Opzioni di trattamento della dislipidemia nel paziente diabetico intollerante alle statine con IRC

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2019 ESC/EAS guidelines: CV risk categories

Very high risk	High risk	Moderate risk	Low risk
People with any of the following: • Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularisation (PCI, CABG, and other arterial revascularisation procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound • **DM with target organ damage,* or at least three major risk factors, or early onset of T1DM of long duration (>20 years)** • Severe CKD (eGFR <30 mL/min/1.73 m²) • A calculated SCORE ≥10% for 10-year risk of fatal CVD • FH with ASCVD or with another major risk factor	**People with:** • Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg • Patients with FH without other major risk factors • **Patients with DM without target organ damage, with DM duration ≥10 years or another additional risk factor** • Moderate CKD (eGFR 30—59 L/min/1.73 m^2) • A calculated SCORE ≥ 5% and <10% for 10-year risk of fatal CVD	• **Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors** • Calculated SCORE ≥1 % and <5% for 10-year risk of fatal CVD	• Calculated SCORE <1% for 10-year risk of fatal CVD

*Defined as microalbuminuria, retinopathy, or neuropathy. ASCVD = atherosclerotic cardiovascular disease; ACS = acute coronary syndrome; BP = blood pressure; CABG = coronary artery bypass graft surgery; CKD = chronic kidney disease; CT = computed tomography; CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; SCORE = Systematic Coronary Risk Estimation; T1DM = type 1 DM; T2DM =type 2 DM; TC = total cholesterol; TIA = transient ischaemic attack.

ESC European Society of Cardiology
European Heart Journal (2019) 00, 1–78
doi:10.1093/eurheartj/ehz455
ESC/EAS GUIDELINES

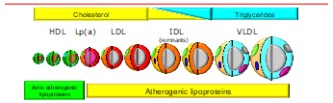
2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

Obiettivi terapeutici raccomandati per la terapia LDL-C e NON-HDL per la prevenzione cardiovascolare

Primo target: COLESTEROLO LDL

Secondo target: COLESTEROLO NON HDL (CT-HDL)

Lipoproteine aterogene e anti-aterogene



Categoria di rischio	goals	
	LDL	NON-HDL (CT-HDL)
Rischio molto elevato	<55 mg/dL >50% ↓	<85 mg/dL
Alto rischio	<70 mg/dL >50%↓	<100 mg/dL >50%↓
Rischio moderato	<100 mg/dL	<130 mg/dL
Basso rischio	<115 mg/dL	<145 mg/dL

Per i pazienti con ASCVD che manifestano un secondo evento vascolare entro 2 anni durante l'assunzione della terapia a base di statine massimamente tollerata, si raccomanda un obiettivo di LDL-C di <1,0 mmol/L (<40 mg / dL)

LDL-C = low-density lipoprotein cholesterol.
Adapted from: Catapano AL, et al. Eur Heart J 2016;37:2999-3058. Mach F, et al. Eur Heart J 2019. doi:10.1093/eurheartj/ehz455.

La maggiore diminuzione della mortalità e morbilità che può essere ottenuta con le statine si osserva nei pazienti a più alto rischio di CVD come il diabete di tipo 2 (4S, HPS, CARE, LIPID, GREACE)

		RR reduction	
DM n. 5618	Statins vs Placebo	All subjects	Diabetes
		-29.7%	-37.7%

PROBLEMI APERTI in tema di INTOLLERANZA ALLE STATINE:

Chi stabilisce l'intollerabilità del sintomo?

Chi deve avviare e seguire il percorso diagnostico?

Come comportarsi sul dato anamnestico?

Table 3 Clinical factors potentially predisposing to statin-associated muscle symptoms

- Advanced age
- Female gender
- Asian ethnicity
- Low body mass index (frailty)
- Pre-existing muscle/joint/tendon conditions
- Chronic pain disorders
- Diabetes mellitus
- Obesity
- Neuromuscular conditions
- Chronic renal or hepatic disease
- Hypothyroidism
- Vitamin D deficiency
- Severe trauma (eg, major surgery)
- Physical exertion
- Family history of myalgia—with or without statin therapy
- Interacting agents—potentially increasing statin serum concentrations
  - Amiodarone
  - Azole antifungals—multiple agents
  - Cyclosporine
  - Gemfibrozil
  - Diltiazem
  - Verapamil
  - Macrolide antibiotics—clarithromycin, erythromycin
  - Protease inhibitors—multiple agents
  - Excess grapefruit/juice consumption
- Other medications/factors associated with musculoskeletal symptoms
  - Substances of abuse—alcohol, amphetamines, caffeine, cocaine, heroin
  - Colchicine
  - Cyclosporine
  - Antiviral agents—zidovudine, ritonavir, didanosine
  - Corticosteroids
  - Antimalarials—hydroxychloroquine
  - Antipsychotics—haloperidol, risperidone
  - Daptomycin
  - Danazol
  - Dipeptidyl peptidase-4 (DPP-4) inhibitors—primarily arthralgia

Definizioni e prevalenza di intolleranza 9.1%

National Lipid Association (NLA): **7.0%**

l'intolleranza alle statine è definita come un effetto avverso che peggiora la qualità della vita tale da determinare una riduzione o una interruzione del farmaco

International Lipid Expert Panel (ILEP): **6.7%**

l'intolleranza alle statine è definita come l'incapacità a tollerare la dose di statina necessaria per ridurre in modo efficace il proprio rischio cardiovascolare.

European Atherosclerosis Association (EAS): **5.9%**

intolleranza muscolare, sindrome clinica caratterizzata da sintomi significativi ed anomalie dei biomarcatori che vengono documentati da un "challenge-dechallange-re-challenge" impiegando almeno due statine differenti

EFFETTI COLLATERALI STATINE:

	TIPO	FREQUENZA
1. MUSCOLO	Mialgie, crampi muscolari Miosite (rara) Rabdomiolisi	Non chiara (10-15%) aspecifica 1/10.000/anno 1-3 casi/100.000/anno
2. FEGATO	Lieve aumento di ALT Insufficienza epatica	0.5-2% Raro
3. DIABETE	Aumentato rischio di alterato metabolismo glucidico e sviluppo di DM	Rischio assoluto incrementato dello 0.2%
4. RENE	Proteinuria	Frequenza aumentata (Rosu)

Dichiarazione da sottoscrivere su scheda AIFA per la diagnosi di intolleranza alle statine

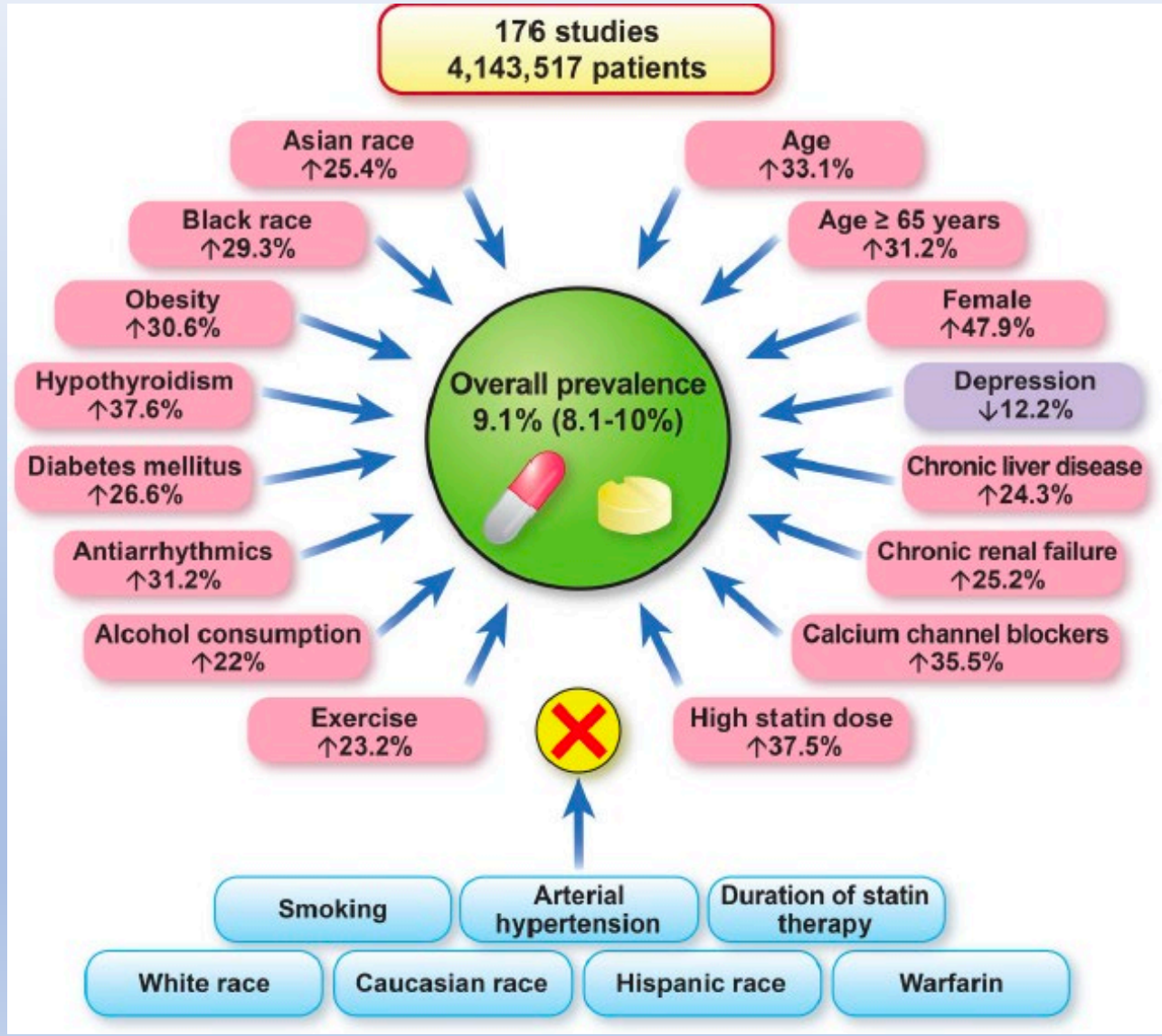
Il motivo del mancato trattamento con statine è l'intolleranza, secondo la seguente definizione: i) impossibilità a tollerare almeno 2 statine di cui una alla dose iniziale (rosuvastatina 5 mg/die, atorvastatina 10 mg/die, simvastatina 10 mg/die, lovastatina 20 mg/die, pravastatina 40 mg/die, fluvastatina 40 mg/die) ed una seconda statina ad una qualsiasi dose; ii) associazione con uno o più eventi avversi correlati all'uso di statine confermati e non tollerabili oppure associazione con significative alterazioni dei biomarkers (CPK > 10 × ULN, eseguito in assenza di sforzi muscolari); iii) risoluzione o netto miglioramento della sintomatologia, normalizzazione o netta riduzione dei biomarkers alla sospensione/riduzione della dose di statina;
iv) sintomatologia/innalzamento dei biomarkers non attribuibile ad altre cause (interazioni farmacologiche o condizioni cliniche note che possono aumentare il rischio di intolleranza alle statine quali ad es. ipotiroidismo, patologie muscolari o importante aumento dell'attività fisica)
(International Lipid Expert Panel - Position paper, Banach 2015) *

Fattori che all'analisi multivariata si sono dimostrati associati ad un rischio aumentato di intolleranza alle statine

- **età**, sia intesa some variabile continua [odds ratio (OR) 1.33, 95% CI 1.25–1.41; P=0.04], sia come **età superiore > 65 anni** (OR 1.31, 95% CI 1.22–1.45; P=0.04)
- **sesso femminile** (OR 1.47, 95% CI 1.38–1.53; P=0.007).
- **obesità** (OR 1.30, P=0.02), il
- **diabete mellito** (OR 1.26, P=0.02)
- **ipotiroidismo** (OR 1.37, P=0.01),
- **malattie epatiche croniche** (OR 1.24, P=0.03) e
- **insufficienza renale** (OR 1.25, P=0.03)
- **consumo di alcool** (OR 1.22, P=0.03) l'
- **esercizio fisico** (OR 1.23, P=0.03),
- Impiego di farmaci: **calcio-antagonisti** (OR 1.31, P=0.03) e di **anti-aritmici** (OR 1.35, P=0.03).
- **l'incremento della dose delle statine** (OR 1.37, P=0.01) ma non la durata del follow-up (OR 1.06, P=0.48) correla con un aumentato rischio di sospensione del trattamento.

La depressione è stata trovata un'associazione negativa (OR 0.88, P=0.04)

L'ipertensione arteriosa e l'abitudine tabagica non hanno dimostrato nessun tipo di influenza



STATIN ASSOCIATED MUSCLE SYMTPOMS (SAMS)

Table 1 Proposed statin myalgia clinical index score

Clinical symptoms—new or increased unexplained muscle symptoms	
Regional distribution/pattern	
Symmetric hip flexors/thigh aches	3
Symmetric calf aches	2
Symmetric upper proximal aches	2
Nonspecific asymmetric—intermittent	1
Temporal pattern	
Symptoms onset <4 wk	3
Symptoms onset 4–12 wk	2
Symptoms onset >12 wk	1
Dechallenge	
Improves on withdrawal—<2 wk	2
Improves on withdrawal—2–4 wk	1
Does not improve upon withdrawal—>4 wk	0
Challenge	
Same symptoms reoccur on rechallenge—<4 wk	3
Same symptoms reoccur on rechallenge—4–12 wk	1
Statin myalgia clinical index score (total points)	
Probable	9–11
Possible	7–8
Unlikely	<7

Rhabdomyolisis (1-3/100.000 pts/years)
Myalgya with or without CK elevation
Myositis myalgia CK >10 times ULN

Higher probability:
- In elderly
- With statin metabolized by CYP3A4 (such as atorvastatin, simvastatin and lovastatin) for interaction with other drugs or food

Stroes, Thompson et al. Statin-associated muscle symtptoms: impact on statin therapy- European Atherosclerosis Society Consensus Panel Statementon assessment, aetiology and managment European Heart Journal 2015
Backes , Ruisinger et al. Statin-associated muscle symptoms—Managing the highly intolerant. J Clin Lipidol Feb 2017
Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA, The National Lipid Association's Muscle Safety Expert P. An assessment by the Statin Muscle Safety Task Force: 2014 update. J Clin Lipidol. 2014;8:S58–S71.

