4° Modulo | Le dimensioni del problema: epidemiologia delle dislipidemie

Relatore: Prof. GIOVANNA LIUZZO

Direttore Cardiologia d'Urgenza

Fondazione Policlinico Universitario A. Gemelli - IRCCS

Università Cattolica del Sacro Cuore - Roma

AGENDA

1. A livello mondiale, i livelli medi di colesterolo sono rimasti sostanzialmente immodificati nelle ultime 4 decadi
2. Target di trattamento del LDL-C nelle linee guida, nel tempo
3. Attuale percezione e pratica nel trattamento delle dislipidemie
4. Gestione subottimale delle dislipidemie nella pratica quotidiana: segnali di allarme dal mondo reale
5. Rischio cardiovascolare residuo a basso LDL-C: Trigliceridi, Colesterolo Remnant, Lipoproteina(a), infiammazione …..

1. A livello mondiale, i livelli medi di colesterolo sono rimasti sostanzialmente immodificati nelle ultime 4 decadi

Article

Repositioning of the global epicentre of non-optimal cholesterol Nature | Vol 582 | 4 June 2020 |

A livello regionale, il non HDL-C è diminuito notevolmente nei paesi occidentali ad alto reddito e nell'Europa centrale e orientale. L'Europa nord-occidentale aveva i livelli più alti nel 1980, ma ha registrato i cali maggiori(>0,3 mmol l^{-1} per decennio). Al contrario, il non HDL-c è aumentato nell'Asia orientale e sudorientale, nell'Africa sub-sahariana ….

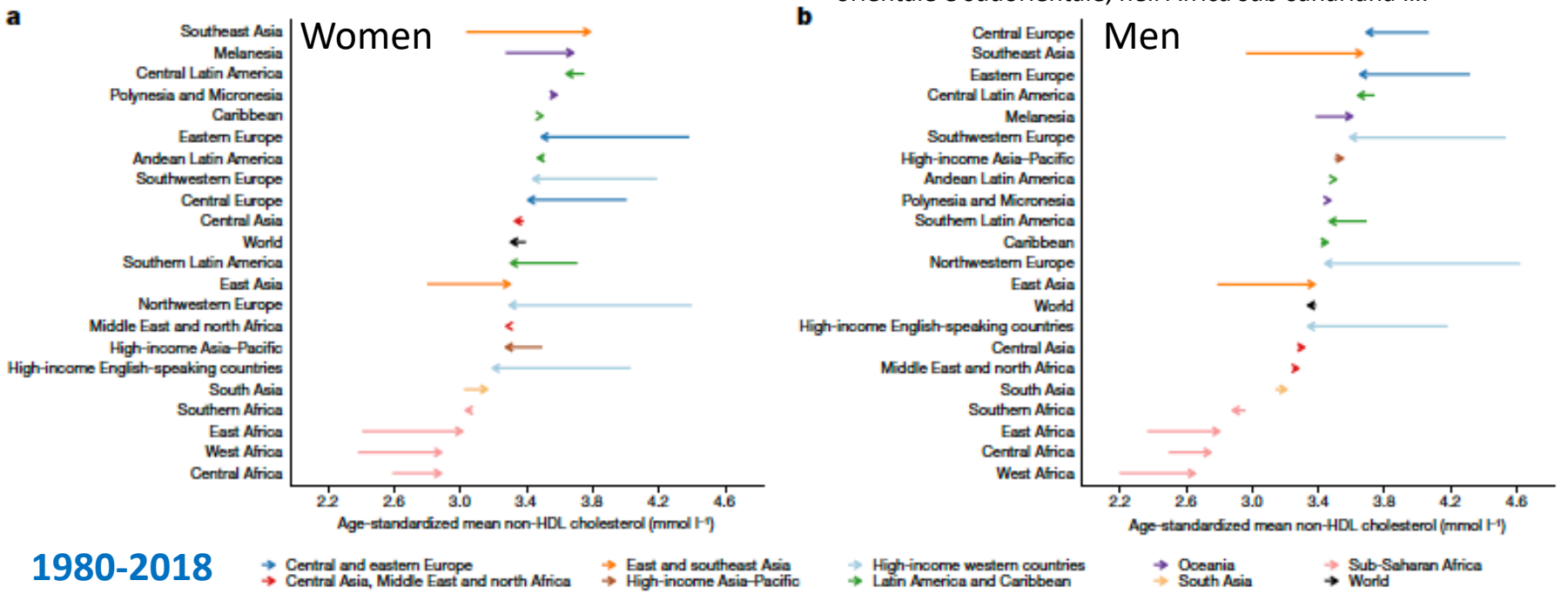
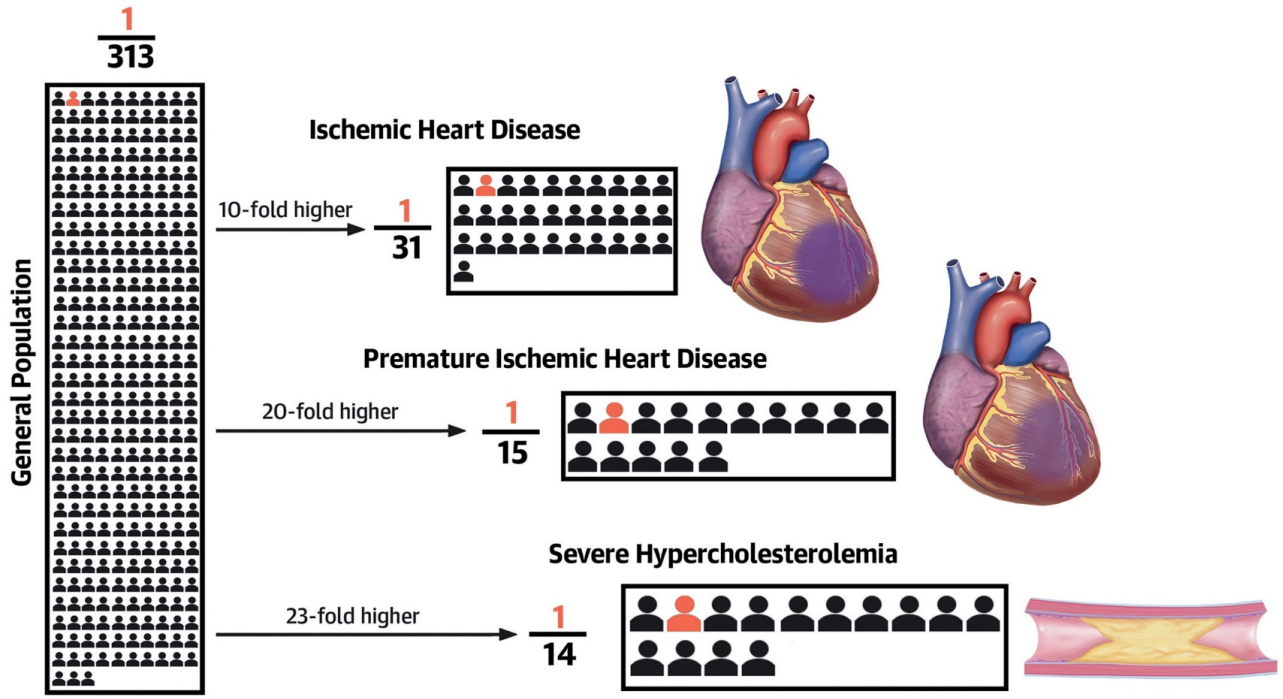


Fig. 2 | Change in age-standardized mean non-HDL cholesterol between 1980 and 2018 by region for women and men. a, Age-standardized mean non-HDL cholesterol in women. **b**, Age-standardized mean non-HDL cholesterol in men. The start of the arrow shows the level in 1980 and the head indicates the level in 2018. See Extended Data Fig. 3 for age-standardized mean HDL cholesterol. One mmol l^{-1} is equivalent to 38.61 mg dl^{-1}.

