

*INTERNATIONAL WORKSHOP*

**THE ROLE OF DYSLIPIDAEMIAS  
IN DETERMINING CARDIOVASCULAR RISK:  
FROM LIFESTYLE TO PHARMACOLOGICAL INTERVENTION**

*Naples - 2018, November 17-18 - Hotel Royal Continental*

Chairs

A.L. Catapano, P. Perrone Filardi and L. Tokgözoğlu

**FAMILIAL DYSLIPIDAEMIAS  
AND VERY HIGH RISK  
PATIENTS**

**THE VERY  
HIGH RISK PATIENTS**

**Alberto Zambon**  
University of Padova  
Italy



# DISCLOSURE

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Prof. A. Zambon reports having received grants, consulting fees and/or honoraria and delivering lectures for:

- Abbott
- AstraZeneca
- Merck Sharp & Dohme
- Amgen
- Sanofi
- Lilly
- Mylan
- Chiesi

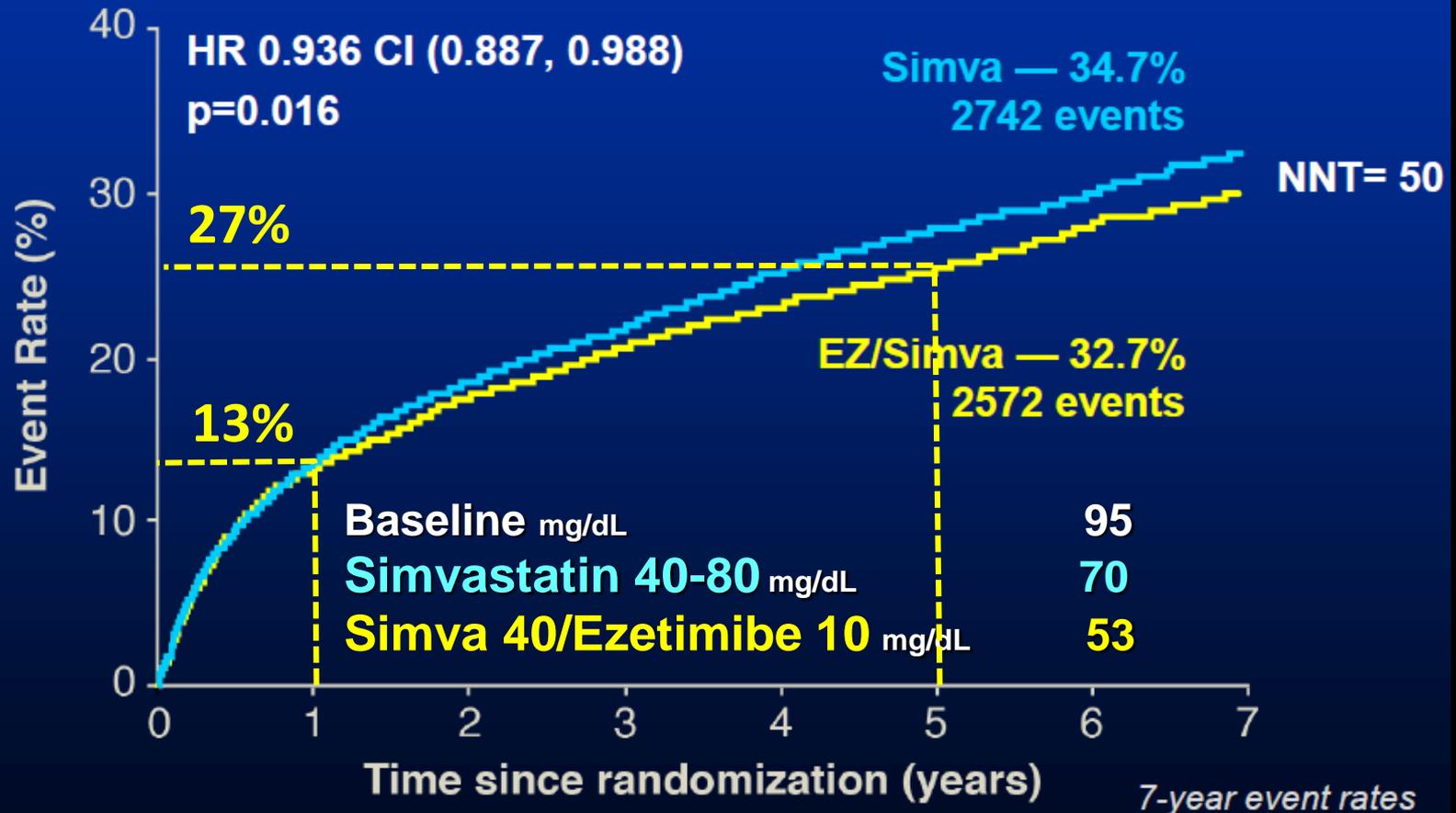
## Risk categories

<b>Very high-risk</b>	<p>Subjects with any of the following:</p> <ul style="list-style-type: none"> <li>• Documented CVD, clinical or unequivocal on imaging. Documented clinical CVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented CVD on imaging includes significant plaque on coronary angiography or carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima-media thickness of the carotid artery.</li> <li>• DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolaemia or marked hypertension.</li> <li>• Severe CKD (GFR &lt;30 mL/min/1.73 m<sup>2</sup>).</li> <li>• A calculated SCORE ≥10%.</li> </ul>
<b>High-risk</b>	<p>Subjects with:</p> <ul style="list-style-type: none"> <li>• Markedly elevated single risk factors, in particular cholesterol &gt;8 mmol/L (&gt;310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg.</li> <li>• Most other people with DM (with the exception of young people with type 1 DM and without major risk factors that may be at low or moderate risk).</li> <li>• Moderate CKD (GFR 30–59 mL/min/1.73 m<sup>2</sup>).</li> <li>• A calculated SCORE ≥5% and &lt;10%.</li> </ul>
<b>Moderate-risk</b>	<p>SCORE is ≥1% and &lt;5% at 10 years. Many middleaged subjects belong to this category.</p>
<b>Low-risk</b>	<p>SCORE &lt;1%.</p>

# IMPROVE-IT

## Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization ( $\geq 30$  days), or stroke



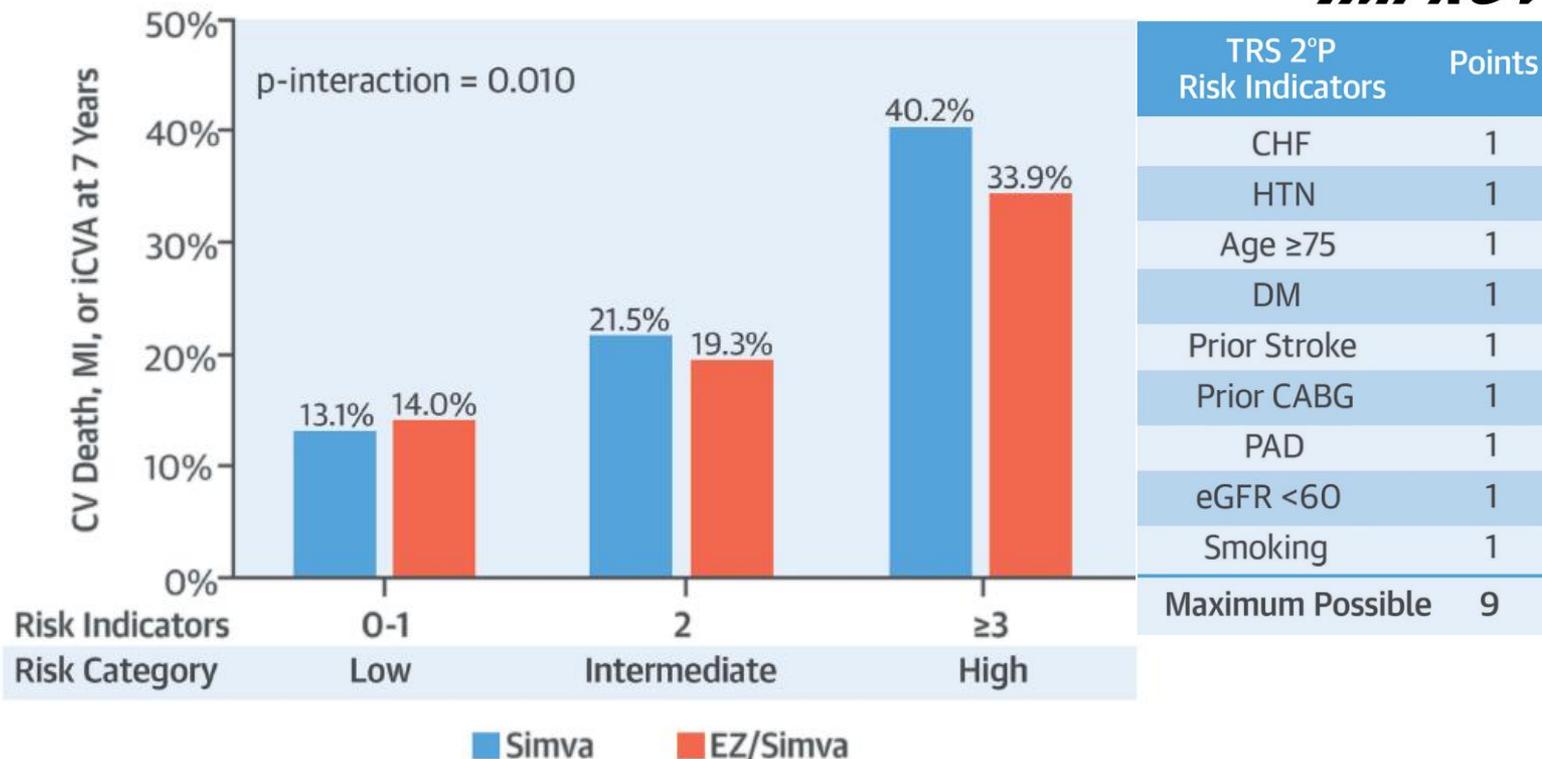
# The ***TIMI Risk Score for Secondary Prevention (TRS 2P)*** is a simple 9-point risk stratification tool for post-ACS patients

