Intravascular Ultrasound Guidance Improves Angiographic and Clinical Outcome of Stent Implantation for Long Coronary Artery Stenoses

Final Results of a Randomized Comparison With Angiographic Guidance (TULIP Study)

Pranobe V. Oemrawsingh, MD; Gary S. Mintz, MD; Martin J. Schalij, MD, PhD; Aeilko H. Zwinderman, PhD; J. Wouter Jukema, MD, PhD; Ernst E. v.d. Wall, MD, PhD

Background—Long coronary lesions treated with stents have a poor outcome. This study compared the 6-month outcome of stent implantation for long lesions in patients randomized to intravascular ultrasound (IVUS; n = 73) or angiographic guidance (n = 71).

Methods and Results—Stenoses >20 mm in length and a reference diameter that permitted a stent diameter ≥3 mm were eligible. Primary end points were 6-month minimal lumen diameter (MLD) and the combined end point of death, myocardial infarction, and target-lesion revascularization (TLR). Baseline clinical and angiographic data were comparable in both groups. At 6 months, MLD in the IVUS group (1.82 ± 0.53 mm) was larger than in the angiography group (1.51 ± 0.71 mm; P = 0.042). TLR and combined end-point rates at 6 months were 4% (n = 3) and 6% (n = 4) in the IVUS group and 14% (n = 10) and 20% (n = 14) in the angiography group, respectively (P = 0.037 for TLR and P = 0.01 for combined events). Restenosis (>50% diameter stenosis) was found in 23% of the IVUS group and 45% of the angiography group (P = 0.008). At 12 months, TLR and the combined end point occurred in 10% (n = 7) and 12% (n = 9) of the IVUS group and 23% (n = 17) and 27% (n = 19) of the angiography group (P = 0.018 and P = 0.026), respectively.

Conclusions—Angiographic and clinical outcome up to 12 months after long stent placement guided by IVUS is superior to guidance by angiography. (Circulation. 2003;107:62-67.)

Key Words: stents ■ restenosis ■ ultrasonics

Patients with long coronary artery stenoses represent a difficult subset in the population considered for percutaneous intervention.1–3 In contrast to shorter lesions, stent placement for longer stenoses is generally avoided because of high restenosis rates.4–6 Final dimensions after stenting are a strong predictor of outcome.7–10 Because lumen and stent dimensions can be accurately determined by intravascular ultrasound (IVUS), guidance of stenting by IVUS has been proposed as a method to reduce restenosis rates.11 However, randomized studies investigating this strategy have yielded inconsistent results.12–17 We hypothesized that the potential advantages of IVUS guidance would be most apparent in complex lesions, such as long stenoses. In this report, we compared the clinical and angiographic outcome after stenting of long coronary artery stenoses with randomization to angiographic or IVUS guidance of the intervention. The acronym TULIP refers to “Thrombocyte activity evaluation and effects of Ultrasound guidance in Long Intracoronary stent Placement,” because platelet activity was evaluated in a subgroup of patients.

Methods

Patients

Consecutive patients referred for elective percutaneous intervention were included. Patients were eligible if they had a de novo, nonostial stenosis ≥20 mm length in a native coronary artery with a reference diameter that permitted implantation of ≥3-mm stents without involvement of significant side branches (diameter ≥2.0 mm). Patients with recent (<2 weeks) myocardial infarction (MI), total occlusion, and/or contraindications for combined antiplatelet therapy with ticlopidine and acetylsalicylic acid were excluded. The institutional ethics committee approved the study protocol. Written informed consent was obtained from all patients. Randomization to IVUS or angiographic guidance was done just before the procedure.
Stent Implantation, Angiography, and IVUS

All patients received 7500 U of heparin twice during the procedure and 240 mg of acetylsalicylic acid plus 500 mg of ticlopidine at the end of the procedure, followed by 250 mg/d of ticlopidine for 4 weeks and ≥80 mg/d of acetylsalicylic acid indefinitely. In this study, AVE GFX-XL (Medtronic/AVE) stents were used exclusively. If more than 1 stent was required, additional AVE GFX stents were used. Stent size and length were selected based on online quantitative angiographic (QCA) measurements. Stent deployment with ≥9 atm was mandatory and, if necessary, supplemented by higher-pressure dilations to achieve the following criteria for angiographically successful stent placement: (1) complete coverage of the stenotic segment; (2) angiographic residual diameter stenosis <30%; and (3) absence of angiographically visible dissections.