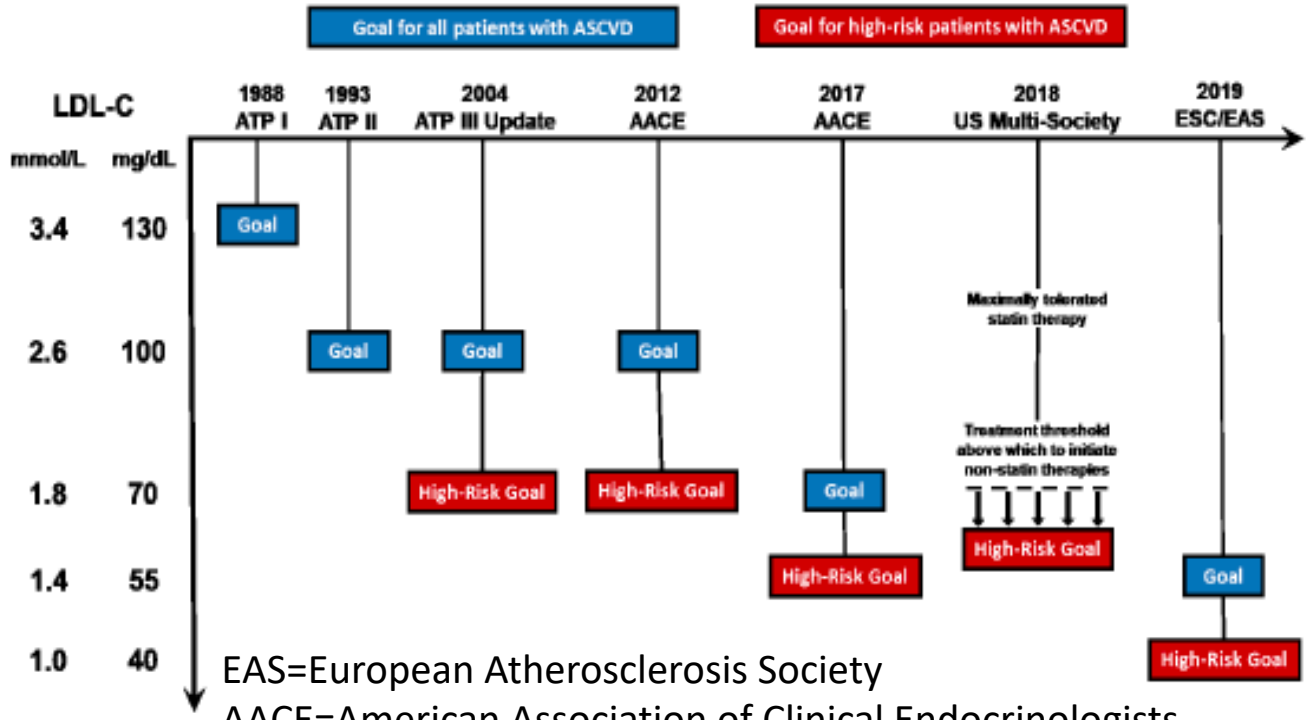
Worldwide Prevalence of Familial Hypercholesterolemia: Meta-Analyses of 11 Million Subjects

CENTRAL ILLUSTRATION: Prevalence of Familial Hypercholesterolemia



Beheshti, S.O. et al. J Am Coll Cardiol. 2020;75(20):2553-66.

2. Target di trattamento del LDL-C nelle linee guida, nel tempo



EAS=European Atherosclerosis Society
AACE=American Association of Clinical Endocrinologists

Le ultime linee guida europee 2019 hanno raccomandato un target di LDL-C < 1,4 mmol/L (55 mg/dL) nelle popolazioni ad alto rischio e un target più aggressivo di < 1 mmol/L (40 mg/dL) nei pazienti con eventi ricorrenti.

I target di LDL-C sono stati suggeriti per la prima volta nel 1988 dalle linee guida del Adult Treatment Panel (ATP) ed ampiamente raccomandati per qualsiasi individuo a rischio di ASCVD. Nei tre decenni successivi, le linee guida hanno suggerito target più bassi per coloro che hanno una ASCVD accertata e per coloro che sono ad alto rischio di eventi ricorrenti.

2. Target di trattamento del LDL-C nelle linee guida, nel tempo

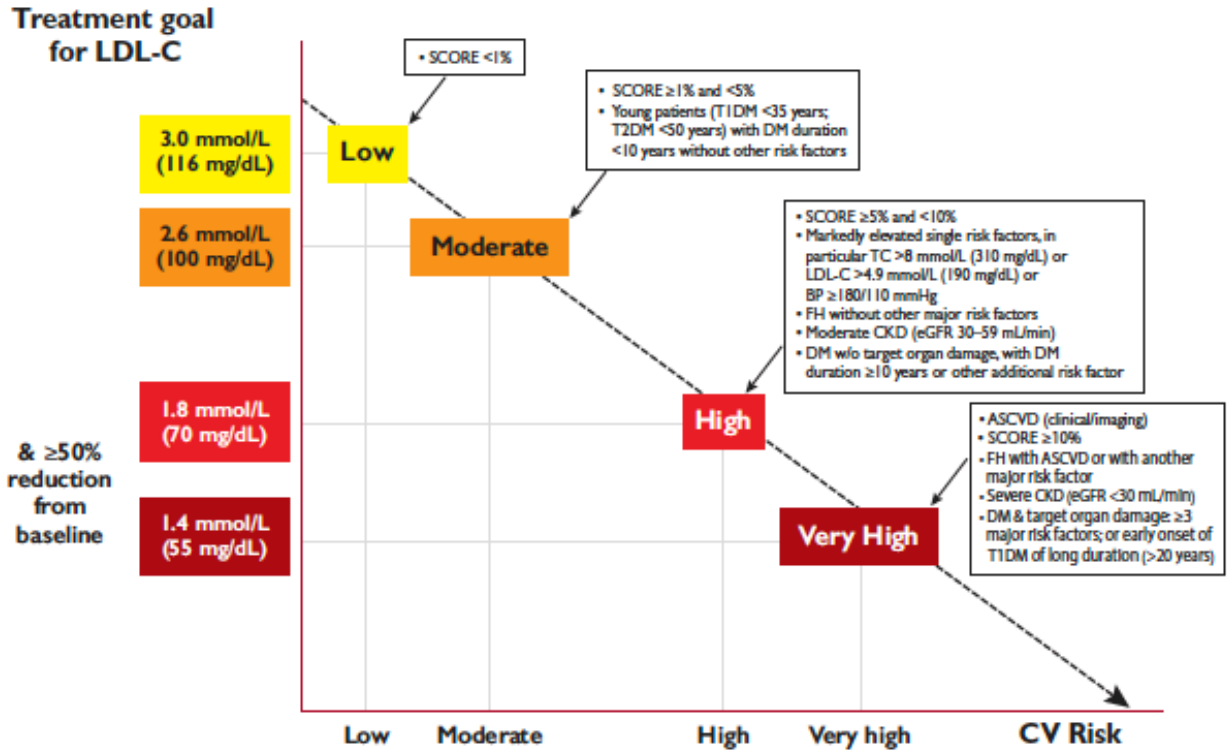
Analisi evidence-based e studi randomizzati controllati (RCT) supportano il concetto di «lower is better» o «lowest is best» riguardo i livelli di colesterolo proaterogenico (LDL-C, non HDL-C, apo B)

Table 1 LDL-C levels achieved in randomized clinical trials influencing changes to guidelines for the highest ASCVD risk individuals and validation of lower outcomes at intensified lower levels

LDL-C Level Achieved	<70 mg/dL, 2004 ATP III Update		<55 mg/dL, 2017 AACE/ACE		<30 mg/dL	
Trial Analysis	RCT	LDL-C, mg/dL	RCT	LDL-C, mg/dL	RCT	LDL-C, mg/dL
Level 1A RCT	PROVE-IT [31]	62	IMPROVE-IT [58]	53.5	FOURIER [71]	30
Prespecified or Post-Hoc Subgroup Analyses	HPS [29] - lowest tertile - sub-group <100	 69 65	PROVE-IT [51] TNT [52] VA Palo Alto Health Care [53] JUPITER [54]	40 54 40 44	IMPROVE-IT [70] FOURIER [72]	<30 <20 <10 (7)
Meta-analyses RCT Statin Trials			8 Statin RCT Trials - divided by Quartiles [55] - divided by Septiles [56]	 Q1, <62; mean, 49 S1, <50		
Imaging (Coronary IVUS)			GLAGOV [65]	36.6		
Coronary IVUS trial PAV changes by linear regression analysis (LRA)	REVERSAL [30] mean 73 mg/dL	LRA 83 → 30	REVERSAL [30] Mean 73 mg/dL	LRA 83 → 30	8 Statin IVUS trials [57] GLAGOV [65]	LRA 93 → 15 LRA 90 → 20

