11° CONGRESSO NAZIONALE

CAMPUS Cuore

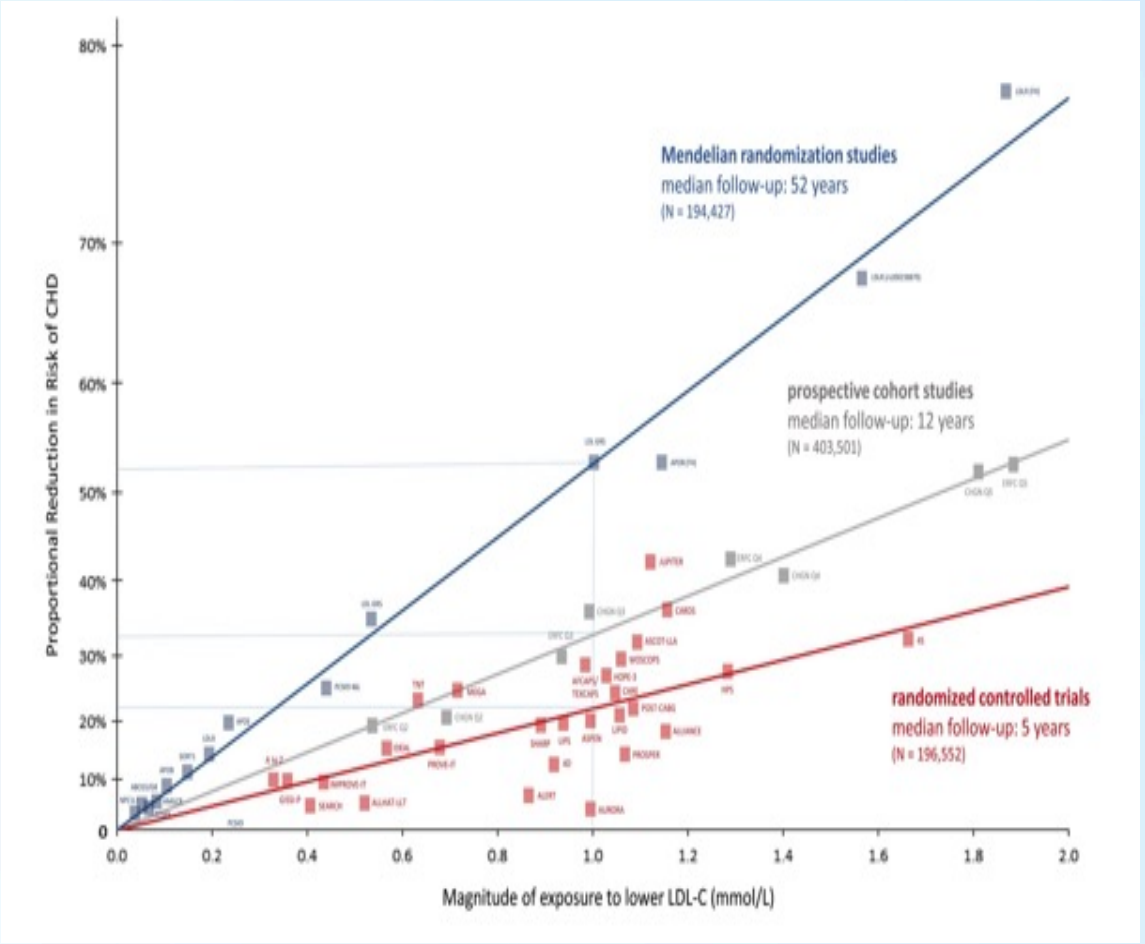
Quello che le Linee Guida Non Dicono

Napoli
5-6 aprile 2024

Doppia inibizione Colesterolo LDL statina/ezetimibe: strategie per una appropriata implementazione nella pratica clinica quotidiana

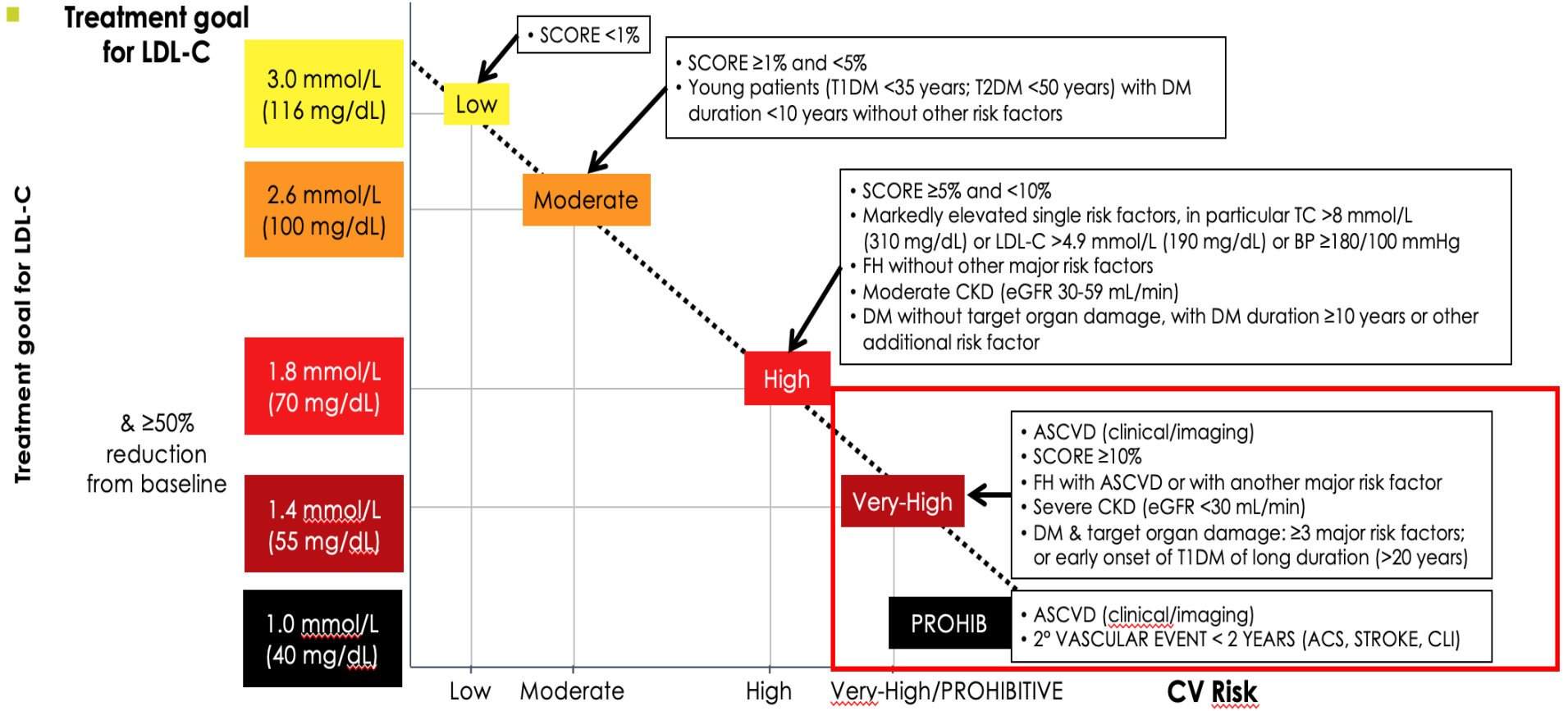
Claudia Concilio, MD
Cardiologia Clinica a Direzione Universitaria con UTIC
AORN Sant'Anna e San Sebastiano, Caserta

L'esposizione temporale e cumulativa al Colesterolo-LDL è un predittore chiave del rischio di malattia cardiovascolare aterosclerotica (ASCVD)



Ference BA, Eur Heart J 2017

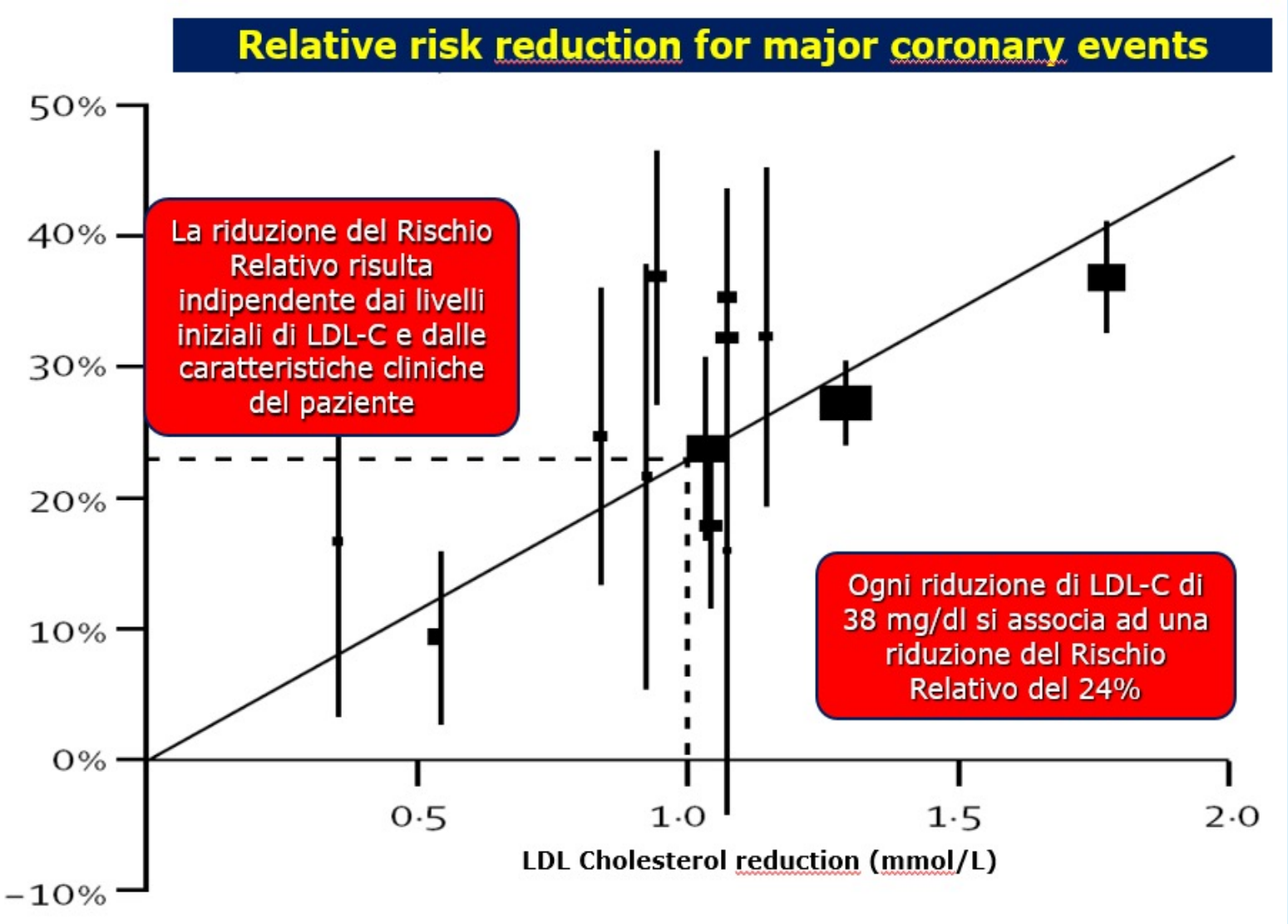
TREATMENT GOALS FOR LOW-DENSITY LIPOPROTEIN CHOLESTEROL (LDL-C) ACROSS CATEGORIES OF TOTAL CARDIOVASCULAR DISEASE RISK



