Il paziente dislipidemico con diabete : rischio cardiovascolare residuo

Antonio Lanzilli
UOSD Malattie endocrine , Nutrizione e Malattie del ricambio
AORN San Giuseppe Moscati Avellino

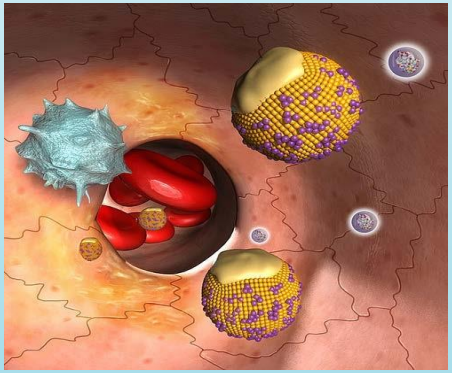
Per **Rischio Cardiovascolare Residuo** si intende la probabilità di sviluppare un evento cardiovascolare nonostante il paziente sia sottoposto al trattamento massimale con le terapie standard raccomandate

Residual Vascular Risk: DEFINITION

Residual Risk of macro-vascular events, including risk from established (such as unhealthy lifestyles, dyslipidemia, high blood pressure, high blood sugar and obesity) and emerging risk factors, that persists in patients in spite of current evidence-based medical care

Approved by the International Steering Committee members of the R³i Foundation and endorsed by its Trustees.

Dislipidemia diabetica aterogena



Alterazioni quantitative

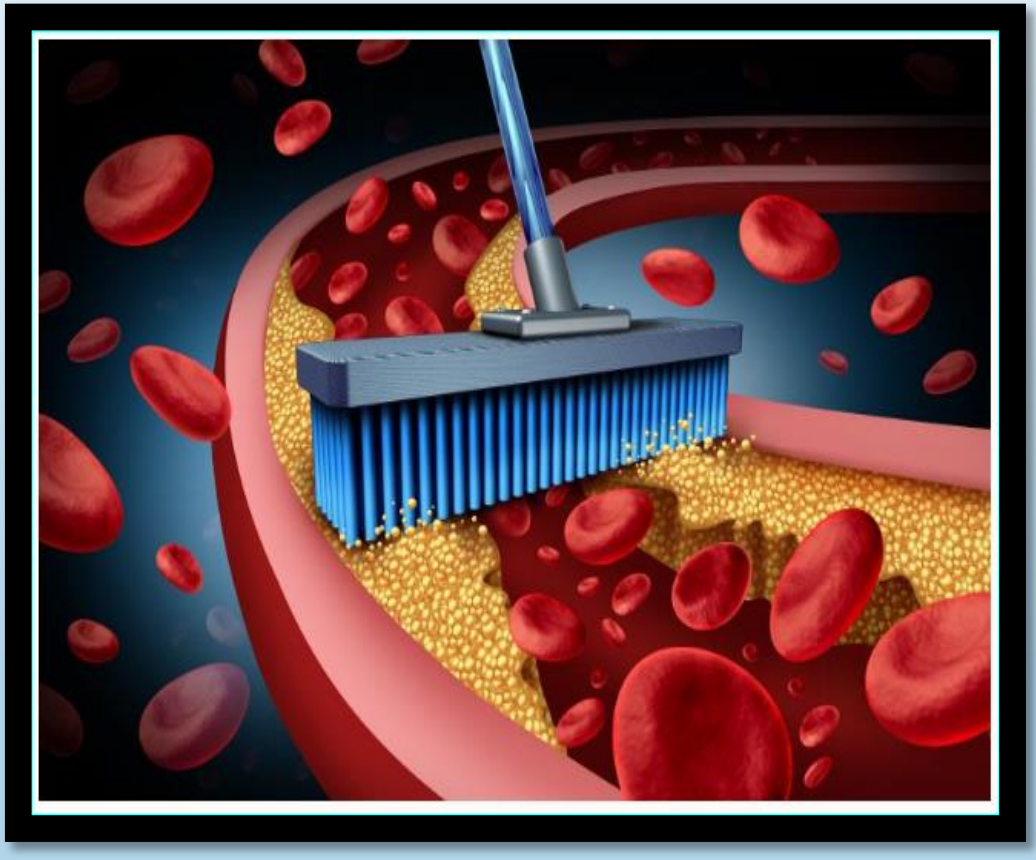
- ***FFA*** ↑↑
- ***Trigliceridi*** ↑↑
- ***HDL-Colesterolo*** ↓
- ***Colesterolo Totale*** ↑↓
- ***Apo B*** ↑↑

Alterazioni qualitative

- ***b-VLDL***
- ***HDL ricche di trigliceridi***
- ***(HDL3 e ↓HDL1 e HDL2)***
- ***LDL piccole e dense***
- ***Iperlipemia postprandiale***

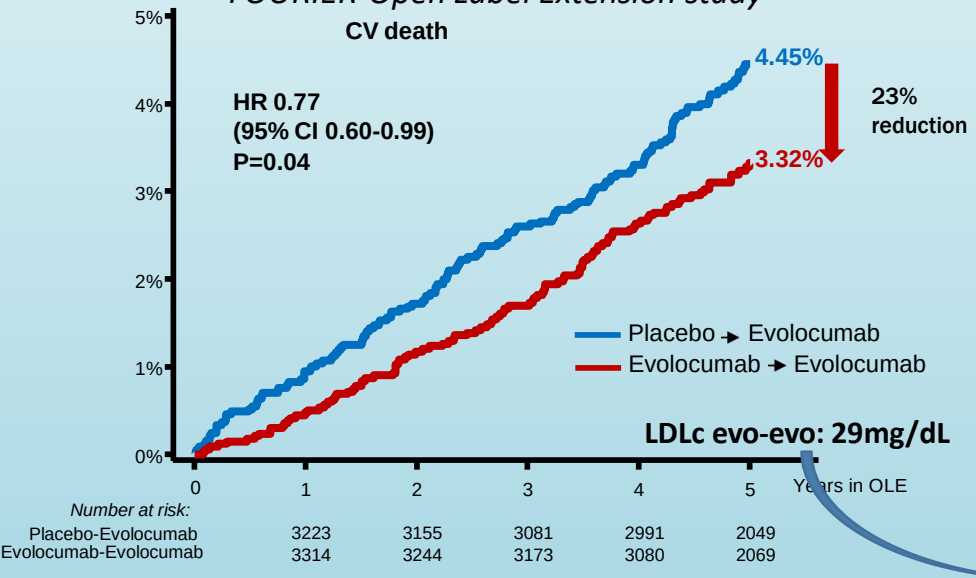
MORE AGGRESSIVE LIPID LOWERING IN PEOPLE WITH DIABETES?

There is ongoing debate as to whether aggressive LDL cholesterol-lowering therapy, as opposed to comprehensive lipid management addressing the hypertriglyceridaemia and low HDL cholesterol, is the optimal approach to reduce atherosclerotic cardiovascular risk in people with diabetes.

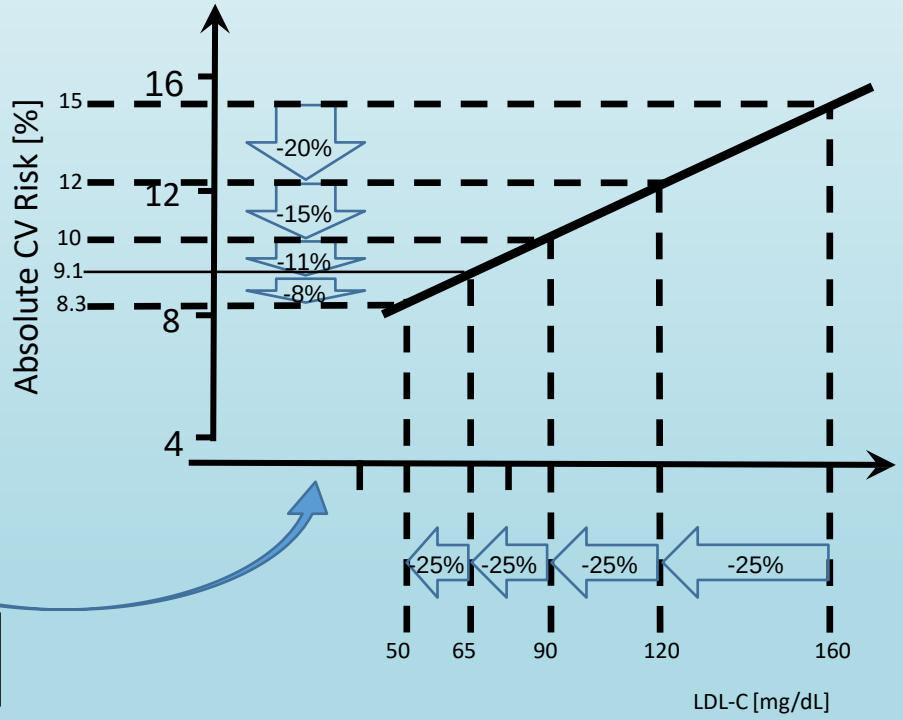


Residual risk in patients with very-low LDLc levels

Significant benefit with marked residual risk
FOURIER-Open Label Extension study



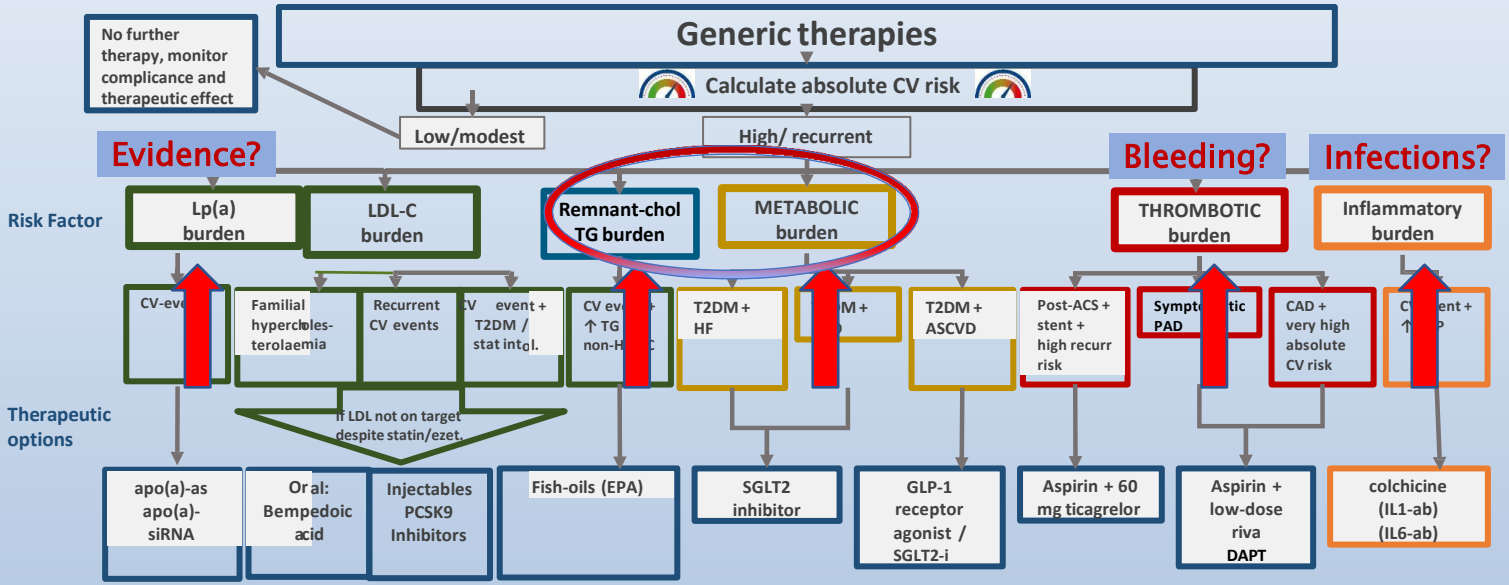
Further LDLc lowering - limited benefit



Recurrent CV-event rate in evo-evolocumab : **14.6% /5yr**
Recurrent CV-event rate in placebo-evolocumab: **16.8% /5yr**

O'Donaghue, *Circulation* 2022; Gaba P, *Circulation* 2023; Laufs, *Eur Heart J* 2014

Other pillars ‘contributing’ to atherogenesis

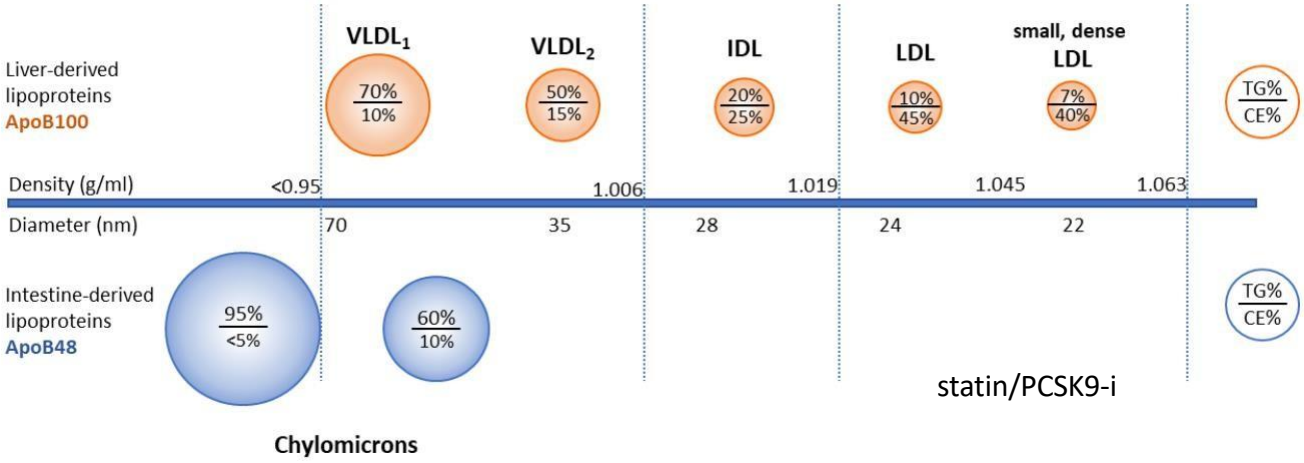


Hoogeveen, Stroes, Neth Heart J 2021

When cardiologist talk about high TGs .

TGs are 'heterogeneous'

Size and density profile of major apolipoprotein-B containing lipoprotein classes



statin/PCSK9-i

apoB containing lipoproteins

Triglycerides / Triglyceride-rich lipoproteins

Triglyceride-remants /
Remnant cholesterol

Ginsberg H, et al. Consensus on HTG. *Eur Heart J 2021*

Review Article | Published: 30 October 2018

Safety and efficacy of statin therapy

Bhavin B. Adhyaru & Terry A. Jacobson

Nature Reviews Cardiology **15**, 757–769(2018) | Cite this article

5822 Accesses | **52** Citations | **48** Altmetric | Metrics

Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials

Cholesterol Treatment Trialists' Collaboration*

AHA Scientific Statement

Statin Safety and Associated Adverse Events

A Scientific Statement From the American Heart Association

Connie B. Newman, MD, FAHA, Chair; David Preiss, FRCPath, PhD; Jonathan A. Tobert, MD, PhD, FAHA; Terry A. Jacobson, MD, FAHA, Vice Chair; Robert L. Page II, PharmD, MSPH, FAHA; Larry B. Goldstein, MD, FAHA; Clifford Chin, MD; Lisa R. Tannock, MD, FAHA; Michael Miller, MD, FAHA; Geetha Raghuveer, MD, MPH, FAHA; P. Barton Duell, MD, FAHA; Eliot A. Brinton, MD, FAHA; Amy Pollak, MD; Lynne T. Braun, PhD, FAHA; Francine K. Welty, MD, PhD, FAHA; on behalf of the American Heart Association Clinical Lipidology, Lipoprotein, Metabolism and Thrombosis Committee, a Joint Committee of the Council on Atherosclerosis, Thrombosis and Vascular Biology and Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular Disease in the Young; Council on Clinical Cardiology; and Stroke Council

Le statine di sintesi si confermano il farmaco di prima scelta laddove il target di LDL non possa essere corretto con il solo regime dietetico o mediante l'utilizzo di nutraceutici
(in particolare per i soggetti a rischio cardiovascolare elevato/molto elevato).

Identifying the right patient

How to Screen Diabetes with ASCVD risk (DYSLIPIDEMIA)

- **For all patients:**
  - history and physical examination
  - standard lipid profile*:* **TC, LDL-C, HDL-C, non-HDL-C*, TG,ApoB**
    - Non-fasting lipid testing is recommended in most adults for screening; however, for individuals with a history of TGs >4.5 mmol/L, fasting lipid levels are recommended.
    - ***it is now generally preferable to follow non-HDL-C or ApoB levels over LDL-C when interpreting lipid results, particularly when TG is ≥1.5 mmol/L**
  - **eGFR**
  - **lipoprotein(a) -- once in patient's lifetime, with initial screening**

- **Optional:**
  - **Urine ACR** (if eGFR <60 mL/min/1.73 m^2, hypertension, or diabetes)

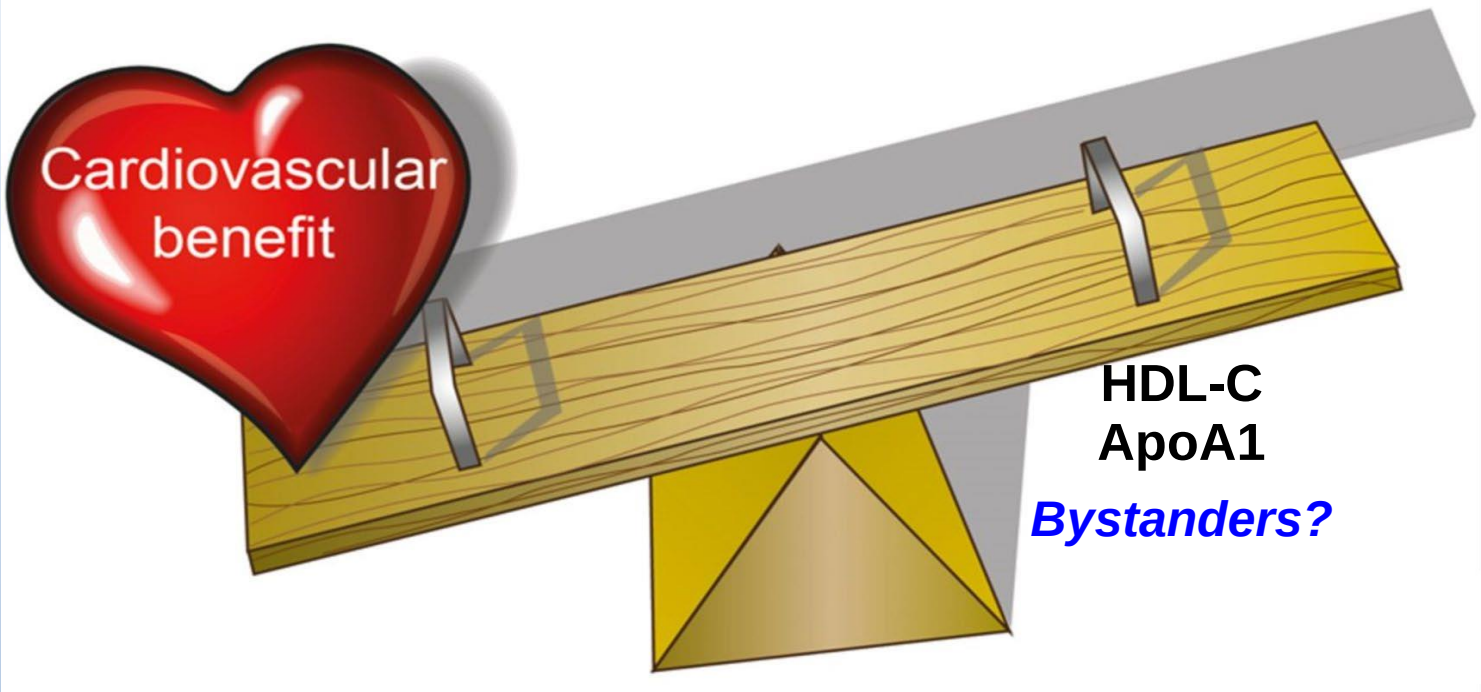
Nuovi marcatori rischio

- **Trigliceridi**
- **HDL**
- **ApoB e non HDL-col**
- **Lp(a)**
- **Infiammazione**

Nuovi marcatori di rischio

- **Trigliceridi**
- HDL
- ApoB e non HDL-col
- Lp(a)
- Infiammazione

Triglycerides a Causal Risk Factor?



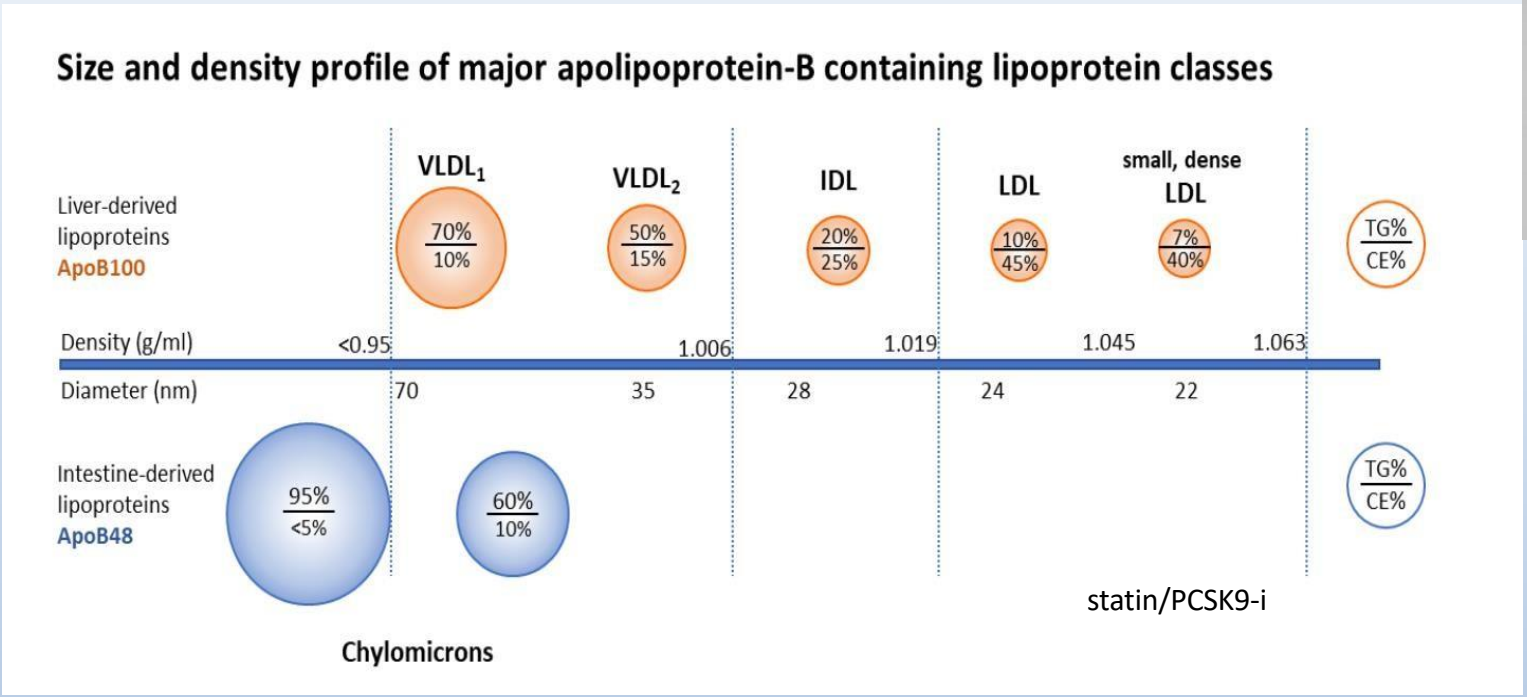
Triglyceride-rich lipoproteins
ApoC3

Causal risk factors?

Adapted with permission from Libby P. Triglycerides on the rise: should we swap seats on the seesaw? *Eur Heart J*. 2015;36:774-776.

When cardiologist talk about high TGs …

TGs are 'heterogeneous'



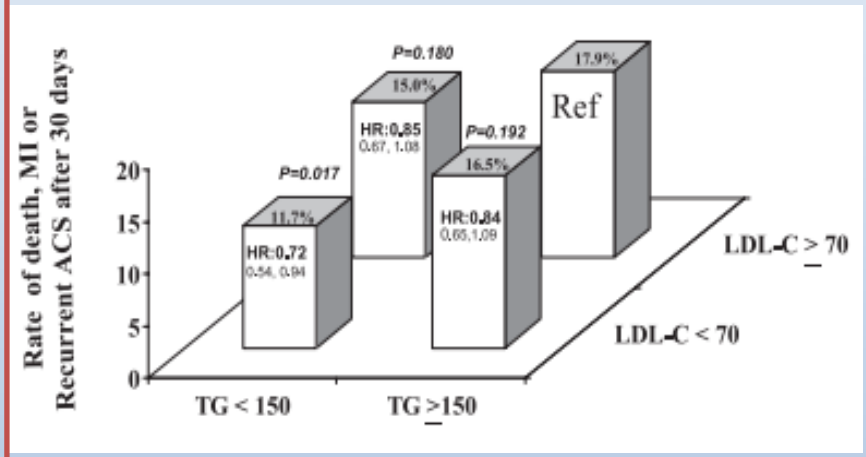
apoB containing lipoproteins

Triglycerides / Triglyceride-rich lipoproteins

Triglyceride-remants /
Remnant cholesterol

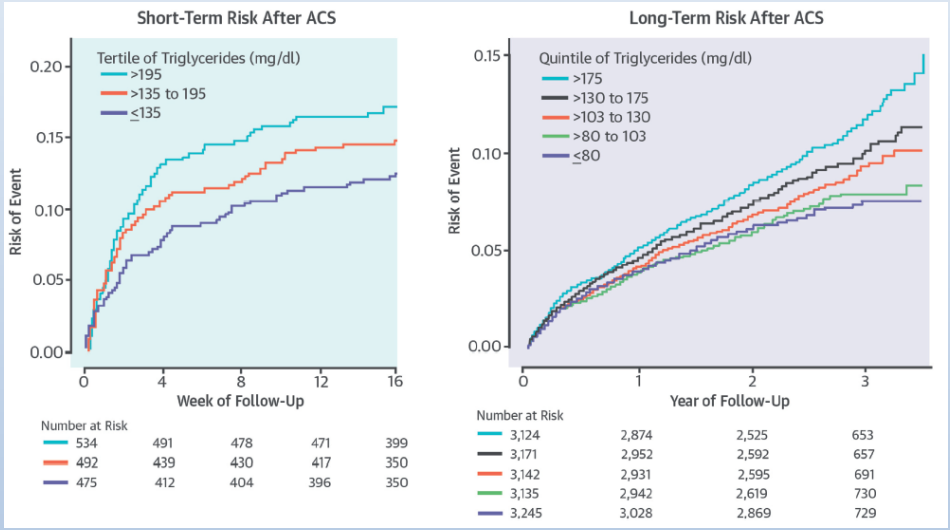
Ginsberg H, et al. Consensus on HTG. ***Eur Heart J 2021***

Fasting Triglycerides Predict Recurrent Ischemic Events in Patients with Acute Coronary Syndrome or ASCVD Treated with High Dose Statins



Risk of recurrent events using selected cut-points of LDL-C and TG

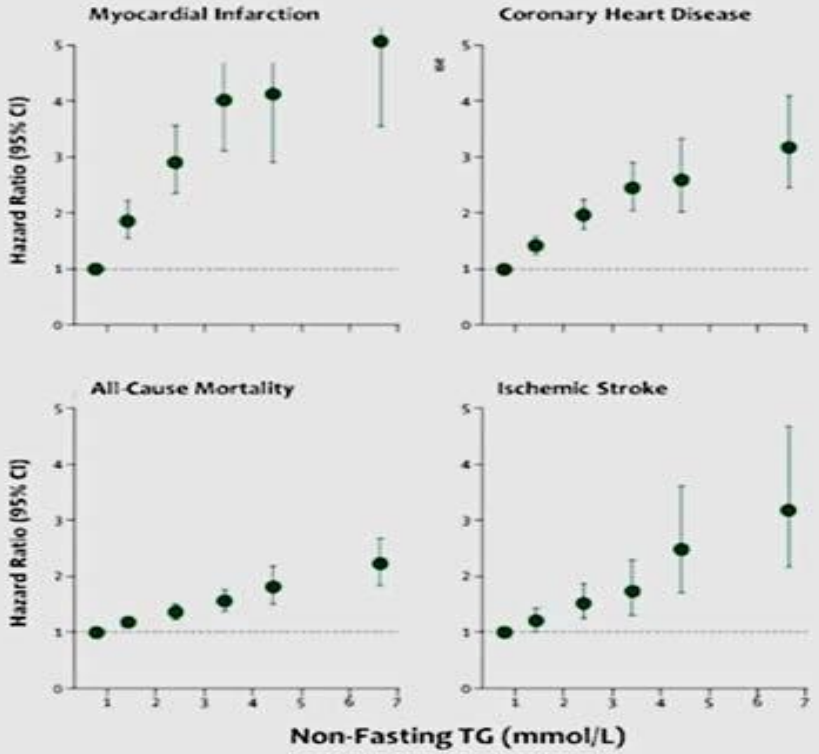
Prove-it[1]



Miracl[2] **dal-OUTCOMES[2]**

1. Miller M, et al., 2008. JACC Vol. 51, No. 7 Pages 724-730, ISSN 0735-1097
2. Schwartz GG, et al. J Am Coll Cardiol. 2015; 65(21):2267-75

Trigliceridi e Rischio CV



Large Population Based Studies Show Consistent Risk Associations

Copenhagen City Heart Study and Copenhagen General Population Study.
Median Follow-Up 6 years

No. Subjects >90,000
MI = 3287
CHD = 7183
Ischemic Stroke = 2994
All Cause Mortality = 14,547

Nordestgard Lancet 2014

Rischio Residuo

LDL colesterolo

↑ TG

- **Fibrati ?**
- **Olio di pesce ?**

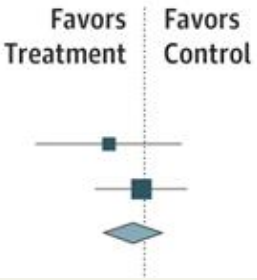
Randomized Control Trials

JAMA Cardiology | Original Investigation

Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks

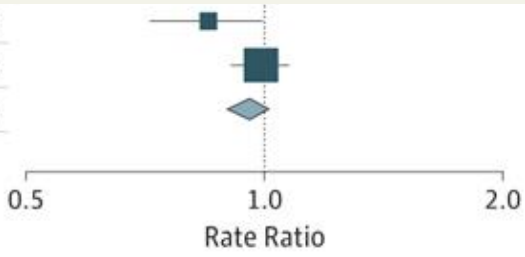
Meta-analysis of 10 Trials Involving 77 917 Individuals

Source	No. of Events (%) Treatment	Control	Rate Ratios (CI)
Nonfatal myocardial infarction			
Open	285 (1.9)	316 (2.1)	0.90 (0.73-1.11)
Blind	836 (3.5)	839 (3.5)	0.99 (0.87-1.13)
All	1121 (2.9)	1155 (3.0)	0.97 (0.89-1.05)
			P = .40



CONCLUSIONS AND RELEVANCE This meta-analysis demonstrated that omega-3 fatty acids had no significant association with fatal or nonfatal coronary heart disease or any major vascular events. It provides no support for current recommendations for the use of such supplements in people with a history of coronary heart disease.

Open	512 (3.4)	598 (4.0)	0.85 (0.72-0.99)
Blind	2573 (10.7)	2590 (10.8)	0.99 (0.91-1.07)
All	3085 (7.9)	3188 (8.2)	0.96 (0.90-1.01)
			P = .12

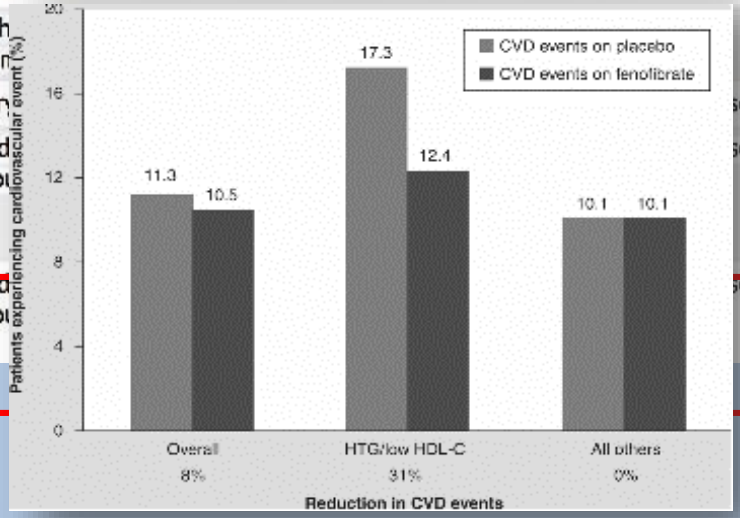


JAMA Cardiol. 2018;3(3):225-234.

RCT con FIBRATI

TABLE 2 Summary of CVD trials with TG lowering drugs

Trial	Drug	Patient population	Statin use	HDL	TG	LDL	CVD outcomes
HHS	Gemfibrozil	Non-HDL-C >5.2 mmol/L. Asymptomatic with no prior CVD	No	19.4% increase	52% decrease	8.4% decrease	34% reduction in CVD, no mortality benefit
VA-HIT	Gemfibrozil	Establish <1 mm				No significant difference	24% reduction MACE
BIP	Bezafibrate	Coronary				6.5% decline	Neutral
FIELD	Fenofibrate	Type 2 d without				5.8% decrease	**Neutral** *(Non fatal MI, CHD death)*
ACCORD	Fenofibrate	Type 2 d without				No significant difference vs placebo	Neutral



Sacks et al NEJM 2010

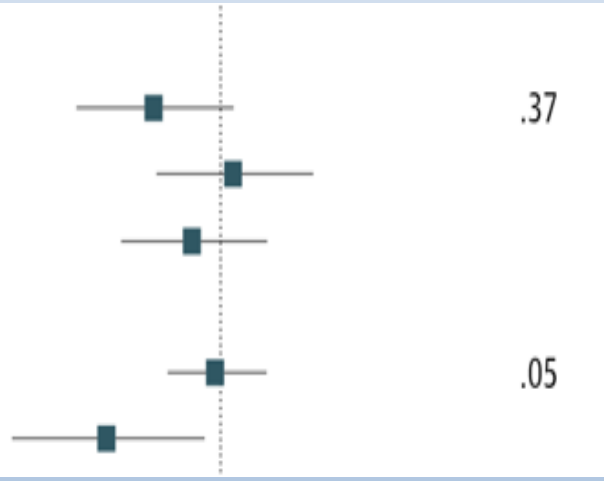
Association of Fenofibrate Therapy With Long-term Cardiovascular Risk in Statin-Treated Patients With Type 2 Diabetes

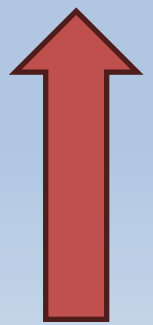
Marshall B. Elam, PhD, MD[1]; Henry N. Ginsberg, MD[2]; Laura C. Lovato, MS[3]; et al

» Author Affiliations | Article Information

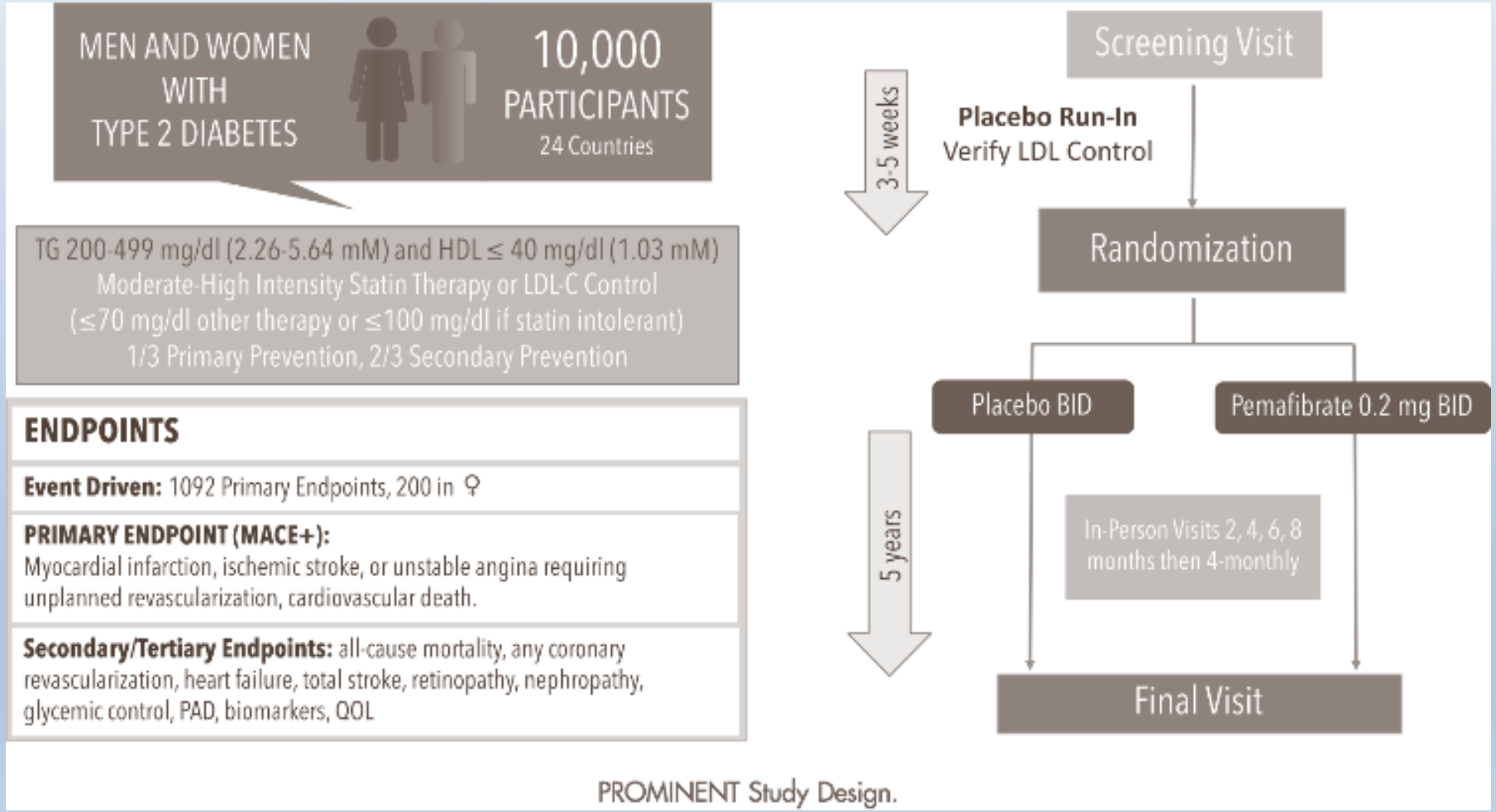
JAMA Cardiol. 2017;2(4):370-380. doi:10.1001/jamacardio.2016.4828

Triglycerides				
<129	146/879 (16.61)	186/930 (20.00)	0.83 (0.67-1.03)	.37
129-203	171/918 (18.63)	160/908 (17.62)	1.04 (0.84-1.29)	
≥204	189/927 (20.39)	190/882 (21.54)	0.93 (0.76-1.13)	
Dyslipidemia				
No	407/2242 (18.15)	415/2266 (18.31)	0.99 (0.86-1.13)	.05
Triglycerides >204 and HDL-C <34	99/482 (20.54)	121/454 (26.65)	0.73 (0.56-0.95)	





PROMINENT: Pemafibrato



PROMINENT Study Design.

Fibrates: Enhancing TG-metabolism?
TG lowering in absence of TRL-reduction not beneficial

Effect Pemafibrate	%change compared to placebo	Abs. difference Vs placebo
TG change	-26.2 %	- 69 mg/dl
Remnant chol	-25.6 %	- 12 mg/dl
LDLc	+12.3 %	+ 10 mg/dl
apoB	+ 4.8 %	+ 5 mg/dl

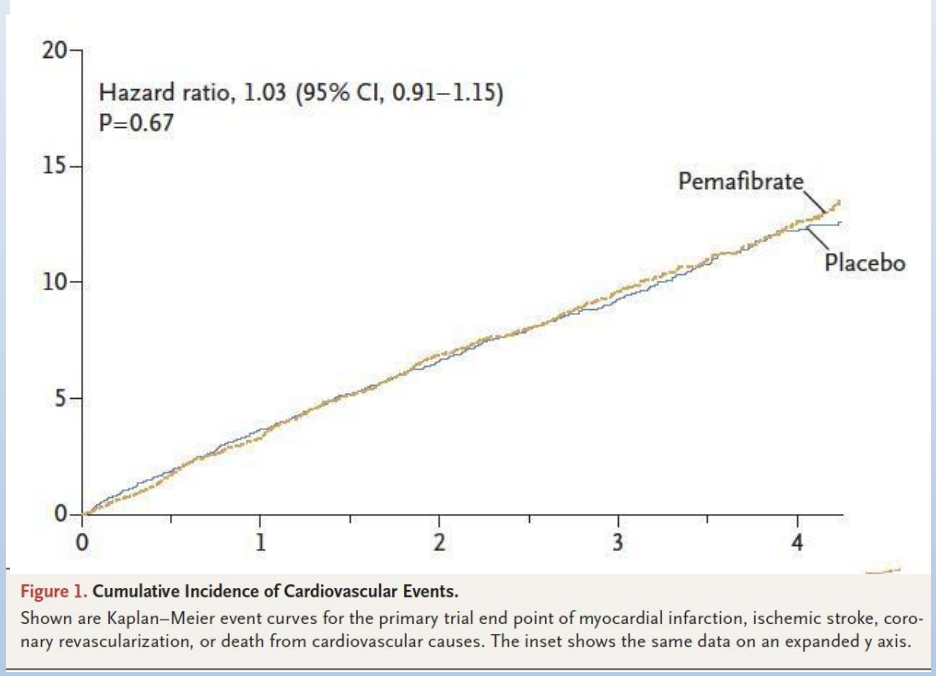


Figure 1. Cumulative Incidence of Cardiovascular Events.
Shown are Kaplan–Meier event curves for the primary trial end point of myocardial infarction, ischemic stroke, coronary revascularization, or death from cardiovascular causes. The inset shows the same data on an expanded y axis.

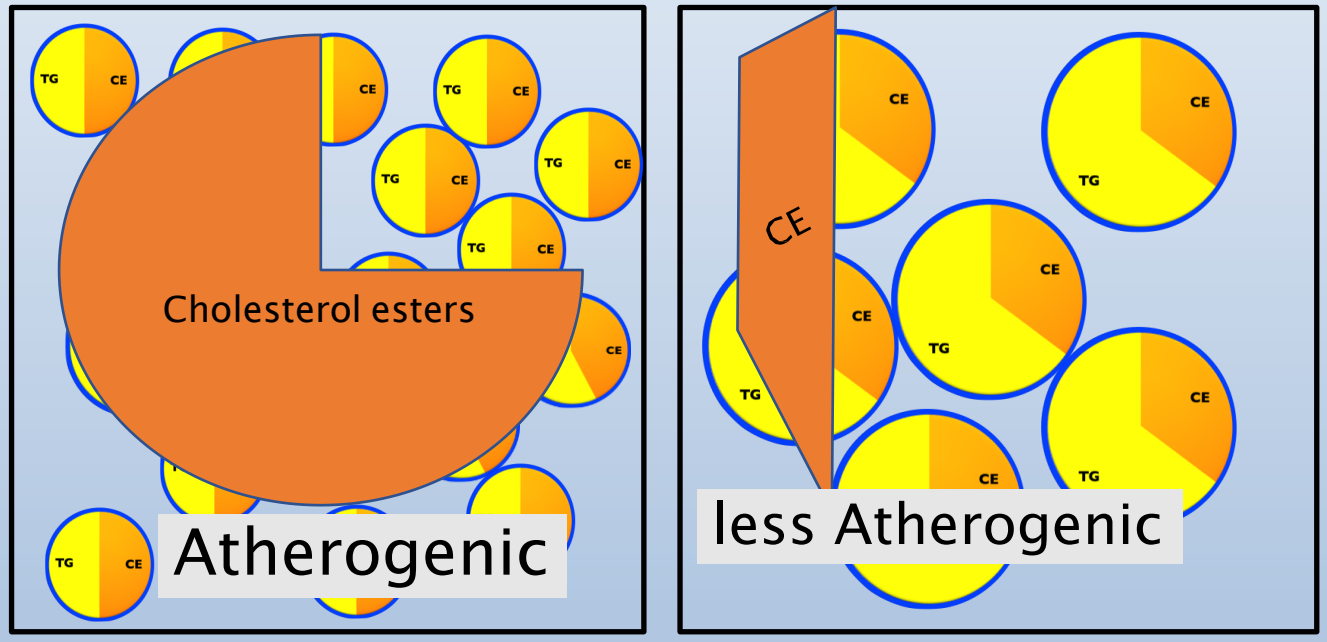
Fibrate **does not 'remove' Triglyceride-rich particles**

It shifts atherogenic particles towards other atherogenic particles

Das-Pradhan N Engl J Med 2022; Ginsberg H, Eur Heart J 2021

But, what is high Triglycerides?
a mixed bag

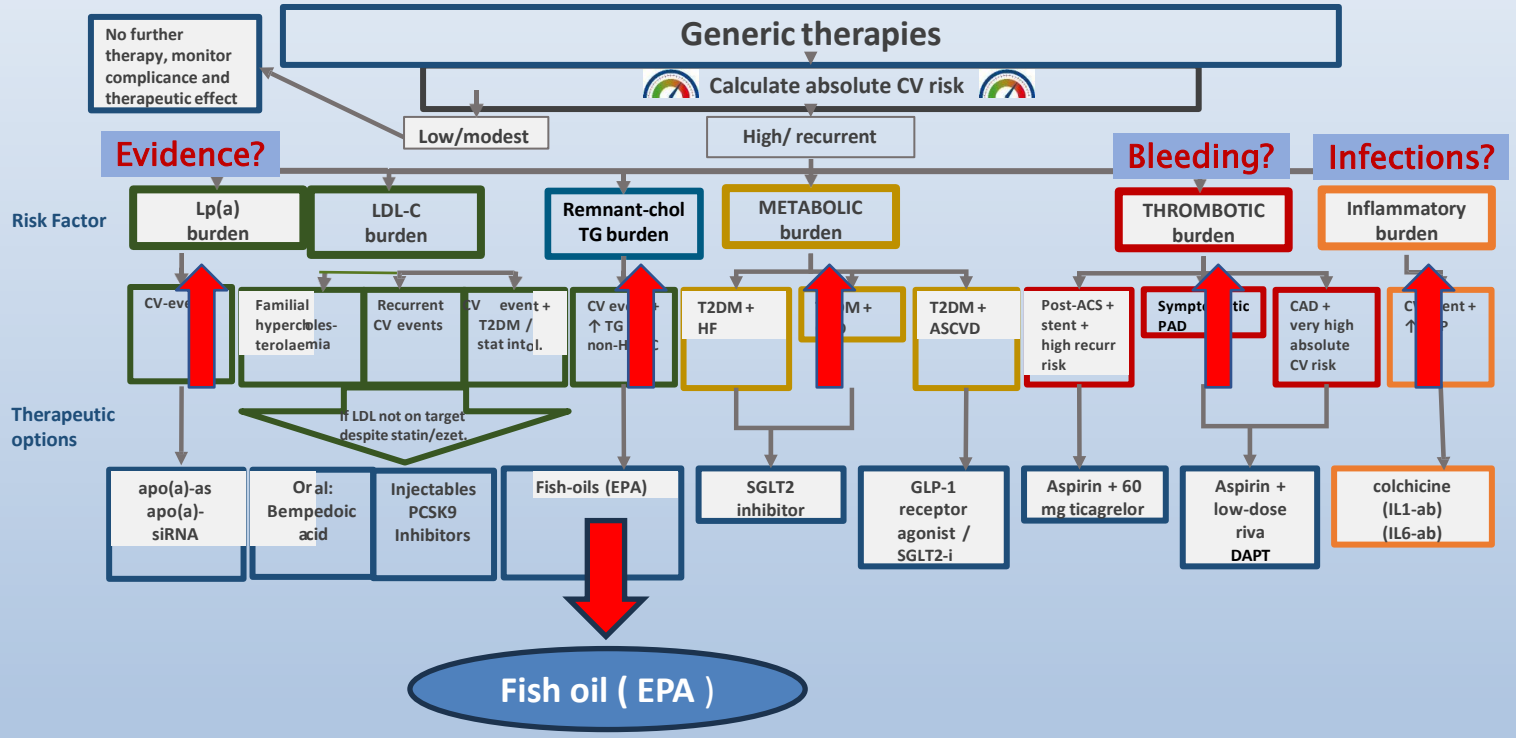
TG 4.5 mmol/l (405 mg/dL)



High apo B 135mg/dl

Low apo B 87 mg/dl

Other pillars ‘contributing’ to atherogenesis



Hoogeveen, Stroes, Neth Heart J 2021

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Effects of Icosapent Ethyl on Total Ischemic Events: From REDUCE-IT

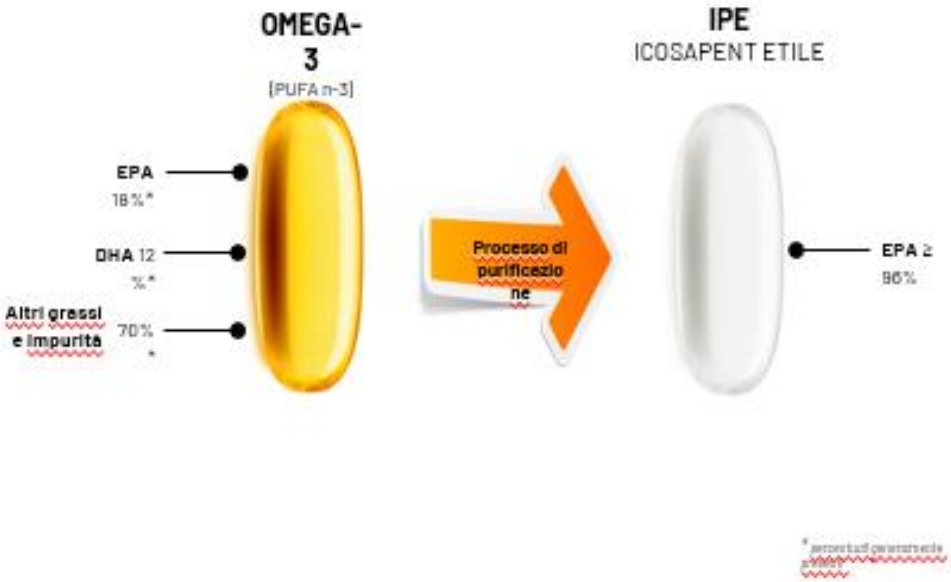
Deepak L. Bhatt, MD, MPH,[a] Ph. Gabriel Steg, MD,[b,c] Michael Miller, MD,[d] Eliot A. Brinton, MD,[e] Terry A. Jacobson, MD,[f] Steven B. Ketchum, PhD,[g] Ralph T. Doyle, Jr, BA,[g] Rebecca A. Juliano, PhD,[g] Lixia Jiao, PhD,[g] Craig Granowitz, MD, PhD,[g] Jean-Claude Tardif, MD,[h] John Gregson, PhD,[i] Stuart J. Pocock, PhD,[i] Christie M. Ballantyne, MD,[j] on Behalf of the REDUCE-IT Investigators*

Article available at http://doi.org/10.1016/j.jacc.2019.02.032
Slides available for download at www.lipid.org

Gli **OMEGA-3**
sono miscele contenenti:
(acidi grassi polinsaturi a catena lunga)

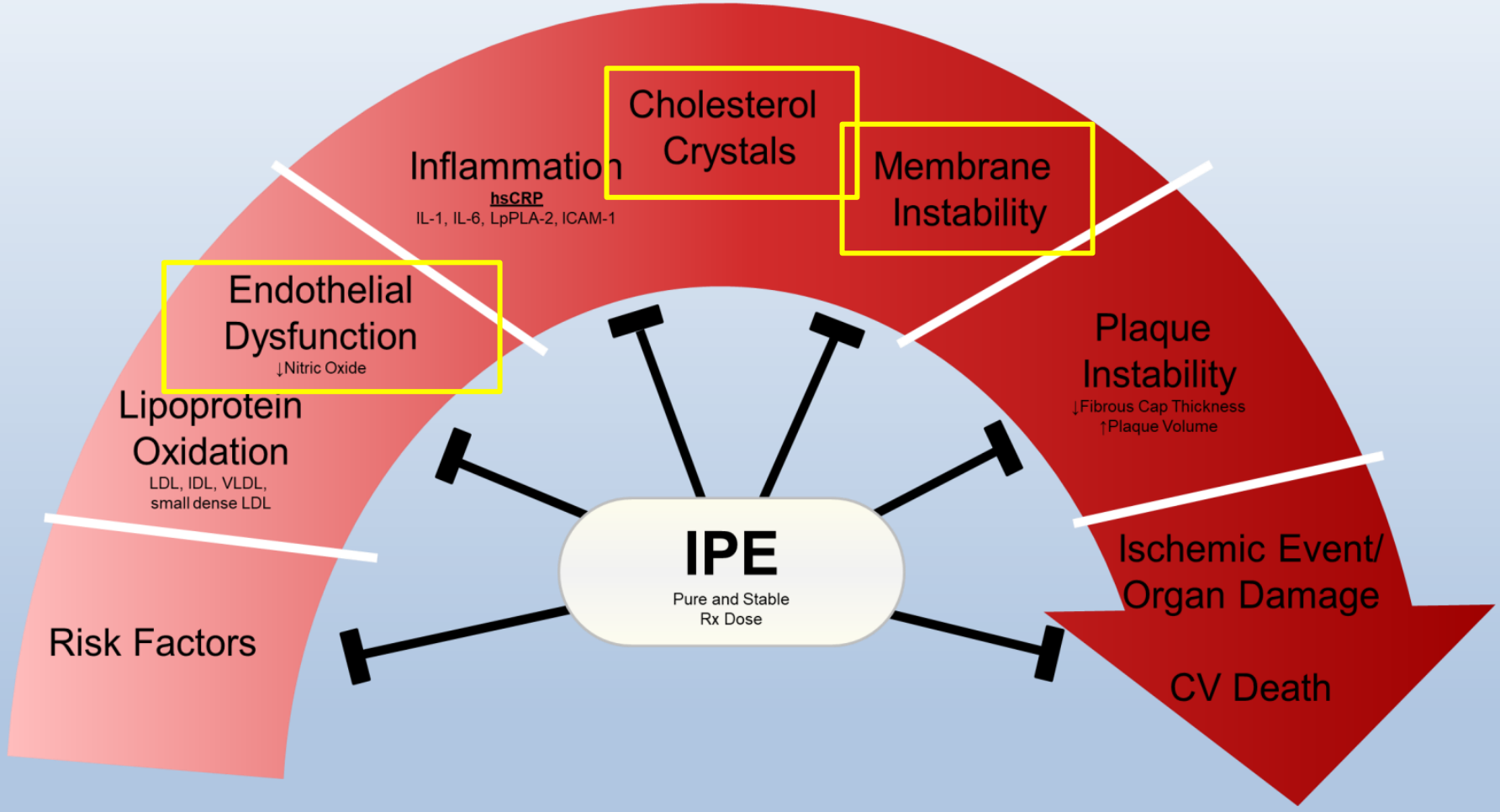
EPA
ACIDO
EICOSAPENTAENOICO

DHA
ACIDO DOCOSAESAENOICO



L'ICOSAPENT ETILE (**IPE**)
è l'estere etilico
dell'**acido eicosapentaenoico**
altamente PURIFICATO.
IPE è stato approvato* come una
NUOVA entità chimica.

IPE Interferes with the CV Disease Continuum at Multiple Points to Reduce Events



Bays HE et al. *Am J Cardiovasc Drugs*. 2013;13; Borow KM, Nelson JR, Mason RP. *Atherosclerosis.* 2015;242; Bhatt DL et al. *N Engl J Med.* 2019;380; Ganda OP et al. *J Am Coll Cardiol*. 2018;72; Jia X et al. *Curr Atheroscler Rep*. 2019;21; Mason RP et al. *Biomed Pharmacother*. 2018;103; Ference BA et al. *JAMA*. 2019;321.

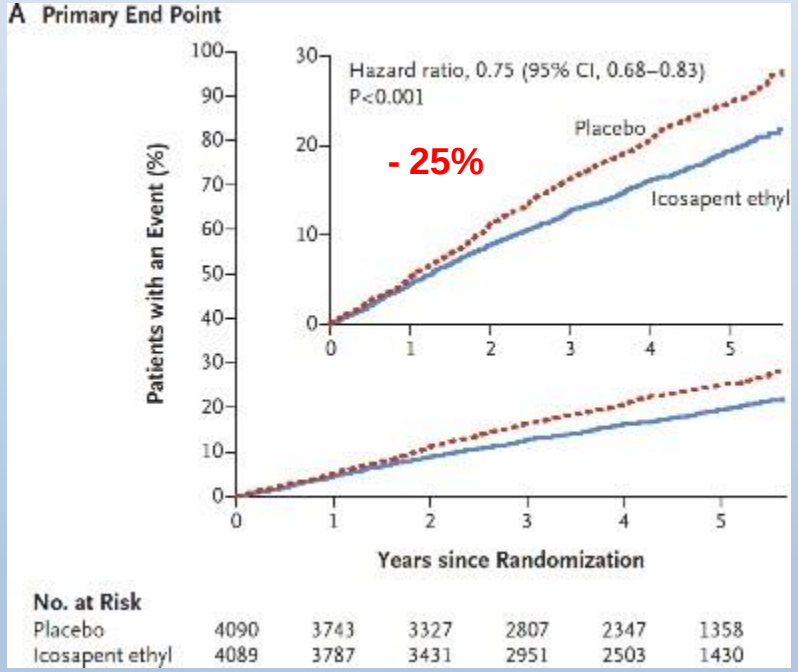
REDUCE-IT: Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

8179 Adulti trattati con statina
Livelli persistentemente elevati di TG
Storia di CVD o DM2 con un FdR aggiuntivo

EPA 2gx2 Placebo

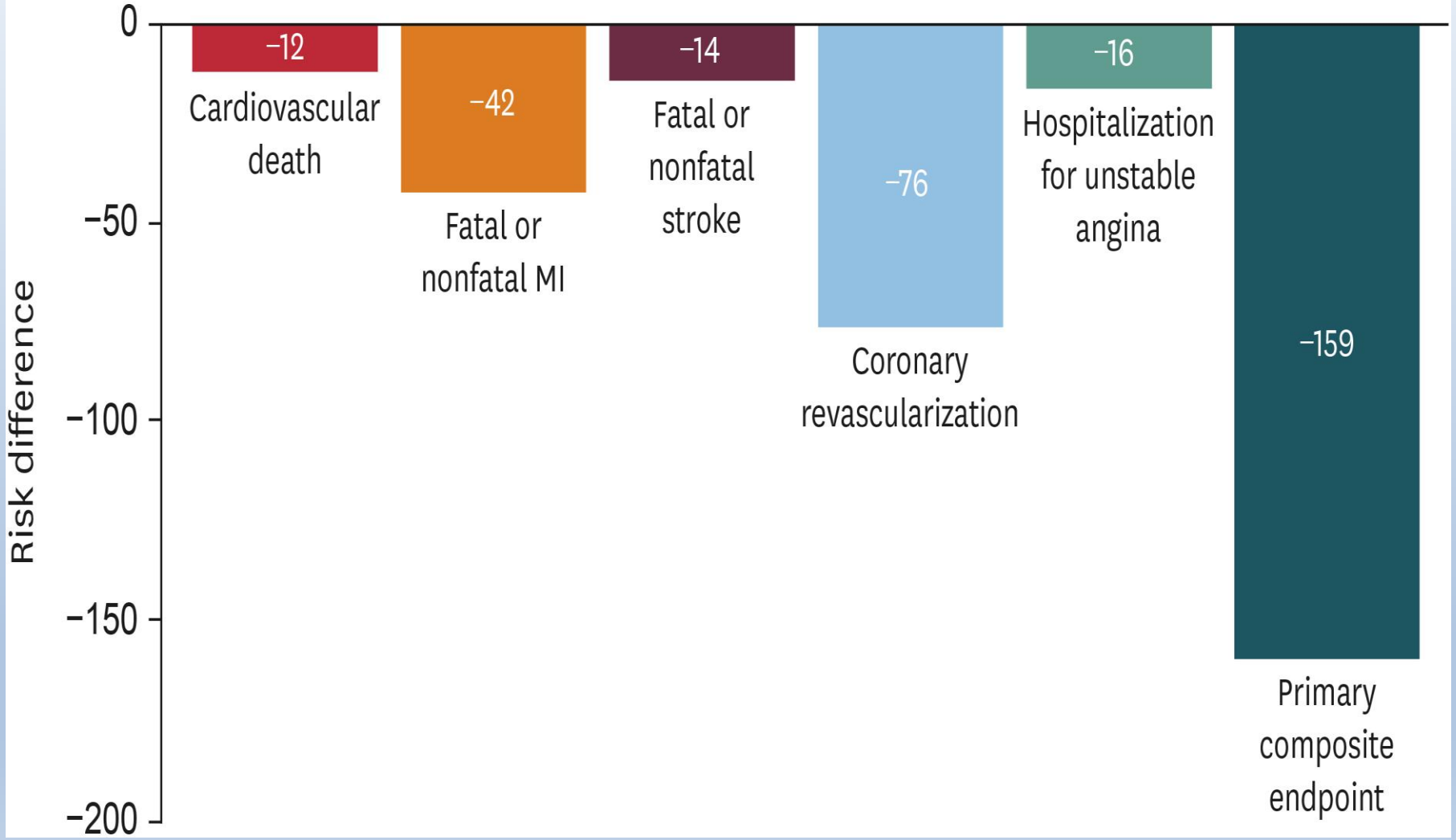
FU= 4.9 yrs

Primary Outcome: CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina



Bhatt DL et al NEJM 2019

For every 1,000 patients treated with icosapent ethyl for 5 years, there are significant reductions in total ischemic events, including deaths from cardiovascular causes.