ESC European Society of Cardiology
European Heart Journal (2020) **41**, 111–188
doi:10.1093/eurheartj/ehz455
ESC/EAS GUIDELINES

Treatment goals for LDL-C across categories of total cardiovascular disease risk

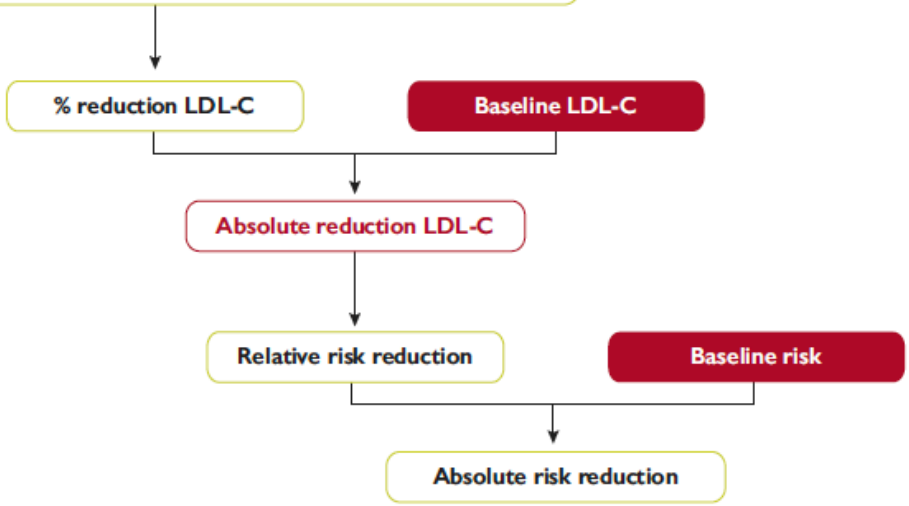


ESC European Society of Cardiology
European Heart Journal (2020) 41, 111–188
doi:10.1093/eurheartj/ehz455
ESC/EAS GUIDELINES

Expected clinical benefits of low-density lipoprotein cholesterol-lowering therapies

Intensity of lipid lowering treatment

Treatment	Average LDL-C reduction
Moderate intensity statin	≈ 30%
High intensity statin	≈ 50%
High intensity statin plus ezetimibe	≈ 65%
PCSK9 inhibitor	≈ 60%
PCSK9 inhibitor plus high intensity statin	≈ 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	≈ 85%

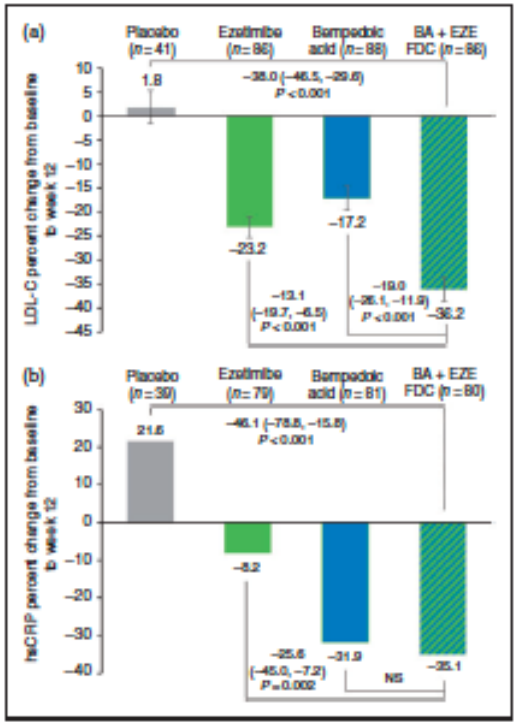


©ESC 2019

- Ogni riduzione assoluta di 1,0 mmol/L in LDL-C è associata ad una riduzione del 20% del rischio di eventi CV
- Riduzioni assolute maggiori di LDL-C portano a maggiori riduzioni proporzionali del rischio.

Table 1 Percent of LDL-C-lowering provided by various lipid modifying therapies. Bempedoic acid is more likely to be used in statin-intolerant patients and provides greater LDL-C percent reduction in this setting. A combination pill of bempedoic acid and ezetimibe is currently available that further lowers LDL-C by 35% in patients on stable background statin therapy.

Treatment Category	Examples	LDL-C % Reduction
High intensity statin		≥50%
Moderate intensity statin		30–49%
Low intensity statin		< 30%
Ezetimibe		20–25% when added to baseline statin therapy
Bile Acid Sequestrants		15% when added to baseline statin therapy
		15–25% when not receiving statin therapy
PCSK9 Inhibitor		50–70% when added to baseline statin therapy
Bempedoic Acid	Bempedoic acid 180 mg daily	16–18% when added to baseline statin therapy 20–22% when not receiving statin therapy
Bempedoic Acid + Ezetimibe Combination	Bempedoic acid 180 mg + Ezetimibe 10 mg daily	35% when added to baseline statin therapy
Inclisiran	Inclisiran 300 mg on day 1, day 90, then q6 months	50% when added to baseline statin therapy



Effetto di una dose fissa di acido bempedoico (180 mg) + ezetimibe (10 mg) in pazienti con iper-COL e alto rischio CVD trattati con statine alla dose massima tollerata

Cambiamenti in LDL-C e hsCRP dal basale alla 12°settimana

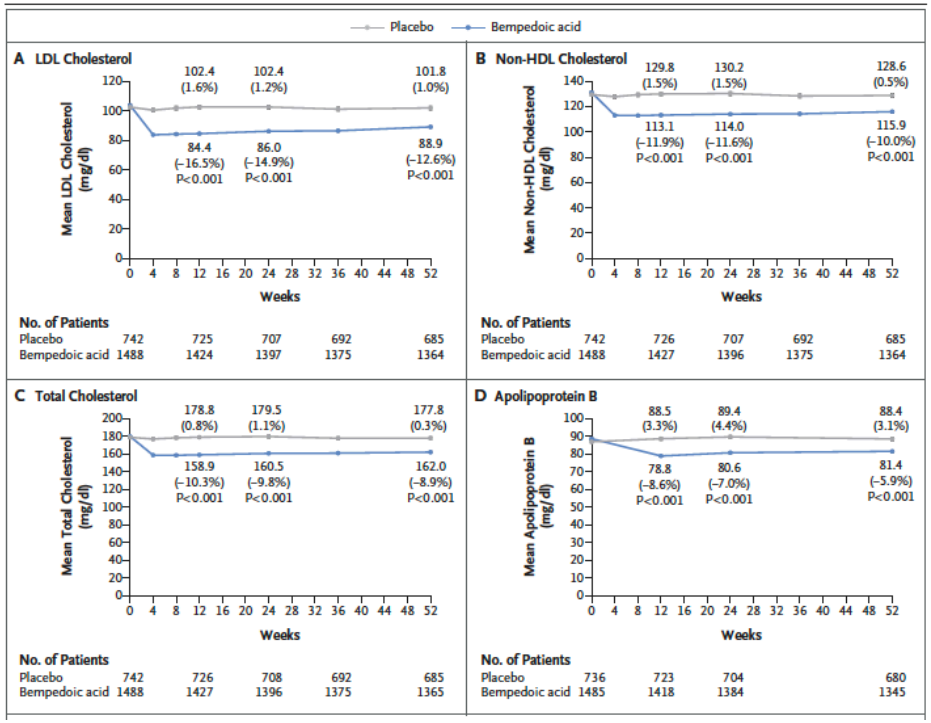
Eur J Prev Cardiol 2020; 27: 593–603

N Engl J Med 2019;380:1022-32.

