Correspondence

Letters to the Editor will be published, if suitable, as space permits. They should not exceed 500 words (typed double-spaced) in length and may be subject to editing or abridgment.

How to Estimate Restenosis Rate

Kuntz et al. correctly note that patients referred for repeat angiography are preferentially selected on the basis of recurrent symptoms or ischemic exercise test responses and that this selection bias results in an overestimation of the restenosis rate following coronary angioplasty. They say that no suitable way to detect and correct the errors resulting from this selection bias has been devised, and they go on to develop what they call a “predictive method” to assess the rate of restenosis following coronary angioplasty. In fact, their approach is identical to one previously developed to correct the errors in sensitivity and specificity resulting from the preferential referral of positive test responders for diagnostic verification.2-6 Unfortunately, the parity of the two approaches (along with a few technical errors) is obscured by a formal appendix that is long on mathematical symbolism and short on verbal description.

Suppose we consider recurrent symptoms or an ischemic exercise test response a “positive” (or what they call a “nonelective”) clinical evaluation with respect to the diagnosis of restenosis and the absence of these observations as a “negative” (or “elective”) clinical evaluation with respect to the diagnosis of restenosis. If we evaluate a population of patients following angioplasty in this way and refer everyone (the “positive” and the “negative” responders) for repeat angiography, we can classify our clinical evaluation according to the 2×2 matrix illustrated in Table 1 and calculate the actual rate of restenosis as:

\[
\text{Actual restenosis rate} = \frac{\text{True-positives (TP)} + \text{false-negatives (FN)}}{\text{Total positives} + \text{total negatives}}
\]

or

\[
\text{Actual restenosis rate} = \frac{\text{TP} + \text{FN}}{\text{TP} + \text{FP} + \text{(FN+TN)}}
\]

where FP is false-positives and TN is true-negatives.

But if we exercise “good clinical judgment” and thereby refer only some proportion \( p \) of the “nonelective” patients with a “positive” test response and some (smaller) proportion \( q \) of all the “elective” patients with a “negative” test response to angiography, we can classify only a portion of the total population (that summarized in Table 2). If \( p \) and \( q \) are not equal—that is, if the proportion of patients referred for angiography depends in some way on the test response—the observed restenosis rate will not be the same as the actual restenosis rate:

\[
\text{Observed restenosis rate} = \frac{\text{TP} \cdot p + \text{FN} \cdot q}{\text{TP} + \text{FP} \cdot p + \text{(FN+TN)} \cdot q}
\]

### TABLE 1. A Conventional Binary Classification Matrix With Respect to Restenosis

<table>
<thead>
<tr>
<th>Test response</th>
<th>Restenosis</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>TP</td>
<td></td>
<td>FP</td>
</tr>
<tr>
<td>Negative</td>
<td>FN</td>
<td></td>
<td>TN</td>
</tr>
</tbody>
</table>

TP indicates number of true-positives; FP, number of false-positives; FN, number of false-negatives; and TN, number of true-negatives.

### TABLE 2. Effect of Selection Bias on the Observed Classification Matrix

<table>
<thead>
<tr>
<th>Test response</th>
<th>Restenosis</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>TP \cdot p</td>
<td></td>
<td>FP</td>
</tr>
<tr>
<td>Negative</td>
<td>FN \cdot q</td>
<td></td>
<td>TN</td>
</tr>
</tbody>
</table>

\( p \) indicates proportion of positive responders referred for verification; and \( q \), proportion of negative responders referred for verification.

We can now substitute the empirical values observed by Kuntz et al into this equation:

\[
\text{Observed number of true-positives: TP} \cdot p = 53
\]
\[
\text{Observed number of false-positives: FN} \cdot q = 19
\]
\[
\text{Observed number of verified positives: (TP+FP)} \cdot p = 100
\]
\[
\text{Observed number of verified negatives: (FN+TN)} \cdot q = 149
\]
\[
\text{Observed restenosis rate} = \frac{53 + 19}{100 + 149} = 0.29
\]

But since the proportions \( p \) and \( q \) are known, we can use these values to compute the actual number of true-positives and false-positives and thereby estimate the actual restenosis rate:

\[
\text{Actual restenosis rate} = \frac{(TP \cdot p) + (FN \cdot q)}{(TP+FP) \cdot p + (FN+TN) \cdot q}
\]

Verification rate for positives: \( p = 100/103 = 0.97 \)
Verification rate for negatives: \( q = 149/198=0.75 \)

\[
\text{Actual restenosis rate} = \frac{53/0.97 + 19/0.75}{100/0.97 + 149/0.75} \approx 0.26
\]

The logarithm of the ratio of \( p \) to \( q \) is a linear measure of the magnitude of the error resulting from selection bias. The standard error and 95% confidence interval associated with the estimated restenosis rate are readily computed but not in the way described by Kuntz et al.1 Their standard errors are computed under the improper assumption that all the component errors are independent and uncorrelated,8,9 and their confidence intervals are based on the assumption that the underlying distributions are gaussian rather than binomial.10 As a result, they underestimate the magnitude of error by 24% and the width of the confidence interval by 27%. A BASIC computer program that performs the appropriate calculations with respect to restenosis rate (the putative binary outcome) is available on request. This program is readily modified to deal also with late percent stenosis (the analogous continuous outcome). Please enclose an MS-DOS formatted diskette.