Conclusions

Compared with placebo, VASCEPA 4g/day significantly reduced important CV events by **25%**, including:

- **20%** reduction in death due to cardiovascular causes
- **31%** reduction in heart attack
- **28%** reduction in stroke

Low rate of adverse effects, including:

- Small but significant increase in atrial fibrillation/flutter
- Non-statistically significant increase in serious bleeding

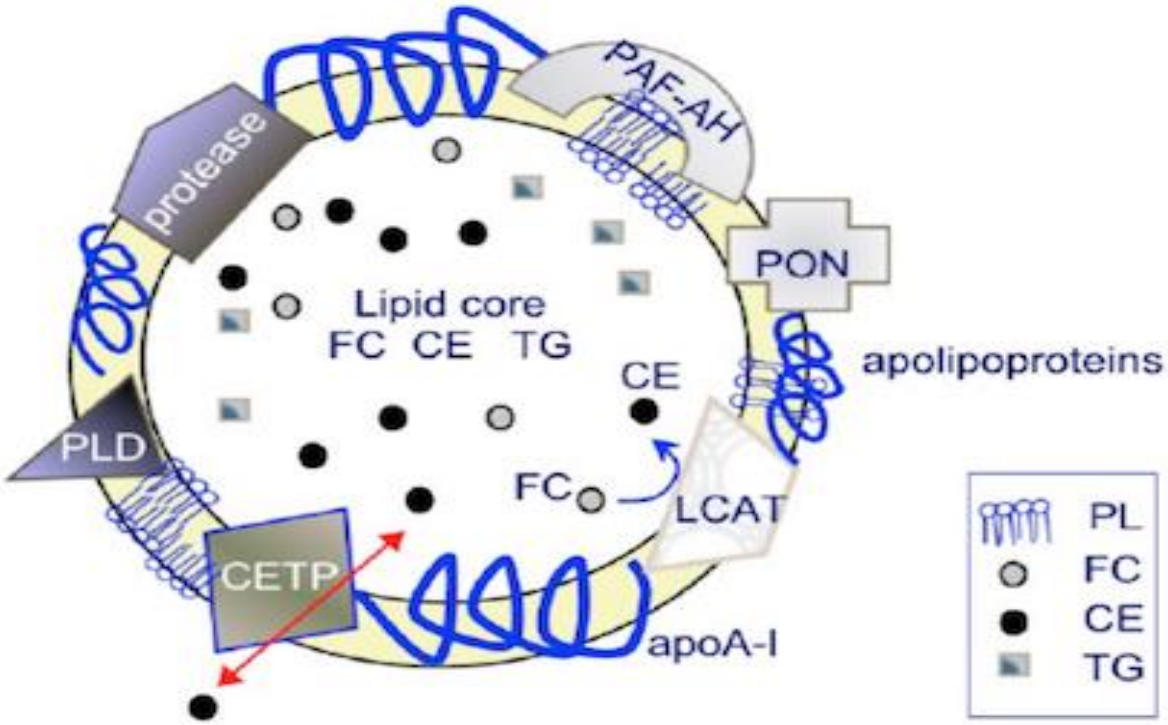
Consistent efficacy across multiple subgroups

Nuovi marcatori di rischio

- Trigliceridi
- **HDL**
- ApoB e non HDL-col
- Lp(a)
- Infiammazione

HDL: UN PLAYMAKER NELLA RIDUZIONE DEL RISCHIO CV

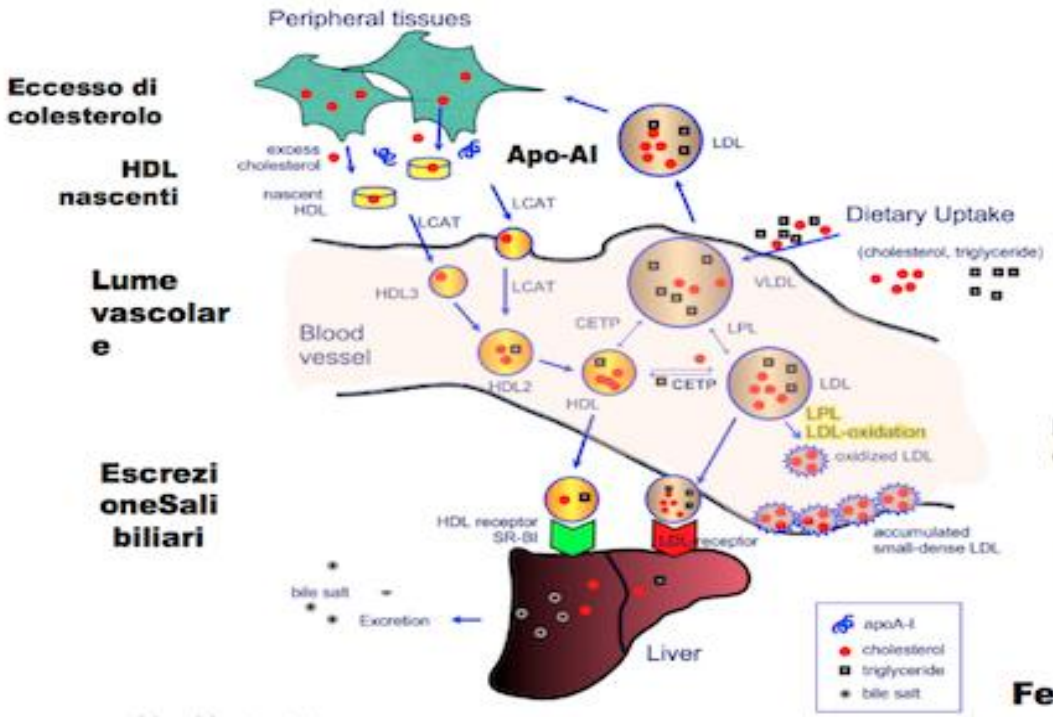
Illustrazione schematica e semplificata di una HDL



HDL: UN PLAYMAKER NELLA RIDUZIONE DEL RISCHIO CV

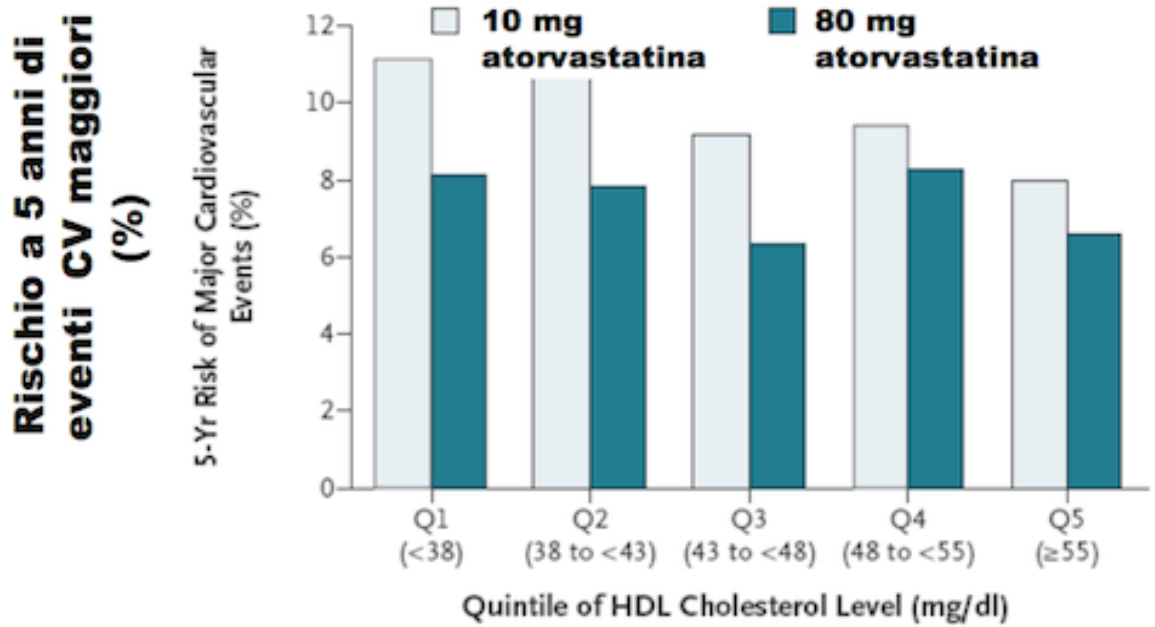
Le HDL nel trasporto inverso del colesterolo

Tessuti periferici



HDL: UN PLAYMAKER NELLA RIDUZIONE DEL RISCHIO CV

Studio TNT: Rischio CV in funzione dei livelli di HDL

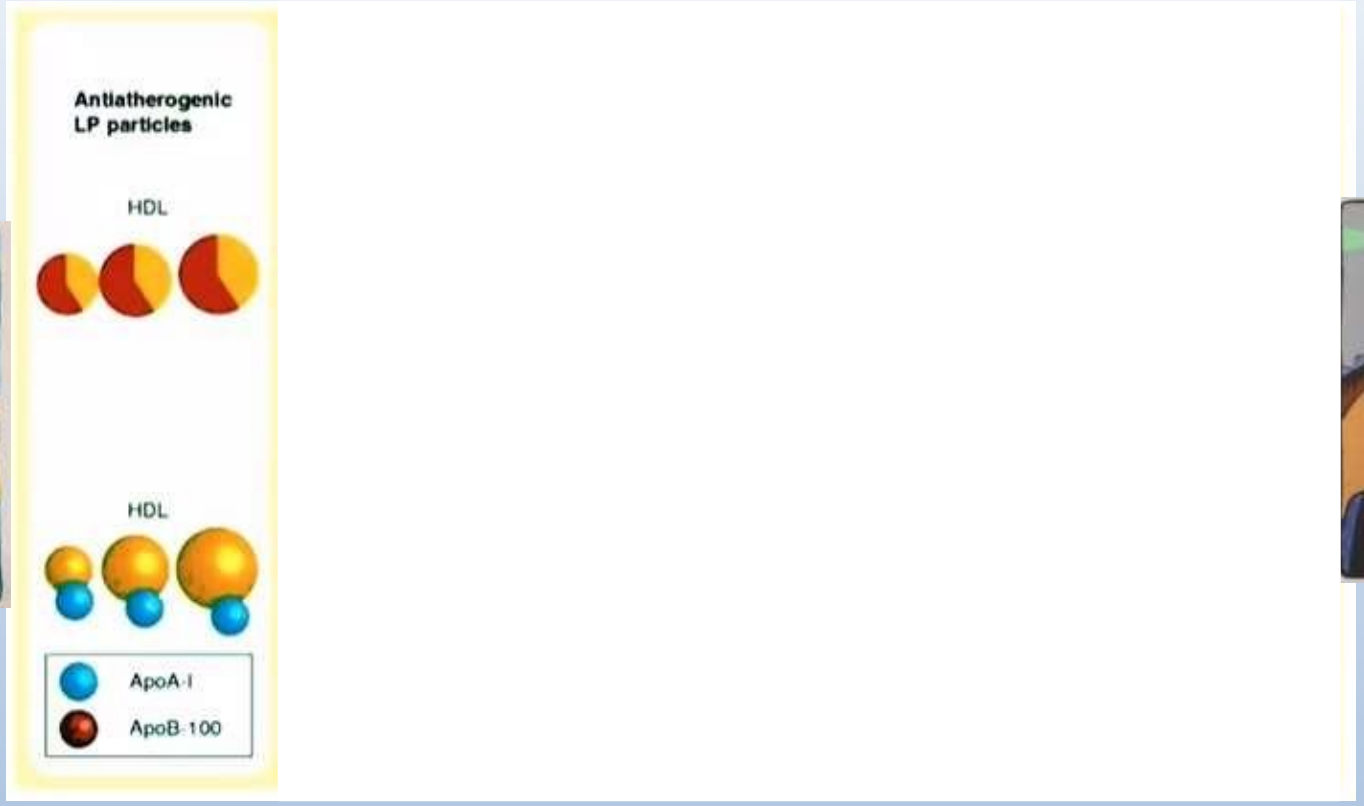


[1]

Nuovi marcatori di rischio

- Trigliceridi
- HDL
- **ApoB e non HDL-col**
- Lp(a)
- Infiammazione

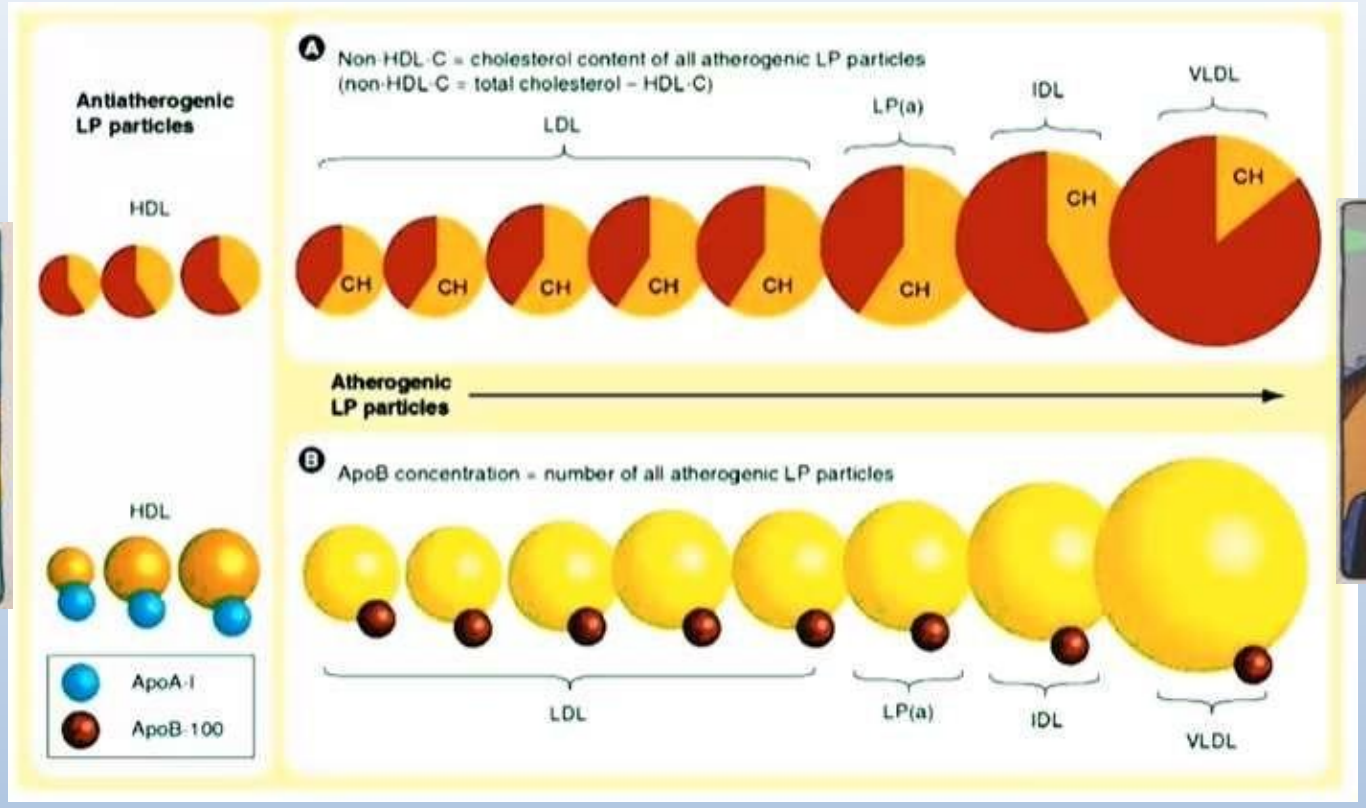
LDL-C measures only a portion of atherogenic particles – although non-HDL or ApoB captures all -



Source: Clin Lipidol © 2011 Future Medicine Ltd

sistent CV Risk Beyond LDL-C: Case examples from 2021 CCS lipid guidelines (2021)

LDL-C measures only a portion of atherogenic particles – although non-HDL or ApoB captures all -



Non-HDL-C = (TC) – (HDL-C)

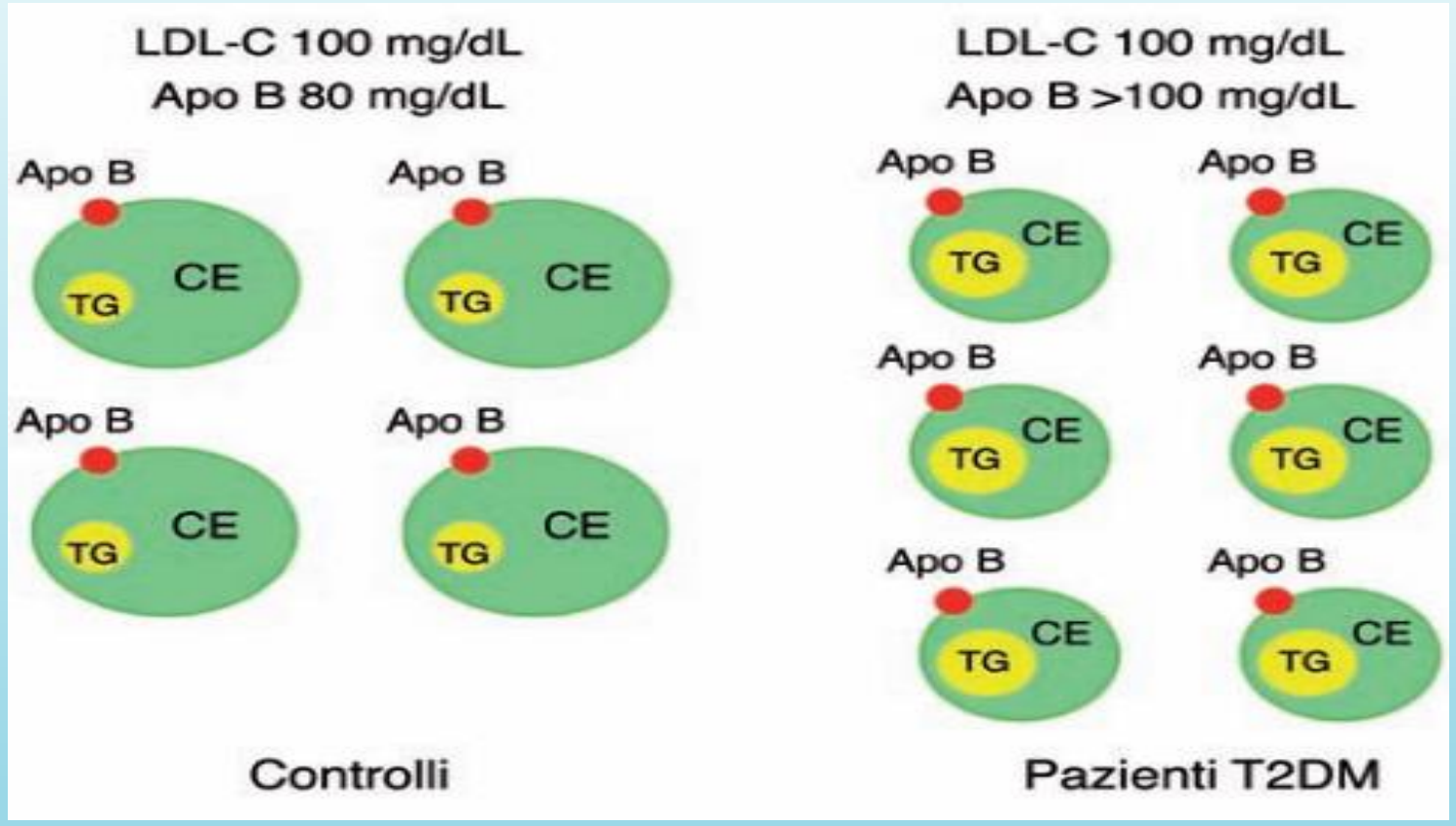
Persistent CV Risk Beyond LDL-C: Case examples from 2021 CCS lipid guidelines (2021)

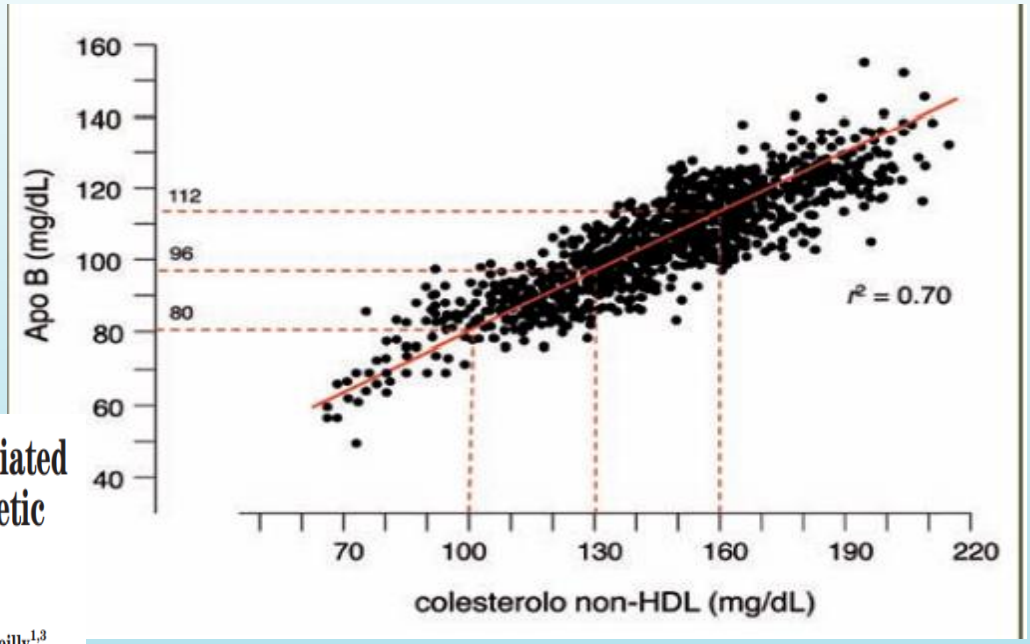
Non-HDL Cholesterol (Non-HDL Chol. = TC – HDL)

- Known predictor of CHD in epidemiology
- Equivalent to total apo B-100, and TC/HDL

- Represents the sum of LDL, Lp(a), IDL, and VLDL: All atherogenic apo B containing lipoproteins

- Lipid Equivalent of “HbA1C”


LDL-C 100 mg/dL
Apo B 80 mg/dL
Apo B
CE
TG
Controlli
LDL-C 100 mg/dL
Apo B >100 mg/dL
Pazienti T2DM



Apolipoprotein B but not LDL Cholesterol Is Associated With Coronary Artery Calcification in Type 2 Diabetic Whites

Seth S. Martin,[1,2] Atif N. Qasim,[1] Nehal N. Mehta,[1] Megan Wolfe,[1] Karen Terembula,[1] Stanley Schwartz,[3] Nayyar Iqbal,[3] Mark Schutta,[3] Roshanak Bagheri,[4] and Muredach P. Reilly[1,3]

Association of plasma levels of apoB and cholesterol parameters with CAC

Variables adjusted for	Type 2 diabetic subjects (n = 611)	Nondiabetic subjects (n = 803)
	*Tobit ratio (95% CI)	*Tobit ratio (95% CI)
ApoB		
Age, sex, medications	*1.36 (1.06–1.75)	1.65 (1.38–1.96)
Age, sex, medications, risk factors	1.37 (1.05–1.79)	1.50 (1.25–1.80)
LDL cholesterol		
Age, sex, medications	1.09 (0.85–1.41)	1.56 (1.30–1.86)
Age, sex, medications, risk factors	1.13 (0.87–1.47)	1.51 (1.27–1.81)
Non-HDL cholesterol		
Age, sex, medications	1.30 (1.01–1.68)	1.68 (1.41–2.00)
Age, sex, medications, risk factors	1.28 (0.99–1.67)	1.54 (1.29–1.85)

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

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

Use of ApoB in risk stratification. ApoB may be a better measure of an individual's exposure to pro atherogenic lipoproteins, and hence its use may be particularly helpful for risk assessment in people where measurement of LDL-C underestimates this burden, such as those with high TG, DM, obesity, or very low LDL-C.

In general, LDL-C, non-HDL-C, and ApoB concentrations are very highly correlated. As a result, under most circumstances, they provide very similar information about ASCVD risk.[45,105–108] However, under certain circumstances—including among people with elevated TG levels, DM, obesity, or very low achieved LDL-C levels—the calculated or directly measured LDL-C level may underestimate both the total concentration of cholesterol carried by LDL and, more importantly, underestimate the total concentration of ApoB-containing lipoproteins, thus underestimating the risk of ASCVD.

In circa il 20% dei casi vi è discordanza tra LDL e ApoB.

- Il target dei livelli di ApoB da raggiungere dovrebbero essere , rispettivamente , inferiore a 65 mg/dl , 80 mg/dl e 100 mg/dl in funzione del rischio CV del paziente (molto alto , alto e moderato)

A Translational Tool to Facilitate Use of Apolipoprotein B for Clinical Decision-Making

J. Cole, J.D. Otvos, A.T. Remaley

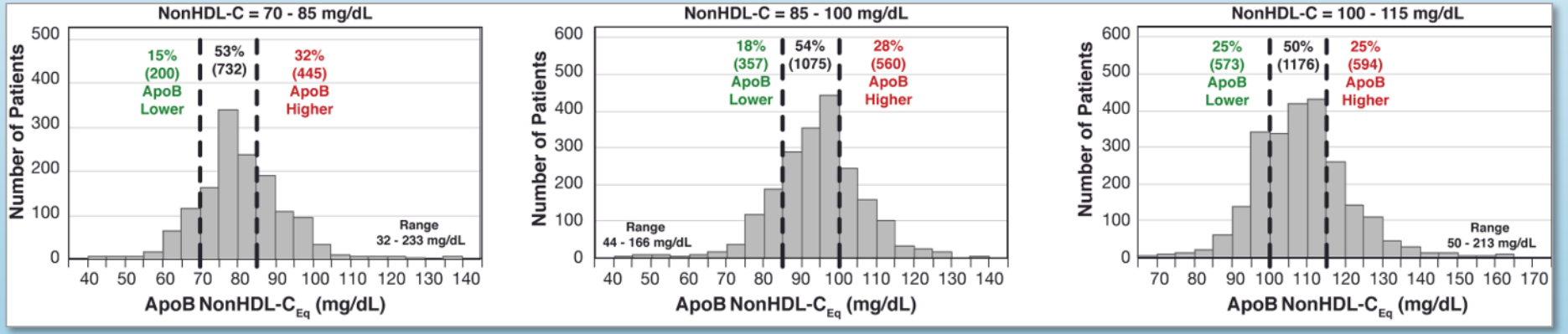
January 2023

https://doi.org/10.1093/clinchem/hvac161

Discordantly higher apoB than LDL-C indicates insulin resistance, small, cholesterol-depleted LDL, increased TG, and low HDL-C

ApoB LDL-C_{Eq} Difference	N (%)	ApoB LDL-C_{Eq} (mg/dL)	LDL-C (mg/dL)	TG (mg/dL)	HDL-C (mg/dL)	LDL Size (nm)	LP-IR (0-100)
ApoB LDL-C_{Eq} Higher than LDL-C							
>30 mg/dL	404 (3.0)	139 [42]	96 [38]	357 [176]	39 [22]	20.0 [0.6]	73 [19]
20–30 mg/dL	443 (3.3)	117 [36]	92 [36]	232 [99]	43 [17]	20.2 [0.5]	66 [19]
10–20 mg/dL	1321 (9.7)	106 [36]	92 [36]	176 [80]	45 [16]	20.3 [0.5]	59 [19]
5-10 mg/dL	1312 (9.7)	95 [34]	88 [34]	144 [64]	49 [17]	20.4 [0.5]	54 [19]
1–5 mg/dL	1422 (10.5)	95 [33]	92 [33]	128 [56]	51 [16]	20.6 [0.4]	49 [19]
ApoB LDL-C_{Eq} Equal to LDL-C							
<1 mg/dL	739 (5.4)	96 [35]	96 [35]	120 [52]	53 [17]	20.7 [0.4]	47 [19]
ApoB LDL-C_{Eq} Lower than LDL-C							
1–5 mg/dL	1690 (12.5)	94 [33]	97 [33]	110 [47]	55 [17]	20.7 [0.4]	42 [19]
5– 10 mg/dL	2027 (14.9)	96 [32]	103 [32]	103 [43]	57 [17]	20.9 [0.4]	38 [19]
10–20 mg/dL	2790 (20.6)	102 [32]	117 [32]	99 [40]	61 [17]	21.0 [0.4]	34 [19]
20–30 mg/dL	1059 (7.8)	114 [33]	138 [34]	96 [42]	65 [17]	21.2 [0.3]	28 [17]
> 30 mg/dL	360 (2.6)	130 [47]	168 [50]	100 [49]	69 [18]	21.4 [0.4]	25 [20]

ApoB non-HDL-C_{Eq} distributions within subgroups of non-HDL-C concentration.



- Non-HDL-C is only slightly less discordant with apoB than LDL-C.
- As it does not indicate particle number and size, it is similar to LDL-C in its limitations as a marker of ASCVD risk.

Conclusions

- **Both LDL-C and non-HDL-C are frequently discordant with apoB, which is the superior marker of residual ASCVD risk.**

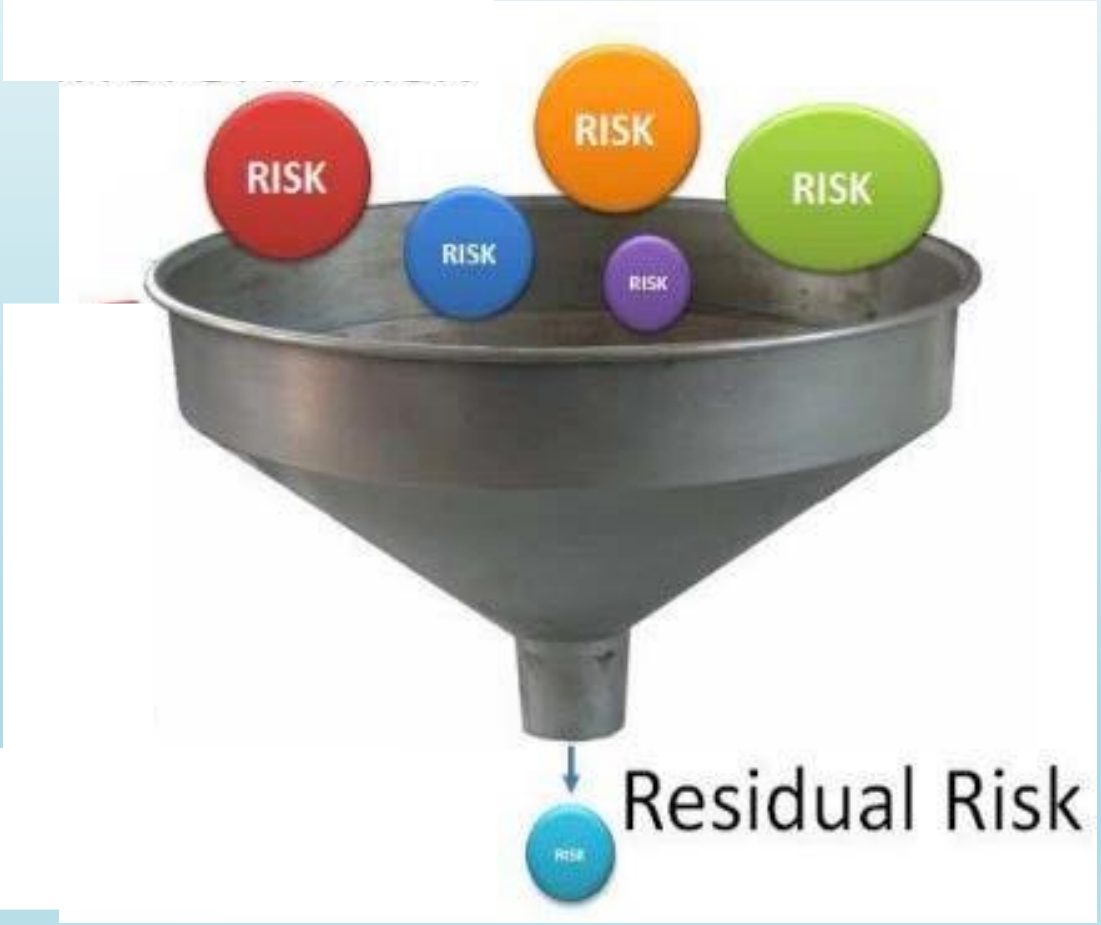
- **When making patient-centered treatment decisions, the most accurate marker of individual risk is desired.**

- **A major impediment to changing over to the use of apoB for this purpose is a lack of guideline-recommended apoB treatment targets.**

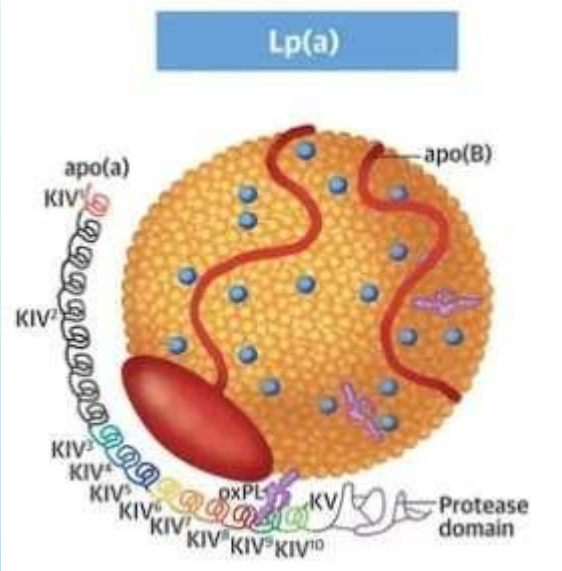
- **Clinical laboratories can effect an immediate positive impact for patients by reporting apoB LDL-C_{Eq} values where apoB testing is available.**

Nuovi marcatori di rischio

- Trigliceridi
- HDL
- ApoB e non HDL-col
- **Lp(a)**
- **Infiammazione**



What is Lipoprotein(a)?

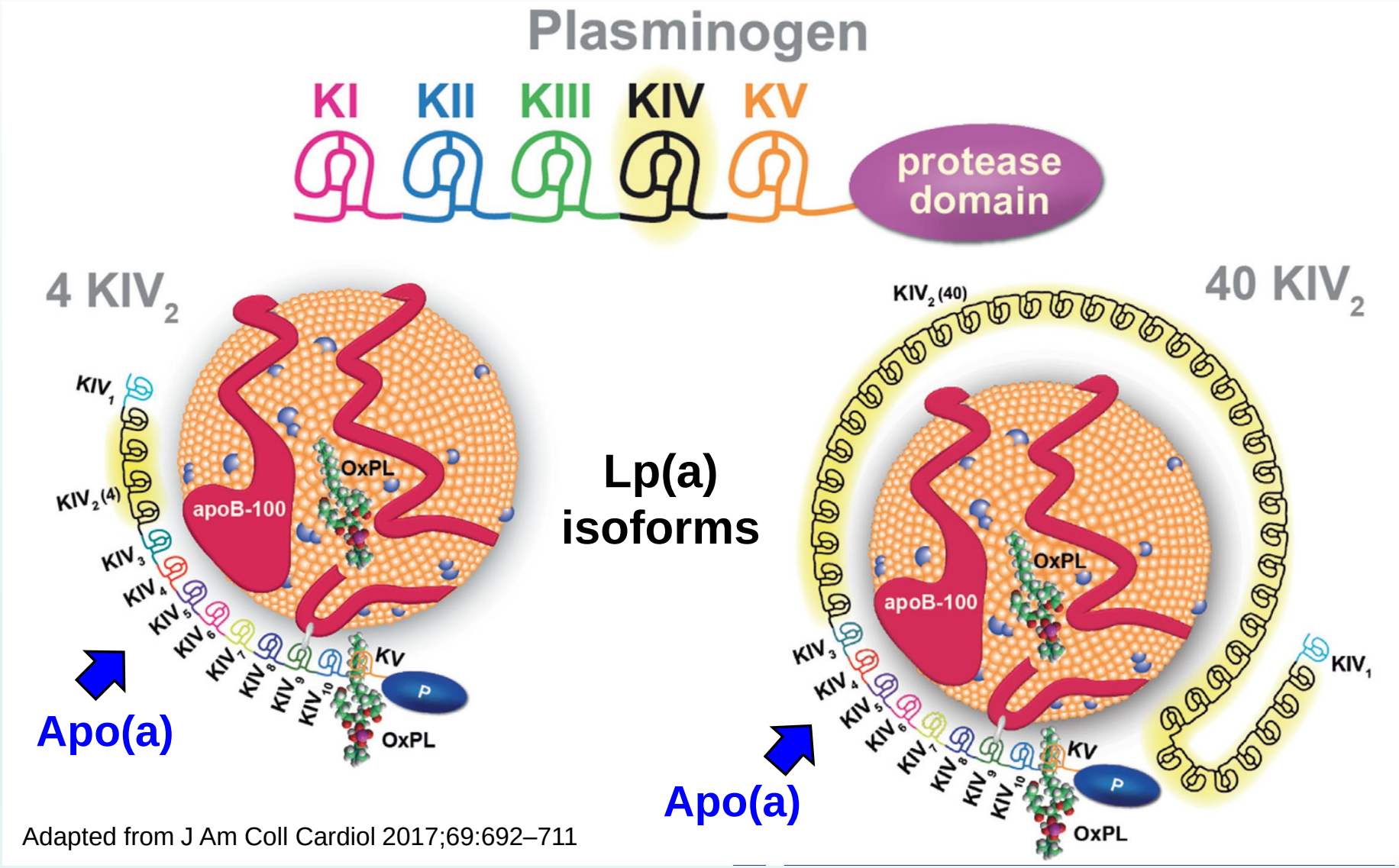


Lp(a) = LDL-C + apo(a)

- A "bad" LDL with a "sticky" tail → highly atherogenic
  - Poorly correlated with LDL-C
- Lp(a) levels are almost entirely genetically determined (levels are determined at birth and remain stable over lifetime).
  - Higher in South Asians, Latin Americans and African Americans
- Independent marker of CV risk (independent of other lipids and risk factors)
  - The higher the Lp(a), the higher the risk for ASCVD and recurrent events
- Most common genetic dyslipidemia
  - Estimated 6 million Canadians have high Lp(a) defined as >50 mg/dL

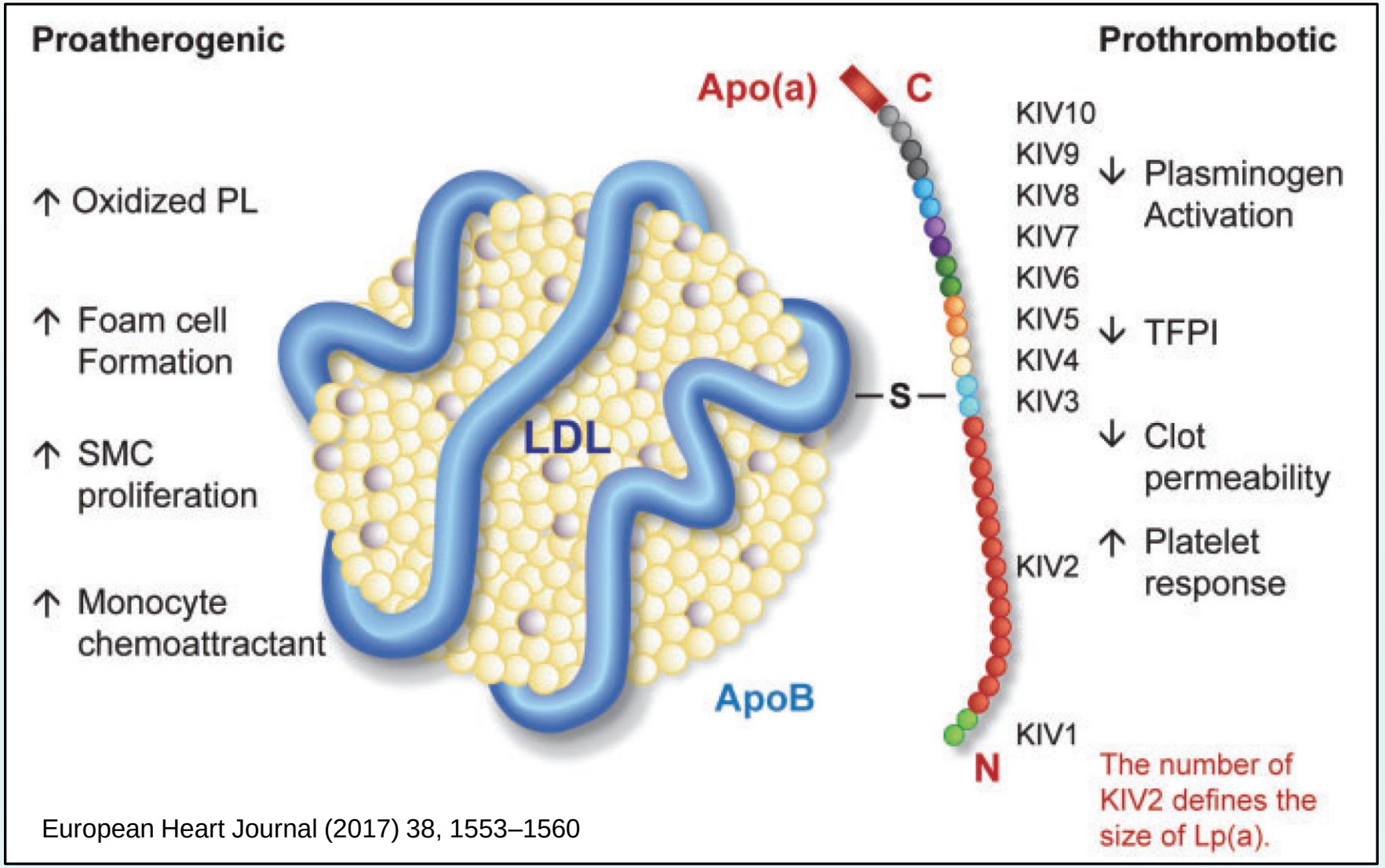
t CV Risk Beyond LDL-C: Case examples from 2021 CCS lipid guidelines (2021)

Lipoprotein(a) and Plasminogen Structure



Adapted from J Am Coll Cardiol 2017;69:692–711

Lp(a) Components: Dual Mechanisms Of Harm



European Heart Journal (2017) 38, 1553–1560

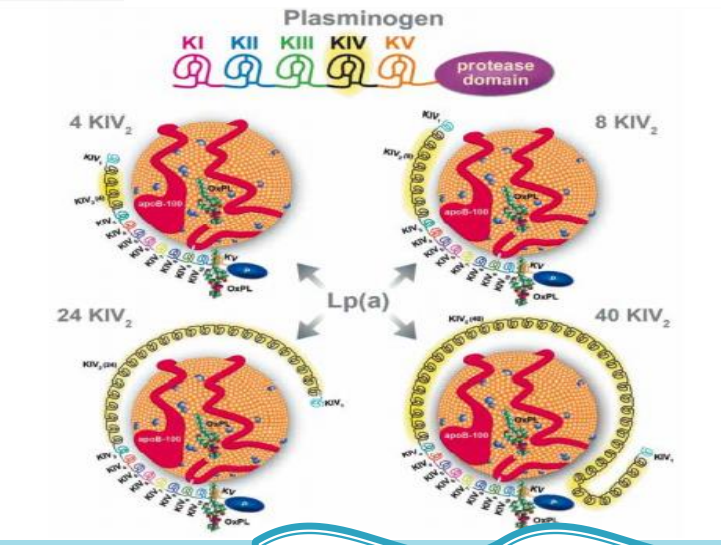
MARCATORI DI MALATTIA

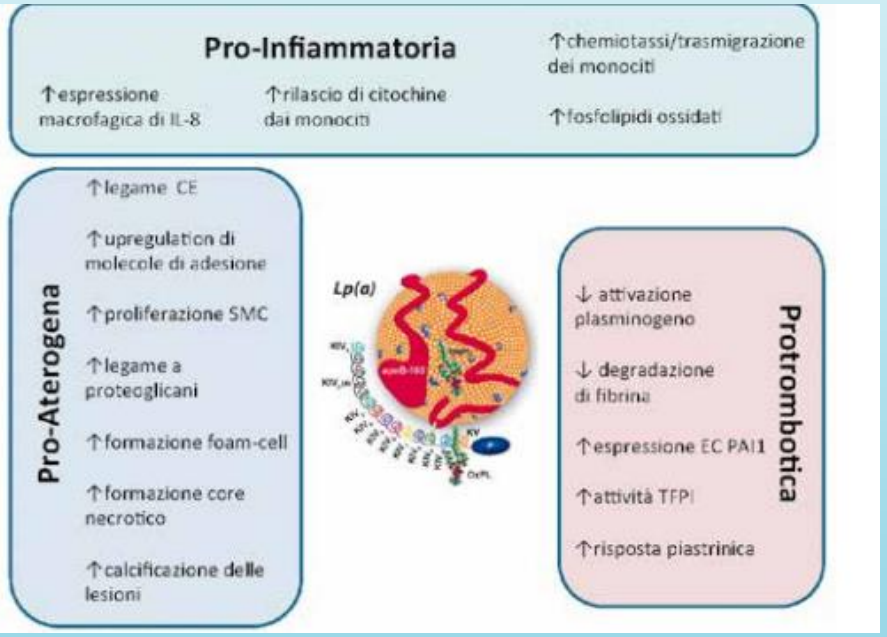
LIPOPROTEINA(a) E ATEROSCLEROSI: È TEMPO DI TRATTARE!

Lipoprotein(a) and Atherosclerosis: it is high time to treat!

MARIA GRAZIA ZENTI, ANNA ALTOMARI, ENZO BONORA

Endocrinologia, Diabetologia e Metabolismo, Dipartimento di Medicina, Università e Azienda Ospedaliera Universitaria Integrata di Verona





Molteplici isoforme, attività peculiare.

Giornale Italiano dell'Arteriosclerosi 2017; 8 (3): 50-61

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

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

Certain individuals declare themselves to be at high or very high CVD risk without needing risk scoring, and all risk factors require immediate attention. This is true for patients with documented CVD, older individuals with long-standing DM, familial hypercholesterolaemia, chronic kidney disease, carotid or femoral plaques, coronary artery calcium score >100, or extreme Lp(a) elevation.

Livelli estremi di Lp(a) modifcano la classe di rischio del paziente

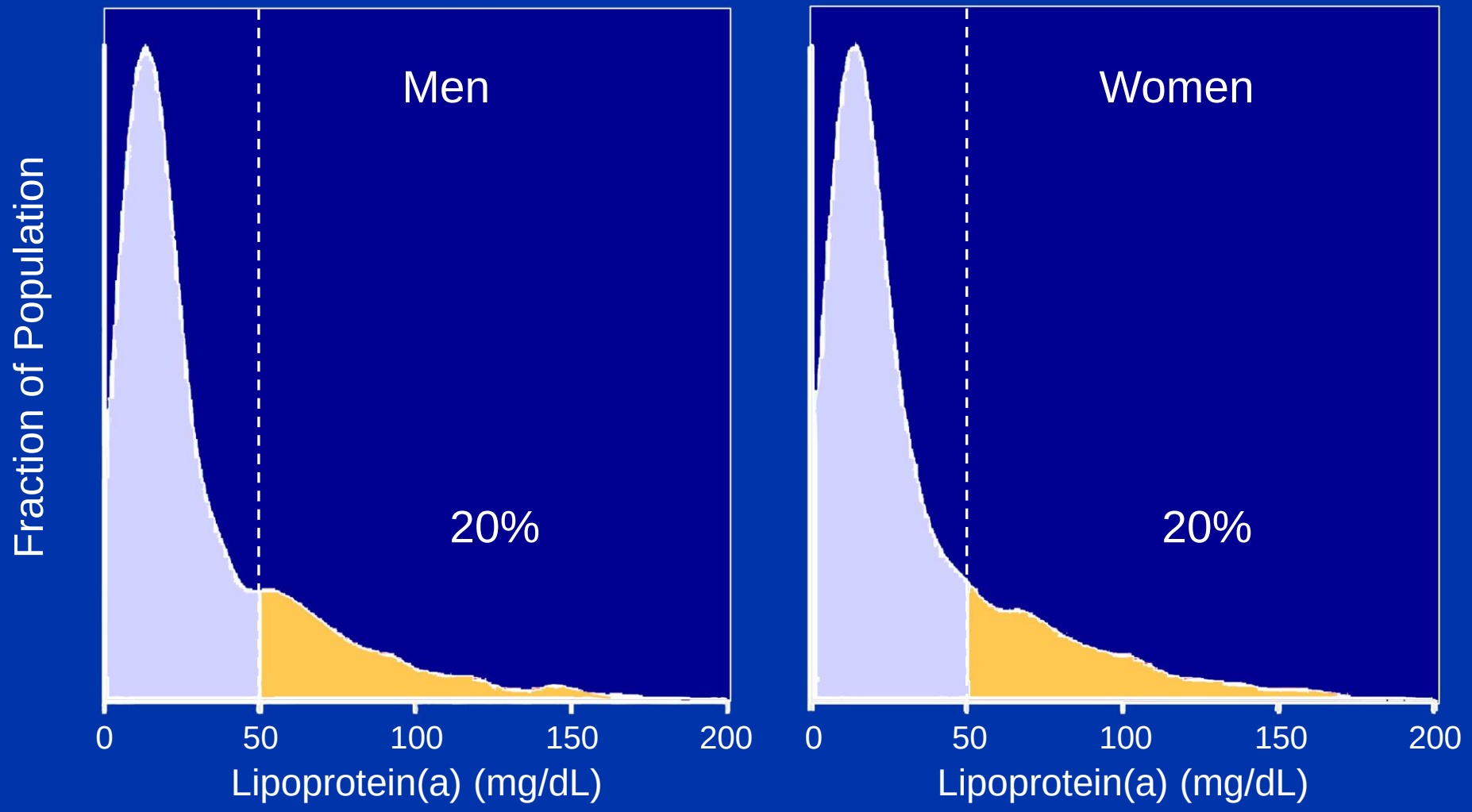
Lipid analyses for CVD risk estimation

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.

Particolarmente significativi i livelli oltre 180 mg/dl

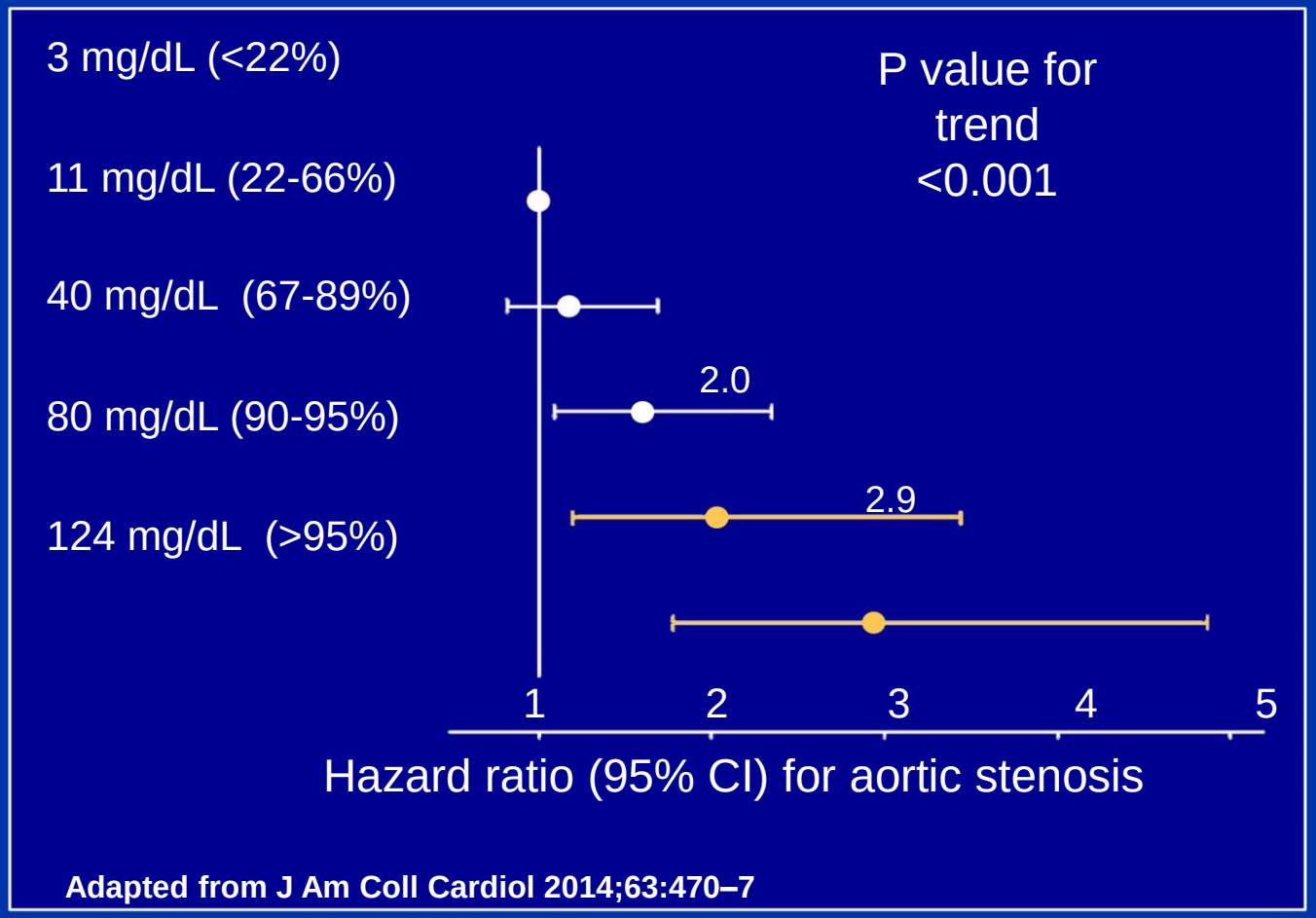
What are Normal and Abnormal Levels of Lipoprotein(a)?

Distribution of Lp(a) in the General Population



Nordestgaard B G et al. Eur Heart J 2010;31:2844-2853

Lipoprotein(a) Levels and Risk of Aortic Stenosis



Adapted from J Am Coll Cardiol 2014;63:470–7

How Does Lipoprotein(a) Contribute to Atherosclerosis?

Lp(a) level and atherosclerotic cardiovascular disease risk

- **INTERHEART Study** of risk factors for first MI: Lp(a) > 50 mg/dL (>500 mg/L) associated with 1.5-fold increased risk of MI, independent of other CVD risk factors including DM, smoking, high blood pressure
- **Copenhagen Heart Study:** Lp(a) between 30-76 mg/dL (300-760 mg/L) had 1.7-fold higher and with level > 117 mg/dL (1170 mg/L) 2.7-fold higher hazard ratio for myocardial infarction
- Higher Lp(a) carries even higher burden of CVD risk in South Asian and Latin American individuals
- With very high levels (>100 mg/L) CVD event rate is similar to individuals with heterozygous FH, a condition for which family screening is recommended

Guidelines Recommendation

RECOMMENDATION

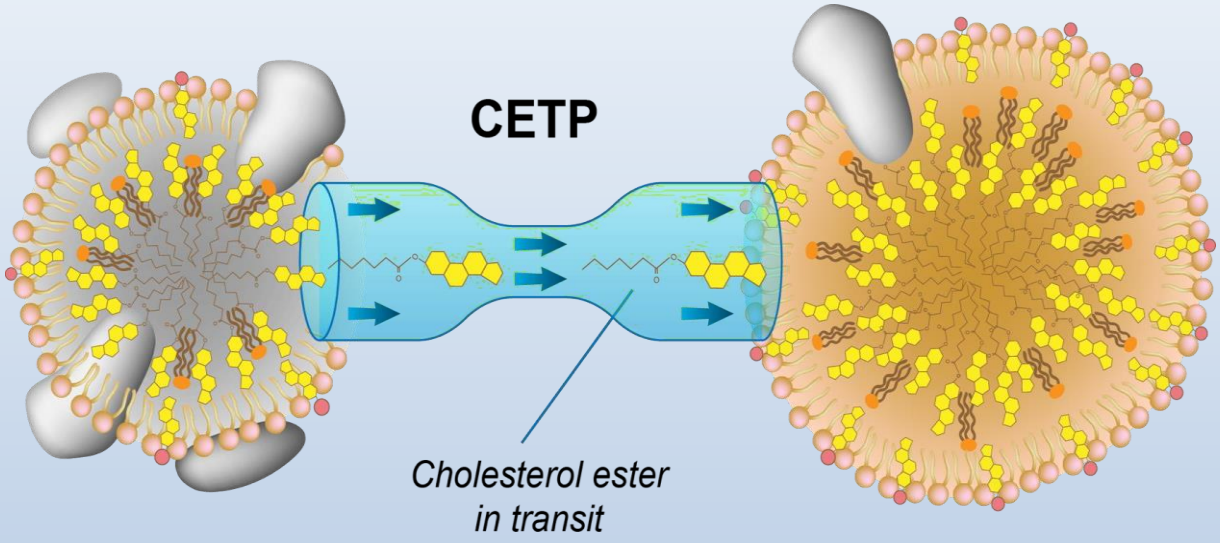
5. We recommend measuring Lp(a) level once in a person's lifetime as a part of the initial lipid screening (Strong Recommendation; High-Quality Evidence).
6. For all patients in the setting of primary prevention with a Lp(a) $\geq$ 50 mg/dL (or $\geq$ 100 nmol/L), we recommend earlier and more intensive health behaviour modification counselling and management of other ASCVD risk factors (Strong Recommendation; Expert Consensus).

