

A Prospective Randomized Trial Comparing Stenting With Off-Pump Coronary Surgery for High-Grade Stenosis in the Proximal Left Anterior Descending Coronary Artery: Three-Year Follow-Up

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OBJECTIVES	This study was done to identify the best treatment for an isolated high-grade stenosis of the proximal left anterior descending coronary artery (LAD).
BACKGROUND	Percutaneous transluminal coronary angioplasty with stenting (PCI) and off-pump coronary artery bypass grafting (surgery) are used to treat single-vessel disease of a high-grade stenosis of the proximal LAD. Midterm results of both treatments are compared in this prospective randomized study.
METHODS	In a single-center prospective trial, we randomly assigned 102 patients with a high-grade stenosis of the proximal LAD (American College of Cardiology/American Heart Association classification type B2 or C) to PCI (n = 51) or surgery (n = 51). Primary composite end point was freedom from Major Adverse Cardiac and Cerebrovascular Events (MACCE) at follow-up, including death, myocardial infarction, cerebrovascular accident, and repeat target vessel revascularization (TVR). Secondary end points were angina pectoris class and need for antianginal medication at follow-up. Analysis was by intention-to-treat (ITT) and received treatment (RT).
RESULTS	Mean follow-up time was three years (90% midrange, two to four years). Incidence of MACCE was 23.5% after PCI and 9.8% after surgery; p = 0.07 ITT (24.1% vs. 8.3%; p = 0.04 RT). After surgery a significantly lower angina pectoris class (p = 0.02) and need for antianginal medication (p = 0.01) was found compared to PCI. Target vessel revascularization was 15.7% after PCI and 4.1% after surgery (p = 0.09).
CONCLUSIONS	At three-year follow-up (range, two to four years), a trend in favor of surgery is observed in regard to MACCE-free survival with a significantly lower angina pectoris status and significantly lower need for antianginal medication. (J Am Coll Cardiol 2002;40:1955-60) © 2002 by the American College of Cardiology Foundation

Percutaneous transluminal coronary angioplasty with primary stenting (PCI) and off-pump coronary bypass surgery (surgery) have become established treatments for symptomatic drug-resistant coronary artery disease. Both can treat a high-grade type B2- or C-lesion in the proximal left anterior descending coronary artery (LAD) (1). This lesion carries a high risk of restenosis after PCI with a reported patency rate at six months follow-up of approximately 75% (2-4). In contrast, six months patency rates after surgery are reported to be approximately 95% (5,6). Surgery is thought to be a major invasive procedure in comparison with PCI, in regard to periprocedural morbidity and mortality. However, no prospective randomized studies have been performed to compare the outcome after both procedures for this type of lesion.

We conducted a prospective randomized study to compare both treatments (PCI and surgery) in 102 patients with a high-grade stenosis of the proximal LAD (7). After six

months follow-up, we found a significantly higher restenosis rate in the PCI group (29%) when compared with the surgery group (4%, p < 0.001) (7). However, differences in periprocedural adverse events did not differ significantly between both procedures (7).

In the present study, we report the two- to four-year follow-up of this ongoing trial comparing the clinical outcome after both procedures.

PATIENTS AND METHODS

Study design. Design and methods of this single-center prospective randomized trial have been described in detail elsewhere (7). In brief, patients with angina pectoris Canadian Cardiovascular Society class 2 or more due to a high-grade stenosis of the proximal LAD were selected. All patients had to be eligible for both PCI and surgery by unanimous forum discussion of cardiologists and cardiac surgeons. Before inclusion, the patient gave written informed consent. Included patients were randomly assigned to PCI or surgery. The Ethics Committee of the University Hospital Groningen approved this study. Cordis Europe

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Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
Gp	= glycoprotein
LAD	= left anterior descending coronary artery
MACCE	= major adverse cardiac and cerebrovascular events
PCI	= percutaneous transluminal coronary angioplasty with stenting
surgery	= off-pump coronary artery bypass grafting with a left internal mammary artery to the left anterior descending coronary artery
TVR	= repeat target vessel revascularization

supported this study financially, but did not take part in the conduct of the study.

Percutaneous coronary angioplasty with stenting. In the PCI group, stent implantation was performed after predilation. All patients received 250 mg ticlopidin daily from the day of stent implantation until one month after the procedure. Also, all patients received 100 mg aspirin daily starting the first postprocedural day. In the study period (1997 to 1999) no platelet glycoprotein (Gp) IIb/IIIa receptor blockers were used.

