



Characterization of Types and Sizes of Myocardial Infarction Reduced with Evolocumab in FOURIER

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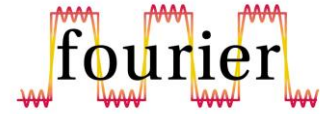
On behalf of the FOURIER Investigators

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Background

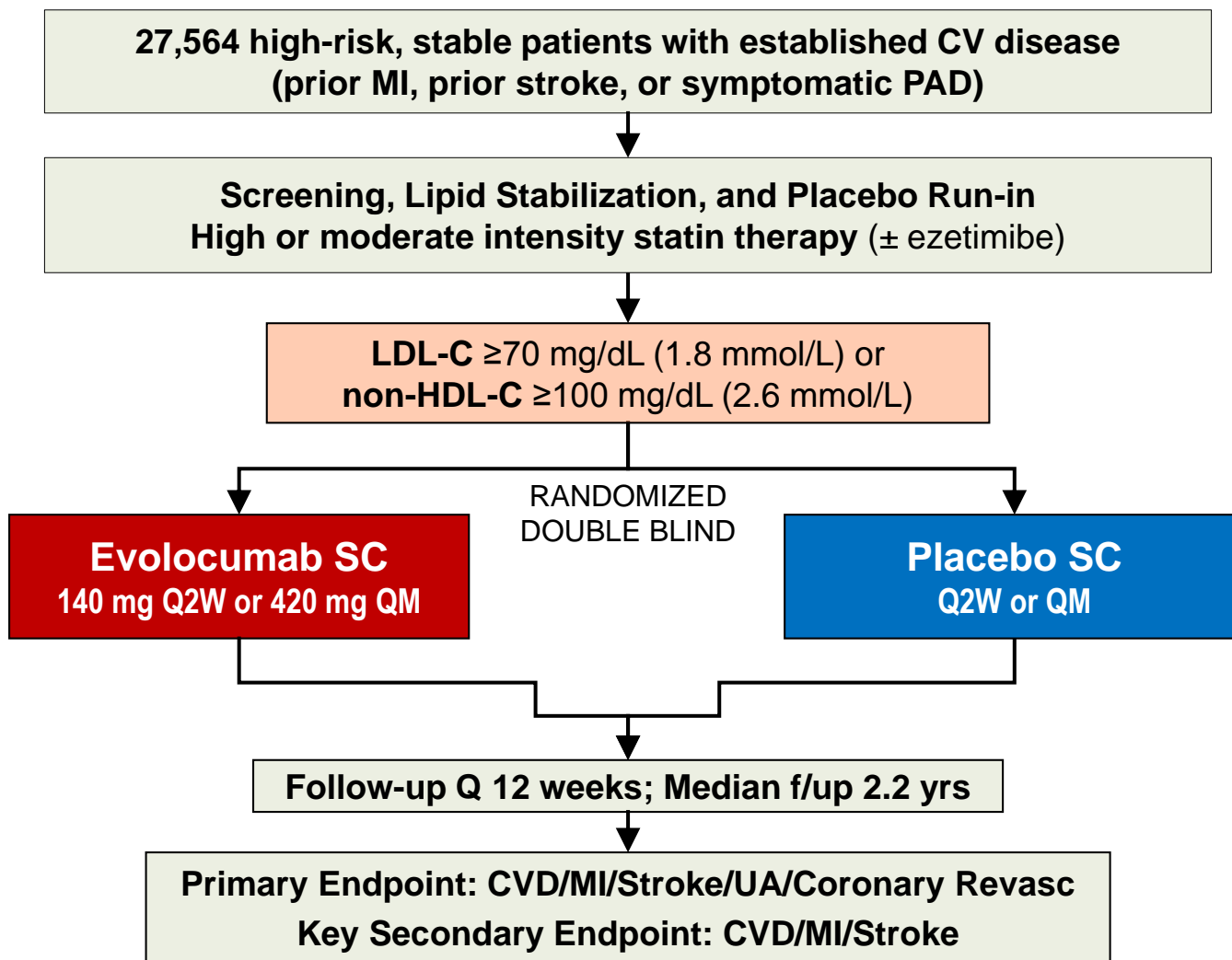


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- **Decades of lipid-lowering trials have shown that LDL reduction with statins reduces myocardial infarction.**
 - **The FOURIER trial compared the PCSK9 inhibitor evolocumab to placebo in patients on statin therapy and showed a significant reduction in cardiovascular events proportional to LDL reduction and time.**
 - **We sought to further characterize the effects of evolocumab on myocardial infarction.**



