Repeat Interventions as a Long-Term Treatment Strategy in the Management of Progressive Coronary Artery Disease

KENNETH G. LEHMANN, MD, FACC, ARTHUR C. MAAS, MD,* RON VAN DOMBURG, MS,* PIM J. DE FLEYTER, MD, PhD, FACC,* MARCEL VAN DEN BRAND, MD, PhD, FACC,* PATRICK W. SERRUYS, MD, PhD*

Rotterdam, The Netherlands and Seattle, Washington

Objective. This study investigates whether repeat coronary interventions, applied over an extended time period, can successfully curtail the progression of ischemic symptoms and angiographic lumen narrowing.

Background. Coronary artery disease is a chronic and generally progressive disorder, and potential treatment strategies should be examined and compared with this chronicity in mind. Percutaneous interventional revascularization procedures could theoretically be useful in controlling progression of the disease through repeated use as new coronary lesions arise. However, the outcome of this long-term management concept has not previously been subjected to detailed investigation.

Methods. From a consecutive series of 4,357 interventional cardiac procedures, 544 patients were identified who received two or more interventions during the 13-year study period. These patients were categorized into one of three groups: restenosis (repeat interventions limited to the same target segment, n = 261), new stenosis (all repeat interventions directed to stenoses not previously treated, n = 155) or both (repeat interventions directed both to the same and to different target lesions, n = 128).

Results. Two to five procedures were performed per patient; the time period (mean ± SD) separating each procedure was significantly less (p < 0.0001) for the restenosis group (4.2 ± 2.3 months) than for the new stenosis (24.2 ± 23.5 months) or the “both” groups (11.4 ± 11.0 months). Despite the need for repeat procedures, the severity of angina (mean New York Heart Association functional class 1.6 ± 0.9) after 6.2 ± 2.3 years of follow-up was substantially better than before the initial procedure (mean functional class 3.2 ± 0.8), with a similar magnitude of change found in all three groups. This long-term functional improvement was mirrored by a corresponding anatomic improvement, with the mean number of diseased vessels remaining constant at the time of each procedure (1.5 ± 0.7, 1.5 ± 0.7 and 1.6 ± 0.7, respectively, for the first, second and third procedures, p = NS). The restenosis and the new stenosis groups also demonstrated statistically similar annual rates of mortality (1.9% vs. 1.8%) and coronary surgery (2.3% vs. 2.6%), although the restenosis group had a lower rate of infarction (1.4% vs. 3.2%, p = 0.002).

Conclusions. Repeat interventional treatment of newly acquired stenoses provides a rational approach for the long-term management of chronic coronary artery disease. In addition to yielding a favorable late outcome, the use of this strategy can result in sustained functional improvement and can check the progression of clinically significant stenoses.

(J Am Coll Cardiol 1996;27:1398–405)
However, repeat procedures can also be used to treat new coronary stenoses that may arise years after a successful initial intervention. Relative to a second or third coronary operation, repeat percutaneous intervention provides a potentially more attractive approach for several reasons. 1) Medical expenses and patient recovery time are generally lower (15-17), reducing the financial and social burden of multiple additional procedures. 2) Repeat intervention can be attempted with anticipated success and complication rates comparable to those of patients undergoing a first intervention. 3) Repeat percutaneous procedures can probably be continued in the future even as a patient ages or acquires comorbidities, factors that could preclude candidacy for repeat bypass operation (18-20).

Despite its inherent appeal, the utility of repeat percutaneous coronary intervention as a long-term management strategy for new lesions has not previously been subjected to detailed formal investigation. This issue is examined in the present study derived from the 13-year experience of a high volume center.

Methods

Study patients. Participants in this investigation were derived from the 4,357 consecutive interventional cardiac procedures performed at the Thoraxcenter between September 1980 and April 1991. This latter date provided a minimum of 2.5 years of follow-up for every patient in the study. Additional criteria for entrance into the current study consisted of 1) two or more interventional procedures performed at this or another facility; 2) a minimum of 7 days separating each procedure to help eliminate planned staged procedures or unplanned repeat intervention due to complications arising from the initial procedure; and, 3) first interventional procedure performed for either stable or unstable angina but not for evolving myocardial infarction. Potential candidates were identified using the Thoraxcenter interventional data base, with final acceptance contingent on verification and thorough review of all clinical and procedural records. The 544 patients who satisfied all these criteria form the basis of this report.