ORIGINAL ARTICLE

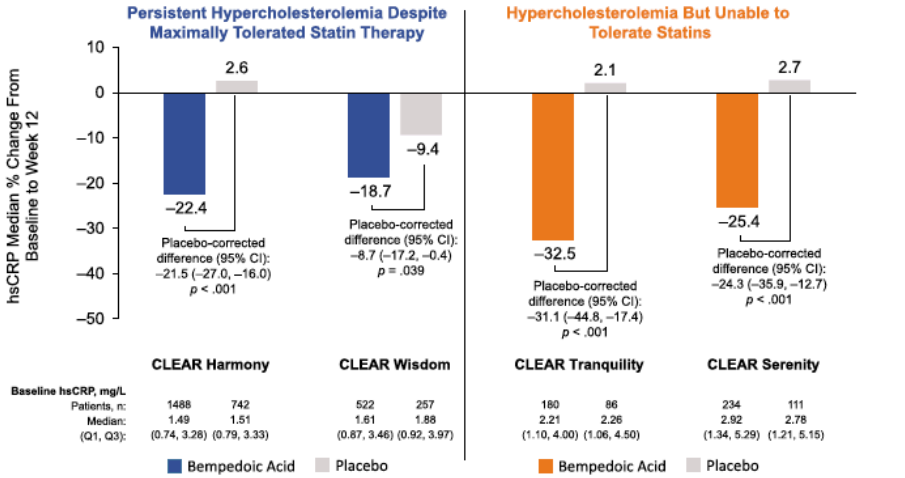
Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol

Kausik K. Ray, M.D., M.Phil., Harold E. Bays, M.D., Alberico L. Catapano, Ph.D., Narendra D. Lalwani, Ph.D., M.B.A., LeAnne T. Bloedon, M.S., R.D., Lulu R. Sterling, Ph.D., Paula L. Robinson, M.S., and Christie M. Ballantyne, M.D., for the CLEAR Harmony Trial*



In 52 settimane, l'acido bempedoico aggiunto alla dose massima tollerata di statine non ha dato una maggiore incidenza di eventi avversi rispetto al placebo e ha ottenuto una < significativa di LDL-C

Ballantyne CM, Cardiovascular Drugs and Therapy https://doi.org/10.1007/s10557-021-07147.



Effect of bempedoic acid on hsCRP after 12 weeks of treatment [33–36]. *CI* confidence interval, *hsCRP* high-sensitivity C-reactive protein

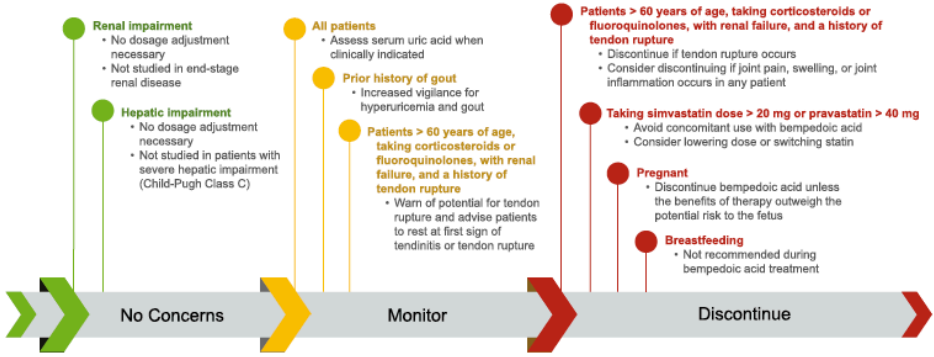


Fig. 5 Management of patients receiving bempedoic acid therapy

ESC European Society of Cardiology
European Journal of Preventive Cardiology
doi:10.1093/eurjpc/zwaa156

FULL RESEARCH PAPER
Lipids

3. Current perceptions and practices in lipid management: results of a European Society of Cardiology/European Atherosclerosis Society Survey

Konstantinos C. Koskinas[1]*, Alberico L. Catapano[2], Colin Baigent [3], Lale Tokgozoglu [4], and Francois Mach[5]

[1]Department of Cardiology, Bern University Hospital, 3010 Bern, Switzerland; [2]Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy; [3]Nuffield Department of Population Health, University of Oxford, Oxford, UK; [4]Department of Cardiology, Hacettepe University, Ankara, Turkey; and [5]Department of Cardiology, Geneva University Hospital, Geneva, Switzerland

Received 12 November 2020; revised 4 December 2020; editorial decision 11 December 2020; accepted 15 December 2020

Aims We sought to evaluate physicians' opinions and practices in lipid management.

Methods and results A web-based survey by the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) was distributed to 70 696 individuals at two time points, before and after publication of the 2019 ESC/EAS dyslipidaemia guidelines. Respondents (1271 in the first and 1056 in the second part) were most commonly cardiologists in Europe. More than 90% of participants reported that they regularly measure lipid levels and discuss lipid-lowering treatment with patients. More than 87% found the use of LDL-C goals useful or potentially useful, although it was acknowledged that recommended goals are frequently not achieved. Regarding the LDL-C goal according to the 2019 guidelines (<1.4 mmol/L for very high-risk patients), more than 70% of respondents felt that it is based on solid scientific evidence, but 31% noted that implementation should also consider available local resources and patient preferences. Statin intolerance was perceived as infrequent, affecting 1–5% of patients according to most respondents but was the main reason for not prescribing a statin to secondary-prevention patients, followed by patient non-adherence. Although most respondents reported that 11–20% of secondary-prevention patients have an indication to add a non-statin medication, fewer patients (<10% according to most respondents) receive these medications.

Conclusions This survey shows a high level of acceptance of the LDL-C treatment goals recommended by current ESC/EAS guidelines. Although patient-related factors were the main reported reasons for suboptimal lipid-lowering therapy, physician inertia to intensify treatment cannot be excluded as an additional contributing factor.

