FOCUS ISSUE: DRUG-ELUTING STENTS: TAXUS-IV   **Editorial Comment**

Surrogates, Substudies, and Real Clinical End Points in Trials of Drug-Eluting Stents*

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"If I had an enemy, I would teach him angioplasty"
Andreas Gruentzig, MD, 1980
(Richard Myler, MD,
personal communication, June 1984)

The words of Andreas Gruentzig reflect the emotional anguish and uncertainty that accompanied inflation of a fluid-filled balloon in a human coronary artery. Abrupt coronary occlusion complicated 4% to 8% of balloon angioplasty procedures, was largely unpredictable, and was associated with considerable morbidity and mortality for the patient (1–3). By scaffolding balloon-mediated plaque disruption and facilitating laminar flow, stents provide a more predictable immediate angiographic result and reduce the risk of procedural complications. Furthermore, multiple randomized comparative trials of coronary balloon angioplasty versus stenting have demonstrated a salutary effect of stents on late (≥6 months) coronary reocclusion/restenosis (4–8). Nevertheless, clinical and/or angiographic restenosis after conventional stent deployment still occurs in a substantial portion of patients and often necessitates repeat revascularization procedures. The cumulative societal burden of coronary restenosis on global health care expenditures and quality of life was considerable in the era of conventional stents. More recently, targeted polymer-based elution of both sirolimus (a cytostatic macrocyclic lactone with anti-inflammatory and antiproliferative properties) and paclitaxel (a lipophilic derivative of the TAXUS Brevifolia tree capable of inhibiting the cellular processes of mitosis, motility, secretion, and signal transduction) from stent platforms have dramatically reduced the neointimal proliferative response to stent-vessel injury and, thus, have reduced the occurrence and cost of restenosis (9–11). These novel devices have rapidly transformed the practice of percutaneous coronary intervention (PCI). Recent estimates

suggest that in the U.S. ≥85% of coronary stents currently deployed are drug-eluting stents. Application of drug-eluting stents to the remaining ≤15% of patients undergoing PCI is limited only by a lack of available U.S. Food and Drug Administration (FDA)-approved stent sizes (<2.5 and ≥4.0 mm diameter) and/or difficulties in deliverability of the current drug-eluting stent platforms.

Although the two available drug-eluting stents (TAXUS–paclitaxel-eluting [Boston Scientific, Natick, Massachusetts] and Cypher–sirolimus-eluting [Cordis Corp., Miami Lakes, Florida]) differ considerably in metal platform design, polymer, and active pharmacologic agent, their use may be perceived as interchangeable by interventional cardiologists in a manner analogous to "therapeutic substitution" and the concept of "class effect" as frequently applied to pharmacotherapies. To what degree these assumptions are correct and how far presumed "class effects" may apply to new drug-eluting stents platforms is unknown. The contributions from six substudies of the pivotal TAXUS-IV trial of the TAXUS stent, which appear in this issue of the *Journal* (12–17), provide perspectives on this new technology as well as the opportunity for reflection on clinical trial design, analysis, and application to clinical practice. Let us first examine the fundamental concepts raised by Ellis et al. (12) regarding the quantitative angiographic end point measure of late coronary lumen loss and its relationship to clinical events.

LATE LOSS, STATISTICS, AND INFERENCE

The measurement of the magnitude of re-narrowing at late (six- to nine-month) follow-up has been a valuable method to gauge the need for repeat intervention of the target lesion (18,19), and to elucidate the mechanism of re-narrowing felt to be predominantly due to intimal hyperplasia within and just outside the stent boundaries (20). The metrics employed to measure this magnitude include the continuous and statistically powerful end points of percent diameter stenosis, late loss in lumen diameter (measured in millimeters), and intimal volume, measured as an absolute or relative volume by intravascular ultrasound (reported in this issue by Weissman et al. [17]). The notion that all fixed balloon-expanded metal stents undergo some level of re-narrowing, summarized as the mean in-stent (or in-

segment) late lumen loss, and that excessive re-narrowing in a minority leads to flow limitation and the need for repeat intervention, summarized as target lesion (or target vessel) revascularization rate, supports the utility of reporting the mean late lumen loss as a surrogate for binary clinical restenosis propensity. While multiple bare-metal stent trials have demonstrated an average late loss (in-stent) of approximately 0.8 to 1.0 mm with corresponding clinical restenosis (target lesion revascularization [TLR]) rates of approximately 15% to 25%, recent successful drug-eluting stent trials have demonstrated a clear beneficial treatment effect evidenced by low mean in-stent late losses of 0.2 to 0.4 mm accompanied by low clinical restenosis (TLR) rates of 5% to 8%. Moreover, the continuous and near normal distribution of late loss (21,22) allows the assumption of monotonicity in the relationship between incremental higher mean late loss values (for any given stent or patient cohort) and higher probabilities of excessive re-narrowing causing binary clinical restenosis.

