

4° G.Meta Open Forum: “al cuore del diabete”

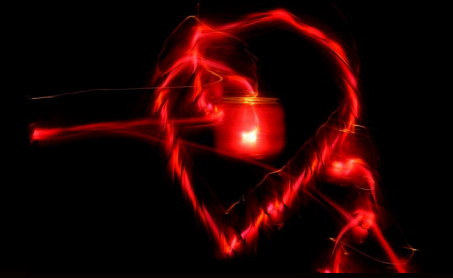
14-15 Marzo 2025

Aula Brasca, Policlinico Gemelli - Roma (RM)

**Gli strumenti che abbiamo (o che AIFA ci permette di avere)
per raggiungere i target di LDL**

Prof. Giuseppe Patti

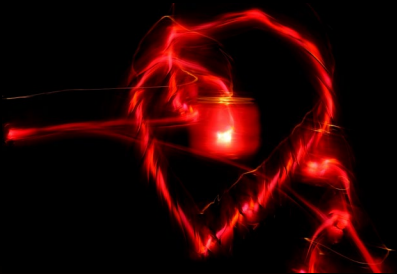
**Direttore Cattedra e Scuola di Specializzazione in Cardiologia, Università del Piemonte Orientale
Direttore Dipartimento Toraco-Cardio-Vascolare, AOU Maggiore della Carità di Novara**



CARDIOLOGIA NOVARA

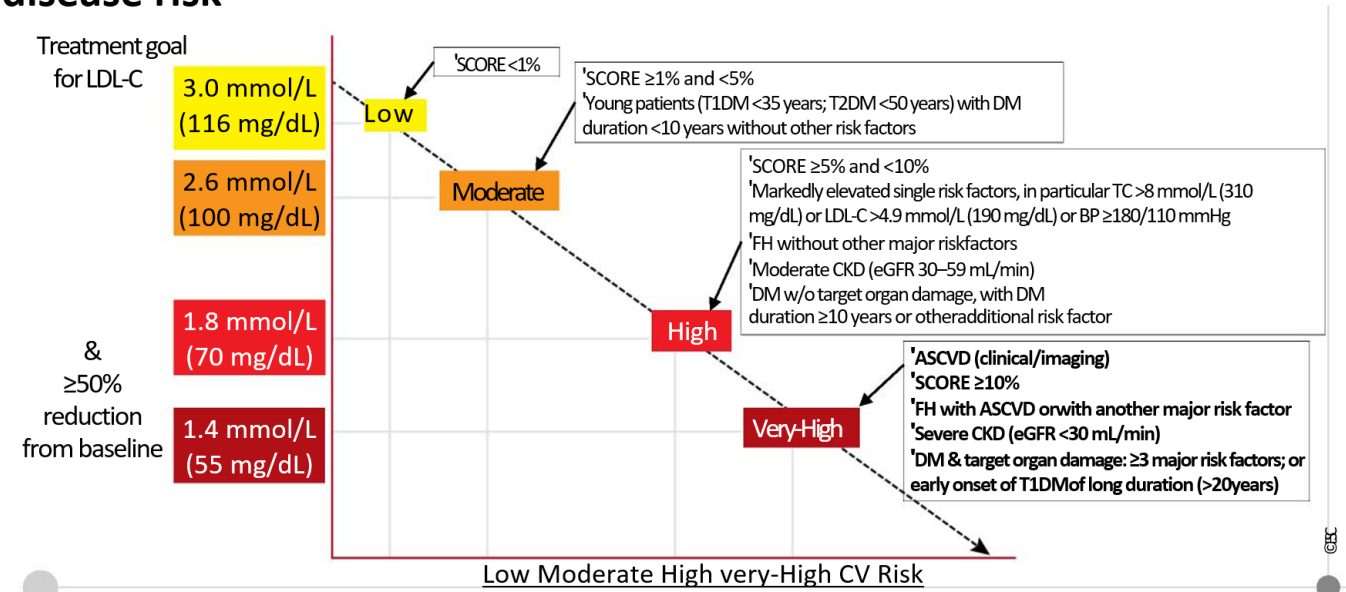
Conflicts of interest

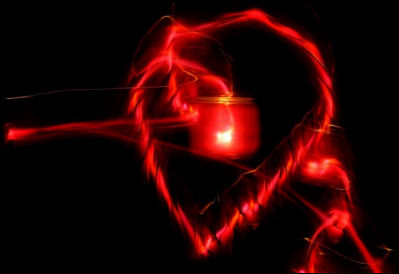
Speaker/Consultant fee for Daiichi Sankyo, Amgen, Novartis, Sanofi, Neopharmed



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

Treatment goals for low-density lipoprotein cholesterol (LDL-C) across categories of total cardiovascular disease risk

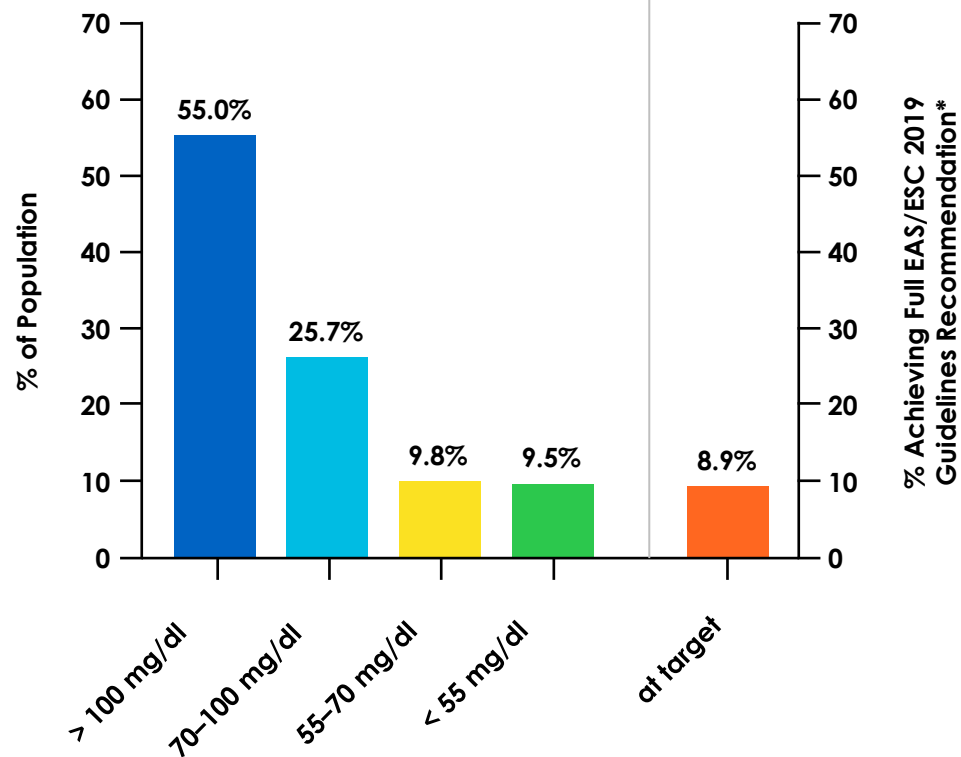




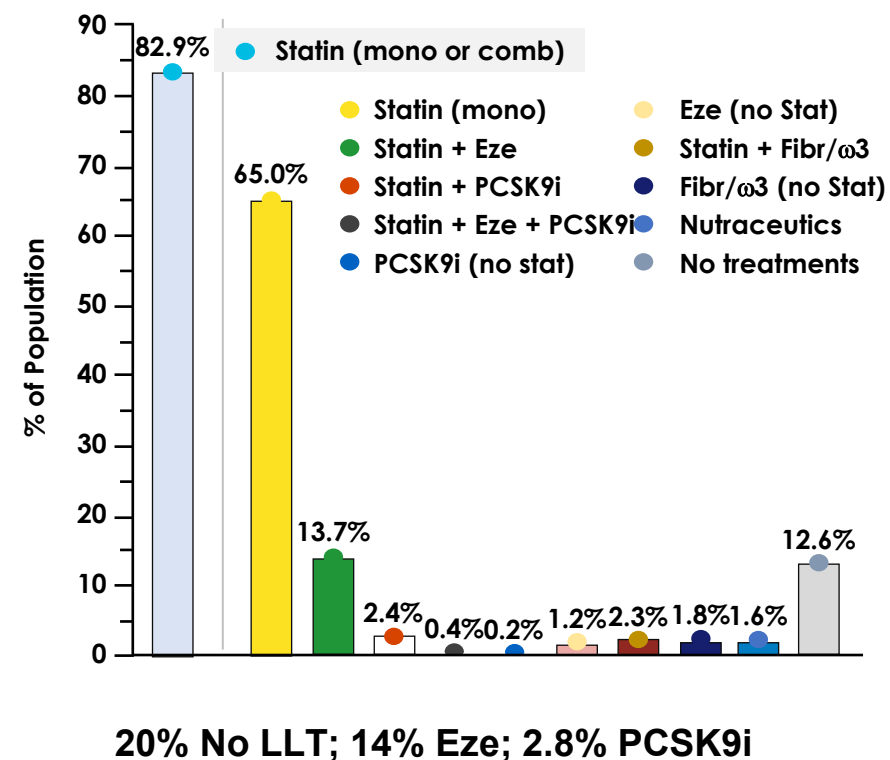
Unmet needs in patients with diabetes and dyslipidemia at very high cardiovascular risk

Cardiologia Novara

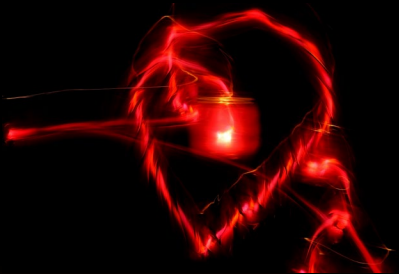
Very High CV Risk n = 2035



Very High CV Risk n = 2035

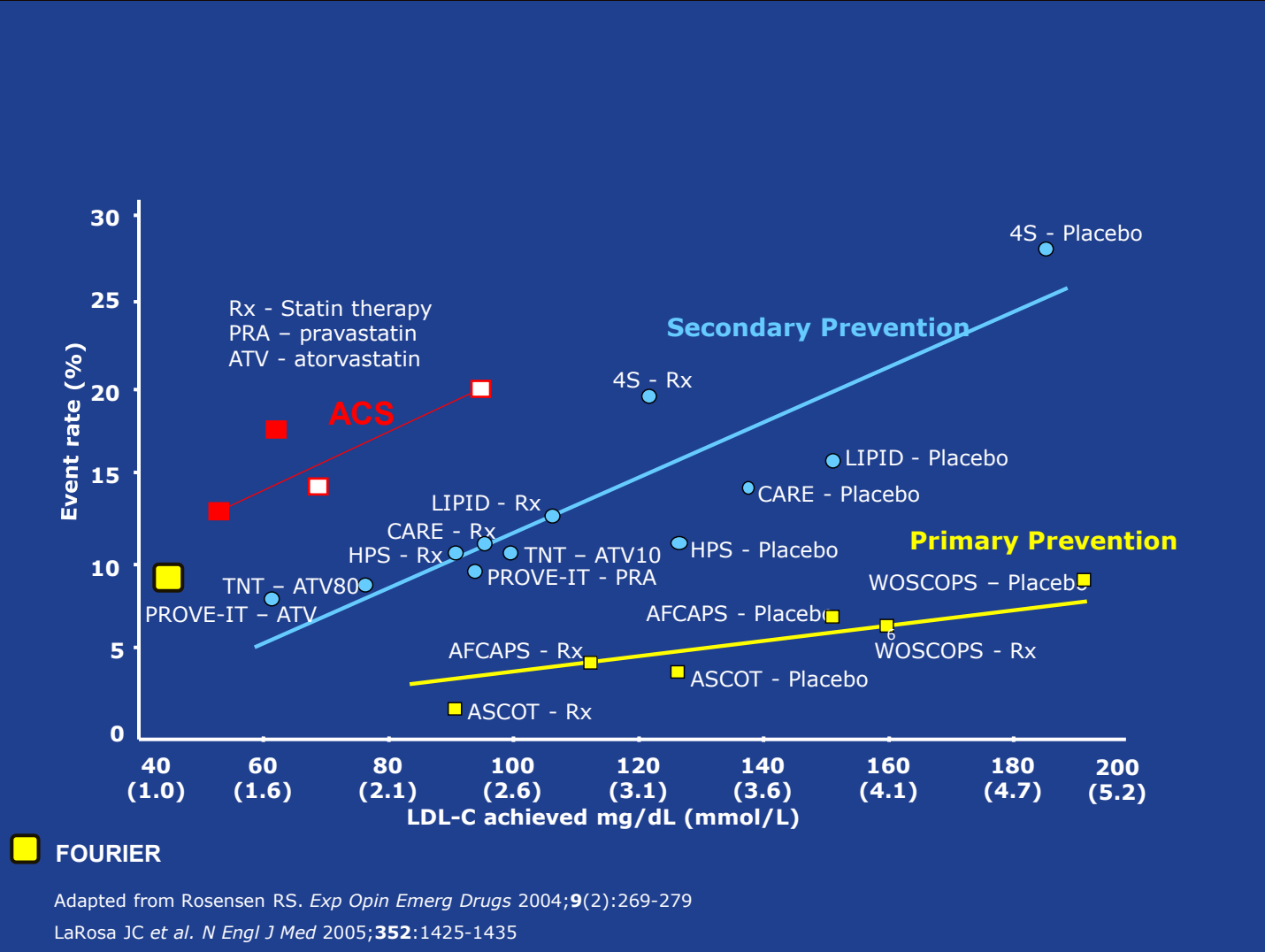


	Statin 	Ezetimibe 	Bempedoic acid 	PCSK9i 	Inclisiran 
Route	Os daily	Os daily	Os daily	Subcutaneous/2 weeks	Subcutaneous/6 months
LDL-C reduction	20-50%	20%	20%	60%	50%
Time to max effect	2 weeks	?	?	7 days (22% reduction at 24 hrs)	2 weeks
Variability in response	High	Low	?	Low	Moderate
Adherence to treatment	Low	High	High	High	High
Off-target effects?	Yes, in the acute phase	Probably no	Probably yes (diabetic pts)	Probably yes	Probably no
Clinical benefit	25% RRR for 40 mg/dL of LDL-C decrease	7% RRR of MACE in ACS with LDL-C from 70 to 55 mg/dL	13% RRR of MACE in stable CVD with LDL from 139 to 109 mg/dL	15% RRR of MACE in stable CAD and ACS from 90 to 30 mg/dL	No data yet



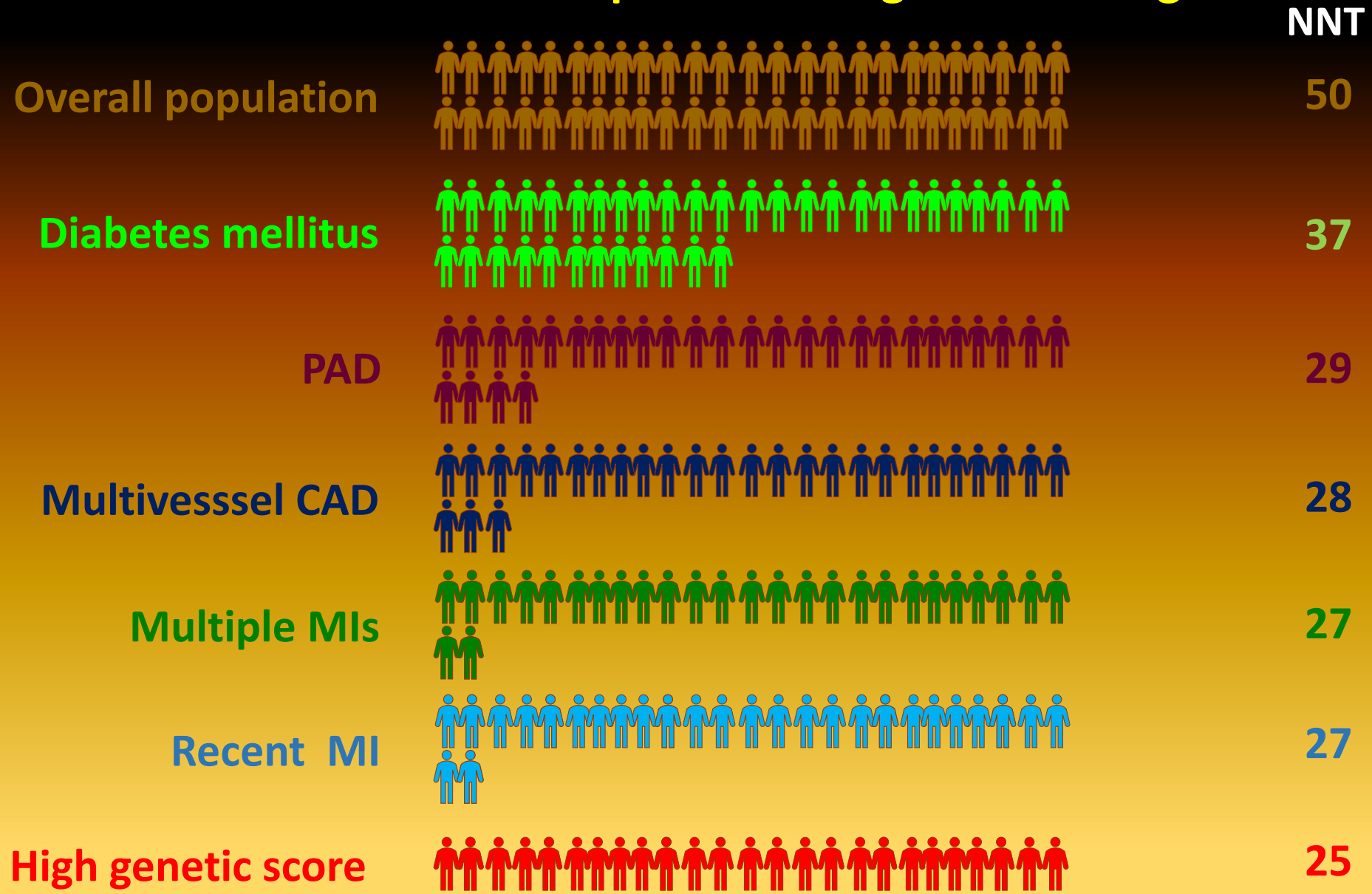
The higher is the baseline risk profile, the higher the event reduction by LDL-C lowering

