Università e Azienda Ospedaliera di Perugia
Cardiologia
e
Fisiopatologia Cardiovascolare

"Trattare l'Aterosclerosi: Il ruolo disease-modifying di GLP1-RA"

Giuseppe Ambrosio

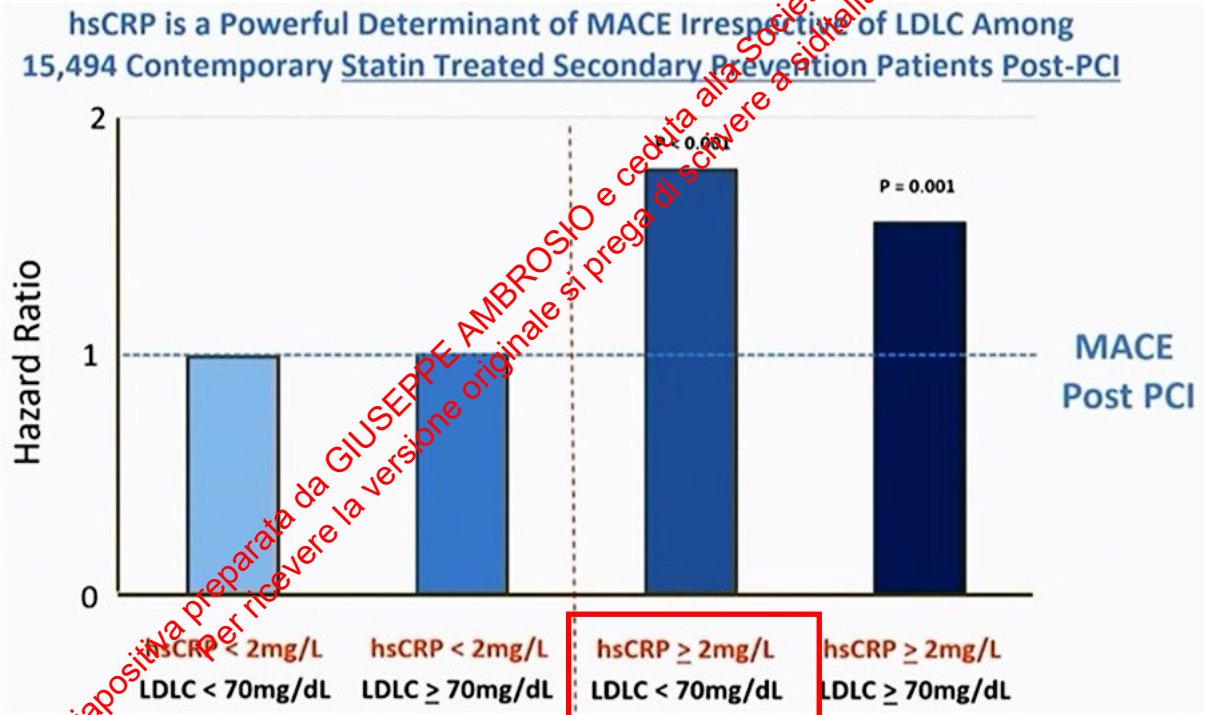
Dichiaro di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Amarin
- CLS
- Menarini
- Novo-Nordisk

Dichiaro altresì l'impegno ad astenermi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

International Atherosclerosis Society (IAS) 2026

Inflammatory Residual Risk in Atherosclerotic Cardiovascular Disease: Do You Still Believe LDL-C Is Everything?



TAMING THE INFLAMED HEART

Charlotte Harrison, Nature Medicine, 5 June 2026

Cardiovascular disease is not just a cholesterol problem. Inflammation is now recognized as a **major, independent** driver of heart attacks and strokes.

WHY THIS MATTERS

LDL

Lowering LDL cholesterol saves lives.

But many patients still have heart attacks or strokes despite optimal lipid control.

Persistent immune activation and vascular **inflammation** drive plaque instability and events.

This **"residual risk"** represents a large, unmet need in cardiovascular prevention.

NEW DIAGNOSTIC APPROACHES

We can now see inflammation in and around the coronary arteries.

Advanced Imaging + AI

CT and other imaging modalities enhanced by artificial intelligence.

Imaging Biomarkers of Inflammation

High

Low

Detect inflamed, high-risk plaques that may rupture and cause events.

Personalized Risk Assessment

Assess both cholesterol burden and inflammatory burden to better predict risk.

NEW THERAPEUTIC APPROACHES

Targeting the immune system to reduce vascular inflammation.

Anti-inflammatory Therapies

Monoclonal antibodies and other agents that reduce key inflammatory pathways.

Immunomodulation

Approaches that enhance regulatory T-cell activity or rebalance immune responses.

Clinical Trials Underway

Multiple trials testing whether controlling inflammation prevents future heart attacks and strokes.

A SHIFT IN PARADIGM

THE OLD VIEW

Heart disease = a lipid disorder

Focus on LDL lowering

THE NEW VIEW

Heart disease = an immune-inflammatory disease

Address lipids AND inflammation

TAKE-HOME MESSAGE

The combination of advanced inflammatory imaging and emerging immunotherapies could usher in a new era of prevention—one that "tames the inflamed heart" and reduces the residual risk that remains today.

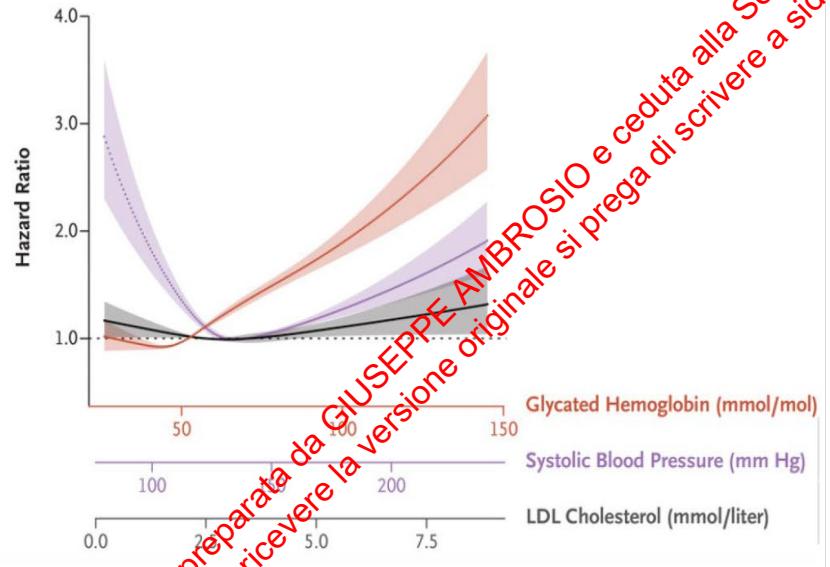
Controlling inflammation—alongside lipids—may be the key to preventing the next heart attack or stroke.

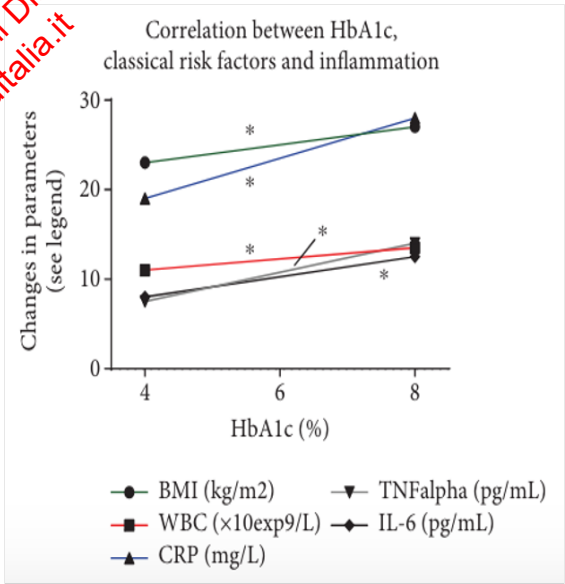
The contribution of systemic inflammation as key driver in T2D and ASCVD

GLP1-RA anti-inflammatory effects

Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Aidin Rawshani, M.D., Araz Rawshani, M.D., Ph.D., Stefan Franzén, Ph.D., Naveed Sattar, M.D., Ph.D., Björn Eliasson, M.D., Ph.D., Ann-Marie Svensson, Ph.D., Björn Zethelius, M.D., Ph.D., Mervete Miftaraj, M.Sc., Darren K. McGuire, M.D., M.H.Sc., Annika Rosengren, M.D., Ph.D., and Soffia Gudbjörnsdottir, M.D., Ph.D.





Steven S, et al. Oxid Med Cell Longev. 2019

Dietary Fat and Meat Intake in Relation to Risk of Type 2 Diabetes in Men

ROB M. VAN DAM, MSC[1,2]
WALTER C. WILLETT, MD[1,3,4]
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FRANK B. HU, MD[1,4]

OBJECTIVE — To examine dietary fat and meat intake in relation to risk of type 2 diabetes.

RESEARCH DESIGN AND METHODS — We prospectively followed 42,504 male participants of the Health Professionals Follow-Up Study who were aged 40–75 years and free of diagnosed diabetes, cardiovascular disease, and cancer in 1986. Diet was assessed by a validated food frequency questionnaire and updated in 1990 and 1994. During 12 years of follow-up, we ascertained 1,321 incident cases of type 2 diabetes.

RESULTS — Intakes of total fat (multivariate RR for extreme quintiles 1.27, CI 1.04–1.55, *P* for trend = 0.02) and saturated fat (1.34, 1.09–1.66, *P* for trend = 0.01) were associated with a higher risk of type 2 diabetes. However, these associations disappeared after additional adjustment for BMI (total fat RR 0.97, CI 0.79–1.18; saturated fat 0.97, 0.78–1.20). Intakes of oleic acid, *trans*-fat, long-chain n-3 fat, and α-linolenic acid were not associated with diabetes risk after multivariate adjustment. Linoleic acid was associated with a lower risk of type 2 diabetes in men <65 years of age (RR 0.74, CI 0.60–0.92, *P* for trend = 0.01) and in women with a BMI <25 kg/m^2 (0.53, 0.33–0.85, *P* for trend = 0.006) but not in older and obese men. Frequent consumption of processed meat was associated with a higher risk of type 2 diabetes (RR 1.46, CI 1.14–1.86 for ≥5/week vs. <1/month, *P* for trend = 0.000

CONCLUSIONS — Total and saturated fat intake were associated with a higher risk of type 2 diabetes, but these associations were not independent of BMI. Frequent consumption of processed meats may increase risk of type 2 diabetes.

Diabetes Care 25:417–424, 2002

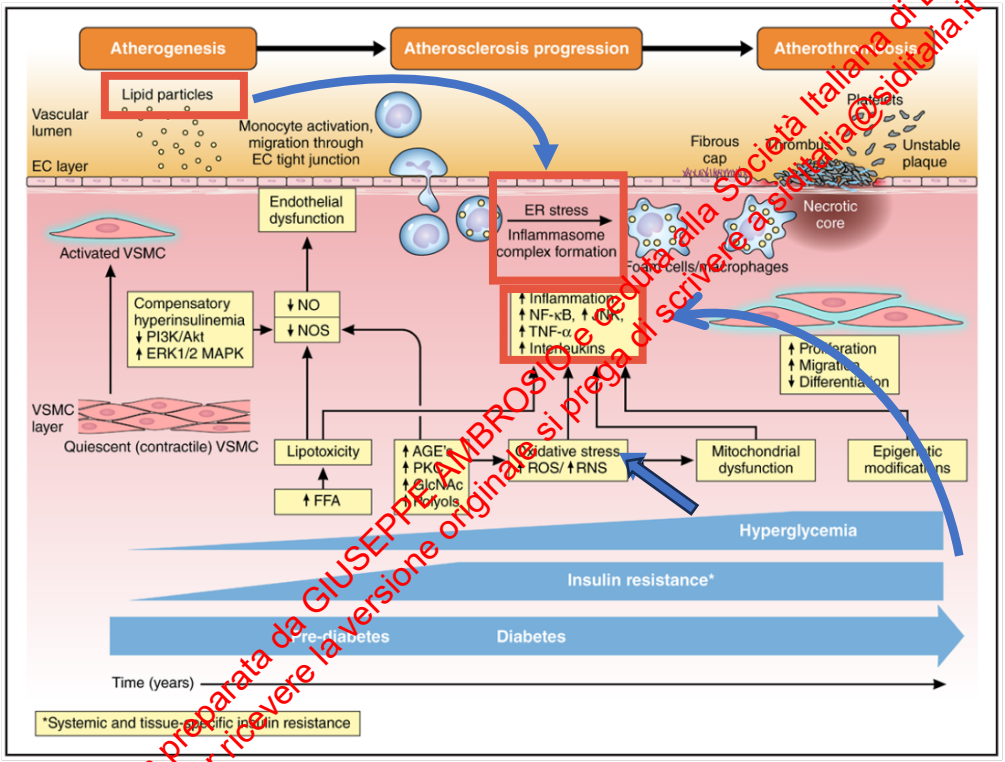
Several studies of hyperinsulinemia and hyperglycemia suggested a detrimental effect of saturated fat (7,12) and a beneficial effect of polyunsaturated fat (8,13). However, other studies did not confirm these results (14–16). Lack of adjustment for confounding by other dietary and nondietary risk factors may have contributed to the inconsistencies in findings. Alternatively, the apparently divergent results observed in different populations may be real because the effects of dietary fat may vary with population characteristics, such as age, BMI, and physical activity, that are associated with insulin sensitivity (17–19).

Few studies have examined the possible role of n-3 fatty acids (9,12,20–22) or *trans*-fat (21,22) in the development of type 2 diabetes. Previously, we reported that *trans*-fat was positively associated and polyunsaturated fat inversely associated with risk of type 2 diabetes in women (21). Meat intake was associated with a higher risk of diagnosed diabetes in a study in Seventh-Day Adventists (23), but it has never been examined in detail.

In 6 years of follow-up in this cohort of male health professionals, we did not

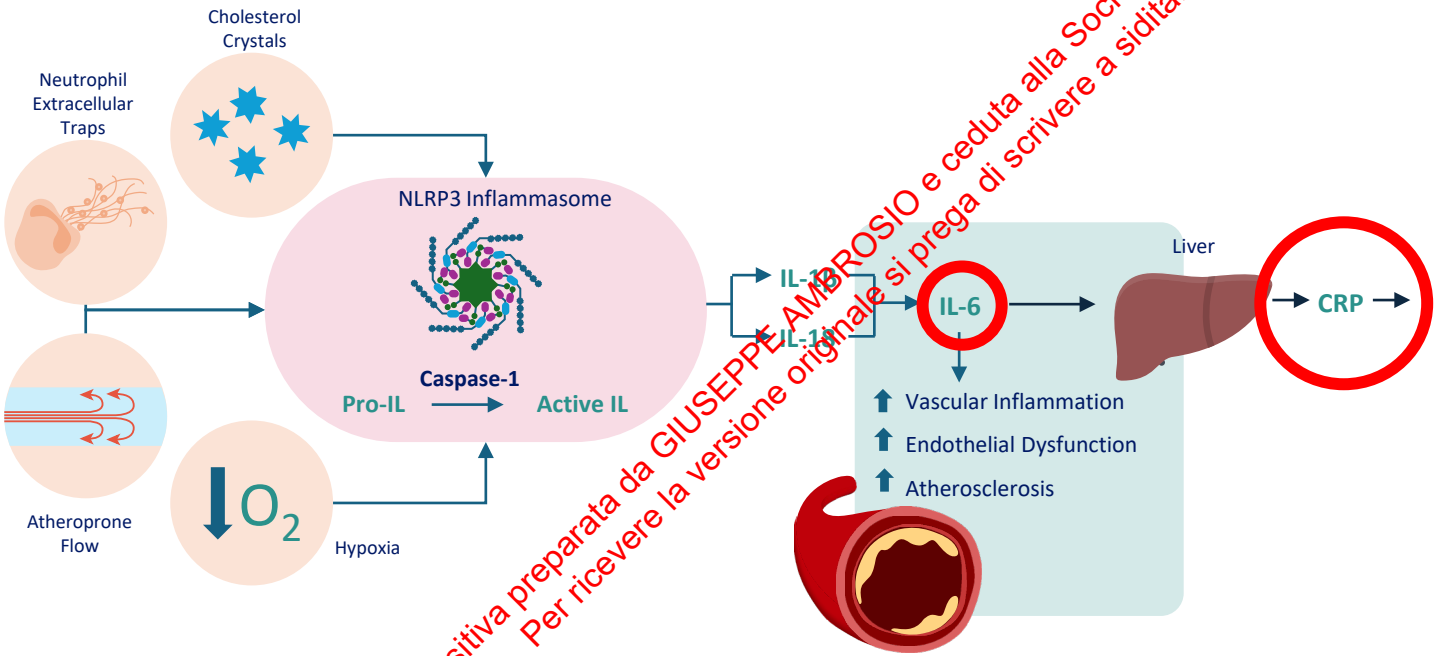
One of the mechanisms linking DM and CAD is the so-called *meta-inflammation,* i.e., metabolic inflammation, which is a low-grade chronic and sterile inflammatory status which accompanies nutrient intake

High Fat Diet induces systemic chronic low-grade inflammation by promoting <u>cytokine production</u> and activating <u>immune cells</u>, particularly macrophages



Role of Inflammasome activation in ASCVD and level of CRP

NLRP3 inflammasome stimulated IL-6 secretion leads to progression of atherosclerosis



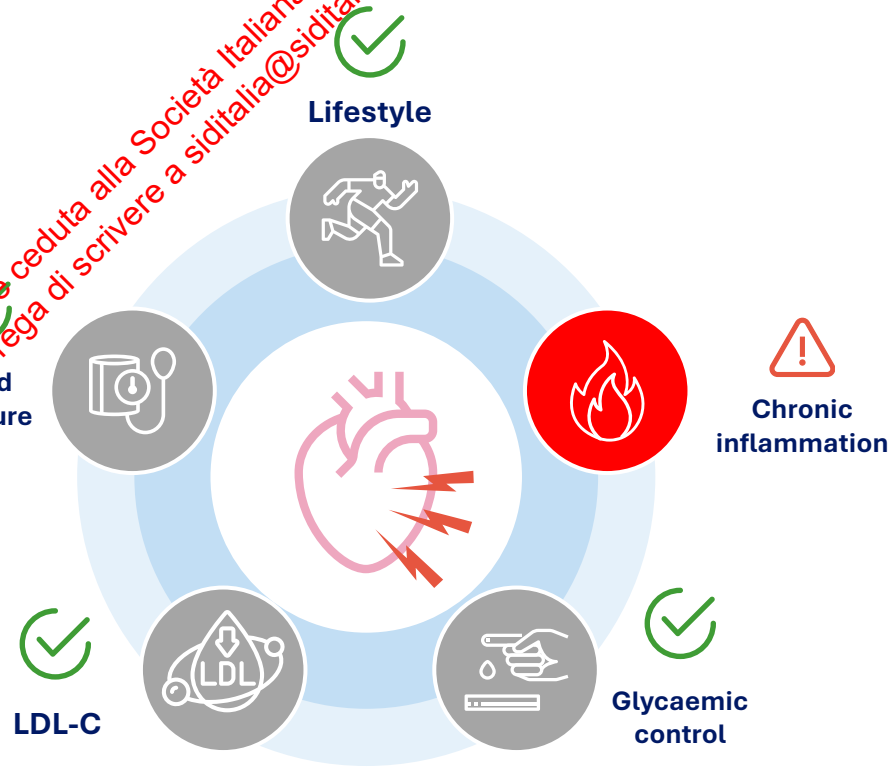
C-reactive Protein as an indicator of underlying inflammation

