodeling was positive in the SES and negative in the BMS (1.7\% versus $-6.4\%$, $P=0.057$). At the distal edge, tendency toward enlargement due to positive
Table 1. Edge Effect of Paclitaxel-Eluting Stents

<table>
<thead>
<tr>
<th>Study Name</th>
<th>First Author</th>
<th>Patients, n</th>
<th>Follow Up, m</th>
<th>Proximal Edge Up to 5 mm</th>
<th>Distal Edge Up to 5 mm</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EEM, mm</td>
<td>P&amp;M, mm</td>
<td>Lumen, mm</td>
</tr>
<tr>
<td>TAXUS II*</td>
<td>Serruys</td>
<td>Moderate-release 107</td>
<td>6</td>
<td>1–2, 3–5</td>
<td>1–5</td>
<td>1–5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slow-release 106</td>
<td></td>
<td>↑↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>TAXUS IV†</td>
<td>Weissman</td>
<td>88</td>
<td>9</td>
<td>1–4, 5</td>
<td>1–5</td>
<td>1–5</td>
</tr>
<tr>
<td>TAXUS IV, V, VI‡</td>
<td>Weissman</td>
<td>287</td>
<td>9</td>
<td>1–5</td>
<td>1–5</td>
<td>1–5</td>
</tr>
<tr>
<td>ASPECT§</td>
<td>Hong</td>
<td>Low dose 28</td>
<td>6</td>
<td>1–5</td>
<td>1–2, 3–5</td>
<td>1–5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High dose 28</td>
<td></td>
<td>↑↓</td>
<td>↑↓</td>
<td>↑</td>
</tr>
<tr>
<td>DiabeDES</td>
<td>Jensen</td>
<td>34</td>
<td>8</td>
<td>1–2, 3–5</td>
<td>1–5</td>
<td>1–5</td>
</tr>
<tr>
<td>HORIZON – AMI**</td>
<td>Maehara</td>
<td>163</td>
<td>13</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>BETAX††</td>
<td>Garcia-Garcia</td>
<td>24</td>
<td>6</td>
<td>1–5</td>
<td>1–4, 5</td>
<td>1, 2–5</td>
</tr>
<tr>
<td>Endeavor IV†‡</td>
<td>Waseda</td>
<td>98</td>
<td>8</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>

Arrows indicate an increase or decrease from baseline to follow-up. EEM indicates external elastic membrane; P&M, plaque and media.

*Data from Serruys PW, et al.\textsuperscript{10}  
†Data from Weissman NJ, et al.\textsuperscript{11}  
‡Data from Weissman NJ, et al.\textsuperscript{12}  
§Data from Hong MK, et al.\textsuperscript{13}  
‖Data from Jensen LO, et al.\textsuperscript{14}  
***Data from Maehara A, et al.\textsuperscript{15}  
††Data from Garcia-Garcia HM, et al.\textsuperscript{16}  
‡‡Data from Waseda K, et al.\textsuperscript{26}
remodeling was observed in the lumen of SES, while lumen loss was detected in the BMS (1.5% versus -8.0%, \(P = NS\)).

In serial IVUS assessments from the DiabeDES trial\(^{14}\), there were no significant changes in vessel, lumen, or plaque volumes at the proximal edge of SES, while significant lumen enlargement (\(P = 0.037\)) was observed at distal edge at follow up. In a much smaller study, Asano et al\(^{21}\) evaluated the edge effect of SES in only 33 lesions and found lumen decreases with significant P&M increases (\(P < 0.01\)) without significant vessel remodeling (\(P = 0.9\)).

Some SES trials have specific patient populations. Diabetic patients were studied with serial IVUS in the DIABETES (Diabetes and Sirolimus-Eluting Stent) trial\(^{22}\), and their out-patients were studied with serial IVUS in the DIABETES** Jiménez-Quevedo\(^{22}\) trial. Across most studies, lumen enlargement (or the lack of lumen reduction as compared with BMS) occurred in the distal edge of SES because of positive remodeling. In general, there was lumen reduction at proximal edge of the stent (in both BMS and SES) in most of these studies.

### Zotarolimus-Eluting Stents

The analysis is limited to the zotarolimus-eluting Endeavor stent. The Resolute platform was not included.

The ENDEAVOR III trial\(^{24}\) compared the efficacy and safety of ZES and SES (Table 2). There was no difference at baseline and at follow up, and between the groups at stent edge segments. At the proximal stent edge of ZES, there was an increase in lumen volume with plaque reduction, while lumen volume did not change at the distal stent edge. There was no statistical difference in vessel response of stent edge segments between ZES and SES.

