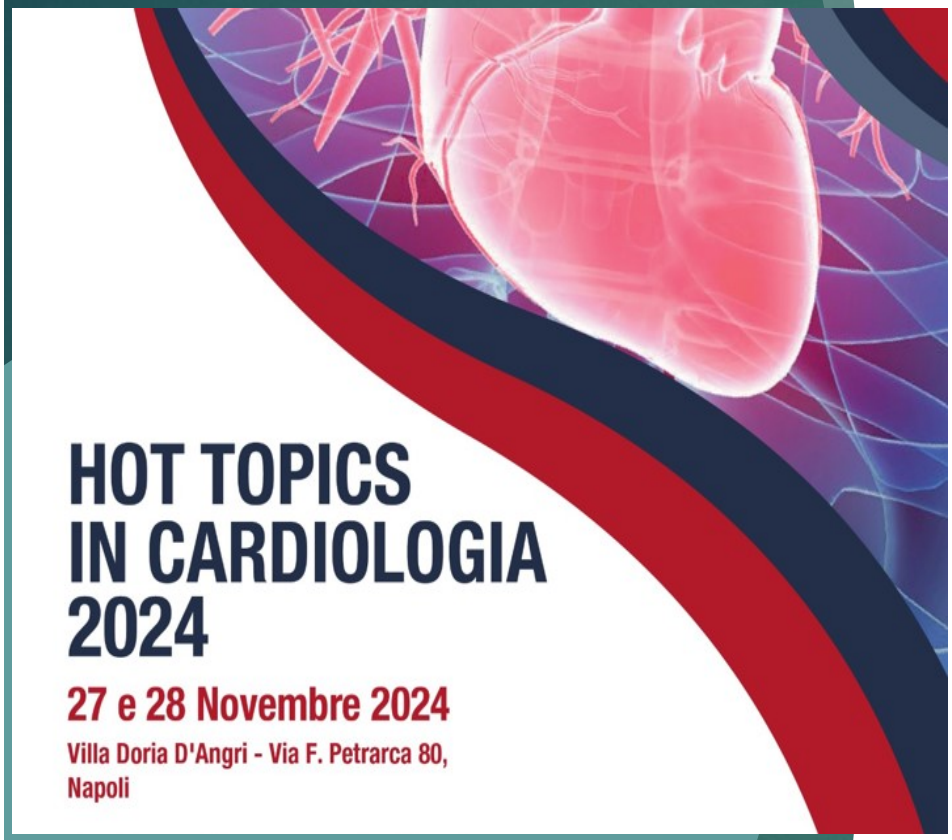


Terapia medica ottimale: gestione del rischio residuo

Dott.ssa Valentina Capone
Cardiologia UTIC - AO "A. Cardarelli"
Direttore Prof. C. Mauro

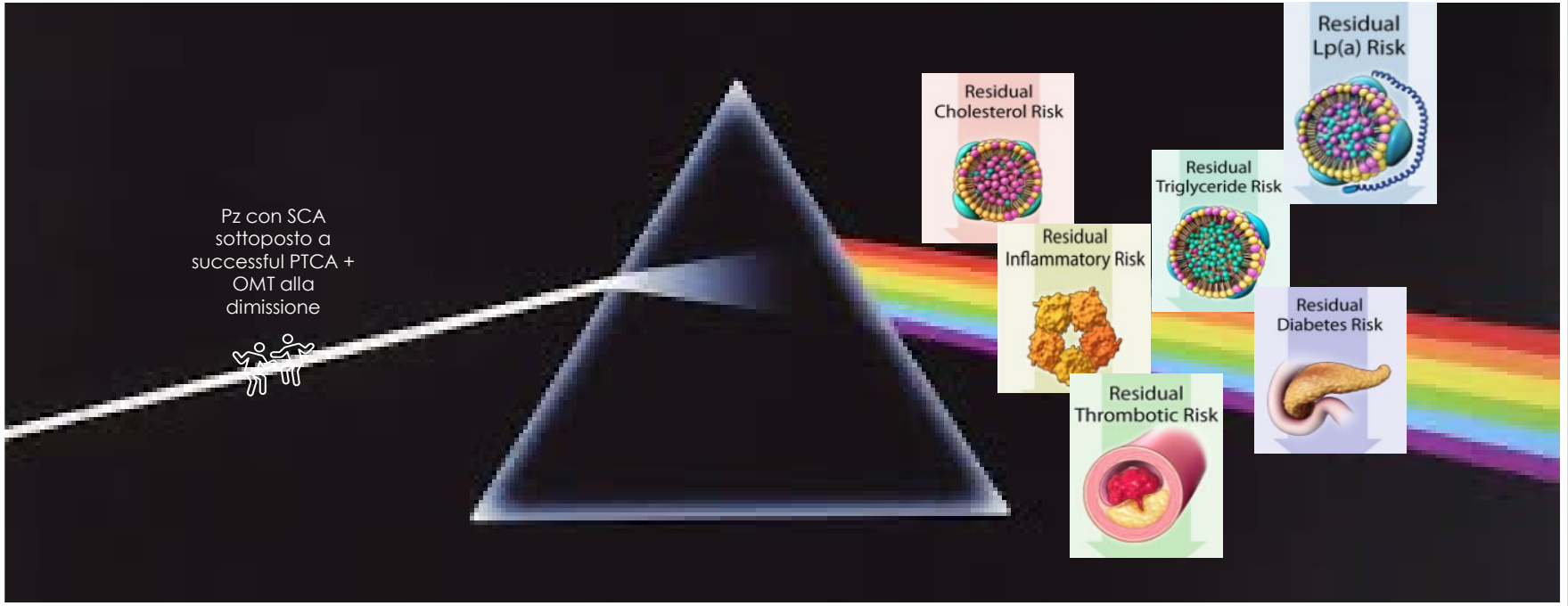
Rischio residuo cardiovascolare

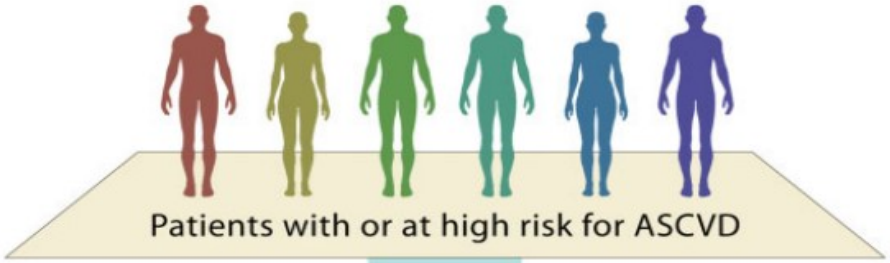
Rischio residuo cardiovascolare

Il rischio cardiovascolare residuo si può definire come la **probabilità di sviluppare un evento cardiovascolare maggiore pur avendo sottoposto il paziente al trattamento ottimale** secondo gli standard di cura raccomandati.

Rischio residuo cardiovascolare: The Dark Side of The Moon

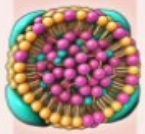
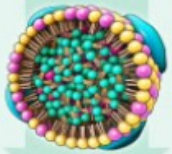
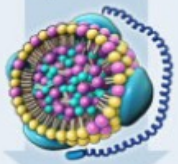
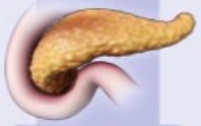
Rischio residuo cardiovascolare: The Dark Side of The Moon





Patients with or at high risk for ASCVD

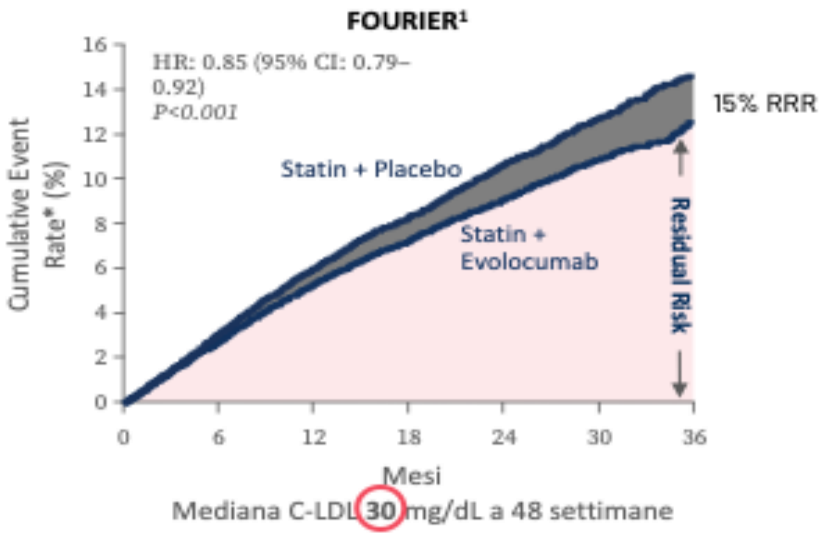
Despite contemporary evidence-based therapies*, residual risk of ASCVD events persists

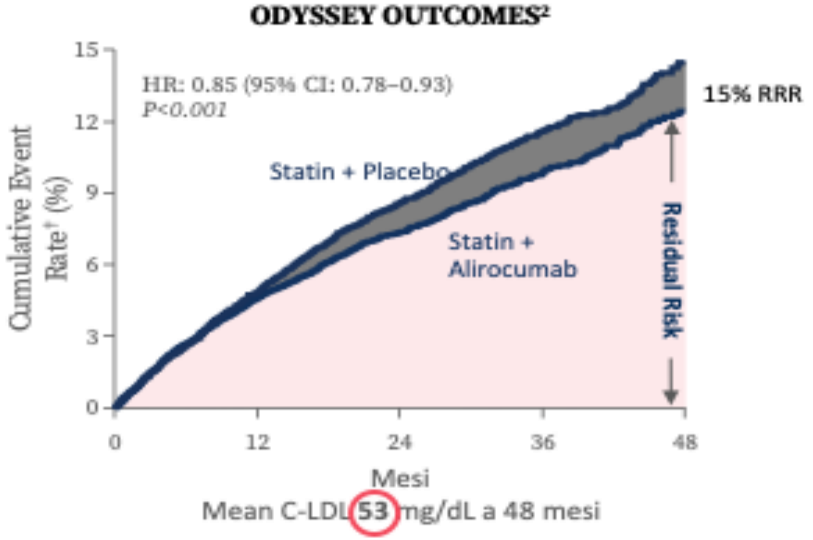
Biological Issue	Residual Cholesterol Risk	Residual Inflammatory Risk	Residual Thrombotic Risk	Residual Triglyceride Risk	Residual Lp(a) Risk	Residual Diabetes Risk
						
Critical Biomarker	LDL-C ≥100 mg/dL	hsCRP ≥2mg/L	No simple biomarker	TG ≥150mg/dL	Lp(a) ≥50mg/dL	HbA1c Fasting glucose
Potential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

Lawler PR, et al. Eur Heart J. 2021 Jan 1;42(1):113-131

Residual Lipidic risk

Il Rischio Residuo persiste nonostante l'aggressiva riduzione del C-LDL con gli inibitori della PCSK9





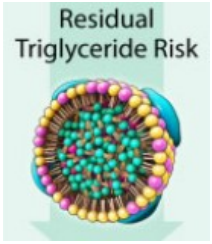
Ulteriore riduzione del rischio di circa il 15% in 2-4 anni

*Composite of CV death, MI, stroke, hospitalisation for unstable angina or coronary revascularisation[1]; †Composite of death due to coronary heart disease, non-fatal MI, fatal or non-fatal ischaemic stroke or hospitalisation for unstable angina.[2] CI: confidence interval; HR: hazard ratio.

FOURIER: Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; LDL-C: low density lipoprotein-cholesterol; MI: myocardial infarction; ODYSSEY-OUTCOMES: Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; PCSK9:Proprotein convertase subtilisin/kexin type 9; RRR: relative risk reduction.

