EAS

GESTIONE DEL PAZIENTE A RISCHIO CARDIOVASCOLARE ALTO E MOLTO ALTO

Prof. Maurizio Averna
Università degli Studi di Palermo

EAS

Webinar EAS

Gestione del paziente a rischio cardiovascolare alto e molto alto

Maurizio Averna

Department of Health Promotion Sciences Maternal and Infantile Care, Internal Medicine and Medical Specialities

PROMISE

UNIVERSITY OF PALERMO

maurizio.averna@unipa.it

Il sottoscritto Maurizio Averna
Ai sensi dell'art. 76 sul Conflitto di Interessi dell'Accordo Stato-Regioni del 02 febbraio 2017 in materia di ECM
Dichiara

che negli ultimi due anni ha avuto rapporti di consulenza con:

Akcea

Amgen

Amrith

Daichii

Novartis

Piam

Sandoz

Sanofi

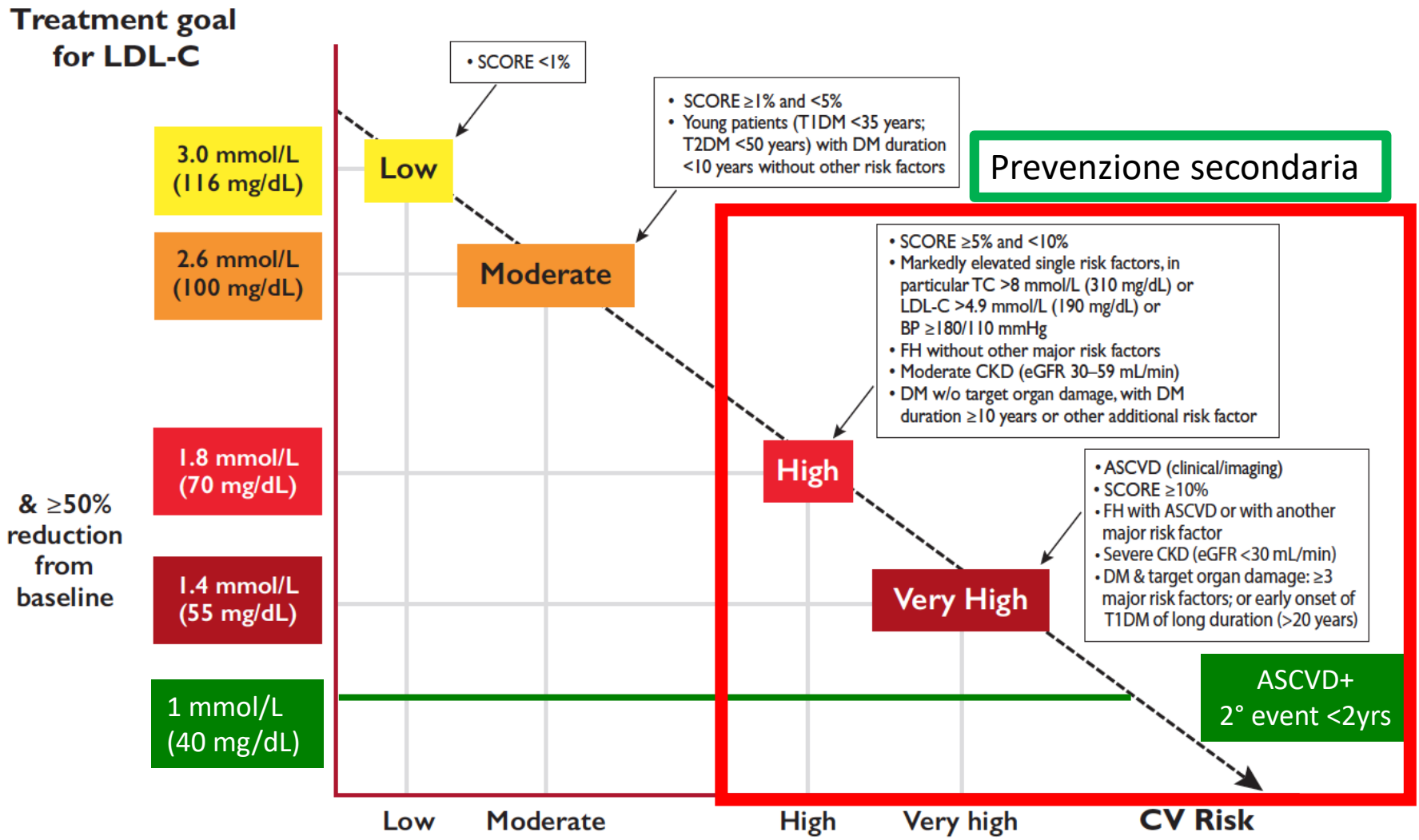
Gli Unmet Medical Needs della Prevenzione secondaria

- La distanza dal Goal LDL-C
- L’ inerzia terapeutica
- La scarsa aderenza
- Il rischio cardiovascolare residuo

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 2019


Treatment goal for LDL-C
3.0 mmol/L (116 mg/dL)
2.6 mmol/L (100 mg/dL)
1.8 mmol/L (70 mg/dL)
1.4 mmol/L (55 mg/dL)
1 mmol/L (40 mg/dL)
& ≥50% reduction from baseline
• SCORE <1%
Low
• SCORE ≥1% and <5%
• Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years without other risk factors
Moderate
Prevenzione secondaria
• SCORE ≥5% and <10%
• Markedly elevated single risk factors, in particular TC >8 mmol/L (310 mg/dL) or LDL-C >4.9 mmol/L (190 mg/dL) or BP ≥180/110 mmHg
• FH without other major risk factors
• Moderate CKD (eGFR 30–59 mL/min)
• DM w/o target organ damage, with DM duration ≥10 years or other additional risk factor
High
• ASCVD (clinical/imaging)
• SCORE ≥10%
• FH with ASCVD or with another major risk factor
• Severe CKD (eGFR <30 mL/min)
• DM & target organ damage: ≥3 major risk factors; or early onset of T1DM of long duration (>20 years)
Very High
ASCVD+
2° event <2yrs
Low
Moderate
High
Very high
CV Risk

Is the novel LDL-cholesterol goal <1.4 mmol/L (55 mg/dl) achievable without a PCSK9 inhibitor in a chronic coronary population from clinical practice?

1018 patients hospitalized with a coronary event median 16 months earlier.

Low-density lipoprotein cholesterol <1.4 mmol/L by intensity of statin therapy and level of adherence

	N (%)	Mean LDL-C (SD)	LDL-C <1.4 mmol/L, *N* (%)
No statin treatment or low adherence[a]	132 (13.0)	2.89 (1.22)	8 (6.1)
Low-intensity statin therapy[b]	380 (37.3)	2.13 (0.69)	42 (11.1)
High-intensity statin therapy[b]	506 (49.7)	1.89 (0.60)	83 (16.4)

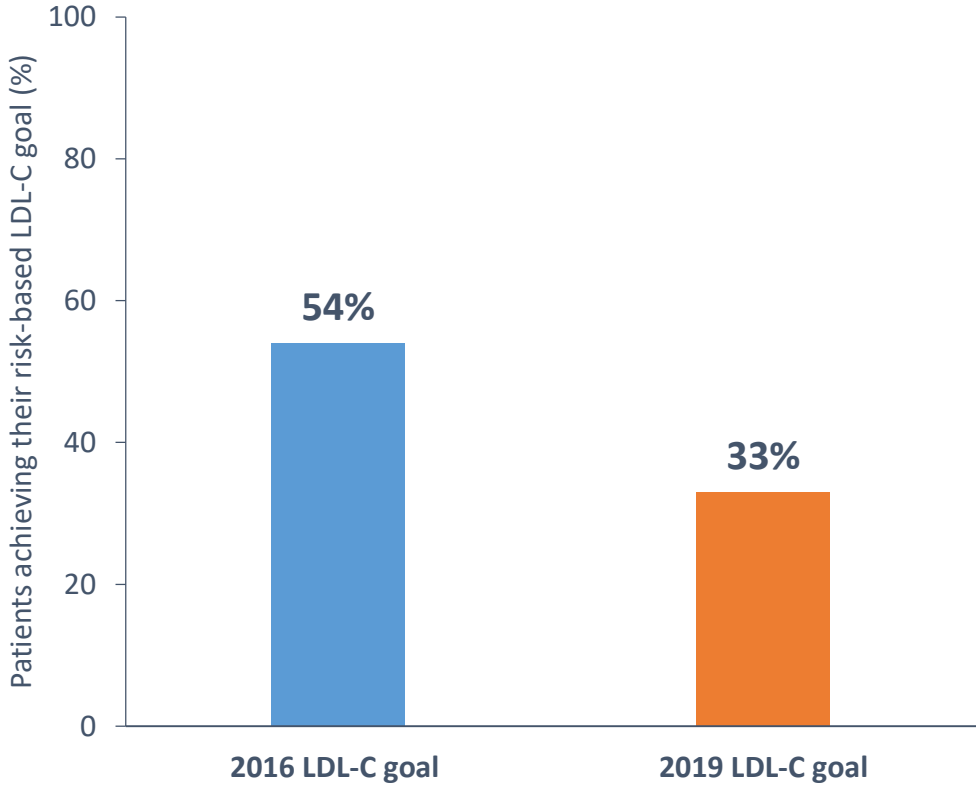
European Journal of Preventive Cardiology 2020

Gli Unmet Medical Needs della Prevenzione secondaria

- La distanza dal Goal LDL-C
- L’ inerzia terapeutica
- La scarsa aderenza
- Il rischio cardiovascolare residuo

Studio DA VINCI: Disegno & Obiettivi

- ***Circa metà dei pazienti non hanno raggiunto i loro obiettivi terapeutici di C-LDL secondo le LG 2016 e circa due terzi non hanno raggiunto gli obiettivi raccomandati dalle LG 2019***

