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Research Article

Two Years Follow-Up Outcome of Synergy™ Coronary Stent: Comparison between Case Control Study-Oriented Definition/Criterion and Real-World Results

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Abstract

Objectives: To clarify the 2 years outcome of Bioabsorbable Polymer Everolimus-Eluting Stent (BP-EES) using several criteria/definitions. Previous reports have showed worse outcomes in Real-World (RW) setting than case-Controlled Clinical trials (CC).

Methods and Materials: We studied consecutive patients who received BP-EES implantation from October 2017 through January 2018. We adopted the parameters used in previous BP-EES associated CC (SYNERGY, EVOLVE), compared the CC inclusion criteria (on-label) with others (off-label) at 2 years follow-up.

Results: There were 678 BP-EESs inserted in 437 patients (283 male, mean age 72.3±11.2 years). Data from 4 patients lacked, and therefore the follow-up rate was 99.1%. There were 381 patients (87.2%) satisfying the CC criteria. Male gender, ejection fraction <40%, smoker, multiple stenting, total stent length, target vessel failure and all death was higher in the off-label group (P<0.05). Regarding revascularization-related parameters (all target lesion/non-target lesion revascularization), there was no difference between the 2 groups (TLR 6.1% vs 3.6%, non-TL TVR 5.6% vs 10.9%; CC vs off-label, p=ns, respectively). On the other hand, comparison of TLR using the CC definition (ischemia-oriented TLR) and real-world definition (any TLR) showed approximately 2-3 times higher frequency in the real-world basis (1.6% vs 5.8% per patient basis and 2.1%vs 5.8% per stent basis).

Conclusions: Different definitions for repeat angioplasty among the reports may be a key cause of the discrepancy in revascularization frequency in dug-eluting stent studies, and it is the different inclusion criteria among studies that are associated with patient vulnerability.

Introduction

Bioabsorbable polymer technology aims to reduce potential polymer-related adverse events and recent studies (both randomized and observational) of bioabsorbable polymer Drug-Eluting Stent (DES) have shown supporting outcomes [1-3]. The SYNERGY stent (Boston Scientific Corporation, Marlborough, MA) is a thin-strut (74–81 µm) Platinum Chromium (PtCr) metal alloy stent that elutes everolimus from thin bioabsorbable poly (DL- lactide-co-glycolide) polymer applied to the abluminal surface. The polymer is absorbed shortly after the drug elution is complete at 3 months, providing optimal healing and freedom from long-term polymer exposure within the vessels [4,5].

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In the landmark study EVOLVE II, SYNERGY demonstrated comparable outcomes to durable polymer PROMUS Element Plus, with low rates of stent thrombosis and adverse events through 5 years of follow-up [6]. However, the clinical data from real-world cases differ from trial-based studies because these pivotal studies have exclusion criteria, and only examine the data which met their strict definitions [2-7].

The aim of this study was to assess the 2-year clinical outcomes with high follow-up rate of bioabsorbable polymer everolimus-eluting stent (BP-EES) using several criteria/definitions.

Methods

Study Design and Definitions

This study was based on a single-center, retrospective, all-comer patients' registry of Sapporo Cardiovascular Clinic (SCVC), designed to reflect the "real-world" practice. We studied all patients who received PCI using BP-EES from October 2017 through January 2018. In reflecting the real-world data, we analyzed overall results similar to previous case-control studies, and added the comparison of label indication; that is, case-control study inclusion criteria (on-label) versus others (off-label) to enhance the differences between the real-world and case control studies.

Procedure

As per routine, both pre- and post-dilatations were mandated, and intracoronary imaging device-assisted angioplasty was performed. Debulking devices, such as at hero ablation, were used by the operator's decision. Staged procedures with allocated stents were permitted within 3 months after the initial percutaneous intervention with coronary stenting. Dual Anti-Platelet Therapy (DAPT) of aspirin (81mg throughout their lifespan) and clopidogrel (75mg feed for at least 1 year from index procedure) was recommended, its duration ultimately being left to the discretion of the attending physicians. Generally, DAPT was prescribed for a lifetime. Laboratory tests included systematic assessment of post-intervention cardiac markers mandatory for all patients, and subsequent serial measurements in case of suspected ischemia. PCI-associated MI was adopted from universal definition of myocardial infarction. (type 4a MI) [8].

