L'approccio terapeutico alle dislipidemie: stato dell'arte

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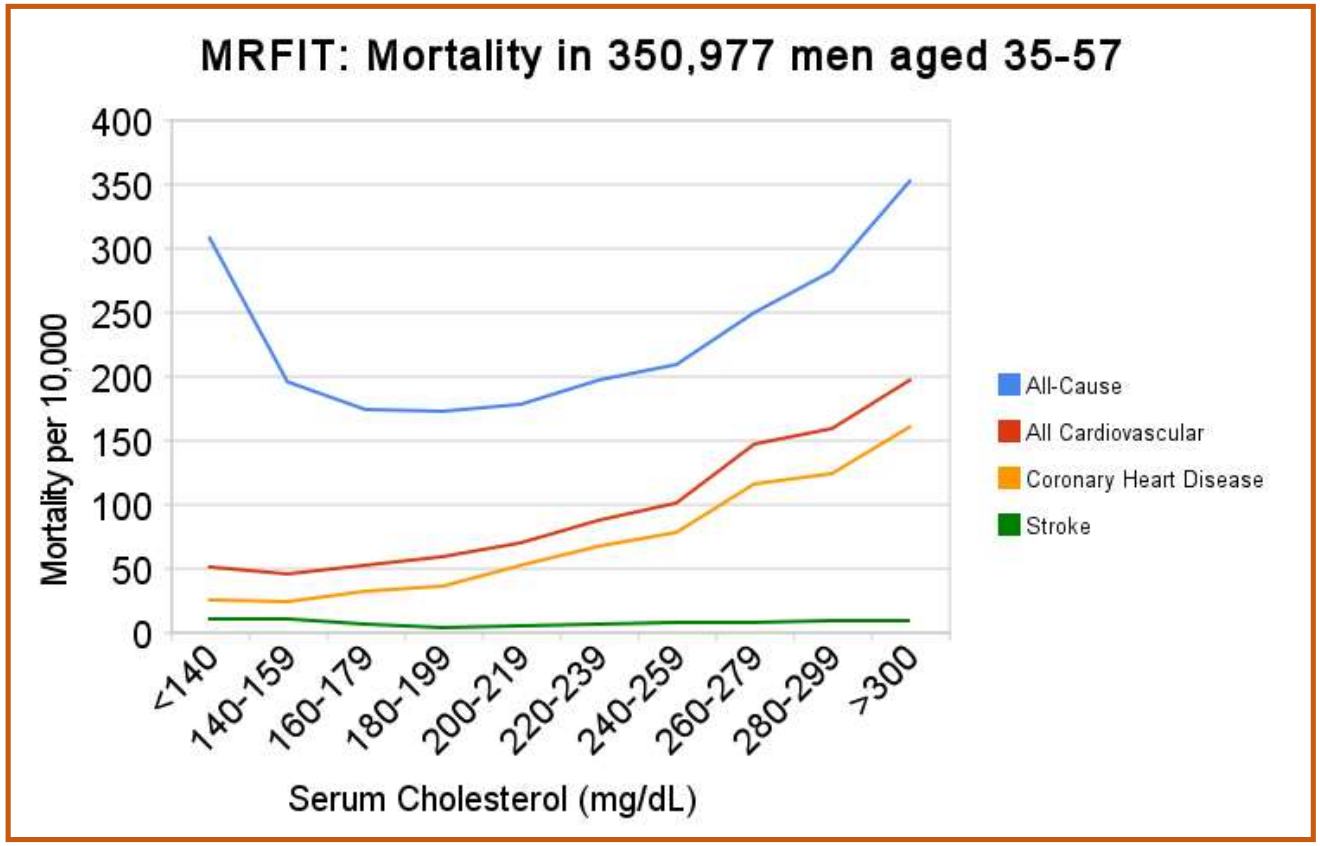
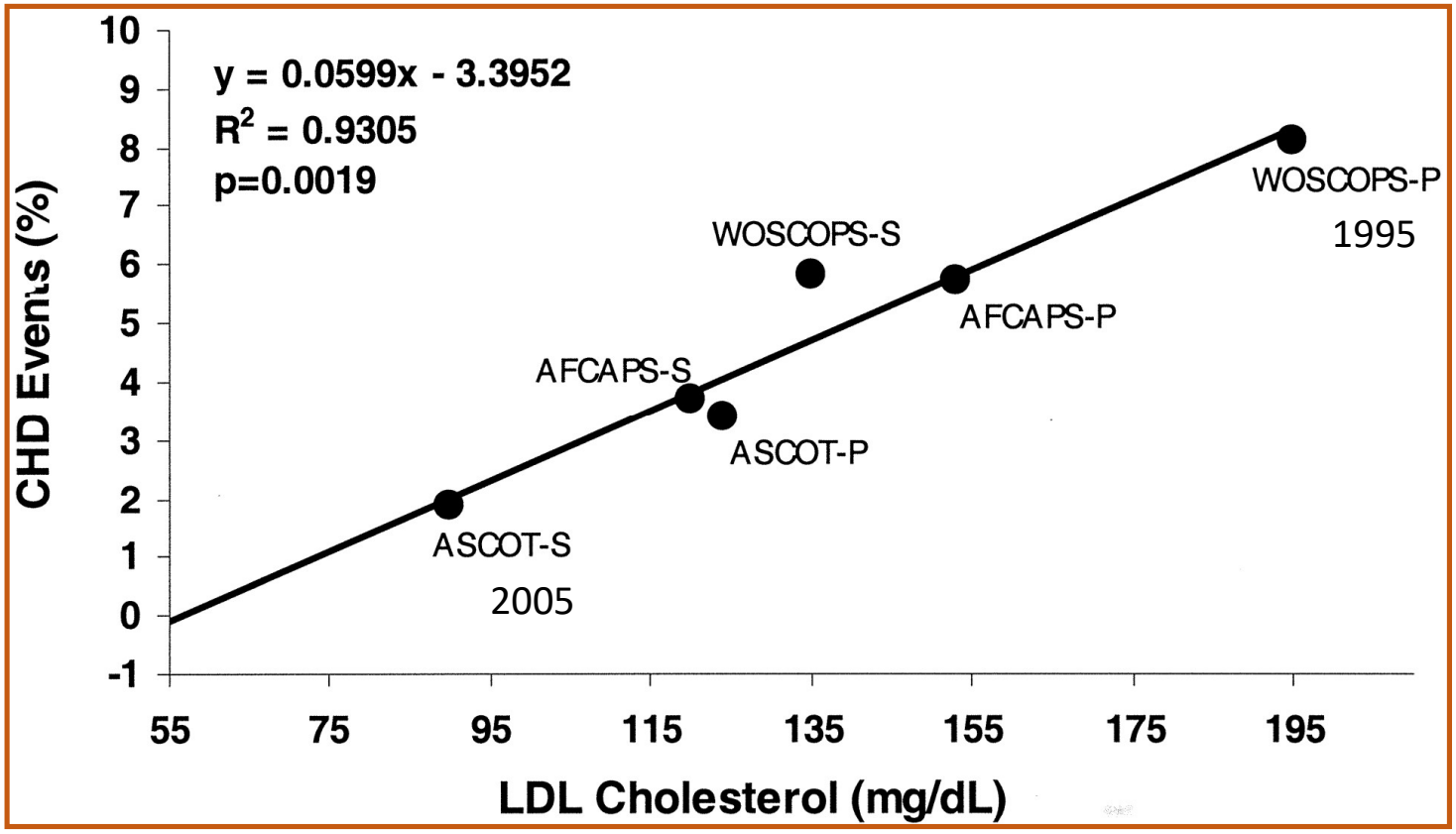
Livelli elevati di colesterolo sono associati ad un aumentato rischio di mortalità per cardiopatia ischemica



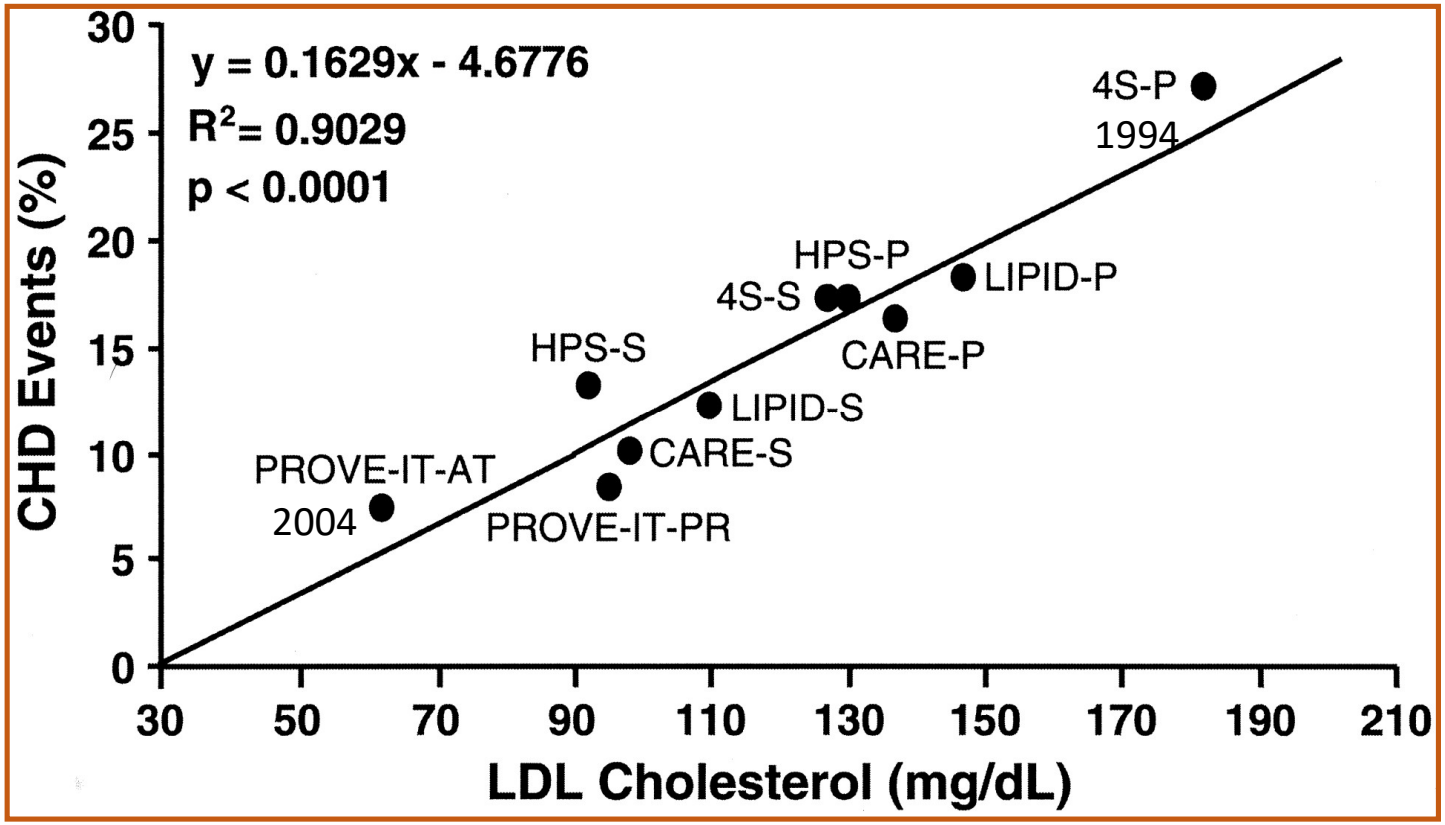
Lancet 1986

Coronary heart disease event rates in primary prevention trials (4 to 5 y duration) are directly proportional to the on-treatment cLDL levels.



O'Keefe J R et al. J Am Coll Cardiol 2004; 43:2142-2146

Coronary heart disease event rates in secondary prevention trials (5 years in duration except the PROVE-IT study, which was 2 y) were directly proportional to c LDL levels

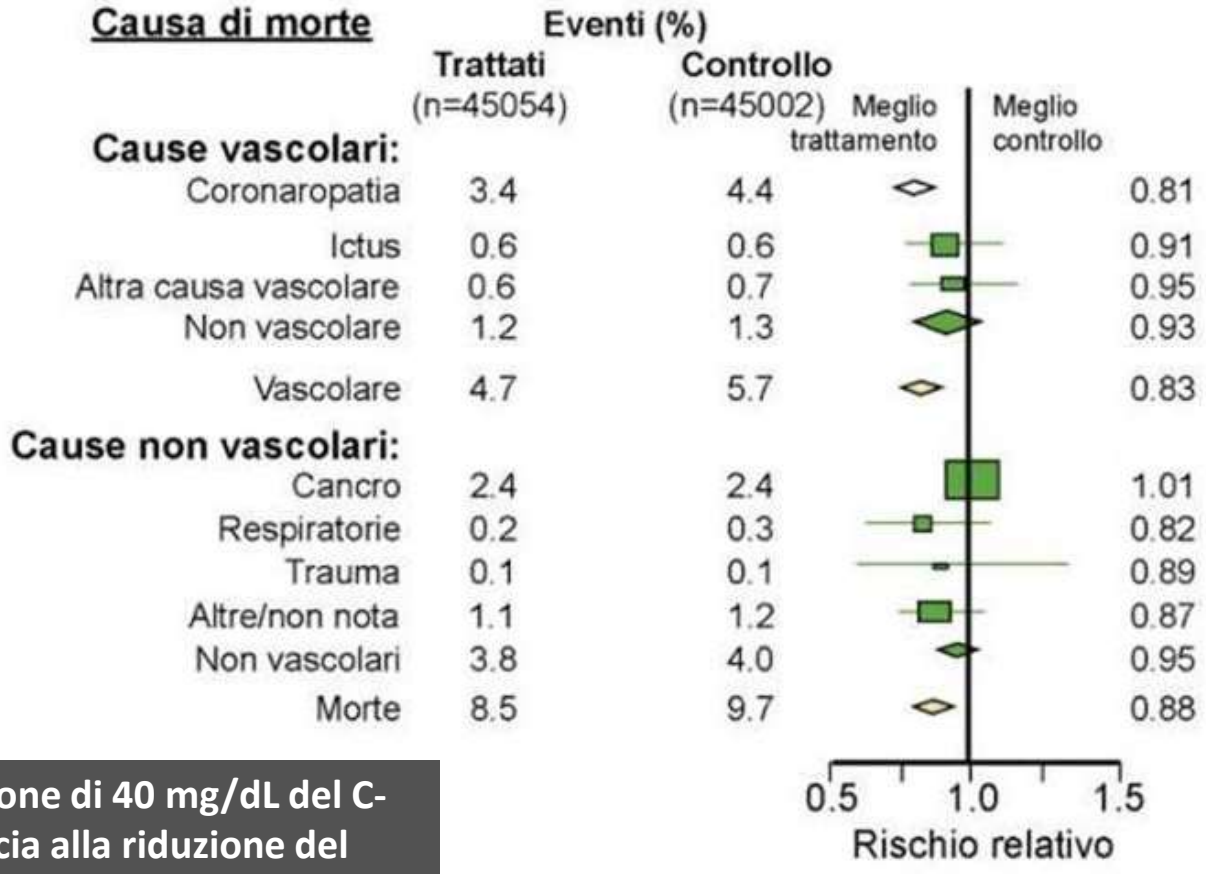


O'Keefe J R et al. J Am Coll Cardiol 2004; 43:2142-2146

Le statine riducono la mortalità per tutte le cause

Meta-analisi di 14 studi

Cholesterol Treatment Trialists' Collaboration



Ogni riduzione di 40 mg/dL del C-LDL si associa alla riduzione del 25% del rischio di eventi.

