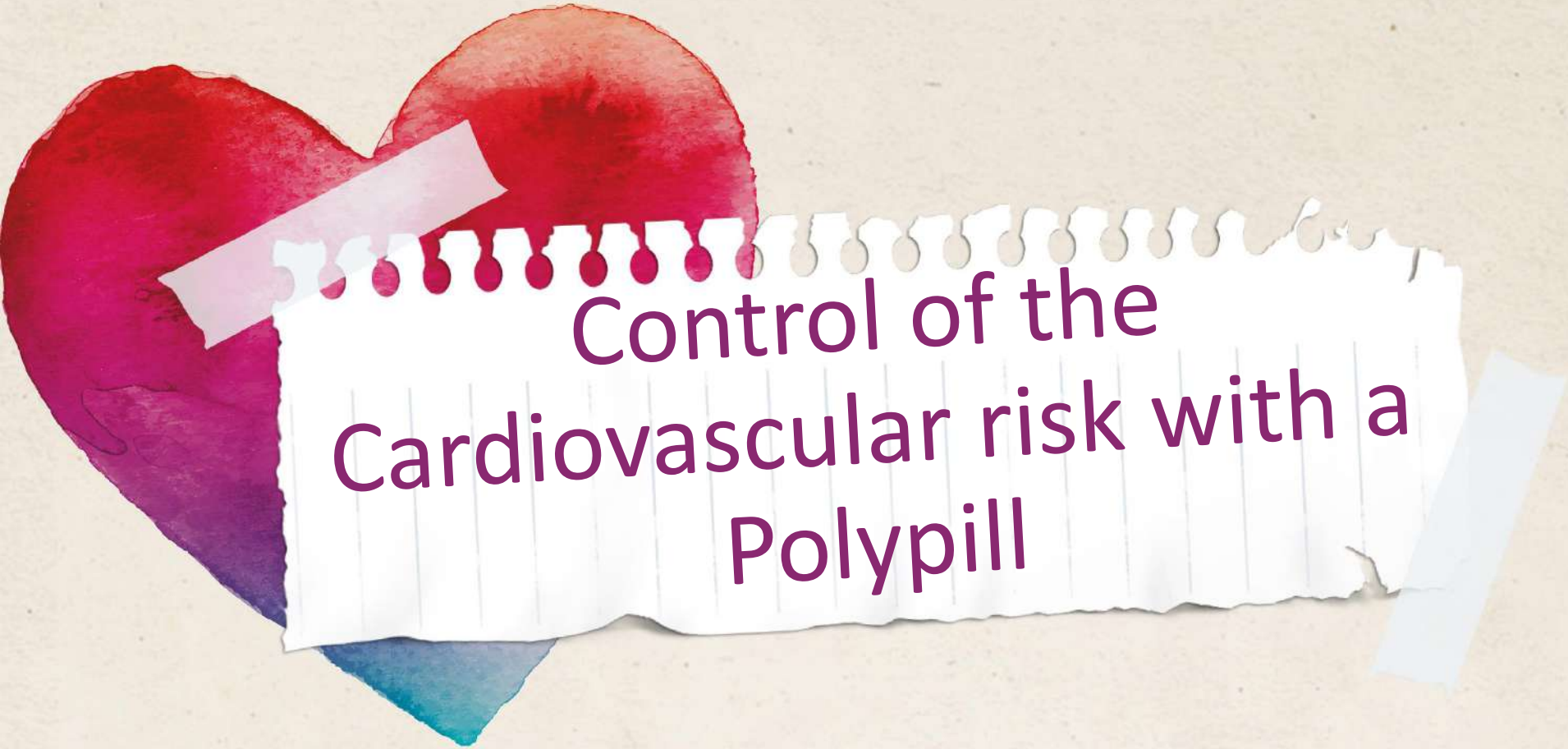


Control of the Cardiovascular risk with a Polypill

Vivencio Barrios
MD, PhD, FESC, FACC
University Hospital Ramón y Cajal, Alcalá University
Madrid (Spain)

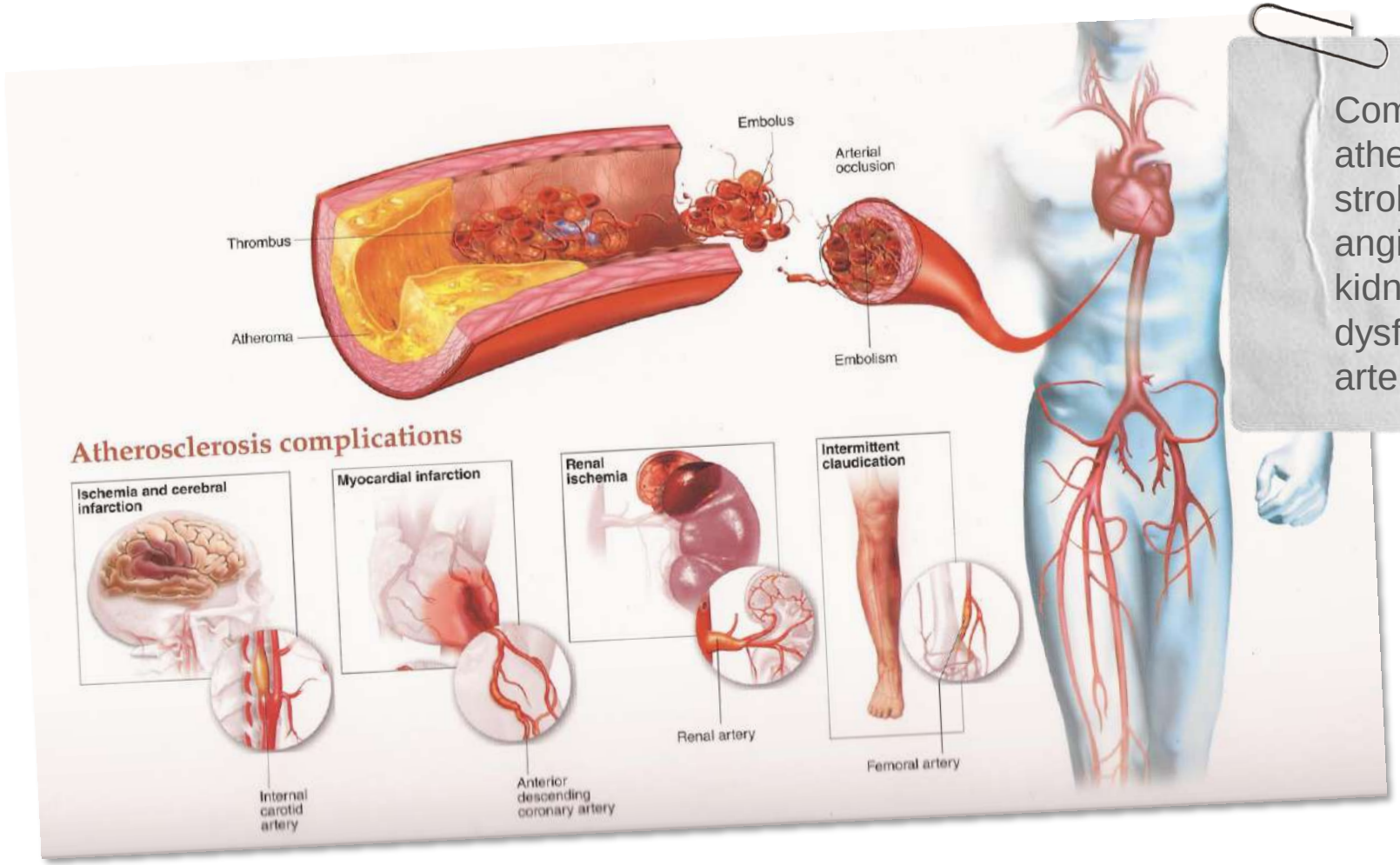
Disclosure

Speaker/consultant for:

Abbott; Amgen; Amstrong; AstraZeneca; Bayer Schering Pharma; Boehringer Ingelheim Pharmaceuticals GmbH; Bristol-Myers Squibb; Daiichi Sankyo Europe GmbH; Ferrer International SA; Janssen; Menarini Group Farma; Mundipharma; Mylan Pharma; Novartis AG; NovoNordisk; Pfizer; Recordati Pharma; Roche Pharma; Sanofi-Aventis; Servier Laboratories; Takeda Pharmaceuticals

Atherosclerosis

Multisystemic disease



Complications of atherosclerosis include: stroke or TIA in the brain, angina or heart attack, kidney failure, erectile dysfunction and peripheral artery disease