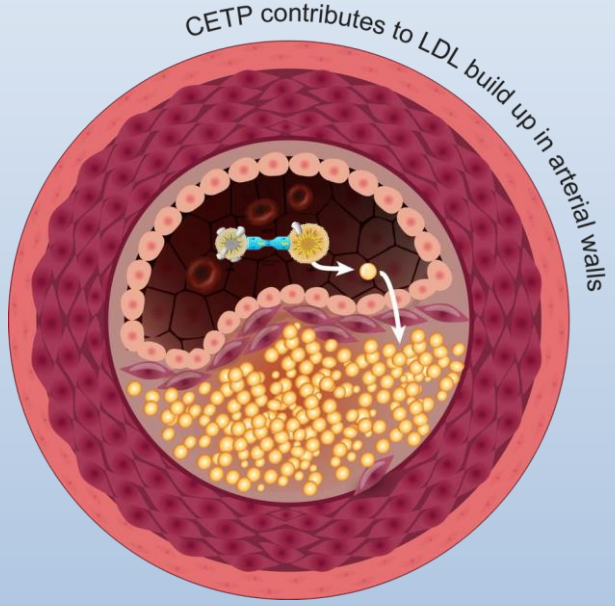
Pearson GJ *et al.*, *Can J Cardiol* 2021;37:1129-1150

Current and emerging Lp(a) lowering therapies

- **PCSK9-inhibition**
- Lipoprotein apheresis
- **CETP-inhibition**
- apo(a)- gal-nac antisense
- apo(a)-siRNA

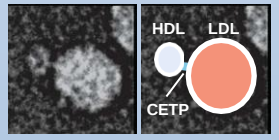
CETP transfers cholesterol esters from HDL to LDL





Cholesteryl ester transfer protein (CETP) promotes the transfer of cholesterol esters from ***anti- atherogenic HDLs*** to ***pro-atherogenic LDLs***

- CETP activity increases circulating LDL-C levels



Electron micrograph of HDL, LDL, CETP

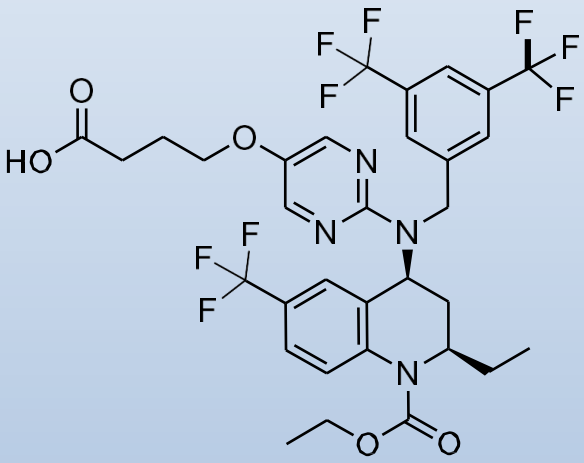
Electron micrograph (key)

- **Note: Figures adapted from Meng Zhang, at al., Assessing the mechanisms of cholesteryl ester transfer protein inhibitors, Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids, 1862(12), 2017, 1606-1617, and from Lei D, et al., Insights into the Tunnel Mechanism of Cholesteryl Ester Transfer Protein through All-atom Molecular Dynamics Simulations, J Biol Chem., 2291(27), 2016, 14034-14044.**

Summary of previous CETP inhibitors

Drug	CETP inhibition	LDL-C reduction	HDL-C increase	ApoB	Significant trials	Results	Other
Torcetrapib	≥80%	-20%	65%	-16%	ILLUMINATE (2006)	Terminated due to increased death and CV events	
Dalcetrapib	37%	-7%	26%	-2%	Dal-OUTCOMES (2012)	Terminated for futility	Decrease in onset of DM
Evacetrapib	83%	-26%	98%	16%	ACCELERATE (2017)	Terminated for futility	Decrease in onset of DM Lp(a) -32% (100mg)
Anacetrapib	90%	-41% (-17%)*	104%	-18%	REVEAL (2017, 2021)	MACE -9% MACE -20% in 2.3 yr f/u	Decrease in onset of DM Lp(a) -25% 4+ year half-life

Obicetrapib



- Obicetrapib is a selective CETP inhibitor undergoing clinical development for reducing both LDL-C and the incidence of major adverse cardiovascular events
- **At equipotent dosages obicetrapib reduces CETP activity to a greater extent than both anacetrapib and evacetrapib resulting in greater efficacy for LDL-C lowering**
- The potency of obicetrapib comes from a series of crystallography experiments that have shown that CETP inhibitors located at the narrow N-terminal neck of the hydrophobic tunnel of CETP are able to restrict the lipid flow through this tunnel
- By introducing hydrophilic structures into obicetrapib, it is the most polar of all CETP inhibitors and has a LogP of 4.9 versus 9.2 for anacetrapib and 7.9 for evacetrapib (less lipophilic)

- Nicholls, SJ et al., Lipid lowering effects of the CETP inhibitor obicetrapib in combination with high-intensity statins: a randomized phase 2 trial, Nature Medicine,11 August 2022, 10.1038/s41591-022-01936-7, https://www.nature.com/articles/s41591-022-01936-7

Nuovi marcatori di rischio

- Trigliceridi
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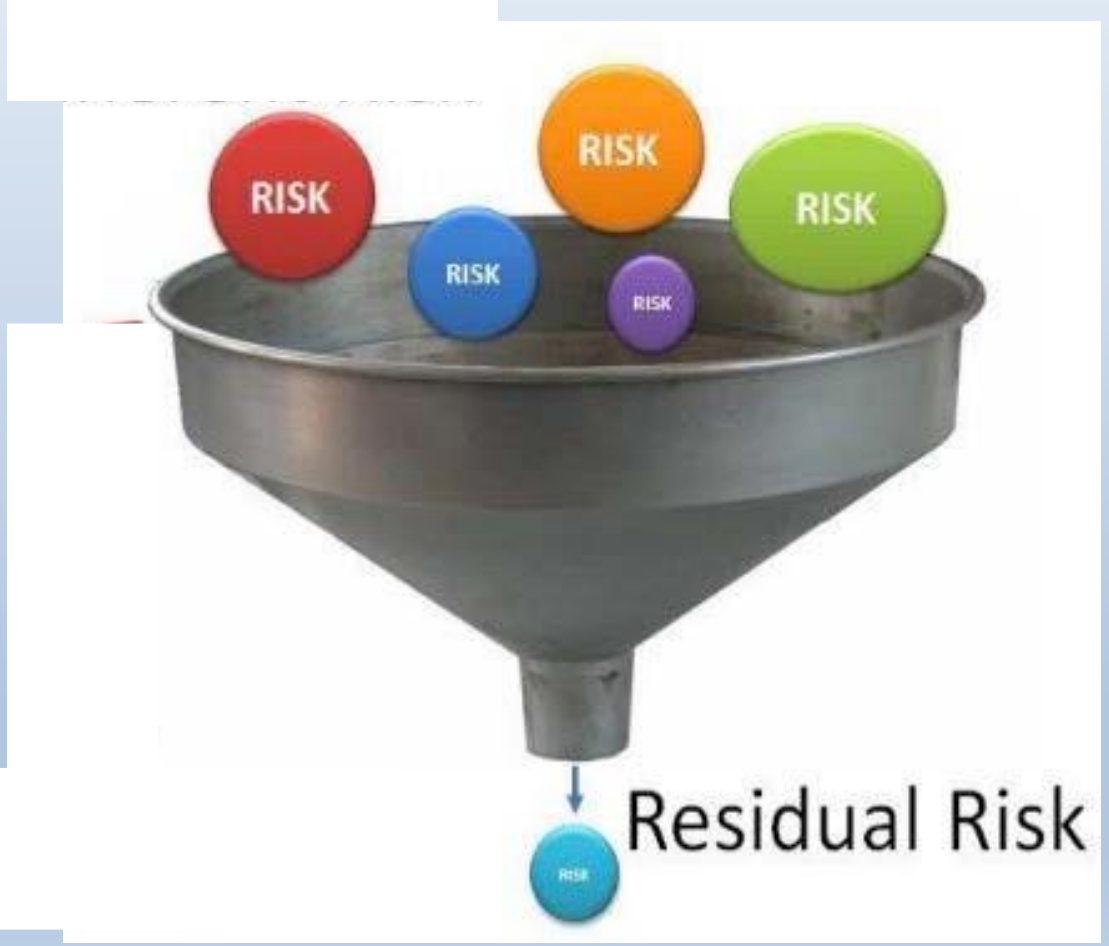
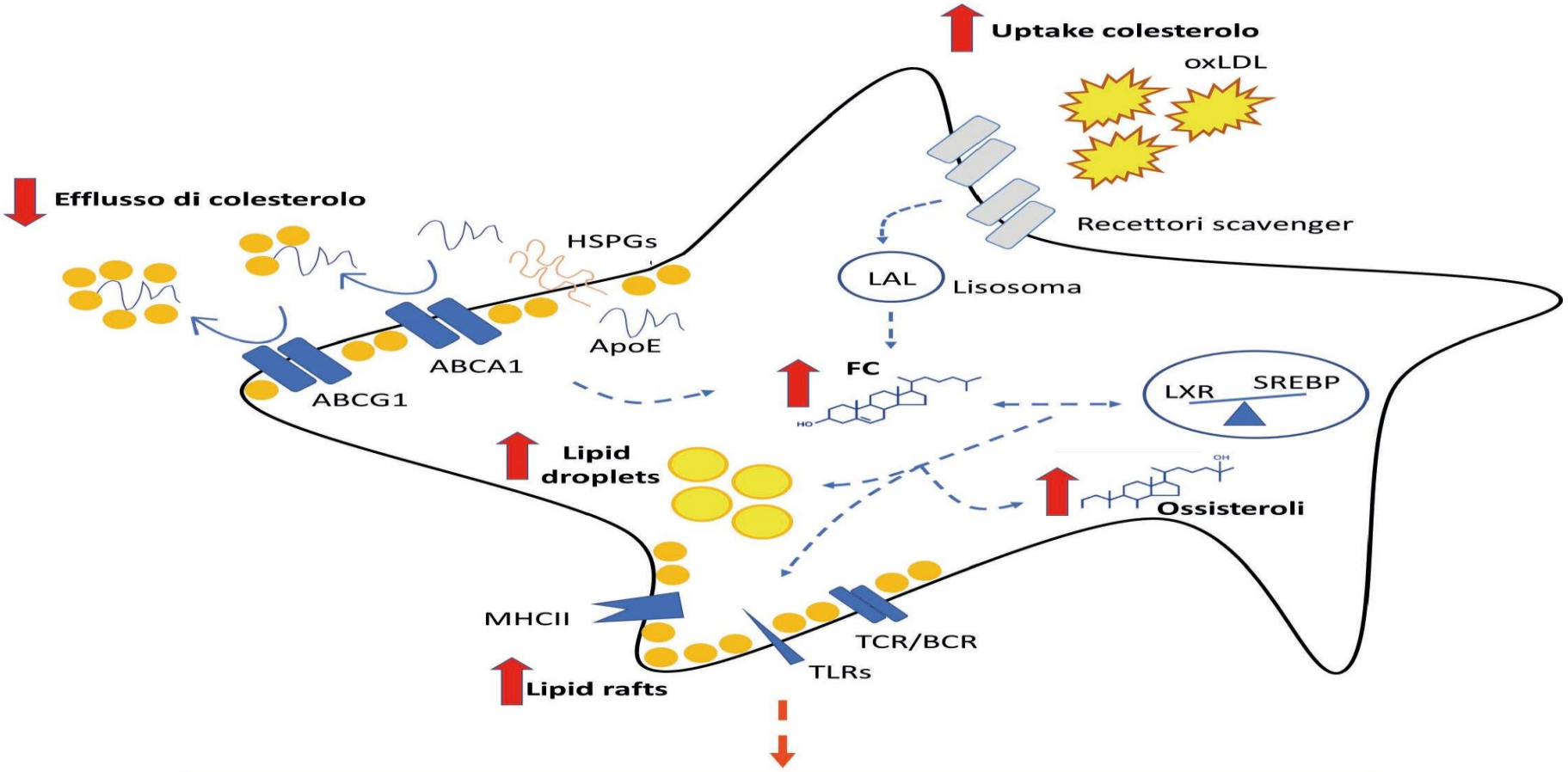




Aumentata risposta immunitaria: Attivazione dell'inflammasoma, produzione di citochine pro-infiammatorie incontrollata proliferazione

Promozione delle malattie a carattere infiammatorio ATEROSCLEROSI

«Inflammation : the next target in atherosclerotic cardiovascular disease care ?»

Paul Ridker
Birmingham e Women’S Hospital Boston
USA

ESC Congress 2023

E’ ormai accettata la definizione di **Rischio infiammatorio residuo** dove Hs-CRP e altre proteine della fase acuta siano dei biomarcatori e le interleuchine (IL-1 b , IL-6 , IL-7) utilizzate come target

Il Canone di Medicina Interna dell'Imperatore Giallo

What's Hot in CVD Prevention?

Lipid Management!!

THANK YOU!

Role of Lipoprotein(a) in Coronary Disease: An Emerging Novel Target

Steven E. Nissen MD MACC
Chairman, Department of Cardiovascular Medicine
Cleveland Clinic

Role of Lipoprotein(a) in Coronary Disease: An Emerging Novel Target

Disclosure

Consulting: Many pharmaceutical companies

Clinical Trials: Abbvie**,** Amgen, AstraZeneca, Eli Lilly, Novartis, Novo Nordisk, The Medicines Company, Cerenis, Orexigen, Takeda and Pfizer.

Companies are directed to pay any honoraria, speaking or consulting fees directly to charity so that neither income nor tax deduction is received.

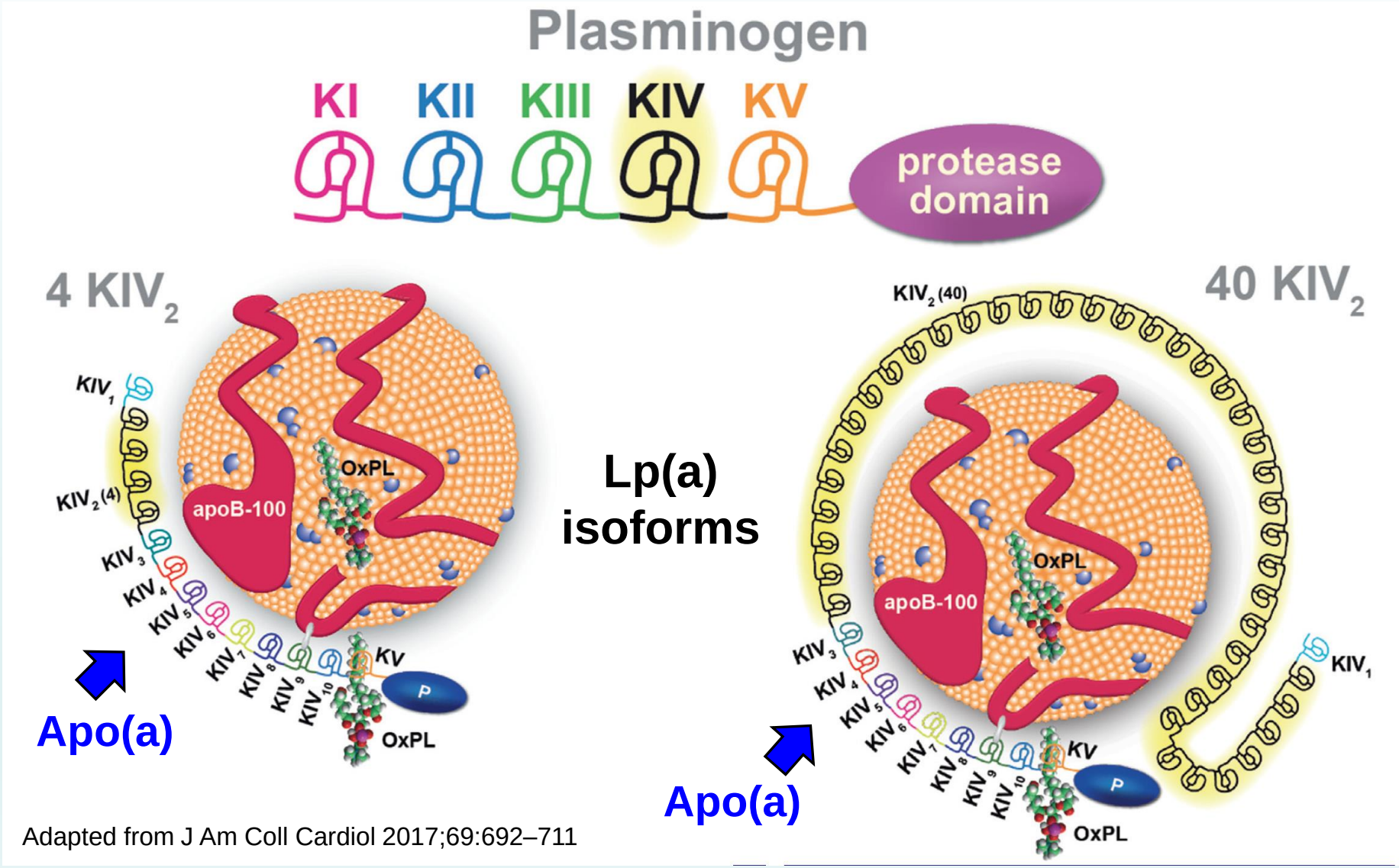
Acknowledgements

Some slides adapted from excellent review
by Dr. Sam Tsimikas
(J Am Coll Cardiol 2017;69:692–711)

What is Lipoprotein(a)?

- An LDL-like particle consisting of apo B covalently bound to apo(a) via a disulfide bond.
- May have evolved from the plasminogen gene, the proenzyme converted to the fibrinolytic enzyme plasmin by activators such as tPA.
- Lp(a) has some similarities to LDL, but is more atherogenic, promoting both inflammation and thrombosis.
- Lp(a) has many isoforms (>40) based on Kringle IV repeats with all isoforms contributing to atherogenic risk.

Lipoprotein(a) and Plasminogen Structure



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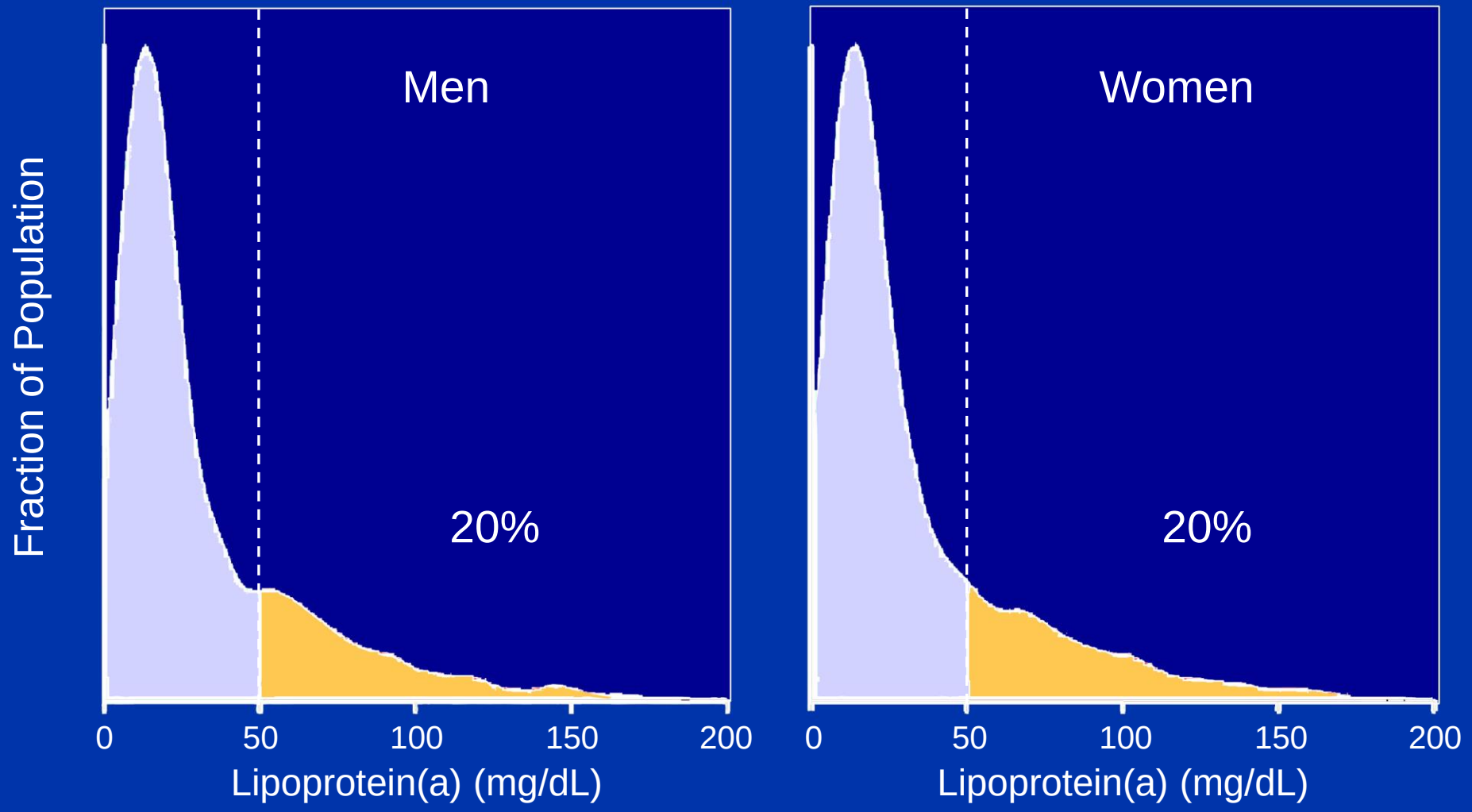
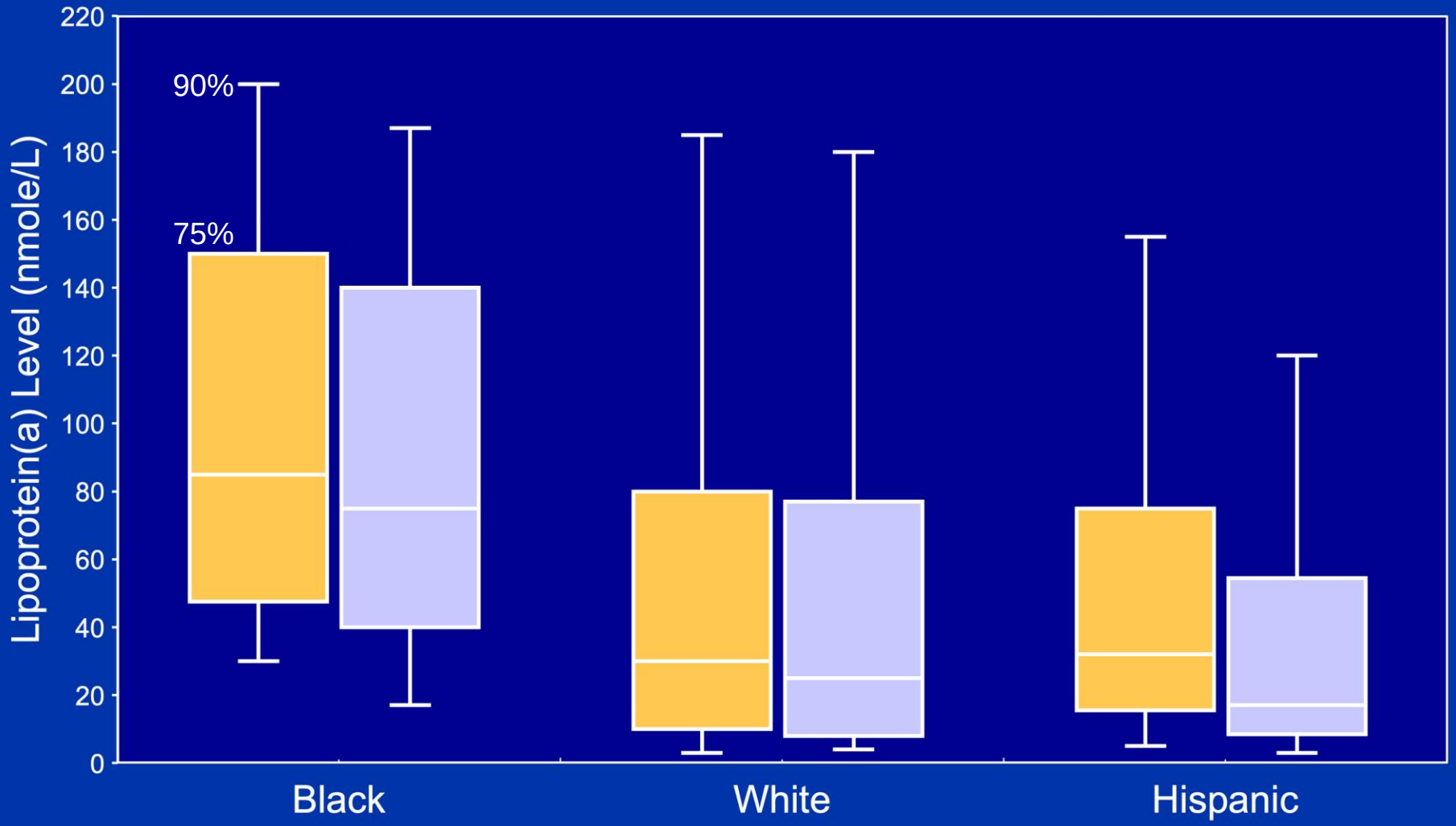
What are Normal and Abnormal Levels of Lipoprotein(a)?

Distribution of Lp(a) in the General Population



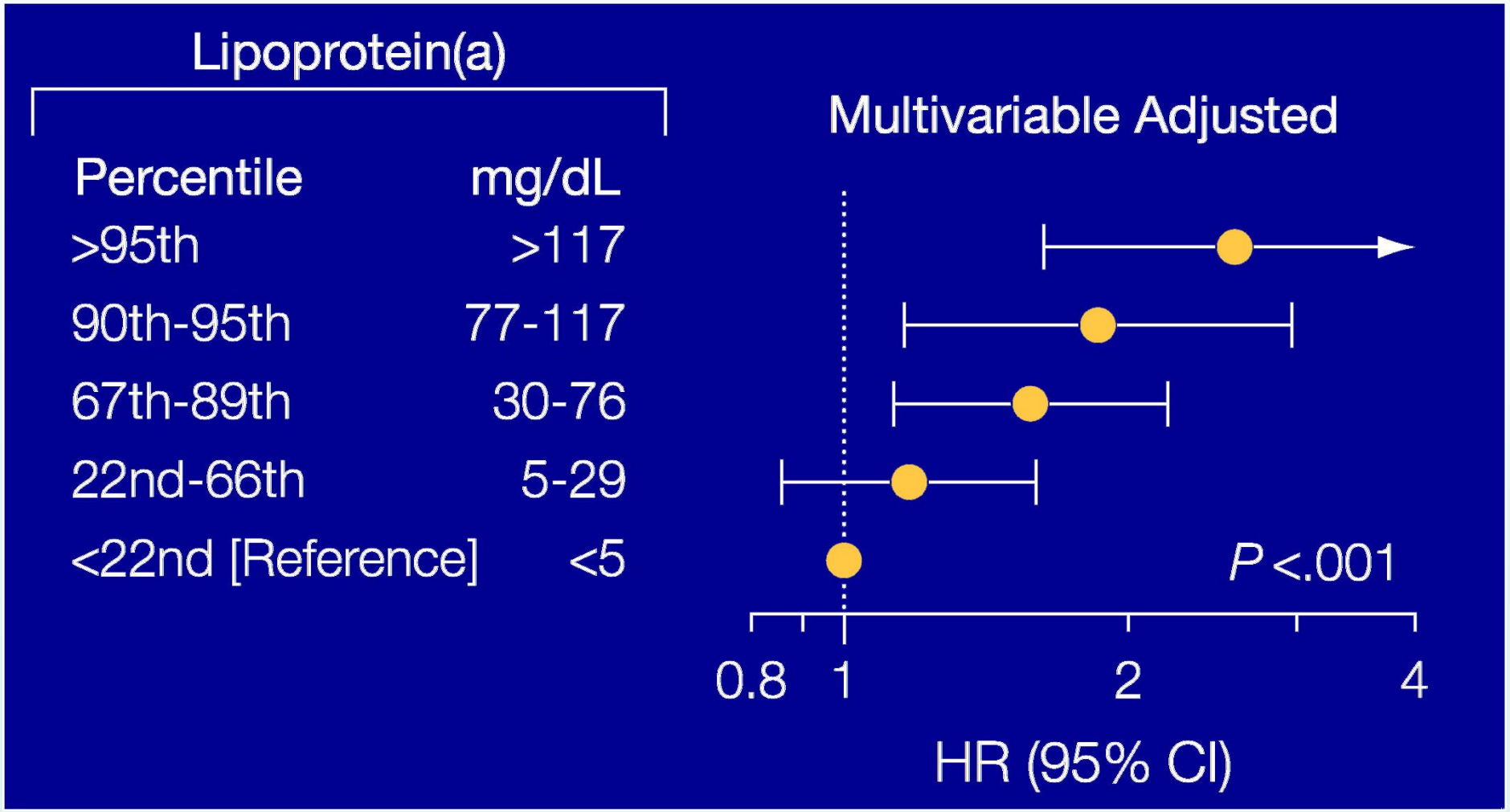
Nordestgaard B G et al. Eur Heart J 2010;31:2844-2853

Dallas Heart Study: Lp(a) Levels by Race/Ethnicity



Circulation. 2009;119:1711-1719

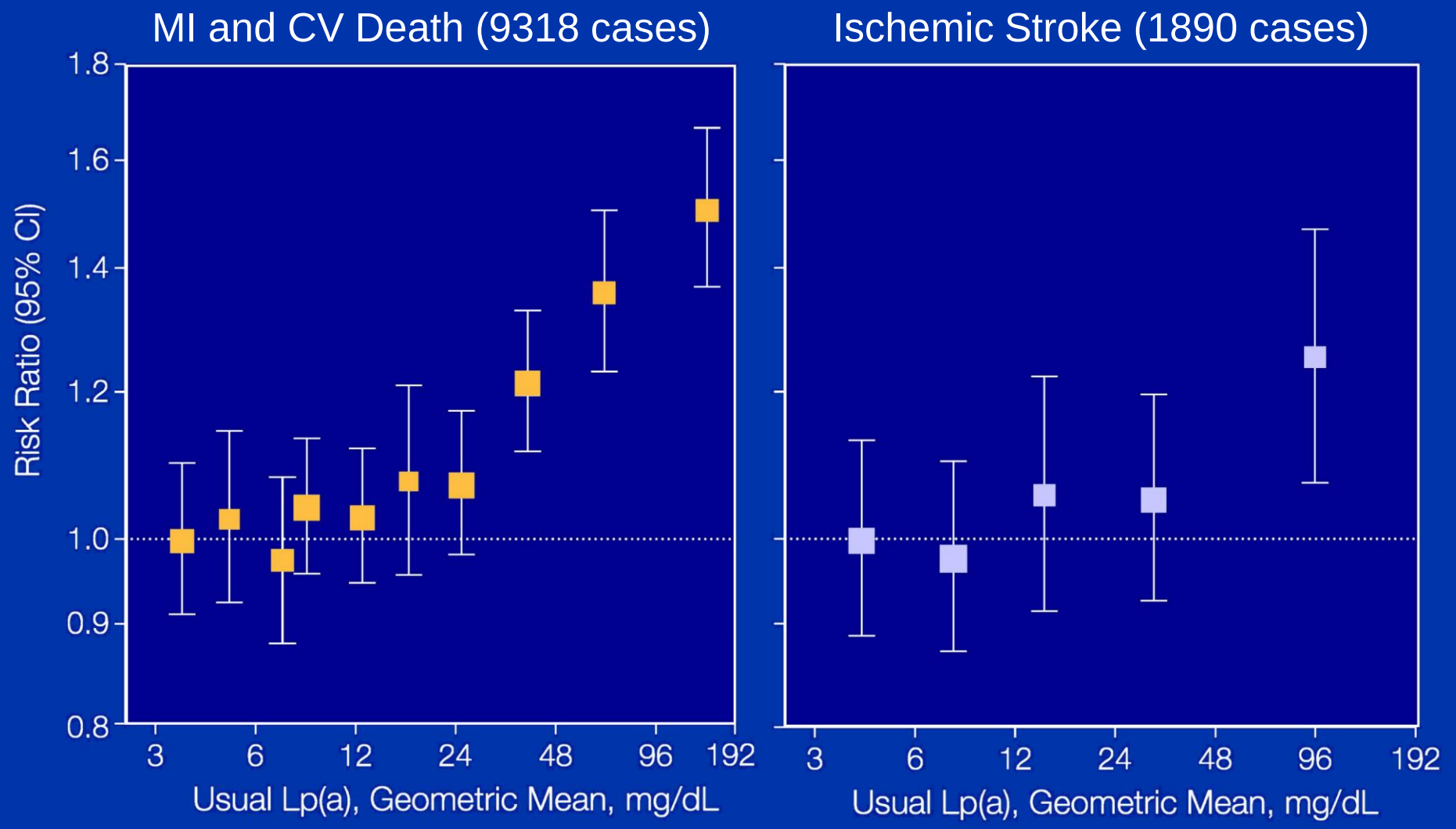
Risk of Elevated Lp(a) in General Population*



JAMA. 2009;301(22):2331-2339

*Data from Copenhagen City Heart Study

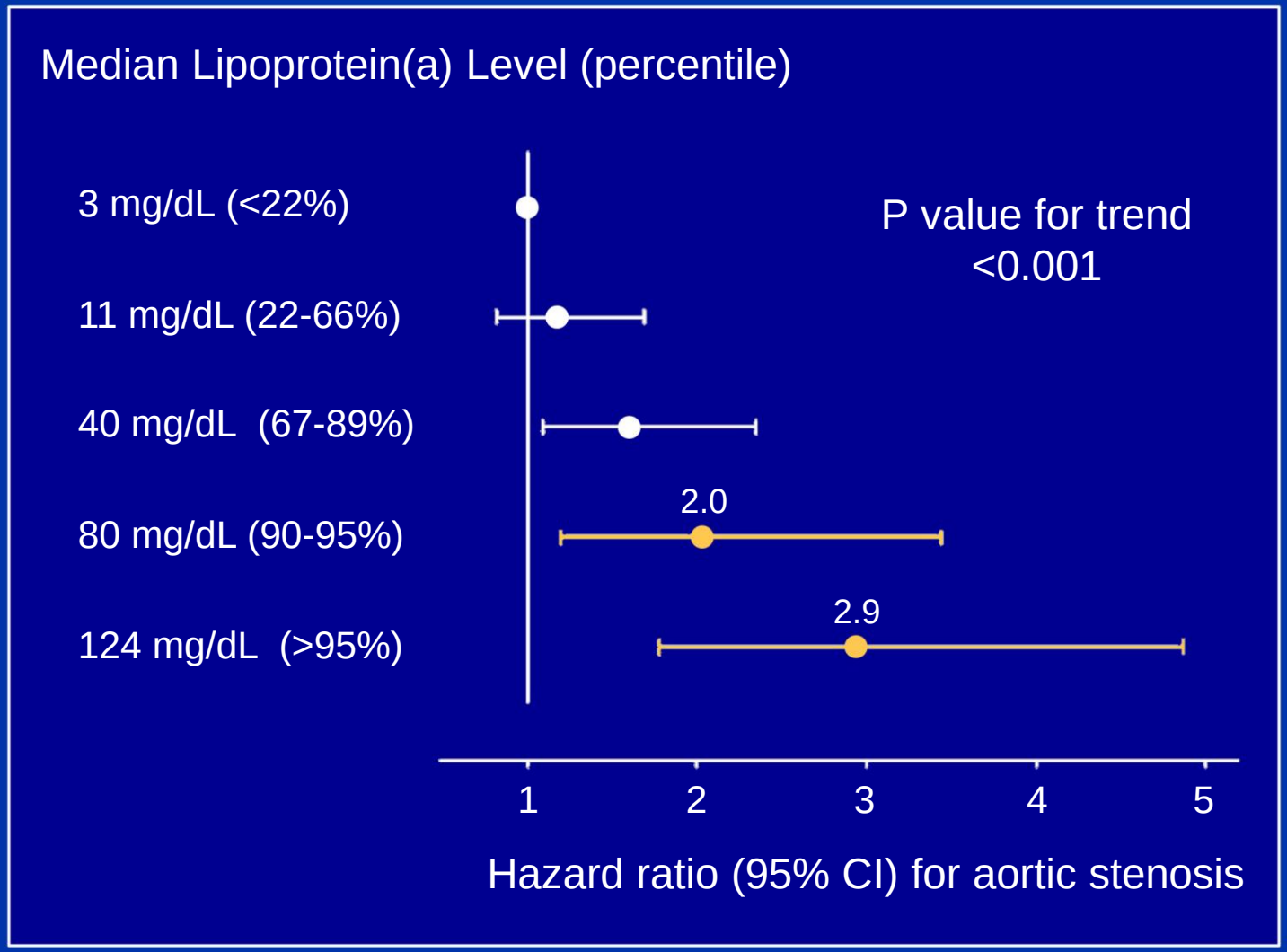
Relationship between Lipoprotein(a) and Outcome*



JAMA. 2009;302(4):412-423

**Emerging Risk Factor Collaboration*

Lipoprotein(a) Levels and Risk of Aortic Stenosis



Adapted from J Am Coll Cardiol 2014;63:470–7

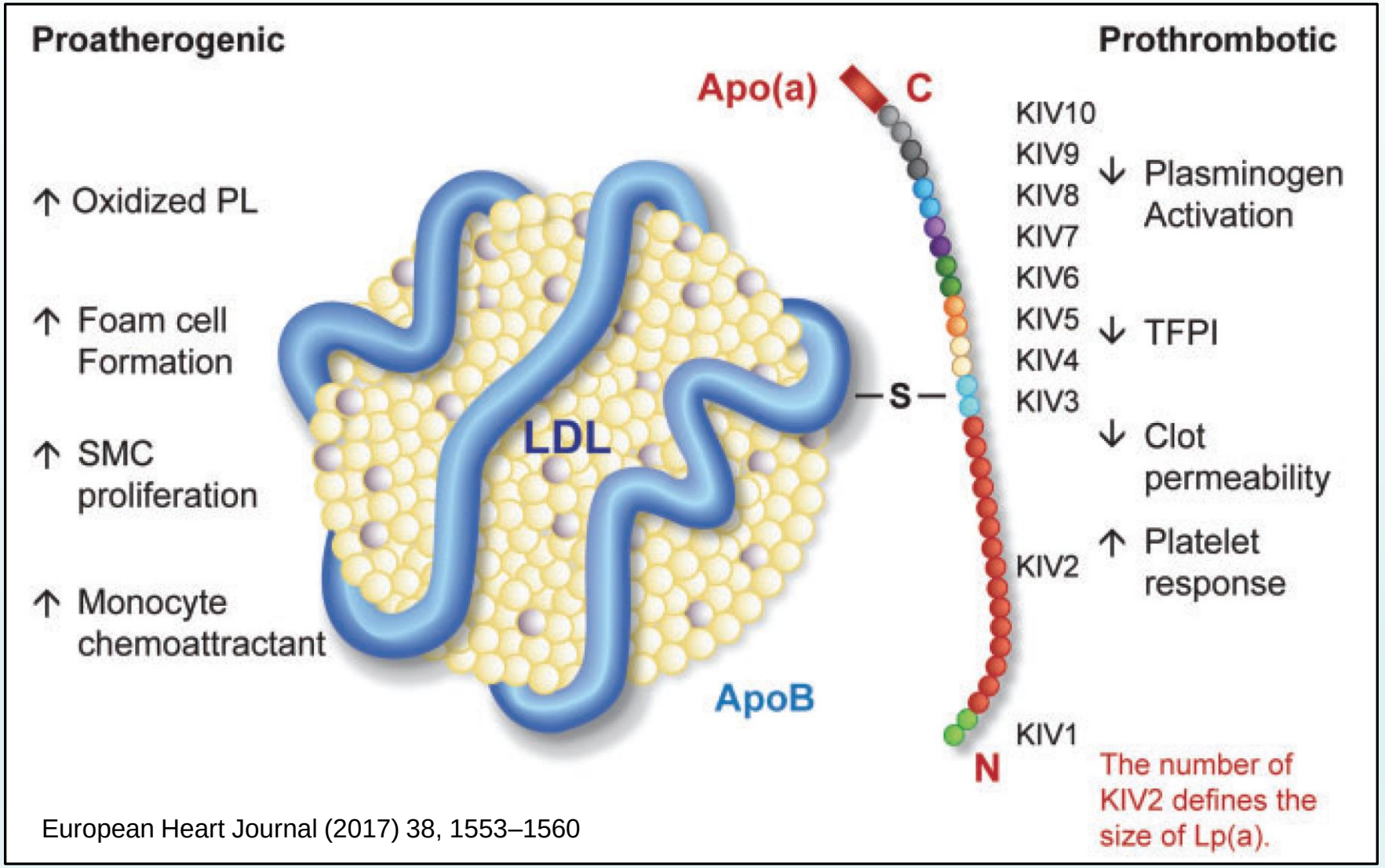
Prevalence of Elevated Lp(a): US and Globally

Prevalence	Top 20%	Top 10%	Top 5%	Top 1%
Lp(a) Level	60 mg/dL	90 mg/dL	116 mg/dL	180 mg/dL
Number (USA)	64 million	30 million	16 million	3.2 million
Number (EU)	150 million	75 million	37.5 million	7.5 million
Number Globally	1.4 billion	700 million	350 million	7 million

Arterioscler Thromb Vasc Biol. 2016;36:2239-2245 and adapted from Tsimikas

How Does Lipoprotein(a) Contribute to Atherosclerosis?

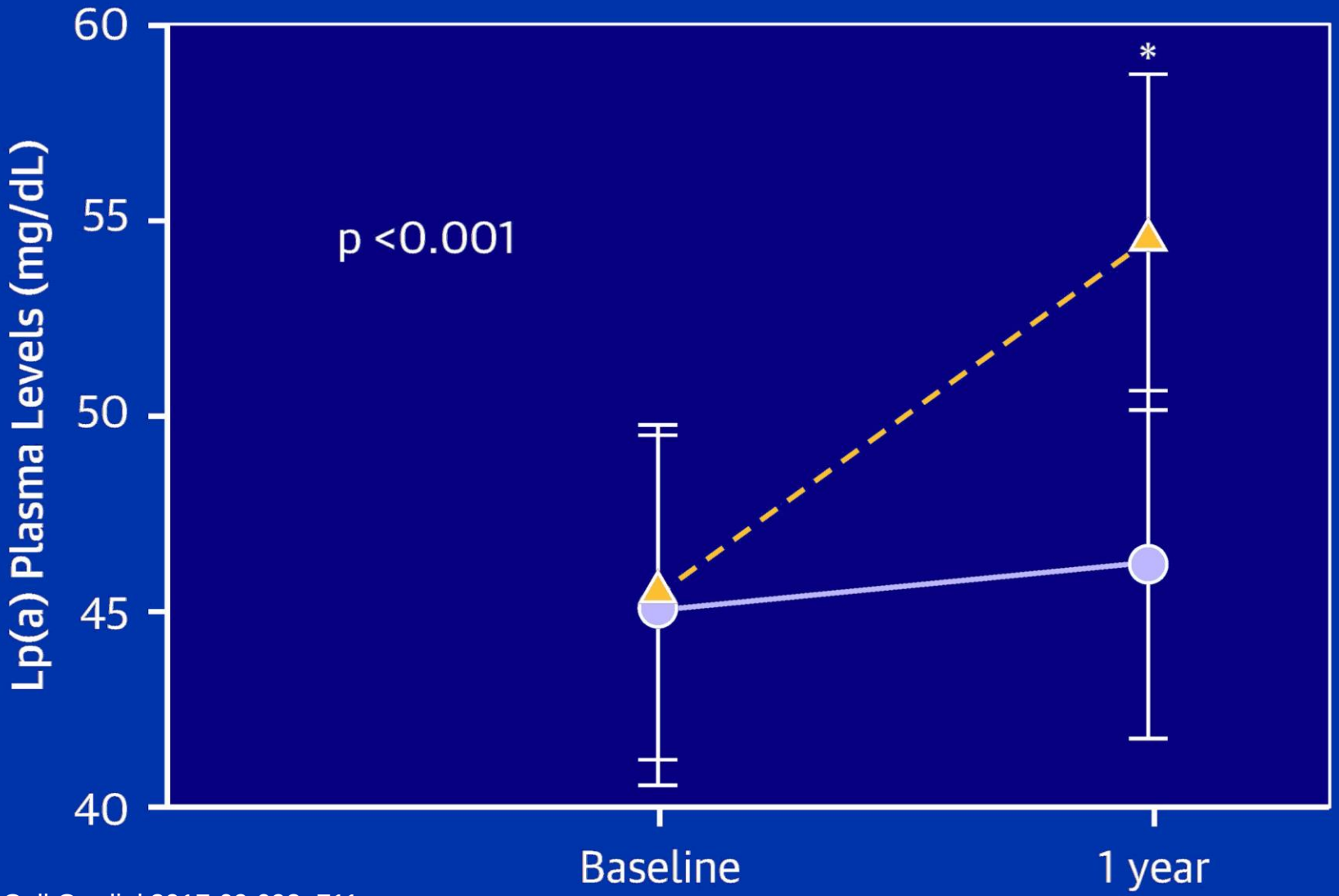
Lp(a) Components: Dual Mechanisms Of Harm



European Heart Journal (2017) 38, 1553–1560

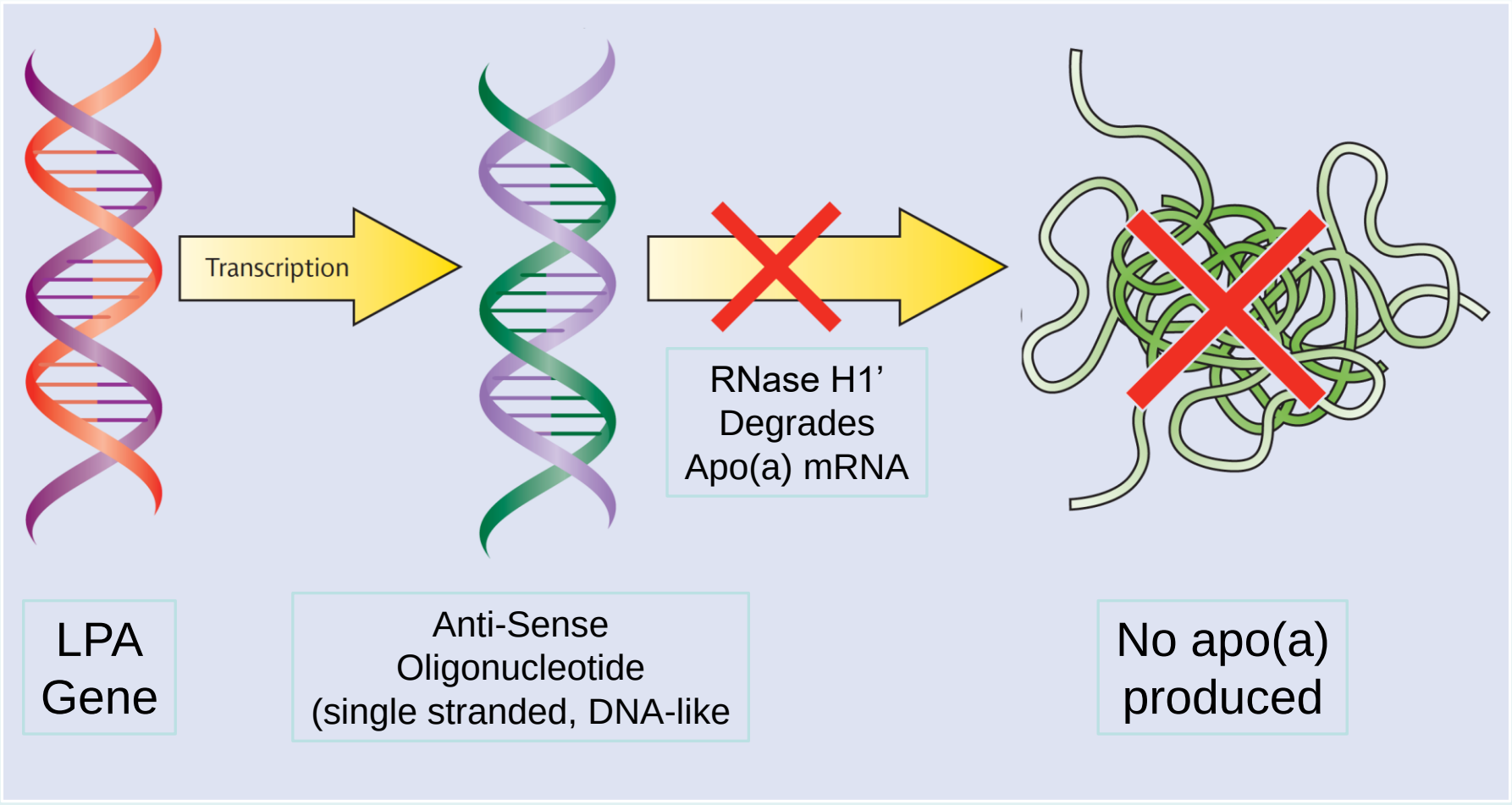
Lipoprotein(a) Levels
are Genetically Determined
Diet and Lifestyle Have No Effect

Effect of Rosuvastatin on Lipoprotein(a) Levels



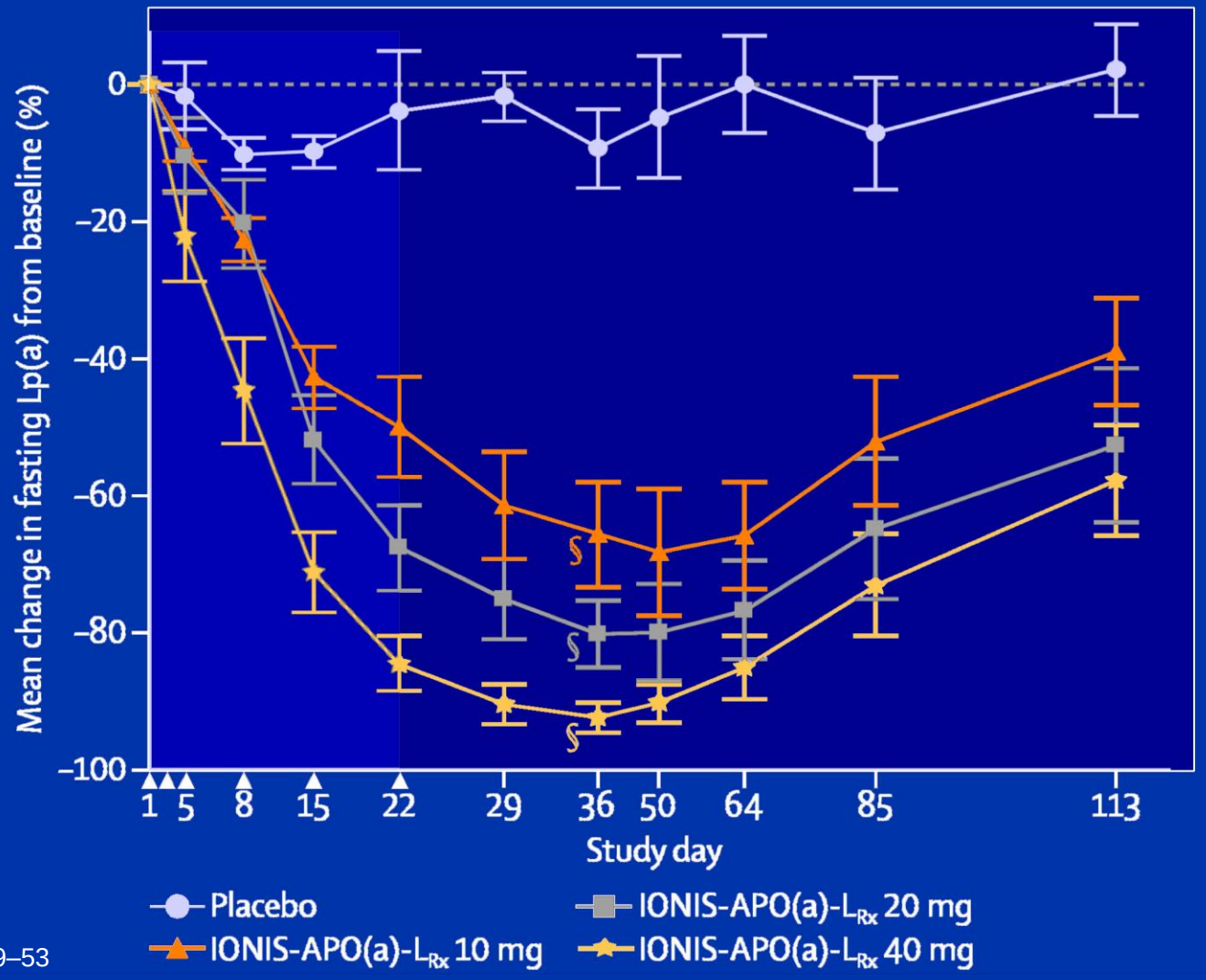
J Am Coll Cardiol 2017;69:692–711

Lp(a) Anti-Sense Oligonucleotide Therapy



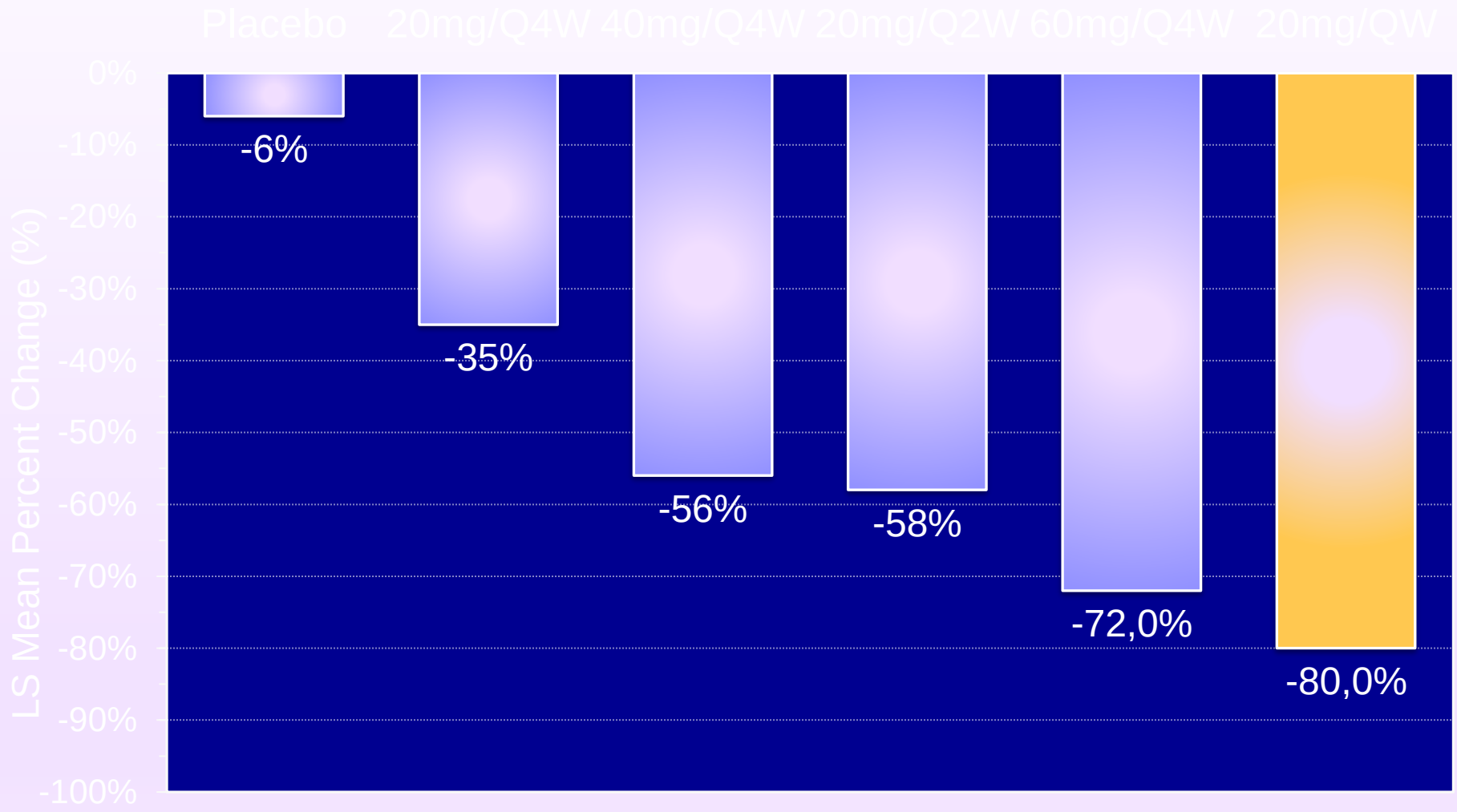
Lancet 2015; 386: 1472–83

GalNAc-Enhanced Lp(a) Oligonucleotide Therapy



Lancet 2016; 388: 2239–53

Phase IIb: Effect of ASO on Lp(a) Levels (n=286)



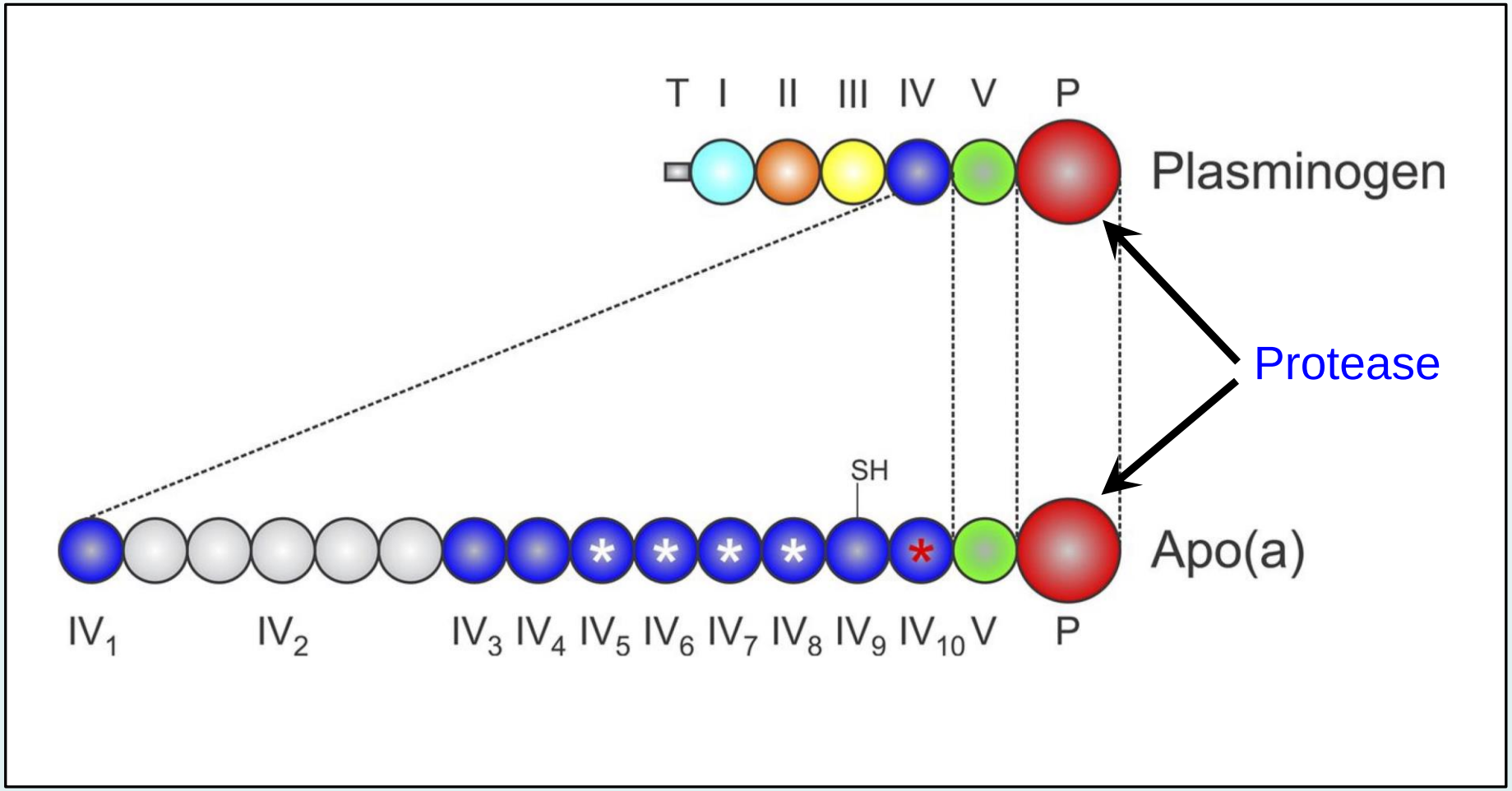
Presented by Tsmikas et al (AHA 2018)

EAS: Screening for Elevated Lipoprotein(a)

- **Premature CVD**
- **Familial hypercholesterolemia**
- **Family history premature CVD or Lp(a)↑**
- **Recurrent CVD despite statins**
- **≥3% 10-year risk of fatal CVD**
- **≥10% 10-year risk** of fatal/nonfatal CHD

Nordestgaard et al. EAS Consensus Panel. Eur Heart J 2010;31:2844-2853

Homology between Apo(a) and Plasminogen

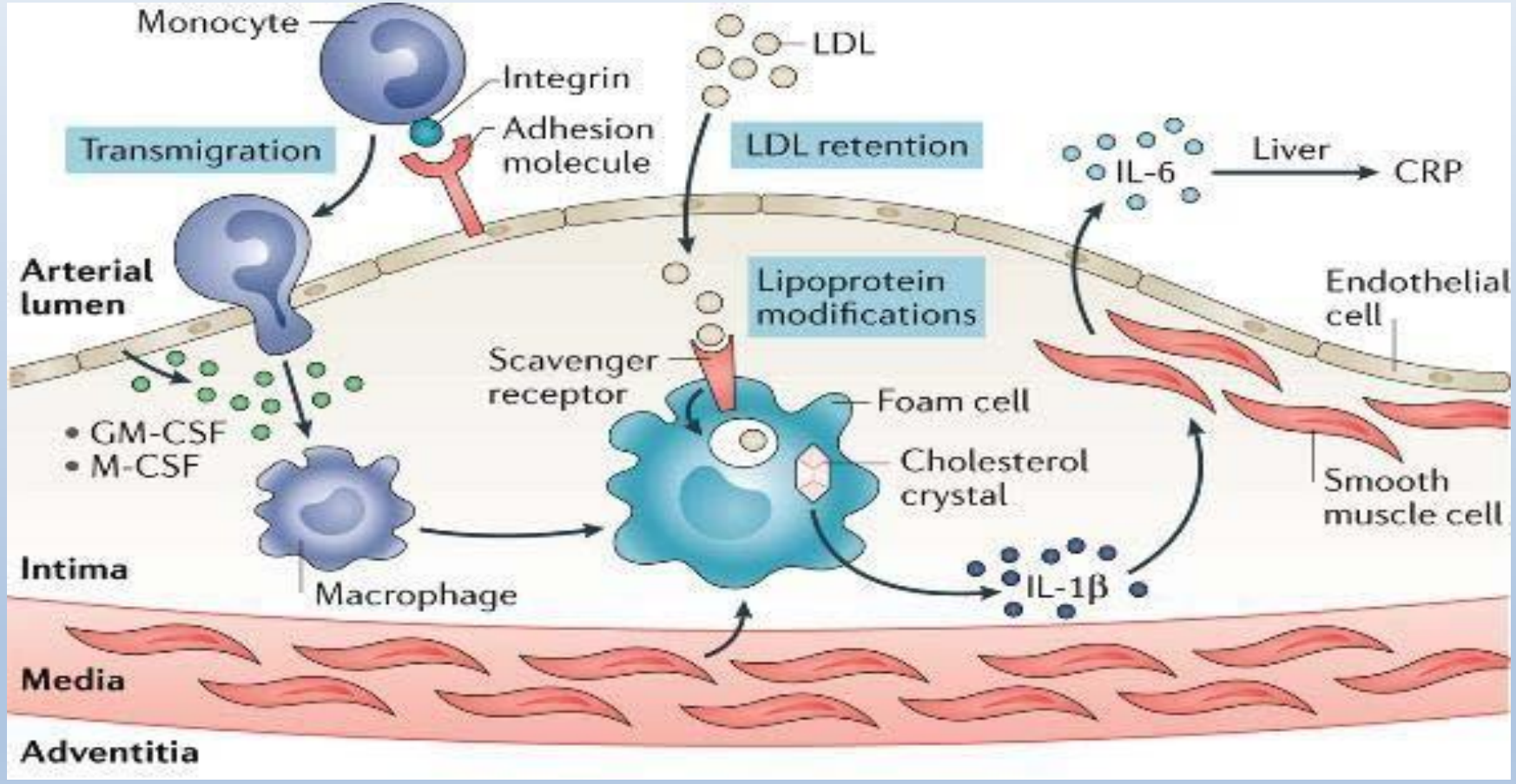


J. Lipid Res. 2016. 57: 745–757

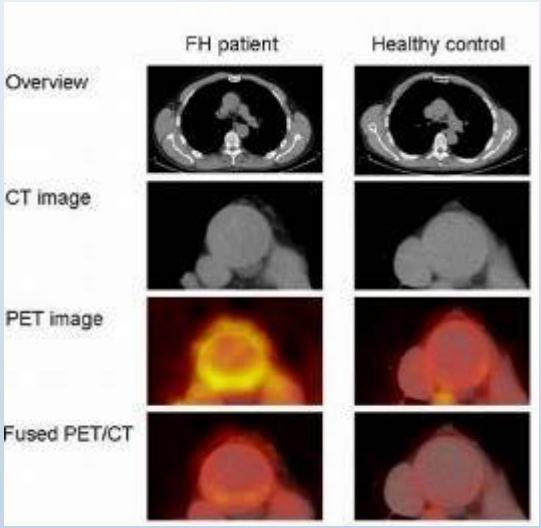
Nuovi Marcatori di Rischio

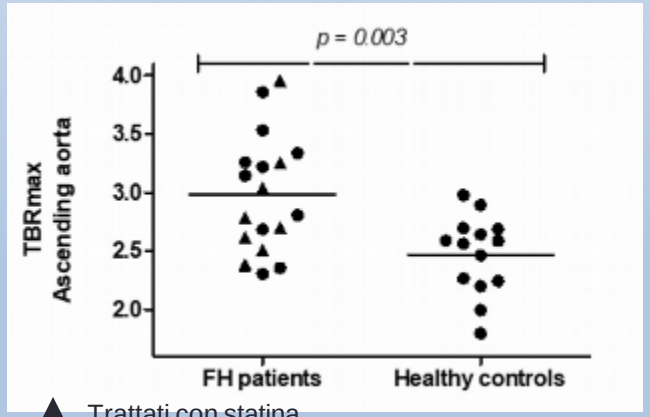
- Acido Urico
- Trigliceridi
- Infiammazione

