A Randomized Controlled Trial of Angiography Versus Intravascular Ultrasound-Directed Bare-Metal Coronary Stent Placement (The AVID Trial)

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Background—AVID (Angiography Versus Intravascular ultrasound-Directed stent placement) is a multicenter, randomized controlled trial designed to assess the effect of intravascular ultrasound (IVUS)-directed stent placement on the 12-month rate of target lesion revascularization (TLR).

Methods and Results—After elective coronary stent placement and an optimal angiographic result (<10% stenosis), 800 patients were randomized to Angiography- or IVUS-directed therapy. Blinded IVUS was performed in the Angiography group without further therapy. In the IVUS group, IVUS criteria for optimal stent placement (<10% area stenosis, apposition, and absence of dissection) were applied. Final minimum stent area was 6.90±2.43 mm² in the Angiography group and 7.55±2.82 mm² in the IVUS group (P=0.001). In the IVUS group, only 37% with inadequate expansion (<90%) received further therapy. The 12-month TLR rate was 12.0% in the Angiography group and 8.1% in the IVUS group (P=0.08, 95% confidence level [CI], [−8.3% to 0.5%]). When vessels with a distal reference diameter <2.5 mm by core laboratory angiography measurement were excluded from analysis, the 12-month TLR rate was 10.1% in the Angiography group and 4.3% in the IVUS group (P=0.01, 95% CI, [−10.6% to −1.2%]). With a prestent angiographic stenosis of ≥70%, the TLR rate was lower in the IVUS group compared with the Angiography group (3.1% versus 14.2%; P=0.002; 95% CI, [−18.4% to −4.2%]).

Conclusions—IVUS-directed bare-metal stent placement results in larger acute stent dimensions without an increase in complications and a significantly lower 12-month TLR rate for vessels ≥2.5 mm by angiography and for vessels with high-grade prestent stenosis. However, for the entire sample analyzed on an intention-to-treat basis, IVUS-directed bare-metal stent placement does not significantly reduce the 12-month TLR rate when compared with stent placement guided by angiography alone. In addition, IVUS evaluation of adequate stent expansion is underutilized by experienced operators. (Circ Cardiovasc Interv. 2009;2:113-123.)

Key Words: angiography ■ intravascular ultrasound ■ randomized controlled trial ■ restenosis ■ stents

Intravascular ultrasound (IVUS) is an invasive imaging technique used to visualize coronary cross-sectional anatomy and is superior to coronary angiography for the assessment of vessel size, calcium content, and lesion severity.1-4 The technology has also been used to evaluate the results of coronary angioplasty and stent placement.5,6

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Much controversy exists regarding the importance of IVUS as a method of determining adequate stent placement and the duration of antiplatelet therapy. Although 2 studies showed a significant benefit of IVUS-guided stent placement,7,8 others...
failed to demonstrate a difference when compared with a procedure guided by angiography alone.\textsuperscript{9,10} Because of the heterogeneity of available studies and varying clinical results, the technique of IVUS-guided stent placement was never satisfactorily evaluated, and the controversy never adequately resolved.

We therefore tested the hypothesis that IVUS-directed bare-metal stent placement is superior to stent placement guided by angiography alone. The primary end point of this study was the rate of target lesion revascularization (TLR) at 12 months determined by clinical follow-up, without the requirement for repeat angiography.

**Methods**

**Study Design**

The Angiography versus Intravascular Ultrasound-Directed (AVID) study is a randomized controlled trial (Figure 1) with 24 centers in the United States. Enrollment occurred between 1995 and 1999, and the follow-up was completed in 2000. Each site was visited by the principal investigator to verify that operators were proficient in both IVUS interpretation and coronary stent placement. The Institutional Review Board at each institution approved the study, and subjects gave written informed consent.

**Subject Selection**

Patients over 18 years who were scheduled for elective coronary stent placement were eligible. They could receive single or multiple stents placed within a native artery or bypass graft with a distal reference vessel diameter \( \geq 2.5 \) mm by visual estimate of angiography.

Exclusion criteria were as follows: dissection not covered by stent; thrombolysis in myocardial infarction flow grade \(<3\) after stent placement; chronic total occlusion, stent placement in a sole remaining circulation or left main equivalent; stent placement within an aneurysmal portion of a vessel such that complete stent-vessel wall contact could not be achieved; a bypass graft supplying a native vessel \(<2.0\) mm by visual estimate; cardiac transplantation; or performance of IVUS during the index procedure before stent placement.

