Effects of Routine Early Treatment with PCSK-9 Inhibitor in Patients Undergoing Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction: A randomized, double-blind, sham-controlled trial

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Disclosure Statement

EPIC STEMI was an investigator-initiated study that was funded by the PHRI and an unrestricted research grant from Sanofi.

Faculty disclosure information can be found on the app

Background

- In patients with STEMI, early initiation of high intensity statin therapy, regardless of baseline LDL level is standard practice worldwide.
- The greater the reduction in LDL with statins, the lower the risk, with no apparent lower limit beyond which a benefit is not observed. Yet, a significant proportion of STEMI patients never achieve optimal LDL levels with statins
- PCSK9 inhibitors further reduce LDL and events but have been not studied when given acutely nor as routine treatment
- Whether a simplified regimen of initiating PCSK9 inhibitor *routinely* in the acute setting of STEMI on top of high intensity statins would add additional benefit by further reducing LDL-cholesterol levels in a much wider population of patients is unknown.
- On a population level, such an approach would be expected to substantially reduce the number of major cardiovascular events in this high-risk population.

Objectives

EPIC-STEMI was designed to evaluate the routine, early administration of PCSK9 inhibitor, regardless of baseline LDL levels or prior statin use, in order to determine:

1. The degree of LDL reduction that might be expected with this approach
2. The time course of LDL lowering during the acute period after STEMI
3. The overall feasibility of this approach.

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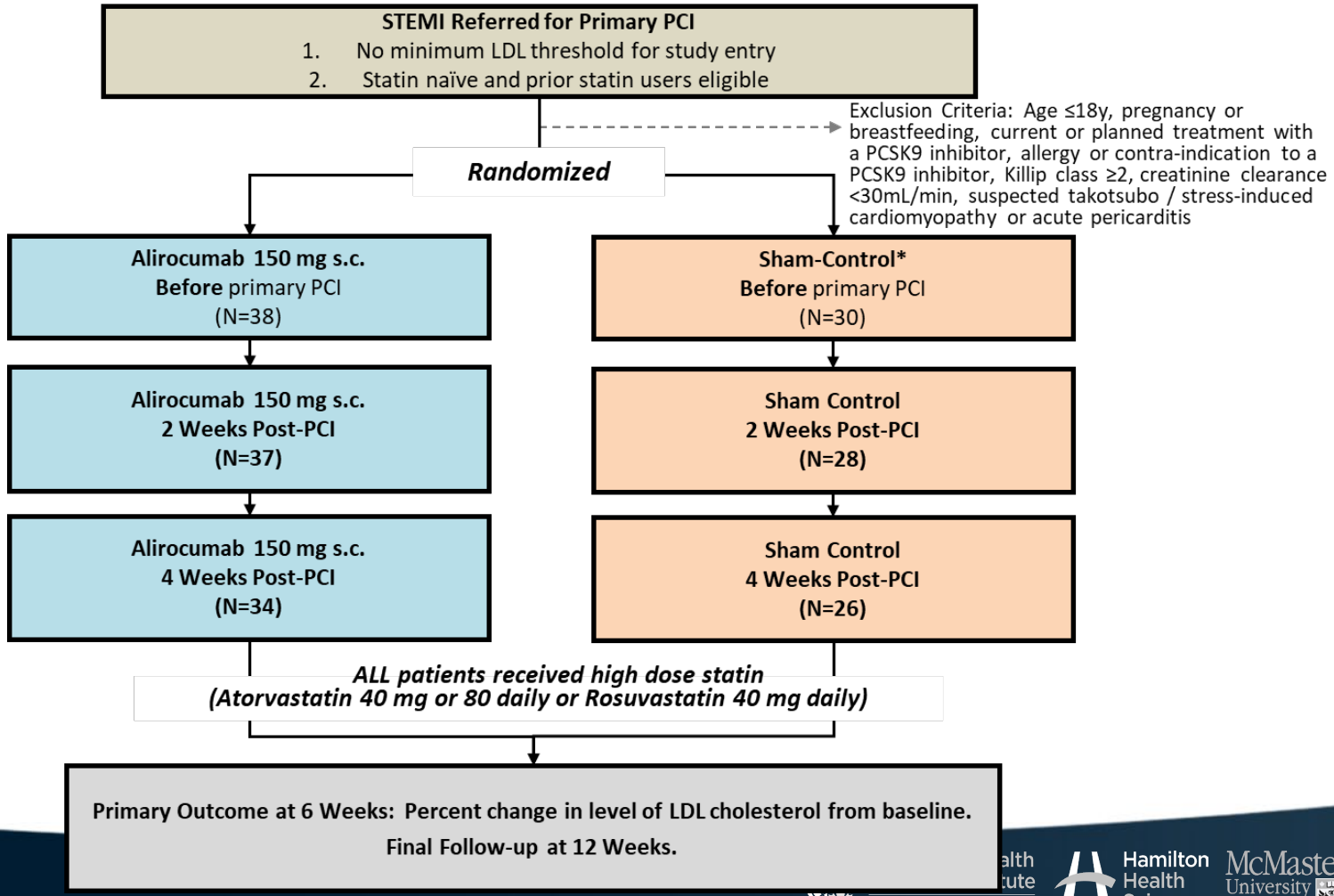
Design Flow



