Update.
Trattamento della dislipidemia nel paziente ad alto rischio cardiovascolare: non solo statine

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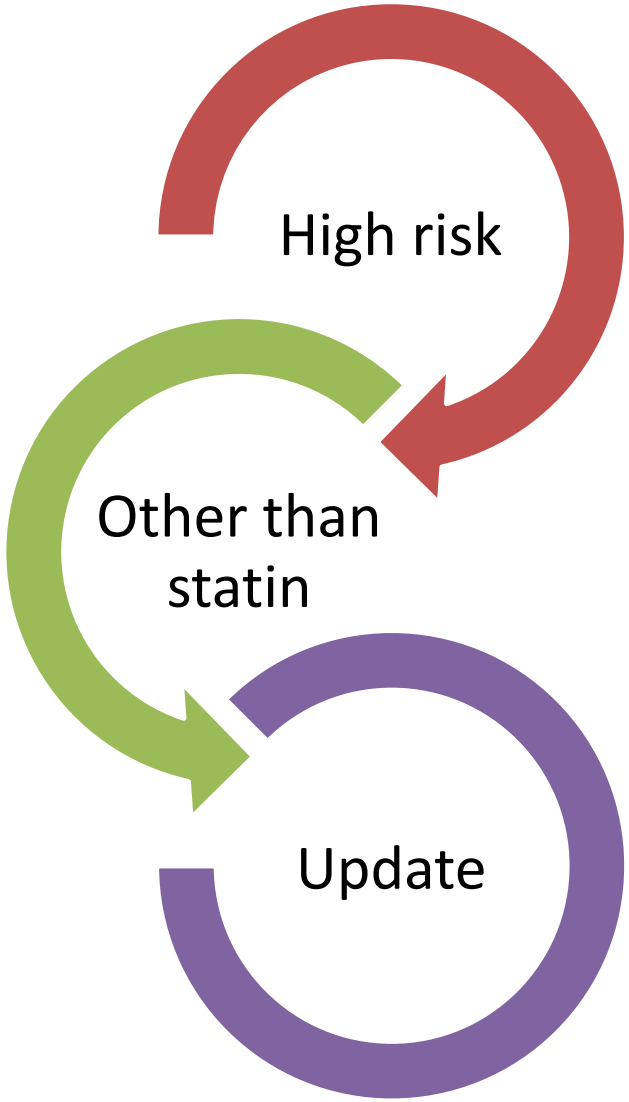
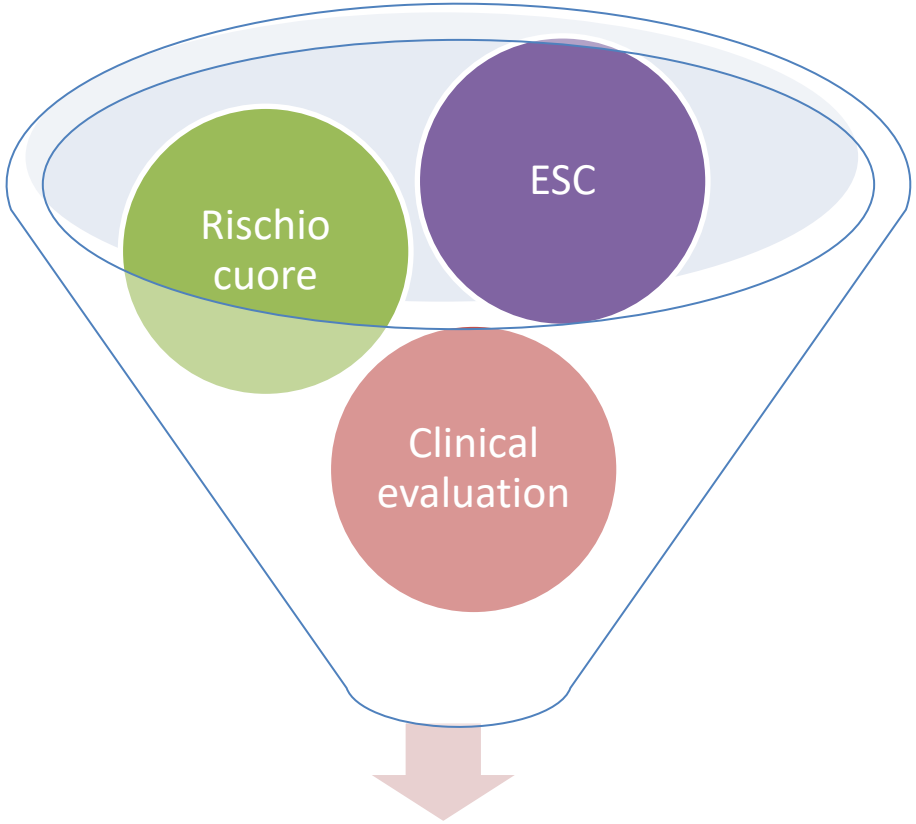
DISCLOSURES

Consultant for Abbott, Chiesi, Medtronic, Edwards


High risk
Other than statin
Update

DEFINITION OF RISK



RISCHIO CUORE

About 18000 people

40-69 years old

449 MI (2.5%)

198 stroke/TIA (1.3%)

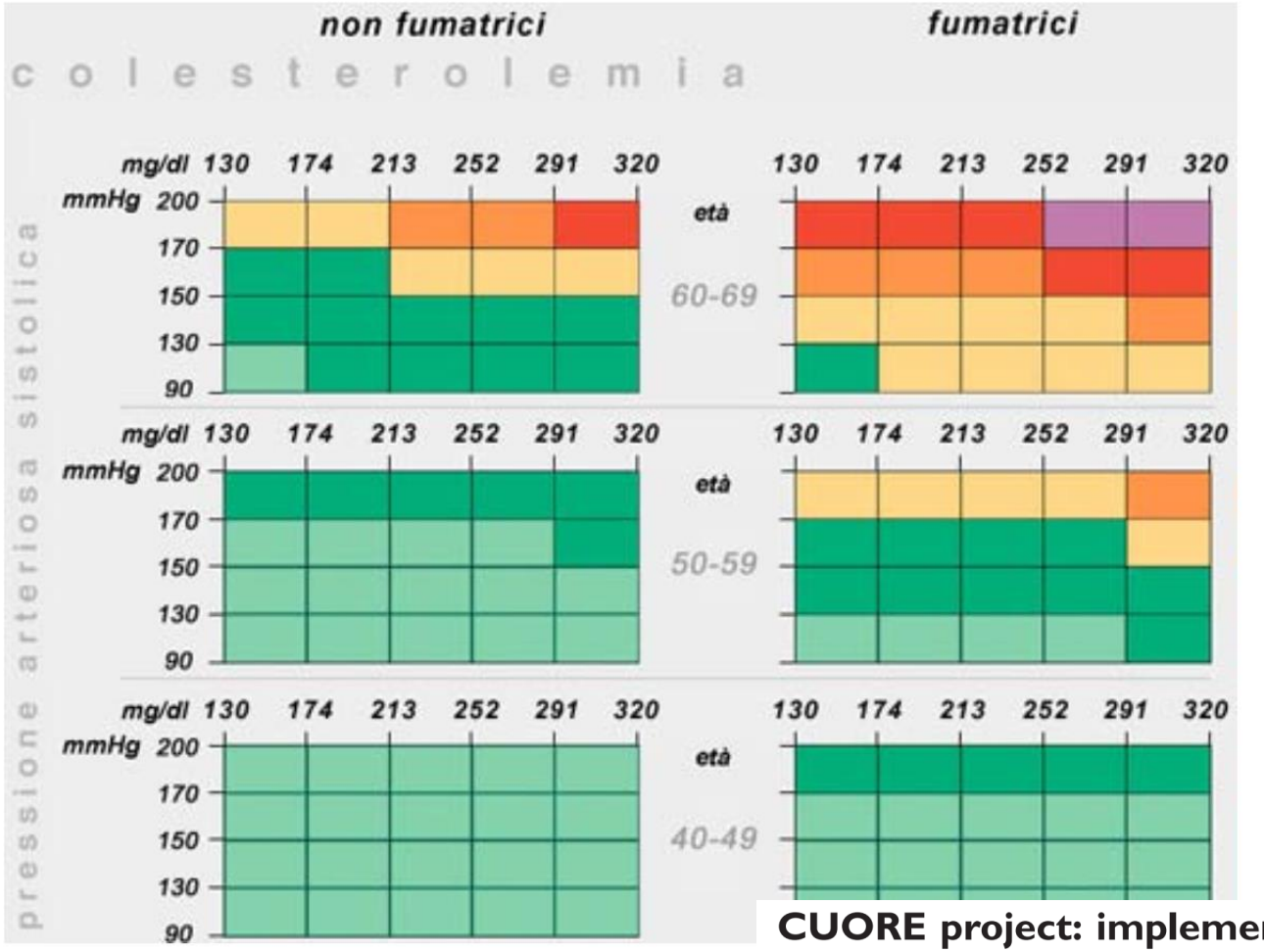
Maximum follow up

10 years

donne diabetiche
rischio cardiovascolare a 10 anni

Come utilizzare la carta

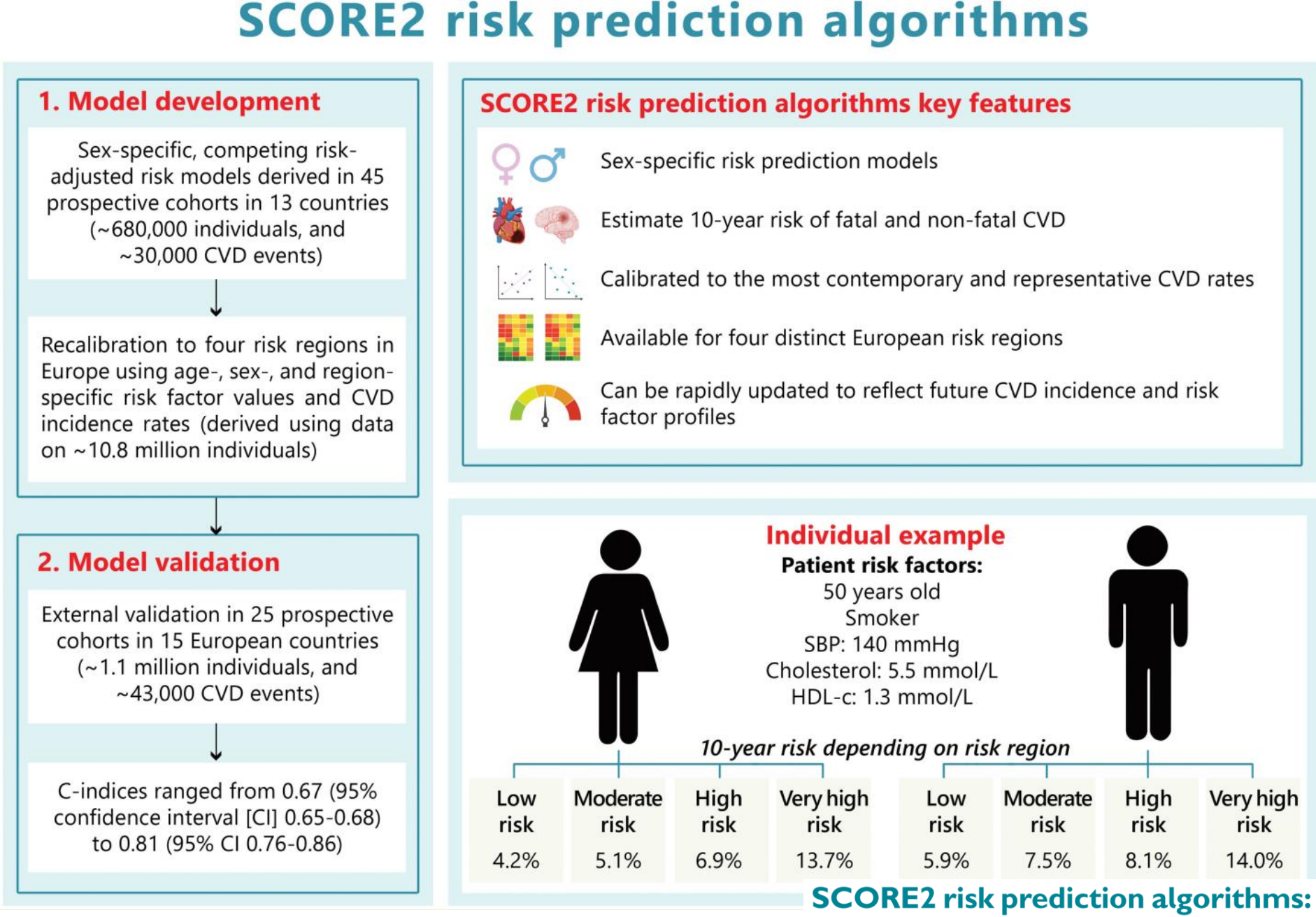
- Posizionarsi nella zona fumatore / non fumatore.
- Identificare il decennio di età.
- Collocarsi sul livello corrispondente a pressione arteriosa sistolica e colesterolemia.
- Identificato il colore, leggere nella legenda a fianco il livello di rischio.



