
Copyright: © 2016. This manuscript version is made available under the [CC-BY-NC-ND 4.0 license](http://creativecommons.org/licenses/by-nc-nd/4.0/)

DOI link to article: [http://dx.doi.org/10.1016/S0140-6736(16)32052-9](http://dx.doi.org/10.1016/S0140-6736(16)32052-9)

Date deposited: 08/03/2018

Embargo release date: 30 April 2017

This work is licensed under a [Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International licence](http://creativecommons.org/licenses/by-nc-nd/4.0/)
Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis: The randomised Nordic–Baltic–British left main revascularisation study (NOBLE)

Timo Mäkikallio, Niels R Holm, Mitchell Lindsay, Mark Spence, Andrejs Erglis, Ian B A Menown, Thor Trovik, Markku Eskola, Hannu Rompanen, Thomas Kellerth, Jan Ravkilde, Lisette O Jensen, Gintaras Kalinauskas, Rikard B A Linder, Markku Pentikainen, Anders Hervold, Adrian Banning, Azfar Zaman, Jamen Cotton, Erlend Eriksen, Sulevi Margus, Henrik T Sørensen, Per H Nielsen, Matti Niemelä, Kari Kervinen, Jens F Lassen, Michael Maeng, Keith Oldroyd, Geoff Berg, Simon J Walsh, Colm G Hanratty, Indulis Kumsars, Peteris Stradins, Terje K Steigen, Ole Fröbert, Alastair NJ Graham, Petter C Endresen, Matthias Corbascio, Olli Kajander, Uday Trivedi, Juha Hartikainen, Vesa Anttila, David Hildick–Smith, Leif Thuesen, and Evald H Christiansen, for the NOBLE investigators*

* A complete list of investigators in the NOBLE–study is provided in the Supplementary Appendix.

Department of Cardiology, Oulu University Hospital, Finland (T Mäkikallio MD, M Niemelä PhD, K Kervinen PhD);
Department of Cardiology, Aarhus University Hospital, Skejby, Aarhus, Denmark (N R Holm MD, J F Lassen PhD, M Maeng PhD, E H Christiansen PhD);
Department of Cardiology, Golden Jubilee National Hospital, Clydebank, Scotland (M Lindsay MD, Professor K Oldroyd MD);
Belfast Heart Centre, Belfast Trust, Northern Ireland (M Spence MD, S J Walsh MD, C G Hanratty MD, A N J Graham MD);
Latvia Centre of Cardiology, Paul Stradins Clinical Hospital, Riga, Latvia (Professor A Erglis PhD, I Kumsars MD, P Stradins PhD);
Craigavon Cardiac Centre, Northern Ireland (I B A Menown FRCP);
Department of Cardiology, University of Northern Norway, Tromsø, Norway (T Trovik PhD, T K Steigen PhD);
Department of Cardiovascular Surgery, University of Northern Norway, Tromsø, Norway (P C Endresen PhD);
Heart Hospital, Tampere University Hospital, Finland (M Eskola PhD, O Kajander PhD);
Heart Center, Kuopio University Hospital, Finland (H Rompanen PhD, Prof J Hartikainen PhD);
Department of Cardiology, Örebro University Hospital, Sweden (T Kellert MD, O Fröbert PhD);
Department of Cardiology, Aalborg University Hospital, Denmark (J Ravkilde DMSc, L Thuesen DMSc);
Department of Cardiology, Odense University Hospital, Denmark (L O Jensen DMSc);
Department of Cardiology, Vilnius University Hospital, Lithuania (G Kalinauskas PhD);
Department of Cardiology, Danderyd Hospital, Stockholm, Sweden (R B A Linder FESC);
Heart and Lung Center, Helsinki University Hospital, Finland (M O Pentikainen PhD);
Department of Cardiology, Oslo University Hospital, Rikshospitalet, Norway (A Hervold MD);
Oxford Heart Centre, UK (Professor A Banning FRCP);
Department of Cardiology, Freeman Hospital and Institute of Cellular Medicine, Newcastle, UK (Professor A Zaman FRCP);
Heart and Lung Centre, New Cross Hospital, Wolverhampton, UK (J Cotton MD);
Department of Cardiology, Haukeland University Hospital, Bergen, Norway (E Eriksen MD);
Department of Cardiology, East Tallinn Hospital, Estonia (S Margus MD);
Department of Clinical Epidemiology, Aarhus University Hospital, Denmark and the Department of Health Research and Policy (Epidemiology), Stanford University, CA, US (Professor H T Sørensen DMSc);
Department of Cardiac Surgery, Aarhus University Hospital, Skejby, Aarhus, Denmark (P H Nielsen MD);
Department of Cardiac Surgery, Golden Jubilee National Hospital, Clydebank, Scotland (G Berg MD);
Department of Cardiology, Karolinska University Hospital, Huddinge, Stockholm, Sweden (M Corbascio PhD);

Department of Cardiac Surgery, Oulu University Hospital, Finland (V Anttila PhD);

Sussex Cardiac Centre, Brighton and Sussex University Hospital, UK (U Trivedi MD, D Hildick-Smith MD)

Correspondence to:
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
Left Main Coronary Artery Stenosis, Coronary Artery Bypass Grafting, Percutaneous Coronary Intervention

Word count: 4281
Summary

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

Methods Patients with LMCA disease were enrolled in 36 centres in Northern Europe and randomised 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 revascularisation and stroke. Non–inferiority of PCI to CABG required the lower end of the 95% confidence interval (CI) not to exceed a hazard ratio (HR) of 1.35 after up to five years of follow–up. Clinicaltrials.gov identifier: NCT01496651.

Findings A total of 1201 patients were randomised, 598 to PCI and 603 to CABG, and 592 in each arm entered analysis by intention to treat. Kaplan–Meier five–year estimates of MACCE were 28·7% for PCI (121 events) and 20·1% for CABG (81 events), [HR 1·46 (95% CI 1·10–1·95)], exceeding the limit for non–inferiority and was significant for superiority of CABG over PCI (p=0·0079). As–treated estimates were 29·1% vs. 21·1% [HR 1·51 (95% CI 1·15–1·99), p=0·0032]. Comparing PCI to CABG, five–year estimates were 11·5% vs. 9·5% [HR 1·04 (95% CI 0·65–1·67), p=0·8625] for all–cause mortality; 6·9% vs. 1·9% [HR 2·9 (95% CI 1·40–5·90), p=0·000] for non–procedural myocardial infarction; 16·2% vs. 10·4% [HR 1·5 (95% CI 1·04–2·17), p=0·0315] for any revascularisation; and 4·9% vs. 1·7% [HR 2·3 (95% CI 0·92–5·48), p=0·0731] for stroke.

Interpretation The findings of this study indicate that CABG may be superior to PCI for treatment of left main stem coronary artery disease.
Funding Biosensors, Aarhus University Hospital, and participating sites

Introduction

Treatment of unprotected left main coronary artery (LMCA) disease using percutaneous coronary intervention (PCI) has increased rapidly during the past decade, following the favourable results of randomised trials\textsuperscript{1–4} and observational registry studies comparing PCI and coronary artery bypass grafting (CABG).\textsuperscript{5–9} At the present time, both options are used to treat LMCA disease.\textsuperscript{10} Current guidelines recommend PCI in LMCA patients with coronary pathology favourable to PCI, \textit{i.e.}, in the absence of complex and diffuse lesions.\textsuperscript{10} The guidelines are based primarily on the pre specified, and powered subgroup of 705 patients with LMCA disease in the SYNTAX trial,\textsuperscript{11,12} 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 randomised LE MANS,\textsuperscript{1} PRECOMBAT\textsuperscript{2} and Boudriot \textit{et al.}\textsuperscript{3} trials, which included 105, 600 and 201 patients with LMCA stenosis, respectively. In the randomised trials, the non–inferiority margin was wide, due to relatively small patient sample sizes and thus the trials were not powered to definitively determine the best treatment for unprotected LMCA disease.