Atherosclerosis

A global therapeutic approach for a multifactorial disease

SMOKING CESATION

DIET

PHYSICAL ACTIVITY

PHARMACOLOGICAL TREATMENT

Piepoli et al., Eur Heart J 2016; 37(29):2315-81

Atherosclerosis

A global therapeutic approach for a multifactorial disease

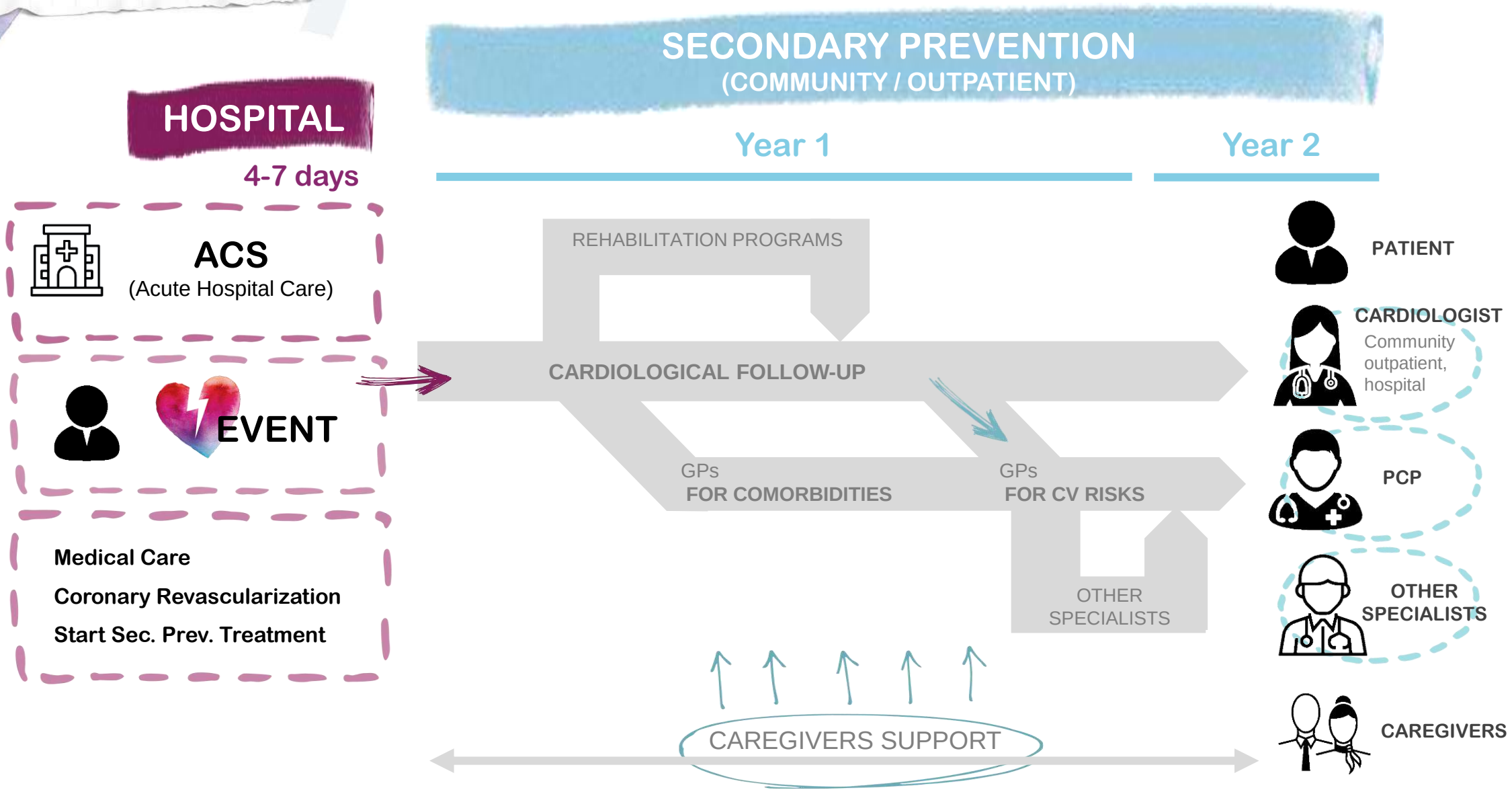
It's Recommended the use of **AAS, Statins and ACE-I** in the Secondary Prevention Guidelines

CORONARY HEART DISEASE

Guideline	Drug class	Recommendation class/ Evidence level
Secondary Prevention of Coronary and Other Atherosclerotic Vascular Disease	ACEi	1A / IIaB
	Statin	1A
	Aspirin	1A

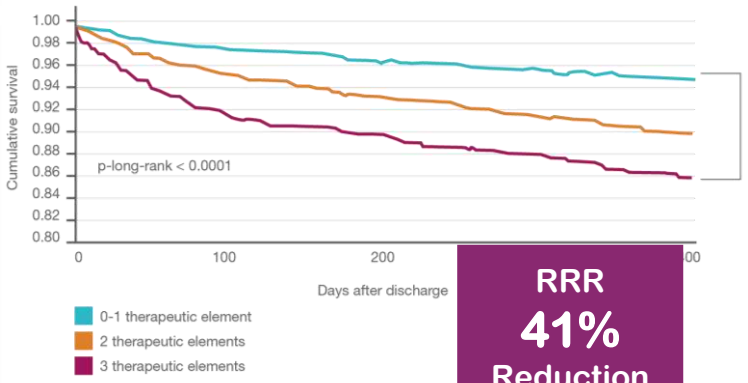
Guideline	Drug class	Recommendation class/ Evidence level
AMI with ↑ST (STEMI) *Ibañez et al., 2017*	ACEi	1A
AMI without ↑ST (NSTE-ACS) *Roffi et al 2015*	Statin	1A
Stable Coronary Disease *Montalescot 2013*	Aspirin	1A

Patient journey after a cardiovascular event



Evidence-based therapy

(EBCP) for secondary prevention of cardiovascular disease

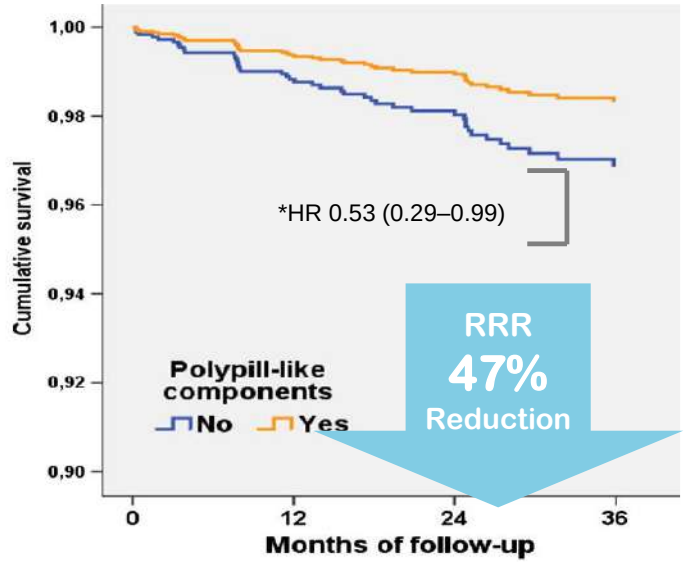


RRR 41% Reduction

A combination therapy with aspirin, an ACE inhibitor and a statin reduces 1-year mortality in patients after AMI.
Previously treated with a beta-blocker.

Prospective, observational study of 9,998 post-MI patients

Curr Med Res Opin.2011;27:1563-70.



RRR 47% Reduction

A global essential CV treatment at discharged improves CV secondary prevention

Retrospective analysis of 1,261 consecutive ACS patients

Int J Cardiol 2014;177:209–210

Essential treatments

Statins alone	47% (OR 0.53 (0.33-0.86)
Statins + ASA	61% (OR 0.39 (0.29-0.52)
Statin + ASA + ACEi	**71%** (OR 0.29 (0.21-0.41)

Statin-ASA-ACEi 71% Reduction

Patients with CHD reduces risk of all-cause mortality.

Open prospective case-control analysis in UK in 13,029 patients with ischemic heart disease

BMJ 2005;330;1059-1063

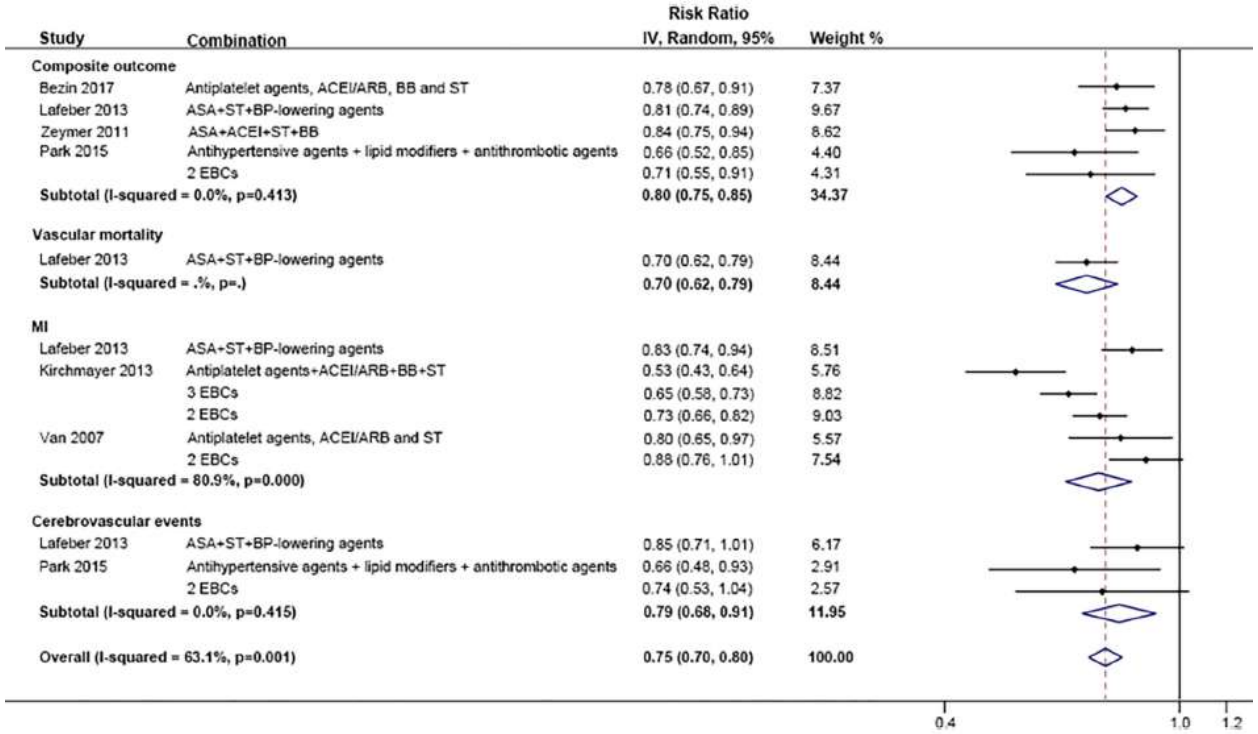
Evidence-based therapy

(EBCP) for secondary prevention of cardiovascular disease

Meta-analysis:
The use of combination therapy reduced the relative risk of major cardiovascular events by 25%

