El impacto de la Adherencia Terapeutica en prevencion secundaria

Resultados del Estudio SECURE

X Jornada Científica de la Adherencia al Tratamiento OAT

Madrid | 15 Noviembre, 2022

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Vocal del Comité Científico del Grupo OAT.

Director Científico, Fundación de Investigación HM

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GOBIERNO DE ESPAÑA MINISTERIO DE CIENCIA, INNOVACIÓN Y UNIVERSIDADES

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fundaciónhm investigación

HOSPITALES CENTRO INTEGRAL DE ENFERMEDADES CARDIOVASCULARES hm CIEC

GRUPOOAT

CENTRO NACIONAL DE INVESTIGACIONES CARDIOVASCULARES (CNIC)

Valentin Fuster | General Director

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MINISTERIO DE ECONOMÍA, INDUSTRIA Y COMPETITIVIDAD

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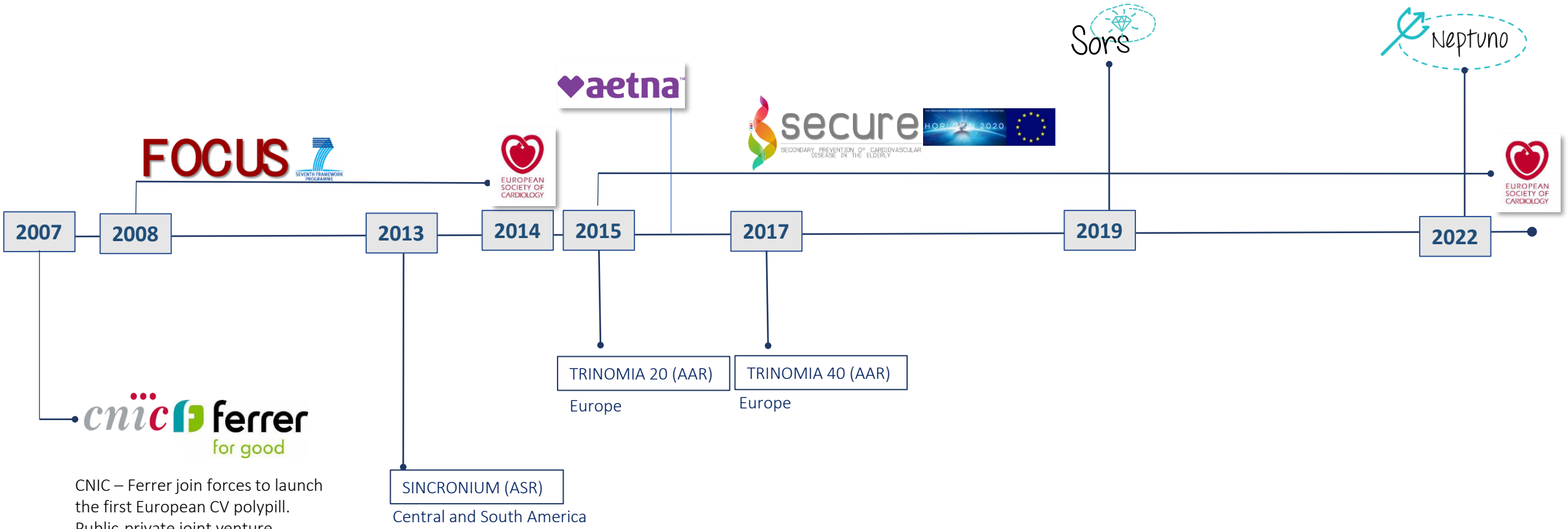
SCIENTIFIC DEVELOPMENT & MILESTONES

CNIC-Ferrer CV Polypill for Secondary Prevention

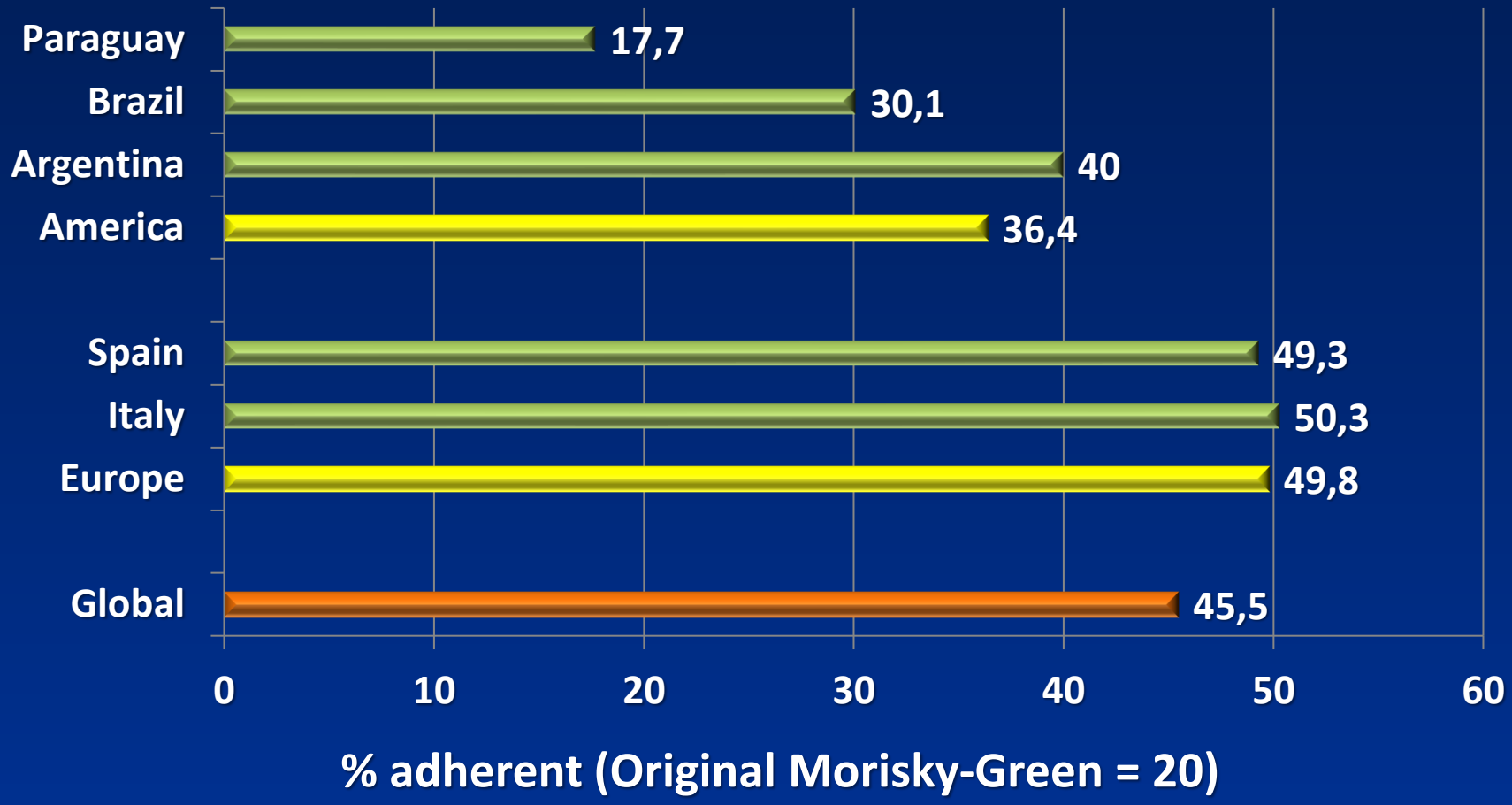


cnic ferrer for good

CNIC – Ferrer join forces to launch the first European CV polypill. Public-private joint venture. Dr. Valentin Fuster.

FOCUS Phase 1 – Results (2)

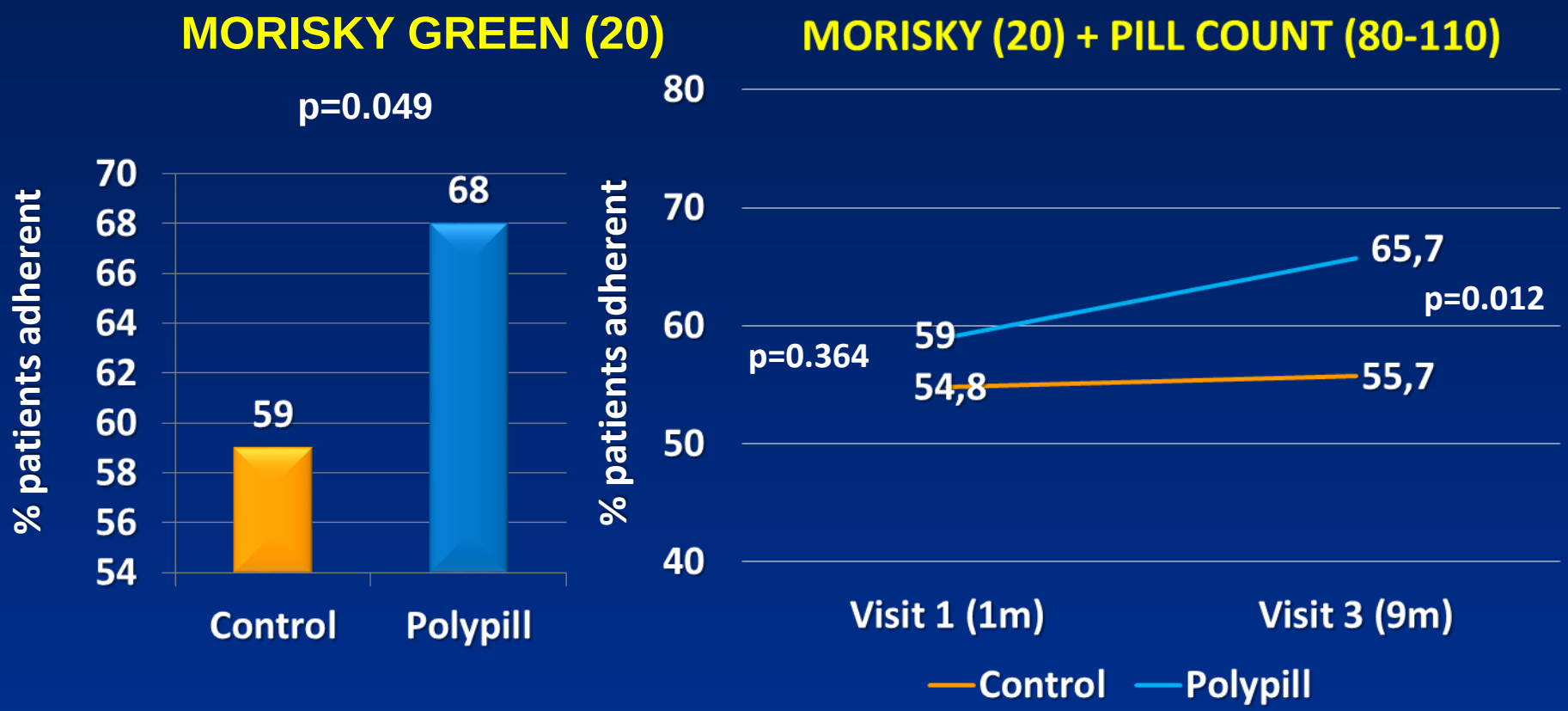
MORISKY GREEN: EVALUATION OF ADHERENCE (N=2118)



Castellano JM, Sanz G, Fuster V et al. *J Am Coll Cardiol*. 2014; 64

FOCUS Phase 2 Results

POLYPILL VS. CONTROL AT 9 MONTHS: EFFECT ON ADHERENCE



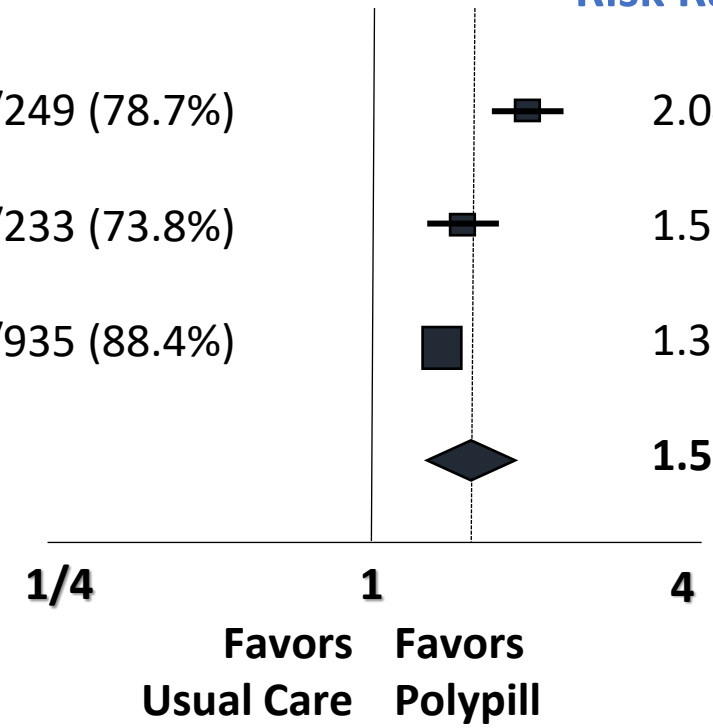
Castellano JM, Sanz G, Fuster V et al. *J Am Coll Cardiol*. 2014; 64

SPACE Program Results

A prospective, individual patient data meta-analysis of 3140 patients in six countries

UMPIRE: n= 2002, India & W. Europe
Kanyini-GAP: n=623 in Australia, half indigenous
IMPACT: n=513 in NZ, half indigenous

