ASCVD Risk Reduction For Patients with High Lp(a) in 2020: Is There a Role for PCSK9 Inhibition?

Vera Bittner, MD, MSPH, FACC, FAHA, FESC
Professor of Medicine
Section Head, General Cardiology, Prevention, and Imaging
University of Alabama at Birmingham

Disclosures: Vera Bittner, MD, MSPH

UAB Contracts		
Sanofi	Steering Committee	ODYSSEY Outcomes
Amgen	Investigator (PI: Muntner)	Pharmacoepidemiology
Amgen	Site PI (under negotiation)	CV Moebius
DalCor	National Coordinator	DalGene
Astra-Zeneca	National Coordinator	STRENGTH
Esperion	National Coordinator	CLEAR
The Medicines Company	Site PI	ORION IV
Other		
Circulation	Senior Guest Editor	
ACC	ACC20 Program Committee; ACC SAP Section Editor	
Sanofi	Participated in Ad Boards in 2018	

Discussion of Off Label Uses

Neither FDA nor EMA have approved PCSK9 inhibitors for the purpose of lowering Lp(a)

Outline

FOURIER and ODYSSEY OUTCOMES

- Does Lp(a) distribution differ from general population?
- Do PCSK9 inhibitors lower Lp(a)?
- Does lowering of Lp(a) by PCSK9 inhibitors relate to cardiovascular risk reduction?

Clinical Guidance

- Current guidelines
- Using PCSK9 inhibitors for patients with high Lp(a) – My Take

FOURIER and ODYSSEY OUTCOMES

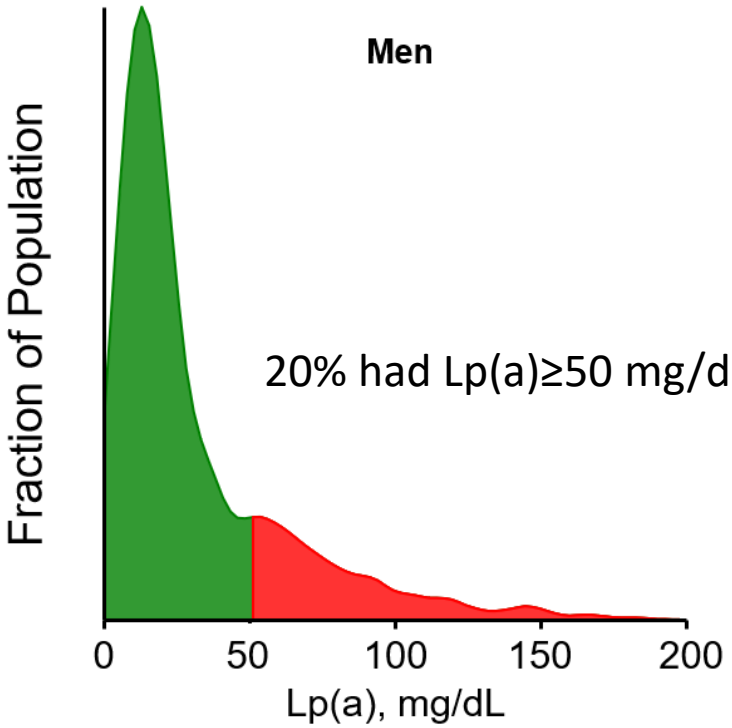
PCSK9 Monoclonal Antibody Trials: Trial Characteristics

Design Feature	FOURIER	ODYSSEY Outcomes
Patient Population	Stable ASCVD: MI, stroke, PAD; median 3 years since index event	Post ACS; median 2.6 months since index event
N (% women)	27,564 (25)	18,294 (25)
Mean age (years)	63	58
LDL-C entry criterion	≥ 70 mg/dL	≥ 70 mg/dL
Baseline LDL-C	92 mg/dL	87 mg/dL
High intensity statin	69%	89%
Ezetimibe	5%	3%
PCSK9 dosing	Evolocumab 140 mg Q 2 weeks or 420 mg Q 4 weeks	Alirocumab 75 mg or 150 mg Q 2 weeks; titrated to target LDL-C 25-50 mg/dL
Follow-up	2.2 years	2.8 years (44% ≥3 years)
Primary Endpoint	MACE: CV death, MI, stroke, UA, coronary revasc	MACE: CHD death, MI, ischemic stroke, UA

