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Pushing Drug-Eluting Stents Into Uncharted Territory Simpler Than You Think—More Complex Than You Imagine

Campbell Rogers, MD; Elazer R. Edelman, MD, PhD

Failures are the preparation for...victories.

Ralph Waldo Emerson¹

Mechanical failure is a characteristic of a material or device and not necessarily an indication of inadequacy. All devices will fail under some specific stress. It is only failure at the lowest levels of stress that may represent inadequacy. Stress on a material, for example, rises with strain until a critical load is exceeded, at which point the material fatigues and loses mechanical integrity. Failure analysis, the science by which these conditions are rigorously defined, is an important component of device design, development, and use. Once the transition point to failure is identified, material use can be restricted to the zone of safety or modified so as to have this zone expanded. Just as the characterization of a material is incomplete unless pushed to the limits of load bearing, characterization of an implantable device is incomplete unless preclinical and clinical environments test the limits of device functionality. It was in this light in 1999 that we noted the impossibility of defining the functional limits of novel bare metal stents in head-to-head trials, which, by necessity, could only include lesions into which the predicate device (the Palmaz-Schatz stent, Cordis, Warren, NJ) could be placed.² Glimpses of superiority of 1 bare metal stent over another were only possible via registry data, “real world” reports, or small studies comparing advanced stent designs³ where more diverse patients and lesions could be considered and more granular determination of lesion- or patient-specific predictors of failure determined.

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New School Percutaneous Interventions

Twelve years after their introduction into the United States, stents have become as complex as the patients into whom they are placed. Over the past 5 years, the number of percutaneous interventions has grown by 40%. This expansion derives from an increased breadth of cases, as percutaneous interventions are now routinely performed in diabetic, small-vessel, multilesion, diffuse disease, and acute coronary

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syndrome settings. Contemporaneously, widespread adoption of drug-eluting stents has emboldened clinicians and provided greater security in the use of these devices in lesions or patients previously thought to be destined for device failure. For this reason, as well as many others, clinically testing stents beyond the limits of “safe and effective” has become the norm. Pushing head-to-head randomized trials into increasingly complex realms is easier than before, and potential differences between stents are much more profound now than when devices were all of similar form and material. Furthermore, the spectacular success of drug-eluting stents is still plagued by an aura of unease and an insistent drumbeat demanding evidence of success and safety. There remains the fear that one gain may be offset by another associated risk and dramatic reductions in restenosis attended by enhanced rates of thrombosis.

We now are prompted to expand upon the set of questions that prompted our editorial 7 years ago. We knew then that preclinical models predicted better outcomes with some metal stent designs than others⁴ but did not know whether late clinical outcomes would differ. Today, implants include different stent platforms that release drugs with vastly different targets, mechanisms of action, and pharmacokinetics and resultant differences in suppression of neointimal hyperplasia.^{5–8} Perhaps conventional wisdom holding that such complex and varied devices behave “the same” is naïve. If so, as head-to-head randomized trial data accumulate, analysis may gain the sophistication to demonstrate differences. The playing field for prospective randomized trials has broadened, bringing greatly enhanced strength of evidence to domains previously restricted to open registries.

Complexity Simplified

Everything is simpler than you think and at the same time more complex than you imagine.

Johann Wolfgang von Goethe⁹

Making the simple complicated is commonplace; making the complicated simple, awesomely simple, that's creativity.

Charles Mingus¹⁰

Musical genius is most appreciated in the setting of the complex and challenging. Yet, complex is not synonymous with complicated, harmony does not need convoluted tones, and virtuosity can be appreciated even in simple rhythms. Critical then to our understanding of clinical performance of avant garde medical devices is defining terms. Drug-eluting stent “failure” can be defined operationally in the same way as material failure: inadequate function in the setting of a

