Quantitative Coronary Angiographic and Intravascular Ultrasound Assessment of a New Nonarticulated Stent: Report From the Advanced Cardiovascular Systems MultiLink Stent Pilot Study

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Objectives. The purpose of this study was to evaluate the safety, feasibility, optimal deployment technique and 1-year clinical outcome for the Advanced Cardiovascular Systems (ACS) MultiLink stent.

Background. Optimal stent deployment assessed by quantitative coronary angiography and intravascular ultrasound (IVUS) is associated with improved clinical outcome.

Methods. Forty-nine consecutive patients with a discrete stenosis in a native coronary artery 3 to 4 mm in diameter were treated with the new, balloon-expandable ACS MultiLink stent. Stent expansion was assessed in all patients using quantitative coronary angiography and serial IVUS imaging after 8-, 12- and 16-atm inflations. Clinical follow-up was obtained at 30 days and 1 year.

Results. All 49 patients had successful placement of a MultiLink stent without death, emergency coronary artery bypass graft surgery or Q wave myocardial infarction. After placement of the MultiLink stent, the minimal lumen diameter increased from 1.24 to 2.98 mm (p < 0.001), and diameter stenosis decreased from 61% to 7% (p < 0.001). Minimal lumen cross-sectional area by IVUS increased progressively after 8, 12 and 16-atm inflations. Clinical follow-up was obtained at 30 days and 1 year.

Conclusions. Treatment of stenoses in native coronary arteries with the MultiLink stent is associated with a high success rate and a low incidence of adverse events by 1 year, despite the fact that the majority of stents did not meet IVUS-defined criteria for “optimal stenting” derived from first-generation devices.

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The use of coronary metallic endovascular prostheses (stents) has risen exponentially since approval by the Food and Drug Administration (FDA) in 1993 to 1994. It is estimated that 30% to 40% of all percutaneous coronary interventions performed currently in the United States involve placement of a stent. By virtue of their ability to seal arterial dissections, reduce elastic recoil, maximize acute lumen diameter and reduce the rates of subsequent angiographic restenosis and revascularization compared with conventional balloon angioplasty, stents have become the technique of choice for urgent treatment of abrupt or threatened closure, as well as an elective treatment for suitable lesions (1,2).

The ability of these “first-generation” stents to improve both short-term procedural and long-term outcome thus represents a major breakthrough in percutaneous coronary revascularization. However, these initial devices have significant mechanical limitations (e.g., excessive rigidity, articulation gaps, nonuniform expansion). A number of second-generation stents have therefore been proposed, whose geometry can simultaneously impart both enhanced flexibility (to facilitate delivery) and excellent radial strength once expanded (to provide uniform scaffolding throughout the stented segment) (3). One such second-generation device is the ACS (Advanced Cardiovascular Systems) MultiLink stent. Before commencement of a large, multicenter, randomized trial comparing this new stent with the approved Palmaz-Schatz coronary stent, an open-label pilot study was performed at three U.S. sites to evaluate the safety, feasibility and optimal deployment technique for the MultiLink stent as assessed by quantitative coronary angiography and serial intravascular...
ultrasound (IVUS). This report describes that initial U.S. experience.

Methods

The ACS MultiLink stent. The MultiLink stent is constructed from a stainless-steel cylinder that is laser-etched into a pattern of repeating, nonoverlapping loops connected by interposed bridges (Fig. 1). All stents deployed in this study were 15 mm in length and were mounted on either a 3.0-mm or 3.5-mm delivery balloon, covered by a retractable 5F sheath.

Study patients. Forty-nine consecutively treated patients were enrolled at three centers (Beth Israel Hospital, Boston; St. Vincent’s Hospital, Indianapolis; and the University of Alabama at Birmingham) under an Investigational Device Exemption from the FDA. The investigational protocol was approved by the respective Institutional Review Boards. Each patient had angina or objective evidence of myocardial ischemia, or both, as well as a single (<12 mm) primary or previously treated lesion in a native coronary artery whose reference diameter was between 3.0 and 3.5 mm. Patients with a recent myocardial infarction (<5 days) or a contraindication to aspirin or anticoagulation were excluded from the study.