Ellis et al. (12) challenge this expected correlative relationship between late loss and clinical restenosis. Over the 0.0 to 1.0 mm range of average late loss values seen in the wide spectrum of bare-metal and drug-eluting stent trials, the authors propose that any stents with average late losses of up to 0.5 to 0.65 mm (in-segment) and 0.75 to 1.0 mm (in-stent) have a low and relatively flat relationship to the risk of restenosis. They propose that stents with mean late loss values below these thresholds have equivalent low clinical restenosis potentials, with no practical discriminating value for differences in average late loss. The basis of their conclusion is derived from an analysis of the relationship between late loss and TLR *for individual patients* from the TAXUS-IV trial (10). However, neither this analysis nor their conclusion is appropriate for a discussion of the relationship between average late loss values of stents and the probability of clinical restenosis. The authors motivate their analysis of late loss in the TAXUS-IV trial by stating that the interrelationship between late loss, binary restenosis, and TLR after bare-metal stenting has not been completely evaluated. The tautology of the interrelationship between these variables *in patients* probably explains the lack of prior formal analysis. For any patient who receives a stent, the interrelationship between late loss and binary restenosis (defined as >50% diameter stenosis), for example, is essentially defined by a simple arithmetic formula. For a 3.0-mm coronary artery, the usual acute result (from virtually all contemporary balloon-expandable stent trials) is an average 5% residual in-stent percent diameter stenosis, or an in-stent minimum lumen diameter of approximately 2.85 mm. In order to qualify for binary restenosis (≥50% diameter stenosis at follow-up), this lumen will have to be reduced to ≤1.50 mm, corresponding to a late loss of ≥1.35 mm. Thus, for a 3.0-mm stented artery, the interrelationship between in-stent late loss and binary restenosis is a step function. That is, late loss up to 1.35 mm would generally not be associated with binary restenosis (because all percent

diameter stenosis possibilities would be below 50%), and late loss >1.35 mm would be associated with binary restenosis (because all possible percent diameter stenosis would be ≥50%). A graph of the relationship between late loss on the abscissa and the probability of binary restenosis on the ordinate would essentially be a square step function: flat and 0 up to 1.35 mm, with an immediate inflection at 1.35 mm, and flat and 100% above 1.35 mm.

Given that stent trials have variable reference vessel sizes, of which the vast majority are between 2.5 and 3.2 mm, the predicted step function of the interrelationship between late loss and binary restenosis would contain a softer inflection point and look less square than in the above 3.0-mm example. The inflection, while still step-like in appearance, would occur less sharply over the 1.1 to 1.4 mm range of in-stent late loss. It is no surprise that any patient with an in-stent late loss below 1.1 mm would have a low probability of binary restenosis, while any patient with a late loss above 1.4 mm would have a high probability of binary restenosis in the typical reference vessel size range. This result holds true whether the tested stent is bare-metal or drug-eluting.

If this example is now extended to examine late loss and TLR, the relationship would still be formulaic, predictable, and step-like. Target lesion revascularization is generally adjudicated (as described by Ellis et al. [12]) as being positive when: 1) the percent diameter stenosis is >70% with symptoms; or 2) there is revascularization and clinical ischemia when the percent diameter stenosis is between 50% to 70%. It is generally adjudicated as negative if the percent diameter stenosis is below 50%. Although these rules further soften the inflection point, there remains a predictable slanted step function that has a flat and near 0 likelihood of TLR when late loss is below 1.0 mm, and near 100% TLR when late loss is above 1.5 mm.