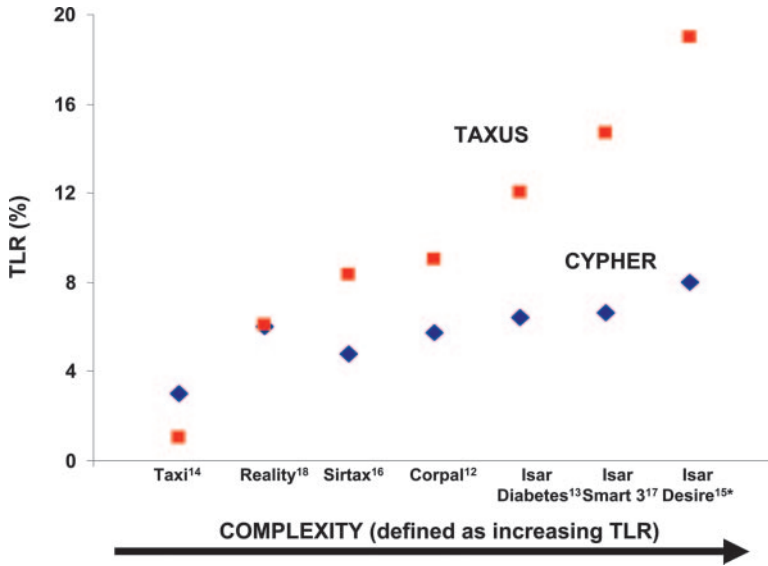


Figure 1. TLR rates differ among head-to-head randomized drug-eluting stent comparison trials and rise differentially for Taxus and Cypher stents. *Target vessel revascularization.

given load or strain. The inability to withstand stress may take many forms that can change over time. Failure may be manifest acutely as the inability to deliver a stent to the desired location, subacutely as stent thrombosis or postprocedural myonecrosis, and later as restenosis. “Simple lesions” are those in which few devices should fail. “Complex” lesions, in contrast, have a heightened risk of failure. To be of value, each scale of advancing complexity must provoke higher failure rates for each device, and one device may fail sooner than another along one such “complexity” scale and later along another.

We predicted that differences between bare metal stents would have become apparent, had randomized trials been “pushed” into more complex lesions, but such trials were difficult to conduct.² As advanced drug-eluting stent designs have enhanced deliverability and reduced restenosis rates, 7 randomized trials comparing directly the 2 Food and Drug Administration (FDA)-approved drug-eluting stents, Cypher (Cordis-Johnson and Johnson) and Taxus (Boston Scientific,

Boston, Mass), have been reported.^{11–17} These trials report a broad range of restenotic failure as evidenced by the need for revascularization. Across these trials, driven by a variety of factors, revascularization rates vary quite widely. In this regard, the clinical end point of target lesion revascularization (TLR) becomes 1 measure of device failure, and when the 7 trials are depicted in order of increasing TLR, the rate of failure increases more slowly with 1 device than the other (the curves diverge, Figure 1). Moreover, the separation between the failure rates of the two devices broadens in direct relation to the degree of “complexity” (Figure 2). Finally, TLR rates for Taxus and Cypher stents correlate remarkably (Figure 3), confirming that trial-specific events and conditions determined TLR. This correlation, however, does not correspond one-to-one, as would be expected if each device responded identically to advancing complexity. On the contrary, the ratio of TLR (the slope) was greater than 3, suggesting that

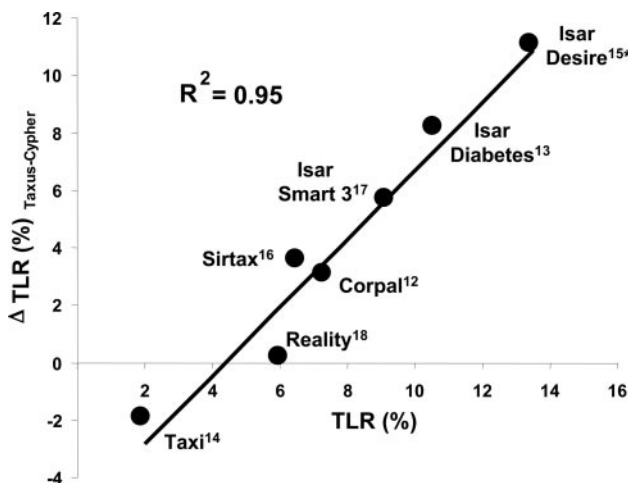


Figure 2. The difference between restenosis (TLR) rates for Cypher and Taxus stents in a given trial correlates with the average TLR for that trial. The higher the risk, the greater the difference in outcomes. *Target vessel revascularization.

