11 WORKSHOP NAZIONALE CISAI

TORINO 2023

20 • 21 APRILE

Tollerabilità dei farmaci antinfettivi e co-morbilità associate all'infezione da HIV

Presidenti del Convegno

Paolo Bonfanti, Antonio Di Biagio, Giancarlo Orofino

FONDAZIONE ASIA

CISAI

Azienda Ospedaliera
Ospedale Niguarda Ca' Granda

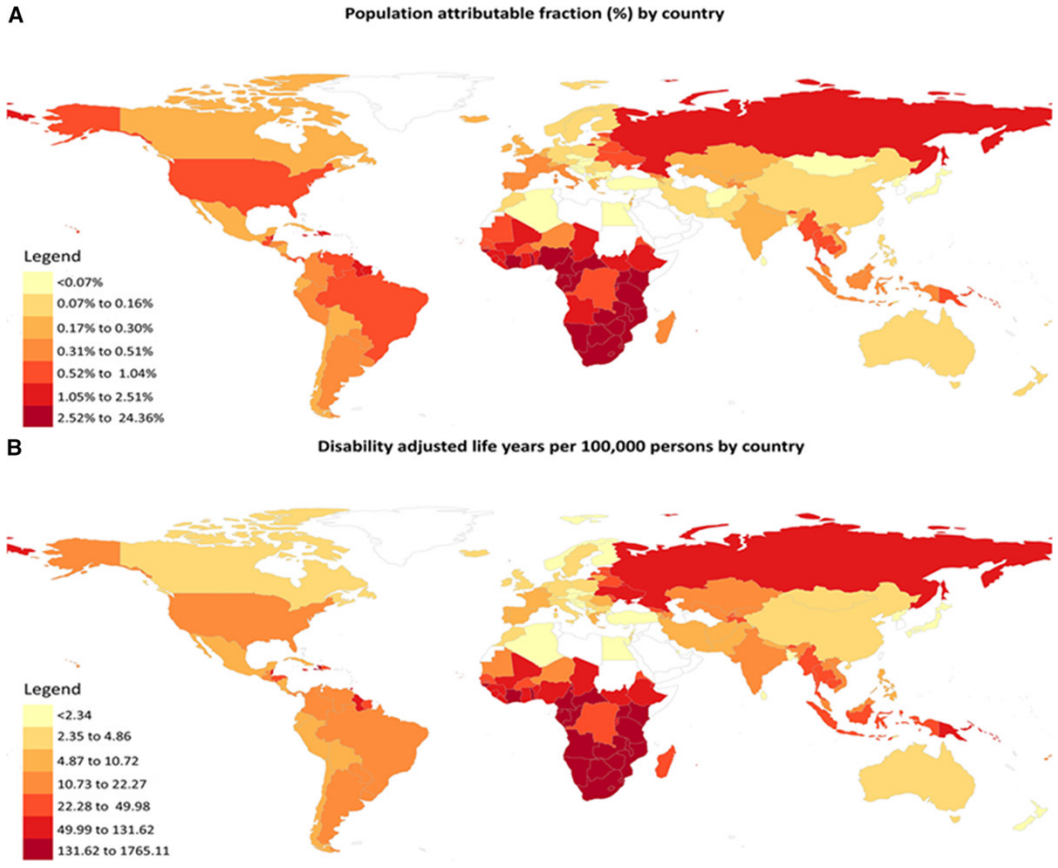
Sistema Sanitario Regione Lombardia

Aprile 2023

Terapia delle dislipidemie: nuove evidenze e strategie terapeutiche

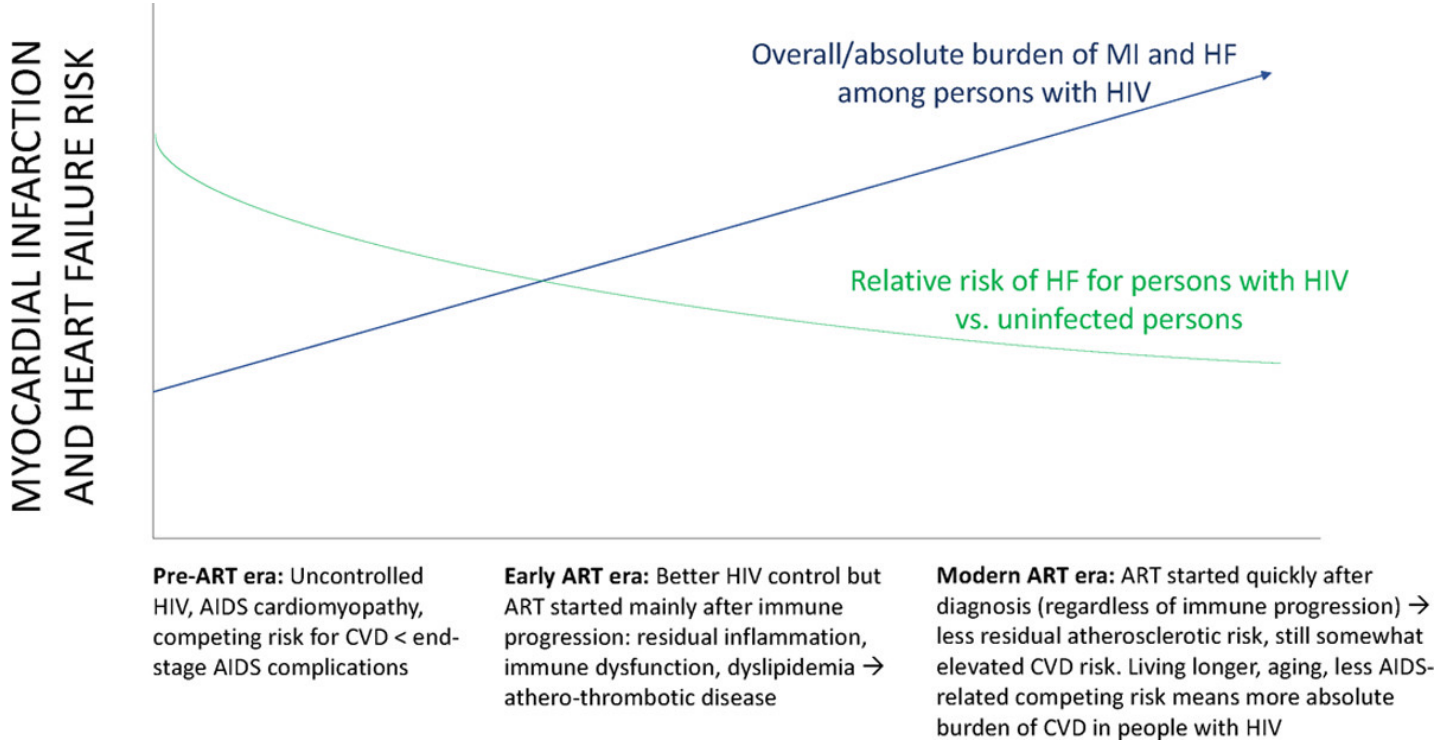
Cristina Giannattasio
De Gasperis Cardio Center Niguarda Milano e
Università di Milano Bicocca Milano

a) Popolazione HIV affetta e/o trattata e b) disabilità per evento cardiovascolare attesa



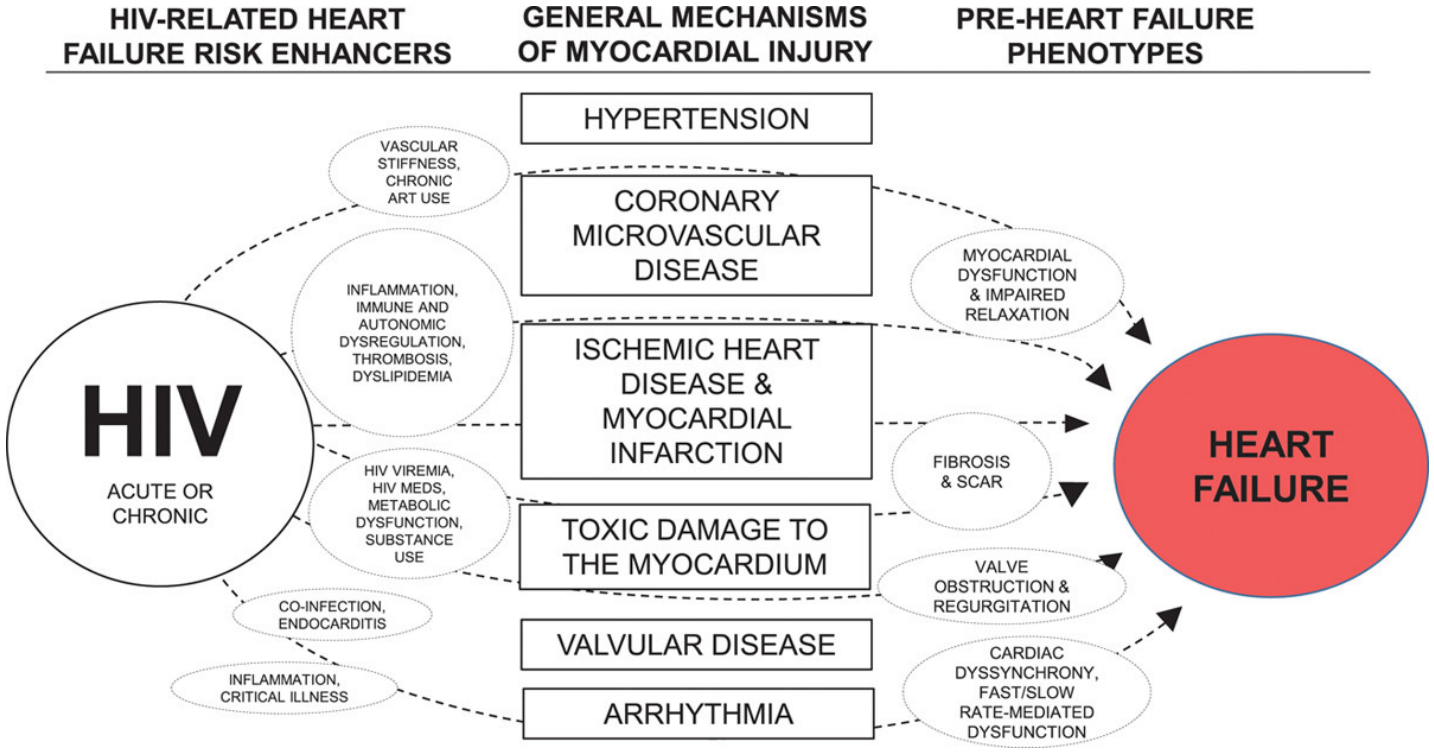
Matthew J. Feinstein. Circulation. Characteristics, Prevention, and Management of Cardiovascular Disease in People Living With HIV: A Scientific Statement From the American Heart Association, Volume: 140, Issue: 2, Pages: e98-e124, DOI: (10.1161/CIR.0000000000000695)

Rischio Assoluto e Relativo di Infarto Miocardico e Scompenso cardiaco nelle Diverse ere di trattamento HIV



Matthew J. Feinstein. Circulation. Characteristics, Prevention, and Management of Cardiovascular Disease in People Living With HIV: A Scientific Statement From the American Heart Association, Volume: 140, Issue: 2, Pages: e98-e124, DOI: (10.1161/CIR.0000000000000695)

Meccanismi «tradizionali» di danno miocardico e Meccanismi specifici HIV relati



Matthew J. Feinstein. Circulation. Characteristics, Prevention, and Management of Cardiovascular Disease in People Living With HIV: A Scientific Statement From the American Heart Association, Volume: 140, Issue: 2, Pages: e98-e124, DOI: (10.1161/CIR.0000000000000695)

Characteristics, Prevention, and Management of Cardiovascular Disease in People Living With HIV: A Scientific Statement From the American Heart Association

Matthew J. Feinstein, Priscilla Y. Hsue,

Originally published Circulation 3 Jun 2019

- There are well-documented disparities in care for CVD among PLWH. PLWH have fewer clinic visits that meet guideline-directed medical therapy for aspirin therapy (5.1% versus 13.8%) and use of statins (23.6% versus 35.8%).[21]

Profilo lipidico e terapia antiretrovirale in una coorte di bambini, adolescenti e giovani adulti con infezione da HIV a trasmissione verticale.

