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Malta

Challenges in the Effective Treatment of Dyslipidemia

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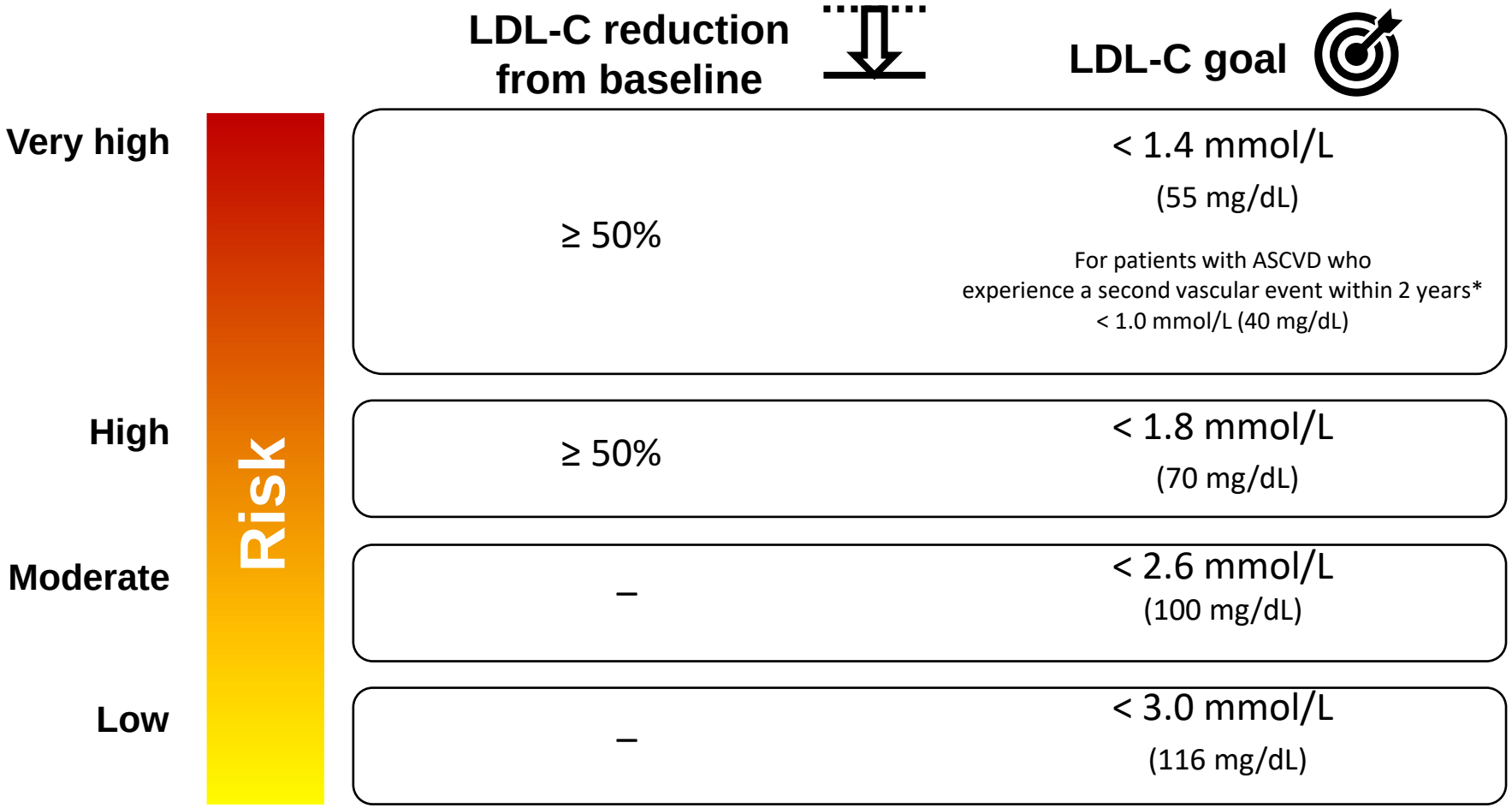
2019 ESC/EAS Guidelines

Very high risk	People with any of the following: • Documented ASCVD, either clinical or unequivocal on imaging • DM with target organ damage, or at least three major risk factors, or early onset of T1DM of long duration (> 20 years) • Severe CKD (eGFR < 30 mL/min/1.73 m^2) • A calculated SCORE ≥ 10% for 10-year risk of fatal CVD • FH with ASCVD or with another major risk factor
High risk	People with: • Markedly elevated single risk factors, in particular TC > 8 mmol/L (310 mg/dL), LDL-C > 4.9 mmol/L (190 mg/dL), or BP ≥ 180/110 mmHg • Patients with FH without other major risk factors • Patients with DM without target organ damage, with DM duration ≥ 10 years or another additional risk factor • Moderate CKD (eGFR 30-59 mL/min/1.73 m^2) • A calculated SCORE ≥ 5% and < 10% for 10-year risk of fatal CVD
Moderate risk	• Young patients (T1DM < 35 years; T2DM < 50 years) with DM duration < 10 years, without other risk factors • Calculated SCORE ≥ 1% and < 5% for 10-year risk of fatal CVD
Low-risk	• Calculated SCORE < 1% for 10-year risk of fatal CVD

ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; SCORE, Systematic Coronary Risk Estimation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TC, total cholesterol. Adapted from Mach F, et al. *Eur Heart J* 2020;41(1):111-88.

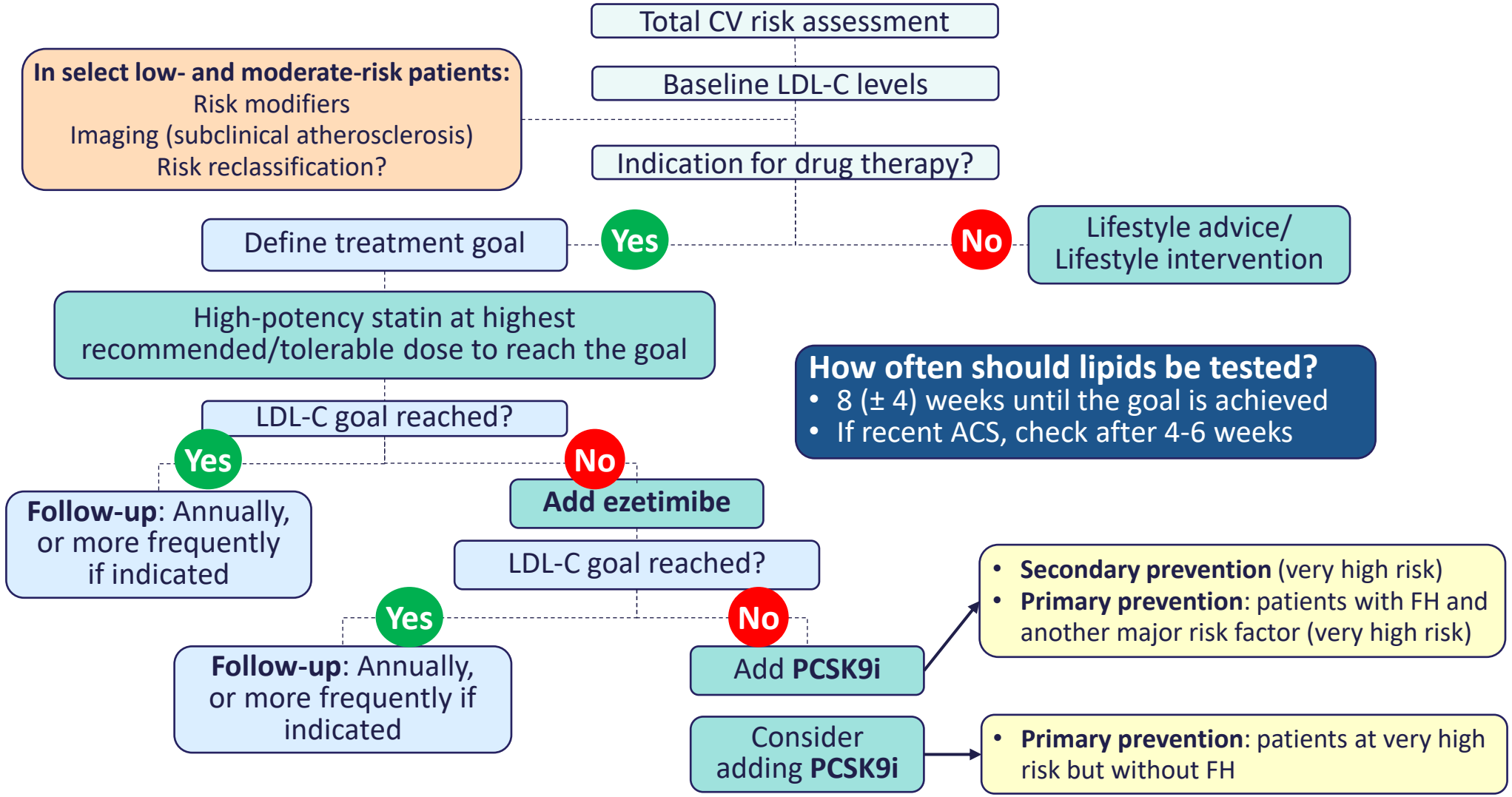
Risk Stratification Dictates LDL-C Lowering Goals



*For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy, an LDL-C goal of < 1.0 mmol/L (< 40 mg/dL) may be considered.

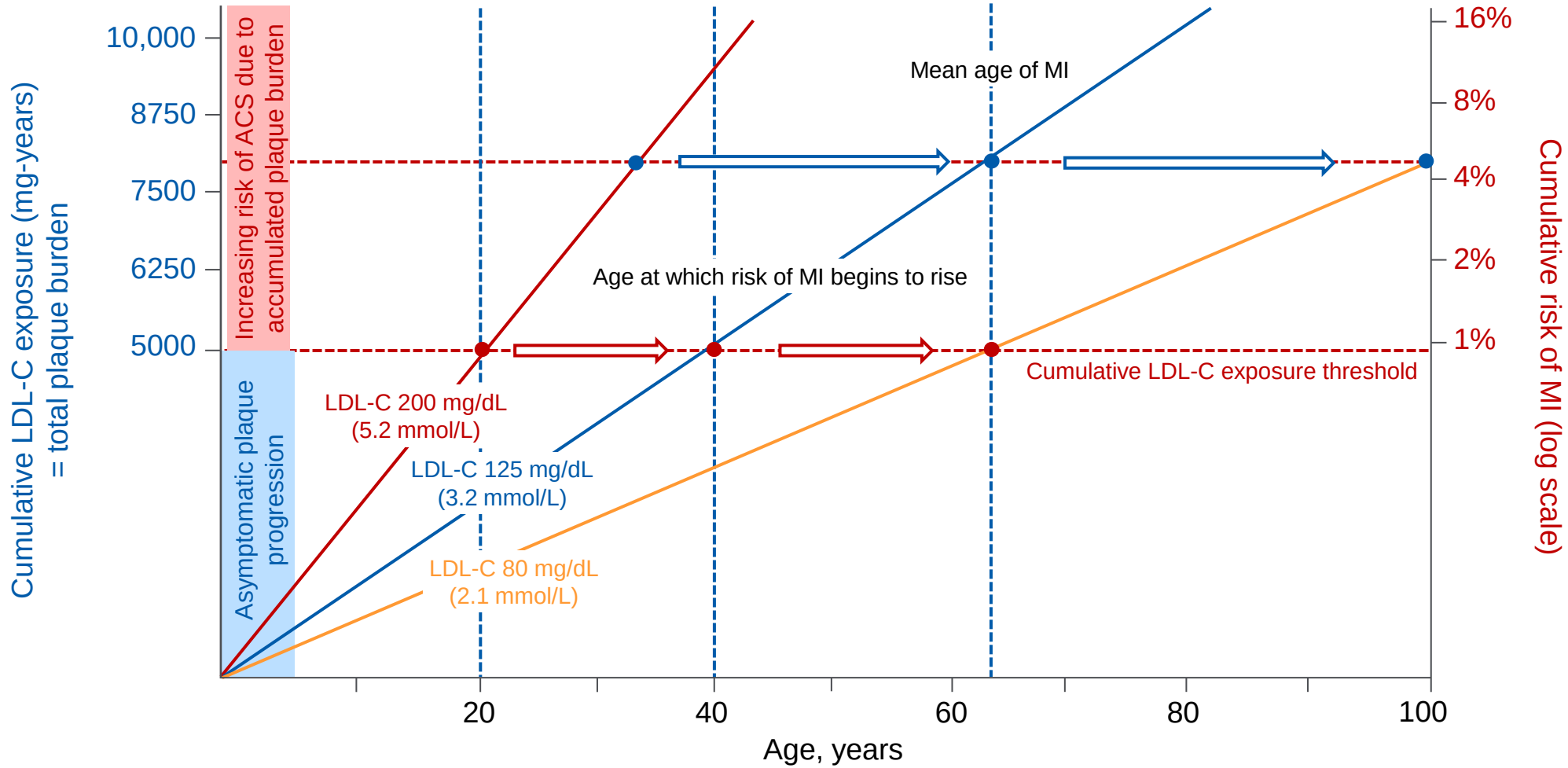
ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol. Adapted from Mach F, et al. *Eur Heart J* 2020;41(1):111-88.

2019 ESC/EAS Treatment Algorithm for Pharmacological LDL-C-Lowering



ACS, acute coronary syndrome; CV, cardiovascular; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor. Adapted from Mach F, et al. *Eur Heart J* 2020;41(1):111-88.

Cumulative Effect of LDL on Risk of Atherosclerotic Cardiovascular Disease

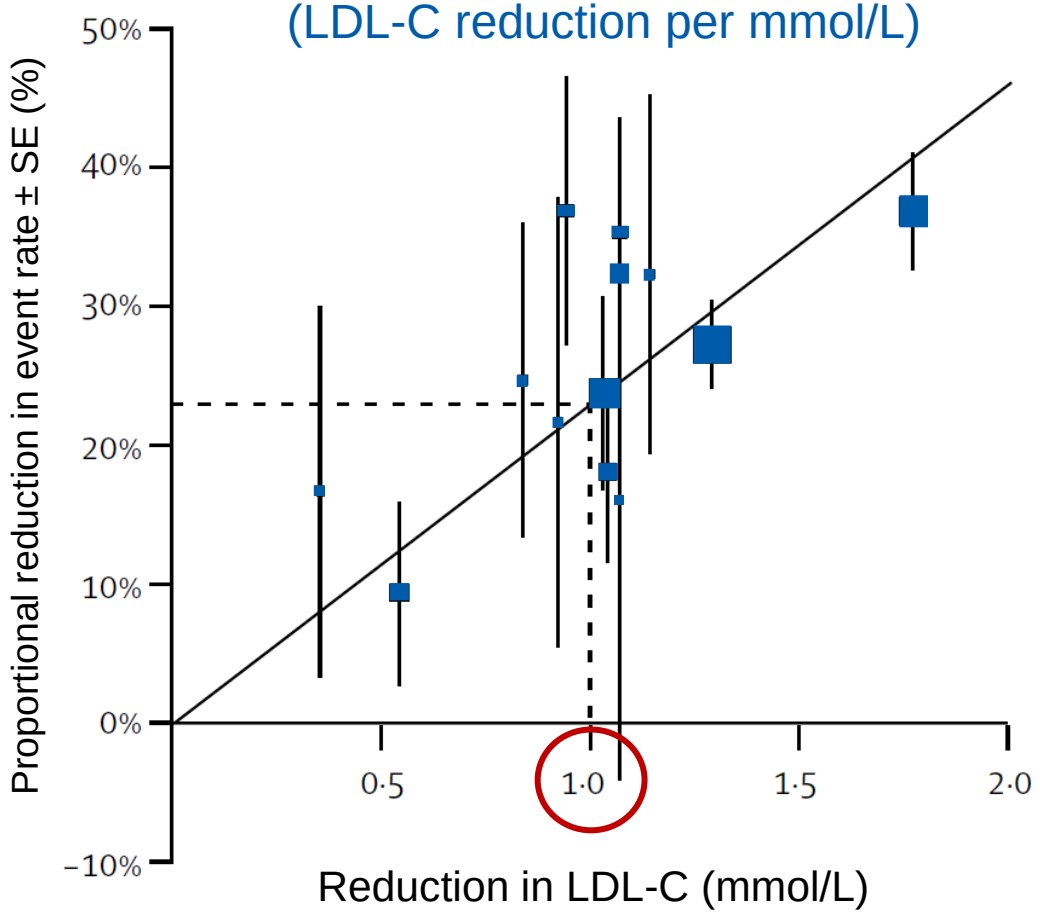


ACS, acute coronary syndrome; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction. Adapted from Ference BA, et al. *J Am Coll Cardiol* 2018;72(10):1141-56.