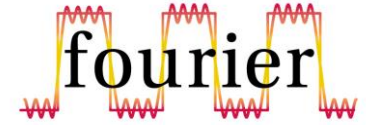


Trial Design

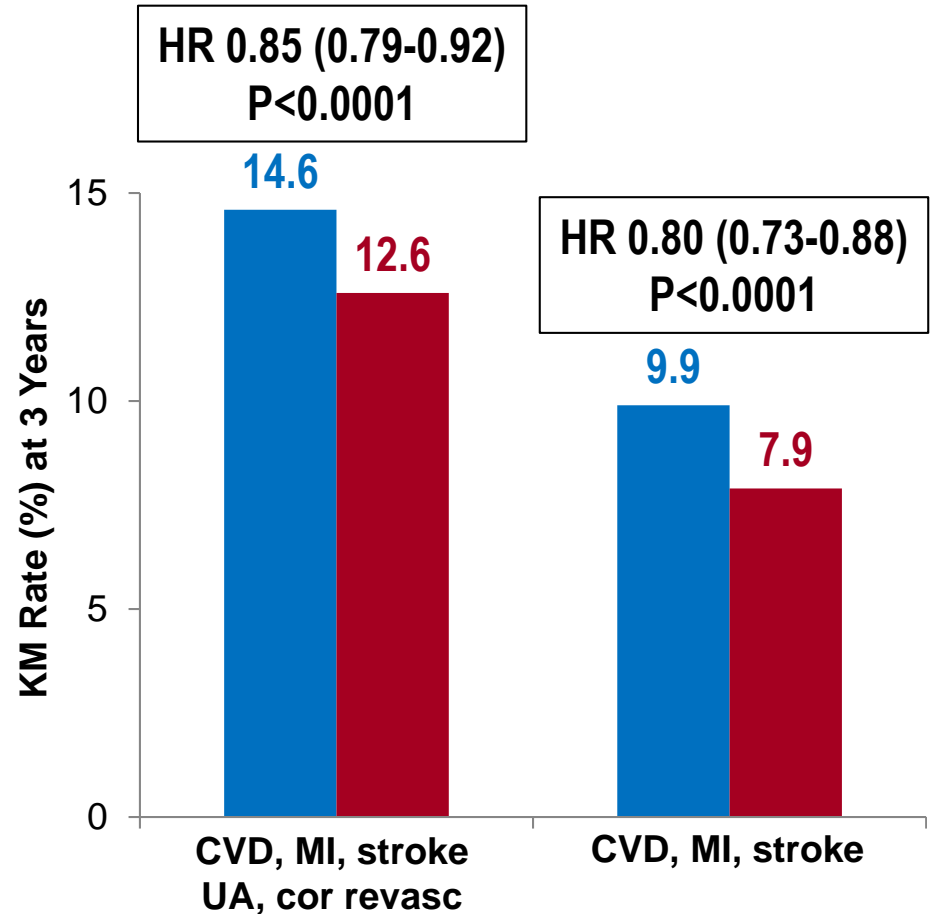
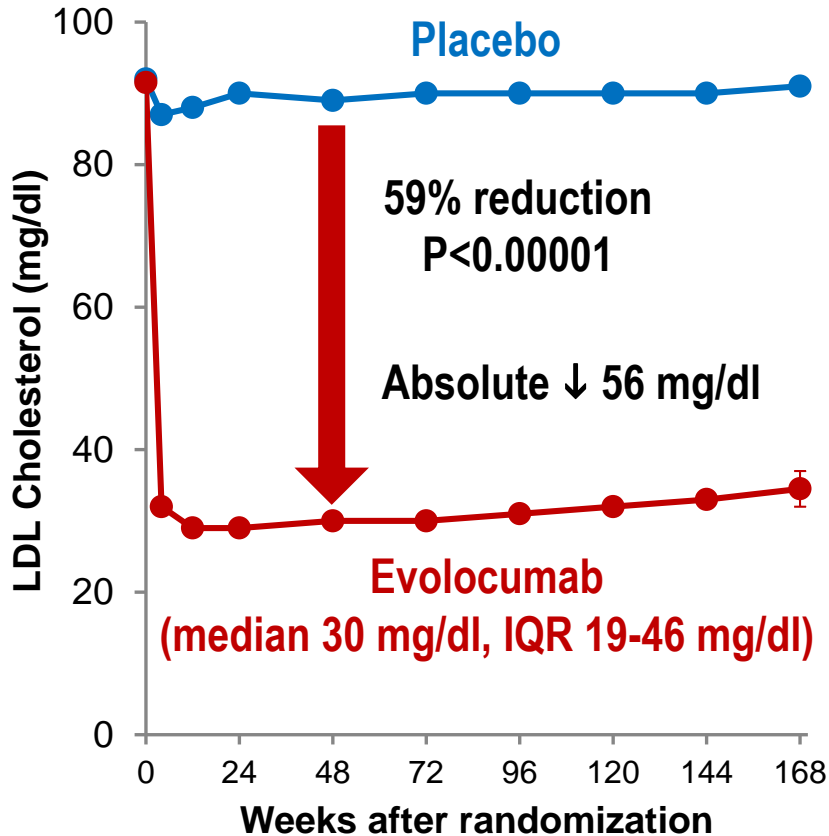




Summary of Effects of PCSK9i Evolocumab



- ↓ LDL-C by 59% down to a median of 30 mg/dl
- ↓ CV outcomes in patients on statin
- Safe and well-tolerated