CRP, C-reactive protein; CV, cardiovascular; IL, interleukin; hsCRP, high-sensitivity CRP; MI, myocardial infarction; NLRP3, nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3; O_2, oxygen. Figure adapted from both references 1 and 2; 1. Ridker PM. Circ Res. 2016;118:145–156; 2. Ridker PM and Luscher TF. Eur. Heart J. 2014;35(27):1782–1791; and 3. Silvis MJ et al. J Cardiovasc Transl Res. 2021;14(1):23-34

The concept of residual inflammatory risk

- **Recurrent cardiovascular events occur frequently despite control of conventional risk factors** (e.g lifestyle intervention, BP, LDL-C and glycaemic control). This is recognized as **"residual cardiovascular risk"**[1]
- **Ongoing chronic inflammation** is an important contributor to the risk of recurrent cardiovascular events and is mainly driven by the NLRP3 inflammasome pathway[2]
- The most widely used marker of this signaling cascade is **hsCRP**, a convenient barometer of the extent of ongoing inflammation[2]

Residual inflammatory risk (RIR) is classified as levels of high-sensitivity **C-reactive protein (hsCRP) ≥2 mg/L**

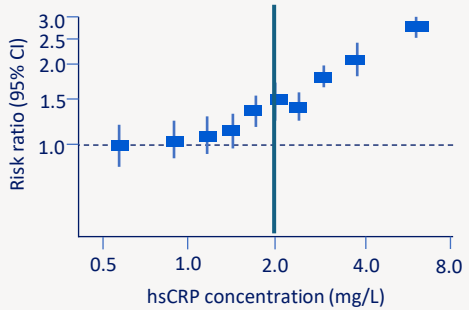


BP, blood pressure; LDL-C, low density lipoprotein – cholesterol; NLRP3, NOD [nucleotide oligomerization domain]-, LRR [leucine-rich repeat]- and PYD [pyrin domain]-containing protein 3
1. Volpe Intern Emerg Med 2011; 6 Suppl 1: 45-51; 2. Ridker et al. Circulation 2020;141:787–789; 3. Ridker Eur Heart J 2016; 37(22): 1720-1722

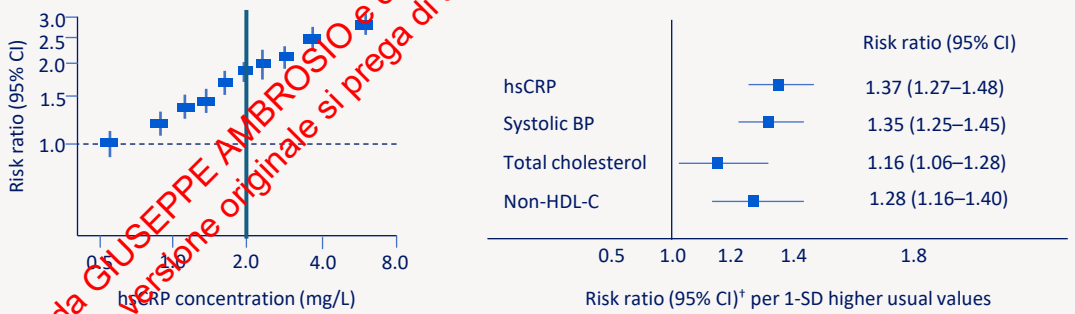
High hsCRP levels are associated with an increased risk of vascular events in healthy individuals

Primary prevention
(meta-analysis of 54 studies including 160,309 participants)

All vascular deaths*



CHD†



37% increased risk of CHD per 1-SD (or 3-fold) increase in hsCRP levels

Median follow-up of **8 years**

Adjusted for age, sex and study (based on 3,430 cases from 37 studies); †Left figure: adjusted for age, sex and study (based on 10,341 cases from 48 studies); right figure: adjusted for age, sex, smoking status, history of diabetes, BMI, Log_e triglycerides and alcohol consumption (based on 91,900 participants from 31 studies with 5,373 CHD events)

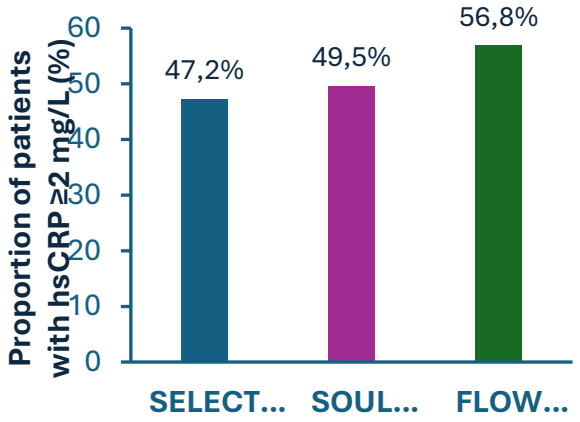
Ref: Emerging Risk Factors Collaboration et al. Lancet 2010;375:132–140

How common are Elevated baseline hsCRP levels in patients with CVD ?

Objective

- To determine the proportion of patients recruited in SELECT, SOUL, and FLOW trials with systemic inflammation (defined as **hsCRP ≥2 mg/L**)

	SELECT	SOUL	FLOW
Persons	N=17,605	N=9,650	N=3,534
Age	≥45 years old	≥50 years old	≥18 years old
Characteristics	• Established **CVD** • **BMI ≥27 kg/m²** • No diabetes	• Established **ASCVD and/or CKD** • **T2D**	• **T2D** • **CKD** • Treated with RAAS-blocking agents
Outcome	MACE	MACE	CV and kidney outcomes

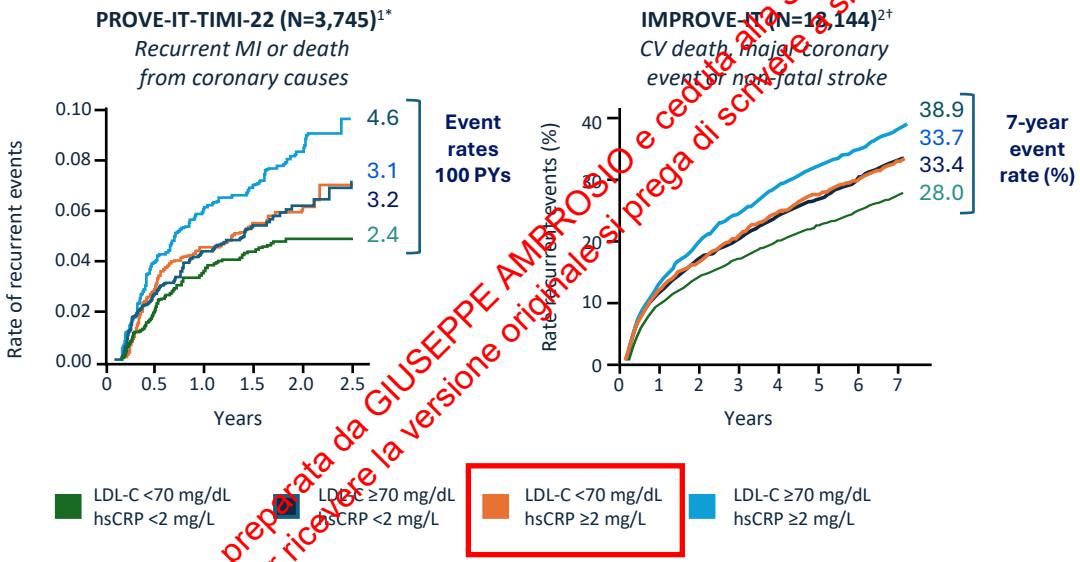


Marx N et al. Eur Heart J 2023;44(suppl 2)

In post-ACS patients, the residual inflammatory risk was a predictor of CV events alongside LDL-C

Patients with prior ACS on statin therapy

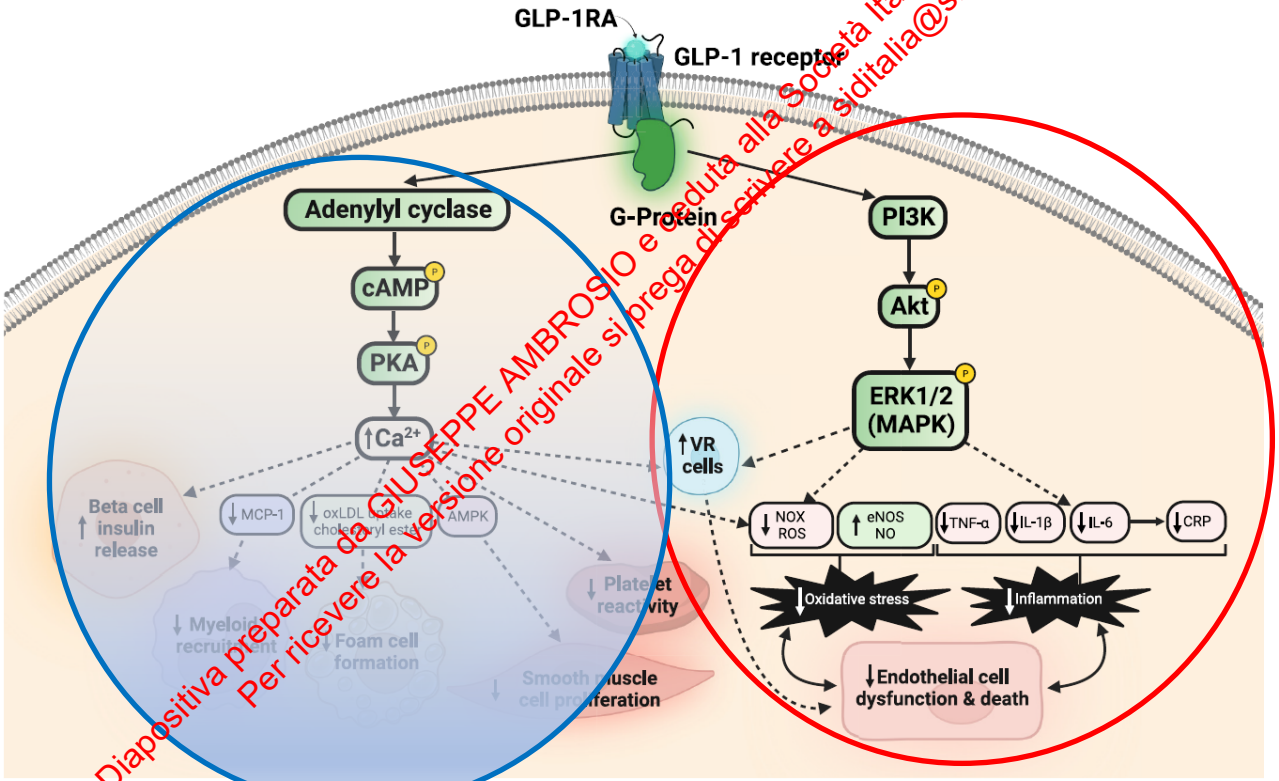
Incidence of recurrent CV events according to hsCRP and LDL-C levels



*Patients *received high-intensity statin therapy (80 mg of atorvastatin orally per day), moderate-intensity statin therapy (40 mg of pravastatin orally per day) or gatifloxacin and placebo; †Patients received simvastatin (40 mg daily) plus placebo or simvastatin (40 mg daily) plus ezetimibe (10 mg daily)*

GLP-1 receptor activation comes into play

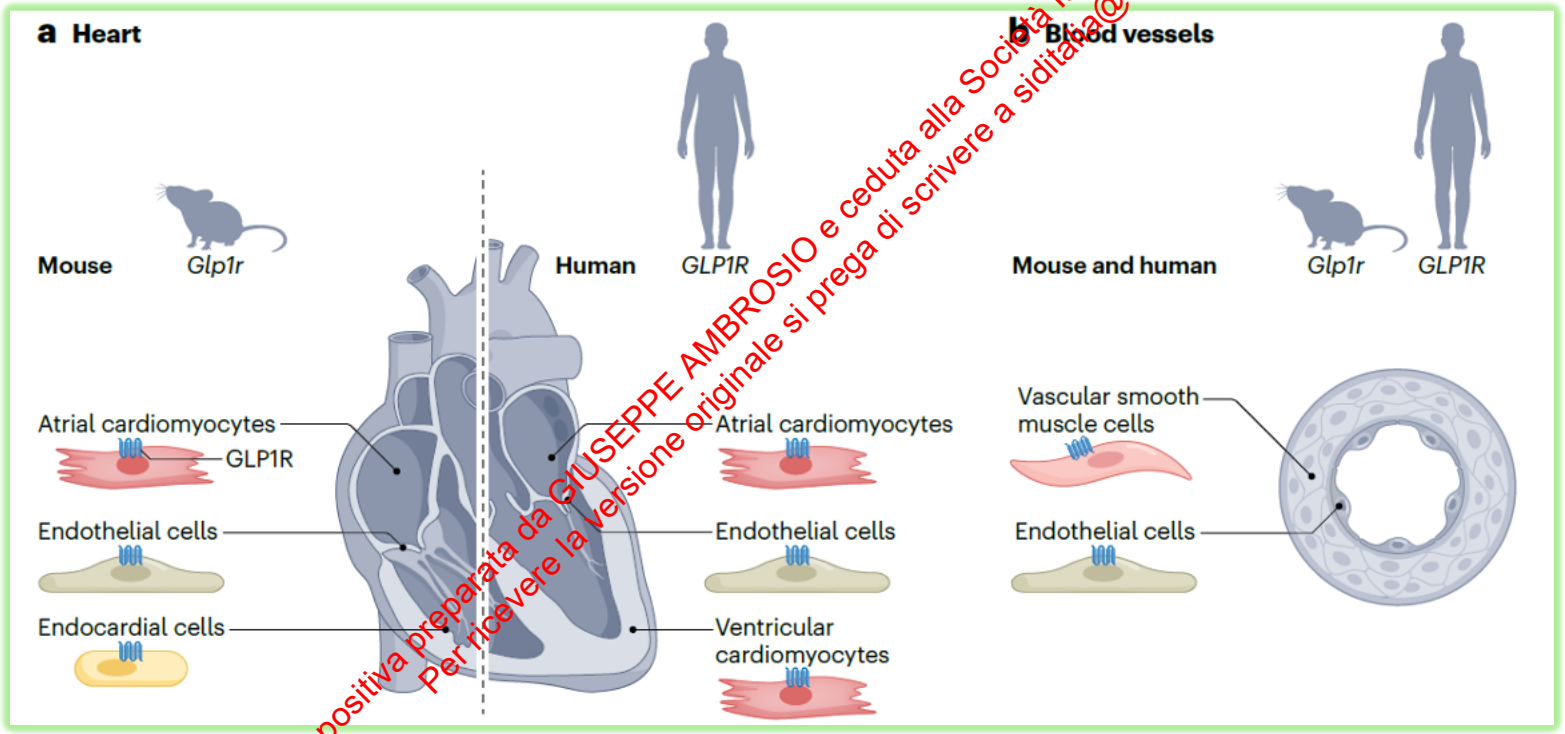
Activation of Class B G protein-coupled GLP-1R drives 2 signaling pathways



Park B, et al. Am J Physiol Heart Circ Physiol. 2024

GLP-1 receptor activation at cardiovascular level comes into play

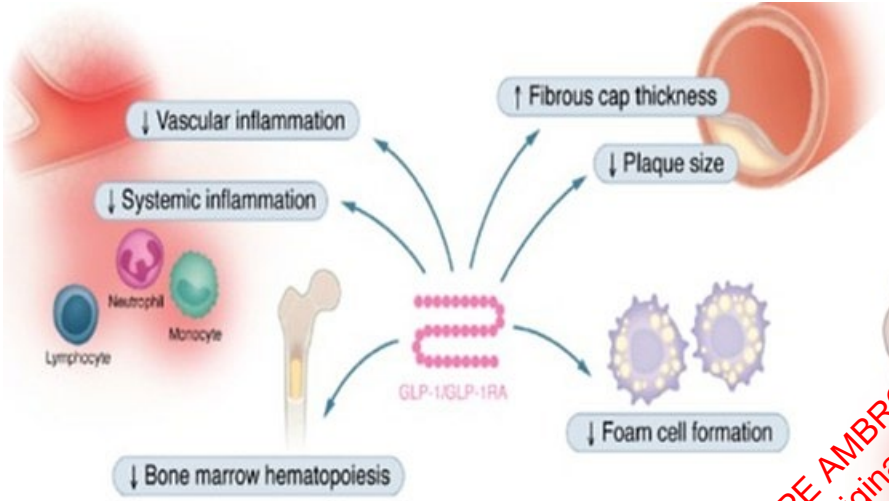
Distribution of mouse GLP1-R and human GLP1-R mRNA expression



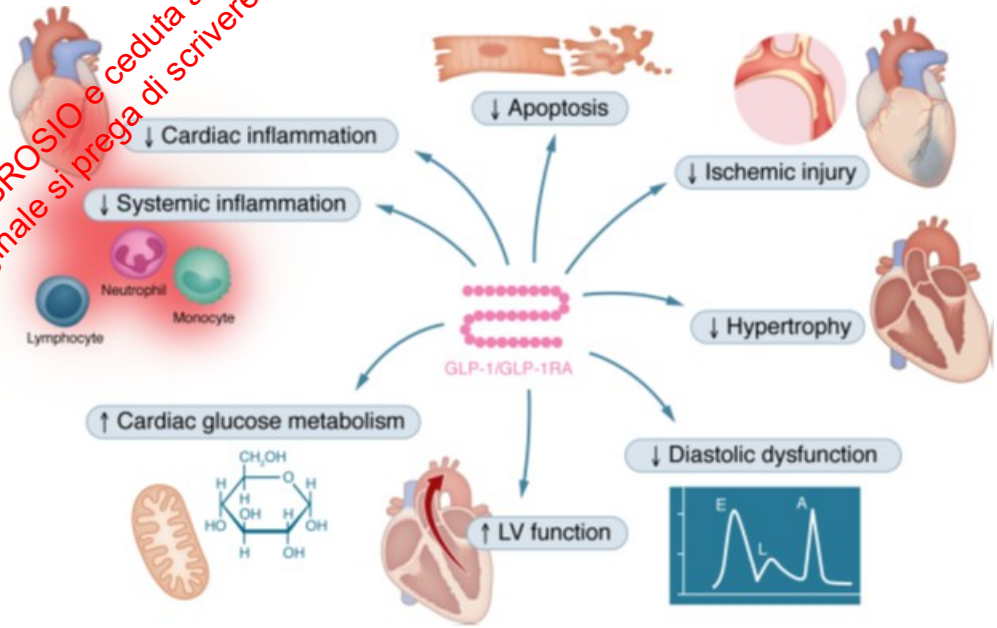
Ussher JR, Drucker DJ. Et al. Nat Rev Cardiol. 2023