CUORE project: implementation of th
10-year risk score

Palmieri et al., EHJ 11

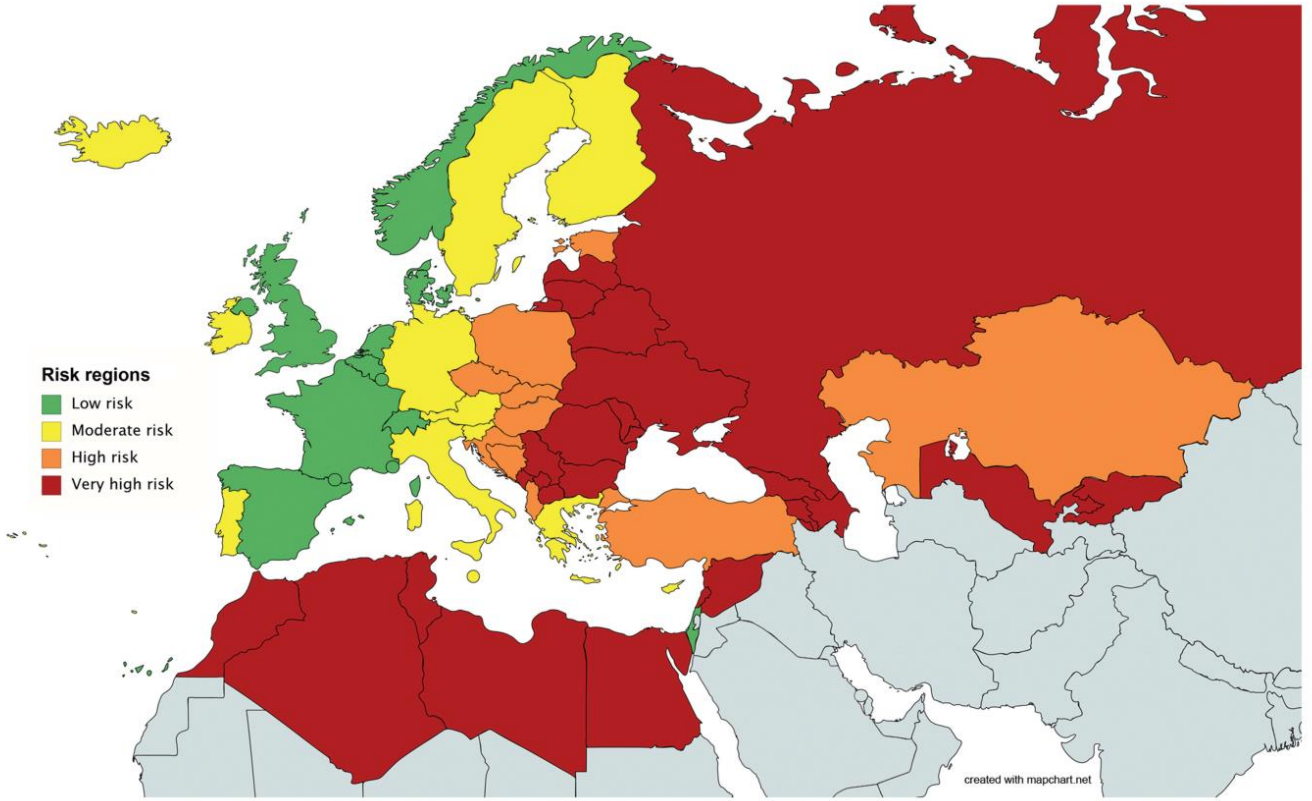
ESC 2022



SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe

Esc WG, EHJ 22

ESC 2022



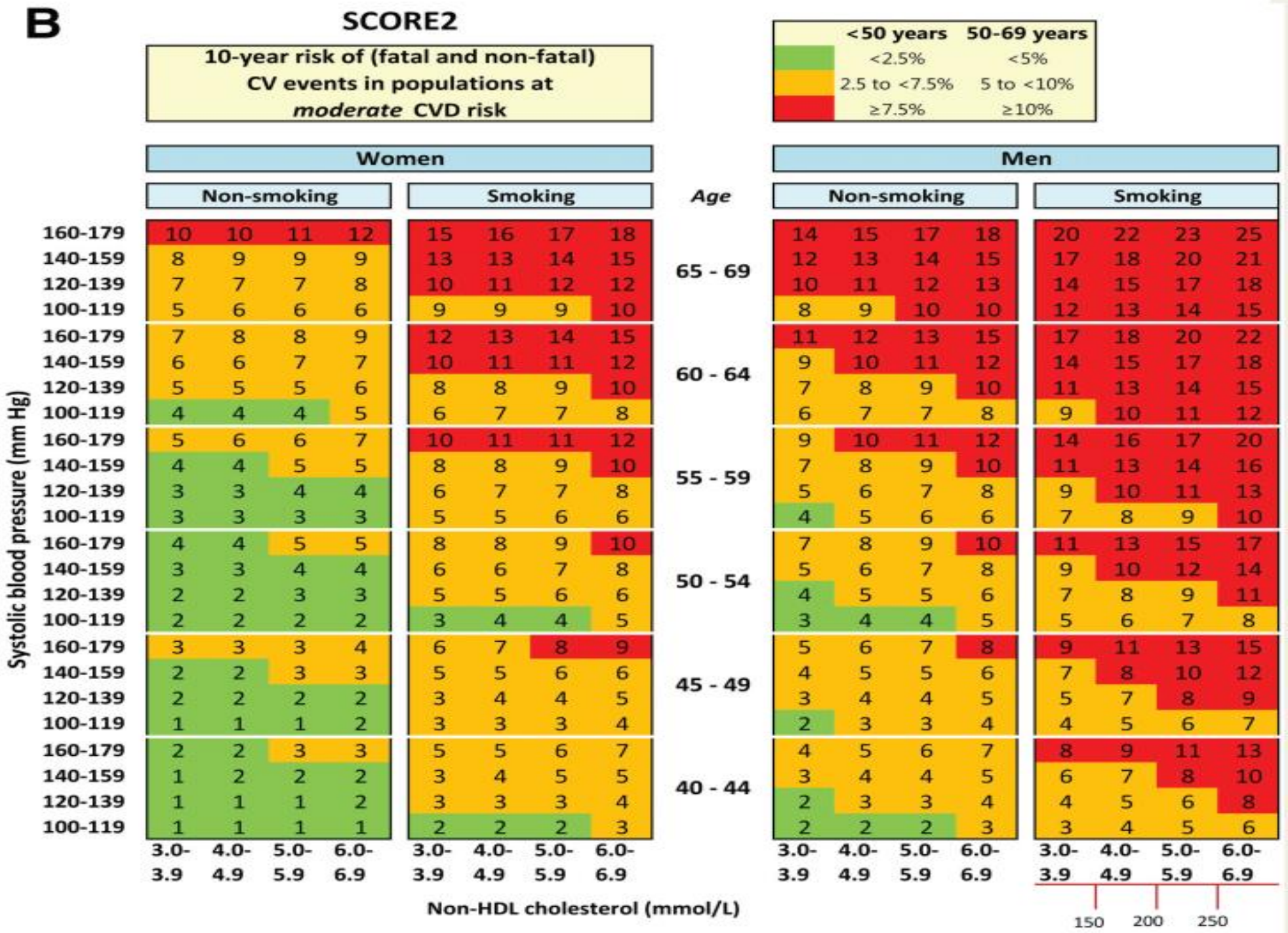
Italy	PAMELA	1250	54
	MONICA-Brianza III	982	60
	Moli-sani	16594	115
	EPIC-CVD	2857	700
	Total	21683	929

0.813 (0.762, 0.863)
0.754 (0.696, 0.813)
0.750 (0.703, 0.797)
0.751 (0.728, 0.773)
0.754 (0.725, 0.784)

SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe

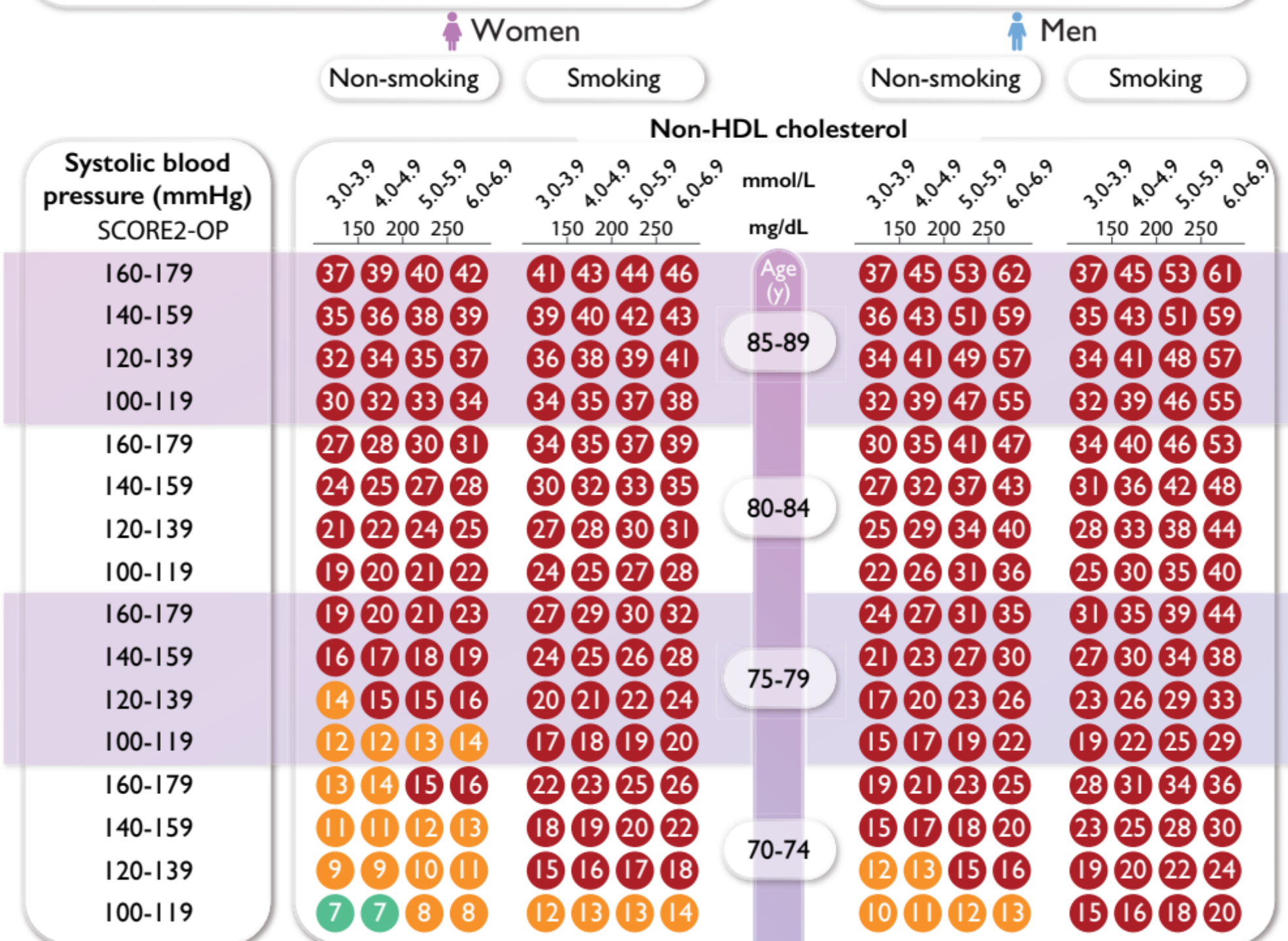
Esc WG, EHJ 22

ESC 2022



Esc WG, EHJ 22

ESC 2022



Esc WG, EHJ 22

Female 50 years old, smoking habit, no DM, 210 mg/dl of cholesterol, SBP more than 160 mmHg

Rischio CUORE 10-15%

SCORE2>10%

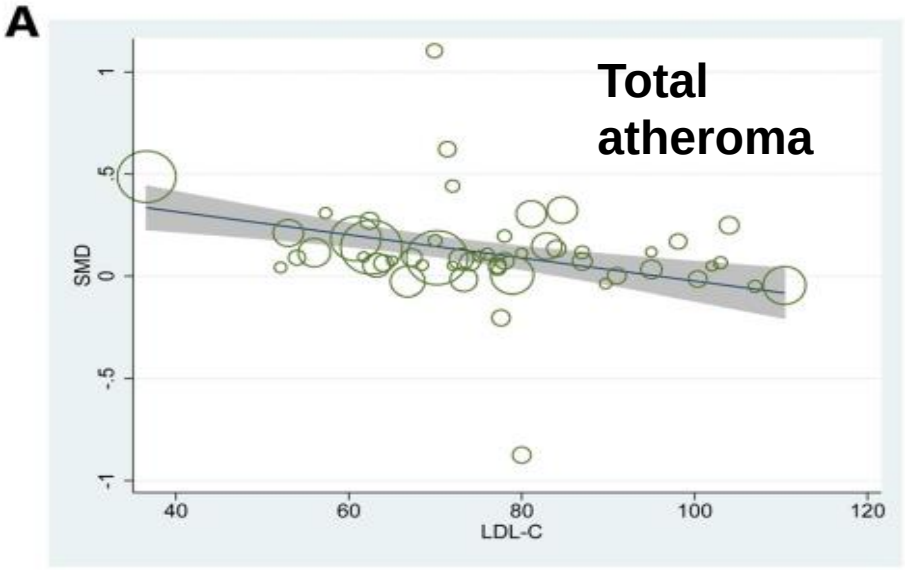
Male, 65 years old, no smoking habit, no DM, 190 mg/dl of cholesterol, SBP 105 mmHg

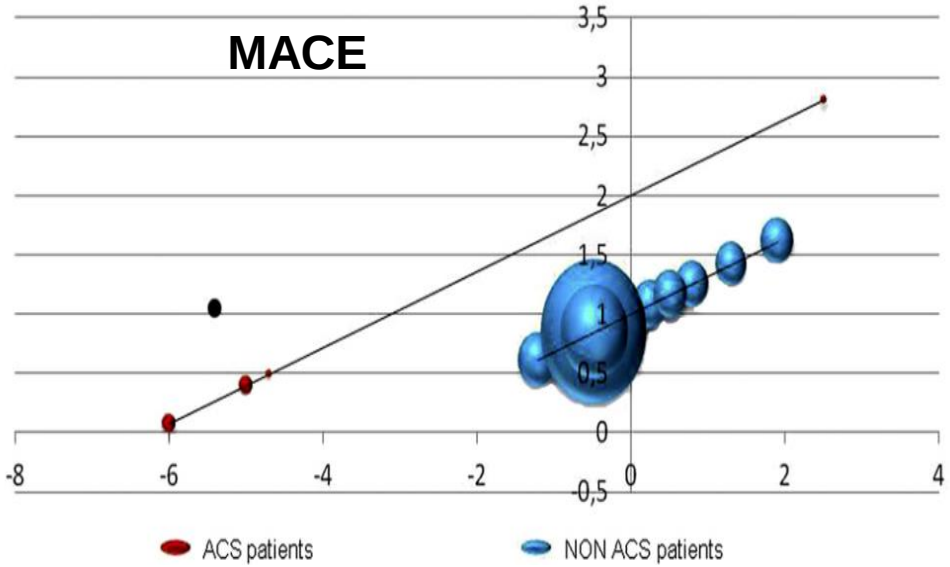
Rischio CUORE 5-10%

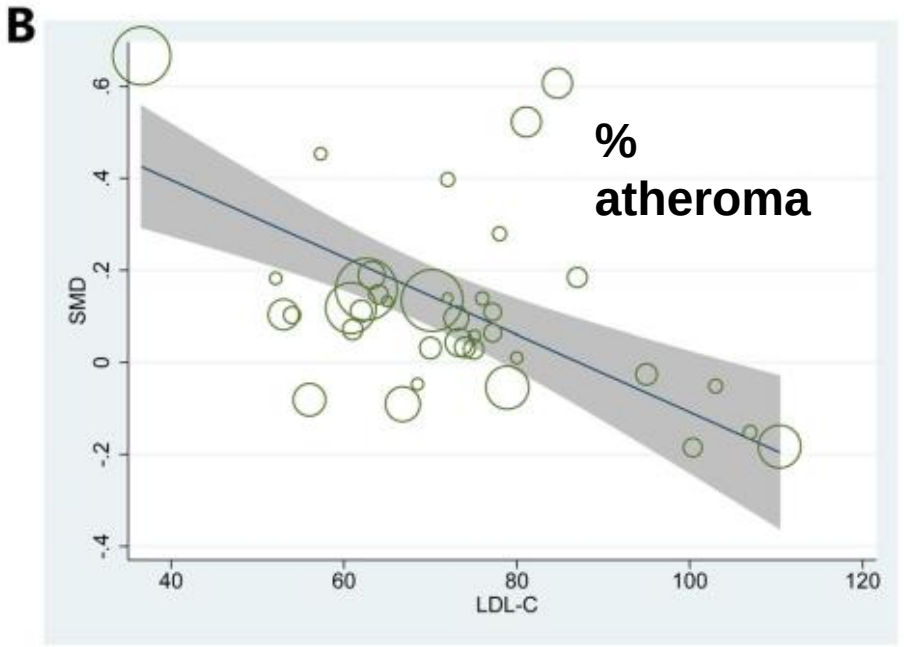
SCORE2 5-10%

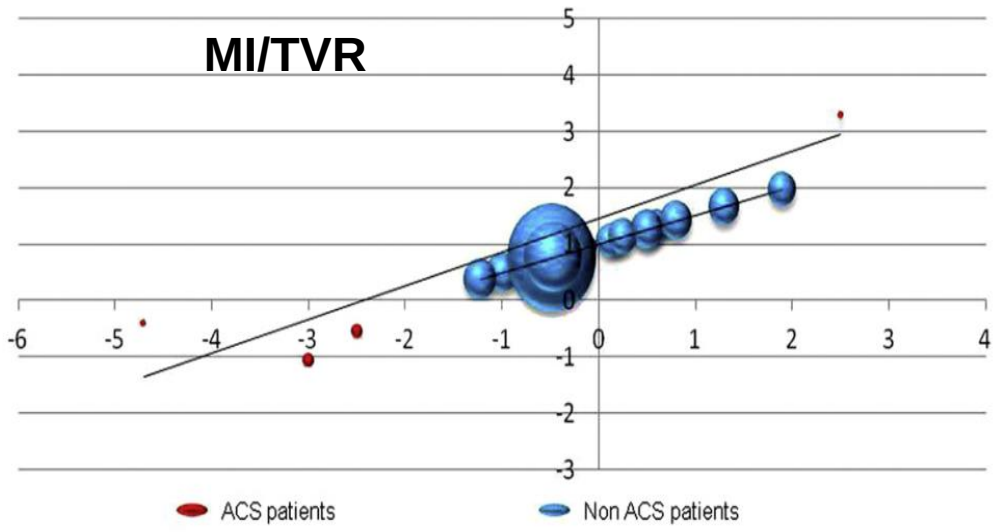
BENEFITS OF REDUCTION

BENEFITS OF REDUCTION ON PLAQUES









Li, Nature 21

D'Ascenzo, Atherosclerosis 13

BENEFITS OF REDUCTION ON EVENTS

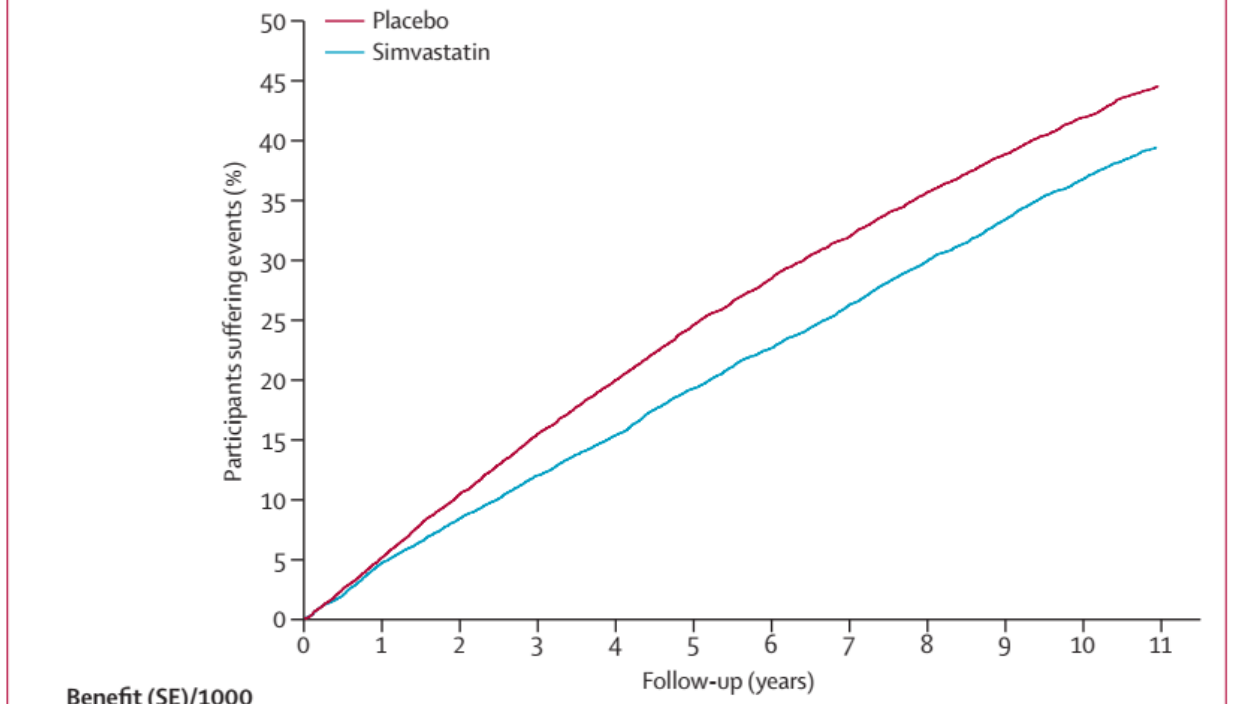
20536 patients

Randomized to

Placebo vs.