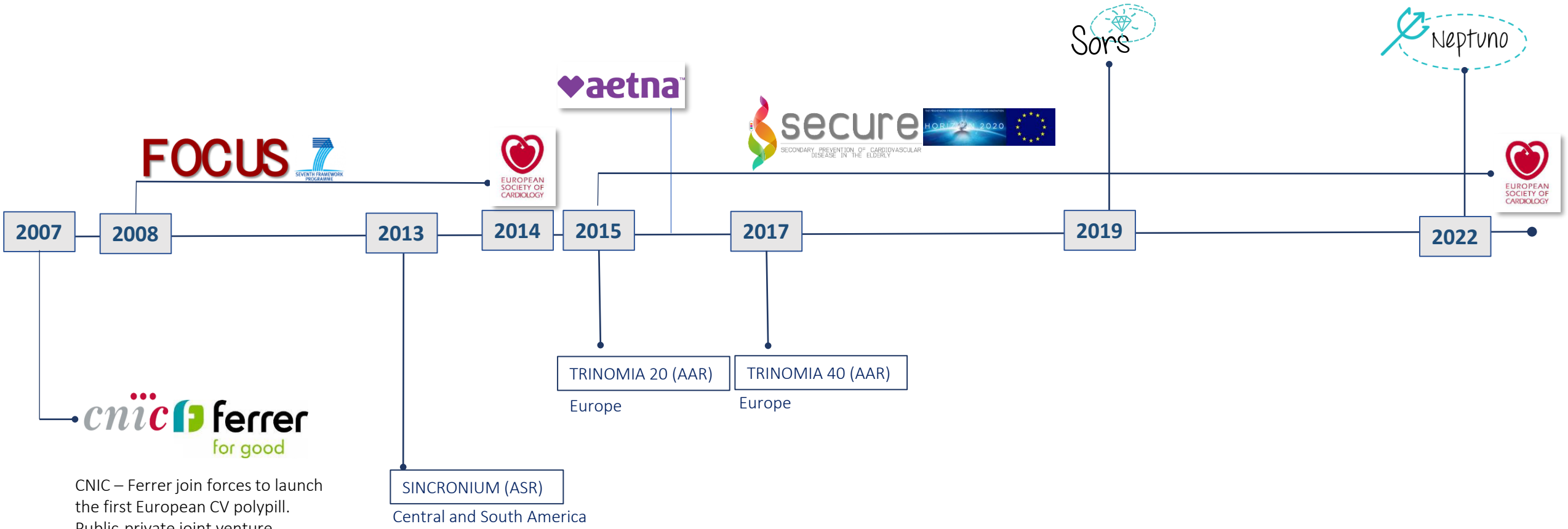
	Usual Care	Polypill	Risk Ratio (95% CI)	P value
Kanyini-GAP	96/249 (38.6%)	196/249 (78.7%)	2.04 (1.72,2.42)	<0.01
IMPACT	106/218 (48.6%)	172/233 (73.8%)	1.52 (1.30,1.78)	<0.01
UMPIRE	602/925 (65.1%)	827/935 (88.4%)	1.36 (1.29, 1.43)	<0.01
Overall			**1.58 (1.32, 1.90)**	**<0.01**



R.Webster et al. / International Journal of Cardiology 205 (2016) 147–156

SCIENTIFIC DEVELOPMENT & MILESTONES

CNIC-Ferrer CV Polypill for Secondary Prevention



cnic ferrer for good

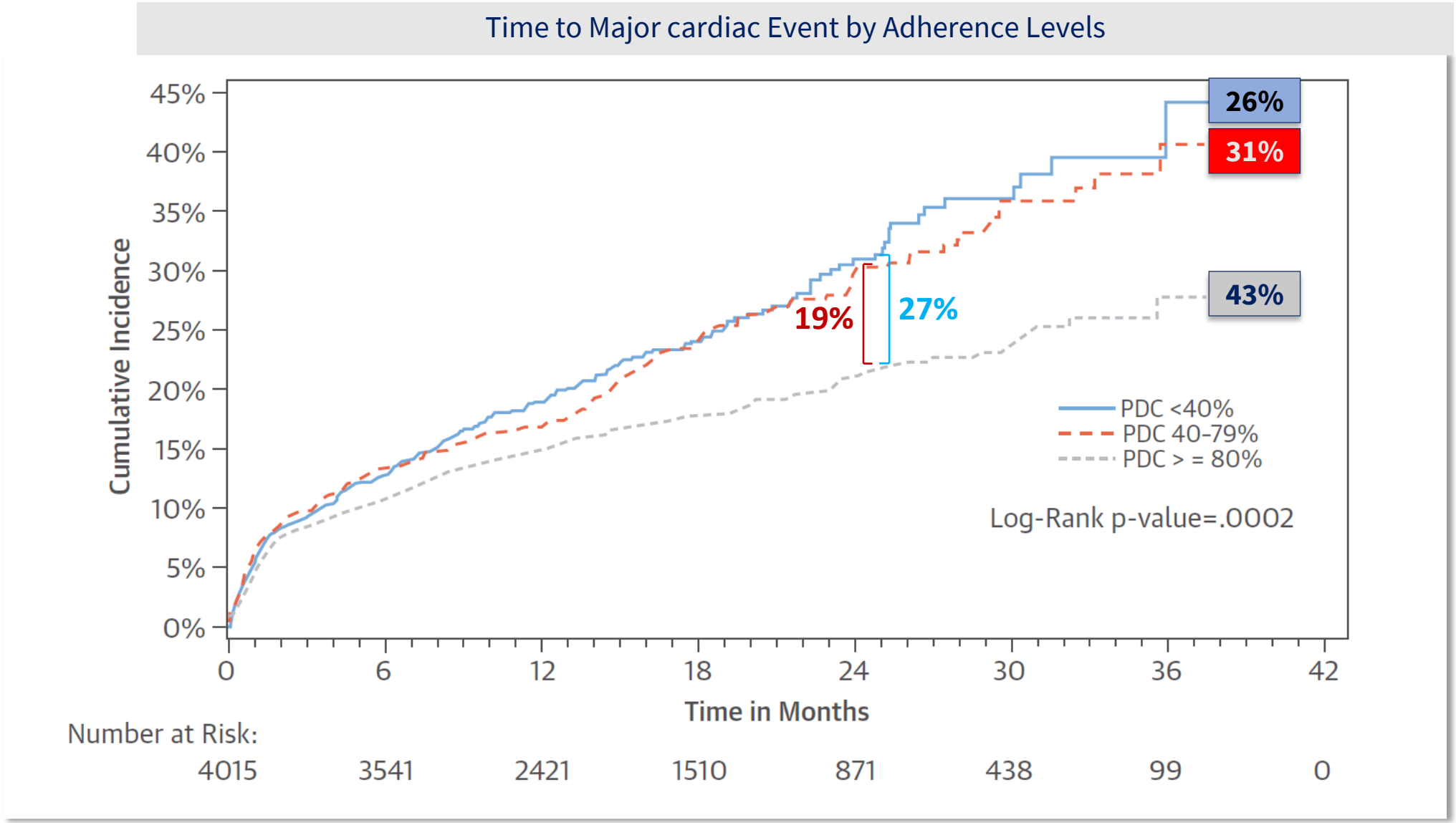
CNIC – Ferrer join forces to launch the first European CV polypill. Public-private joint venture. Dr. Valentin Fuster.

Assessing the impact of medication adherence on long-term cardiovascular outcomes

Objective: to determine the association between adherence levels and long term MACE in secondary CV prevention.

Bansilal S, Castellano JM, Fuster V et al, . *J Am Coll Cardiol*. 2016 Aug 23;68(8):789-801

Assessing the impact of medication adherence on long-term cardiovascular outcomes



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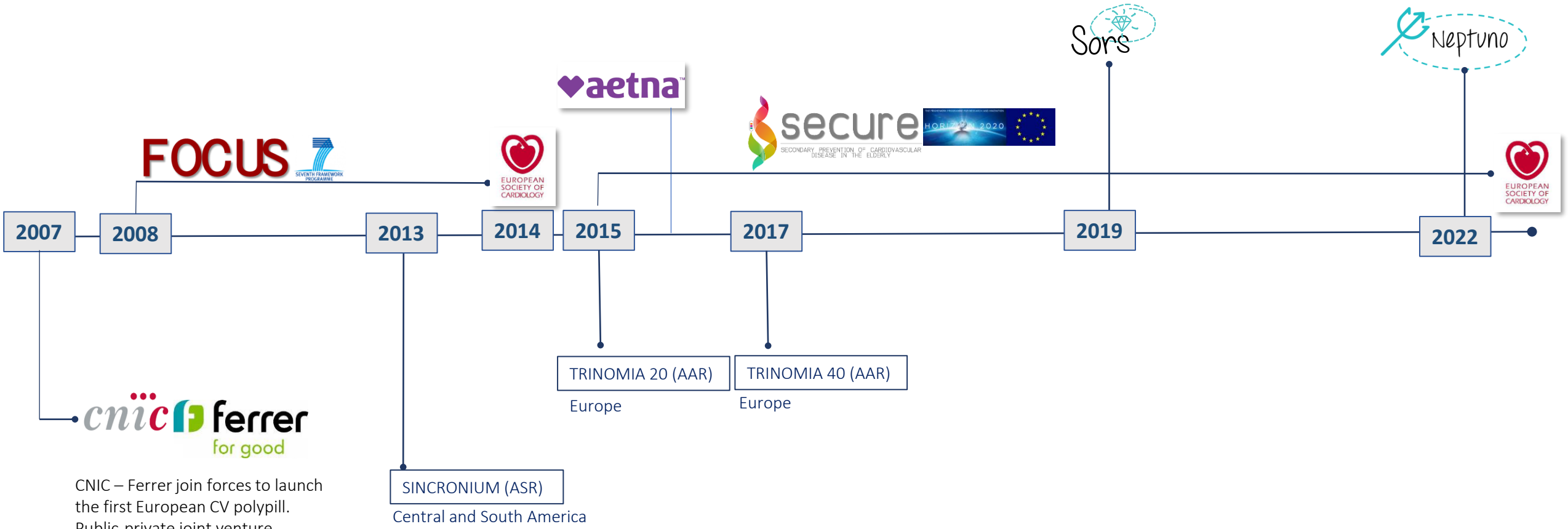
SCIENTIFIC DEVELOPMENT & MILESTONES

CNIC-Ferrer CV Polypill for Secondary Prevention

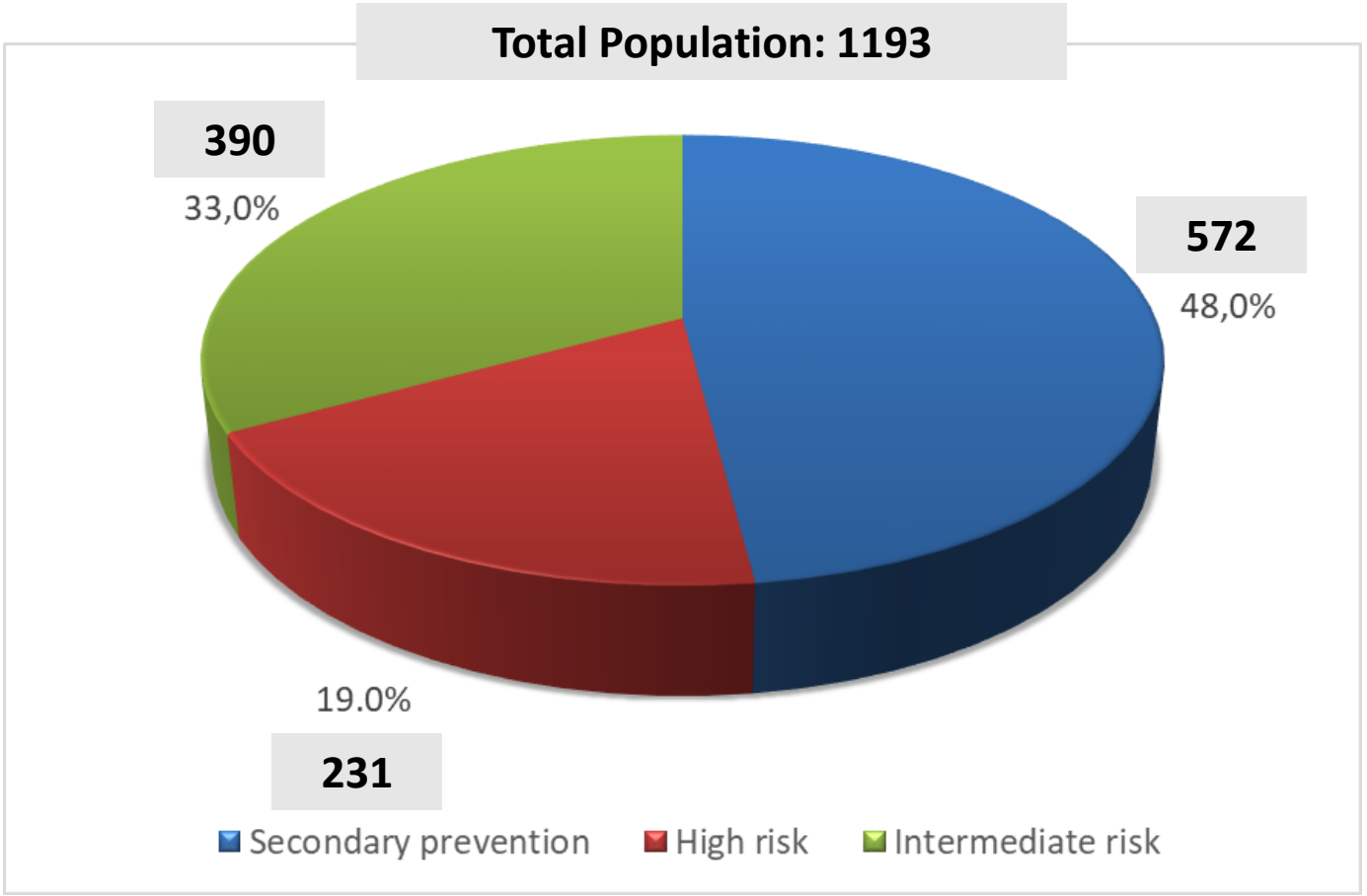


cnic ferrer for good

CNIC – Ferrer join forces to launch the first European CV polypill. Public-private joint venture. Dr. Valentin Fuster.

