Beyond Restenosis

Five-Year Clinical Outcomes From Second-Generation Coronary Stent Trials

Donald E. Cutlip, MD; Amit G. Chhabra, MBBS, MPH; Donald S. Baim, MD; Manish S. Chauhan, MD; Sachin Marulkar, MBBS, MPH; Joseph Massaro, PhD; Ameet Bakhai, MD; David J. Cohen, MD, MSc; Richard E. Kuntz, MD, MSc; Kalon K.L. Ho, MD, MSc

Background—In the first year after coronary stent implantation, clinical failures are driven mainly by procedural complications and restenosis, but the subsequent relative contributions of restenosis and disease progression to late failures are less clear.

Methods and Results—We observed 1228 patients for 5 years after the implantation of stents as part of pivotal second-generation coronary stent trials. Clinical events of death, myocardial infarction, repeat revascularization, and repeat hospitalization for acute coronary syndrome or congestive heart failure were attributed to the index stented (target) lesion or other distinct sites (either in the target or other coronary vessels) and further classified as procedural, restenosis, or nonrestenosis. During the first year the hazard rate was 18.3% for target-lesion events and 12.4% for events unrelated to the target lesion. After the first year the average annual hazard rate was 1.7% for target-lesion events and 6.3% for nontarget-lesion events. By the fifth year, restenosis events occurred in 20.3% of patients, whereas 30-day procedural complications or later nonrestenosis events occurred in 37.9%, including 11.4% who also experienced a restenosis event, for a combined cumulative event rate of 46.4%. Diabetes mellitus and multivessel disease were independently associated with increased risk for both restenosis and nonrestenosis events.

Conclusion—In a low-risk clinical trial population, the clinical outcome beyond 1 year after stenting is determined by a high rate of events related to disease progression in segments other than the stented lesion, which itself remains relatively stable. (Circulation. 2004;110:1226-1230.)

Key Words: stents □ restenosis □ prevention

Clinical events after coronary stent implantation can result from procedural complications, restenosis of the index (target) lesion, or the progression of disease at other sites in the coronary tree. Most studies have focused on early events, with clinical follow-up limited to 9 to 12 months. The few studies including longer-term follow-up of the first-generation Palmaz-Schatz stent also have focused on late stability of the target lesion.1-3 Repeat revascularization of the target lesion resulting from restenosis is the most common event during this interval. The interest in restenosis events recently reached a crossroads with the advent of drug-eluting stents that have demonstrated their ability to reduce restenosis rates by roughly 70% compared with bare metal stents.4,5 The true impact of drug-eluting stents and other strategies designed to limit or prevent restenosis, however, can only be fully evaluated against the backdrop of other events resulting from disease progression outside the stented segment(s).

Long-term follow-up of study stent patients enrolled in the second-generation coronary stent trials was mandated after US Food and Drug Administration approval of these devices. We sought to determine the risk and predictors for events related to restenosis and those events that were likely the result of disease progression at other sites during a 5-year period after stenting. The relative contributions of procedural ischemic complications, restenosis, and other late nonrestenosis events to the overall 5-year outcome also were analyzed.

Methods

Study Design

Three randomized trials (ASCENT [ACS Stent Clinical Equivalence in de Novo lesions Trial; ACS MultiLink stent {Guidant}], NIRVANA [NIR Vascular Advanced North American investigational trial; NIR stent {Boston Scientific}], and SMART [Study of Microstent’s Ability to limit Restenosis Trial; AVE Micro II stent...
End Point Definitions