Simvastatin 40 mg 1 cp

	Simvastatin allocation		Risk ratio (95% CI)	p value
	Simvastatin	Placebo		
In-trial events				
Major coronary event	959/10269 (9·3%)	1287/10267 (12·5%)	0·73 (0·67–0·79)	
Stroke	480/10269 (4·7%)	619/10267 (6·0%)	0·76 (0·68–0·86)	
Revascularisation	981/10269 (9·6%)	1258/10267 (12·3%)	0·76 (0·70–0·83)	
Major vascular event	**2153/10269 (21·0%)**	**2712/10267 (26·4%)**	**0·77 (0·72–0·81)**	**p<0·0001**

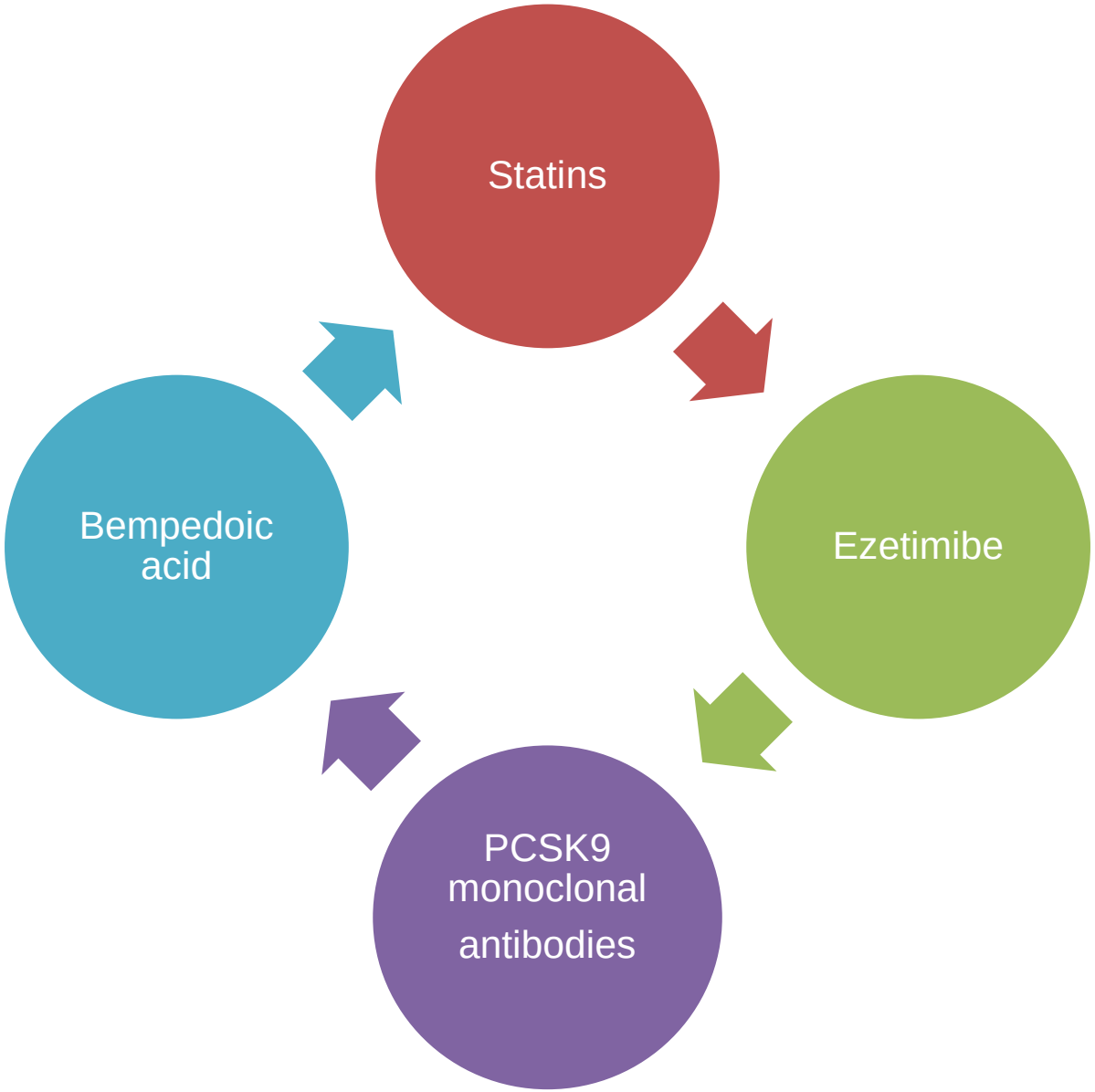


Benefit (SE)/1000 allocated simvastatin		5 (3)	20 (4)	35 (5)	46 (5)	53 (6)	58 (6)	58 (7)	57 (7)	55 (7)	52 (8)	51 (11)
Number at risk												
Placebo	10267	9682	9055	8464	7894	7314	6785	6326	5848	5410	4822	2120
Simvastatin	10269	9744	9287	8814	8352	78						

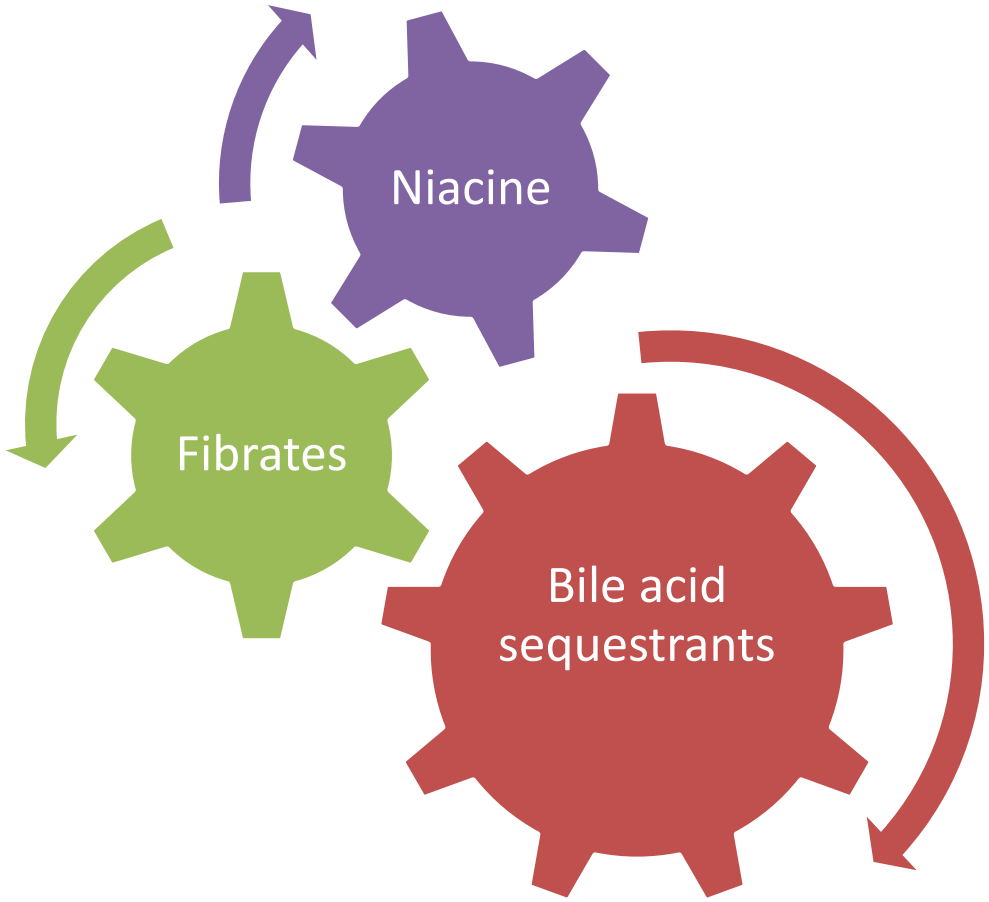
Heart Protection Study Collaborative Group, Lancet 11

Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20 536 high-risk individuals: a randomised controlled trial