Lipid profile and antiretroviral therapy in a cohort of children, adolescents and young adults infected with HIV by vertical transmission.

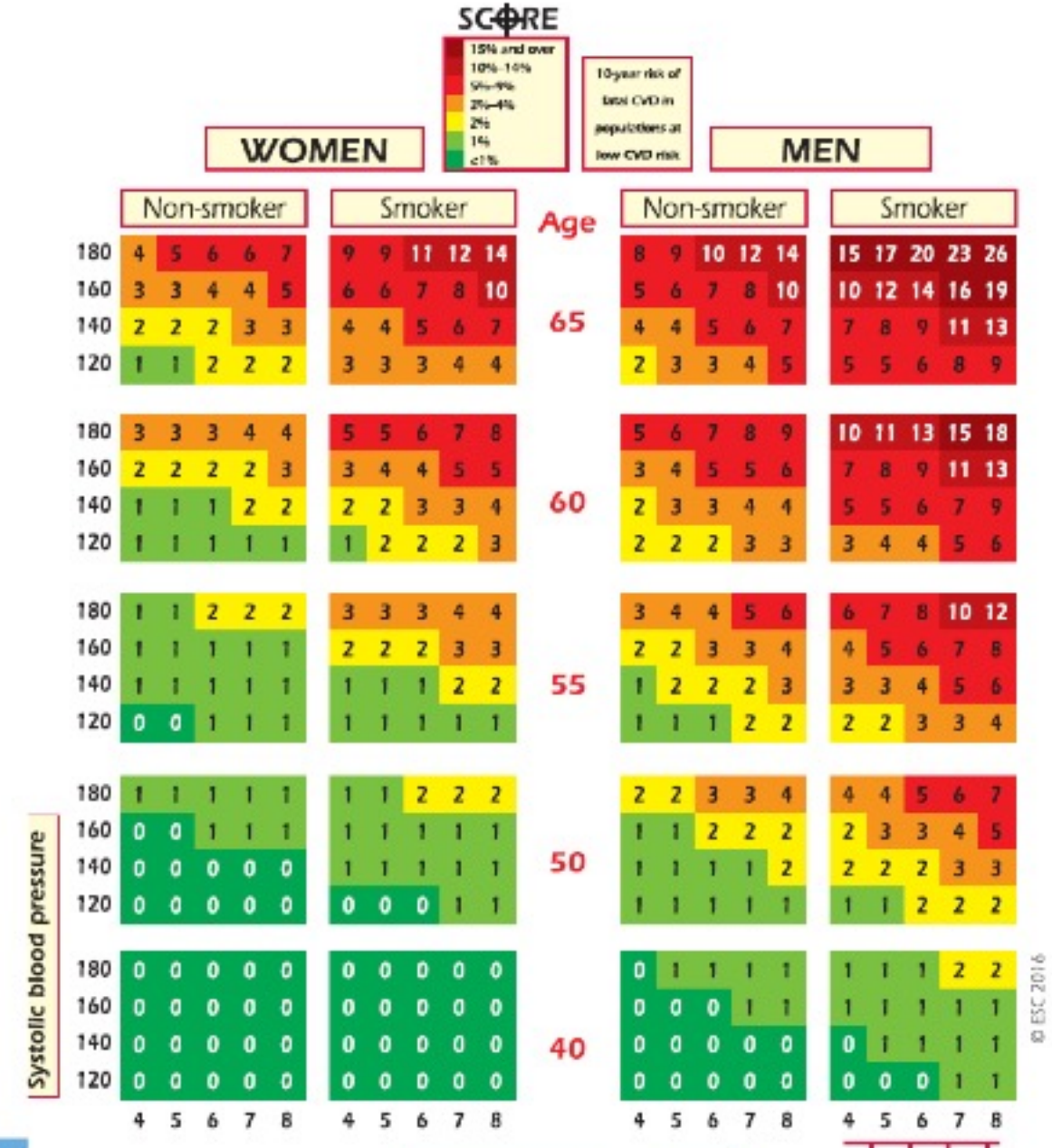
Laura Bisoffi, Daniele Donà, Carlo Giaquinto, Osvalda Rampon
Dipartimento per la Salute della Donna e del Bambino, Università degli Studi di Padova, Azienda Ospedaliera

JHA 2017; 2(3): 65-70

Lo studio ha evidenziato una quota elevata (57.9%) di pazienti con uno o più parametri lipidici alterati tra colesterolo totale, LDL, HDL e trigliceridi; per quanto riguarda la relazione tra alterazioni del profilo lipidico e terapia antiretrovirale, non abbiamo però rilevato associazioni significative. Quella dei pazienti pediatrici e giovani adulti con infezione verticale da HIV è quindi una popolazione ad elevato rischio di aterosclerosi precoce ed eventi cardiovascolari; la prevenzione è perciò fondamentale, sia a livello primario, sia a livello di screening e diagnosi precoce della patologia cardiovascolare

RISCHIO IN HIV

- FATTORI DI RISCHIO TRADIZIONALI ESASPERATI NELLA POPOLAZIONE IN OGGETTO
- FATTORI SPECIFICI LEGATI ALLA MALATTIA ED ALLA TERAPIA
- INVECCHIAMENTO DELLA POPOLAZIONE



LINEE GUIDA EUROPEE ESH/ESC

Recommendations for cardiovascular risk assessment

Recommendations	Class[a]	Level[b]
Systematic CV risk assessment is recommended in individuals at increased CV risk, i.e. with family history of premature CVD, familial hyperlipidaemia, major CV risk factors (such as smoking, high BP, DM or raised lipid levels) or comorbidities increasing CV risk.	I	C
It is recommended to repeat CV risk assessment every 5 years, and more often for individuals with risks close to thresholds mandating treatment.	I	C
Systematic CV risk assessment may be considered in men >40 years of age and in women >50 years of age or post-menopausal with no known CV risk factors.	IIb	C
Systematic CV risk assessment in men <40 of age and women <50 years of age with no known CV risk factors is not recommended.	III	C

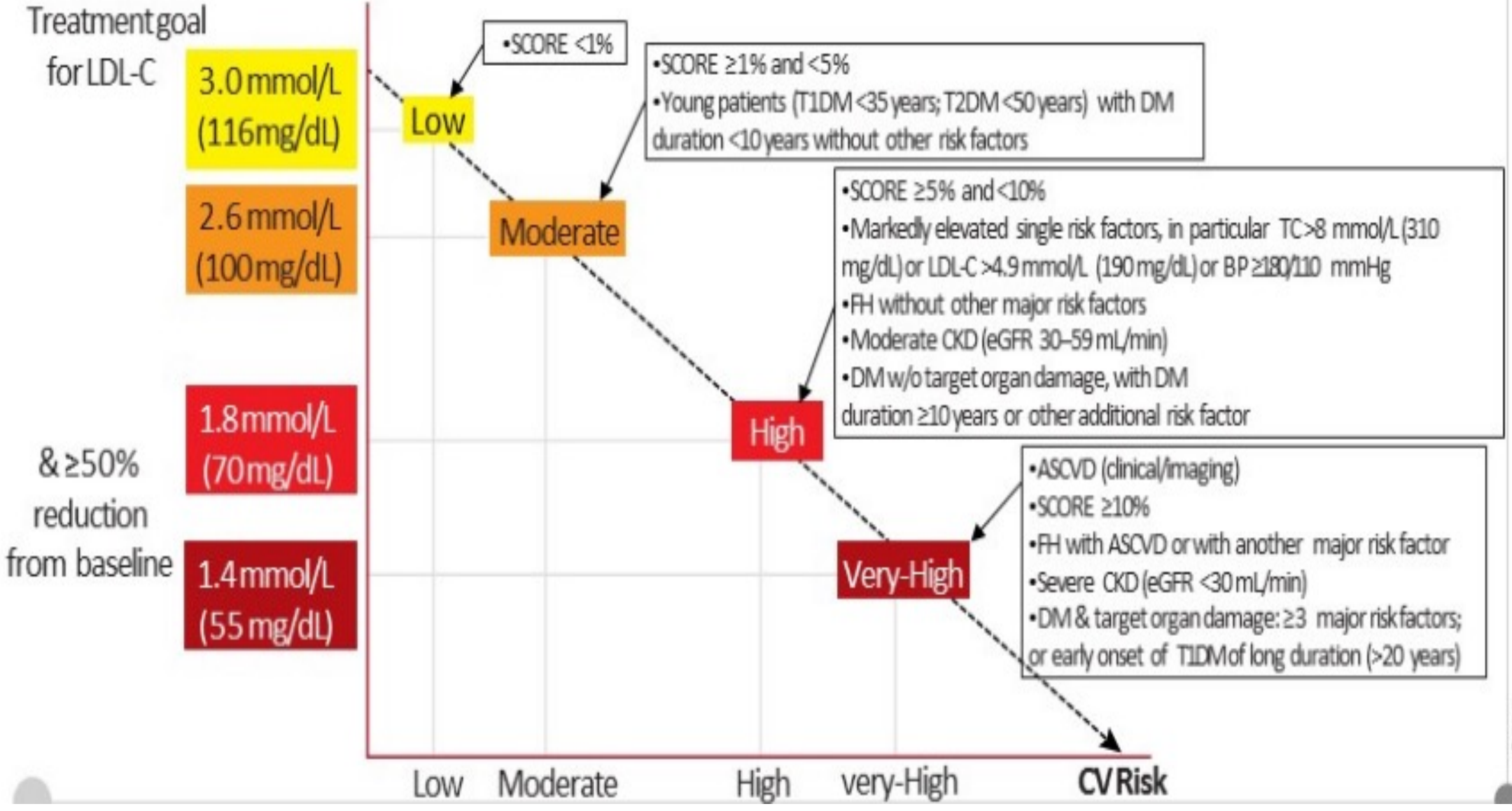
Table 6 Risk factor goals and target levels for important cardiovascular risk factors

Smoking	No exposure to tobacco in any form.
Diet	Low in saturated fat with a focus on wholegrain products, vegetables, fruit and fish.
Physical activity	At least 150 minutes a week of moderate aerobic PA (30 minutes for 5 days/week) or 75 minutes a week of vigorous aerobic PA (15 minutes for 5 days/week) or a combination thereof.
Body weight	BMI 20–25 kg/m^2. Waist circumference <94 cm (men) or <80 cm (women).
Blood pressure	<140/90 mmHg[a]
Lipids[b] LDL[c] is the primary target	**Very high-risk: <1.8 mmol/L (<70 mg/dL),** or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL)[d] **High-risk: <2.6mmol/L (<100 mg/dL)**, or a reduction of at least 50% if the baseline is between 2.6 and 5.1 mmol/L (100 and 200 mg/dL) **Low to moderate risk: <3.0 mmol/L (<115 mg/dL).**
HDL-C	No target but >1.0 mmol/L (>40mg/dL) in men and >1.2 mmol/L (>45 mg/dL) in women indicate lower risk.
Triglycerides	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)

LINEE GUIDA 2019

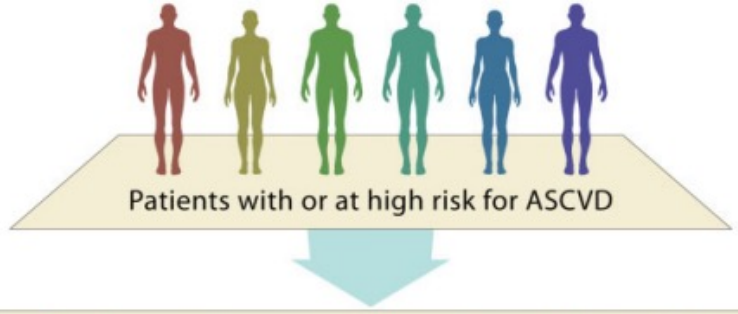
	2016 LDL-C Goals[1]	2019 LDL-C Goals[2]
Low Risk	< 3.0 mmol/L (116 mg/dL)	
Moderate Risk	< 3.0 mmol/L (116 mg/dL)	< 2.6 mmol/L (100 mg/dL)
High Risk	50% reduction OR < 2.6 mmol/L (100mg/dL)	50% reduction AND < 1.8 mmol/L (70 mg/dL)
Very high risk	50% reduction OR < 1.8 mmol/L (70 mg/dL)	50% reduction AND < 1.4 mmol/L (55 mg/dL)
Second CV event within 2 years	NA	50% reduction AND < 1.0 mmol/L (40 mg/dL)

