Lipoprotein(a) Lowering by Alirocumab Contributes to Event Reduction Independent of Low-Density Lipoprotein Cholesterol in the ODYSSEY OUTCOMES Trial

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On behalf of the ODYSSEY OUTCOMES Investigators and Committees

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*Equal contributions
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Disclosures

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Lipoprotein(a)

- A low-density lipoprotein containing apo B and apo(a)
- Atherogenic, pro-inflammatory, pro-thrombotic and pro-oxidant properties
- Associated with incident CHD in population studies
- Levels primarily genetically determined
- Levels lowered by several drug classes, including PCSK9i
- Limited data to date linking pharmacologic lowering of Lp(a) to reduction in cardiovascular events

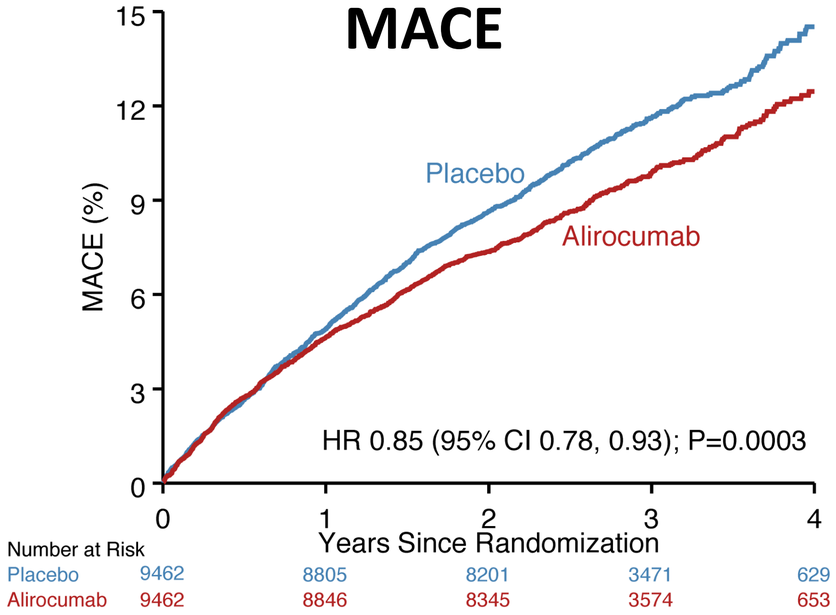
The ODYSSEY OUTCOMES Trial

- 18,924 patients with **recent ACS and LDL-C ≥70 mg/dL*** despite intensive or maximum tolerated statin
  (*or non-HDL-C ≥100 mg/dL or apoB ≥80 mg/dL)
- Randomization: **alirocumab (75 mg) or placebo** q 2 wks
  (blinded adjustment of alirocumab dose to target achieved LDL-C 25-50 mg/dL)
- **Primary endpoint (MACE):** CHD death, non-fatal MI, ischemic stroke, hospitalization for unstable angina
- **Secondary endpoints** included all-cause death, hospitalization for HF, and ischemia-driven coronary revascularization
- **Median follow-up 2.8 years**

