BIELLA CUORE
12-13 Settembre 2025

Lettura Magistrale
“Il trattamento delle dislipidemie: presente e futuro”

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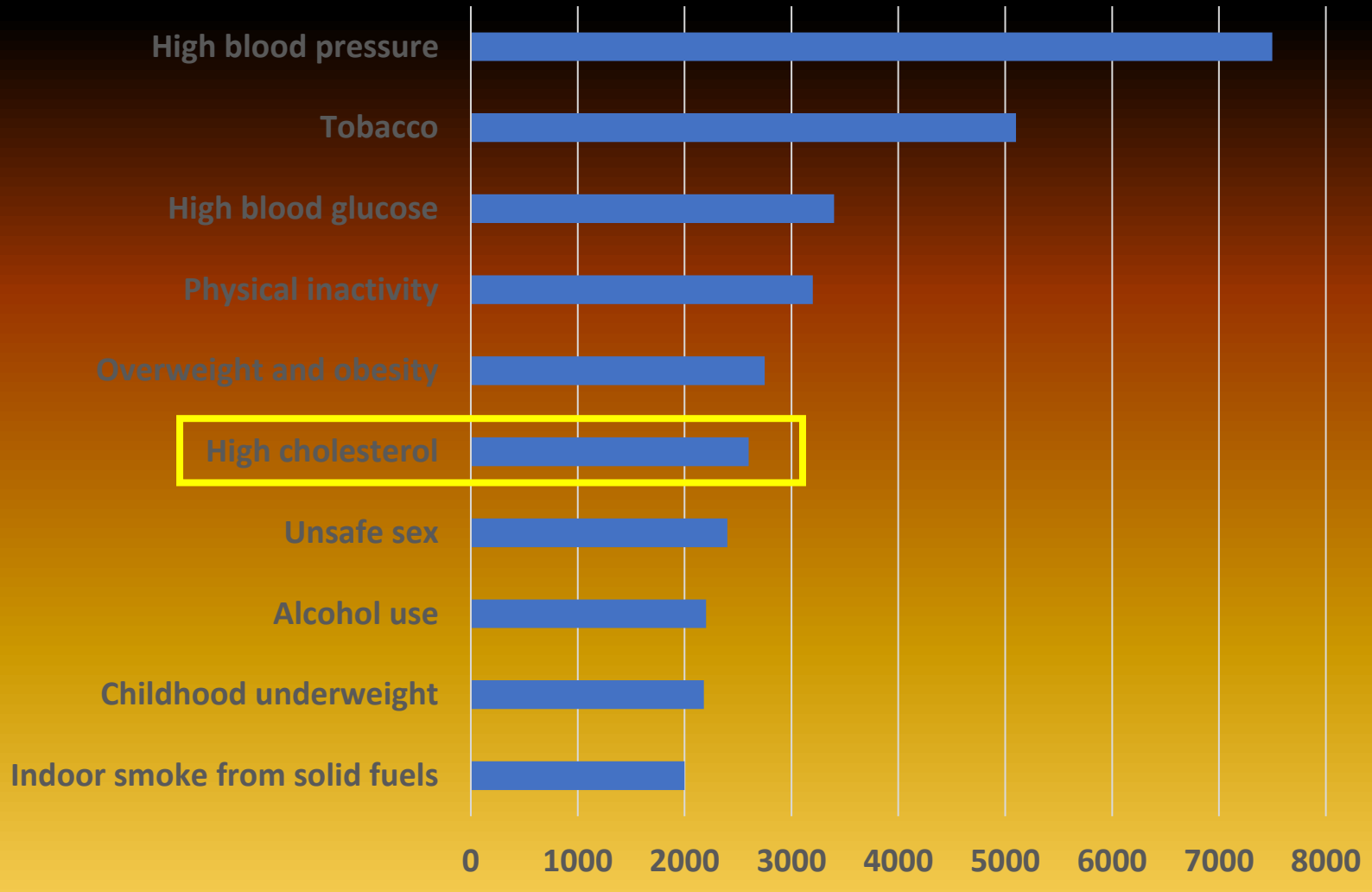
Direttore Dipartimento Toraco-Cardio-Vascolare, AOU Maggiore della Carità di Novara

CARDIOLOGIA NOVARA

Ranking of 10 selected risk factors of cause of death



Attributable deaths due to selected risk factors (in thousands)

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Evolution of Lipid Lowering Therapies:

Statins* → Oral combination → MoAb → ASO → siRNA → Vaccination → Gene editing

Statins*	Oral combination	MoAb	ASO	siRNA	Vaccination	Gene editing
	Ezetimibe* Icosapent ethyl* Bempedoic acid Fibrate	Alirocumab* Evolocumab* Evinocumab	Volanesorsen Vupanorsen Pelacarsen	Inclisiran Olpasiran		
Daily		Monthly Bimonthly	Weekly Monthly	Bianually	Annual?	For life?

- LDL-C — Main target
- Non-HDL (including remnants) — Secondary target
- Lp (a) — New target

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Lipoproteins in the blood

HDL

Apo A1

LDL

Apo B100

Apo B100

LP(a)

IDL

Apo B100

VLDL

Apo B100

Chylomicron remnant

Apo B48

Non-HDL-C

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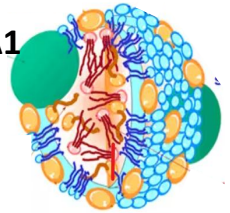
Lipoproteins in the blood

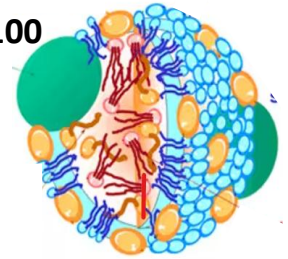
HDL

Apo A1

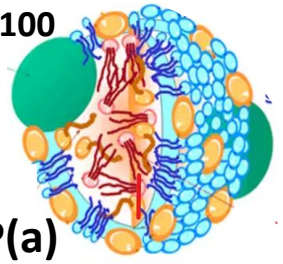


LDL

Apo B100



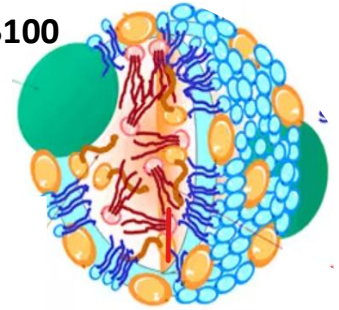
Apo B100



LP(a)

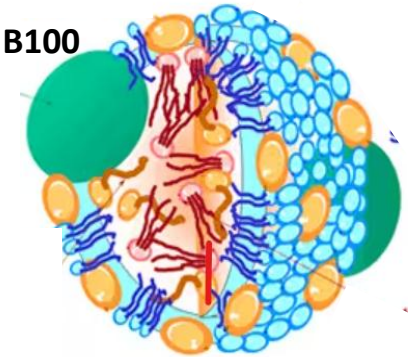
IDL

Apo B100



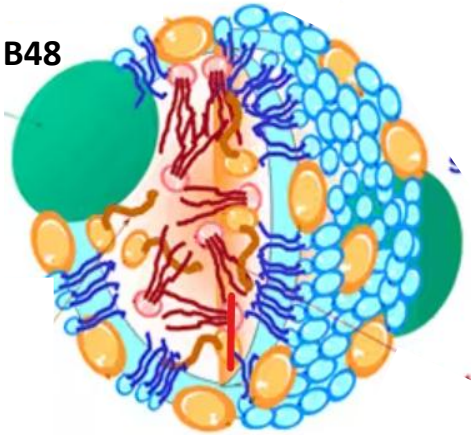
VLDL

Apo B100



Chylomicron remnant

Apo B48



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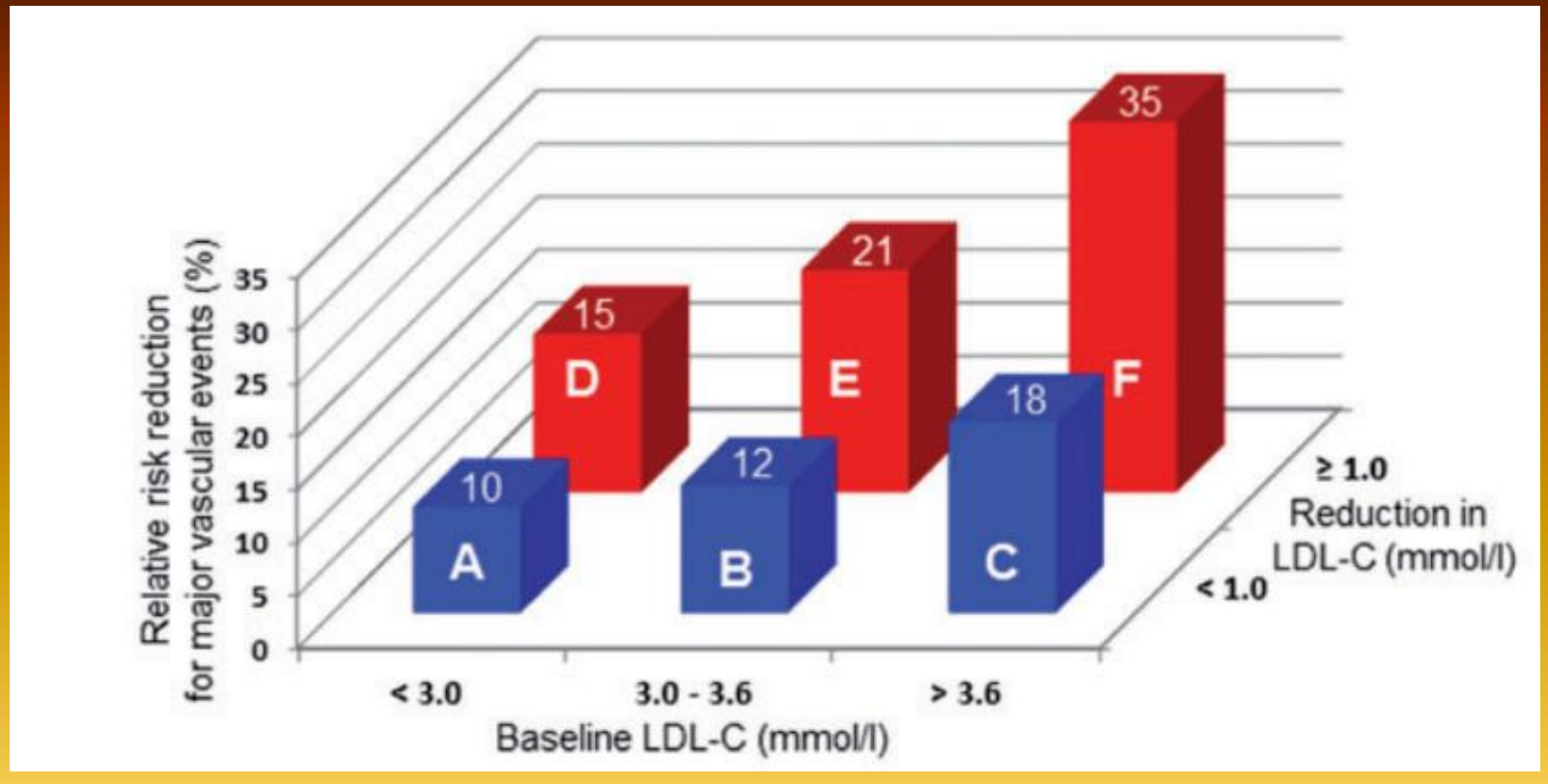
The higher the baseline LDL value and the higher the absolute reduction with lipid-lowering therapy, the higher is the reduction of CV events with treatment



Koskinas K et al. Eur Heart J 2018

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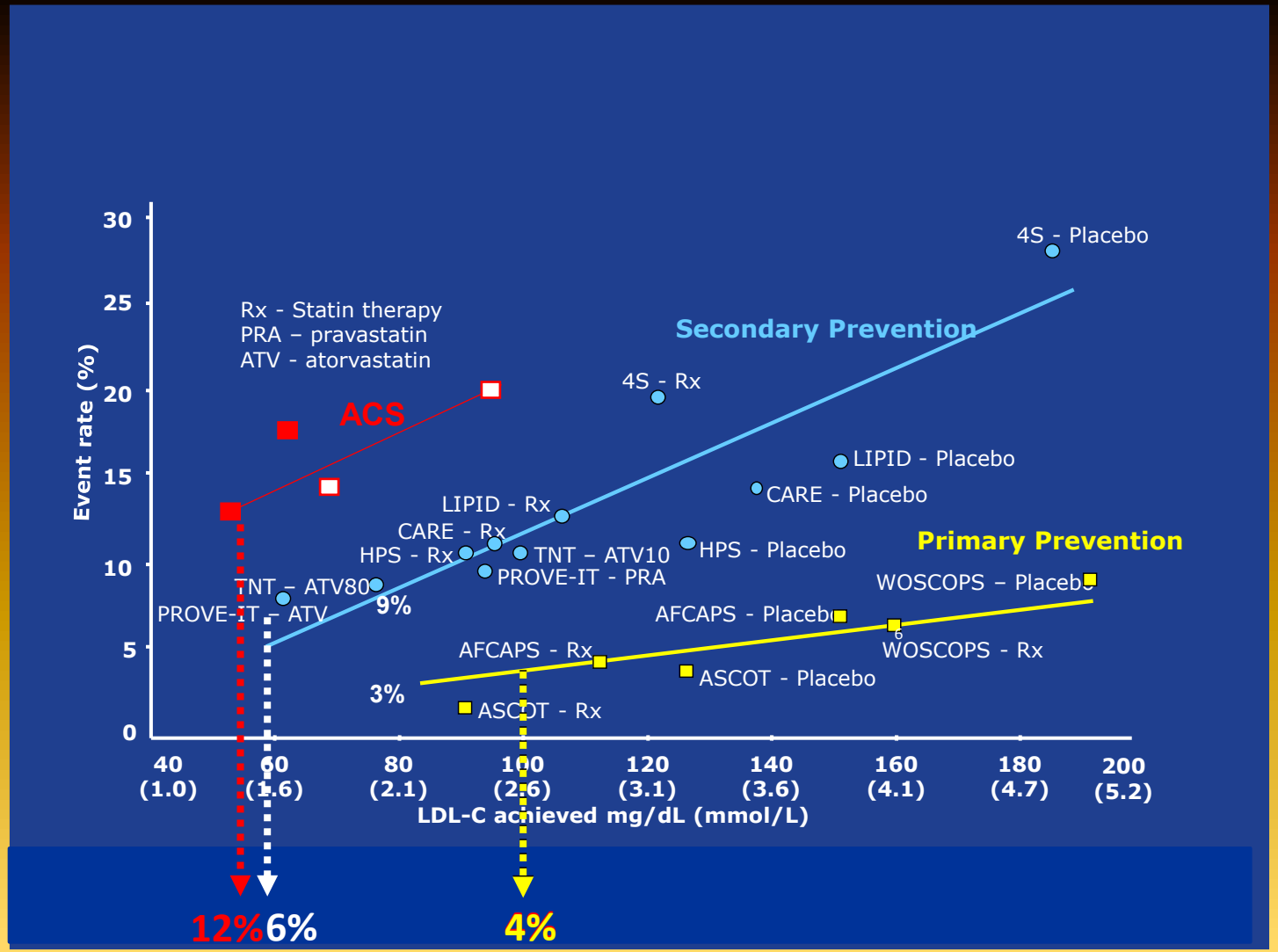
Absolute risk of events in patients with different risk profile not achieving the target LDL-C value



