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Retroinfusion-Supported Stenting in High-Risk Patients for Percutaneous Intervention and Bypass Surgery: Results of the Prospective Randomized Myoprotect I Study

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The objective of this study was to assess event-free survival and total treatment costs of retroinfusion-supported stenting in high-risk patients compared to bypass surgery. An increasing number of patients with main-stem and main-stem-equivalent stenosis are treated by stent implantation, which appears to be safe in the short-term follow-up. However, there is a lack of randomized studies comparing conventional bypass surgery with stent implantation, particularly in patients with high risk for both treatments. We here report on the 1-year results of a prospective randomized single-center study in patients with symptomatic main-stem and main-stem-equivalent lesions with substantially increased risk for bypass surgery. Patients where randomized to undergo either percutaneous transluminal coronary angioplasty/stent procedure (n = 23) or bypass surgery (n = 21). Patients randomized to stent implantation were supported by selective pressure-regulated retroinfusion of the anterior cardiac vein during ischemia. Patients of the stent group and the bypass group did not differ in baseline characteristics, including Parsonnet score and quality-of-life score. Twenty-eight-day mortality and 1-year mortality rate as well as quality-of-life scores were similar in both groups. Event-free survival after 1 year was higher in the bypass group (71.4% vs. 52.3%; $P = 0.02$) due to a lower target lesion revascularization rate. With regard to total treatment costs, however, the stent group compared favorably to the bypass group (9,346 ± 807 vs. 26,874 ± 3,985 euro), predominantly as a result of a shorter intensive care and hospital stay. In this first randomized study in high-risk patients for stent implantation and bypass surgery, patients with retroinfusion-supported stent implantation had a similar 1-year outcome and quality of life compared to patients with bypass surgery. Though in the stent group event-free survival was lower and target lesion revascularization rate was higher, retroinfusion-supported stent implantation was associated with substantially lower costs and might be considered as an alternative treatment option in this selected group of high-risk patients.

INTRODUCTION

The number of patients undergoing percutaneous transluminal coronary angioplasty (PTCA) and coronary bypass surgery has been growing distinctly during the last years. With increasing number of interventions, older patients and patients with an aggravated risk for peri- and postinterventional complications have been treated by these revascularization procedures. Implementation of coronary stents improved the safety of percutaneous interventions, the predictability of the acute result, and the restenosis rate. As a consequence, percutaneous treatment has also been reported for main-stem and main-stem-equivalent lesions [1–4]. In general, patients with main-stem stenosis or main-stem-equivalent stenosis are considered to be at high risk for PTCA, because myocardial perfusion is dependent to a large extent on the patency of the treated coronary vessel.

As a consequence, different support devices [5–8] have been applied in these patients to increase the safety of the procedure. However, there is a lack of randomized

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studies showing the feasibility, safety, and the impact on prognosis and cost effectiveness of this treatment option.

With regard to treatment costs, the application of coronary stenting appears to be reasonable, particularly in patients with high-risk lesions who at the same time are at a high risk for bypass surgery. The risk factors influencing peri- and postoperative mortality of bypass surgery have been extensively investigated [9–13]. Assessment of these risk factors makes it possible to determine the risk of bypass surgery with a high predictive value [9].

We here report on the 1-year results of a prospective randomized single-center study (Myoprotect I) in 44 patients with symptomatic main-stem or main-stem-equivalent lesions who were at a substantially increased risk for bypass surgery. In all patients randomized to percutaneous treatment, selective pressure-regulated retroinfusion of arterial blood into the anterior cardiac vein was applied during ischemia, which has been shown previously to preserve perfusion and regional myocardial function in high-risk patients for PTCA [14].