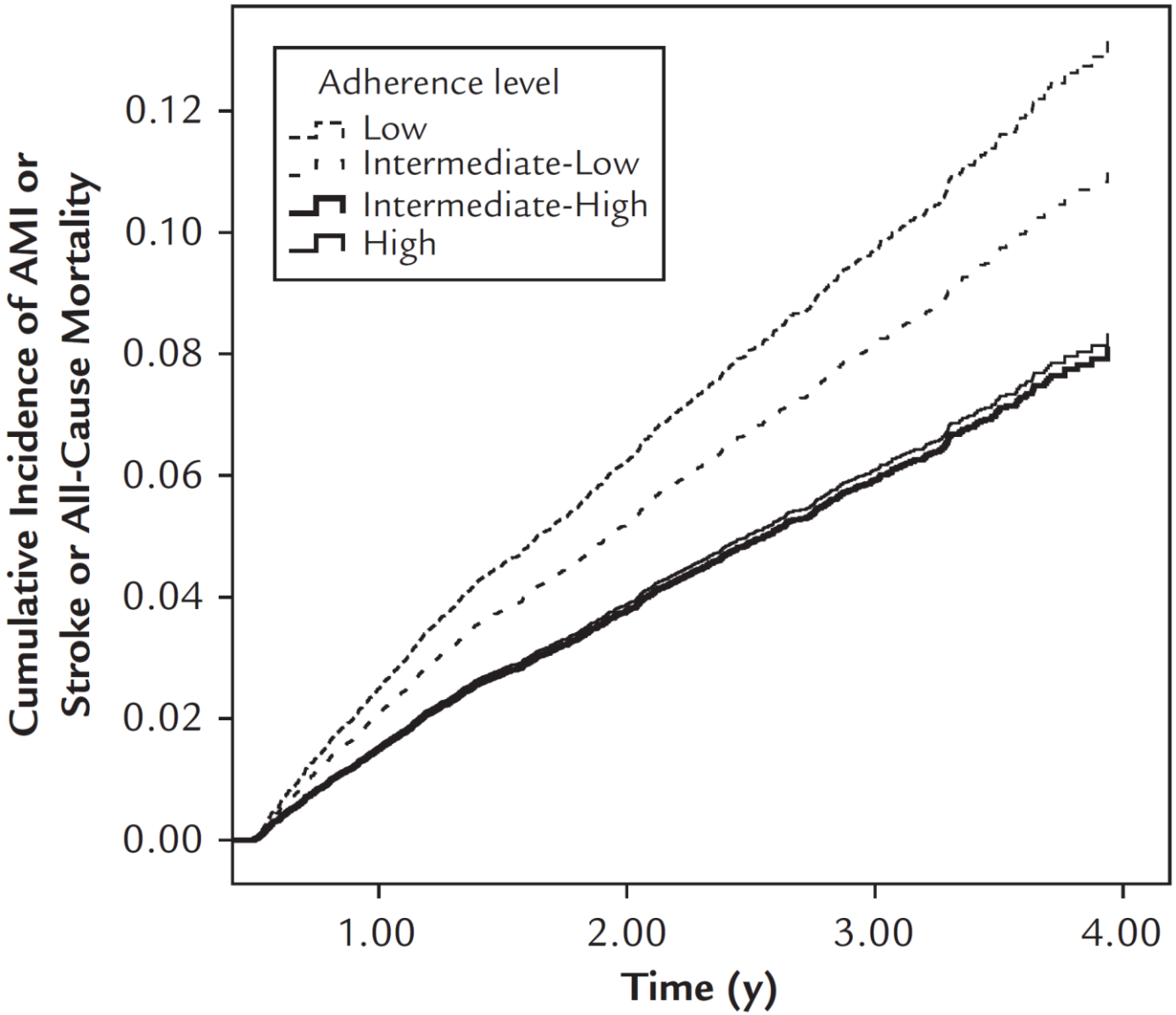


- **Ray, KK et al. Eur. J. Prev. Cardiol. 2020**

Gli Unmet Medical Needs della Prevenzione secondaria

- La distanza dal Goal LDL-C
- L’ inerzia terapeutica
- La scarsa aderenza
- Il rischio cardiovascolare residuo

Association of patients' levels of adherence with first-ever hospitalization for acute myocardial infarction (AMI) or stroke or with all-cause death



Clinical Therapeutics/Volume 34, Number 1, 2012

Long-term adherence to statins was associated with decreased 5-year MACE in a linear-fashion.

Those with a PDC ≥80% over 5 years of follow-up demonstrated a 48% reduction in MACE risk compared to those with a PDC <80% throughout.

5 year MACE (death, myocardial infarction [MI], or stroke) outcomes among the different proportion of days covered (PDC) categories for patients with atherosclerotic cardiovascular disease (ASCVD), defined as coronary artery disease (CAD)/MI, cerebrovascular disease (CVD), and peripheral arterial disease (PAD).

	PDC ≥80% years 1-5, n=351 (6.4%)	**PDC ≥80% years 1-3, n=324 (5.9%)**	**PDC ≥80% year 1, n=851 (15.6%)**	**PDC <80% years 1-5, n=3,942 (72.1%)**	**p-trend**
Frequency of 5 year outcomes					
MACE	15 (4.3%)	21 (6.5%)	60 (7.1%)	331 (8.4%)	0.002
Multivariable hazard ratios and 95% confidence intervals					
	PDC ≥80% years 1-5 vs. PDC <80% years 1-5 (referent)	**PDC ≥80% years 1-3 vs. PDC <80% years 1-5 (referent)**	**PDC ≥80% year 1 vs. PDC <80% years 1-5 (referent)**	**PDC ≥80% years 1-3 vs. PDC ≥80% years 1-5 (referent)**	**PDC ≥80% year 1 vs. PDC ≥80% years 1-5 (referent)**
MACE	0.52 (0.31, 0.88)	0.79 (0.51, 1.23)	0.86 (0.66, 1.14)	1.51 (0.78, 2.93)	1.65 (0.94, 2.91)
p-trend	*0.007*				

*variables evaluated in the multivariable models included sex, age, hypertension, hyperlipidemia, diabetes, smoking, history of depression, renal failure, heart failure, atrial fibrillation, COPD, sleep apnea, history of malignancy, ASCVD group, statin prescription at ASCVD diagnosis hospitalization

JACC March 12, 2019 Volume 73, Issue 9

Gli Unmet Medical Needs della Prevenzione secondaria

- La distanza dal Goal LDL-C
- L’ inerzia terapeutica
- La scarsa aderenza
- Il rischio cardiovascolare residuo

Residual Risk and a Movement Toward Personalized Medicine

Known Cardiovascular Disease

↓

High Intensity Statin

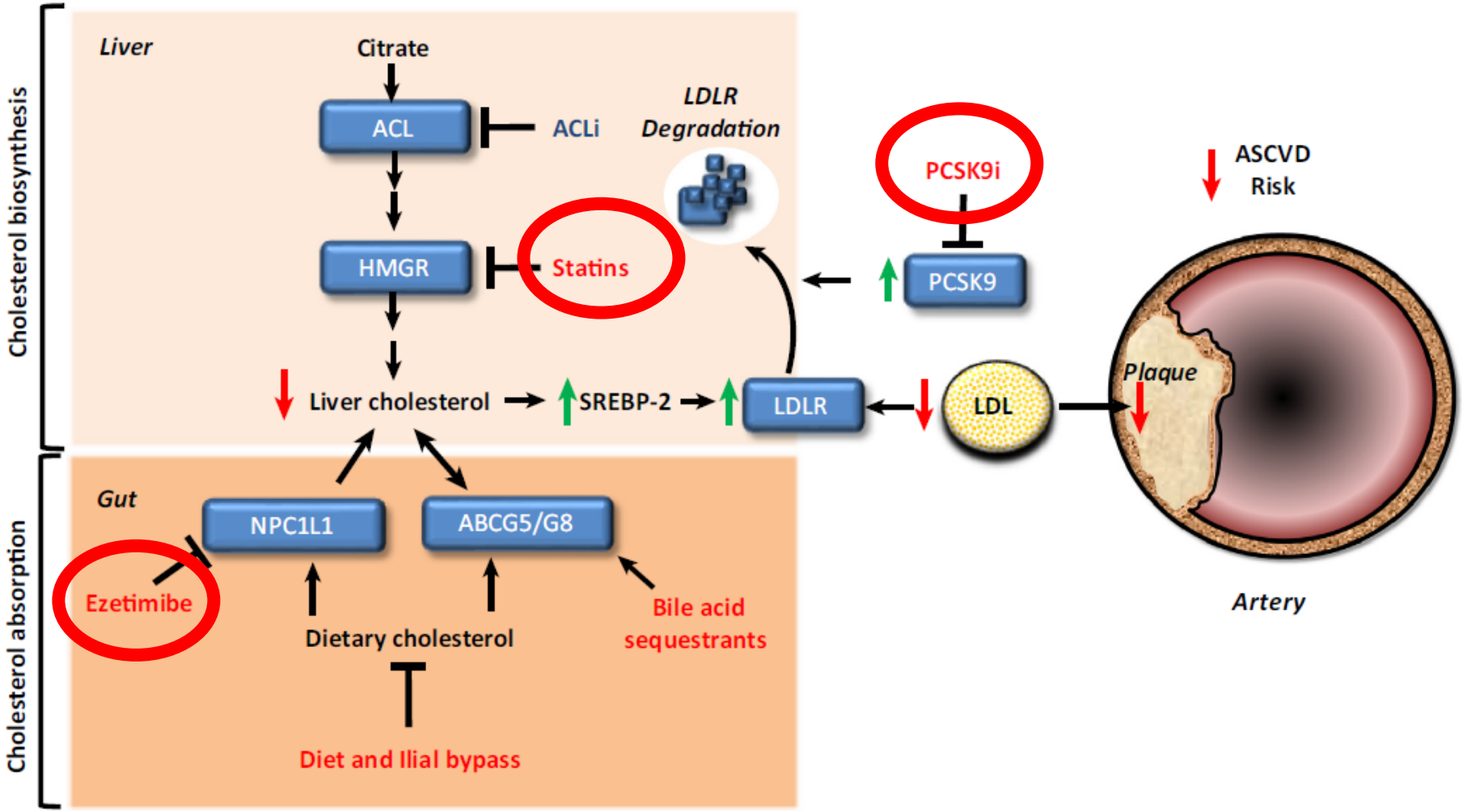
Biologic Issue	Residual Cholesterol Risk	Residual Inflammatory Risk	Residual Thrombotic Risk	Residual Triglyceride Risk	Residual Lp(a) Risk
Critical Biomarker	LDL-C >100 mg/dl	hsCRP >2 mg/l	No simple biomarker	TG >200 mg/dl HDL <40 mg/dl	Lp(a) >50 mg/dl
Potential Intervention	Targeted LDL / Apo B Reduction	Targeted Inflammation Reduction	Targeted Antithrombotic Reduction	Targeted Triglyceride Reduction	Targeted Lp(a) Reduction
Randomized Trial Evidence	IMPROVE-IT FOURIER, SPIRE ODYSSEY	CANTOS	COMPASS DAPT	REDUCE-IT STRENGTH PROMINENT	Planned