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References
1. Kuntz RE, Keaney KM, Senerchia C, Bain DS. A predictive method for estimating the late angiographic results of coronary...

Reply

We appreciate the similarities that Diamond has pointed out between our predictive method2 (which corrects for bias introduced by incomplete angiographic follow-up when patients with or without anginal symptoms are recruited differentially) and a method that he previously adapted to correct for errors in diagnostic test sensitivity and specificity given differential referral based on patient test response. Both algorithms extrapolate the outcome of interest from an incomplete sample composed of two different underlying groups—stratified by a confounder such as symptom status or positive test response. While verification bias described by Diamond thus has similarities to selection bias as discussed in our article, the contrast between coronary restenosis as a continuous process and the necessary dichotomization of disease in assessing diagnostic test characteristics underscores the substantial differences in the derivation and application of any correction. While the extrapolation concept used by the two methods (outlined in Diamond's letter) is thus quite simple and logical, the estimation of variance and confidence intervals for our predictive result was unique and differs substantially from that found in Diamond's confidence coverage (according to his program written in BASIC). Moreover, his method proves to be overly conservative using our simulation models. We therefore stand by our predictive method as the preferred way to estimate coronary restenosis when incomplete ascertainment is present and continue to recommend it over the approach suggested by Diamond.

We also reemphasize that the goal of our study was to adjust estimates of coronary restenosis for biases due to incomplete angiographic follow-up. We and others have developed concepts that regard restenosis as a continuous rather than dichotomous process,2-4 in which the late percent stenosis is a continuous outcome that is normally distributed. While this unconditional mean estimate was our preference, we also considered binary restenosis as an unconditional probability, using a binomial distribution (see "Appendix"). Diamond correctly points out the latter is mathematically equivalent to the one he obtained by using the conventional binary classification matrix of test response and disease (see Table 1 of Diamond's letter). Once his notation (e.g. true-positive/false-negative) is matched to our end points, the revision of his previous BASIC program is straightforward for the binary case (restenosis rate). In the continuous case (i.e., late percent stenosis), Diamond's attempt to expand his model of test positivity (positive test and disease present) to the continuous end point of restenosis is unintuitive and imprecise.

The previous work developed by Begg and Greenes5 on which Diamond's methods are based was designed to assess the discriminatory properties of a diagnostic test rather than to assess disease prevalence. Specifically, Begg and Greenes derived adjustments for estimates of sensitivity and specificity in the presence of verification bias. While their adjustment for verification bias has mathematical similarities to our adjustments for selection bias, we object to the notion that these two conceptually different paradigms are interchangeable. On the one hand, Begg and Greenes' method calculates sensitivity and specificity conditionally on the presence or absence of disease, without determining the prevalence of disease. Indeed, in the diagnosis of a rare disease, a sampling scheme that preferentially selects diseased individuals ensures adequate patients for analysis. Our study, on the other hand, was aimed at determining restenosis prevalence, using a design predicated on random selection. Thus, there appears to be no natural connection between the two methods which Diamond described as "identical."

Moreover, our derivations of variance were different for the continuous and binary cases. It is thus unclear what Diamond meant by the statement, "Their confidence intervals are based on the assumption that the underlying distributions are gaussian rather than binomial," and equally unclear whether these confidence intervals would be different using Diamond's method. Our method intentionally avoids the dichotomization of restenosis (i.e., disease) in the continuous case, assuming that late percent stenosis is distributed normally and thus uses variance calculations appropriate for normal random variables. Diamond, on the other hand, still tries to apply binary methodology to a continuous outcome. In the binary case, we assume that the prevalence of restenosis (25% late diameter stenosis) was a binomial parameter and thus calculate the variance under the binomial distribution (see "Appendix").

Finally, we have investigated his suggestions further by performing simulations based on the dataset presented in our article and a nominal value coverage probability of 0.95 to evaluate the confidence interval estimation procedures of each method. Under the assumption that the proportion of nonelectives is a random quantity, the coverage probabilities were 0.923 for our predictive variance versus 0.987 for Diamond's variance, suggesting that our variance was slightly underestimated, whereas Diamond's variance was overestimated. However, we actually feel that the proportion of nonelectives should be considered as a known value, unique for each treatment population. Simulations under these assumptions increased our coverage probability to 0.944 but further inflated Diamond's coverage probability to 0.993. We also calculated a bootstrap variance6 of 0.00073, which should be fairly close to the true theoretical variance. Although this was larger than our predictive variance (0.00062), it was considerably smaller than the variance calculated by Diamond's formula (0.00111).

Given these failures of Diamond's application of the methodology for binary test results to the more complex case of a continuous restenosis outcome, we stand by our methods and results, in full.

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References

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G A Diamond

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