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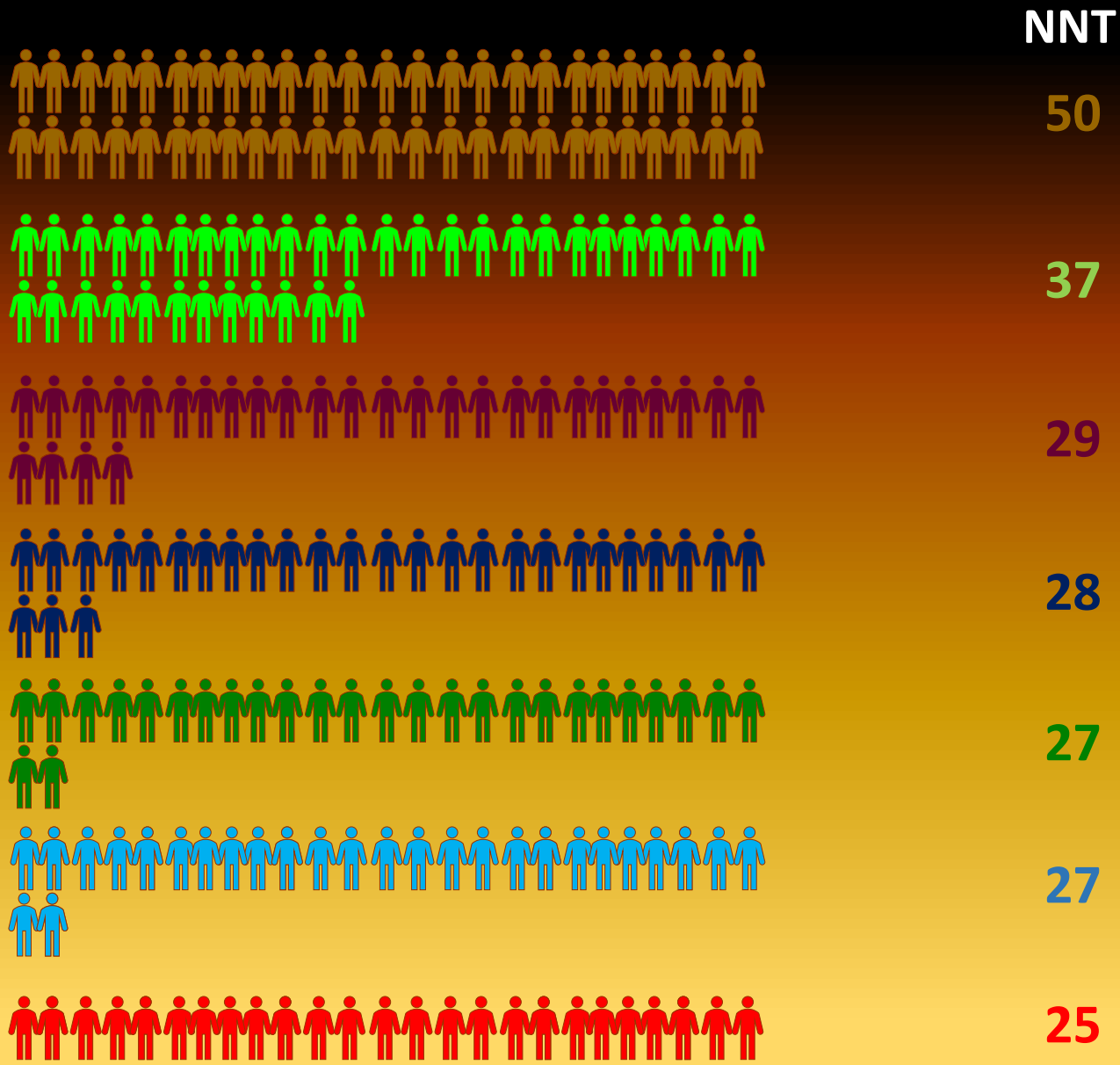
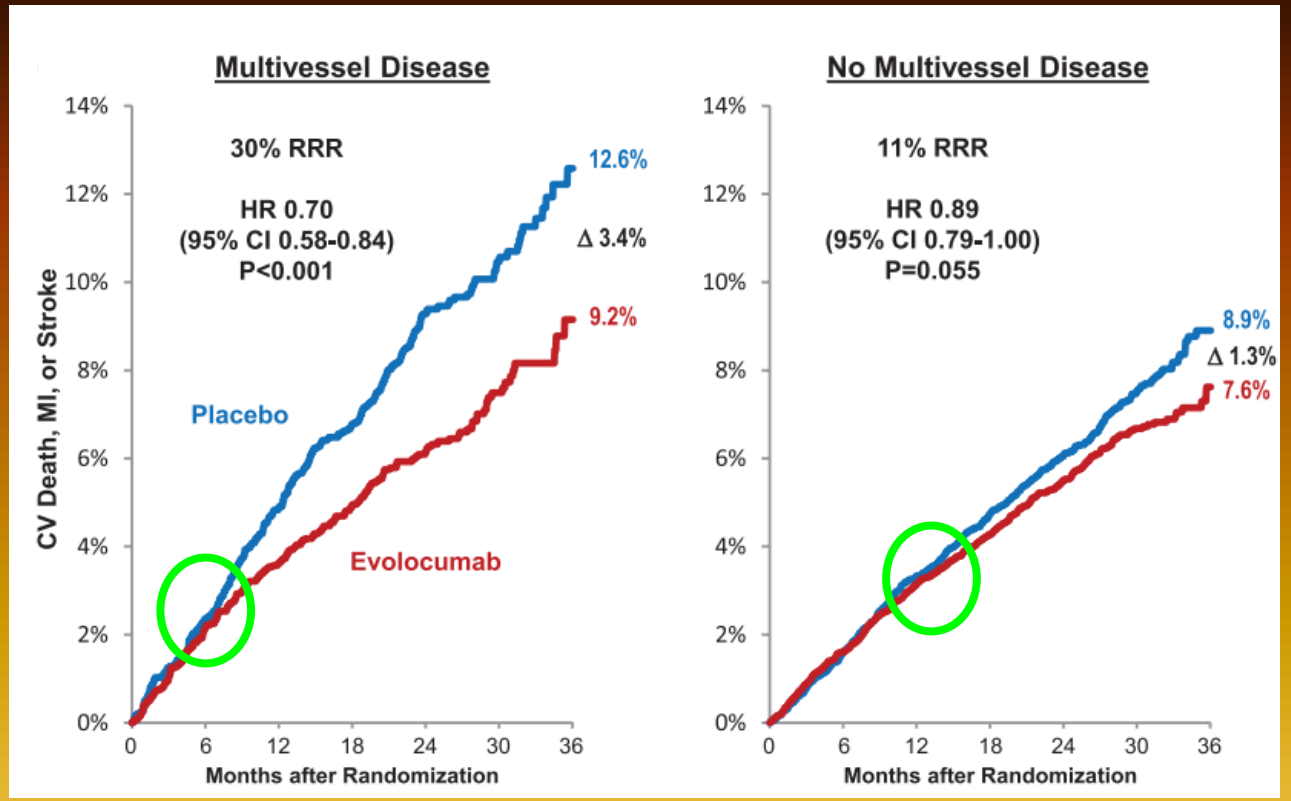
FOURIER trial: NNT for the primary endpoint with evolocumab vs placebo in high-risk settings (personal data)



CARDIOLOGIA NOVARA

FOURIER trial: Clinical Benefit of Evolocumab by Severity and Extent of Coronary Artery Disease



Sabatine MS, et al. Circulation 2018

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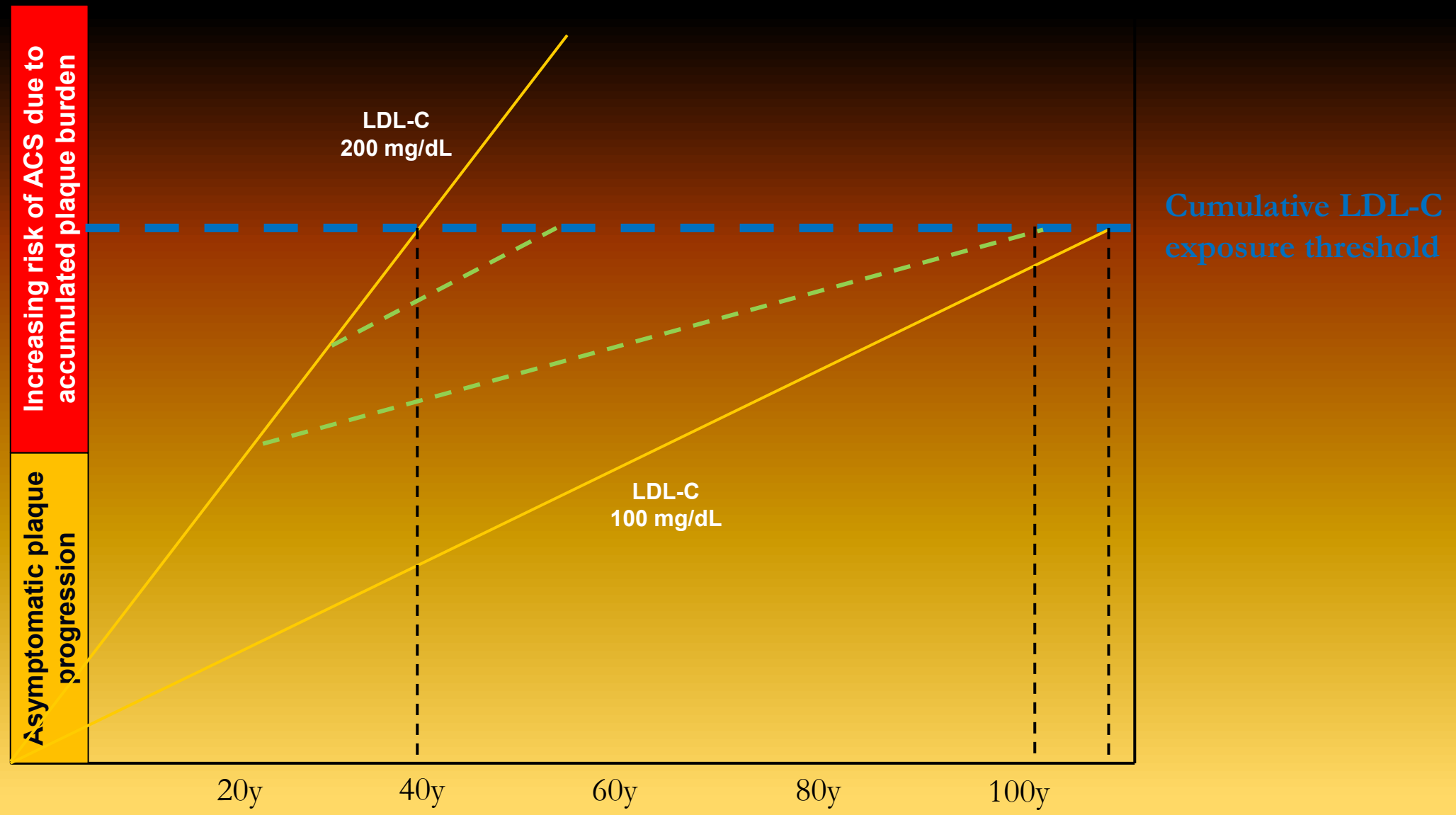
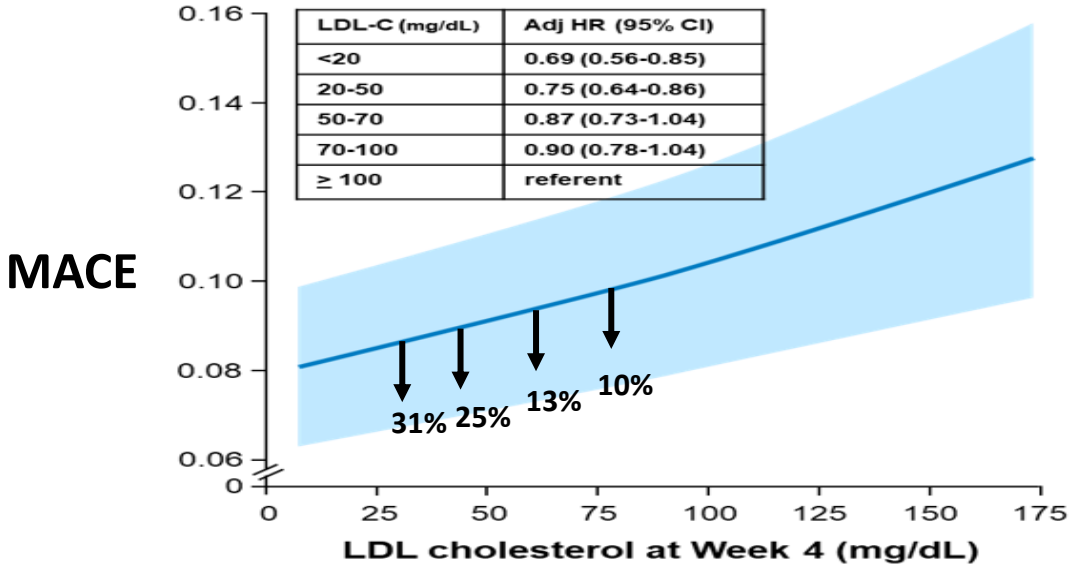
Role of long-term exposition to high LDL-C levels



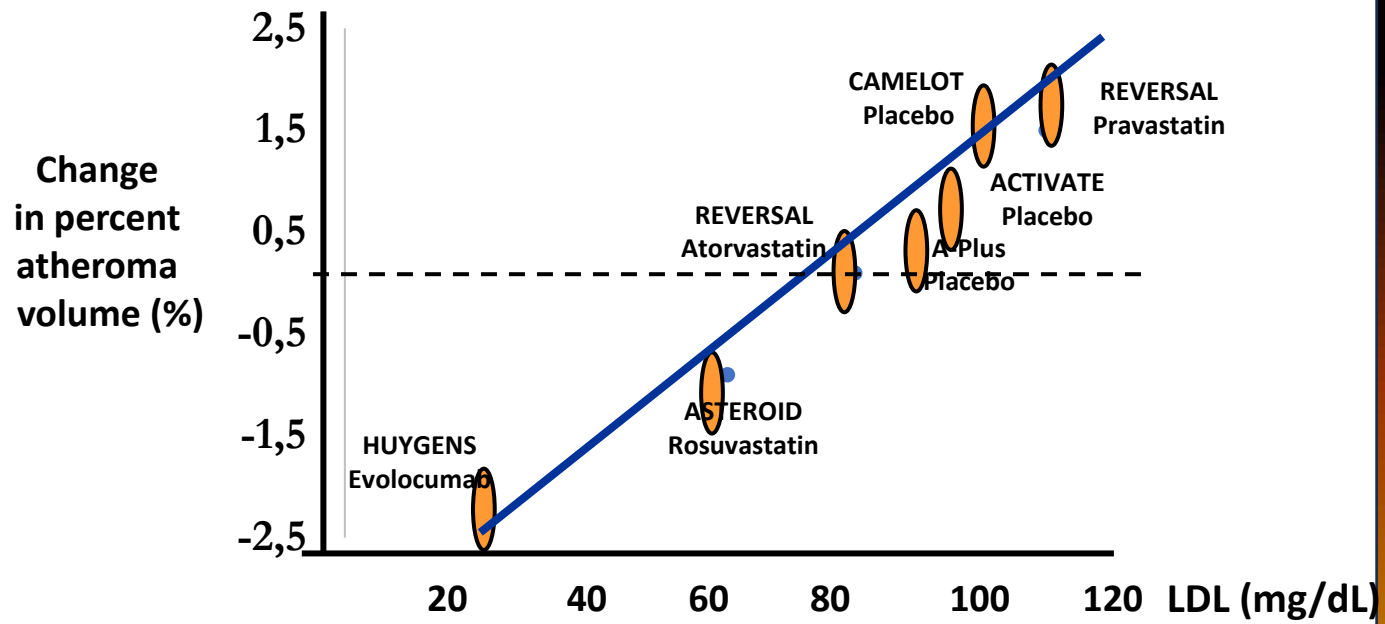
Event risk according to achieved LDL-C values and coronary plaque features

39 mg/dL LDL-C decrease= 22% MACE reduction

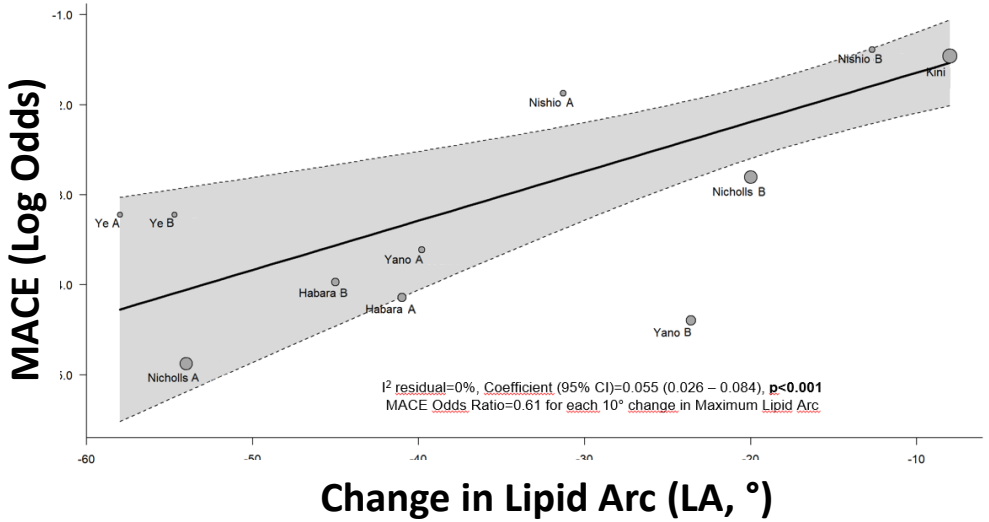


LDL-C (mg/dL)	Adj HR (95% CI)
<20	0.69 (0.56-0.85)
20-50	0.75 (0.64-0.86)
50-70	0.87 (0.73-1.04)
70-100	0.90 (0.78-1.04)
≥ 100	referent