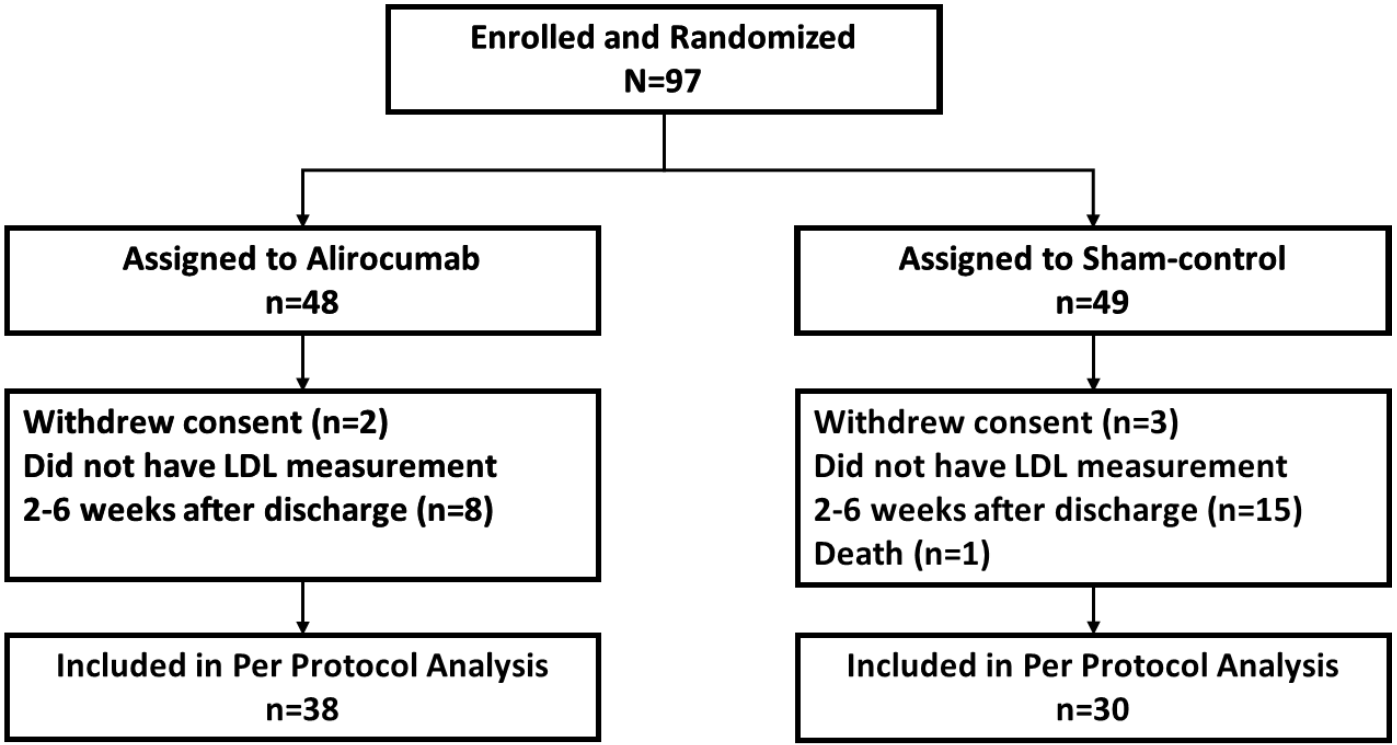
Methods: Analysis

- **Study Power:** 58 patients gave 95% power to detect a mean between-group LDL–C difference of 25%* from baseline to week 6, 2-sided alpha=0.05, SD=25%, 5% non-compliance/LTFU. 100 patients ultimately planned to increase feasibility/safety data.

**A slightly more modest reduction than in prior trials was postulated given (1) no LDL threshold required at entry and (2) statin naïve patients were eligible*

- **Recruitment Period:** May 9, 2019 – April 7, 2021
- **Population:** Modified ITT: at least 1 LDL measurement 2-6 wks + at least 1 study drug administered 2 weeks prior
- **Analysis:** Mixed model with repeated measures. For biomarker outcomes collected only at 6-weeks: linear regression. Non-normally distributed outcomes summarized with median, IQR and compared with Wilcoxon rank-sum test.