Schwartz GG, et al *NEJM* 2018;379:2097-2107

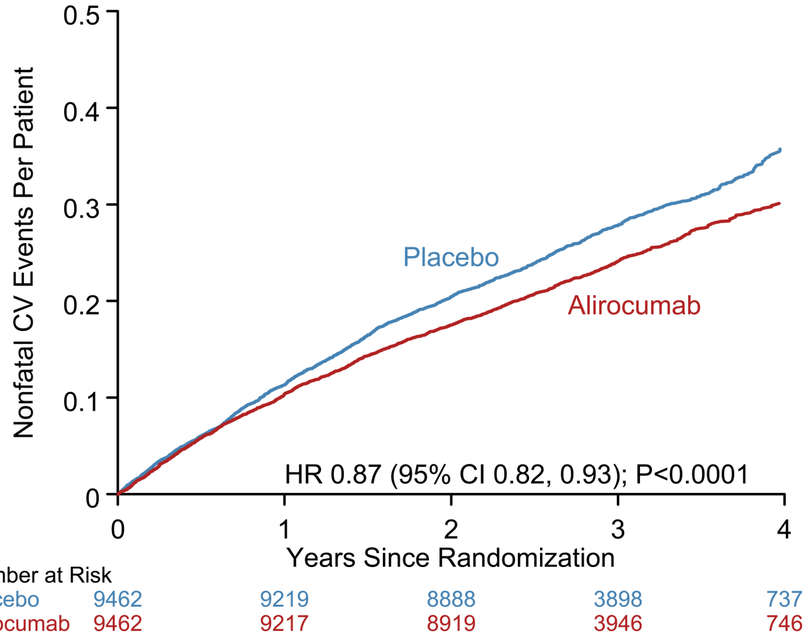
Summary of Efficacy

MACE



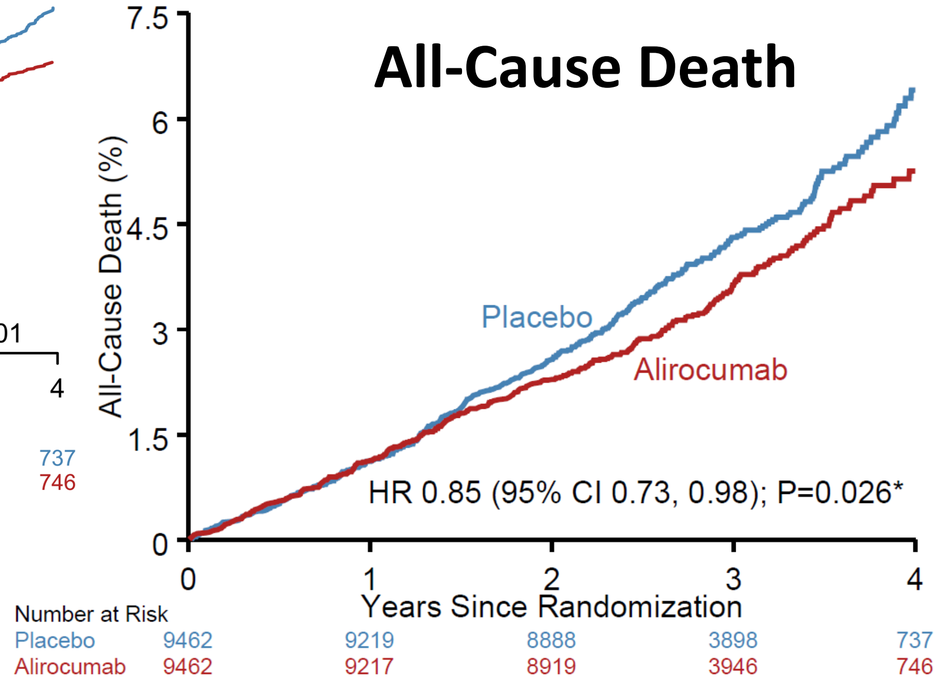
Schwartz GG, et al *NEJM* 2018;379:2097

Total Non-Fatal CV Events



Szarek M et al. *JACC* 2019;73:387

All-Cause Death



Schwartz GG, et al *NEJM* 2018;379:2097
* Nominal p-value

Placebo
Alirocumab

Objective

To determine whether the risks of first primary endpoint (MACE) and total endpoint events were related to lowering of Lp(a) by alirocumab, **independent of the concurrent effect of alirocumab to lower LDL-C**.

