

# **Percutaneous Coronary Angioplasty versus Coronary Artery Bypass Grafting in Treatment of Unprotected Left Main Stenosis: The Nordic-Baltic-British Left Main Revascularization Study (NOBLE)**

Authors

Corresponding author:

Evald Høj Christiansen, Aarhus University Hospital, Department of Cardiology, Palle Juul-Jensens

Boulevard 99, 8200 Aarhus N, Denmark. Phone +45 78452254. Email: evald.christiansen@dadlnet.dk

Keywords

Conflicts of interest

## **ABSTRACT**

### **BACKGROUND**

Coronary artery bypass grafting (CABG) is the standard treatment for revascularization in patients with left main coronary artery (LMCA) disease, but use of percutaneous coronary intervention (PCI) for this indication is increasing. We compared PCI and CABG for treatment of LMCA disease.

### **METHODS**

Patients with LMCA disease were enrolled in 36 centers and randomized 1:1 to treatment with PCI or CABG. Eligible patients had stable angina pectoris, unstable angina pectoris or non-ST elevation myocardial infarction. The primary endpoint was major adverse cardiac or cerebrovascular events (MACCE) - a composite of all-cause mortality, non-procedural myocardial infarction, any repeat coronary revascularization and stroke. The primary outcome was test for non-inferiority of PCI to CABG after up to 5 years of follow-up. Clinicaltrials.gov identifier: NCT01496651.

### **RESULTS**

A total of 1201 patients were randomized. Kaplan-Meier five-year estimates of MACCE were 28.7% for PCI and 20.1% for CABG, HR 1.46 [95% confidence interval (CI), 1.10 to 1.95], exceeding the limit for non-inferiority and significant for superiority of CABG over PCI ( $p=0.0078$ ). Comparing PCI to CABG, five-year estimates were 11.5% vs. 9.5% [HR 1.04 (95% CI, 0.65 to 1.67),  $p=0.86$ ] for all-cause mortality; 6.9% vs. 1.9% [HR 2.9 (95% CI, 1.40 to 5.90),  $p=0.004$ ] for non-procedural myocardial infarction; 16.2% vs. 10.4% [HR 1.5 (95% CI, 1.04 to 2.17),  $p=0.03$ ] for any revascularization; and 4.9% vs 1.7% [HR 2.3 (95% CI, 0.92 to 5.48),  $p=0.07$ ] for stroke.

### **CONCLUSION**

CABG provided a clinical outcome superior to PCI for treatment of LMCA disease.

## INTRODUCTION

Treatment of unprotected left main coronary artery (LMCA) disease using percutaneous coronary intervention (PCI) has increased rapidly during the past decade, following the favorable results of randomized trials{ {273;274;275;276}} and observational registry studies comparing PCI and coronary artery bypass grafting (CABG){ {277;278;279;280;281}}. At the present time, both options are used to treat LMCA disease{ {282}} Current guidelines recommend PCI in LMCA patients with coronary pathology favorable to PCI, *i.e.*, in the absence of complex and diffuse lesions{ {282,345}}. The guidelines are based primarily on the 705-patient LMCA disease subgroup analysis of the SYNTAX trial,{ {284}} which compared PCI with the drug-eluting Taxus stent to CABG in patients with 3-vessel or LMCA disease. The guidelines also refer to the findings of the randomized LE MANS{ {273}}, PRECOMBAT{ {274}} and Boudriot *et al.*{ {275}} trials, which included 105, 600 and 201 LCMA patients, respectively. In the randomized trials, the non-inferiority margin was wide, due to relatively small patient sample sizes. Furthermore, the LMCA subgroup results of the SYNTAX trial were hypothesis-generating in nature.

In the NOBLE trial we hypothesized that PCI with drug-eluting stents would produce non-inferior clinical results compared with CABG in revascularization of 1200 patients with unprotected LMCA stenosis..

## Methods

### Study Design

The Nordic-Baltic-British Left Main Revascularization Study (NOBLE) trial, a prospective randomized clinical trial was conducted at 36 sites in 9 countries in Northern Europe. The authors designed the study, wrote the manuscript and vouch for the completeness and accuracy of data collection and analysis. All patients provided written informed consent. The protocol and consent forms were consistent with Good Clinical Practice, the Declaration of Helsinki and all relevant regulations. The study was approved by local or national ethics committees and by the Danish Data Protection Agency. Clinicaltrials.gov identifier: NCT01496651.

## **Patient Selection and Randomization**

A local interventional cardiologist and a cardiac surgeon at each site prospectively evaluated eligible patients with LMCA disease. Inclusion criteria for study enrollment were stable angina pectoris, unstable angina pectoris or acute coronary syndrome, together with a significant lesion (visually assessed stenosis diameter  $\geq 50\%$  or fractional flow reserve  $\leq 0.80$ ) of the LMCA ostium, mid-shaft and/or bifurcation and with no more than three additional non-complex lesions. Complex lesions were defined as chronic total occlusions, bifurcation lesions requiring two stent techniques or lesions with calcified or tortuous vessel morphology. Exclusion criteria were ST-elevation infarction within 24 hours, patient considered too high risk for CABG or PCI, or expected survival  $< 1$  year. Patients for whom it was determined that equivalent revascularization could be achieved with CABG or PCI were randomly assigned (1:1) to undergo either treatment. Randomization was performed in permuted blocks by country and center with stratification by gender, presence of a distal LMCA bifurcation lesion, and diabetes mellitus. A screening log was maintained in 5 centers which recruited 506 of the 1201 patients.

## **Revascularization and Pharmacologic Treatment**

Patients were treated with the intention of achieving complete revascularization of all vessels with significant lesions. In the PCI group, ostial and mid-shaft lesions were treated with a single stent. Distal bifurcation lesions could be treated with two-stent techniques, preferably the culotte technique. Mini crush, T-stenting, V-stenting or a single-stent strategy could be used if appropriate to lesion morphology and the operator's experience. High-pressure post-dilatation after stent implantation was recommended for all cases. Final kissing balloon dilatation was encouraged after main-vessel-only stenting and was mandatory when a two-stent technique was used. Intravascular ultrasound (IVUS) was strongly recommended pre- and post-stent placement. Use of drug-eluting stents was mandatory. In March 2010, after treatment of 73 patients with PCI, the biolimus-eluting stent (Biomatrix Flex, Biosensors, Switzerland) became the recommended study stent.

Patients randomized to the CABG group were treated according to current clinical practice. The left internal mammary artery was recommended for revascularization of the left anterior descending coronary artery, whenever feasible. For other lesion locations, saphenous venous grafts, free arterial grafts or the right internal mammary artery could be used.