	Rate of CV Events in the Placebo Group	Rate of CV Events in the active Tx Group
CANTOS **Placebo group nr: 2.284** Canakinumab 50/150/300 mg	**4,5%/yr**	**3,9%/yr***
REDUCE-IT **Placebo group nr: 4.090** Icosapent 4 g	**4,5%/yr**	**3,5%/yr**
FOURIER **Placebo group nr: 13.780** Evolocumab 140/420 mg	**5,1%/yr**	**4,4%/yr**
ODYSSEY OUTCOMES **Placebo group nr: 9.462** Alirocumab 75/150 mg	**4,0%/yr**	**3,4%/yr**

Ridker PM et al. N Engl J Med. 2017
Sabatine MS et al. N Engl J Med 2017
Bhatt DL, N Engl J Med. 2019
Schwartz GG, et al. N Engl J Med 2018

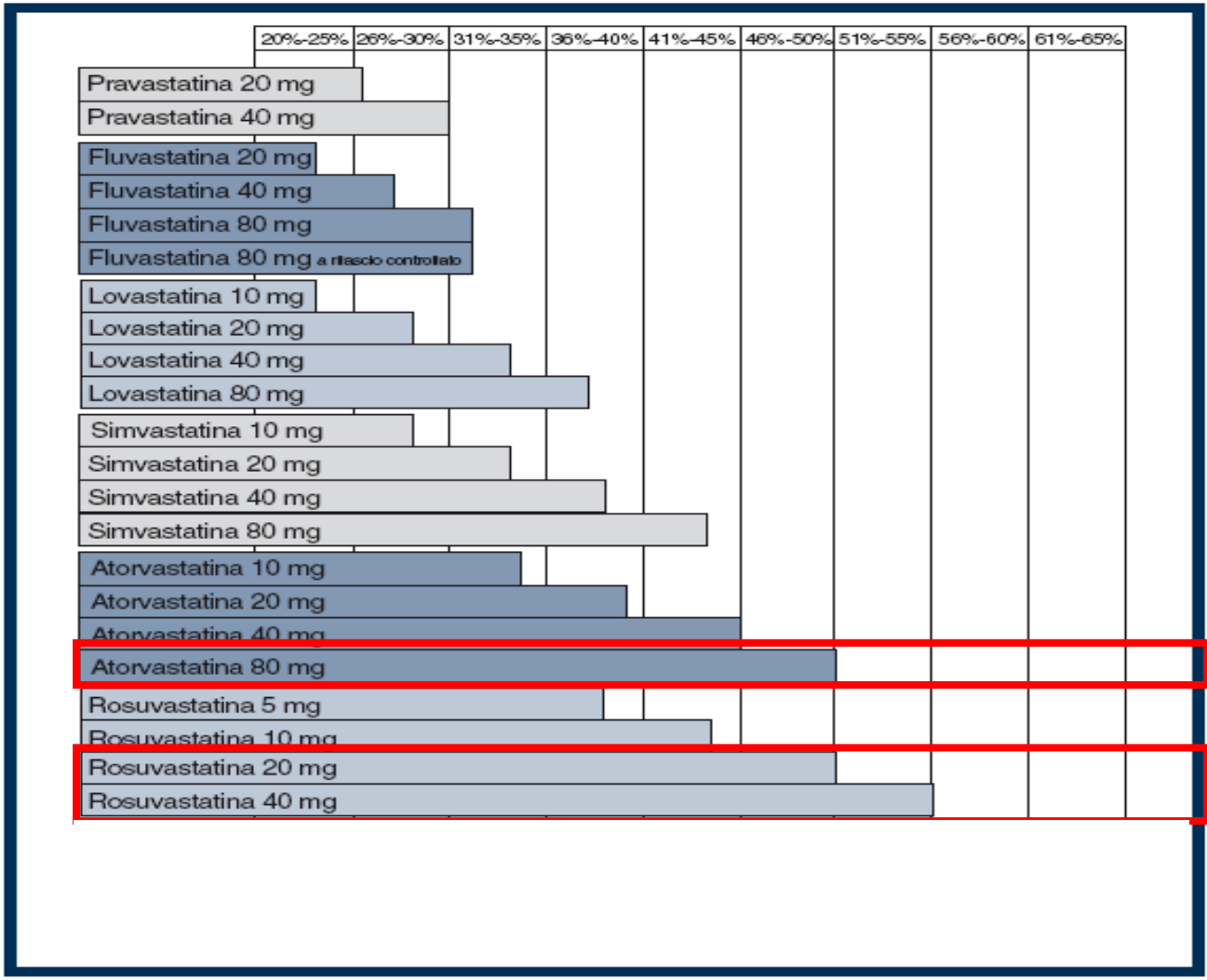
Prevenzione secondaria nei pazienti ad alto ed altissimo rischio pazienti: le strategie

I farmaci che promuovono l' aumento dell'espressione del recettore delle LDL nel fegato riducono il rischio CV



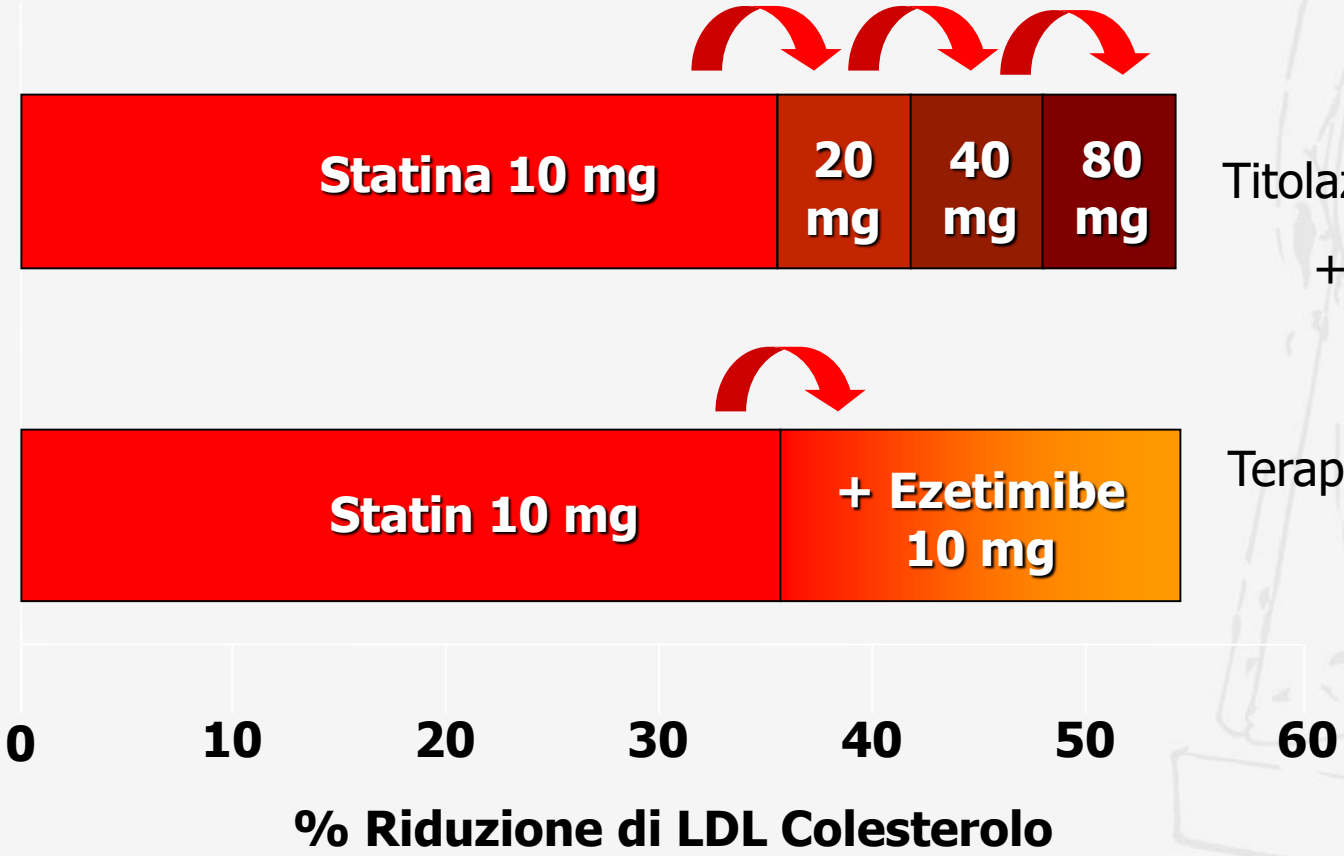
Trends in Molecular Medicine, November 2017

Conoscendo la riduzione percentuale necessaria per raggiungere il target terapeutico, è possibile individuare quale opzione terapeutica consente di ottenerla.



