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Randomized Comparison of Primary Stenting and Provisional Balloon Angioplasty Guided by Flow Velocity Measurement

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Background—Coronary stenting improves outcomes compared with balloon angioplasty, but it is costly and may have other disadvantages. Limiting stent use to patients with a suboptimal result after angioplasty (provisional angioplasty) may be as effective and less expensive.

Methods and Results—To analyze the cost-effectiveness of provisional angioplasty, patients scheduled for single-vessel angioplasty were first randomized to receive primary stenting (97 patients) or balloon angioplasty guided by Doppler flow velocity and angiography (523 patients). Patients in the latter group were further randomized after optimization to either additional stenting or termination of the procedure to further investigate what is "optimal." An optimal result was defined as a flow reserve >2.5 and a diameter stenosis <36%. Bailout stenting was needed in 129 patients (25%) who were randomized to balloon angioplasty, and an optimal result was obtained in 184 of the 523 patients (35%). There was no significant difference in event-free survival at 1 year between primary stenting (86.6%) and provisional angioplasty (85.6%). Costs after 1 year were significantly higher for provisional angioplasty (EUR 6573 versus EUR 5885; $P=0.014$). Results after the second randomization showed that stenting was also more effective after optimal balloon angioplasty (1-year event free survival, 93.5% versus 84.1%; $P=0.066$).

Conclusions—After 1 year of follow-up, provisional angioplasty was more expensive and without clinical benefit. The beneficial value of stenting is not limited to patients with a suboptimal result after balloon angioplasty. **(*Circulation*. 2000;102:2930-2937.)**

Key Words: stents ■ angioplasty ■ balloon ■ random allocation ■ cost-benefit analysis

Over the last 2 decades, percutaneous transluminal coronary angioplasty has proven to be a safe and effective option for treating patients with coronary artery disease.[1] However, treatment results may be transient because of recoil, restenosis, and reocclusion. Although these disadvantages are partly overcome by coronary stenting,[2–6] the costs of coronary stenting are high compared with balloon angioplasty, and the long-term outcome remains a matter of concern.[7,8]

It has been suggested that optimal balloon angioplasty could yield a clinical outcome similar to stenting.[9–12] The Doppler Endpoints Balloon Angioplasty Trial Europe (DEBATE) I results support this hypothesis in that the outcome for patients with both a diameter stenosis (DS) ≤35% and a coronary flow reserve (CFR) >2.5 was comparable to that achieved with stenting in the Belgian Netherlands Stent (BENESTENT) trials.[3,13] Thus, the following provisional approach emerges: stent only those patients likely to reap an additional benefit. Such an approach challenges the intervener who must decide on overall patient care. "Provisional

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A complete list of the DEBATE II study group investigators can be found in the Appendix.

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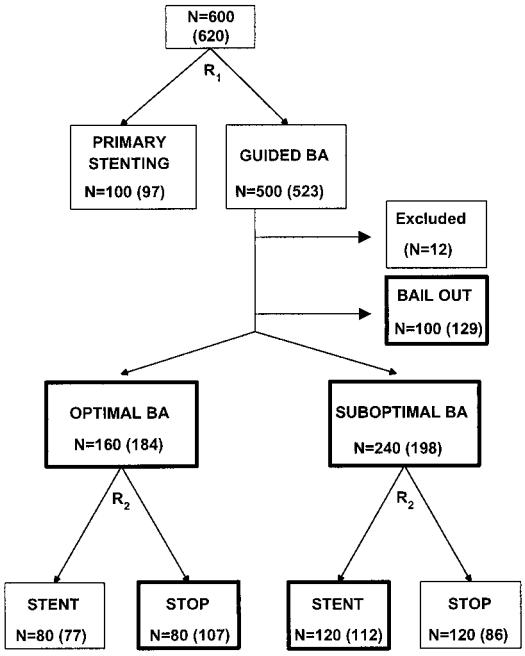

Figure 1. Study flowchart. R_1 indicates first randomization; R_2, second randomization; and BA, balloon angioplasty. Patient groups with provisional stenting are framed in bold. Actual number of patients in clinical subsets lie between parentheses; theoretical assumptions are denoted by n. Twelve patients were excluded from study between randomizations 1 and 2 (10 due to inconsistencies between randomization service and investigators, and 2 due to missing CFR values).

angioplasty" refers to a status of angioplasty that satisfies predefined criteria of optimal results based on pressure gradients,[11] early loss of minimal lumen diameter,[10] or intravascular ultrasound measurements.[12] A failure to meet the criteria would change the intended treatment and results in stent implantation.