MODIFICATO *from: Mach F, et al. Eur Heart J 2019. doi:10.1093/eurheartj/ehz455.*

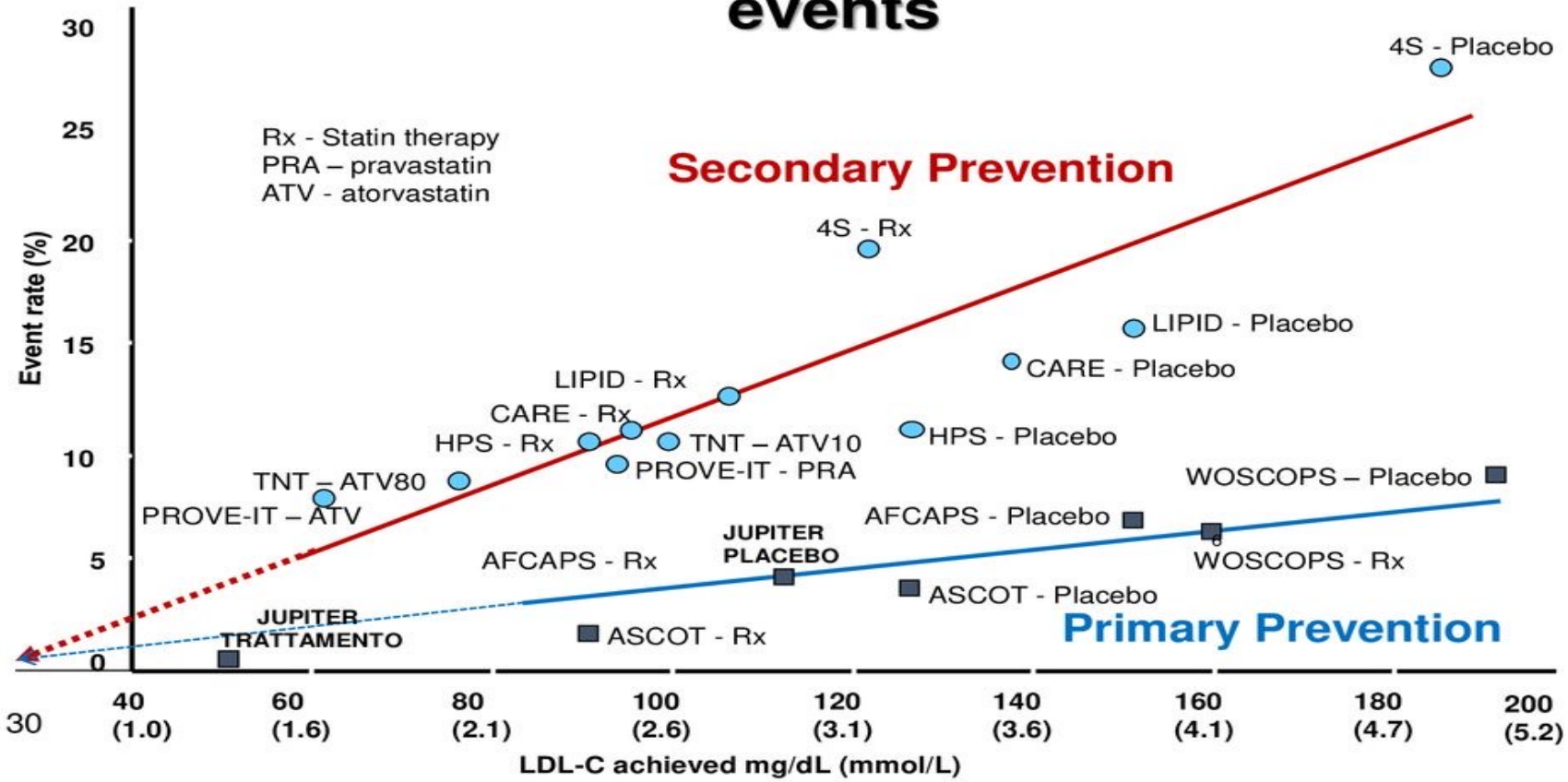
Several large randomized controlled trials that included hundreds of thousands of patients have shown the benefit of statins in reducing LDL-C levels and coronary heart disease risk.

Year	Trial	References	Patient Category	Statin(s)	n
1994	4S	69	CHD	Simvastatin	4444
1995	WOSCOPS	70	Healthy hypercholesterol.	Pravastatin	6595
1996	CARE	71	CHD	Pravastatin	4159
1997	Post CABG	85	CHD	Lovastatin	1351
1998	AFCAPS/TEXCAPS	84	Healthy	Lovastatin	6605
1998	LIPID	76	CHD	Pravastatin	9014
2000	GISSI Prevenzione	86	CHD	Pravastatin	4271
2001	MIRACL	87	CHD	Atorvastatin	3086
2002	HPS	88	CHD	Simvastatin	20536
2002	LIPS	89	Post PCI	Fluvastatin	1677
2002	GREACE	90	CHD	Atorvastatin	1600
2002	PROSPER	91	Elderly (70–82 y) high risk	Pravastatin	5804
2002	ALLHAT-LLT	92	Hypertensive high risk	Pravastatin	10355
2002	ASCOT	93	Hypertensive	Atorvastatin	10305
2003	ALERT	94	Renal transplant	Fluvastatin	2102
2003	CARDS	95	Diabetes mellitus type 2	Atorvastatin	2838
2004	ALLIANCE	96	CHD	Atorvastatin	2442
2004	PROVE IT	78	CHD	Pravastatin-atorvastatin	4162
2004	A to Z	79	CHD	Simvastatin	4497
2004	TNT	80	CHD	Atorvastatin	10001
2005	4D	97	Dialysis patients w. diabetes	Atorvastatin	1255
2005	IDEAL	81	CHD	Atorvastatin -simvastatin	8888
2006	MEGA	98	Healthy hypercholesterol.	Pravastatin	8214
2006	SPARCL	99	Stroke	Atorvastatin	4731
2007	CORONA	100	Heart failure	Rosuvastatin	5011
2008	GISSI HF	101	Heart failure	Rosuvastatin	4574
2008	JUPITER	102	Healthy CRP elevation	Rosuvastatin	17802
2009	AURORA	103	Chronic kidney disease on dialysis	Rosuvastatin	2776
2010	SEARCH	82	CHD	Simvastatin	12064
2011	SHARP	104	Chronic kidney disease	Simvastatin+ezetimibe	9270



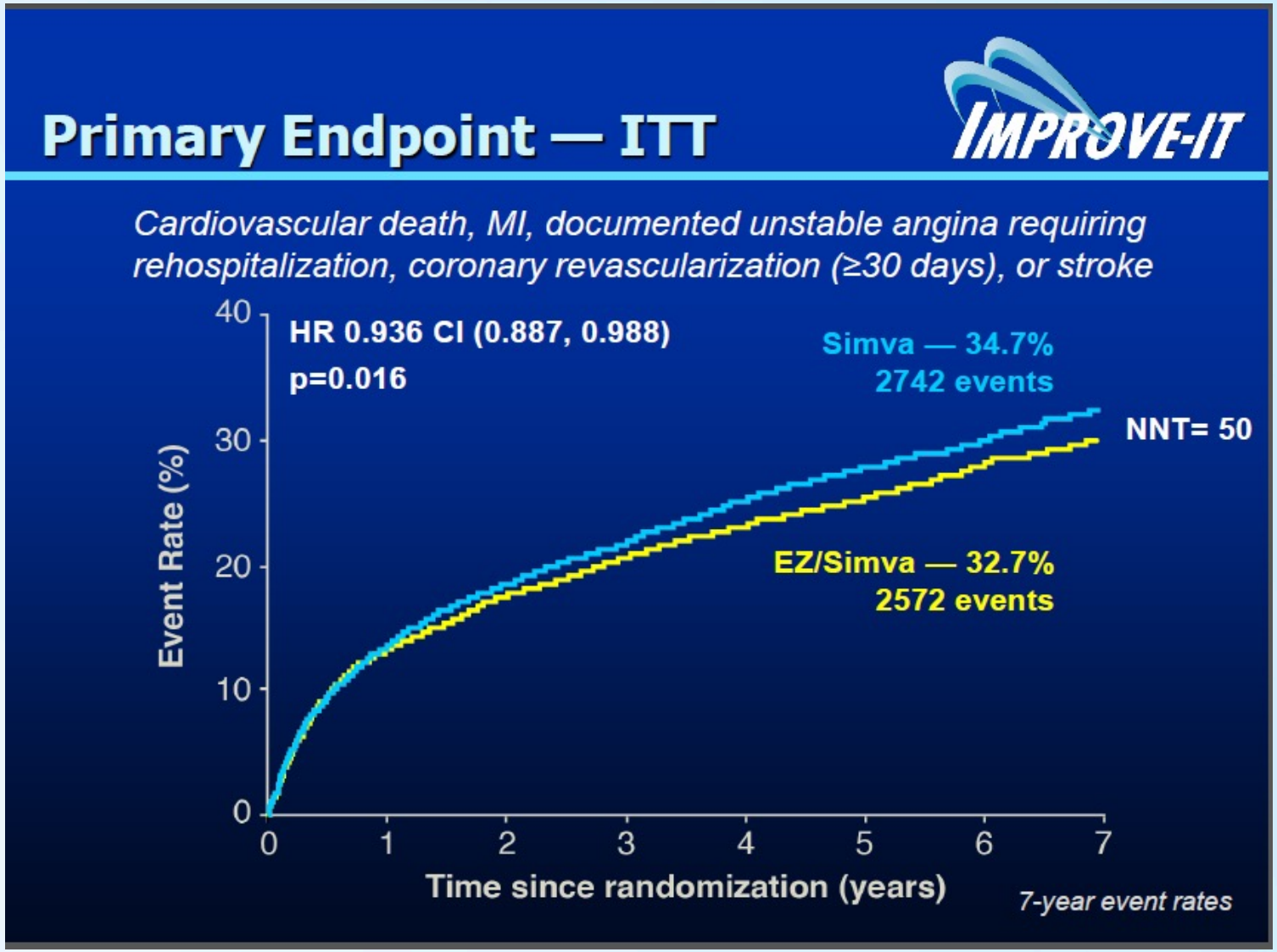
Baigent C, Lancet 2005

Every reduction in LDL-C with STATINS is associated with a corresponding reduction in CVD events



Adapted from Rosensen RS. *Exp Opin Emerg Drugs* 2004; 9(2):269-279
LaRosa JC et al. *NEJM* 2005; 352:1425-1435
Ridker PM et al. *NEJM* 2008; 359: 2195-2207

When added to statins, ezetimibe reduces LDL cholesterol levels by an additional 16%.

