11° CONGRESSO NAZIONALE

CAMPUS Cuore

Quello che le Linee Guida Non Dicono

Napoli
5-6 aprile 2024

Strategie terapeutiche “Fixed Dose Combination” per la riduzione del rischio cardiovascolare

Mario Crisci
AORN dei Colli – Ospedale Monaldi – UOC di Cardiologia e UTIC

OSPEDALI DEI COLLI
MONALDI - COTUGNO - C.T.O.

ESC European Society of Cardiology

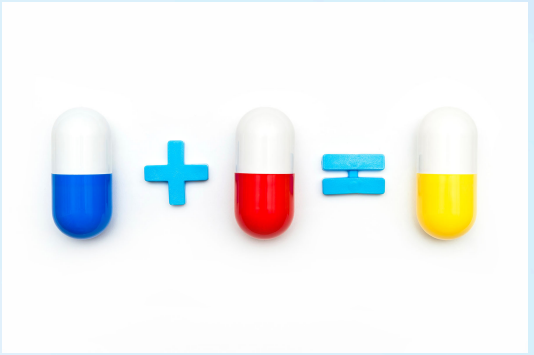
European Heart Journal (2018) **39**, 3021–3104
doi:10.1093/eurheartj/ehy339

ESC/ESH GUIDELINES

2018 ESC/ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH)

Authors/Task Force Members: Bryan Williams* (ESC Chairperson) (UK),



Drug treatment strategy for hypertension

Recommendations	Class[a]	Level[b]
Among all antihypertensive drugs, ACE inhibitors, ARBs, beta-blockers, CCBs, and diuretics (thiazides and thiazide-like drugs such as chlorthalidone and indapamide) have demonstrated effective reduction of BP and CV events in RCTs, and thus are indicated as the basis of antihypertensive treatment strategies.[2]	I	A
Combination treatment is recommended for most hypertensive patients as initial therapy. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or diuretic. Other combinations of the five major classes can be used.[233,318,327,329,341–345]	I	A
It is recommended that beta-blockers are combined with any of the other major drug classes when there are specific clinical situations, e.g. angina, post-myocardial infarction, heart failure, or heart rate control.[300,341]	I	A
It is recommended to initiate an antihypertensive treatment with a two-drug combination, preferably in an SPC. Exceptions are frail older patients and those at low risk and with grade 1 hypertension (particularly if SBP is <150 mmHg).[342,346,351]	I	B
It is recommended that if BP is not controlled[c] with a two-drug combination, treatment should be increased to a three-drug combination, usually a RAS blocker with a CCB and a thiazide/thiazide-like diuretic, preferably as an SPC.[349,350]	I	A
It is recommended that if BP is not controlled[c] with a three-drug combination, treatment should be increased by the addition of spironolactone or, if not tolerated, other diuretics such as amiloride or higher doses of other diuretics, a beta-blocker, or an alpha-blocker.[310]	I	B
The combination of two RAS blockers is not recommended.[291,298,299]	III	A

© ESC 2018

Several reasons need to be considered to identify why the current treatment strategy has failed to achieve better BP control rates:

(1) **Efficacy of pharmacological therapies**. Are the best available treatments, in whatever combination, incapable of controlling BP in most patients? The evidence from RCTs demonstrating that BP control can be achieved in most recruited patients, and that no more than 5-10% of these patients exhibit resistance to the selected treatment regimen, suggests that ineffective drug therapy is not the source of the problem.

(2) **Physician or treatment inertia**. (i.e. failure to adequately uptitrate treatment). Evidence suggests that inertia[311] contributes to suboptimal BP control, with many patients remaining on monotherapy and/or suboptimal doses, despite inadequate BP control.[12]

(3) **Patient adherence to treatment**. Evidence is accumulating that adherence is a much more important factor than previously recognised. Studies using urine or blood assays for the presence or absence of medication have shown that adherence to treatment is low. This is supported by studies in the general population in which adherence to treatment, based on prescription refilling, was <50% of the treatment in half of the patients.[312] Poor adherence has also be shown to be associated with increased CV risk in various studies[313] (see section 10).

(4) **Insufficient use of combination treatment**. BP is a multiregulated variable depending on many compensating pathways. Consequently, combinations of drugs, working through different mechanisms, are required to reduce BP in most people with hypertension. Thus, monotherapy is likely to be inadequate therapy in most patients. Indeed, almost all patients in RCTs have required combinations of drugs to control their BP.[314]

(5) **Complexity of current treatment strategies**. There is also evidence that adherence to treatment is adversely affected by the complexity of the prescribed treatment regimen. In a recent study, adherence to treatment was strongly influenced by the number of pills that a patient was prescribed for the treatment of hypertension.[315] Non-adherence was usually <10% with a single pill, rising to ~20% with two pills, ~40% with three pills, and very high rates of partial or complete non-adherence in patients receiving five or more pills.[315]

ELSEVIER Check for updates

Canadian Journal of Cardiology 34 (2018) 506–525

Guidelines

Hypertension Canada's 2018 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults and Children

Guidelines

1. Initial therapy should be with either monotherapy or single pill combination.
   i. Recommended monotherapy choices are:
      a. A thiazide/thiazide-like diuretic (Grade A), with longer-acting diuretics preferred (Grade B);
      b. A β-blocker (in patients younger than 60 years; Grade B);
      c. An ACE inhibitor (in nonblack patients; Grade B);
      d. An ARB (Grade B); or
      e. A long-acting calcium channel blocker (CCB) (Grade B).
   ii. Recommended single pill combination choices are those in which an ACE inhibitor is combined with a CCB (Grade A), ARB with a CCB (Grade B), or ACE inhibitor or ARB with a diuretic (Grade B).

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

8.1.6.1. Choice of Initial Monotherapy Versus Initial Combination Drug Therapy

Recommendations for Choice of Initial Monotherapy Versus Initial Combination Drug Therapy*

COR	LOE	Recommendations
I	C-EO	1. Initiation of antihypertensive drug therapy with 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP more than 20/10 mm Hg above their BP target.
IIa	C-EO	2. Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal <130/80 mm Hg with dosage titration and sequential addition of other agents to achieve the BP target.

*Fixed-dose combination antihypertensive medications are listed in Online Data Supplement D.

ESC ESC/ESH GUIDELINES

2018 ESC/ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH)

A single-pill strategy to treat hypertension. Poor adherence to longer-term BP-lowering medication is now recognised as a major factor contributing to poor BP control rates. Research has shown a direct correlation between the number of BP-lowering pills and poor adherence to medications. Moreover, SPC therapy has been shown to improve adherence to treatment. SPC therapy is now the preferred strategy for initial two-drug combination treatment of hypertension and for three-drug combination therapy when required. This will control the BP of most patients with a single pill and could transform BP control rates.