CTT Collaborators. Lancet. 2005;366:1267-78

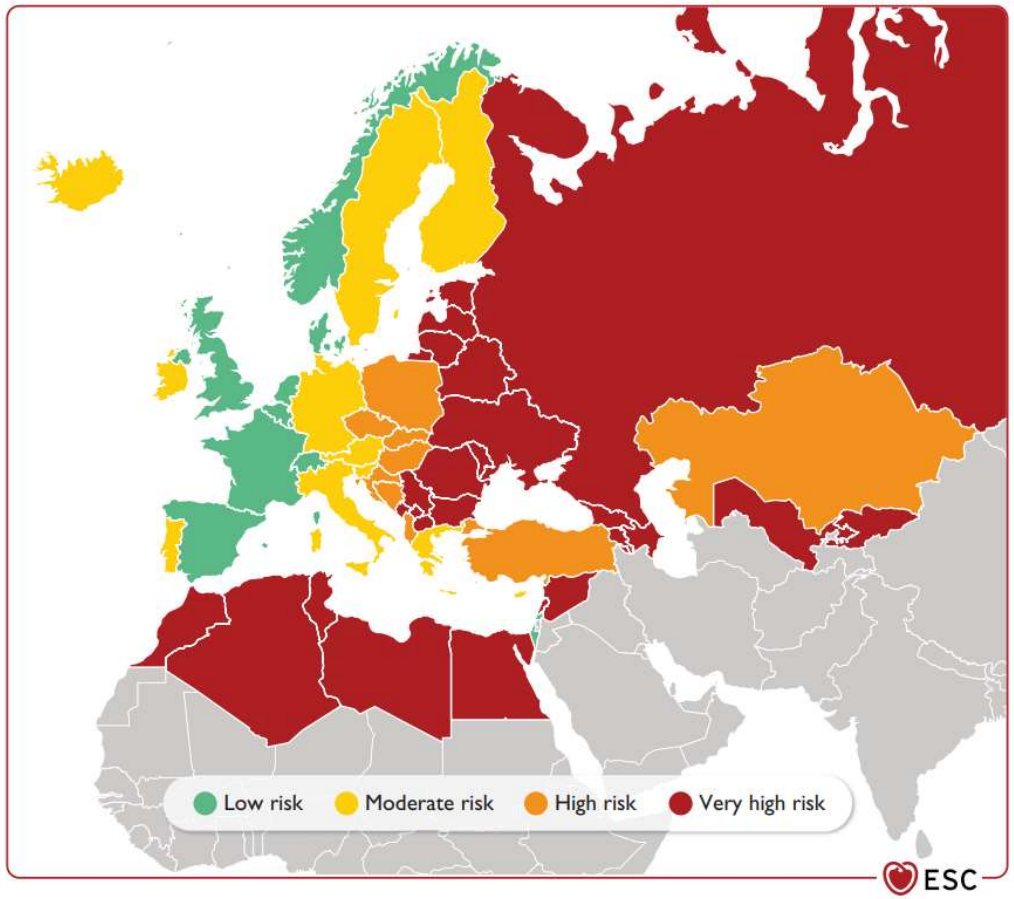
What is cardiovascular disease prevention?

- Prevention is defined as a co-ordinated set of actions, either at the population or individual level, aimed at eliminating or minimizing the impact of CV diseases and their related disabilitie.

The importance of atherosclerotic cardiovascular disease (ASCVD) prevention remains undisputed and should be delivered at:

- the general population level by promoting healthy lifestyle behaviour,
- **at the individual level by tackling unhealthy lifestyles and by reducing increased levels of causal CV risk factors, such as LDL cholesterol or blood pressure (BP) levels.**

Risk regions based on World Health Organization cardiovascular mortality rates.



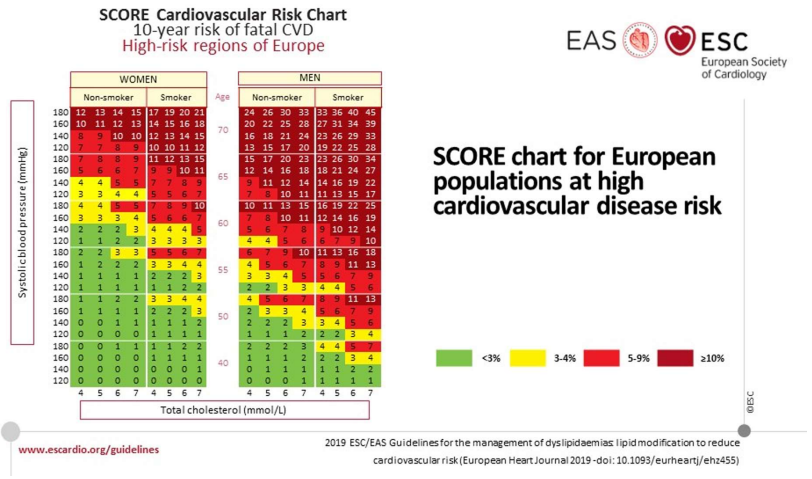
Low risk: < 100 CVD deaths per 100.000

Moderate risk: 100 to <150 deaths per 100.000

High risk: 150 to <300 deaths per 100.000

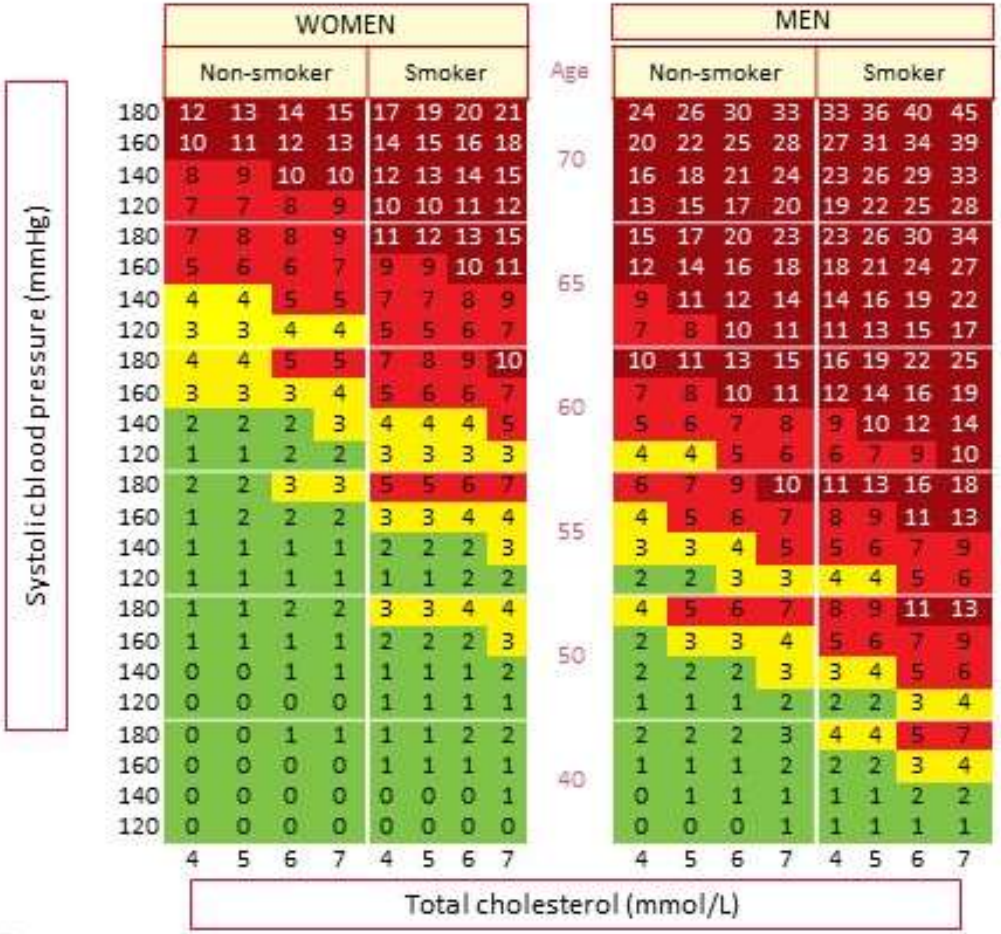
Very high risk: ≥ 300 deaths per 100.000

SCORE Chart for European population



Persons with **documented ASCVD**, type 1 or type 2 **DM** (T1DM and T2DM, respectively), very high levels of individual risk factors, or **chronic kidney disease (CKD)** are generally at very-high or high total CV risk. No risk estimation models are needed for such persons.

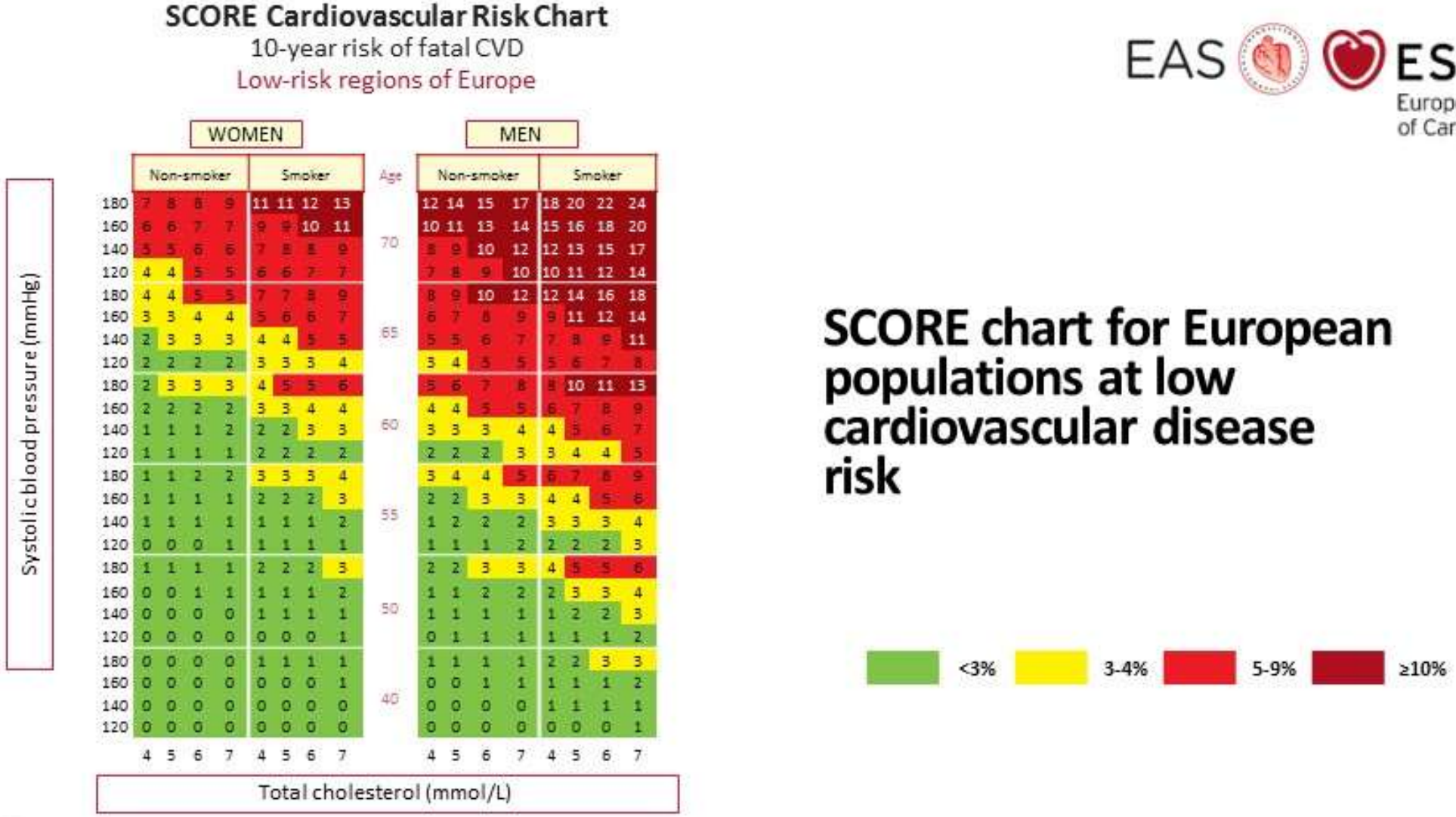
SCORE Cardiovascular Risk Chart
10-year risk of fatal CVD
High-risk regions of Europe



SCORE chart for European populations at high cardiovascular disease risk

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)



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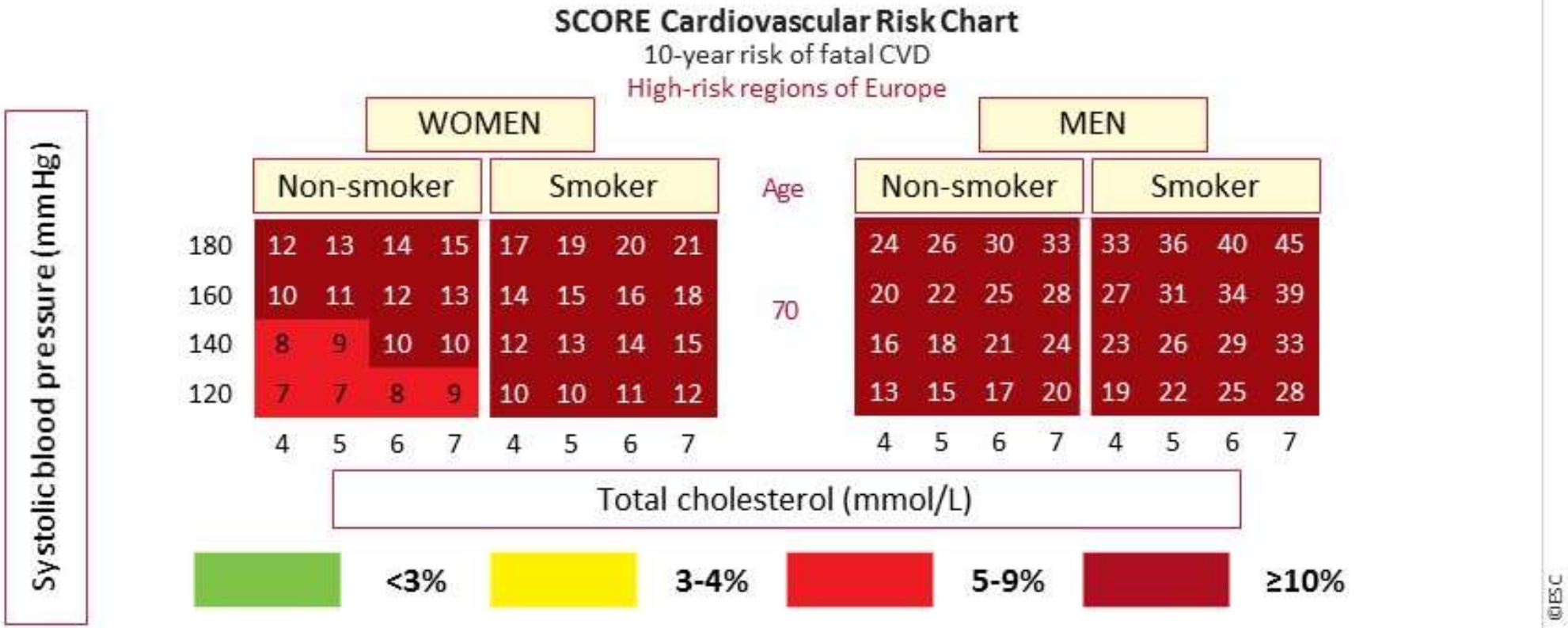
2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