After the index procedure, patients were treated according to local practice. The treatment included 75-150 mg of aspirin lifelong. In both arms, patients with acute coronary syndrome received 75 mg clopidogrel daily for 12 months. All PCI patients also received 75 mg clopidogrel daily for 12 months. Prasugrel or ticagrelor could be substituted for clopidogrel at the discretion of the operator.

### **Primary Endpoint**

The primary endpoint was a composite of major adverse cardiac and cerebrovascular events (death from any cause, stroke, non-procedural myocardial infarction<sup>{346}</sup> or repeat revascularization) (MACCE). The main hypothesis was non-inferiority of PCI to CABG, assessed as the hazard ratio (HR) of PCI to CABG not exceeding 1.35 during up to five years of follow-up and also assessed after 275 MACCE events had occurred. Due to a lower-than-expected event rate, the target number of events could not be reached within the full five-year follow-up period. The primary endpoint thus was assessed after a median of 3.1 years of follow-up. See supplementary information for details and definitions of individual primary and secondary endpoints.

### **Secondary Endpoints**

Other clinical endpoints were the individual components of the primary MACCE endpoint, definite stent thrombosis and symptomatic graft occlusion. Procedural myocardial infarctions were documented. Repeat revascularizations were categorized as target lesion revascularization, LMCA target lesion revascularization or de novo lesion revascularization.

### **Angiographic Evaluation**

Diagnostic angiograms were reviewed by staff at an independent core laboratory [European Cardiovascular Research Center (CERC), France] who were unaware of treatment assignment. Diagnostic angiograms were scored according to the SYNTAX I score algorithm at both the recruitment site and the core laboratory{{283}}

### **Data Acquisition and Monitoring**

Data were collected using a secure, web-based trial management system. Remote monitoring was performed by Qmed Consulting ApS, Denmark, and by professional staff at Aarhus University Hospital, Denmark. Site visits were not performed systematically.

### **Clinical endpoint adjudication**

An independent clinical events committee consisting of cardiologists and a cardiac surgeon adjudicated all possible events concerning cause of death, stroke, myocardial infarction, revascularization, graft occlusion, and stent thrombosis. See supplementary information for details.

### **Data safety monitoring board**

The study was overseen by an independent data safety monitoring board, which received information on clinical events. Details are provided in the supplementary information.

### **Sample size**

The sample size calculation was based on estimated occurrence of the composite primary endpoint of MACCE after mean follow-up of two years. A HR of 1.36, comparing PCI and CABG at one year, was derived from previous studies,{{284}} and translated into 30% of PCI patients and 23% of CABG patients

experiencing MACCE after two years of follow-up. A HR of 1.35 was set as the non-inferiority limit. This corresponded to a total of 275 events, with 1200 patients, 600 in each treatment group, required to detect non-inferiority of PCI to CABG. As the total number of events could not be reached within the full five-year follow-up period for MACCE, as stipulated in the study protocol, the primary endpoint was assessed at a median of 3.1 years of follow-up. See supplementary information for details.

## Statistics

The intention-to-treat principle was used in the analysis if not specified otherwise. Continuous variables were reported as means  $\pm$  standard deviations (SDs) and compared by t-test if they followed a Gaussian distribution. Continuous variables not following a Gaussian distribution were reported as their median value and interquartile range [IQR] and compared using the Mann-Whitney test. Binary variables were reported as counts and percentages, and baseline and in-hospital differences between the two groups were assessed using the Chi-square or Fisher's exact test if a cell value was lower than 5. Follow-up began at randomization. In the analysis of individual endpoints, follow-up continued until the date of a clinical endpoint event, death, emigration, or 5 years after randomization, whichever occurred first. All patients were followed for at least one year. Clinical outcomes occurring during the 30 days following the index procedure and at 12 months were presented with risk differences (RDs) and compared using the log-rank test. Extended follow-up to 5 years was reported using 5-year Kaplan-Meier estimates and hazard ratios (HRs) with 95% CIs based on Cox regression analysis. Cumulative rates of major adverse cardiac or cerebrovascular events were stratified into three groups based on the core laboratory SYNTAX score ("low":  $\leq 22$ ; "intermediate": 23 to 32; and "high":  $\geq 33$ ), and presented by Kaplan-Meier curves. A p value  $< 0.05$  was considered significant. All analyses were performed using STATA12.

## Results

A total of 1201 patients were enrolled from December 2008 to January 2015 in 36 centers. Fourteen withdrew consent, 3 were lost to follow-up, and 1184 were included in the analysis (592 patients in each group, Figure 1). Patients were followed for at least one year and extended follow-up was available for a median of 3.1 [IQR: 2.0:5.0] years. Follow-up was available for 90% of the study population at two years, 68% at three years, 51% at four years, and 35% at five years.

### Baseline characteristics

In the PCI and CABG groups, median ages were  $66.2 \pm 9.9$  years and  $66.2 \pm 9.4$  years ( $p=0.91$ ), percent female were 19.6% and 23.7% ( $p=0.09$ ) and percent with diabetes were 14.6% and 15.2%, respectively. The logistic EUROSCORE was 2[IQR 2:4] in both groups and the SYNTAX scores were  $22.3 \pm 7.8$  and  $22.4 \pm 7.4$  ( $p=0.70$ ) in the PCI and CABG groups, respectively. The procedure indication was stable angina pectoris in 78.7% of patients in the PCI group and 80.5% in the CABG group ( $p=0.61$ ). Distal LMCA disease was present in 80.8% of patients in the PCI group and 81.4% of patients in the CABG group. Additional characteristics are provided in Table 1.

### PCI Procedural Characteristics

Among PCI-treated patients (Supplement Table 1), 53.4% had isolated LMCA treatment, 32.5% had one additional lesion treated, and 9.6% had two additional lesions treated. LMCA treatment involved the bifurcation in 86.8% of PCI cases and two-stent techniques were applied in 35.3% of PCI cases. A first-generation drug-eluting stent was implanted in the LMCA in 10.3% of PCI cases. The nominal diameter of stents in LMCA was 4.0 [IQR 4.0:4.5] mm, inflated to  $18$  [IQR 16:20] atm. Kissing balloon inflation was performed in 52.5% of PCI patients, and any ostial circumflex post-dilatation was performed in 72.0% of patients. Complete revascularization was achieved in 94.1% of cases. IVUS of the LMCA was performed pre-PCI in 46.8% of patients and post-PCI in 74.9% of patients.



