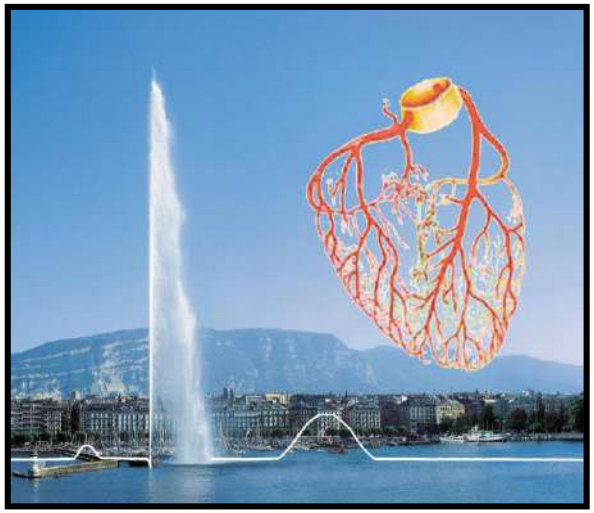
Wrap-up session of my experience at the TIMI study group

Baris Gencer, MD
Cardiology Division
Geneva University Hospitals
April 1, 2021

Acknowledgments



Special Thanks to Professor François Mach and the Geneva University Hospitals

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

HUG Hôpitaux Universitaires Genève

From TIMI 1 to TIMI 70

The New England Journal of Medicine

Established in 1812 as The NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

VOLUME 312 APRIL 4, 1985 NUMBER 14

Special Report

The Thrombolysis in Myocardial Infarction (TIMI) Trial: Phase I Findings 932

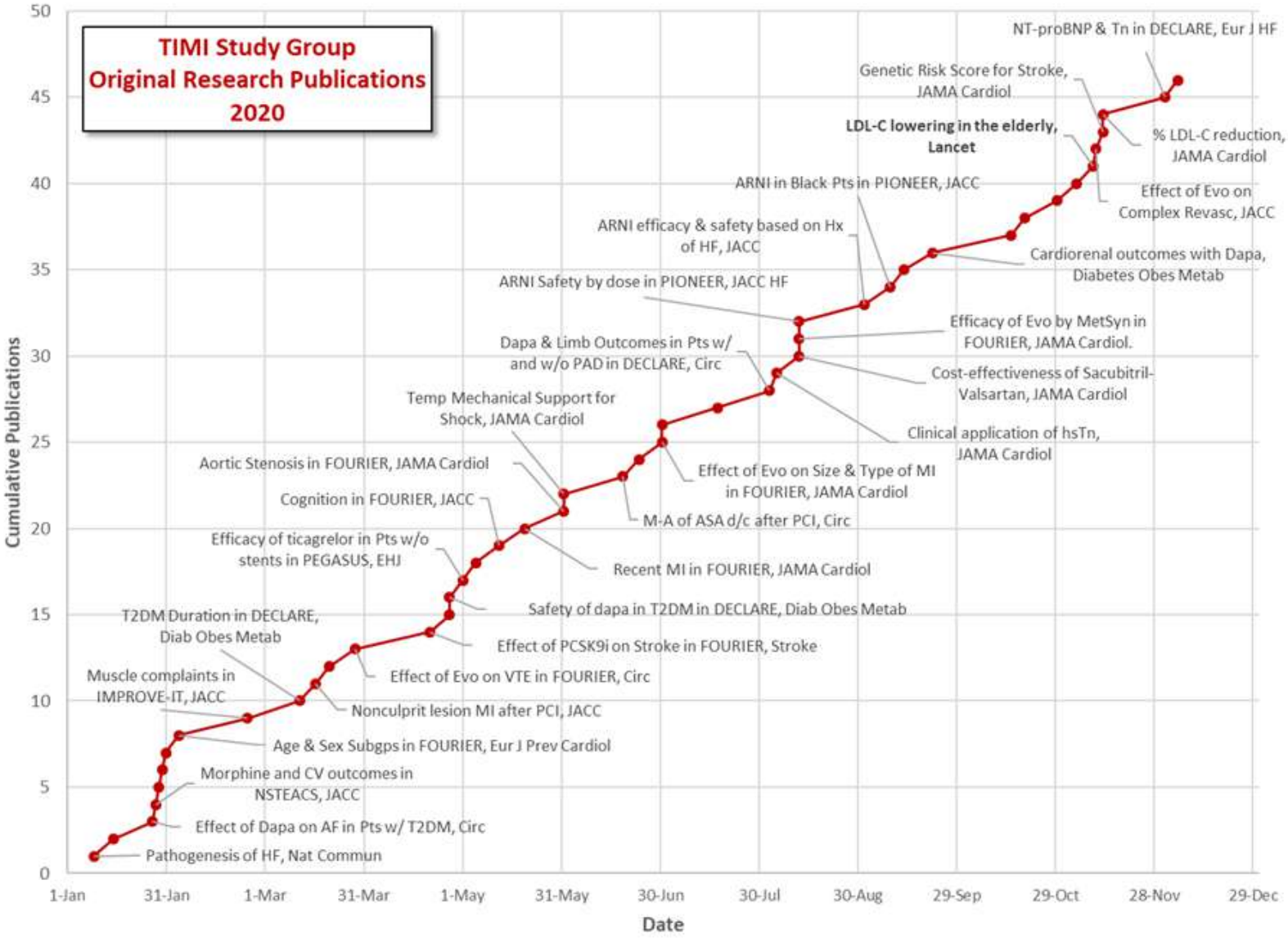
THE TIMI STUDY GROUP

Fibrinolytic Antithrombotic Antiplatelet Lipid-modifying

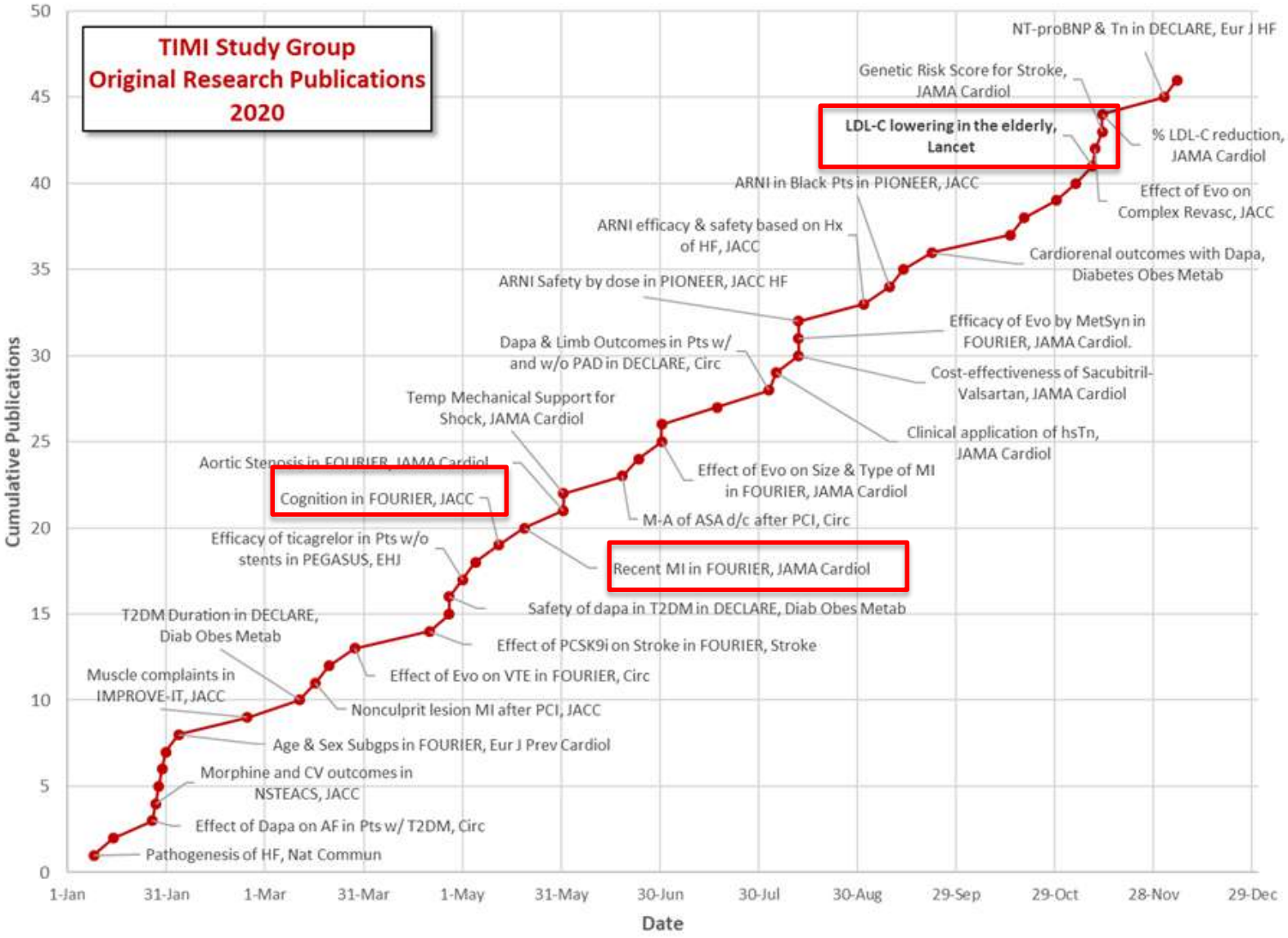
Anti-diabetes Anti-inflammatory Anti-ischemic Anti-obesity

TIMI Risk Score Genetic and biomarker

Publications in 2020



Publications in 2020



Activities of the TIMI Study Group

- Academic Trial Leadership
- Global Trial Management
- Biostatistics
- Clinical Events Committee
- Safety Desk
- Medical Hotline
- Core Lab
- Scientific publications

Scientific Proposal Template

Lead Author	
Working Short Title of Proposed Analyses	
Background	
What question will this research answer?	
Hypothesis	
Trial database(s)	
Brief analytic plan	
Target scientific meeting	

Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials

Baris Gencer, Nicholas A Marston, KyungAh Im, Christopher P Cannon, Peter Sever, Anthony Keech, Eugene Braunwald, Robert P Giugliano, Marc S Sabatine

Lancet 2020,396:1637-43

Background

- The clinical trials of therapies **lowering low-density lipoprotein cholesterol (LDL-C) levels have consistently demonstrated cardiovascular (CV) event reduction.**
- However, the clinical benefit from LDL-C lowering therapy in the **elderly remains debated** because participants **aged ≥75 years** were not well represented in individual trials.
- Practice guidelines have noted that the **level of evidence in the elderly population is low** and some have lower strength recommendations for older patients.