Razionale della Terapia di combinazione con Ezetimibe + Statina

1 Step o 3 Step?



Titolazione a 3 STEP

+6% a step

Terapia di combinazione

+15-20%

Adapted from Stein E Eur Heart J Suppl 2001;3(suppl E):E11-E16.

Il raggiungimento degli obiettivi terapeutici nell' era degli inibitori di PCSK9

Rosuva 20 mg + Eze 10 mg

Alirocumab 75/150 mg QW2
Evolocumab 140mg QW2
Evolocumab 420mg QW4

-65% LDL-C

Contents lists available at ScienceDirect

Atherosclerosis

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

From the EAS

Practical guidance for combination lipid-modifying therapy in high- and very-high-risk patients: A statement from a European Atherosclerosis Society Task Force

Maurizio Averna [a], Maciej Banach [b], Eric Bruckert [c], Heinz Drexel [d,e,f], Michel Farnier [g], Dan Gaita [h], Paolo Magni [i], Winfried März [j,k], Luis Masana [l], Alberto Mello e Silva [m], Zeljko Reiner [n], Emilio Ros [o,p], Michal Vrablik [q], Alberto Zambon [r], Jose L. Zamorano [s], Jane K. Stock [t], Lale S. Tokgözoğlu [u], Alberico L. Catapano [i,*]

Contents lists available at ScienceDirect

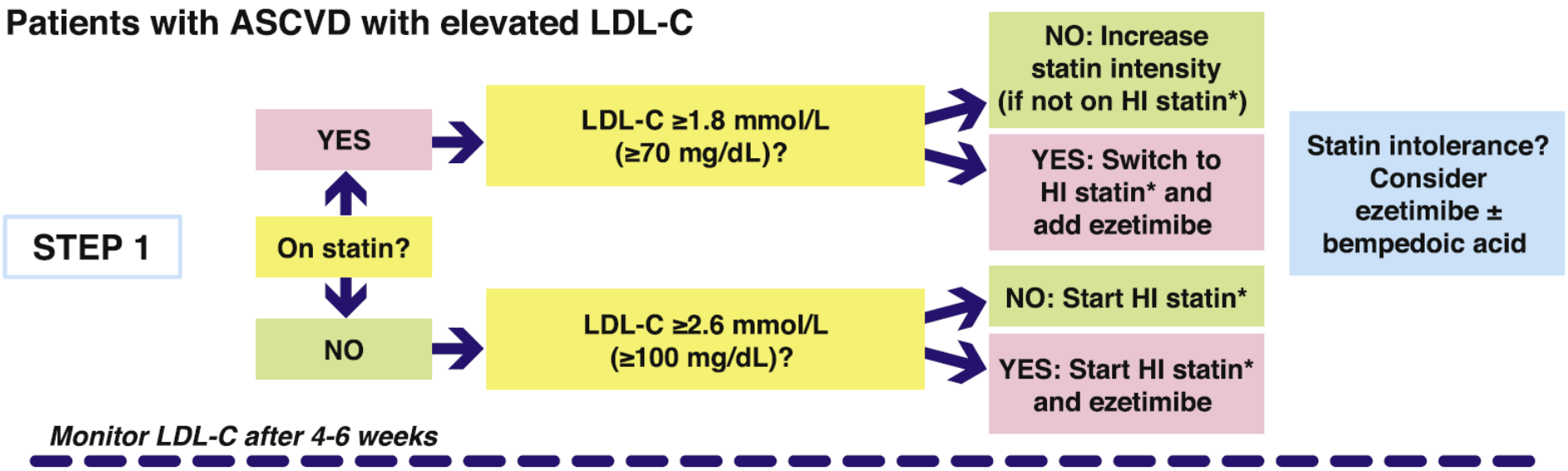
Atherosclerosis

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

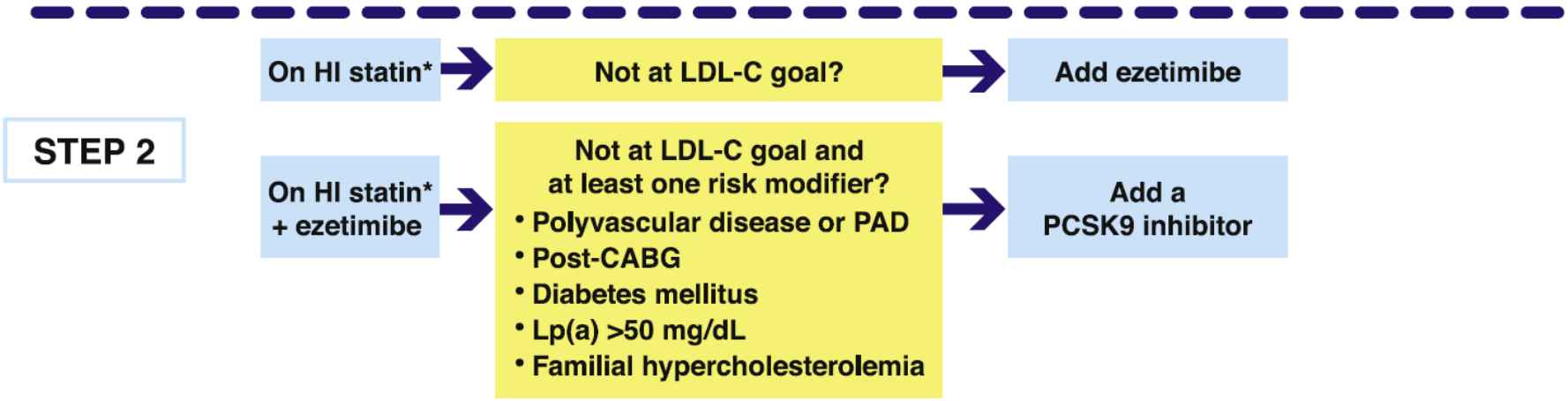
From the EAS

Practical guidance for combination lipid-modifying therapy in high- and very-high-risk patients: A statement from a European Atherosclerosis Society Task Force

Maurizio Averna [a], Maciej Banach [b], Eric Bruckert [c], Heinz Drexel [d,e,f], Michel Farnier [g], Dan Gaita [h], Paolo Magni [i], Winfried März [j,k], Luis Masana [l], Alberto Mello e Silva [m], Zeljko Reiner [n], Emilio Ros [o,p], Michal Vrablik [q], Alberto Zambon [r], Jose L. Zamorano [s], Jane K. Stock [t], Lale S. Tokgözoğlu [u], Alberico L. Catapano [l,*]



Algorithm for managing high LDL-C levels in ASCVD patients



Atherosclerosis 325 (2021) 99–

Statin-ezetimibe combination treatment is the FIRST CHOICE for managing elevated LDL-C and should be given UPFRONT in very-high-risk patients with high LDL-C unlikely to reach goal with a statin, and in primary prevention familial hypercholesterolaemia patients

La Terapia di Combinazione è sempre la scelta iniziale quando il goal LDL-C è molto distante

Case 1.

High-risk CVD

ESC/EAS GOAL <1.8 mmol/L

Age
55 years

BMI
28.2 kg/m²

Diabetic
No

Smoker
No

Hypertensive before ACEi treatment
Yes, BP 138/94

Receiving
Perindopril 4 mg

Family history
Brother with FH and recent MI

Lipid profile and current treatments

Jun 2019: LDL-C 5.1, TG 1.9 no Rx
Dec 2019: LDL-C 4.5 dietary changes only
Mar 2020: LDL-C 2.3 on rosuvastatin 20 mg

Therapeutic options

Increase statin to 40 mg/day
Predicted 6% drop to achieved LDL-C of 2.0; >50% LDL-C reduction from baseline

Add ezetimibe to statin
Predicted 20% drop to achieved LDL-C of 1.7

Case 2.

Very high-risk CVD

ESC/EAS GOAL <1.4 mmol/L

Age
58 years

BMI
33.8 kg/m²

Diabetic
Yes, type 2

Smoker
No

Hypertensive before ACEi treatment
Yes, BP 148/98

Receiving
Metformin 1000 mg and ramipril 5 mg

Presents with stable angina; significant disseminate disease in LAD and RCA on coronary CT imaging

Lipid profile and current treatments

Predicted baseline: LDL-C 4.0
Jan 2019: LDL-C 2.4, TG 2.0 on atorvastatin 20 mg
Mar 2020: LDL-C 2.2, TG 1.9 on atorvastatin 40 mg (intolerant of higher dose)

Therapeutic options

Add ezetimibe to statin
Predicted 20% reduction to achieved LDL-C of 1.8; >50% LDL-C reduction from baseline

Add PCSK9i to statin
Predicted 60% drop to achieved LDL-C of 0.9

Case 3.