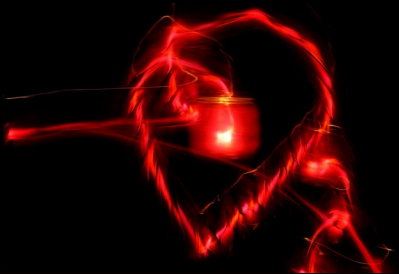
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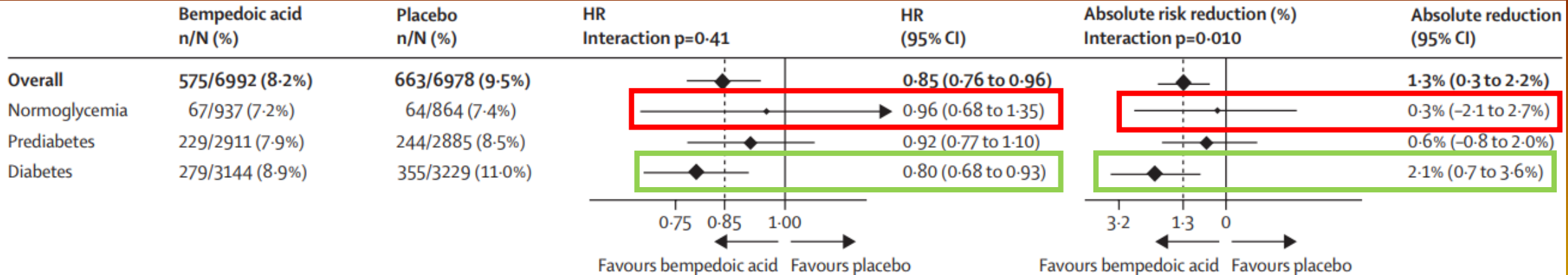
FOURIER trial: NNT for the primary endpoint with evolocumab vs placebo in high-risk settings





Reduction of 3-point MACE with Bempedoic acid and Placebo according to diabetes status in the CLEAR OUTCOMES trial

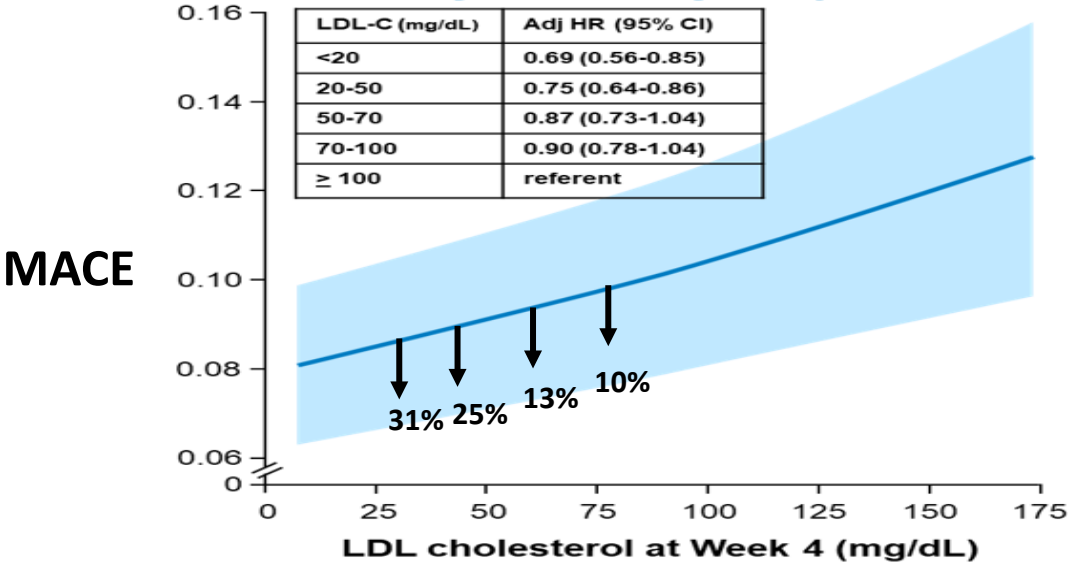
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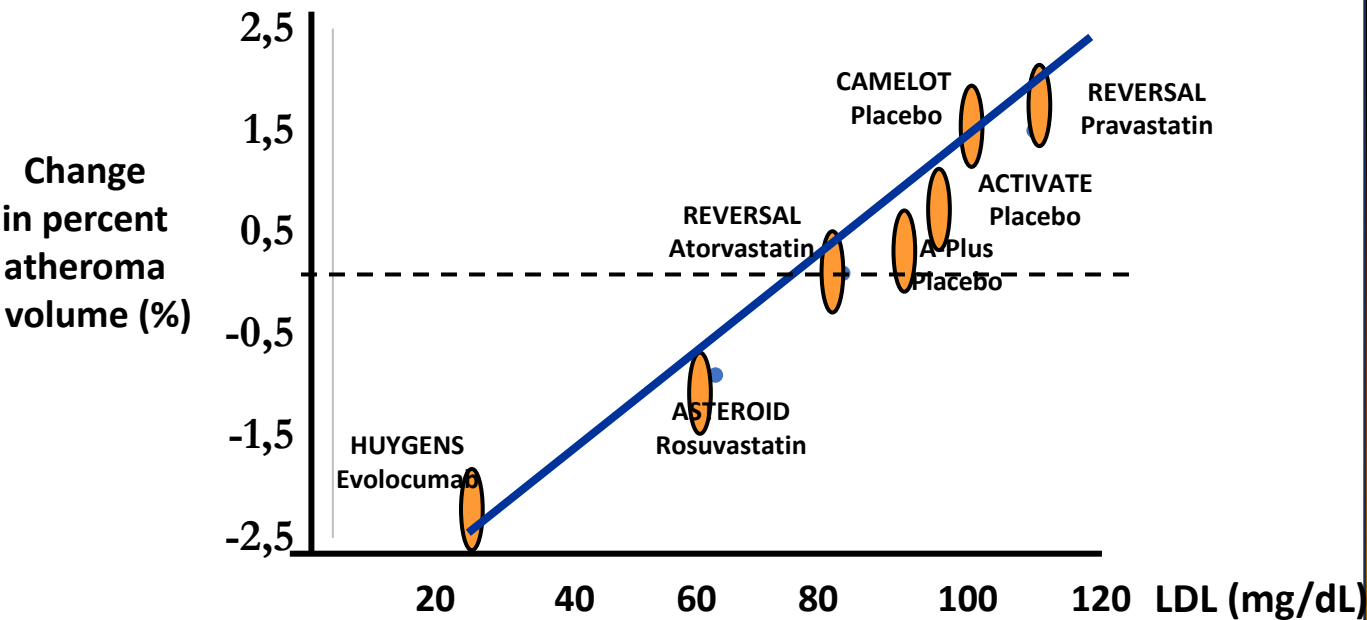
NNT no diabetes 333
NNT diabetes 48

Event risk according to achieved LDL-C values and coronary plaque features (Patti G, et al. Submitted)

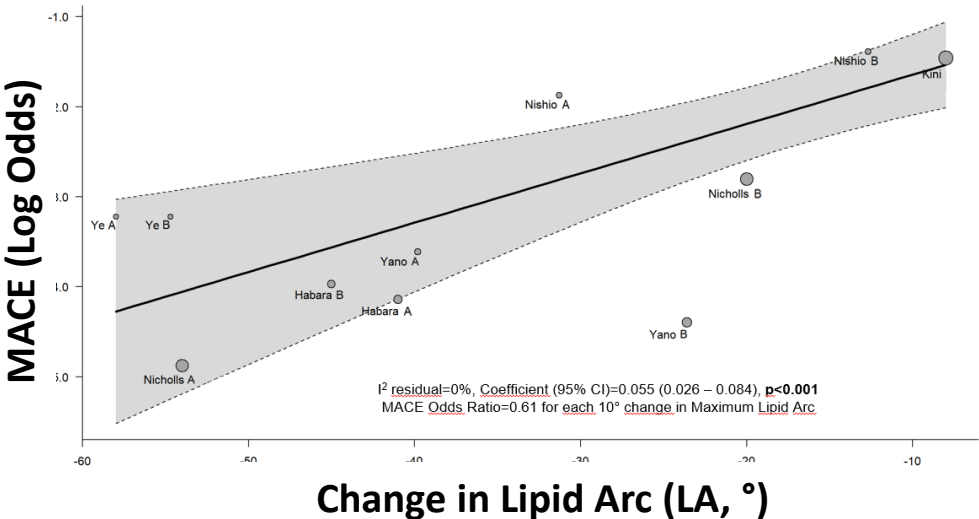
39 mg/dL LDL-C decrease= 22% MACE reduction

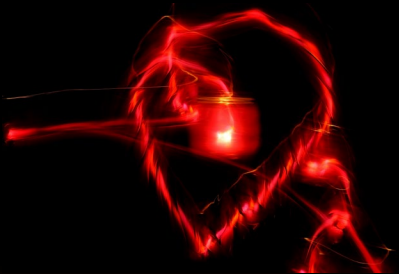


1% PAV reduction= 25% MACE reduction



10° LA decrease= 39% MACE reduction





AIFA – Bempedoic acid

A DIAGNOSI

- ☐ Ipercolesterolemia primaria familiare eterozigote
- ☐ Ipercolesterolemia primaria non familiare
- ☐ Dislipidemia mista

B CLASSE DI RISCHIO CARDIOVASCOLARE (**fare riferimento alla Nota 13** per la classificazione del livello di rischio)

- ☐ Medio
- ☐ Moderato
- ☐ Alto
- ☐ Molto alto

D DISTANZA DAL TARGET TERAPEUTICO NON SUPERIORE AL 20% nonostante il trattamento di 1° e 2° livello (per i target raccomandati rispetto ai livelli di rischio **fare riferimento alla Nota 13**) ☐

Es.	per target LDL < 130 mg/dl	----	(valore LDL non superiore a 162 mg/dl)
	per target LDL < 115 mg/dl	----	(valore LDL non superiore a 145 mg/dl)
	Per target LDL < 100 mg/dl	----	(valore LDL non superiore a 125 mg/dl)
	Per target LDL < 70 mg/dl	----	(valore LDL non superiore a 88 mg/dl)

E TERAPIA IN ATTO

- Statine alla massima dose tollerata ☐ oppure Intolleranza alle statine ☐
- Ezetimibe ☐ oppure Intolleranza all'ezetimibe ☐

(in questo caso escludere NUSTENDI)



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

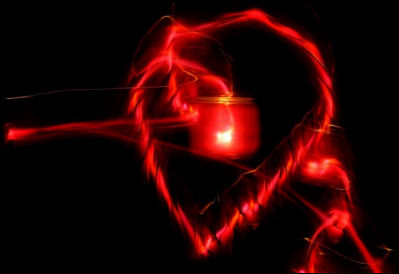
>20%

≤20%

PCSK9-i

Bempedoic acid **

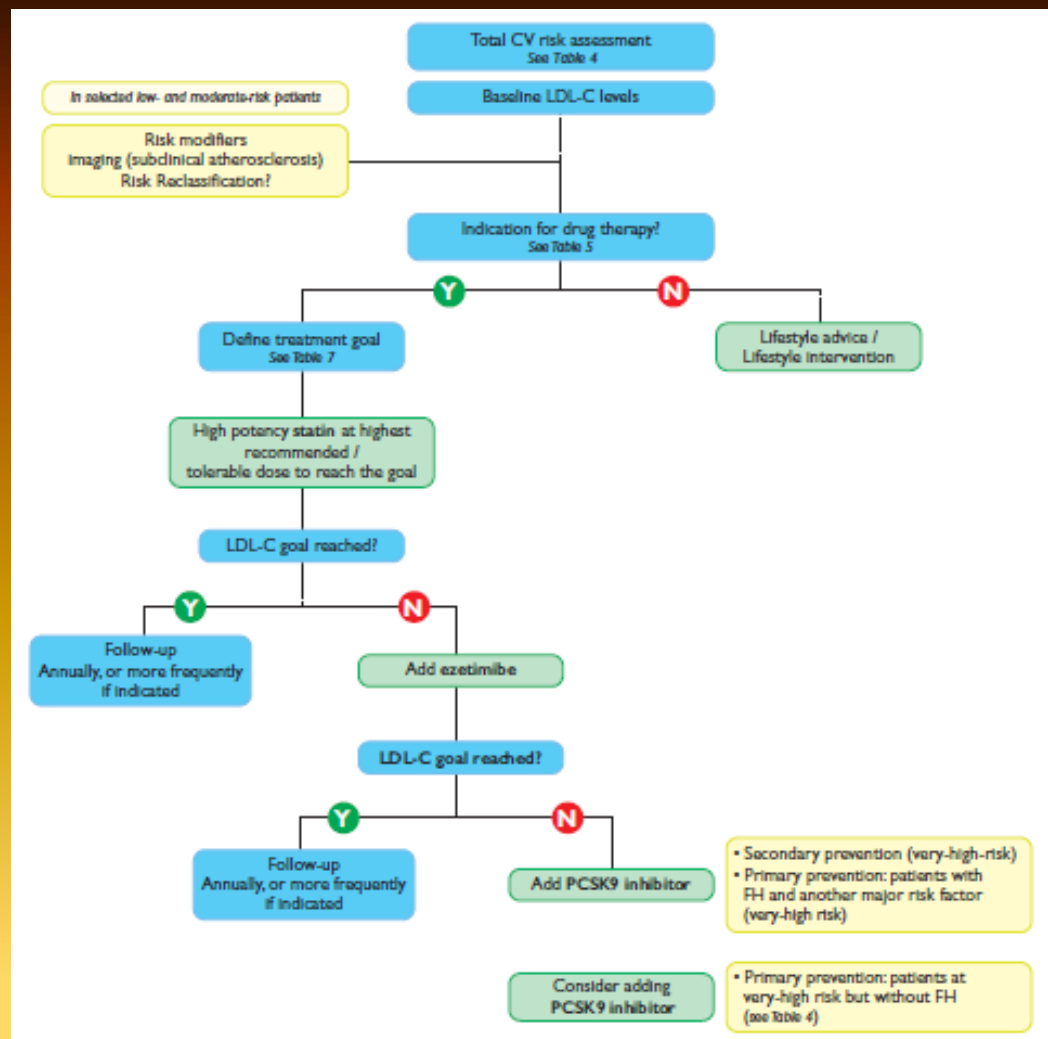
**** Additional candidates:**
- Statin-intolerance
- Age >80 years

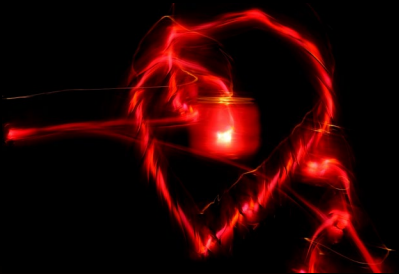


The earlier is the achievement of LDL-C target, the earlier and the greater the clinical benefit

