Appropriate Uses of Angiographic Follow-up in the Evaluation of New Technologies for Coronary Intervention

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The choice of a primary end point for evaluating the long-term results of percutaneous coronary interventions has come full circle since Andreas Gruentzig first evaluated the initial Zurich experience. At that time, he equated the long-term success of percutaneous transluminal coronary angioplasty (PTCA) (predominantly in patients with single-vessel disease) to ongoing freedom from a composite of ischemic clinical events that included death, myocardial infarction, angina, and repeat revascularization. Subsequently (after 1986), these broad-based clinical end points were largely supplanted by follow-up quantitative angiography, which provided a more precise measurement of late-term failure in terms of the extent of local renarrowing at the initial treatment site. Given the then-current view of restenosis as a binary outcome (prevalent until 1992), however, a variety of definitions of restenosis were used to dichotomize late angiographic findings, many of which did not completely parallel the late clinical recurrence of ischemia. This clinical-angiographic disparity has increasingly troubled many investigators and has led to their devaluing the importance of follow-up angiography. Within the past year, there has been a renewed interest in bringing back composite clinical events as the principal outcome by which the long-term benefits of coronary intervention are measured.

How we choose to evaluate coronary restenosis, however, has tremendous impact on our ability to sort out the winners from the losers among the plethora of current coronary devices and drugs that seek to address what is arguably the most costly ongoing limitation of coronary intervention. Unless the primary end point by which long-term success is judged is sufficiently precise, extraneous noise may obscure the important late clinical events that derive from late failure at the initial treatment site, and thereby lead to misleading conclusions about device efficacy. The composite end points (e.g., death, myocardial infarction, and repeat revascularization) that have served as clinical surrogates for coronary restenosis are attractive because they are easily ascertainable and subsume important cardiac events, but unfortunately they are less precisely linked to failure at the initial coronary treatment site than are the more direct measures derived from follow-up angiography. The purpose of this editorial is to examine the reasons why late angiography (or combined angiographic-clinical end points such as target-vessel revascularization) should remain the gold standard for evaluating restenosis rather than being abandoned in favor of simplistic and purely clinical measures.

Unusual Features of Coronary Restenosis

Unlike other medical or surgical interventions, the pattern of recurrent angina after coronary angioplasty is unusual in that its occurrence is time-limited to between 2 and 8 months after successful angioplasty. By contrast, recurrent symptoms after successful medical therapy or bypass surgery are characterized by a failure rate that increases progressively over the course of many years. The reason for the discrete period of symptom recurrence after angioplasty has been clarified by serial follow-up angiography, which demonstrates variable degrees of renarrowing of initial treatment site in the first 6 months after successful angioplasty, with relative stability of the treatment lumen thereafter.

Once this time course of angiographic restenosis was appreciated, follow-up angiography (generally at 6 months when the healing/renarrowing process was largely completed) was combined with quantitative coronary angiography (QCA), providing a more precise way to describe restenosis compared with the wide variety of less specific clinical signs and symptoms that had been used previously. Since then, angiographic follow-up has remained firmly ensconced as the mainstay of clinical trials involving both conventional angioplasty and newer devices for coronary intervention. The apparent precision of angiographic follow-up as an end point reflecting the durability of a coronary intervention, however, should not be taken as blanket endorsement of the angiogram as the absolute or only meaningful instrument for evaluation. Like all other outcome measures, the late angiogram has both strengths and weaknesses.

Strengths of Angiographic Follow-up

There can be little doubt that routine angiographic follow-up has provided important insights into the ex-
tent to which various interventions acutely enlarge the coronary lumen and how that enlargement relates to subsequent arterial narrowing. Coupled with various computer-assisted quantitative systems for the analysis of coronary angiograms, the classic serial restudies performed separately by Nobuyoshi et al. and Serruys et al. demonstrated that significant loss of lumen diameter is rare before 1 month and has reached a steady state by 6 months after intervention. Nobuyoshi recently demonstrated a similar pattern for loss of lumen after coronary stent placement, explaining why the stented lumen diameter at 6 months and 1 year are nearly identical. Comparisons between acute and follow-up angiograms have provided the underpinnings of newer concepts such as acute gain, late loss, and loss index (the ratio of acute gain to late loss), which form the basis of current restenosis analyses.10,11

With the increasing awareness that both neointimal growth (smooth muscle cell hyperplasia and matrix elaboration) and fibrotic vessel contraction can play a role in the “late loss” that occurs after coronary intervention,12,13 the value of the 6-month angiogram can be enhanced by simultaneous performance of follow-up intravascular ultrasound examination. Coupled with intravascular ultrasound performed immediately after intervention, this technique can discriminate the relative contributions of proliferation and contraction.14 Finally, the performance of angiographic follow-up provides an end point that is specific for the site of coronary intervention. The ability to perform angiographic measurements on the treatment site is not compromised by the persistence or progression of disease at other coronary locations, which may inject confusing “noise” into purely clinical (nonangiographic) end points such as death, myocardial infarction, or recurrent ischemia.15