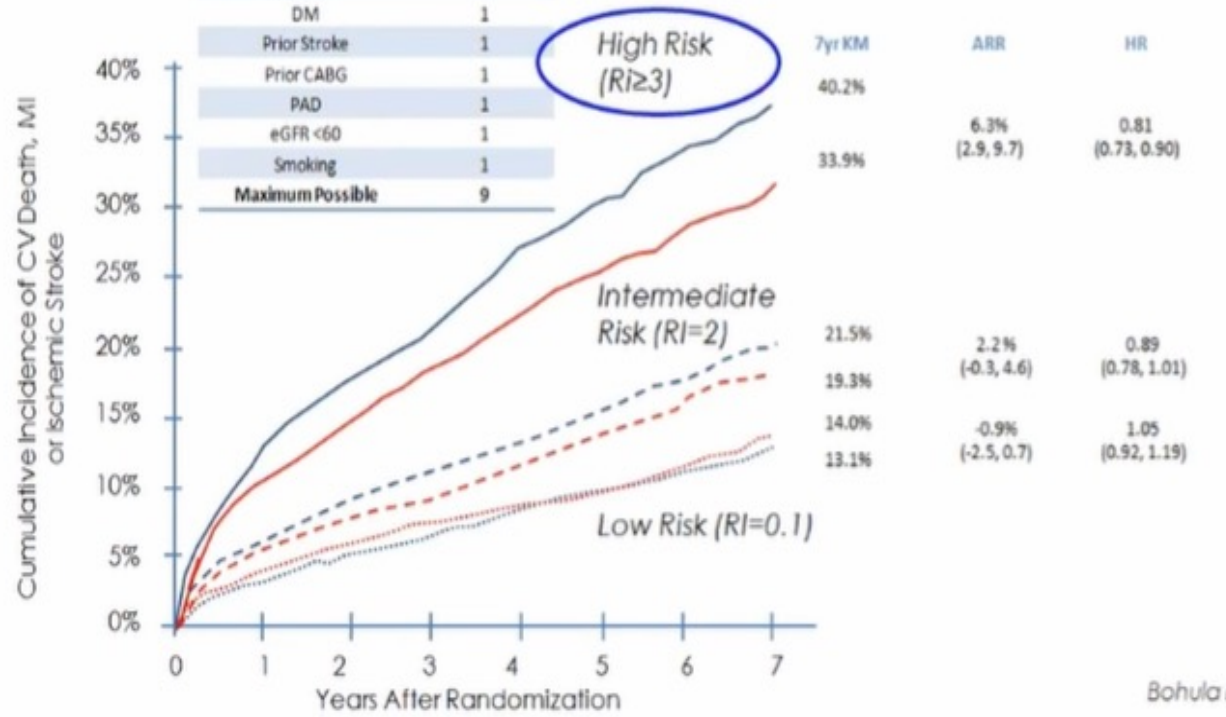


Cannon CP, N Engl J Med 2015

Statina + ezetimibe nei pazienti a più elevato rischio

La stratificazione secondo lo score TRA2P-TIMI 50

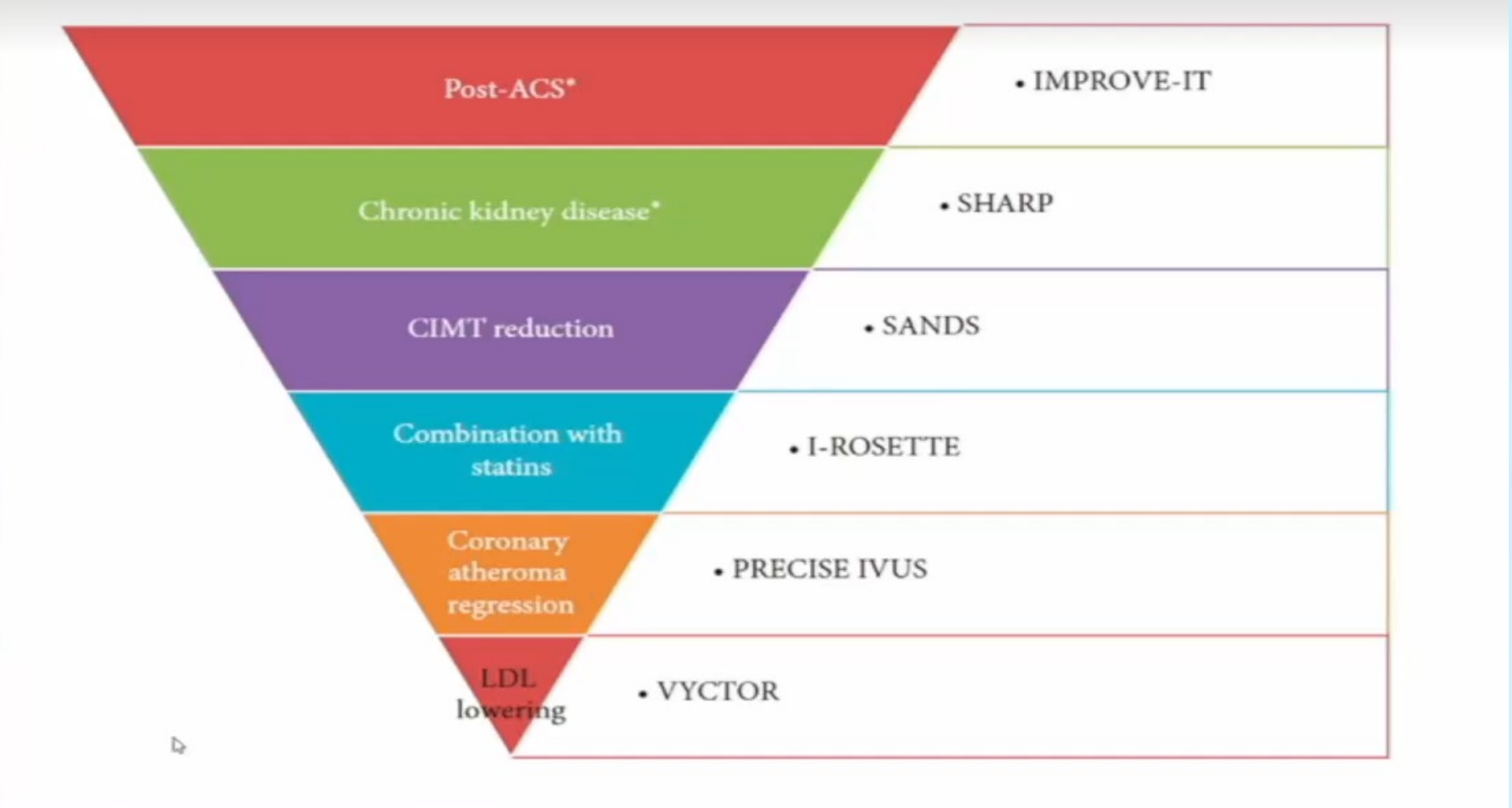
TRS 2°P Risk Indicators	Points
CHF	1
HTN	1
Age ≥75	1
DM	1
Prior Stroke	1
Prior CABG	1
PAD	1
eGFR <60	1
Smoking	1
Maximum Possible	9



Bohula EA, Morrow DA, Giugliano RP et al. JAC

Bahula EA, JACC 2017

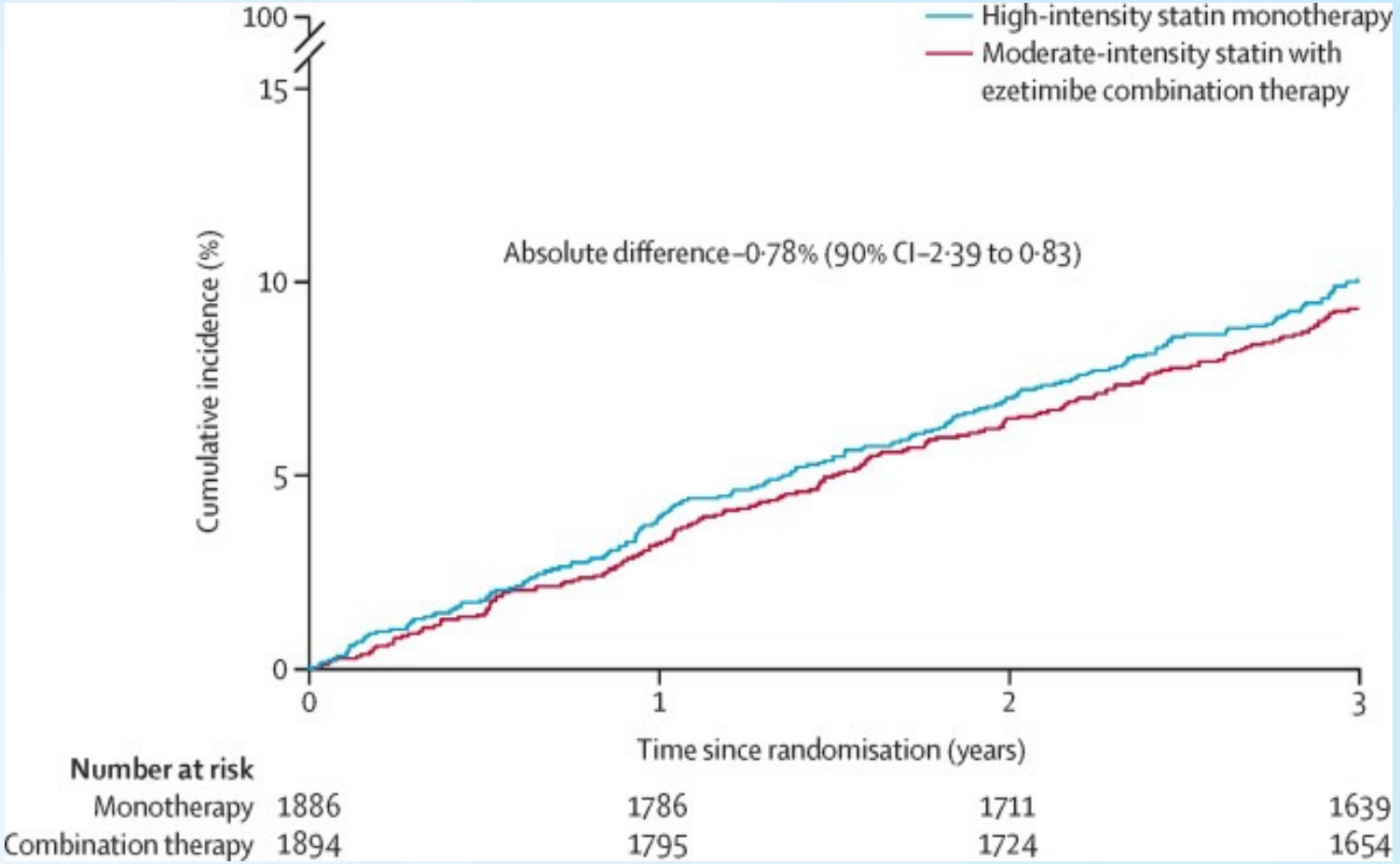
Scenari clinici dove la terapia di combinazione ha dimostrato la sua efficacia ed utilità



Cardiology Research and Practice 2020

RACING TRIAL

The primary endpoint was the 3-year composite of cardiovascular death, major cardiovascular events, or non-fatal stroke, in the intention-to-treat population with a non-inferiority margin of 2·0%.



