

## Drug-Eluting Stents: Making Sense of the Clinical Data

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The ability to open blocked blood vessels via percutaneous coronary interventions (PCI) such as balloon angioplasty has revolutionized the treatment of coronary artery disease, a leading cause of death worldwide. The introduction of stents, small mesh tubes that help prevent the re-closure of blood vessels (restenosis) following PCI, was a major breakthrough in the evolution of angioplasty. Another major milestone was the recent development of specialized stents capable of releasing drugs that inhibit the overgrowth of blood vessel cells inside the stent. Drug-eluting stents (DES) have dramatically improved the outcomes of PCI by reducing the rates of restenosis and the need for repeat interventions.<sup>1,2</sup> As a consequence, they have helped to make coronary angioplasty one of the most common medical interventions in the world, with more than one million procedures performed annually.

Numerous clinical trials involving tens of thousands of patients worldwide have established the safety and efficacy of DES, and continue to clarify how best to use this technology and which patients are most likely to benefit. DES trials employ various designs and a broad spectrum of endpoints. The sheer number of different measurements that can be used to assess the safety and efficacy of DES – as well as ongoing debates about the relative predictive value of some endpoints – can make interpreting data from clinical studies a difficult task even for interventional cardiologists. Furthermore, variations in study designs and the way particular endpoints are defined often make cross-study comparisons of DES data difficult or impossible.

This primer provides an accessible overview of DES trial designs and endpoints. It is designed to help writers evaluate DES data communicated through medical congresses and literature, as well as the media.

### Types of Clinical Studies

Two main types of studies are used to evaluate DES: randomized controlled trials (RCTs) and registry studies. RCTs measure the performance of a DES under highly controlled conditions and within a well-defined patient population. They are required to establish the efficacy and safety of a device for approval or for indication extension by regulatory agencies such as the U.S. Food and Drug Administration (FDA)

Registries, on the other hand, are conducted after a device has already been approved, and are designed to observe safety under “real-world” conditions. Procedures and patient characteristics may vary widely. Key differences between RCTs and registries are summarized in the table below.

<b>Randomized Controlled Trials</b>	<b>Registries</b>
Homogeneous patient population	Heterogeneous patient population
Statistical proof of safety and/or efficacy	Not statistically valid for efficacy or safety comparisons
Treatment randomized to comparator	Open label (patients not randomized)
Blinded when possible	Observational
Complete independent monitoring, oversight and core lab analysis	Variable monitoring and oversight with visual angiographic estimates

Thus, data from registries and RCTs are complementary, but not comparable.

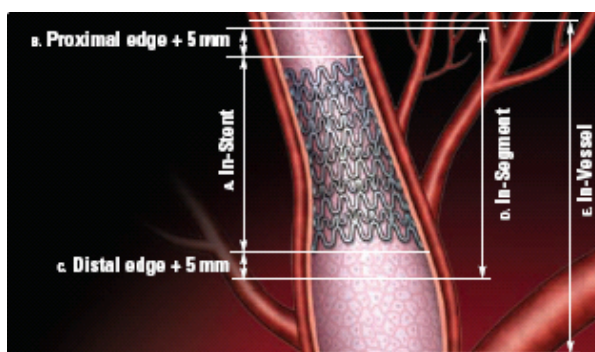
### Clinical Endpoints

Endpoints are specific outcomes that are measured during clinical studies. The two basic types of endpoints are clinical and non-clinical. The classic clinical endpoint for DES studies is major adverse cardiac events (MACE), which comprise a number of individual outcomes, including coronary death, cardiac death, death from any cause and myocardial infarction (MI). Different trials have used different definitions of MACE. Thus, rates of MACE between studies are not comparable.<sup>3</sup>

The need to re-open or bypass a blood vessel (revascularize) following PCI is another clinical measurement that is increasingly used as an endpoint in DES studies. Target lesion revascularization (TLR) and target vessel revascularization (TVR) are the two main types of revascularization.

TLR refers to a repeat PCI or a bypass surgery within or immediately adjacent to the stented area (see Figure 1). Clinical trials often measure the incidence rate of TLR to assess performance of a DES.

TVR refers to a repeat PCI anywhere in a vessel that has received a stent (Figure 1). Thus, although TVR is an



**Figure 1**

important clinical endpoint, it does not directly reflect the performance of the stent.

Not all serious events involving target lesions or target vessels require additional PCI or bypass surgery. For example, the patient may develop angina or a blood clot (thrombosis) that can be treated by other means. To capture these types of events, some clinical trials include a measurement known as target vessel failure (TVF). Like MACE, definitions of TVF may vary significantly from trial to trial, complicating or precluding cross-study comparisons.

