Atherothrombotic Risk Stratification and Magnitude of Benefit of Evolocumab in FOURIER

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BACKGROUND

- Evolocumab (EvoMab) significantly reduced cardiovascular (CV) death, MI or stroke by 20% (absolute risk reduction [ARR] of 2% at 3 years) in pts with atherosclerosis
- However, pts with atherosclerosis vary in their risk for recurrent CV events.
- The TIMI Risk Score for Secondary Prevention (TRS 2ºP), a simple risk stratification tool previously derived and validated for prediction of recurrent CV events in a large population with a history of prior MI (TRA 2ºP-TIMI 50), predicted benefit from lipid lowering with ezetimibe added to simvastatin in post-ACS pts (IMPROVE-IT). [1-2]
- We hypothesized that the TRS 2ºP would identify pts who have the greatest potential for benefit from EvoMab in the FOURIER trial.

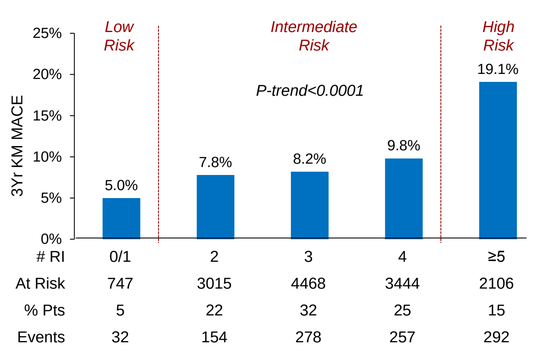
METHODS

- We prospectively applied TRS 2ºP to 27,564 pts with atherosclerosis and an LDL-C≥70mg/dL or non-HDL-C≥100mg/dL randomized to EvoMab or placebo (Pbo) in FOURIER.
- The total risk for each pt was defined by the arithmetic sum of the number of risk indicators (RI) present (range 0-10). Simple risk categories were defined as low (RI=0-1), intermediate (2-4), and high (≥5).
- As the TRS 2ºP was applied here in a broader population of pts with CAD with and without a prior MI, the score was modified to add 1 point for prior MI, when present
- The absolute risk as well as the relative (RRR) and absolute (ARR) risk reductions in the key secondary endpoint of CV death, MI or stroke (MACE) with EvoMab versus Pbo were calculated by TRS 2ºP strata.

RESULTS

Figure 1: Risk Stratification for MACE with Placebo

Risk Indicators	Points
CHF	1
HTN	1
Age≥75	1
DM	1
Prior Stroke	1
Prior CABG	1
PAD	1
eGFR<60	1
Current Smoking	1
Prior MI	1
Max Possible	10



- The integer-based scheme showed a strong, graded relationship with the rate of CV death, MI or CVA and the components at 3 yrs in both treatment arms (Fig 1; p-trend < 0.0001 for all endpoints; c-statistic = 0.61 [0.67 in prior validation set]).

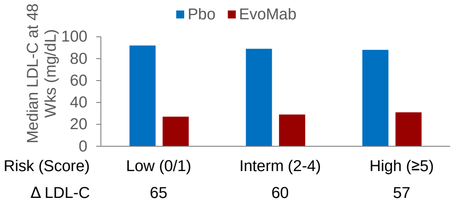
RESULTS

Table 1: Baseline Characteristics by Risk Category

	Low (0-1) (N=1524, 5%)	Intermediate (2-4) (N=21726, 79%)	High (≥5) (N=4314, 16%)
Age in yrs (median, IQR)	64 [54, 68]	62 [56, 68]	66 [59, 74]
Age≥75 yrs	0	7	25
Female	16	25	27
Diabetes	0	32	71
Current smoking	0.1	28	37
Hypertension	0.1	82	98
Peripheral arterial disease	3	11	30
Prior CABG	0	15	48
Prior stroke	11	18	30
eGFR <60 ml/min/1.73m2	0	13	54
Prior MI	86	80	86
High intensity statin use	69	69	71
LDL-C - mg/dL (median, IQR)	91 [80, 106]	92 [80, 109]	92 [80, 110]

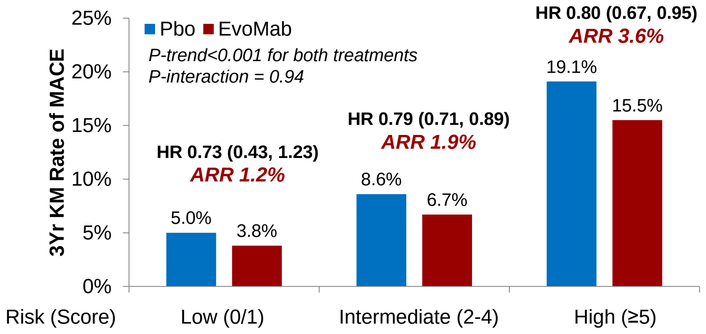
Number denotes proportion (%) unless otherwise specified. P-value <0.05 for all variables for comparison across risk categories.