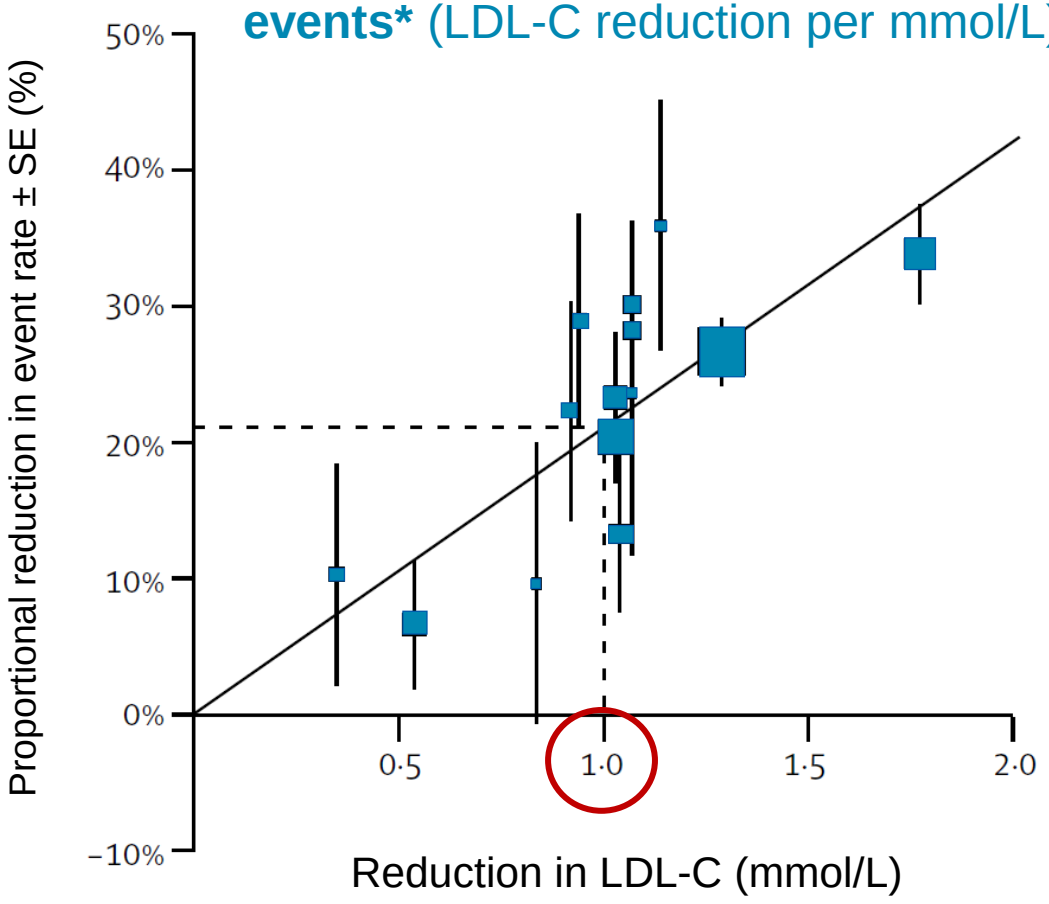
CTT Collaborators: Reduction in LDL-C Is Associated With Reduction in Coronary and Major Vascular Events

14 clinical trials (N = 90,056)

23% reduction in coronary events
(LDL-C reduction per mmol/L)

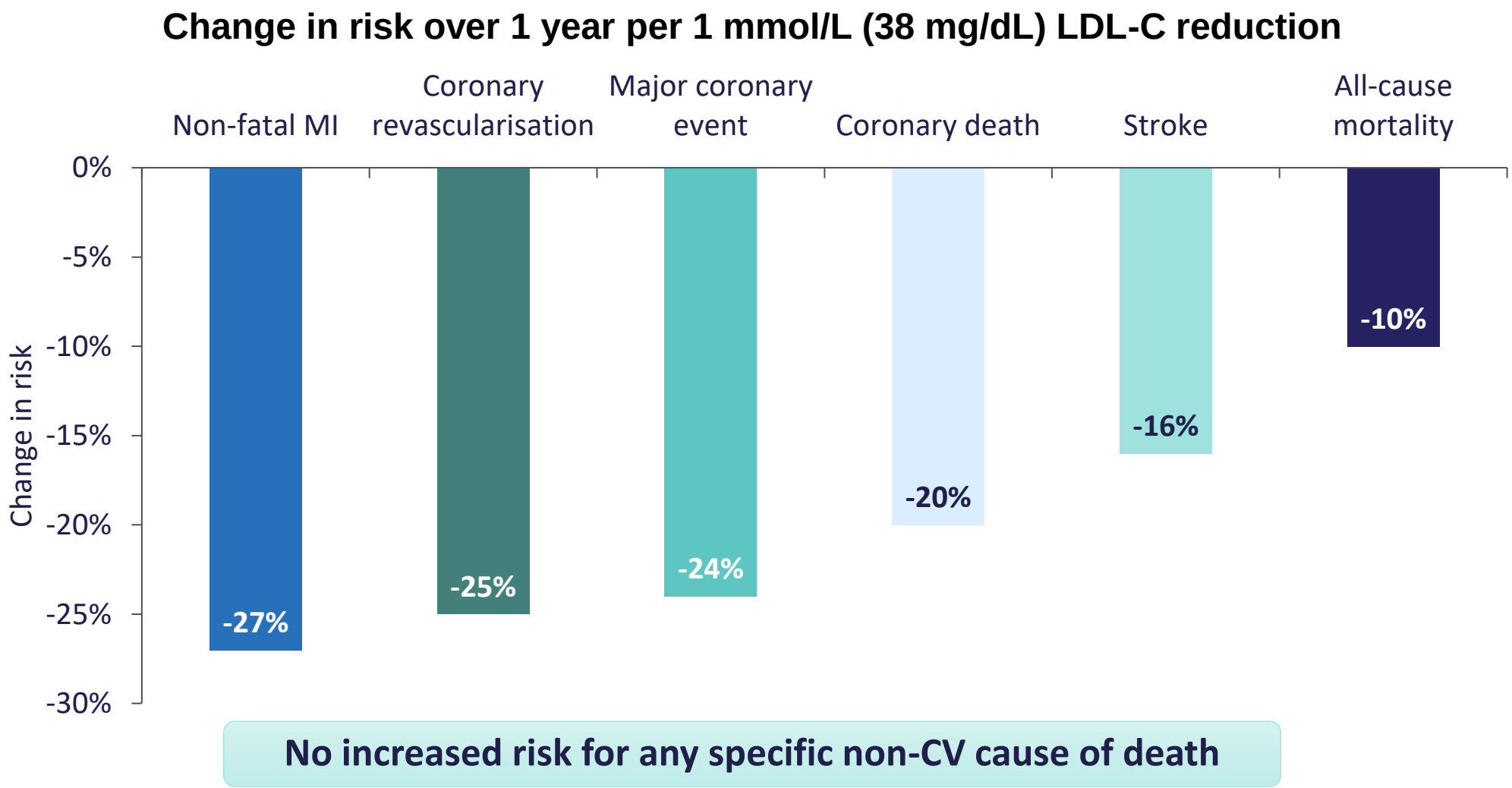


21% reduction in major vascular events* (LDL-C reduction per mmol/L)



*Defined as non-fatal myocardial infarction or mortality due to coronary heart disease.
CTT, Cholesterol Treatment Trialists; LDL-C, low-density lipoprotein cholesterol; SE, standard error.
Adapted from Baigent D, et al. *Lancet* 2005;366(9493):1267-78.

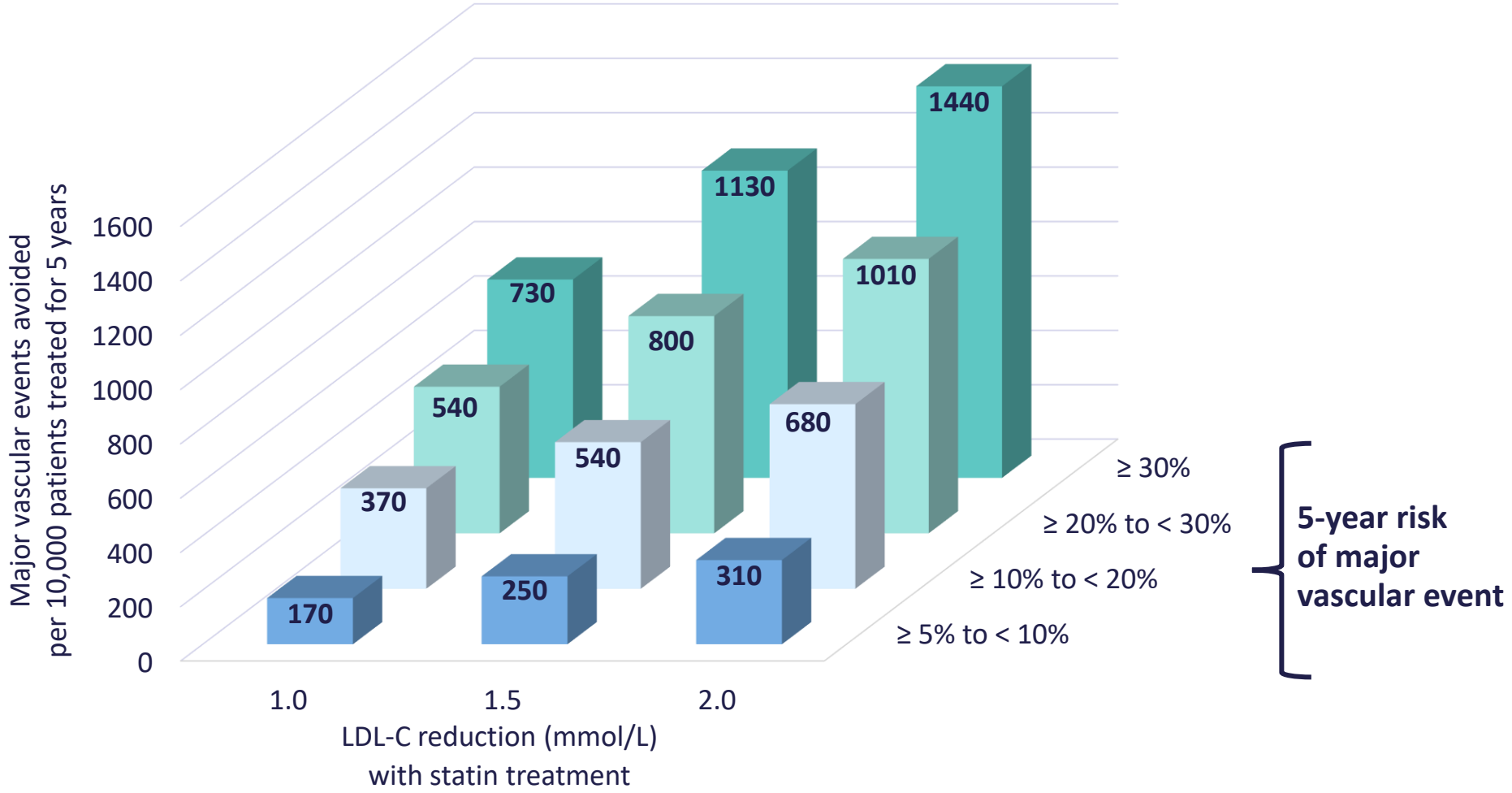
Benefits of Intensive Statin Therapy Are Well Documented



CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.
Adapted from Cholesterol Treatment Trialists' (CTT) Collaboration. *Lancet* 2010;376:1670-81.

Lower Is Better: Greater Reduction of LDL-C Improves Risk of Vascular Events

Predicted absolute risk reduction in major vascular events (after first year) by lowering LDL-C with statin therapy for 5 years in people at different levels of absolute risk



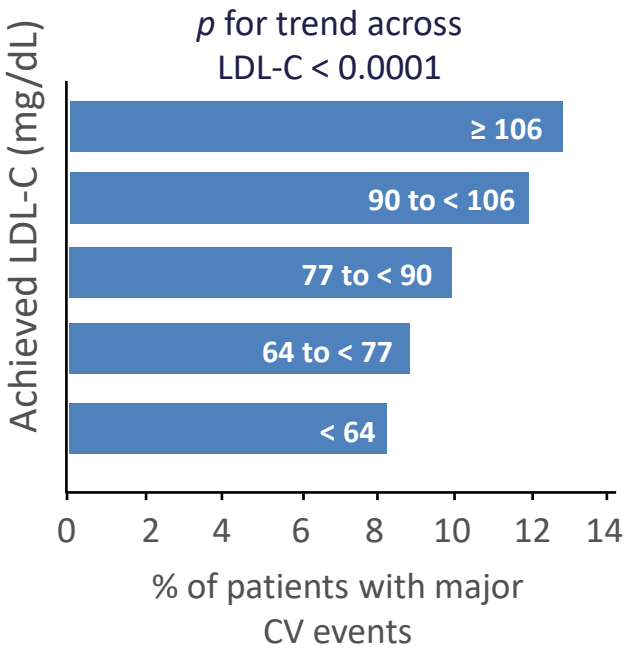
LDL-C, low-density lipoprotein cholesterol.

Adapted from Cholesterol Treatment Trialists' (CTT) Collaborators, et al. *Lancet* 2012;380:581-90.

No Evidence for a Lower LDL-C Limit in Reducing Major CV Events

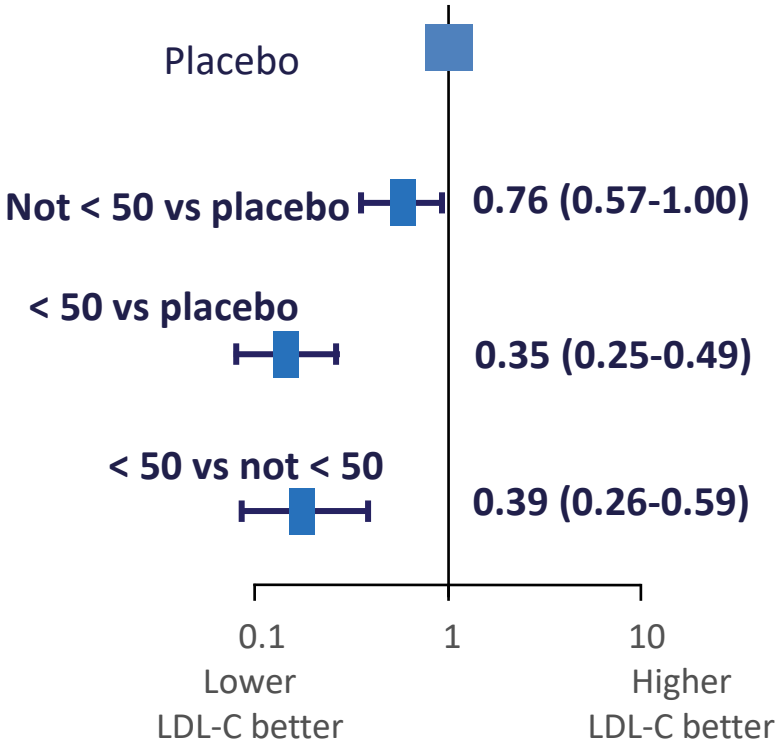
TNT[1]

Rate of major CV events



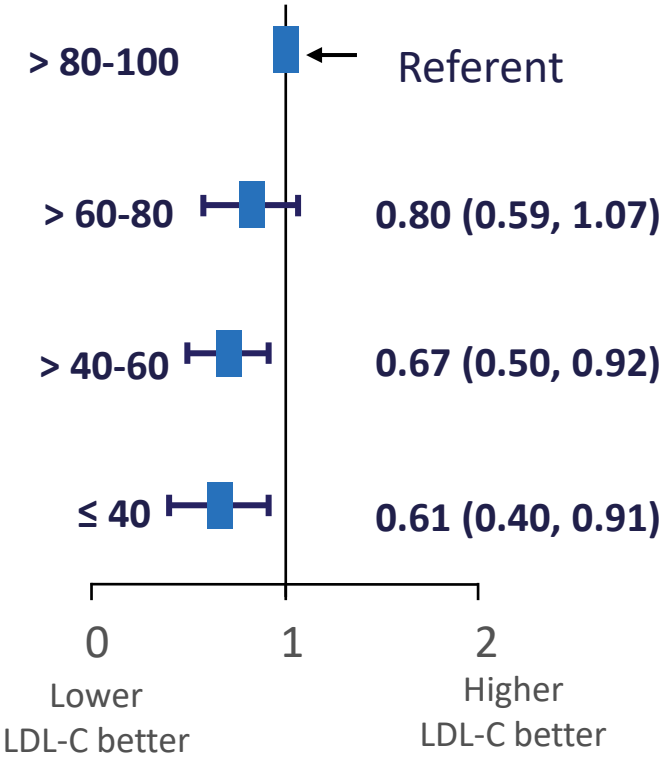
JUPITER[2]

Risk of primary endpoint*



PROVE-IT[3]

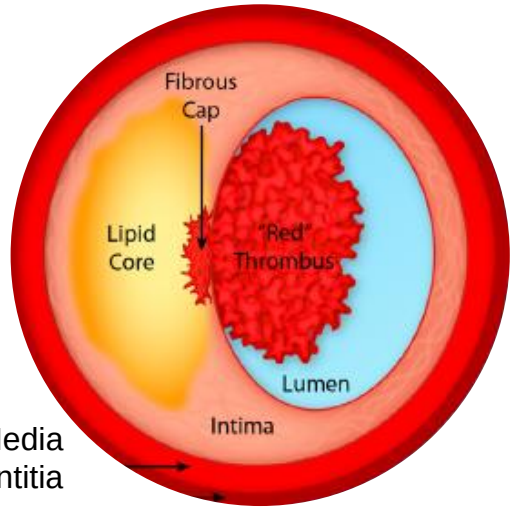
Risk of primary endpoint†



CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol.