The study by Ellis et al. (12) confirms this intuition, that is, there is an inflection point in the fitted logit model of late loss and TLR at about 1.0 mm for in-stent late loss and 0.6 mm for in-segment late loss (which is a softer measure of late loss and has a narrower range of values than in-stent late loss). The authors have reaffirmed this generally well-appreciated concept that it takes about 50% or more re-narrowing, measured by the amount of in-stent or in-lesion late loss, to drive TLR in a given individual.

However, of greater interest to clinicians is the interrelationship between *average* late loss (of different stent types or different patient risk subsets) and the probability of clinical restenosis. This relationship has direct implications on how one might chose a drug-eluting stent for a patient with a coronary obstruction. One would like to know whether a stent with an average late loss of 0.17 mm (Cypher stent: a U.S. multicenter, randomized, double-blind study of the SIRolImUS-eluting stent in de novo native coronary lesions [SIRIUS] [9] trial), or 0.39 mm (TAXUS stent: TAXUS-IV trial [10]), or 0.81 mm (non-polymer paclitaxel elution ACHIEVE stent [Cook and Guidant Corp., Indianapolis, Indiana]: DELIVER trial [23]) have differences in

clinical restenosis risk. Such an analysis requires one to estimate the fraction of patients who exceed the already known 1.2- to 1.4-mm late loss threshold required for *individual* TLR, when their expected mean late loss is 0.17, 0.39, or 0.81 mm. This interrelationship was not examined by Ellis et al. (12). Although the authors point out that probability distributions of late loss are affected by theoretical differences in spread (variance) and skew (right-shift), they do not provide an analysis that relates varying mean late loss values to the density of the zone of the continuous distribution beyond the threshold where late loss is high and associated with clinical restenosis, as already defined by the individual patient late loss-TLR analysis.

The actual distribution of continuous angiographic restenosis metrics has been examined for drug-eluting stents (24,25) and has been shown to be right-skewed when mean late loss is low. In fact, the magnitude of right skew is inversely proportional to the mean until the mean is in the bare-metal stent range of 0.8 to 1.0 mm, where the distribution is near normal (21,22,24,25). Moreover, late loss variance estimates are proportional to the late loss means over the range from right skew to near normal (25) as seen with similar biological near Gaussian distributions. One would assume, therefore, under parametric continuous probability distribution theory, that the higher the late loss mean, the higher the likelihood that any patient may achieve the fixed late loss threshold that is associated with TLR. In other words, the baseline null assumption to be disproved would be the notion that a family of ordered distributions with different mean values (such as distributions of average in-stent late loss from different drug-eluting stents or at-risk patient cohorts) would be associated with increasing risks of restenosis, defined precisely as the density of their distribution above some fixed threshold of late loss, such as 1.2- to 1.5-mm in-stent late loss. The pivotal question is how much separation in mean values is clinically important, not whether the interrelationship between the mean and right-sided density is correlated and ordered.

The flat square-like curve reported by Ellis et al. (12), which describes the *individual patient* late loss-TLR interrelationship, does not address this latter concern for mean values. Although the authors correctly state knowledge of the population distribution of late loss is also required to accurately predict overall late loss, confusion arises in their discussion where inferences are made about relating *average* late losses (mean in-stent and in-segment) to the probability of TLR. The authors conclude that:

> "A mean analysis segment late loss of 0.5 mm (or in-stent late loss of 0.75 mm) after drug-eluting stent implantation is adequate to achieve TLR rates <5%. Greater reduction of late loss may not translate into significantly lower TLR rates, because the relatively flat portion of the TLR/late loss curve has been reached."

Unfortunately, they use the individual patient-based analysis and curve to reach conclusions on the average late loss-TLR relationship. The authors quote the similarity in clinical restenosis rates between two trials, SIRIUS and TAXUS-IV, which have corresponding in-stent late loss mean values of 0.17 and 0.39 mm, respectively, to substantiate this claim although the confidence intervals about the clinical restenosis rates from these studies are too wide to provide adequate support for equating restenosis risk based on different late loss values.