Types of CV Outcomes



Endpoint	Evolocumab (N=13,784)	Placebo (N=13,780)	HR (95% CI)
	<i>3-yr Kaplan-Meier rate</i>		
CVD, MI, stroke, UA, or revasc	12.6	14.6	0.85 (0.79-0.92)
CV death, MI, or stroke	7.9	9.9	0.80 (0.73-0.88)
Cardiovascular death	2.5	2.4	1.05 (0.88-1.25)
MI	4.4	6.3	0.73 (0.65-0.82)
Stroke	2.2	2.6	0.79 (0.66-0.95)
Hosp for unstable angina	2.2	2.3	0.99 (0.82-1.18)
Coronary revasc	7.0	9.2	0.78 (0.71-0.86)





Hypothesis



We hypothesized that:

- 1. In this stable population, spontaneous MI would predominate**
- 2. PCSK9 inhibition with evolocumab would reduce spontaneous MI and more severe MIs**
- 3. Longer durations of treatment would result in greater MI reduction**





Methods



- Myocardial Infarction (MI) was identified locally and adjudicated centrally by the independent TIMI Clinical Events Committee using source documentation
- MI definition was based on the 3rd Universal MI definition[^]
- MI was further categorized by:
 - ECG Type (STEMI/ NSTEMI)
 - Size (peak troponin “fold” elevation) vs to local report ULN
 - Universal MI Type:
 - Type 1 – Spontaneous Atherothombotic
 - Type 2 – Ischemic Imbalance (secondary)
 - Type 3 – Death due to MI without evaluation*
 - Type 4 – PCI Related MI (types A-C collapsed)
 - Type 5 – CABG related MI*



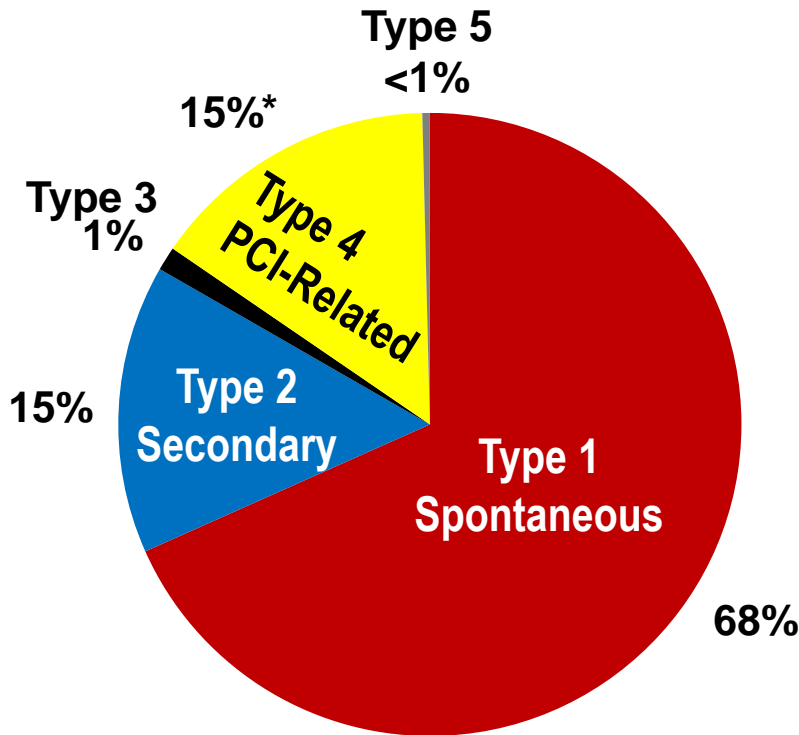


Type of MI



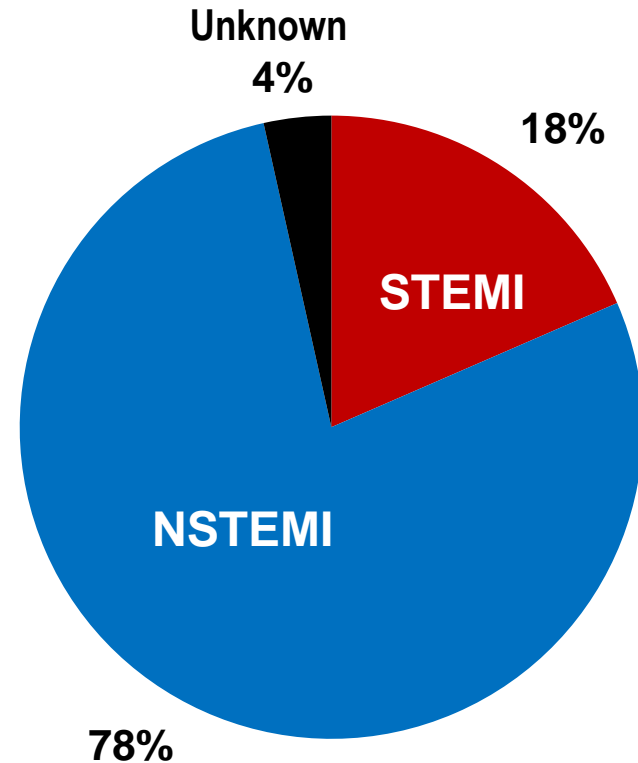
1288 total myocardial infarctions occurred in the trial

