GRG-Gruppo di Ricerca Geriatrica Brescia

I seminari del Venerdì del GRG

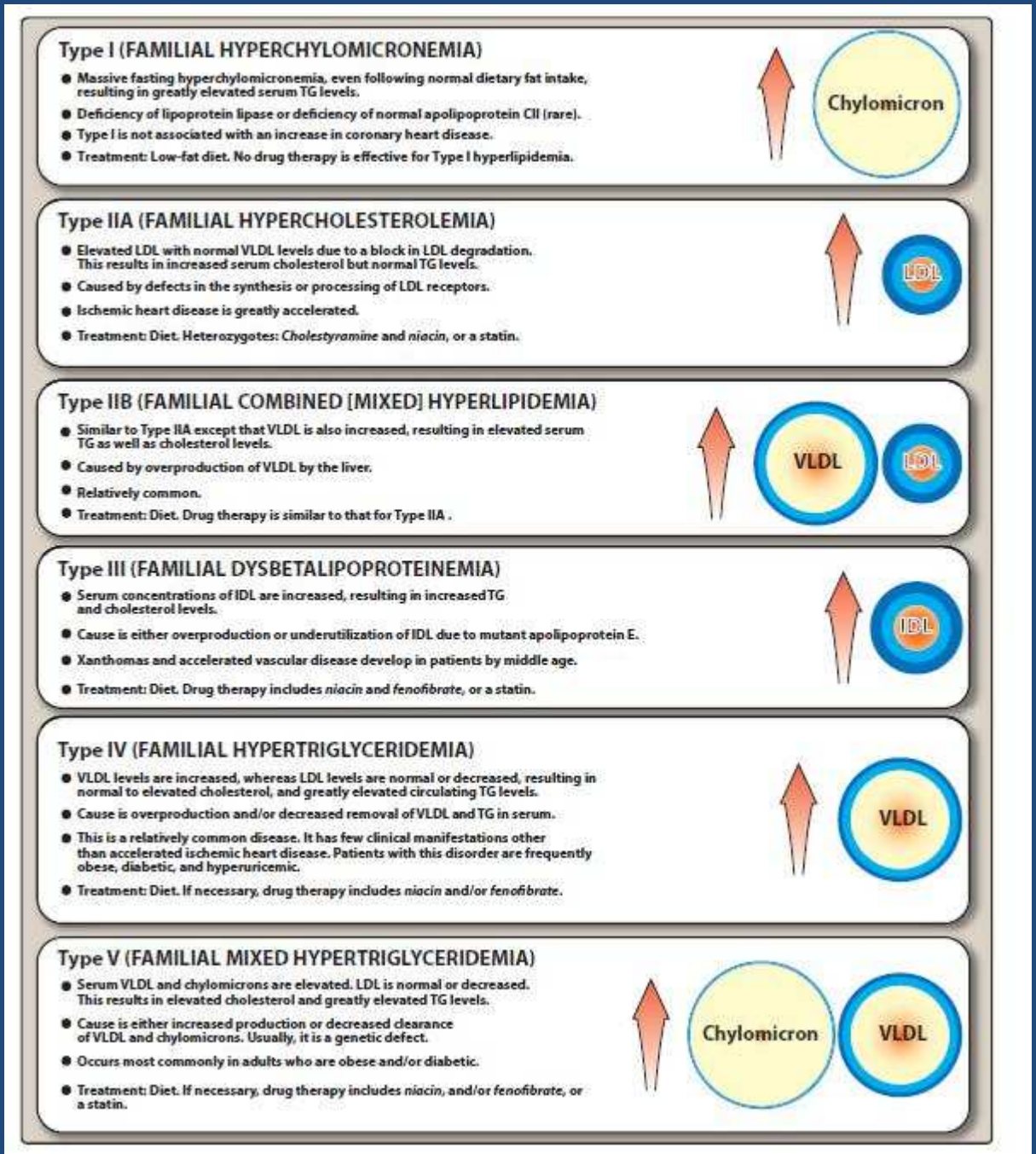
LE STATINE E L'ANZIANO: PER UN INQUADRAMENTO RAZIONALE