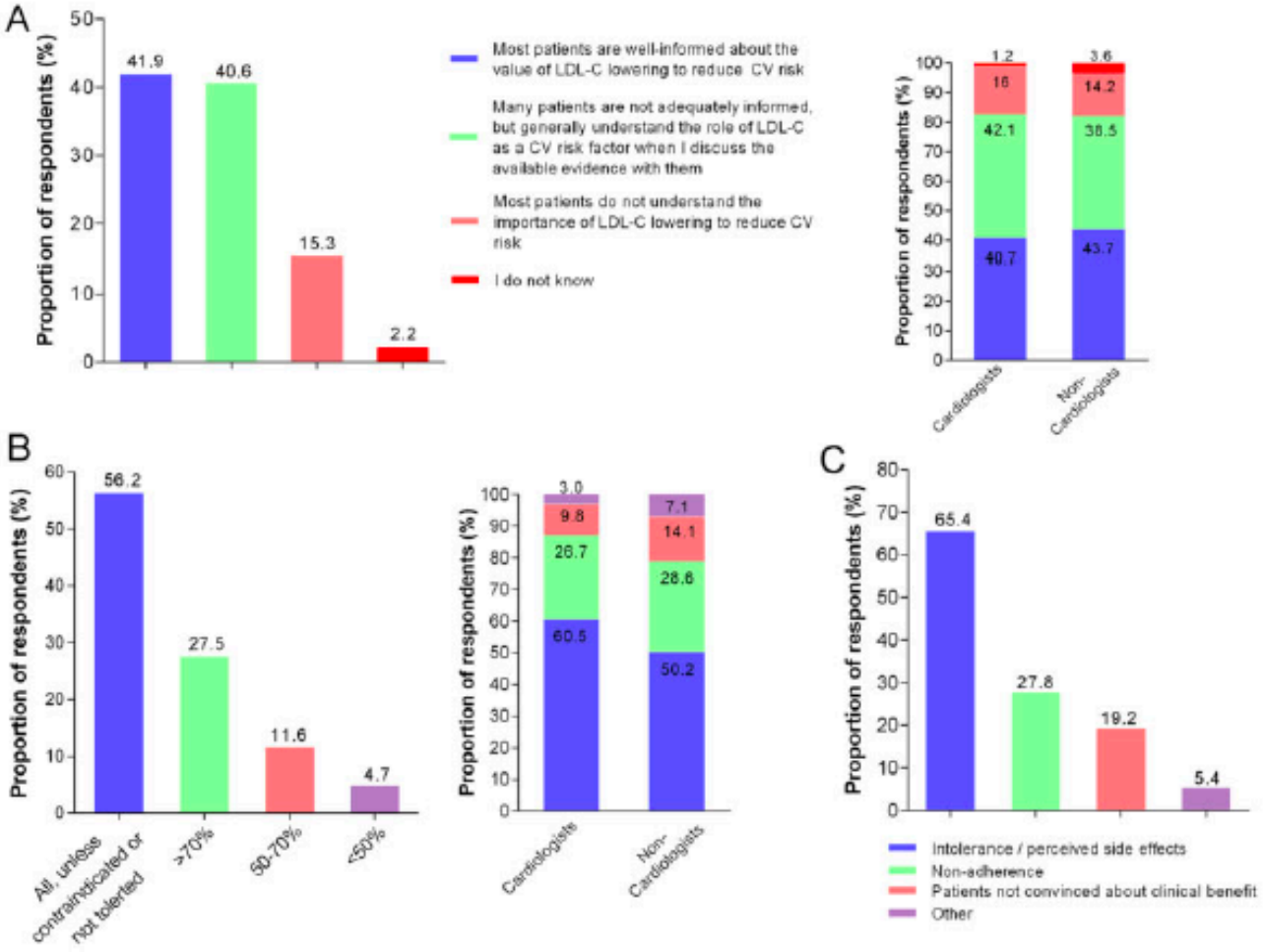
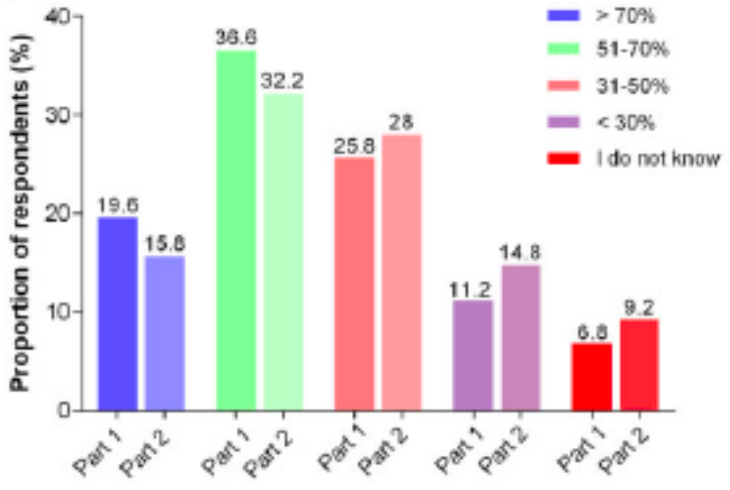
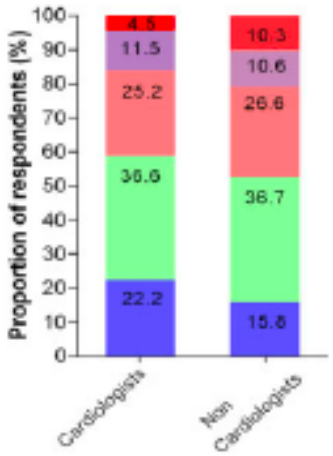
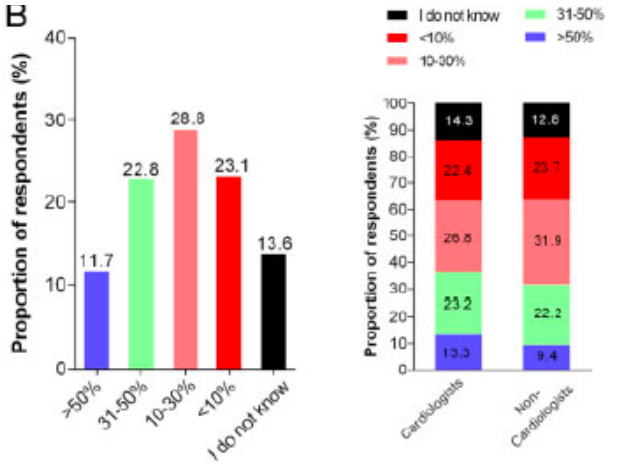


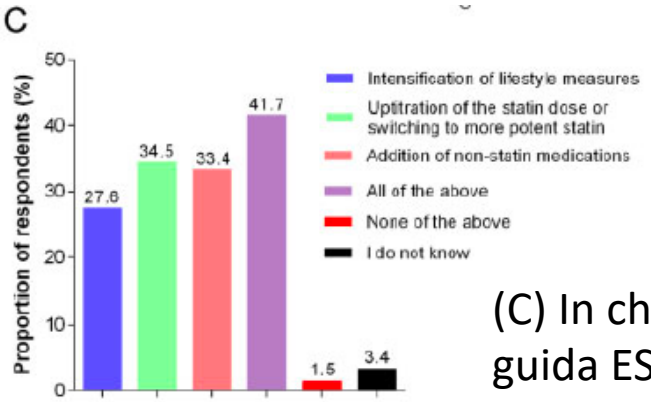
Figure 1 (*A*) How is LDL-C perceived as a risk factor by your patients with ASCVD? (single answer possible). (*B*) How many of your patients with ASCVD are on statin treatment? (single answer possible). (*C*) From your experience, the most common reason(s) for not prescribing a statin in patients with atherosclerotic cardiovascular disease include (multiple answers possible). For questions (*A*) and (*B*), stratified analyses for cardiologists vs. non-cardiologists are also shown.





Qual è la proporzione approssimativa di pazienti con ASCVD che raggiungono: (A) il target di LDL-C raccomandato dalle linee guida ESC/EAS 2016 (<1.8mmol/L)?
(B) Il target di LDL-C raccomandato dalle linee guida ESC/EAS 2019 (<1,4 mmol/L)?





(C) In che modo le nuove linee guida ESC/EAS sulle dislipidemie cambieranno la pratica clinica quotidiana nei pazienti a rischio di eventi CV alto o molto alto?

4. Gestione subottimale delle dislipidemie nella pratica quotidiana: segnali allarmanti dal mondo reale

Current lipid lowering treatment and attainment of LDL targets recommended by ESC/EAS guidelines in very high-risk patients with established atherosclerotic cardiovascular disease: Insights from the START registry

Leonardo De Luca [a,*], Marcello Arca [b], Pier Luigi Temporelli [c], Jennifer Meessen [d], Carmine Riccio [e], Paolo Bonomo [f], Angela Rita Colavita [g], Domenico Gabrielli [h], Michele Massimo Gulizia [i], Furio Colivicchi [j], on behalf of the START Investigators [1]

International Journal of Cardiology 316 (2020) 229–235

ABSTRACT

Background: Current European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines for the management of dyslipidemias have further reduced low density lipoprotein-cholesterol (LDL-C) targets, as compared to the guidelines released in 2016. These targets are particularly restraining for patients at very high risk (VHR).

Methods: Using the data from a nationwide, prospective registry on patients with established atherosclerotic cardiovascular disease (ASCVD), we sought to assess: 1) the contemporary use of conventional cholesterol-lowering therapies and the achievement of LDL-C goals according to previous and current ESC guidelines in subjects at VHR; 2) the proportion of VHR patients potentially eligible for proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) treatment.

Results: Among the 5053 patients with data available, 4751 (94.0%) were deemed as VHR. Among these patients, the mean LDL-C levels were 62.4 ± 47.7 mg/dl at enrollment. A high dose of statin was used in 54.9%, while the association of high dose statin and ezetimibe was prescribed in 4.8% of VHR patients. A target level of LDL-C < 70 mg/dl recommended by 2016 ESC guidelines was reached by 58.1%, while a target of <55 mg/dl and LDL-C reduction ≥50% recommended by 2019 ESC guidelines, would be reached by 3.2% of patients at VHR. Accordingly, 9.4% and 1.4% of VHR patients would be eligible for PCSK9i according to ESC guidelines and Italian regulations, respectively.

Conclusions: In VHR patients enrolled in this large cohort of established ASCVD managed by cardiologists, the lipid management and LDL-C targets attainment is largely suboptimal.