**Randomization, Treatment Allocation, and Blinding**

Balanced, blocked randomization was used to allocate equal numbers of subjects at each site to Angiography- or IVUS-directed stent placement. Computer-generated treatment assignments were placed in serially numbered, sealed, opaque envelopes by the coordinating center. After entry criteria had been met, a treatment allocation envelope was opened in the catheterization laboratory. Patients and staff members of the angiography and IVUS core laboratories who performed image measurements, nurses who conducted telephone follow-up, and physicians at the coordinating center who adjudicated outcome events were blinded to the treatment allocation assignment. However, treating physicians who performed stent placement and IVUS imaging and cardiac catheterization laboratory staff were not blinded.

**Stent Selection and Placement**

Initially, stent placement was restricted to the Palmaz-Schatz coronary stent. In January 1998, a protocol amendment was approved by the Institutional Review Board at each site to allow the use of the SCIMED NIR, Cordis Crown, AVE MicroStent II, and ACS Rx MultiLink coronary stents, alone or in combination. All had received FDA approval and had demonstrated restenosis rates comparable with the Palmaz-Schatz design. No restrictions were placed on the type, size or number of stents or balloons used, or the minimum or maximum stent placement or postdilatation balloon inflation pres-
sures. IVUS was not performed before stent placement in either group.

**Angiography-Directed Group**

For patients randomized to Angiography-directed therapy, procedural success was defined as <10% stent diameter stenosis compared with the distal reference vessel by visual estimate of angiography. If the patient fulfilled angiographic criteria, blinded IVUS was performed. The imaging catheter was placed 5 mm distal to the stent and automatic pullback performed at 0.5 mm/s. In the event of a significant dissection (through the media), the IVUS results were unblinded, and the operator was given the option to place an additional stent. No other crossover options were provided.

**IVUS-Directed Group**

For the IVUS-directed group, identical criteria were applied for angiographic success before study entry. Then, unblinded IVUS was performed. The distal reference vessel lumen area (segment with the smallest quantity of plaque within 5 mm of the distal stent margin) was measured and compared against the minimal stent area. If the patient failed to meet IVUS criteria for optimal stent placement, further therapy was recommended. No limit was placed on the number of iterative IVUS assessments that could be performed.

**IVUS Criteria for Optimal Stent Placement**

The study criteria for optimal stent placement had been previously tested in a single-center trial of IVUS-guided stent placement. The criteria were as follows: the smallest cross-sectional area within the stent should be ≥90% of the distal reference vessel lumen cross-sectional area; full apposition of the stent to vessel wall; and dissections involving exposure of the media should be covered by stent placement.

**IVUS Equipment**

IVUS imaging was performed using a Boston Scientific Corporation 30-MHz, 3.2F imaging catheter. Images were recorded on S-VHS videotape for analysis by the core laboratory.

**Postprocedure Medications**

Ticlopidine 250 mg was administered twice a day for 2 to 4 weeks. Aspirin 325 mg/day was administered for an indefinite period. After August 1998, investigators were given the option of administering clopidogrel 75 mg per day for 2 weeks rather than ticlopidine. No patient received a glycoprotein IIb/IIIa inhibitor.

**Quantitative Coronary Angiography**

Angiograms were analyzed by the Washington Hospital Center Angiographic Core Laboratory (Washington, DC). Cine frames were selected from 2 views before intervention, after a final angiographic result, and after further therapy. Frames were digitized and analyzed using an automated edge-detection algorithm (CAAS-II). Minimum lumen diameters within and at the margins of the stent and reference diameter were calculated to determine the percent diameter stenosis before intervention, after stent deployment, and after final balloon dilatation.

**Quantitative IVUS**

IVUS images were evaluated by the Center for Research in Cardiovascular Interventions IVUS Core Laboratory (Stanford University) and were digitized with TapeMeasure (Indec Systems, Santa Clara, Calif). Measurements were performed at te following 5 locations: the smallest lumen within the stent; the proximal and distal stent edges; and the proximal and distal reference segments (the segment with the least amount of plaque within 5 mm of the proximal and distal stent edges and before a major side branch). The average of the minimum and maximum lumen diameters at each location was used for diameter-related calculations. When 2 stents in a vessel overlapped, they were treated as a single segment. Two nonoverlapping stents in a single vessel were treated as 2 segments.

