Randomized trials and registries have clearly demonstrated that drug-eluting stents (DES) are effective in reducing restenosis. After their introduction and an initial period of unbridled enthusiasm, it was recognized that there was a significant increase in very late stent thrombosis (VLST) compared with bare metal stents, and this late complication has been the subject of continued concern and intensive investigation. Very late ST is fortunately infrequent, but it is associated with very high rates of death and myocardial infarction. Understanding the frequency, duration, and potential mechanisms of VLSLT has been hampered by the lack of large studies where low-frequency events can be more accurately determined and evaluated. Randomized trials, typically evaluating low-risk patients, have shown a low rate of VLST averaging 0.2%/y, but rates in registries with off-label use are higher, averaging 0.6%/y. Some studies have suggested a plateau after 5 years whereas others have not. Because of the selective nature of these trials, the incidence and time course in an unrestricted population is unclear.

**Table. Incidence of VLST With First-Generation DES in Large Registries With 3- to 5-Year Follow-Up**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patients, n</th>
<th>Stent</th>
<th>FU, y</th>
<th>VLST, %/y</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESTROFA*</td>
<td>2008</td>
<td>23,500</td>
<td>SES/PES</td>
<td>3</td>
<td>0.27</td>
</tr>
<tr>
<td>SCAAR</td>
<td>2009</td>
<td>42,150</td>
<td>SES/PES</td>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td>DESIRE-LATE15</td>
<td>2010</td>
<td>10,100</td>
<td>SES/PES</td>
<td>5</td>
<td>0.22</td>
</tr>
<tr>
<td>Jensen*</td>
<td>2010</td>
<td>12,374</td>
<td>SES/PES</td>
<td>3</td>
<td>0.21</td>
</tr>
<tr>
<td>Simsek10</td>
<td>2010</td>
<td>14,444</td>
<td>SES/PES</td>
<td>4</td>
<td>0.2</td>
</tr>
<tr>
<td>BERN/Rotterdam3</td>
<td>2011</td>
<td>8,146</td>
<td>SES/PES</td>
<td>4</td>
<td>0.53</td>
</tr>
<tr>
<td>EVASTENT11</td>
<td>2011</td>
<td>1,564</td>
<td>SES</td>
<td>4</td>
<td>0.18</td>
</tr>
<tr>
<td>Kimura* (current study)</td>
<td>2011</td>
<td>12,812</td>
<td>SES</td>
<td>5</td>
<td>0.26</td>
</tr>
</tbody>
</table>

*SES indicates sirolimus-eluting stent; PES, paclitaxel-eluting stent; FU, follow-up; VLST, very late stent thrombosis; ESTROFA, Estudio Español Sobre Trombosis de Stents Farmacoeutivos; SCAAR, Swedish Coronary Angiography and Angioplasty Registry; DESIRE-LATE, Drug-Eluting Stents in the Real World-LATE; and EVASTENT, Evaluation coût/efficacité du stent actif au sirolimus chez les patients diabétiques et non diabétiques.

In this issue of Circulation, Kimura and colleagues report on the outcome of 12,812 patients receiving the first generation sirolimus-eluting stent. In this large unrestricted registry from Japan, the cumulative incidence of definite ST was low (0.3% early, 0.6% late, and 1.6% at 5 years). Most disturbing, however, was the observation of the continued steady rate of VLST of 0.26%/y without any evidence of a plateau up to 5 years. The rate of VLST is consistent with other large registries with long follow-up (the Table) and is compatible with smaller Drug-Eluting Stents in the Real World-LATE (DESIRE-LATE) study, the only other registry to have 5-year data. The continued low but persistent rate of VLST is concerning and suggests that this may be a problem that continues for a very long period of time, perhaps indefinitely, after stenting.

The study by Kimura confirms that target-lesion revascularization (TLR), primarily a problem in the first year, also continues at a low but steady rate after the first year, with a 5-year cumulative incidence of TLR of 15.9% or 2.2%/y. Compared with prior randomized trials, the TLR rate is higher, likely reflecting the higher-risk patient profile and more complex coronary disease in this registry. The current trial also confirms that, over 5 years, nontarget revascularization is more common than TLR (31.2% [3.8%/y]), an observation made by others as well.

The advantage of looking at both ST and TLR is that they represent the stent-related complications rather than progression of disease in the nonstented segments. In addition, the distinction between VLST and TLR is difficult because both can present with a myocardial infarction or with only angina, a factor that can confound the estimation of the incidence of these events. In this study, stent-related complications (ST and TLR) occurred in 17.5% whereas any major adverse cardiovascular event occurred in 49% of patients (death in 14.4%, myocardial infarction in 3.8%, stroke in 5.9%, and any coronary revascularization in 38.6%), reflecting the progressive nature of chronic coronary artery disease. Stent thrombosis was the cause of the myocardial infarction in 37%. In those with very late ST, 91% presented with a myocardial infarction with a mortality of 6.9%, attesting to the serious consequences of this adverse event. This is not a rosy picture given that one half of the patients had an adverse event in the first 5 years, and stent related events accounted for one third of these.