MATERIALS AND METHODS

The protocol of this prospective randomized monocenter Myoprotect I study was approved by the local institutional ethics committee of the University of Munich. Forty-four patients (age, 70 ± 7.6) were included from March 1998 to March 2001 on the basis of the following criteria: symptomatic coronary artery disease; substantially increased risk for bypass surgery (Parsonnet score > 6); main-stem ($n = 13$) or a main-stem-equivalent lesion ($n = 31$) viable and normokinetic anterior ventricular wall. Main-stem-equivalent lesion was defined as a leading proximal left anterior descending coronary artery (LAD) stenosis or stenosis of an LAD bypass ($\geq$ 75%) with a concomitantly documented proximal occlusion of the right coronary artery and/or the left circumflex artery and a history of myocardial infarction.

Exclusion criteria were life expectancy < 12 months; myocardial infarction < 28 days; indication for valve replacement; contraindication against clopidogrel or aspirin; participation in another study.

A total of 67 patients who fulfilled the inclusion criteria were presented to the cardiac surgeon who decided whether or not the patient was eligible for cardiac surgery on the basis of the risk profile and the accessibility of the vessels for bypass grafting. Of the 67 patients, 19 patients were not eligible for bypass surgery. Of the remaining 48 patients, 4 patients did not give written informed consent to participate in the study at least 24 hr before the procedure.

All other 44 patients were randomly (external randomization) assigned to the stent group ($n = 23$) or the bypass group ($n = 21$). The primary endpoint of the study was event-free survival (death, myocardial infarction, or need for target lesion revascularization) 1 year after the procedure. Secondary endpoints consisted of quality-of-life evaluation and total treatment costs.

Interventional Procedures

In all patients randomized to the stent group, a retroinfusion catheter was placed as described previously [14] through the femoral vein selectively into the anterior cardiac vein ($n = 19$) or into the great cardiac vein in case of a main-stem stenosis ($n = 4$). The systolic coronary venous occlusion pressure (SCVOP) was determined by balloon occlusion of the vein (30 sec) and the preset target retroinfusion pressure was chosen 20 mm Hg higher than the SCVOP (Table I). Selective pressure-regulated retroinfusion with arterial blood [14] was started 10 sec before each balloon inflation required for PTCA or stent implantation and was stopped 10 sec after each balloon inflation. The retroinfusion catheter was removed after successful stent implantation in all patients.

PTCA and stent implantation were performed in the standard manner using a PTCA balloon of adequate size. Stent implantation was performed after predilatation using a PUVA stent (Devon, Germany) or a MAC stent (AMG, Germany) of adequate length and diameter.

Coronary Artery Bypass Surgery

Seventeen patients randomized for bypass surgery underwent on-pump coronary bypass surgery following the standard protocol of the Department of Heart Surgery. Four patients underwent off-pump coronary artery bypass (OPCAB) procedure.

Follow-Up Evaluation

All patients were monitored on the intensive care unit (ICU) for at least 24 hr. Serum parameters for myocardial damage were measured before, immediately after the procedure, as well as 6 and 24 hr after the procedure. One-month and 1-year follow-up included quality-of-life score analyzed by an SF-12 questionnaire and the assessment of the angina score according to the Canadian Cardiovascular Society (CCS) classification. In all patients randomized to the stent group, a diagnostic catheter was mandatory 6 months after the procedure. In case of recurrence of angina or a positive stress test during follow-up, a repeat diagnostic catheter was performed in all patients. In case of restenosis or the development of new hemodynamically relevant coronary lesions, the decision and the kind of second treatment (i.e., PTCA/stent,