LINEE GUIDA 2019



Very high risk	**People with any of the following:** **Documented CVD, either clinical or unequivocal on imaging.** • **Clinical CVD** includes; acute myocardial infarction, acute coronary syndrome, coronary or other arterial revascularization, stroke, TIA, aortic aneurysm, PAD • **Unequivocal documented CVD on imaging** includes: significant plaque (i.e. ≥ 50% stenosis) on angiography or ultrasound. It does not include increase in carotid intima-media thickness. **Diabetes mellitus with target organ damage**, e.g. proteinuria or a with a major risk factor such as grade 3 hypertension or hypercholesterolaemia **Severe CKD** (eGFR < 30 mL/min/1.73 m^2) **A calculated 10-year SCORE of ≥ 10%**
High risk	**People with any of the following:** **Marked elevation of a single risk factor**, particularly cholesterol > 8 mmol/L (> 310 mg/dL) e.g. familial hypercholesterolaemia, grade 3 hypertension (BP ≥ 180/110 mmHg) **Most other people with diabetes mellitus** (except some young people with type 1 diabetes mellitus and without major risk factors, that may be moderate risk) **Hypertensive LVH** **Moderate CKD eGFR 30–59 mL/min/1.73 m^2)** **A calculated 10-year SCORE of 5–10%**
Moderate risk	**People with:** **A calculated 10-year SCORE of 1% to < 5%** **Grade 2 hypertension** **Many middle-aged people** belong to this category
Low risk	**People with:** **A calculated 10-year SCORE of < 1%**

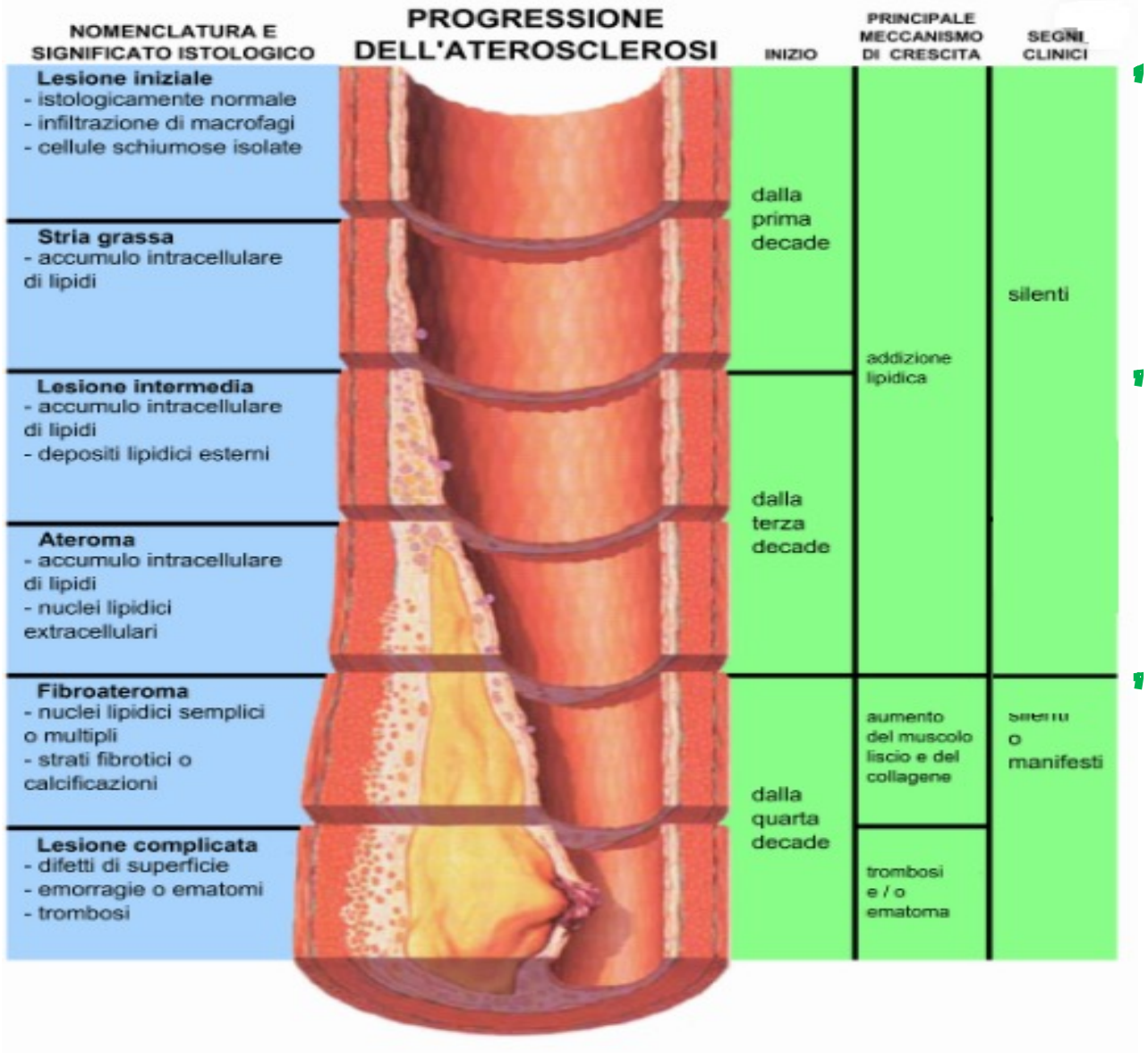
RISCHIO ESTREMO



Despite contemporary evidence-based therapies*, residual risk of ASCVD events persists

Biological Issue	Residual Cholesterol Risk	Residual Inflammatory Risk	Residual Thrombotic Risk	Residual Triglyceride Risk	Residual Lp(a) Risk	Residual Diabetes Risk
Critical Biomarker	LDL-C ≥100 mg/dL	hsCRP ≥2mg/L	No simple biomarker	TG ≥150mg/dL	Lp(a) ≥50mg/dL	HbA1c Fasting glucose
Potential Intervention	Targeted LDL/Apo B Reduction	Targeted Inflammation Reduction	Targeted Antithrombotic Reduction	Targeted Triglyceride Reduction	Targeted Lp(a) Reduction	SGLT2 Inhibitors GLP-1 Agonists
Randomized Trial Evidence	IMPROVE-IT FOURIER SPIRE ODYSSEY	CANTOS COLCOT *LoDoCo2* *OASIS-9*	PEGASUS COMPASS THEMIS	REDUCE-IT *PROMINENT*	Planned	EMPA-REG CANVAS DECLARE CREDENCE LEADER SUSTAIN-6 REWIND