1% PAV reduction= 25% MACE reduction



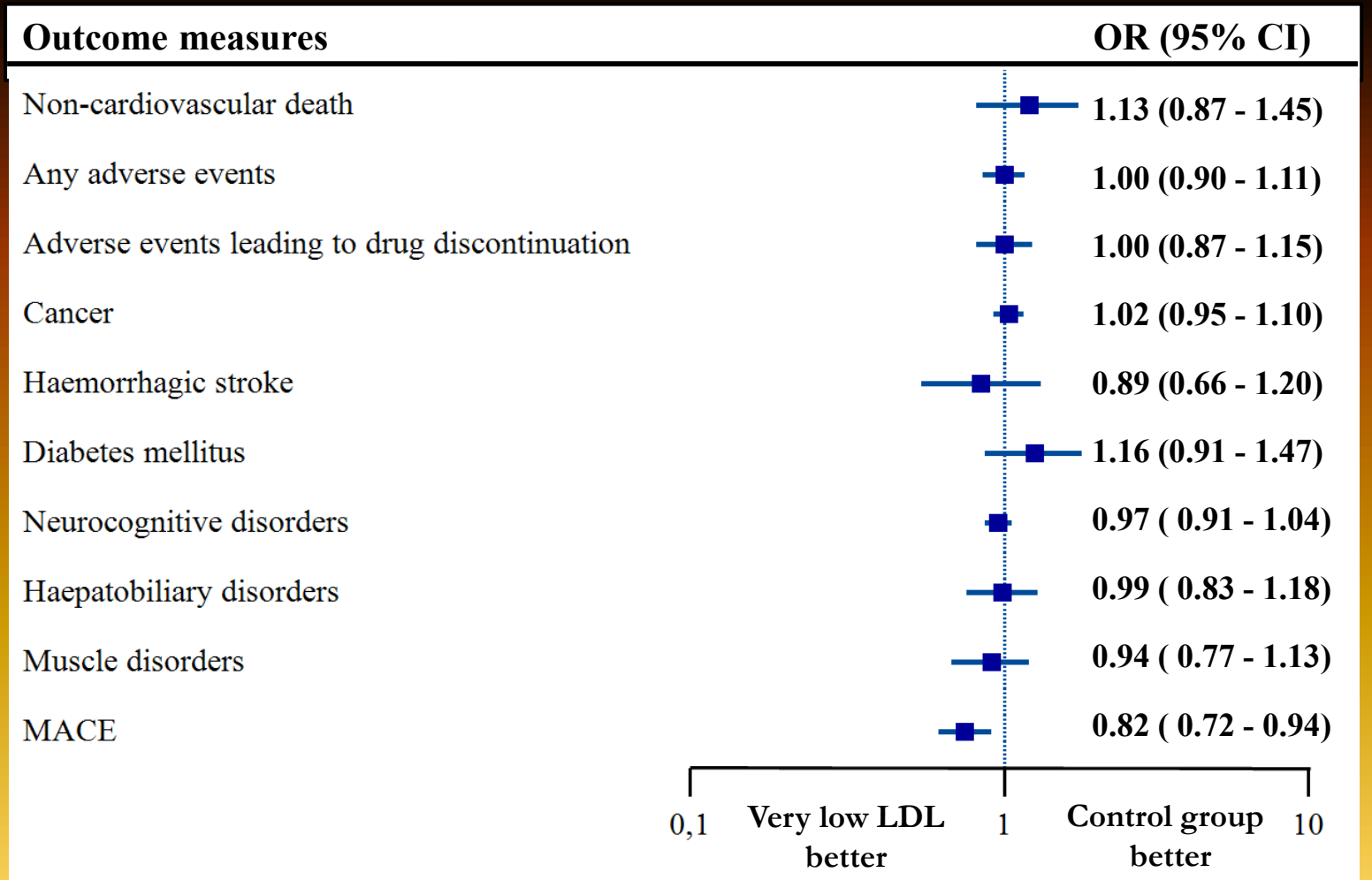
10° LA decrease= 39% MACE reduction



Patti G, et al. Atherosclerosis 2025

CARDIOLOGIA NOVARA

Study-level meta-analysis on 9 randomized trials and approximately 109,000 patients to evaluate the safety and efficacy of LDL-C levels <40 mg/dL



Patti G, et al. Eur Heart J-Cardiovasc Pharmacother 2022 https://doi.org/10.1093/ehjcvp/pvac049

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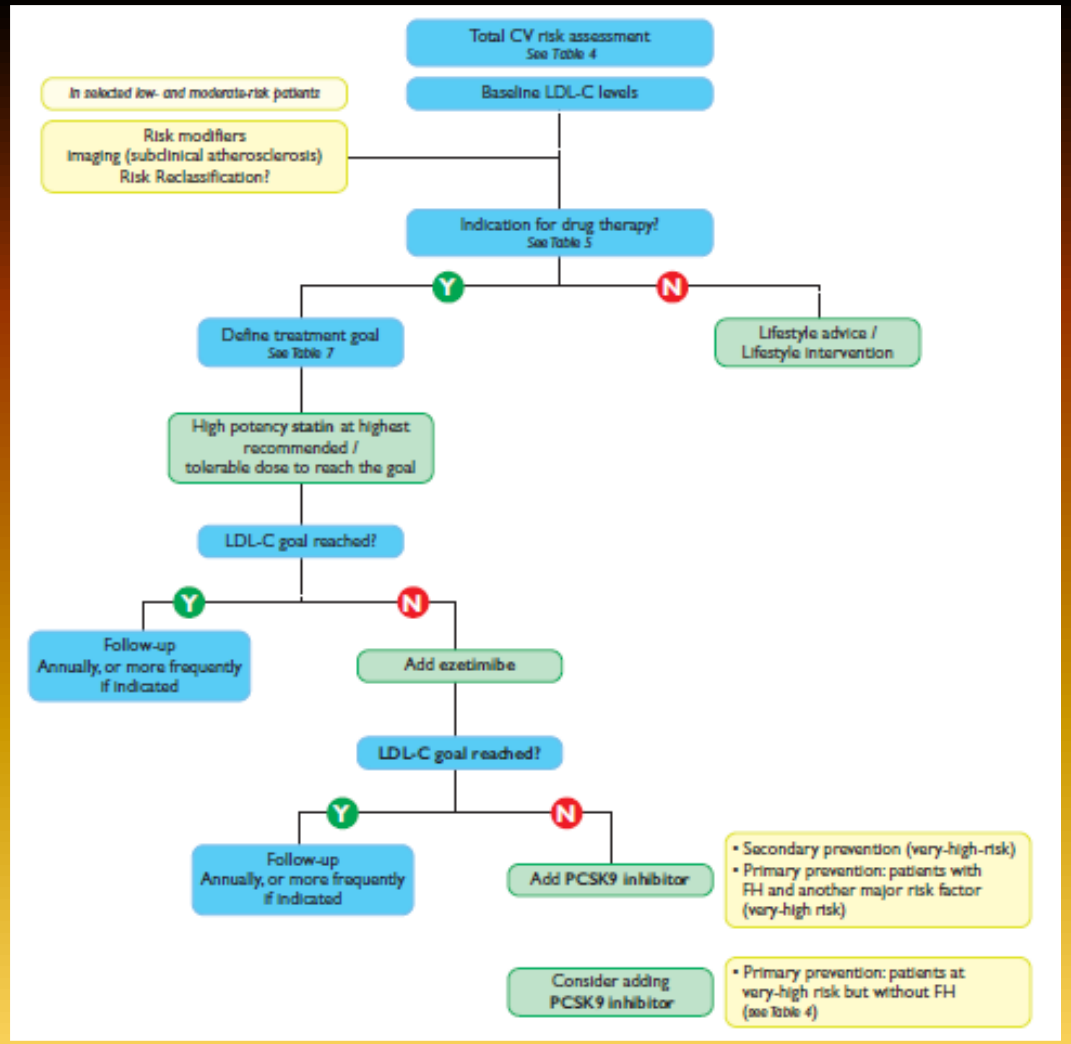
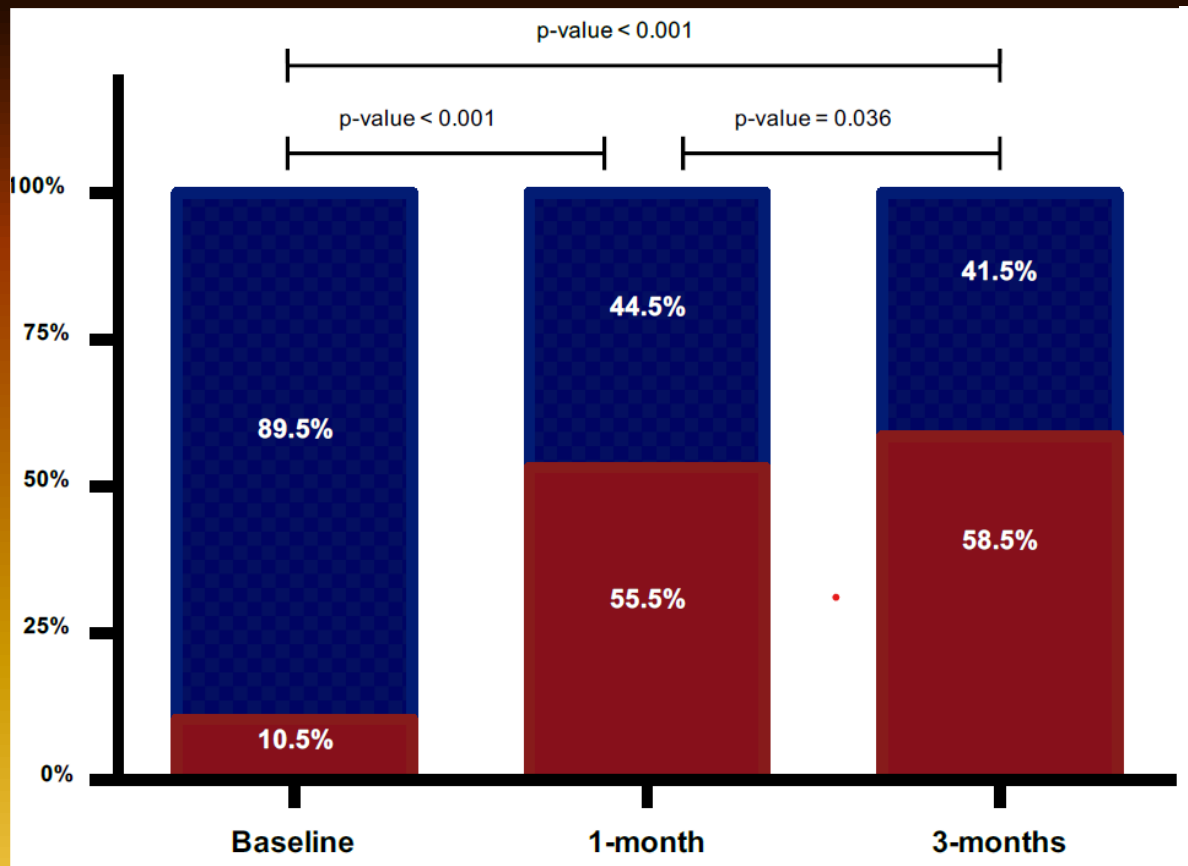
2019 ESC Guidelines

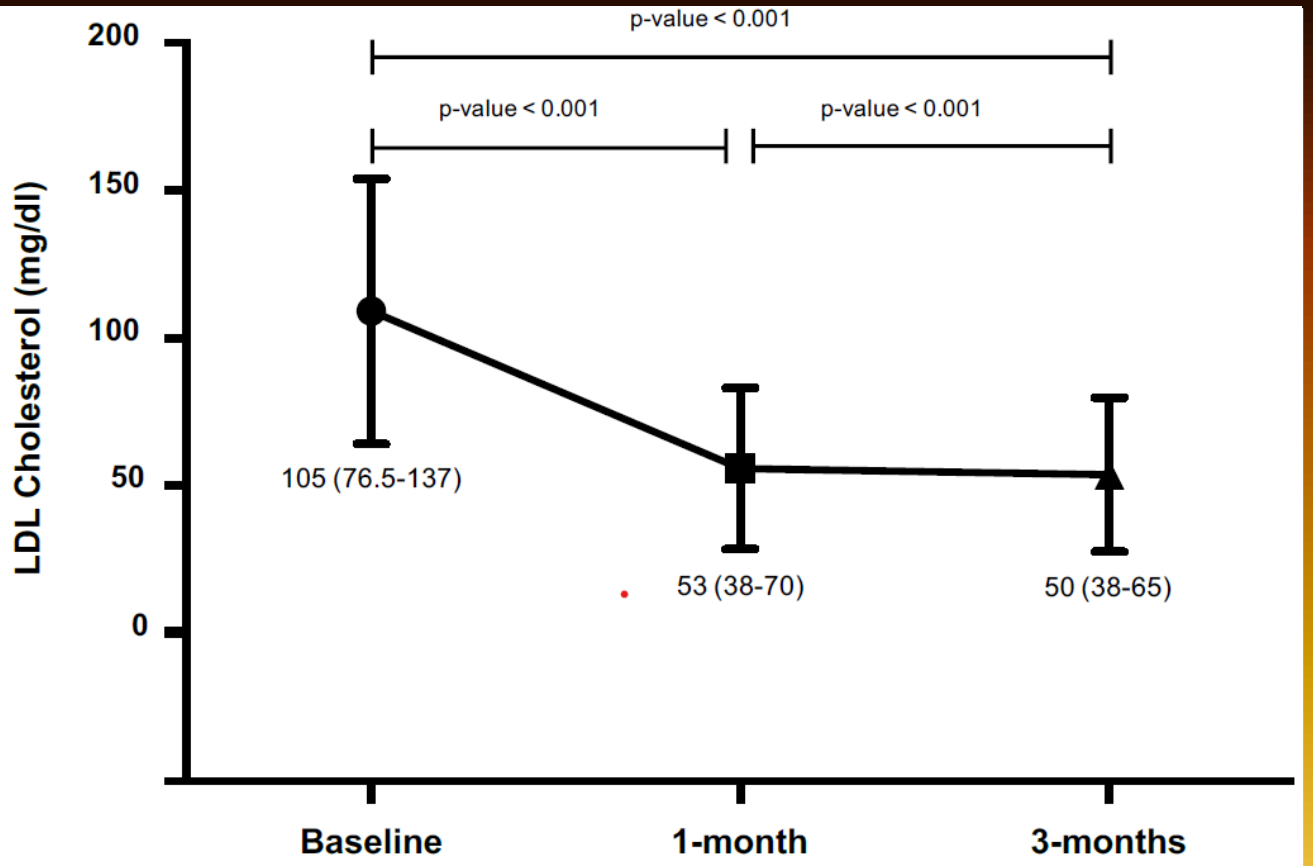


JET-LDL Registry - N=1,095 pts with ACS

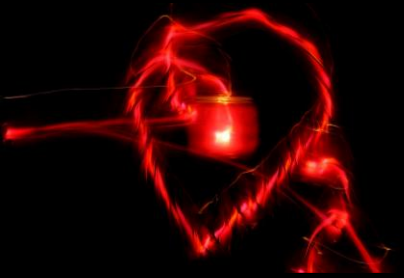
Ferlini M, Patti G, …. Musumeci G, et al. Int J Cardiol 2023 Dec 14; 131659

CARDIOLOGIA NOVARA





At discharge, 40% of patients received high-dose statin, 50% statin plus ezetimibe and 8.5% a PCSK9i



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LDL-C in ACS: GO LOWER AND FASTER!!!!!!!
AIFA: in patients with multiple CV events or ACS, one LDL-C determination allows PCSK-9i initiation

Not at target for LDL-C
Statin Rx?

- **YES**
  - **LDL <100** → Increase statin dose, modify statin type and/or add ezetimibe
  - **LDL ≥100** → Ezetimibe + PCSK-9 i (if LDL >70 and age ≤80 yrs)
- **NO**
  - **LDL <150** → HD potent statin ± ezetimibe and 1-mo re-evaluation
  - **LDL ≥150** → Statin + Ezetimibe + PCSK-9 i

CARDIOLOGIA NOVARA

Impact of a personalized, strike early and strong lipid-lowering approach on LDL-C levels and cardiovascular outcome in patients with acute myocardial infarction

FAST-NOTE REGISTRY

Outcome comparison between the following 3 periods

Period A (N=198; January-June 2019): target LDL-C <70 mg/dL

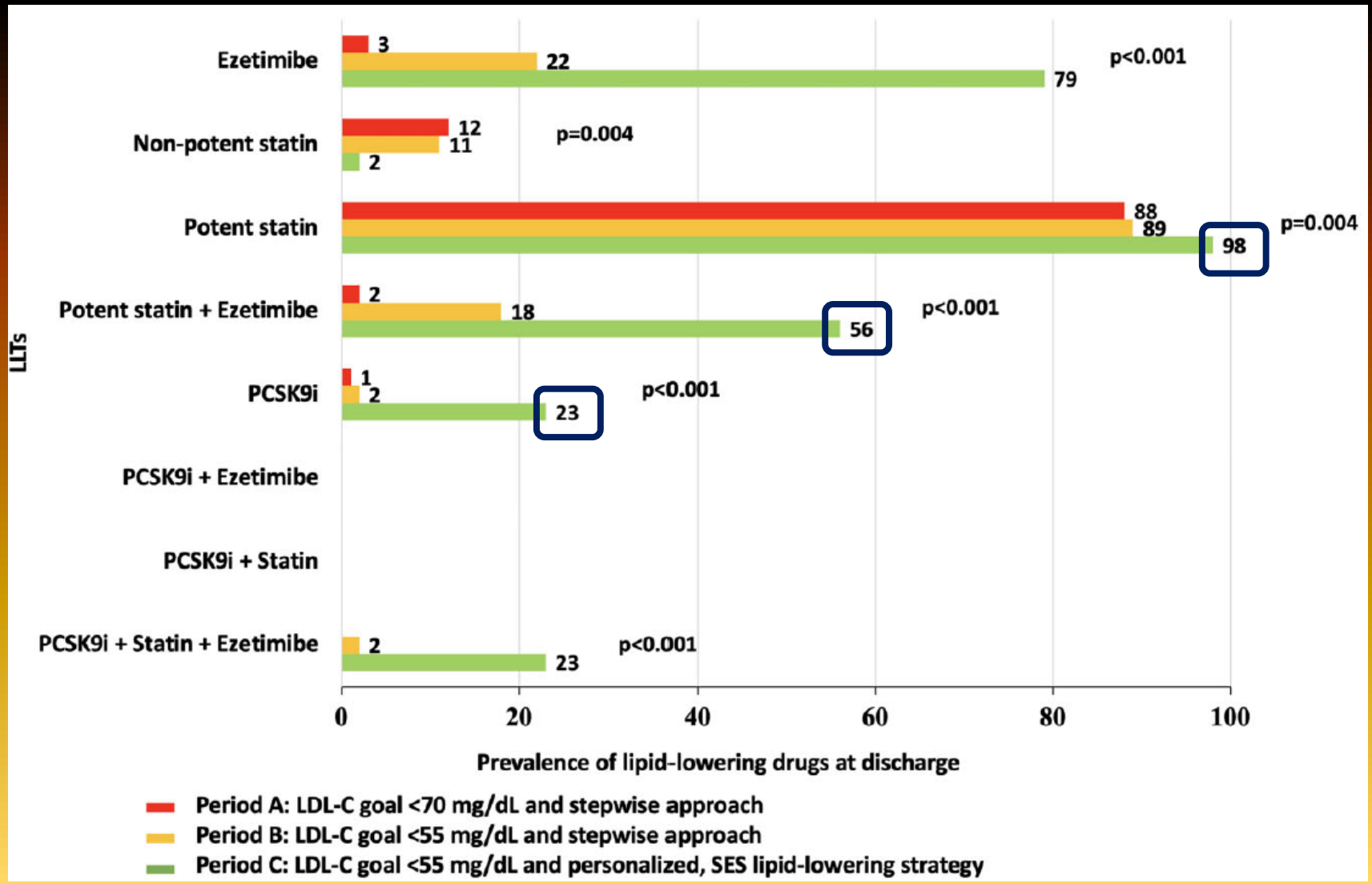
Period B (N=180; January-June 2021): target LDL-C <55 mg/dL and stepwise approach