Residual Triglyceride risk

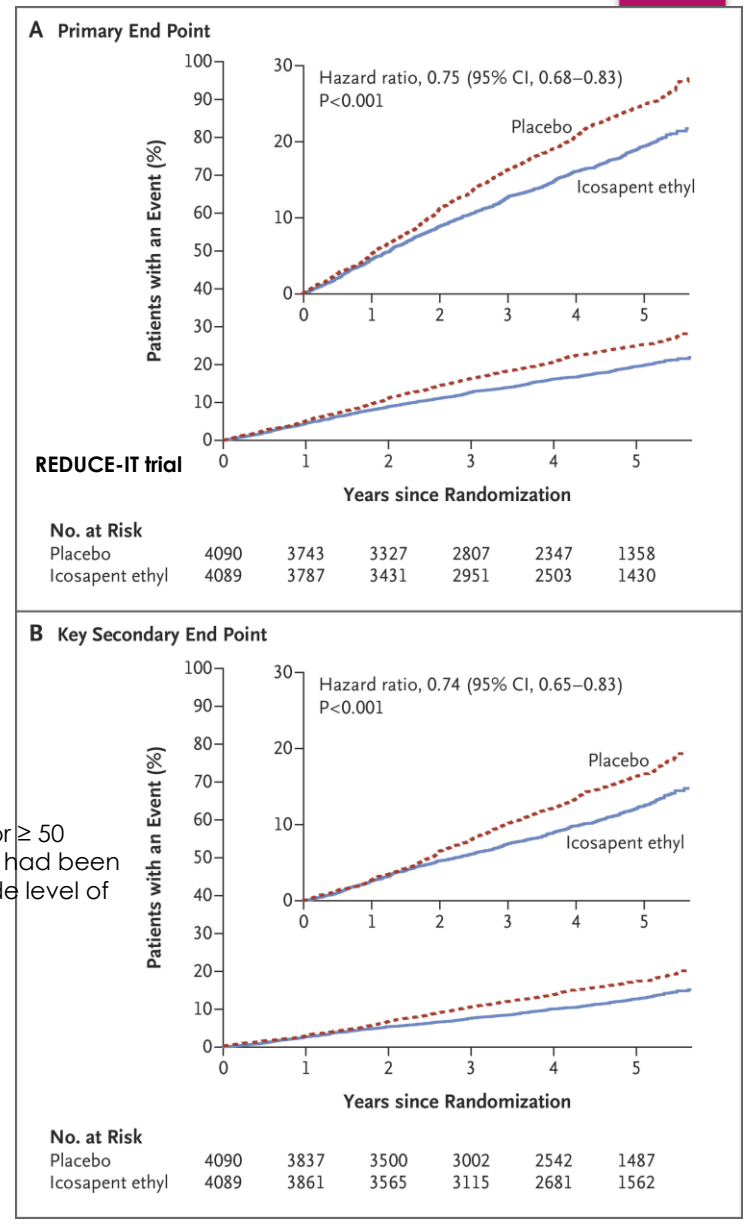
Biological Issue:

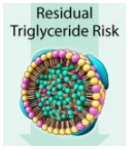


Critical biomarker:

TG ≥150 mg/dL

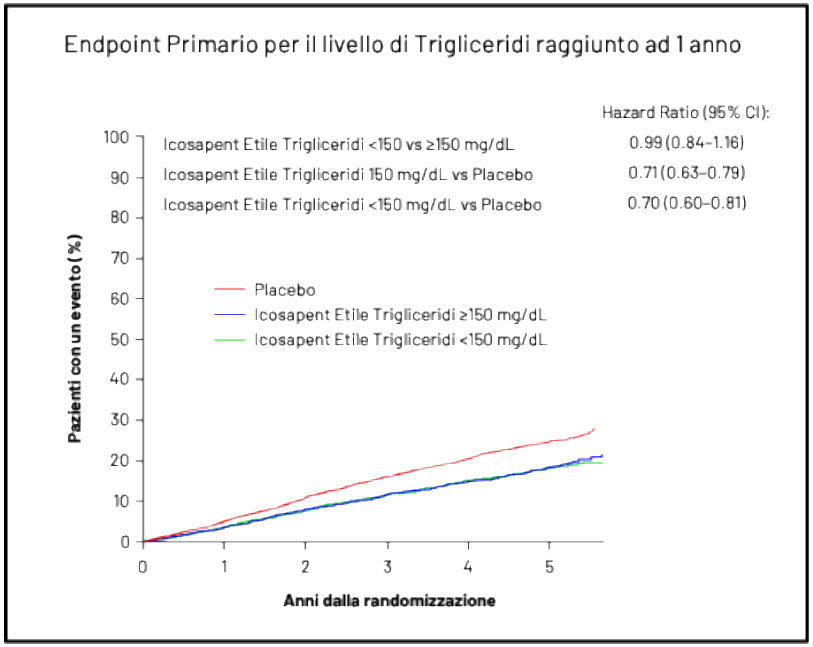
8179 pt with established CVD or ≥ 50 years with DM and ≥ 1 RF, who had been receiving statins and triglyceride level of 135 ≤ TG ≤ 499 m/dl
IPE 2g twice daily vs placebo
FU 4.9 years

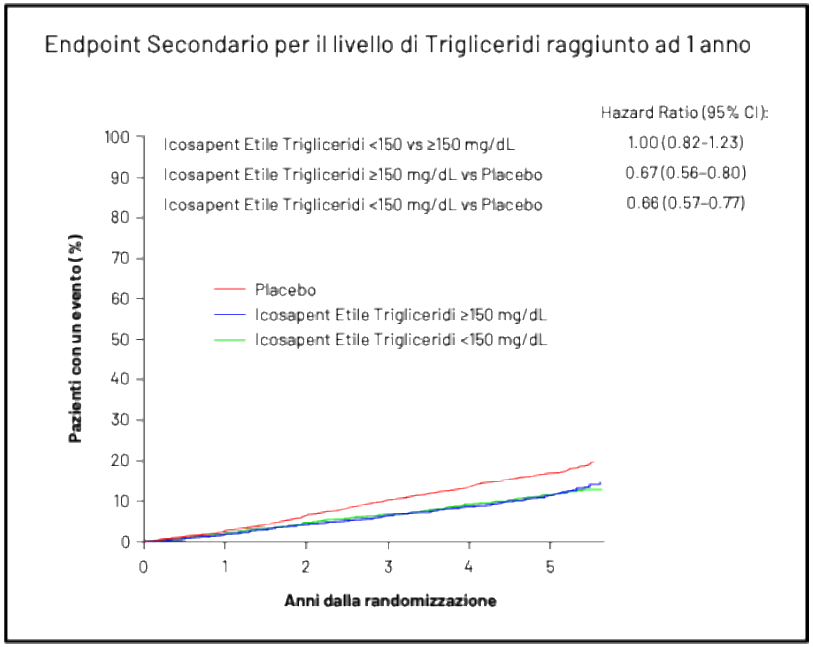




Residual Triglyceride risk

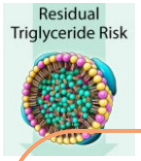
REDUCE-IT: beneficio CV di IPE indipendente dai livelli di TG raggiunti





Trigliceridi come target della terapia

Trigliceridi come marker di rischio

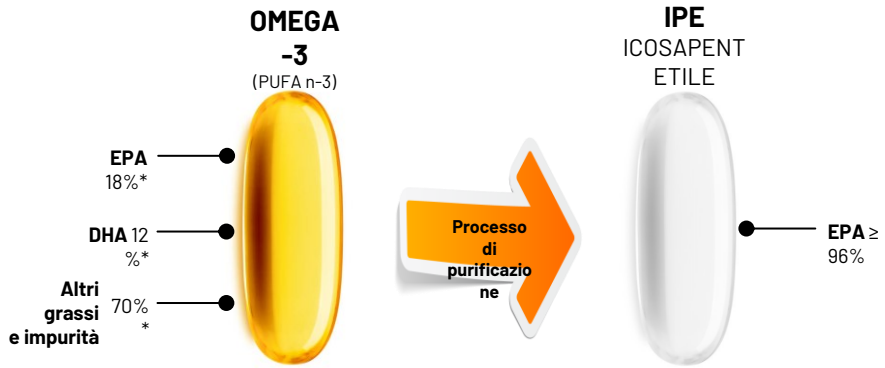


Residual Triglyceride risk

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

EPA
ACIDO
EICOSAPENTAENOICO

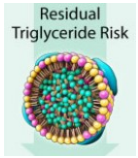
DHA
ACIDO
DOCOSAESAENOICO



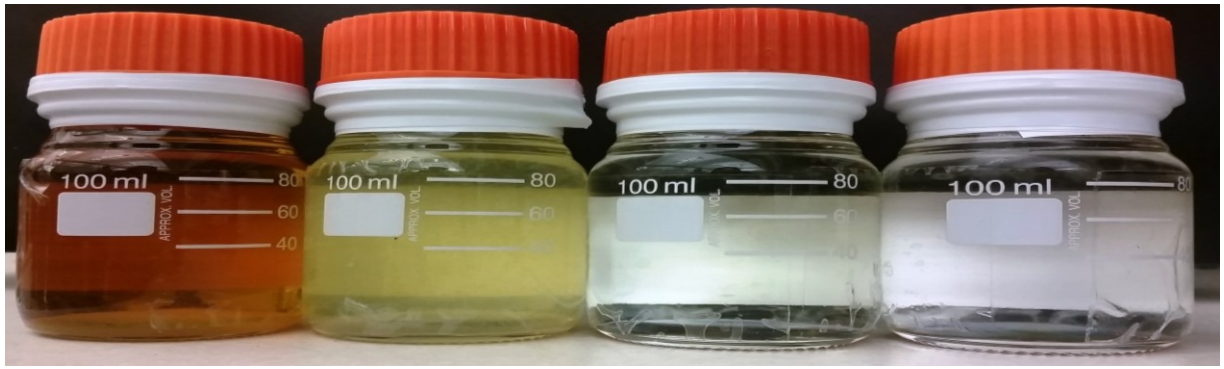
* *percentuali generalmente presenti*

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

* da EMA e FDA



IPE: un EPA altamente purificato



Maggioranza degli integratori di olio di pesce *
EPA 18%
DHA 12%

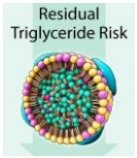
→ **EPA 26%**
DHA 16%

→ **EPA 65%**
DHA <5%

→ **VAZKEPA®**
≥EPA 96%
DHA non rilevato

Purezza VAZKEPA

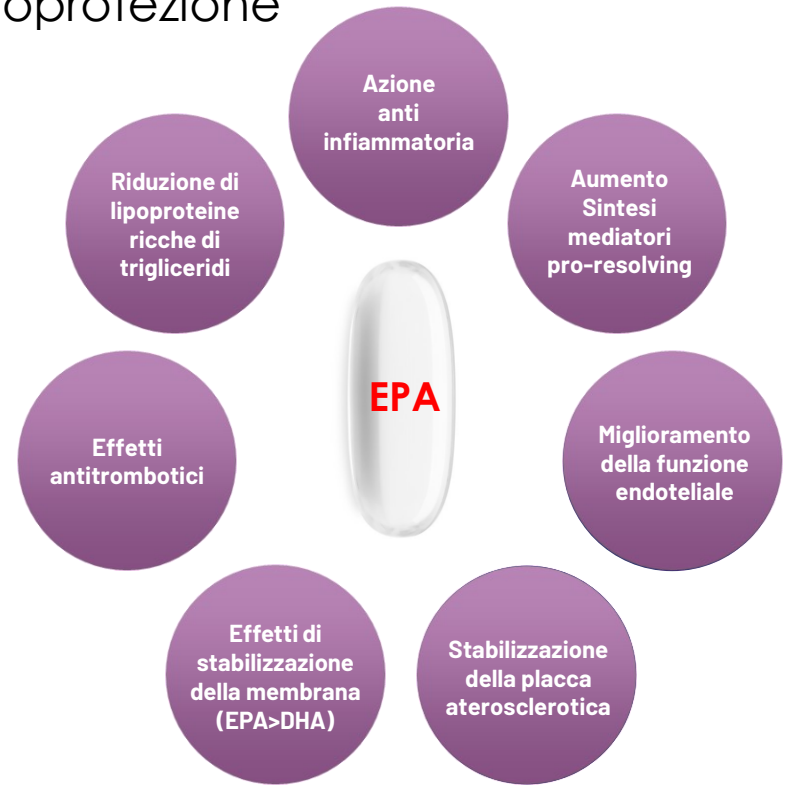
Amarin, data on file. *Based on Fish Oil Capsules containing 18% EPA, 12% DHA, and 70% other undisclosed fatty acids.



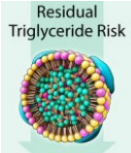
Residual Triglyceride risk

Acidi Grassi Omega-3: potenziali meccanismi di cardioprotezione

Gli acidi grassi omega-3 possono ridurre il rischio di eventi cardiovascolari attraverso una serie di meccanismi che contribuiscono alla loro complessiva azione protettiva.



Mason RP, et al., 2020

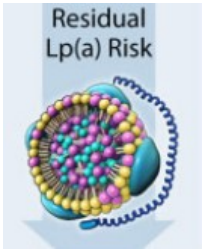


Residual Triglyceride risk

Acidi Grassi Omega-3: cosa ci dicono le Linee Guida?