New Guidelines suggests to start with SPCs

ESH
EUROPEAN SOCIETY OF CARDIOLOGY®

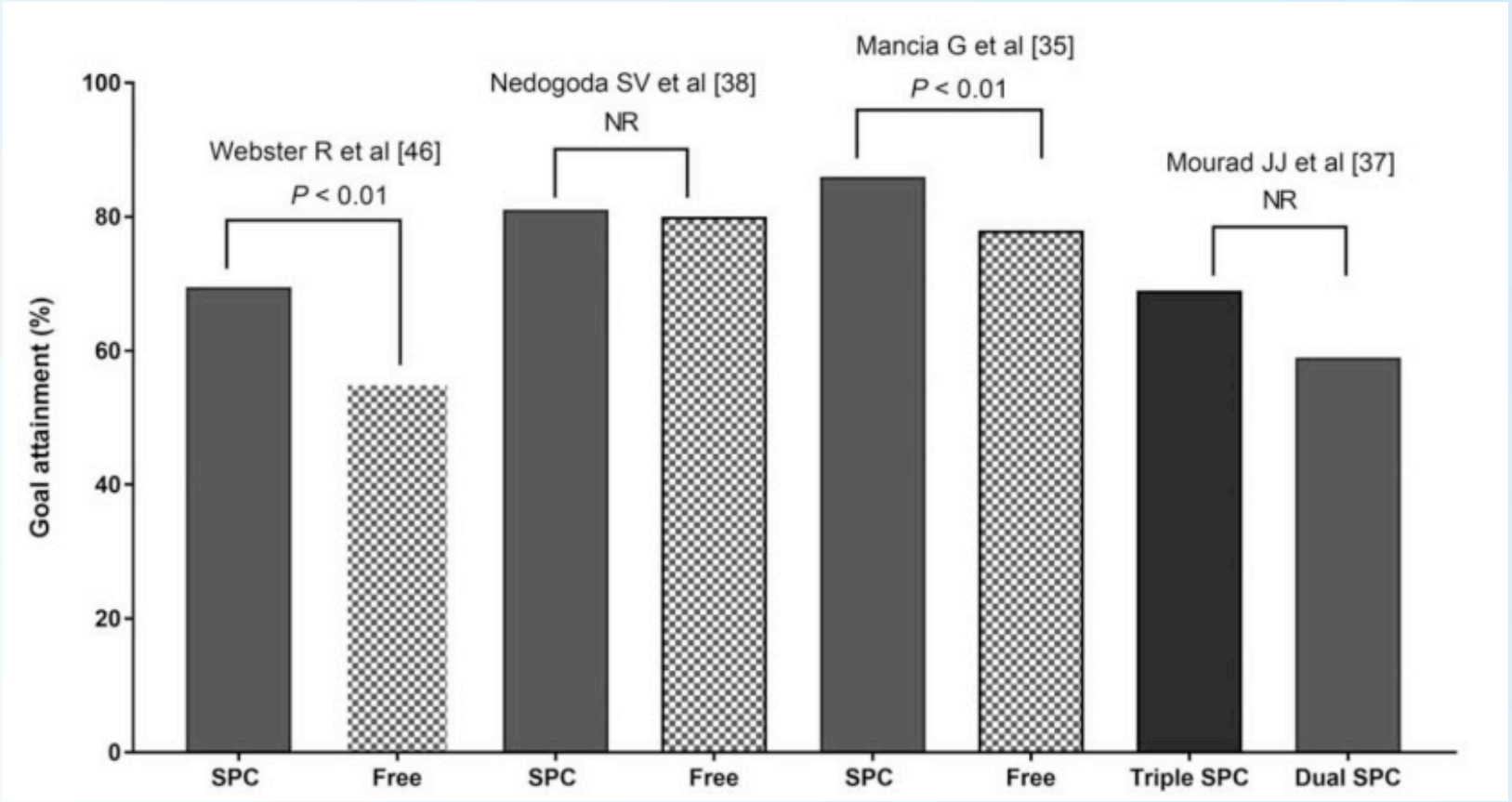
1 pill	**Initial Therapy** Dual Combination	ACEi or ARBs + CCB or Diuretics
1 pill	**Step 2** Triple Combination	ACEi or ARBs + CCB + Diuretics
2 pills	**Step 3** Triple Combination + spironolactone or other drug	**Resistant Hypertension** Add spironolactone or other drugs (alpha blocker or Beta Blocker)

Monotherapy:
Low risk
Grade I Hypertension
Very elderly patients >80
Frailer patients

Considerer **beta-blocker** at any treatment step, when there is a specific indication for their use, e.g. heart failure, angina, post-MI, atrial fibrillation or younger women with, or planning, pregnancy

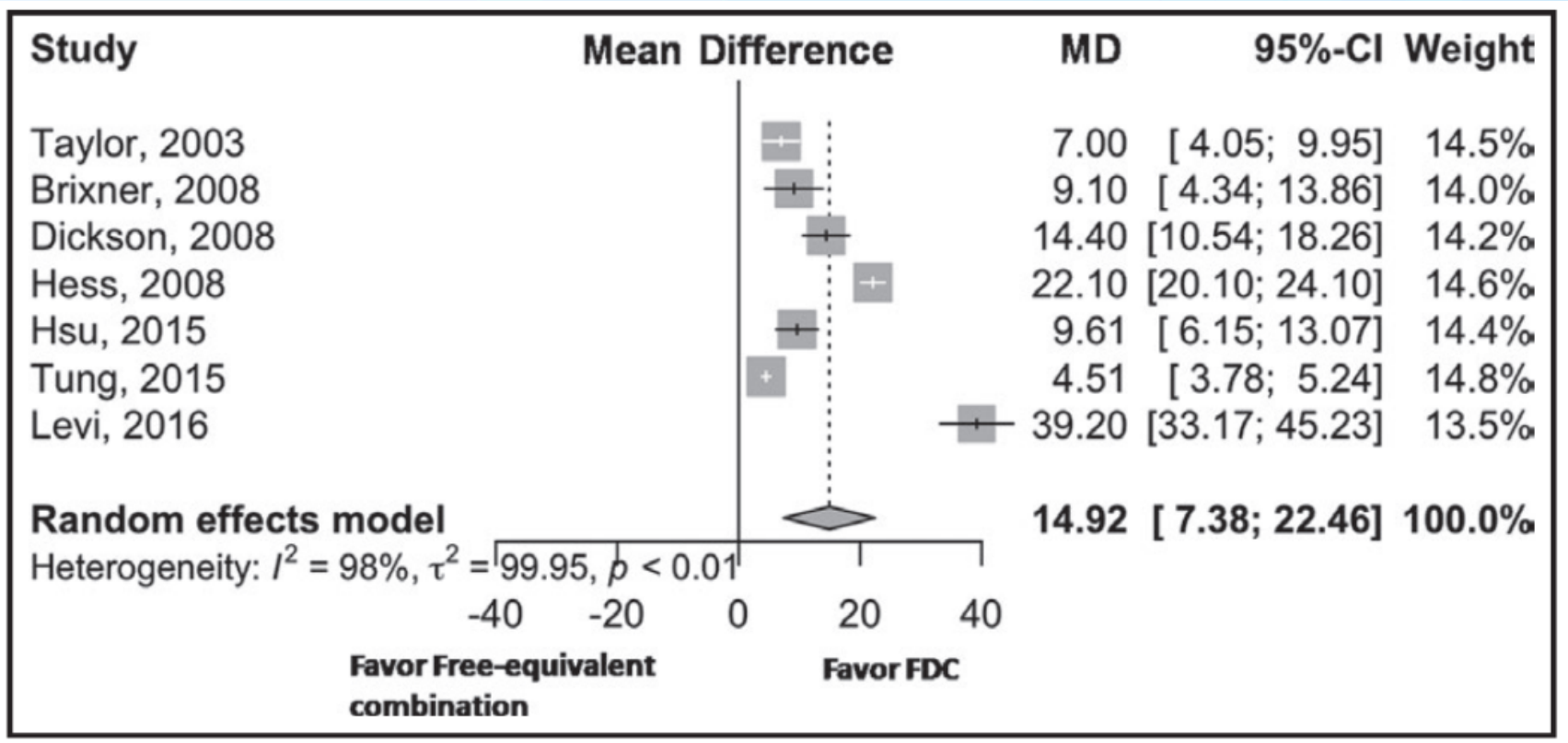
Williams B. et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal (2018) 00, 1–98 doi:10.1093/eurheartj/ehy339