Kim B-K, Lancet 2022

RACING TRIAL

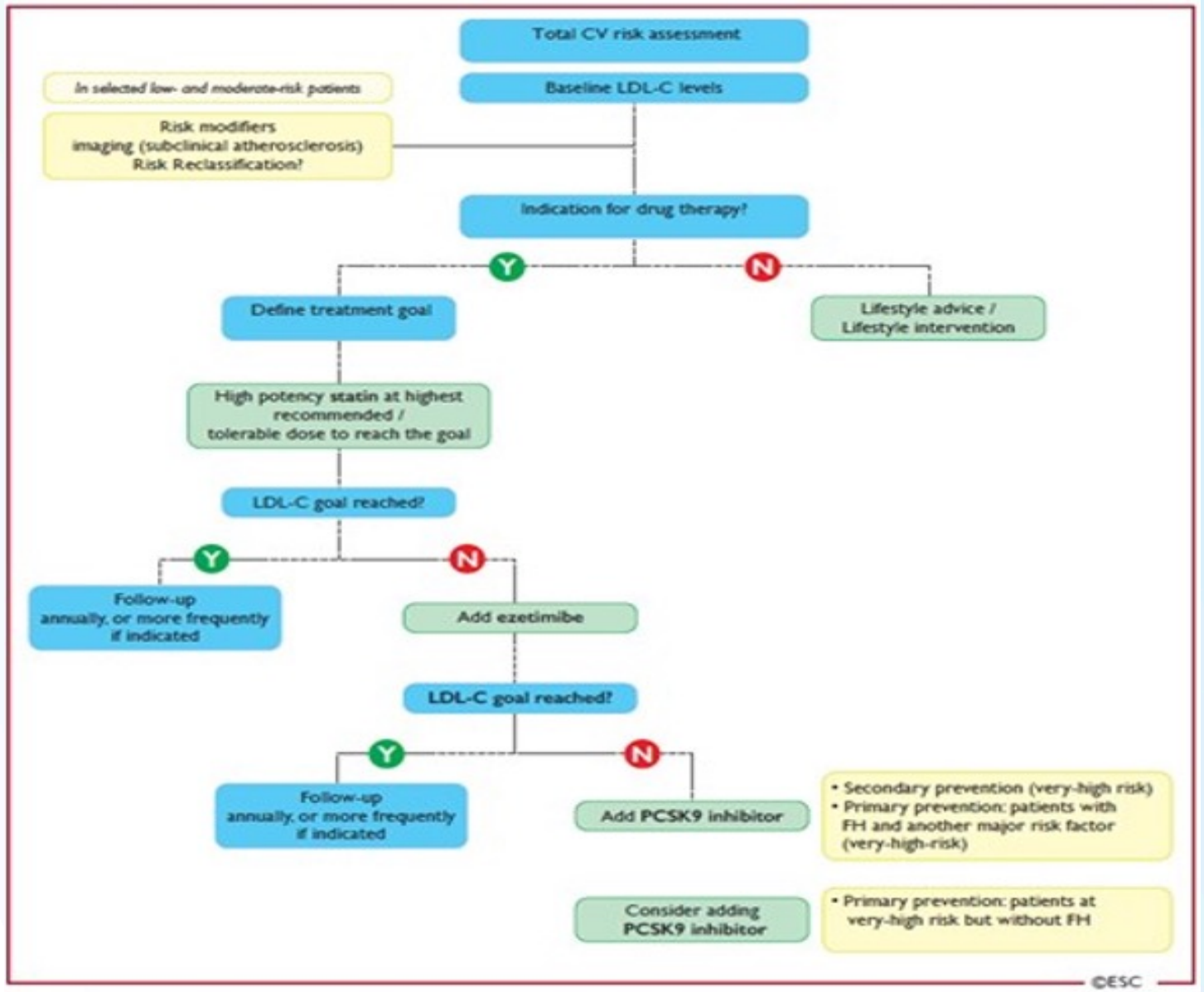
	Moderate-intensity statin with ezetimibe combination therapy (n=1846)	High-intensity statin monotherapy (n=1832)	Absolute difference (95% CI)
Serious adverse events			
Death	26 (1·4%)	22 (1·2%)	0·21 (−5·88 to 1·01)
Adverse events			
Discontinuation or dose reduction of study drug due to intolerance	88 (4·8%)	150 (8·2%)	−3·42 (−5·07 to −1·80)
Reported symptoms			
Dizziness or general weakness	10	21	..
Chest discomfort or headache	7	12	..
Gastrointestinal symptoms	4	9	..
Urticaria or itching sensation	6	7	..
Myalgia	7	22	..
Other	5	3	..
Physician discretion			
Liver enzyme elevation	15	32	..
Creatine kinase elevation	25	33	..
Fasting glucose concentration elevation	5	6	..
Other	4	5	..
New-onset diabetes	145 (7·9%)	159 (8·7%)	−0·82 (−2·65 to 1·00)
New-onset diabetes with anti-diabetic medication initiation	95 (5·1%)	107 (5·8%)	..
Muscle-related adverse events	21 (1·1%)	34 (1·9%)	0·69 (−2·22 to 0·82)
Myalgia	17 (0·9%)	29 (1·6%)	0·66 (−1·46 to 1·06)
Myopathy	2 (0·1%)	4 (0·2%)	−0·11 (−0·50 to 0·25)
Myonecrosis*	11 (0·6%)	13 (0·7%)	0·11 (−0·72 to 0·48)
Mild	8	9	..
Moderate	2	3	..
Severe including rhabdomyolysis	1	1	..
Gallbladder-related adverse events	13 (0·7%)	7 (0·4%)	0·32 (−0·22 to 0·89)
Major bleeding	17 (0·9%)	13 (0·7%)	0·21 (−0·44 to 0·87)
Cancer diagnosis	37 (2·0%)	28 (1·5%)	0·48 (−0·43 to 0·14)
New-onset neurocognitive disorder	4 (0·2%)	2 (0·1%)	0·11 (−0·25 to 0·50)
Cataract surgery	19 (1·0%)	21 (1·1%)	−0·12 (−0·86 to 0·62)

Data are n (%). These events were adverse events of special interest in this study. ULN=upper limit of normal. *Severity of myonecrosis was classified by an elevation of creatine kinase concentration compared with either baseline concentration or the ULN: mild >3 times ULN; moderate ≥10 times ULN; severe ≥50 times ULN.

Table 4: **Secondary safety endpoint of the safety population**

Higher proportion of patients with LDL cholesterol concentrations of less than 70 mg/dL and lower intolerance-related drug discontinuation or dose reduction.

Kim B-K, Lancet 2022



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

ESC European Society of Cardiology
EAS

March F. Eur Heart J 2019

ESC European Society of Cardiology

European Heart Journal (2022) **43**, 830–833
https://doi.org/10.1093/eurheartj/ehab718

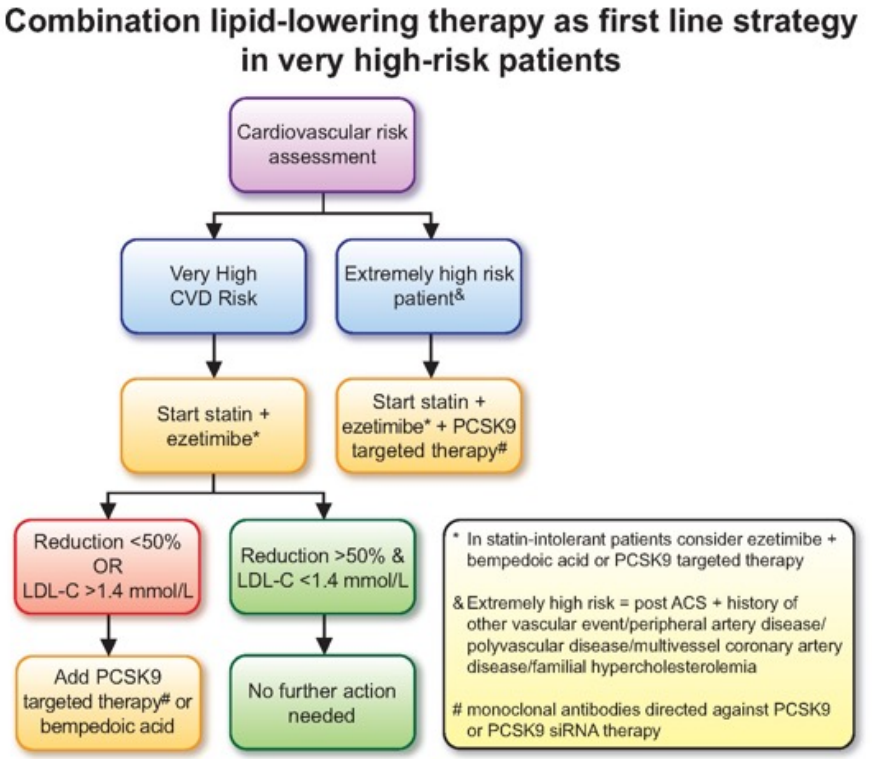
VIEWPOINT
Epidemiology and prevention

Combination lipid-lowering therapy as first-line strategy in very high-risk patients

Kausik K. Ray[1]*, Laurens F. Reeskamp [2], Ulrich Laufs [3], Maciej Banach [4], François Mach [5], Lale S. Tokgözoğlu [6], Derek L. Connolly[7], Anja J. Gerrits[8], Erik S. G. Stroes [2], Luis Masana [9], and John J. P. Kastelein [2]

Graphical Abstract Combination lipid-lowering therapy as first line strategy in very high-risk patients.