Their principal finding, that patients need about 1 mm or more of in-stent late loss to have restenosis, is translated into a conclusion that stents with average late losses of up to 0.5 mm (in-segment) and 0.75 mm (in-stent) have similar low risk of restenosis. This is counter-intuitive, because the mean in-stent late loss observed for Cypher, TAXUS, and ACHIEVE drug-eluting stents as well as their bare-metal controls were all well below or only slightly above this 0.75-mm threshold. Despite the closeness between their proposed 0.75-mm late loss threshold and the average late loss values reported for many bare-metal stents, the authors state that a reduction of 0.2 to 0.4 mm (from bare-metal 0.8- to 1.0-mm average in-stent late loss values to the 0.75-mm threshold value, below which all stents have the same low restenosis rate) would have a marked impact on reducing restenosis. This conclusion would suggest that many bare-metal stents (with in-stent late loss of 0.75 mm or lower) already possess drug-eluting stent-like antirestenosis properties. Thus, although Ellis et al. (12) have demonstrated the intuitive relationship between in-stent late loss and clinical restenosis for any given patient to be a step function with an inflection above 0.75-mm late loss (in-stent), the more practical relationship between average (mean in-stent or in-segment) late loss and clinical restenosis (likely not a step function) was not analyzed. The authors observed right skewness in the low mean late loss distribution of a drug-eluting stent, but did not provide estimates of the probability of reaching the high late loss threshold (1.0- to 1.5-mm in-stent late loss) from varying mean values. A more workable approximation of restenosis (that estimates the actual density of high late loss) for drug-eluting stents may be derived by employing one of several transformation procedures of the late loss distribution (25). The mean late loss values and the propensity for high late loss density beyond a given threshold are correlated, but the minimum difference in late loss means that has clinical relevance cannot be estimated by such a patient-based analysis, and remains unknown.

"PIVOTAL" DRUG-ELUTING STENT TRIALS IN PERSPECTIVE: A LOOK TOWARD THE FUTURE

The TAXUS-IV trial and other pivotal drug-eluting stent clinical trials are inherently limited in inferential capacity by their very design. Although they serve as primary evidence for breakthrough technologies (such as paclitaxel-eluting stents) in the safe treatment of coronary stenosis, they balance the need for homogeneity of subjects to allow definitive measure of the

behavior of the investigational device being tested, with the need for heterogeneity to allow generalizability. These relatively small and limited (initially) duration follow-up trials derive valuable mechanistic and safety information from subjecting even asymptomatic patients to invasive evaluations such as angiography or intravascular ultrasound. Safety concerns regarding the use of protocol angiography or ultrasound must carefully balance the insights provided with which to better profile rare or late clinical events with the fact that these invasive evaluations provide only surrogate measures for real clinical outcomes. For example, the issue of optimal adjustment for skew in angiographic measures raised previously is based on a correlation with clinically meaningful events (i.e., coronary revascularization).

After U.S. FDA approval of two drug-eluting stent platforms, newer drug-eluting stent platforms can no longer be defined by clinical trials (such as TAXUS-IV and SIRIUS), which test superiority versus placebo (i.e., bare-metal stent controls). Both ethical and practical issues dictate a shift to active control noninferiority studies, as neither patients nor physicians will support clinical trials with clearly inferior treatment arms. Although a shift to "active control" studies with relatively lower clinical event rates might appear to support the need for surrogate angiographic end points in order to make these studies feasible, this perception implies a shift from use of protocol angiography primarily for safety concerns to its use instead as a primary measure of device effectiveness. However, the necessity for requiring invasive evaluations in follow-up becomes both an ethical and practical question when patients can be treated with an approved "active control" drug-eluting stent without participating in the research study.

An assumption central to the conclusion that low clinical event rates mandate angiographic surrogates for feasible device trials deserves scrutiny. Low event rates are driven not only by enhanced drug-eluting stent effectiveness, but also by the "plain vanilla" low-risk patient selection criteria typically used in pre-market pivotal studies. Thus, in both the TAXUS-IV and SIRIUS trials, patients with single-vessel/single-lesion disease, a relatively low incidence of diabetes, and a virtual absence of comorbidities contributed to the low overall event rates observed. Modification of subject enrollment criteria could dramatically influence the feasibility for measuring "real" clinical end points in trials and reduce the dependence on surrogate angiographic measures. For example, a robust approach for understanding a new drug-eluting stent platform that could also provide clinicians and regulatory authorities with valuable prospective data on an already approved drug-eluting stent device would be to enroll a more complex patient population than was studied in prior pivotal superiority trials. This "enriched population" could step beyond the historical pre-market study population by: 1) increasing the density of clinical end points and thus promoting feasible trials based on real outcomes measures; 2) being more reflective of post-market "real world" use, so that data obtained in the pre-market study should be more predictive of actual post-market risk and benefit; 3) more closely approximating patients treated in clinical practice so that enthusiasm of physicians to recruit patients and for patients to enroll in clinical research should be enhanced; and 4) being an exploratory population so that statistical analysis plans would uniquely accommodate for unknowns in both the active control and treatment arms for determination of noninferiority.