An independent clinical events committee adjudicated all deaths, MIs, and repeat revascularization procedures and assigned attribution to target lesion, target vessel, or nontarget vessel for MIs and repeat revascularizations throughout the follow-up of each study. Death was classified as cardiac unless clear noncardiac causes were identified. Before this analysis, a separate committee assigned attribution to target lesion or nontarget lesion for all deaths. All cardiac deaths within the first year were attributed to the target lesion unless clear evidence of a nontarget-vessel distribution was demonstrated, and later deaths were classified as target lesion if directly related to an MI, which itself was attributed to the target lesion or a complication of a target-lesion revascularization (TLR) procedure. In the periprocedural period, MI was defined as creatine kinase-MB (CK-MB) ≥3 times normal or as the development of new pathological Q waves. During the follow-up period, MI was defined as new onset of ischemic symptoms or ischemic ECG changes with either total CK >2 times normal or new pathological Q waves. MI was attributed to the target lesion unless angiography confirmed a separate lesion in the target vessel or angiographic or electrocardiographic evidence of a nontarget vessel was noted as the only potential source of acute ischemia. TLR was defined as any repeat percutaneous revascularization or surgical bypass of the original target lesion that was driven by clinical findings (presence of ischemic symptoms, a positive functional ischemia study, or both) in the presence of a diameter stenosis ≥50% by quantitative angiography at the angiographic core laboratory. Even if ischemic symptoms and a positive functional ischemia study were absent, revascularization for a diameter stenosis ≥70% determined by the angiographic core laboratory also was considered to be clinically driven. The target lesion was considered to be the area covered by the stent plus a 5-mm margin proximal and distal to the edges of the stent. Target-vessel revascularization (TVR) was defined as clinically driven percutaneous revascularization or bypass of the target lesion or any segment of the epicardial coronary artery containing the target lesion. TLR and TVR that were not adjudicated as clinically driven by the clinical events committee were not included as end points for this analysis. Nontarget-vessel revascularization (non-TVR) was defined as any percutaneous revascularization or surgical bypass of an epicardial vessel other than the target vessel. Acute coronary syndrome (ACS) was defined as new-onset or worsening angina that required hospitalization and was associated with ischemic ST-segment abnormalities, any elevation of cardiac enzymes, or both. Attribution to the target lesion was assigned with the use of the algorithm that was described for MI. Congestive heart failure (CHF) was defined as a new diagnosis of CHF requiring hospitalization and was attributed to the target lesion if it was associated with target-lesion MI or target-lesion ACS. The overall composite end point was defined as any death, any MI, any repeat revascularization, ACS, or CHF. All deaths, MIs, and TVRs occurring within 30 days of the index procedure were considered to be procedure-related complications. Events were considered restenosis events if attributed to the target lesion at any time after 30 days or if attributed to any segment of the target vessel between 30 days and 1 year. Nonrestenosis events were defined as all other events beyond 30 days and any non-TVRs. For multiple occurrences of the same event, the time to the first event was considered to be the time an event point was reached.

Statistics

Heterogeneity among the 4 studies was evaluated for key baseline variables by using χ² or Fisher’s exact tests and for the 5-year composite end-point rate by using Cox proportional hazards regression. No significant differences were detected at the P<0.05 level of significance. Event rates were reported with the Kaplan-Meier survival method. Hazard rates were determined from survival analyses as the rate of occurrence of the event of interest during a subsequent time interval that was contingent on survival free of the event to the end of the preceding time interval. The correlates of restenosis events, nonrestenosis events, mortality, and the 5-year cardiac composite outcome were assessed with the use of Cox proportional hazards regression with forward stepwise selection censoring at 5 years or at the time of the last follow-up. The variables considered for each model were age, gender, diabetes, hypertension, hyperlipidemia, number of diseased vessels, left anterior descending coronary artery target vessel, current smoking, previous MI, previous bypass surgery, lesion length, vessel diameter, periprocedural MI, and baseline left ventricular ejection fraction (LVEF). Baseline patient characteristic data were 97% complete. Values for missing LVEF (158 patients) and lesion length (50 patients) were imputed as minimum median value.

Results

Patient and Lesion Characteristics

Baseline patient and lesion characteristics are shown in Table 1. Patients enrolled in the representative studies were relatively young, with only 12.7% >75 years old. Previous MI or history of previous revascularization procedures was infrequent, and mean LVEF was normal. The treated lesions tended to be focal and were found within large-diameter

Table 1. Clinical and Baseline Angiographic Characteristics (n=1228)

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Median, mean±SD or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y (quartiles)</td>
<td>63 (54, 71)</td>
</tr>
<tr>
<td>Women</td>
<td>388 (31.6)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>263 (21.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>692 (56.7)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>540 (44.4)</td>
</tr>
<tr>
<td>Prior MI</td>
<td>390 (32.3)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>488 (39.7)</td>
</tr>
<tr>
<td>Cigarette smoking in past year</td>
<td>272 (22.1)</td>
</tr>
<tr>
<td>Prior restenosis lesion</td>
<td>207 (16.0)</td>
</tr>
<tr>
<td>Left anterior descending lesion</td>
<td>510 (41.5)</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>394 (32.1)</td>
</tr>
<tr>
<td>LVEF, %, mean±SD</td>
<td>56±11</td>
</tr>
</tbody>
</table>

Quantitative angiography, mm

| Reference diameter, median (quartiles) | 2.92 (2.60, 3.25) |
| Pretreatment MLD, median (quartiles)   | 1.00 (0.76, 1.32) |
| Lesion length, median (quartiles)      | 10.63 (7.86, 15.42) |
| Final MLD, median (quartiles)          | 2.77 (2.53, 3.06)  |

Values are given as n (%), median (quartiles), or mean±SD. MLD indicates minimum lumen diameter.
vessels. Baseline characteristics in the long-term follow-up cohort were similar to those previously reported for the overall population from the pooled studies.6