2018 US Guidelines – 1st Prevention

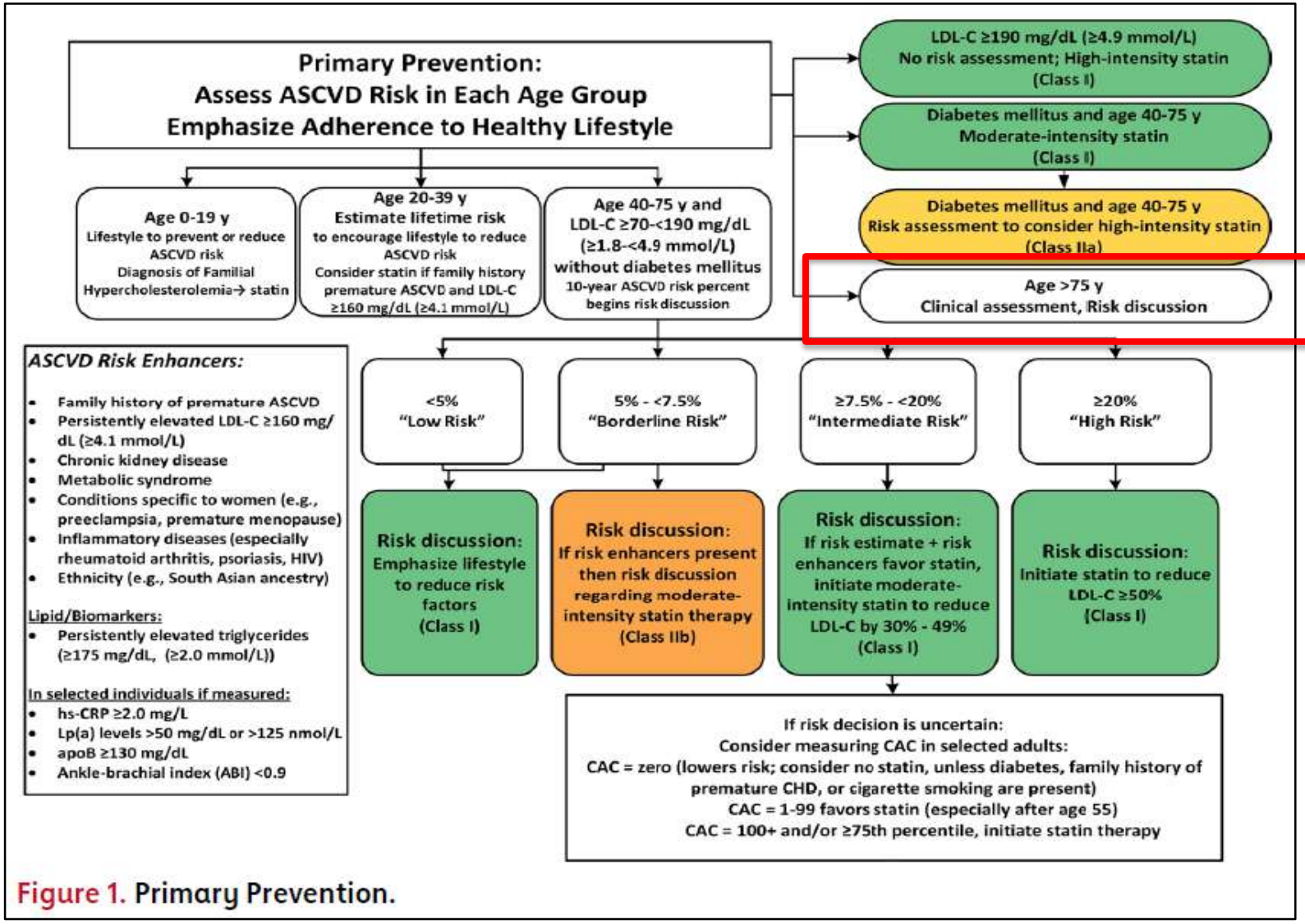
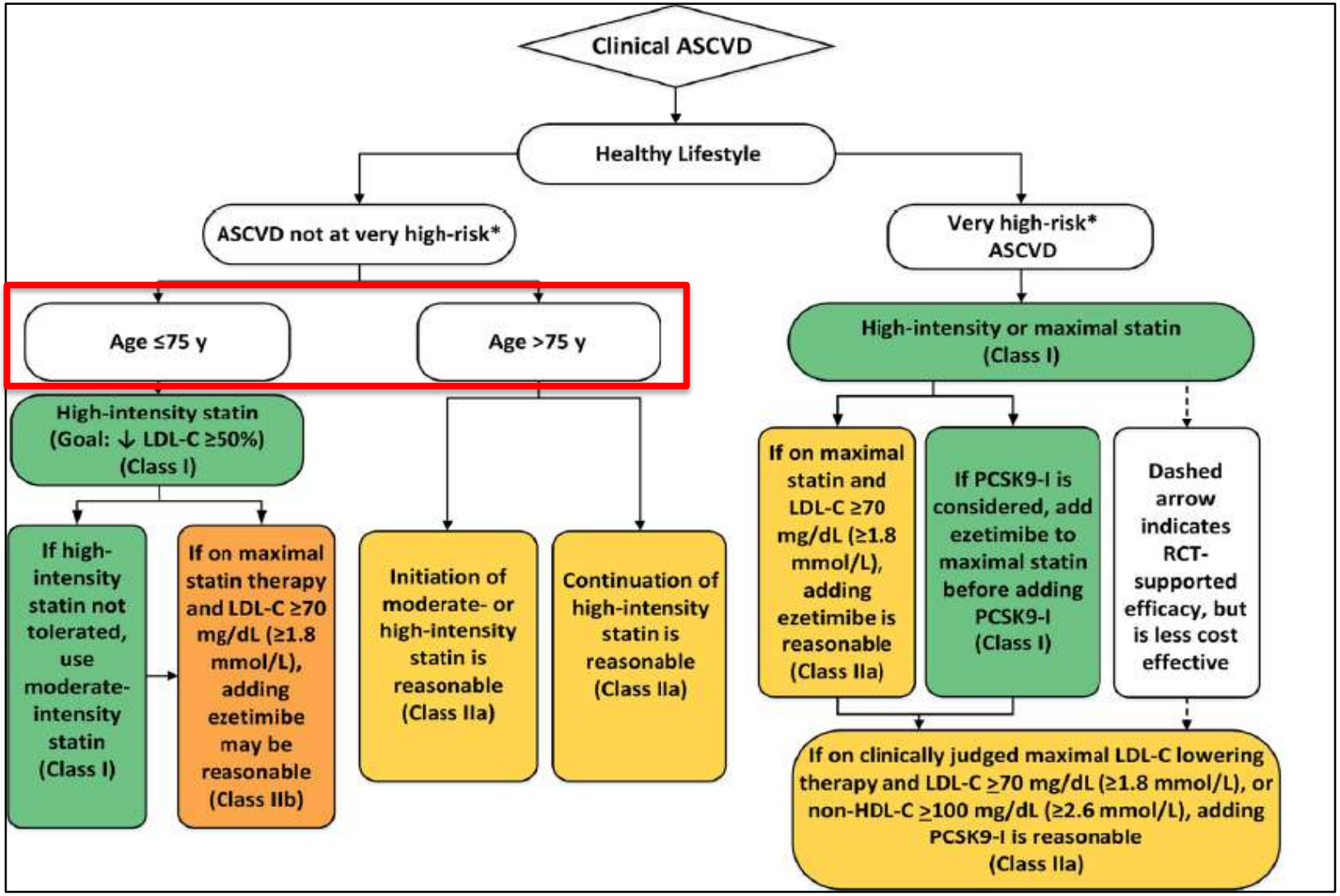


Figure 1. Primary Prevention.

J Am Coll Cardiol. 2019 Jun 25;73(24):e285-e350.

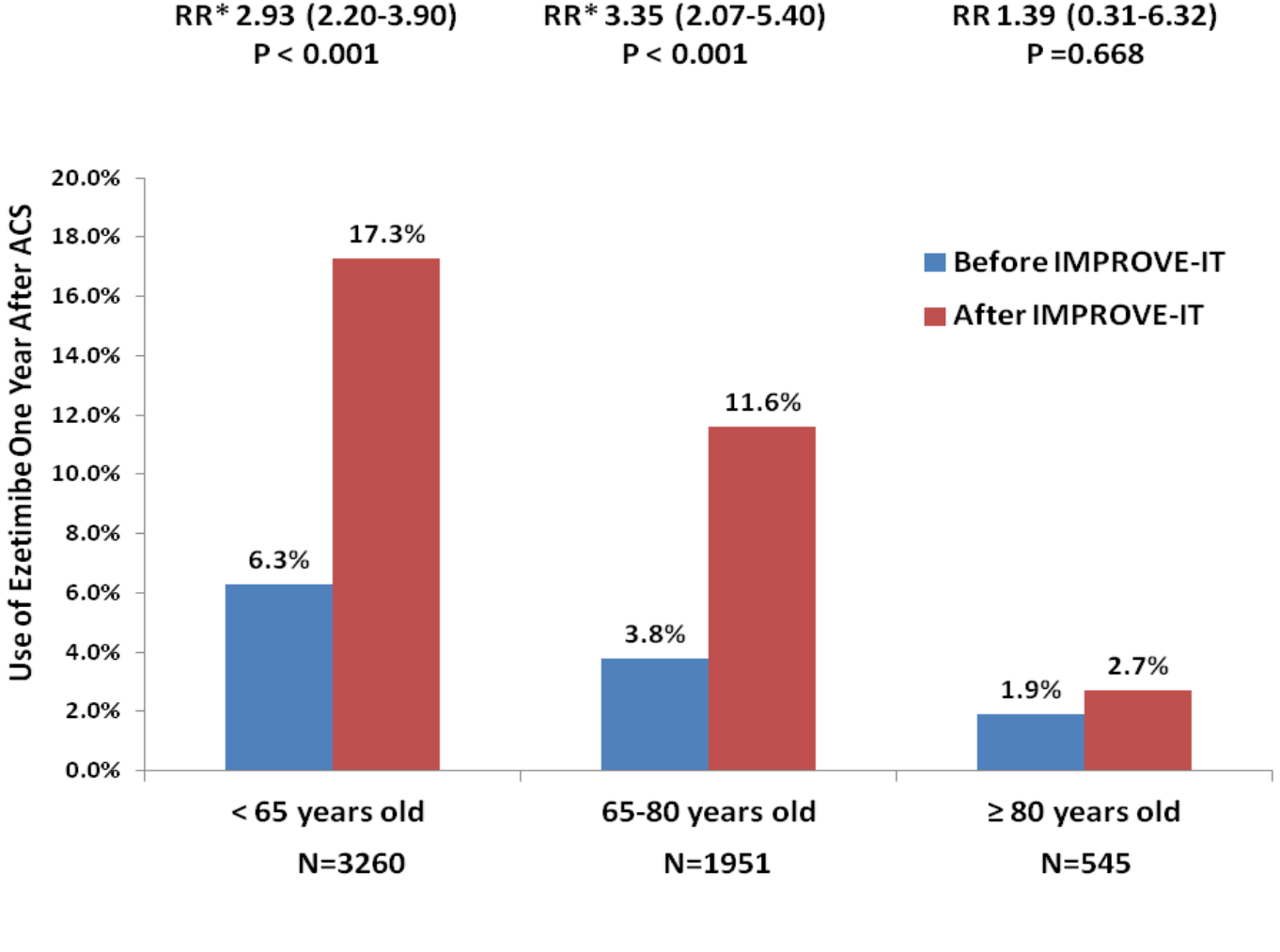
2018 US Guidelines – 2nd Prevention



J Am Coll Cardiol. 2019 Jun 25;73(24):e285-e350.