In patients assigned to IVUS-guided stenting, final balloon diameter and additional stent size were determined by ultrasound measurements. Balloon dilations were performed until the following IVUS criteria were fulfilled: (1) complete stent apposition; (2) in-stent minimal lumen diameter (MLD) ≥80% of the mean of proximal and distal reference diameters; and (3) in-stent minimal lumen area (MLA) greater than or equal to distal reference lumen area. We used the Endosonics/Jomed IVUS system, which allows digital storage of pullback sequences. Automated pullbacks at 1 mm/s were performed before intervention and repeated after stenting and after every dilation until all IVUS criteria were fulfilled. Trained catheterization laboratory personnel performed online IVUS measurements, according to previously described methods.16

Each angiogram or ultrasound sequence was preceded by 200 to 300 μg of intracoronary nitroglycerin. Three angiograms in 2 orthogonal projections were obtained in each patient: before intervention, immediately after the intervention, and at 6-month follow-up. Angiograms were analyzed with validated QCA systems (CMS 4.1; Medis) by an independent core laboratory (HeartCore, Leiden, the Netherlands) that was blinded as to IVUS assignment.

Follow-Up and End Points

Clinical follow-up included an interview, physical examination, blood chemistry, electrocardiography, and exercise testing at 1 and 6 months, as well as a telephone interview at 12 months. Repeat angiography was scheduled at 6 months. Angiography performed at ≤3 months was only used as follow-up if restenosis was present; otherwise, it was repeated at 6 months. Angiographic MLD at 6 months and the combined event rate of cardiac death, MI, and emergency bypass surgery. Cardiac death included all fatal events unless a cardiac cause was unequivocally ruled out. MI was defined as angina or a positive exercise test.18

Sample Size Calculation and Statistics

Sample size calculation was based on the presumption that a difference ≥0.25 mm in MLD at 6 months was clinically relevant. With a standard deviation of 0.5 mm, a sample size of 64 patients per group was calculated to achieve a power of 0.8 at a significance level of 0.05. Assuming 10% to 15% loss to follow-up, 75 patients per group were to be included. Analysis was done according to the intention-to-treat principle. Continuous variables were compared with the Student’s t test, and the χ² statistic was used for categorical data. Multivariate analysis was done by the stepwise logistic regression method or Cox regression analysis where applicable, and log rank testing was used for comparison of the Kaplan-Meier survival curves (SPSS version 10.0.7).

Results

Patient Characteristics

From June 1998 to January 2001, 150 patients were enrolled, of whom 74 were randomized to IVUS-guided stenting and 76 to angiographic guidance. Just before the intervention, 4 patients were secondarily excluded and referred for bypass surgery because of disease progression (1 patient in each group) had previously unrecognized left main stenoses, and 2 patients assigned to angiographic guidance had progression to total occlusion. Two patients randomized to angiographic guidance refused the allocated strategy and were excluded from intention-to-treat analysis. Angiography at 6 months was available in 125 (87%) of 144 patients (64 [88%] of 73 IVUS-guided patients and 61 [86%] of 71 patients in the angiography group). In both groups, the stent could not be delivered to the target in 1 patient. In the angiography group, 2 patients did not receive stents after predilation (operator choice). In the IVUS group, coronary rupture after predilation necessitated acute bypass surgery in 1 patient. Ultimately, 71 patients in the IVUS group (97%) and 68 in the angiography group (96%) received the assigned treatment (P = NS). At 6 months, clinical follow-up was available for 144 patients (100%), and at 12 months, 70 IVUS-guided patients (96%) and 68 patients in the angiography group (96%) were interviewed (Figure 1). Baseline clinical characteristics were similar in both groups (Table 1). Because lesion lengths...
>20 mm were required for inclusion, by definition all lesions were type C. 19

