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ORIGINAL ARTICLE

## Coronary angioplasty in drug eluting stent era for the treatment of unprotected left main stenosis compared to coronary artery bypass grafting

TIMO H. MÄKIKALLIO, MATTI NIEMELÄ, KARI KERVINEN, VESA JOKINEN, JARI LAUKKANEN, KARI YLITALO, MIKKO P. TULPPU, JUKKA JUVONEN & HEIKKI V. HUIKURI

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### Abstract

**Background.** Improved outcomes of percutaneous coronary interventions (PCI) with drug-eluting stents (DES) have resulted in their expanded use for left main coronary artery (LMCA) stenosis.

**Aim.** We compared outcomes of patients undergoing PCI for unprotected LMCA stenosis and patients treated by coronary artery bypass grafting (CABG).

**Method.** Between January 2005 and January 2007, 6705 patients were studied with coronary angiography in northern Finland. All subjects treated with revascularization of LMCA stenosis ( $n=287$ ) were included and followed up for a mean of  $12 \pm 6$  months.

**Results.** From 287 patients, 238 underwent CABG, and 49 had PCI with DES. The incidence of 1-year mortality was 4% among the PCI-treated and 11% among CABG-treated patients ( $P=0.136$ ). After the first month, mortality among PCI- or CABG-treated patients did not differ statistically significantly (2% versus 7%,  $P=0.133$ ). The most significant independent predictor of mortality was reduced left ventricular systolic function (hazard ratio 14.9, 95% CI 5.5–40.0,  $P<0.001$ ).

**Conclusions.** PCI with DES for selected LMCA disease patients results in short- and midterm outcomes comparable to results of CABG in general. PCI is a viable therapeutic option in selected patients with LMCA stenosis.

**Key words:** Left main coronary artery stenosis, mortality, percutaneous coronary intervention

The treatment of unprotected left main coronary artery (LMCA) disease by percutaneous coronary intervention (PCI) has rapidly increased during past few years, although surgical revascularization is currently recommended for this disorder (1–5). Until the recent years, restenosis has limited the widespread application of PCI among patients with LMCA stenosis (6–10). The availability of drug-eluting stents (DES), associated with low angiographic restenosis rate, has led to renewed interest in PCI for LMCA stenosis. Preliminary results from various studies

show that the implantation of DES for LMCA lesions is a safe and feasible approach in various patient populations (11–18). Comparable clinical outcomes have been reported with the treatment of LMCA stenosis by PCI versus coronary artery bypass grafting (CABG) (15–20). This study was designed to compare consecutive series of patients with LMCA stenosis treated with CABG, or with PCI and DES. We hypothesized that PCI results are comparable to those of CABG for short- and midterm outcomes when performed in selected patients.

## Methods

### Subjects

In the specified geographical area of northern Finland, 6705 patients underwent coronary angiography for evaluation of chest pain in four angiographic centers between January 2005 and January 2007. From these patients all subjects with significant LMCA stenosis treated with CABG or with PCI were included and followed up for a mean of  $12 \pm 6$  months. All LMCA revascularization CABG and PCI procedures were performed in one experienced university hospital. LMCA stenosis was observed in 287 patients of which 238 underwent CABG and 49 patients underwent PCI. All patients treated with PCI received a DES in the LMCA. The following predefined criteria were used for selection of eligibility for PCI of LMCA: 1) patients considered by a cardiac surgeon to be at a high surgical risk ( $n = 11$ , Euroscore  $> 12$ ); 2) patient refusal of CABG despite the recommendation ( $n = 4$ ); and 3) coronary anatomy particularly suitable for PCI (no need for more than maximum one additional stent after LMCA stenting procedure), patient preferred PCI and agreed to return for surveillance angiography to exclude restenosis ( $n = 34$ ). In other words, the majority of the PCI-treated patients ( $n = 34$ ) had mainly isolated or almost isolated LMCA disease; these were the most feasible candidates for PCI treatment. The majority of the treatment decisions were made in weekly meetings between cardiologists and surgeons. The cardiologist was always the responsible decision-maker of the treatment when a PCI procedure was conducted without cardiologist-surgeon meeting enforcement. In these patients the PCI procedure was conducted directly after coronary angiography. The cardiologist was also the responsible decision-maker in cases where PCI was still evaluated to be a feasible treatment option when perioperative risk for CABG was considered to be too high by the surgeon. All patients received detailed information about the different treatment options.