**End Points**

The primary end point was TLR, defined as the clinical requirement for a repeat revascularization procedure (angioplasty, stent, or coronary artery bypass graft) due to in-stent restenosis within 1 year of the index stent procedure. TLR was chosen to avoid both the need for a follow-up angiogram as a requirement of study entry and potential investigator bias. Secondary end points were death from any cause, myocardial infarction (MI), stent thrombosis, coronary artery bypass grafting, and a composite end point consisting of any major adverse cardiac event. MI was defined as an elevation of creatine phosphokinase (CPK) 2 times the institutional upper limit of normal with an associated rise in CPK-MB fraction. Additional secondary end points included 30-day and 6-month clinical events. Procedural costs were not collected as part of this study.

**Follow-Up**

A nurse from the coordinating center telephoned subjects at 1, 6, and 12 months after the index procedure. If a patient could not be reached, the patient’s cardiologist was contacted. The Social Security Death Index was searched for patients lost to follow-up. For subjects who underwent repeat angiography within 1 year, films and procedural reports were reviewed by 2 physicians, blinded to treatment assignment, at the coordinating center to determine whether the patient required TLR within the stent placed at the time of study entry.

**Sample Size**

In both the STRESS and BENESTENT trials, the TLR rate at 6 months was ∼10%.6,12 Our protocol allowed for stent placement in saphenous vein graft lesions as well as native lesions, complex lesions, restenotic lesions, and lesions requiring multiple stents. Thus, the TLR rate was expected to climb to ∼12% at 12 months. With a 50% anticipated reduction in TLR, from 12% to 6%, α = 0.05 and 80% power, 356 subjects were required in each group. To accommodate a 10% anticipated loss to follow-up, the sample size was increased to 400 subjects per group.

**Statistical Analysis**

Categorical variables were compared between the Angiography- and IVUS-directed groups with Pearson χ² test or Fisher exact, 2-tailed test. Ninety-five percent confidence intervals (CI) were calculated using the Wilson score method without continuity correction. Continuous variables, reported as means ± standard deviations, were compared using 2-sample, 2-sided t-tests. For the total number of stents, the data were right-skewed, and both the 2-sample t test and the Mann-Whitney U test were performed. Data were not analyzed by study center or by performing physician.

The primary intention-to-treat analysis was a χ² comparison of randomization assignment (Angiography-directed therapy versus IVUS-directed therapy) with respect to the occurrence of 12-month TLR (yes versus no). Then, after the database had been locked, an unplanned post hoc analysis was performed that excluded cases with a distal reference diameter <2.5 mm by angiography core laboratory measurement. For the 8% of patients who underwent stent placement in more than one lesion, one was randomly chosen for analysis. If 2 lesions were stented and one required TLR, that lesion was chosen for analysis.

Forward, stepwise logistic regression analysis was conducted to determine significant predictors of TLR using 4 preplanned variables: treatment allocation, diabetes, saphenous vein graft, and angiographic prestenot distal reference vessel lumen diameter (treated as a continuous variable). P values <0.05 were considered to be statistically significant. SPSS version 13.0 was used. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.
Results

Baseline Characteristics
A total of 811 patients were enrolled at 24 centers. Eleven patients were excluded from the analysis. One subject withdrew consent before stent placement, and 10 were excluded because of protocol violations: cardiac transplantation (1); Institutional Review Board approval not current (1); IVUS used before stent placement (5); and protocol not followed during index procedure (3). Of the remaining 800 subjects, 406 were randomized to Angiography-directed treatment and 394 were randomized to IVUS-directed treatment (Figure 1). Twelve-month follow-up data are available for 744 (93%) patients. The target enrollment of 712 subjects with 12-month follow-up was achieved. Patients who were lost to follow-up had similar baseline characteristics to those who were not (data not shown).

