Long-term PCSK9 Inhibition with Evolocumab and Aortic Stenosis Events

An Analysis from FOURIER and FOURIER-Open Label Extension (OLE)

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Disclosure of Relevant Financial Relationships

I, Prakriti Gaba, am a member of the Thrombolysis in Myocardial Infarction Study Group, which has received grant support through Brigham and Women's Hospital (Boston, MA, USA) from Abbott, Amgen, Anthos Therapeutics, AstraZeneca, Bayer HealthCare Pharmaceuticals, Daiichi-Sankyo, Eisai, Intarcia, Ionis, MedImmune, Merck, Novartis, Pfizer, Quark Pharmaceuticals, Regeneron Pharmaceuticals, Roche, Siemens Healthcare Diagnostics, The Medicines Company, and Zora Biosciences.

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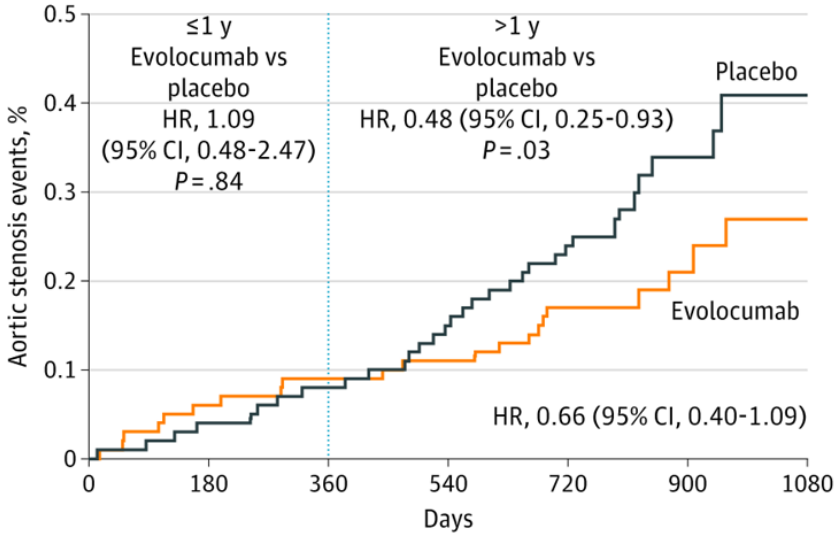
Faculty disclosure information can be found on the app

Background

Aortic valve stenosis (AS) is a progressive, life-threatening condition with no approved disease-modifying pharmacotherapy



In the parent FOURIER trial, evolocumab was associated with a lower risk of AS events in patients with atherosclerotic cardiovascular disease (ASCVD) beyond the 1st year of treatment

Bergmark et al. JAMA Card 2020; 5(6): 709-713.

Objectives

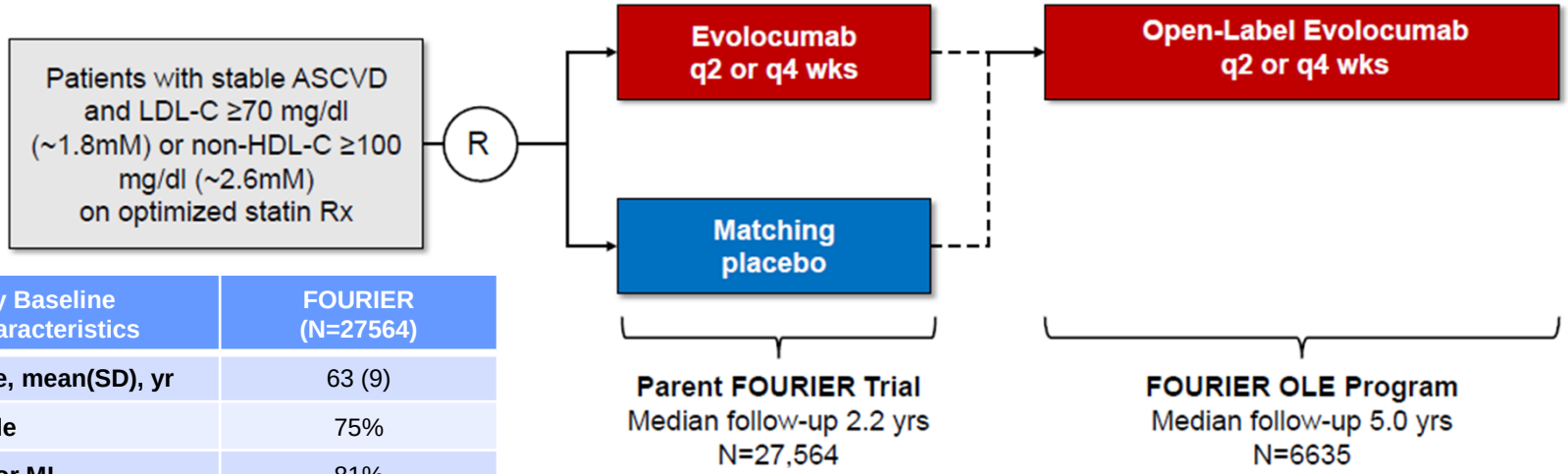
- To explore the associations between week 12 lipoprotein(a) and low-density lipoprotein cholesterol (LDL-C) levels and the risk of AS events