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

Methods

Study design

The Nordic–Baltic–British Left Main Revascularisation Study (NOBLE) trial, a prospective, randomised, open label, clinical, non-inferiority trial was conducted at 36 sites in Latvia, Estonia, Lithuania, Germany,
Norway, Sweden, Finland, United Kingdom and Denmark. The authors designed the study, wrote the manuscript and vouch for the completeness and accuracy of data collection and analysis. The protocol and consent forms were consistent with Good Clinical Practice, the Declaration of Helsinki and all relevant regulations. The study was approved by The Central Denmark Region Committees on Health Research Ethics, and by national or local ethics committees for the individual sites as appropriate, and by the Danish Data Protection Agency. The trial was registered with ISRCTN87206264 and clinicaltrials.gov identifier: NCT01496651.

Patient selection

A local interventional cardiologist and a cardiac surgeon at each site prospectively evaluated eligible patients with LMCA disease. Inclusion criteria for study enrolment 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 were enrolled in the study by site investigators or designated staff. A screening log was maintained in 5 centres which recruited 506 of the 1201 patients. All enrolled patients provided written informed consent.

Randomisation and masking

Patients for whom it was determined that equivalent revascularisation could be achieved with CABG or PCI were randomly assigned (1:1) to undergo either treatment. Randomisation was performed by a web based computer randomization system (Trialpartner, random allocation sequence generated by Jakob Hjort, Institute of Clinical Medicine, Aarhus University, Denmark) in permuted blocks by country and centre with stratification by gender, presence of a distal LMCA bifurcation lesion, and presence of diabetes.
Revascularisation and pharmacologic treatment

Patients were treated with the intention of achieving complete revascularisation 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 deployment. 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 randomised to the CABG group were treated according to current clinical practice. The left internal mammary artery was recommended for revascularisation 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. 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, non–procedural myocardial infarction, repeat revascularisation or stroke) (MACCE)]. The main hypothesis was non–inferiority of PCI to CABG, assessed as the lower limit of the 95% CI of the hazard ratio (HR) of PCI to CABG, not exceeding 1.35 assessed at median three years follow-up.

**Summary of change to the primary endpoint**

The original primary endpoint was evaluation of non-inferiority of PCI to CABG assessed by MACCE at full two years follow-up. Due to low event rates the primary endpoint assessment was primo 2015 changed to a median follow-up including all MACCE endpoints up to five years follow-up and timing of evaluation when the originally stipulated 275 primary endpoint events were reached. Ultimo 2015 it was forecasted that the 275 events would not be reached within full five years follow-up, and the primary endpoint assessment was changed to median 3 years. See Supplementary Appendix for detailed information.

**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 (post hoc). Repeat revascularisations were categorized as target lesion revascularisation, LMCA target lesion revascularisation or de novo lesion revascularisation. Functional class was reported as maximal New York Heart Association (NYHA) score and chest pain was reported by the maximal Canadian Cardiovascular Society (CCS) score at up to five years follow-up.

**Angiographic evaluation**

Diagnostic angiograms were reviewed an independent core laboratory [European Cardiovascular Research Center (CERC), France] who were blinded to the assigned treatment. Diagnostic angiograms were scored according to the SYNTAX I score algorithm at both the recruitment sites and the core laboratory.
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, revascularisation, graft occlusion, and stent thrombosis. (See Supplementary Appendix for list of members).

Data and Safety Monitoring Board

The study was overseen by an independent Data and Safety Monitoring Board, which received information on clinical events. (See Supplementary Appendix for list of members).

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 the SYNTAX trial,\textsuperscript{11,12} 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 were defined accordingly as the clinical acceptable non-inferiority limit not to be exceeded by the on-sided 95% confidence interval (CI). 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 at two-years follow-up. As the total number of events could not be reached within the full five-year follow-up period for MACCE, the primary endpoint was assessed at a median of three years of follow-up. (See Supplementary Appendix for details of sample size calculation and changes to the primary endpoint reporting).

Statistics

The intention-to-treat principle was used in the analysis if not specified otherwise. Continuous variables were reported as means ± 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 randomisation. In the analysis of individual endpoints, follow–up continued until the date of a clinical endpoint event, death, emigration, or five years after randomisation, 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 five years was reported using 5–year Kaplan–Meier estimates and HRs with 95% CIs computed on unadjusted 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”: ≤22; “intermediate”: 23 to 32; and “high”: ≥33), and presented by Kaplan–Meier curves. A p value <0·05 was considered significant. All analyses were performed using STATA12.

Role of the funding source

Aarhus University Hospital was the main sponsor of the trial. Biosensors provided an institutional research grant for the trial but had no role in the study design; in the collection, analysis, and interpretation of the data, in the writing of this report; or in the decision to submit the paper for publication. The corresponding author, NRH and HTS had full access to all the data in the study and had together with the Writing group (see supplementary material) the final responsibility for the decision to submit for publication.

Results

A total of 1201 patients were enrolled from Dec 2008 to Jan 2015 in 36 centres. Fourteen withdrew consent, three 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 for the primary endpoint was continued until May 1st 2016 and was available for 89.7% and 89.9% of the study population at two years, 68.8% and 67.2% at three years, 52.0% and 49.5% at four years, and 37.8% and 35.1% at five years in the PCI and CABG arm respectively, corresponding to 69% of the total study follow-up completed.

Baseline characteristics

In the PCI and CABG groups, median ages were 66·2±9·9 years and 66·2±9·4 years (p=0·91), female were 116 (19·6%) and 140 (23·7%) (p=0·0902) and patients with diabetes were 86 (14·6%) and 90 (15·2%) (p=0·9410), respectively. The logistic EUROSCORE was 2[IQR 2:4] (p=0.1884) in both groups and the SYNTAX scores were 22·3±7·8 and 22·4±7·4 (p=0·7062) in the PCI and CABG groups, respectively. The procedure indication was stable angina pectoris or silent ischemia in 466 (78·7%) of patients in the PCI group and 476 (80·5%) in the CABG group (p=0·4358). Distal LMCA disease was present in 477 (80·8%) of patients in the PCI group and 482 (81·4%) of patients in the CABG group (p=0·7111). Additional characteristics of the study population are provided in table 1.

PCI procedural characteristics

Among PCI–treated patients (Supplementary table 1), 312 (53·4%) had isolated LMCA treatment, 191 (32·5%) had one additional lesion treated, and 55 (9·6%) had two additional lesions treated. LMCA treatment involved the bifurcation in 508 (87·7%) of PCI cases and two–stent techniques were applied in 176 (34·6%) of LMCA bifurcation treatments. A first–generation drug–eluting stent was implanted in the LMCA in 10·9% of PCI cases. The nominal diameter of stents in the LMCA was 4·0 [IQR 4·0:4·5] mm, inflated to 18 [IQR16:20] atm. Kissing balloon inflation was performed in 277 (54·5%) and any ostial circumflex post–dilatation was performed in 79·8% of LMCA bifurcation treatments. Complete revascularisation was achieved in 543 (93·6%) of cases. IVUS of the LMCA was performed pre–PCI in 270 (46·3%) and post–PCI in 430 (74·1%) of PCI treated patients.
CABG procedural characteristics

CABG was performed using the on-pump technique in 476 (84.4%) patients, 526 (93.4%) underwent arterial grafting of the left anterior descending artery and 480 (85.7%) underwent left internal mammary artery plus venous grafting. Grafting using the right internal mammary artery was performed in 44 (7.9%) cases. The number of grafts per patient were one in 23 (4.1%) patients; two in 294 (52.0%) of patients; three in 220 (39.0%) of patients; four in 25 (4.4%) of patients; and 5 in 3 (0.6%) of patients (Supplementary table 2).