Roberto Schepisi

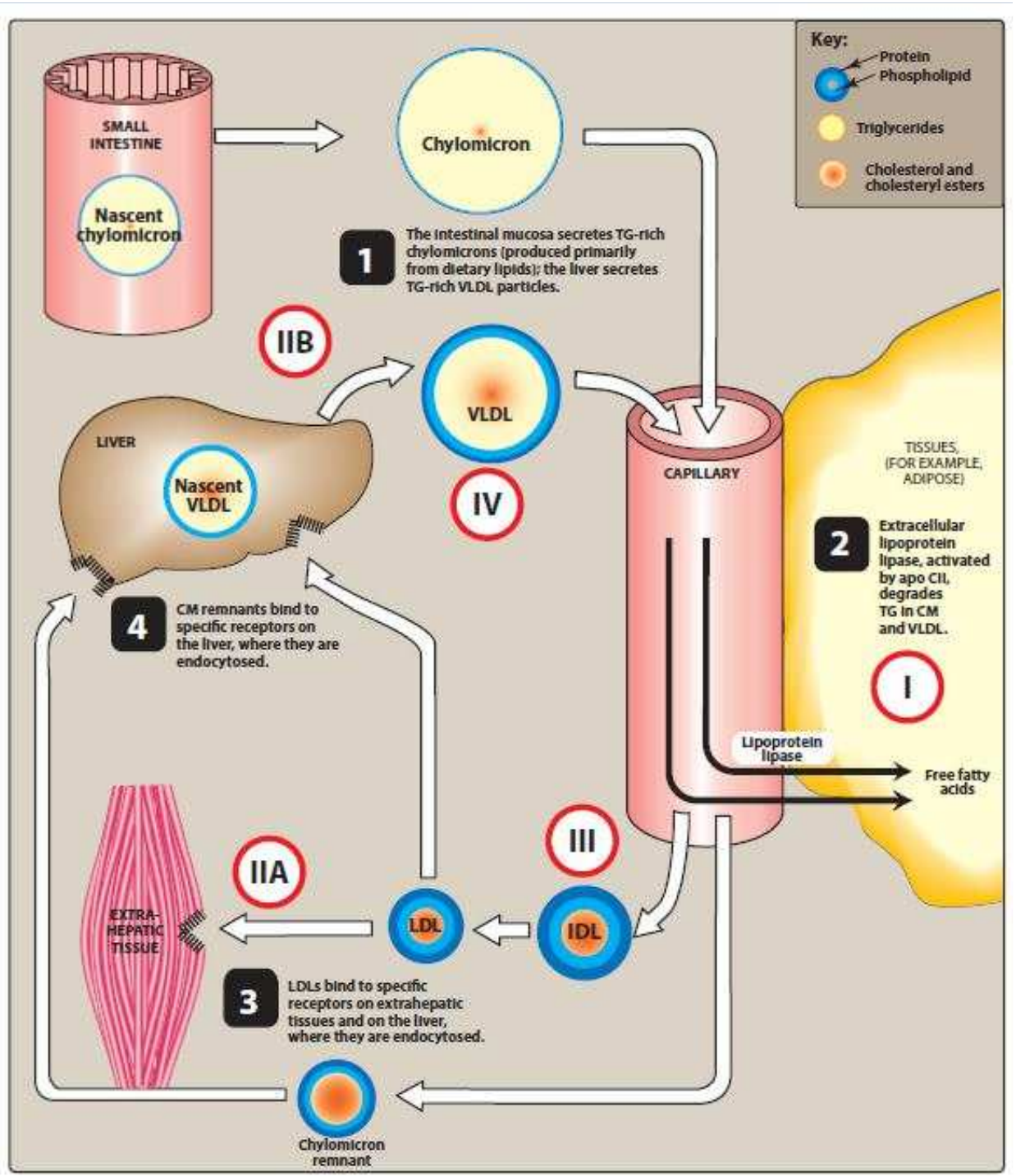
U.O. Medicina IC S.Anna - Brescia

Venerdì, 09 Marzo 2018

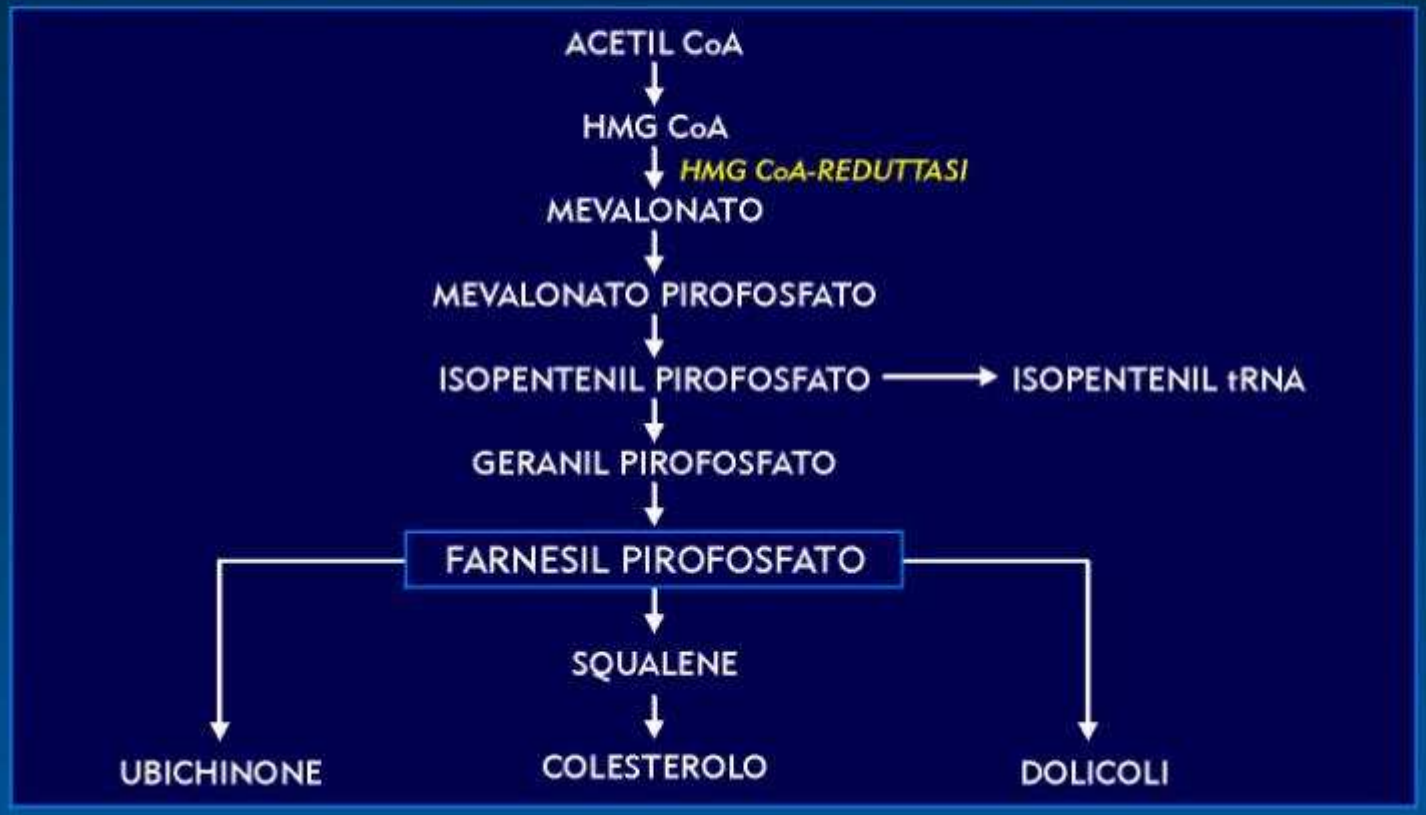
DISLIPIDEMIE: CLASSIFICAZIONE



DISLIPIDEMIE: CLASSIFICAZIONE

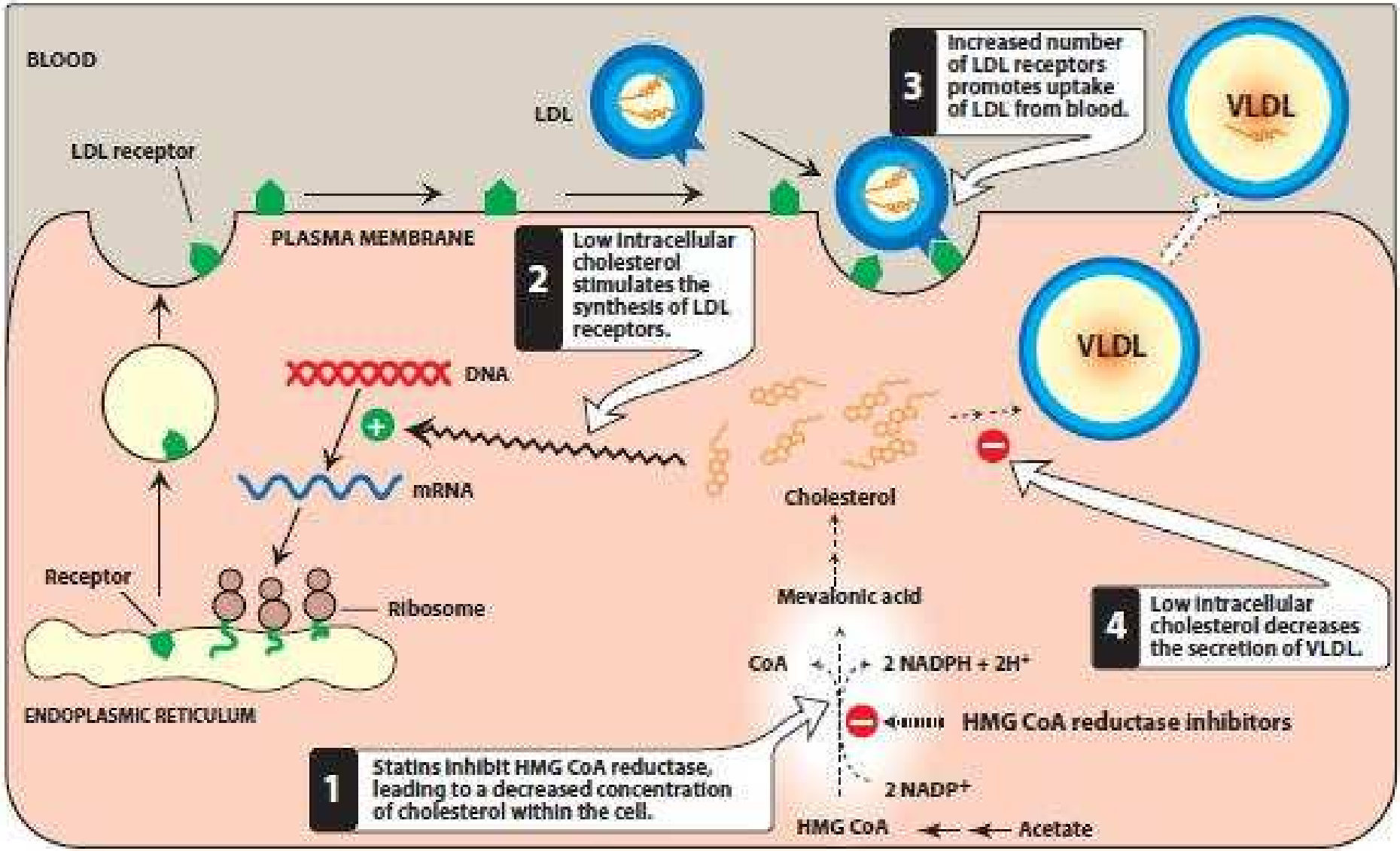


LE STATINE: INIBIZIONE DELLA SINTESI DEL COLESTEROLO

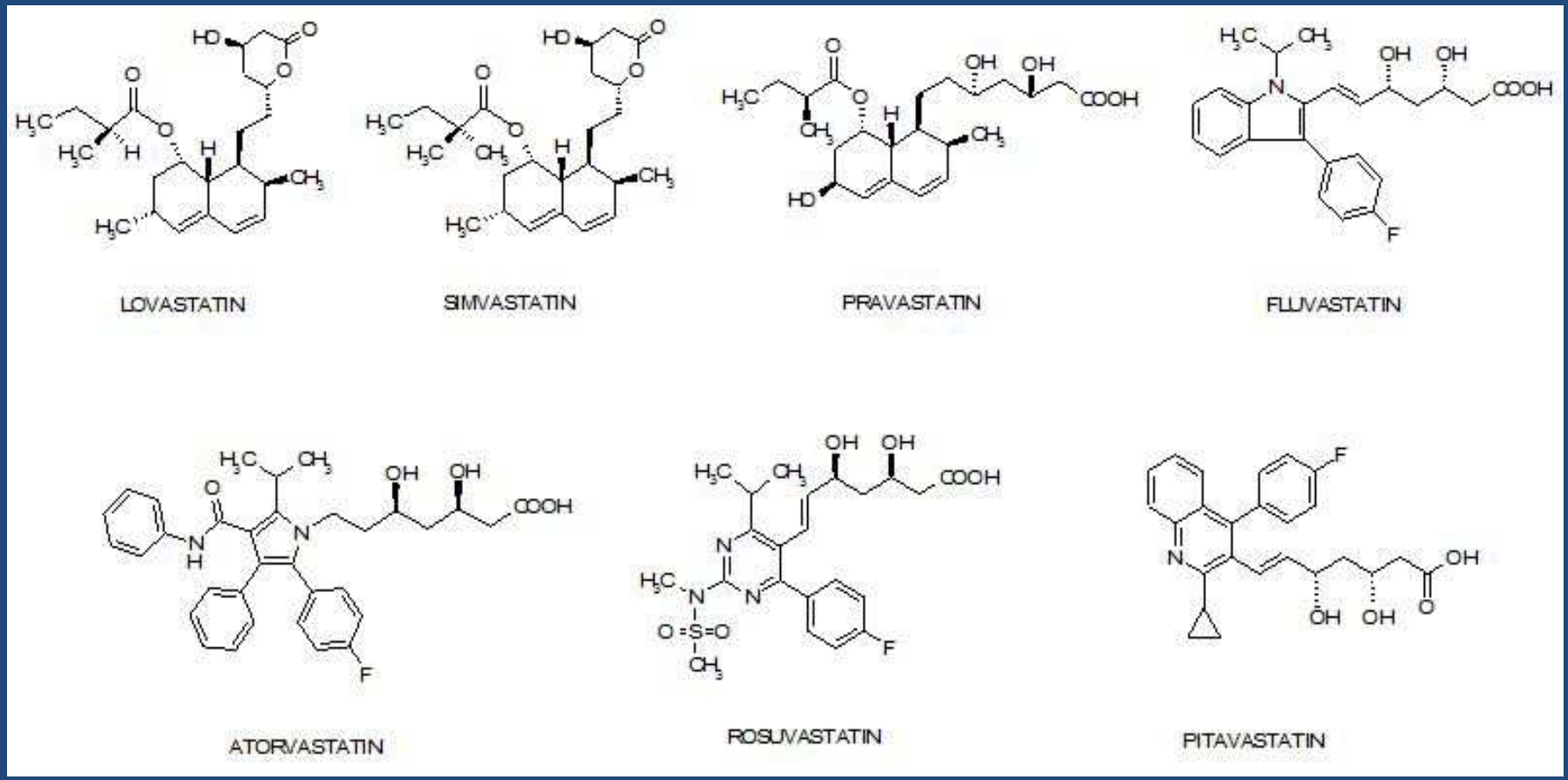


SISA- Sez. Lombardia

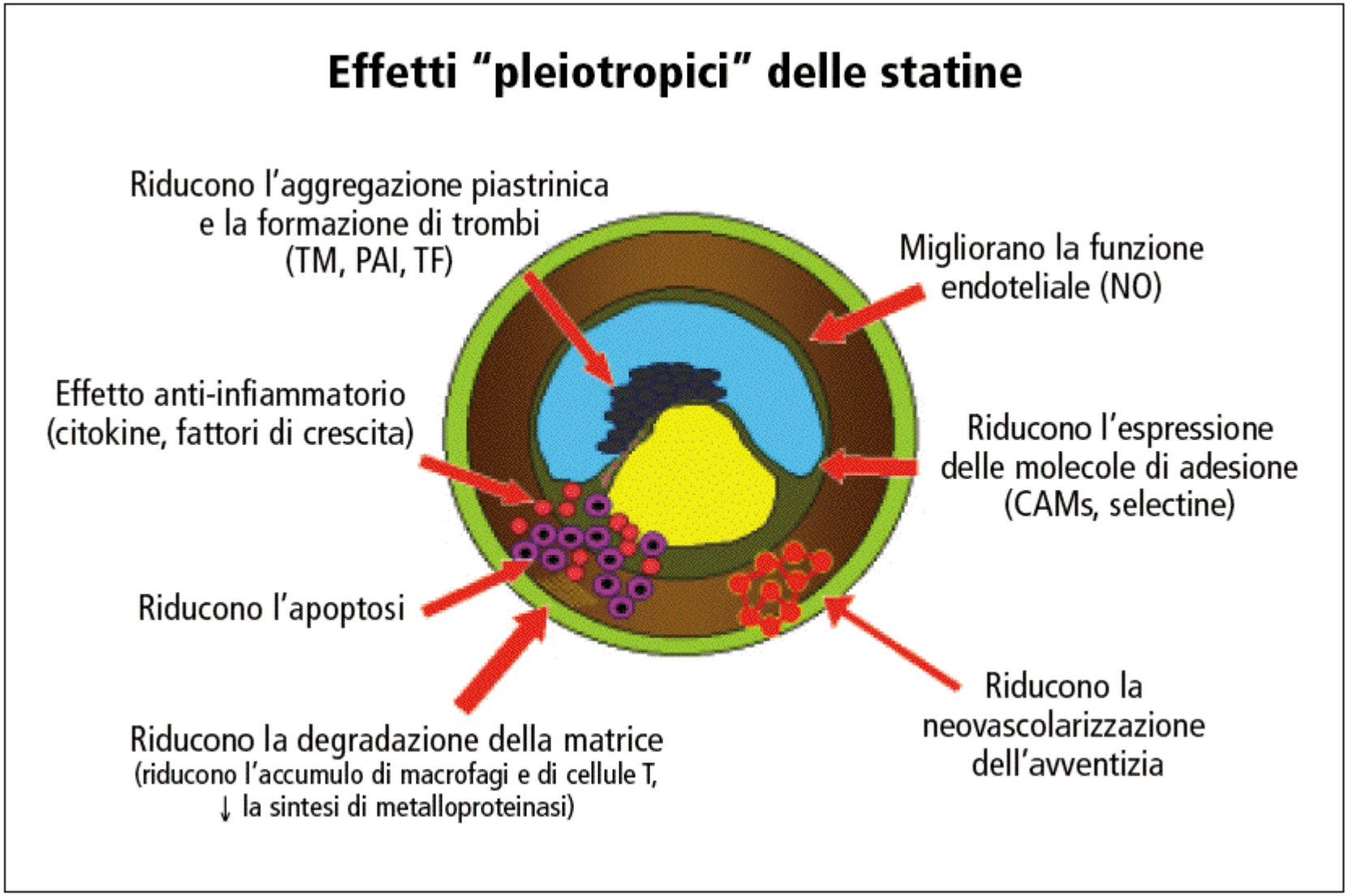
MECCANISMO D'AZIONE



STATINE:
STRUTTURA MOLECOLARE



PLEIOTROPISMO DELLE STATINE



Liao, JK. Am J Cardiol. 2005;96(Suppl. 1):24F-33F

PLEIOTROPISMO DELLE STATINE

- Upregulation of nitric oxide synthase
- Enhanced endothelial function
- Decreased vascular and valvular inflammation
- Downregulation of matrix metalloproteinases
- Decreased platelet clumping and aggregation
- Coronary plaque stabilization and atheroma regression
- Improved myocardial perfusion
- Decreased negative cardiac remodeling
- Stabilization of autonomic and beta-adrenergic myocardial stimulation
- Increase myocardial parasympathetic responsiveness
- Enhanced cerebromotor reactivity and reduced cerebral vasospasm
- Upregulation of angiogenesis
- Downregulation of angiotensin II type I receptor expression
- Increased baroreceptor sensitivity

Mihos CG et al.,Ph. Res. 88-2014, 12-19

STATINE e DEMENZA

- Livelli elevati di Colesterolo correlano con la deposizione di placche di β-amiloide e con sviluppo di Demenza di Alzheimer (Reed B, JAMA 2014; Lesser GT, Curr Alzheimer Res 2011)

STATINE e DEMENZA

JAMA Neurol. 2017 February 01; 74(2): 225–232. doi:10.1001/jamaneurol.2016.3783.

Sex and Race Differences in the Association Between Statin Use and the Incidence of Alzheimer Disease

METABOLISMO delle STATINE

- Simvastatina, Atorvastatina, Lovastatina sono metabolizzate da Citocromo CYP3A4 (Amiodarone,Amlodipina, Citalopram agiscono sul medesimo)
- Fluvastatina , Pitavastatina,Rosuvastatina sono metabolizzate da Citocromo CYPC9 (Warfarin, Dicoflenac agiscono sul medesimo)
- Pravastatina è l'unica statina a non avere metabolismo epatico

Elenco di farmaci interagenti potenzialmente con le statine, metabolizzati dal CYP3A4, con un incrementato rischio di miopatia e rabdomiolisi

Anti-infective agents	Calcium antagonists	Other
Itraconazole	Verapamil	Ciclosporin
Ketoconazole	Diltiazem	Danazol
Posaconazole	Amlodipine	Amiodarone
Erythromycin		Ranolazine
Clarithromycin		Grapefruit juice
Telithromycin		Nefazodone
HIV protease inhibitors		Gemfibrozil

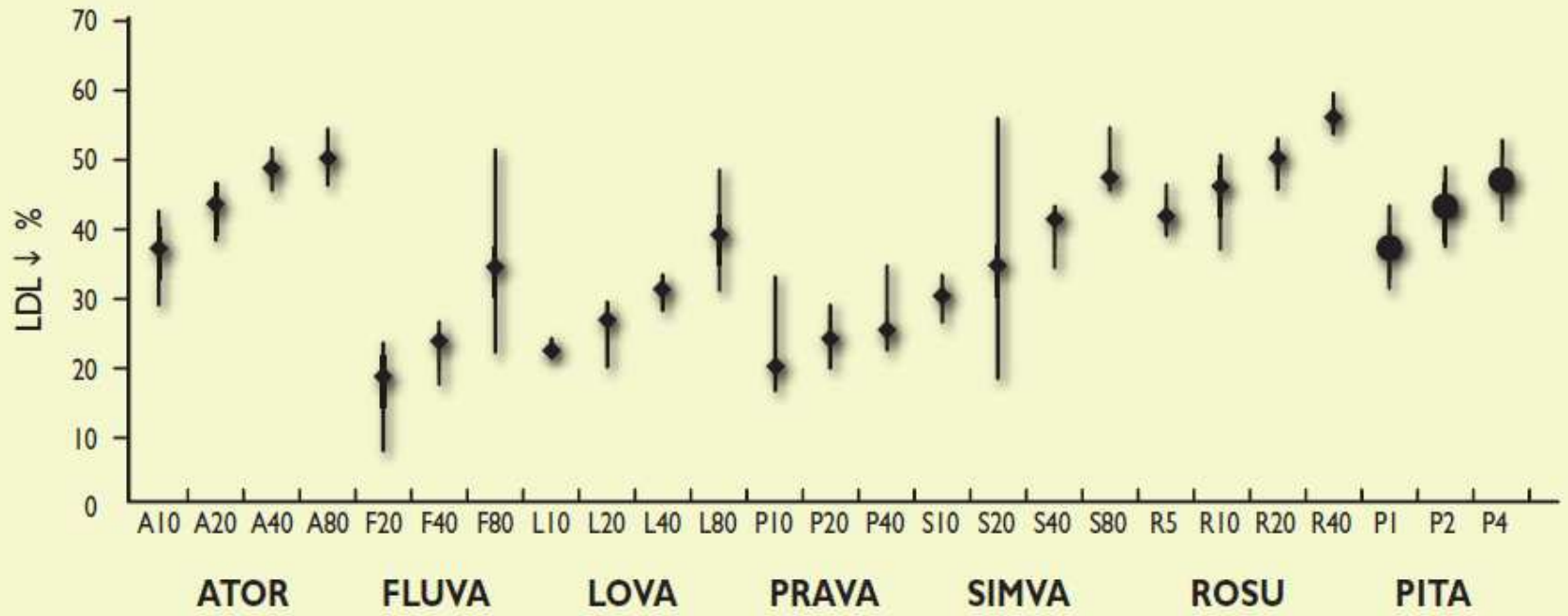
European Heart Journal (2016) 37, 2999–3058
doi:10.1093/eurheartj/ehw272

LE STATINE: PROPRIETA' FARMACOCINETICHE

Parametro farmacocinetico	LOVASTATINA	SIMVASTATINA	PRAVASTATINA	FLUVASTATINA	ATORVASTATINA
Metabolismo via CYP450	Si	Si	No	Si	Si
Lipofilia	Si	Si	No	Si	Si
Legame alle proteine plasmatiche (%)	>95	95-98	~50	>98	>98
Emivita di eliminazione (ore)	~2	~3	~2	~3	~15

SISA- Sez Lombardia

LE STATINE E LE LINEE GUIDA ESC



Weng TC, *et al. J Clin Pharm Ther* . 2010;35:139-151
Mukhtar RY, *et Al. Int J Clin Pract* . 2055;59(2):239-252

European Heart Journal (2016) **37**, 2999–3058
doi:10.1093/eurheartj/ehw272

Efficacia comparata delle diverse statine

Atorvastatina	Simvastatina	Pravastatina	Fluvastatina	Rosuvastatina	Riduzione C-LDL
	10 mg	20 mg	40 mg		20-31%
10 mg	20 mg	40 mg	80 mg	5 mg	32-36%
20 mg	40 mg			10 mg	37-42%
40 mg				20 mg	43-50%
80 mg				40 mg	51-60%

STATINE

PREVENZIONE PRIMARIA

ESC 2016:
Categorie di rischio

Very high-risk	Subjects with any of the following: • Documented cardiovascular disease (CVD), clinical or unequivocal on imaging. Documented CVD includes previous myocardial infarction (MI), acute coronary syndrome (ACS), coronary revascularisation (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)) and other arterial revascularization procedures, stroke and transient ischaemic attack (TIA), and peripheral arterial disease (PAD). Unequivocally documented CVD on imaging is what has been shown to be strongly predisposed to clinical events, such as significant plaque on coronary angiography or carotid ultrasound. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia. • Severe CKD (GFR <30 mL/min/1.73 m^2). • A calculated SCORE ≥10% for 10-year risk of fatal CVD.
High-risk	Subjects with: • Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg. • Most other people with DM (some young people with type 1 diabetes may be at low or moderate risk). • Moderate CKD (GFR 30–59 mL/min/1.73 m^2). • A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	SCORE is ≥1% and <5% for 10-year risk of fatal CVD.
Low-risk	SCORE <1% for 10-year risk of fatal CVD.

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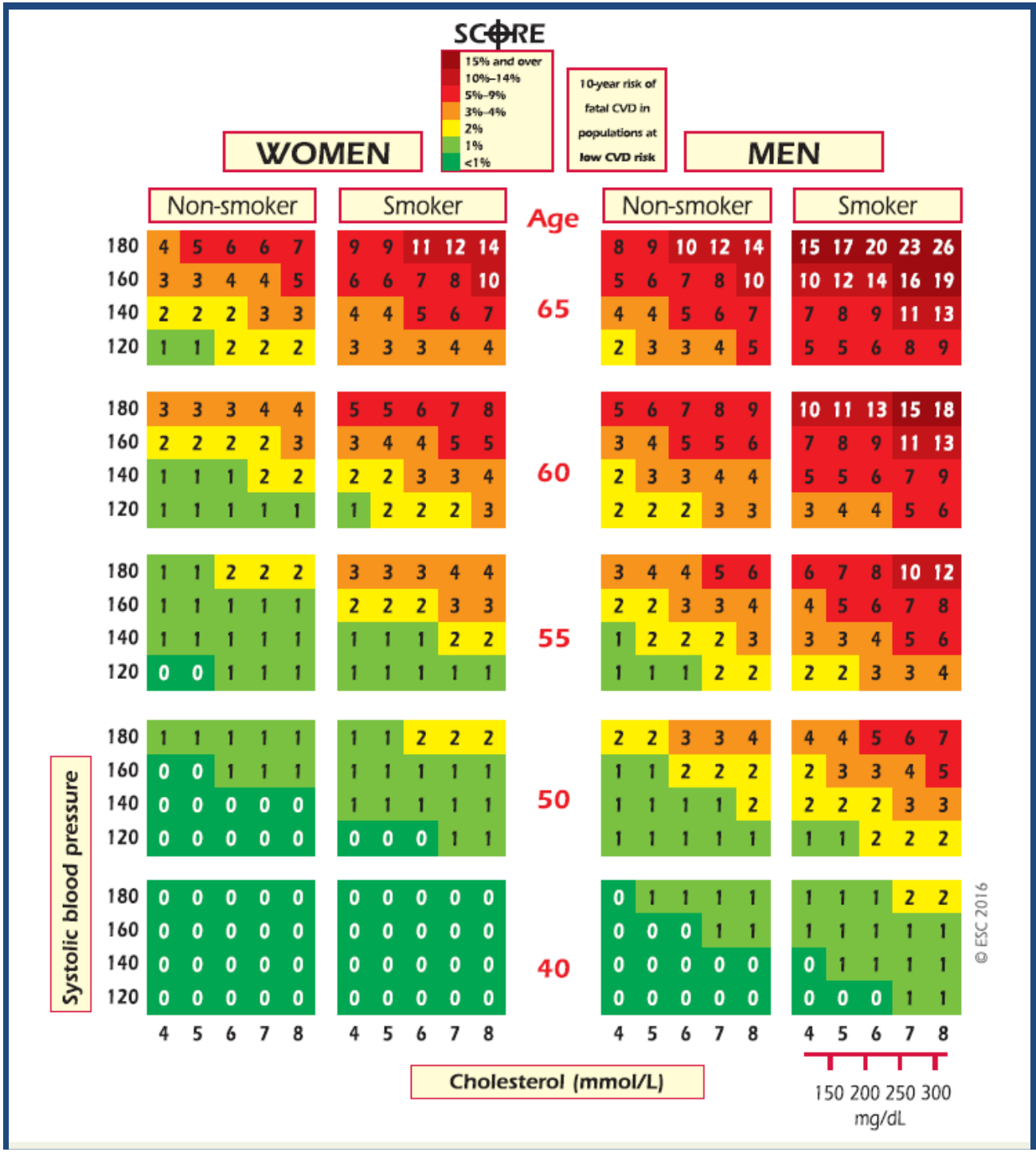
doi:10.1093/eurheartj/ehw272



ESC 2016:

rischio a 10 anni di malattia cardiovascolare fatale in popolazione a **basso** rischio in base ai seguenti fattori:
età, sesso, PAS, colesterolo totale

European Heart Journal (2016) **37**, 2999–3058
doi:10.1093/eurheartj/ehw272

ESC 2016:
Effetto della modifica degli stili di vita

	Magnitude of the effect	Level of evidence
Lifestyle interventions to reduce TC and LDL-C levels		
Reduce dietary trans fat	+++	A
Reduce dietary saturated fat	+++	A
Increase dietary fibre	++	A
Use functional foods enriched with phytosterols	++	A
Use red yeast rice supplements	++	A
Reduce excessive body weight	++	A
Reduce dietary cholesterol	+	B
Increase habitual physical activity	+	B
Use soy protein products	+/-	B
Lifestyle interventions to reduce TG-rich lipoprotein levels		
Reduce excessive body weight	+++	A
Reduce alcohol intake	+++	A
Increase habitual physical activity	++	A
Reduce total amount of dietary carbohydrate	++	A
Use supplements of n-3 polyunsaturated fat	++	A
Reduce intake of mono- and disaccharides	++	B
Replace saturated fat with mono- or polyunsaturated fat	+	B
Lifestyle interventions to increase HDL-C levels		
Reduce dietary trans fat	+++	A
Increase habitual physical activity	+++	A
Reduce excessive body weight	++	A
Reduce dietary carbohydrates and replace them with unsaturated fat	++	A
Modest consumption in those who take alcohol may be continued	++	B
Quit smoking	+	B
Among carbohydrate-rich foods prefer those with low glycaemic index and high fibre content	+/-	C
Reduce intake of mono- and disaccharides	+/-	C

European Heart Journal (2016) **37**, 2999–3058
doi:10.1093/eurheartj/ehw272

ESC 2016:
Obiettivi nella prevenzione del rischio cardiovascolare

Smoking	No exposure to tobacco in any form.
Diet	Healthy diet low in saturated fat with a focus on whole grain products, vegetables, fruit and fish.
Physical activity	2.5–5 h moderately vigorous physical activity per week or 30–60 min most days.
Body weight	BMI 20–25 kg/m^2, waist circumference <94 cm (men) and <80 cm (women).
Blood pressure	<140/90 mmHg[a]
Lipids LDL-C is the primary target	**Very high-risk: LDL-C <1.8 mmol/L (70 mg/dL)** or a reduction of at least 50% if the baseline[b] is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL).
	High-risk: LDL-C <2.6 mmol/L (100 mg/dL) or a reduction of at least 50% if the baseline[b] is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL).
	Low to moderate risk: LDL-C <3.0 mmol/L (115 mg/dL).
	Non-HDL-C secondary targets are <2.6, 3.4 and 3.8 mmol/L (100, 130 and 145 mg/dL) for very high-, high- and moderate-risk subjects, respectively.
	HDL-C: no target, but >1.0 mmol/L (40 mg/dL) in men and >1.2 mmol/L (48 mg/dL) in women indicates lower risk.
	TG: no target but <1.7 mmol/L (150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.
Diabetes	HbA1c: <7% (<53 mmol/mol).