Universal MI Type



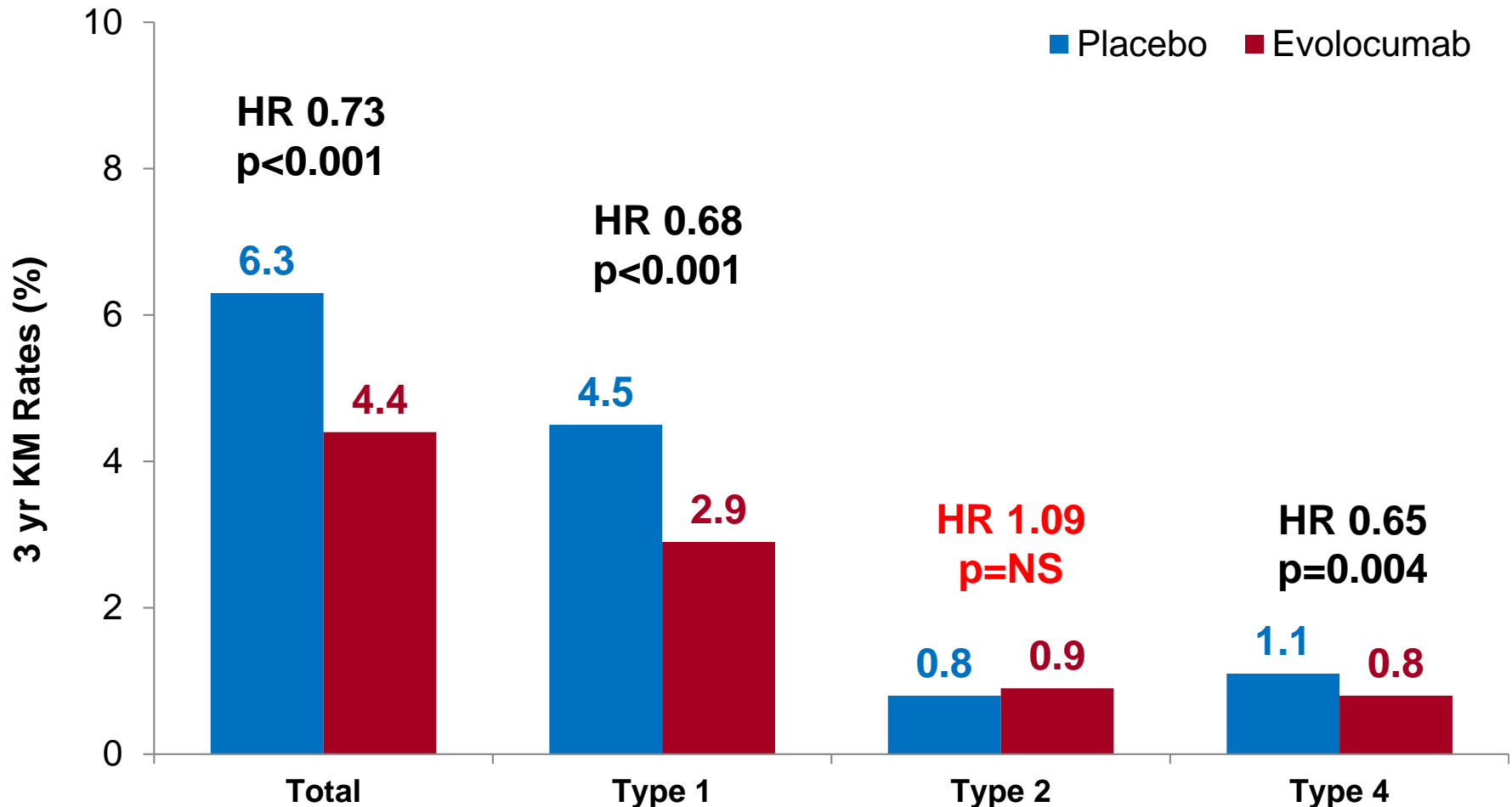
*25 Type 4a, 99 Type 4b, 70 Type 4c

ECG Categorization





Effect of Evolocumab by Universal MI Type