One example of an enriched population would be the inclusion of patients with multivessel disease, which should include a higher proportion of diabetics and could promote a clinical event density rate sufficient to support a feasible study of real clinical end points.

The need for angiographic information and "invasive risk" for patients who participate in an enriched population study could be more specifically tailored to the novelty of the drug-eluting stent platform per se.

ACTIVE CONTROL STUDIES: THE VALUE OF THE IMPUTED PLACEBO

Two issues to be addressed for active control clinical trials of drug-eluting stents in "enriched" populations are: 1) the potential for "creep" back toward placebo event rates in a noninferiority trial design; and 2) the need to develop performance boundaries to define noninferiority in an "enriched" population not previously systematically studied using the active control therapy (26–29). Both issues may be addressed by the development of an imputed-placebo-relative-risk boundary. The techniques for creating indirect comparisons of a new treatment to placebo have been described (29). Using these methods it is possible to estimate how the experimental drug-eluting stent will perform versus placebo if a placebo were present. For example, in constructing a comparative study that uses the TAXUS stent in a multivessel population (not studied in the TAXUS-IV trial), the primary clinical end point in the experimental drug-eluting stent arm would be compared with the TAXUS arm using relative risk as a measure because the noninferiority margin (delta) can be stated in terms of a relative risk. The imputed placebo calculations for the trial could be based on the results of all TAXUS studies reported, as shown in Figure 1. These results are combined using a random effects empirical Bayes estimator. The combined estimate of the relative risk for major adverse cardiovascular events to nine months is 0.52 with 95% confidence limits of 0.40 to 0.67. The reciprocal of this upper confidence limit forms a natural delta for noninferiority. This delta insures that the imputed placebo relative risk will be significantly lower than 1, indicating that the experimental drug-eluting stent is significantly better than placebo. This statistical methodology and design will likely chart the course for future active control, noninferiority trials of newer drug-eluting stent platforms.
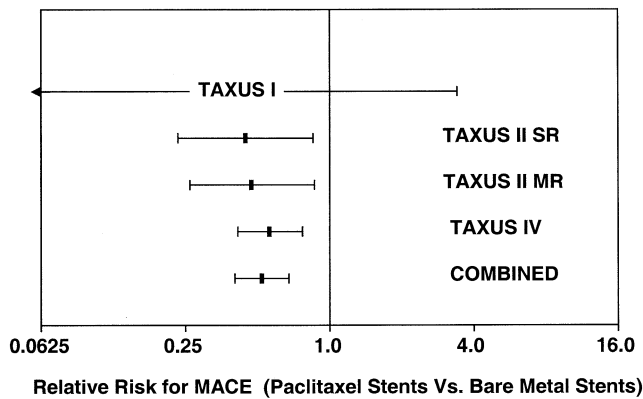
Figure 1. Relative risk for major adverse cardiovascular events (MACE) up to nine months in randomized trials of the TAXUS paclitaxel-eluting stent; MACE is composite occurrence of cardiovascular death, myocardial infarction, or target vessel revascularization (see text). MR = moderate release; SR = slow release.

SUBSET ANALYSES FROM PIVOTAL TRIALS

One must acknowledge that simple, non-prespecified subgroup analyses such as those described in the TAXUS-IV substudy reports (only presentation of the stratified results by vessel size and diabetes were prespecified in the TAXUS-IV trial protocol) have limited power to provide assurances as to safety or efficacy of a new device and are, at best, hypothesis-generating. Furthermore, the main effect analysis methodology of the primary end point used for two of these reports (left anterior descending target lesion location and diabetes) essentially repeats the findings reported in the primary publications (with expanded secondary end point analysis) showing a similar positive treatment effect as in the overall TAXUS subject sample (10,30). What is absent from these multiple subgroup analyses is a comparison of treatment effect between complementary subsets (i.e., a test of interaction) (31). Because these subsets are concluded to have similar outcomes as the overall randomized cohort, an estimation of the power to detect a given difference in treatment effect would help to put the findings into perspective.