### **CABG Procedural Characteristics**

CABG was performed using the on-pump technique in 84.4% of patients, 93.4% underwent arterial grafting of the left anterior descending (LAD) artery and 85.7% underwent left internal mammary artery plus venous grafting. Grafting using the right internal mammary artery was performed in 7.9% of cases. The number of grafts per patient were 1 in 4.1% of patients; 2 in 52.0% of patients; 3 in 39.0% of patients; 4 in 4.4% of patients; and 5 in 0.6% of patients (Supplement Table 2).

### **Primary Endpoint**

Kaplan-Meier estimates of MACCE after five years were 28.7% for PCI and 20.1% for CABG (Figure 2). The HR was 1.46 (95% CI, 1.10 to 1.95), exceeding the limit for non-inferiority (1.35), and was significant for superiority of CABG compared to PCI ( $p=0.0078$ ). One-year rates of MACCE in the two groups were 7.1% vs. 7.1%, (RD 0.0, 95% CI -2.9 to 2.9,  $p=1.00$ ).

### **Secondary Clinical Endpoints**

Five-year risk estimates comparing PCI and CABG (Table 2) were 11.5% vs. 9.5% [HR 1.04 (95% CI, 0.65 to 1.67),  $p=0.86$ ] for all-cause mortality; 6.9% vs. 1.9% [HR 2.9 (95% CI, 1.40 to 5.90),  $p=0.004$ ] for non-procedural myocardial infarction; 4.9% vs 1.7% [HR 2.3 (95% CI, 0.92 to 5.48),  $p=0.07$ ] for stroke (all were ischemic), 16.2% vs. 10.4% [HR 1.5 (95% CI, 1.04 to 2.17),  $p=0.03$ ] for total repeat revascularization; 10.0% vs 7.5% [HR 1.2 (95% CI, 0.78 to 1.94),  $p=0.37$ ] for repeat revascularization of the LMCA; and 6.2% vs 2.6% [HR 2.3 (95% CI, 1.16 to 4.74),  $p=0.02$ ] for de-novo lesion revascularization during follow-up.

### **30-Day Outcomes Following the Index Procedure**

Rates of outcomes, comparing the PCI and CABG groups, during the 30 days following the index procedure, were 5.4% vs. 6.7% [RD -1.3% (95% CI, -5.4 to 2.8),  $p=0.40$ ] (assessable in 45.1% of patients) for procedural myocardial infarction, 0.2% vs 3.9% [RD -3.7% (95% CI, -5.3 to -2.1),  $p<0.0001$ ] for reoperation

for bleeding, 2.0% vs. 27.5% [RD -25.4% (95% CI, -29.3 to -21.5),  $p<0.0001$ ] for blood transfusion, 0.0% vs. 0.5% [RD -0.5% (95% CI, -1.1 to 0.07),  $p=0.08$ ] for surgery for a sternum infection, and 0.4% vs. 0.7% [RD 0.3% (95% CI, -1.2 to 0.5),  $p=0.41$ ] for surgery to address access site complications. The duration of the index treatment admission was 2 [IQR 1:4] days for PCI and 9 [IQR 7:13] days for CABG. Comparing the PCI and CABG groups, rates of all-cause mortality were 0.3% vs. 1.2% [RD -0.8% (95% CI, -1.8 to 0.1),  $p=0.09$ ], rates of non-procedural myocardial infarction were 0.5% vs. 0.0% [RD 0.5 (95% CI, -0.06 to 1.1),  $p=0.08$ ], rates of revascularization were 1.2% vs. 1.7% [RD -0.5% (95% CI, -1.8 to 0.8),  $p=0.46$ ] and rates of stroke were 0.0% vs. 0.7% [RD -0.7% (95% CI, -1.3 to -0.01),  $p=0.04$ ], respectively (Table 3).

### **One-year Clinical Outcomes**

One-year clinical outcomes are shown in Table 4. One-year RDs comparing PCI and CABG (Table x) were 1.5% vs. 2.9% [RD -1.3% (95% CI, -3.0 to 0.3),  $p=0.11$ ] for all-cause mortality; 1.4% vs. 2.2% [RD -0.8 (95% CI, -2.3 to 0.6),  $p=0.27$ ] for cardiac death, 1.9% vs. 1.4% [RD 0.5 (95% CI, -0.9 to 1.9) for non-procedural myocardial infarction,  $p=0.49$ ], 0.3% vs. 1.0% [RD -0.7% (95% CI, -1.6 to 0.3),  $p=0.16$ ] for stroke, and 5.4% vs. 4.0% [RD 1.4 (95% CI, -1.1 to 3.8),  $p=0.27$ ] for total repeat revascularization.

### **Outcomes According to SYNTAX Score Groups**

Comparing the PCI and CABG groups, five-year Kaplan-Meier estimates for MACCE in the SYNTAX score subgroups were as follows: “low” 1-22: 29.7% vs. 16.2% [HR 1.85, 95% CI (1.20 to 2.85),  $p=0.004$ , 51.8% of study population]; “intermediate” 23-32: 27.1% vs. 21.9% [HR 1.16, 95% CI (0.76 to 1.78),  $p=0.48$ , 39.6% of study population], and “high” >32: 32.9% vs. 23.6% [HR 1.41, 95% CI (0.62 to 3.20),  $p=0.41$ , 8.6% of study population] (Figure 3).

## Discussion

The EXCEL and NOBLE studies are the largest international randomized studies of left main coronary artery PCI vs. surgery to date<sup>{341}</sup>. The key findings of the NOBLE study are (1) CABG was superior to PCI for the composite endpoint of MACCE, (2) all-cause mortality was similar in the two groups, (3) non-procedural myocardial infarction and need for repeat revascularization were increased after PCI, (4) a higher rate of stroke was observed in the CABG group after 30 days, but an unexpected, numerically higher rate of stroke was found among PCI patients in 5-year estimates, (5) the differences in outcomes were mainly seen beyond one year, and (6) the SYNTAX score was not predictive of MACCE.

Our findings of similar mortality but higher rates of myocardial infarction and repeat revascularization in patients undergoing PCI compared to CABG are consistent with previous major studies of coronary revascularization in patients with LMCA disease<sup>{273;274;275;276}</sup>. The low mortality following treatment in both groups demonstrates that modern revascularization techniques and adjunctive therapy can lead to excellent survival in stable LMCA patients. Still, the increased rates of non-procedural myocardial infarction, repeat revascularization and stroke associated with PCI are important considerations in selecting optimal treatment for individual patients.

The reason for the increase in myocardial infarctions during follow-up after PCI may be multifactorial, as both target lesion-related myocardial infarctions and de-novo lesion myocardial infarctions were contributory. The main advantage of CABG may be bypassing of long lesion segments by grafting, which protects to a greater extent against target lesion myocardial infarctions and proximal de-novo lesion myocardial infarctions. Although the increased rate of myocardial infarctions after PCI did not translate into differences in cardiac deaths, all reported myocardial infarctions were diagnosed during symptom-driven hospitalizations, signaling a disadvantage for the patient.