Period C (N=122; January-June 2023): target LDL-C <55 mg/dL and personalized, SES lipid-lowering strategy

Patti G, et al. Eur Heart J Cardiovascular Pharmacotherapy 2025; doi 10.1093/ehjcvp/pvaf004

Impact of a personalized , strike early and strong lipid-lowering approach on LDL-C levels and cardiovascular outcome in patients with acute myocardial infarction FAST-NOTE REGISTRY

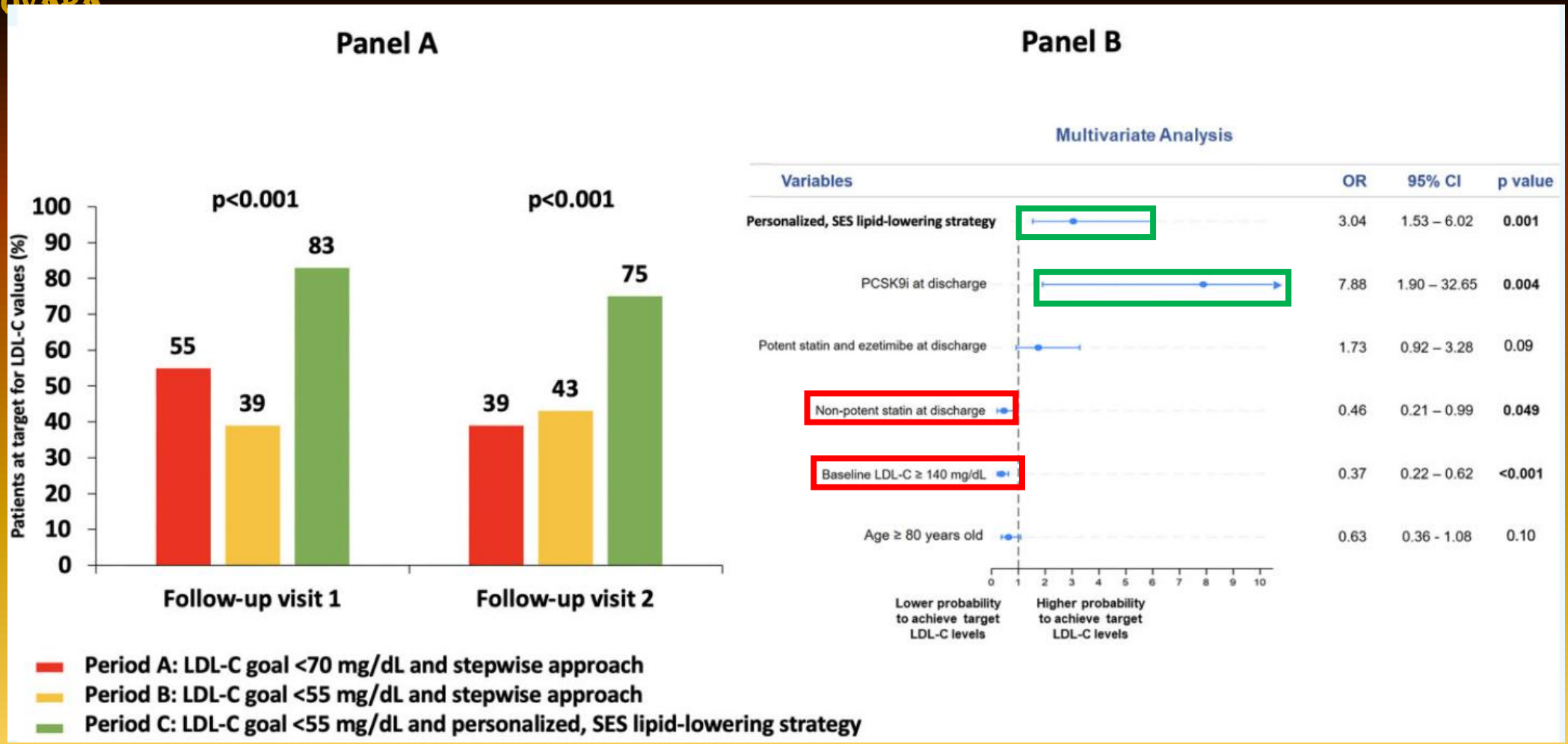
CARDIOLOGIA NOVARA



Patti G, et al. Eur Heart J Cardiovascular Pharmacotherapy 2025; doi 10.1093/ehjcvp/pvaf004

Impact of a personalized, strike early and strong lipid-lowering approach on LDL-C levels and cardiovascular outcome in patients with acute myocardial infarction
FAST-NOTE REGISTRY

CARDIOLOGIA NOVARA

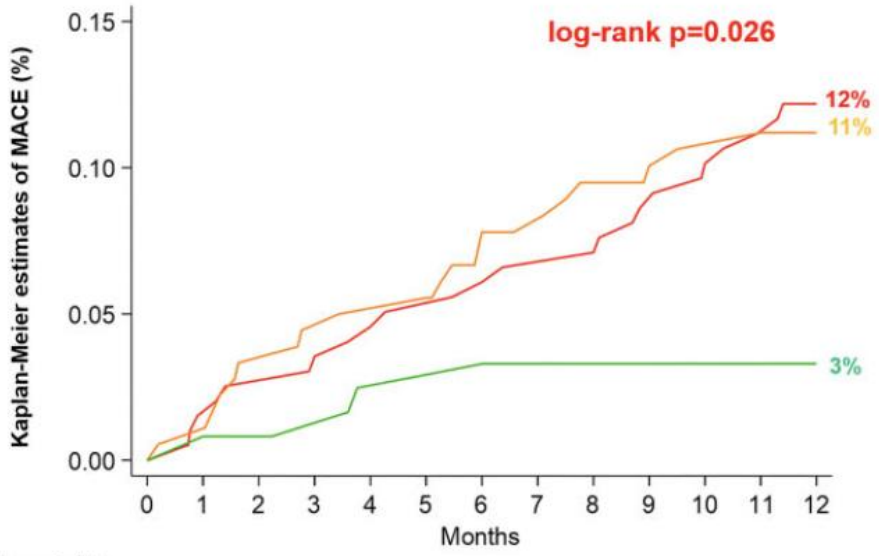


Patti G, et al. Eur Heart J Cardiovascular Pharmacotherapy 2025; doi 10.1093/ehjcvp/pvaf004

Impact of a personalized, strike early and strong lipid-lowering approach on LDL-C levels and cardiovascular outcome in patients with acute myocardial infarction FAST-NOTE REGISTRY

CARDIOLOGIA [illegible]

Panel A

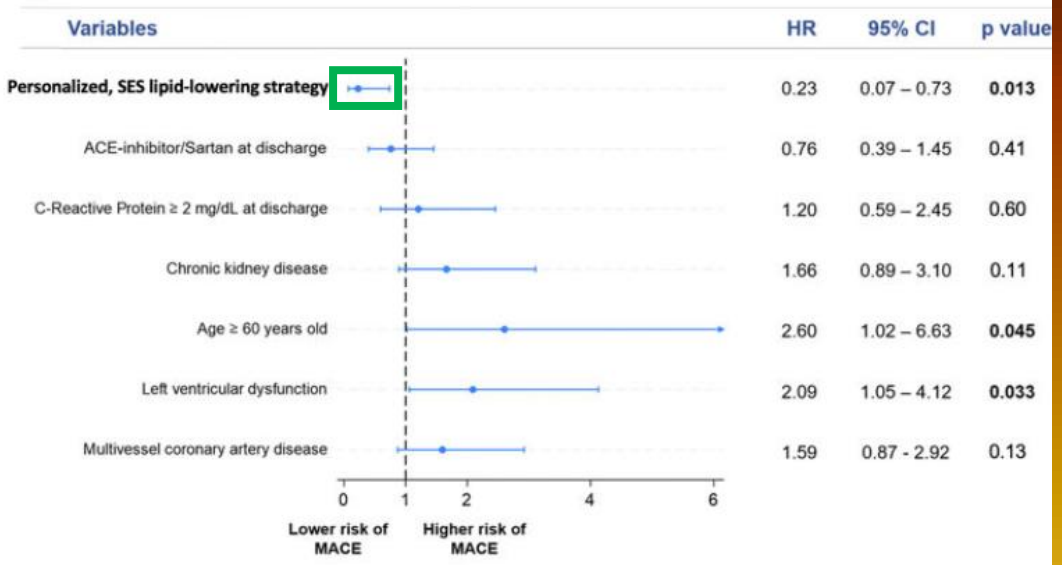


Number at risk

Period A	198	194	192	191	189	187	186	184	184	180	178	175	173
Period B	180	179	174	172	171	171	166	163	160	159	157	157	156
Period C	122	122	121	120	118	118	118	117	117	117	117	117	117

Period A: LDL-C goal <70 mg/dL and stepwise approach
Period B: LDL-C goal <55 mg/dL and stepwise approach
Period C: LDL-C goal <55 mg/dL and personalized, SES lipid-lowering strategy

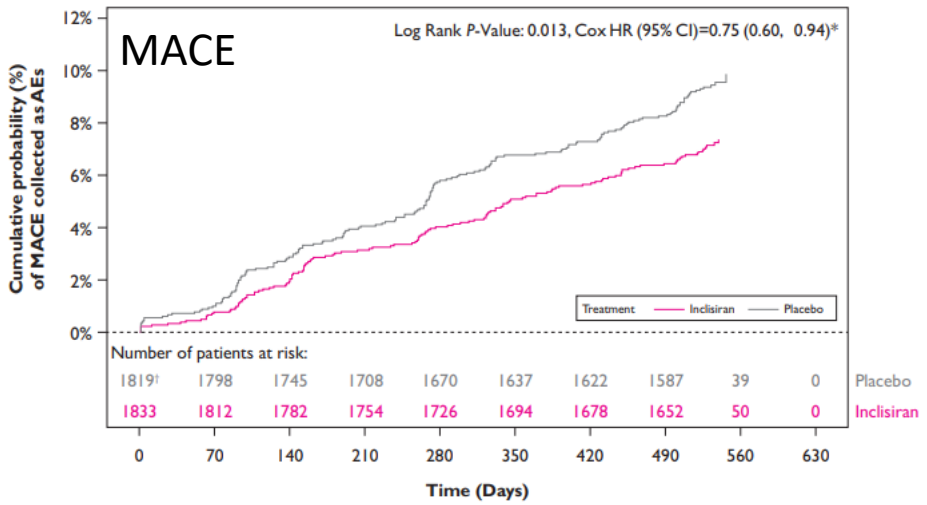
Panel B

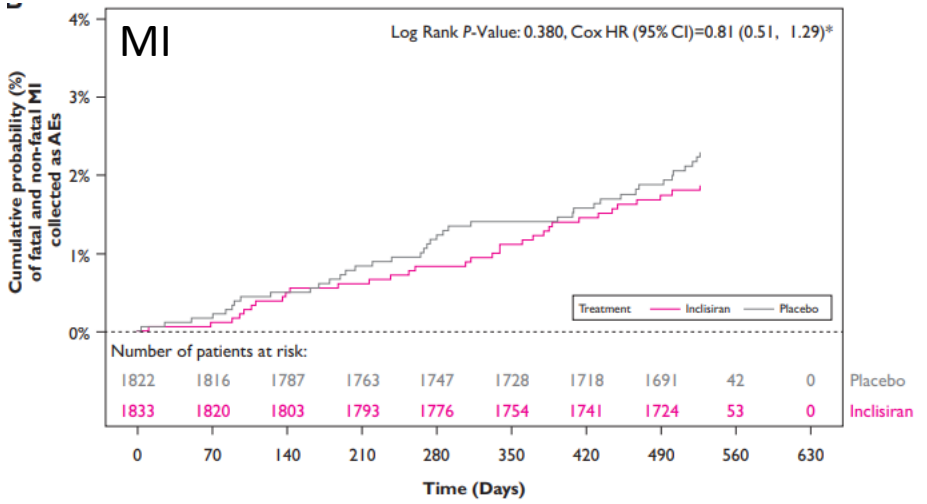


Patti G, et al. Eur Heart J Cardiovascular Pharmacotherapy 2025; doi 10.1093/ehjcvp/pvaf004

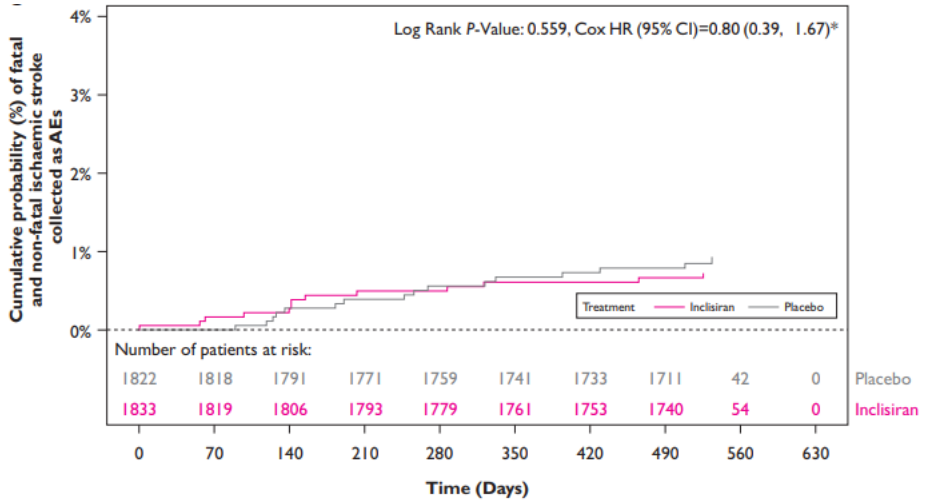
Patient-level, pooled analysis of ORION-9,–10, –11, on 36,052 patients with heterozygous familial hypercholesterolaemia, ASCVD or ASCVD risk equivalent on maximally tolerated statin-therapy - Ray KK, et al. Eur Heart J 2023;44:129

CARDIOLOGIA NOVARA



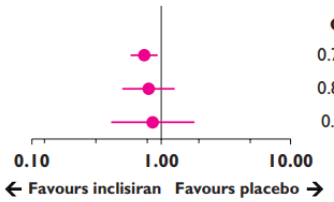


Stroke



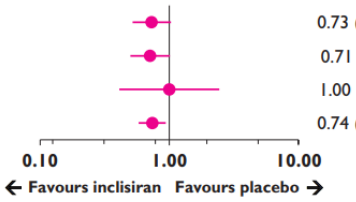
A Summary effects of MACE, fatal and non-fatal MI and fatal and non-fatal stroke

Treatment	Inclisiran*	Placebo†	OR (95% CI)
MACE	131 (7.1%)	172 (9.4%)	0.74 (0.58, 0.94)
Fatal and non-fatal MI	33 (1.8%)	41 (2.3%)	0.80 (0.50, 1.27)
Fatal and non-fatal stroke	13 (0.7%)	15 (0.8%)	0.86 (0.41, 1.81)



B MACE by individual study

Treatment	Inclisiran*	Placebo†	OR (95% CI)
ORION-11	63 (7.8%)	83 (10.3%)	0.73 (0.52, 1.03)
ORION-10	58 (7.4%)	79 (10.2%)	0.71 (0.50, 1.01)
ORION-9	10 (4.1%)	10 (4.2%)	1.00 (0.41, 2.44)
Fixed-effects model	131 (7.1%)	172 (9.4%)	0.74 (0.58, 0.94)