SCORE chart for European populations at high cardiovascular disease risk (1)

EAS ESC European Society of Cardiology



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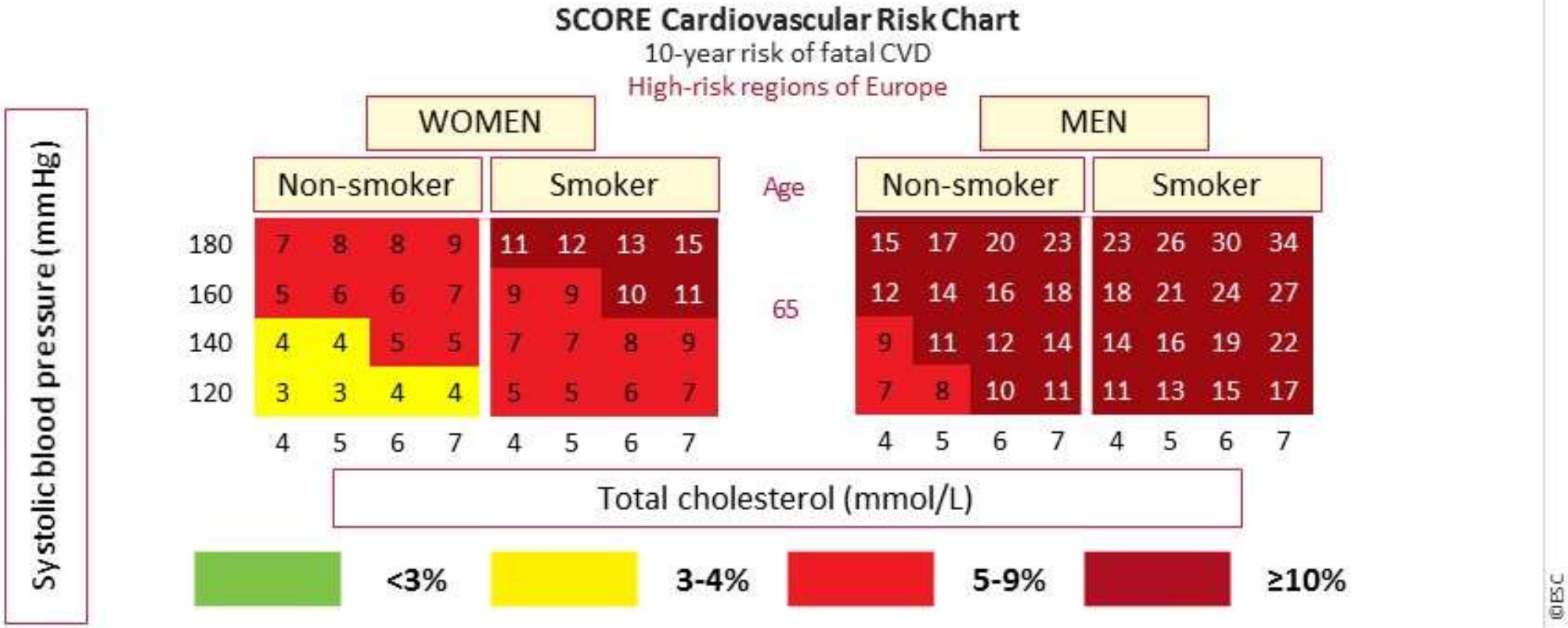
2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

SCORE chart for European populations at high cardiovascular disease risk (2)

EAS ESC European Society of Cardiology

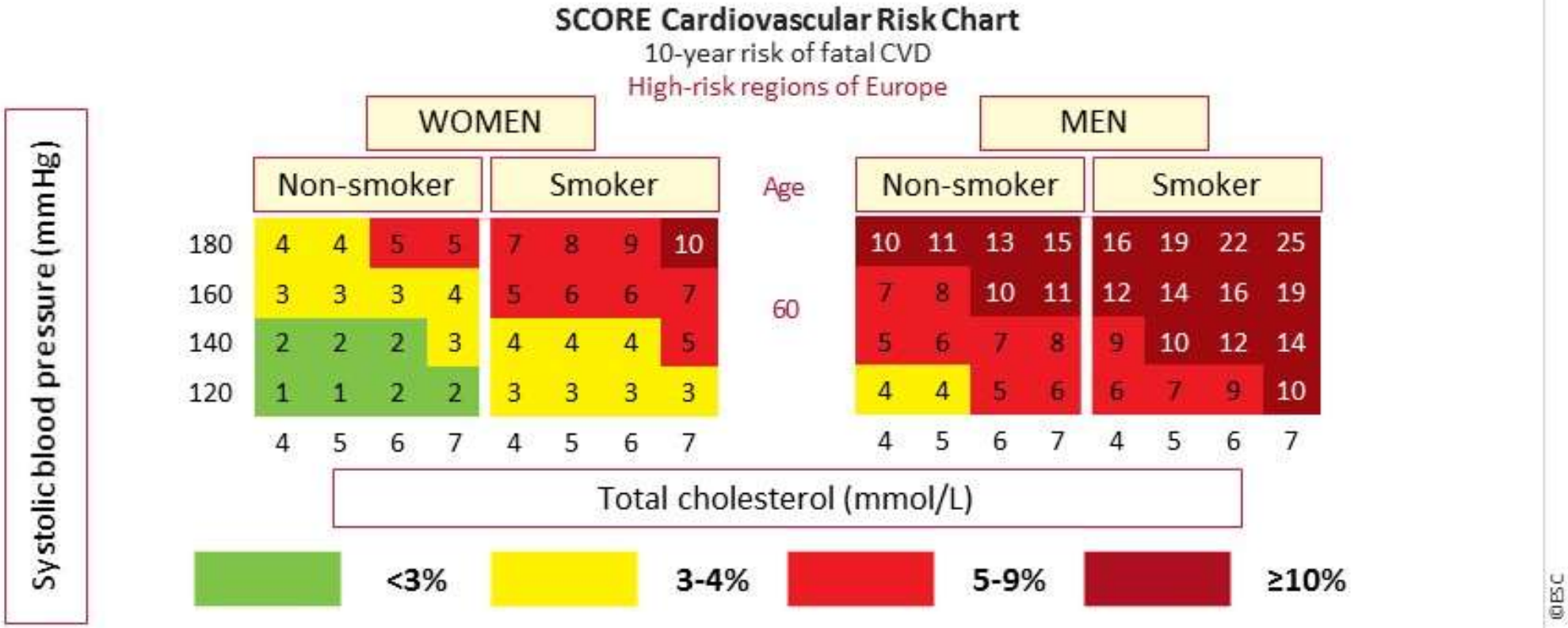


www.escardio.org/guidelines

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

SCORE chart for European populations at high cardiovascular disease risk (3)

EAS ESC European Society of Cardiology



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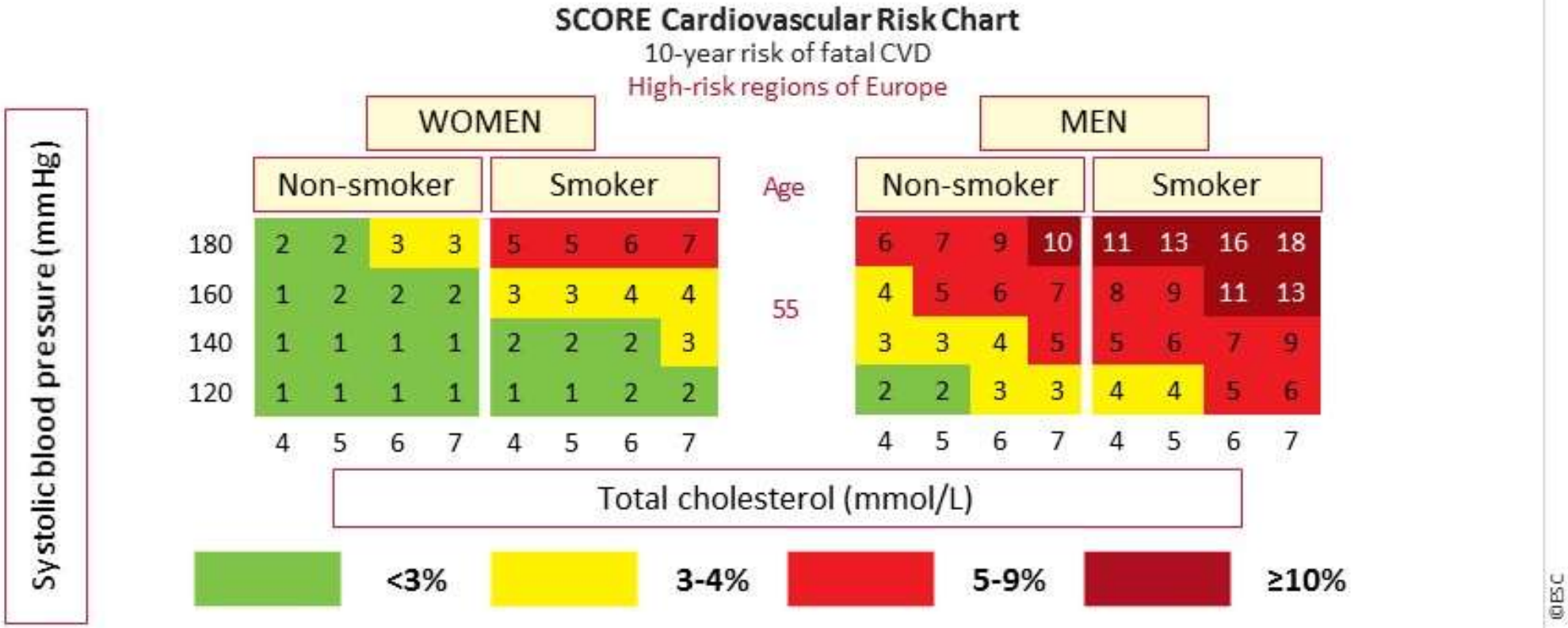
2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

SCORE chart for European populations at high cardiovascular disease risk (4)

EAS ESC European Society of Cardiology



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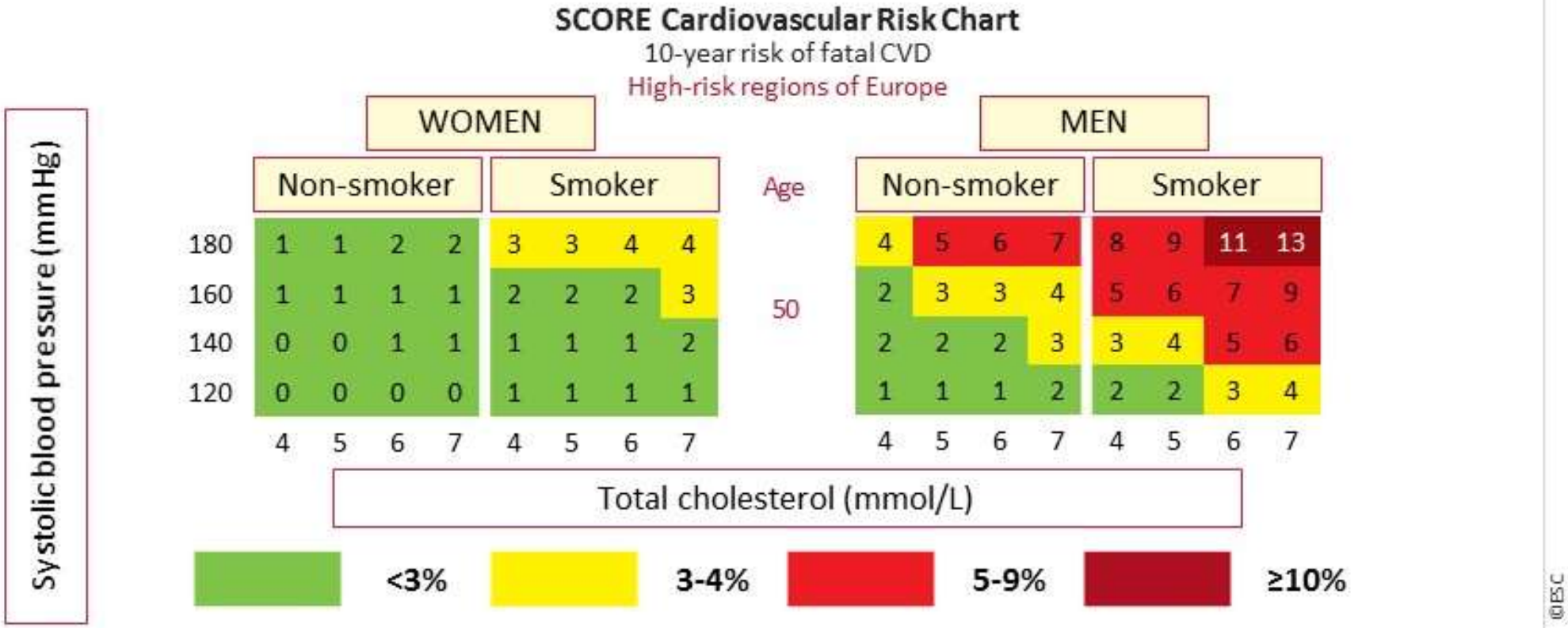
2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

SCORE chart for European populations at high cardiovascular disease risk (5)