Very high-risk CVD
multiple previous events

ESC/EAS GOAL <1.0 mmol/L

Age
62 years

BMI
29.5 kg/m²

Diabetic
No

Hypertensive before ACEi treatment
Yes, BP 138/87

Receiving
Lisinopril 20 mg and amlodipine 5 mg

Jan 2017: positive stress ECG; >50% stenosis in LAD and CFX; angioplasty + stent

Mar 2019: NSTEMI; successful PCI with further stent in LAD

Lipid profile and current treatments

Predicted baseline: LDL-C 4.9
Mar 2017: LDL-C 3.0, TG 2.4 on atorvastatin 20 mg
Jul 2019: LDL-C 1.9, TG 1.7 on atorvastatin 80 mg

Therapeutic options

Add ezetimibe to statin
Predicted 20% reduction to achieved LDL-C of 1.5; >50% LDL-C reduction from baseline

Add PCSK9i to statin
Predicted 60% drop to achieved LDL-C of 0.9

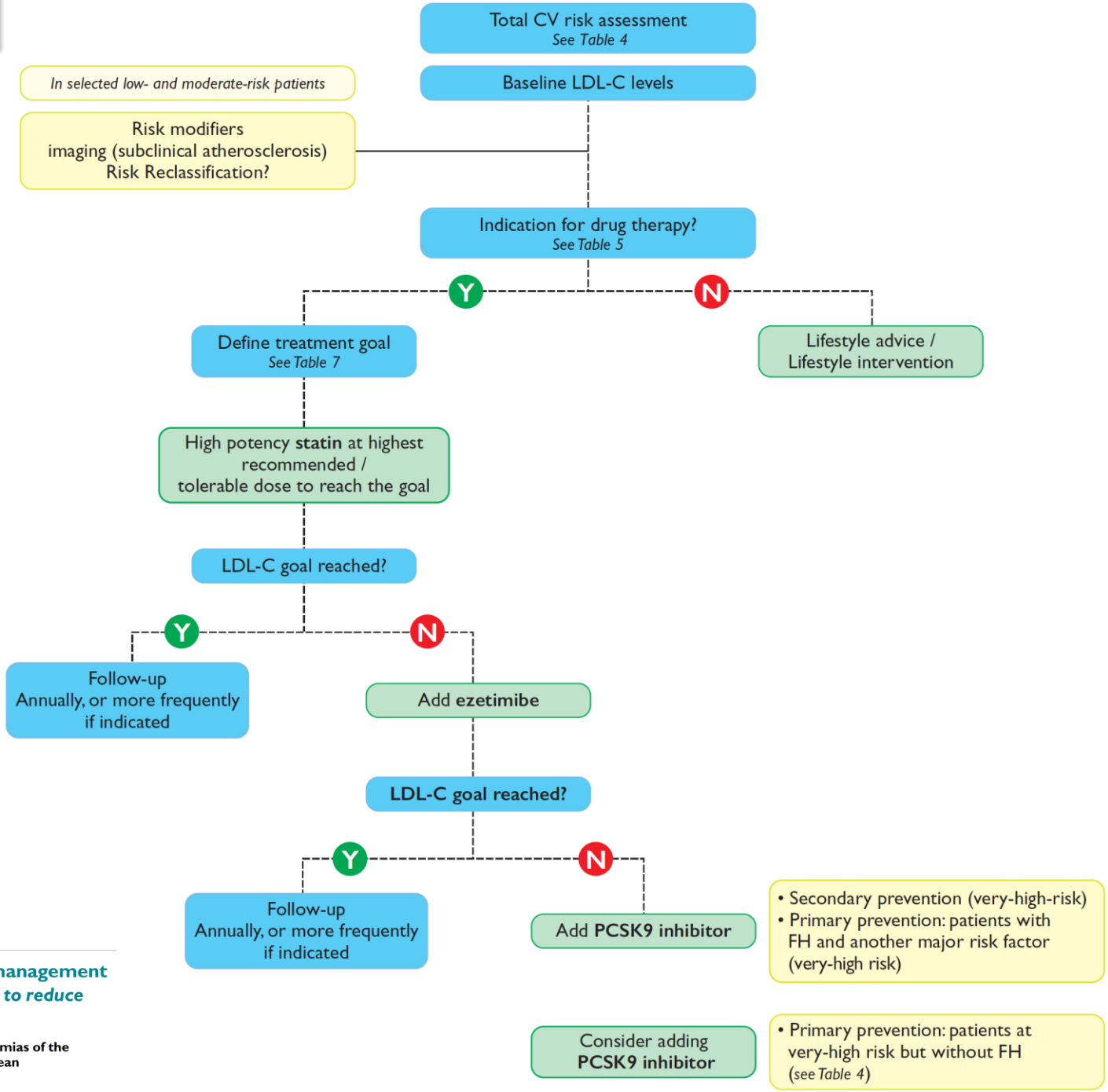
Packard C, et al. Heart 2021

In quali casi ridurre ulteriormente LDL-C?

Categories of 'highest risk' for ASCVD (around or above a benchmark of 30% 10-year risk) on statin therapy, based on published trial data

Category	Projected 10-year risk on moderate- or high-intensity statin therapy (%)
Patients with ASCVD/stroke/AOP/FH	
With CKD	28–43
Patients with recent ACS and comorbidities	
CHD and poorly controlled risk factors	28–41
CHD and peripheral vascular disease	43–55
CHD and age ≥65 years	21–54
Stroke/transient ischaemic attack and male	31
CHD and familial hypercholesterolaemia (baseline LDL-C ≥190 mg/dL)	41

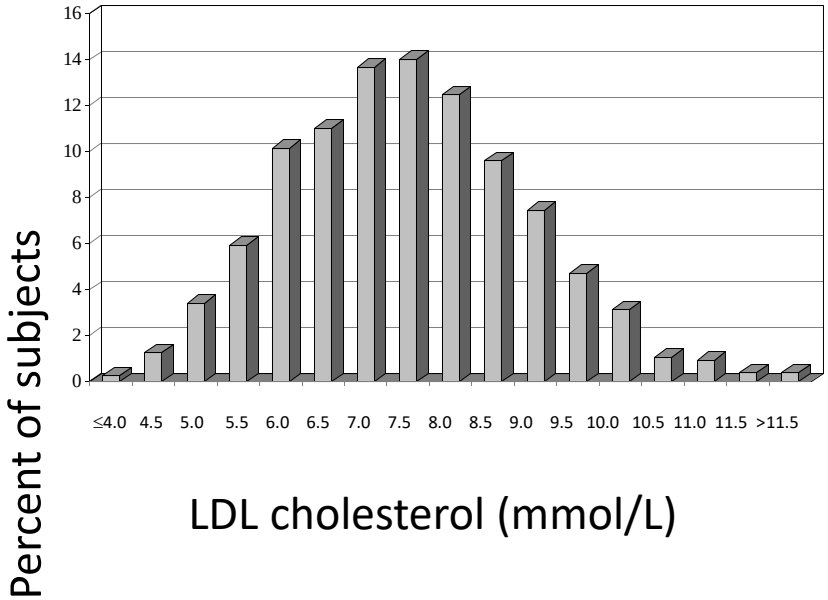
European Heart Journal 2018



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)

Distribution of LDL cholesterol levels (adjusted for gender, age and familial relations) in 1769 ADH-1 heterozygous patients carrying pathogenic mutations of *LDLR* gene



5th p.	5.00 mmol/L
10th p.	5.45 mmol/L
25th p.	6.11 mmol/L
50th p.	7.08 mmol/L
75th p.	8.15 mmol/L
90th p.	9.05 mmol/L
95th p.	9.64 mmol/L