Elderly Undertreated after ACS

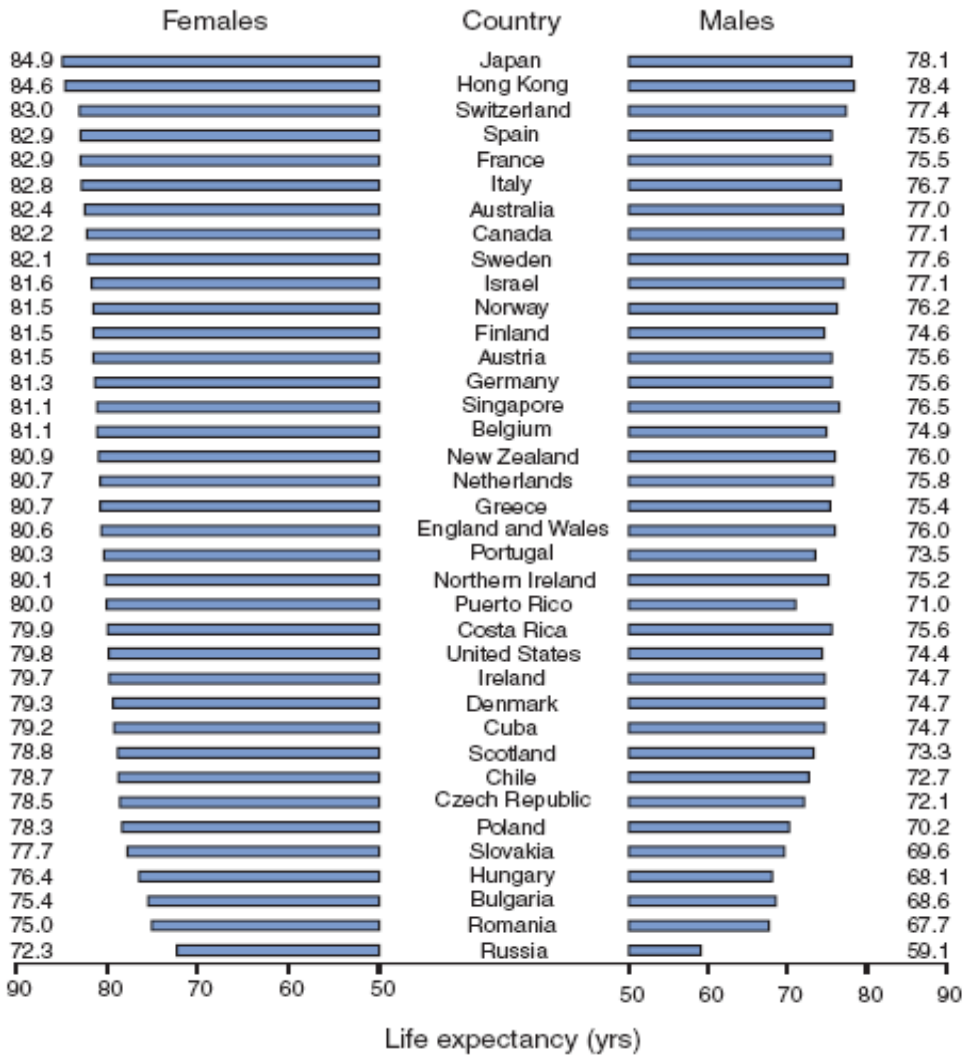
Swiss ACS Patients N=5756



Gencer B et al, Int J Cardiol. 2020 Mar 15;303:8-1

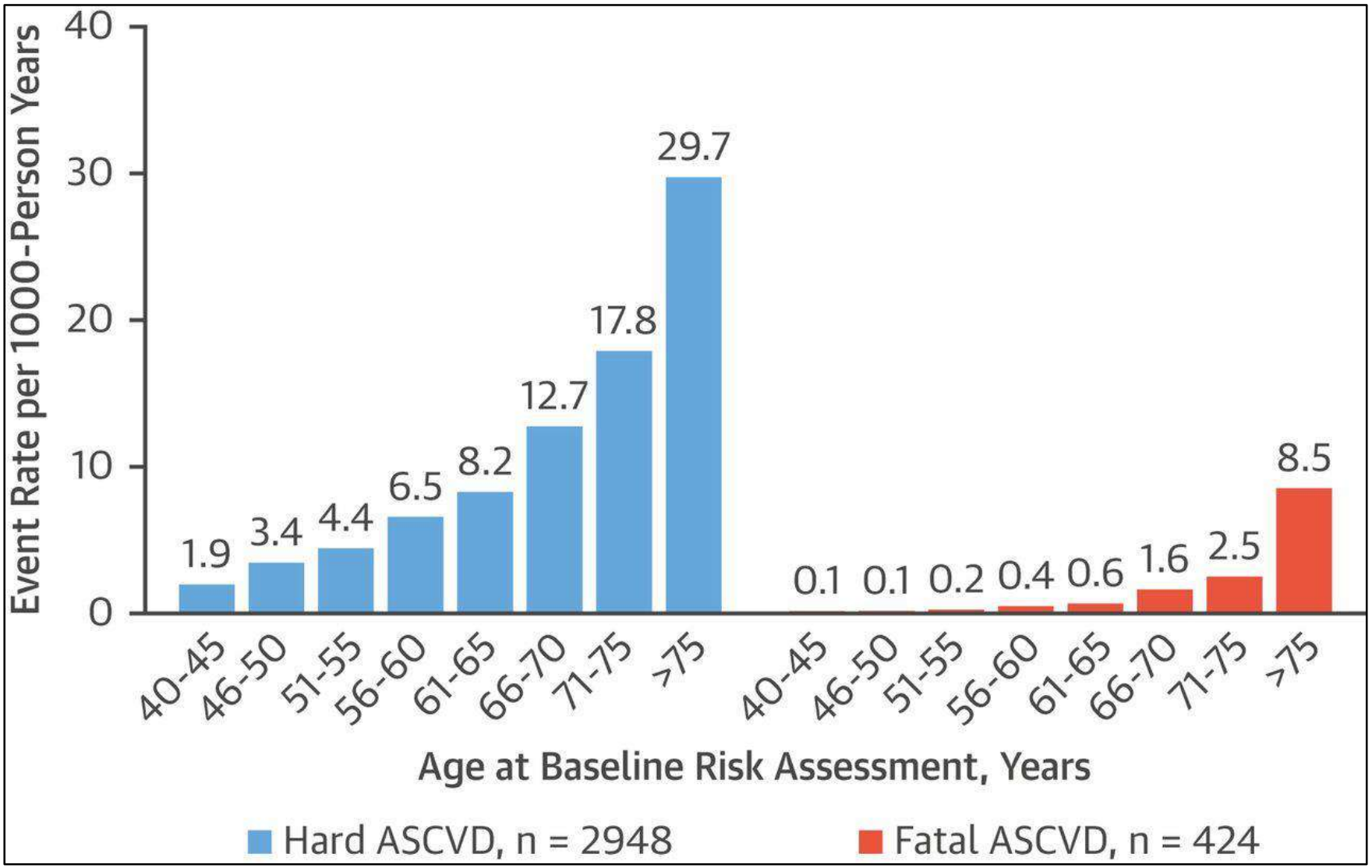
Life Expectancy

75-85 yrs



National Center for Health Statistics, Health, United States, 2005.

CV morbidity and mortality



J Am Coll Cardiol. 2018 Jan 2;71(1):85-94.

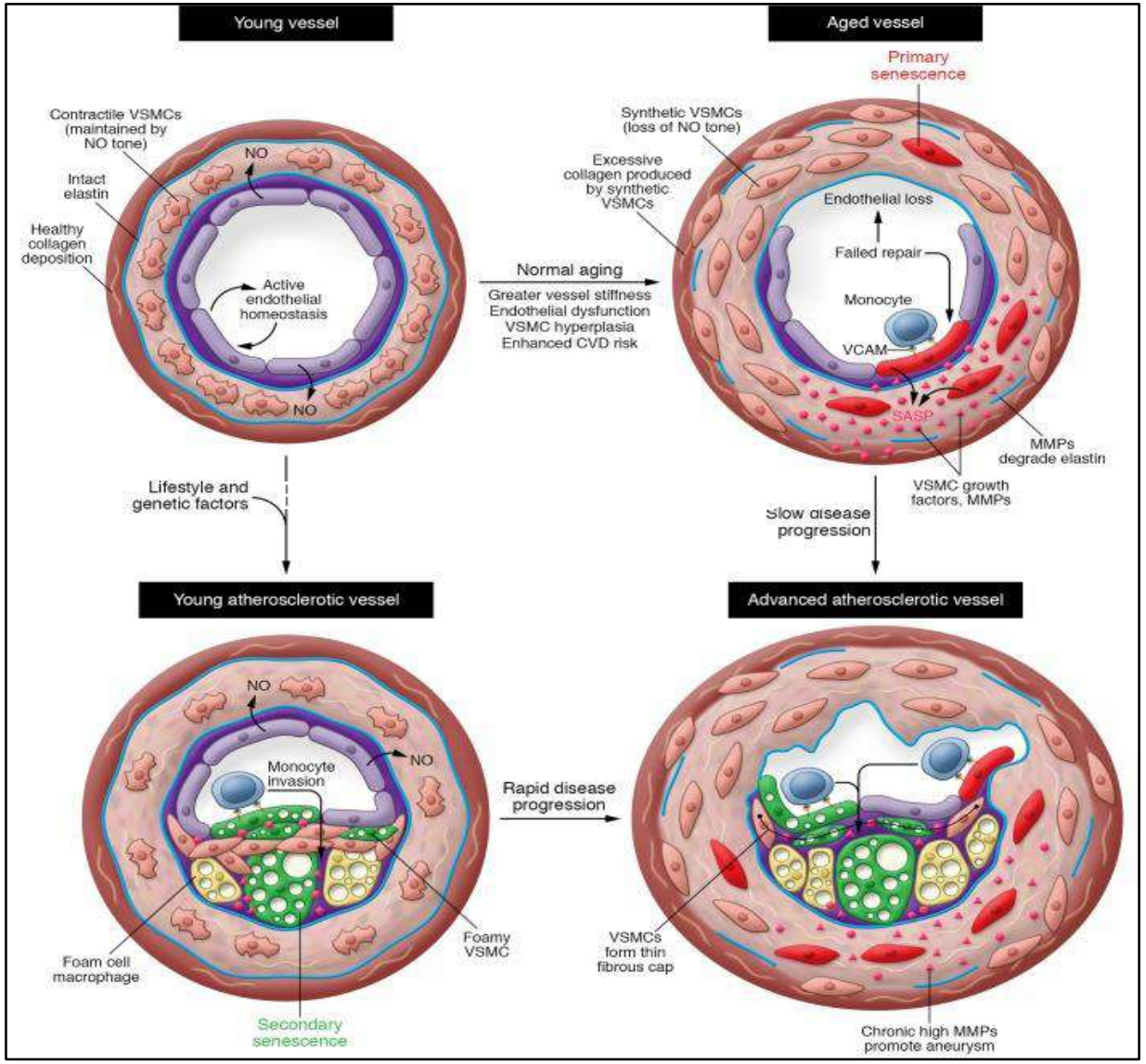
Lack of an association or an inverse association between low-density-lipoprotein cholesterol and mortality in the elderly: a systematic review

Uffe Ravnskov,[1] David M Diamond,[2] Rokura Hama,[3] Tomohito Hamazaki,[4] Björn Hammarskjöld,[5] Niamh Hynes,[6] Malcolm Kendrick,[7] Peter H Langsjoen,[8] Aseem Malhotra,[9] Luca Mascitelli,[10] Kilmer S McCully,[11] Yoichi Ogushi,[12] Harumi Okuyama,[13] Paul J Rosch,[14] Tore Schersten,[15] Sherif Sultan,[6] Ralf Sundberg[16]

Conclusions: High LDL-C is inversely associated with mortality in most people over 60 years. This finding is inconsistent with the cholesterol hypothesis (ie, that cholesterol, particularly LDL-C, is inherently atherogenic). Since elderly people with high LDL-C live as long or longer than those with low LDL-C, our analysis provides reason to question the validity of the cholesterol hypothesis. Moreover, our study provides the rationale for a re-evaluation of guidelines recommending pharmacological reduction of LDL-C in the elderly as a component of cardiovascular disease prevention strategies.

BMJ Open. 2016; 6(6): e010401.

Biology of CV Aging



J Clin Invest. 2018 Apr 2;128(4):1217-1228

Key publications in 2019-2020

Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials

*Cholesterol Treatment Trialists' Collaboration**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke

Effect of alirocumab on cardiovascular outcomes after acute coronary syndromes according to age: an ODYSSEY OUTCOMES trial analysis

ORIGINAL RESEARCH ARTICLE

Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older (EWTOPIA 75)

JAMA Cardiology | Original Investigation

Effect of Simvastatin-Ezetimibe Compared With Simvastatin Monotherapy After Acute Coronary Syndrome Among Patients 75 Years or Older
A Secondary Analysis of a Randomized Clinical Trial

LDL-cholesterol lowering with evolocumab, and outcomes according to age and sex in patients in the FOURIER Trial

Objectives

These new data give the opportunity:

- To summarize the evidence of lipid-lowering therapies in the elderly population with a meta-analysis.
- To address whether elderly patients should be treated less intensively than younger patients.

Literature Search

- A data search (BG, NM) of all CV outcome trials of LDL-C lowering and published between March 2015 1st and August 14th 2020 was done on MEDLINE and Embase.
- The literature search was done independently by two co-authors for the screening of the titles, abstracts and full text of papers and risk of bias assessment (BG, NM).

Selection Criteria

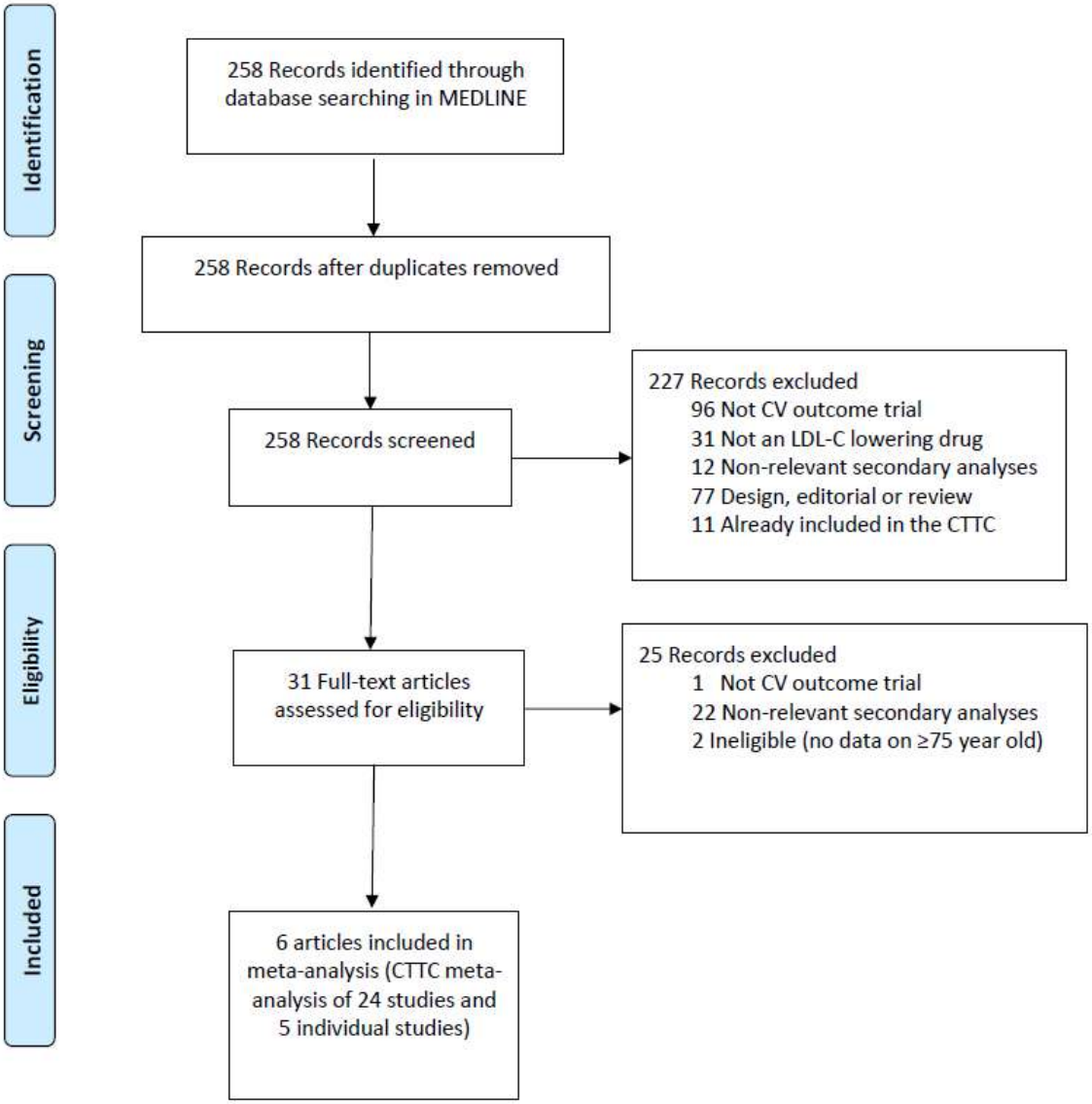
1) Randomized Controlled Trial
2) Cardiovascular outcomes
3) Recommended LDL-C lowering drugs (statin, ezetimibe or PCSK9 inhibitors)
4) At least a median follow-up of 2 years
5) Data in older patients aged ≥75 years old