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2019

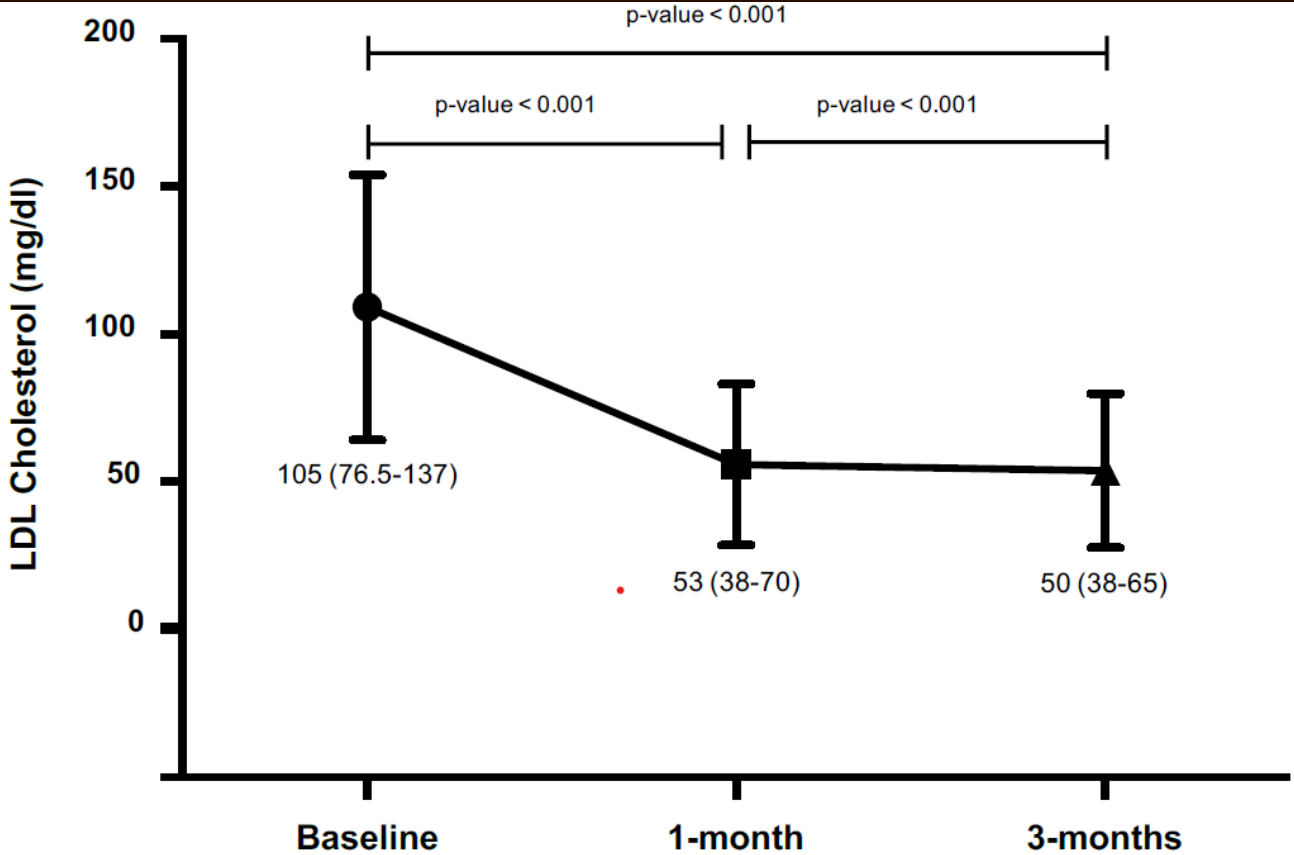
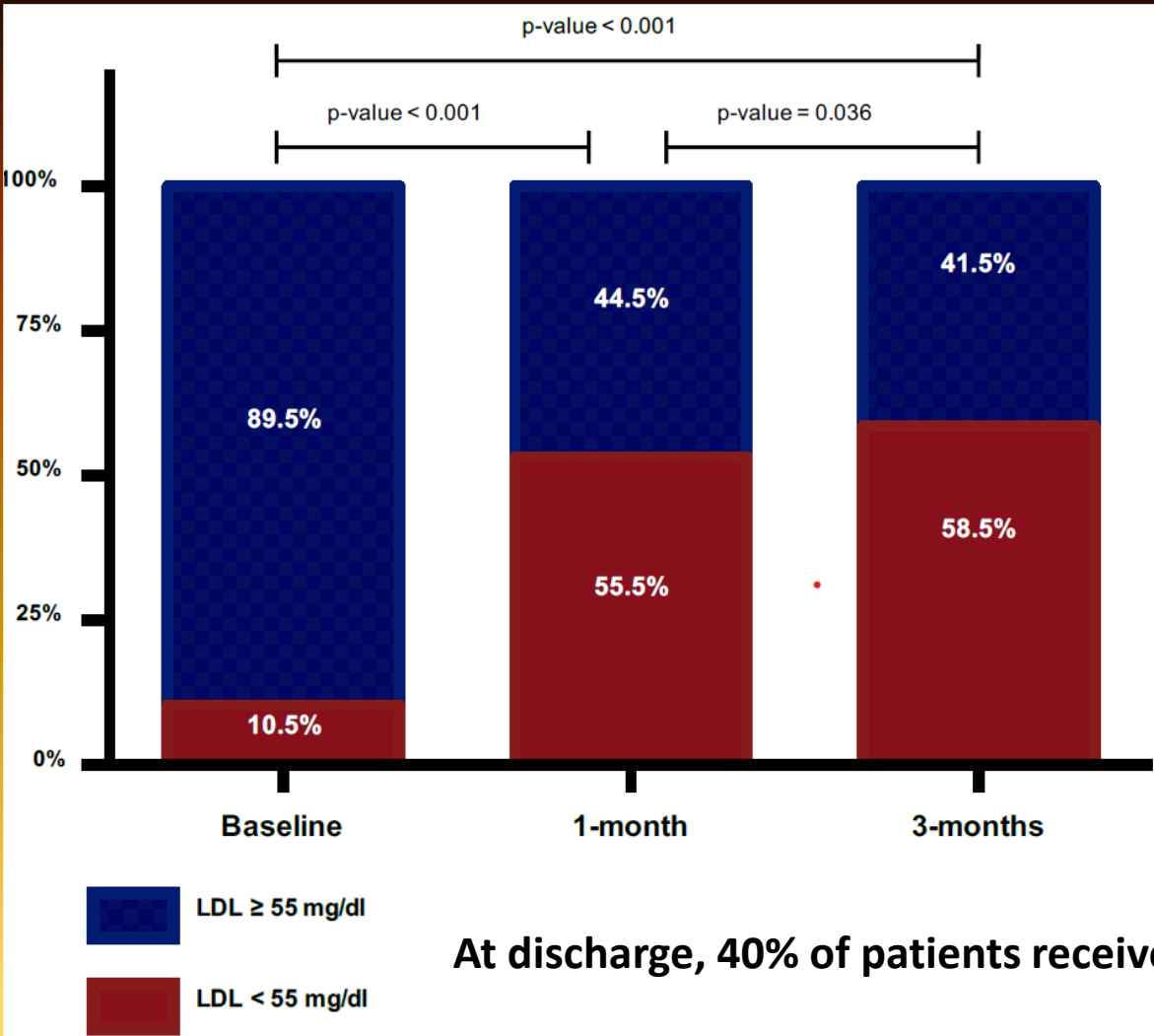




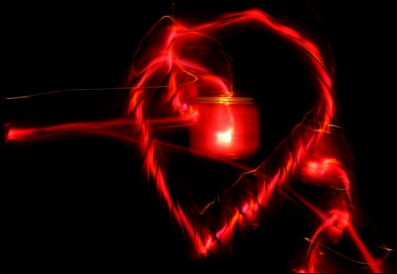
JET-LDL Registry - N=1,095 pts with ACS

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

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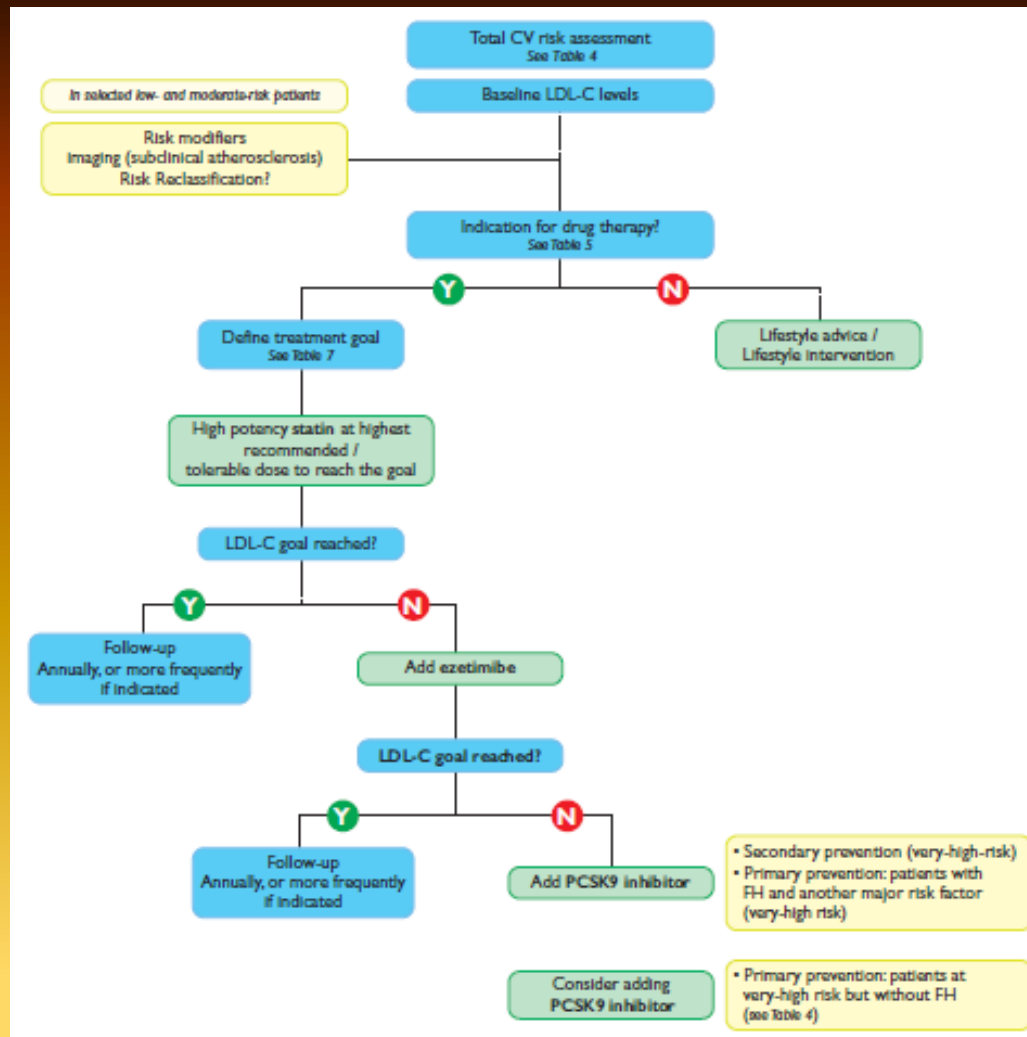
At discharge, 40% of patients received high-dose statin, 50% statin plus ezetimibe and 8.5% a PCSK9i



The earlier is the achievement of LDL-C target, the earlier and the greater the clinical benefit

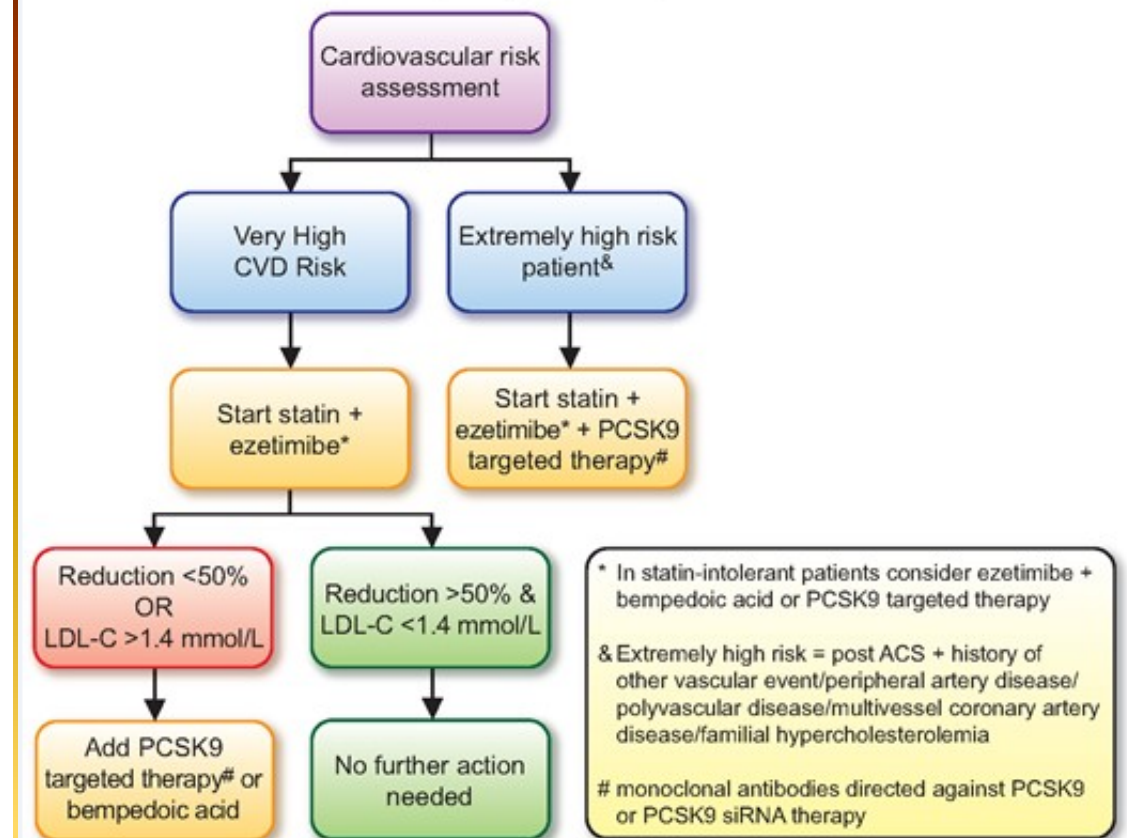
CARDIOLOGIA NOVARA

2019



2022

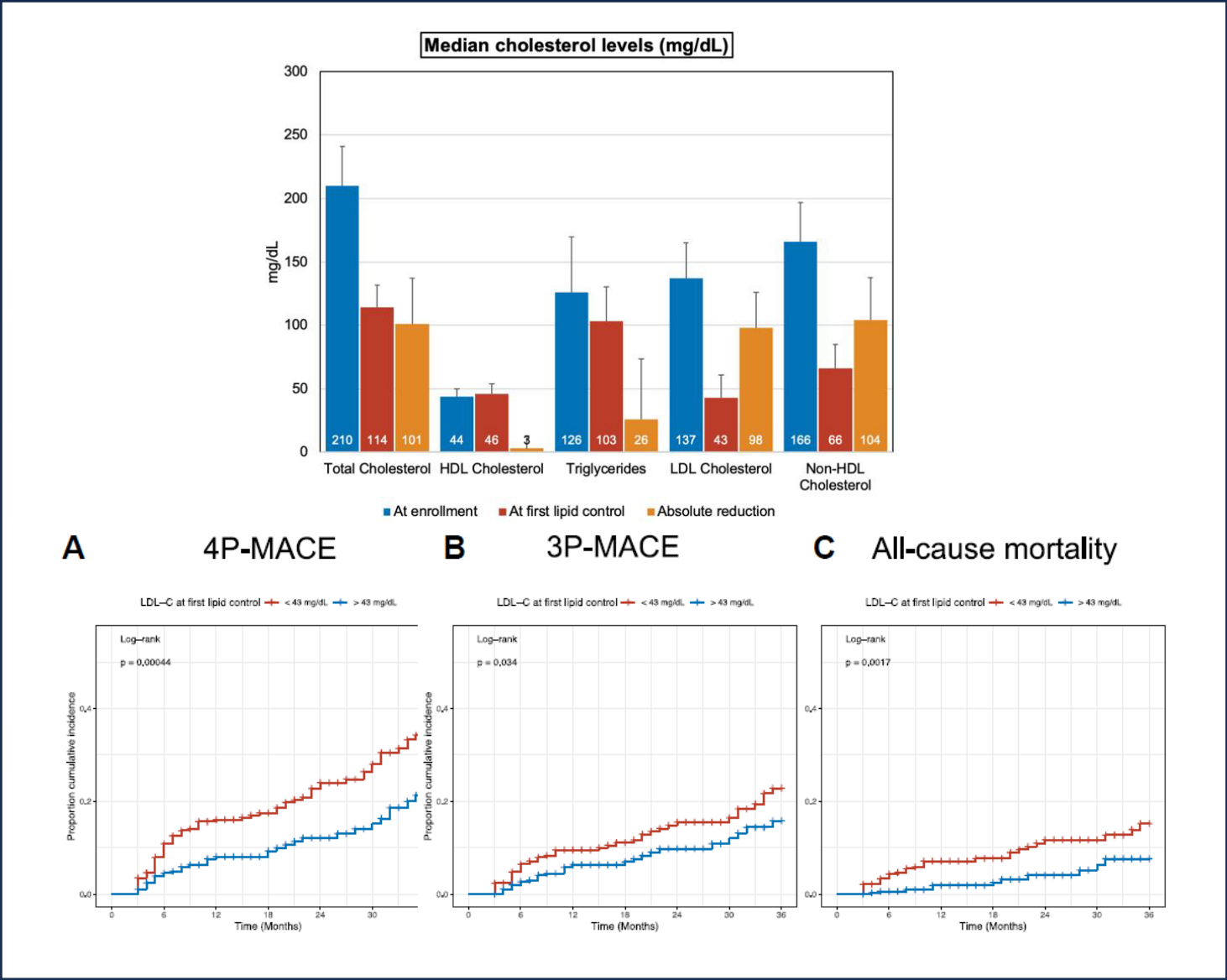
Combination lipid-lowering therapy as first line strategy in very high-risk patients

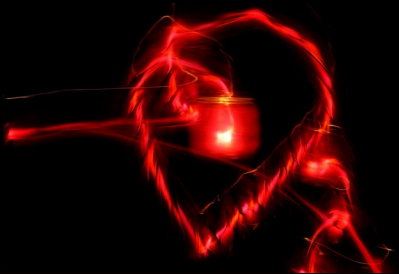




AT-TARGET Registry: n=771 pts with ACS on early PCSK9-i in 22 Italian centers

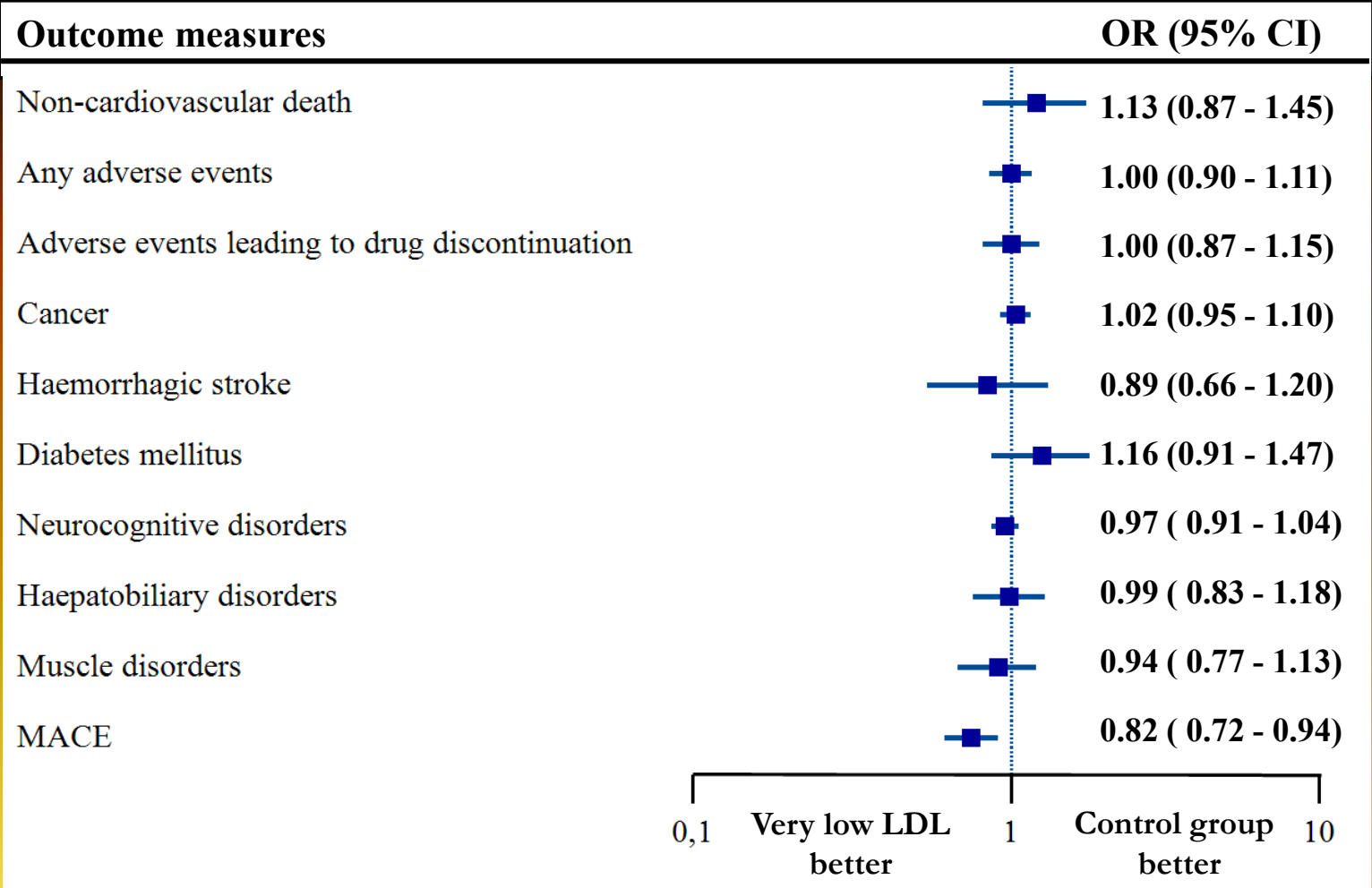
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Study-level meta-analysis on 9 randomized trials and approximately 109,000 patients to evaluate the safety and efficacy of LDL-C levels <40 mg/dL