© 2020 Elsevier B.V. All rights reserved.

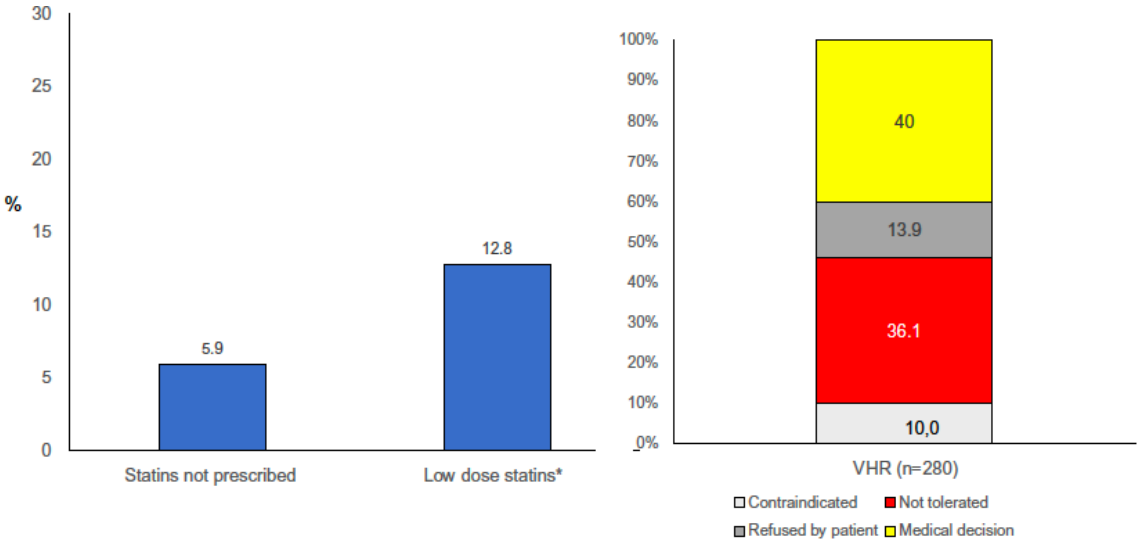
L'accumulo di dati dall'Europa e da altri continenti ha mostrato una cattiva gestione della dislipidemia in pazienti a rischio di eventi CV alto o molto alto con conseguenze potenzialmente dannose per la salute.

Il registro START include un ampio campione di 5000 pazienti a rischio Cv molto alto, reclutati dalla pratica clinica quotidiana in Italia

Current lipid lowering treatment and attainment of LDL targets recommended by ESC/EAS guidelines in very high-risk patients with established atherosclerotic cardiovascular disease: Insights from the START registry

Leonardo De Luca [a,*], Marcello Arca [b], Pier Luigi Temporelli [c], Jennifer Meessen [d], Carmine Riccio [e], Paolo Bonomo [f], Angela Rita Colavita [g], Domenico Gabrielli [h], Michele Massimo Gulizia [i], Furio Colivicchi [j], on behalf of the START Investigators [1]

International Journal of Cardiology 316 (2020) 229–235



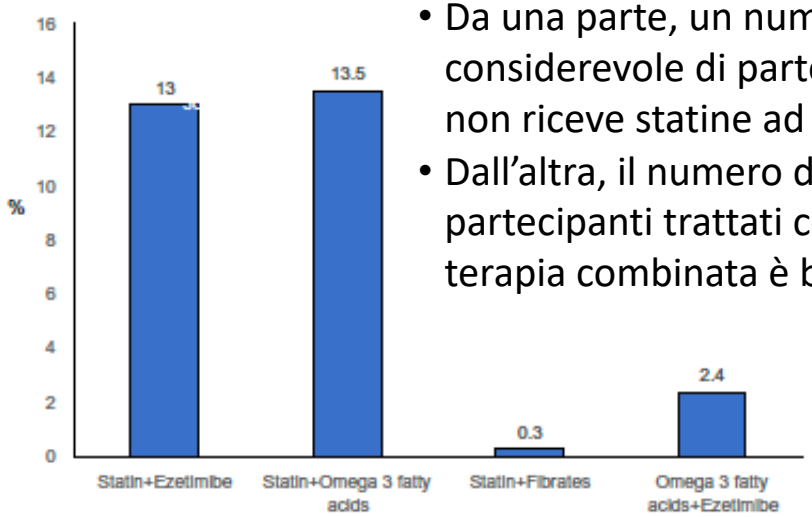
Percentuale dei pazienti rischio CV molto alto inclusi nel registro START (n=280) che non ricevono statine o ricevono statine a bassa dose (Atorvastatina ≤10 mg/die, Fluvastatina ≤40 mg/die, Lovastatina ≤20 mg/die, Pravastatina ≤20 mg/die, Rosuvastatina ≤5 mg/die, Simvastatina ≤20 mg/die) al momento della dimissione/visita finale (pannello sinistro).

I motivi della mancata prescrizione delle statine o della prescrizione di statine a bassa dose sono mostrati nel pannello destro.

International Journal of Cardiology 316 (2020) 229–235

Current lipid lowering treatment and attainment of LDL targets recommended by ESC/EAS guidelines in very high-risk patients with established atherosclerotic cardiovascular disease: Insights from the START registry

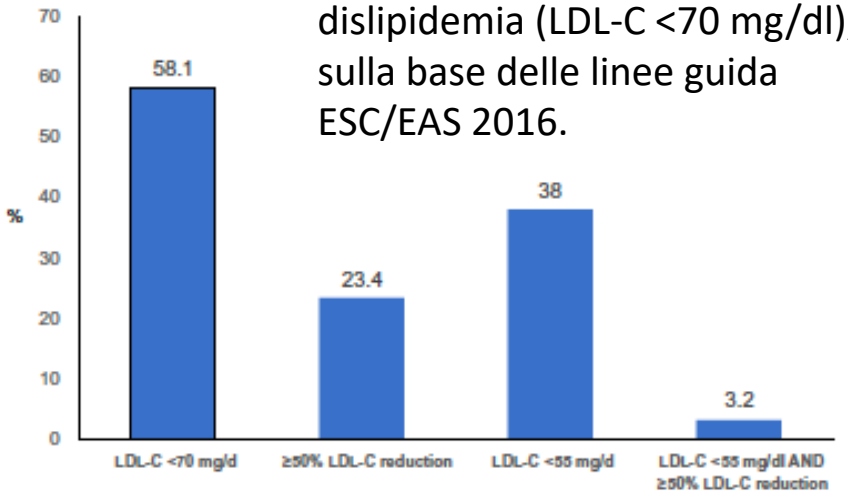
Leonardo De Luca [a,*], Marcello Arca [b], Pier Luigi Temporelli [c], Jennifer Meessen [d], Carmine Riccio [e], Paolo Bonomo [f], Angela Rita Colavita [g], Domenico Gabrielli [h], Michele Massimo Gulizia [i], Furio Colivicchi [j], on behalf of the START Investigators [1]



- Da una parte, un numero considerevole di partecipanti non riceve statine ad alte dosi
- Dall'altra, il numero di partecipanti trattati con terapia combinata è basso

Associazioni terapeutiche per la riduzione del LDL-C in pazienti a rischio molto alto. Altre possibili combinazioni utilizzate in meno dello 0,5% dei casi non sono riportate.

Circa il 42% dei pazienti a rischio CV molto alto non aveva una gestione sufficiente della dislipidemia (LDL-C <70 mg/dl), sulla base delle linee guida ESC/EAS 2016.



Frequenza dei pazienti a rischio molto alto che raggiungono i target di LDL-C raccomandati dalle linee guida ESC/EAS 2016 e 2019.