1. LaRosa JC, et al. *Am J Cardiol* 2007;100:747-52. 2. Hsia J, et al. *J Am Coll Cardiol* 2011;57:1666-75. 3. Wiviott SD, et al. *J Am Coll Cardiol* 2005;46:1411-6.

Very Low LDL-C Levels Are Associated With More Stable Plaque Features

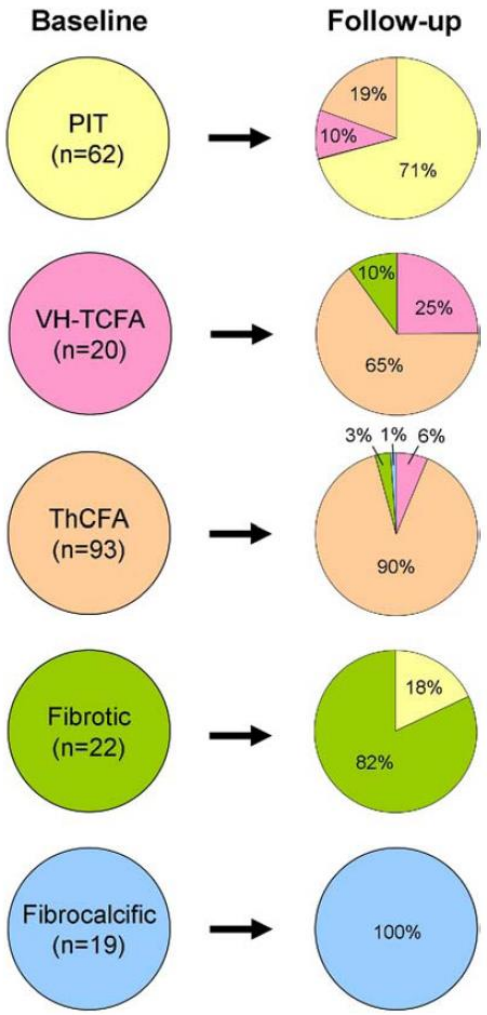


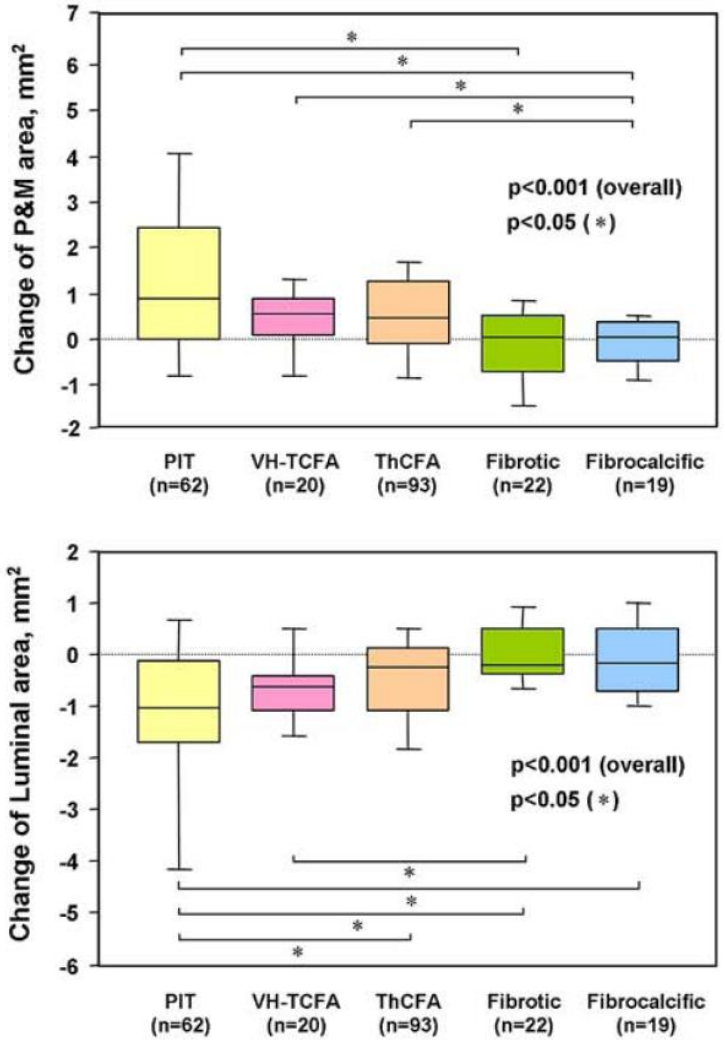
	LDL-C < 50 mg/dL (1.3 mmol/L) (87 plaques)	LDL-C 50-70 mg/dL (1.3-1.8 mmol/L) (81 plaques)	LDL-C 70-100 mg/dL (1.8-2.6 mmol/L) (117 plaques)	LDL-C > 100 mg/dL (2.6 mmol/L) (130 plaques)	*p*
Plaque microstructures in lipid plaques (n = 293)					
Fibrous cap thickness (μm)	139.9 ± 93.9	103.1 ± 66.4	92.5 ± 48.5	92.1 ± 47.8	0.001
Plaque rupture, n (%)	1/42 (2.3)	2/46 (4.3)	7/91 (7.6)	12/114 (10.5)	0.17
Thrombus, n (%)	0/42 (0.0)	1/46 (2.1)	2/91 (2.1)	3/114 (2.6)	0.18

LDL-C, low-density lipoprotein cholesterol.

Kataoka Y, et al. *Atherosclerosis* 2015;242:490-5.

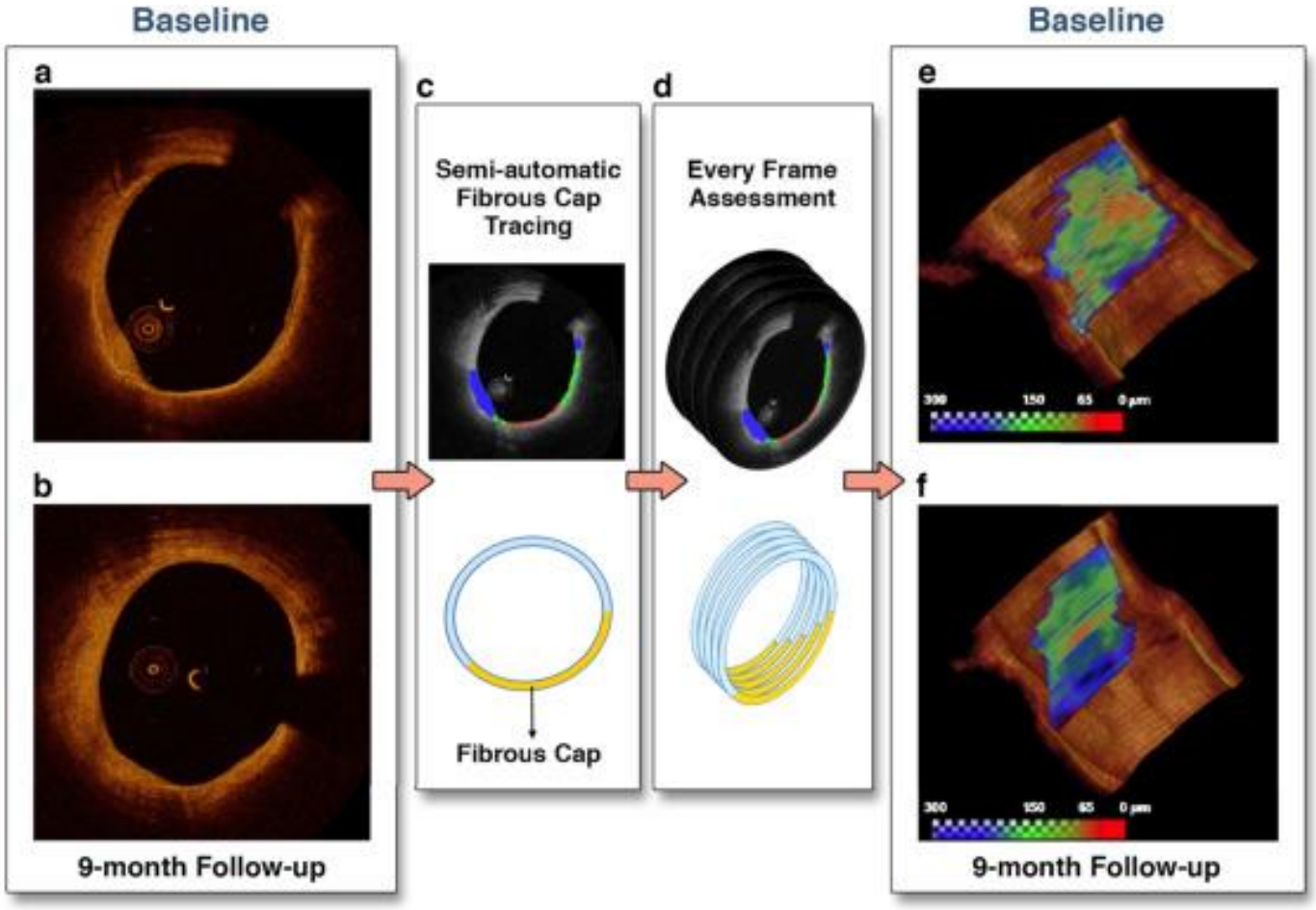
The Dynamic Nature of Coronary Artery Lesion Morphology Assessed by Serial VH-IVUS





Kubo T, et al. *J Am Coll Cardiol* 2010;55:1590

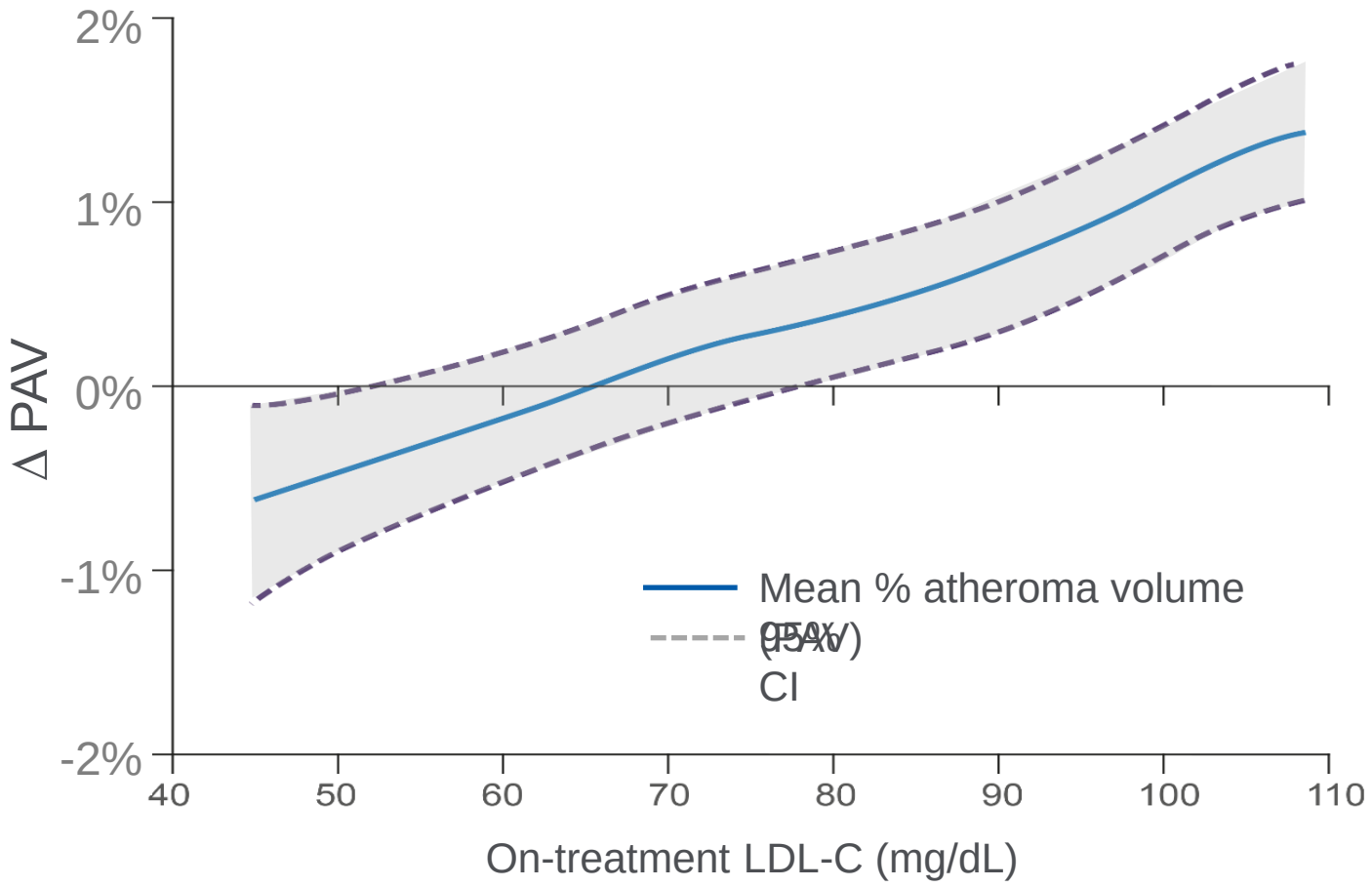
Fate of Nonculprit Plaques after pPCI Followed by Statin Therapy: A Serial OCT Analysis From the OCTAVIA Study



The proportion of TCFA decreased significantly from baseline to follow-up in the high-intensity statin group (26.4% [n = 19] vs. 9.7% [n = 7]; p = 0.002) compared with the lower-intensity group (38.9% [n = 14] vs. 25% [n = 9]; p = 0.180).