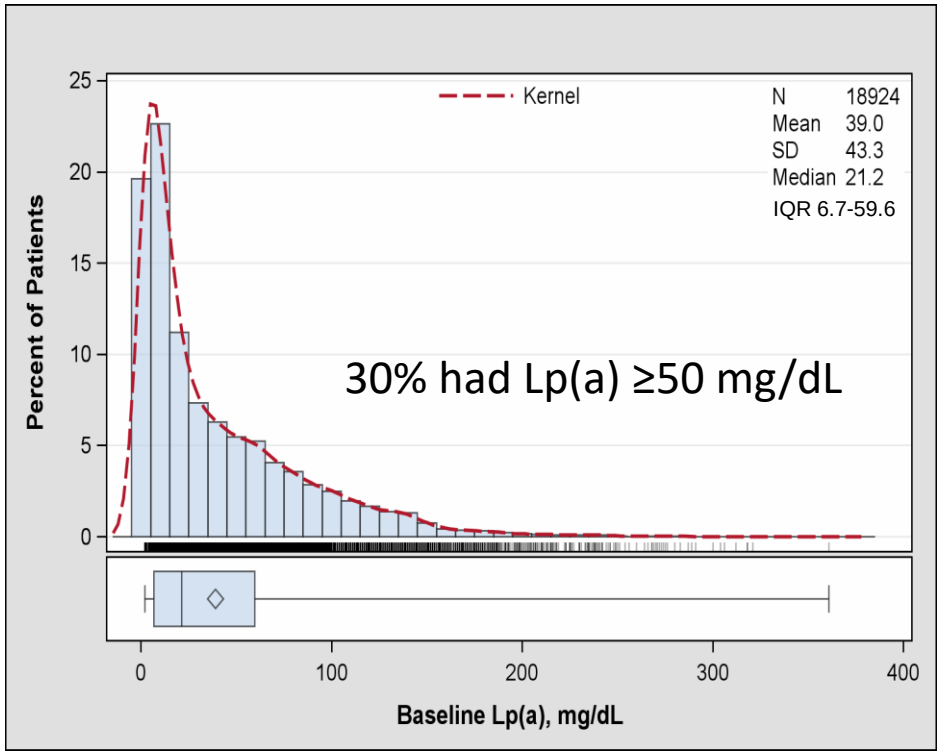
Sabatine M, et al. NEJM 2017; Schwartz G, et al. NEJM 2018

Distribution of Lp(a)

Copenhagen General Study



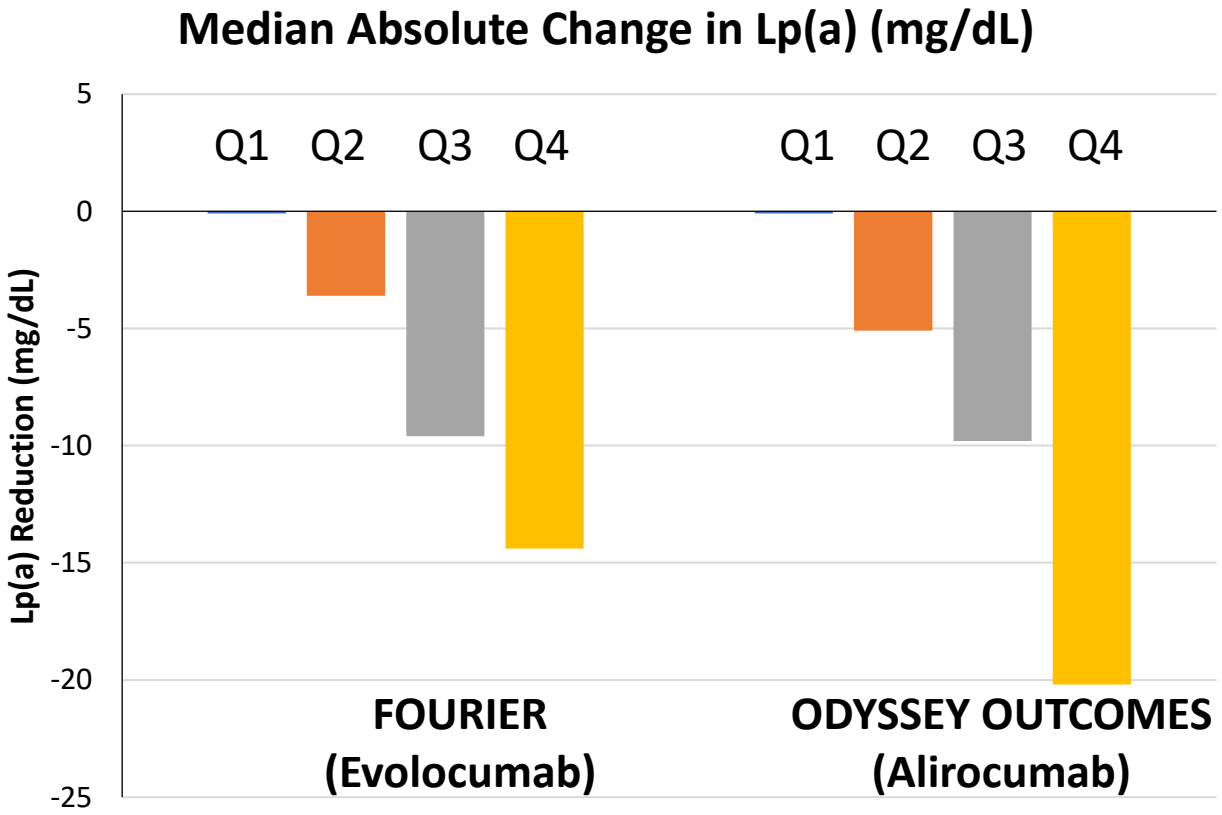
ODYSSSEY OUTCOMES



FOURIER: Lp(a) median 14.8 mg/dL (IQR 5.2, 66)