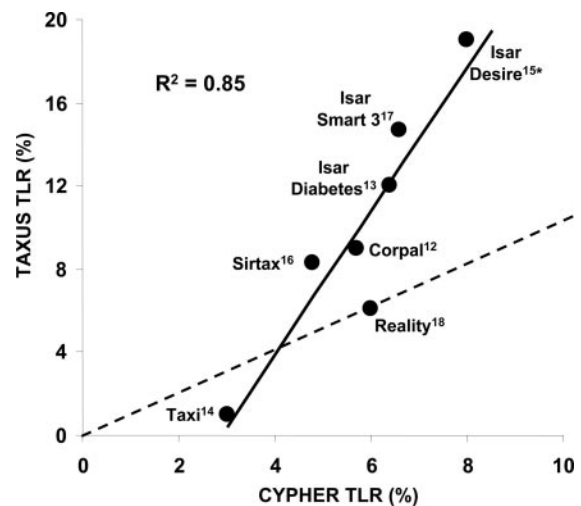


Figure 3. TLR rates for 7 comparison trials demonstrate remarkable correlation between Taxus and Cypher stents. Yet, rather than falling on the unity (dashed) line indicating identical response, TLR rates rise 3.5 times faster with one device than with the other. *Target vessel revascularization.

although both devices are subject to increasing failure as complexity increases, 1 device becomes ever-more likely than the other to fail when applied in settings with ever-higher TLR risk. In other words, composite medical devices with a wide range of structural, geometric, and pharmacological differences can be shown to produce different clinical effects as the environments in which they are tested become increasingly complex.

What the Individual Trials Cannot Tell Us

The progressive difference between the performances of the 2 FDA-approved drug-eluting stents as they are pushed into more complex settings is precisely what one would anticipate from medical devices with different performance signatures. However, a central limitation of most randomized trials, even those that push the limits of complexity, is the inability to identify predictors of failure because of the low numbers of patients enrolled. From the perspectives of investigation, device development, and clinical practice, knowing which patient or lesion characteristics confer higher failure rates is critical information. Our analysis has centered on restenosis. Other failure modes such as stent thrombosis, postprocedural myonecrosis, or even late processes such as plaque rupture, enhanced disease at a distance, and excitation of a heightened immune state are no less critical and may be determined by completely different device or patient characteristics.

It is in this light that the registry report of Kastrati et al¹⁸ in the current issue of *Circulation* is of greatest value. There are 2 ways in which well-executed registry or pooled data can be most complementary to randomized trials. First, large numbers of patients provide a higher incidence of rare failure modes as well as allow more granular determination of lesion- or patient-specific predictors of failure. For example, a pooled analysis of several head-to-head randomized bare metal stent trials allowed identification of clear risk factors for stent thrombosis that had eluded analysis of the individual (smaller) trials.¹⁹ Second, registry or pooled data may incorporate a broader range of patient characteristics, allowing greater discrimination between devices. The report of Kastrati et al¹⁸ may fall into this category as well, as it includes "high risk" populations from several randomized trials.

Kastrati et al¹⁸ report on more than 2000 lesions in 1845 patients treated with either Taxus or Cypher drug-eluting stents at 2 hospitals. Although described as consecutive patients, the population is reported elsewhere as stemming from a series of randomized trials comparing Taxus and Cypher stents (making it unlikely that the patients were indeed consecutive). That methodological issue notwithstanding, the authors use multivariate analysis for just the purpose described above, namely, to identify what lesion and patient characteristics predict failure (restenosis). Risk factors identified included prior history of coronary bypass surgery, calcification, smaller vessel size, and greater degree of pre-stent and post-stent stenosis. Use of a Cypher rather than Taxus stent was independently associated with lower restenosis risk. An interesting negative finding was the absence of diabetes as a significant predictor, at odds with strong suggestions from some²⁰ but not all other analyses. Divergent definitions of diabetes and smaller numbers of diabetic

patients in some studies (with resultant wide confidence intervals) may in part explain these discrepancies. Nevertheless, better understanding from preclinical or clinical studies of how different diabetic states may affect restenosis after stenting is critical.²¹

