TITLE PAGE

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

First Author’s Surname & Short Title: Russo, AVID Trial

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Background: AVID (Angiography Vs. 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% CI [-8.3%, 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%, -1.2%]). With a prestent angiographic stenosis of ≥70%, the TLR rate was lower in the IVUS group compared to the Angiography group (3.1% vs. 14.2%; P=0.002; 95% CI [-18.4%, -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 to stent placement guided by angiography alone. In addition, IVUS evaluation of adequate stent expansion is underutilized by experienced operators.

**Key Words:** Angiography; Intravascular ultrasound; Randomized controlled trial; Restenosis; Stents
Introduction

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. The technology has also been used to evaluate the results of coronary angioplasty and stent placement.

Much controversy exists regarding the importance of IVUS as a method of determining adequate stent placement and the duration of antiplatelet therapy. While two studies showed a significant benefit of IVUS-guided stent placement, others failed to demonstrate a difference when compared to a procedure guided by angiography alone. Due to 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 endpoint of this study was the rate of target lesion revascularization 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 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 (IRB) 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 ≥2.5 mm by visual estimate of angiography.

Exclusion criteria were: dissection not covered by stent; TIMI 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 prior to 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, 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 IRB 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 to 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 post-dilatation balloon inflation pressures. IVUS was not performed prior to 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 to 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/sec. 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 prior to 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: (1) The smallest cross-sectional area within the stent should be ≥90% of the distal reference vessel lumen cross-sectional area; (2) Full apposition of the stent to vessel wall; and (3) 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 two to four 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 two 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 used to calculate the percent diameter stenosis before intervention, after stent deployment, and after final balloon dilatation.

Quantitative Intravascular Ultrasound

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, CA). Measurements were performed at five 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 two stents in a vessel overlapped, they were treated as a single segment. Two non-overlapping stents in a single vessel were treated as two segments.

Endpoints

The primary endpoint was target lesion revascularization (TLR), defined as the clinical requirement for a repeat revascularization procedure (angioplasty, stent, or CABG) due to in-stent restenosis within one 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 endpoints were death from any cause, myocardial infarction, stent thrombosis,
CABG, and a composite endpoint consisting of any major adverse cardiac event. Myocardial infarction (MI) was defined as an elevation of CPK two times the institutional upper limit of normal with an associated rise in CPK-MB fraction. Additional secondary endpoints 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 one year, films and procedural reports were reviewed by two physicians, blinded to treatment assignment, at the coordinating center to determine if the patient required target lesion revascularization within the stent placed at the time of study entry.

**Sample Size**

In both the STRESS and BENESTENT trials, the TLR rate at six months was approximately 10%. 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 approximately 12% at 12 months. With a 50% anticipated reduction in TLR, from 12% to 6%, \( \alpha=0.05 \) 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-directed and IVUS-directed groups with Pearson’s chi-squared test or Fisher’s exact, two-tailed test. Ninety-five percent confidence intervals were calculated using the Wilson score method without continuity correction.\textsuperscript{13} Continuous variables, reported as means±standard deviations, were compared using two-sample, two-sided t-tests. For the total number of stents, the data were right-skewed, and both the two-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 chi-square comparison of randomization assignment (Angiography-directed therapy vs. IVUS-directed therapy) with respect to the occurrence of 12-month target lesion revascularization (yes vs. 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 lab measurement. For the 8% of patients who underwent stent placement in more than one lesion, one was randomly chosen for analysis. If two 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 four preplanned variables: treatment allocation, diabetes, saphenous vein graft, and angiographic prestent 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 prior to stent placement, and 10 were excluded because of protocol violations: cardiac transplantation (1); IRB approval not current (1); IVUS used prior to 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 patients (93%). 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 to the Angiography-directed group, a greater number of stents (1.53±0.88 vs. 1.38±0.68, \(P=0.01\) by the two-sample t-test and \(P=0.11\) by the Mann-Whitney U test), and balloons (2.79±1.68 vs. 1.93±1.14; \(P<.001\)) were utilized. The maximum balloon size used was significantly larger in the IVUS group compared to the Angiography group (3.71±0.62 vs. 3.53±0.49; \(P<0.001\)), although the maximum balloon inflation pressures were similar in both groups (17.0±3.5 atm vs. 16.6±3.7 atm; \(P=0.14\)).