Patient classification. Each enrolled patient was assigned to one of three mutually exclusive groups based on location of the target lesion or lesions. The restenosis group had repeat interventions limited to the same target segments treated during the initial procedure for each and every subsequent intervention. In the new stenosis group, all subsequent interventions occurred in coronary segments not treated at any time previously. The both group included all remaining patients and consisted of those undergoing repeat interventions directed both to the same and to different target segments; these interventions may or may not have been performed during the same repeat procedure. Target coronary segments treated >12 months after the last intervention in that same segment were considered new stenoses and not restenosis (21). Coronary segmentation was based on the classification scheme of the American Heart Association (22), with stenoses >50% considered clinically significant. All patients with one or more repeat procedures performed in a contiguous coronary artery segment (such as the proximal left anterior descending artery in the first procedure and the mid left anterior descending artery in the second) were analyzed for possible target segment misclassification. Those found by careful analysis of records and cine films to be categorized incorrectly were reassigned to the appropriate group.

Long-term follow-up. Follow-up data were obtained by using two complementary strategies. First, written inquiries on patient whereabouts and vital status were sent to the local Civil Registration Service for each of the 544 participants using their last known address. In The Netherlands, municipal records such as these are generally quite accurate and complete. For patients who had moved to new areas, additional inquiries were undertaken until the location of their current residence was firmly established. Questionnaires were then mailed to all living participants. Patients were queried as to current angina status with the use of a series of questions designed to reliably replicate the New York Heart Association classification scheme. Information on the occurrence, location and timing of cardiac admissions, myocardial infarctions, repeat revascularization procedures and medication use was also requested. Nonresponders were contacted by repeated mailings and ultimately by telephone. Ambiguous responses were also clarified by phone. Overall, 92.7% of personal patient responses were obtained.

Second, additional follow-up data were obtained by record review. This source was used to verify positive patient responses to questions on interval myocardial infarctions and revascularization procedures. Outside records were also sought and obtained for infarctions and procedures occurring at other medical centers. Because of the inherent inaccuracy of the remote recall of symptoms, the medical record was used as the sole source of data regarding the presence and severity of angina pectoris preceding each interventional procedure. The follow-up rate by record review was 97.2%.

Data analysis. The data were analyzed by using the CLINT data base system (23) in conjunction with Biomedical Data Processor version 7.0. Categorical data were compared by using the chi-square statistic. Continuous variables were analyzed by using one-way analysis of variance, with the Tukey multiple range test employed for post hoc intergroup comparisons. Life tables were calculated according to the Kaplan-Meier method, and the generalized Wilcoxon test was selected to detect potential differences between groups. Plus over minus values represent mean value ± SD. Mean differences associated with a p value ≤0.05 were deemed statistically significant.

Results

Baseline patient characteristics. Of the 544 enrolled patients who underwent repeat procedures, 261 (48%) had all subsequent interventions limited to retreatment of their initial target stenoses or stenoses (restenosis group), 155 (28%) underwent repeat interventions limited to stenoses that had
not been treated previously (new stenosis group) and 128 (24%) had subsequent procedures directed both to prior target stenoses and to new target stenoses ("both" group). As detailed in Table 1, the three groups were similar with respect to mean age (57 years), gender (78% men) and the presence of previous myocardial infarction (39%). Prior coronary artery surgery was slightly more common (p < 0.05) in patients in the "both" group. Most patients had severe angina pectoris before intervention (72% in New York Heart Association class III or IV), but the pain pattern was deemed stable in the majority (59%). No statistically significant differences in angina severity or stability were found among groups.

At the time of the initial procedure (Table 1), single-vessel disease was more prevalent in the restenosis group than in either the new stenosis or the "both" group (66% vs. 56% and 53%, respectively, p < 0.01). This observation might be explained in part by a greater propensity of patients with initially more severe disease to develop new lesions requiring intervention in the future. Despite more single-vessel disease, patients in the restenosis group initially received more multi-lesion angioplasty (33% vs. 20% for the new stenosis group, p < 0.05).

Complete angiographic success rates for the initial procedures were high overall (98% vs. 94% vs. 93%, p = NS). The complete failure rate of 0 for the restenosis group reflects the study's requirement of angiographic success in at least one target stenosis in all patients experiencing restenosis in the future. Major complications consisted of urgent coronary bypass surgery in five patients and acute myocardial infarction in nine, with differences between groups statistically nonsignificant.

Repeat procedures. On average, each patient underwent 2.36 interventional procedures; 13 patients underwent the maximal number of 5 interventions. In addition to the per patient analyses described, the data on all 740 repeat procedures were analyzed on a per procedure basis (Table 2). A total of 946 target stenoses were treated during these procedures; the mean number of target stenoses per procedure ranged from 1.08 for the restenosis group to 1.52 for the "both" group.