The Journal of Clinical Investigation 2026

Vascular effects



Cardiac effects



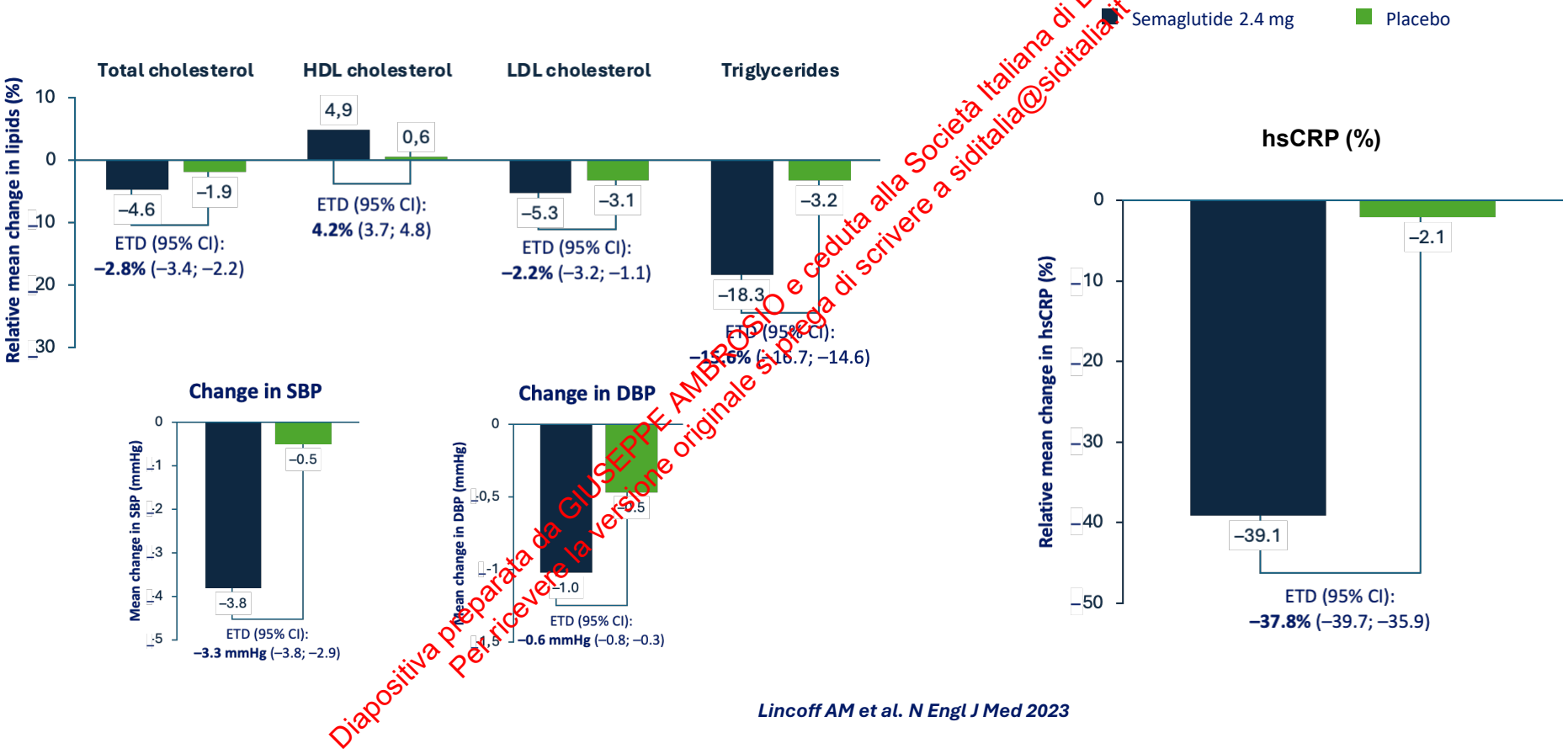
Anti-inflammatory therapies in cardiovascular diseases: evidences, controversies and future directions. A Scientific Statement of the Heart Failure Association of the ESC, in collaboration with the ESC Working Groups on Cardiovascular Pharmacotherapy, Myocardial and Pericardial Diseases, and Cellular Biology of the Heart

Davide Stolfo[1,2]*, Sophie Van Linthout[3-5]*, Ahmed Khaled Elsanhoury[3,4], Magdy Abdelhamid[6], Amr Abdin[7], Giuseppe Ambrosio[8,9], Antonio Cannata[10,11], Ovidiu Chioncel[12,13], Dobromir Dobrev[14-16], Alberto Esteban-Fernández[17,18], Andrea Frustaci[19], Nicolas Girerd[20], Nazha Hamdani[21-24], Massimo Imazio[25,26], Riccardo Maria Inciardi[27], Pardeep Jhund[28], Juan Carlos Kaski[29], Felix Lindberg[30], Pasquale Maffia[31-33], Marco Metra[34,35], Mark Petrie[28], Marija Polovina[36,37], Paul Ridker[38], Bianca Rocca[39], Carsten Tschoepe[3-5,40], Peter Van der Meer[41], Gianluigi Savarese[30]

GDMT Class	Key Anti-inflammatory Mechanisms	Evidence/References
β-blockers	↓ TNF-α, IL-6, IL-1β; NF-κB inhibition; ↓ oxidative stress; improved endothelial function	Ohtsuka 2001[27]; Mayer 2005[29]; Toyoda 2020[30]; Nasoufidou 2025[28]
RAASi (ACEI/ARB)	↓ IL-6, MCP-1, TNF-α, CRP; ↑ M2 macrophage polarization; ↓ T-cell activation; anti-fibrotic	Haliga 2025[31]; Ghafoury 2025[38]
MRA	↓ TNF-α, IL-6, MCP-1; ↓ ROS; ↓ fatty acid-induced inflammation; anti-fibrotic	Fu 2022[33]; Savarese 2024[143]
SGLT2i	↓ IL-6,* TNF-α, NLRP3 inflammasome activity; M2 macrophage shift; ↓ ROS; improved endothelial function	Crispino 2025[15]; Metra 2025[16]; Dihoum 2024[144]; Docherty 2025[26]*
GLP-1RA	**↓ IL-6, TNF-α, CRP; AMPK-mediated antioxidant effects; ↓ ROS; improved endothelial repair; anti-fibrotic**	Ren 2025[21]; Skrobucha 2024[22]; Bonfioli 2025[23]

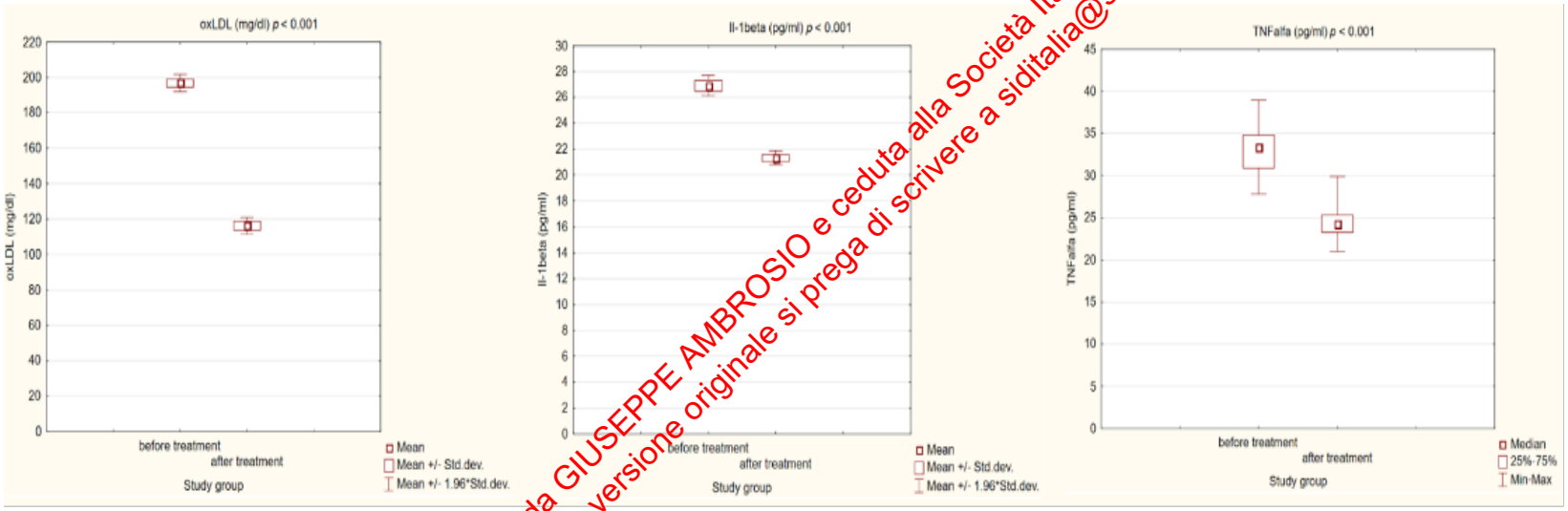
Eur J Heart Failure 2026

Change in CV Risk Factors (SELECT)



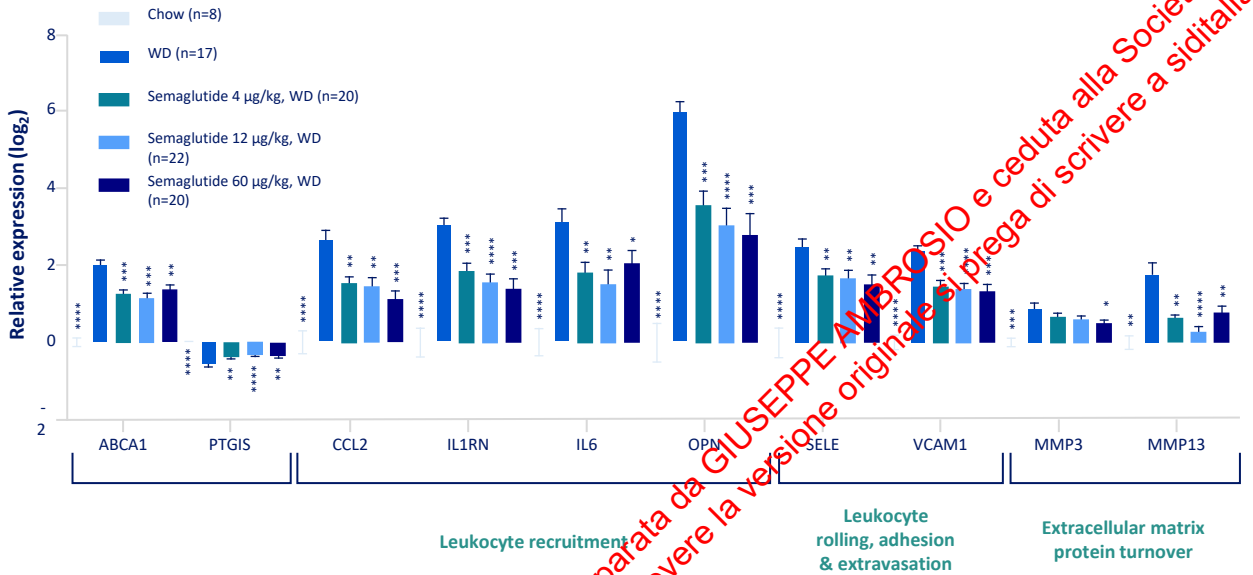
Lincoff AM et al. N Engl J Med 2023

GLP-1 RA administration and biochemical markers of inflammation (at 180 days f-u) [Hachuda et al., Int J Mol Sci 2024; 25:1854]

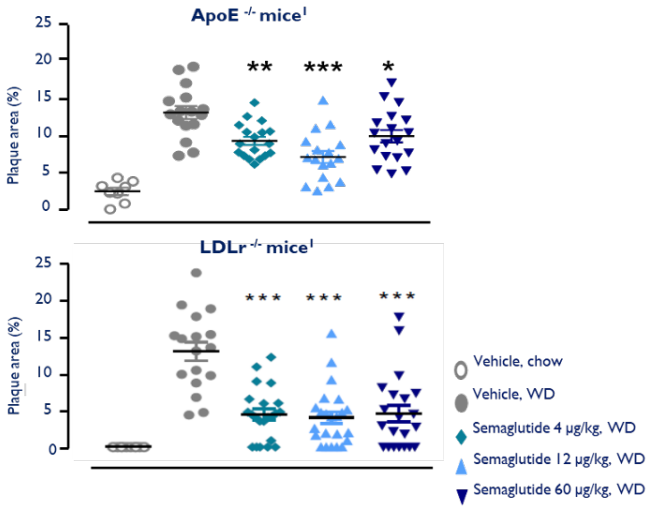


Anti-atherosclerotic effects of Semaglutide in animal models

Gene expression in LDLR$^{-/-}$ or APOE$^{-/-}$ mice treated with semaglutide



Atherosclerotic plaque size in LDLR$^{-/-}$ or APOE$^{-/-}$ mice treated with semaglutide



Rakipovski G et al. JACC Basic Transl Sci 2018

Atherosclerosis 352 (2022) 88–95

Contents lists available at ScienceDirect

Atherosclerosis

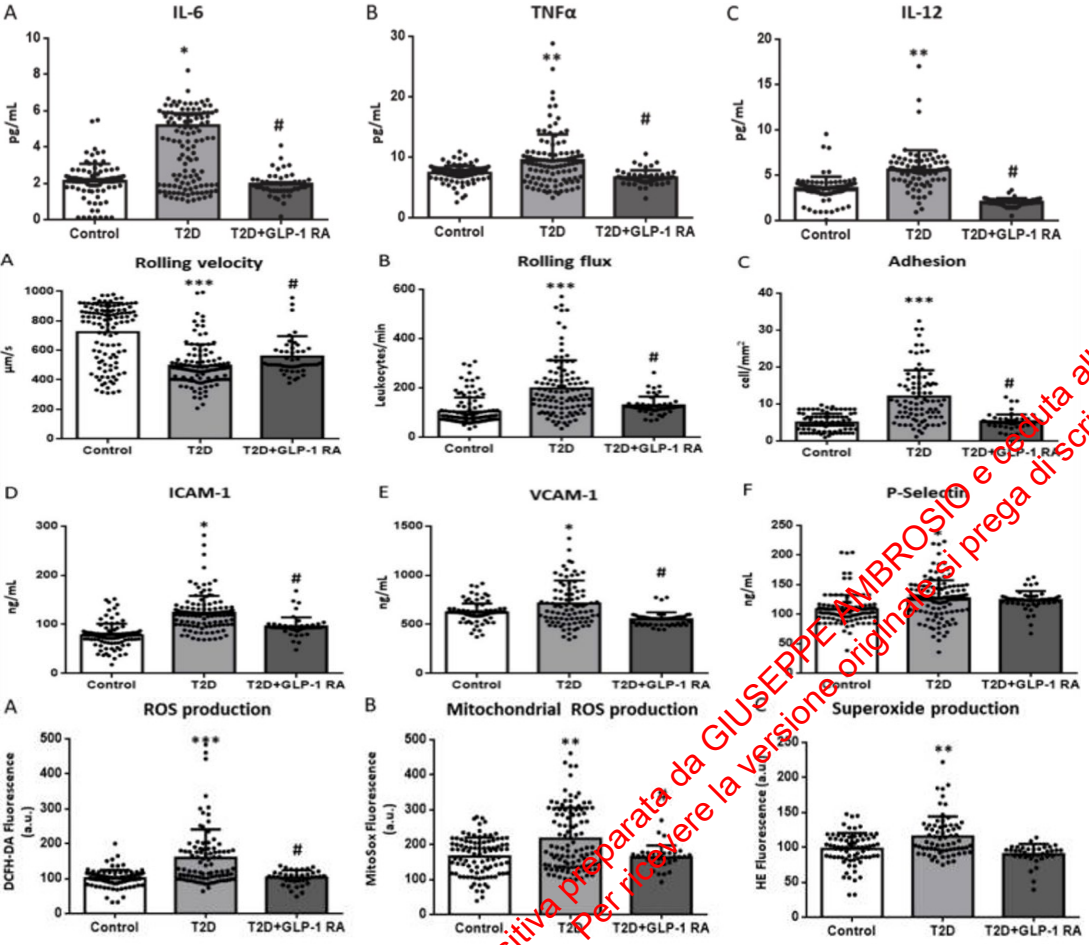
journal homepage: www.elsevier.com/locate/atherosclerosis

Semaglutide reduces vascular inflammation investigated by PET in a rabbit model of advanced atherosclerosis

Jacob K. Jensen *, Tina Binderup, Constance E. Grandjean, Simon Bentsen, Rasmus S. Ripa, Andreas Kjaer

Dept. of Clinical Physiology, Nuclear Medicine & PET and Cluster for Molecular Imaging, Dept. of Biomedical Sciences, Rigshospitalet and University of Copenhagen, Copenhagen, Denmark

Conclusions: Semaglutide decreased vascular uptake of tracers imaging activated macrophages and cellular metabolism but not micro-calcifications compared to a saline placebo. This supports the hypothesis that semaglutide reduces atherosclerotic inflammation by means of decreased activated macrophage activity.



Real-world Type 2 diabetic patients and control subjects

T2D divided into 2 groups: without GLP-1 RA treatment (196), and treated with GLP-1 RA (59).

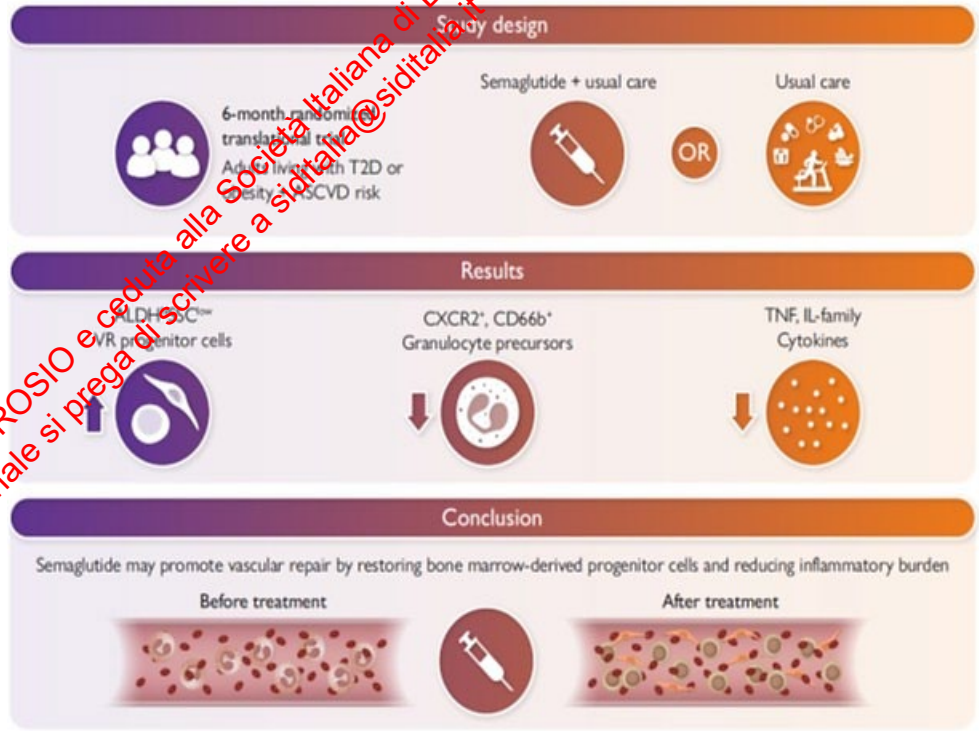
Peripheral blood polymorphonuclear leukocytes (PMNs) isolated to measure reactive oxygen species (ROS) production by flow cytometry and oxygen consumption. PMNs were also used to assess leukocyte-endothelial interactions. Circulating levels of adhesion molecules and inflammatory markers were quantified by Luminex's technology.