TABLE I. Group Characteristics*

	Stent group	Bypass group	*P*
n	23	21	
Male	19 (83%)	12 (57%)	NS
Age (years)	69 ± 8	71 ± 7	NS
Quality-of-life score	37.3 ± 9.5	35.1 ± 9	NS
Angina CCS score	3.0 ± 0.9	2.6 ± 1.5	NS
LVEF	52%	56%	NS
Number of vessels diseased	2.7	2.6	NS
Number of vessels treated	1	2.6 ± 1	< 0.001
Number of patient with three-vessel disease	15	17	NS
Number of patient with two-vessel disease	4	7	NS
Main-stem lesion	4	8	NS
Main-stem-equivalent lesion (LAD)	12	9	NS
Main-stem-equivalent lesion (LAD byass graft)	7	4	NS
Vessel size (mm diameter)	3.2 ± 0.3		
Total stent length (mm)	13 ± 4		
Coronary venous pressure and retroinfusion flow			
SCVOP (mm/Hg)	57 ± 12		
reached pressure (mm/Hg)	64 ± 10		
Retroinfusion flow (ml/min)	98 ± 52		
Retroinfusion duration (sec)	87 ± 28		
Main risk factors contributing to preoperative risk assessment in the Parsonnet score			
Main-stem lesion	4 (17%)	8 (38%)	NS
Instable angina	18 (78%)	12 (57%)	NS
Reoperation	10 (43%)	10 (48%)	NS
LVEF 30–49%	8 (39%)	7 (33%)	NS
Diabetes mellitus	9 (39%)	8 (38%)	NS
Hypertension	22 (96%)	18 (86%)	NS
Parsonnet score	8.9 ± 1.9	9.2 ± 2.0	NS
Pre interventional drug treatment			
Calcium antagonists	3 (13%)	0	NS
β-blockers	16 (70%)	13 (62%)	NS
Nitrats	17 (74%)	13 (62%)	NS
ASA	20 (87%)	17 (81%)	NS
ACE inhibitors	11 (48%)	11 (52%)	NS
Statins	5 (22%)	10 (48%)	NS
Diuretics	6 (26%)	9 (43%)	NS
Post interventional drug treatment			
Calcium antagonists	0	3 (14%)	NS
β-blockers	16 (70%)	7 (33%)	0.03
Nitrats	11 (48%)	0	< 0.001
ASA	21 (91%)	18 (86%)	NS
ACE inhibitors	10 (43%)	14 (67%)	NS
Statins	9 (39%)	2 (10%)	NS
Diuretics	8 (35%)	15 (71%)	NS
Clopidogrel[a]	10 (44%)	1 (5%)	0.008
Ticlopidin[a]	9 (39%)	0	0.004

*ASA, acetylsalicylic acid; ACE, angiotensin converting enzyme; LVEF, left ventricular ejection fraction.
[a]Given for 1 month after intervention.

bypass surgery, or medication) was based on clinical judgement and not regulated by the study protocol.

Cost Analysis

Total treatment costs were analyzed after 1 year, including costs for the primary procedure, hospitalization time, rehabilitation, reintervention, and medication. Primary procedure costs for the patients undergoing bypass surgery included a hospital stay of 14 days and a 2-day stay on ICU, whereas for patients undergoing PTCA/stent procedure, costs only covered the interventional procedure.

Statistics

Data were analyzed using SPSS software; categorical variables are expressed as the number and the percentage of patients. For continuous variables, data are reported as

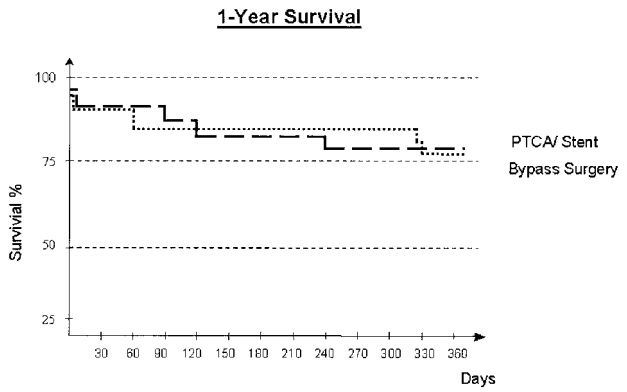

Fig. 1. Comparison of 1-year survival (%) of patients in the stent and bypass groups.

