Long-Term Follow-Up After Percutaneous Transluminal Coronary Angioplasty Was Not Performed Based on Intravascular Ultrasound Findings

Importance of Lumen Dimensions

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Background—Angiography is limited in determining the anatomic severity of coronary artery stenoses. Clinical decision-making in patients with symptoms and intermediate lesions remains challenging.

Methods and Results—The current analysis included 300 patients (357 intermediate native artery lesions) in whom intervention was deferred based on intravascular ultrasound (IVUS) findings. Standard clinical, angiographic, and IVUS parameters were collected. Patients were followed for >1 year. Events occurred in 24 patients (8%). They included 2 cardiac deaths, 4 myocardial infarctions, and 18 target-lesion revascularizations (TLR; 12 percutaneous transluminal coronary angiographies and 6 coronary artery bypass grafts; only 3 TLRs occurred within 6 months after the IVUS study). All significant univariate clinical, angiographic, and IVUS parameters (*P*<0.05) were tested in multivariate models. These included diabetes mellitus, IVUS lesion lumen area, maximum lumen diameter, minimum lumen diameter, plaque area, plaque burden, and area stenosis (AS). No angiographic measurement was significant at *P*<0.05. The only independent predictors of an event (death, myocardial infarction, or TLR) were IVUS minimum lumen area and AS. The only independent predictors of TLR were diabetes mellitus, IVUS minimum lumen area, and AS. In 248 lesions with a minimum lumen area ≥4.0 mm², the event rate was only 4.4% and the TLR rate 2.8%.

Conclusions—Long-term follow-up after IVUS-guided deferred interventions in patients with de novo intermediate native artery lesions showed a low event rate. In patients with a minimum lumen area ≥4.0 mm², the event rate was especially low. IVUS imaging is an acceptable alternative to physiological assessment in these patients. (*Circulation*. 1999;100:256-261.)

Key Words: lesion □ ultrasonography, interventional □ coronary disease

Angiography is an imperfect technique for determining coronary artery stenosis severity, especially for intermediate lesions.1-3 Clinical decision-making in these patients remains challenging. Symptoms may be typical or atypical, and noninvasive functional testing is often unavailable or inconclusive. Invasive functional data (coronary flow reserve [CFR] or fractional flow reserve [FFRMYO]) are ways of differentiating significant from nonsignificant stenoses.4,5 Alternatively, intravascular ultrasound (IVUS) provides transmural tomographic images of coronary arteries in vivo, which allows the atherosclerotic disease process to be studied in a manner that would otherwise not be possible. Previous studies comparing angiography and IVUS have shown disparities in the presence, location, distribution, composition, and severity of atherosclerosis.6-10 Recently, we showed that IVUS minimum lumen area correlated strongly with preintervention CFR.11

The purposes of the current study were (1) to determine the event rate in patients with chest pain and angiographically intermediate de novo native coronary artery lesions after intervention was deferred on the basis of IVUS findings and (2) to identify the clinical, angiographic, and IVUS predictors of late cardiac events in these patients.

Methods

Patient Population

From December 30, 1992 to April 30, 1997, IVUS was performed in 7168 patients (8891 lesions) for diagnostic purposes or during catheter-based intervention. Of these, 756 patients (900 lesions) were studied specifically to quantify the severity of an intermediate stenosis (<70% diameter stenoses [DS] by visual estimation) in a major epicardial vessel other than the left main artery and not in the setting of a recent myocardial infarction (MI). If the stenosis was deemed significant, intervention was performed; if not, intervention
was deferred. None of these patients had intervention in another lesion. We excluded the following patients from the current analysis: the 196 patients (233 lesions) who underwent in-hospital revascularization on the basis of IVUS findings and (2) the 260 patients with 310 previously treated lesions. Therefore, the current analysis included a consecutive series of 300 patients (357 de novo intermediate native artery lesions) in whom intervention was deferred because of IVUS findings. In general, the criteria for deferred intervention were a minimum lumen area $\geq 4.0 \text{ mm}^2$ or a minimum lumen diameter (MLD) $\geq 2.0$ mm.

### Quantitative Coronary Angiography

Angiograms were reviewed by a core laboratory blinded to the IVUS or clinical findings. Quantitative coronary angiography (QCA) was performed using a computer-assisted, automated, edge-detection algorithm (Cardiovascular Measurement System, CMS-GFT, MEDIS). With the outer diameter of the contrast-filled catheter as the calibration, the MLD in diastole from the “worst” view was recorded. The reference diameter was averaged from 10-mm-long angiographically normal segments proximal and distal to the lesion; when a normal proximal segment could not be identified (eg, ostial lesion location), only a distal segment was analyzed. The percent DS was calculated.