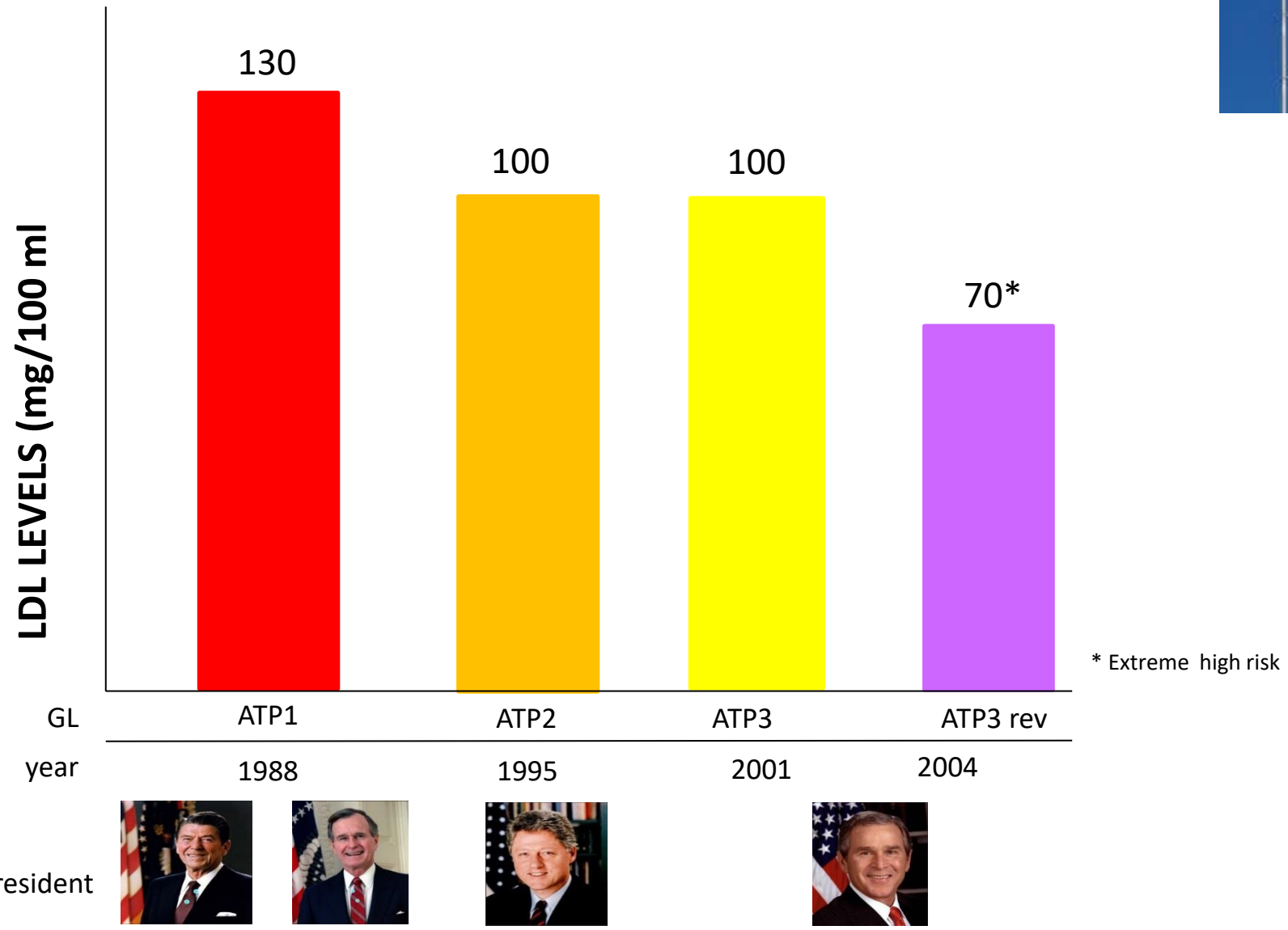
STRATEGIES TO ACHIEVE REDUCTION



FORGOTTEN STRATEGIES

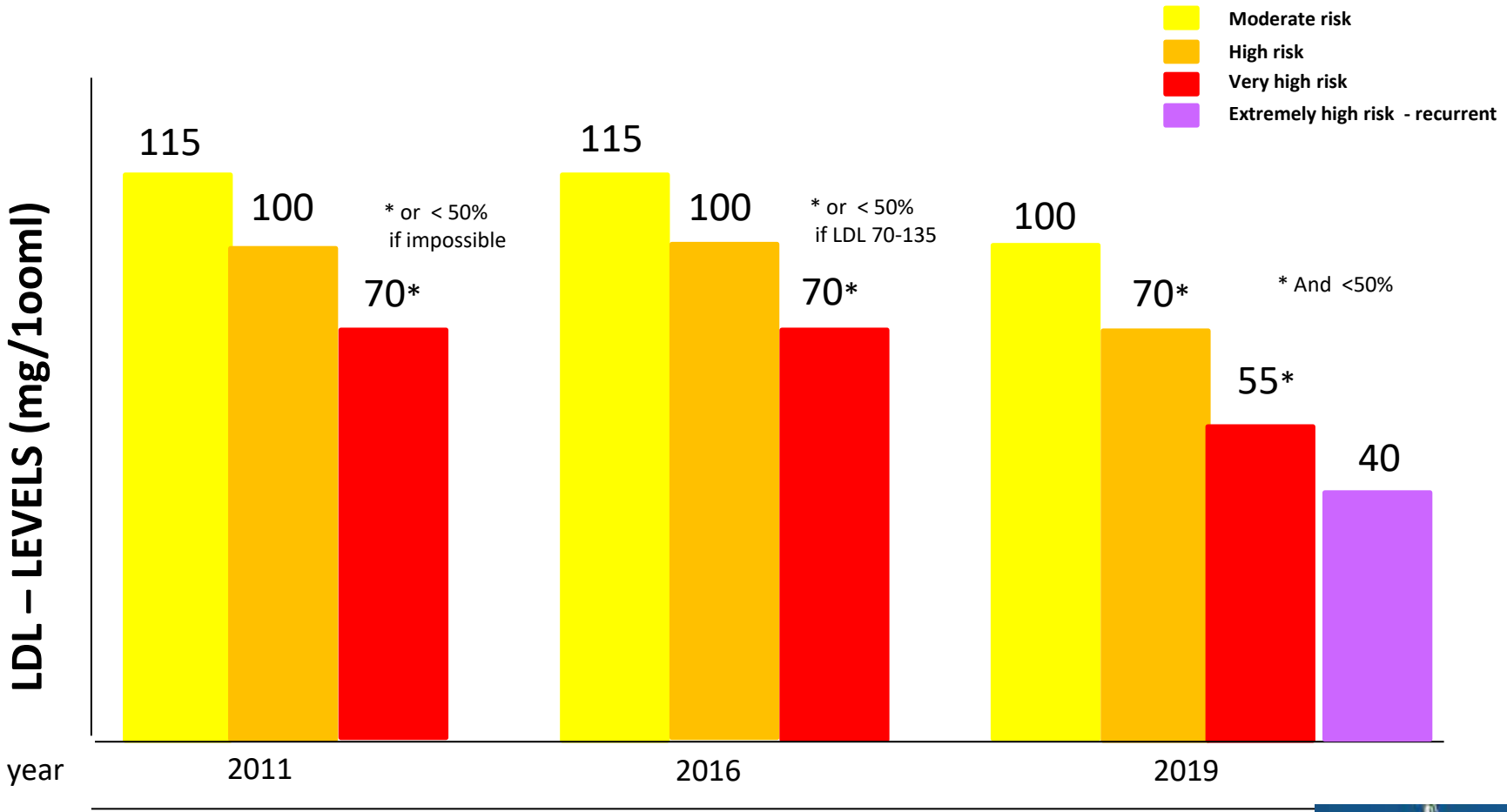


LDL GOAL U.S. 1998-2004



* Extreme high risk

LDL GOAL ESC/EAS 2001-2019

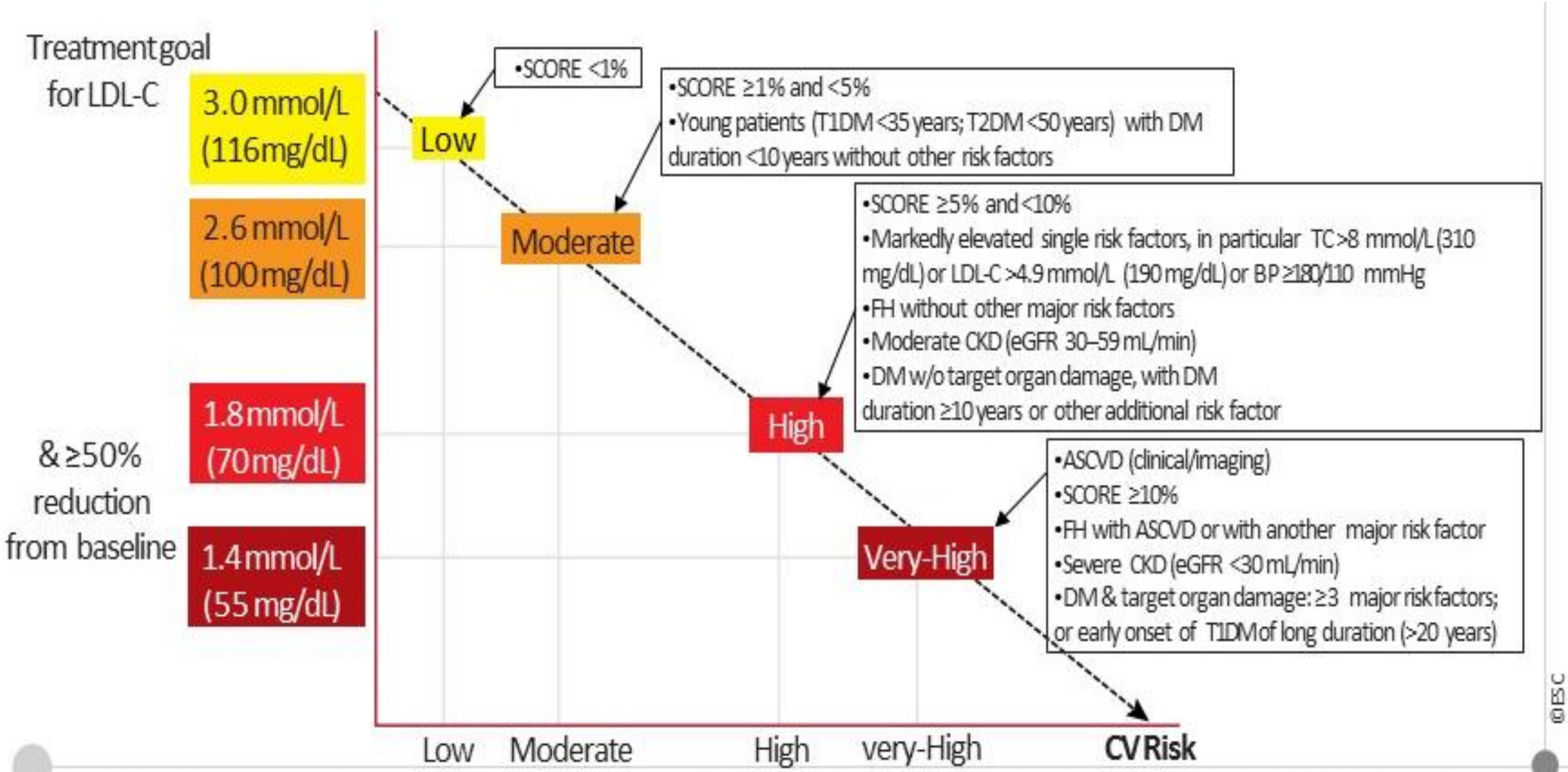


Italian Prime Minister






LDL GOAL ESC/EAS 2019

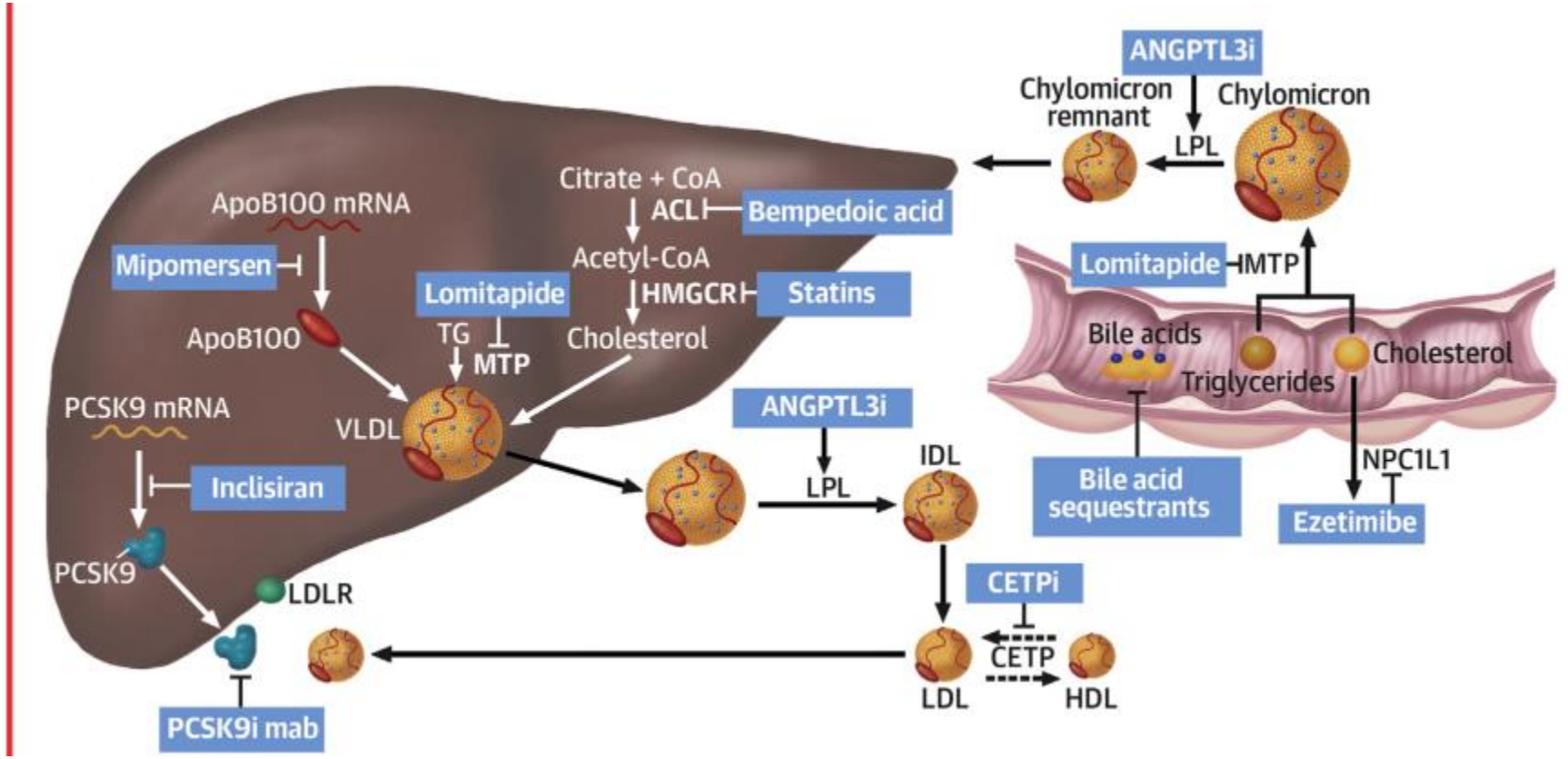


www.escardio.org/guidelines

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

EZETIMIBE

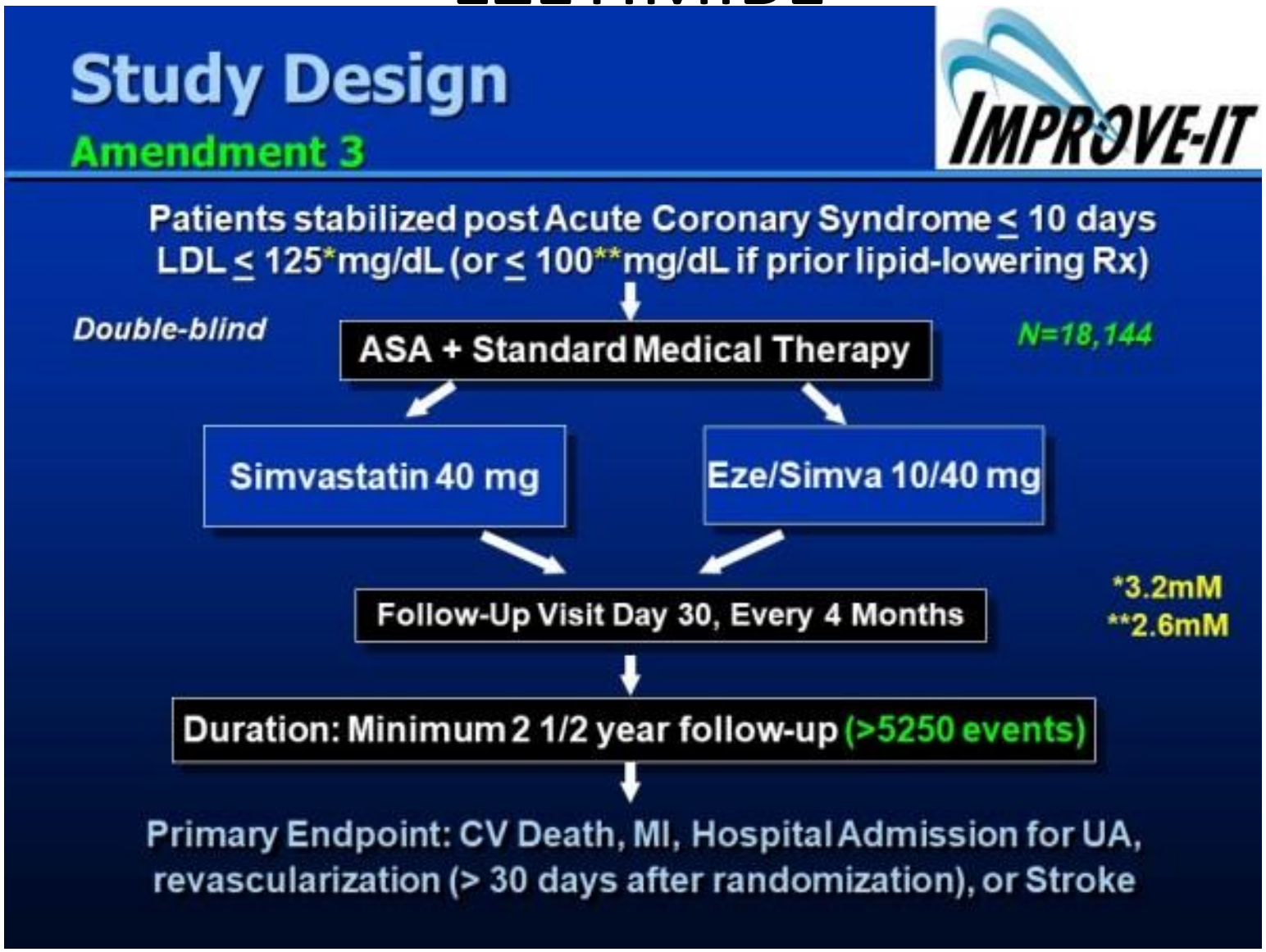
Ezetimibe reduces intestinal absorption of cholesterol through targeting of the Niemann-Pick C1-like 1 (NPC1L1) protein



New and Emerging Therapies for Reduction of LDL-Cholesterol and Apolipoprotein B

Nurmohamed, Jacc 2021

EZETIMIBE



Cannon et al., IMPROVE-IT Nejm 2015

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

EZETIMIBE

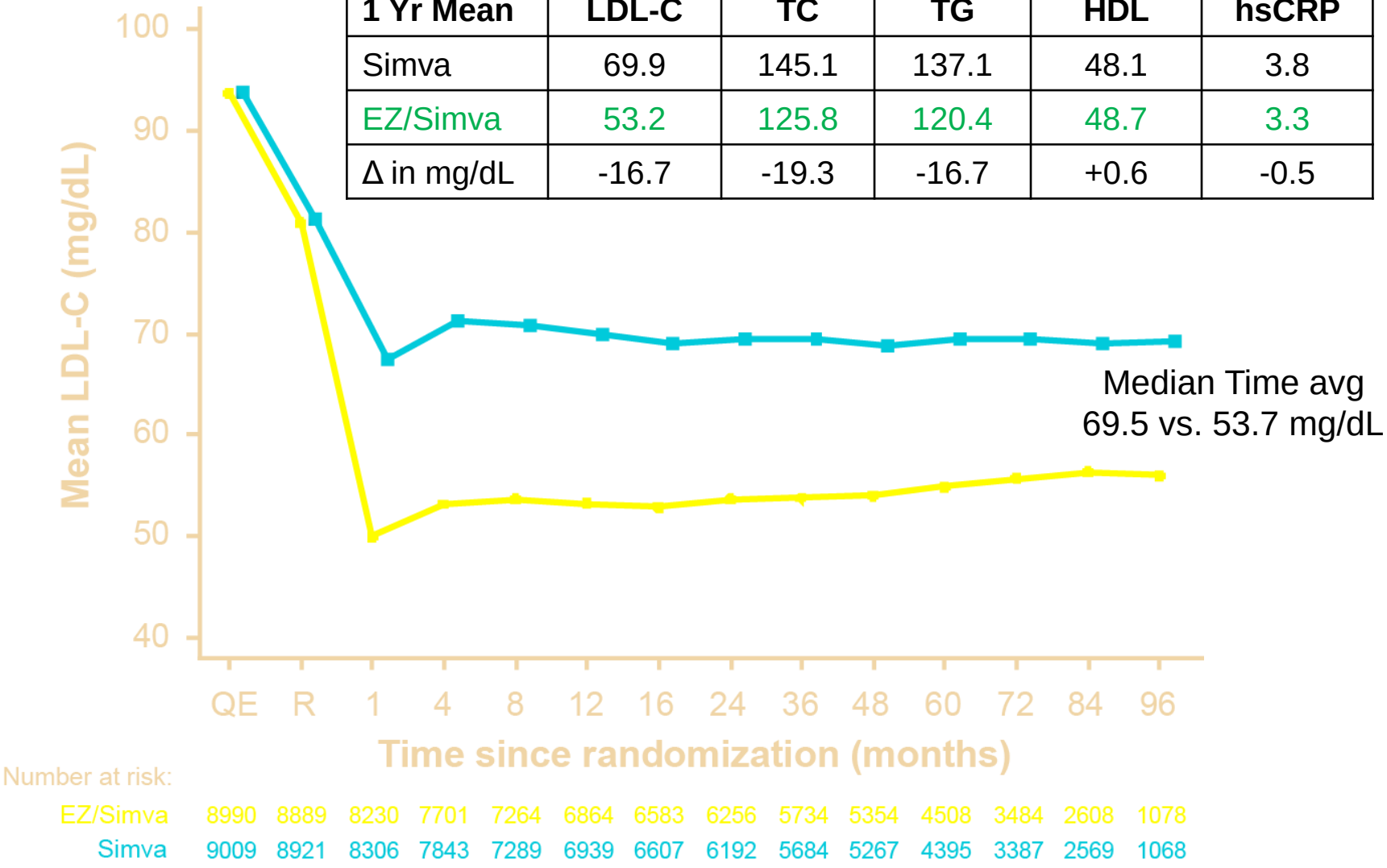
- Inclusion Criteria:
  - Hospitalization for STEMI, NSTEMI/UA < 10 days
  - Age ≥ 50 years, and ≥ 1 high-risk feature:
    - New ST chg, + troponin, DM, prior MI, PAD, cerebrovasc, prior CABG > 3 years, multivessel CAD
  - LDL-C 50-125 mg/dL (50–100 mg/dL if prior lipid-lowering Rx)
- Major Exclusion Criteria:
  - CABG for treatment of qualifying ACS
  - Current statin Rx more potent than simva 40mg
  - Creat Cl < 30mL/min, active liver disease