Measurement of Lipoproteins

Lipoprotein(a)

- Automated nephelometry*, mg/dL

LDL-cholesterol

- Friedewald or beta-quantification
- Measured LDL-C = LDL-C_{corr} + Lp(a)-C

Corrected LDL-cholesterol†

- LDL-C_{corr} = LDL-C – 0.3×Lp(a) mass

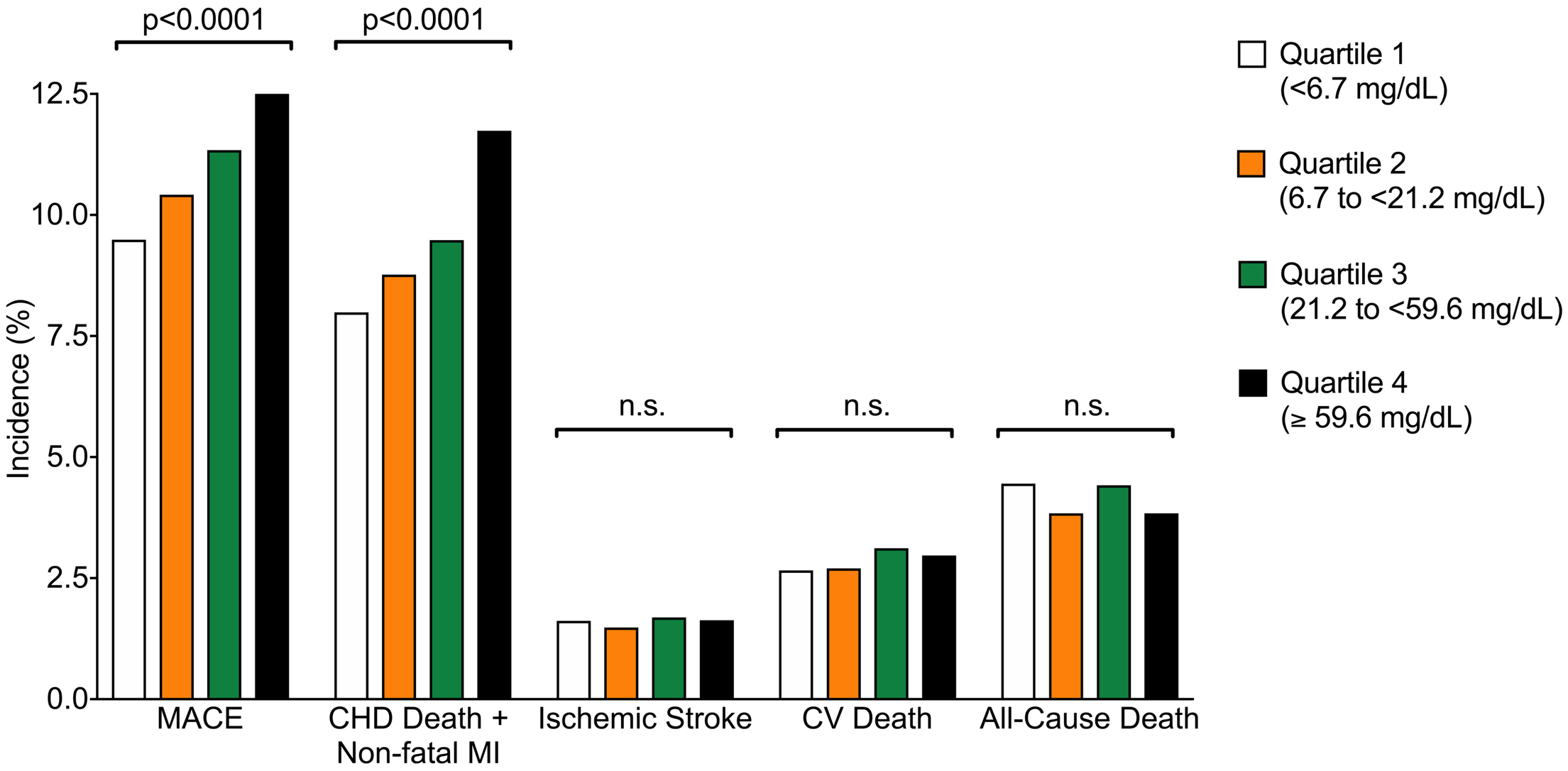
*Siemens BNII ; March 22, 2017; † Kinpara K et al. *Clin Chim Acta* 2011;412:1783-87

