3° Congresso Nazionale

ORGANI DI SENSO, NEUROINFIAMMAZIONE e NEURODEGENERAZIONE

14-16 maggio 2024

LA DISLIPIDEMIA: TRA PREVENZIONE E NUOVE TERAPIE

Obiettivi preventivi e terapeutici nell'anziano

Prof. P. Abete

Dipartimento di Scienze Mediche Traslazionali

Università di Napoli Federico II

Journal of the American College of Cardiology
© 2014 The Expert Panel Members
Published by Elsevier Inc.

Vol. 63, No. 25, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.11.002

PRACTICE GUIDELINE

2013 ACC/AHA Guideline on the

CrossMark

CLINICAL PRACTICE GUIDELINE: EXECUTIVE SUMMARY

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the

esterol:

iation

ESC European Society of Cardiology

European Heart Journal (2020) **41**, 111–188
doi:10.1093/eurheartj/ehz455

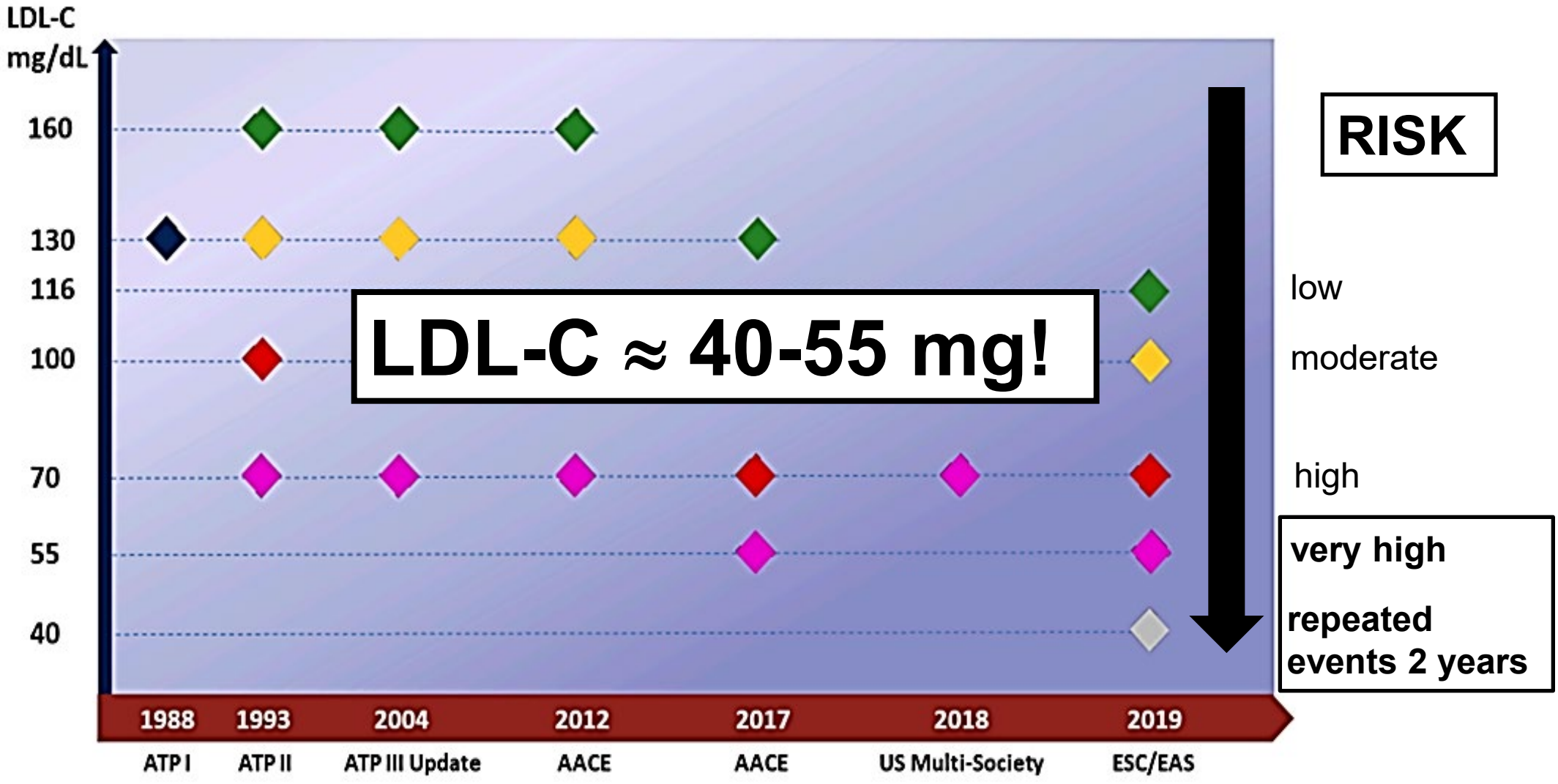
ESC/EAS GUIDELINES

ESC Guidelines 25 YEARS

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

LDL-C goals evolution across guidelines over time



Agnello F et al. Journal of Clinical Medicine 2024

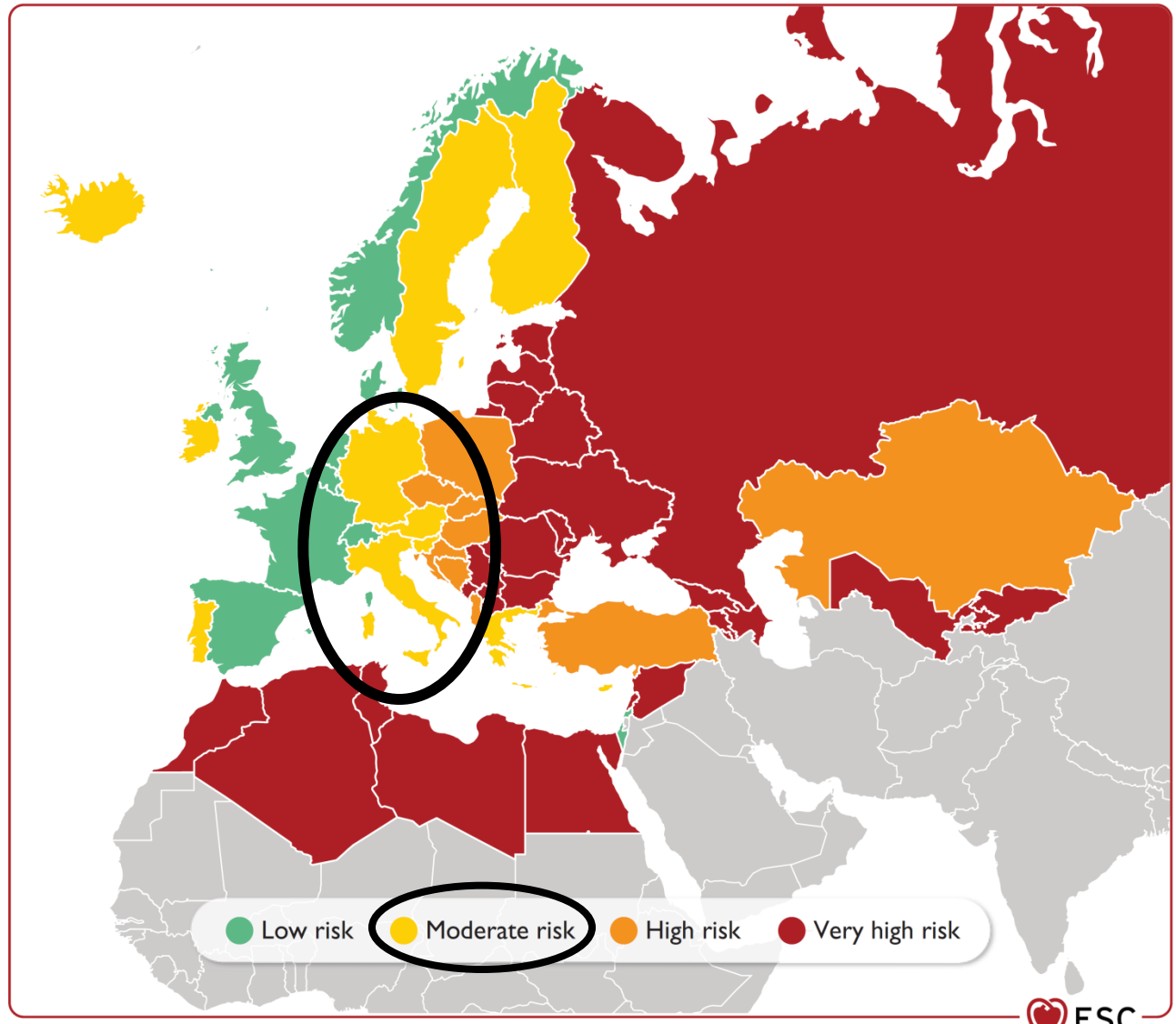
SIONG
SOCIETÀ ITALIANA
OTONEUROGERIATRIA

LA DISLIPIDEMIA: TRA PREVENZIONE E NUOVE TERAPIE

Obiettivi preventivi e terapeutici nell'anziano

- **Cholesterol, ageing and risk score**
- Primary and secondary prevention
- Nonadherence and discontinuation
- Focus on newer agents
- Frail elderly: the "catabolic" syndrome

Risk regions based on World Health Organization cardiovascular mortality rates



2019 ESC/EAS Guidelines

Cardiovascular risk categories

VERY HIGH RISK PATIENT	**People with any of the following:** – ***Documented AtheroSclerotic CardioVascular Disease (ASCVD),*** either clinical or unequivocal on imaging. Documented ASCVD includes previous Acute Coronary syndrome (ACS) MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, andperipheral arterial disease.. – ***Diabetes Mellitus*** with target organ damage,a or at least three majorrisk factors, or early onset of T1DM of long duration(>20 years). – ***Severe Chronic Kidney Disease*** (eGFR <30 mL/min/1.73 m2). – **Familiar Hypercholsterolemia with ASCVD or with another major risk factor**.