Serial IVUS data along each millimeter of the stent edge is available in a subset of the Endeavor II trial\(^{25}\), which compared the efficacy and safety of ZES with BMS. In volumetric analysis of the stent edge during follow up, significant lumen reduction (proximal \(P < 0.0001\), distal \(P = 0.01\)) due to negative remodeling (proximal \(P < 0.0001\), distal \(P = 0.01\)) was observed at the edges of ZES, similar to BMS (Table 3). After examination of the changes that occurred along the length of the stent edge, the area closest to the proximal edge had less negative remodeling and less plaque, while the area closest to the distal edge had less plaque increase.

The ENDEAVOR IV trial\(^{26}\) compared the efficacy and safety between ZES and PES for the treatment of de novo coronary artery lesions. A significant decrease in lumen volume with negative remodeling and plaque increase was observed at

### Table 2. Edge Effect of Sirolimus-Eluting Stents

<table>
<thead>
<tr>
<th>Study Name</th>
<th>First Author</th>
<th>Patients, n</th>
<th>Follow Up, m</th>
<th>Proximal Edge Up to 5 mm</th>
<th>Distal Edge Up to 5 mm</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIM registry*</td>
<td>Degertekin</td>
<td>43</td>
<td>4 or 6</td>
<td>(\uparrow) (\uparrow) (\downarrow)</td>
<td>(\uparrow) (\uparrow) (\uparrow)</td>
<td>Volume</td>
</tr>
<tr>
<td>E-SIRIUS†</td>
<td>Hoffmann</td>
<td>31</td>
<td>8</td>
<td>(\uparrow) (\uparrow) (\downarrow)</td>
<td>(\uparrow) (\uparrow) (\downarrow)</td>
<td>Volume</td>
</tr>
<tr>
<td>N/‖</td>
<td>Degertekin</td>
<td>24</td>
<td>5.5</td>
<td>(\uparrow) (\uparrow) (\downarrow)</td>
<td>(\uparrow) (\uparrow) (\downarrow)</td>
<td>Volume</td>
</tr>
<tr>
<td>DiabeDES§</td>
<td>Jensen</td>
<td>40</td>
<td>8</td>
<td>(\uparrow) (\uparrow) (\downarrow) (\downarrow) (\uparrow) (\downarrow)</td>
<td>(\uparrow) (\downarrow) (\downarrow) (\uparrow) (\downarrow) (\uparrow)</td>
<td>mm by mm</td>
</tr>
<tr>
<td>N/‖</td>
<td>Asano</td>
<td>33</td>
<td>9</td>
<td>(\uparrow) (\uparrow) (\downarrow) (\downarrow) (\uparrow) (\downarrow)</td>
<td>(\uparrow) (\downarrow) (\downarrow) (\uparrow) (\downarrow) (\uparrow)</td>
<td>mm by mm</td>
</tr>
<tr>
<td>DIABETES**</td>
<td>Jiménez-Quevedo</td>
<td>75</td>
<td>9</td>
<td>(\uparrow) (\uparrow) (\downarrow) (\downarrow) (\uparrow) (\downarrow)</td>
<td>(\uparrow) (\uparrow) (\downarrow) (\downarrow) (\uparrow) (\downarrow)</td>
<td>Volume</td>
</tr>
<tr>
<td>Mission††</td>
<td>Atary</td>
<td>20</td>
<td>9</td>
<td>(\downarrow) (\downarrow) (\uparrow) (\uparrow) (\downarrow) (\uparrow)</td>
<td>(\uparrow) (\uparrow) (\uparrow) (\uparrow) (\downarrow) (\uparrow)</td>
<td>Volume 5–10 mm</td>
</tr>
<tr>
<td>Endeavor III‡‡</td>
<td>Miyazawa</td>
<td>42</td>
<td>8</td>
<td>(\rightarrow) (\uparrow) (\downarrow) (\uparrow) (\downarrow) (\uparrow)</td>
<td>(\uparrow) (\uparrow) (\uparrow) (\uparrow) (\downarrow) (\uparrow)</td>
<td>Volume</td>
</tr>
</tbody>
</table>

Arrows indicate an increase or decrease from baseline to follow-up.

EEM indicates external elastic membrane; P&M, plaque and media.

*Data from Degertekin M, et al.\(^{18}\)
†Data from Hoffmann R, et al.\(^{19}\)
‡Data from Degertekin M, et al.\(^{20}\)
§Data from Jensen LO, et al.\(^{14}\)
‖Data from Asano T, et al.\(^{21}\)
**Data from Jiménez-Quevedo P, et al.\(^{22}\)
††Data from Atary JZ, et al.\(^{23}\)
‡‡Data from Miyazawa A, et al.\(^{24}\)
both proximal and distal edges of ZES during the follow up (Table 3). There was no statistical difference in vessel response of stent edge segments between ZES and PES.

Although the data are limited, no negative edge effects of ZES were detected compared with BMS or other DES. Consecutive ENDEAVOR trials overall demonstrated that lumen area decreased at both proximal and distal edges of the ZES because of negative remodeling or plaque increase.