DEBATE II was a prospective, randomized study that used criteria identified in DEBATE I. It addressed the following questions. (1) Should elective treatment be by stenting or balloon angioplasty (provisional angioplasty being guided by the stated criteria)? (2) What is the relative cost/benefit ratio of these strategies? (3) Do patients with optimal balloon angioplasty obtain an additional benefit from stenting?

Methods

Patient Selection

Patients were eligible for the study if they were scheduled to undergo angioplasty for stable or unstable angina pectoris (excluding Braunwald classification III),[14] documented myocardial ischemia due to a single de novo coronary stenosis potentially amenable to stent implantation, or both. The target lesion was to supply viable myocardium and be <25 mm long. Excluded patients manifested total coronary occlusion; lesions that were ostial or at a bifurcation; lesions in vessels that were previously bypassed, tortuous, or contained thrombus; or previous Q-wave infarction (in the target vessel territory or from an evolving myocardial infarction of the previous week). The study was performed according to the principles in the Declaration of Helsinki. Every patient provided written, informed consent.

Study Objectives and Trial Design

The primary trial objective was to compare the cost-effectiveness of elective stent implantation (primary stenting) with provisional bal-

TABLE 1. Baseline Clinical and Angiographic Characteristics

	First Randomization	
	Primary Stenting	Guided Balloon Angioplasty
n	97	523
Male sex	72	73
Age, y	60±10	59±11
Previous conditions		
Q-wave myocardial infarction	6	10
Non Q-wave myocardial infarction	18	17
Coronary artery bypass grafting	1	1
Angioplasty	9	11
Diabetes mellitus	10	10
Insulin-dependent	2	2
Hypertension	46	39
Hypercholesterolemia	48	53
Family history	43	38
History of stroke	2	2
Peripheral vascular disease	7	5
Smoking history		
Never smoked	35	36
Previous smoker	38	37
Current smoker	27	27
Stable angina	59	58
Canadian Cardiovascular Society classification		
1	5	5
2	32	31
3	19	20
4	3	2
Unstable angina	39	34
Braunwald classification[14]		
IB	8	12
IIB	24	17
IC	4	2
IIC	3	3
Silent ischemia	2	8
No. of diseased vessels		
1	91	90
2	9	8
3	0	2
Target vessel		
Right coronary	26	30
Left anterior descending	61	53
Left circumflex	13	18
Lesion type[27]		
A	12	18
B1	23	26
B2	59	51
C	6	6
DS,* %	70±12	70±11

Values are mean±SD or % of patients, unless otherwise indicated.
*Assessed by the investigator during the procedure.

TABLE 2. Angiography and CFR During the Procedure

	First Randomization			GBA: Second Randomization			
	PS	GBA	GBA Bailout	Stent: Optimal	Stent: Suboptimal	Balloon: Optimal	Balloon: Suboptimal
n	97	523	129	77	112	107	86
Initial DS, %	70±12	70±11	72±11	67±11	70±11	69±12	69±11
Initial CFR	...	1.6±0.6	1.6±0.6	1.7±0.6	1.5±0.6	1.7±0.6	1.4±0.4
DS before second randomization, %	...	...	...	22±8	22±9	23±8	24±11
CFR before second randomization	...	...	...	3.1±0.5	2.0±0.4	3.1±0.6	2.0±0.4
Lesion length, mm				9±4	9±4	9±3	9±4
Reference diameter, mm				2.78±0.42	2.73±0.44	2.71±0.47	2.62±0.45
Final DS, %	9±8	...	...	8±8	7±8	...	...
Stent length, mm				15±4	16±4	...	...
Balloon length, mm				...	...	20±2	20±4
Final CFR	...	...	...	3.3±0.7	2.4±0.7	...	...