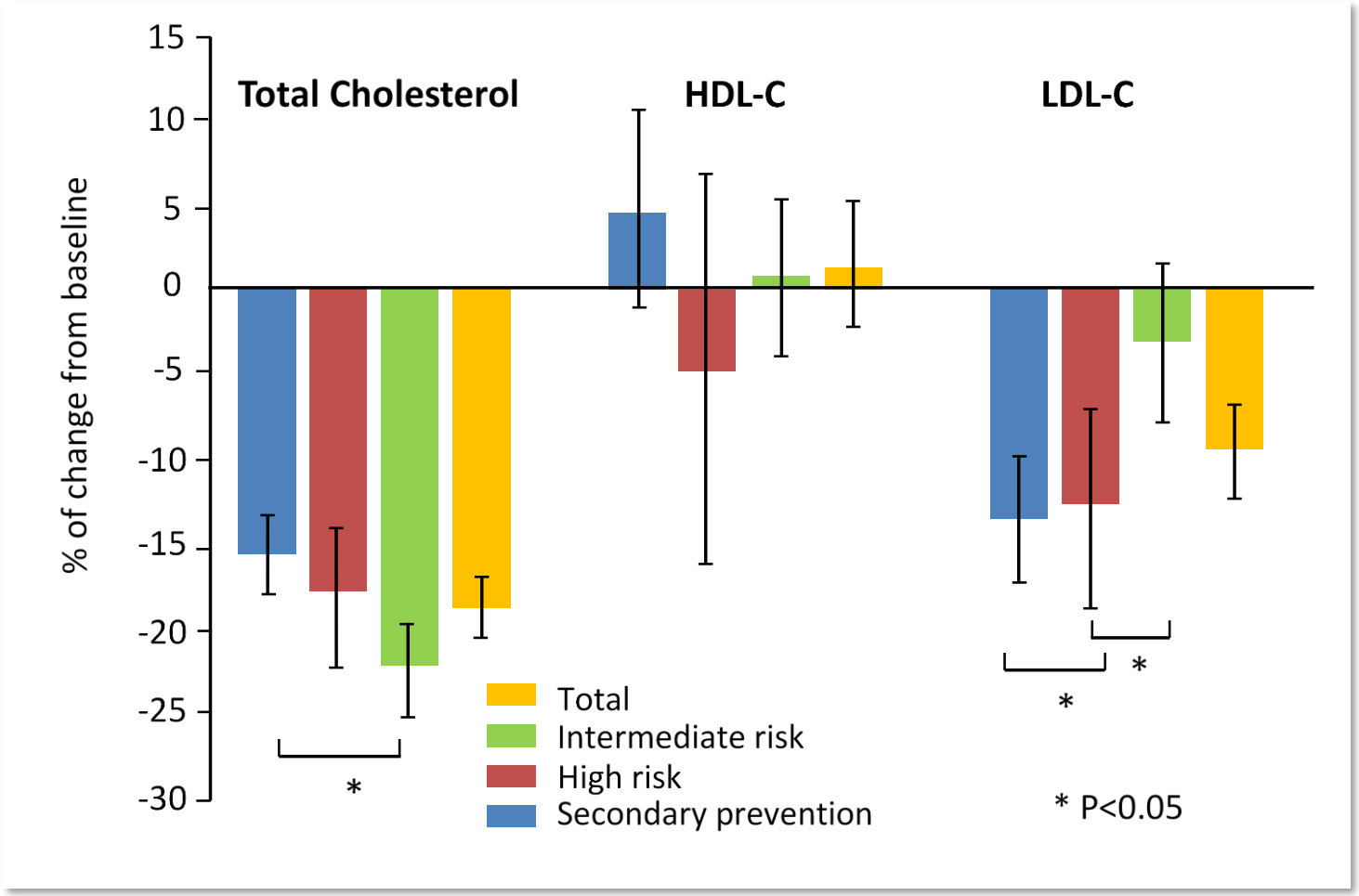
Clinical effectiveness of the Cardiovascular Polypill in a real-life setting in patients with cardiovascular risk in Mexico

Objective. To determine the **impact of a cardiovascular polypill on risk factor control** in a population of **high risk cardiovascular patients after one year follow up**.



Castellano JM, Fuster V, et al. . Archives of Medical Research 50 (2019) 31-40.

Clinical effectiveness of the Cardiovascular Polypill in a real-life setting in patients with cardiovascular risk in Mexico



LDL.C:
-24.9 mg/dL
(18.7%)

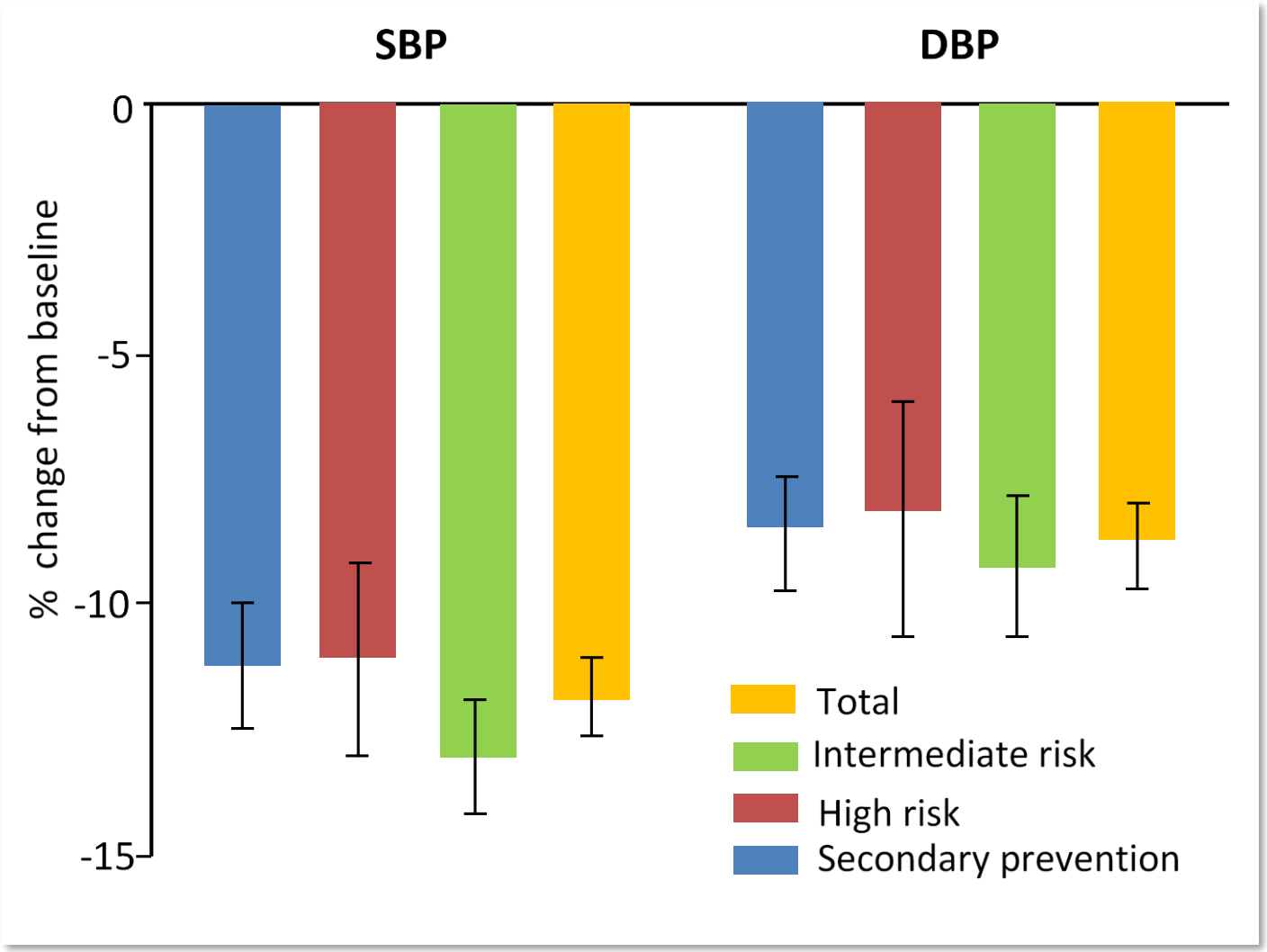
Total C:
-59.3mg/dL
(24.3%)

TG:
-72.7mg/dL
30.7%

Sors

Castellano JM, Fuster V, et al. . Archives of Medical Research 50 (2019) 31-40.

Clinical effectiveness of the Cardiovascular Polypill in a real-life setting in patients with cardiovascular risk in Mexico



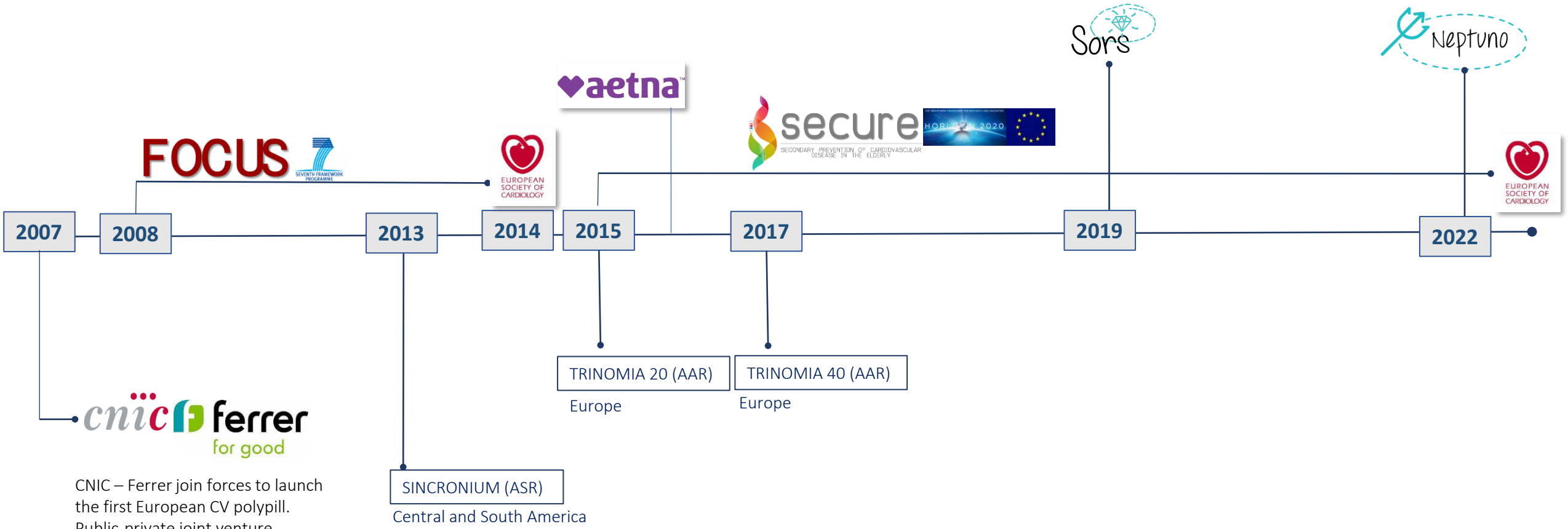
SBP
-18.9mmHg
(12.8%)

DBP
-8.7mmHg
9.7%

Castellano JM, Fuster V, et al. . Archives of Medical Research 50 (2019) 31-40.

SCIENTIFIC DEVELOPMENT & MILESTONES

CNIC-Ferrer CV Polypill for Secondary Prevention

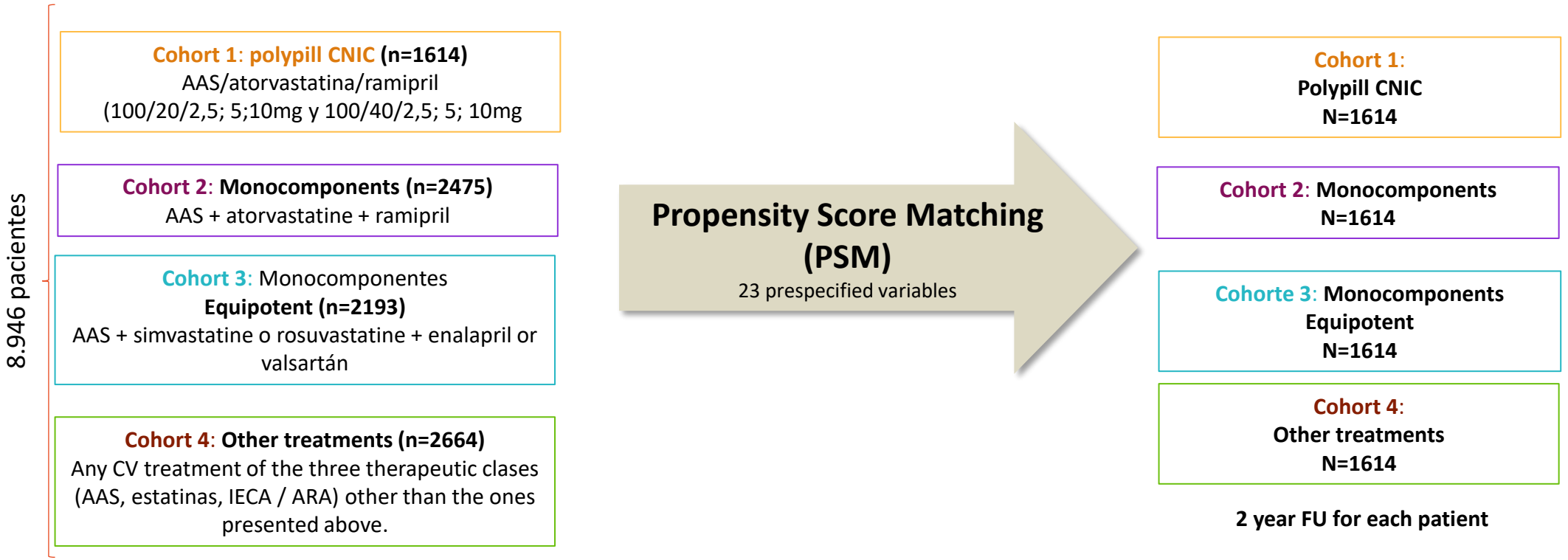


cnic ferrer for good

CNIC – Ferrer join forces to launch the first European CV polypill. Public-private joint venture. Dr. Valentin Fuster.

