Consistency of LDL-C Reduction with Evolocumab: An Analysis from FOURIER

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BACKGROUND

- Evolocumab, a fully human mAb against PCSK9, decreased LDL-C by 59% & reduced the risk of CV death, MI or stroke by 20% in pts with stable atherosclerotic cardiovascular disease[1]. Development of neutralizing antibodies was not seen in any patient.
- Recently, concerns have been raised about significant interindividual variability in LDL-C reduction in response to bococizumab, a humanized but not fully human mAb against PCSK9, against which neutralizing antibodies developed[2].
- We evaluated the interindividual variability in LDL-C reduction in response to PCSK9 inhibition with evolocumab in the FOURIER trial.

METHODS

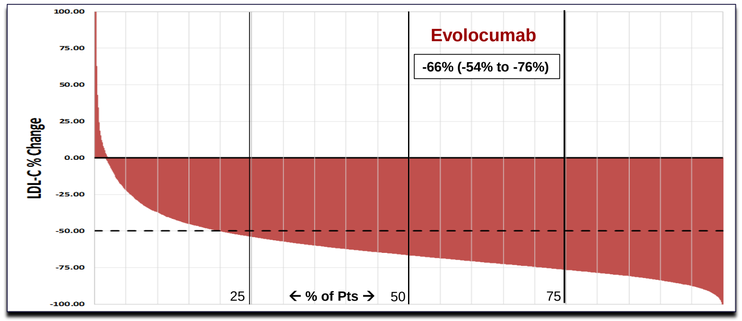
- FOURIER was a randomized trial of 27,564 pts with ASCVD & LDL-C ≥70 mg/dL on background statin therapy. Pts had to be on optimized, stable lipid-lowering regimen for ≥4 wks prior to randomization. Pts were randomized to evolocumab or placebo. The median f/u was 2.2 years.
- At the first 2 or 3 study drug administrations, pts were to be instructed and supervised in the administration of study drug. After the wk 4 visit, pts could administer study drug on their own.
- **In this exploratory analysis, we analyzed the interpatient variability in % LDL-C reduction with evolocumab compared with placebo at 4 weeks after randomization.**
- For this analyses, we excluded following pts:
  - Did not receive study drug, acknowledged an alteration in background lipid-lowering therapy, or had missing LDL-C levels at wk 4 (n=2,250).
  - High baseline LDL-C variability prior to randomization (>90th percentile on difference between screening phase and randomization lab values; n=3,533).
- The final cohort consisted of 21,781 pts.

STATISTICAL ANALYSIS

- We analyzed the % change in LDL-C between baseline & 4 wks.
- Waterfall plots were used to display the interindividual variation in LDL-C reduction with evolocumab & placebo.
- To generate placebo-controlled difference, the % LDL-C reduction was rank ordered among pts in each arm & the value in the placebo arm was subtracted from the corresponding value in the evolocumab arm.

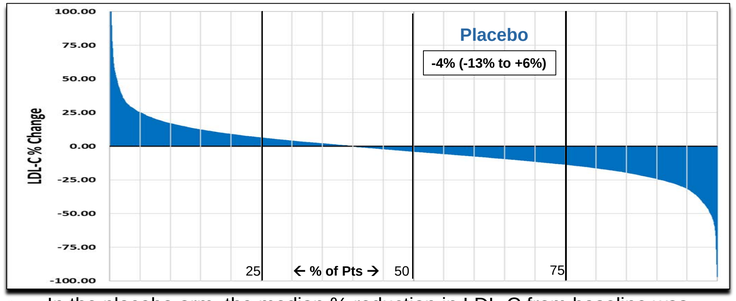
RESULTS

Fig 1. Waterfall plot showing distribution of % change in LDL-C at 4 wks in the evolocumab arm.



- In the evolocumab arm, the median % reduction in LDL-C from baseline was 66% (IQR 54-76%) at 4 wks **(Fig 1)**.
- 80% of pts on evolocumab had a LDL-C reduction ≥50%.
- 93% of pts on evolocumab had a LDL-C reduction ≥30%.
- 98% of pts on evolocumab had at least some reduction in LDL-C.
- Of the 20% with <50% reduction in LDL-C at 4 wks, 98% had LDL-C measured later within 1st year, and of those 74% had a LDL-C reduction ≥50%.