Figure 2: 48 Wk Achieved LDL-C by Risk Category & Treatment



EvoMab resulted in a 57-65mg/dL absolute difference in LDL-C at 48 wks compared to Pbo across TRS 2ºP risk categories (Fig 2).

Figure 3: MACE by Risk Category & Randomized Treatment



- Low-risk pts had a 1.2% ARR, intermediate-risk a 1.9% ARR and high-risk a 3.6% ARR in MACE at 3 years with EvoMab vs Pbo, ***translating to a NNT$_{3Yr}$ of 83, 53 and 28***, respectively (Fig 3).

RESULTS

Figure 4: Individual Outcomes by Risk Category & Randomized Treatment

Fig 4A: Cardiovascular Death

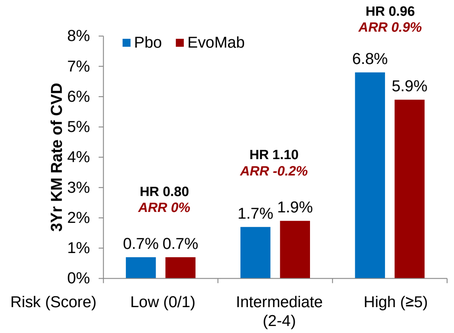
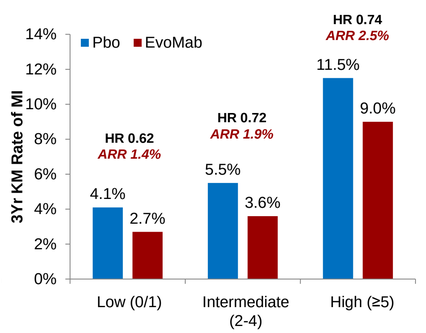
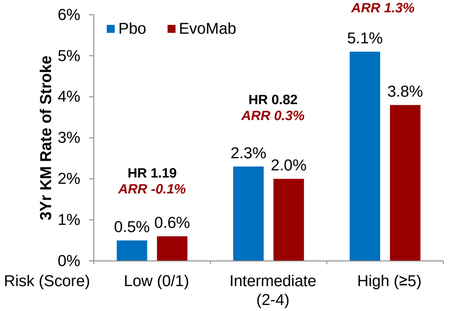


Fig 4B: Myocardial Infarction



P-trend<0.001 for all endpoints for both treatments
P-interaction > 0.05 for all endpoints

Fig 4C: Stroke



Evaluation of individual endpoints showed a ARR in high-risk pts of 0.9% for CV death, 1.3% for CVA, and 2.5% for MI, respectively (Fig 4A-C).

CONCLUSIONS

- In FOURIER, the TIMI Risk Score for Secondary Prevention (TRS 2ºP):
  - Predicted a gradient of risk for major adverse CV events
  - Identified high-risk pts w/ ASCVD who demonstrate a pattern of ***greater ARR*** in major CV events with EvoMab, with an **NNT$_{3Yr}$ of 28** in the highest risk.
- This strategy may prove useful to personalize the intensification of secondary preventative therapies.

DISCLOSURE OF FACULTY RELATIONSHIPS: EAB: Research Grant; Significant; Amgen, DaiichiSankyo, Eisai, Merck, Takeda, Novartis. Honoraria; Modest; Novartis, Lexicon. Consultant/Advisory Board; Modesmay be a t; Merck, Novartis. Consultant/Advisory Board; Significant; Daiichi Sankyo, Servier. DAM: Research Grant; Significant; Amgen, Abbott Laboratories, AstraZeneca, Critical Diagnostics, DaiichiSankyo, Eisai, GlaxoSmithKline, Intarcia, Merck, Roche Diagnostics, Takeda, Gilead, Poxel, Novartis, MedImmune, Janssen, Genzyme. T.R. Pedersen: None. E. Kanevsky: 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. RPG: Research Grant; Significant; Amgen, DaiichiSankyo, Merck. Honoraria; Modest; BoehringerIngelheim, BMS, CVS Caremark, GSK, Portola, Pfizer. Honoraria; Significant; Amgen, Amarin, Merck, DaiishiSankyo, Lexicon. P.S. Sever: None. ACK: Honoraria; Modest; Abbott, Amgen. Consultant/Advisory Board; Modest; Abbott, Amgen. Other; Modest; Lecture fees: AstraZeneca, Pfizer. Support of an education activity: Mylan. 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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