Lesion-to-Lesion Independence of Restenosis After Treatment by Conventional Angioplasty, Stenting, or Directional Atherectomy
Validation of Lesion-Based Restenosis Analysis

C. Michael Gibson, MD, MS; Richard E. Kuntz, MD, MS; Masakiyo Nobuyoshi, MD; Bernard Rosner, PhD; and Donald S. Baim, MD

Background. Since many restenosis trials include patients in whom more than one lesion is treated, analysis of the angiographic data on a “per lesion” basis might be confounded by potential correlations of restenosis among multiple treated lesions within each patient. The goals of this study were 1) to determine whether there was any correlation in the rate of restenosis among multiple lesions that underwent conventional angioplasty, stenting, or directional atherectomy within the same patient and 2) to determine whether lesions treated in a multilesion intervention experience a different magnitude of restenosis than lesions undergoing single-lesion procedures.

Methods and Results. Of 441 patients treated by Palmaz-Schatz stenting (n=114), directional atherectomy (n=100), or conventional balloon angioplasty (n=227), 67 underwent multilesion procedures involving treatment of 146 lesions. A general linear model with intraclass correlation (GLIMIC) was used to calculate the coefficient of correlation (ρ) of the change in the measured minimum luminal diameter (late loss) from the time of the initial procedure to 6-month angiogram among the multiple lesions within the same patient for all 441 patients. This showed no correlation among multiple lesions within the same patient for the late loss in minimum luminal diameter (ρ=−0.12 [95% CI: −0.40, 0.12]), among lesions in the same vessel (ρ=0.14 [95% CI: −0.34, 0.62]), or among different vessels (ρ=−0.18 [95% CI: −0.52, 0.16]), suggesting that the magnitude of late loss is independent among multiple lesions within the same patient. There was no difference (p=0.96) between the observed incidence of zero-, one-, and two-vessel restenosis (≥50% diameter stenosis at follow-up) for patients with multiple-lesion treatment and that predicted assuming lesion-to-lesion independence. Similarly, there was no difference in late loss or in the overall binary restenosis rate when single-lesion procedures were compared with multilesion procedures. Multivariable analysis of the late loss in lumen diameter (which adjusted for the effects of the acute result and the device used) demonstrated no independent effect (p=0.20) of single-lesion versus multilesion status.

Conclusions. Luminal encroachment appears to occur at independent rates among multiple lesions treated in a single patient. The observed incidence of restenosis for patients with multiple treated lesions is accurately predicted assuming independent probabilities of restenosis. Lesion-based analysis, even when including multiple treated lesions within the same patient, is thus valid for evaluating conventional angioplasty, stenting, or directional atherectomy. (Circulation 1993;87:1123–1129)

Key Words • restenosis • lesions

The analysis of coronary restenosis after conventional or new device interventions has traditionally been based on either late patient end points (recurrent symptoms or need for revascularization) or late angiographic end points (luminal renarrowing). Because follow-up angiography provides objective quantitative data, a lesion-based angiographic analysis would be preferable. Many published retrospective and prospective trials that attempted to determine the effect of patient characteristics, lesion characteristics, or specific interventions (device or adjunctive pharmacologic therapy) on restenosis have thus relied on lesion-based analyses, even though many patients received treatment for more than one coronary obstruction. 1-10 Such analysis requires two untested assumptions. First, for multiple lesions treated in the same patient, it is assumed that there is no correlation in the restenosis rate among the treated lesions. Otherwise, the calculated variance used for statistical comparison of the treated population would be underestimated. 11-14 One approach to avoid this problem is to choose one lesion per patient for the analysis, 15,16 but this method does not make efficient use...
of all the available angiographic data and introduces obvious selection bias. The second untested assumption for lesion-based analysis is that restenosis behaves equivalently in patients with single-lesion intervention versus patients with multileesion intervention.

We have previously reported that coronary restenosis is a continuous and near normally distributed process. Analysis of restenosis data as a continuous variable by regression techniques and application of a specialized statistical technique that analyzes the intraclass correlation can thus be helpful in determining whether restenosis occurs at independent rates within the same patient. Accordingly, the purpose of this study is both to test the validity of lesion-based analysis by determining whether there is correlation in the rate of restenosis among multiple lesions within the same patient and to test whether the magnitude of restenosis is equivalent among patients undergoing single-lesion or multileesion interventions.