EAS ESC European Society of Cardiology



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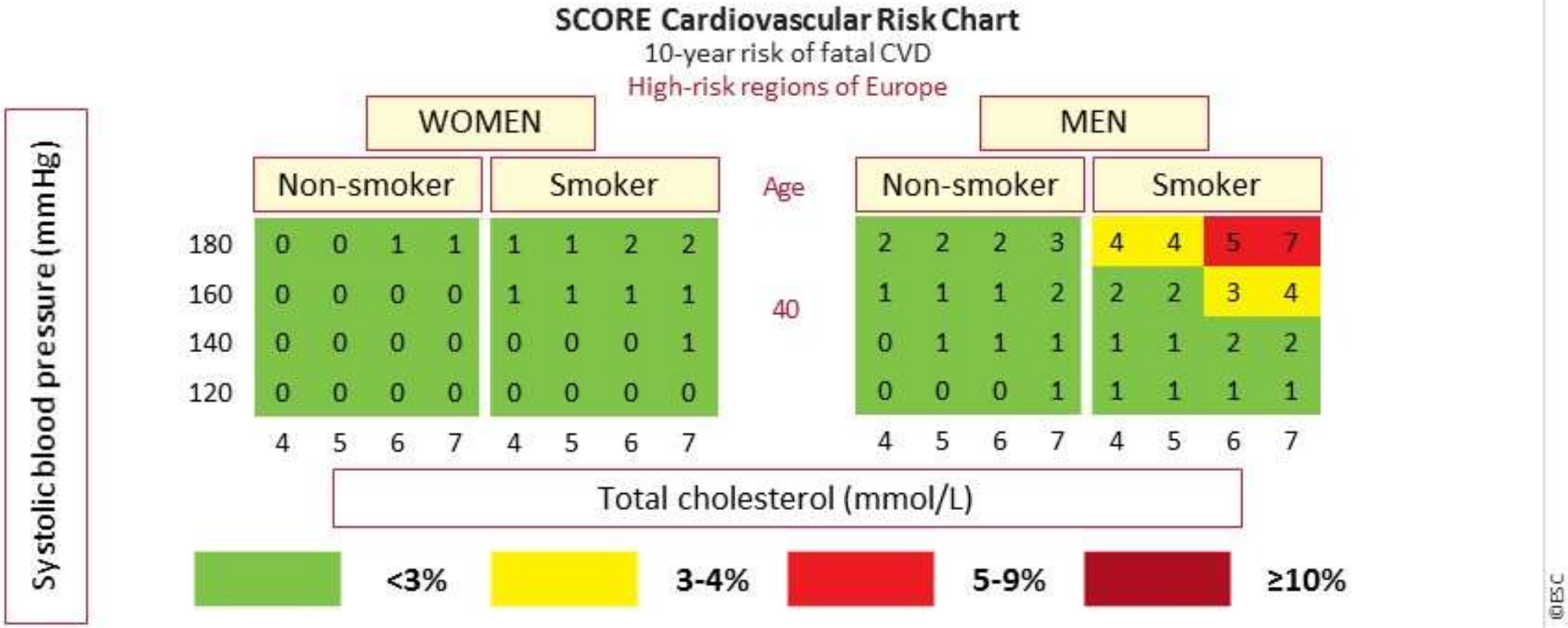
2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

SCORE chart for European populations at high cardiovascular disease risk (6)

EAS ESC European Society of Cardiology



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)

10-year risk of fatal CVD

Low-risk regions of Europe (age interactions included)

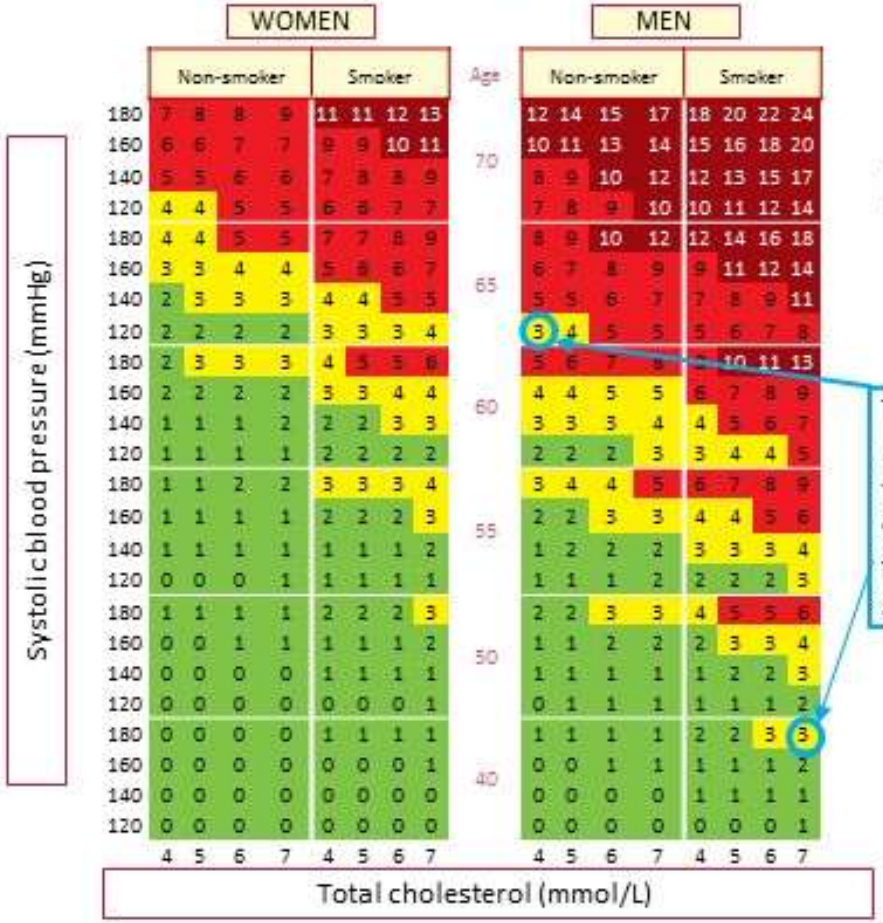


Illustration of the risk age concept

The risk of this 40 – year old male smoker with risk factors is the same (3-4%) as that of a 65 year – old man with ideal risk factor levels– therefore his risk age is 65 years.

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

Factors modifying SCORE risks (1)

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Social deprivation – the origin of many of the causes of CVD.
Obesity and central obesity as measured by the body mass index and waist circumference, respectively.
Physical inactivity.
Psychosocial stress including vital exhaustion.
Family history of premature CVD (men: <55 years; women: <60 years).
Chronic immune-mediated inflammatory disorder.

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

Factors modifying SCORE risks (2)

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- Major psychiatric disorders.
- Treatment for human immunodeficiency virus (HIV) infection.
- Atrial fibrillation.
- Left ventricular hypertrophy.
- Chronic kidney disease.
- Obstructive sleep apnoea syndrome.
- Non-alcoholic fatty liver disease.

Air Pollution

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

Cardiovascular risk categories (1)

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Very-high-risk	People with any of the following: Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularisation (PCI, CABG and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis) or on carotid ultrasound. DM with target organ damage, or at least three major risk factors, or early onset of T1DM of long duration (>20 years). (>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.

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

Cardiovascular risk categories (2)

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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 factors. 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.

*Target organ damage is defined as microalbuminuria, retinopathy or neuropathy

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

Intervention strategies as a function of total cardiovascular risk and untreated low-density lipoprotein cholesterol levels

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	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 uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A	IIa/A
	≥1 to <5, or moderate risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	IIa/A	IIa/A
	≥5 to <10, or high- risk	Lifestyle advice	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
	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	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
	Class[a]/Level[b]	IIa/B	IIa/A	I/A	I/A	I/A	I/A
Secondary Prevention	Very-high risk	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	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	IIa/A	I/A	I/A	I/A	I/A	I/A

www.escardio.org/guidelines

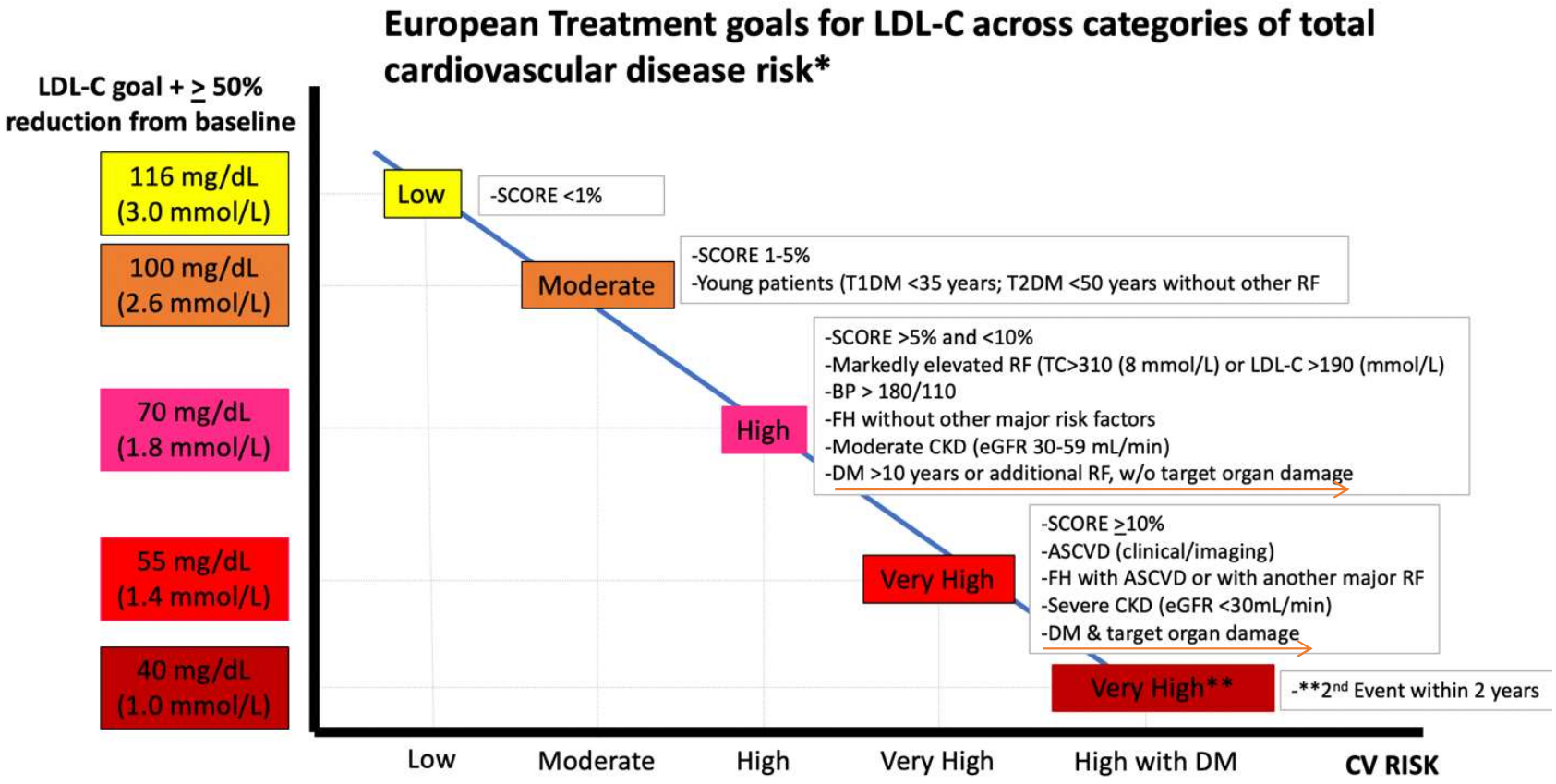
2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Intervention strategies as a function of total cardiovascular risk and untreated low-density lipoprotein cholesterol levels