Clinical Outcomes
The median follow-up interval was 1830 days (5.0 years), with follow-up beyond 4 years in 86% of patients. Follow-up included planned angiographic follow-up at 6 to 9 months in 519 (42%) patients. During the first year, the clinical outcome was determined by perprocedural complications, which were represented mainly by MI and repeat revascularization of the target lesion beyond 30 days resulting from restenosis. During the next 4 years, target-lesion events occurred less frequently, and nontarget-lesion events dominated (see Table 2 and Figure 1). Moreover, some of the target-lesion events beyond 1 year were triggered by nontarget-lesion progression. Of the 57 target-lesion events beyond 1 year, 29 (52%) were performed in association with nontarget-vessel revascularization, including multivessel coronary artery bypass surgery in 19 (32%). Figure 2 shows the overlap and isolated frequencies of procedural, restenosis, and nonrestenosis events. Figure 3 depicts the 5-year event rates for restenosis events, nonrestenosis events, and the overall cardiac composite, demonstrating a steady increase in restenosis events during the first year and virtual absence of restenosis thereafter, despite the ongoing development of other major events, to yield a cumulative 5-year event rate of 46.4%.

Predictors of Restenosis and Nonrestenosis Outcomes
The independent correlates for each of the study end points are shown in Table 3. Notably, the presence of diabetes mellitus and multivessel disease were strong predictors of

<table>
<thead>
<tr>
<th>End Point</th>
<th>Failures</th>
<th>HR</th>
<th>Failures</th>
<th>HR</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Annualized</td>
</tr>
<tr>
<td>Composite</td>
<td>321</td>
<td>26.1</td>
<td>221</td>
<td>25.3</td>
<td>7.2</td>
</tr>
<tr>
<td>All-cause death</td>
<td>11</td>
<td>0.9</td>
<td>78</td>
<td>6.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>9</td>
<td>0.7</td>
<td>44</td>
<td>3.9</td>
<td>1.0</td>
</tr>
<tr>
<td>MI or ACS</td>
<td>104</td>
<td>8.5</td>
<td>76</td>
<td>7.4</td>
<td>2.0</td>
</tr>
<tr>
<td>TLR</td>
<td>146</td>
<td>12.0</td>
<td>57</td>
<td>5.7</td>
<td>1.5</td>
</tr>
<tr>
<td>TVR (excluding TLR)</td>
<td>40</td>
<td>3.2</td>
<td>47</td>
<td>4.5</td>
<td>1.2</td>
</tr>
<tr>
<td>Total TVR</td>
<td>185</td>
<td>15.1</td>
<td>86</td>
<td>8.9</td>
<td>2.4</td>
</tr>
<tr>
<td>Non-TVR</td>
<td>109</td>
<td>8.9</td>
<td>133</td>
<td>12.8</td>
<td>3.5</td>
</tr>
<tr>
<td>CHF</td>
<td>2</td>
<td>0.2</td>
<td>17</td>
<td>1.5</td>
<td>0.4</td>
</tr>
</tbody>
</table>

HR indicates hazard rate, which is the probability of event within a given interval if survived before interval free of event. Cumulative event rates were determined using survival analysis estimates at 5 years.

Figure 1. Hazard rates per year for target-lesion and nontarget-lesion events derived from life table survival analysis. Target-lesion events include any repeat TLR or other event (ie, death, MI, ACS, or CHF) attributed to the target lesion. Nontarget-lesion events include all repeat revascularizations involving the target vessel outside the target lesion, any non-TVR, and any death, MI, ACS, or CHF that was clearly not attributable to the target lesion.

Figure 2. Venn diagram schematic showing relationship of procedural (30-day), restenosis, and nonrestenosis events (see Methods for definitions).
both restenosis and nonrestenosis events. Advanced age, reduced LVEF, and index lesion length were the major predictors of 5-year mortality.

### Discussion

In this study containing long-term clinical follow-up after the implantation of second-generation coronary stents, we found that the stented target lesion was clinically stable after the first 12 months. Thereafter, new events resulted almost exclusively from the progression of disease within other segments of the target vessel or in nontarget vessels and continued to accrue steadily. During years 2 through 5, new TLR was performed in only 5.7% of patients, which may be an overestimate of late clinically significant restenosis events because most late TLR was performed in conjunction with a non-TVR (including surgical revascularization in one third of patients). Although nontarget-lesion events were less common than were target-lesion events during year 1 (12.4% versus 18.3%), they dominated the events during years 2 through 5 (average annual hazard rate 6.3% versus 1.7%). Over the 5-year follow-up, these nontarget-lesion events contributed importantly to the 46.4% overall event rate in our study. This outcome is consistent with earlier studies of the Palmaz-Schatz stent1–3 and suggests that late clinical outcomes have not substantially improved in the modern stent era. Of particular interest, >50% of patients with restenosis events also sustained a nonrestenosis event.