INFIAMMAZIONE

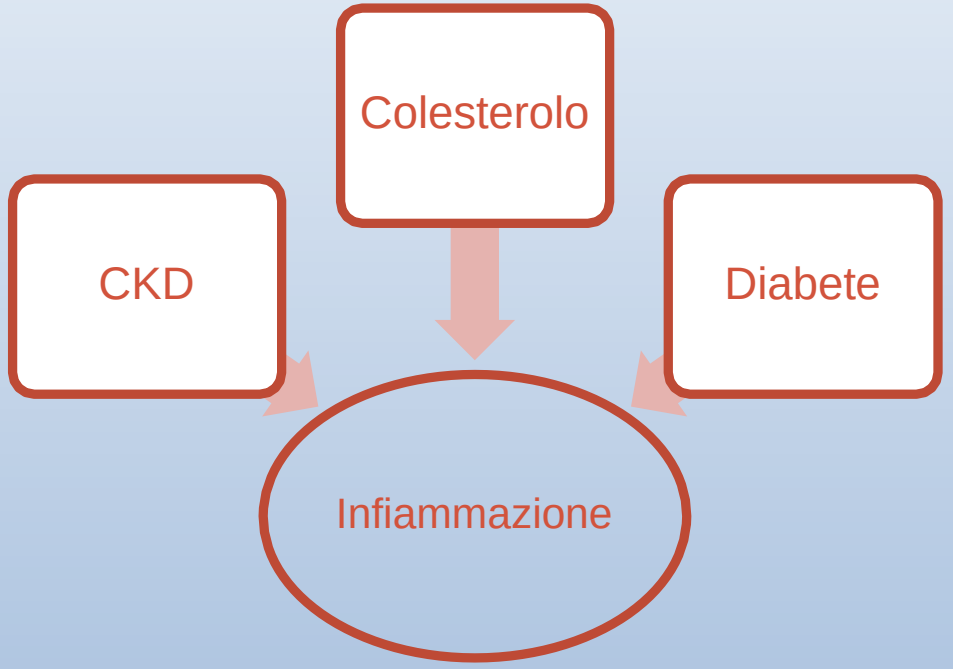


Gisterå, A Nat. Rev. Nephrol. **2017**





▲ Trattati con statina



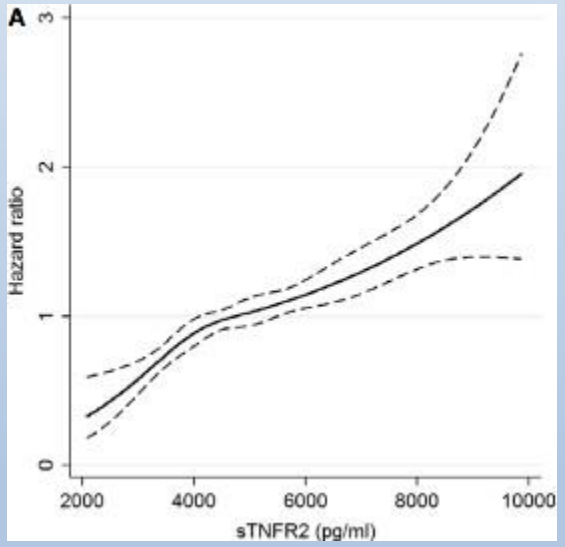
Wan WijK et al JACC 2014; Sophie J. Bernelot Moens JASN 2017

Biomarcatori di Infiammazione

sTNFR1 and sTNFR2 associated with CV events and mortality (FU 10 yrs) in patients with stable CHD at baseline

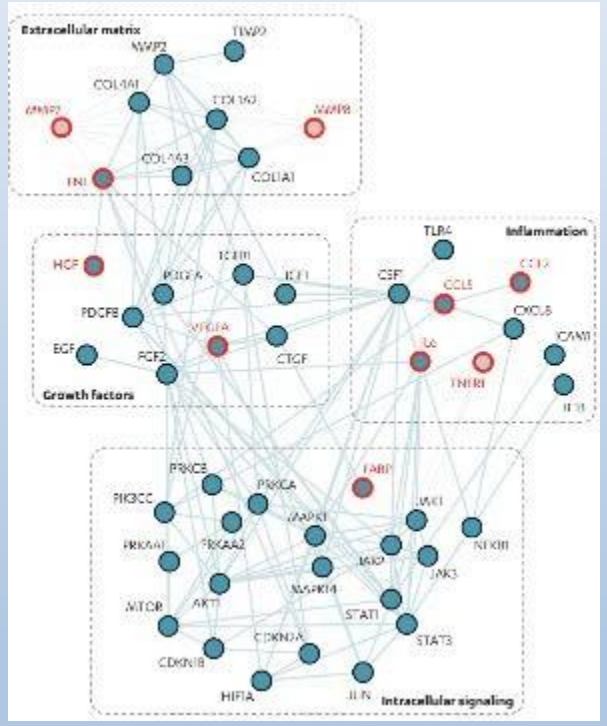
Recettori del TNF-α

- Marcatori di progressione DKD

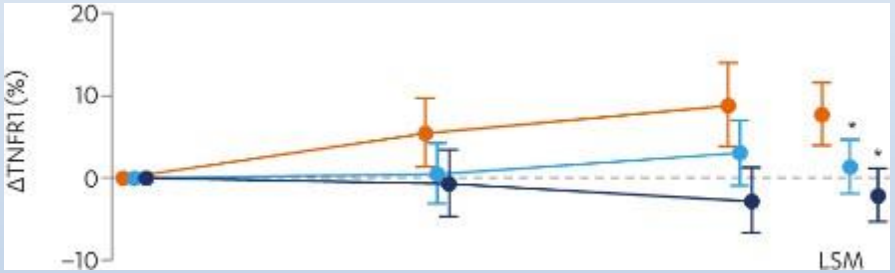


Carlsson AC et al. J Am Heart Assoc. 2018

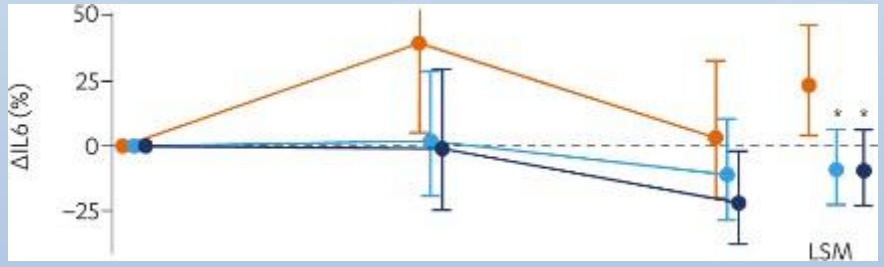
SGLT2i – Biomarcatori di Infiammazione



TNFR1



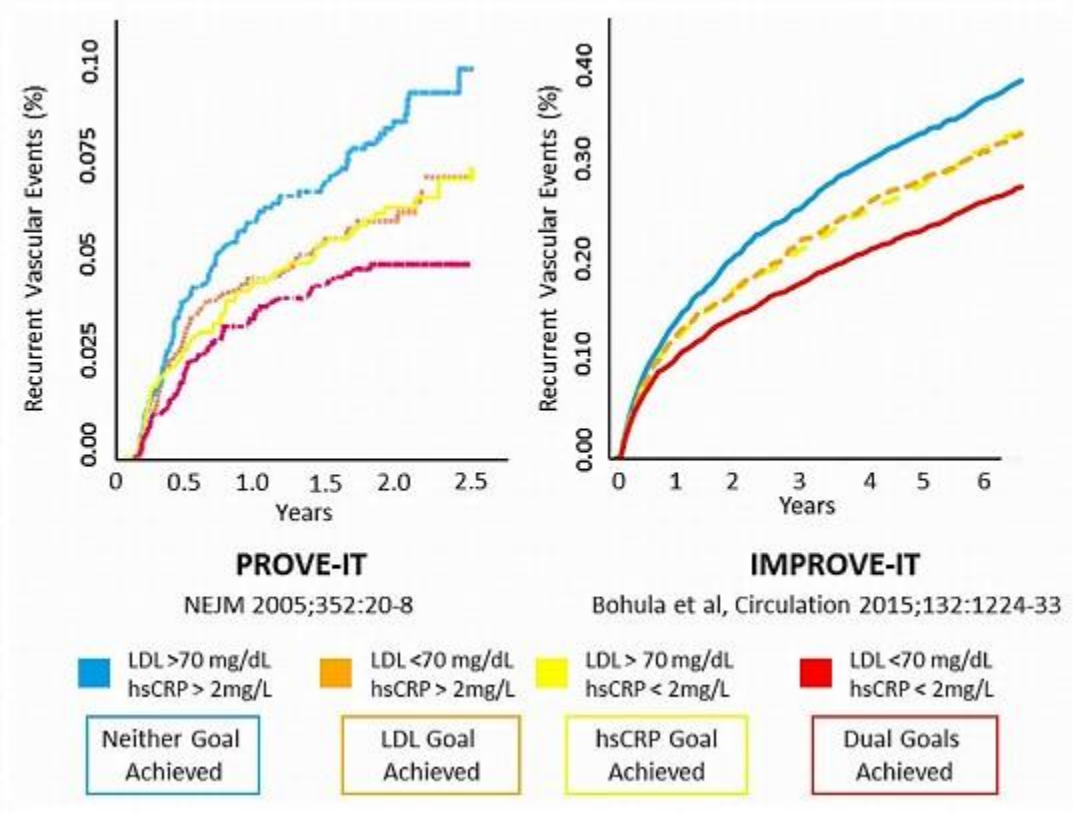
IL-6

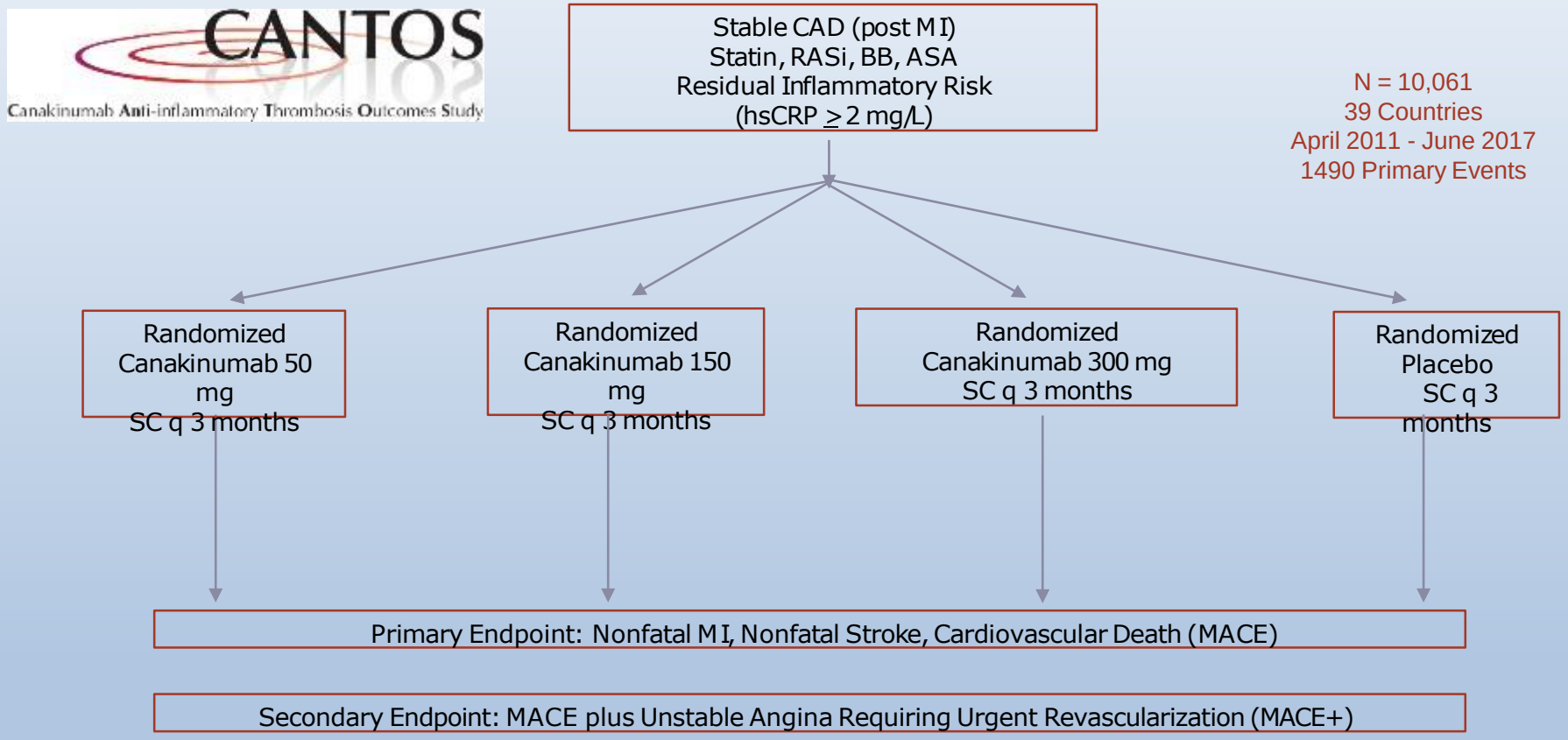


GLIM — CANA 100 mg — CANA 300 mg

Heerspink H et al. Diabetologia 2019

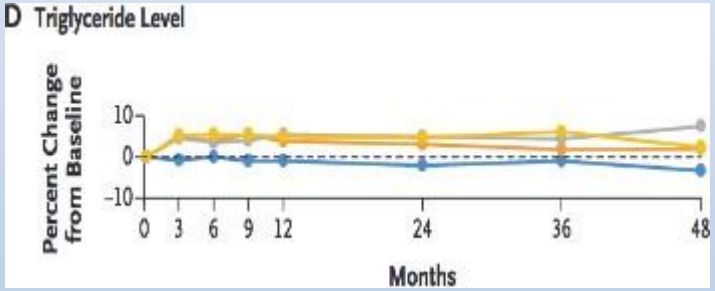
hs-PCR per la Stratificazione del Rischio Residuo

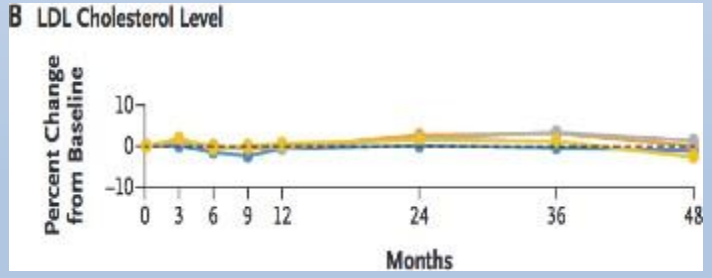


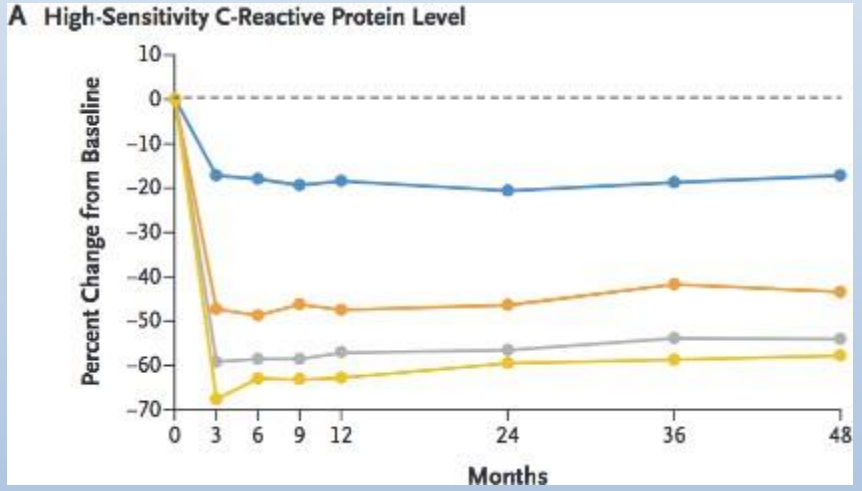


Ridker PM et al. N Engl J Med. 2017

CANTOS Trial: Anti-inflammatory Therapy with Canakinumab for Atherosclerotic Disease



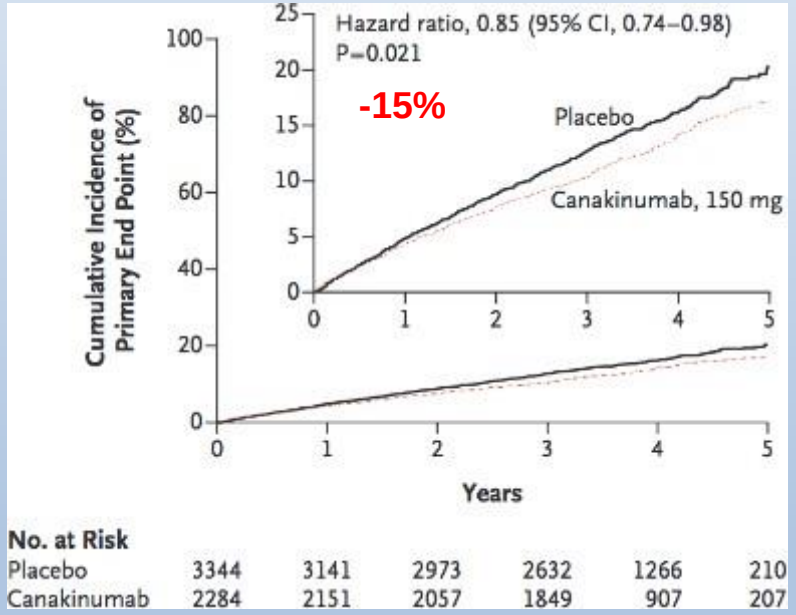


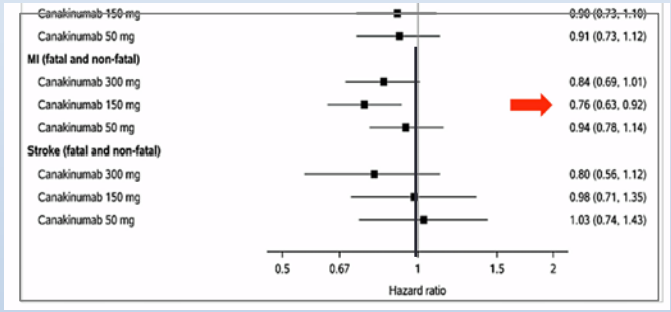


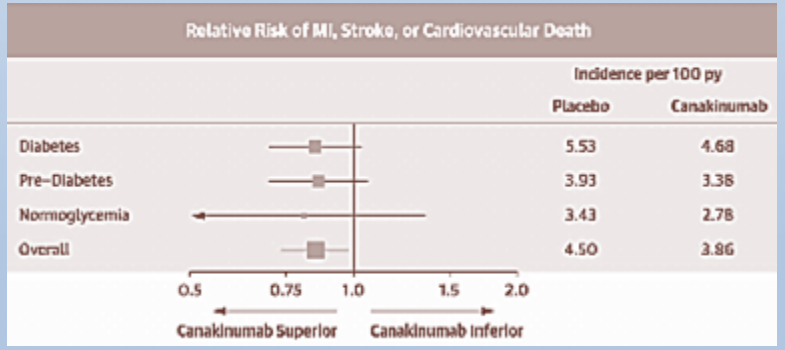
Ridker PM et al NEJM 2019

CANTOS Trial: Anti-inflammatory Therapy with Canakinumab for Atherosclerotic Disease

MACE: CV death, non-fatal stroke, non-fatal MI







Ridker PM et al NEJM 2017; Everett BM JACC 2018

CANTOS Trial: Anti-inflammatory Therapy with Canakinumab for Atherosclerotic Disease

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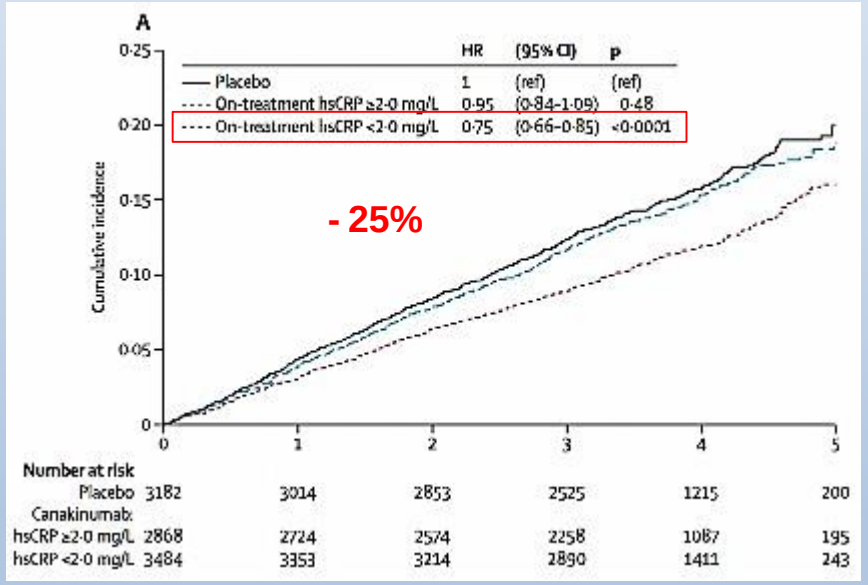
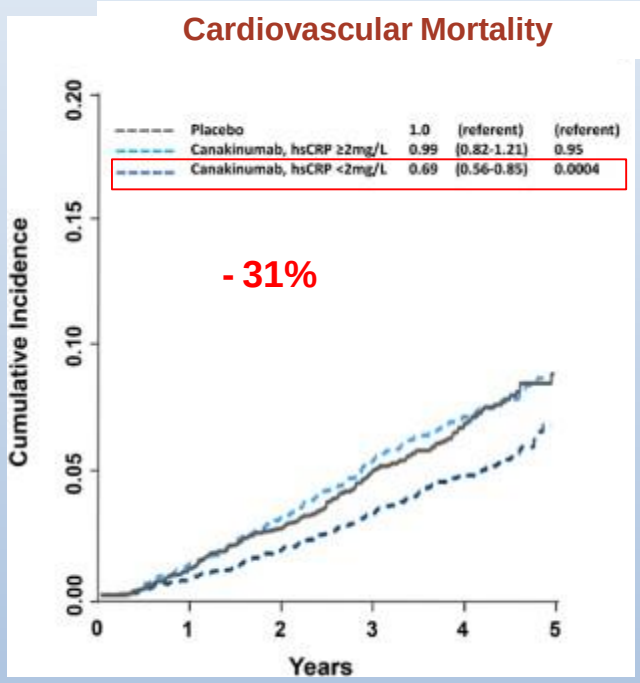
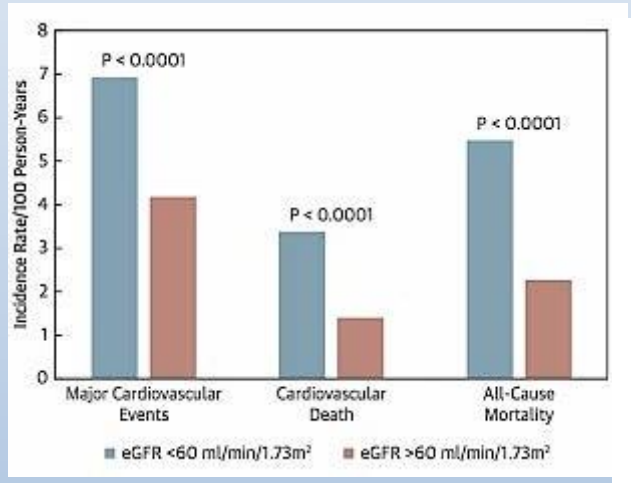


Cardiovascular Mortality

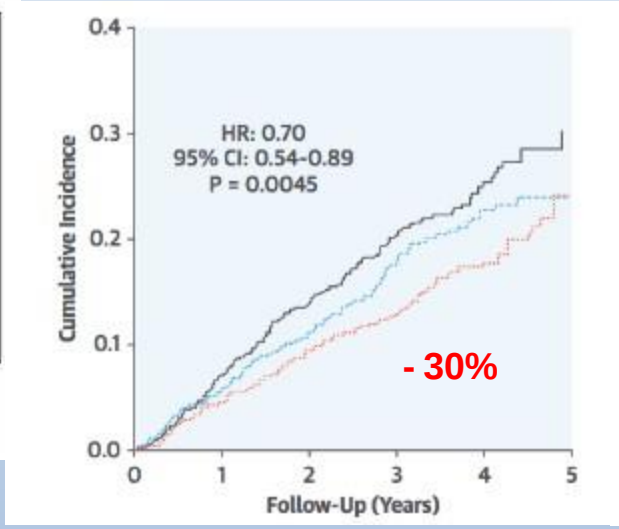


Ridker PM et al Lancet 2018, Ridker PM et al Circulation 2018

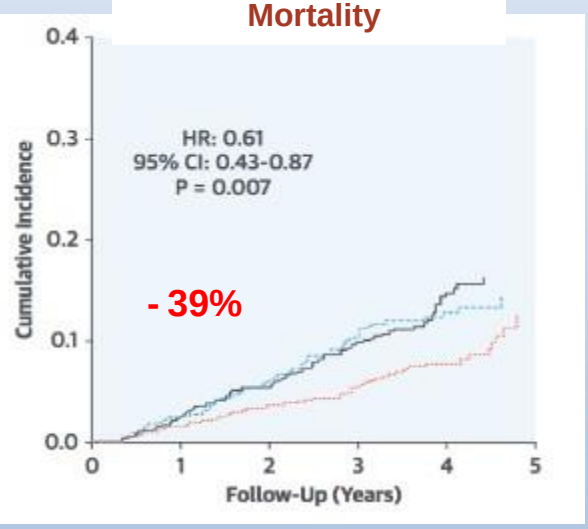
CANTOS: Efficacy in Patients with CKD



MACE



Cardiovascular Mortality



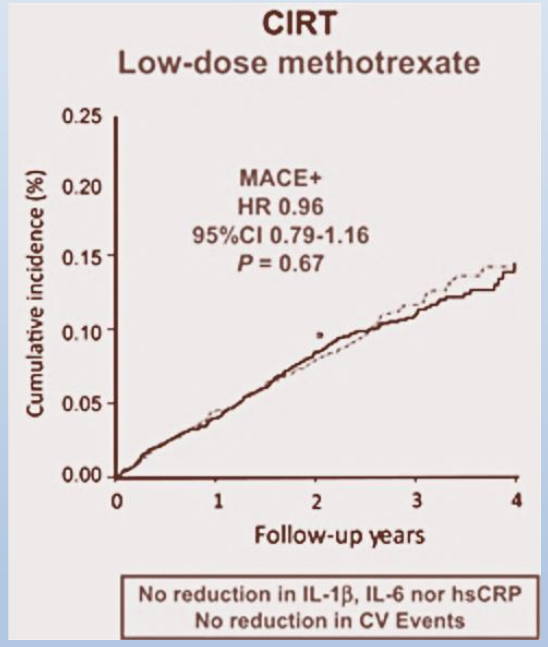
placebo group
canakinumab group with on-treatment hsCRP > 2 mg/l
canakinumab group with on-treatment hsCRP < 2 mg/l

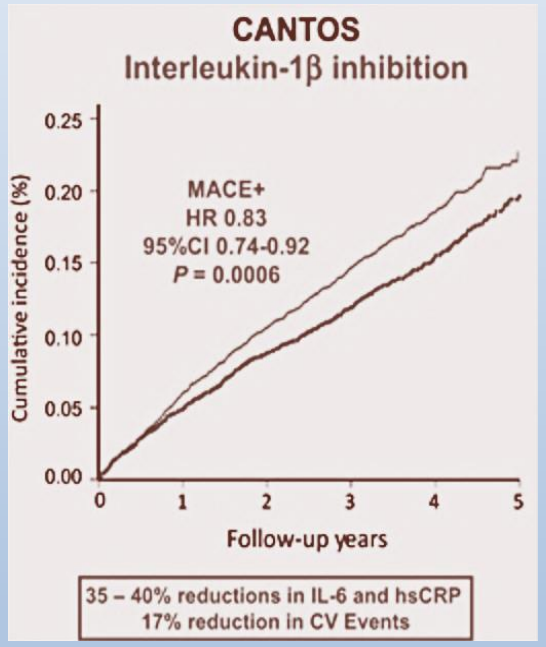
Ridker PM et al JACC 2018

Effetti Avversi

Adverse Event or Laboratory Variable	Placebo Group (N=3344)	Canakinumab				P Value	
		50-mg Group (N=2170)	150-mg Group (N=2284)	300-mg Group (N=2263)	All Doses (N=6717)	For Trend across Doses vs. Placebo	For Combined Dose Groups vs. Placebo
Event — incidence rate per 100 person-yr (no. of patients with event)							
Any serious adverse event	11.96 (1202)	11.41 (741)	11.71 (812)	12.33 (836)	11.82 (2389)	0.43	0.79
Any serious adverse event of infection	2.86 (342)	3.03 (230)	3.13 (258)	3.25 (265)	3.14 (753)	0.12	0.14
Cellulitis	0.24 (30)	0.24 (19)	0.37 (32)	0.41 (35)	0.34 (86)	0.02	0.09
Pneumonia	0.90 (112)	0.94 (74)	0.94 (80)	0.99 (84)	0.95 (238)	0.56	0.62
Urinary tract infection	0.22 (27)	0.18 (14)	0.24 (21)	0.20 (17)	0.21 (52)	0.84	0.87
Opportunistic infection†	0.18 (23)	0.16 (13)	0.15 (13)	0.20 (17)	0.17 (43)	0.97	0.78
Pseudomembranous colitis	0.03 (4)	0.13 (10)	0.05 (4)	0.12 (10)	0.10 (24)	0.13	0.03
Fatal infection or sepsis	0.18 (23)	0.31 (25)	0.28 (24)	0.34 (29)	0.31 (78)	0.09	0.02
Any cancer‡	1.88 (231)	1.85 (144)	1.69 (143)	1.72 (144)	1.75 (431)	0.31	0.38
Fatal cancer‡	0.64 (81)	0.55 (44)	0.50 (44)	0.31 (27)	0.45 (115)	<0.001	0.02
Other adverse event							
Injection-site reaction†	0.23 (29)	0.27 (21)	0.28 (24)	0.30 (26)	0.28 (71)	0.49	0.36
Arthritis	3.32 (385)	2.15 (164)	2.17 (180)	2.47 (201)	2.26 (545)	0.002	<0.001
Osteoarthritis	1.67 (202)	1.21 (94)	1.12 (95)	1.30 (109)	1.21 (298)	0.04	<0.001
Gout	0.80 (99)	0.43 (34)	0.35 (30)	0.37 (32)	0.38 (96)	<0.001	<0.001
Drug-induced liver injury†	0.18 (23)	0.15 (12)	0.13 (11)	0.05 (4)	0.11 (27)	0.004	0.05
Leukopenia	0.24 (30)	0.30 (24)	0.37 (32)	0.52 (44)	0.40 (100)	0.002	0.01
Neutropenia	0.06 (7)	0.05 (4)	0.07 (6)	0.18 (15)	0.10 (25)	0.01	0.17
Any hemorrhage	4.01 (462)	3.33 (249)	4.15 (327)	3.82 (301)	3.78 (877)	0.94	0.31
Thrombocytopenia	0.43 (53)	0.56 (44)	0.54 (46)	0.71 (60)	0.60 (150)	0.02	0.03
Hepatic variable — percent of patients with condition (no.)							
Alanine aminotransferase >3× normal value	1.4 (46)	1.9 (42)	1.9 (44)	2.0 (45)	2.0 (131)	0.19	0.06
Aspartate aminotransferase >3× normal value	1.1 (36)	1.5 (32)	1.5 (35)	1.5 (34)	1.5 (101)	0.30	0.11
Alkaline phosphatase >3× normal value	0.4 (15)	0.5 (11)	0.4 (10)	0.5 (12)	0.5 (33)	0.67	0.82
Bilirubin >2× normal value	0.8 (26)	1.0 (21)	0.7 (15)	0.7 (15)	0.8 (51)	0.34	0.83

CIRT: Low dose Methotrexate





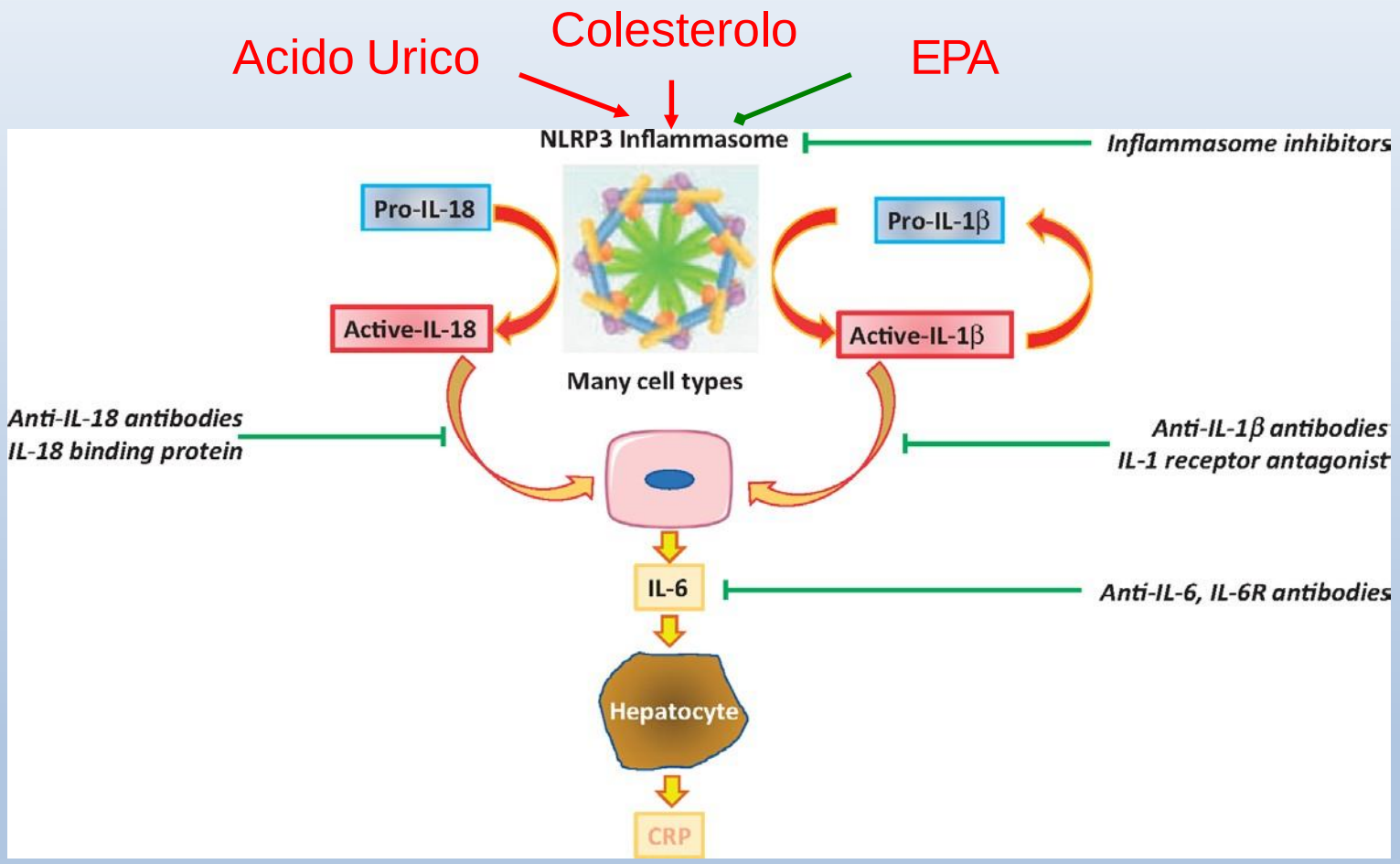
Casistica

- CANTOS: ↑CRP
- CIRT: DM2-SM

Pathway

- CANTOS: NLRP3 IL1-IL6-CRP
- CIRT: generico

Ridker PM JIM 2019



Ridker PM et al European Heart Journal 2019

Target Tradizionali

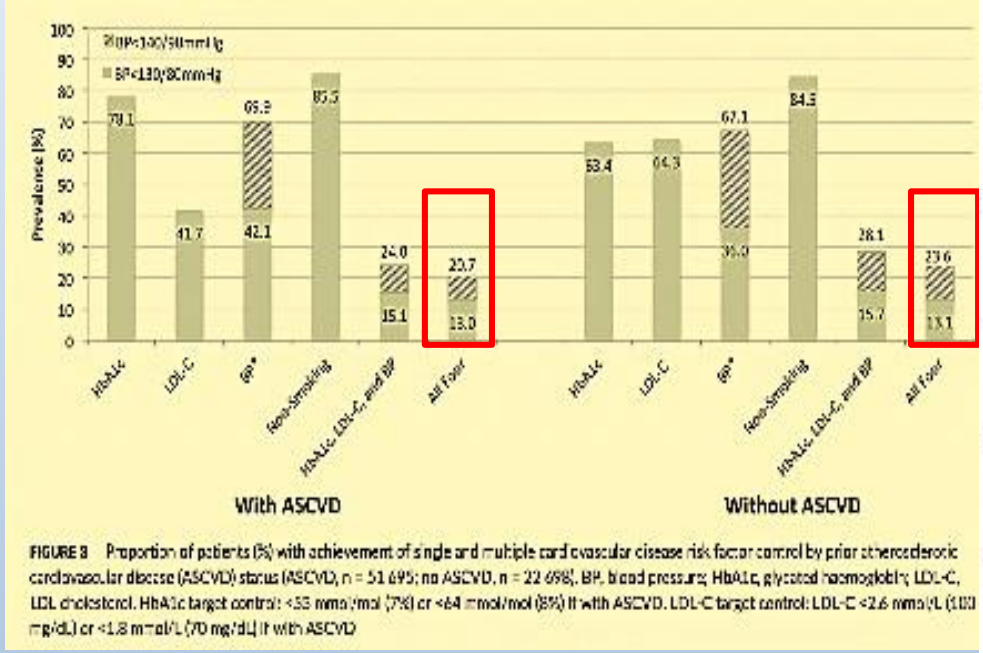
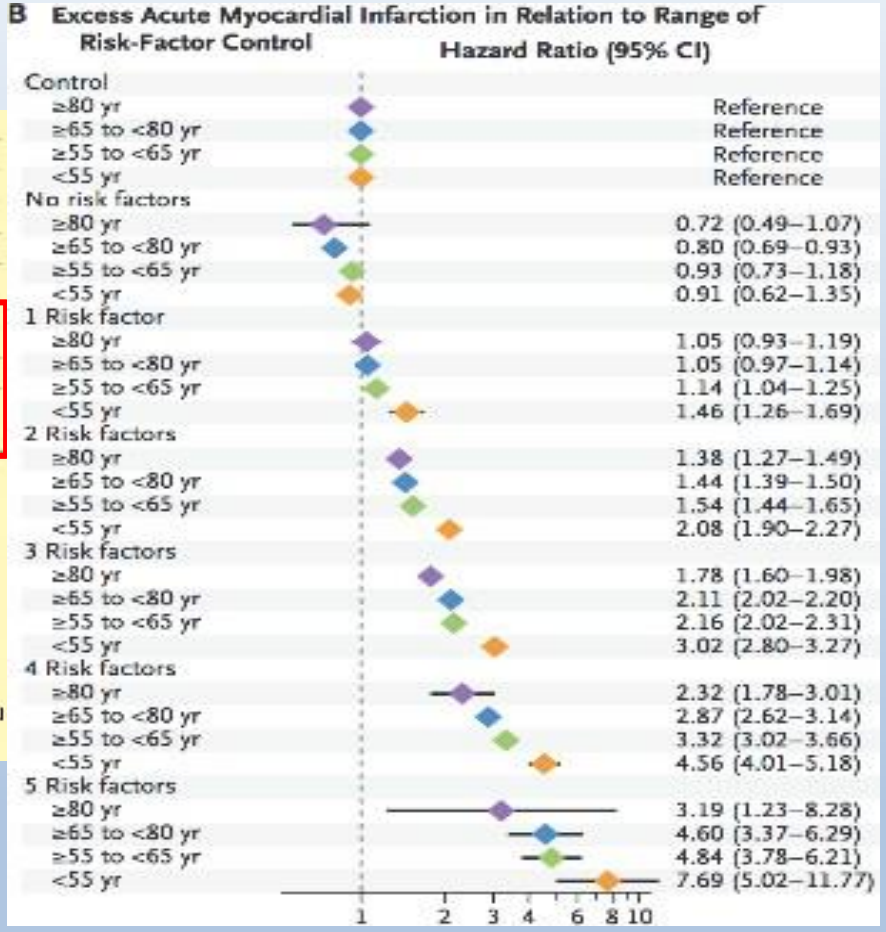


FIGURE 3 Proportion of patients (%) with achievement of single and multiple cardiovascular disease risk factor control by prior atherosclerotic cardiovascular disease (ASCVD) status (ASCVD, n = 51 695; no ASCVD, n = 22 698). BP, blood pressure; HbA1c, glycated haemoglobin; LDL-C, LDL cholesterol. HbA1c target control: <53 mmol/mol (7%) or <64 mmol/mol (8%) if with ASCVD. LDL-C target control: LDL-C <2.6 mmol/L (100 mg/dL) or <1.8 mmol/L (70 mg/dL) if with ASCVD

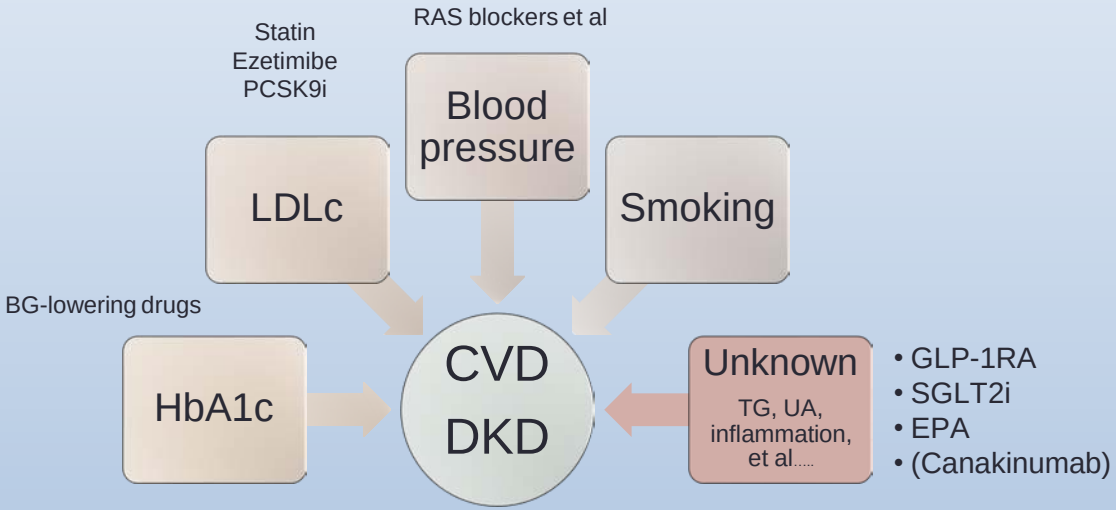
A1C, BP, fumo, LDL



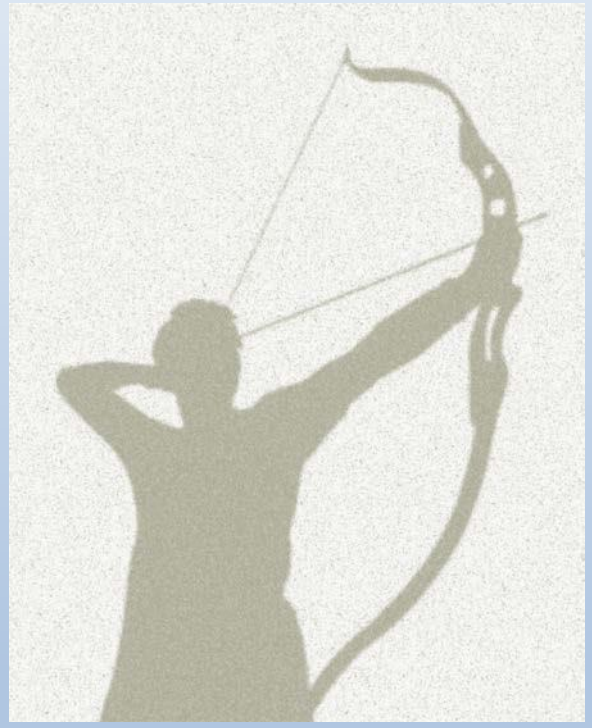
A1C, BP, fumo, LDL, albuminuria

Fan W et al Diabetes, Obesity and Metabolism 2019
Rawshani A et al NEJM 2018

Conclusione…



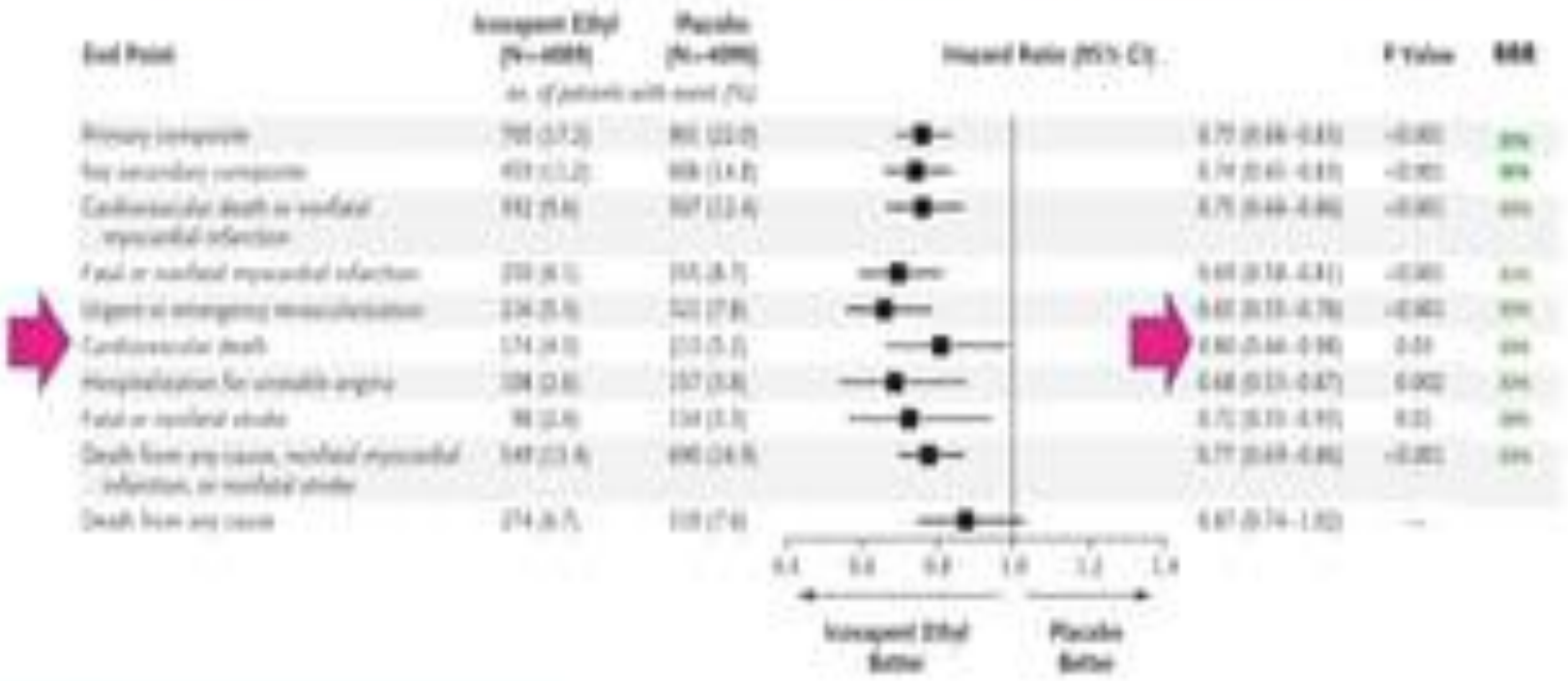
Implementazione
Aderenza terapeutica



Clinical Implication 3

Reduction in CV Death

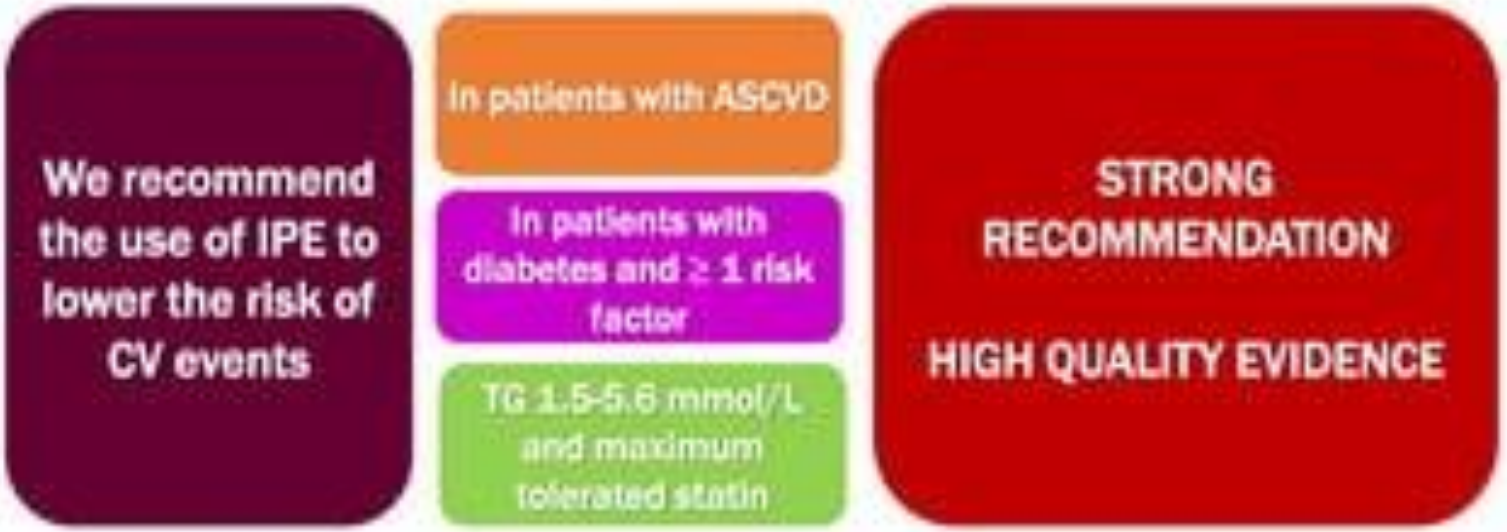
20% reduction in CV Death in REDUCE-IT



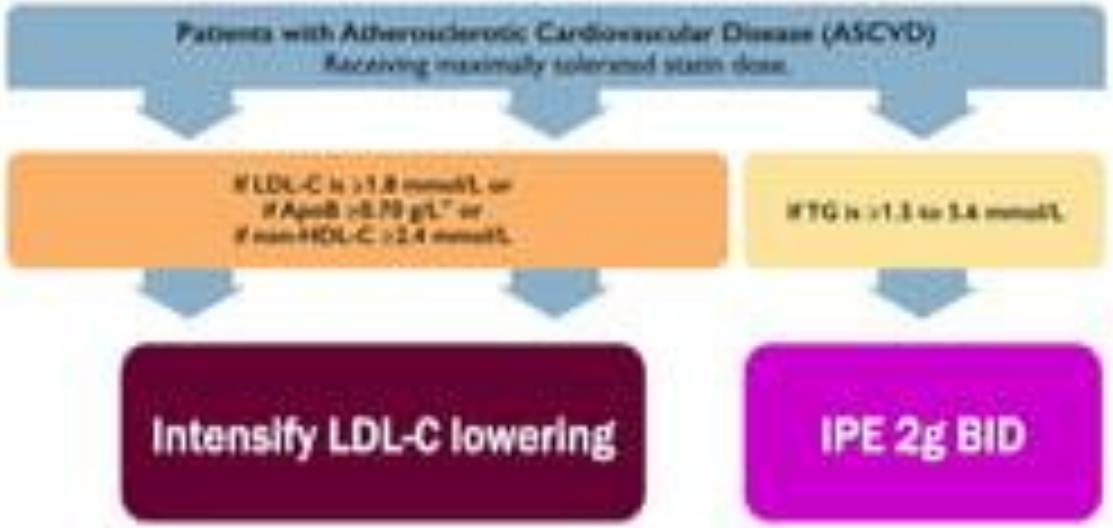
Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2018

Leading Global Medical Societies Recognize IPE as an Important CV Treatment Option

The 2021 Canadian Lipid Guidelines for Icosapent Ethyl (IPE)



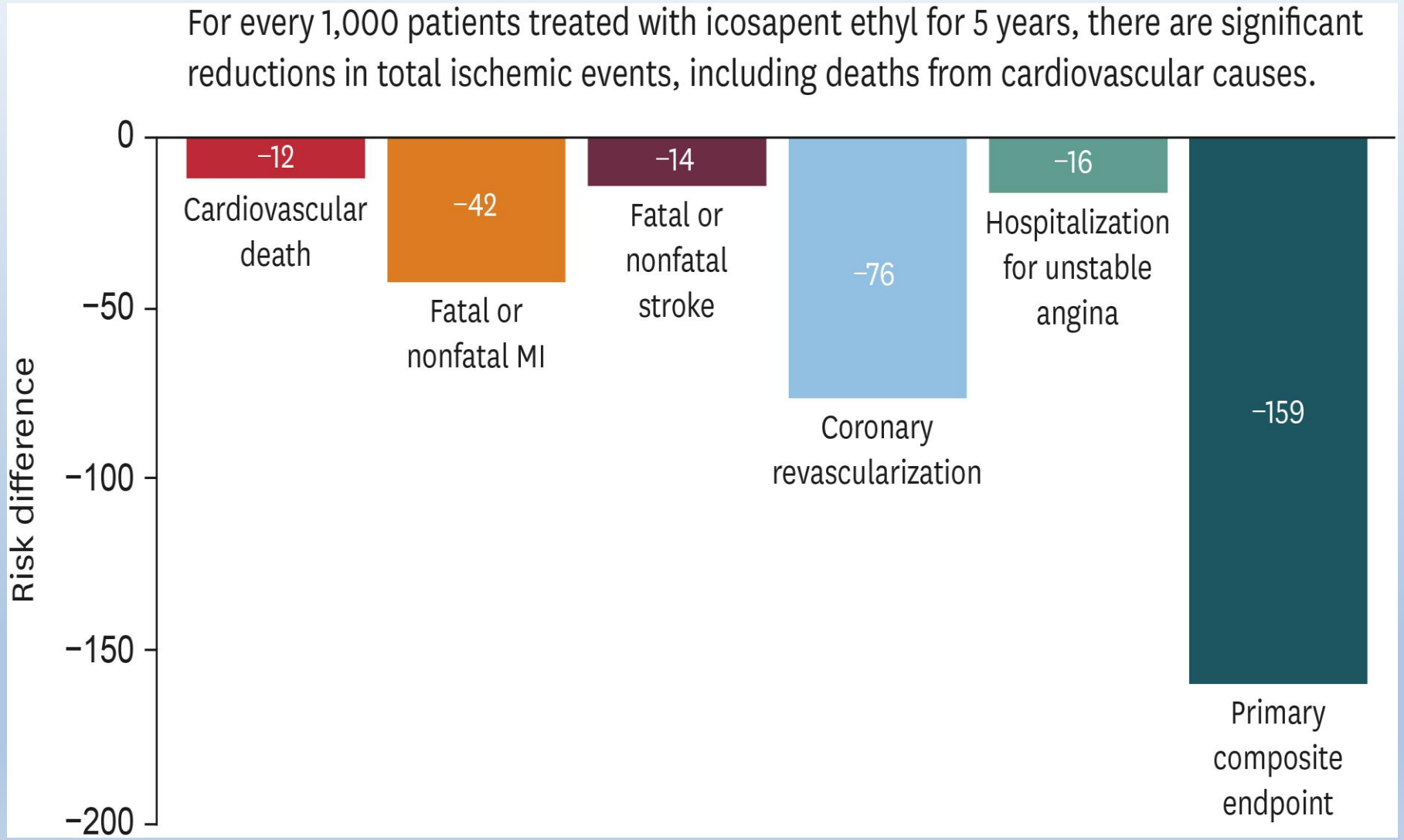
It's not sequential – but horizontal integration



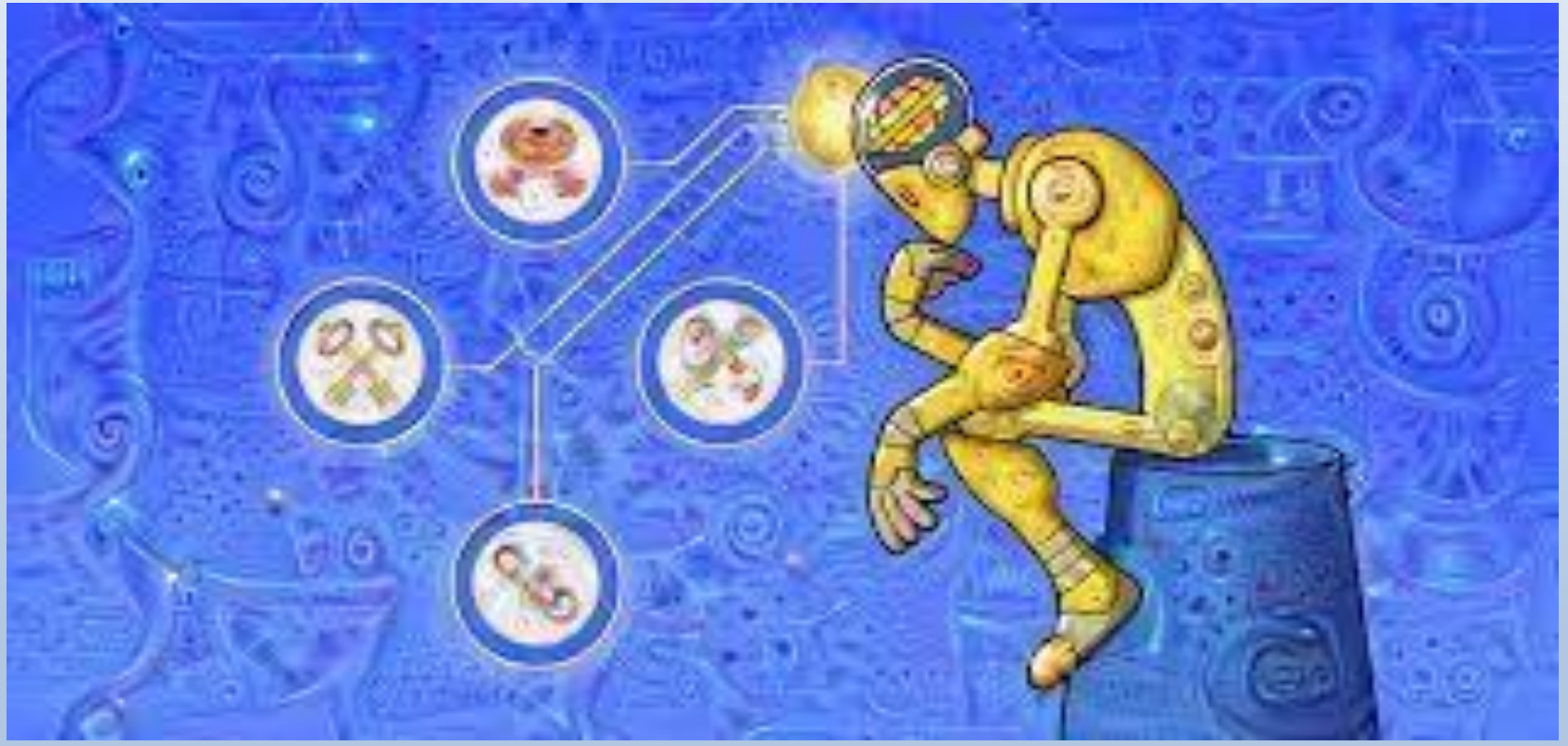

The 2021 Canadian Lipid Guidelines
We do not recommend the use of OTC omega-3 PUFA supplements to lower the risk of CV events
These are marketed as natural health products in Canada
STRONG RECOMMENDATION
HIGH QUALITY EVIDENCE

Key contemporary residual risk pathways in secondary prevention

Eur Heart J Volume 42, Issue 1, 7 January 2021, Pages 113–131, https://doi.org/10.1093/eurheartj/ehaa943


For every 1,000 patients treated with icosapent ethyl for 5 years, there are significant reductions in total ischemic events, including deaths from cardiovascular causes.
Risk difference
0
−50
−100
−150
−200
−12
Cardiovascular death
−42
Fatal or nonfatal MI
−14
Fatal or nonfatal stroke
−76
Coronary revascularization
−16
Hospitalization for unstable angina
−159
Primary composite endpoint

Interesting questions and answers

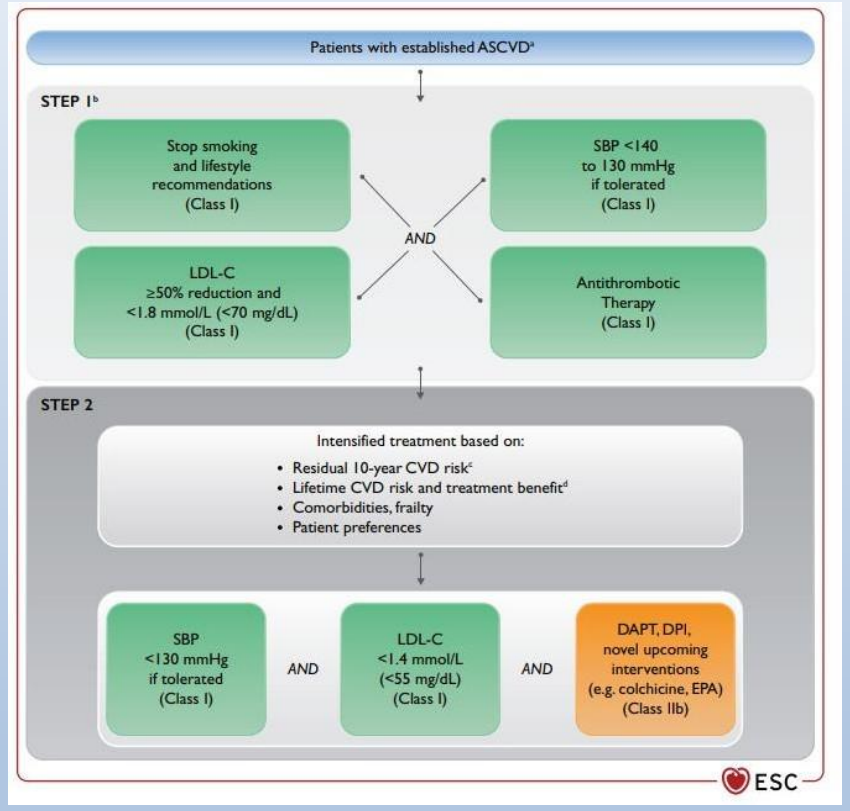


ESC guidelines: recommendations for use of icosapent ethyl

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

ESC/EAS guidelines 2019[1]



ESC guidelines on CVD prevention 2021[2]

Conclusions

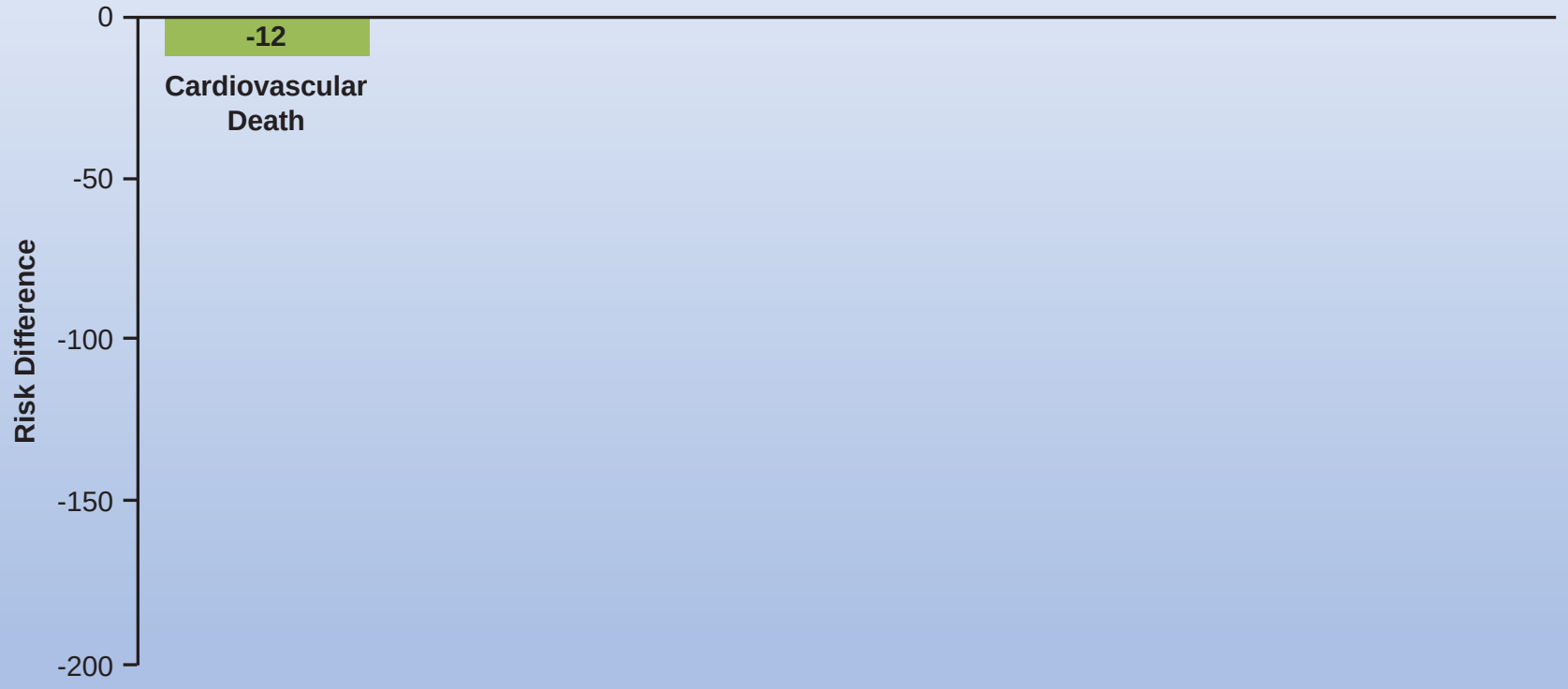
Compared with placebo, icosapent ethyl 4g/day significantly reduced total cardiovascular events by **30%**, including:

- **25%** reduction in first cardiovascular events
- **32%** reduction in second cardiovascular events
- **31%** reduction in third cardiovascular events
- **48%** reduction in fourth or more cardiovascular events

Analysis of first, recurrent, and total events demonstrates the large burden of ischemic events in statin-treated patients with baseline triglycerides > ~100 mg/dL and the potential role of icosapent ethyl in reducing this residual risk

Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019. Bhatt DL. ACC 2019, New Orleans.