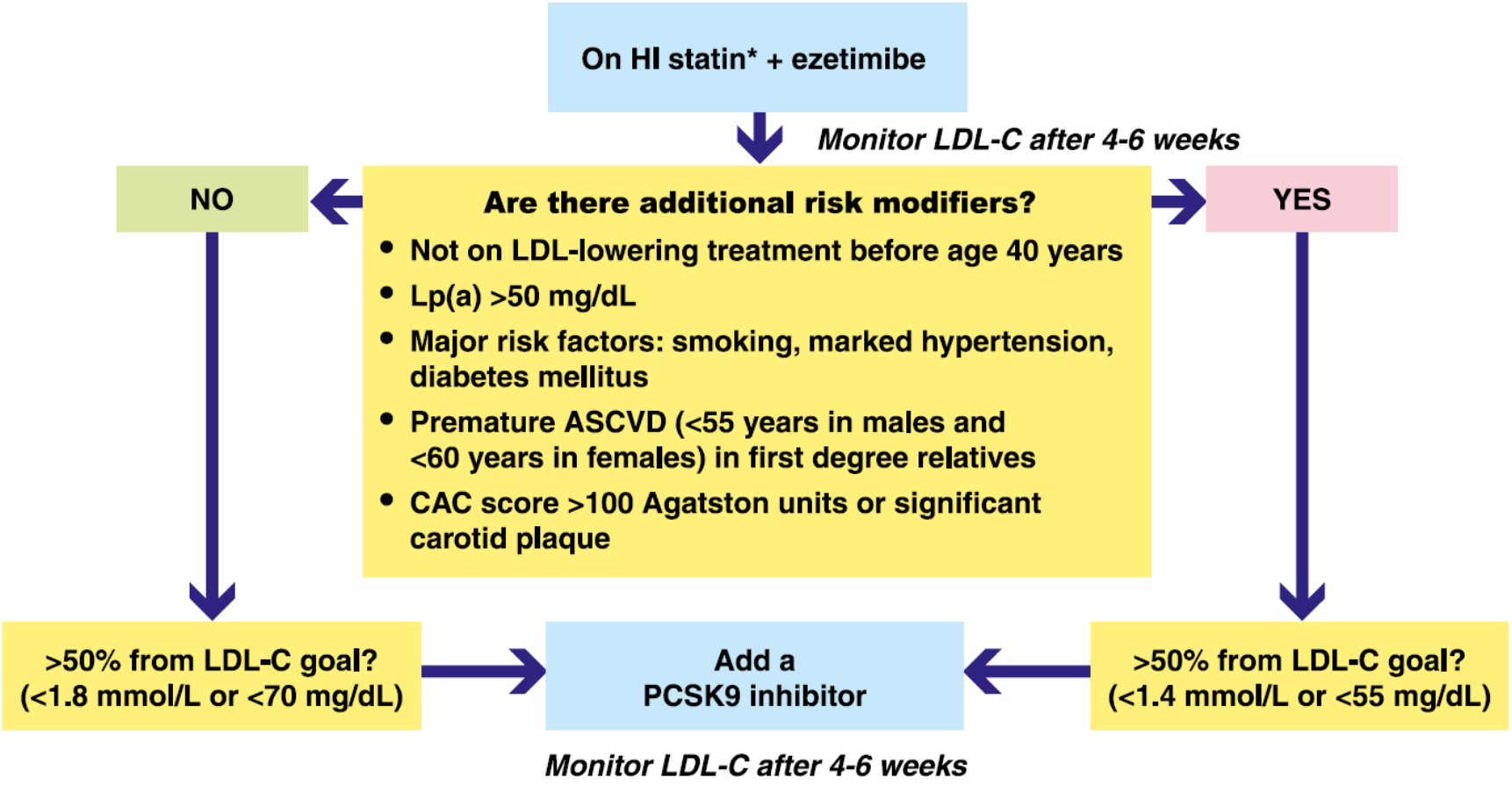
I LIVELLI MEDI DI LDL-C NEGLI FH SONO MOLTO ALTI ≥ 280 MG / DL

Bertolini S., Calandra S., Averna M. et Al, Atherosclerosis 2013

SISA Lipigen Network

Algorithm for managing high LDL-C levels in FH patients without ASCVD

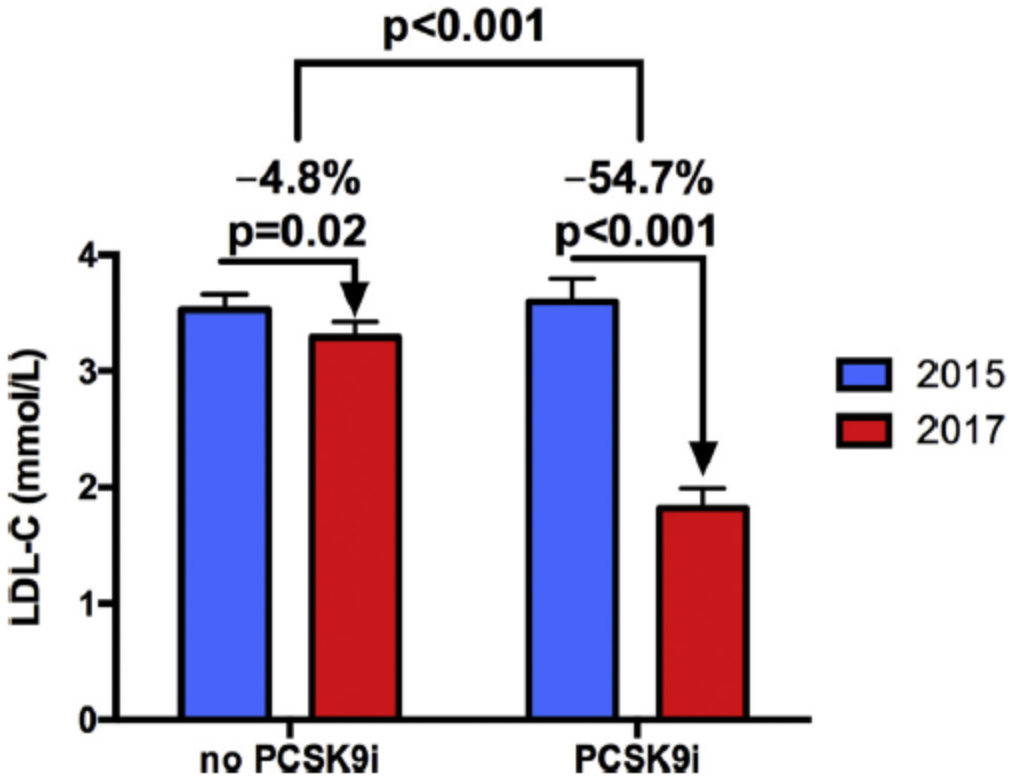
Primary prevention adult patients with familial hypercholesterolaemia



Atherosclerosis 325 (2021) 99–

Changes in LDL-C levels in patients in the British Columbia FH Registry from 2015 to 2017, corresponding to the period immediately before, and the first 2 years after, availability of PCSK9 inhibitors in Canada.

A large percentage of patients with FH using a PCSK9 inhibitor are able to reach a target of 50% reduction or LDL-C < 2 mmol/L



Il raggiungimento degli obiettivi terapeutici nell' era degli inibitori di PCSK9

Statina ad alta intensità +

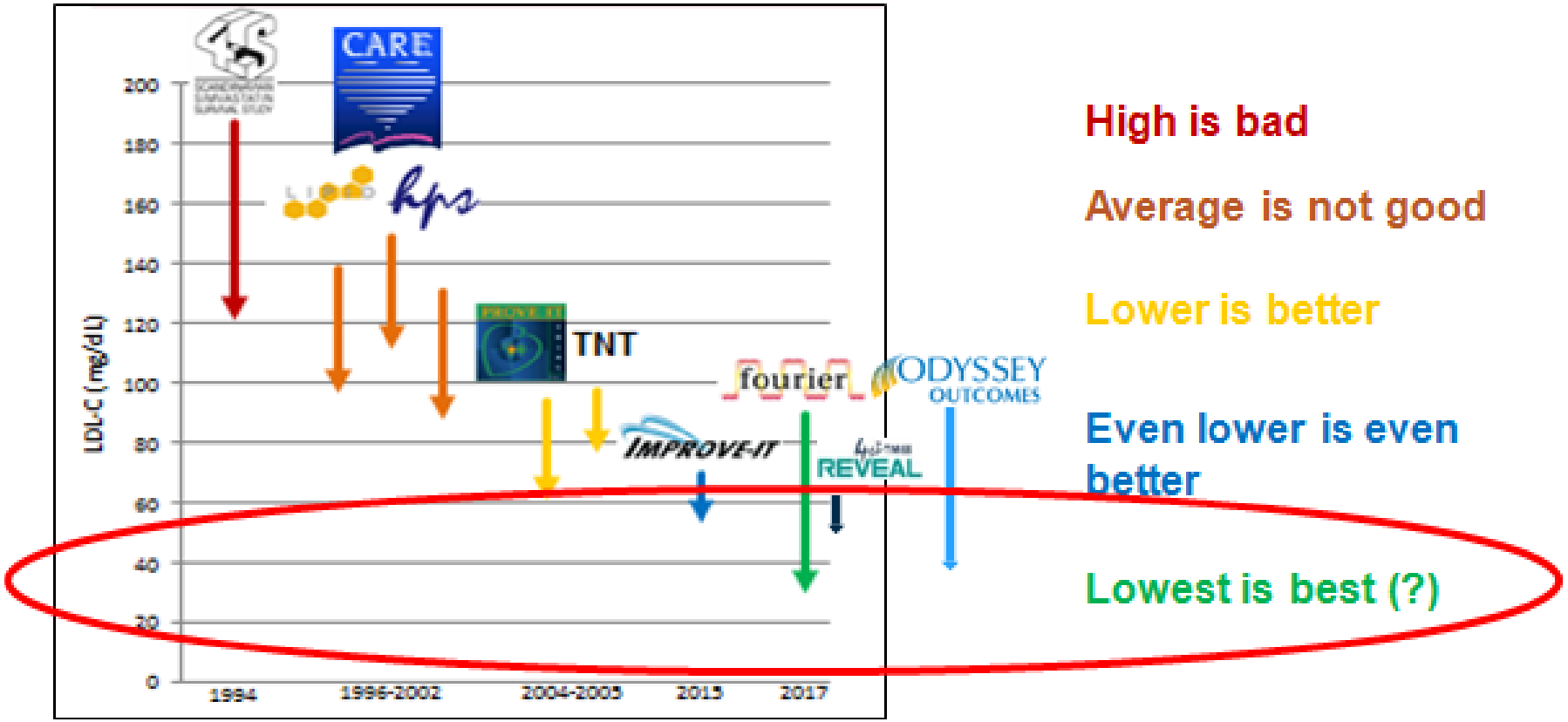
Ezetimibe +

PCSK9i

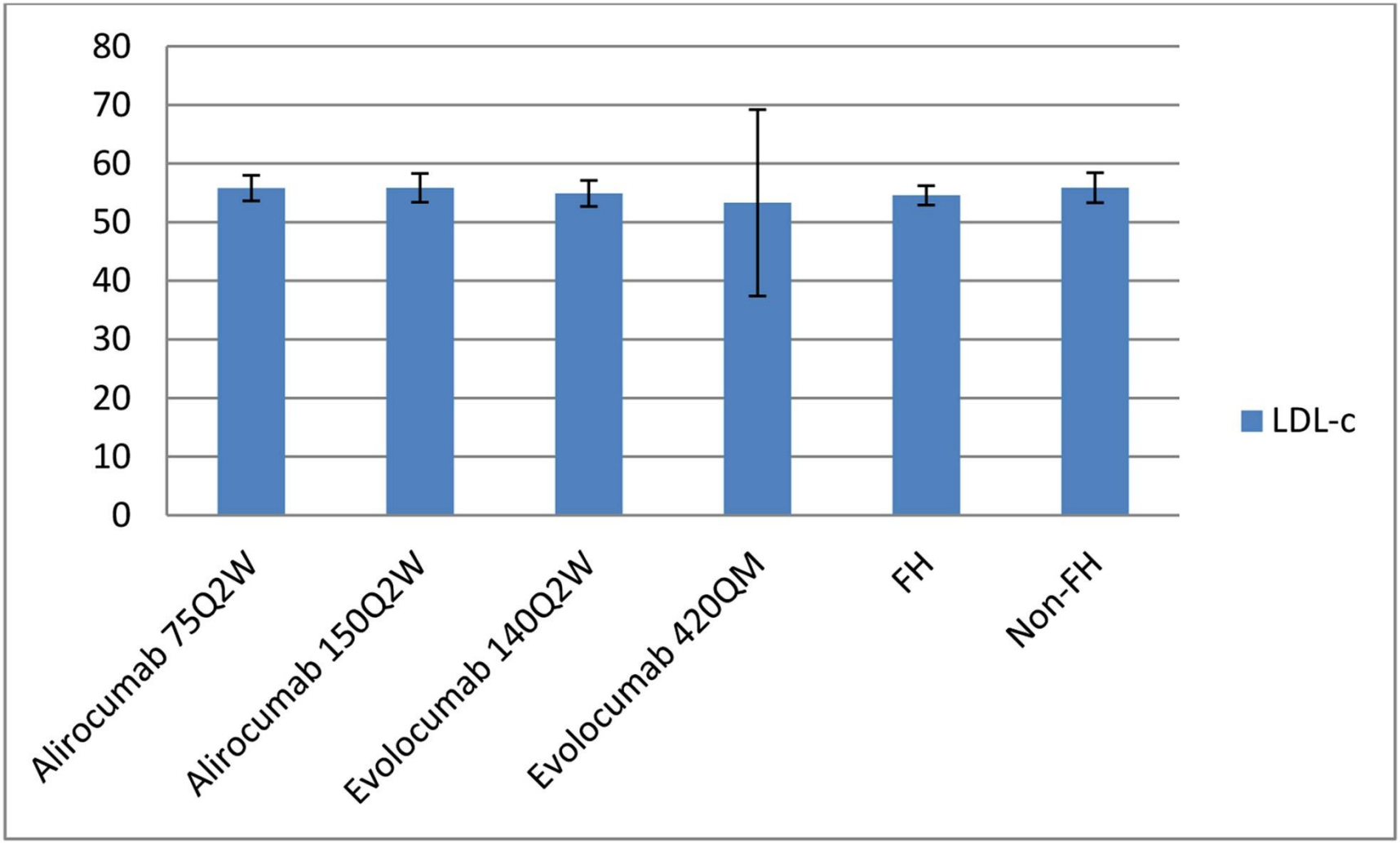
↓

LDL-C
- 84 %

LDL-C Levels for optimal CV Risk Reduction:



Riduzione percentuale dei livelli di LDL-C in pazienti trattati con iPCSK9

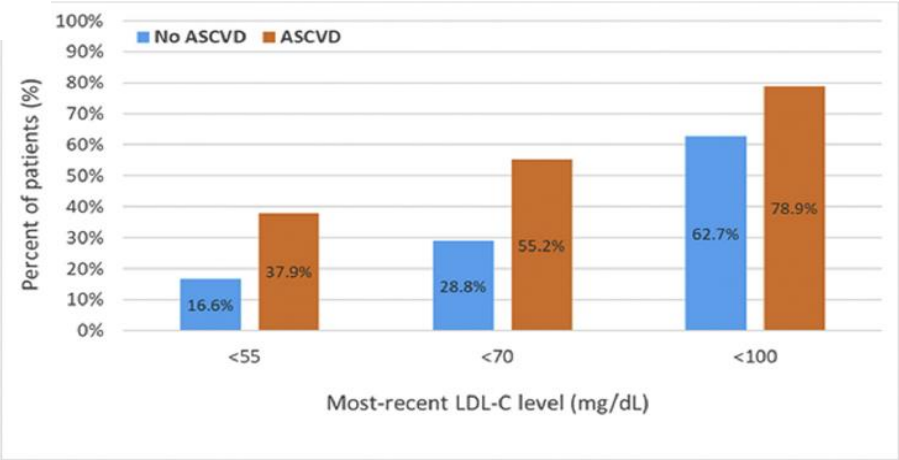


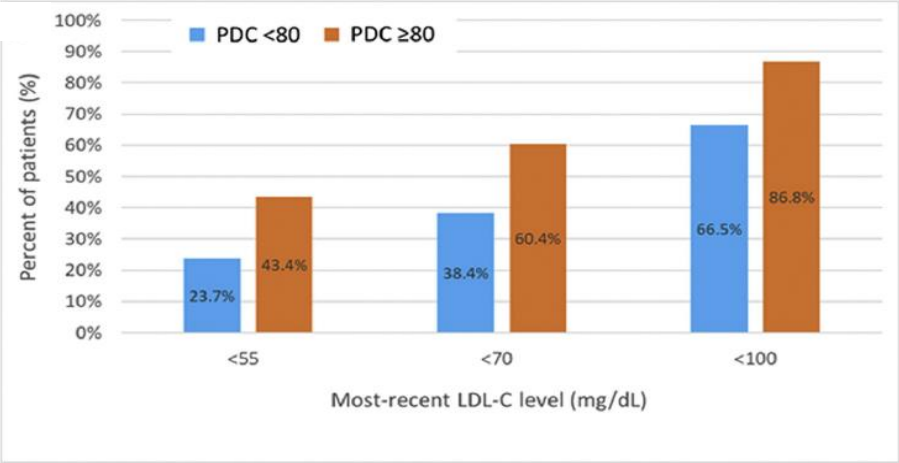
Stoekenbroek RM, et al. Atherosclerosis. 2018

PCSK9 inhibition in clinical practice: Treatment patterns and attainment of lipid goals in a large health maintenance

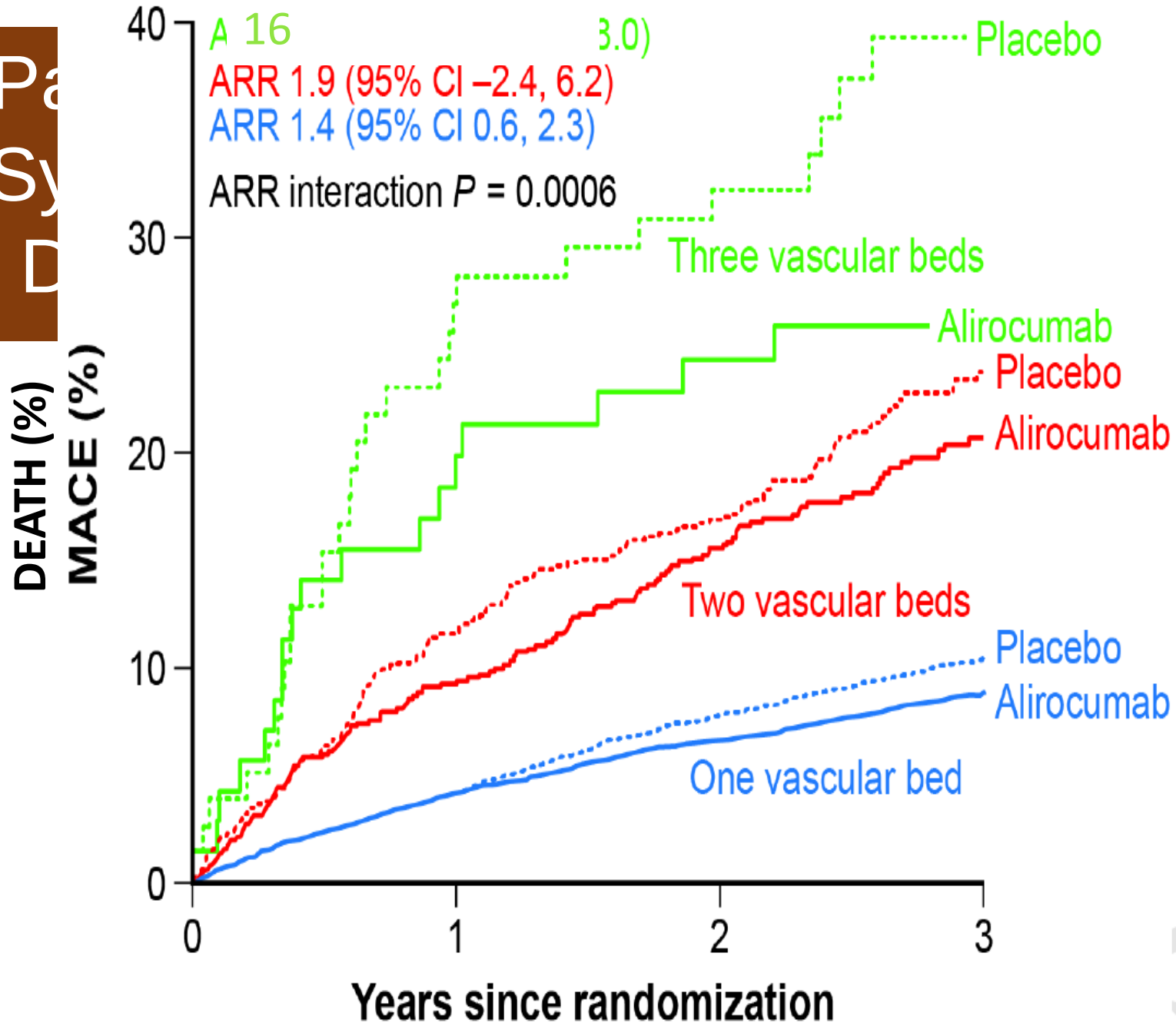
Attainment of LDL cholesterol treatment goals according to clinical parameters

Atherosclerotic cardiovascular disease (ASCVD);
Proportion of days covered (PDC)