Luna Marco C, et al. Redox Biology 2023

ESC European Society of Cardiology
European Heart Journal (2026) 47, 1171–1182
https://doi.org/10.1093/eurheartj/ehaf690
FASTTRACK – CLINICAL RESEARCH
Vascular biology and medicine

Semaglutide promotes bone marrow–derived progenitor cell flux towards an anti-inflammatory and pro-regenerative profile in high-risk patients: the SEMA-VR CardioLink-15 trial

Brady Park[1,2,3], Fallon Dennis[1,2,3], Arianna Z. He[1,2,3], Aishwarya Krishnaraj[1,2,3], Ehab Bakbak[4], Cole J. Dennis[1,2,3], Yi Pan[1,2], Elizabeth Misner[1], Veena Thayanithy[5,6], Bhavaani Lambotharan[6], Vaasudevan Lambotharan[6,7], Aruna Lambotharan[6], C. David Mazer[8,9,10], Adrian Quan[1,2], Hwee Teoh[1,2,11], David A. Hess[2,3,12,13], and Subodh Verma[1,2,3,14,*]

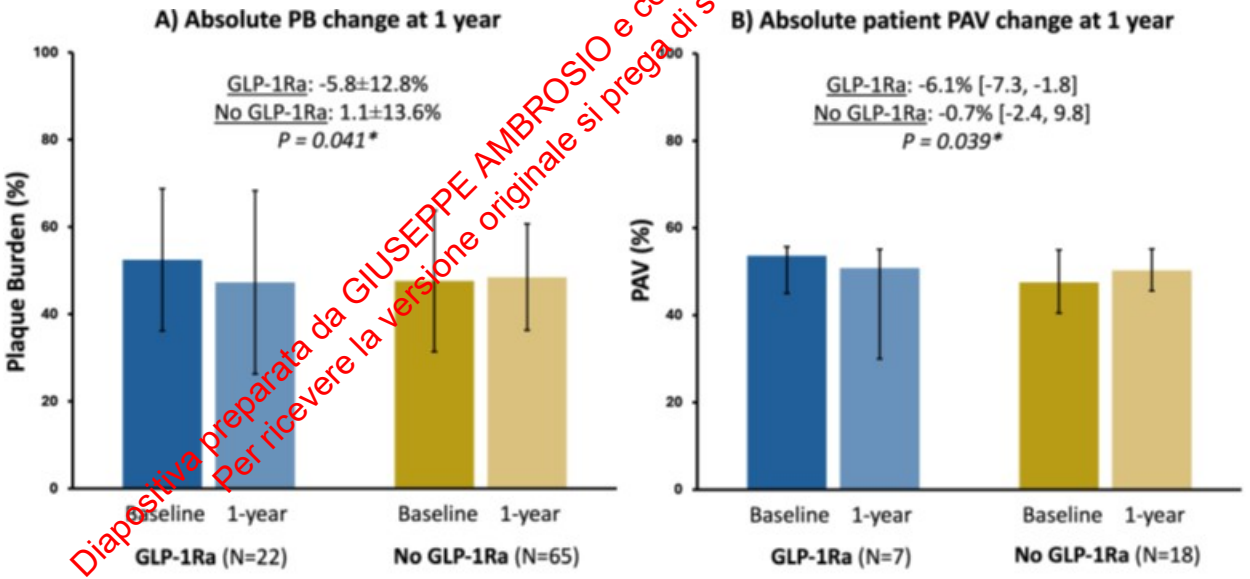


Acta Diabetologica (2026) 63:179–191
https://doi.org/10.1007/s00592-025-02606-z

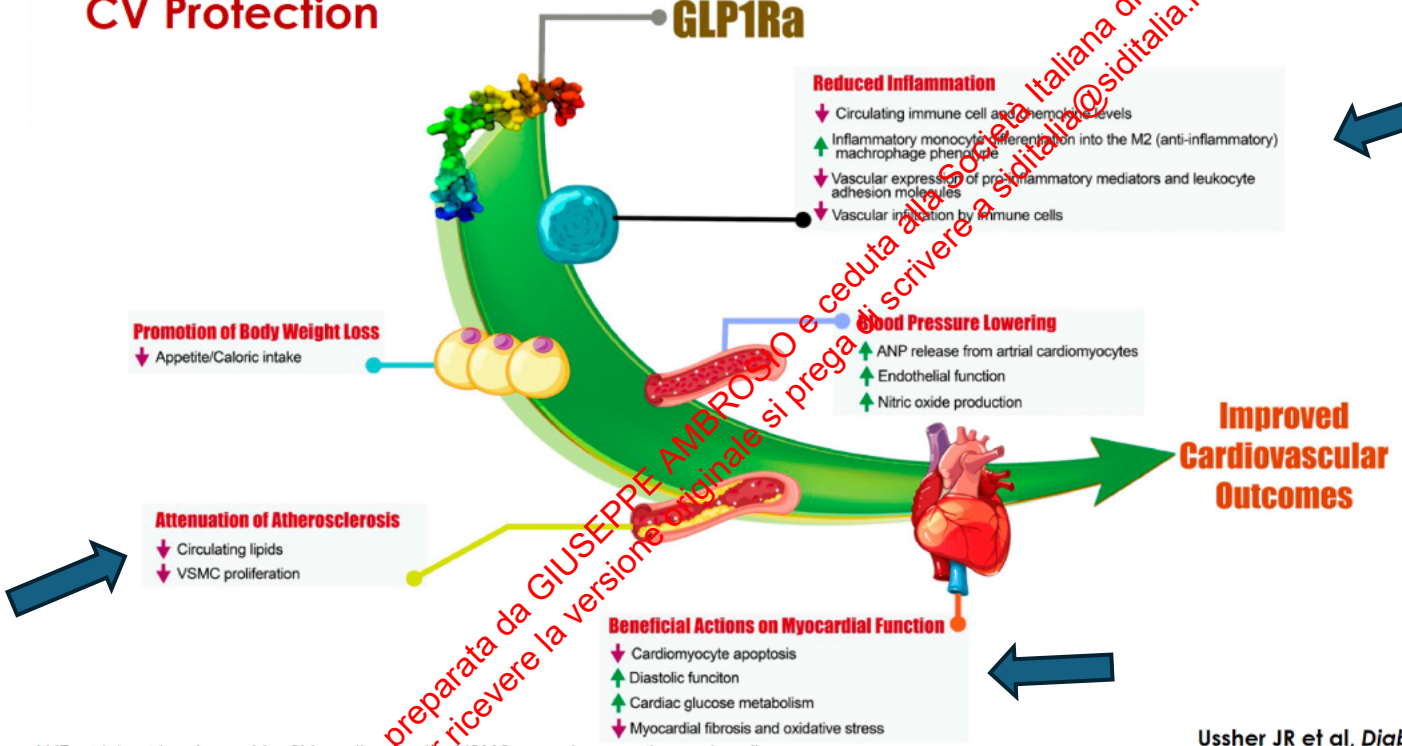
ORIGINAL ARTICLE

GLP-1 receptor agonists and coronary plaques regression in diabetic patients after acute coronary syndromes

Mauro Gitto[1,2] · Federica Catapano[1,2] · Marco Francone[1,2] · Gianluca Mincione[1,2] · Vincenzo Scialò[1,2] · Carlo A. Pivato[1,2] · Costanza Lisi[1,2] · Damiano Regazzoli[1,2] · Davide Cao[1,2] · Roberta Maria Fiorina[1] · Alessandra Petrelli[3,4] · Loredana Bucciarelli[4] · Cristian Loretelli[3,4] · Gianluigi Condorelli[1,2] · Paolo Fiorina[3,4,5] · Giulio Stefanini[1,2]

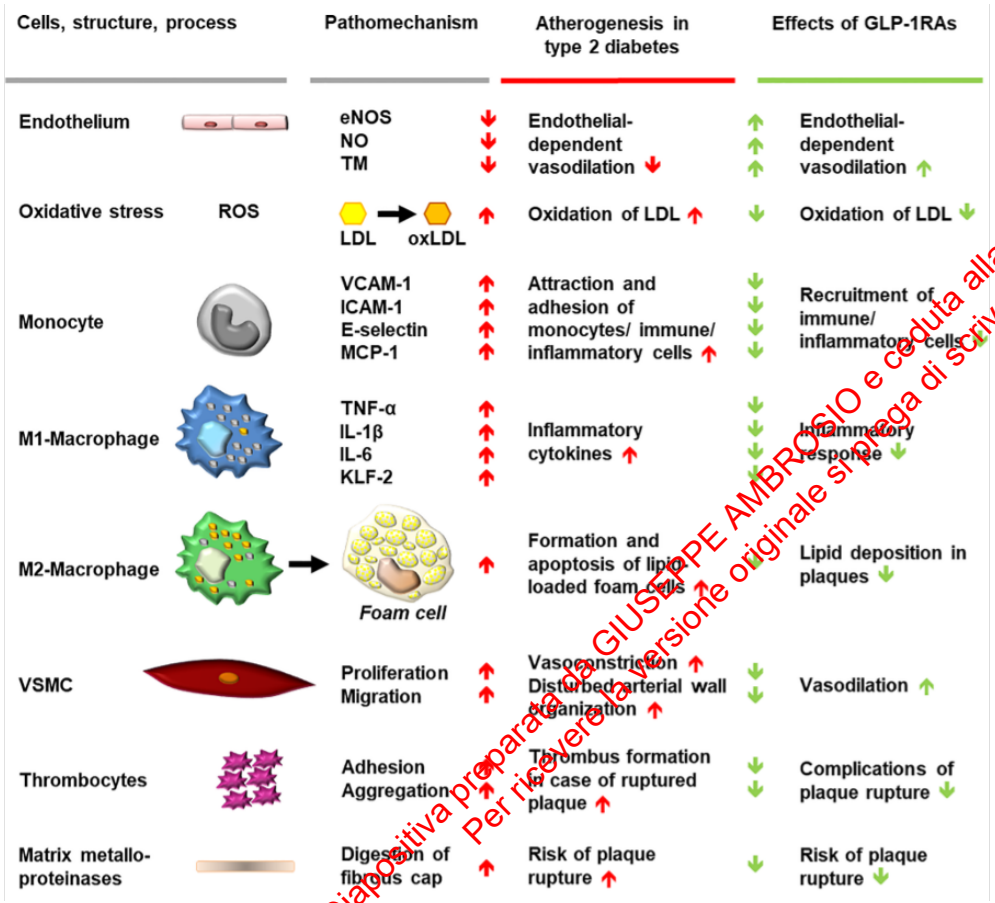


Potential Mechanisms Contributing to GLP-1RA-mediated CV Protection



ANP, atrial natriuretic peptide; CV, cardiovascular; VSMC, vascular smooth muscle cells

Ussher JR et al, *Diabetes* 2022



Anti-atherosclerotic effects of GLP-1 receptor agonists

Nauck and Quast , 2021

JACC: BASIC TO TRANSLATIONAL SCIENCE 2023

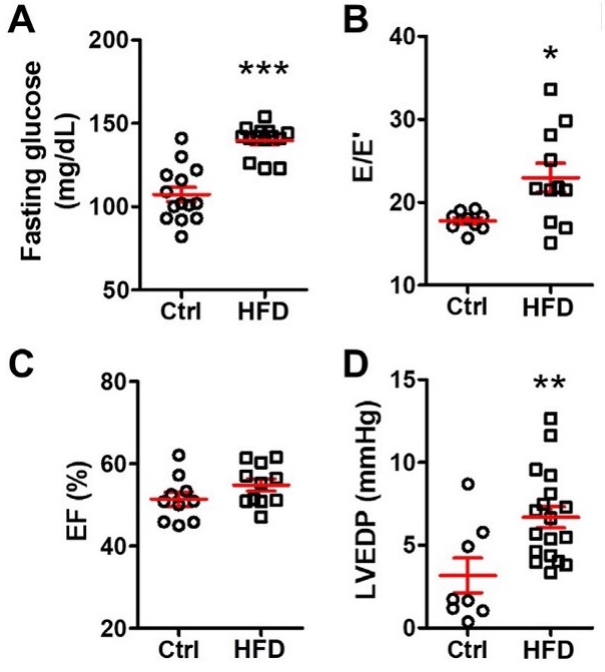
EDITORIAL COMMENT

Revisiting IL-1β

Linking Metainflammation to Diastolic Dysfunction

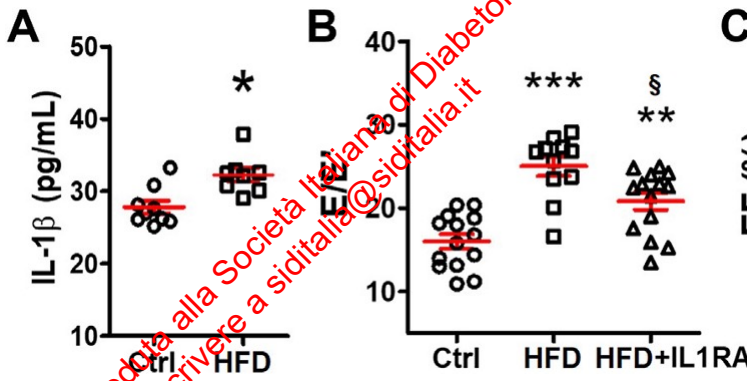
Mallory Filipp, MS, Edward B. Thorp, PHD

Interleukin-1b produced by inflammatory macrophages mediates High-Fat Diet-induced hyperglycemia, and Heart Failure with Preserved Ejection Fraction

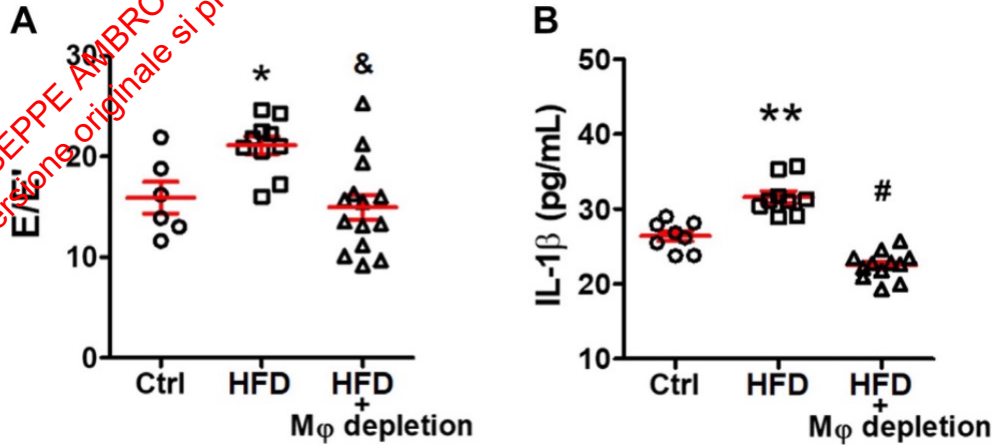


High-fat diet (HFD)-induced (A) hyperglycemia, (B) increased ratio of transmitral Doppler early filing velocity to tissue Doppler early diastolic mitral annular velocity (E/E0), and (D) left ventricular end-diastolic pressure (LVEDP) elevation with (C) preserved ejection fraction (EF)

Liu H et al, JACC Basic to Translational Science 2023



HFD-induced DD was accompanied by increased cardiac MCP-1 and IL-1β, an increase in pro-inflammatory and decrease in anti-inflammatory macrophages, and increased CM mitoROS



Inhibiting IL-1β or mitoROS improved DD, as was macrophage depletion or anti-inflammatory macrophage phenotypic modulation

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

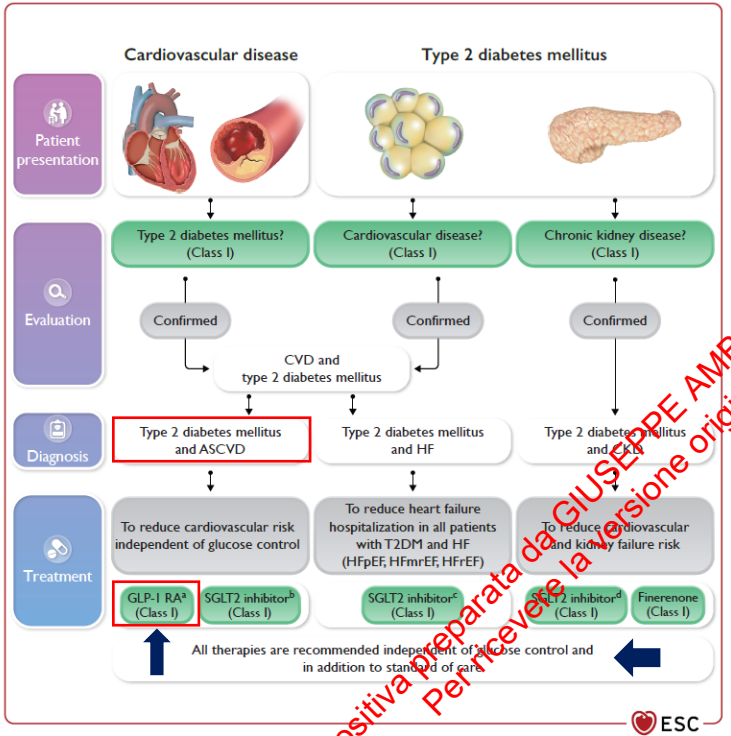


Figure 1 Management of cardiovascular disease in patients with type 2 diabetes: clinical approach and key recommendations. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; s.c. subcutaneous; SGLT2, sodium–glucose co-transporter 2; T2DM, type 2 diabetes mellitus. [a]GLP-1 RAs with proven cardiovascular benefit: lixisenatide, semaglutide s.c., dulaglutide, efpeglenatide. [b]SGLT2 inhibitors with proven cardiovascular benefit: empagliflozin, canagliflozin, dapagliflozin, sotagliflozin. [c]Empagliflozin, dapagliflozin, sotagliflozin in HFrEF; empagliflozin, dapagliflozin in HFpEF and HFmrEF. [d]Canagliflozin, empagliflozin, dapagliflozin.

2024 ESC Guidelines for the management of chronic coronary syndromes

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

[a]Class of recommendation.
[b]Level of evidence.
[c]Canaglifozin, dapagliflozin, empagliflozin, sotagliflozin (listed in alphabetical order).
[d]Dulaglutide, efpeglenatide, liraglutide, semaglutide (listed in alphabetical order).