Effectiveness of the CNIC Polypill in patients with previous cardiovascular events in hospitals and primary care centers in Spain: NEPTUNO study

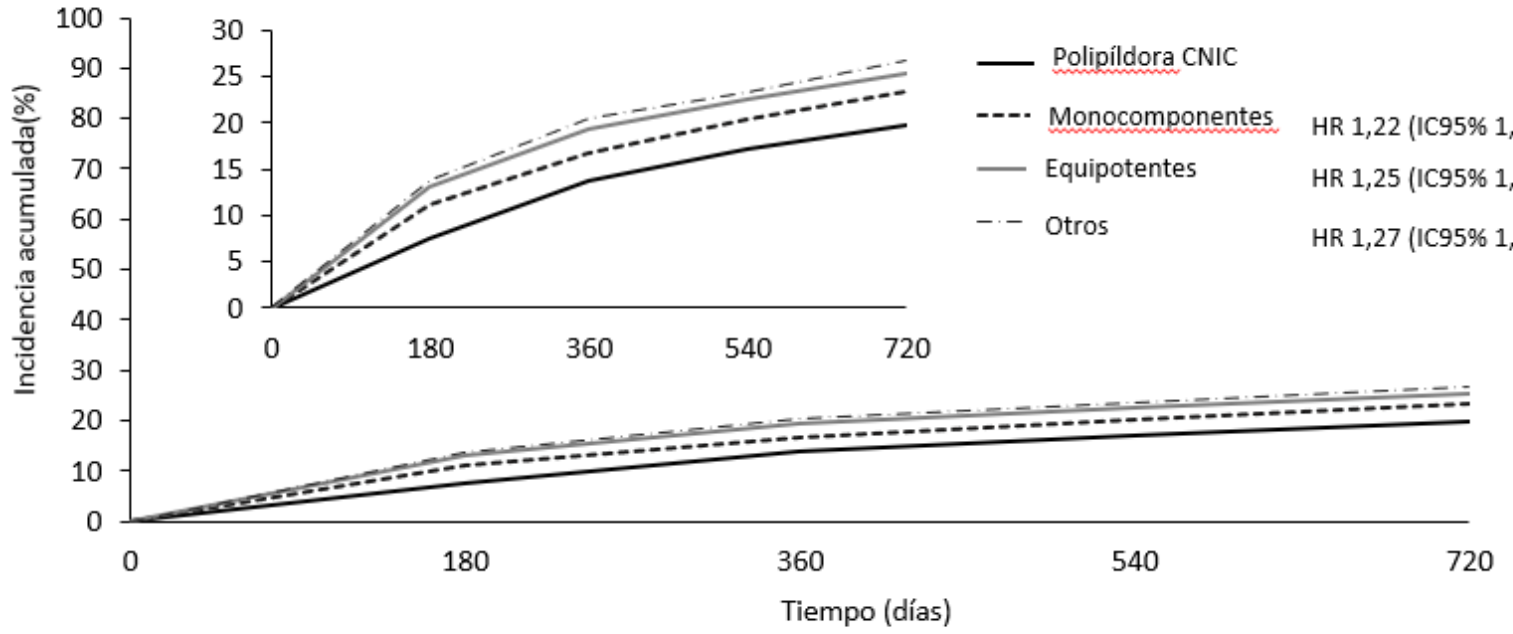
Objective: To evaluate the effectiveness of a cardiovascular polypill including aspirin, ramipril and atorvastatin (CNIC-Polypill), on the incidence of recurrent major cardiovascular events (MACE) and risk factor control in patients with established atherosclerotic cardiovascular disease (ASCVD) vs different pharmacological therapeutic strategies.



González-Juanatey JR, Cordero A, Castellano JM, Masana L, Dalmau R, Ruiz E, Sicras-Mainar A, Fuster V. The CNIC-Polypill reduces recurrent major cardiovascular events in real-life secondary prevention patients in Spain: The NEPTUNO study. Int J Cardiol. 2022 May 12:S0167-5273(22)00666-0. doi: 10.1016/j.ijcard.2022.05.015. Epub ahead of print. PMID: 35569611

Effectiveness of the CNIC Polypill in patients with previous cardiovascular events in hospitals and primary care centers in Spain: NEPTUNO study

Cumulative Incidence of MACE after 2 year follow up



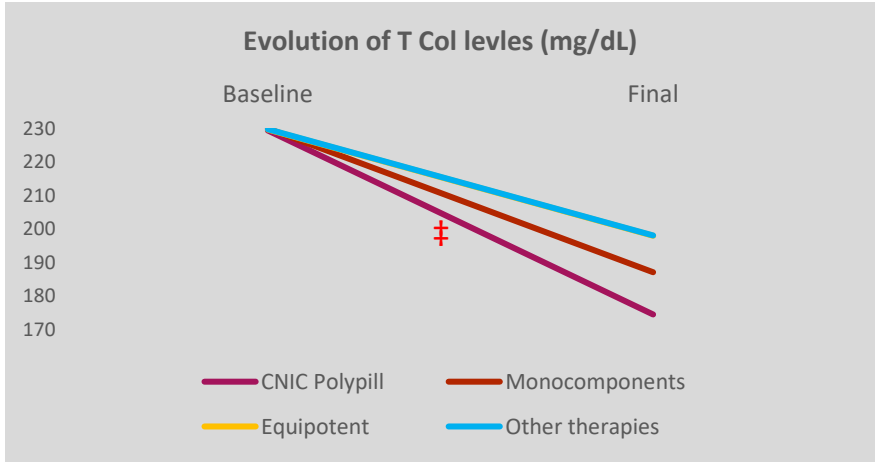
No. en riesgo	Día 0	Día 180	Día 360	Día 540	Día 720
Polipíldora CV	1614	1491	1393	1336	1294
Monocomponentes	1614	1434	1344	1285	1236
Equipotentes	1614	1404	1302	1285	1203
Otros	1614	1391	1282	1236	1182

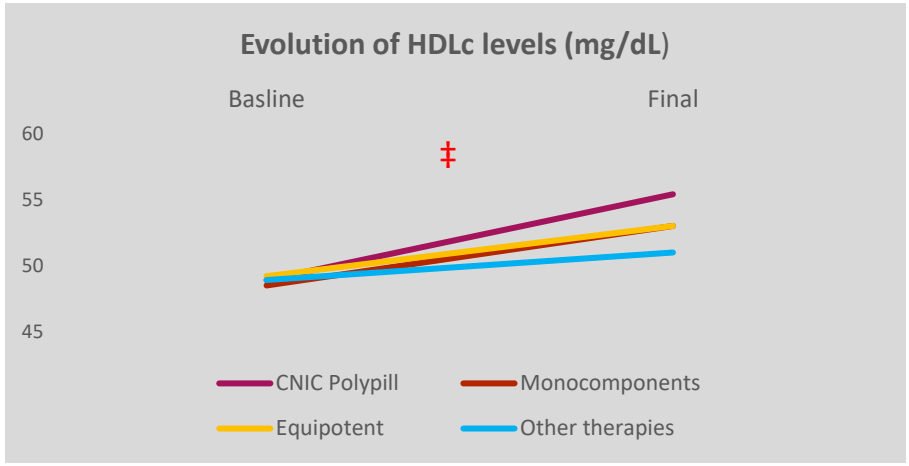
HR: Hazard Ratio. IC: intervalo de confianza. p: significación estadística

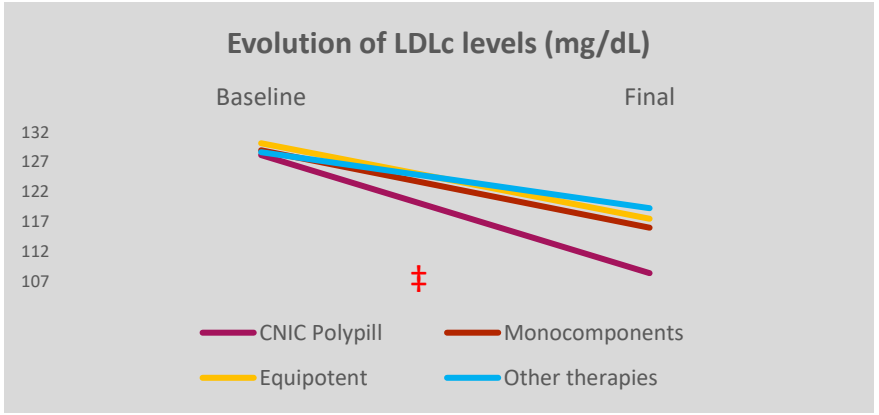
González-Juanatey JR, Cordero A, Castellano JM, Masana L, Dalmau R, Ruiz E, Sicras-Mainar A, Fuster V. The CNIC-Polypill reduces recurrent major cardiovascular events in real-life secondary prevention patients in Spain: The NEPTUNO study. Int J Cardiol. 2022 May 12:S0167-5273(22)00666-0. doi: 10.1016/j.ijcard.2022.05.015. Epub ahead of print. PMID: 35569611

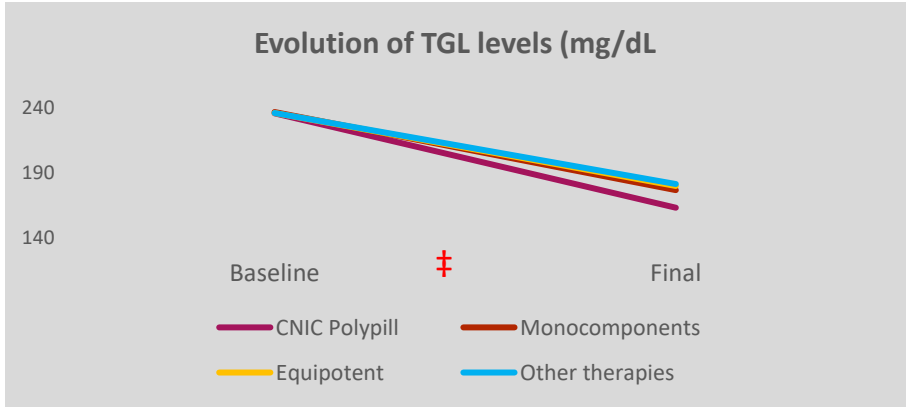
Effectiveness of the CNIC Polypill in patients with previous cardiovascular events in hospitals and primary care centers in Spain: NEPTUNO study

Evolution of the lipidic parameters in the 2-year follow-up period.







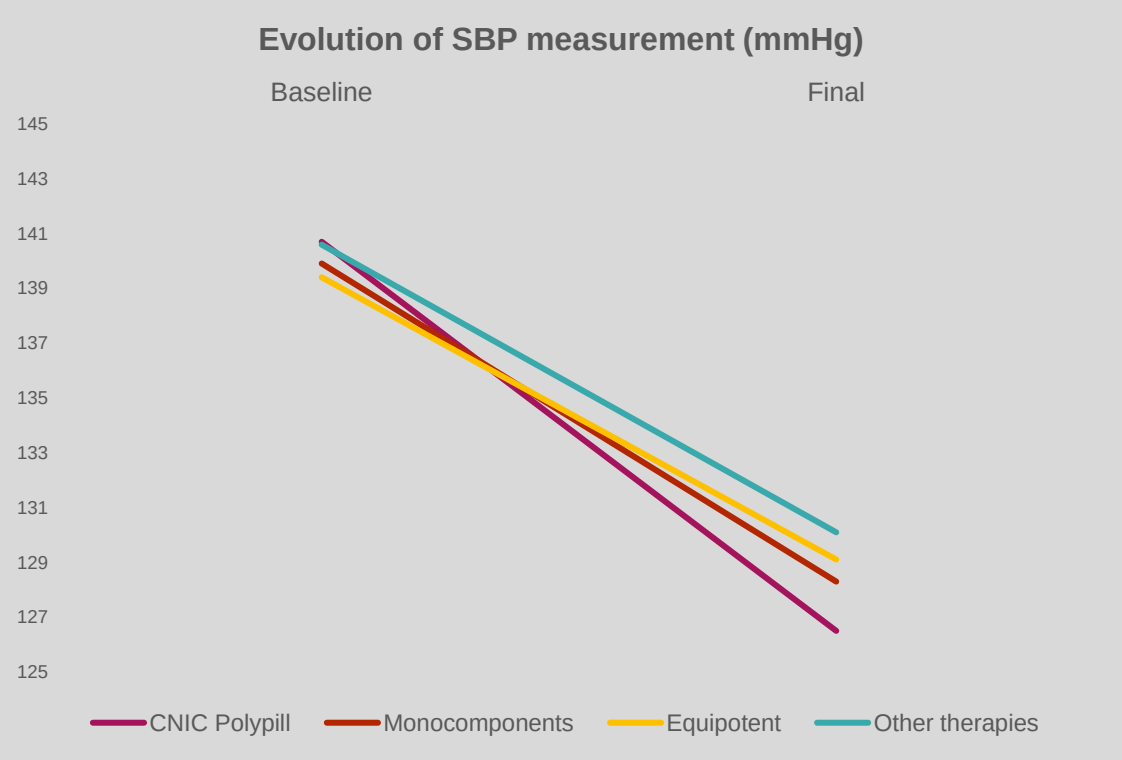


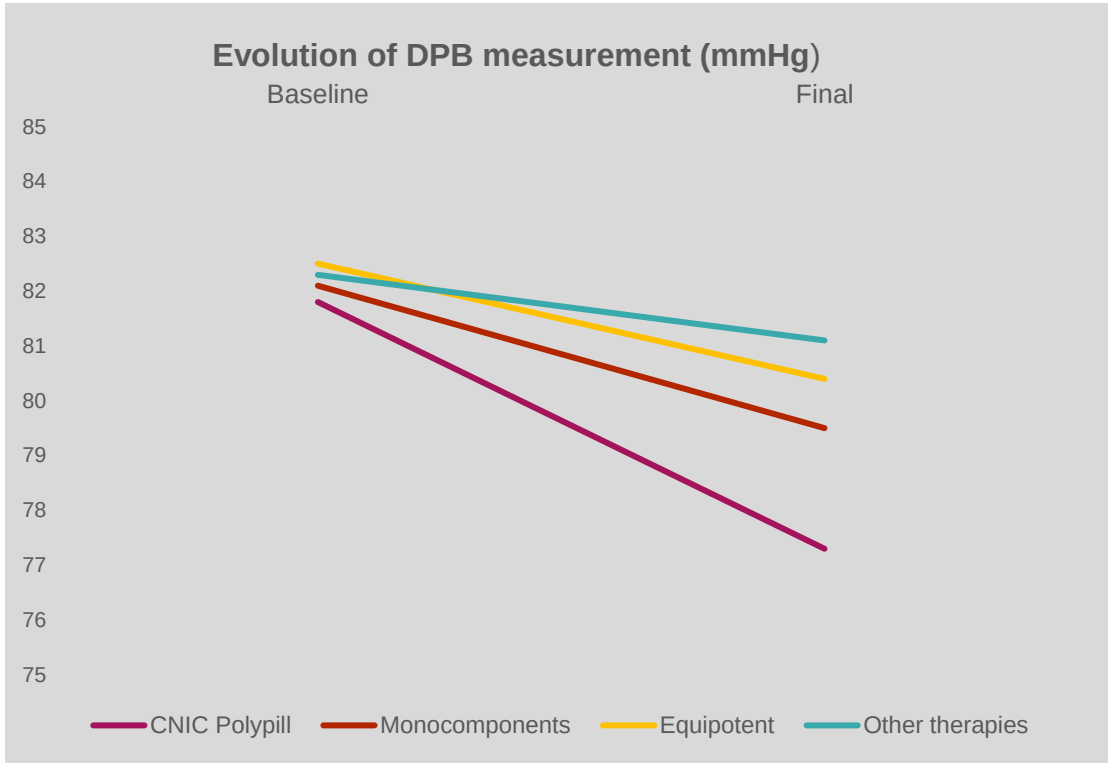
‡p<0.001 CNIC Polypill cohort vs control cohorts