Optimal EBCP reduced the risk of:

- Composite outcome by **14%**
(95% CI 11%-18%)
- Vascular mortality by **27%**
(95% CI 22%-33%)
- MI by **16%**
(95% CI 10%-21%)
- Cerebrovascular events by **19%**
(95% CI 9%-28%)



Meta-analysis of existing observational studies that investigated the impact of the EBCP on mortality and cardiovascular events in the secondary prevention of CVD.
EBCP: combination of antiplatelet agents, lipid-modifiers, ACEi/ARBs and beta-blockers

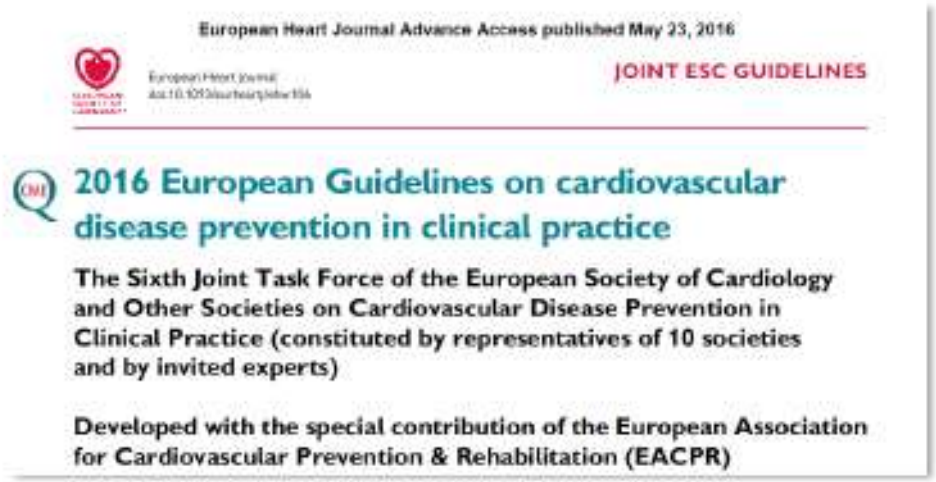
Ma T-T et al., 2019. PLoS ONE 14(1): e0210988. https://doi.org/10.1371/journal.pone.0210988

Polypill in Cardiovascular Prevention

Characteristics of the treatment with a polypill

- Multifactorial treatment for a multifactorial disease
- The baseline treatment for an optimal control in patients after a CV event
- Simplicity in the posology (once daily)
- Implementation strategy to favour the use of essential drugs in secondary prevention
- Better risk factor control than monocomponents taking separately

Guidelines



European Heart Journal Advance Access published May 23, 2016

JOINT ESC GUIDELINES

2016 European Guidelines on cardiovascular disease prevention in clinical practice

The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)

Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)

"The polypill should not be considered in isolation, but as an integral part of a comprehensive CVD prevention strategy that includes efforts to reduce tobacco use, increase physical activity and increase consumption of a heart-healthy diet"

"The polypill may increase adherence to treatment and improve CV risk factor control"

Recommendations for achieving medication adherence

Recommendations	Class[a]	Level[b]	Ref[c]
Simplifying the treatment regimen to the lowest acceptable level is recommended, with repetitive monitoring and feedback. In case of persistent non-adherence, multi-session or combined behavioural interventions are recommended.	I	A	481
It is recommended that physicians assess medication adherence, and identify reasons for non-adherence in order to tailor further interventions.	I	C	482–484
The use of the polypill and combination therapy to increase adherence to drug therapy may be considered.	IIb	B	485, 486

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Piepoli et al., Eur Heart J 2016; 37(29):2315-2381.

Polypill in the control of CV risk

Available data with polypills: Control of CV risk

SBP

-6,34 mmHg*

Additional effect over usual care or placebo

LDL-C

-26,3 mg/dL**

Additional effect over usual care or placebo

* -6.34 mmHg (95% IC: -9.03 a -3.64)
**-0.70 mmol/L=26,3mg/dL (95% IC: -0.98 a -0.41)

Cochrane Library

An additional control of CV risk with a polypill

Bahiru E, et al., Cochrane Database of Systematic Reviews 2017. DOI: 10.1002/14651858.CD009868.pub3

Polypill in the control of CV risk

2016 ESC guidelines on the prevention of CVD

27%

More patients achieve global control with a Polypill vs usual care

Blood pressure

8%

More patients on ESC target for SBP

LDL-C

13%

More patients on ESC target for LDLc

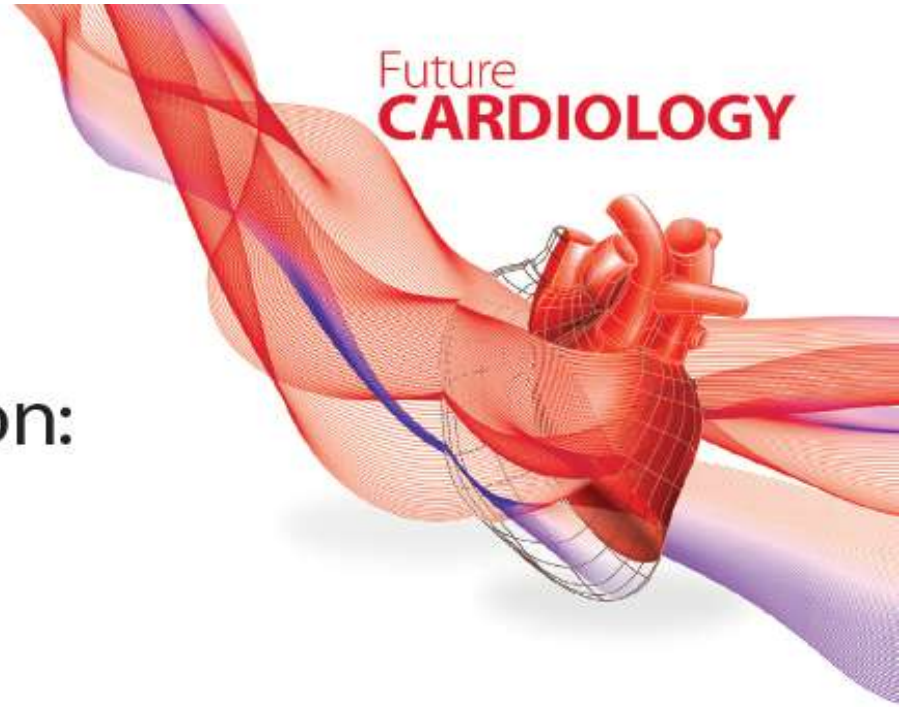
antiplatelet therapy

96% vs 96%

3140 patients from Australia, England, India, Ireland, the Netherlands and New Zealand (75% male, mean age 62 years and 76% with a prior CVD event or who were at high risk of their first event.

Selak V, et al. Heart 2018; 105 9-10

Polypill



REVIEW

Improving cardiovascular protection: focus on a cardiovascular polypill

Vivencio Barrios*[1] & Carlos Escobar[2]

Future Cardiol 2016; 12(2):181-96

Polypill

Composition of different CV polypills used in clinical practice

Table 3. Most relevant fixed-dose combinations.

Study	Composition of polypill
TIPS	Aspirin 100 mg, ramipril 5 mg, simvastatin 20 mg, hydrochlorothiazide 12.5 mg, atenolol 50 mg
Poly-Iran	Aspirin 81 mg, enalapril 2.5 mg, atorvastatin 20 mg, hydrochlorothiazide 12.5 mg
Combination Therapy Trial	Aspirin 75 mg, lisinopril 10 mg, simvastatin10 mg, hydrochlorothiazide 10 mg
PILL Collaborative Group Study	Aspirin 75 mg, lisinopril 10 mg, simvastatin 20 mg, hydrochlorothiazide 12.5 mg
IMPACT	Aspirin 75 mg, lisinopril 10 mg, simvastatin 40 mg, atenolol 50 mg/ hydrochlorothiazide 12.5 mg
FOCUS Trial in Secondary Prevention	Aspirin 100 mg, ramipril 2.5/ 5/10 mg, simvastatin 40 mg
UMPIRE	Aspirin 75 mg, lisinopril 10 mg, simvastatin 40 mg, atenolol 50 mg ('red heart pill 1') or aspirin 75 mg, lisinopril 10 mg, simvastatin 40 mg, hydrochlorothiazide 12.5 mg ('red heart pill 2')

Data taken from [45–47].

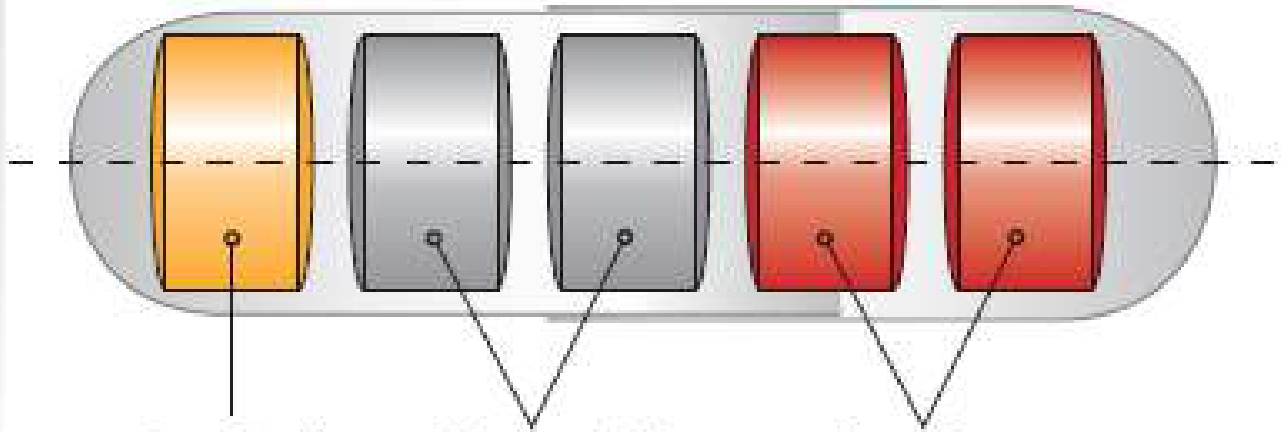
Barrios V, et al. Future Cardiol 2016;12(2):181-96

CNIC-Fuster-Ferrer (Trinomia®)

Hard gelatin 0 size capsule containing 5 coated inmediate release pills:

- Aspirin (100 mg (2 x 50mg))
- Statin (Atorvastatin 40 mg (2 x 20 mg))
- ACE inhibitor (Ramipril 2,5mg; 5mg or 10 mg)

New technology that allows avoiding chemicophysical incompatibilities between components.