BMI = body mass index; HbA1C = glycated haemoglobin; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; TG = triglycerides.

[a]The BP target can be lower in some patients with type 2 diabetes127 and in some high-risk patients without diabetes who can tolerate multiple antihypertensive drugs.[70]

[b]The term "baseline LDL-C" refers to the level in a subject not taking any lipid lowering medication.

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Recommendations	Class [a]	Level [b]
In patients at VERY HIGH CV risk[c], an LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C[a] is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.	I	B
In patients at HIGH CV risk[c], an LDL-C goal of <2.6 mmol/L (100 mg/dL), or a reduction of at least 50% if the baseline LDL-C[a] is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.	I	B
In subjects at LOW or MODERATE risk[d] an LDL-C goal of <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C

ESC 2016:

Raccomandazioni per ottimizzare i livelli di colesterolo LDL in base al rischio cardiovascolare

European Heart Journal (2016) 37, 2999–3058
doi:10.1093/eurheartj/ehw272

Strategie d'intervento in funzione del rischio CVD totale e del livello di colesterolo in LDL

Total CV risk (SCORE) %	LDL-C levels				
	<70 mg/dL <1.8 mmol/L	70 to <100 mg/dL 1.8 to <2.6 mmol/L	100 to <155 mg/dL 2.6 to <4.0 mmol/L	155 to <190 mg/dL 4.0 to <4.9 mmol/L	≥190 mg/dL ≥4.9 mmol/L
<1	No lipid intervention	No lipid intervention	No lipid intervention	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A
≥1 to <5	No lipid intervention	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	I/A
≥5 to <10, or high-risk	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
Class[a]/Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A
≥10 or very high-risk	Lifestyle intervention, consider drug	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
Class[a]/Level[b]	IIa/A	IIa/A	I/A	I/A	I/A

CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol; SCORE = Systematic Coronary Risk Estimation.
[a]Class of recommendation.
[b]Level of evidence.
[c]In patients with myocardial infarction, statin therapy should be considered irrespective of total cholesterol levels

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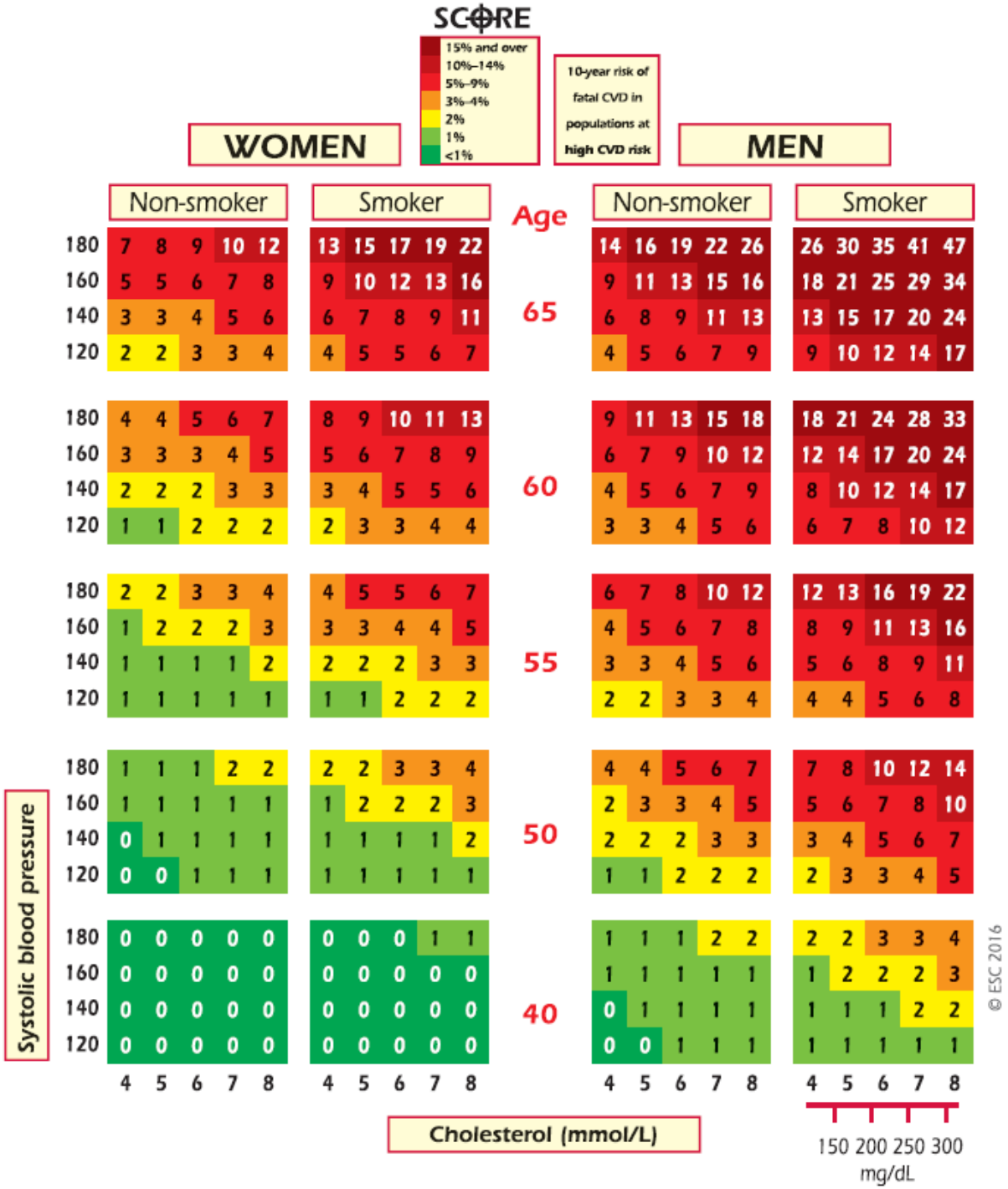


ESC 2016:

rischio a 10 anni di malattia cardiovascolare fatale in popolazione ad **alto** rischio in base ai seguenti fattori:
età, sesso, PAS, fumo, colesterolo totale

European Heart Journal (2016) **37**, 2999–3058
doi:10.1093/eurheartj/ehw272

QUANDO TRATTARE?

REVIEW TOPIC OF THE WEEK

Primary Prevention With Statins in the Elderly

Martin Bødtker Mortensen, MD, PhD, Erling Falk, MD, DMSc

Journal of American College of Cardiology, Vol 71, N.1, 2018

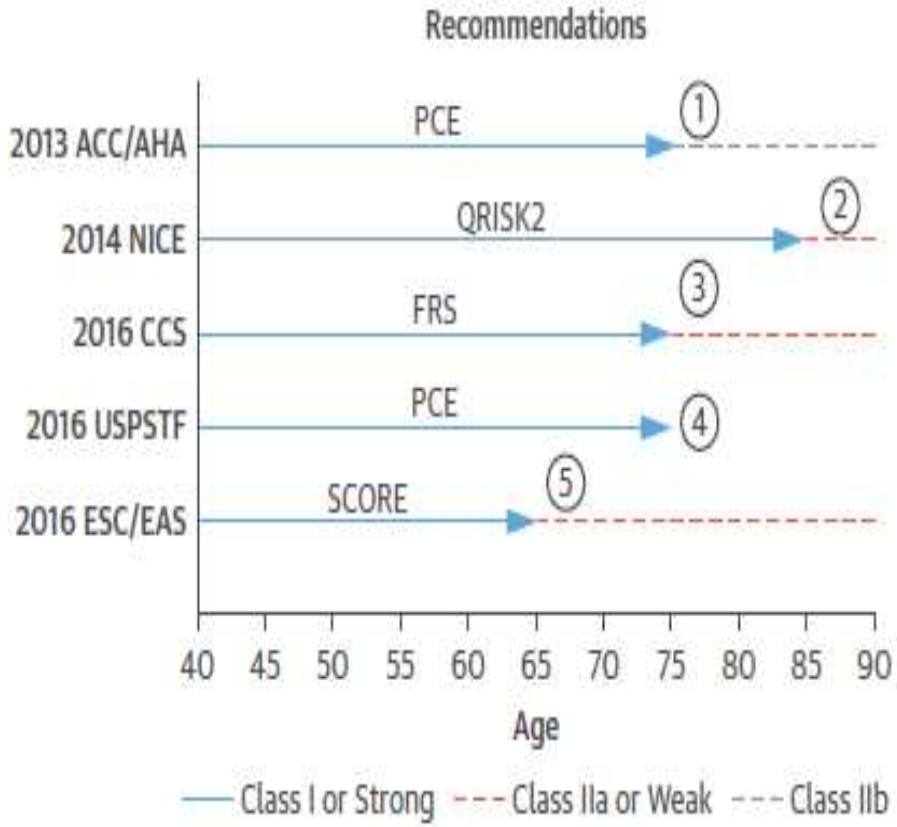
TABLE 1 Eligibility for Primary Prevention With Statins (Class I or Strong Indication)

Indication for Statin Therapy	ACC/AHA 2013 (5)	NICE-UK 2014/2016 (6)	CCS 2016 (7)	USPSTF 2016 (8)	ESC/EAS 2016 (9)
High estimated 10-yr risk					
Age range, yrs	40-75	30-84	30-75*	40-75	40-65†
Risk model	PCE	QRISK2	Modified FRS-CVD	PCE	SCORE
Predicted endpoints	Nonfatal MI, CHD death, stroke	CHD, stroke, TIA (fatal and nonfatal)	MI, angina, CHD death, heart failure, stroke, TIA, PAD	Similar to ACC/AHA	Fatal ASCVD
Risk threshold for therapy	≥7.5%	≥10%	10%-19% (intermediate), ≥20% (high risk)	≥10%	5% to <10% (high risk), ≥10% (very high risk)
Risk factor requirements	No	No	Yes if 10%-19% risk* No if ≥20% risk	≥1‡	No
LDL-C before treatment, mg/dl	70-189	No	≥135 if 10%-19% risk* No if ≥20% risk	≤190	≥155 if high risk ≥100 if ≥10% risk
LDL-C treatment target, mg/dl	No	High intensity: >40%↓§	<77/>50%↓*	No	<100/≥50%↓ if high risk <70/≥50%↓ if ≥10% risk
High-risk clinical condition					
FH and/or high cholesterol, mg/dl	LDL-C ≥190 ≥21 yrs of age	No§	LDL-C ≥190	No‡	FH or TC >310
Diabetes mellitus	40-75 yrs of age LDL-C ≥70	High-risk type 1§	≥40 yrs of age*	No‡	>40 yrs of age
CKD (eGFR), ml/min/1.73 m^2	No	<60§	<60†	No	30-59 = high risk <30 = very high risk†

*The Framingham Risk Score for general cardiovascular disease (FRS-CVD) is not well validated after 75 years of age. In the modified version, the risk is doubled in case of family history of premature cardiovascular disease (CVD). Equivalent values are provided for low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (HDL-C), and apolipoprotein B. Required risk factors in intermediate risk: men ≥50 years of age and women ≥60 years of age and 1 additional CVD risk factor. Diabetes: ≥40 years of age or ≥15-year duration for ≥30 years of age (type 1) or microvascular disease. Chronic kidney disease (CKD): ≥50 years of age and estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 or albumin/creatinine ratio >3 mg/mmol (those on dialysis optional). †Systematic COronary Risk Evaluation (SCORE) is only applicable up to 65 years of age. Statin therapy is not recommended in end-stage renal disease. ‡These recommendations do not pertain to persons with familial hypercholesterolemia (FH) and/or LDL-C >190 mg/dl. Required risk factor includes dyslipidemia, diabetes, hypertension, or smoking. §Patients with FH or receiving renal replacement therapy are not covered under this guideline. Diabetes, high risk: type 1 diabetes >40 years of age or diabetes >10 years or nephropathy or cardiovascular risk factors. In type 2 diabetes, QRISK2-guided statin therapy is recommended. CKD: eGFR <60 ml/min/1.73 m^2 and/or albuminuria. Treatment goal: >40% reduction in non-HDL-C.

ACC/AHA = American College of Cardiology/American Heart Association; ASCVD = atherosclerotic cardiovascular disease; CCS = Canadian Cardiovascular Society; CHD = coronary heart disease; ESC/EAS = European Society of Cardiology/European Atherosclerosis Society; MI = myocardial infarction; NICE-UK = NICE = UK National Institute for Health and Care Excellence; PAD = peripheral artery disease; PCE = pooled cohort equation; TC = total cholesterol; TIA = transient ischemic attack; USPSTF = U.S. Preventive Services Task Force.

FIGURE 1 Recommendations for Primary Prevention With Statins in Apparently Healthy People



Guideline Recommendations in Elderly

1. "Statin therapy may be considered in selected individuals" (age >75, Class IIb)
2. "For people 85 years or older consider atorvastatin 20 mg as statins may be of benefit in reducing the risk of non-fatal myocardial infarction"
3. FRS is not well validated beyond age 75, and indications for statins are less well defined in this age group
4. There is no recommendation for statins in people >75 years old
5. SCORE is not applicable beyond age 65, but "statin therapy should be considered in older adults, particularly in the presence of hypertension, smoking, diabetes and dyslipidemia" (Class IIa)

Handling of individuals >65 years of age differs substantially among contemporary European and North American guidelines, partly because of the performance (applicability) of the risk model used. ACC/AHA = American College of Cardiology/American Heart Association; CCS = Canadian Cardiovascular Society; ESC/EAS = European Society of Cardiology/European Atherosclerosis Society; FRS = Framingham Risk Score for general cardiovascular disease; NICE = National Institute for Health and Care Excellence; PCE = pooled cohort equation; SCORE = Systematic COronary Risk Evaluation; USPSTF = U.S. Preventive Services Task Force.