Cannon et al., IMPROVE-IT Nejm 2015

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

EZETIMIBE

1 Yr Mean	LDL-C	TC	TG	HDL	hsCRP
Simva	69.9	145.1	137.1	48.1	3.8
EZ/Simva	53.2	125.8	120.4	48.7	3.3
Δ in mg/dL	-16.7	-19.3	-16.7	+0.6	-0.5

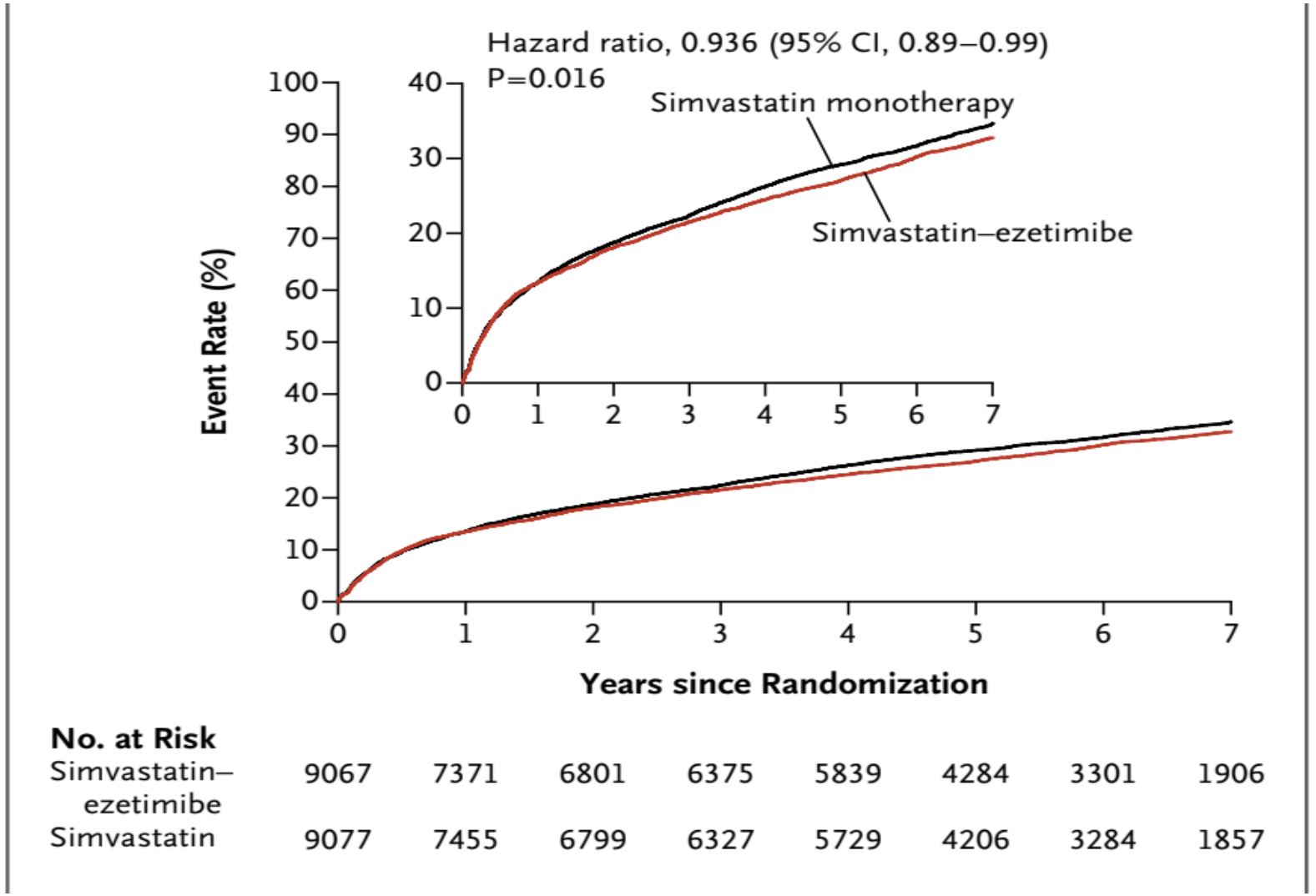


Median Time avg
69.5 vs. 53.7 mg/dL

Cannon et al., IMPROVE-IT Nejm 2015

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

EZETIMIBE



No. at Risk								
Simvastatin–ezetimibe	9067	7371	6801	6375	5839	4284	3301	1906
Simvastatin	9077	7455	6799	6327	5729	4206	3284	1857

Cannon et al., IMPROVE-IT Nejm 2015

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

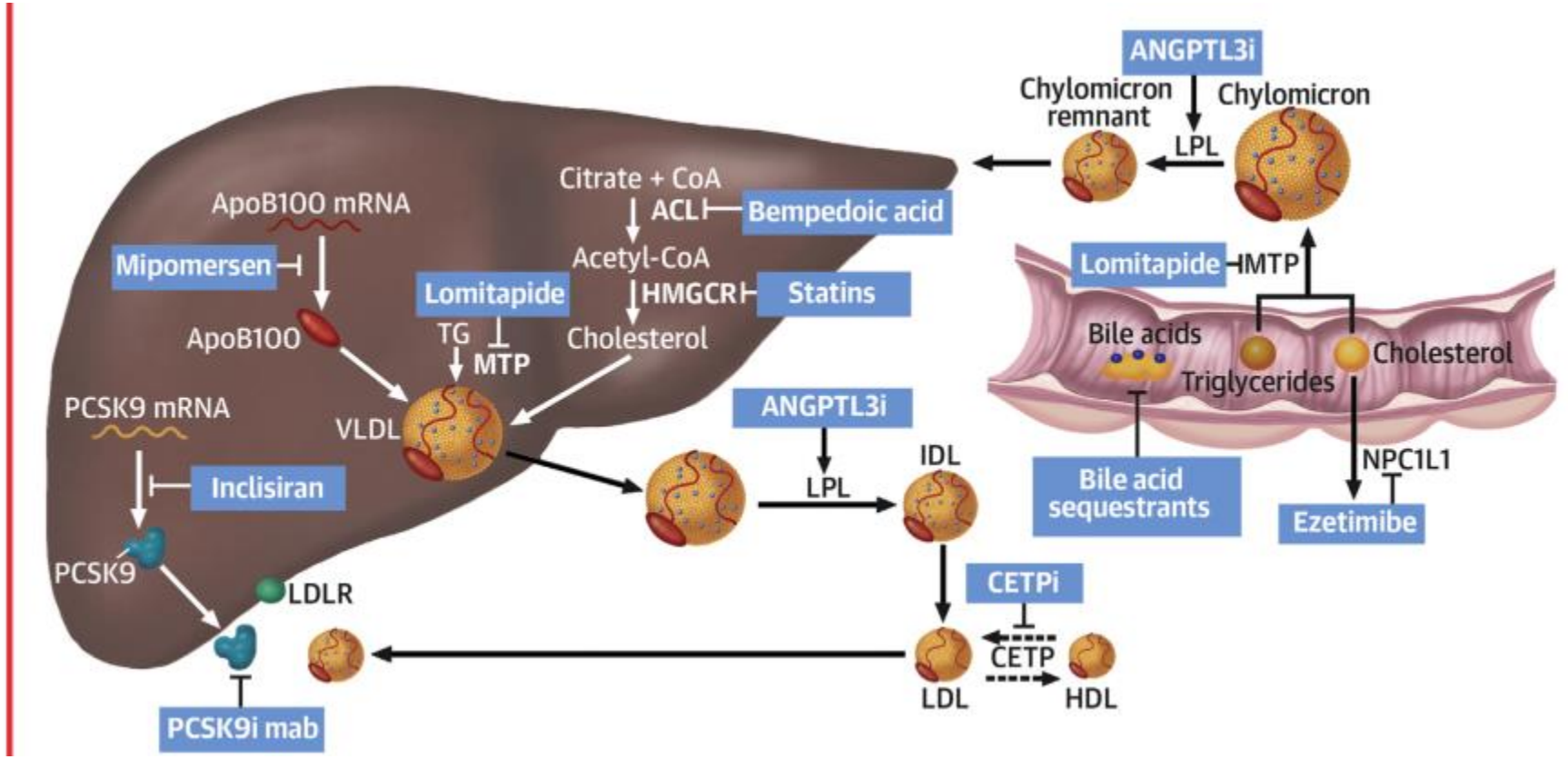
Outcome	Simvastatin Monotherapy (N=9077)	Simvastatin–Ezetimibe (N=9067)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Primary end point: death from cardiovascular causes, major coronary event, or nonfatal stroke	2742 (34.7)	2572 (32.7)	0.936 (0.89–0.99)	0.016
Secondary end points				
Death from any cause, major coronary event, or nonfatal stroke	3246 (40.3)	3089 (38.7)	0.95 (0.90–1.0)	0.03
Death from coronary heart disease, nonfatal MI, urgent coronary revascularization ≥30 days	1448 (18.9)	1322 (17.5)	0.91 (0.85–0.98)	0.02
Death from cardiovascular causes, nonfatal MI, hospitalization for unstable angina, all revascularization ≥30 days, nonfatal stroke	2869 (36.2)	2716 (34.5)	0.95 (0.90–1.0)	0.04
Tertiary end points†				
Death from any cause	1231 (15.3)	1215 (15.4)	0.99 (0.91–1.07)	0.78
Death from cardiovascular causes	538 (6.8)	537 (6.9)	1.00 (0.89–1.13)	1.00
Death from coronary heart disease	461 (5.8)	440 (5.7)	0.96 (0.84–1.09)	0.50
Any MI	1118 (14.8)	977 (13.1)	0.87 (0.80–0.95)	0.002
Nonfatal MI	1083 (14.4)	945 (12.8)	0.87 (0.80–0.95)	0.002
Fatal MI	49 (0.7)	41 (0.5)	0.84 (0.55–1.27)	0.41
Any stroke	345 (4.8)	296 (4.2)	0.86 (0.73–1.00)	0.05
Ischemic stroke	297 (4.1)	236 (3.4)	0.79 (0.67–0.94)	0.008
Hemorrhagic stroke	43 (0.6)	59 (0.8)	1.38 (0.93–2.04)	0.11
Coronary revascularization ≥30 days after randomization	1793 (23.4)	1690 (21.8)	0.95 (0.89–1.01)	0.11
Urgent coronary revascularization ≥30 days after randomization	626 (8.6)	510 (7.0)	0.81 (0.72–0.91)	0.001
Any revascularization ≥30 days after randomization	1962 (25.6)	1871 (24.2)	0.96 (0.90–1.02)	0.18
Hospitalization for unstable angina	148 (1.9)	156 (2.1)	1.06 (0.85–1.33)	0.62
Other prespecified end points				
Death from cardiovascular causes, MI, or stroke	1704 (22.2)	1544 (20.4)	0.90 (0.84–0.96)	0.003
Major vascular events: death from coronary heart disease, MI, stroke, or coronary revascularization ≥30 days after randomization‡	2685 (34.0)	2498 (31.9)		

Cannon et al., IMPROVE-IT Nejm 2015

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

PCSK9 monoclonal antibodies

The secretory serine protease PCSK9 is responsible for extracellular binding and subsequent degradation of the LDLR, which impedes LDL clearance from the circulation. Monoclonal antibodies targeting PCSK9 increase the number of LDLRs and reduce LDL-C levels.



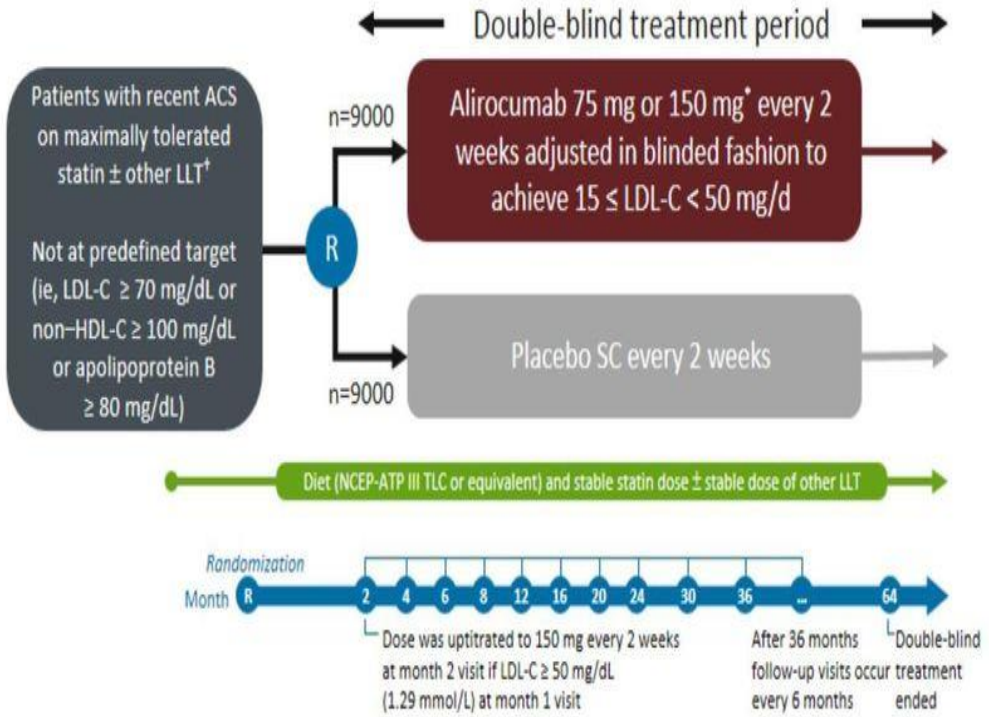
New and Emerging Therapies for Reduction of LDL-Cholesterol and Apolipoprotein B