ESC European Society of Cardiology

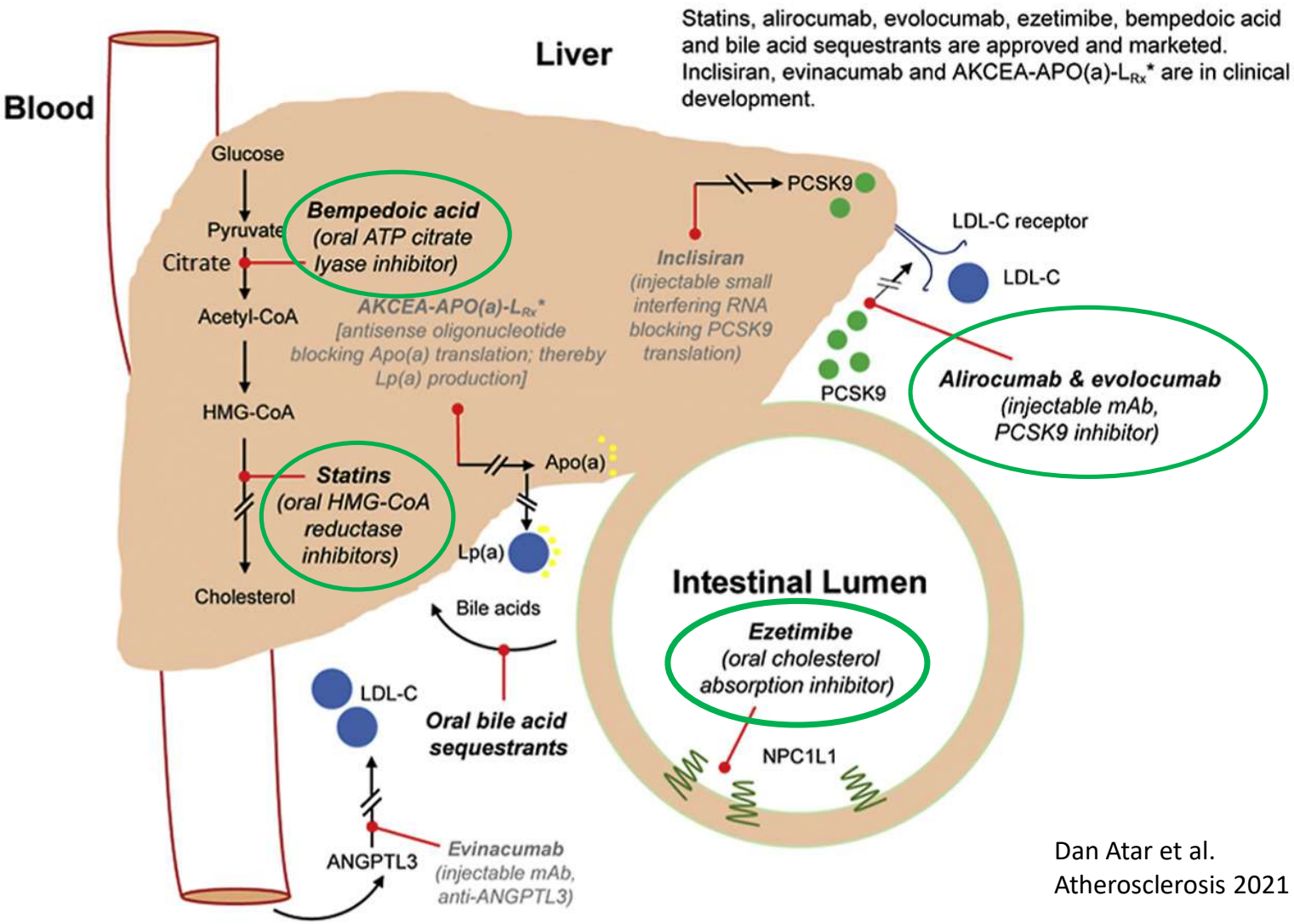
EAS

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

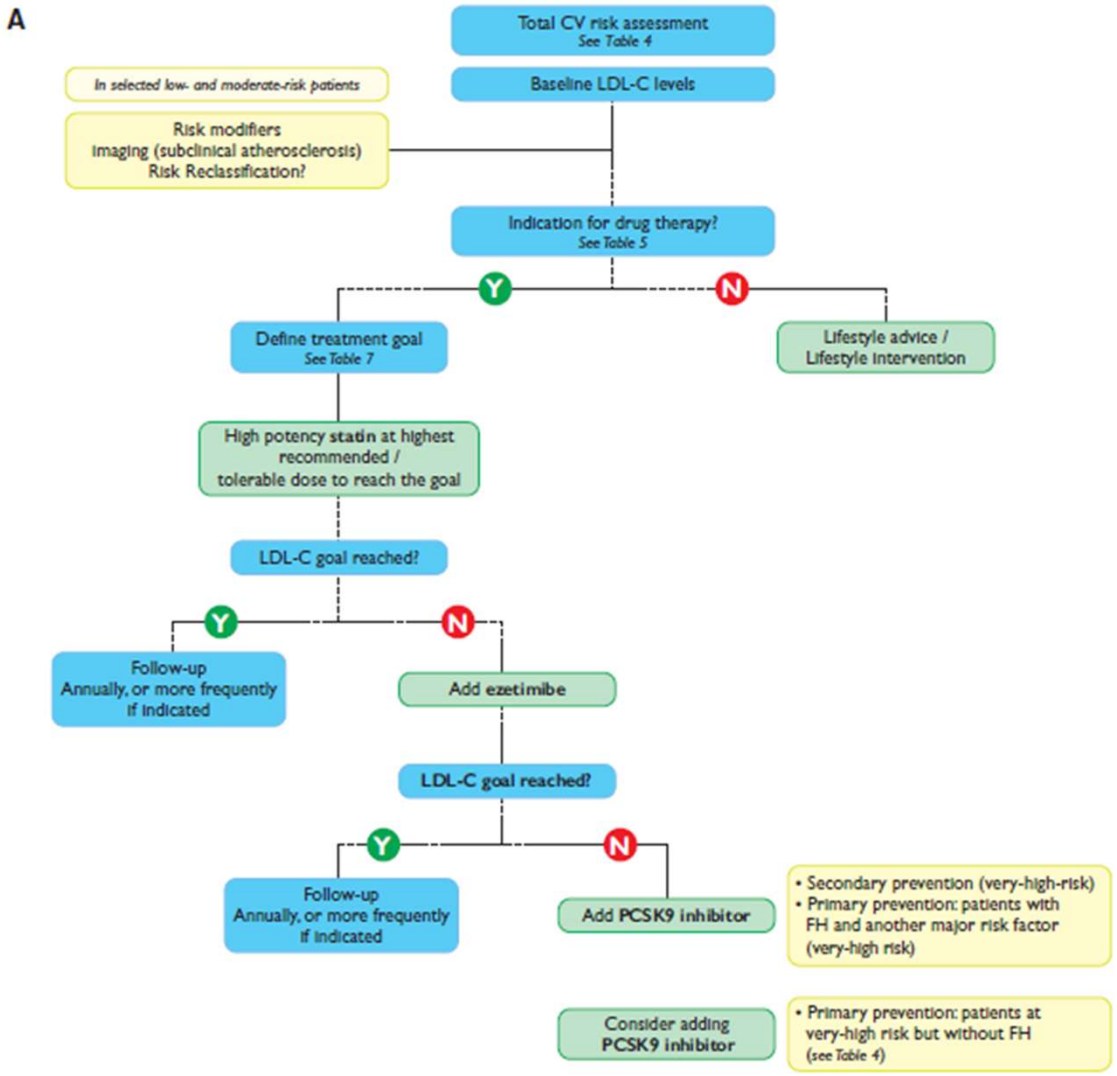


*Adapted from slideset available on www.escardio.org/guidelines which is from 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk

Sites and targets of lipid-lowering therapies



Dan Atar et al.
Atherosclerosis 2021



EAS ESC
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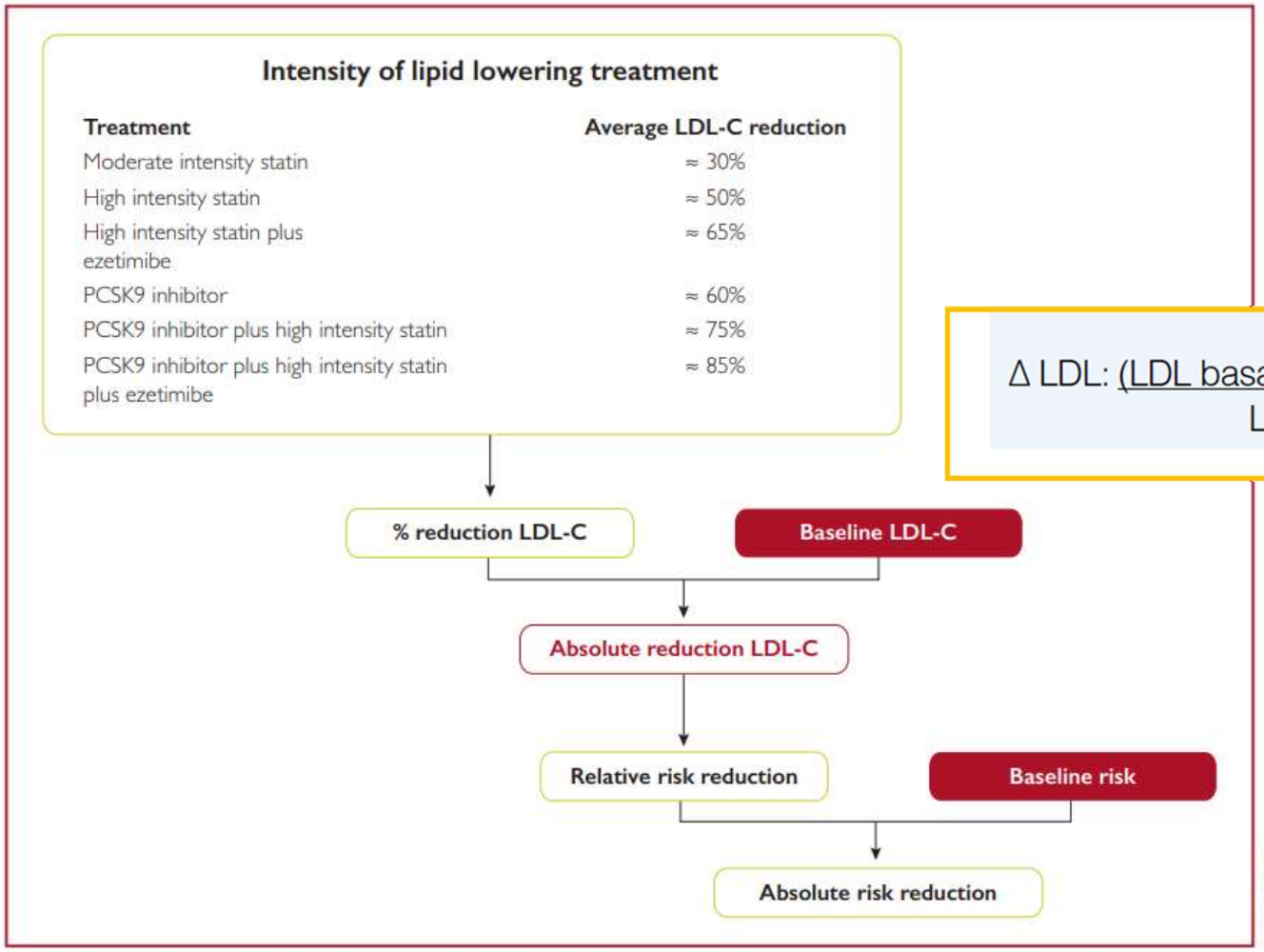
Treatment algorithm for pharmacological LDL-C lowering

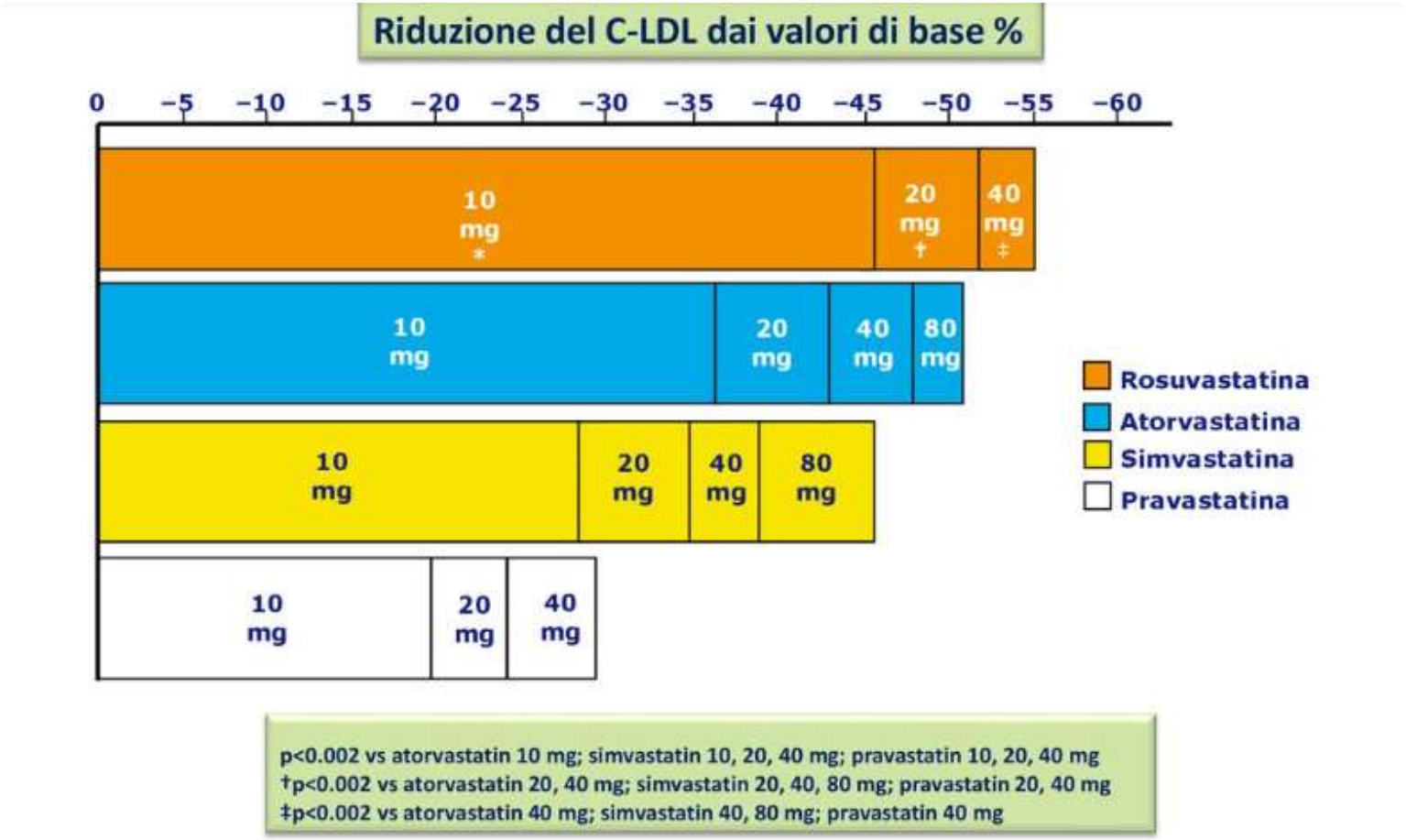
2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Expected clinical benefits of low-density lipoprotein cholesterol-lowering therapies

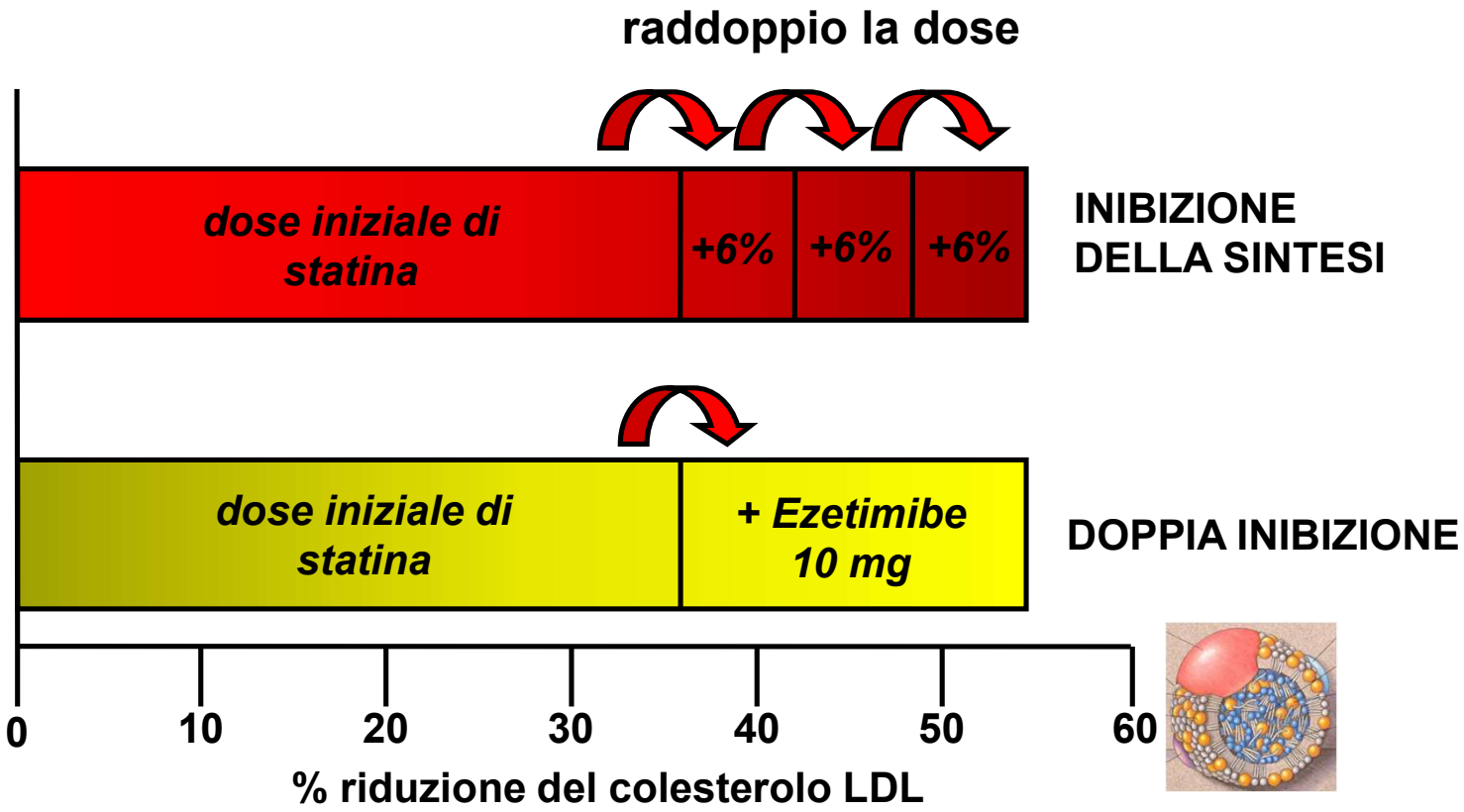


Δ LDL: (LDL basale – target LDL) espressa in % LDL basale

Effetto delle varie statine sulla riduzione del C-LDL



Razionale della terapia di combinazione



Statine: problemi aperti

- **Pazienti ad alto rischio cardiovascolare:**

  Mancato raggiungimento dei target di colesterolo-LDL

  nonostante l'impego di statine ad alta efficacia

- **Ipercolesterolemia familiare**

- **Intolleranza alle statine** (intolleranza ad almeno due statine di cui una a base dosi)

