Inflammatory and Cholesterol Risk in the FOURIER Trial

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On behalf of the FOURIER Investigators

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An Academic Research Organization of
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Background

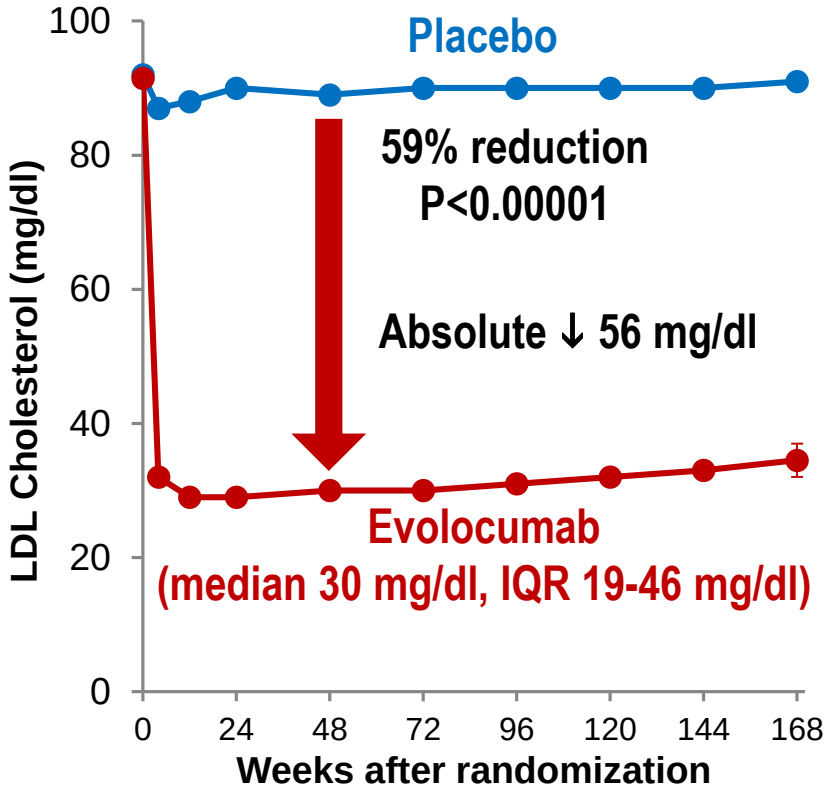
- LDL-C is a well-recognized risk factor for atherosclerotic CV disease (ASCVD)
- CV benefit of ↓ LDL-C, including w/ PCSK9i evolocumab in the FOURIER trial
- Inflammation also plays a role in ASCVD; hsCRP is a marker of inflammation and increased CV risk
- The CANTOS trial of the anti-IL-1β Ab, canakinumab, demonstrated that inflammation was a modifiable risk factor with a ↓ hsCRP and MACE