Stent procedure. Baseline angiography was performed after the administration of 150 μg of intracoronary nitroglycerin. After predilation with a conventional angioplasty balloon, the ACS MultiLink coronary stent was delivered to the target lesion over a 0.014-in. (0.035-cm) exchange length guide wire. The delivery sheath was withdrawn and appropriate stent position was reconfirmed by angiography. The stent delivery balloon was inflated to 8 atm for 30 s. After removal of the delivery system and administration of 150 μg of intracoronary nitroglycerin, angiography was repeated and IVUS imaging was performed using a 2.9F or 3.2F UltraCross Catheter (CardioVascular Imaging Systems). Balloon inflation was then performed to 12 atm within the stent using a noncompliant balloon (balloon/artery ratio 1:1.1). After repeat angiography and IVUS, the same noncompliant balloon was inflated to 16 atm within the stent. Angiography and IVUS were then repeated. The protocol prohibited postdilation with a balloon whose nominal size was >3.5 mm.

Medical therapy and clinical follow-up. All patients received 325 mg of aspirin before the procedure. All patients also received 10 mg of warfarin on the evening before the procedure, and then warfarin was titrated to an international normalized ratio (INR) of 2 to 3 for 4 weeks. Heparin boluses were given during the procedure to raise the activated clotting time to >300 s. Heparin was restarted 6 h after sheath removal (timed to an activated clotting time of 150 to 170 s) and titrated to an activated partial thromboplastin time of 60 to 80 s until a therapeutic INR was achieved. Clinical follow-up was obtained at 30 days, 6 months and 1 year.

Quantitative coronary angiography. All cine angiograms were forwarded to the Washington Hospital Center Angiographic Core Laboratory for review by observers who had no knowledge of the early and late clinical outcomes. Standard qualitative morphologic criteria were used to evaluate stenosis complexity before and after stent deployment. Using the contrast-filled guiding catheter as the calibration source, reference and minimal lumen diameters were determined before stent deployment, after stent deployment at 8 atm and after 16 atm using a validated algorithm. The final residual minimal lumen diameter and percent diameter stenosis were identified within the segment (“lesion”) as well as within the axial length of the stent (“stent”).

Intravascular ultrasound. The IVUS catheter was delivered distal to the treated segment. Imaging was performed during slow (1 mm/s), motorized pullback through the treated segment and into the proximal reference vessel. Images were recorded on high quality S-VHS videotape and analyzed at the Center for Research in Cardiovascular Interventions under the direction of Dr. Paul G. Yock. Lumen and vessel minimal diameter and maximal diameter and cross-sectional area (CSA) were measured distal and proximal to the stent, as well as at the proximal, distal and narrowest areas within the stent. Additional variables were calculated as follows:

Reference CSA

= (CSA [proximal to stent] + CSA [distal to stent])/2.

Eccentricity ratio

= Minor axis (tightest stent)/Major axis (tightest stent).

Percent expansion

= Lumen CSA (stent)/Lumen CSA (reference).
Table 1. Baseline Demographics

| Age (yr) | 59 ± 11 |
| Male     | 42 (86%) |
| Female   | 7 (14%)  |
| Hypertension | 27 (55%) |
| Diabetes mellitus | 8 (16%)  |
| Dyslipidemia   | 18 (38%)  |
| Previous MI   | 25 (51%)  |
| Family history of premature CAD | 18 (39%)  |
| Cigarette smoking within 1 year | 17 (35%)  |
| Previous CABG | 5 (10%)  |
| Previous PTCA of the target vessel | 8 (17%)  |

Angina class according to CCS

0 | 5 (10%)
I | 6 (12%)
II| 6 (12%)
III| 12 (25%)
IV | 20 (41%)

Vessel treated

LAD | 16 (33%)
RCA | 21 (43%)
LCx | 12 (25%)

Data presented are mean value ± SD or number (%) of patients. CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery.

Data analysis. All data were collected and processed at the Cardiovascular Data Analysis Center under the direction of Dr. Richard E. Kuntz. Statistical analyses were performed using the SAS for Windows statistical program (version 6.10–6.12). Data are expressed as the mean value ± SD. Comparisons between groups were made using analysis of variance.