Single-vessel disease at the time of the initial procedure was substantially more common in the restenosis group (73% vs. 56% for the new stenosis and 51% for the "both" group, p < 0.0001) as were single-lesion interventional procedures (93% vs. 76% and 56%, respectively, p < 0.0001). The left anterior descending artery was a more typical target in the restenosis group (54% vs. 31% and 38%, p < 0.0001). Balloon angioplasty was the sole device used in 86% of repeat interventions, a finding consistent with the era selected for patient enrollment. The use of other devices was equally distributed among groups (p = NS).

Complete angiographic success was significantly less frequent (p < 0.0001) in the new stenosis group (79%) than in the restenosis (91%) or the "both" (89%) group. However, major complications were rare in all three groups (p = NS).

The mean time interval separating each interventional procedure differed considerably among groups (p < 0.0001) (Fig. 1). Whereas patients with restenosis had an interprocedural interval averaging 4.2 ± 2.3 months, patients with new stenosis underwent intervention after a much longer interval of 24.2 ± 23.5 months. Patients in the "both" group had an intermediate interprocedural interval (11.4 ± 11.0 months).

Long-term effect on symptoms and disease severity. Overall, the strategy of repeat interventions appears to have had a favorable impact on angina status (Fig. 2). For this analysis, we censored patients who had incomplete data on initial or final angina status; however, the results were virtually identical when the analysis was repeated without censoring. At the end of 6.2 ± 2.3 years of follow-up, 211 patients (57%) were in functional class I. This group includes 61% of the patients who were in class III or IV before their initial procedure. The mean initial functional class of 3.2 ± 0.8 decreased to 1.6 ± 0.9 at the end of follow-up (p < 0.0001).

This analysis can be further expanded by considering symptom status segregated by groups and stratified by time. Figure 3 reveals that mean functional class was visually and statistically...

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics at Initial Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
</tr>
<tr>
<td>Restenosis (n = 261)</td>
</tr>
<tr>
<td>Age (yr) (mean range)</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Previous MI</td>
</tr>
<tr>
<td>Previous CABG</td>
</tr>
<tr>
<td>Angina severity (NYHA class)</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
<tr>
<td>Indication for procedure</td>
</tr>
<tr>
<td>Unstable angina</td>
</tr>
<tr>
<td>Stable angina</td>
</tr>
<tr>
<td>Coronary disease severity†</td>
</tr>
<tr>
<td>Single vessel</td>
</tr>
<tr>
<td>Double vessel</td>
</tr>
<tr>
<td>Triple vessel</td>
</tr>
<tr>
<td>Extent of procedure*</td>
</tr>
<tr>
<td>Single lesion/single vessel</td>
</tr>
<tr>
<td>Multivessel/single vessel</td>
</tr>
<tr>
<td>Multivessel/multivessel</td>
</tr>
<tr>
<td>Angiographic procedural success</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Partial‡</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Major complications</td>
</tr>
<tr>
<td>Urgent operation</td>
</tr>
<tr>
<td>Acute MI</td>
</tr>
</tbody>
</table>

*p < 0.05, †p < 0.01. ‡Successful treatment... some but not all attempted target stenoses. Values represent means of continuous variables and counts of categoric variables, with percentages indicated by parentheses. CABG = coronary artery bypass surgery; MI = myocardial infarction; NYHA class = New York Heart Association functional class.
### Table 2. Characteristics of Repeat Procedures

<table>
<thead>
<tr>
<th>Procedure Type</th>
<th>Restenosis (no.)</th>
<th>New Stenosis (no.)</th>
<th>Both (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single vessel</td>
<td>230 (71)</td>
<td>100 (56)</td>
<td>126 (51)</td>
</tr>
<tr>
<td>Double vessel</td>
<td>53 (17)</td>
<td>53 (30)</td>
<td>73 (30)</td>
</tr>
<tr>
<td>Triple vessel</td>
<td>33 (10)</td>
<td>24 (14)</td>
<td>48 (19)</td>
</tr>
</tbody>
</table>

**Coronary disease severity**
- Single vessel: 230 (71) vs. 100 (56) vs. 126 (51)
- Double vessel: 53 (17) vs. 53 (30) vs. 73 (30)
- Triple vessel: 33 (10) vs. 24 (14) vs. 48 (19)

**Indication for procedure**
- Acute MI: 3 (1) vs. 10 (6) vs. 7 (3)
- Unstable angina: 72 (23) vs. 41 (25) vs. 76 (31)
- Stable angina: 239 (76) vs. 126 (71) vs. 164 (66)