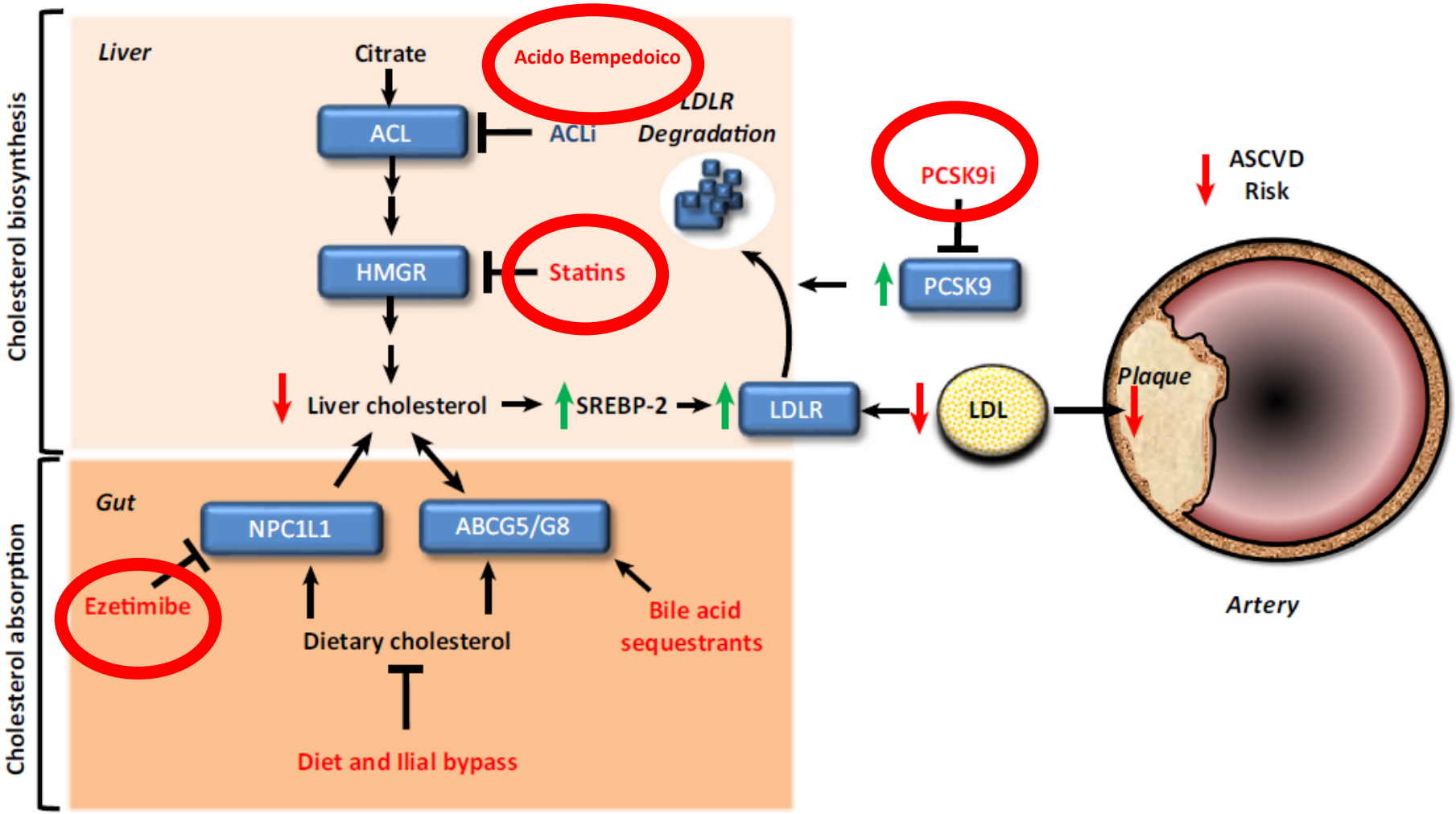




Journal of Clinical Lipidology 2021 15, 202–211


A 16
3.0)
ARR 1.9 (95% CI –2.4, 6.2)
ARR 1.4 (95% CI 0.6, 2.3)
ARR interaction P = 0.0006
Placebo
Three vascular beds
Alirocumab
Placebo
Alirocumab
Two vascular beds
Placebo
Alirocumab
One vascular bed
DEATH (%)
MACE (%)
40
30
20
10
0
0
1
2
3
Years since randomization

I farmaci che promuovono l' aumento dell'espressione del recettore delle LDL nel fegato riducono il rischio CV



Trends in Molecular Medicine, November 2017

Il raggiungimento degli obiettivi terapeutici nell' era degli inibitori di PCSK9 E DI ACIDO BEMPEDOICO

Statina ad alta intensità+
Ezetimibe+
PCSK9i

-84

Statina ad alta intensità+
Ezetimibe+
PCSK9i+
Acido Bempedoico

-100

Current Cardiology Reports 2020

Ministero della Salute

DIREZIONE GENERALE DELLA PREVENZIONE SANITARIA – Ufficio 8

Prevenzione delle malattie cardiovascolari lungo il corso della vita

COMPONENTI DEL GRUPPO

Marco Bacchini (Federazione nazionale unitaria titolari di farmacIa - FEDERFARMA)
Paolo Bellisario (Ministero della salute)
Fulvio Bellocci (Gruppo Intervento Emergenze Cardiologiche – GIEC)
Cristina Bolsi (Associazione Fondazione Italiana per il Cuore-Italian Heart Foundation)
Giuseppe Boriani (Associazione Italiana di Aritmologia e Cardiostimolazione – AIAC)
Elena Bozzola (Società Italiana di Pediatria – SIP)
Giuseppe Ciancamerla (Coordinamento Nazionale Associazioni del Cuore - CONACUORE)
Susanna Conti (Società Italiana di Statistica Medica ed Epidemiologia Clinica – SISMEC)
Vincenzo Contursi (Società Italiana Interdisciplinare di Cure Primarie - SIICP)
Vitaliano Corapi (Federazione degli Ordini Farmacisti Italiani – FOFI)
Giovanni Corrao (Consulta delle società scientifiche per la riduzione del rischio cardiovascolare)
Claudio Ferri (Società Italiana dell'Ipertensione Arteriosa - Lega Italiana contro l'Ipertensione Arteriosa – SIIA)
Emanuela Folco (Associazione Fondazione Italiana per il Cuore-Italian Heart Foundation)
Giovanni Forleo (Associazione Italiana di Aritmologia e Cardiostimolazione – AIAC)
Claudio Fresco (Gruppo di Studio Aterosclerosi, Trombosi, Biologia Vascolare – ATBV)
Domenico Gabrielli (Associazione Nazionale Medici Cardiologi Ospedalieri – ANMCO)
Antonio Vittorino Gaddi (Società Italiana di salute digitale e Telemedicina – SIT)
Daniela Galeone (Ministero della salute)
Gianfranco Gensini (Società Italiana di salute digitale e Telemedicina – SIT)
Ignazio Grattagliano (Società Italiana di Medicina Generale e delle Cure Primarie – SIMG)
Pasquale Guarini (Società Italiana Cardiologia Ospedalità Accreditata – SICOA)
Michele Massimo Gulizia (Fondazione per il tuo cuore Onlus - HCF Onlus)
Ciro Indolfi (Società Italiana di Cardiologia – SIC)
Giovanna Laurendi (Ministero della salute)
Paolo Magni (Associazione Fondazione Italiana per il Cuore-Italian Heart Foundation)
Giuseppe Mancia (Consulta delle società scientifiche per la riduzione del rischio cardiovascolare)
Dario Manfellotto (Federazioni delle Associazioni dei Dirigenti Ospedalieri Internisti – FADOI)
Giuseppe Marceca (Gruppo Intervento Emergenze Cardiologiche – GIEC)
Walter Marrocco (Federazione Italiana Medici di Medicina Generale – FIMMG)
Marco Masci (Società Italiana di Pediatria – SIP)
Tiziana Menegon (Società Italiana di Igiene Medicina Preventiva e Sanità Pubblica – SItI)
Giuseppe Mercuro (Società Italiana di Cardiologia – SIC)
Renato Nami (Associazione nazionale cardiologi extraospedalieri - Cardiologia italiana del territorio - ANCE)
Enrico Orsini (Associazioni Regionali Cardiologi Ambulatoriali)
Roberto F.E. Pedretti (Associazione Italiana di Cardiologia clinica, Preventiva e Riabilitativa - AICPR)
Antonio Pelliccia (Società Italiana di Cardiologia dello Sport - SIC Sport)
Barbara Pellizzari (Società Italiana di Igiene Medicina Preventiva e Sanità Pubblica – SItI)
Francesco Perticone (Società Italiana Medicina Interna - SIMI)
Enzo Pirrotta (Società Nazionale di Aggiornamento per il Medico di Medicina Generale - SNAMID)
Renato Pietro Ricci (Associazione Italiana di Aritmologia e Cardiostimolazione – AIAC)
Adamo Ripani (Comitato Italiano Scienze Motorie - CISM)
Giancarlo Roscio (Società italiana di formazione permanente per la medicina specialistica - SIFOP)
Lidia Rota Vender (Associazione per la Lotta alla Trombosi e alle malattie cardiovascolari onlus - ALT onlus)
Paola Santalucia (Associazione per la Lotta alla Trombosi e alle malattie cardiovascolari onlus - ALT onlus)
Fabio Tarantino (Società Italiana di Cardiologia Interventistica – GISE)
Giovanna Tassoni (Associazione Onlus CardioSalus)
Giuliano Tocci (Società italiana per la prevenzione cardiovascolare- SIPREC)
Annarita Vestri (Società Italiana di Statistica Medica ed Epidemiologia Clinica – SISMEC)
Alberto Villani (Società Italiana di Pediatria – SIP)
Massimo Volpe (Società italiana per la prevenzione cardiovascolare- SIPREC)
Roberto Volpe (Società Italiana per lo Studio dell'Aterosclerosi – SISA)

Coordinatori del gruppo di lavoro: Paolo Bellisario, Daniela Galeone, Michele Massimo Gulizia, Giovanna Laurendi.
Coordinatori dei sottogruppi di lavoro: Domenico Gabrielli, Gianfranco Gensini, Michele Massimo Gulizia, Marco Masci, Roberto F.E. Pedretti, Lidia Rota Vender, Giuliano Tocci, Massimo Volpe.

Un Modello organizzativo per La Prevenzione Secondaria deve prevedere:

- l'***empowerment***, sia a livello individuale che di comunità, ovvero l'acquisizione della capacità di operare scelte e di agire per migliorare la propria salute in modo consapevole;

- il ***patient engagement***, ovvero il coinvolgimento attivo del paziente in tutto ciò che riguarda il suo percorso di cura, in modo da favorire una maggiore autonomia e proattività della persona nella gestione la propria salute anche in relazione con il sistema sanitario.

- **le linee guida diagnostico-terapetiche.**

- **i Percorsi Preventivo-Diagnostico-Terapeutico-Assistenziali (PPDTA).**

- **L' integrazione tra cure primarie, ospedale e territorio.**

TAKE HOME MESSAGE

- ***L'ulteriore riduzione di LDL-C con i PCSK9i ha dimostrato un significativo incrementale beneficio nei pazienti ad alto ed altissimo rischio cardiovascolare***

- **L'unica strategia «evidence based» per ridurre il rischio residuo è rappresentata dalla ulteriore riduzione di LDL-C con le nuove terapie**

- ***Per i pazienti appartenenti alle categorie di rischio altissimo o estremo le nuove LG raccomandano un goal di LDL-C inferiore a 55 mg/dl***