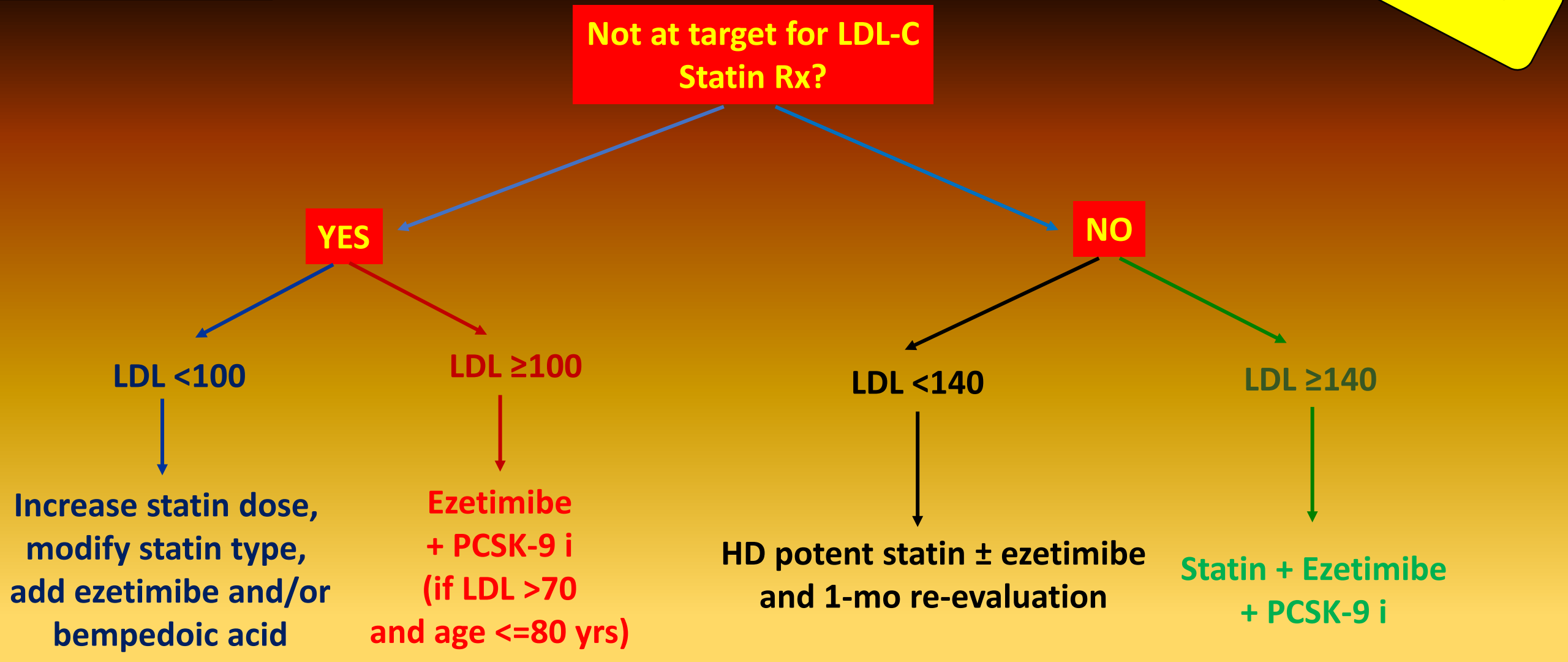
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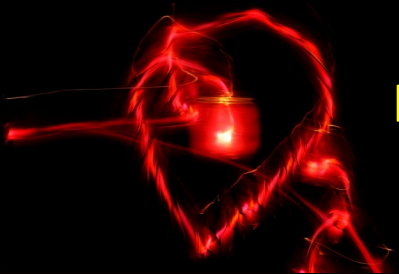




LDL-C in ACS: GO LOWER AND FASTER!!!!!!
AI/FA: in patients with multiple CV events or ACS,
one LDL-C determination allows PCSK-9i initiation

CAD: admission for ACS





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

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Outcome comparison between the following 3 periods

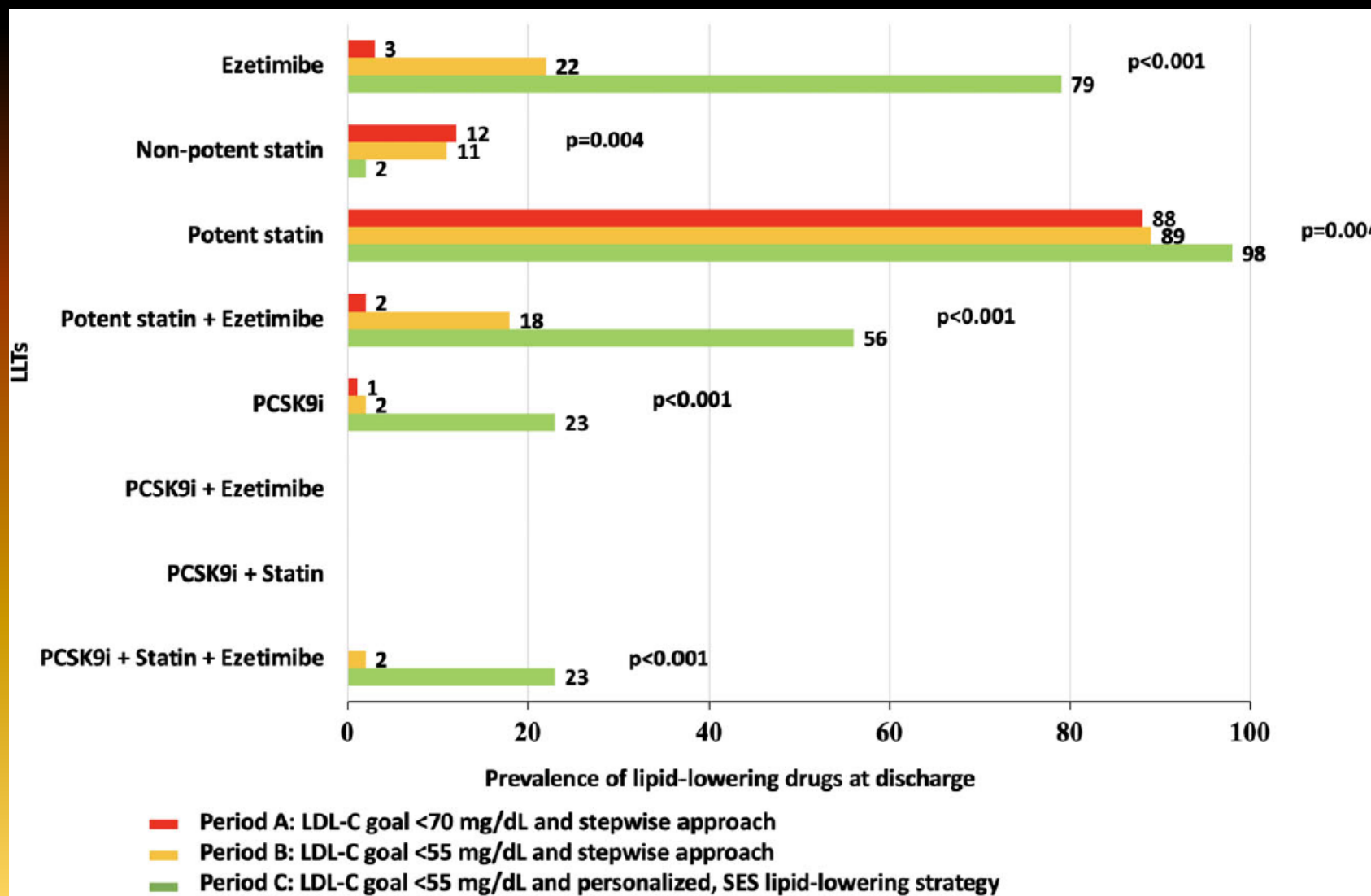
Period A (N=198; January-June 2019): target LDL-C <70 mg/dL

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

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

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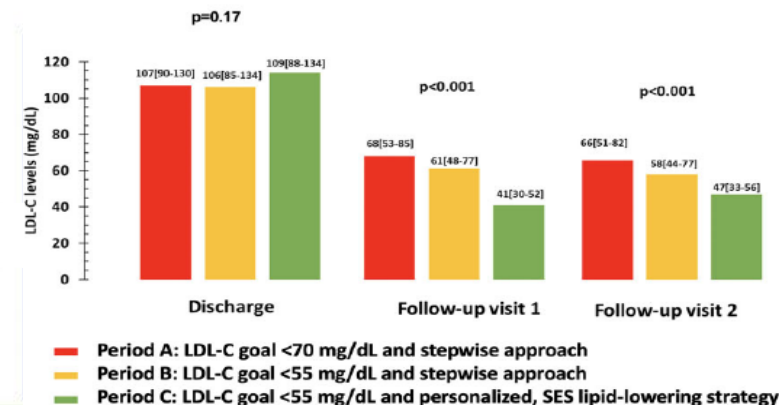
Impact of a personalized , strike early and strong lipid-lowering approach on LDL-C levels and cardiovascular outcome in patients with acute myocardial infarction

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

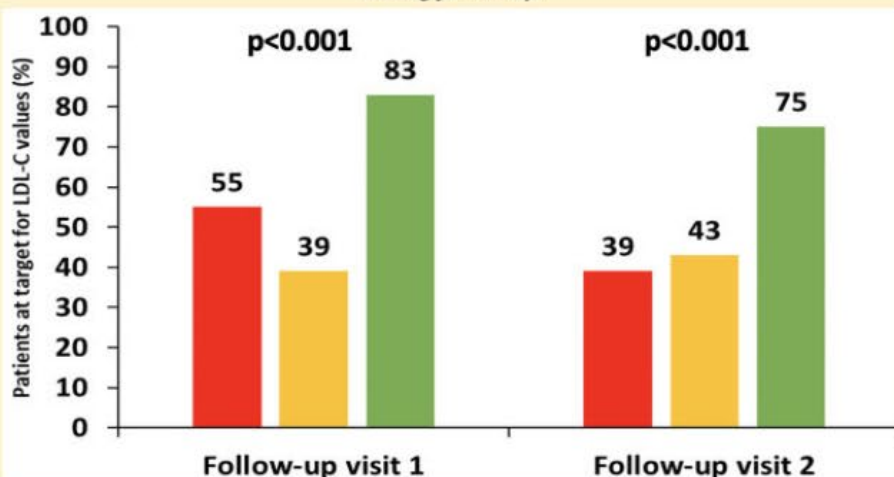
Period B (N=180; January-June 2021): LDL-C goal <55 mg/dL and stepwise approach

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



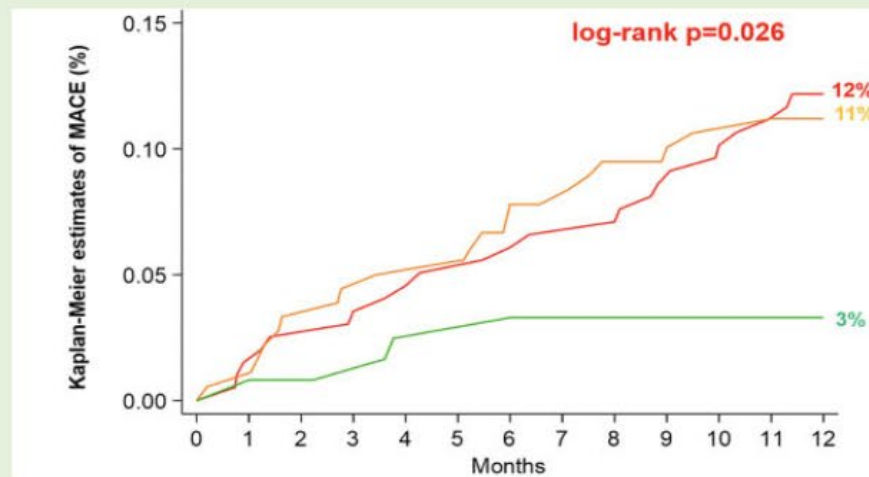
Primary Laboratory Endpoint

Prevalence of patients who achieved LDL-C goal in at least one visit during follow-up



Primary Clinical Endpoint

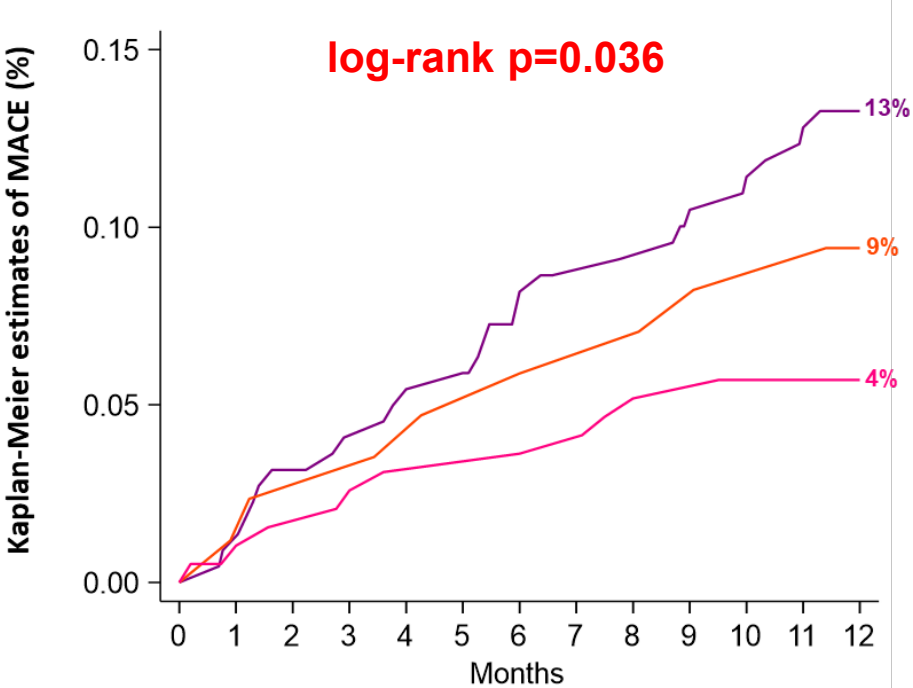
Kaplan-Meier curves for the incidence of MACE at one year in the three periods





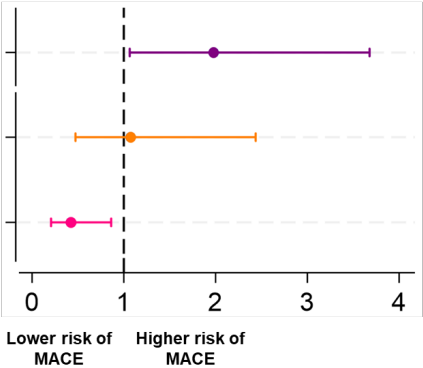
Impact of a personalized , strike early and strong lipid-lowering approach on LDL-C levels and cardiovascular outcome in patients with acute myocardial infarction

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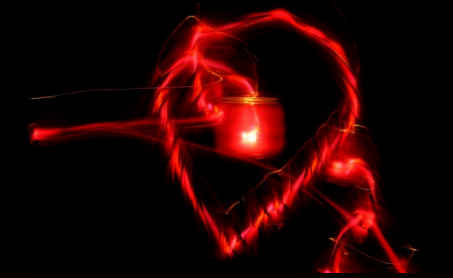


Number at risk	
Late or never LDL-C at target	221 219 214 211 209 208 202 198 197 194 192 189 187
Early but non-sustained LDL-C at target	85 84 83 83 82 81 81 80 80 79 78 78 77
Early and sustained LDL-C at target	194 192 190 189 187 187 187 186 184 183 182 182 182

Variables	Adjusted HR	95% CI	p value
Never or late LDL-C at target	1.97	1.06 – 3.67	0.031
Early and non-sustained LDL-C at target	1.07	0.47 – 2.43	0.863
Early and sustained LDL-C at target	0.42	0.20 – 0.86	0.018



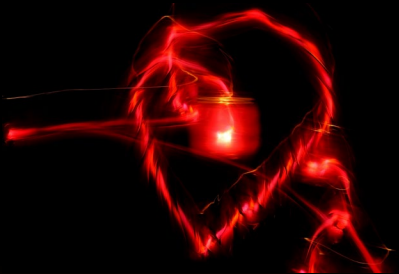
p for trend = 0.013



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«The lower is the better» for LDL-C should be amended as:

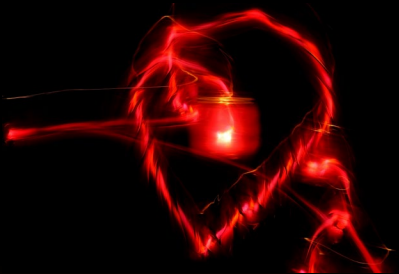
«The lower, the earlier and the longer are the better», especially in patients at higher CV risk, such as those with diabetes mellitus



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Thank you very much for your attention!!!