### IVUS Imaging

Operators were not blinded to the images. IVUS imaging was performed after administration of 0.2 mg of intracoronary nitroglycerin. Studies were performed using a system made by 1 of the following manufacturers: CVIS/InterTherapy Inc, Hewlett-Packard and Boston Scientific Corporation, or Cardiovascular Imaging Systems/Boston Scientific Corporation. The IVUS catheter was advanced approximately 10 mm distal to the lesion, the video recorder was turned on, the transducer pullback device was activated or the manual pullback was initiated, and the artery was imaged retrograde to the aorto-ostial junction. Studies were recorded on 0.5-inch high-resolution s-VHS tape for off-line analysis.

### IVUS Analysis

Validation of normal coronary anatomy, plaque composition, and measurements determined using IVUS have been reported.\(^{12-16}\) The external elastic membrane (EEM) cross-sectional area (CSA) was measured by tracing the leading edge of the adventitia. The lesion site was the cross-sectional slice with the smallest lumen; among sections with the same lumen area, the one with the most plaque was selected. If the plaque was “packed” around the catheter, the lumen was assumed to be the physical (not acoustical) size of the catheter. Because IVUS cannot measure media thickness accurately, plaque and media (P&M) were the measure of plaque mass. Cross-sectional narrowing (CSN) has also been called the plaque burden or percent stenosis (AS) as shown:

\[
\text{AS} = \left( \frac{\text{mean reference lumen CSA} - \text{lesion lumen CSA}}{\text{mean reference lumen CSA}} \right) \times 100
\]

Lesion and reference selection and their measurement reproducibility were reported previously.\(^{9,17}\)

**Clinical Data, Definitions, and Outcomes**

Baseline demographics were confirmed by hospital chart review. Prior MI occurred $>6$ weeks before the study. Symptoms included unstable angina (at rest or progressive pain, with or without ECG changes) and congestive heart failure (class III or IV using the guidelines of the Canadian Cardiovascular Society). Risk factors included diabetes mellitus (oral agent or insulin treated), hypertension (medication-dependent), and hypercholesterolemia (medication-dependent or $>240 \text{ mg/dL}$).

Follow-up clinical events were obtained by serial telephone interviews 1, 3, 6, and 12 months and then every year after the IVUS measurements. All events were source-documented, including cardiac death, MI, and target-lesion revascularization (by percutaneous transluminal coronary angioplasty [PTCA] or coronary artery bypass grafting [CABG]) related to the assessed lesion.

**Statistical Analysis**

Statistical analysis was performed using StatView 4.5 (Abacus Concepts) or SAS (Statistical Analysis Systems, SAS Institute Inc). Continuous data were compared using unpaired Student’s t tests. Categorical data were compared using $\chi^2$ analysis or Fisher’s Exact Test. Cox regression analysis was used to identify the independent predictors of late cardiac events (including relative risk and 95% confidence intervals).

**Cardiac Events**

Complete follow-up data were available for 99% of the 300 patients over a mean follow-up time of 13 months (range, 1 to 24 months). Events occurred in 24 patients (8%). The minimum follow-up in patients who were event-free was 12 months.

There were 2 cardiac deaths (0.7%) after 7 and 21 months, respectively. One patient had sudden cardiac death, and the other died of severe heart failure and ventricular arrhythmias. There were no noncardiac deaths. Four patients (1.3%) had a MI at a mean follow-up time of 13.5 months (range, 3 to 15 months).

During follow-up, 18 patients (6%) had lesion-related revascularization; 12 (4%) underwent PTCA of the target lesion a mean of 14.0 months (range, 1 to 24 months) after the original IVUS measurements, and 6 (2%) underwent CABG (including a graft to the target vessel) a mean of 12.5 months (range, 4 to 22 months) after the IVUS measurements. Only 3 revascularizations (2 PTCA and 1 CABG) were performed within 6 months of the diagnostic IVUS study. Event-free survival curves are shown in Figure 1.