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TRS 2°P Risk Indicators
CHF
HTN
Age $\geq$ 75
DM
Prior Stroke
Prior CABG
PAD
eGFR <60
Current Smoking

# Atherothrombotic Risk Stratification and Ezetimibe for Secondary Prevention

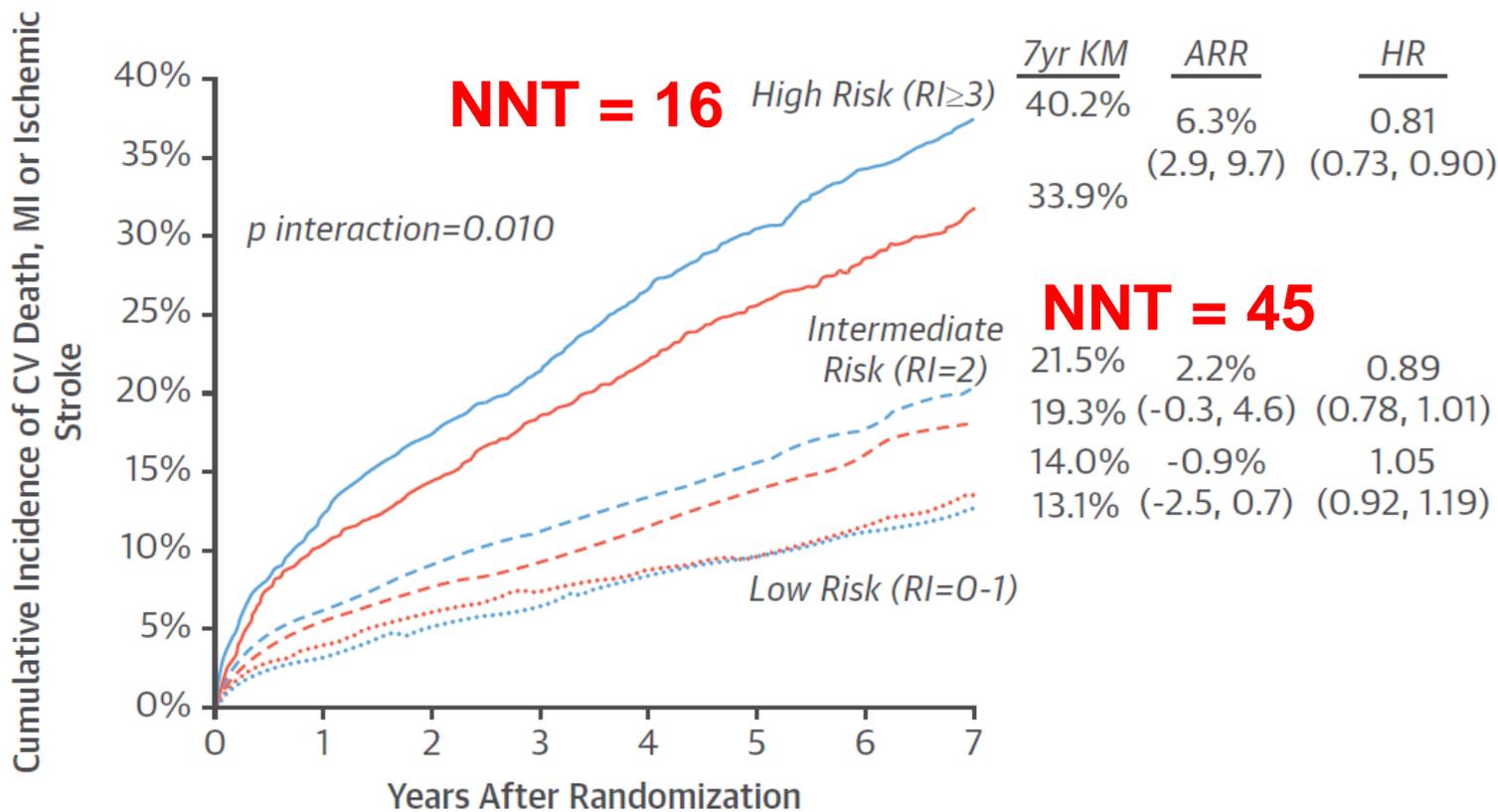


In patients stabilized after acute coronary syndrome in IMPROVE-IT, the TRS 2P, a simple risk stratification tool using 9 readily available clinical characteristics, **identifies a strong gradient of risk for cardiovascular death, MI, or ischemic stroke and an increasingly favorable relative and absolute benefit from the addition of ezetimibe to simvastatin therapy with increasing risk profile**

# The **TIMI Risk Score for Secondary Prevention (TRS 2P)** is a simple 9-point risk stratification tool for post-ACS patients



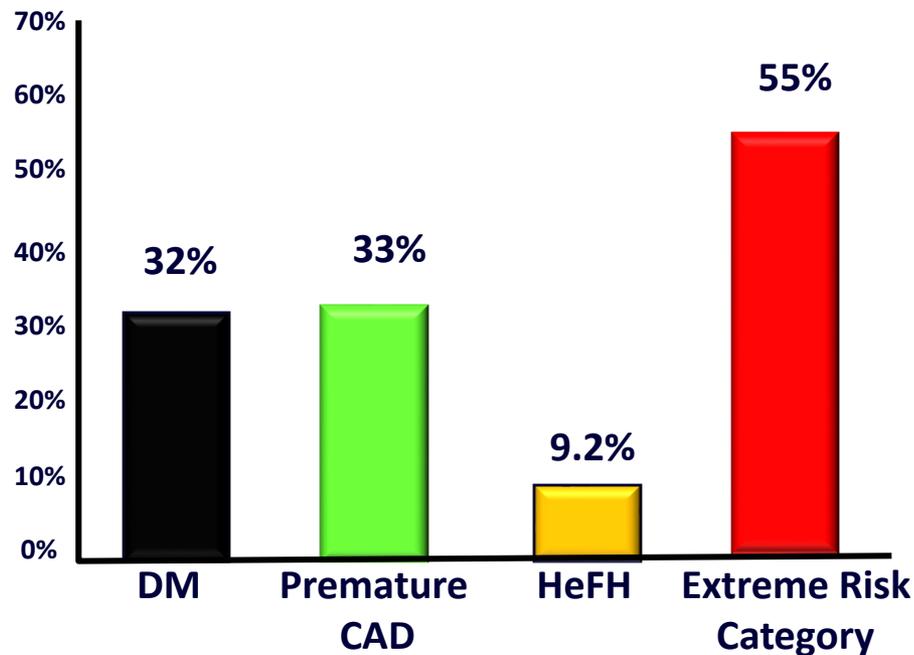
## **A** Outcomes by Risk Category and Randomized Treatment



Extreme-risk category: High prevalence among stable coronary patients and an emerging widening treatment gap in achieving LDL-cholesterol less than 55 mg/dL



Loukianos S. Rallidis <sup>a,\*</sup>, Estela Kiouri <sup>a</sup>, Andreas Katsimardos <sup>a</sup>, Christos Kotakos <sup>b</sup>



## PREVALENCE OF

- **Diabetes mellitus (DM),**
- **Recurrent coronary artery disease (CAD) and**
- **Heterozygous familial hypercholesterolaemia (HeFH)**

among 1629 patients with stable CAD. The last bar shows the proportion of patients who constitute the extreme cardiovascular risk category.

## AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE

**Table 6**  
**Atherosclerotic Cardiovascular Disease Risk Categories and LDL-C Treatment Goals**

Risk category	Risk factors <sup>a</sup> /10-year risk <sup>b</sup>	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	<ul style="list-style-type: none"> <li>– Progressive ASCVD including unstable angina in patients after achieving an LDL-C &lt;70 mg/dL</li> <li>– Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH</li> <li>– History of premature ASCVD (&lt;55 male, &lt;65 female)</li> </ul>	<55	<80	<70
Very high risk	<ul style="list-style-type: none"> <li>– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk &gt;20%</li> <li>– Diabetes or CKD 3/4 with 1 or more risk factor(s)</li> <li>– HeFH</li> </ul>	<70	<100	<80
High risk	<ul style="list-style-type: none"> <li>– ≥2 risk factors and 10-year risk 10-20%</li> <li>– Diabetes or CKD 3/4 with no other risk factors</li> </ul>	<100	<130	<90
Moderate risk	≤2 risk factors and 10-year risk <10%	<100	<130	<90
Low risk	0 risk factors	<130	<160	NR

Abbreviations: ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; MESA = Multi-Ethnic Study of Atherosclerosis; NR = not recommended; UKPDS = United Kingdom Prospective Diabetes Study.

<sup>a</sup> Major independent risk factors are high LDL-C, polycystic ovary syndrome, cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or on hypertensive medication), low HDL-C (<40 mg/dL), family history of coronary artery disease (in male, first-degree relative younger than 55 years; in female, first-degree relative younger than 65 years), chronic renal disease (CKD) stage 3/4, evidence of coronary artery calcification and age (men ≥45; women ≥55 years). Subtract 1 risk factor if the person has high HDL-C.

<sup>b</sup> Framingham risk scoring is applied to determine 10-year risk.