ESC European Society of Cardiology
European Journal of Preventive Cardiology (2021) 28, 380–382
doi:10.1177/2047487320915662
INVITED EDITORIAL

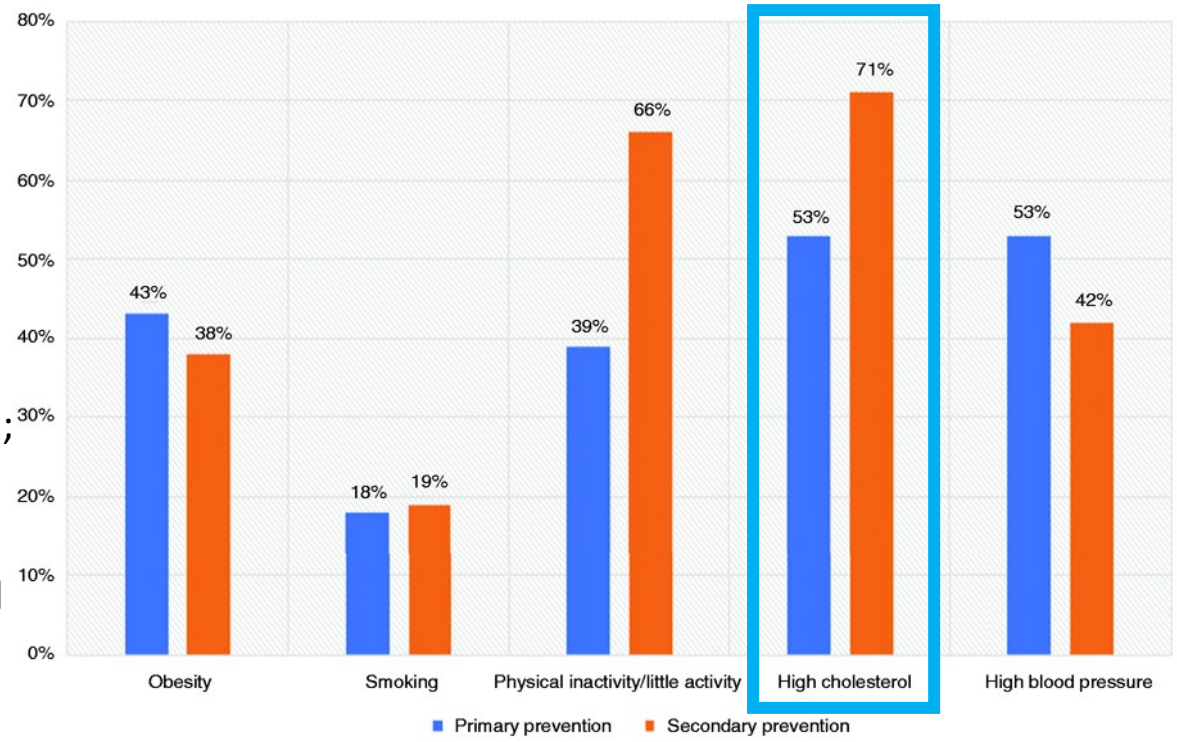
EUROASPIRE V and uncontrolled risk factors in primary prevention: Atherosclerotic cardiovascular disease in the making

L'EUROASPIRE V, analizza il controllo dei fattori di rischio in 2759 individui senza malattia CV ed in 8261 pazienti in prevenzione secondaria.

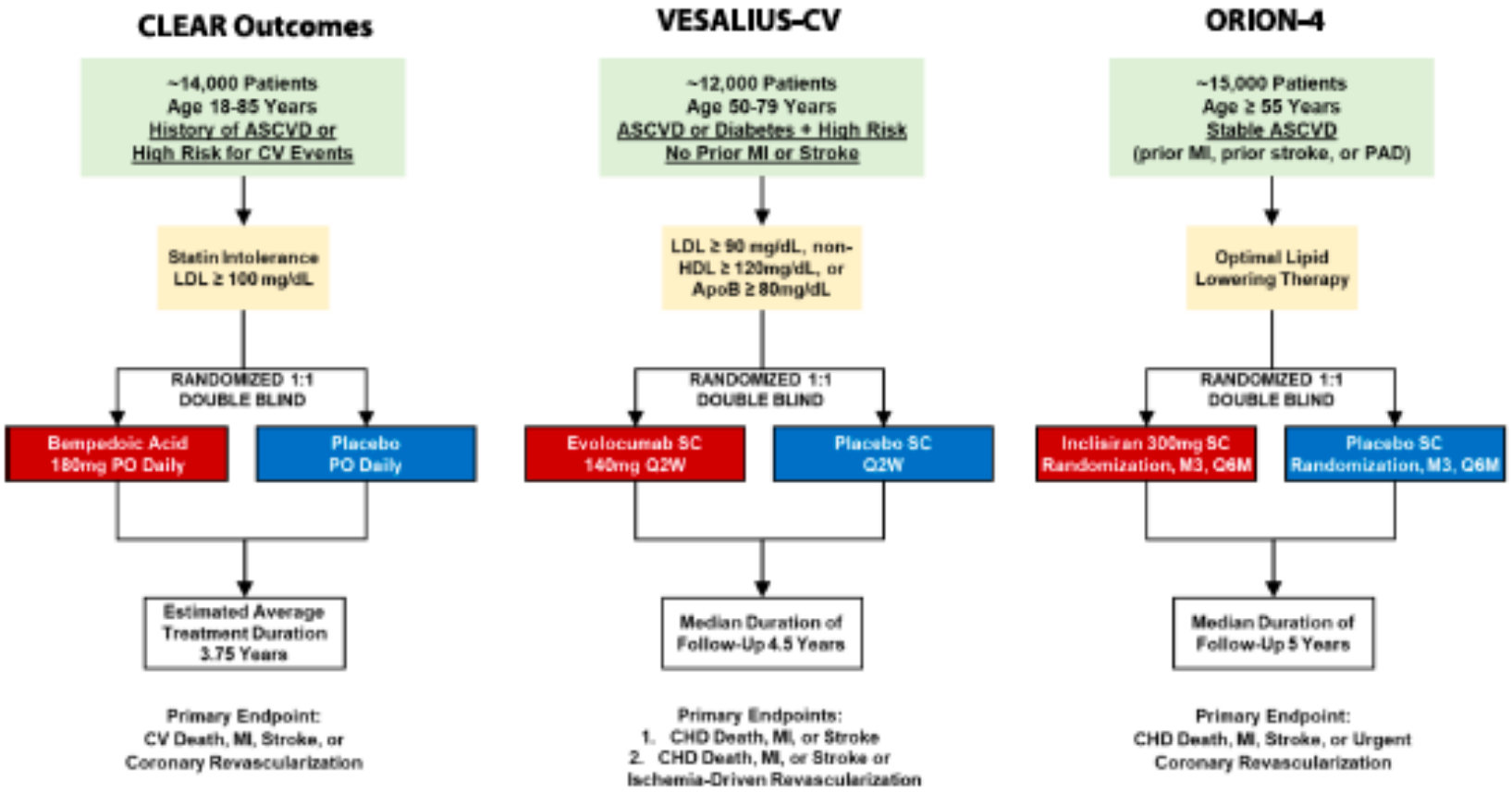
Obiettivo principale: determinare se le linee guida 2016 delle Società Europee sulla prevenzione sono implementate nella pratica clinica.

- Obesità=body mass index >30 kg/m2;
- Target di di PA: <140/90 mmHg e <140/85 mmHg nei diabetici;
- Target di colesterolo: LDL-cholesterol <2.6 mmol/L e <1.8mmol/L in prevenzione primaria e secondaria, rispettivamente.

Un-controlled risk factors



Key ongoing CV outcome trials of LDL-C lowering therapy



Il CLEAR Outcomes (NCT02993406) studierà l'efficacia dell'acido bempedoico nel ridurre gli eventi CV maggiori. Il VESALIUS-CV (NCT03872401) valuterà il potenziale dell'inibizione di PCSK9 nel prevenire il primo evento CV. L'ORION-4 (NCT03705234) sta investigando il vantaggio clinico di inclisiran, un first-in-class siRNA somministrato in due dosi all'anno, per ridurre il colesterolo.