Values are mean±SD. PS indicates primary stenting; GBA, guided balloon angioplasty.

Twelve patients were excluded from the study after the first randomization: 10 patients due to inconsistencies between randomization service and investigators, and 2 patients due to missing CFR values.

loon angioplasty guided by quantitative angiography and Doppler flow velocity measurements. The strategy after provisional angioplasty was to limit stent implantation to bailout situations and cases in which an "optimal result" (DS ≤35% and CFR >2.5)[13] was not achievable. The secondary objective was to evaluate the benefit differences from additional stenting in patients with and without an optimal result. Therefore, double randomization was required (Figure 1).

It would be incorrect to estimate the costs and benefits of provisional angioplasty using average costs and benefits combining (1) patients with bailout stents, (2) patients with optimal balloon angioplasty, and (3) patients with stenting after a suboptimal result. Patients left after bailout stenting would then receive too much weight, because the bailout decision was made before the second randomization, leading to 4 groups instead of the 2 created by the provisional angioplasty strategy. Therefore, a weighted average was used that weighted bailout stenting by the probability of bailout stenting and stenting in patients who did not require bailout stenting by the probabilities of belonging to either the optimal balloon angioplasty or suboptimal angioplasty groups. Thus, the provisional angioplasty group is a constructed or virtual group.

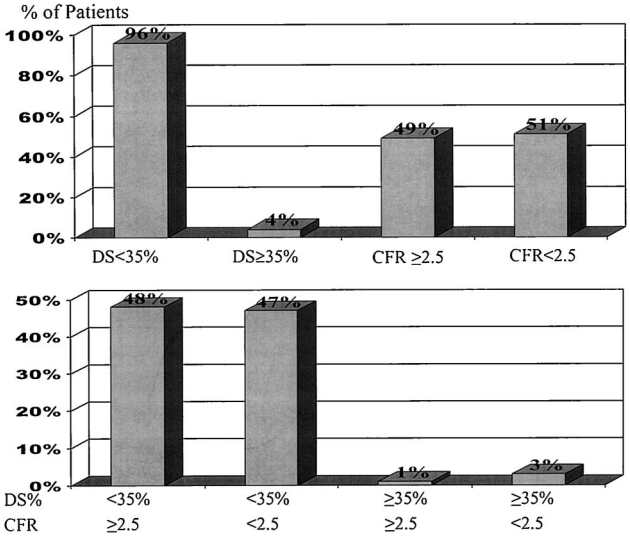

Figure 2. Relative role of DS and CFR in classifying patients in balloon angioplasty group (bailout patients not included).

Primary Stenting

A conventional guidewire was used in patients randomized to primary stenting, and predilatation was performed in all patients before stent implantation.

Guided Balloon Angioplasty

During guided balloon angioplasty, quantitative angiography and CFR measurements were made using standardized protocols[13,15] to achieve an optimal result (criteria defined earlier in article).

A 0.014-inch Doppler guidewire (Cardiometrics FloWire, EndoSonics) was advanced distal to the lesion, and velocity recordings were obtained under basal and hyperemic conditions. Maximal hyperemia was induced by adenosine, which was administered as an intracoronary bolus (right coronary artery, 12 μg; left coronary artery, 18 μg) or as an intravenous infusion (140 $\mu g \cdot kg^{-1} \cdot min^{-1}$).[16,17] These 2 methods were proven to be equivalent.

If an optimal result was not achieved, the operator was urged to perform iterative dilatations by upsizing the balloon, increasing the inflation pressure, or both. Bailout stenting was allowed in the presence of residual stenosis >50%; dissection types D, E, or F; persistent myocardial ischemia with dissection type C; reduction of TIMI flow[18] by ≥1 grade; or the existence of TIMI grades 0 or 1. The final DS and CFR were assessed after an optimal result was achieved or when the operator considered further improvement attempts unsafe. A second randomization was then performed that disregarded the measurements.