La prescrizione di associazioni pre-costituite di farmaci anti-ipertensivi favorisce il raggiungimento degli obiettivi pressori (PA<140/90 mmHg): Studi Clinici Randomizzati e Controllati



Journal of Hypertension 2020, 38:1016–1028

La prescrizione di associazioni pre-costituite di farmaci anti-ipertensivi favorisce l'Aderenza: una Meta-analisi



J Clin Hypertens. 2018;20:902–907.

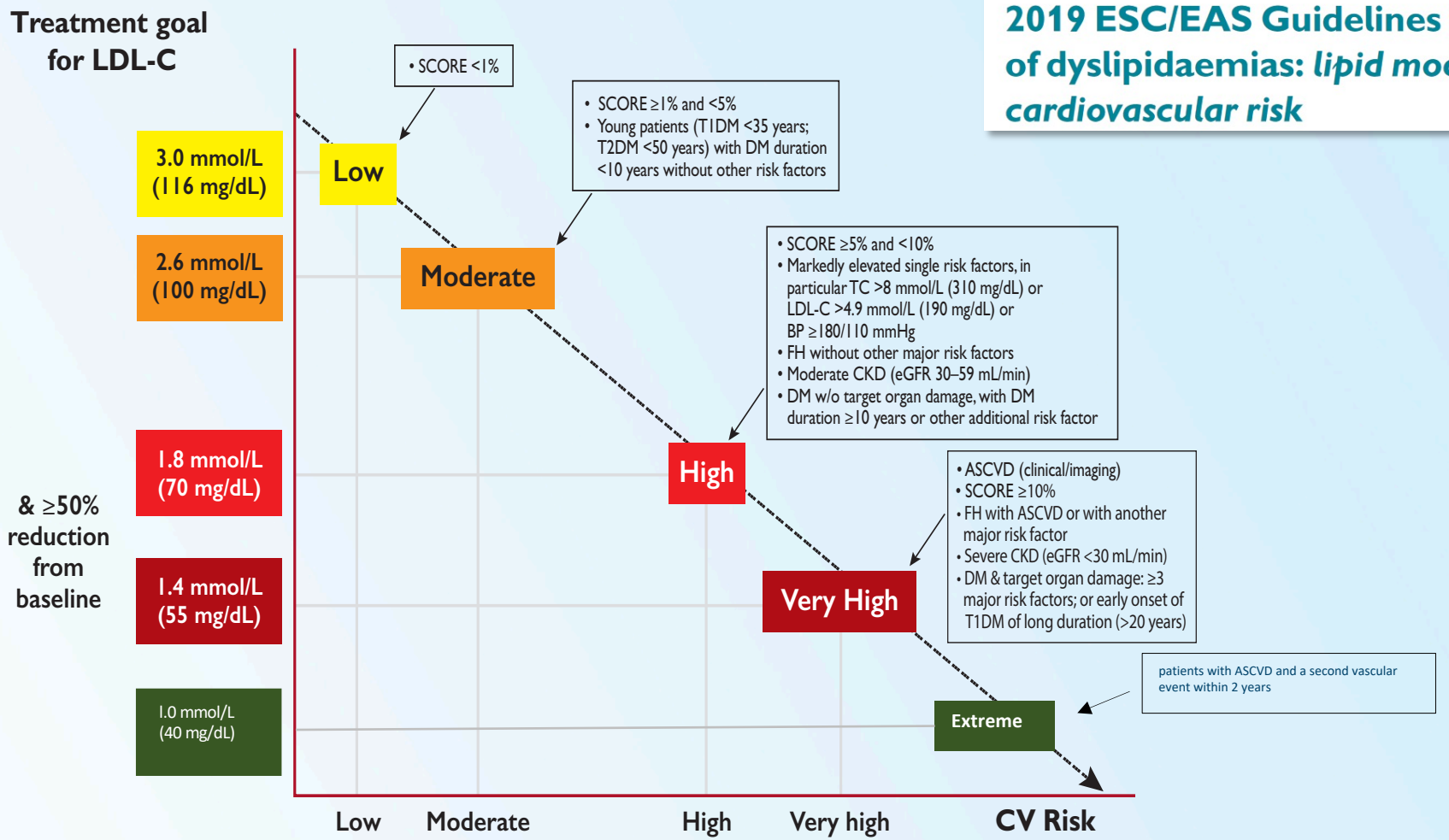
ESC European Society of Cardiology

European Heart Journal (2020) **41**, 111–188
doi:10.1093/eurheartj/ehz455

ESC/EAS GUIDELINES

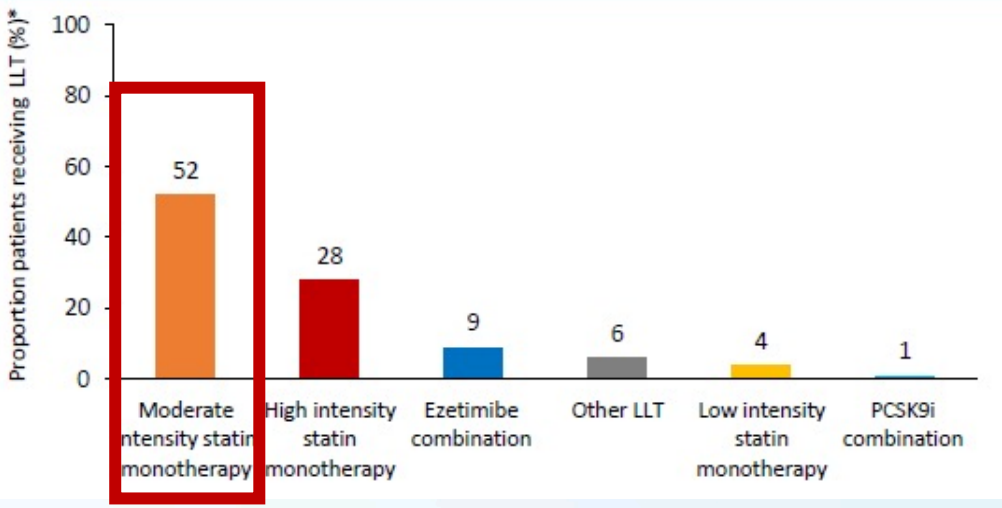
2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