Methods

Study Population

Between June 1988 and January 1991, 143 lesions in 132 patients were treated by Palmaz-Schatz stenting, and 160 lesions in 134 patients were treated by directional coronary atherectomy at the Beth Israel Hospital (Boston). Between January 1986 and January 1988, 229 patients underwent conventional angioplasty of 288 coronary segments at Kokura Memorial Hospital. Protocols approved by the committee on clinical investigations were followed. Follow-up angiography was performed at 3–6 months after coronary intervention in 441 patients (123 stent lesions, 112 directional atherectomy lesions, and 285 conventional angioplasty lesions) representing 89% angiographic follow-up. “Multileesion” intervention was performed on 146 lesions using the same device in the same patient either within the same vessel (68 [46.5%]) or in different vessels (78 [53.5%]).

Angiographic Analysis

Angiographic analysis was performed immediately before and after each new intervention and was repeated 6 months after intervention using the view in which the initial stenosis appeared most severe. Coronary arterial dimensions were determined by caliper measurements made on projected flat images of selected optically magnified cineframes and referenced to the known diameter of the angiographic catheter for stent and atherectomy lesions, with videodensitometry using a Vanguard XR-70 coronary analyzer for conventional angioplasty lesions. Almost all views for analysis were performed on a magnified 5-in. mode with the target lesion and reference guide catheter centered whenever possible. Measurements included the minimal luminal diameter of the treated coronary segment and the reference diameter (taken as the mean diameter of the normal-appearing proximal and distal segment) before and after each intervention and at follow-up. Intravenous nitroglycerin (200 μg) was administered immediately before and after intervention.

Statistical Analysis

Values are reported as mean±SD. Categorical variables were compared by χ² analysis, and continuous data was compared by t test or ANOVA. The late (3–6-month follow-up angiogram) percent diameter stenosis for single-lesion versus multileesion procedures was also compared using a display of the complement of a cumulative distribution. This function plots the proportion of patients exceeding a given percent diameter stenosis on the y-axis versus the percent diameter stenosis of interest on the x-axis.

The independent effect of multileesion intervention versus single-lesion intervention on restenosis was examined using multivariable techniques. Restenosis was analyzed in two ways: 1) as the late loss or the absolute loss in minimum luminal diameter between the immediate postprocedure lumen and the late (3–6-month) lumen and 2) as binary restenosis defined as >50% diameter stenosis at follow-up angiography. The association between the late loss in luminal diameter and selected explanatory variables was tested using linear regression. Independent determinants of restenosis were constructed using step-up multivariable regression techniques in which significant (p<0.10) explanatory variables from univariable models were entered into the multiple model.

A general linear model with intraclass correlation was used to analyze potential correlation among lesions within patients who had multileesion intervention. This method tests for the presence of significant correlation between treated lesions within individual patients, since such correlation would introduce important methodological errors for the variance calculation. The finding of no significant correlation would thus validate lesion-based analysis. The statistical details of this method are presented in the “Appendix.”

The probability of zero-, one-, or two-lesion restenosis per patient may be accurately estimated by simple multiplication of independent probabilities of restenosis if binary restenosis occurs as an independent event in multiple treated lesions within any given patient. The per-lesion restenosis rate was first calculated from all lesions in patients undergoing a two-lesion procedure. Based on this per-lesion restenosis rate, the predicted incidence of zero-, one-, or two-lesion restenosis on a per-patient basis was then calculated. The predicted incidence of zero-, one-, or two-lesion restenosis was then compared with the observed incidence rate of zero-, one-, or two-lesion restenosis on a per-patient basis, using the χ² test.