The potential relationship between anti-inflammatory effect of GLP-1 and CAD

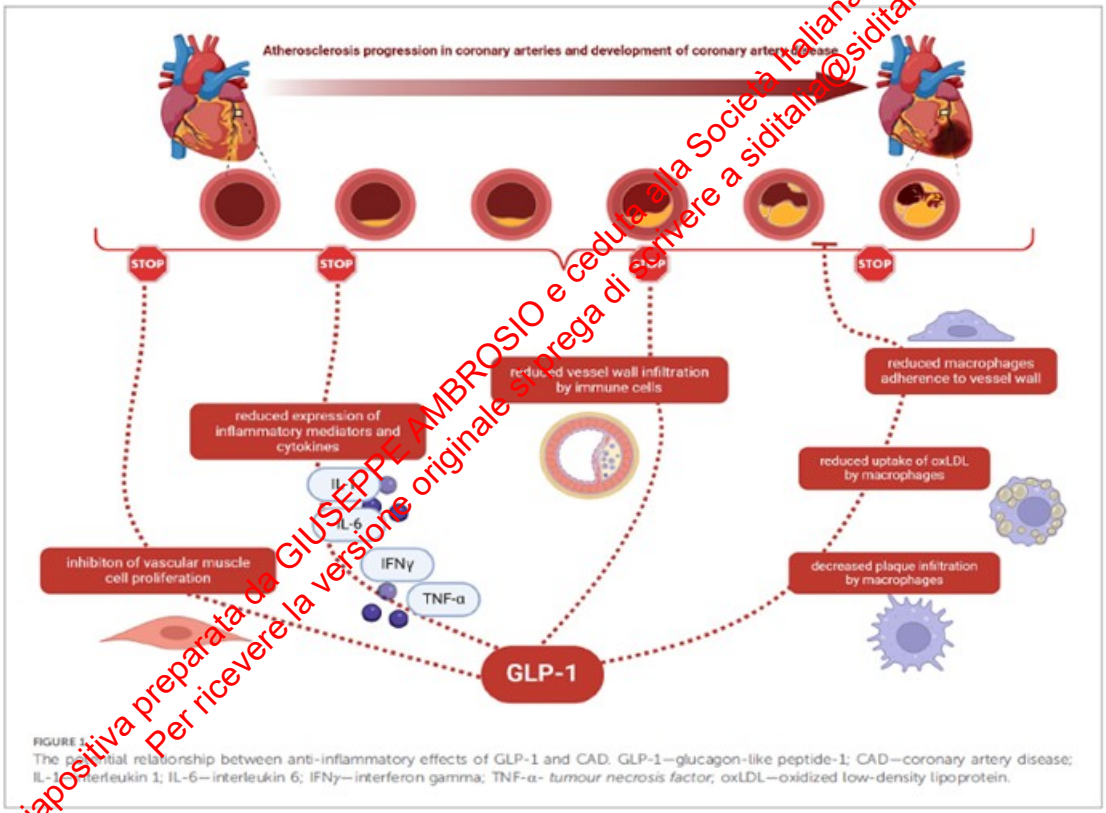
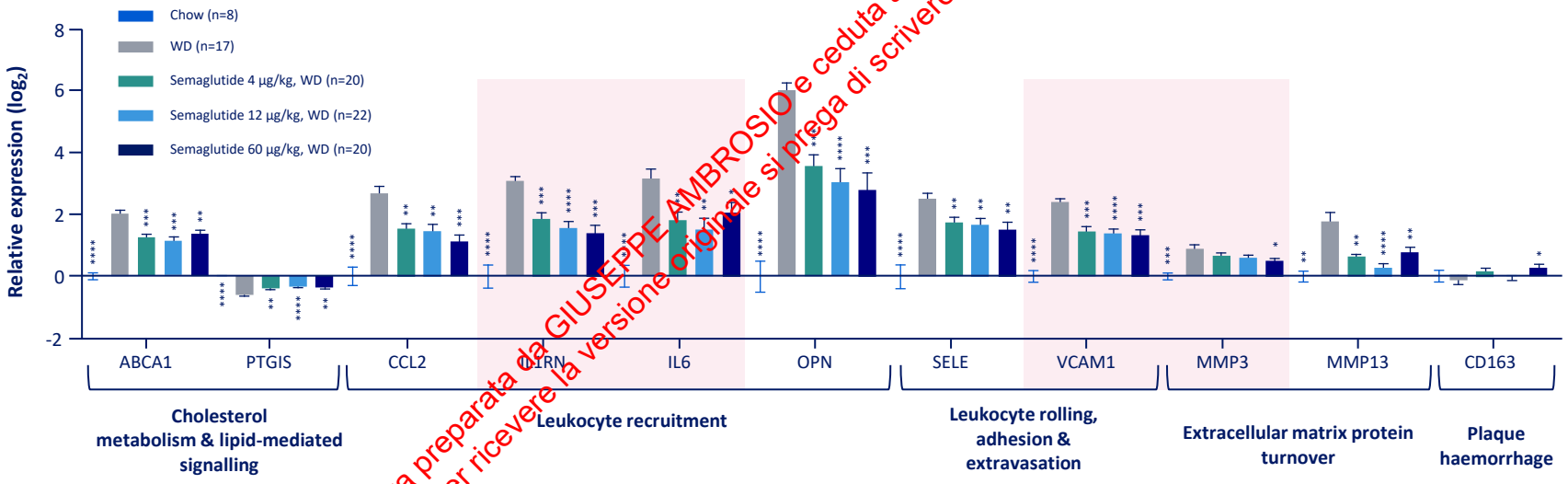


FIGURE 1
The potential relationship between anti-inflammatory effects of GLP-1 and CAD. GLP-1—glucagon-like peptide-1; CAD—coronary artery disease; IL-1—interleukin 1; IL-6—interleukin 6; IFNγ—interferon gamma; TNF-α- *tumour necrosis factor*; oxLDL—oxidized low-density lipoprotein.

CAD, Coronary artery disease
Skrobucha A, et al. Front Cardiovasc Med. 2024;11:1446468.

Semaglutide downregulates genes related to the process of atherosclerosis in a non-clinical study†

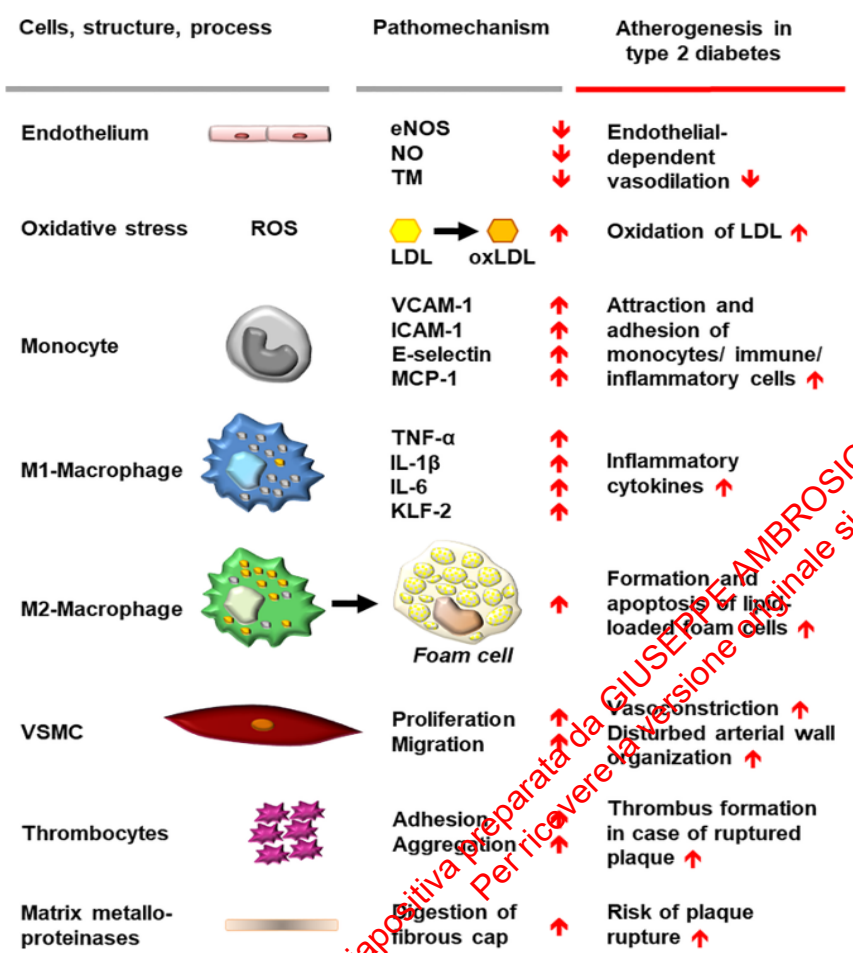
Expression of genes relevant to atherosclerosis pathogenesis



†Experiments performed in $Ldlr^{-/-}$ mice. All p-values calculated vs LDLr-/- WD control; ****p<0.0001; ***p<0.001; **p<0.01; *p<0.05.
ABCA1, ATP-binding cassette transporter 1; CCL2, chemokine ligand 2; CD163, cluster of differentiation 163; IL1RN, interleukin-1 receptor antagonist; IL6, interleukin-6; $LDLr^{-/-}$, low-density lipoprotein receptor knockout; MMP3, matrix metalloproteinase-3; MMP13, matrix metalloproteinase-13; OPN, osteopontin; PTGIS, prostaglandin I2 synthase; SELE, selectin E; VCAM1, vascular cell adhesion molecule; WD, Western diet.
Adapted from Rakipovski G et al. JACC Basic Transl Sci 2018;3:844–57.

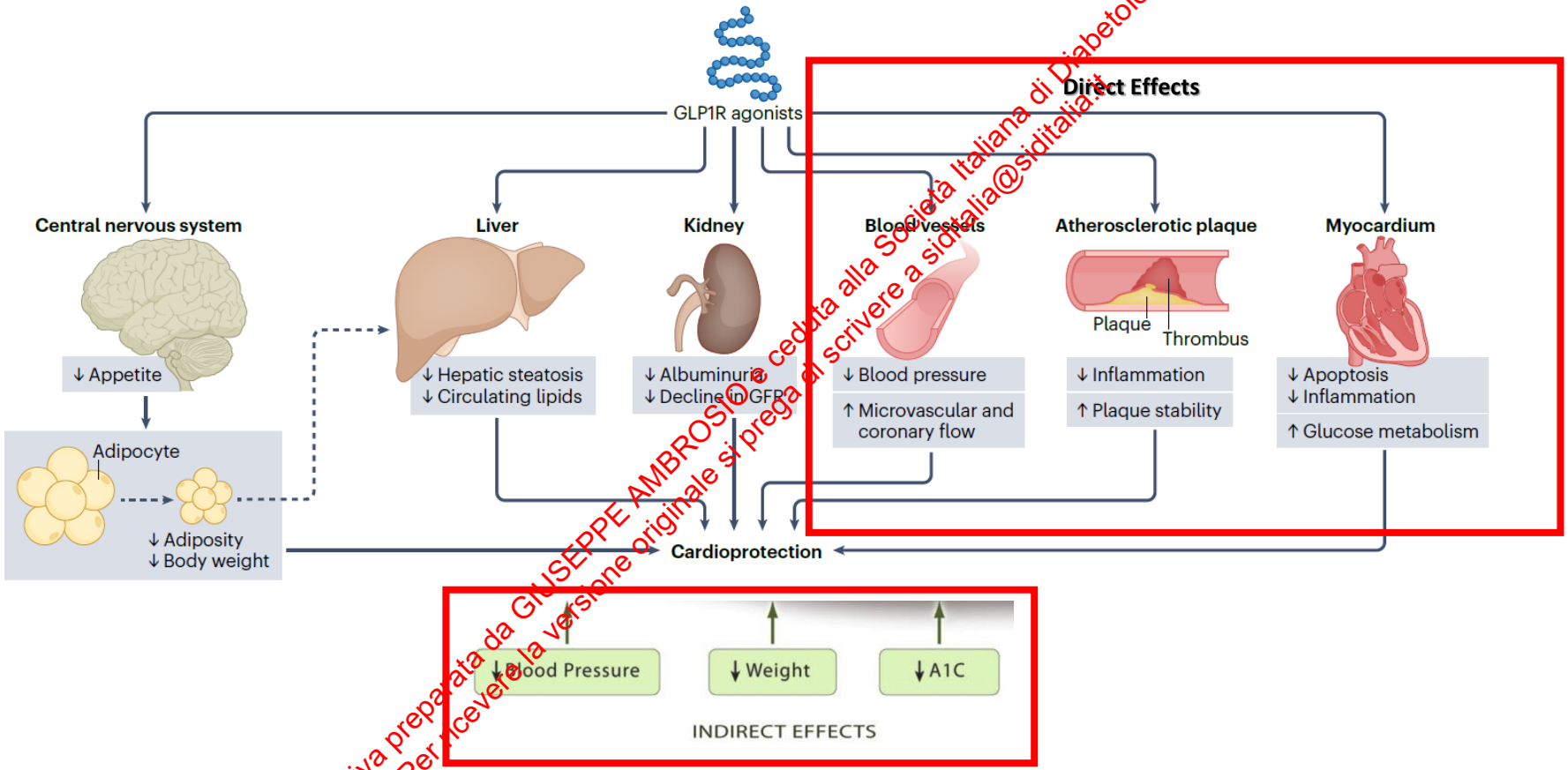
Semaglutide and CV risk reduction in diabetes

- **Inflammation, atherosclerosis, and diabetes**
- **Role of GLP1 in inflammation**
- **Mechanisms of Semaglutide effects on inflammation**
- **Oral semaglutide as a new approach**



Mechanism involved in atherosclerotic lesion formation in patients with T2 diabetes

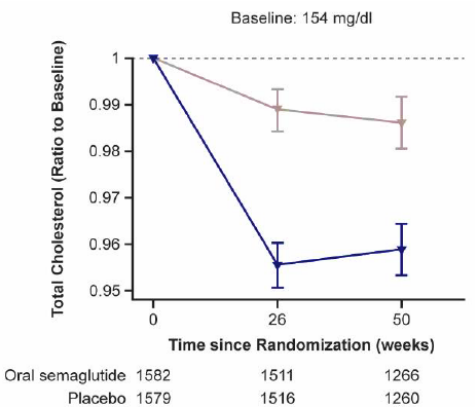
Nauck and Quast , 2021



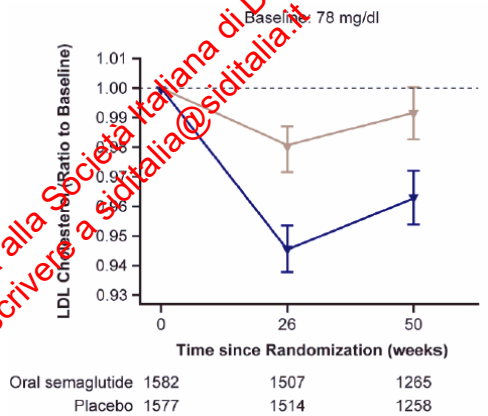
John R. Ussher 1,2 & Daniel J. Drucker. Nature reviews cardiology 2023. https://doi.org/10.1038/s41569-023-00849-3

Effetti sul metabolismo lipidico

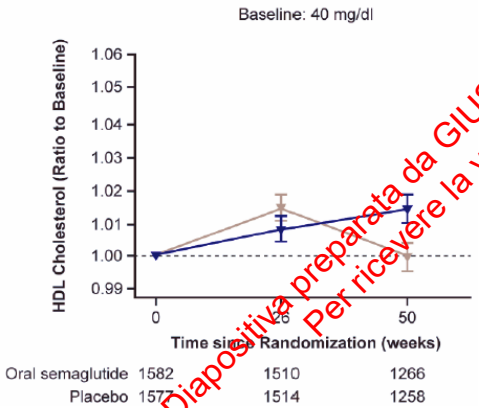
TC



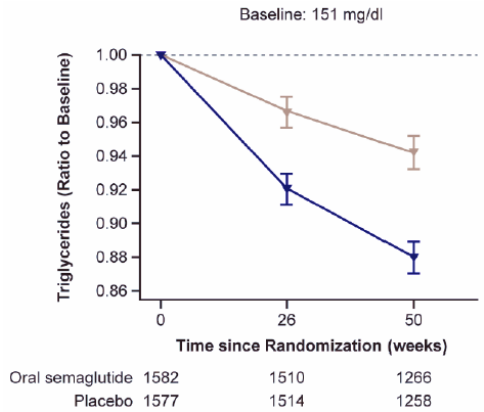
LDL



HDL



TG

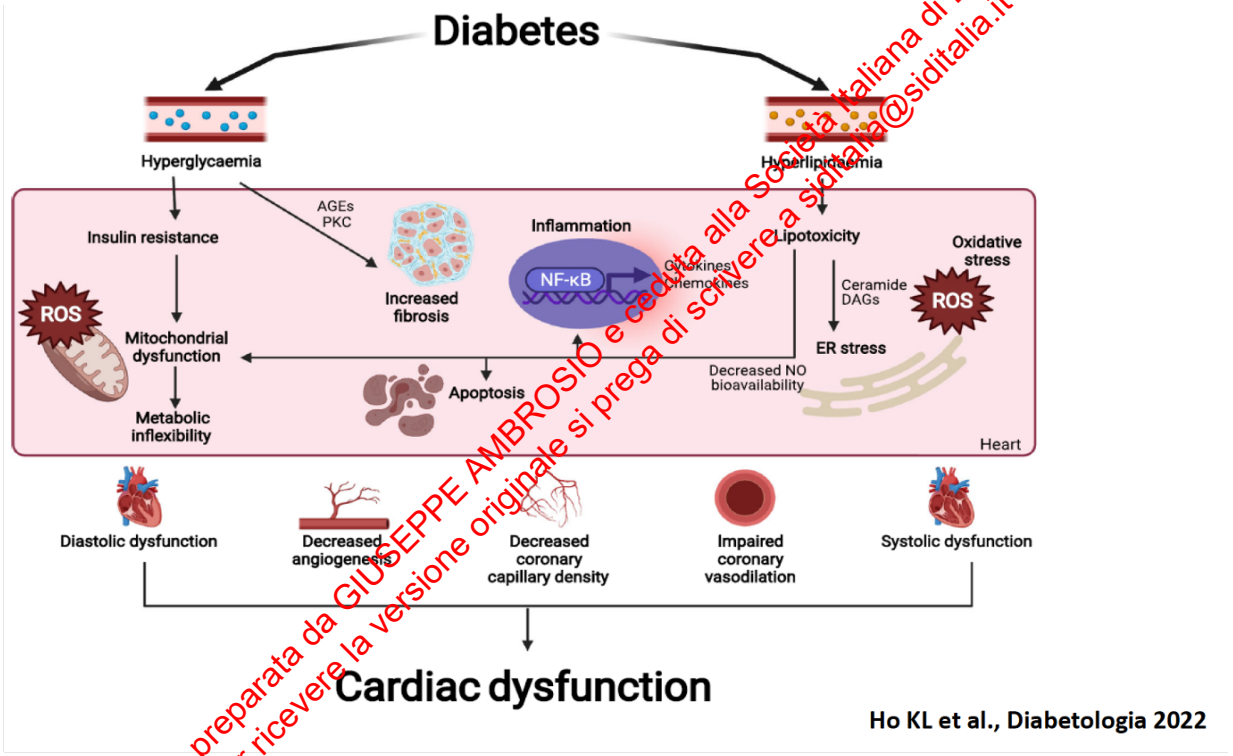


Husain M, et al. N Engl J Med 2019;381:841–51

Oral Semaglutide improves «classical» CV risk factors

Changes at 26 weeks		HbA_{1c}	SBP (mmHg)	Lipids	Weight (kg)	Waist (cm)
PIONEER 2	Semaglutide	-1.3*	-5	↓TC*, ↓LDL*	-3.8	-3.7*
	PO	-0.9	-5		-3.7	-3.0
	Empagliflozin					
PIONEER 3	Semaglutide	-1.3*	-3	↓TC*, ↓LDL*, ↓TG*	-3.1*	-2.3*
	PO	-0.8	-2		-0.6	-0.6
	Sitagliptin					
PIONEER 4	Semaglutide	-1.2	-4		-4.4*	-4.2*
	PO	1.1	3		3.1	2.9