Nurmohamed, Jacc 2021

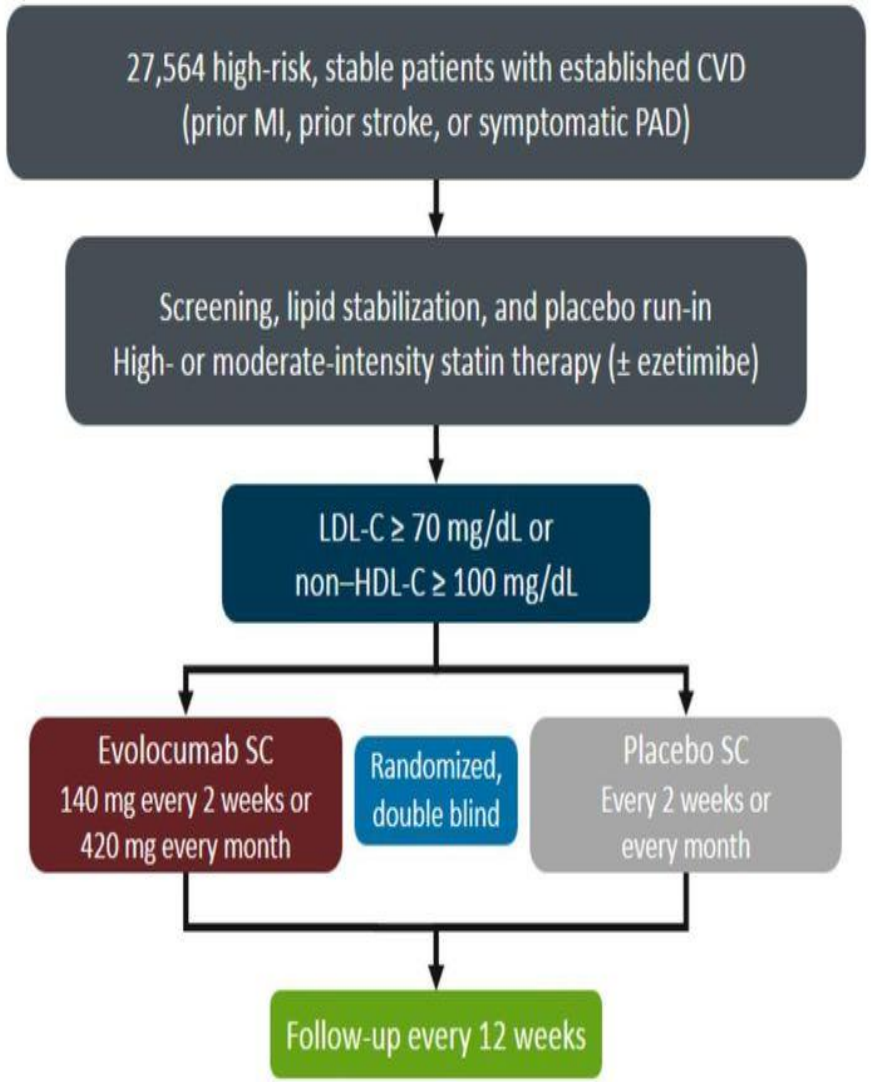
PCSK9 monoclonal antibodies

ODYSSEY OUTCOMES: Study Design

A randomized, double-blind, placebo-controlled study



FOURIER Trial Design



PCSK9 monoclonal antibodies

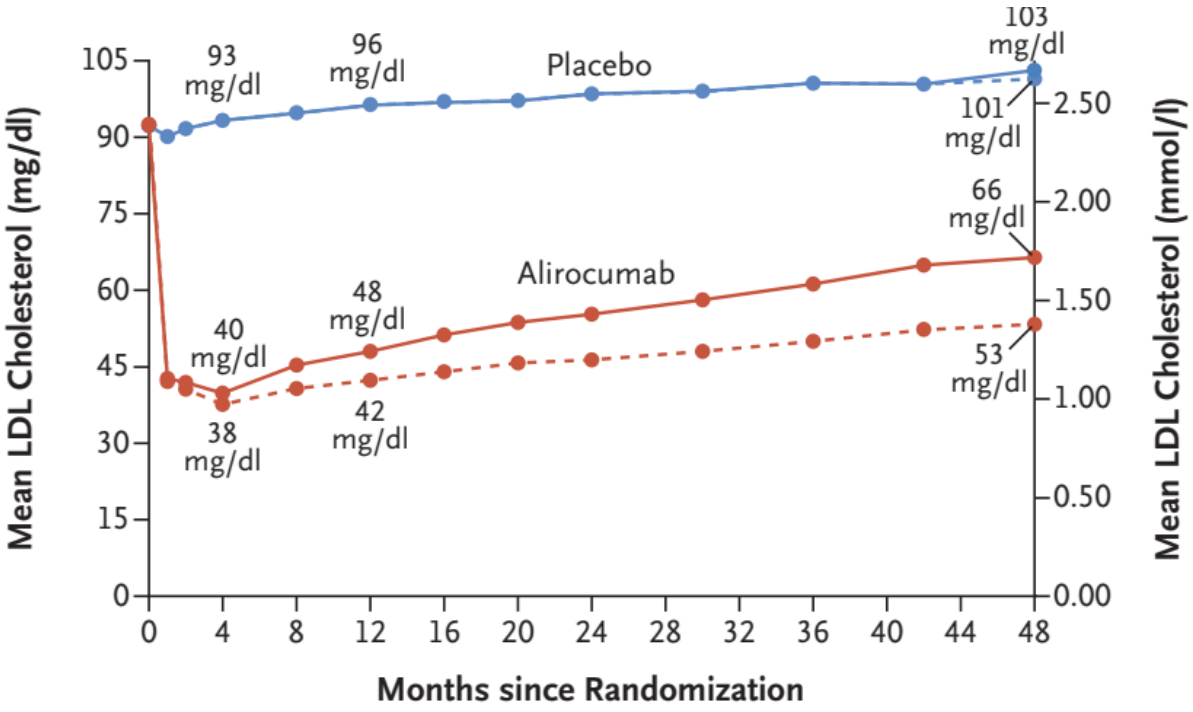
	ODYSSEY OUTCOMES[a] (n=18,312)	FOURIER[b] (n=27,564)
Age (mean)	58.6	62.5
Male, %	74.8	75.4
Hypertension, %	63.3	80.0
Diabetes, %	28.9	33.9
Current smoker, %	23.9	28.2
History of MI, %	100% ACS (mean time from index event 3.6 months, 75% <4 months) including 35% prior CAD + 20% with recurrent event	81.1 (31% MI < 1 y)
History of stroke, %	2.9	19.3
History of PAD, %	3.7	13.2

PCSK9 monoclonal antibodies

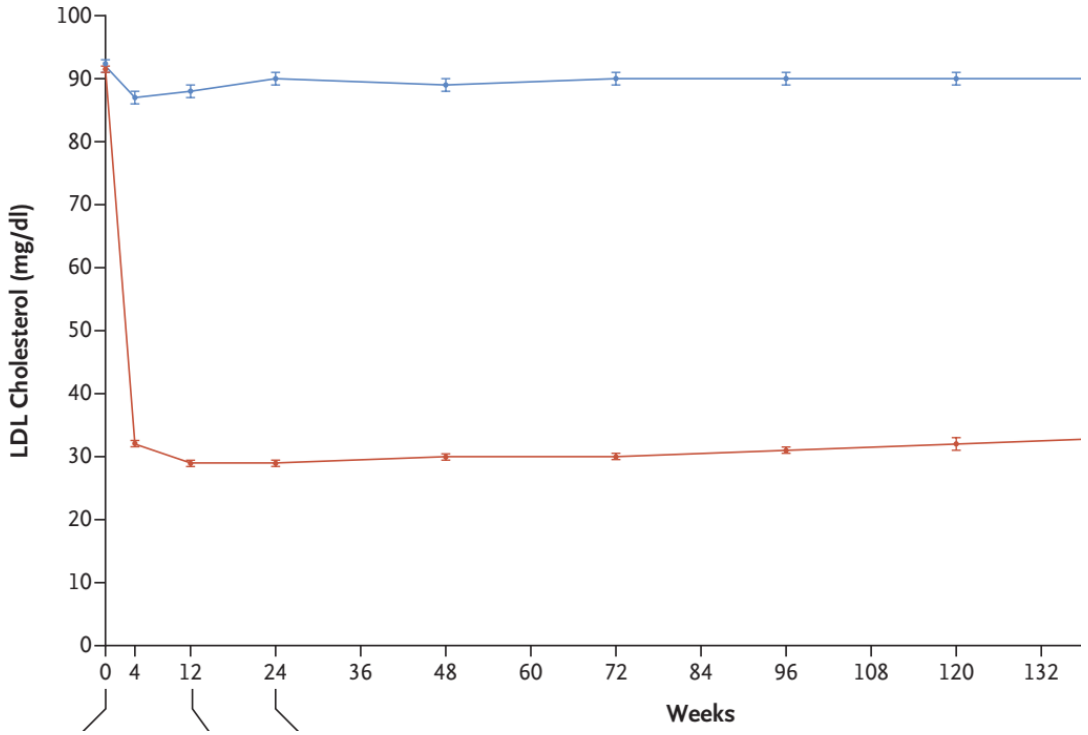
	ODYSSEY OUTCOMES[a] (n=18,312)	FOURIER[b] (n=27,564)
LLTs		
High-intensity stain, %	89.5	69.2
Moderate-/low-intensity statin, %	7.8	30.7
Ezetimibe, %	2.9	5.1
Lipid parameters		
Median LDL-C, mg/dL	86.5	91.5
Total cholesterol, mg/dL	160.0	167.0
HDL-C, mg/dL	42.5	44.0
Triglycerides, mg/dL	129.2	133.0

PCSK9 monoclonal antibodies

ODISSEY OUTCOMES

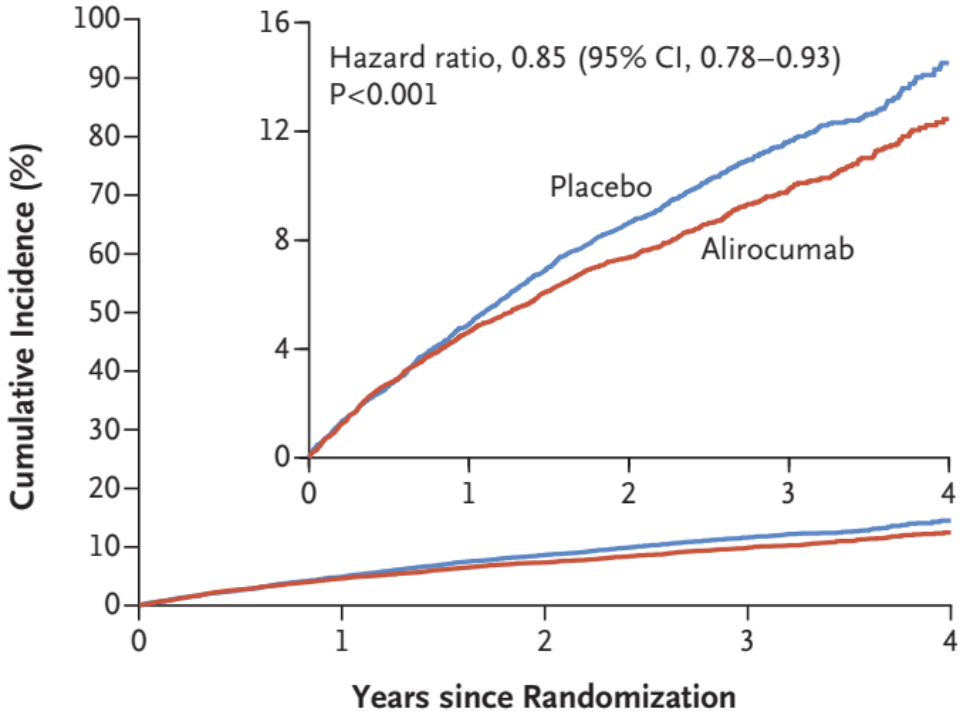


FOURIER



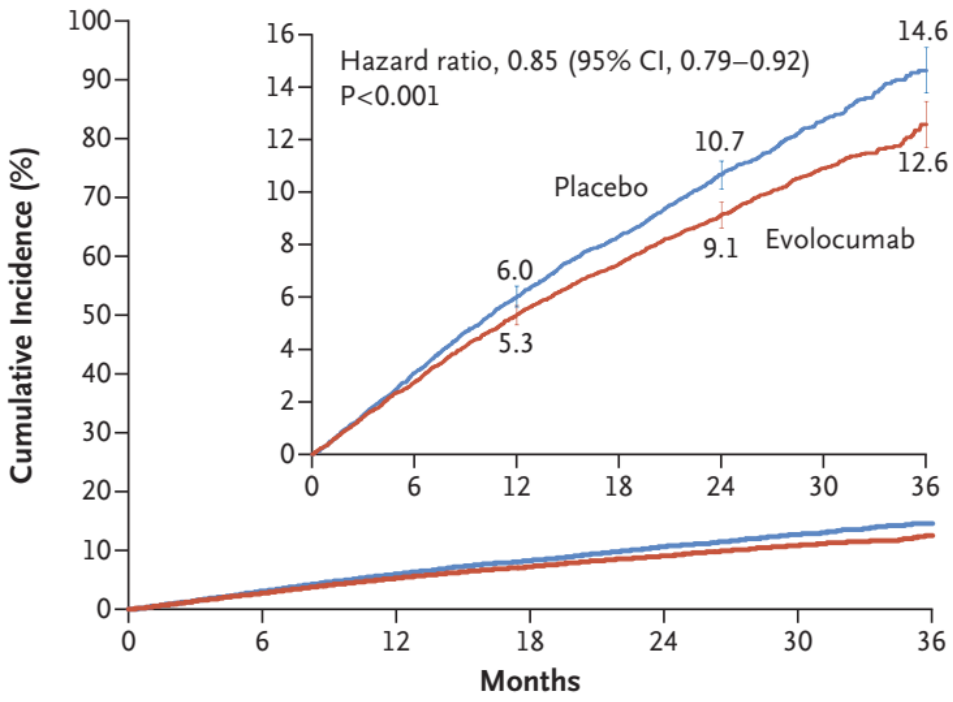
PCSK9 monoclonal antibodies

ODISSEY OUTCOMES



No. at Risk					
Placebo	9462	8805	8201	3471	629
Alirocumab	9462	8846	8345	3574	653

FOURIER

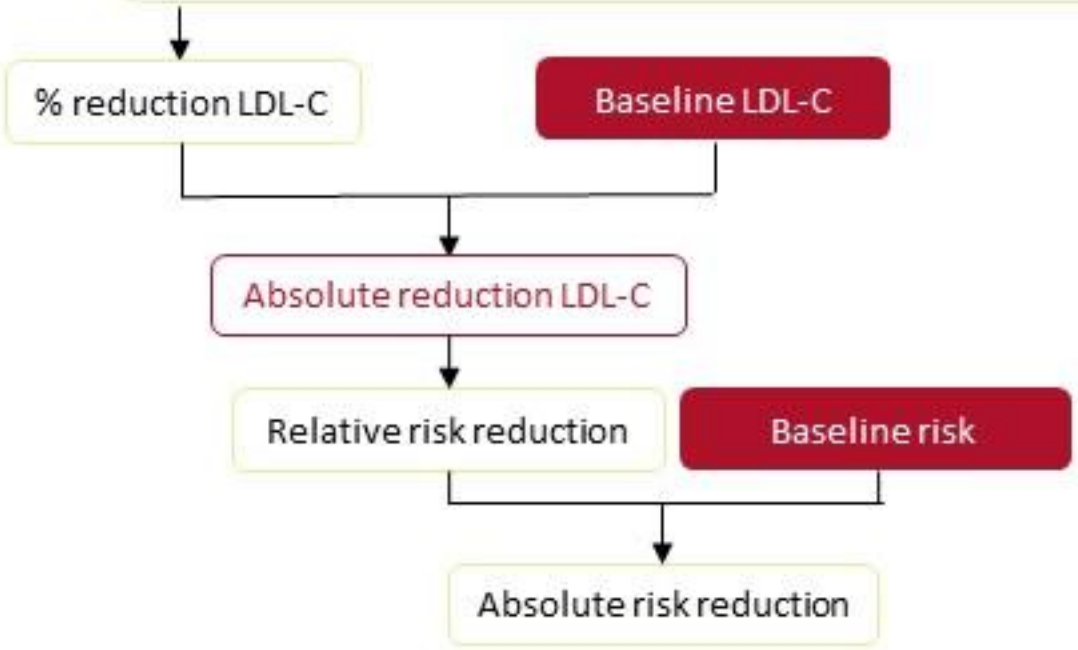


No. at Risk							
Placebo	13,780	13,278	12,825	11,871	7610	3690	686
Evolocumab	13,784	13,351	12,939	12,070	7771	3746	689

Expected clinical benefit of low-density lipoprotein cholesterol lowering therapies

Intensity of lipid lowering treatment

Treatment	Average LDL-C reduction
Moderate intensity statin	≈ 30%
High intensity statin	≈ 50%
High intensity statin plus ezetimibe	≈ 65%
PCSK9 inhibitor	≈ 60%
PCSK9 inhibitor plus high intensity statin	≈ 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	≈ 85%