In our study, the predictors of restenosis events and nonrestenosis events at 5 years were similar, with diabetes mellitus and multivessel disease being the strongest independent variables. The finding of an increased risk of restenosis in people with diabetes mellitus and in smaller vessels (which also predicted restenosis events but not nonrestenosis events) is consistent with other studies that evaluated restenosis in the first year after stenting.6,7 The finding of multivessel disease at the time of the index stent procedure as a significant predictor of restenosis events is surprising, however, and may suggest the presence of other risk factors in patients with more diffuse disease at presentation. The finding also may suggest that some of the late restenosis outcomes may have been driven by events related to the progression of disease in nontarget vessels rather than to restenosis or disease progression within the target lesion. These results highlight the particularly high risk of diabetic patients for both restenosis and disease progression.

The 5-year mortality rate of 8.2% was similar to other studies of patients with coronary artery disease,8 despite the baseline low-risk profile of these selected clinical trial patients. The finding of advanced age as a predictor is completely expected in a long-term follow-up study and should not be interpreted necessarily as evidence that stenting poses a unique long-term risk for older patients. The protective effect of hyperlipidemia is interesting: Because the definition of hyperlipidemia included cholesterol >200 mg/dL, or a requirement for medical therapy, it is possible that the protective effect is related to medical therapy. Unfortunately, specific data on medical therapy were not available. Longer lesions were associated with higher mortality risk and may be a marker of more severe atherosclerosis. In this analysis, the occurrence of a periprocedural MI was not a predictor of late mortality. This outcome is in contrast to several other studies and could be the result of better tolerance of periprocedural complications in this low-risk population, or it may indicate that CK-MB elevation is an imperfect marker of diffuse atherosclerosis or other potential confounders.9

The results of our study must be interpreted in light of the data for the latest generation of coronary stents that elute antirestenosis drugs and offer the promise of virtually eliminating the clinical events related to restenosis.4,5 This advance, however, makes the findings of our study even more important. Even if restenosis had been eliminated, the 5-year event rate in our study population would have approached 40% because of the combination of periprocedural and
nonrestenosis events. This result highlights the importance of continuing efforts to reduce early complications, including emergency bypass surgery, stent thrombosis, and distal embolization leading to large MIs. Although drug-eluting stents have reduced events related to restenosis, the reduction of late events unrelated to restenosis also remains a clear target for intervention and future study. In fact, the greatest opportunity for improvement in long-term outcomes is in the prevention of disease progression at other sites through aggressive risk-factor modification with statin therapy and the consideration of long-term therapy with clopidogrel and angiotensin-converting enzyme inhibitors.

Limitations
The study has several limitations. First, the data for stability of the target lesion after 1 year were limited to clinical outcomes, with planned angiographic follow-up in only 42% of the patients. Thus, clinically silent late restenosis or target-lesion atherosclerotic disease progression cannot be evaluated. Furthermore, given that routine angiographic follow-up artificially increases TLR, it is possible that the differential in restenotic events and nonrestenotic events is even greater in real-world experience than it is in this observation. Adjudication of TLR required a clinically driven procedure to help control for this potential bias. Second, patients were pooled from clinical trial cohorts and may not be representative of the general population undergoing coronary stenting. It is likely that event rates would be even higher in a real-world population, but we cannot exclude the possibility that the relative frequencies of target-lesion and nontarget-lesion events would be different. Third, we cannot exclude that some early (year 1) nontarget-lesion revascularizations were performed in the setting of restenosis and may not have come to clinical attention if restenosis had not occurred or may have been performed as planned staged procedures. Fourth, mortality assessment was limited to annual contact reports from the investigators at the participating clinical centers. Social Security identification data were not available to investigators for them to query the National Death Index to verify the survival of those patients for whom 5-year follow-up was not complete. Thus, the actual late mortality rate in our study population could be underestimated.

Conclusion
In just 5 years since the approval of second-generation coronary stents, and now with the potent advance of drug-eluting stents, the landscape has changed dramatically. The promise of long-term successful clinical control of coronary artery disease will remain elusive until the challenge of preventing disease progression at other sites in the coronary tree can be addressed. In the meantime, we must still view catheter-based coronary intervention as an inherently episodic and recurrent technique for the management of coronary artery disease.

References
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*Circulation.* 2004;110:1226-1230; originally published online August 30, 2004;
doi: 10.1161/01.CIR.0000140721.27004.4B
*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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