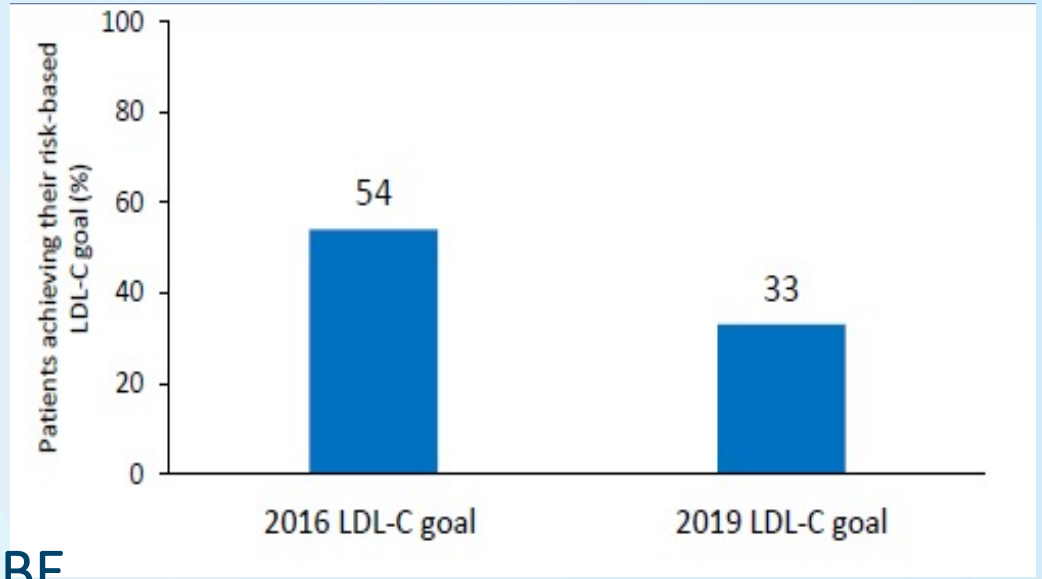
Recommendations	
Class[a]	Level[b]
IIb	A
IIa	A
I	A
I	A
IIb	B



ESC European Society of Cardiology
European Journal of Preventive Cardiology (2021) **28**, 1279–1289
doi:10.1093/eurjpc/zwaa047
FULL RESEARCH PAPER

EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DA VINCI study



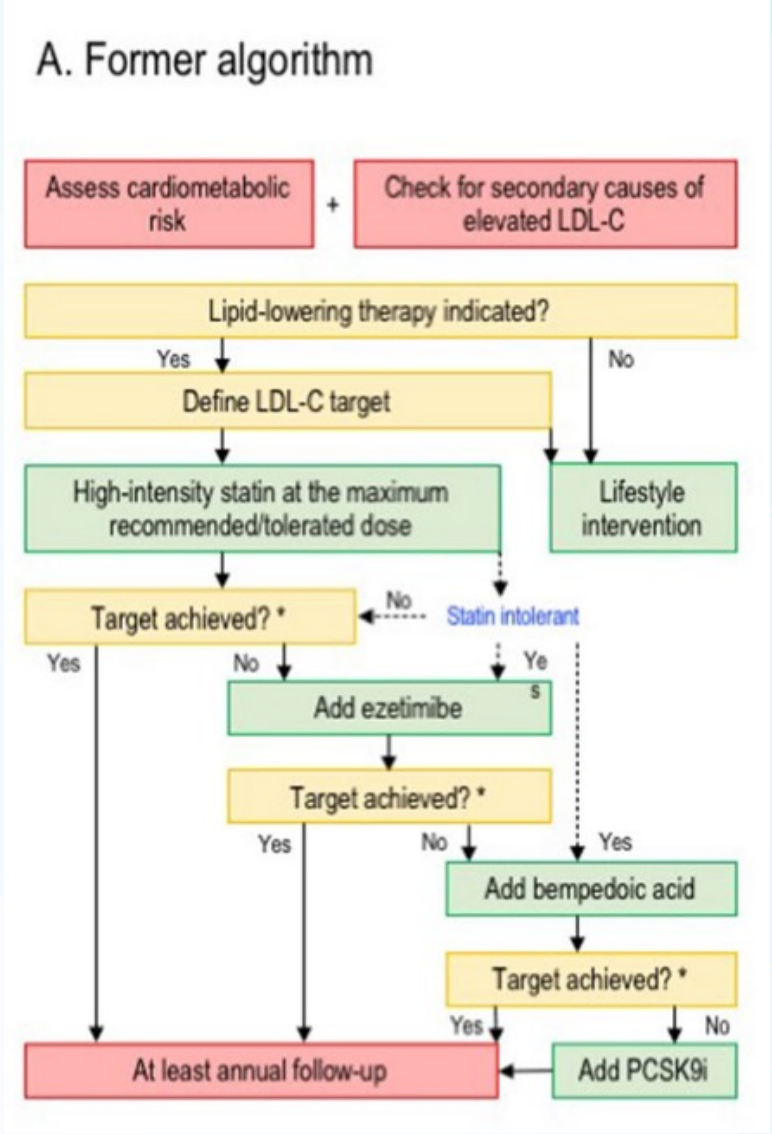


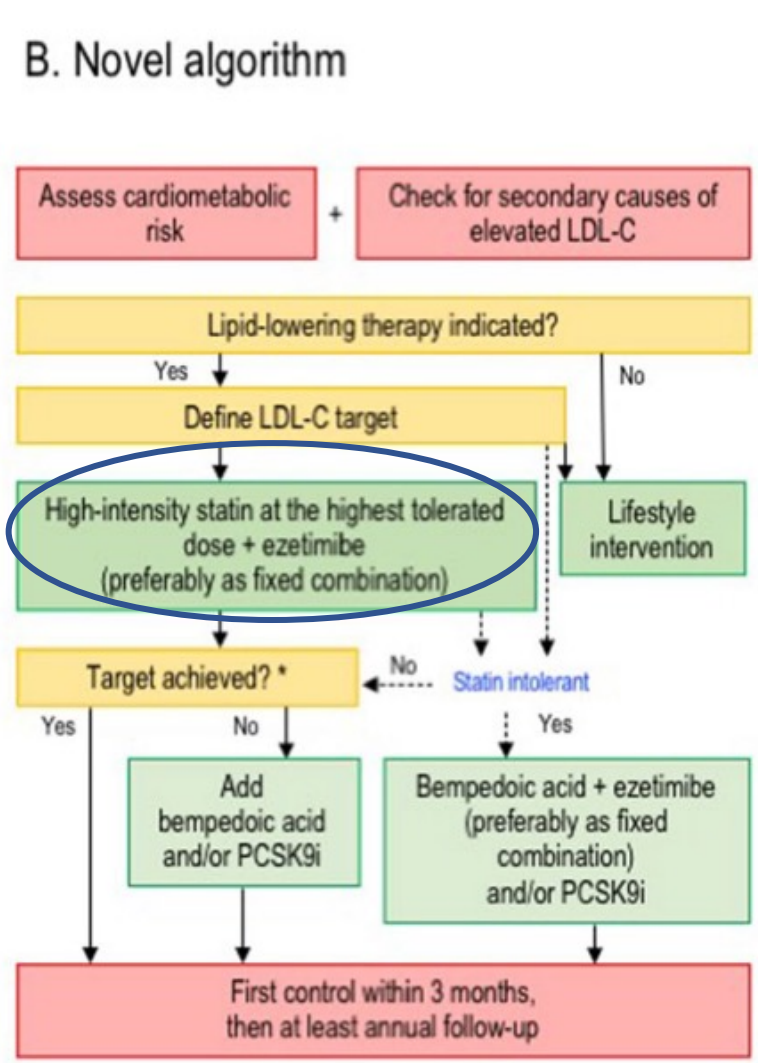
La maggior parte dei pazienti riceve LLT con statine a moderata intensità