3 Trinomia® presentations:
- Trinomia® 100/40/2,5
- Trinomia® 100/40/5
- Trinomia® 100/40/10

Trinomia® should be taken orally as a single capsule per day, preferably after a meal

Polypill, A New therapeUtic tool to impRove Adherence in secondary prevention

The AURA clinical program

trinomia

acetylsalicylic acid • atorvastatin • ramipril

Treatment and adherence available for everyone

ferrer | cnic

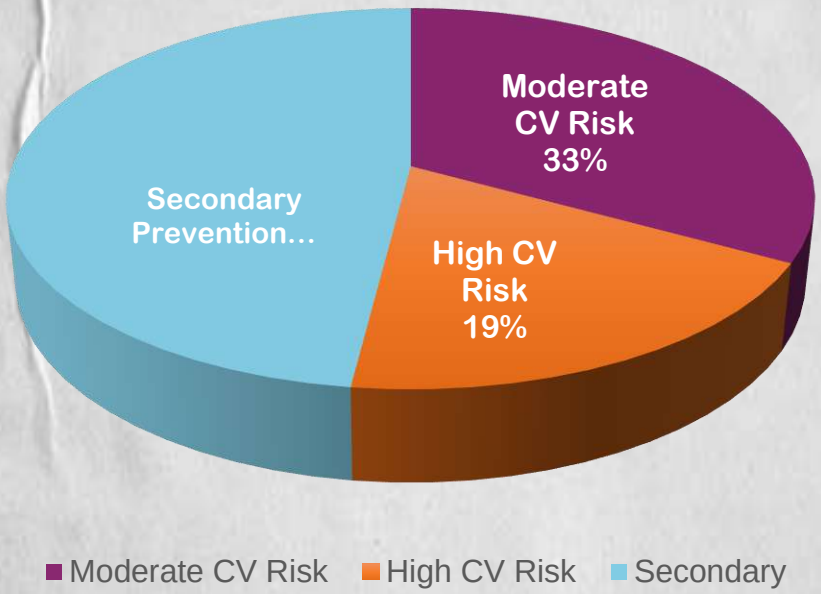
Polypill, A New therapeUtic tool to impRove Adherence in secondary prevention

Control of the CV Risk with a Polypill

reducing risks,

SORS STUDY

Risk control in real-life patients with the Polypill CNIC



Baseline	Total	Secondary prevention	High risk	Intermediate risk	P
Patients, n (%)	1193 (100%)	572 (47.9)	231(19,4)	390 (32.7)	
Age (years), mean(SD)	57.4 (14.2)	59,4 (13.9)	57.5 (13,4)	54.3 (14.5)	<0.01
Males, n (%)	644 (54.0)	328 (57.3)	109 (47.2)	207 (53.1)	0.03
Obesity, n (%)*	478 (40.2)	243 (42.7)	94 (40.9)	141 (36.2)	
Arterial Hypertension, n (%)	1038 (87.0)	491 (85.8)	201 (87.0)	346 (88.7)	0.427
Hypercholesterolemia, n (%)	1018 (85.3)	497 (86.9)	199 (86.1)	322 (82.6)	0.164
Diabetes Mellitus, n (%)	380 (31.9)	178 (31.1)	195 (84.4)	7 (1.8)	<0.001

Observational study, multicentric, cohort of 1193 patients treated with Polypill CNIC (ASA 100mg, simvastatin 40mg, ramipril 5 or 10mg) for 12 months in Mexico.

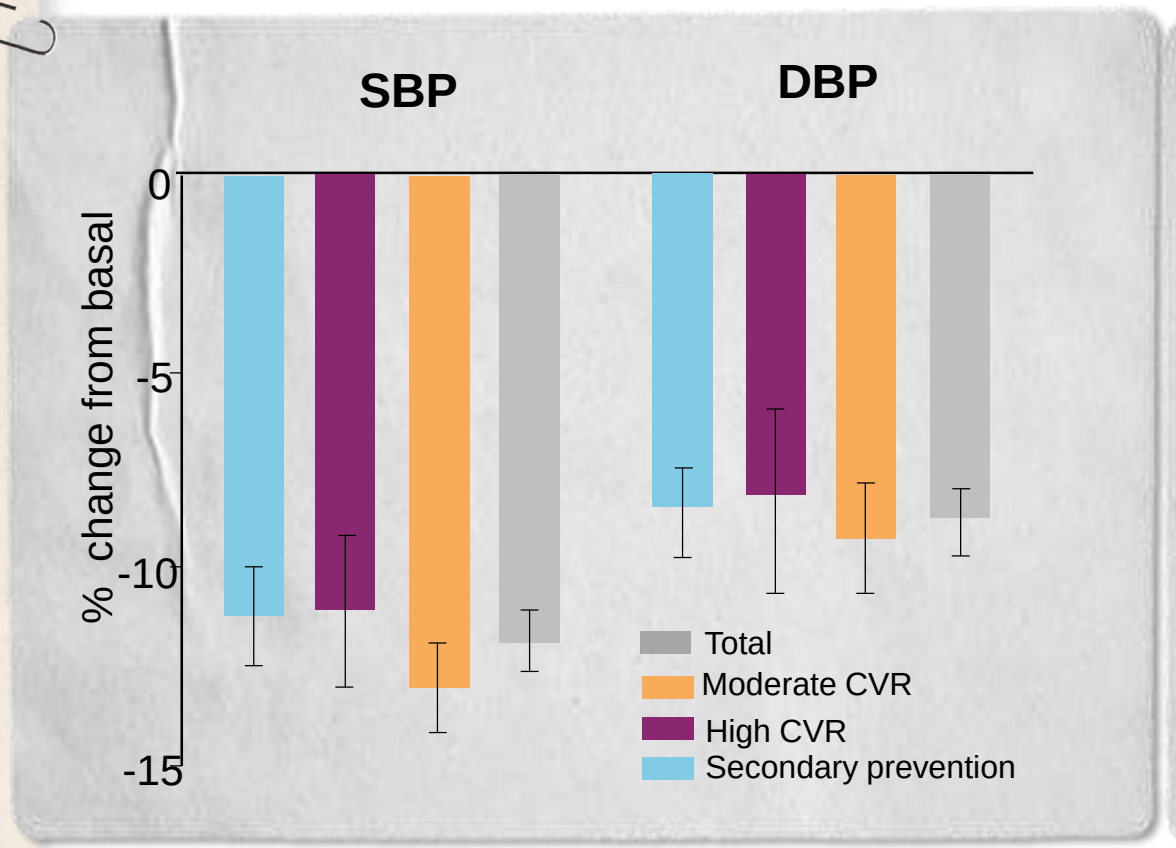
This study contains off label information of Polypill CNIC.
The use of the drug is recommended within the approved indication

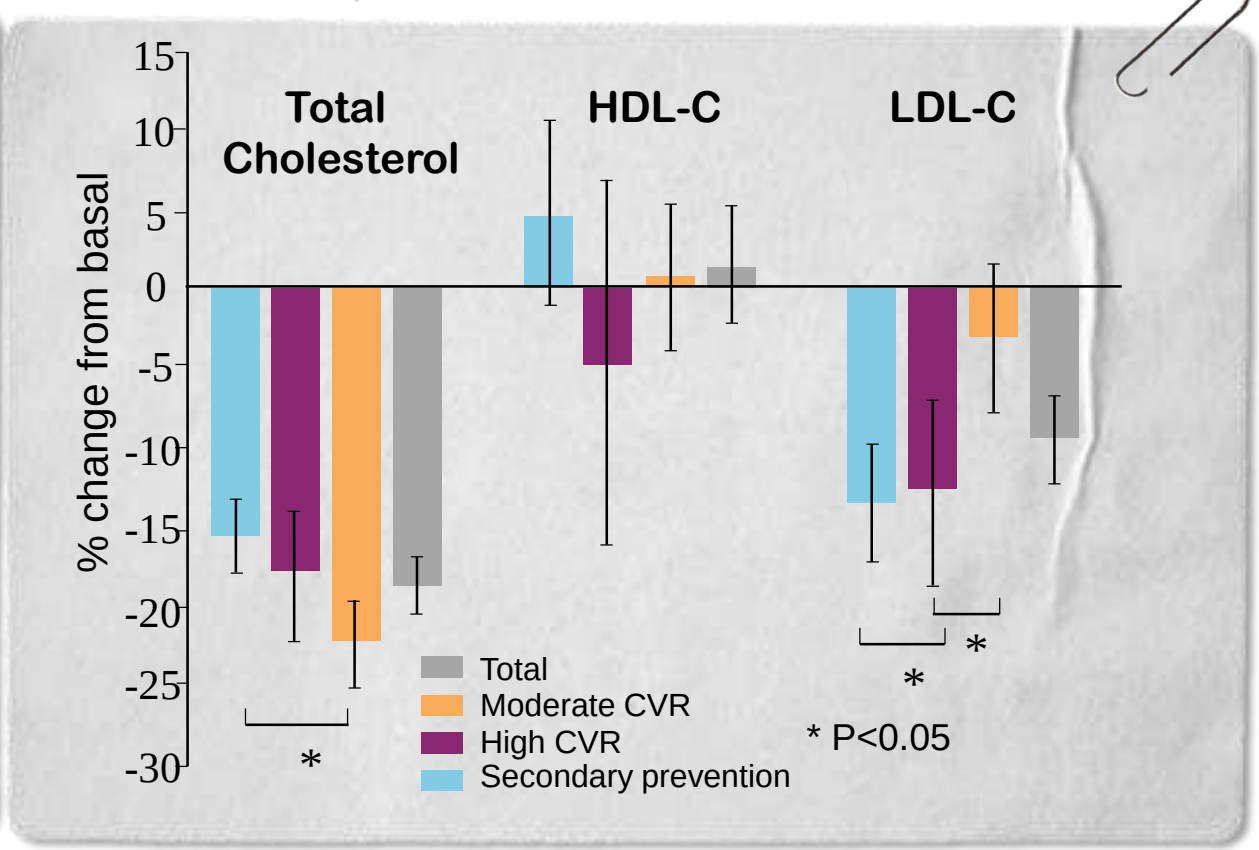
Castellano JM et al. Archives Int Med 2019 (in press)