### Procedures and follow-up

All CABG and PCI procedures were performed according to current standard clinical techniques. Both off-pump and on-pump techniques in CABG procedures were used, and the selection of the method used was operator-dependent. Standard bypass techniques included a left internal mammary artery for the revascularization of the left anterior descending coronary artery whenever feasible. PCI was performed via transfemoral approach for all

### Key messages

- Percutaneous coronary interventions (PCI) with drug-eluting stents for selected left main coronary artery (LMCA) disease patients results in short- and midterm outcomes comparable to results of coronary artery bypass grafting in general.
- PCI is a viable therapeutic option in selected patients with LMCA stenosis.

patients. All patients received DES (sirolimus or paclitaxel) in the LMCA. Ostial lesions without distal bifurcation involvement were determined to treatment with a single stent. For the treatment of distal bifurcation lesions crush, culotte, T-stenting, or single stent techniques were used. Post dilation with additional balloons was performed for optimal stent apposition. All PCI-treated patients received acetylsalicylic acid indefinitely and a loading dose of 300 mg of clopidogrel, which was continued for at least 9 months after the procedure. During PCI, patients were treated with unfractionated heparin (70 U/kg i.v.) or alternatively with low molecular weight heparin (0.7 mg/kg s.c.) or bivalirudin. Glycoprotein IIb/IIIa antagonists, intra-aortic balloon pump, and intravascular ultrasound use was left to the discretion of the operator.

A routine surveillance coronary angiography was performed 6–8 months after intervention or at appearance of clinical symptoms. For patients who underwent repeated revascularization by PCI new control angiography was scheduled. Among CABG-treated patients, new coronary angiography was performed only if clinically indicated. The patients were followed up for a mean of  $12 \pm 6$  months. After the follow-up the clinical outcome of the patients was defined by reviewing their medical records supplemented by an interview of the patients or family members. In the case of death, the hospital records and death certificates were reviewed to verify the deaths. The primary end point was all-cause mortality. Secondary end points were stroke, documented ST-elevation myocardial infarction after discharge, target vessel revascularization of symptomatic patient, and unplanned new hospitalization.

### Definitions

Successful PCI procedure was defined as thrombolysis in myocardial infarction (TIMI) flow grade 3 with a final residual stenosis  $< 30\%$  without death, myocardial infarction, or emergency CABG before hospital discharge. All post- or periprocedure deaths

without exclusions were included. Myocardial infarction was defined as chest pain symptoms associated with cardiac enzyme elevation >3 times the upper limit of normal value (troponin I, troponin T, or creatine kinase MB isoenzyme) and ST-segment elevation of more than 1 mm in two different leads. A cerebrovascular event with permanent impairment was defined as stroke. Transient ischemic attacks were not included. Unplanned new hospitalization was defined as acute hospitalization due to heart failure. Target lesion revascularization was defined as a repeat revascularization to treat a stenosis anywhere within the LMCA or within 10 mm distal to the left anterior descending or circumflex artery. The reason for target lesion revascularization was documented.

### Statistics

The data were analyzed using the SPSS software (SPSS 14.0, SPSS Inc. Chicago, Illinois, USA). Continuous variables are presented as mean  $\pm$  standard deviation and were compared by Student's *t* test or Mann-Whitney U test if the group distributions were skewed. The chi-square test or Fisher exact test was used to determine of differences in categorical variables. The value of  $P < 0.05$  was considered significant. Kaplan-Meier estimates of the distribution of times from baseline to end points were computed, and log-rank analysis was performed to compare survival curves between the groups. The Cox regression model for clinical

variables was created with all-cause mortality and any secondary events as the end points. Risk ratio (RR) and 95% confidence intervals (CI) were calculated for each variable. Univariate predictors were included in a Cox proportional hazards regression analysis after adjusting for left ventricular function, acute coronary syndrome, and medication to estimate also their independent predictive powers.

## Results

### Patient characteristics

Clinical characteristics of the patient populations are listed in Tables I and II. PCI-treated patients were more often females, they had more often elective procedures, they had higher preoperative risk scores, and they were more often on cardiac medication tailored according to contemporary guidelines than patients treated with CABG.

### Mortality

After the follow-up of  $12 \pm 6$  months, 27 patients (10%) died, and 260 patients were still alive. There were two deaths in the PCI group (4%): one suicide and one due to heart failure of patients considered by a cardiac surgeon too high-risk for CABG. Twenty-five patients (11%) died in the CABG group. The lower mortality rate after follow-up among PCI-treated patients compared to CABG-treated patients

Table I. Characteristics of the study patients.