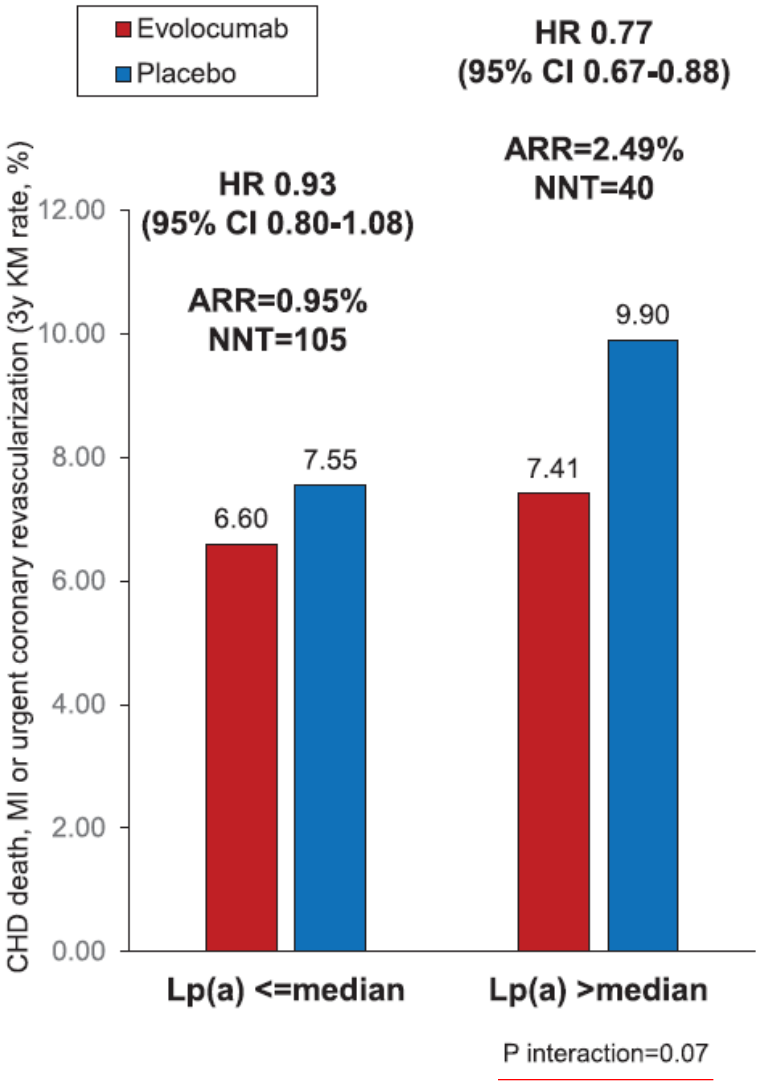
Nordestgaard et al. EHJ 2010;31:2844-2853
Bittner et al. JACC 2020;75:133-144 (suppl)
O'Donoghue et. al. Circ 2019;139:1483–1492 (suppl)

Lp(a) Reduction with PCSK9 Inhibitors Varies by Baseline Lp(a)



Bittner et al. JACC 2020;75:133-144 (suppl) – Baseline to Month 4
O'Donoghue et. al. Circ 2019;139:1483–1492 (suppl) – Baseline to Week 48

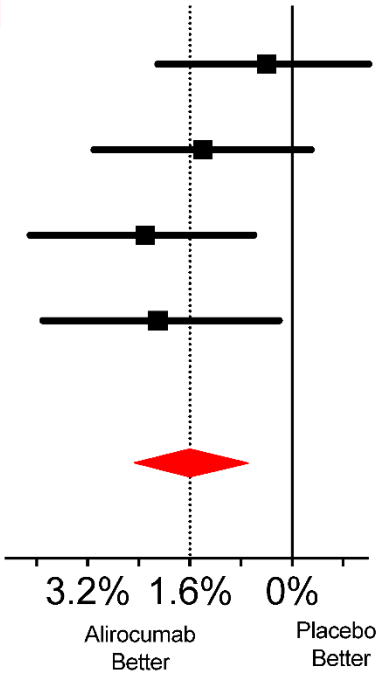
FOURIER: Treatment Effect by Baseline Lp(a)



O'Donoghue et. al. Circulation 2019;139:1483–1492

ODYSSEY OUTCOMES: Treatment Effect on MACE by Baseline Lp(a)