SORS STUDY

Risk factors control in real-life patients with the Polypill CNIC

Polypill CNIC reduces LDL and BP additionally to usual care





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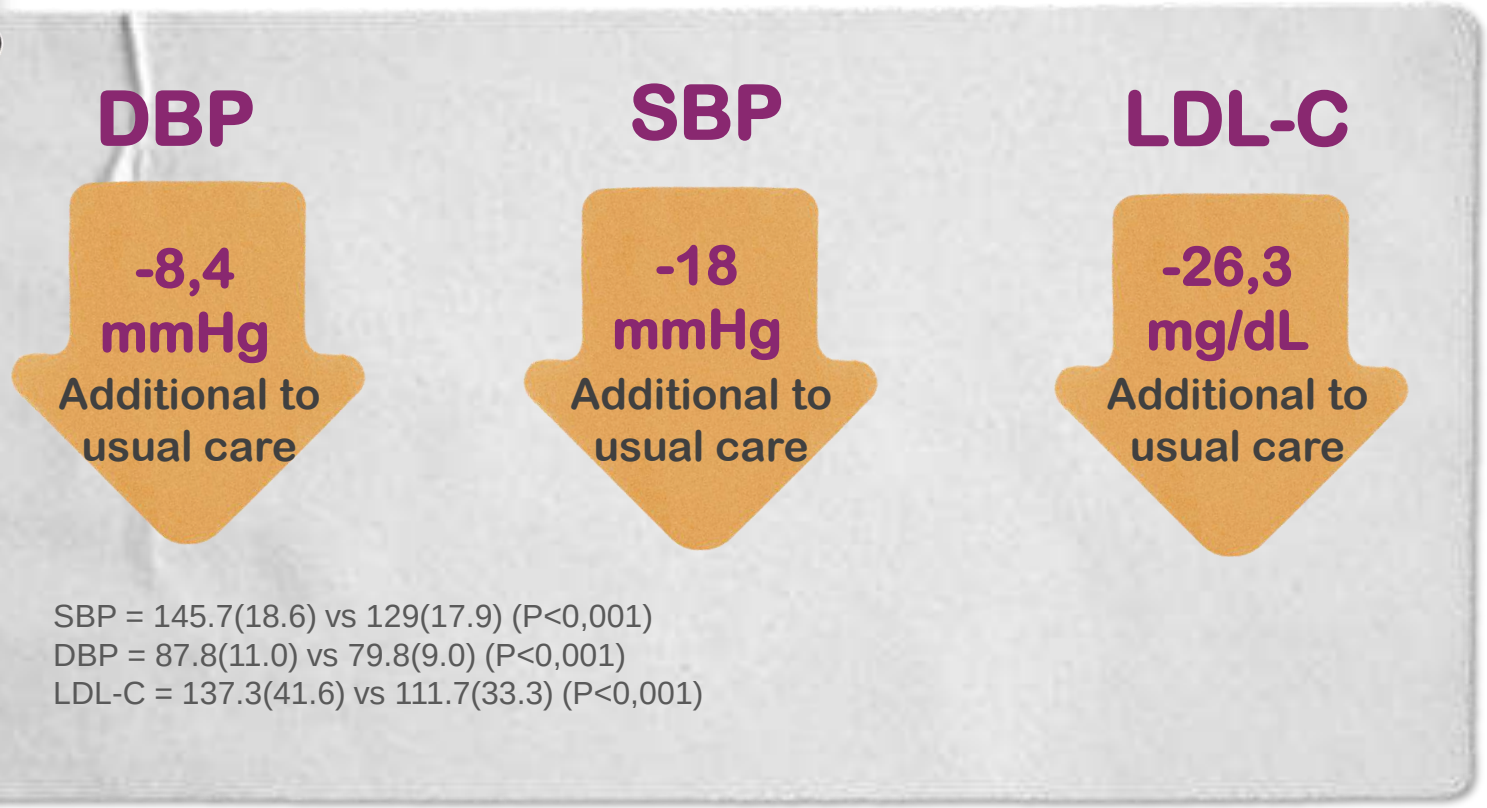
Castellano JM et al. Archives Int Med 2019 (in press)

SORS STUDY

Risk factors control in real-life patients with the Polypill CNIC

Polypill CNIC reduces LDL-C and BP additionally to usual care



SBP = 145.7(18.6) vs 129(17.9) (P<0,001)
DBP = 87.8(11.0) vs 79.8(9.0) (P<0,001)
LDL-C = 137.3(41.6) vs 111.7(33.3) (P<0,001)

This study contains off label information of Polypill CNIC. The use of the drug is recommended within the approved indication

Castellano JM et al. Archives Int Med 2019 (in press)

SORS STUDY

Risk factors control in real-life patients with the Polypill CNIC

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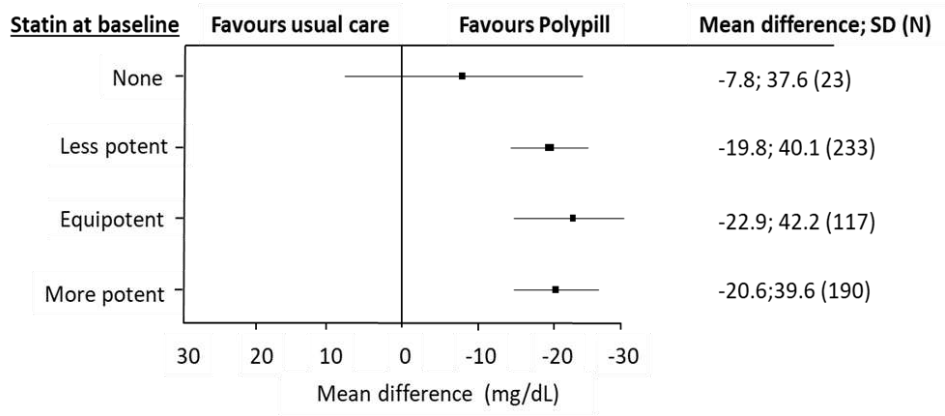
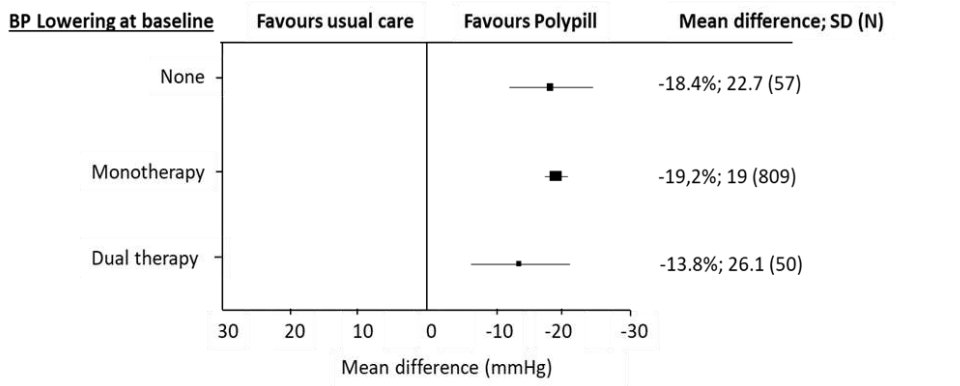