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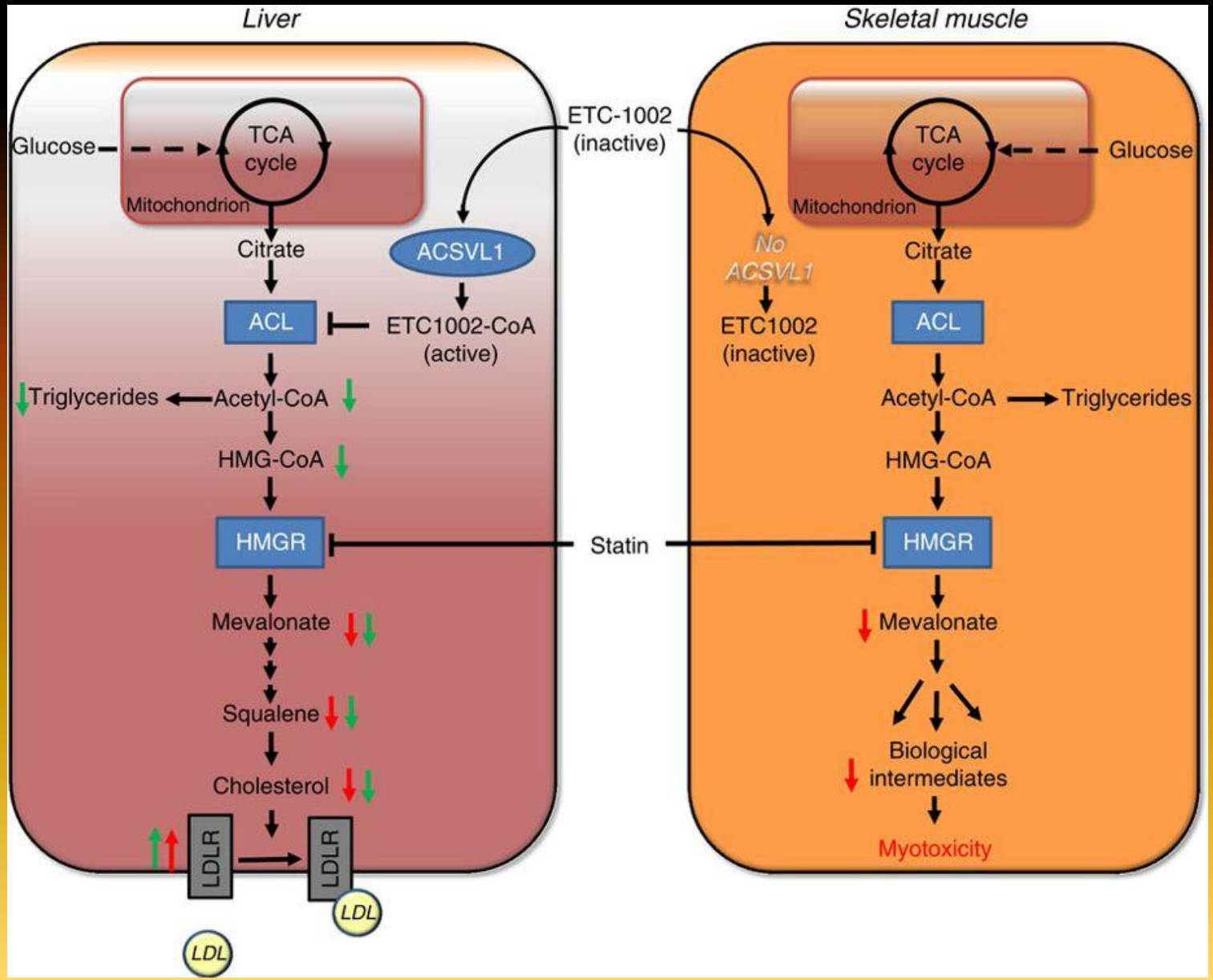
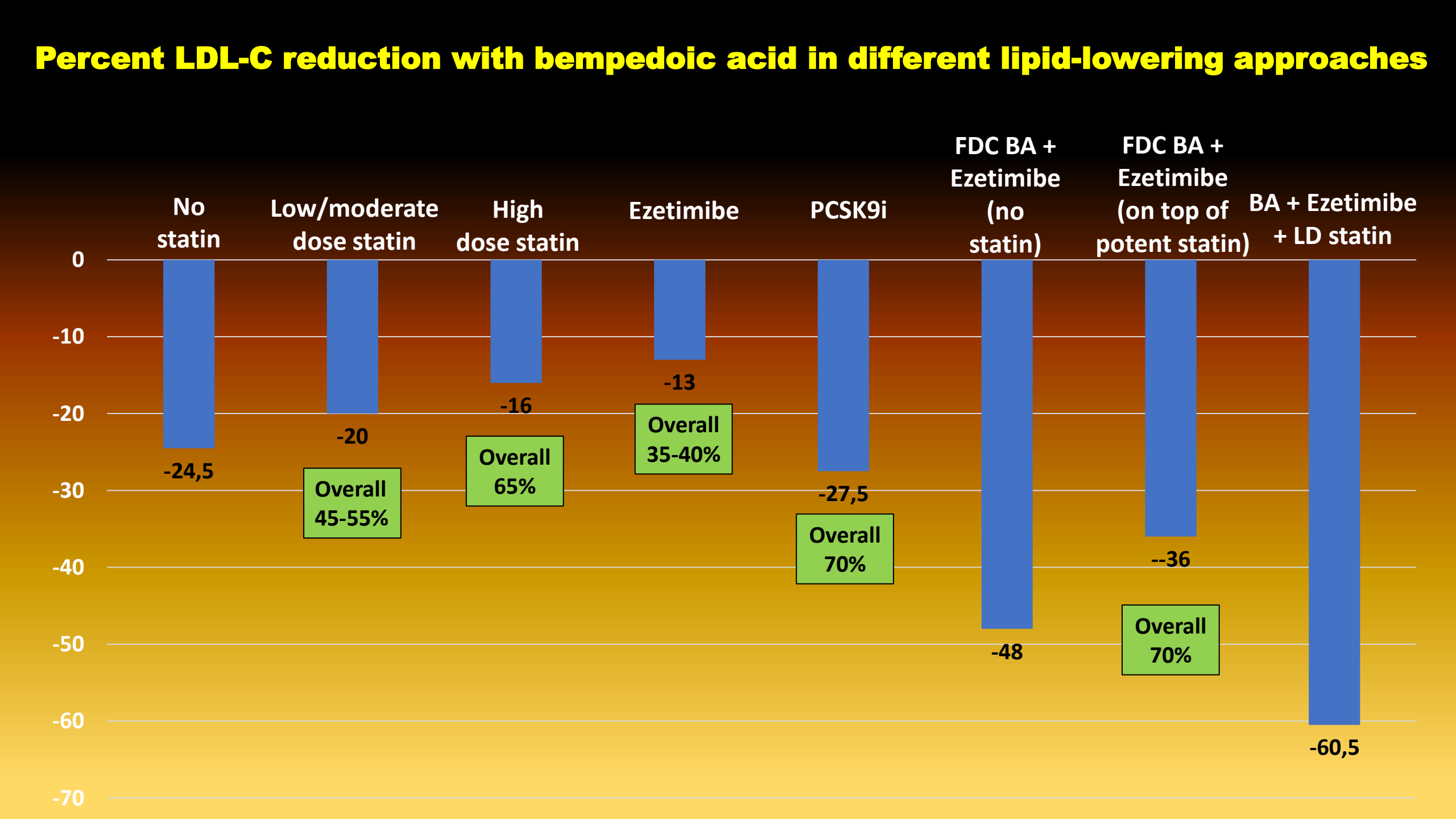
Bempedoic Acid is not Activated in the Skeletal Muscle



Pinkosky S et al. Nat Commun. 2016;7:13457. doi: 10.1038/ncomms1345

Percent LDL-C reduction with bempedoic acid in different lipid-lowering approaches



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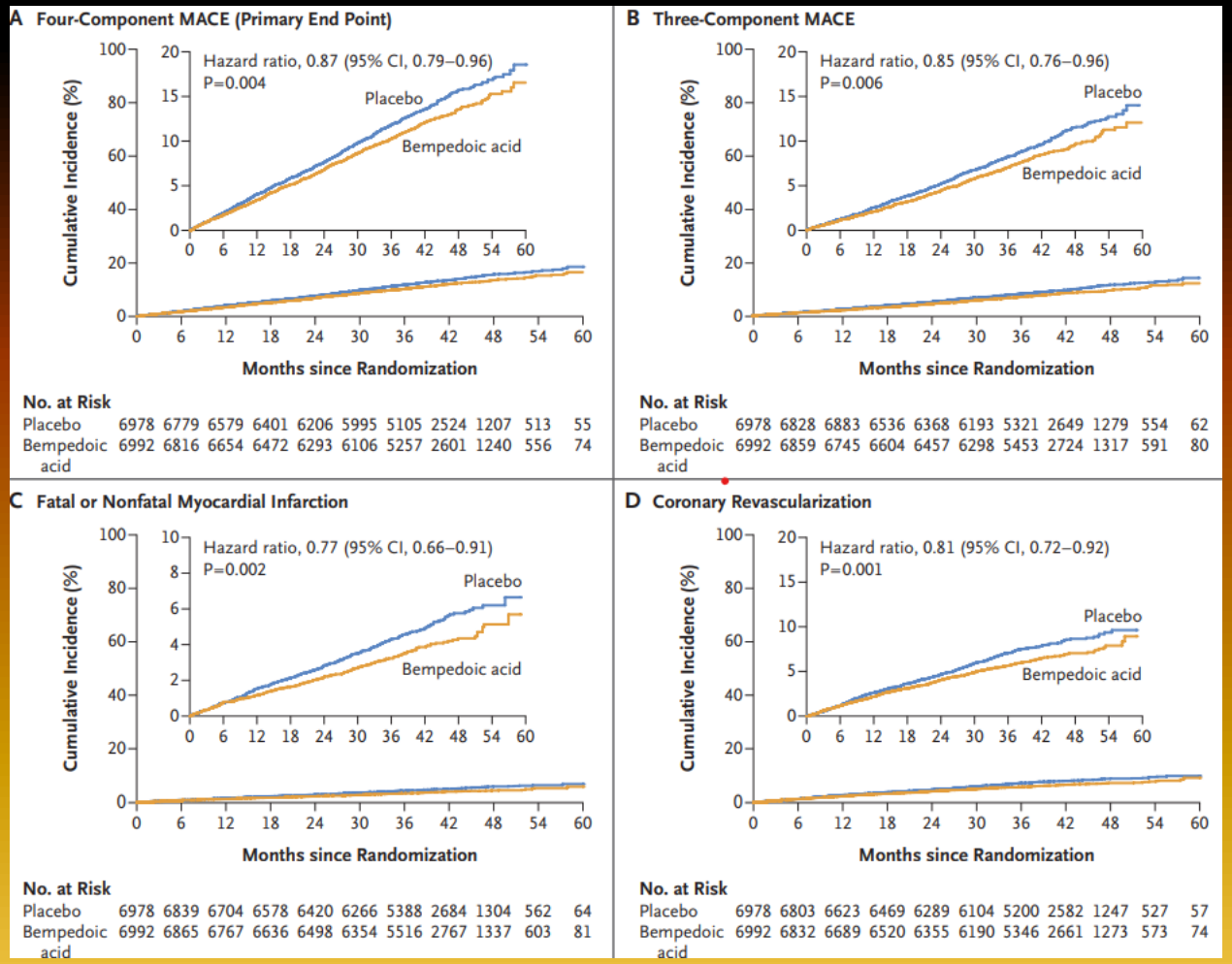
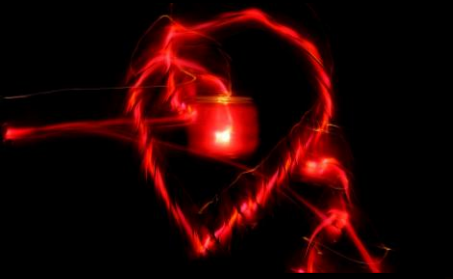
CLEAR OUTCOMES: Main results



Four-component MACE: death from CV, nonfatal MI, nonfatal stroke, or coronary revascularization

Nissen SE, et al. N Engl J Med 2023



CARDIOLOGIA NOVARA

Bempedoic acid: a guide for clinical use
(Patti G. et al. Vascul Pharmacol 2023 Feb;148:107137)

CAD: Chronic phase

LDL-C not at target

Statin monotherapy at highest recommended / tolerable dose without/with ezetimibe

LDL-C at target

LDL-C not at target: required LDL-C reduction

>20%

PCSK9-i

≤20%

Bempedoic acid **

** Additional candidates:
- Statin-intolerance
- Age >80 years

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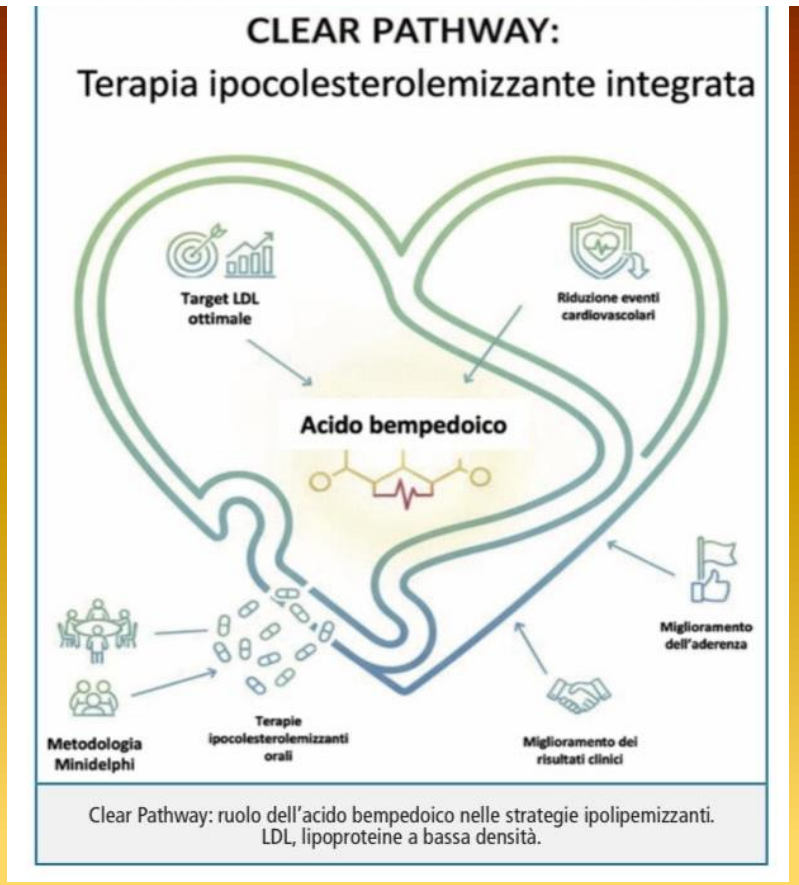
STUDIO OSSERVAZIONALE

Clear Pathway: ruolo dell'acido bempedoico nelle strategie ipolipemizzanti. Il parere dei cardiologi del Piemonte e della Valle d'Aosta

Federico Nardi[1], Giuseppe Patti[2], Giorgio Quadri[3], Luigi Pollarolo[1], Gianluca Alunni[4], Monica Andriani[4], Andrea Angelini[5], Marzia Bertolazzi[6], Giacomo Boccuzzi[7], Michele Capriolo[8], Alessandra Chinaglia[9], Michele De Benedictis[10], Ovidio De Filippo[4], Pierfranco Dellavesa[11], Fabrizio Delnevo[3], Sara Ferrillo[1], Massimo Giammaria[12], Antonio Lanfranchi[11], Piergiuseppe Greco Lucchina[13], Stefano Maffè[2], Marco Pavani[11], Elisa Pelloni[14], Davide Presutti[15], Maria Elena Rovere[16], Paolo Scacciatella[17], Gaetano Senatore[8], Erika Taravelli[18], Orazio Viola[19], Greca Zanda[20], Maurizio D'Amico[21], Gaetano Maria De Ferrari[4], Antonio Della Valle[22], Mauro Feola[23], Walter Grosso Marra[15], Alessandro Lupi[24], Claudio Moretti[19], Gianfranco Pistis[25], Francesco Rametta[6], Andrea Rognoni[20], Roberta Rossini[18], Marco Scaglione[5], Ferdinando Varbella[20], Giuseppe Musumeci[3]