La lezione del GAUSS-3…..

Research

Original Investigation

Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance The GAUSS-3 Randomized Clinical Trial

Steven E. Nissen, MD; Erik Stroes, MD, PhD; Ricardo E. Dent-Acosta, MD; Robert S. Rosenson, MD; Sam J. Lehman, MBBS, PhD; Naveed Sattar, MD, PhD; David Preiss, MD; Eric Bruckert, MD; Richard Ceška, MD; Norman Lepor, MD; Christie M. Ballantyne, MD; Ioanna Gouni-Berthold, MD; Mary Elliott, MS; Danielle M. Brennan, MS; Scott M. Wasserman, MD; Ransi Somaratne, MD, MBA; Rob Scott, MD; Evan A. Stein, MD, PhD; for the GAUSS-3 Investigators

IMPORTANCE Muscle-related statin intolerance is reported by 5% to 20% of patients.

OBJECTIVE To identify patients with muscle symptoms confirmed by statin rechallenge and compare lipid-lowering efficacy for 2 nonstatin therapies, ezetimibe and evolocumab.

DESIGN, SETTING, AND PARTICIPANTS Two-stage randomized clinical trial including 511 adult patients with uncontrolled low-density lipoprotein cholesterol (LDL-C) levels and history of intolerance to 2 or more statins enrolled in 2013 and 2014 globally. Phase A used a 24-week crossover procedure with atorvastatin or placebo to identify patients having symptoms only with atorvastatin but not placebo. In phase B, after a 2-week washout, patients were randomized to ezetimibe or evolocumab for 24 weeks.

INTERVENTIONS Phase A: atorvastatin (20 mg) vs placebo. Phase B: randomization 2:1 to subcutaneous evolocumab (420 mg monthly) or oral ezetimibe (10 mg daily).

MAIN OUTCOME AND MEASURES Coprimary end points were the mean percent change in LDL-C level from baseline to the mean of weeks 22 and 24 levels and from baseline to week 24 levels.

RESULTS Of the 491 patients who entered phase A (mean age, 60.7 [SD, 10.2] years; 246 women [50.1%]; 170 with coronary heart disease [34.6%]; entry mean LDL-C level, 212.3 [SD, 67.9] mg/dL), muscle symptoms occurred in 209 of 491 (42.6%) while taking atorvastatin but not while taking placebo. Of these, 199 entered phase B, along with 19 who proceeded directly to phase B for elevated creatine kinase (N = 218, with 73 randomized to ezetimibe and 145 to evolocumab; entry mean LDL-C level, 219.9 [SD, 72] mg/dL). For the mean of weeks 22 and 24, LDL-C level with ezetimibe was 183.0 mg/dL; mean percent LDL-C change, −16.7% (95% CI, −20.5% to −12.9%), absolute change, −31.0 mg/dL and with evolocumab was 103.6 mg/dL; mean percent change, −54.5% (95% CI, −57.2% to −51.8%); absolute change, −106.8 mg/dL ($P < .001$). LDL-C level at week 24 with ezetimibe was 181.5 mg/dL; mean percent change, −16.7% (95% CI, −20.8% to −12.5%); absolute change, −31.2 mg/dL and with evolocumab was 104.1 mg/dL; mean percent change, −52.8% (95% CI, −55.8% to −49.8%); absolute change, −102.9 mg/dL ($P < .001$). For the mean of weeks 22 and 24, between-group difference in LDL-C was −37.8%; absolute difference, −75.8 mg/dL. For week 24, between-group difference in LDL-C was −36.1%; absolute difference, −71.7 mg/dL. Muscle symptoms were reported in 28.8% of ezetimibe-treated patients and 20.7% of evolocumab-treated patients (log-rank $P = .17$). Active study drug was stopped for muscle symptoms in 5 of 73 ezetimibe-treated patients (6.8%) and 1 of 145 evolocumab-treated patients (0.7%).

CONCLUSIONS AND RELEVANCE Among patients with statin intolerance related to muscle-related adverse effects, the use of evolocumab compared with ezetimibe resulted in a significantly greater reduction in LDL-C levels after 24 weeks. Further studies are needed to assess long-term efficacy and safety.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01984424

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Supplemental content at jama.com

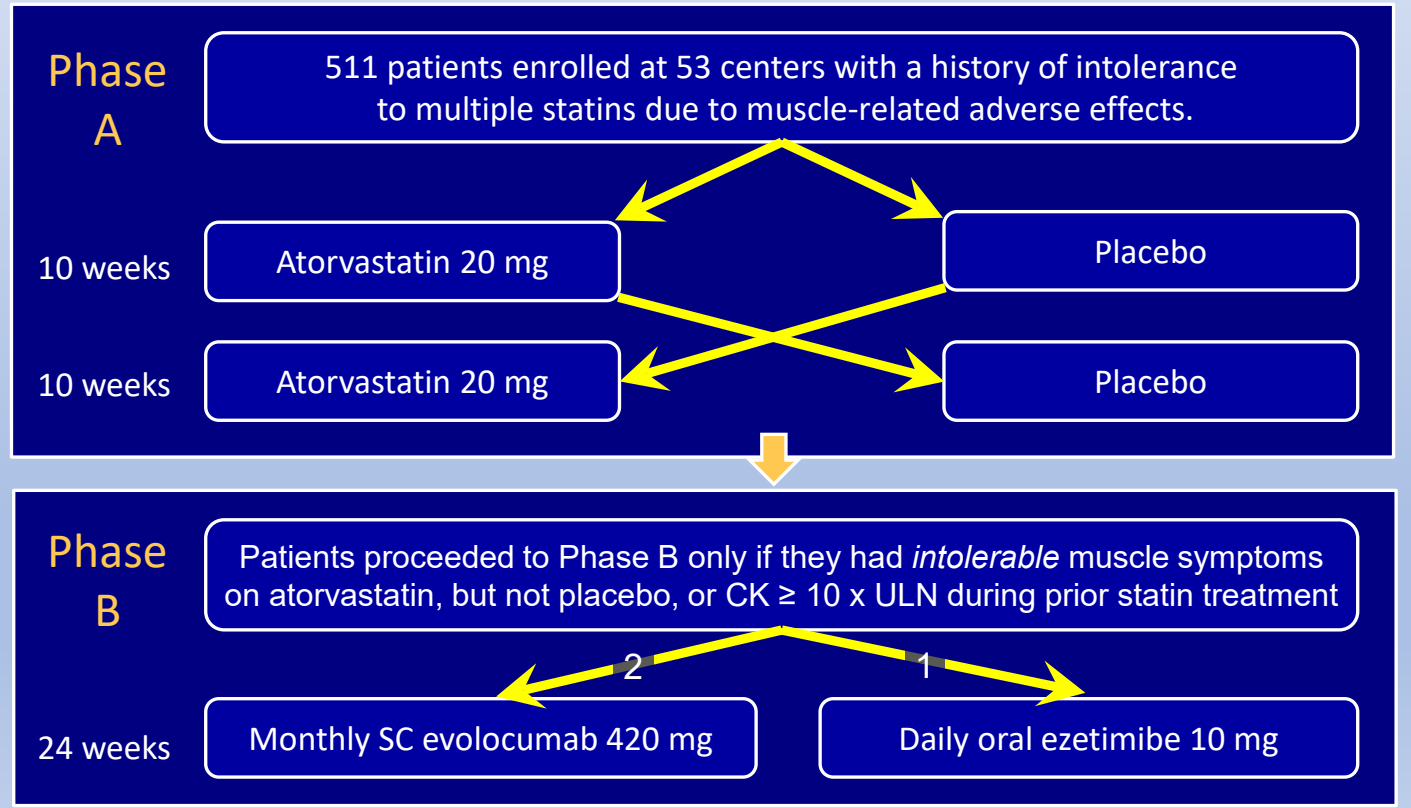
CME Quiz at jamanetworkcme.com

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The Goal Achievement after Utilizing an anti-PCSK9 Antibody in Statin-Intolerant Subjects 3 (GAUSS-3) Investigators are listed at the end of this article.

JAMA. 2016;315(15):1580-1590. doi:10.1001/jama.2016.3608
Published online April 3, 2016.

GAUSS-3: Study Design: Two Double-Blind Phases



GAUSS-3: Phase A: Study Drug Discontinuation Events

Intolerable Muscle Symptoms	N = 491
On atorvastatin, but not placebo	209 (42.6%)*
On placebo, but not atorvastatin	130 (26.5%)
On both placebo and atorvastatin	48 (9.8%)
No symptoms on either treatment	85 (17.3%)
Did not complete Phase A	*20/511*
Bypassed Phase A due to CK elevation ≥ 10 x ULN	19 (3.9%)*

**218 of these 228 eligible patients proceeded to Phase B*

Phase B: Adverse Effects and Drug Discontinuations

	Ezetimibe (n=73)	Evolocumab (n=145)
Total muscle-related events	21 (28.8%)	30 (20.7%)
Myalgia, muscle pain or weakness	17 (23.3%)	25 (17.2%)
Investigator reported CK Increase	1 (1.4%)	4 (2.8%)
Discontinuation of Treatment for Any Reason		
Discontinuation of oral treatment	14 (19.2%)	23 (15.9%)
Discontinued SC drug treatment	4 (5.5%)	7 (4.8%)
Discontinuation of Treatment for Muscle Symptoms		
Discontinued oral drug treatment	5 (6.8%)	**11 (7.6%)**
Discontinued SC drug treatment	**0 (0%)**	**1 (0.7%)**

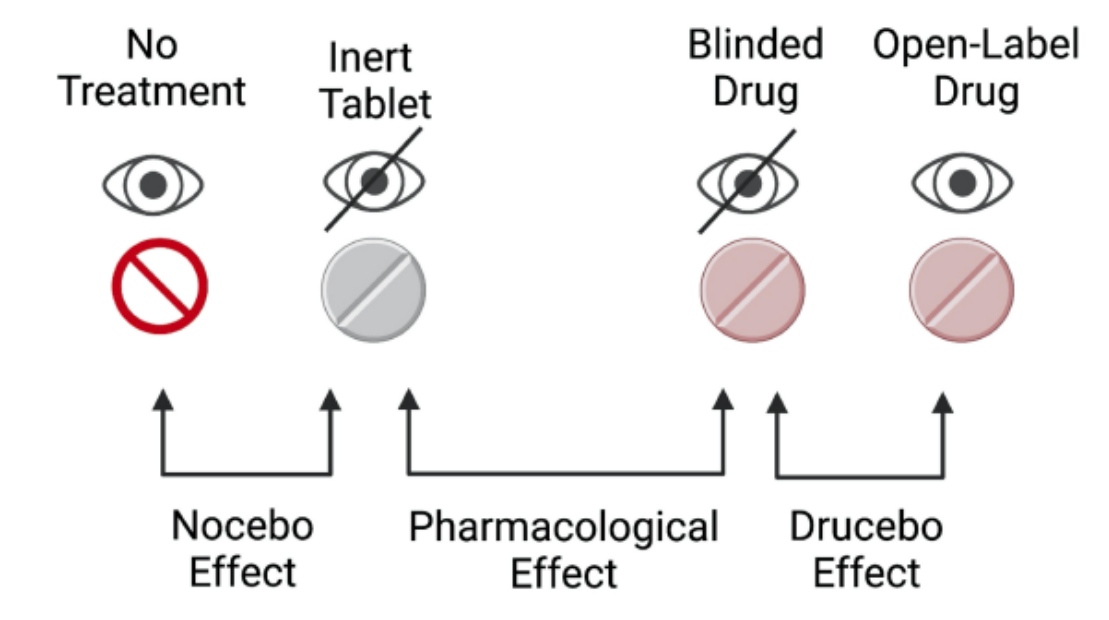
Variabile	Gruppo trattato	Gruppo placebo	p
Qualsiasi disturbo			
CK >5x ULN			
CK >10x ULN			
Rabdomiolisi			
Interruzione della			

CK, creatinchinasi

Va sottolineato che l'affermazione diffusa dai media che la terapia statinica provochi effetti collaterali in molti pazienti, e la mancata smentita di tali affermazioni fuorvianti, ha portato pazienti ad alto rischio di eventi vascolari o con malattie cardiovascolari conclamate ad interrompere la terapia. È stato stimato che tali riduzioni nell'uso di statine abbiano causato migliaia di attacchi cardiaci e ictus fatali o disabilitanti, che avrebbero potuto essere evitati.

Gli autori dello studio segnalano che raramente, nella storia della terapia moderna, i benefici sostanziali dimostrati da un trattamento sono stati compromessi in misura tale da gravi errori nella presentazione delle evidenze relative al profilo di sicurezza, e forse è bene porsi la domanda se comunicazioni irresponsabili non siano da condannare ufficialmente.

L'effetto «drucebo»



REVIEW

Journal of Cachexia, Sarcopenia and Muscle 2022; **13**: 1596–1622
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Step-by-step diagnosis and management of the nocebo/drucebo effect in statin-associated muscle symptoms patients: a position paper from *the International Lipid Expert Panel* (ILEP)

Peter E. Penson[1,2], Eric Bruckert[3], David Marais[4], Željko Reiner[5], Matteo Pirro[6], Amirhossein Sahebkar[7,8,9], Gani Bajraktari[10,11], Erkin Mirrakhimov[12], Manfredi Rizzo[13,14], Dimitri P. Mikhailidis[15], Alexandros Sachinidis[13,16], Dan Gaita[17,18], Gustavs Latkovskis[19,20], Mohsen Mazidi[21,22], Peter P. Toth[23,24], Daniel Pella[25], Fahad Alnouri[26], Arman Postadzhiyan[27], Hung-I Yeh[28], G.B. John Mancini[27], Stephan von Haehling[29,30], Maciej Banach[31,32,33]* & International Lipid Expert Panel (ILEP)[†]

Molti eventi avversi sono erroneamente attribuiti [alle statine] e i sintomi soggettivi si manifestano per via del fatto che i pazienti si aspettano che compaiano dopo l'assunzione del farmaco (effetto drucebo), il che potrebbe essere vero per più del 50% di tutti i pazienti con debolezza muscolare/dolore".