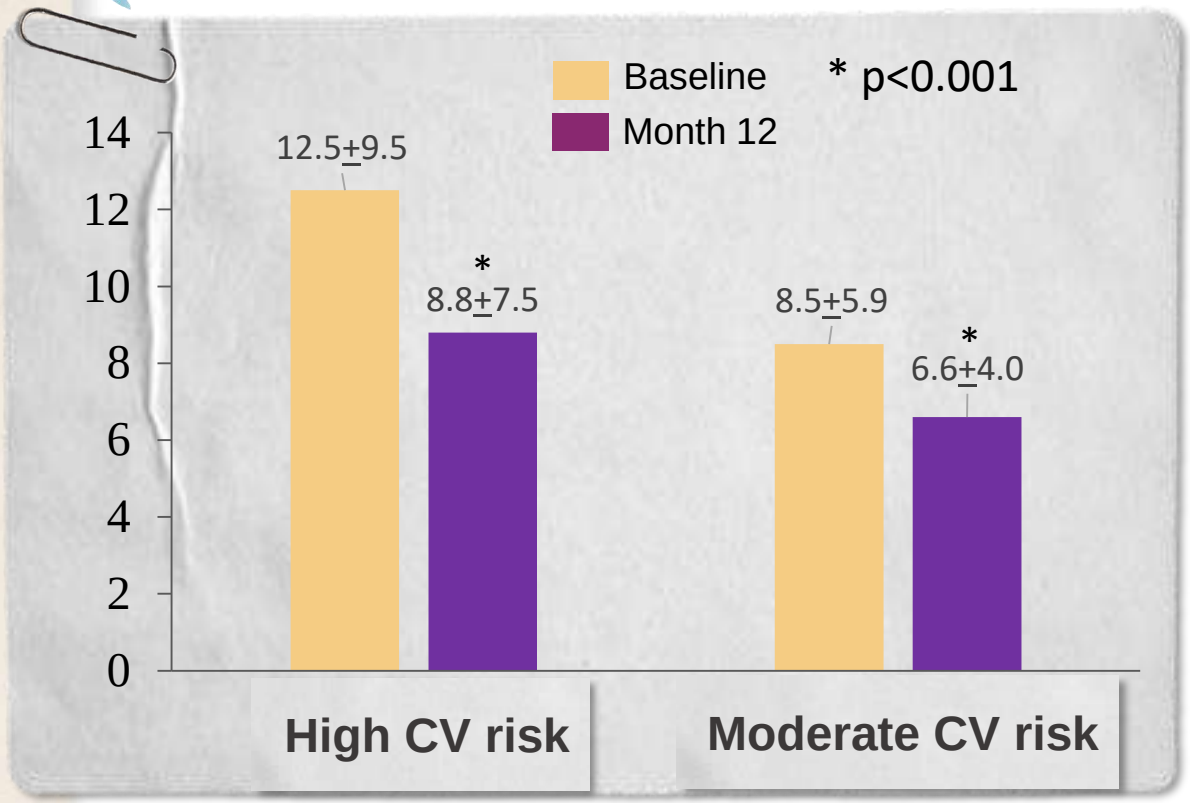
This study contains off label information of Polypill CNIC. The use of the drug is recommended within the approved indication

Castellano JM et al. Archives Int Med 2019 (in press)

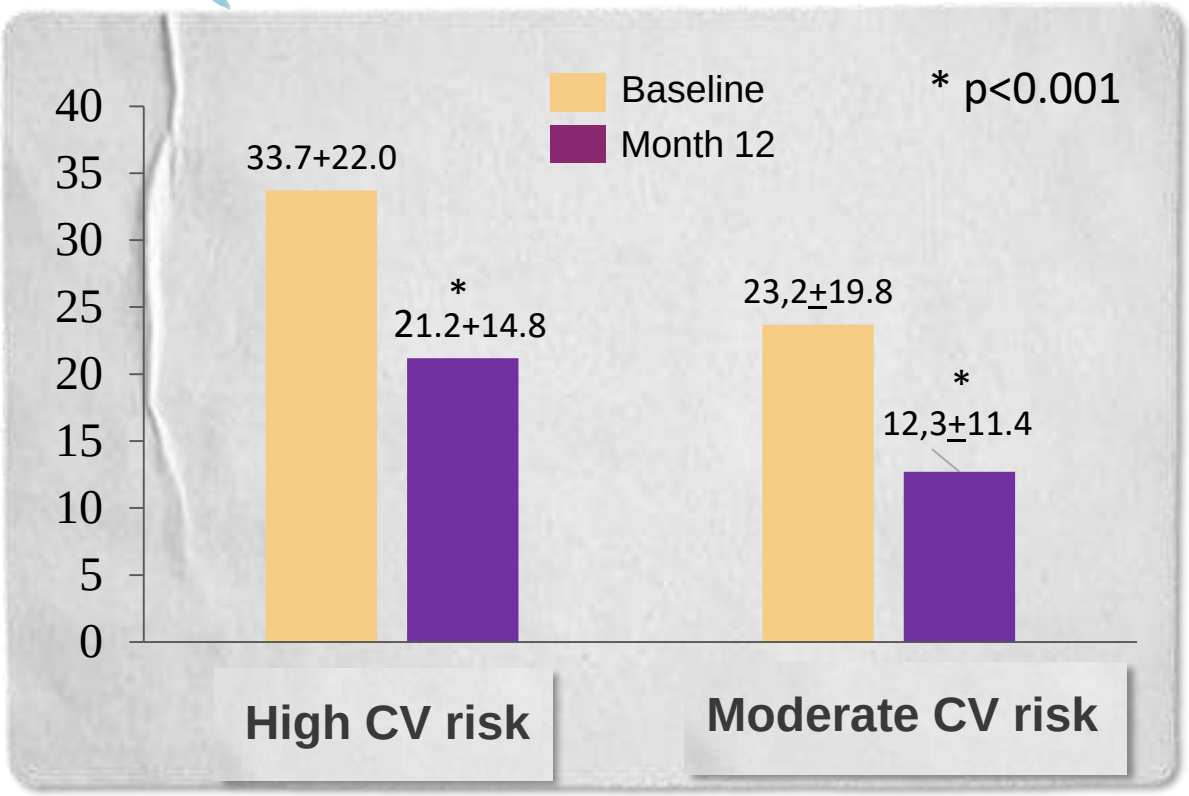
SORS STUDY

CV risk reduction in real-life patients with the Polypill CNIC

Changes in the 10-year Framingham risk score (%) for cerebrovascular events



Changes in the 10-year Framingham risk score (%) for cardiovascular disease



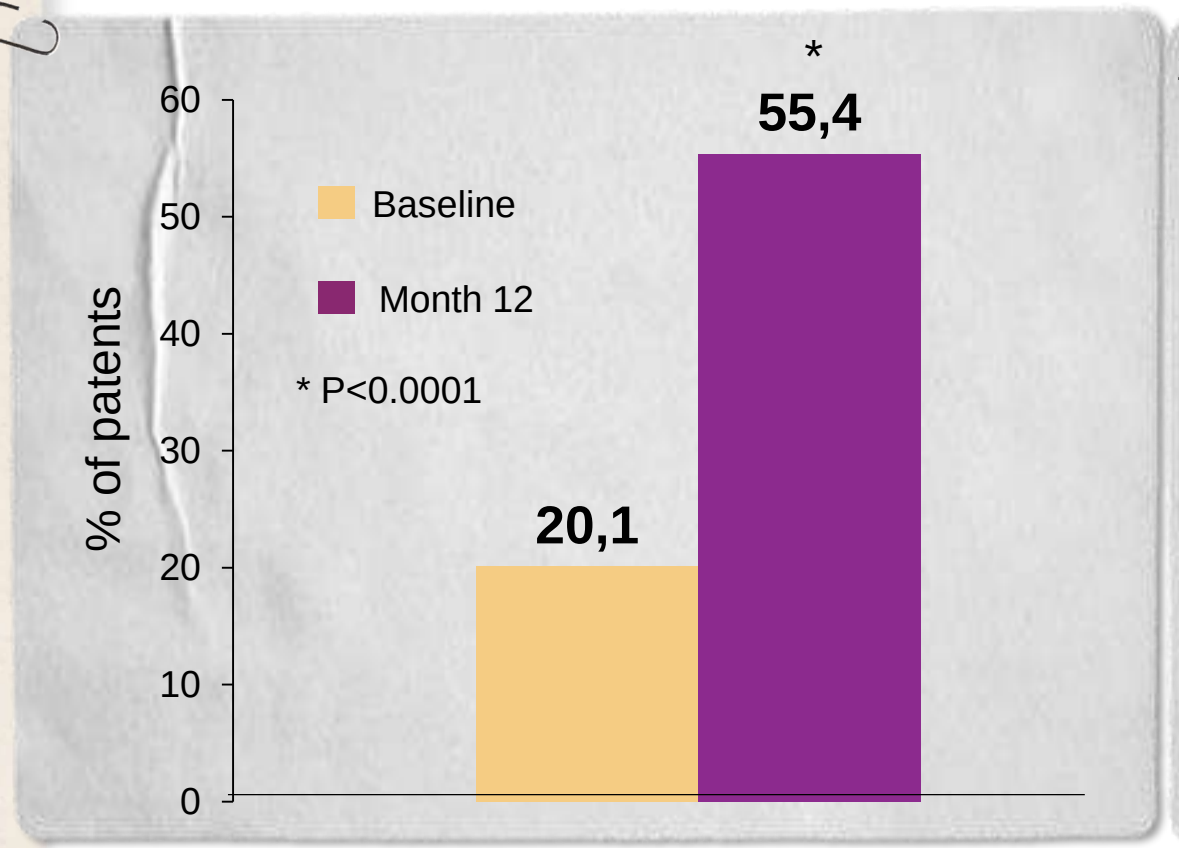
This study contains off label information of Polypill CNIC. The use of the drug is recommended within the approved indication