ESC European Society of Cardiology

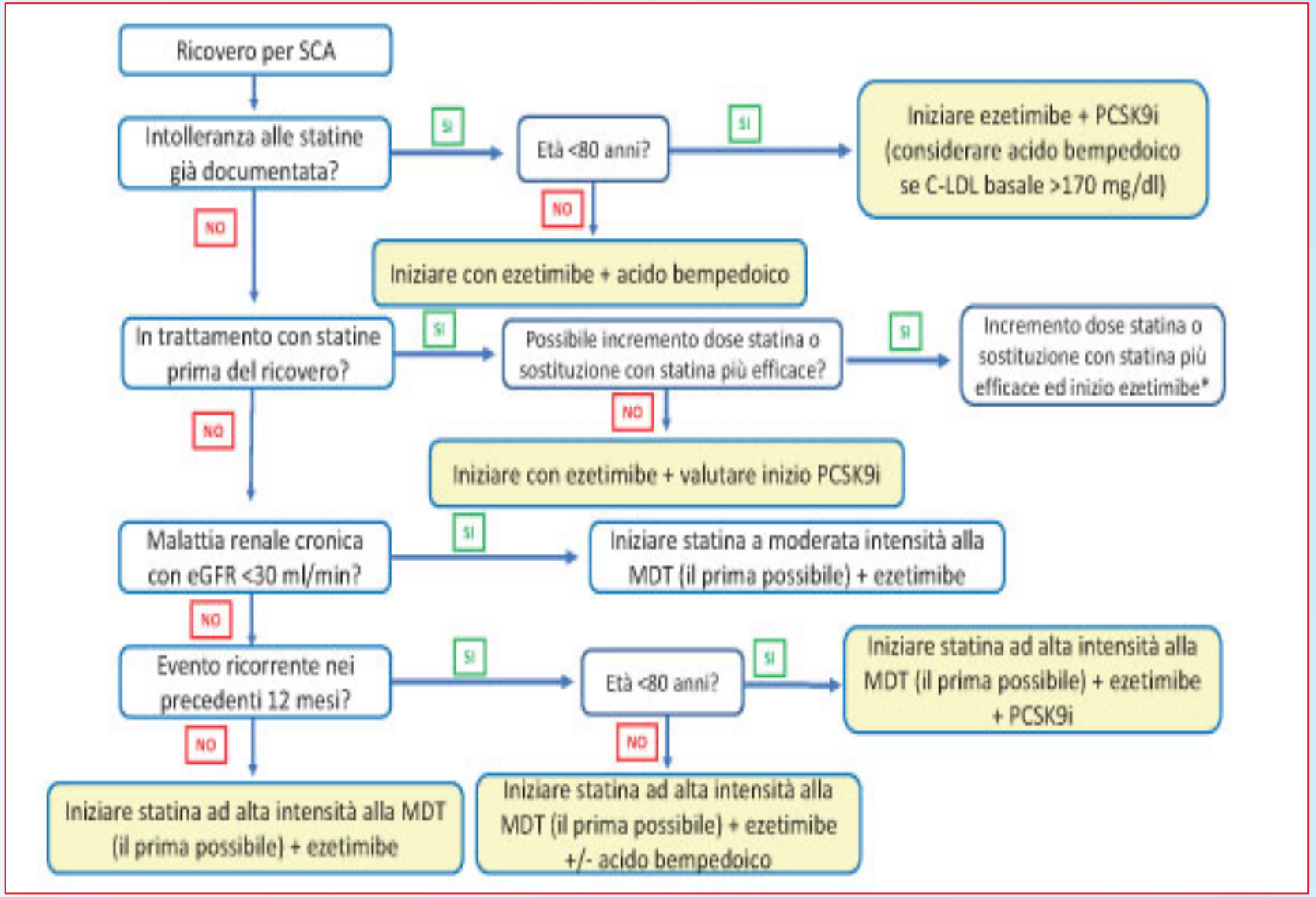


Eur Heart J, Volume 43, Issue 8, 21 February 2022, Pages 830–833, https://doi.org/10.1093/eurheartj/ehab718

Kausik KR, Eur Heart J 2022

Position paper ANMCO: Gestione dell'ipercolesterolemia nei pazienti con sindrome coronarica acuta

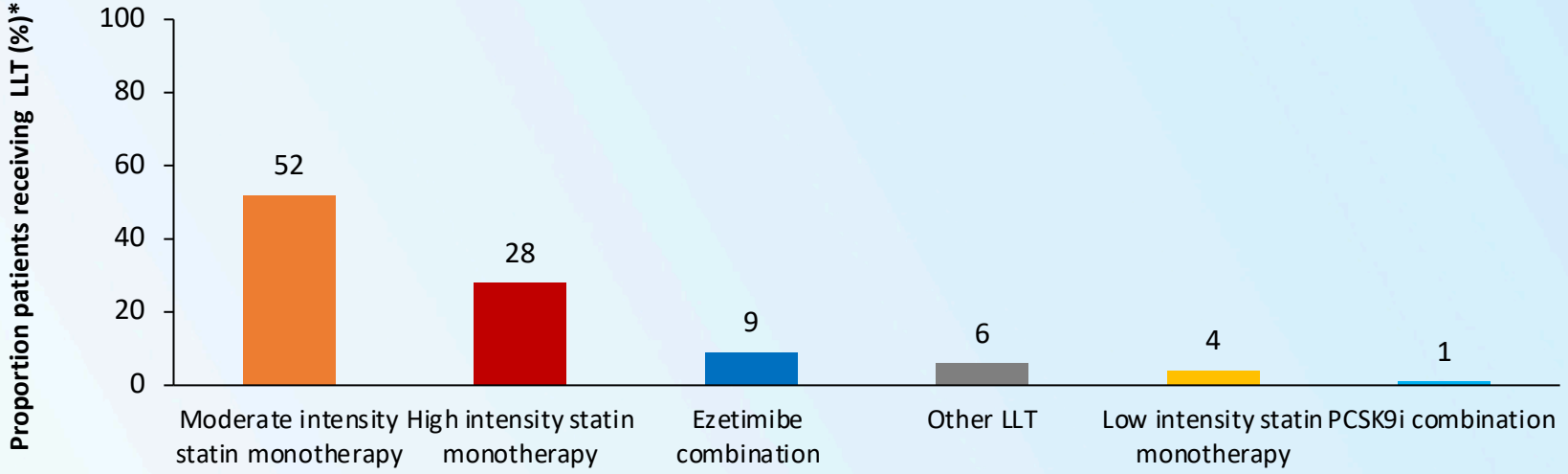
Leonardo De Luca[1], Carmine Riccio[2], Alessandro Navazio[3], Serafina Valente[4], Manlio Cipriani[5], Marco Corda[6], Alfredo De Nardo[7], Giuseppina Maura Francese[8], Cosimo Napoletano[9], Emanuele Tizzani[10], Loris Roncon[11], Pasquale Caldarola[12], Michele Massimo Gulizia[8], Domenico Gabrielli[1,13], Fabrizio Oliva[14], Furio Colivicchi[15]



De Luca L, G Ital Cardiol. 2023

DA VINCI Sought to Determine Attainment of ESC/EAS LDL-C Goals In Clinical Practice Across Europe

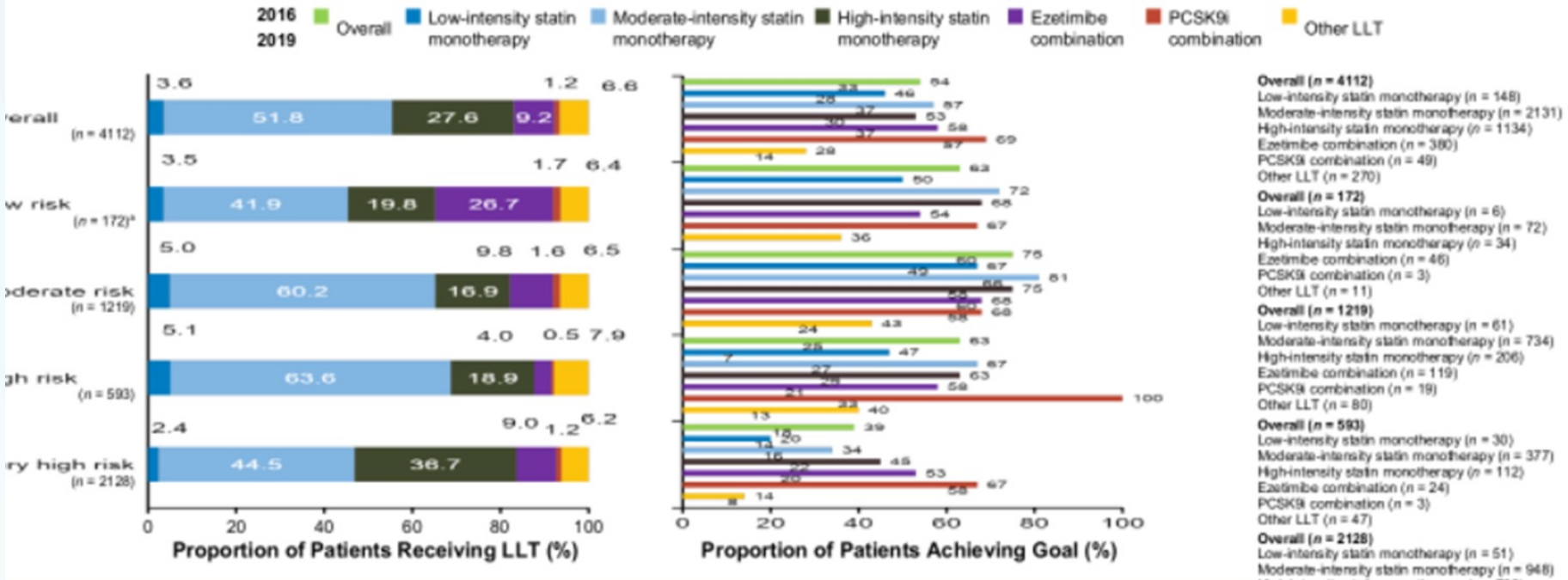
Implementation of both 2016 and 2019 ESC/EAS guideline LDL-C goal attainment for patients (n=5888) across 18 countries in Europe in primary and secondary healthcare settings



- **Only 28% of patients were receiving high intensity statin monotherapy**
- **Few patients (9%) were receiving ezetimibe combo**
- **Even fewer patients (1%) received PCSK9i combo**

*Stabilised LLT at time of LDL-C measurement. combo, combination
LDL-C = low-density lipoprotein cholesterol; LLT = lipid lowering therapy; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor.
Ray, KK, et al. *Eur J Prev Cardiol*. 2020. doi:10.1093/eurjpc/zwaa047.

Only 18% of Very-High Risk Patients Achieved LDL-C Goals of < 1.4 mmol/L (< 55 mg/dL)



Among very-high risk patients receiving statin monotherapy, goal attainment was 14%, 16% and 22% in those receiving low-, moderate- and high-intensity statins. Overall, 37% of patients receiving ezetimibe combination therapy and 57% receiving PCSK9 inhibitor combination therapy achieved their risk-based LDL-C goal.

Overall (*n* = 4112)
Low-intensity statin monotherapy (*n* = 148)
Moderate-intensity statin monotherapy (*n* = 2131)
High-intensity statin monotherapy (*n* = 1134)
Ezetimibe combination (*n* = 380)
PCSK9i combination (*n* = 49)
Other LLT (*n* = 270)

Overall (*n* = 172)
Low-intensity statin monotherapy (*n* = 6)
Moderate-intensity statin monotherapy (*n* = 72)
High-intensity statin monotherapy (*n* = 34)
Ezetimibe combination (*n* = 46)
PCSK9i combination (*n* = 3)
Other LLT (*n* = 11)

Overall (*n* = 1219)
Low-intensity statin monotherapy (*n* = 61)
Moderate-intensity statin monotherapy (*n* = 734)
High-intensity statin monotherapy (*n* = 206)
Ezetimibe combination (*n* = 119)
PCSK9i combination (*n* = 19)
Other LLT (*n* = 80)

Overall (*n* = 593)
Low-intensity statin monotherapy (*n* = 30)
Moderate-intensity statin monotherapy (*n* = 377)
High-intensity statin monotherapy (*n* = 112)
Ezetimibe combination (*n* = 24)
PCSK9i combination (*n* = 3)
Other LLT (*n* = 47)