Revascularization rates were also greater over time for the PCI group than for the CABG group. These rates are comparable with previous publications on both left main stem stenting {{273;274;275;276;277;278;279;280;281}} and three-vessel coronary artery disease stenting{{340;276}} Although restenosis of drug-eluting stents has diminished over time with introduction of high-pressure deployment,{{287}}use of IVUS,{{288}}and improved stent design,{{286}}it remains a weakness of PCI for treatment of LMCA disease. This may again reflect the superiority of “bypassing” the lesion territory as well as segments with potentially progressive disease. Accordingly, we found more than doubling of the need for de-novo lesion revascularization in the PCI group, compared with the CABG group during follow-up. Repeat revascularization was performed mainly using PCI, but an estimated 4.4% of PCI patients required revascularization using CABG during 5 years of follow-up. As no angiographic follow-up was performed, rates of asymptomatic graft or stent failure are unknown.

Stroke rates were remarkably low in this study, especially during the first 30 days post-procedure. During follow-up, stroke rates in the surgical cohort remained almost static, whereas in the PCI group, the very low early procedural stroke rate (0.0%) gradually increased over time to an estimated 4.9% at 5 years. These findings contrast with previous studies, which have tended to show a higher stroke rate for CABG, with limited differences between PCI and CABG patients with longer follow-up. All strokes were ischemic with no clear explanation for the rate among PCI patients. The strokes in the PCI arm mainly occurred after one year coinciding with completion of dual antiplatelet inhibition treatment.

In contrast to previous studies{{284}}, the SYNTAX score was not predictive of outcomes. The lowest and highest scores favored CABG, while the middle score showed equivalence. This may represent a weakness of the SYNTAX score for treatment selection in patients with LMCA disease. Perhaps the SYNTAX score is better suited (as it was designed) for multivessel disease.

Thirty-day outcomes were noteworthy. The death rate among patients treated with PCI was only 0.3%, compared to 1.2% among patients undergoing CABG. Only 1.2% of PCI patients and 1.7% of CABG

patients required repeat revascularization during the first 30 days post-procedure. Disadvantages of CABG manifested during early follow-up, with a 3.9% reoperation rate for bleeding, a 0.5% reoperation rate for sternum infection, and a 27.5% rate of blood transfusion. The median hospitalization period--2 days for PCI and 9 days for CABG--represented a significant difference between the revascularization modalities.

The one-year MACCE was exactly the same in the two treatment group, but there was a significant difference in the long term outcomes between PCI and CABG. Selecting PCI over CABG can therefore be justified in patients with reduced life expectancy. However our data clearly show that the tradition in PCI revascularization trials of only reporting event rates at one year{ {1}} is not reliable for predicting the long-term prognosis.

In terms of surgical technique, the majority of CABG patients received one or more arterial grafts. While high long-term patency of the internal mammary artery is expected,{ {344}} some vein graft degeneration can be expected beyond 5 years{ {343}}. We will follow all patients for MACCE for a full 5 years and for all-cause mortality until 10 years.

Among PCI patients, the vast majority had bifurcation LMCA involvement, consistent with previous studies{ {284}} A single-stent provisional approach was used for two-thirds of patients, and one-third underwent dual stenting, chiefly with the culotte technique. Half of patients underwent a kissing balloon procedure. The optimal stent implantation technique in LMCA is unknown{ {289}}, but adequate expansion and full lesion coverage are required{ {338}}. IVUS can be helpful in this regard, but less than half of PCI patients had a pre-PCI IVUS assessment and 75% had a post-PCI IVUS assessment. Detailed analysis of the IVUS data and stenting techniques may improve our understanding of implantation results in this trial. The majority of patients with LMCA disease have diameters above 4 mm (average 5.7 mm) indicating the requirement for post dilation beyond nominal diameter{ {347}}. Bench testing of the BioMatrix stent in 3.5 and 4.0 mm (similar platform) showed the ability to expand to 5.9 mm{ {339}}. Larger LMs were possibly

excluded by the local heart teams. The majority had post-dilatation of the LM but only half of the patients had post-dilatation with balloons larger than 4 mm. Stent under-expansion and mal-apposition in the LM can have contributed to the numerically higher target LMCA revascularization in the PCI group.

The primary endpoint of this study clearly favored surgical revascularization. However, it was a composite endpoint, and the results may be interpreted in various ways. In some patients' view, the need for surgery, the long hospitalization, the risk of reoperation for bleeding, and a longer recovery time may not be worth the lower risk of repeat revascularization and myocardial infarction, as no mortality difference was found.

In conclusion, the NOBLE trial showed that CABG provided a superior clinical outcome compared to PCI for treatment of LMCA disease.

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<b>Table 1. Baseline Characteristics by Treatment Group.</b>			
	<b>PCI</b>	<b>CABG</b>	<b>P-value</b>
Age (yrs)	66.2±9.9	66.2±9.4	0.91
Gender (female)	19.6%	23.7%	0.09
BMI (kg/m <sup>2</sup> )	27.9±4.5	28.1±4.4	0.53
Diabetes type I or type II	14.6%	15.2%	0.94
Family history of IHD	57.9%	55.7%	0.45
Statin treatment	81.6.0%	78.4%	0.17
Hypertension	65.4%	65.7%	0.91
Active smoking	18.5%	21.6%	0.18
Previous PCI	19.7%	20.0%	0.90
Previous CABG	0.68%	0.34%	0.41
Ejection fraction (% [IQR])	60 [55;65]	60 [52;64]	0.27
NYHA class			
I	52.8%	42.6%	0.013
II	29.6%	33.1%	
III	12.5%	17.0%	
IV	5.0%	7.3%	
EUROSCORE	2 [2;4]	2 [2;4]	0.18
SYNTAX score	22.5±7.5	22.4±8.0	0.74
Indication			
Stable angina pectoris	78.7%	80.5%	0.61
Unstable angina pectoris	17.9%	16.9%	0.65
Lesions to be treated (n [IQR])	2[1;3]	2[2;3]	<0.0001

Distal LMCA lesion	80.8%	81.4%	0.77
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BMI: body mass index; IHD: ischemic heart disease; NYHA class: New York heart association class;  
LMCA: left main coronary artery