Primary endpoint

Kaplan–Meier estimates of MACCE by intention-to-treat after five years were 28.7% (121 events) for PCI and 20.1% (81 events) for CABG (figure 2). The HR was 1.46 (95% CI 1.10–1.95), exceeding the limit for non-inferiority (1.35), and was significant for superiority of CABG compared to PCI (p=0.0079). Notably, one-year rates of MACCE in the two groups were the same [7.1% (42) vs. 7.1% (42), (RD 0.0, 95% CI –2.9–2.9, p=1.00)]. Outcome by actual treatment was 28.1% (120 events) vs. 19.2% (78 events), HR 1.46 (95% CI 1.10–1.95), p=0.0032.

Secondary clinical endpoints

Five-year risk estimates comparing PCI to CABG (table 2) were 11.5% (36) vs. 9.5% (33) [HR 1.04 (95% CI 0.65–1.67), p=0.8625] for all-cause mortality; 6.9% (29) vs. 1.9% (10) [HR 2.9 (95% CI 1.40–5.90), p=0.0040] for non-procedural myocardial infarction; 4.9% (16) vs. 1.7% (7) [HR 2.3 (95% CI 0.92–5.48), p=0.0731] for stroke (all were ischemic), 16.2% (71) vs. 10.4% (47) [HR 1.5 (95% CI 1.04–2.17), p=0.02315] for total repeat revascularisation; 10.0% (41) vs. 7.5% (33) [HR 1.2 (95% CI 0.78–1.94), p=0.3714] for repeat revascularisation of the LMCA; and 6.2% (24) vs. 2.6% (11) [HR 2.3 (95% CI 1.16–4.74), p=0.00180] for de-novo lesion revascularisation during follow-up. Maximal NYHA score at up to five years follow-up was 1 in 57% and 54%, 2 in 37% and 36%, 3 in 5% and 10%, and 4 in 1 and 0.2% (p=0.0110), further was CCS class during up to 5 years follow-up 0 in 42% and 50%, 1 in 41% and 35%, 2 in 14% and 13%, 3 in 3% and 2%, 4 in 1% and 1% (p=0.0932) in PCI and CABG, respectively.
30–day outcomes following the index procedure

Rates of outcomes, comparing the PCI group to the CABG group, during the 30 days following the index procedure were; 16 (5·4%) vs. 16 (6·7%) [RD –1·3% (95% CI –5·4–2·8), p=0·5238] for procedural myocardial infarction (assessable in 238 (41·8%) and 296 (50·6%) of patients), 1 (0·2%) vs. 23 (3·9%) [RD –3·7% (95% CI –5·3–2·1), p<0·0001] for reoperation for bleeding, 11 (2·0%) vs. 150 (27·5%) [RD –25·4% (95% CI –29·3–21·5), p<0·0001] for blood transfusion, 0 (0·0%) vs. 3 (0·5%) [RD –0·5% (95% CI –1·1–0·07), p=0·0825] for surgery for a sternum infection, and 2 (0·4%) vs. 4 (0·7%) [RD 0·3% (95% CI –1·2–0·5), p=0·4162] 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] (p<0·0001) days for CABG. Comparing the PCI group to the CABG group, rates of 30 days all–cause mortality were 2 (0·3%) vs. 7 (1·2%) [RD –0·8% (95% CI –1·8–0·1), p=0·0943], rates of non–procedural myocardial infarction were 3 (0·5%) vs. 0 (0·0%) [RD 0·5% (95% CI –0·06–1·1), p=0·0829], rates of revascularisation were 7 (1·2%) vs. 10 (1·7%) [RD –0·5% (95% CI –1·8–0·8), p=0·4636] and rates of stroke were 0 (0·0%) vs. 0·4% [RD –0·7% (95% CI –1·3–0·01), p=0·0451], respectively (table 3).

One–year clinical outcomes

One–year clinical outcomes are shown in table 4. One–year outcome comparing the PCI group to the CABG group were 9 (1·5%) vs. 17 (2·9%) [RD –1·3% (95% CI –3·0–0·3), p=0·1126] for all–cause mortality; 8 (1·4%) vs. 13 (2·2%) [RD –0·8 (95% CI –2·3–0·6), p=0·2709] for cardiac death, 11 (1·9%) vs 8 (1·4%) [RD 0·5 (95% CI –0·9–1·9) for non–procedural myocardial infarction, p=0·4878], 2 (0·3%) vs. 6 (1·0%) [RD –0·7% (95% CI –1·6–0·3), p=0·1559] for stroke, and 32 (5·4%) vs. 24 (4·0%) [RD 1·4 (95% CI –1·1–3·8), p=0·2734] for total repeat revascularisation.

Outcomes according to SYNTAX score groups

Comparing the PCI group to the CABG group, five–year Kaplan–Meier estimates for MACCE in the SYNTAX score subgroups were as follows: “low” 1–22: 29·7% (57 of 297) vs. 16·2% (33 of 316) [HR 1·85,
95% CI (1.20–2.85), p=0.0050, 51.8% of study population); “intermediate” 23–32: 27.1% (52 of 249) vs. 21.9% (37 of 220) [HR 1.16, 95% CI (0.76–1.78), p=0.4763, 39.6% of study population], and “high” >32: 32.9% (12 of 46) vs. 23.6% (11 of 56) [HR 1.41, 95% CI (0.62–3.20), p=0.4099, 8.6% of study population] (figure 3).
Discussion

The EXCEL and NOBLE studies are the largest international randomised studies comparing PCI and CABG in the treatment of LMCA disease to date.\textsuperscript{15} 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 revascularisation 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) maximal angina pectoris score was higher after PCI at up to 5 years follow-up (6) the differences in outcomes were seen mainly after one year of follow-up, and (7) the SYNTAX score was not associated with MACCE after PCI.

The composite primary MACCE endpoint was similar in NOBLE and the SYNTAX trial except NOBLE did not include peri-procedural myocardial infarction. We found no difference in large peri-procedural myocardial infarctions between PCI and CABG in NOBLE, and similar to NOBLE, no difference was observed at one year in the SYNTAX trial comparing the PCI group to the CABG group (MACCE: 13·7\% vs. 15·8\%, p=0·44).\textsuperscript{12} At five year follow-up in the SYNTAX trial, the MACCE rate was higher in the PCI group compared to the CABG group (36·9\% vs. 31·0\%, p=0·12).\textsuperscript{16} A recent meta-analysis of the SYNTAX LMCA subgroup and PRECOMBAT\textsuperscript{17} showed that PCI was associated with significantly higher MACCE after 5 years (28·3\% vs. 23·0\%, p=0·045), as confirmed by the NOBLE trial.

Our findings of similar mortality but higher rates of myocardial infarction and repeat revascularisation in patients undergoing PCI compared to CABG are consistent with previous major studies of coronary revascularisation in patients with LMCA disease.\textsuperscript{1-4,16-17} The low mortality following treatment in both groups demonstrates that modern revascularisation techniques and adjunctive therapy can lead to excellent survival in stable LMCA patients. Still, the increased rates of non-procedural myocardial infarction, repeat revascularisation 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, signalling a disadvantage for the patient.