A calculated SCORE ≥ 10% for 10-year risk of fatal ASCVD!

2019 ESC/EAS Guidelines for the Management of Dyslipidaemias

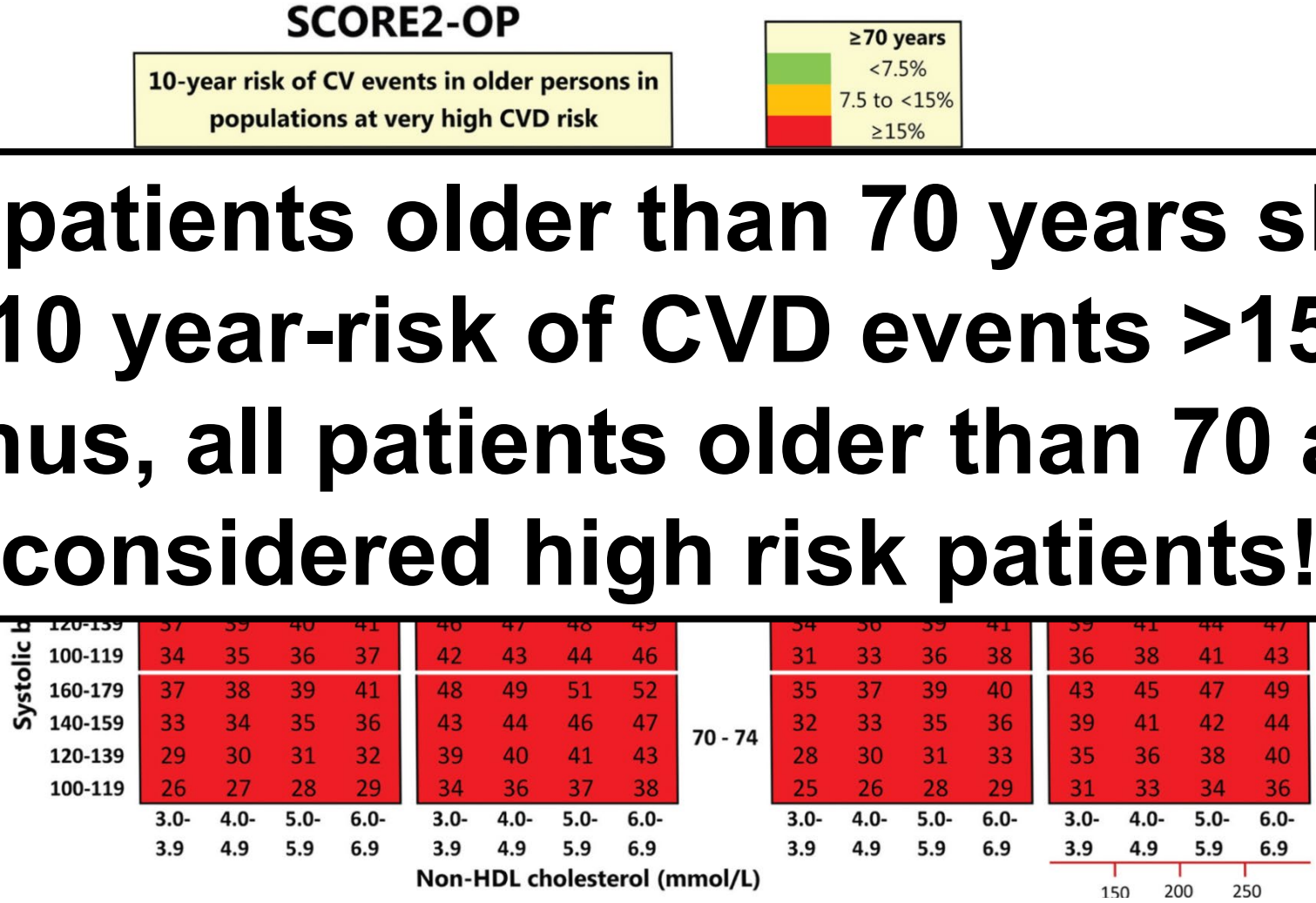
Prevalence of CVD risk factors (%) by age and sex in the Framingham Study

Age	ECG-LVH[a]	ECG-LVH	DM[b]	DM	HT[c]	HT
	M	F	M	F	M	F
55–64	2.7	1.7	5.5	4.2	26.8	31.5
65–74	3.6	3.2	10.9	7.2	38.0	47.6
75–84	4.2	4.9	13.2	10.2	48.4	59.9
85–94	5.9	9.4	14.2	11.1	47.8	65.6

Abbreviations: CVD, cardiovascular disease; ECG, electrocardiographic evidence; LVF, left ventricular hypertrophy; DM, diabetes mellitus; HT, hypertension; M, male; F, female.

Petersen LK et al. Age & Ageing 2010

SCORE2-Older People risk prediction algorithms: estimating incident cardiovascular event risk in older persons



All patients older than 70 years show a 10 year-risk of CVD events >15%. Thus, all patients older than 70 are considered high risk patients!!

SCORE2-OP working group and ESC Cardiovascular risk collaboration 2021

Intervention strategies as a function of total cardio-vascular risk and untreated low-density lipoprotein cholesterol levels Primary prevention

	Total CV risk (SCORE) %	Untreated LDL-C levels					
		<1.4 mmol/L (55 mg/dL)	1.4 to <1.8 mmol/L (55 to <70 mg/dL)	1.8 to <2.6 mmol/L (70 to <100 mg/dL)	2.6 to <3.0 mmol/L (100 to <116 mg/dL)	3.0 to <4.9 mmol/L (116 to <190 mg/dL)	≥4.9 mmol/L (≥190 mg/dL)
Primary prevention	<1, low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if	Lifestyle intervention and concomitant drug
	Class[a]/Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A	I/A
	≥10, or at very-high risk due to a risk condition (see *Table 4*)	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention

"PRIMARY" prevention consider adding drug in very-high risk patient

Low-Density Lipoprotein-Cholesterol from 55 to 70 mg%

2019 ESC/EAS Guidelines

Intervention strategies as a function of total cardio-vascular risk and untreated low-density lipoprotein cholesterol levels Secondary prevention

Total CV risk (SCORE) %	Untreated LDL-C levels					
	<1.4 mmol/L (55 mg/dL)	1.4 to <1.8 mmol/L (55 to <70 mg/dL)	1.8 to <2.6 mmol/L (70 to <100 mg/dL)	2.6 to <3.0 mmol/L (100 to <116 mg/dL)	3.0 to <4.9 mmol/L (116 to <190 mg/dL)	≥4.9 mmol/L (≥190 mg/dL)

SECONDARY prevention consider adding drug in very-high risk patient

Low-Density Lipoprotein-Cholesterol lower than 55 mg%!