Off-pump coronary artery bypass grafting (CABG). Off-pump coronary artery bypass surgery (surgery) was performed through a small left anterolateral thoracotomy on the beating heart without cardiopulmonary bypass using a mechanical coronary stabilizer (Guidant, Indianapolis, Indiana) (8). All patients received 100 mg aspirin daily starting the first postoperative day.

End points. Primary end point of this study was the three-year freedom from major adverse cardiac and cerebrovascular events (MACCE). The MACCE were death, myocardial infarction, stroke, and need for repeat target vessel revascularization (TVR). The TVR was performed only in patients with angiographic restenosis of more than 50% in combination with objective signs of myocardial ischemia. Secondary end points were angina pectoris class, use of antianginal medication, other clinical events, and MACCE without revascularization.

Follow-up. Follow-up was done by hospital and/or telephone contacts and mailed questionnaires each at six-month intervals and after three years annually. Clinical events were checked by contact with the treating physicians and adjudicated by an event-monitoring committee of an experienced cardiologist and cardiac surgeon.

Analyses and statistics. Primary analysis of the data was performed according to the principle of "intention to treat." A secondary analysis was performed by the principle of "received treatment."

The baseline descriptive statistics for the continuous variables are the mean and standard error of the mean. For the normally distributed continuous variables, differences between the two treatments were evaluated by the Student *t* test. For skewed distributed continuous end points (p value Shapiro-Wilk test for normality <0.05), the Mann-

Table 1. Baseline Demographic and Clinical Characteristics of the Randomized Patients

	PCI (n = 51)	Surgery (n = 51)	p Value
Age (yrs)	61 ± 1.3	60 ± 1.6	0.73*
Male	75%	78%	0.82†
Weight, median (kg)	85	82	0.27*
Hypercholesterolemia	45%	41%	0.80‡
Diabetes	18%	8%	0.23†
Hypertension	33%	16%	0.08‡
CAD in family	50%	46%	0.84†
Smoking past/current	28/30%	25/37%	0.74‡
Previous myocardial infarction	18%	24%	0.63†
Duration of angina pectoris (months)	16	16	0.38§
CCS classification			0.06‡
Class II	27%	31%	
Class III	46%	24%	
Class IV	27%	45%	
Triple therapy			0.98‡
No beta/ca-ant/l.a.nit.	6%	6%	
One of beta/ca-ant/l.a.nit	31%	33%	
At least 2 of beta/ca-ant/l.a.nit.	63%	61%	
Percentage stenosis	75 ± 1.5	75 ± 1.7	0.96‡

*Student *t* test; †Fisher exact test; ‡chi-square test; §Mann-Whitney *U* test.
beta = beta-blocker; ca-ant = calcium antagonist; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; l.a.nit. = long-acting nitrate; PCI = percutaneous transluminal coronary angioplasty with stenting.

Whitney *U* test was used. For qualitative parameters (categorical or ordered), frequency counts and percentages of each category were calculated by treatment strategy. A Fisher exact test or chi-square test was used to evaluate the differences between PCI and surgery.

At three-year follow-up, the effect of PCI and surgery on number of sustained MACCE was evaluated with a survival analysis, both according to the intention-to-treat and the received treatment principles. Survival was estimated by the method of Kaplan-Meier. Using a log-rank test, the distribution of event-free survival between the two treatment strategies was compared. A second survival analysis was performed on MACCE without TVR, both according to the intention to treat and the received treatment principles. All tests performed in order to test the (null-) hypothesis of no treatment difference were two-sided. A p value < 0.05 was considered statistically significant. For all analyses, commercially available computer software (Statistical Analysis System version 6.12, SAS Institute, Cary, North Carolina) was used.