Maximal angina pectoris score was higher after PCI than after CABG probably contributing to the increased revascularisation rates in the PCI group. Increased revascularisation rates after PCI compared to CABG are consistent with previous publications on both LMCA stenting\(^1\)–\(^9\) and three–vessel coronary artery disease stenting.\(^{4,18}\) Although restenosis of drug–eluting stents has diminished over time with introduction of high–pressure deployment,\(^{19}\) use of IVUS,\(^{20}\)and improved stent design,\(^{21}\)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 a small difference in target LMCA revascularization but a more than two-fold increase in the need for de–novo lesion revascularisation in the PCI group compared with the CABG group during follow–up. Repeat revascularisation was performed mainly using PCI, but an estimated 4·4% of PCI patients required revascularisation using CABG during the up to five 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 five years. These findings contrast with previous studies, which have tended to show a higher stroke rate for CABG, persisting at long-term follow-up in the 5-year report of the SYNTAX LMCA trial, whereas the differences in stroke
rates were limiting at longer follow-up in the other randomised trials. 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 termination of dual antiplatelet inhibition treatment. Still, the low number of strokes and the late separation of the stroke event curves do not exclude that this finding was due to chance.

The SYNTAX score was not associated with outcomes after PCI in contrast to the SYNTAX study. The unexpected finding of a substantial better outcome after CABG in the low SYNTAX score group could be the result of the fact that 87% of PCI treatments involved the LMCA bifurcation which is known to predict worse outcome. This may therefore represent a limitation of the SYNTAX score for treatment selection in patients with LMCA disease. The clinical utility of the SYNTAX score may be better in patients with multivessel disease, based on whom the score was developed.

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 revascularisation 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 revascularisation modalities.

While MACCE was exactly the same for the two treatment groups at one year, there was a significant difference in the long term outcomes between the PCI and CABG groups. This suggests that selecting PCI over CABG can be justified in patients with reduced life expectancy. However our data clearly show that the practice of only reporting event rates at one year in PCI revascularisation trials is not reliable for predicting 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, some vein graft degeneration can be
expected beyond five years.\textsuperscript{21} We will follow all patients for MACCE for a full five years and for all–cause mortality for ten years.

Among PCI patients, the vast majority had bifurcation LMCA involvement, consistent with previous studies.\textsuperscript{11} 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,\textsuperscript{25} but adequate expansion and full lesion coverage are required.\textsuperscript{26} 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 dilatation beyond the nominal diameter.\textsuperscript{27} Bench testing of the 3·5 and 4·0 mm BioMatrix stent (similar platform) showed the ability to expand to 5·9 mm.\textsuperscript{28} Larger left mains were possibly excluded by the local cardiac teams. The majority had post–dilatation of the LMCA but only half of the patients had post–dilatation with balloons larger than 4 mm. Stent under–expansion and mal–apposition in the LMCA may have contributed to the numerically higher target LMCA revascularisations in the PCI group.

The NOBLE results should be generalized with caution and in particular the SYNTAX stratified results as they are rather different from previous publications. The change to the primary endpoint timing is a major limitation but was carefully considered by investigators and statisticians in response to the low event rates to avoid a vastly underpowered and likely inconclusive primary non-inferiority endpoint reporting. The reporting by Kaplan-Meier estimates could be influenced by a change in risk for those entering the study early and late as will be determined at the full five-year follow-up. Still, the main five-year KM outcome estimates in NOBLE are in line with the results presented in the recent metaanalysis of 5-year outcome in the SYNTAX LMCA and PRECOMBAT trials.\textsuperscript{17} As patients in NOBLE were elective or stabilized patients results may not be applicable in the acute setting where PCI may be preferred over CABG if the anatomy is suitable for PCI. The centres in the trials were selected according to interest in LMCA and bifurcation
treatment and the result might not be translated into centres with low volume in bifurcation treatment. A small fraction of patients were treated with first generation drug eluting stents and the study stent had a strut thickness above most types of presently used permanent metallic stents. Still, the study stent is a proven device with good clinical results in general use\textsuperscript{29,30} and it is therefore uncertain if the applied stent types affects the generalizability of the results.

The primary endpoint of this study clearly favoured surgical revascularisation. However, it was a composite endpoint, and the results may be interpreted in various ways. We saw a slight difference in patients refusing the allocated treatment in favor of PCI and in some patients’ view, the need for surgery, the long hospitalization, the risk of reoperation for bleeding and infection, and a longer recovery time may not be worth the lower risk of repeat revascularisation and myocardial infarction, as no difference in all–cause mortality was found.

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

TM and LT designed the trial and wrote the protocol. Contracts and funding was handled by JFL, LT, EHC and NRH. Statistical analysis was performed by NRH with advice from HTS. The writing committee (MS, ANJG, IM, DHS, ML, TM, MN, KK, AE, PS, TT, PCE, VA, LT, EHC, NRH, PHN, HTS) interpreted results and wrote the report. All authors contributed to implementation of the study, data acquisition, and approved the report for publication.

Declaration of interests

TM has received grants from Biosensors to the institution during the conduct of the study; NRH received institutional research grants from Biosensors, Abbott, Cordis, Medtronic, Biotronik, Reva Medical, Elixir and Boston Scientific, and received speaker fees from Boston Scientific, St. Jude Medical and Terumo ML received grants from Biosensors during the conduct of the study; MS received personal fees from Edwards Lifesciences, Medtronic, Boston Scientific, outside the submitted work; AE received personal fees from Biosensors, outside the submitted work, IM received grants from Biosensors, during the conduct of the study and other grants from Biosensors, grants from Boston Scientific, outside the submitted work. TT, ME, HR, and TK reports nothing to disclose. JR reports grants from Biosensors to his institution, outside the submitted work. LOJ reports grants from Biosensors to her institution, grants from Biotronik to her institution, personal fees from Biotronik, grants from Terumo and St. Jude Medical to her institution, outside the submitted work; GK reports no conflicts of interest; RL reports grants from Biosensors to his institution, outside the submitted work. MP reports grants from Biosensors, Switzerland, during the conduct of the study; AH reports no conflicts of interest; AB reports personal fees from Abbott Vascular, Medtronic, Boston scientific, outside the submitted work and is partially funded by the NIHR Oxford Biomedical Research Centre. AZ has nothing to disclose; JC reports non-financial support from Biosensors, during the conduct of the study; other from Travel Support Medtronic, outside the submitted work; EE has nothing to disclose; SM, HTS and PHN has nothing to disclose. MN and KK reports grants from Biosensors to his institution, during the conduct of the study. JFL reports grants from Boston Scientific, St. Jude Medical, Biosensors, Biotronik, and Terumo outside the submitted work. MM reports grants from Boston Scientific,
BioSensors International, Volcano, outside the submitted work. KO reports grants from Biosensors, during the conduct of the study; personal fees from Biosensors, outside the submitted work. GB reports personal fees from Vascutek Ltd, outside the submitted work. SW and CH have nothing to disclose. IK reports grants from Biosensors to his Institution, personal fees from Astra Zeneca, outside the submitted work. PS, AG, PCE, MC, TS, OK and UT reports nothing to disclose, JH reports grants from Biosensors to his institution, during the conduct of the study. VA and OF has nothing to disclose, has nothing to disclose. DHS reports other support from BioSensors, during the conduct of the study; LT has nothing to disclose. EHC reports grants from Biosensors to his institution.

Acknowledgement

The study secretary Helle Bargsteen and study coordinators Pia Stycke Ottosen and Lars Peter Jørgensen, all Aarhus University Hospital, Denmark are acknowledged for their major contribution during the conduct of the trial. Data manager Jakob Hjort, Aarhus University, is acknowledged for his important contribution during all phases of the trial.
Research in Context

Evidence before this study

We searched PubMed reports on randomised trials comparing percutaneous coronary intervention (PCI) with coronary artery bypass grafting (CABG) in treatment of left main coronary artery (LMCA) disease with the search terms “percutaneous coronary intervention”, “coronary artery bypass operation”, “coronary artery bypass grafting”, “randomised”, or “randomized”, published after the introduction of drug eluting stents, between January 1, 2003, and September 1st, 2016. We identified four randomised trials1–3,16. Three trials were underpowered for clinical end-points1–3 and in the SYNTAX trial16, included only 705 patients with LMCA disease. Although, the randomised trials suggested that PCI was a valid alternative to CABG, we found a need for further documentation with a large randomised trial.