TABLE II. Follow-Up Data

	Stent group	Bypass group	*P*
28-day mortality	2 (8.7%)	2 (9.5%)	NS
1-year mortality	5 (21.7%)	5 (23.8%)	NS
Event-free survival	12 (52.3%)	15 (71.4%)	0.02
Myocardial infarction during follow-up	1 (4.3%)	0	NS
Reangiographie	15 (65.2%)	5 (23.8%)	0.006
Target lesion revascularisation rate	5 (21.7%)	1 (4.8%)	0.01
Total revscularisation rate	7 (30.4%)	1 (4.8%)	< 0.001
Bypass surgery during follow-up	2 (8.7%)	0	0.004
28-day quality-of-life score	32.2 ± 8	33.9 ± 7	NS
1-year quality-of-life score	32.8 ± 9	30.6 ± 8	NS
28-day angina CCS score	1.9 ± 0.3	2.0 ± 0.4	NS
1-year angina CCS score	2.5 ± 0.4	2.4 ± 0.3	NS
In-hospital time (days)	16.1 ± 2.9	36.5 ± 6.6	0.02
ICU stay (days)	1.0 ± 0.5	11.9 ± 4.3	0.02

mean ± SD, and values were compared by unpaired Student's *t*-tests after testing for normal distribution. Fisher's exact test or a chi-square test was used for categorical variables with nominal scales, and the Wilcoxon or Mann-Whitney rank-sum test was used for those with ordinal scales. Event-free survival was estimated by Kaplan-Meier method and differences were assessed by means of the log-rank test. Rates of events were compared by the calculation of unadjusted relative risks with 95% confidence intervals. All statistical tests were two-tailed. A *P* value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Patient Characteristics

There were no significant differences between the two groups with regard to age, gender, cardiovascular risk factors, and medical treatment prior to treatment (Table I).

The Parsonnet score, required to be higher than 6 by the inclusion criteria, was similar in both groups (8.9 ± 1.9 vs. 9.2 ± 2.0) as well as severity of coronary artery disease with regard to the number of diseased vessels (Table I). In the group undergoing bypass surgery, significantly more vessels were treated during the procedure. In the bypass group, eight patients had main-stem stenosis. In the group undergoing PTCA, four patients had main-stem stenosis. The total average length of the implanted stents was 13 ± 4 mm; the average vessels diameter was 3.2 ± 0.3 mm (Table I).

Twenty-Eight-Day and 1-Year Mortality

Twenty-eight-day mortality was similar in the two groups with two patients in the stent group (8.7%) and two patients in the bypass group (9.5%). In the bypass group, one patient died during surgery and one patient on the second day after bypass surgery. Both patients died due to catecholamine refractory cardiac failure. In the stent group, one patient died 12 hr after the intervention who developed subacute stent thrombosis and one patient died 2 days after the intervention (Table II).

One-year mortality was also similar in both groups; five patients died in each group (21.7% vs. 23.8%) (Fig. 4). In one case, it was not possible to clarify the cause of death; all other nine patients died of cardiac dysfunction. Of those patients died within 1 year, one patient of the stent group underwent bypass surgery because of recurrent angina and died during surgery.

Event-Free Survival, Revascularization Rate, and Quality of Life

Event-free survival rate after 1 year was significantly lower in the stent group (52.3%) than in the bypass group (71.4%; Table II, Fig. 2). This was predominantly due to a higher target lesion revascularization rate (21.7% vs. 4.8%; $P = 0.01$). Total revascularization rate was also higher in the stent group (30.4% vs. 4.8%; $P < 0.001$; Table II). Two patients of the stent group underwent coronary bypass surgery as a second revascularization procedure during follow-up.

Quality-of-life score significantly improved in both groups, with no statistically significant differences between the two groups 28 days and 1 year after the procedure (Fig. 3). CCS angina score significantly improved 28 days after the procedure, with Δ 1.1 ± 0.6 in the stent group and Δ 0.9 ± 0.6 in the bypass group. CCS score was similar 1 year after the procedure in both groups (2.5 ± 0.4 vs. 2.4 ± 0.3; P = NS).