Selected Clinical Characteristics By Baseline Lp(a) Quartiles

Variable	Q1 <6.7 mg/dL (n=4730)	Q2 6.7 to <21.2 mg/dL (n=4731)	Q3 21.2 to <59.6 mg/dL (n=4729)	Q4 ≥59.6 mg/dL (n=4734)	P-value*
Age, years	58 (52–65)	58 (52–65)	58 (52–65)	58 (52–65)	0.14
Female (%)	20	24	25	32	**<0.001**
Black (%)	0.6	1.0	3.1	5.2	**<0.001**
Lp(a), mg/dL	2.0 (2.0–4.8)	12.2 (9.3–15.9)	37.6 (28.3–47.7)	92.2 (73.2–119.0)	
LDL-C, mg/dL	83 (69–101)	85 (72–102)	86 (73–104)	92 (78–109)	<0.001
ApoB, mg/dL	79 (68–93)	78 (68–92)	78 (68–92)	82 (71–95)	<0.001
High intensity statin (%)	88	87	89	91	<0.0001
BMI (kg/m^2)	28.5 (25.7–31.6)	27.9 (25.2–30.9)	27.7 (24.9–30.8)	27.7 (25.0–31.0)	<0.001
Diabetes	31	29	29	27	**0.001**
Current smoking	26	25	24	22	**<0.001**

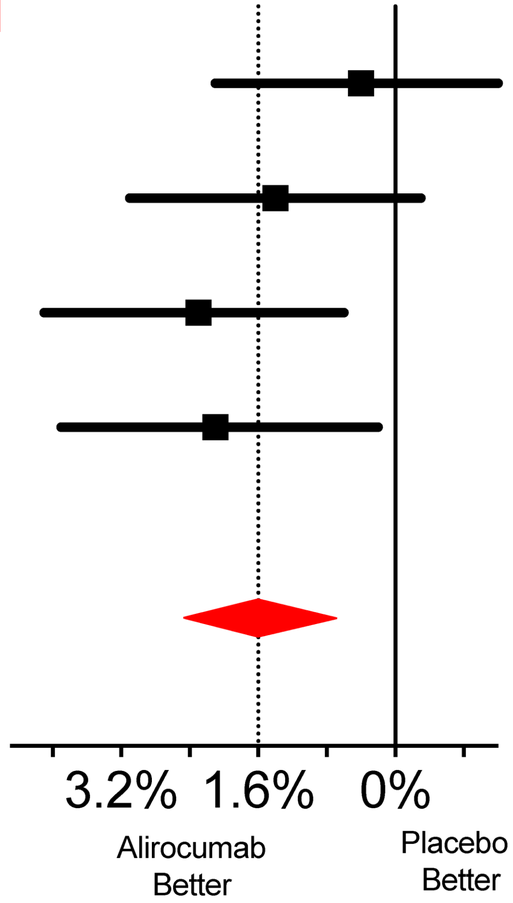
*P value: Kruskal Wallis or Chi square; percentages are rounded to nearest whole number