Research Algorithm

The following algorithm was used :

("Cholesterol"[Mesh] OR "LDL"[tiab] OR "Lipid"[tiab]) AND ("Ezetimibe"[tiab] OR "PCSK9 inhibitors"[tiab] OR "Alirocumab"[tiab] OR "statin" OR "Evolocumab"[tiab] OR "Anticholesteremic Agent"[tiab] OR "Hypolipidemic Agent"[tiab] OR "Non-statin"[tiab]) AND (random[tw] OR "trial"[tiab]) AND ("Myocardial Infarction"[Mesh] OR "Myocardial Infarction"[tiab] OR "stroke"[Mesh] OR "stroke"[tiab] OR "death"[Mesh] OR "death"[tiab] OR "MACE"[tiab] OR "major adverse cardiovascular events"[tiab] OR "major adverse cardiac events"[tiab]) NOT (Review[ptyp]).*

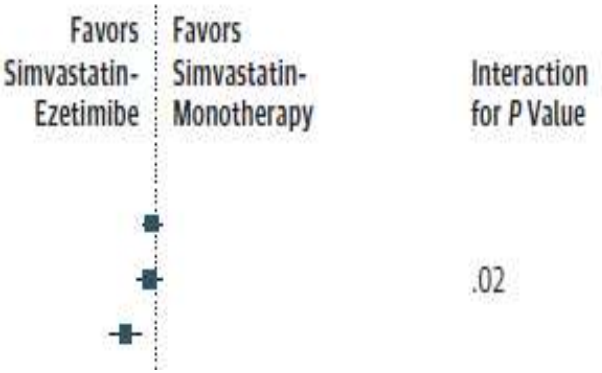
PRISMA Flow Diagram



Data extraction (example)

IMPROVE-IT (*JAMA Cardiol.* 2019;4(9):846-854).

Event	Total No. of Events	Event Rate at 7 y[a] Simvastatin-Ezetimibe	Simvastatin-Monotherapy	HR (95% CI)[b]
Primary composite end point, age, y				
<65	2707	29.9	30.8	0.97 (0.90-1.05)
65-74	1590	35.1	35.9	0.96 (0.87-1.06)
≥75	1017	38.9	47.6	0.80 (0.70-0.90)



HR	Lower 95%CI HR	Higher 95%CI HR
0.80	0.70	0.90

LDL-C reduction ezetimibe vs. placebo: 0.3525 mmol/L

=HR^(1/Difference LDL-C mmol/l)
=0.80^(1/0.3525)=0.53

Normalization to
1 LDL-C reduction

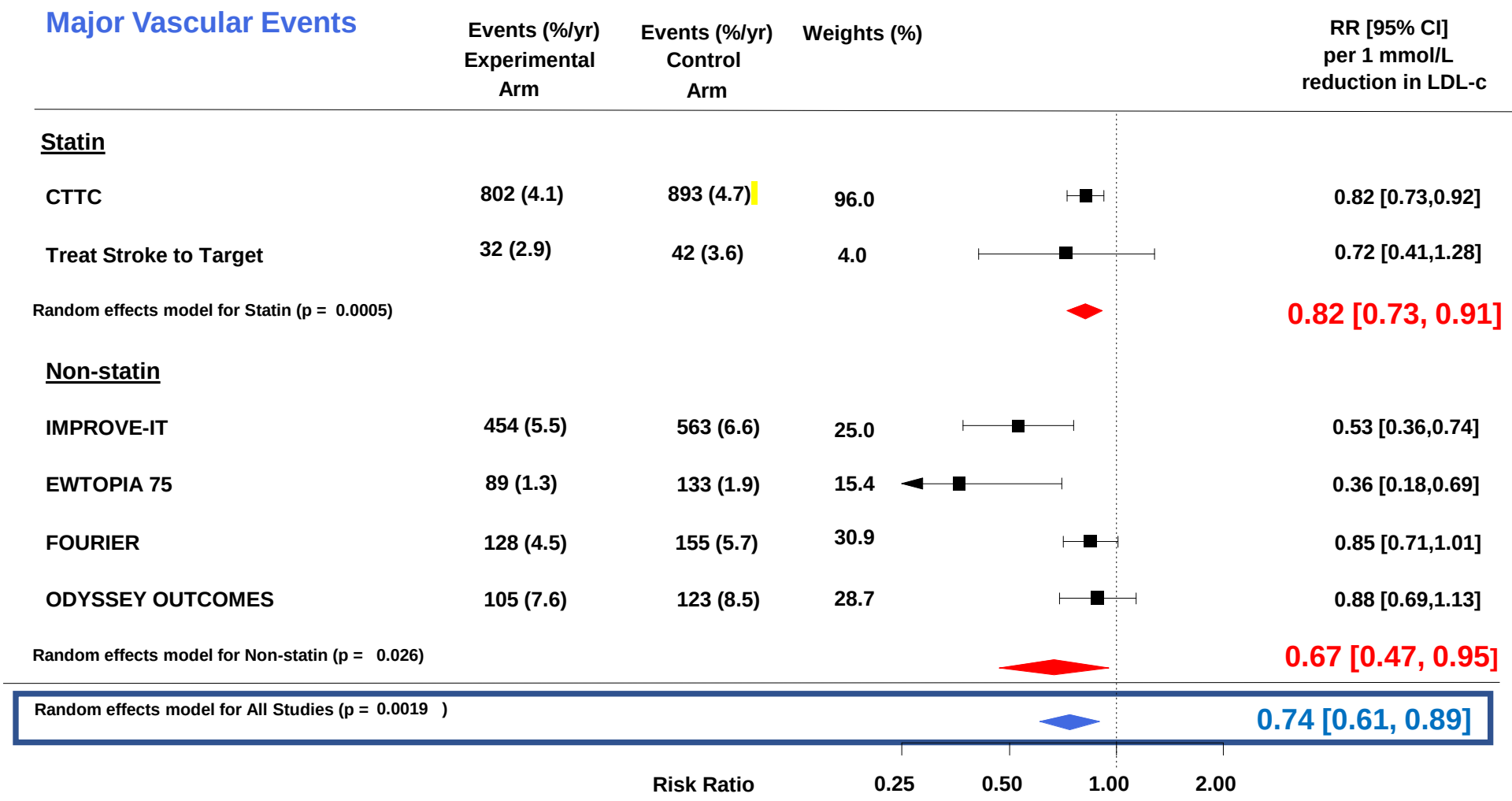
Baseline Table

Studies	Number Elderly	1st vs. 2nd Prevention	Experimental Arm	Control Arm	Delta LDL-C mmol/L	Median of follow-up in years	Number Major Vascular Events
Statin							
CTTC of 24 Trials	11,108	Mixed	Statin or more intensive statin	Placebo or less intensive statin	1.0	4.9	**1,695**
Treat Stroke To Target	642	2nd	Target LDL-C <1.8 mmol/L	Target LDL-C 2.3-2.8 mmol/L	0.8	3.5	**74**
Non-statin							
IMPROVE-IT	2,798	2nd	Ezetimibe+ Simvastatin	Placebo+ Simvastatin	0.4	6.0	**1,017**
EWTOPIA 75	3,411	1st	Ezetimibe	Usual care	0.4	4.1	**222**
FOURIER	2,526	2nd	Evolocumab	Placebo	1.3	2.2	**283**
ODYSSEY	1,007	2nd	Alirocumab	Placebo	1.0	2.8	**228**
TOTAL of 29 trials	**21,492**	**Mixed**			**0.9**	**3.3 (2.2-4.6)**	**3,519**

Risk of Bias Summary

	Random Sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personal (performance bias)	Blinding of outcome assessment (detection-bias)	Incomplete outcome data addressed (attrition bias)	Selective reporting (reporting bias)
CTTC	Low	Low	Low	Low	Low	Low
Treat Stroke to Target trial	Low	Low	Moderate	Low	Low	Low
IMPROVE-IT	Low	Low	Low	Low	Low	Low
EWTOPIA 75	Low	Low	Moderate	Low	Moderate	Low
FOURIER	Low	Low	Low	Low	Low	Low
ODYSSEY OUTCOMES	Low	Low	Low	Low	Low	Low

Effect of 1-mmol/L LDL-C lowering on the risk of major vascular events in the elderly

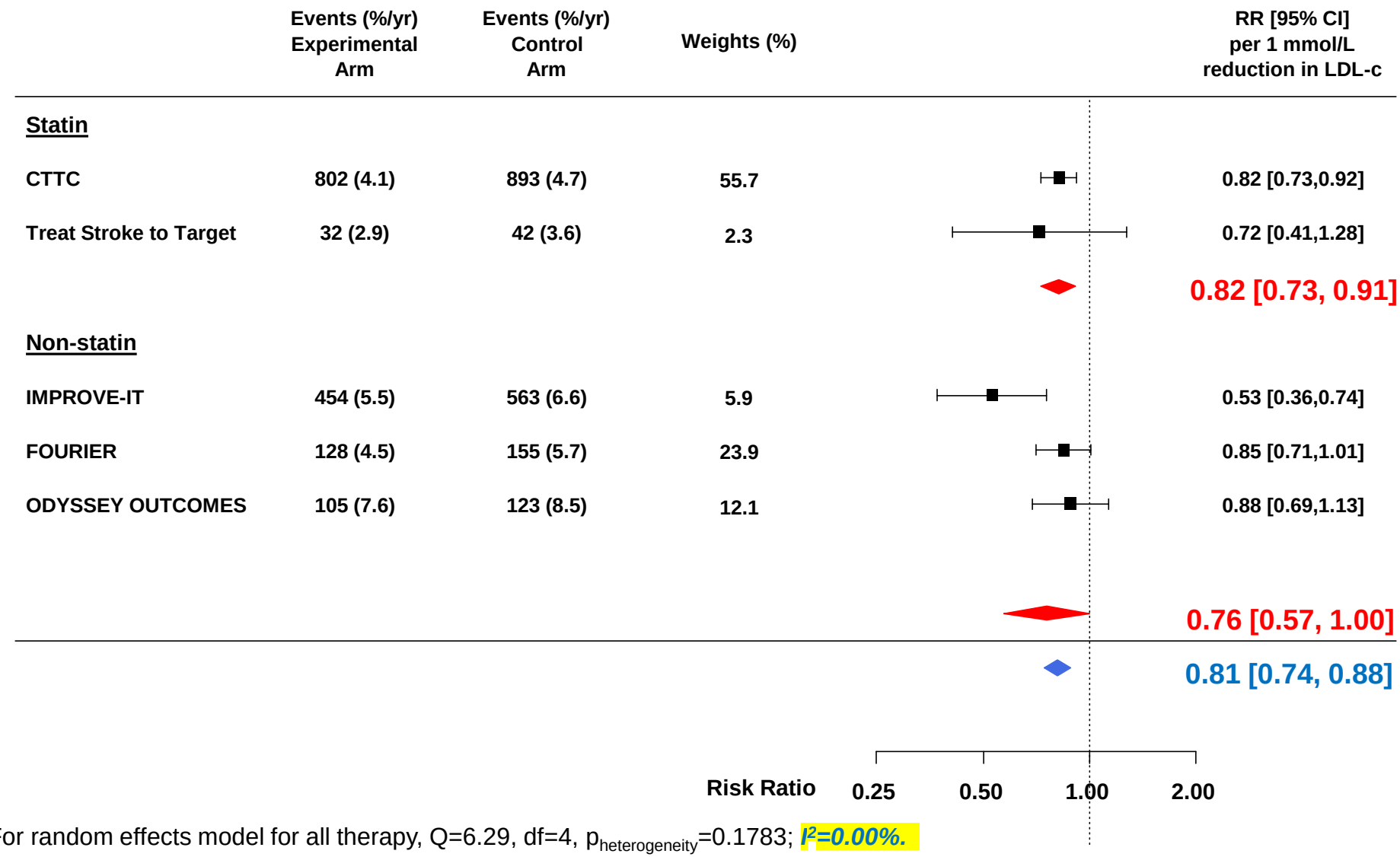


The interaction between statins and non-statin trials was not significant ($P_{interaction}=0.64$).

For random effects model for all therapy, Q=11.85, df=5, $p_{heterogeneity}=0.0369$; $I^2=67.61\%$.