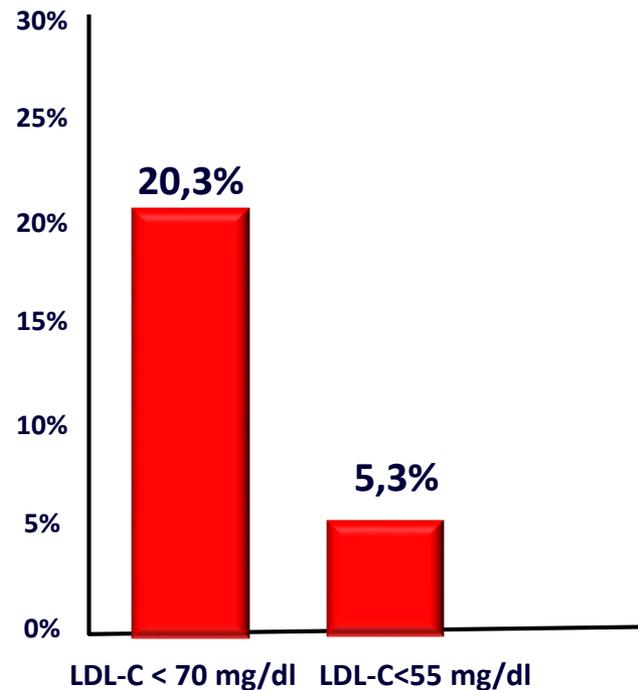
Reproduced with permission from Garber et al. *Endocr Pract.* 2017;23:207-238.

Extreme-risk category: High prevalence among stable coronary patients and an emerging widening treatment gap in achieving LDL-cholesterol less than 55 mg/dL



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Proportion of extreme cardiovascular risk patients on lipid-lowering therapy (n= 779) achieving LDL-C levels <70 mg/dL and <55 mg/dL.

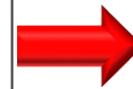


# 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

## Recommendations for the treatment of dyslipidaemia in diabetes

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.	I	A	62, 64, 68
In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered.	IIa	C	239, 256, 257
If <u>the goal is not reached, statin combination with a cholesterol absorption inhibitor</u> should be considered.	IIa	B	63
In patients at very high-risk, with <u>persistent high LDL-C despite treatment with maximal tolerated statin dose</u> , in combination with <u>ezetimibe</u> or in patients with statin intolerance, a <u>PCSK9 inhibitor</u> may be considered.	IIb	C	115, 116



**Choice #1**  
**Statin high dose**



**LDL-C NOT AT GOAL**

**Statin-Ezetimibe**

**↓ LDL-C by 20%**

**PCSK9 INHIBITORS**



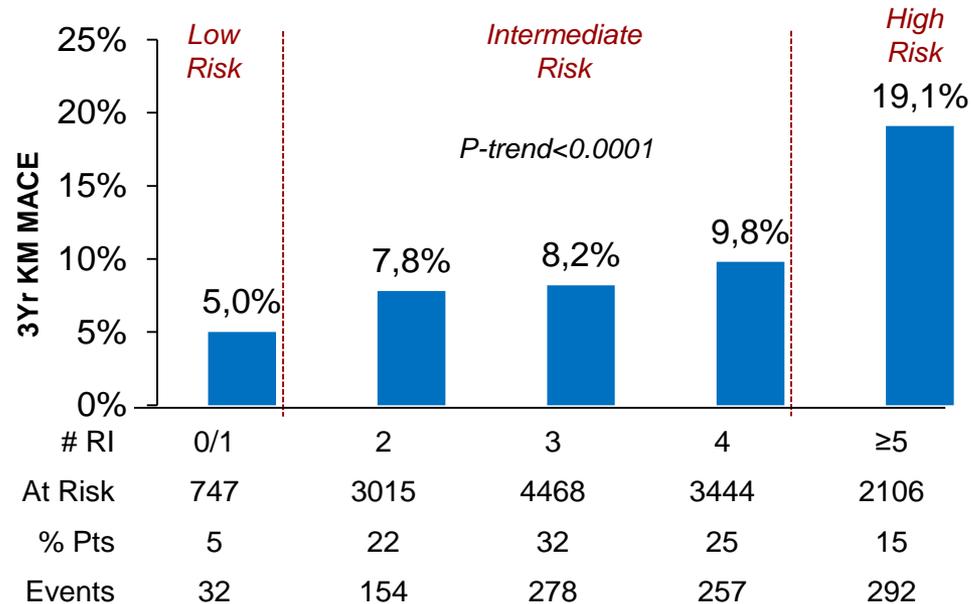
**+ Statin-Ezetimibe**

**↓ LDL-C 55-70%**

# TIMI SIHD Risk Score and Events in the Placebo Group



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



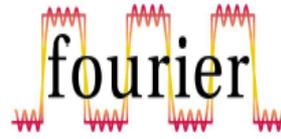
SIHD: Stable Ischemic Heart Disease MACE: CV death, MI, stroke



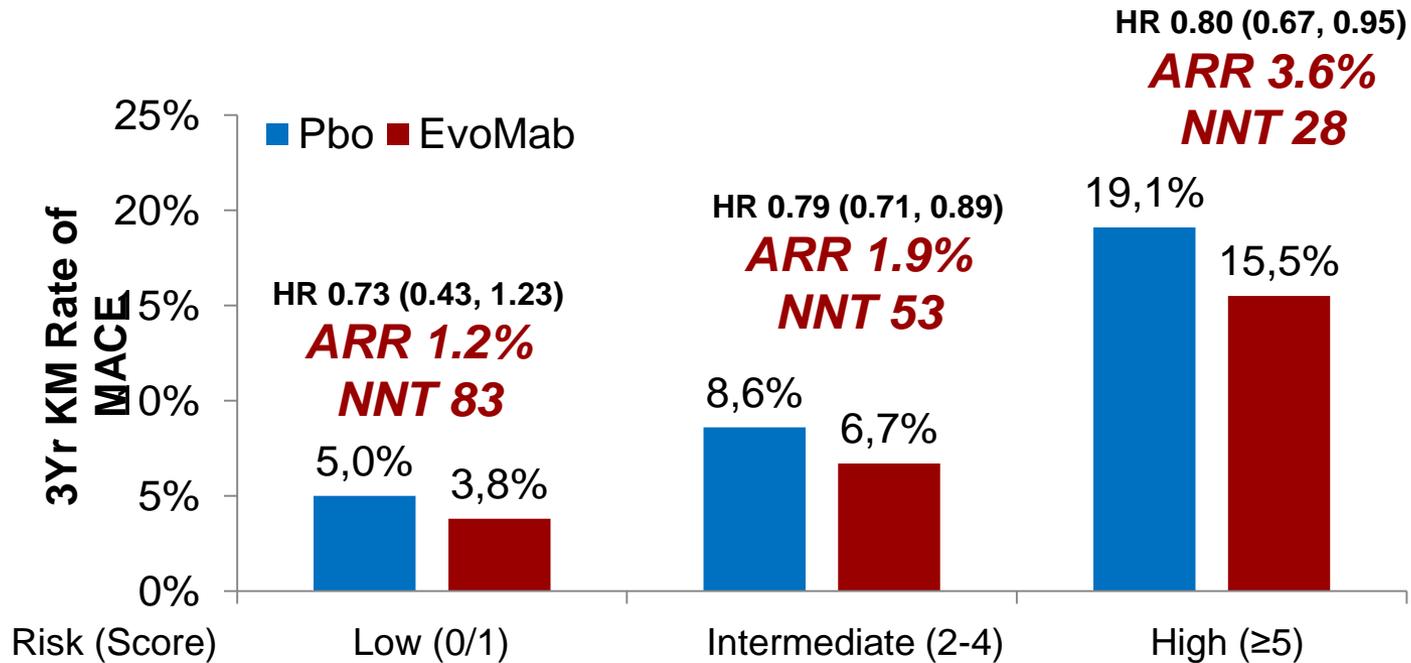
# Atherothrombotic Risk Stratification and Magnitude of Benefit of Evolocumab in FOURIER

Erin A Bohula<sup>1</sup>, David A Morrow<sup>1</sup>, Terje R. Pedersen<sup>2</sup>, Estella Kanevsky<sup>1</sup>, Sabina A Murphy<sup>1</sup>, Robert P Giugliano<sup>1</sup>, Peter S. Sever<sup>3</sup>, Anthony C. Keech<sup>4</sup>, and Marc S Sabatine<sup>1</sup>

<sup>1</sup>TIMI Study Group, Brigham & Women's Hospital, Boston, MA, USA <sup>2</sup>Ullevål University Hospital, Oslo, Norway <sup>3</sup>Imperial College, London, UK, <sup>4</sup>University of Sydney, Sydney, Australia