Nakamura D, et al. JACC Cardiovasc Imaging 2017;10:827

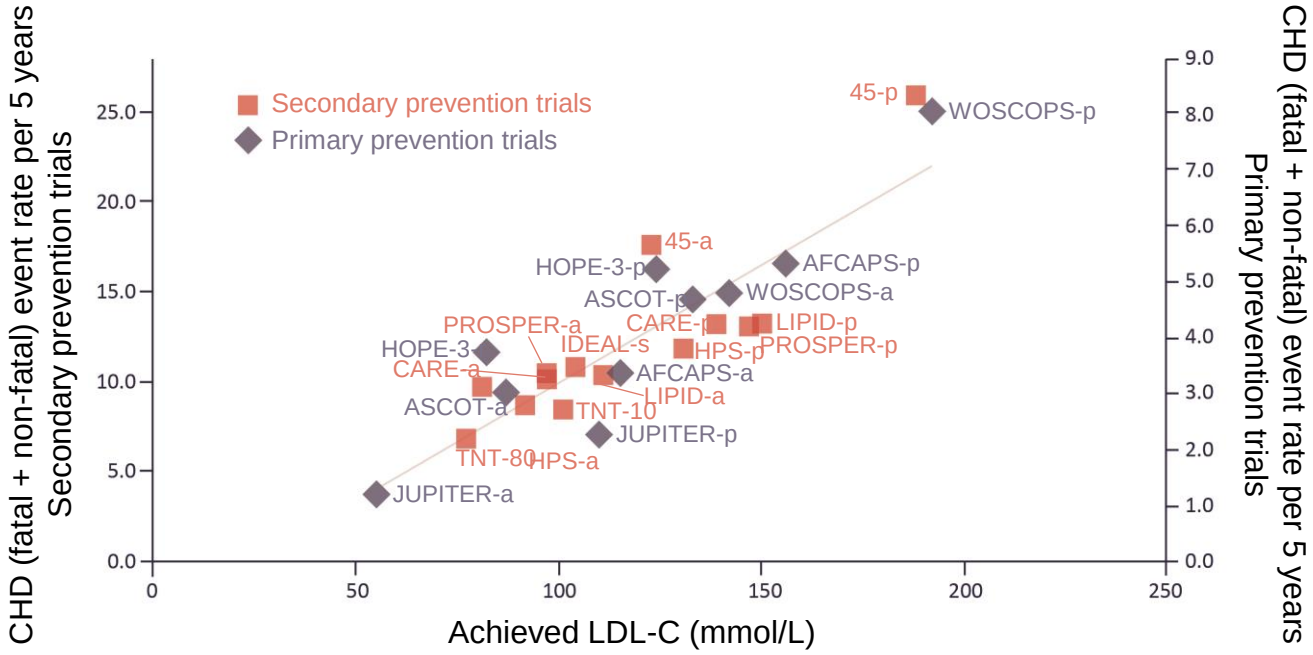
Very Potent LDL-C Lowering Is Associated With Atherosclerosis Regression



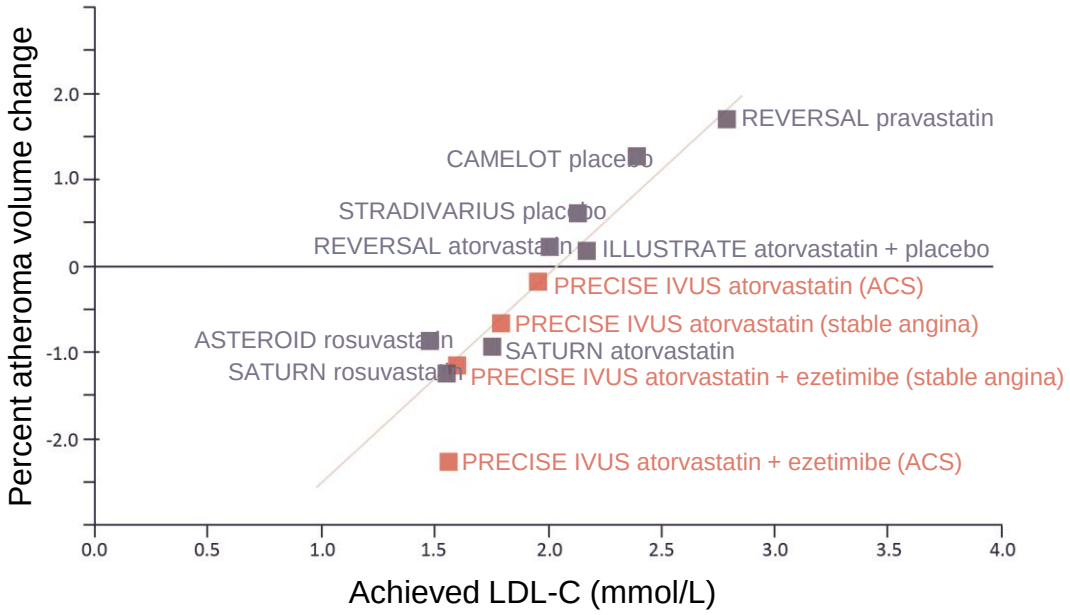
N = 1455 patients with angiographic coronary disease.
LDL-C, low-density lipoprotein cholesterol; PAV, percent atheroma volume.
Adapted from Nicholls SJ, et al. *JAMA* 2007;297:499-508.

Correlation Between Decrease in LDL-C, CHD Events, and Percent Atheroma

Absolute cardiovascular event rates



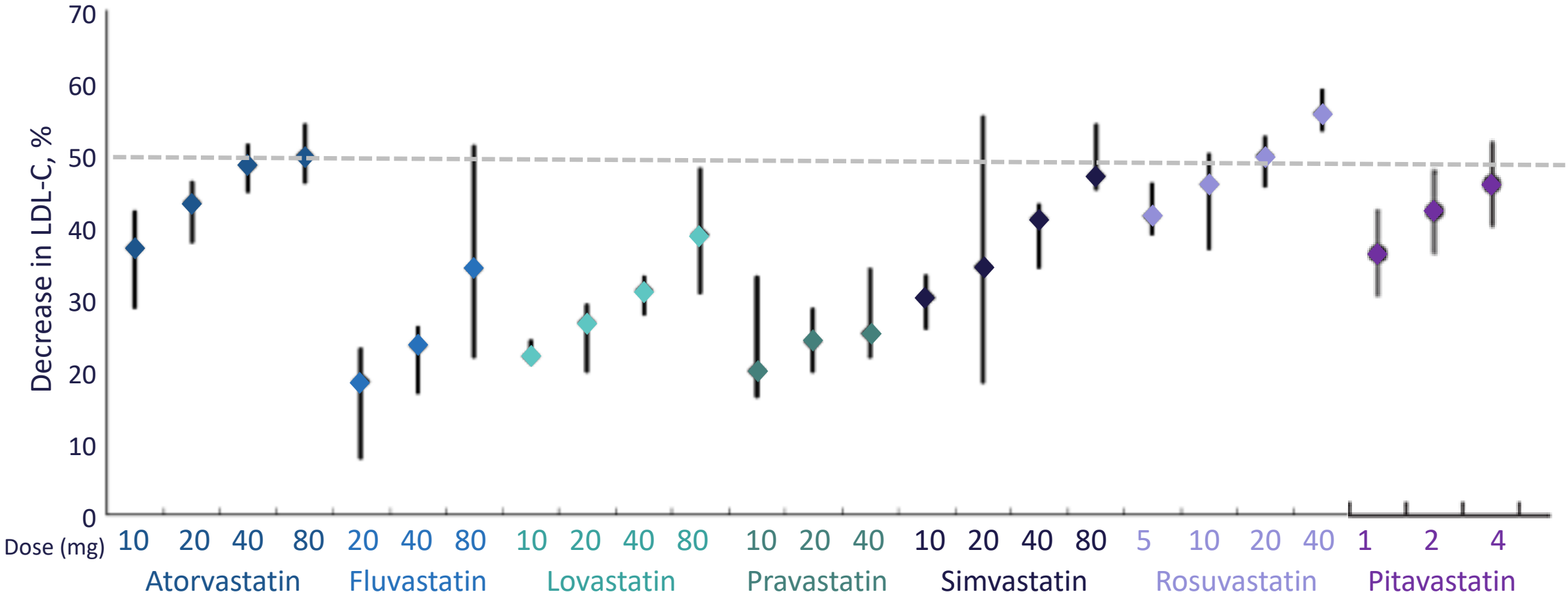
Progression of atherosclerosis
(as measured by intravascular ultrasound)



Linear association between achieved LDL-C level and absolute CHD event rate or progression of atherosclerosis

p, placebo; a, active treatment arm, except for IDEAL, where s, simvastatin and a, atorvastatin; and HOPE-3, where r, rosuvastatin; and TNT, where reference is made to atorvastatin 10- and 80-mg doses. CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol.
Adapted from Ference BA, et al. *Eur Heart J* 2017;38(32):2459-72.

Efficacy of Different Statins on LDL-C Lowering



LDL-C, low-density lipoprotein cholesterol.

Adapted from Weng TC, et al. *J Clin Pharm Ther* 2010;35:139-51. Mukhtar RY, et al. *Int J Clin Pract* 2005;59(2):239-52.

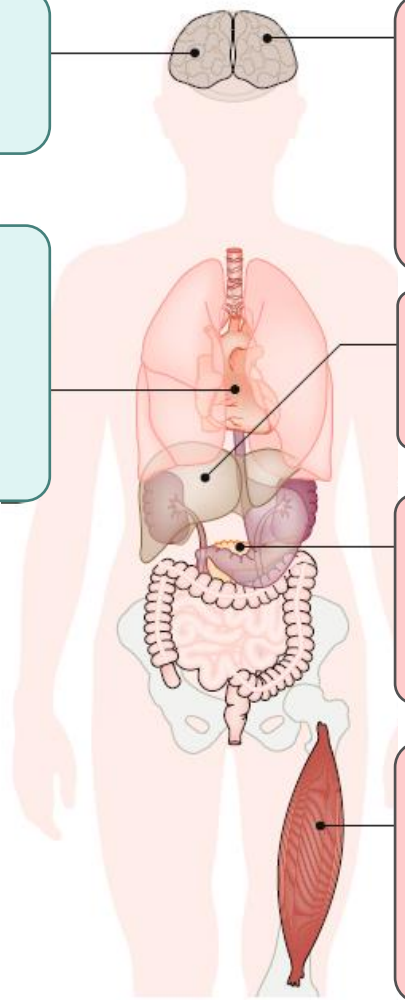
Benefits vs Risks of Statin Therapy

Benefits

Risk of stroke
- ↓ 16% for total stroke
- ↓ 21% for ischaemic stroke

Risk of major coronary events
- ↓ 27% for non-fatal MI
- ↓ 20% for CHD death

Risk of revascularisation procedures
- ↓ 25%



Adverse effects

Cognitive dysfunction
- No evidence

Risk of haemorrhagic stroke
- Small increase in individuals with prior haemorrhagic stroke in one study*

Liver symptoms/diseases
- Clinically insignificant liver enzyme elevations
- Incidence of liver failure: 1/100,000

Incidence of new-onset diabetes mellitus
- Moderate-intensity statin therapy: 0.1% per year
- High-intensity statin therapy: 0.2% per year

Incidence of muscle symptoms/diseases
- SAMS: 10-29% in observational studies and 1-2% in RCTs
- Myopathy: 1/1000
- Rhabdomyolysis: 1/10,000

*Not confirmed by any other studies.
CHD, coronary heart disease; MI, myocardial infarction;
RCT, randomised controlled trial; SAMS, statin-associated muscle symptoms.
Adapted from Adhyaru BB, Jacobson TA. *Nat Rev Cardiol* 2018;15(12):757-69.

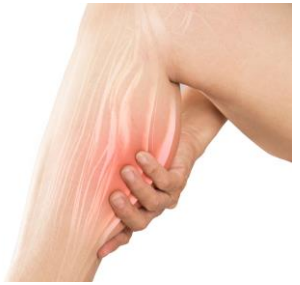
Muscle Adverse Event Terminology

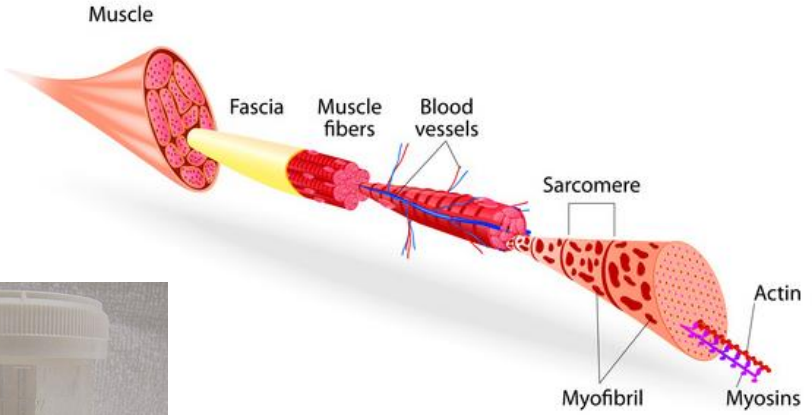
SAMS
Muscle symptoms reported during statin therapy but not necessarily caused by the statin

Myalgia
Muscle pain or aches

Myopathy
Unexplained muscle pain or weakness accompanied by CK concentration > 10 x ULN

Rhabdomyolysis
Severe form of myopathy, with CK typically > 40 ULN, which can cause myoglobinuria and acute renal failure





CK, creatinine kinase; SAMS, statin-associated muscle symptoms; ULN, upper limit of normal.

Newman CB, et al. *Arterioscler Thromb Vasc Biol* 2019;39:e38-e81.

Landmark Studies: Clinical Implications

PRIMO[1]

- Observation study (N = 7924)
- Pravastatin, atorvastatin, simvastatin, fluvastatin XL
- Muscle symptoms in 10.5% of patients

STOMP[2]

- RCT (N = 420)
- High dose (80 mg) atorvastatin vs placebo
- Myalgia: 9.4% in statin group vs 4.6% in placebo group (p = 0.05)

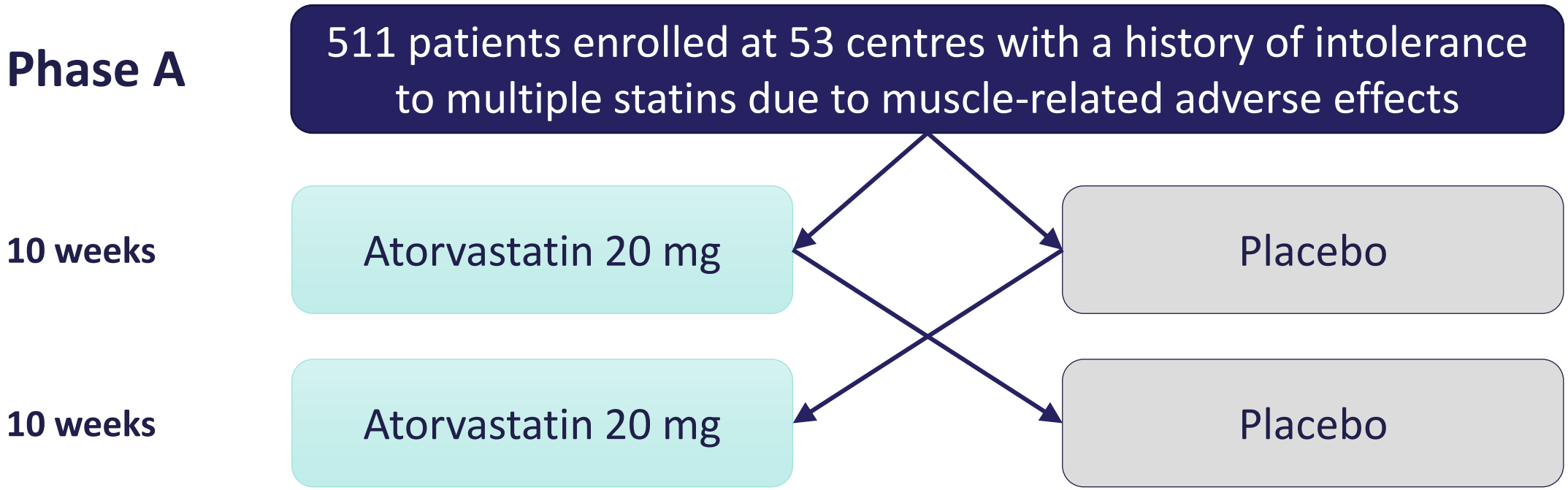
Systematic review[3]

- 42 trials
- Muscle problems: 12.7% in statin group vs 12.4% in placebo group (p = 0.06)

RCT, randomised controlled trial.

1. Bruckert E, et al. *Cardiovasc Drugs Ther* 2005;19:403-414. 2. Parker BA, et al. *Circulation* 2013:127:96-103. 3. Ganga HV, et al. *Am Heart J* 2014; 168(1):6-15.

GAUSS-3 Study Design: Phase A



Nissen SE, et al. *JAMA* 2016;315:1580-90.

GAUSS-3:
Phase A Study Drug Discontinuation Events

Intolerable muscle symptoms	N = 491
On atorvastatin, but not placebo	**209 (42.6%)**
On placebo, but not atorvastatin	130 (26.5%)
On both placebo and atorvastatin	48 (9.8%)
No symptoms on either treatment	85 (17.3%)
Did not complete Phase A	20/511
Bypassed Phase A due to CK elevation ≥ 10 x ULN	19 (3.9%)

43.8%
are NOT statin intolerant

CK, creatinine kinase; ULN, upper limit of normal.
Nissen SE, et al. *JAMA* 2016;315:1580-90.

There Is a Nocebo Effect of Muscle-Related Symptoms for People Who Know They Are Taking a Statin

ASCOT-LLA design

- Blinded, randomised phase (N = 10,180)
- Non-blinded, non-randomised extension phase (n = 9899)

Blinded randomised phase

Risk of muscle-related adverse event in statin group

HR 1.03 (0.88-1.21); *p* = 0.72

Un-blinded non-randomised phase

Risk of muscle-related adverse event in statin group

HR 1.41 (1.10-1.79); *p* = 0.006

Nocebo effect, an excess rate of muscle-related AE reports, only when patients/doctors were aware of statin therapy use

AE, adverse event; HR, hazard ratio.

