Relationship Between Baseline LDL-C and %LDL-C Reduction with Evolocumab in the FOURIER Trial

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Background

Background

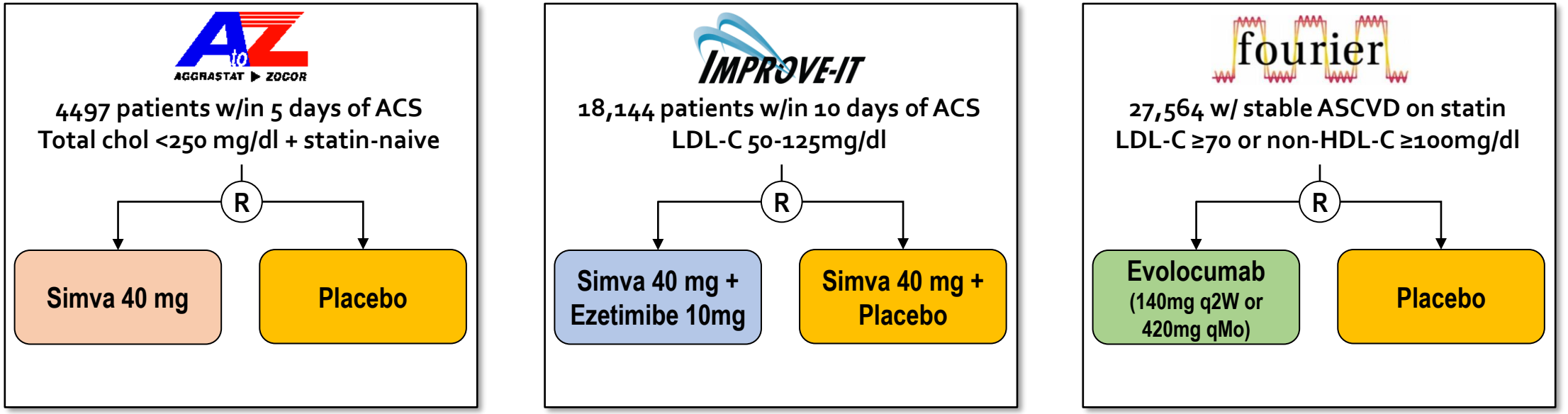
- Statins, ezetimibe and PCSK9 inhibitors are commonly used to lower LDL-C and therefore to lower ASCVD risk
- Intensity of lipid lowering therapy is defined by %LDL-C reduction
- It is commonly assumed %LDL-C lowering is intrinsic to a drug with little variation by patient characteristics

Objective

- To evaluate association between baseline LDL-C and %LDL-C reduction with a statin, ezetimibe and a PCSK9 inhibitor