Baseline Lp(a) Predicts MACE Risk in the Placebo Group

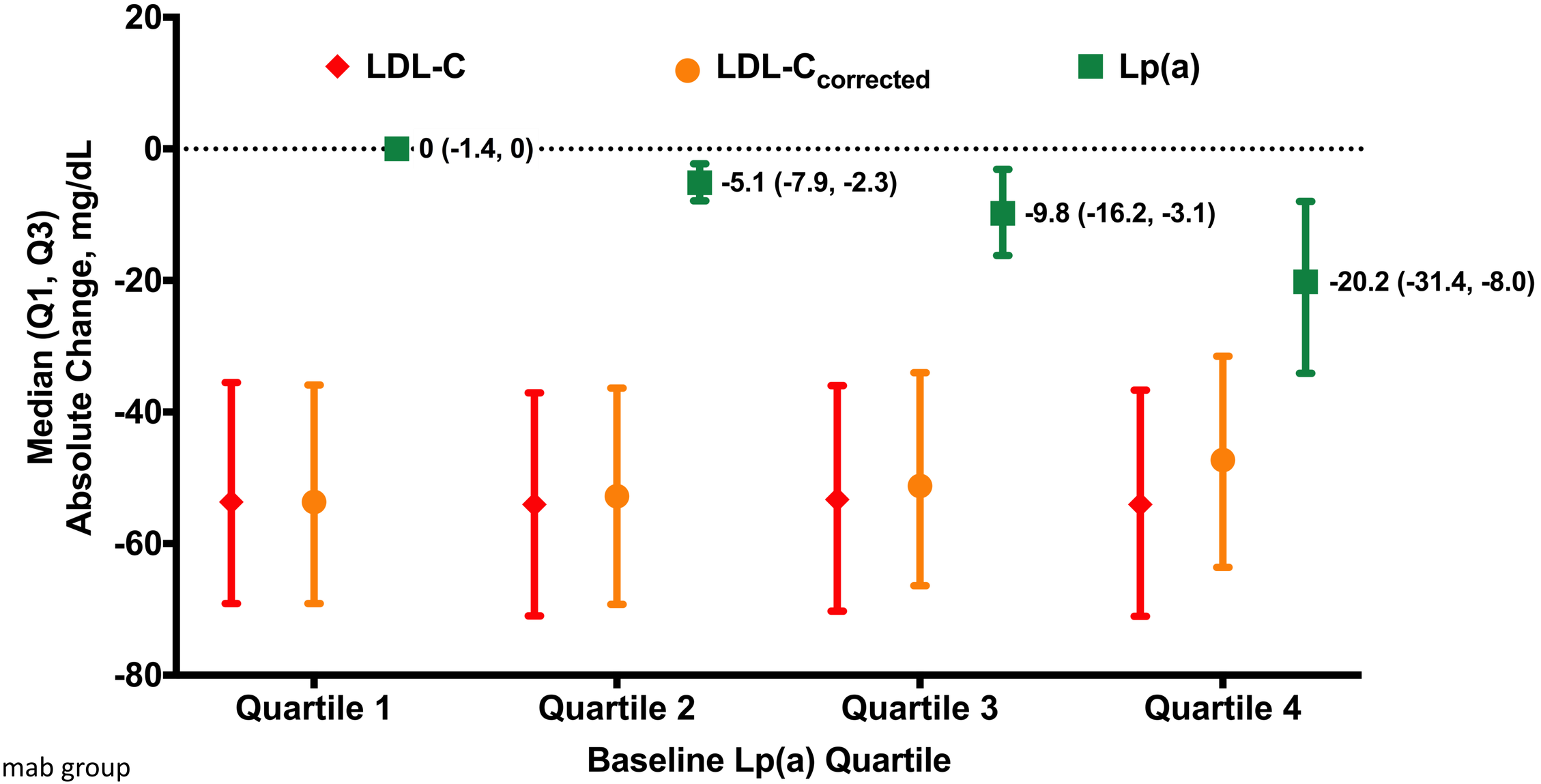


Greater Absolute Treatment Effect on MACE With Higher Baseline Lp(a)

Subgroup	MACE Incidence Alirocumab n/N (%)	MACE Incidence Placebo n/N (%)	Absolute Risk Reduction (95% CI) ($p_{interaction}$= 0.0011)
Quartile 1	211/2327 (9.1)	228/2403 (9.5)	0.4% (-1.2%, 2.1%)
Quartile 2	219/2438 (9.0)	239/2293 (10.4)	1.4% (-0.3%, 3.1%)
Quartile 3	212/2356 (9.0)	269/2373 (11.3)	2.3% (0.6%, 4.1%)
Quartile 4	261/2341 (11.2)	316/2393 (13.2)	2.1% (0.2%, 3.9%)
Overall	903/9462 (9.5)	1052/9462 (11.1)	1.6% (0.7%, 2.4%)



Baseline Lp(a) Predicts Absolute Change in Lp(a), but not LDL-C



Alirocumab group

Relationships between Change in Lp(a) with Alirocumab (Baseline to Month 4) and CV Outcomes after Month 4