Results

Demographics. From August 1995 through May 1996, 49 patients were enrolled in the MultiLink Pilot Study. The patients’ mean age was 59 years and 86% were men (Table 1). Fifty-one percent of patients had a previous myocardial infarction and 65% had either Canadian Cardiovascular Society class III or IV angina. Forty-three percent of stents were placed in the right coronary artery, with 33% in the left anterior descending coronary artery and 25% in the left circumflex coronary artery.

Procedural outcome. All 49 patients had successful placement of a MultiLink stent, with no instances of procedural death, emergency bypass surgery or Q wave myocardial infarction. Fourteen dissections (29%) occurred after predilation, but only three dissections remained evident after stent placement (6%) (Table 2). Forty-three patients received only one MultiLink stent, but five patients received two MultiLink stents, and one patient received three stents to cover a dissection proximal or distal to the original stent. One patient had a Palmaz-Schatz coronary stent placed in addition to the MultiLink stent. There was no angiographic evidence of abrupt closure, distal embolization or perforation in any patient. One patient had reduced flow (Thrombolysis in Myocardial Infarction flow grade 2) after stent placement. Four patients (8.0%) had non–Q wave myocardial infarctions (creatine kinase, MB fraction greater than twice the normal level). Two patients (4.0%) developed femoral hematomas, but neither required surgical repair or transfusion.

Clinical follow-up at 30 days was available for 48 patients. No major adverse events occurred during this period. Specifically, no patient had stent thrombosis or required repeat revascularization of the target vessel. One-year clinical follow-up was available for 43 patients (91%). No patients died; one patient (2.0%) required repeat angioplasty for restenosis of the target site; and two other patients (4.6%) underwent revascularization of other vessels.

Quantitative coronary angiography. Complete angiographic data were available for 47 patients (two films were unavailable for analysis). The majority of lesions treated were in American Heart Association/American College of Cardiology (AHA/ACC) class B2 or C, with a mean lesion length of 9.6 mm (Table 2). Before intervention, the mean reference vessel diameter was 3.18 ± 0.49 mm, and the minimal lumen diameter was 1.24 ± 0.46 mm, corresponding to a baseline diameter stenosis 61 ± 13% (Table 3). After placement of the MultiLink stent, the minimal lumen diameter increased to 2.49 ± 0.42 mm, corresponding to a diameter stenosis 21 ± 11%. After dilation, the minimal lumen diameter within the stent increased further to 2.98 ± 0.28 mm, corresponding to a diameter stenosis 7.0 ± 9.0%.
Intravascular ultrasound. Intravascular ultrasound data were available for 43 patients. Minimal lumen CSA measured within the stent increased progressively after 8-, 12- and 16-atm inflations (5.6 ± 1.0 to 6.8 ± 1.0 to 7.4 ± 1.2 mm², p < 0.001) (Fig. 2). Percent expansion also increased from 8 to 12 atm (60 ± 16% to 73 ± 16%, p < 0.001), but did not increase further from 12 to 16 atm (73 ± 16% to 75 ± 17%, p = NS), owing to a concomitant increase in the reference vessel CSA (9.6 ± 2.2 to 10.1 ± 2.0 mm², p < 0.001). When the minimal lumen CSA within the stent is normalized for the reference CSA measured before high pressure dilation (to avoid the confounding increase in reference area), there is a progressive rightward shift in the cumulative distribution function curves at 12 and 16 atm (Fig. 3). The mean recovery of measured balloon CSA at 16 atm is ∼80% (Fig. 4). The eccentricity ratio was similar after all three dilation pressures (84 ± 4% vs. 84 ± 6% vs. 83 ± 5%, p = NS [8, 12 and 16 atm, respectively]).

Discussion

Randomized trials have consistently demonstrated that the use of the Palmaz-Schatz coronary stent is associated with a reduction in angiographic restenosis and the need for subsequent recanalization compared with conventional balloon angioplasty (1,4,5). By favorably addressing the problems of acute mechanical instability and late restenosis, stents represent a true breakthrough in interventional cardiology.

Despite the increasingly important role played by stents in the percutaneous treatment of complex coronary artery disease, the presently available devices (Palmaz-Schatz and Gianturco-Roubin) are limited by mechanical problems, including excessive rigidity, articulation site defects, nonuniform expansion and recoil (Gianturco-Roubin). These mechanical limitations contribute to difficulties in delivering stents through tortuous vessels and in achieving optimal acute results. A number of newer “second-generation” stents have thus been proposed to overcome the limitations of the initial devices and have recently entered clinical evaluation.