Recommendations	Class [a]	Level [b]
Treatment with statins is recommended for older adults with established CVD in the same way as for younger patients.	I	A
Since older people often have co-morbidities and have altered pharmacokinetics, lipid-lowering medication should be started at a lower dose and then titrated with caution to achieve target lipid levels that are the same as in younger subjects.	IIa	C
Statin therapy should be considered in older adults free from CVD, particularly in the presence of hypertension, smoking, diabetes and dyslipidaemia.	IIa	B

ESC 2016:
Raccomandazioni per il trattamento della dislipidemia nell'anziano

European Heart Journal (2016) 37, 2999–3058
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TABLE 2 Enrollment of Elderly and Very Elderly in Primary Prevention Statin Trials

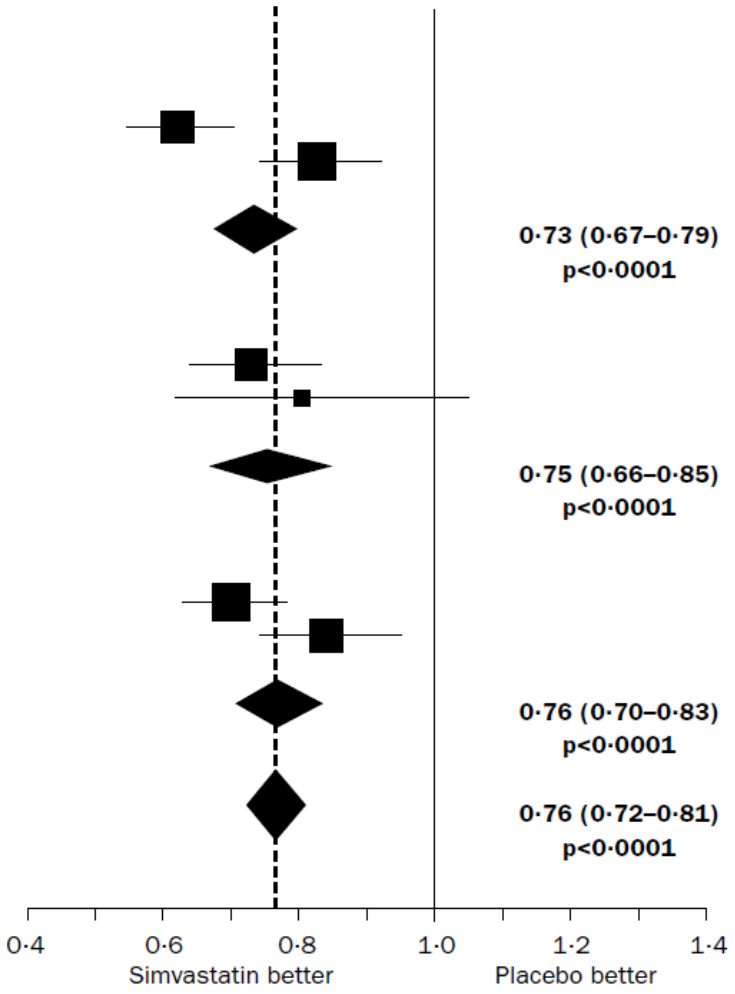
Study Name, Year (Ref. #)	No.	Mean Age (yrs)	Age Range (yrs)	Elderly	Very Elderly (≥75 yrs of Age)
WOSCOPS, 1995 (10)	6,595	55	Men 45–64	0	0
AFCAPS/TexCAPS, 1998 (11)	6,605	Men 58 Women 62	Men 45–73 Women 55–73	Men 20% ≥65 yrs of age Women 33% ≥65 yrs of age	0
ALLHAT-LLT, 2002 (12)	10,355	66	≥55	28% ≥65 yrs of age*	7%*
PROSPER, 2002 (13)	3,239 (no ASCVD)	75 (whole cohort)	70–82 (whole cohort)	100% ≥70 yrs of age	NR
ASCOT-LLA, 2003 (14)	10,305	63	40–79	64% >60 yrs of age 23% >70 yrs of age	NR
CARDS, 2004 (15)	2,838	62	40–75	40% ≥65 yrs of age 12% >70 yrs of age	0
MEGA, 2006 (16)	7,832	58	40–70	23% ≥65 yrs of age	0
JUPITER, 2008 (17)	17,802	66	Men ≥50 Women ≥60	58% ≥65 yrs of age† 32% ≥70 yrs of age†	NR
HOPE-3, 2016 (18)	12,705	66	Men ≥55 Women ≥65/60	52% ≥65 yrs of age† 24% ≥70 yrs of age†	NR

*Primary prevention data reported by Han et al. (19). †Reported by Ridker et al (20).

AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid Lowering Trial; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; CARDS = Collaborative Atorvastatin Diabetes Study; HOPE-3 = Heart Outcomes Prevention Evaluation-3; JUPITER = Justification for the Use of Statins in prevention: An Intervention Trial Evaluating Rosuvastatin; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; NR = not reported; PROSPER = Pravastatin in elderly individuals at risk of vascular disease; WOSCOPS = West of Scotland Coronary Prevention Study.

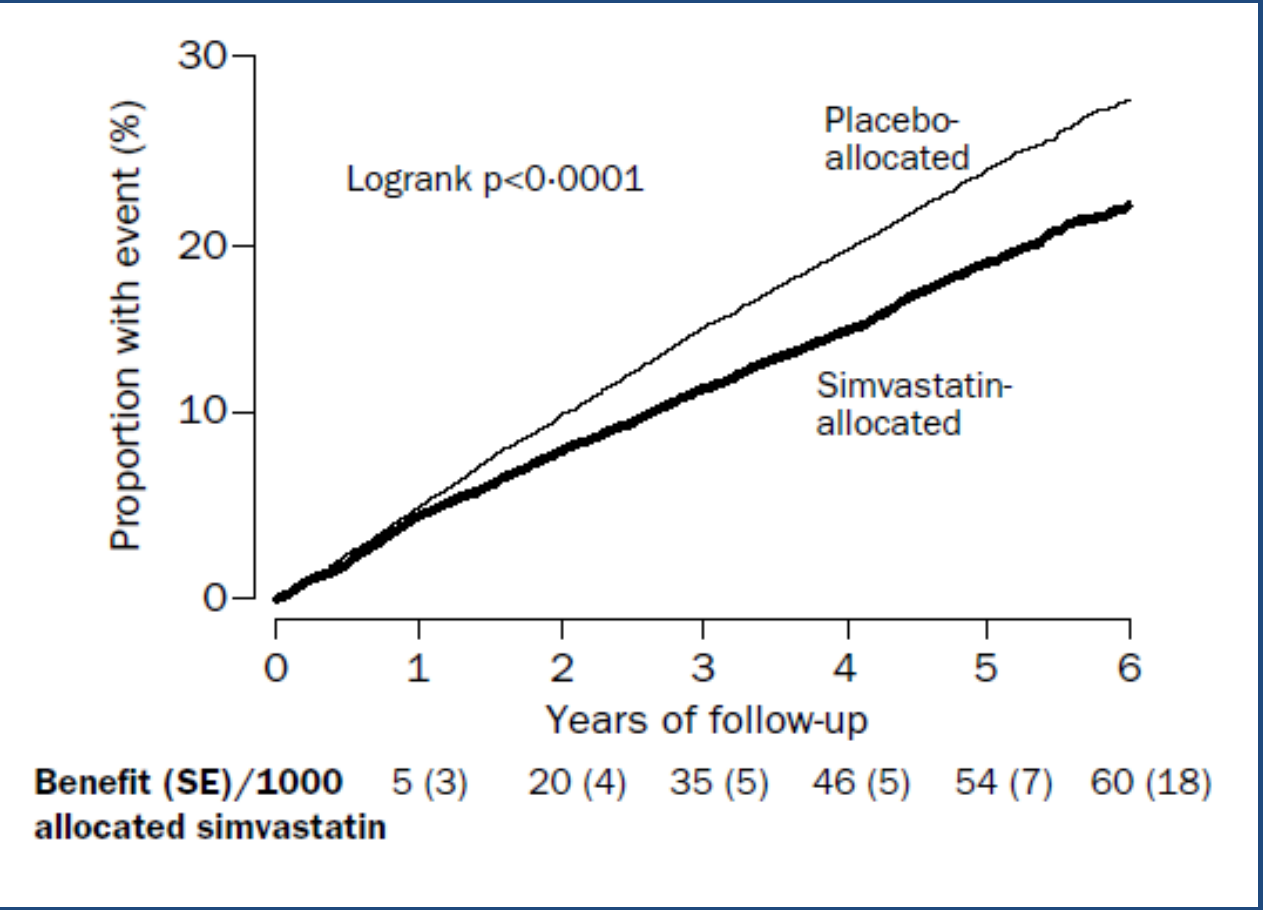
STUDIO HPS

Type of major vascular event	Simvastatin-allocated (10 269)	Placebo-allocated (10 267)	Event rate ratio (95% CI)
Coronary events			
Non-fatal MI	357 (3·5%)	574 (5·6%)	
Coronary death	587 (5·7%)	707 (6·9%)	
Subtotal: major coronary event	**898 (8·7%)**	**1212 (11·8%)**	**0·73 (0·67–0·79) p<0·0001**
Strokes			
Non-fatal stroke	366 (3·6%)	499 (4·9%)	
Fatal stroke	96 (0·9%)	119 (1·2%)	
Subtotal: any stroke	**444 (4·3%)**	**585 (5·7%)**	**0·75 (0·66–0·85) p<0·0001**
Revascularisations			
Coronary	513 (5·0%)	725 (7·1%)	
Non-coronary	450 (4·4%)	532 (5·2%)	
Subtotal: any revascularisation	**939 (9·1%)**	**1205 (11·7%)**	**0·76 (0·70–0·83) p<0·0001**
ANY MAJOR VASCULAR EVENT	**2033 (19·8%)**	**2585 (25·2%)**	**0·76 (0·72–0·81) p<0·0001**



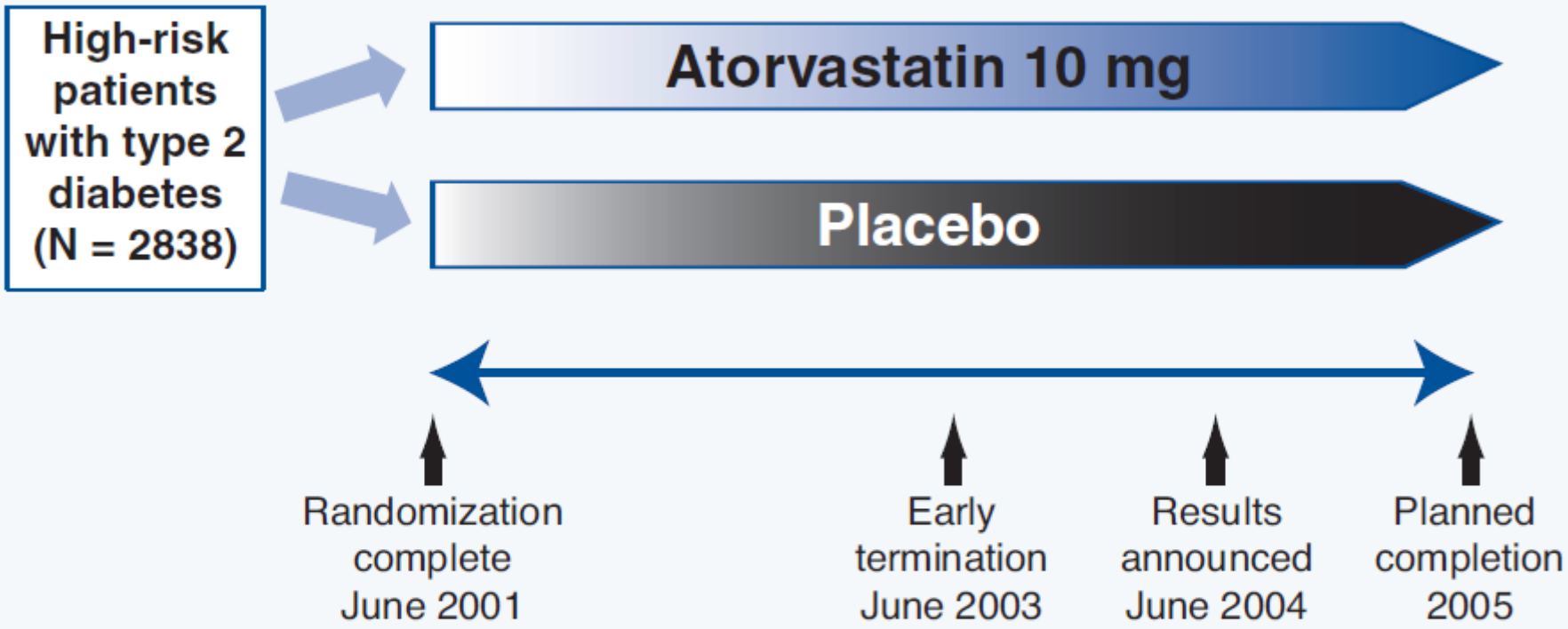
Collins R, et al. Lancet 2003;361:2005-16

STUDIO HPS



Collins R, et al. Lancet 2003;361:2005-16

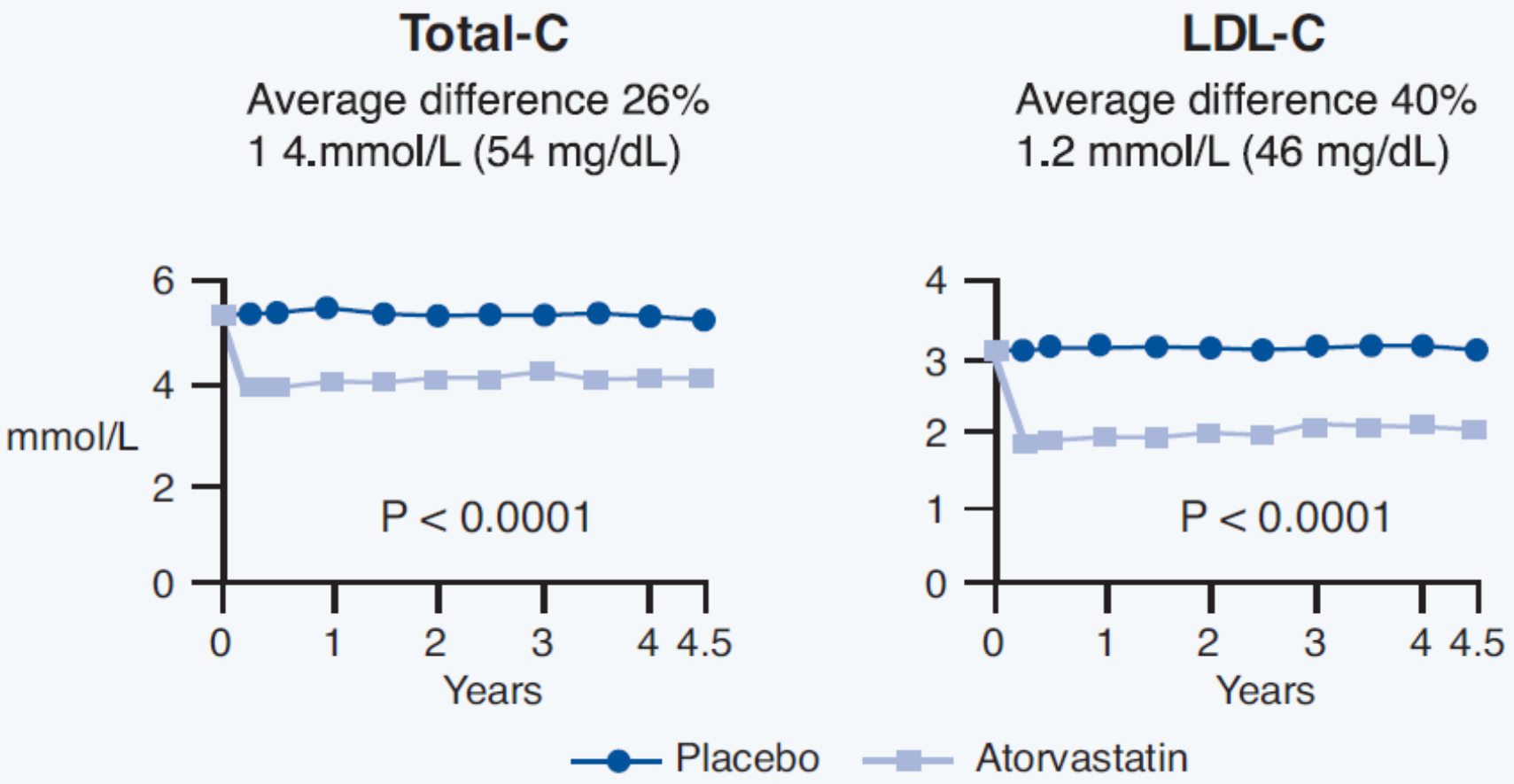
STUDIO CARDS



Primary outcome: Composite of major coronary events, revascularizations, unstable angina, resuscitated cardiac arrest, and stroke

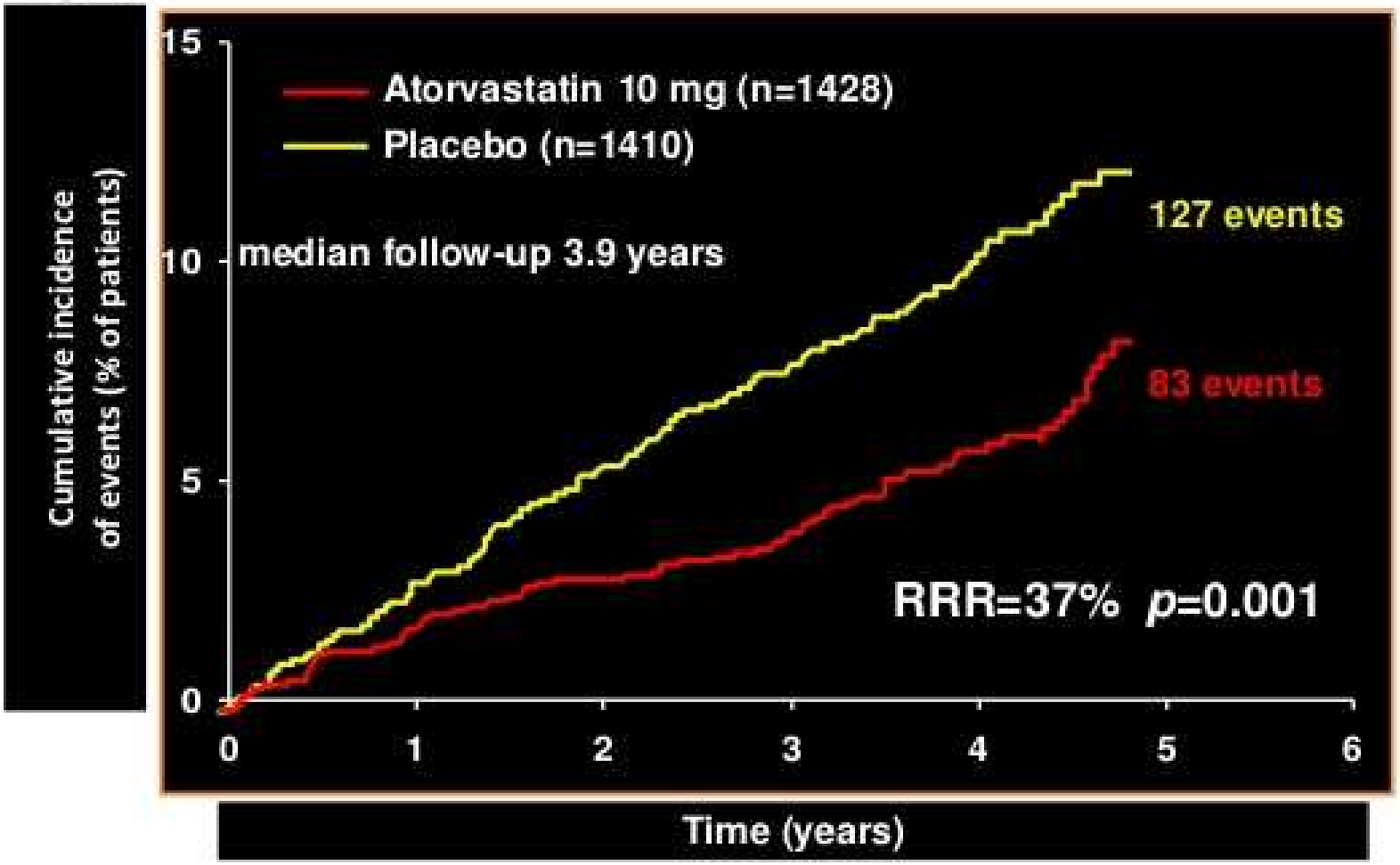
Colhoun HM, et al. Lancet 2004;364:685-96

STUDIO CARDS: Effetto sui lipidi



Colhoun HM, et al. Lancet 2004;364:685-96

CARDS: Atorvastatin reduces CV events by 37%

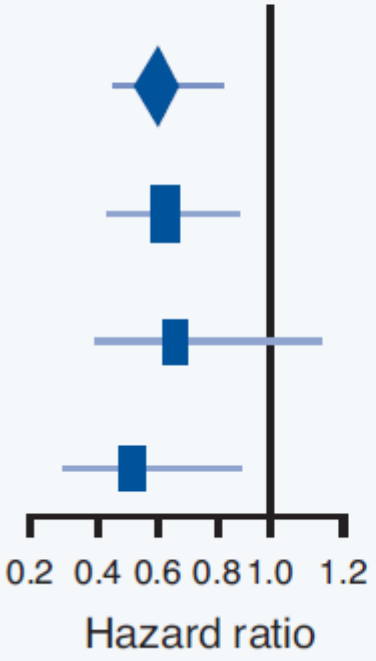


*Acute CHD event, coronary revascularization, stroke.
RRR: Relative risk reduction

Colhoun HM et al. *Lancet*. 2004;364:685-696.