Ipercolesterolemia familiare (FH)

Ipercolesterolemia genetica a trasmissione AD, caratterizzata da:

- **Elevati livelli di LDL** (160-300 mg/dL nelle forme di eterozigosi; 500-800 mg/dL nelle forme di omozigosi)

- **Presenza di xantomi cutanei e tendinei; arco corneale**

- **Malattia coronarica precoce**: eFH eventi cardiovascolari (IMA) prima dei 50 anni; i soggetti con omozigosi FH muoiono precocemente (prima dei venti anni) per complicanze cardiovascolari

- **Prevalenza**: Eterozigote 1:200 – 1:250
  Monozigote: 1: 1.000.000

- **Circa l'80% dei pazienti con FH non raggiunge il target di LDLc < 100 mg/dl**

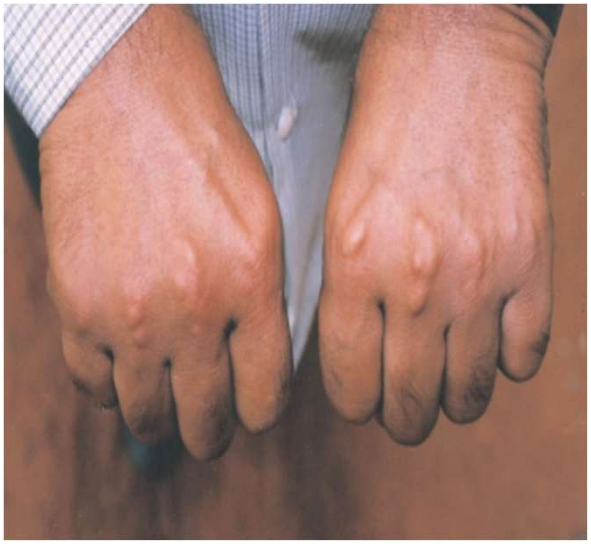
Ipercolesterolemia familiare (ADH): cause

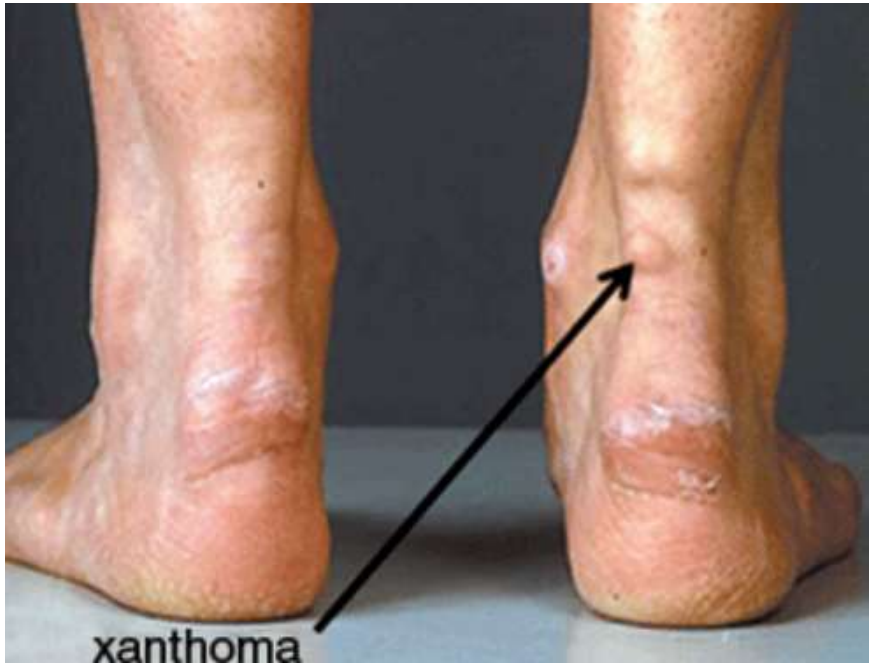
Mutazioni del:

1) **Gene del recettore delle LDL (LDL-R**), che causano un ridotto legame e catabolismo delle LDL plasmatiche (ADH-1); In Italia, come in altri paesi occidentali, la frequenza stimata di ADH-1 nella forma eterozigote è di circa 1:500 individui e quella nella forma omozigote è di 1:1.000.000. Si prevede pertanto che in Italia siano presenti circa 120.000 eterozigoti e 55 omozigoti.

2) **Gene dell'apolipoproteina B-100 (apoB**) con conseguente produzione di una apoB-100 difettiva che ha una ridotta affinità di legame per il LDL-R (ADH-2);

3) **Gene di PCSK9** con alterazione della normale funzione dell'enzima proteolitico PCSK9 (ADH-3)




xanthoma

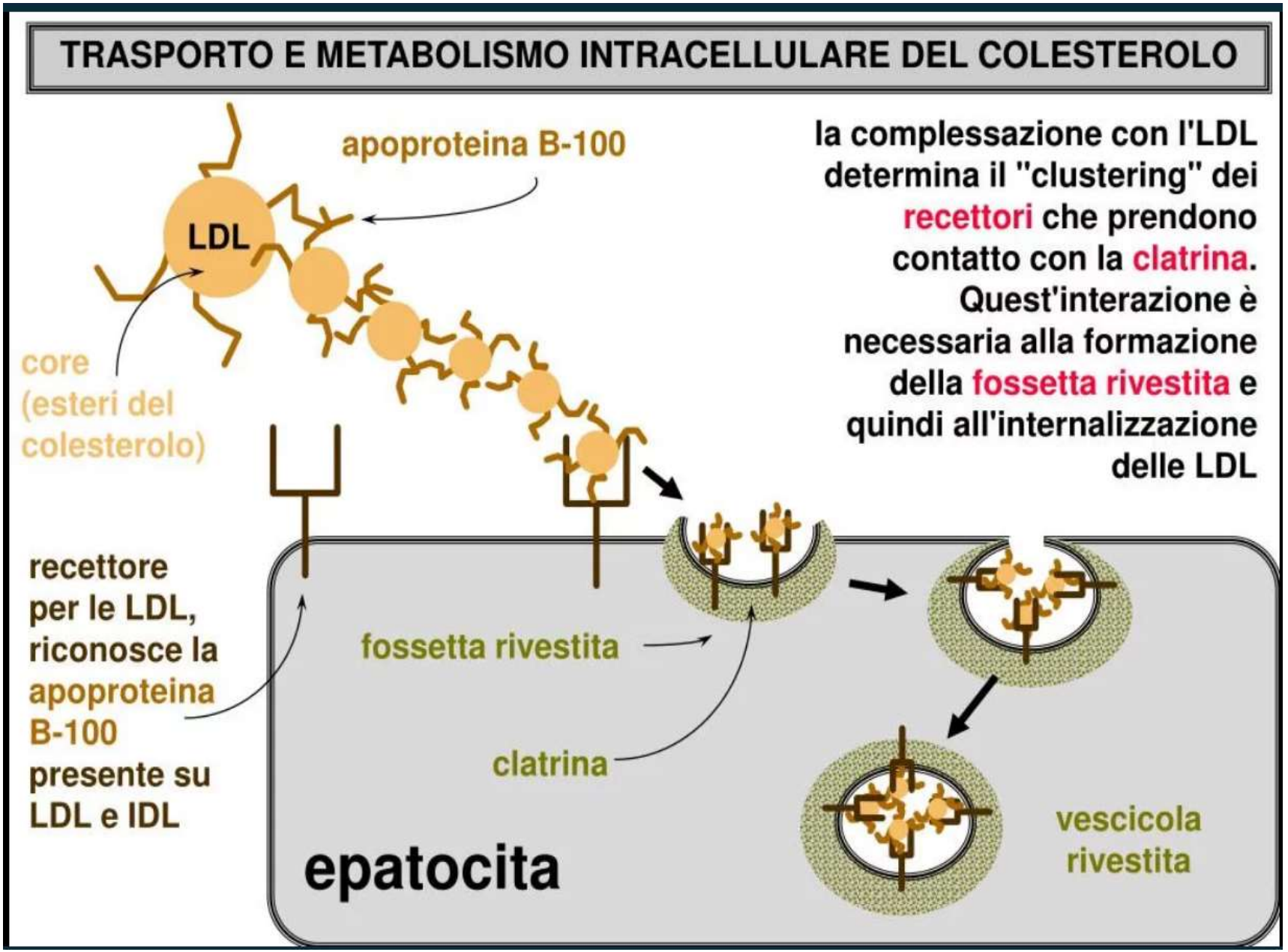
Clinical scores for FH screening

✓ Dutch Lipid Score

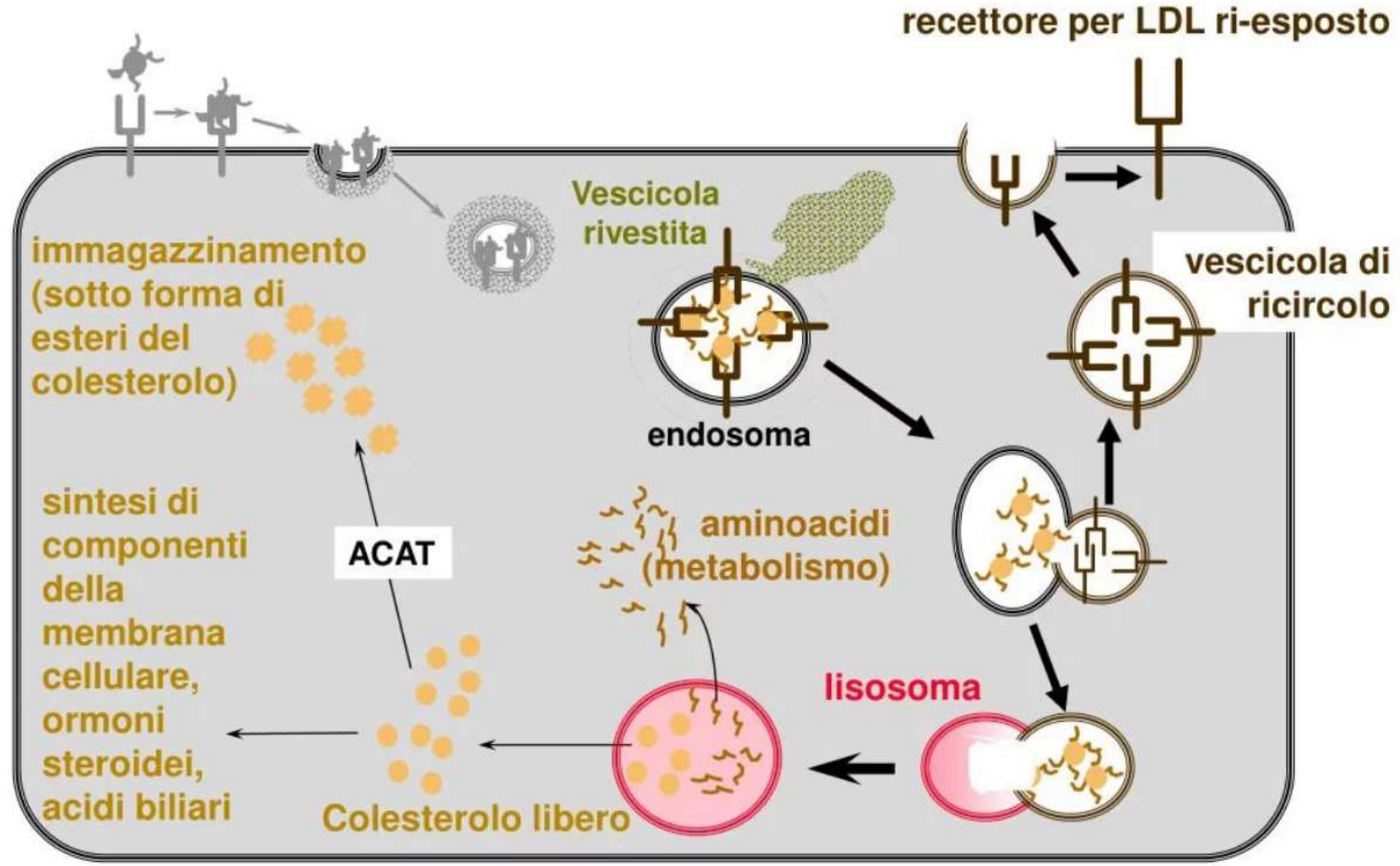
		Punti
Storia familiare		
a) Parenti di primo grado con coronaropatia (CHD) prematura (<55 anni negli uomini; <60 anni nelle donne)		1
b) Parenti di primo grado con colesterolo >8 mmol/L (≥310 mg/dL) (o >95° percentile del Paese)		1
c) Parenti di primo grado con xantomi tendinei e/o arco corneale		2
d) Bambini <18 anni con colesterolo >6 mmol/L (≥230 mg/dL) (o >95° percentile del Paese)		2
Storia clinica		
a) Soggetto con CHD prematura (<55 anni negli uomini; <60 anni nelle donne)		2
b) Soggetto con malattia vascolare cerebrale o periferica prematura (<55 anni negli uomini; <60 anni nelle donne)		1
Esame fisico		
a) Xantoma tendineo		6
b) Arco corneale in un soggetto con <45 anni		4
Risultati biochimici (colesterolo LDL)	>8,5 mmol/L (>325 mg/dL)	8
	6,5-8,4 mmol/L (251-325 mg/dL)	5
	5,0-6,4 mmol/L (191-250 mg/dL)	3
	4,0-4,9 mmol/L (155-190 mg/dL)	1
Analisi del DNA		
a) Mutazione causative nota nei geni		8
Diagnosi "certa" con un punteggio >8 punti. Diagnosi "probabile" con un punteggio tra 6 e 8 punti. Diagnosi "possibile" con un punteggio tra 3 e 5 punti. Diagnosi "improbabile" con un punteggio tra 0 e 2 punti.		