The most common causes of CK elevation

Chronic diseases	Medications	Toxins	Metabolic disturbances	Muscle trauma/disorders	Others
Endocrine disorders *Hyperthyroidism* *Hypothyroidism* *Hypoparathyroidism* *Acromegaly* *Cushing syndrome* Connective tissue disorders Rheumatological diseases Cardiac disease (heart failure, valvular, tachycardia, myocarditis, ACS) Acute kidney disease Viral illnesses Celiac disease	Statins Fibrates Antiretrovirals Beta-blockers Clozapine Angiotensin receptor blocking agents Hydroxychloroquine Isotretinoin Colchicine Steroids	Ethanol Cocaine Heroin Amphetamine	Hyponatraemia Hypokalaemia Hypophosphataemia	Muscle dystrophies Metabolic and mitochondrial disorders of muscle Inflammatory myopathies Others *Familial elevated CK* *Sarcoid myopathy* *Motor neuron diseases* *Charcot–Marie–Tooth disease* *Other congenital diseases* Intramuscular injections Needle electromyography Seizures	Ethnicity (black Americans may have elevated baseline CK levels) Intensive exercise Surgery Malignancy MacroCK Ssevere chills Predisposition to malignant hyperthermia Idiopathic hyperCKaemia

Very-high-risk	People with any of the following: Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound. DM with target organ damage,[a] or at least three major risk factors, or early onset of T1DM of long duration (>20 years). Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.
High-risk	People with: Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage,[a] with DM duration ≥10 years or another additional risk factor. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1 % and <5% for 10-year risk of fatal CVD.
Low-risk	Calculated SCORE <1% for 10-year risk of fatal CVD.

Dislipidemia nella malattia renale cronica

- La **malattia cardiovascolare** (CVD) **è una delle principali cause di mortalità** nei pazienti con malattia renale cronica (CKD) da lieve a moderata e malattia renale allo stadio terminale (ESRD).
- Circa il **50% dei pazienti con ESRD muore per un evento cardiovascolare.**
- La mortalità cardiovascolare **>30 volte superiore nei pazienti in dialisi e 500 volte superiore nei pazienti con ESRD** rispetto agli individui della popolazione generale della stessa età e razza.
- I pazienti con insufficienza renale cronica presentano **alterazioni significative nel metabolismo delle lipoproteine**,

Tsimihodimos V et al. Dyslipidemia in chronic kidney disease: an approach to pathogenesis and treatment. Am J Nephrol. 2008;28(6):958-73

Mach F et al. 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), European Heart Journal, Volume 41, Issue 1, 1 January 2020, Pages 111–188

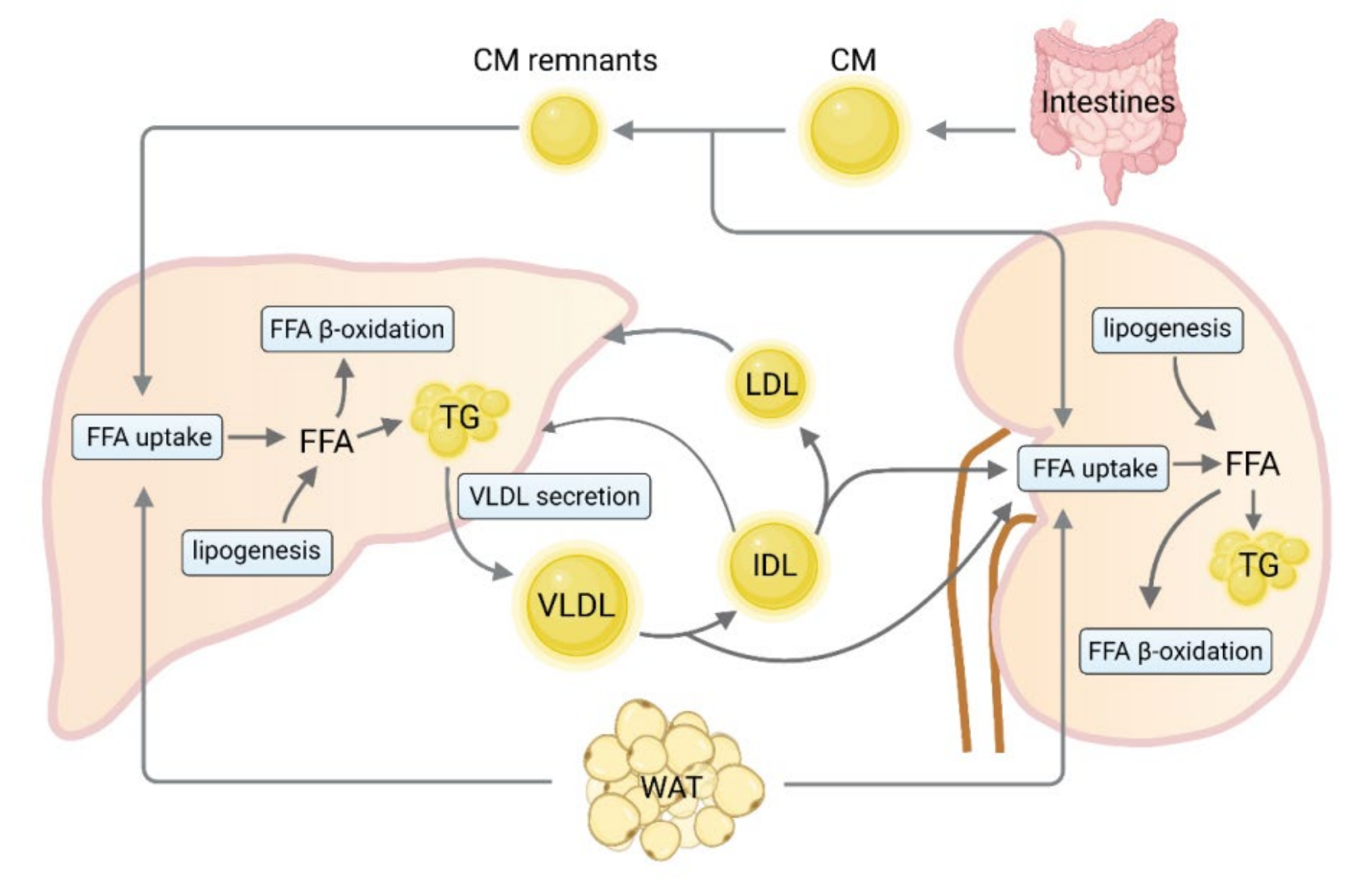
Dislipidemia nel paziente nefropatico

	Nephrotic syndrome	CKD (stages 1–2)	CKD (stages 3–4)	HD	PD	KTR
Total Cholesterol	↑↑	=	=	= or ↓	↑	↑
LDL	↑↑	=	= or ↓	= or ↓	↑	↑
HDL	↓	↓	↓	↓	↓	= or ↓
Triglycerides	↑↑	↑↑	↑↑	= or ↑	↑↑	↑ or ↑↑

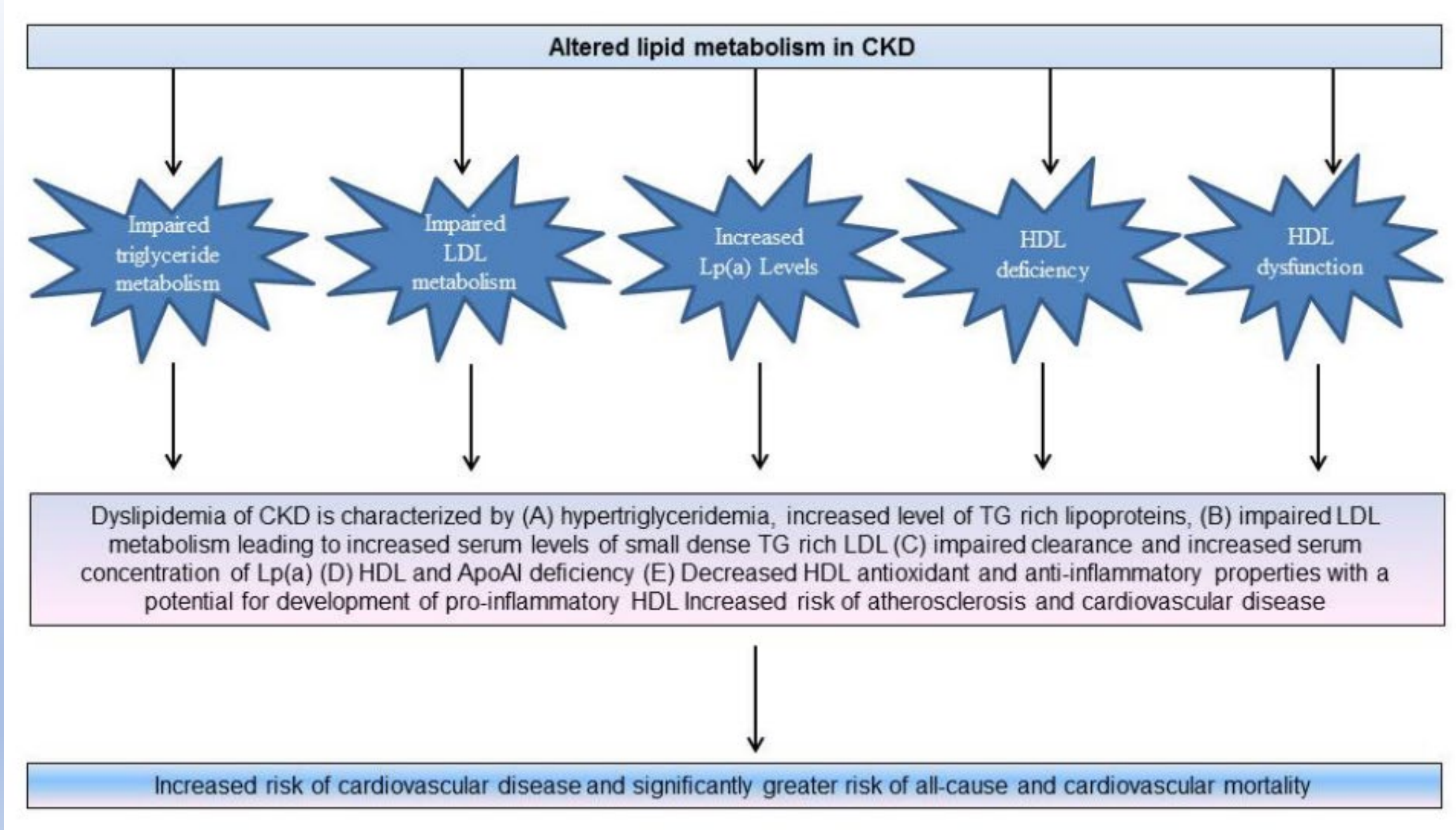
HD haemodialysis, *HDL* high-density lipoprotein cholesterol, *KTR* kidney transplant recipient, *LDL* low-density lipoprotein cholesterol, *PD* peritoneal dialysis

Pontremoli R et al. Management of dyslipidaemia in patients with chronic kidney disease: a position paper endorsed by the Italian Society of Nephrology. J Nephrol. 2020 Jun;33(3):417-430.

Cross-talk tra fegato e rene nel metabolismo lipidico



Yang M, Geng CA, Liu X, Guan M. Lipid Disorders in NAFLD and Chronic Kidney Disease. Biomedicines. 2021 Oct 6;9(10):1405.



Moradi H et al. Molecular mechanisms of disorders of lipid metabolism in chronic kidney disease. Front Biosci (Landmark Ed). 2018 Jan 1;23(1):146-161.

The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial

Lancet 2011; 377: 2181–92

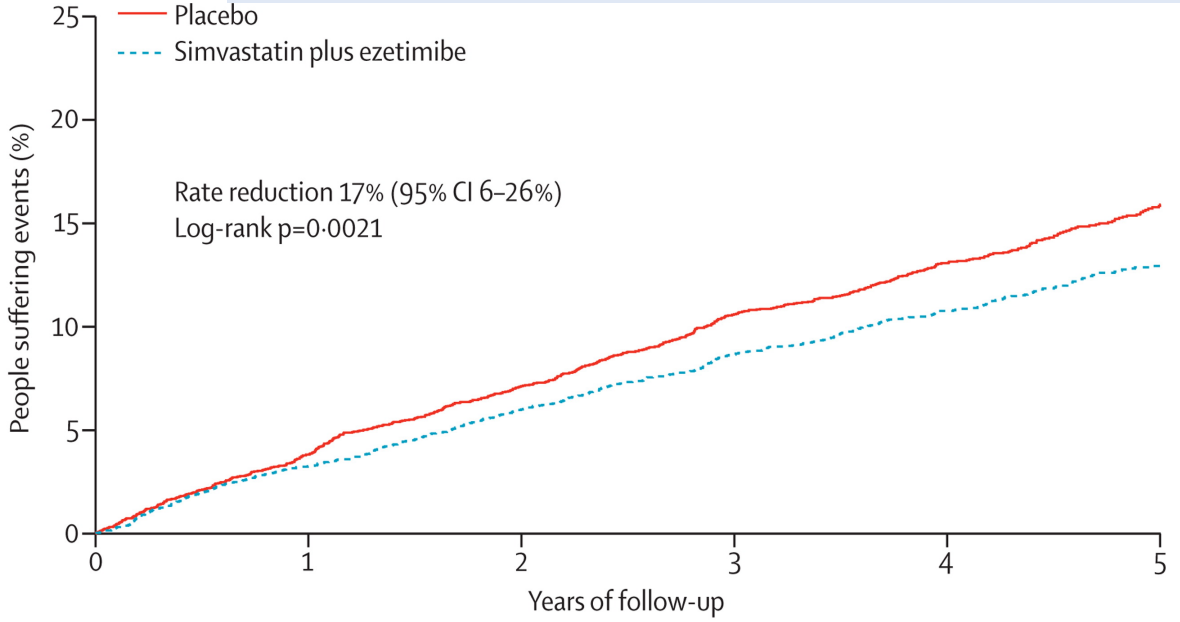
Summary

Background Lowering LDL cholesterol with statin regimens reduces the risk of myocardial infarction, ischaemic stroke, and the need for coronary revascularisation in people without kidney disease, but its effects in people with moderate-to-severe kidney disease are uncertain. The SHARP trial aimed to assess the efficacy and safety of the combination of simvastatin plus ezetimibe in such patients.