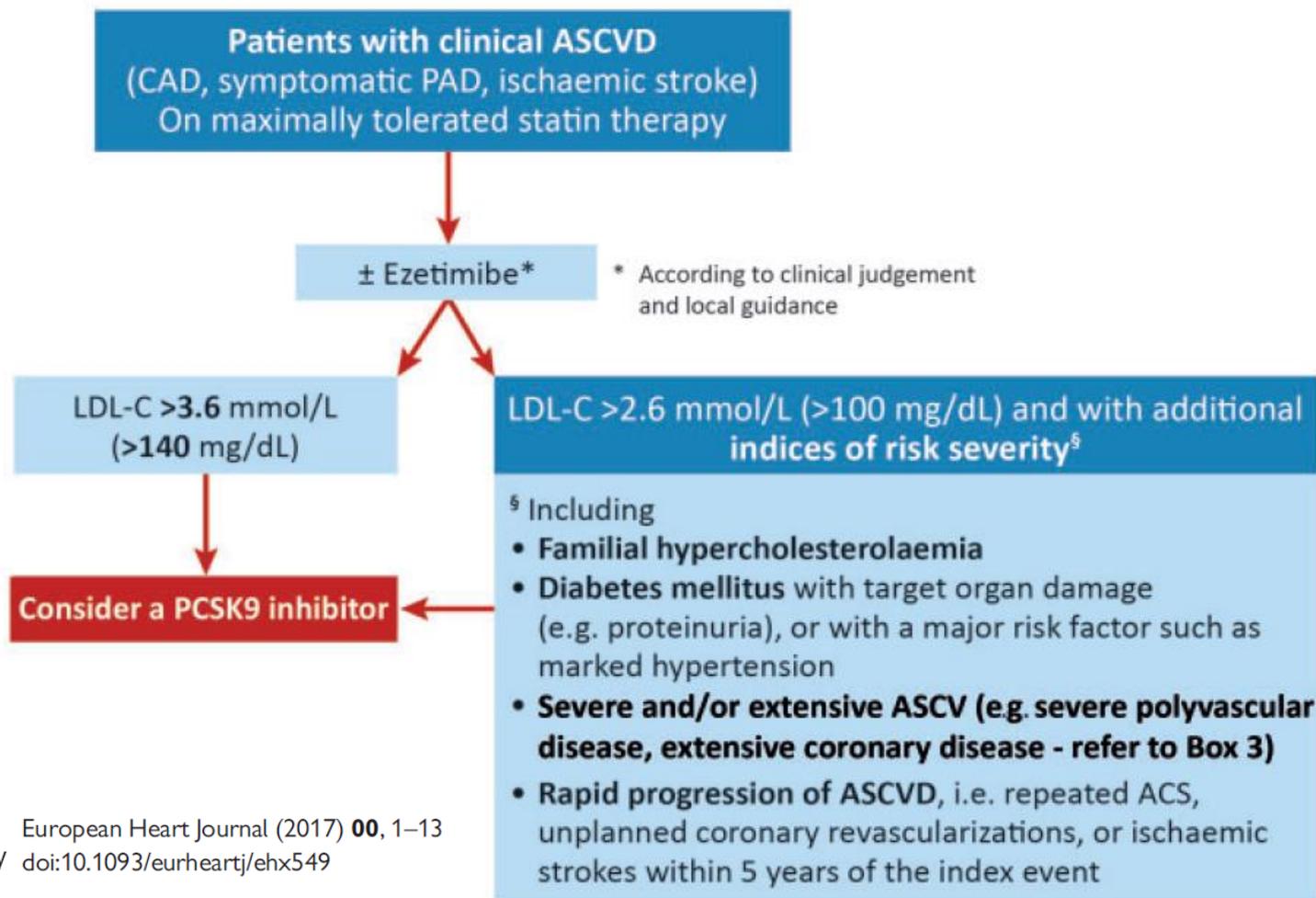
## MACE by Risk Category and Treatment



MACE: CV death, MI, stroke

*P-trend < 0.001 for both treatments*  
*P-interaction = 0.94*

# 2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia





# Clinical Benefit of Evolocumab in Patients with a History of MI: An Analysis from FOURIER

Marc S. Sabatine, Gaetano M. De Ferrari, Robert P. Giugliano,  
Kurt Huber, Basil S. Lewis, Jorge Ferreira, Julia F. Kuder,  
Sabina A. Murphy, Stephen D. Wiviott, Christopher Kurtz,  
Narimon Honarpour, Anthony C. Keech,  
Peter S. Sever, and Terje R. Pedersen,  
for the FOURIER Steering Committee & Investigators

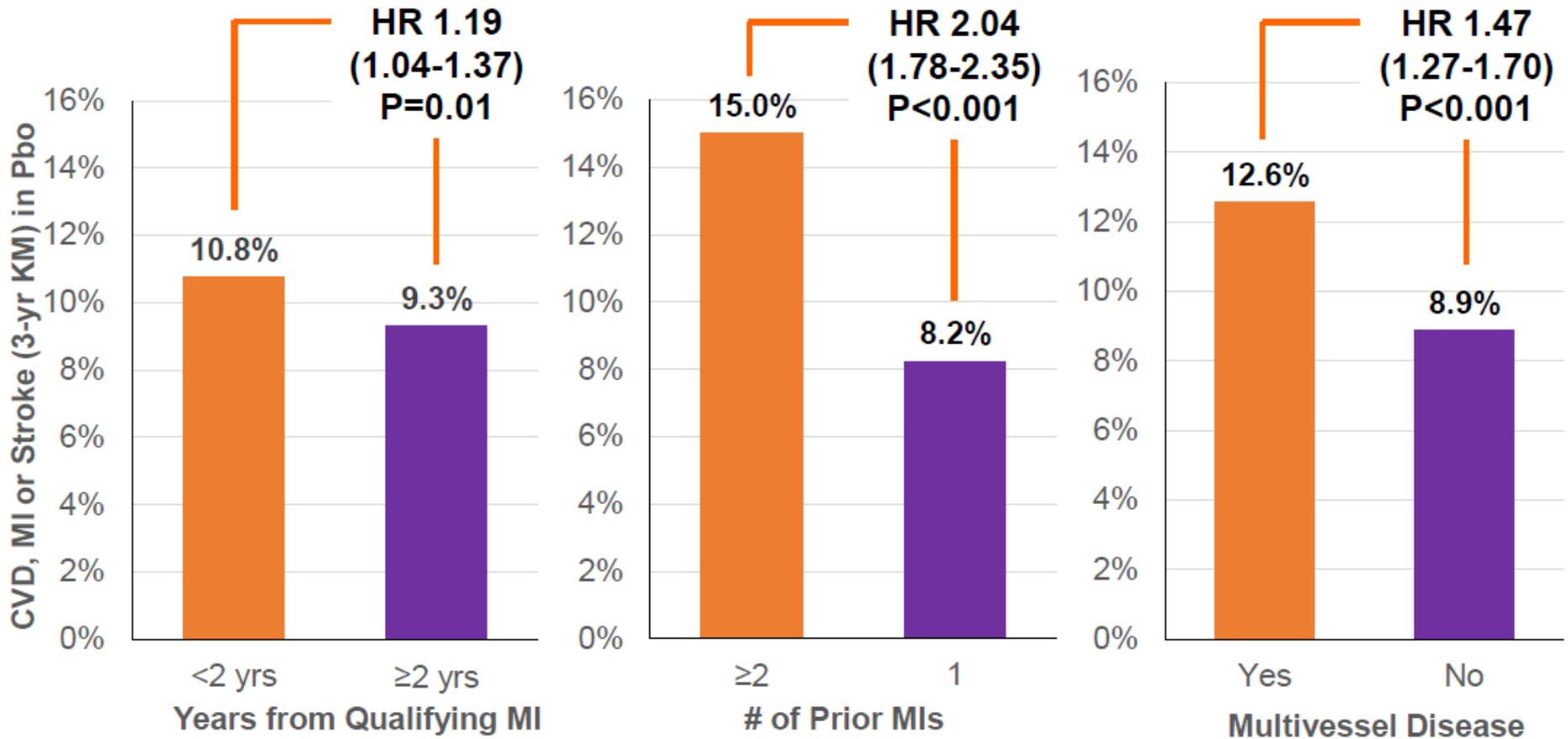
*American Heart Association – Annual Scientific Session  
Late-Breaking Science in Prevention  
November 13, 2017*



An Academic Research Organization of  
Brigham and Women's Hospital and Harvard Medical School



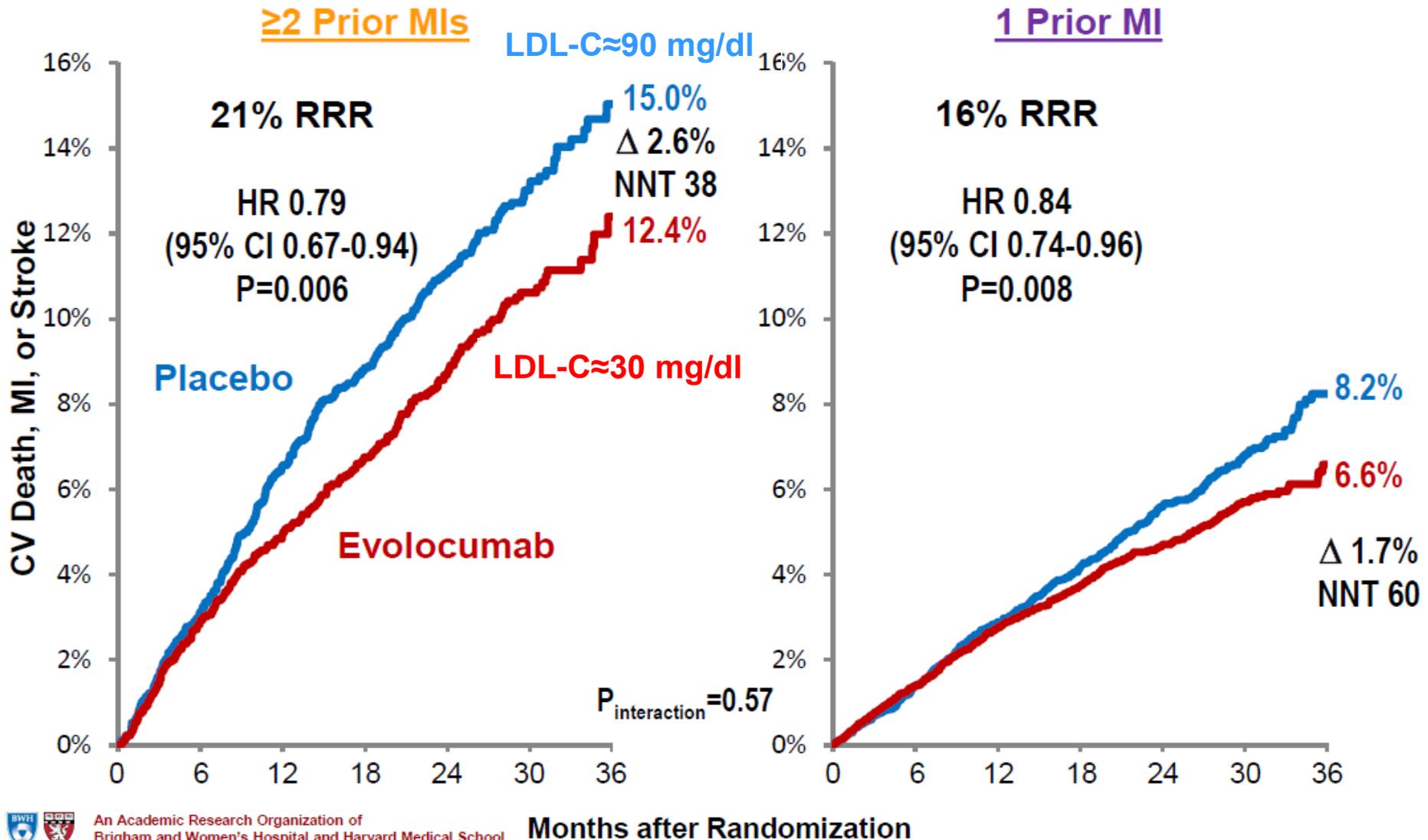
# Risk of CV Death, MI or Stroke with Each Risk Factor