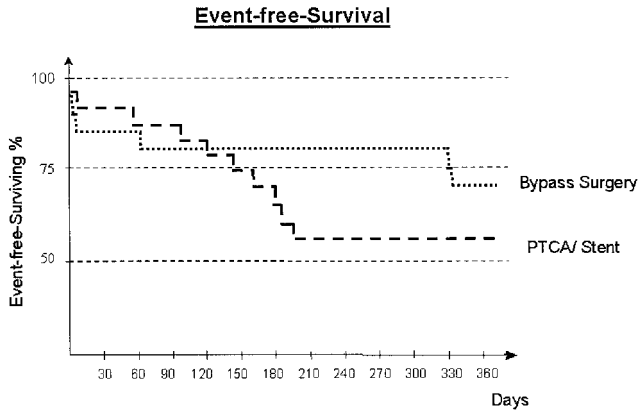

Fig. 2. Comparison of event-free survival (no death, myocardial infarction, target lesion revascularization) after 1 year of patients in the stent and bypass groups.

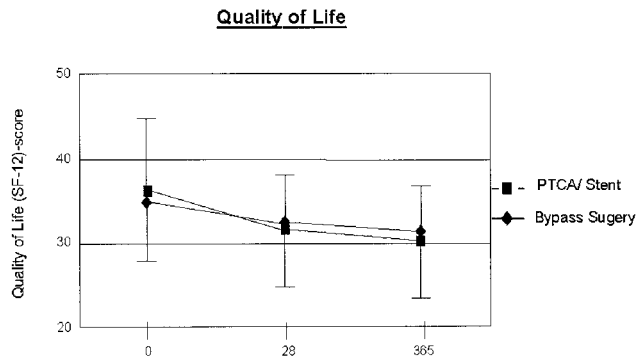

Fig. 3. Comparison of quality of life before intervention, after 1 month, and after 1 year in the stent and bypass groups.

Coronary Venous Pressure-Flow Data During Retroinfusion

Catheterization of the anterior cardiac vein or into the great cardiac vein through the femoral vein was successful in all patients. The mean SCVOP was 57 ± 12 mm Hg determined by balloon occlusion of the vein; the reached target retroinfusion pressure was 64 ± 10 mm Hg. Mean retroinfusion flow of selective pressure-regulated retroinfusion with arterial blood was 98 ± 52 ml/min and the mean duration of retroinfusion was 87 ± 28 sec. All retroinfusion catheters were removed after successful stent implantation.

ICU Stay, In-Hospital Time, and Cost Analysis

There was a statistically significant difference in the duration of ICU stay (1.0 ± 0.5 vs. 11.9 ± 4.3 days; $P < 0.02$) and in-hospital time (16.1 ± 2.9 vs. 36.5 ± 6.6 days; $P < 0.02$) in favor of the stent group compared to the bypass group (Fig. 4).

Total costs per patient after 1 year, including costs for the primary procedure, hospitalization, rehabilitation, re-

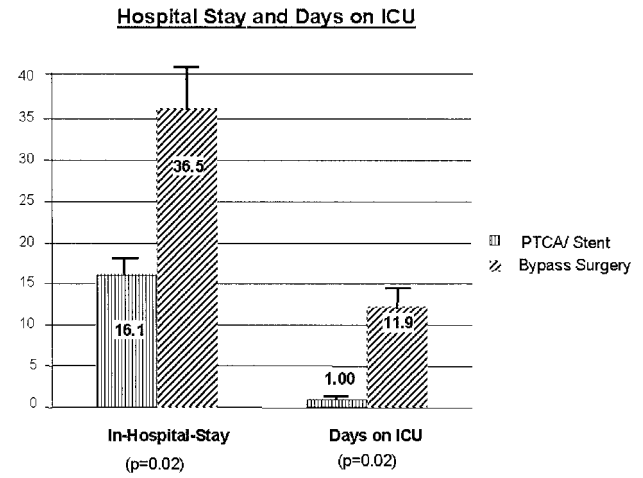

Fig. 4. Comparison of hospital stay and days on ICU in the stent and bypass groups.