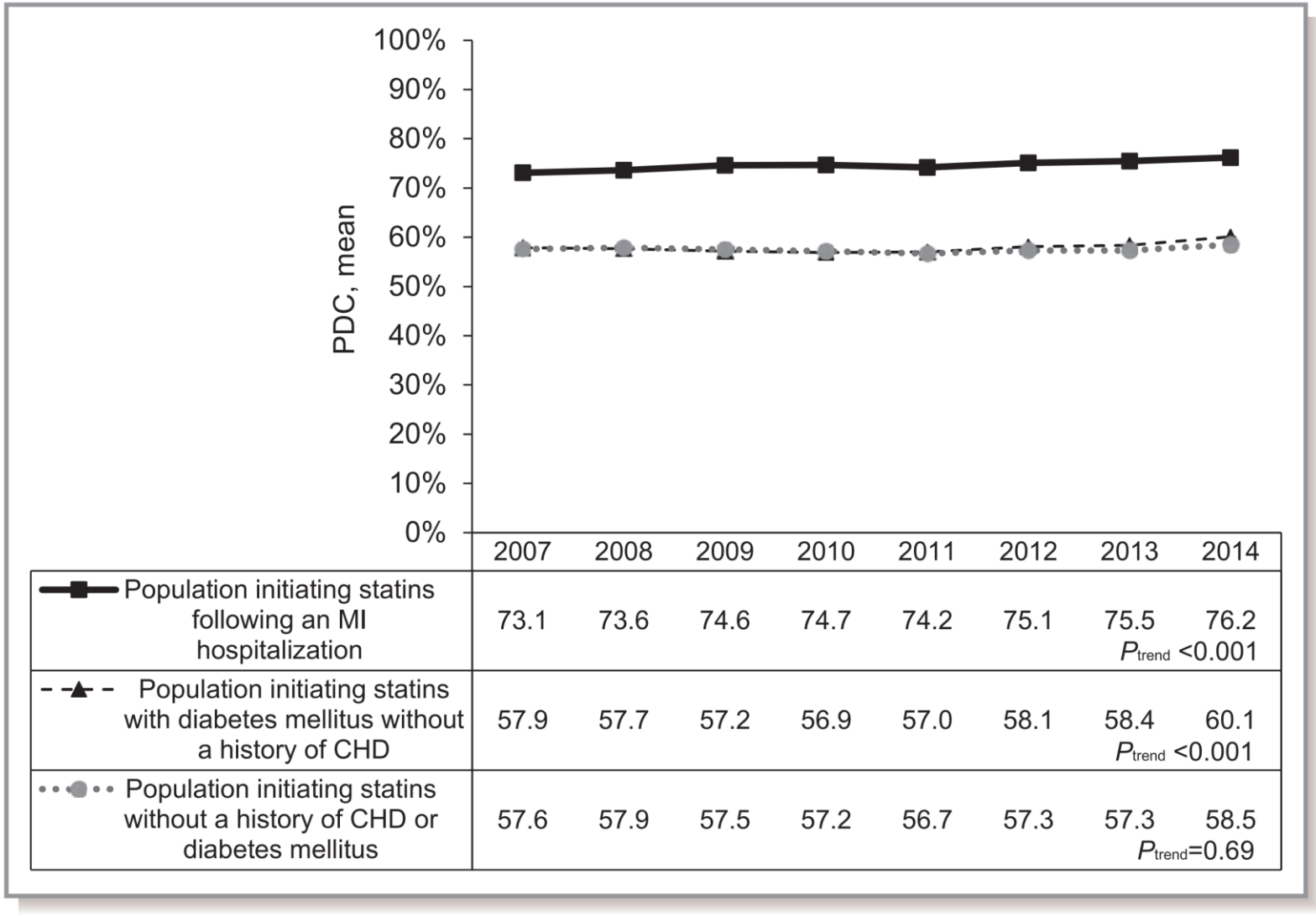


LDL-C = low-density lipoprotein cholesterol;
PCSK9 = proprotein convertase subtilisin/kexin type 9.

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

What else?

Adherence to statins from 3 million of Medicare people



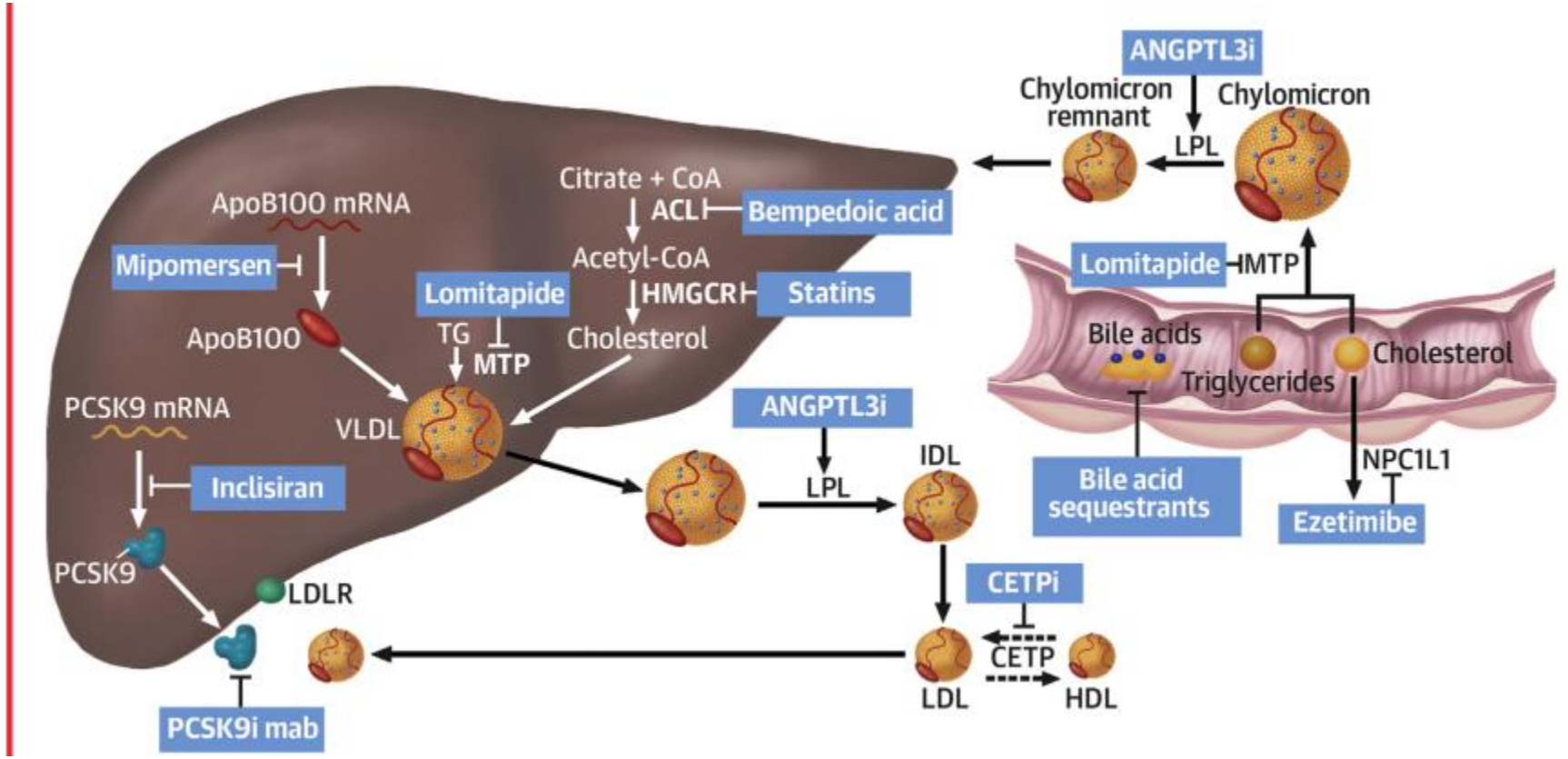
	2007	2008	2009	2010	2011	2012	2013	2014
Population initiating statins following an MI hospitalization	73.1	73.6	74.6	74.7	74.2	75.1	75.5	76.2 P_{trend} <0.001
Population initiating statins with diabetes mellitus without a history of CHD	57.9	57.7	57.2	56.9	57.0	58.1	58.4	60.1 P_{trend} <0.001
Population initiating statins without a history of CHD or diabetes mellitus	57.6	57.9	57.5	57.2	56.7	57.3	57.3	58.5 P_{trend}=0.69

Adherence to Statin Therapy Among US Adults Between 2007 and 2014

Lisandro et al, Jaha 19

Bempedoic acid

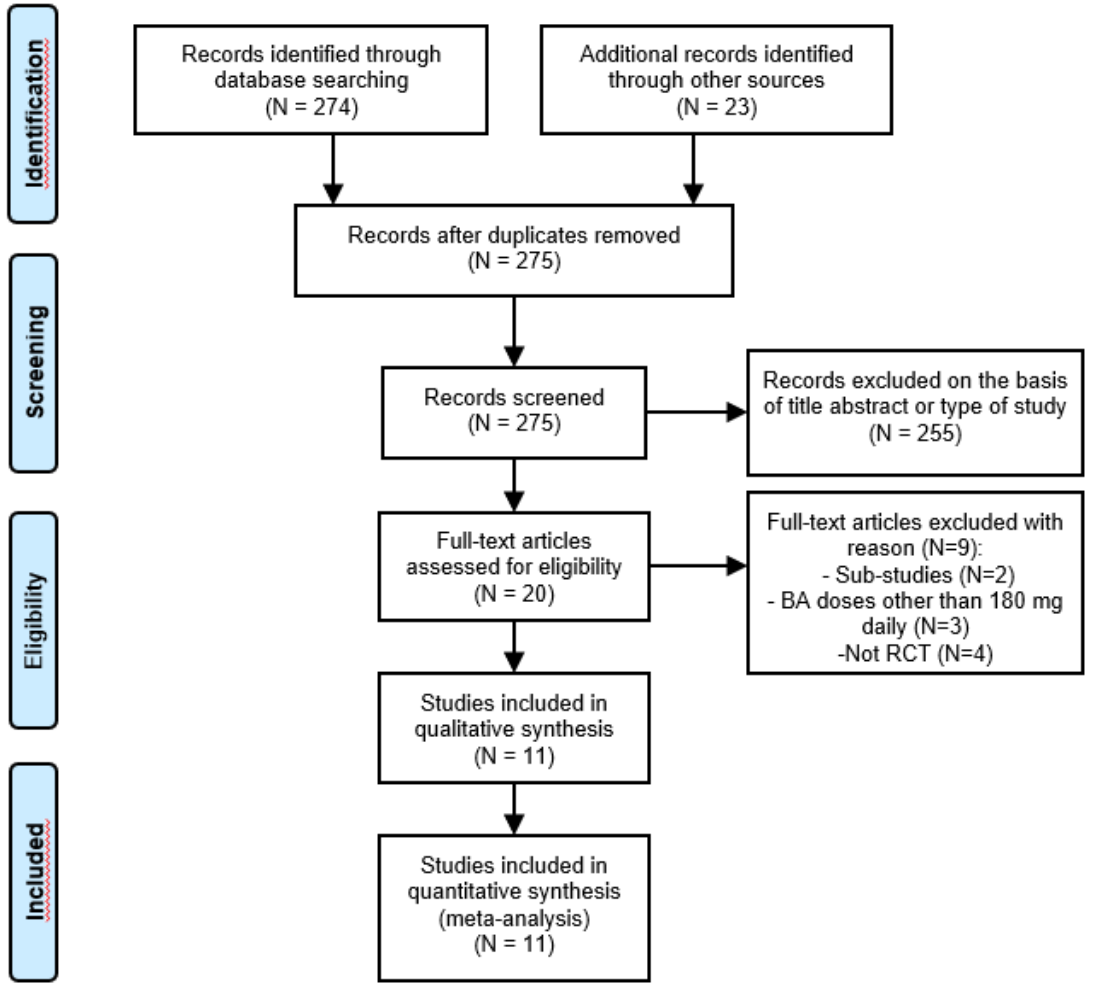
BA is metabolized in the liver to a CoA thioester form, which suppresses metabolites downstream of ACL in the same pathway of HMG-CoA reductase, up-regulating LDLRs and lowering LDL-C



New and Emerging Therapies for Reduction of LDL-Cholesterol and Apolipoprotein B

Nurmohamed, Jacc 2021

Bempedoic acid



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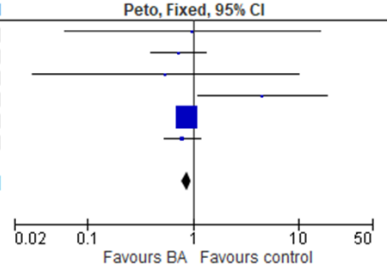
Safety and efficacy of Bempedoic Acid: a systematic review and meta-analysis of randomised controlled trials.

Bempedoic acid

MACE

Study or Subgroup	BA Events	BA Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bays, Am J Prev Cardiol. 2021 (vs. placebo)	1	61	1	60	0.1%	0.98 [0.06, 15.91]
Goldberg, JAMA 2019	32	522	21	257	2.6%	0.73 [0.40, 1.31]
Lalwani, J Clin Lipidol. 2019	1	42	1	24	0.1%	0.55 [0.03, 10.02]
Laufs, JAHA 2019	9	234	0	111	0.5%	4.52 [1.10, 18.63]
Nissen, NEJM 2023	819	6992	927	6978	91.2%	0.87 [0.78, 0.96]
Ray, NEJM 2019	68	1488	42	742	5.5%	0.79 [0.53, 1.19]
Total (95% CI)		**9339**		**8172**	**100.0%**	**0.86 [0.79, 0.95]**
Total events	930		992			

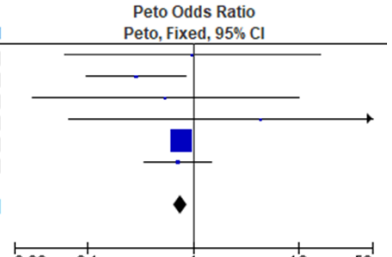
Heterogeneity: Chi² = 5.87, df = 5 (P = 0.32); I² = 15%
Test for overall effect: Z = 2.99 (P = 0.003)



Myocardial infarction

Study or Subgroup	BA Events	BA Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bays, Am J Prev Cardiol. 2021 (vs. placebo)	1	61	1	60	0.3%	0.98 [0.06, 15.91]
Goldberg, JAMA 2019	6	522	9	257	2.1%	0.29 [0.10, 0.85]
Lalwani, J Clin Lipidol. 2019	1	42	1	24	0.3%	0.55 [0.03, 10.02]
Laufs, JAHA 2019	1	234	0	111	0.1%	4.37 [0.07, 290.03]
Nissen, NEJM 2023	261	6992	334	6978	92.6%	0.77 [0.66, 0.91]
Ray, NEJM 2019	19	1488	13	742	4.6%	0.71 [0.34, 1.50]
Total (95% CI)		**9339**		**8172**	**100.0%**	**0.76 [0.64, 0.88]**
Total events	289		358			

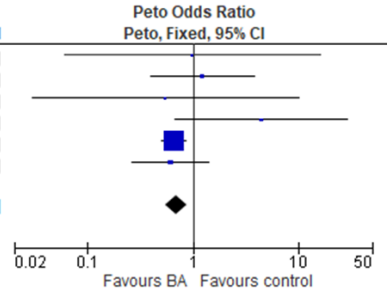
Heterogeneity: Chi² = 3.87, df = 5 (P = 0.57); I² = 0%
Test for overall effect: Z = 3.48 (P = 0.0005)



Unstable angina

Study or Subgroup	BA Events	BA Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bays, Am J Prev Cardiol. 2021 (vs. placebo)	1	61	1	60	0.7%	0.98 [0.06, 15.91]
Goldberg, JAMA 2019	10	522	4	257	4.6%	1.23 [0.40, 3.77]
Lalwani, J Clin Lipidol. 2019	1	42	1	24	0.7%	0.55 [0.03, 10.02]
Laufs, JAHA 2019	5	234	0	111	1.6%	4.44 [0.67, 29.34]
Nissen, NEJM 23	91	6992	137	6878	84.1%	0.65 [0.50, 0.85]
Ray, NEJM 2019	14	1488	11	742	8.2%	0.61 [0.27, 1.42]
Total (95% CI)		**9339**		**8072**	**100.0%**	**0.69 [0.54, 0.88]**
Total events	122		154			

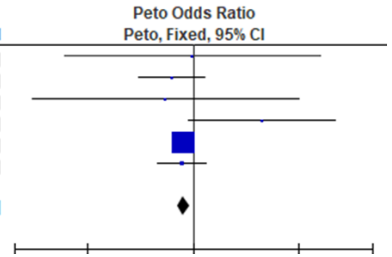
Heterogeneity: Chi² = 5.08, df = 5 (P = 0.41); I² = 2%
Test for overall effect: Z = 3.02 (P = 0.003)



Coronary revascularization

Study or Subgroup	BA Events	BA Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bays, Am J Prev Cardiol. 2021 (vs. placebo)	1	61	1	60	0.2%	0.98 [0.06, 15.91]
Goldberg, JAMA 2019	20	522	15	257	3.0%	0.63 [0.31, 1.29]
Lalwani, J Clin Lipidol. 2019	1	42	1	24	0.2%	0.55 [0.03, 10.02]
Laufs, JAHA 2019	7	234	0	111	0.6%	4.48 [0.91, 22.21]
Nissen, NEJM 2023	435	6992	529	6978	90.6%	0.81 [0.71, 0.92]
Ray, NEJM 2019	38	1488	24	742	5.4%	0.78 [0.46, 1.33]
Total (95% CI)		**9339**		**8172**	**100.0%**	**0.81 [0.71, 0.92]**
Total events	502		570			

Heterogeneity: Chi² = 4.99, df = 5 (P = 0.42); I² = 0%
Test for overall effect: Z = 3.33 (P = 0.0009)



Safety and efficacy of Bempedoic Acid: a systematic review and meta-analysis of randomised controlled trials.