![Figure 1. Kaplan-Meyer survival curves (any event and target lesion revascularization [TLR] are separate) in 300 patients with deferred intervention after IVUS imaging. At 24 months, TLR-free survival was 94% and event-free survival was 92%.](image-url)
Clinical Predictors of Cardiac Events
Diabetes mellitus was more common in patients with clinical events. There was also a tendency for a reduced left ventricular ejection fraction in these patients. Age, male sex, prior MI, prior CABG, unstable angina, congestive heart failure, hypertension, hypercholesterolemia, and family history were similar in all patients (Table 1).

Angiographic Predictors of Cardiac Events
The angiographic reference, MLD, and DS measured 3.04 ± 0.61 mm, 1.69 ± 0.53 mm, and 46 ± 11%, respectively. Overall, by QCA analysis, 107 lesions (30%) had a DS between 50% and 72%, 160 lesions (45%) had a DS between 40% and 49%, and 90 lesions (25%) had a DS < 40%.

Importantly, the QCA MLD and DS were similar in patients with and without events (Table 2).

IVUS Predictors of Cardiac Events
Plaque composition was dominantly hyperechoic in 58% of patients, dominantly hypoechoic in 26%, and a combination of both in 16%. None of the plaques were dominantly calcific; the arc of calcium measured 32 ± 80°. Plaque composition was similar in patients with and without events. However, patients with events had a smaller lesion-site lumen CSA (4.2 ± 1.2 versus 6.2 ± 2.4 mm²), a smaller MLD (2.00 ± 0.42 versus 2.40 ± 0.48 mm), a larger CSN (62 ± 13% versus 56 ± 12%), and a larger AS (51 ± 15% versus 37 ± 16%) (Table 3).

Predictors of Cardiac Events
The variables tested as possible predictors of cardiac events included diabetes mellitus, IVUS lesion-site lumen CSA, MLD, P&M CSA, CSN, and AS. IVUS lesion-site lumen CSA and AS were the only independent predictors of cardiac events at follow-up. The predictors for target lesion revascularization (PTCA and CABG) were diabetes mellitus, IVUS lesion-site lumen CSA, and IVUS AS. Although the number of patients with death and MI was small, the only independent predictor was IVUS MLD (relative risk, 0.113; 95% confidence interval, 0.013 to 0.998; P = 0.0498) (Table 4, Figure 2).

Discussion
The current study of intermediate native coronary artery stenoses showed the following: (1) coronary angiography could not differentiate lesions with events from those without events; (2) the event rate (death, MI, or need for revascularization) in patients with IVUS-guided deferred intervention was 8%, with a 2% chance of major events (death or MI); and

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<th>TABLE 1. Clinical Variables</th>
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<tr>
<td>Age, y</td>
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<tr>
<td>Male, n (%)</td>
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<td>Prior MI, n (%)</td>
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<td>Prior bypass surgery, n (%)</td>
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<td>Unstable angina, n (%)</td>
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<td>CHF (CCS class III–IV), n (%)</td>
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<td>Diabetes, n (%)</td>
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<td>Hypertension, n (%)</td>
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<td>Hypercholesterolemia, n (%)</td>
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<td>Left ventricular ejection fraction, %</td>
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Values are mean ± SD or n (%). n = 300 patients. CCS indicates Canadian Cardiovascular Society and CHF, congestive heart failure.

<table>
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<th>TABLE 2. Angiographic Findings</th>
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<td>Vessel</td>
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<td>LAD, n (%)</td>
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<td>LCX, n (%)</td>
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<td>RCA, n (%)</td>
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<td>Ostial location, n (%)</td>
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<td>Reference diameter, mm</td>
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<td>Minimum lumen diameter, mm</td>
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<td>Diameter stenosis, %</td>
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Values are mean ± SD or n (%). LAD indicates left anterior descending artery; LCX, left circumflex artery; and RCA, right carotid artery. n = 357 lesions.
*34 patients had multiple intermediate lesions.
†4 patients had multiple intermediate lesions.
The occurrence of any event (death, MI, or revascularization) decreased with increasing minimum lumen CSA and was similar in diabetics and nondiabetics. Target lesion revascularization decreased with increasing minimum lumen CSA, but it was lower in nondiabetic than diabetic patients. DM indicates diabetes mellitus. (r=0.831; P<0.0001). A preintervention minimum lumen CSA≥4.0 mm² had a diagnostic accuracy of 92% in predicting a CFR≥2.0. The current study validates the clinical usefulness of this cutoff. Although the event rate decreased with increasing lumen area, an important difference seemed to exist between lesions with minimum lumen areas above and below 4.0 mm². In 248 lesions with a minimum lumen CSA≥4.0 mm², the event rate was only 4.4% and the revascularization rate only 2.8%.