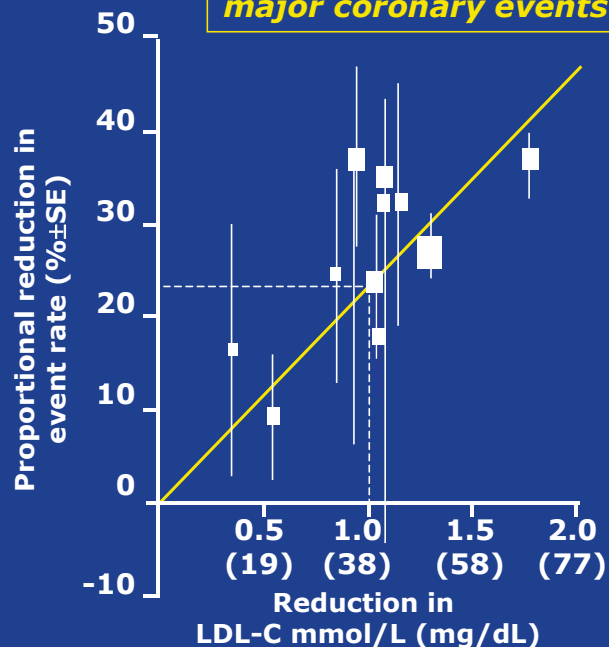
For LDL-C values the lower is the better

A meta-analysis from 90,056 individuals from 14 statin trials

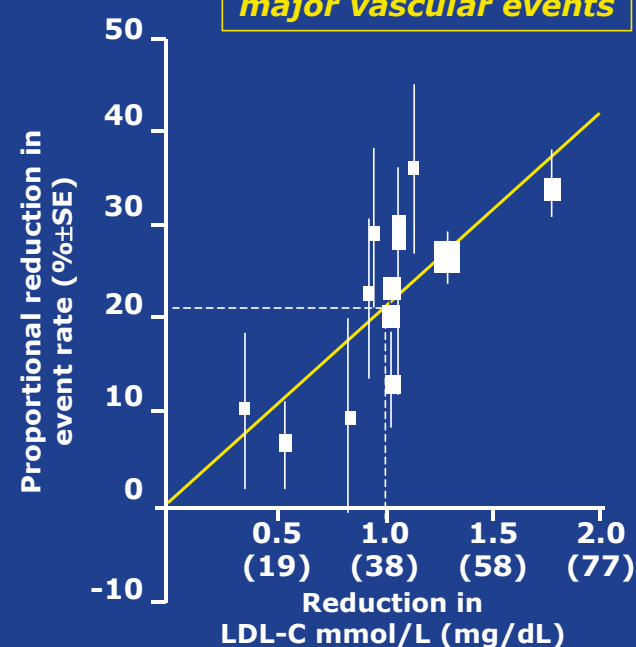
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A 1 mmol/L (39 mg/dL) reduction in LDL-C was associated with a

.... 23% reduction in major coronary events

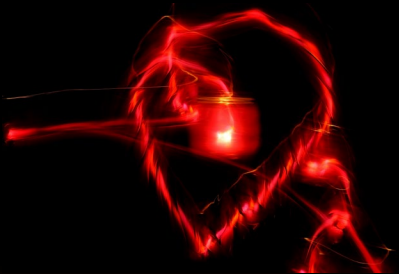


.... 21% reduction in major vascular events



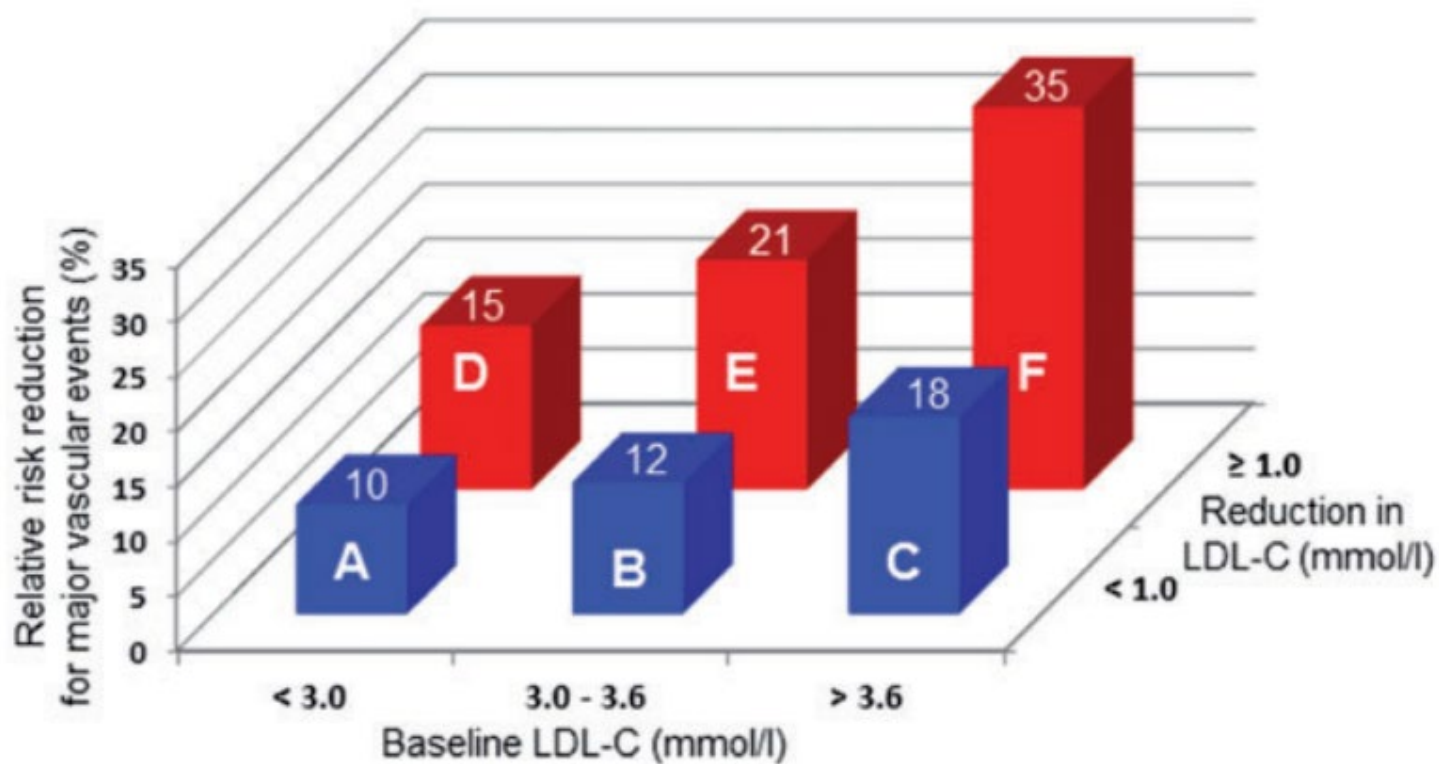
Linear relationship

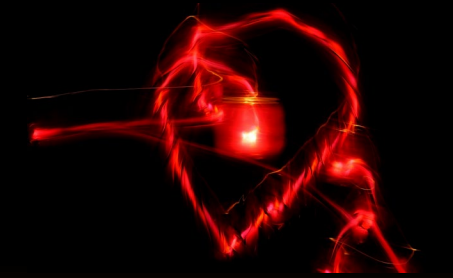
1. CTT Collaborators. *Lancet* 2005;366:1267-1278.



**The higher the baseline LDL value,
the higher the reduction of CV events with treatment**

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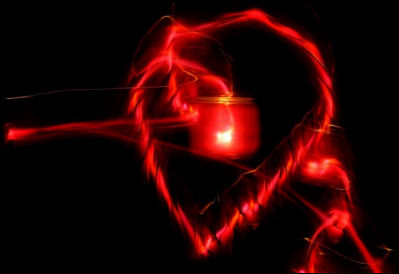




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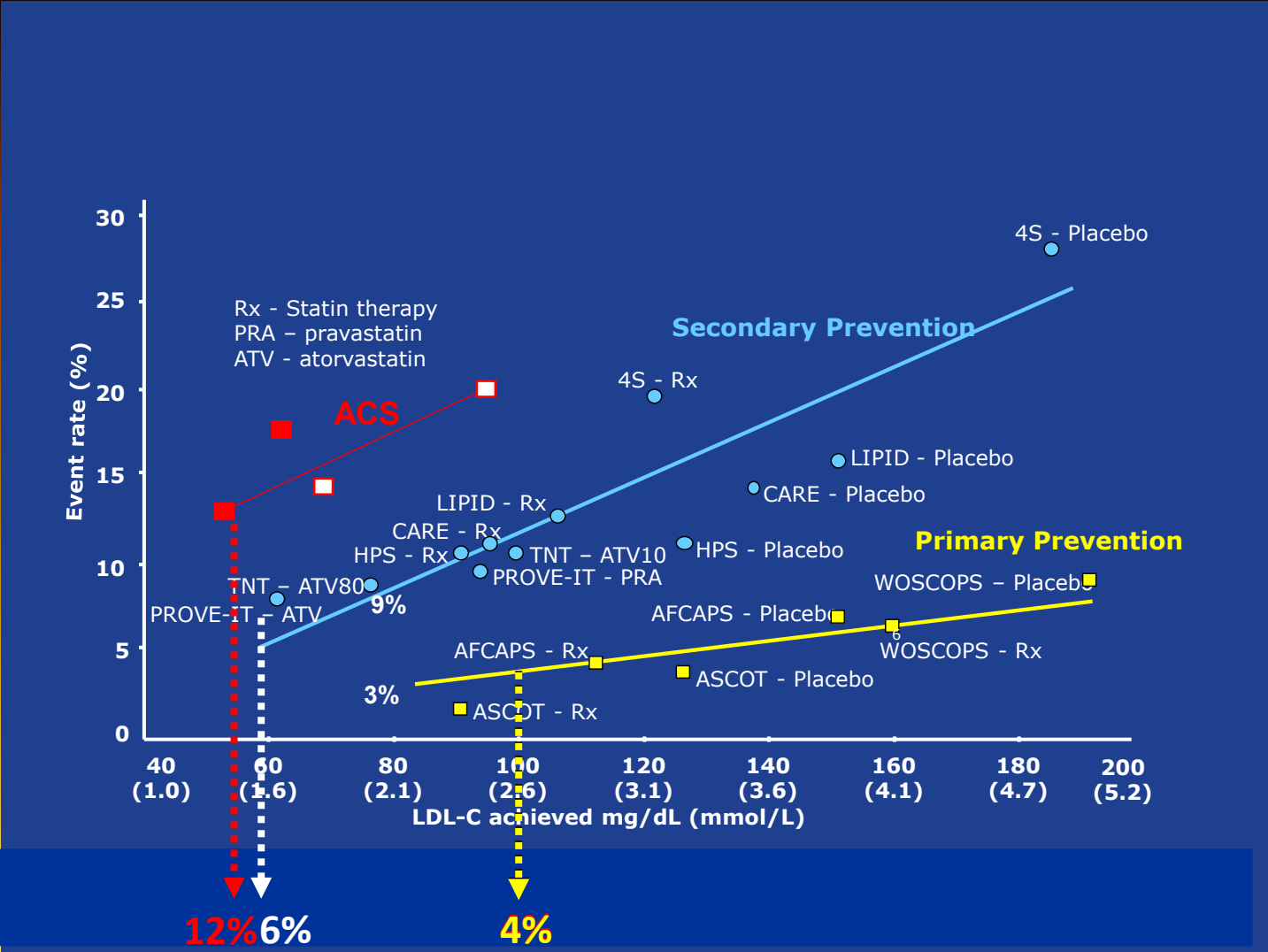
Patients deriving the highest clinical benefit from lipid-lowering treatments:

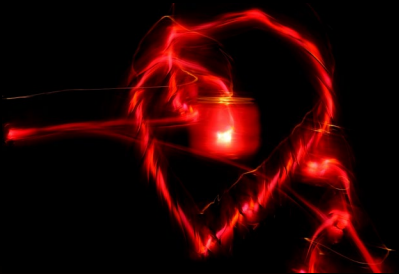
- ❖ **With high baseline LDL-C levels**
- ❖ **With high clinical risk**
- ❖ **Achieving strong LDL-C reduction**
- ❖ **Achieving lowest LDL-C levels**



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

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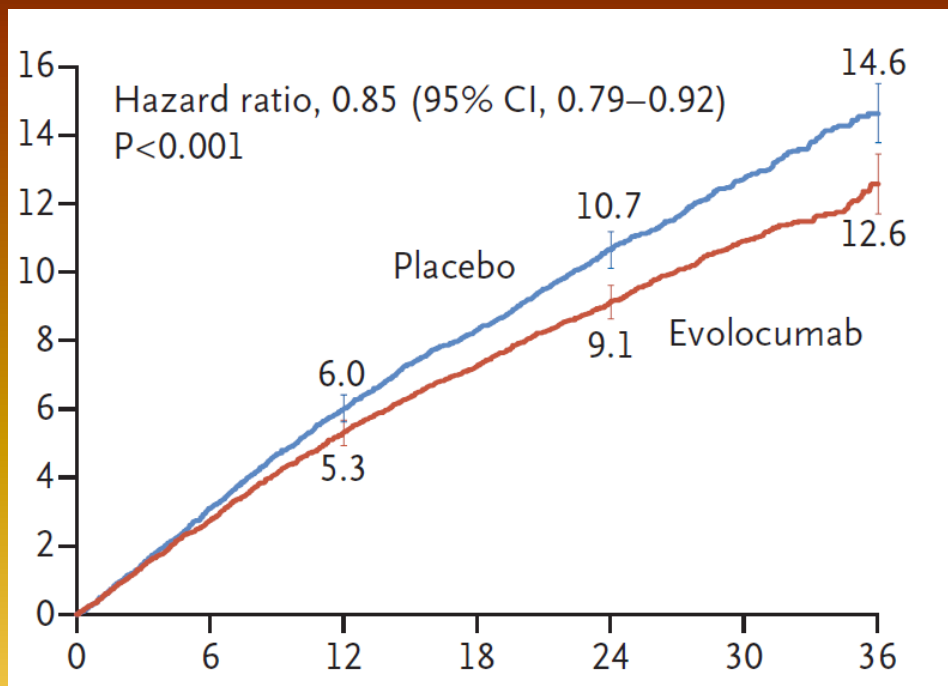




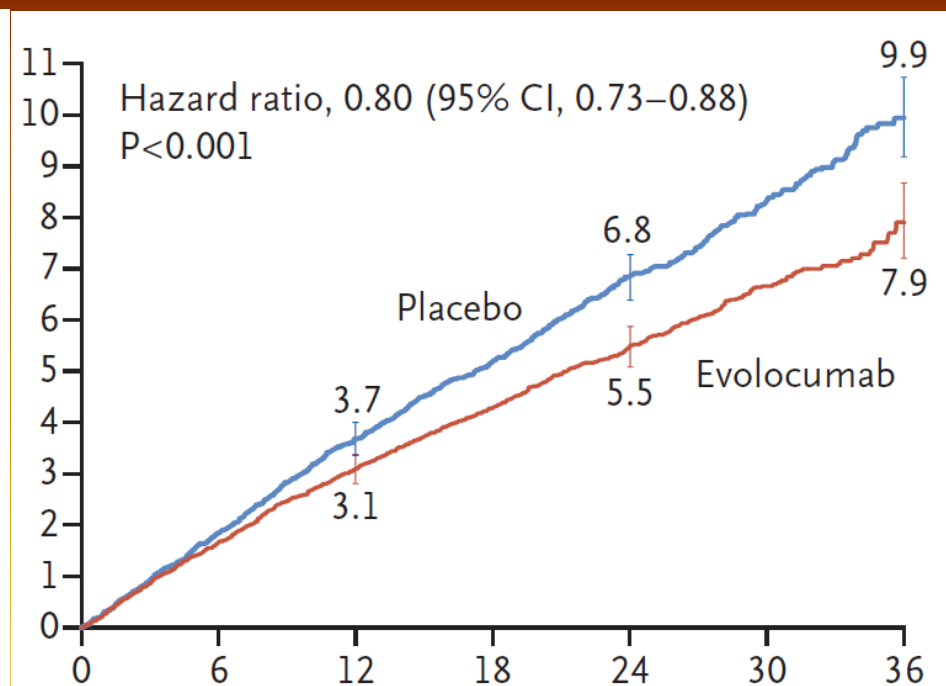
FOURIER trial: Main results

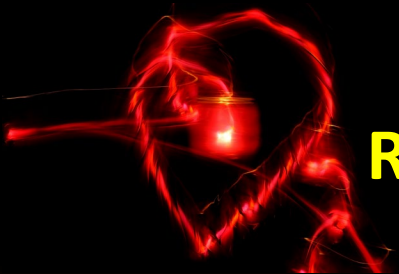
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Cumulative incidence (%) of CV death, MI, stroke, hosp. for UA, coronary revascularization