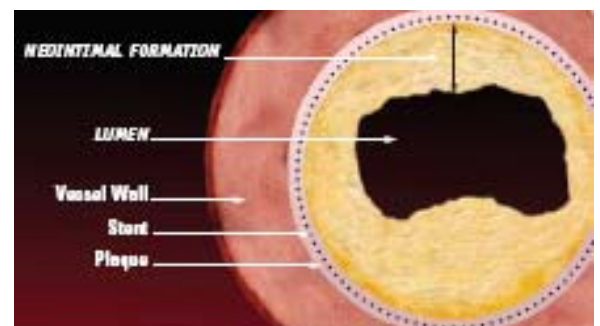
### **Non-clinical Endpoints**

Several non-clinical measurements are used as “surrogate” endpoints in DES studies. Although these measurements may correlate to clinical endpoints such as TLR, in some cases the association is controversial or complex. Non-clinical endpoints are based on either quantitative coronary angiography (QCA) or intravascular ultrasound (IVUS).

### ***QCA-based endpoints***

The two most important angiographic endpoints are in-segment binary restenosis and in-segment late lumen loss. Binary restenosis occurs when the opening (lumen) of a stented vessel closes by 50 percent or more (Figure 2).

Late lumen loss, also known as “late loss,” is a measure of the growth of blood vessel cells within or near the stent. In the healing process following the implantation of a stent, a new layer of blood vessel cells (neointimal layer) forms over the inside surface and architecture (struts) of the stent. Adequate growth is required for normal blood-flow through the stent. However, excessive growth of the new cell layer can impede blood flow and lead to repeat interventions.



**Figure 2. Restenosis**

Late loss measures the difference of the diameter of the vessel opening (in millimeters) immediately following PCI and at later time points. When late loss is a positive number, it

means that the diameter of the blood vessel opening has become smaller (see Figure 3). Research has shown that when late loss is more than 0.6 mm, there is a correlation between the amount of late loss and restenosis.<sup>2</sup> However, there does not appear to be an association between restenosis and late loss below this threshold. For example, a late loss of 0.17mm was associated with a TLR rate of 4 percent in a study of the Cypher<sup>®</sup> DES<sup>4</sup>, while a “higher” late loss of 0.39mm was associated with a TLR rate of 3 percent in a similar study of the Taxus<sup>™</sup> DES.<sup>2</sup>

When late loss is negative, it means that the blood vessel opening is wider than it was immediately following stent implantation, and that a normal layer of cells has not covered the struts of the stent (Figure 3). This is important, since inadequate growth of a new cell layer over the stent may correlate with the formation of blood clots months after the procedure (late thrombosis).<sup>5</sup>

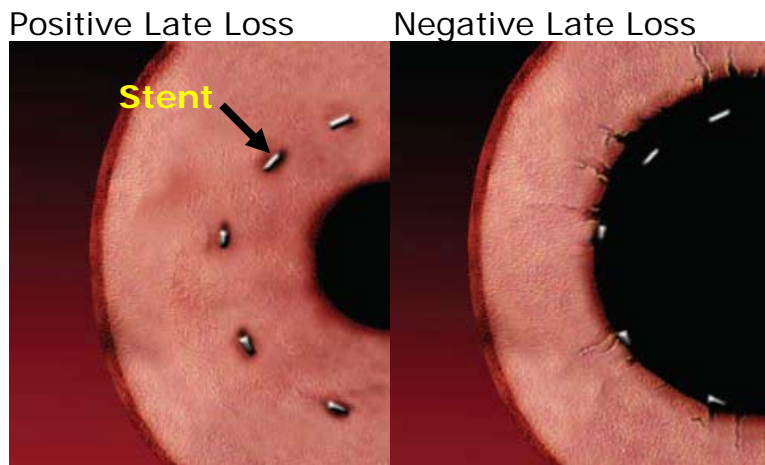



Figure 3. Late loss

### ***Intravascular ultrasound (IVUS)-based endpoints***

IVUS measures the three-dimensional area of the blood vessel, the stent and the opening of the blood vessel. These measurements can be used to assess the extent of growth of the new blood vessel cell layer, or the “neointimal hyperplasia area” (NIHA).



Unlike angiographic measurements, IVUS can also detect when the stent is not flush with the wall of the blood vessel, which allows blood to flow around the stent.<sup>3</sup>

### **Conclusion**

In order to accurately interpret the results of DES studies, it is critical to understand the various types of trials and endpoints used to assess the devices, as well as the often-subtle differences between similar endpoints. Both clinical and non-clinical endpoints have variable definitions, and even trials using identical endpoints may differ significantly in design, thus precluding cross-study comparisons. Finally, it is important to remember that non-clinical endpoints provide useful information about DES, but their relationship to clinical outcomes is often unclear.<sup>3</sup>

## Glossary of Key Terms

[http://www.bostonscientific.co.uk/common\\_templates/glossary.jsp?task=tskFinancialGlossary.jsp&sectionId=2&rellId=1,23](http://www.bostonscientific.co.uk/common_templates/glossary.jsp?task=tskFinancialGlossary.jsp&sectionId=2&rellId=1,23)

## References

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