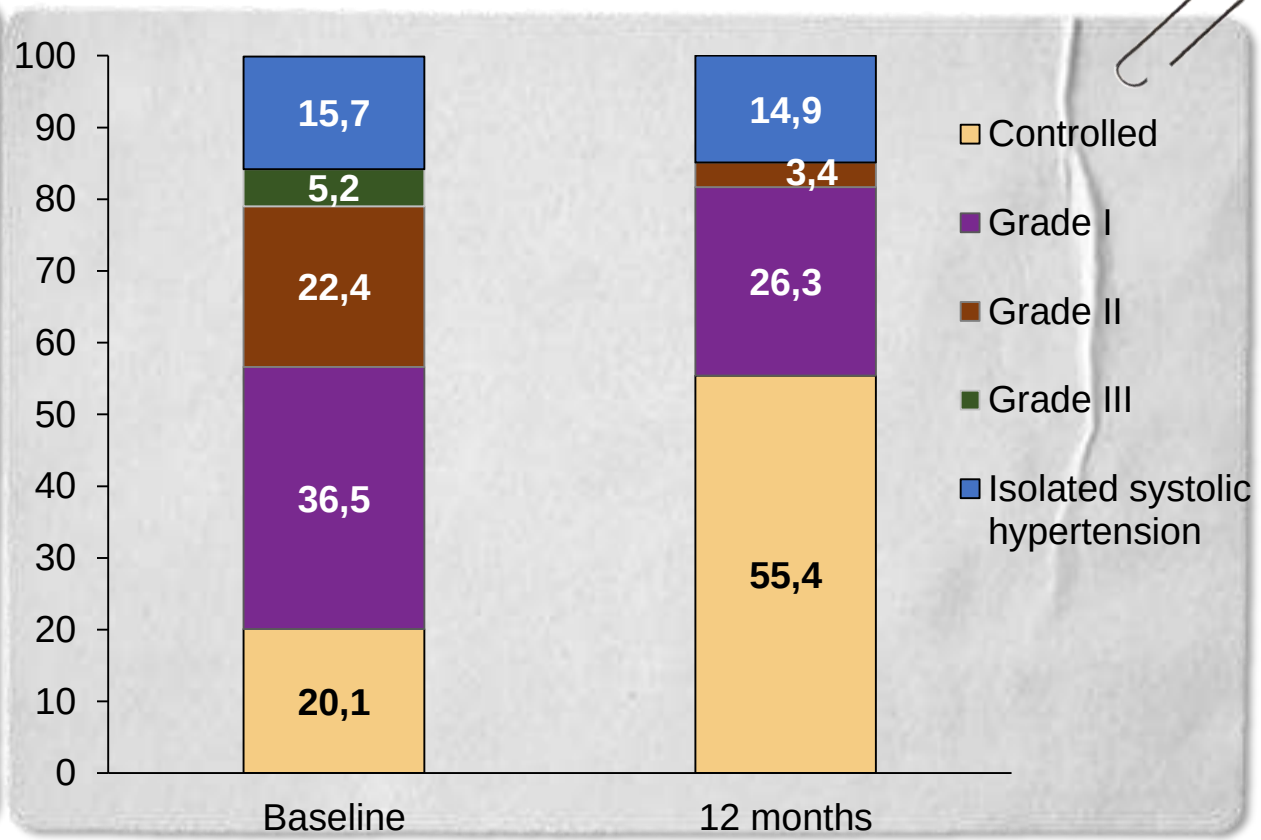
Castellano JM et al. Archives Int Med 2019 (in press)

SORS STUDY

Reaching of BP target with the CNIC polypill in patients in secondary prevention in Mexico

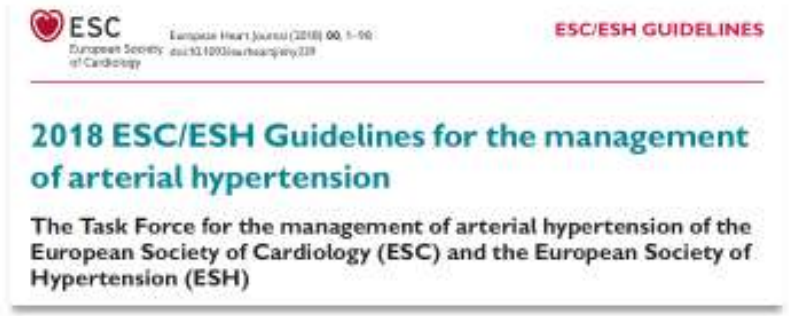
More patients with BP under control with Polypill CNIC





Gomez Alvarez E et al., SIAC Congress 2019

Guidelines


ESC European Society of Cardiology

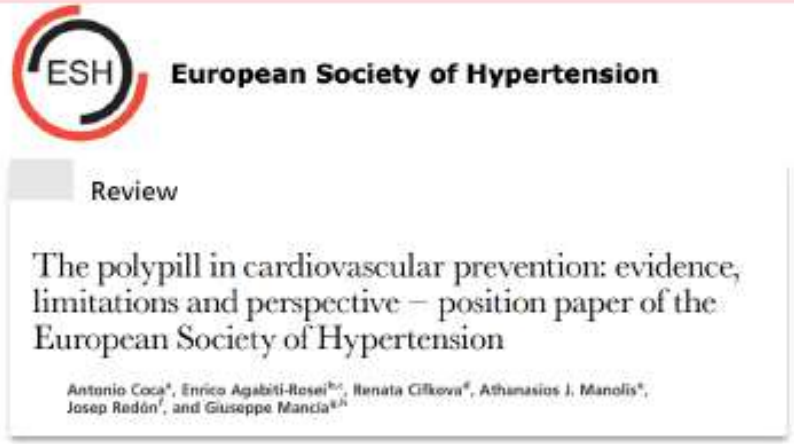
ESC/ESH GUIDELINES

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)

Williams et al., Eur Hear J. 2018; doi:10.1093/eurheartj/ehy33

- "Polypills have also emerged as SPCs (i.e. a fixed-dose combination of one or more antihypertensive agents with a statin and low-dose aspirin), with the rationale that hypertensive patients are often at sufficient CV risk to benefit from statin therapy".


ESH **European Society of Hypertension**

Review

The polypill in cardiovascular prevention: evidence, limitations and perspective – position paper of the European Society of Hypertension

Antonio Coca[a], Enrico Agabiti-Rosei[b,c], Renata Cifkova[d], Athanasios J. Manolis[e], Josep Redón[f], and Giuseppe Mancia[g,h]

Coca A et al., J Hypertension. 2017; 35:1546–1553.

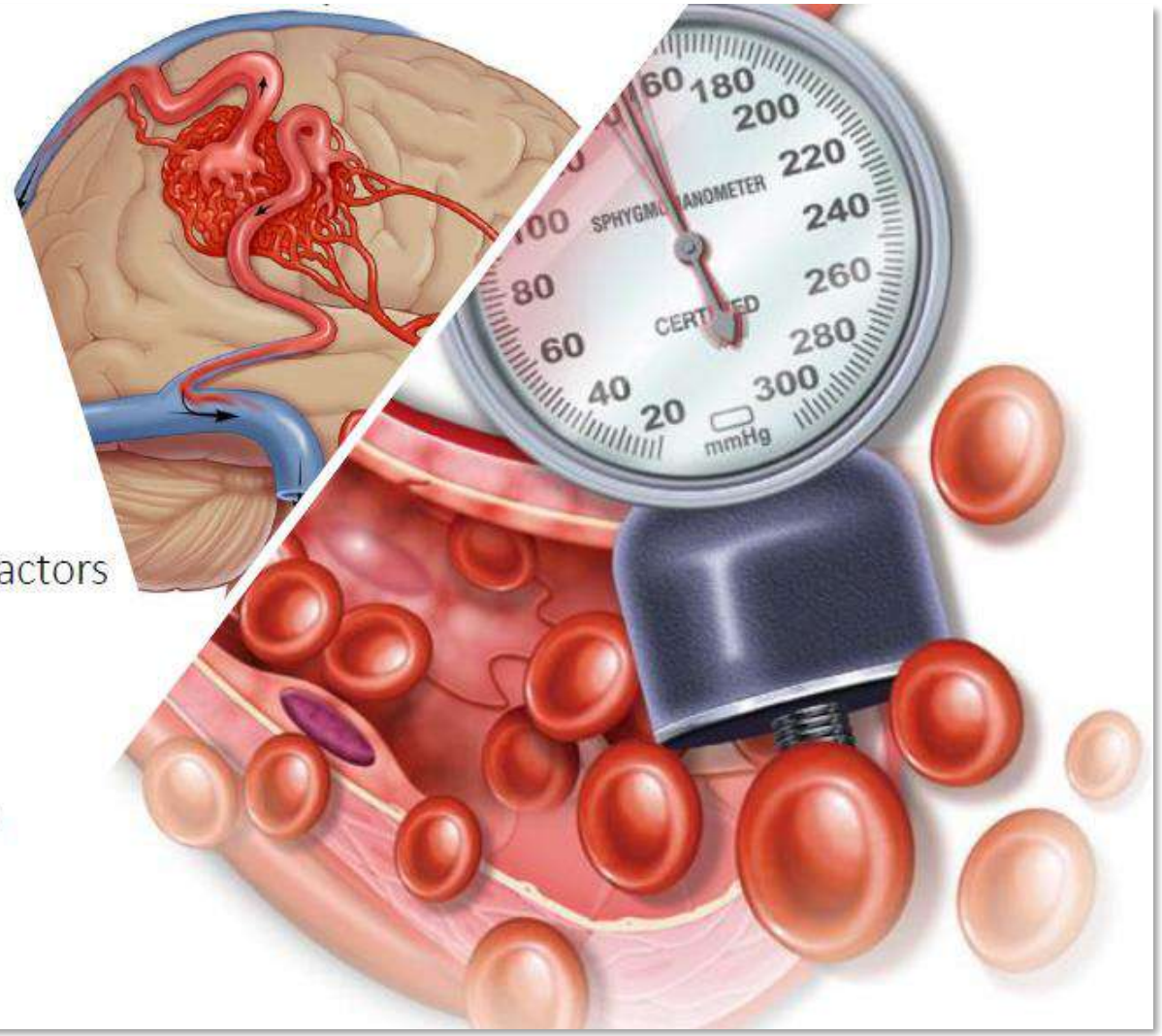
- Hypertensive patients are suitable candidates for Polypill since they have multiple comorbidities, remain in a high cardiovascular risk and they are candidates to antiplatelet treatment.
- The Polypill has been predominantly investigated in the context of secondary cardiovascular prevention. Patients without a history of cardiovascular disease, with a high cardiovascular risk profile might appear as a reasonable option.