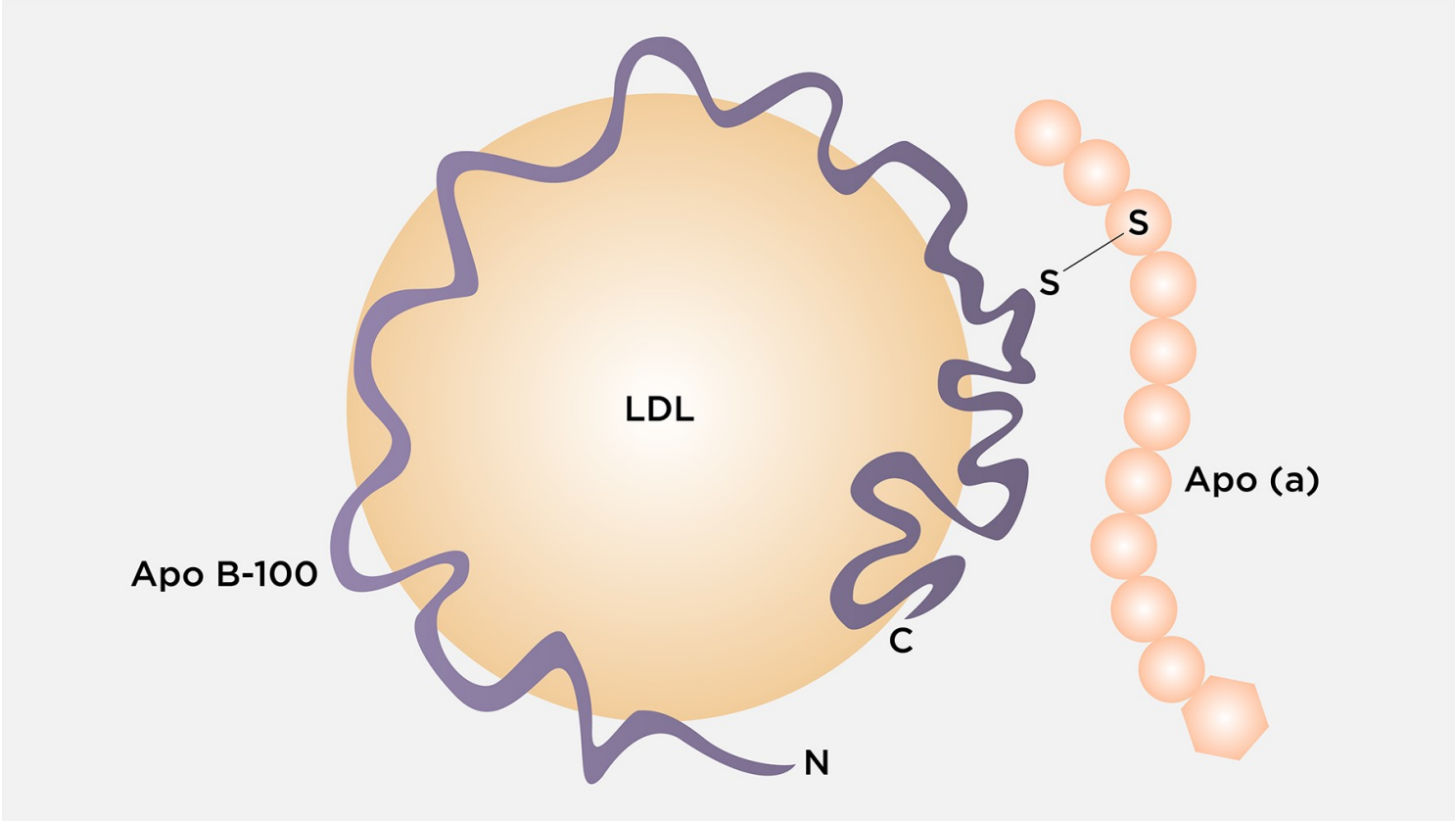
Raccomandazioni	Classe	Livello
Il trattamento con statine è raccomandato come farmaco di prima scelta per ridurre la CVD in individui ad alto rischio con trigliceridemia [TG>2.3 mml/L (>200mg/dL)].	I	B
In pazienti ad alto rischio o superiore con TG tra 1.5 e 5.6 mmol/L (135-499 mg/dL) nonostante il trattamento con statine, dovrebbe essere considerato il trattamento con i PUFA n-3 (*icosapent etile* 2x2g/die) in combinazione con le statine.	IIa	B

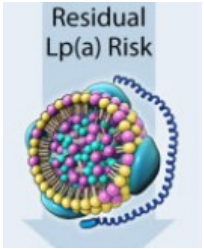
François Mach et al. European Heart Journal 2020 Nov 21;41(44):4255. doi: 10.1093/eurheartj/ehz455.



Residual Lp(a) risk

Struttura della Lipoproteina a





Residual Lp(a) risk

Meccanismo di danno CV mediato da Lp(a)

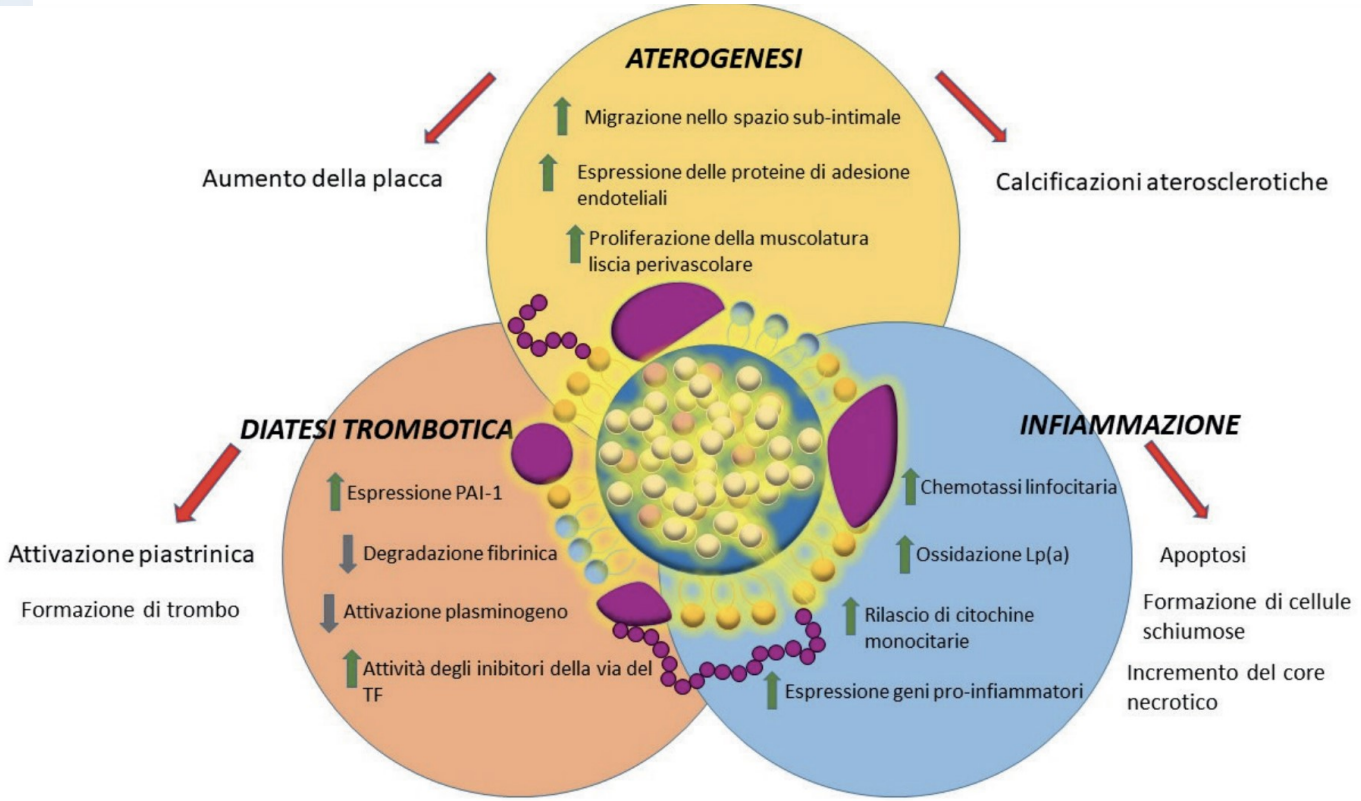
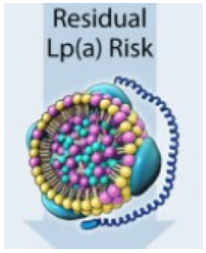


Figura 3. Schema dei tre principali meccanismi di danno cardiovascolare da lipoproteina(a) [Lp(a)].
PAI-1, inibitore dell'attivatore del plasminogeno di tipo 1; TF, fattore tissutale.
Riprodotta con permesso da Maloberti et al.[8].

Abrignani MG, et al. Lipoproteina(a): associazione con la malattia aterosclerotica e valvolare e terapie emergenti. *G Ital Cardiol* 2024;25(2):76-87. doi 10.1714/4187.41756

Residual Lp(a) risk

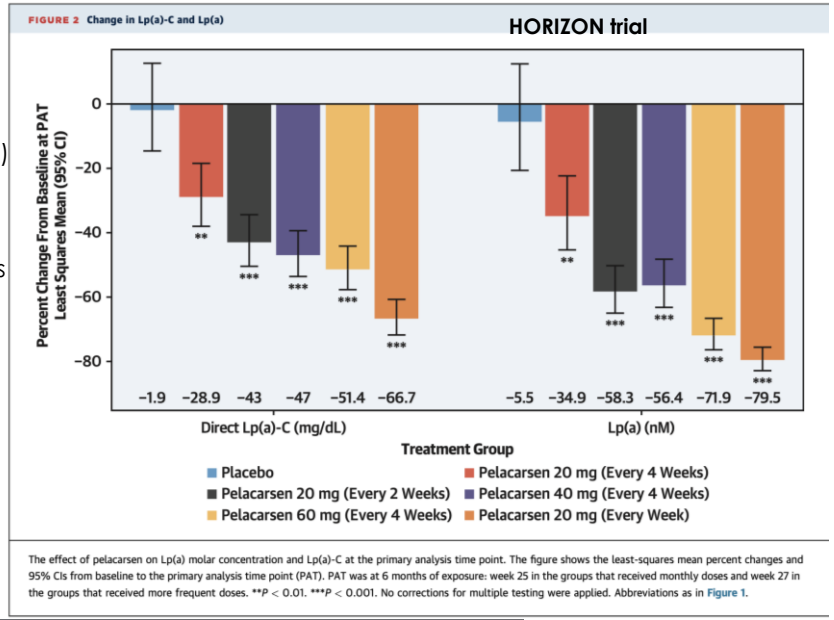
Biological Issue:

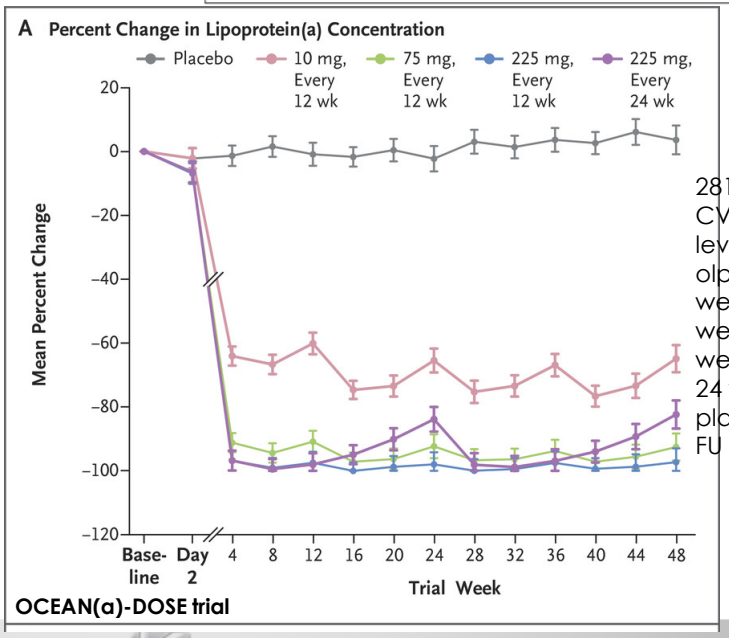


Critical biomarker:

Lp(a) ≥ 50 mg/dL

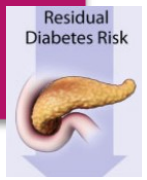
286 pt with established CVD and screening Lp(a) levels ≥ 60 mg/dL
cumulative doses of 20, 40, 60, and 80 mg pelacarsen sc monthly vs placebo
FU 6-12 months



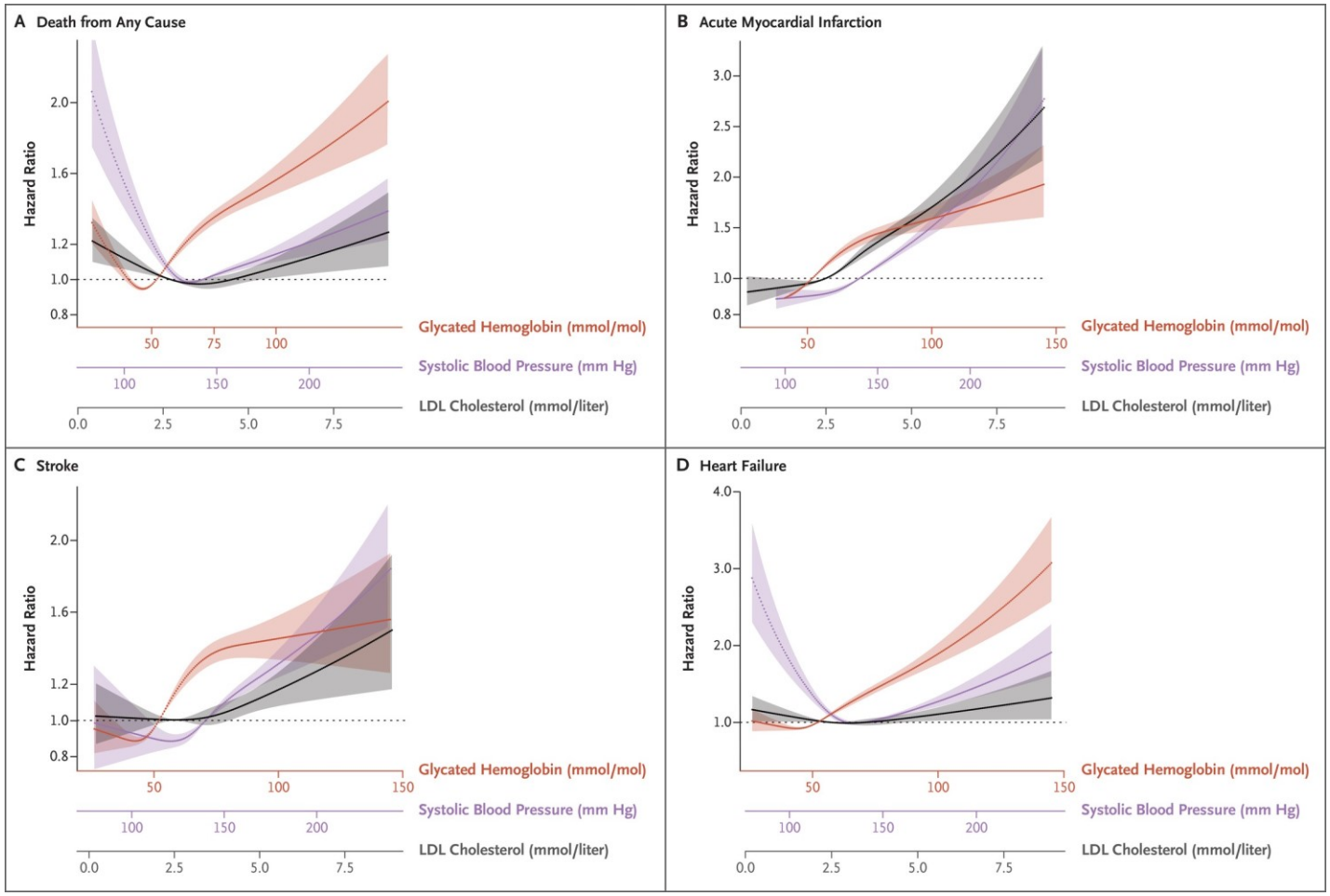


281 pt with established CVD and screening Lp(a) levels ≥ 70 mg/dL
olpasiran (10 mg every 12 weeks, 75 mg every 12 weeks, 225 mg every 12 weeks, or 225 mg every 24 weeks) vs matching placebo
FU 48 weeks

Residual Diabetes risk



271,174 patients with type 2 diabetes who were registered in the Swedish National Diabetes Register and matched them with 1,355,870 controls on the basis of age, sex, and country.



Rawshani A et al. N Engl J Med2018;379:633-644

Residual Diabetes risk

Aspettativa di vita, incremento ponderale e fattori ambientali stanno rendendo l'iperglicemia una pandemia.

Table 3. Adjusted Hazard Ratios for Death from Any Cause and Death from Cardiovascular Causes among Patients with Type 2 Diabetes versus Controls, According to Time-Updated Mean Glycated Hemoglobin Level or Renal Disease Status and Time-Updated Age Category in Model 3.*

Variable	Death from Any Cause				Death from Cardiovascular Causes			
	<55 Yr	55–64 Yr	65–74 Yr	≥75 Yr	<55 Yr	55–64 Yr	65–74 Yr	≥75 Yr
Time-updated mean glycated hemoglobin level†								
Reference	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
≤6.9%	1.92 (1.75–2.11)	1.40 (1.34–1.46)	1.11 (1.08–1.14)	0.95 (0.94–0.96)	2.18 (1.81–2.64)	1.57 (1.46–1.70)	1.13 (1.08–1.18)	0.92 (0.90–0.94)
7.0–7.8%	2.00 (1.77–2.27)	1.55 (1.47–1.63)	1.25 (1.21–1.29)	1.03 (1.02–1.05)	2.59 (2.04–3.28)	1.92 (1.75–2.10)	1.34 (1.27–1.41)	1.02 (0.99–1.04)
7.9–8.7%	2.50 (2.17–2.87)	1.71 (1.60–1.83)	1.56 (1.49–1.62)	1.20 (1.18–1.23)	3.76 (2.93–4.82)	2.16 (1.93–2.41)	1.86 (1.75–1.98)	1.15 (1.11–1.19)
8.8–9.6%	2.92 (2.44–3.49)	2.31 (2.13–2.52)	1.84 (1.74–1.95)	1.34 (1.29–1.39)	4.06 (2.94–5.61)	2.96 (2.58–3.40)	2.22 (2.03–2.43)	1.29 (1.23–1.36)
≥9.7%	4.23 (3.56–5.02)	2.77 (2.51–3.05)	2.48 (2.31–2.67)	1.55 (1.47–1.63)	5.38 (3.89–7.43)	3.51 (2.99–4.11)	3.10 (2.78–3.45)	1.42 (1.32–1.53)

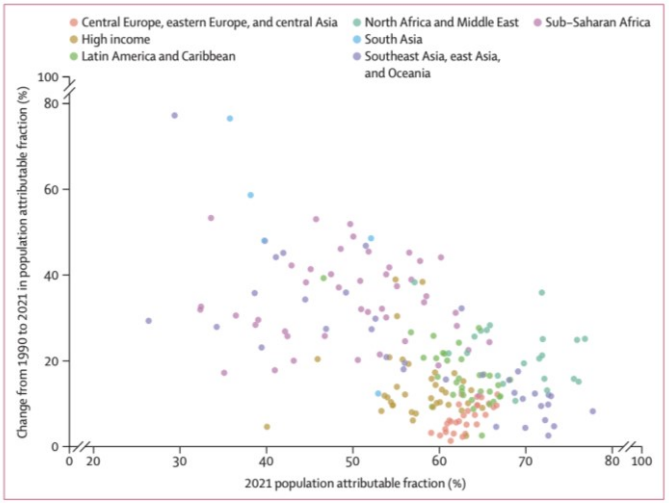


***Figure 3*: Change from 1990 to 2021 in population attributable fraction for high BMI in relation to type 2 diabetes, by GBD super-region**
BMI=body-mass index. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study.

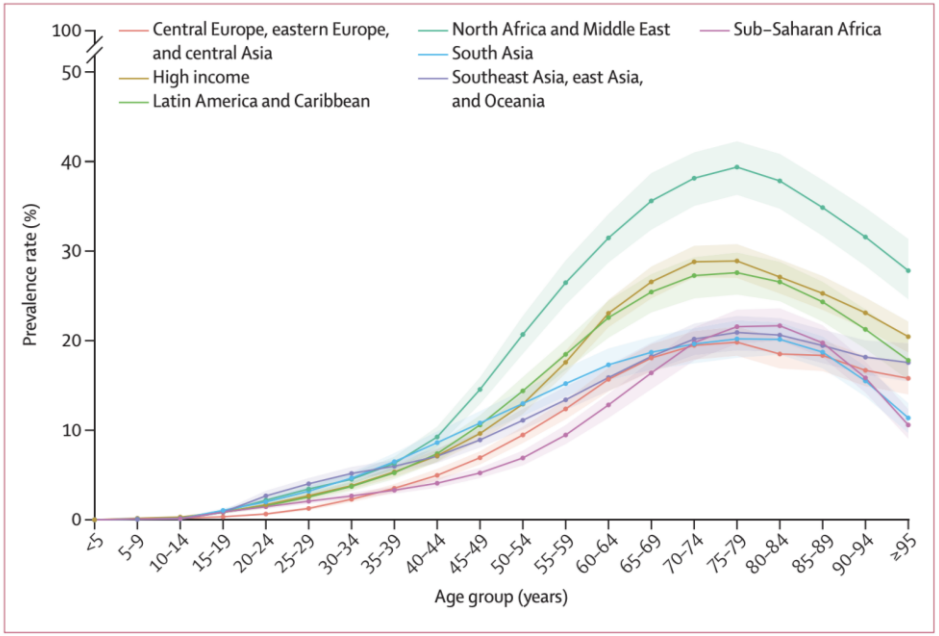
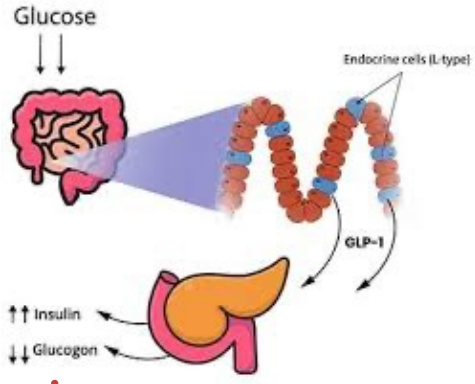


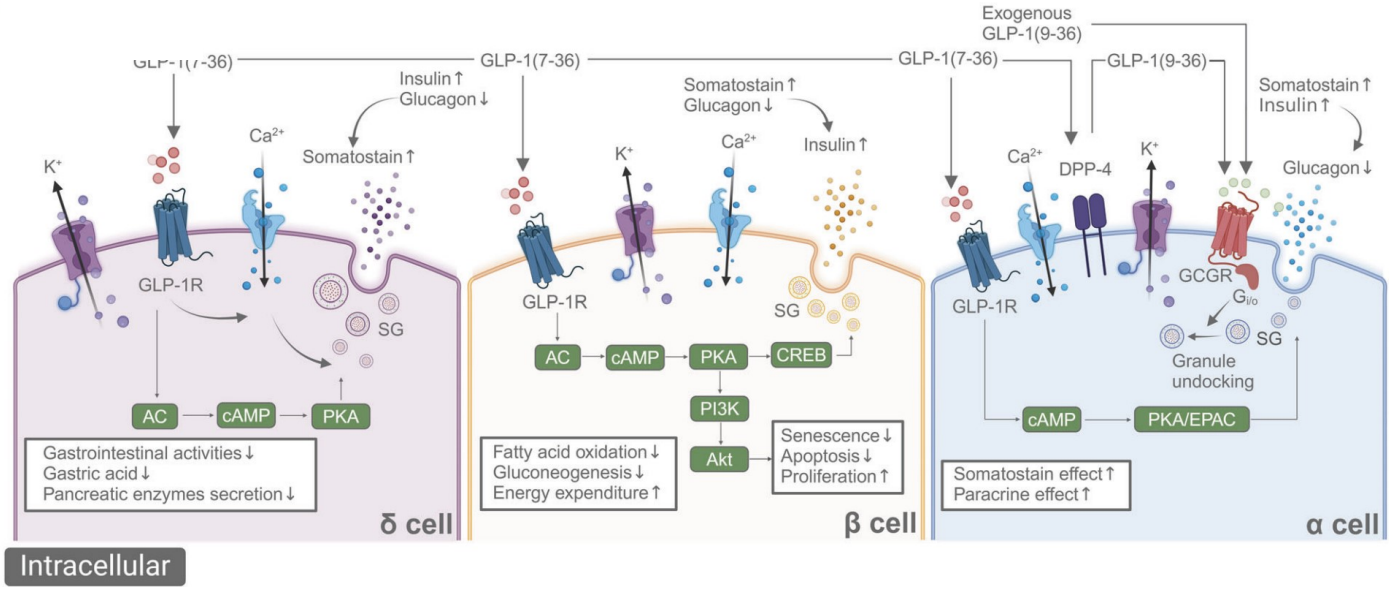
***Figure 2*: Prevalence of total diabetes by age and GBD super-region in 2021**
The shaded areas represent 95% uncertainty intervals. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study.