**Table 3. Outcomes between Index Procedure and 30 days of Follow-up by Treatment Group.**

	PCI	CABG	Risk difference	95% CI	P-value
Death	0.3%	1.2%	-0.8%	-1.8 to 0.1	0.09
Cardiac death	0.3%	1.2%	-0.8%	-1.8 to 0.1	0.09
Vascular death	0.0%	0.0%	0.0%	-	1.00
Procedural MI*	5.4%	6.7%	-1.3%	-5.4 to 2.8	0.40
Non-procedure-related MI	0.5%	0%	0.5%	-0.06 to 1.1	0.08
Definite stent thrombosis or symptomatic graft occlusion	0.2%	0.3%	-0.1%	-0.7 to 0.4	0.56
Repeat revascularization	1.2%	1.7%	-0.5%	-1.8 to 0.8	0.46
Stroke	0.0%	0.7%	-0.7%	-1.3 to -0.01	0.04
Re-operation for bleeding	0.2%	3.9%	-3.7%	-5.3 to -2.1	<0.0001
Blood transfusion	2.0%	27.5%	-25.4%	-29.3 to -21.5	<0.0001
Operation for sternum infection	0.0%	0.5%	-0.5%	-1.1 to 0.07	0.08
Operation for access site complications	0.4%	0.7%	0.3%	-1.2 to 0.5	0.41
CT-verified pulmonary embolus	0.2%	0.2%	0.0%	-0.4 to 0.9	0.99
Duration of index treatment admission	2[1:4]	9[7:13]			<0.0001

\* Assessable in 45.1% of patients

**Table 4. One-Year Clinical Outcome by Treatment Group**

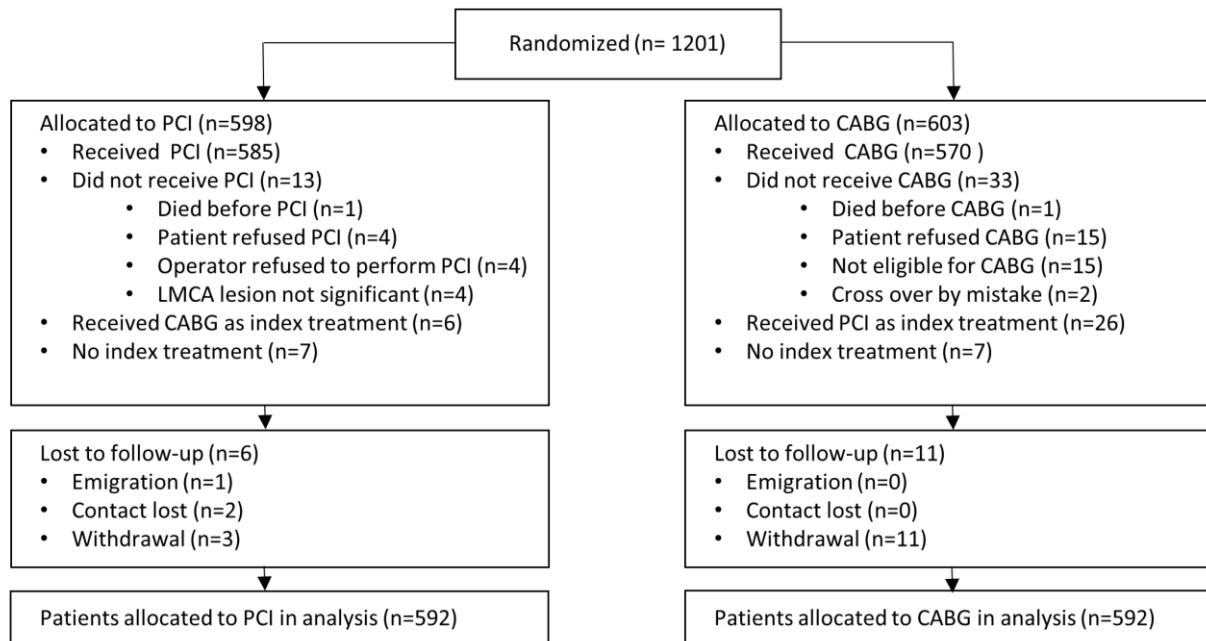
	<b>PCI</b>	<b>CABG</b>	<b>Risk difference</b>	<b>95% CI</b>	<b>p-value</b>
MACCE	7.1%	7.1%	0.0	-2.9 to 2.9	1.00
All-cause mortality	1.5%	2.9%	-1.3%	-3.0 to 0.3	0.11
Cardiac death	1.4%	2.2%	-0.8%	-2.3 to 0.6	0.27
Vascular death	0.0%	0.2%	0.1	-0.1 to 0.3	0.32
Non-procedural MI	1.9%	1.4%	0.5%	-0.9 to 1.9	0.49
Revascularization (total)	5.4%	4.0%	1.4%	-1.1 to 3.8	0.27
Symptomatic graft occlusion or definite stent thrombosis	0.3%	1.2%	-0.8%	-1.8 to 0.1	0.09
Stroke	0.3%	1.0%	-0.7%	-1.6 to 0.3	0.16