RESULTS

Patient population. From March 1997 until September 1999, 102 patients were included in this study. Follow-up is complete for all patients. Mean follow-up time was 2.9 years (90% midrange, 1.9 to 3.9 years). Baseline demographic and clinical characteristics of both groups did not significantly differ between both treatments (Table 1). Three patients

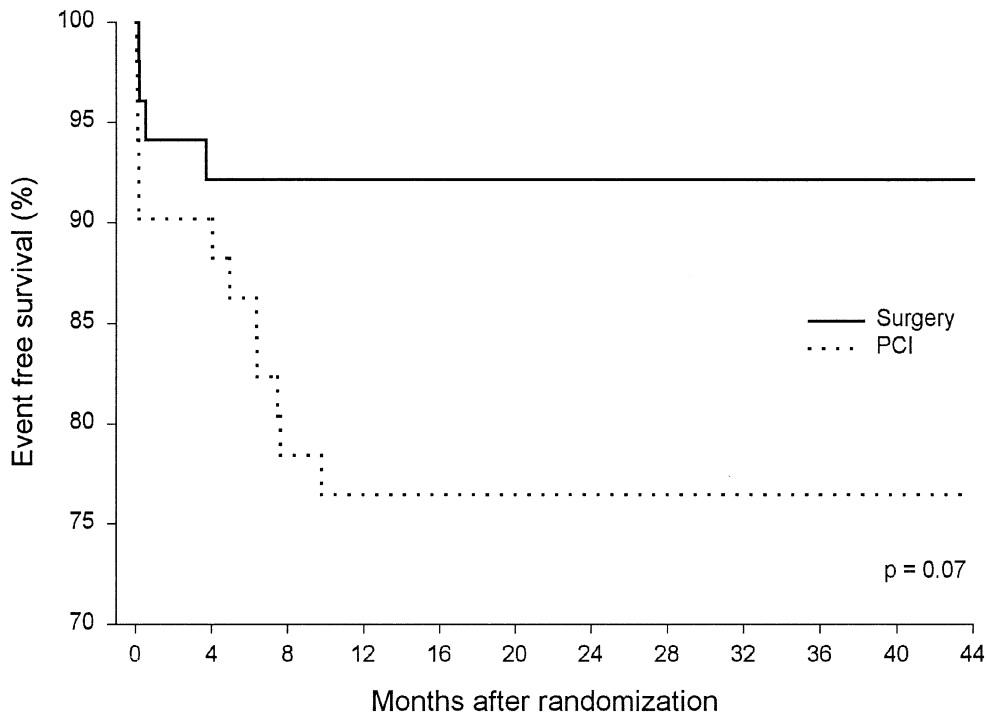


Figure 1. Major adverse cardiac and cerebrovascular events by intention-to-treat analysis. PCI = percutaneous transluminal coronary angioplasty with stenting.

assigned to surgery underwent PCI: one because of severe chronic obstructive pulmonary disease, implicating a high operation risk according to the anesthetist, and two patients finally refused surgery and preferred PCI instead. According to the intention-to-treat principle, these three patients were analyzed as surgery patients (= primary analysis). However, in the secondary analysis, they were analyzed as PCI patients.

Clinical outcome and analyses. In-hospital and six-month clinical and angiographic follow-up has been previously reported (7). Almost all MACCE occurred during the first nine months after stenting and during hospitalization after surgery (Figs. 1 and 2). Table 2 shows the MACCE at two- to four-year follow-up.

After surgery two patients died. One patient died three days postoperatively due to an ongoing inferoposterior myocardial infarction by unknown causes. Autopsy showed a patent anastomosis of the left internal mammarian artery to the LAD, but revealed a proximal luminal diameter of 40% in the right coronary artery already known from the preoperative angiography but not identified as significantly stenotic. One week after discharge, the other patient died at home for unknown reasons after an uncomplicated operation and hospitalization period.

At three-year follow-up, incidence of MACCE by intention-to-treat analysis was 23.5% after PCI and 9.8% after surgery. Risk for MACCE was 2.5 times higher after PCI compared with surgery (95% confidence interval, 0.1 to 1.1; log-rank test, $p = 0.07$; Fig. 1). However, the analysis by received treatment showed a significantly higher

freedom from MACCE after surgery (log-rank test, $p = 0.04$, Fig. 2).

Need for TVR did not significantly differ in the intention-to-treat analysis (Fisher exact test, $p = 0.09$) between both treatments, but was significantly higher after PCI in the analysis by received treatment (Fisher exact test, $p = 0.02$). Diabetes mellitus or the number of stents used in the primary procedure did not influence the need for TVR.

In addition, MACCE-free survival without TVR was analyzed. Intention-to-treat and received treatment analysis showed no significant differences at midterm follow-up between both treatments (log-rank test, $p = 0.45$ resp. $p = 0.55$; Fig. 3 and 4). The MACCE without TVR occurred mainly during the periprocedural period for either treatment.