Zhang Y, Niu J, Choi HK. Excess Mortality among Persons with Type 2 Diabetes. *N Engl J Med*. 2016;374(8):788. doi:10.1056/NEJMc1515130

Residual Diabetes risk



Mechanisms of Blood Glucose Reduction by GLP-1 on different pancreatic cell types (pancreatic α, β, and δ Cells).



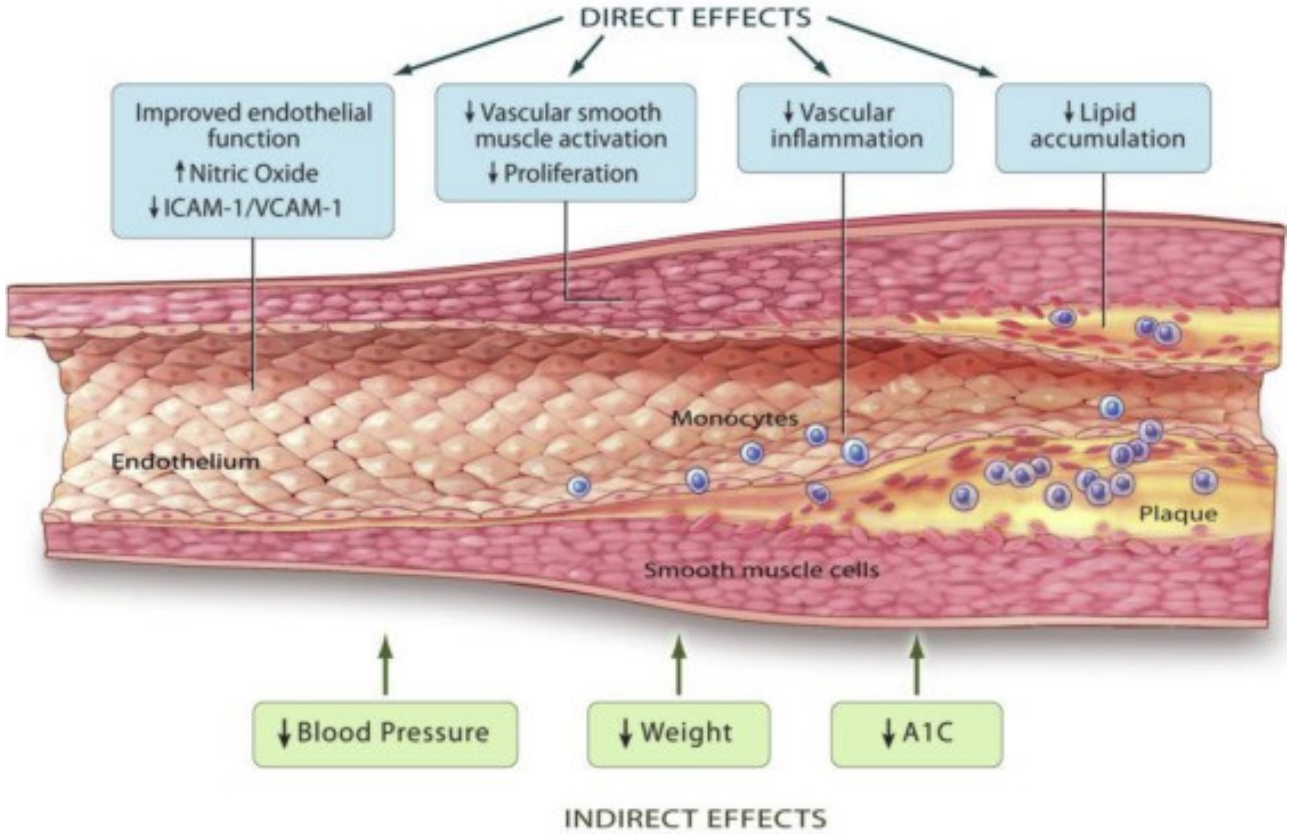
Zheng, Z. *et al.* Glucagon-like peptide-1 receptor: mechanisms and advances in therapy. *Sig Transduct Target Ther* **9**, 234 (2024).

Residual Diabetes risk

Ryan DH, Lingvay I, Colhoun HM, et al. Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity (SELECT) rationale and design. *Am Heart J*. 2020;229:61-69.

Residual Diabetes risk

Mechanisms whereby glucagon-like-peptide-1 receptor agonists modify the risk of cardiovascular outcomes.



A1C, glycated hemoglobin; *ICAM-1*, intercellular adhesion molecule 1; *VCAM-1*, vascular cell adhesion molecule 1.

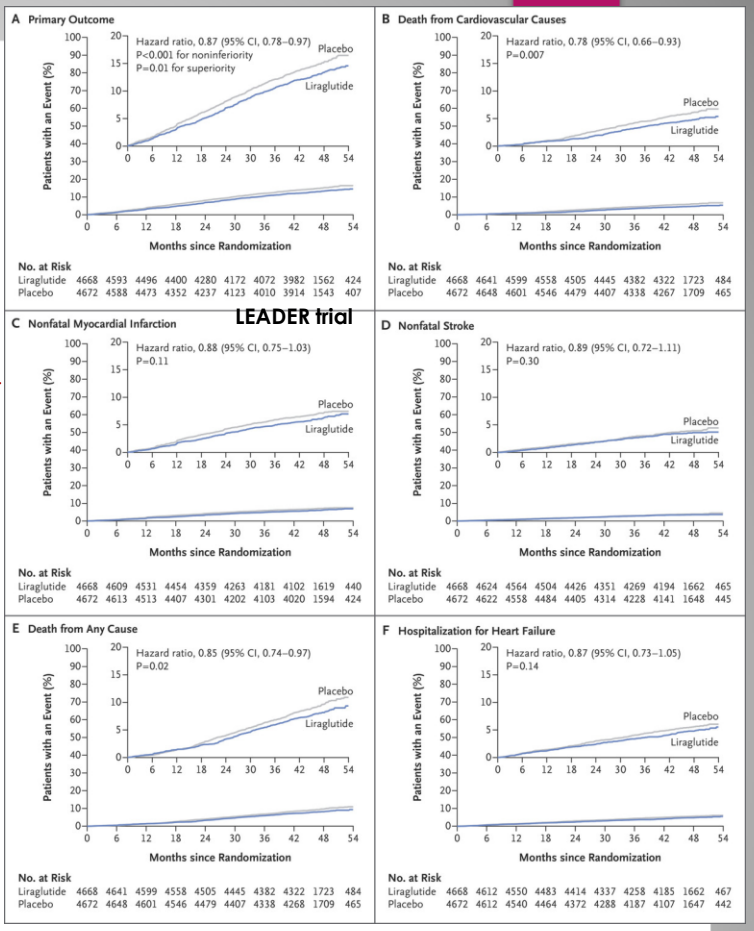
Sharma A. et al. Mechanisms by Which Glucagon-Like-Peptide-1 Receptor Agonists and Sodium-Glucose Cotransporter-2 Inhibitors Reduce Cardiovascular Risk in Adults With Type 2 Diabetes Mellitus. *Can J Diabetes*. 2020;44(1):93-102.

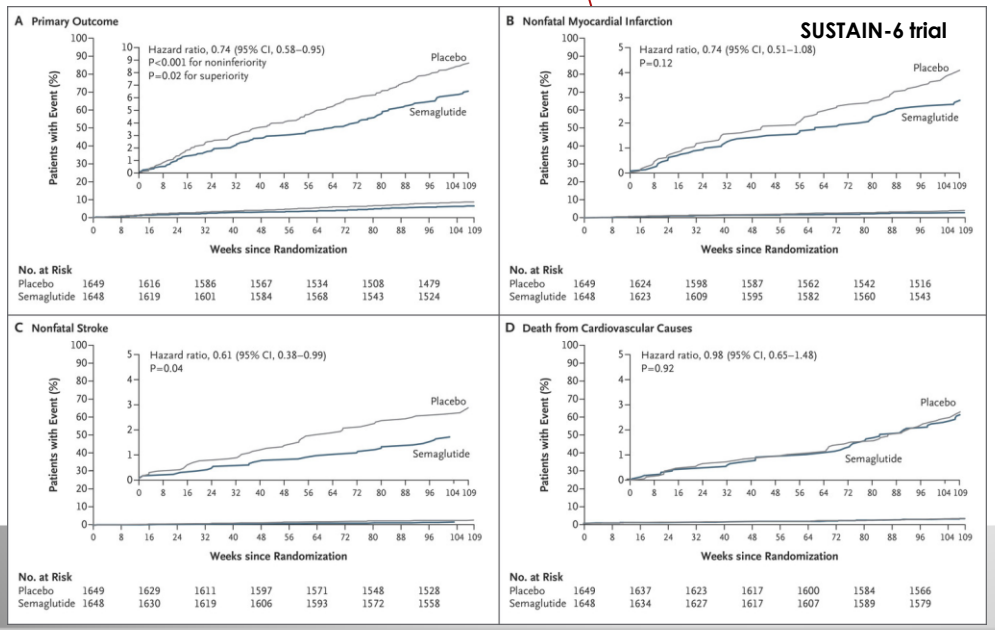
Residual Diabetes risk

Biological Issue:

Critical biomarker:

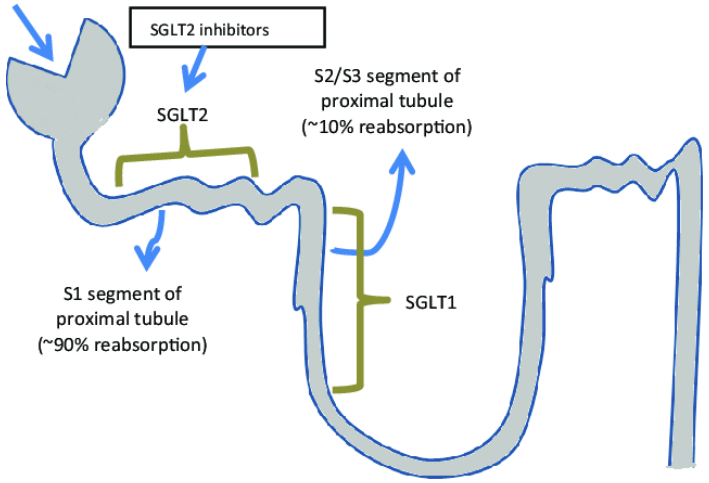
hbA1c
Fasting glucose



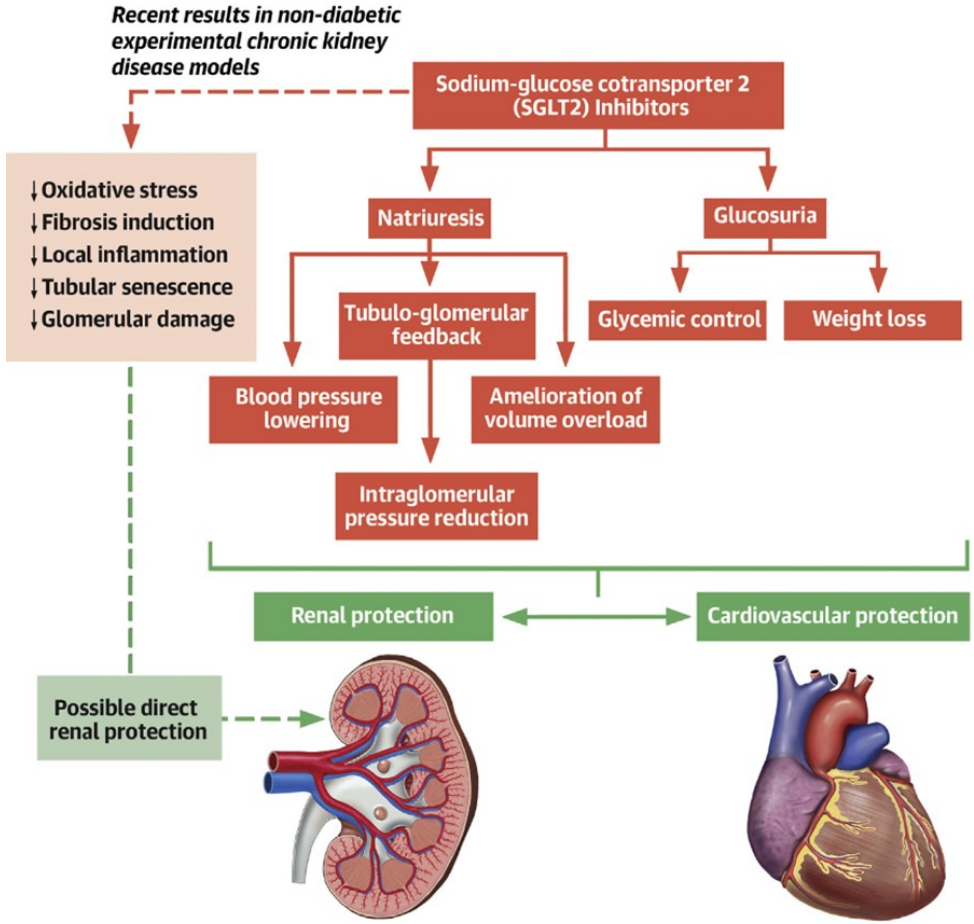


Residual Diabetes risk

Meccanismo d'azione degli SGLT2-i



Meccanismo cardio- e nefro-protettivo degli SGLT2-i



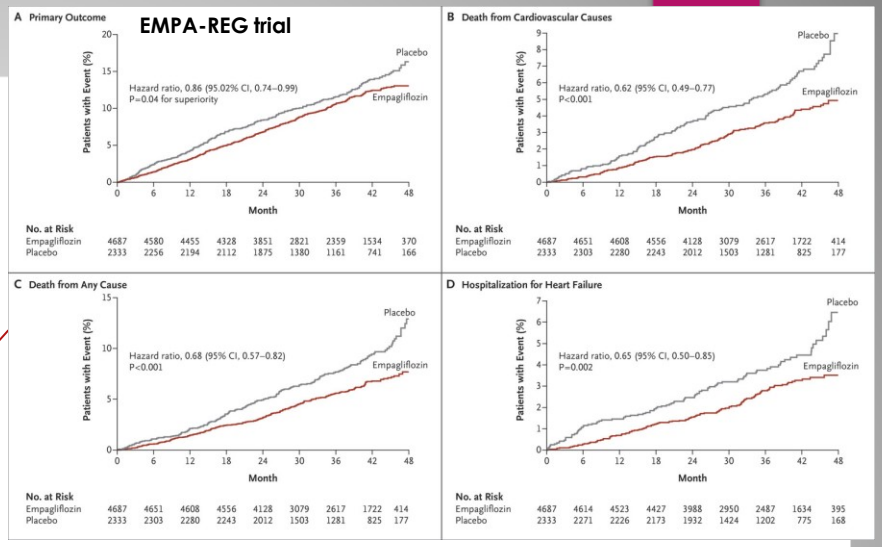
Residual Diabetes risk

Biological Issue:

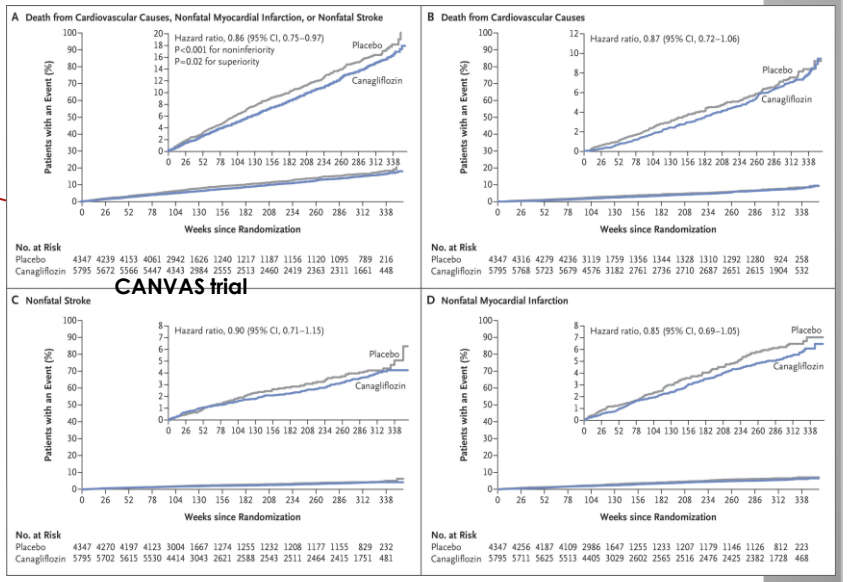
Critical biomarker:

hbA1c
Fasting glucose

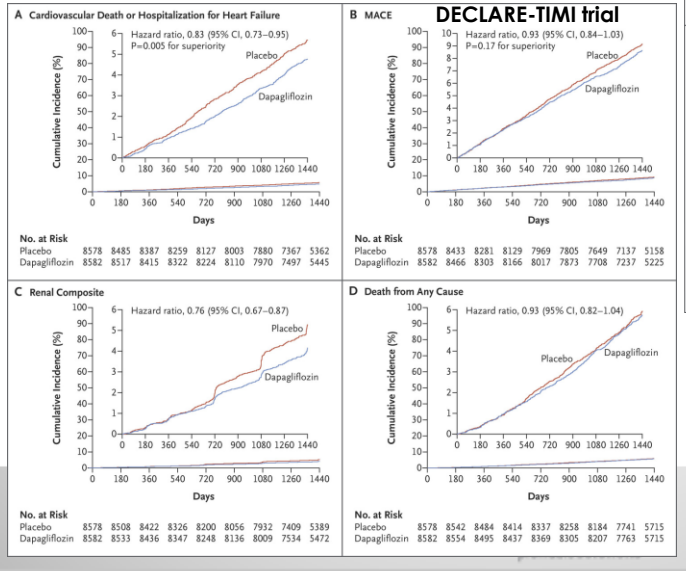
EMPA-REG trial



CANVAS trial



DECLARE-TIMI trial



Residual Diabetes risk

RESEARCH Open Access

SGLT2-inhibitors effects on the coronary fibrous cap thickness and MACEs in diabetic patients with inducible myocardial ischemia and multi vessels non-obstructive coronary artery stenosis

Celestino Sardu[1*], Maria Consiglia Trotta[2], Ferdinando Carlo Sasso[1], Cosimo Sacra[3], Gerardo Carpinella[4], Ciro Mauro[4], Fabio Minicucci[5], Paolo Calabrò[6], Michele D'Amico[2], Fabrizio D'Ascenzo[7], Ovidio De Filippo[7], Mario Iannaccone[8], Carmine Pizzi[9], Giuseppe Paolisso[1] and Raffaele Marfella[1]

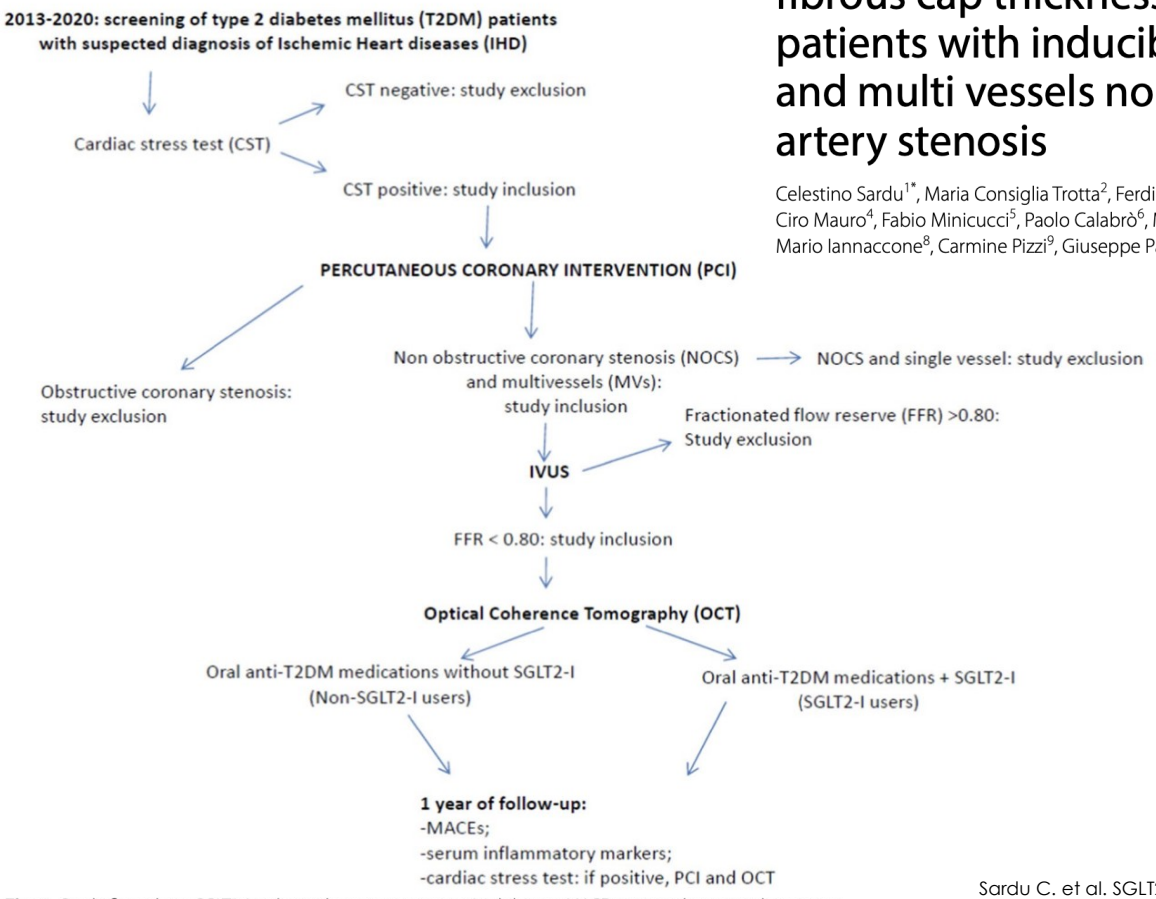
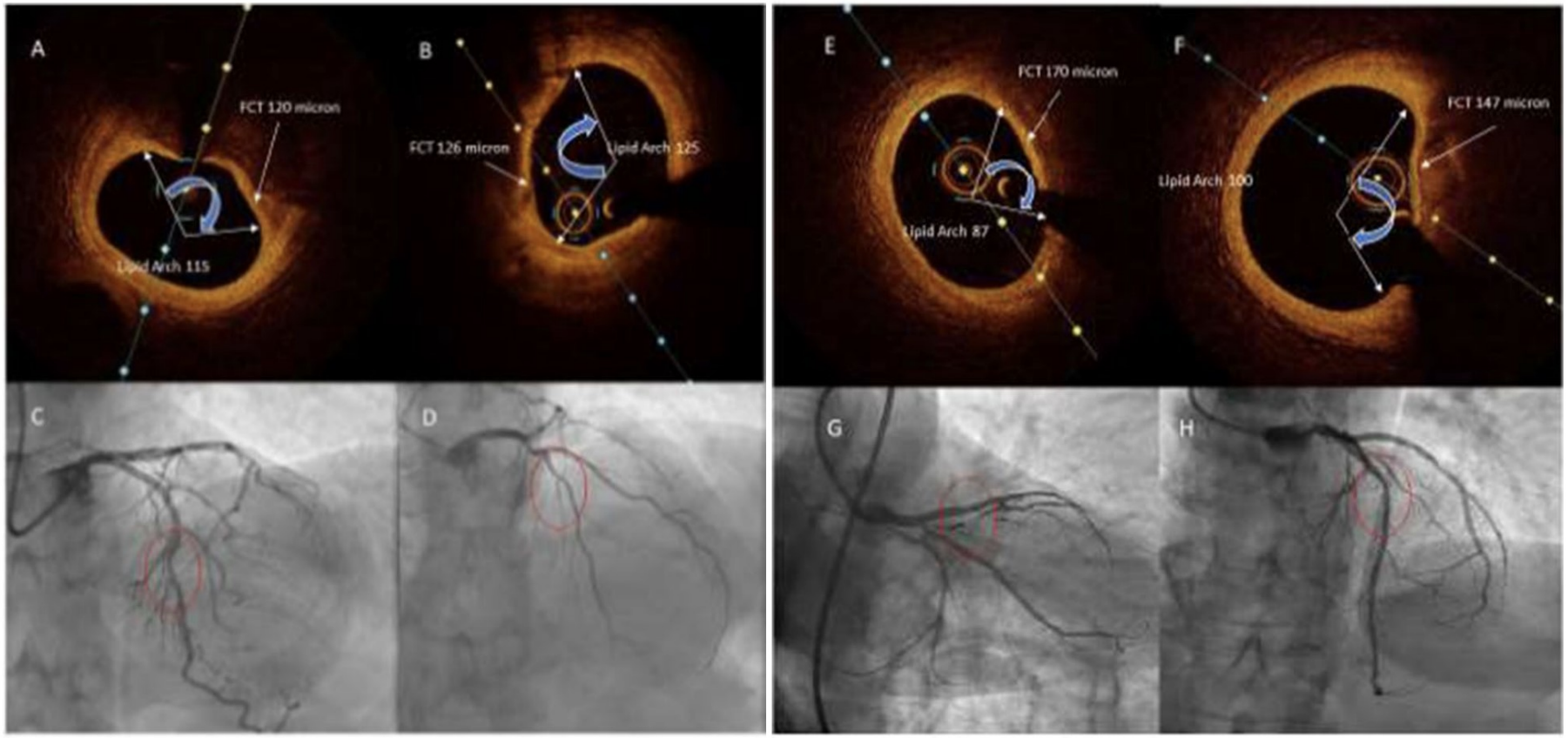


Fig. 1 Study flow chart. *SGLT2-I* sodium glucose transporter 2 inhibitors, *MACEs* major adverse cardiac events

Sardu C. et al. SGLT2-inhibitors effects on the coronary fibrous cap thickness and MACEs in diabetic patients with inducible myocardial ischemia and multi vessels non-obstructive coronary artery stenosis. Cardiovasc Diabetol. 2023;22(1):80.