**Procedural Characteristics**

There was a significant increase in stent length and number of stents associated with IVUS guidance (Table 2). The final balloon was larger in the IVUS group, whereas maximal inflation pressures were equivalent. Angiographic success was achieved in 97% of patients in both groups (P = NS). Abciximab was used more often in the IVUS group because of flow-limiting thrombus or side-branch dissections (Table 2).

Online IVUS measurements at the end of the procedure showed an MLA of 6.0 ± 3.3 mm², with proximal and distal reference areas of 8.8 ± 3.3 and 5.9 ± 2.5 mm², respectively; the MLD was 2.8 ± 0.3 mm, with proximal and distal reference diameters of 3.3 ± 0.4 and 2.7 ± 0.4 mm, respectively. All criteria for optimal stent placement were achieved in 65 patients (89%). In the other 8 patients (10%), final in-stent MLA remained smaller than the distal reference lumen despite a balloon-to-vessel ratio up to 1.3 and/or high-pressure inflations.

**Angiographic Analysis**

QCA showed that the preintervention lesion parameters were equivalent (Table 2). Final and follow-up MLDs in the IVUS group were significantly larger than in the angiography group (Table 2). Angiographic restenosis occurred in 15 (23%) of 64 IVUS-guided patients and in 28 (46%) of 61 patients in the angiography group (P = 0.0082). Figure 2 depicts the cumulative frequency curves of the MLD before stent placement, after stent placement, and at 6-month follow up for both groups.

Angiographic 6-month MLD in diabetics was smaller than in nondiabetics (1.69 ± 0.6 versus 1.4 ± 0.5 mm; P = 0.044). Statin use was associated with a significantly larger 6-month MLD (1.8 ± 0.6 versus 1.4 ± 0.6 mm; P = 0.003). No other medication, including abciximab, had a significant effect on follow-up MLD.

Significant correlations could be demonstrated between follow-up MLD and initial reference diameter (r = 0.56, P < 0.001), initial MLD (r = 0.20, P = 0.001), final balloon size

**Figure 2.** Cumulative distribution of MLD. Pre indicates before intervention; Post, after intervention; and FU, follow-up.
TABLE 3. Clinical Events

<table>
<thead>
<tr>
<th></th>
<th>IVUS Group (n=73)</th>
<th>Angiography Group (n=71)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>MI</td>
<td>1 (1)</td>
<td>2 (3)</td>
<td>NS</td>
</tr>
<tr>
<td>TLR</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Non-TLR</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Death+MI+TLR</td>
<td>2 (3)</td>
<td>2 (3)</td>
<td>NS</td>
</tr>
<tr>
<td>Any event</td>
<td>2 (3)</td>
<td>2 (3)</td>
<td>NS</td>
</tr>
<tr>
<td>0–1 Month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>MI</td>
<td>1 (1)</td>
<td>2 (3)</td>
<td>NS</td>
</tr>
<tr>
<td>TLR</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Non-TLR</td>
<td>1 (1)</td>
<td>2 (3)</td>
<td>NS</td>
</tr>
<tr>
<td>Death+MI+TLR</td>
<td>2 (3)</td>
<td>2 (3)</td>
<td>NS</td>
</tr>
<tr>
<td>Any event</td>
<td>2 (3)</td>
<td>2 (3)</td>
<td>NS</td>
</tr>
<tr>
<td>0–6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>NS</td>
</tr>
<tr>
<td>MI</td>
<td>1 (1)</td>
<td>5 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>TLR</td>
<td>3 (4)</td>
<td>10 (14)</td>
<td>0.037</td>
</tr>
<tr>
<td>Death+MI+TLR</td>
<td>4 (6)</td>
<td>14 (20)</td>
<td>0.01</td>
</tr>
<tr>
<td>Non-TLR</td>
<td>8 (11)</td>
<td>8 (11)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are n (%).

