

# Effects of routine early treatment with PCSK9 inhibitors in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: a randomised, double-blind, sham-controlled trial

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## KEYWORDS

- ACS/NSTE-ACS
- multiple vessel disease
- myocardial infarction
- STEMI

## Abstract

**Background:** In patients with ST-segment elevation myocardial infarction (STEMI), early initiation of high-intensity statin therapy, regardless of low-density lipoprotein (LDL) cholesterol levels, is the standard of practice worldwide.

**Aims:** We sought to determine the effect of a similar early initiation strategy, using a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor added to the high-intensity statin, on LDL cholesterol in acute STEMI.

**Methods:** In a randomised, double-blind trial we assigned 68 patients with STEMI undergoing primary percutaneous coronary intervention (PCI) to early treatment with alirocumab 150 mg subcutaneously or to a matching sham control. The first injection was given before primary PCI regardless of the baseline LDL level, then at 2 and 4 weeks. The primary outcome was the percent reduction in direct LDL cholesterol up to 6 weeks, analysed using a linear mixed model.

**Results:** High-intensity statin use was 97% and 100% in the alirocumab and sham-control groups, respectively. At a median of 45 days, the primary outcome of LDL cholesterol decreased by 72.9% with alirocumab (2.97 mmol/L to 0.75 mmol/L) versus 48.1% with the sham control (2.87 mmol/L to 1.30 mmol/L), for a mean between-group difference of -22.3% ( $p < 0.001$ ). More patients achieved the European Society of Cardiology/European Atherosclerosis Society dyslipidaemia guideline target of LDL  $\leq 1.4$  mmol/L in the alirocumab group (92.1% vs 56.7%;  $p < 0.001$ ). Within the first 24 hours, LDL declined slightly more rapidly in the alirocumab group than in the sham-control group ( $-0.01$  mmol/L/hour;  $p = 0.03$ ) with similar between-group mean values.

**Conclusions:** In this randomised trial of routine early initiation of PCSK9 inhibitors in patients undergoing primary PCI for STEMI, alirocumab reduced LDL cholesterol by 22% compared with sham control on a background of high-intensity statin therapy. A large trial is needed to determine if this simplified approach followed by long-term therapy improves cardiovascular outcomes in patients with acute STEMI. (ClinicalTrials.gov: NCT03718286)

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## **Supplementary data**

### **Supplementary Appendix 1. Study Committees.**

#### **Steering Committee:**

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#### **Data Safety Monitoring Committee:**

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Todd Anderson, University of Calgary, Calgary, AB, Canada

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## Supplementary Appendix 2. Methods: pre-analytical and analytical process.

Specimens were collected, transported to the central lab (CRLB-GMEL), and processed within 2 hours of collection. After processing, samples were stored in liquid nitrogen vapor (-165°C) until analysis.

Prior to analysis, specimens underwent controlled thaw and vortexing. Samples were analyzed within 1 hour of thaw, or placed in the refrigerator.

**Supplementary Table 1. Analytical methods.**

Analyte	Manufacturer	Instrument	Method
Direct LDL	Beckman Coulter	Unicel DxC 600	Automated colorimetric timed-endpoint
Cholesterol	Beckman Coulter	Unicel DxC 600	Automated colorimetric timed-endpoint
HDL	Beckman Coulter	Unicel DxC 600	Automated colorimetric timed-endpoint
Trig	Beckman Coulter	Unicel DxC 600	Automated colorimetric timed-endpoint (glycerophosphate oxidase)
ApoB	Beckman Coulter	Unicel DxC 600	Automated turbidimetric (antibody/antigen complex)
Lp(a)	Roche/Randox	Cobas 6000	Automated immunoturbidimetric
CRP	Beckman Coulter	Unicel DxC 600	Automated turbidimetric (antibody/antigen complex)
CKMB	Roche	Cobas 8000	Automated ECLIA (electrochemiluminescence immunoassay)

### Direct LDL

The method depends on a unique detergent which solubilizes only the non-LDL lipoprotein particles and releases cholesterol to react with cholesterol esterase and cholesterol oxidase to produce a non-colour forming reaction. A second detergent solubilizes the remaining LDL particles, and a chromogenic coupler allows for colour formation.