2019 ESC/EAS Guidelines

SIONG
SOCIETÀ ITALIANA
OTONEUROGERIATRIA

LA DISLIPIDEMIA: TRA PREVENZIONE E NUOVE TERAPIE

Obiettivi preventivi e terapeutici nell'anziano

- Cholesterol, ageing and risk score
- **Primary and secondary prevention**
- Nonadherence and discontinuation
- Focus on newer agents
- Frail elderly: the "catabolic" syndrome

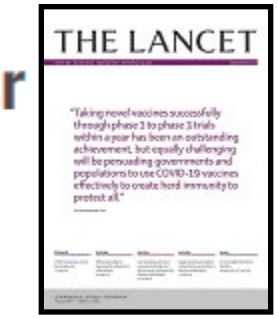
Drugs for treatment of dyslipidaemias

DRUG	Mechanism of action
Statin	Inhibition of HMG-CoA reductase
Ezetimibe	Cholesterol absorption inhibitor
Evolocumab, Alirocumab	Humanized monoclonal antibody against PCSK9
Inclisiran	siRNA against PCK9 Mrna
Evinacumab	Humanized monoclonal antibody against ANGPTL3
Bempedoic Acid	ACL inhibitor

Abbreviations: HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; PCSK9, proprotein convertase subtilisin/ kexin type 9; siRNA, small-interfering ribonucleic acid; mRNA, messenger ribonucleic acid; ANGPTL3, angiopoietin-like 3; ACL, adenosine triphosphate citrate lyase;

Agnello F et al. Journal of Clinical Medicine 2024

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

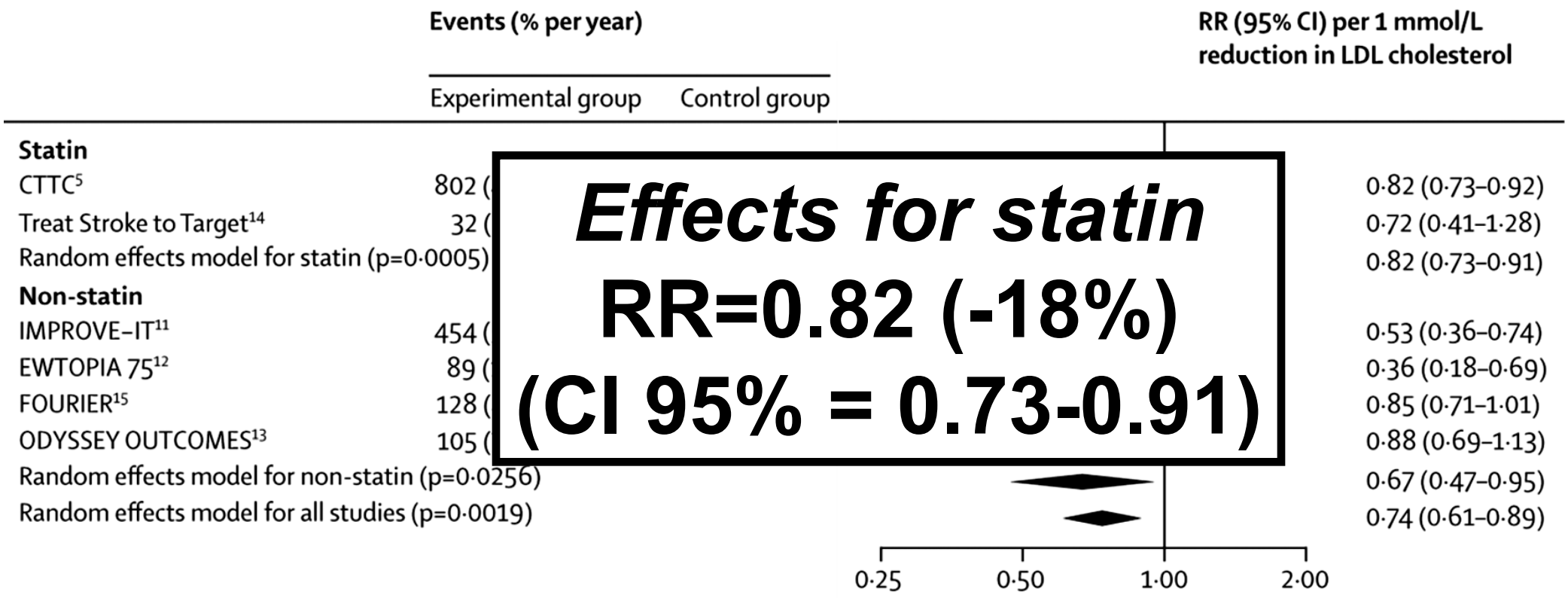


Baris Gencer, Nicholas A Marston, KyungAh Im, Christopher P Cannon, Peter Sever, Anthony Keech, Eugene Braunwald, Robert P Giugliano, Marc S Sabatine

- 24 trials from the Cholesterol Treatment Trialists' Collaboration meta-analysis plus five individual trials.
- Among 244.090 patients from 29 trials, **21.492 (8.8%) were aged at least 75 years.**
- Median follow-up ranged from 2·2 years to 6·0 years.
- Participants with heart failure or on dialysis were excluded.
- Tisk ratio (RR) for major vascular events (a composite of cardiovascular death, myocardial infarction or other acute coronary syndrome, stroke, or coronary revascularisation) **per 1 mmol/L reduction in LDL cholesterol**.

Gencer B et al., Lancet 2020

Effect of LDL cholesterol lowering on the risk of major vascular events *with "statin" and "non-statin" treatment in older patients "PRIMARY PREVENTION"*



Effects for statin

RR=0.82 (-18%)

(CI 95% = 0.73-0.91)

Gencer B et al., Lancet 2020

Effects on major vascular events per mmol/L reduction in LDL cholesterol, subdivided by age at randomisation

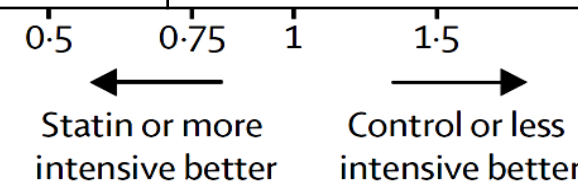
"*SECONDARY PREVENTION*"

Events (% per annum)

RR (CI) per 1 mmol/L reduction in LDL cholesterol

Statin or more intensive | Control or less intensive

Age (yr)	RR	95% CI
> 60 to ≤70	0.79(-22%)	(0.73-0.86)
> 70 to ≤75	0.80 (-20%)	(0.73-0.88)
>75	0.85 (-15%)	(0.73-0.98)



Cholesterol Treatment Trialists' Collaboration Lancet 2019

SIONG
SOCIETÀ ITALIANA
OTONEUROGERIATRIA

LA DISLIPIDEMIA: TRA PREVENZIONE E NUOVE TERAPIE

Obiettivi preventivi e terapeutici nell'anziano

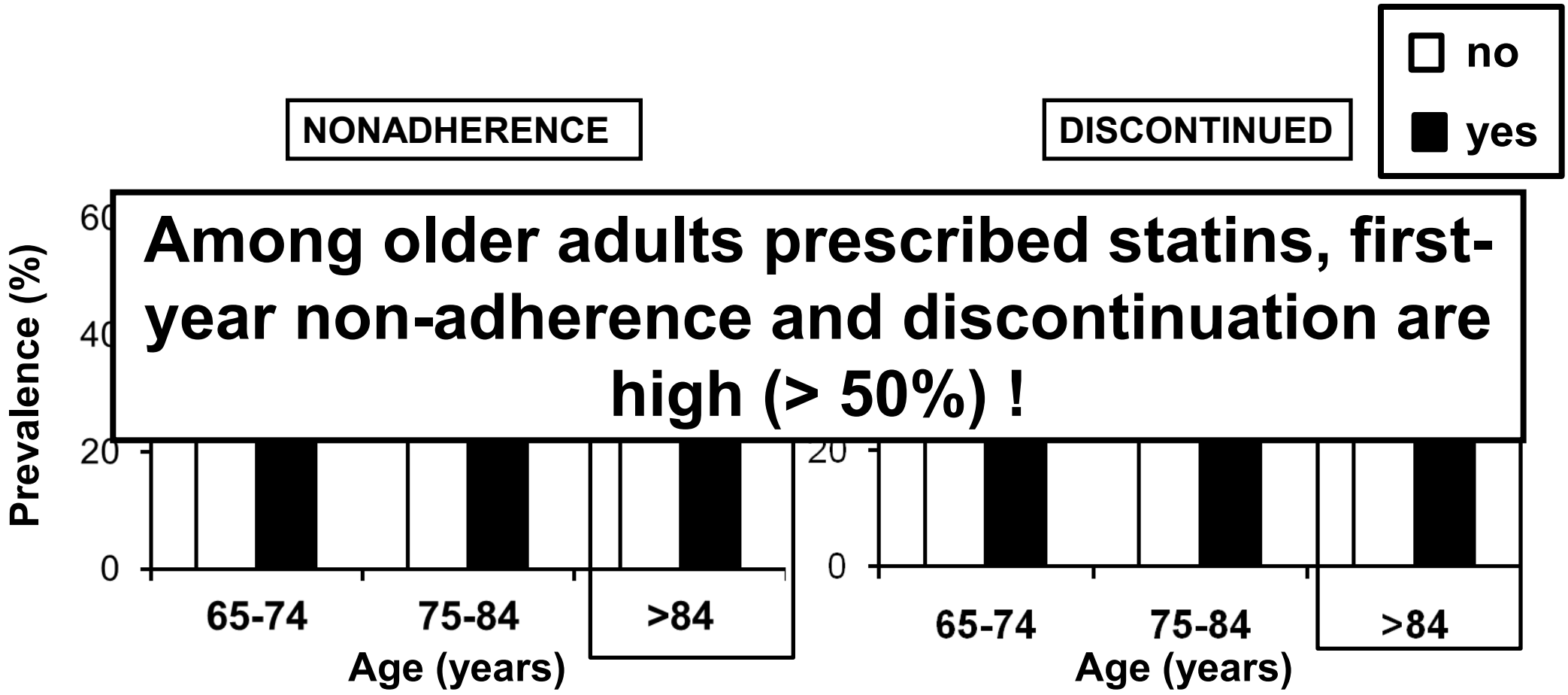
- Cholesterol, ageing and risk score
- Primary and secondary prevention
- **Nonadherence and discontinuation**
- Focus on newer agents
- Frail elderly: the "catabolic" syndrome