For Every 1000 Patients Treated with Icosapent Ethyl for 5 Years:



Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019.

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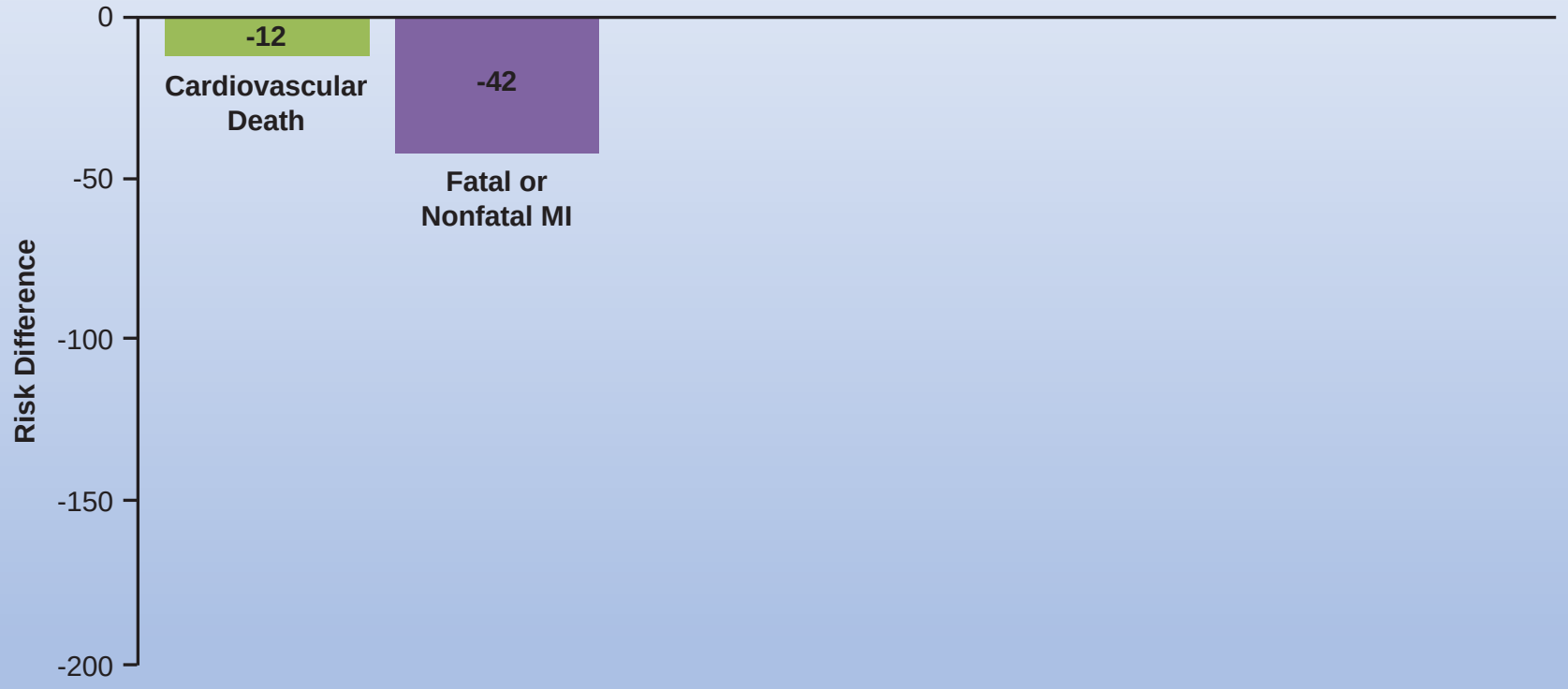

Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019.

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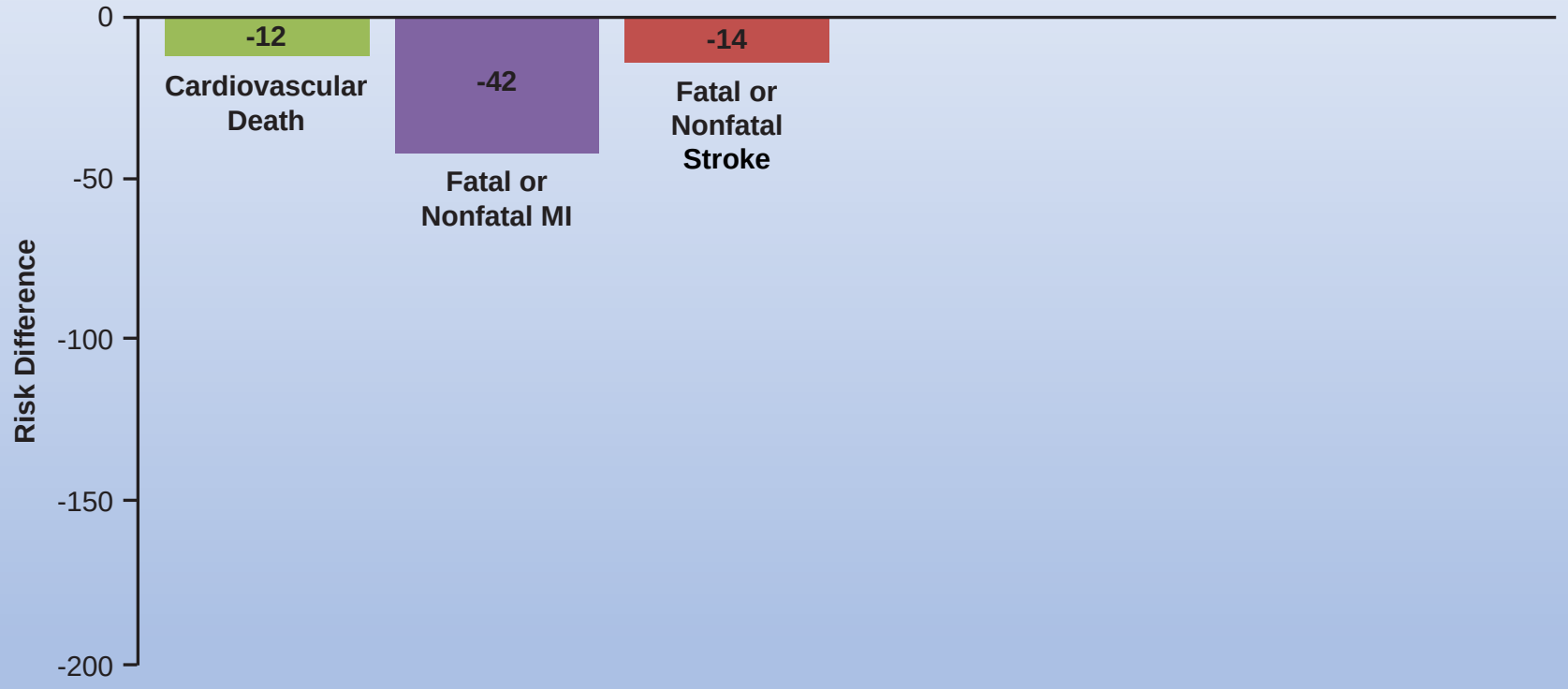
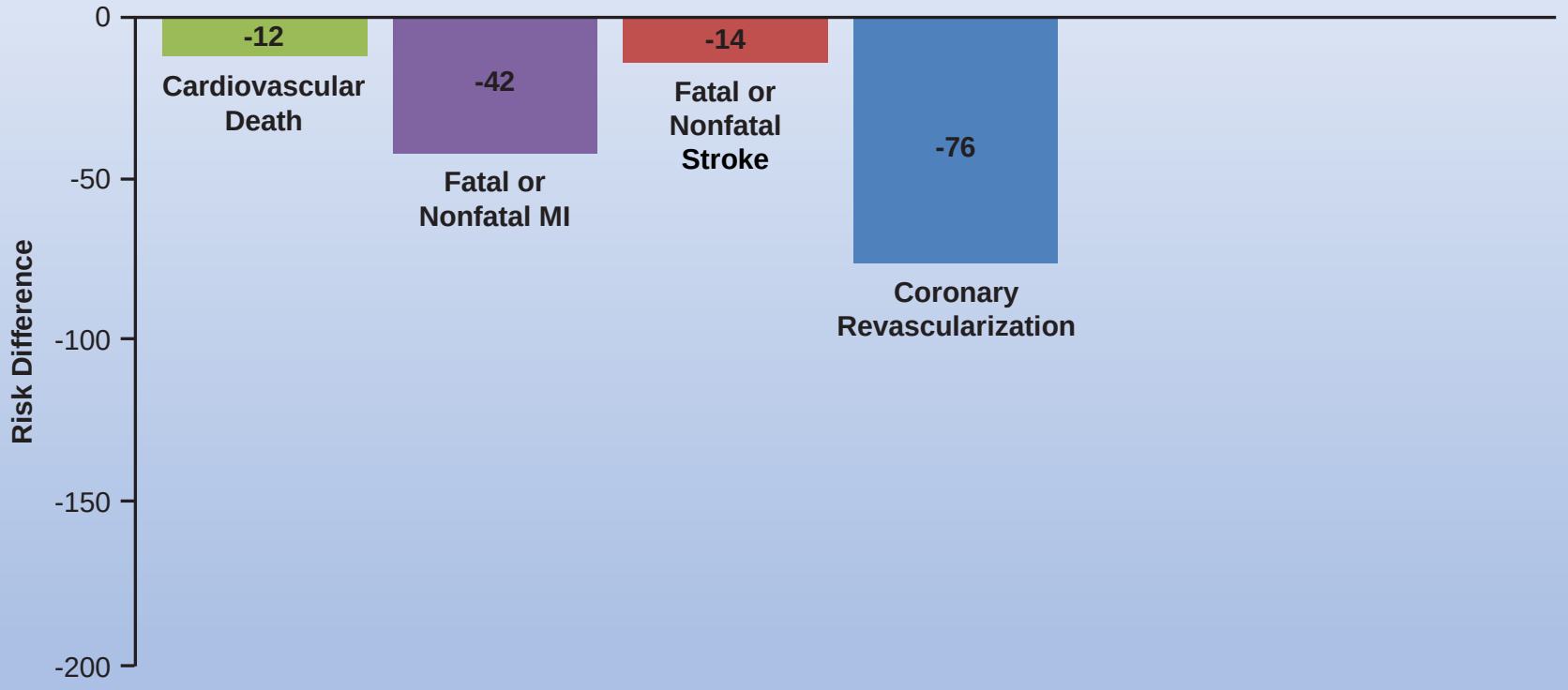


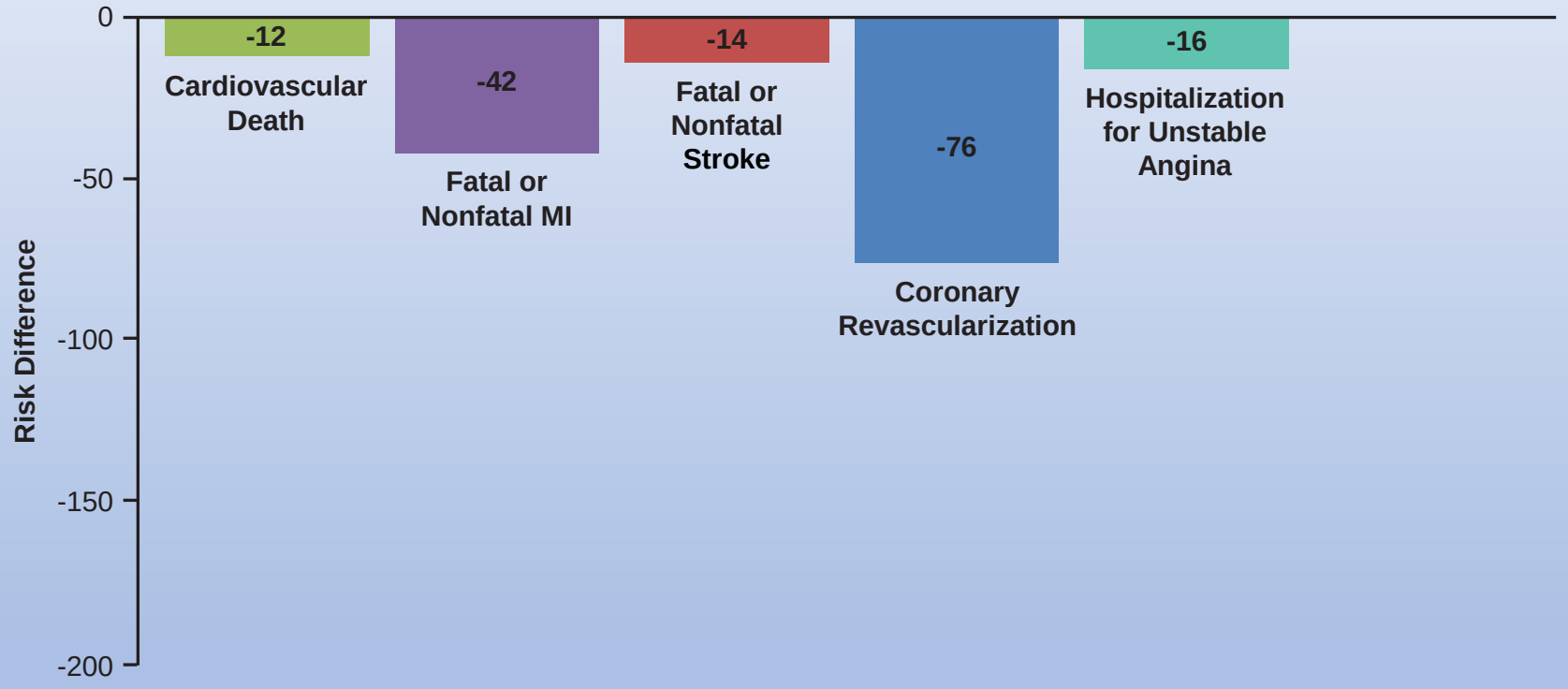
Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019.

For Every 1000 Patients Treated with Icosapent Ethyl for 5 Years:



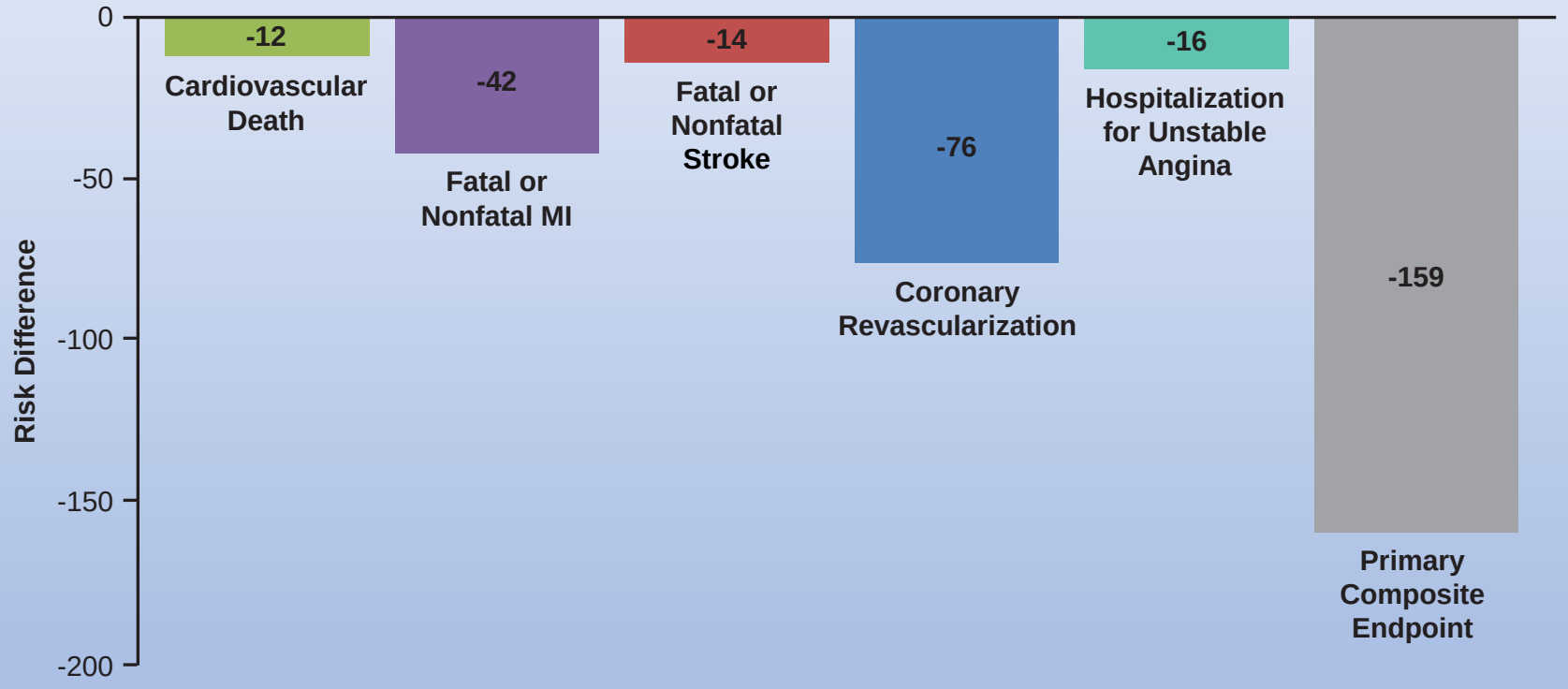
Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019.

For Every 1000 Patients Treated with Icosapent Ethyl for 5 Years:



Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019.

For Every 1000 Patients Treated with Icosapent Ethyl for 5 Years:



Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019.

CONCLUSIONS

- Statin therapy is recommended as the first-line lipid-lowering drug therapy for the management of dyslipidemia in individuals with DM
- In major statin trials, significant residual cardiovascular risk remains even after acceptable reduction of LDL-C, especially in patients with diabetes
- Ezetimibe and PCSK9 inhibitors have some beneficial effects to address the residual risk
- **The results of REDUCE-IT trial have introduced a new tool to address the residual risk…!**

ADA UPDATES, MARCH 27, 2021

- Based on findings from the Reduction of Cardiovascular Event with Icosapent Ethyl-Intervention Trial (**REDUCE-IT**), an additional recommendation has been officially added to the section "Treatment of Other Lipoprotein Fractions or Targets." The new recommendation reads as follows:

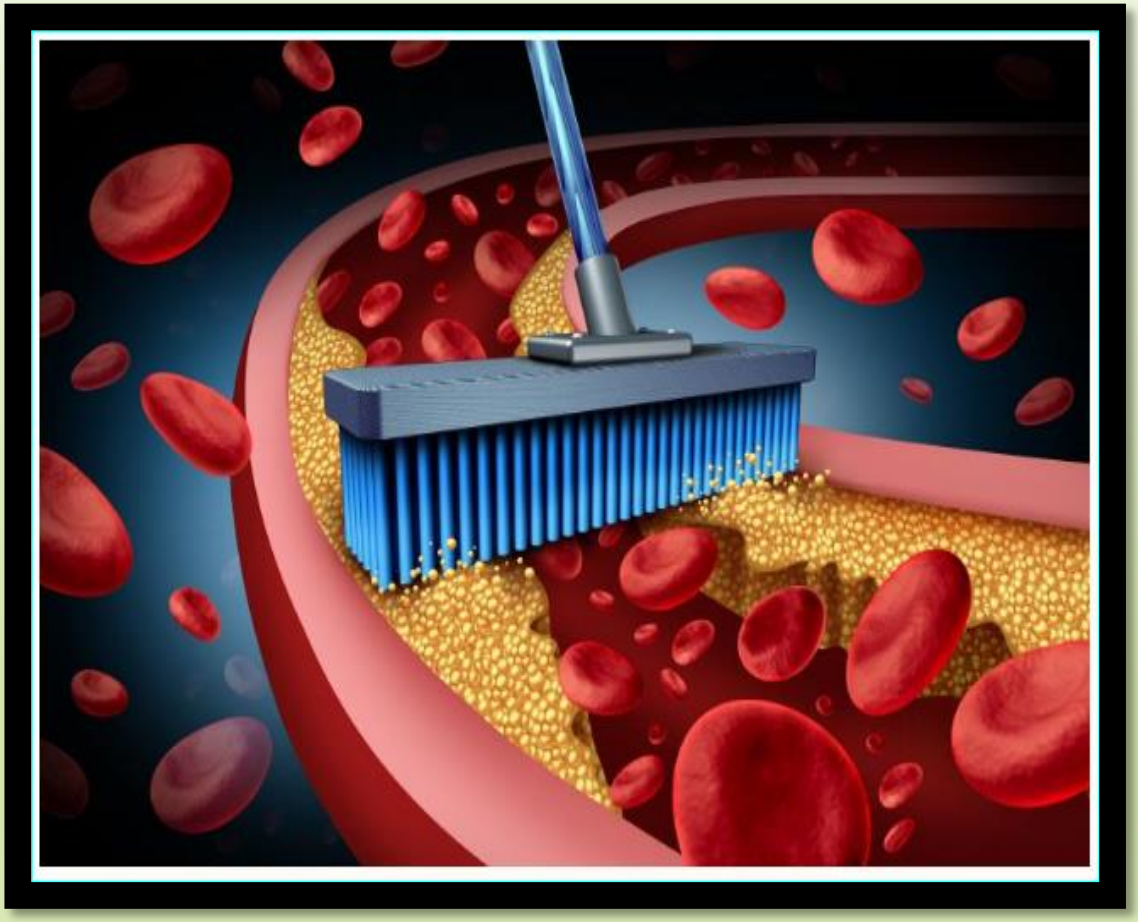
- In patients with ASCVD or other cardiac risk factors on a statin with controlled LDL-C, but elevated triglycerides (135-499), the addition of **icosapent ethyl** should be considered to reduce cardiovascular risk. **A**

- Reference: Bhatt DL, Steg G, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT, Juliano RA, Jiao L, Granowitz C, Tardif JC, Ballantyne CM; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med 2019;380:11-22.

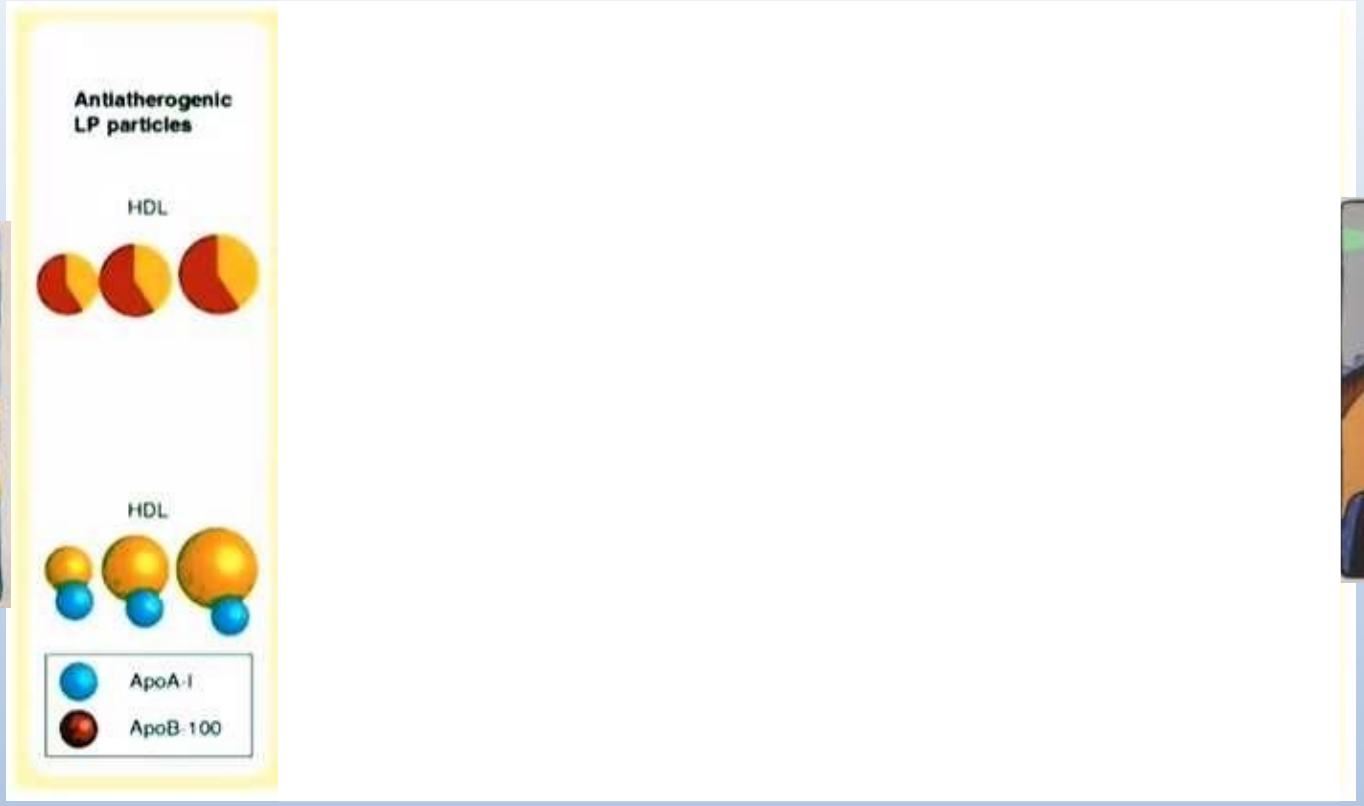
- Suggested citation: American Diabetes Association. 10. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes—2019 [web annotation]. Diabetes Care 2019;42(Suppl. 1):S103–S123. Retrieved from https://hyp.is/JHhz_JCrEembFJ9LIVBZlw/care.diabetesjournals.org/content/42/Supplement_1/S103

MORE AGGRESSIVE LIPID LOWERING IN PEOPLE WITH DIABETES?

There is ongoing debate as to whether aggressive LDL cholesterol-lowering therapy, as opposed to comprehensive lipid management addressing the hypertriglyceridaemia and low HDL cholesterol, is the optimal approach to reduce atherosclerotic cardiovascular risk in people with diabetes.



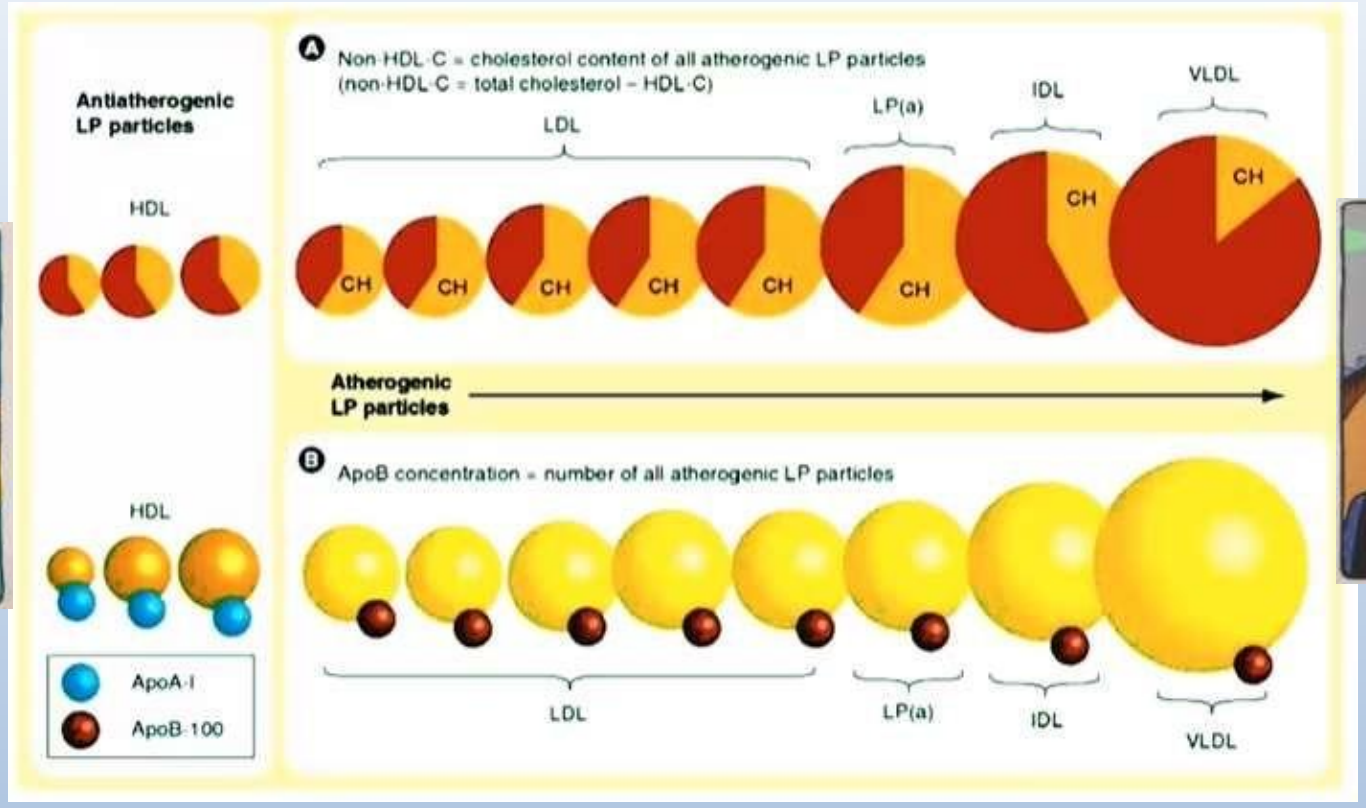
LDL-C measures only a portion of atherogenic particles – although non-HDL or ApoB captures all -



Source: Clin Lipidol © 2011 Future Medicine Ltd

Persistent CV Risk Beyond LDL-C: Case examples from 2021 CCS lipid guidelines (2021)

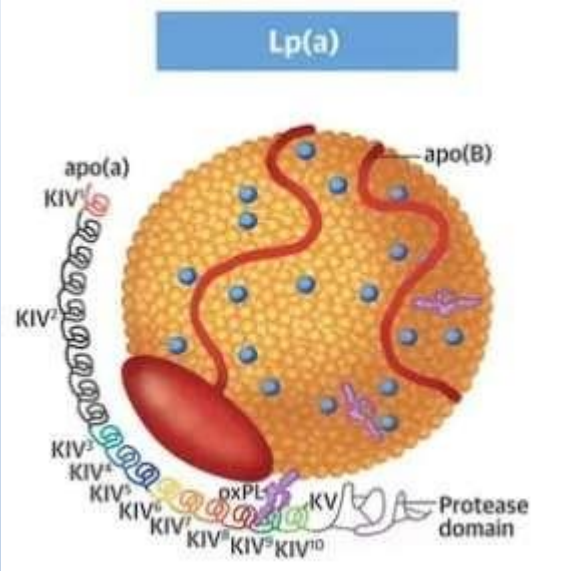
LDL-C measures only a portion of atherogenic particles – although non-HDL or ApoB captures all -



Non-HDL-C = (TC) – (HDL-C)

Persistent CV Risk Beyond LDL-C: Case examples from 2021 CCS lipid guidelines (2021)

What is Lipoprotein(a)?



Lp(a) = LDL-C + apo(a)

- A "bad" LDL with a "sticky" tail → highly atherogenic
  - Poorly correlated with LDL-C
- Lp(a) levels are almost entirely genetically determined (levels are determined at birth and remain stable over lifetime).
  - Higher in South Asians, Latin Americans and African Americans
- Independent marker of CV risk (independent of other lipids and risk factors)
  - The higher the Lp(a), the higher the risk for ASCVD and recurrent events
- Most common genetic dyslipidemia
  - Estimated 6 million Canadians have high Lp(a) defined as >50 mg/dL

t CV Risk Beyond LDL-C: Case examples from 2021 CCS lipid guidelines (2021)

Lp(a):

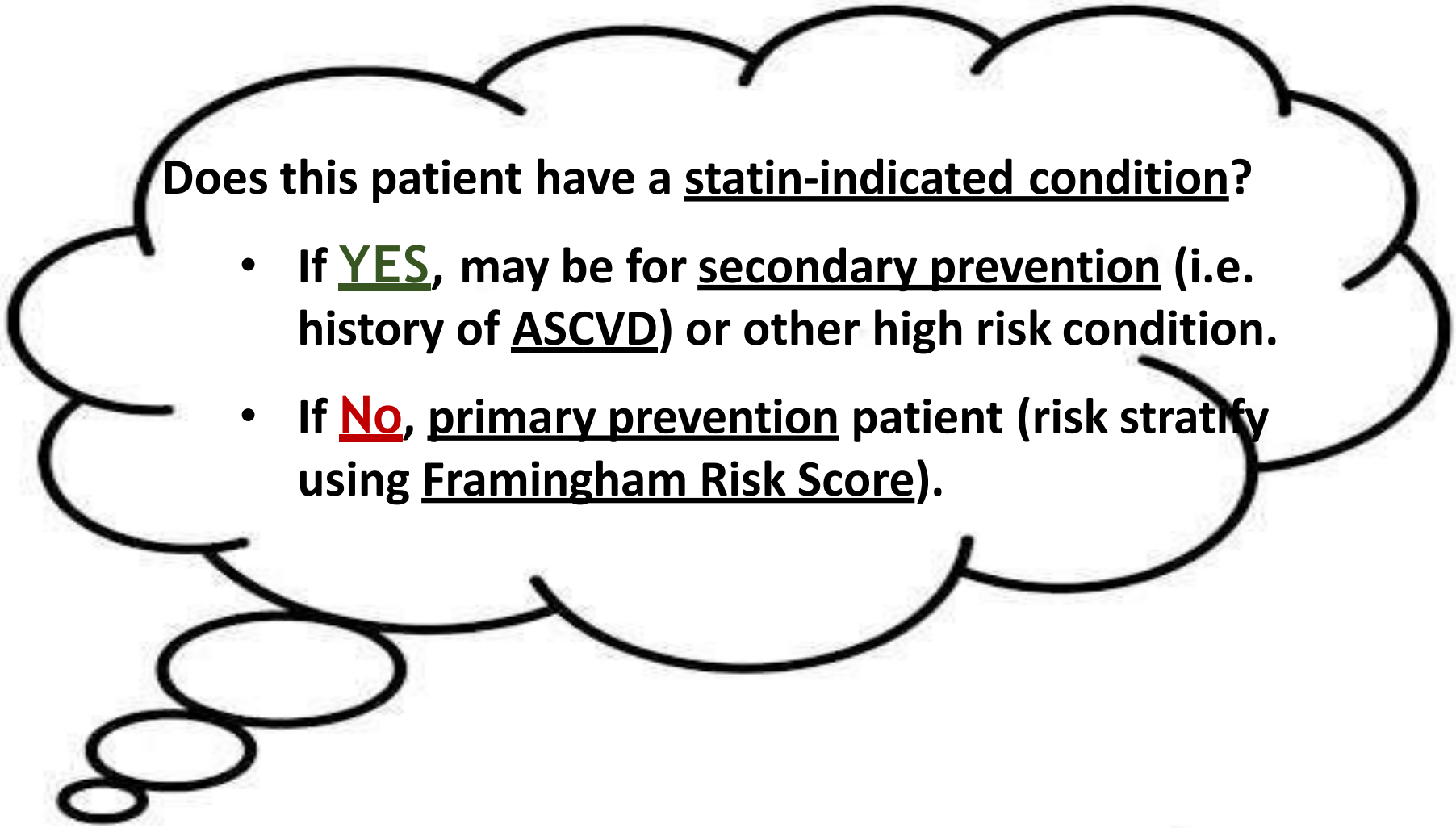
Clinical Pearls

- CCS recommends measuring Lp(a) level **once** in a person's lifetime as part of the initial lipid screening

- For all patients with Lp(a) ≥50 mg/dL (or ≥100 nmol/L), this is associated with a >2-fold increased CV risk and thus recommend earlier screening, health behaviour counselling and management of other CV risk factors in the setting of primary prevention.

- Currently a **marker of risk and not a treatment target** – only test once in each adult's lifetime
  - Patients with high Lp(a) should have **earlier consideration of LDL-lowering therapies** (and be more aggressive in when to start therapy).
  - Possible future therapies reducing Lp(a) (?early thoughts re: PCSK9i)

Who to Treat to reduce ASCVD



Does this patient have a statin-indicated condition?

- **If YES, may be for secondary prevention (i.e. history of ASCVD) or other high risk condition.**
- **If No, primary prevention patient (risk stratify using Framingham Risk Score).**

Step 3 – Who to Treat to reduce ASCVD risk?

A. Based on Clinical Factors (Framingham Risk Calculation not req'd):

1. Patients with Statin-Indicated Conditions:
   a. Clinical ASCVD *("**secondary prevention**")* or AAA
   b. Diabetes mellitus if >40 yo, or >30 yo with microvascular disease or >15 yrs duration
   c. Chronic kidney disease (non-dialysis, eGFR <60 mL/min or urine ACR ≥ 3.0 mg/mmol)
   d. FH or LDL-C ≥5.0 or non-HDL-C ≥5.8 mmol/L or ApoB ≥ 1.45 g/L

Secondary Prevention

2. Patients with very high TG ≥10 mmol/L and/or history of TG-related pancreatitis → fibrates.

Step 3 – Who to Treat to reduce ASCVD risk?

Primary Prevention

B. Based on Calculation of Framingham Risk Score (FRS):

1. High FRS (≥20%/10yrs) – all patients should be treated with statins

2. Intermediate FRS (10-19.9%/10-yrs) and LDL-C ≥3.5 mmol/L or non-HDL-C ≥4.2 mmol/L or ApoB ≥ 1.05 g/L

3. Intermediate FRS (10-19.9%/10-yrs) and LDL-C <3.5 mmol/L or nonHDL-C <4.2 mmol/L or ApoB <1.05 g/L or other risk enhancers:
   - Men ≥50 yrs and women ≥60 yrs with one additional risk factor: low HDL-C, IFG, high waist circumference, smoker or HTN **or the presence of other risk modifiers: hsCRP ≥2.0 mg/L, CAC >0 AU, family history of premature CAD, Lp(a) ≥ 50 mg/dL (100 nmol/L)**

4. Low FRS (<10%/10-yrs) – statin therapy (beyond health behaviour modification) not recommended for most low-risk individuals, exceptions include:
   - LDL-C ≥ 5.0 mmol/L (or non-HDL-C ≥ 5.8 mmol/L or ApoB ≥ 1.45 g/L) or
   - FRS (5-9%/10 years) LDL-C ≥ 3.5 mmol/L (or non-HDL-C ≥ 4.2 mmol/L or ApoB ≥ 1.05 g/L), particularly with **other CV risk modifiers (e.g., FHx, Lp(a) ≥50 mg/dL [or ≥100 nmol/L] or CAC >0 AU)**

Step 4 – How to treat patients (dyslipidemia)?

**Reminder: multimodal approach to CV risk reduction and addressing all vascular risk factors (BP, glucose, lipids), diet, exercise, weight goals, alcohol and smoking.

- Start with health behaviour modifications
- Pharmacotherapy: Statins
  - Shift from 'targets' to 'thresholds' – *lower is better!*
  - What are ' thresholds to intensify therapy' beyond maximally tolerated statins with Ezetimibe and/or PCSK9i (FH and secondary prevention).
- Reducing Residual Risk: Secondary Prevention (ASCVD) or DM w/ RFs (and elevated TG): Icosapent ethyl (IPE)

Simultaneous Publication

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk

A. Das Pradhan, R.J. Glynn, J.-C. Fruchart, J.G. MacFadyen, E.S. Zaharris, B.M. Everett, S.E. Campbell, R. Oshima, P. Amarenco, D.J. Blom, E.A. Brinton, R.H. Eckel, M.B. Elam, J.S. Felicio, H.N. Ginsberg, A. Goudev, S. Ishibashi, J. Joseph, T. Kodama, W. Koenig, L.A. Leiter, A.J. Lorenzatti, B. Mankovsky, N. Marx, B.G. Nordestgaard, D. Páll, K.K. Ray, R.D. Santos, H. Soran, A. Susekov, M. Tendera, K. Yokote, N.P. Paynter, J.E. Buring, P. Libby, and P.M Ridker, for the PROMINENT Investigators*

CENTER FOR CARDIOVASCULAR DISEASE PREVENTION
BRIGHAM AND WOMEN'S HOSPITAL

ClinicalTrials.gov Identifier: NCT03071692

Challenges in Atherosclerotic Cardiovascular Disease reduction and Triglyceride-related risk

Erik Stroes, MD

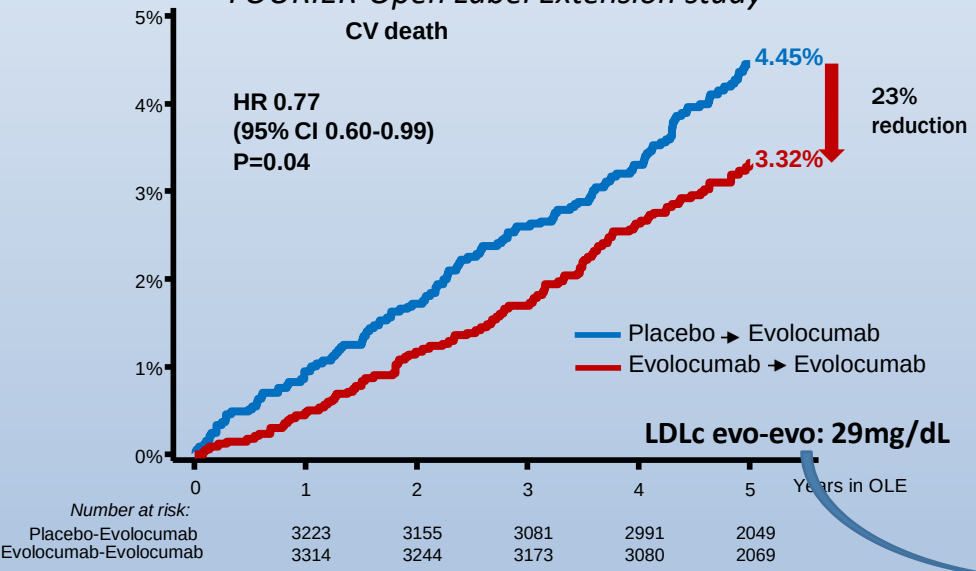
Amsterdam UMC, The Netherlands

Improving the management of patients with atherosclerotic cardiovascular disease - The evolving role of icosapent ethyl

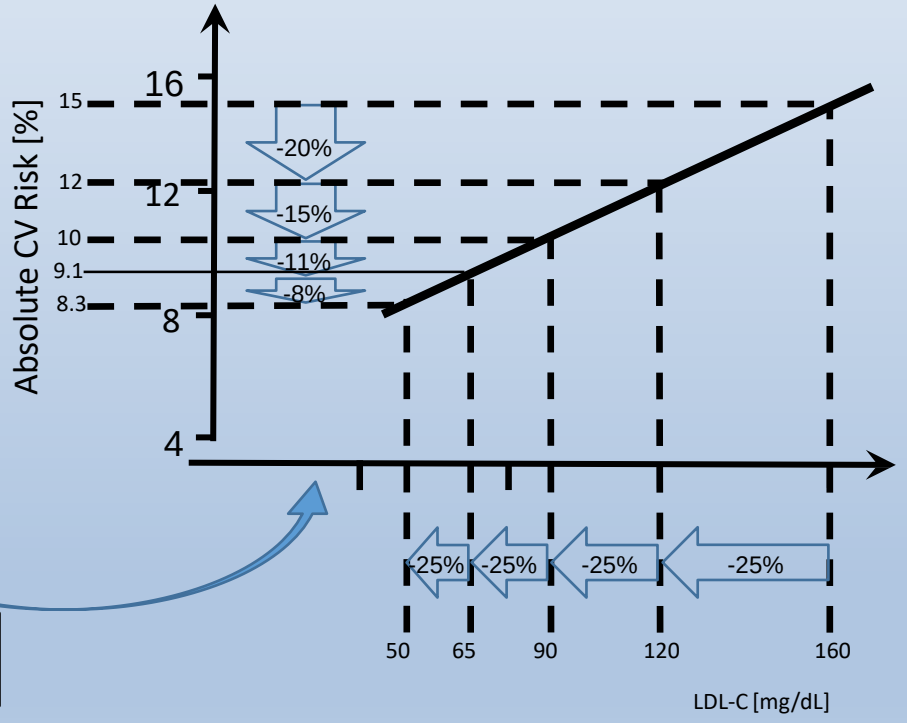
PHYSICIANS' ACADEMY FOR CARDIOVASCULAR EDUCATION
PACE-CME

Residual risk in patients with very-low LDLc levels

Significant benefit with marked residual risk
FOURIER-Open Label Extension study



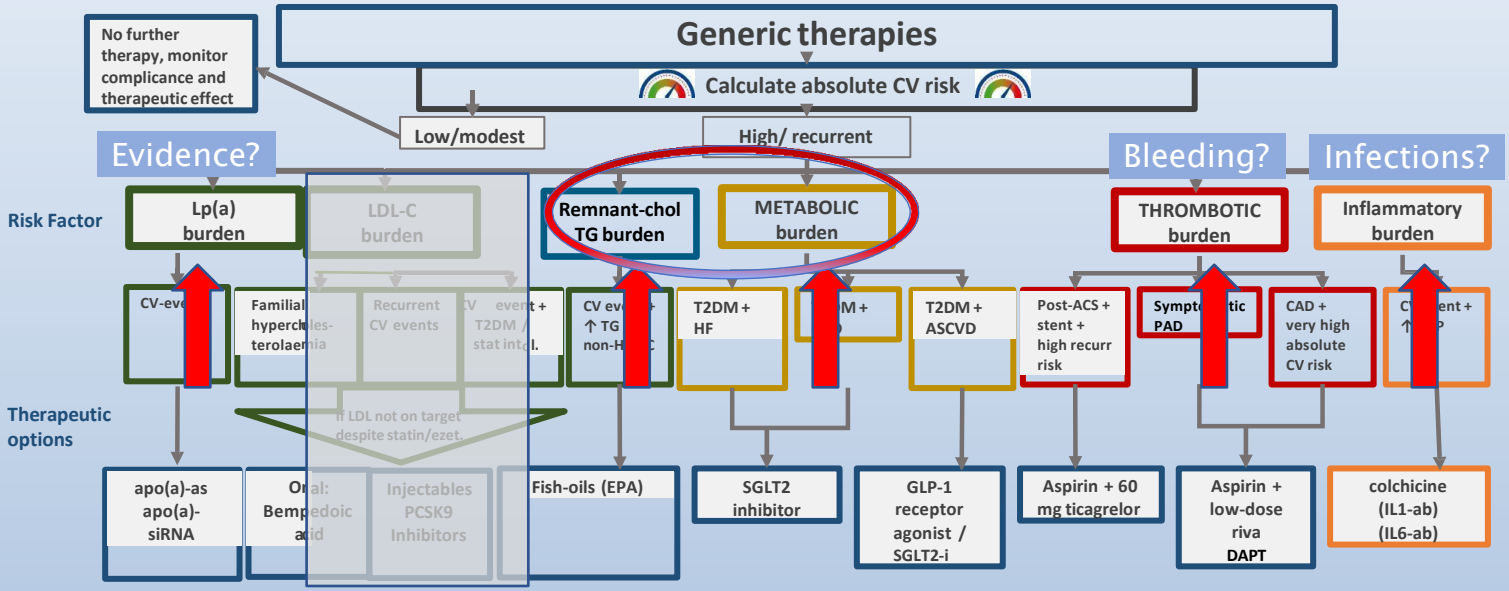
Further LDLc lowering - limited benefit



Recurrent CV-event rate in evo-evolocumab : **14.6% /5yr**
Recurrent CV-event rate in placebo-evolocumab: **16.8% /5yr**

O'Donaghue, *Circulation* 2022; Gaba P, *Circulation* 2023; Laufs, *Eur Heart J* 2014

Other pillars ‘contributing’ to atherogenesis

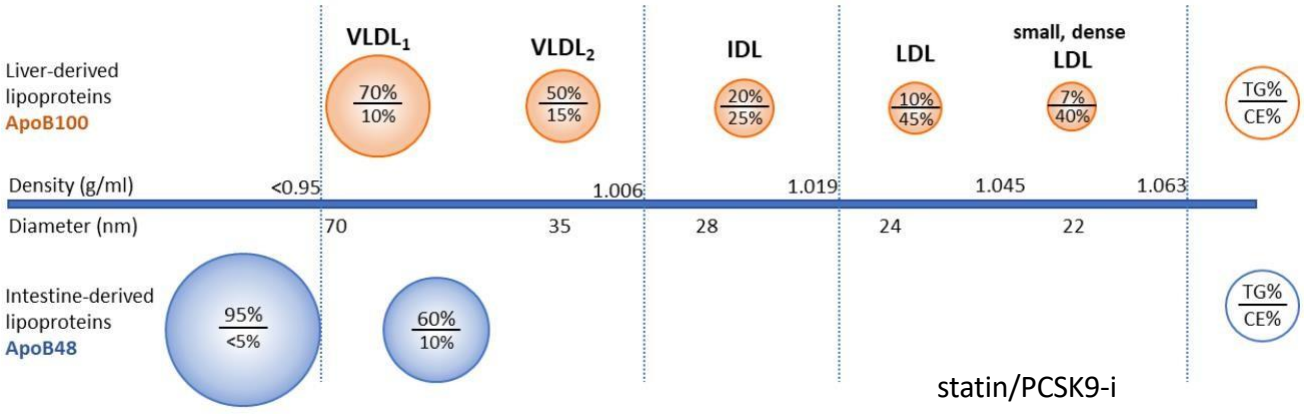


Hoogeveen, Stroes, Neth Heart J 2021

When cardiologist talk about high TGs .

TGs are 'heterogeneous'

Size and density profile of major apolipoprotein-B containing lipoprotein classes



statin/PCSK9-i

apoB containing lipoproteins

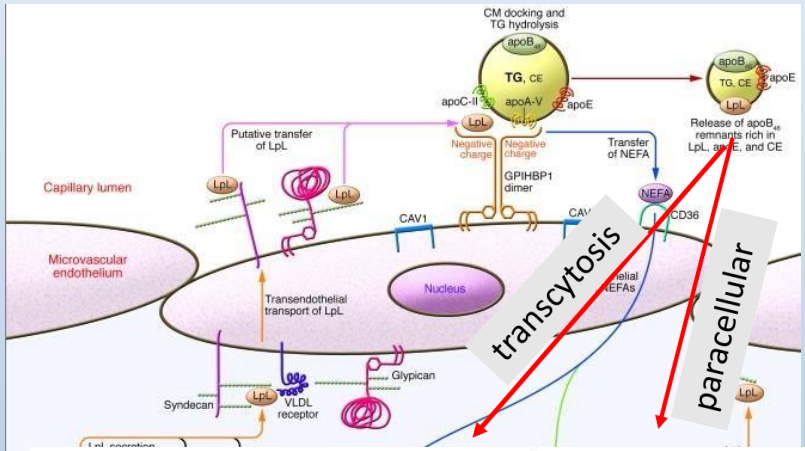
Triglycerides / Triglyceride-rich lipoproteins

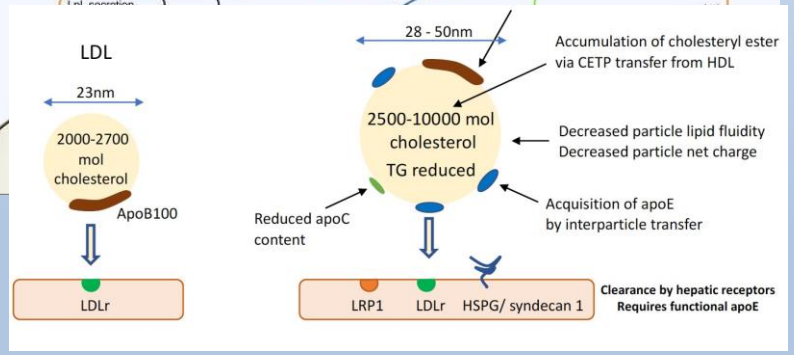
Triglyceride-remants /
Remnant cholesterol

Ginsberg H, et al. Consensus on HTG. *Eur Heart J 2021*

Why are Triglyceride-rich particles atherogenic?