Baseline characteristics, history of cardiovascular disease, coronary risk factors, medications, and procedural data were obtained and recorded by the physicians and research associates of the Cardiovascular-Institute of Therapeutic Evaluation and Creation (CiTEC). Follow-up data were obtained through a chart review and lacking information was collected via telephone interview or from referring physicians. Although angiographic follow-up assessment was not mandatory, coronary Computed Tomography (CT) angiography follow-up evaluations were basically recommended at 6, 12 and 24 months after PCI in SCVC.

Definitions and Outcomes

Basic outcomes followed the pivotal BP-EES trial (EVOLVE-II) and consensus document of the standardized definition for clinical research [5,6,8]. Briefly, rate of Target Lesion Failure (TLF) was defined as a composite of any ischemia-driven revascularization of the target lesion, Myocardial Infarction (MI) related to the target vessel or any cardiac death from discharge to 24 months follow-up. Individual components were further presented as follows: repeat treatment to the inside of the implanted stent or within 5 mm proximal/distal to the stent was defined as Target Lesion Revascularization (TLR), but when done elsewhere within the target vessel it was recorded as non-target lesion revascularization (non-TL TVR). At least receiving revascularization anywhere during follow-up period is defined as any revascularization. To reflect real-world data, we listed not only ischemia-driven revascularization (i.e., case-control study definition) but also other all events separately (clinically driven revascularization). In this study, ischemia-driven revascularization only indicated fractional flow reserve positive (≤0.8) or presenting ischemic sign during diagnosis, e.g., chest pain, electrocardiogram abnormalities). Deaths were classified as cardiac, non-cardiac and unidentified. Uncertain-cause death including sudden death was included into cardiac death incomposite analysis. MI was defined on the basis of ECG changes and rise in creatine kinase enzyme concentration above three times the upper normal limit. Stent thrombosis was also classified based on Standardization of clinical trials defined by the Academic Research Consortium (ARC) [7]. Both cerebral infarction and hemorrhagic strokes were noted. Off-label indication included the lesion and strategy subsets that were eliminated from pivotal BP-EES studies [4-6]: briefly,>4 lesions within a vessel, triple-vessel disease, ST-segment-elevation myocardial infarction, stenting for Left Main Trunk (LMT) or saphenous vein graft lesions, chronic total occlusion, in-stent restenosis, and bifurcations requiring ≤2 stents. Multiple stenting was defined as requiring ≥2 stents in the target vessel within a procedure.

Statistical Analysis and Ethics

All analyses were performed using R version 4.0.2. [9] Continuous variables are presented as mean ± standard deviation. Continuous variables were compared using the Student's t-test. Categorical variables were compared using the chi-square test or Fisher's exact test. The threshold for significance was $p<0.05$. The study was approved by the institutional review board, and written informed consent was obtained from all patients. SCVC belongs to the Japanese Association of Cardiovascular Intervention and Therapeutics (CVIT) and participates in J-PCI registry, and therefore the study/procedure basically followed their definitions/recommendations [10].

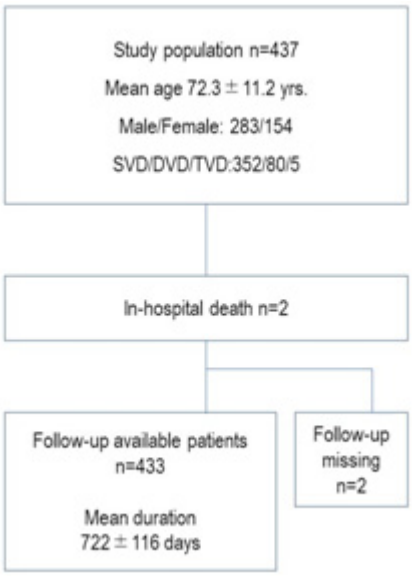

Figure 1: Flow of 437 consecutive patients who received BP-EES implantation.