**Table 2. Kaplan-Meier Five-Year Estimates by Intention-to-Treat.**

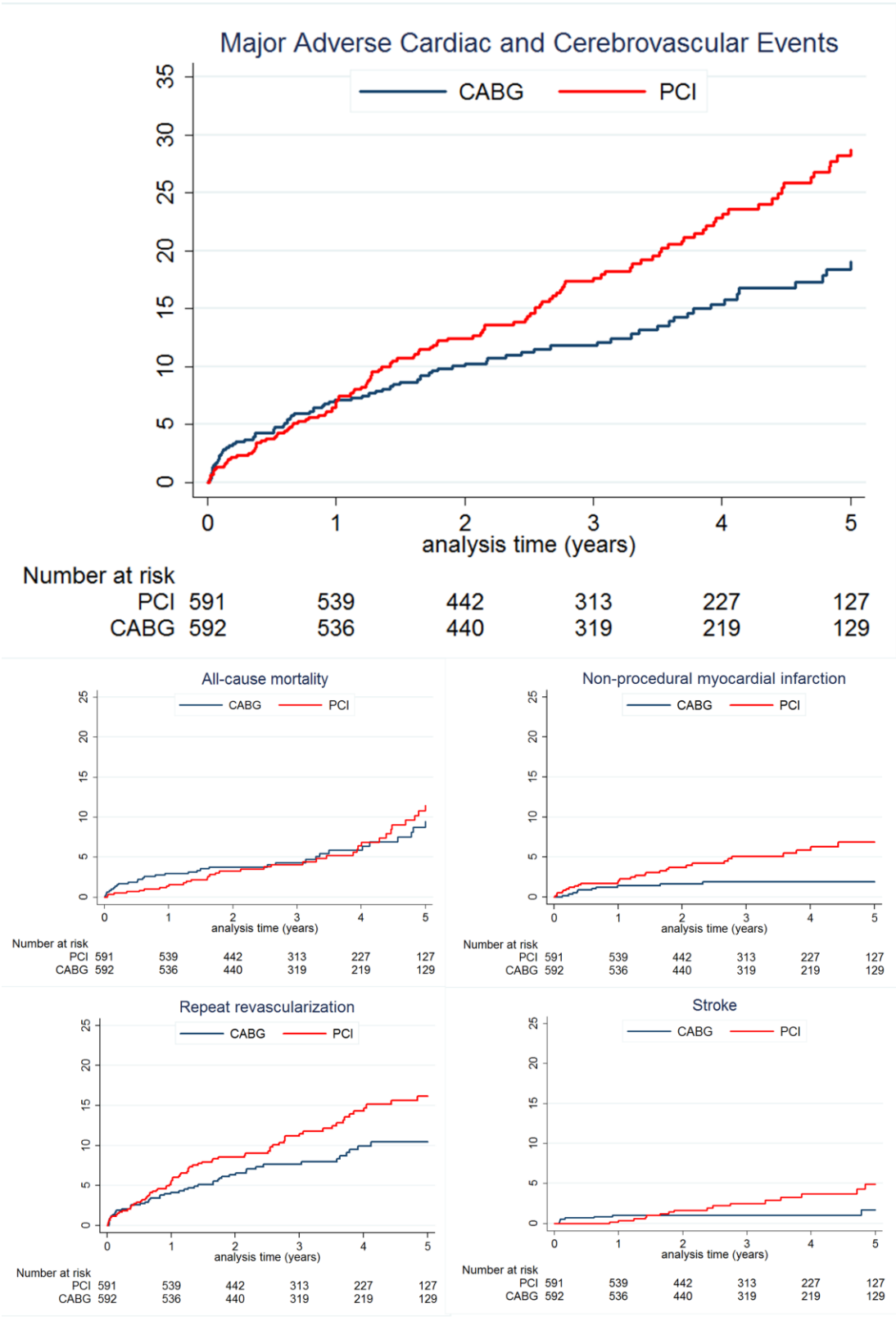
	PCI	CABG	Hazard ratio	95% CI	p-value
All-cause mortality	11.5%	9.5%	1.04	0.65 to 1.67	0.86
Cardiac death	3.1%	3.1%	0.86	0.41 to 1.81	0.69
Vascular death	0.7%	0.2%	1.96	0.18 to 21.66	0.55
Non-procedural MI	6.9%	1.9%	2.88	1.40 to 5.90	0.004
Revascularization (total)	16.2%	10.4%	1.50	1.04 to 2.17	0.03
Revascularization with PCI	12.9%	10.1%	1.23	0.83 to 1.83	0.29
Revascularization with CABG	4.4%	0.3%	9.41	2.20 to 40.38	0.003
Target lesion revascularization	11.7%	8.0%	1.38	0.90 to 2.12	0.14
Target LMCA revascularization	10.0%	7.5%	1.23	0.78 to 1.94	0.37
De-novo lesion revascularization*	6.2%	2.6%	2.34	1.16 to 4.74	0.02
Symptomatic graft occlusion or definite stent thrombosis	2.6%	4.1%	0.59	0.26 to 1.36	0.22
Possible stent thrombosis	1.3%	0.0%	-	-	-
Probable stent thrombosis	0.3%	0.0%	-	-	-
Stroke	4.9%	1.7%	2.25	0.92 to 5.48	0.07

\* New lesion in non-stented segment or non-grafted vessel.

**Figure 1. Patient Flow Chart**



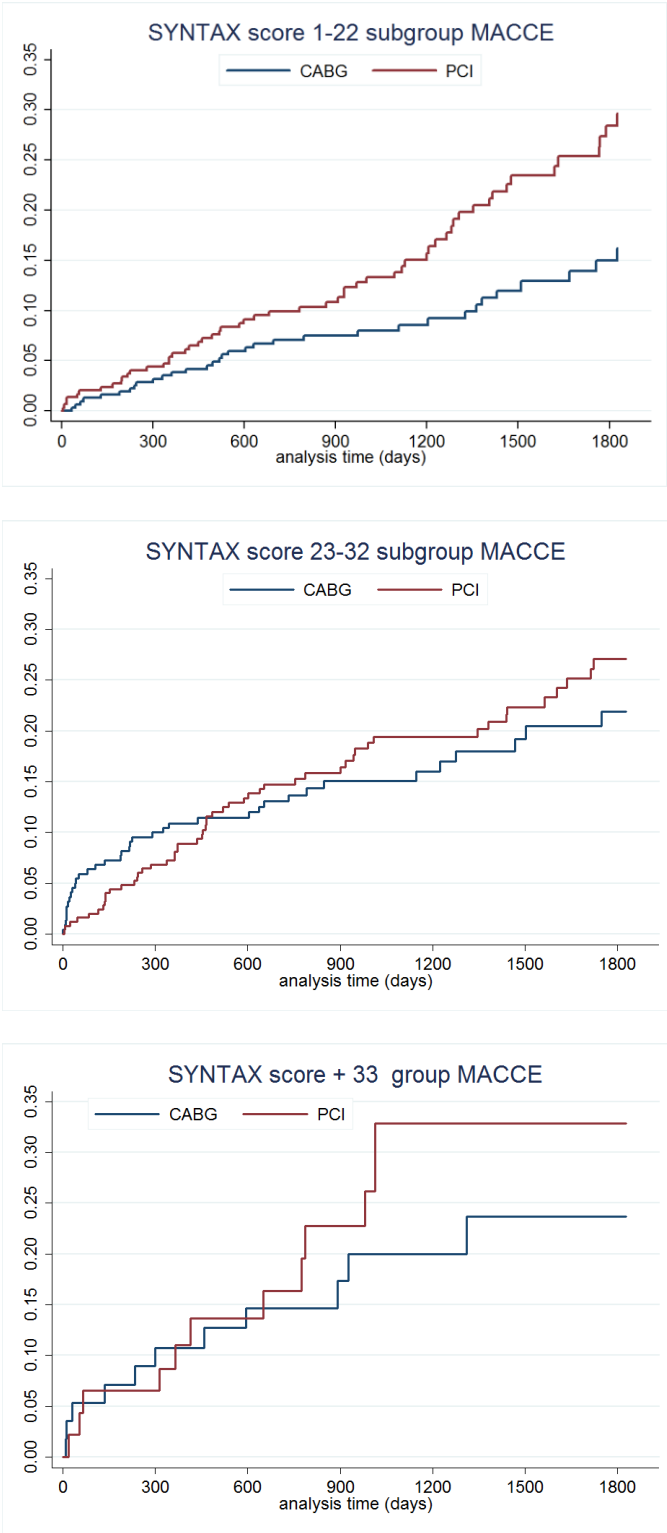
**Figure 2. Outcomes According to Intention-to-Treat.**