5. Rischio cardiovascolare residuo a basso LDL-C

Evidenze a favore dei trigliceridi come fattore di rischio cardiovascolare	
Evidenze epidemiologiche	• Grandi studi di popolazione e studi di prevenzione secondaria in pazienti trattati con statina identificano i trigliceridi come marcatore di rischio ASCVD*
Evidenze genetiche	• Il colesterolo trasportato nei TGRL (RLP-C)⁺ è un fattore causale per le malattie cardiovascolari e la mortalità per tutte le cause • Diverse varianti nei geni coinvolti nel metabolismo dei TGRL sono associate all'ASCVD
Evidenze terapeutiche	Le statine sono raccomandate come terapia di prima linea nei pazienti a rischio alto / e molto alto con trigliceridi elevati Solo uno studio (REDUCE-IT) ha mostrato un beneficio significativo nei pazienti con elevate concentrazioni di trigliceridi trattati con statina (beneficio inspiegabile dalla sola riduzione dei trigliceridi) Sono necessarie ulteriori prove che dovrebbero essere ottenute usando nuovi agenti sviluppati per la riduzione delle concentrazioni dei trigliceridi

*ASCVD: atherosclerotic cardiovascular disease; ⁺RLP-C: remnant lipoprotein cholesterol; TGRLs: triglyceride-rich lipoproteins

5. Rischio CV residuo a basso LDL-C

ESC European Society of Cardiology
European Journal of Preventive Cardiology
doi:10.1093/eurjpc/zwaa152

FULL RESEARCH PAPER
Risk prediction

Triglyceride-rich lipoproteins, apolipoprotein C-III, angiopoietin-like protein 3, and cardiovascular events in older adults: Atherosclerosis Risk in Communities (ARIC) study

Aliza Hussain[1,2], Caroline Sun[1,2], Elizabeth Selvin[3], Vijay Nambi[1,2,4], Josef Coresh[3], Xiaoming Jia[1,5], Christie M. Ballantyne[1,2,5], and Ron C. Hoogeveen[1,2]*

[1]Section of Cardiovascular Research, Department of Medicine, Baylor College of Medicine, 6565 Fannin Street, MS F701, Houston, TX 77030, USA; Department of Medicine, Center for Cardiometabolic Disease Prevention, Baylor College of Medicine, 6565 Fannin Street, MS F701, Houston, TX 77030, USA; [3]Department of Epidemiology and Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins Bloomberg School of Public Health, 2024 East Monument Street, Baltimore, Maryland (MD), 21287, Baltimore, MD, USA; [4]Section of Cardiology, Michael E. DeBakey Veterans Affairs Medical Center, 2002 Holcombe Boulevard, Houston, Texas (TX), 77030, USA; and [5]Section of Cardiology, Department of Medicine, Baylor College of Medicine, 6565 Fannin Street, MS F701, Houston, TX 77030, USA

Received 11 November 2020; revised 3 December 2020; editorial decision 6 December 2020; accepted 8 December 2020

Aims Despite statin and antihypertensive therapies, older Americans have high atherosclerotic cardiovascular disease (ASCVD) risk. Novel measures of triglyceride-rich lipoproteins, low-density lipoprotein triglycerides (LDL-TG), and remnant-like particle cholesterol (RLP-C), are associated with ASCVD in middle-aged adults. Polymorphisms in genes encoding angiopoietin-related protein 3 (ANGPTL3) and apolipoprotein C-III (apoC-III), two proteins involved in triglyceride catabolism, are associated with increased risk for hypertriglyceridaemia and ASCVD and are potential therapeutic targets. We examined associations of LDL-TG, RLP-C, apoC-III, and ANGPTL3 levels with ASCVD events in older adults in the Atherosclerosis Risk in Communities (ARIC) study.

Methods and results In 6359 participants (mean age 75.8 ± 5.3 years) followed for ASCVD events [coronary heart disease (CHD) or ischaemic stroke] up to 6 years, associations between LDL-TG, RLP-C, apoC-III, and ANGPTL3 and ASCVD events were assessed using Cox regression. With adjustment for age, sex, and race, RLP-C, LDL-TG, apoC-III, and ANGPTL3 (as continuous variables) were significantly associated with CHD. However, after adjustment for traditional risk factors and lipid-lowering medications, only LDL-TG and ANGPTL3 were significantly associated with ASCVD events [hazard ratio (HR) 1.72, 95% confidence interval (CI) 1.25–2.37 per log unit increase in LDL-TG; HR 1.63, 95% CI 1.17–2.28 per log unit increase in ANGPTL3].

Conclusions In older adults, LDL-TG, RLP-C, apoC-III, and ANGPTL3 were associated with CHD events in minimally adjusted models; LDL-TG and ANGPTL3 remained independent predictors of ASCVD events with further adjustment. Future studies should assess potential benefit of lowering hepatic apoC-III or ANGPTL3 expression in patients with elevated triglyceride-rich lipoproteins.

5. Rischio CV residuo a basso LDL-C

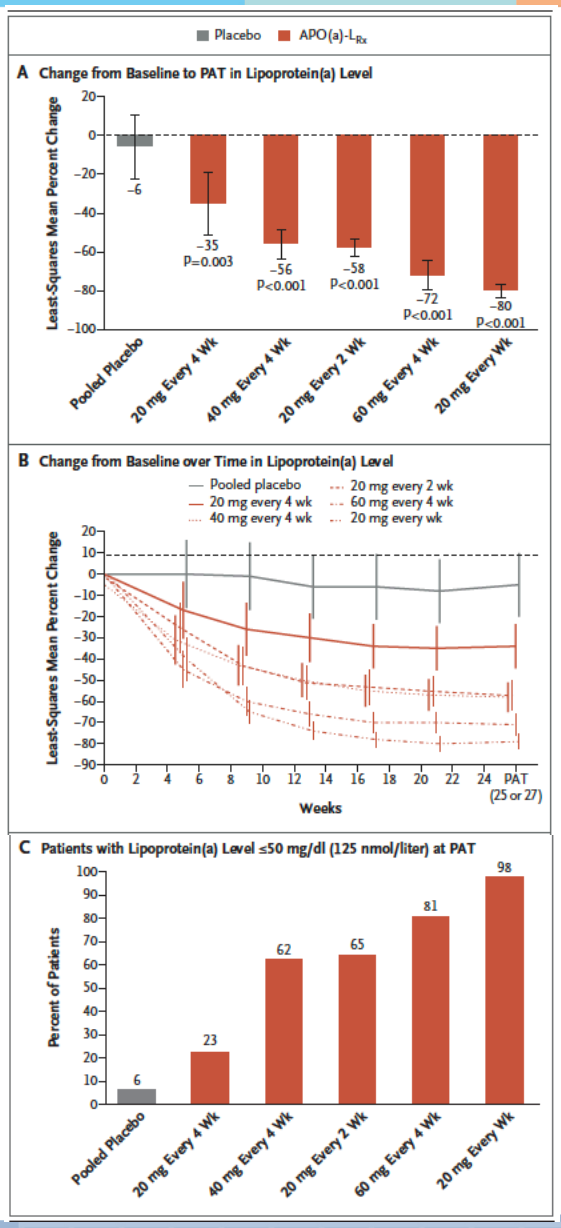
N Engl J Med 2020;382:244-55

ORIGINAL ARTICLE

Lipoprotein(a) Reduction in Persons with Cardiovascular Disease

Sotirios Tsimikas, M.D., Ewa Karwatowska-Prokopczuk, M.D., Ph.D., Ioanna Gouni-Berthold, M.D., Jean-Claude Tardif, M.D., Seth J. Baum, M.D., Elizabeth Steinhagen-Thiessen, M.D., Michael D. Shapiro, D.O., Erik S. Stroes, M.D., Patrick M. Moriarty, M.D., Børge G. Nordestgaard, M.D., D.M.Sc., Shuting Xia, M.S., Jonathan Guerriero, M.B.A., Nicholas J. Viney, B.Sc., Louis O'Dea, M.B., B.Ch., B.A.O., and Joseph L. Witztum, M.D., for the AKCEA-APO(a)-L_{Rx} Study Investigators*

In 286 pazienti che avevano livelli elevati di Lp(a) (almeno 60 mg per decilitro) e malattia cardiovascolare accertata, APO(a)-LRx, un oligonucleotide antisenso diretto verso gli epatociti, riduce i livelli di Lp(a) dal basale al 6°mese di trattamento in modo dose-dipendente.



4° Modulo | Le dimensioni del problema: epidemiologia delle dislipidemie

Grazie dell'attenzione