	PCI ( <i>n</i> = 49)	CABG ( <i>n</i> = 238)	<i>P</i> -value
Clinical features			
Age (years)	72 $\pm$ 10	70 $\pm$ 9	0.006
Gender—male/female	29/20 (59/41%)	190/48 (80/20%)	<0.001
Smoking (current)	10 (20%)	43 (18%)	0.698
Diabetes	10 (20%)	40 (17%)	0.711
Hypertension	23 (46%)	108 (46%)	0.698
CCS class (II/III/IV)	7/22/18	50/99/89	0.471
Prior PCI	3 (6%)	8 (3%)	0.365
LVEF	55 $\pm$ 12	54 $\pm$ 11	0.541
Cholesterol (mmol/L)	4.6 $\pm$ 0.9	4.7 $\pm$ 0.9	0.691
Low Density Lipoprotein (mmol/L)	2.7 $\pm$ 0.9	2.9 $\pm$ 1.0	0.385
Medication			
Aspirin	44 (90%)	195 (82%)	0.121
Beta-blockers	44 (90%)	190 (80%)	0.024
Statins	41 (84%)	173 (73%)	0.012
ACE inhibitors/AT II blockers	25 (51%)	88 (37%)	0.114
Ca-channel blockers	9 (18%)	21 (9%)	0.145
Status prior procedure			
Euroscore	7.7 $\pm$ 7.5	5.2 $\pm$ 4.4	0.002
Elective/UAP/AMI	23/13/13 (47/27/27%)	65/113/60 (27/47/25%)	0.037

ACE = angiotensin-converting enzyme; AMI = acute myocardial infarction; AT II = angiotensin II receptor; CCS = Killip class; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; UAP = unstable angina pectoris.

Table II. Procedural characteristics of the patients.

	PCI (n=49)
Lesion type; ostial/distal	10/39
Stent deployment technique:	
Single stent	20 (41%)
Culotte/crush	5 (10%)
Final stent diameter	3.9±0.7
Glycoprotein inhibitors	29 (59%)
Guidance with IVUS	29 (59%)
	CABG (n=238)
Number of grafts	3.7±0.9
On-pump/off-pump	114/124

CABG = coronary artery bypass grafting; IVUS = intravascular ultra sound; PCI = percutaneous coronary intervention.

was not statistically significant (4% versus 11%,  $P=0.136$ ; Figure 1, Table III). Similarly after the first month, the mortality rate did not differ significantly between PCI- and CABG-treated patients (2% versus 7%,  $P=0.133$ ; Table III). The impacts of different clinical variables as predictors of death are listed in Table IV. The most significant independent

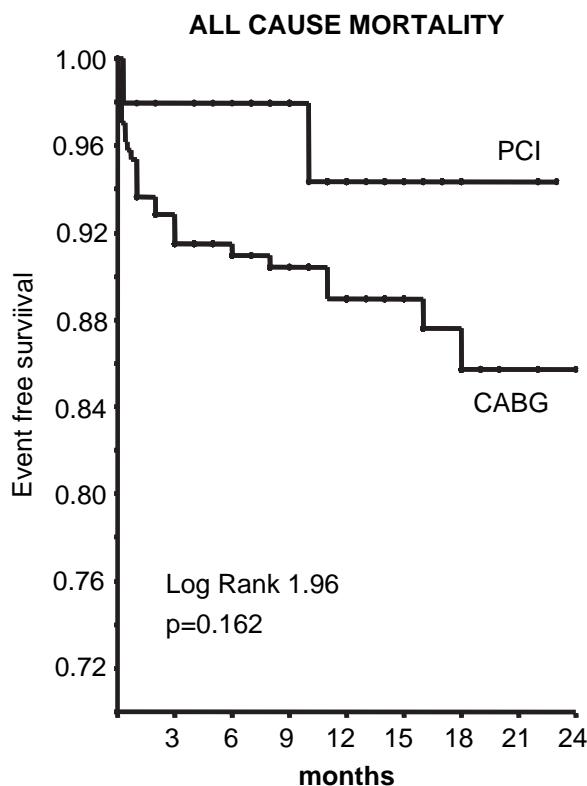


Figure 1. Kaplan-Meier survival curve for death among patients with percutaneous coronary interventions (PCI) and coronary artery bypass grafting (CABG) treatment for left main coronary artery stenosis. Patients with PCI had nonsignificant tendency to lower death rate than patients treated with CABG during the follow-up.