Clinical outcome at three-year follow-up for angina pectoris status and need for antianginal medication was significantly lower after surgery than after PCI (chi-square test, $p = 0.02$ resp. $p = 0.01$; Table 3).

DISCUSSION

This study shows a trend towards a beneficial effect of surgery over PCI for high-grade stenosis of the proximal LAD in periprocedural events and MACCE-free survival at two- to four-year follow-up (7). Although surgery is thought to be a major invasive procedure in terms of periprocedural complications compared with PCI, we find a higher periprocedural complication rate after PCI (Fig. 1). After three-year follow-up, a trend in favor of better MACCE-free survival was found after surgery, which was

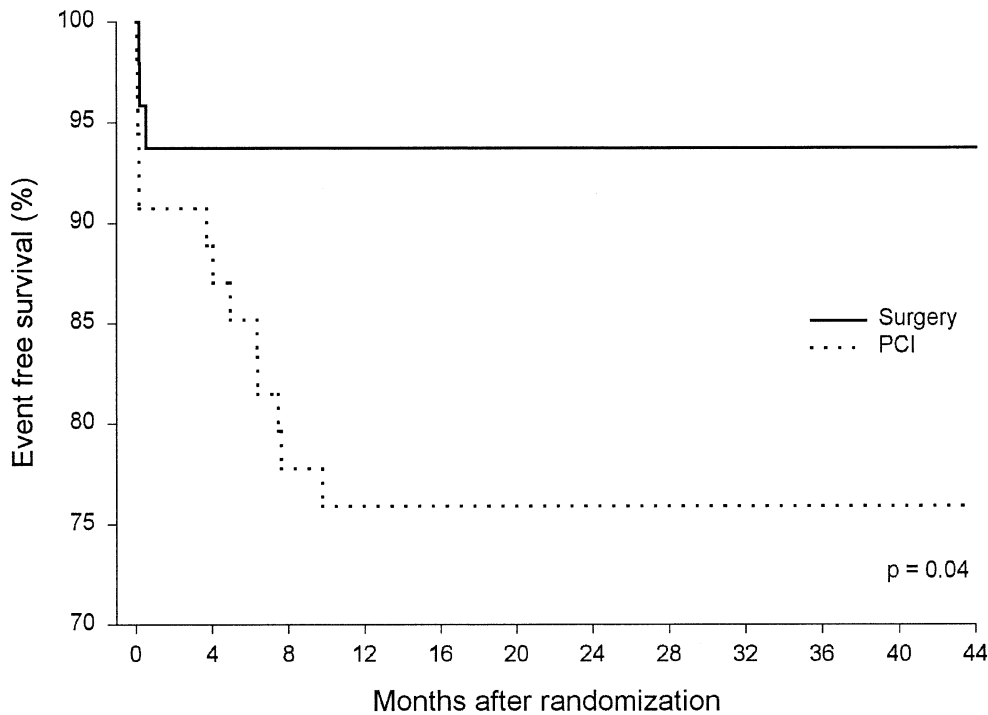


Figure 2. Major adverse cardiac and cerebrovascular events by received treatment analysis. PCI = percutaneous transluminal coronary angioplasty with stenting.

already apparent in the early postprocedural period (Fig. 1). Therefore, no scientific basis could be found in this study supporting this thought.

At two- to four-year follow-up, anginal status is significantly better after surgery than after PCI despite successful TVR and a significantly higher antianginal medication use after PCI. Probably this is a reflection of our angiographic findings at six-month follow-up in which 29% restenosis was found after PCI and 4% after surgery ($p < 0.001$) (7). The finding that these restenotic lesions after PCI are not symptomatic at six-month follow-up was also reported by others (9).

In our study outcome, after surgery is better than after PCI. This is supported by our analysis by received treatment. This means that the three patients that were assigned to surgery, but underwent PCI, were analyzed as PCI

patients. This analysis showed a significant MACCE-free survival in favor of surgery ($p = 0.04$, Fig. 2). A probable explanation for our finding could be the high periprocedural risk and risk of restenosis after PCI for the studied high-grade stenosis of the proximal LAD, while surgery is not hampered by the severity of this lesion. However, in the recently published new guidelines for percutaneous coronary interventions, the proximal LAD is not anymore identified as a high-risk location for restenosis (10). Diffuse lesions (length, >20 mm) with an inability to protect major side branches remain high-risk lesions in the stent era (10). Other known risk factors for restenosis, like diabetes, and procedural-related variables, like number of stents used, could not be identified in our PCI population (11). Apparently, the treated lesion is the basis of our findings and not the location of the lesion.