Rodbard HW et al Diabet



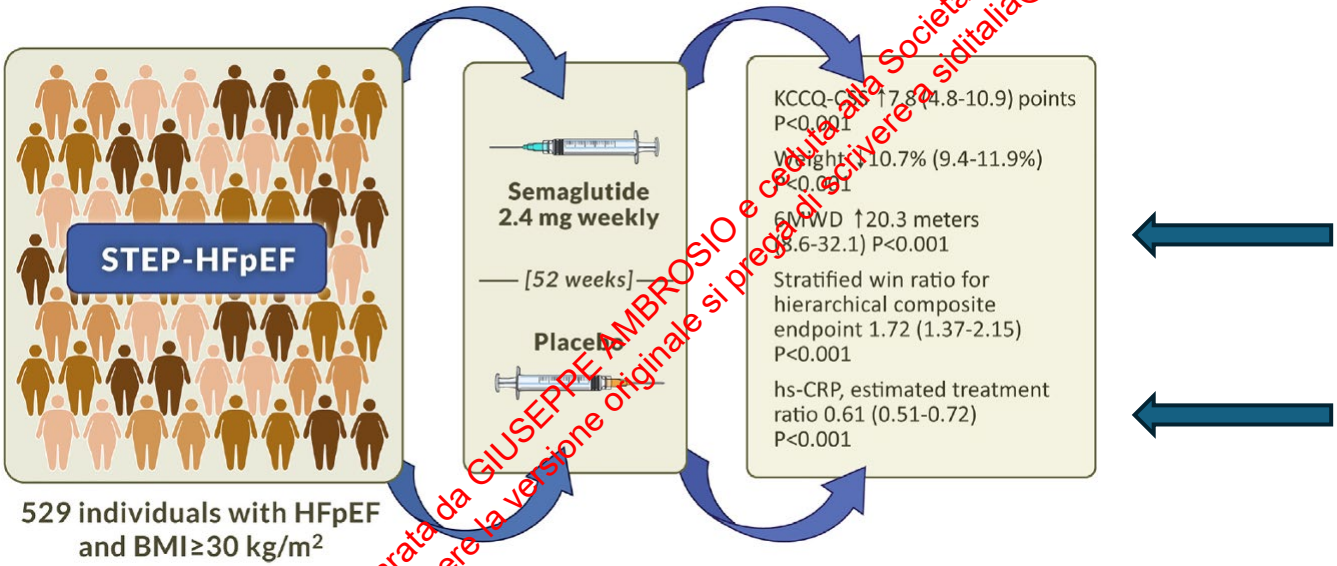
Ho KL et al., Diabetologia 2022

Cell Metabolism

CellPress

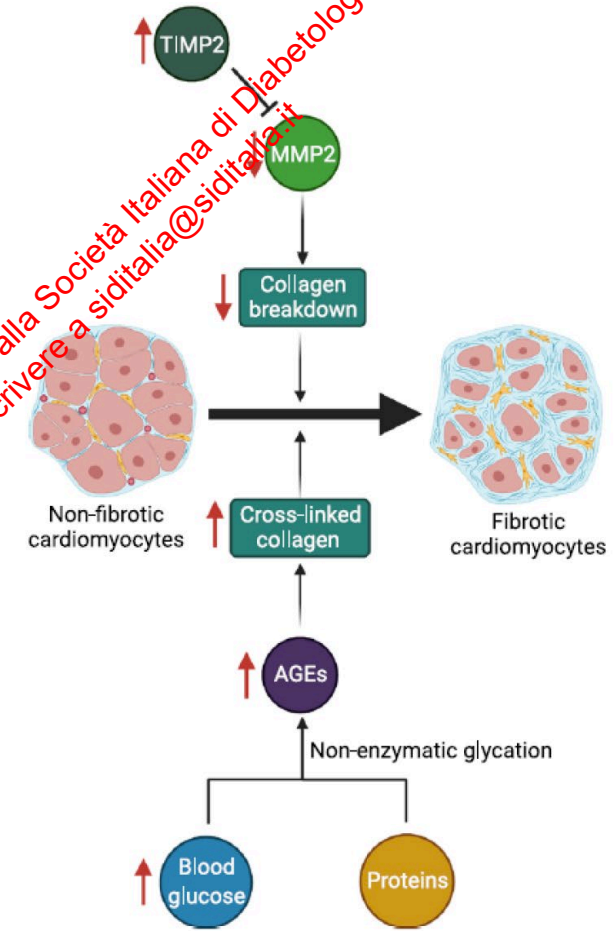
Commentary

A big STEP for treatment of heart failure with preserved ejection fraction



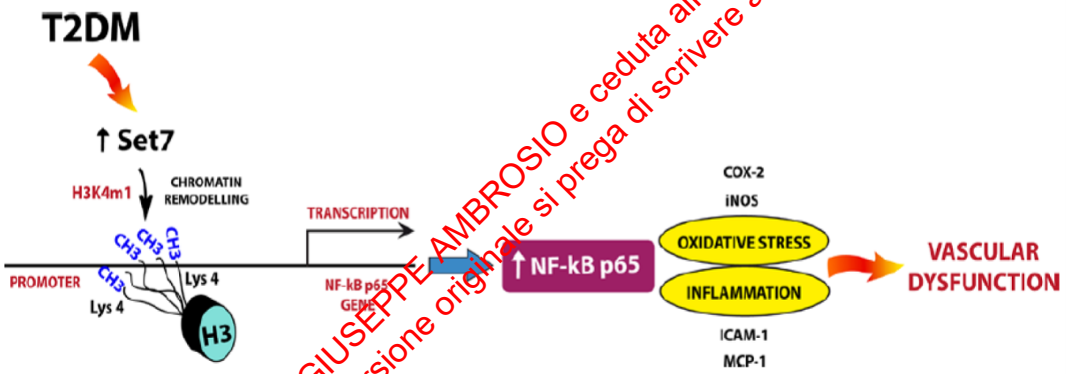
CONCLUSIONS: In patients with HFpEF and obesity, semaglutide produced large improvements in HF-related symptoms, physical limitations, exercise function, inflammation, body weight, and N-terminal pro-brain natriuretic peptide, regardless of baseline health status. The benefits of semaglutide extended to all key KCCQ domains.

MECHANISMS FOR CARDIAC FIBROSIS IN DIABETES



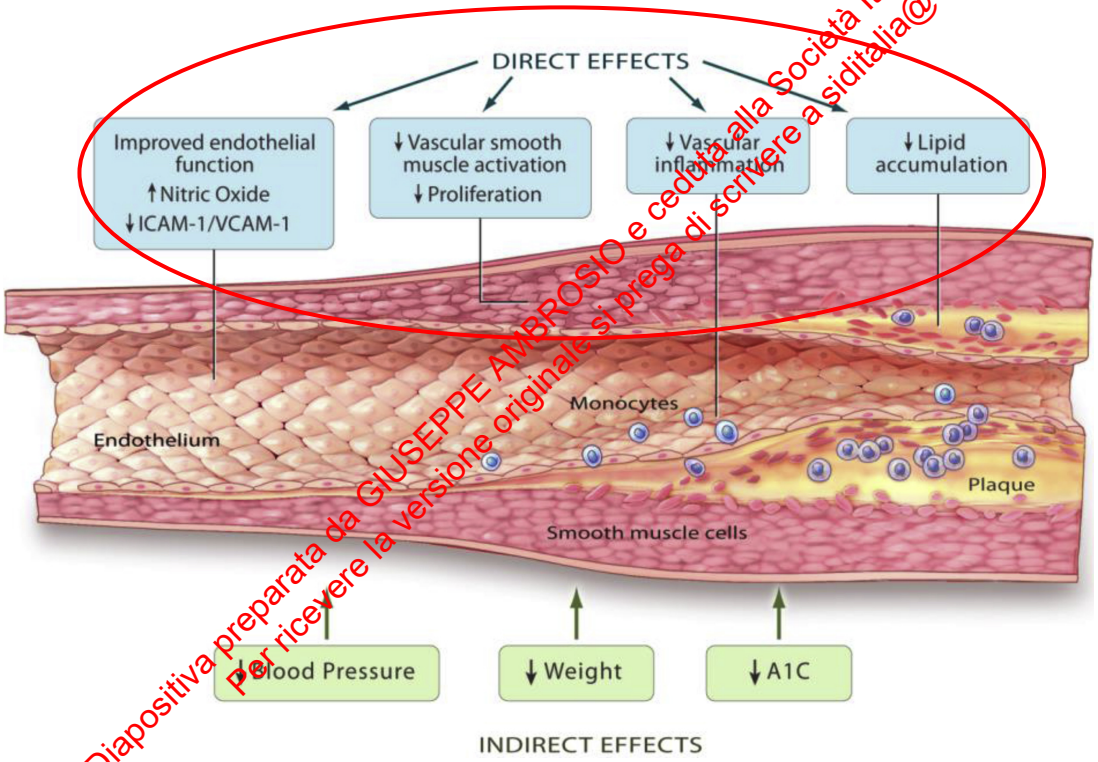
Ho KL et al., Diabetologia 2022

From T2DM to vascular dysfunction through epigenetic modifications



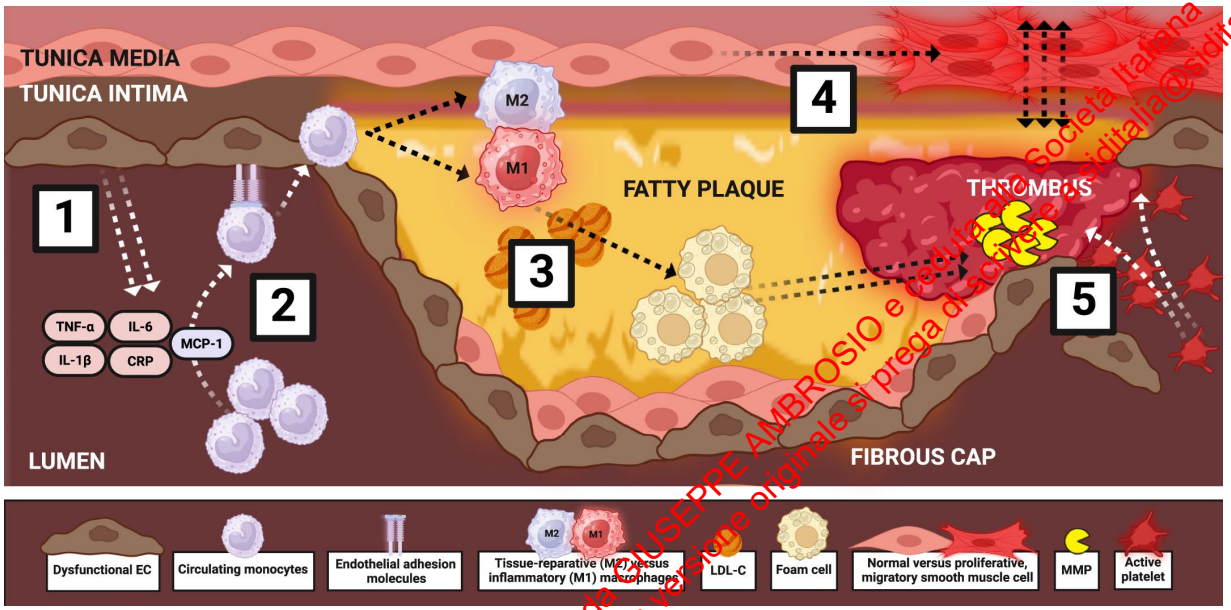
Paneni F et al, *Circ Cardiovasc Genet*. 2015

Beneficial effects of GLP-1 receptor activation at the vascular level



Drucker D. Cell Metabolism 2016;24(1):15-30; Sharma and Verma, Can J Diabetes, 2020;44(1):93.102

The anti-atherosclerotic targets of GLP-1RAs during endothelial dysfunction

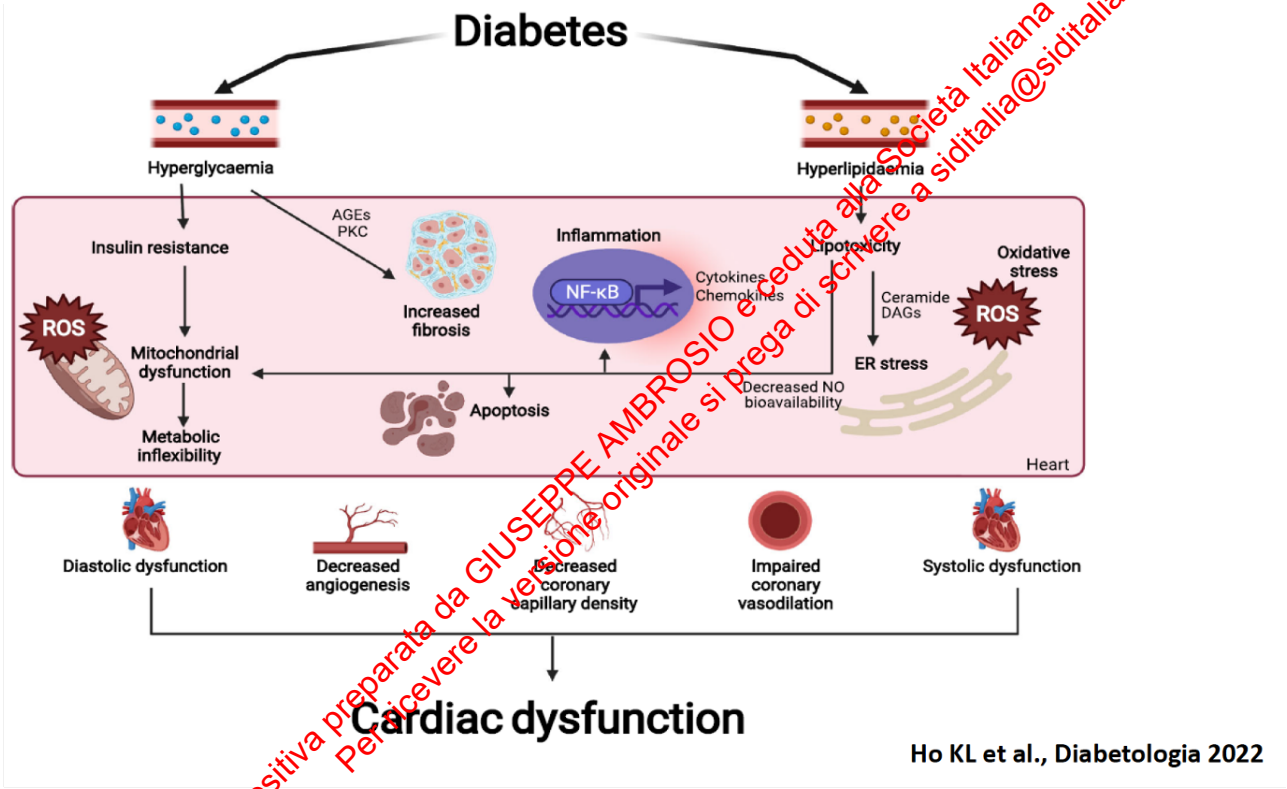


CRP, C-reactive protein; IL-1b, interleukin-1b; IL-6, interleukin-6; LDL-C, low-density lipoprotein cholesterol; MCP-1, monocyte chemoattractant protein-1; MMP, matrix metalloproteinase; TNF-α, tumor necrosis factor-α.

The **anti-atherosclerotic targets** of **GLP-1RAs** include:

(1) suppression of **inflammatory cytokine** production and secretion;
(2) monocyte recruitment, **adhesion**, and **infiltration**;
(3) M1 pro-inflammatory macrophage polarization and **foam cell formation**;
(4) intimal thickening induced by the differentiation of **vascular smooth muscle cells** into a proliferative, migratory phenotype;
(5) fatty lesion formation, **plaque rupture**, and thrombosis.

Park B, et al. Am J Physiol Heart Circ Physiol. 2024;326(5):H1159-H1176.



Ho KL et al., Diabetologia 2022

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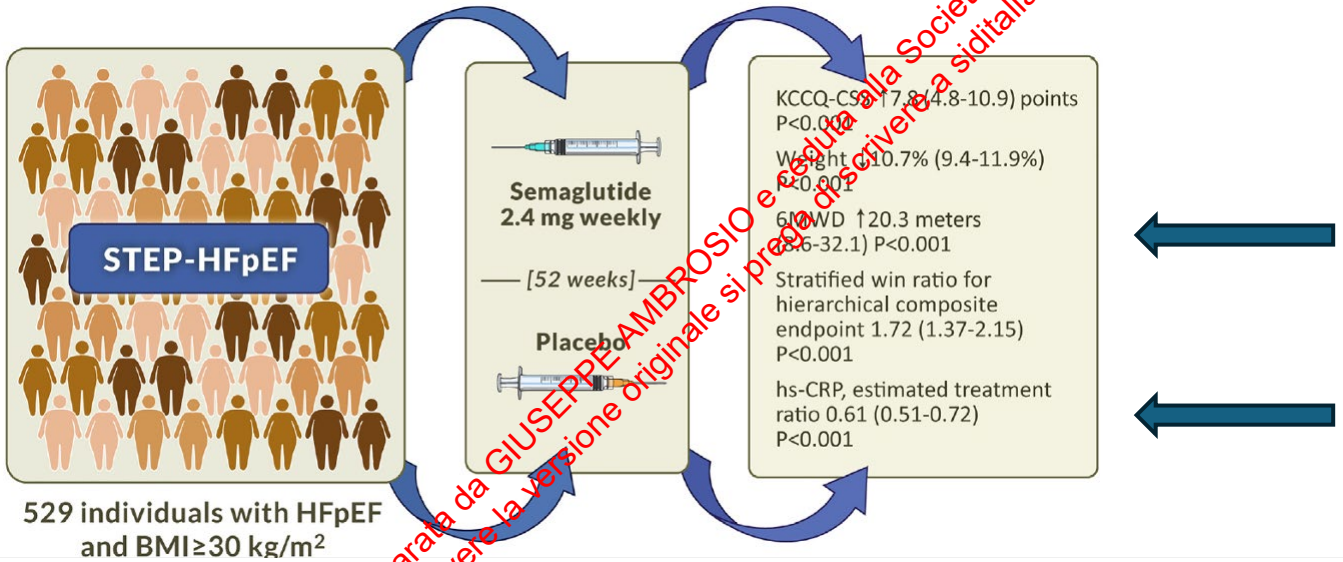

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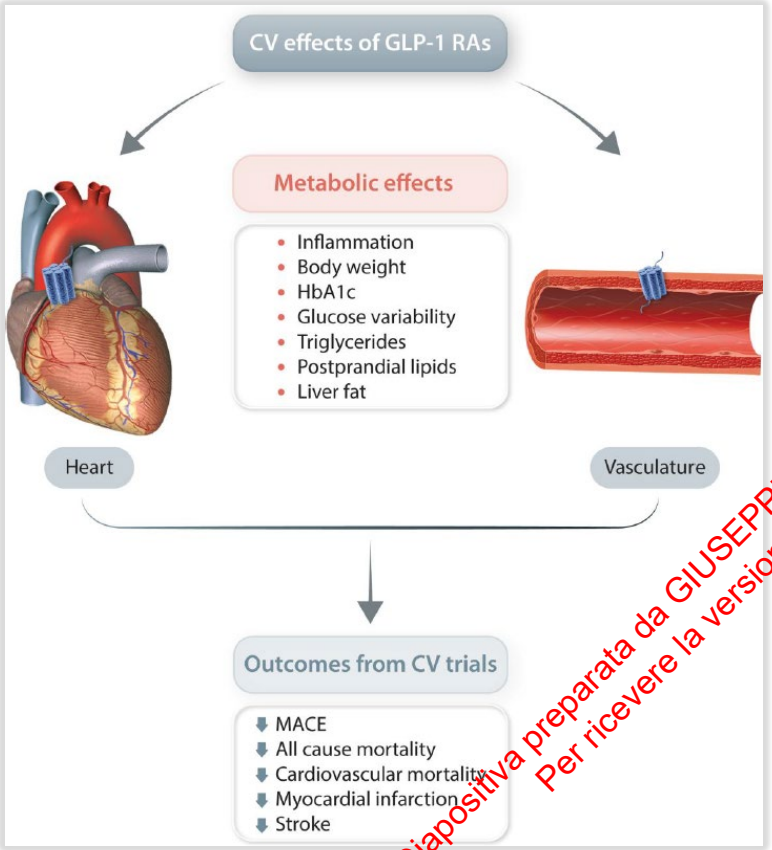
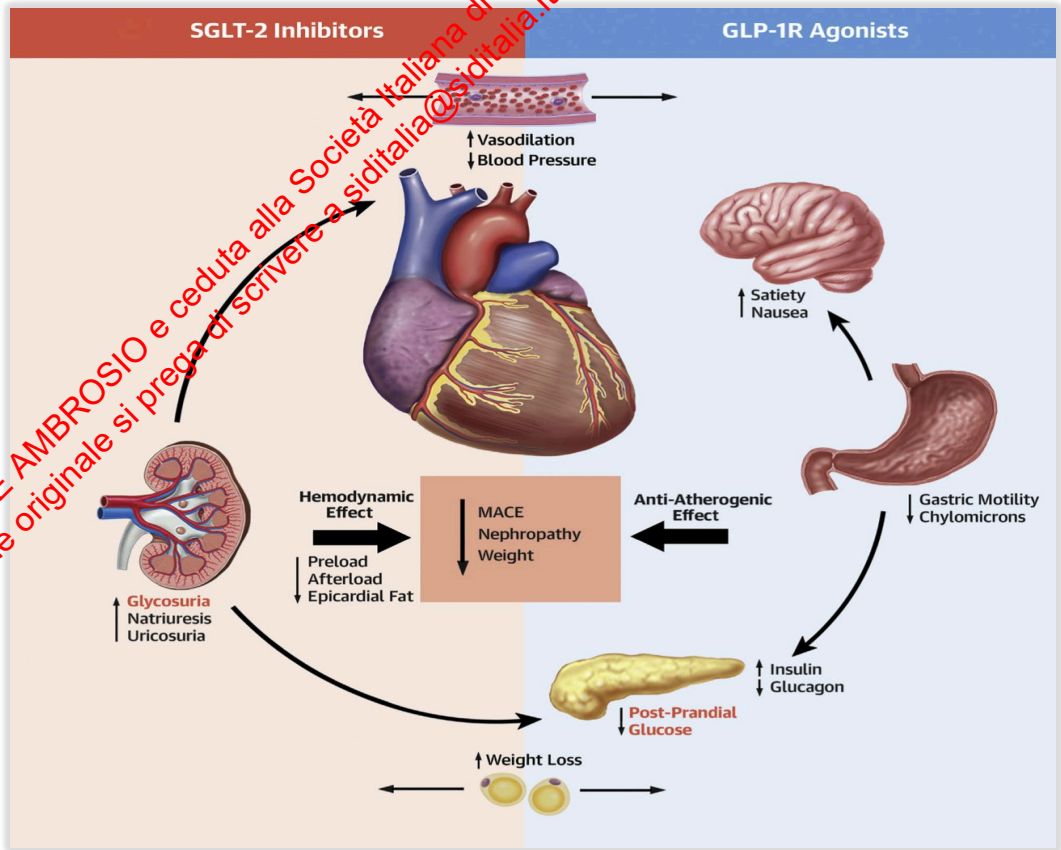
Diversity of Physiologic Effects of GLP-1RA and SGLT-2i