Evidence of generalizability for treatment effect across subgroups of interest should be addressed in the initial trial design, with special attention to eligibility criteria, rather than reliance on subgroup analyses from an already positive study. Any added value in showing similarity of treatment effect among subgroups is limited by both statistical power (type 2 error) and multiple comparisons (type 1 error) (32). Subset analyses, always done with a test for interaction should be reserved for subgroups suspected of having a differential treatment effect, and this suspected difference should be quantified and prespecified.

Nevertheless, for patients with treated diabetes, the TAXUS stent appears relatively safe and effective for reducing clinical or angiographic restenosis in comparison to the bare-metal EXPRESS-2 stent platform. Furthermore, the magnitude of TAXUS benefit (vs. EXPRESS-2) does not

appear different by diabetic treatment (insulin vs. oral agents) (13). Similarly, the subgroup analysis of patients undergoing TAXUS stent deployment for left anterior descending coronary artery stenosis reported by Dangas et al. (14) supports the relative safety and efficacy of TAXUS compared with the EXPRESS-2 stent. In addition, the analysis of gender-based outcomes for TAXUS versus EXPRESS-2 stent deployment presented by Lansky et al. (15) supports the relative safety and efficacy of TAXUS. Finally, an analysis of patients classified as having an acute coronary syndrome (unstable angina or non–ST-segment elevation myocardial infarction) demonstrates the salutary effects of TAXUS compared with EXPRESS-2 stent deployment for reducing angiographic and clinical restenosis as well as major adverse cardiovascular events (16). Although 20% of patients classified as having an acute coronary syndrome in the TAXUS-IV trial had non–ST-segment elevation myocardial infarction, angiographically demonstrable thrombus was an exclusion from enrollment into this trial (10). Surprisingly, two-thirds of patients enrolled into the TAXUS-IV trial had a history of angina pectoris at rest. Unfortunately, these underpowered analyses do not provide definitive evidence from which conclusive statements regarding safety and efficacy in the populations studied can be made. Similar limitations are applicable to prior subgroup analyses reported from the SIRIUS trial (33,34).

TENSION BETWEEN PROOF OF PRINCIPLE AND GENERALIZABILITY

New technologies require first evaluation under controlled, almost experimental conditions that emphasize validity and proof of principle. Such trials aim to reduce confounding design features by using uncomplicated subjects and simple end points. Once proof of principle is validated, trials that emphasize broader clinical application and generalizability may relax the "experimental" conditions, and test the new technology on more complex patient cohorts using more practical clinical outcomes. Unfortunately, the burden of generalizability has previously been relegated largely to post-market studies, which have been less effective than desired.

As experience with drug-eluting stent and clinical practice expands, the landscape for clinical trial evaluation of new drug-eluting stent platforms is rapidly evolving. Thus, two clinical trial methodologies emerge. For first- or second-in-class experimental therapies, the pivotal trial method used in the TAXUS-IV and SIRIUS randomized trials, where emphasis is placed on validation and mechanism of action and which requires protocol-driven invasive evaluation in a prespecified portion of patients will be employed. This pivotal trial format will comprise a sample size of 1,000 to 2,000 randomized patients and will likely incorporate a subset in which several surrogate end points (such as late loss) are measured. These powerful continuous

angiographic measures will also likely have been employed in smaller preliminary studies used to screen out ineffective therapies or test new doses before initiating larger randomized trial evaluations.

As an experimental therapy becomes standard-of-care, a second trial method with a trial sample that more closely approximates the target population will be employed. Thus, a shift from an evaluation methodology aimed at proof of concept with multiple surrogate end points, obtained by invasive techniques in a relatively low-risk patient sample, to an evaluation methodology that employs more clinically relevant end points in a higher-risk "enriched" patient cohort will occur. As the noninferiority active control trial methodology becomes dominant, methods to assure prevention of recession to mediocrity, or "placebo creep" back to a treatment effect no better than "placebo" (i.e., bare-metal stent) standard, must be utilized (26–29).