Methods This randomised double-blind trial included 9270 patients with chronic kidney disease (3023 on dialysis and 6247 not) with no known history of myocardial infarction or coronary revascularisation. Patients were randomly assigned to simvastatin 20 mg plus ezetimibe 10 mg daily versus matching placebo. The key prespecified outcome was first major atherosclerotic event (non-fatal myocardial infarction or coronary death, non-haemorrhagic stroke, or any arterial revascularisation procedure). All analyses were by intention to treat. This trial is registered at ClinicalTrials.gov, NCT00125593, and ISRCTN54137607.

Findings 4650 patients were assigned to receive simvastatin plus ezetimibe and 4620 to placebo. Allocation to simvastatin plus ezetimibe yielded an average LDL cholesterol difference of 0·85 mmol/L (SE 0·02; with about two-thirds compliance) during a median follow-up of 4·9 years and produced a 17% proportional reduction in major atherosclerotic events (526 [11·3%] simvastatin plus ezetimibe *vs* 619 [13·4%] placebo; rate ratio [RR] 0·83, 95% CI 0·74–0·94; log-rank p=0·0021). Non-significantly fewer patients allocated to simvastatin plus ezetimibe had a non-fatal myocardial infarction or died from coronary heart disease (213 [4·6%] *vs* 230 [5·0%]; RR 0·92, 95% CI 0·76–1·11; p=0·37) and there were significant reductions in non-haemorrhagic stroke (131 [2·8%] *vs* 174 [3·8%]; RR 0·75, 95% CI 0·60–0·94; p=0·01) and arterial revascularisation procedures (284 [6·1%] *vs* 352 [7·6%]; RR 0·79, 95% CI 0·68–0·93; p=0·0036). After weighting for subgroup-specific reductions in LDL cholesterol, there was no good evidence that the proportional effects on major atherosclerotic events differed from the summary rate ratio in any subgroup examined, and, in particular, they were similar in patients on dialysis and those who were not. The excess risk of myopathy was only two per 10 000 patients per year of treatment with this combination (9 [0·2%] *vs* 5 [0·1%]). There was no evidence of excess risks of hepatitis (21 [0·5%] *vs* 18 [0·4%]), gallstones (106 [2·3%] *vs* 106 [2·3%]), or cancer (438 [9·4%] *vs* 439 [9·5%], p=0·89) and there was no significant excess of death from any non-vascular cause (668 [14·4%] *vs* 612 [13·2%], p=0·13).

Interpretation Reduction of LDL cholesterol with simvastatin 20 mg plus ezetimibe 10 mg daily safely reduced the incidence of major atherosclerotic events in a wide range of patients with advanced chronic kidney disease.



Number at risk

Placebo	4620	4204	3849	3469	2566	1269
Simvastatin plus ezetimibe	4650	4271	3939	3546	2655	1265

SHARP
STUDY OF HEART AND RENAL PROTECTION

LINEE GUIDA DI TRATTAMENTO DELLA DISLIPIDEMIA NEL PAZIENTE NEFROPATICO

Guideline	Population	CKD stage	Treatment recommendations
KDIGO (2013)	Adults ≥ 50 years	1–2	Statin
		3–5 (not on dialysis)	Statin; Statin + Ezetimibe
	Adults 18–49 years + ≥ 1 of the following: 1. known coronary disease 2.DM 3. Prior ischemic stroke 4. estimated 10 years incidence of coronary death or non fatal MI > 10%	1–5 (not on dialysis)	Statin
	Adults with dialysis-dependent CKD	5 (HD or PD)	Statins or statin combinations should not be initiated; they can be continued if already received at the time of dialysis initiation
	Adult kidney transplant recipient	1–5	Statin
ACC/AHA (2018)	Adults with clinical ASCVD	1–5 (not on dialysis)	High-intensity statin preferred; moderate-intensity statin if not a candidate for high-intensity
	Adults with LDL-cholesterol ≥ 190 mg/dL	1–5 (not on dialysis)	High-intensity statin preferred; moderate-intensity statin if not a candidate for high-intensity
	Adults 40–75 years with DM and LDL-cholesterol 70–189 mg/dL (no ASCVD)	1–5 (not on dialysis)	High-intensity statin if estimated 10-years ASCVD risk ≥7.5%; moderate-intensity statin if not a candidate for high-intensity
	Adults 40–75 years with estimated 10-years ASCVD risk ≥ 7.5% (no DM or ASCVD)	1–5 (not on dialysis)	Moderate- or high-intensity statin
	Adults with dialysis-dependent CKD and kidney transplant recipients	5 (HD or PD) or 1–5 in kidney transplant recipient	No recommendation
ESC/EAS (2019)	Adults	1–5 (not on dialysis)	Statin; Statin + Ezetimibe
	Patients with dialysis-dependent CKD and free of atherosclerotic CVD	5 (HD or PD)	Statins should not be initiated; in patients already on treatment at the time of dialysis initiation, these drugs should be continued, particularly in patients with CVD
	Adult kidney transplant recipients	1–5	Treatment with statins may be considered

Pontremoli R et al. Management of dyslipidaemia in patients with chronic kidney disease: a position paper endorsed by the Italian Society of Nephrology. J Nephrol. 2020 Jun;33(3):417-430.

Statin therapy in patients with CKD

Target/mechanism of action	Inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase		
Therapeutic target	LDL-cholesterol < 70 mg/dL in patients at high CV risk and < 55 mg/dL in patients at very high CV risk [55]		
Potential pleiotropic effects	Pro-inflammatory cytokines and CRP reduction, increased eNOS expression and activity, ROS reduction, atherosclerotic plaque stabilization, platelet aggregation inhibition, fibrosis and left ventricular hypertrophy decrease, reduction in migration and proliferation of vascular smooth muscle cells, nephroprotection, antitumor activity, immunomodulation [56, 57]		
Main adverse events	Myopathy (including myositis), rhabdomyolysis with or without AKI, myalgia, muscle cramps, asthenia, hepatitis/jaundice, increased blood levels of liver enzymes, alkaline phosphatase, CPK, HbA1c, and fasting glucose		
	CKD under conservative therapy	Haemodialysis and Peritoneal dialysis patients	Renal transplantation
Indications according to guidelines KDIGO [37] Joint British Societies for the prevention of CV disease [58] NICE [59] Canadian CV Society [60] ESC/EAS [55]	Estimation of CV risk not required if GFR < 60 ml/min/1.73 m^2 or if albuminuria is present Indications: Adults ≥ 50 yrs with GFR < 60 ml/min/1.73 m^2: statin or statin/ezetimibe therapy recommended Adults ≥ 50 yrs with CKD and GFR ≥ 60 ml/min/1.73 m^2: statin therapy recommended Adults 18–49 yrs: statin therapy suggested in the presence of one or more of the following: DM, known coronary disease, estimated 10-year incidence of non-fatal MI or coronary death > 10%, previous ischaemic stroke	It is suggested not to start statin or statin/ezetimi-be therapy It is suggested to continue treatment in patients already on statin or statin/ezetimi-be therapy at the time of dialysis initiation	Statin therapy suggested
Molecules and dosages resulted effective in clinical studies	Lovastatin (20 mg/day) [61]		Lovastatin (20 mg/day) [81–83]
	Pravastatin (10–20 mg/day) [62–65]		Pravastatin (20 mg/day) [84–86]
	Atorvastatin (10–80 mg/day) [32, 66–71]		Atorvastatin (10 mg/day) [87, 88]
	Simvastatin (10–40 mg/day) [72–76]		Simvastatin (5–40 mg/day) [81, 85, 89–95] or Simvastatin-Ezetimibe (extrapolated from the SHARP trial)
	Simvastatin-Ezetimibe (SHARP trial) [33]		Fluvastatin (20–80 mg/day) [51, 82, 96–98]
	Fluvastatin (10–30 mg/day) [77]		Rosuvastatin (10 mg/day) [99]
	Rosuvastatin (2.5–20 mg/day) [78–80]		

STATINE nel paziente NEFROPATICO

- TERAPIA DI PRIMA SCELTA IN PAZIENTI IN TERAPIA CONSERVATIVA o TRAPIANTATI. Indicate anche nella SINDROME NEFROSICA
- NON INDICATO INIZIARE IL TRATTAMENTO IN PAZIENTI IN EMODIALISI, MA CONTINUARE SE IN ATTO
- CONTROINDICATE LE ALTE DOSI DI ROSUVASTATINA (40 mg) IN IRC MODERATA, TUTTE LE DOSI ROSUVASTATINA IN IRC GRAVE
- **ATORVASTATINA SICURA FINO A 80 mg**
- TARGET LDL-C<70 mg/dl <55 mg/dl
- EFFETTI PLEIOTROPICI POTENZIALI

	Rosuva	Atorva	Simva	Prava	Fluva	Lova
Insuff. renale lieve-moderata	40 mg CI	X	X	10 mg (iniziale)	X	X
Insuff. renale grave	CI	X	Cautela con dosi >10 mg	10 mg (iniziale)	NR	Attenta valutazione dosi >20 mg

Pontremoli R et al. Management of dyslipidaemia in patients with chronic kidney disease: a position paper endorsed by the Italian Society of Nephrology. J Nephrol. 2020 Jun;33(3):417-430.

EZETIMIBE IN PAZIENTE NEFROPATICO

Table 3 Ezetimibe therapy in patients with CKD

EZETIMIBE				
Target/mechanism of action	Selective inhibition of NPC1L1 protein, transporter of food cholesterol from intestinal lumen into enterocytes [101, 102]			
Therapeutic targets in CKD	LDL-cholesterol < 70 mg/dL in patients at high CV risk and < 55 mg/dL in patients at very high CV risk [55]			
Potential pleiotropic effects	Enhancement of plaque regression through: inhibition of intestinal absorption of plant sterols (associated with early atherosclerosis in some studies); modulation of genes involved in inflammation and/or oxidative stress, inhibition of the differentiation of monocytes and/or macrophages, inhibition of proliferation of smooth muscle cells; inhibition of platelet aggregation and activation; modulation of atherosclerotic plaque composition [117–123]			
Main adverse effects	Asthenia, myalgia, arthralgia, increased levels of liver enzymes and creatine phosphokinase, diarrhoea, dyspepsia, gastritis, headache			
	CKD on conservative therapy	Extracorporeal dialysis	Peritoneal dialysis	Renal transplantation
Dosages tested in clinical studies and indications according to guidelines KDIGO [37] Joint British Societies for the prevention of CV disease [56] NICE [57] Canadian CV Society [58] ESC/EAS [55]	Ezetimibe monotherapy not recommended Adults ≥ 50 yrs with GFR < 60 ml/min/1.73 m2: statin or statin/ezetimibe therapy recommended	It is suggested not to start statin or statin/ezetimi-be therapy It is suggested to continue treatment in patients already on statin or statin/ezetimi-be therapy at the time of dialysis initiation	Ezetimibe 10 mg + simvastatin 10 or 20 mg/day [33]	No specific indication for ezetimibe therapy

- NON RACCOMANDATA IN MONOTERAPIA MA IN ASSOCIAZIONE A STATINA
- NON INIZIARE SE IL PAZIENTE E' IN DIALISI MA CONTINUARE SE ERA GIA' IN TERAPIA
- TARGET LDL-C<70 mg/dl <55 mg/dl
- EFFETTI PLEIOTROPICI POTENZIALI

Pontremoli R et al. Management of dyslipidaemia in patients with chronic kidney disease: a position paper endorsed by the Italian Society of Nephrology. J Nephrol. 2020 Jun;33(3):417-430.

FENOFIBRATO NEL PAZIENTE NEFROPATICO

Controindicazioni

Insufficienza renale

Posologia

Pazienti con compromissione renale: è richiesta la riduzione del dosaggio.
In questi pazienti è raccomandato l'uso di forme farmaceutiche contenenti una dose più bassa di principio attivo (100 mg o 67 mg di fenofibrato).
N.B. La compressa non è divisibile.

Avvertenze speciali e precauzioni di impiego

Funzionalità renale: Il trattamento deve essere interrotto in caso di aumento dei livelli di creatinina maggiori del 50% del limite superiore di normalità (ULN).
Controllare la creatinina nei primi tre mesi successivi all'inizio del trattamento e poi periodicamente.

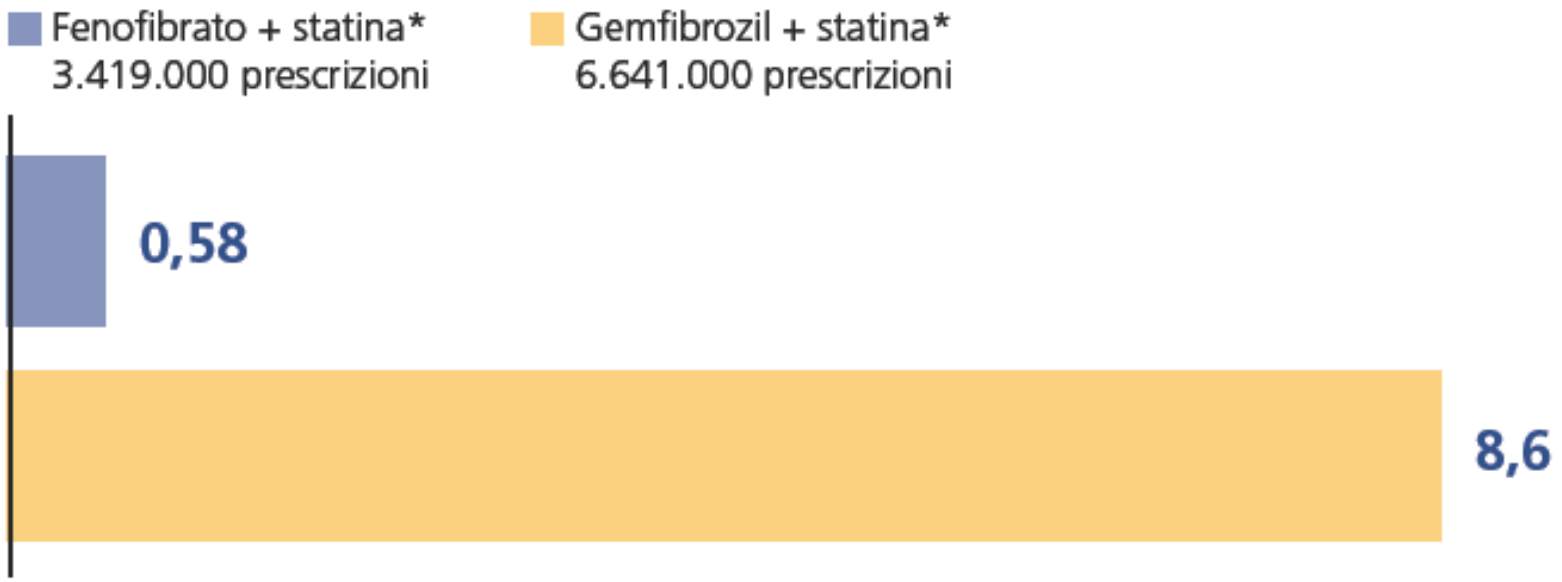
Farmacocinetica

L'acido fenofibrico non viene eliminato con l'emodialisi.