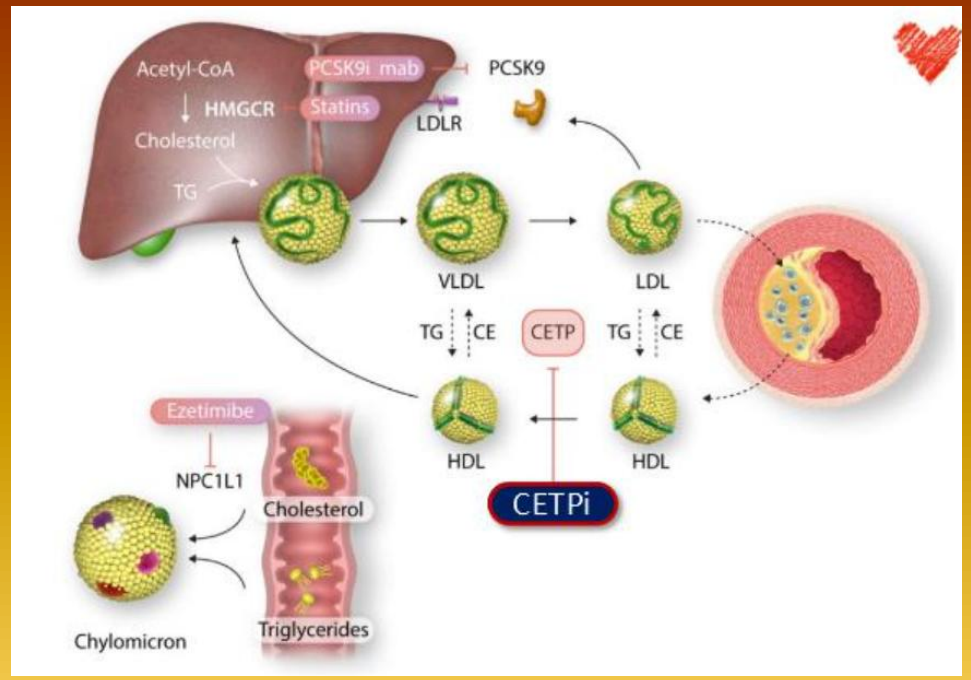


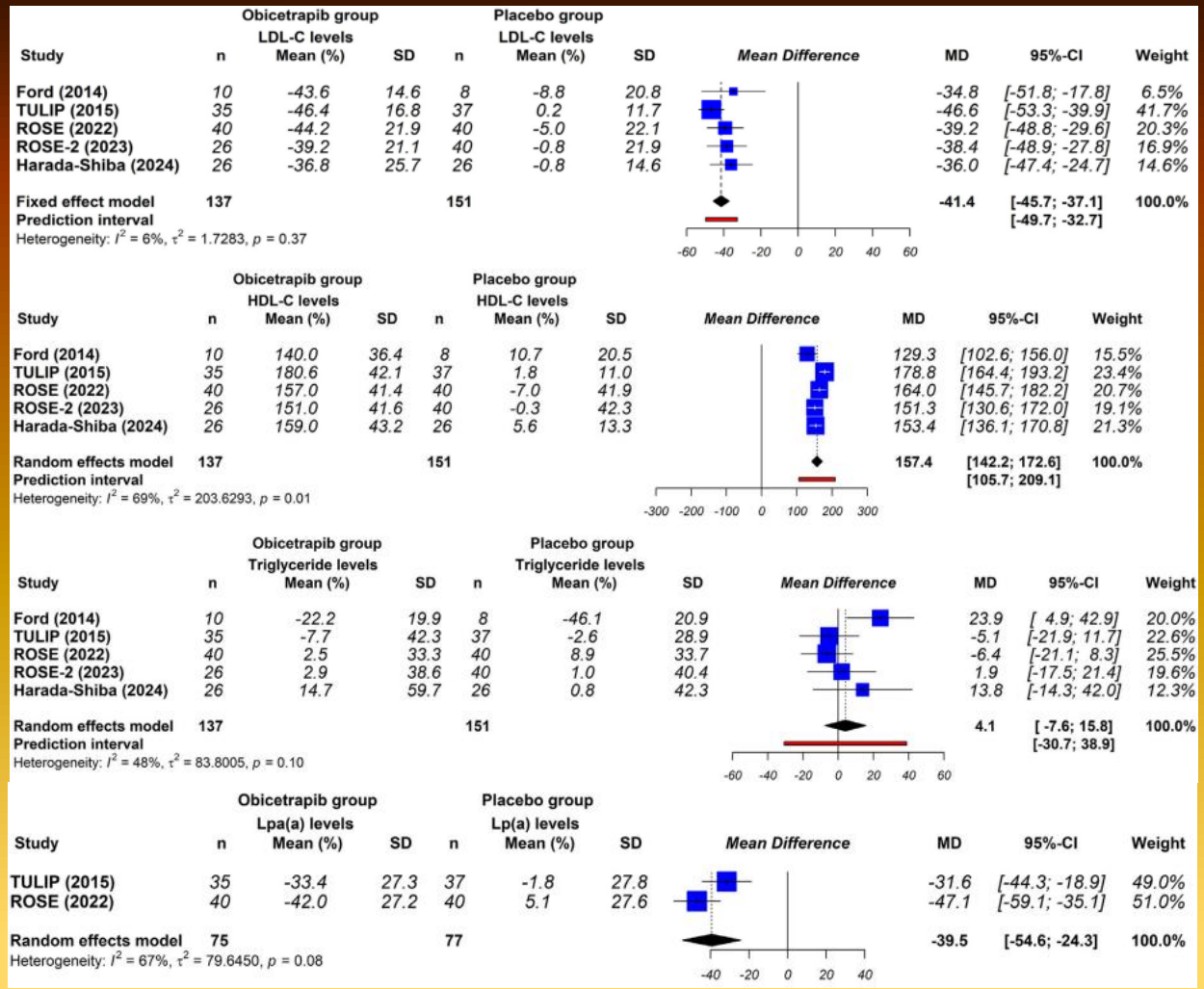
Clear Pathway: ruolo dell'acido bempedoico nelle strategie ipolipemizzanti.
LDL, lipoproteine a bassa densità.

CARDIOLOGIA NOVARA

The future … Newer agents

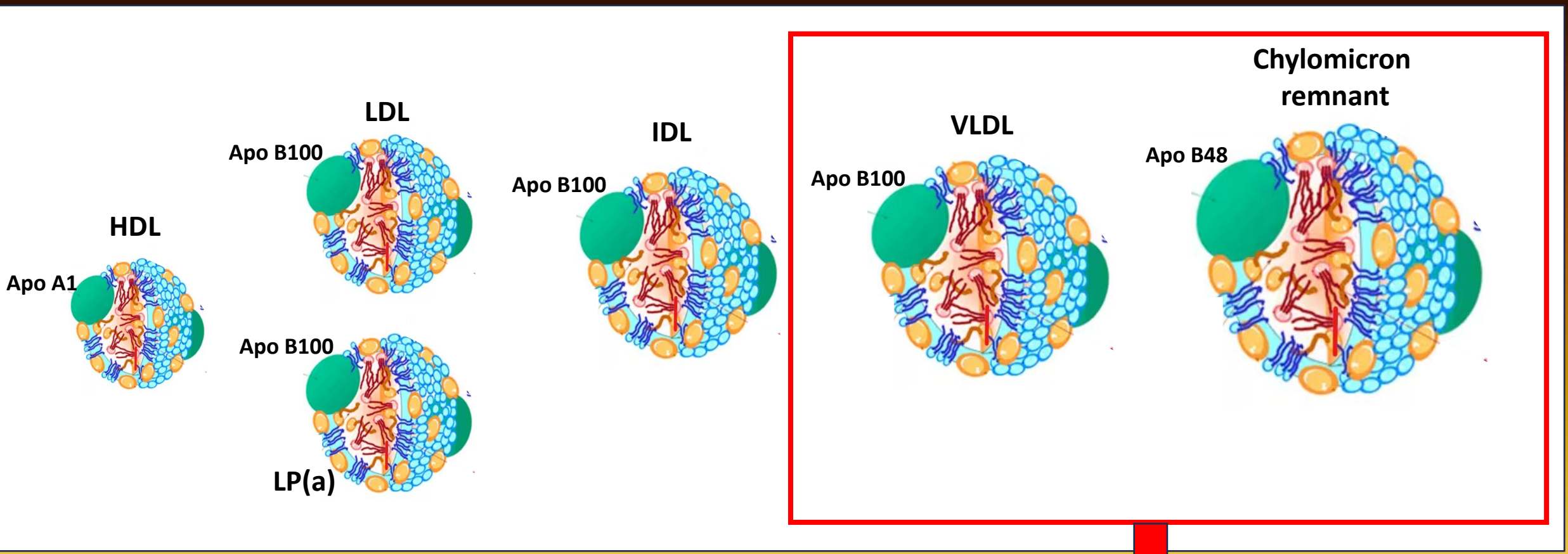
- Oral PCSK9-i
- Lomitapide; Evinacumab
- Obicetrapib





CARDIOLOGIA NOVARA

Lipoproteins in the blood



Triglycerides-rich lipoproteins

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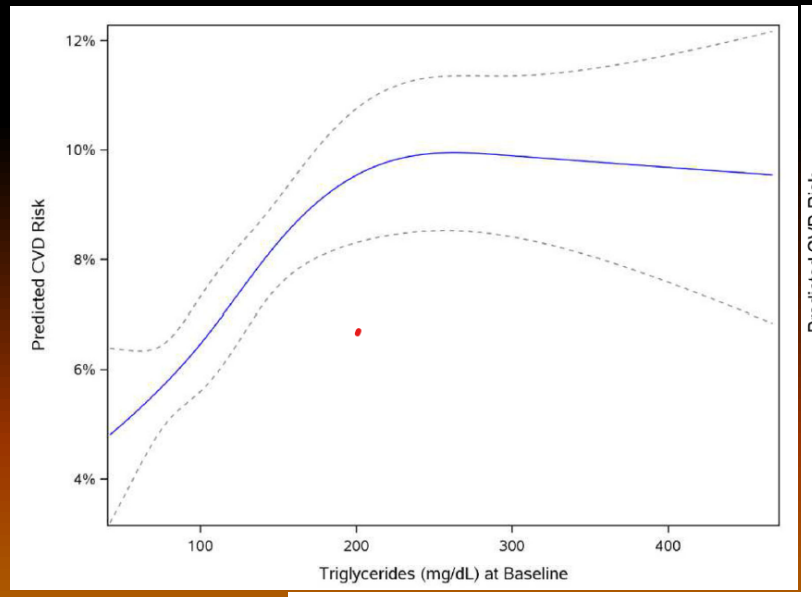
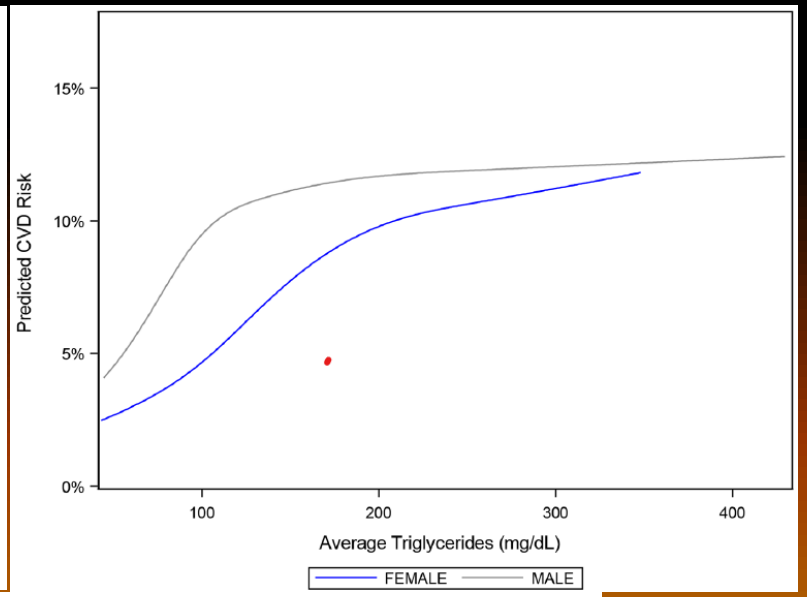
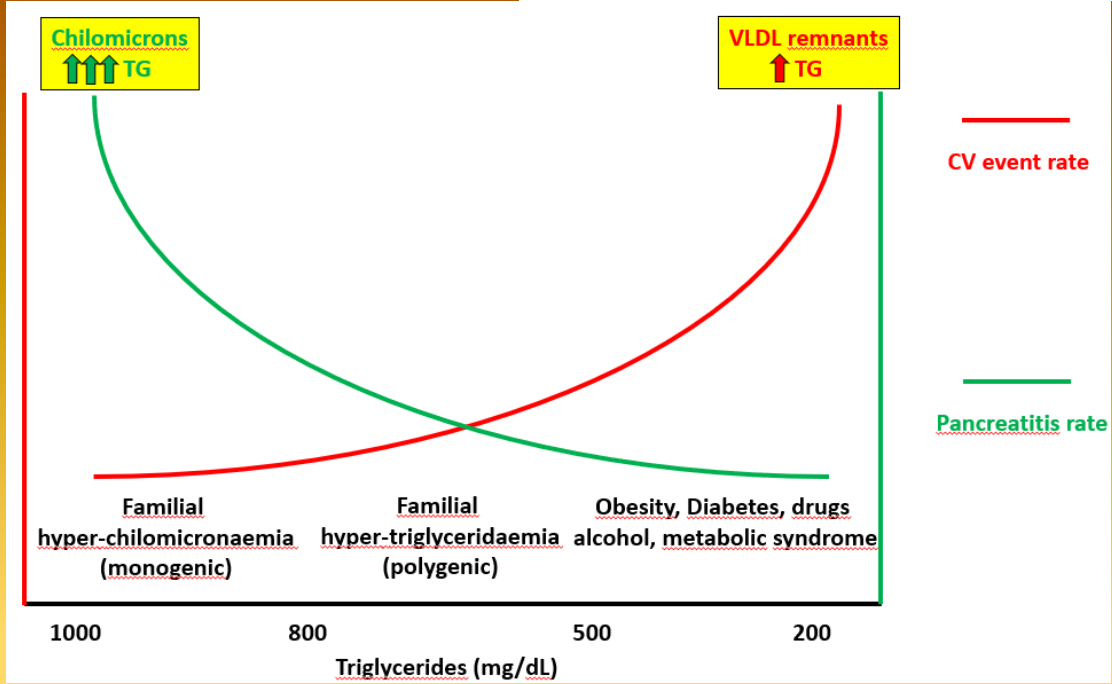
Triglycerides and cardiovascular risk







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Secondary causes of Hypertriglyceridemia

TABLE 1 Secondary Causes of Hypertriglyceridemia (2,41-43)

Categories	Conditions and Medications Contributing to Hypertriglyceridemia
Diseases	■ Poorly controlled diabetes mellitus ■ Chronic kidney disease, nephrotic syndrome ■ Familial partial lipodystrophy ■ Uncontrolled hypothyroidism ■ Cushing syndrome ■ Glycogen storage disease, acute hepatitis ■ Rheumatoid arthritis ■ Psoriasis ■ Systemic lupus erythematosus ■ Multiple myeloma ■ Sepsis (*repeat measurement is recommended if lipids were measured during an episode of sepsis*)
Diet/lifestyle	■ History of alcohol abuse or alcohol excess ■ Diets high in saturated fat, sugar, or high-glycemic-index foods ■ Sedentary lifestyle ■ Total parenteral nutrition with lipid emulsions

Drugs* (Medications)	**Anesthesia:**
	■ Propofol
	Cardiology:
	■ Beta adrenergic blocking agents
	■ Thiazide and loop diuretic agents
	■ Bile acid sequestrants (cholestyramine, colestipol, colesevelam)
	Endocrine:
	■ Glucocorticosteroids
	■ Anabolic steroids
	■ Oral estrogens
	  ■ Raloxifene
	  ■ Clomiphene citrate
	  ■ Estradiol
	  ■ Ethinyl estradiol
	  ■ Conjugated estrogens
	  ■ Tamoxifen
	Dermatology:
	■ Isotretinoin
	Infectious Disease
	■ HIV protease inhibitors
	Oncology:
	■ Tamoxifen
	■ L-asparaginase
	■ Bexarotene
	■ Cyclophosphamide
	Psychiatry:
	■ Atypical antipsychotic agents (eg, olanzapine, mirtazapine, clozapine)
	Immunosuppressive agents:
	■ Tacrolimus
	■ Sirolimus
	■ Cyclosporine
	■ Interferons

Disorders of metabolism	■ Overweight and obesity ■ Metabolic syndrome/insulin resistance ■ Weight gain after weight loss ■ Pregnancy (*especially third trimester when triglyceride elevation associated with pregnancy is peaking*)

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ESC 2019 Guidelines on Dyslipidemias

Table 11. Effects of Nutrition Practices on Triglyceride Lowering

Nutrition Practice	TG-Lowering Response, %
Weight loss (5% to 10% of body weight)	20
Implement a Mediterranean-style diet vs a low-fat diet	10–15
Add marine-derived PUFA (EPA/DHA) (per gram)	5–10
Decrease carbohydrates	
1% Energy replacement with MUFA/PUFA	1–2
Eliminate *trans* fats	
1% Energy replacement with MUFA/PUFA	1

Table 12. Effect of Lipid-Lowering Therapies on Triglyceride Reduction[504,480a–480d]

Drug	% Triglyceride Reduction
Fibrates	30–50
Immediate-release niacin	20–50
Omega-3	20–50
Extended-release niacin	10–30
Statins	10–30
Ezetimibe	5–10

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

reduce-it

PATIENTS	AT RISK FOR	RANDOMISATION
8179 Patients… ▪ Men and women aged ≥45 years on stable statin therapy +/- ezetimibe ▪ LDL-C 40 – 100 mg/dl ; median at baseline 74 mg/dl	**At High Risk for CV Events due to:** **Mild to moderate TG elevation** ▪ TG 135 –500 mg/dl; (median at baseline 216 mg/dl) **- AND -** ▪ Established CVD (secondary prevention cohort) **- OR -** ▪ Diabetes mellitus + age ≥50 years + at least 1 risk factor for CVD (primary prevention cohort)	**Randomisation 1:1** **Study Treatment** ▪ Stable statin + IPE 4 g/day (2 g twice daily with meals) **- OR -** ▪ Stable statin + placebo ▪ Follow-up duration: median 4.9 yrs, maximum 6.2 yrs

PRIMARY ENDPOINT: Composite of CV death, non-fatal MI (including silent MI), non-fatal stroke, coronary revascularization, or unstable angina in a time-to-event analysis

SECONDARY ENDPOINT: Composite of CV death, non-fatal MI, non-fatal stroke

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Outcomes - Biomarkers

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	Icosapent Ethyl (N=4089) Median		Placebo (N=4090) Median		Median Between Group Difference at Year 1		
Biomarker*	Baseline	Year 1	Baseline	Year 1	Absolute Change from Baseline	% Change from Baseline	% Change P-value
Triglycerides (mg/dL)	216.5	175.0	216.0	221.0	-44.5	-19.7	<0.0001
Non-HDL-C (mg/dL)	118.0	113.0	118.5	130.0	-15.5	-13.1	<0.0001
LDL-C (mg/dL)	74.0	77.0	76.0	84.0	-5.0	-6.6	<0.0001
HDL-C (mg/dL)	40.0	39.0	40.0	42.0	-2.5	-6.3	<0.0001
Apo B (mg/dL)	82.0	80.0	83.0	89.0	-8.0	-9.7	<0.0001
hsCRP (mg/L)	2.2	1.8	2.1	2.8	-0.9	-39.9	<0.0001
Log hsCRP (mg/L)	0.8	0.6	0.8	1.0	-0.4	-22.5	<0.0001
EPA (µg/mL)	26.1	144.0	26.1	23.3	+114.9	+358.8	<0.0001

*Apo B and hsCRP were measured at Year 2.