- Two analyses conducted within the alirocumab group:
  - **First MACE event** (prespecified; Cox proportional hazards model)
  - **Total CV events and all-cause death** (post hoc; frailty model)

- Same co-variates for **both** analyses
  - ***Model 1:*** Adjusted for baseline Lp(a)
  - ***Model 2:*** Adjusted for baseline Lp(a), baseline LDL-C_{corr}, and **the change from baseline to Month 4 in LDL-C_{corr}**

- Model results expressed as HR for 1 mg/dL reduction in Lp(a) or LDL-C_{corr}
- Compare relative benefit associated with reduction in Lp(a) and LDL-C_{corr}

Change in Lp(a) Predicts MACE, Independent of LDL-C_{corr}

Model	Model Adjustments	Change Parameter	HR (95% CI) per 1 mg/dl decrease	p-value
1	Baseline Lp(a)	Lp(a)	0.993 (0.989, 0.998)	0.0027
2	Baseline Lp(a), Baseline LDL-C_{corr}, Change from Baseline to Month 4 in LDL-C_{corr}	Lp(a) LDL-C_{corr}	0.994 (0.990, 0.999) 0.996 (0.994, 0.998)	0.0081 0.0002

Changes in lipoproteins measured between baseline and Month 4

Change in Lp(a) Predicts MACE, Independent of LDL-C_{corr}

Model	Model Adjustments	Change Parameter	HR (95% CI) per 1 mg/dl decrease	p-value
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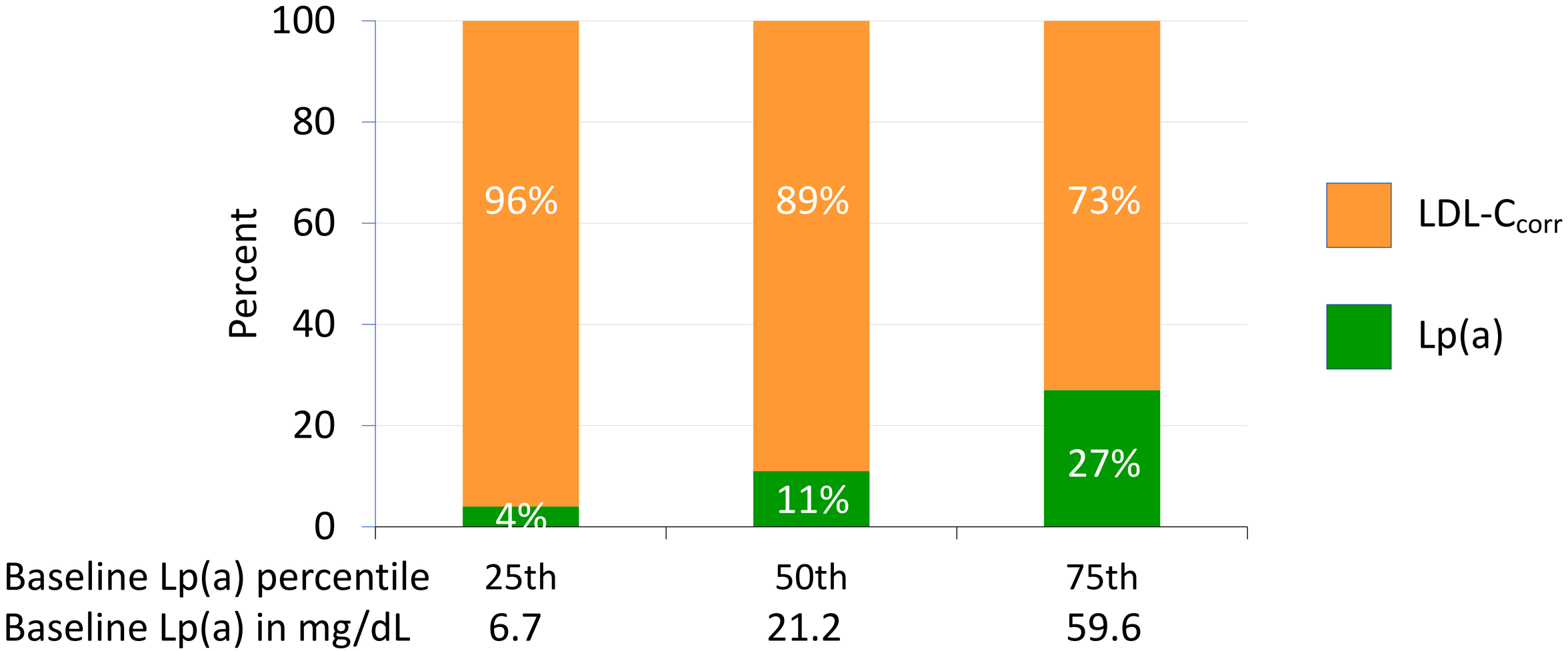
Implications of Hazard Ratios: Some Examples