- SOLO IL 28% riceve una statina AD ALTA INTENSITÀ
- SOLO IL 9% riceve una COMBINAZIONE CON EZETIMIBE

Intensità del trattamento ipolipemizzante

Trattamento	Riduzione media di C-LDL
Statina a moderata intensità	≈30%
Statina ad elevata intensità	≈50%
Statina ad elevata intensità + ezetimibe	**≈65%**
Inibitore di PCSK9	≈60%
Inibitore di PCSK9 + statina ad elevata intensità	≈75%
Inibitore di PCSK9 + statina ad elevata intensità + ezetimibe	≈85%





High Blood Pressure & Cardiovascular Prevention (2022) 29:105–113
https://doi.org/10.1007/s40292-021-00501-6

CONSENSUS DOCUMENT

Reduction of High Cholesterol Levels by a Preferably Fixed-Combination Strategy as the First Step in the Treatment of Hypertensive Patients with Hypercholesterolemia and High/Very High Cardiovascular Risk: A Consensus Document by the Italian Society of Hypertension

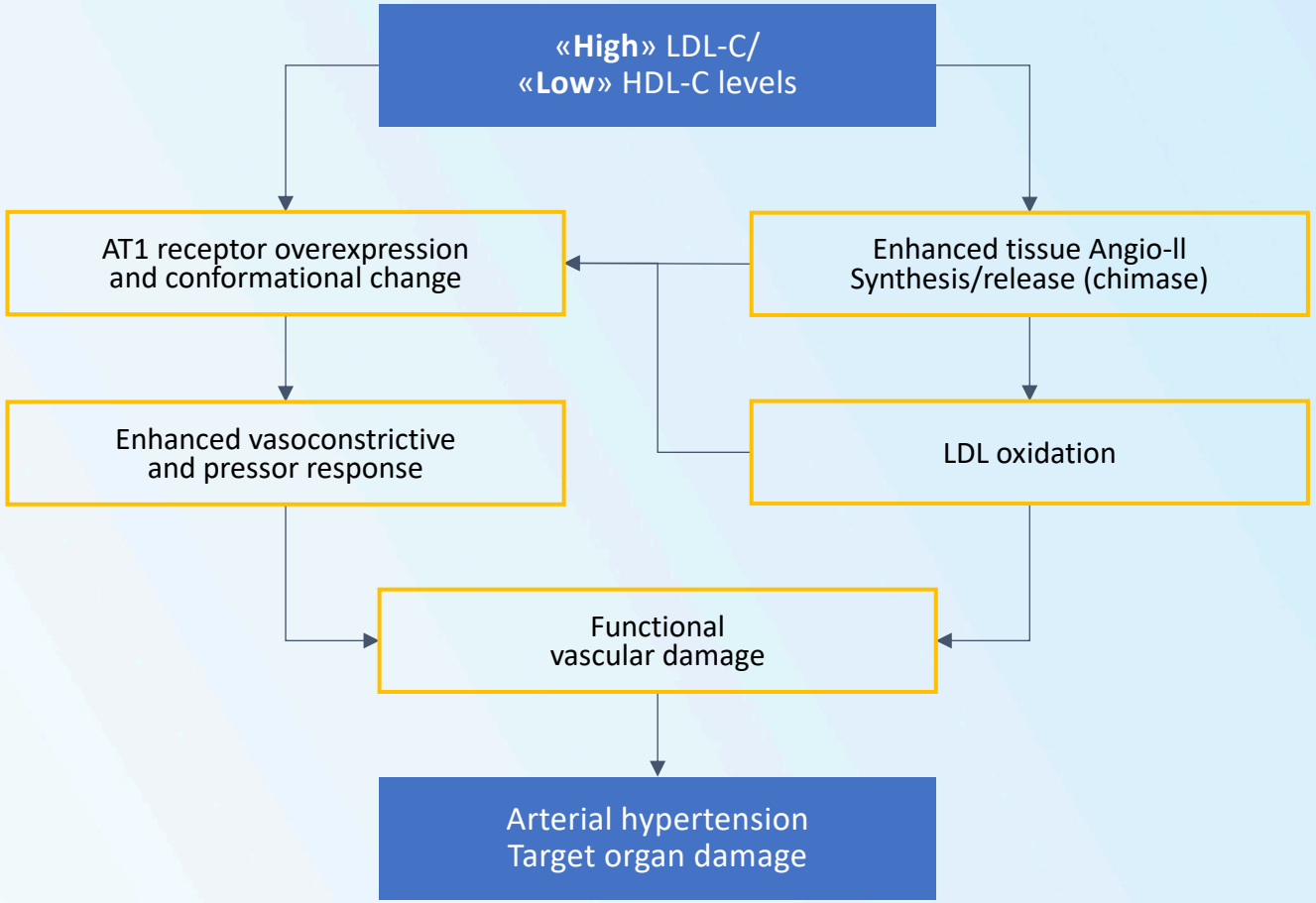
Il nuovo algoritmo prevede come ***prima linea di trattamento*** *statina ad alta intensità + ezetimibe preferibilmente in combinazione fissa*

Riduzioni ≥50% di C-LDL


rosuasa
aspirina
rosuvastatina
What the hell is this?


13:58
5G
Memedical
oro · 20 h ·
Commenti più popolari
Aspetto con ansia che mi accettino la Xanapirina per togliere ogni male dalla terra
19 h
Mi piace
Rispondi
60

Razionale dell'Associazione Statina/ACE-I

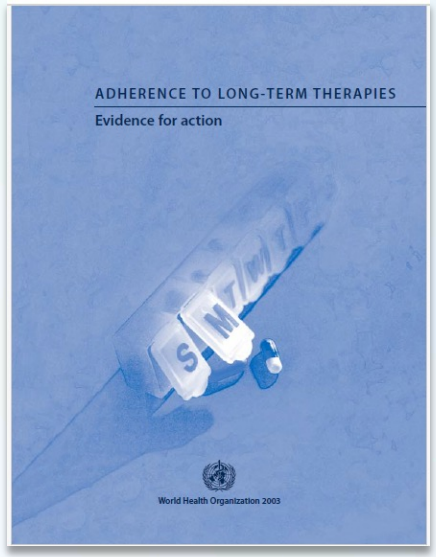


Comparative Study of Rosuvastatin as Monotherapy Versus Rosuvastatin with Ramipril in Dyslipidemia and Their Effects on Atherosclerosis

88 patients of newly diagnosed dyslipidemia, aged 30-70 years. 12 weeks FU

	Group I Rosuvastatin (10 mg/day)	Group II Rosuvastatin + Ramipril (10/5 mg/day)
Mean IMT (CCA, ICA, mm)	+ 0.01224 %, p>0.05	**-0.0704** %, p>0.05
Average Plaque size in Carotid Arteries (cm^2)	+0.006 %, p>0.05	**-4.551** %, p>0.05

Adapted from Raj K et al. Am J of Med Sci and Med, 2014, Vol. 2, No. 3, 58-63



«L'effettiva aderenza agli interventi terapeutici può avere un maggior impatto sulla salute della popolazione rispetto a qualsiasi miglioramento di trattamenti specifici» (WHO 2003)

WHO updates list of essential medicines to include heart 'polypills,' MS treatments but not weight-loss drugs

By Giri Viswanathan, CNN
Published 6:34 PM EDT, Wed July 26, 2023

«La polipillola in ambito cardiovascolare entra a far parte della lista dei farmaci essenziali» (WHO 2023)

ESC European Society of Cardiology
European Heart Journal (2023) 00, 1–107
https://doi.org/10.1093/eurheartj/ehad191
ESC GUIDELINES

2023 ESC Guidelines for the management of acute coronary syndromes

Developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC)

La polipillola dovrebbe essere considerata come un'opzione per migliorare l'aderenza e gli esiti clinici nella prevenzione secondaria post-SCA (ESC 2023)

From 2003...