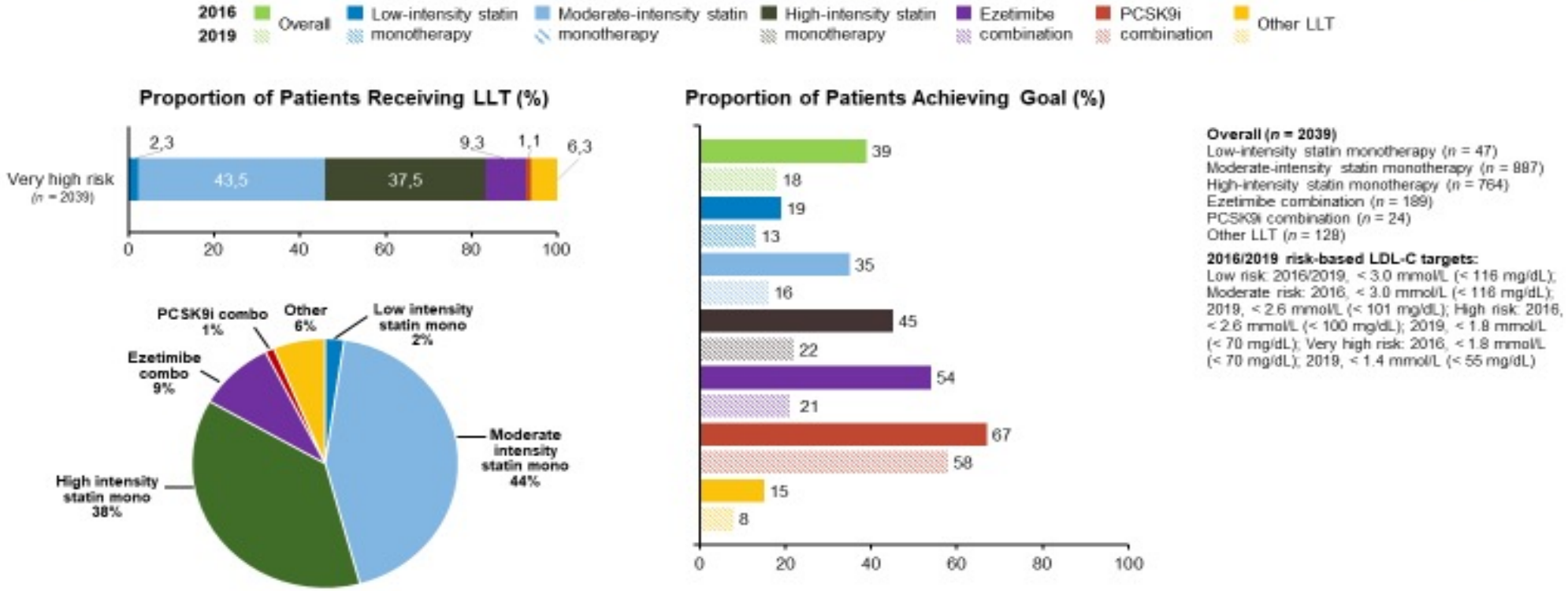
Overall (*n* = 2128)
Low-intensity statin monotherapy (*n* = 51)
Moderate-intensity statin monotherapy (*n* = 948)
High-intensity statin monotherapy (*n* = 782)
Ezetimibe combination (*n* = 191)
PCSK9i combination (*n* = 24)
Other LLT (*n* = 132)

2016/2019 risk-based LDL-C targets:
Low risk: 2016/2019, < 3.0 mmol/L (<
Moderate risk: 2016, < 3.0 mmol/L (<
2019, < 2.6 mmol/L (< 101 mg/dL); H
< 2.6 mmol/L (< 100 mg/dL); 2019, <
(< 70 mg/dL); Very high risk: 2016,
< 1.8 mmol/L (< 70 mg/dL); 2019,
< 1.4 mmol/L (< 55 mg/dL)

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; EAS = European Atherosclerosis Society; ESC = European Society of Cardiology; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor.
Goal attainment for low risk is the same for 2016 and 2019 (< 3.0 mmol/L [< 116 mg/dL]) so only one bar is displayed. *N* is the number of patients in the category with non-missing LDL-C goal data. Patients enrolled as secondary prevention whose first ASCVD event occurred after the date LDL-C levels were stabilised are included in the primary prevention group. Among patients enrolled as secondary prevention, 142 had their first CV event recorded after their most recent LDL-C measurement, hence they were analysed as primary prevention patients for outcomes assessed at LDL-C measurement, such as goal attainment. For outcomes assessed at enrollment, these 142 patients were analysed as secondary prevention. Ray, KK, et al. *Eur J Prev Cardiol.* 2020. doi:10.1093/eurjpc/zwaa047.

Kausik KR, Eur J of Prev Card 2020

In Very High Risk Patients with Established ASCVD, Goal Attainment was More Likely Seen in those Receiving Combination Therapy



ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor.
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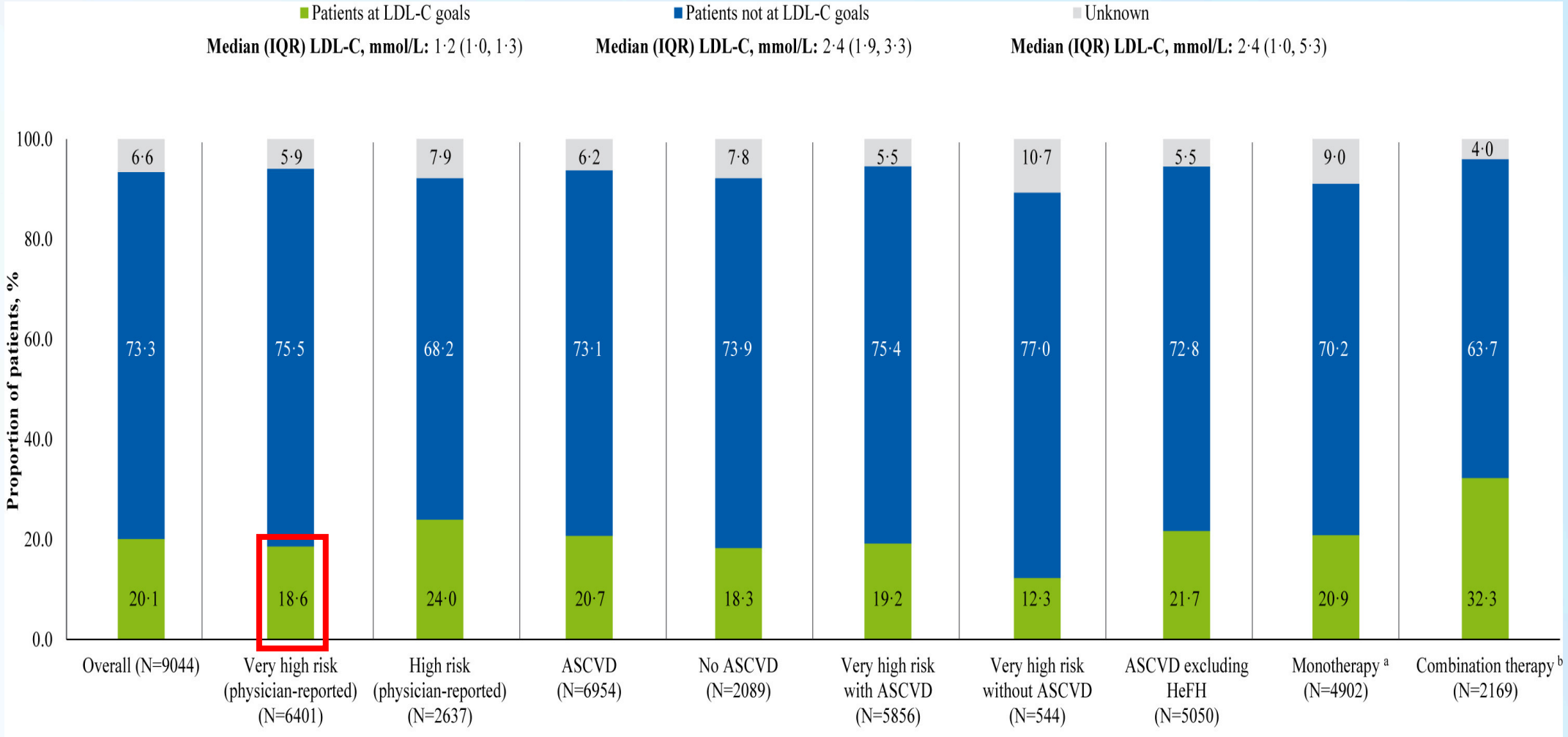
Ray, KK, et al. *Eur J Prev Cardiol*. 2020. doi:10.1093/eurjpc/zwaa047.

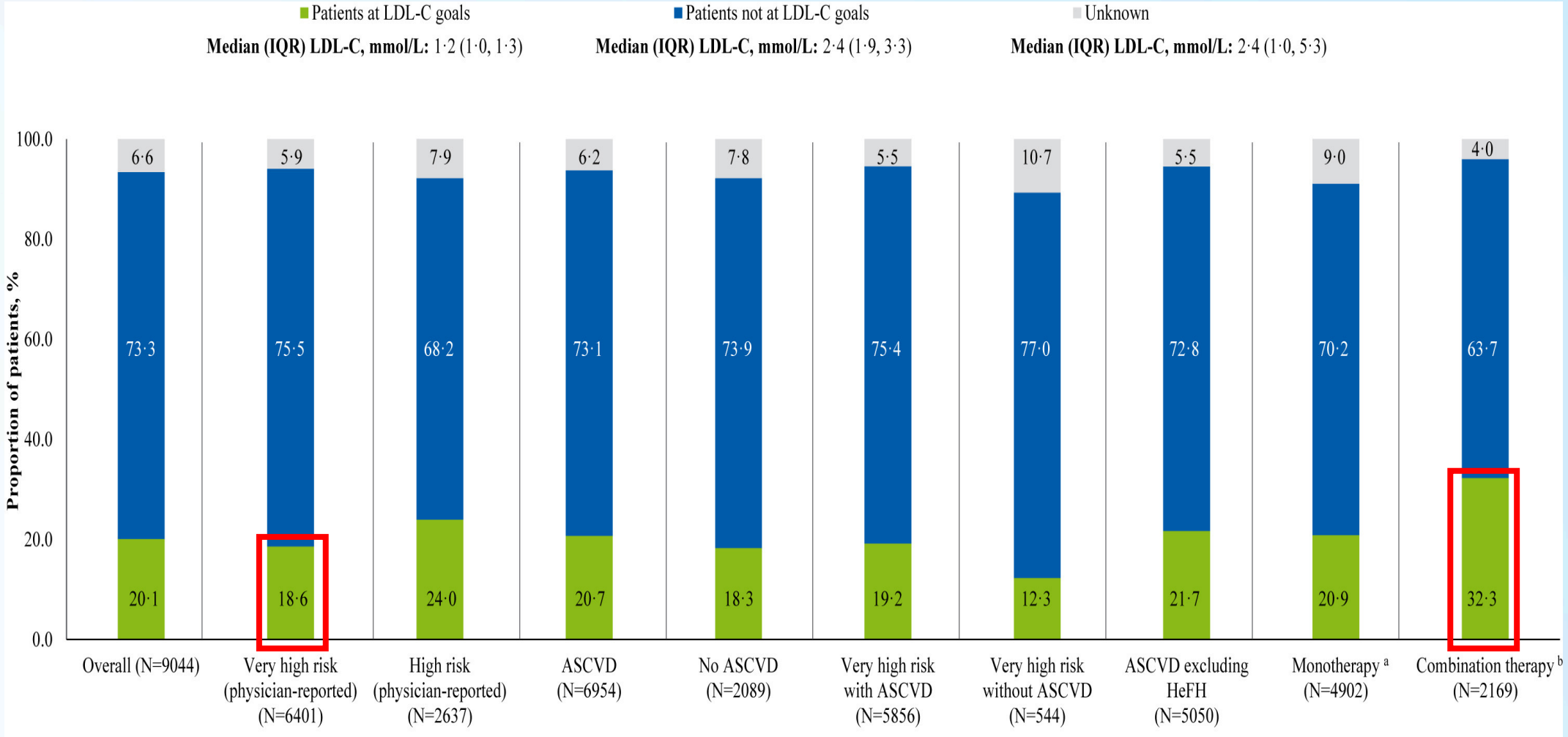
Kausik KR, Eur J of Prev Card 2020

SANTORINI STUDY



Ray KK, Lancet Reg Health Eur. 2023

SANTORINI STUDY



Ray KK, Lancet Reg Health Eur. 2023

Medication Adherence

Table III. Medication adherence after discharge, defined according to the medication possession ratio (MPR).