Lp(a) Reduction (mg/dL)	HR*	RRR for MACE
1	0.994	0.6%
5	$0.994^5 = 0.970$	3.0%
10	$0.994^{10} = 0.942$	5.8%
15	$0.994^{15} = 0.914$	8.6%
20	$0.994^{20} = 0.890$	11.0%

* independent of baseline Lp(a), baseline LDL-C_{corr} and change in LDL-C_{corr}

5 mg/dL reduction = median; 15 mg/dL reduction = 75th percentile

Proportion of MACE Reduction Attributable to Changes in Lp(a) and Corrected LDL-C



From model with baseline and change in Lp(a), baseline and change in LDL-C_{corr} (Model 2)

Change in Lp(a) Predicts Total Events, Independent of LDL-C_{corr}

Model	Model Adjustments	Change Parameter	HR (95% CI) per 1 mg/dl decrease	p-value
1	Baseline Lp(a)	Lp(a)	0.994 (0.990, 0.999)	0.0109
2	Baseline Lp(a), Baseline LDL-C_{corr}, Change from Baseline to Month 4 in LDL-C_{corr}	Lp(a) LDL-C_{corr}	0.995 (0.991, 0.999) 0.996 (0.994, 0.998)	0.0224 0.0004

Changes in lipoproteins measured between baseline and Month 4

Change in Lp(a) Predicts Total Events, Independent of LDL-C_{corr}

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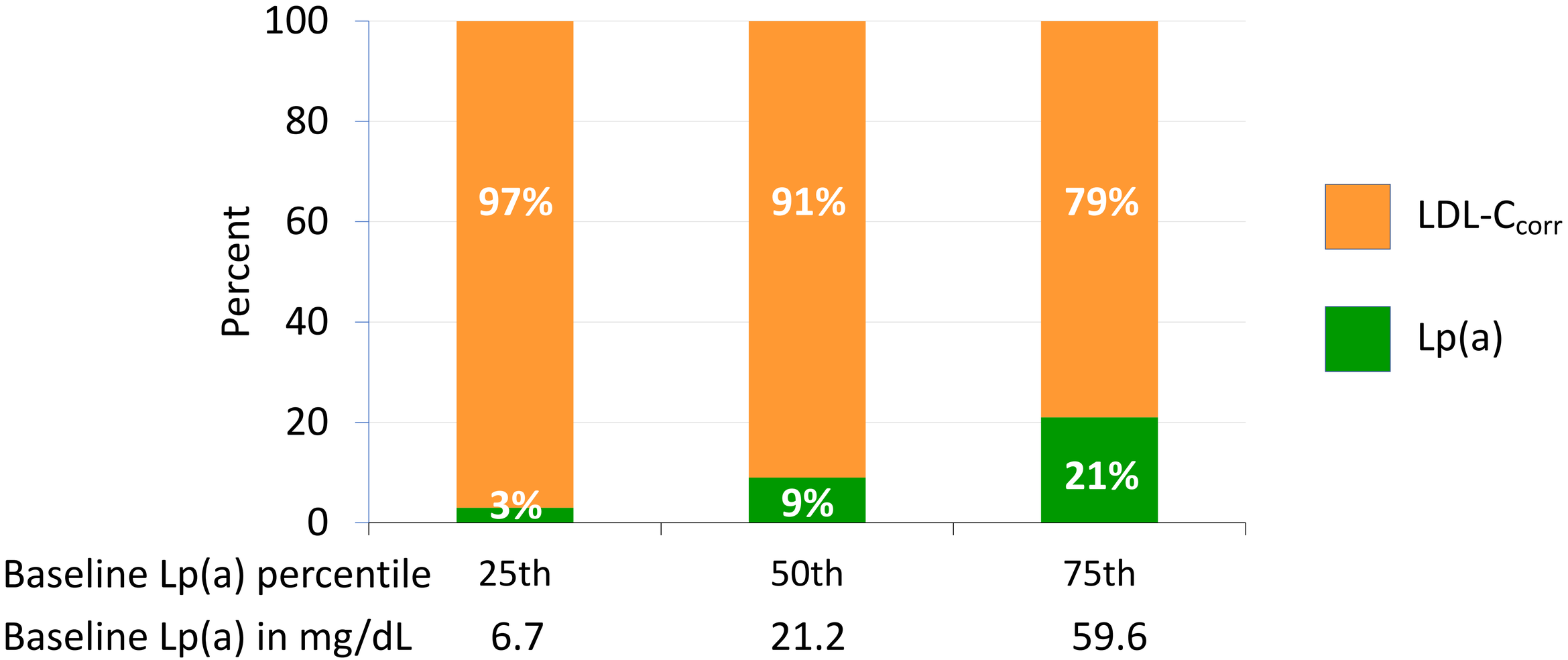
Changes in lipoproteins measured between baseline and Month 4