A strategy to reduce cardiovascular disease by more than 80%

N J Wald, M R Law

		% reduction in risk (95% CI)*			
Risk factor	Agent	Reduction in risk factor	IHD event	Stroke	Source of evidence
LDL cholesterol	Statin†	1.8 mmol/l (70 mg/dl) reduction in LDL cholesterol	61 (51 to 71)	17 (9 to 25)	Law et al[1]
Blood pressure	Three classes of drug at half standard dose	11 mm Hg diastolic	46 (39 to 53)	63 (55 to 70)	Law et al[16]
Serum homocysteine	Folic acid (0.8 mg/day)	3 µmol/l	16 (11 to 20)	24 (15 to 33)	Wald et al[9]
Platelet function	Aspirin (75 mg/day)	Not quantified	32 (23 to 40)	16 (7 to 25)	Table A on bmj.com
Combined effect	All		88 (84 to 91)	80 (71 to 87)	

LDL=low density lipoprotein

*95% confidence intervals include imprecision of the estimates of both the agent reducing the risk factor and the risk factor reduction decreasing risk

What this study adds

Intervening on all four risk factors reduces heart attacks and strokes by over 80%

To achieve this large effect in a population requires a combination treatment taken by everyone above a specified age (say 55) and younger people with a clinical history of occlusive arterial disease

A combination pill containing six active components could be widely used

Each component has been used in medical practice for more than 10 years with substantial evidence on safety and efficacy

...to 2023

2023 ESC Guidelines for the management of acute coronary syndromes

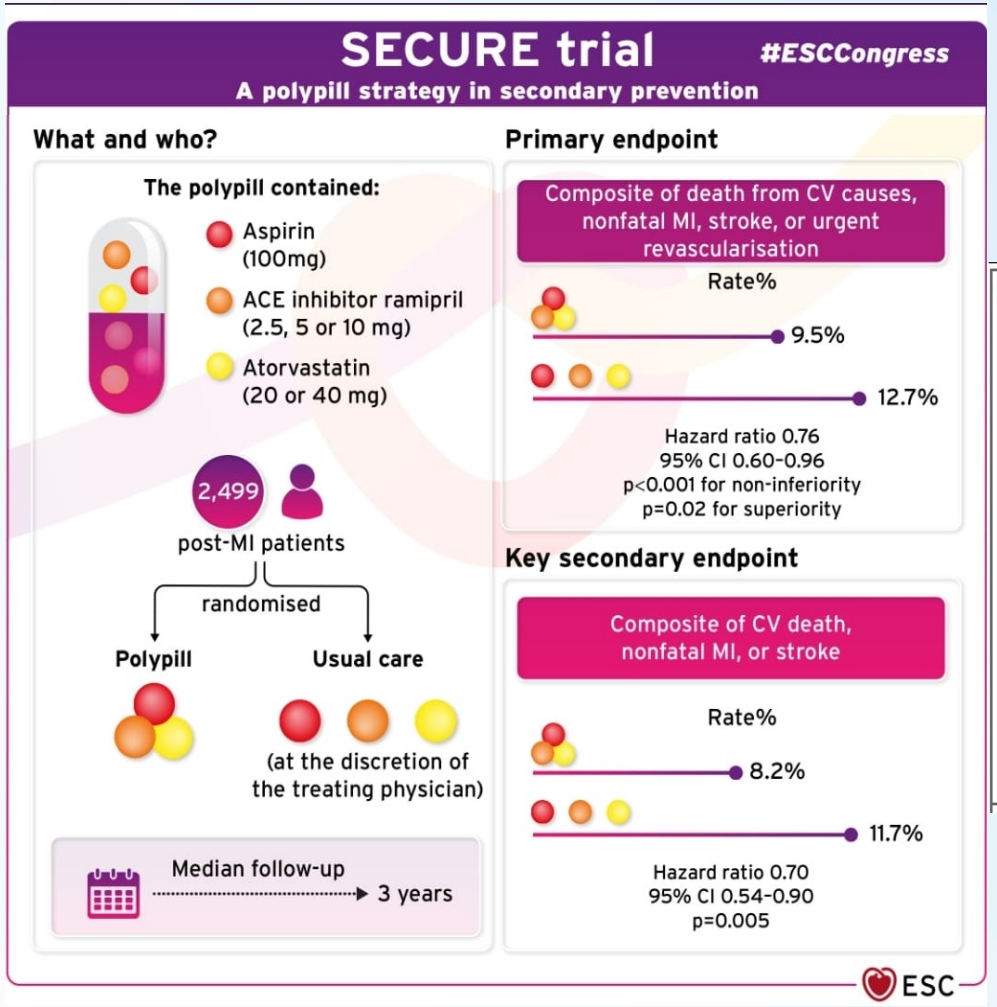
Developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC)

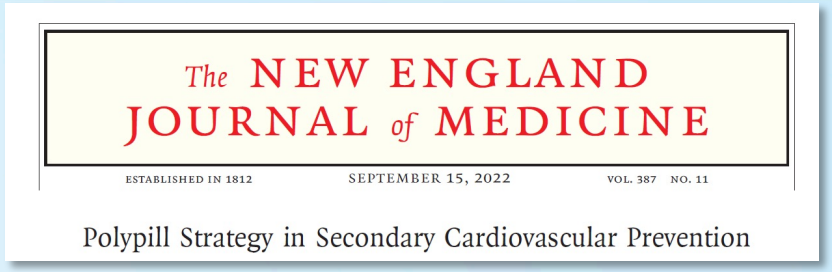
Adherence to medication		
A polypill should be considered as an option to improve adherence and outcomes in secondary prevention after ACS.[753]	IIa	B