Natural History of Intermediate Lesions
Crenshaw et al²⁸ found a 10-year survival rate of 85.5% in 2184 patients with noncritical lesions (<70% DS). In the Thrombosis in Myocardial Ischemia trial (TIMI-IIIA), 53 patients (14% of the total) who underwent angiography for unstable angina and did not have critical narrowings had 14% of the total who underwent angiography for unstable angina and did not have critical narrowings had excellent short-term prognoses.²⁹ The Multicenter Anti-Atheroma Study examined progression in mild disease: a minority of lesions progressed (4.4%), but spontaneous regression was rare (2.3%).³⁰ Conversely, The Harvard Atherosclerosis Reversibility Project Study Group found that lesions with a larger MLD progressed more rapidly than those with a smaller MLD.³¹ As shown in trials of lipid-lowering agents, most patients with noncritical disease do well.³²-³⁷ In the current study, predictors of late cardiac events were IVUS lumen CSA and AS. Diabetes was also an important predictor of late revascularization. Coronary disease is more aggressive in diabetics; they have more diffuse disease, 4 to 5 times the mortality, and worse outcomes after intervention.³⁸-⁴¹ Several factors promote accelerated atherosclerosis in diabetics.³²-⁴⁶ In the current study, it is unclear why diabetes was a predictor of revascularization but not of all events; however, few patients had death or MI.

Other studies have analyzed patients with unstable angina and nonsevere stenoses. Clinical predictors of mortality were older age, male sex, diabetes, and hypertension—not the presence of noncritical stenoses.²⁸ Conversely, Stone et al³¹ showed no effect of patient characteristics on progression in moderate stenoses; the only determinant of progression in their study was lesion severity.
Myocardial Infarction
There were four MIs during follow-up. In the Coronary Artery Surgery Study (CASS), high-grade stenoses more frequently led to a Q-wave MI. In other studies, most infarctions occurred on previously “insignificant” lesions. This apparent conflict is resolved by recognizing that patients with coronary disease have a large number of angiographically insignificant lesions but only a few “significant” stenoses. Thus, the “relatively more significant” stenosis is more likely to lead to an MI. However, the sheer number of insignificant lesions makes it more likely that a culprit lesion was initially insignificant. In the current study, half of the lesions had a minimum lumen area \( \geq 4.0 \text{ mm}^2 \).

Technical Considerations
The diagnostic use of IVUS depends on technique. Because of the importance of the minimum lumen CSA, it is necessary to interrogate carefully to identify the image slice with the smallest lumen, especially in very focal stenoses. Poor technique (too rapid or uneven transducer withdrawal or not interrogating the stenosis carefully) may miss the true minimum lumen CSA. Once the smallest lumen is identified, careful measurement is required.

Limitations
Limitations of the study exist. One was that plaque composition did not predict events. IVUS does not determine lipid content, and the propensity of plaques to become unstable and cause events is related to the amount of extracellular lipid. Although most of the patients had symptoms indicating significant coronary artery disease, few had noninvasive testing or invasive physiological assessment. In the United States, only 29% of patients referred for angioplasty undergo exercise testing. The IVUS data could have biased the decision toward revascularization; however, only 3 revascularizations were performed within 6 months of the IVUS study.

Another limitation was that the angiograms taken at the time of revascularization were not all available for review, making it difficult to assess disease progression versus persistent symptoms. It was also difficult to absolutely relate the MI events to the lesions.

The findings in the current study are only true for patients with intermediate lesions. These findings are not applicable to other situations (ie, postintervention lesion assessment). Also, relatively few patients had a lumen CSA <4.0 mm².

Conclusions
A low event rate during follow-up after IVUS-based deferred coronary interventions existed in patients with de novo intermediate native artery lesions. IVUS minimum lumen CSA was the major anatomic predictor of events. In patients with a minimum lumen CSA \( \geq 4.0 \text{ mm}^2 \), the event rate was especially low. IVUS imaging is an acceptable alternative to physiological assessment in these patients.

Acknowledgement
This study was supported, in part, by the Cardiovascular Research Foundation, Washington, DC.

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Long-Term Follow-Up After Percutaneous Transluminal Coronary Angioplasty Was Not Performed Based on Intravascular Ultrasound Findings: Importance of Lumen Dimensions

*Circulation*. 1999;100:256-261
doi: 10.1161/01.CIR.100.3.256
*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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