Our understanding of other modes of failure, especially stent thrombosis, will be deepened greatly by registries of similar rigor to the one reported by Kastrati et al,¹⁸ and we look forward eagerly for analyses of these events. Pooled data with rigorous ascertainment and careful statistical methodology, taken together with randomized trial data, open a door to device choice based on the knowledge that risk of failure (complexity) does vary, and the higher the complexity, the greater the incremental benefit of choosing one device over another. A decision algorithm is therefore possible, whereby multiple failure modes and risk factors are weighed, and an optimum stent choice made which balances safety and efficacy based on the totality of evidence, rather than anecdote and loose comparisons of disparate subgroups from individual trials.

Evaluating Clinical Trials

*The subject of trial(s) is also very difficult... the aim and meaning of all the trials... is to let people know what they ought to do or what they must believe.*²²

The great 12th century physician, theologian, and philosopher Moses Maimonides discussed the concepts of biblical trials at length. He concluded that mortal man tests those things that he does not know in advance. Only divinity knows the results of trials in advance and uses them to validate what He already has determined to be the case. Clinical trials should support clinical science, not divinely inspired prophecy. It was perhaps naïve to imagine that devices as different one from another as the 2 current FDA-approved drug-eluting stents would produce identical clinical results. If so, it ought not to come as a surprise that head-to-head randomized trial data from many different countries in complex settings are now indicating just how differently the 2 devices may perform. It is not our intention to comment on selection of one drug-eluting stent over another but only to highlight that differences between devices can emerge if comparative testing is performed in complex domains.

Future trials should be designed and evaluated to examine why these differences exist. Trials residing only in previous safety and complexity domains are unlikely to offer deeper insights into device performance, patient care decisions, or discrimination of alternative therapies. We tend to embrace simplicity as a virtue, but, in the words of Albert Einstein, "Everything should be made as simple as possible, but not simpler." Complexity is a tool of differentiation, and when used properly can simplify our understanding of the clinical behavior of complex devices. We look forward to more trials that will examine what we currently believe to be the limits of drug-eluting stents and interventional cardiology and to help define in simple terms differences between complex devices applied to complex problems.