Final stent area expansion (at the stent minimum lumen diameter) compared to the cross-sectional area of the 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 three patients due to a dissection. However, three patients, crossed over for indications not included in the protocol (one each for stent non-apposition, stent underexpansion, and treatment of a lesion noted by IVUS). Data from all six 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 post-stent expansion criteria (≥90% cross-sectional area [CSA]), 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 to 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 patients (105/163=64%). 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 underwent repeat balloon treatment using a higher inflation pressure (27/55=49%).

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, one after
acute stent thrombosis and one after a non-hemorrhagic cerebrovascular accident (CVA) unrelated to stent placement. Two patients in the IVUS-directed group died within 30-days; one after a non-hemorrhagic CVA and one of urosepsis.

At 12-month follow-up, the rates of MI, death, or non-TLR-related CABG or PTCA were similar for the two treatment groups. In the intention-to-treat analysis, the 12-month TLR rate was lower in the IVUS-directed treatment group compared to the angiography directed group, but the difference was not statistically significant (8.1% vs. 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 target lesion revascularization, stent thrombosis, MI, or CABG prior to being lost to follow-up. In the multivariable logistic regression analysis, significant predictors of TLR were smaller angiographic prestent lumen diameter (P<.001) and randomization to the Angiography-directed group (P=0.04). The Hosmer and Lemeshow goodness-of-fit test P-value was 0.94, indicating the model adequately fit the data.

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% vs. 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% vs. 4.0%, P=0.005; Figure 3B). In vessels with a pre-stent angiographic stenosis
of ≥70%, by core lab measurement, the TLR rate was lower in the IVUS-directed group
compared to the Angiography-directed group (14.2% vs. 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 two 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
two measurement techniques increases as angiographic reference vessel size decreases. At the
same time, the rate of target lesion revascularization increases with decreasing vessel diameter.
Thus, these two 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 ≥2.5 mm and
<3.25 mm (363/800 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% CI [-13.6%, -1.3%]).

Non-Apposition and Dissection

The criteria for optimal stent placement specifically addressed stent non-apposition 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 to those without, there was no difference in the rate of TLR (12.5% vs. 10.0%; P=0.54, and 10.5% vs. 10.2%, respectively; P=1.00) or stent thrombosis (1.4% vs. 1.2%; P=1.00, and 0.0% vs. 1.3%, respectively; P=1.00) at 12 months.

IVUS Procedural Complications

In the IVUS-directed group, two patients (0.5%) experienced a complication as a result of further therapy. In one 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 LAD. 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 to a procedure guided by angiography alone. However, IVUS-directed therapy did not significantly reduce the overall primary endpoint, the 12-month TLR rate, when compared to angiography-directed stent placement. It was only in subsets that a benefit was identified. With respect to our secondary endpoints, there was no difference in the rate of death, MI, stent thrombosis, or a composite endpoint 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 three 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-directed group were likely affected by the less than optimal treatment of stent underexpansion.

**The Effect of Prestent Vessel Size and Lesion Severity**
The protocol specified an angiographic distal reference vessel diameter $\geq 2.5$ 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 60-70%. 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, while 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 appears 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 four previous trials of IVUS-guided stent placement (Table 5). In RESIST, patients first underwent PTCA followed by stent placement prior to being randomized to either IVUS-directed or IVUS-documented therapy. Stents were placed as a primary planned procedure, or after a suboptimal PTCA result. Interestingly, the IVUS-directed group had a significantly larger stent CSA immediately post-procedure and at six-month follow-up. However, the anticipated improvement in clinical outcome at 12 months was not reported. The primary endpoint was angiographic restenosis at six months, which showed no difference between the two treatment strategies.