Efficacy End Points

The efficacy end point compiled major adverse cardiac events within 12 months of the procedure; these included death from any cause, nonfatal myocardial infarction, and percutaneous or surgical target lesion revascularization. Myocardial infarction was defined as the development of a new Q-wave or a rise of serum creatinine kinases with an abnormal plasma concentration of myocardial isoenzymes. Enzymes were sampled twice in the first 24 hours. Patients visited the outpatient clinic 1, 6, and 12 months after hospital discharge. At each visit, records were kept of anginal status, cardiac medication, 12-lead ECG, and complete physical examination. No follow-up angiogram was performed unless clinically indicated.

TABLE 3. Frequency of Primary Clinical End Points at 12 Months in Descending Order of Severity

	First Randomization			GBA: Second Randomization			
	PS	GBA	GBA Bailout	Stent: Optimal	Stent: Suboptimal	Balloon: Optimal	Balloon: Suboptimal
n	97	523	129	77	112	107	86
Death	2.1	1.3	0.8	2.6	0.9	0.9	2.3
MI	4.1	3.6	7.0	0.0	3.6	1.9	3.5
Q-wave	2.1	1.9	3.1	0.0	1.8	1.9	1.2
Non–Q-wave	2.1	1.7	3.9	0.0	1.8	0.0	2.3
CABG	0.0	1.1	2.3	0.0	0.9	0.9	0.0
TLPR	7.2	9.8	7.8	3.9	5.4	12.1	20.9
MACE-free	86.6	84.1	82.2	93.5	89.3	84.1	73.3
Any MACE	13.4	15.9	17.8	6.5	10.7	15.9	26.7

All values except n are percent. MI indicates myocardial infarction; CABG, coronary artery bypass grafting; TLPR, target lesion percutaneous revascularisation; MACE, major adverse clinical events; PS, primary stenting; and GBA, guided balloon angioplasty.

Twelve patients were excluded from the study after the first randomization: 10 patients due to inconsistencies between the randomization service and investigators, and 2 patients due to missing CFR values.

Costs

Cost analysis was limited to direct medical costs, which were calculated as resource utilization volume × unit costs in 1999 at the University Hospital Rotterdam-Dijkzigt, the Netherlands.[19] Resources included the materials used in the initial procedure (eg, stents, balloons, and Doppler wires); length of stay in the intensive care unit, coronary care unit, or general ward; major curative and diagnostic procedures; and rehospitalization within 12 months of the initial procedure. Although it could be expected that a guided strategy would lengthen procedures, we decided not to estimate the cost consequences of such an action. We hypothesized that the increased duration would not reduce the number of procedures possible per day; thus, the "fixed costs" would remain fixed. Also, the data may be biased by the time taken for a second randomization, thus breaking the continuity of procedures.

Cost Effectiveness

The balance between costs and benefits was addressed by calculating incremental cost-effectiveness ratios (ie, additional costs per additional event-free survivor after 1 year) and by estimating the probabilities that the provisional angioplasty was (1) more effective and cost saving, (2) more effective and more costly, (3) less effective and cost saving, or (4) less effective and more costly.

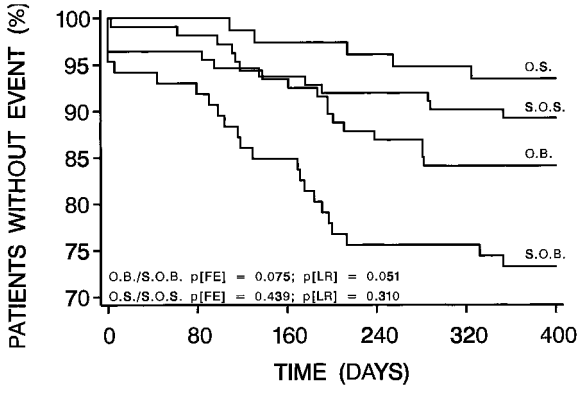

Figure 3. Event-free survival (Kaplan-Meier curves) at 12 months. Patients with suboptimal and optimal balloon angioplasty were randomized to additional stenting or no further treatment. OS indicates optimal stenting (n=77); SOS, suboptimal stenting (n=112); OB, optimal balloon angioplasty (n=107); SOB, suboptimal balloon angioplasty (n=86); FE, Fisher's exact test; and LR, log-rank test. For definitions of optimal and suboptimal, see text.