PREVENZIONE



THE EARLIER

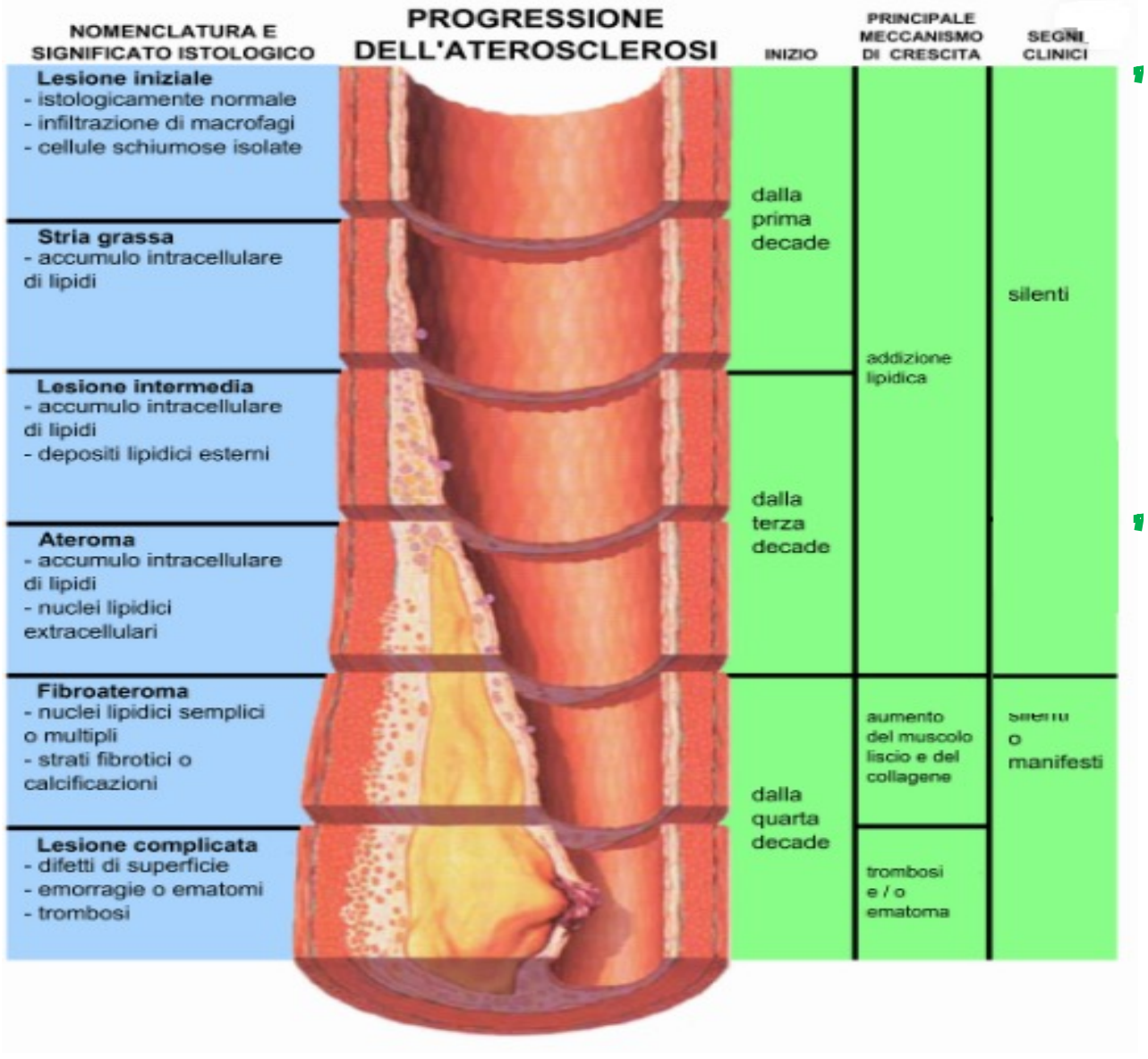
–

THE BETTER

PRIMARIA

SECONDARIA

PREVENZIONE



PRIMARIA

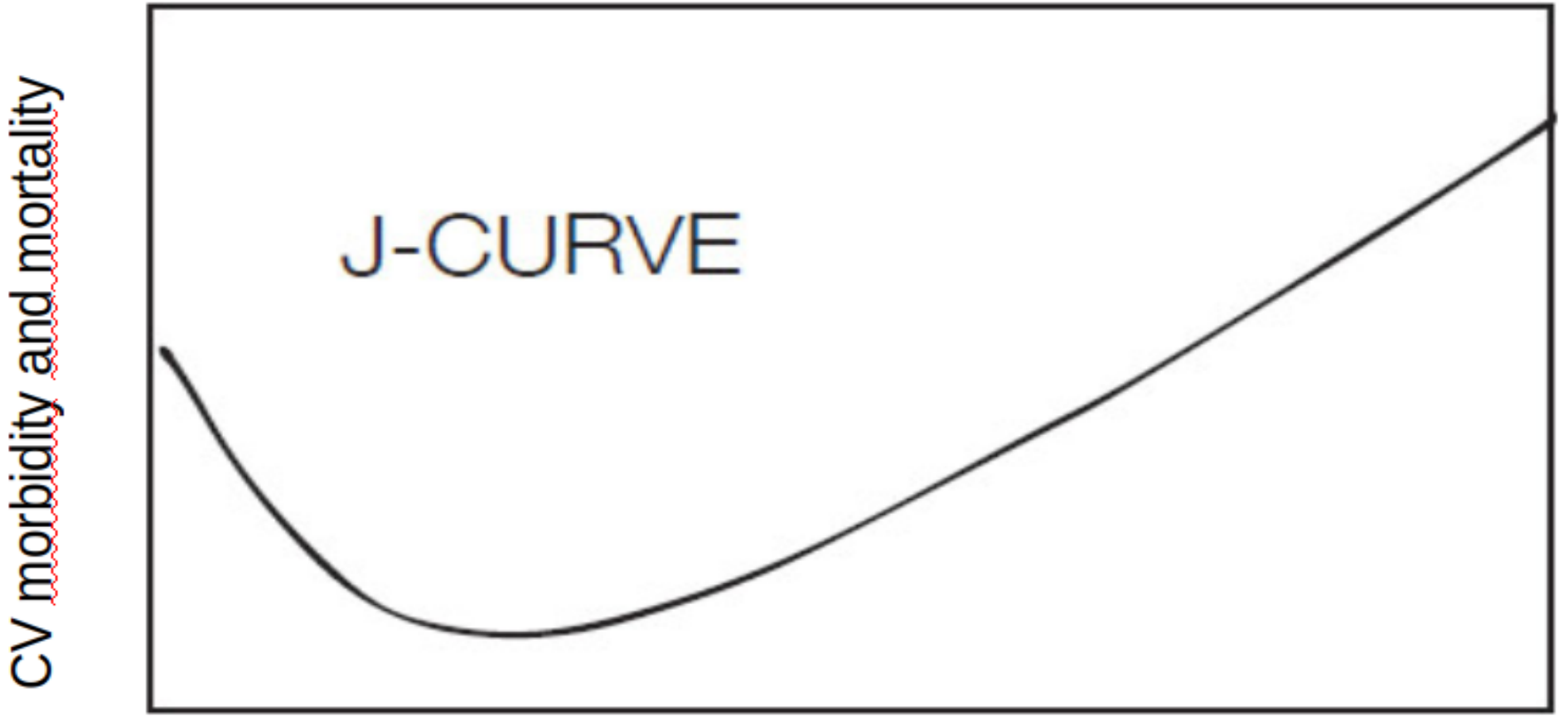
THE LOWER

–

THE BETTER

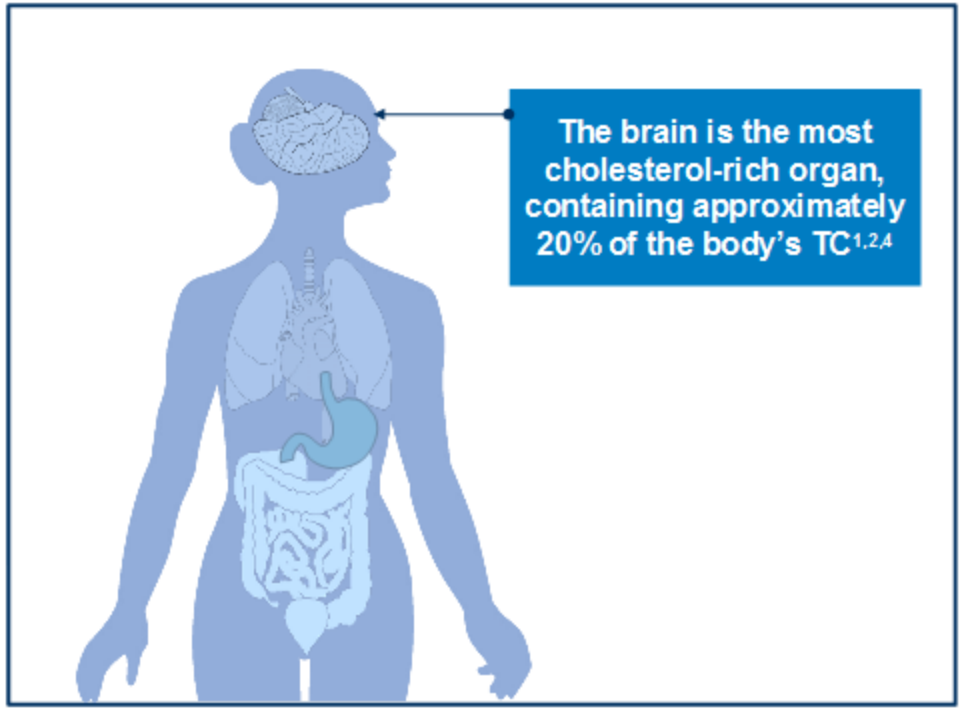
SECONDARIA

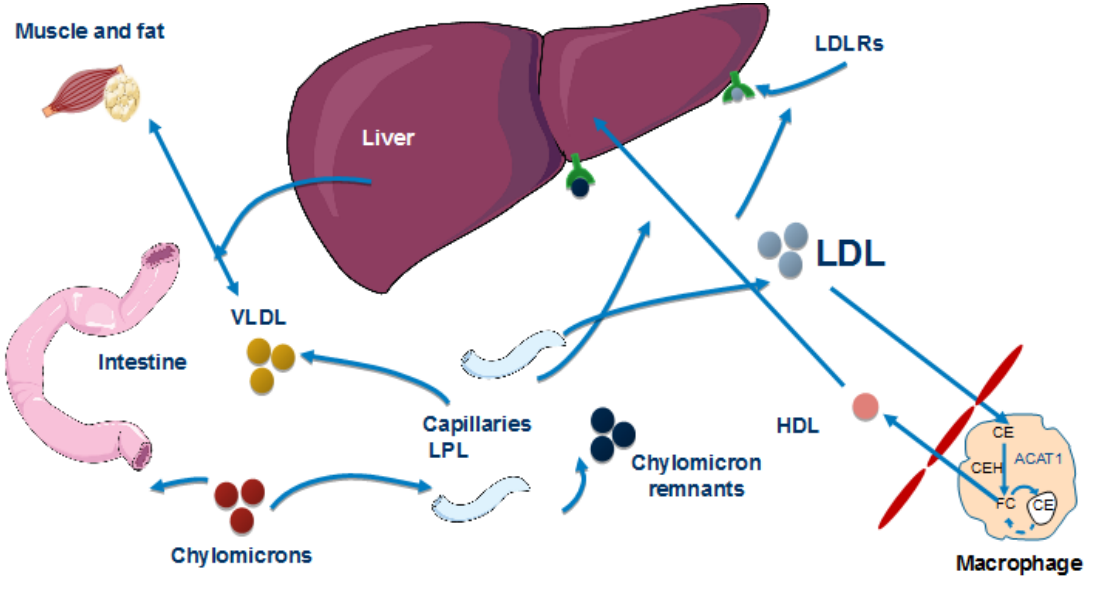
CURVA J



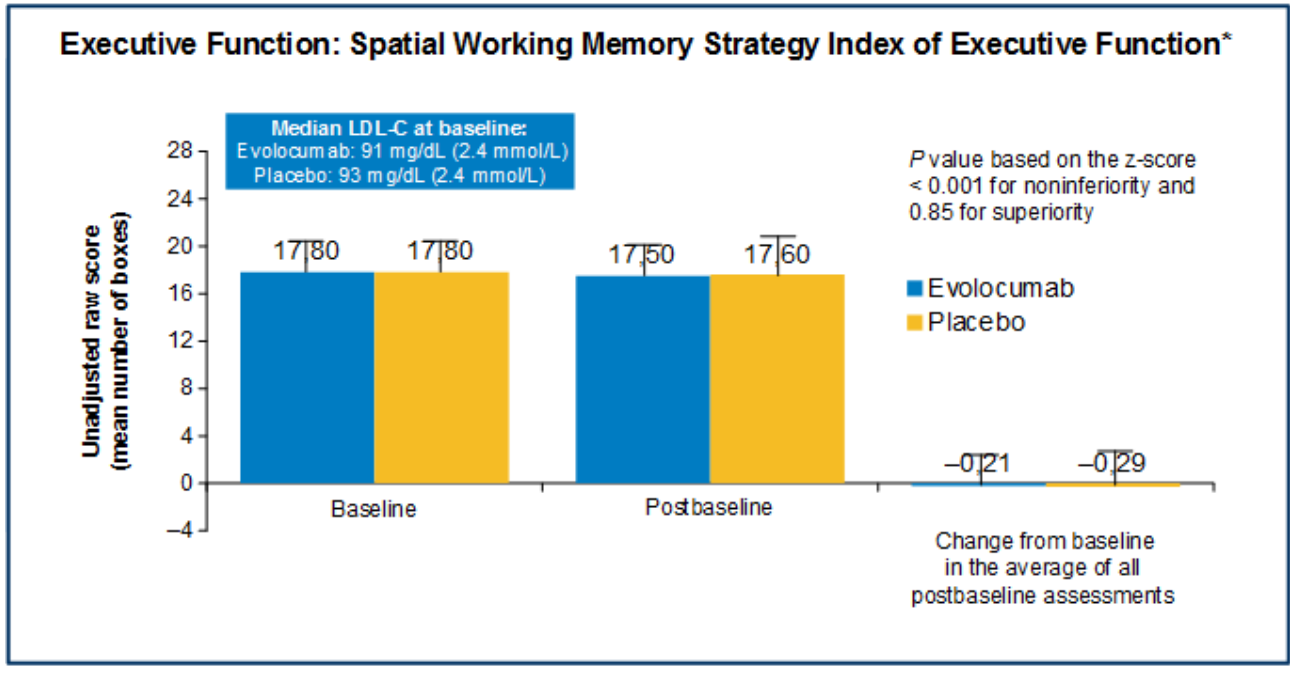
BASSI LIVELLI DI COLESTEROLO E ENCEFALO

Cholesterol in the Brain Is Supplied by De Novo Synthesis





BASSI LIVELLI DI COLESTEROLO



10.1161/CIRCULATIONAHA.122.061620

Long-Term Evolocumab in Patients with Established Atherosclerotic Cardiovascular Disease

Leucker TM, Gerstenblith G, et al. Evolocumab, a PCSK9-Monoclonal Antibody, Rapidly Reverses Coronary Artery Endothelial Dysfunction in People Living With HIV and P