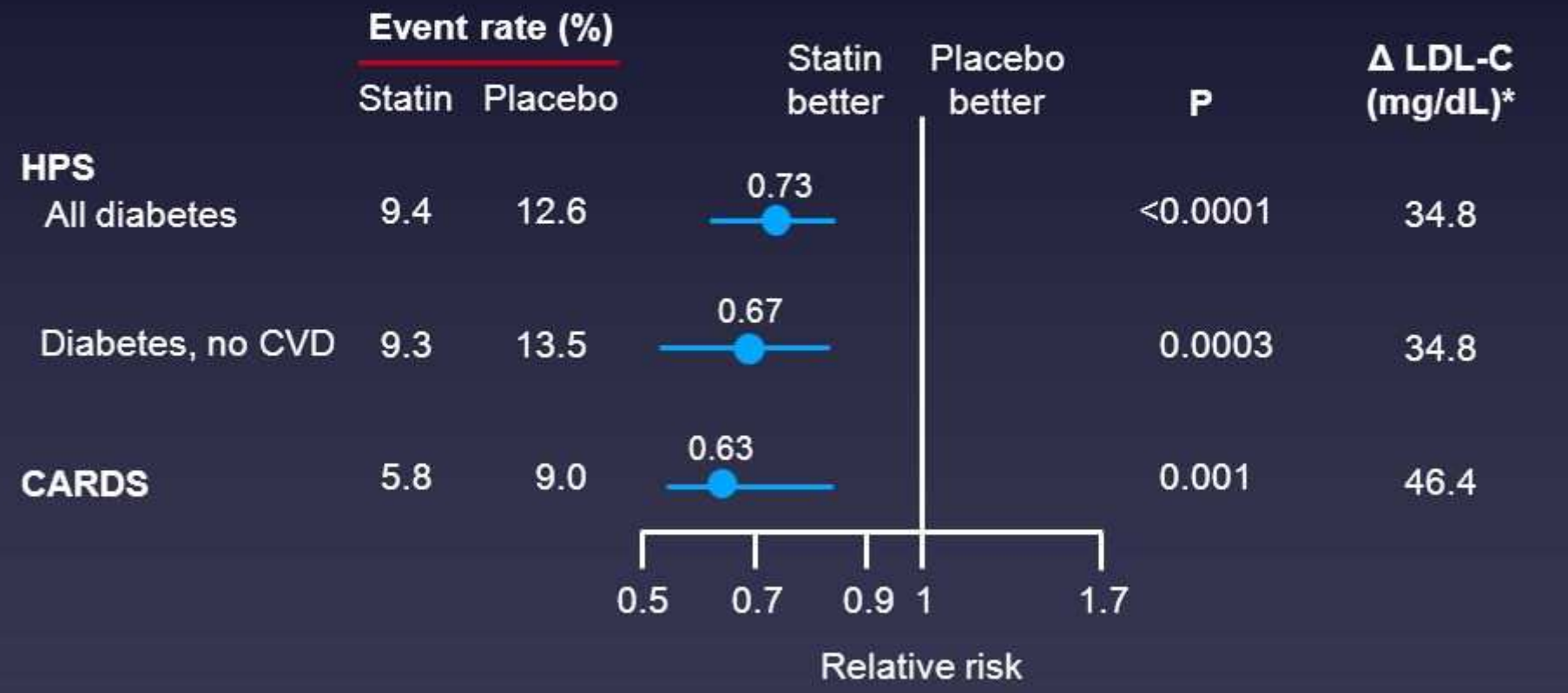
STUDY CARDS: Forest plot

Event	n (% randomized) Placebo	Atorvastatin	Risk reduction (95% CI)
Primary outcome	127 (9.0)	83 (5.8)	37% (17–52) P = 0.001
Acute coronary events	77 (5.5)	51 (3.6)	36% (9–55)
Coronary revascularization	34 (2.4)	24(1.7)	31% (−16–59)
Stroke	39 (2.8)	21(1.5)	48% (11–69)



Colhoun HM, et al. Lancet 2004;364:685-96

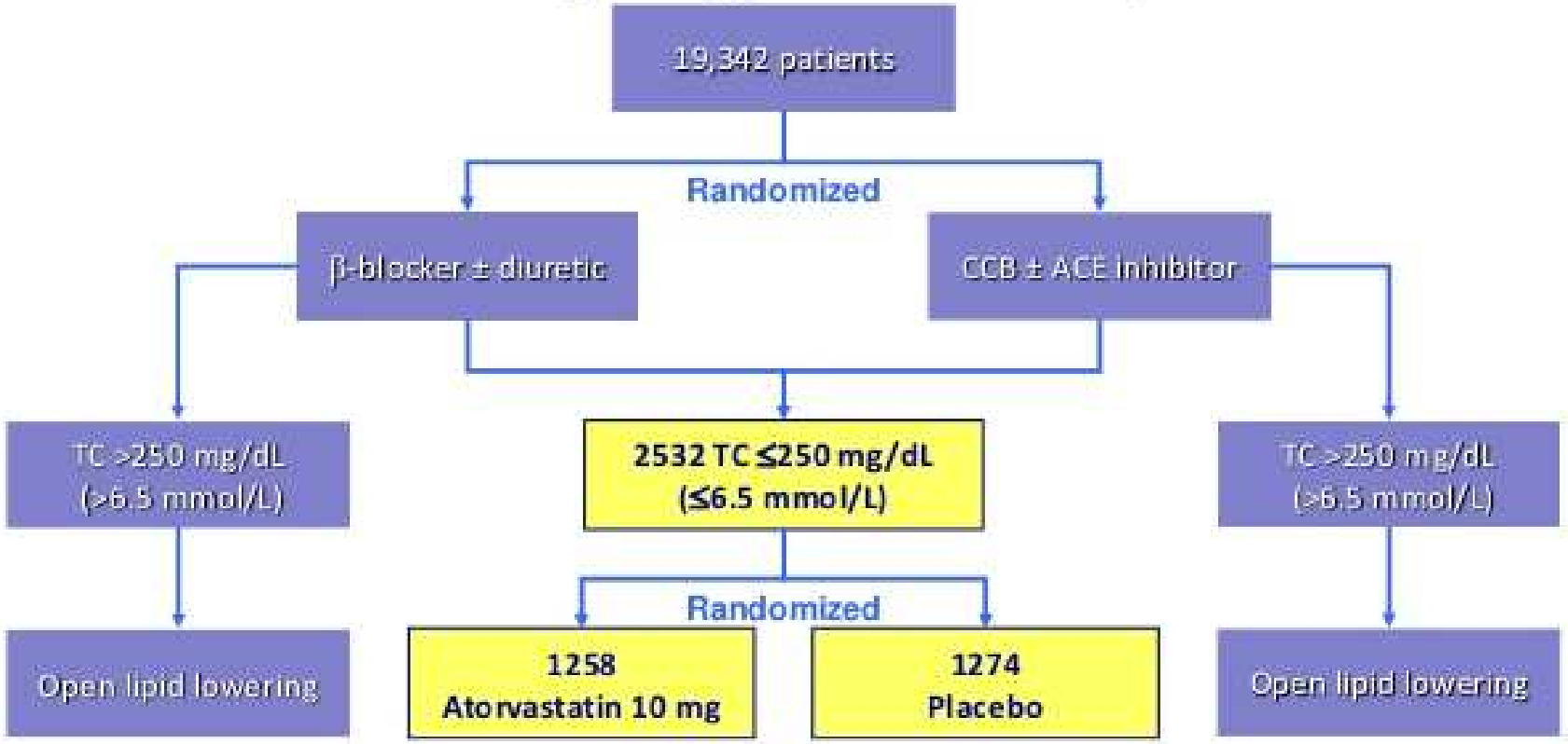
HPS and CARDS: Benefits of lowering LDL-C in diabetes



*Statin vs placebo
HPS = Heart Protection Study
CARDS = Collaborative Atorvastatin Diabetes Study

HPS Collaborative Group. *Lancet*. 2003;361:2005-16.
Colhoun HM et al. *Lancet*. 2004;364:685-96.

ASCOT-LLA: Primary prevention– DM Sub-analysis (yellow cells)



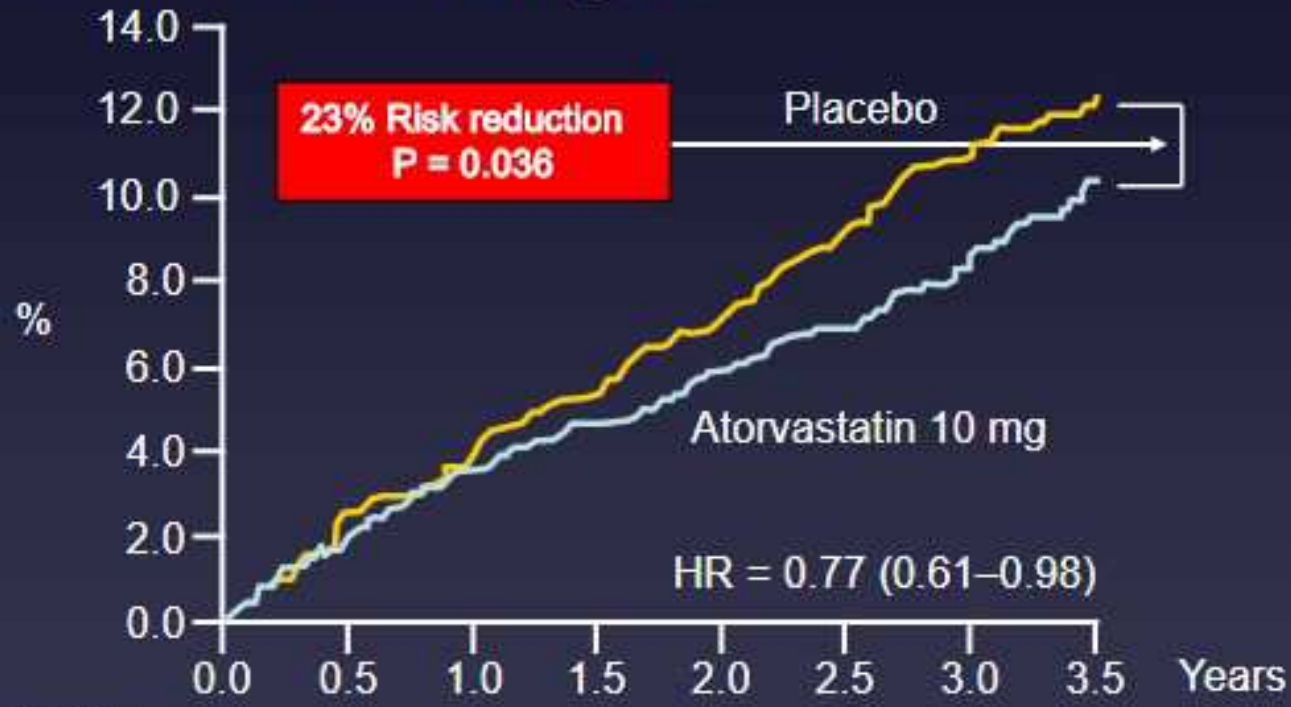
Primary end point: Composite of fatal CHD and nonfatal MI

Highlighted boxes indicate diabetes patients enrolled in lipid-lowering arm.

ASCOT: LLA: Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm
Sever PS et al. *J Hypertens.* 2001;19:1139-1147. CCB: Calcium Channel Blocker
ACE: Angiotension Convertase Inhibitor TC: Total Cholesterol

ASCOT-LLA: Atorvastatin reduces CV events in patients with diabetes and hypertension

N = 2532, baseline LDL-C 128 mg/dL



Number at risk								
Placebo	1258	1231	1209	1191	1171	1065	699	370
Atorvastatin	1274	1237	1219	1200	1175	1058	714	375

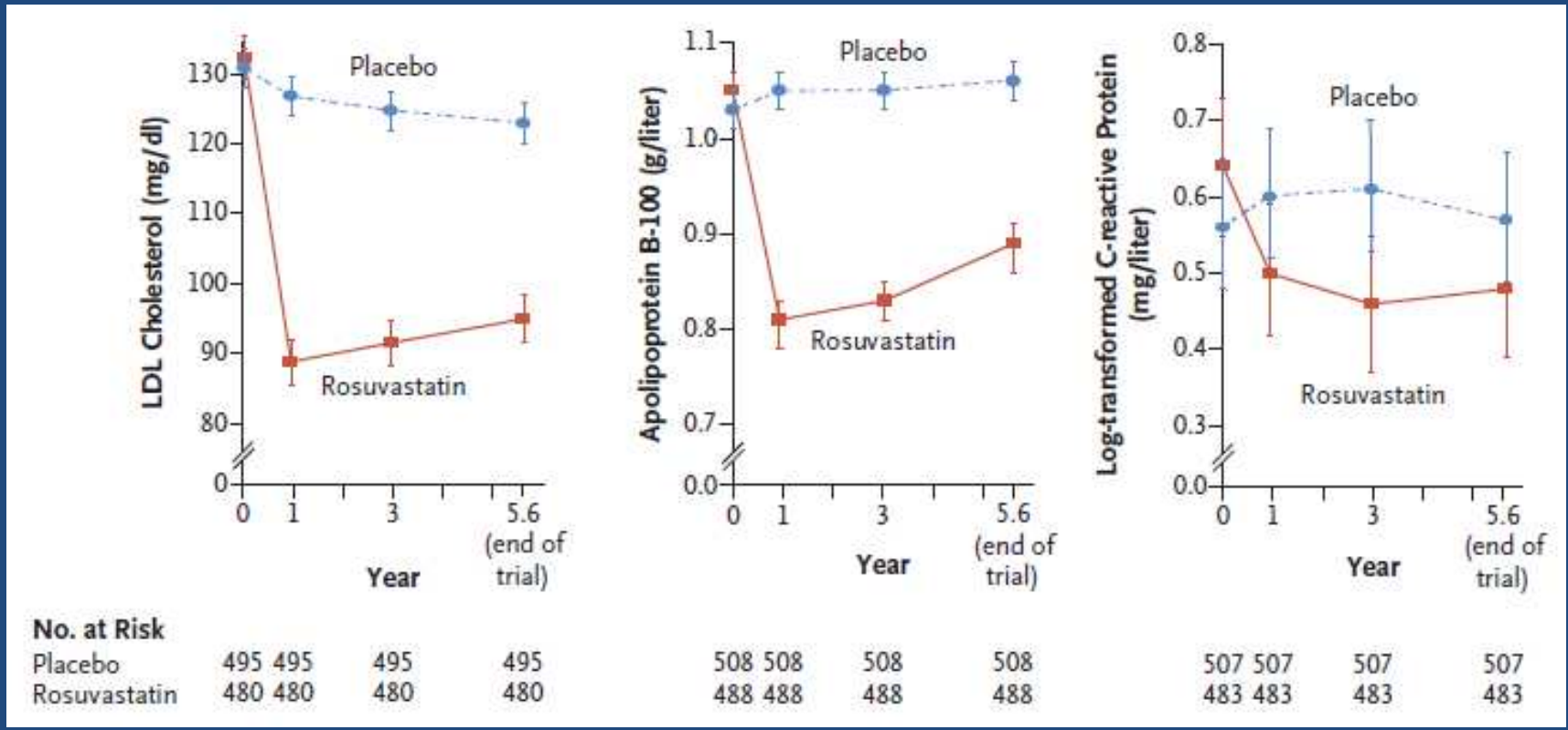
Nonfatal MI, CV mortality, UA, stable angina, arrhythmias, stroke, TIA, PAD, retinal vascular thrombosis, revascularization

ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm

Sever PS et al. *Diabetes Care*. 2005;28:1151-7.