Experimental evidence: direct uptake in the arterial wall





Yang, Int J Mol Sciences 2018; Hassing, BBA 2012;
Ginsberg, Eur H J 2022; Steender & Zilversmit, Atherosclerosis 1981

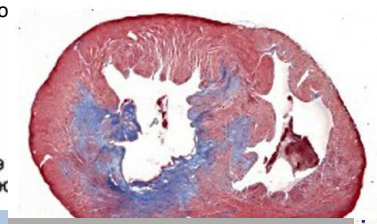
Table 1. Labeled Esterified Cholesterol in Plasma and Tissues after Injection of ^{14}C-Cholesterol-Labeled Chylomicrons and ^{3}H-Cholesterol-Labeled d < 1.019 Lipoproteins

Animal*	Duration (hr)	Mean plasma ^{14}C (% of d	Mean plasma ^{3}H	Intima-media†	Liver† ^{14}C	Liver† ^{3}H
1	1.4	0.78				
2	1.8	0.61				
3	3.2	0.74				
4	3.3	0.64				
5	3.8	0.53				
6	4.3	0.42				
7	4.4	0.47				

Anitschkow

Chylomicro

Figure 4. The
take of labelec



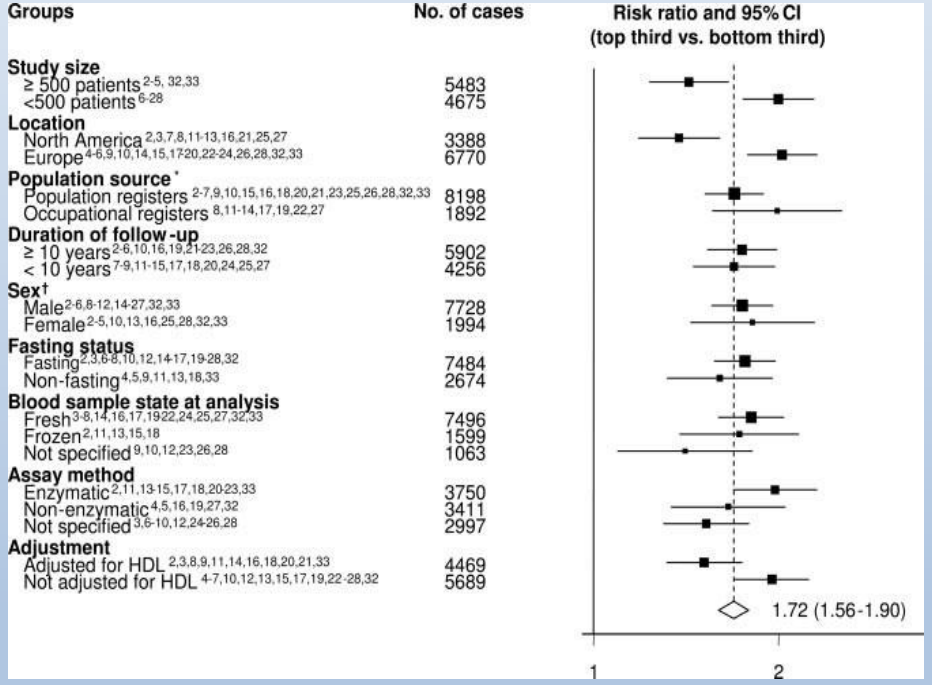
Atherosclerosis in rabbits

Vulnerable coronary plaque

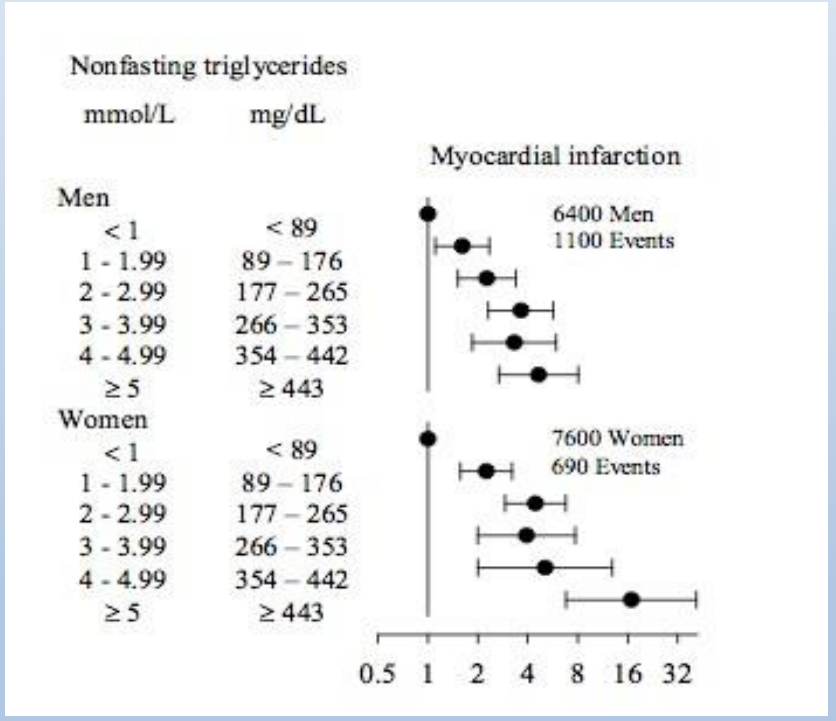
Are Triglycerides associated with Atherogenesis?

Epidemiological evidence: TG associated with CV-risk

TGs association with CV-risk
10.158 Cases in 262.525 subjects



non-fasting TGs associate with CV-risk
in both men and women

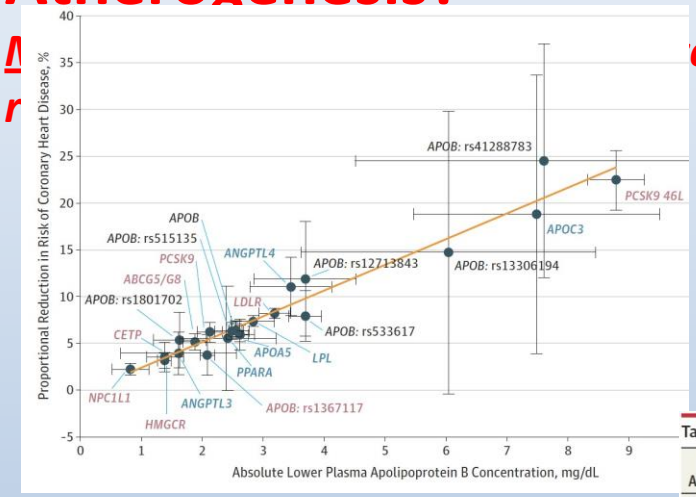


Sarwar. Circulation 2007; Nordestgaard B, Circ Res 2016

Kolovou etal Curr Vasc Rep 2011, 9:258-270

Are Triglycerides a 'causal' factor in Atherogenesis?

M… …e: TRL-C (particle number)
r…



Clinical benefit of LDL-C or TG/TRL-C lowering is proportional to the reduction in the number of atherogenic particles, i.e. apoB reduction

Table 3. Multivariable Mendelian Randomization Analysis of the Association Between Plasma Triglycerides, LDL-C, and ApoB With the Risk of CHD[a]

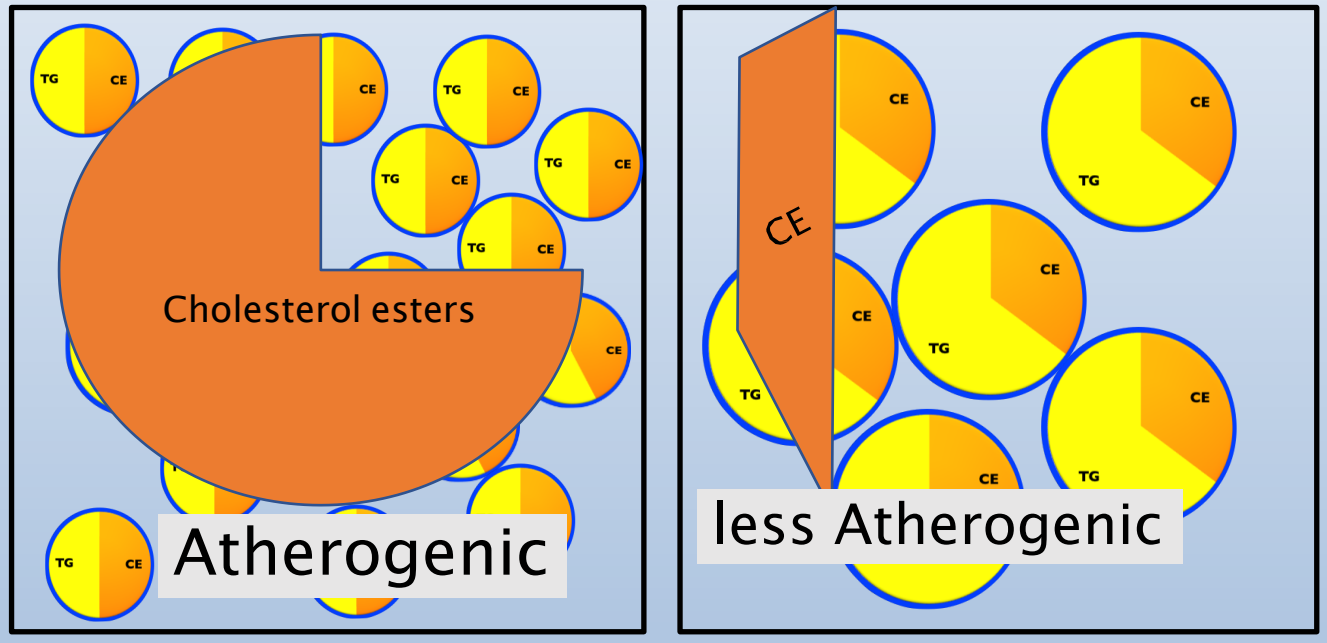
Analysis	Variables	Odds Ratio for CHD (95% CI)	*P* Value
Association of 10-mg/dL lower ApoB with risk of CHD	ApoB	0.770 (0.760-0.781)	1.42E-170
Association of 10-mg/dL lower LDL-C with risk of CHD	LDL-C	0.846 (0.833-0.858)	8.16E-77
Association of 50-mg/dL lower triglycerides with risk of CHD	Triglycerides	0.815 (0.785-0.846)	1.37E-18
Association of 10-mg/dL lower LDL-C and 50-mg/dL lower triglycerides with risk of CHD included in same model	LDL-C	0.862 (0.849-0.875)	6.92E-65
	Triglycerides	0.876 (0.850-0.902)	1.36E-14
Association of 10-mg/dL lower LDL-C, 50-mg/dL lower triglycerides, and 10-mg/dL lower ApoB with risk of CHD included in same model	ApoB	0.761 (0.723-0.798)	7.51E-20
	LDL-C	1.010 (0.967-1.055)	.19
	Triglycerides	1.014 (0.965-1.065)	.19

Varbo, Circ 2013; Jorgenson, NEJM 2014; TG working group, NEJM 2014
Cardiogram consortium, NEJM 2016; Helgadottir, Nature genetics 2016
Dewey, NEJM 2016; Dewey, NEJM 2017; …..

Ference, JAMA 2019

But. what is high Triglycerides?
a mixed bag

TG 4.5 mmol/l (405 mg/dL)



High apo B 1350mg/l

Low apo B 870 mg/l

Triglyceride-rich particles ‘drive’ atherogenic risk

	Mg/dl	Mmol/l
TC	231	6.0
HDL-C	37	0,97
LDL-C	126	3.27

VLDL

	Mg/dl	Mmol/l
TC	308	8.0
TG	835	5.95
HDL-C		1,05
Non-HDL-c	268	6,95
LDL-C	nm	nm
apoB	140	1.4 g/l

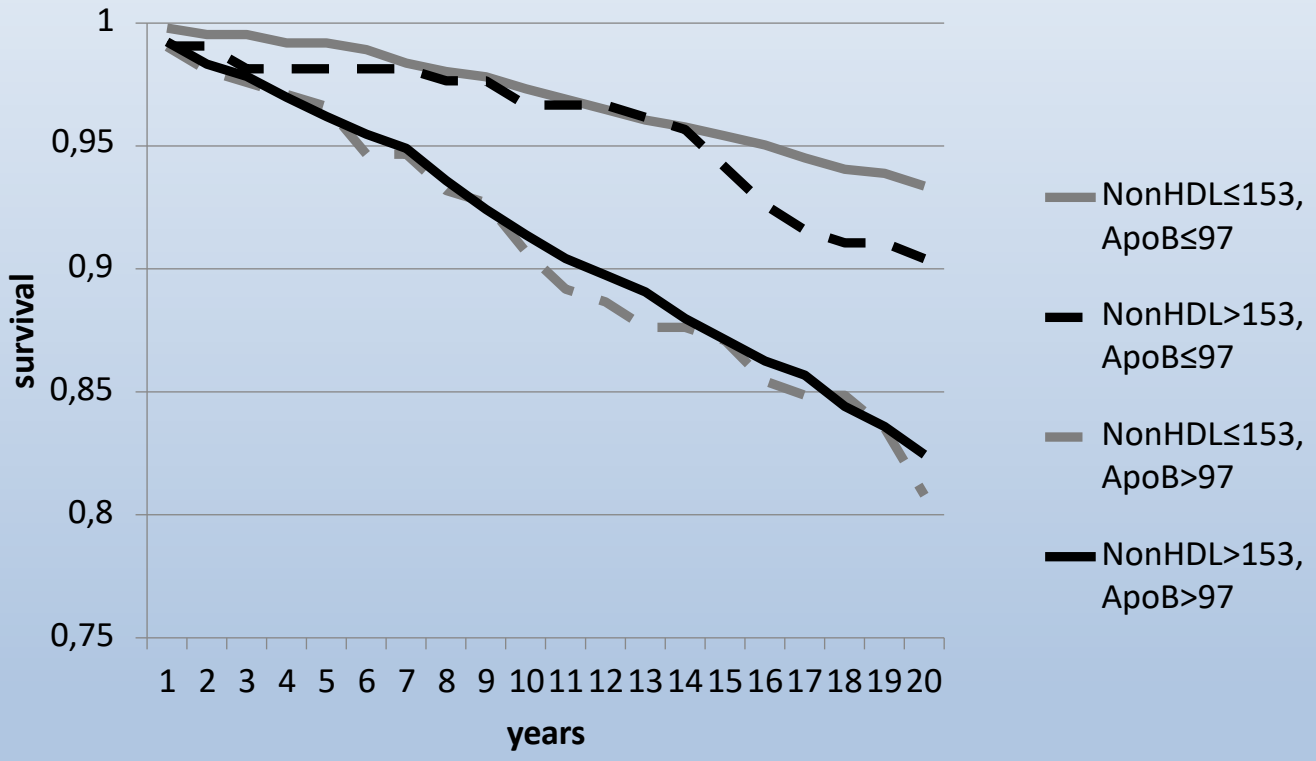
VLDL and LDL

	Mg/dl	Mmol/l
TC	316	8,2
TG	974	11,0
HDL-C		0.60
Non-HDL-c	29[illegible]	[illegible]6
LDL-C	nm	nm
apoB	100	1,0 g/l

VLDL + chylomicrons

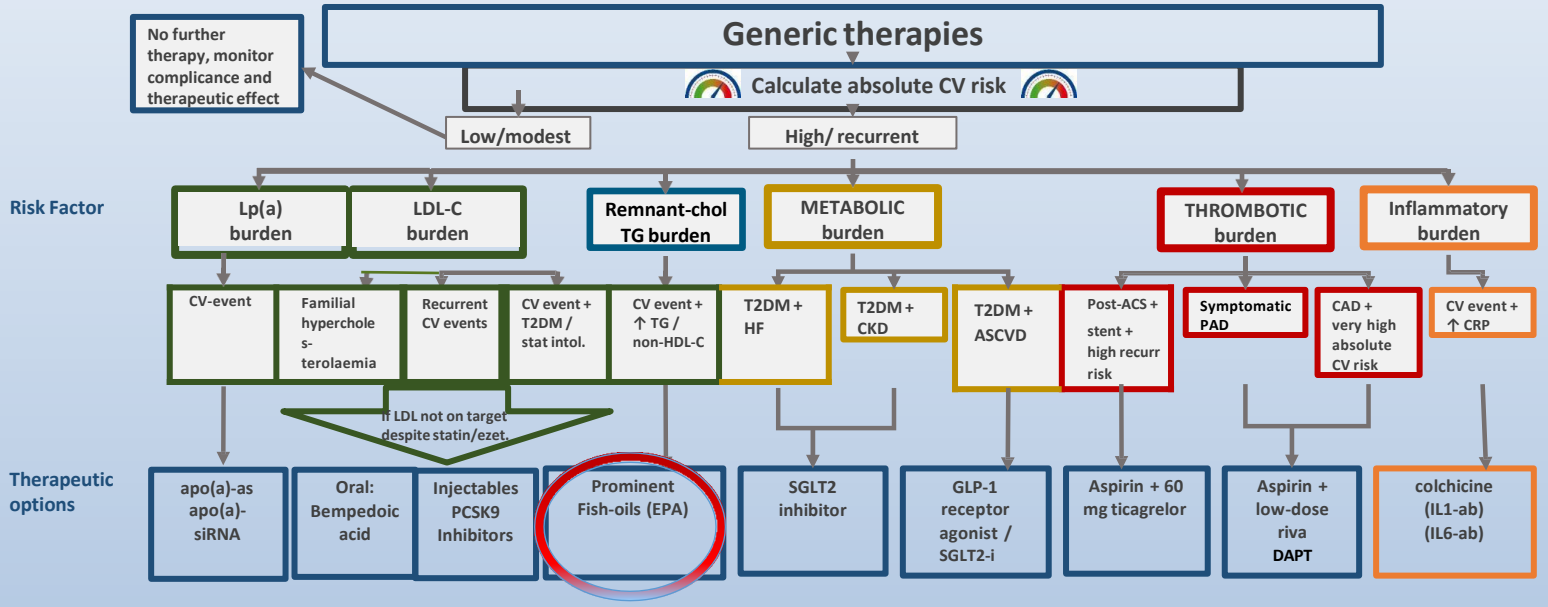
And we have known this for decades: Only an increased 'number' of TRLs associate with risk

Framingham Heart Study



Schaeffer E, et al, J Lip Res 1994

Does 'TG'-lowering reduce residual CV-risk?



Hoogeveen R, Neth J Med 2021

PROMINENT:

Pemafibrate in high-risk hypertriglyceridemic DM-II patients

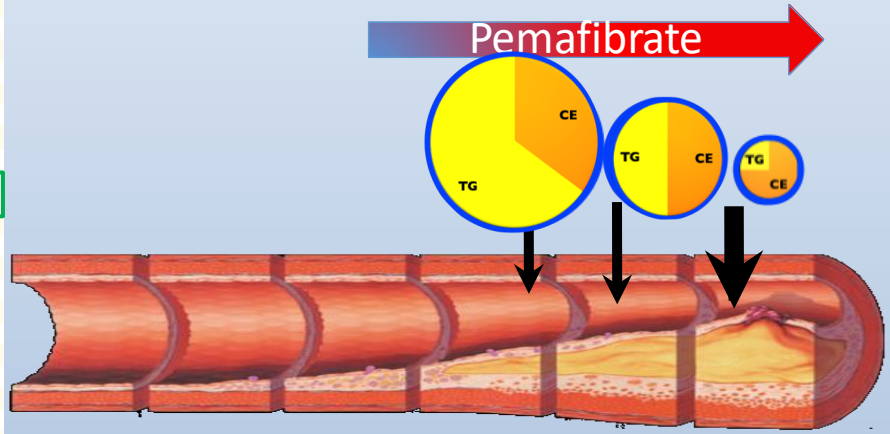
Variable	Pemafibrate (N = 5240)	Placebo (N = 5257)	Treatment Effect†
	Median Value (IQR)		Mean % Change (95% CI)
Triglyceride-related biomarkers			
Triglyceride level, measured			
Baseline — mg/dl	273 (22[illegible] to 342)		
4 Mo — mg/dl	189 (1[illegible] to 253)		
Median change from baseline — %	−31.1 (−48.9 to −9.6)	−6.9 (−28.4 to 20.2)	−26.2 (−28.4 to −24.10)
VLDL cholesterol level, calculated — mg/dl‡			
Baseline — mg/dl	49 (39 to 63)	49 (39 to 62)	
4 Mo — mg/dl	31 (23 to 42)	43 (32 to 59)	
Median change from baseline — %	−35.0 (−54.1 to −11.5)	−10.5 (−33.3 to 17.4)	−25.8 (−27.8 to −23.9)
Remnant cholesterol level, calculated§			
Baseline — mg/dl	47 (38 to 60)	47 (37 to 59)	
4 Mo — mg/dl	32 (24 to 42)	39 (29 to 52)	
Median change from baseline — %	−31.3 (−49.1 to −8.2)	−15.6 (−36.8 to 10.8)	−18.2 (−20.3 to −16.1)
Remnant cholesterol level, measured			
Baseline — mg/dl	56 (4[illegible] to 73)		
4 Mo — mg/dl	30 (2[illegible] to 41)		
Median change from baseline — %	−43.6 (−57.8 to −24.1)	−20.2 (−38.3 to 3.8)	−25.6 (−27.3 to −24.0)
Apolipoprotein C-III level, measured			
Baseline — mg/dl	15 (13 to 19)	15 (13 to 18)	
4 Mo — mg/dl	11 (9 to 14)	15 (12 to 19)	
Median change from baseline — %	−27.8 (−43.8 to −9.1)	0.0 (−18.8 to 18.8)	−27.6 (−29.1 to −26.1)
Other lipid biomarkers			
Total cholesterol level, measured			
Baseline — mg/dl	161 (139 to 193)	161 (137 to 191)	
4 mo — mg/dl	162 (138 to 190)	158 (134 to 190)	
Median change from baseline — %	−0.5 (−12.2 to 13.2)	−1.2 (−12.1 to 11.0)	0.8 (−0.1 to 1.6)
HDL cholesterol level, measured			
Baseline — mg/dl	33 (29 to 37)	33 (29 to 37)	
4 Mo — mg/dl	36 (30 to 42)	34 (30 to 39)	
Median change from baseline — %	8.3 (−5.3 to 25.0)	3.1 (−7.4 to 15.6)	5.1 (4.2 to 6.1)
LDL cholesterol level, measured			
Baseline — mg/dl	79 (6[illegible] to 104)		
4 Mo — mg/dl	91 (7[illegible] to 115)		
Median change from baseline — %	14.0 (−6.3 to 41.4)	2.9 (−13.5 to 24.6)	12.3 (10.7 to 14.0)
Apolipoprotein B level, measured			
Baseline — mg/dl	90 (7[illegible] to 108)		
4 Mo — mg/dl	93 (7[illegible] to 111)		
Median change from baseline — %	3.2 (−12.0 to 19.7)	−1.6 (−13.4 to 11.8)	4.8 (3.8 to 5.8)

84 mg/dl TG decrease

26 mg/dl RC decrease

12 mg/dl LDL-C increase

3 mg/dl apoB increase



Das-Pradhan N Engl J Med 2022;

Fibrates: Enhancing TG-metabolism?

TG lowering in absence of TRL-reduction not beneficial

Effect Pemafibrate	%change compared to placebo	Abs. difference Vs placebo
TG change	-26.2 %	- 69 mg/dl
Remnant chol	-25.6 %	- 12 mg/dl
LDLc	+12.3 %	+ 10 mg/dl
apoB	+ 4.8 %	+ 5 mg/dl

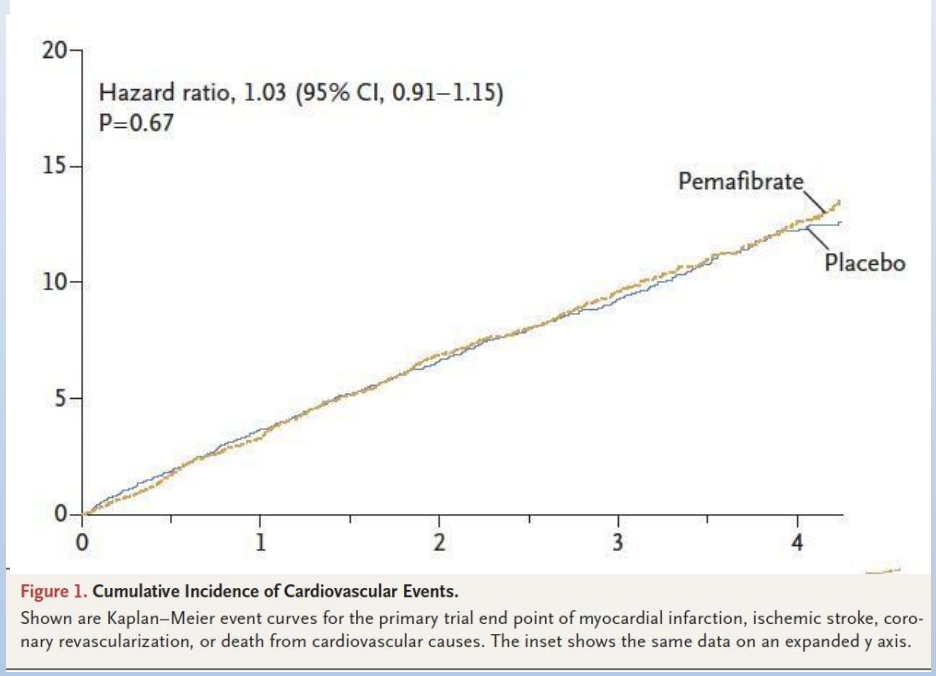


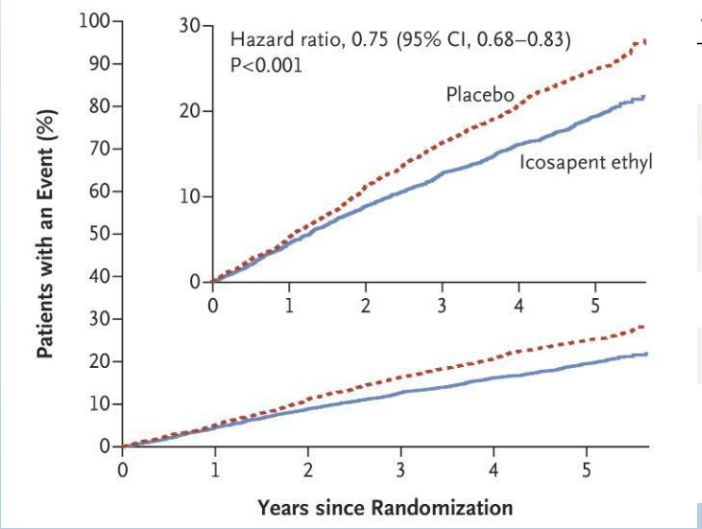
Figure 1. **Cumulative Incidence of Cardiovascular Events.**
Shown are Kaplan–Meier event curves for the primary trial end point of myocardial infarction, ischemic stroke, coronary revascularization, or death from cardiovascular causes. The inset shows the same data on an expanded y axis.

Fibrate does not 'remove' Triglyceride-rich particles
It shifts atherogenic particles towards other atherogenic particles

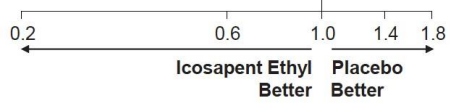
Das-Pradhan N Engl J Med 2022; Ginsberg H, Eur Heart J 2021

REDUCE-IT: Icosapent-ethyl in hyperTG-patients

Benefit 'independent' of TG-effect?



TOTAL EVENTS – Primary Composite Endpoint/Subgroup	Icosapent Ethyl	Placebo	RR (95% CI)	P-value
	Rate per 1000 Patient Years	Rate per 1000 Patient Years		
Primary Composite Endpoint (ITT)	61.1	88.8	0.70 (0.62–0.78)	<0.0001
Baseline Triglycerides by Tertiles*				
≥81 to ≤190 mg/dL	56.4	74.5	0.74 (0.61–0.90)	0.0025
>190 to ≤250 mg/dL	63.2	86.8	0.77 (0.63–0.95)	0.0120
>250 to ≤1401 mg/dL	64.4	107.4	0.60 (0.50–0.73)	<0.0001



*P (interaction) = 0.1

TG-reduction: 39 mg/dl *(pemafibrate: -84mg/dl)*

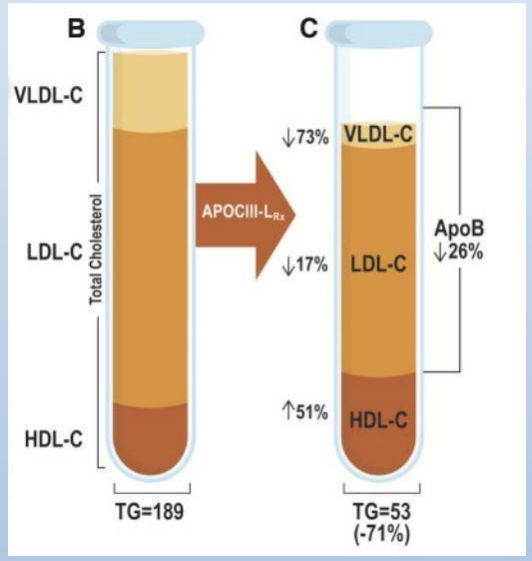
Icosapent ethyl is not a TG-lowering drug,
Mechanism of benefit? Prof G Steg

Bhatt, N Engl J Med 2019

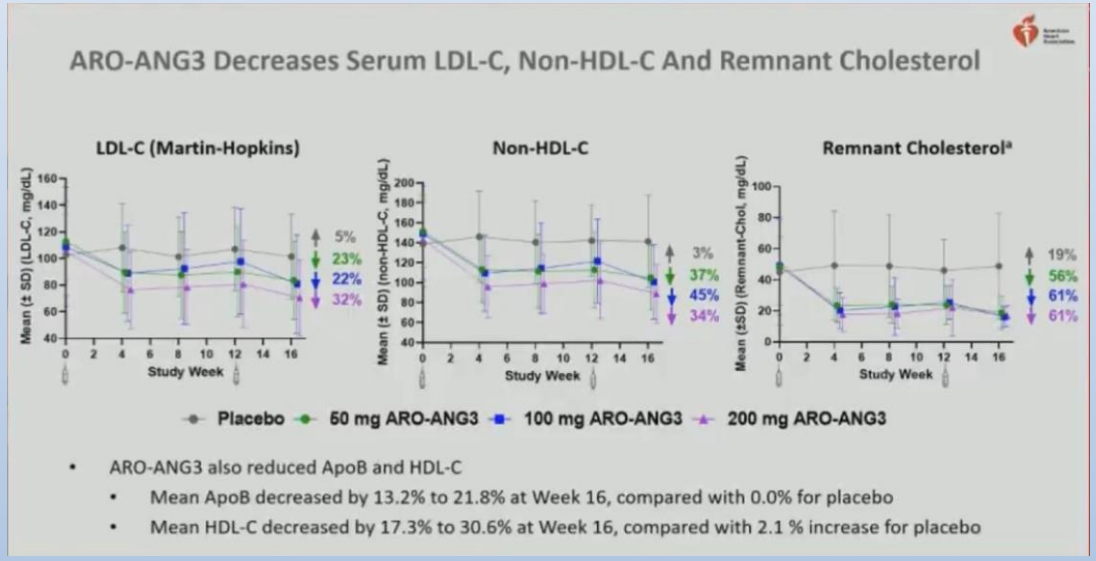
Benefit of TLR-lowering on CVD needs to be tested

using TRL-lowering therapies

apoCIII antisense therapy



ANGPTL3 siRNA therapy



Alexander V, Eur Heart J 2019 Rosenson, AHA 2022

Summary: Challenges in Atherosclerotic Cardiovascular Disease reduction and Triglyceride-related risk

- **TG reduction should not be used as target** for CVD-reduction
- **Triglyceride-rich lipoprotein** (**TRL**) **reduction**, i.e. reduction apoB + TG, **best surrogate** for CVD-reduction
- **Beta-lipoprotein reduction, comprising LDLc + TRL-C, is best target**

ONGOING THERAPY AND MONITORING WITH LIPID PANEL

- In adults not taking statins or other lipid-lowering therapy, it is reasonable to obtain a lipid profile at the time of diabetes diagnosis, at an initial medical evaluation, and every 5 years thereafter if under the age of 40 years, or more frequently if indicated. E

- Obtain a lipid profile at initiation of statins or other lipid lowering therapy, 4–12 weeks after initiation or a change in dose, and annually thereafter as it may help to monitor the response to therapy and inform medication adherence. E

American Diabetes Association®

STATIN TREATMENT PRIMARY PREVENTION

- For patients with diabetes aged 40–75 years without ASCVD, use moderate-intensity statin in addition to lifestyle therapy. A

- For patients with diabetes aged 20–39 years with additional ASCVD risk factors, it maybe reasonable to initiate statin in addition to lifestyle therapy. C

- In patients with diabetes at higher risk, especially those with multiple ASCVD risk factors or aged 50–70 years, it is reasonable to use high-intensity statin. B

- In adults with diabetes and 10-year ASCVD risk of 20% or higher(equivalent documented ASCVD) , it may be reasonable to add ezetimibe to maximally tolerated statin to reduce LDL levels by 50% or more. C

PRIMARY PREVENTION (PTS WITHOUT ASCVD)

- The evidence is lower for aged >75 years; relatively few older patients with diabetes have been enrolled in primary prevention trials. However, heterogeneity by age has not been seen in the relative benefit of lipid-lowering therapy in trials that included older participants ,and because older age confers higher risk, the absolute benefits are actually greater .

Moderate-intensity statin therapy is recommended in patients with diabetes who are 75 years or older. However, the risk-benefit profile should be routinely evaluated in this population, with downward titration of dose performed as needed.

American Diabetes Association.

AGE <40 YEARS AND/OR TYPE 1 DIABETES

- Very little clinical trial evidence exists for patients with DM2 under 40 years or DM1 of any age.
- Patients below the 40y have lower risk of developing a cardiovascular event over a 10-year horizon; however, their lifetime risk of developing CVD and suffering an MI, stroke, or cardiovascular death is high. For patients who are younger than 40 years of age and/or have type 1 diabetes with other ASCVD risk factors, it is recommended that the patient and health care provider discuss the relative benefits and risks and consider the use of moderate-intensity statin therapy

American Diabetes Association®

SECONDRAY PREVENTION

- For patients of all ages with diabetes and ASCVD, high-intensity statin should be added to lifestyle therapy. A
- **(based on the Cholesterol Treatment Trialists' Collaboration involving 26 statin trials, of which 5 compared high-intensity versus moderate-intensity statins. Together, they found reductions in nonfatal cardiovascular events with more intensive therapy, in patients with and without diabetes .)**

- For patients with diabetes and ASCVD considered very high risk using specific criteria, if LDL is >=70 mg/dL on maximally tolerated statin dose, consider additional LDL-lowering therapy (ezetimibe or PCSK9 inhibitor). A Ezetimibe may be preferred due to lower cost.
- following a clinician patient discussion about the net benefit, safety, and cost.
- **(Definition of very high-risk patients with ASCVD = (major ASCVD events & high-risk conditions)**

- For patients who do not tolerate the intended intensity, the maximally tolerated statin dose should be used. E
- In adults with diabetes aged >75 years already on statin therapy, it is reasonable to continue statin. B
- In adults with diabetes aged>75 years, it may be reasonable to initiate statin therapy after discussion of potential benefits and risks. C
- Statin is contraindicated in pregnancy. B

American Diabetes Association.

- Combination Therapy for LDL Lowering Statins and Ezetimibe The IMPROVE-IT was a randomized controlled trial in 18,144 patients comparing the addition of ezetimibe to simvastatin therapy versus simvastatin alone. Individuals were>50 years of age, had experienced a recent ACS, and were treated for an average of 6 years.

- Overall, the addition of ezetimibe led to a 6.4% relative benefit and a 2% absolute reduction in major adverse cardiovascular events, with the degree of benefit being directly proportional to the change in LDL, which was 70 mg/dL in the statin group on average and 54 mg/dL in the combination group .In those with diabetes (27% of participants), the combination of moderate-intensity simvastatin (40 mg) and ezetimibe (10 mg) showed a significant reduction of major adverse cardiovascular events with an absolute risk reduction of 5% (40% vs. 45% cumulative incidence at 7 years) and a relative risk reduction of 14% over moderate-intensity simvastatin (40 mg) alone

INITIATING STATIN BASED ON RISK

statins are the drugs of choice for LDL lowering and cardioprotection.

two statin dosing are recommended for clinical practice: high-intensity approximately a >50% reduction in LDL, and moderate-intensity statin 30–49% reductions in LDL.

Low-dose statin therapy is generally not recommended in pts with diabetes but is sometimes the only dose of statin that tolerate.

Table 10.2—High-intensity and moderate-intensity statin therapy*

High-intensity statin therapy (lowers LDL cholesterol by ≥50%)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30–49%)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 1–4 mg

*Once-daily dosing. XL, extended release.

TREATMENT OF OTHER LIPOPROTEIN FRACTIONS OR TARGETS

- For patients with fasting TG>500 mg/dL, evaluate for secondary causes of hyper TG and consider medical therapy to reduce the risk of pancreatitis. C
- In adults with moderate hyper TG (TG 175–499 mg/dL), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that raise triglycerides. C
- In patients with ASCVD or other CV risk factors on a statin with controlled LDL but elevated triglycerides (135–499 mg/dL), the addition of icosapent ethyl can be considered to reduce CV risk. A

American Diabetes Association.

OTHER COMBINATION THERAPY

- Statin plus fibrate combination therapy has not been shown to improve ASCVD outcomes and is generally not recommended. A
- A prospective trial of a newer fibrate in this specific population of patients is ongoing

- Statin plus niacin combination therapy has not been shown to provide additional CV benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended. A

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LIPID-LOWERING AGENTS AND COGNITIVE FUNCTION

- Potential adverse impact of lipid-lowering agents on cognitive function have been raised

several lines of evidence point against this association, as detailed in a 2018 European Atherosclerosis Society Consensus Panel statement :

- 1-First, there are three large randomized trials of statin versus placebo where specific cognitive tests were performed, and no differences were seen between statin and placebo .
- 2-In addition, no change in cognitive function has been reported in studies with the addition of ezetimibe or PCSK9 inhibitors to statin therapy.
- 3-In addition, the most recent systematic review of the U.S. FDA's post marketing surveillance databases, randomized controlled trials, and cohort, case-control, and cross-sectional studies evaluating cognition in patients receiving statins found that published data **do not reveal an adverse effect of statins on cognition .**

- Therefore, a concern that statins or other lipid-lowering agents might cause cognitive dysfunction or dementia is not currently supported by evidence and should not deter their use in individuals with diabetes at high risk for ASCVD

MORE AGGRESSIVE LIPID LOWERING IN PEOPLE WITH DIABETES?

There is ongoing debate as to whether aggressive LDL cholesterol-lowering therapy, as opposed to comprehensive lipid management addressing the hypertriglyceridaemia and low HDL cholesterol, is the optimal approach to reduce atherosclerotic cardiovascular risk in people with diabetes.

www.thelancet.com/diabetes-endocrinology 2019

- The focus on large statin outcome trials: the reduction in major cardiovascular events is independent of the baseline LDL .
- Despite high-intensity statin therapy, residual cardiovascular risk remains and further lowering of LDL might be of value.

- beneft with the addition of ezetimibe benefit was seen in the IMPROVE-IT trial. Notably, despite only a small further reduction in LDL (0·43 mmol/L) with ezetimibe, cardiovascular benefit was apparent.

- In The **Lancet Diabetes & Endocrinology,** of a **prespecifed secondary analysis of the ODYSSEY OUTCOMES** of the PCSK9 inhibitor alirocumab: assessing cardiovascular outcomes in participants with and without diabetes at baseline and exploring the drug's effects on glycaemia and diabetes risk among those without diabetes at baseline.
- LDL cholesterol concentration was lowered to a median of **0·8** mmol/L with alirocumab by 4 months.
- After almost 3 years of median follow-up, the relative risk reduction for the primary endpoint was similar across glycaemic categories, but with greater absolute risk reduction in those with diabetes (−2·3%) compared with those with prediabetes or normoglycaemia at baseline (both −1·2%).
-
- This finding is similar to prespecifed analysis of the PCSK9 inhibitor evolocumab after the **FOURIER** trial:LDL cholesterol concentration was also lowered to a median of **0·8** mmol/L, with a greater absolute risk reduction in patients with diabetes (2·7%) than in those without diabetes (1·6%).

- In terms of lipid management, should we just be targeting LDL in people with diabetes???
- Newer fbrates are under development and a large cardiovascular outcomes study (PROMINENT) is being done to assess whether *pemafbrate* can reduce the risk of CVD in high-risk patients with diabetes.
- In the REDUCE-IT trial, the risk of ischaemic events after a median follow-up of 4·9 years was signifcantly reduced in those receiving icosapent ethyl
- The reduction in cardiovascular events could not be explained by the modest reduction in triglyceride concentrations.
- Novel therapies targeting triglyceride synthesis or enhancing triglyceride clearance as well as LDL reduction, such as *bempedoic acid and angiopoietin-like 3 inhibitors*, are also under study.

Should LDL targets be lowered further in people with diabetes???

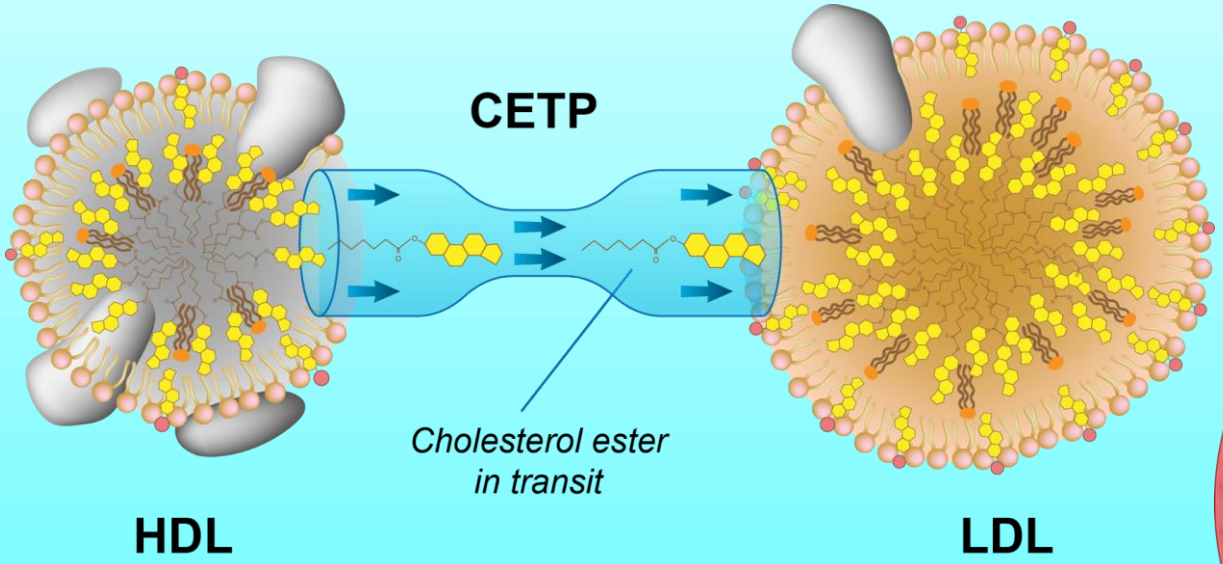
- While we await the results of outcomes studies with these newer agents, we should aim to reduce LDL aggressively in people with diabetes, since their absolute cardiovascular risk is high and there does not seem to be a threshold below which LDL lowering is not associated with further cardiovascular beneft.

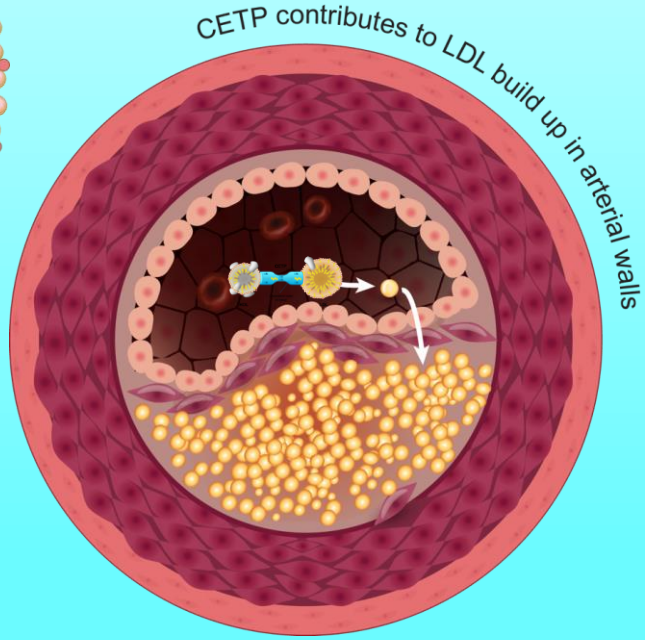
- LDL cholesterol lowering is therefore recommended for most, if not all, people with diabetes, especially those with established vascular disease.

- First-line therapy remains a high-intensity statin with the addition of ezetimibe if necessary.
- The addition of a PCSK9 inhibitor should be considered in patients who are intolerant to statins, those who do not achieve optimal LDL with existing therapy, or in those with progressive atherosclerosis despite this therapy

THANK YOU…

CETP transfers cholesterol esters from HDL to LDL



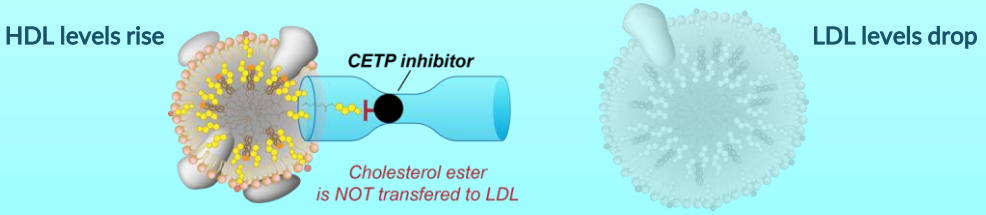


Cholesteryl ester transfer protein (CETP) promotes the transfer of cholesterol esters from ***anti-atherogenic HDLs*** to ***pro-atherogenic LDLs***, causing LDL-C to build up in the walls of arteries

Biology: CETP inhibition has multiple actions that are beneficial for CHD risk

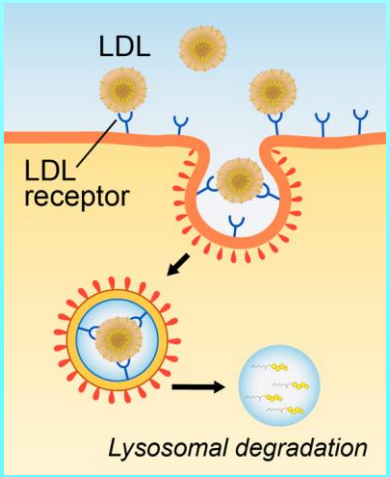
1 In Circulation

CETP inhibition ***blocks transportation of cholesterol esters*** from HDL > LDL, lowering LDL and increasing HDL



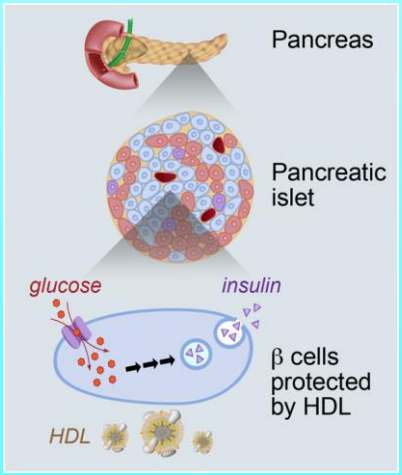
2 In Liver

CETP inhibition also upregulates LDL catabolism in the liver by causing an ***increase in LDL receptors***, resulting in drop in LDL levels in circulation



3 In Pancreas

CETP inhibition also protects vital pancreatic β cells by increasing small functional HDLs, ***supporting islet cell survival*** and ***increasing insulin production*** in the pancreas



Challenges in Atherosclerotic Cardiovascular Disease reduction and Triglyceride-related risk

Erik Stroes, MD

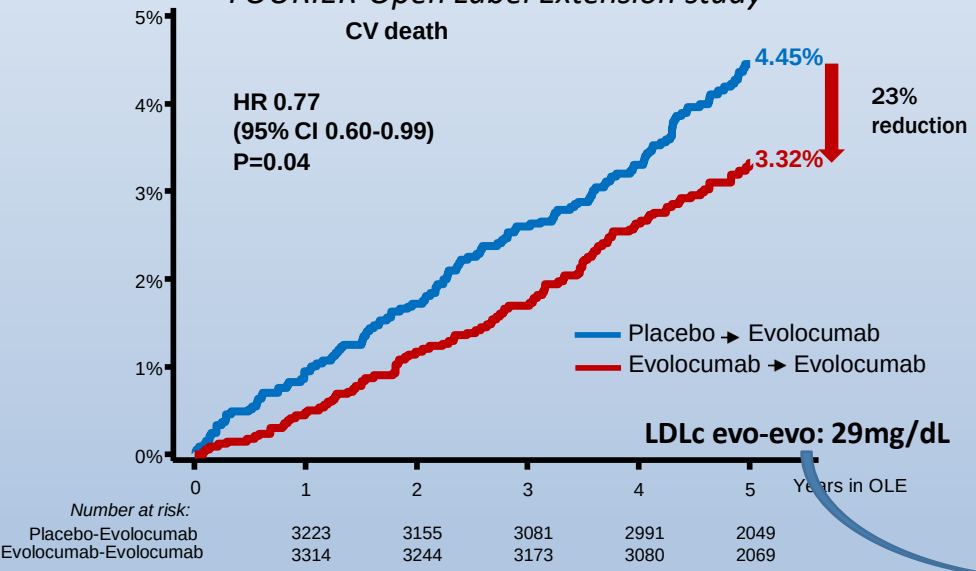
Amsterdam UMC, The Netherlands

Improving the management of patients with atherosclerotic cardiovascular disease - The evolving role of icosapent ethyl

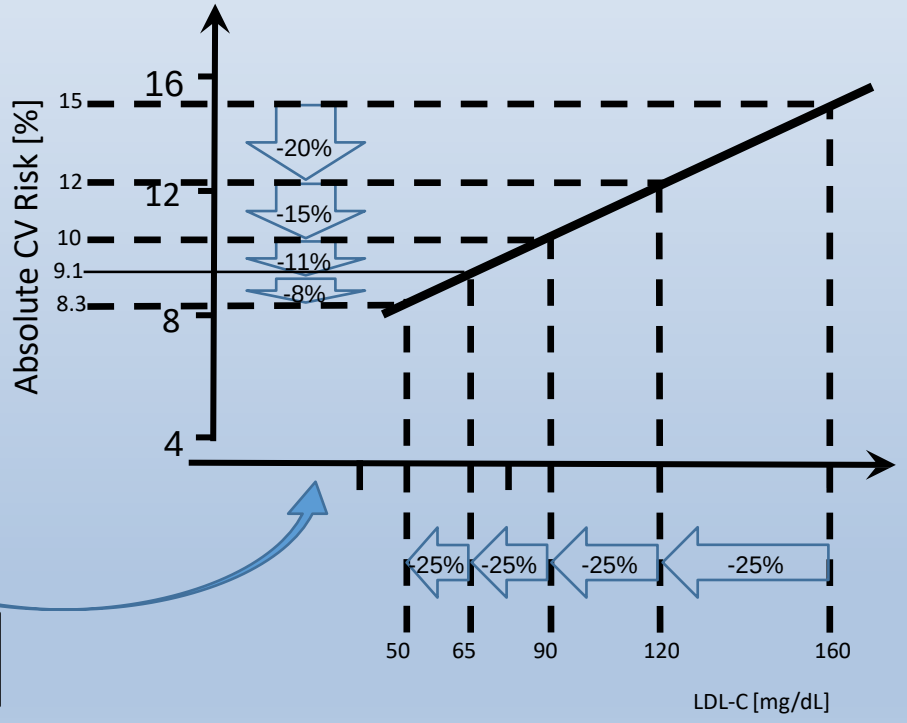
PHYSICIANS' ACADEMY FOR CARDIOVASCULAR EDUCATION
PACE-CME

Residual risk in patients with very-low LDLc levels

Significant benefit with marked residual risk
FOURIER-Open Label Extension study



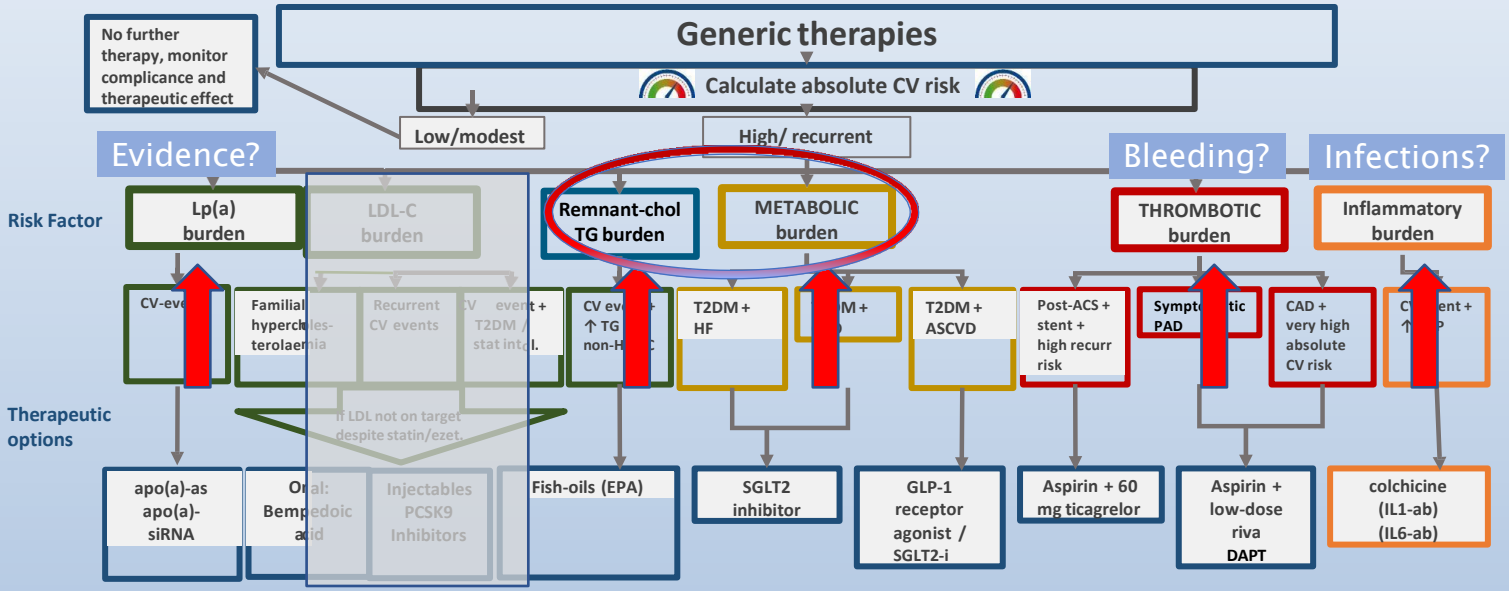
Further LDLc lowering - limited benefit



Recurrent CV-event rate in evo-evolocumab : **14.6% /5yr**
Recurrent CV-event rate in placebo-evolocumab: **16.8% /5yr**

O'Donaghue, *Circulation* 2022; Gaba P, *Circulation* 2023; Laufs, *Eur Heart J* 2014

Other pillars ‘contributing’ to atherogenesis

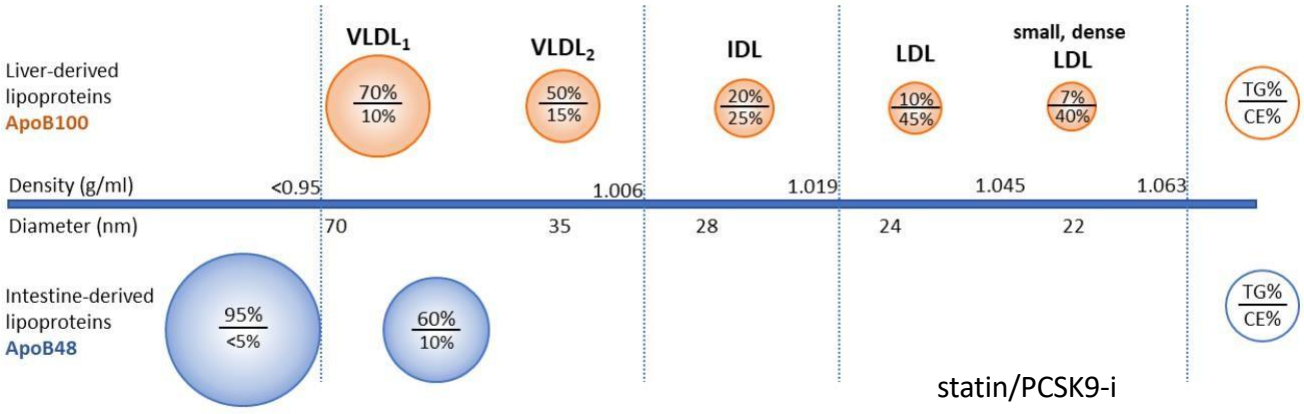


Hoogeveen, Stroes, Neth Heart J 2021

When cardiologist talk about high TGs .

TGs are 'heterogeneous'

Size and density profile of major apolipoprotein-B containing lipoprotein classes



statin/PCSK9-i

apoB containing lipoproteins

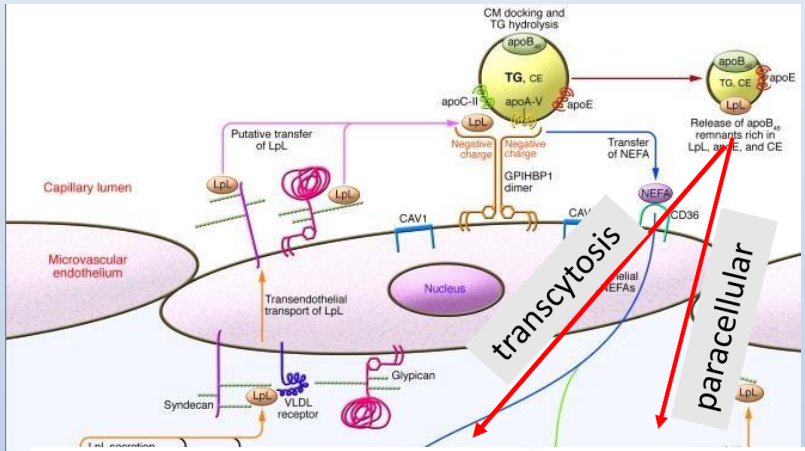
Triglycerides / Triglyceride-rich lipoproteins

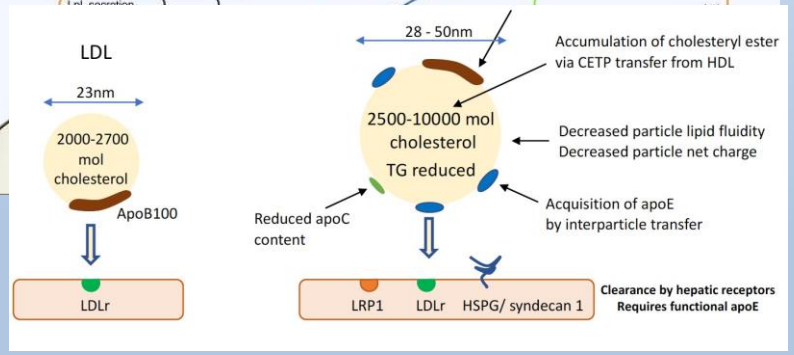
Triglyceride-remants /
Remnant cholesterol

Ginsberg H, et al. Consensus on HTG. *Eur Heart J 2021*

Why are Triglyceride-rich particles atherogenic?

Experimental evidence: direct uptake in the arterial wall





Yang, Int J Mol Sciences 2018; Hassing, BBA 2012;
Ginsberg, Eur H J 2022; Steender & Zilversmit, Atherosclerosis 1981

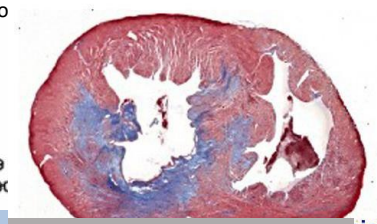
Table 1. Labeled Esterified Cholesterol in Plasma and Tissues after Injection of ^{14}C-Cholesterol-Labeled Chylomicrons and ^{3}H-Cholesterol-Labeled d < 1.019 Lipoproteins

Animal*	Duration (hr)	Mean plasma ^{14}C (% of d	Mean plasma ^{3}H	Intima-media†	Liver† ^{14}C	Liver† ^{3}H
1	1.4	0.78				
2	1.8	0.61				
3	3.2	0.74				
4	3.3	0.64				
5	3.8	0.53				
6	4.3	0.42				
7	4.4	0.47				

Anitschkow

Chylomicro

Figure 4. The
take of labelec



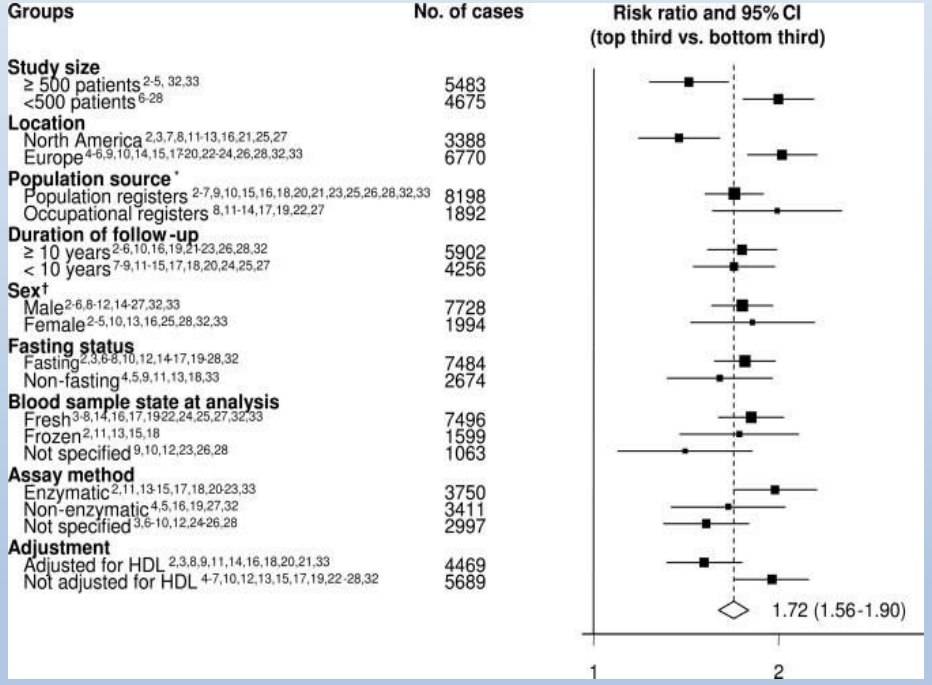
Atherosclerosis in rabbits

Vulnerable coronary plaque

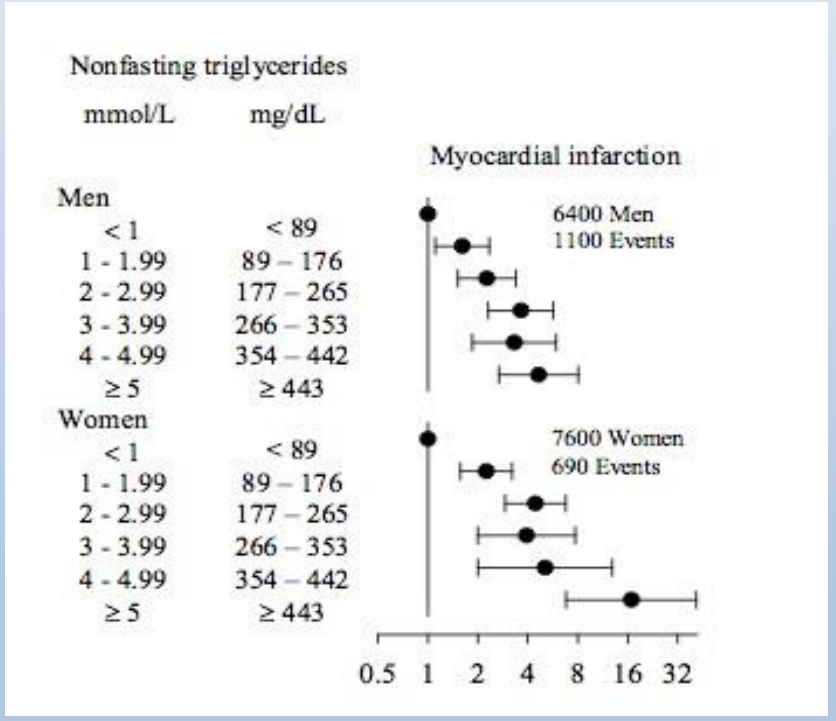
Are Triglycerides associated with Atherogenesis?