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Outcomes - Endpoints

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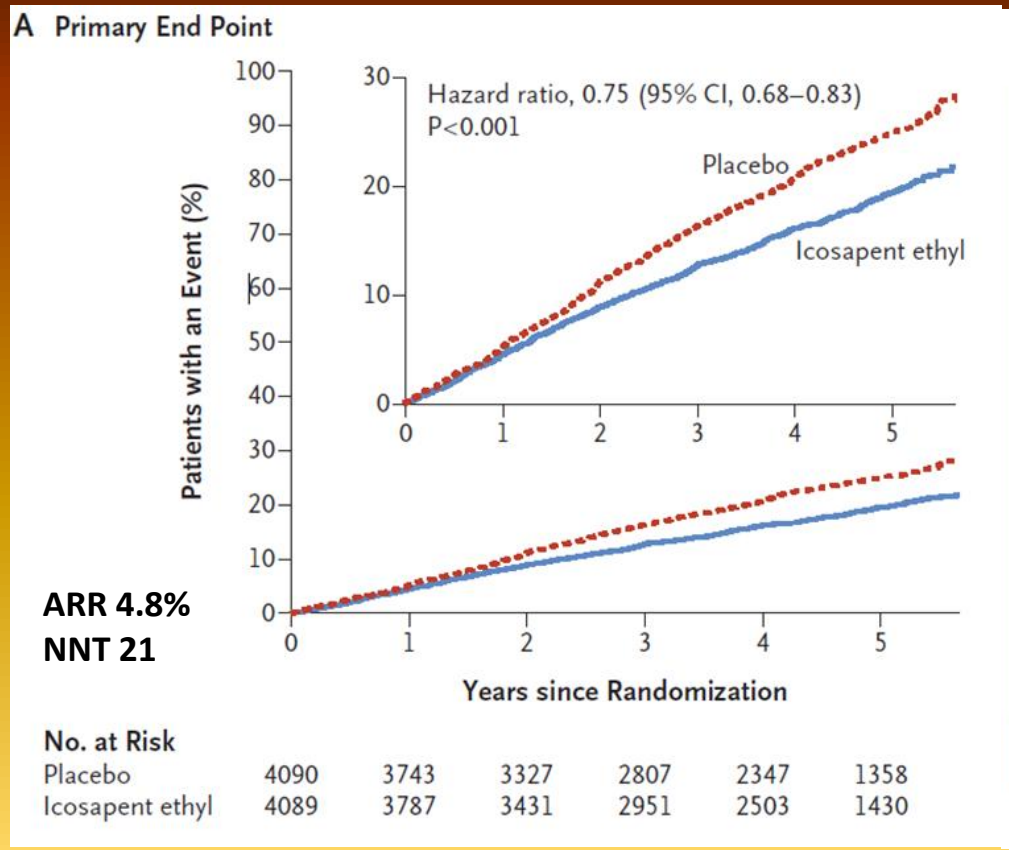
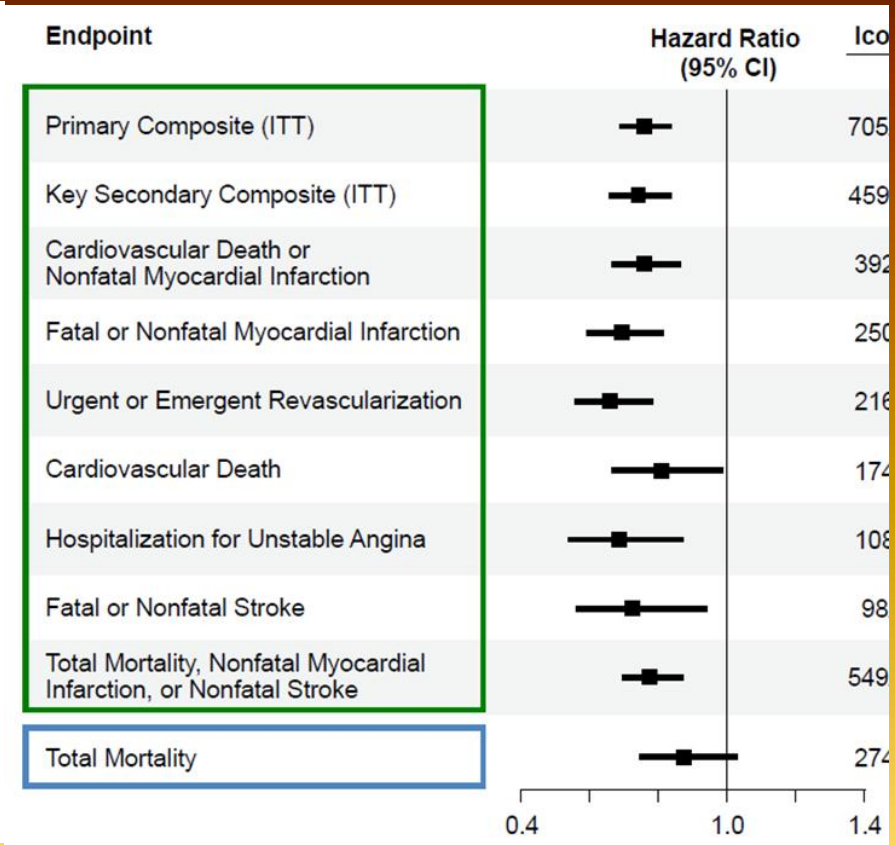


ARR 4.8%
NNT 21



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When can we use icosapent ethyl in Italy?

Recommendations for drug treatment of patients with hypertriglyceridaemia

Recommendations	Class[a]	Level[b]
Statin treatment is recommended as the first drug of choice to reduce CVD risk in high-risk individuals with hypertriglyceridaemia [TG levels >2.3 mmol/L (>200 mg/dL)].[355]	I	B
In high-risk (or above) patients with TG levels between 1.5–5.6 mmol/L (135–499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2×2 g/day) should be considered in combination with a statin.[194]	IIa	B
In primary prevention patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.[305–307,356]	IIb	B
In high-risk patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.[305–307,356]	IIb	C

- Patients with at least one of these cardiovascular diseases:
  - previous MI
  - previous coronary revascularization with PCI or CABG
  - documented coronary disease in medical treatment
  - symptomatic PAD
  - previous stroke/TIA

AND

- TG levels ≥200 mg/dl at 3 determinations

AND

- BMI ≥27
- Age 18-80 years
- On high-potency statin + ezetimibe
- LDL-C <70 mg/dl
- Not receiving PCSK9i

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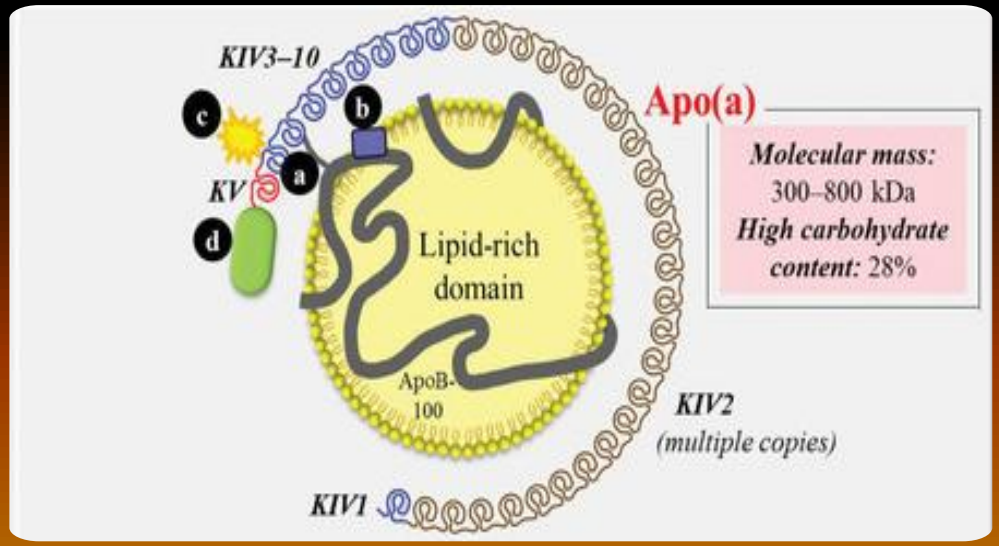
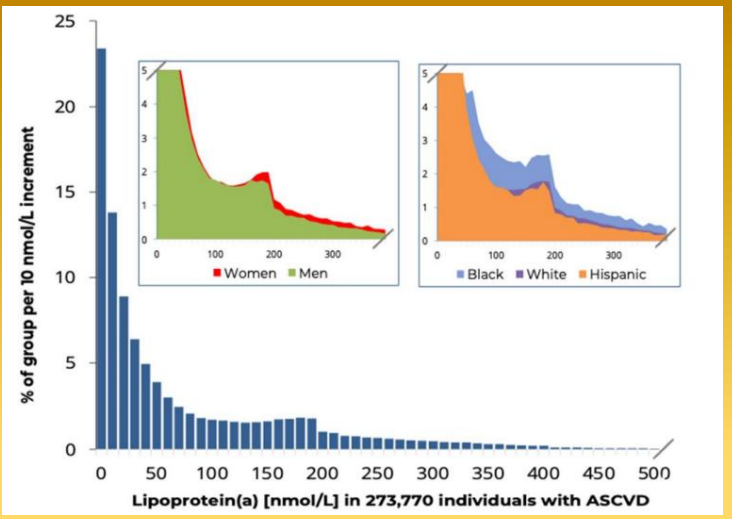
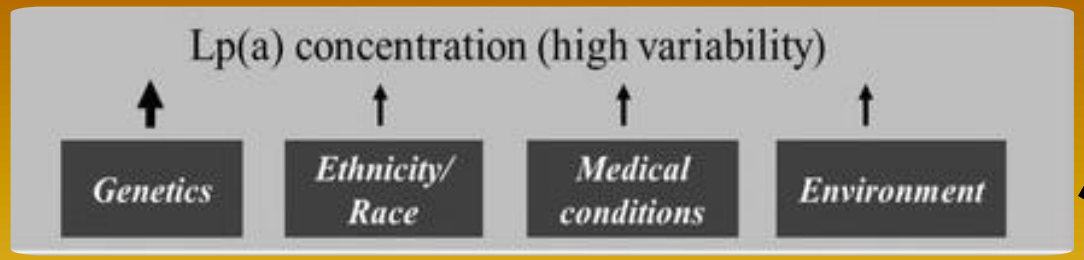
Structure of Lp(a)



- Lipoprotein(a) consists of a lipid-rich domain, primarily cholesteryl esters, and Apo(a).
- Apo(a) binds to apolipoprotein B100 (apoB) via a single disulfide bond (a) at a location close the low-density lipoprotein receptor binding site of apoB (b).
- There are 10 different subtypes of apo(a) KIV, where type 2 is present in multiple copies, resulting in a highly variable molecular mass (300–800 kDa).





- K-IV repeat polymorphism
- South Asian
- Black
- Hispanic
- CKD
- Chronic inflammation
- Liver disease (reduction)
- Low carbohydrate/saturated fat diet (-10%)

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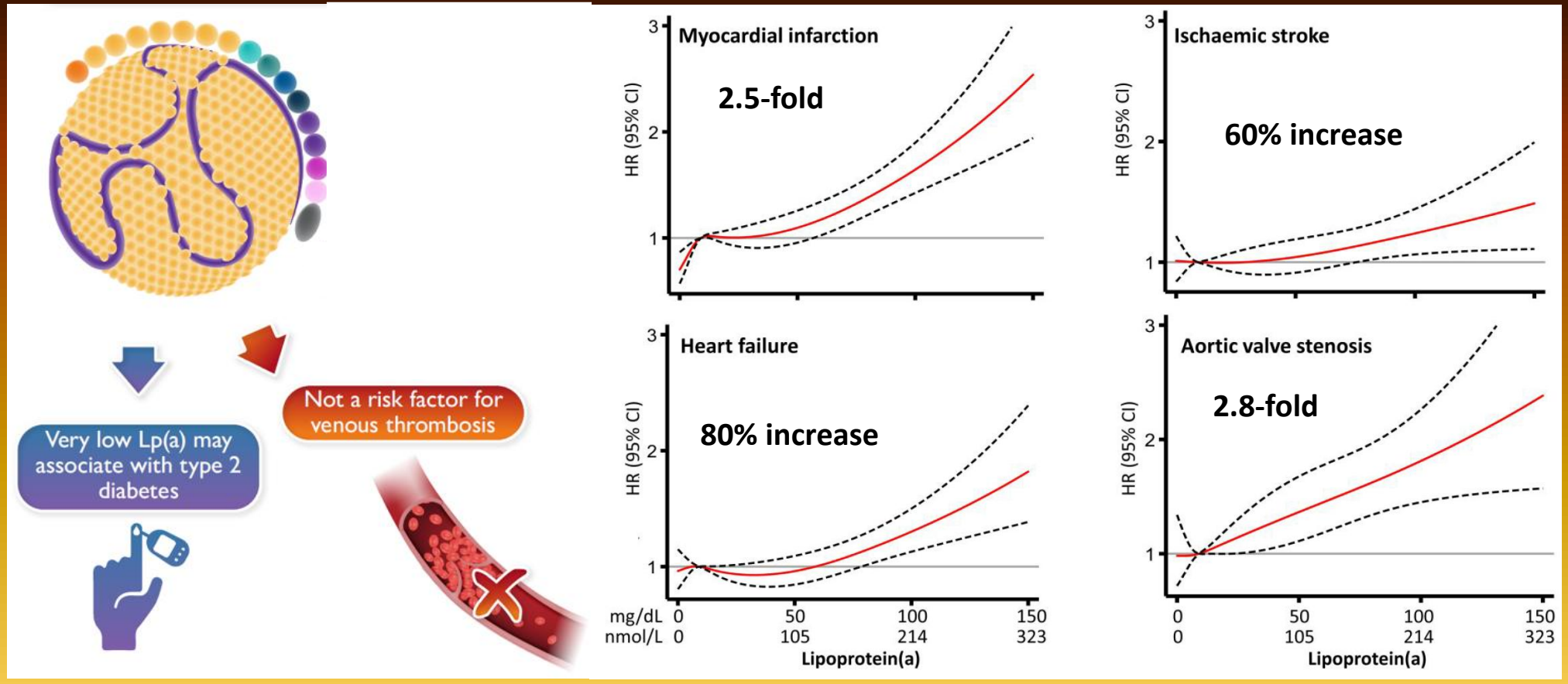
Risk of clinical outcomes with Lp(a) concentration



Kronenberg, F. et al. Eur Heart J vol. 43,39 (2022): 3925-3946

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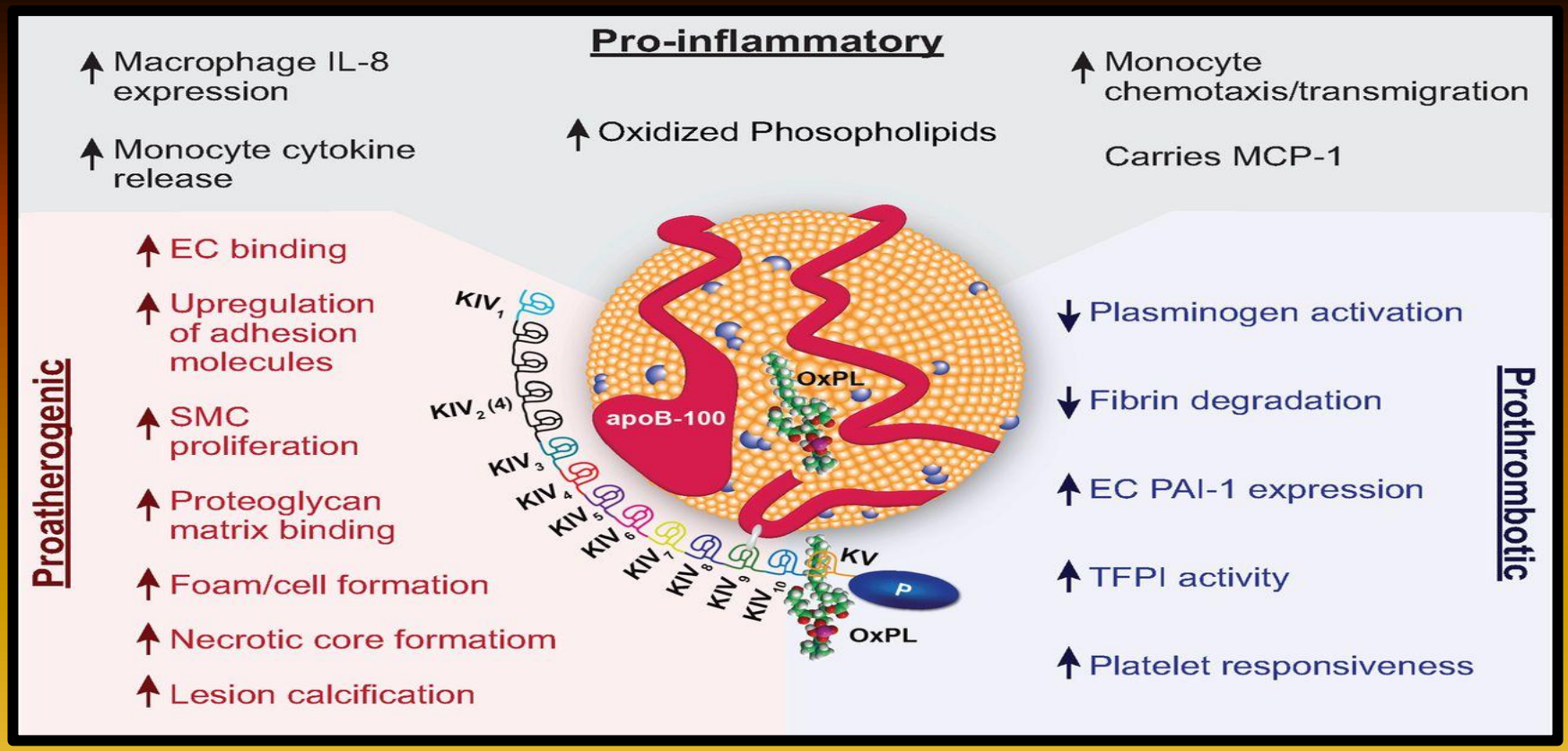
Pathogenesis of Lp(a)-mediated damage