The CRUISE trial compared IVUS-guided and IVUS-documented stent placement in a non-randomized study. 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 nine-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. At the conclusion of the procedure, IVUS was not performed in the angiography-guided group and, thus, acute results could not be compared. At six-month follow-up there was no difference in the dichotomous angiographic rate of restenosis, and at 12 months there was no difference in the rate of repeat intervention. The failure of the IVUS-guided group to achieve clinical or angiographic superiority may be due to the IVUS criteria used for optimal stent expansion, adherence to the IVUS criteria, or an aggressive approach in the angiography-guided group not representative of operators in other studies.

Finally, TULIP, a single-center, randomized trial, evaluated the benefit of IVUS-guided stent placement in long lesions. The primary endpoint was angiographic diameter at six months. A significantly larger final balloon was used in the IVUS-directed group. However, the immediate results could not be compared as IVUS was not performed in the angiography-directed group. Significant clinical and angiographic benefits were noted in the IVUS-directed group at six-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 utilized.
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 prestent angiographic stenosis of ≥70%. In addition, when compared to 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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Disclosures

Dr. Russo reports having received an unrestricted educational grant for the AVID study from Boston Scientific Corporation and having received honoraria from Boston Scientific. Dr. Teirstein reports having received research grants from Cordis, Boston Scientific, Medtronic, and Accumetrics; 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 co-inventor 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 vs. Boston Scientific; and serving as a consultant/advisory board member for Baxter. Dr. Leon reports 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.
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9. Schiele F, Meneveau N, Vuillemeot A, Zhang DD, Gupta S, Mercier M, Danchin N,
Bertrand B, Bassand JP. Impact of intravascular ultrasound guidance in stent deployment on
6-month restenosis rate: a multicenter, randomized study comparing two strategies--with and
without intravascular ultrasound guidance. RESIST Study Group. REStenosis after Ivus

W, Voudris V, Regar E, Henneke KH, Schachinger V, Zeiher A, OPTICUS (OPTimization
with ICUS to reduce stent restenosis) Study Investigators. Randomized comparison of
coronary stent implantation under ultrasound or angiographic guidance to reduce stent


**Figure Legends**

**Figure 1.** Study flow diagram. CSA indicates cross-sectional area. IRB indicates Institutional Review Board. In the Angiography-directed group, 19 patients were lost to follow-up at one month; two at six months, and an additional 10 at twelve months, for a total of 31 patients lost to follow-up (7.6%). In the IVUS-directed group, 16 patients were lost to follow-up at one month; 5 at six months, and an additional 4 at twelve months, for a total of 25 patients lost to follow-up (6.3%).

**Figure 2.** Histograms of (A) angiography core laboratory measurements of prestent distal reference lumen diameter in 767 vessels, identifying the subgroup of patients with a prestent reference vessel <2.5 mm; and (B) vessels with a prestent lesion of <50%, using the average reference vessel diameter. Although entry criteria required a distal reference vessel diameter (DRV) ≥2.5 mm by visual estimate of angiography, 31% of vessels had a DRV <2.5 mm.

**Figure 3.** Subgroup analyses of 12-month target lesion revascularization rates (TLR) by distal reference vessel diameter (A), which demonstrates a significant clinical benefit in vessels ≥2.5 mm; by vessel treated (B); and by prestent % diameter stenosis (C), with a significant improvement in IVUS-directed group in patients with a high-grade prestent lesion severity. Vessel measurements made by angiography core laboratory. ∆: Intravascular ultrasound-directed group – Angiography-directed group TLR rate difference. 95% confidence intervals (CI) are for ∆. SVG indicates saphenous vein graft; LAD, left anterior descending; LCX, left circumflex;
RCA, right coronary artery.

**Figure 4.** Lumen diameter by Angiography compared to the IVUS-minus-Angiography difference in 1273 proximal and distal reference vessels from 800 patients in AVID. The angiographic reference vessel diameter value is the average of two orthogonal views as measured by the angiographic core laboratory. The IVUS reference lumen diameter is the average of major and minor lumen diameters as measured by the IVUS core laboratory. Due to lesion location, not all patients had an appropriate proximal or distal reference vessel diameter for measurement by both imaging techniques.
Table 1. Baseline patient characteristics and presten angiographic measurements.