Added value of this study

Our findings of similar mortality but higher rates of myocardial infarction and repeat revascularisation in LMCA patients undergoing PCI compared to CABG are consistent with the previous randomised studies1–3,16. With 1201 patients included in our study the increased rates of major adverse cardiac or cerebrovascular events (MACCE) associated with PCI beyond one year became significant, and confirms a recent metaanalysis also showing increased MACCE after PCI at five years. 17 Contrasting to the SYNTAX trial16, our study suggested that patients with LMCA disease had inferior outcome after PCI compared to CABG irrespective of coronary lesion complexity evaluated with the SYNTAX score.14

Implications of all the available evidence

Despite similar mortality, the 5-year risk of MACCE is higher after PCI compared to CABG for treatment of unprotected LMCA disease.

References


### Table 1. Baseline characteristics by treatment group

<table>
<thead>
<tr>
<th></th>
<th>PCI</th>
<th>CABG</th>
<th>P–value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>66·2±9·9</td>
<td>66·2±9·4</td>
<td>0·91</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>116 (19·6%)</td>
<td>140 (23·7%)</td>
<td>0·09</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27·9±4·5</td>
<td>28·1±4·4</td>
<td>0·53</td>
</tr>
<tr>
<td>Diabetes type I or type II</td>
<td>86 (14·6%)</td>
<td>90 (15·2%)</td>
<td>0·94</td>
</tr>
<tr>
<td>Family history of IHD</td>
<td>321 (57·9%)</td>
<td>307 (55·7%)</td>
<td>0·45</td>
</tr>
<tr>
<td>Statin treatment</td>
<td>482 (81·6%)</td>
<td>464 (78·4%)</td>
<td>0·17</td>
</tr>
<tr>
<td>Hypertension</td>
<td>386 (65·4%)</td>
<td>389 (65·7%)</td>
<td>0·91</td>
</tr>
<tr>
<td>Active smoking</td>
<td>108 (18·5%)</td>
<td>127 (21·6%)</td>
<td>0·18</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>116 (19·7%)</td>
<td>118 (20·0%)</td>
<td>0·90</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>4 (0·68%)</td>
<td>2 (0·34%)</td>
<td>0·41</td>
</tr>
<tr>
<td>Ejection fraction (% [IQR])</td>
<td>60 [55;65]</td>
<td>60 [52;64]</td>
<td>0·27</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>244 (52·8%)</td>
<td>195 (42·6%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>135 (29·6%)</td>
<td>150 (33·1%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>57 (12·5%)</td>
<td>77 (17·0%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>23 (5·0%)</td>
<td>33 (7·3%)</td>
<td>0·0120</td>
</tr>
<tr>
<td>SYNTAX score</td>
<td>22·5±7·5</td>
<td>22·4±8·0</td>
<td>0·74</td>
</tr>
</tbody>
</table>

### Indication

<table>
<thead>
<tr>
<th></th>
<th>PCI</th>
<th>CABG</th>
<th>P–value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable angina pectoris</td>
<td>466 (78·7%)</td>
<td>476 (80·5%)</td>
<td>0·61</td>
</tr>
<tr>
<td>Unstable angina pectoris</td>
<td>106 (17·9%)</td>
<td>100 (16·9%)</td>
<td>0·65</td>
</tr>
<tr>
<td>Lesions to be treated (n [IQR])</td>
<td>2[1:3]</td>
<td>2[2:3]</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Distal LMCA lesion</td>
<td>477 (80·8%)</td>
<td>482 (81·4%)</td>
<td>0·77</td>
</tr>
</tbody>
</table>

BMI: body mass index; IHD: ischemic heart disease; NYHA class: New York Heart Association class; LMCA: left main coronary artery
<table>
<thead>
<tr>
<th>Event</th>
<th>PCI</th>
<th>CABG</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>36 (11.5%)</td>
<td>33 (9.5%)</td>
<td>1.04</td>
<td>0.65–1.67</td>
<td>0.86</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>14 (3.1%)</td>
<td>15 (3.1%)</td>
<td>0.86</td>
<td>0.41–1.81</td>
<td>0.69</td>
</tr>
<tr>
<td>Vascular death</td>
<td>2 (0.7%)</td>
<td>1 (0.2%)</td>
<td>1.96</td>
<td>0.18–21.66</td>
<td>0.55</td>
</tr>
<tr>
<td>Non-procedural MI</td>
<td>29 (6.9%)</td>
<td>10 (1.9%)</td>
<td>2.88</td>
<td>1.40–5.90</td>
<td>0.0040</td>
</tr>
<tr>
<td>Revascularisation (total)</td>
<td>71 (16.2%)</td>
<td>47 (10.4%)</td>
<td>1.50</td>
<td>1.04–2.17</td>
<td>0.0232</td>
</tr>
<tr>
<td>Revascularisation with PCI</td>
<td>56 (12.9%)</td>
<td>45 (10.1%)</td>
<td>1.23</td>
<td>0.83–1.83</td>
<td>0.29</td>
</tr>
<tr>
<td>Revascularisation with CABG</td>
<td>19 (4.4%)</td>
<td>2 (0.3%)</td>
<td>9.41</td>
<td>2.20–40.38</td>
<td>0.0031</td>
</tr>
<tr>
<td>Target lesion revascularisation</td>
<td>50 (11.7%)</td>
<td>36 (8.0%)</td>
<td>1.38</td>
<td>0.90–2.12</td>
<td>0.14</td>
</tr>
<tr>
<td>Target LMCA revascularisation</td>
<td>41 (10.0%)</td>
<td>33 (7.5%)</td>
<td>1.23</td>
<td>0.78–1.94</td>
<td>0.37</td>
</tr>
<tr>
<td>De-novo lesion revascularisation*</td>
<td>24 (6.2%)</td>
<td>11 (2.6%)</td>
<td>2.34</td>
<td>1.16–4.74</td>
<td>0.0180</td>
</tr>
<tr>
<td>Symptomatic graft occlusion or definite stent thrombosis</td>
<td>9 (2.6%)</td>
<td>15 (4.1%)</td>
<td>0.59</td>
<td>0.26–1.36</td>
<td>0.22</td>
</tr>
<tr>
<td>Possible stent thrombosis</td>
<td>4 (1.3%)</td>
<td>0 (0.0%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Probable stent thrombosis</td>
<td>2 (0.3%)</td>
<td>0 (0.0%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Stroke</td>
<td>16 (4.9%)</td>
<td>7 (1.7%)</td>
<td>2.25</td>
<td>0.92–5.48</td>
<td>0.07</td>
</tr>
</tbody>
</table>