Sample Size

Assumptions for sample size calculation were based on BENESTENT-1, BENESTENT-2 pilot, and DEBATE I experiences.[2,3,13] All additional benefits of stenting were attributed to patients with suboptimal results. With these assumptions, it was calculated that for the randomization scheme in Figure 1, 600 patients were needed to detect, with 80% power, a difference (α=0.05) of EUR 680 between provisional angioplasty and primary stenting in cost-effectiveness per survivor (no major adverse cardiac event) after 1 year.[20]

Statistical Analysis

Continuous variables are expressed as means±SD. Differences between patient groups were studied using Student's unpaired *t* test or 1-way ANOVA, whichever was appropriate. Categorical variables are presented as percentages, and differences between groups were evaluated using Fisher's exact test. Kaplan-Meier event-free survival curves were calculated, and differences between patient groups were compared by a log-rank test.

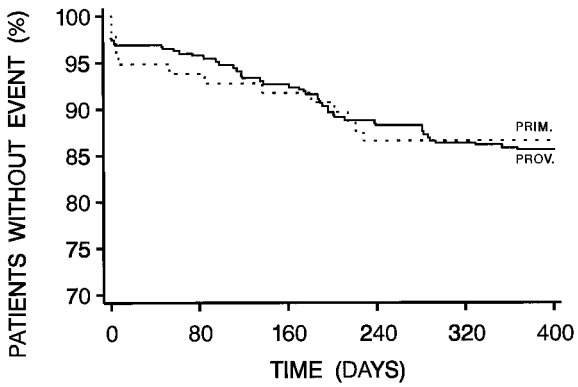

Figure 4. Event-free survival (Kaplan-Meier curves) at 12 months in patients who had primary stenting (PRIM; n=97) or provisional angioplasty (PROV; n=523).

TABLE 4. Costs and Event-Free Survival After 12 Months

	Unit Cost per Patient, €	PS	PA*	Optimal Stenting	Optimal Balloon	Suboptimal Stenting	Suboptimal Balloon	Bailout
No. of patients		97	523	77	107	112	86	129
Procedure and initial hospitalization								
Fixed procedure costs, €		1167	1167	1167	1167	1167	1167	1167
Resource use, Unit per patient								
Guiding catheter	82	1.20	1.20	1.19	1.24	1.21	1.14	1.13
Guidewire	95	1.03	0.55	0.40	0.42	0.56	0.44	0.70
FloWire	483	0.26	1.09	1.12	1.11	1.07	1.07	1.07
Balloon	368	1.52	1.55	1.52	1.27	1.67	1.31	1.78
Mounted stent	817	0.58	0.41	0.57	0.04	0.49	0.07	0.82
Nonmounted stent	454	0.56	0.37	0.49	0.04	0.60	0.05	0.49
Reoperation	1021	0.02	0.03	0.04	0.01	0.04	0.03	0.05
IVUS catheter	545	0.05	0.04	0.03	0.02	0.06	0.09	0.05
Contrast medium, mL	0	249	284	333	253	301	307	307
CCU days	856	0.58	0.62	0.53	0.49	0.58	0.84	0.86
ICU days	941	0.00	0.01	0.00	0.00	0.00	0.03	0.05
Non–CCU/ICU days	305	3.36	2.76	2.43	2.27	3.06	2.40	3.00
Follow-up, Unit per patient								
Second interventions	2800	0.16	0.16	0.12	0.19	0.15	0.22	0.15
CABG	8622	0.00	0.02	0.00	0.01	0.01	0.01	0.05
Recatheterization	1934	0.20	0.23	0.27	0.21	0.27	0.31	0.22
Vascular surgery	1157	0.00	0.01	0.00	0.00	0.00	0.00	0.02
CCU days	856	0.22	0.21	0.09	0.18	0.15	0.40	0.35
ICU days	941	0.00	0.03	0.00	0.03	0.02	0.01	0.05
Non–CCU/ICU days	305	1.38	2.62	0.82	2.55	2.72	2.11	2.56
Costs of initial hospitalization, €		4456	4486	4493	3606	4769	4084	5305
Costs of follow-up, €		1420	2055	1139	1927	1995	2352	2330
Total cost, €		5885	6573	5632	5533	6764	6519	7763
Event-free survival, %		86.6	85.6	93.5	84.1	89.3	73.3	82.2