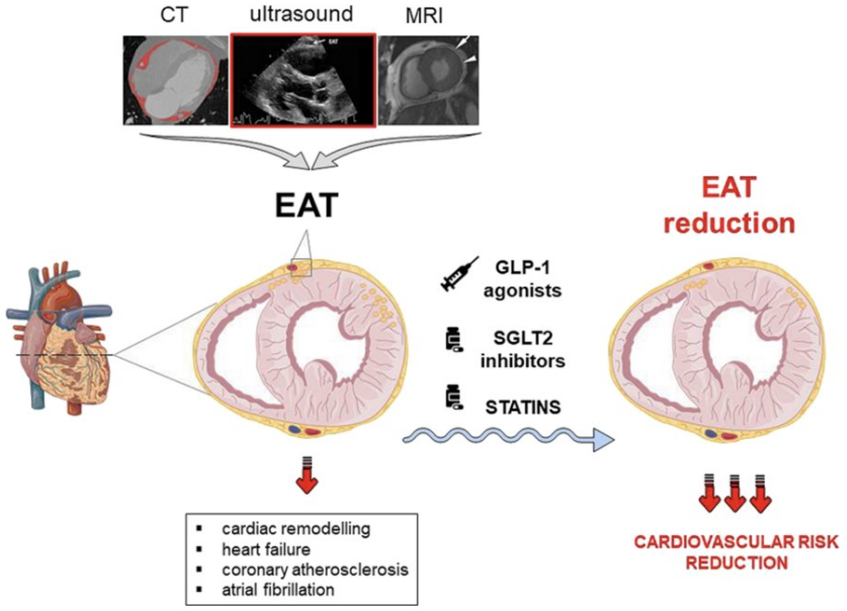
Residual Diabetes risk

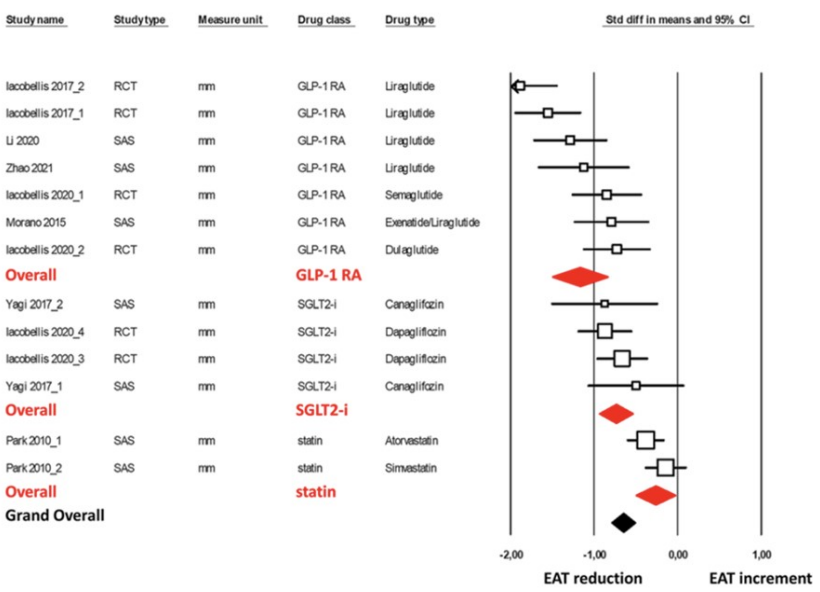


Sardu C. et al. SGLT2-inhibitors effects on the coronary fibrous cap thickness and MACEs in diabetic patients with inducible myocardial ischemia and multi vessels non-obstructive coronary artery stenosis. Cardiovasc Diabetol. 2023;22(1):80.

Residual Diabetes risk

Tessuto Adiposo Epicardico (EAT)



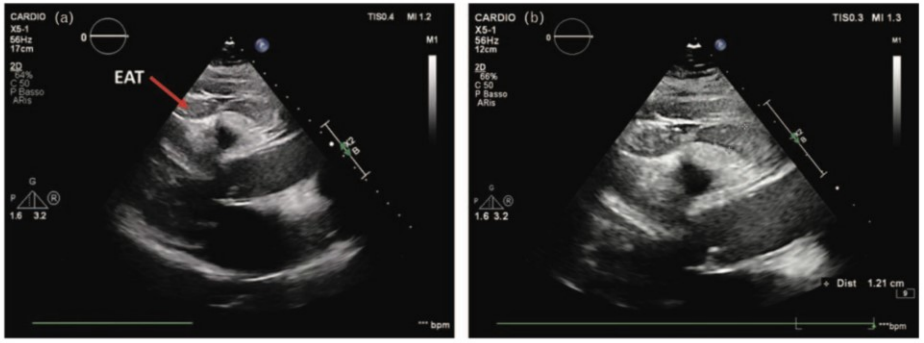


Myasoedova, V.A. *et al.* Efficacy of cardiometabolic drugs in reduction of epicardial adipose tissue: a systematic review and meta-analysis. *Cardiovasc Diabetol* **22**, 23 (2023)

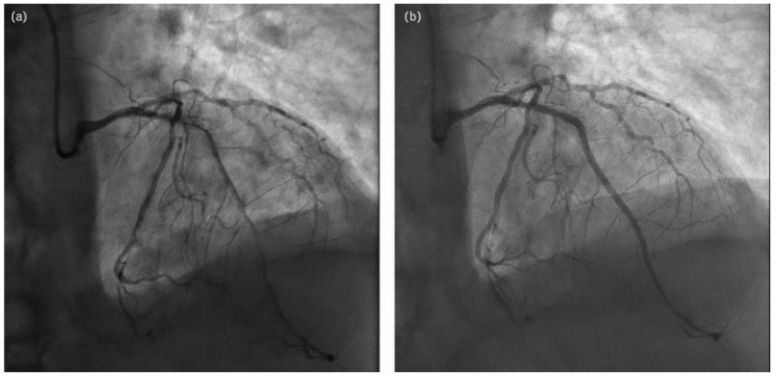
Residual Diabetes risk

Epicardial adipose tissue and residual cardiovascular risk: a comprehensive case analysis and therapeutic insights with Liraglutide

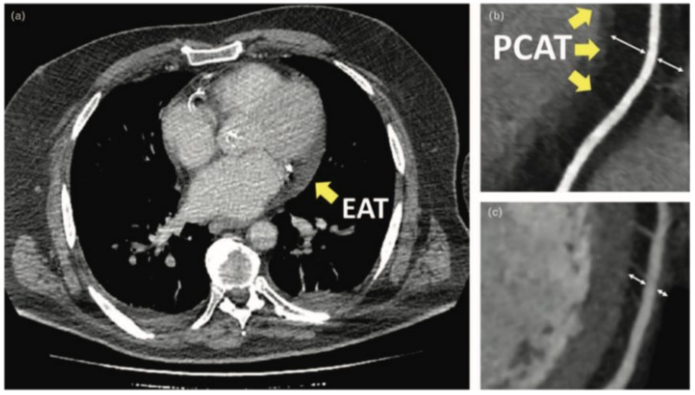
Fulvio Cacciapuoti[a], Ciro Mauro[a], Davide D'Andrea[a], Valentina Capone[a,b], Carlo Liguori[c] and Federico Cacciapuoti[d]



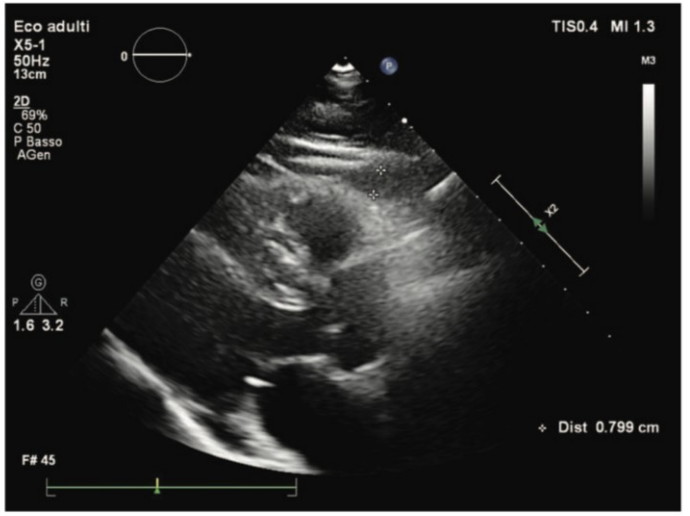
Two-dimensional echocardiography in parasternal long-axis view. Evidence of epicardial adipose tissue (arrow) (a); measurement of EAT thickness (b).



Coronary angiography showing evidence of intrastent restenosis on the left anterior descending artery and disease progression (a); postrevascularization examination (b).



Thoracic computed tomography (CT) showing evidence of epicardial adipose tissue (a); detailed coronary CT showing evidence of pericoronary adipose tissue (b); detailed coronary CT at follow-up showing reduction of pericoronary adipose tissue thickness (c).



Follow-up 2D echocardiography in long-axis parasternal view showing a reduction in EAT thickness.

Residual Diabetes risk

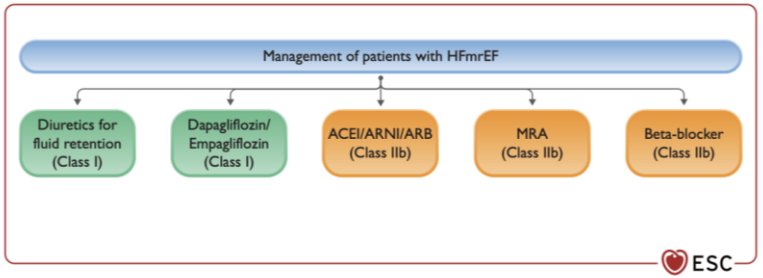


Figure 1 Management of patients with heart failure with mildly reduced ejection fraction. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; HFmrEF, heart failure with mildly reduced ejection fraction; MRA, mineralocorticoid receptor antagonist.

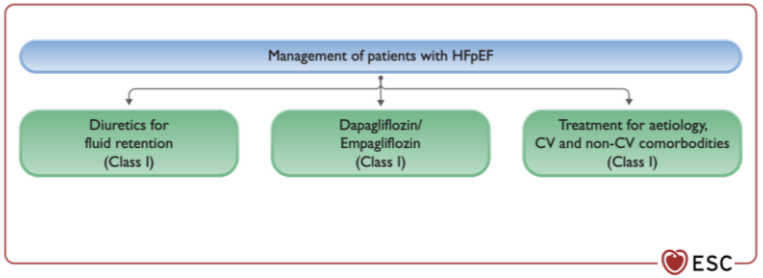


Figure 2 Management of patients with heart failure with preserved ejection fraction. CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction.