Drugs for treatment of dyslipidaemias
Adverse Reactions

DRUG	Mechanism of action
Statin	**Muscle toxicity** (myalgia, myopathy, myositis, rhabdomyolysis), transaminase elevation with rare risk for liver toxicity, risk for new-onset diabete
Ezetimibe	Arthralgia, diarrhea, **upper respiratory tract infections**
Evolocumab, Alirocumab	Injection-site reactions, **nasopharyngitis**, influenza
Inclisiran	Injection-site reactions, arthralgia, **urinary tract infections**, diarrhea, bronchitis, pain in extremity, dyspnea
Evinacumab	Flu-like symptoms, **nasopharyngitis**, dizziness, rhinorrhea, nausea
Bempedoic Acid	Hyperuricemia, gout, cholelithiasis, **upper respiratory tract infections**, muscle spasms, back pain, abdominal pain, pain in extremity, bronchitis, anemia, elevated liver enzymes

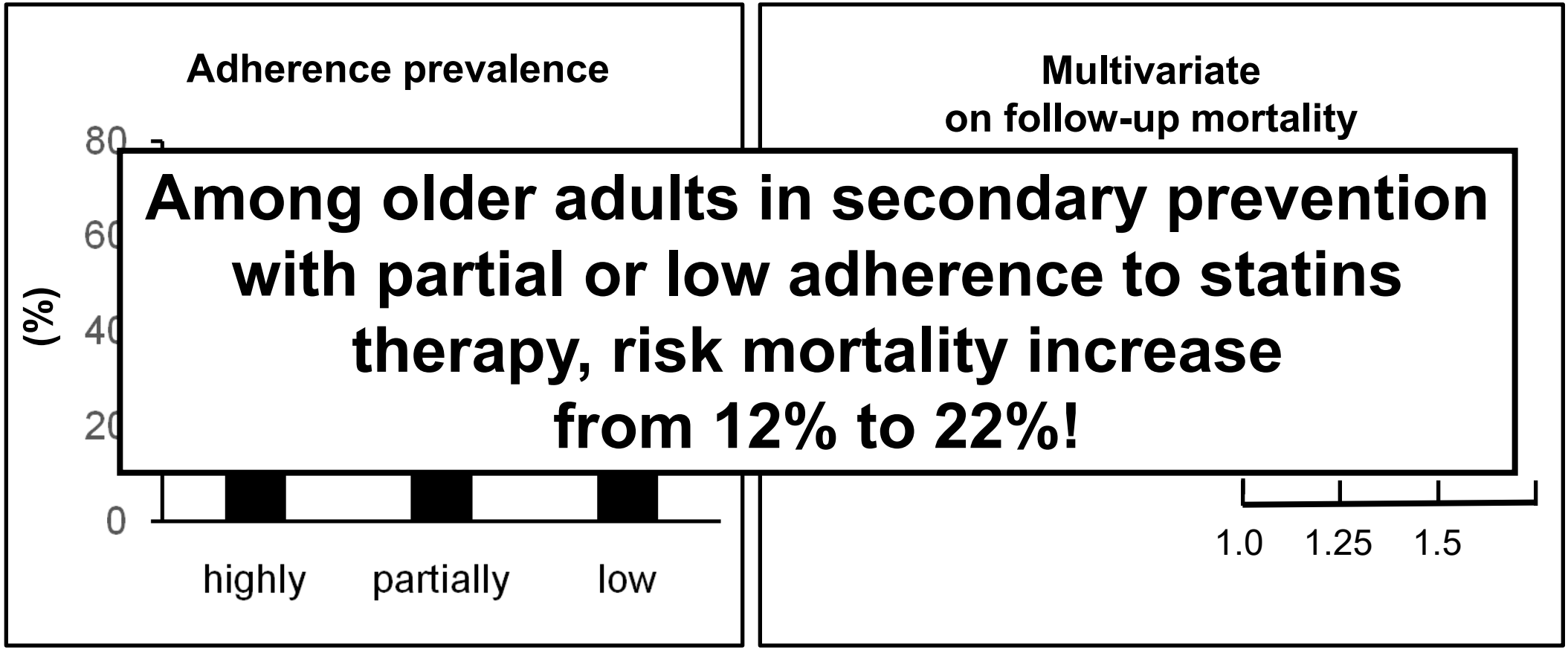
Agnello F et al. Journal of Clinical Medicine 2024

Predictors of first-year nonadherence and discontinuation of statins among older adults: a retrospective cohort study



Ofori-Asenso R et al., Br J Pharmacol 2019

Statin adherence and mortality in patients aged 80 years and older after acute myocardial infarction



Among older adults in secondary prevention with partial or low adherence to statins therapy, risk mortality increase from 12% to 22%!

Phan DQ et al., JAGS 2019

SIONG
SOCIETÀ ITALIANA
OTONEUROGERIATRIA

LA DISLIPIDEMIA: TRA PREVENZIONE E NUOVE TERAPIE

Obiettivi preventivi e terapeutici nell'anziano

- Cholesterol, ageing and risk score
- Primary and secondary prevention
- Nonadherence and discontinuation
- **Focus on newer agents**
- Frail elderly: the "catabolic" syndrome

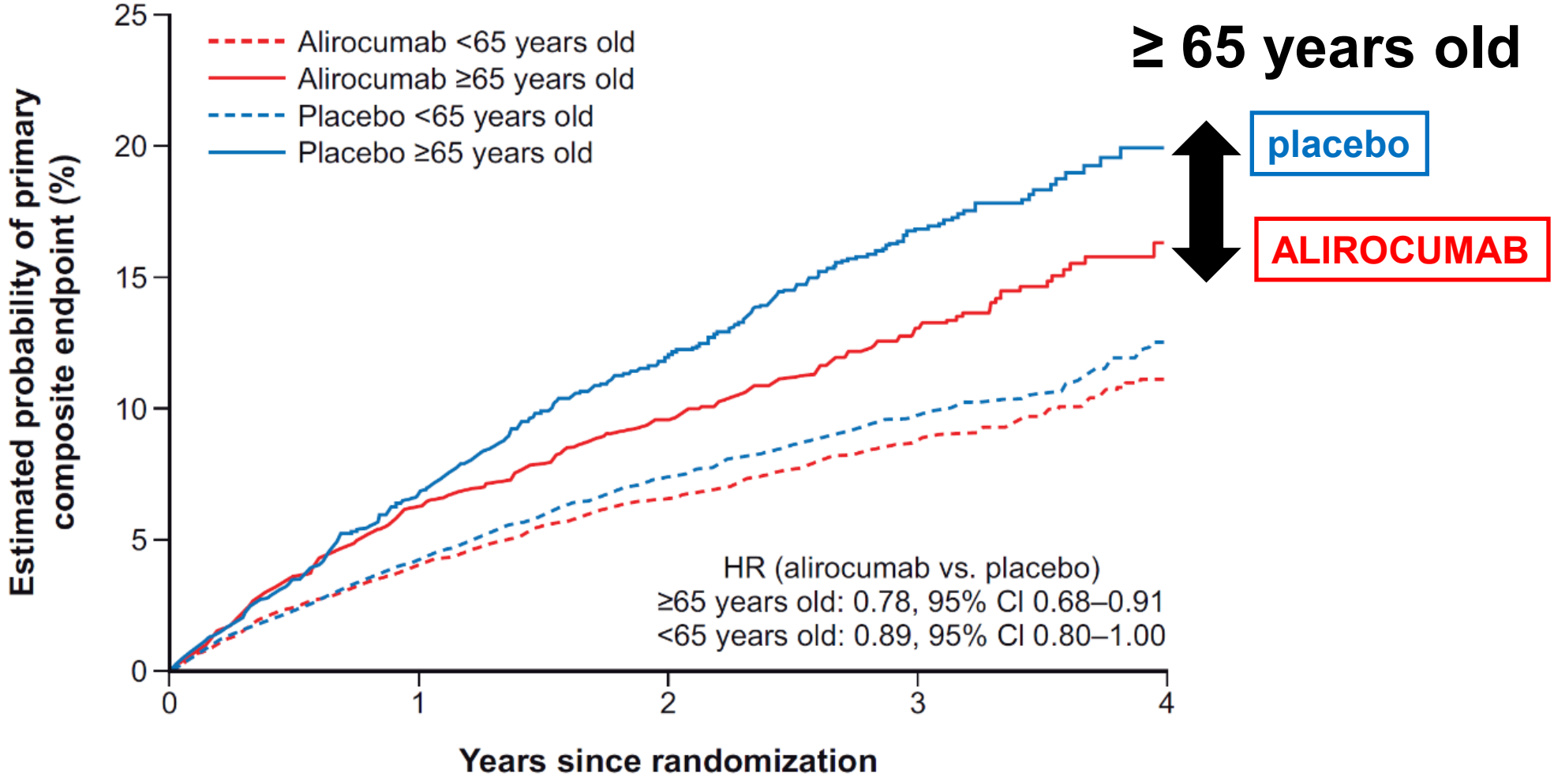
LDL-cholesterol lowering with EVOLOCUMAB, and outcomes according to age and sex in patients "FOURIER Trial"

Double blind trial, comparing evolocumab with placebo in 27,564 patients with atherosclerotic cardiovascular disease receiving statin therapy (median follow-up 2.2 years).