Cumulative incidence (%) of CV death, MI, stroke



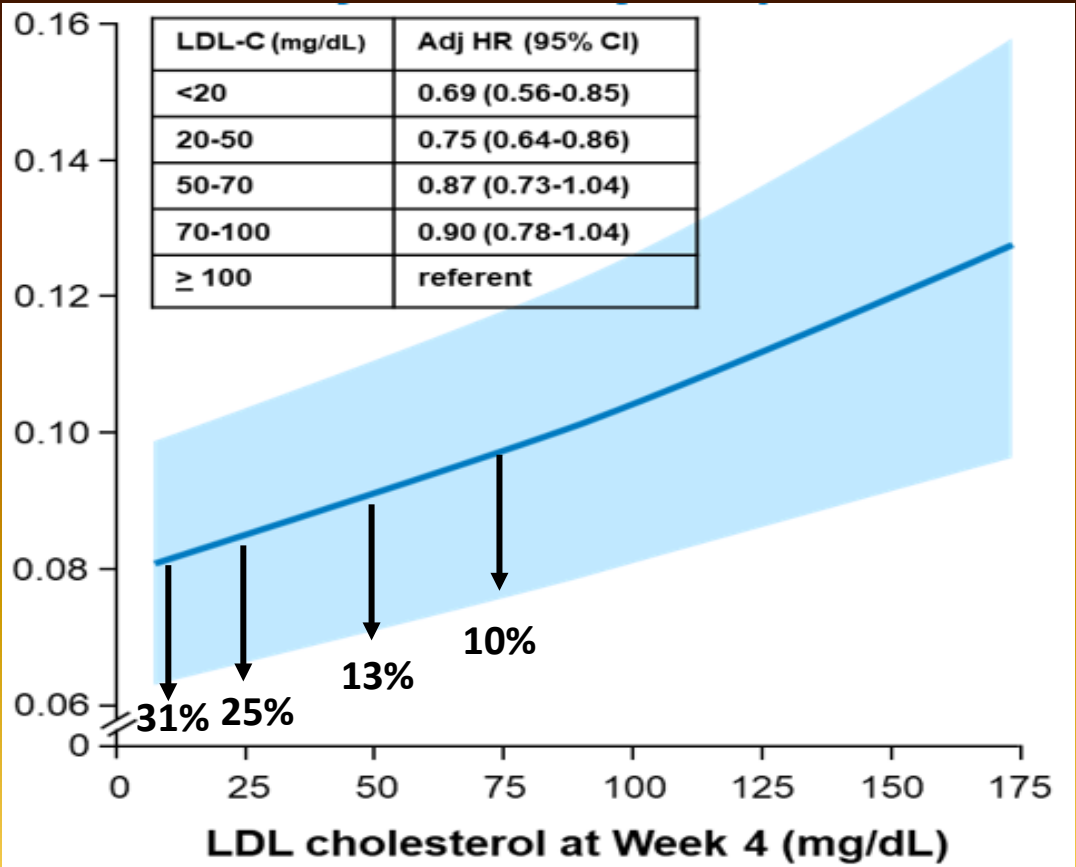


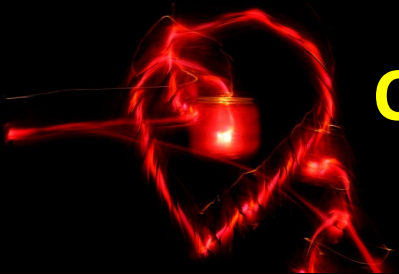
FOURIER trial

Risk of events according to different LDL-C values achieved at week 4

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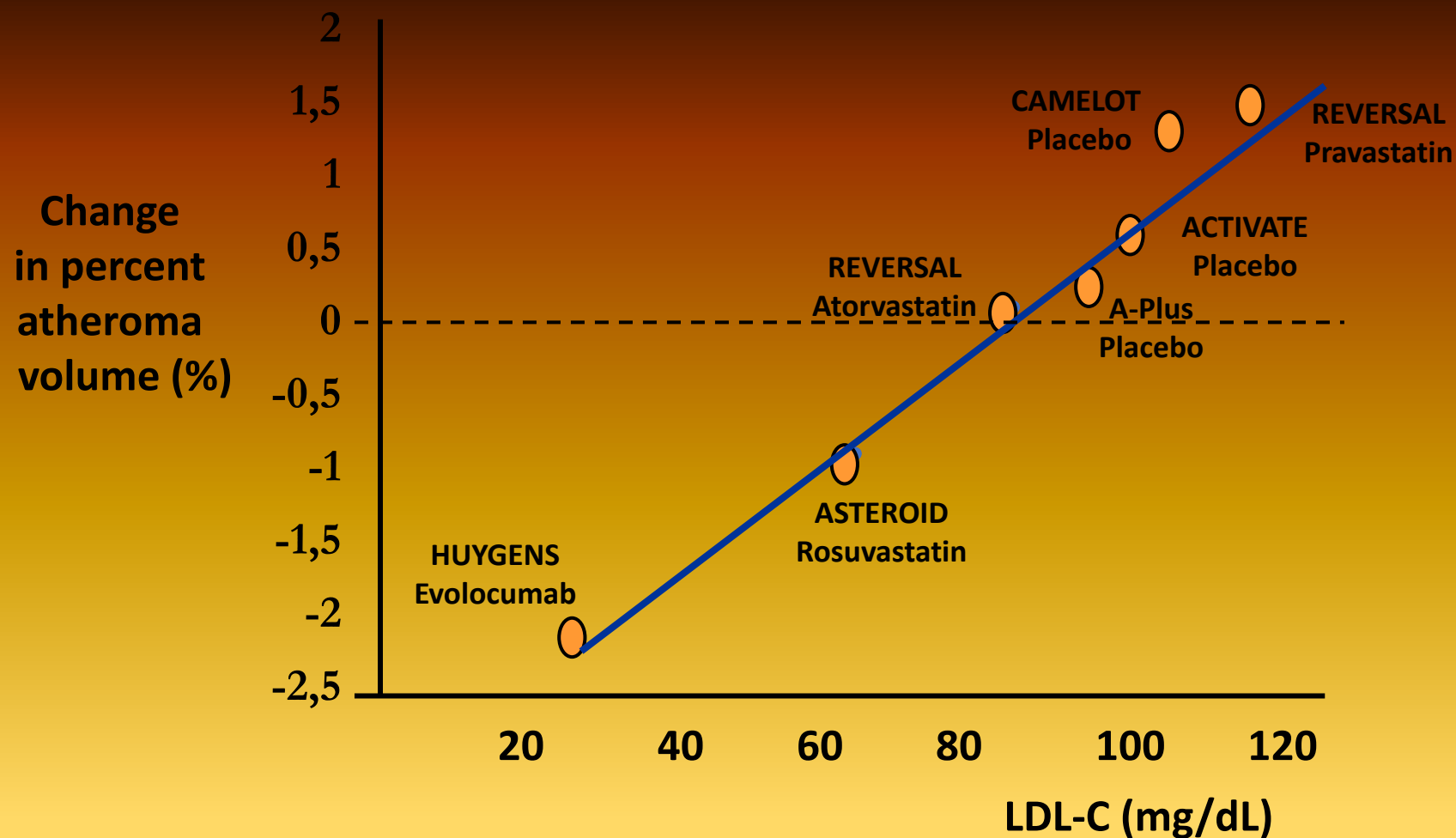
CV death, MI, stroke, hosp. for UA,
coronary revascularization

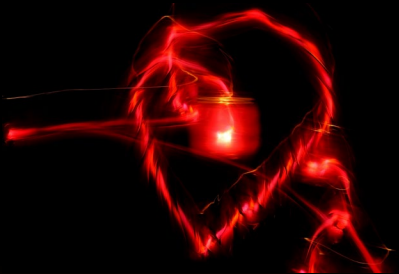




Change in progression of coronary percent atheroma volume versus LDL-C in randomized studies

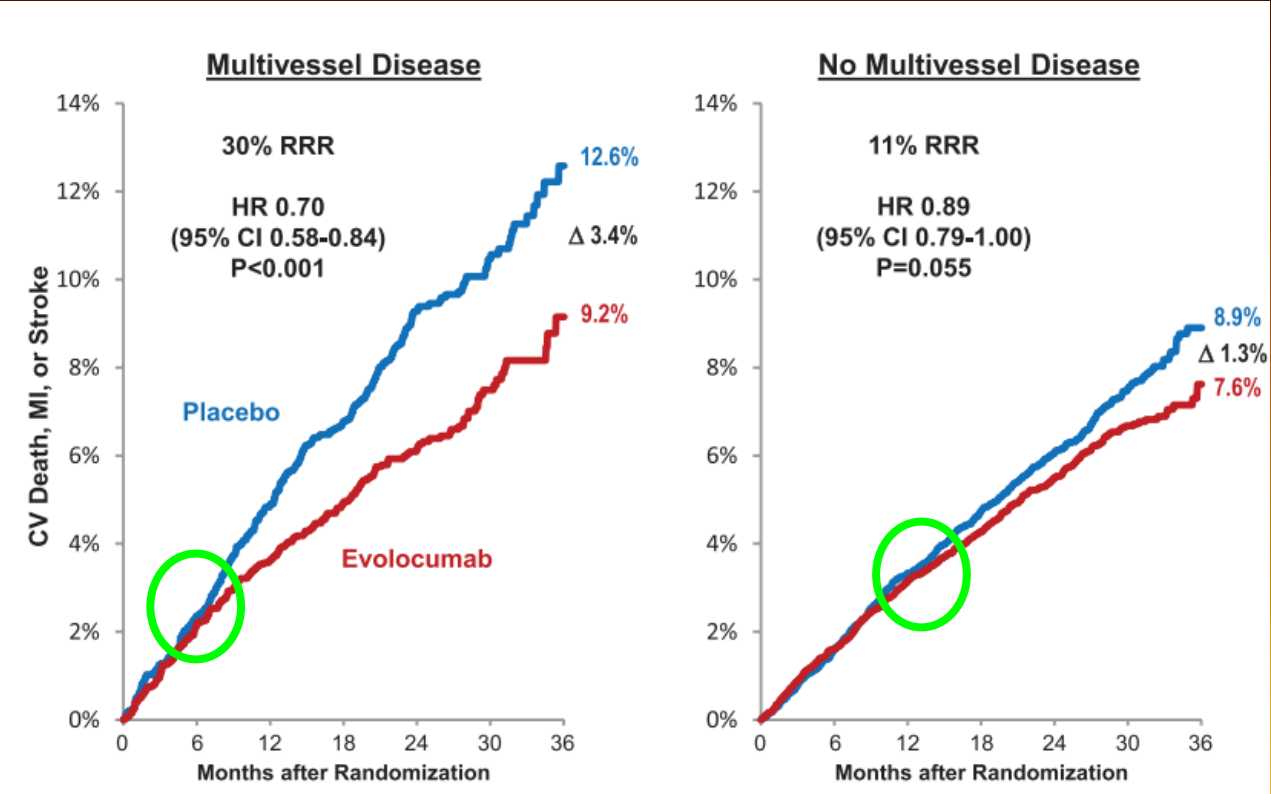
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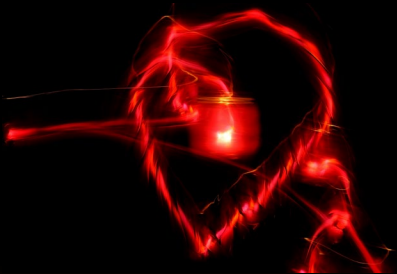




FOURIER trial: Clinical Benefit of Evolocumab by Severity and Extent of Coronary Artery Disease

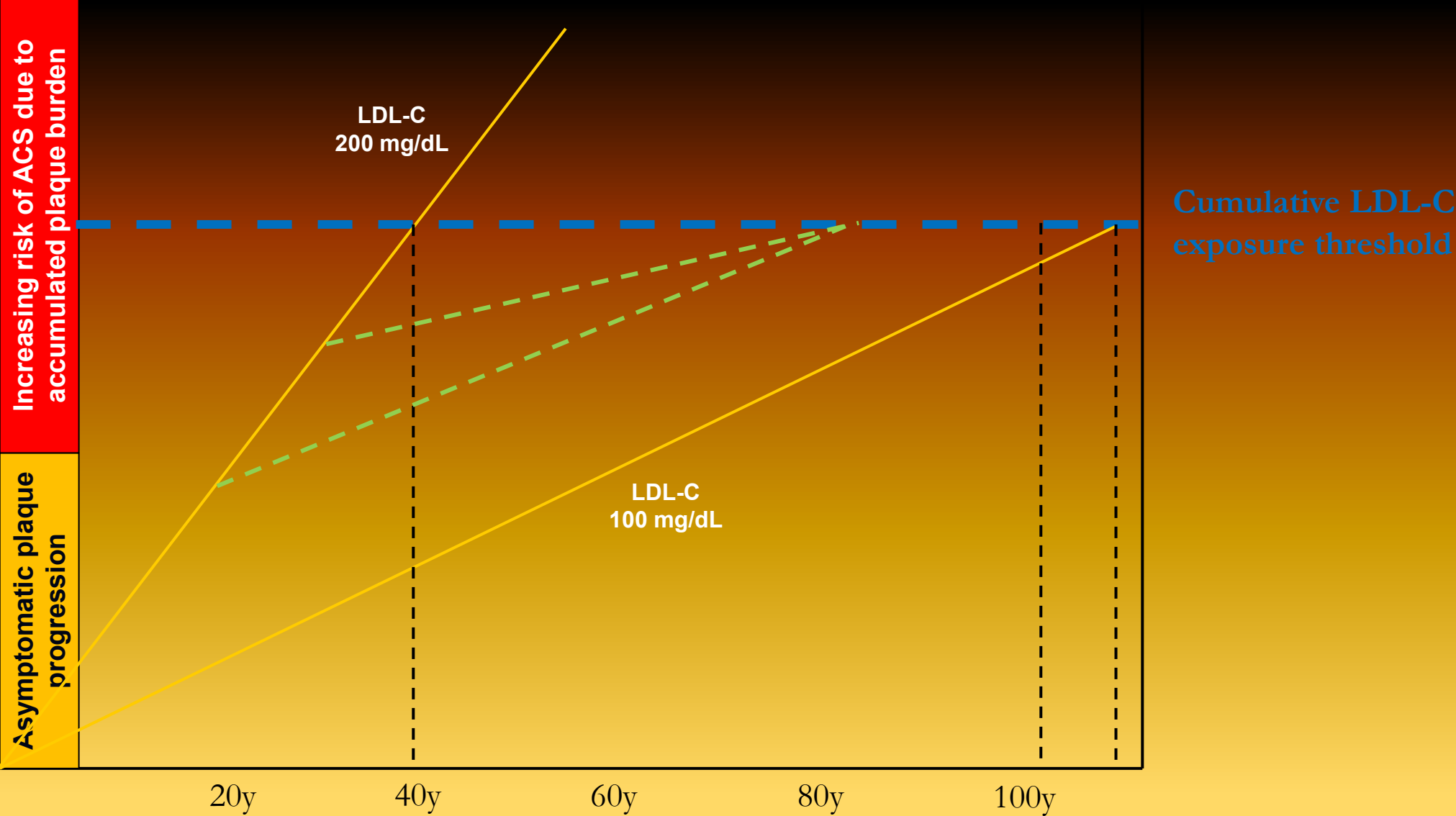
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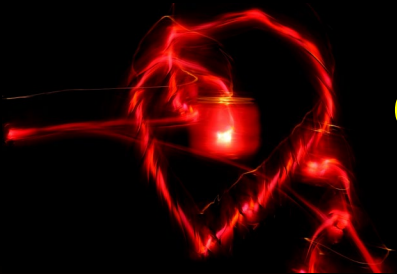




Role of long-term exposition to high LDL-C levels

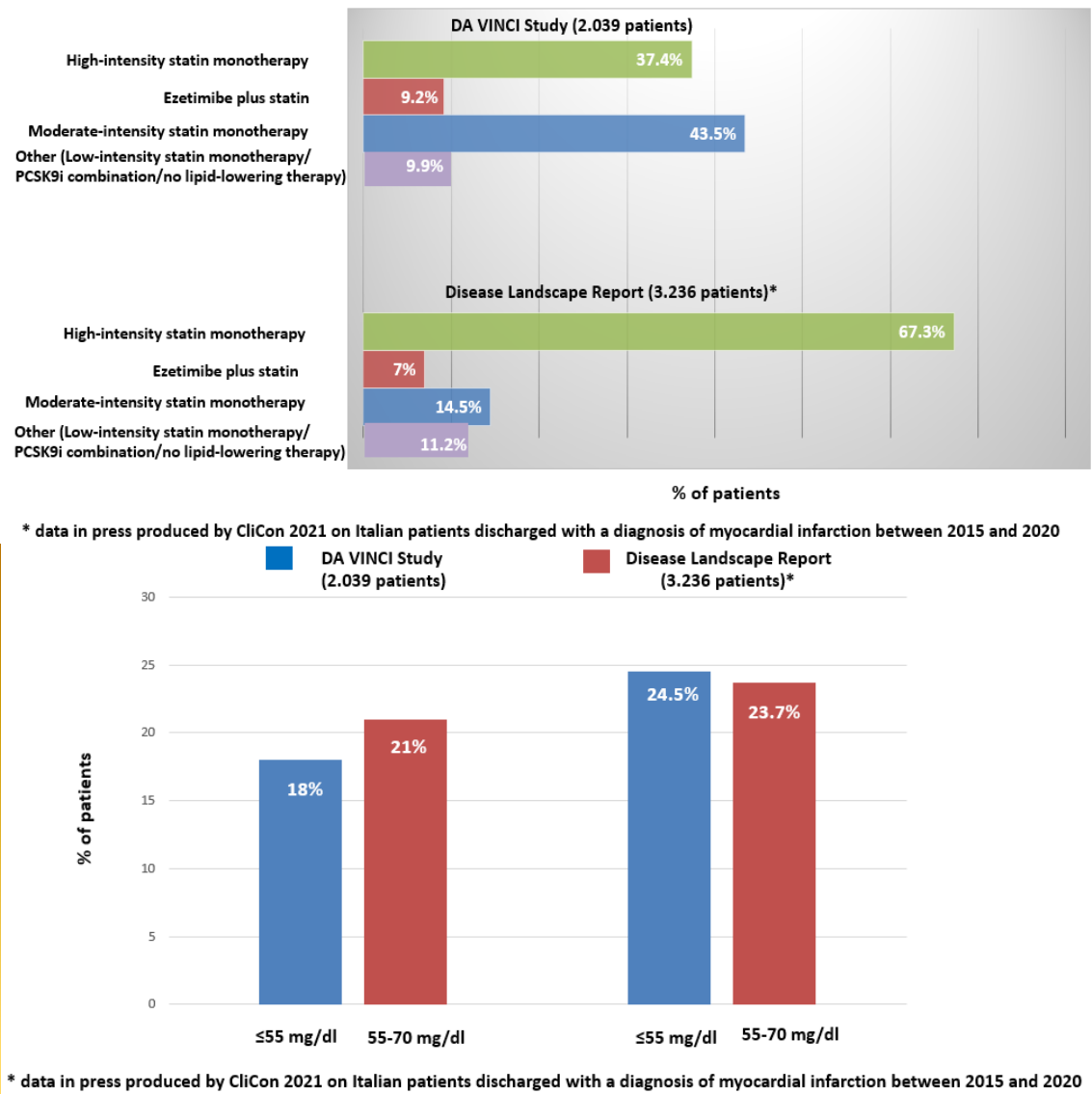
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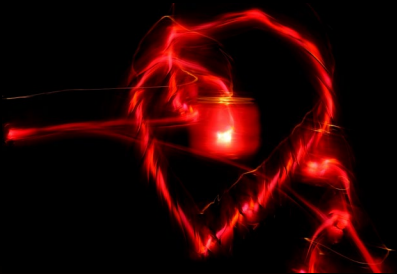