González-Juanatey JR, Cordero A, Castellano JM, Masana L, Dalmau R, Ruiz E, Sicras-Mainar A, Fuster V. The CNIC-Polypill reduces recurrent major cardiovascular events in real-life secondary prevention patients in Spain: The NEPTUNO study. Int J Cardiol. 2022 May 12:S0167-5273(22)00666-0. doi: 10.1016/j.ijcard.2022.05.015. Epub ahead of print. PMID: 35569611

Effectiveness of the CNIC Polypill in patients with previous cardiovascular events in hospitals and primary care centers in Spain: NEPTUNO study

Evolution of the BP in the 2-year follow-up period.





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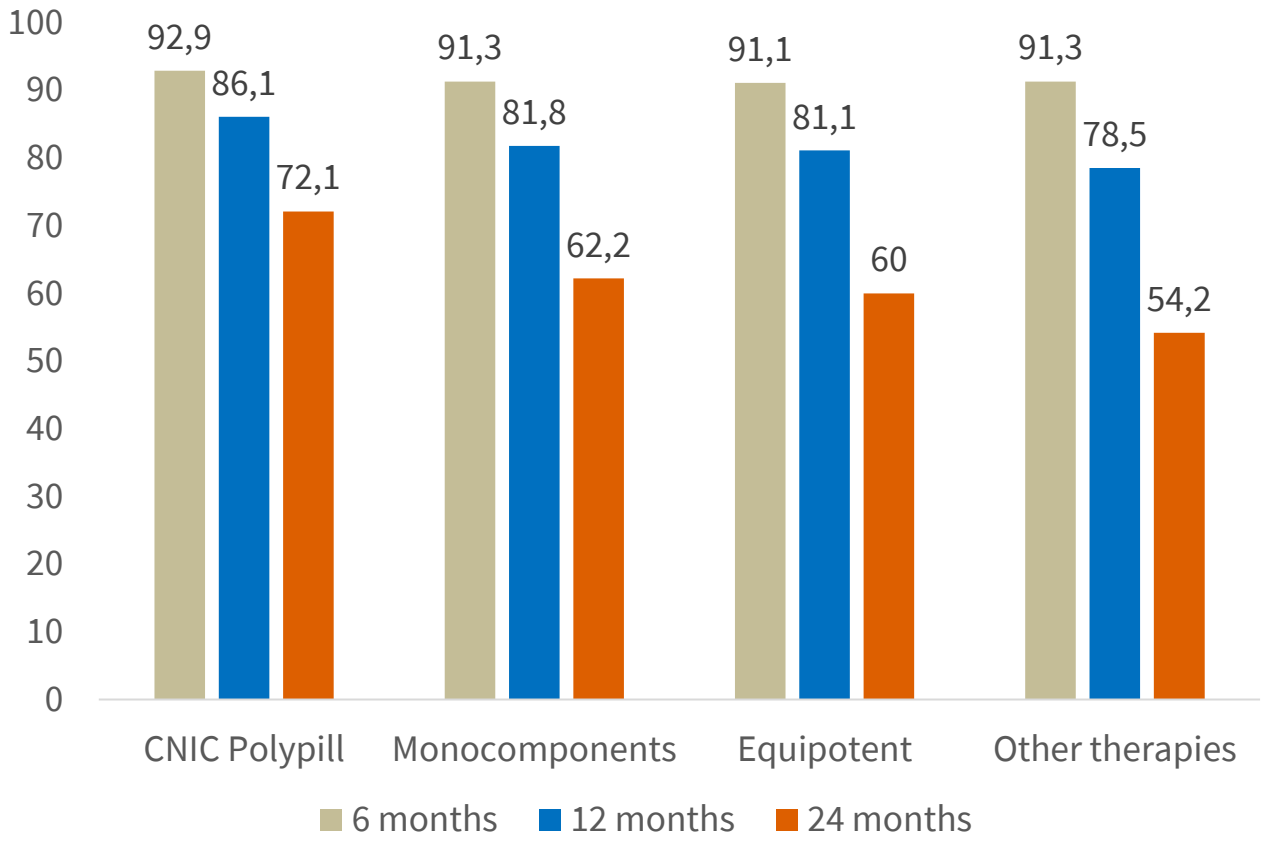
Effectiveness of the CNIC Polypill in patients with previous cardiovascular events in hospitals and primary care centers in Spain: NEPTUNO study

Evolution of treatment persistance



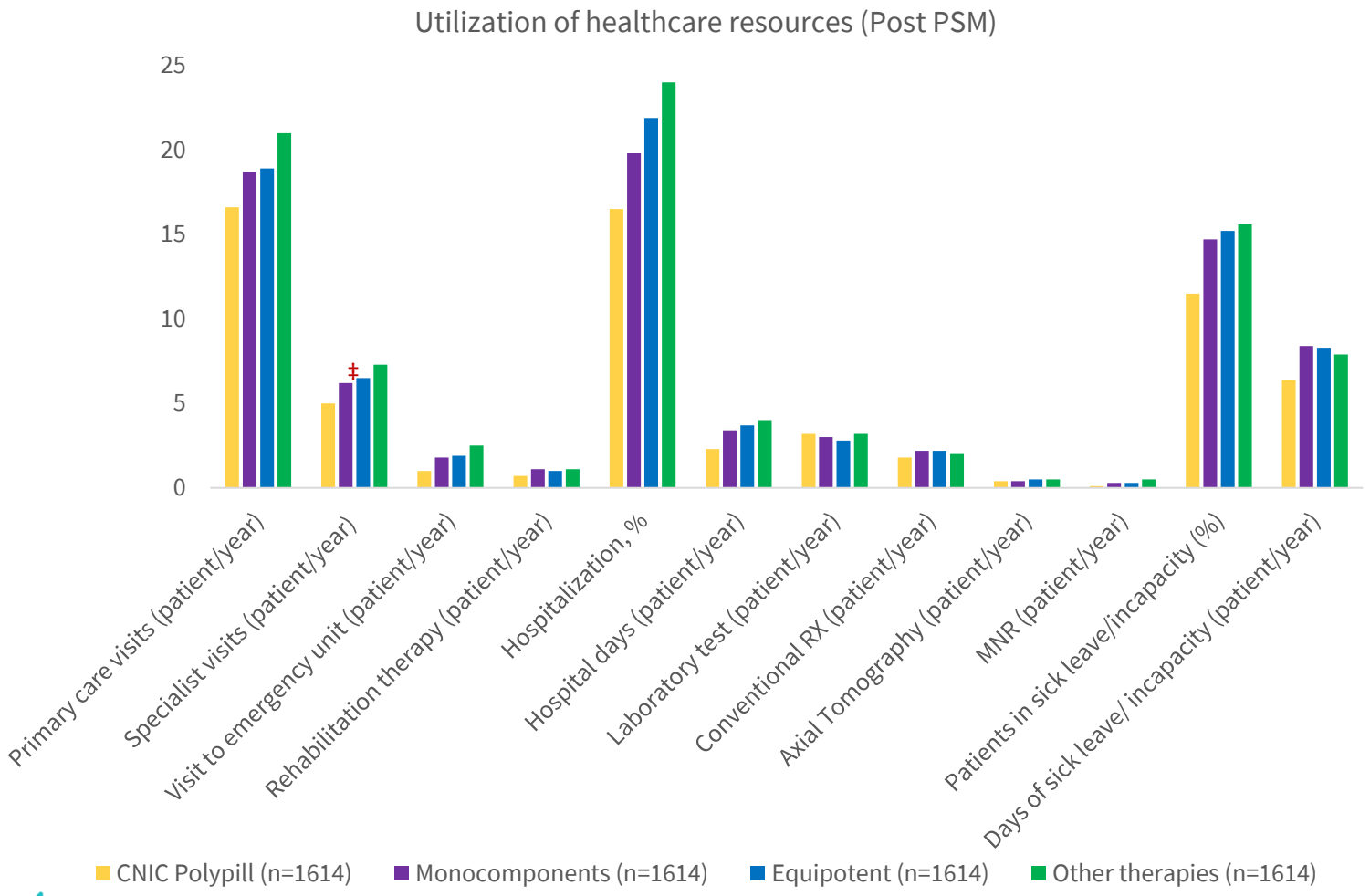
Greater long-term persistence to treatment after 2 years with the CNIC-Polypill

Persistence to treatment:
CNIC Polypill: 72.1% (95% CI: 69.9 - 74.3)
Monocomponents: 62.2% (95% CI: 58.8 - 64.6*
Equipotent: 60.0% (95% CI: 59 . 6 - 64.4) *
Other treatments: 54.2% (95% CI: 51.8 - 56.6)*

González-Juanatey JR, Cordero A, Castellano JM, Masana L, Dalmau R, Ruiz E, Sicras-Mainar A, Fuster V. The CNIC-Polypill reduces recurrent major cardiovascular events in real-life secondary prevention patients in Spain: The NEPTUNO study. Int J Cardiol. 2022 May 12:S0167-5273(22)00666-0. doi: 10.1016/j.ijcard.2022.05.015. Epub ahead of print. PMID: 35569611

Effectiveness of the CNIC Polypill in patients with previous cardiovascular events in hospitals and primary care centers in Spain: NEPTUNO study

Use of Healthcare Resources



Pharmacoeconomic data support the sustainability and scalability of the CNIC Polypill strategy

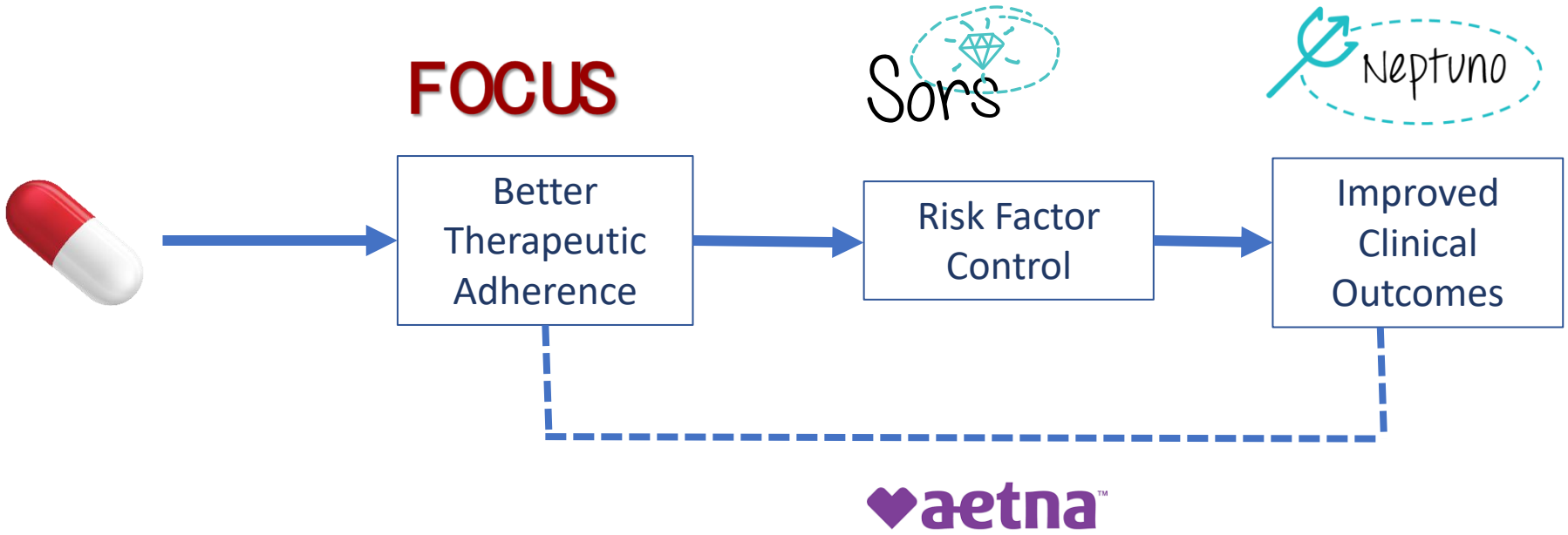
The CNIC Polypill compared with the control cohorts (monocomponents, equipotent and other therapies) showed a **significant reduction in the use of healthcare resources.**

The total **cost per patient** with the CNIC Polypill compared to the control cohorts, corrected for covariates, **was significantly lower** (€ 4668 vs € 5587. € 5682 and € 6016; p <0.001).