*Analyses in placebo arm*

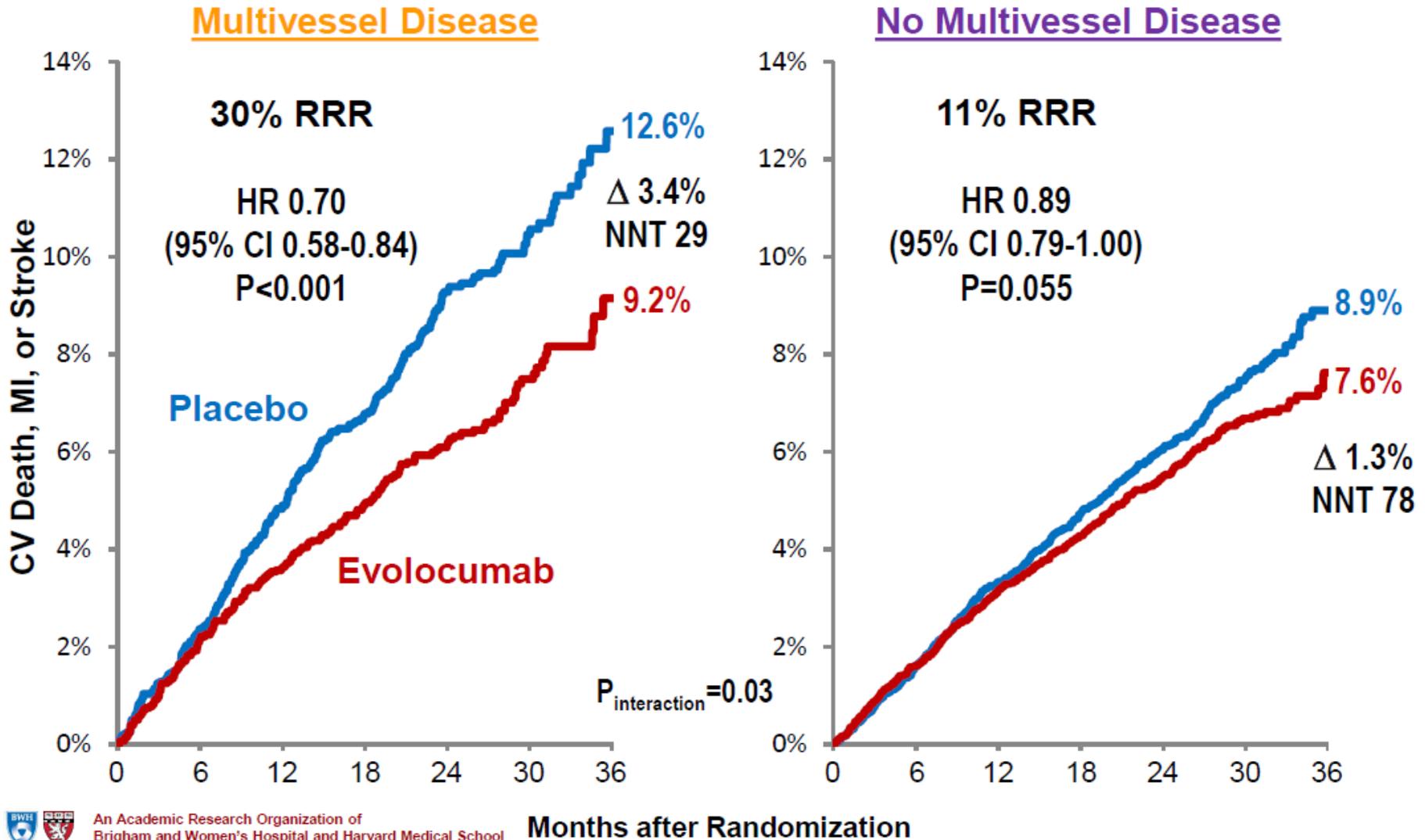
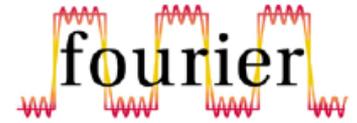


# Benefit of EvoMab Based on # of Prior MIs





# Benefit of EvoMab Based on Multivessel Disease





# LDL Cholesterol Lowering with Evolocumab and Outcomes in Patients with Peripheral Artery Disease: Insights from the FOURIER Trial

Marc P. Bonaca, Patrice Nault, Robert P. Giugliano, Anthony C. Keech, Armando Lira Pineda, Estella Kanevsky, Julia Kuder, Sabina A. Murphy, J. Wouter Jukema, Basil S. Lewis, Lale Tokgozoglu, Ransi Somaratne, Peter S. Sever, Terje R. Pedersen, Marc S. Sabatine