- *Sulla base dell'esperienza clinica nell'uso dell'associazione fibrato + statine, la FDA ha rilevato un'incidenza di casi di rabdomiolisi per milione di prescrizioni significativamente inferiore per l'associazione fenofibrato + statina rispetto a gemfibrozil + statina (p<0,0000001).* [24]

FDA Report 2005

Numero di casi di rabdomiolisi per milione di prescrizioni [25]

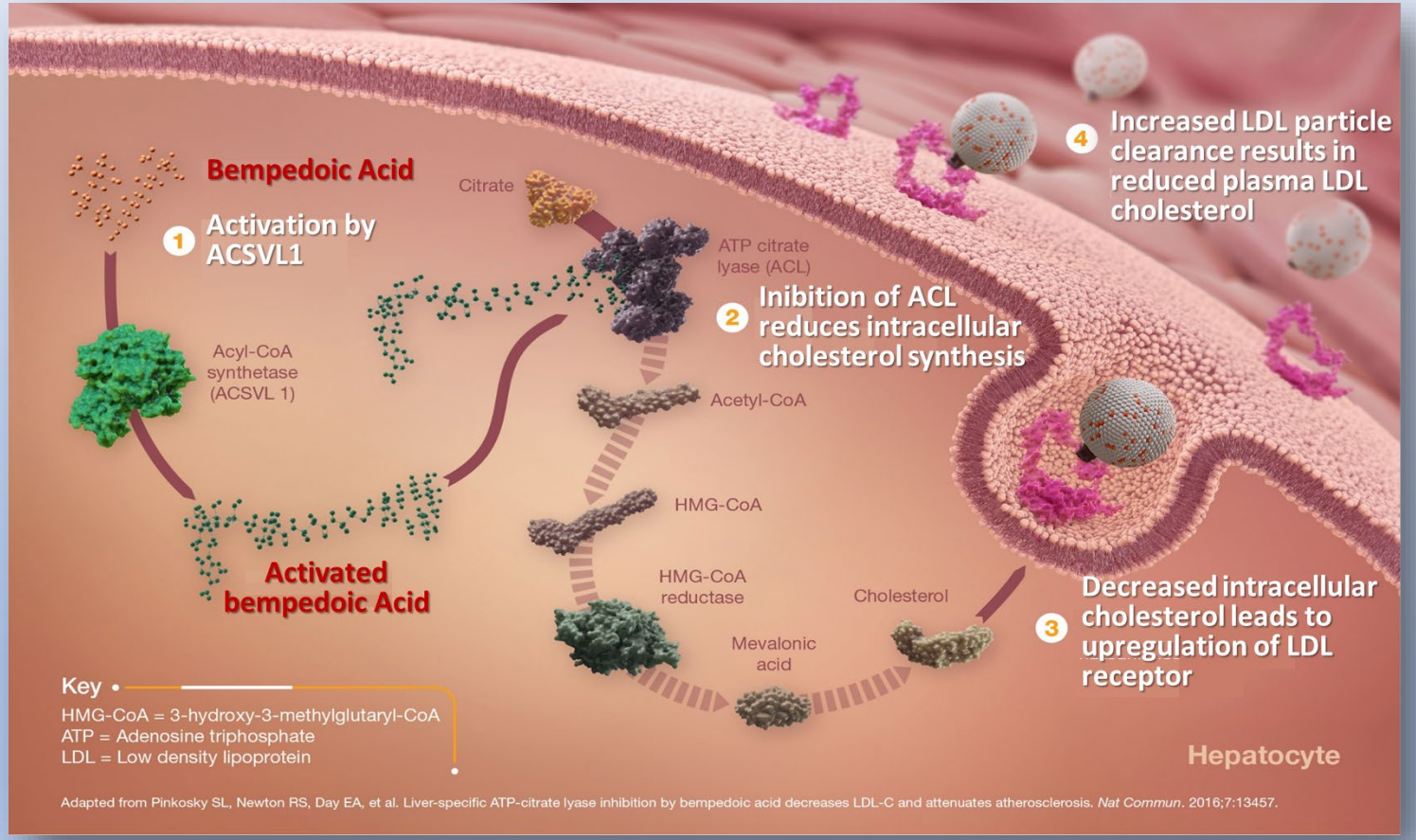


* esclusa la combinazione con cerivastatina

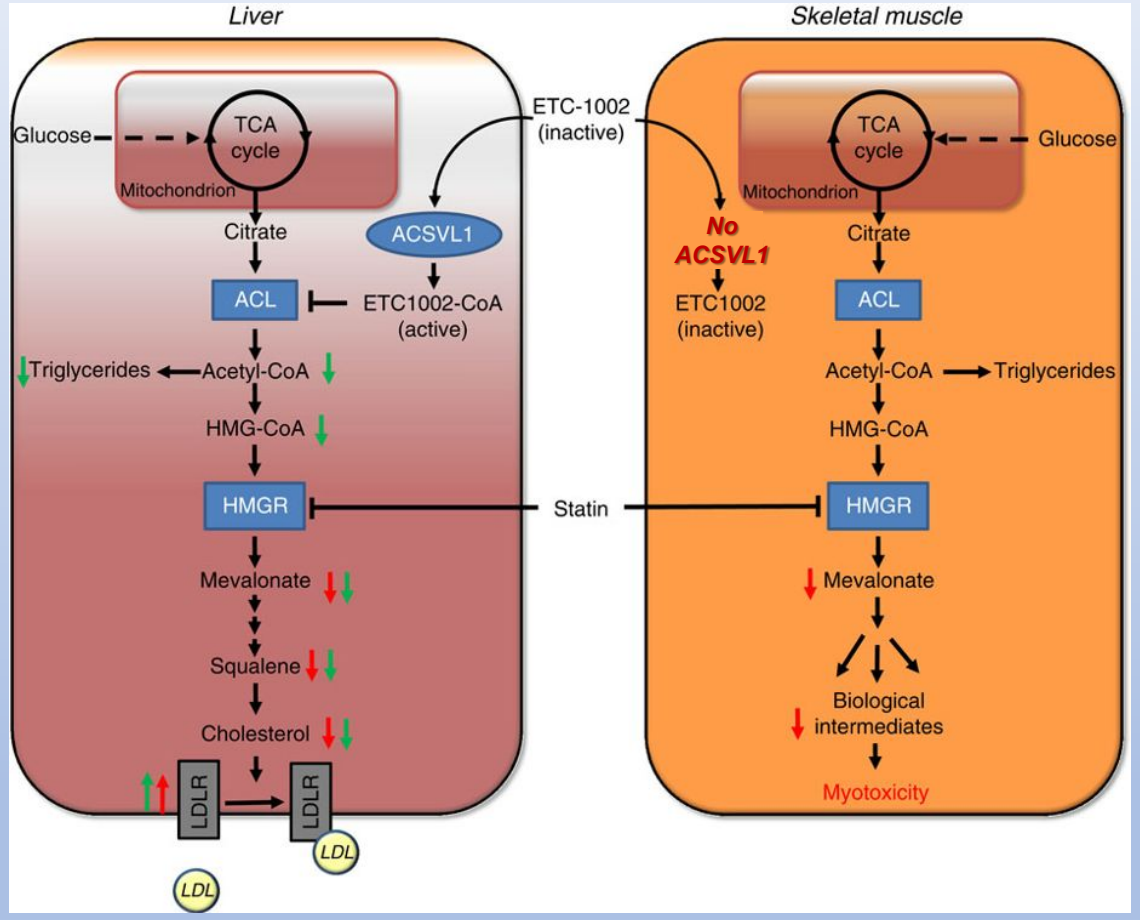
ACIDO BEMPEDOICO

- Attivato principalmente a livello epatico, l'acido bempedoico <u>inibisce l'enzima ATP citrato liasi</u> (ACL) nella nota via di sintesi del colesterolo, a monte rispetto al target delle statine

- La conseguente up-regolazione dei recettori per le LDL determina un'aumentata captazione di LDL da parte delle cellule epatiche con relativa riduzione dei livelli plasmatici di C-LDL



L’Acido Bempedoico non è attivato nel muscolo scheletrico



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

ACIDO BEMPEDOICO E COMPROMISSIONE RENALE

- **Nessun aggiustamento di dosaggio è necessario in pazienti con compromissione renale lieve o moderata**

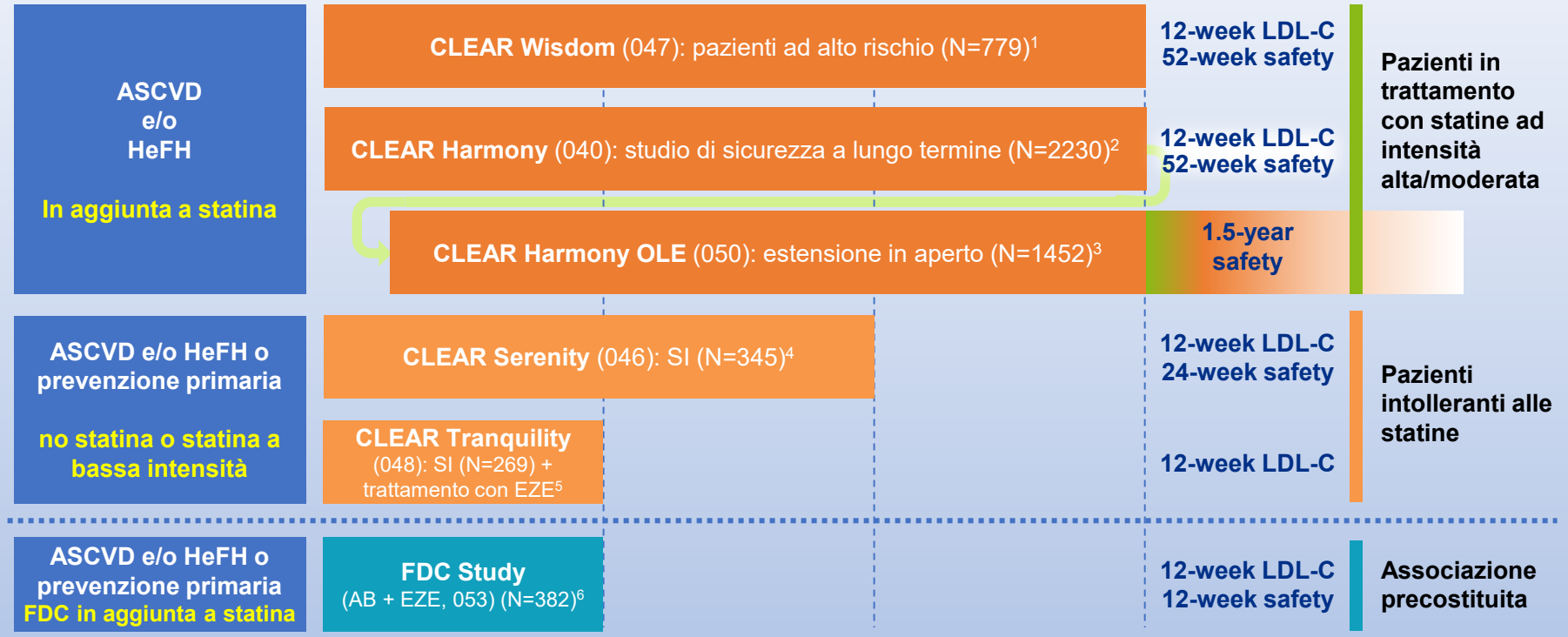
- I dati circa l'utilizzo di acido bempedoico in pazienti con compromissione renale severa (eGFR <30 mL/min/1.73 m^2) sono limitati e la molecola non è stata studiata in pazienti con malattia renale in stadio terminale o in pazienti dializzati.

- In RCP si riporta che nei pazienti in trattamento con acido bempedoico sono stati segnalati **aumenti dei valori di creatinina** ma tra gli eventi avversi NON comunemente riportati (frequenza ≥1/1.000, <1/100):

Negli studi aggregati, controllati con placebo, è stato osservato con l'acido bempedoico un aumento medio di 0,05 mg/dL (4,4 micromoli/L) dei valori di creatinina sierica e un aumento medio di 1,7 mg/dL (0,61 mmol/L) di BUN rispetto al basale, alla settimana 12 nello **0.8% (19/2424) dei pazienti in trattamento** con acido bempedoico e nello **0.3% (4/1197) dei pazienti del gruppo placebo**.

Tali variazioni si sono verificate di solito **entro le prime 4 settimane di trattamento**, i valori sono rimasti stabili e sono **tornati al basale a seguito della sospensione del trattamento.** Il motivo di queste variazioni è legato ad una lieve inibizione che l'acido bempedoico esercita su un trasportatore di anioni organici espresso a livello del tubulo renale (OAT2), implicato nell'escrezione di creatinina e quindi si tratta di un'interazione farmaco-endogena del substrato e non sembra indicare un peggioramento della funzione renale.