Results

Patient Flow and Background

The patient flow of this study is shown in (Figure 1). From October 2017 through January 2018, 437 patients (282 males, 64.5%) were enrolled and analyzed. Baseline patient demographics were as follows: diabetic mellitus 28.4% (124/437), hypertension 78.5% (343/437), dyslipidemia 83.5% (365/437), smoker 20.4% (89/437) and hemodialysis 4.1% (18/437). The history of myocardial infarction and aorto-coronary bypass surgery were 22.7% (99/437) and 5.0% (22/437), respectively.

Implanted Stent and Vessel Characteristics

Stent and lesion characteristics are listed in (Table 1). Bifurcation-related stenting was performed in 339 segments. Of these, 286 stents were implanted using the kissing dilatation technique. There were 617 type B2/C lesions (91.0%) and most lesions were de novo (n=652, 96.2%).

Lesion preparation by at hero ablation before stent implantation was attempted in 4 vessels (2with the rotablator and 2 with the excimer laser). As a result, all attempted BE-EES were inserted successfully to the target lesions (100% delivery success). Of the BP-EES, 50.3% were very long (38mm), 33.3% (114/342) of which were used for multiple implantations within a vessel.

Table 1: Details of used stent.

Location	544 vessels (678 stents)
LMT	20 (21)
LAD	228 (260)
LCX	112 (128)
RCA	182 (267)
SVG	1 (1)
RAG	1 (1)
Used stent	n=678
Diameter, # (%)	
2.25mm	86, (12.7)
2.5	151, (22.3)
2.75	2, (0.3)
3.0	228, (33.6)
3.5	117, (17.3)
4.0	95, (14.0)
Length, # (%)	
12 mm	12, (1.8)
16mm	35, (5.2)
20 mm	103, (15.2)
24mm	81, (11.9)
28mm	71, (10.5)
32mm	3, (0.4)
38mm	342, (50.4)

LMT: Left Main Trunk, LAD: Left Anterior Descending Artery, LCX: Left Circumflex Artery, RCA: Right Coronary Artery, SVG: Saphenous Vein Graft, RA: Radial Artery Graft.

Outcomes

There were 2 in-hospital deaths due to ST-segment elevation acute myocardial infarction (STEMI) at admission. Although they received mechanical device-assisted primary PCI, circulatory dysfunction did not improve after revascularization. The current study followed up on all of the remaining (n=435) patients except 2 (99.5%, male/female: 279/154). The details are listed in (Table 2).

Table 2: Outcomes (per patients).

Follow-up available, # (%)	433, (99.1)
Missing, # (%)	2, (0.5)
In-hospital death, # (%)	2, (4.7)
Alive, # (%)	392 (90.3)
Revascularization, any	95 (21.9)
TVF # (%)	17 (3.9)
Death, # (%)	41 (9.5)
Cardiac, # (%) including sudden death	5 (1.6)
Non-cardiac, # (%)	30, (6.9)
Unknown cause, # (%)	6, (14.0)
Stroke, # (%)	4 (1.0)
Bleeding, # (%)	2, (0.5)
Infarction, # (%)	2, (0.5)
Acute coronary syndrome	
AMI, #, (%)	0 (0)
Unstable angina, # (%)	1 (0.2)
Stent thrombosis, n, (%)	7 (1.6)
Definite, # (%)	1 (0.2)
Possible, # (%)	5 (1.1)
Probable, # (%)	1 (0.2)
DAPT continuation, # (%)	413 (95.4)

TVF: Target Vessel Failure, AMI: Acute Myocardial Infarction, DAPT: Dual Anti-Platelet Therapy.