* New lesion in non-stented segment or non-grafted vessel.
<table>
<thead>
<tr>
<th></th>
<th>PCI</th>
<th>CABG</th>
<th>Risk difference</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2 (0.3%)</td>
<td>7 (1.2%)</td>
<td>−0.8%</td>
<td>−1.8−0.1</td>
<td>0.09</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>2 (0.3%)</td>
<td>7 (1.2%)</td>
<td>−0.8%</td>
<td>−1.8−0.1</td>
<td>0.09</td>
</tr>
<tr>
<td>Vascular death</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0.0%</td>
<td>−</td>
<td>1.00</td>
</tr>
<tr>
<td>Procedural MI*</td>
<td>16 (5.4%)</td>
<td>16 (6.7%)</td>
<td>−1.3%</td>
<td>−5.4−2.8</td>
<td>0.40</td>
</tr>
<tr>
<td>Non-procedure–related MI</td>
<td>3 (0.5%)</td>
<td>0 (0.0%)</td>
<td>0.5%</td>
<td>−0.06−1.1</td>
<td>0.08</td>
</tr>
<tr>
<td>Definite stent thrombosis or symptomatic graft occlusion</td>
<td>1 (0.2%)</td>
<td>2 (0.3%)</td>
<td>−0.1%</td>
<td>−0.7−0.4</td>
<td>0.56</td>
</tr>
<tr>
<td>Repeat revascularisation</td>
<td>7 (1.2%)</td>
<td>10 (1.7%)</td>
<td>−0.5%</td>
<td>−1.8−0.8</td>
<td>0.46</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 (0.0%)</td>
<td>4 (0.7%)</td>
<td>−0.7%</td>
<td>−1.3−0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>Re–operation for bleeding</td>
<td>1 (0.2%)</td>
<td>23 (3.9%)</td>
<td>−3.7%</td>
<td>−5.3−2.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>11 (2.0%)</td>
<td>150 (27.5%)</td>
<td>−25.4%</td>
<td>−293−21.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Operation for sternum infection</td>
<td>0 (0.0%)</td>
<td>3 (0.5%)</td>
<td>−0.5%</td>
<td>−1.1−0.07</td>
<td>0.08</td>
</tr>
<tr>
<td>Operation for access site complications</td>
<td>2 (0.4%)</td>
<td>4 (0.7%)</td>
<td>0.3%</td>
<td>−1.2−0.5</td>
<td>0.41</td>
</tr>
<tr>
<td>CT–verified pulmonary embolus</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
<td>0.0%</td>
<td>−0.4−0.9</td>
<td>0.99</td>
</tr>
<tr>
<td>Duration of index treatment admission</td>
<td>2[1:4]</td>
<td>9[7:13]</td>
<td>−</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

* Assessable in 45·1% of patients

Table 3. Outcomes between index procedure and 30 days of follow–up by treatment group
<table>
<thead>
<tr>
<th>Treatment Event</th>
<th>PCI</th>
<th>CABG</th>
<th>Risk difference</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACCE</td>
<td>42 (7.1%)</td>
<td>42 (7.1%)</td>
<td>0.0</td>
<td>–2.9 – 2.9</td>
<td>1.00</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>9 (1.5%)</td>
<td>17 (2.9%)</td>
<td>–1.3%</td>
<td>–3.0 – 0.3</td>
<td>0.11</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>8 (1.4%)</td>
<td>13 (2.2%)</td>
<td>–0.8%</td>
<td>–2.3 – 0.6</td>
<td>0.27</td>
</tr>
<tr>
<td>Vascular death</td>
<td>0 (0.0%)</td>
<td>1 (0.2%)</td>
<td>0.1</td>
<td>–0.1 – 0.3</td>
<td>0.32</td>
</tr>
<tr>
<td>Non-procedural MI</td>
<td>11 (1.9%)</td>
<td>8 (1.4%)</td>
<td>0.5%</td>
<td>–0.9 – 1.9</td>
<td>0.49</td>
</tr>
<tr>
<td>Revascularisation (total)</td>
<td>32 (5.4%)</td>
<td>24 (4.0%)</td>
<td>1.4%</td>
<td>–1.1 – 3.8</td>
<td>0.27</td>
</tr>
<tr>
<td>Symptomatic graft occlusion or definite stent thrombosis</td>
<td>2 (0.3%)</td>
<td>7 (1.2%)</td>
<td>–0.8%</td>
<td>–1.8 – 0.1</td>
<td>0.09</td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (0.3%)</td>
<td>6 (1.0%)</td>
<td>–0.7%</td>
<td>–1.6 – 0.3</td>
<td>0.16</td>
</tr>
</tbody>
</table>

*Table 4. One-year clinical outcome by treatment group*
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 Revascularisation Study (NOBLE)”
List of Writing Committee members

Mark Spence, M.D., Belfast Heart Centre, United Kingdom

Alastair N. J. Graham, M.D., Belfast Heart Centre, United Kingdom

Ian Menown, M.D., FRCP, Craigavon Cardiac Centre, Belfast, United Kingdom

David Hildick-Smith, M.D., Sussex Cardiac Centre, Brighton, United Kingdom

Mitchell Lindsay, M.D., Department of Cardiology, Golden Jubilee National Hospital, Clydebank, United Kingdom

Timo Mäkikallio, M.D., Department of Cardiology, Oulu University Hospital, Finland

Matti Niemelä, M.D., Ph.D., Department of Cardiology, Oulu University Hospital, Finland

Kari Kervinen, M.D., Ph.D., Department of Cardiology, Oulu University Hospital, Finland

Andrejs Erglis, Professor, M.D., Ph.D., Paul Stradins Clinical University Hospital, Riga, Latvia

Peteris Stradins, M.D., Ph.D., Paul Stradins Clinical University Hospital, Riga, Latvia

Thor Trovik, M.D., Ph.D., Department of Cardiology, University Hospital of Northern Norway, Tromsø, Norway

Petter Cappelen Endresen, M.D., Ph.D., Department of Cardiology, University Hospital of Northern Norway, Tromsø, Norway

Vytautas Abraitis, M.D., Vilnius University Hospital, Lithuania

Leif Thuesen, M.D., D.M.Sc., Department of Cardiology, Aalborg University Hospital, Denmark
List of Clinical Endpoint Committee members

Julian Strange, MBChB, FRCP, M.D., Department of Cardiology, Spire The Glen Hospital, Bristol

Anders Jepsson, professor, Department of Cardiothoracic Surgery, Sahlgrenska University Hospital, Gothenburg

Kjeld Nikus, M.D., Heart Hospital, Tampere University Hospital and University of Tampere, School of Medicine, Tampere
List of members of the Data Monitoring Safety Committee

Name: John Walsh
Address: Nottingham University Hospitals Trust
Email: john.walsh@nuh.nhs.uk
Telephone: –
Discipline: Cardiology

Name: Knut Rasmussen
Address: Head Department of Cardiology, University Hospital of Northern Norway, Tromsø
Email: knut.rasmussen@unn.no
Telephone: –
Discipline: Cardiology

Name: Dag Sørlie
Address: Head Department of Cardiology, University Hospital of Northern Norway, Tromsø
Email: dag.glen.sorlie@unn.no
Telephone: –
Discipline: Cardiology

Name: Janne Martikainen
Address: School of Pharmacy, University of Eastern Finland, Kuopio, Finland
Email: janne.martikainen@uef.fi
Telephone: –
Discipline: Pharmacy

Name: Juha Hartikainen
Address: Heart Center, Kuopio University Hospital, Kuopio, Finland
Email: juha.hartikainen@kuh.fi
Telephone: –
Discipline: Cardiology
List of Investigators and Collaborators

Listed in alphabetical order by institution.