**Type of procedure**
- Balloon angioplasty: 265 (84) vs. 159 (50) vs. 215 (67)
- Coronary stent: 30 (9) vs. 11 (6) vs. 4 (1)
- Directional atherectomy: 19 (6) vs. 4 (2) vs. 6 (2)
- Other: 2 (1) vs. 3 (2) vs. 6 (2)

**Angiographic procedural success**
- Yes: 287 (91) vs. 140 (79) vs. 221 (69)
- Partial: 1 (0) vs. 6 (3) vs. 14 (6)
- No: 26 (9) vs. 31 (18) vs. 13 (5)

**Major complications**
- Death: 3 (1) vs. 0 (0) vs. 1 (1)
- Urgent operation: 6 (2) vs. 6 (3) vs. 4 (2)
- MI: 9 (3) vs. 14 (6) vs. 10 (4)

**Target vessel (946 lesions)***
- RCA: 83 (24) vs. 81 (35) vs. 125 (33)
- LAD: 184 (54) vs. 71 (31) vs. 141 (38)
- LCx: 52 (15) vs. 67 (29) vs. 80 (21)
- Graft: 22 (6) vs. 11 (5) vs. 31 (8)

**Prior procedures (no.)***
- One: 261 (82) vs. 155 (48) vs. 126 (52)
- Two: 44 (14) vs. 22 (12) vs. 79 (32)
- Three: 9 (3) vs. 0 (0) vs. 29 (12)
- Four: 2 (1) vs. 0 (0) vs. 11 (4)

**Time interval between procedures (mo.)***
- Procedure 1 vs. 2: 4.2 ± 2.3 vs. 23.5 ± 23.8 vs. 11.5 ± 17.2
- Procedure 2 vs. 3: 4.4 ± 4.0 vs. 32.0 ± 23.2 vs. 15.2 ± 20.7
- Procedure 3 vs. 4: 6.8 ± 5.3 vs. — vs. 16.6 ± 19.5
- Procedure 4 vs. 5: 4.3 ± 1.5 vs. — vs. 19.3 ± 15.8

*p < 0.0001. **p < 0.05. *Successful treatment of some but not all attempted target stenoses. Values represent means of continuous variables and counts of categoric variables, with percentages indicated by parentheses. LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MI = myocardial infarction; RCA = right coronary artery.

We sought to assess whether this substantial functional improvement in coronary disease severity was mirrored by a corresponding anatomic improvement. Figure 4 displays overall coronary disease severity (quantified by using the mean number of vessels containing significant stenoses) at six different points in time (before and immediately after the first, second and third procedures). As shown, each procedure is accompanied by a statistically similar improvement in disease severity. Moreover, the severity at the start of each procedure does not increase with time but remains relatively constant (1.5 ± 0.7 for the first, 1.5 ± 0.7 for the second and 1.6 ± 0.7 for the third procedure, p = NS).

**Prognosis and clinical endpoints.** The occurrence of major clinical events (death, coronary artery surgery and nonfatal...
Figure 1. Three-dimensional bar graph depicting the mean time interval separating the current percutaneous coronary interventional procedure from its most immediate predecessor. The procedure number is displayed on the x axis, patients segregated into groups on the y axis, and the number of months since the last procedure on the z axis. The difference between groups was highly significant for each procedure number (p < 0.0001), whereas the apparent trend toward greater mean time intervals with later procedures was statistically nonsignificant. There were no fourth or fifth procedures in the new stenosis group.

Figure 2. New York Heart Association classification of angina severity in 366 patients assessed immediately before the initial procedure and at final follow-up. Patients with incomplete data on angina status for either period were excluded. The columns of Roman numerals represent angina classes I through IV; the values in the squares represent the number of patients in that specific angina class at each time period; the thickness of the lines interconnecting the boxes is directly proportional to the number of patients involved; the outside circles present mean values of angina class for the two periods. The overall changes observed were highly significant (p < 0.0001).

Figure 3. Angina severity represented by mean New York Heart Association (NYHA) class, grouped by patients in the restenosis, new stenosis or “both” groups. Data are presented for before the first procedure (one), before the second procedure (two), before the third procedure (three) and for final follow-up (follow-up). The small number of patients undergoing more than three procedures precluded inclusion of additional data points. The groups did not differ significantly from one another at any time point, nor did the overall data differ significantly among the first, second and third procedures. However, the differences between angina status before each procedure and angina status at final follow-up were all highly significant (p < 0.0001).

Discussion

Characteristics of repeat procedures. The clinical decision to attempt repeat intervention obviously depends on many factors, including the likelihood of success, the anticipated frequency of complications and the viability of alternative modes of treatment. Nevertheless, in the current study the threshold for percutaneous intervention, as gauged by preprocedural angina severity, proved to be similar between the initial procedure and all subsequent repeat procedures. This pattern was found with both restenosis and new stenosis. In contrast, the timing of the repeat procedures was quite different.
the current study, and suggest that the anticipated success rates for repeat interventions of new stenoses...by be comparable to that of initial interventions of new lesions.