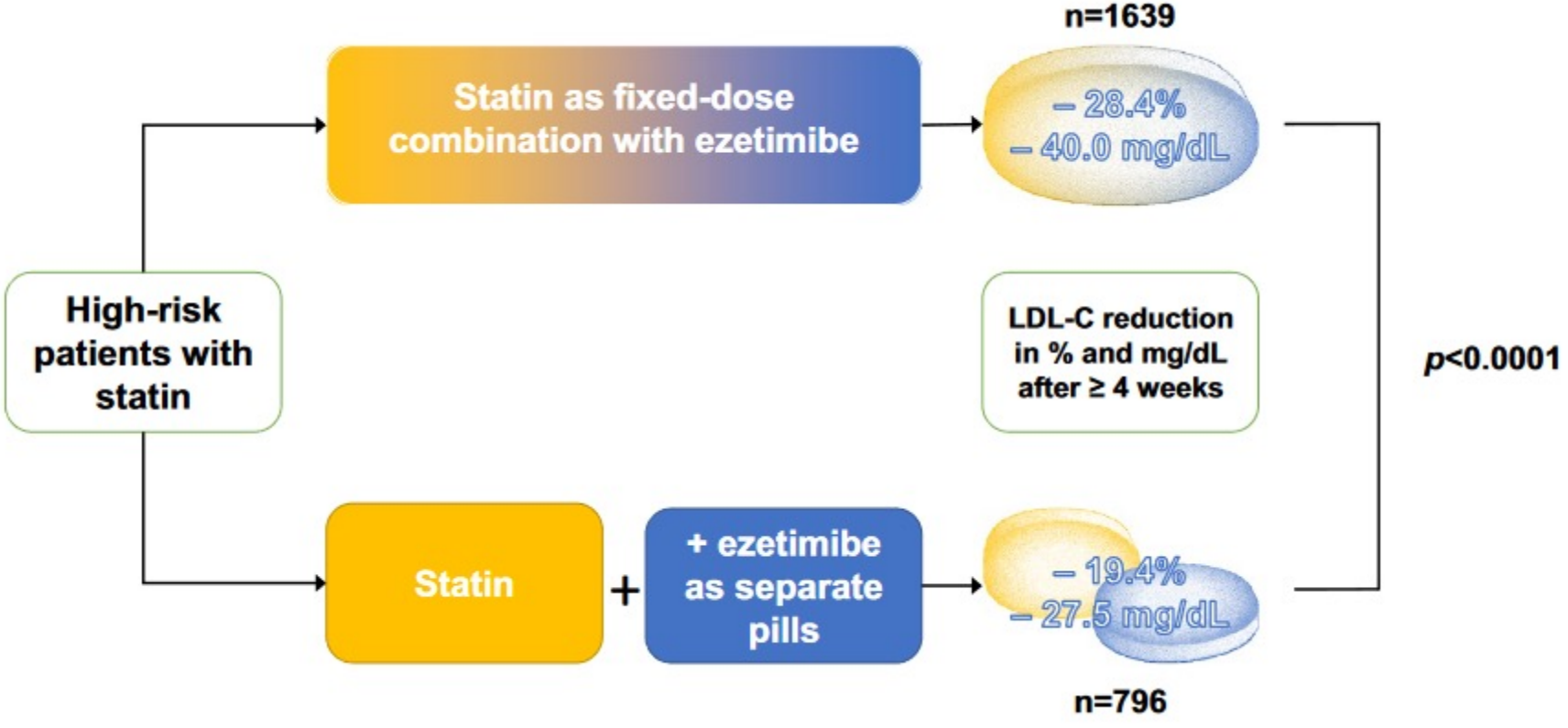
HIV infection and cardiovascular risk: the role of PCSK9.Vanessa Bianconi[1], Jessica Fusaro[1], Elisa Venanzi[1], Elisabetta Schiaroli[2], Matteo Pirro[1]; JHA 2019; 4(4):77-82

STATINA-EZETIMIBE

Non-statin lipid-lowering therapy over time in very-high-risk patients: effectiveness of fixed-dose statin/ezetimibe compared to separate pill combination on LDL-C

Clinical Research in Cardiology (2022) 111:243–252

Julius L. Katzmann[1] · Francesc Sorio-Vilela[2] · Eugen Dornstauder[3] · Uwe Fraas[3] · Timo Smieszek[4] · Sofia Zappacosta[4] · Ulrich Laufs[1]



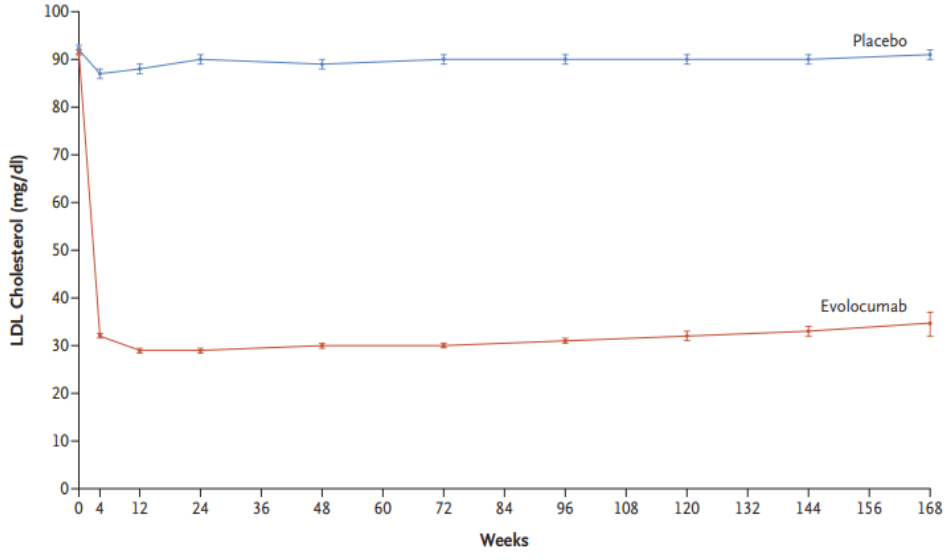
NOVITA' 2017: AB ANTI PCS-K9

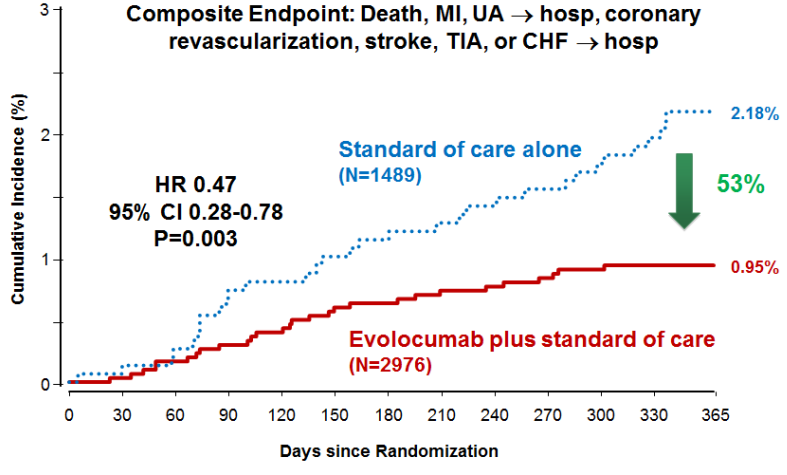
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 4, 2017 VOL. 376 NO. 18

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*



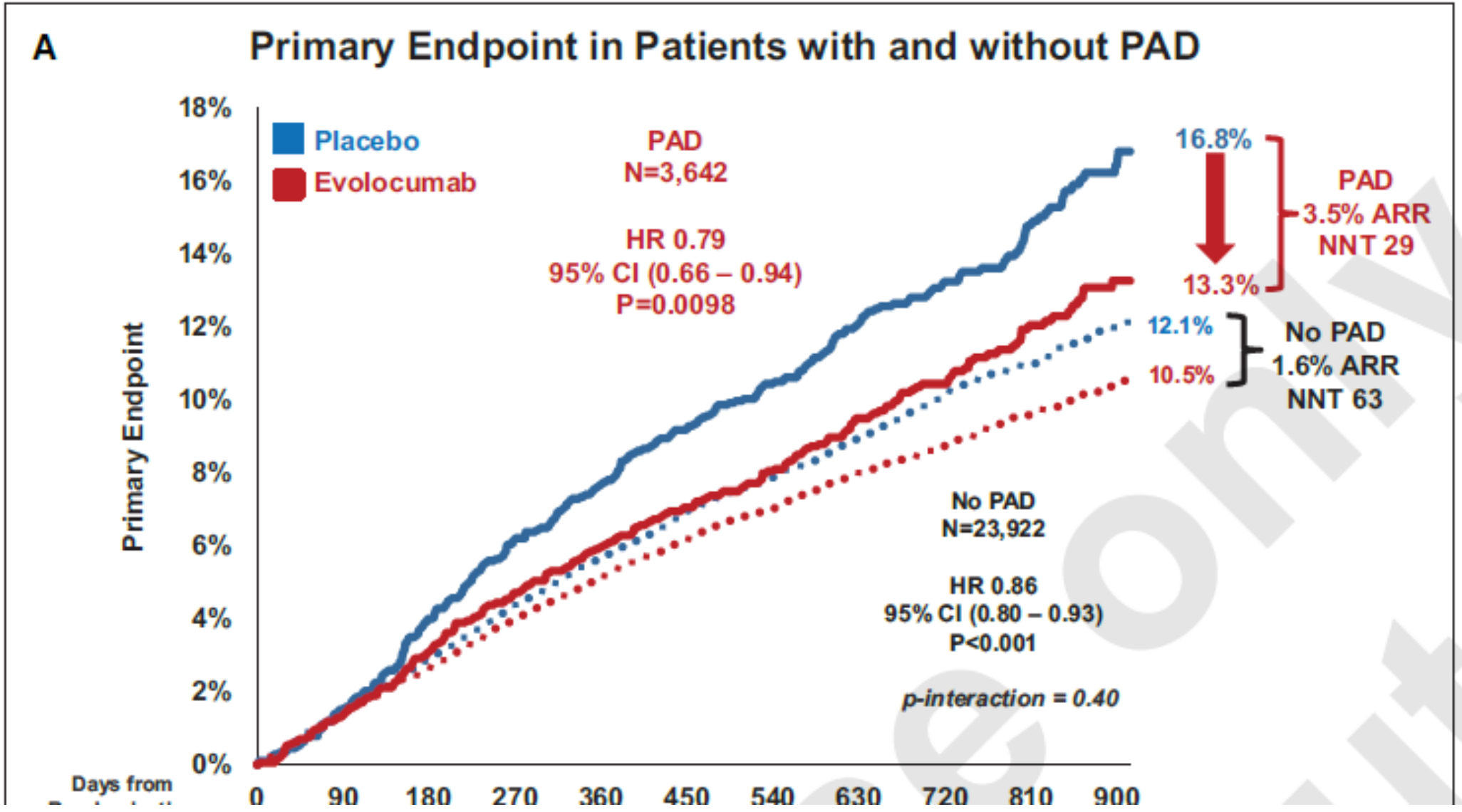


ODYSSEY OUTCOMES

>40y, ACS history withing past 1-12 months, on high dose statin, Inadequate control of lipids.

Myocardial infarction — no. (%)	11,145 (80.9)
Median time from most recent previous myocardial infarction (IQR) — yr	3.4 (1.0–7.4)

PAD


A
Primary Endpoint in Patients with and without PAD
Placebo
Evolocumab
PAD
N=3,642
HR 0.79
95% CI (0.66 – 0.94)
P=0.0098
16.8%
13.3%
PAD
3.5% ARR
NNT 29
12.1%
10.5%
No PAD
1.6% ARR
NNT 63
No PAD
N=23,922
HR 0.86
95% CI (0.80 – 0.93)
P<0.001
p-interaction = 0.40
Primary Endpoint
18%
16%
14%
12%
10%
8%
6%
4%
2%
0%
Days from
0
90
180
270
360
450
540
630
720
810
900

TAKE HOME MESSAGE

- Statine ad alta intensità + ezetimibe dall'inizio
- nei pazienti ad alto rischio CV.

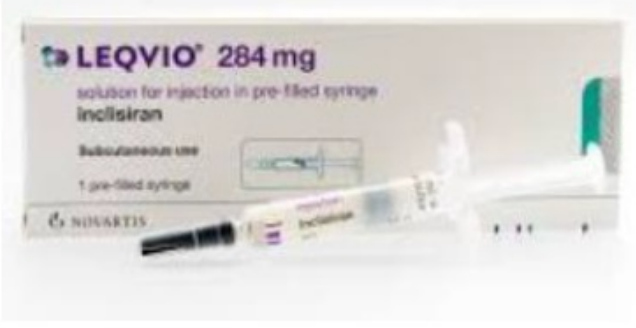
- Obiettivo 55 mg/dL (e riduzione del 50%).