Contemporary real-world evidence of lipid-lowering approaches in ACS

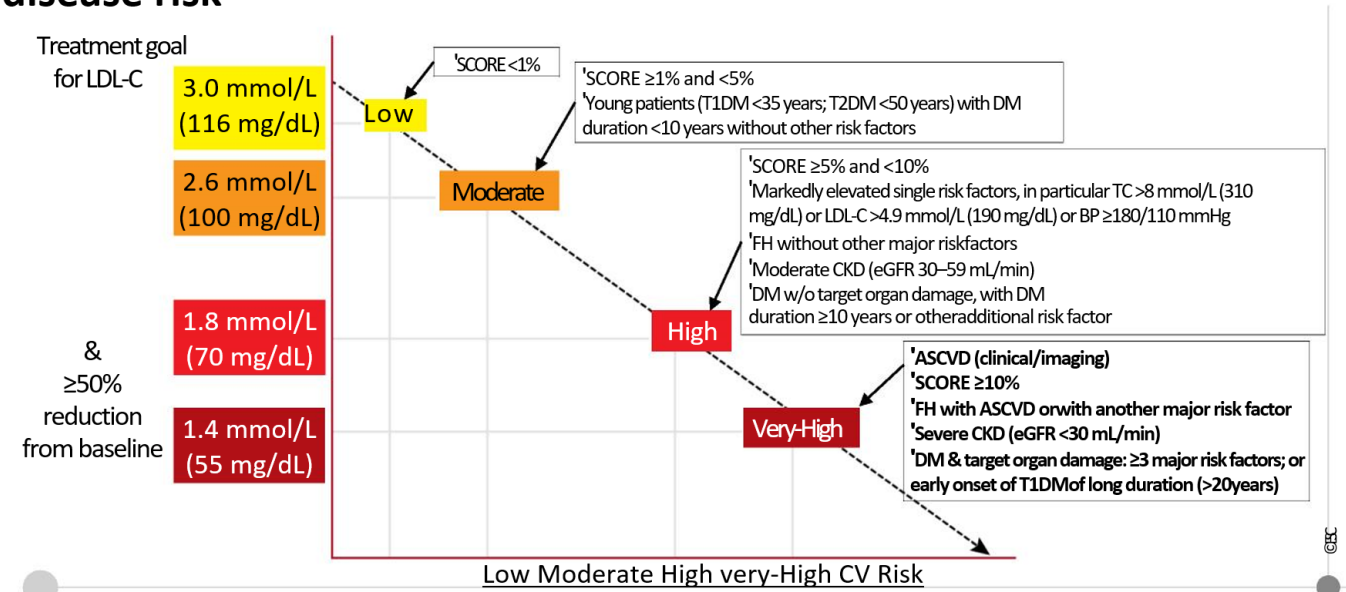
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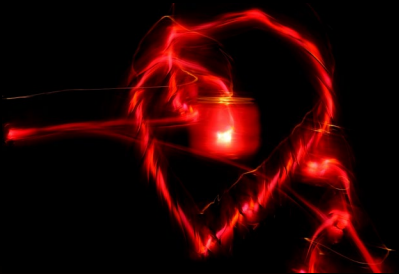




2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk

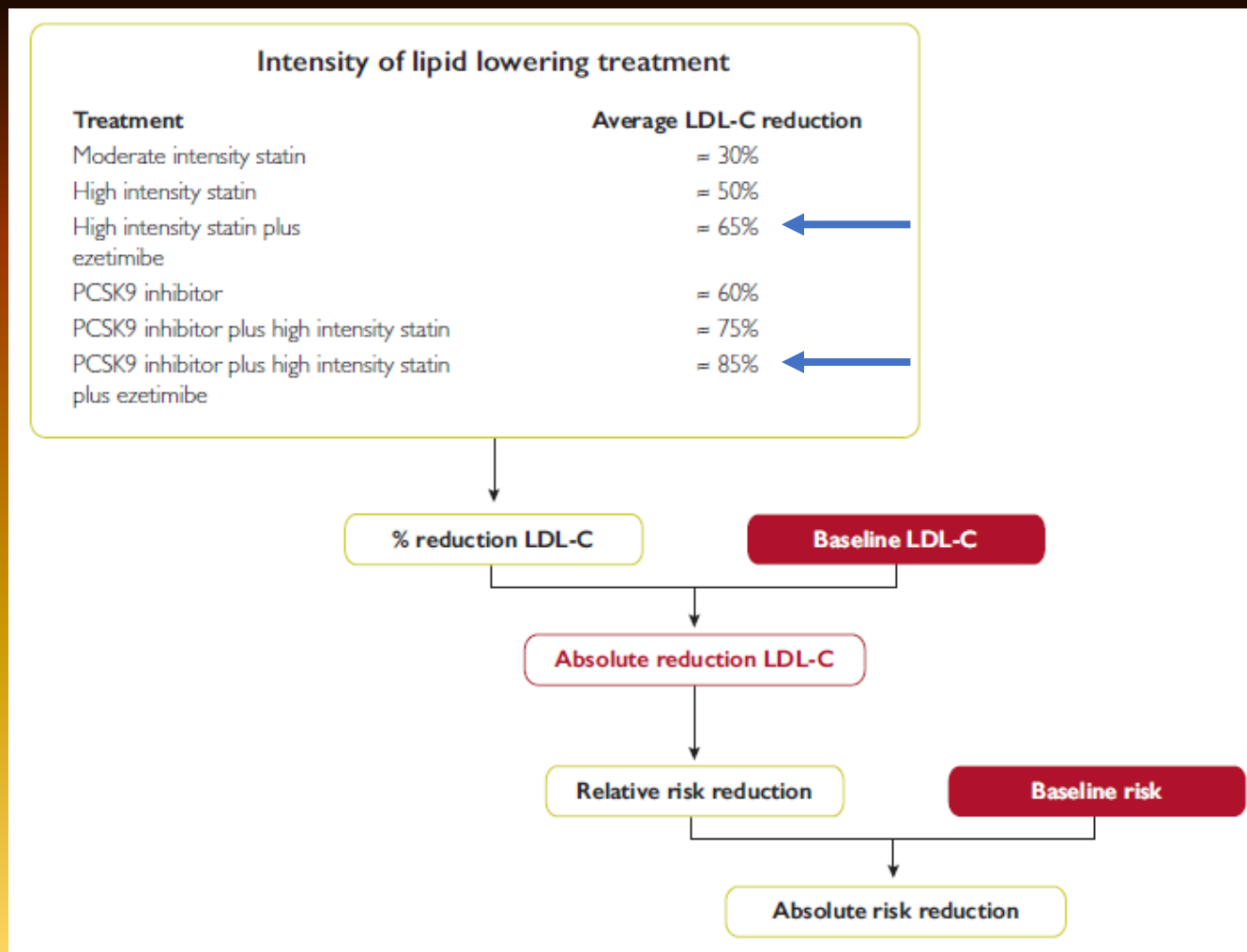
Treatment goals for low-density lipoprotein cholesterol (LDL-C) across categories of total cardiovascular disease risk

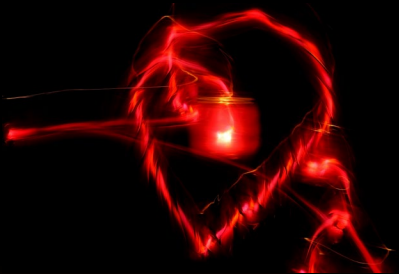




2019 ESC Guidelines on dyslipidaemias

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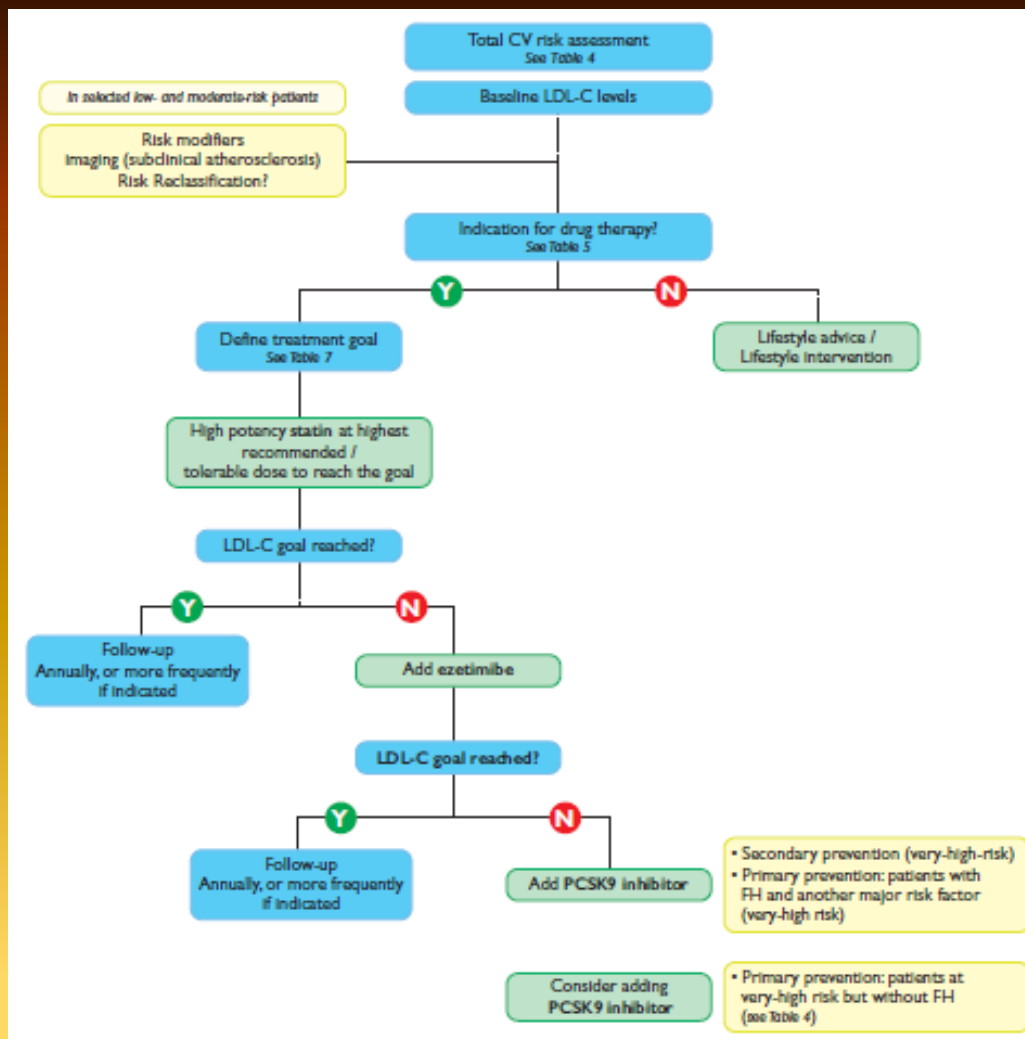




The earlier is the achievement of LDL-C target, the earlier and the greater the clinical benefit

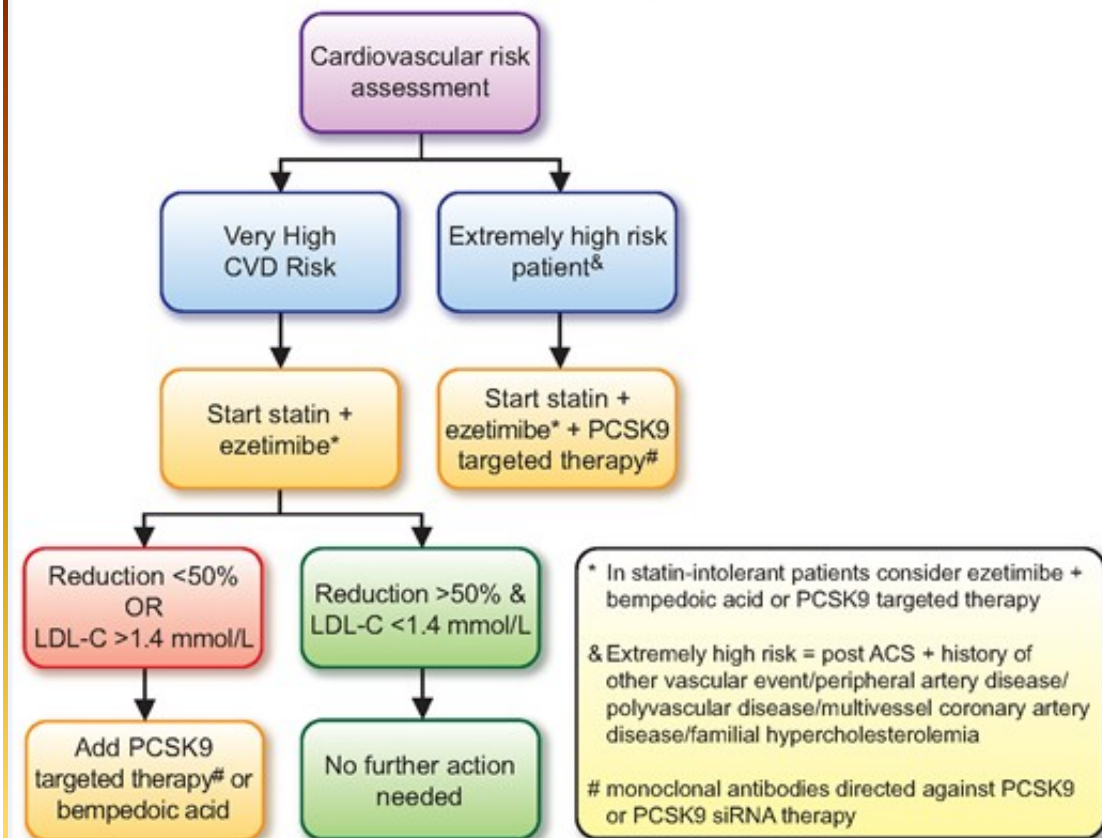
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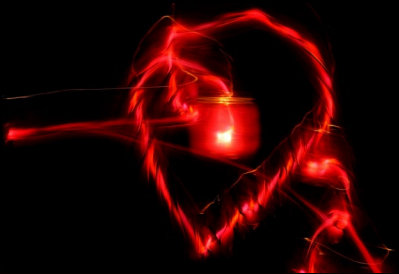
2019



2022

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

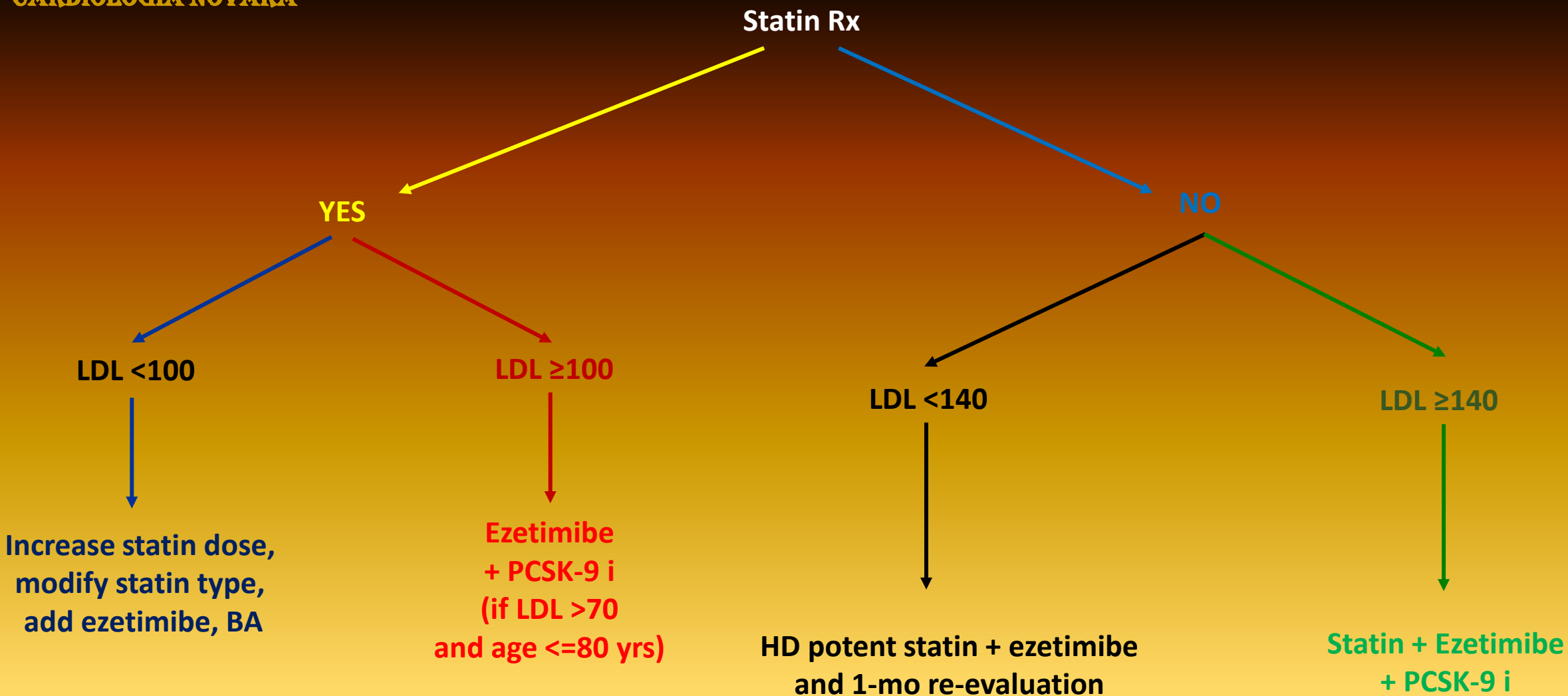


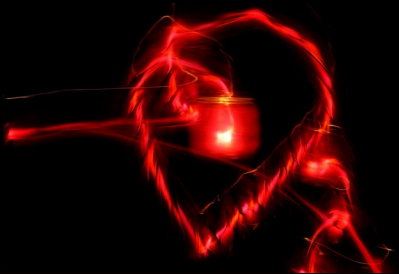


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LDL-C in ACS: GO LOWER AND FASTER!!!!!!!