Weaknesses of Angiographic Follow-up

Incomplete Ascertainment

If an end point is to represent the behavior of the treated population as a whole, it must be measured in essentially every patient. Otherwise, inference made from a smaller “follow-up” subpopulation may be highly confounded by “selection bias” if the choice of which patients were and were not followed up was nonrandom. Such nonrandom bias clearly exists in the case of angiographic follow-up, since patients with recurrent symptoms are clearly more highly motivated to return for follow-up compared with patients who remain free of recurrent symptoms (and are thus less likely to have restenosis).16 When the angiographic follow-up rate falls <80%, extrapolating from the symptom-selected restudy population may give a misleadingly high estimate of restenosis in the patient population as a whole. We have previously estimated the magnitude of this effect by showing a clear difference in the incidence of >50% diameter stenosis between symptomatic (53% restenosis) and asymptomatic (13% restenosis) patients undergoing angiographic follow-up. We thus proposed that symptom status might be exploited statistically to compute the angiographic status of the nonrestudied patients, and thus refine the estimation of outcome for the entire population whenever angiographic follow-up is <80%.16

Cost and Risk

Without question, routine angiographic follow-up adds significantly to the cost of performing clinical trials with new devices. Even in a “no-frills,” two-arm, 600-patient trial (as required to provide adequate statistical power to evaluate a device hoped to reduce restenosis from 41% to 29%), follow-up angiography may cost nearly $2 million. Any such costs not borne by third-party payers must be picked up by device manufacturers when they reimburse study centers for follow-up examinations that are not necessary on purely clinical grounds. With growing FDA insistence on randomized trials as part of the premarket evaluation of new devices, the cost of follow-up angiography adds significantly to the +$20 million cost of bringing a new device through the FDA process.

While Litvack et al. are correct in pointing out that there are small but real patient risks to the performance of routine follow-up angiograms,2 these risks are substantially less than those for clinically driven angiography (which is performed on a population including more patients with unstable ischemic syndromes). These risks should be further minimized by insistence that follow-up examinations for study protocols be performed by the most experienced angiographers at each site. In no event, however, does the risk of such follow-up exceed 0.1%, a level deemed acceptable by both Human Subjects Committees and the patients who give their informed consent for participation in these trials. Another risk not mentioned by Litvack et al is the risk that the angiographer performing the follow-up angiogram will succumb to the “oculostenotic” reflex and perform a repeat intervention to treat a borderline lesion detected by follow-up angiography in a patient with no clinical indications of ischemia, with a 1% risk. In current trials coordinated at our center, eg, the Balloon versus Optimal Atherectomy Trial (BOAT), the protocol design thus calls for the operator to review clinical and exercise data and to then commit before the follow-up angiogram is performed as to whether repeat intervention would be clinically necessary if significant treatment site renarrowing is found.

Accuracy of Measurement

Although some clinical trials have been performed with visual estimation of late stenosis severity or with hand-held digital calipers, the current standard is computer-assisted QCA.17,18 These systems project and enlarge a selected cineangiographic frame into a high-resolution TV camera. The resulting scanned image is digitized, and a computer is used to define the edge of the index vessel by looking at pixel-by-pixel gradients in optical density. This provides precision as fine as 0.1 mm (100 μm) for repeated measurements.

High precision of repeat measurement on the same QCA system, however, does not guarantee high levels of agreement among trials performed with different QCA systems. Because of differences in the edge-detection algorithm used by such systems (eg, relative weighting of the first and second derivatives of the density gradient), the angiographic restenosis rate of similar de novo native lesions treated by conventional angioplasty has varied from 57% in the CAVEAT trial19 to 43% in STRESS20 to 32% in BENESTENT,21 reflecting differ-
ences in which specific QCA systems were used rather than any true biological differences in conventional PTCA results among these three trials. While these issues are not a problem within any single randomized trial, they must be kept in mind when results are compared between trials.

**Measurement of Long-term Success and Failure**

How we interpret treatment success and treatment failure after coronary angioplasty lies at the heart of the current disagreement about the superiority of clinical versus angiographic follow-up. While we agree with Litvack et al. that late success must be grounded in real clinical events, the definition of long-term success must take into account the somewhat limited treatment aims of coronary angioplasty.

Unlike many other medical or surgical treatments that are aimed at prolonging life (such as chemotherapy for cancer or bypass surgery for left main disease), coronary interventions are directed primarily at improving quality of life by the treatment, in most cases, of a single “culprit” stenosis. Long-term survival per se is thus far from a sensitive measure of how well a coronary interventional success has met its long-term aims, particularly when the intervention does not provide complete revascularization or prevent progression of coronary disease at other sites. Since myocardial infarction frequently results from plaque rupture of previously nonobstructing atherosclerotic plaques (and is rarely the consequence of restenosis), the measurement of myocardial infarction is also an insensitive end point for assessing the long-term outcome of coronary intervention. While restenosis lesions may cause angina or trigger repeat revascularization, too many of these late events are the result of disease elsewhere, compromising their ability to serve as a clean measure of the long-term success of an intervention that has treated one particular 10-mm-long segment of coronary artery.