LDLD reagent is used to measure the cholesterol concentration by a timed-endpoint method. The Beckman Coulter Synchron System(s) automatically proportions the appropriate LDL cholesterol sample and reagent volumes into a cuvette. The ratio used is one part sample to 93 parts reagent. The System monitors the change in absorbance at 560 nanometers. This change in absorbance is directly proportional to the concentration of LDL cholesterol in the samples and is used by the System to calculate the express the LDL cholesterol concentration.

**Supplementary Table 2. Baseline characteristics (included vs excluded).**

	<b>Included</b>	<b>Excluded</b>	
	<b>Mean (SD)</b>	<b>Mean (SD)</b>	<b>p-value</b>
	N=68	N=29	
Age (yrs)	62.37 (10.74)	65.48 (14.14)	0.24
BMI	28.98 (5.60)	28.29 (5.42)	0.59
Systolic blood pressure (mm/Hg)	144.1 (23.79)	148.9 (23.47)	0.36
Diastolic blood pressure (mm/Hg)	89.22 (15.80)	87.31 (16.21)	0.59
Heart rate (bpm)	88.84 (23.89)	88.17 (29.92)	0.91
Male	55 (80.88)	20 (68.97)	0.29
White	61 (89.71)	26 (89.66)	1.00
Current smoker	23 (33.82)	14 (48.28)	0.18
Medical history			
Previous MI	6 (8.82)	4 (13.79)	0.48
Previous stroke	1 (1.47)	0 (0.00)	1.00
Family history of early onset coronary artery disease	7 (10.29)	3 (10.34)	0.99
Atrial fibrillation/flutter	2 (2.94)	0 (0.00)	0.35
History of heart failure	0 (0.00)	0 (0.00)	---
Peripheral arterial disease	1 (1.47)	1 (3.45)	0.53
Hypertension	30 (44.12)	13 (44.83)	0.95
Dyslipidemia	25 (36.76)	9 (31.03)	0.59
Diabetes	6 (8.82)	4 (13.79)	0.46
Chronic renal insufficiency	0 (0.00)	0 (0.00)	---
Other relevant ongoing medical condition	10 (14.71)	5 (17.24)	0.75
Time from symptom onset to primary PCI	3.65 (2.25)	3.28 (2.07)	0.46
Prior statin use	16 (23.53)	1 (3.45)	0.02

**Supplementary Table 3. Baseline measurements (included vs excluded).**

	<b>Included</b>	<b>Excluded</b>	<b>p-value</b>
N	68	29	.
LDL-cholesterol (mmol/L), mean(SD)	2.92 ( 1.01)	2.89 ( 1.10)	0.88
ApoB (g/L), mean(SD)	0.86 ( 0.30)	0.85 ( 0.31)	0.91
Non HDL-cholesterol (mmol/L), mean(SD)	3.58 ( 1.22)	3.46 ( 1.31)	0.67
Total cholesterol (mmol/L), mean(SD)	4.63 ( 1.21)	4.58 ( 1.35)	0.87
Triglycerides (mmol/L), median(IQR)	1.09 (0.63, 1.62)	0.92 (0.60, 1.36)	0.29
HDL-cholesterol (mmol/L), mean(SD)	1.04 ( 0.28)	1.12 ( 0.28)	0.25
Lp (a) (mg/L), median(IQR)	73 (34, 427)	158 (47, 447)	0.41