Methods and Materials

3 double-blind, placebo-controlled RCTs of lipid-lowering therapies



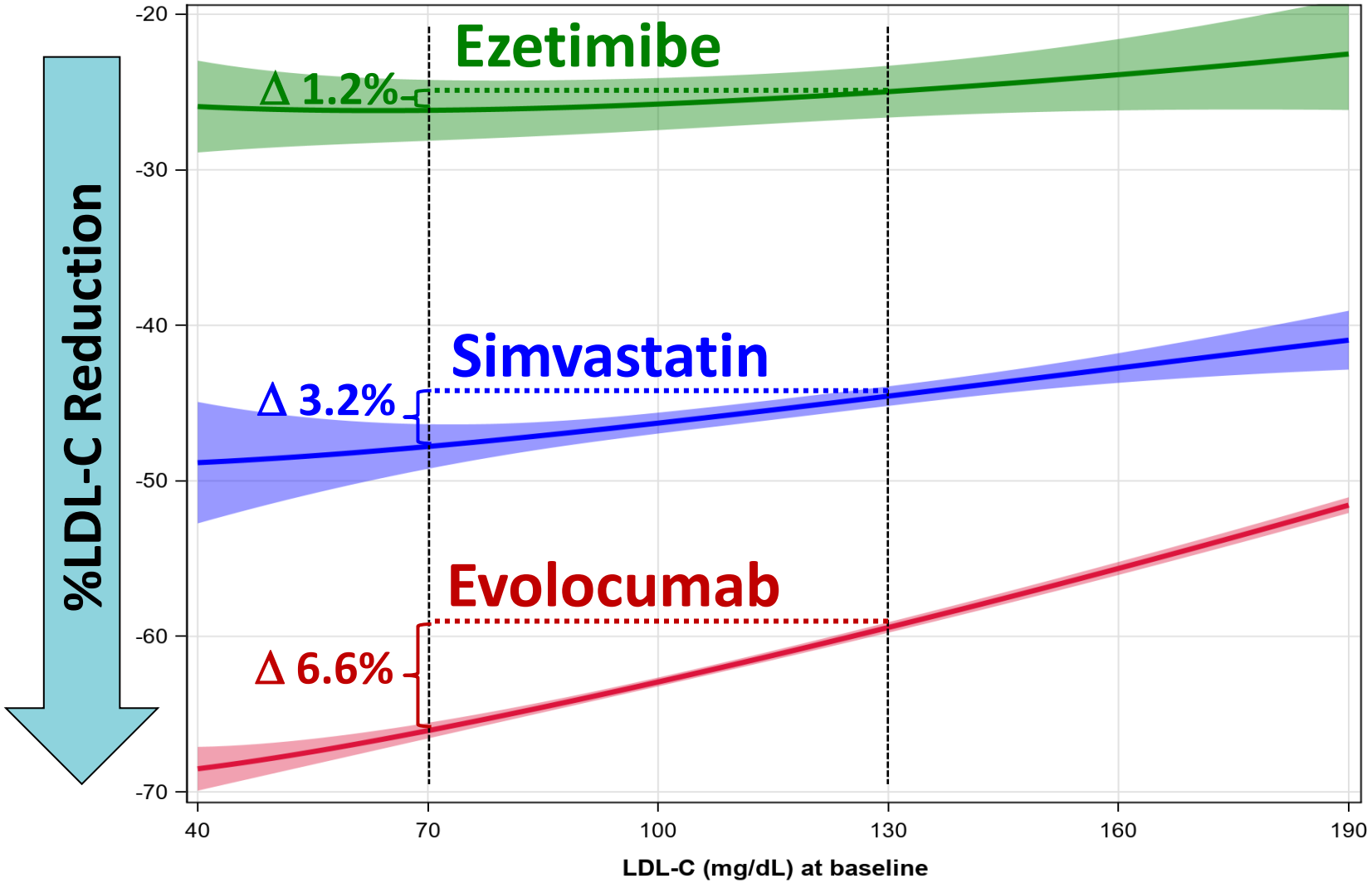
- Analyses restricted to patients on study drug with LDL-C values at baseline and follow-up timepoint (1 month for simvastatin & ezetimibe; 3 months for evolocumab).

- %LDL-C calculated as follows: used generalized linear regression to model achieved LDL-C as function of baseline LDL-C in each arm of each trial; %LDL-C reduction estimated from the difference between treatment and placebo achieved LDL-C.