Results

Clinical Characteristics

Among 441 patients who had angiographic follow-up after either coronary angioplasty (n=227), Palmaz-Schatz stenting (n=114), or directional coronary atherectomy (n=100), 374 had single-lesion intervention and 67 had multileesion intervention. The distribution of the number of lesions treated per patient stratified by the device type is displayed in Table 1. The single-lesion intervention group had a higher percent prior restenosis (43% versus 29%, p<0.002, Table 2) than the multileesion group, but there was no difference in age or the proportion of men between the two groups. Examination of the coronary distribution demonstrated that single-lesion interventions were performed on a higher percentage of left anterior descending arteries...
(51.3% versus 40.4%, p=0.03). Single-lesion procedures were performed in men in 78% of cases while multivessel procedures were performed in men in 68% of cases, but this 10% difference did not achieve statistical significance (p=0.09).

Analysis of the Intraclass Correlation of Late Loss

The intraclass correlation (ρ) of late loss in minimum luminal diameter for multiple treated lesions was −0.12 (95% CI: −0.40, 0.12). Thus, late loss in minimum luminal diameter for multiple lesions within the same patient was not significantly correlated, implying that luminal renarrowing was an independent process among multiple treated lesions within the same patient. Furthermore, subset analysis demonstrated no significant correlation for the late loss among multileisions within the same coronary vessel (n=68, ρ=0.14 [95% CI: −0.34, 0.62]) or among different coronary vessels (n=78, ρ= −0.18 [95% CI: −0.52, 0.16]).

Actual and Predicted Incidence of Restenosis in Patients With Single-Lesion and Multileesion Intervention

In the above continuous-variable analysis, luminal renarrowing (late loss) occurred at independent rates among multiple treated lesions within individual patients. To confirm this independent behavior in a traditional restenosis model, we compared observed incidence of zero-, one-, or two-lesion restenosis as a binary outcome in patients with two-lesion intervention with the predicted incidence assuming independent rates of restenosis. Using a restenosis rate of 36.6% (the per-lesion restenosis rate among two-vessel procedures) the predicted rate of zero-, one-, or two-lesion restenosis per patient was calculated by multiplying probabilities of restenosis assuming independence of the events. The observed incidence of zero-, one-, and two-lesion restenosis among 56 patients undergoing two- vessel angioplasty was not statistically different from the predicted incidence, assuming lesion independence as shown in Figure 1 (p=0.958).

Angiographic Measurements Comparing Single-Lesion Multileesion Intervention

Comparison of single-lesion and multileesion angiographic measurements on a per-lesion basis using ANOVA demonstrated no significant differences in the baseline, procedural, or late (6-month) angiographic measurements for the lesions treated by stenting or directional atherectomy or conventional angioplasty (Table 3) except for a larger preprocedure minimum lumen diameter in the multileesion conventional angioplasty group (p=0.03). The overall binary restenosis rate was 37.4% for single-lesion intervention and 34.9%

TABLE 1. Distribution of the Number of Lesions Treated Per Patient Stratified by Device Type

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Single-vessel</th>
<th>Two-vessel</th>
<th>Three-vessel</th>
<th>Four-vessel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stent</td>
<td>106</td>
<td>14</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Atherectomy</td>
<td>88</td>
<td>24</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Conventional PTCA</td>
<td>180</td>
<td>74</td>
<td>27</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>374</td>
<td>112</td>
<td>30</td>
<td>4</td>
</tr>
</tbody>
</table>

PTCA, percutaneous transluminal coronary angioplasty.

FIGURE 1. Bar graph shows observed incidence of zero-, one-, and two-lesion restenosis in patients undergoing two-vessel angioplasty compared with the predicted incidence assuming that the lesions restenose at independent rates. The restenosis rate in two-vessel procedures was first calculated on a per-lesion basis. Based on this per-lesion rate of restenosis, the rate of zero-, one-, and two-lesion restenosis in multileesion procedures was predicted using multiplication of the per-lesion rates. As shown here, there was no difference between the observed incidence of zero-, one-, or two-lesion restenosis compared with the predicted incidence assuming that the lesions behave independently.