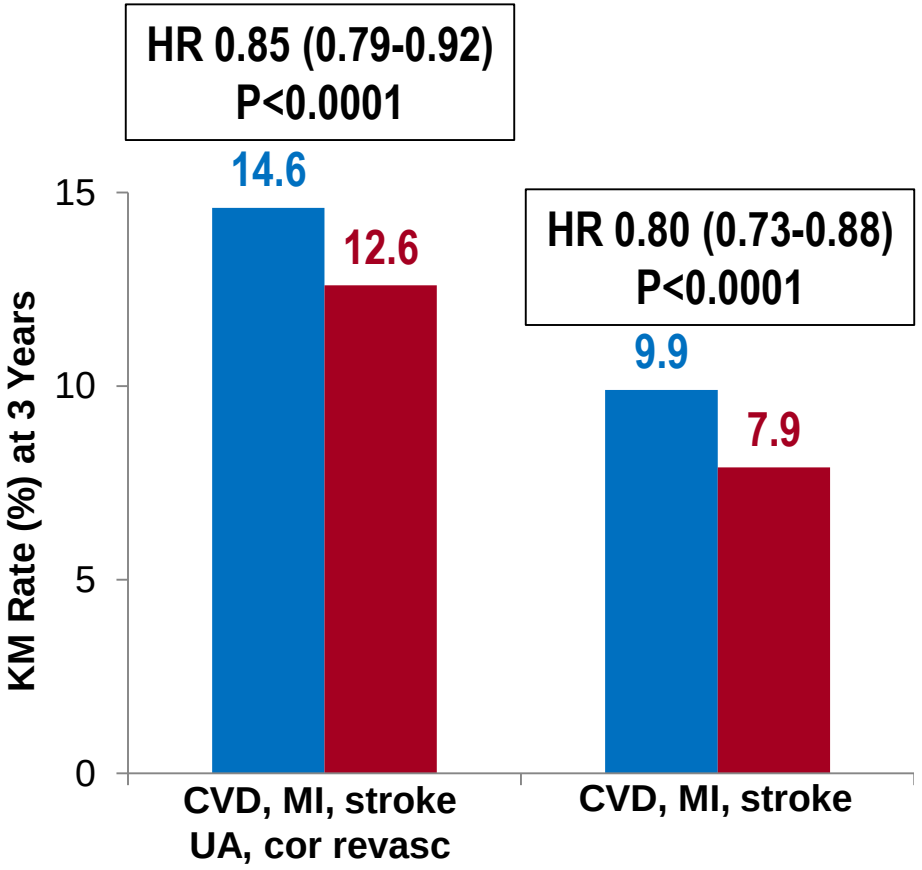
Objectives

- To explore the consistency of benefit of evolocumab for prevention of CV events by baseline hsCRP
- To investigate the importance of inflammatory and residual cholesterol risk as defined by hsCRP and LDL-C levels

Summary of Effects of PCSK9i Evolocumab

- 27,564 pts w/ stable ASCVD & LDL-C ≥70mg/dL on a statin
- ↓ LDL-C by 59% down to a median of 30 mg/dl
- ↓ CV outcomes in patients on statin
- Safe and well-tolerated