<table>
<thead>
<tr>
<th></th>
<th>Angiography-directed therapy (n=406)</th>
<th>IVUS-directed therapy (n=394)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>68</td>
<td>73</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>63±11</td>
<td>62±12</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>55±13</td>
<td>53±13</td>
</tr>
<tr>
<td>Prior history (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>29</td>
<td>35</td>
</tr>
<tr>
<td>CABG</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>PCI</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>45</td>
<td>46</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>44</td>
<td>40</td>
</tr>
<tr>
<td>Vessel treated (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>37</td>
<td>40</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>32</td>
<td>35</td>
</tr>
<tr>
<td>Circumflex</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Saphenous vein graft</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Left main</td>
<td>0.5</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>&gt;1 vessel stented (%)</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>De novo lesions (%)</td>
<td>88</td>
<td>90</td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>12.99±7.79</td>
<td>13.04±7.71</td>
</tr>
<tr>
<td>Distal reference vessel diameter (mm)</td>
<td>2.82±0.61</td>
<td>2.80±0.67</td>
</tr>
<tr>
<td>Average reference diameter (mm)</td>
<td>3.00±0.54</td>
<td>3.05±0.64</td>
</tr>
<tr>
<td>Minimum pre-stent lumen diameter (mm)</td>
<td>1.09±0.47</td>
<td>1.11±0.50</td>
</tr>
<tr>
<td>Stenosis (%)</td>
<td>63.5±14.3</td>
<td>63.4±14.1</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as mean±SD.
Table 2. Summary statistics for angiographic and intravascular ultrasound variables. In the IVUS-directed therapy group, a significant increase in minimum stent lumen diameter and minimum stent area is noted when compared to the Angiography-directed group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Angiography-directed therapy (n=406)</th>
<th>IVUS-directed therapy (n=394)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angiography core laboratory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Post-stent</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balloon:artery ratio</td>
<td>1.29±0.26</td>
<td>1.38±0.29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stent minimum diameter (mm)</td>
<td>2.87±0.48</td>
<td>2.93±0.55</td>
<td>0.11</td>
</tr>
<tr>
<td>Diameter expansion (%)</td>
<td>97.1±14.9</td>
<td>97.9±16.5</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>Final</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stent minimum diameter (mm)</td>
<td>2.87±0.48</td>
<td>2.97±0.56</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Intravascular ultrasound core laboratory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Post-stent</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal reference average lumen diameter (mm)</td>
<td>3.22±0.66</td>
<td>3.22±0.64</td>
<td>0.97</td>
</tr>
<tr>
<td>Lumen diameter at minimum stent area (mm)</td>
<td>2.89±0.51</td>
<td>2.95±0.49</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
<td>p-value</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Distal reference lumen area (mm²)</td>
<td>8.59±3.67</td>
<td>8.61±3.64</td>
<td>0.94</td>
</tr>
<tr>
<td>Minimum stent area (mm²)</td>
<td>6.88±2.43</td>
<td>7.17±2.45</td>
<td>0.11</td>
</tr>
<tr>
<td>Area expansion (%)</td>
<td>84.4±20.8</td>
<td>86.6±20.0</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Final</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumen diameter at minimum stent area (mm)</td>
<td>2.90±0.52</td>
<td>3.02±0.54</td>
<td>0.001</td>
</tr>
<tr>
<td>Minimum stent area (mm²)</td>
<td>6.90±2.43</td>
<td>7.55±2.82</td>
<td>0.001</td>
</tr>
<tr>
<td>Area expansion (%)</td>
<td>84.6±20.8</td>
<td>90.4±20.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gain in minimum stent area (mm²)</td>
<td>Not applicable</td>
<td>0.39±1.18</td>
<td>—</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as mean±SD.
Table 3. IVUS procedural results for patients in the Angiography- and IVUS-directed groups demonstrating improvement after IVUS-directed further therapy. 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.