CONSORT Diagram



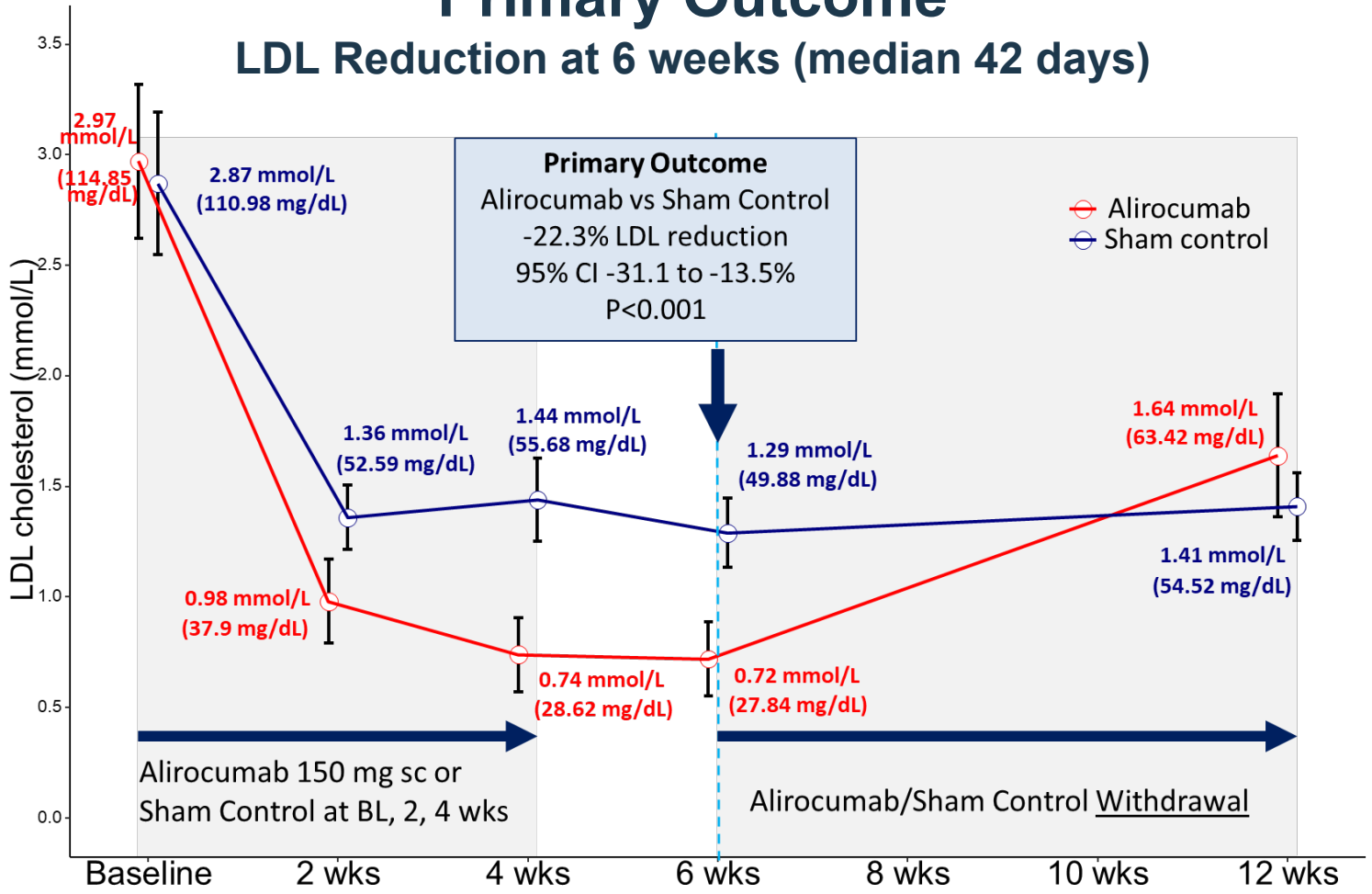
Baseline Characteristics

Median follow-up 45 days

	Alirocumab N=38	Sham-Control N=30
Age (year)	61.37 (11.04)	63.63 (10.38)
Sex (male) - no.(%)	27 (71.05)	28 (93.33)
Medical History		
Diabetes - no.(%)	5 (13.16)	1 (3.33)
Prior myocardial infarction - no.(%)	3 (7.89)	3 (10.00)
Current smoker - no.(%)	16 (42.11)	7 (23.33)
Hypertension - no.(%)	17 (44.74)	13 (43.33)
Dyslipidemia - no.(%)	13 (34.21)	12 (40.00)
Prior stroke - no.(%)	1 (2.63)	0 (0.00)
Time from symptom onset to primary PCI (hours)	3.40 (2.23)	3.96 (2.26)
Statin use within 7 days of randomization no.(%)	8 (21.05)	8 (26.67)
Statin use after randomization		
Atorvastatin 40-80 mg or Rosuvastatin 40 mg daily	37 (97.37)	30 (100)
Atorvastatin 80 mg or Rosuvastatin 40 mg daily	37(97.37)	27(90.00)
Ezetimibe	2 (5.26)	1 (3.33)

Primary Outcome

LDL Reduction at 6 weeks (median 42 days)



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Primary and Secondary Outcomes