The MultiLink stent. Like the Palmaz-Schatz coronary stent, the ACS MultiLink stent is constructed by laser etching of a stainless-steel tube. The unique geometric arrangement of interposed loops (as opposed to the “stacked” rectangular pattern of the Palmaz-Schatz coronary stent) improves flexibility in the nonexpanded state, which may facilitate delivery through tortuous vessels. When open, this design imparts a high degree of axial and radial strength, rendering the stent resistant to axial and radial collapse (6). Finally, uniform cell

Table 3. Quantitative Coronary Angiography

<table>
<thead>
<tr>
<th></th>
<th>No. of Pts</th>
<th>Reference Vessel Diameter (mm)</th>
<th>Minimal Lumen Diameter (mm)</th>
<th>Percent Stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>47</td>
<td>3.18 ± 0.49</td>
<td>1.24 ± 0.46</td>
<td>61 ± 13</td>
</tr>
<tr>
<td>After stent placement (8 atm)</td>
<td>41</td>
<td>3.20 ± 0.46</td>
<td>2.49 ± 0.42</td>
<td>22 ± 11</td>
</tr>
<tr>
<td>Final lesion</td>
<td>47</td>
<td>3.23 ± 0.45</td>
<td>2.64 ± 0.46</td>
<td>18 ± 10</td>
</tr>
<tr>
<td>Final stent</td>
<td>47</td>
<td>3.23 ± 0.45</td>
<td>2.98 ± 0.28*</td>
<td>7 ± 9†</td>
</tr>
</tbody>
</table>

*p < 0.001 (before treatment vs. after stent vs. final stent minimal lumen diameter). †p = 0.001 (before treatment vs. after stent vs. final stent percent stenosis). Data presented are number of patients (Pts) or mean value ± SD.
size and the ability to provide flexibility without a discrete articulation site (invariably the portion with the smallest CSA within the Palmaz-Schatz–treated lesion) largely overcome the problem of plaque prolapse into the lumen.

Although these unique properties of the MultiLink stent may offer theoretic advantages over earlier designs, direct comparison cannot be made without a prospective, randomized clinical trial. This multicenter pilot study, however, used quantitative coronary angiography and serial IVUS to address issues pertaining to clinical safety and the response of the stent to adjunctive high pressure dilation, before commencement of the randomized trial.

Figure 3. Cumulative distribution function curves (after 8, 12 and 16 atm) are shown for the ratio of the minimal lumen CSA within the stent to the reference lumen CSA at 8 atm.

Figure 4. Cumulative distribution function curves are shown for the ratio of the minimal lumen CSA within the stent to the nominal balloon CSA (solid squares) and the measures of balloon CSA (open circles). QCA = quantitative coronary angiography.
Clinical and angiographic outcome. In this study, MultiLink stents were deployed successfully in all 49 patients without major adverse clinical events. Because the majority of lesions were AHA/ACC grade B2 or C and a significant percentage of lesions (30%) were in angulated segments (>45°), this excellent deliverability suggests that the MultiLink stent can be delivered safely and reliably in complex lesion subsets. The absence of major ischemic complications (particularly subacute thrombosis) within 30 days of stent placement supports the thromboresistance of the MultiLink stent observed in earlier animal studies (7). However, the small sample size in this study precludes direct comparison of the rate of uncommon events such as thrombosis with the rate reported for the Palmaz-Schatz stent. With the planned conversion to an antiplatelet regimen (aspirin and ticlopidine) in the randomized trial, acceptably low rates (<1%) of subacute thrombosis are expected (8). The low incidence (2.0%) of revascularization of the target site at 12 months is consistent with the attainment of a large lumen after the procedure and lack of plaque prolapse through an articulation site. Whether the performance of the MultiLink stent procedure in these aspects exceeds that of the Palmaz-Schatz stent cannot be determined from this pilot registry, but will be addressed directly in the larger ACS MultiLink Stent Clinical Equivalence in De Novo Lesions Trial (ASCENT) now in progress.