Although recorded as a definite stent thrombosis according to the ARC definition, a case presented ACS not to an intrastent event but due sub-occlusion of side branch covered by crossover stenting. This stable angina case with a single vessel disease had been treated by regular-length stent (2.5x20mm).

Comparison of the Label Indication

Off-label indication was seen in 70 lesions from 56 patients (12.8%, 56/437 patients; 17.3%, 117/678 stents). The details of the off-label indication and number of patients were as follows; STEMI (n=18), left main trunk disease (n=9), graft disease (n=2), chronic total occlusion (n=25), bifurcation requiring>1 stent (n=2), in-stent restenosis (n=1), >4discrete native coronary lesions (n=8) and triple epicardial vessel disease (n=5).

Differences between label indications are listed in (Table 3). Off-label population had a higher incidence of male gender (P=0.002), multiple stenting (P=0.007) and EF<40% population (P=0.002) than on-label. Distribution of diabetes and the elderly were similar between the two groups.

Discussion

Usually, “all-comer use” or “real-world data” presents worse outcomes compared with trial-based case control studies. The current study presents an overall comparison between these two, and adds other analyses to clarify the cause of any differences; specifically, it conducts label-indication comparison, presents different revascularization definitions (ischemia- or clinically driven), and offers the details of the outcome parameters including death. These analyses revealed that the composite endpoint and revascularization parameters were higher in current all-comer data. However, adjusted results (to an on-label basis) in the current study did not differ from previous case-controlled studies. Clinically oriented revascularization was 3 times higher than ischemia-oriented decisions. Regarding label indication comparison, there was no difference in revascularization parameters among the groups, then being similar to previous case control studies, but death-related composite

Table 3: Comparison between on- and off-label indication.

	Case control study criterion compatibles (on-label)	*Other populations (off-label)*	*P*
Per patient	381	56	
Male gender, # (%)	237, (62.2)	46, (82.1)	0.004
Mean Age	72+11	70±10	0.1
Diabetes, # (%)	104, (27.5)	17, (31.5)	0.5
EF<40%, # (%)	13, (3.4)	8, (14.3)	0.002
Smoker	68, (18.0)	19, (35.2)	0.006
MVD (single/double/triple)	318/63/0	34/17/5	<0.001
Multiple stenting, # (%)	89, (23.4)	32, (57.1)	0.007
Total stent length, mm	45.3±15.1	54.7±19.9	0.02
Outcomes			
Follow up available, # (%)	378 (99.2)	55 (98.2)	
Death, any, # (%)	32, (8.5)	9, (16.4)	0.01
Prognosis, # (%)			0.009
Cardiac death	3, (0.8)	1, (1.8)	
Non-cardiac death	26, (6.8)	4, (7.3)	
Sudden death	1, (0.3)	0, (0)	
Unknown cause death	2, (0.5)	4, (7.3)	
Alive	346, (90.8)	46, (82.1)	
TVF, # (%)	11, (2.9)	6, (10.9)	0.01
TLR, overall, # (%)	23, (6.1)	2, (3.6)	0.8
Non-TL TVR overall, # (%)	21, (5.6)	6, (10.9)	0.1
Per lesion	561	117	
TVF, # (%)	16, (2.9)	10, (8.8)	<0.001
TLR, overall, # (%)	34, (6.1)	5, (4.4)	0.7
Non-TL TVR, overall	30, 5.4%	8, 7.0%	0.5

EF: Ejection Fraction, MVD: Multi Vessel Disease, TLR: Target Lesion Revascularization, Non-TL TVR: Non Target Lesion (but) Target Vessel Revascularization.

Table 4: Label-based assessment of revascularization parameters (follow-up available 668 stented segments in 538 vessels from 433 patients).

	Case control trial (on-label definition); ischemia driven revascularization alone	**Real-world data basis; actual revascularization number**
TLR (per patient), #, %	7, 1.6%	25, 5.8%
TLR (per stent), #, %	14, 2.1%	39, 5.8%
Non-TL TVR (per patient)	9, 2.1%	27, 6.2%
Non-TL TVR (per vessel)	8, 1.5%	38, 7.1%

TLR: Target Lesion Revascularization, TLR: Target Lesion Revascularization, Non-TL TVR: Non Target (but) Target Vessel Revascularization.

endpoint was markedly different between the indications.