Proportion of Total Event Reduction Attributable to Change in Lp(a) and Corrected LDL-C



From model with baseline and change in Lp(a), baseline and change in LDL-C_{corr} (Model 2)

Conclusions

- Baseline Lp(a) predicts MACE in patients with recent ACS.
- Lowering of both Lp(a) and LDL-C_{corr} by alirocumab contributed **independently** to the reduction of MACE and total CV events.
- Reduction of LDL-C_{corr} is the **dominant factor** contributing to event reduction with alirocumab.
- The contribution of Lp(a) lowering to event reduction with alirocumab increases with higher baseline Lp(a) levels, and **becomes clinically meaningful** in patients with high baseline Lp(a) levels.

Clinical Implication

- Our findings suggest that Lp(a) could be a therapeutic target in selected patients after recent ACS.

Backup

Survival Analysis Methods Involving Lp(a) Change

- Analyses involving 710 first MACE events were by prespecified Cox regression models
- Analyses involving 1636 total nonfatal CV events and 299 all-cause deaths were by post hoc shared frailty models
  - Allows multiple events within a given patient
  - Total nonfatal CV events: MI, stroke (including hemorrhagic), UA and HF requiring hospitalization, ischemia-driven coronary revascularization
  - Frailty is a random effect that accounts for risk heterogeneity between patients; specified to have a Gamma distribution
  - Assumes multiple events times within a patient are independent conditional on the predictors in the model and the random frailty effect
- All analyses were ITT, including all adjudicated events after a patient's month 4 assessment through the common study end date (11 Nov 2017)

Survival Analysis Methods Involving Lp(a) Change

- Proportions of the combined relative risk reduction by change in Lp(a) and LDL-C_{corr} attributed to each factor determined by log hazard ratios at specified percentiles of baseline Lp(a)
  - Attributed to Lp(a) = $\log(HR)_{Lp(a)} / [\log(HR)_{Lp(a)} + \log(HR)_{LDL\text{-}Ccorr}]$
  - Attributed to LDL-C_{corr} = $\log(HR)_{LDL\text{-}Ccorr} / [\log(HR)_{Lp(a)} + \log(HR)_{LDL\text{-}Ccorr}]$
- Expected change in Lp(a) and LDL-C_{corr} at each baseline Lp(a) percentile determined by linear regression models with baseline Lp(a) as predictor