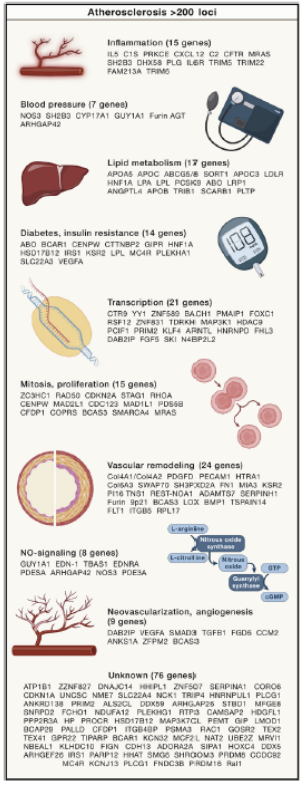


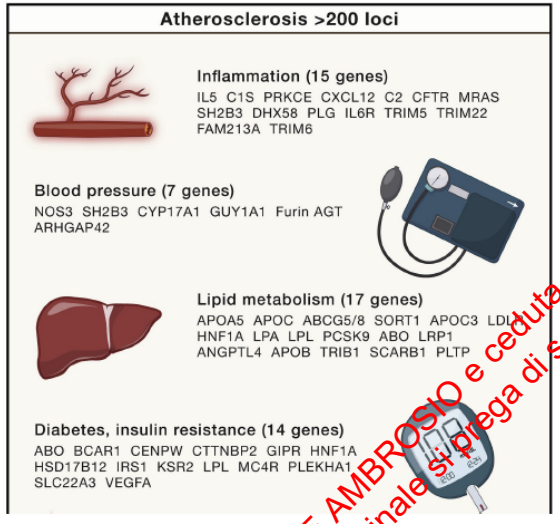


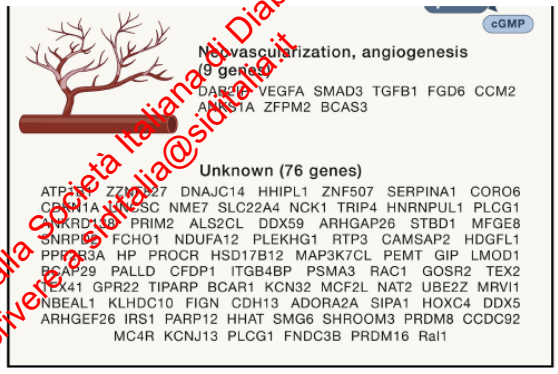
Madsbad S and Holst JJ. Cardiovasc Res. 2023;119(4):886-904.

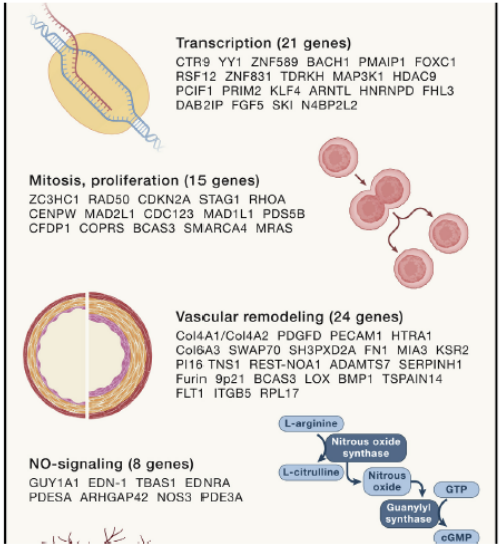
Wilcox T, et al. J Am Coll Cardiol. 2020;75(16):1956-1974.

Genetic factors contributing to atherosclerosis susceptibility



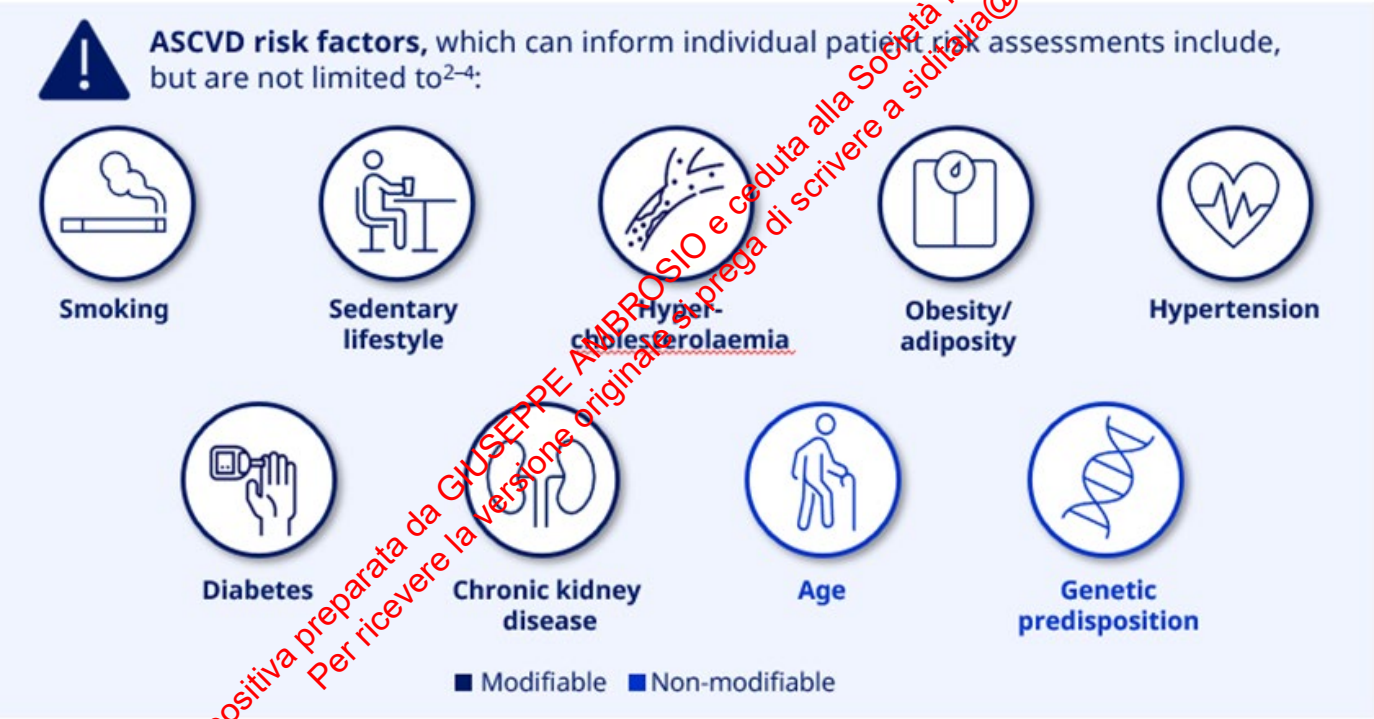






Cell 2022 1851630-1645DOI: (10.1016/j.cell.2022.04.004)

Over 70% of ASCVD worldwide is caused by modifiable risk factors[1]



ASCVD, atherosclerotic cardiovascular disease.

1. Yusuf S, et al. Lancet. 2020; 395:795–808; 2. An J et al. J Am Heart Assoc. 2020;9:e017310; 3. Lampreo-Montealegre JA et al. Hypertension 2018;72:602–609; 4. Herrington W et al. Circ Res 2016;118:535–546.

Presentation Overview

Historical Perspective

1858 Virchow proposes inflammation as central to atherogenesis

1976 Ross & Glomset publish 'Response-to-Injury' hypothesis

1997 Ridker et al. link CRP to future MI risk (NEJM)

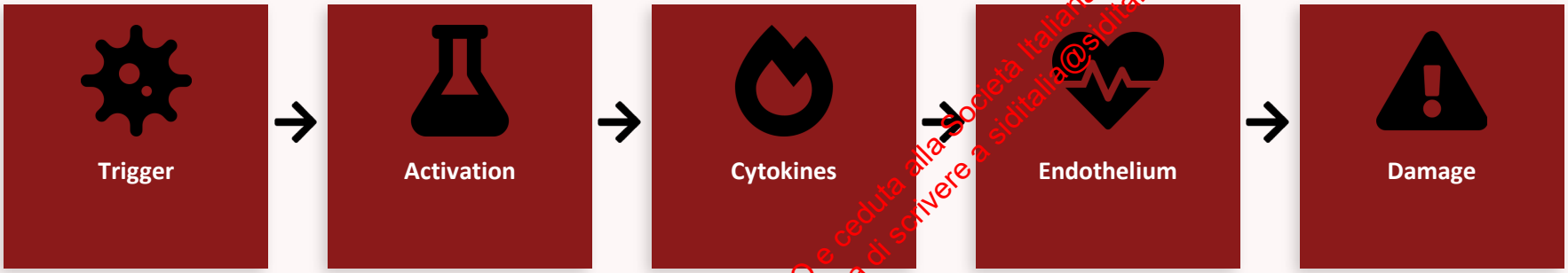
1999 Ross reframes atherosclerosis as 'Inflammatory Disease'

2008 JUPITER trial: Rosuvastatin + CRP reduction → ↓ CV events

2017 CANTOS: Canakinumab ↓ recurrent MI independent of lipids

2019 COLCOT: Colchicine post-MI reduces ischemic cardiovascular events

Innate Immunity & Vascular Inflammation



oxLDL, DAMPs, PAMPs activate PRRs (TLR4, NLRP3)

Monocyte / macrophage polarization (M1 phenotype)

TNF-α, IL-1β, IL-6 IL-18, MCP-1 release

ICAM-1, VCAM-1, E-selectin upregulation

Leukocyte recruitment Foam cell formation

Key Concept: Chronic, low-grade vascular inflammation differs fundamentally from acute inflammatory responses. Persistent activation of innate immune pathways within the arterial wall drives disease progression through self-amplifying feedback loops involving oxidative stress, NF-κB signaling, and efferocytosis failure.

Atherosclerosis: The Inflammatory Paradigm

Pathological Stages

Endothelial activation

oxLDL retention, shear stress → VCAM-1/ICAM-1

Monocyte recruitment

MCP-1–driven diapedesis, differentiation to macrophage

Foam cell formation

Unregulated SR-A/CD36 uptake of oxLDL

Fatty streak

Earliest visible lesion; T-cell infiltration

Fibrous plaque

SMC migration, collagen synthesis, necrotic core

Vulnerable plaque

Thin fibrous cap, lipid-rich core, high macrophage burden

Key Molecular Players

ox-LDL

Triggers endothelial TLR activation; promotes foam cell formation

MCP-1 (CCL2)

Monocyte chemoattractant; drives plaque infiltration

TNF-α / IL-1β

Pro-inflammatory cytokines; amplify NF-κB signaling

NLRP3 inflammasome

Caspase-1 activation → IL-1β / IL-18 maturation

MMPs (1, 3, 9)

Extracellular matrix degradation; cap thinning

IFN-γ

Inhibits SMC collagen synthesis; destabilizes fibrous cap

Clinical Inflammatory Biomarkers

hsCRP

High-sensitivity C-Reactive Protein

Risk Stratification

- <1 mg/L → Low risk
- 1–3 mg/L → Intermediate
- >3 mg/L → High risk

Pentameric acute-phase reactant; synthesized by hepatocytes in response to IL-6. Independent predictor of MACE (OR ~2x).

IL-6

Interleukin-6

Risk Stratification

- Quartile 4 vs 1: HR ~1.8
- Mendelian randomization supports causality

Pleiotropic cytokine linking inflammation to thrombosis; activates hepatic CRP / fibrinogen synthesis.

Lp-PLA2

Lipoprotein-associated Phospholipase A_2

Risk Stratification

- Mass >200 ng/mL → ↑ risk
- Activity >200 nmol/min/mL

Vascular-specific inflammatory marker; generated by macrophages in plaques; produces pro-inflammatory lysophospholipids.

Endothelial Dysfunction & NF-κB Signaling

Endothelial Dysfunction

- **↓ eNOS / NO bioavailability**
  Impaired vasodilation, ↑ vascular tone
- **↑ Reactive Oxygen Species**
  Superoxide quenches NO; peroxynitrite formation
- **↑ ICAM-1, VCAM-1 expression**
  Leukocyte adhesion and transmigration
- **Glycocalyx degradation**
  Barrier function loss; platelet activation
- **↑ PAI-1, TF expression**
  Prothrombotic shift of endothelial phenotype
- **Paracrine IL-6 / IL-8**
  Amplifies local and systemic inflammation

NF-κB Pathway

Stimulus
oxLDL, cytokines, ROS, AGEs

→

IKKβ activation
Phosphorylates IκBα → ubiquitination

→

IκBα degradation
26S proteasome-mediated proteolysis

→

p65/p50 nuclear translocation
Binding to κB response elements

→

Target gene expression
COX-2, iNOS, IL-6, TNF-α, VCAM-1, MCP-1

→

Amplification
Autocrine / paracrine cytokine loops

Plaque Vulnerability & Rupture

~70%

of ACS events

arise from non-obstructive plaques (<70% stenosis)

TCFA

Thin-Cap Fibroatheroma

Cap thickness <65 µm; macrophage density >26%

4–5×

↑ MMP expression

in vulnerable vs stable plaques (MMP-1, -3, -9, -13)

Determinants of Plaque Rupture

- **Biomechanical stress**
  Circumferential wall stress peak at plaque shoulders
- **Inflammatory cell burden**
  Macrophage-derived proteases degrade collagen matrix
- **Necrotic core expansion**
  Efferocytosis failure → secondary necrosis → DAMP release
- **Intraplaque hemorrhage**
  Vasa vasorum neovascularization → hemorrhage & rapid growth
- **Cap thinning**
  ↓ TGF-β / ↑ IFN-γ impairs SMC collagen synthetic capacity

Therapeutic Targets: Anti-inflammatory Strategies

Statins

HMG-CoA reductase inhibition

Mechanism

↓ CRP, ↓ NF-κB, ↑ eNOS, ↓ ROS

Evidence

Multiple RCTs; ↓ MACE 25-35%

Canakinumab

Anti-IL-1β monoclonal antibody

Mechanism

NLRP3 inflammasome blockade

Evidence

CANTOS: ↓ non-fatal MI (HR 0.83)

Colchicine

Tubulin polymerization inhibitor

Mechanism

↓ NLRP3 activation, ↓ IL-1β, ↓ neutrophil function

Evidence

COLCOT, LoDoCo2: ↓ CV events ~30%

Methotrexate

Folate antagonist / adenosine ↑

Mechanism

↓ IL-1, IL-6, TNF-α

Evidence

CIRT: No CV benefit vs placebo (2019)

Ziltivekimab

Anti-IL-6 ligand antibody

Mechanism

↓ CRP, fibrinogen, SAA

Evidence

RESCUE: Phase 2 positive; ZEUS ongoing

Tocilizumab

IL-6 receptor antagonist

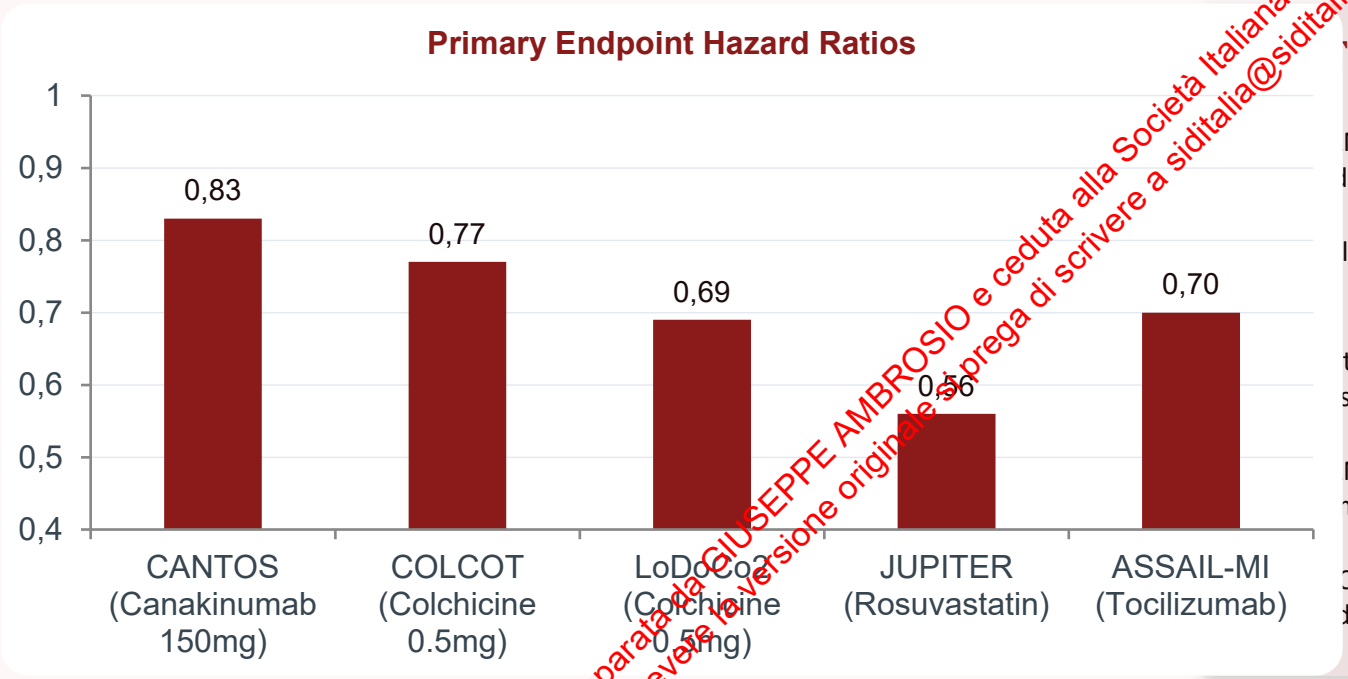
Mechanism

↓ CRP, fibrinogen

Evidence

Post-ACS trials ongoing (ASSAIL-MI)

Landmark Trials: CANTOS, COLCOT & Beyond



akeaways

NTOS confirmed inflammation causality lependent of LDL-C

lchicine benefits consistent across post- & chronic CAD populations

ti-inflammatory benefit independent of seline hsCRP or statin use

NTOS: ↑ fatal infections offset CV gain in me risk strata

CRP reduction correlates with CV event duction

Proof of concept established: targeting IL-1β and tubulin pathways reduces recurrent cardiovascular events in high-risk patients.

Emerging Targets & Precision Medicine

NLRP3 Inflammasome Inhibitors

MCC950 / Dapansutrile: preclinical MI protection. Phase 2 trials underway.

Trained Immunity Modulation

Epigenetic reprogramming of monocytes via β-glucan / BCG; may reduce CV inflammation.