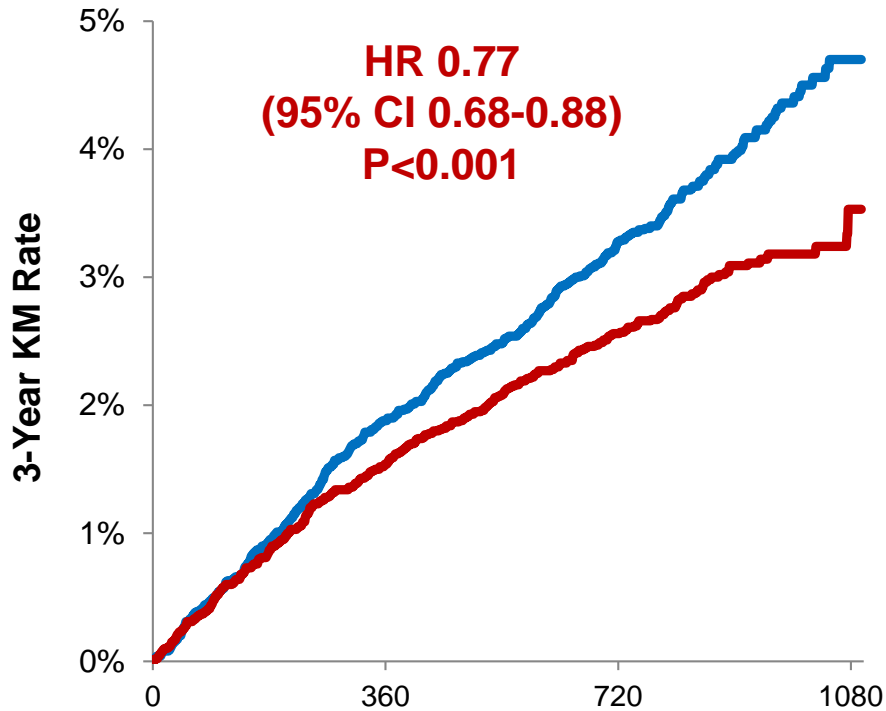




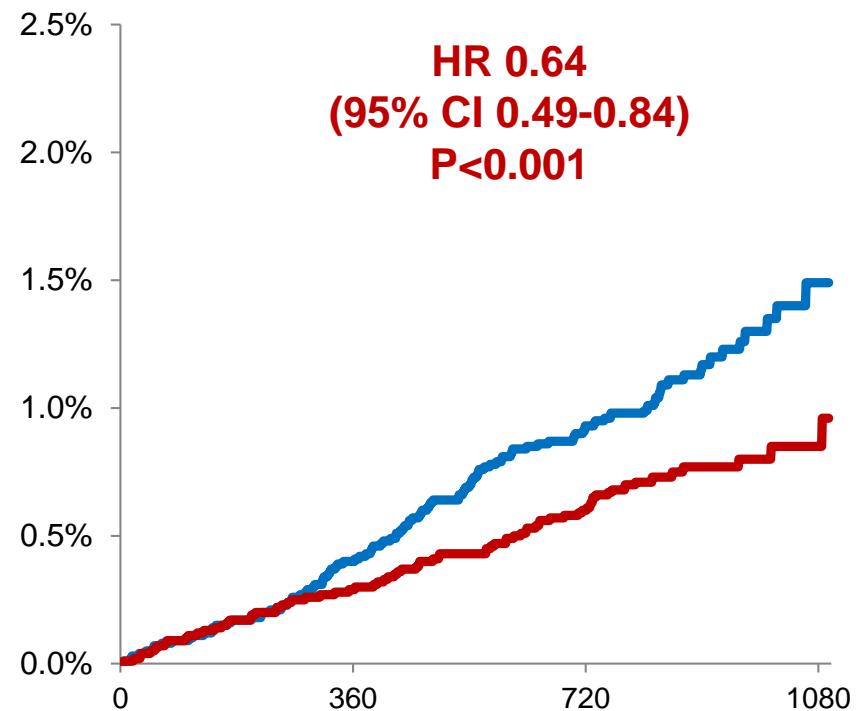
Effect of Evolocumab by MI Type: NSTEMI and STEMI