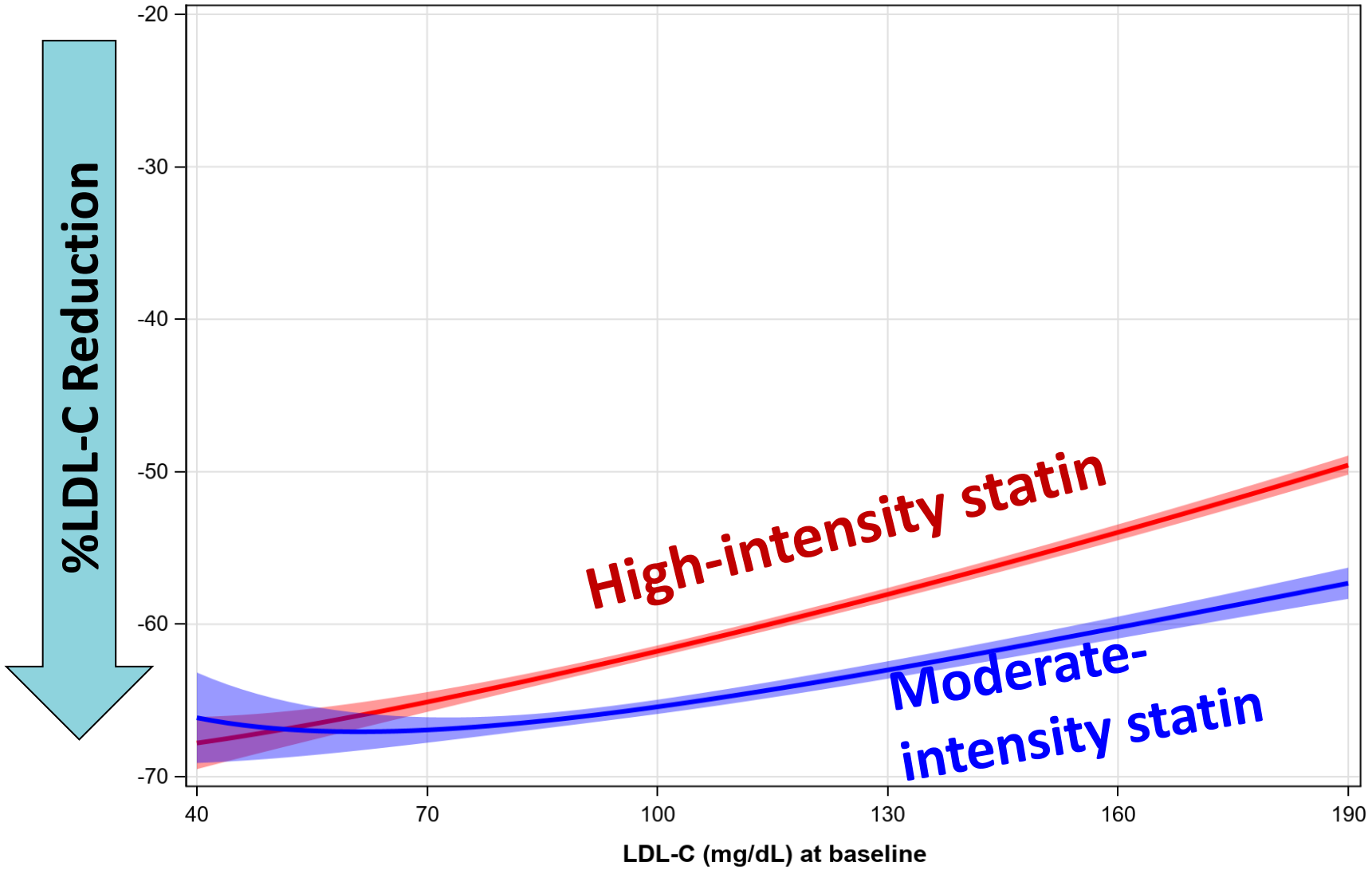
Study Population

	A to Z – TIMI 21	IMPROVE-IT	FOURIER
Lipid Lowering Agent	Simvastatin	Ezetimibe	Evolocumab
N in analysis population	3187	10,680	25,847
Age, median (IQR), yrs	61	62	63
Female (%)	23	23	24
Caucasian (%)	86	83	85
Diabetes Mellitus (%)	20	21	36
Baseline LDL-C, median (IQR), mg/dL	113 (95-131)	83 (67-99)	91.5 (79.5-108.5)
Achieved LDL-C in placebo arm, median (IQR), mg/dL	124 (105-145)	62 (51-76)	88 (75-106)
Achieved LDL-C in treatment arm, median (IQR), mg/dL	67 (53 – 82)	45 (36-57)	28 (19-43)