Belfast Heart Centre, Belfast Trust, Northern Ireland (Mark Spence, Simon J. Walsh, Colm G. Hanratty, Paul W. Johnston, Colum G. Owens, Alastair N. J. Graham); Blackpool Victoria Hospital (Jonas Eichofer);
Brighton and Sussex University Hospital, Sussex Cardiac Centre (David Hildick-Smith, Uday Trivedi, Adam J de Belder, James A Cockburn); Coventry University Hospital (Peter Glennon); Craigavon Cardiac Centre, Northern Ireland (Ian Brian Alexander Menown); Danderyd Hospital, Stockholm (Rikard Linder, Jonas Persson, Nikolaos Östlund Papadogeorgos); East Tallinn Hospital (Sulev Margus); Elisabeth–Krakenhaus, Klinik für Kardiologie und Angiologie, Essen (Christoph K. Naber, Thomas Schmitz); Freeman Hospital and Institute of Cellular Medicine, Newcastle (Azfar Zaman, Amr Gamal, Javed Ahmed); Glenfield Hospital, Leicester (Anthony Gershlick); Golden Jubilee National Hospital, Clydebank (Mitchell Lindsay, Keith Oldroyd, Geoff Berg, Hany Eteiba, Margaret McEntegart); Guy's & St Thomas' Hospital, London (Martyn Thomas); Haukeland University Hospital, Bergen (Erlend Eriksen); Helsinki University Hospital, Heart and Lund Center (Markku O. Pentikäinen, Mika Laine, Antti Vento); James Cook University Hospital, Middlesbrough (Mark A. de Belder, Paul D. Williams); Karolinska University Hospital, Huddinge, Stockholm (Matthias Corbascio, Shams Younis Hassan, Giovanna Sarno); Kings College Hospital, London (Asif Qasim); Kuopio University Hospital, Heart Center (Hannu Rompannen, Juha Hartikainen, Antti Valtola, Anssi Perälä); Manchester Royal Infirmary (Doug Fraser); New Cross Hospital, Heart & Lung Centre, Wolverhampton (James Cotton); Odense University Hospital (Lisaette Okkels Jensen, Knud Erik Pedersen, Poul Erik Mortensen); Oslo University Hospital, Rikshospitalet (Anders Hervold, Knut Endresen);
Oulu University Hospital (Timo Mäkikallio, Matti Niemelä, Kari Kervinen, Vesa Anttila, Olli–Pekka Piira, Jari Laukkanen); Oxford Heart Centre (Adrian Banning, Rajesh Kharbanda, Rana Sayeed); Paul Stradins Clinical Hospital, Riga (Andrejs Erglis, Indulis Kumsars, Peteris Stradins, Inga Narbute, Janis Volkolakovs);
Satakunta Central Hospital, Pori (Antti Ylitalo, Pasi Karjalainen); Spire Southampton Hospital (Nick Curzen); Södersjukhuset, Stockholm (Nikolai Fedchenko); Tampere University Hospital (Markku Eskola, Olli Kajander, Juha Nissinen, Mika Kohonen); Trondheim University Hospital (Rune Wiseth, Dag Ole Nordhaug); Universitetsklinikum Essen (Markus Kamler); University of Northern Norway, Tromsø (Thor Trovik, Petter Cappelen Endresen, Terje Steigen, Truls Myrmel); Uppsala University Hospital (Stefan James); Vilnius University Hospital (Gintaras Kalinauskas, Giedrius Davidavicius, Arvydas Baranauskas);
Örebro University Hospital (Thomas Kellerth, Ole Fröbert, Örjan Friberg); Aalborg University Hospital (Jan Ravkilde, Leif Thuesen, Jan Jesper Andreasen, Jens Aarøe); Aarhus University Hospital, Skejby, Aarhus (Evald H. Christiansen, Niels R. Holm, Per H. Nielsen, Jens Flensted Lassen, Michael Maeng, Ivy Susanne Modrau, Hans Henrik Kimose, Henrik Toft Sørensen).
Data acquisition and monitoring

Data were collected using a secure, web-based trial management system, Trialpartner, Institute of Clinical Medicine, Aarhus University Denmark. Remote monitoring was performed by Qmed Consulting ApS, Denmark, and by professional staff at Aarhus University Hospital, Denmark according to the monitoring plan specified before start of the monitoring process. Site visits were not performed systematically. Deidentified source material was transferred to the study organization at Aarhus University Hospital, Denmark by participating sites. Source material for the clinical event committee was monitored. In case the clinical endpoint committee requested additional documentation, this was requested from the sites, and the adjudication postponed to a subsequent meeting.
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. All procedure–related deaths, including those related to concomitant treatment, were classified as cardiac death. The endpoint was included post hoc. (Modified from Cutlip et al. Circulation. 2007;115:2344–2351) The information on cause of death was obtained from hospital patient files, from general practitioners, or from families if no other source was available.

Vascular death
Death caused by non–coronary vascular causes, including cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular diseases. The endpoint was included post hoc. (Modified from Cutlip et al. Circulation. 2007;115:2344–2351)

Non–procedure–related myocardial infarction
A rise in biochemical markers exceeding the decision limit for 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), and (3) development of a pathologic Q–wave with no relation to a PCI procedure.

Repeat revascularisation
Any new PCI or CABG operation performed during follow–up. If an index revascularisation was attempted or successful, any subsequent revascularisation was counted as repeat revascularisation. Attempted PCI was defined as an advancement of a wire in the coronary tree at least. Attempted CABG was defined as at least initiation of an index operation.

Procedure–related biomarker release
The diagnosis of a procedure–related biomarker increase required a rise in total creatine kinase (CK) and/or Troponin–T/I. Due to the great heterogeneity of biomarkers and various assays used during the study in participating centres, this comparison was omitted from the final analysis.
Diagnosis of procedural MI for both PCI and CABG patients was based on CK–MB elevations when available. Patients needed to have stable angina pectoris as the clinical indication OR a normal baseline CK–MB, TnI, TnT, or highly sensitive TnT, to be assessable for procedural MI. Diagnosis required a CK–MB value above 10 x URL or ULN to establish the diagnosis. The diagnosis could also be placed by the combination of a CK–MB value 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 left bundle branch block, 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. Peri-procedural MI due to repeat revascularization during follow-up were assessed applying the 3rd Universal definition as CK-MB was not available in all event patients. A procedural MI according to this definition was counted as a non-index procedural myocardial infarction.

**Target lesion revascularisation**
Repeat revascularisation by PCI of any target segment treated during the index procedure. A target lesion segment was defined as a stented or balloon treated segment and its 5 mm margins.

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

**Definite stent thrombosis**
Stent thromboses were categorized as acute, subacute, late and very late and as definite, probable and possible according to ARC criteria. (Cutlip et al. Circulation 2007;115:2344–51)

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

**Stroke**
Ischemic or haemorrhagic cerebrovascular event verified by brain computed tomography (CT) or magnetic resonance imaging (MRI).

Pulmonary embolus

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

NYHA class and CCS class Patients were queried yearly by telephone regarding symptoms of angina pectoris and heart failure; if they reported angina, they were categorized as Canadian Cardiovascular Society (CCS) classes 1 through 4. If they reported heart failure symptoms, they were categorized as New York Heart Association (NYHA) functional classes 1 through 4.

Recommendations for angiography and re-revascularisation

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 tachyarrhythmia (ventricular fibrillation or ventricular tachycardia). Revascularisation 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 limited to the shaft without involvement of the LMCA ostium and the LMCA bifurcation.

Sample size calculation and primary endpoint reporting

The sample size calculation was based on the combined primary endpoint of death, stroke, non-index treatment related MI and new revascularisation (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 being exponential

• zero dropout

• randomisation into 2 equally sized groups

• $\alpha = 0.05$ (one-sided)

• $1 - \beta$ (power) = 80%

The non-inferiority limit was based on a 12-month MACCE rate of 12% in the CABG group and 16% in the PCI group (the SYNTAX study). With exponential event curves ($\text{CABG}(t) = \exp(-\lambda t)$), this corresponded to a hazard ratio of 1.36 for PCI versus CABG and, with $t$ in months, $\lambda = 0.0107$ in the CABG group. In line with the SYNTAX study, the present study used a hazard ratio of 1.35 for PCI versus CABG, as the limit for non-inferiority, and $\lambda = 0.011$ to describe MACCE in the CABG group. These figures corresponded to 24-month MACCE rates of 30% and 23% in the PCI and CABG groups, respectively. The above preconditions and assumptions resulted in the number of patients needed in each randomisation group equalling 593 (and a total number of events – in both groups – equalling 275). Consequently, 1186 patients needed to be randomised. It was decided to include 600 patients in each group to account for possible dropouts before follow-up and for estimation errors.