The relative efficacy of EVOLOCUMAB was consistent regardless of patient age both for the primary (-14%) and secondary (-18%)

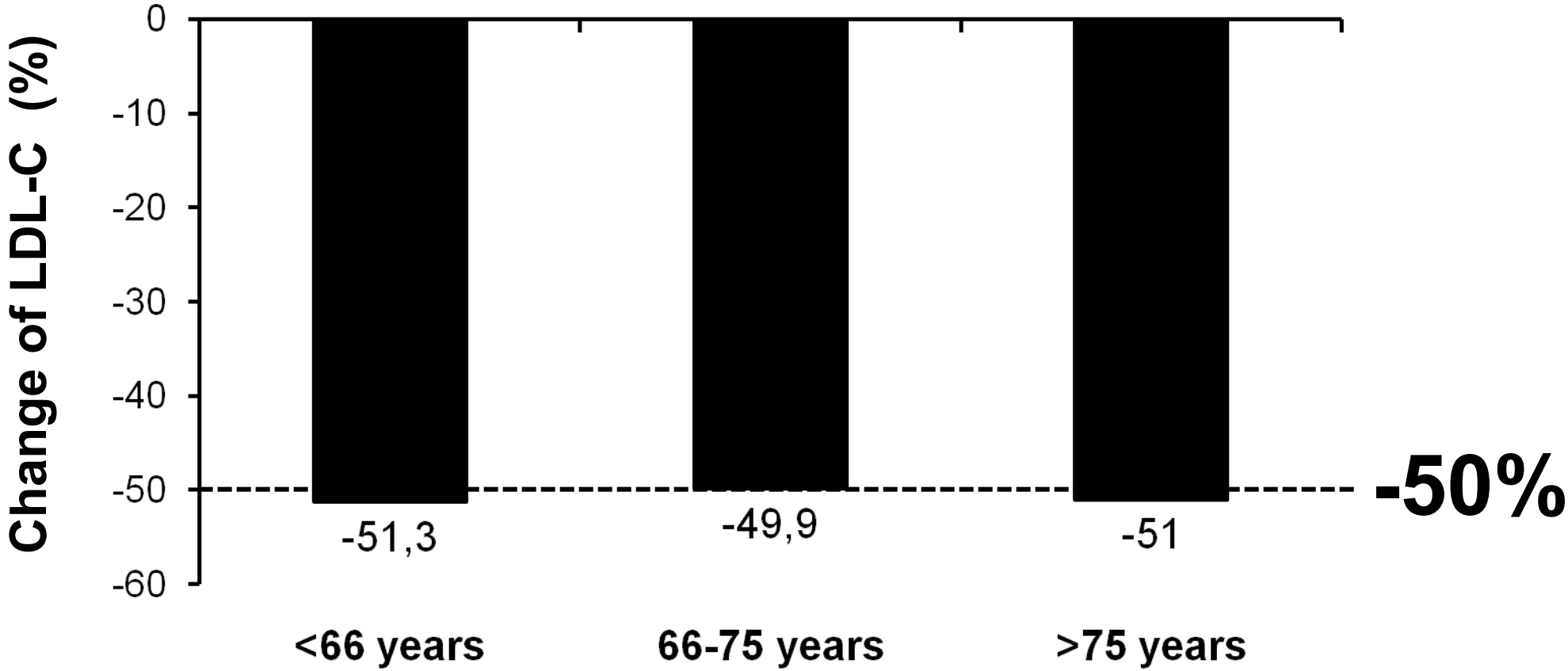
	Age >56–63	3493	344	12.84	3661	409	13.56	0.88 (0.76–1.01)	0.077	
	Age >63–69	3512	315	11.81	3543	381	14.32	0.82 (0.71–0.95)	0.009	
	Age >69	3178	331	13.58	3055	366	15.62	0.86 (0.74–0.99)	0.049	
Secondary: endpoint	Age ≤56	3601	188	6.69	3521	243	9.33	0.74 (0.61–0.89)	0.002	0.813
	Age >56–63	3493	197	7.71	3661	249	8.84	0.83 (0.69–0.99)	0.047	
	Age >63–69	3512	191	7.57	3543	244	9.50	0.78 (0.65–0.94)	0.010	
	Age >69	3178	240	9.93	3055	277	12.42	0.82 (0.69–0.98)	0.029	

Effect of ALIROCUMAB on cardiovascular outcomes after acute coronary syndromes according to age "ODYSSEY trial"



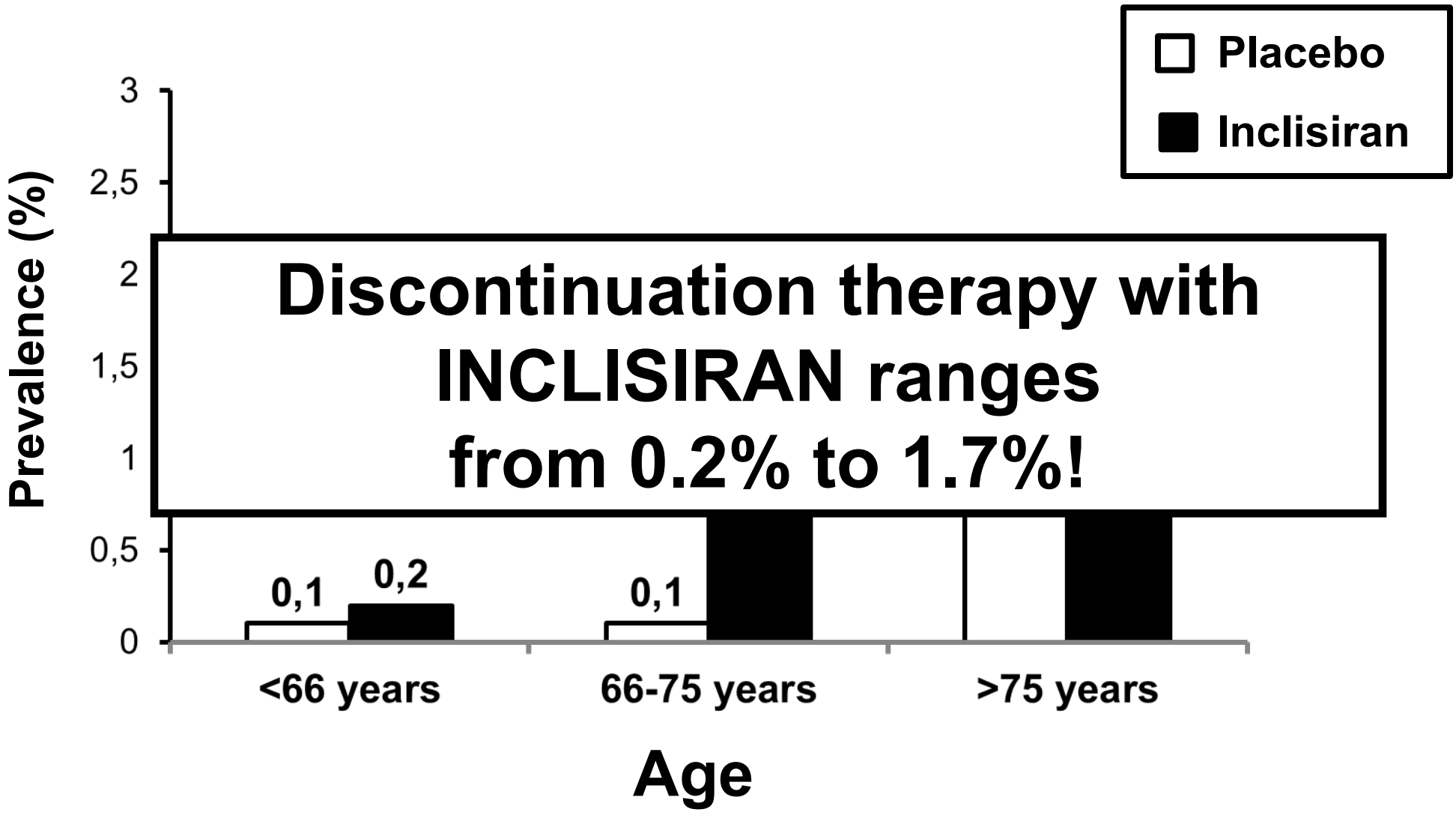
Sinnaeve PR et al., Eur Heart J 2020

Efficacy and safety of INCLISIRAN according to age: a pooled analysis of phase III studies (ORION 9, 10 e 11)