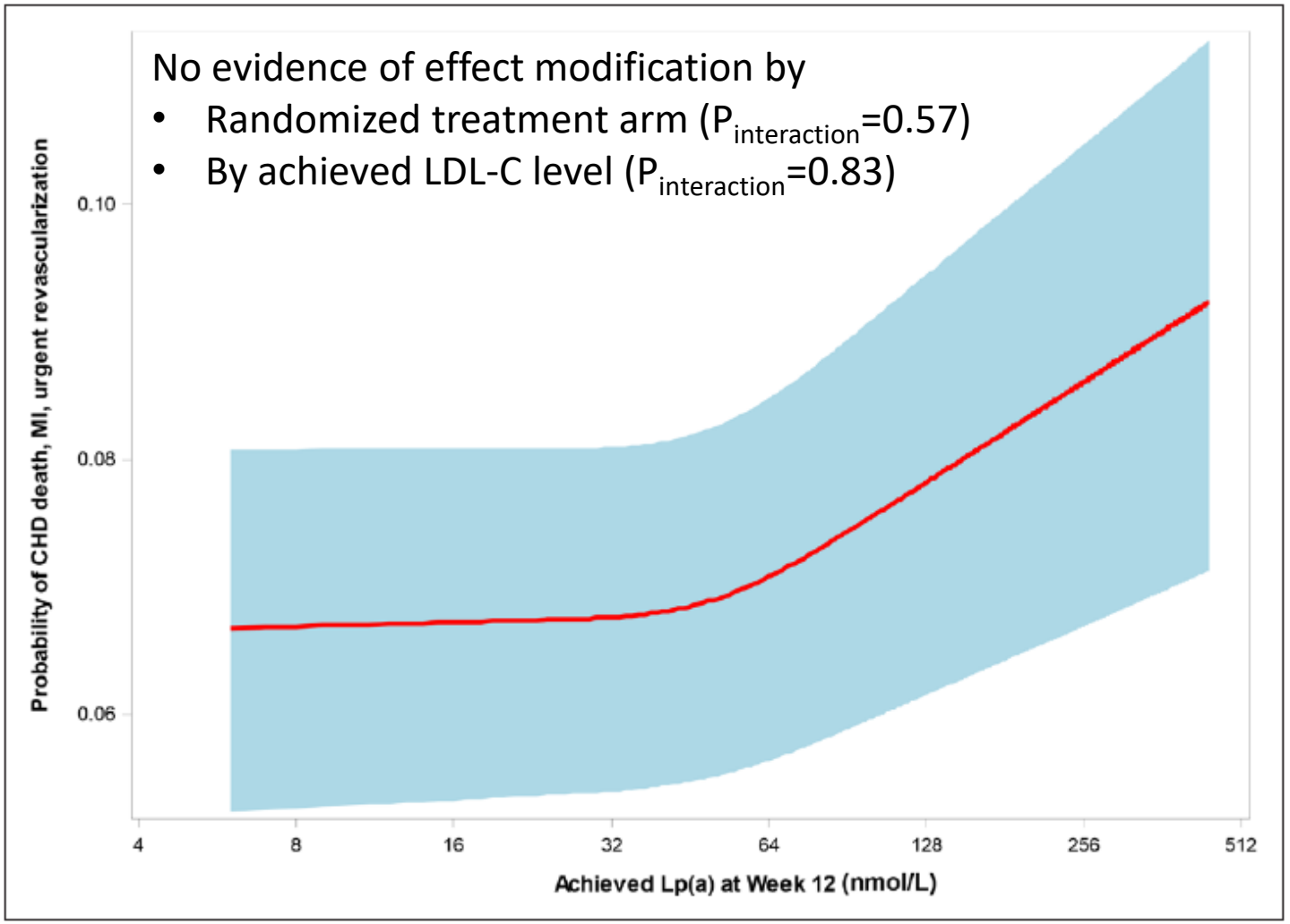
Subgroup	MACE Incidence Alirocumab n/N (%)	MACE Incidence Placebo n/N (%)	Absolute Risk Reduction (95% CI) ($p_{interaction}$= 0.0011)
Quartile 1	211/2327 (9.1)	228/2403 (9.5)	0.4% (-1.2%, 2.1%)
Quartile 2	219/2438 (9.0)	239/2293 (10.4)	1.4% (-0.3%, 3.1%)
Quartile 3	212/2356 (9.0)	269/2373 (11.3)	2.3% (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%)



No significant interaction by baseline Lp(a) for relative risk reduction.

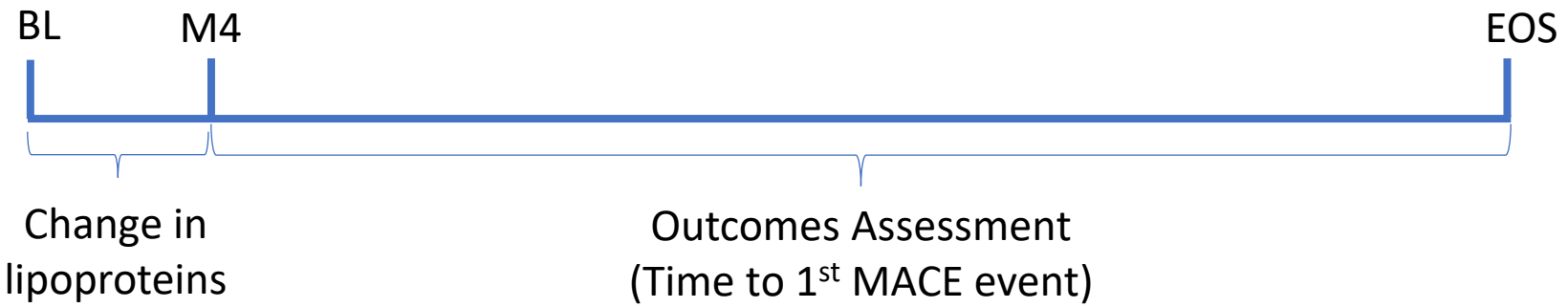
Bittner et al. JACC 2020;75:133-144

Probability of CHD Event by Achieved Lp(a)
FOURIER Landmark Analysis (Week 12)



O'Donoghue et. al. Circulation 2019;139:1483–1492

ODYSSEY OUTCOMES: Analyses by Absolute Change in Lp(a) in the Alirocumab Group



- Pre-specified analysis
- Corrected LDL-C for cholesterol contained in Lp(a)
  - $LDL\text{-}C_{corr} = LDL\text{-}C - 0.3 \times Lp(a)\ mass$
- Does absolute change in Lp(a) contribute to event reduction independently from absolute change in $LDL\text{-}C_{corr}$?