Intravascular ultrasound assessment. Other than demonstrating the preliminary safety of the MultiLink stent, however, the primary goal of this pilot trial was to evaluate the proposed technique for stent deployment. By quantitative angiography, the residual stenosis after stent deployment at 8 atm was 22%, but decreased to 7% after adjunctive balloon dilation to 16 atm. These data are similar to those observed after placement of Palmaz-Schatz stents and support the use of routine high pressure (14 to 16 atm) after dilation to achieve optimal angiographic results with the MultiLink stent (9). In addition, the fact that the MultiLink stent lacks a discrete articulation site may allow for more uniform scaffolding throughout the length of the stent. In contrast, Ikari et al. (10) demonstrated that the smallest mean lumen diameter within the Palmaz-Schatz stent is at the articulation site immediately after deployment. Hoffman et al. (11) confirmed this finding using serial IVUS. In this cohort without significant lesion calcification, the lack of a discrete articulation site may also have obviated the need for extremely high pressure (>18 atm) after dilation, as is often used to overcome recoil at the articulation site within the Palmaz-Schatz stent (11).

The use of serial IVUS allows for more precise quantification of variables of stent expansion (12). In the present study, progressive increases in lumen CSA within the stent are observed from 8 to 12 to 16 atm. Percent stent expansion increased significantly from 8 to 12 atm, and to a lesser extent from 12 to 16 atm, given a concomitant increase in the reference vessel area at the higher pressures. When the minimal lumen CSA within the stent is normalized to the reference lumen CSA at 8 atm (to avoid the confounding issue of reference vessel enlargement after high pressure dilation), there is additional gain from 12 to 16 atm. This is reflected by the progressive rightward shift of the cumulative distribution function curve from 8 to 12 to 16 atm (Fig. 2).

The criteria proposed for IVUS-guided “optimal stenting” have become more stringent over the past several years. They currently include the attainment of a 0.7 ratio of lumen CSA within the stent to reference lumen CSA (9,12,13). In this study, however, only 64% of stents achieved a lumen to mean reference area ratio ≥0.70. Because the ratio of stent lumen CSA to measured balloon CSA was ~0.70 (similar to the 0.60 to 0.70 reported by IVUS for the Palmaz-Schatz stent [9]), it may be necessary to use balloons with an inflated diameter 10% to 20% over the reference lumen diameter to overcome lumen recoil and to achieve 90% of the reference vessel CSA.

The use of slightly oversized balloons or adjunctive high pressure (>16 atm) dilation was prohibited by the study protocol; thus, these traditional strategies used to expand the stent more fully could not be used. However, the excellent clinical results of this pilot study (absence of occlusive thrombosis and low incidence [2.0%] of target lesion revascularization) suggest that the attainment of an arbitrary, IVUS-defined criterion (such as lumen/reference CSA ratio >0.70) may not be clinically necessary. Even at current levels of expansion, the MultiLink stent appears to have a relatively high ratio of the minor to major axes (eccentricity ratio >0.80), suggesting its uniform expansion from the collapsed to the deployed state. Recently, Stone et al. (14) reported similar observations using serial IVUS in Palmaz-Schatz stents.

Study limitations. The small sample size and narrow inclusion criteria of this pilot study do not permit generalization of the findings to a much larger population of patients in whom coronary stents are placed. The lack of routine angiographic follow-up also precludes any precise quantification of angiographic restenosis or biologic response to injury. Finally, the absence of a control group treated with approved stents or other catheter-based modalities does not allow for direct comparison with other devices. Such comparisons must be deferred until the larger, randomized ASCENT trial is completed.

Conclusions. This pilot study suggests that the ACS MultiLink stent has favorable characteristics in terms of deformability, expansion of minimal lumen diameter, thromboresistance on an aspirin/warfarin regimen and freedom from clinically driven, target-driven revascularization during 6 to 12 months of follow-up. Final inflation pressures in the 12 to 16 atm range appear to be adequate to obtain expansion to 7% residual stenosis by quantitative angiography. Intravascular ultrasound, however, suggests that use of postdilating balloons with inflated diameters of 10% to 20% over the reference diameter would be necessary to achieve a final stent CSA >80% of the reference lumen. The preliminary data, however, are encouraging for the completion of the large, randomized ASCENT trial comparing the ACS MultiLink stent with the approved Palmaz-Schatz stent in focal disease in native coronary arteries.
References