	Alirocumab N=38			Sham-control N=30			Difference (95% CI)	P
	Baseline	Follow-up	Percent Change	Baseline	Follow-up	Percent Change		
LDL-cholesterol mean (SD) **mmol/L** mg/dL	**2.97 (1.09)** 114.85 (42.15)	**0.75 (0.46)** 29 (17.79)	**-72.9% (17.5)**	**2.87 (0.90)** 110.98 (34.8)	**1.30 (0.45)** 50.27 (17.4)	**-48.1% (29.5)**	**-22.3% (-31.1, -13.5)**	**<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)**	**-11.2% (-17.5, -4.8)***	**<0.001**
Non HDL-cholesterol mean(SD) **mmol/L** mg/dL	**3.68 (1.37)** 142.3 (57.98)	**1.13 (0.62)** 43.7 (23.98)	**-67.3% (18.8)**	**3.46 (1.01)** 133.8 (39.06)	**1.79 (0.50)** 69.22 (19.33)	**-48.2% (20.0)**	**-19.07% (-29.42, -8.71)**	**0.001**
Total cholesterol mean (SD) **mmol/L** mg/dL	**4.73 (1.35)** 182.91 (52.2)	**2.22 (0.65)** 85.85 (25.14)	**-50.9% (18.0)**	**4.51 (1.01)** 174.4 (39.06)	**2.84 (0.65)** 109.82 (25.14)	**-38.0% (18.4)**	**-12.98% (-22.70, -3.26)**	**0.010**