Baseline characteristics were similar in both groups (Table 1). Prestent distal reference vessel diameter was 2.81±0.64 mm for the entire study group. Although entry criteria specified a distal reference vessel diameter of ≥2.5 mm, 31% of vessels had a distal reference lumen diameter <2.5 mm by angiographic core laboratory analysis (Figure 2A). For the entire study group, the average prestent lesion severity by angiography was 63.4±14.2%. Prestent angiographic lesion severity was <50% in 17% of all patients enrolled and was equal in both groups (Figure 2B).

Procedural Results
In the IVUS-directed therapy group, compared with the Angiography-directed group, a greater number of stents (1.53±0.88 versus 1.38±0.68; P=0.01 by the 2-sample t test and P=0.11 by the Mann-Whitney U test) and balloons (2.79±1.68 versus 1.93±1.14; P<0.001) were used. The maximum balloon size used was significantly larger in the IVUS group compared with the Angiography group (3.71±0.62 versus 3.53±0.49; P<0.001), although the maximum balloon inflation pressures were similar in both groups (17.0±3.5 atm versus 16.6±3.7 atm; P=0.14).

Final stent area expansion (at the stent minimum lumen diameter) compared with the cross-sectional area of the diameter <2.5 mm by angiographic core laboratory analysis (Figure 2A). For the entire study group, the average prestent lesion severity by angiography was 63.4±14.2%. Prestent angiographic lesion severity was <50% in 17% of all patients enrolled and was equal in both groups (Figure 2B).
distal reference vessel lumen was 84.6±20.8% in the Angiography-directed group and 90.4±20.6% in the IVUS-directed group (P<0.001; Table 2). Although optimal stent expansion was defined as 90% of the cross-sectional area of the distal reference vessel lumen by IVUS, only 48% of vessels in the IVUS-directed group fulfilled this criterion (Table 3).

Six subjects in the Angiography-directed group crossed over to IVUS-directed treatment after blinded IVUS images were obtained (Table 3). IVUS was unblinded and additional stents were placed in 3 patients because of a dissection. However, 3 patients, crossed over for indications not included in the protocol (1 each for stent nonapposition, stent underexpansion, and treatment of a lesion noted by IVUS). Data from all 6 subjects were analyzed with the Angiography-directed group.

### IVUS-Directed Further Therapy

In the IVUS-directed group, after an optimal angiographic result, 42% of patients received additional therapy in an attempt to fulfill IVUS criteria for optimal stent placement (Table 3). However, of the subjects in the IVUS-directed group who did not meet study poststent expansion criteria (≥90% cross-sectional area), only 37% received further therapy for an underexpanded stent. Patients in the IVUS-directed group who did not fulfill criteria after the initial IVUS assessment, but did receive further therapy for an underdilated stent were compared with those who did not receive further therapy. There was no significant difference in preprocedure distal reference vessel diameter, diameter stenosis, stent diameter, or size of final balloon used.

In the IVUS-directed group, 163 of 165 patients who underwent further therapy after the initial IVUS assessment had complete balloon diameter data available for analysis. A larger balloon was used for additional therapy in 105 (64%) of 163 patients. Of the 58 patients who underwent additional therapy after the initial IVUS assessment, but without the use of a larger diameter balloon, 3 had missing inflation pressure data. For the remaining 55 patients, 27 (49%) patients underwent repeat balloon treatment using a higher inflation pressure.

### Clinical Results

There was no significant difference in clinical events between the Angiography-directed and IVUS-directed groups at 30-day or 6-month follow-up. At 30 days the rate of stent thrombosis was 1.3% in the IVUS-directed group and 1.0% in the Angiography-directed group (Δ=0.3%; 95% CI, −1.5 to 2.1%; P=0.75). All deaths within 30 days occurred during hospitalization for stent placement. Two patients in the Angiography-directed group died within 30 days; 1 after acute stent thrombosis and 1 after a nonhemorrhagic cerebrovascular accident unrelated to stent placement. Two patients in the IVUS-directed group died within 30 days; 1 after a nonhemorrhagic cerebrovascular accident and 1 of urosepsis.