Sabatine MS et al. *NEJM* 2017;376:1713-22

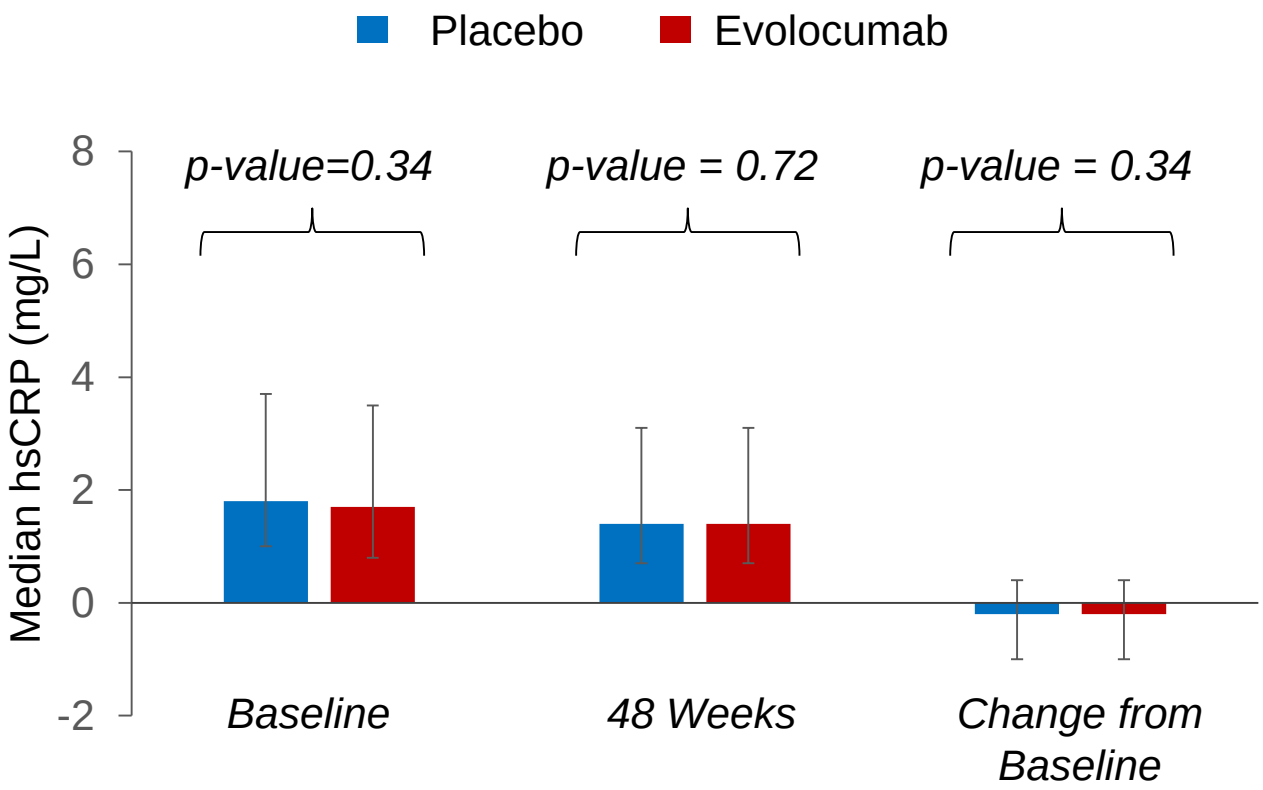
Methods

- Effect of evolocumab on hsCRP levels
- In pts stratified by baseline hsCRP according to AHA/CDC risk groups (hsCRP<1, 1-3, >3 mg/L) determine:
  - Rate of CV outcomes by hsCRP levels
  - Effect of evolocumab on CV outcomes stratified by hsCRP
    - PEP (CV death, MI, stroke, UA, cor revasc)
    - Key SEP (CV death, MI, stroke)
- Prognostic value for CV outcomes of inflammatory & cholesterol risk according to baseline hsCRP and 1 mo achieved LDL-C, adjusted for variables independently associated w/ hsCRP or LDL-C