NSTEMI



STEMI



Days from Randomization

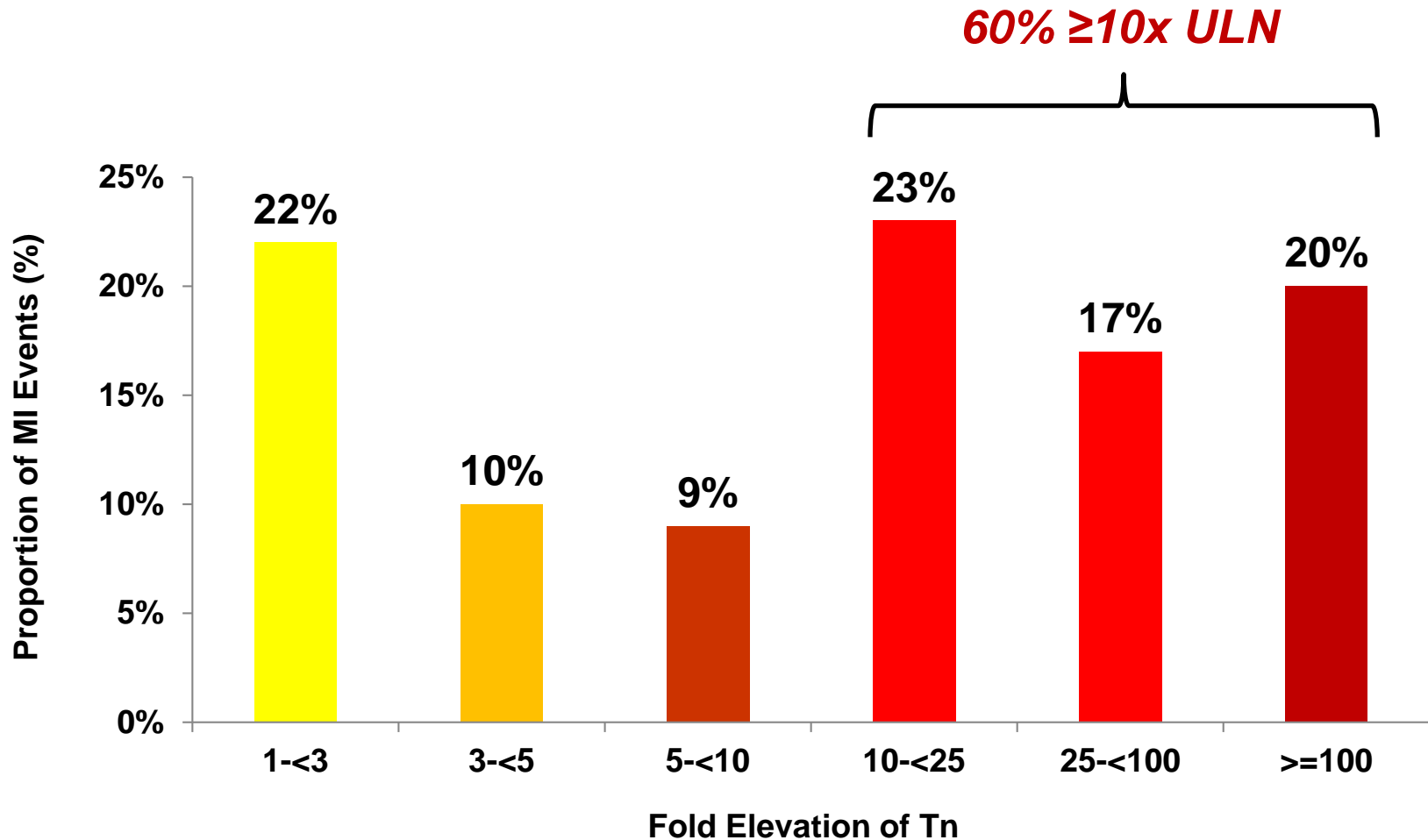




MI Size

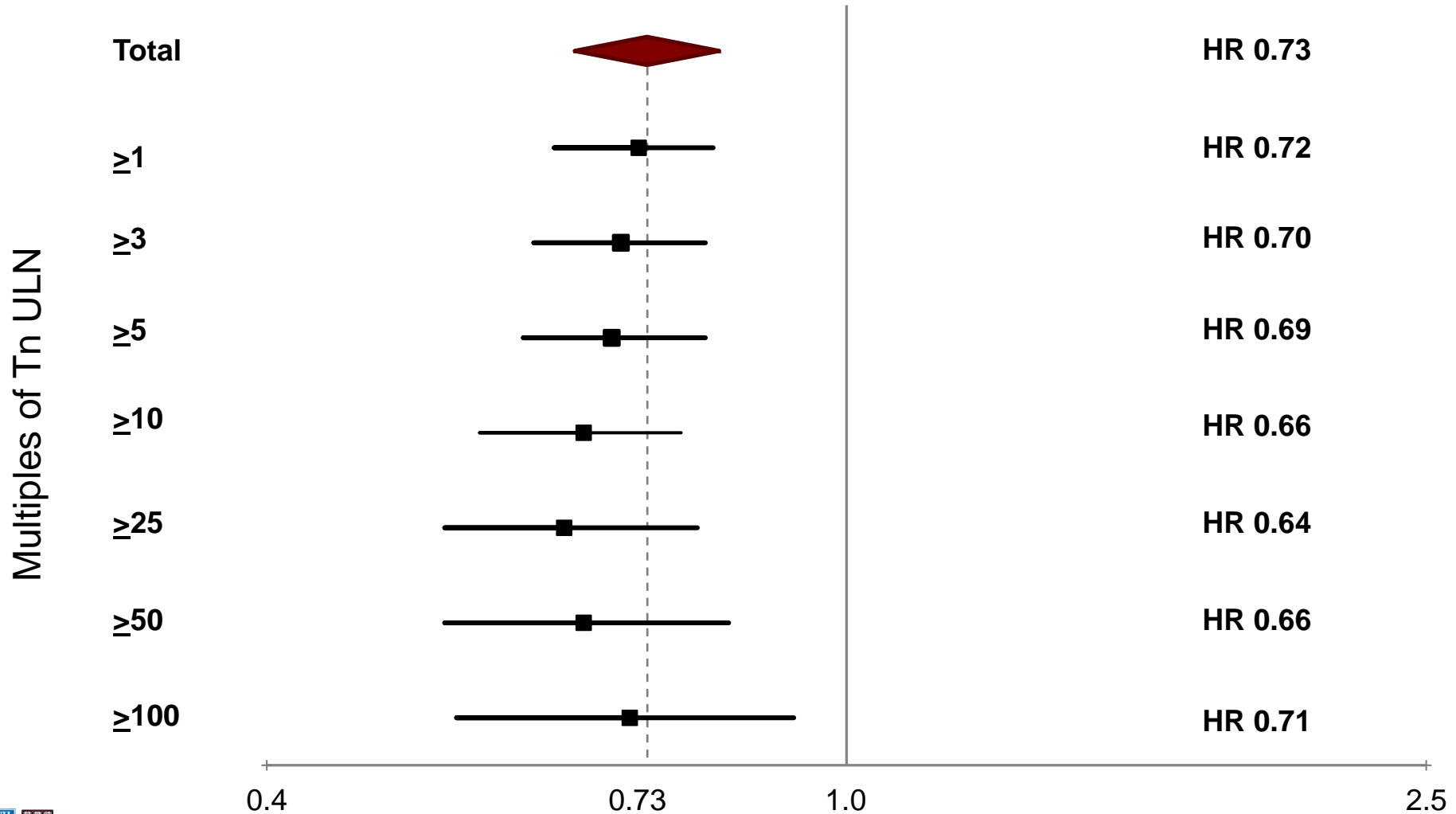


1288 total MI, 1150 with Tn Size Data