TABLE 2. Baseline Clinical Variables for Patients Treated by Either Single-Lesion or Multileesion Intervention

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Single-lesion procedure (n=374 lesions, 374 patients)</th>
<th>Multileesion procedure (n=146 lesions, 67 patients)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.9±10.5</td>
<td>58.6±10.6</td>
<td>60.4±10.0</td>
<td>0.21</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>76.6%</td>
<td>76.1%</td>
<td>68.6%</td>
<td>0.09</td>
</tr>
<tr>
<td>Prior restenosis (%)</td>
<td>39.2%</td>
<td>43.3%</td>
<td>28.8%</td>
<td>0.002</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
<td>0.03*</td>
</tr>
<tr>
<td>Left main</td>
<td>3 (0.6%)</td>
<td>3 (0.8%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>251 (48.3%)</td>
<td>192 (51.3%)</td>
<td>59 (40.4%)</td>
<td></td>
</tr>
<tr>
<td>Circumflex</td>
<td>91 (17.5%)</td>
<td>54 (14.4%)</td>
<td>37 (25.3%)</td>
<td></td>
</tr>
<tr>
<td>Right coronary</td>
<td>124 (23.9%)</td>
<td>89 (23.8%)</td>
<td>35 (24.0%)</td>
<td></td>
</tr>
<tr>
<td>Saphenous vein graft</td>
<td>51 (9.8%)</td>
<td>36 (9.6%)</td>
<td>15 (10.3%)</td>
<td></td>
</tr>
</tbody>
</table>

*Overall, the proportion of lesions in single-lesion and multileesion procedures was significantly different by χ² analysis.
for multilesion intervention \( (p=0.60) \). Figure 2 shows similar cumulative distributions of the late percent stenosis between single-lesion and multilesion intervention for the overall group. Thus, the binary restenosis rate is similar for single-lesion and multilesion procedures irrespective of the dichotomous definition of restenosis.

**Multiple Linear Regression Model**

There was no difference in binary restenosis \( (p=0.60) \) between single-lesion versus multilesion intervention. To examine the possibility that patients with multilesion intervention had different restenosis characteristics than patients with single-lesion intervention (based on continuous variables), a linear regression model of late loss in lumen diameter was constructed (Table 4). Linear regression demonstrated that the immediate postprocedure luminal diameter was an independent determinant of late loss but not whether the treated lesions were from a single-lesion intervention or multilesion intervention.

**FIGURE 2.** This complement of a cumulative distribution function presents a definition-independent view of restenosis. The percent stenosis at follow-up is displayed as a cumulative distribution of all multilesion and single-lesion procedures. The value on the y-axis represents the percent of lesions whose percent stenosis at follow-up is greater than the corresponding value on the x-axis. Thus, restenosis can be defined as any follow-up percent stenosis, and the proportion of the study group satisfying that definition can be calculated. For instance, if a \( \geq 50\% \) stenosis definition is used, then 37.4\% of single-lesion procedures and 34.9\% of multilesion procedures experienced restenosis.

**Table 3. Angiographic Measurements Stratified by Single-Lesion Versus Multilesion Intervention and by Device Type**

<table>
<thead>
<tr>
<th></th>
<th>Stents</th>
<th>Atherectomy</th>
<th>PTCA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single-lesion</td>
<td>Multilesion</td>
<td>Single-lesion</td>
</tr>
<tr>
<td></td>
<td>( n=106 )</td>
<td>( n=8 )</td>
<td>( n=88 )</td>
</tr>
<tr>
<td>Reference diameter (mm)</td>
<td>3.38±0.66</td>
<td>3.60±0.60</td>
<td>3.15±0.69</td>
</tr>
<tr>
<td>Initial lesion diameter (mm)</td>
<td>0.77±0.54</td>
<td>1.0±0.61</td>
<td>0.68±0.34</td>
</tr>
<tr>
<td>Postprocedure diameter (mm)</td>
<td>3.48±0.65</td>
<td>3.64±0.62</td>
<td>2.96±0.57</td>
</tr>
<tr>
<td>Acute gain (mm)</td>
<td>2.71±0.72</td>
<td>2.64±0.76</td>
<td>2.29±0.62</td>
</tr>
<tr>
<td>Follow-up lumen diameter (mm)</td>
<td>2.13±0.96</td>
<td>2.34±1.06</td>
<td>1.84±0.98</td>
</tr>
<tr>
<td>Follow-up stenosis (%)</td>
<td>33.8±26.2</td>
<td>33.9±28.9</td>
<td>39.3±28.7</td>
</tr>
<tr>
<td>Late loss (mm)</td>
<td>1.35±1.0</td>
<td>1.30±1.48</td>
<td>1.12±0.95</td>
</tr>
</tbody>
</table>

PTCA, percutaneous transluminal coronary angioplasty.