Effect of 1-mmol/L LDL-C lowering on the risk of major vascular events in the elderly without EWTOPIA

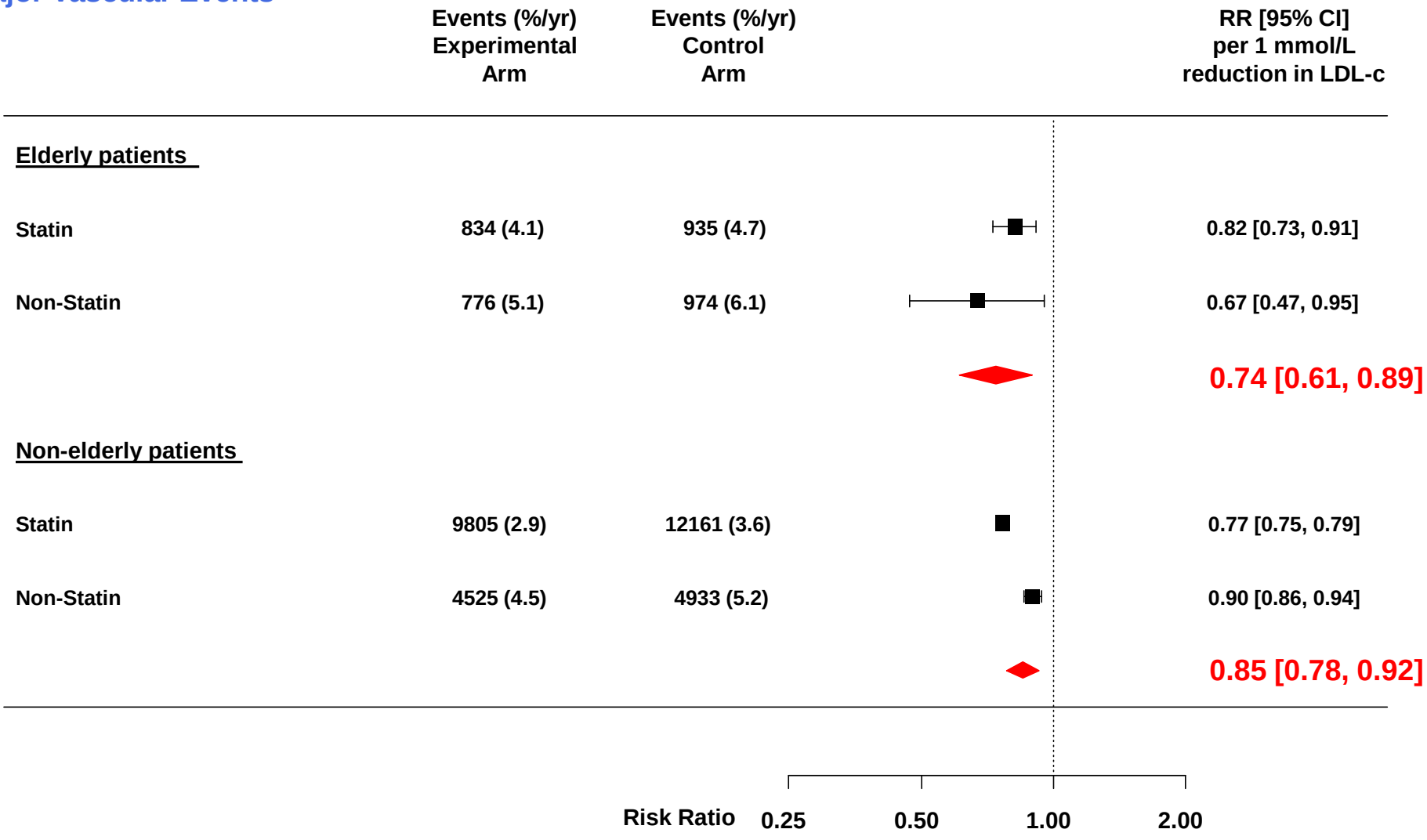
Major Vascular Events



For random effects model for all therapy, Q=6.29, df=4, $p_{heterogeneity}$=0.1783; I^2=0.00%.

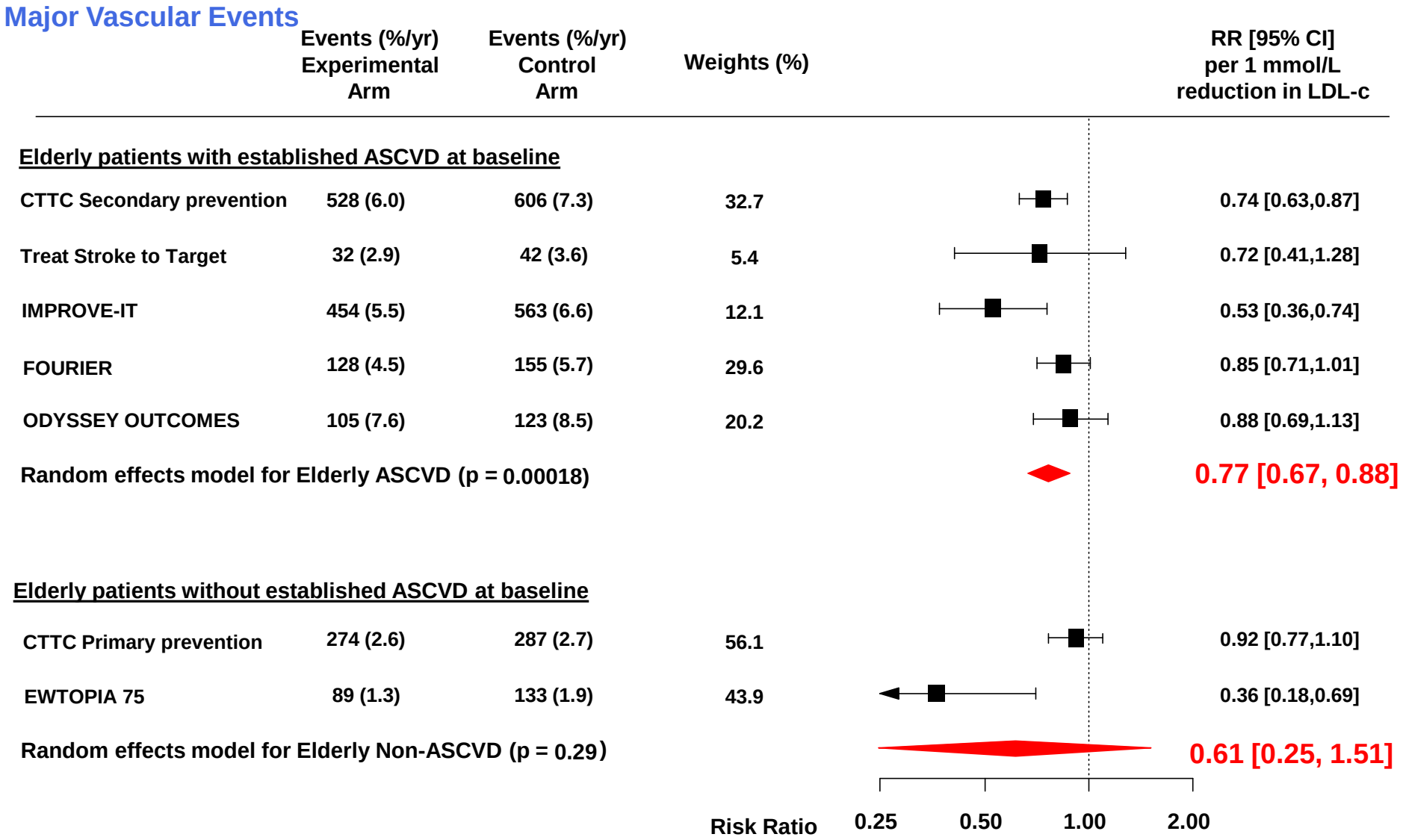
Effect of 1-mmol/L LDL-C lowering on the risk of major vascular events in the elderly vs. the non-elderly

Major Vascular Events



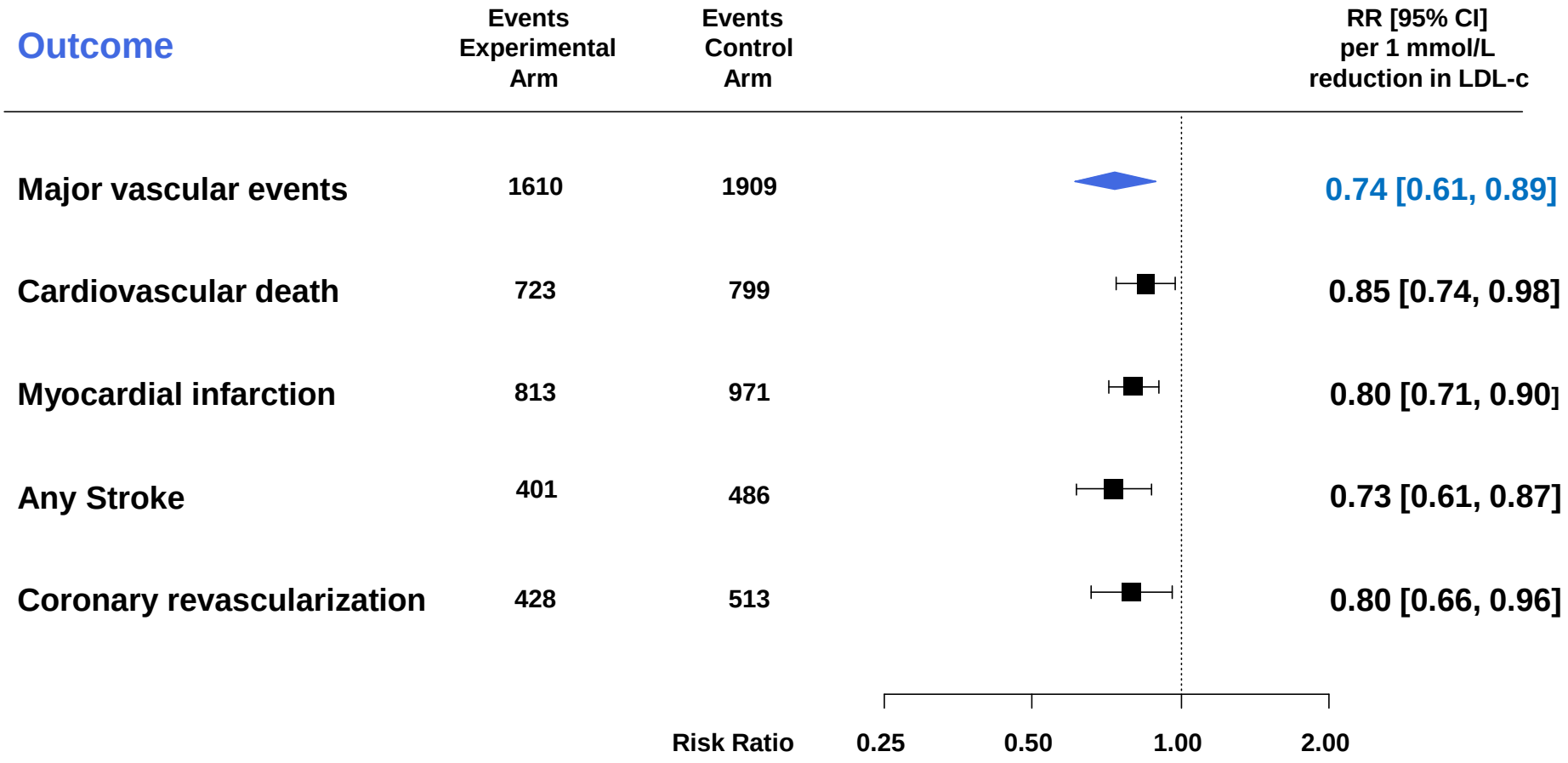
The interaction between the elderly vs. non elderly was not significant ($P_{interaction}=0.37$).