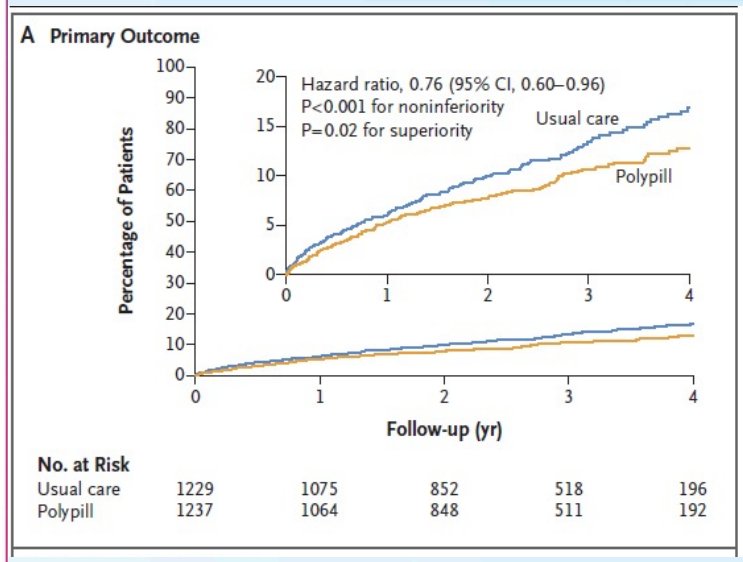
2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

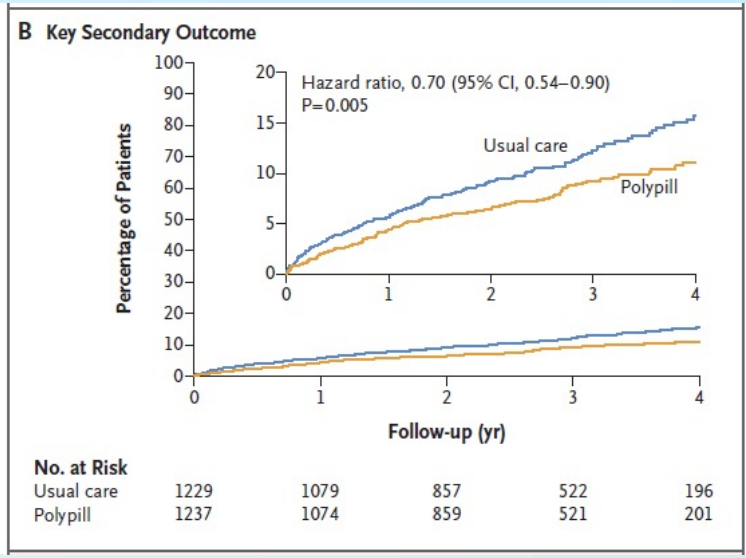
Developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC)

only achieved in 18% and 28% of patients, respectively. This was explained by low prescription rates of the combination of all cardioprotective drugs (antiplatelet therapy, beta-blockers, RAS inhibitors, and statins) in only 55% of patients with newly detected T2DM, and in 60% of patients with previously known T2DM.[34] The concept of a polypill, e.g. containing aspirin, ramipril, and atorvastatin, may even improve clinical events in secondary cardiovascular prevention.[368]







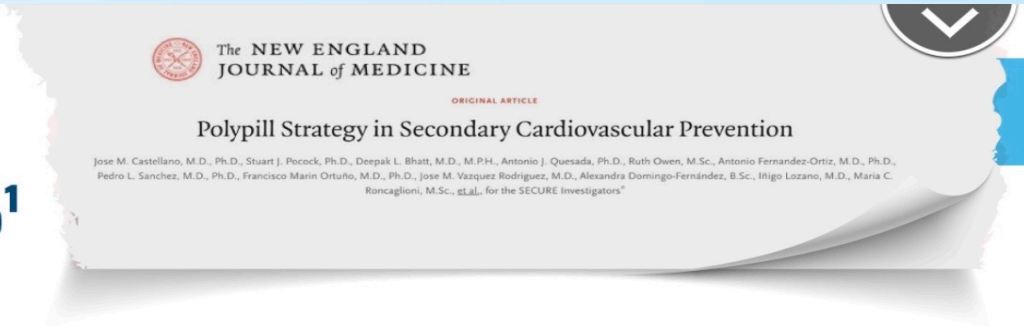


Primary outcome: cardiovascular death, nonfatal type 1 myocardial infarction, nonfatal ischemic stroke, or urgent revascularization

Secondary outcome: composite of cardiovascular death, nonfatal type 1 myocardial infarction, or nonfatal ische- mic stroke.

Castellano et al. (2022), N Engl J Med; 387: 967-77.

LE POLIPILLOLE RIDUCONO IL RISCHIO DI EVENTI CARDIOVASCOLARI DEL 27%[1]



RIDUZIONE DEL NUMERO DELLE COMPRESSE[2]

+

AUMENTATA ADERENZA TERAPEUTICA[1]

=

RIDUZIONE DEL 27% DEL RISCHIO di EVENTI CV[1]

A review of polypills for the prevention of atherosclerotic cardiovascular disease

Federica Agnello, MD, Simone Finocchiaro, MD, Claudio Laudani, MD, Marco Legnazzi, MD, Maria Sara Mauro, MD, Carla Rochira, MD, Lorenzo Scalia, MD, and Davide Capodanno, MD, PhD (Catania, Italy)

- Polypills is a promising strategy in both primary and secondary prevention of ASCVD.
- Its benefits have been proven in populations with different ASCVD risk classes.
- Efficacy has been tested in both polypills vs placebo and polypills vs usual care trials.

Am Heart J
2023;266:74–85

Table 1. Randomized clinical trials of polypill to control cardiovascular risk factors