SUMMARY

The TAXUS-IV trial reports and accompanying commentary provide several global perspectives that are pertinent to all drug-eluting stents as well as strategies for future drug-eluting stent evaluation. First, drug-eluting stent platforms elicit a biologic response with respect to angiographic late coronary lumen loss that differs in its distribution from the late loss distribution previously observed in response to bare-metal stent deployment. The precedent statistical methodology used to describe this response and its relationship to restenosis is no longer accurate. Late loss retains a close correlation with late outcomes when appropriate statistical methodology is applied. Thus, the "game" (importance of late loss) remains the same in the era of drug-eluting stent; only the "rules" (statistical methodology) have changed. Therefore, we might predict that in a randomized comparative trial of two drug-eluting stents with differing levels of late loss, if reference vessel diameter and post-procedural gains are equivalent, late loss will remain a valuable and ordinal variable directly related to adverse late clinical events including restenosis. Second, the recent focus on angiographic "surrogate" end points need not blind us to the importance of meaningful clinical outcomes. Although angiographic end points may be adopted to screen therapies for effectiveness, they have limited ability to detect unusual but important events such as stent thrombosis. Furthermore, the challenges of "real" clinical practice (multivessel and complex subset intervention) will likely exaggerate differences in clinical outcomes associated with specific drug-eluting stent platforms. Third, the practice of underpowered post-hoc subgroup analyses from pivotal trials offers limited assurance of device safety or efficacy in a relatively well-circumscribed "lower-risk" cohort than would be treated in routine clinical practice. These analyses must not take the place of larger randomized clinical trials which, in turn, may be supplemented by more comprehensive and complete registry data. Finally, we may be forced to consider alternative algorithms for new device testing and approval that could incorporate more rigorous and comprehensive post-market surveillance evaluation to both assure patient safety and yet (hopefully) facilitate the pre-market approval process.

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REFERENCES

1. Lincoff AM, Popma JJ, Ellis SG, et al. Abrupt vessel closure complicating coronary angioplasty; clinical, angiographic and therapeutic profile. J Am Coll Cardiol 1992;19:926–35.
2. Kuntz RE, Piana R, Pomerantz RM, et al. Changing incidence and management of abrupt closure following coronary intervention in the new device era. Cathet Cardiovasc Diagn 1992;27:183–90.
3. Scott NA, Weintraub WS, Carlin SF, et al. Recent changes in the management and outcome of acute closure after percutaneous transluminal coronary angioplasty. Am J Cardiol 1993;71:1158–63.
4. Serruys PW, deJaegere P, Kiemeneij F, et al., for the Benstent Study Group. A comparison of balloon expandable stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med 1994;31:489–95.
5. Fischman DL, Leon MD, Baim DS, et al. A randomized comparison of coronary stent placement and balloon angioplasty in the treatment of coronary artery disease. N Engl J Med 1994;331:496–501.
6. Serruys PW, Emanuelsson H, van der Giessen W, et al. Heparin-coated Palmaz-Schatz stents in human coronary arteries. Early outcome of the Benestent-II pilot study. Circulation 1996;93:412–22.
7. Betriu A, Masotti M, Serra A, et al. Randomized comparison of coronary stent implantation and balloon angioplasty in the treatment of de novo coronary artery lesions (START): a four-year follow-up. J Am Coll Cardiol 1999;34:1498–506.
8. Moreno R, Fernandez C, Alfonso F, et al. Coronary stenting versus balloon angioplasty in small vessels: a meta-analysis from 11 randomized studies. J Am Coll Cardiol 2004;43:1964–72.
9. Moses JW, Leon MB, Popma JJ, et al., for the SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–23.
10. Stone GW, Ellis SG, Cox DA, et al., for the TAXUS-IV Investigators. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221–31.
11. Cohen DJ, Bakhai A, Shi C, et al. Cost-effectiveness of sirolimus-eluting stents for treatment of complex coronary stenoses: results from the Sirolimus-Eluting Balloon Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions (SIRIUS) trial. Circulation 2004;110:508–14.
12. Ellis SG, Popma JJ, Lasala JM, et al. Relationship between angiographic late loss and target lesion revascularization after coronary stent implantation: analysis from the TAXUS-IV trial. J Am Coll Cardiol 2005;45:1193–200.
13. Hermiller JB, Raizner A, Cannon L, et al., for the TAXUS-IV Investigators. Outcomes with the polymer-based paclitaxel-eluting TAXUS stent in patients with diabetes mellitus: the TAXUS-IV trial. J Am Coll Cardiol 2005;45:1172–9.
14. Dangas G, Ellis SG, Shlofmitz R, et al., for the TAXUS-IV Investigators. Outcomes of paclitaxel-eluting stent implantation in patients with stenosis of the left anterior descending artery. J Am Coll Cardiol 2005;45:1186–92.
15. Lansky AJ, Costa RA, Mooney M, et al., for the TAXUS-IV Investigators. Gender-based outcomes after paclitaxel-eluting stent implantation in patients with coronary artery disease. J Am Coll Cardiol 2005;45:1180–5.
16. Moses JW, Mehran R, Nikolsky E, et al. Outcomes with the paclitaxel-eluting stent in patients with acute coronary syndromes: analysis from the TAXUS-IV trial. J Am Coll Cardiol 2005;45:1165–71.