The study has its weaknesses, however. It was a voluntary industry-sponsored registry with events determined by chart
review and patient recall, likely leading to underreporting of events. The follow-up rate at 5 years was only 77%. Only patients with a sirolimus-eluting stent and not other types of DES were enrolled, and selection bias at each site could have impacted the results. The relevance of the study can also be questioned because the sirolimus-eluting stent, a first-generation stent, is no longer available and recent studies have shown that the rates of ST and TLR are lower with the second-generation drug-eluting stents such as the everolimus-eluting stents.23

The current study suggests that the pathophysiology of VLST may not be the same as early and late ST because the predictors for VLST are quite different from those for early and late ST. The large Spanish Estudio Espanol Sobre Trombosis de Stents Farmacoactivos 1 (ESTROFA-1) registry demonstrated that the predictors for early and late ST were different, but it did not separately analyze very late ST.24 In the Japanese Registry of Stent Thrombosis for Review and Reevaluation (RESTART), the VLST group had significantly different baseline demographic features from those of late ST, also supporting a different pathophysiology.15

The exact mechanisms for VLST, however, remain elusive. Evidence from angiography, intravascular ultrasound, and optical coherence tomography studies suggests that delayed healing and late-acquired stent malapposition are frequent in LST and very late ST.16,17 Cook showed that 8 of 11 stents with VLST had malapposition, and the clot aspirated from these patients showed a high percentage of eosinophils.18 These findings are consistent with pathological studies and support the contention that a late inflammatory process is responsible.19 The culprit for this reaction has been felt to be the polymer coating on the stent because the drugs have been eluted far earlier, making it hard to incriminate them in the process.

Emerging information suggests that in some patients with very late ST and perhaps most patients with very late restenosis, neoatherosclerosis is the cause for these events. Yokoyama showed by serial angiography that the neointima turned from white to yellow over 4 years with bare metal stents, suggesting conversion of the neointima to atherosclerosis.20 A similar angiographic change has been shown with sirolimus-eluting stents where thrombus was also seen in conjunction with the yellow atherosclerotic plaque within the stent.21 In a study of 50 DES in-stent restenotic lesions with a mean follow-up of 32.2 months, Kang showed by intravascular ultrasound and optical coherence tomography that 52% had an in-stent thin-capped fibroatheroma, and 58% had at least 1 neointimal rupture.22 The longer the follow-up, the greater was the incidence of a thin-capped fibroatheroma. Pathological series have confirmed this conversion with DES as well as with bare metal stents, but the average time for this conversion was sooner for DES (1.5 versus 6 years).23

Recently, Yamaji showed that aspiration of the thrombus in 42 patients with very late ST after bare-metal-stent thrombosis showed fragments of atherosclerotic plaques and suggested that disruption of in-stent neoatherosclerosis could play a role in VLST.24 These observations suggest that neoatherosclerosis may be responsible for VLST in some patients. How often neoatherosclerosis occurs and how often it leads to plaque rupture and thrombosis versus restenosis is not known, and further serial studies are needed. It is interesting to speculate that perhaps inflammation and stent malapposition diminish over time but neoatherosclerosis increases with time.

A key unanswered question is whether either VLST or TLR can be prevented. In the current study, the only multivariable predictors of VLST were current smoking and total stent length. Whether continued dual antiplatelet therapy can prevent VLST cannot be answered by this study, but it is interesting that whereas 50% remained on dual antiplatelet therapy it was not a predictor of VLST. Theoretically, dual antiplatelet therapy should decrease both ST and plaque rupture with thrombosis. We will need to await the results of large ongoing randomized trials to help answer this important question. The use of second-generation stents and other newer stents including those without polymers and biodegradable stents may be helpful.14,25 Aggressive medical therapy should help attenuate the development of in-stent neoatherosclerosis, but this remains to be demonstrated.

This report also highlights the importance of prospective observational cohort studies in augmenting our knowledge about new therapies. The long-term outcomes of DES in large registries have made it apparent that the stented segment continues to be at risk for thrombosis and neoatherosclerosis for many years after implantation. The observation that VLST and TLR continue at a steady rate up to 5 years is sobering and suggests that there may be no end in sight for these serious events. The hope is that, through a better understanding of the processes responsible, targeted therapy can improve the long-term durability and safety of DES.

Disclosures

None.

References


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Very Late Stent Thrombosis and Late Target Lesion Revascularization: No End in Sight

David P. Faxon

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