Baseline Characteristics

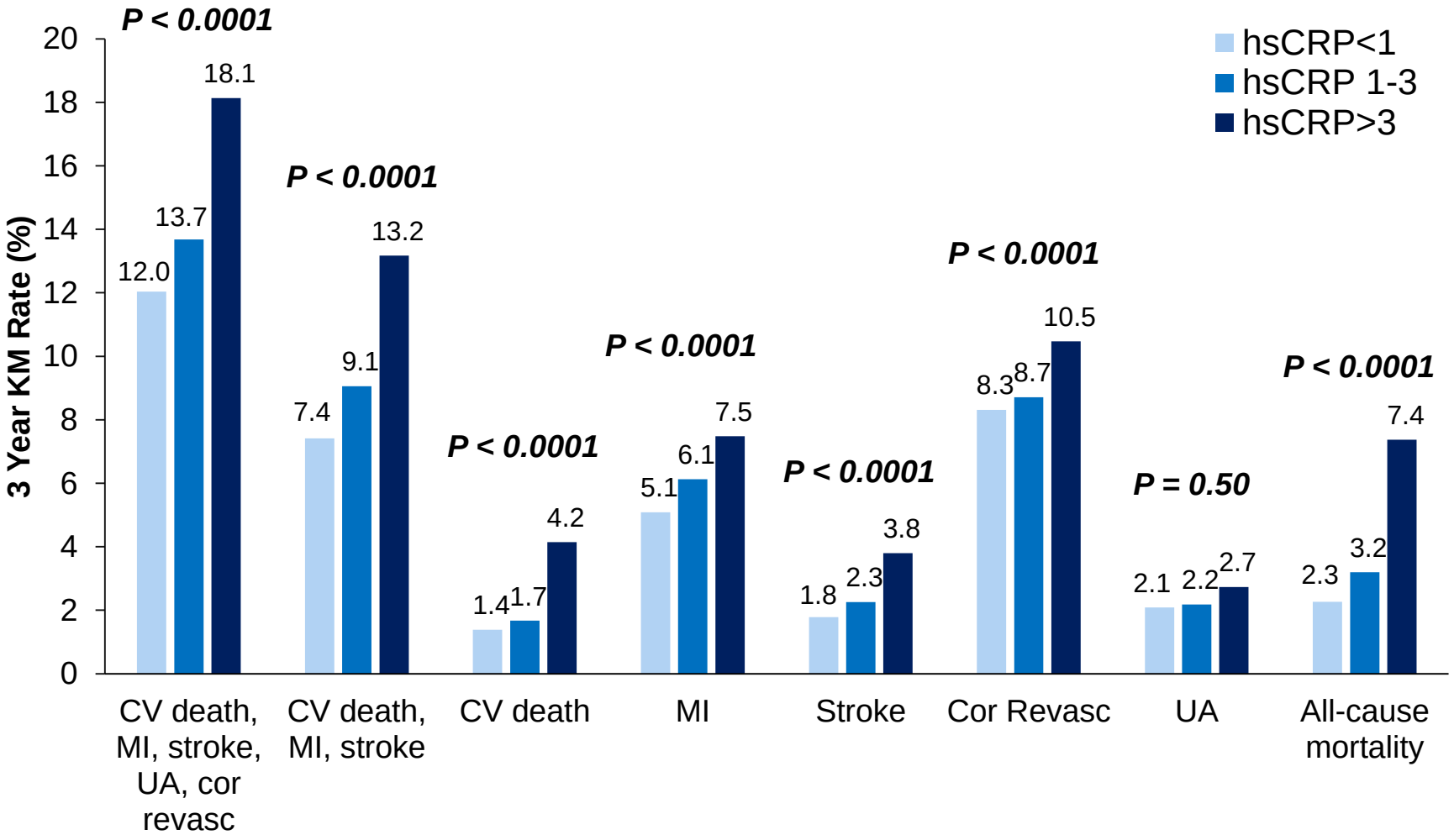
Baseline characteristics	hsCRP<1 (N=7981, 29%)	hsCRP 1-3 (N=11,177, 41%)	hsCRP>3 (N=8337, 30%)