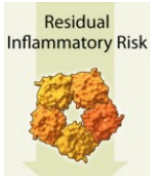
Recommendation Table 19 — Recommendations for sodium–glucose cotransporter 2 inhibitors and/or glucagon-like peptide-1 receptor agonists in patients with chronic coronary syndrome (see also Evidence Table 19)

Recommendations	Class[a]	Level[b]
CCS patients with type 2 diabetes		
SGLT2 inhibitors with proven CV benefit[c] are recommended in patients with T2DM and CCS to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.[86,688,695,697,700]	I	A
GLP-1 receptor agonists with proven CV benefit[d] are recommended in patients with T2DM and CCS to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.[710,711]	I	A
CCS patients without type 2 diabetes		
The GLP-1 receptor agonist semaglutide should be considered in overweight (BMI >27 kg/m^2) or obese CCS patients without diabetes to reduce CV mortality, MI, or stroke.[465]	IIa	B

BMI, body mass index; CCS, chronic coronary syndrome; CV, cardiovascular; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; MI, myocardial infarction; SGLT2, sodium–glucose cotransporter 2; T2DM, type 2 diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.
[c]Canagliflozin, dapagliflozin, empagliflozin, sotagliflozin (listed in alphabetical order).
[d]Dulaglutide, efpeglenatide, liraglutide, semaglutide (listed in alphabetical order).

2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

2024 ESC Guidelines for the management of chronic coronary syndromes



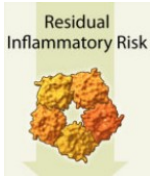
Residual Inflammatory risk

	Persistent high RIR	Increased RIR	Attenuated RIR	Persistent low RIR
Baseline hsCRP	High	Low	High	Low
Follow-up hsCRP	High	High	Low	Low
Adjusted HR[a] for				
1-year Death	3.22	1.37	0.53	ref.
1-year MI	1.60	1.43	0.96	ref.
1-year MACE	1.72	1.31	0.93	ref.
1-year MACE+	1.21	1.08	1.13	ref.

Take home figure Concept of residual inflammatory risk and the main findings of this study. High high sensitive C-reactive protein is defined as >2 mg/L. [a]Adjusted for age, gender, body mass index, acute coronary syndrome, diabetes mellitus, hypertension, chronic kidney disease, previous coronary artery bypass graft, and baseline low-density lipoprotein cholesterol. Red hazard ratio indicates a *P*-value <0.01. MACE, major adverse cardiovascular events, composite of death, MI, and CVA; MACE+, MACE with any revascularization; MI, myocardial infarction.

Deborah N Kalkman, et al. Residual inflammatory risk and the impact on clinical outcomes in patients after percutaneous coronary interventions, *European Heart Journal*, Volume 39, Issue 46, 07 December 2018, Pages 4101–4108

Residual Inflammatory risk



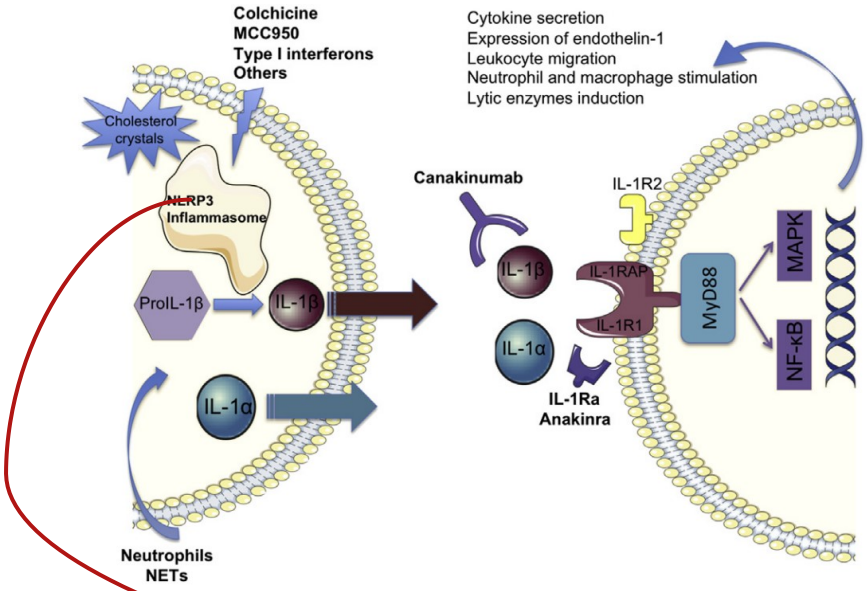


Fig. 1. Interleukin 1α and β activity, natural regulators and inhibitors.

L'interleuchina 1 è un sistema complesso. Mentre IL-1a agisce immediatamente dopo l'attivazione, IL-1b richiede la conversione del suo precursore nella molecola attiva da parte dell'inflammasoma NLRP3. Sia IL-1a che IL-1b agiscono sul complesso IL-1R1/IL-1RAP per attivare la segnalazione NFkB e MAPK. Ciò si traduce in una serie di effetti pro-aterogenici. Questi effetti possono essere inibiti agendo sull'inflammasoma NLRP3 (diminuendo i livelli di IL-1b e IL-18) o modulando l'interazione con il complesso IL-1R1/IL-1RAP (ad esempio canakinumab, anakinra). IL-1Ra e IL-1R2 sono regolatori naturali dell'attività di IL-1.

Sono stati descritti almeno quattro presunti meccanismi di inibizione dell'inflammasoma NLRP3 da parte della colchicina. 1) Inibizione del gene MEFV con conseguente inibizione della pirina (recettore); 2) inibizione della co-localizzazione citoplasmatica dell'inflammasoma dovuta all'interferenza della tubulina; 3) blocco diretto della caspasi-1; 4) inibizione della formazione dei pori mediata da P2X7 con conseguente diminuzione dell'efflusso di Kþ. Il risultato finale è l'inibizione della produzione della forma attiva IL1b (e probabilmente IL-18).

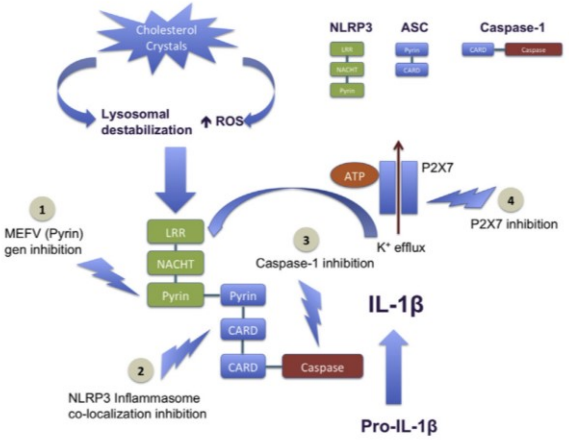
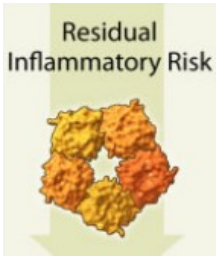


Fig. 2. Colchicine inhibition of the NLRP3 inflammasome.

Martínez GJ. et al. The NLRP3 inflammasome and the emerging role of colchicine to inhibit atherosclerosis-associated inflammation. Atherosclerosis. 2018 Jun;273:157.

Residual Inflammatory risk

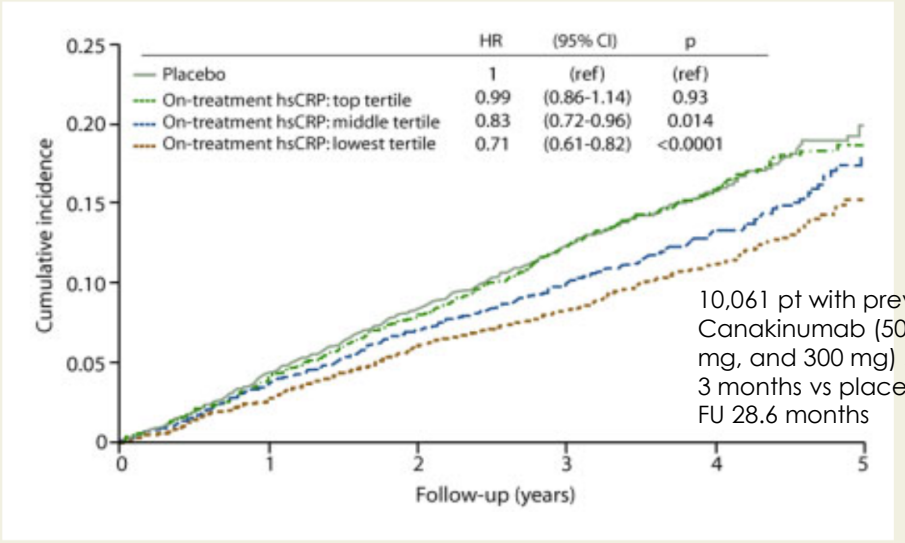
Biological Issue:



Critical biomarker:

hsCRP ≥ 2 mg/dL

CANTOS trial

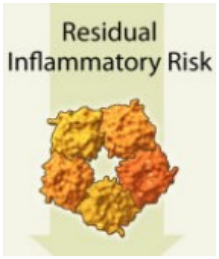


10,061 pt with previous MI
Canakinumab (50 mg, 150 mg, and 300 mg) sc every 3 months vs placebo
FU 28.6 months

Figure 5 Cumulative incidence of the primary composite atherosclerotic cardiovascular disease endpoint (non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death) in the CANTOS trial, in the placebo and canakinumab arms, the latter stratified by tertiles of achieved on-canakinumab high-sensitivity C-reactive protein (Reproduced from Ridker *et al.*[171] with permission).

Residual Inflammatory risk

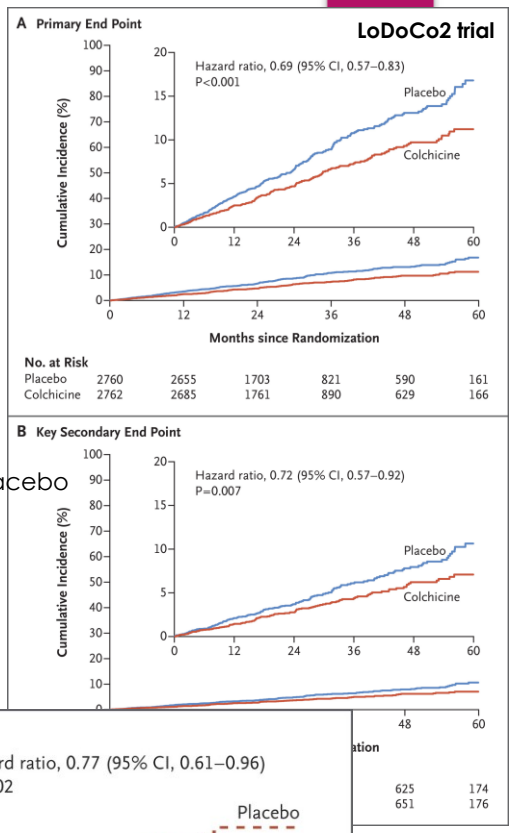
Biological Issue:



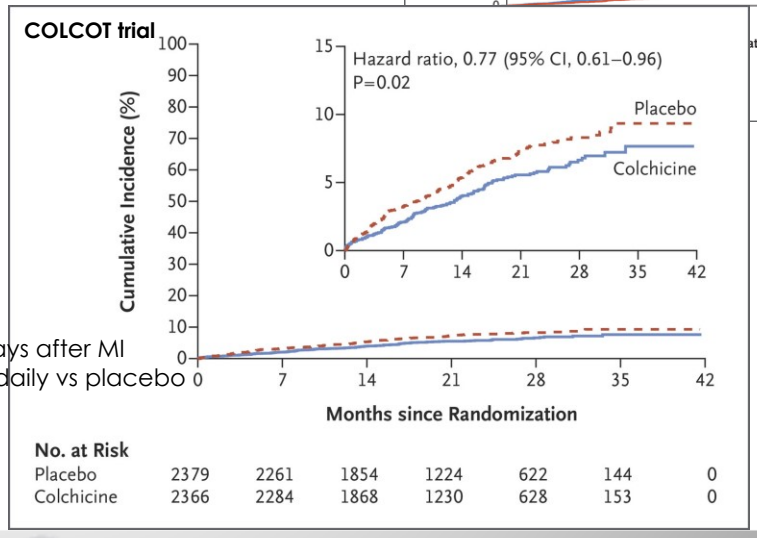
Critical biomarker:

hsCRP ≥ 2 mg/dL

5522 pt with CCS
colchicine 0.5 mg/daily vs placebo
FU 28.6 months



4745 pt within 30 days after MI
colchicine 0.5 mg/daily vs placebo
FU 22.6 months



Rischio residuo cardiovascolare: The ~~Dark Side of The~~ Moon