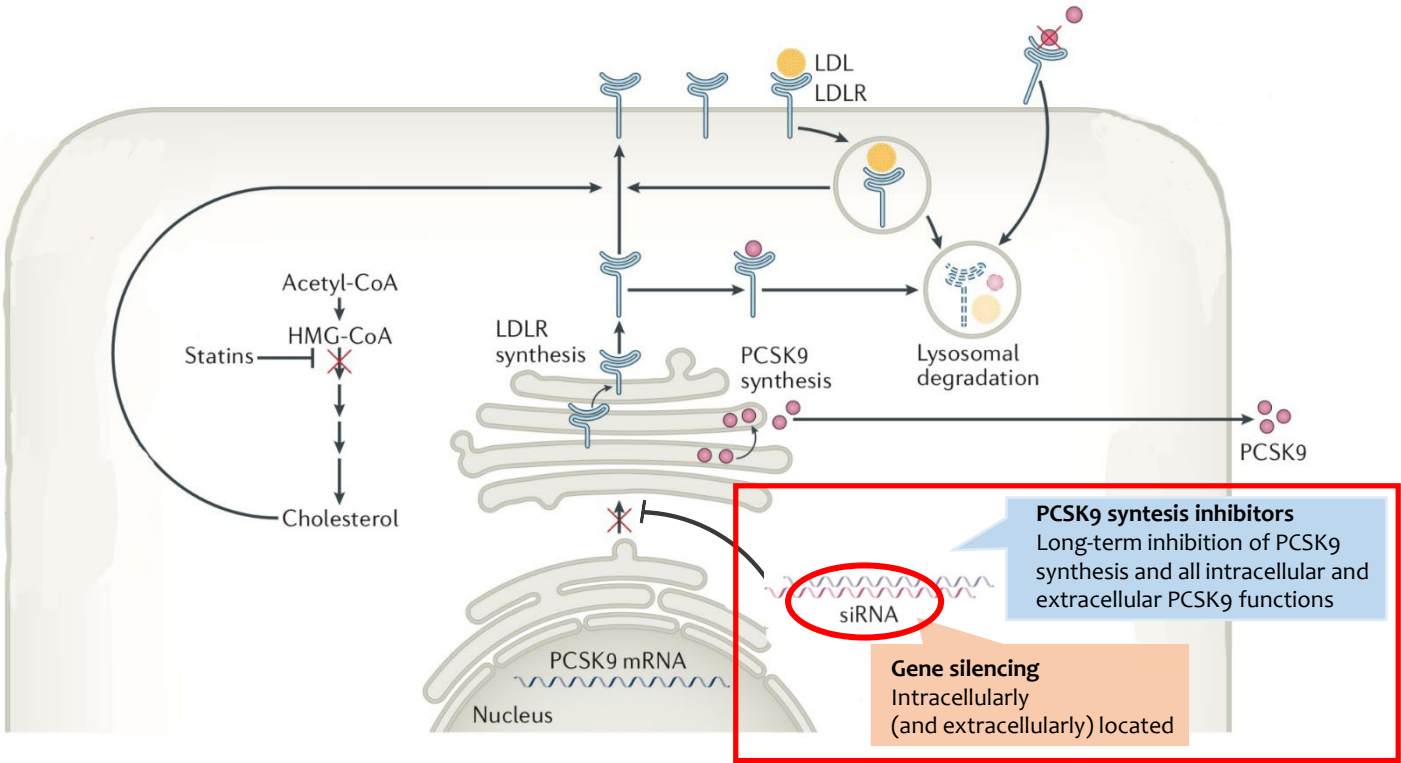
AIFA document: in patients with multiple CV events or ACS, one single LDL-C determination allows PCSK-9i initiation

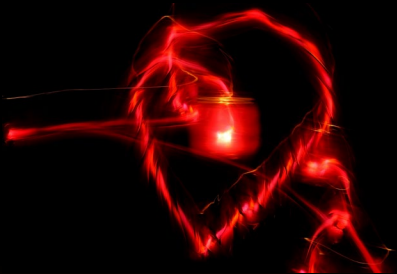




Newer therapeutic approaches to LDL-C lowering: siRNA

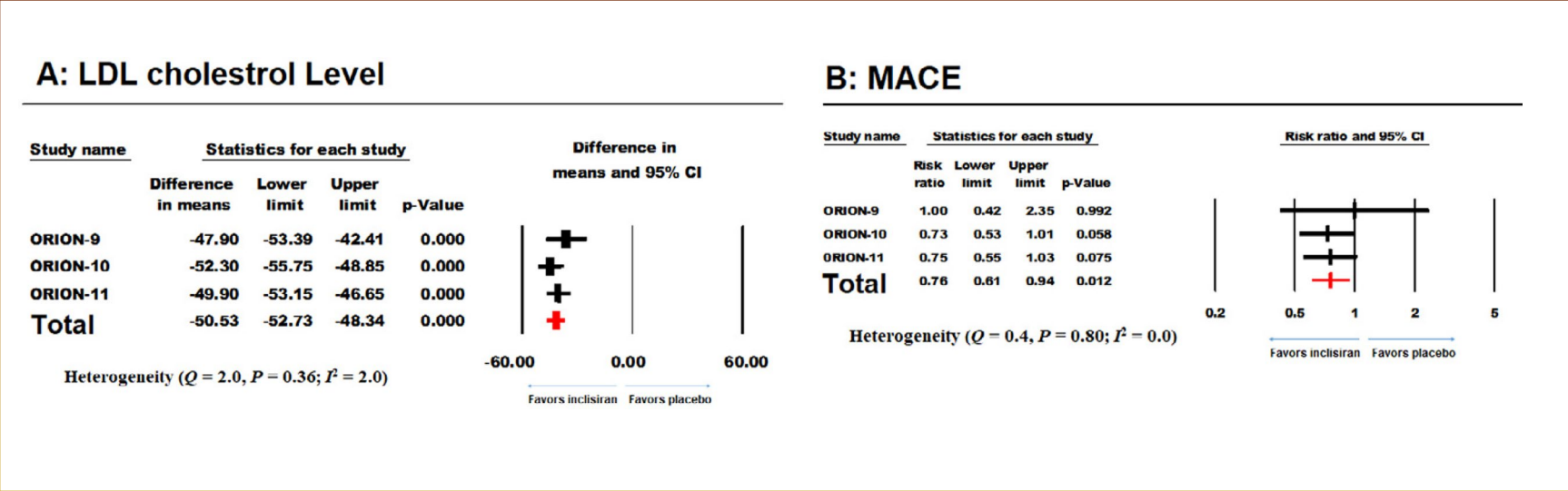
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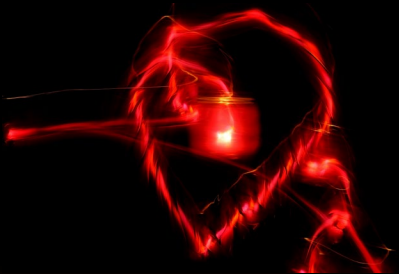




Meta-analysis of Orion 9-10-11 trials

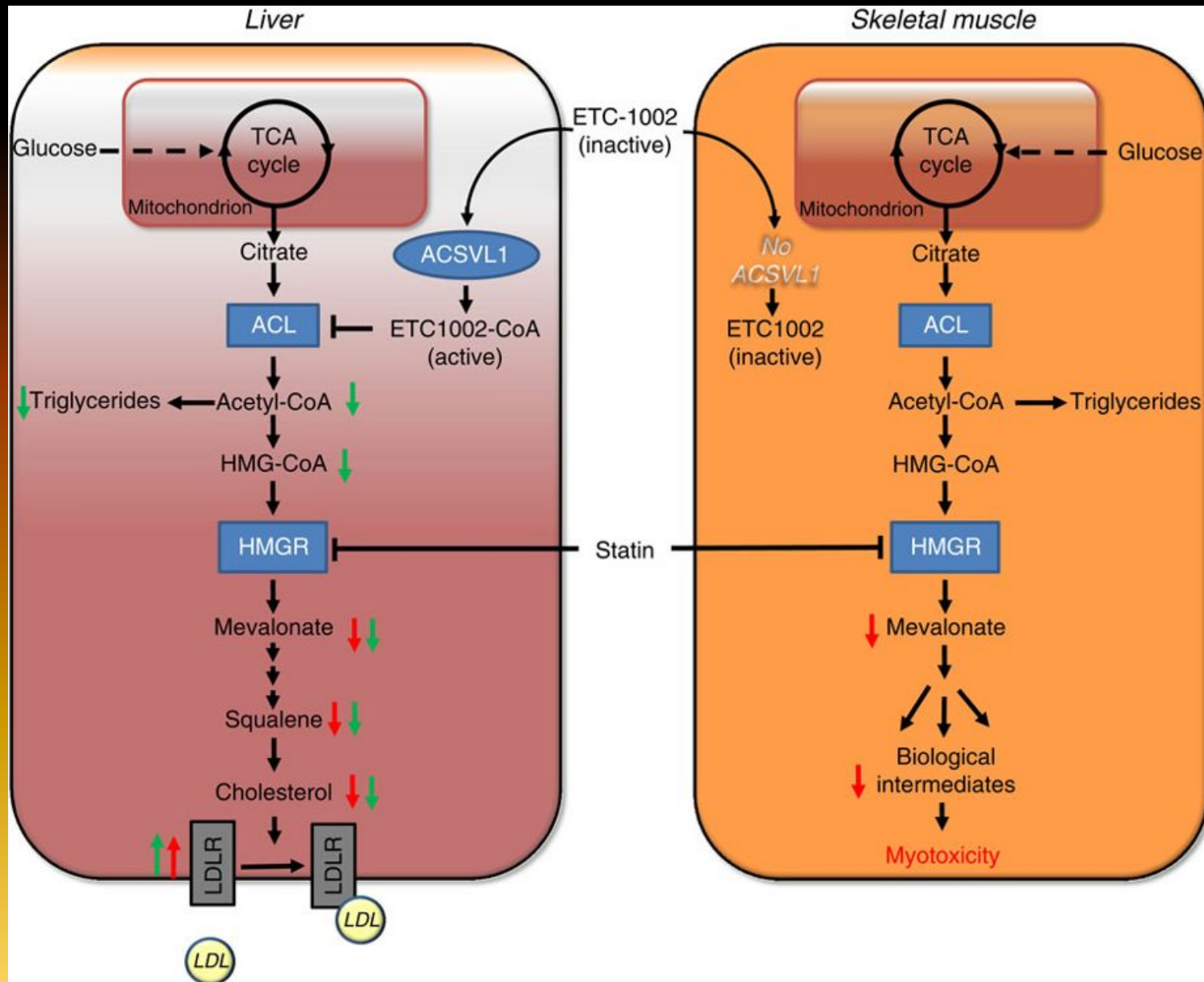
LDL reduction and MACE prevention



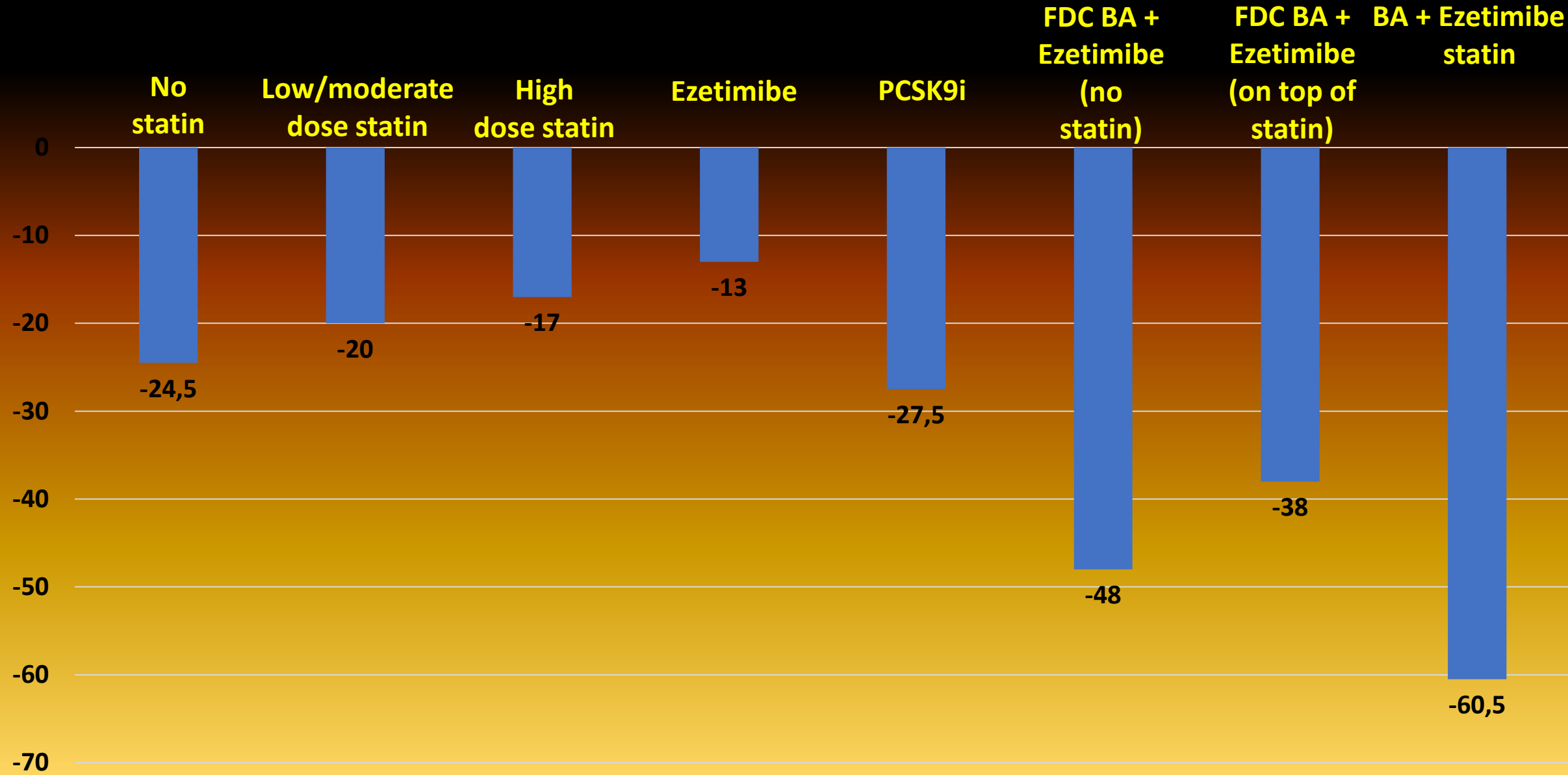


Barriers to lipid-lowering therapy implementation	
Patient-related	Physician-related
Low perception of hypercholesterolemia as a risk factor for CV disease	“Indulgence” in cholesterol levels due to weak awareness that cholesterol is causal in atherosclerosis
Statin-specific side effects	Reduced awareness of LDL-C targets
Statins nocebo effect	Clinical inertia
Aversion to pharmaceuticals	Inadequate follow-up plan for therapy implementation
Non-adherence	Poor patient-physician relationship
Polypharmacy	Reduced awareness of the safety of low LDL-C levels
Tips to overcome barriers to lipid-lowering therapy implementation	
Removal of cholesterol reference values in the reports of blood tests	
Screening programs for hypercholesterolemia and tests for early detection of subclinical atherosclerosis	
Healthy diet advertising campaigns	
Involvement of general practitioners in the management of hypercholesterolemia	
Increased knowledge and awareness of CV risk categories and recommended LDL-C targets	
Improve doctor-patient relationship	
Statin re-challenge in the case of side effects	
Combination therapy to reach LDL-C targets as early as possible	

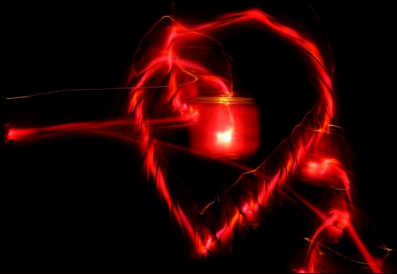
Bempedoic Acid is not Activated in the Skeletal Muscle



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



Bempedoic acid: safety analysis in >3,600 patients



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Treatment-Emergent Adverse Events	Bempedoic Acid N=2424, % (n)	Placebo N=1197, % (n)	p value
Overview of AEs in All Patients			
Any AE	73.1 (1771)	72.5 (868)	NS
Serious AEs	14.1 (341)	13.3 (159)	NS
Discontinuation due to AEs	11.3 (273)	7.8 (93)	NS
Muscular weakness	0.5 (13)	0.6 (7)	NS
New-onset diabetes/hyperglycemia	4.0 (96)	5.6 (67)	0.03
Blood uric acid increased	2.1 (51)	0.5 (6)	< 0.001
Hyperuricemia	1.7 (40)	0.6 (7)	0.007
Gout	1.4 (33)	0.4 (5)	0.008
Blood creatinine increased	0.8 (19)	0.3 (4)	NS
Glomerular filtration rate decreased	0.7 (16)	<0.1 (1)	0.02
Hepatic enzyme elevation	2.8 (67)	1.3 (15)	0.004
> 3 times the upper reference limit	0.7 (18)	0.3 (3)	NS
> 5 times the upper reference limit	0.2 (6)	0.2 (2)	NS
Neurocognitive disorderse	0.7 (16)	0.8 (9)	NS

Bempedoic acid: a guide for clinical use