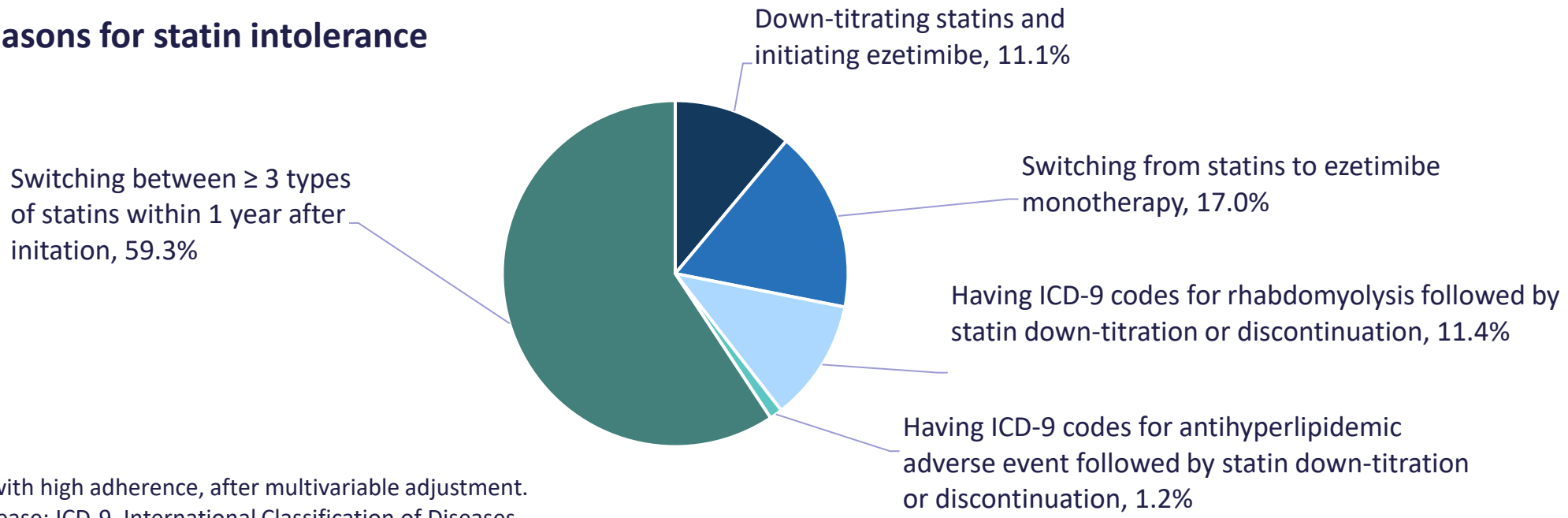
Gupta A, et al. *Lancet* 2017;389(10088):2473-81.

Excess Risk From Statin Intolerance

MI (N = 105,329)

- **High adherence 52.8%**
- **Statin intolerance 1.65%** → **50%** higher risk for recurrent MI*; **51%** higher risk for CHD*

Reasons for statin intolerance



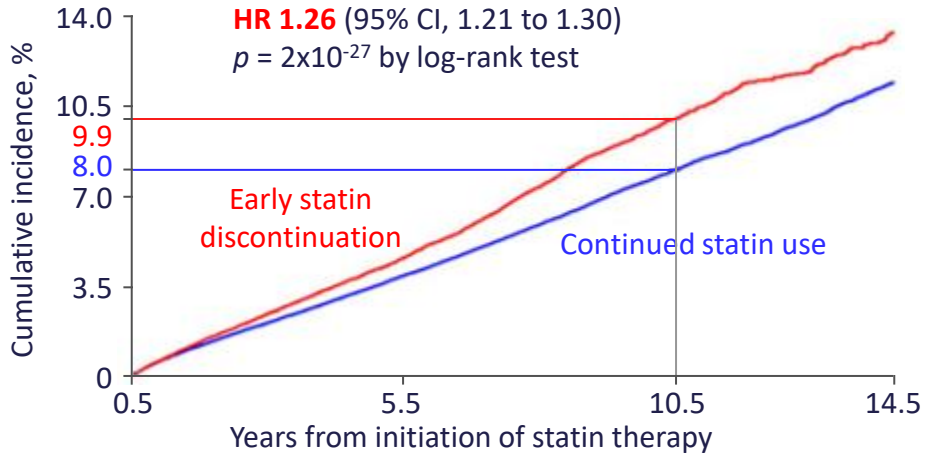
*Excess risk compared with high adherence, after multivariable adjustment.
CHD, coronary heart disease; ICD-9, International Classification of Diseases, Ninth Revision; MI, myocardial infarction.

Serban MC, et al. *J Am Coll Cardiol* 2017;69(11):1386-95.

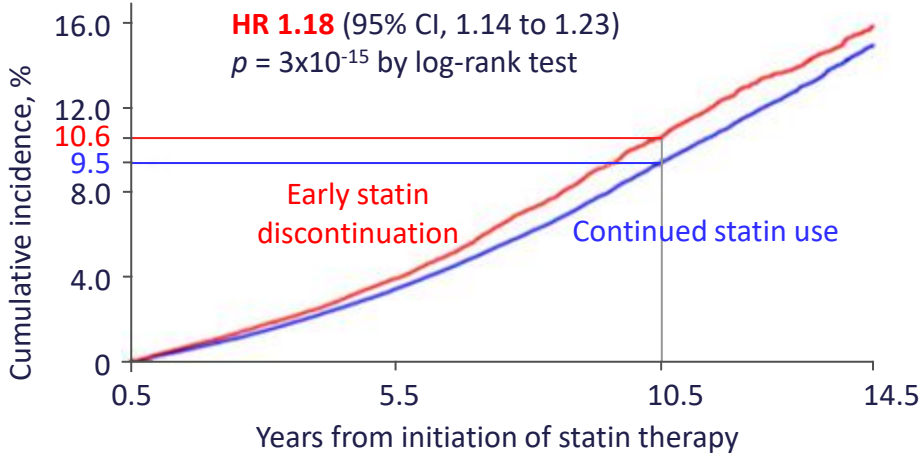
Predictors and Consequences of Early Statin Discontinuation

Predictor	Odds ratio of early discontinuation
Negative nationwide statin-related news story	1.09 (1.06-1.12)
Neutral nationwide statin-related news story	0.98 (0.96-1.01)
Positive nationwide statin-related news story	0.92 (0.90-0.94)

MI



Death from CV disease

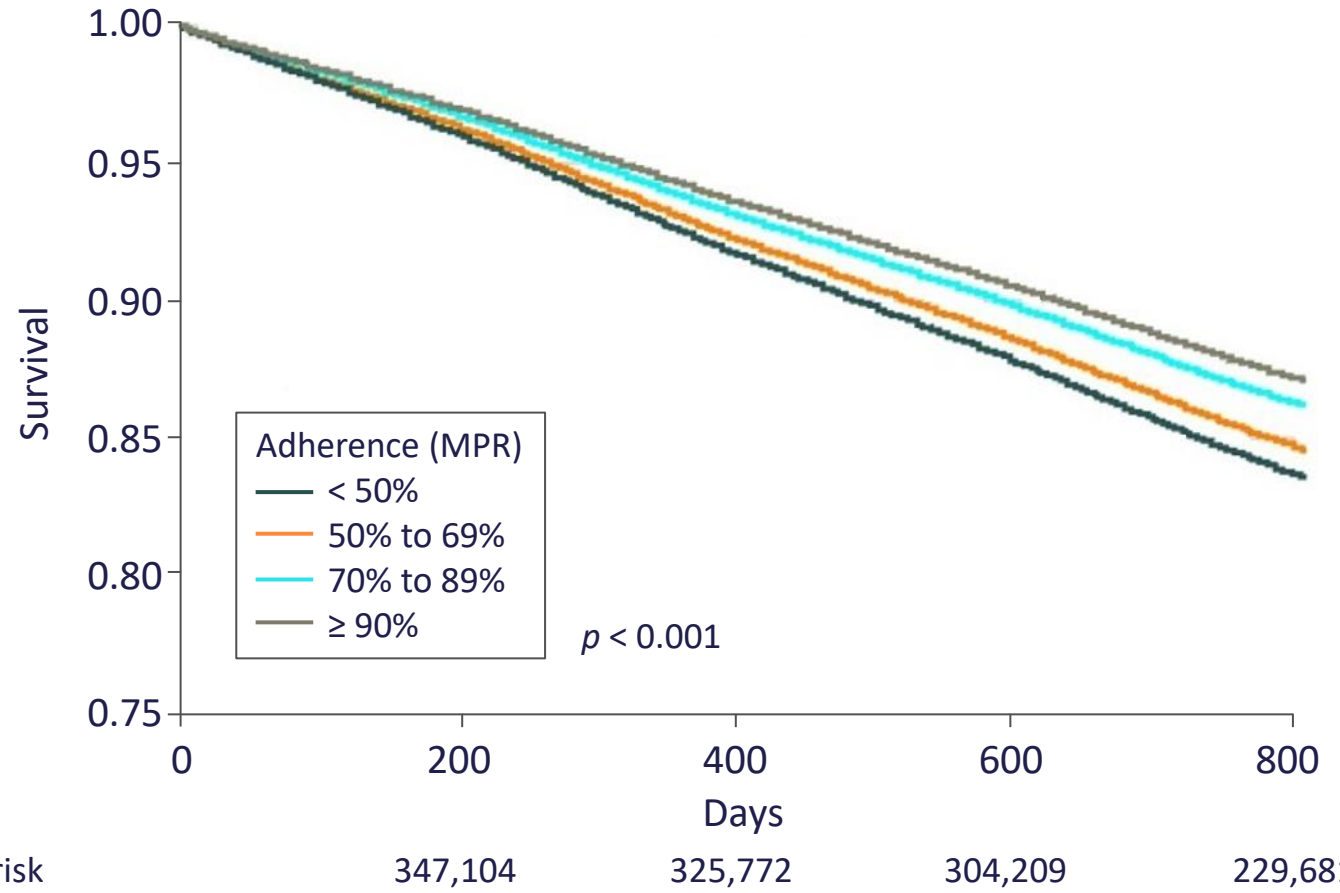


Negative statin-related news stories decrease statin persistence and increase MI and CV mortality

CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.
Adapted from Nielsen SF, Nordestgaard BG. *Eur Heart J* 2016;37:908-16.

Higher Statin Adherence Is Associated with Better Survival Rates

Survival curves by statin adherence level as defined by medication possession ratios (MPRs)

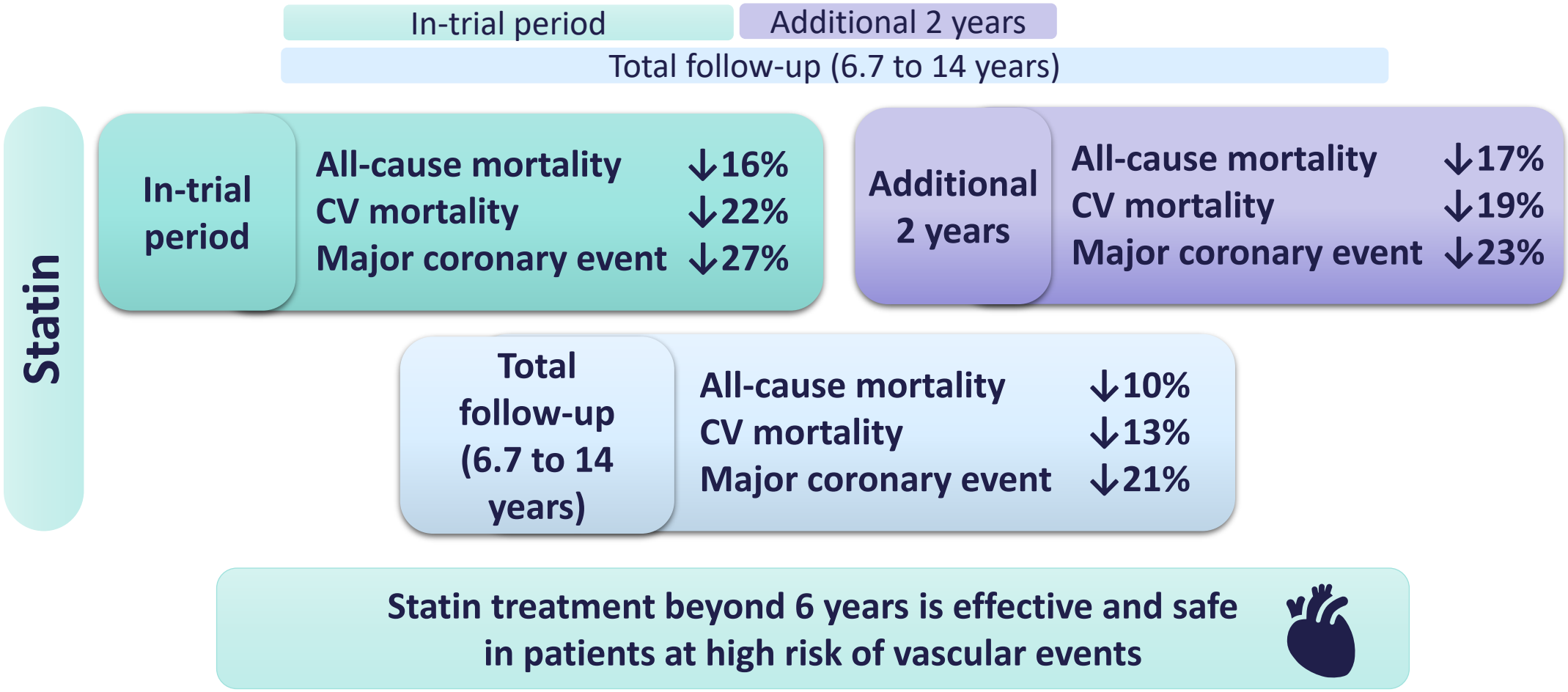


Cohort study of patients with atherosclerotic cardiovascular disease. Plotted values include point estimates and 95% CIs. There is a dose-response association between adherence and survival, with the greatest survival among the most adherent patients. No., number.

Adapted from Rodriguez F, et al. *JAMA Cardiol* 2019;4(3):206-13.

Long-term Benefits of Statin Treatment

6 RCTs with post-trial follow-up beyond 6 years (N = 42,296)

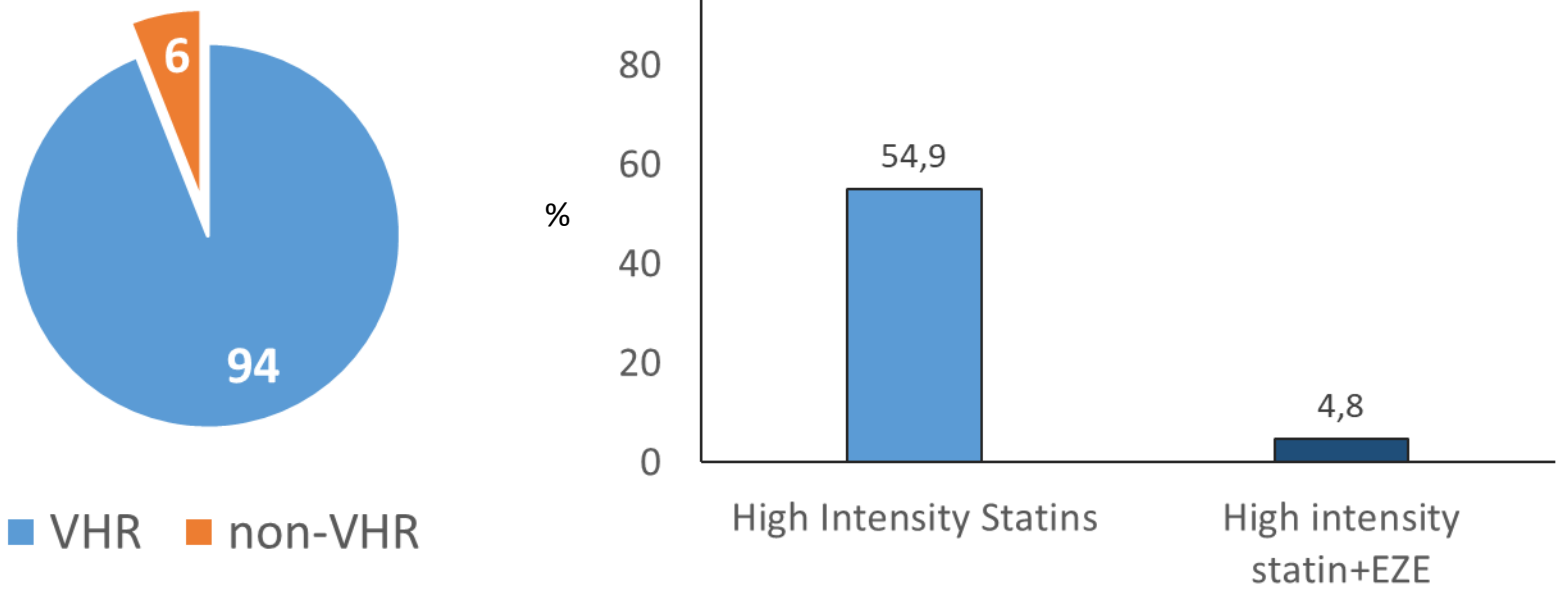


Statin treatment beyond 6 years is effective and safe in patients at high risk of vascular events

CV, cardiovascular RCT, randomised controlled trial.
Adapted from Lv H, et al. *Pharmacol Res* 2014;81:64-73.