17. Weissman NJ, Koglin J, Cox DA, et al. Polymer-based, paclitaxel-eluting stents reduce in-stent neointimal tissue proliferation: a serial volumetric intravascular ultrasound analysis from the TAXUS-IV trial. J Am Coll Cardiol 2005;45:1201–5.
18. Kuntz RE, Baim DS. Defining coronary restenosis: newer clinical and angiographic paradigms. Circulation 1993;88:1310–23.
19. Cutlip DE, Chauhan MS, Baim DS, et al. Clinical restenosis after coronary stenting: perspectives from multicenter clinical trials. J Am Coll Cardiol 2002;40:2082–9.
20. Post MJ, Borst C, Kuntz RE. The relative importance of arterial remodeling compared to intimal hyperplasia in lumen renarrowing following balloon angioplasty: a study in the normal rabbit and the hypercholesterolemic Yucatan micropig. Circulation 1994;89:2816–21.
21. Kuntz RE, Safian RD, Levine MJ, et al. Novel approach to the analysis of restenosis after the use of three new coronary devices. J Am Coll Cardiol 1992;91:1493–9.
22. Rensing BJ, Hermans WR, Deckers JW, de Feyter PJ, Tijssen JG, Serruys PW. Lumen narrowing after percutaneous transluminal coronary balloon angioplasty follows a near Gaussian distribution: a quantitative angiographic study in 1,445 successfully dilated lesions. J Am Coll Cardiol 1992;19:939–45.
23. Lansky AJ, Costa RA, Mintz GS, et al. Non-polymer-based paclitaxel-coated coronary stents for the treatment of patients with de novo coronary lesions: angiographic follow-up of the DELIVER clinical trial. Circulation 2004;109:1948–54.
24. Lemos PA, Mercado N, van Domburg RT, Kuntz RE, O'Neill WW, Serruys PW. Comparison of late luminal loss response pattern after sirolimus-eluting stent implantation or conventional stenting. Circulation 2004;110:3199–20.
25. Mauri L, Orav EJ, O'Malley AJ, et al. Relationship of late loss in lumen diameter to coronary restenosis in sirolimus-eluting stents. Circulation 2005;111:321–7.
26. Fisher LD. Active control trials: what about a placebo? A method illustrated with clopidogrel, aspirin and placebo. Am J Cardiol 2001;141:26–32.
27. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997;50:683–91.
28. Hauck WW, Anderson S. Some issues in the design and analysis of equivalence trials. Drug Inf J 1999;33:109–18.
29. Hasselblad V, Kong DF. Statistical methods for comparison to placebo in active-control trials. Drug Inf J 2001;35:435–49.
30. Stone GW, Ellis SG, Cox DA, et al. One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. Circulation 2004;109:1942–7.
31. Pocock SJ, Assmann SE, Enos LE, Kasten LE. Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems. Stat Med 2002;21:2917–30.
32. Pocock SJ. Clinical trials with multiple outcomes: a statistical perspective on their design, analysis and interpretation. Control Clin Trials 1997;18:530–45.
33. Moussa I, Leon MB, Baim D, et al. Impact of sirolimus-eluting stents on outcome in diabetic patients: a SIRIUS (SIRolImUS-coated BX Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions) substudy. Circulation 2004;109:2273–8.
34. Sawhney N, Moses JW, Leon MB, et al. Treatment of left anterior descending coronary artery disease with sirolimus-eluting stents. Circulation 2004;110:374–9.