Triglycerides median (IQR) **mmol/L** mg/dL	**1.20 (0.68, 1.89)** 106.29 (60.23, 167.4)	**1.01 (0.82, 1.40)** 89.46 (72.63, 124)	**-8.9% (-41.1, 50.6)**	**0.85 (0.55, 1.32)** 75.29 (48.72, 116.92)	**1.19 (0.88, 1.62)** 105.4 (77.95, 143.49)	**25.9% (-8.9, 61.0)**	**-**	**0.044**
HDL-cholesterol median (IQR) **mmol/L** mg/dL	**0.97 (0.82, 1.28)** 37.51 (31.71, 49.5)	**1.09 (0.92, 1.23)** 42.15 (35.58, 47.56)	**5.8% (-12.0, 21.1)**	**1.06 (0.83, 1.26)** 40.99 (32.1, 48.72)	**0.98 (0.86, 1.23)** 37.9 (33.26, 47.56)	**-1.7% (-15.6, 8.3)**	**-**	**0.29**
Lp (a) median (IQR) **mg/L**	**68 (34, 431)**	**87 (34, 489)**	**5.3% (0, 40.2)**	**101 (50, 414)**	**171 (43, 482)**	**34.8% (14.7, 68.6)**	**-**	**0.024**

*68.4% vs 26.7% had Apo B levels ≤ the assay lower detection limit of 0.35 mmol/L (P=0.001)

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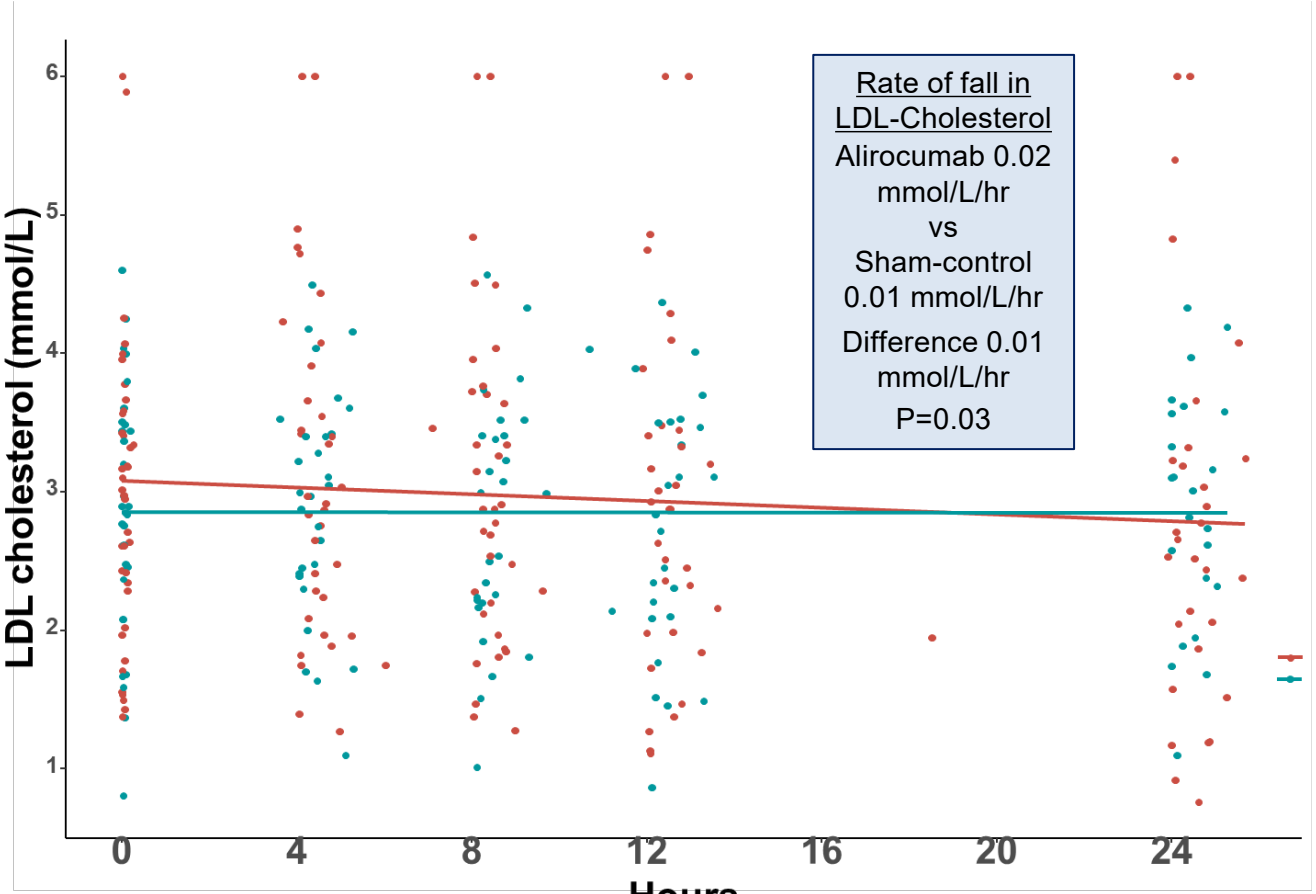
Acute LDL Reduction (First 24 h)