**Everolimus-Eluting Stents**

One registry study provides some IVUS data of EES edge effect. Shimohama et al.27 addressed the vascular response after EES implantation in the SPIRIT III Japan Registry (JAPAN) compared with EES implantation in the SPIRIT III United States trial. Enlargement of lumen volume and vessel volume were observed at the distal stent edge, while lumen reduction with negative remodeling was detected at the proximal edge (Table 4). Because information regarding EES stent edges is limited, the tendency of response on the stent edge is still unclear.

**Lessons Learned**

The summary above demonstrates the disparate data across DES studies on edge effect. Despite differences in methodology or definitions, when reviewing all of the studies, some patterns emerge.

1. First and foremost, all DES studies reviewed demonstrated no negative edge effects in any DES when compared with the edge effect of a BMS.

2. Secondly, most of studies show that the edge effect is different at the proximal edge as compared with the distal edge of the DES. This finding is unique to DES and was not found in BMS studies (nor in the BMS control arm of these DES studies). A beneficial distal stent edge effect on the lumen from DES, as compared with the BMS, is particularly notable in the first few millimeters distal to the DES.

3. The mechanism of the beneficial distal edge effect is not consistent across studies but appears to be a combination of reduced plaque growth and positive remodeling, suggesting drug effects downstream to the DES. This finding also could explain the relatively higher restenosis rates at the proximal edge of DES detected in previous trials.2,28,29

Does the type of DES influence the pattern of stent edge effect? Reviewing the studies by DES type, there appears to be different rates of “efficacy” on the distal stent edge lumen, with different drugs used in the DES (Tables 1–4). Enlargement of the distal lumen with positive remodeling was observed in many of the larger SES trials, while lumen reduction with negative remodeling was detected in PES in the majority of large trials. PES attenuate the degree of lumen reduction and remodeling, as compared to BMS, but do not eliminate it entirely. Although the detailed data with millimeter by millimeter IVUS analysis along the length of the edge is limited, the beneficial effects appear stronger closer to the edge, particularly with SES. Zotarolimus, despite being a sirolimus analogous drug, did not have the beneficial findings at the distal edge in consecutive Endeavor trials.24–26 Everolimus is also a sirolimus analogous drug and has very limited IVUS data on the stent edges; while very preliminary data in a registry suggests a similar beneficial distal edge effect, further studies are needed to confirm this finding.

Because the follow up period in most of studies was ≤9 months, edge effect of DES >1 year is unknown. In 1 study, it was reported that no significant change in lumen or vessel volume was observed in either proximal or distal edges of SES from 6 months to 20 months.30

This review indicates the beneficial effect of the drug on a DES, especially in the distal edge, and suggests the effect differs among DES type. IVUS assessment of stent edge

**Table 3. Edge Effect of Zotarolimus-Eluting Stents**

<table>
<thead>
<tr>
<th>Study Name</th>
<th>First Author</th>
<th>Patients, n</th>
<th>Follow Up, m</th>
<th>Proximal Edge Up to 5 mm</th>
<th>Distal Edge Up to 5 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EEM, mm</td>
<td>P&amp;M, mm</td>
</tr>
<tr>
<td>Endeavor II*</td>
<td>Sakurai</td>
<td>178</td>
<td>8</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Endeavor III†</td>
<td>Miyazawa</td>
<td>122</td>
<td>8</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Endeavor IV‡</td>
<td>Waseda</td>
<td>100</td>
<td>8</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

Arrows indicate an increase or decrease from baseline to follow-up. EEM indicates external elastic membrane; P&M, plaque and media.

*Data from Sakurai R, et al.25
†Miyazawa A, et al.24
‡Waseda K, et al.26

**Table 4. Edge Effect of Everolimus-Eluting Stents**

<table>
<thead>
<tr>
<th>Study Name</th>
<th>First Author</th>
<th>Patients, n</th>
<th>Follow Up, m</th>
<th>Proximal Edge Up to 5 mm</th>
<th>Distal Edge Up to 5 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EEM</td>
<td>P&amp;M</td>
</tr>
<tr>
<td>SPIRIT III*</td>
<td>Shimohama</td>
<td>Japan 70</td>
<td>8</td>
<td>↓</td>
<td>→</td>
</tr>
<tr>
<td></td>
<td></td>
<td>USA 71</td>
<td></td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

Arrows indicate an increase or decrease from baseline to follow-up. EEM indicates external elastic membrane; P&M, plaque and media.

*Data from Shimohama T, et al.27
should be continued in next generation DES to extend our knowledge about the distal benefit of DES.

Disclosures

None.

References


Key Words: drug-eluting stent □ edge effect □ intravascular ultrasound
Edge Effect From Drug-Eluting Stents as Assessed With Serial Intravascular Ultrasound: A Systematic Review
Kohei Wakabayashi, Ron Waksman and Neil J. Weissman

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