Other studies. We do not know other prospective randomized studies comparing PCI and off-pump CABG in high-grade single-vessel disease of the LAD. Both only balloon angioplasty and conventional CABG is compared, or a retrospective analysis has been made. Also, the severity of the studied lesion (high- and low-grade lesions) has been mixed and, thereby, influences the outcome because outcome of a PCI procedure is related to the severity of the lesion (10). A comparable study by Goy et al. (12) reported a better MACCE-free survival after conventional on-pump CABG than after PCI, but does not find a difference in functional class or need for antianginal medication. We feel that this difference with our study can be explained by the severity of the studied lesion as explained above.

Table 2. MACCE at Midterm Follow-Up (by Intention-to-Treat Analysis)

	PCI (n = 51)	Surgery (n = 51)	p Value
Death	0	2	0.50*
Myocardial infarction	5	1	0.21*
Stroke	1	0	1.00*
TVR	8	2	0.09*

*Fisher exact test. Values are number of patients per clinical event category. The number of patients with at least one event are presented; no patient double counting for multiple events within a category was done. Between categories patients are double counted in case of multiple events.

MACCE = major adverse cardiac and cerebrovascular events; PCI = percutaneous transluminal coronary angioplasty with stenting; TVR = repeat target vessel revascularization.

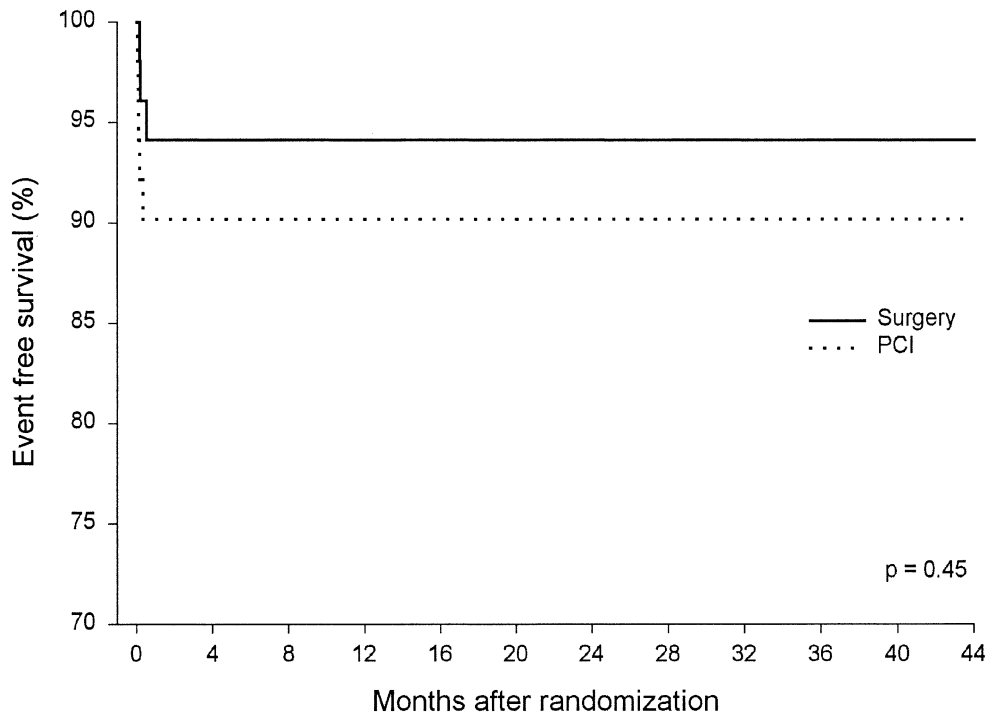


Figure 3. Major adverse cardiac and cerebrovascular events without revascularization by intention-to-treat analysis. PCI = percutaneous transluminal coronary angioplasty with stenting.