Bittner et al. JACC 2020;75:133-144

Relationships between Change in Lp(a) with Alirocumab (BL to M4) and MACE after M4

- Outcome: Time to first MACE event
- Predictor Variable: Change in Lp(a) (BL to M4)
- Cox Proportional Hazard Model; Co-variates:
  - ***Model 1:*** Baseline Lp(a)
  - ***Model 2:*** Baseline Lp(a), baseline LDL-C_{corr}, and ***change from baseline to Month 4 in LDL-C_{corr}***
  - ***Model 3:*** Model 2 additionally adjusted for clinical and demographic characteristics
- Model results expressed as HR for 1 mg/dL reduction in Lp(a) or LDL-C_{corr}
- Compare benefit associated with reduction in Lp(a) and LDL-C_{corr}

Bittner et al. JACC 2020;75:133-144

Change in Lp(a) Predicts MACE, Independent of Change in Corrected LDL-C

Model	Model Adjustments	Change Parameter	HR (95% CI) per 1 mg/dl decrease
1	BL Lp(a)	Lp(a)	0.993 (0.989, 0.998)
3	BL Lp(a), BL LDL-C_{corr} Change in LDL-C_{corr} Demographics / clinical variables	Lp(a) LDL-C_{corr}	0.994 (0.990, 0.998) 0.995 (0.993, 0.997)

Changes in lipoproteins measured between baseline and Month 4

Bittner et al. JACC 2020;75:133-144

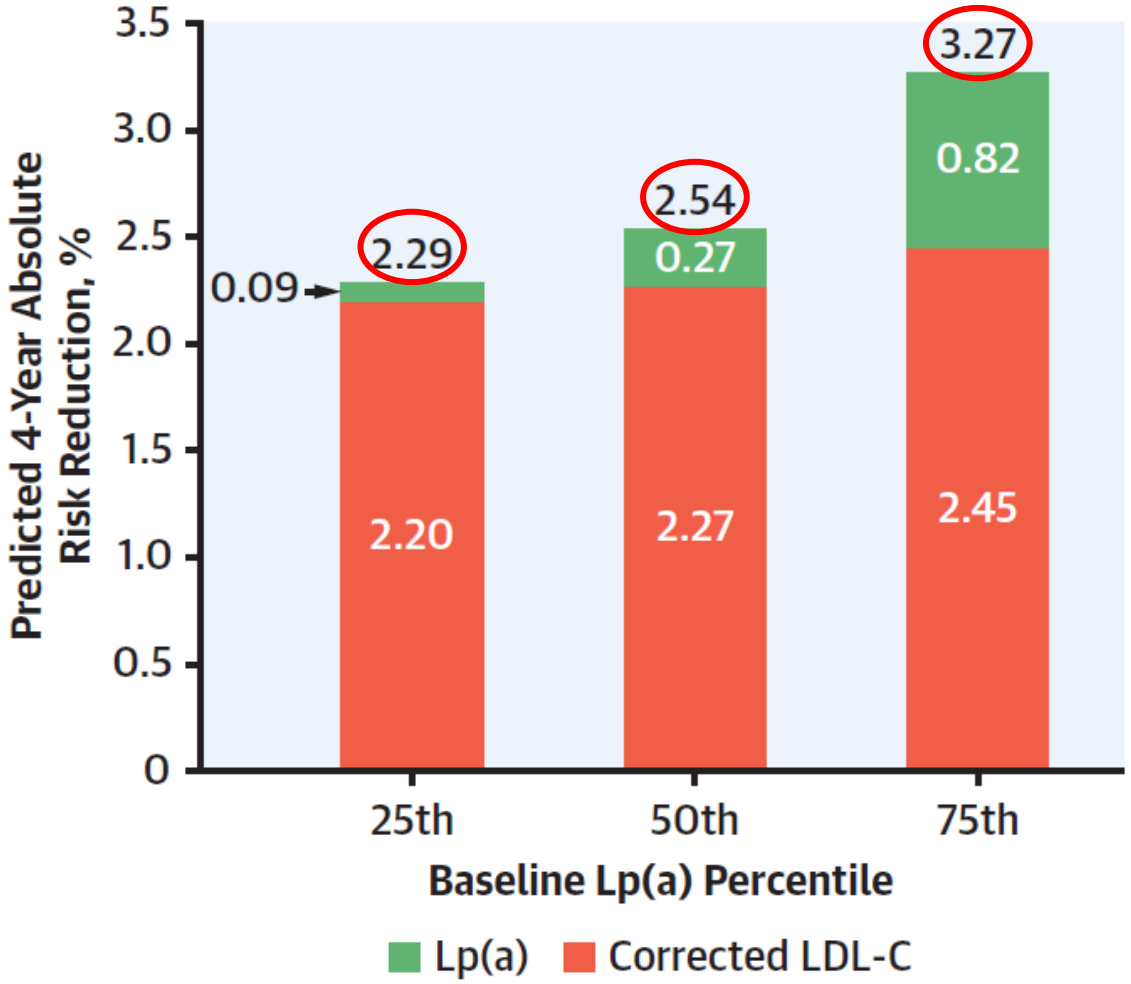
Change in Lp(a) Predicts MACE, Independent of Change in Corrected LDL-C