Wright RSR et al, abstract AHA 2020

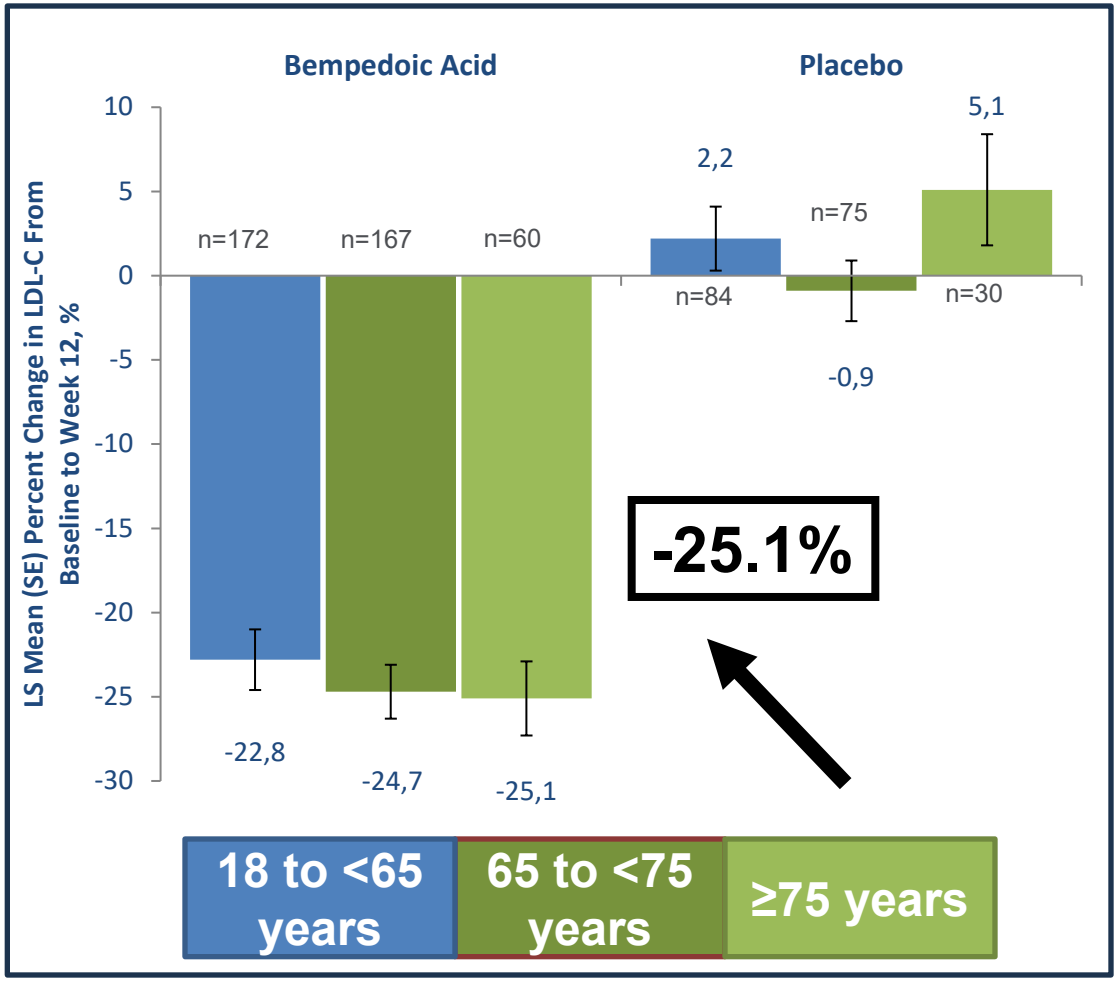
Patients with at least one event leading to drug discontinuation receiving placebo or INCLISIRAN



BEMPEDOIC ACID safety analysis
Pooled data from four phase 3 clinical trials

Δ LDL-C from Baseline a 12 settimane

Statin Intolerant Pool



Age, years	Placebo-corrected difference (95% CI)
18 to <65 years	**-25.0 (-30.3, -19.7)**
65 to <75 years	**-23.9 (-28.6, -19.2)**
≥75 years	**-30.2 (-38.8, -21.5)**

Age group and treatment Interaction p=0.51

Bays HE et al., Journal of Clinical Lipidology, 2020

SIONG
SOCIETÀ ITALIANA
OTONEUROGERIATRIA

LA DISLIPIDEMIA: TRA PREVENZIONE E NUOVE TERAPIE

Obiettivi preventivi e terapeutici nell'anziano

- Cholesterol, ageing and risk score
- Primary and secondary prevention
- Nonadherence and discontinuation
- Focus on newer agents
- **Frail elderly: the "catabolic" syndrome**

Guideline recommendations of of Lipid Lowering Drugs (LLD) treatment in the elderly

Guideline	Primary prevention	Secondary Prevention
ESC 2019	Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients. Initiation of statin treatment for primary **prevention in older people aged >75 years may be considered, if at high-risk or above.**	Treatment with statins is recommended for older people with ASCVD **in the same way as for younger patients.**

Guideline recommendations of of Lipid Lowering Drugs (LLD) treatment in the elderly

Guideline	Primary prevention	Secondary Prevention
AHA/ACC 2018	**70–75 years**: treat in the same way as younger adults. **>75 years**: clinical assessment, risk discussion. It may be reasonable to stop statins when functional decline, multimorbidity, ***FRAILTY*** or reduced life-expectancy limits the potential benefits of statins.	**70–75 years**: treat in the same way as younger adults; **>75 years**: it is reasonable to initiate moderate/high intensity statins. Weigh potential CV risk reduction against adverse effects, drug–drug interactions, **FRAILTY** before initiating therapy. Continue high-intensity statins if well-tolerated

REVIEW

LAURIE HERZIG MALLERY, MD, FRCPC, MSM
Department of Medicine, Division of Geriatric Medicine, Dalhousie University, Halifax, Nova Scotia, Canada

PAIGE MOORHOUSE, MD, MPH, FRCPC, MSM
Department of Medicine, Division of Geriatric Medicine, Dalhousie University, Halifax, Nova Scotia, Canada

PAM McLEAN VEYSEY, BSc (Pharm)
Team Lead, Drug Evaluation Unit, Department of Pharmacy, Nova Scotia Health Authority, Halifax, Nova Scotia, Canada