\*\( p<0.05 \) comparing single-lesion and multilesion procedures for the same device.

**Discussion**

**The Problem of Multilesion Intervention in Restenosis Analysis**

The analysis of restenosis data is complicated by the fact that there are often multilesion procedures performed within the same patient, making several lesions available for analysis. One approach to the analysis of multiple treated lesions within the same patient is to average the data from each of the multiple lesions to provide single values comparable to patients who had single-lesion intervention. An analogous patient-based analysis has been used in atherosclerosis regression trials\(^2\) in which the single data point reflects the average lesion change within the patient as a whole. Such analysis may be oversimplistic, since the behavior of individual lesions that are responsible for clinical events such as angina and myocardial infarction is obscured.\(^2\) For instance, in a patient who has undergone a multilesion procedure, severe restenosis within a single lesion may result in recurrent angina, whereas the other dilated lesions within the same patient may remain quiescent. Averaging the data from all the lesions in such a patient would thus dissociate the clinical event of angina from an unremarkable or favorable average change in percent stenosis.

A lesion-based approach would be desirable compared with the patient-based approach because it makes more efficient use of limited angiographic data and increases the statistical power of the study.\(^4\) Although a lesion-based analysis is appealing, potential methodological problems limit its use.\(^11-14\) If there is homogeneity or correlation in the magnitude of restenosis (luminal narrowing) among multiple lesions within the same patient, then the variance of the population will be underestimated, leading to spurious significant differences between groups, when in fact, no such differences exist.\(^11-14\) Because of these concerns, some investigators have selected only one lesion at random for restenosis analysis in patients in whom multiple lesions were dilated.\(^15,16\) This approach, however, is limited by potential selection bias and by its failure to make the most efficient use of all the available angiographic data.

Previously, we have applied a general linear model with intraclass correlation to the analysis of atherosclerosis regression data to correct for any correlation among multiple lesions within individual patients in a
Multilesion restenosis was defined as the incidence of restenosis in patients undergoing multilesion procedures, based on the findings of Vandormael et al. The cumulative distribution of late loss due to restenosis was similar to that expected based on the number of lesions treated. However, the incidence of restenosis was higher in patients undergoing multilesion procedures compared to single-lesion procedures, indicating that the presence of multiple lesions may be an important determinant of restenosis.

Our finding that the incidence of zero-, one-, and two-lesion restenosis in patients with multilesion procedures follows the distribution that was predicted assuming lesion independence differs from the findings of Lambert et al., who found that the incidence of restenosis in patients with multilesion procedures did not follow the expected binomial distribution. This study may have been limited, however, by a low angiographic follow-up rate (64%) and the fact that more symptomatic than asymptomatic patients were available for re-study, potentially biasing estimates of the restenosis rate.

**Comparison of Single-Lesion and Multilesion Procedures**

Coronary stenoses undergoing single-lesion intervention did not experience more late loss in lumen diameter compared with lesions involved in multilesion procedures. In the multivariable model of lumen narrowing, the postprocedure lumen diameter was the only significant explanatory variable in the determination of the late loss in lumen diameter, not the variable denoting single-lesion versus multilesion intervention. There was also no difference in restenosis according to a traditional definition (≥50% diameter stenosis) for single-lesion and multilesion procedures. Furthermore, the cumulative distribution of late percent stenosis shown in Figure 2 shows that the late results were nearly identical for single-lesion and multilesion procedures independent of the definition of restenosis used.

The higher incidence of restenosis in patients undergoing multilesion procedures reported in some studies is probably due to the fact that there are simply more arteries available to experience restenosis in these patients rather than a higher rate of restenosis on a per-lesion basis in these lesions. This is demonstrated clearly in the per-patient analysis of the current data set. Whereas 37.4% of patients undergoing single-lesion procedures experienced restenosis, 10.4% of multilesson patients experienced multilesson restenosis (all lesions restenosed), and 52.2% of these patients experienced restenosis of at least one lesion (mixed restenosis response), for a total of 62.6% of multilesson patients experiencing restenosis in at least one lesion.