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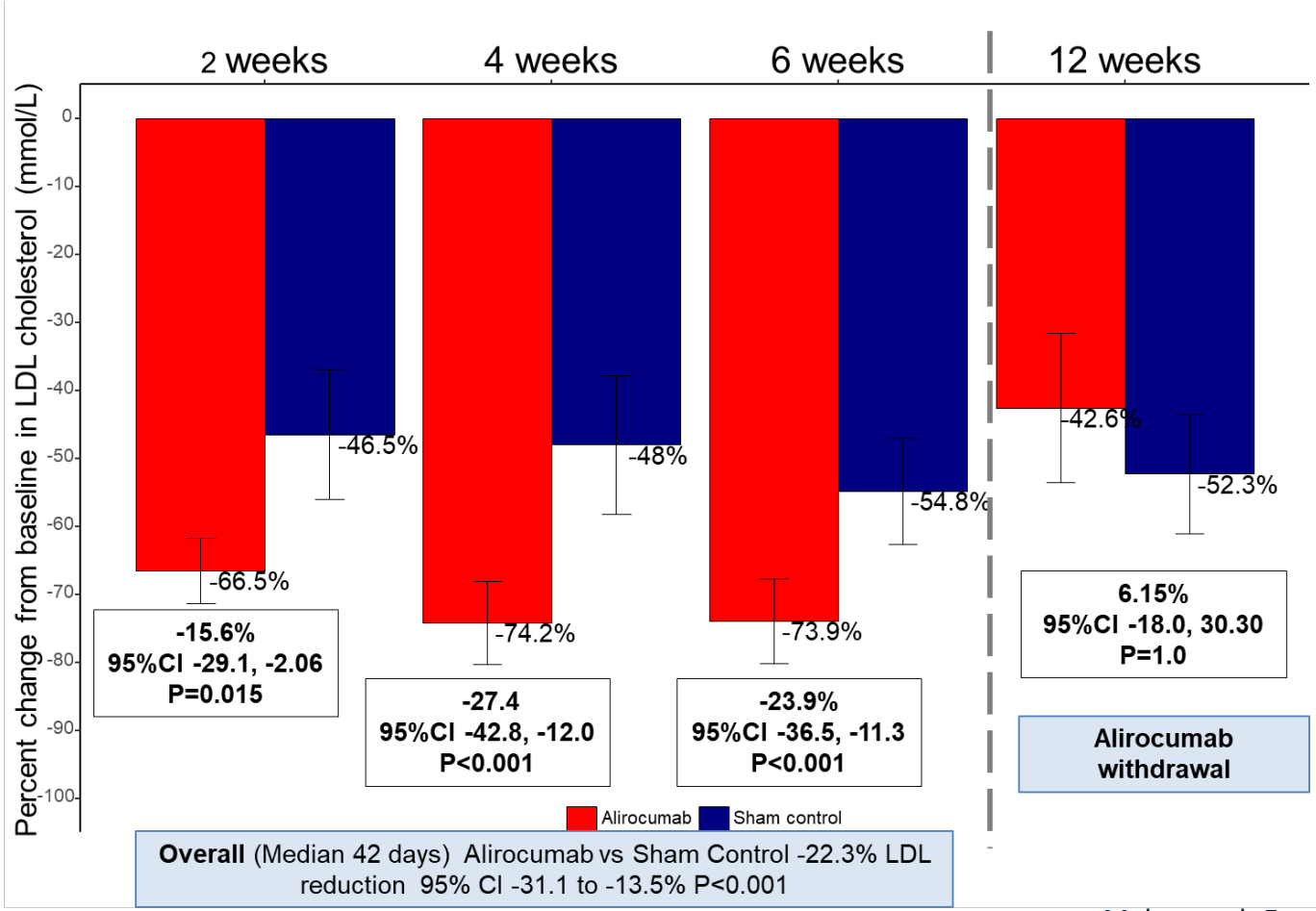
Infarct Size, NT pro BNP and CRP