At 12-month follow-up, the rates of MI, death, or non-TLR-related coronary artery bypass graft or percutaneous transluminal coronary angioplasty were similar for the 2 treatment groups. In the intention-to-treat analysis, the 12-month TLR rate was lower in the IVUS-directed treatment group.
group compared with the Angiography-directed group, but the difference was not statistically significant (8.1% versus 12.0%; Δ = −3.9%; 95% CI, −8.3 to 0.5%; P = 0.08; Table 4). Forty-five patients in the Angiography-directed group and 30 patients in the IVUS-directed group underwent TLR. None of the patients who were lost to follow-up had undergone TLR, stent thrombosis, MI, or coronary artery bypass graft before being lost to follow-up. In the multivariable logistic regression analysis, significant predictors of TLR were smaller angiographic prestent lumen diameter when core laboratory measurements of proximal and distal reference vessel diameter by angiography and IVUS were compared against angiography measurements, a significant difference between the 2 techniques was found with IVUS values being 0.25 to 0.75 mm larger (Figure 4). Using angiographic measurements as a point of reference, the greatest difference angiography and IVUS is observed for vessels <3.25 mm. The maximum balloon size used was larger in the IVUS group, although the maximum balloon inflation pressures were similar in both groups. Independent of randomization, the maximum inflation pressures for patients with and without TLR were 17.4±3.9 atm and 16.7±3.6 atm, respectively (P = 0.15). There was no significant interaction effect between randomization assignment and inflation pressure on TLR.

Sample size estimation was performed assuming the protocol entry criteria of a distal reference vessel ≥2.5 mm in diameter. Post hoc analysis showed that when vessels <2.5 mm by angiography core laboratory analysis were excluded (31% of the total enrollment), final minimum stent area by IVUS core laboratory was 7.42±2.54 mm² in the Angiography group and 8.34±3.06 mm² in the IVUS group (P < 0.001). For vessels ≥2.5 mm, the 12-month TLR rate was 10.1% in the Angiography-directed group and 4.3% in the IVUS-directed group (Δ = −5.9%; 95% CI, −10.6% to −1.2%; P = 0.01) (Figure 3A).

Post hoc subgroup analysis demonstrated that for saphenous vein graft lesions, the TLR rate was also lower in the IVUS-directed treatment group (20.8% versus 5.1%; P = 0.03; Figure 3B). A similar advantage was found for lesions in the right coronary artery treated with IVUS-directed therapy (14.3% versus 4.0%, P = 0.005; Figure 3B). In vessels with a prestent angiographic stenosis of ≥70%, by core laboratory measurement, the TLR rate was lower in the IVUS-directed group compared with the Angiography-directed group (14.2% versus 3.1%; P = 0.002; Figure 3C). No sex-based differences were present.

When core laboratory measurements of proximal and distal reference vessel diameter by angiography and IVUS were compared against angiography measurements, a significant difference between the 2 techniques was found with IVUS values being 0.25 to 0.75 mm larger (Figure 4). Using angiographic measurements as a point of reference, the greatest difference angiography and IVUS is observed for vessels <3.25 mm. The difference between the 2 measure-

| Table 3. IVUS Procedural Results for Patients in the Angiography- and IVUS-Directed Groups Demonstrating Improvement After IVUS-Directed Further Therapy |
|----------------------------------|---------------------|---------------------|---------------------|
|                                   | Angiography-Directed Therapy | All Subjects        | IVUS-Directed Therapy |
|                                   | (n=406)                | (n=394)             | (n=165)             | (n=229)             |
| Final IVUS evaluation             |                      |                     |                     |                     |
| Subjects who met all IVUS criteria, % | 35.6                | 43.5                | 46.0                | 41.6                |
| Final IVUS cross-sectional area expansion |                     |                     |                     |                     |
| ≥90%                              | 39.1%                | 48.2%               | 52.0%               | 45.4%               |
| ≥80%                              | 56.5%                | 68.2%               | 74.3%               | 63.8%               |
| ≥70%                              | 74.7%                | 88.6%               | 89.5%               | 87.9%               |
| Final untreated dissection, %     | 3.1                  | 3.4                 | 3.9                 | 3.0                 |
| Final incomplete apposition, %    | 11.6                 | 9.8                 | 7.4                 | 11.6                |
| Received additional therapy       |                      |                     |                     |                     |
| Subjects, %                       | 6 (1.5)*             | 165 (41.9)†         |                     |                     |
| Reasons, %                        |                      |                     |                     |                     |
| Stenosis >10%                     | 1 (0.2)              | 115 (29.2)          |                     |                     |
| Nonapposition                     | 1 (0.2)              | 42 (10.7)           |                     |                     |
| Dissection                        | 3 (0.7)              | 19 (4.8)            |                     |                     |
| Occult disease                    | 1 (0.2)              | 10 (2.5)            |                     |                     |
| Increase at the minimum lumen diameter by IVUS (mean ± SD) |                      |                     |                     |                     |
| Major axis                        | 0.30±0.22 mm         |                     |                     |                     |
| Cross-sectional area (relative)   | 20.3±16.7%           |                     |                     |                     |
| Cross-sectional area (absolute)   | 1.27±1.23 mm²        |                     |                     |                     |