Variable	Low Adherence: MPR 0%–79%	High Adherence: MPR ≥80%
Drugs		
Clopidogrel, prasugrel, ticagrelor, or aspirin	517 (11.9%)	3832 (88.1%)
DAPT	2069 (47.6%)	2280 (52.4%)
Lipid-lowering drugs	1023 (23.5%)	3326 (76.5%)
ACE inhibitors/ARBs	2059 (47.3%)	2290 (52.7%)
Beta-blockers	3831 (88.1%)	518 (11.9%)
All 3 drugs (LLDs, ACE/ARBs, BBs)	4051 (93.1%)	298 (6.9%)
All 5 drugs(+ DAPT)	4159 (95.6%)	190 (4.4%)

ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; BBs = beta-blockers; DAPT = dual antiplatelet therapy; LLDs = lipid-lowering drug.

Carola A, Clinical Therapeutics 2019

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Carola A, Clinical Therapeutics 2019

Medication Adherence

Figure 1. The one-year proportion of days covered (PDC) for antihypertensive (AH) and lipid-lowering (LL) therapy, by level of prescription burden.

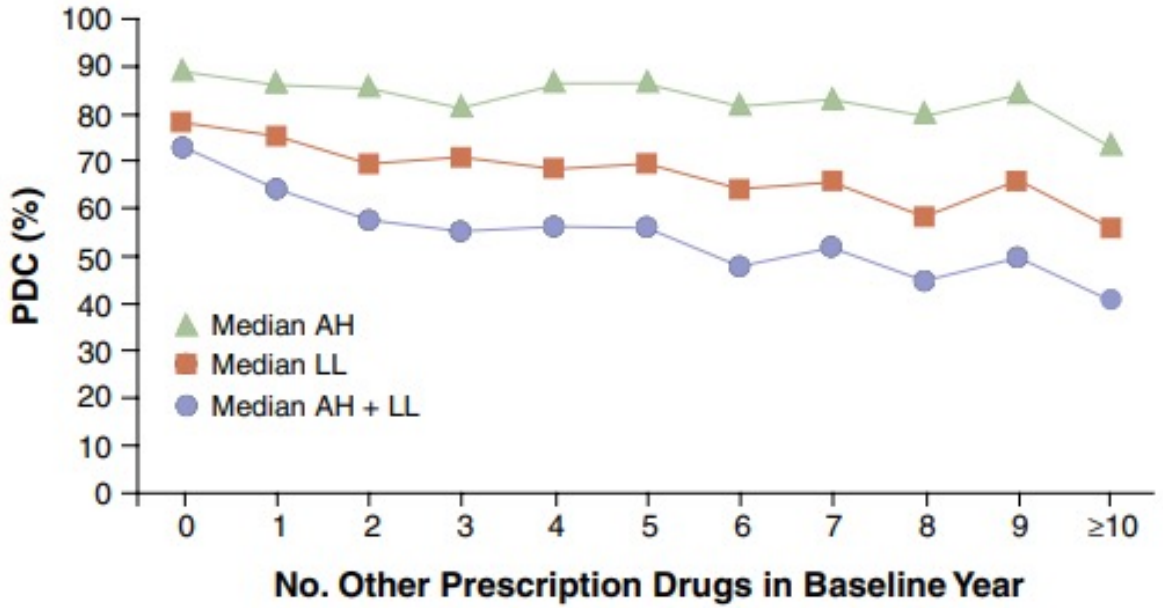
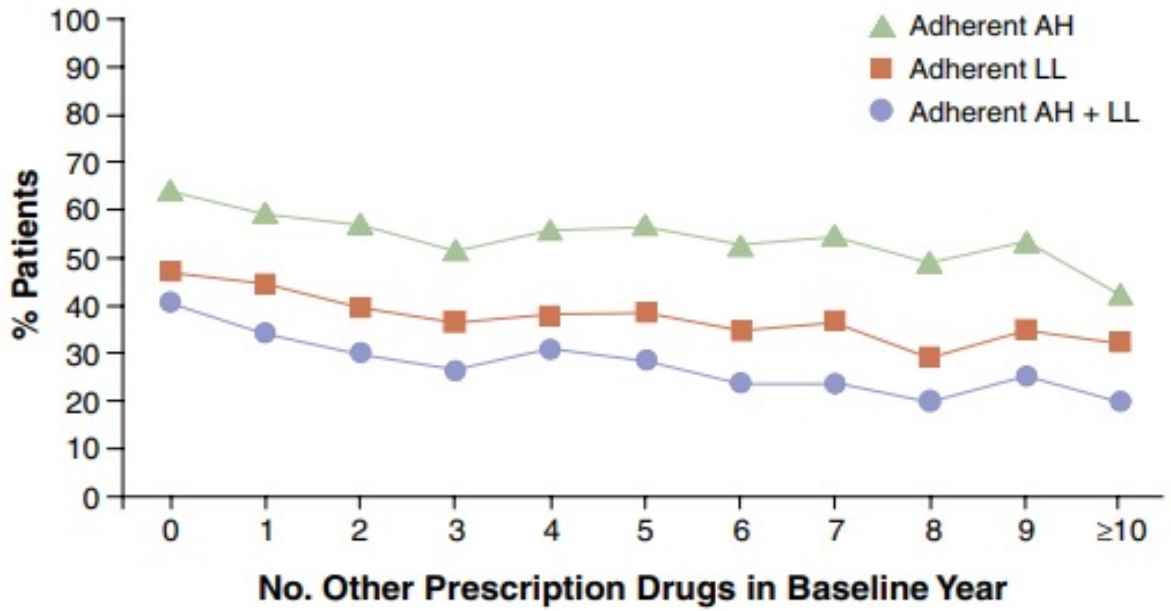
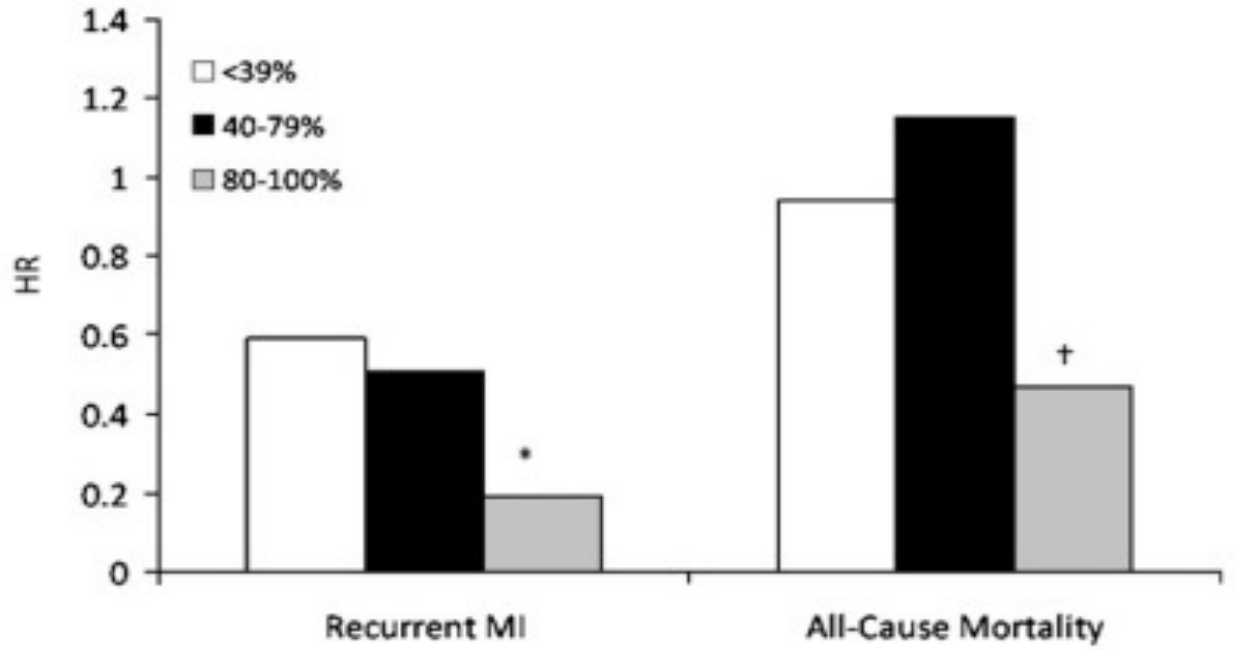


Figure 2. Percentage of patients adherent (proportion of days covered of ≥80%) to antihypertensive (AH) and lipid-lowering (LL) therapy, by level of prescription burden.



Benner JS, Am J Health Syst Pharm 2009

Medication Adherence



*P<.01; †P<.05

Figure 1 Effects of adherence on recurrent MI and all-cause mortality in patients with a history of MI.[20] HR, hazard ratio; MI, myocardial infarction.

Simpson RJ, J of Clinic Lipidology 2010

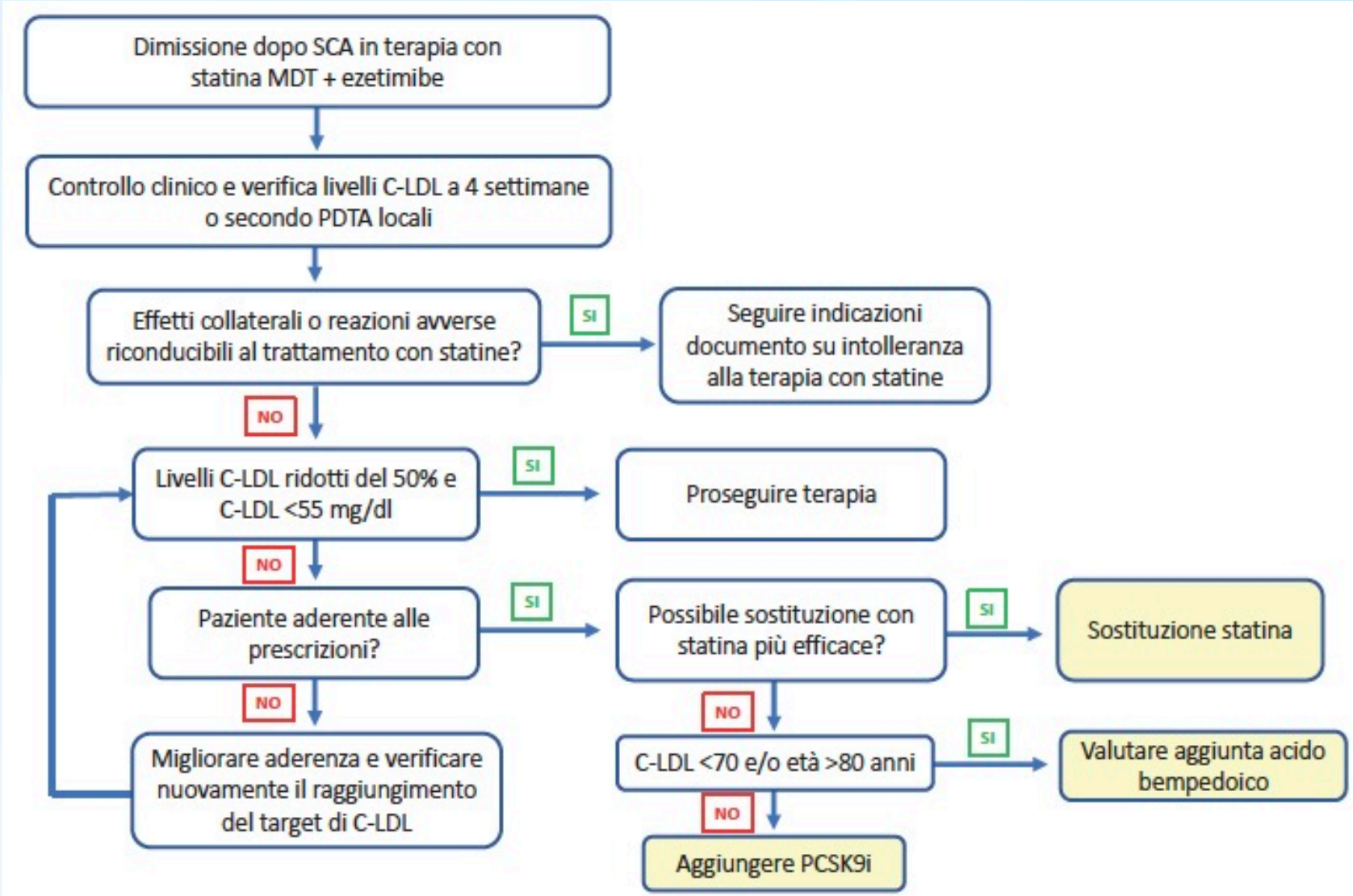
Pilastri pratici nella scelta della terapia ipolipemizzante nei pazienti post-SCA