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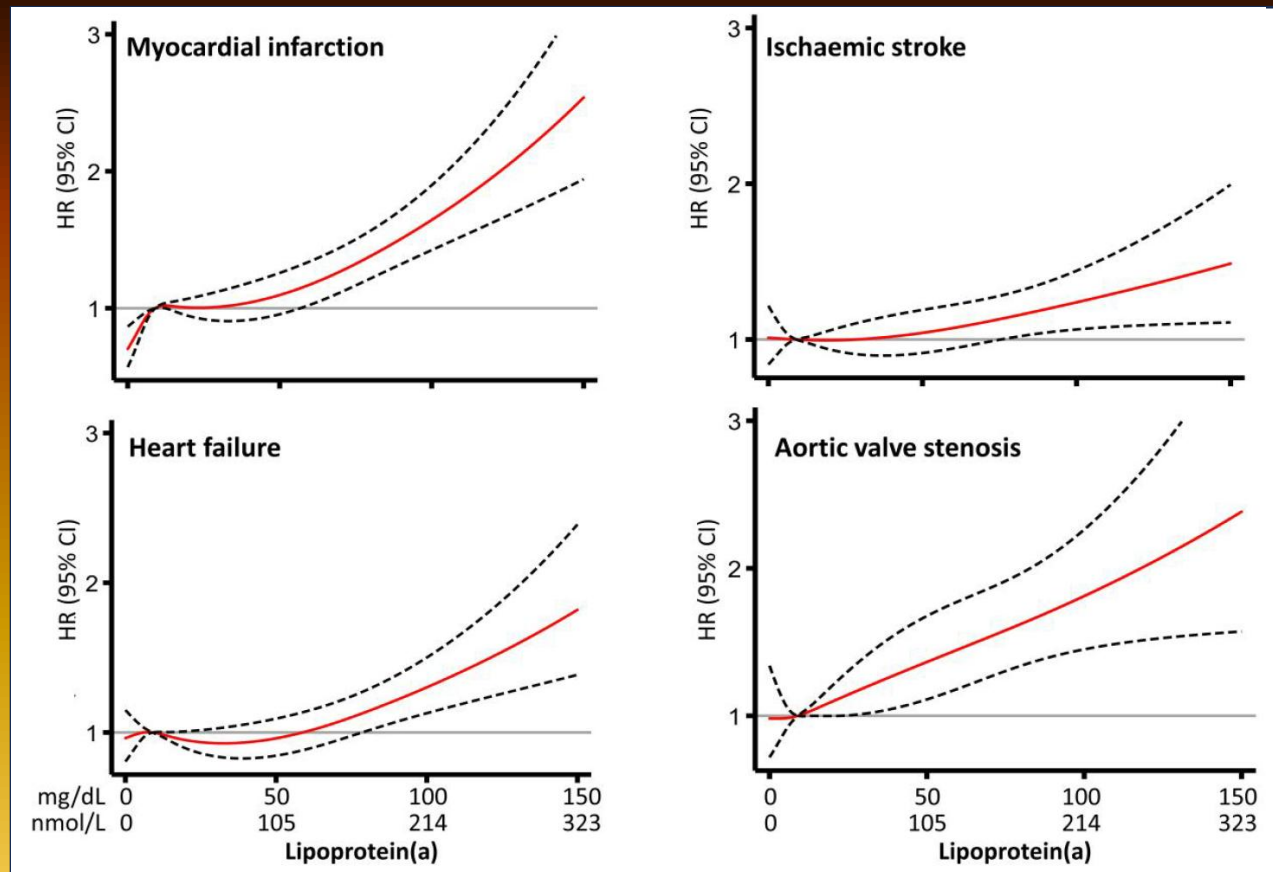
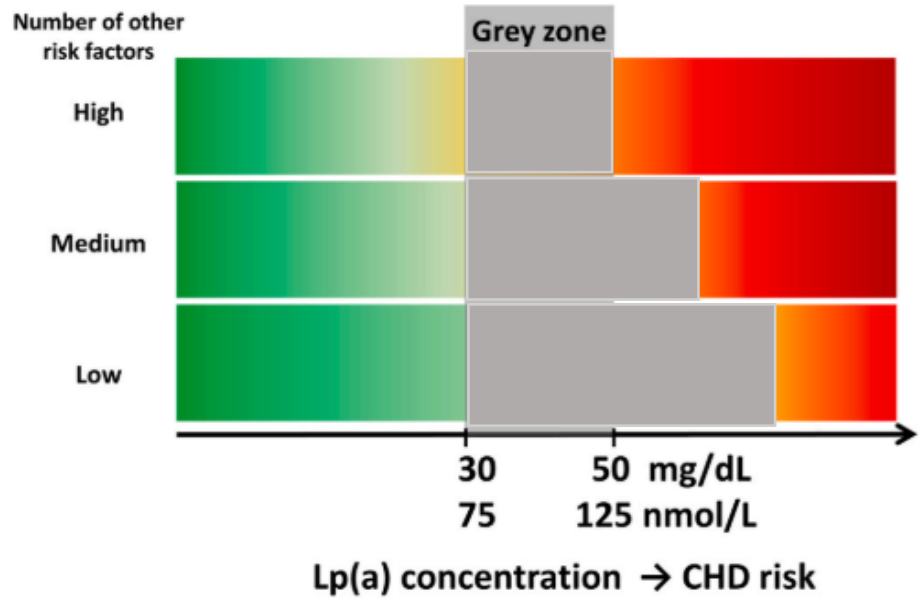
Clinical outcomes with Lp(a) concentration





Kronenberg, Florian et al. EHJ vol. 43,39 (2022): 3925-3946

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Lipoprotein(a) and recurrent atherosclerotic cardiovascular events according to LDL-C levels

US Family Heart Database - N=273,770 individuals (57% men) with ASCVD anf followed at a median of 5.4 yrs for recurrence of CV events (MI, ACS, stroke, PCI, CABG)

Lipoprotein(a) Category nmol/L	n	n with events	HR (95% CI)	p value
Recurrent ASCVD events in individuals using no LDL cholesterol lowering therapy, adjusted for sex, race/ethnicity and age				
<15	36,589	4,254	1	Reference
15-79	42,201	5,132	1.05 (1.00-1.09)	0.03
80-179	19,400	2,594	1.15 (1.09-1.20)	6×10^{-08}
180-299	10,939	1,659	1.32 (1.25-1.40)	7×10^{-22}
≥300	4,714	844	1.57 (1.46-1.69)	8×10^{-33}

MacDougall DE, et al. Eur Heart J 2025

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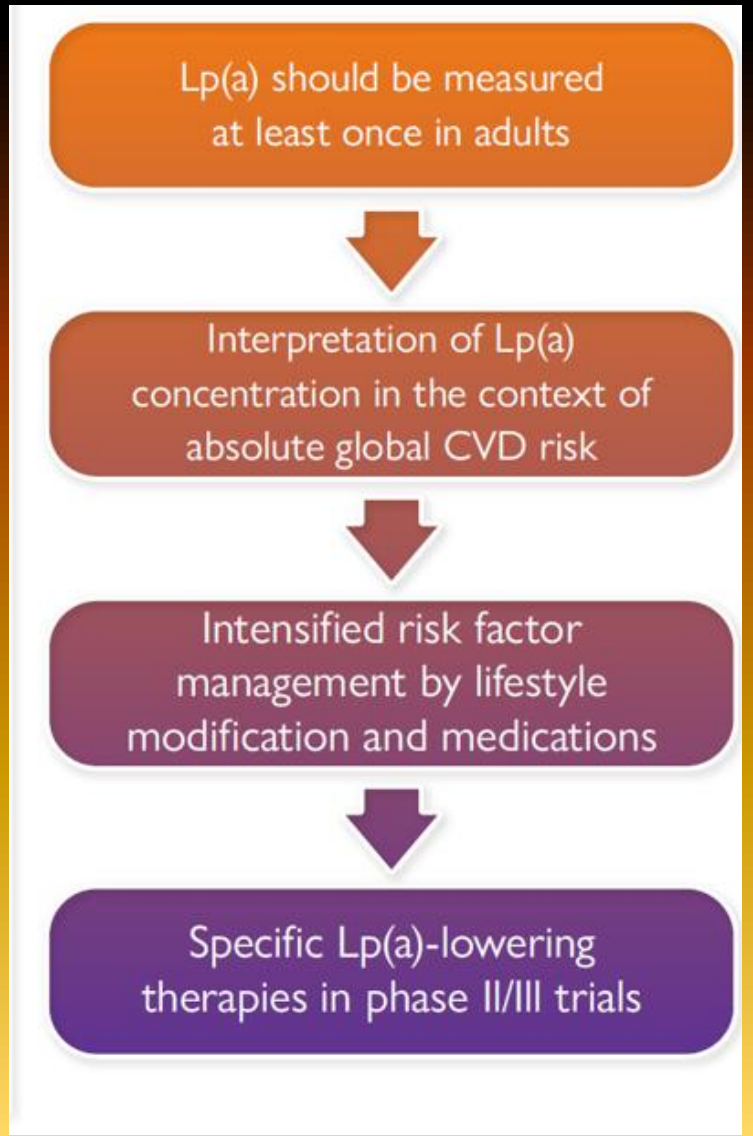
EAS/ESC recommendations on Lp(a)

Recommendations for lipid analyses for cardiovascular disease risk estimation (3)

EAS ESC European Society of Cardiology

Recommendations	Class	Level
Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >180 mg/dL (>430 nmol/L) who may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolaemia.	IIa	C
Lp(a) should be considered in selected patients with a family history of premature CVD, and for reclassification in people who are borderline between moderate and high-risk.	IIa	C



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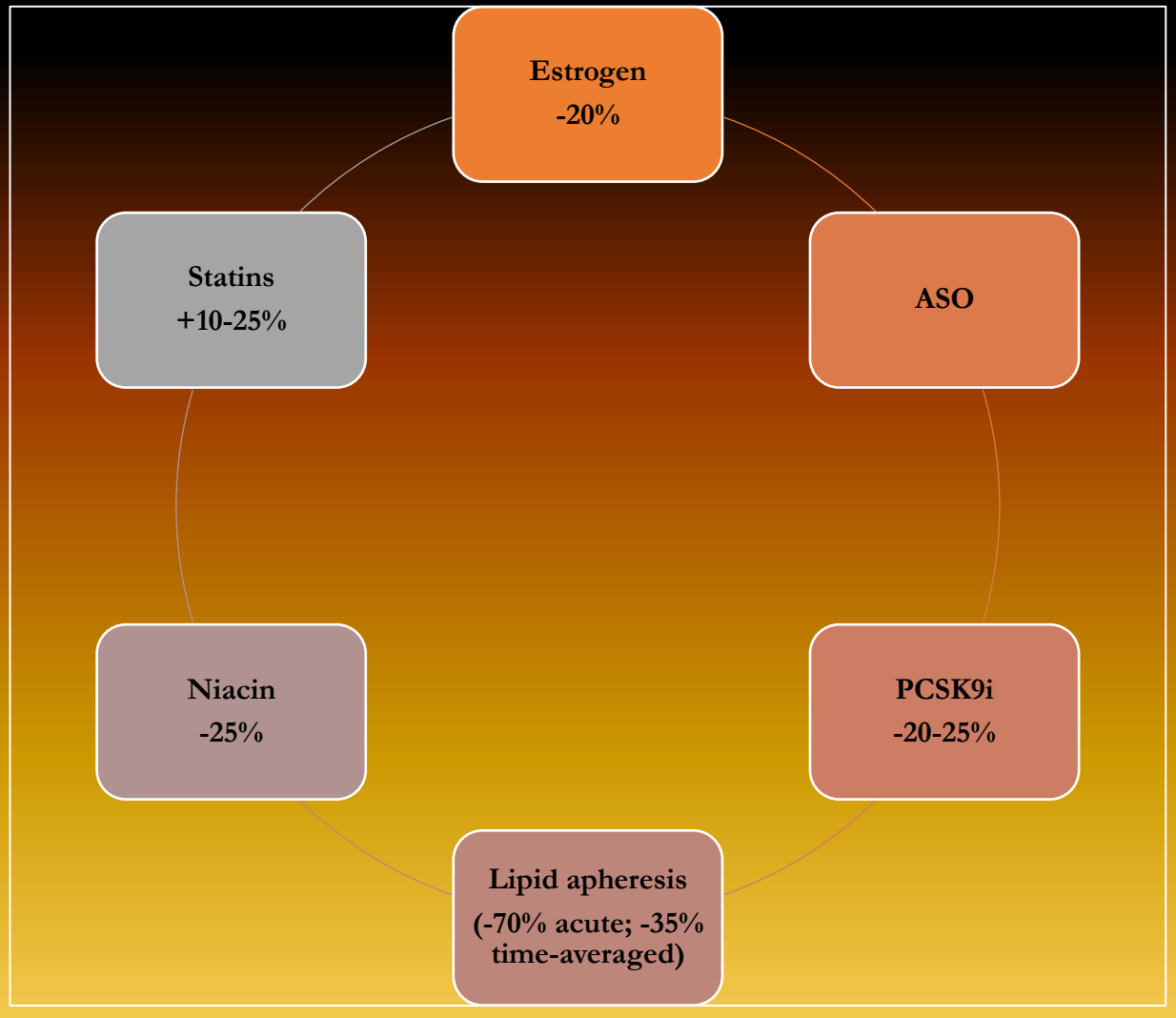
Therapies affecting Lp(a) levels



Therapies affecting Lp(a) levels

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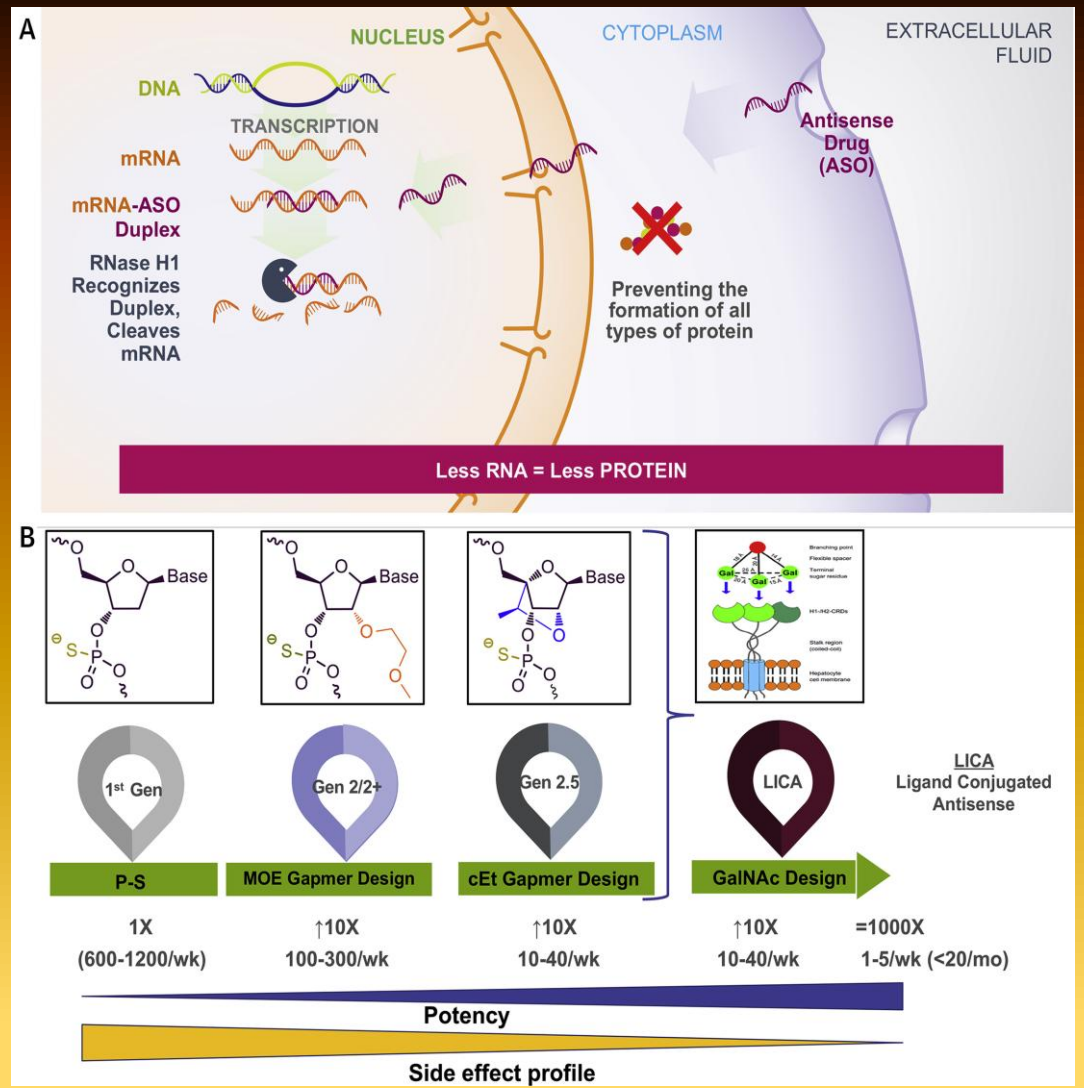

	Route and dosing	LP(a) % reduction
ISIS-APO(a)	S.C. weekly	40-78%
IONIS-APO(a)	S.C. weekly	67-72%
Pelacarsen (AS0)	S.C. monthly	72-80%
Olpasiran (siRNA)	S.C. 3 months	81-94%
SLN360 – Zerlasiran (siRNA)	S.C. 1 or 2 months	98%
Lepodisiran (siRNA)	S.C. 6 months	98%
Muvalaplin	Oral OD	50%
CRISPR-Cas9	Gene editing	

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Thank you very much for your attention!!!

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