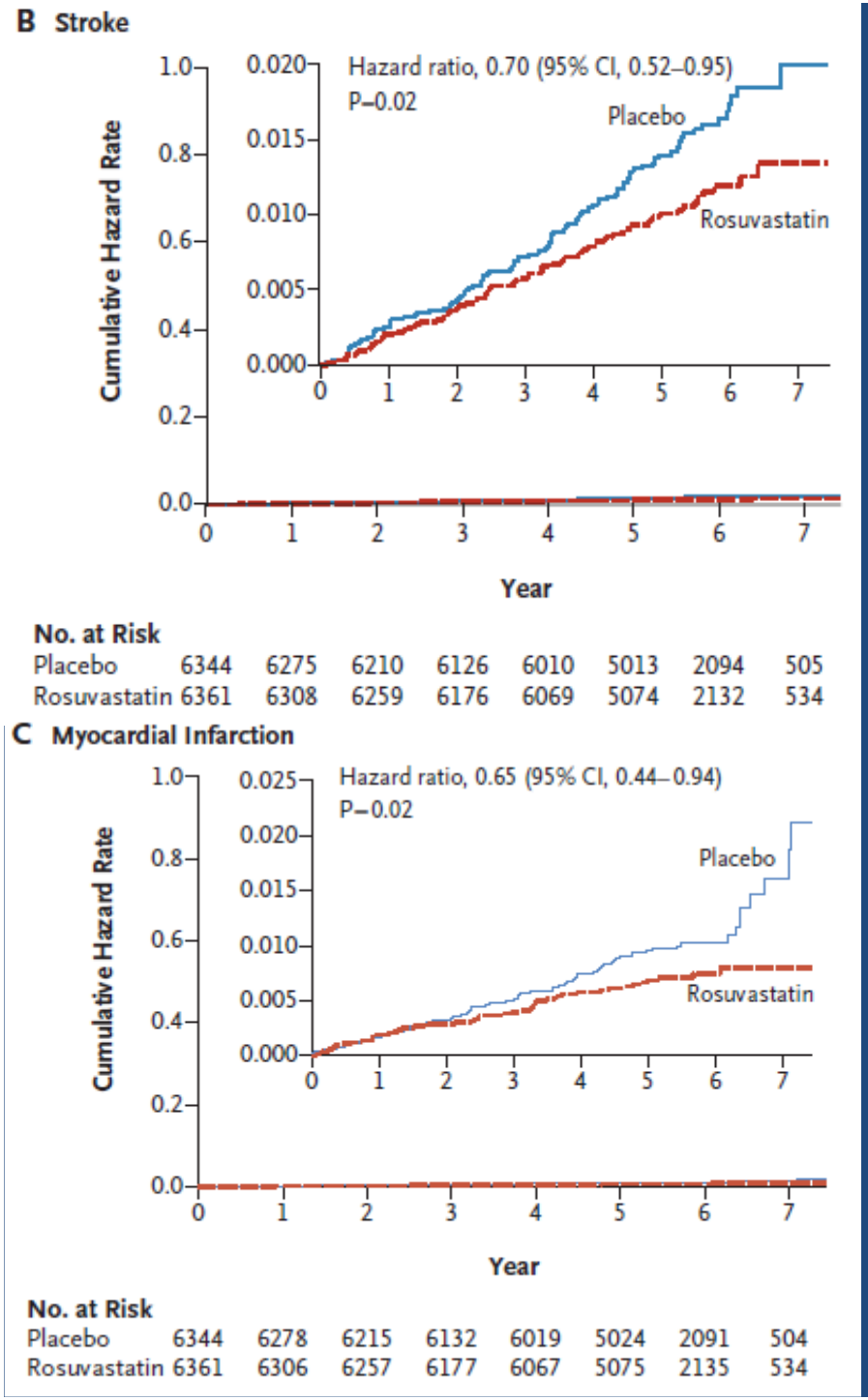
STUDIO HOPE-3

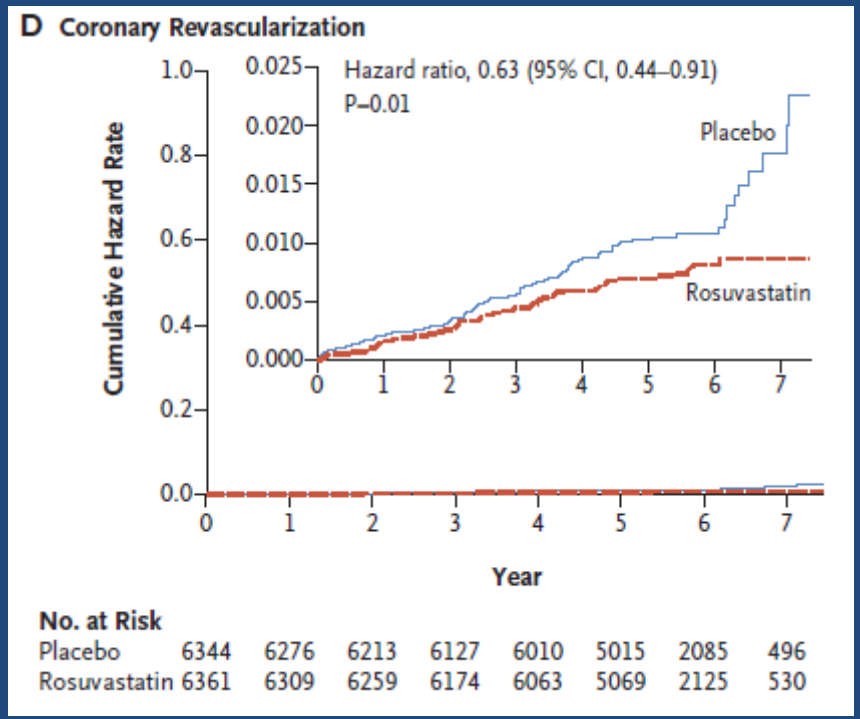
12705 pz, da 21 Paesi, senza patologie cardiovascolari, randomizzati a ricevere Rosuvastatina 10 mg versus placebo



Yusuf S, et al. NEJM 2016

STUDIO HOPE-3

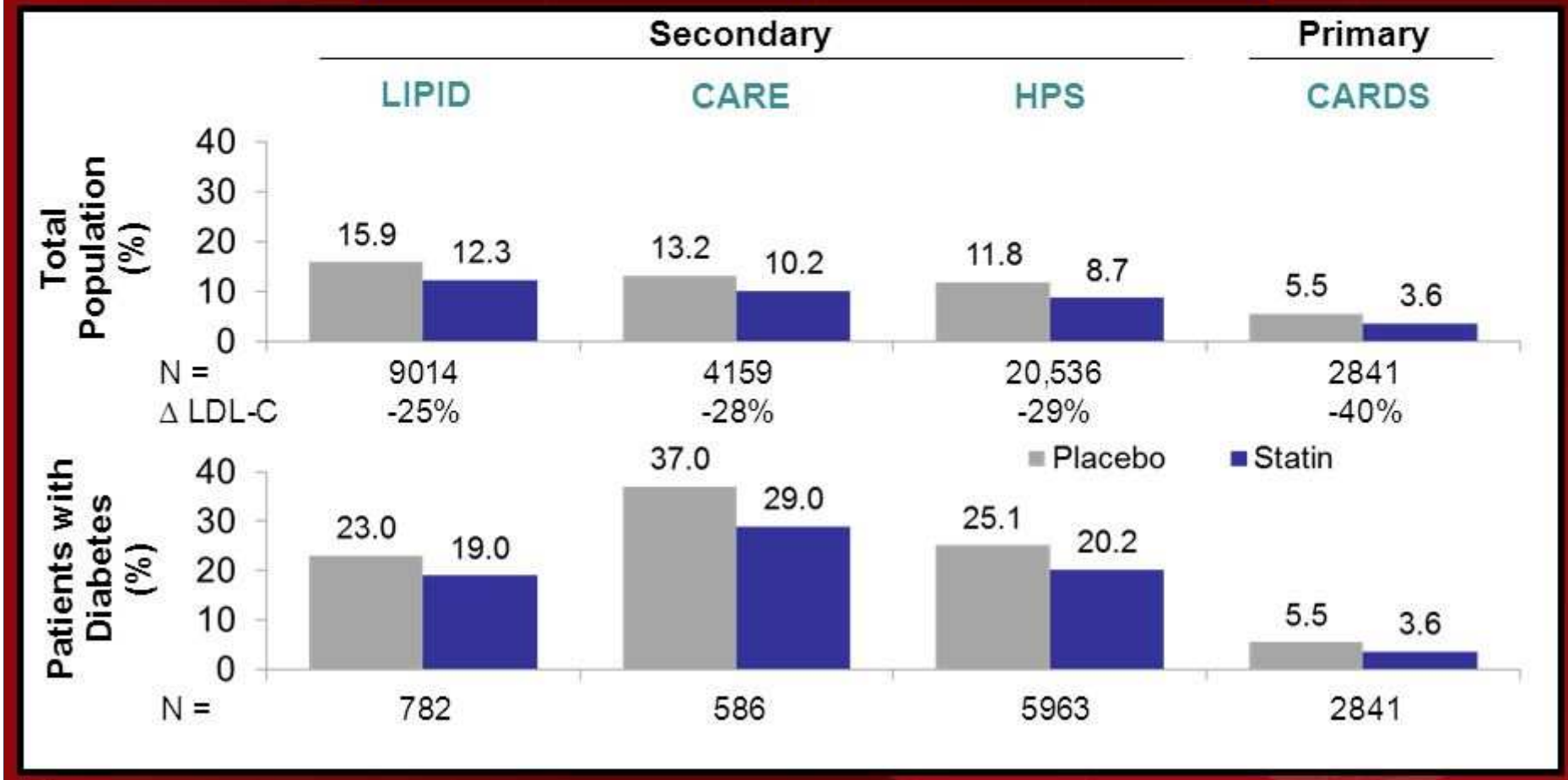




Yusuf S, et al. NEJM 2016

Residual Cardiovascular Risk in Major Statin Trials

CHD events still occur in patients treated with statins

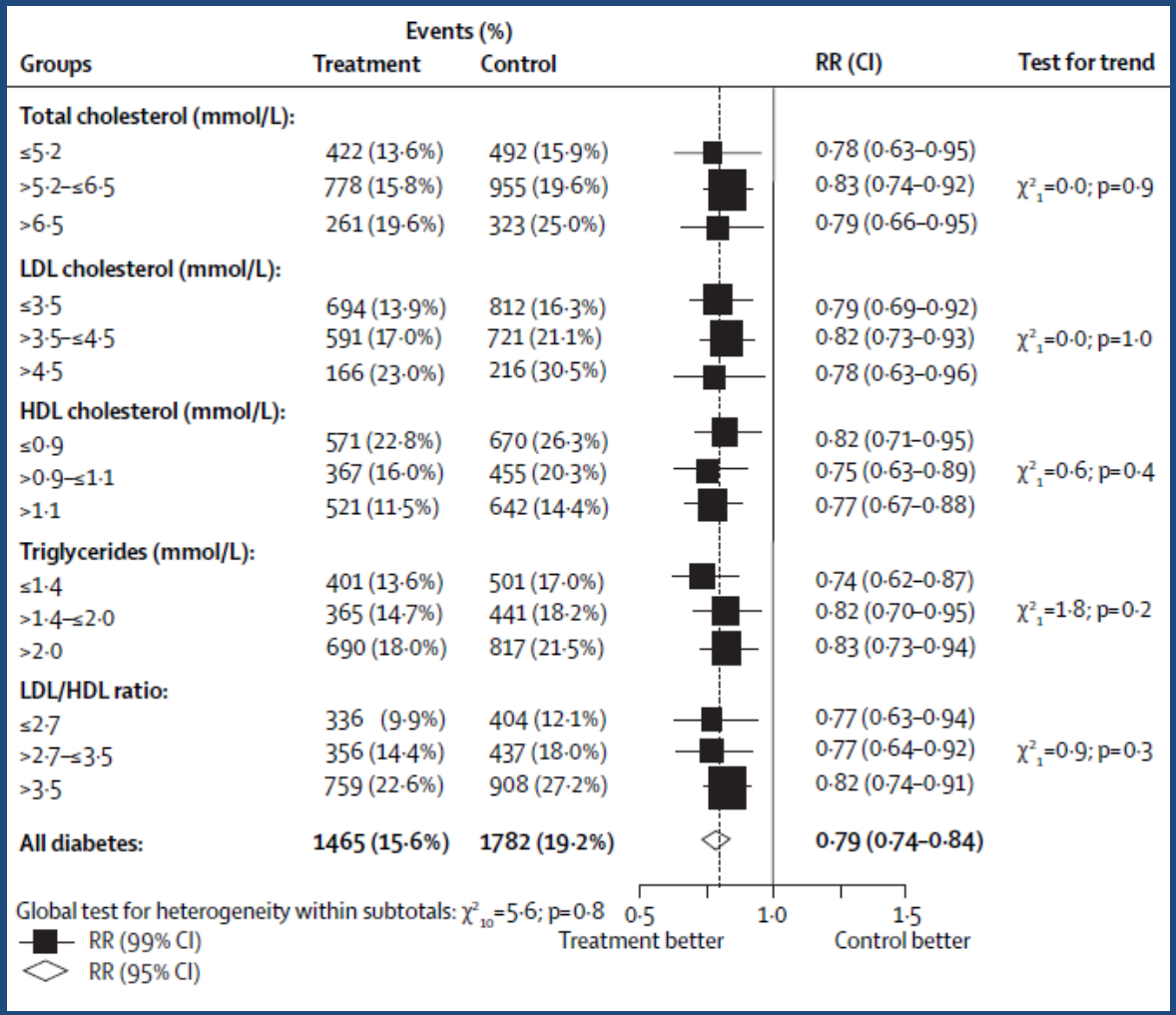


LIPID Study Group. *N Engl J Med.* 1998;339:1349-1357. Sacks FM, et al. *N Engl J Med.* 1996;335:1001-1009.
HPS Collaborative Group. *Lancet.* 2002;360:7-22. Colhoun HM, et al. *Lancet.* 2004:364:685-696.

Metanalisi CTT

Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis

*Cholesterol Treatment Trialists' (CTT) Collaborators**



Groups	Events (%) Treatment	Control	RR (CI)	Test for trend
Total cholesterol (mmol/L):				
≤5·2	422 (13·6%)	492 (15·9%)	0·78 (0·63–0·95)	
>5·2–≤6·5	778 (15·8%)	955 (19·6%)	0·83 (0·74–0·92)	χ^2_1=0·0; p=0·9
>6·5	261 (19·6%)	323 (25·0%)	0·79 (0·66–0·95)	
LDL cholesterol (mmol/L):				
≤3·5	694 (13·9%)	812 (16·3%)	0·79 (0·69–0·92)	
>3·5–≤4·5	591 (17·0%)	721 (21·1%)	0·82 (0·73–0·93)	χ^2_1=0·0; p=1·0
>4·5	166 (23·0%)	216 (30·5%)	0·78 (0·63–0·96)	
HDL cholesterol (mmol/L):				
≤0·9	571 (22·8%)	670 (26·3%)	0·82 (0·71–0·95)	
>0·9–≤1·1	367 (16·0%)	455 (20·3%)	0·75 (0·63–0·89)	χ^2_1=0·6; p=0·4
>1·1	521 (11·5%)	642 (14·4%)	0·77 (0·67–0·88)	
Triglycerides (mmol/L):				
≤1·4	401 (13·6%)	501 (17·0%)	0·74 (0·62–0·87)	
>1·4–≤2·0	365 (14·7%)	441 (18·2%)	0·82 (0·70–0·95)	χ^2_1=1·8; p=0·2
>2·0	690 (18·0%)	817 (21·5%)	0·83 (0·73–0·94)	
LDL/HDL ratio:				
≤2·7	336 (9·9%)	404 (12·1%)	0·77 (0·63–0·94)	
>2·7–≤3·5	356 (14·4%)	437 (18·0%)	0·77 (0·64–0·92)	χ^2_1=0·9; p=0·3
>3·5	759 (22·6%)	908 (27·2%)	0·82 (0·74–0·91)	
All diabetes:	**1465 (15·6%)**	**1782 (19·2%)**	**0·79 (0·74–0·84)**	