L'Acido Bempedoico è stato valutato in un solido programma clinico che ha incluso un ampio spettro di pazienti

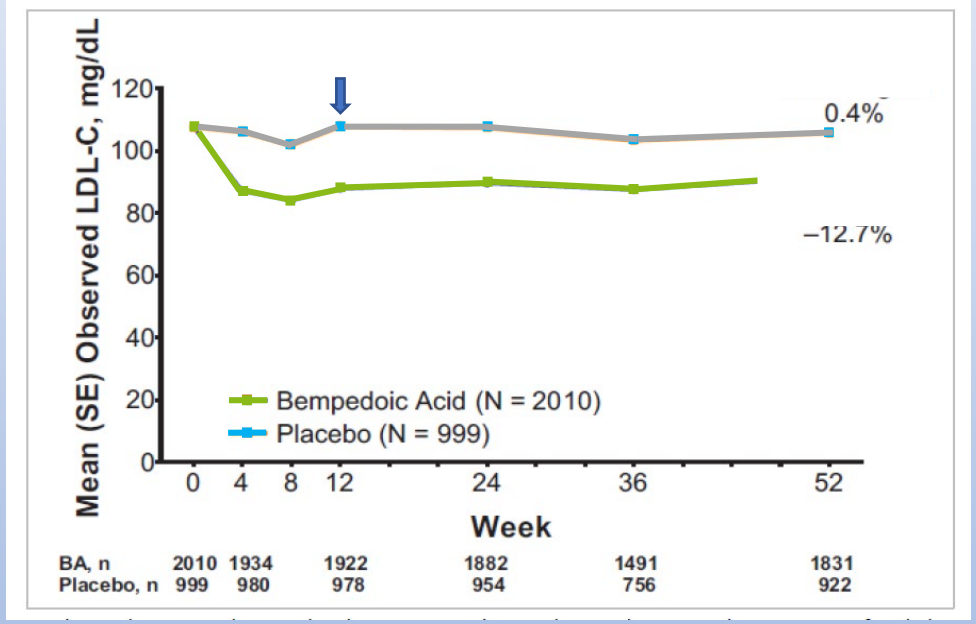


- ASCVD = malattia cardiovascolare su base aterosclerotica; AB = acido bempedoico; EZE = ezetimibe; HeFH = iperholesterolemia familare eterozigote;
  LDL-C Colesterolo LDL; OLE = open-label extension; SI = statino-intolleranti

- **1**.Goldberg AC et al. JAMA. 2019;322(18):1780-1788. doi:10.1001/jama.2019.16585; **2.** Ray KK, et al. *N Engl J Med*. 2019;380:1022-32; **3.** ClinicalTrials.gov identifier NCT03067441; **4.** Laufs U, et al. *J Am Heart Assoc*. 2019;8:e011662; **5.** Ballantyne CM, et al. *Atherosclerosis*. 2018;277:195-2036. **6.** Ballantyne CM et al. *Eur J Prev Cardiol*. 2020;27(6):593-603.

Pazienti in trattamento con statine ad intensità alta/moderata

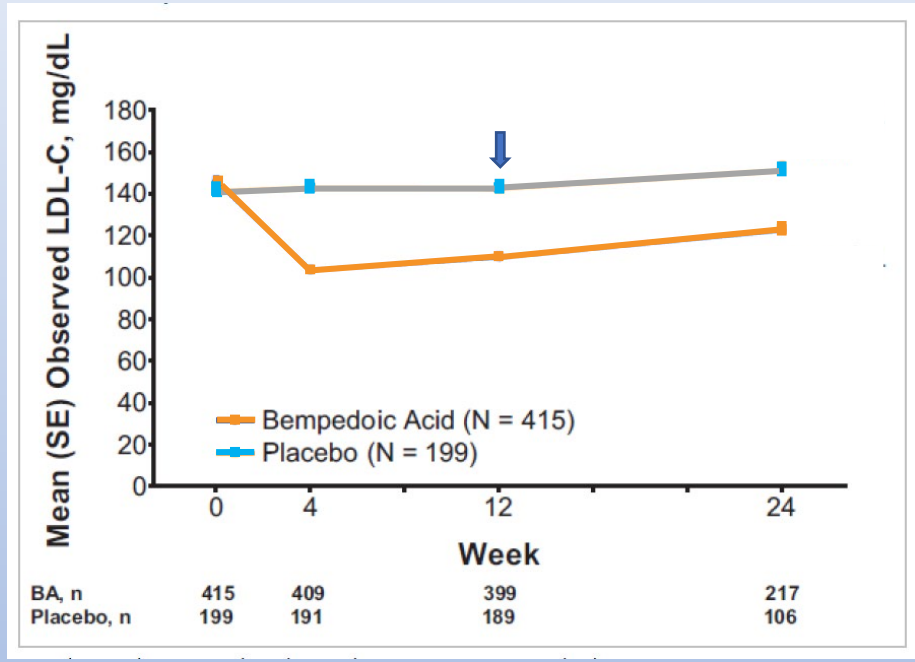
L’acido bempedoico riduce i livelli di LDL-C in maniera significativa rispetto a placebo
(Analisi “pooled” degli studi CLEAR Harmony e CLEAR Wisdom)



Variazione percentuale media di LDL-C:
−16.0% nel gruppo acido bempedoico vs
+1.8% nel gruppo placebo (**−17.8**%, *P* < 0.001)

Pazienti intolleranti alle Statine

L’acido bempedoico riduce i livelli di C-LDL in maniera significativa rispetto a placebo
(Analisi “pooled” degli studi CLEAR Serenity e CLEAR Tranquility)

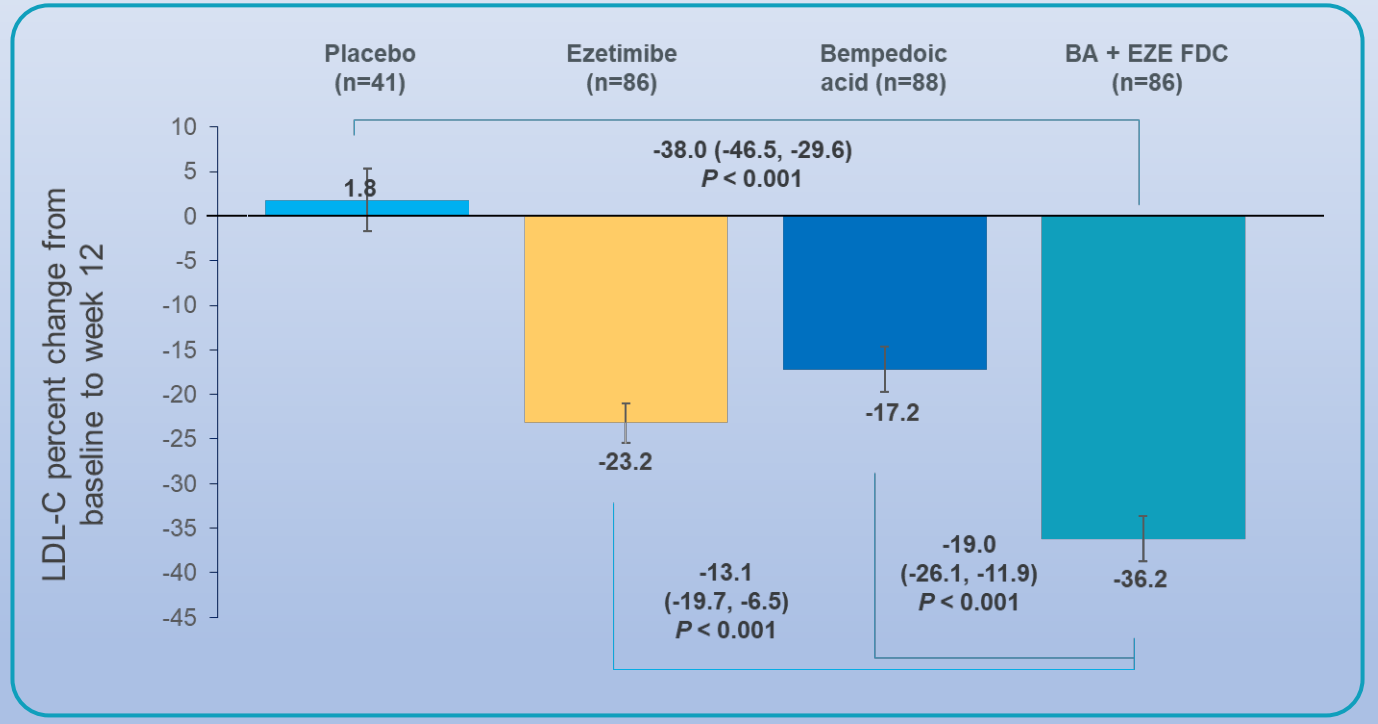


Variazione percentuale media di LDL-C:
−23.0% nel gruppo acido bempedoico vs
+1.5% nel gruppo placebo (**−24.5%**, *P* < 0.001)

Banach M. et al., JAMA Cardiology, published online July 1, 2020

Acido Bempedoico + Ezetimibe FDC

Studio FDC: la combinazione a dose fissa Ac. Bempedoico + EZE riduce i livelli di LDL-C in maniera significativa rispetto al placebo



Post hoc population
BA, bempedoic acid; EZE, ezetimibe; FDC, fixed-dose combination.

L'associazione fissa acido bempedoico + EZE ha ridotto il colesterolo-LDL in maniera coerente nei vari sottogruppi considerati, compresi i sottogruppi trattati con terapia statinica sottostante a diversa intensità.

- Ballantyne CM et al. *Eur J Prev Cardiol*. 2020;27(6):593-603.

Acido bempedoico in pazienti diabetici

- Poichè i pazienti con diabete sono ad elevato rischio di malattia cardiovascolare aterosclerotica, gli studi clinici condotti con acido bempedoico hanno incluso pazienti con diabete mellito

- L'acido bempedoico, con o senza ezetimibe, ha ridotto i valori di LDL-C, non-HDL-C, TC e hsCRP in pazienti con ipercolesterolemia e diabete metllito di tipo 2, senza compromettere il controllo glicemico [1-3]

- Nel sottogruppo di pazienti diabetici, sono stati riportati valori inferiori di emoglobina glicata (HbA1c) nel braccio di trattamento con acido bempedoico rispetto a quanto osservato nel gruppo placebo (in media 0,2%) [4]

- L'acido bempedoico è risultato ben tollerato nei pazienti con storia di diabete[1-3]

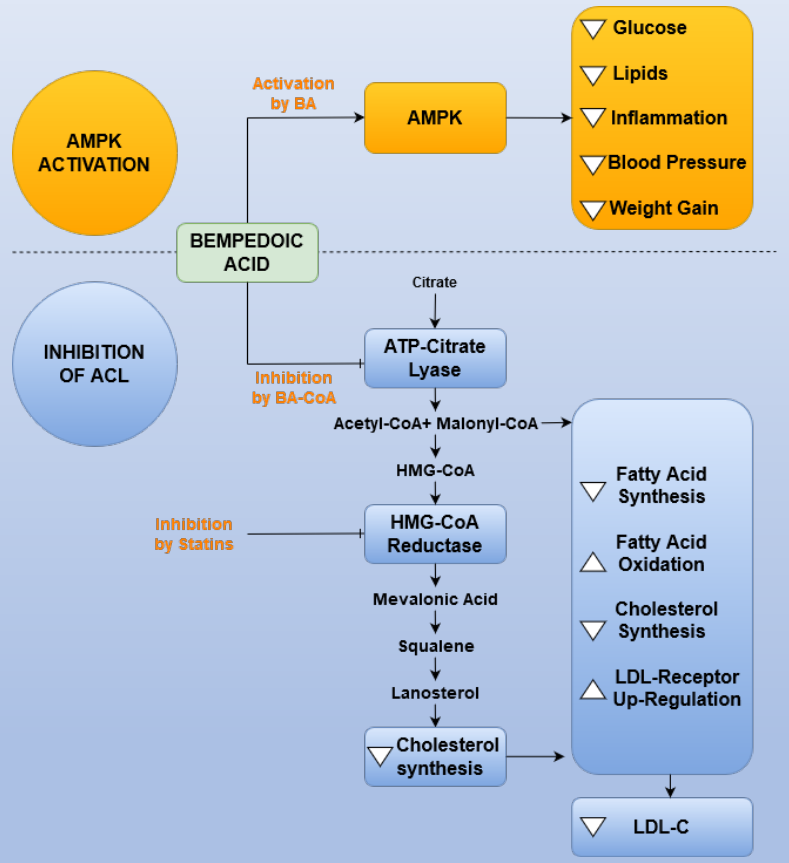
- Abbiamo la disponibilità anche di dati derivanti da studi di fase 2 e metanalisi

References

1. Gutierrez MJ, Rosenberg NL, Macdougall DE, et al. *Arterioscler Thromb Vasc Biol*. 2014;34(3):676-83.
2. Bays HE, Baum SJ, Brinton EA, et al. *American College of Cardiology/World Congress of Cardiology 2020*.
3. Leiter LA, Banach M, Catapano AL, et al. *American Diabetes Association. 80th Scientific Sessions*, 185-OR
4. NILEMDO® (bempedoic acid) Summary of Product Characteristics.