CCU indicates coronary care unit; ICU, intensive care unit; CABG, coronary artery bypass grafting; PS, primary stenting; and PA, provisional angioplasty.
*Costs and effects of the provisional angioplasty group were assessed by calculating a weighted average.

Because the costs and benefits of provisional angioplasty were calculated as weighted averages, bootstrapping techniques were used to evaluate differences in the balance between costs and benefits after primary stenting and provisional angioplasty.[21,22] A total of 3000 bootstrap samples were drawn iteratively, with replacement when sample sizes equalled the total number of patients studied. Odds ratios and 95% confidence intervals are presented; a Breslow-Day test for homogeneity of odds ratios between subgroups and χ^2 tests were also applied.

Statistical tests were 2-tailed, with significance stated at the 0.05 level. Uncertainties surrounding cost, benefits, and cost-effectiveness were addressed by probability ellipses in the "cost-effectiveness plane."[21]

Results

Patient Characteristics

Baseline characteristics of the patients in this trial are presented in Table 1. There were no significant differences between patients allocated to primary stenting and to guided balloon angioplasty. Of the 523 patients randomized to guided balloon angioplasty, 129 (25%) underwent bailout stenting at the time of initial dilatation (n=103) or during the optimization process (n= 26). Of the remaining 394 patients, 382 underwent the second randomization. Twelve were not subrandomized for technical and logistical reasons.

Procedural Results

Table 2 summarizes the procedural results, and Figure 2 shows the relative roles of DS and CFR in classifying patients. Optimal results, with an average DS of 22±8% and a CFR of 3.1±0.6, were achieved in 35% of patients. In the suboptimal group, DS was 23±10% and CFR was 2.0±0.4. Additional stenting in patients with optimal balloon angioplasty resulted in a DS of 8±8% and a CFR of 3.3±0.7; in patients with suboptimal balloon angioplasty, additional stenting resulted in a DS of 7±8% but a CFR of 2.4±0.7.

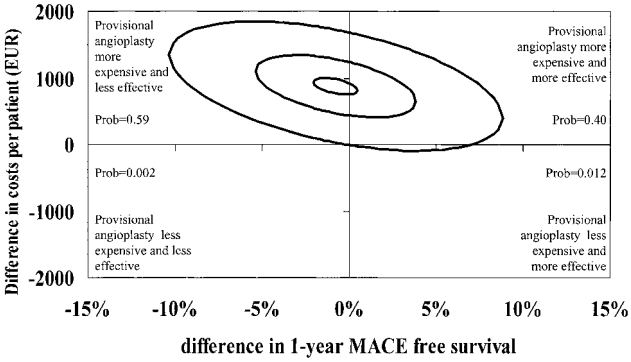

Figure 5. Incremental cost-effectiveness of provisional angioplasty vs primary stenting. Outer ellipse defines smallest area (95% probability) containing incremental costs and effectiveness of provisional angioplasty compared with primary stenting. Middle and inner ellipses define smallest areas (50% and 5% probabilities, respectively). Center of ellipse represents point estimate of incremental costs and effects. Prob indicates estimated probability that cost and effect are in respective quadrant; MACE, major adverse cardiac events.