Neptuno

González-Juanatey JR, Cordero A, Castellano JM, Masana L, Dalmau R, Ruiz E, Sicras-Mainar A, Fuster V. The CNIC-Polypill reduces recurrent major cardiovascular events in real-life secondary prevention patients in Spain: The NEPTUNO study. Int J Cardiol. 2022 May 12:S0167-5273(22)00666-0. doi: 10.1016/j.ijcard.2022.05.015. Epub ahead of print. PMID: 35569611

SECURE RATIONALE



SECURE | Consortium

2499 patients recruited in 113 centers across 7 European Countries

Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) | **SPAIN** |Valentin Fuster, MD, PhD (PI) Jose M. Castellano MD, PhD (Co-PI)

Istituto di Ricerche Farmacologiche "Mario Negri" (IRFMN) | **ITALY** |Maria Carla Roncaglioni, Biol Sci Dr

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General University Hospital in Prague| **CZECH REPUBLIC** |Aleš Linhart, MD, PhD

Fundación Investigación Biomédica Hospital Clínico San Carlos | **SPAIN** |Antonio Fernandez Ortiz MD, PhD

London School of Hygiene and Tropical Medicine (LSHTM) | **UK** | Stuart Pocock, BSc MSc PhD

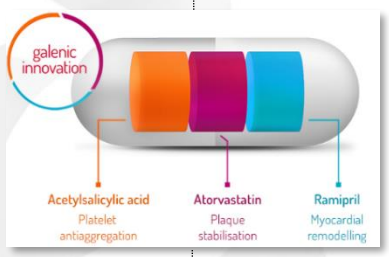
ferrer

Study Overview

n=2500
Post MI >65

+ at least one

a. Documented DM
b. Mild to moderate CKD
c. Prior MI
d. Prior coronary revascularization
e. Prior stroke
f. Age ≥ 75 years



Median FU
3 years

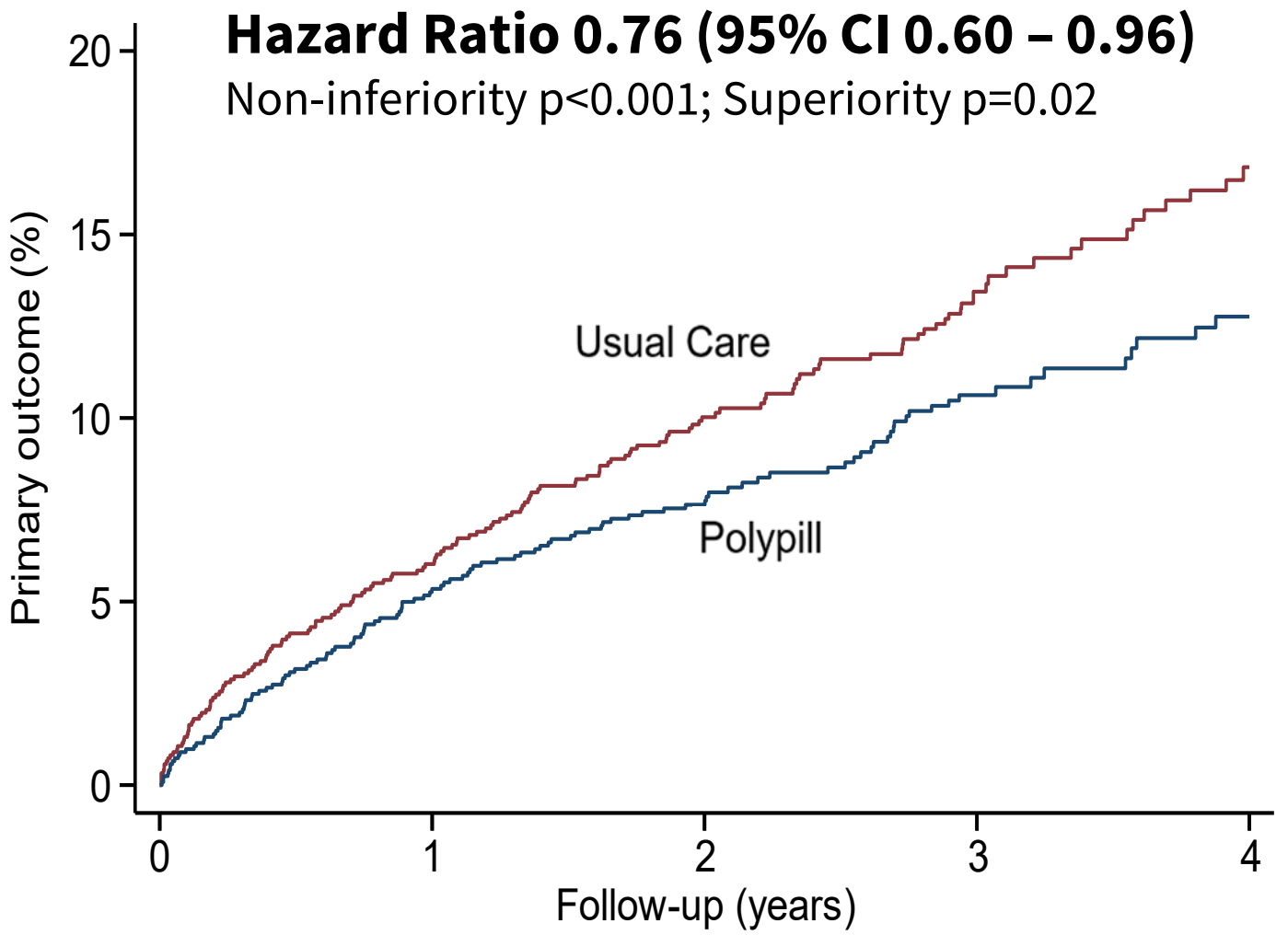
MACE
Cardiovascular death
Nonfatal myocardial infarction
Nonfatal ischemic stroke
Urgent revascularization

The **primary composite endpoint** was cardiovascular death, MI, stroke, or urgent revascularization.

The **key secondary endpoint** was the composite of cardiovascular death, nonfatal MI, or stroke.

Primary Outcome

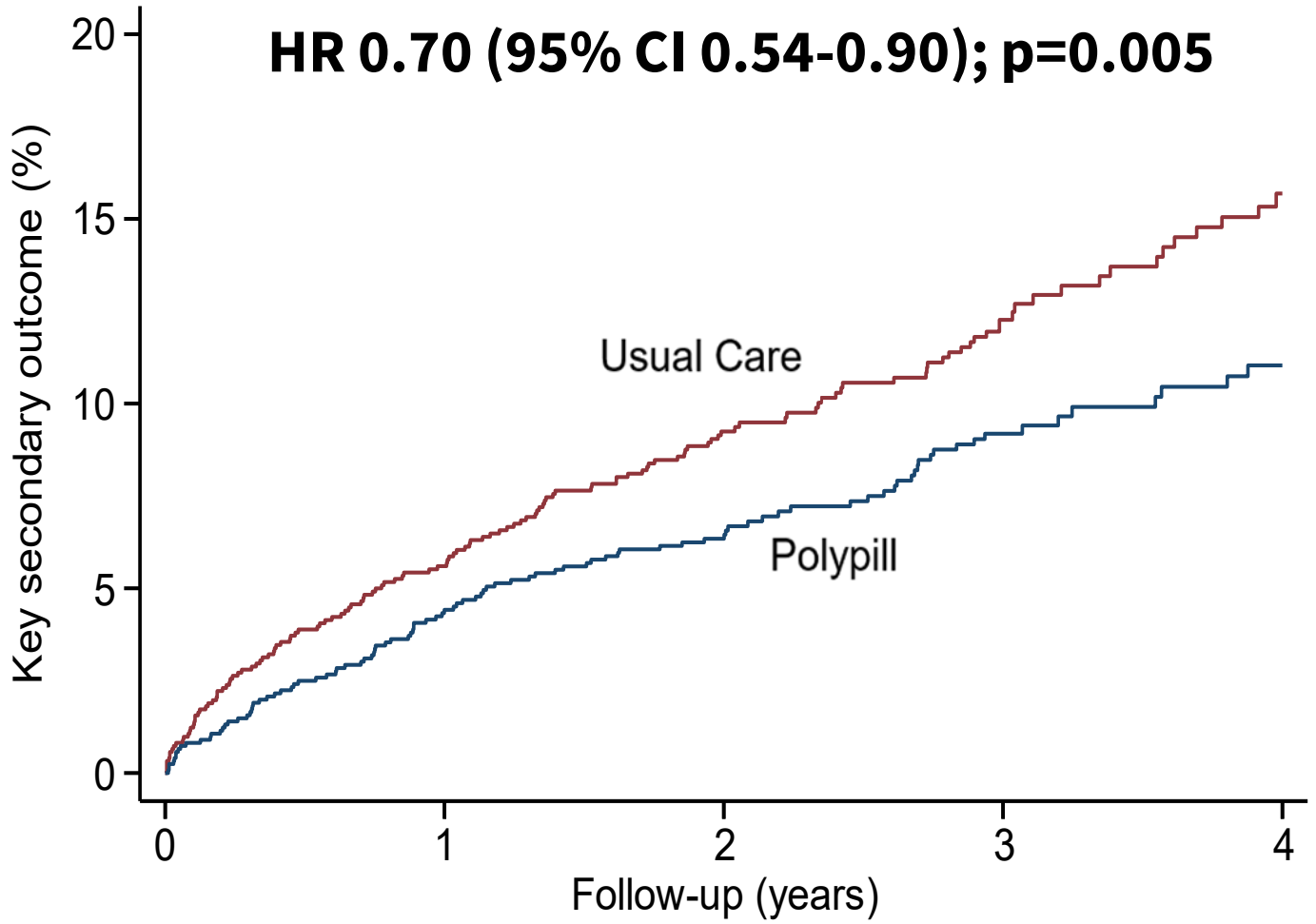
Composite of CV Death, MI, Stroke, and Urgent



Number at risk					
Usual Care	1229	1075	852	518	196
Polypill	1237	1064	848	511	192

Key Secondary Outcome

Composite of CV Death, MI, Stroke



Number at risk

Usual Care	1229	1079	857	522	196
Polypill	1237	1074	859	521	201

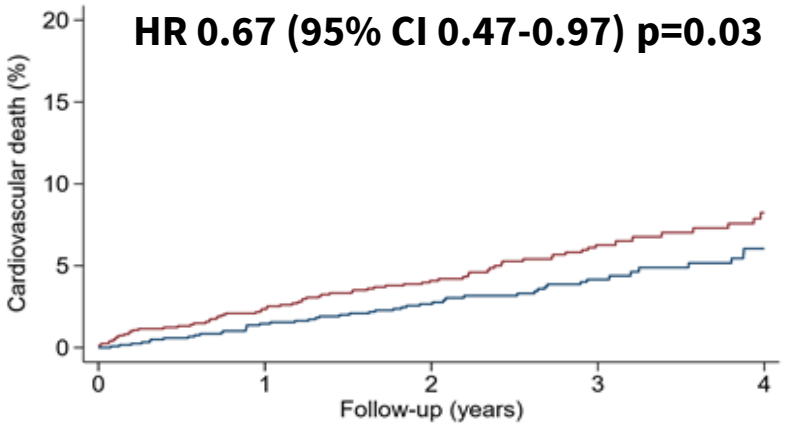
Primary and Secondary Outcomes ITT Analysis

	Polypill (n=1258)		Usual Care (n=1241)		HR (95% CI)	P
	N	%	N	%		
Primary outcome	118	9.5	156	12.7	0.76 (0.60, 0.96)	Non-inferiority p<0.001 Superiority p=0.02
Key secondary outcome						
Composite of CV death, type 1 MI or ischemic stroke	101	8.2	144	11.7	0.70 (0.54, 0.90)	0.005
Components of primary outcome						
CV death	48	3.9	71	5.8	0.67 (0.47, 0.97)	0.03
Type 1 MI	44	3.6	62	5.0	0.71 (0.48, 1.05)	0.09
Ischemic stroke	19	1.5	27	2.2	0.70 (0.39, 1.26)	0.24
Urgent revascularization	27	2.2	28	2.3	0.96 (0.57, 1.63)	0.88
Safety						
All-cause death	115	9.3	117	9.5	0.97 (0.75, 1.25)	0.79
Non-CV death	67	5.4	46	3.7	1.42 (0.97, 2.07)	0.07

Individual Components of the Primary Outcome

Cardiovascular Death

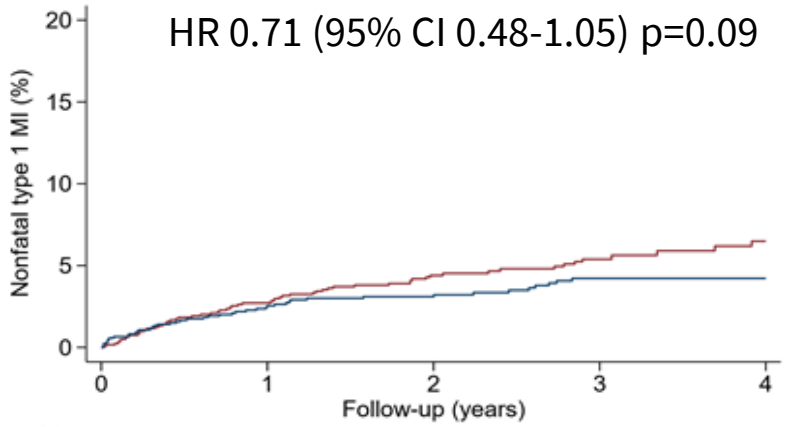
HR 0.67 (95% CI 0.47-0.97) p=0.03



Number at risk				
Usual Care 1229	1115	908	557	210
Polypill 1237	1108	890	550	209

Nonfatal type 1 MI

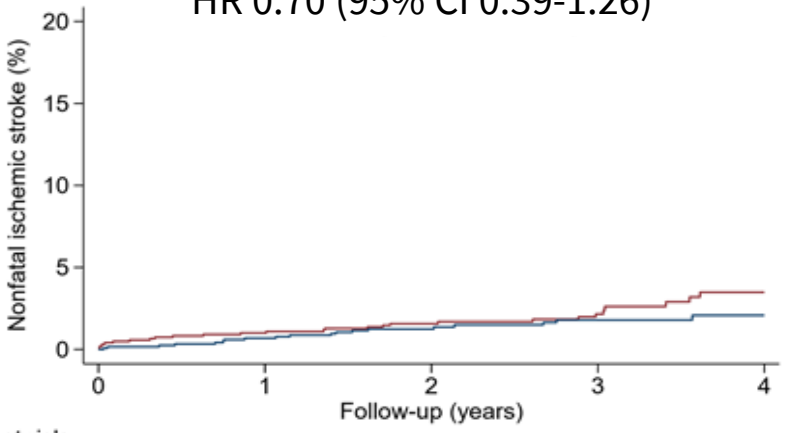
HR 0.71 (95% CI 0.48-1.05) p=0.09



Number at risk				
Usual Care 1229	1090	873	533	204
Polypill 1237	1079	867	530	204