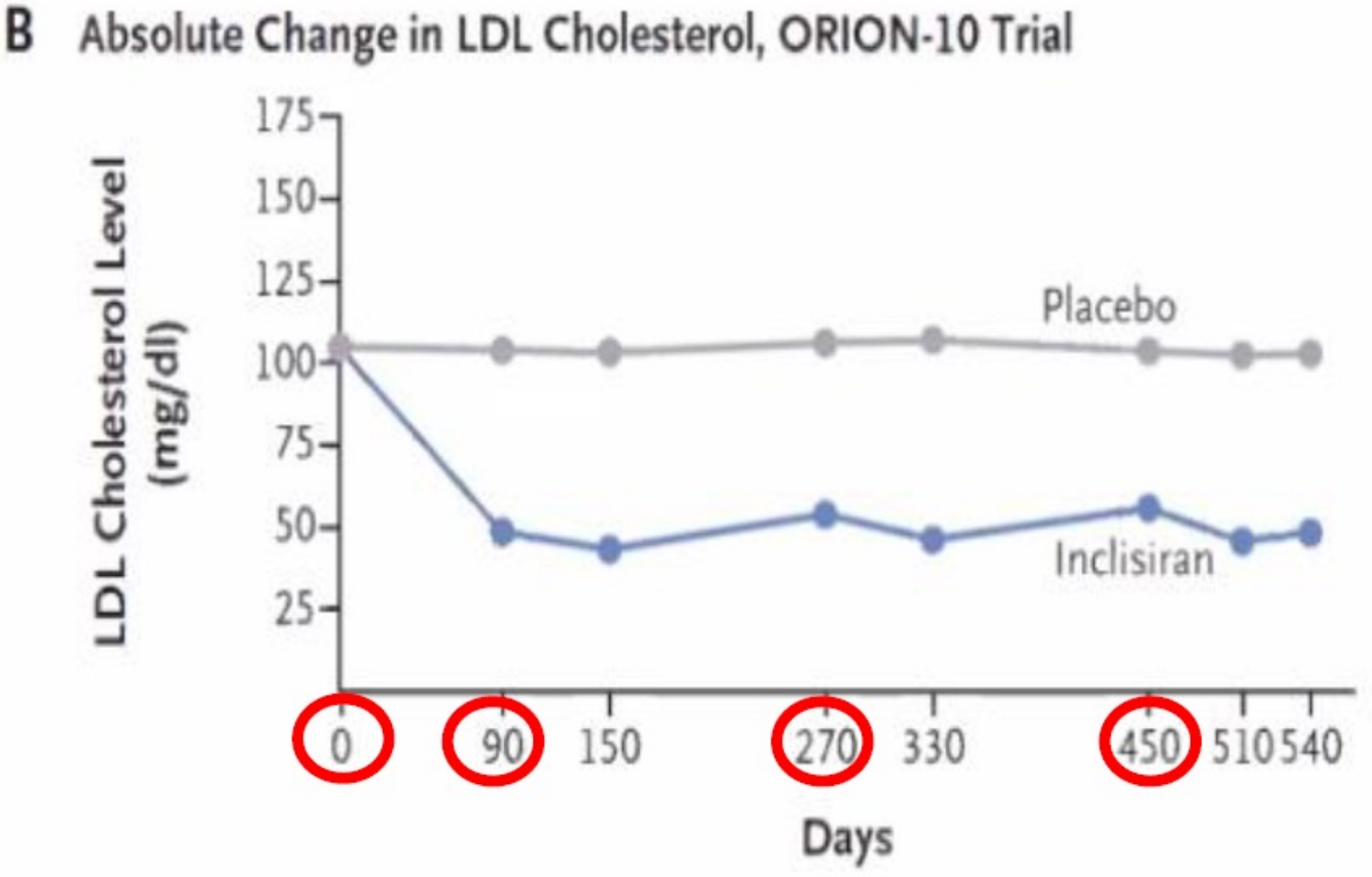
- Nessuna paura dei bassi livelli di LDL.

- PCSK-9 se ancora > 70 mg/dL o intollerante.

COSA C'E' DI NUJOVO:INCLISIRAN:

2 sc all'anno

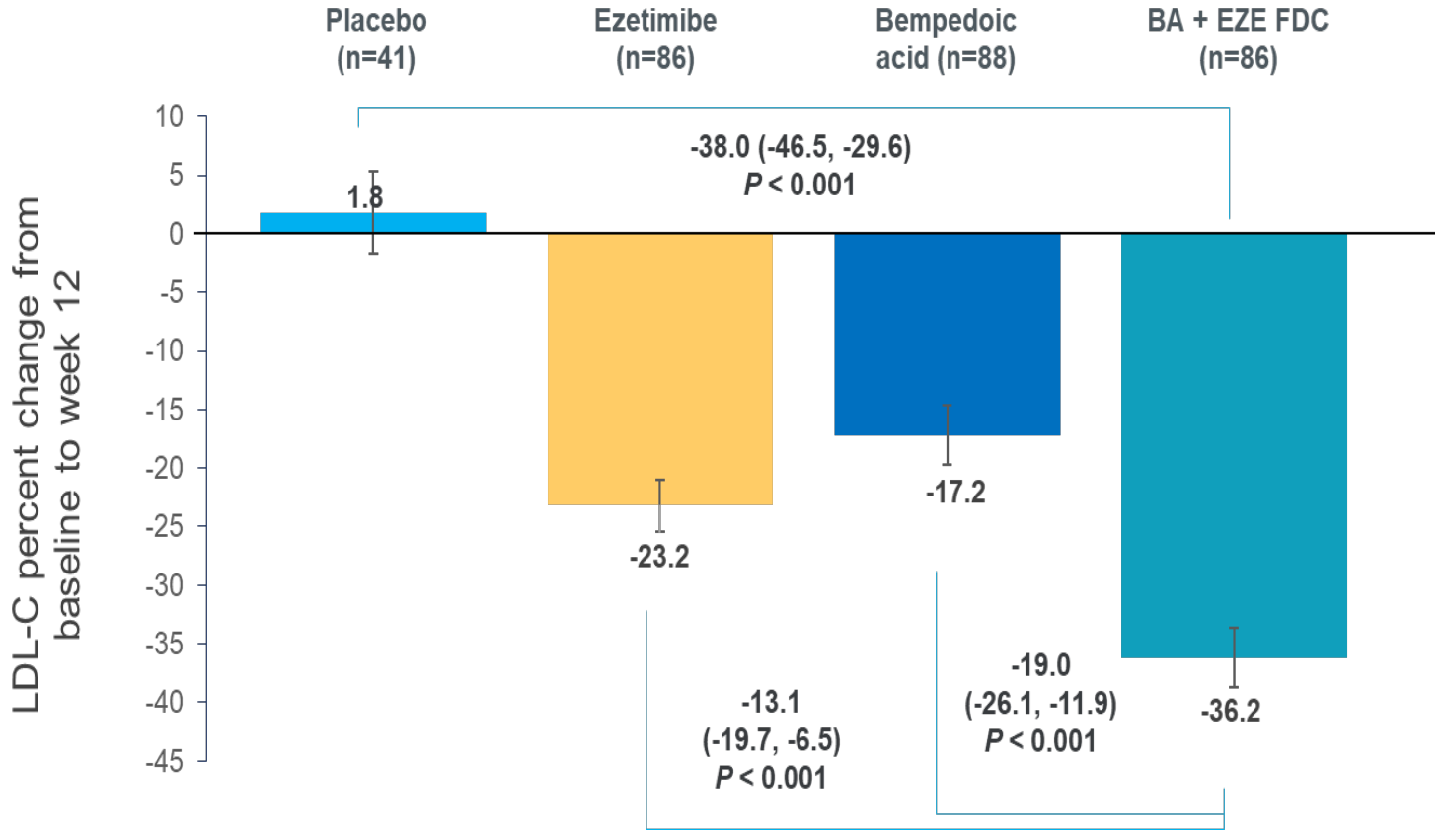




COSA C'E' DI NUOVO: ACIDO BEMPEDOICO

Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy

European Journal of Preventive Cardiology
2020, Vol. 27(6) 593–603



NEL FUTURO: LIPOPROTEINA A

ESC European Society of Cardiology
European Heart Journal (2022) **0**, 1–22
https://doi.org/10.1093/eurheartj/ehac361

Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement

Florian Kronenberg [1], Samia Mora [2], Erik S.G. Stroes [3], Brian A. Ference[4], Benoit J. Arsenault [5], Lars Berglund[6], Marc R. Dweck [7], Marlys Koschinsky [8], Gilles Lambert [9], François Mach[10], Catherine J. McNeal [11], Patrick M. Moriarty[12], Pradeep Natarajan [13], Børge G. Nordestgaard [14,15], Klaus G. Parhofer [16], Salim S. Virani [17], Arnold von Eckardstein [18], Gerald F. Watts[19], Jane K. Stock[20], Kausik K. Ray[21], Lale S. Tokgözoğlu[22], and Alberico L. Catapano [23,24]

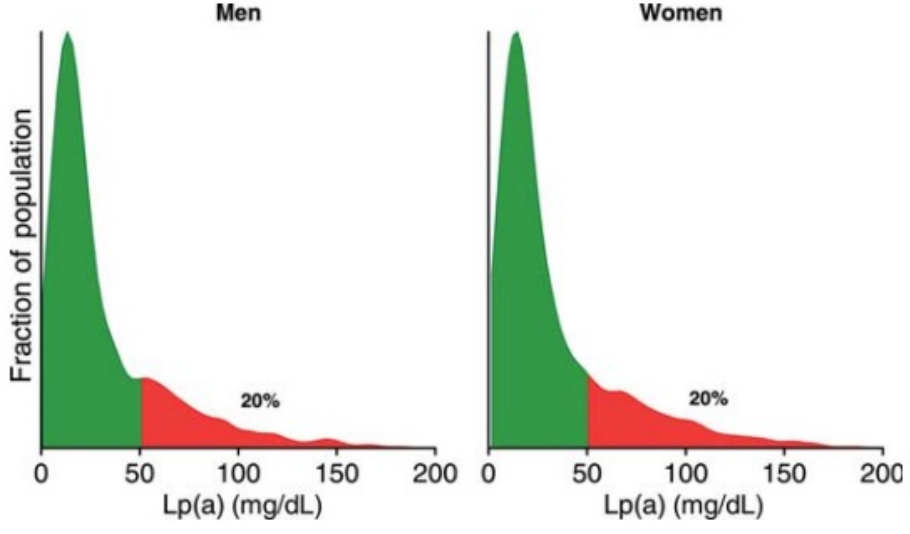
LIPOPROTEINA A

La Lipoproteina(a) è composta da una **LDL** e da una apolipoproteina chiamata **apolipoproteina(a) [apo(a)].**

La apo(a) è legata covalentemente alla apolipoproteina B100 (apoB100) mediante formazione di un ponte disolfuro tra la cisteina 4326 della apoB e la cisteina 4057 della apo(a).
Il gene che codifica la apo(a) è definito LPA

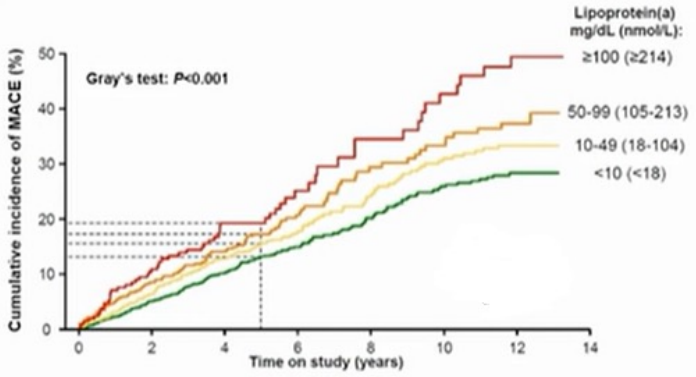
I livelli circolanti di Lp(a) sono principalmente determinati dal gene LPA, senza effetti significativi della dieta o di altri fattori ambientali

GENETICAMENTE DETERMINATA: non modificabile con lo stidle di vita



LIPOPROTEINA A

Lp(a) and recurrent MACE in the CGPS, N=2527



Lipoprotein(a) mg/dL (nmol/L)	Individuals	Events	Multifactorially adjusted hazard ratio for MACE (95% CI)	P for Trend
<10 (<18)	1,086	178	1 (Reference)	
10-49 (18-104)	792	156	1.26 (1.01-1.56)	
50-99 (105-213)	437	100	1.38 (1.08-1.77)	
≥100 (≥214)	212	59	2.07 (1.52-2.82)	<0.001

MACE=major adverse cardiovascular event.

Adapted with permission.

Madsen CM, et al. *ATVB*. 2020;40:255-266.