Effect of 1-mmol/L LDL-C lowering on the risk of major vascular events by baseline cardiovascular disease in the elderly

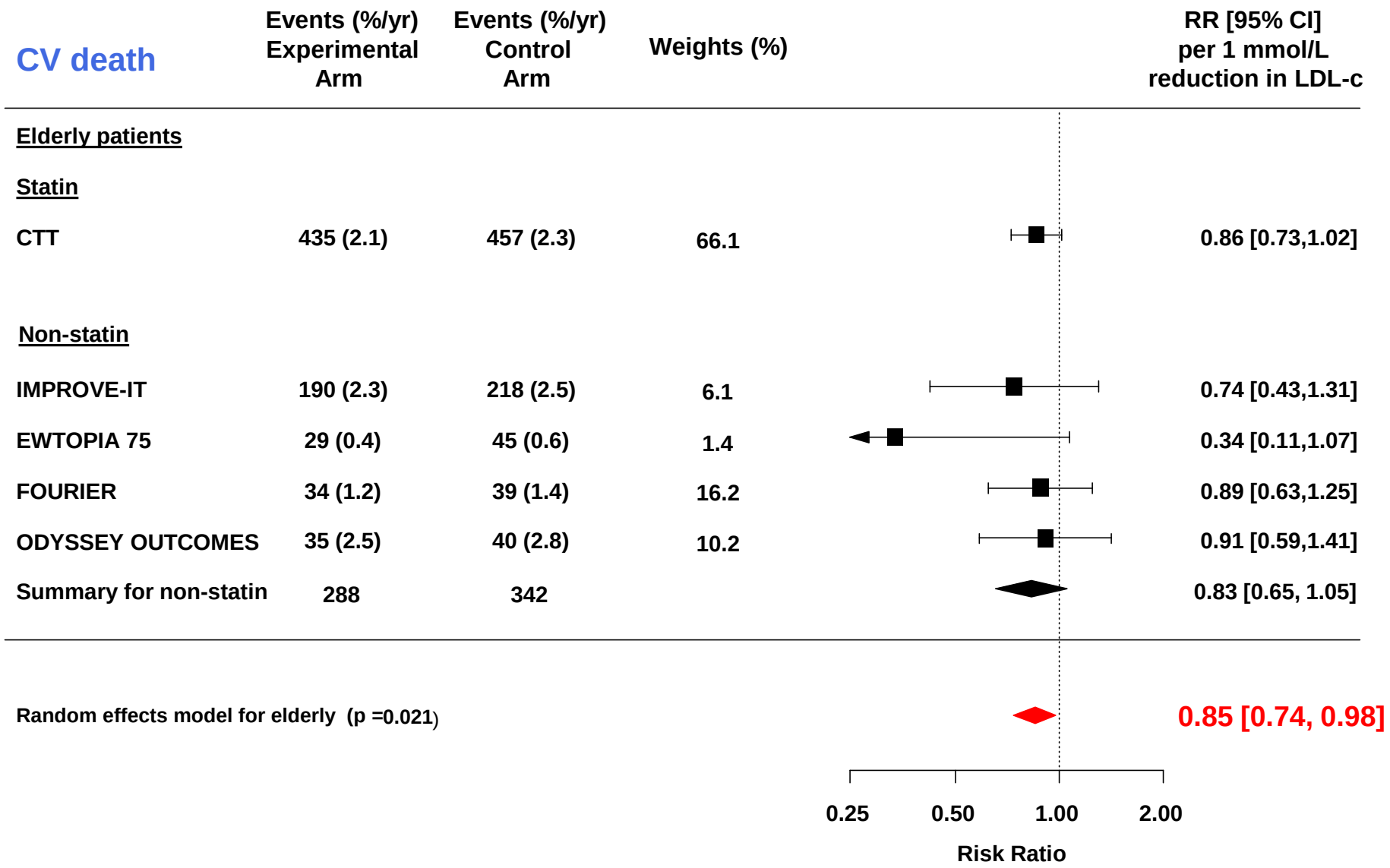


The interaction between established vs. non established ASCVD was not significant ($P_{interaction}=0.89$).

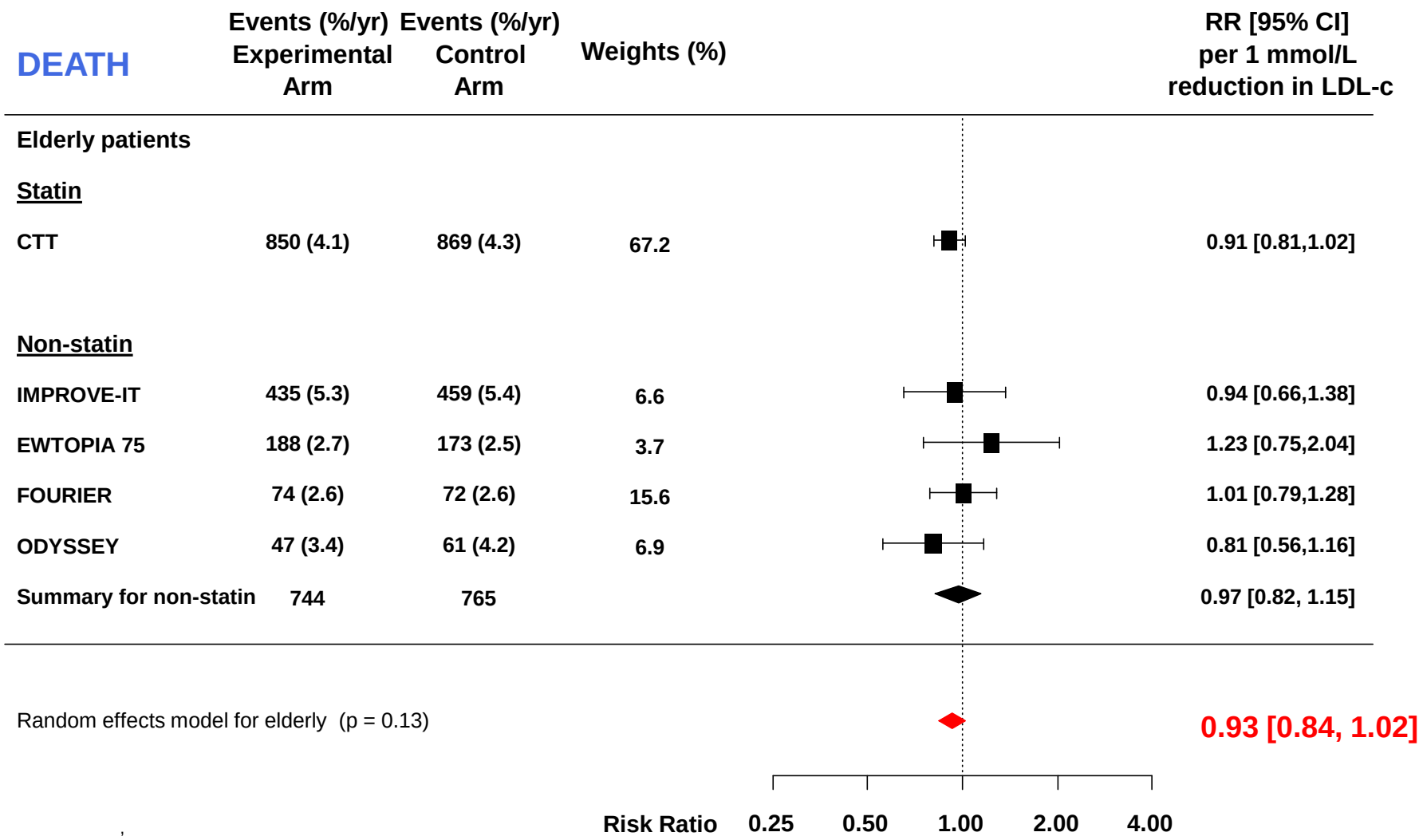
Effect of 1-mmol/L LDL-C lowering on the risk of individual efficacy endpoints in the elderly



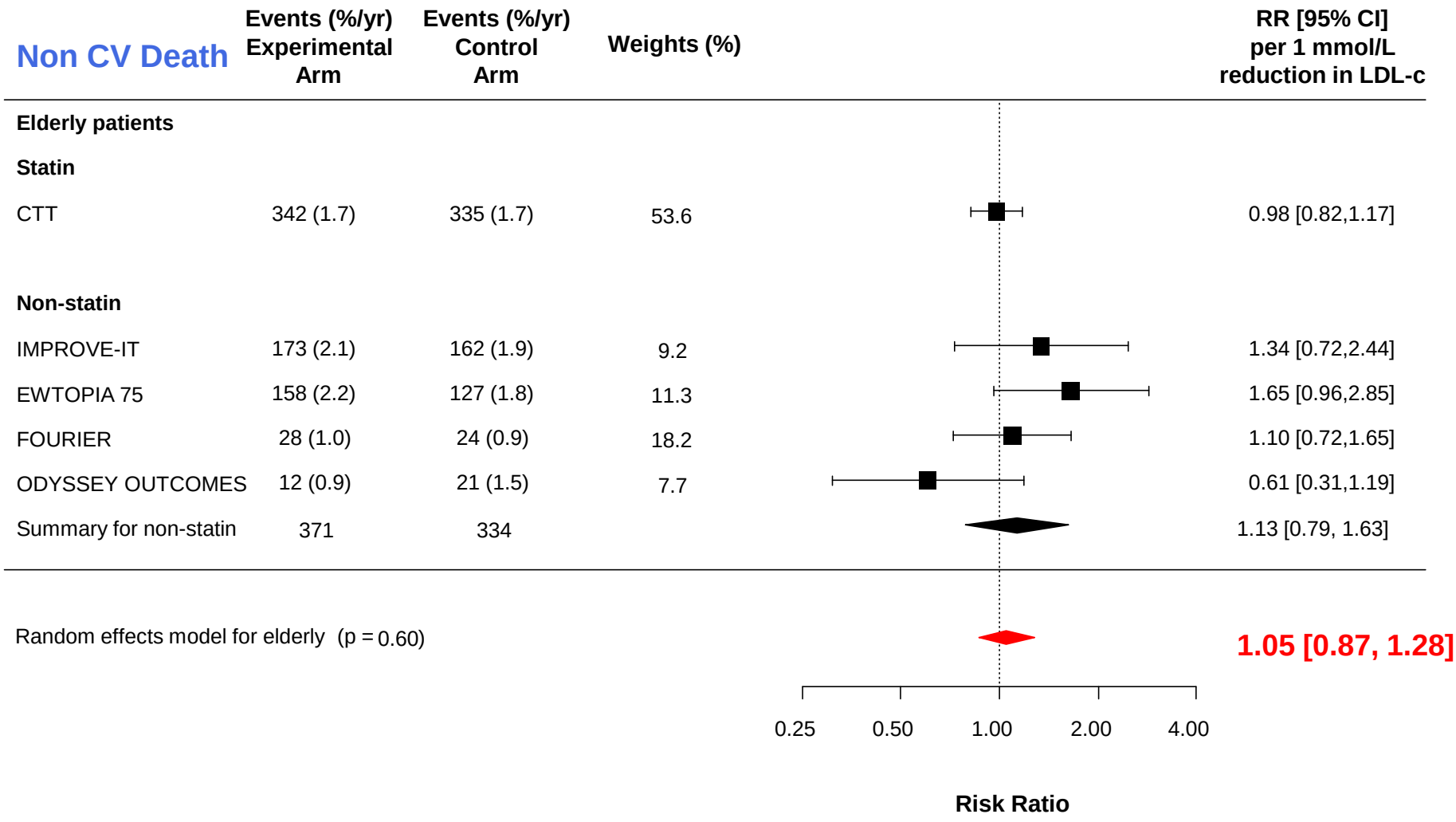
Effect of 1-mmol/L LDL-C lowering on the risk of CV death in the elderly



Effect of 1-mmol/L LDL-C lowering on the risk of all-cause death in the elderly

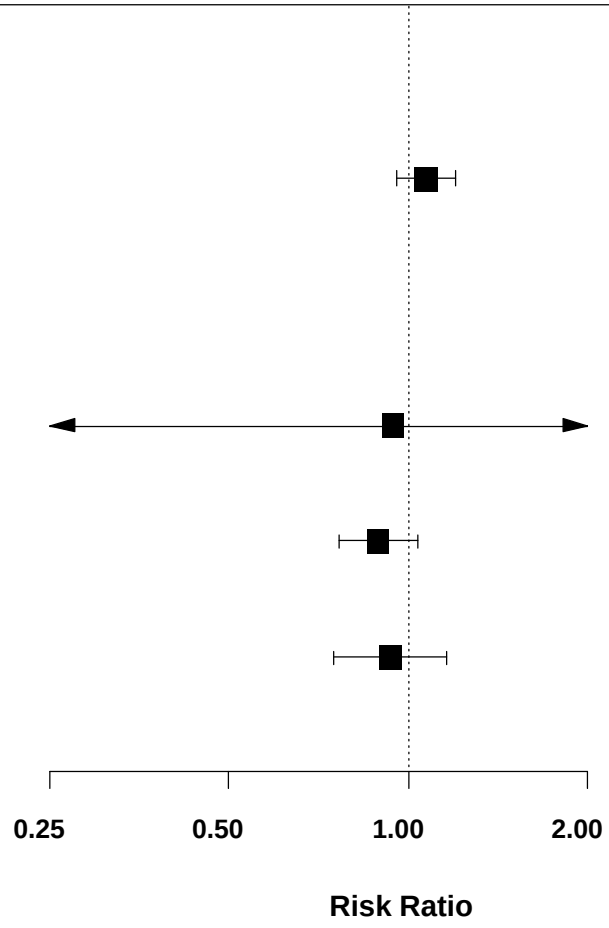


Effect of 1-mmol/L LDL-C lowering on the risk of non-CV death in the elderly



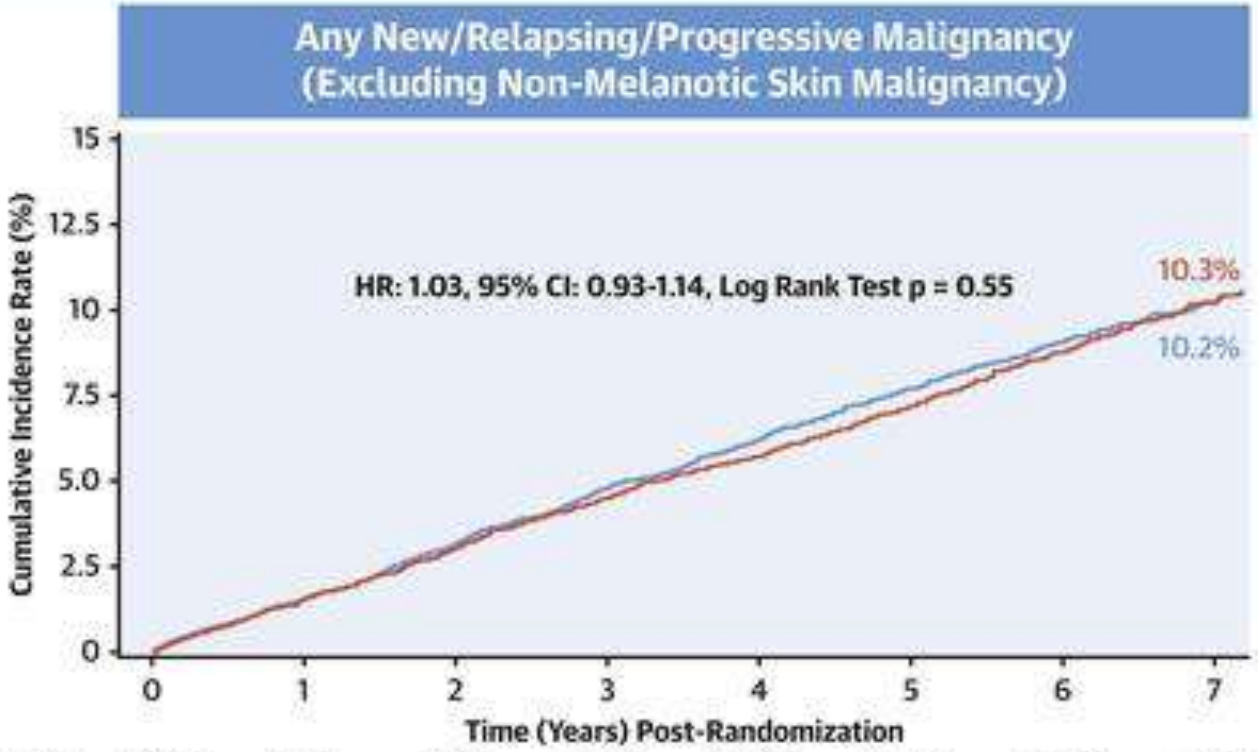
Effect of 1-mmol/L LDL-C lowering on the risk of safety endpoints in the elderly