(r=0.42, \(P<0.001\)), and postprocedural MLD (r=0.56, \(P<0.001\)). However, follow-up MLD had no relationship with lesion length, stent length, or number of stents. Because final balloon size, final MLD, stent length, and the number of stents were consequences of IVUS guidance, these variables were excluded from the model, consistent with the intention-to-treat principle. All other variables with a univariate \(P=0.10\) (diabetes, statin use, IVUS guidance, initial reference diameter, and sex) were included in the multivariate analysis. Independent predictors of 6-month MLD were initial reference diameter (\(P<0.001\)), IVUS guidance (\(P=0.03\), and statin use (\(P=0.045\)).

**Clinical Outcome**

Table 3 summarizes the clinical events. Side-branch occlusion resulted in 1 Q-wave and 1 non–Q-wave MI in the angiography group and 1 non–Q-wave MI in the IVUS group. Procedural success was similar (96%) in both groups (\(P=NS\)). The in-hospital combined event rate was 3% for both groups (\(P=NS\)). At 1 month, 1 patient in each group had an episode of chest pain that could not be attributed to the treated vessel after repeated angiography.

Within 6 months, 1 patient with in-stent restenosis in the angiography group died of complications after bypass surgery. The ischemia-driven TLR rate was 4% (n=3) in the IVUS group and 14% (n=10) in the angiography group (\(P=0.037\)). In each group, 8 patients (11%) had a non–target-lesion intervention. At 6 months, the combined event rate (death plus MI plus TLR) was 6% in the IVUS group (n=4) and 20% in the angiography group (n=14; \(P=0.01\)).

From 6 to 12 months, 2 patients in the IVUS group died within 4 weeks after a non–target-lesion intervention: 1 due to heart failure, another of vascular complications (a Jehovah’s Witness who refused transfusions). The combined event rate (death plus MI plus TLR) at 12 months (Figure 3A) was 12% (n=9) in the IVUS group versus 27% (n=19) in the angiography group (\(P=0.026\)). The cumulative TLR rate at 12 months (Figure 3B) was 10% (n=7) in the IVUS-guided group versus 23% (n=17) in the angiography group (\(P=0.018\)). Cox regression analysis of the clinical events was done with a model that included all variables with \(P=0.10\) in univariate comparison (diabetes, statin use, IVUS guidance, and initial reference diameter). Guidance by IVUS was independently associated with a lower frequency of the combined end point of cardiac death, MI, and TLR at 6 months (\(P=0.025\)) and 12 months (\(P=0.016\)). Nonuse of a statin before the intervention was also an independent risk factor for occurrence of the combined clinical end point at 6 months (\(P=0.027\)) but not at 12 months.

**Discussion**

The improved angiographic and clinical outcome of stenting long coronary stenoses with IVUS guidance is the principal finding of this study. This occurred despite the fact that patients randomized to IVUS guidance received more and/or longer stents, 2 characteristics notorious for their association with restenosis.4–6 Long lesions are a challenging subset because they are traditionally associated with poor outcome after balloon angioplasty or stenting.1–6 The only randomized study to