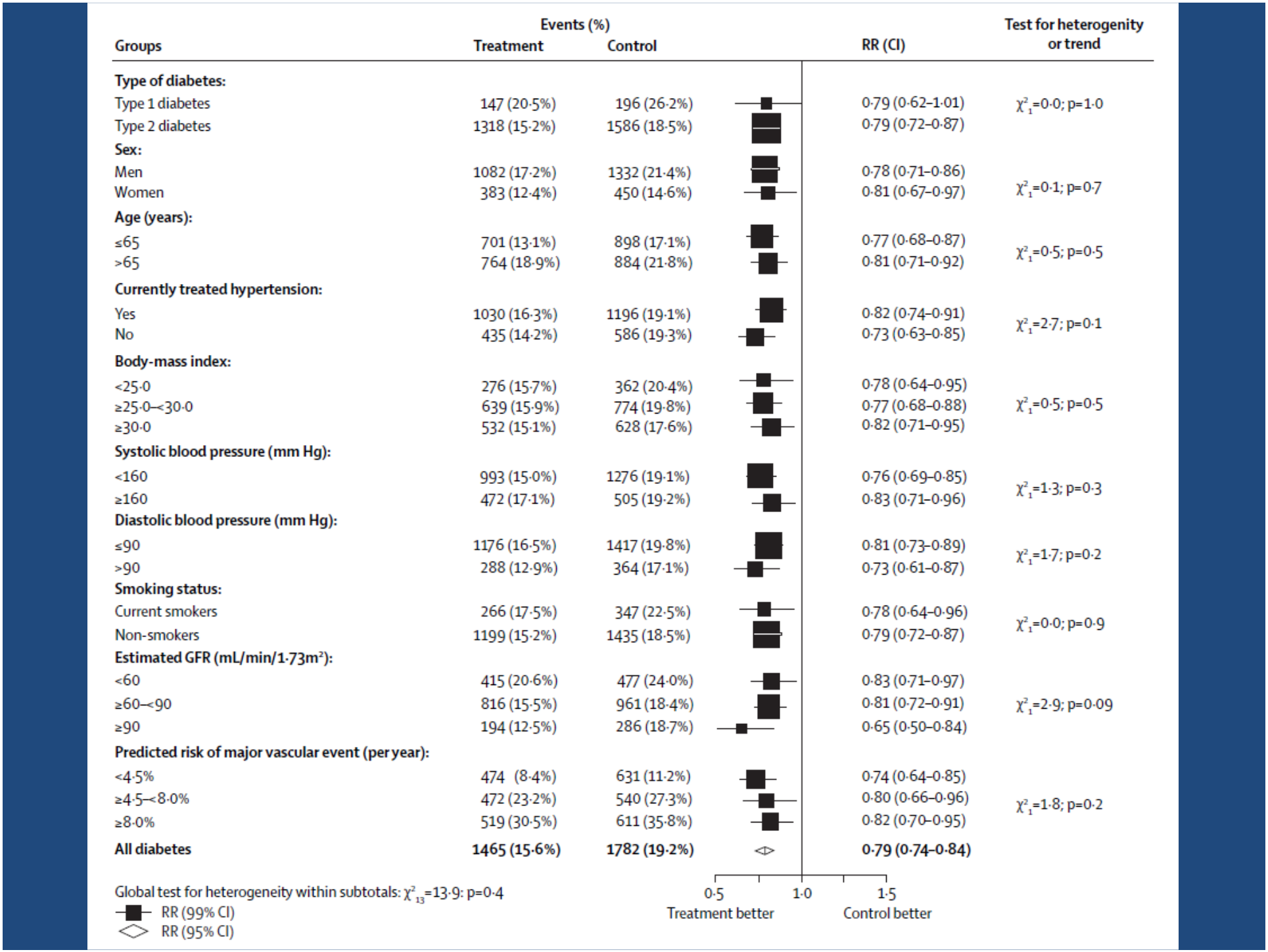
Global test for heterogeneity within subtotals: χ^2_{10}=5·6; p=0·8

0·5 Treatment better — 1·0 — 1·5 Control better

RR (99% CI)

RR (95% CI)

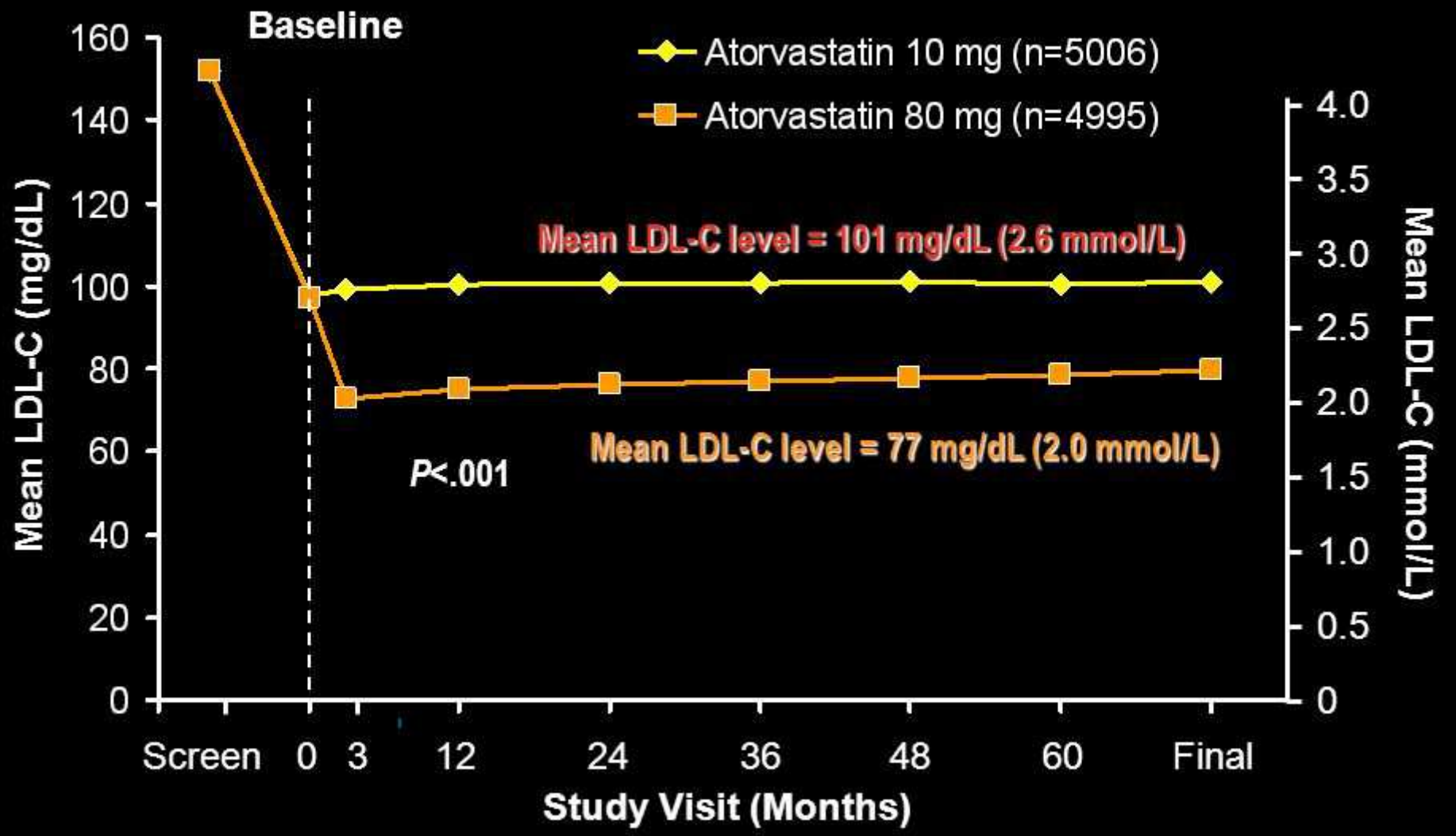
Kearney PM, et al.Lancet 2008;371:117-25


Groups
Events (%)
Treatment
Control
RR (CI)
Test for heterogenity or trend
Type of diabetes:
Type 1 diabetes 147 (20·5%) 196 (26·2%) 0·79 (0·62–1·01) χ²₁=0·0; p=1·0
Type 2 diabetes 1318 (15·2%) 1586 (18·5%) 0·79 (0·72–0·87)
Sex:
Men 1082 (17·2%) 1332 (21·4%) 0·78 (0·71–0·86)
Women 383 (12·4%) 450 (14·6%) 0·81 (0·67–0·97) χ²₁=0·1; p=0·7
Age (years):
≤65 701 (13·1%) 898 (17·1%) 0·77 (0·68–0·87)
>65 764 (18·9%) 884 (21·8%) 0·81 (0·71–0·92) χ²₁=0·5; p=0·5
Currently treated hypertension:
Yes 1030 (16·3%) 1196 (19·1%) 0·82 (0·74–0·91)
No 435 (14·2%) 586 (19·3%) 0·73 (0·63–0·85) χ²₁=2·7; p=0·1
Body-mass index:
<25·0 276 (15·7%) 362 (20·4%) 0·78 (0·64–0·95)
≥25·0–<30·0 639 (15·9%) 774 (19·8%) 0·77 (0·68–0·88) χ²₁=0·5; p=0·5
≥30·0 532 (15·1%) 628 (17·6%) 0·82 (0·71–0·95)
Systolic blood pressure (mm Hg):
<160 993 (15·0%) 1276 (19·1%) 0·76 (0·69–0·85)
≥160 472 (17·1%) 505 (19·2%) 0·83 (0·71–0·96) χ²₁=1·3; p=0·3
Diastolic blood pressure (mm Hg):
≤90 1176 (16·5%) 1417 (19·8%) 0·81 (0·73–0·89)
>90 288 (12·9%) 364 (17·1%) 0·73 (0·61–0·87) χ²₁=1·7; p=0·2
Smoking status:
Current smokers 266 (17·5%) 347 (22·5%) 0·78 (0·64–0·96)
Non-smokers 1199 (15·2%) 1435 (18·5%) 0·79 (0·72–0·87) χ²₁=0·0; p=0·9
Estimated GFR (mL/min/1·73m²):
<60 415 (20·6%) 477 (24·0%) 0·83 (0·71–0·97)
≥60–<90 816 (15·5%) 961 (18·4%) 0·81 (0·72–0·91) χ²₁=2·9; p=0·09
≥90 194 (12·5%) 286 (18·7%) 0·65 (0·50–0·84)
Predicted risk of major vascular event (per year):
<4·5% 474 (8·4%) 631 (11·2%) 0·74 (0·64–0·85)
≥4·5–<8·0% 472 (23·2%) 540 (27·3%) 0·80 (0·66–0·96) χ²₁=1·8; p=0·2
≥8·0% 519 (30·5%) 611 (35·8%) 0·82 (0·70–0·95)
All diabetes 1465 (15·6%) 1782 (19·2%) 0·79 (0·74–0·84)
Global test for heterogeneity within subtotals: χ²₁₃=13·9: p=0·4
RR (99% CI)
RR (95% CI)
0·5
1·0
1·5
Treatment better
Control better

STATINE

- PREVENZIONE SECONDARIA

TNT: Changes in LDL-C by Treatment Group



LaRosa et al. *N Engl J Med.* 2005;352:1425-1435.

HMG-CoA Reductase Inhibitor Evidence: Secondary Prevention

Treating to New Targets (TNT) Trial

10,001 patients with stable CHD randomized to atorvastatin (80 mg) or atorvastatin (10 mg) for 4.9 years

High-dose statin therapy provides benefit in chronic CHD

Helping Cardiovascular Professionals Learn. Advance. Heal.

*Includes CHD death, nonfatal MI, resuscitation after cardiac arrest, or stroke

CHD=Coronary heart disease, CV=Cardiovascular, MI=Myocardial infarction, RRR=Relative risk reduction

Source: LaRosa JC et al. *NEJM* 2005;352:1425-35

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Colesterolo e rischio cardiovascolare: percorso diagnostico-terapeutico in Italia

Paziente in prevenzione cardiovascolare secondaria

Rischio cardiovascolare globale assoluto molto alto

↓

Target lipidico: colesterolo-LDL < 70 mg/dl (o riduzione di colesterolo-LDL ≥ 50%): necessaria statina ad alta intensità, cioè a dosi elevate e potente

↓

Nota 13 AIFA:

Atorvastatina
Simvastatina
Fluvastatina
Lovastatina
Pravastatina

↓

Non raggiungimento del target o evidenza di effetti collaterali severi nei primi 6 mesi di terapia con altre statine?

↓

Rosuvastatina (come seconda scelta)
Statina + ezetimibe (per non raggiungimento del target terapeutico con la dose massima di statina)

Gulizia, M et al. G Ital Card 2017

STATINE: quando sospendere ?

- «Molti studi hanno evidenziato tendenza a sospensione della terapia statinica durante I anno di terapia sia in Prevenzione primaria che secondaria…mancanza di benefici in pazienti dializzati, con Scompenso cardiaco avanzato con grave depressione della FE, età>75 anni senza malattie cardiovascolari» (Mars JC, 2016)

STATINE: quando sospendere?

J Am Geriatr Soc. 2014 November ; 62(11): 2095–2101. doi:10.1111/jgs.13105.

Statin Discontinuation Among Nursing Home Residents with Advanced Dementia

Jennifer Tjia, MD, MSCE[1], Sarah L. Cutrona, MD, MPH[1], Daniel Peterson, MS[1], George Reed, PhD[1], Susan E. Andrade, ScD[1], and Susan L. Mitchell, MD, MPH[2]

Nel 37% dei casi Statine venivano sospese nel primo mese di soggiorno; erano somministrate in paz con DM e Ipertensione Arteriosa, Stroke; causa principale è Polifarmcoterapia; nel 47% dei casi veniva stoppato anche un altro farmaco

LINEE GUIDA e RACCOMANDAZIONI per USO > 75 anni

Table 1

Recommendations about the use of statin therapy in the elderly (> 75 years of age).

ACC/AHA 2013[20, 21]	USPSTF[22]	NLA 2015[23]	ESC/EAS 2016[24, 25]
Primary prevention			
• No recommendations for primary prevention in people > 75 years of age **Note:** "In persons with diabetes who are >75 years of age statin therapy should be individualized on the basis of considerations of ASCVD risk-reduction benefits, the potential for adverse effects and drug–drug interactions, and patient preferences"	• No recommendations	• "Statin-eligible patients should undergo a patient-centered discussion with their provider about the risks and benefits of statin therapy"	• "Statin therapy should be considered in older adults free from CVD, particularly in the presence of hypertension, smoking, diabetes and dyslipidaemia" **Note:** "Since older people often have co-morbidities and have altered pharmacokinetics, lipid-lowering medication should be started at a lower dose and then titrated with caution to achieve target lipid levels that are the same as in younger subjects."

Ruscica M 2018, Eur J Intern Med

LINEE GUIDA e RACCOMANDAZIONI per USO > 75 anni

Secondary prevention			
• Moderate-intensity statin therapy should be considered for individuals >75 years of age with clinical ASCVD" **Note**: consider adverse effects, drug–drug interactions, and patient preferences	• No recommendations	• "Patients who are >75 to <80 years of age may be treated with similar regimens after a careful consideration of the risk-benefit ratio of such therapy" • "In patients ≥80 years of age, moderate intensity statin therapy should be considered based upon a provider-patient discussion of the risks and benefits of such therapy"	• "Treatment with statins is recommended for older adults with established CVD in the same way as for younger patients" **Note:** "Since older people often have co-morbidities and have altered pharmacokinetics, lipid-lowering medication should be started at a lower dose and then titrated with caution to achieve target lipid levels that are the same as in younger subjects."

Ruscica M 2018, Eur J Intern Med

TRIALS e BENEFICI delle STATINE per ETA'

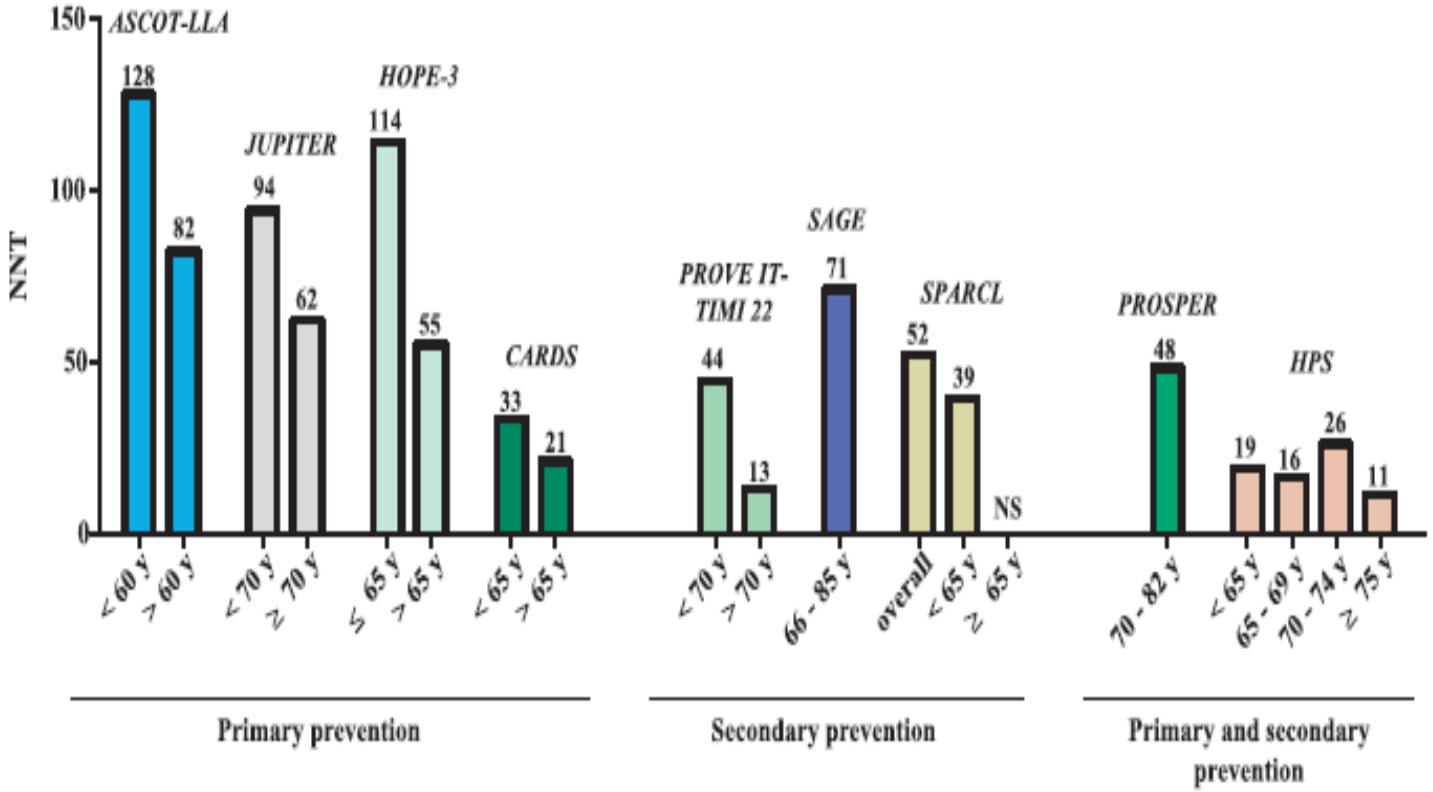


Fig. 1. Graphic representation of the number needed to treat (NNT) for each randomized controlled trial (RCT) described in this review. For each RCT the NNT has been graphically depicted accordingly to the different age-group. Y axis reports NNT whereas X axis reports ages; ALLHAT-LLT trial shows no-significant reduction in mortality. y, years; NS, not significant.