- To examine whether patients initially randomized to evolocumab in the parent trial have a lower risk of AS events

Methods

- **FOURIER**: 27,564 pts w/ stable ASCVD on optimized statin therapy
  - Randomized to evolocumab vs placebo (median f/u 2.2 yrs)
- **FOURIER-OLE**: 6635 pts from FOURIER
  - All transitioned to open-label evolocumab (additional median f/u 5 yrs)
- Aortic stenosis events defined as *new or worsening AS or SAVR/TAVR*
  - Review of the safety database blinded to treatment assignment and lipid levels
- Associations between week 12 Lp(a) and LDL-C levels and risk of AS events were examined
  - Adjusted for age, sex, DM, HTN, smoking, eGFR, and week 12 LDL-C or Lp(a)
- Effect of initial Rx randomization on risk of AS events was calculated for the overall period, 1st yr, and beyond 1st yr

Study Schema & Key Characteristics



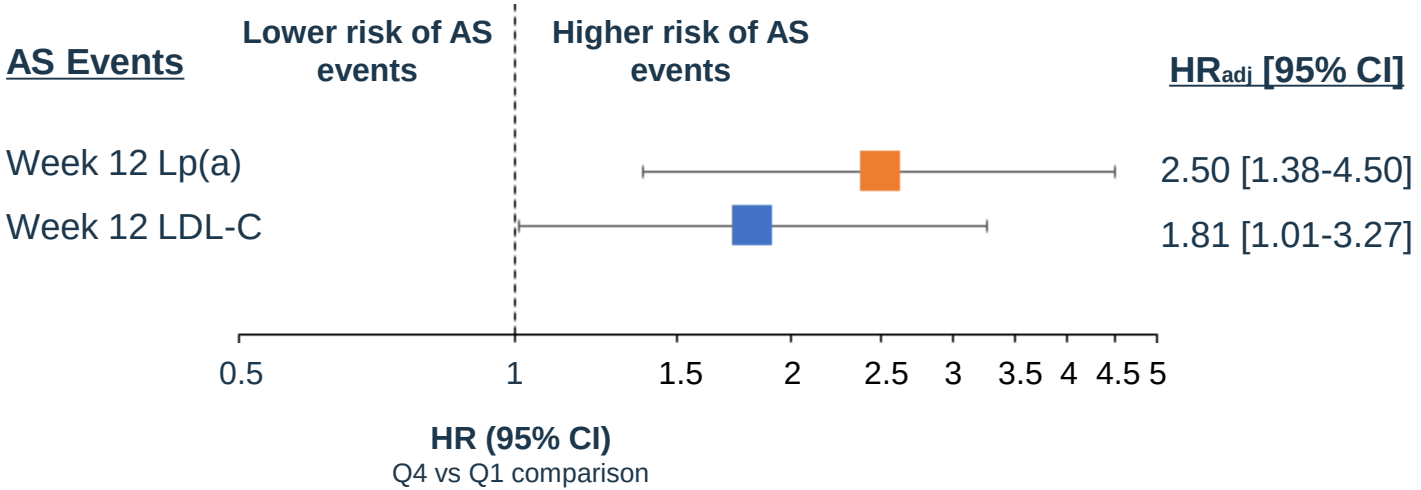
Key Baseline Characteristics	FOURIER (N=27564)
Age, mean(SD), yr	63 (9)
Male	75%
Prior MI	81%
High-intensity statin	69%
Lp(a), nmol/L*	37 (13-165)
LDL-C, mg/dL*	92 (80-109)