<table>
<thead>
<tr>
<th>Final IVUS evaluation</th>
<th>All subjects (n=394)</th>
<th>Received further therapy (n=165)</th>
<th>No further therapy (n=229)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects who met all IVUS criteria</td>
<td>35.6%</td>
<td>43.5%</td>
<td>46.0%</td>
</tr>
<tr>
<td>Final IVUS cross-sectional area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>expansion</td>
<td>39.1%</td>
<td>48.2%</td>
<td>52.0%</td>
</tr>
<tr>
<td>≥90%</td>
<td>39.1%</td>
<td>48.2%</td>
<td>52.0%</td>
</tr>
<tr>
<td>≥80%</td>
<td>56.5%</td>
<td>68.2%</td>
<td>74.3%</td>
</tr>
<tr>
<td>≥70%</td>
<td>74.7%</td>
<td>88.6%</td>
<td>89.5%</td>
</tr>
<tr>
<td>Final untreated dissection</td>
<td>3.1%</td>
<td>3.4%</td>
<td>3.9%</td>
</tr>
</tbody>
</table>
Final incomplete apposition 11.6% 9.8% 7.4% 11.6%

**Received additional therapy**

<table>
<thead>
<tr>
<th>Subjects (%)</th>
<th>6 (1.5)*</th>
<th>165 (41.9)†</th>
</tr>
</thead>
</table>

**Reasons (%):**

<table>
<thead>
<tr>
<th>Reason</th>
<th>Subjects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenosis &gt;10%</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Non-apposition</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Dissection</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>Occult disease</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

Increase at the minimum lumen diameter by IVUS (mean±SD)

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major axis</td>
<td>0.30±0.22 mm</td>
</tr>
<tr>
<td>Cross-sectional area (relative)</td>
<td>20.3±15.7%</td>
</tr>
<tr>
<td>Cross-sectional area (absolute)</td>
<td>1.27±1.23 mm²</td>
</tr>
</tbody>
</table>

*Due to rounding, 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.
Table 4. Twelve-month clinical event rates demonstrating the improvement in clinical outcome in the IVUS-directed therapy group. A significant improvement in TLR is noted when vessels <2.5 mm are removed from the analysis.

<table>
<thead>
<tr>
<th>Angiography-directed therapy</th>
<th>IVUS-directed therapy</th>
<th>Δ</th>
<th>95% confidence interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>375</td>
<td>369</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical events (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLR</td>
<td>12.0</td>
<td>8.1</td>
<td>-3.9</td>
<td>-8.3, 0.5</td>
</tr>
<tr>
<td>Death</td>
<td>1.9</td>
<td>3.3</td>
<td>1.4</td>
<td>-1.0, 3.9</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5.1</td>
<td>6.8</td>
<td>1.7</td>
<td>-1.7, 5.2</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>1.1</td>
<td>1.4</td>
<td>0.3</td>
<td>-1.5, 2.2</td>
</tr>
<tr>
<td>CABG</td>
<td>2.7</td>
<td>2.7</td>
<td>0.0</td>
<td>-2.5, 2.6</td>
</tr>
<tr>
<td>Any MACE</td>
<td>18.7</td>
<td>18.4</td>
<td>-0.2</td>
<td>-5.8, 5.4</td>
</tr>
</tbody>
</table>

Subjects with an angiographic pre-stent distal reference diameter ≥2.5 mm

<p>| Subjects                     | 257                   | 235  |
| Clinical events (%)          |                       |      |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR</td>
<td>10.1</td>
<td>4.3</td>
<td>-5.9</td>
<td>-10.6</td>
<td>-1.2</td>
</tr>
<tr>
<td>Death</td>
<td>1.2</td>
<td>3.8</td>
<td>2.7</td>
<td>-0.2</td>
<td>0.06</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5.1</td>
<td>5.5</td>
<td>0.5</td>
<td>-3.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>1.2</td>
<td>1.7</td>
<td>0.5</td>
<td>-1.9</td>
<td>3.2</td>
</tr>
<tr>
<td>CABG</td>
<td>2.3</td>
<td>2.1</td>
<td>-0.2</td>
<td>-3.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Any MACE</td>
<td>15.6</td>
<td>14.5</td>
<td>-1.1</td>
<td>-7.4</td>
<td>5.3</td>
</tr>
</tbody>
</table>

Δ indicates IVUS-directed group minus Angiography-directed group; TLR, target lesion revascularization; MACE, major adverse cardiac event.
Table 5. Summary of five trials of IVUS-guided stent placement.