![Figure 3. Kaplan-Meier survival curves. A, Cumulative combined event-free survival. B, Cumulative freedom from TLR. ANGIO indicates angiographic guidance.](http://circ.ahajournals.org/doi/10.1161/CIRCULATIONAHA.107.712681)
investigate the use of stents in this subset showed less 6-month angiographic restenosis in the stent group (27%) than in the balloon group (42%; P<0.05) but no clinical benefit at 9 months.20 In a nonrandomized comparison, balloon angioplasty with IVUS-guided provisional spot stenting had a better long-term outcome than stenting with full lesion coverage.21 IVUS-guided patients in the present study had better angiographic and clinical outcomes than patients in either of these previous studies. In the present study, information obtained with IVUS apparently motivated the operators to stent athroesclerotic segments more extensively, despite similar lesion lengths in the angiography group. The extent of athroesclerotic disease is not accurately identified by angiography, and consequently, automated quantitative techniques may define stenosis borders as the place where compensatory vessel enlargement fails to preserve luminal dimensions, not where significant disease begins or ends.22 The present results indicate that complete coverage of the target lesion plus IVUS-guided optimal stent expansion offsets the unfavorable influence of more metal on late outcome. One explanation could be that stent dimension rather than length is the primary determinant of long-term outcome. Alternatively, the favorable flow characteristics associated with smooth transitions of slightly or nondiseased vessel to stented parts, as opposed to the disturbed flow that occurs with an abrupt transition of a significantly diseased vessel segment to a relatively smoother stented part, could positively influence the local reaction and late outcome.

Generally, greater acute gain produces more injury and more late loss. However, similar to other reports,14 it did not result in increased late loss in the IVUS-guided group in the present study. Analogous to our findings regarding stent length and restenosis, we tend to ascribe this effect to optimization of the luminal geometry.

The angiographic criteria for optimal stent placement (<30% residual stenosis) in the present protocol could be considered conservative, but because QCA data of the final result were similar in both groups, a bias of the interventionists in favor of the IVUS approach is unlikely. Because of a perceived difference in initial MLD in the cumulative frequency distribution curves, multivariate analyses were repeated to force baseline MLD into the model. This analysis confirmed that initial MLD was not an independent predictor of angiographic or clinical outcome at 6 or 12 months.23

We also found that statin use was independently associated with better angiographic and clinical outcome. Although several researchers have found that smooth muscle cell proliferation is inhibited by statin use,24,25 only a few studies directly investigated the possible effects of this therapy on restenosis after stenting. The present data corroborate the reduction of in-stent restenosis and improved clinical outcome reported by Walter et al26 in a nonrandomized study of the effects of statins after stenting.

Study Limitations

This was a single-center study with a relatively small sample size, but it was adequately powered to demonstrate the assumed difference between the strategies. Because we used 2 end points, an angiographic and a clinical parameter, to evaluate the difference between the 2 treatment strategies, it could be argued that correction for multiple testing (Bonferroni) should be used. This type of correction, however, would imply independence of angiographic and clinical outcome, but in our experience, these are highly correlated, which forms the basis for the use of angiographic outcome parameters as surrogate markers for event rate.27–29 The exclusive use of 1 stent type prohibits extension of these findings to the liberal use of other stents, but stent design may influence late outcome.30,31 Because only lesions >20 mm were included, these results may not be applicable to shorter lesions in which “baseline” restenosis rates are lower. Finally, there was a difference in abciximab use due to more difficulties in the IVUS group that resulted in flow impairment, but without an increase in clinical events.

Conclusions

This study demonstrates an improved angiographic and clinical outcome after stent placement for long coronary stenoses guided by IVUS compared with angiographic guidance only. The initial results of drug-eluting stents for shorter lesions are promising, and in view of this report, the use of these new devices should be compared with the strategy of IVUS guidance when investigated in a lesion set comparable to that in the present study.

Acknowledgment

This study was supported by an unrestricted research grant from Medtronic/AVE.

References


Intravascular Ultrasound Guidance Improves Angiographic and Clinical Outcome of Stent Implantation for Long Coronary Artery Stenoses: Final Results of a Randomized Comparison With Angiographic Guidance (TULIP Study)
Pranobe V. Oemrawsingh, Gary S. Mintz, Martin J. Schalij, Aeilko H. Zwinderman, J. Wouter Jukema and Ernst E.v.d. Wall

Circulation. 2003;107:62-67; originally published online December 9, 2002;
doi: 10.1161/01.CIR.0000043240.87526.3F
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/107/1/62

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/