Non Fatal Ischemic Stroke

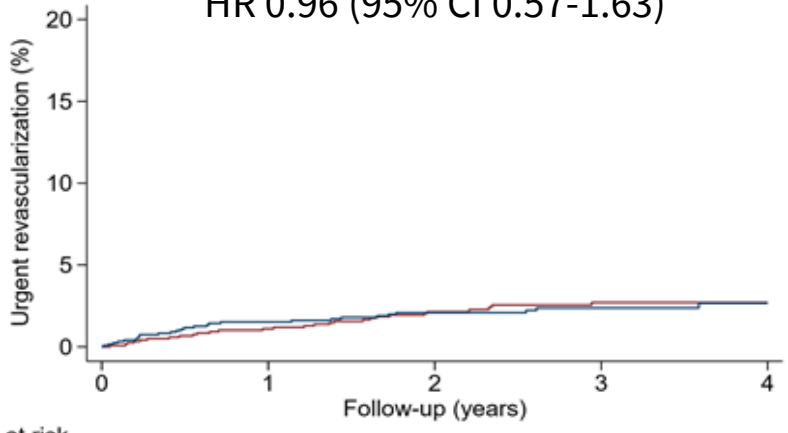
HR 0.70 (95% CI 0.39-1.26)



Number at risk				
Usual Care 1229	1104	892	546	201
Polypill 1237	1102	881	540	206

Urgent Reavascularization

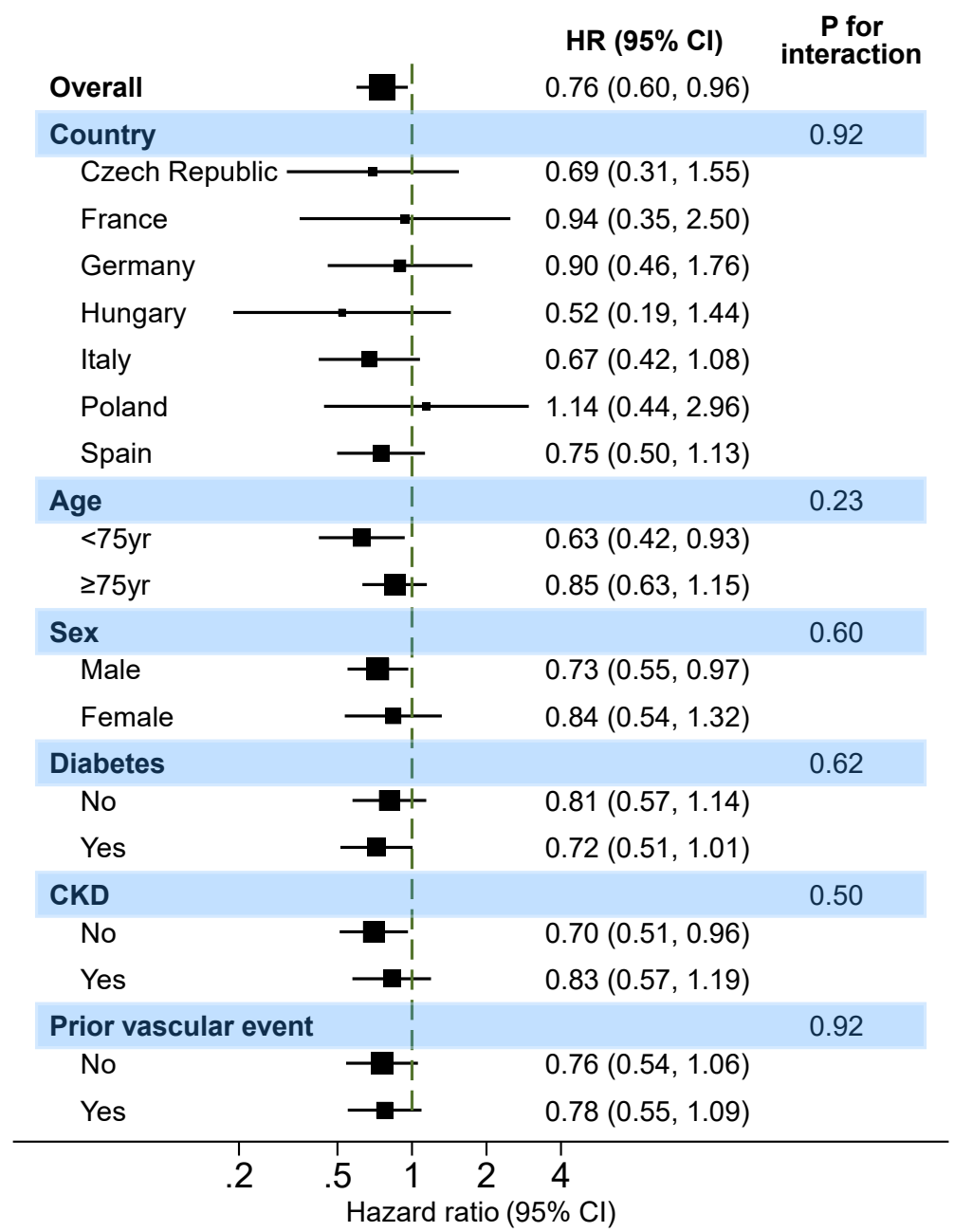
HR 0.96 (95% CI 0.57-1.63)



Number at risk				
Usual Care 1229	1106	895	547	210
Polypill 1237	1091	872	535	200

Usual Care — Polypill

Primary Outcome in Prespecified Subgroups



Secondary Endpoints | Adherence

Adherence was measured using the Morisky Medication Adherence Scale which categorizes patients to low (< 6 points), medium (6-7 points), or high levels of adherence (8 points)

	Adherence At 6 Months			*Adherence At 24 Months*		
	Low (<6)	**Medium (6 to <8)**	**High (8)**	**Low (<6)**	**Medium (6 to <8)**	**High (8)**
Polypill	5.5	23.9	70.6	4.2	21.7	74.1
Usual Care	9.5	27.8	62.8	6.9	29.8	63.2
Common OR (95% CI)	1.46 (1.22, 1.74) $p < 0.001$			1.67 (1.36, 2.04) $p < 0.001$		

Secondary Endpoints | SBP, DBP, LDL

	Polypill			Usual Care		
	N	Mean (SD)	Change from baseline, mean (SD)	N	Mean (SD)	Change from baseline, mean (SD)
SBP, mmHg						
Baseline	1235	129.1 (17.6)		1226	129.1 (17.9)	
6 months	1067		5.2 (21.3)	1053		5.7 (22.1)
12 months	986		7.5 (22.5)	972		5.7 (22.4)
24 months	882		6.3 (21.9)	830		6.3 (22.1)
DBP, mmHg						
Baseline	1235	71.1 (11.0)		1226	71.4 (11.4)	0.0 (0.0)
6 months	1067		3.0 (12.7)	1052		2.7 (13.0)
12 months	986		3.5 (12.7)	972		2.3 (13.1)
24 months	882		3.6 (12.6)	829		3.1 (13.3)
LDL cholesterol, mg/dL						
Baseline	1144	90.3 (37.9)		1144	88.3 (36.3)	
12 months	874		-20.3 (35.6)	871		-20.5 (36.9)
24 months	781		-22.3 (36.7)	715		-20.7 (38.4)

No evidence of treatment differences over time

Study Treatments

Study treatment used in the polypill arm (N=1237)

	No. patients (%)
Polypill	
Ramipril 10mg - Atorvastatin 40mg - ASA 100mg	229 (18.5)
Ramipril 5mg - Atorvastatin 40mg - ASA 100mg	400 (32.3)
Ramipril 2.5mg - Atorvastatin 40mg - ASA 100mg	506 (40.9)
Ramipril 10mg - Atorvastatin 20mg - ASA 100mg	22 (1.8)
Ramipril 5mg - Atorvastatin 20mg - ASA 100mg	31 (2.5)
Ramipril 2.5mg - Atorvastatin 20mg - ASA 100mg	49 (4.0)

Lipid lowering treatment in the usual care arm (N=1229)

	No. patients (%)
High-intensity statin therapy	1020 (83.0)
Atorvastatin 40mg	520 (42.3)
Atorvastatin 80mg	446 (36.3)
Rosuvastatin 20-40mg	51 (4.1)
Moderate-intensity statin therapy	167 (13.6)
Atorvastatin 10-20mg	99 (8.1)
Rosuvastatin 5-10mg	15 (1.2)
Simvastatin 20-40mg	47 (3.8)
Pravastatin 40-80mg	3 (0.2)
Lovastatin 40mg	2 (0.2)
Pitavastatin 2-4mg	1 (0.1)
Low-intensity statin therapy	4 (0.3)
Pravastatin 10-20mg	1 (0.1)
Lovastatin 20mg	1 (0.1)
Fluvastatin 20-40mg	2 (0.2)
No statin	38 (3.0)

Study Treatments

Concomitant Medications

	Polypill (n=1237)	Usual care (n=1229)
Non-ASA antiplatelet agent	1163 (94.0)	1172 (95.4)
Beta-blocker	1014 (82.0)	1037 (84.4)
Calcium channel blocker	229 (18.5)	252 (20.5)
Diuretic	385 (31.1)	419 (34.1)
Nitrate	119 (9.6)	148 (12.0)
Ezetimibe	97 (7.8)	98 (8.0)

Distribution of the number of cardiovascular therapies per patient at baseline by treatment arm

No. cardiovascular therapies	Polypill (n=1237)	Usual care (n=1229)
Mean (SD)	3.4 (0.9)	5.4 (0.9)
Median (IQR)	3 (3-4)	5 (5-6)

Limitations

- No adjustment was made for multiple comparisons of secondary endpoints, so these should be viewed as hypothesis-generating.
- Withdrawal and loss to follow-up may potentially bias comparison between the groups, though with similar withdrawal rates in both arms this seems less likely.
- All patients were enrolled by the end of 2019. Given the high-risk nature and average age of the participants, it is reasonable to infer that the pandemic precluded some patients from completing study visits

Strengths

- Kaplan meyer curves for primary endpoint and key secondary endopoint for polypill vs. usual care diverge early and differences increase over time.
- Control group probably displayed better adherence than real world patients who are not enrolled on a RCT where adherence is measured at 6 and 24 months.
- It is reasonable to infer differences may be larger in the real world in similar settings and even larger in LMICs.

Conclusions

A treatment strategy based on **a polypill containing aspirin, atorvastatin, and ramipril**, led to **reductions in recurrent cardiovascular** events following MI in elderly patients.

- 24% RRR composite MACE
- 30% RRR in key secondary endpoint
- 33% RRR in CV death

The **use of a polypill strategy is safe**, there were no significant differences in adverse events between groups.

The use of a cardiovascular polypill as a substitution approach could be an integral part of a **global strategy to improve secondary prevention**.