**Figure 3. Outcomes by SYNTAX Score Group.**



## Supplementary appendix

Additional information regarding the trial “Percutaneous Coronary Angioplasty versus Coronary Artery Bypass Grafting in Treatment of Unprotected Left Main Stenosis: The Nordic-Baltic-British Left Main Revascularization Study (NOBLE)”

**List of Steering Committee members**

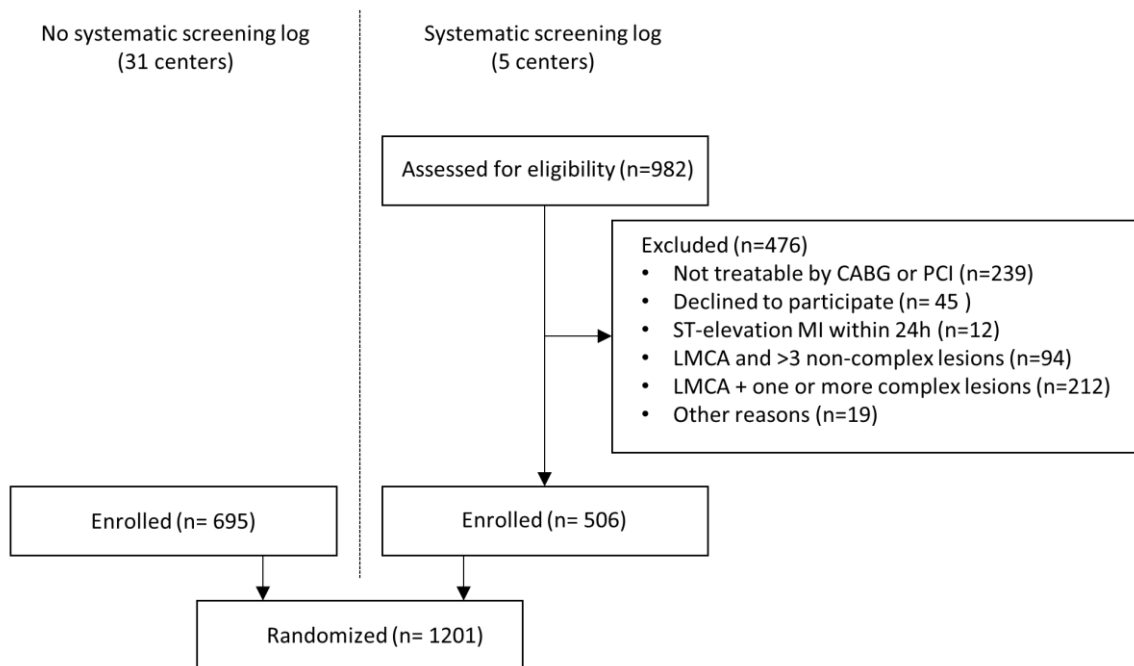
**List of Clinical Endpoint Committee members**

**List of members of the Data Monitoring Safety Committee**

**List of Investigators and Collaborators**

## Screening of Patients

The predefined screening log was maintained in five participating centers. Eight centers entered five or fewer patients in the screening log during the enrollment period and are omitted from the diagram.



## Clinical Endpoint Definitions

### **All-cause mortality**

Death from any cause.

### **Cardiac death.**

Cardiac death was defined as any death due to a suspected cardiac cause (myocardial infarction, low-output heart failure, fatal arrhythmia), unwitnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment, will be classified as cardiac death. (Modified from Cutlip et al. Circulation. 2007;115:2344-2351)

### **Vascular death**

Death caused by non-coronary vascular causes, including cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular diseases. (Modified from Cutlip et al. Circulation. 2007;115:2344-2351)

### **Non-procedure related myocardial infarction**

A rise of biochemical markers exceeding the decision limit of myocardial infarction (99th percentile including < 10% CV) with at least one of the following; 1) ischemic symptoms, 2) ECG changes indicative of ischemia (ST segment elevation or depression, 3) development of pathologic Q-wave and with no relation to a PCI procedure.

### **Repeat revascularization**

Any new PCI or CABG operation performed during follow-up. If index revascularization was attempted or successful, any subsequent revascularization was counted as repeat revascularization. Attempted PCI was defined as if at least a wire was advanced in the coronary tree. Attempted CABG was defined as at least initiated index operation.

### **Procedure related biomarker release**

The diagnosis of procedure related biomarker increase required a rise of Total CK and/or Troponin-T/I. Due to major heterogeneity of biomarkers and various assays used during the study in participating centers the comparison was omitted from final analysis.

### **Procedural myocardial infarction**



Diagnosis of procedural MI for both PCI and CABG patients was based on CK-MB elevations when available. The patient was to have stable angina pectoris as clinical indication, OR a normal baseline CK-MB, TnI, TnT, or high sensitive TnT, to be assessable for procedural MI. Diagnosis required a CK-MB above 10 x URL or ULN, OR a CK-MB above 5 x URL or ULN, AND one or more of the following: 1) new pathological Q waves in at least 2 contiguous leads or new persistent non-rate related LBBB, or 2) angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow, or 3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. The endpoint of procedural myocardial infarction was included post hoc and the definition was adapted to match the definition applied in the EXCEL trial on PCI vs. CABG for LMCA stenosis.

### **Target lesion revascularization**

By PCI: repeat revascularization of any target segment treated at the index procedure. A target lesion segment was defined as a stented or balloon treated segment and its 5 mm margins.

### **LMCA revascularization**

By PCI: any subsequent revascularization of the segments within 5 mm of any treated segment related to the LMCA or the LMCA bifurcation. By CABG: any revascularization of native LMCA including the LMCA bifurcation, or revascularization of a graft supplying the left anterior descending artery or circumflex arteries.

### **Definite stent thrombosis**

Stent thromboses are categorized as acute, subacute, late and very late and as definite, probable and possible according to ARC criteria (Cutlip et al. Circulation. 2007;115:2344-2351)

### **Symptomatic graft occlusion**

Diagnosis of symptomatic graft occlusion required it to be detected during a clinically indicated coronary angiography.

### **Stroke**

Ischemic or hemorrhagic cerebrovascular event verified by brain computed tomography (CT) or magnetic resonance imaging

### **Pulmonary embolus**

The diagnosis of pulmonary embolus required verification by appropriate computed tomography scan.