Although IVUS-directed further therapy resulted in an increase in stent cross-sectional area, a significant underutilization of IVUS information was found, with most patients not meeting IVUS criteria for optimal stent placement.

*Because of rounding off, percentages do not sum to 1.5%. Denominator for percentages is 406.
†Some patients had additional therapy for more than one reason. Denominator for percentages is 394.
ment techniques increases as angiographic reference vessel size decreases. At the same time, the rate of TLR increases with decreasing vessel diameter. Thus, these 2 opposing observations create a procedural window of opportunity where the use of IVUS leads to accurate balloon sizing and an improvement in TLR. For vessels \( \geq 2.5 \) mm and \( <3.25 \) mm (363 of 800 patients, 45.4%) by angiographic measurement, the rate of TLR was 5.1% in the IVUS-directed group, and 12.6% in the Angiography group (\( P=0.02; 95\% \text{ CI}, 13.6\% \) to \( 1.3\% \)).

### Nonapposition and Dissection

The criteria for optimal stent placement specifically addressed stent nonapposition and dissection not covered by a stent. After final assessment by IVUS, 79 patients had incomplete stent apposition (38 in the IVUS group and 41 in the Angiography group), and 24 patients had a dissection of any grade not covered by stent placement (13 in the IVUS group and 11 in the Angiography group). However, for those patients with incomplete apposition of any severity or any grade of dissection noted on final IVUS compared with those without, there was no difference in the rate of TLR (12.5% versus 10.0%; \( P=0.54 \) and 10.5% versus 10.2%, respectively; \( P=1.00 \)) or stent thrombosis (1.4% versus 1.2%; \( P=1.00 \), and 0.0% versus 1.3%, respectively; \( P=1.00 \)) at 12 months.

### IVUS Procedural Complications

In the IVUS-directed group, 2 (0.5%) patients experienced a complication as a result of further therapy. In 1 patient, further therapy was performed due to an underdilated stent as judged by IVUS. This resulted in a distal dissection requiring an additional stent. In the second, a lesion was discovered by IVUS distal to the initial stent in the left anterior descending artery. Placement of a second stent resulted in closure of a diagonal branch and a non-Q-wave MI. No complications due to the use of the IVUS catheter were reported in either group.

### Discussion

In this study, we showed that IVUS-directed bare-metal stent placement results in a lower TLR rate compared with a procedure guided by angiography alone. However, IVUS-directed therapy did not significantly reduce the overall primary end point, the 12-month TLR rate, when compared with Angiography-directed stent placement. It was only in subsets that a benefit was identified. With respect to our secondary end points, there was no difference in the rate of death, MI, stent thrombosis, or a composite end point of any major adverse cardiac event. We also showed that IVUS-directed stent placement results in larger acute stent dimensions without an increase in procedural complications.

### IVUS Criteria for Optimal Stent Placement

Previous IVUS criteria for optimal stent expansion were complex and, as a result, were difficult to apply in routine clinical practice. We therefore sought to develop simpler guidelines that could be applied to everyday use without compromising clinical outcome. We hypothesized that these criteria would minimize TLR as well as stent thrombosis.
We adopted 3 study criteria that addressed stent expansion, apposition, and dissection. The criteria were previously tested in a pilot study and arose from the observation that an obstruction of >10% of the cross-sectional area of a 3.0-mm vessel results in turbulent flow. Accurate lumen definition by IVUS would allow the operator to safely match the stent lumen to the distal reference vessel. We assumed this IVUS-guided approach would result in a larger final stent size without dissection of the proximal or distal reference vessel and a lower 12-month TLR rate.