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References

- Emerson RW. *The Writer in Representative Men: Seven Lectures*. New York: Modern Library; 2004.
- Edelman ER, Rogers C. Stent vs stent equivalency trials: are some stents more equal than others? *Circulation*. 1999;100:896–898.
- Hausleiter J, Kastrati A, Mehilli J, Schühlen H, Pache J, Dotzer F, Sattelberger U, Dirschinger J, Schömig A. Impact of lesion complexity on the capacity of a trial to detect differences in stent performance: results from the ISAR-STEREO trial. *Am Heart J*. 2003;146:882–886.
- Rogers C, Edelman ER. Endovascular stent design dictates experimental restenosis and thrombosis. *Circulation*. 1995;91:2995–3001.
- Rogers C. Clinical perspectives on drug and design differences. *Rev Cardiovasc Med*. 2005;6:S3–S12.
- Levin A, Jonas M, Hwang C, Edelman ER. Local and systemic drug competition in drug-eluting stent tissue deposition properties. *J Control Release*. 2005;109:236–243.
- Levin AD, Vukmirovic N, Hwang CW, Edelman ER. Specific binding to intracellular proteins determines arterial transport properties for rapamycin and paclitaxel. *Proc Natl Acad Sci*. 2004;101:9463–9467.
- Serruys PW, Kutryk MJB, Ong ATL. Coronary artery stents. *N Engl J Med*. 2006;354:483–495.
- Goethe JW. Quoted in: *Johann Wolfgang Goethe, Gedenkausgabe der Werke, Briefe und Gesproche [Johann Wolfgang Goethe, Collected Works, Letters and Conversations]*. Beutler E, ed. Vol. 9. Zurich, Switzerland: Artemis-Verlag; 1962:651.
- Charles Mingus, as quoted by his wife, Sue Mingus, and confirmed by telephone conversation between Sue Mingus and Elazer Edelman. Also available at: <http://www.startliving.org.uk/2005/11/charles-mingus-quote.html>. Accessed on May 2, 2006.
- de Lezo JS, Medina A, Pan M, Romero M, Delgado A, Segura J, Hernandez E, Pavlovic D, Ojeda S, Fernandez-Duenas J, Ariza J, Mellan F. Drug-eluting stent for complex lesions: latest angiographic data from the randomized rapamycin versus paclitaxel CORPAL study. *J Am Coll Cardiol*. 2005;45:75A-76A. Abstract.
- Dibra A, Kastrati A, Mehilli J, Pache J, Schühlen H, von Beckerath N, Ulm K, Wessely R, Dirschinger J, Schömig A. Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. *N Engl J Med*. 2005;353:663–670.
- Goy J-J, Stauffer J-C, Siegenthaler S, Benoît A, Seydoux C. A prospective randomized comparison between paclitaxel and sirolimus stents in the real world of interventional cardiology: the TAXi trial. *J Am Coll Cardiol*. 2005;45:308–311.
- Kastrati A, Mehilli J, von Beckerath N, Dibra A, Hausleiter J, Pache J, Schühlen H, Schmitt C, Dirschinger J, Schömig A. Sirolimus-eluting stent or paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. *JAMA*. 2005;293:165–171.
- Windecker S, Remondino A, Eberli FR, Jüni P, Räber L, Wenaweser P, Togni M, Billinger M, Tüller D, Seiler C, Roffi M, Corti R, Sütsch G, Maier W, Lüscher T, Hess OM, Egger M, Meier B. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. *N Engl J Med*. 2005;353:653–662.
- Mehilli J, Dibra A, Kastrati A, Pache J, Dirschinger J, Schömig A. Randomized trial of paclitaxel- and sirolimus-eluting stents in small coronary vessels. *Eur Heart J*. 2006;27:260–266.
- Morice M-C, Colombo A, Meier B, Serruys P, Tamburino C, Guagliumi G, Sousa E, Stoll H-P. Sirolimus- vs paclitaxel-eluting stents in de novo coronary artery lesions: the REALITY trial. *JAMA*. 2006;295:895–904.
- Kastrati A, Dibra A, Mehilli J, Mayer S, Pinieck S, Pache J, Dirschinger J, Schömig A. Predictive factors of restenosis after coronary implantation of sirolimus- or paclitaxel-eluting stents. *Circulation*. 2006;113:2293–2300.
- Cutlip DE, Baim DS, Ho KKL, Popma JJ, Lansky AJ, Cohen DJ, Carrozza JP, Chauhan MS, Rodriguez O, Kuntz RE. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. *Circulation*. 2001;103:1967–1971.
- Lemos PA, Hoye A, Goedhart D, Arampatzis CA, Saia F, van der Giessen WJ, McFadden E, Sianos G, Smits PC, Hofma SH, de Feyter PJ, van Domburg RT, Serruys PW. Clinical, angiographic, and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation in complex patients: an evaluation from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) study. *Circulation*. 2004;109:1366–1370.
- Jonas M, Edelman ER, Groothuis A, Baker AB, Seifert P, Rogers C. Vascular neointimal formation and signaling pathway activation in response to stent injury in insulin resistant and diabetic animal models. *Circ Res*. 2005;97:725–733.
- Maimonides M. Chapter 24. In: *The Guide of the Perplexed*. Pines S, trans. Vol. 2, Book III. Chicago, Ill: University of Chicago Press; 1963:497.

KEY WORDS: Editorials ■ registries ■ restenosis ■ stents ■ failure