Severely frail elderly patients do not need lipid-lowering drugs

EDITORIAL

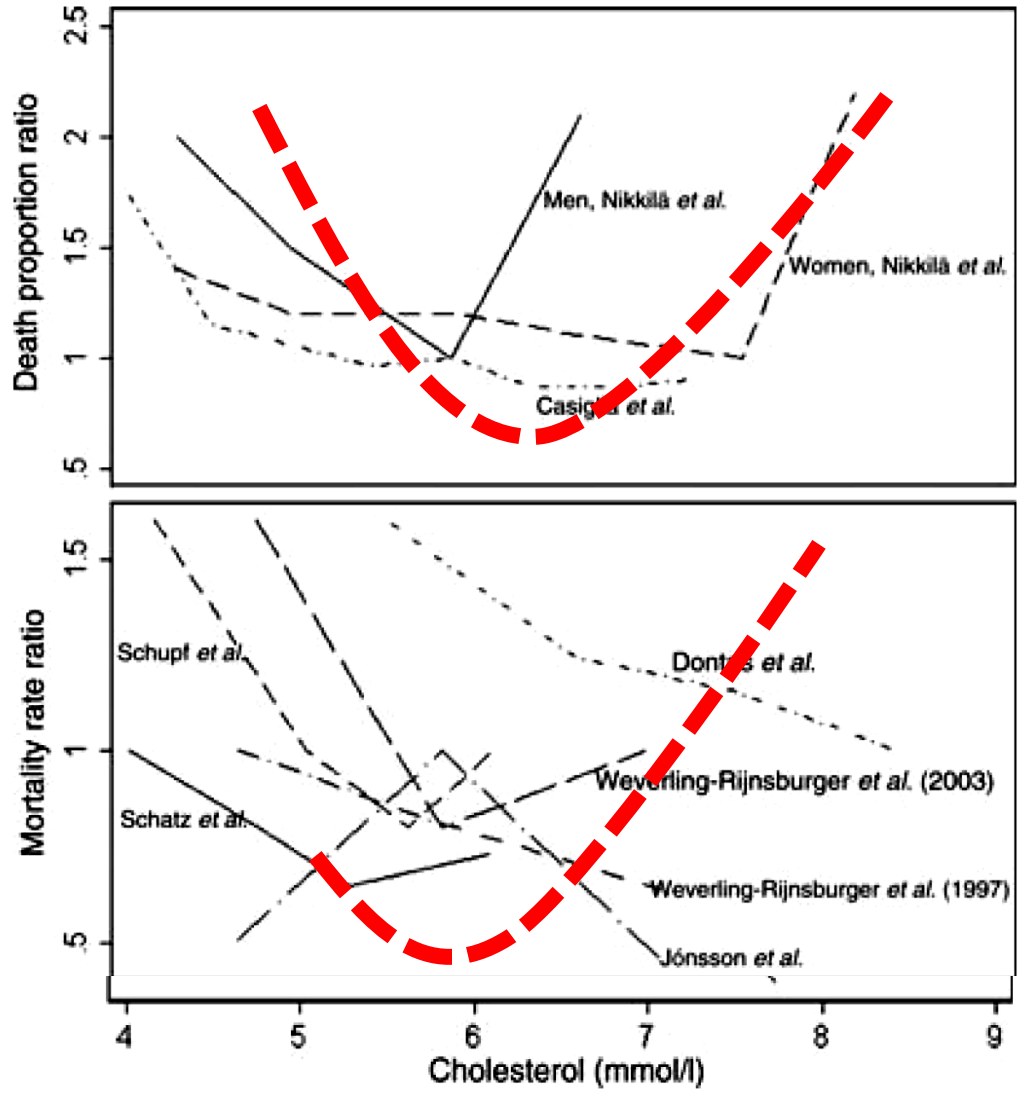
DONALD CLARK III, MD
Department of Cardiovascular Medicine, Cleveland Clinic

LESLIE S. CHO, MD
Section Head, Preventive Cardiology & Rehabilitation, and Director, Women's Cardiovascular Center, Department of Cardiovascular Medicine, Cleveland Clinic

Statin therapy in the frail elderly: A nuanced decision

Cleveland Clinic Journal Of Medicine, 2017

All-cause mortality and cholesterol in the elderly

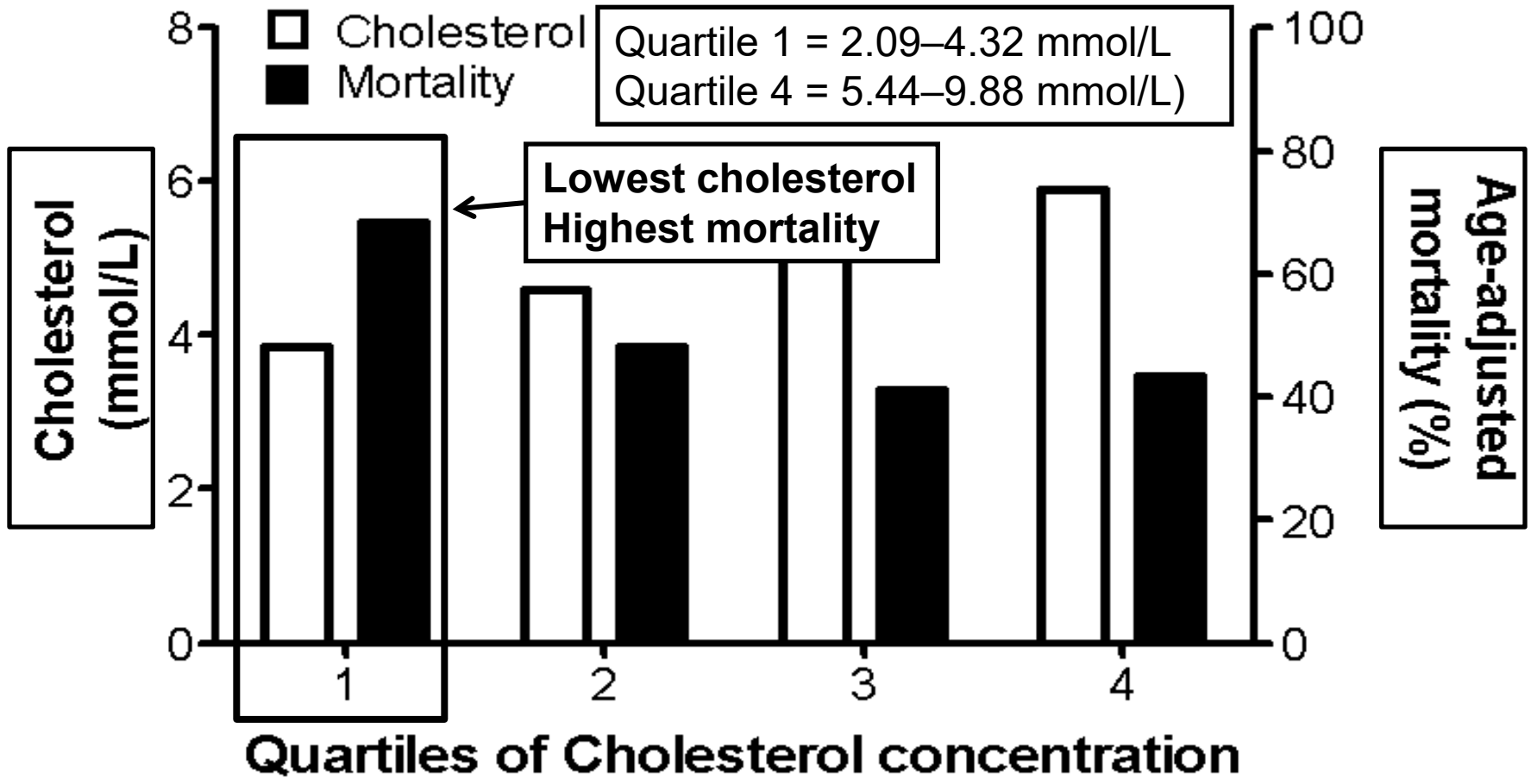


U curve

J curve

Petersen LK et al. Age & Ageing 2010

Relationship between total cholesterol level and mortality in elderly people from the "*Honolulu Heart Program*"