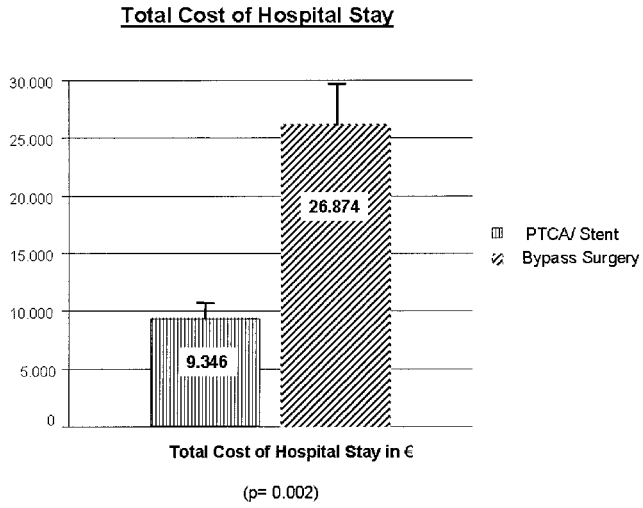

Fig. 5. Comparison of total interventional costs in euro of patients in the stent and bypass groups.

intervention, and medication, were substantially lower in the stent group than in the bypass group (Fig. 5). Cost analysis also revealed that procedure-related costs, hospitalization costs, and rehabilitation costs were significantly higher in the bypass group, whereas reintervention and medication costs were significantly higher in the stent group (Table III).

DISCUSSION

Interventional treatment of high-risk lesions such as main-stem stenosis and main-stem-equivalent stenosis has been controversial [14–16], and there is a lack of randomized prospective studies comparing this treatment option to bypass surgery.

TABLE III. Cost Analysis*

	Stent group	Bypass group	*P*
Total costs	9,346 ± 807	26,887 ± 2,096	< 0.001
Procedure-related costs	3,653 ± 0	12,271 ± 0	< 0.001
Additionally hospital costs	3,878 ± 3,236	8,062 ± 16,804	0.003
Reintervention-related costs	1,815 ± 3,104	174 ± 797	< 0.001
Rehabiltiation costs	0	6,367 ± 9,504	< 0.001
Medication costs in the first year	676 ± 416	394 ± 270	0.018

*Average values (euro) per patient.

As patients at very high risk for bypass surgery may benefit from a less invasive procedure, coronary stenting supported by selective retroinfusion of the coronary veins was compared to bypass surgery in this prospective randomized Myoprotect I study for the first time.

The most striking finding of the Myoprotect I study was significant lower costs for the stent group at 1-year follow-up despite a significant higher reintervention rate, which was associated with a significantly lower event-free survival rate. As expected in this high-risk group for cardiac surgery, the lower costs in the stent group predominantly resulted from a shorter intensive care and overall hospital stay. In addition, higher procedure-related costs and higher rehabilitation costs in the surgical group contributed significantly to the observed lower costs in the stent group (Table III).

The higher reintervention rate in the stent group is in agreement with previous studies comparing bypass surgery to stenting [17]. Though reintervention rate was considerably higher in the stent group, the improvement in quality of life after the initial procedure tended to be higher after 28 days and was similar after 1 year compared to bypass surgery. Furthermore, 28-day mortality was similar in both groups. Due to the small number of patients in each group, however, similarity between the two groups must be interpreted with caution. Interestingly, the preoperative assessment of the Parsonnet score (9.2) well matched with the actual mortality in the bypass group (9.5%) 28 days after operation, which is in agreement with the excellent predictive value of the Parsonnet score in larger patient cohorts [9]. The finding of similar mortality rates and quality-of-life scores even 1 year after the initial procedure supports the assumption that coronary stenting might be equivalent to bypass surgery in this selected very high risk patient group, but this has to be proven in a larger-scale study.