Study limitations. This study is based on the controversy whether PCI or surgery is the most suitable treatment for high-grade lesions of the proximal LAD. At the time this study was conducted, these kinds of lesions were the most prone for restenosis (1). Now, almost four years after the

start of the study, more is known about the restenosis mechanism and options to prevent it. The biggest gains in this field are use of Gp IIb/IIIa receptor blockers, newer stent designs, and drug-eluted stents (10,11,13-15). However, at the start of the study, these advantages were not

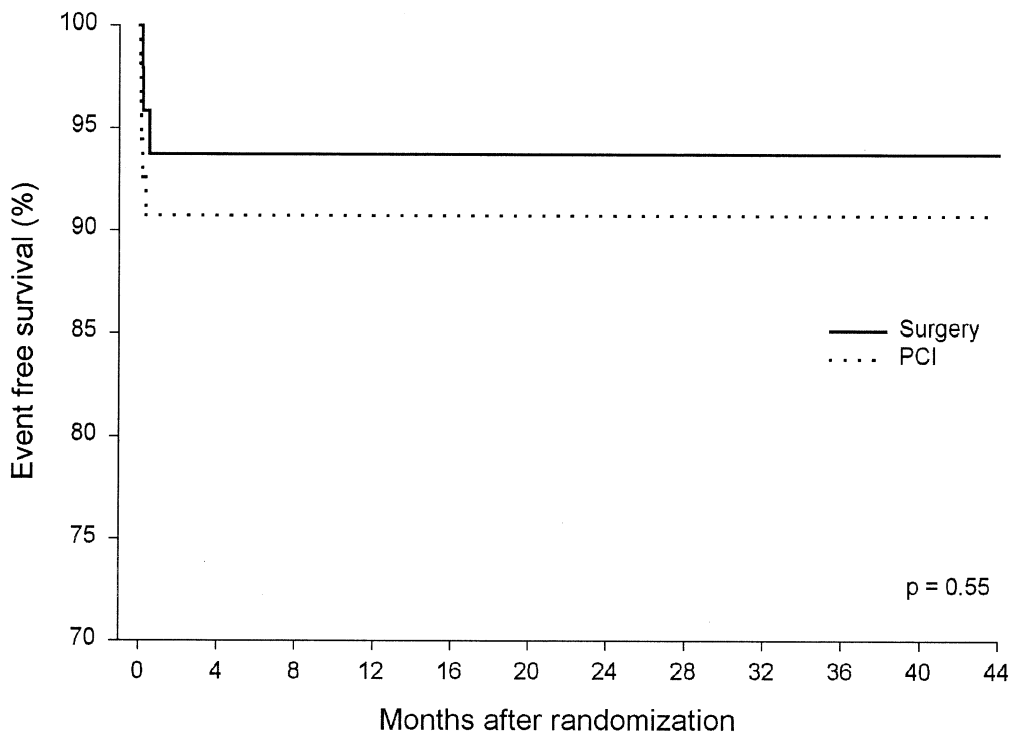


Figure 4. Major adverse cardiac and cerebrovascular events without revascularization by received treatment analysis. PCI = percutaneous transluminal coronary angioplasty with stenting.

Table 3. Clinical Outcome at Midterm Follow-Up (by Intention-to-Treat Analysis)

	PCI (n = 51)	Surgery (n = 49)	p Value
CCS classification			0.02*
Class 0	65%	88%	
Class 1	2%	4%	
Class 2	21%	4%	
Class 3	12%	4%	
Class 4	0%	0%	
Triple therapy			0.01*
No beta/ca-ant/l.a.nit.	28%	31%	
One of beta/ca-ant/l.a.nit.	39%	48%	
At least 2 of beta/ca-ant/l.a.nit.	33%	21%	

*Chi-square test.

beta = beta-blocker; ca-ant = calcium antagonist; CCS = Canadian Cardiovascular Society; l.a.nit. = long-acting nitrate; PCI = percutaneous transluminal coronary angioplasty with stenting.

available. The number of patients included is a limitation of our study. Although not affecting significance for anginal class and need for antianginal medication, significance in MACCE-free survival could only be obtained by received treatment analysis.

Clinical implications. If a patient with a high-grade stenosis of the LAD accepts a higher chance for repeat TVR, PCI is a good alternative for surgery. However, our study indicates that after three-year follow-up his anginal status and need for antianginal medication will be significantly higher after PCI compared with surgery. Whether the above-described improvements in PCI treatment that are not implicated in this study will be beneficial in the long-term for this patient group has to be sought out in future trials containing these recent improvements of PCI. Long-term MACCE-free and angina-free survival can be expected after off-pump CABG with a LIMA to the LAD.

Conclusions. At three-year follow-up (range, two to four years), a trend in favor of surgery is observed in regard to MACCE-free survival with a significantly lower angina pectoris status and significantly lower need for antianginal medication.

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