Table III. Outcomes during the mean follow-up of 12 months.

	PCI	CABG	P-value
Death (30 days)	1 (2%)	15 (6%)	0.133
Death (follow-up)	2 (4%)	25 (11%)	0.136
Stroke	0 (0%)	12 (5%)	0.082
ST-elevation myocardial infarction	1 (2%)	4 (2%)	0.861
Symptom-based new revascularization	2 (4%)	4 (2%)	0.285
Primary or secondary end point event <sup>a</sup>	5 (10%)	49 (20%)	0.044

<sup>a</sup> Primary or secondary end point: death, stroke, ST-elevation myocardial infarction, symptom-based new revascularization, or unplanned new hospitalization.

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

predictor of mortality was reduced left ventricular systolic function (Hazard Ratio [HR] 14.9, 95% CI 5.5–40.0,  $P<0.001$ ).

#### Secondary end points

After the follow-up of  $12 \pm 6$  months, the event rate of any primary or secondary end point did not differ significantly between the study groups. A stroke rate of 5% was observed among CABG-treated patients, while none of the PCI-treated patients had stroke (5% versus 0%,  $P=0.082$ ; Table III). Combined end point of all end points showed higher incidence among CABG-treated patients ( $P<0.05$ ) but remained nonsignificant after adjustment with other clinical risk factors and follow-up time. The impacts of different clinical variables as predictors of primary

Table IV. Cox proportional hazard model results using death as an end point.

	Hazard ratio (95% CI)	P-value
Univariate analysis		
Left ventricular function (EF <40%)	14.9 (5.5–40.0)	<0.001
COPD	3.1 (1.2–8.2)	0.021
Age (>70 years)	1.5 (0.7–3.2)	0.279
High preoperative risk score (Euroscore >6)	1.6 (5.6–3.6)	0.245
Urgent revascularization (ACS or UAP)	1.5 (0.6–3.6)	0.416
CABG versus PCI treatment	2.7 (0.6–3.7)	0.179
Multivariate analysis (adjusted by medication, EF and ACS)		
COPD	2.1 (0.7–6.8)	0.176
Age (>70 years)	1.3 (0.6–2.8)	0.571
CABG versus PCI treatment	2.5 (0.6–10.8)	0.227

ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; PCI = percutaneous coronary intervention; UAP = unstable angina pectoris.

or secondary events are listed in Table V. The most significant independent predictor of any event was reduced left ventricular systolic function (HR 4.3, 95% CI 2.5–7.4,  $P < 0.001$ ). During the follow-up 10% ( $n = 5$ ) of the PCI-treated subjects needed target vessel revascularization. Three of these were asymptomatic, but control angiograms revealed marked restenosis. In all cases, restenoses occurred in distal bifurcation lesions and always in left circumflex ostium. Only five CABG-treated patients had target vessel revascularization during the follow-up.

## Discussion

We report three main findings in this study of patients with LMCA stenosis. First, the incidence of death after PCI with DES for LMCA stenosis is low when patients with PCI-suitable anatomy are selected for the procedure. Second, coronary revascularization by PCI and DES is a viable therapeutic option in selected patients with LMCA stenosis resulting overall short- and midterm outcomes comparable to CABG in general. Third, PCI with DES of the unprotected LMCA is feasible and safe, but relatively frequent restenosis exists, often involving the left circumflex ostium.

The present study results are in accordance with previous studies assessing the results of PCI with DES and CABG (11–18). Recent nonrandomized studies have shown that LMCA stenosis treatment with PCI and DES results in outcomes equivalent to CABG after adjustment for clinical risk variables (15–17). Also, a small randomized trial showed favorable outcomes among patients with LMCA stenosis treated with PCI compared to subjects treated with CABG (21). An evident difference between the present study and the previous ones is that the patient population here comprised of all

patients undergoing coronary angiography in a specific geographical area, and the PCI and CABG procedures were centralized in one experienced center. Furthermore, this series included all consecutive revascularized LMCA stenosis patients without any exclusions in this area. Therefore, it should be noted that the present results may not be generalized in other cardiology service systems.