for the FOURIER Steering Committee & Investigators

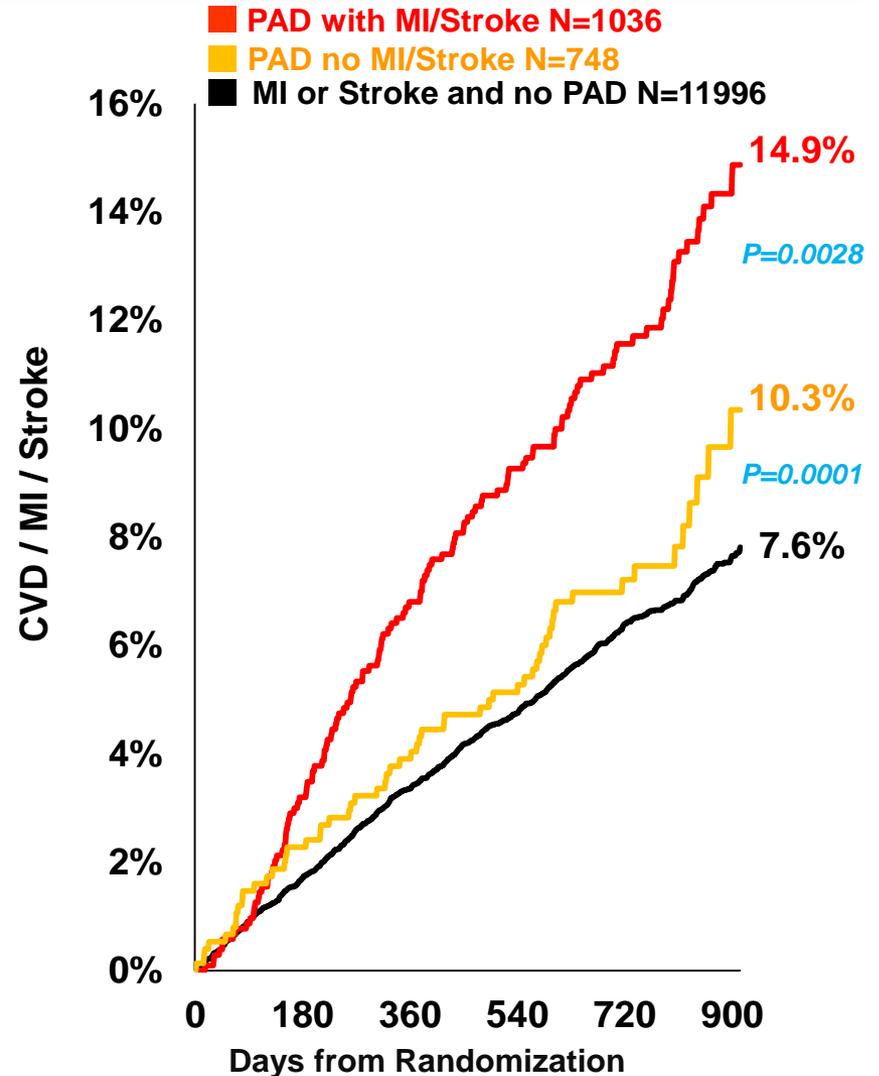
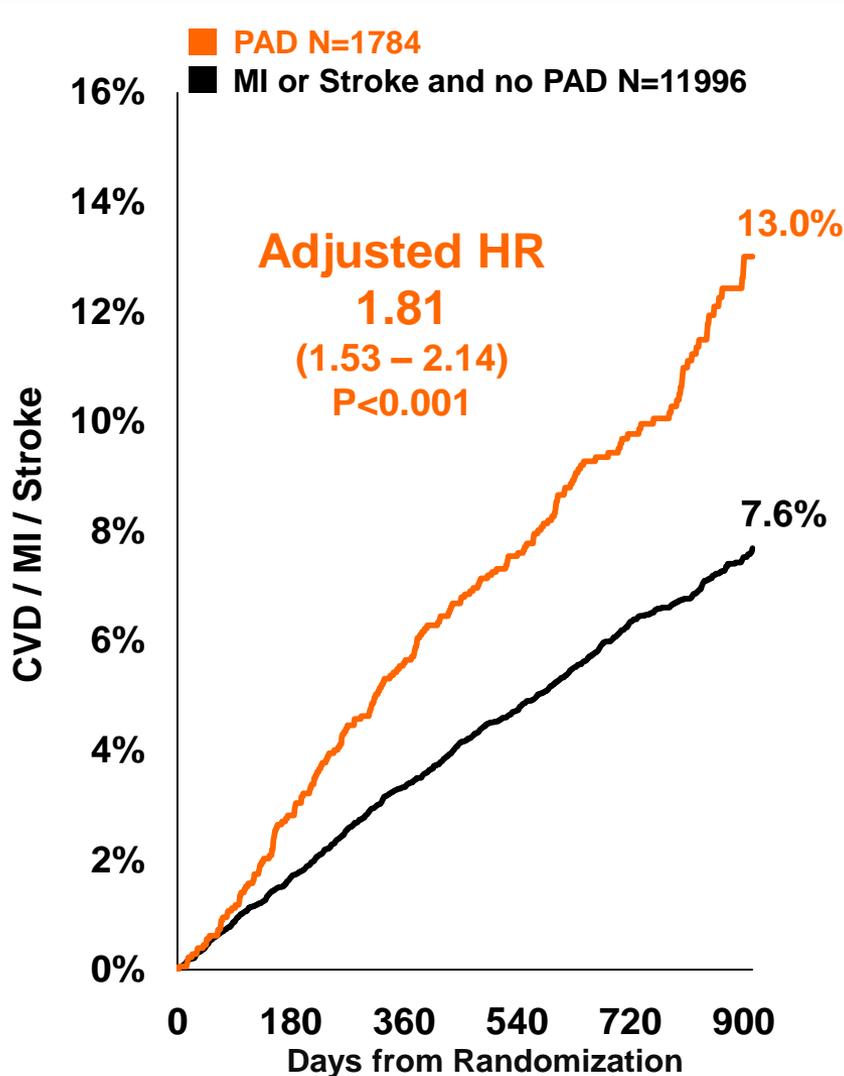
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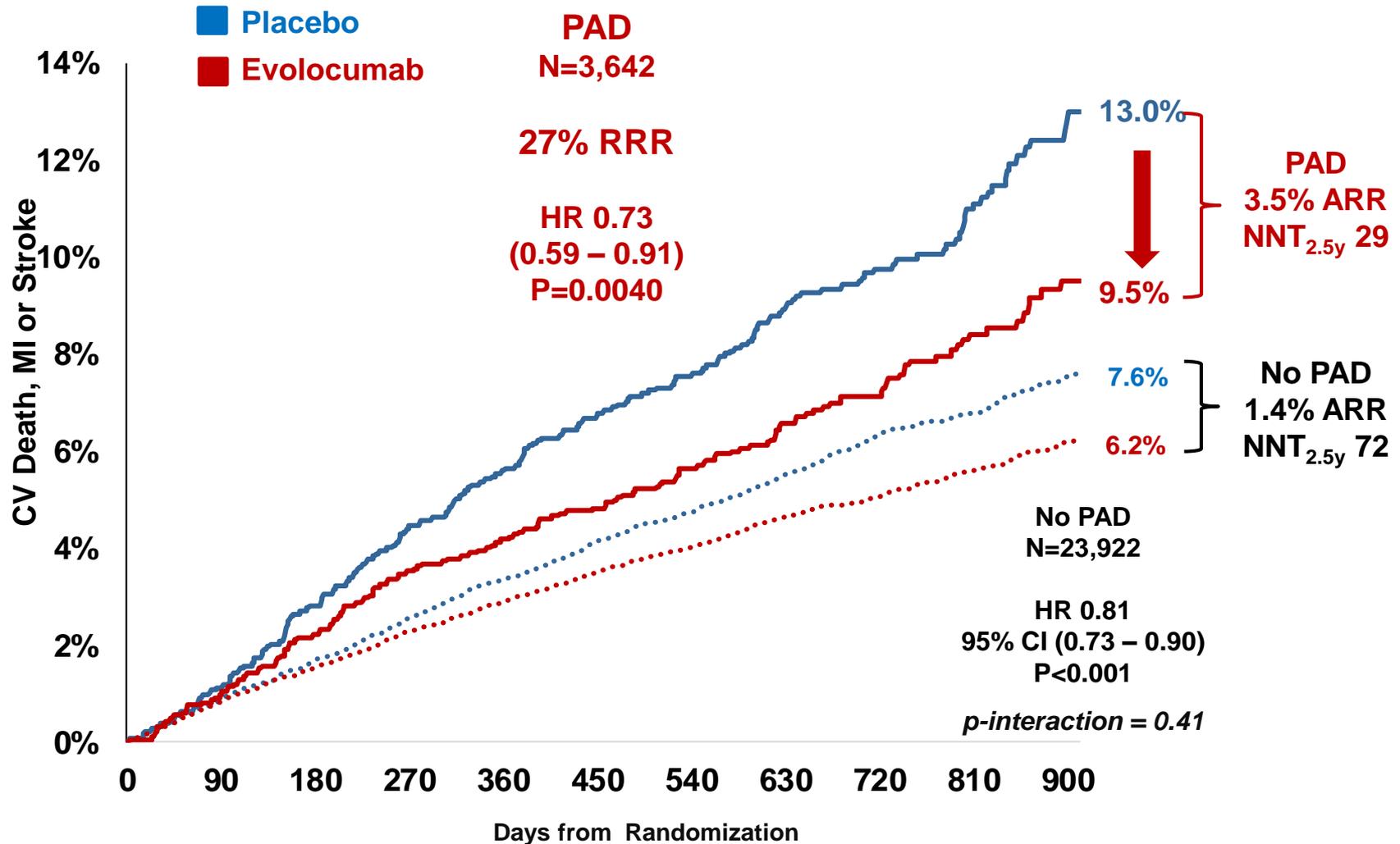
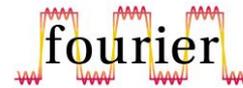