Study	*N*	Intervention	Comparator	Key results
Low risk of ASCVD events				
TIPS[28] (2009)	2,053	Combination of aspirin 100 mg, atenolol 50 mg, ramipril 5 mg, HTZ 12.5 mg and simvastatin 20 mg	Aspirin alone, simvastatin alone, HTZ alone, combination of 2 or 3 BP-lowering drugs, or combination of 3 BP-lowering drugs and aspirin	• Systolic BP (vs groups without BP-lowering drugs): difference −7.4 mmHg, 95% CI, −6.1 to −8.1 • Diastolic BP (vs groups without BP-lowering drugs): difference −5.6 mmHg, 95% CI, −4.7 to −6.4 • LDL-C (vs simvastatin): difference −0.13 mmol/L, 95% CI, −0.25 to −0.01
Malekzadeh et al.[32] (2010)	475	Combination of aspirin 81 mg, enalapril 2.5 mg, HTZ 12.5 mg and atorvastatin 20 mg	Placebo	• Systolic BP: difference −4.5 mmHg; $P < .001$ • Diastolic BP: difference −1.6 mmHg; $P < .032$ • LDL-C: difference −0.4 mmol/L; $P < .001$ • Total cholesterol: difference −0.63 mmol/L; $P < .001$
SCCS[35] (2019)	303	Combination of amlodipine 2.5 mg, losartan 25 mg, HTZ 12.5 mg and atorvastatin 10 mg	Usual care	• Systolic BP: difference −7 mmHg, 95% CI, −12 to −2 • Diastolic BP: difference −3 mmHg, 95% CI, −5 to −1 • LDL-C: difference −11 mg/dL, 95% CI, −18 to −5
Intermediate risk of ASCVD events				
PILL[27] (2019)	378	Combination of aspirin 75 mg, lisinopril 10 mg, HTZ 12.5 mg and simvastatin 20 mg	Placebo	• Systolic BP: difference −9.9 mmHg, 95% CI, −7.7 to 12.1 • Diastolic BP: difference −5.3 mmHg, 95% CI, −3.9 to −6.7 • LDL-C: difference −0.8 mmol/L, 95% CI, 0.6 to −0.9
Soliman, et al.[33] (2011)	216	Combination of aspirin 75 mg, lisinopril 10 mg, HTZ 12.5 mg and simvastatin 20 mg	Usual care	• Systolic BP: difference −1.9 mmHg, 95% CI, −5.1 to 8.9 • Total cholesterol: difference −0.4 mmol/L, 95% CI, 0.0 to −0.8
High risk of ASCVD events				
TIPS 2[29] (2012)	518	Combination of aspirin 100 mg, atenolol 50 mg, ramipril 5 mg, HTZ 12.5 mg and simvastatin 20 mg (2 doses)	Same as one dose	• Systolic BP: difference −2.8 mmHg, 95% CI, −4.70 to −1.0 • LDL-C: difference -6.6 mg/DL, 95% CI, −11.3 to −1.9
UMPIRE[19] (2013)	2,004	Combination of aspirin 75 mg, lisinopril 10 mg, HTZ 12.5 mg and simvastatin 40 mg ± atenolol 50 mg	Usual care	• Systolic BP: difference −2.6 mmHg, 95% CI, −4.0 to −1.1 • Diastolic BP: difference −2.5 mmHg, 95% CI, −3.3 to −1.6 • LDL-C: difference −4.2 mg/dL; 95% CI, −6.6 to −1.9
IMPACT[18] (2014)	513	Combination of aspirin 75 mg, simvastatin 40 mg, and lisinopril 10 mg with either atenolol 50 mg or HTZ 12.5 mg	Usual care	• Systolic BP: difference −2.2 mmHg, 95% CI, −5.6 to 1.2; $P = .21$ • Diastolic BP: difference −1.2 mmHg, CI −3.2 to 0.8; $P = .22$ • LDL-C: difference: −0.05 mmol/L, 95% CI, −0.17 to 0.08; $P = .46$
KANYNI[40] (2015)	623	Combination of aspirin 75 mg, lisinopril 10 mg, HTZ 12.5 mg or atenolol 50 mg and simvastatin 40 mg	Usual care	• Systolic BP: difference −1.5 mmHg, 95% CI, −4.0 to 1.0 • Diastolic BP: difference −0.9 mmHg, 95% CI, −2.3 to −0.5 • Total cholesterol: difference 0.08 mmol/L, 95% CI, −0.06 to 0.2

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; HTZ: hydrochlorothiazide; LDL-C: low-density lipoprotein cholesterol.

TRA I FARMACI ESSENZIALI LA POLIPILLOLA PER PATOLOGIE CARDIOVASCOLARI:

26 Luglio 2023: L'ULTIMO AGGIORNAMENTO DELL'OMS

WHO updates list of essential medicines to include heart 'polypills,' MS treatments but not weight-loss drugs

By Giri Viswanathan, CNN
Published 6:34 PM EDT, Wed July 26, 2023

World Health Organization

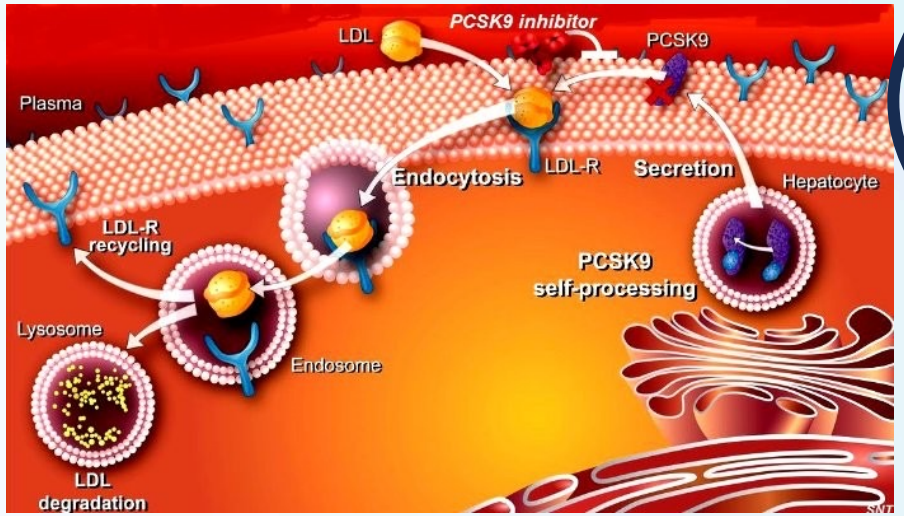
"Le polipillole possono essere un modo economico ed efficace per ridurre il rischio di problemi cardiaci, con studi che indicano che possono ridurre il rischio di problemi cardiovascolari di quasi il 40%.

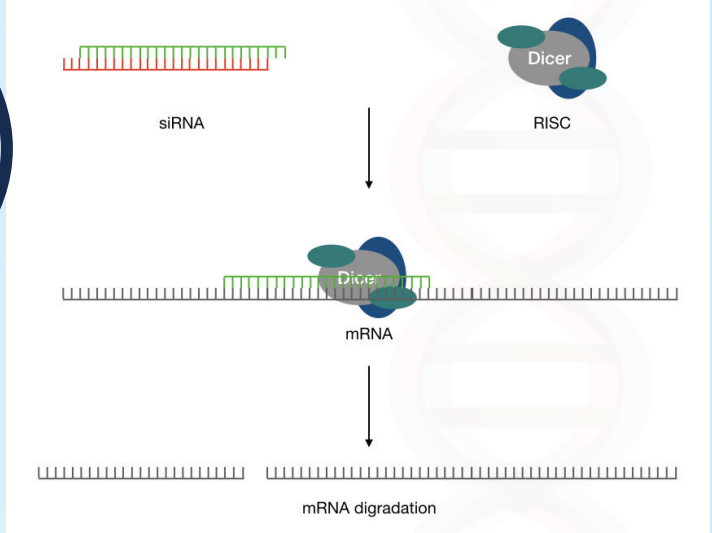
Solo poche aziende producono e commercializzano polipillole, e poche persone le prendono, anche se le malattie cardiache e gli infarti uccidono 18 milioni di persone ogni anno."

"Questi trattamenti potrebbero avere un grande impatto sulla salute pubblica a livello globale, senza compromettere i bilanci sanitari dei paesi a basso e medio reddito."

ha detto il Dr. Tedros Adhanom Ghebreyesus, direttore generale dell'OMS.

Prospettive future





Grazie per l'attenzione

Pantorc 20 mg 1 cp ore 7.30
Cardioaspirina 100 mg 1 cp/die
Ticagrelor 90 mg 1 cp x2/die
Ramipril 10 mg 1 cp/die
Atorvastatina 80 mg 1 cp/die
Ezetimibe 10 mg 1 cp/die
Amlodipina 5 mg
Bisoprolo

Pantorc 20 m
Ramipril + Bis
ASA + Statina
Ticagrelor 90 m

mg 1 cp ore 7.30
ina 100 mg 1 cp/die
0 mg 1 cp x2/die
lodipina
40 + 10 Ezetimibe 1 cp/die
mg 1 cp/die

1 cp ore 7.30
prololo 1 cp/die
tina 1 cp/die
icagrelor 90 mg 1 cp x2/die
Amlodipina 1 cp/die