Impact on symptoms and adverse events. The strategy of repeat percutaneous interventions proved to be quite capable of lessening symptoms of angina pectoris over the long term, with treatment of new stenosis as successful in this regard as treatment of restenosis. During a follow-up interval extending to 13 years, 58% of patients with angina class III or IV initially changed to class I. Each repeat procedure on average was able to reestablish the magnitude of angina relief experienced with the initial intervention.

Outcomes analysis also established a relatively low rate of adverse events for all groups in the study. The 10-year survival rate for our restenosis (81%) and new stenosis (82%) groups was similar to the survival figures observed in the Coronary Artery Surgery Study (24) for both the medical (79%) and the surgical (82%) cohort, although disease severity was probably different in these two studies. The rate of bypass surgery was also statistically similar among three patient groups. Overall, despite a higher prevalence of multivessel disease at baseline, the patients undergoing repeat procedures for new stenoses did as well in three outcome domains (death, bypass surgery and symptomatic relief) as did those who underwent repeat procedures for restenosis, the latter representing a well established and widely accepted treatment strategy.

The observation of a somewhat higher rate of infarction in the new stenosis group than in the restenosis group remains both intriguing and unexplained. It is due in part to the higher rate of periprocedural myocardial infarction observed in the former group during repeat procedures and to the more frequent use of interventional procedures for the treatment of acute infarction in previously untreated stenoses. However, these two factors combined account for only a 10% difference in the observed 10-year infarction rates. Other contributory factors may include a higher prevalence of multivessel disease at baseline and the possibility of “more aggressive” disease associated with the rapid development of new lesions.

Impact on coronary anatomy. Ideally, repeat interventional procedures performed solely for restenosis might be expected to maintain the overall extent of coronary disease at or near a constant level over a prolonged period. In the current study this theory was borne out by the patients in whom this approach was used. In addition, interventions directed exclusively to newly developed stenoses accomplished this same goal. Patients in the new stenosis group had an average of 1.54 vessels with significant disease before the initial intervention, but this number was statistically similar before the second (1.55) and third (1.73) procedures despite a time span of several years. Similarly, the mean number of diseased vessels was 0.55, 0.72 and 0.82, respectively, immediately after the first, second and third interventional procedures. The treatment strategy of multiple repeat percutaneous intervention may therefore be able to check the progression of coronary disease in selected patients over the lifetime of the patient.

Potential limitations of the study. Among possible limitations of the present study is the fact that precise categorization of a new, visualized lesion as either restenotic or new can be difficult or impossible if the stenosis develops near the site of an earlier interventional procedure. Although a prospective investigation of this issue would have enhanced the reliability of our findings, it would probably have proved logically difficult. Second, our conclusions are directly applicable only to the subset of patients whose coronary anatomy and clinical status permit serial interventions. Third, the outcomes observed are derived from procedures performed up to a decade or more in the past. Because interventional cardiology is such a rapidly evolving field, conclusions derived from work done in the 1980s may not be directly applicable to the 1990s. Nevertheless, relative to the current study, the superior safety and efficacy of modern percutaneous interventions may predict an even more favorable outcome for repeat interventional procedures in the future.

Clinical implications. The acute manifestations of coronary artery disease, such as unstable angina pectoris or myocardial infarction, rightly command the greatest attention of cardiologists and cardiac interventionalists. However, this focus often overshadows the inherently chronic nature of the underlying atherosclerotic process. When coronary athrosclerotic is viewed as a lifelong disease, it becomes obvious that procedures performed during a period of heightened symptoms should be considered not as isolation but rather as a single step in a long-term management strategy that may span several decades.

This study helps validate the use of repeat interventional procedures in the management of progressive coronary artery disease. This approach resulted in a clear decrease in symptoms during follow-up of up to 13 years, a period during which coronary bypass surgery used as a single procedure tends to lose its effectiveness (4). Adverse events were relatively infrequent, with a good 10-year survival rate observed. Perhaps most remarkable was the ability of this strategy of multiple repeat procedures to maintain the severity of angiographic disease below its level at initial presentation, even though new stenoses developed during follow-up with regular frequency. These data suggest that the use of repeat coronary interventions should be considered a rational long-term treatment strategy for appropriate patients with atherosclerotic heart disease.

References
4. Talley JD, Hurst JW, King SB III, et al. Clinical outcome 5 years after...