Ruscica M 2018, Eur J Intern Med

LOW-, MODERATE-, HIGH-INTENSITY

Table 2
Statin dose intensity as defined by 2013 ACC/AHA Adult Cholesterol Guidelines.

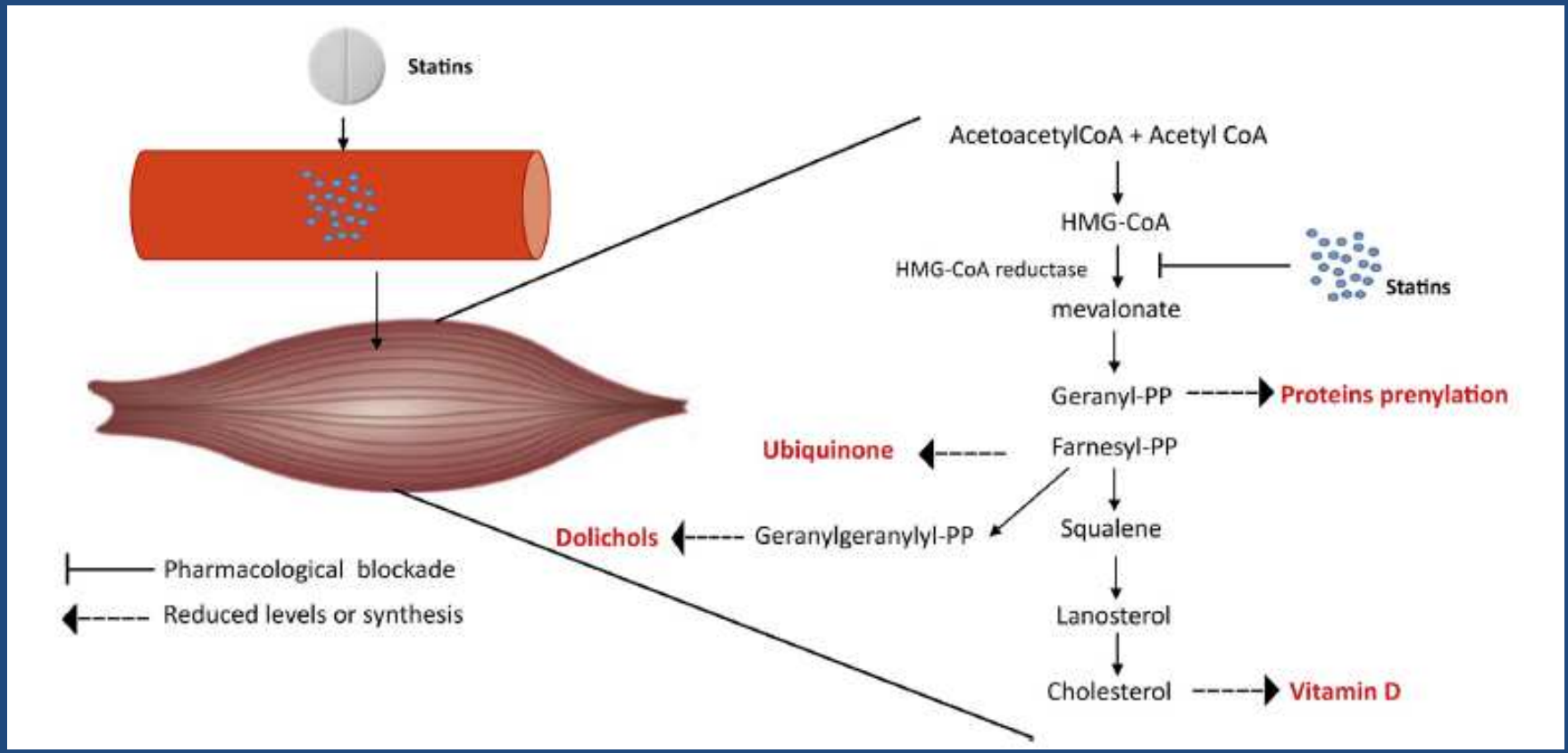
Statin	Low-intensity	Moderate-intensity	High-intensity
Atorvastatin		10–20 mg	40–80 mg
Rosuvastatin		5–10 mg	20–40 mg
Simvastatin	10 mg	20–40 mg	
Pravastatin	10–20 mg	40–80 mg	
Lovastatin	20 mg	40 mg	
Fluvastatin	20–40 mg	40 mg BID	
Fluvastatin XL		80 mg	
Pitavastatin	1 mg	2–4 mg	

Ruscica M 2018, Eur J Intern Med

STATINE: EFFETTI COLLATERALI

- MIALGIE
- RABDOMIOLISI
- EPATOPATIA
- DIABETE MELLITO (>insulinoresistenza, Rosuvastatina)
- PROTEINURIA
- CATARATTA (controverso)
- Altri effetti identificati solo a livello sperimentale su Statine idrofobe (atorvastatina) e disfunzione mitocondriale delle cellule endoteliali (Broniarek I, 2018)

ETIOPATOGENESI DELLA RABDOMIOLISI DA STATINE



Norata GD et al. Pharmacological Research 88 (2014) 107–113

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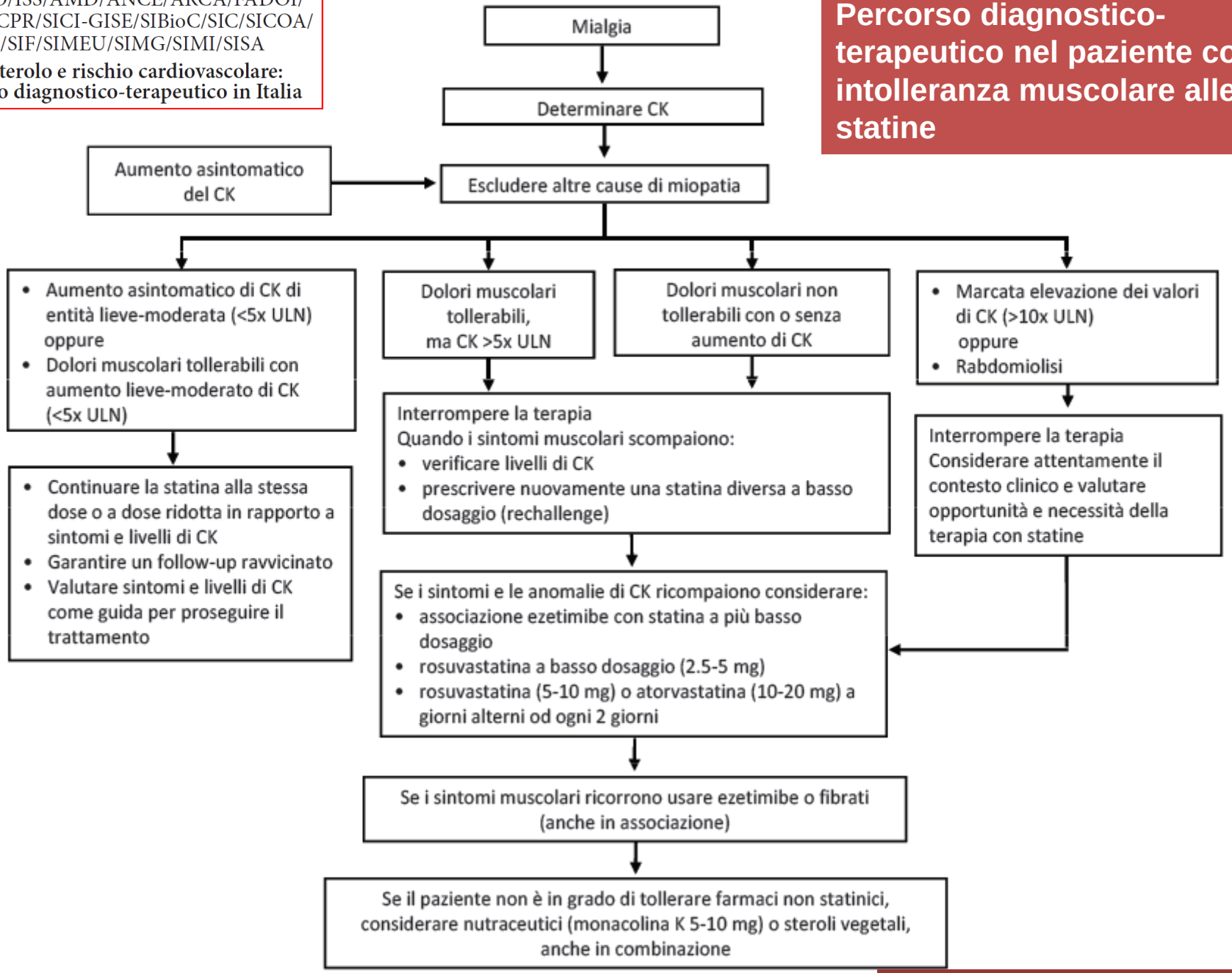
Colesterolo e rischio cardiovascolare: percorso diagnostico-terapeutico in Italia

Percorso diagnostico-terapeutico nel paziente con intolleranza muscolare alle statine



Gulizia, M et al. G Ital Card 2017

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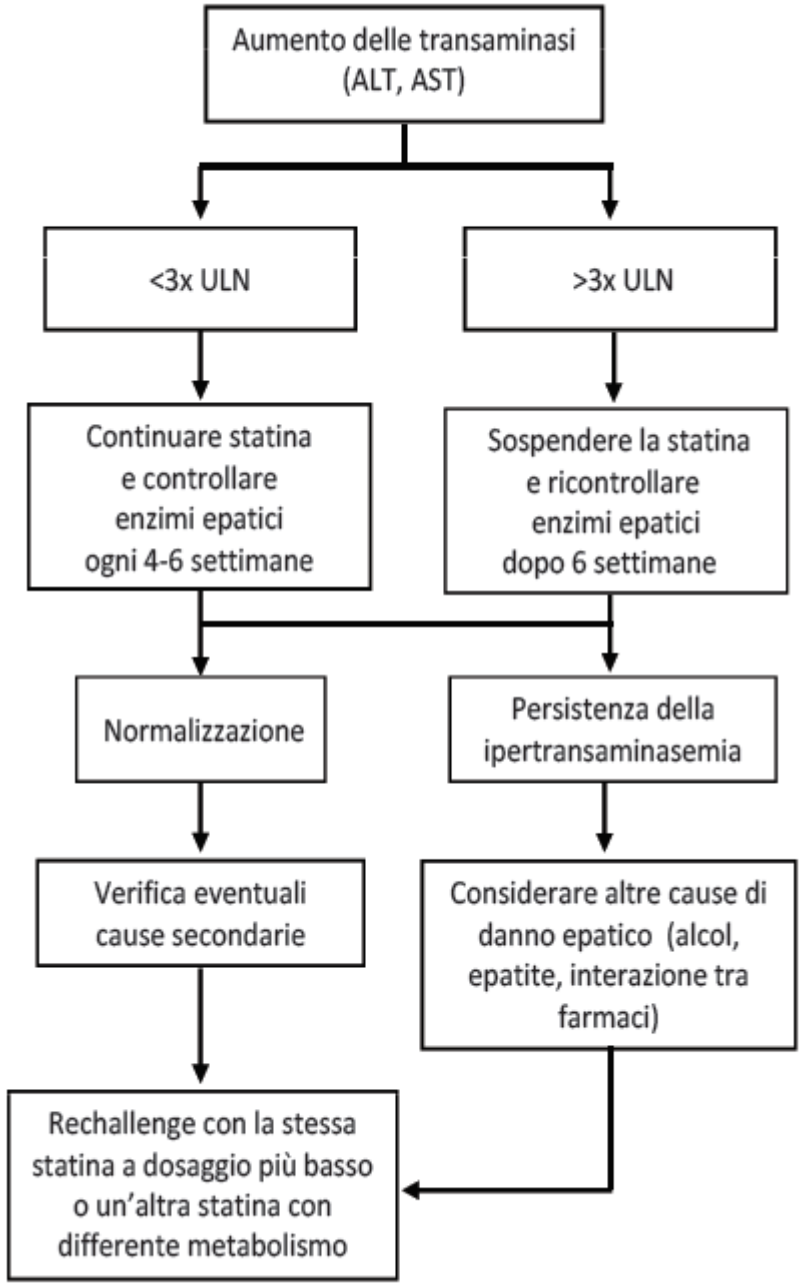
SID/SIF/SIMEU/SIMG/SIMI/SISA

Colesterolo e rischio cardiovascolare: percorso diagnostico-terapeutico in Italia

Percorso diagnostico-terapeutico nel paziente con intolleranza ***epatica*** alle statine



Gulizia, M et al. G Ital Card 2017

STATINE e RISCHIO di DIABETE MELLITO

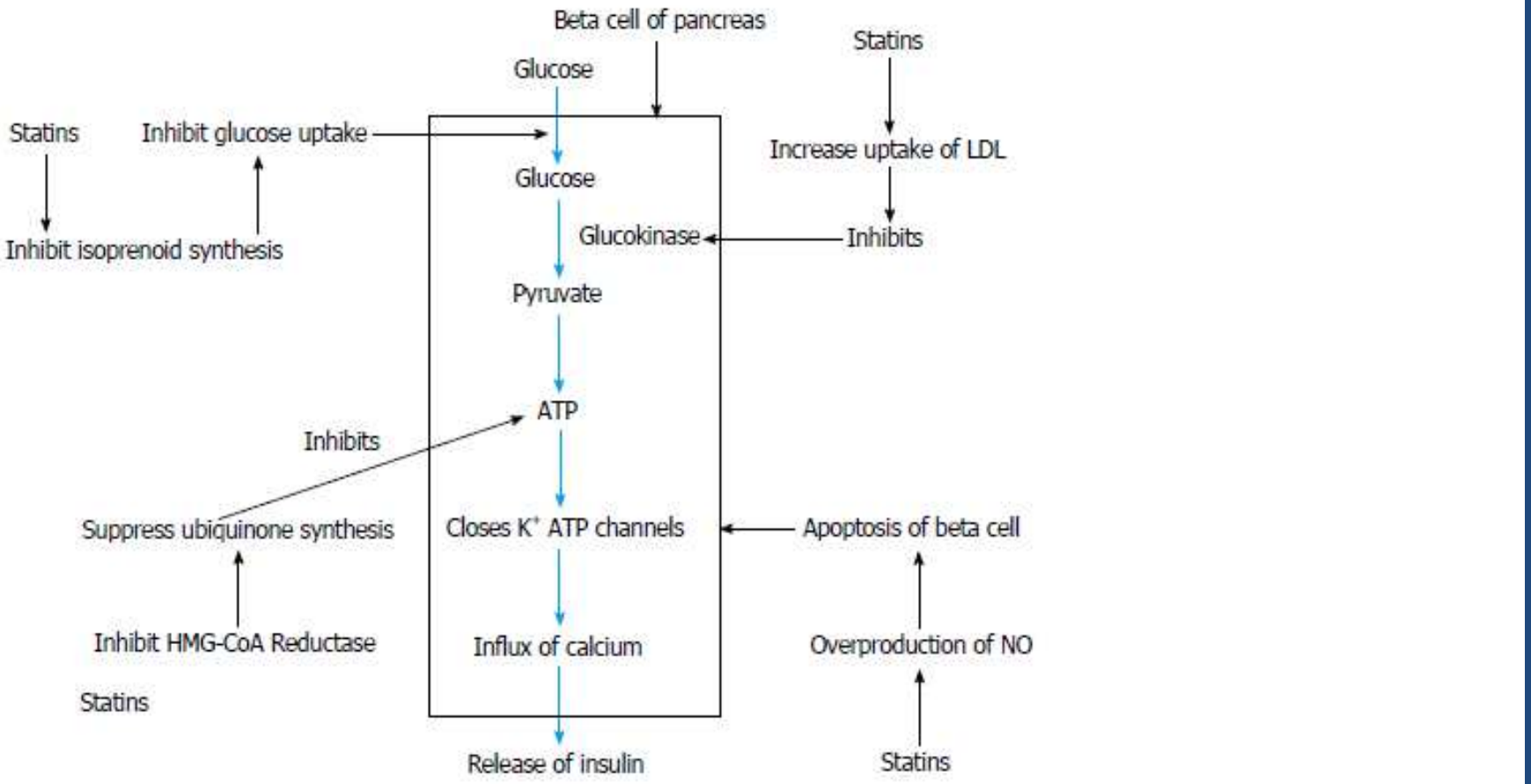


Figure 1 Actions of statins on beta cell of pancreas[43]. HMG-CoA: 3-hydroxy-methylglutaryl coenzyme A; NO: Nitric oxide; LDL: Low density lipoprotein.

Chogtu B 2015, World J Diabetes

STATINE e NON ADERENZA

THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2018, Vol. 00, No. 00, 1–8
doi:10.1093/gerona/glx256
Advance Access publication January 19, 2018

OXFORD

Review

A Systematic Review and Meta-analysis of the Factors Associated With Nonadherence and Discontinuation of Statins Among People Aged ≥65 Years

STATINE e NON ADERENZA

- Fattori correlati con Non Aderenza: età avanzata, comorbilità non vascolari (Depressione, BPCO,Asma, Demenza, Tumori), scarsa percezione del rischio (specie in pazienti in Prevenzione Primaria)