Outcome	Events Experimental Arm	Events Control Arm	n/N (%) Experimental Arm	n/N (%) Control Arm	RR [95% CI] per 1 mmol/L reduction in LDL-C
Statin and non-statin					
Cancer	878	807	n/a	n/a	1.07 [0.96, 1.20]
Non-statin					
Hemorrhagic Stroke	27/6589	26/6677	0.4	0.4	0.94 [0.23, 3.85]
New onset diabetes	257/3449	286/3505	7.5	8.2	0.89 [0.77, 1.04]
Neurocognitive adverse events	165/5155	179/5239	3.2	3.4	0.93 [0.75, 1.16]



Risk of malignancy in 17,708 patients randomized to ezetimibe vs. placebo: IMPROVE-IT trial

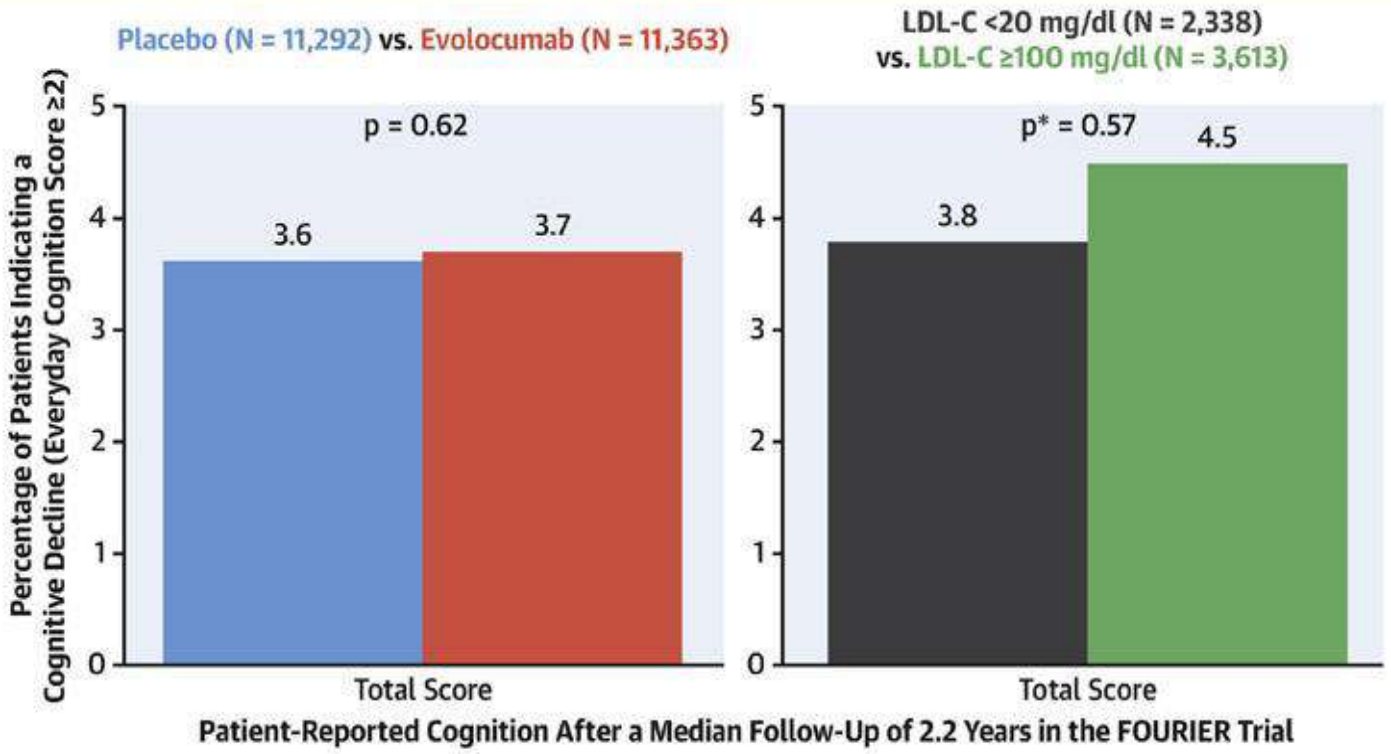
CENTRAL ILLUSTRATION: Cumulative Incidence Rates for the Primary Malignancy Endpoint by Treatment Arm



Giugliano, R.P. et al. J Am Coll Cardiol CardioOnc. 2020;2(3):385-96.

Cognition after LDL-C Lowering with Evolocumab N=22,655

CENTRAL ILLUSTRATION: Percentage of Patients Indicating Cognitive Decline (Everyday Cognition Score ≥2) at the End of the Study by Treatment Arm and Achieved Low-Density Lipoprotein-Cholesterol Target at 4 Weeks

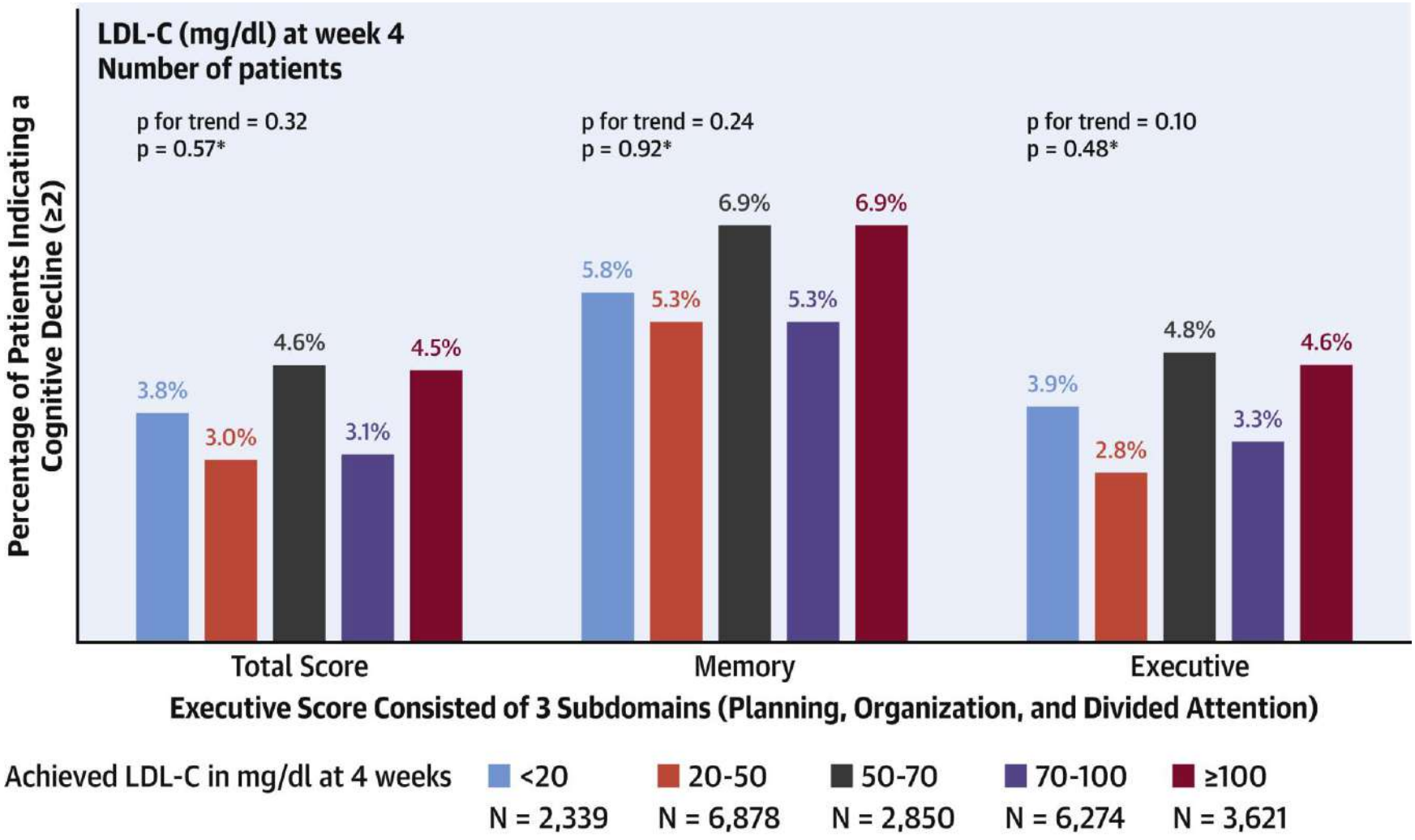


Patient-Reported Cognition After a Median Follow-Up of 2.2 Years in the FOURIER Trial

Gencer, B. et al. J Am Coll Cardiol. 2020;75(18):2283-93.

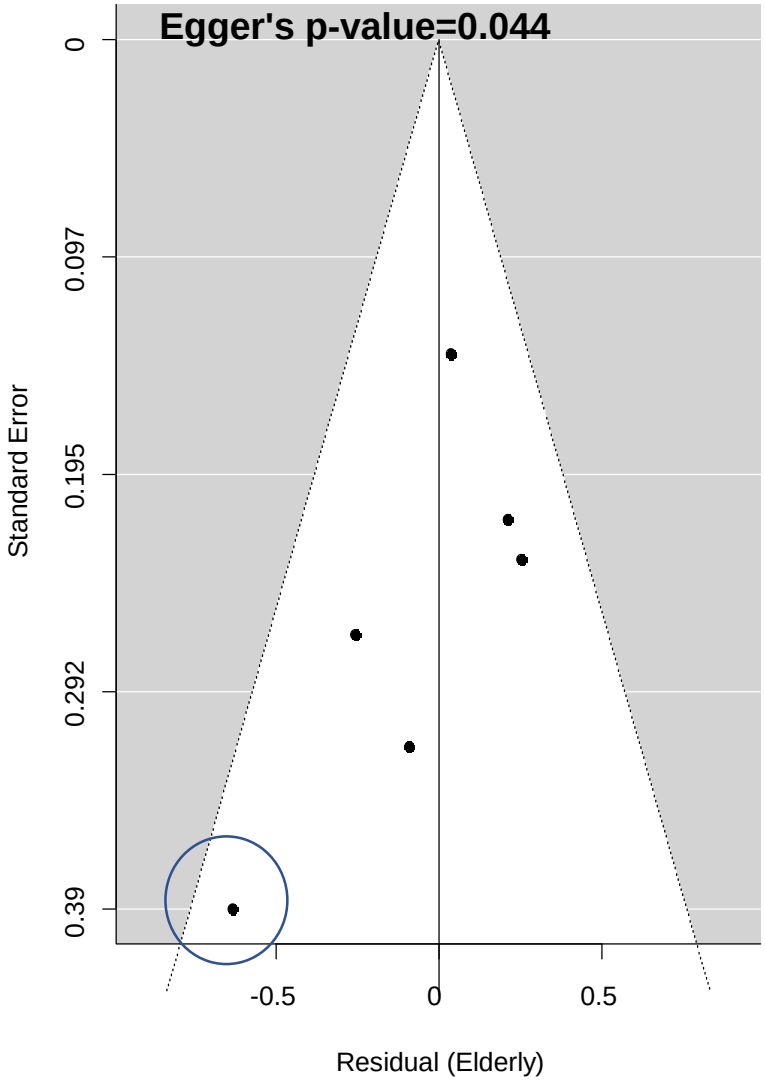
*Adjustment for randomization arm and baseline characteristics differences