LIPOPROTEINA A

Lp(a) Heritage
Prevalence Study

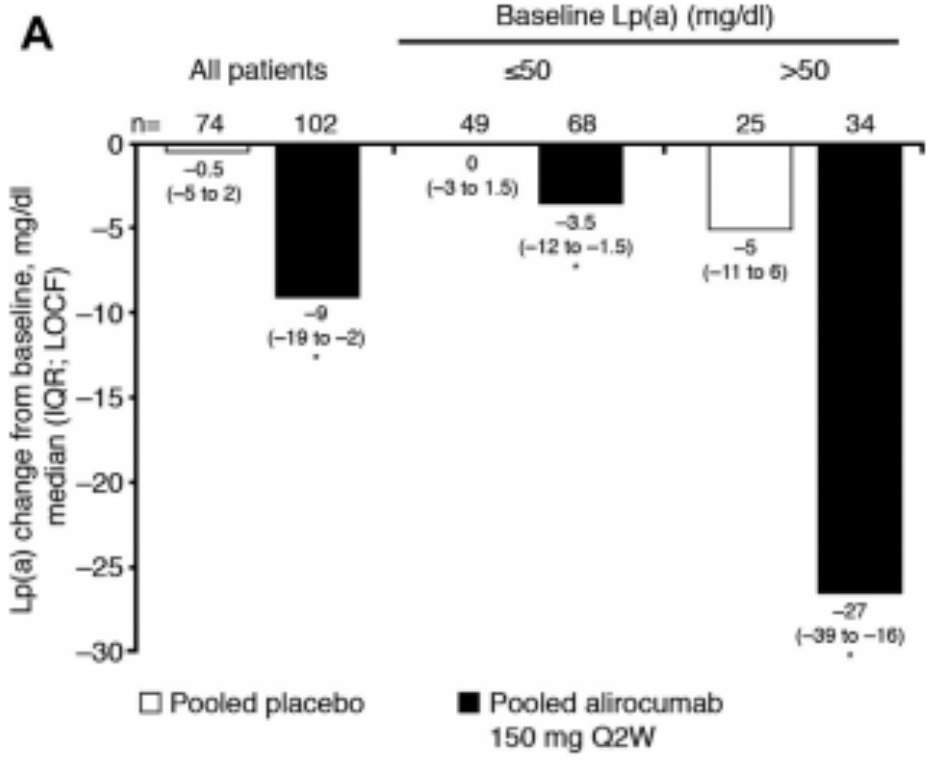
PI	City	Pts. Screened	Pts. with reported Lp(a)	Sum of Pts. with elevated Lp(a)	% of Pts. with elevated Lp(A)
Maloberti	Milano	100	100	18	18%
	Cona				
	Milano				
	Milano				
	Cortona (AR)				
	Ancona				
	Napoli				
	Pozzilli (IS)				
	Roma				
	Milano				
	Salerno				
	Milano				
	Roma				
	Milano				
	Bologna				
	Brescia				
	Pisa				
	Varese				
	Bergamo				
	Palermo				
	Napoli				
	Perugia				
	Bari				
	Milano				
	Pavia				
	Treviglio (BG)				
	Milano				
	Novara				
Total		**1219**	**1199**	**325**	**27%**

LIPOPROTEINA A

(Am J Cardiol 2014;114:711–715)

Effect of Alirocumab, a Monoclonal Proprotein Convertase Subtilisin/Kexin 9 Antibody, on Lipoprotein(a) Concentrations (a Pooled Analysis of 150 mg Every Two Weeks Dosing from Phase 2 Trials)☆

Daniel Gaudet, MD, PhD[a,*], Dean J. Kereiakes, MD[b], James M. McKenney, PharmD[c], Eli M. Roth, MD[d], Corinne Hanotin, MD[e], Daniel Gipe, MD[f], Yunling Du, PhD[f], Anne-Catherine Ferrand, MSc[e], Henry N. Ginsberg, MD[g], and Evan A. Stein, MD, PhD[h]



TRIGLICERIDI

ESC European Society of Cardiology

European Heart Journal (2021) **42**, 4791–4806
doi:10.1093/eurheartj/ehab551

SPECIAL ARTICLE

Triglyceride-rich lipoproteins and their remnants: metabolic insights, role in atherosclerotic cardiovascular disease, and emerging therapeutic strategies—a consensus statement from the European Atherosclerosis Society

STORIA

VOLUME 312, ISSUE 8081, P117-119, JULY 15, 1978

EICOSAPENTAENOIC ACID AND PREVENTION OF THROMBOSIS AND ATHEROSCLEROSIS?

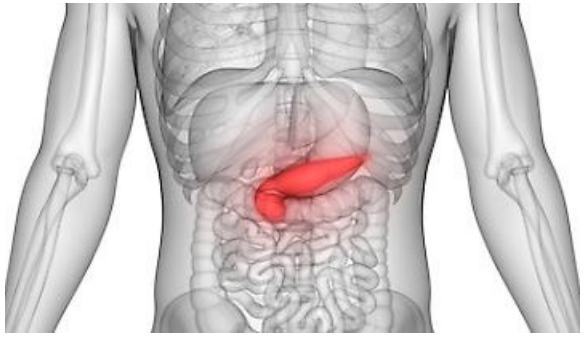
J. Dyerberg • H.O. Bang • E. Stoffersen • S. Moncada • J.R. Vane

Published: July 15, 1978 • DOI: https://doi.org/10.1016/S0140-6736(78)91505-2

Death from cardiovascular disease is rare among Inuits.

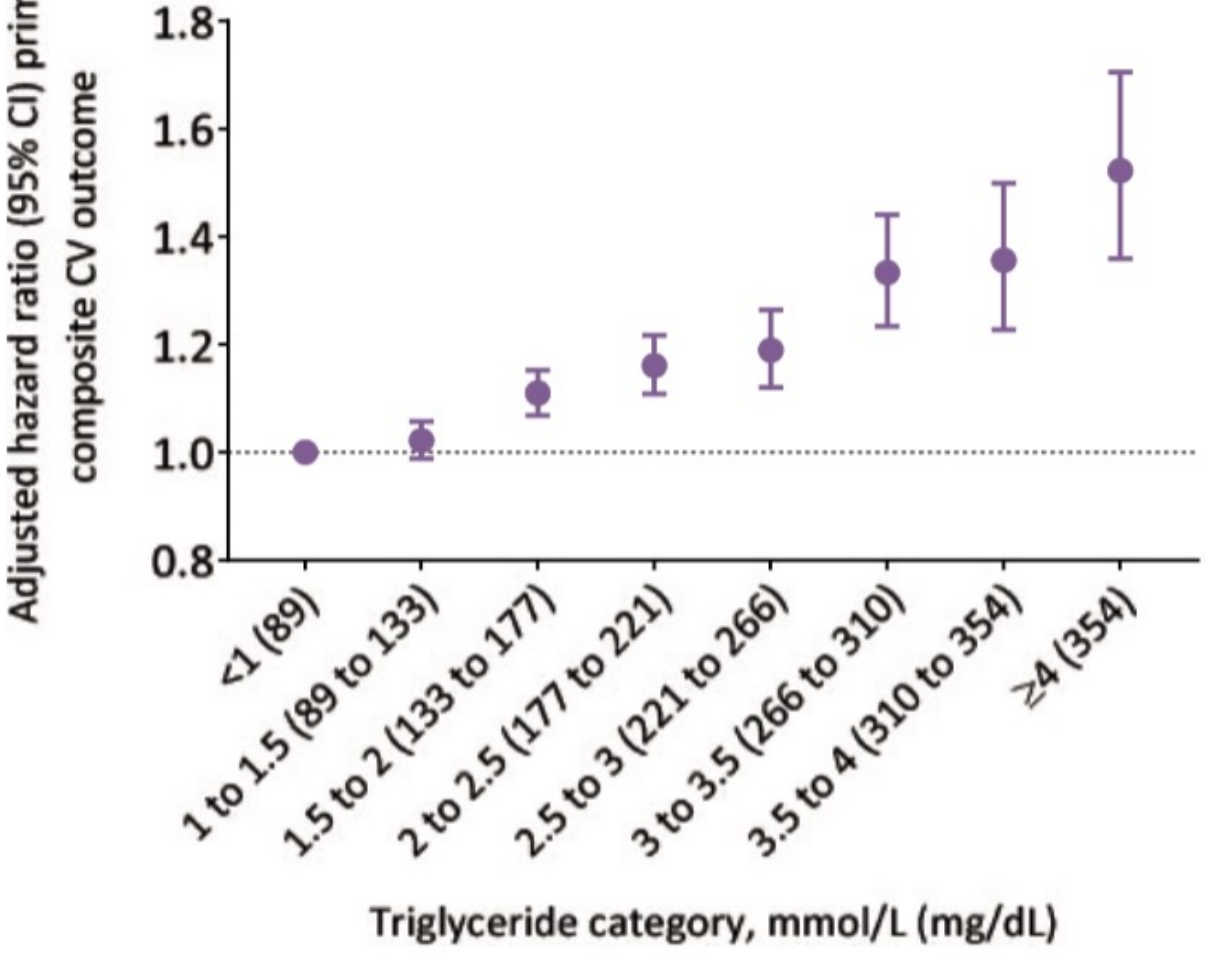
CLASSIFICAZIONE

> 800-1000 mg/dL



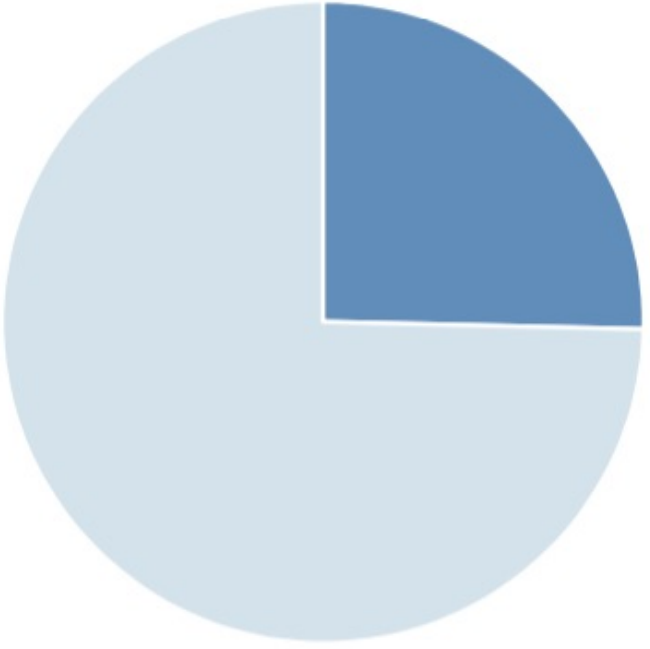
EPIDEMIOLOGIA: RELAZIONE CON EVENTI CV

Risk of ASCVD events associated with triglyceride level among 196,717 patients with prevalent ASCVD in the population



EPIDEMIOLOGIA

Approximately 1 in 4 patients with ASCVD in the general population may have hypertriglyceridemia and controlled LDLc*



*defined as triglyceride 1.52-5.63 mmol/L (135-499 mg/dL) and LDLc 1.06-2.59 mmol/L (41-100 mg/dL)

TERAPIA: IPA

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REDUCE-IT

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

Key Inclusion Criteria

- Statin-treated men and women ≥45 yrs
- Established CVD (~70% of patients) or DM + ≥1 risk factor
- TG ≥150 mg/dL and <500 mg/dL*
- LDL-C >40 mg/dL and ≤100 mg/dL

Icosapent Ethyl
4 g/day
(n=4089)

Placebo
(n=4090)

Primary Endpoint

Time from randomization to the first occurrence of composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina requiring hospitalization