Dual Mechanism of Action of BA: ACL inhibition and AMPK activation

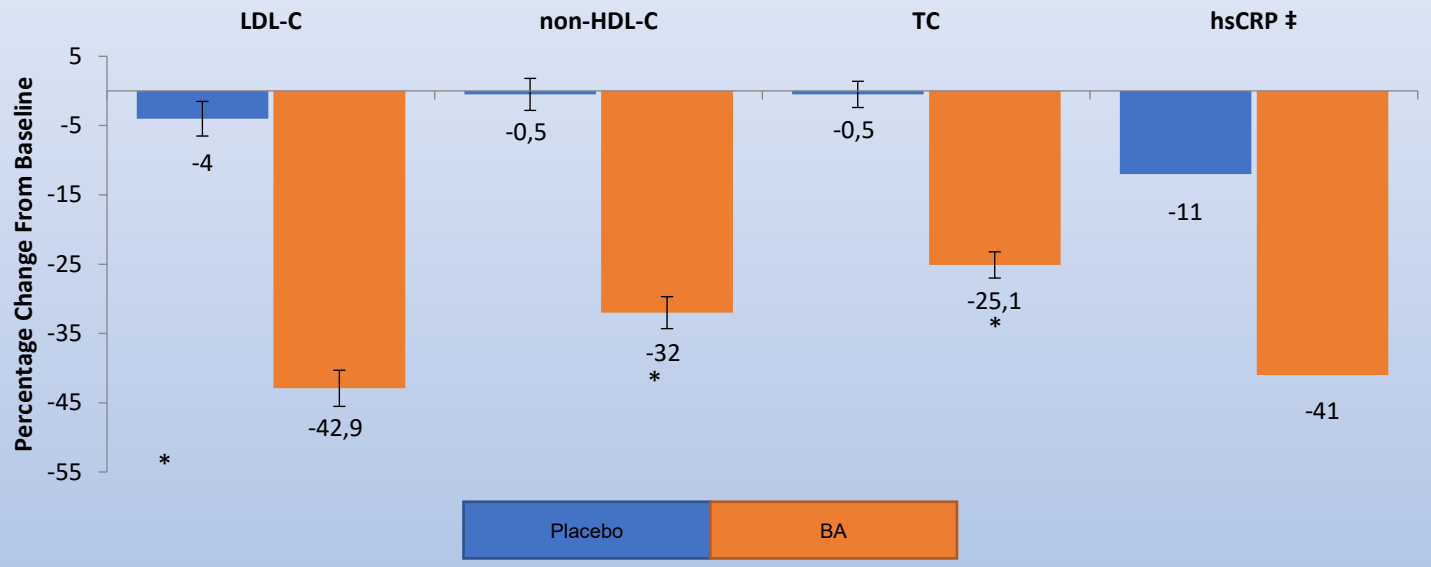
BA inhibits ACL to reduce cholesterol synthesis resulting in the reduction of low-density lipoprotein cholesterol (LDL-C).



BA also activates AMPK. This pathway has known effects on glucose, lipids, inflammation, blood pressure, and weight gain

Pinkosky SL et al. Nat Commun. 2016;7:13457.

Efficacy of bempedoic acid in patients With Hypercholesterolemia and Type 2 Diabetes Mellitus (Study 005)

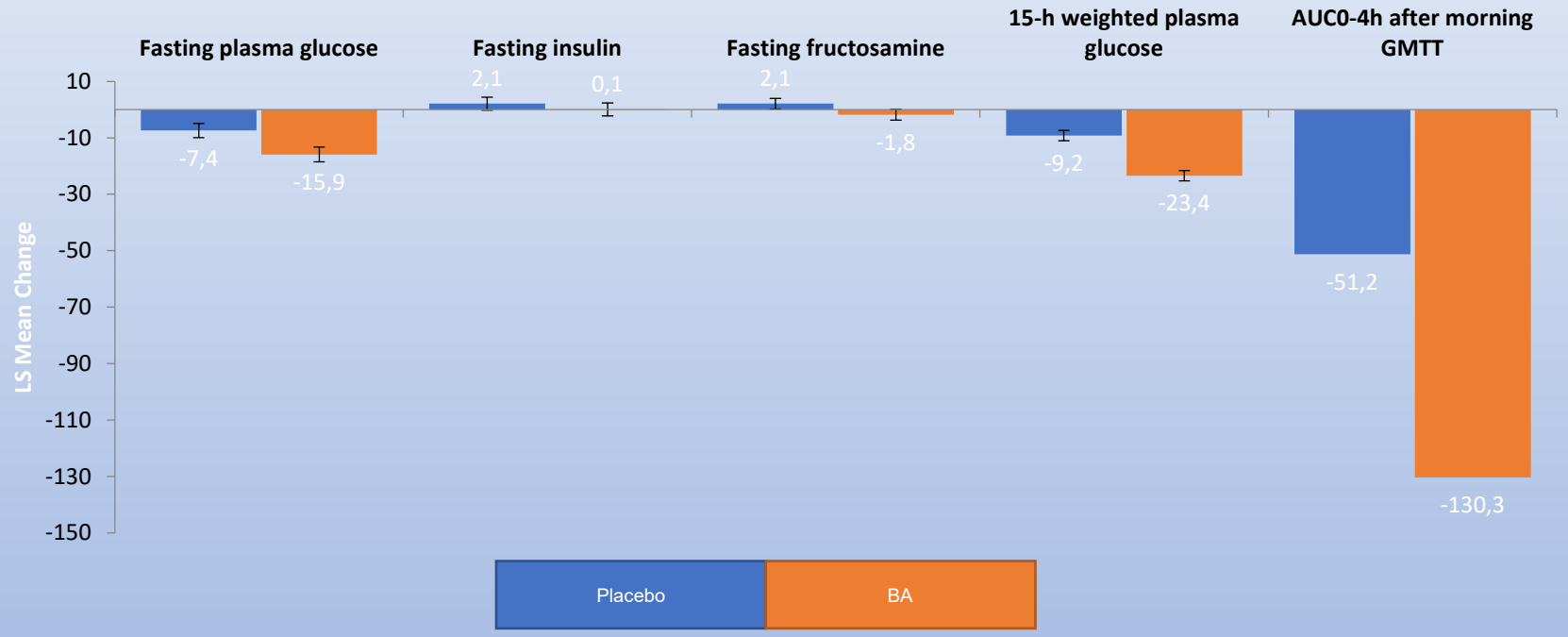


Least squares mean percent change in lipid and inflammation parameters from baseline to Week 4.Values are least-squares mean±SE.
*p < 0.0001 versus placebo. ‡ Median percentage change.

Gutierrez MJ et al., Arterioscler Thromb Vasc Biol. 2014;34(3):676-83

Efficacy of bempedoic acid in patients With Hypercholesterolemia and Type 2 Diabetes Mellitus (Study 005)

Glycaemic Endpoints at Week 4

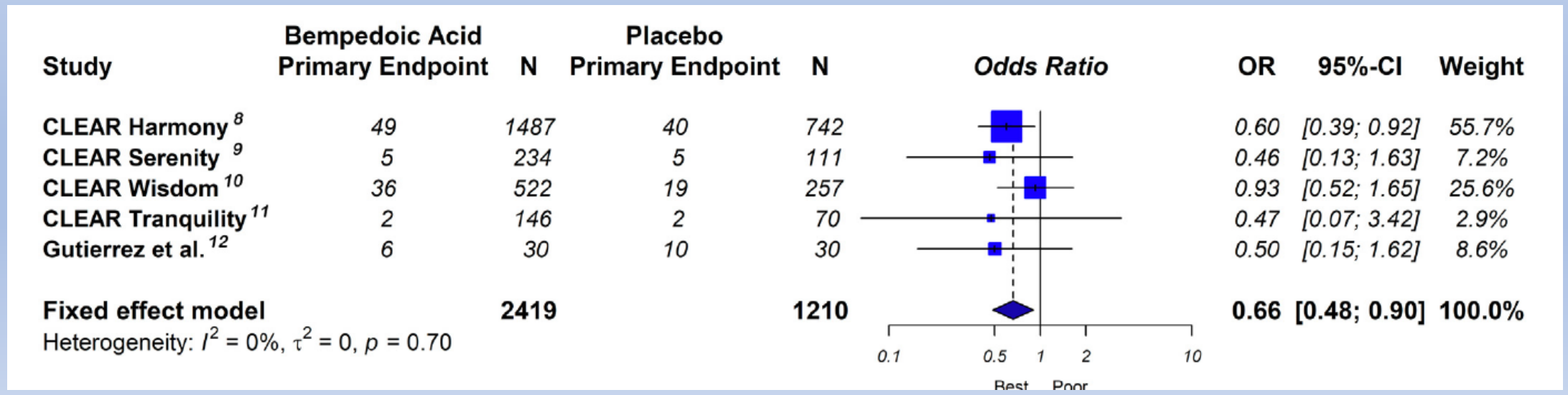


Least squares mean change from baseline to end point (Week 4) in glycaemic markers. Values are least-squares mean±SE $AUC_{0\text{-}4\ h}$ indicates area under the concentration-time curve from time 0 to 4 hours; GMTT, glucose meal tolerance test; and LS, least squares.

Gutierrez MJ et al., Arterioscler Thromb Vasc Biol. 2014;34(3):676-83

Effect of bempedoic acid on new onset or worsening diabetes
A meta-analysis

Study	Treatment arm	N	Baseline characteristics	Control Arm	N	Baseline characteristics	Population included	Follow-up (weeks)
CLEAR Harmony	Bempedoic Acid (180 mg/day)	1488	Age 65.8 ± 9.1 y Female: 26.1% Diabetes: 28.6%	Placebo	742	Age 66.8 ± 8.6 y Female: 28.7% Diabetes: 28.6%	ASCVD and/or HeFH LDL-C > 70 mg/dl	52
CLEAR Serenity	Bempedoic Acid (180 mg/day)	224	Age 65.2 ± 9.7 y Female: 56.8% Diabetes: 26.9%	Placebo	107	Age 65.1 ± 9.2 y Female: 55.0% Diabetes: 23.4%	Statin intolerance LDL-C > 130 mg/dl (primary prevention) LDL-C > 100 mg/dl (ASCVD or HeFH)	24
CLEAR Wisdom	Bempedoic Acid (180 mg/day)	522	Age 64.1 ± 8.8 y Female: 37.2% Diabetes: 29.7%	Placebo	257	Age 64.7 ± 8.7 y Female: 34.6% Diabetes: 31.5%	ASCVD and/or HeFH LDL-C > 70 mg/dl	52
CLEAR Tranquility	Bempedoic Acid (180 mg/day)	181	Age 63.8 ± 10.8 y Female: 60.2% Diabetes: 19.3%	Placebo	88	Age 63.7 ± 11.3 y Female: 63.6% Diabetes: 19.3%	Statin intolerance C-LDL > 100 mg/dl	12
Gutierrez et al.	Bempedoic Acid (80–120 mg/day)	30	Age 55.3 ± 6.9 y Female: 43.3% Diabetes: 100% (HbA1c 8.0 ± 0,7%)	Placebo	30	Age 56.0 ± 9.9 y Female: 33.3% Diabetes: 100% (HbA1c 8,2 ± 0,9%)	Type 2 Diabetes C-LDL > 100 mg/dl	4



CLEAR OUTCOMES

The NEW ENGLAND JOURNAL of MEDICINE

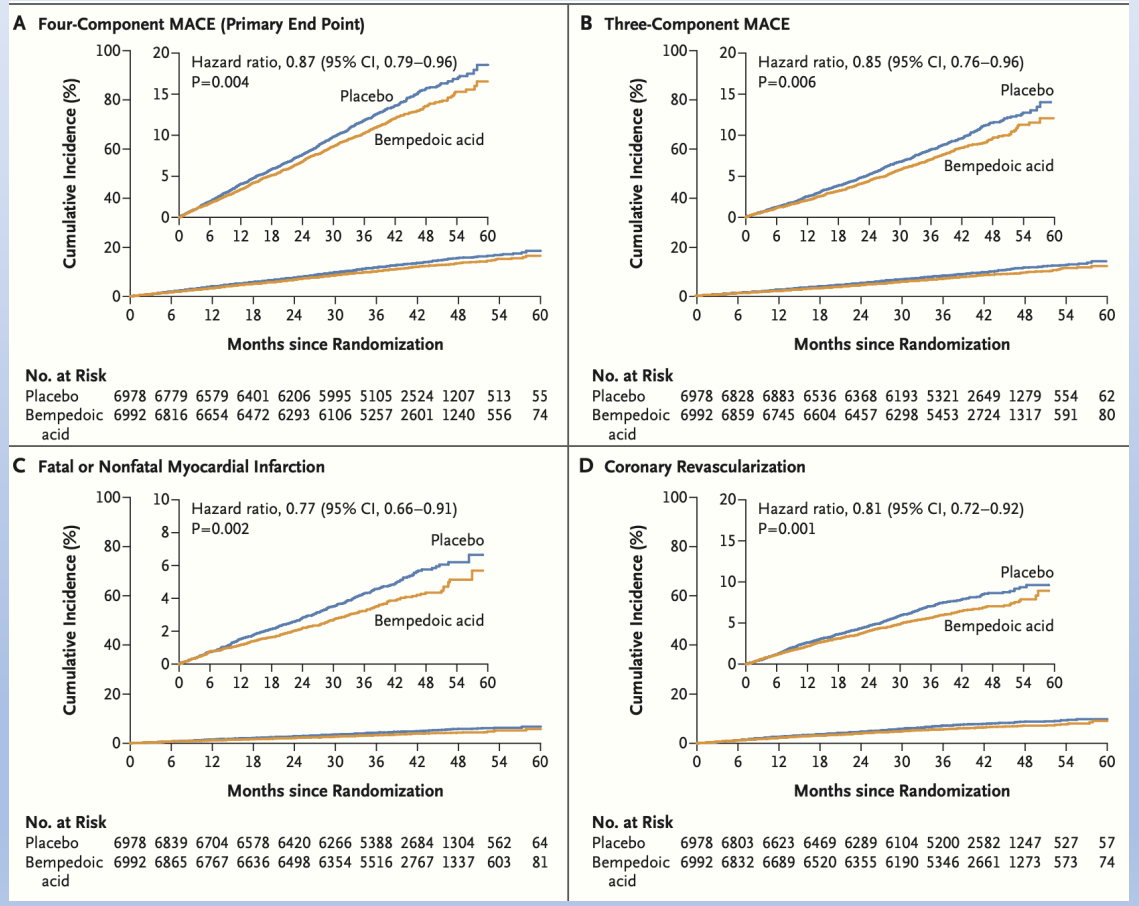
ESTABLISHED IN 1812 APRIL 13, 2023 VOL. 388 NO. 15

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

S.E. Nissen, A.M. Lincoff, D. Brennan, K.K. Ray, D. Mason, J.J.P. Kastelein, P.D. Thompson, P. Libby, L. Cho, J. Plutzky, H.E. Bays, P.M. Moriarty, V. Menon, D.E. Grobbee, M.J. Louie, C.-F. Chen, N. Li, L.A. Bloedon, P. Robinson, M. Horner, W.J. Sasiela, J. McCluskey, D. Davey, P. Fajardo-Campos, P. Petrovic, J. Fedacko, W. Zmuda, Y. Lukyanov, and S.J. Nicholls, for the CLEAR Outcomes Investigators*

13,970 soggetti (6992 acido bempedoico; 6978 placebo) in follow-up per 40 mesi:

- **Riduzione** del **rischio** relativo (RRR) del **20%** di eventi avversi cardiovascolari maggiori (**MACE-4**)
- **Riduzione** del **rischio** di un **primo evento MACE-4 del 13**% tra i soggetti ad alto rischio di malattia cardiovascolare che non potevano o non volevano assumere statine
- **Assenza** di nuovi casi di **DM** (neutralità su glicemia e HbA1c)
- iperuricemia (10,9% vs. 5,6%), gotta (3,1% vs. 2,1%) e colelitiasi (2,2% vs. 1,2%).