All percutaneous interventions in this study were supported by selective suction and pressure-regulated retroinfusion of arterial blood during balloon inflations and stent implantation, which has been shown previously to preserve regional myocardial function and hemodynamics during ischemia [14]. It has to be stressed, however, that the Myoprotect I study was not designed to demonstrate the necessity of selective pressure-regulated retroinfusion for the successful performance of the percutaneous high-risk intervention. As a consequence and different from previous investigations [14], we did not perform a control group without retroinfusion and also no coronary artery occlusions without support. Hence, all ischemic periods were supported as we were able to apply the retroinfusion procedure in all patients. Moreover, no complications associated to the retroinfusion procedure occurred, underscoring the previously reported safety of the procedure [14]. The increase in coronary venous pressures during ischemia (Table I) to the preset and intended levels, which were higher than the coronary venous systolic occlusion pressure, supports the assumption of effective selective retroinfusion of arterial blood in all patients.

Because no other support devices, such as the intraaortic balloon pump [8], were used in this study, no conclusions can be drawn on the superiority or inferiority of selective pressure-regulated retroinfusion to other support devices in terms of myocardial protection or clinical efficacy. As we also did not experience a bailout situation with prolonged ischemia, the definite need for a prophylactically inserted support device for high-risk coronary interventions remains uncertain. Furthermore, it has to be emphasized that with the high and increasing success rate of direct stenting [18–20], nowadays prolonged ischemia can be avoided even in most of the complex and high-risk percutaneous procedures. Our results also support the concept of primary stenting with successful stent implantation after predilation in all of these high-risk patients to achieve predictable results and lower restenosis rates compared to balloon dilatation without subsequent stent implantation.

Due to the lower reintervention rate, event-free survival after 1 year was significantly higher in the bypass group, which is in agreement with previous studies comparing bypass surgery to balloon dilatation [15,21] or provisional stenting [22]. Interestingly, quality of life as well as mortality was not different between the groups, although significantly more vessels were revascularized in the bypass group than in the stent group. Following the inclusion criteria, only one target lesion was treated in the initial procedure in the stent group, whereas the number of treated vessels in the bypass group was at the discretion of the cardiac surgeon. The target vessel reintervention rate (21.7%) in the stent group was in the expected range after single stent implantation [23–25]. However, the considerably higher total reintervention rate (30.4%) indicated rapid progression of coronary artery disease in nontarget lesions, which were considered to be hemodynamically irrelevant at the time of the initial procedure.

With the emerging potential of drug-eluting stents to lower or eliminate completely restenosis [26–30], the percutaneous treatment of patients with very high risk for cardiac bypass surgery might be further improved. Therefore, the impact of drug-eluting stents on mortality, reintervention rate, quality of life, and treatment costs will be addressed in a subsequent study with a similar prospective randomized design. Other factors such as minimally invasive or off-pump bypass surgery will be taken into account but were not relevant for the Myoprotect I study.

In summary, retroinfusion-supported stent implantation was highly associated with lower treatment costs in the 1-year follow-up compared to bypass surgery in a selected group of patients with high risk for bypass surgery and at the same time high risk for percutaneous treatment. The major drawback of percutaneous intervention, the higher reintervention rate, was present also in this study, leading to a significantly lower event-free survival rate in the stent group. Although this study was not powered to show equivalence between the two treatment groups, similar 28-day and 1-year mortality rates as well as similar improvement of quality of life argue for the potential of percutaneous treatment to be a reasonable treatment option in these patients despite a higher reintervention rate.

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