Underutilization of IVUS Information
The decision to perform further therapy in the IVUS group was based on interpretation of the IVUS images by each investigator. Overall, 42% of patients in the IVUS group received further therapy, most (70%) for an underexpanded stent. We presumed that all investigators would recognize an underdilated stent and that larger balloons would be used when appropriate to achieve a final area stenosis of less than 10%.

To ensure adherence to the protocol and expertise in the performance of IVUS, we visited each site during the early phase of the study and stressed the importance of fulfilling criteria for optimal stent expansion. Despite the earnest efforts of many experienced investigators, only 37% of the patients in the IVUS group with inadequate stent expansion received further therapy. This underutilization of IVUS information may be due to a discrepancy between measurements at the time of the procedure and subsequent off-line IVUS core laboratory analysis or the unwillingness of an investigator to use larger balloons or higher expansion pressures due to concerns regarding procedural safety. Regardless of the reasons, the overall clinical results in the IVUS-
Table 5. Summary of Five Trials of IVUS-Guided Stent Placement

<table>
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<tr>
<th>Subjects</th>
<th>RESIST³</th>
<th>CRUISE⁷</th>
<th>OPTICUS¹⁰</th>
<th>TULIP⁶</th>
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<td>Target vessel</td>
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Continuous variables are expressed as mean±SD. For Treatment Group, Angio indicates angiography-directed or guided therapy; IVUS, intravascular ultrasound-directed or guided therapy; NA, not applicable.

The Effect of Prestent Vessel Size and Lesion Severity
The protocol specified an angiographic distal reference vessel diameter >2.5 mm for study entry. We chose this minimum size to exclude smaller vessels that would cause the clinical event rate to rise sharply, as well as the sample size necessary to demonstrate a meaningful difference between the groups. We did not anticipate that 31% of vessels would be <2.5 mm, which were responsible for 49% of the total 12-month TLR events. This underscores the need for accurate prestent reference vessel assessment, perhaps by IVUS, to determine the appropriate revascularization strategy for smaller vessels with inherently higher rates of TLR.

Prestent lesion severity was not prespecified, but we assumed a mean diameter stenosis of 60% to 70%. We found 17% of patients had a prestent lesion of <50% by core laboratory evaluation. These patients enjoyed a better clinical outcome if included in the Angiography-directed group, whereas those patients with a higher degree of prestent obstruction fared better with an IVUS-directed approach. We postulated that a less diseased artery poorly tolerates an aggressive approach with large balloons. The resulting vascular injury may trigger a process that culminates in a greater degree of intimal hypertrophy and clinical symptoms. Conversely, the bulky, calcified plaque found in a more diseased artery may better tolerate the aggressive approach of IVUS-directed therapy. This observation suggests that lesions of <50% diameter stenosis should not be treated with an aggressive approach due to the potential of significant late lumen loss.

Focused Use of IVUS-Directed Stent Placement
It seems that the strategy of IVUS-directed stent placement has its greatest value in a subset of patients based on prestent vessel size. If the use of IVUS-directed therapy is restricted to vessels with a reference vessel diameter of >2.5 mm and <3.25 mm by angiography, then this strategy would be applied to 47.3% of patients in the present study, with a 12-month TLR rate of 5.1% in the IVUS-directed group and 12.6% in the Angiography-directed group.

Comparison With Previous Studies
The benefit of IVUS noted in AVID should be compared to the 4 previous trials of IVUS-guided stent placement (Table 5). In RESIST, patients first underwent percutaneous transluminal coronary angioplasty followed by stent placement before being randomized to either IVUS-directed or IVUS-documentation therapy.⁹ Stents were placed as a primary planned procedure or after a suboptimal percutaneous transluminal coronary angioplasty result. Interestingly, the IVUS-directed group had a significantly larger stent cross-sectional area immediately postprocedure and at 6-month follow-up. However, the anticipated improvement in clinical outcome at 12 months was not reported. The primary end point was angiographic restenosis at 6 months, which showed no difference between the 2 treatment strategies.

The CRUISE trial compared IVUS-guided and IVUS-documentation stent placement in a nonrandomized study.⁷ Treatment assignment was determined by institutional preference. IVUS criteria for optimal stent placement were not specified, and the use of IVUS was left to the discretion of the operator. A significant improvement in TLR was observed in the IVUS-guided group at 9-month follow-up. The results of this trial may be due to the advantage of IVUS-guided stent placement or to the expertise of the treating physicians in the IVUS-guided institutions.