Effect of Evolocumab by MI Size Based on Peak Tn/ULN*

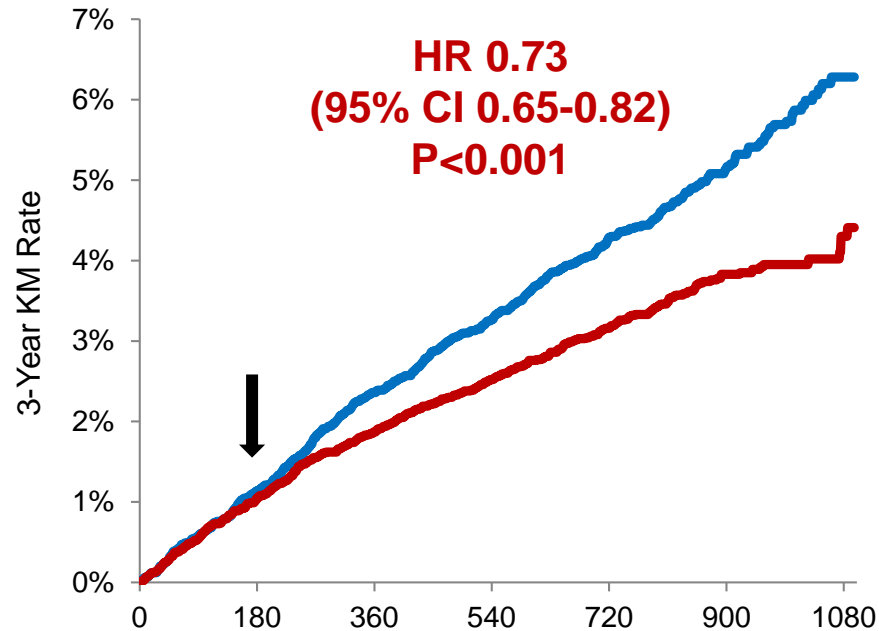




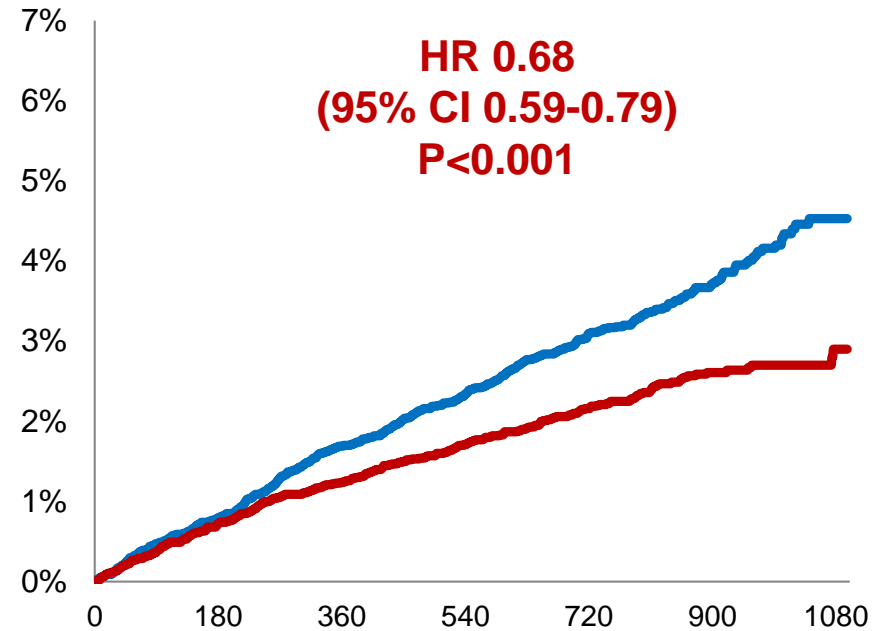
Effect of Evolocumab on Total and Spontaneous MI