Epidemiological evidence: TG associated with CV-risk

TGs association with CV-risk
10.158 Cases in 262.525 subjects



non-fasting TGs associate with CV-risk
in both men and women

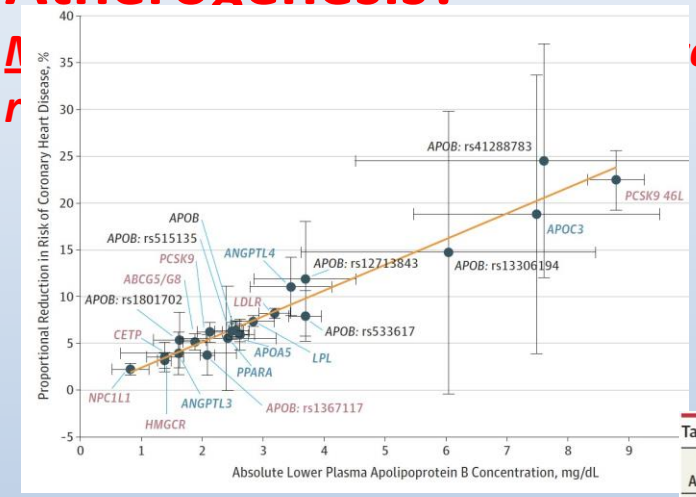


Sarwar. Circulation 2007; Nordestgaard B, Circ Res 2016

Kolovou etal Curr Vasc Rep 2011, 9:258-270

Are Triglycerides a 'causal' factor in Atherogenesis?

M… …e: TRL-C (particle number)
r…



Clinical benefit of LDL-C or TG/TRL-C lowering is proportional to the reduction in the number of atherogenic particles, i.e. apoB reduction

Table 3. Multivariable Mendelian Randomization Analysis of the Association Between Plasma Triglycerides, LDL-C, and ApoB With the Risk of CHD[a]

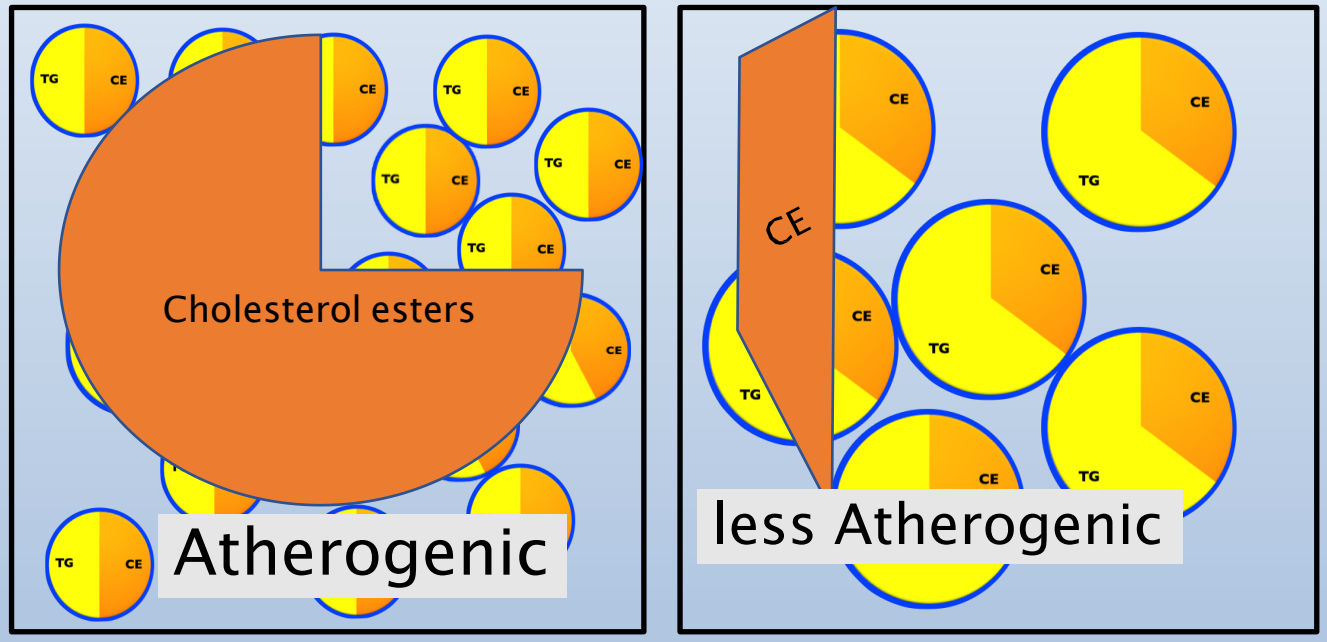
Analysis	Variables	Odds Ratio for CHD (95% CI)	*P* Value
Association of 10-mg/dL lower ApoB with risk of CHD	ApoB	0.770 (0.760-0.781)	1.42E-170
Association of 10-mg/dL lower LDL-C with risk of CHD	LDL-C	0.846 (0.833-0.858)	8.16E-77
Association of 50-mg/dL lower triglycerides with risk of CHD	Triglycerides	0.815 (0.785-0.846)	1.37E-18
Association of 10-mg/dL lower LDL-C and 50-mg/dL lower triglycerides with risk of CHD included in same model	LDL-C	0.862 (0.849-0.875)	6.92E-65
	Triglycerides	0.876 (0.850-0.902)	1.36E-14
Association of 10-mg/dL lower LDL-C, 50-mg/dL lower triglycerides, and 10-mg/dL lower ApoB with risk of CHD included in same model	ApoB	0.761 (0.723-0.798)	7.51E-20
	LDL-C	1.010 (0.967-1.055)	.19
	Triglycerides	1.014 (0.965-1.065)	.19

Varbo, Circ 2013; Jorgenson, NEJM 2014; TG working group, NEJM 2014
Cardiogram consortium, NEJM 2016; Helgadottir, Nature genetics 2016
Dewey, NEJM 2016; Dewey, NEJM 2017; …..

Ference, JAMA 2019

But, what is high Triglycerides?
a mixed bag

TG 4.5 mmol/l (405 mg/dL)



High apo B 135mg/dl

Low apo B 87 mg/dl

Triglyceride-rich particles ‘drive’ atherogenic risk

	Mg/dl	Mmol/l
TC	231	6.0
HDL-C	37	0,97
LDL-C	126	3.27

VLDL

	Mg/dl	Mmol/l
TC	308	8.0
TG	835	5.95
HDL-C		1,05
Non-HDL-c	268	6,95
LDL-C	nm	nm
apoB	140	1.4 g/l

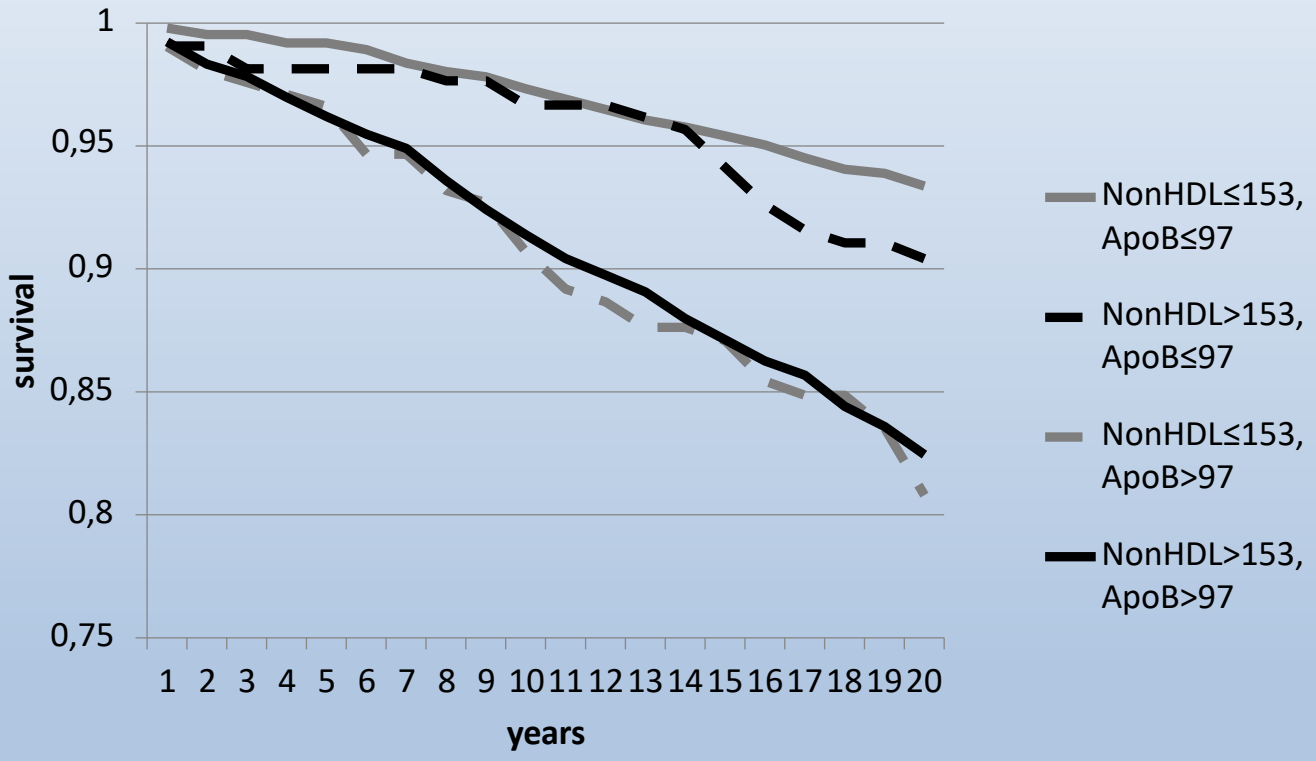
VLDL and LDL

	Mg/dl	Mmol/l
TC	316	8,2
TG	974	11,0
HDL-C		0.60
Non-HDL-c	29[illegible]	[illegible]6
LDL-C	nm	nm
apoB	100	1,0 g/l

VLDL + chylomicrons

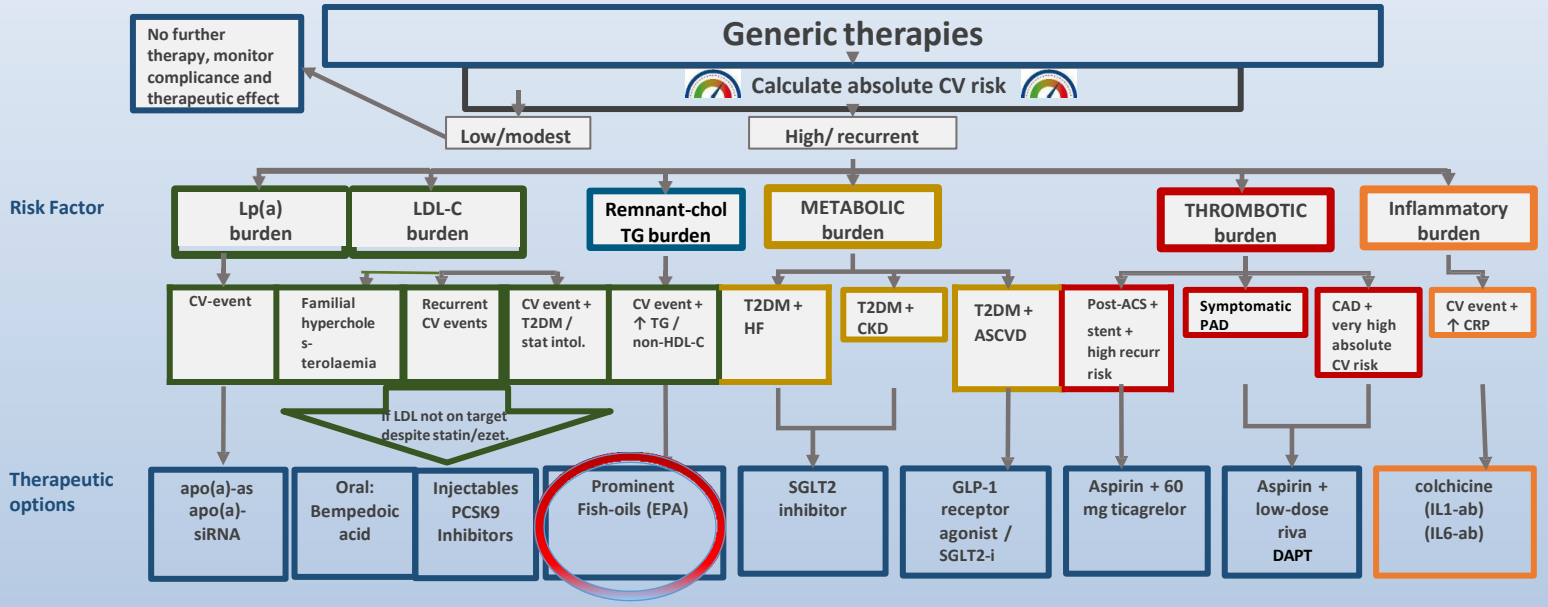
And we have known this for decades: Only an increased 'number' of TRLs associate with risk

Framingham Heart Study



Schaeffer E, et al, J Lip Res 1994

Does 'TG'-lowering reduce residual CV-risk?



Hoogeveen R, Neth J Med 2021

PROMINENT:

Pemafibrate in high-risk hypertriglyceridemic DM-II patients

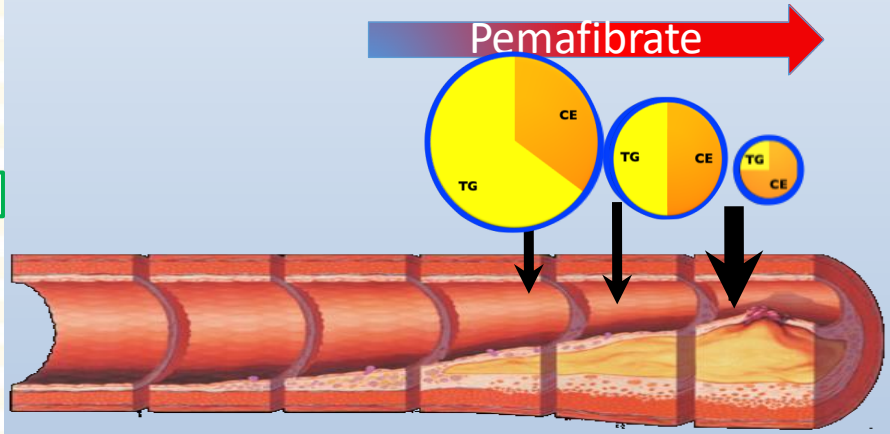
Variable	Pemafibrate (N = 5240)	Placebo (N = 5257)	Treatment Effect†
	Median Value (IQR)		Mean % Change (95% CI)
Triglyceride-related biomarkers			
Triglyceride level, measured			
Baseline — mg/dl	273 (22[illegible] to 342)		
4 Mo — mg/dl	189 (1[illegible] to 253)		
Median change from baseline — %	−31.1 (−48.9 to −9.6)	−6.9 (−28.4 to 20.2)	−26.2 (−28.4 to −24.10)
VLDL cholesterol level, calculated — mg/dl‡			
Baseline — mg/dl	49 (39 to 63)	49 (39 to 62)	
4 Mo — mg/dl	31 (23 to 42)	43 (32 to 59)	
Median change from baseline — %	−35.0 (−54.1 to −11.5)	−10.5 (−33.3 to 17.4)	−25.8 (−27.8 to −23.9)
Remnant cholesterol level, calculated§			
Baseline — mg/dl	47 (38 to 60)	47 (37 to 59)	
4 Mo — mg/dl	32 (24 to 42)	39 (29 to 52)	
Median change from baseline — %	−31.3 (−49.1 to −8.2)	−15.6 (−36.8 to 10.8)	−18.2 (−20.3 to −16.1)
Remnant cholesterol level, measured			
Baseline — mg/dl	56 (4[illegible] to 73)		
4 Mo — mg/dl	30 (2[illegible] to 41)		
Median change from baseline — %	−43.6 (−57.8 to −24.1)	−20.2 (−38.3 to 3.8)	−25.6 (−27.3 to −24.0)
Apolipoprotein C-III level, measured			
Baseline — mg/dl	15 (13 to 19)	15 (13 to 18)	
4 Mo — mg/dl	11 (9 to 14)	15 (12 to 19)	
Median change from baseline — %	−27.8 (−43.8 to −9.1)	0.0 (−18.8 to 18.8)	−27.6 (−29.1 to −26.1)
Other lipid biomarkers			
Total cholesterol level, measured			
Baseline — mg/dl	161 (139 to 193)	161 (137 to 191)	
4 mo — mg/dl	162 (138 to 190)	158 (134 to 190)	
Median change from baseline — %	−0.5 (−12.2 to 13.2)	−1.2 (−12.1 to 11.0)	0.8 (−0.1 to 1.6)
HDL cholesterol level, measured			
Baseline — mg/dl	33 (29 to 37)	33 (29 to 37)	
4 Mo — mg/dl	36 (30 to 42)	34 (30 to 39)	
Median change from baseline — %	8.3 (−5.3 to 25.0)	3.1 (−7.4 to 15.6)	5.1 (4.2 to 6.1)
LDL cholesterol level, measured			
Baseline — mg/dl	79 (6[illegible] to 104)		
4 Mo — mg/dl	91 (7[illegible] to 115)		
Median change from baseline — %	14.0 (−6.3 to 41.4)	2.9 (−13.5 to 24.6)	12.3 (10.7 to 14.0)
Apolipoprotein B level, measured			
Baseline — mg/dl	90 (7[illegible] to 108)		
4 Mo — mg/dl	93 (7[illegible] to 111)		
Median change from baseline — %	3.2 (−12.0 to 19.7)	−1.6 (−13.4 to 11.8)	4.8 (3.8 to 5.8)

84 mg/dl TG decrease

26 mg/dl RC decrease

12 mg/dl LDL-C increase

3 mg/dl apoB increase



Das-Pradhan N Engl J Med 2022;

Fibrates: Enhancing TG-metabolism?

TG lowering in absence of TRL-reduction not beneficial

Effect Pemafibrate	%change compared to placebo	Abs. difference Vs placebo
TG change	-26.2 %	- 69 mg/dl
Remnant chol	-25.6 %	- 12 mg/dl
LDLc	+12.3 %	+ 10 mg/dl
apoB	+ 4.8 %	+ 5 mg/dl

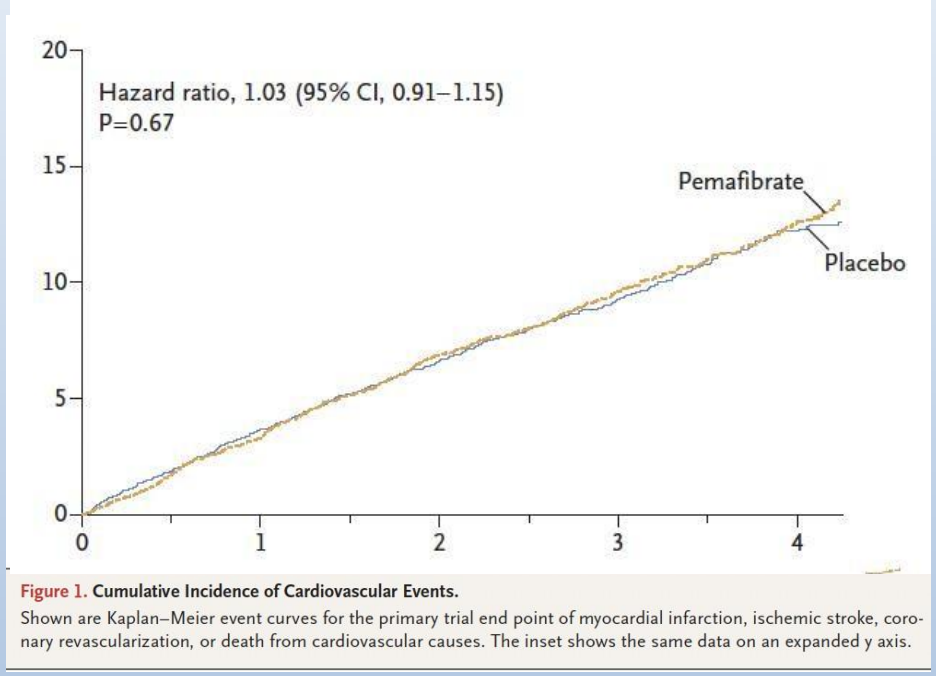


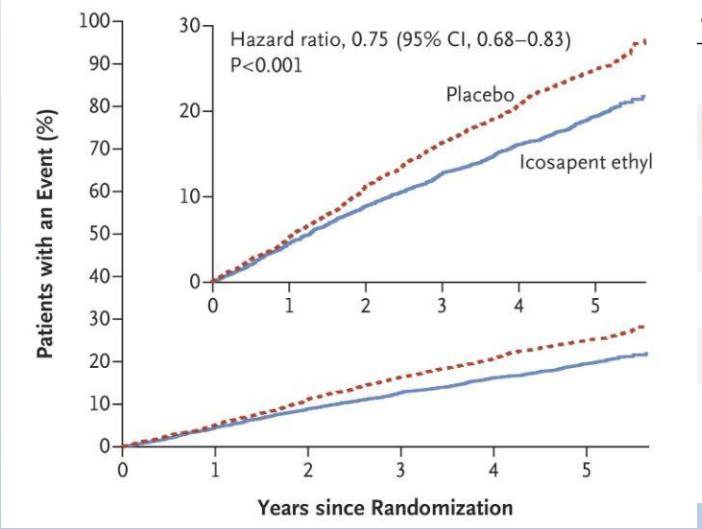
Figure 1. **Cumulative Incidence of Cardiovascular Events.**
Shown are Kaplan–Meier event curves for the primary trial end point of myocardial infarction, ischemic stroke, coronary revascularization, or death from cardiovascular causes. The inset shows the same data on an expanded y axis.

Fibrate does not 'remove' Triglyceride-rich particles
It shifts atherogenic particles towards other atherogenic particles

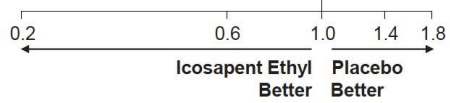
Das-Pradhan N Engl J Med 2022; Ginsberg H, Eur Heart J 2021

REDUCE-IT: Icosapent-ethyl in hyperTG-patients

Benefit 'independent' of TG-effect?



TOTAL EVENTS – Primary Composite Endpoint/Subgroup	Icosapent Ethyl	Placebo	RR (95% CI)	P-value
	Rate per 1000 Patient Years	Rate per 1000 Patient Years		
Primary Composite Endpoint (ITT)	61.1	88.8	0.70 (0.62–0.78)	<0.0001
Baseline Triglycerides by Tertiles*				
≥81 to ≤190 mg/dL	56.4	74.5	0.74 (0.61–0.90)	0.0025
>190 to ≤250 mg/dL	63.2	86.8	0.77 (0.63–0.95)	0.0120
>250 to ≤1401 mg/dL	64.4	107.4	0.60 (0.50–0.73)	<0.0001



*P (interaction) = 0.1

TG-reduction: 39 mg/dl *(pemafibrate: -84mg/dl)*

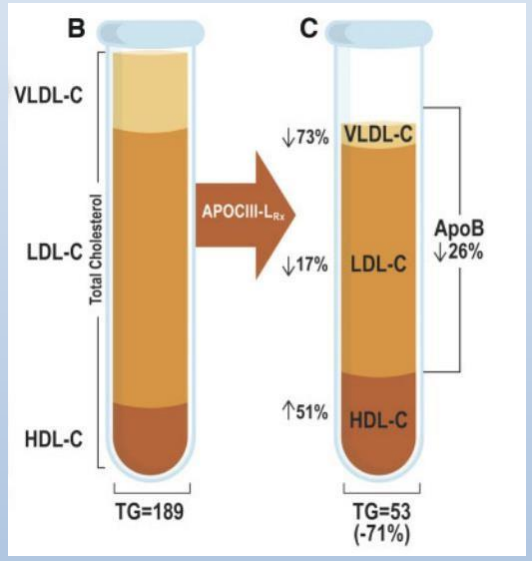
Icosapent ethyl is not a TG-lowering drug,
Mechanism of benefit? Prof G Steg

Bhatt, N Engl J Med 2019

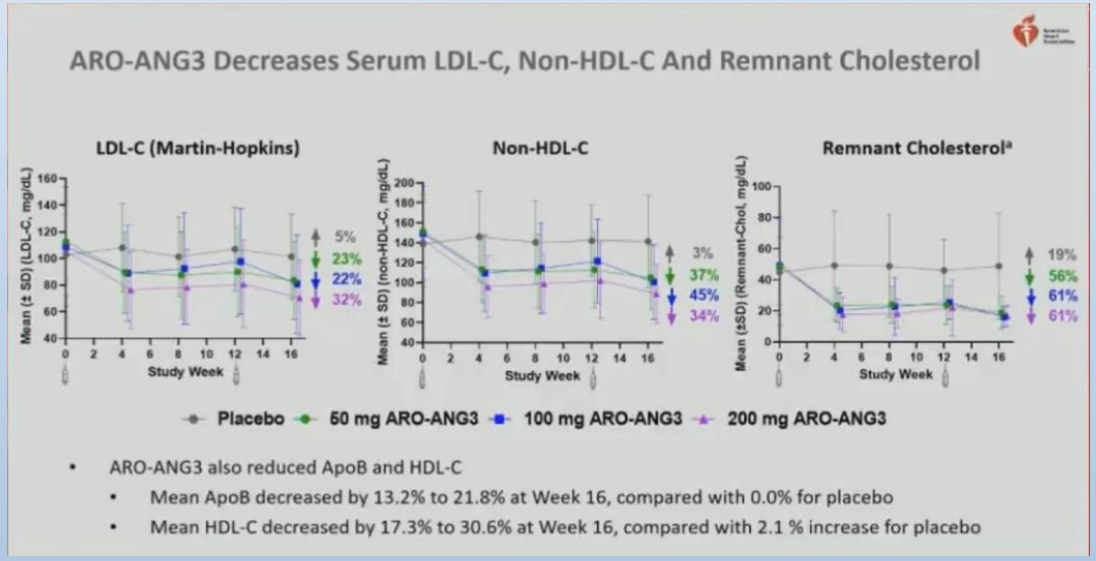
Benefit of TLR-lowering on CVD needs to be tested

using TRL-lowering therapies

apoCIII antisense therapy



ANGPTL3 siRNA therapy

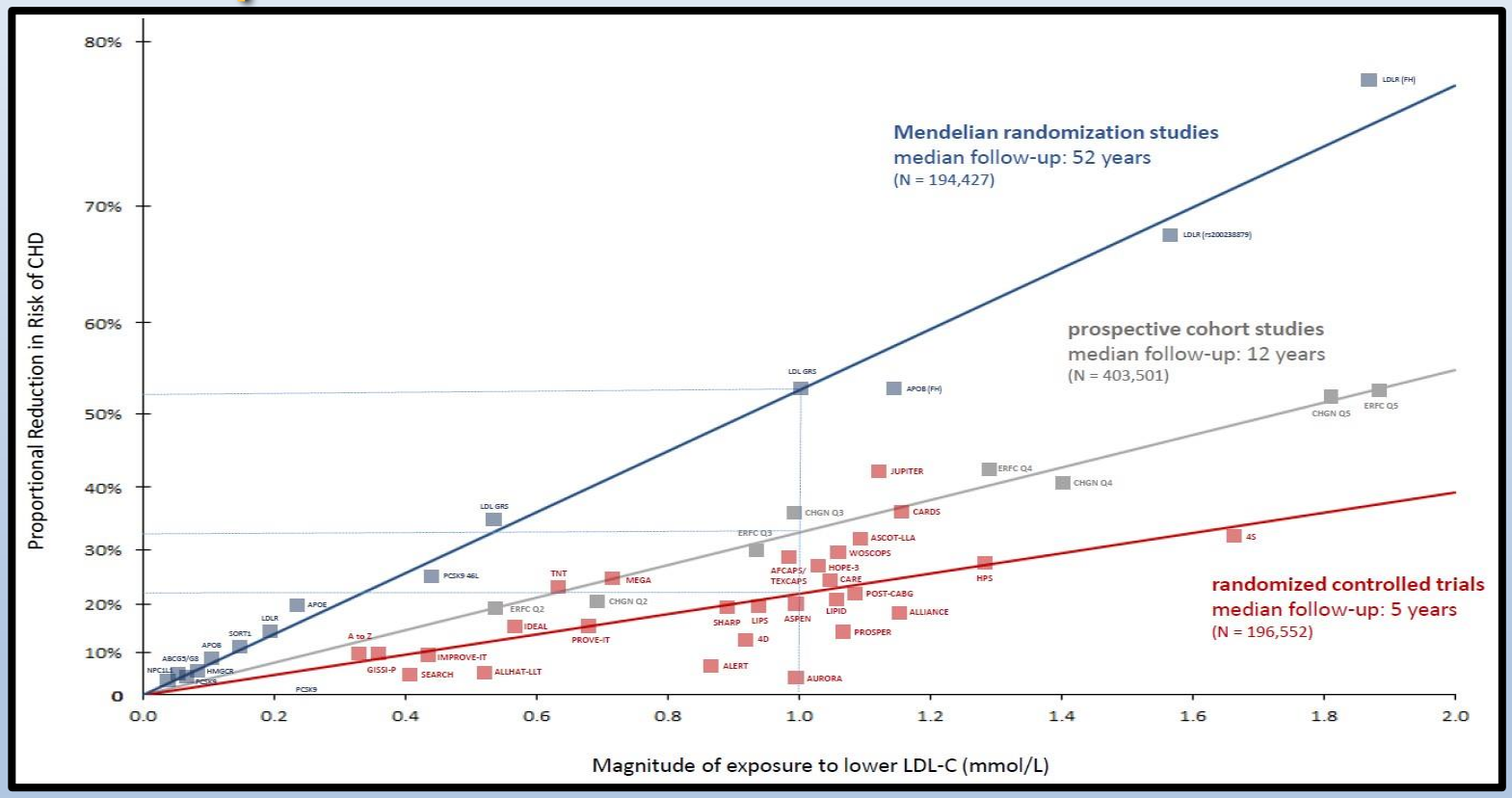


Alexander V, Eur Heart J 2019 Rosenson, AHA 2022

Summary: Challenges in Atherosclerotic Cardiovascular Disease reduction and Triglyceride-related risk

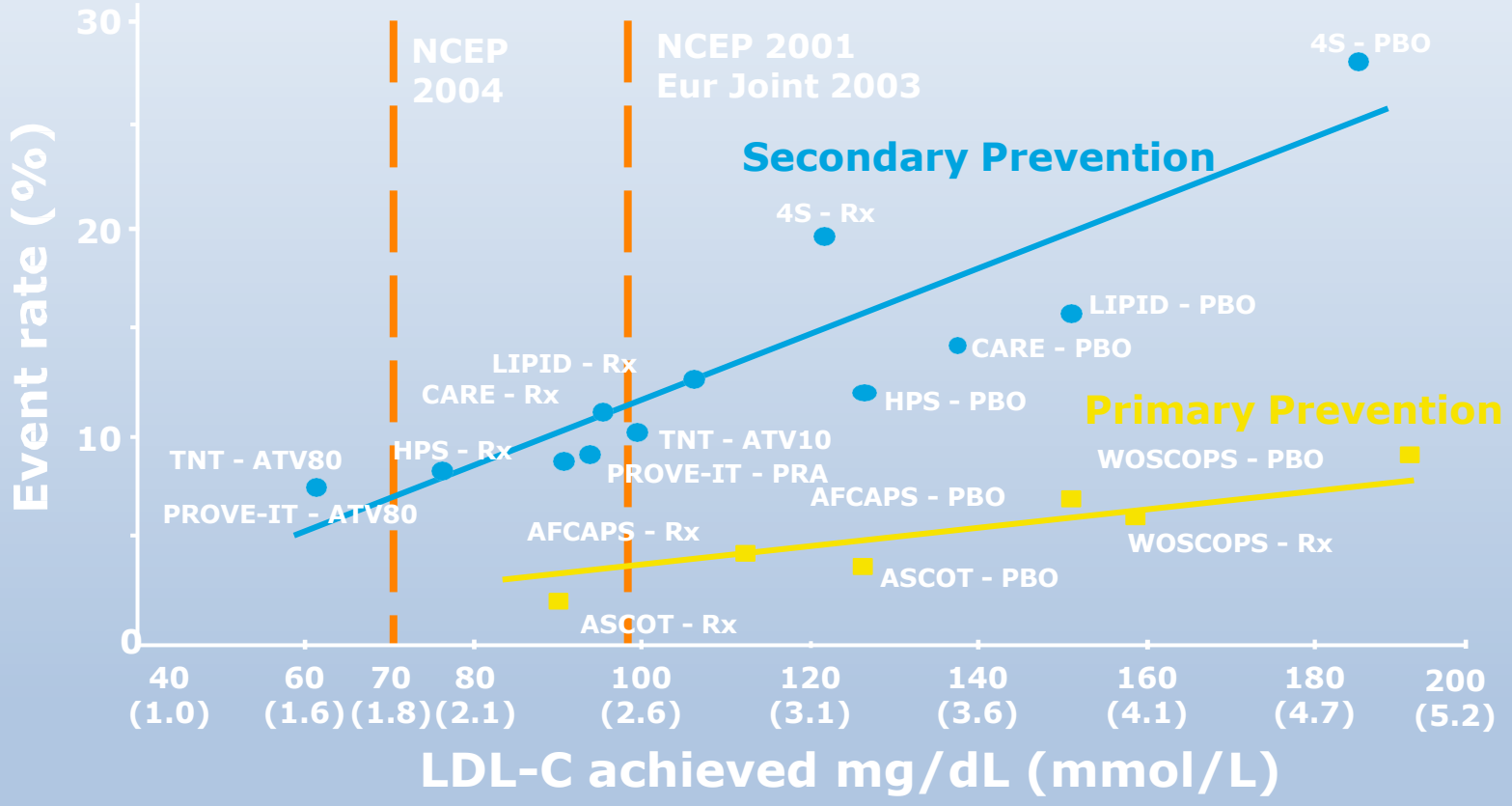
- **TG reduction should not be used as target** for CVD-reduction
- **Triglyceride-rich lipoprotein** (**TRL**) **reduction**, i.e. reduction apoB + TG, **best surrogate** for CVD-reduction
- **Beta-lipoprotein reduction, comprising LDLc + TRL-C, is best target**

Genetic Benefits of Early Exposure to Lower LDL-C Levels



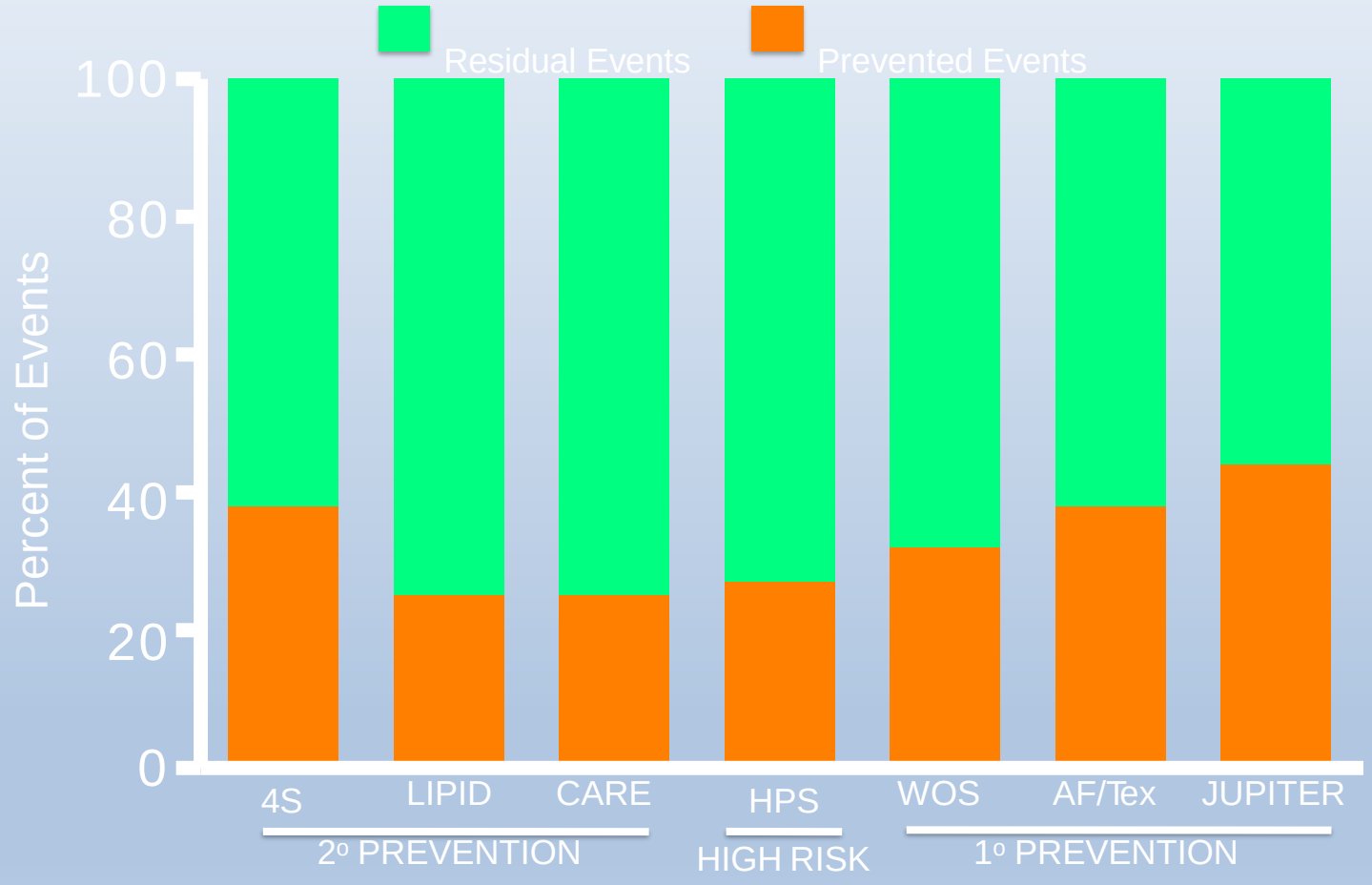
Ference, Nicholls et al. *Eur Heart J* 2017;38:2459-72.

LDL-C Lowering and Benefit of Statins



Adapted from Rosensen, Exp Opin Emerg Drugs 2004;9:269; LaRosa J et al, N Engl J Med,2005;352:1425

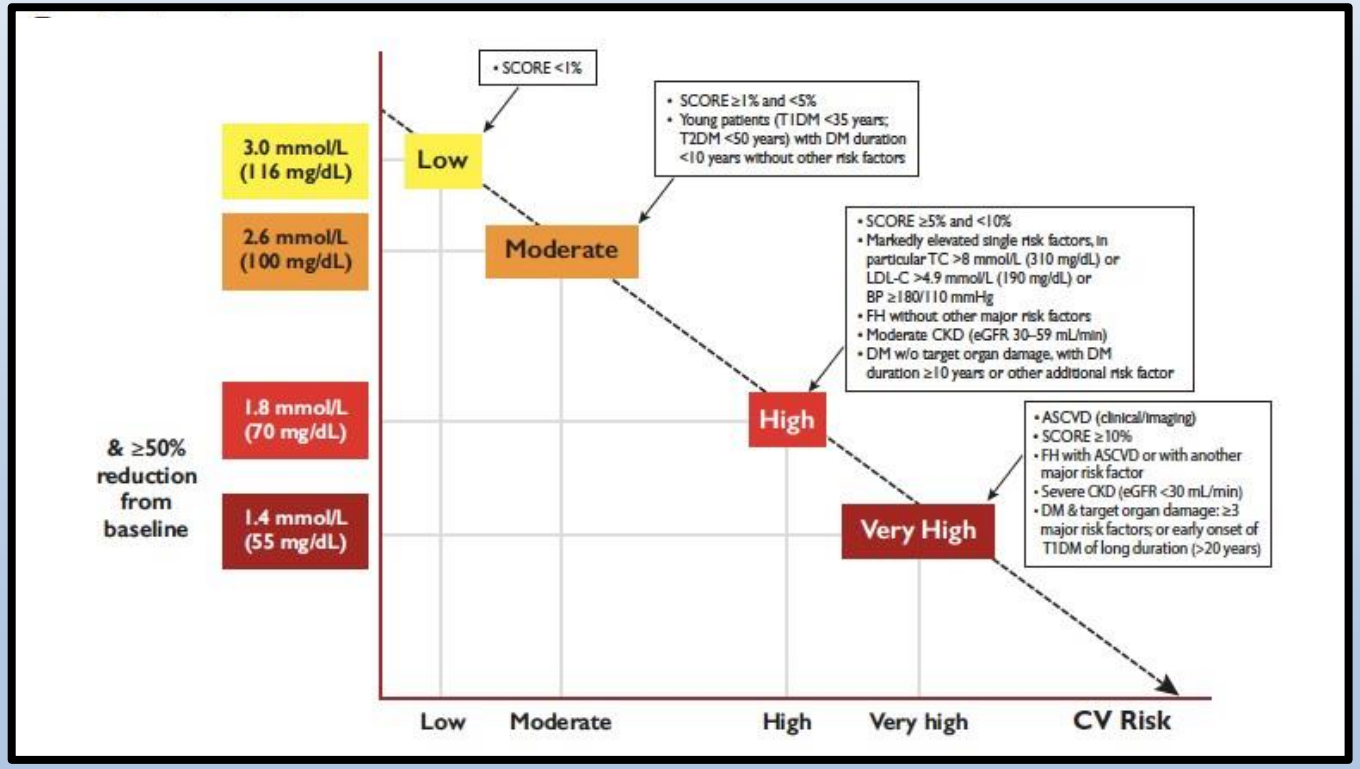
Residual Clinical Risk in Statin Trials



Outcomes: Non-Statin LDL-C Lowering Therapies

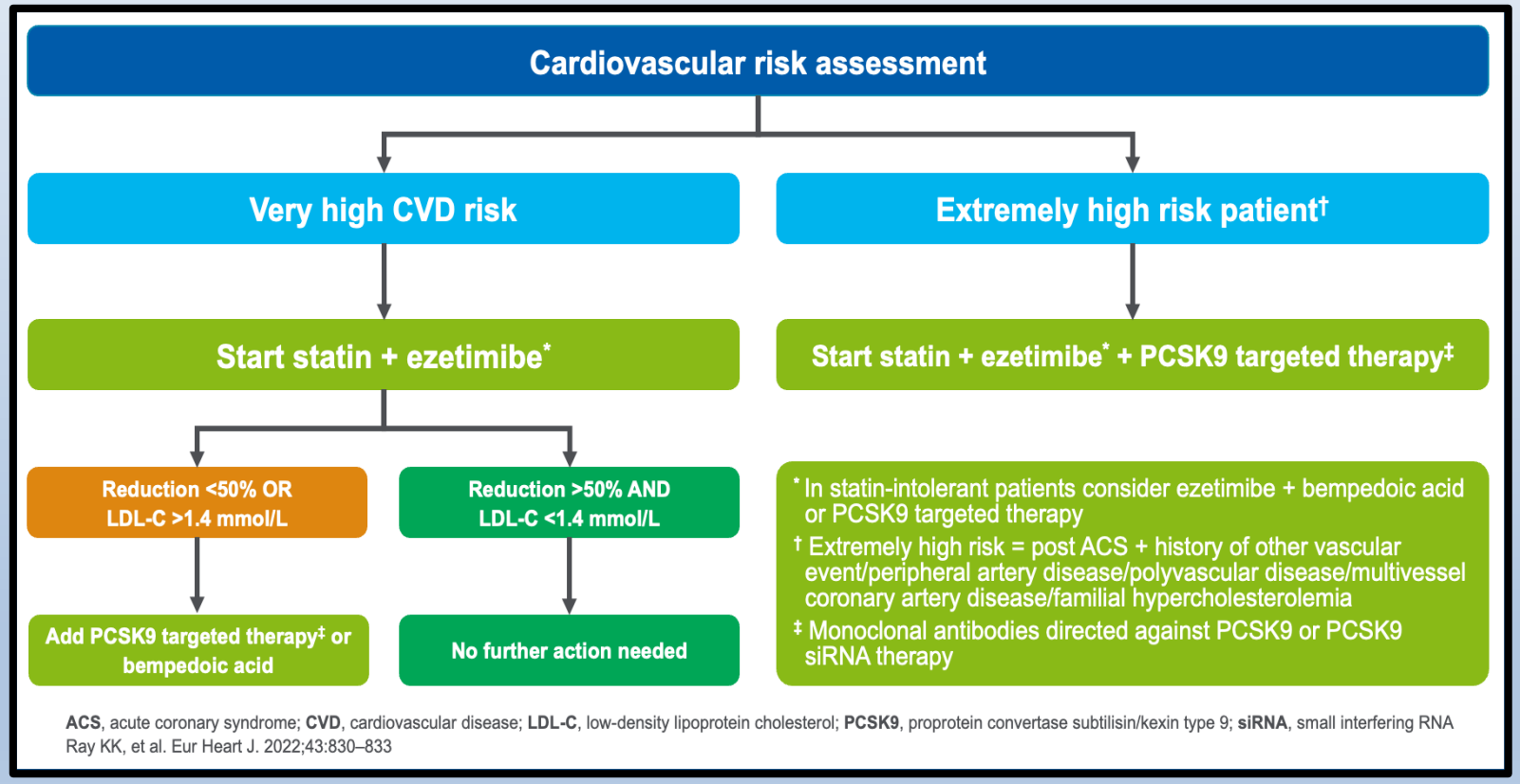
	3-Component MACE	Nonfatal MI
IMPROVE-IT Ezetimibe	0.90	0.87
FOURIER Evolocumab	0.80	0.73†
ODYSSEY Outcomes Alirocumab	0.86*	0.86
CLEAR Outcomes Bempedoic Acid	0.85	0.73

High Risk Patients Need Very Low LDL-C Levels



Mach *Eur Heart J* 2020;41:111-88

Integration of Combination of Lipid Lowering in Treatment Guidelines



ACS, acute coronary syndrome; **CVD**, cardiovascular disease; **LDL-C**, low-density lipoprotein cholesterol; **PCSK9**, proprotein convertase subtilisin/kexin type 9; **siRNA**, small interfering RNA

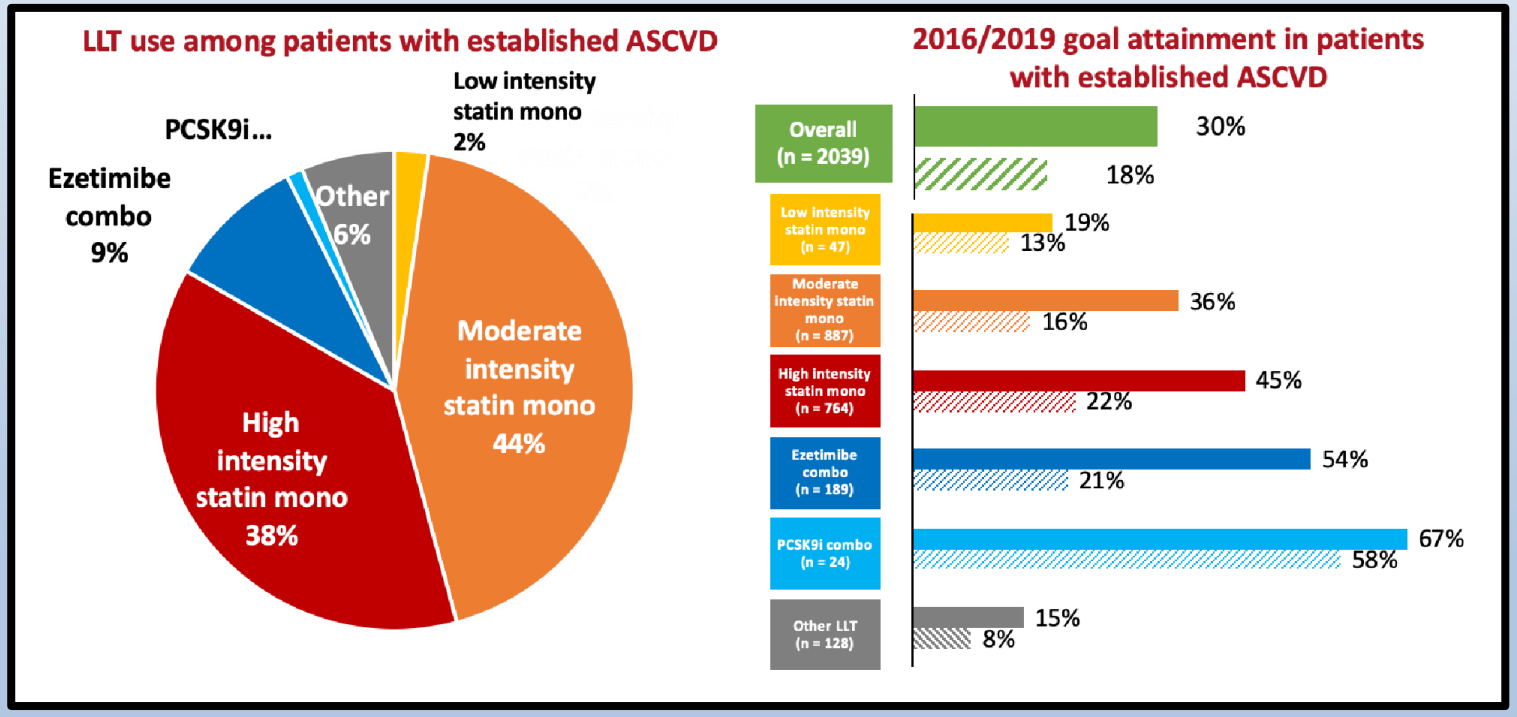
Ray KK, et al. Eur Heart J. 2022;43:830–833

Intensity of Lipid Lowering Treatment

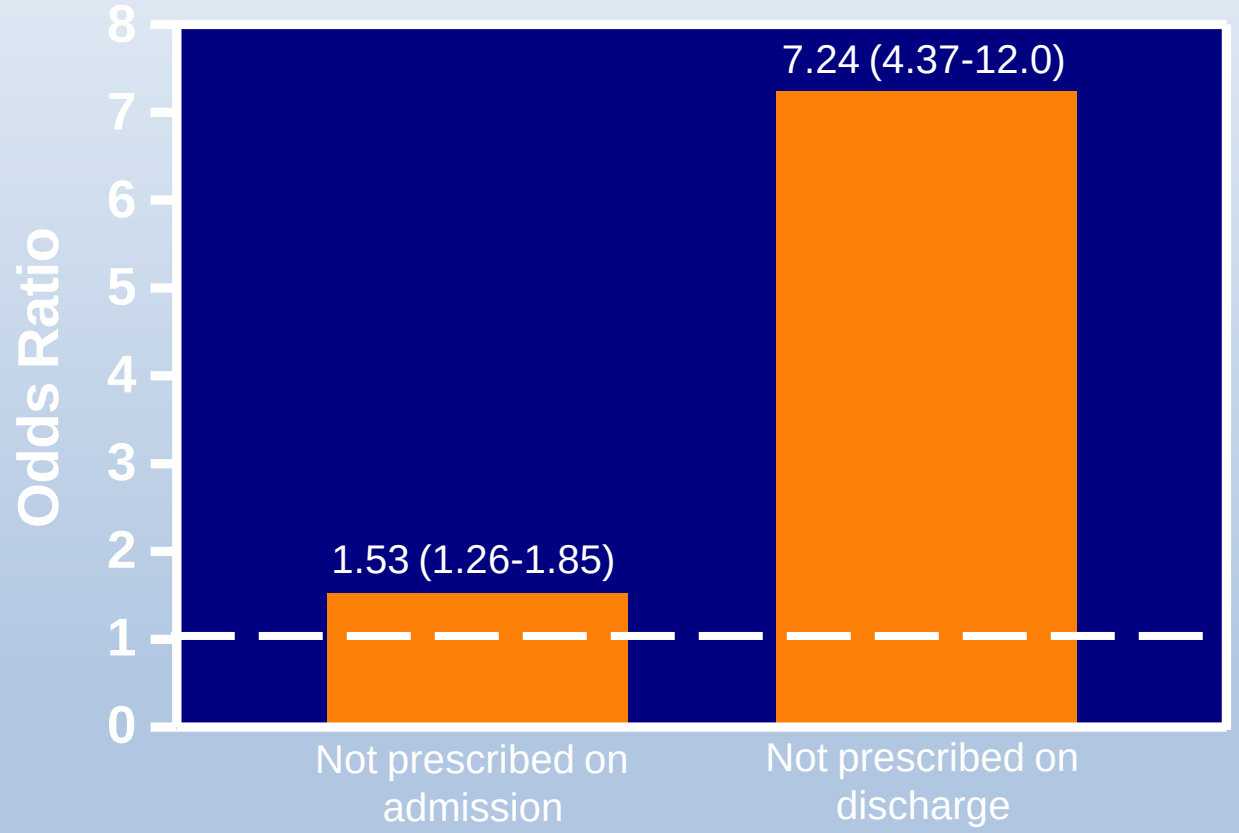
Treatment	LDL-C Reduction
Moderate intensity statin	~30%
Ezetimibe + bempedoic acid	~45%
High intensity statin	~50%
High intensity statin + ezetimibe	~65%
Moderate statin + ezetimibe + bempedoic acid	~65%
PCSK9 inhibitor	~60%
PCSK9 inhibitor + high intensity statin	~75%
PCSK9 inhibitor + high intensity statin + ezetimibe	~85%

Mach *Eur Heart J* 2020;41:111-88. Thompson et al *J Clin Lipidol* 2016; 10: 556-567. Rubino, et al *Athero* 2021

Lipid Lowering Therapy and LDL-C Goal Attainment in Patients with ASCVD



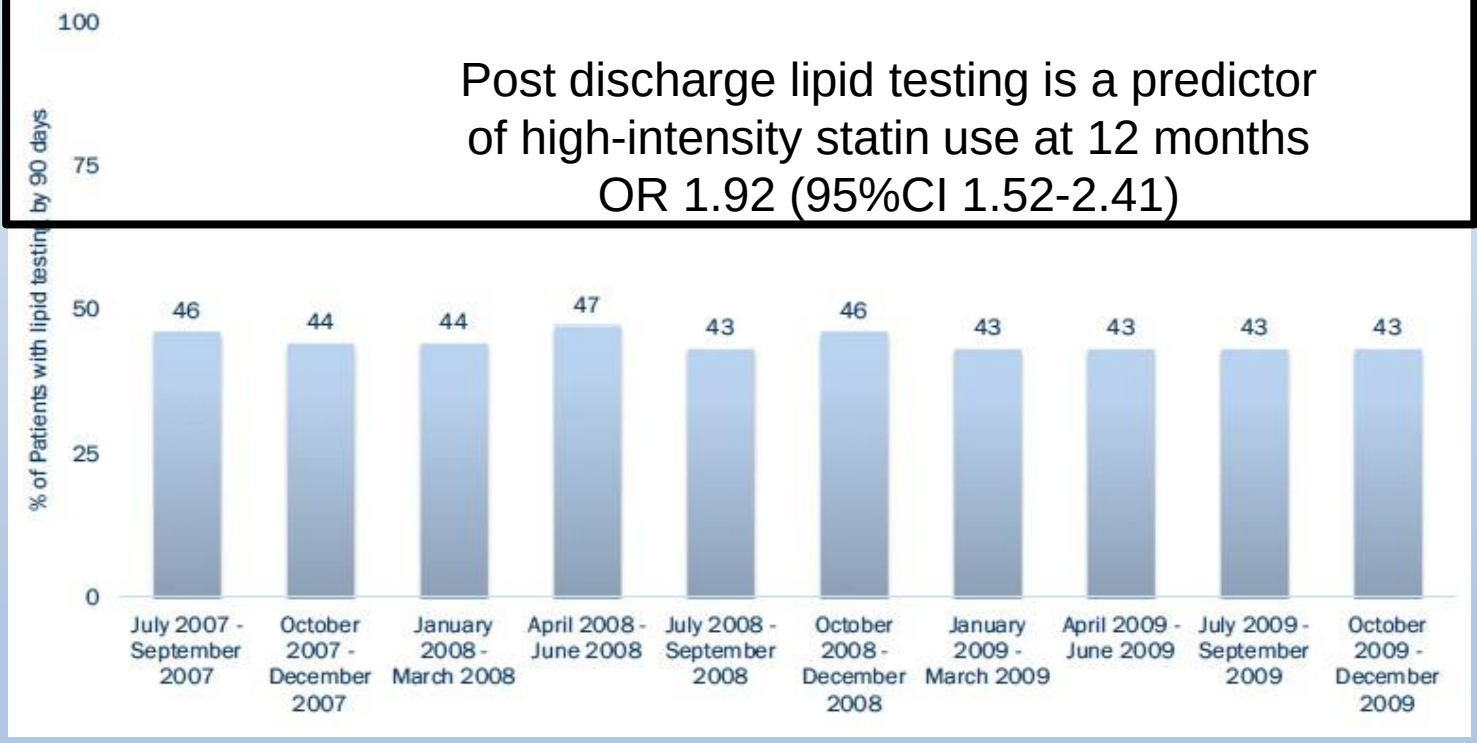
Predictors of Intensive Lipid Lowering Use 12 Months Post ACS



Brieger *Med J Aust* 2019;210(2):80-5

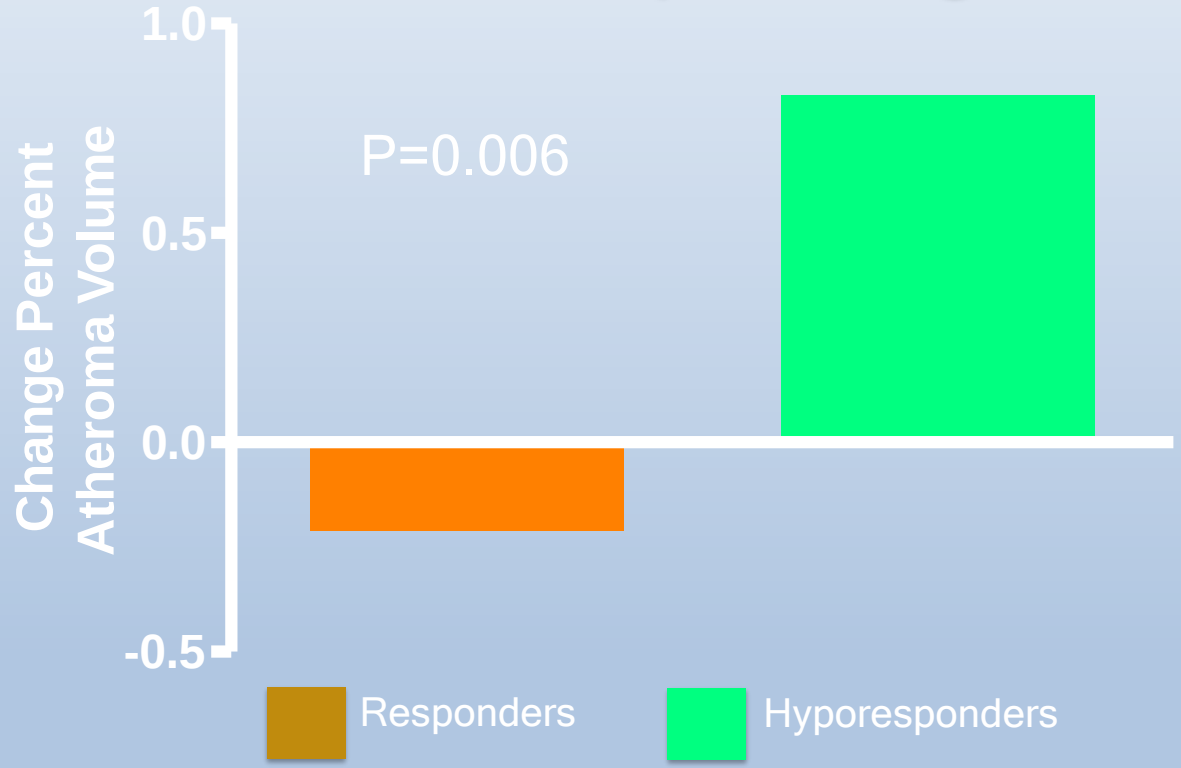
We Don't Follow up with Lipid Tests

Post discharge lipid testing is a predictor of high-intensity statin use at 12 months
OR 1.92 (95%CI 1.52-2.41)

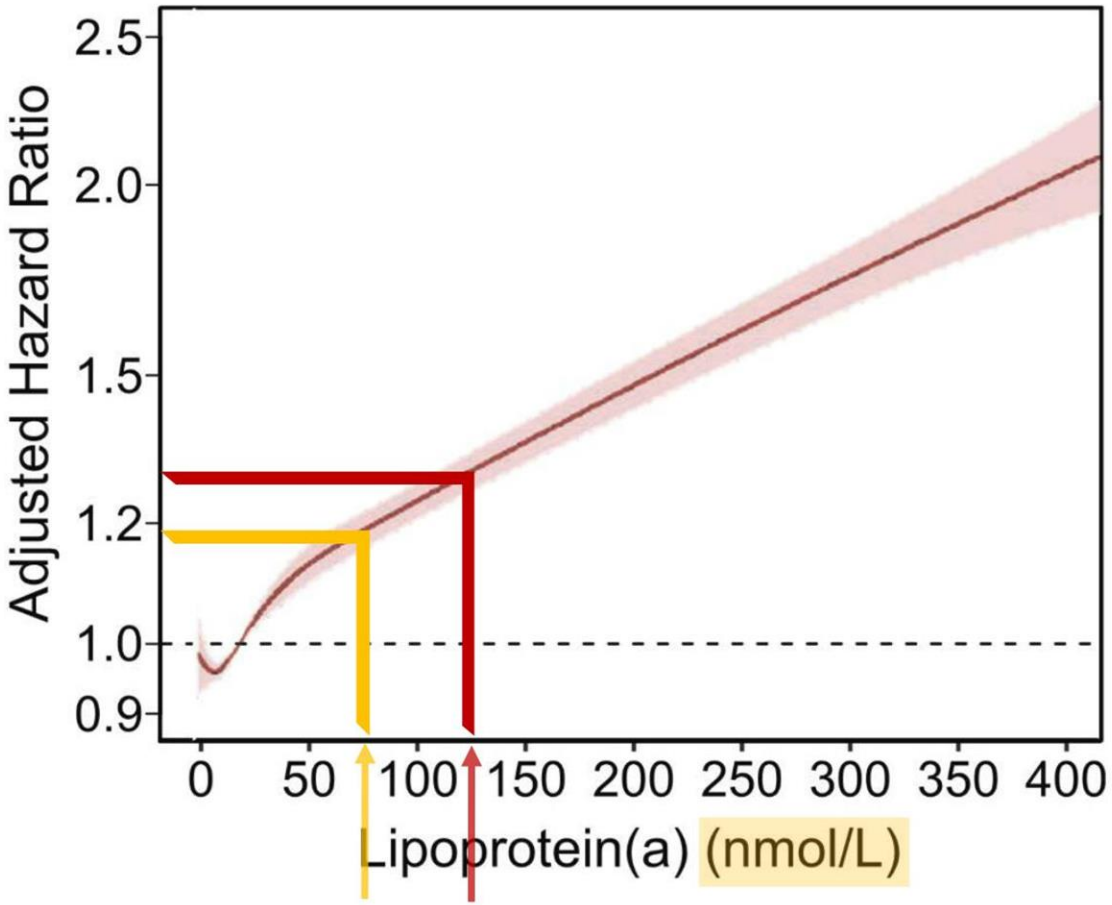


Wang *J Amer Heart Assoc* 2018;7:e006460

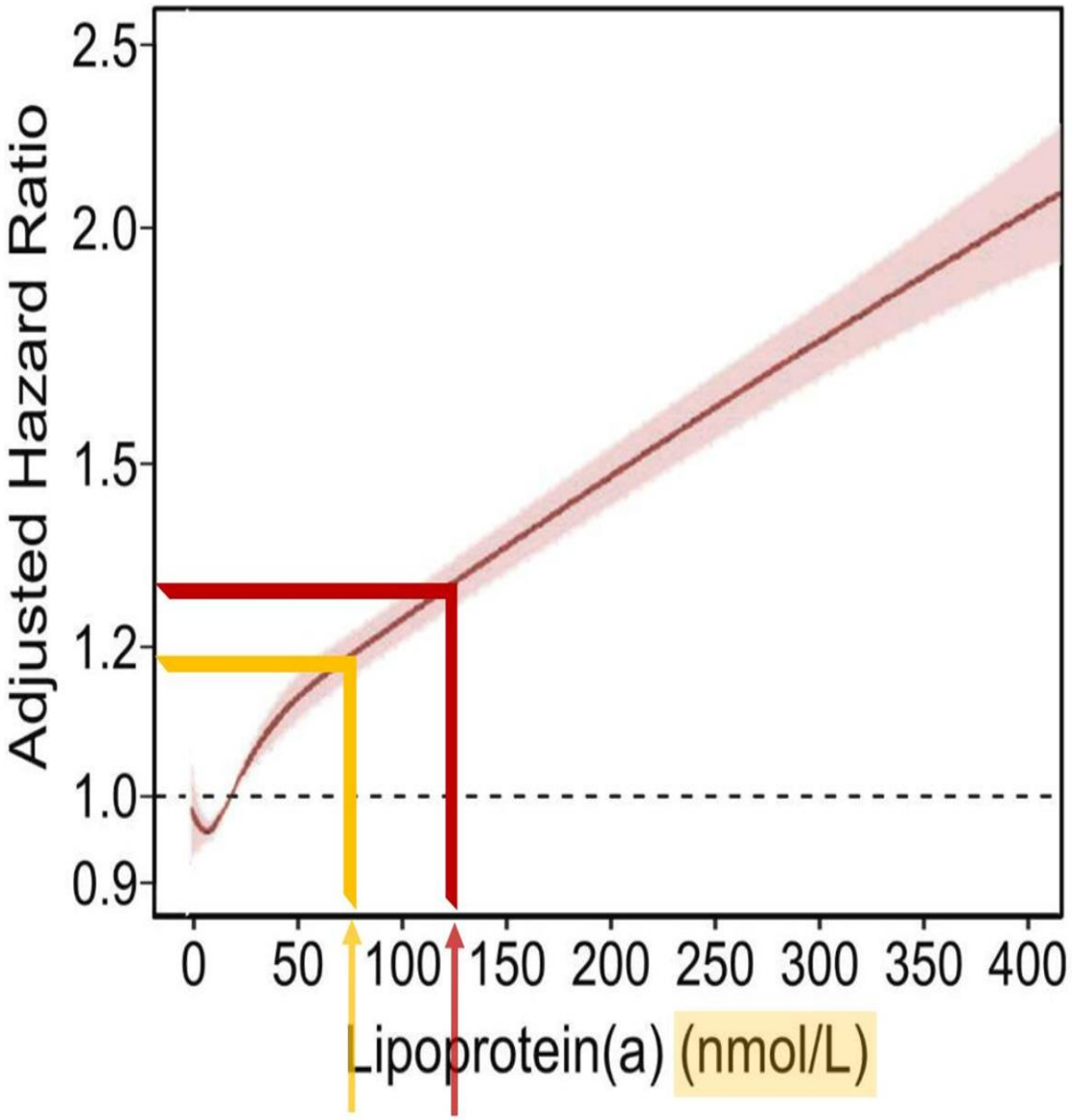
Suboptimal LDL Response to Statins Associate with Plaque Progression



Kataoka *Arterioscler Thromb Vasc Biol* 2015



GENEPI INNSBRUCK



GENEPI INNSBRUCK

So, why should I measure Lp(a) now?