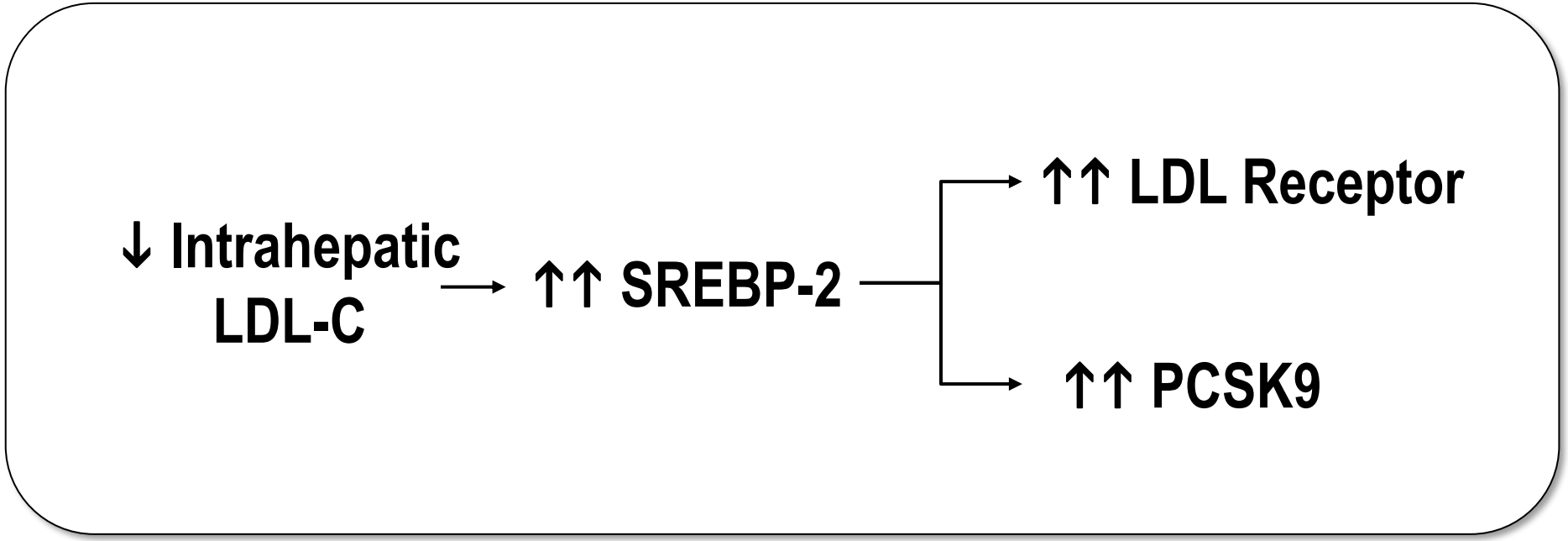
%LDL-C Lowering By Baseline LDL-C



FOURIER %LDL-C Lowering, Stratified By Statin



Possible Mechanism



- In the setting of lower intrahepatic LDL-C, SREBP-2 is upregulated
- Higher levels of SREBP-2 → ↑ synthesis of both the LDL receptor and, as a counter-regulatory brake, PCSK9
- **In that setting, PCSK9 inhibition may lead to particularly greater LDL receptor activity**

Limitations

- A-to-Z and IMPROVE-IT both enrolled immediately post-ACS, whereas FOURIER did not
- Although baseline LDL-C associated with magnitude of % LDL-C reduction, cannot prove causality; other factors could also be at play
- Observations should be repeated in studies with other PCSK9 inhibitors to confirm class-effect

Conclusion

- **Lower baseline LDL-C is associated with 6.6% absolute greater LDL-C reduction for evolocumab**

- **These data are encouraging for reaching the progressively lower LDL-C targets that are being set**