Clonal Hematopoiesis (CHIP)

TET2/DNMT3A mutations → hyperinflammatory macrophages → 2× CVD risk. Emerging target.

Neutrophil Extracellular Traps

NETs activate platelets and endothelium; PAD4 inhibitors under investigation post-ACS.

Gut Microbiome & TMAO

Dysbiosis-driven TMAO promotes macrophage cholesterol accumulation; dietary/FMT interventions.

RNA Therapeutics

siRNA targeting PCSK9, lipoprotein(a), ANGPTL3; dual lipid + inflammation targeting.

Summary & Future Directions

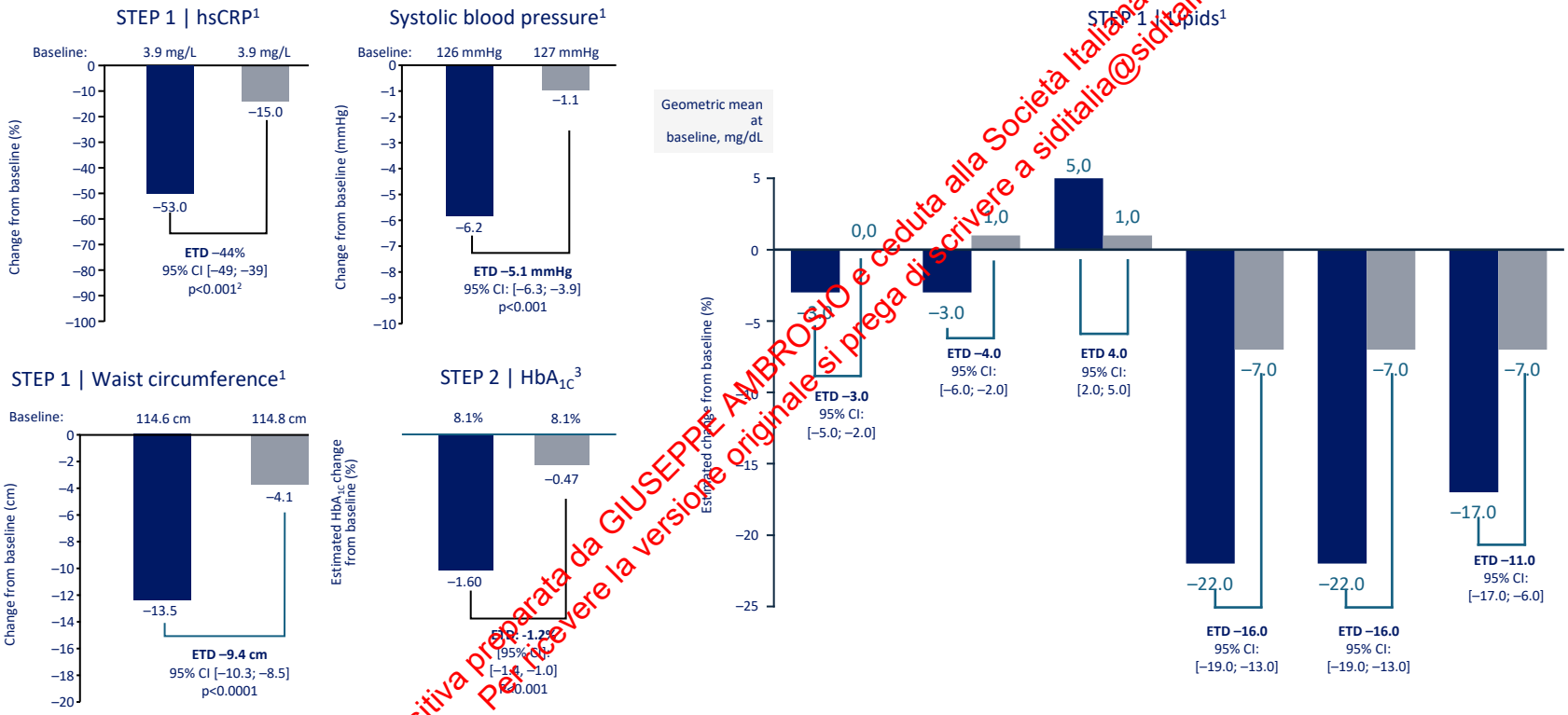
- Inflammation is a causal, not merely associative, driver of atherosclerosis and acute coronary syndromes
- The NLRP3 → IL-1β → IL-6 → CRP axis represents a key therapeutic pathway with validated clinical evidence
- Colchicine is now guideline-endorsed (ACC/AHA 2023) for secondary prevention in stable CAD
- Residual inflammatory risk (hsCRP >2 mg/L on statin therapy) identifies patients for targeted anti-inflammatory therapy
- Emerging science: CHIP, NETs, trained immunity, and gut microbiome expand the inflammatory CVD paradigm
- Precision medicine approaches matching biomarker profiles to specific anti-inflammatory therapies represent the frontier

"Inflammation is not merely a consequence of heart disease — it is its engine."

Oral Semaglutide improves «classical» CV risk factors

Changes at 26 weeks		HbA_{1c}	SBP (mmHg)	Lipids	Weight (Kg)	Waist (cm)
PIONEER 2	Semaglutide PO	-1.3*	-5	↓TC*, ↓LDL*	-3.7*	-3.7*
	Empagliflozin	-0.9	-5		-3.7	-3.0
PIONEER 3	Semaglutide PO	-1.3*	-3	↓TC*, ↓LDL*, ↓TG*	-3.1*	-2.3*
	Sitagliptin	-0.8	-2		-0.6	-0.6
PIONEER 4	Semaglutide PO	-1.2	-4		-4.4*	-4.2*
	Liraglutide	-1.1	-3		-3.1	-2.9
PIONEER 7	Semaglutide PO	-1.3*	-4	↓TC*, ↓LDL*	-2.6*	na
	Sitagliptin	-0.8	-2		-0.7	

Semaglutide 2.4 mg has benefits on CV risk factors: STEP



CI, confidence interval; CV, cardiovascular; ETD, estimated treatment difference; ETR, estimated treatment ratio; HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

1. Wilding et al. N Engl J Med 2021;384:989-1002; 2. Kosoribod M et al. Poster presented at the American College of Cardiology (ACC) conference, May 15–17 2021, virtual meeting; 3. Davies M et al. Lancet 2021;397:971–84.

Research Article

Effect of GLP-1/GLP-1R on the Polarization of Macrophages in the Occurrence and Development of Atherosclerosis

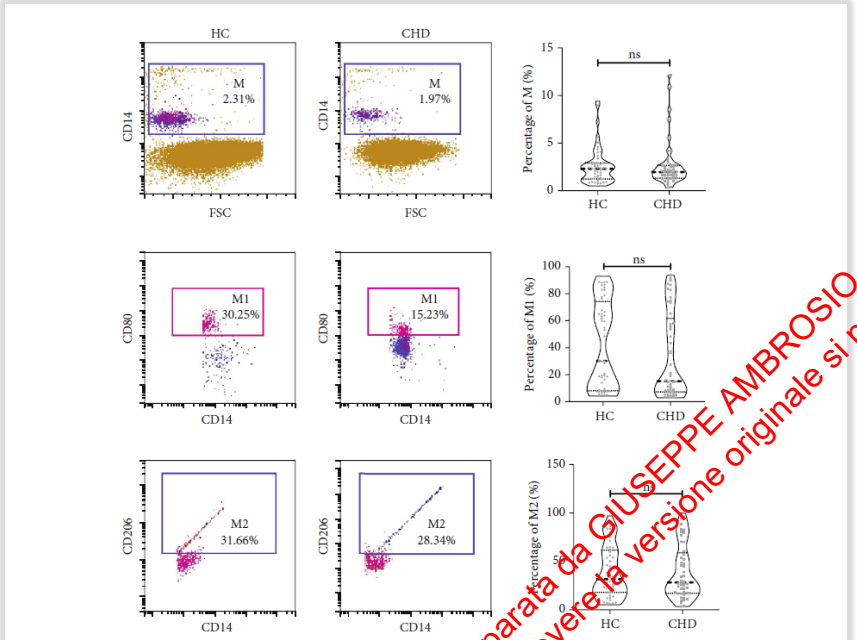


Figure 1: Expression difference of total macrophage, M1, and M2 macrophage between CHD group and HC group. Data are represented as mean ± SEM. $^{*}P < 0.05$, $^{**}P < 0.01$. M: macrophage, labeled by CD14+ molecule; M1: M1 macrophage, labeled by CD14+ and CD80+ molecule; M2: M2 macrophage, labeled by CD14+ and CD206+ molecule.

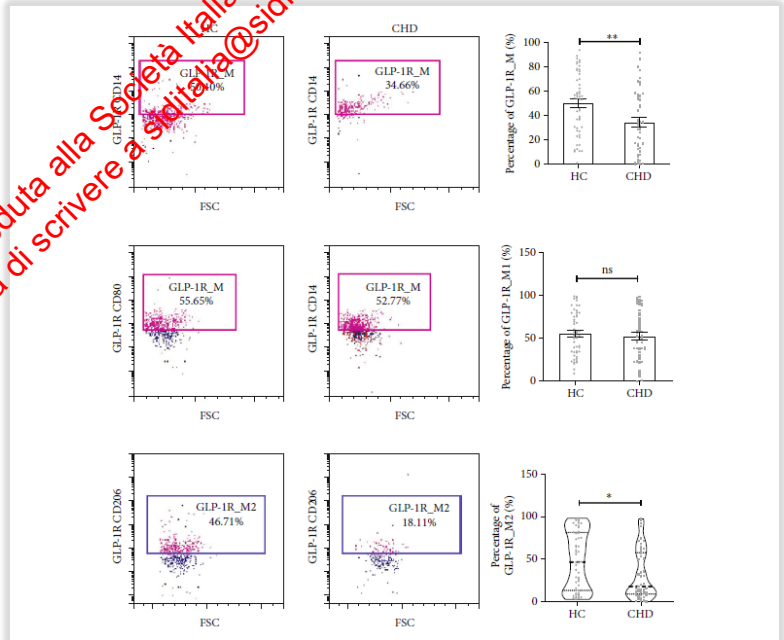
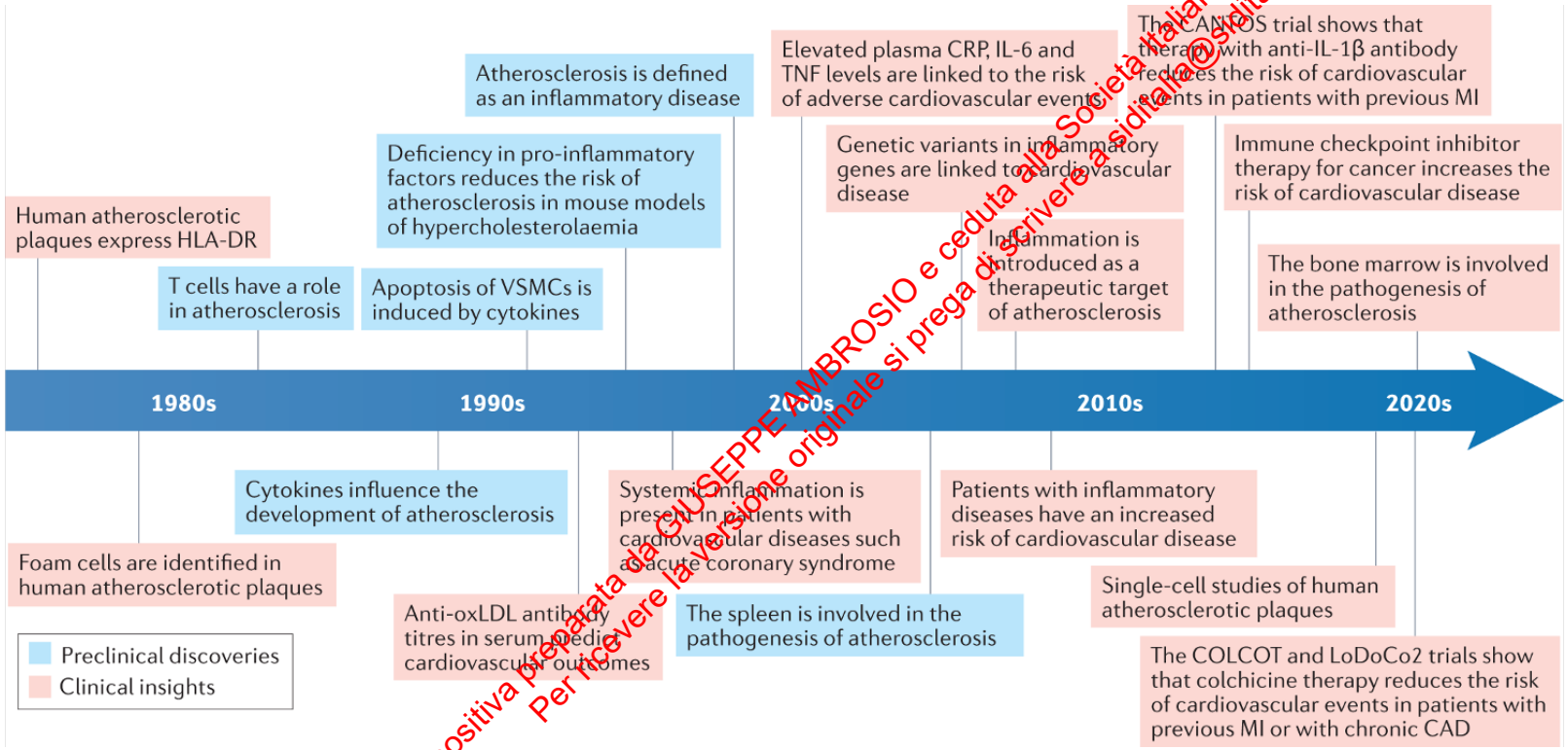


Figure 2: Expression difference of GLP-1R on the surface of total macrophage, M1, and M2 macrophage between two groups. Data are represented as mean ± SEM. $^{*}P < 0.05$, $^{**}P < 0.01$. GLP-1R_M: GLP-1R on the surface of macrophage, labeled by CD14+ and GLP-1R+ molecule; GLP-1R_M1: GLP-1R on the surface of M1 macrophage, labeled by CD14+, CD80+, and GLP-1R+ molecule; GLP-1R_M2: GLP-1R on the surface of M2 macrophage, labeled by CD14+, CD206+, and GLP-1R+molecule.

Conclusion: GLP-1R agonist is independent of the hypoglycemic effect of T2DM and has protective effect on cardiovascular system. GLP-1R may regulate the polarization of macrophages toward M2, thus playing a protective role in the progression of coronary atherosclerosis.

How Inflammation made its way through atherosclerosis



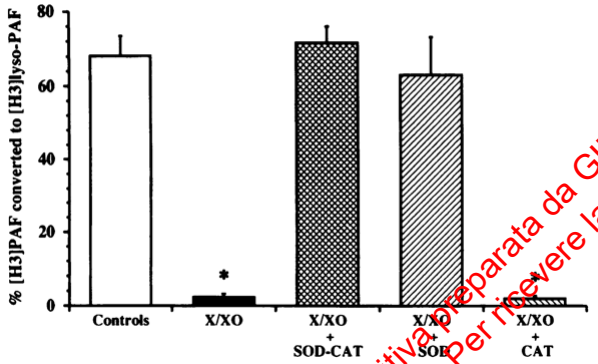
Additional pro-inflammatory effects of oxidants in Diabetes

Oxygen Radicals Inhibit Human Plasma Acetylhydrolase, the Enzyme That Catabolizes Platelet-activating Factor

Giuseppe Ambrosio, Alfonso Oriente,* Claudio Napoli, Giuseppe Palumbo,‡ Paola Chiariello, Gianni Marone,* Mario Condorelli, Massimo Chiariello, and Massimo Triggiani*

J. Clin. Invest. **1994**

Exposure of low density lipoproteins to oxidants



C Napoli, M Triggiani, G Palumbo, M Condorelli, M Chiariello, G Ambrosio

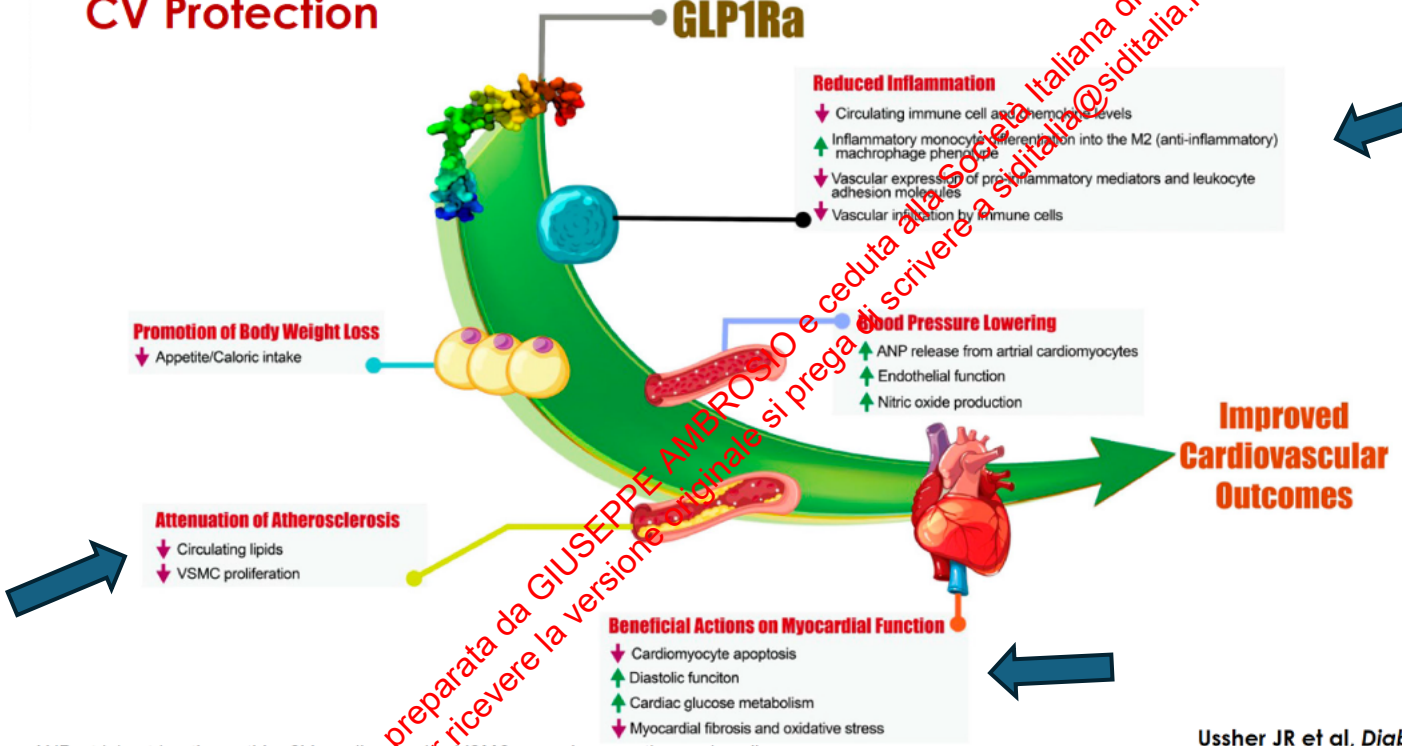
Basic Res Cardiol, 1997

Hyperglycemia induces glycosylation of low density lipoproteins

LDL Glycosylation:
- **enhances oxygen radical-induced modifications of human LDL**
- **decreases their acetylhydrolase activity**

These phenomenona may synergistically contribute to enhance and/or accelerate the progression of atherosclerosis in diabetic patients

Potential Mechanisms Contributing to GLP-1RA-mediated CV Protection



ANP, atrial natriuretic peptide; CV, cardiovascular; VSMC, vascular smooth muscle cells

Ussher JR et al, *Diabetes* 2022