Thus, although it may be appropriate to analyze “any event” when comparing two different strategies for managing coronary disease (eg, a comparison of angioplasty versus surgery for patients with multivessel coronary disease), hesitantly application of the composite “any event” end point to measure the durability of an intervention that addresses only a specific site in the coronary tree is fraught with problems. The consequent “noise” injected by the persistence or progression of disease at other sites may even create the impression that there is a frank dissociation between angiographic follow-up findings and late patient clinical status. With the increasing FDA focus on demonstrating clinical benefit, this apparent discrepancy between clinical and angiographic end points has brought the latter into questionnable status.

While the stochastic behavior of traditional “any event” end points after coronary intervention does not always parallel coronary restenosis as defined by serial angiographic studies, we feel that this low correlation is not a true disparity but rather an artifact that results from differences in measurement efficiency. Current composite clinical end points, which are used to infer treatment site failure, are simply no match for the angiogram with its computerized quantitative precision. Much of this apparent discrepancy between angiographic and clinical end points, moreover, can be resolved by simply filtering late clinical events into those that are and are not related to the index treatment site. This is generally possible even in trials that have less than complete angiographic follow-up, since patients with clinical problems usually undergo angiography during the evaluation and treatment of their symptoms. The result of such angiography then allows the clinical problem to be “filtered” as to whether it does or does not reflect a “target-vessel” or “target-lesion” failure. As such, trials like STRESS or BENESTENT (which failed to show an overall clinical benefit of stenting using “any event”) did show statistically significant reductions in “target-vessel revascularization” (clinically indicated repeat revascularization of the target site) for stenting compared with conventional angioplasty.

**Balanced Role for Angiographic Follow-up**

When the strengths and weaknesses of angiographic follow-up as an end point for new device evaluation are balanced, several points emerge.

1. Routine follow-up angiography continues to provide important mechanistic information, particularly if it is combined with follow-up intravascular ultrasound. Although most current devices have demonstrated a similar relation between acute and late results (by virtue of a loss index of 0.4 to 0.6) that points toward the need for obtaining optimal acute results, there is no guarantee that newer interventions (therapeutic ultrasound, biodegradable stents, coated stents, stand-alone rotablator, etc) will fall into this narrow range or even obey the “proportional injury” model that is the foundation of the loss index. All new devices should thus be subjected to routine angiographic follow-up and QCA evaluation in a first cohort of 100 to 200 patients to define this behavior.

2. Although clinical events should be tabulated, analyzed, and reported for both the acute and follow-up phases of device evaluation, raw “any event” scoring of the 6-month outcome should be deemphasized, because it tends to be excessively contaminated by the persistence and progression of disease at other (nontreated) coronary sites. This contamination underlies the apparent discrepancy between angiographic and “any event” clinical outcomes, but its existence does not impeach the ongoing fundamental value of angiographic end points. Randomized trials designed to show meaningful reduction in restenosis can and should continue to use an angiographic primary end point. With this approach, combined end points would be preserved as a measure of safety, rather than serving as the primary end point itself.

3. Our continued endorsement of the value of angiographic follow-up should not be interpreted as a suggestion that clinical outcomes are unimportant. With increased pressures on health care costs, clinical benefit remains an important leg for the determination of cost effectiveness and should be tabulated. If the goal, however, is to establish the clinical relevancy of improved late angiographic outcomes with new coronary interventions, this should be done using “filtered” clinical end points, such as target-vessel revascularization, that make use of clinically driven angiographic fol-
low-up and more closely reflect the status at the treatment site.

4. The statistical power of the precisely measured and continuously distributed lumen dimensions (obtained by angiography and intravascular ultrasound) is much higher than binary clinical event end points. This discrepancy allows for a trial to be structured favorably so that only a small subset of patients is required to have angiographic follow-up. The overall sample size for such a trial may thus be determined based on the less powerful binary clinical event (such as target-vessel/site revascularization), while only a smaller subset (chosen in an unbiased way from clinical sites with proven records of high angiographic follow-up) need be designated to undergo angiographic follow-up. If anything, such a compromise enhances the importance of the “filtered” clinical end point, without sacrificing the precision of follow-up angiography to measure a more quantitative interventional outcome.

In summary, we believe that recent progress in evaluating the late outcomes of coronary intervention do warrant a reconsideration of the primary role of angiographic follow-up in the evaluation of new devices. This is particularly true in light of newer “filtered” clinical end points such as target-vessel revascularization. Even so, QCA follow-up remains critically important to understanding mechanistic issues. In the future, randomized trials may move away from an angiographic primary end point (with important secondary end points such as target-vessel revascularization, as well as death, myocardial infarction, etc.) and toward more purely clinical primary end points (such as target-vessel revascularization, with follow-up angiography restricted to patients with clinical symptoms). If so, this will pose important questions for the FDA, device manufacturers, and the medical community in general. For now, however, we believe that angiographic follow-up remains the gold standard.

References


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