TERAPIA: FIBRATI

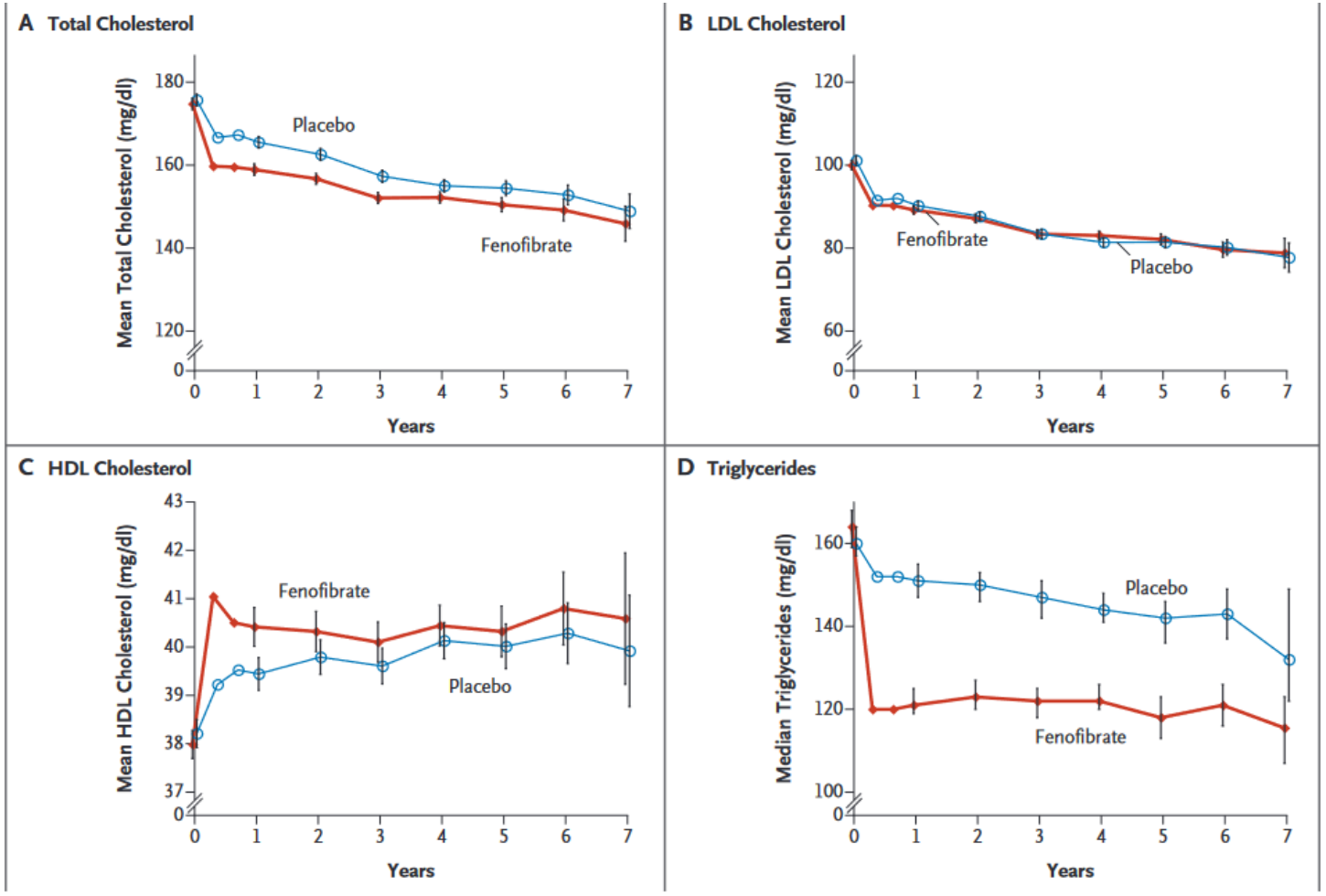
- I fibrati interagiscono tramite recettori nucleari simili a quelli che legano gli ormoni steroidei: i PPAR (Peroxysome proliferative activated receptors).
- L'attivazione dei PPAR comporta la sintesi di enzimi che aumentano i processi intracellulari degradativi degli acidi grassi, e la lipolisi delle lipoproteine VLDL (maggior sintesi di LPL).
- La minore disponibilità di acidi grassi costringe il fegato ad un minore rilascio di VLDL.

TERAPIA: FIBRATI

Randomized Controlled Trial > N Engl J Med. 2010 Apr 29;362(17):1563-74.
doi: 10.1056/NEJMoa1001282. Epub 2010 Mar 14.

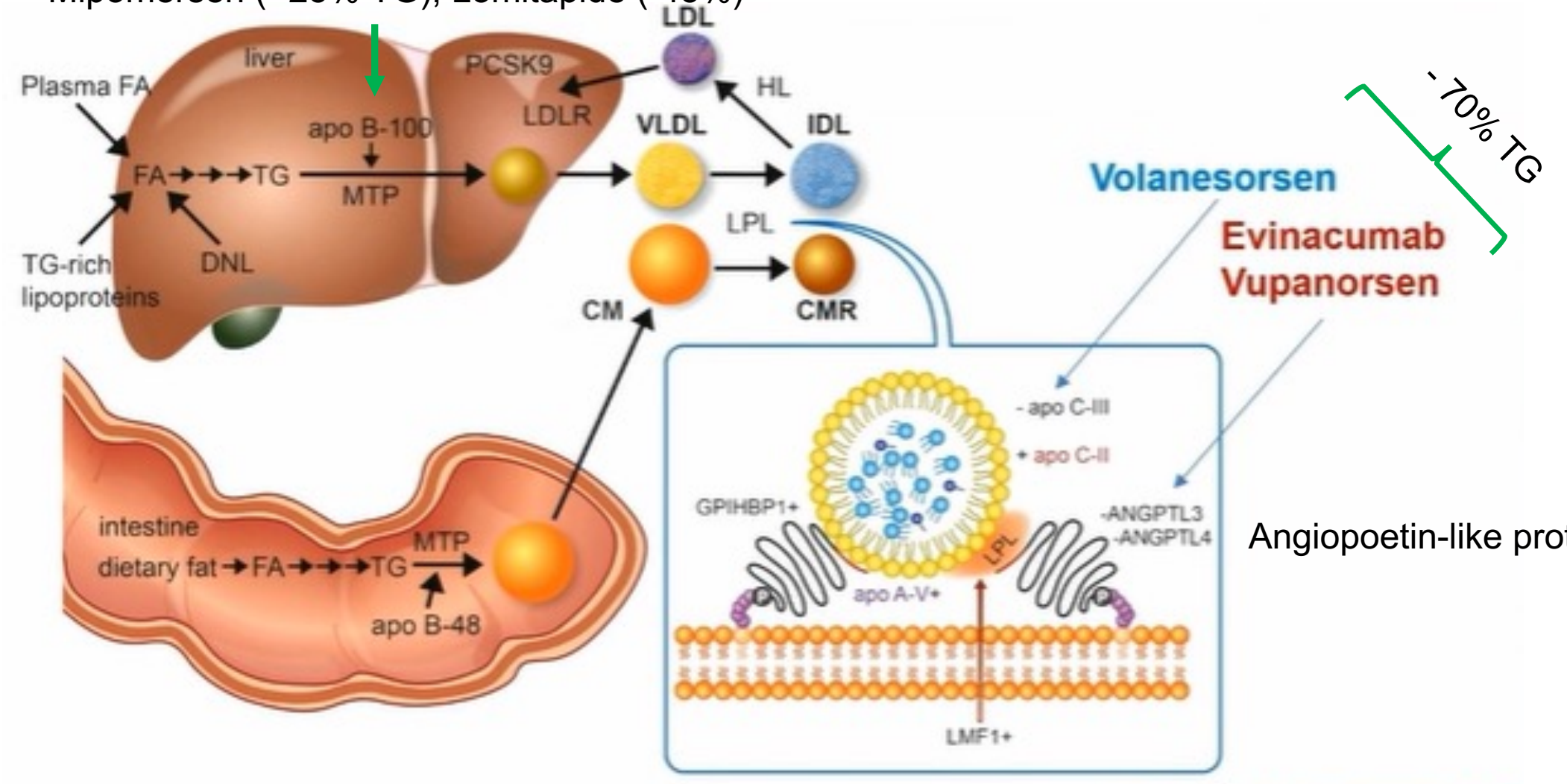
ACCORD TRIAL

Effects of combination lipid therapy in type 2 diabetes mellitus



ALTRE TERAPIE

Mipomersen (- 25% TG); Lomitapide (-45%)



Angiopoetin-like protein

Laufs et al., EHJ 2020;41(1):99-109

TAKE HOME MESSAGES

- Prima linea di trattamento: statine ad alta intensità e portare a target LDL.

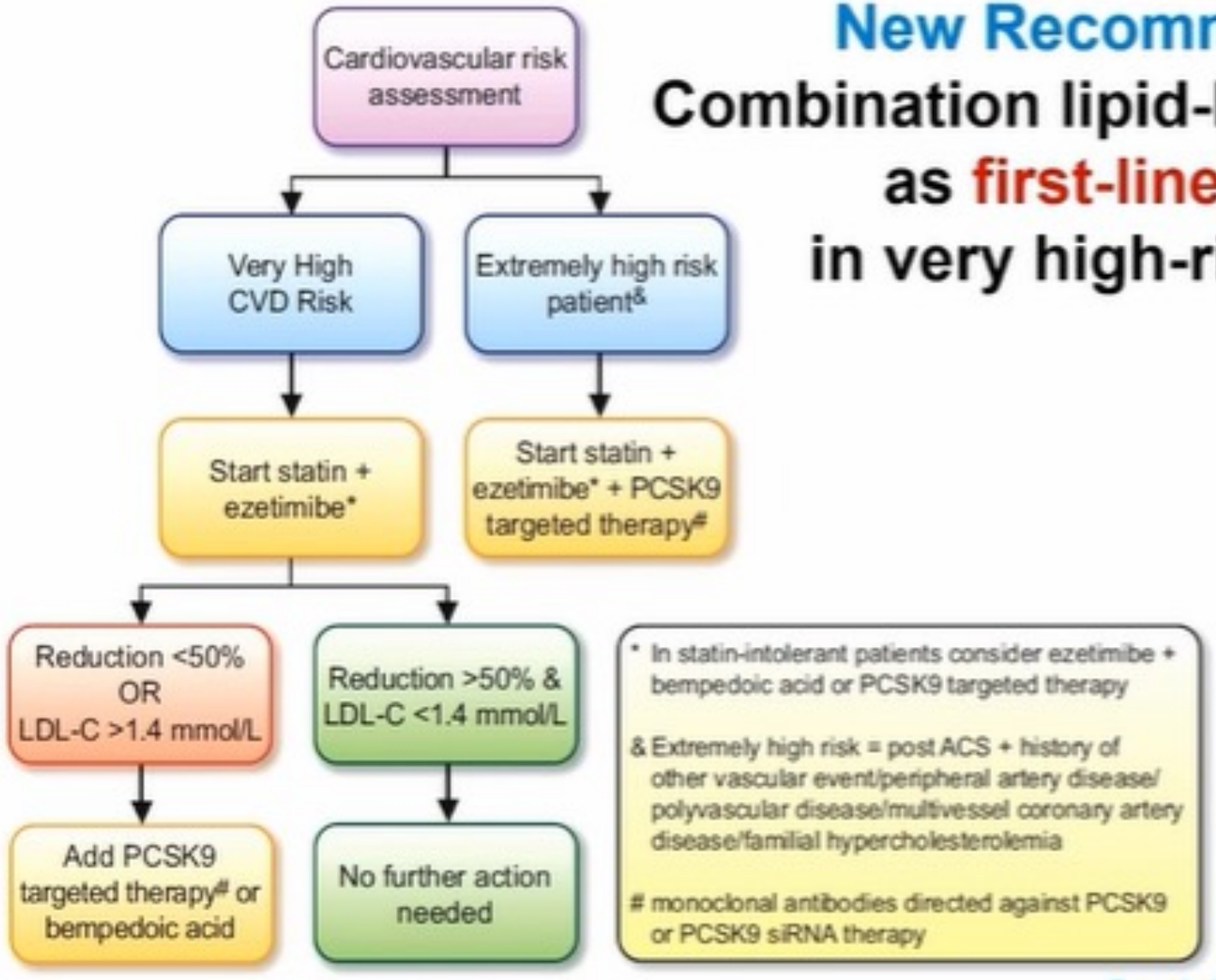
- Se > 150 mg/dL → IPA 4 gr/die (non formulazioni attualmente in circolazione).

- Se severa → centri dislipidemie.

NUOVA STRATEGIA

New Recommendation:

Combination lipid-lowering therapy as first-line strategy in very high-risk patients



Ray et al., EHJ 2021; doi:10.1093/eurheartj/ehab718