In the present study, the majority of the patients treated with PCI and DES were selected in the light of high procedural success rate expectations. Therefore a comparable overall outcome of these patients compared to CABG-treated patients is not a surprise. These patients consisted of only a small proportion of the total patient population with LMCA stenosis, however. After adjustment for other clinical risk factors, PCI with DES still showed comparable results with CABG. However, despite statistical adjustment, regression analysis or any scoring techniques cannot provide complete statistical adjustment for all confounding variables that often exist in the nonrandomized patient cohorts. Furthermore, the lower mortality in the PCI group did not reach statistical significance. Of note, from two deaths occurring among the PCI-treated patients, one was not a cardiac death, and the other occurred in a patient considered by a cardiac surgeon to be too high a surgical risk for CABG. These observations highlight the viability of PCI treatment with DES in selected patients with LMCA stenosis (22).

The observational nature of our study does not allow any definite conclusions on comparisons of CABG and PCI as treatment strategies of LMCA stenosis per se. Patient selection to PCI with DES treatment has, no doubt, contributed to the results observed. The good results obtained by PCI compared to CABG must be interpreted only in the light of suitability of the patient for PCI treatment with

Table V. Cox proportional hazard model results using any primary or secondary event as an end point.

	Hazard ratio (95% CI)	P-value
Univariate analysis		
Left ventricular function (EF <40%)	4.6 (2.6–8.1)	<0.001
COPD	2.7 (1.2–5.6)	0.024
Age (>70 years)	1.2 (0.7–2.0)	0.587
High preoperative risk score (Euroscore >6)	1.8 (1.1–3.1)	0.033
Urgent revascularization (ACS or UAP)	1.7 (0.8–3.4)	0.108
CABG versus PCI treatment	2.0 (0.8–4.9)	0.113
Multivariate analysis (adjusted by medication, EF, and ACS)		
COPD	2.2 (0.8–5.9)	0.086
Age (>70 years)	1.1 (0.6–2.0)	0.811
CABG versus PCI treatment	2.1 (0.7–5.8)	0.180

ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; PCI = percutaneous coronary intervention; UAP = unstable angina pectoris.

DES. This is in accordance with other studies, which have found that better outcome than expected is seen among patients carefully selected by physician judgment for one treatment rather than another (23).

The limited size of the study population and duration of the follow-up in the present study as well as in the previous studies are facts that may underestimate the results of surgical therapy. The durability of surgical revascularization has been demonstrated to be superior to PCI in previous studies (1,2). Moreover, complex anatomies in distal LMCA stenosis as well as in the rest of the coronaries are critically important to outcomes of PCI treatment but have little or no influence on results of surgery. Indeed, with current DES technology for branch vessel application, late restenosis and stent thrombosis are observed in some patients with distal LMCA bifurcation stenosis limiting generalizations of results of the present and previous studies to the nonselected patient populations. Target vessel revascularization was relatively frequent in the present study as well as in previous studies among PCI-treated patients compared to CABG-treated patients. Most frequently target vessel revascularization is needed in distal bifurcation lesions, where we currently do not have an optimal stenting technique even in the DES era (11,12,24). Notably, all patients treated with PCI underwent routine coronary angiography, and the majority of the revascularization procedures were driven by angiographic findings rather than by symptoms. Moreover, control angiographies are not generally done on CABG patients, but in a recent study with control angiography for CABG almost half of the patients had at least one graft totally occluded 1 year after the CABG procedure, and among these patients over a quarter experienced death, myocardial infarction, or new revascularization during the first year after the CABG procedure (25). Despite the fact that revascularization procedures are more common among PCI-treated patients, recent studies show that total costs are lower among patients treated with PCI, even among patients with multi-vessel disease (26).

Ongoing randomized trials are welcomed efforts to compare PCI and CABG as a treatment for LMCA stenosis (27). It is important to realize, however, that randomization eliminates clinical judgment in patient selection and carries a potential for being misleading as a predictor of outcomes in actual clinical practice. Current excellent results of PCI in treatment of LMCA stenosis are mainly based on suitable patient selection although this patient population is expanding (28–30). However,

CABG is still a major revascularization strategy for treatment of LMCA stenoses providing a solution to many of the shortcomings of PCI treatment. Especially when there are several stenoses in addition to LMCA stenosis, CABG is a feasible alternative.

In conclusion, the current clinical practice of unprotected LMCA stenting with DES platforms is an acceptable treatment strategy when coronary anatomy is suitable and if performed in a well organized centralized system. PCI of LMCA stenosis is especially attractive in proximal and midshaft stenoses that can be treated with a simple treatment strategy, while treatments of distal LMCA lesions have a relatively high risk for repeated PCI procedure.

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