Very Late Stent Thrombosis and Late Target Lesion Revascularization:

No End in Sight

Running title: Faxon; Very late ST and TLR

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Randomized trials and registries have clearly demonstrated that drug-eluting stents (DES) are effective in reducing restenosis.\textsuperscript{1, 2} Following their introduction and an initial period of unbridled enthusiasm, it was recognized that there was a significant increase in very late stent thrombosis (VLST) when compared to bare metal stents (BMS) 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 VSLT have 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\%/year but rates in registries with off label use are higher, averaging 0.6\%/year\textsuperscript{2, 3} Some studies have suggested a plateau after 3 years while others have not.\textsuperscript{4} Due to the selective nature of these trials, the incidence and time course in an unrestricted population is unclear.

In this issue of \textit{Circulation}, Kimura and colleagues report on the outcome of 12,812 patients receiving the first generation sirolimus-eluting stent (SES). 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).\textsuperscript{5} Most disturbing, however, was the observation of the continued steady rate of VLST of 0.26\%/year without any evidence of a plateau up to 5 years. The rate of VLST is consistent with other large registries with long follow-up (Table 1) and is compatible with the smaller DESIRE-LATE study, the only other registry to have 5-year data.\textsuperscript{3, 6-11} 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, and perhaps indefinitely, following 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%/year. Compared to 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, non-target revascularization is more common than TLR (31.2% (3.8%/year)) an observation made by others as well. 4,12,13

The advantage of looking at both ST and TLR is that they represent the stent-related complications and not progression of disease in the non-stented segments. In addition the distinction between VLST and TLR is difficult since 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% while any MACE 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 MI in 37%. In those with very late ST, 91% presented with an MI with a mortality of 6.9%, attesting to the serious consequences of this adverse event. This is not a rosy picture as one half of the patients had an adverse event in the first five years and stent related events accounted for 1/3 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 an SES and not other DES were enrolled and selection bias at each site could have impacted the results. The relevance of the
study can also be questioned as SES, 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. 

The current study suggests that the patho-physiology of VLST may not be the same as early and late ST as the predictors for VLST are quite different from those for early and late stent thrombosis. The large Spanish ESTROFA-1 registry demonstrated that the predictors for early and late ST were different but it did not separately analyze very late ST. In the Japanese RESTART registry, the VLST group had significantly different baseline demographic features from those the late ST also supporting a different pathophysiology.

The exact mechanisms for VLST however remain elusive. Evidence from angioscopy, IVUS and OCT studies suggest that delayed healing and late acquired stent mal-apposition are frequent in LST and very late ST. Cook showed that 8/11 stents with VLST had mal-apposition and the clot aspirated from these patients showed a high percentage of eosinophils. These findings are consistent with pathological studies and support the contention that a late inflammatory process is responsible. The culprit for this reaction has been felt to be the polymer coating on the stent since 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, neo-atherosclerosis is the cause for these events. Yokoyma showed that by serial angioscopy, that the neointima turned from white to yellow over 4 years with bare
metal stents suggesting conversion of the neointima to atherosclerosis.\textsuperscript{20} A similar angioscopic change has been shown with SES where thrombus was also seen in conjunction with the yellow atherosclerotic plaque within the stent.\textsuperscript{21} In a study of 50 DES in-stent restenotic lesions with a mean follow-up of 32.2 months, Kang showed that by IVUS and optical coherence tomography (OCT), 52\% had an in-stent thin capped fibroatheroma (TCFA) and 58\% had at least one neointimal rupture.\textsuperscript{22} The longer the follow-up, the greater was the incidence of a TCFA. Pathological series have confirmed this conversion with DES as well as with BMS but with an average time for this conversion was sooner for DES (1 ½ vs 6 years).\textsuperscript{23} Recently Yamaji showed that aspiration of the thrombus in 42 patients with very late ST following bare metal stent thrombosis showed fragments of atherosclerotic plaques and suggested that disruption of in-stent neo-atherosclerosis could play a role in VLST.\textsuperscript{24} These observations suggest that neo-atherosclerosis may be responsible for VLST in a proportion of patients. How often neo-atherosclerosis occurs and how often does 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 mal-apposition diminish over time but neo-atherosclerosis 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 while 50\% remained on DAPT it was not a predictor of VLST. Theoretically DAPT should decrease both ST and plaque rupture with thrombosis. We will need to await the large on-going randomized trials to help answer this important question.
second-generation stents and other newer stents including those without polymers and biodegradable stents may be helpful.\textsuperscript{14,25} Aggressive medical therapy should help attenuate the development of in-stent neo-atherosclerosis 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 drug eluting stents in large registries have made it apparent that the stented segment continues to be at risk for thrombosis and neo-atherosclerosis 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 drug eluting stents.

\textbf{Conflict of Interest Disclosures:} none

\textbf{References:}


**Table 1.** The incidence of very late stent thrombosis with first generation DES in large registries with 3 to 5 year follow-up.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N Pts</th>
<th>Stent</th>
<th>FU (y)</th>
<th>VLST %/y</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESTROFA⁶</td>
<td>’08</td>
<td>23,500</td>
<td>SES/PES</td>
<td>3</td>
<td>0.27</td>
</tr>
<tr>
<td>SCAAR²</td>
<td>’09</td>
<td>42,150</td>
<td>SES/PES</td>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td>DESIRE-late¹⁵</td>
<td>’10</td>
<td>1,010</td>
<td>SES/PES</td>
<td>5</td>
<td>0.22</td>
</tr>
<tr>
<td>Jensen⁹</td>
<td>’10</td>
<td>12,374</td>
<td>SES/PES</td>
<td>3</td>
<td>0.21</td>
</tr>
<tr>
<td>Simsek¹⁰</td>
<td>’10</td>
<td>1,444</td>
<td>SES/PES</td>
<td>4</td>
<td>0.2</td>
</tr>
<tr>
<td>BERN/Rotterdam³</td>
<td>’11</td>
<td>8,146</td>
<td>SES/PES</td>
<td>4</td>
<td>0.53</td>
</tr>
<tr>
<td>EVASTENT¹¹</td>
<td>’11</td>
<td>1,564</td>
<td>SES</td>
<td>4</td>
<td>0.18</td>
</tr>
<tr>
<td>Kimura⁵</td>
<td>’11</td>
<td>12,812</td>
<td>SES</td>
<td>5</td>
<td>0.26</td>
</tr>
<tr>
<td>(Current study)</td>
<td></td>
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SES- sirolimus-eluting stent, PES- paclitaxel-eluting stent
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