Effect of Evolocumab on hsCRP

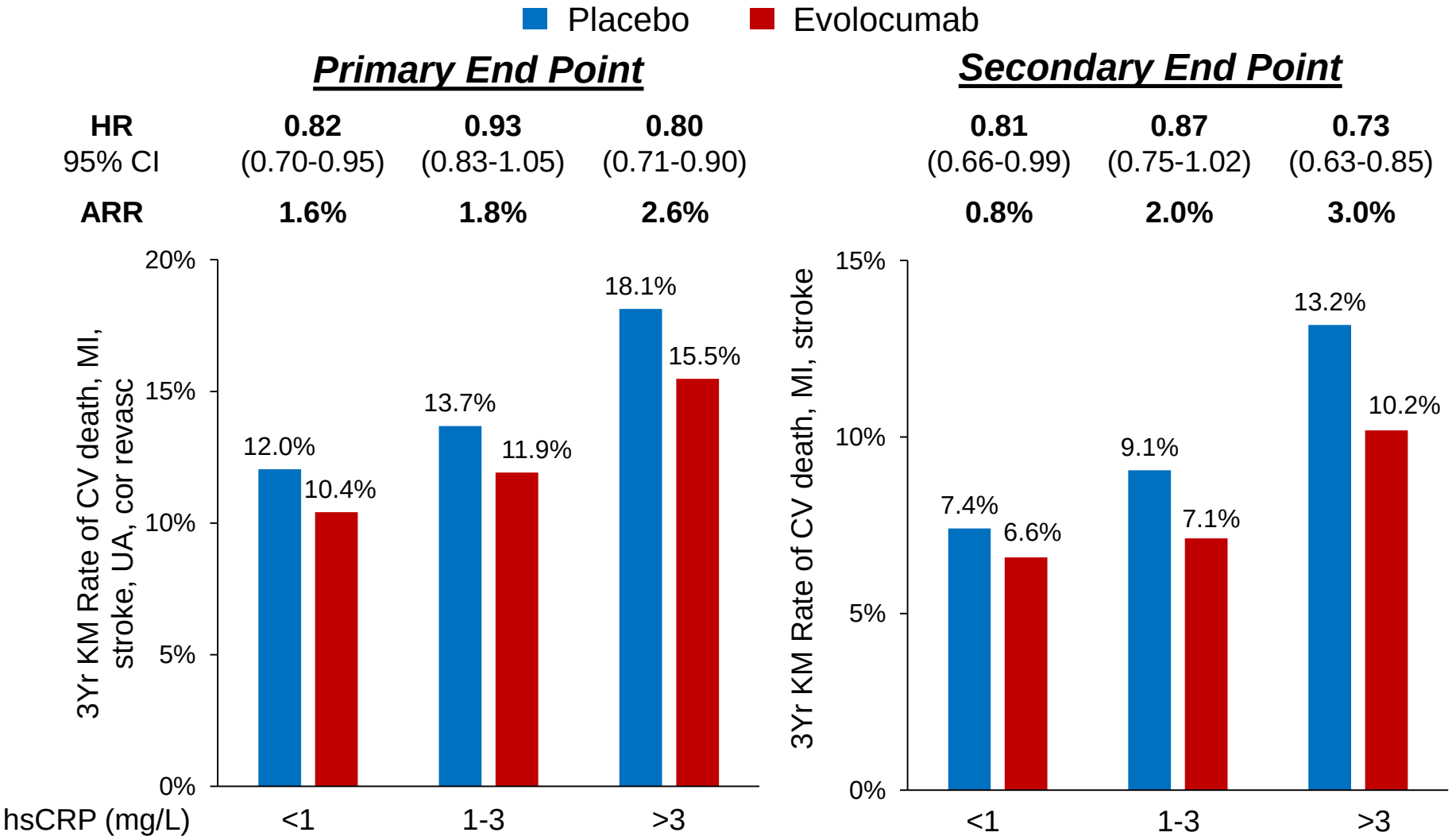


Minimal change in hsCRP from baseline (-0.2mg/L)
&
No difference between treatment arms