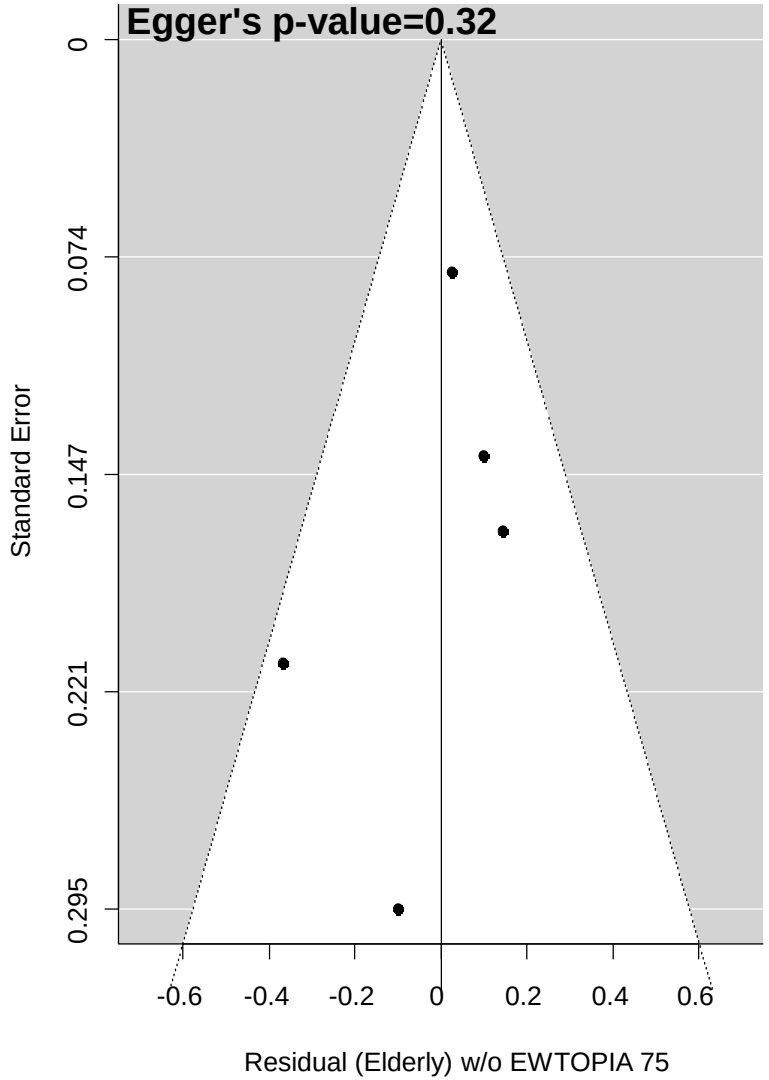
Cognition after LDL-C Lowering with Evolocumab



*Adjustment for randomization arm and baseline characteristics differences

Publication bias assessment for the primary endpoint of major vascular events





Limitations

- The trials were of different durations.
- The data for the benefit of lipid-lowering on the reduction of CV events for primary prevention in the elderly are sparse, with slightly less than a quarter of the major vascular events in primary prevention patients.
- It is also important to note that elderly patients included in clinical trials might not be representative of everyday practice.

Upcoming Statin Trials in the Elderly

- **STAREE (A Clinical Trial of STAtin Therapy for Reducing Events in the Elderly)**
  - N=18,000 men and women aged 70 or older
  - Atorvastatin 40mg daily vs placebo
  - Primary outcome: disability-free survival
  - Recruiting

- **PREVENTABLE (Pragmatic Evaluation of Events and Benefits of Lipid-lowering in Older Adults)**
  - N=20,000 men and women aged 75 and older
  - Moderate-intensity statin vs placebo
  - 3 outcomes: dementia, disability and CV events
  - Funded by the NIH, but not yet commenced

Summary

- In patients 75 years and older, lipid-lowering therapy is as effective in reducing CV events as it is in younger adults.

- Significant reductions were seen for all of the individual components of the composite endpoint, including CV death, myocardial infarction, stroke, and coronary revascularization.

- These results should strengthen guideline recommendations for the use of lipid-lowering therapies in the elderly.

Future Projects

- Design and conduct of clinical trials in cardiovascular sciences in Switzerland.
- International and national multidisciplinary collaborations.
- Promote local projects to improve care of patients.

Lack of Association Between Cholesterol and Coronary Heart Disease Mortality and Morbidity and All-Cause Mortality in Persons Older Than 70 Years

Harlan M. Krumholz, MD; Teresa E. Seeman, PhD; Susan S. Merrill, PhD; Carlos F. Mendes de Leon, PhD; Viola Vaccarino, MD; David I. Silverman, MD; Reiko Tsukahara, MD; Adrian M. Ostfeld, MD; Lisa F. Berkman, PhD

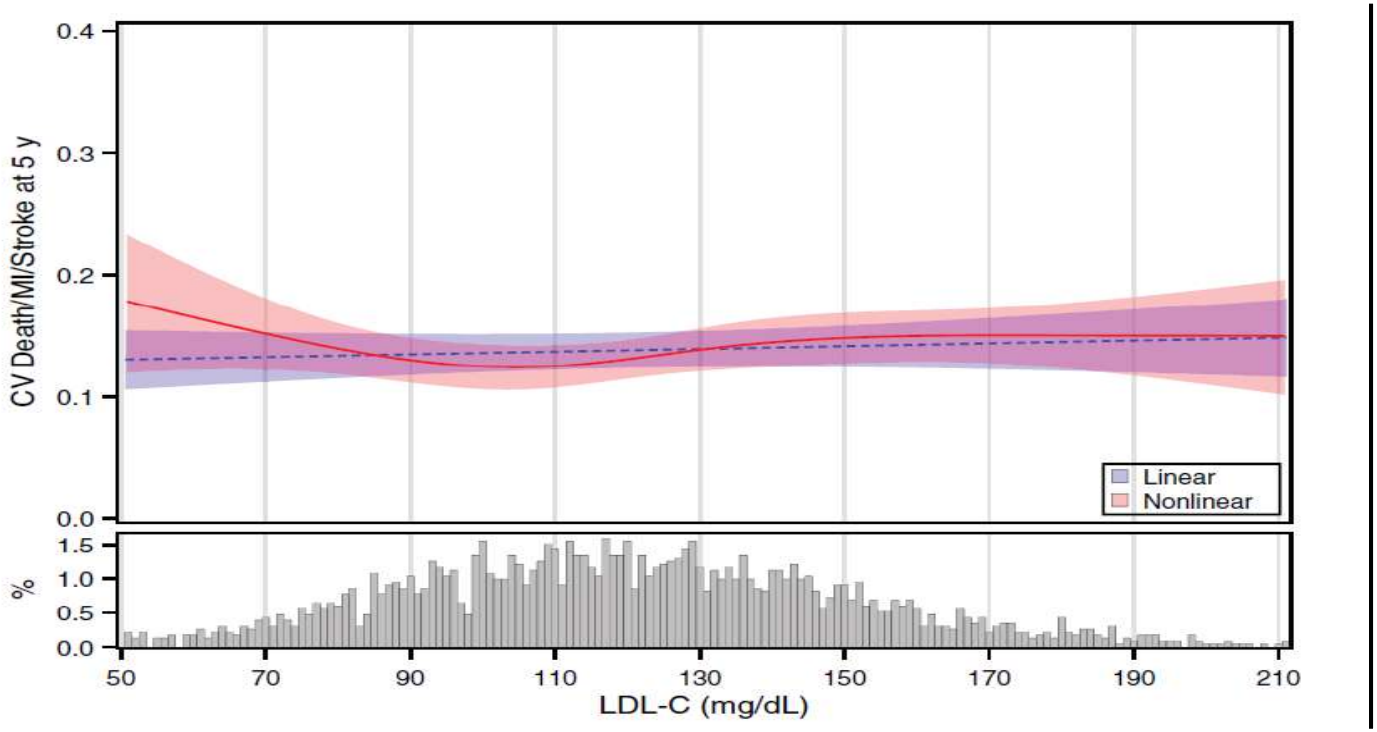
Conclusions.—Our findings do not support the hypothesis that hypercholesterolemia or low HDL-C are important risk factors for all-cause mortality, coronary heart disease mortality, or hospitalization for myocardial infarction or unstable angina in this cohort of persons older than 70 years.

(*JAMA*. 1994;272:1335-1340)

JAMA 1994: 272:1335-1340.

The Association Between Low-Density Lipoprotein Cholesterol and Incident Atherosclerotic Cardiovascular Disease in Older Adults: Results From the National Institutes of Health Pooled Cohorts

Michael G. Nanna, MD, Ann Marie Navar, MD, PhD, Daniel Wojdyla, MSc, and Eric D. Peterson, MD, MPH



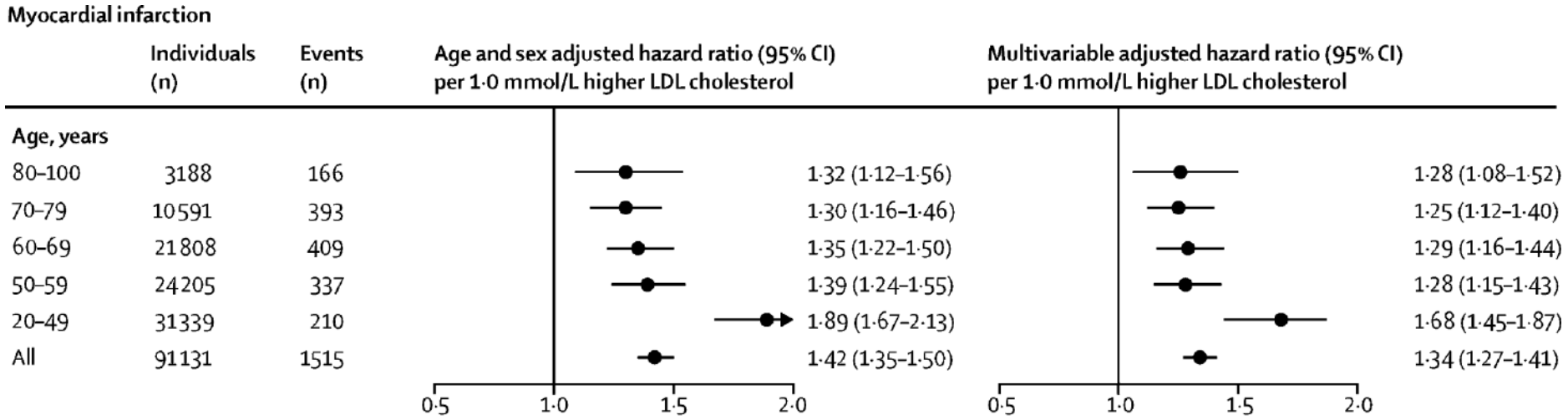
CONCLUSION: Among a well-characterized cohort, LDL-C was not associated with CVD risk among adults aged 75 years or older, even in the presence of other risk factors.

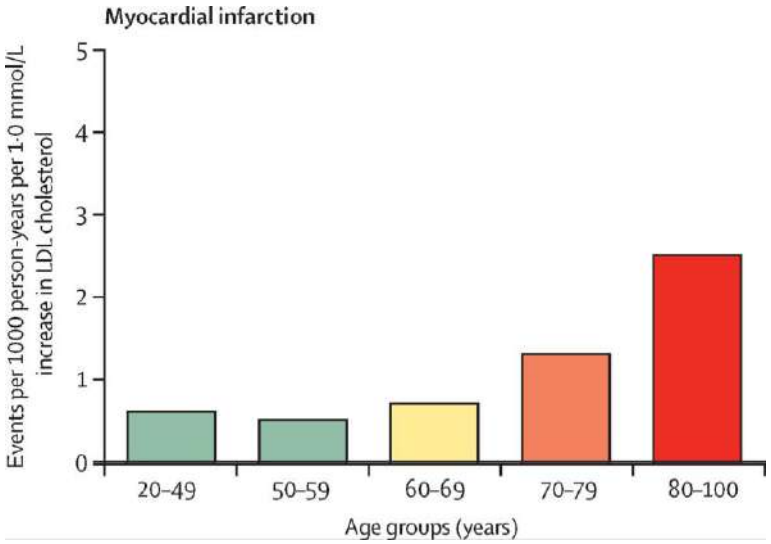
J Am Geriatr Soc 67:2560-2567, 2019.

Standards for Abstract Submission

≥10 weeks prior: Submit proposal for review & approval.
≥8 weeks prior: Initial request for analyses (including draft table shells) to be sent to statistician leaders.
4-8 weeks prior: Initial analyses performed. Data reviewed by lead author & trial PI during Work-in-Progress. Follow-up analyses performed, as needed.
4 weeks prior: Draft abstract (1 page handout) prepared by lead author, reviewed by trial PI, and ready to be reviewed at upcoming TIMI mtg.
0-4 weeks prior: Review of abstract at TIMI meetings. Additional analyses as needed based on feedback at TIMI mtg. Circulation of abstract to co-authors outside of TIMI and trial sponsor(s). Submit final abstract to stats for final numbers check prior to submission of abstract.

Increased relative risk of MI with higher LDL-C levels in all age groups





Lancet. 2020 Nov 21,396(10263):1644-1652