Nordestgaard BG et al. Eur Heart J 2013

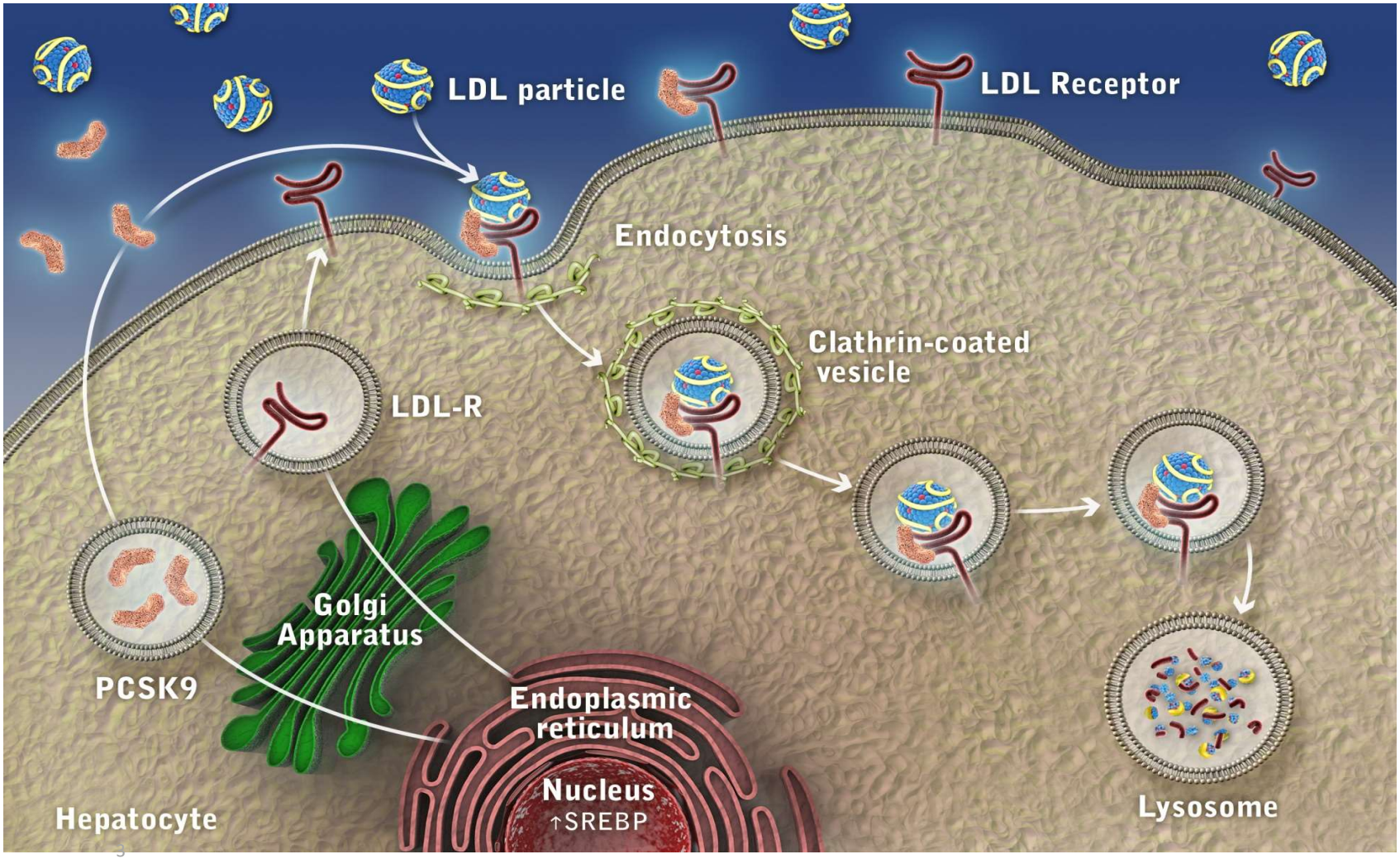
TRASPORTO E METABOLISMO INTRACELLULARE DEL COLESTEROLO



TRASPORTO E METABOLISMO INTRACELLULARE DEL COLESTEROLO

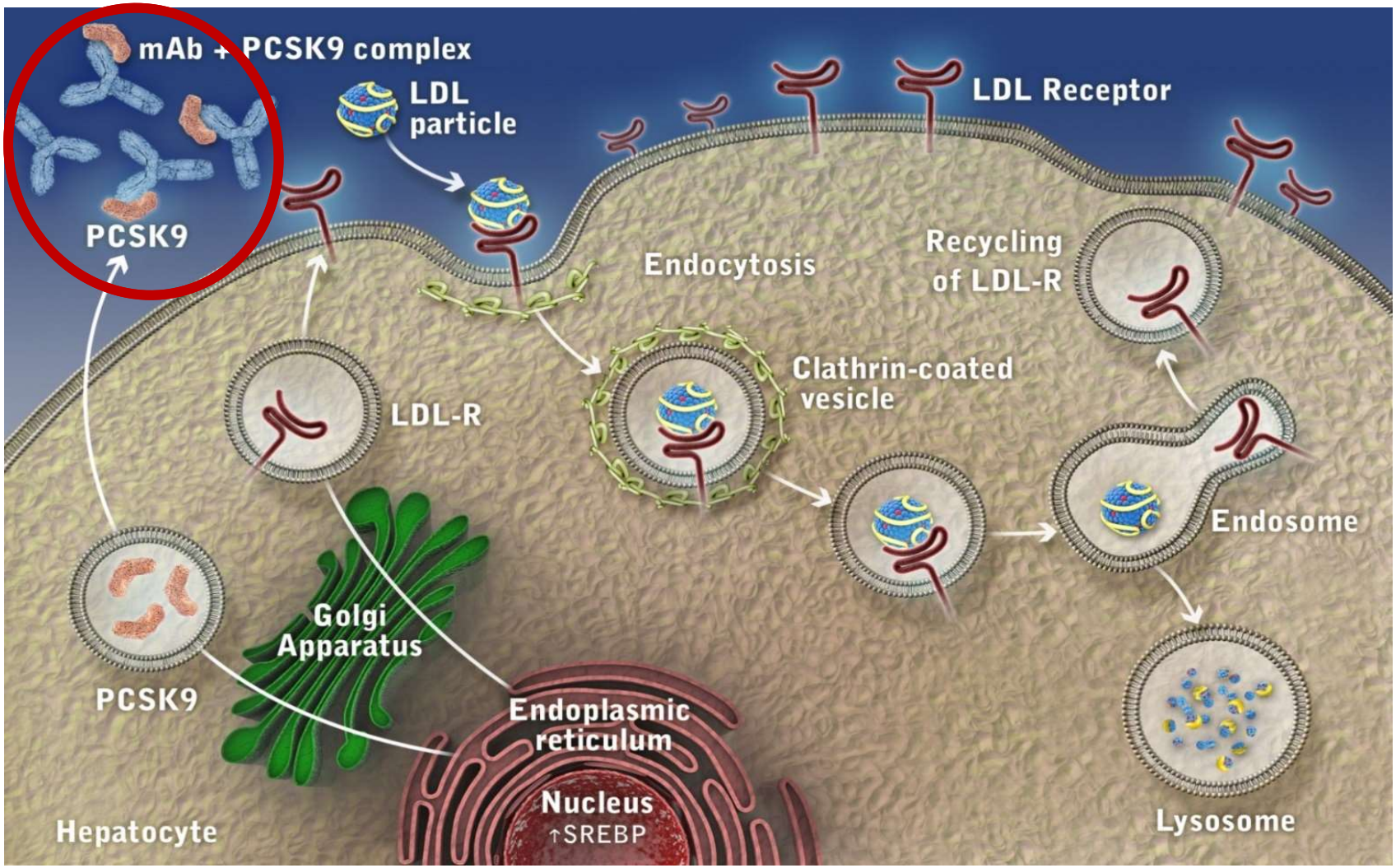


Ruolo del PCSK9 nella regolazione dell'espressione of recettore per LDL



Adapted from Catapano & Papadopoulos Atherosclerosis 2013;228:18–28

Impact of a PCSK9 Monoclonal Antibody on LDL Receptor Expression



Adapted from Catapano & Papadopoulos *Atherosclerosis* 2013;228:18–28

Overview of the ODYSSEY program for efficacy and safety of alirocumab

14 global Phase 3 trials including >23 500 patients across >2000 study centres

HeFH population

Add-on to max tolerated statin (± other LLT)

ODYSSEY FH I (NCT01623115; EFC12492)
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=486; 18 months

ODYSSEY FH II (NCT01709500; CL1112)
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=249; 18 months

ODYSSEY HIGH FH (NCT01617655; EFC12732)
LDL-C ≥160 mg/dL
n=107; 18 months

ODYSSEY OLE (NCT01954394; LTS 13463)
Open-label study for FH from EFC 12492, CL 1112, EFC 12732 or LTS 11717
n≥1000; 30 months

ODYSSEY LONG TERM (NCT01507831; LTS11717)
LDL-C ≥70 mg/dL
n=2,341; 18 months

HC in high CV-risk population

Add-on to max tolerated statin (± other LLT)

ODYSSEY COMBO I (NCT01644175; EFC11568)
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=316; 12 months

***ODYSSEY COMBO II (NCT01644188; EFC11569)**
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=720; 24 months

ODYSSEY CHOICE I (NCT01926782; CL1308)
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=700; 12 months

ODYSSEY OUTCOMES (NCT01663402; EFC11570)
LDL-C ≥70 mg/dL
n=18,000; 64 months

Additional populations

ODYSSEY MONO (NCT01644474; EFC11716)
Patients on no background LLTs
LDL-C ≥100 mg/dL
n=103; 6 months

ODYSSEY ALTERNATIVE (NCT01709513; CL1119)
Patients with defined statin intolerance
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=314; 6 months

ODYSSEY CHOICE II (NCT02023879; EFC13786)
Patients not treated with a statin
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=200; 6 months

ODYSSEY OPTIONS I (NCT01730040; CL1110)
Patients not at goal on moderate-dose atorvastatin
LDL-C ≥70 mg/dL OR LDL-C ≥100 m
n=355; 6 months

ODYSSEY OPTIONS II (NCT01730053; CL1118)
Patients not at goal on moderate-dose rosuvastatin
LDL-C ≥70 mg/dL OR LDL-C ≥100 n
n=305; 6 months

ODYSSEY

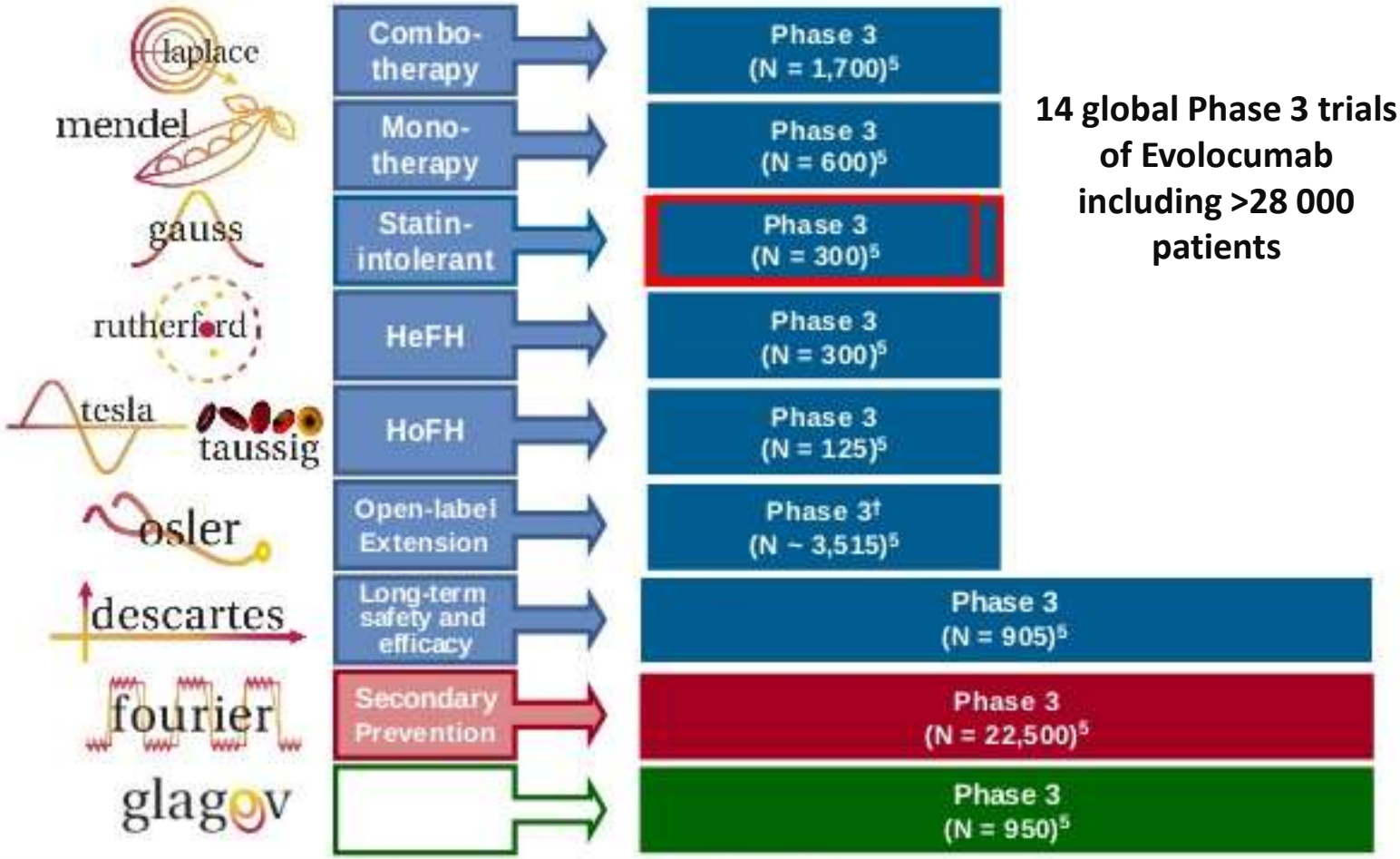
Significant and Consistent LDL-C Reduction across All 10 Reported Trials

	Study	Dosing q2w	Baseline LDL-C (mg/dL)	LDL-C Change from Baseline at 24 Weeks			
				Alirocumab	Comparator		
HeFH	HIGH FH	150 mg	198	↓ **46%**	↓ 7%	placebo	On top of max statin doses
	FH I	75/150 mg[1]	145	↓ **49%**	↑ 9%	placebo	
	FH II	75/150 mg[1]	134	↓ **49%**	↑ 3%	placebo	
High CV Risk	LONG TERM	150 mg	122	↓ **61%**	↑ 1%	placebo	
	COMBO I	75/150 mg[1]	102	↓ **48%**	↓ 2%	placebo	
	COMBO II	75/150 mg[1]	108	↓ **51%**	↓ 21%	ezetimibe	
	OPTION I	75/150 mg[1]	105	↓ **44-54%**	↓ 21-23% ↓ 5% ↓ 21%	ezetimibe statin x2 statin switch	On top of regular statin doses
	OPTION II	75/150 mg[1]	111	↓ **36-51%**	↓ 11-14% ↓ 16%	ezetimibe statin switch	
Statin Intolerant	ALTERNATIVE	75/150 mg[1]	191	↓ **45%**	↓ 15%	ezetimibe	Not receiving statins
Moderate CV Risk	MONO	75/150 mg[1]	140	↓ **48%**	↓ 16%	ezetimibe	

Primary efficacy endpoint met in all 10 reported trials

PROFICIO

Program to **R**educe **L**DL-**C** and **C**ardiovascular **O**utcomes **F**ollowing **I**nhibition of **P**CSK9 **I**n Different **P**opulations



14 global Phase 3 trials of Evolocumab including >28 000 patients

*Subjects completed a qualifying Phase 2 study. †Subjects completed a qualifying Phase 3 study.