<table>
<thead>
<tr>
<th></th>
<th>RESIST⁹</th>
<th>CRUISE⁷</th>
<th>OPTICUS¹⁰</th>
<th>TULIP⁸</th>
<th>AVID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>155</td>
<td>525</td>
<td>550</td>
<td>144</td>
<td>800</td>
</tr>
<tr>
<td>Comparison endpoint</td>
<td>Angiographic restenosis</td>
<td>Target vessel revascularization</td>
<td>Repeat PTCA (secondary endpoint)</td>
<td>TLR</td>
<td>TLR</td>
</tr>
<tr>
<td>Follow-up (mos)</td>
<td>6</td>
<td>9</td>
<td>12</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Angiographic follow-up</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Treatment group</td>
<td>Angio</td>
<td>IVUS</td>
<td>Angio</td>
<td>IVUS</td>
<td>Angio</td>
</tr>
<tr>
<td>Endpoint results (%)</td>
<td>28.8</td>
<td>22.5</td>
<td>15.2</td>
<td>8.5</td>
<td>8.7</td>
</tr>
<tr>
<td>Largest balloon (mm)</td>
<td>3.30±0.33</td>
<td>3.30±0.29</td>
<td>3.69±0.59</td>
<td>3.88±0.51</td>
<td>3.4±0.5</td>
</tr>
<tr>
<td>% who had further therapy to achieve IVUS criteria</td>
<td>NA</td>
<td>39%</td>
<td>NA</td>
<td>36%</td>
<td>NA</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Prestent IVUS?</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Poststent IVUS?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Final minimum stent area (mm²)</td>
<td>7.16±2.48</td>
<td>7.95±2.21</td>
<td>7.06±2.13</td>
<td>7.76±1.72</td>
<td>NA</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as mean±SD. IVUS indicates intravascular ultrasound-directed or guided therapy; Angio, angiography-directed or guided therapy; TLR, target lesion revascularization; NA, not applicable.
Patient signed consent (n=811)

Patient underwent elective coronary stent placement with clinical & angiographic success

Randomized (n=800)

Angiography-directed therapy (n=406)

Post-stent placement IVUS
- Operator blinded to post-procedure IVUS results
- No further therapy performed

Lost to follow-up (n=31)

Analyzed (n=375)

IVUS-directed therapy (n=394)

Post-stent placement IVUS
- IVUS criteria for optimal stent placement applied
- Additional therapy when required to fulfill IVUS criteria

Lost to follow-up (n=25)

Analyzed (n=369)

Withdraw consent (n=1)

Excluded (n=10)
- Cardiac transplantation (n=1)
- IRB approval not current (n=1)
- IVUS used prior to stent (n=5)
- Protocol not followed during index procedure (n=3)

Lost to follow-up (n=31)

Analyzed (n=369)

*IVUS criteria
(1) Minimum stent lumen CSA ≥90% of distal reference lumen CSA
(2) Full apposition of stent
(3) No major dissection

Figure 1
Figure 2

A

Prestent distal reference vessel diameter (mm)

Percent of vessels

<2.5 mm
31% of vessels

B

Prestent % diameter stenosis

Percent of vessels

<50% stenosis
17% of vessels

Figure 2
Figure 3
Figure 4

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

Robert J. Russo, Patricia D. Silva, Paul S. Teirstein, Michael J. Attubato, Charles J. Davidson, Anthony C. DeFranco, Peter J. Fitzgerald, Steven L. Goldberg, James B. Hermiller, Martin B. Leon, Frederick S. Ling, Jennifer E. Lucisano, Richard A. Schatz, S. Chiu Wong, Neil J. Weissman and David M. Zientek

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