*median[IQR]

Sabatine et al. *NEJM* 2017; 376: 1713-1722.
O'Donoghue et al. *Circulation* 2022; 146: 1109-1119

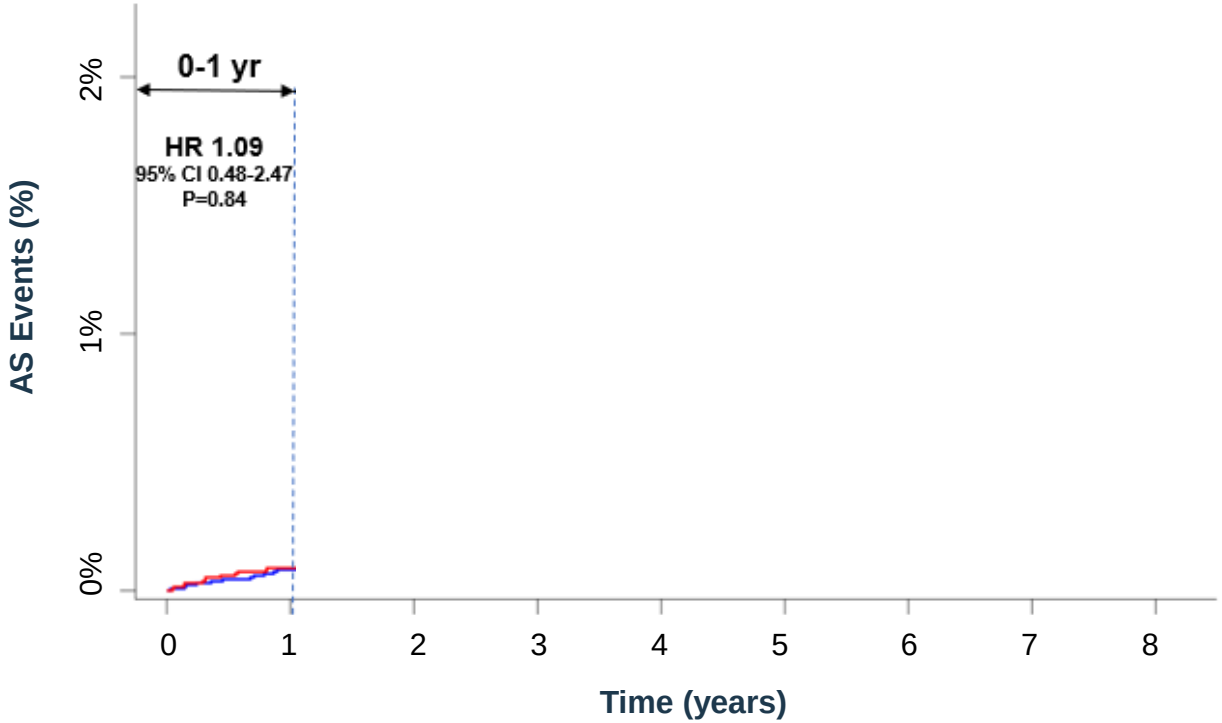
Lp(a), LDL-C & AS Events

120 pts experienced AS events over 90,661 person-yrs of follow-up (max 8.7 yrs)



Adjusted for age, sex, DM, HTN, smoking, eGFR, and week 12 LDL-C or Lp(a)

Risk of AS Events in the Long-Term with Evolocumab vs Placebo



AS events were defined as new or worsening aortic stenosis or undergoing SAVR/TAVR

Limitations

- FOURIER pts had stable ASCVD with baseline LDL-C ≥70 mg/dL or non-HDL ≥ 100 mg/dL on optimized statin therapy; thus results may not apply to all pts in clinical practice
- To enter OLE, pts had to be alive and on study drug at the end of FOURIER and be willing to participate in the extension
- Modest number of AS events requires further confirmation in larger study
- Crossover into OLE among placebo pts may have influenced the ability to discern a difference between Rx arms in later years

Conclusions

- Among pts with ASCVD, higher week 12 Lp(a) and LDL-C levels were associated with higher rates of AS events in the long-term
- Risk of AS events tended to be lower with initial randomization to evolocumab, particularly after the 1st year of treatment
- The effect of PCSK9 inhibition on AS progression warrants investigation in a dedicated randomized trial