Total MI



Spontaneous MI

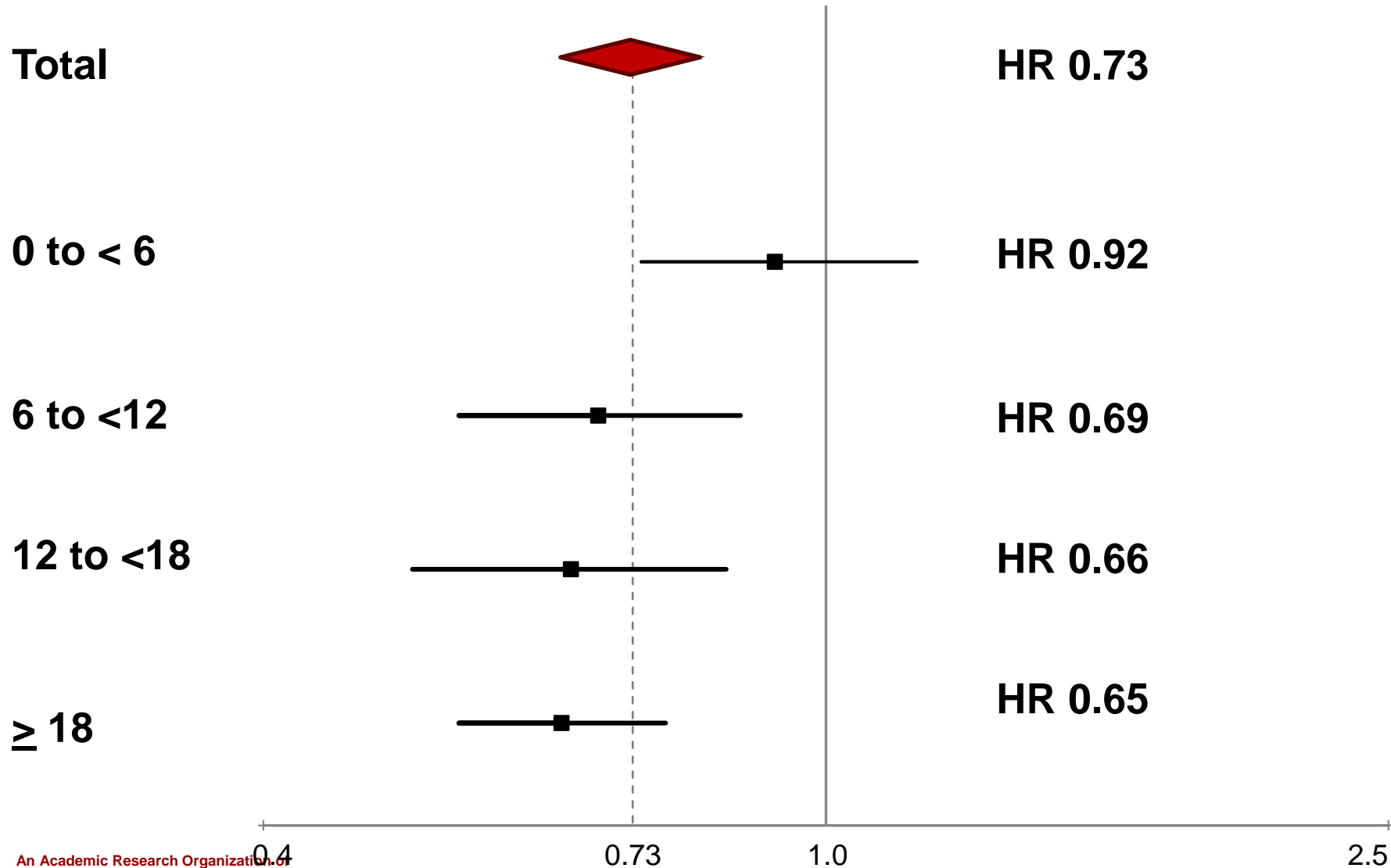


Days from Randomization





Effect of Evolocumab By Timing All MI by Months of Treatment





Summary



- **MI was the commonest of the first primary composite outcomes in this population with stable atherosclerosis**
- **Type 1 (spontaneous) and NSTEMI categories predominated**
- **Addition of the PCSK9 inhibitor evolocumab to statin therapy reduced MI, with consistent reductions of:**
 - **Larger MI**
 - **Spontaneous & PCI-related MI [w/ no effect on Type 2 (ischemic mismatch)]**
 - **STEMI and NSTEMI**
- **MI reduction tended to be greater after the 1st 6 months of therapy. The relatively short trial period may, therefore have limited the overall effect.**





Conclusions/Implications



- **LDL-C reduction with the PCSK9 inhibitor evolocumab resulted in substantial and consistent reductions in MI, including the most severe events.**
- **These data underscore the importance of LDL lowering in prevention of MI.**
- **For future trials of lipid lowering therapy, particularly with shorter time horizons, MI evaluation may wish to focus on spontaneous events.**