- causal risk factor
- frequent risk factor
- helpful for risk estimation

Effectiveness of GLP1RAs in Real –Life Studies

Punti di forza

Popolazione ben definita
Disegno dello studio
Trattamento somministrato in condizioni strettamente controllate
Massima compliance

Punti di Forza

Più ampio spettro di popolazioni e di setti assistenziali (esclusi nei trials)
Effetti lungo periodo
Effetti su outcomes che non erano stati considerati nei trials Eventi avversi rari /tossicità in sottogruppi
Valutare la persistenza in terapia e la compliance Analisi farmaco-economiche

Limiti

Esclusione di molti pazienti
Difficoltà a generalizzare i risultati
Centri specializzati
Durata e dimensioni campione limitate, no info su lungo termine
Trial effect"

Limiti

Rischio di selection bias
Limitato numero di informazioni Dati mancanti o eterogeneità nella definizione dei dati

Tabella 1. Fattori determinanti l'aterogenicità delle lipoproteine contenenti apolipoproteina B[11].

1. Concentrazione plasmatica
2. Dimensioni e affinità per i proteoglicani della parete arteriosa
3. Instabilità delle lipoproteine intrappolate e rapidità di aggregazione (dipendente dalla composizione lipidica delle lipoproteine a bassa densità, a sua volta influenzata dalla dieta)
4. Suscettibilità delle lipoproteine aggregate a subire ulteriori modifiche all'interno della parete arteriosa
5. Capacità delle lipoproteine modificate di indurre risposte cellulari alterate

Figura 1. Livelli target di colesterolo LDL (C-LDL) per le diverse categorie di rischio cardiovascolare (CV). ASCVD, malattia cardiovascolare aterosclerotica; DM1/2, diabete mellito di tipo 1/2; IRC, insufficienza renale cronica.
Elaborata da Mach et al.[6]

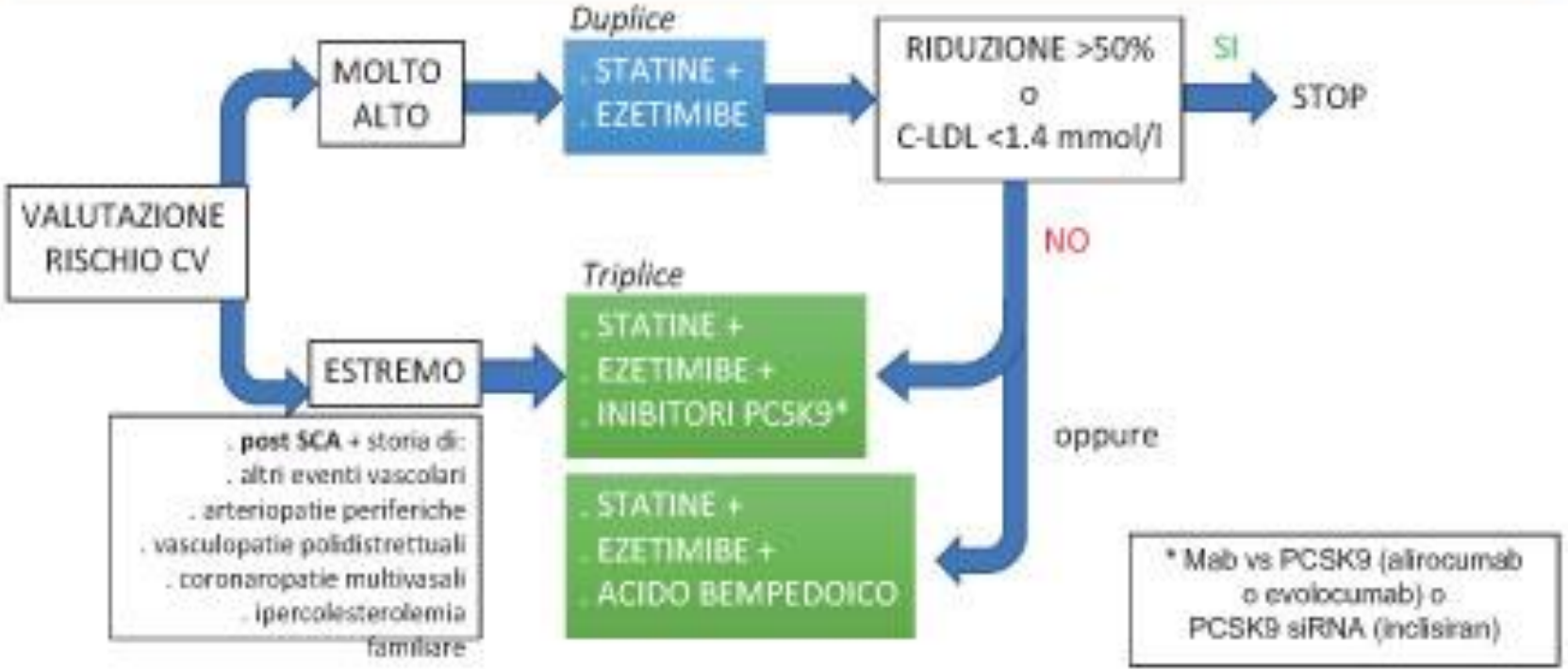


Figura 3. Terapia ipolipemizzante di combinazione come prima linea di trattamento nei pazienti ad elevato rischio cardiovascolare (CV).
C-LDL, colesterolo LDL; PCSK9, proproteina convertasi subtilisina/kexina tipo 9; SCA, sindrome coronarica acuta; siRNA, small interfering RNA.
Elaborata da Ray et al.[17]

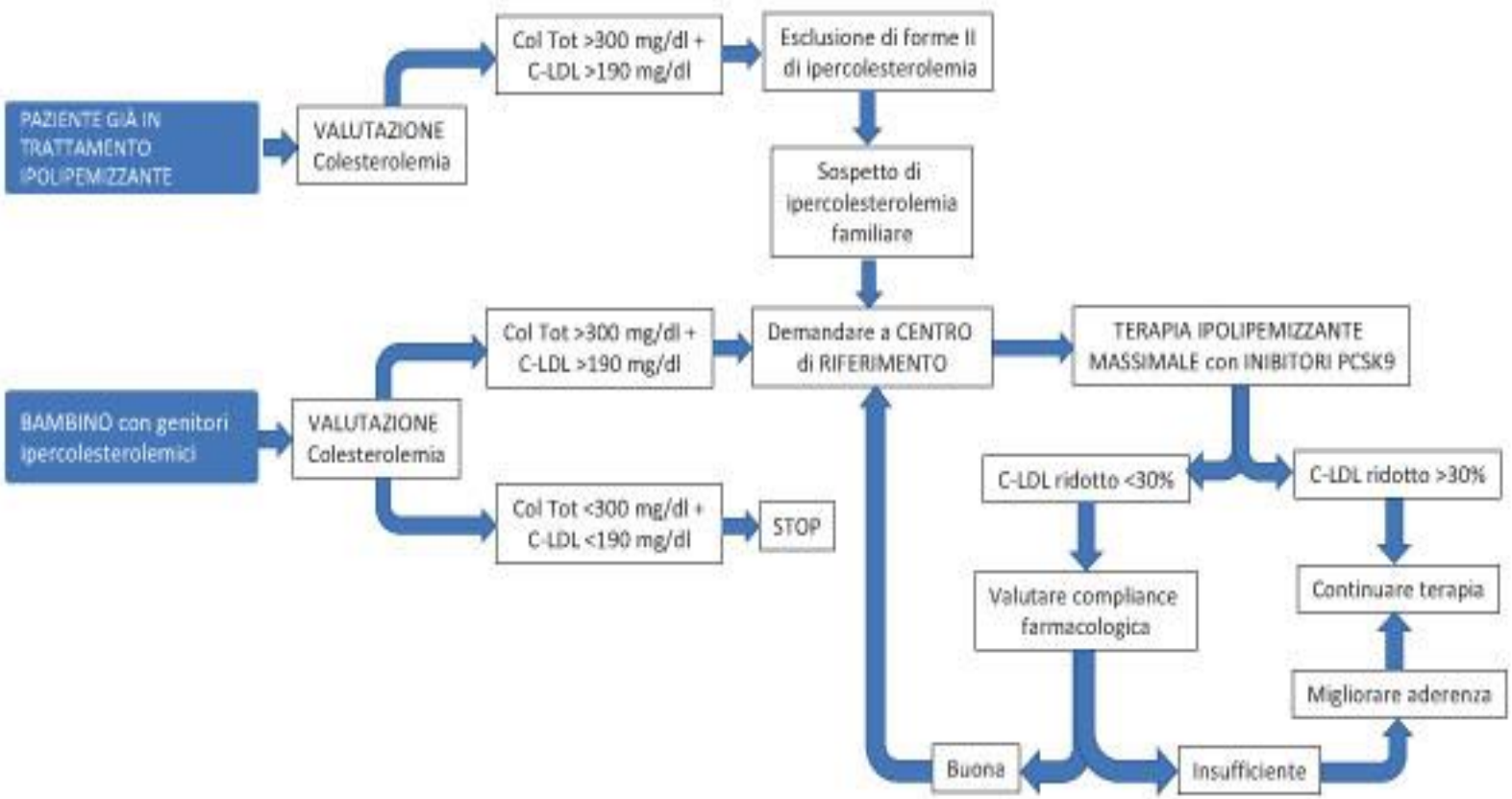
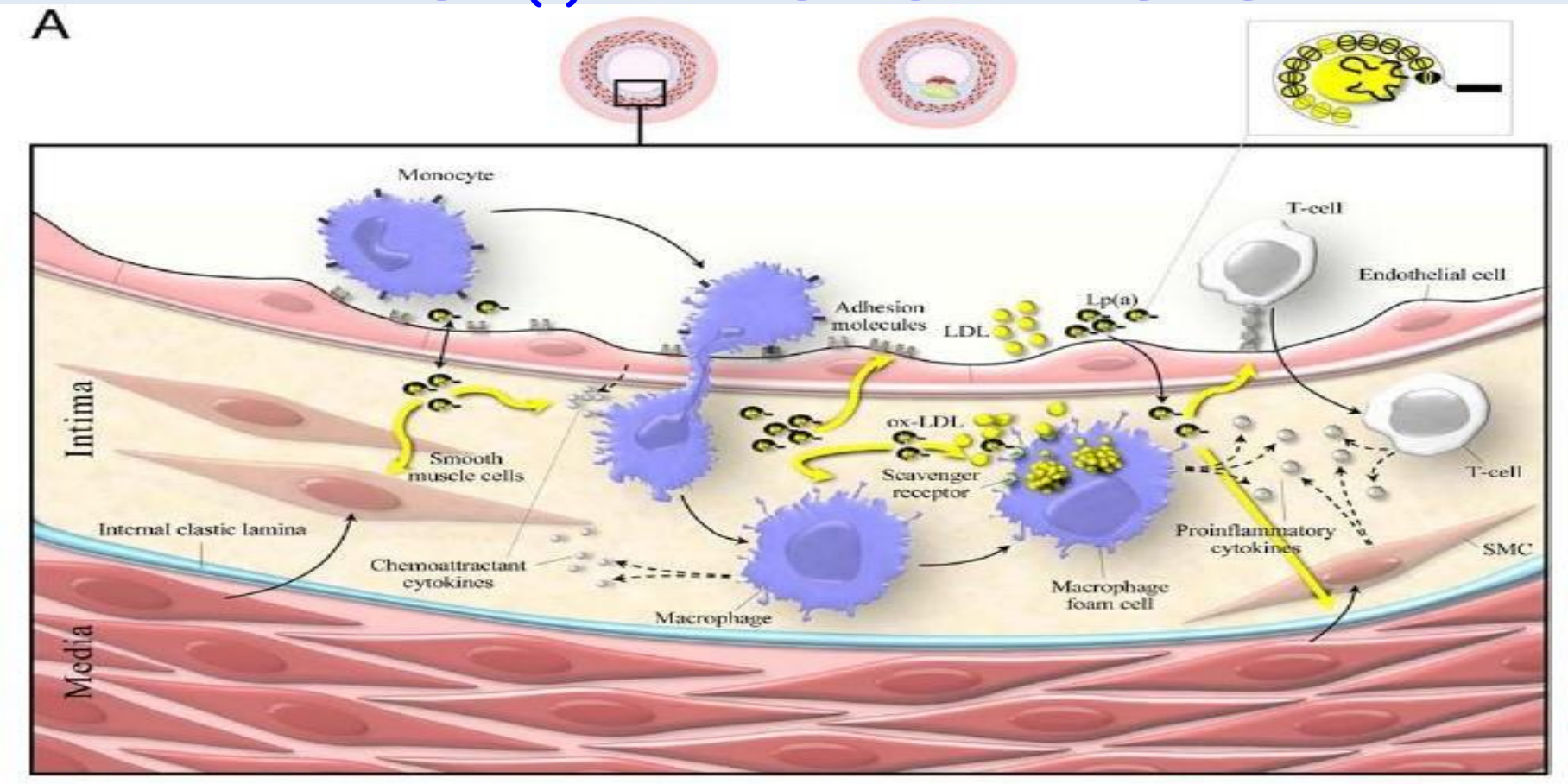


Figura 5. Algoritmo per l'identificazione e la gestione dei pazienti con ipercolesterolemia familiare.
C-LDL, colesterolo LDL; Col Tot, colesterolo totale; PCSK9, proproteina convertasi subtilisina/kexina tipo 9.
Elaborata da Bilato et al.[49]

Lipoprotein (a)

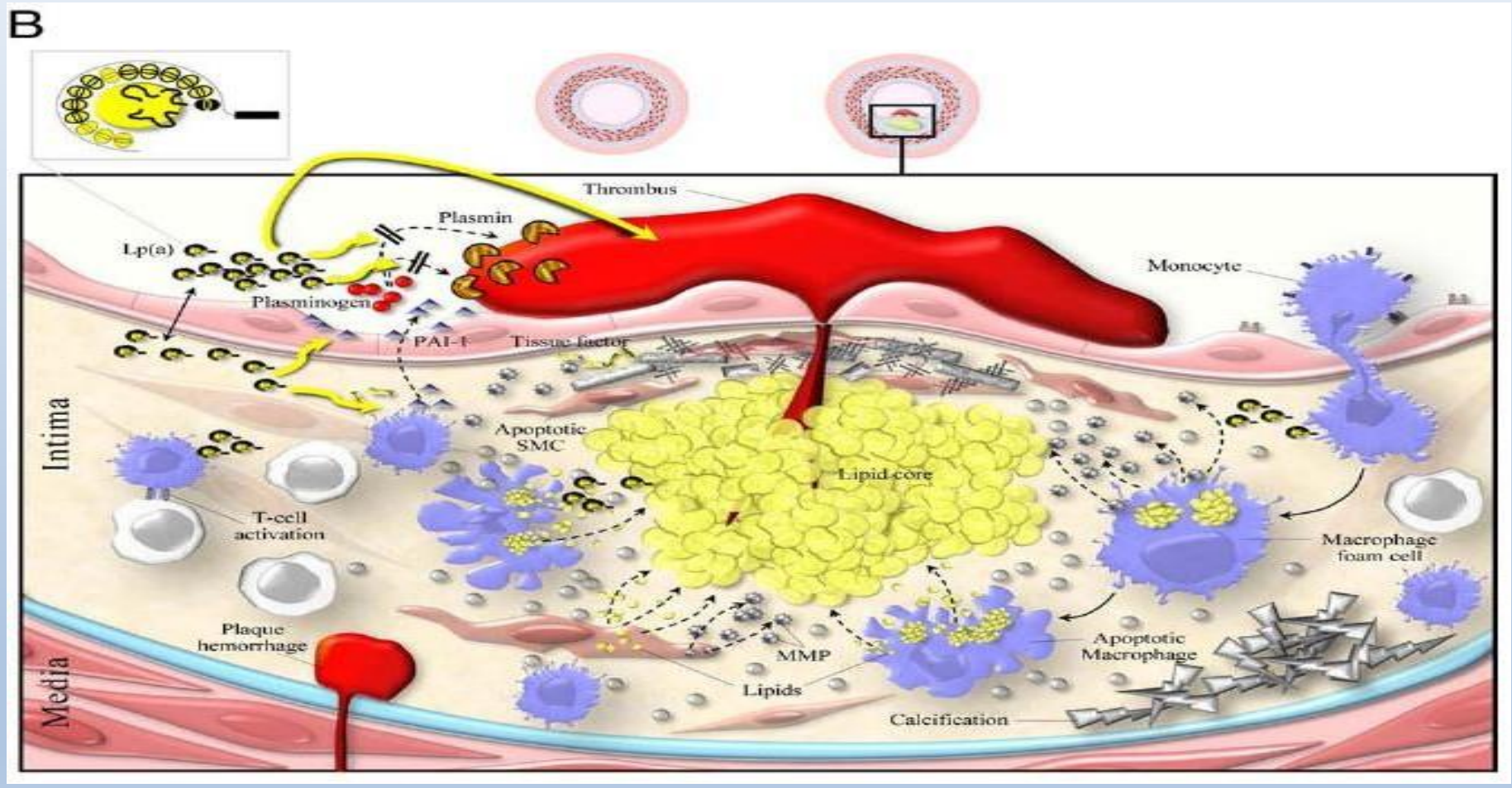
LIPOPROTEIN (a): PROATHEROGENIC PROPERTIES



Lipoprotein (a)

APO (a)

LIPOPROTEIN (a): PROTHROMBOTIC PROPERTIES



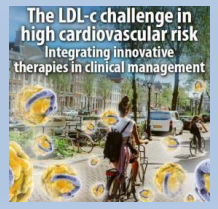
Novel oral pathways in LDL-C lowering therapy: The new promise of CETPi

Erin D. Michos

Johns Hopkins School of Medicine

Baltimore, MD, USA

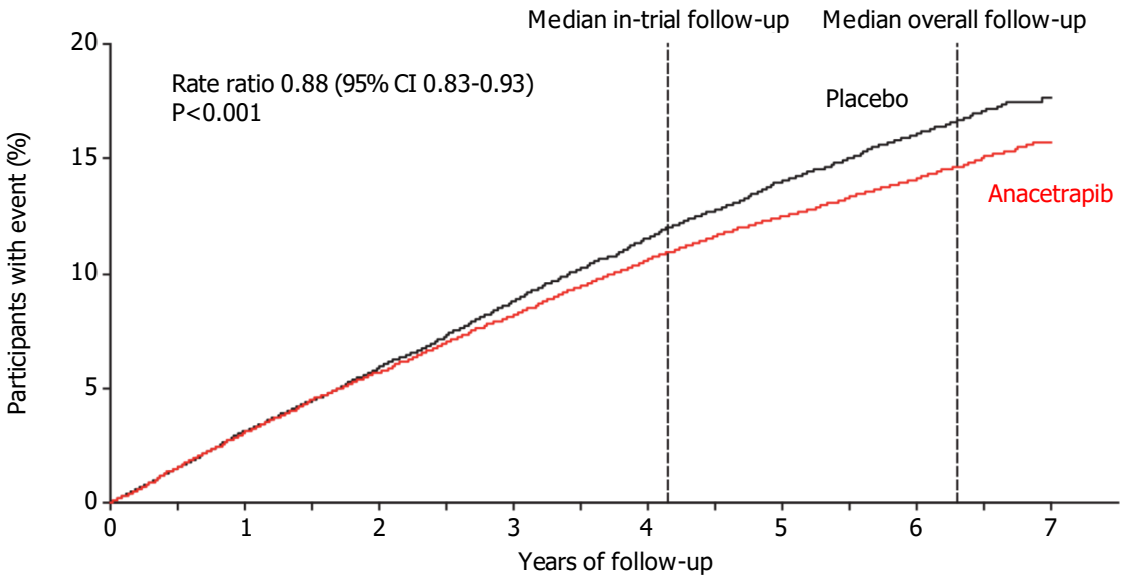
The LDL-c challenge in high cardiovascular risk - Integrating innovative therapies in clinical management



PHYSICIANS' ACADEMY FOR CARDIOVASCULAR EDUCATION
PACE-CME

Historical effects of CETP inhibitors were found in reducing cardiovascular events

REVEAL: Effects of anacetrapib on first major coronary event



Reduction of MACE

At 4.1 years

Additional reduction at 6.3 years

The positive impacts of CETP inhibition on major coronary incidents increased with extended follow-up, with no unfavorable outcomes in non-vascular death or illness

- CETP, cholesteryl ester transfer protein; MACE, major adverse cardiovascular events.
- HPS3/TIMI55-REVEAL Collaborative Group; et al. *Eur Heart J*. 2022;43(14):1416-1424.

ROSE study: Obicetrapib and High Intensity Statin therapy (HIS)

Objective **To evaluate the effect of obicetrapib on top of HIS on LDL-C**

Inclusion criteria

- A stable dose of HIS (A 40 / 80; R 20 / 40) 8 weeks prior to screening
- Fasting LDL-C levels >1.8 mmol/L

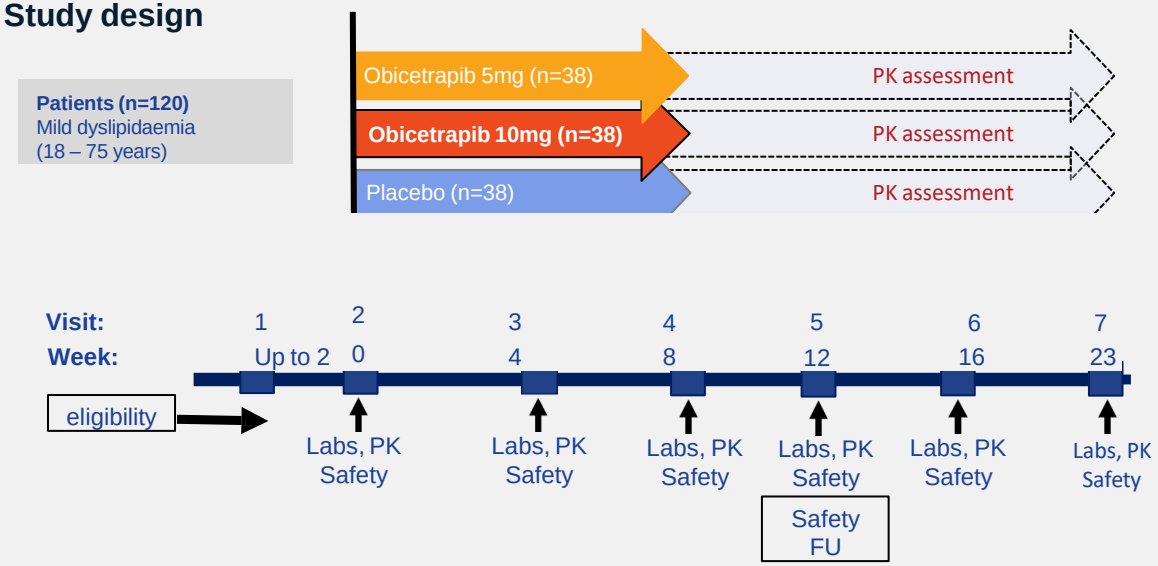
Exclusion criteria

- Current significant CV disease
- Diagnosis of type 1 or type 2 diabetes mellitus;
- Uncontrolled hypertension

Primary efficacy endpoint

- Percent change from baseline in LDL-C compared to the placebo group

Study design

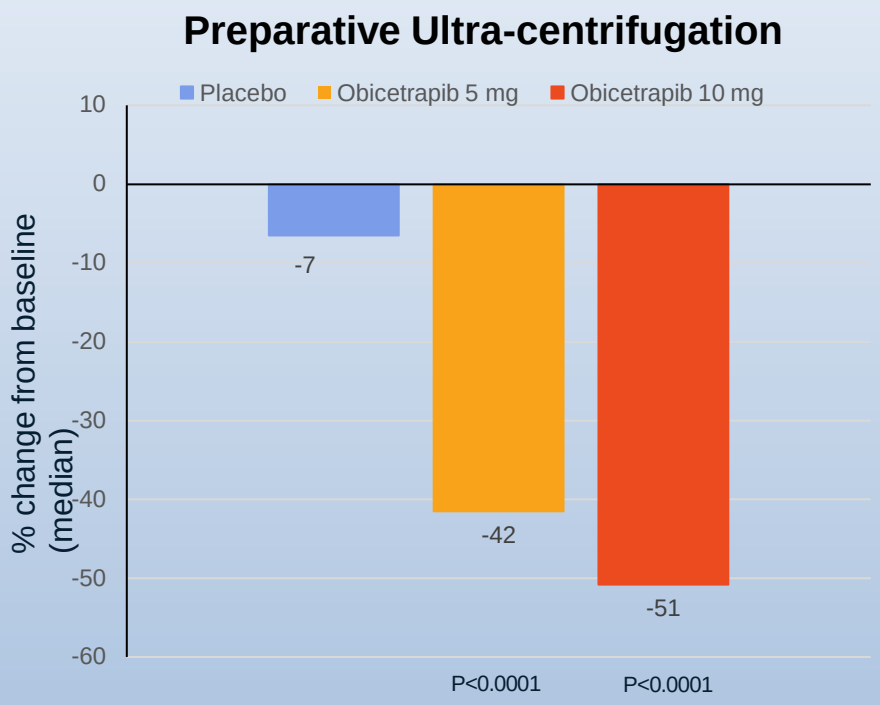


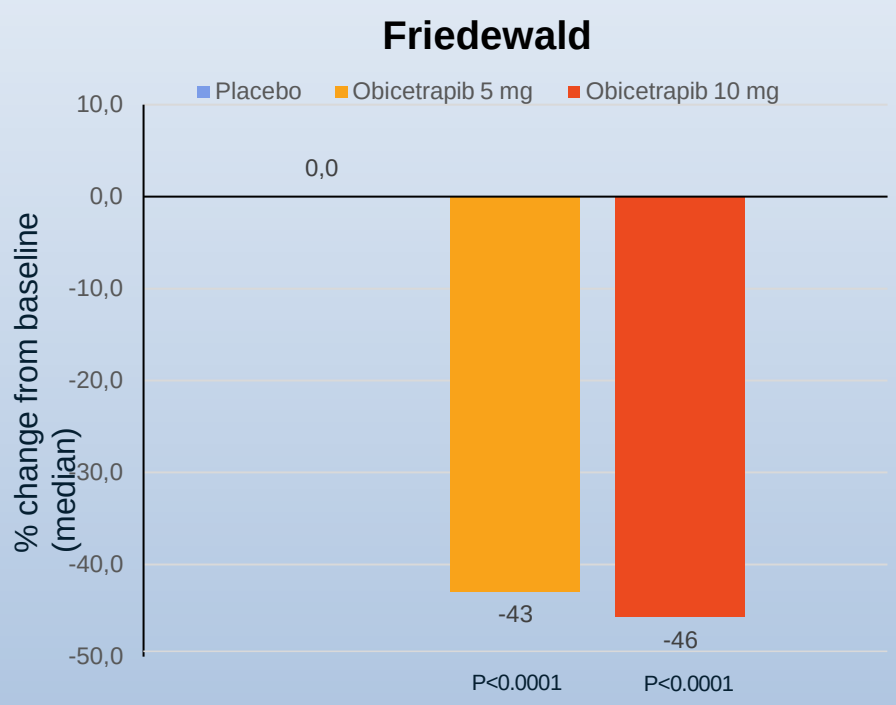
Pre-specified assessment of LDL-C levels by preparative ultra-centrifugation and Friedewald

NLA Scientific Session, Late Breaking Sessions, June 4, 2022

Nicholls SJ et al. Nature Medicine 2022; 28: 1672-1678

LDL-C Percent change from baseline by different measurement approaches



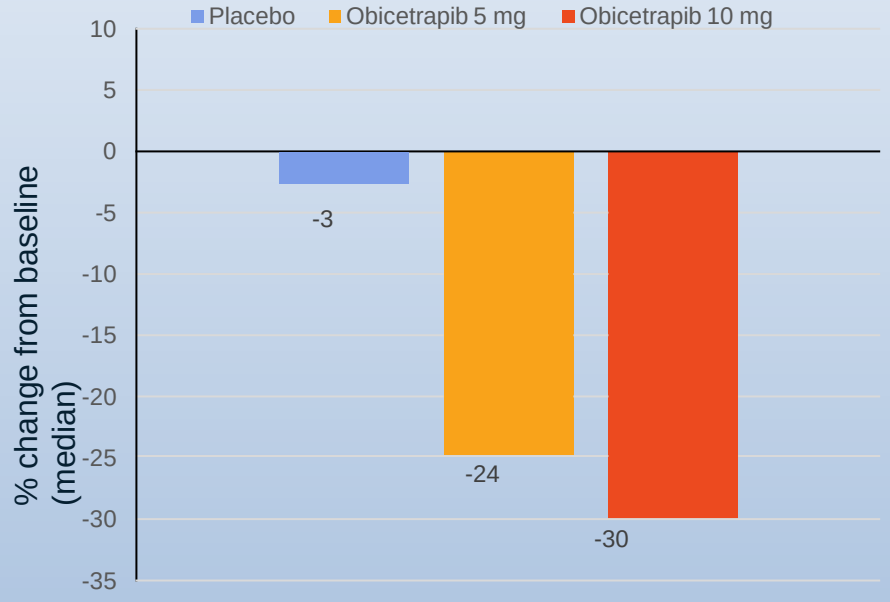


NLA Scientific Session, Late Breaking Sessions, June 4, 2022

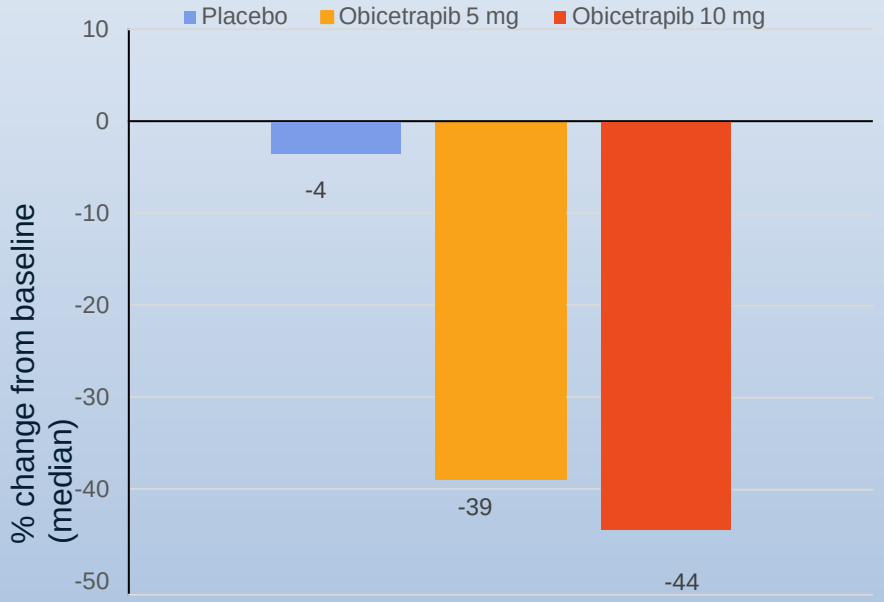
Nicholls SJ et al. Nature Medicine 2022; 28: 1672-1678

ApoB & non-HDL-C Percent change from baseline

ApoB



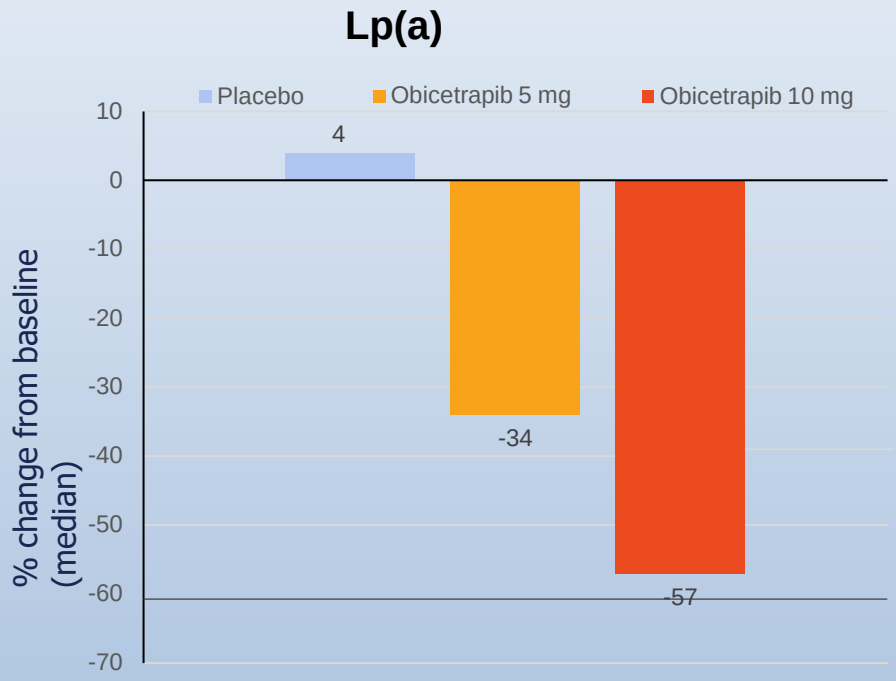
Non-HDL-C

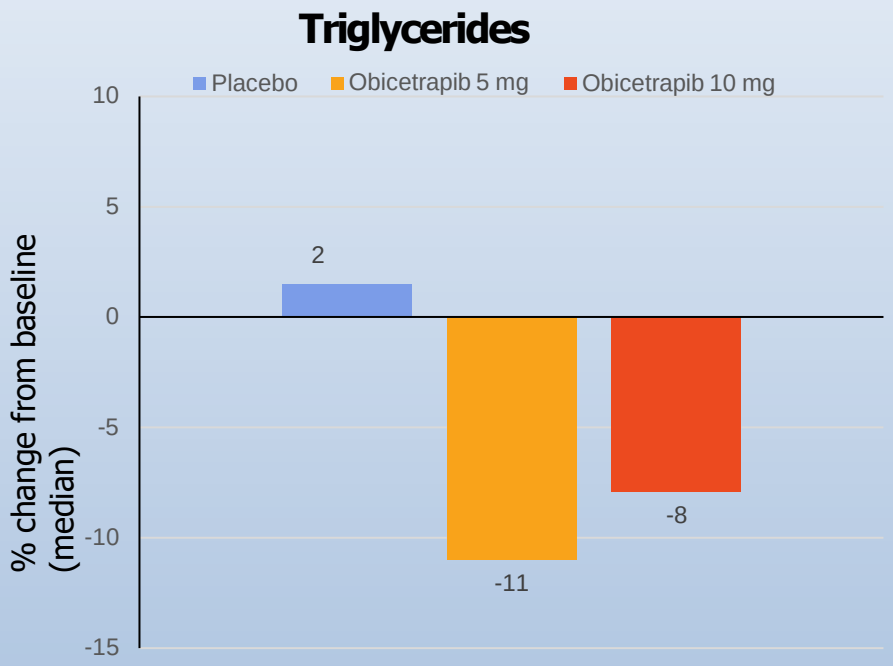


NLA Scientific Session, Late Breaking Sessions, June 4, 2022

Nicholls SJ et al. Nature Medicine 2022; 28: 1672-1678

Lp(a) and Triglycerides Percent change from baseline





NLA Scientific Session, Late Breaking Sessions, June 4, 2022

Nicholls SJ et al. Nature Medicine 2022; 28: 1672-1678

ROSE Conclusions

- Obicetrapib 5 and 10 mg on top of HIS therapy was well tolerated
- Obicetrapib 5 and 10 mg on top of HIS therapy reduced median LDL-C levels by -42% and -51% from baseline, respectively
- Obicetrapib LDL-C lowering comparable at all baseline LDL-C levels
- Obicetrapib LDL-C lowering is not mitigated in combination with HIS
- Obicetrapib LDL-C lowering is similar with both LDL-C quantitation methods
- Obicetrapib has potential to be a valuable addition for high risk ASCVD patients who do not achieve their target LDL-C guideline goals despite the use of HIS therapy.

NLA Scientific Session, Late Breaking Sessions, June 4, 2022
Nicholls SJ et al. Nature Medicine 2022; 28: 1672-1678

ROSE 2 Trial: obicetrapib + ezetimibe and high- intensity statin therapy

Objective

To evaluate the effect of obicetrapib 10mg in combination with ezetimibe 10mg on top of HIS on LDL-C

Inclusion criteria

- Stable dose of high-intensity statins (A 40/80, R 20/40) 8 weeks before screening
- Fasting LDL-C levels >70 mg/dL (1.8 mmol/L)

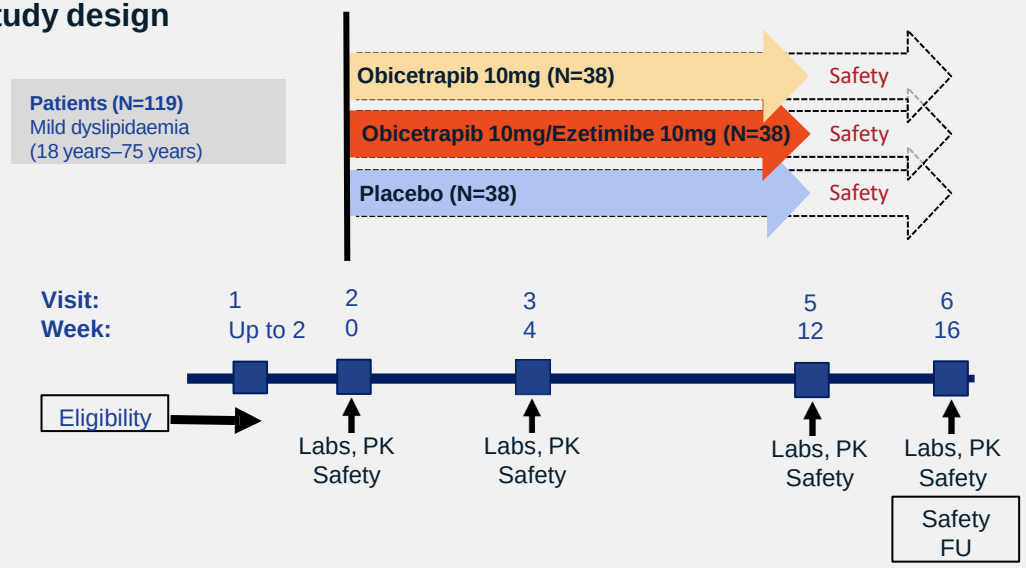
Exclusion criteria

- Current significant CV disease
- HbA1c ≥10%
- Uncontrolled hypertension

Primary efficacy endpoint

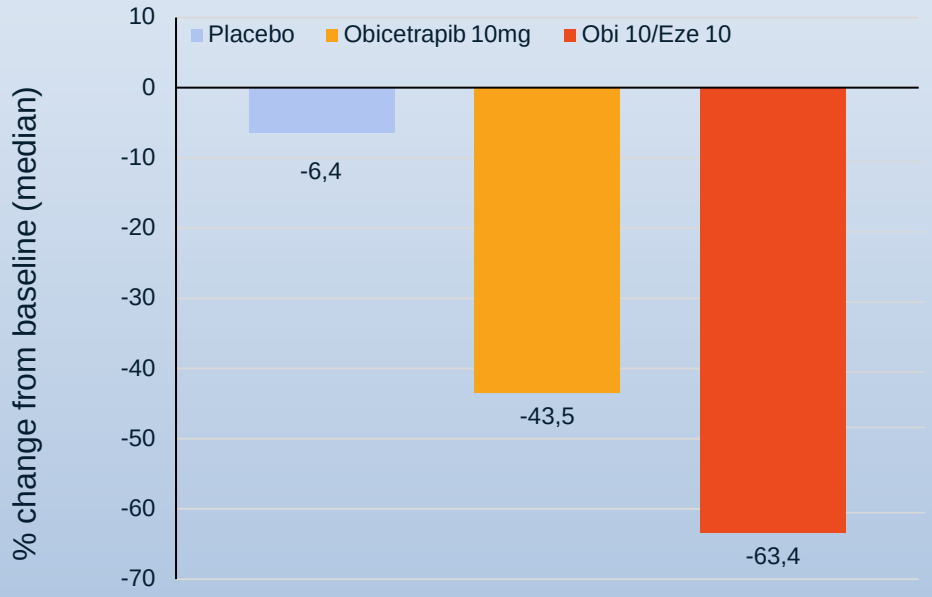
- Percent change from baseline in LDL-C compared with the placebo group

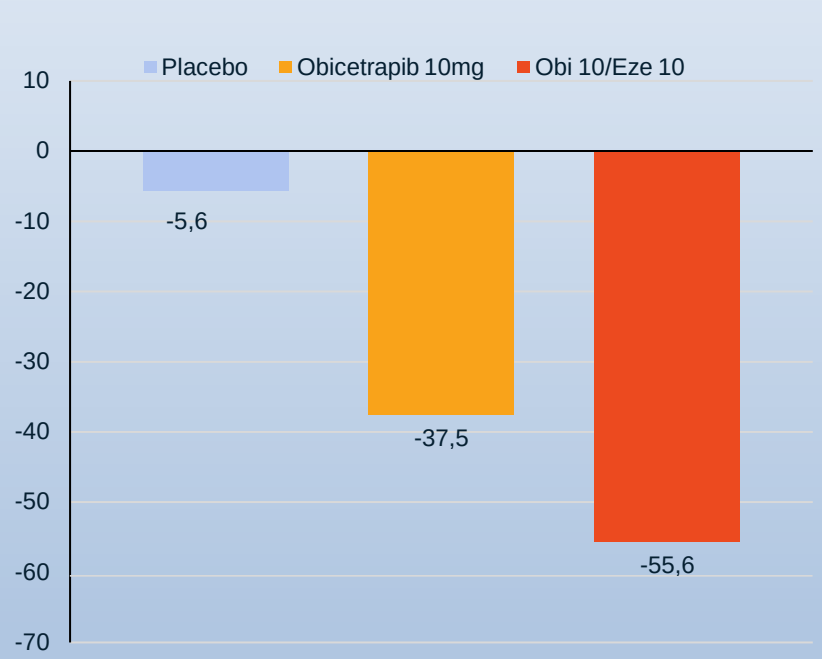
Study design



Ballantyne CM, et al. J. of Clinical Lipidology 2023

LDL-C in mg/dL and percent change from baseline





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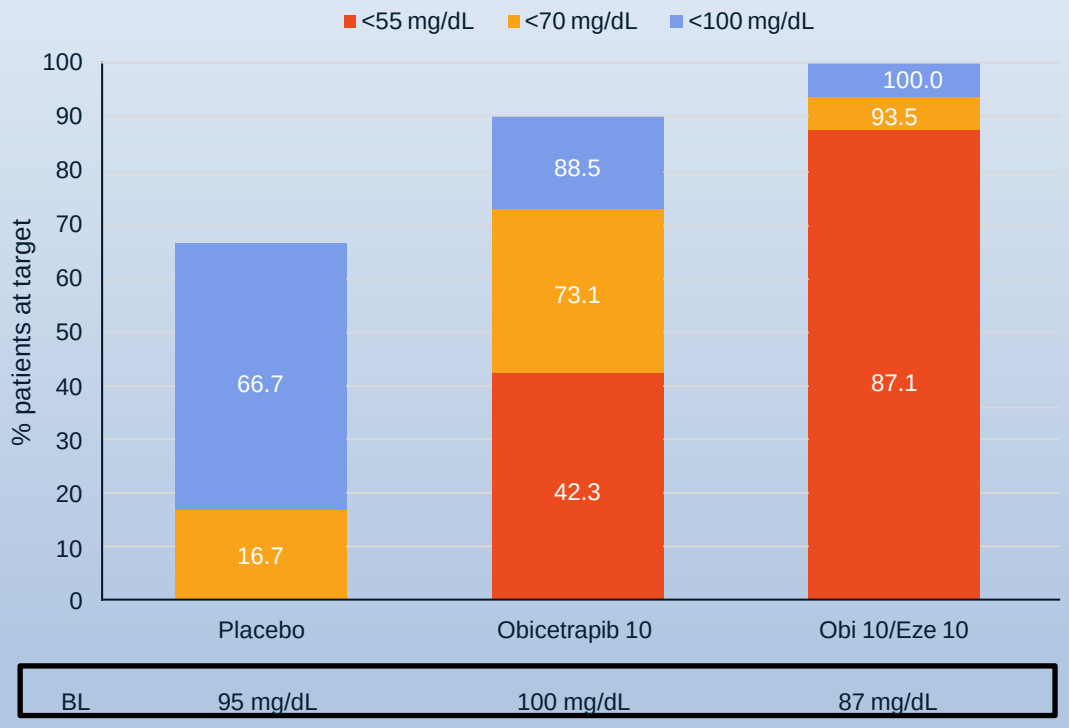
LDL-C target attainment



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Safety: TEAEs, TESAEs, and withdrawal overview (safety population)

	Placebo N= 40, N (%)	Obicetrapib 10 mg N= 39, N (%)	Obi 10 mg / Eze 10 mg N= 40, N (%)
TEAEs (%)			
TEAEs	16 (40)	8 (20.5)	11 (27.5)
Related TEAEs	2 (5.0)	4 (10.3)	5 (12.5)
Severe TEAEs	2 (5.0)	1 (2.6)	0 (0)
TESAEs			
TESAEs, total	1 (2.5)	1 (2.6)	0 (0)
Deaths	0	0	0
Withdrawal's study / medication			
TEAEs leading to discontinuation of study drug	2 (5.0)	2 (5.1)	1 (2.5)

N=total number of subjects in each treatment group.
n=number of subjects who experienced an event.
%=100 x n/N.

Treatment emergent adverse events (TEAE)

Ballantyne CM, et al. J. of Clinical Lipidology 2023

Rose 2 Trial Conclusions

- Obicetrapib 10 mg and the combination of obicetrapib 10 mg + ezetimibe 10 mg were observed to reduce median LDL-C levels by -43.5% and -63.4%, respectively, on top of HIS therapy
- The combination of obicetrapib 10 mg + ezetimibe 10 mg was observed to reduce total LDL particles and small LDL particles by 72.1% and 95.4%, respectively
- 87.1% of patients taking the combination of obicetrapib 10 mg + ezetimibe 10 mg were observed to achieve an LDL-C level <55 mg/dL
- Obicetrapib 10 mg and the combination of obicetrapib 10 mg and ezetimibe 10 mg on top of HIS therapy were well tolerated
- These data support the continued development of a fixed dose combination of obicetrapib 10 mg plus ezetimibe 10 mg

Obicetrapib Cardiovascular Outcome Trial in ASCVD patients

PREVAIL

Rationale

Patients with established ASCVD on maximally tolerated lipid-lowering therapy, including high-intensity statins, who are unable to get to their guideline goals, are at high risk for cardiovascular events, have an unmet medical need and therefore require additional lipid-lowering therapy

Objective

To evaluate the potential of Obicetrapib to reduce cardiovascular mortality and morbidity in patients with established ASCVD

Main inclusion criteria

- Established ASCVD
- Max tolerated lipid-modifying therapy
- LDL-C level ≥ 70 < 100 mg/dL + 1 RF
  - Recent MI (3-12 months)
  - T2DM
  - TG >150 mg/dL
  - HDL-C <40 mg/dL

  Or

  LDL-C≥ 100 mg/dL

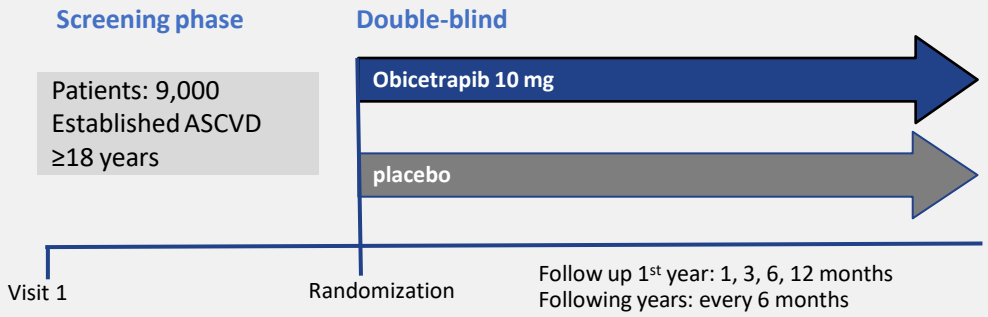
Main exclusion criteria

- Poorly controlled diabetes (HbA1c >10%)
- Hypertension
- Congestive heart failure
- Severe anemia
- Liver disease
- Chronic kidney disease

Strategy

- Duration if 959 primary endpoint events occur or the last randomized patient has been followed for a minimum of 2.5 years

Study design: Randomized, double-blind, placebo-controlled



Primary endpoint

- 4 point MACE (CVD death, non-fatal MI, non-fatal stroke, non-elective coronary revascularization)

Secondary objective

- LDL-c at 12 weeks
- New-onset diabetes mellitus;

NCT05202509

What's Hot in CVD Prevention?

Lipid Management!!

THANK YOU!

Questions??

@ErinMichos

MARCATORI DI MALATTIA

LIPOPROTEINA(a) E ATEROSCLEROSI: È TEMPO DI TRATTARE!

Lipoprotein(a) and Atherosclerosis: it is high time to treat!

MARIA GRAZIA ZENTI, ANNA ALTOMARI, ENZO BONORA

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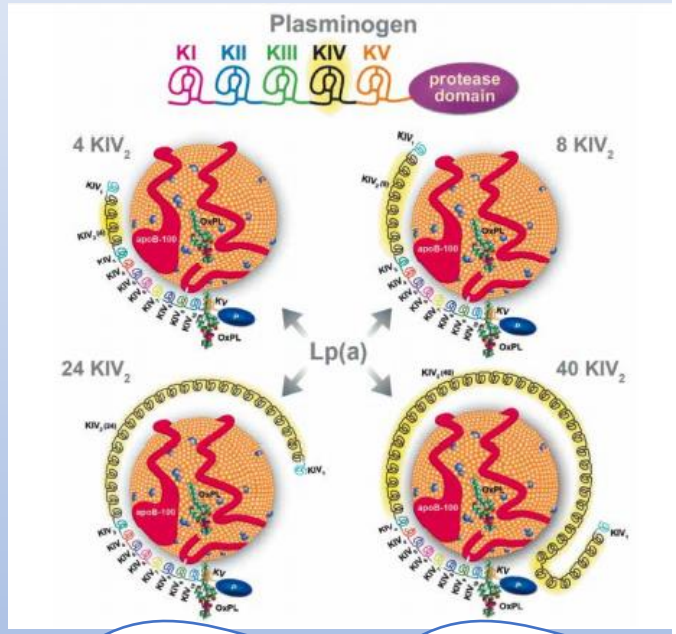

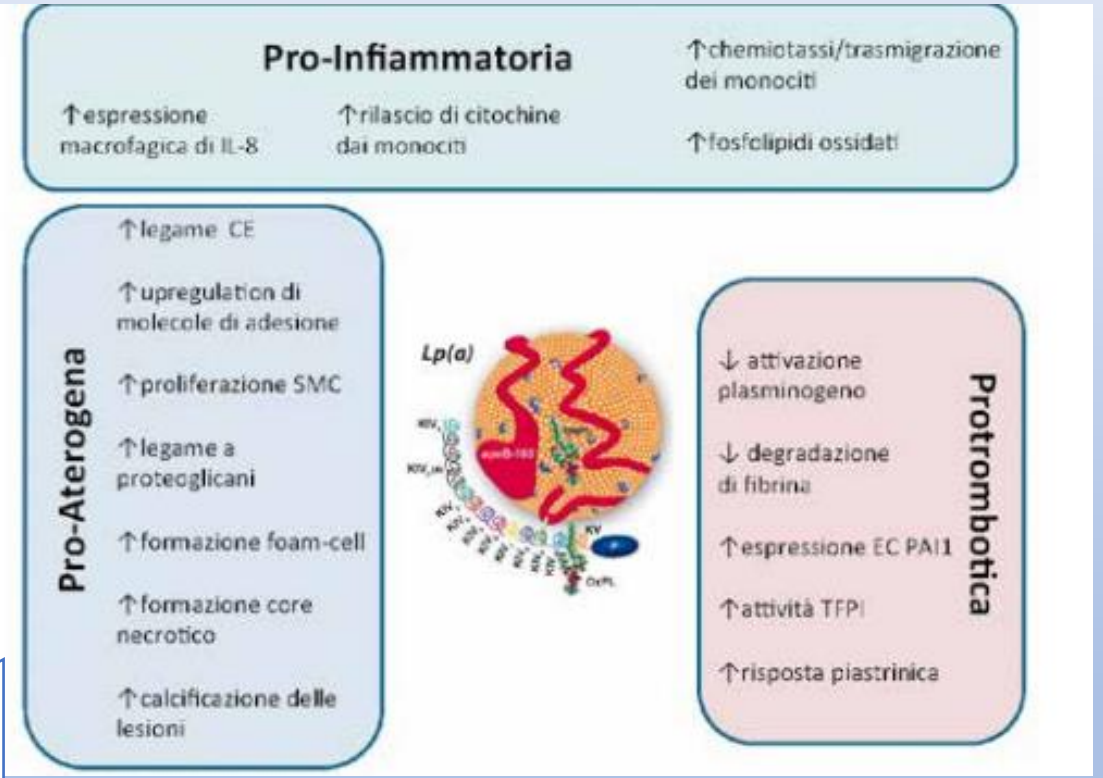

Molteplici isoforme, attività peculiare.

Giornale Italiano dell'Arteriosclerosi 2017; 8 (3): 50-61

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

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

Certain individuals declare themselves to be at high or very high CVD risk without needing risk scoring, and all risk factors require immediate attention. This is true for patients with documented CVD, older individuals with long-standing DM, familial hypercholesterolaemia, chronic kidney disease, carotid or femoral plaques, coronary artery calcium score >100, or extreme Lp(a) elevation.

Livelli estremi di Lp(a) modifcano la classe di rischio del paziente

Lipid analyses for CVD risk estimation

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.

Particolarmente significativi i livelli oltre 180 mg/dl

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