FIDUCIA	POTENZA	PRECOCITÀ
Scegliere un trattamento **efficace** in rapporto al target: • **duplice terapia** (statina ad alta intensità + ezetimibe) • **triplice terapia** (statina ad alta intensità + ezetimibe + inibitore di PCSK9)	Scegliere un trattamento in grado di garantire il raggiungimento di **valori di C-LDL <40 mg/dl** nei **pazienti a rischio estremo** ricorrendo alla **triplice terapia**.	Iniziare **precocemente** la terapia appropriata, ricorrendo quando possibile all'**approccio "fast-track"**, per sfruttare i vantaggi di un raggiungimento anticipato del target (mantenimento nel tempo, esiti clinici favorevoli nel medio-lungo termine, effetti positivi sulla placca aterosclerotica).

Arca M, GIC 2023

Position paper ANMCO: Gestione dell'ipercolesterolemia nei pazienti con sindrome coronarica acuta

Leonardo De Luca[1], Carmine Riccio[2], Alessandro Navazio[3], Serafina Valente[4], Manlio Cipriani[5], Marco Corda[6], Alfredo De Nardo[7], Giuseppina Maura Francese[8], Cosimo Napoletano[9], Emanuele Tizzani[10], Loris Roncon[11], Pasquale Caldarola[12], Michele Massimo Gulizia[8], Domenico Gabrielli[1,13], Fabrizio Oliva[14], Furio Colivicchi[15]



De Luca L, G Ital Cardiol. 2023

Factor	Referral system		P value
	Conventional	IHD registry	
Number of patients	2241	1417	
All-cause death (%)	254 (11.3)	93 (6.6)	<0.001***
CV death (%)	82 (3.7)	19 (1.3)	<0.001***
MACCE (%)	551 (24.6)	272 (19.2)	<0.001***
Major bleeding (%)	104 (4.6)	43 (3.0)	0.016*
Net clinical event (%)	618 (27.6)	304 (21.5)	<0.001***
Follow-up term	1254.64 ± 1089.29	1548.12 ± 1066.60	<0.001***

Values are mean ± standard deviation.

*P<0.05

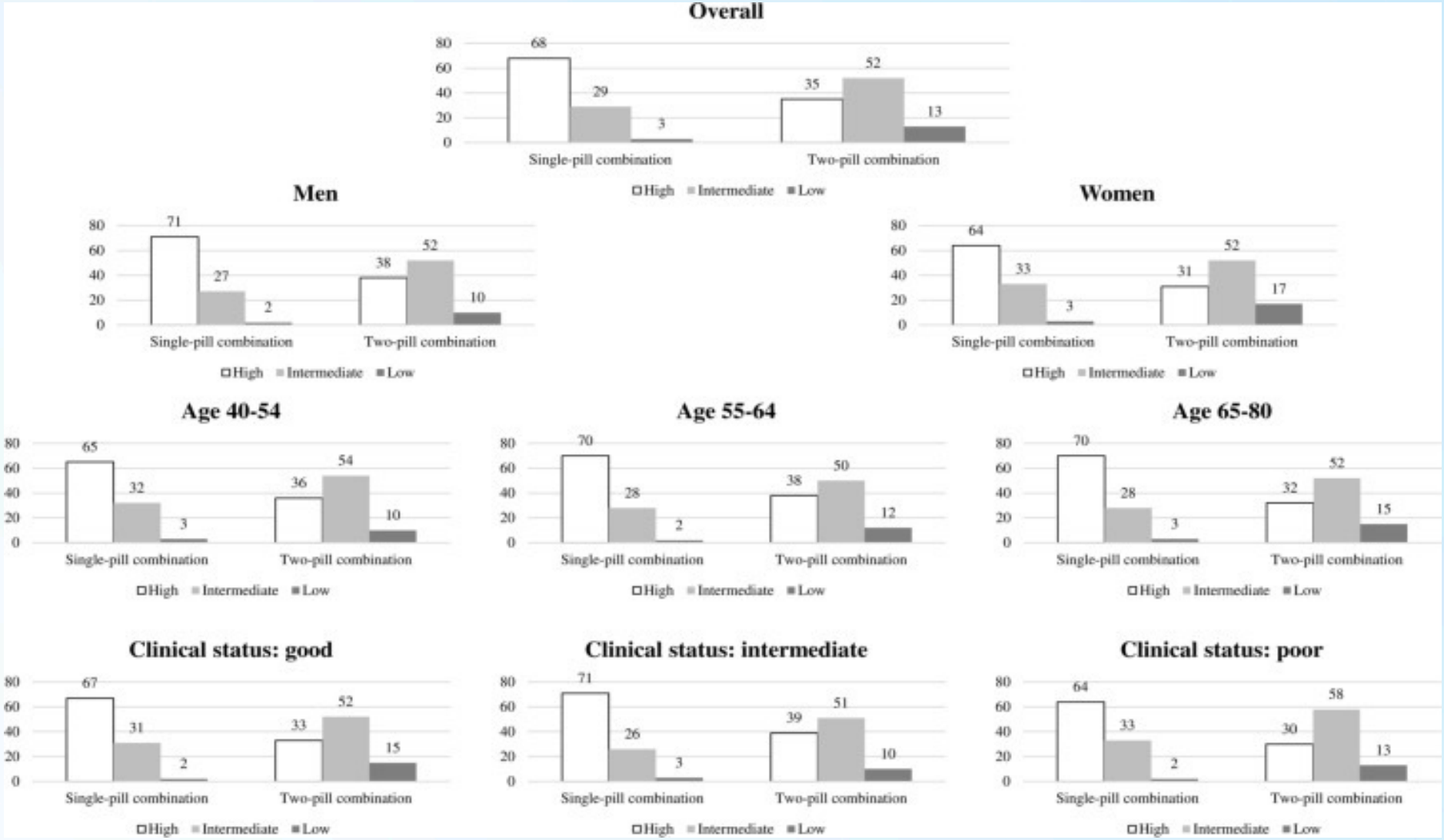
**P<0.01, and

***P<0.001.

Abbreviations: IHD, ischemic heart disease; CV, cardiovascular; MACCE, major adverse cardiac and cerebrovascular event.

https://doi.org/10.1371/journal.pone.0242707.t002

Kageyama S, PLoS ONE, 2020



Rea F, Adv Ther 2021

Tabella 5. Combinazioni fisse precostituite di agenti ipolipemizzanti e indicazioni terapeutiche secondo la scheda tecnica.

Componenti dell'associazione precostituita	Dosaggi (mg)	Indicazione	Forma farmaceutica	Classe di rimborsabilità*
Rosuvastatina[80] + Ezetimibe	5, 10, 20, 40 10	ipercolesterolemia primaria (eterozigote e omozigote familiare e non familiare) o con iperlipidemia mista	Capsula	A
Atorvastatina[81] + Ezetimibe	10, 20, 40 10	Ipercolesterolemia primaria (eterozigote e omozigote familiare e non familiare) o con iperlipidemia mista	Capsula	A
Simvastatina[82] + Ezetimibe	10, 20, 40, 80 10	Ipercolesterolemia primaria (eterozigote familiare e non-familiare) o con iperlipidemia mista	Compressa	A
Acido bempedoico[83] + Ezetimibe	180 10	Ipercolesterolemia primaria o dislipidemia mista, in aggiunta alla dieta e alla massima dose tollerata di statina, o in monoterapia in pazienti intolleranti o con controindicazioni alle statine e che non raggiungono i livelli target di C-LDL con la sola ezetimibe, e in pazienti già trattati con i due principi attivi separatamente	Compressa	A (con compilazione di scheda di prescrizione)

C-LDL, colesterolo legato alle lipoproteine a bassa densità.
*Classe di rimborsabilità A: farmaci a carico dal Servizio Sanitario Nazionale.

De Luca L, GIC 2024

Tabella 4. Possibili strategie disponibili per migliorare l'aderenza del paziente al trattamento[53].

1. Educazione del paziente (tramite consulti personalizzati)
2. Semplificazione del regime terapeutico (tramite utilizzo di combinazioni a dose fissa)
3. Coinvolgimento del farmacista per la gestione delle patologie croniche (tramite interventi educazionali, monitoraggio telefonico o "reminder" per la fornitura periodica dei farmaci)
4. Terapie cognitivo-comportamentali (quali interventi motivazionali da parte di consulenti specializzati)
5. "Reminder" per l'assunzione dei farmaci (tramite contatto telefonico o sistemi elettronici di monitoraggio dell'assunzione)
6. Incentivi per promuovere l'aderenza (quali riduzione della quota a carico del paziente in caso di raggiungimento del goal terapeutico)

Arca M, GIC 2023

Tabella 4. Possibili strategie disponibili per migliorare l'aderenza del paziente al trattamento[53].

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Arca M, GIC 2023

TAKE HOME MESSAGE

- La combinazione statina/ezetimibe è efficace nel ridurre LDL-c e gli eventi cardiovascolari
- La combinazione statina/ezetimibe rappresenta la terapia di prima linea per raggiungere gli obiettivi delle linee guida 2019
- È necessario un implemento nella pratica clinica dell'associazione statina/ezetimibe:
  - attraverso interventi strutturali volti a migliorare la collaborazione tra le strutture ospedaliere e le strutture territoriali
  - attraverso l'implementazione del numero di figure coinvolte nella gestione del paziente dislipidemico (infermieri specializzati, farmacisti)
  - attraverso l'utilizzo di combinazioni fisse precostituite largamente presenti in commercio


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