Protocol change of January 22, 2015

Due to lower than expected endpoint rates, the total number of events needed to assess inferiority would not be reached within a fixed two-year follow-up period. Determining if the primary endpoint of non-inferiority by PCI was met would likely be inconclusive. The response was carefully considered by investigators and statisticians. To accommodate, the total follow-up time of up to five years for each patient was included in the primary endpoint calculation. The time point for assessment was defined as when reaching a total of 275 primary endpoint events corresponding to a median 3.7 years (at the time).

Change in primary outcome reporting

September 2015. Due to changes in forecasting it was estimated that 275 primary endpoint events would not be reached within the full 5-year follow-up period. Statistical support was consulted and at the investigator meeting at TCT in San Francisco on October 12, 2015, it was decided to report the primary outcome based on a median 3-year follow-up (effective follow-up time was median 3.1 years) commencing collection of events for the primary endpoint until May 1st, 2016. Options regarding the primary endpoint were the following: (1) to return to the full two-year endpoint, accepting that the study would be vastly underpowered for assessing whether non-inferiority was met and that the study would likely be inconclusive; (2) to await
the full 5 years of follow-up, available in 2020, still not reaching the prespecified number of events; or (3) reporting results both after a median of three years of follow-up, based on roughly 75% of the total number of expected events occurring within the full five-year follow-up, and then again after reaching the full five-year follow-up to confirm the estimates. The third option allowed to determine with confidence whether non-inferiority was met after a median of 3 years of follow-up, based on the predefined hazard ratio, without withholding these important results for another almost 4 further years.

**Data safety monitoring committee (DSMC)**

The safety of the study was monitored by an independent Data and Safety Monitoring Committee (DSMC) headed by Prof. Juha Hartikainen, Kuopio University Hospital, Finland. The DSMC received information on rates of all–cause mortality, non–index procedure–related myocardial infarction, definite stent thrombosis, target lesion revascularisation and stroke. The DSMC made independent decisions on continuation or stopping the study. Termination of the study was to be recommended if at any time a significant difference (p-value of < 0·003 by χ²–test) was found between rates of all–cause mortality, non–index procedure–related myocardial infarction definite stent thrombosis, target lesion revascularisation or stroke.
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMCA stenting involving ostium and not bifurcation</td>
<td>59 (10.2%)</td>
</tr>
<tr>
<td>Shaft LMCA stenting only</td>
<td>11 (1.8%)</td>
</tr>
<tr>
<td>LMCA bifurcation lesion stenting</td>
<td>508 (87.7%)</td>
</tr>
<tr>
<td>Angulation less than 70 degrees*</td>
<td>110 (22.3%)</td>
</tr>
<tr>
<td>Visible calcification*</td>
<td>213 (42.5%)</td>
</tr>
<tr>
<td>Severe tortuosity*</td>
<td>55 (10.8%)</td>
</tr>
<tr>
<td>Stenting of LMCA–LAD only*</td>
<td>300 (59.4%)</td>
</tr>
<tr>
<td>Stenting of LMCA–Cx only*</td>
<td>21 (4.2%)</td>
</tr>
<tr>
<td>Culotte*</td>
<td>119 (23.9%)</td>
</tr>
<tr>
<td>Crush*</td>
<td>20 (4.0%)</td>
</tr>
<tr>
<td>T–stenting*</td>
<td>41 (8.4%)</td>
</tr>
<tr>
<td>V–stenting*</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Other technique*</td>
<td>4 (0.8%)</td>
</tr>
<tr>
<td>Total stent length in LMCA lesion (mm)</td>
<td>24 [IQR 15:35]</td>
</tr>
<tr>
<td>Total number of stents in LMCA lesion (n)</td>
<td>1 [IQR 1:2]</td>
</tr>
<tr>
<td>IVUS pre–evaluation</td>
<td>270 (46.8%)</td>
</tr>
<tr>
<td>IVUS post–evaluation</td>
<td>430 (74.9%)</td>
</tr>
<tr>
<td>Pre–dilatation of LMCA</td>
<td>498 (86.6%)</td>
</tr>
<tr>
<td>Pre–dilatation of LAD*</td>
<td>426 (76.9%)</td>
</tr>
<tr>
<td>Pre–dilatation of Cx*</td>
<td>204 (40.8%)</td>
</tr>
<tr>
<td>Post–dilatation of LMCA</td>
<td>515 (89.7%)</td>
</tr>
<tr>
<td>Post–dilatation of LAD*</td>
<td>249 (53.4%)</td>
</tr>
<tr>
<td>Post–dilatation of Cx*</td>
<td>399 (79.8%)</td>
</tr>
<tr>
<td>Max pressure of largest balloon in LMCA</td>
<td>18 [IQR 16:20]</td>
</tr>
<tr>
<td>Max pressure of largest balloon in treated LAD</td>
<td>18 [IQR 14:20]</td>
</tr>
<tr>
<td>Max pressure of largest balloon in treated Cx</td>
<td>16 [IQR 12:18]</td>
</tr>
</tbody>
</table>
Nominal diameter of largest balloon or stent in LMCA \(4.0 \text{ [IQR 4.0:4.5]}\)

Nominal diameter of largest balloon or stent in treated LAD \(3.5 \text{ [IQR 3.5:4.0]}\)

Nominal diameter of largest balloon or stent in treated Cx \(3.0 \text{ [3.0:3.5]}\)

Kissing balloon post inflation* \(277 (54.5\%\))

Number of treated lesions

<table>
<thead>
<tr>
<th>Number</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>312</td>
<td>53.4%</td>
</tr>
<tr>
<td>2</td>
<td>191</td>
<td>32.5%</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>9.6%</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>2.4%</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Total stent length in non–LM lesions if treated (mm) \(28 \text{ [IQR 18:42]}\)

Total number of stents in non–LM lesions if treated \(1 [1:2]\)

Procedure time (min) \(62 \text{ [IQR 47:85]}\)

Fluoroscopy time (min) \(26 \text{ [IQR 11:24]}\)

Contrast volume (mL) \(200 \text{ [IQR 150:280]}\)

Complete revascularisation \(543 (94.1\%\))

LMCA treated by 1st generation drug–eluting stent \(42 (10.9\%\))

Antithrombotic treatment

Unfractionated heparin \(411 (72.6\%\))

Low molecular weight heparin \(81 (14.2\%\))

Bivalirudine \(108 (18.9\%\))

GPIIbIIa inhibitor \(110 (19.1\%\))

Aspirin \(539 (92.9\%\))

Clopidogrel/Ticlopidine/Ticagrelor \(566 (97.4\%\))
Table S1. Treatment characteristics in the PCI group
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On–pump technique</td>
<td>476 (84·4%)</td>
</tr>
<tr>
<td>Off–pump technique</td>
<td>88 (15·6%)</td>
</tr>
<tr>
<td>Arterial graft</td>
<td>532 (94·5%)</td>
</tr>
<tr>
<td>Arterial graft to LAD</td>
<td>526 (93·4%)</td>
</tr>
<tr>
<td>LIMA + RIMA grafts</td>
<td>44 (7·9%)</td>
</tr>
<tr>
<td>LIMA + venous graft</td>
<td>480 (85·7%)</td>
</tr>
<tr>
<td>Radial artery graft</td>
<td>26 (4·8%)</td>
</tr>
<tr>
<td>Venous grafts only</td>
<td>27 (5·0%)</td>
</tr>
<tr>
<td>Grafts per patient</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>23 (4·1%)</td>
</tr>
<tr>
<td>2</td>
<td>294 (52·0%)</td>
</tr>
<tr>
<td>3</td>
<td>220 (39·0%)</td>
</tr>
<tr>
<td>4</td>
<td>25 (4·4%)</td>
</tr>
<tr>
<td>5</td>
<td>3 (0·6%)</td>
</tr>
</tbody>
</table>

*Table S2. Treatment characteristics in the CABG group*