## Recommendations for angiography and re-revascularization

Re-angiography was indicated by the presence of new symptoms of angina pectoris or new onset of acute coronary syndrome, angina pectoris Canadian Cardiovascular Score class >2, heart failure or severe tachy arrhythmia (ventricular fibrillation or ventricular tachycardia). Revascularization was indicated if a stenosis exceeded a diameter stenosis of 70% by visual assessment or if fractional flow reserve was measured and had a value below 0.75.

## Classification of left main coronary artery stenosis

Distal LMCA lesions were bifurcation lesion involving the left anterior descending artery and/or left circumflex artery. Ostial LMCA lesions were defined as lesions with or without shaft involvement and no distal bifurcation involvement. Shaft lesions were lesions isolated to the shaft without involvement of the LMCA ostium and the LMCA bifurcation.

## Sample size calculation and primary endpoint reporting

Sample size calculation was based on the combined primary endpoint of death, stroke, non-index treatment related MI and new revascularization (PCI or CABG) after 2 years.

The study was planned as a non-inferiority study, where PCI was considered the experimental treatment of LMCA disease and was compared to CABG as the standard treatment. PCI was not allowed to be more than clinically insignificantly inferior to CABG to be declared non-inferior. Calculations were based on the following:

- mean follow-up time of 24 months
- all event curves should be exponential
- zero dropout
- randomization into 2 equally sized groups

- $\alpha = 0.05$  (one-sided)
- $1 - \beta$  (power) = 80%

The non-inferiority limit was based on a 12 months MACCE rate of 12% in the CABG group and 16% in the PCI group (the SYNTAX study). With exponential event curves ( $CABG(t) = \exp(-\lambda \cdot t)$ ) this corresponds to a hazard ratio of 1.36, PCI versus CABG, and, with  $t$  in months,  $\lambda = 0.0107$  in the CABG group. In continuation of this, the present study used a hazard ratio of 1.35 for PCI versus CABG, as limit for non-inferiority, and  $\lambda = 0.011$  to describe MACCE in the CABG group. These figures correspond to a 24-month MACCE rate of 30% and 23% in the PCI and CABG group, respectively. The above preconditions and assumptions result in a necessary number of patients in each randomization group of 593 (and a total number of events - in both groups - of 275). Consequently, 1,186 patients should be randomized. I was decided to include 600 patients in each group to account for possible dropouts before follow-up and treatment estimation errors.

Protocol change of January 22<sup>nd</sup> 2015

Due to lower than expected endpoint rates, the total number of events needed to assess inferiority would not occur within a fixed two-year follow-up. To accommodate, the total follow-up time of up to 5 years in each patient was included in the primary endpoint calculation. The time point for assessment was defined by reaching a total of 275 primary endpoint events.

Change in primary outcome reporting

In September 2015 it was estimated that 275 primary endpoint events would not be reached within the full 5-year follow-up period. At the investigator meeting at TCT in San Francisco on October 12<sup>th</sup> 2015 it was decided to report the primary outcome based on clinical events received before May 1<sup>st</sup> 2016 thus all patients having at least one year follow-up and a mean 3-year follow-up.

### **Data safety monitoring committee (DSMC)**

The safety of the study was monitored by an independent Data monitoring safety committee (DMSC) headed by Prof. Juha Hartikainen, Kuopio University Hospital, Finland. The DMSC received information on rates of all-cause mortality, non-index procedure related myocardial infarction, definite stent thrombosis, target lesion revascularization and stroke. The DMSC was to make independent decision on continuation or stopping the study. Termination of the study should be recommended if there at any time was found a significant ( $p$ -value of  $< 0.003$  by  $\chi^2$ -test) difference between rates of all-cause mortality, non-index procedure related myocardial infarction definite stent thrombosis, target lesion revascularization or stroke.

<b>Table 1. Treatment Characteristics in the PCI Group.</b>	
LMCA stenting involving ostium and not bifurcation	10.2%
Shaft LMCA stenting only	3.0%
LMCA bifurcation lesion stenting	86.8%
Angulation less than 70 degrees	21.9%
Visible calcification	42.1%
Severe tortuosity	10.8%
Stenting of LMCA-LAD only	57.1%
Stenting of LMCA-Cx only	4.0%
Culotte	22.7%
Crush	3.8%
T-stenting	8.0%
V-stenting	0.2%
Other technique	1.6%
Total stent length in LMCA lesion (mm)	24 [IQR 15:35]
Total number of stents in LMCA lesion (n)	1 [IQR 1:2]
IVUS pre-evaluation	46.8%
IVUS post-evaluation	74.9%
Pre-dilatation of LMCA	86.6%
Pre-dilatation of LAD	76.9%
Pre-dilatation of Cx	40.3%
Post-dilatation of LMCA	89.7%
Post-dilatation of LAD	50.1%

Post-dilatation of Cx	72.0%
Max pressure of largest balloon in LMCA	18 [IQR 16:20]
Max pressure of largest balloon in treated LAD	18 [IQR 14:20]
Max pressure of largest balloon in treated Cx	16 [IQR 12:18]
Nominal diameter of largest balloon or stent in LMCA	4.0 [IQR 4.0:4.5]
Nominal diameter of largest balloon or stent in treated LAD	3.5 [IQR 3.5:4.0]
Nominal diameter of largest balloon or stent in treated Cx	3.0 [3.0:3.5]
Kissing balloon post inflation	52.5%
Number of treated lesions	
1	53.4%
2	32.5%
3	9.6%
4	2.4%
5	0.5%
Total stent length in non-LM lesions if treated (mm)	28 [IQR 18:42]
Total number of stents in non-LM lesions if treated	1 [1:2]
Procedure time (min)	62 [IQR 47:85]
Fluoroscopy time (min)	26 [IQR 11:24]
Contrast volume (mL)	200 [IQR 150:280]
Complete revascularization	94.1%
LMCA treated by 1st generation drug-eluting stent	10.9%
Antithrombotic treatment	
Unfractionated heparin	72.6%
Low molecular weight heparin	14.2%

Bivalirudine	18.9%
GPIIb/IIIa inhibitor	19.1%
Aspirin	92.9%
Clopidogrel/Ticlopidine/Ticagrelor	97.4%

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**Table 2. Treatment Characteristics in the CABG group.**

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On-pump technique	84.4%
Off-pump technique	15.6%
Arterial graft	94.5%
Arterial graft to LAD	93.4%
LIMA + RIMA grafts	7.9%
LIMA + venous graft	85.7%
Radial artery graft	4.8%
Venous grafts only	5.0%
Grafts per patient	
1	4.1%
2	52.0%
3	39.0%
4	4.4%
5	0.6%

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