These results show not only the actual ability of BP-EES (as new generation DES), but also that the composite endpoint itself reflects patient vulnerability.

What Were the Differences between Case-Control Study vs Real World Data?

In general, a first-in-man study is designed by a company to assess the safety and efficacy of a device in a clinical setting. This is usually performed under strict regulations/rules. On the other hand, physicians expect to be able to utilize newer device to treat all lesion/patient without the regulation. This would account for some discrepancies in indications (so-called off-label use). Previous studies have reported on the difference in the indications (standard use and off-label use) and outcomes. Win et al. showed an increase in both stent thrombosis and death/MI or TVR in off-label use compared with on-label use [11]. Another study examined cumulative number of off-label indication and outcomes. In the study, 86% of patients exhibited at least one off-label indication. While the number of off-label indication gradually increased events such as MACE and TVF, marked differences were observed from >3 off-label accumulation [12].

Although off-label indication was observed in only 12.8% of patients in the current study, there was a profonde difference in the lesion/patient characteristics and death-included outcomes including TVF. In other words, the outcomes of the off-label group in the current study was mostly affected by non-revascularization related factors. Consensus document of clinical research (ARC) stated that repeat treatment of target lesion (stent) reflects device effectiveness and death/MI reflects patient-oriented factors [7]. In this study, off-label indication involved more vulnerable patients including the elderly rather than those at high risk for revascularization. And this may support the exclusion of any off-label indication from case-controlled stent studies as being reasonable for pure *"assessment of device safety"*. That is, the existence of off-label indication led to involvement of vulnerable patients who were associated with higher incidence of death but irrelevant to restenosis.

On the other hand, to our knowledge, previous studies that compared on- and off-label indications have not strictly defined revascularization. Case control studies have defined it, most of them adopting the evidence of an ischemia-driven cause. This may create discrepancies between case-control studies and real-world data. In fact, our current results associated with revascularization parameters revealed discrepancies caused by label-induced definitions (counts for ischemia-driven revascularization alone vs. all clinical events). Also, the incidence of revascularization in the case-control definition of our data (on-label) are quite similar to previous case control studies for BP-EES. Therefore the interpretation of real-world data needs not only consider the different inclusion criteria of label indication but also make adjustments according to the label-based definitions of the outcomes.

An increase in the actual revascularization number, i.e., clinically driven revascularization, would have been caused by clinical symptoms or oculo-stenotic reflex including visually estimated coronary stenosis [13]. The oculo-stenotic reflex may affect even CT era; at least, coronary-CT instead of coronary angiography following PCI would have been influence this phenomenon in this study, too.

In the current study, approximately half of very long stents (38mm) were inserted as mono- or multiple use. Although the long stent has an advantage, such as cost effectiveness and avoiding stent gap/overlapping which is associated with worse outcome, off-label indication and stent length were also an independent predictor of death/MI, TVR or thrombosis [11,14,15]. Nevertheless, the similar revascularization and thrombosis frequencies in the current all-comer subsets compared to previous case-control studies may be explained by intracoronary imaging-guided angioplasty. Imaging device, such as IVUS/OCT, can detect at hero sclerosis within the coronary tree and diseased segments that had been treated by stent appropriately [16,17]. Taken together, new generation stent (abluminal coating of bioabsorbable polymer on thin-strut with evelolimus) implantation

with intravascular imaging contributed to similar outcomes to previous case control study even with the use of very long stent or very long segment coverage.

Study Limitations

This is not a prospective study. Therefore, all events could not be detected immediately or annually. Population was relatively small, but there are few reports that exceed a 98% follow-up rate. There was no 8mm stent in this series, although included in the commercially available line-up of BP-EES. Because the current study was a retrospective analysis, only patients that underwent adequate follow-up were counted in the denominator. This increased the frequency of the event than had the study-inclusion number been used.