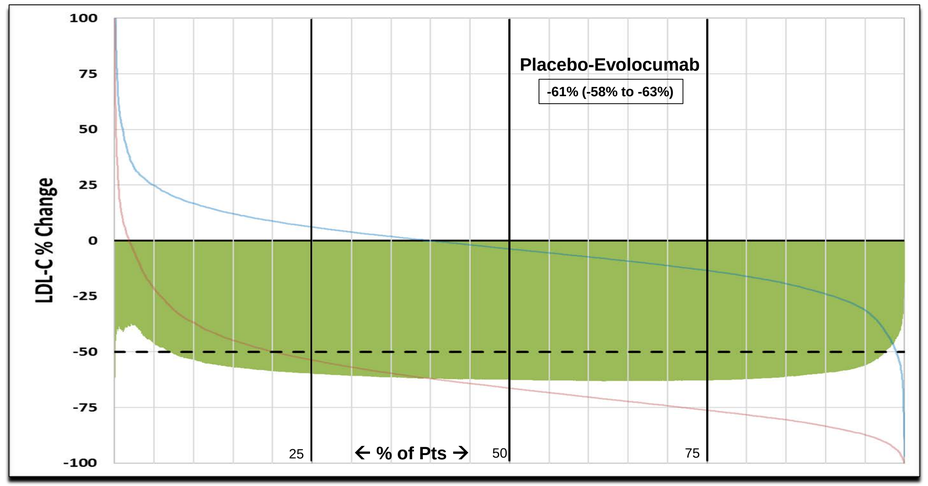
Fig 2. Waterfall plot showing distribution of % change in LDL-C at 4 wks in the placebo arm.



- In the placebo arm, the median % reduction in LDL-C from baseline was 4% (IQR 13% reduction to 6% increase) at 4 wks **(Fig 2)**.
- Despite the exclusion of pts who altered background lipid-lowering therapy, ~5% at both ends of the distribution showed large (≥25%) increases & decreases in LDL-C.

RESULTS

Fig 3. Waterfall plot showing distribution of placebo-adjusted % change in LDL-C at 4 wks (Placebo-Evolocumab).



- In the placebo-controlled analysis, the median % reduction in LDL-C from baseline was 61% (IQR 58-63) at 4 wks **(Fig 3)**.
- 91% of pts on evolocumab had a LDL-C reduction ≥50%**.**
- 97% of pts on evolocumab had a LDL-C reduction ≥40%.

CONCLUSIONS

- In a large clinical trial, variability of LDL-C levels is seen even in the placebo arm and likely reflects:
  - unacknowledged changes in background medications
  - unappreciated errors in study drug administration
  - mistakes in lab sample labeling/handling, or errors with assays
- **Taking such variability into account, there is a highly consistent robust reduction in LDL-C (≥50% in >90% of pts) with evolocumab.**

DISCLOSURE OF FACULTY RELATIONSHIPS: AQ: Research Grant; Significant; NHLBI T32007604. **RPG:** Research Grant; Significant; Amgen, DaiichiSankyo, Merck. Honoraria; Modest; BoehringerIngelheim, BMS, CVS Caremark, GSK, Portola, Pfizer. Honoraria; Significant; Amgen, Amarin, Merck, DaiichiSankyo, Lexicon. **ACK:** Honoraria; Modest; Abbott, Amgen. Consultant/Advisory Board; Modest; Abbott, Amgen. Other; Modest; Lecture fees: AstraZeneca, Pfizer, Support of an education activity: Mylan. **JFK:** Research Grant; Significant; Amgen, Abbott Laboratories, AstraZeneca, Critical Diagnostics, DaiichiSankyo, Eisai, GlaxoSmithKline, Intarcia, Merck, Roche Diagnostics, Takeda, Gilead, Poxel, Novartis, MedImmune, Janssen, Genzyme. **SAM:** Research Grant; Significant; Amgen, Abbott Laboratories, AstraZeneca, Critical Diagnostics, DaiichiSankyo, Eisai, GlaxoSmithKline, Intarcia, Merck, Roche Diagnostics, Takeda, Gilead, Poxel, Novartis, MedImmune, Janssen, Genzyme. **TL**: Employee of Amgen **CK**: Employee of Amgen. **SMW**: Employee of Amgen. **PSS**: Research Grant; Amgen; Consultant; Amgen, Pfizer. **TRP**: Research Grant; Significant; Amgen; Honoraria; Amgen, Sanofi, Merck, BI, MDCO. **MSS**: Research Grant; Significant; Amgen, AstraZeneca, DaiichiSankyo, Eisai, GSK, Intarcia, Janssen Research and Development, MedImmune, Merck, Novartis, Pfizer, Poxel, Takeda. Consultant/Advisory Board; Modest; CVS Caremark, Intarcia, Janssen Research and Development, MedImmune, Merck. Consultant/Advisory Board; Significant; Amgen, Esperion, Ionis.

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