**Limitations**

The angiographic follow-up rate is incomplete (89%); however, it is higher than that reported in a previous study (64%) that addressed related questions. Electronic calipers were used to quantitate the lumen diameters; it has been shown in the past that there is no difference between electronic calipers and videodensi-
tometric measurements in undilated lesions.18,19,21 This study assumes that there is also good agreement between electronic caliper and videodensitometric edge detection measurements in the assessment of post-PTCA lesions. There was a mean of 2.1 lesions per multilession patient (range, 2–4). A larger number of lesions per patient would permit a more precise calculation of the intraclass correlation. The confidence intervals for the estimate of ρ are wide, but even if one assumes that ρ is the largest value in the 95% confidence interval (0.12), then this value is still small and indicates that the magnitude of intraclass correlation is minimal at best. In the subgroup analysis of multiple lesions within the same vessel, the 95% confidence interval for the intraclass correlation coefficient did extend as high as 0.62, indicating that a moderate correlation may exist. Further studies with a large number of lesions dilated in each patient would be needed to independently confirm these results. Although the majority of multilession cases were conventional PTCA procedures, the general linear model of intraclass correlation controls for each of the various device types as a potential covariate. Further studies with a larger number of new devices per patient would also be useful. Although many years of follow-up would be useful to detect concordance in the behavior of lesions in an atherosclerosis regression trial, restenosis usually occurs within months of the procedure, and a longer period of follow-up in these patients would be unlikely to detect a significant correlation among lesions.

Conclusions

Luminal renarrowing occurs at independent intervals within the same patient when multiple lesions are dilated. The fact that multiple lesions within the same patient seem to behave independently justifies a lesion-based analysis of angiographic restenosis data. There is also no apparent difference between single-lesion and multilession procedures in the magnitude or incidence of restenosis, and therefore angiographic data from these two types of procedures can be analyzed together.

Acknowledgments

We would like to thank Marion McPhee for her statistical programming assistance and Cynthia Senerchia, RN, MS, for her assistance in creating the new device data base.

Appendix

A general linear model with intraclass correlation11–14 was used to calculate the coefficient of correlation ρ among multiple lesions within the same patient for the late loss in luminal diameter according to the following procedure:

\[ y_{ij} = \alpha + \beta x_{ij} + \gamma z_{ij} + \sum_{l=1}^{q} \lambda_l w_{il} + \epsilon_{ij} \]  

(1)

where \( y_{ij} \) = late loss in arterial diameter over 30 months, \( i = \text{subject; } j = \text{lesion within subject, } x_{ij} = \text{initial arterial diameter, } z_{ij} = \text{device type indicator variables, } w_{ij} = \ldots, w_{iq} \) are a group of other covariates, and

\[ \epsilon_{ij} \sim N(0, \sigma^2), \rho(\epsilon_{ij}, \epsilon_{jk}) = \rho, i = 1, \ldots, n, j = 1, \ldots, k_i \]  

(2)

where \( \rho \) is the correlation between residuals. Thus, there are \( n \) persons where the \( i^{th} \) person contributes \( k_i \) lesions to the analysis. Therefore, one can treat this as a general linear model problem with intraclass correlation and estimate both the regression coefficients and their statistical significance as well as the correlation among multiple lesions all in the same analysis. The covariates controlled for in this model included the initial lesion diameter, the postprocedure luminal diameter, the reference segment diameter, the lesion location, whether the lesion had restenosed previously, and patient age and sex. All lesions were included in the model in order to estimate the \( \beta \)-coefficients in the regression model. The calculation of the intraclass correlation coefficient of correlation was based on the analysis of all 520 lesions from 441 patients.

References

Lesion-to-lesion independence of restenosis after treatment by conventional angioplasty, stenting, or directional atherectomy. Validation of lesion-based restenosis analysis.

C M Gibson, R E Kuntz, M Nobuyoshi, B Rosner and D S Baim

_Circulation_. 1993;87:1123-1129
doi: 10.1161/01.CIR.87.4.1123

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/87/4/1123

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/