# Peripheral Artery Disease and Risk in Placebo Patients



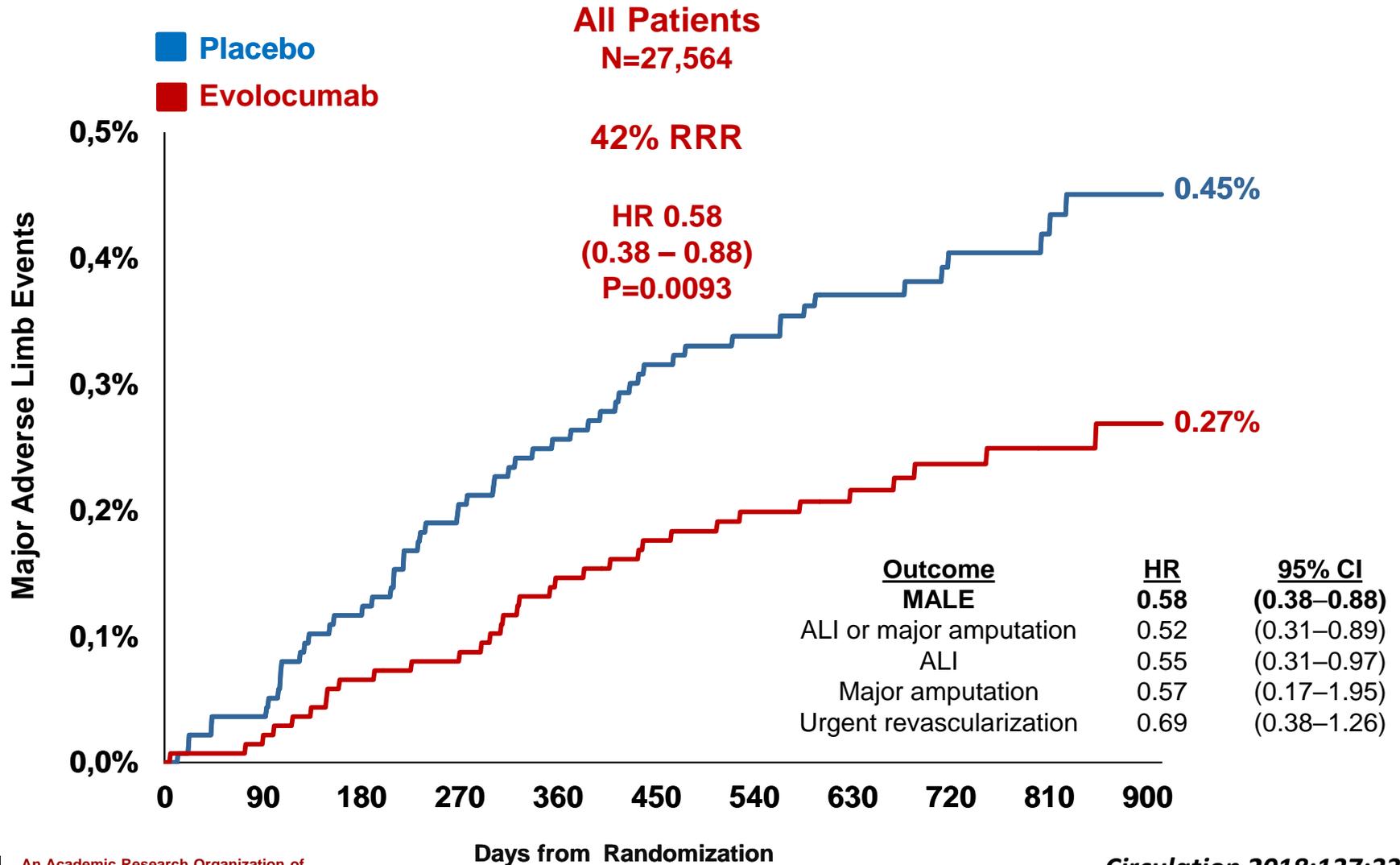


# CV Death, MI or Stroke in Patients with and without Peripheral Artery Disease

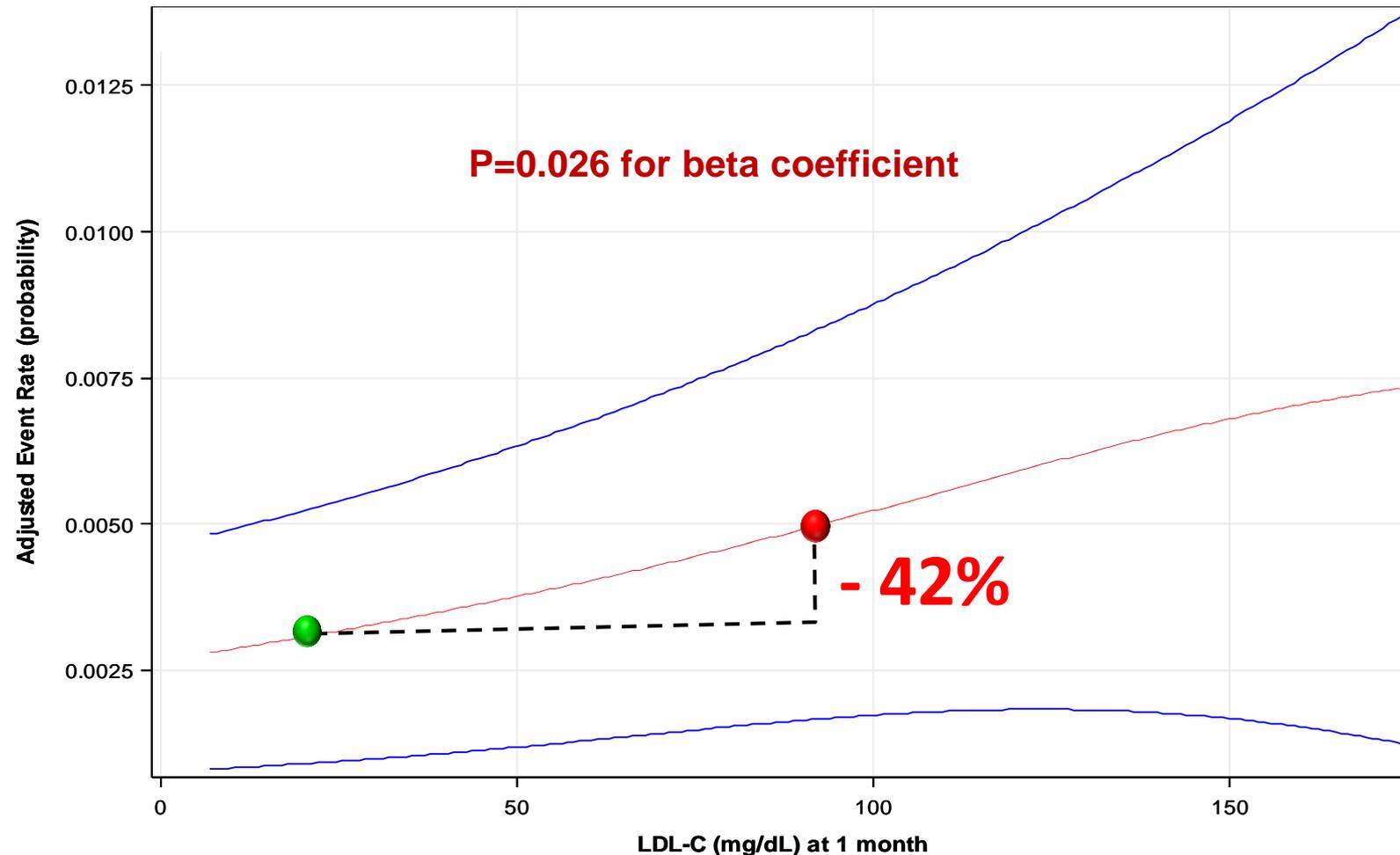




# Major Adverse Limb Events



# Achieved LDL-C and Major Adverse Limb Events



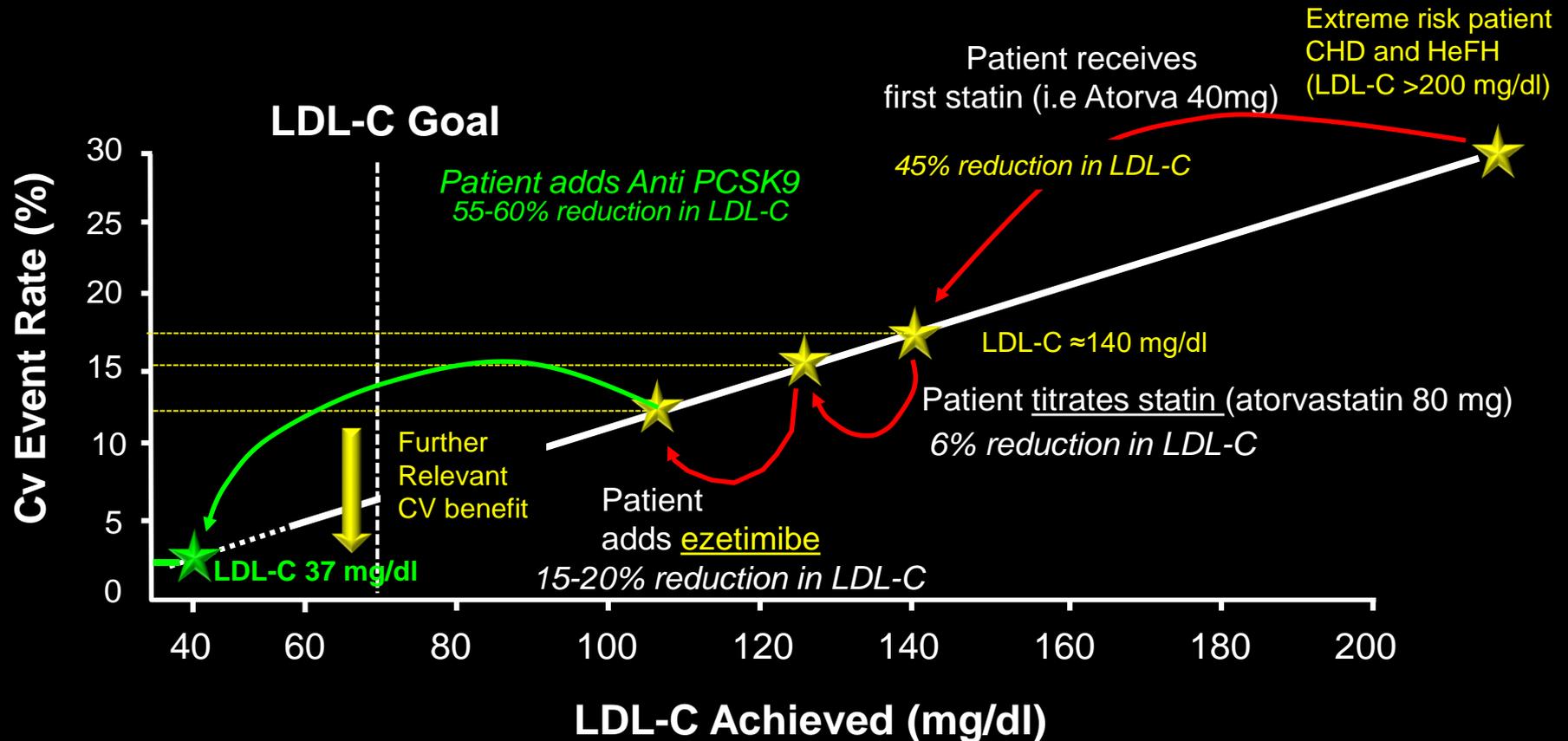
adjusted for significant ( $p < 0.05$ ) predictors of LDL-C cholesterol at 1 month after randomization including age, BMI, LDL-C at baseline, male sex, race, randomized in North America, current smoker, high intensity statin.

# The Very High CVD Risk Patients

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- Atherothrombotic risk stratification using the **TIMI Risk Score for 2P** identifies patients, in the IMPROVE-IT trial, at **extremely high CV risk** who derive greatest benefit from the addition of ezetimibe to statin therapy for secondary prevention after ACS
- In **FOURIER** the use of evolocumab (in combination mostly with high intensity statin therapy) was associated with a greater CVD event reduction and a **cost/effective NNT** in patients with:
  - Multivessel disease
  - Recurrent MI and progressive CVD
  - Diabetes
  - PAD
- In these patients it may be appropriate to aim for **the lowest LDL-C achievable**
- Should we aim for **LDL-C ERADICATION** (rather than LDL-C lowering)?