Current lipid lowering treatment and attainment of LDL targets recommended by ESC/EAS guidelines in very high-risk patients

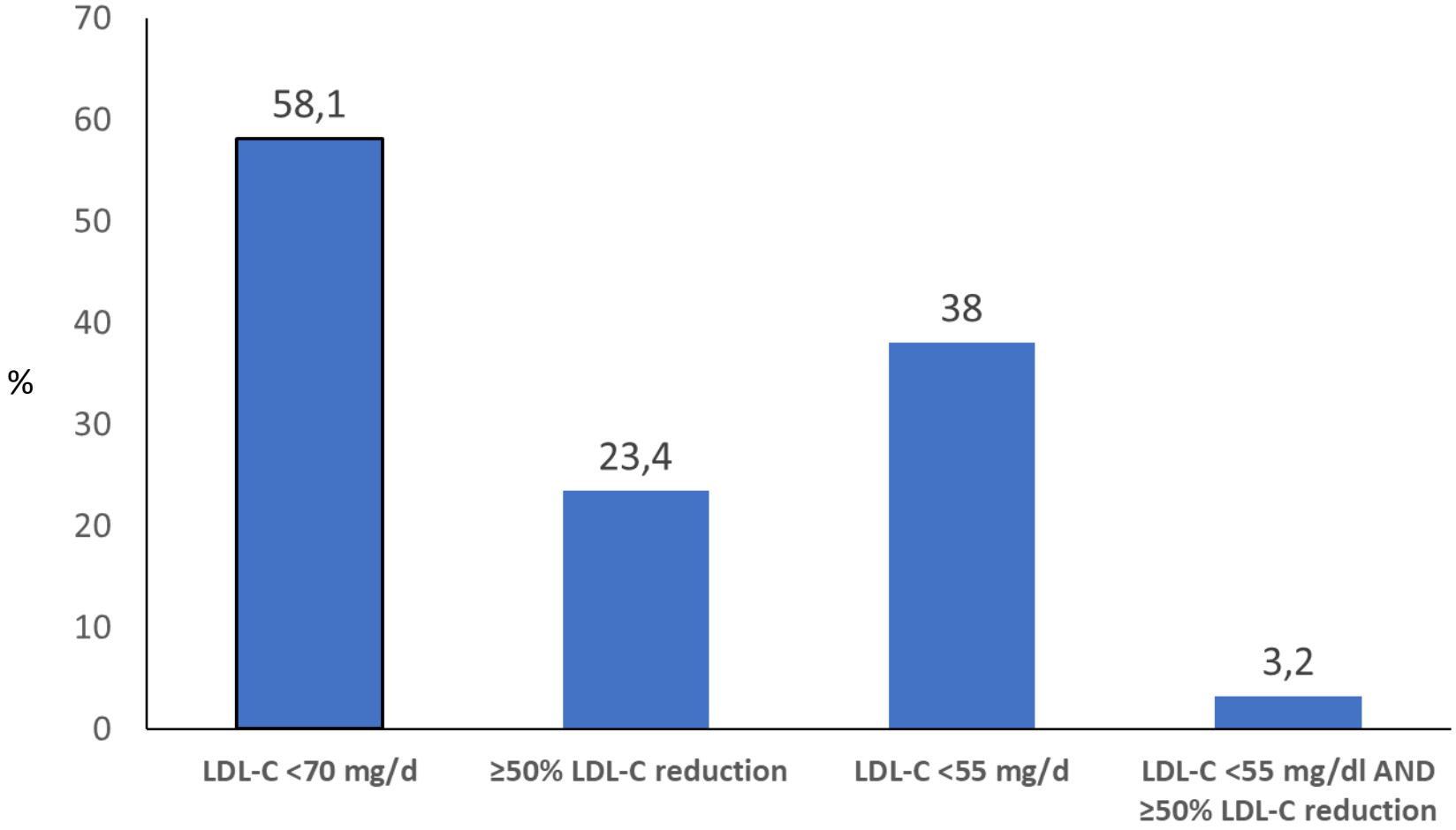
Very High Risk Pts*



*Established CVD, DM2, DM1 with target organ damage, moderate-severe CKD or a SCORE level ≥10%

De Luca L, et al. Int J Cardiol. 2020;316:229-235

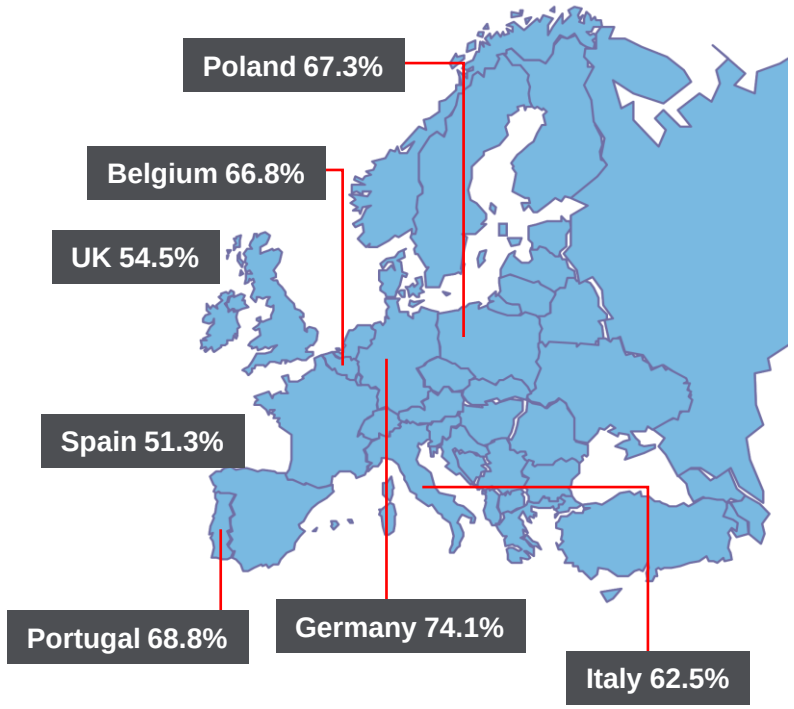
Attainment of LDL targets recommended by ESC/EAS Guidelines in very high-risk patients



De Luca L, et al. Int J Cardiol. 2020;316:229-235

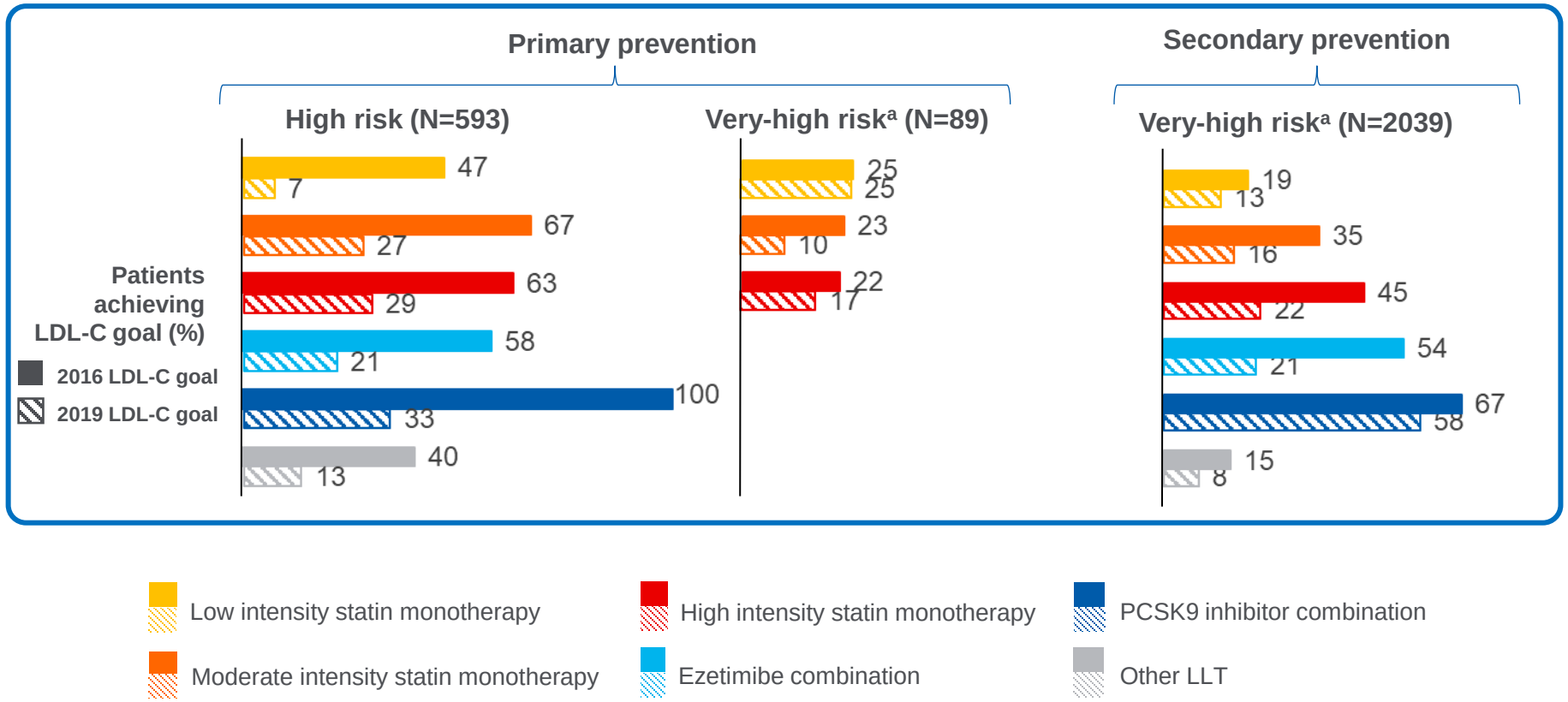
Unmet Need: Very High Risk Patients with LDL-C ≥70 mg/dl Across EUROPE

- Analysis of the hospital arm of the EUROASPIRE V survey of risk factors and management in coronary heart disease patients with/without diabetes
- Carried out in 27 European countries, 2016–17
- Coronary patients followed up n=7,824
- 84.3% of patients were receiving LLT
  - 49.9% were receiving high intensity LLT
  - 34.1% were receiving low/moderate intensity LLT
- Overall, 71.0% of coronary patients across Europe were not at LDL-C goal (<70 mg/dL)



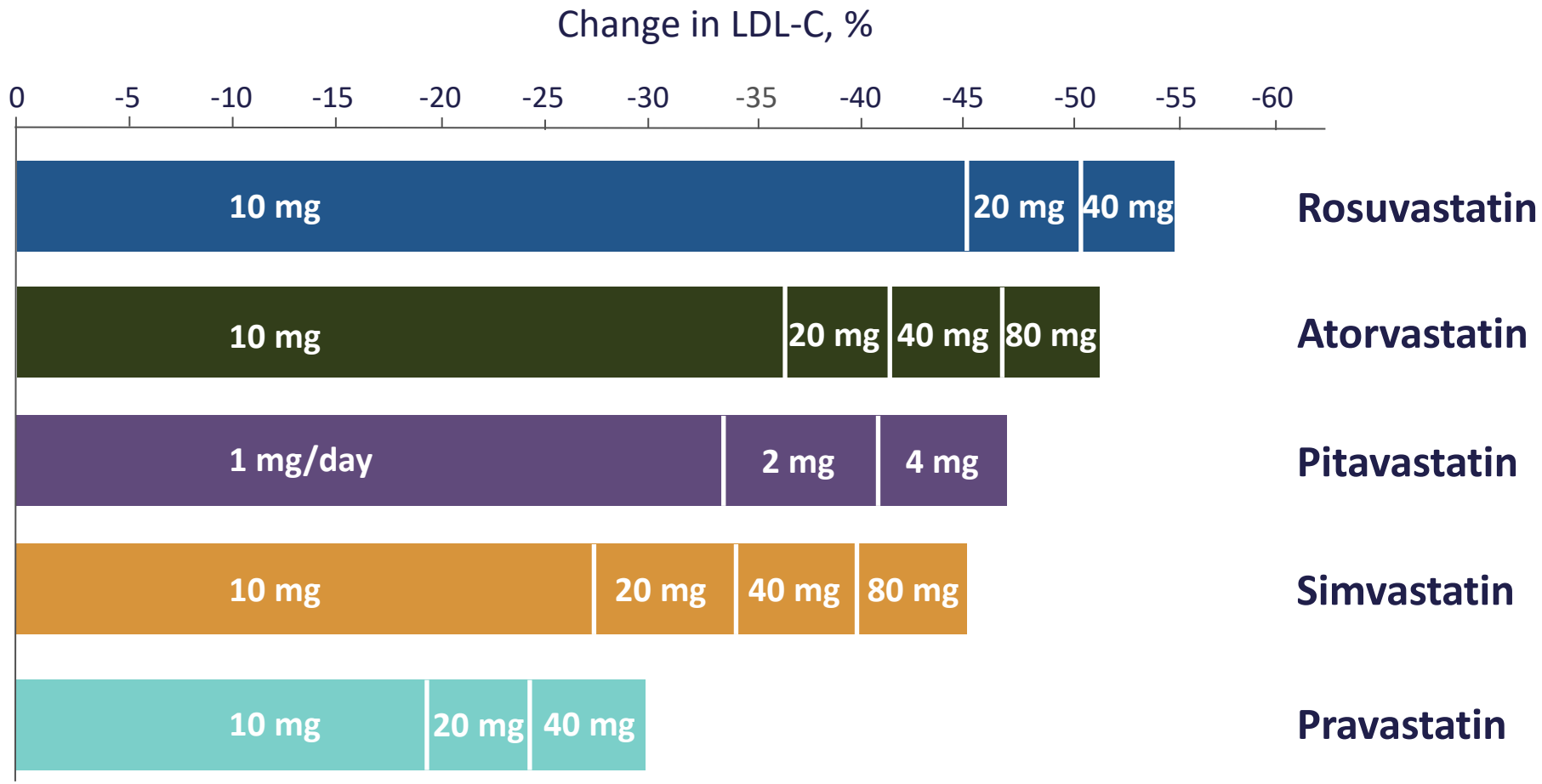
de Backer G et al. Atherosclerosis. 2019;285:135