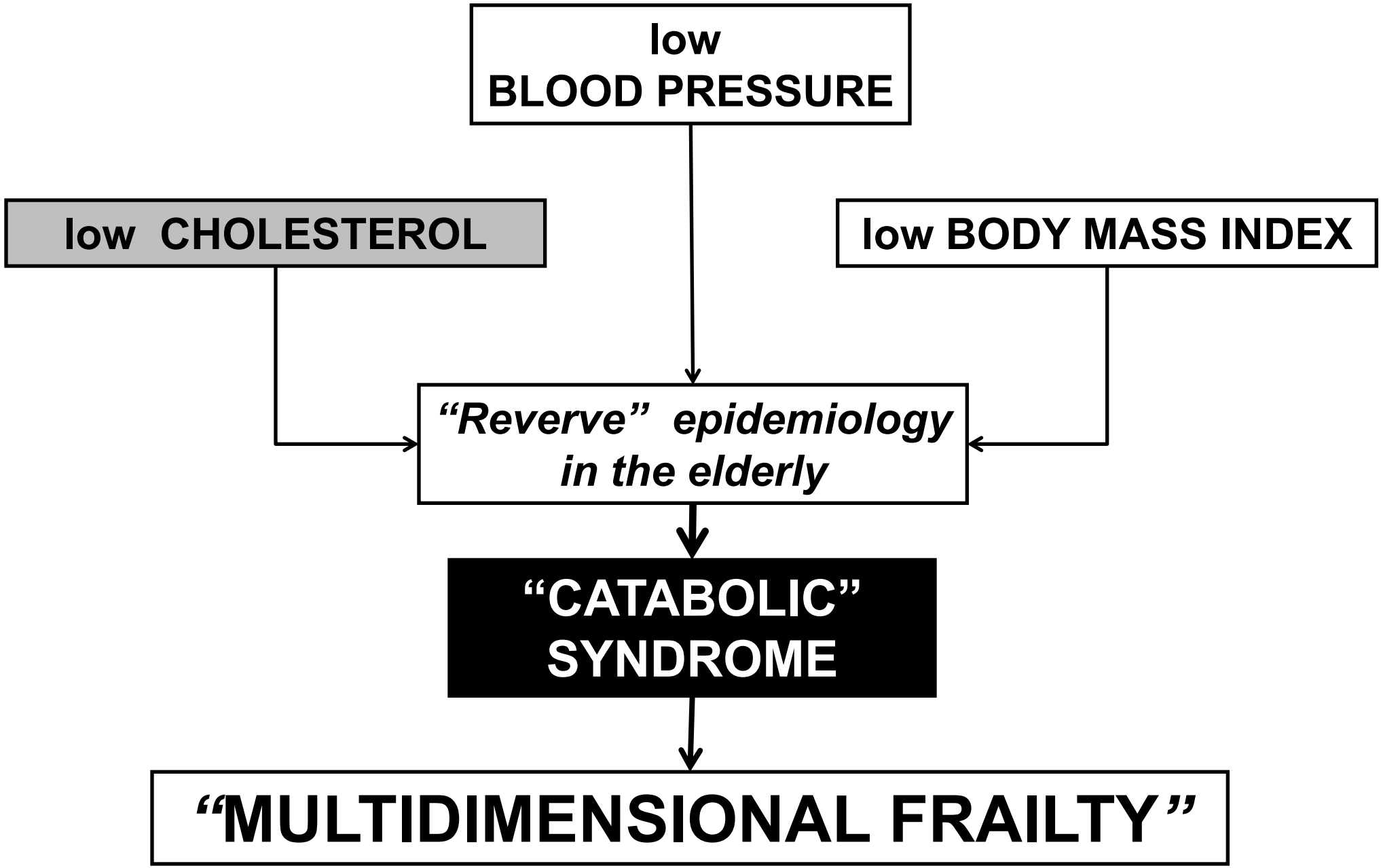
Schatz I et al. Lancet. 2001

Aging Clin Exp Res (2018) 30:547–554
DOI 10.1007/s40520-017-0815-7

REVIEW

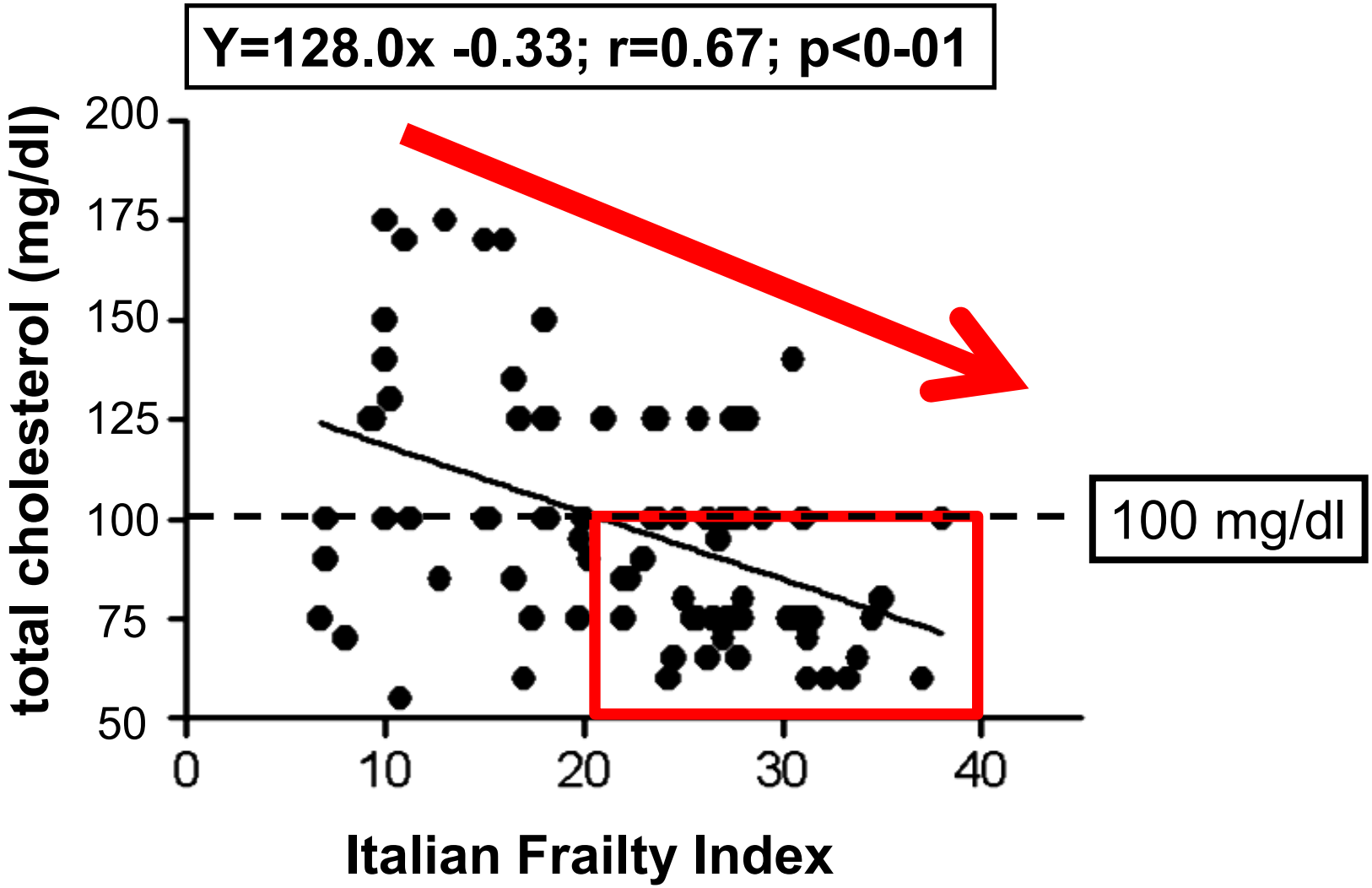
The reverse metabolic syndrome in the elderly: Is it a "catabolic" syndrome?

Francesco Curcio[1] · Giuseppe Sasso[1] · Ilaria Liguori[1] · Gaetana Ferro[2] · Gennaro Russo[1] · Michele Cellurale[1] · David Della-Morte[3,4] · Gaetano Gargiulo[5] · Gianluca Testa[1,6] · Francesco Cacciatore[1,7] · Domenico Bonaduce[1] · Pasquale Abete[1]



Curcio F et al.,. Aging Clin Exp Res 2018

Clinical frailty is inversely related to total cholesterol in the elderly



Curcio F et al.,. Aging Clin Exp Res 2018

British Cardiovascular Society
BMJ
Heart

Review

Treatment of hypercholesterolaemia in older adults calls for a patient-centred approach

Emma EF Kleipool ,[1] Johannes AN Dorresteijn,[2] Yvo M Smulders,[1] Frank LJ Visseren ,[2] Mike JL Peters,[1] Majon Muller[1]

Kleipool EEF et al. Heart 2020

Treatment of hypercholesterolaemia in older adults calls for "*a patient-centred approach*"

LDL-C = 150 mg/ml

10-year CV risk = 13%
Life expectancy ≈ 14 years

Patient 1

Female, 75 years
Osteoarthritis

RR 140/85 mmHg
HDL 1.3, LDL-c 3.8 mmol/L
Total no. drugs 3
eGFR 60 mL/min/1.73m^2

Do not initiate Lipid-Lowering Drug (LLD)

Kleipool EEF et al. Heart 2020

Treatment of hypercholesterolaemia in older adults calls for "*a patient-centred approach*"

LDL-C = 150 mg/ml

10-year CV risk = 26%
Life expectancy ≈ 10 years

Patient 2

Female, 75 years
Smoker, osteoporosis, HT

RR 160/90 mmHg
HDL 1.3, LDL-c 3.8 mmol/L
Total no. drugs 6
eGFR 60 mL/min/1.73m^2

Initiate Lipid-Lowering Drug (LLD)

Kleipool EEF, et al. Heart 2020

Treatment of hypercholesterolaemia in older adults calls for "*a patient-centred approach*"

LDL-C = 150 mg/ml

Life expectancy < 2 years
Calculator not applicable to this frail patient

Patient 3

Male, 75 years
Diabetes, MI, heart failure (NYHA III), cognitive impairment
RR 140/85 mmHg
HDL 1, LDL-c 3.8 mmol/L
Diabetes, total no. drugs 9 (incl. statin)
eGFR 30 mL/min/1.73m^2

Consider discontinue Lipid-Lowering Drug (LLD), especially in case of side effects

Kleipool EEF, et al. Heart 2020

Take home messages (1)

- Dyslipidemia treatment **in patients older than 75 years is still uncertain**.
- **Statins** treatment in advancing age is well studied and it should be considered both **in primary prevention,** in the presence of **cardiovascular very-high risk pattern,** and **in secondary prevention**.
- **Nonadherence and discontinuation** of statins in older adults represent a critical point.
- Newer agents as **Evolocumab, Alirocumab and Inclisiran and bempedoic acid** could be useful in overcoming this phenomenon.

Take home messages (2)

"A patient-centred approach" may be considered for **patients older than 75 years** in whom the **FRAILTY should be always evaluated and quantified!**