OPTICUS, a multicenter randomized trial comparing an angiography-guided to an IVUS-guided stent placement procedure used MUSIC criteria for optimum stent placement.¹⁰,¹⁴ At the conclusion of the procedure, IVUS was not performed in the angiography-guided group and, thus, acute results...
appears to be in vessels of small to medium size. The greatest value of IVUS-directed therapy was the benefit of IVUS-guided stent placement in long lesions. The primary end point was angiographic diameter at 6 months. A significantly larger final balloon was used in the IVUS-directed group. However, the immediate results could not be compared, because IVUS was not performed in the angiography-directed group. Significant clinical and angiographic benefits were noted in the IVUS-directed group at 6-month follow-up.

Limitations
The most important limitation of our study is the underutilization of IVUS information. Only 37% of underdilated stents in the IVUS-directed group underwent further therapy in an attempt to optimize the final result. In addition, drug-eluting stents were not used.

Clinical Implications and Impact
This study represents the largest controlled, multicenter randomized trial to compare IVUS-directed stent placement with a procedure guided by angiography alone in a real-world setting. The results establish for the first time that IVUS-directed therapy using AVID criteria for optimal stent placement, particularly in vessels ≥2.5 mm, improves TLR within the first year after stent placement without an increase in complications. The greatest value of IVUS-directed therapy appears to be in vessels ≥2.5 mm and <3.25 mm by angiography and in vessels with a preexistent angiographic stenosis of ≥70%. In addition, when compared with an experienced IVUS core laboratory, individual operators commonly fail to recognize IVUS findings that may be important for improved clinical outcome.

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Dr. Russo reports having received an unrestricted educational grant for the AVID study from Boston Scientific Corporation and having received honoraria from Medtronic. Dr. Teirstein reports having received research grants from Cordis, Boston Scientific, Medtronic, and Accuraytics; having served on the speakers’ bureau and having received honoraria from Cordis, Boston Scientific, and Medtronic; and having served as a consultant/advisory board member for Boston Scientific and Medtronic. Dr. Schatz reports being a coinventor of the Palmaz-Schatz stent, being on the speakers’ bureau and receiving honoraria from Medtronic; having an ownership interest in Cardium and BDS; serving as an expert witness for Johnson & Johnson, and Conor Medical versus Boston Scientific; and serving as a consultant/advisory board member for Baxter. Dr. Leon reports of being a member of the scientific advisory board of Boston Scientific, Volcano, and Cordis, and having an ownership interest in Volcano. Dr. Weissman reports having received research grant support from Boston Scientific. The other authors report no conflicts.

References
Much controversy exists regarding the importance of intravascular ultrasound (IVUS) as a method of determining adequate stent placement. Although 2 studies showed a significant benefit of IVUS-guided bare-metal stent placement, others failed to demonstrate a difference when compared with a procedure guided by angiography alone. Because of the heterogeneity of available studies and varying clinical results, the technique of IVUS-guided stent placement was never satisfactorily evaluated, and the controversy never adequately resolved. The present study (A Randomized Controlled Trial of Angiography Versus Intravascular Ultrasound-Directed Bare-Metal Coronary Stent Placement [The AVID Trial]) represents the largest multicenter, randomized controlled trial to compare IVUS-directed stent placement with a procedure guided by angiography alone in a real-world setting. The results establish that IVUS-directed therapy using AVID criteria for optimal stent placement, particularly in vessels $\geq 2.5$ mm, improves TLR within the first year after stent placement without an increase in complications. However, in the intention-to-treat analysis, whereas the 12-month TLR rate was lower in the IVUS-directed treatment group compared with the Angiography-directed group, the difference was not statistically significant. The greatest value of IVUS-directed therapy seems to be in vessels $\geq 2.5$ and $< 3.25$ mm by angiography and in vessels with a prestent angiographic stenosis of $\geq 70\%$. In addition, when compared with an experienced IVUS core laboratory, individual operators commonly fail to recognize IVUS findings that may be important for improved clinical outcome. Only 37% of underdilated stents in the IVUS-directed group underwent further therapy in an attempt to optimize the final result.
A Randomized Controlled Trial of Angiography Versus Intravascular Ultrasound-Directed Bare-Metal Coronary Stent Placement (The AVID Trial)

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