1. Giugliano RP, et al. *Lancet*. 2012;380:2007-2017. 2. Koren MJ, et al. *Lancet*. 2012;380:1995-2006. 3. Sullivan D, et al. *JAMA*. 2012;308:2497-2506.
4. Raal F, et al. *Circulation*. 2012;126:2408-2417. 5. Clinical Trials.gov. Available at: http://www.clinicaltrials.gov. Accessed Oct. 2, 2013.

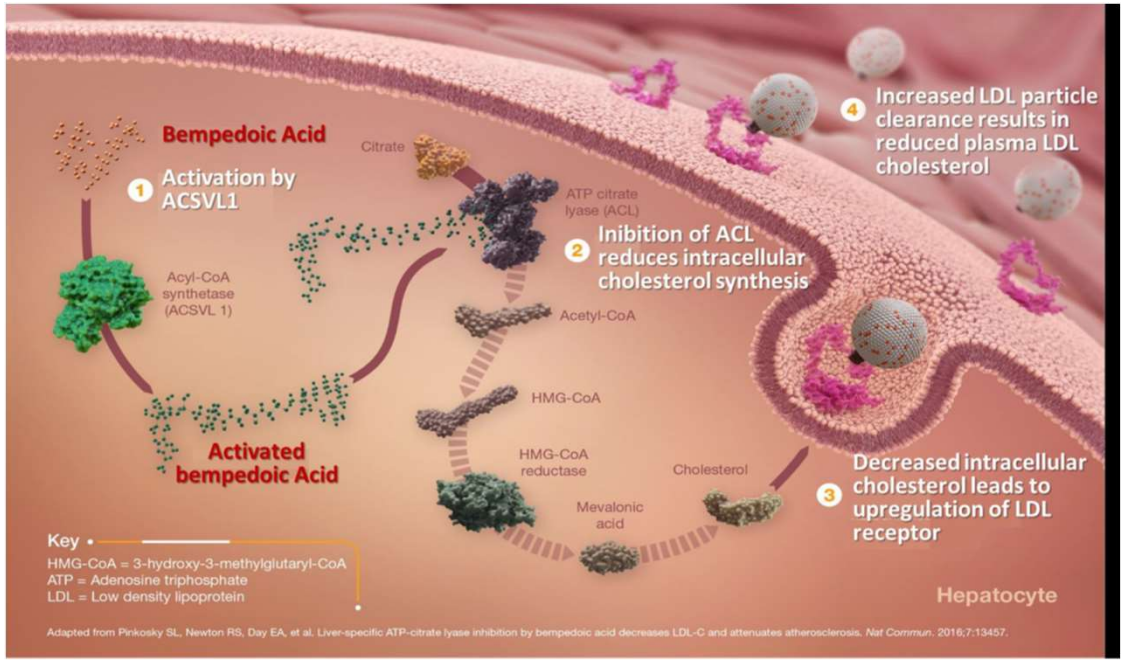
Quando impiegare gli anti-PCSK9?

- **Ipercolesterolemia in pazienti ad alto rischio cardiovascolare, non controllati con dosi massime tollerate di statine in associazione ad ezetimibe**
- **Ipercolesterolemia familiare**
- **Intolleranza alle statine**

Possiamo usare nuovi farmaci? Parola all'acido bempedoico

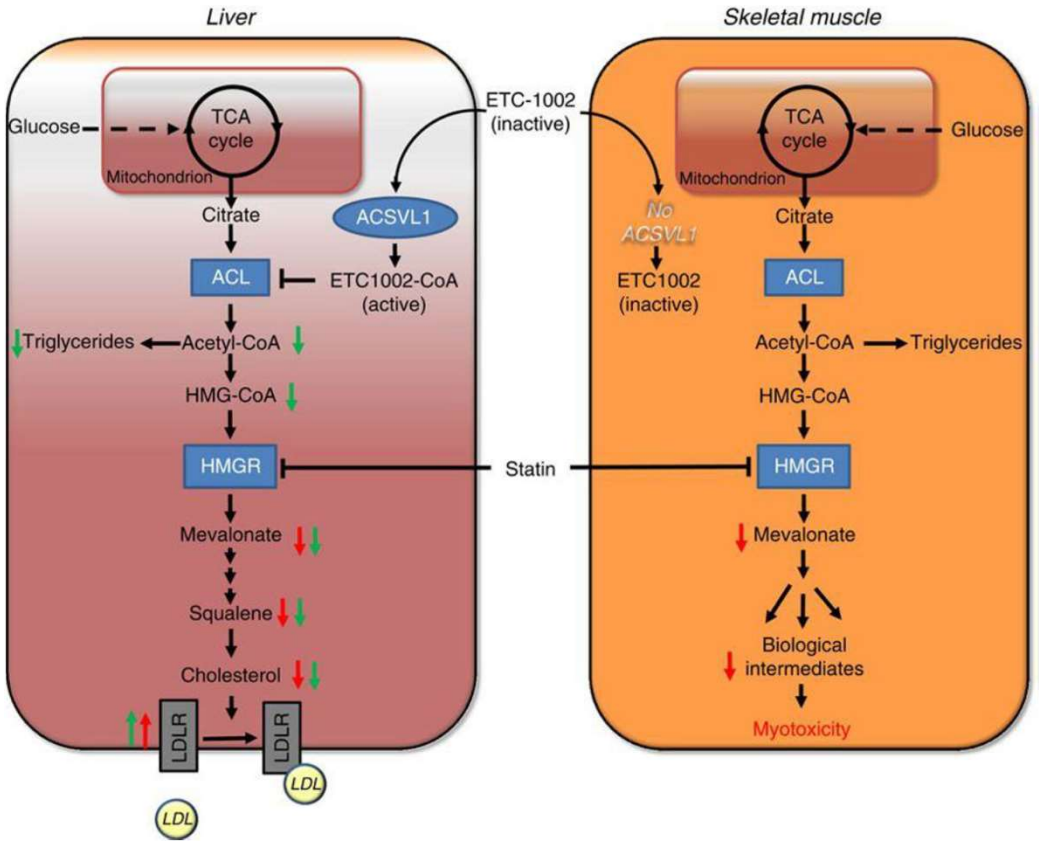
L'acido bempedoico inibisce l'enzima ATP citrato liasi (ACL) nella via di sintesi del colesterolo , a monte rispetto al target delle statine

La conseguente up regolazione dei recettori per le LDL determina un'aumentata captazione di LDL da parte delle c. epatiche con relativa riduzione dei livelli plasmatici di C LDL

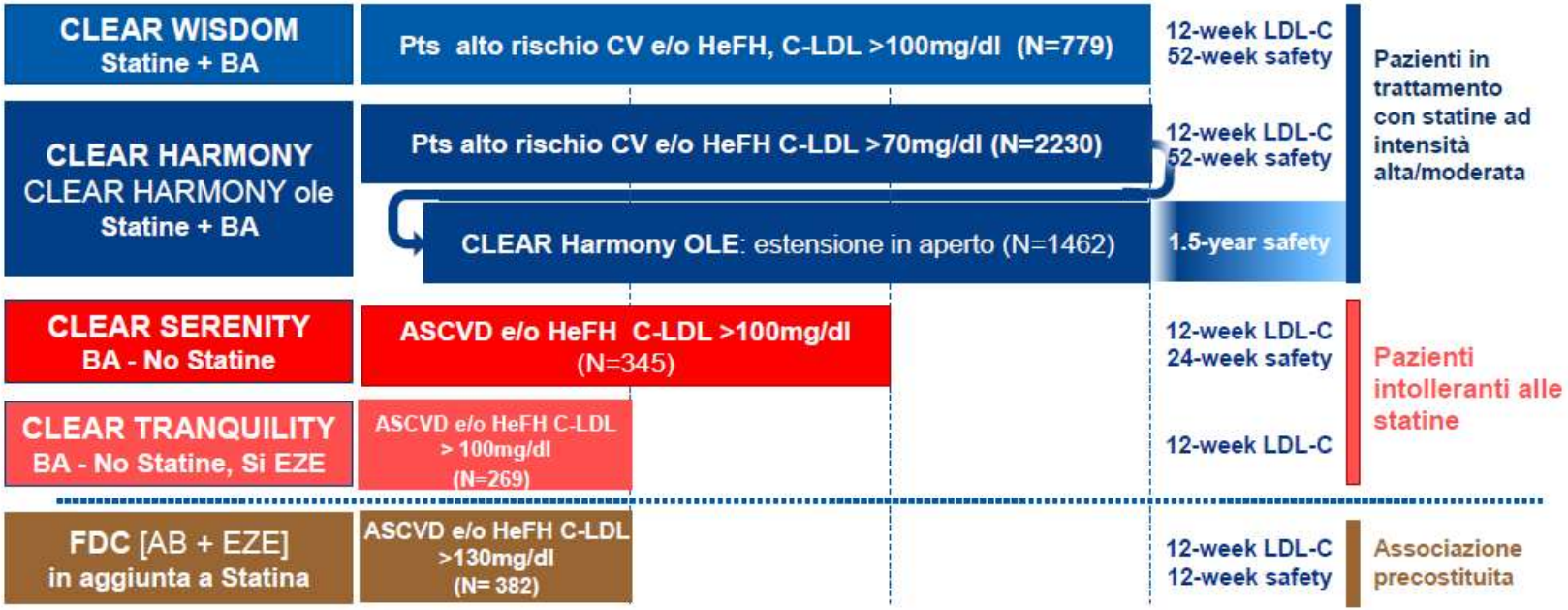


L’acido bempedoico non è attivato nel muscolo scheletrico

ACSVL: Acyl CoA synthetase



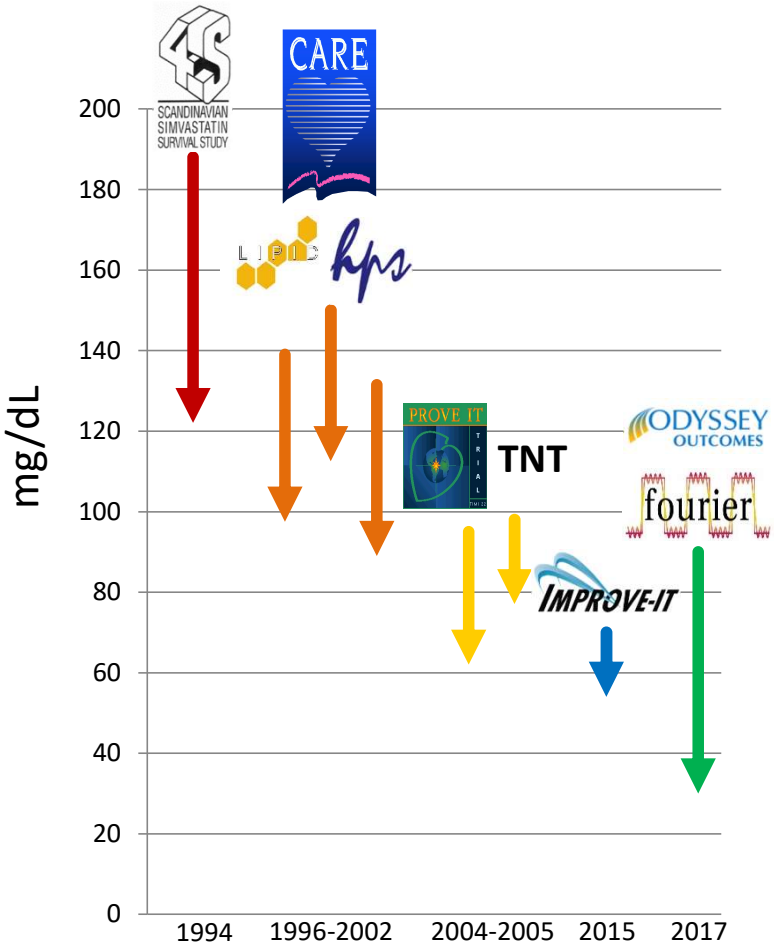
Studi clinici di fase 3 con Acido Bempedoico



ASCVD = malattia cardiovascolare su base aterosclerotica; AB = acido bempedoico; EZE = ezetimibe; HeFH = ipercolesterolemia familare eterozigote; LDL-C Colesterolo LDL; OLE = open-label extension; SI = statino-intolleranti

1.Goldberg AC et al. JAMA. 2019;322(18):1780-1788. doi:10.1001/jama.2019.16565; 2. Ray KK, et al. *N Engl J Med*. 2019;380:1022-32; 3. Ballantyne et al. Poster presented virtually at the European Society of Cardiology Congress, 29 August – 1 September 2020; 4. Laufs U, et al. *J Am Heart Assoc*. 2019;8:e011662; 5. Ballantyne CM, et al. *Atherosclerosis*. 2018;277:195-2036. 6. Ballantyne CM et al. *Eur J Prev Cardiol*. 2020;27(6):593-603.

Even below LDL-c target further LDL-c reduction gives additional CV benefit



- A quarter of a century of treating LDL-C

High is bad

Average is not good

Lower is better

Even lower is even better

Lowest is best

I ♥ DACHSHUNDS

Arrivederci a Bari per il
XX Congresso Regionale
FADOI PUGLIA!!!!!
E XVII ANIMO PUGLIA