DA VINCI Study:
LDL-C 2019 Goal Attainment by Risk and LLT



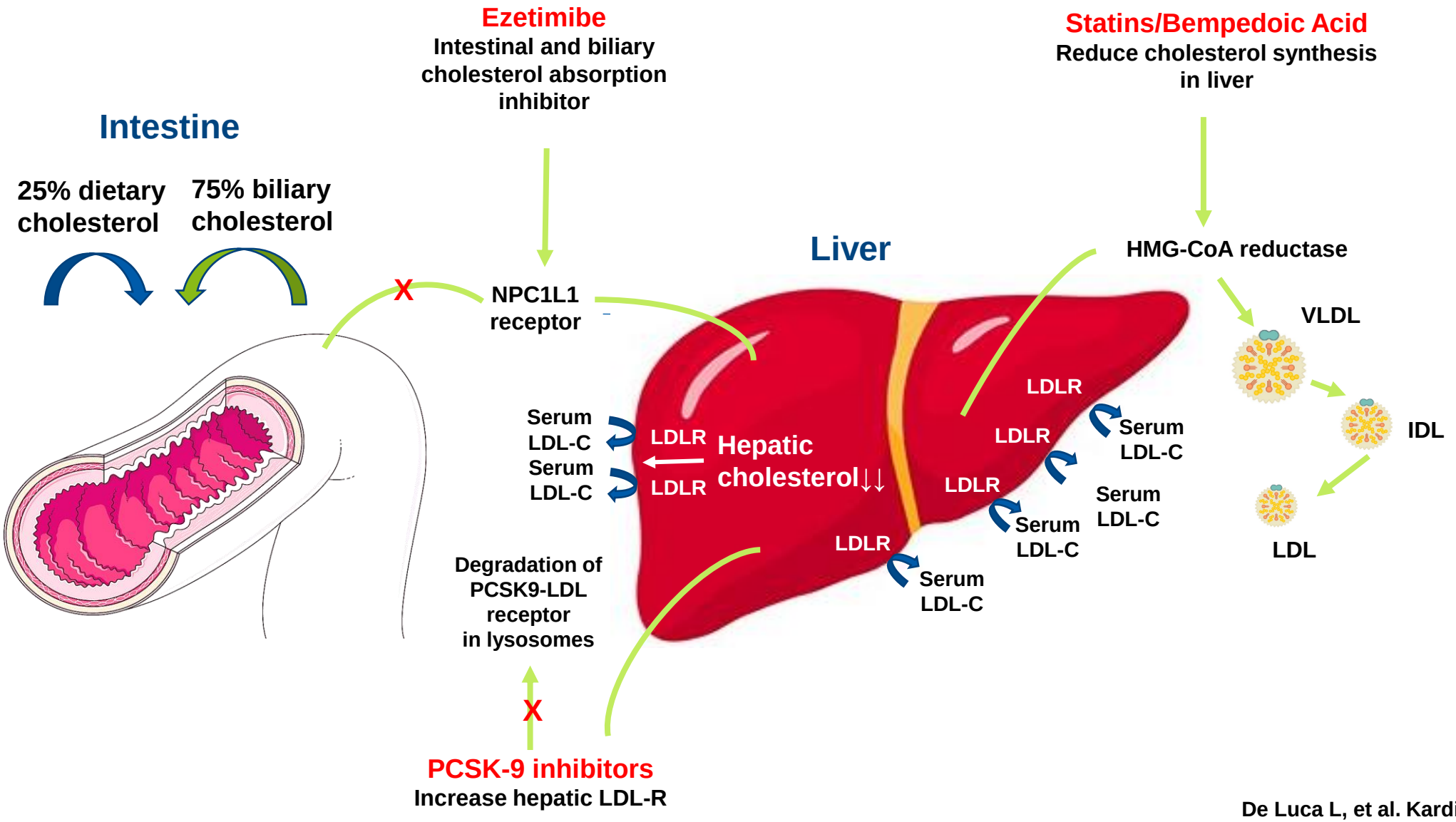
Ray, KK et al. Eur J Prev Cardiol 2020

Doubling Statin Dose Achieves ~6% Additional LDL-C Reduction



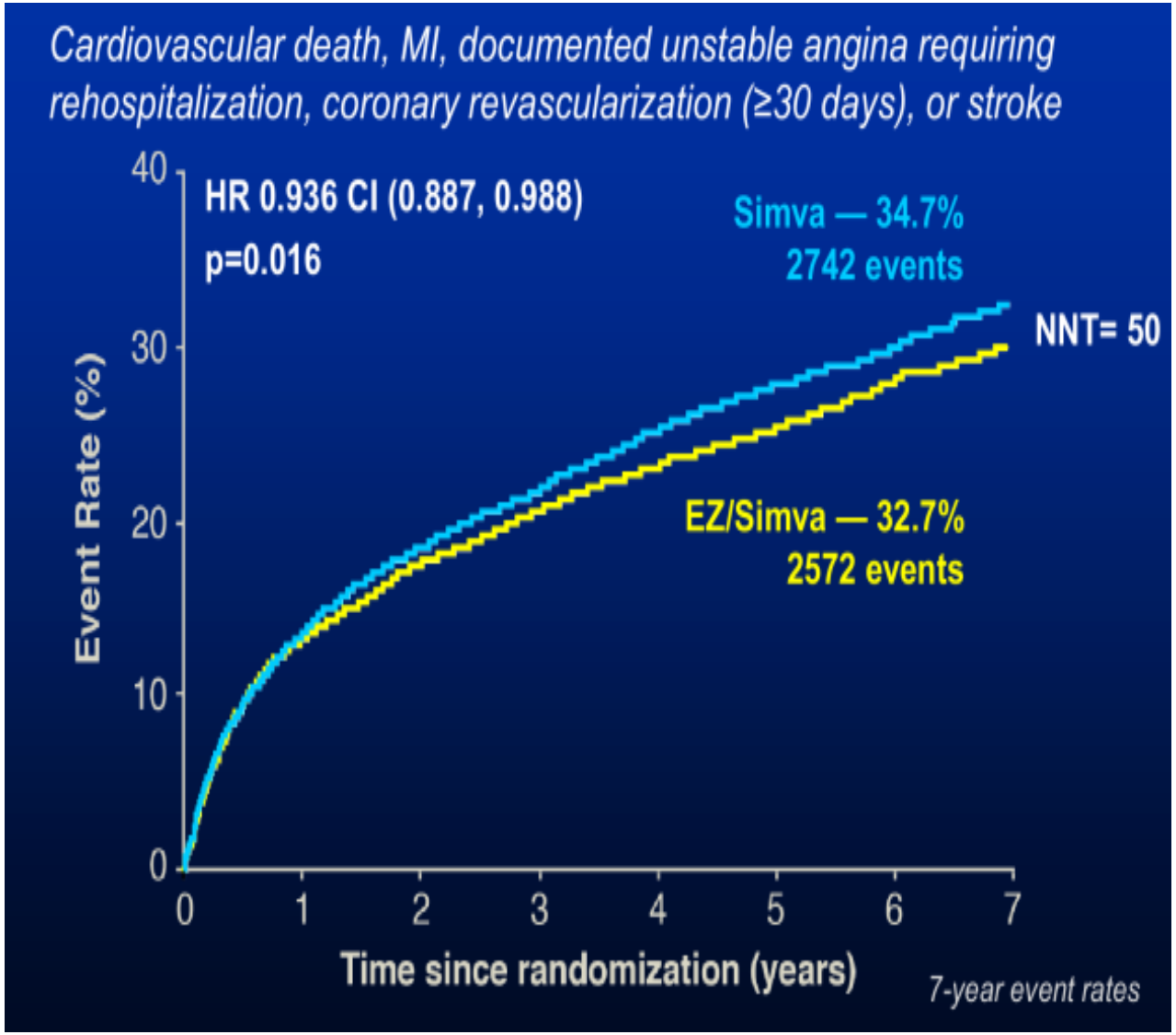
LDL-C, low-density lipoprotein cholesterol. Adapted from "FDA drug safety communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury." US Food & Drug Administration website. Accessed June 2020.

Available LDL Lowering Agents



De Luca L, et al. Kardiol Pol. 2020;78:850

Ezetimibe in IMPROVE-IT



Cannon C, N Engl J Med 2015 (372):2387-97

POSITION PAPER

Position paper ANMCO: Gestione dell'ipercolesterolemia nei pazienti con sindrome coronarica acuta

Leonardo De Luca[1], Carmine Riccio[2], Alessandro Navazio[3], Serafina Valente[4], Manlio Cipriani[5], Marco Corda[6], Alfredo De Nardo[7], Giuseppina Maura Francese[8], Cosimo Napoletano[9], Emanuele Tizzani[10], Loris Roncon[11], Pasquale Caldarola[12], Michele Massimo Gulizia[8], Domenico Gabrielli[1,13], Fabrizio Oliva[14], Furio Colivicchi[15]

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European Heart Journal Supplements (2023) **25** (Supplement D), D299–D309
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suad100

ESC European Society of Cardiology

ANMCO position paper on the management of hypercholesterolaemia in patients with acute coronary syndrome

Leonardo De Luca [1]*, Carmine Riccio[2], Alessandro Navazio[3], Serafina Valente[4], Manlio Cipriani[5], Marco Corda[6], Alfredo De Nardo[7], Giuseppina Maura Francese[8], Cosimo Napoletano[9], Emanuele Tizzani[10], Loris Roncon[11], Pasquale Caldarola[12], Michele Massimo Gulizia[8], Domenico Gabrielli[1], Fabrizio Oliva[13], and Furio Colivicchi[14]

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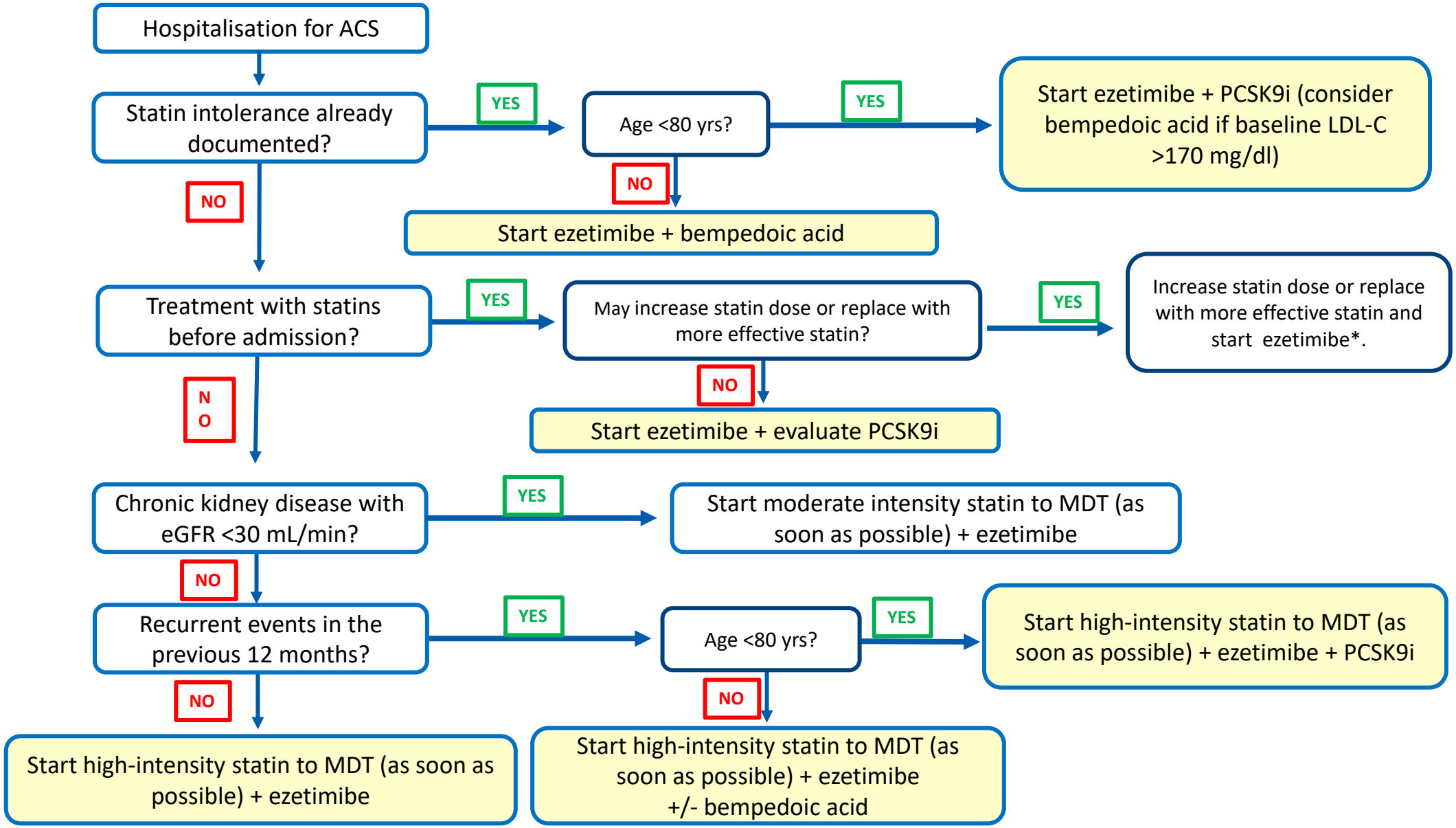
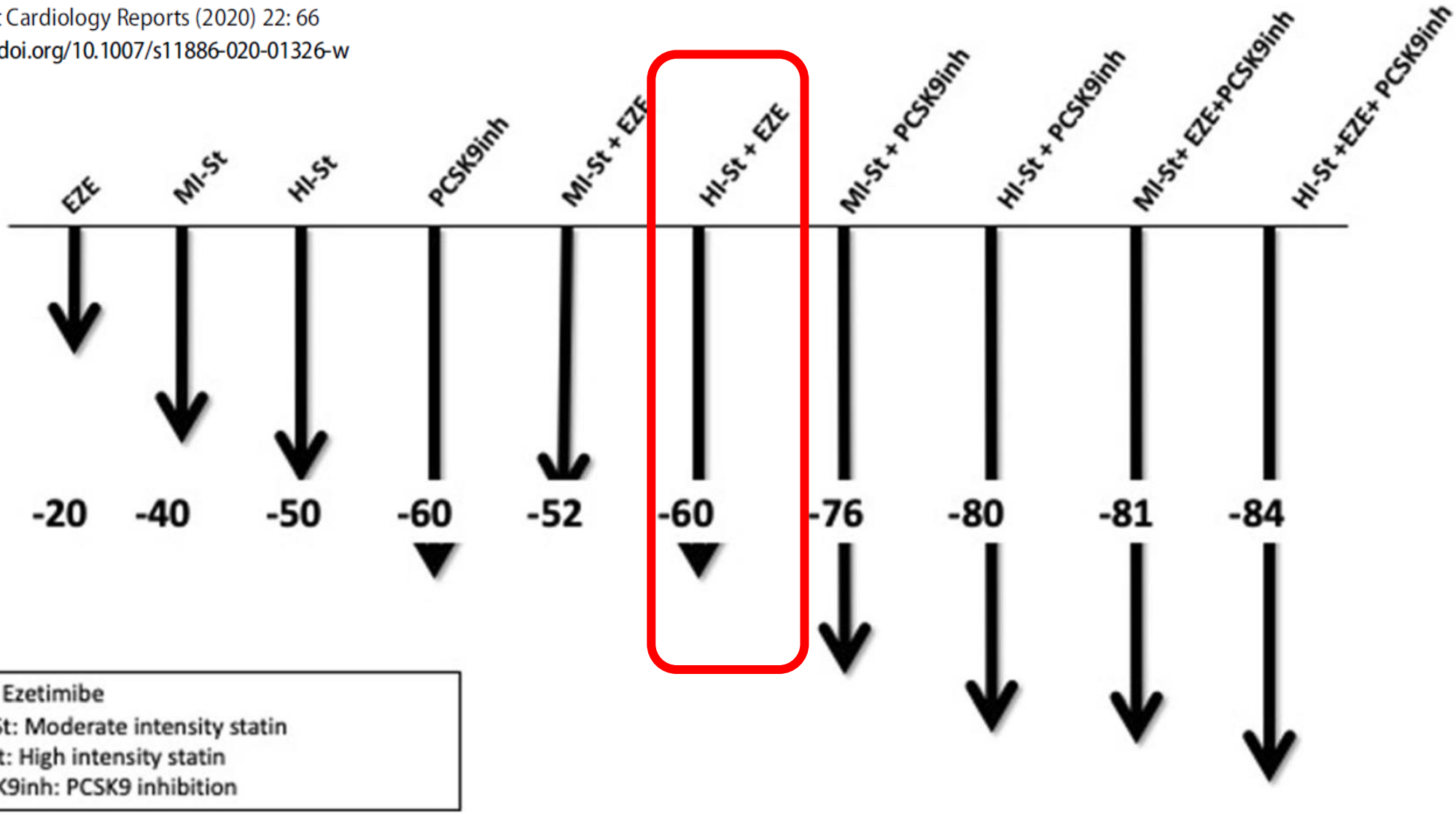
ANMCO
Position Paper



Estimated Efficacy of Different Lipid Lowering Strategies

Current Cardiology Reports (2020) 22: 66
https://doi.org/10.1007/s11886-020-01326-w



Eze: Ezetimibe
MI-St: Moderate intensity statin
HI-St: High intensity statin
PCSK9inh: PCSK9 inhibition

Putting Together the Best in Class

Rosuvastatin

Ezetimibe

First Recommendations for the Use of Polypills

- **2001**: Recommended for secondary prevention of CVD at the Wellcome-WHO meeting
- **First polypills** consisted of:
  - Statin
  - 3 BP-lowering agents (thiazide diuretics, β-blockers, ACEi)
  - Folic acid
  - Aspirin

*The **polypill strategy** could largely **prevent heart attacks and stroke** if taken by **everyone aged 55 and older** and **everyone with existing CVD**.*

*It would be acceptably safe and, with widespread use, would have a **greater impact on the prevention of disease** in the Western world **than any other single intervention**.*

ACEi, angiotensin-converting-enzyme inhibitors; BP, blood pressure; CVD, cardiovascular disease; WHO, World Health Organization.

Wald N, Law M. *BMJ* 2003;326:1419-23.

Rationale and Advantages of the Polypill

Aging population

Westernisation of LMICs

Obesity/DM epidemic

Low adherence to treatment

Cost of treatment

Low compliance to healthy lifestyles

↑ Patient affordability

↑ Patient convenience

↑ Patient adherence

↑ Ease of distribution

ACEi, angiotensin-converting enzyme inhibitor; DM, diabetes mellitus; LMIC, low- and middle-income country.
Adapted from Castellano J, et al. *Can J Cardiol* 2014;30(5):520-6.