Consensus

Consensus recommendations 2018: use of CV polypills for the secondary prevention of cerebrovascular disease

- Atherothrombotic stroke
- Lacunar stroke
- Cryptogenic stroke with CV risk factors

This document is the first to establish recommendations for the use of the CV polypill in cerebrovascular disease



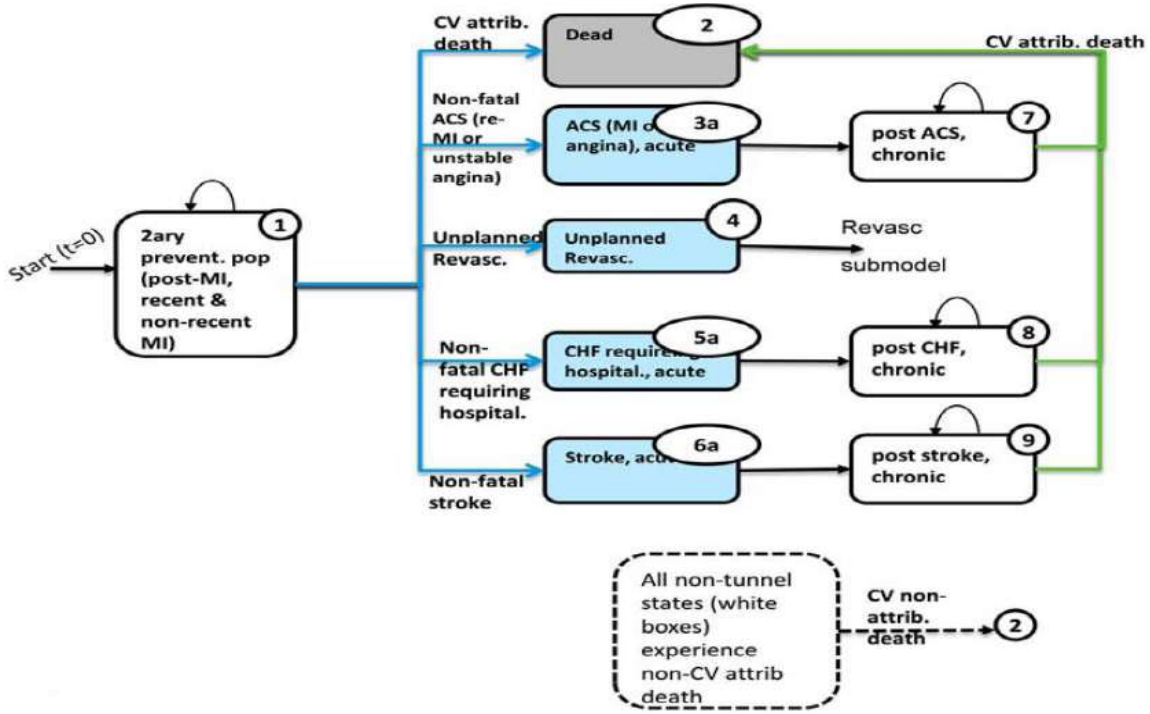
Neurologia 2018 Jan 8. pii: S0213-4853(17)30366-3

Control of the CV Risk with a Polypill

saving lifes and.....

Trinomia® and cost-effectiveness studies: The DIANA study (UK)

Study	Design	Patients	Variable
DIANA	Markov-model based cost-effectiveness analysis.	Post-AMI patients prescribed with secondary cardiovascular prevention medications.	Cardiovascular events prevented per 1000 patients, cost per life-year gained and QALYs gained.



Becerra V. et al.
BMJ Open 2015;5:e007111. doi:10.1136/bmjopen-2014-007111

Trinomia® and cost-effectiveness studies: The DIANA study (UK)

Cost-effectiveness and public health benefit of Trinomia® in the UK

Table 2 Undiscounted public health and discounted economic outcomes in base–case analysis (per 1000 population)

CV disease events and economic outcomes	Polypill	Monocomponents	Difference (% reduction/gain)
ACS events	61.06	75.31	−14.25 (−21.9)
Revascularisation (unplanned and unrelated to other CV events)	104.49	120.76	−16.26 (−15.5)
Congestive heart failure with hospitalisation	32.35	33.86	−1.51 (−5.2)
Stroke	23.20	28.90	−5.70 (−22.8)
CV death	54.62	64.19	−9.57 (−17.3)
Total LY (discounted)	6338.57	6307.69	30.88 (0.5)
Total QALY (discounted)	5278.46	5248.92	29.54 (0.6)
Drug costs (discounted)	£790 229	£326 701	£463 528 (141)
Cost of acute CV events and deaths (discounted)	£2 064 865	£2 195 567	−£130 702 (−6.0)
Cost of patient management (discounted)	£1 139 719	£1 230 203	−£90 484 (−7.4)
Total costs (discounted)	£3 994 814	£3 752 473	£242 341
ICER (discounted)	–	–	£8205 per QALY

ACS, acute coronary syndrome; CV, cardiovascular; ICER, incremental cost-effectiveness ratio; LY, life-years; QALYs, quality-adjusted life-years.

The use of Trinomia® that increase the % of fully adherent patients by 20% in patients with myocardial infarction (MI) could prevent 47.3 fatal and non-fatal CV events per 1,000 population over a 10-year period in the UK.

Becerra V. et al.
BMJ Open 2015;5:e007111. doi:10.1136/bmjopen-2014-007111

Spanish study of cost/effectiveness
The DIANA study

Original article

Usefulness of a Cardiovascular Polypill in the Treatment of Secondary Prevention Patients in Spain: A Cost-effectiveness Study

Vivencio Barrios,[a,*] Lisette Kaskens,[b] José María Castellano,[c,d,e] Juan Cosin-Sales,[f] José Emilio Ruiz,[b] Ilonka Zsolt,[b] Valentín Fuster,[c,d] and Alfredo Gracia[b]

[a] *Departamento de Cardiología Adultos, Hospital Universitario Ramón y Cajal, Madrid, Spain*
[b] *Departamento Científico, Ferrer, Barcelona, Spain*
[c] *Fundación Centro Nacional de Investigaciones Cardiovasculares Carlos III, Madrid, Spain*
[d] *Icahn School of Medicine Mount Sinai, New York, United States*
[e] *Servicio de Cardiología, HM Hospitales, Hospital Universitario HM Montepríncipe, Boadilla del Monte, Madrid, Spain*
[f] *Servicio de Cardiología, Hospital Arnau de Vilanova, Valencia, Spain*

Barrios V, et al. Rev Esp Cardiol 2017;70(1):42-49

Trinomia® and cost-effectiveness studies: The DIANA study (Spain)

Cost-effectiveness and public health benefit of Trinomia® in Spain

Cardiovascular events	Trinomia®	Monocomponents	Incremental
ACS	67.96	85.44	**-17.48**
Revascularization	112.45	132.07	**-19.62**
Congestive HF with hospitalization	33.10	34.94	**-1.84**
Stroke	25.96	32.95	**-6.99**
CV death	59.23	71.18	**-11.95**
Total non-fatal CV events	239.47	285.4	**-45.93**
Total fatal CV events	59.23	71.18	**-11.95**

The use of Trinomia® that increase the % of fully adherent patients by 20% in patients with myocardial infarction (MI) could prevent 45.93 non-fatal and 11.85 fatal CV events per 1,000 population over a 10-year period in Spain.

Barrios V, et al. Rev Esp Cardiol 2017;70(1):42-49

Trinomia® and cost-effectiveness studies: The DIANA study (Spain)

Cost-effectiveness and public healthcare system benefits of Trinomia® in Spain

Cardiovascular events	Trinomia®	Monocomponents	Incremental
Cost (€)	5,963,464.15	6,473,325.79	**-509,861.64**
Cost of drugs (€)	1,245,373.41	1,236,573.49	
Direct cost of acute events (€)	2,815,782.94	3,161,686.53	
Direct cost of chronic events (€)	1,902,307.94	2,075,065.77	
Cost for LY (€)	7,386.12	7,335.06	**51.06**
Cost for QALY (€)	6,147.32	6,098.98	**48.34**
ICER for LY (€)	-	-	**Polypill dominant**
ICER for QALY (€)	-	-	**Polypill dominant**

ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

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Trinomia® and cost-effectiveness in Worse Scenarios

Discounted Health Outcomes for the Alternative Scenarios

Scenarios/number of events avoided	Adherence to 3, 2, 1, or no monocomponents	Polypill price is double that of the base case	Summed price of monocomponents is half that of base case	Adherence to polypll and its monocomponents decreases indefintely	Adherence to polypill decreases until equaling that of the mnocomponents
ACS	-3.62	-17.48	-17.48	-20.21	-5.05
Revascularization	-3.71	-19.62	-19.62	-21.82	-5.63
CHF with hospitalization	-1.37	-1.84	-1.84	-2.09	-0.44
Stroke	-2.27	-6.99	-6.99	-8.08	-2.03
CV death	-5.43	-11.95	-11.95	-14.48	-3.46
Nonfatal CV events avoided (ACS, revasc, CHF & stroke)	-10.97	-45.93	-45.93	-52.20	-13.15

Discounted Economic Outcomes for the Alternative Scenarios

Scenarios/number of events avoided	Adherence to 3, 2, 1, or no monocomponents	Polypill price is double that of the base case	Summed price of monocomponents is half that of base case	Adherence to polypll and its monocomponents decreases indefintely	Adherence to polypill decreases until equaling that of the mnocomponents
Incremental costs (€)	-118,941.93	735,511.78	108,425.33	-590,398.33	-172,037.50
Incremental LYs	21.99	51.06	51.06	63.91	22.44
Incremental QALYs	20.03	48.34	48.34	60.19	22.44
ICER per LY gained (€)	Polypill dominant	14,404.88	2,123.49	Polypill dominant	Polypill dominant
ICER per QALY gained (€)	Polypill dominant	15,214.88	2,242.89	Polypill dominant	Polypill dominant

ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

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A roadmap for reducing cardiovascular premature mortality through secondary prevention interventions