# Extreme CVD Risk Patients LDL-C lowering ROADMAP

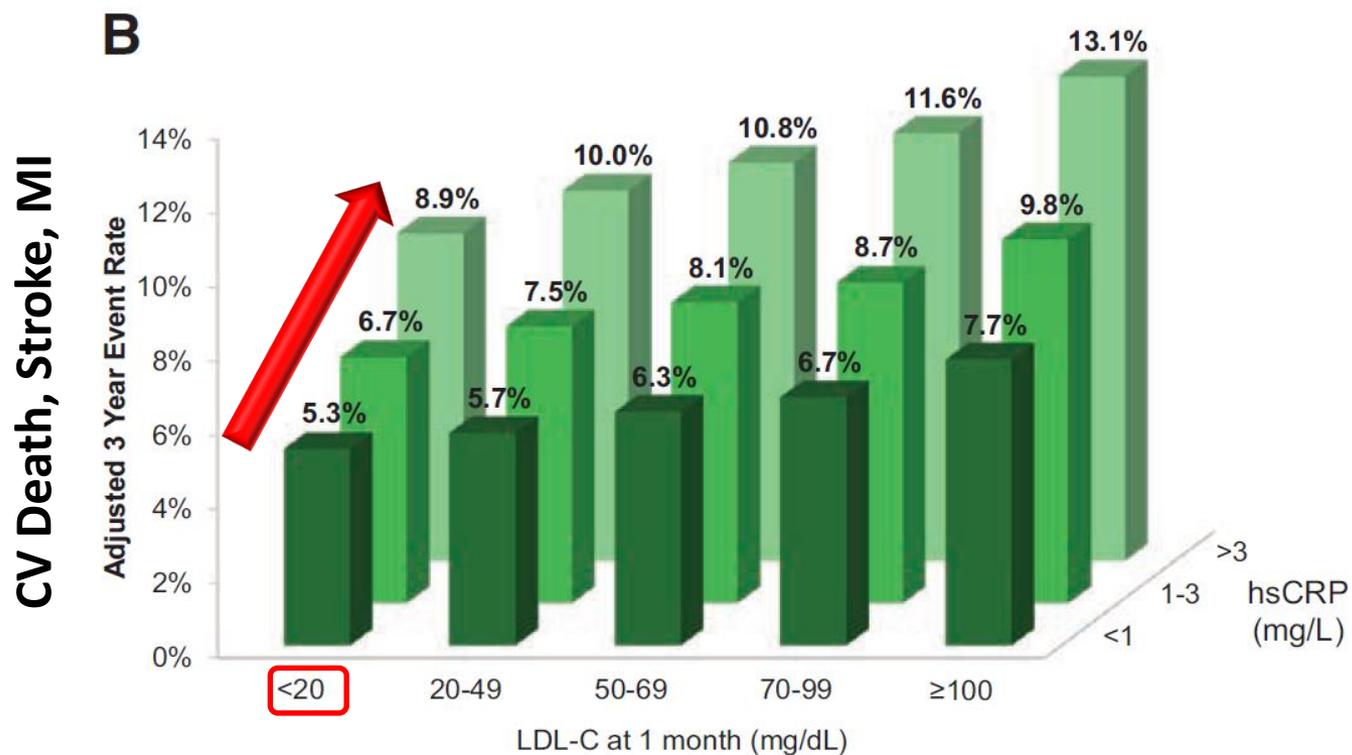


≈ 80% LDL-C reduction vs. baseline; 30-35% ABSOLUTE CV RISK REDUCTION!

\* LDL-C goal for High-risk and Very high-risk patients as defined by ESC/EAS guidelines for the management of dyslipidemias.

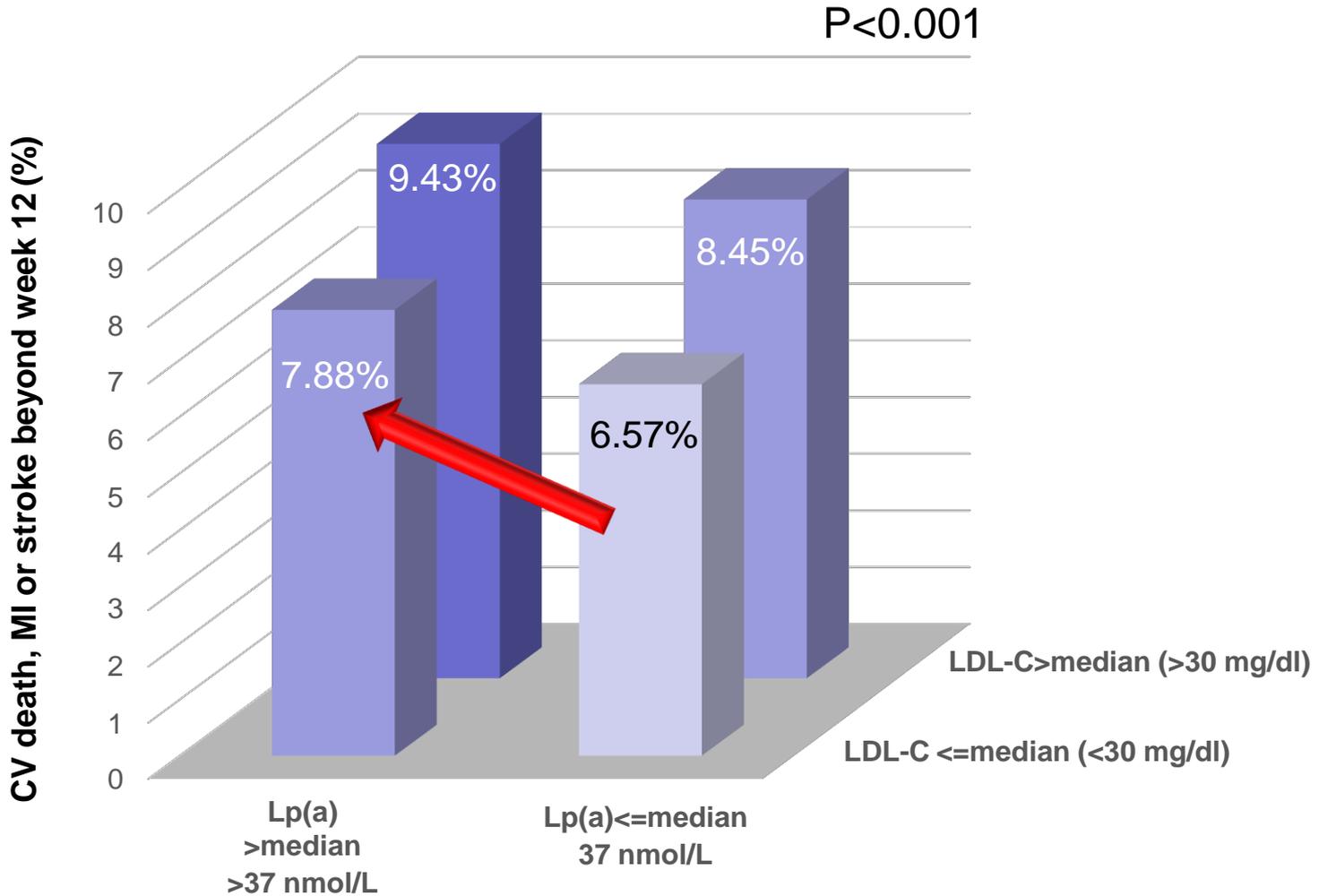
Reiner Z et al. Eur Heart J 2011;32:1769-818

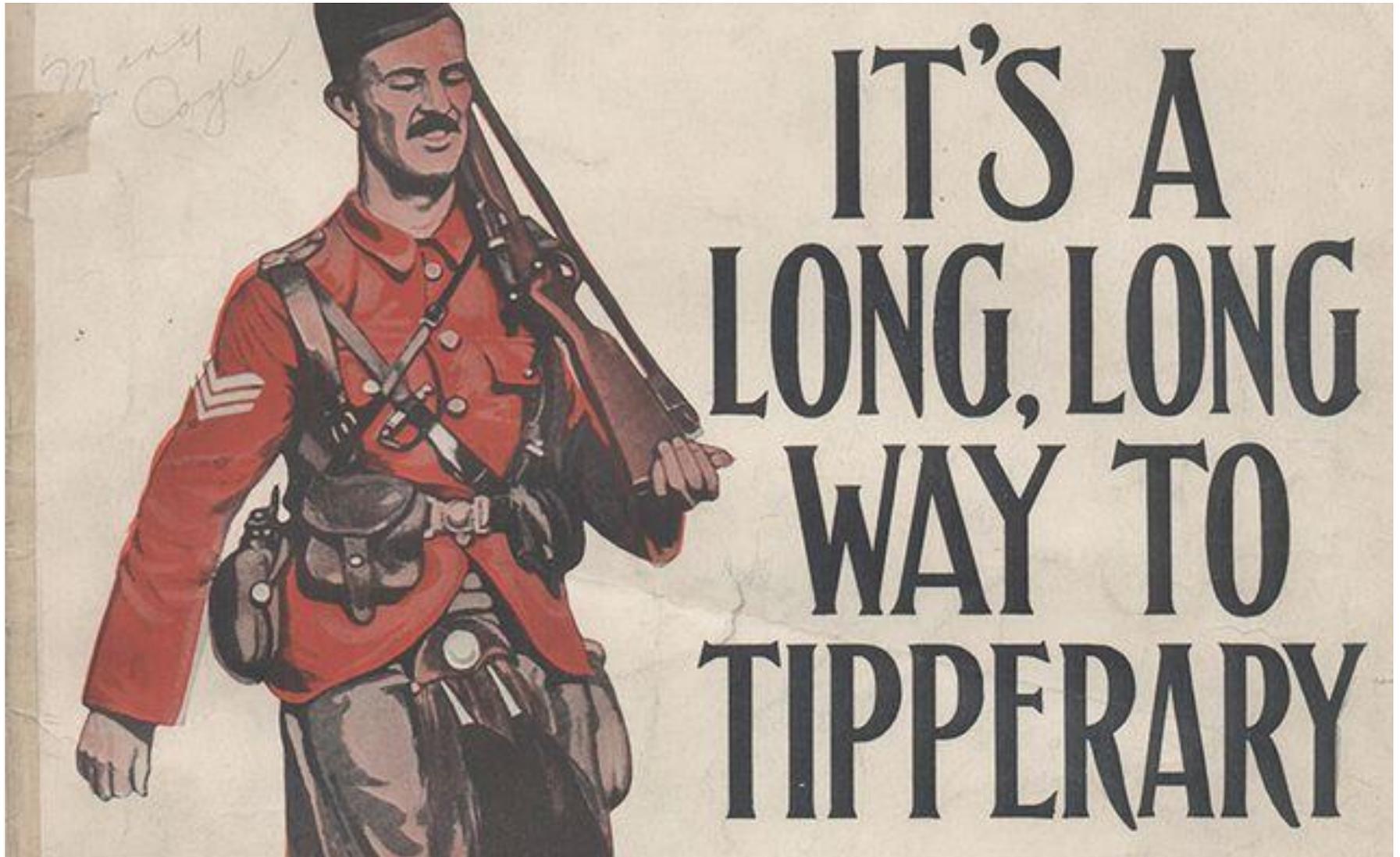
# Inflammatory and Cholesterol Risk in the FOURIER Trial





# Achieved Lp(a), LDL and CV Risk





**IT'S STILL A LONG, LONG WAY TO TIPPERARY!!!**