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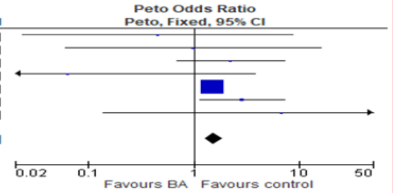
Bempedoic acid

Gout

Study or Subgroup	BA Events	BA Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Ballantyne, Atherosclerosis 2018	1	182	1	89	0.5%	0.46 [0.02, 8.81]
Bays, Am J Prev Cardiol. 2021 (vs. placebo)	1	62	1	61	0.5%	0.98 [0.06, 15.91]
Goldberg, JAMA 2019	11	522	2	257	3.0%	2.25 [0.70, 7.20]
Lalwani, J Clin Lipidol. 2019	0	42	1	24	0.2%	0.06 [0.00, 3.76]
Nissen, NEJM 2023	215	6992	143	6978	91.0%	1.51 [1.22, 1.86]
Ray, NEJM 2019	18	1488	2	742	4.6%	2.88 [1.13, 7.33]
Rubino, Atherosclerosis 2021	1	30	0	28	0.3%	6.91 [0.14, 349.18]
Total (95% CI)		**9318**		**8179**	**100.0%**	**1.55 [1.27, 1.90]**
Total events	247		150			

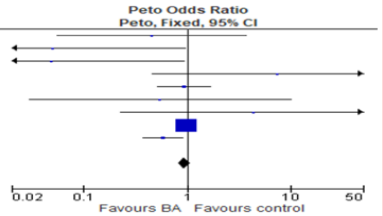
Heterogeneity: Chi² = 5.81, df = 6 (P = 0.45); I² = 0%
Test for overall effect: Z = 4.32 (P < 0.0001)



New onset diabetes

Study or Subgroup	BA Events	BA Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Ballantyne, Atherosclerosis 2018	2	181	2	88	0.4%	0.45 [0.06, 3.69]
Ballantyne, Eur J Prev Cardiol. 2020 (BA +eze)	0	108	2	55	0.2%	0.05 [0.00, 0.96]
Ballantyne, Eur J Prev Cardiol. 2020 (BA alone)	0	110	2	55	0.2%	0.05 [0.00, 0.93]
Bays, Am J Prev Cardiol. 2021 (vs. placebo)	2	61	0	60	0.2%	7.39 [0.46, 119.56]
Goldberg, JAMA 2019	36	522	19	257	4.8%	0.93 [0.52, 1.66]
Lalwani, J Clin Lipidol. 2019	1	42	1	24	0.2%	0.55 [0.03, 10.02]
Laufs, JAHA 2019	2	234	0	111	0.2%	4.39 [0.22, 85.60]
Nissen, NEJM 2023	429	6992	433	6978	85.8%	0.99 [0.86, 1.13]
Ray, NEJM 2019	49	1488	40	742	8.1%	0.58 [0.37, 0.91]
Total (95% CI)		**9738**		**8370**	**100.0%**	**0.94 [0.82, 1.06]**
Total events	521		499			

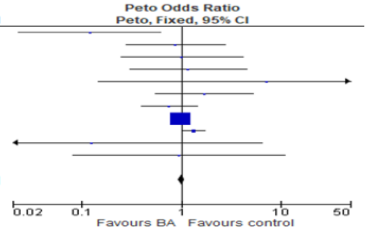
Heterogeneity: Chi² = 16.36, df = 8 (P = 0.04); I² = 51%
Test for overall effect: Z = 1.02 (P = 0.31)



Muscle-related AE

Study or Subgroup	BA Events	BA Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Ballantyne, Atherosclerosis 2016	0	45	6	45	0.3%	0.12 [0.02, 0.62]
Ballantyne, Atherosclerosis 2018	9	181	5	88	0.6%	0.87 [0.28, 2.72]
Ballantyne, Eur J Prev Cardiol. 2020 (BA +eze)	6	108	3	55	0.4%	1.02 [0.25, 4.21]
Ballantyne, Eur J Prev Cardiol. 2020 (BA alone)	7	110	3	55	0.4%	1.17 [0.30, 4.53]
Bays, Am J Prev Cardiol. 2021 (vs. placebo)	1	60	0	59	0.0%	7.27 [0.14, 366.28]
Goldberg, JAMA 2019	11	522	3	257	0.6%	1.70 [0.55, 5.24]
Laufs, JAHA 2019	30	234	18	111	1.7%	0.75 [0.39, 1.45]
Nissen, NEJM 2023	1051	6992	1070	6978	85.8%	0.98 [0.89, 1.07]
Ray, NEJM 2019	195	1488	75	742	10.1%	1.33 [1.01, 1.74]
Rubino, Atherosclerosis 2021	0	31	1	29	0.0%	0.13 [0.00, 6.38]
Rubino, J Clin Lipidol, 2020	2	44	1	21	0.1%	0.95 [0.08, 11.13]
Total (95% CI)		**9815**		**8440**	**100.0%**	**1.00 [0.92, 1.09]**
Total events	1312		1185			

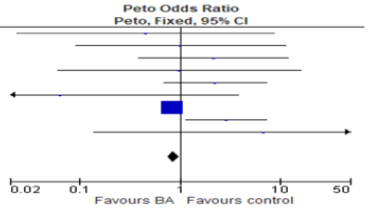
Heterogeneity: Chi² = 14.53, df = 10 (P = 0.15); I² = 31%
Test for overall effect: Z = 0.01 (P = 0.99)



Myalgia

Study or Subgroup	BA Events	BA Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Ballantyne, Atherosclerosis 2018	1	182	1	89	0.2%	0.46 [0.02, 8.81]
Ballantyne, Eur J Prev Cardiol. 2020 (BA +eze)	2	108	1	55	0.3%	1.02 [0.09, 11.32]
Ballantyne, Eur J Prev Cardiol. 2020 (BA alone)	5	110	1	55	0.6%	2.17 [0.39, 12.15]
Bays, Am J Prev Cardiol. 2021 (vs. placebo)	1	62	1	61	0.2%	0.98 [0.06, 15.91]
Goldberg, JAMA 2019	11	522	2	257	1.3%	2.25 [0.70, 7.20]
Lalwani, J Clin Lipidol. 2019	0	42	1	24	0.1%	0.06 [0.00, 3.76]
Nissen, NEJM 2023	393	6992	471	6978	95.0%	0.82 [0.72, 0.94]
Ray, NEJM 2019	18	1488	2	742	2.1%	2.88 [1.13, 7.33]
Rubino, Atherosclerosis 2021	1	30	0	28	0.1%	6.91 [0.14, 349.18]
Total (95% CI)		**9536**		**8289**	**100.0%**	**0.86 [0.75, 0.98]**
Total events	432		480			

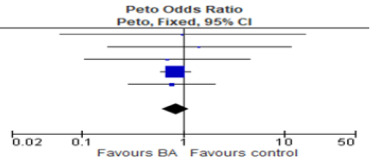
Heterogeneity: Chi² = 13.37, df = 8 (P = 0.10); I² = 40%
Test for overall effect: Z = 2.19 (P = 0.03)



Neurocognitive disorders

Study or Subgroup	BA Events	BA Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bays, Am J Prev Cardiol. 2021 (vs. placebo)	1	61	1	60	1.3%	0.98 [0.06, 15.91]
Goldberg, JAMA 2019	3	522	1	257	2.3%	1.44 [0.18, 11.60]
Laufs, JAHA 2019	3	234	2	111	2.8%	0.70 [0.11, 4.59]
Nissen, NEJM 2023	58	6992	69	6978	83.1%	0.84 [0.59, 1.19]
Ray, NEJM 2019	11	1488	7	742	10.5%	0.78 [0.29, 2.07]
Total (95% CI)		**9297**		**8148**	**100.0%**	**0.84 [0.61, 1.15]**
Total events	76		80			

Heterogeneity: Chi² = 0.33, df = 4 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.08 (P = 0.28)



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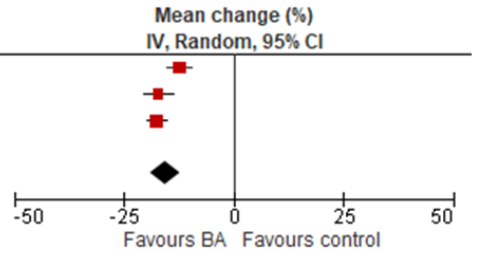
Bempedoic acid

High intensity statin

Study or Subgroup	Mean change (%)	SE	Weight	Mean change (%) IV, Random, 95% CI
Ballantyne, Eur J Prev Cardiol. 2020 (BA alone)	-12.3	1.4	33.4%	-12.30 [-15.04, -9.56]
Goldberg, JAMA 2019	-17.2	1.7	30.2%	-17.20 [-20.53, -13.87]
Ray, NEJM 2019	-17.5	1.1	36.4%	-17.50 [-19.66, -15.34]
Total (95% CI)			**100.0%**	**-15.67 [-19.05, -12.29]**

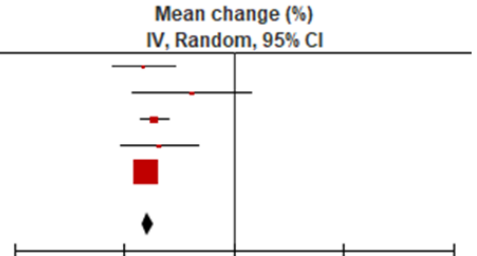
Heterogeneity: Tau² = 6.96; Chi² = 9.31, df = 2 (P = 0.010); I² = 79%
Test for overall effect: Z = 9.09 (P < 0.00001)



Low/moderate intensity statin

Study or Subgroup	Mean change (%)	SE	Weight	Mean change (%) IV, Random, 95% CI
Ballantyne, Atherosclerosis 2018	-20.5	3.7	2.8%	-20.50 [-27.75, -13.25]
Ballantyne, Eur J Prev Cardiol. 2020 (BA alone)	-9.5	6.9	0.8%	-9.50 [-23.02, 4.02]
Goldberg, JAMA 2019	-18.1	1.6	15.2%	-18.10 [-21.24, -14.96]
Laufs, JAHA 2019	-17	4.5	1.9%	-17.00 [-25.82, -8.18]
Ray, NEJM 2019	-20	0.7	79.3%	-20.00 [-21.37, -18.63]
Total (95% CI)			**100.0%**	**-19.58 [-20.80, -18.36]**

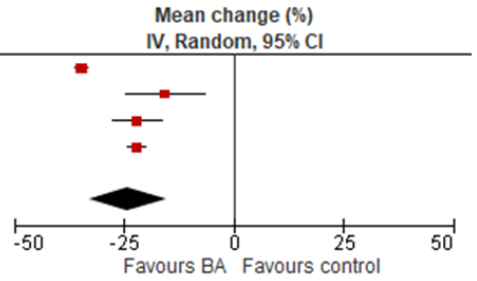
Heterogeneity: Tau² = 0.00; Chi² = 3.74, df = 4 (P = 0.44); I² = 0%
Test for overall effect: Z = 31.42 (P < 0.00001)



No statin

Study or Subgroup	Mean change (%)	SE	Weight	Mean change (%) IV, Random, 95% CI
Ballantyne, Atherosclerosis 2018	-34.7	0.8	27.1%	-34.70 [-36.27, -33.13]
Ballantyne, Eur J Prev Cardiol. 2020 (BA alone)	-15.7	4.6	21.4%	-15.70 [-24.72, -6.68]
Goldberg, JAMA 2019	-22	2.9	24.6%	-22.00 [-27.68, -16.32]
Laufs, JAHA 2019	-22.1	1.1	26.9%	-22.10 [-24.26, -19.94]
Total (95% CI)			**100.0%**	**-24.13 [-33.03, -15.22]**

Heterogeneity: Tau² = 75.50; Chi² = 103.11, df = 3 (P < 0.00001); I² = 97%
Test for overall effect: Z = 5.31 (P < 0.00001)



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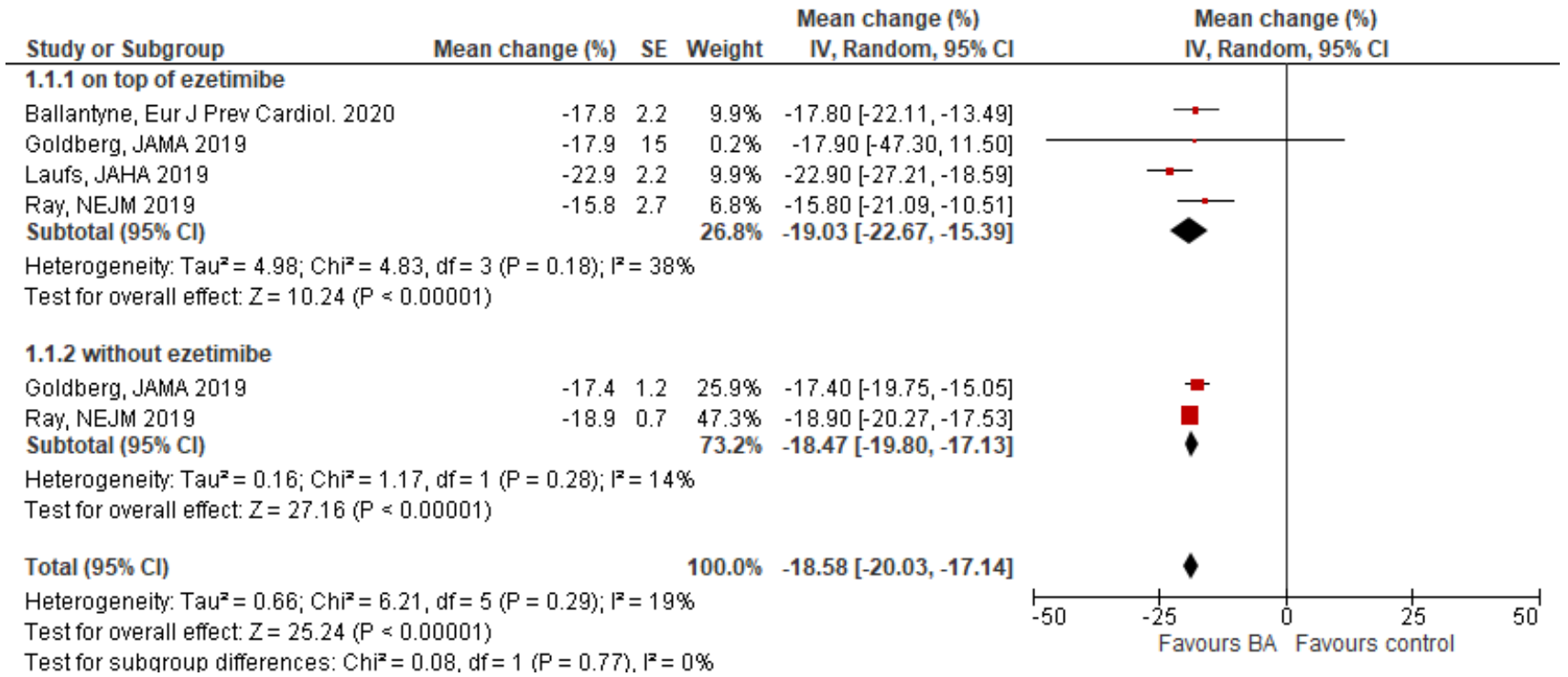
Bempedoic acid



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TAKE HOME MESSAGES

Risk stratification is mandatory, especially to stratify a tailored therapy

Statins represent the milestones of therapy, although limited by side effects/low adherence

Ezetimibe and PCSK9 monoclonal antibodies may represent reasonable choices

BA represent an alternative/add-on choice for high risk patients

QUESTIONS?