Association Between hsCRP & CV Outcomes in Placebo Arm

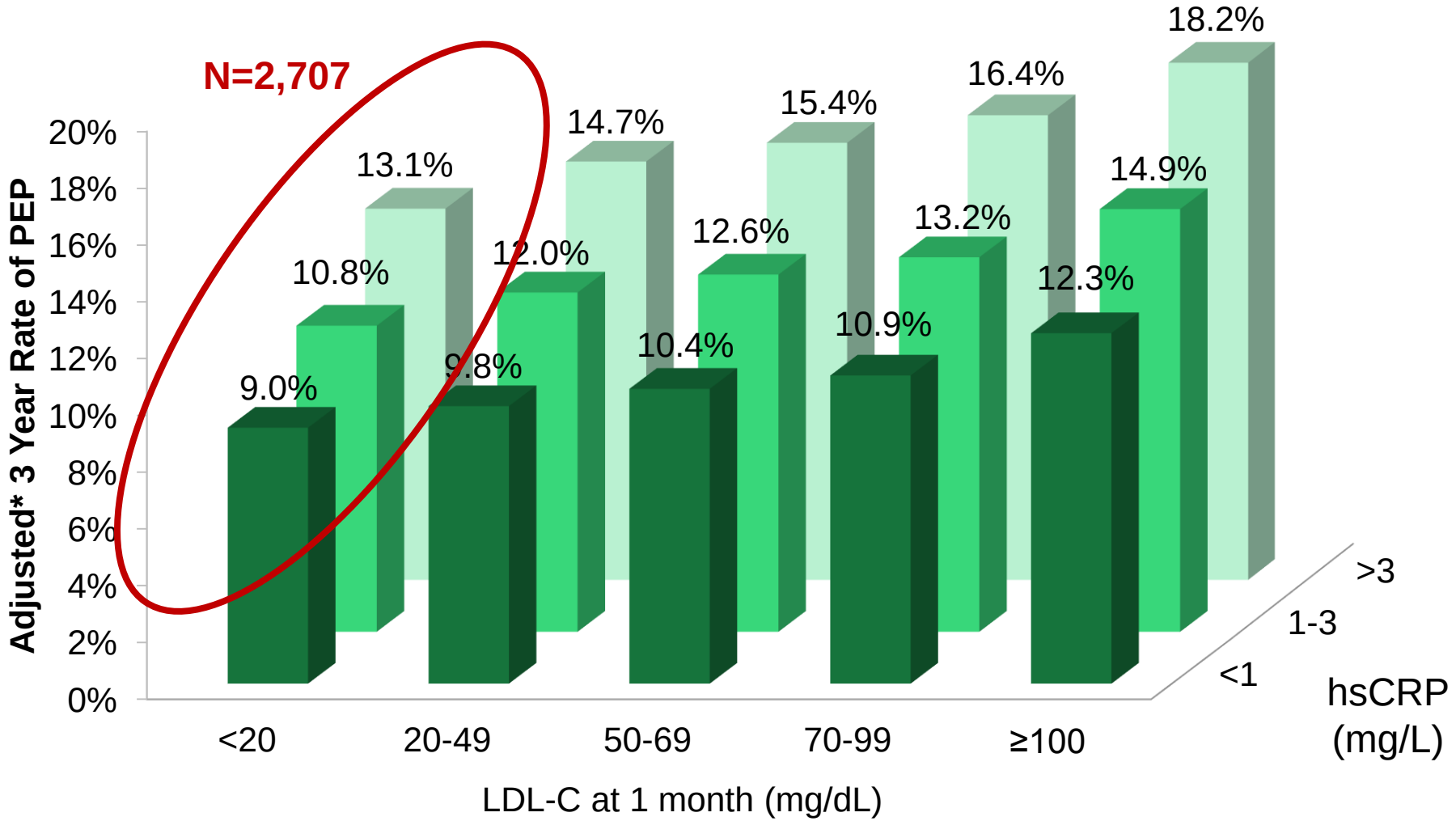


Clinical Benefit of Evolocumab by Baseline hsCRP



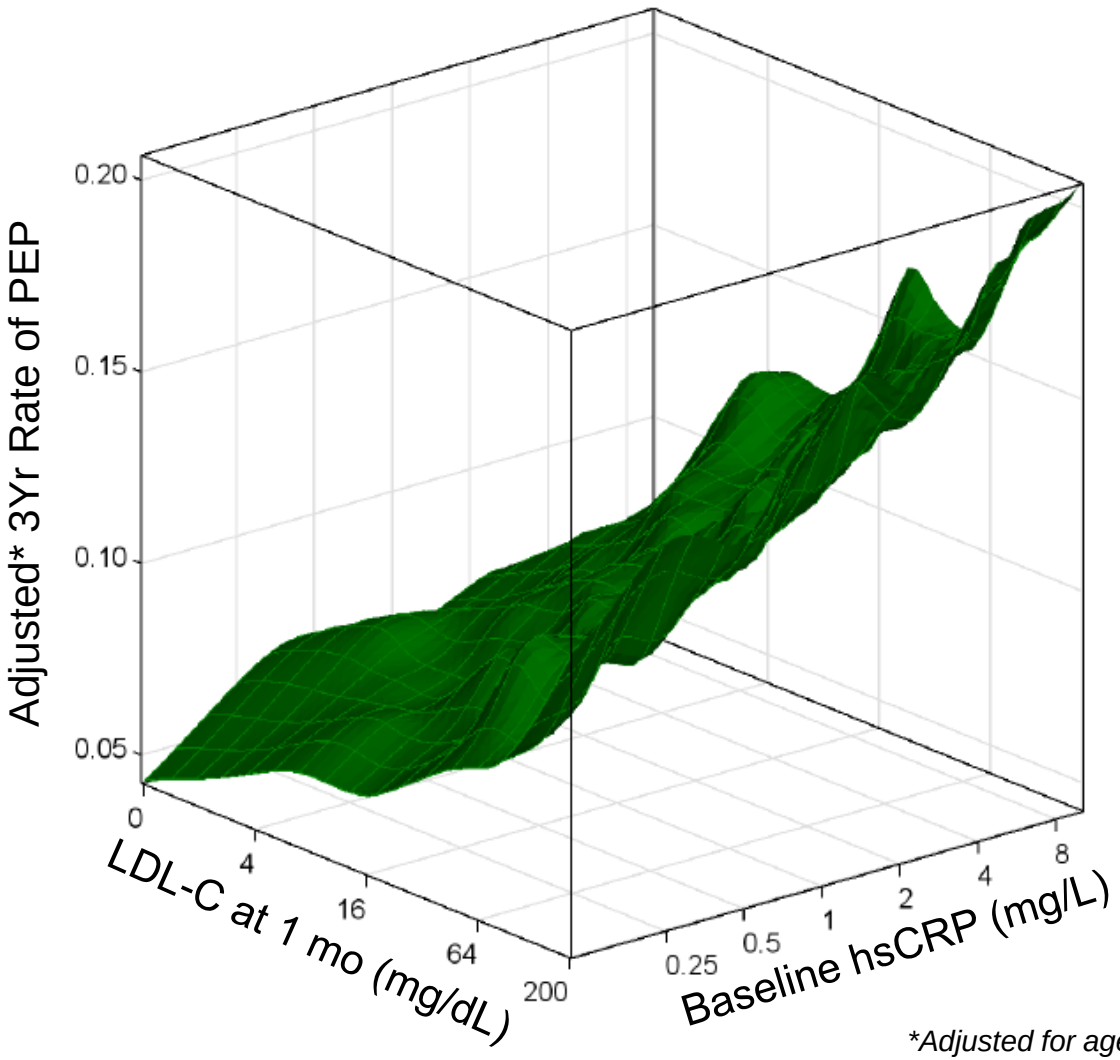
P-interaction for HR >0.05 for both

hsCRP Levels Risk Stratify for PEP Even When LDL-C<20mg/dL



*Adjusted for age, BMI, sex, race, region, prior MI, prior stroke, PAD, HTN, DM, CHF, smoking, eGFR<60, high-intensity statin, ezetimibe, baseline LDL-C, HDL-C and log(TG)

Inflammatory & Cholesterol Risk for PEP



LDL-C (per doubling):

- ***Adj* HR 1.09 (1.05-1.14)***
- ***p<0.0001***

hsCRP (per doubling):

- ***Adj* HR 1.09 (1.07-1.12)***
- ***p<0.0001***

**Adjusted for age, BMI, sex, race, region, prior MI, prior stroke, PAD, HTN, DM, CHF, smoking, eGFR<60, high-intensity statin, ezetimibe, baseline LDL-C, HDL-C and log(TG)*

Limitations

- **Analyses w/ on-treatment LDL-C values were not randomized; multivariable adjustment used to limit confounding due to differences in baseline characteristics by achieved LDL-C**

- **hsCRP was not measured at 1 month; simultaneous assessment of achieved LDL-C & hsCRP not possible.**
  - Stable ASCVD population
  - Minimal change in hsCRP over time
  - On statin at baseline → baseline hsCRP reflects residual inflammatory risk after standard LDL-C lowering Rx

Summary

- Relative benefit of evolocumab for ↓ risk of CV events was consistent irrespective of baseline hsCRP
- Pts w/ higher hsCRP had higher event rates;
  ∴ tended to experience greater <u>absolute</u> CV risk reduction with evolocumab
- CV event rates were independently associated with <u>both</u> LDL-C and hsCRP, even in pts with very low achieved LDL-C levels (<20 mg/dL)

Conclusions/Implications

- In pts with stable ASCVD
  - LDL-C reduction with evolocumab is beneficial across hsCRP strata with a trend towards greater absolute benefit in pts with higher hsCRP
  - LDL-C and hsCRP were independently associated with outcomes supporting the importance of both inflammatory and residual cholesterol risk in secondary prevention

Additional Details Available

Circulation

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