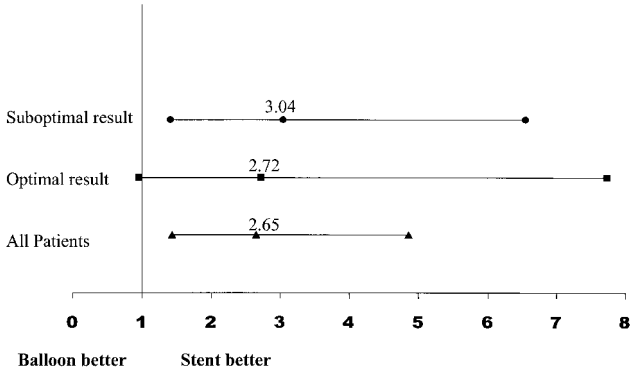

Figure 6. Relative risk ratios at 12 months for patients with suboptimal or optimal balloon angioplasty who survived event-free and were randomized to additional stenting or no further treatment. Bars indicate 95% confidence intervals.

Primary Stenting Versus Provisional Angioplasty

Table 3 shows the incidence of major adverse cardiac events in both the initial groups and the 4 subgroups, ranked in hierarchical order. In general, patients with optimal results experienced fewer major adverse cardiac events than patients with suboptimal results, and stented patients fared better than those undergoing balloon angioplasty alone (Figure 3).

Freedom from these events, which were calculated as weighted averages, was similar for patients undergoing primary stenting (86.6%) and provisional angioplasty (85.6%) (Figure 4). The weight for patients needing bailout stenting was 129/(129+107+112+86+77) or 25.2%; the weight for patients stented after a suboptimal result was 38.7% (calculated as the probability of not needing a bailout stent [100.0%–25.2%=74.8%] multiplied by the probability of a suboptimal result {[112+86]/[77+107+112+86]=51.8%}); and the weight for patients with a stent after an optimal result was 36.0% (calculated as the probability of not needing a bailout stent [74.8%] multiplied by the probability of an optimal result [100%–51.8%=48.2%]).

Table 4 presents cost estimates for the 2 initial groups and 4 subgroups. The cost of FloWire in the initial procedure was only partially covered by the lower stent use. Costs for the provisional angioplasty group during follow-up were higher due to longer hospitalizations and surgical revascularization. After 1 year, the costs of provisional angioplasty outweighed those of direct stenting by EUR 688. Figure 5 presents the estimates of costs, benefits, and cost effectiveness. The point estimate of the incremental cost-effectiveness ratio suggests that provisional angioplasty is less effective and more expensive.

Stenting Versus Balloon Angioplasty After the Second Randomization

The analysis of subrandomized patients in the balloon angioplasty group (Figure 6) indicates that stenting was associated with fewer major adverse cardiac events than balloon angioplasty alone in both patients with suboptimal (10.7% versus 26.7%; odds ratio, 3.0; $P=0.005$) and optimal results (6.5% versus 15.9%; odds ratio, 2.7; $P=0.066$). The Breslow-Day test for homogeneity of odds ratios was not significant ($P=0.865$). The higher cumulative costs of balloon angioplasty alone during the follow-up period almost matched the high initial costs of balloon angioplasty followed by stenting.

Discussion

The main result of this study was a lack of significant difference between clinical outcomes when comparing primary stenting and provisional balloon angioplasty. However, with the current unit costs of FloWire and stents, a strategy of provisional angioplasty is more costly than primary stenting.

Relevance and Critical Appraisal of Cost-Effectiveness Analysis

Cost considerations dominate many decisions about therapeutic interventions and are very relevant from a societal viewpoint. As emphasized in the literature, an independent person without commercial affiliations must analyze cost-effectiveness in such studies to avoid financial bias.[23] However, cost-effectiveness analyses are limited by multiple factors. First, cost data are transient and are affected by product acceptance, market dynamics, and reimbursement systems. Second, changing patterns of practice affect the selection of treatment devices, how they are used, and overall procedure time. Thus, the costs used here represent only a snapshot in time. For example, direct stenting without predilatation (an increasingly used technique) will undoubtedly affect cost-effectiveness in the future, but this method of treatment was not applied here.

Two crucial factors in the present study exerted a major influence on overall costs: the costs of FloWire and those of stenting. When the study was designed, its power calculation was based on market prices in 1996 and the cost estimates related to bleeding complications and the longer hospital stays associated with stenting. The reported cost estimates were based on unit costs in 1999 (costs of primary stenting versus provisional angioplasty, EUR 5916 versus EUR 6724;

$P=0.029$). However, an application of 1996 unit costs does not change the conclusion. The absence of expected differences is mainly because in the year 2000, stenting is no longer associated with bleeding complications and longer hospital stays, whereas the bailout rate with the balloon angioplasty group has increased from 15% to 25%.