Conclusion

Intravascular imaging-guided BP-EES implantation for unselected consecutive patient contributed gratified results compared with previous case control studies. The "selection bias" did not reflect lesion revascularization, rather associated with patient vulnerability. Different criteria for repeat intervention among the reports may be a key cause for discrepancy of revascularization frequency in this evolved DES era.

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Disclosure

Dr. Fujita has contracted with Termo Corporation as technical advisor. The remaining authors have no conflicts of interest to declare.

References

1. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol. 2006; 48: 193-202.
2. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet. 2008; 372: 1163-1173.
3. Serruys PW, Farooq V, Kalesan B, Vries T, Buszman P, Linke A, et al. Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease: final 5-year report of the LEADERS (limus eluted from a durable versus erodable stent coating) randomized, noninferiority trial. JACC Cardiovasc Interv. 2013; 6: 777-789.
4. Meredith IT, Verheye S, Dubois CL, Dens J, Fajadet J, Carrié D, et al. Primary endpoint results of the EVOLVE trial: a randomized evaluation of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent. J Am Coll Cardiol. 2012; 59: 1362-1370.
5. Kereiakes DJ, Meredith IT, Windecker S, Jobe RL, Mehta SR, Sarembock IJ, et al. Efficacy and safety of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent the EVOLVE II randomized trial. Circ Cardiovasc Interv. 2015; 8: e002372.
6. Kereiakes DJ, Windecker S, Jobe RL, Mehta SR, Sarembock IJ, Feldman RL, et al. Clinical outcomes following implantation of thin-strut, bioabsorbable polymer-coated, everolimus-eluting SYNERGY stents. Circ Cardiovasc Interv. 2019; 12: e008152.
7. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, Es GA, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007; 115: 2344-2351.
8. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD: Writing Group on behalf of the Joint ESC/ACC/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. J Am Coll Cardiol. 2012; 16: 1582-1598.
9. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplantation. 2013; 48: 452-458.
10. Sawano M, Yamaji K, Kohsaka S, Inohara T, Numasawa Y, Ando H, et al. Contemporary use and trends in percutaneous coronary intervention in Japan: an outline of the J-PCI registry. Cardiovasc Interv Ther. 2020; 35: 218-226.
11. Win HK, Caldera AE, Maresh K, Lopez J, Rihal CS, Parikh MA, et al. Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. JAMA. 2007; 297: 2001–2009.
12. Kotani J, Ikari Y, Kyo E, Nakamura M, Yokoi H. Long-term outcomes following off-label use of sirolimus-eluting stent. J Cardiol. 2013; 62: 151-157.
13. Nakamura M, Muramatsu T, Yokoi H, Okada H, Ochiai M, Suwa S, et al. Outcomes of the largest multi-center trial stratified by the presence of diabetes mellitus comparing sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) in patients with coronary artery disease. The Japan drug-eluting stents evaluation: a randomized trial (J-DESsERT). Cardiovasc Interv Ther. 2015; 30: 103-114.
14. Tanabe K, Serruys PW, DegertekinaM, Grube E, Guagliumi G, Urbaszek W, et al. Incomplete stent apposition after implantation of paclitaxel-eluting stents or bare metal stents: insights from the randomized TAXUS II trial. Circulation. 2005; 111: 900-905.
15. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA. 2005; 293: 2126–2130.
16. Sonoda S, Morino Y, Ako J, Terashima M, Hassan AHM, Bonneau HN, et al. Impact of final stent dimensions on long-term results following sirolimus-eluting stent implantation: serial intravascular ultrasound analysis from the sirius trial. J Am Coll Cardiol. 2004; 43: 1959-1963.
17. Oemrawsingh PV, Mintz GS, Schalij MJ, Zwinderman AH, Jukema JW, Wall EE. 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). Circulation. 2003; 107: 62-67.