Nissen SE, Lincoff AM, Brennan D, et al. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. *N Engl J Med*. 2023;388(15):1353-1364. doi:10.1056/NEJMoa2215024

Alirocumab-Evolocumab (PCSK9i)
CRITERI DI ESCLUSIONE DAL TRATTAMENTO
anche se rispettano le indicazioni

PAZIENTI>80 ANNI

IRC GRAVE (anche se a rischio CV molto alto)

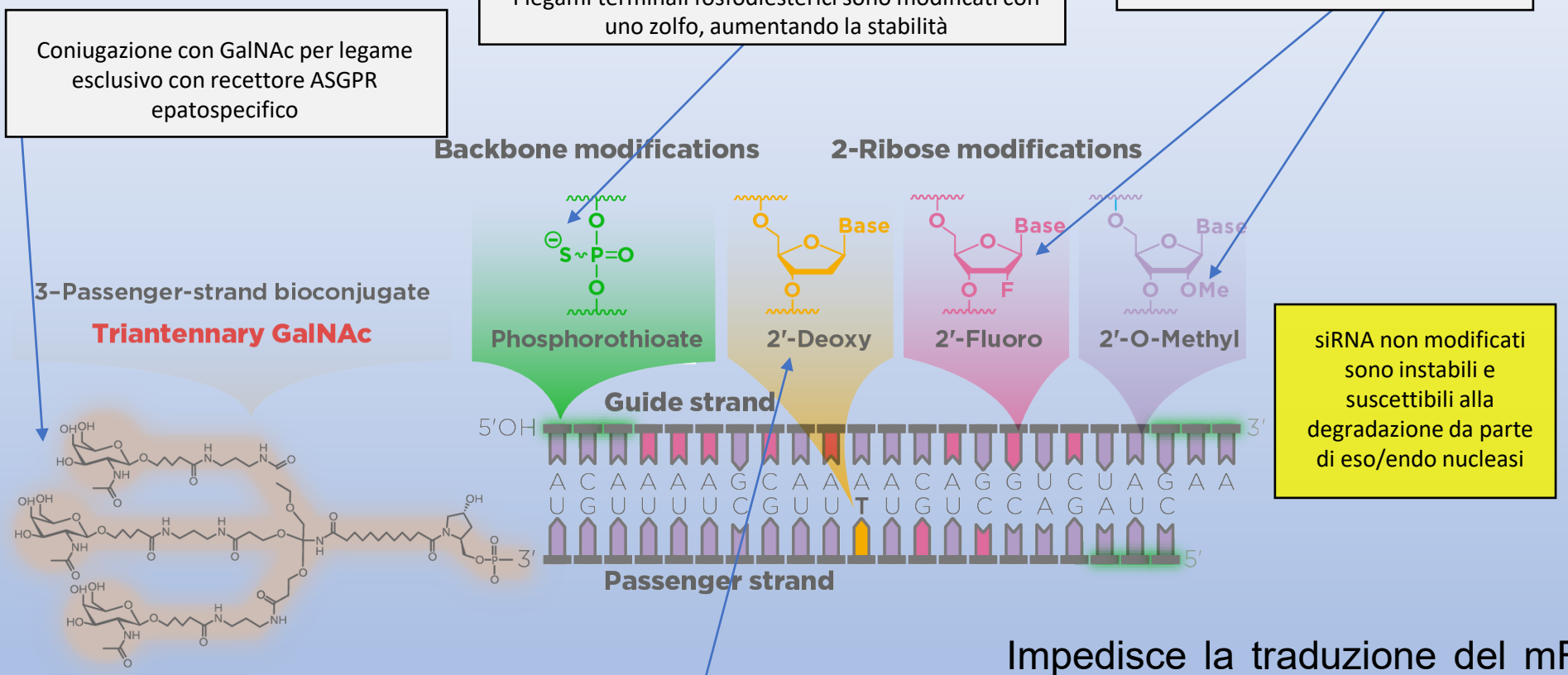
INSUFFICIENZA EPATICA GRAVE (valutata con punteggio di CHILD PUGH C)

Struttura chimica di Inclisiran

Le modificazioni in posizione 2 sui ribosi strutturali, permettono la stabilizzazione del composto

I legami terminali fosfodiesterici sono modificati con uno zolfo, aumentando la stabilità

Coniugazione con GalNAc per legame esclusivo con recettore ASGPR epatospecifico



siRNA non modificati sono instabili e suscettibili alla degradazione da parte di eso/endo nucleasi

Nella sequenza della catena senso vi è una desossitimidina che favorisce il legame con il RISC

Impedisce la traduzione del mRNA di *PCSK9* attraverso l'RNA interference

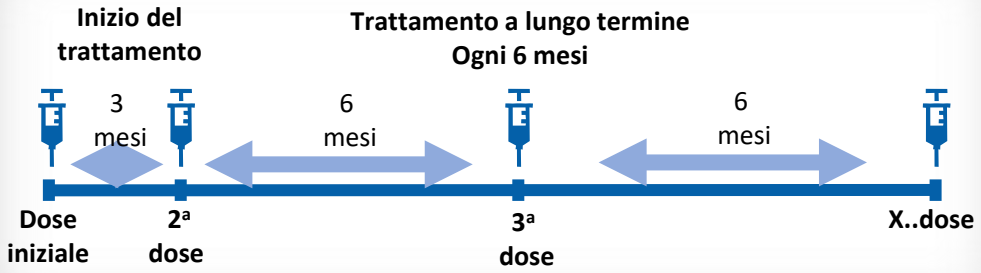
1. Khvorova A Engl J Med. 2017;376(1):4-7: 2. Leqvio | European Medicines Agency (europa.eu)
EPAR Leqvio 3. SmPC Incliriran/Leqvio

Trattamento con inclisiran
Dosaggio e somministrazione

Formulazione[1,2]

- Siringa preriempita
- Ogni siringa preriempita contiene inclisiran sodico equivalente a 284 mg di inclisiran in 1,5 mL di soluzione
- Conservazione a temperatura ambiente

Regime posologico[1,2]



Sviluppo[1]

programma di sviluppo ORION per determinarne l'efficacia, la sicurezza e la tollerabilità

Somministrazione[1,2]

Uso sottocutaneo.

Inclisiran è somministrato tramite iniezione sottocutanea nell'addome; siti di iniezione alternativi comprendono il braccio o la coscia.

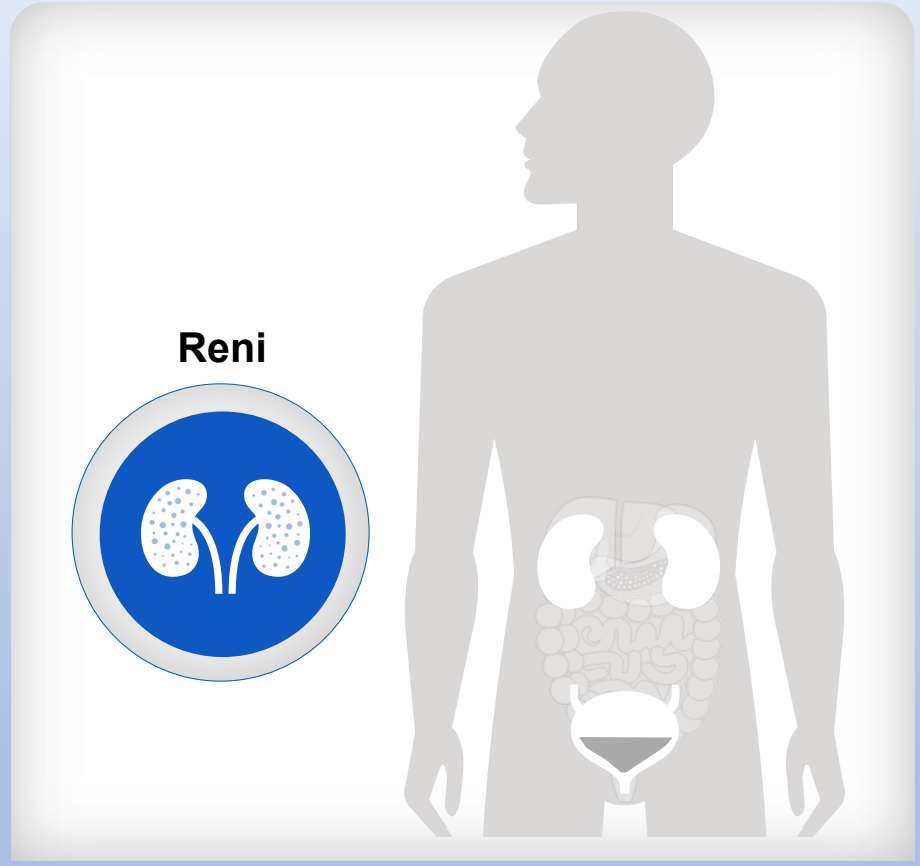
Ogni dose da 284 mg viene somministrata utilizzando una singola siringa preriempita.

Ogni siringa preriempita è solo monouso.

Inclisiran è destinato alla somministrazione da parte di un operatore sanitario.

Proprietà farmacocinetiche di inclisiran
Reni

- I reni sono l'organo principale per l'eliminazione di inclisiran
- Concentrazioni di inclisiran sono presenti anche nei reni, ma sono da 2 a 5 volte inferiori rispetto a quelle riscontrate nel fegato[1]
- Il 16% di inclisiran viene eliminato attraverso i reni e la sua emivita terminale è di ~9 ore[2]



INCLISIRAN E DISFUNZIONE RENALE

ORION-7 studio nella disfunzione renale

Non sono necessari aggiustamenti di dose in pazienti con problematiche renali

Studio di fase 1 PK/PD singola-dose su in pazienti con fx renale normale, o lieve, moderata o severa insufficienza renale* trattati con singola dose di 300 mg di inclisiran† (N=31)

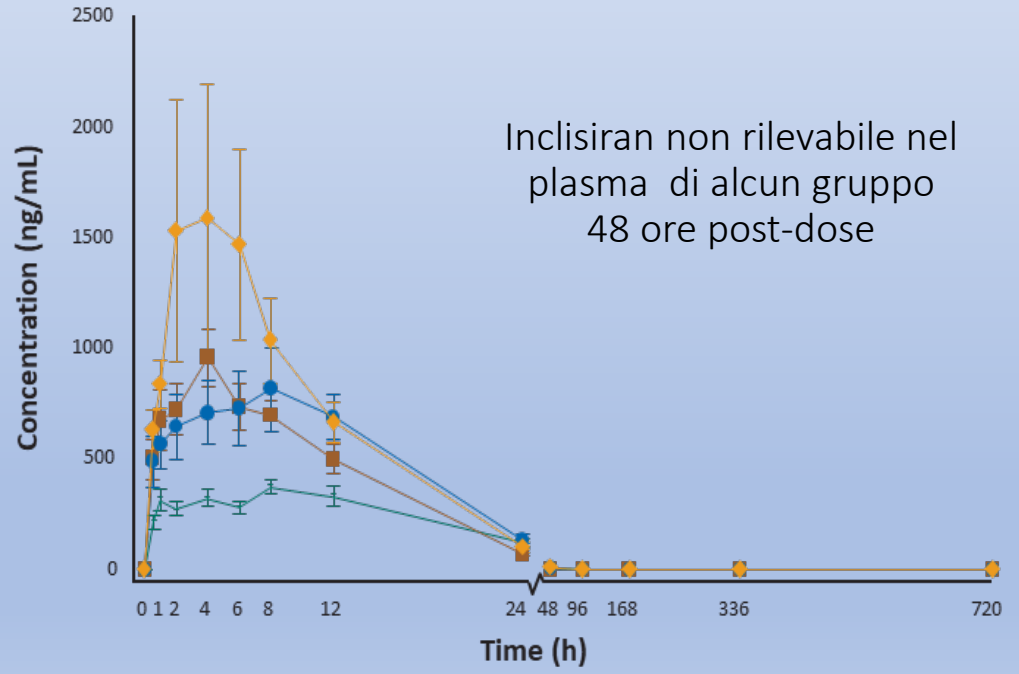
Risultati

L'AUC0-inf di inclisiran è aumentata con maggiori gradi di compromissione renale

La concentrazione plasmatica massima è aumentata con gradi maggiori di compromissione renale, con un aumento di >4 volte della compromissione renale grave.

Il profilo di sicurezza di inclisiran non è stato influenzato da compromissione renale

Concentrazione plasmatica media di inclisiran



Wright RS, et al. *Mayo Clin Proc.* 2020;95(1):77-89.

*Normal renal function: estimated CrCl level, >90 mL/min; mild renal impairment: CrCl level, 60-89 mL/min; moderate renal impairment: CrCl level, 30-59 mL/min; severe renal impairment: CrCl level, 15-29 mL/min.
†300 mg inclisiran sodium salt, equivalent to 284 mg of inclisiran.

TAKE HOME MESSAGES

1) Il paziente diabetico nefropatico è un soggetto a rischio cardiovascolare molto elevato la cui dislipidemia deve essere trattata in fase conservativa con statine+ezetimibe come prima scelta
2) L'intolleranza alle statine è frequente in questa sottopopolazione di pazienti e deve essere diagnosticata con accuratezza
3) Se il paziente è intollerante alle statine si può prendere in considerazione ezetimibe+ PCSK9i o Acido Bempedoico (IRC lieve e moderata) ma spesso i targets non vengono raggiunti
4) L'IRC avanzata e la dialisi sono controindicazioni ai farmaci di nuova generazione

GRAZIE PER L’ATTENZIONE