Moreover, we did not take into account differences in procedure time. The time for guided angioplasty in the present study was 26 minutes longer (mean) than that of stenting, which further tipped the cost-effectiveness balance in favor of primary stenting.

The Additional Value of Stenting After Optimal Angioplasty: A Flow-Mediated Phenomenon?

An unexpected observation in this study was a further reduction in the rate of major adverse cardiac events in patients stented after optimal balloon angioplasty. This observation was made possible by the trial's double randomization design. On the basis of stent-like angioplasty results in other trials,[9,13,24] we had hypothesized no such additional benefits. However, the perceived benefits of additional stenting may have resulted from a selection process that ignored the outcome of patients with unsatisfactory or complicated balloon angioplasty (ie, bailout and suboptimal groups).

Although a similar DS was achieved in all patients stented after angioplasty (7%), a diminished CFR persisted after stenting in the suboptimal group (2.4) compared with the optimal group (3.3). Fewer major cardiac events were observed in the latter group (10.7% versus 6.5%). Further investigations are needed to fully understand the underlying mechanisms.

Clinical Relevance of the Findings of This Study

The present study failed to demonstrate a favorable economic profile for provisional angioplasty (guided by quantitative angiography and Doppler flow velocity measurements) compared with primary stenting. Indeed, although there was no significant difference in clinical effectiveness, the data pointed to higher costs with provisional angioplasty. Thus, the current data do not provide economic arguments to switch from primary stenting, even though clinical benefits result when stenting follows optimal balloon angioplasty. A limitation of our study was the inclusion of patients with only a single, relatively short lesion. However, it would seem from a literature survey that the patients studied represented possibly up to 70% of patients presently treated by percutaneous techniques worldwide.[25,26]

Appendix

Study Investigators, Their Location, and Number of Patients Treated

The Netherlands: P.W. Serruys, M.v.d. Brand, S.G. Carlier, P. de Feyter, D. Foley, W.v.d. Giessen, J. Hamburger (n=67); J.J. Piek, F.v.d. Wal (n=36); N.H.J. Pijls, J.P.M. van Asseldonk (n=20); V.A.W.M. Umans (n=13); G.J. Laarman, F. Kiemeneij (n=13); Belgium: B. de Bruyne, W. Wijns, G.R. Heyndrickx (n=60); C. Vrints (n=29); O. Gurné (n=24); C. Hanet, N. Debbas, D. Huyberechts (n=13); Brazil: J.E. Sousa, I. Pinto, L. Mattos, A. Chaves, A. Abizaid, A. Sousa (n=43); Japan: T. Muramatu (n=32); K. Kurogane (n=5); S. Mizuno (n=3); Austria: P. Probst, G. Porenta (n=28); Portugal: R. Seabra-Gomes, J. Baptista, J.L. Palos, F.P. Machado (n=28); United Kingdom: I.A. Simpson, K.D. Dawkins, H.H. Gray (n=28); P.M. Schofield (n=14); C. Ilsley, M. Mason, M. Bustami (n=13); K.G. Oldroyd (n=4); Greece: V. Voudris, J. Malakos, D.Y. Cokkinos (n=27); Argentina: J. Belardi, L. Guzmán, Rubén Piraino, F. Cura (n=17); France: J.-L.Guermonprez, F. Ledru (n=15); P. Dupouy (n=7); M. Bory (n=4); J. Puel (n=3); F. Tarragano (n=2); Italy: E. Verna (n=13); Germany: A.W. Frey, A. Grove, A. Henning, V. Bassignana (n=12); E. Fleck, E. Wellnhofer (n=11); R. Simon, M. Lins, P. Papechrysanthou (n=10); Israel: R. Beyar, M. Kapeliovich (n=10); M.S. Gotsman, M. Mosseri (n=4); Denmark: P. Thayssen (n=7); Czech Republic: P. Widimsky (n=5).

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