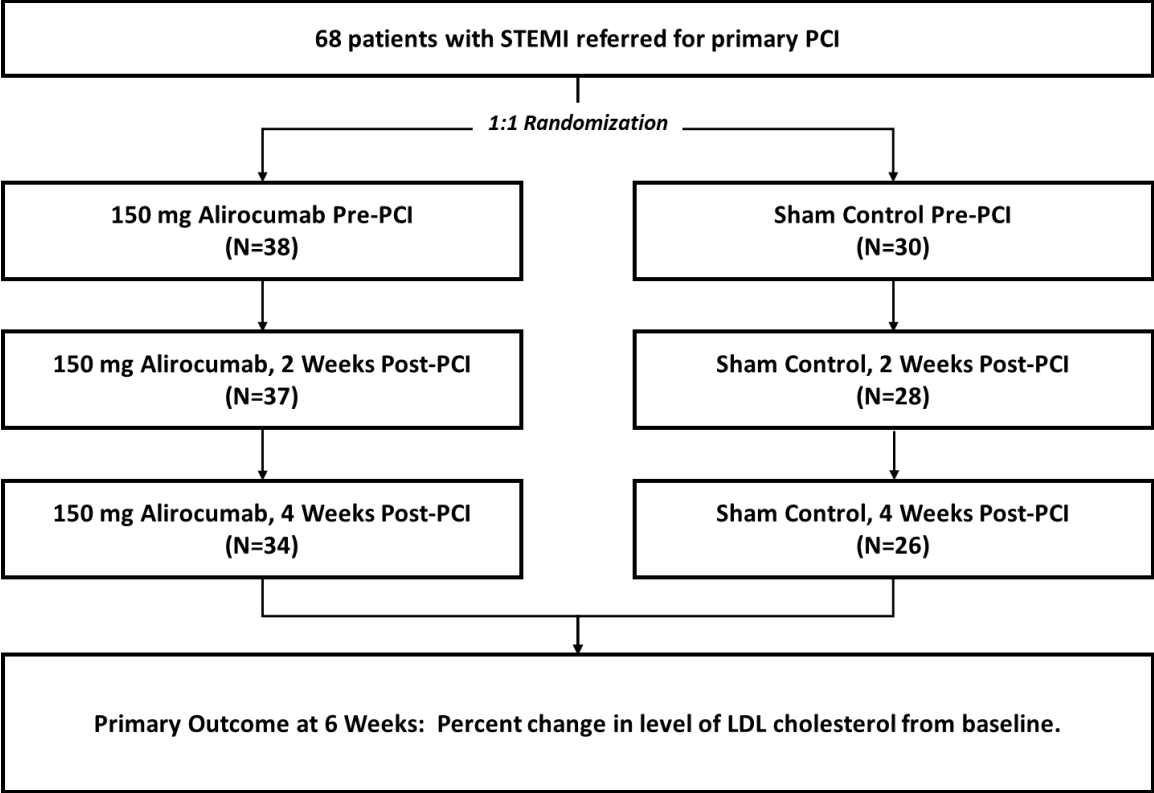
**Supplementary Table 4. LDL- and ApoB-adjusted analyses with gender.**

	Alirocumab N=38			Sham Control N=30			Between Group Difference (95% CI)	P
	Baseline	Follow-up	Percent Change	Baseline	Follow-up	Percent Change		
LDL-cholesterol (mean [SD], mmol/L)	2.97 ( 1.09)	0.75 (0.46)	-72.9% (17.5)	2.87(0.90)	1.30 (0.45)	-48.1% (29.5)	-23.7% (-32.7, -14.7)	<0.001
ApoB (mean [SD], g/L)	0.88 ( 0.33)	0.40 ( 0.11)	-50.6(17.7)	0.83 ( 0.25)	0.49 ( 0.13)	-36.3 (24.4)	-12.2 ( -18.7, -5.7)*	<0.001

\*68.4% of patients in the alirocumab group versus 26.7% in the sham control group had ApoB levels  $\leq$  the assay lower detection limit of 0.35 g/L (P=0.001). All of these patients were assigned a value of 0.35 g/L.

**Supplementary Table 5. Adverse events.**

<b>Event</b>	<b>Treatment Allocation</b>	<b>Summary</b>
Death	Sham Control	Death reported 11 days post 1st injection. Unknown cause.
Heart failure	Alirocumab	Heart failure reported 2 days post 1st injection.
Heart failure	Alirocumab	Heart failure reported 2 hours post 1st injection.
Heart failure	Alirocumab	Heart failure reported 1 hour post 1st injection.
Heart failure	Alirocumab	Heart failure reported 2 days post 1st injection.
Minor bleeding	Sham Control	Minor bleeding reported 48 days post 3rd injection.



Supplementary Figure 1. Trial flow diagram.