	Alirocumab N=38			Sham-control N=30			Between Group Difference (95% CI)	P
	Baseline	Follow-up	Percent Change	Baseline	Follow-up	Percent Change		
NT proBNP (mean [SD, pmol/L)	-	83.33 (99.43)	-	-	75.02 (79.47)	-	8.31 pmol/L (-40.50, 57.13)	0.71
CRP (median [IQR] mg/L)	2.70 (1.14, 5.53)	1.84 (0.69, 5.97)	-34.5% (-67.7, 17.86)	1.86 (0.43, 4.88)	0.99 (0.56, 2.54)	-33.3% (-57.9, 30.0)	1.02% (0.57, 1.60)	0.93
CKMB Area Under the Curve (mean [SD], units)	-	4436 (3512)	-	-	4416 (3079)	-	-180 units (-1803, 1443)	0.67

Timing of LDL reduction



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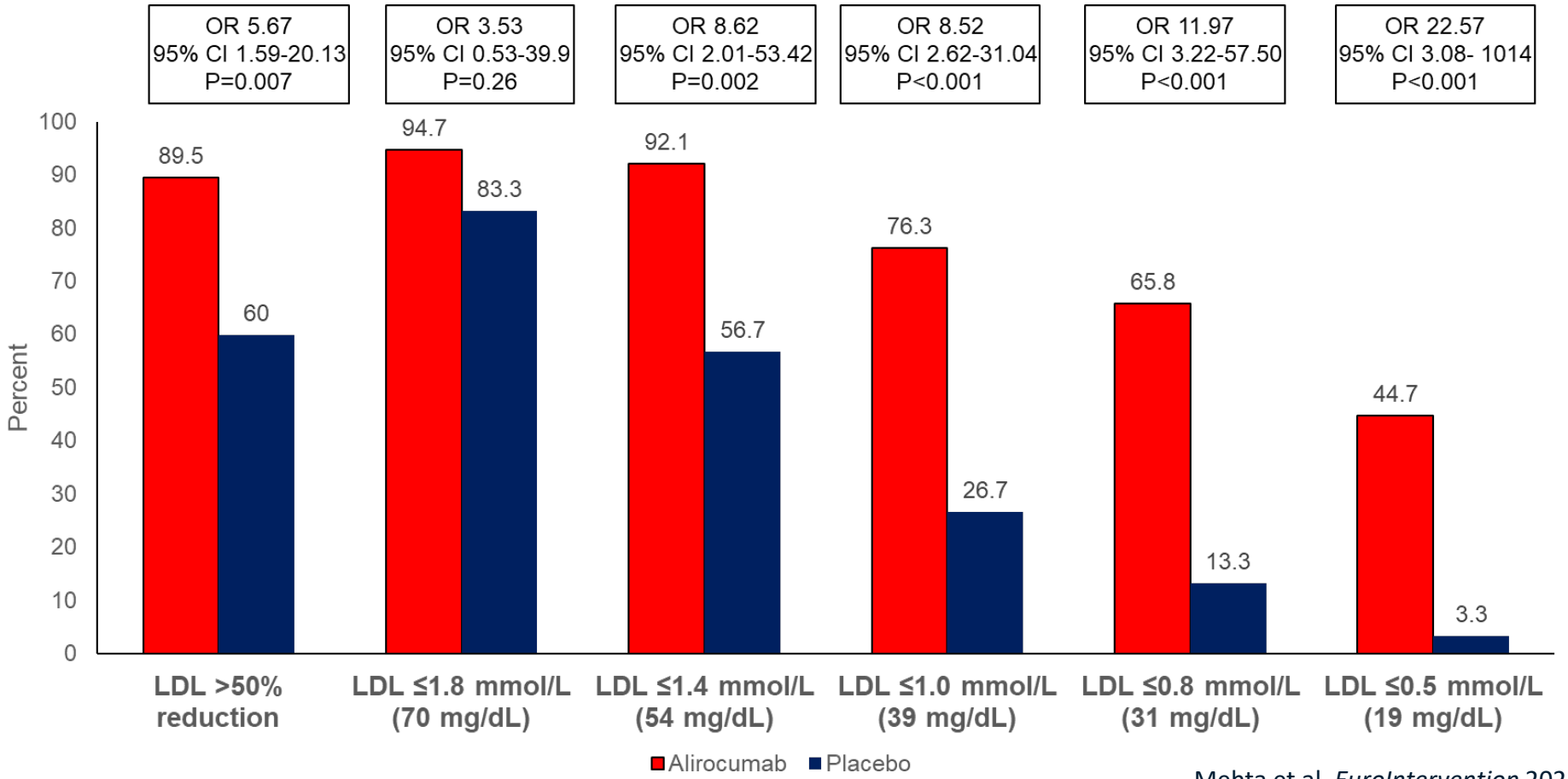
LDL Targets



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Clinical Events

Event	Alirocumab	Sham Control
Death	0	1
MI	0	0
Stroke	0	0
Heart Failure	4	0
Allergic Reaction	0	0
Intracranial Hemorrhage	0	0
Major Bleeding	0	0
Minor bleeding	0	1

Limitations

- Primary outcome could not be assessed in 23 pts due to Covid-19 clinic closure. The initial sample size calculation of 58 pts gave 95% power for a 25% reduction in LDL-C. With 68 pts in the primary analysis, there was high statistical power to evaluate the main hypothesis.
- The alirocumab sham-control training pen was identical in appearance to active alirocumab pen but without internal needle. It's possible that some patients could have been unblinded as they may not have felt the needle puncture despite firm pressure of pen on skin. However, main outcomes were *lab based* and unlikely to be influenced by patient knowledge of treatment allocation.

Conclusions

In patients with STEMI undergoing primary PCI, the routine early initiation of PCSK9 inhibitor *(regardless of baseline LDL level or prior statin use)* compared with sham-control:

1. Reduced LDL-cholesterol by 22% at 6 weeks (median 45 days) on a background of high intensity statin therapy.
2. Resulted in a greater proportion of patients achieving >50% reduction or ESC LDL target of ≤ 1.4 mmol/L (70 mg/dL).
3. Appeared to be feasible and safe.

Implications

- Routine, early administration of PCSK9 inhibitor has the potential to *substantially reduce morbidity and mortality globally* after high-risk ACS by further reducing LDL beyond statins in a *much* greater number of high-risk patients than is currently treated with these agents.
- A large outcomes trial evaluating this simplified strategy is needed

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Simultaneous Publication
EuroIntervention 2022;17:1-1

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