Model	Model Adjustments	Change Parameter	HR (95% CI) per 1 mg/dl decrease
1	BL Lp(a)	Lp(a)	0.993 (0.989, 0.998)
3	BL Lp(a), BL LDL-C_{corr} Change in LDL-C_{corr} Demographics / clinical variables	Lp(a) LDL-C_{corr}	0.994 (0.990, 0.998) 0.995 (0.993, 0.997)

Changes in lipoproteins measured between baseline and Month 4

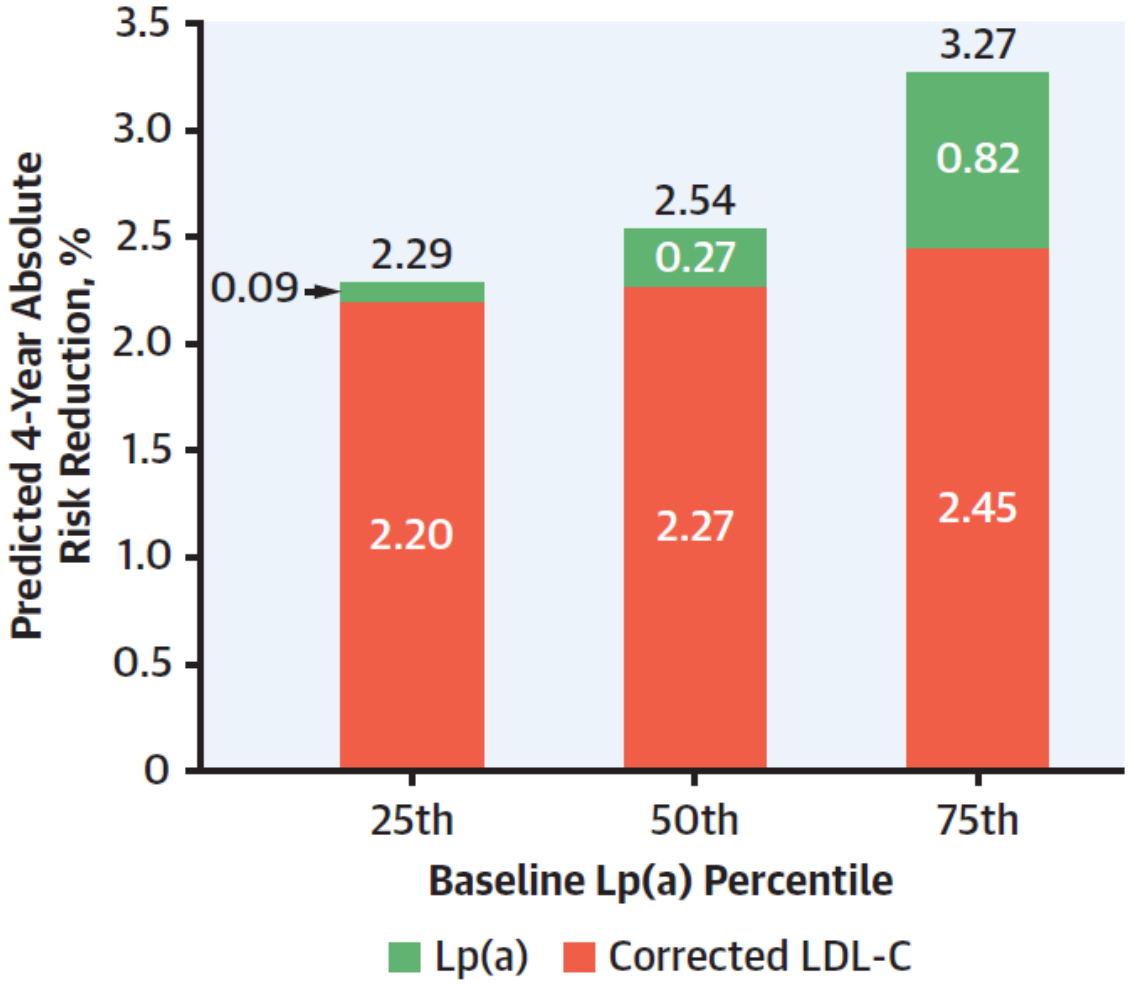
Bittner et al. JACC 2020;75:133-144

Contribution of Change in Lp(a) and Corrected LDL-C to Absolute Risk Reduction



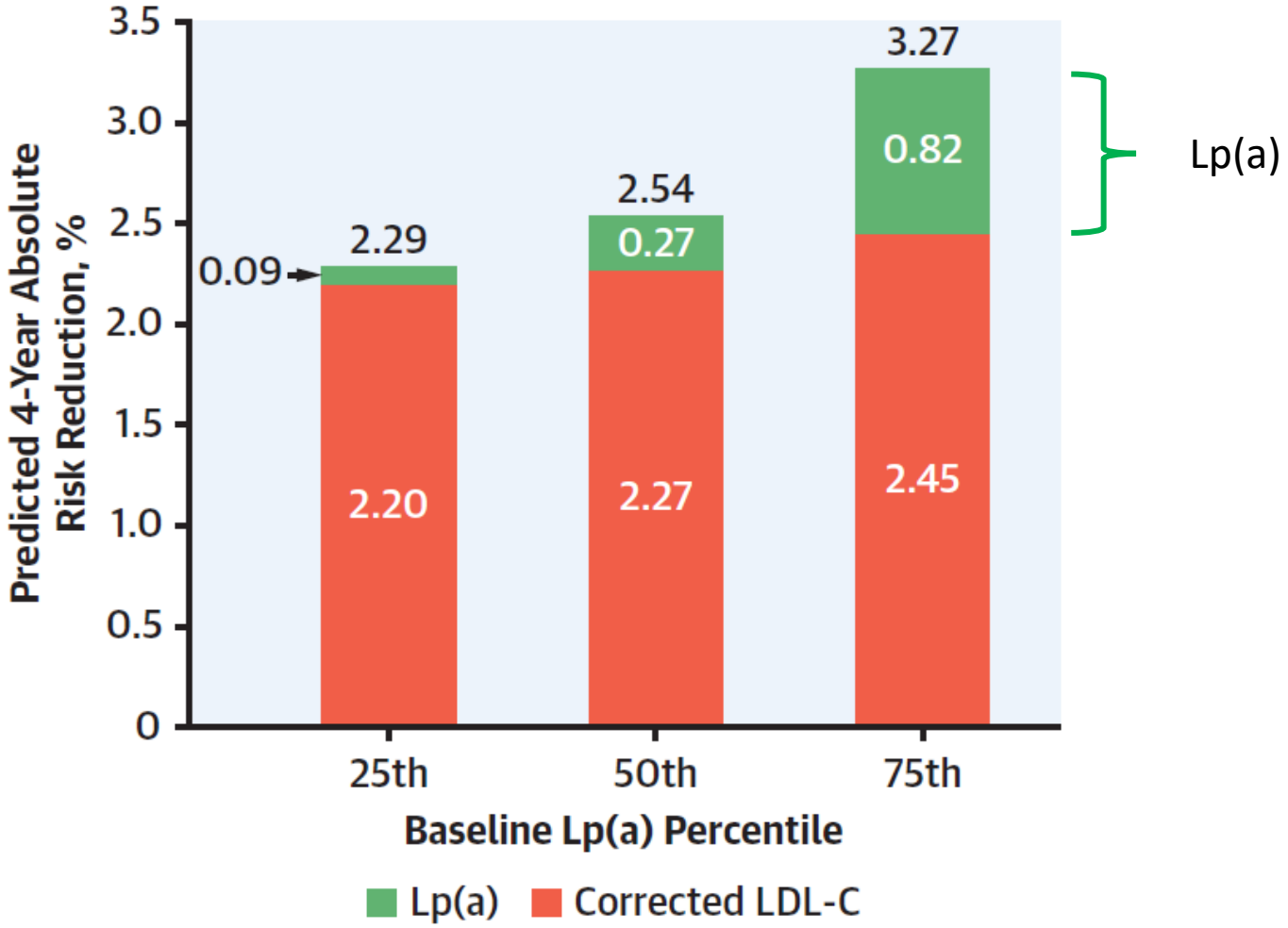
Bittner et al. JACC 2020;75:133-144

Contribution of Change in Lp(a) and Corrected LDL-C to Absolute Risk Reduction



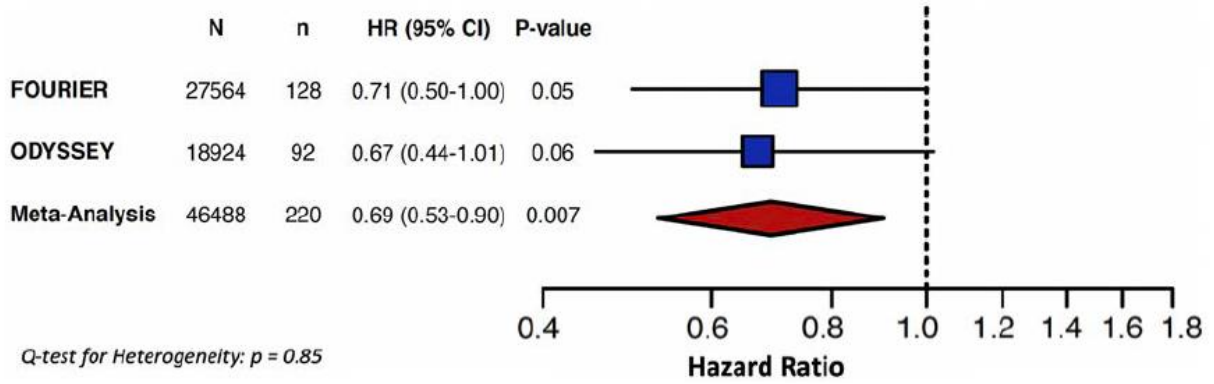
Bittner et al. JACC 2020;75:133-144

Contribution of Change in Lp(a) and Corrected LDL-C to Absolute Risk Reduction

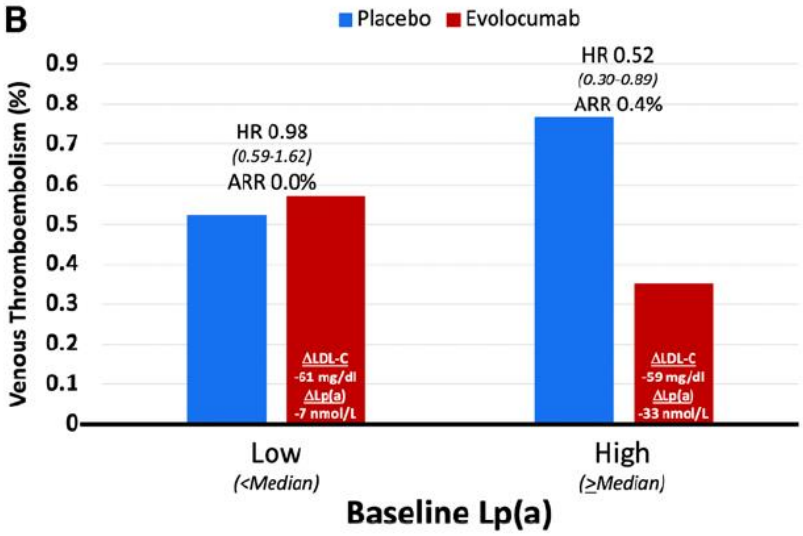


Bittner et al. JACC 2020;75:133-144

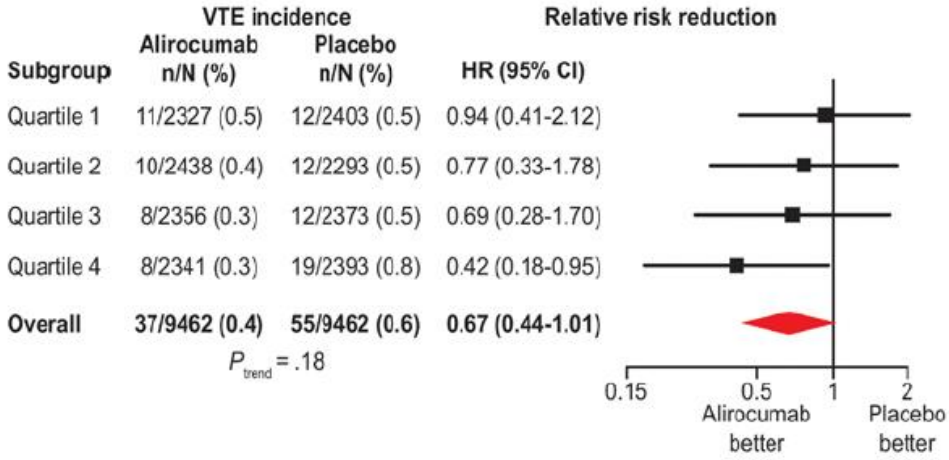
Baseline Lp(a) and Reduction in VTE
FOURIER and ODYSSEY OUTCOMES



FOURIER



ODYSSEY OUTCOMES



