Reduction in Total Cardiovascular Events with the PCSK9 Inhibitor Evolocumab in Patients with Cardiovascular Disease in the Combined FOURIER and FOURIER Open-Label Extension (OLE) Studies

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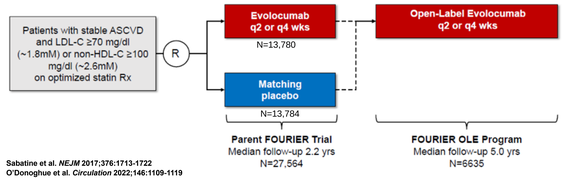
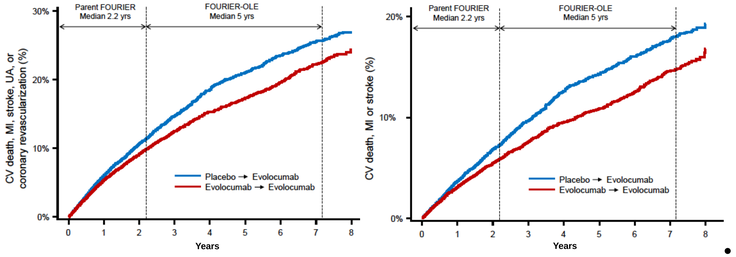
BACKGROUND

FOURIER & FOURIER-OLE Study Design



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

- Earlier intensive LDL-C lowering with the PCSK9i evolocumab (EVO) reduced first major vascular events in patients with stable ASCVD in FOURIER and for the first 3 years in FOURIER-OLE (akin to the legacy effects seen with statins)



- ***However, traditional survival analyses only focus on 1st events***

OBJECTIVE

To examine the long-term impact of earlier initiation of intensive LDL-C lowering with evolocumab on total (first+recurrent) CV events in patients with ASCVD on statin therapy

DISCLOSURES

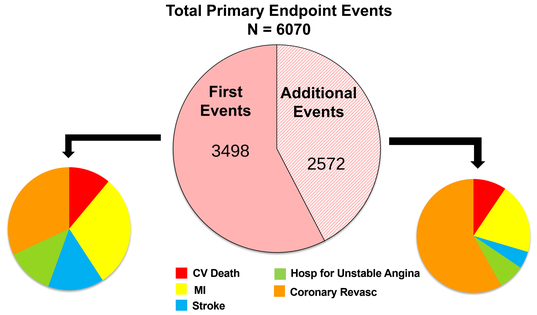
FOURIER & FOURIER-OLE were funded by research grants from Amgen Inc. SAM and MSS are members of the TIMI Study Group, which has received institutional grant support through the Brigham and Women's Hospital from: Abbott, Amgen, Anthos Therapeutics, ARCA Biopharma, AstraZeneca, Daiichi-Sankyo, Eisai, Intarcia, Ionis Pharmaceuticals, Janssen Research and Development, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals, Roche, Siemens Healthcare Diagnostics, Softcell Medical Limited, Zora Biosciences. MSS has consulted for Althera, Amgen, Anthos Therapeutics, AstraZeneca, Beren Therapeutics, Boehringer Ingelheim, Fibrogen, Intarcia, Merck, Moderna, Novo Nordisk, Precision BioSciences, Silence Therapeutics

METHODS

- We evaluated all primary endpoint events (PEP: CV Death, MI, stroke, UA, or coronary revasc) in 27,564 Pts in the parent FOURIER trial (median f/u 2.2 yrs) + 3 yr f/up in 6,635 Pts who continued in FOURIER-OLE, in which all Pts received EVO
- Negative binomial regression was used for the primary analysis
- Wei, Lin, Weissfeld model was used for the sensitivity analysis

RESULTS

Figure 1. Breakdown of First and Additional Types of Event



- Evolocumab prevented 290 1st PEP events (Hazard ratio [HR 0.83, 0.78-0.89) and **382 additional recurrent events** (Risk ratio [RR] 0.74, 0.66-0.83), for a total of 672 events prevented with EVO (RR 0.81, 0.74-0.87) (Fig 2A)
- A similar pattern was seen for CVD/MI/stroke (Fig 2B)
- The magnitude of benefit grew for later events: HR 0.83 → 0.76 → 0.71 → 0.60 (P-trend <0.001) (Fig 3)
- There were significant reductions in total MIs (RR 0.72, p<0.001), ischemic strokes (RR 0.78, p=0.007), & revascs (RR 0.78, p<0.001) (Fig 4)

LIMITATIONS

- All patients in the extension were treated with open-label EVO, resulting in no concurrent placebo arm during this period

RESULTS

Fig 2A & B. Total Primary & Key Secondary Endpoint Events by Initial Allocation in FOURIER

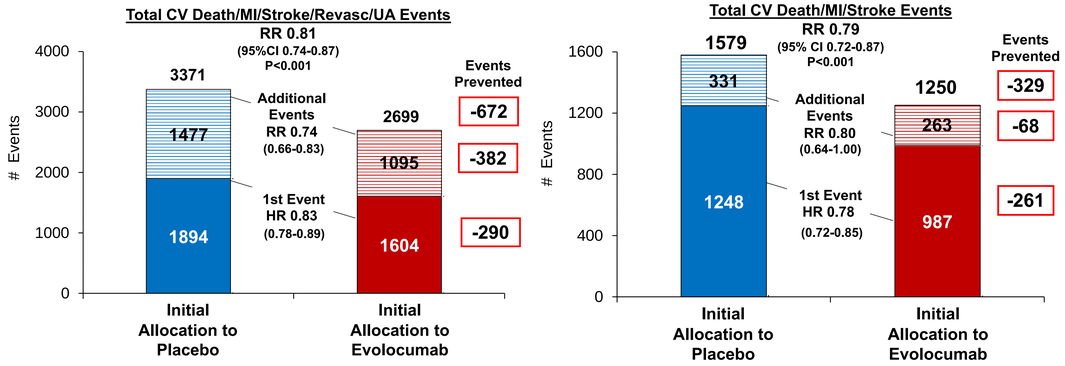


Figure 3. Primary Endpoint Events using Wei, Lin, Weissfeld Model

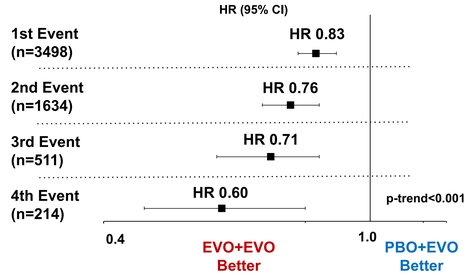
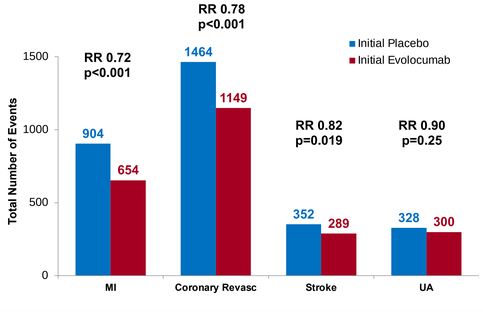


Figure 4. Total Events by Type of Event



CONCLUSIONS

- **Over >5 yrs of follow-up in patients with ASCVD on statin therapy, earlier initiation of intensive LDL-C lowering with evolocumab significantly reduced both first & recurrent CV events, with more than double the number of total events prevented as compared with 1st events only**
- **These data support earlier and long-term use of evolocumab to prevent CV events**