Position of Experts on Polypills

2016 European Guidelines on CVD Prevention in Clinical Practice[1]

The **use of polypill** and combination therapy to **increase adherence** to drug therapy may be considered

2017 Polypill in CV Prevention Position Paper of the ESH[2]

The **use of polypill** and combination therapy to **increase adherence** to drug therapy may be considered

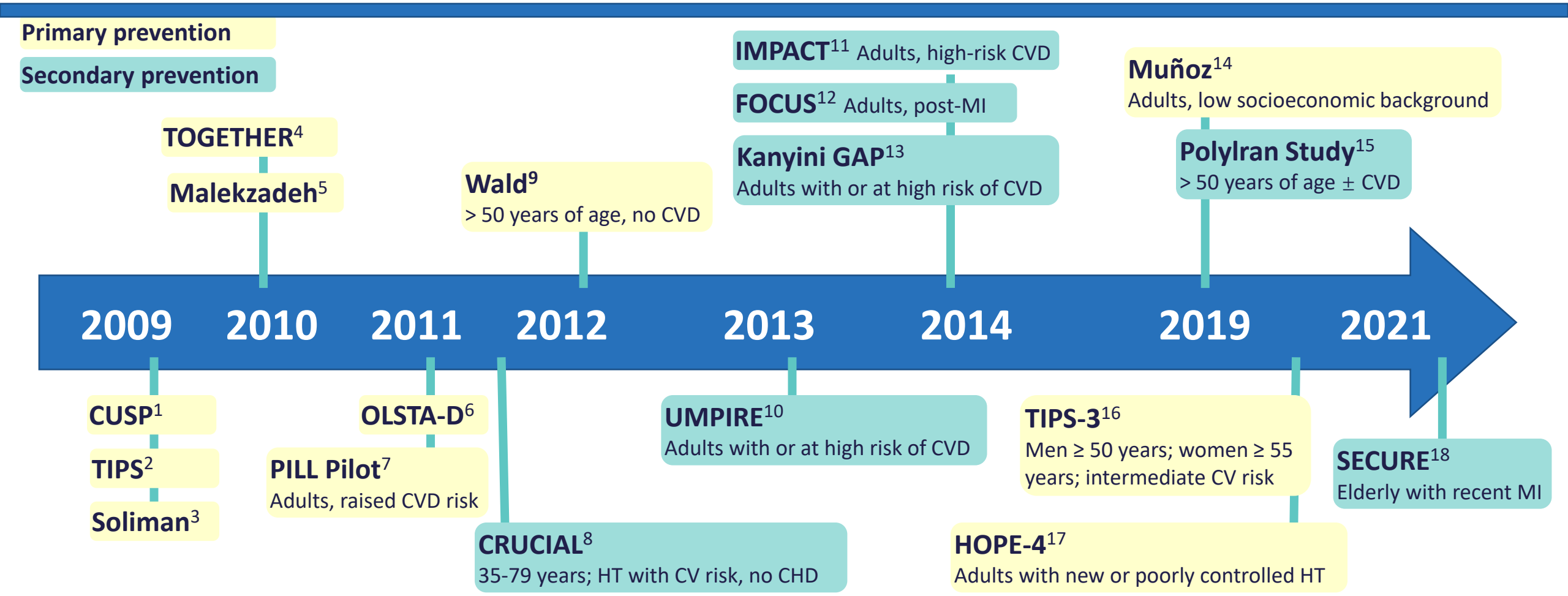
2018 ESC/ESH Guidelines for Management of Arterial Hypertension[3]

The **advantage** of **treatment simplification** and **adherence** suggests that **use of the polypill** may be **considered** in patients with hypertension as a substitution when the need and effectiveness of each polypill component has been previously established by their administration in separate tablets

CV, cardiovascular; CVD, cardiovascular disease; ESC, European Society of Cardiology; ESH, European Society of Hypertension.

1. Piepoli MF, et al. *Eur Heart J* 2016;37(29):2315-81. 2. Coca A, et al. *J Hypertens* 2017;35(8):1546-53. 3. Williams B, et al. *Eur Heart J* 2018;39(33):3021-104.

Key Clinical Trials for Polypills

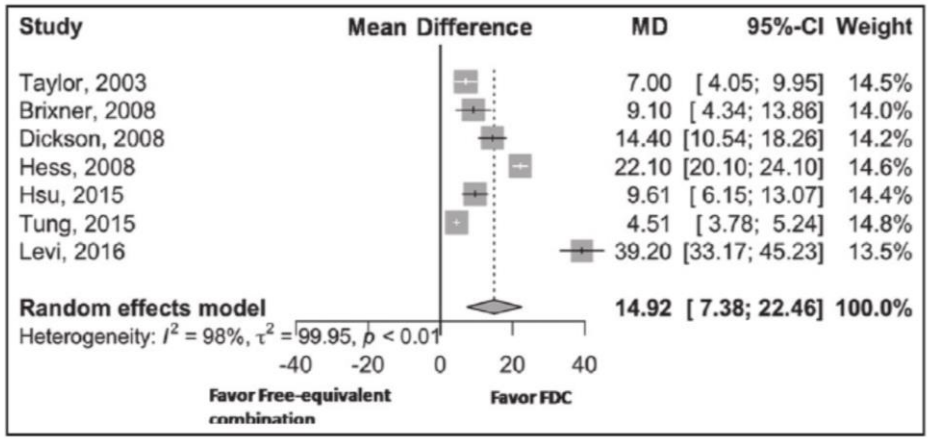


CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; HT, hypertension; MI, myocardial infarction. 1. Neutel JM, et al. *J Clin Hypertens* 2009;11:22-30. 2. Yusuf S, et al. *Lancet* 2009;373:1341-51. 3. Soliman EZ, et al. *Trials* 2011;12:3. 4. Grimm R, et al. *Vasc Health Risk Manag* 2010;6:261-71. 5. Malekzadeh F, et al. *Int J Clin Prac* 2010;64:1220-7. 6. Park J-S, et al. *Drug Des Devel Ther* 2016;10:2599-609. 7. PILL Collaborative Group. *PLoS One* 2011;6(5):e19857. 8. Zamorano J, et al. *Curr Med Res Opin* 2011;27(4):821-33. 9. Wald DS, et al. *PLoS One* 2012;7(7):e41297. 10. Thom S, et al. *JAMA* 2013;310:918-29. 11. Salek V, et al. *BMJ* 2014;348:g3318. 12. Castellano JM, et al. *J Am Coll Cardiol* 2014;64:2071-82. 13. Patel A, et al. *Eur J Prev Cardiol* 2015;22(7):920-30. 14. Muñoz D, et al. *N Engl J Med* 2019;381:1114-23. 15. Roshandel G, et al. *Lancet* 2019;394(10199):672-83. 16. Joseph P, et al. *Am Heart J* 2018;206:72-9. 17. Heart Outcomes Prevention and Evaluation 4 (HOPE-4). ClinicalTrials.gov website. Accessed July 2020. 18. Secondary Prevention of Cardiovascular Disease in the Elderly Trial (SECURE). ClinicalTrials.gov website. Accessed July 2020.

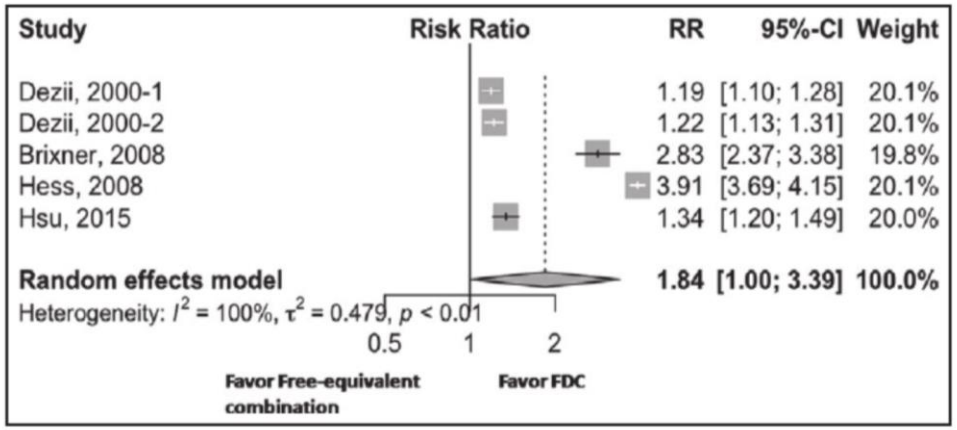
The impact of fixed-dose combination versus free-equivalent combination therapies on adherence for hypertension

Meta-analysis of 7 studies (62,481 patients with hypertension)

Adherence

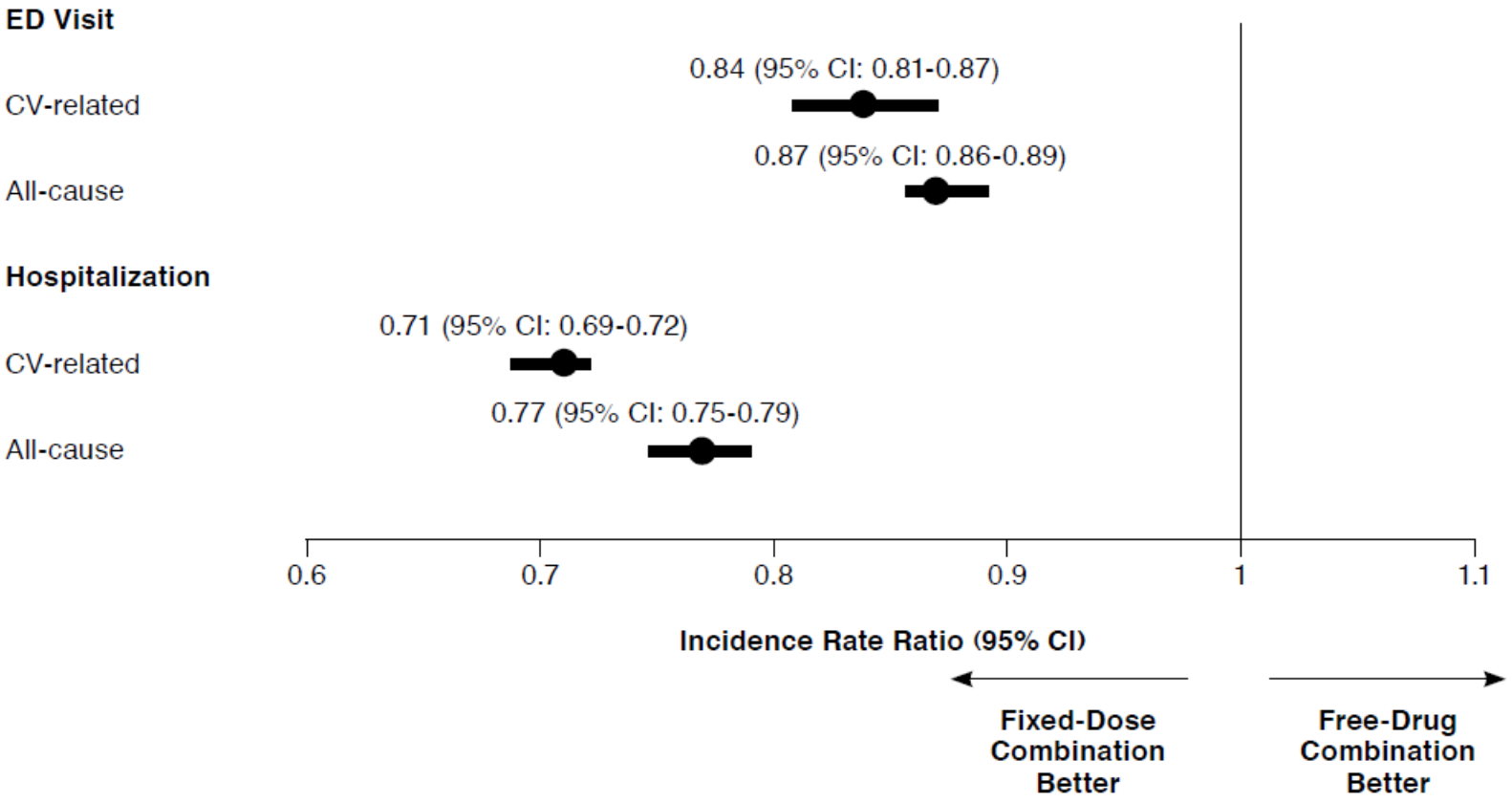


Persistence



Du L, et al. J Clin Hypertens 2018

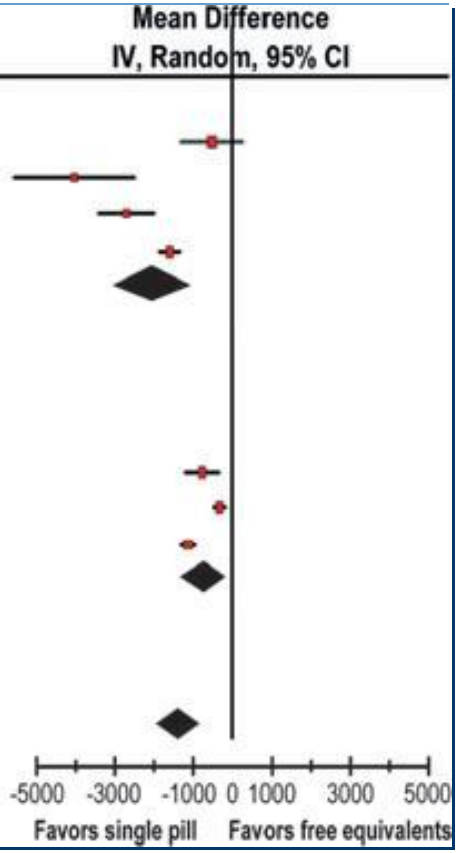
Evaluation of health care utilization in patients treated with single pill vs. free combination antihypertensives



Yang W, et al. Curr Med Res Opin. 2010

Single-pill vs free-equivalent combination therapies for hypertension: a meta-analysis of health care costs

Study or Subgroup	Single Pill Mean Costs	SD	N	Free Equivalent Mean Costs	SD	N	Weight	Mean Difference IV, Random, 95% CI
1.1.1 Total costs								
Brixner 2008	3,449	8,070	7991	3,938	9,214	559	13.0%	-489.00 [-1273.04, 295.04]
Dickson 2008	4,751	11,116	3363	8,802	20,593	713	7.6%	-4051.00 [-5608.54, -2493.46]
Dickson-elderly 2008	4,181	9,782	2336	6,886	16,112	3368	13.8%	-2705.00 [-3378.38, -2031.62]
Malesker 2010	5,495	876	100	7,084	915	100	16.5%	-1589.00 [-1837.27, -1340.73]
Subtotal (95% CI)			**13790**			**4740**	**50.9%**	**-2039.37 [-3047.84, -1030.90]**
Heterogeneity: $Tau^2 = 870104.21$; $Chi^2 = 27.18$, df = 3 ($P < 0.00001$); $I^2 = 89\%$								
Test for overall effect: Z = 3.96 ($P < 0.0001$)								
1.1.2 Hypertension- or cardiovascular-related costs								
Barron 2008	1,361	4,737	4530	2,100	6,639	1095	15.6%	-739.00 [-1155.72, -322.28]
Hess 2008	1,175	4,192	7224	1,469	5,201	7225	16.8%	-294.00 [-448.04, -139.96]
Taylor 2003	918	2,148	2754	2,023	4,733	2978	16.7%	-1105.00 [-1292.97, -917.03]
Subtotal (95% CI)			**14508**			**11298**	**49.1%**	**-709.90 [-1302.17,-117.62]**
Heterogeneity: $Tau^2 = 254852.59$; $Chi^2 = 43.07$, df = 2 ($P < 0.00001$); $I^2 = 95\%$								
Test for overall effect: Z = 2.35 ($P = 0.02$)								
Total (95% CI)			**28298**			**16038**	**100.0%**	**-1357.01 [-1935.49, -778.53]**
Heterogeneity: $Tau^2 = 512373.32$; $Chi^2 = 137.62$, df = 6 ($P < 0.00001$); $I^2 = 96\%$								
Test for overall effect: Z = 4.60 ($P < 0.00001$)								



Sherrill B, et al. J Clin Hypertens. 2011

Summary

LDL-C is the causal factor of coronary plaque development and activation and LDL-C concentrations directly correlate with CV events;

Recent guidelines further reduced LDL-C targets;

Rosu/Ezetimibe is the combination of the best in class oral agents for the reduction of LDL-C levels

Fixed dose combination of rosu/ezetimibe might enhance adherence and increase the percentage of patients reaching the recommended therapeutic goals