Schwartz G et al. Circ2020;141:1608–1617
Marston et al. Circ2020;141:1600-1607

What Have We Learned From FOURIER and ODYSSEY OUTCOMES?

- Alirocumab and evolocumab lower Lp(a) levels with greater reductions at higher baseline Lp(a) levels.
- Baseline Lp(a) predicts MACE in patients with ASCVD.
- Absolute reduction in MACE is greater at higher baseline Lp(a) concentration.
- Data from Odyssey Outcomes suggest that lowering of Lp(a) and LDL-C_{corr} contributed **independently** to the reduction of MACE.
- While reduction in LDL-C_{corr} drives most of the event reduction, the contribution of Lp(a) lowering to event reduction with alirocumab increases with higher baseline Lp(a) levels.
- PCSK9i therapy was associated with reduction in VTE at higher baseline Lp(a) levels

Clinical Guidance

EAS Consensus Panel on Lp(a) 2010

- Elevated Lp(a), like elevated LDL-C, is causally related to premature CVD/CHD
  - Continuous association without a threshold
  - Independent of LDL-C or non-HDL-C levels
  - Prothrombotic effect and/or may accelerate atherosclerosis
- Lp(a) reduction is 2º priority after LDL-C reduction
  - Recommend desirable level for Lp(a) <50 mg/dL (80th percentile)
- Treatment
  - Treatment should primarily be niacin 1-3 g/day
  - In extreme cases, LDL-apheresis is efficacious in removing Lp(a)

Nordestgaard et al. EAS Consensus Panel on Lp(a). EHJ 2010

AHA/ACC Cholesterol Guidelines 2018

- Lp(a) increases ASCVD risk especially at higher levels
- An Lp(a) ≥50 mg/dL or ≥125 nmol/L may be considered a “risk-enhancing factor”
- No treatment recommendations

Grundy SM, Stone NJ et al. 2018 cholesterol guidelines. Circulation 2018

My Take: Clinical Implication of the PCSK9 Inhibitor Outcomes Trials

- The data suggest that Lp(a) could be a therapeutic target in selected patients with ASCVD and very high Lp(a) levels, particularly after recent ACS

- No RCT data with PCSK9i in primary prevention
  - FH patients with high Lp(a) are at particularly high risk, so may be a reasonable group to target for PCSK9 inhibition pending further data