The NEW ENGLAND JOURNAL of MEDICINE

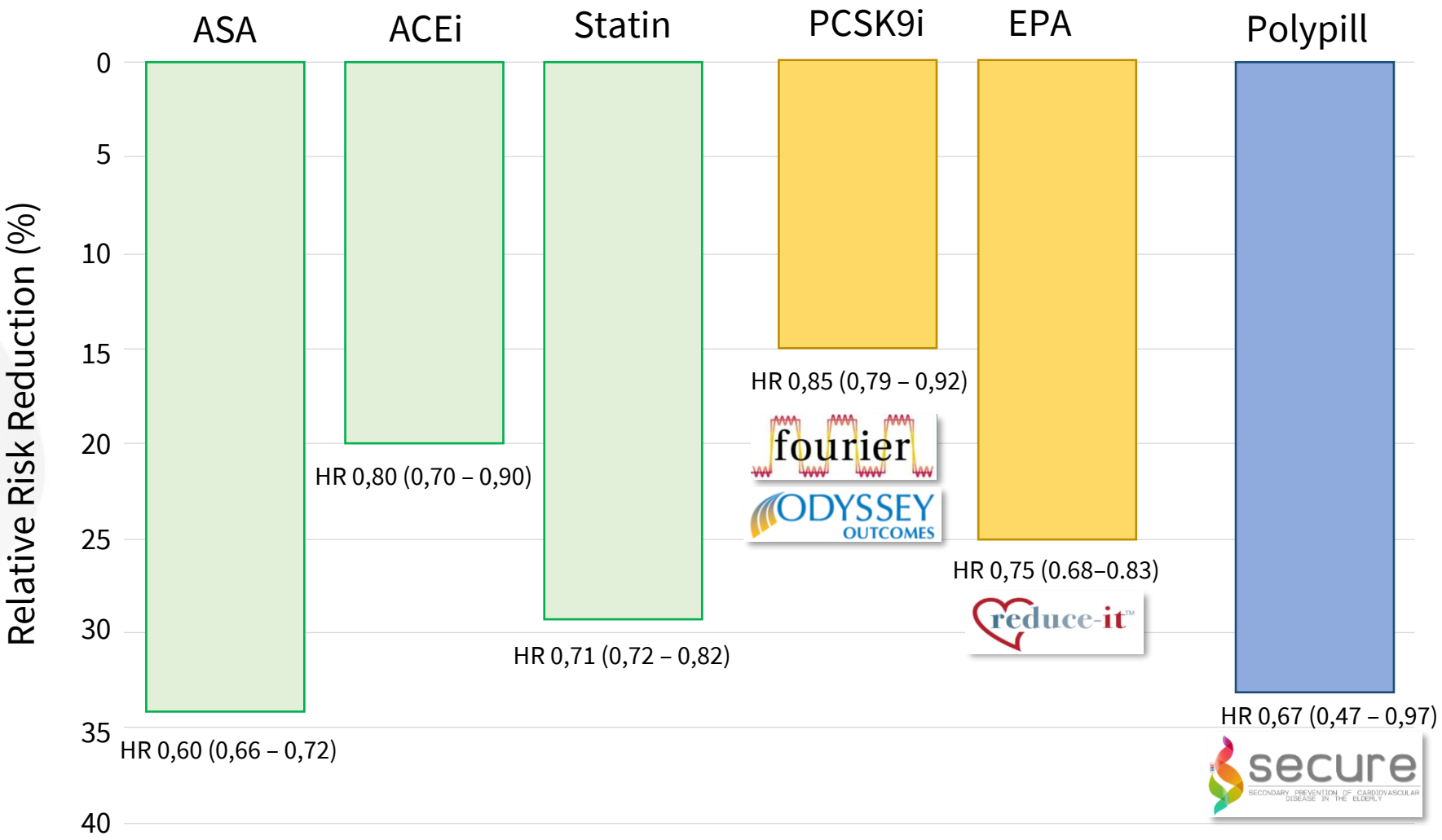
ORIGINAL ARTICLE

Polypill Strategy in Secondary Cardiovascular Prevention

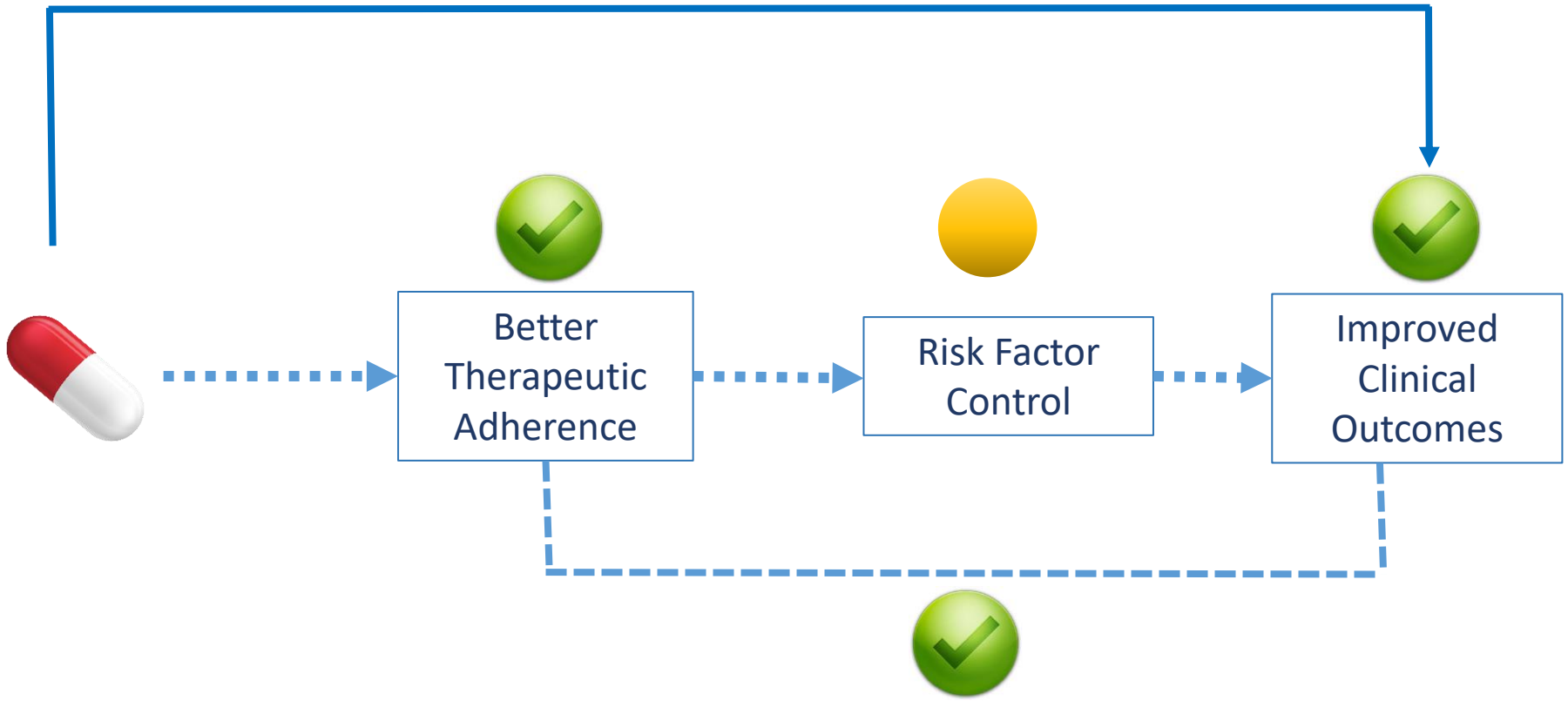
J.M. Castellano, S.J. Pocock, D.L. Bhatt, A.J. Quesada, R. Owen, A. Fernandez-Ortiz, P.L. Sanchez, F. Marin Ortuño, J.M. Vazquez Rodriguez, A. Domingo-Fernández, I. Lozano, M.C. Roncaglioni, M. Baviera, A. Foresta, L. Ojeda-Fernandez, F. Colivicchi, S.A. Di Fusco, W. Doehner, A. Meyer, F. Schiele, F. Ecarnot, A. Linhart, J.-C. Lubanda, G. Barczi, B. Merkely, P. Ponikowski, M. Kasprzak, J.M. Fernandez Alvira, V. Andres, H. Bueno, T. Collier, F. Van de Werf, P. Perel, M. Rodriguez-Manero, A.A. Garcia, M. Proietti, M.M. Schoos, T. Simon, J. Fernandez Ferro, N. Lopez, E. Beghi, Y. Bejot, D. Vivas, A. Cordero, B. Ibañez, and V. Fuster, for the SECURE Investigators*

Results in Context | Reductions in CV Death

Estimated Efficacy of Pharmacotherapy in Secondary Prevention



SECURE RESULTS



Baseline Medical History

	Polypill (n=1237)	Usual care (n=1229)
Smoking status,		
Current	175 (15.0)	161 (13.8)
Former	459 (39.4)	471 (40.4)
Never	532 (45.6)	534 (45.8)
Diabetes mellitus,	520 (42.0)	531 (43.2)
Not insulin-dependent	370 (29.9)	412 (33.5)
Insulin-dependent	149 (12.1)	119 (9.7)
Hypertension,	952 (77.0)	966 (78.8)
Hyperlipidemia,	702 (57.4)	724 (59.6)
Angina pectoris,	280 (22.6)	317 (25.8)
Angina class,		
I	66 (28.2)	82 (29.3)
II	84 (35.9)	106 (37.9)
III	49 (20.9)	49 (17.5)
IV	35 (15.0)	43 (15.4)
Missing (%)	46 (16.4)	38 (12.0)
Previous MI,	260 (21.0)	276 (22.5)
Coronary artery disease,	373 (30.2)	389 (31.7)
Previous PCI,	273 (22.1)	274 (22.3)
Previous CABG,	71 (5.7)	92 (7.5)
Previous stroke,	88 (7.1)	79 (6.4)
Prior vascular event,	406 (32.8)	417 (33.9)
Previous heart failure,	25 (2.0)	25 (2.0)
CKD,	465 (37.6)	435 (35.4)
Peripheral arterial disease,	104 (8.4)	106 (8.6)
History of COPD/asthma,	123 (10.0)	116 (9.5)
History of cancer,	140 (11.3)	150 (12.2)

Study Treatments

Study treatment used in the polypill arm (N=1237)

	No. patients (%)
Polypill	
Ramipril 10mg - Atorvastatin 40mg - ASA 100mg	229 (18.5)
Ramipril 5mg - Atorvastatin 40mg - ASA 100mg	400 (32.3)
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	No. patients (%)
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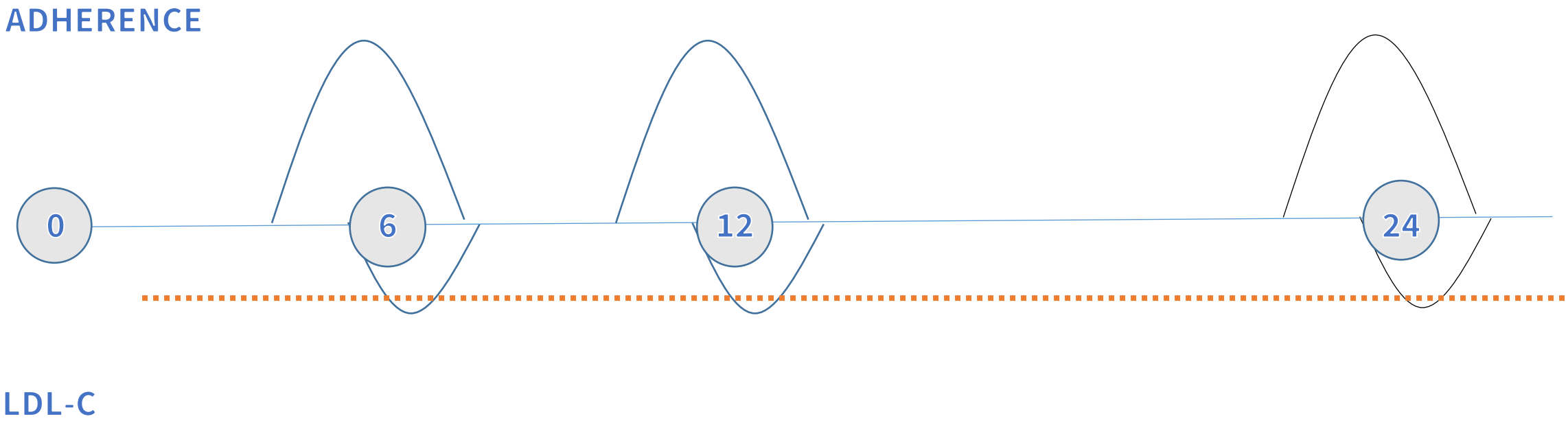
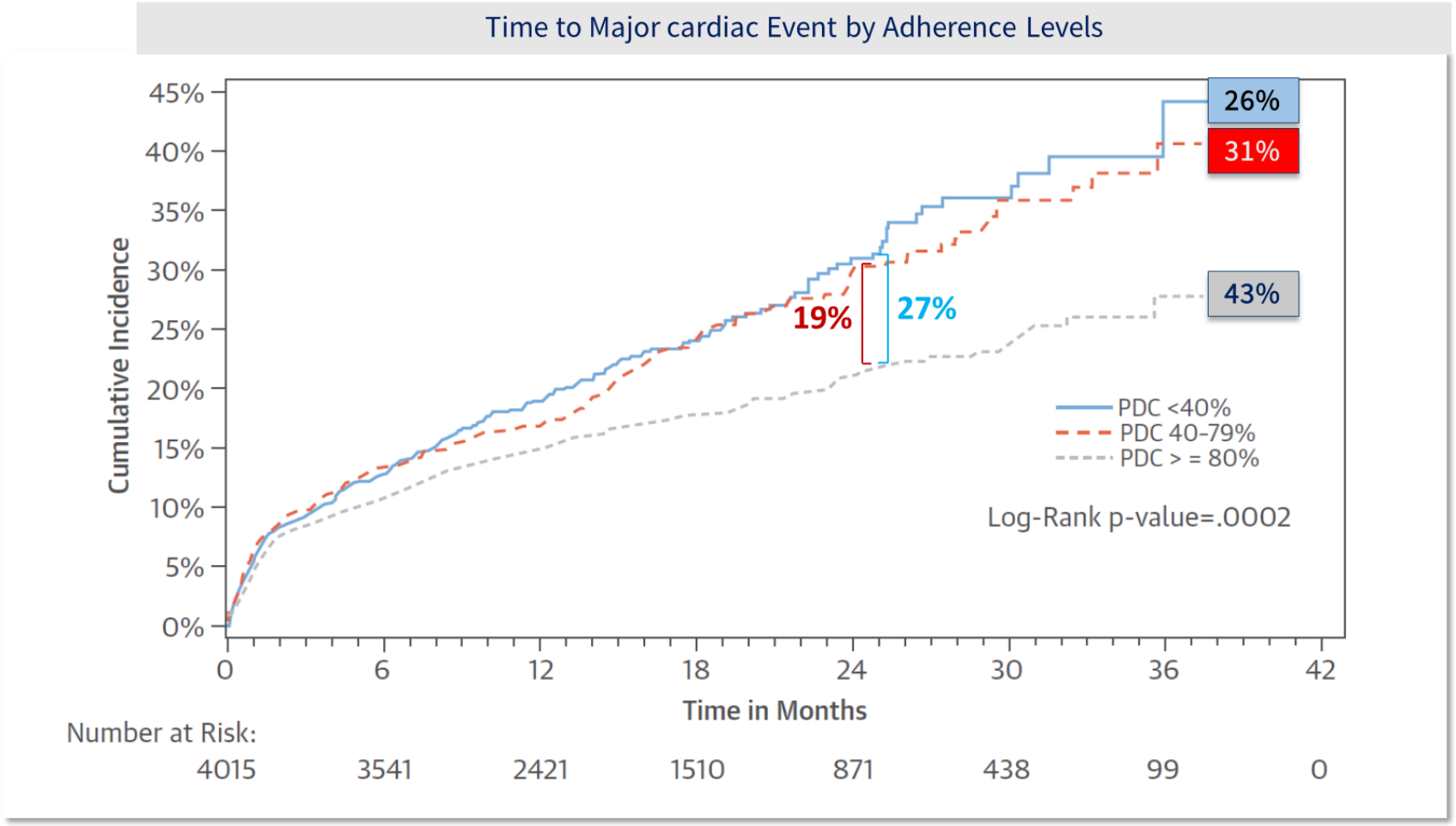
Pravastatin 40-80mg	3 (0.2)
Lovastatin 40mg	2 (0.2)
Pitavastatin 2-4mg	1 (0.1)
Low-intensity statin therapy	4 (0.3)
Pravastatin 10-20mg	1 (0.1)
Lovastatin 20mg	1 (0.1)
Fluvastatin 20-40mg	2 (0.2)
No statin	38 (3.0)

Results in Context | Control in LDL



Results in Context | Reductions in MACE

Assessing the impact of medication adherence on long-term cardiovascular outcomes

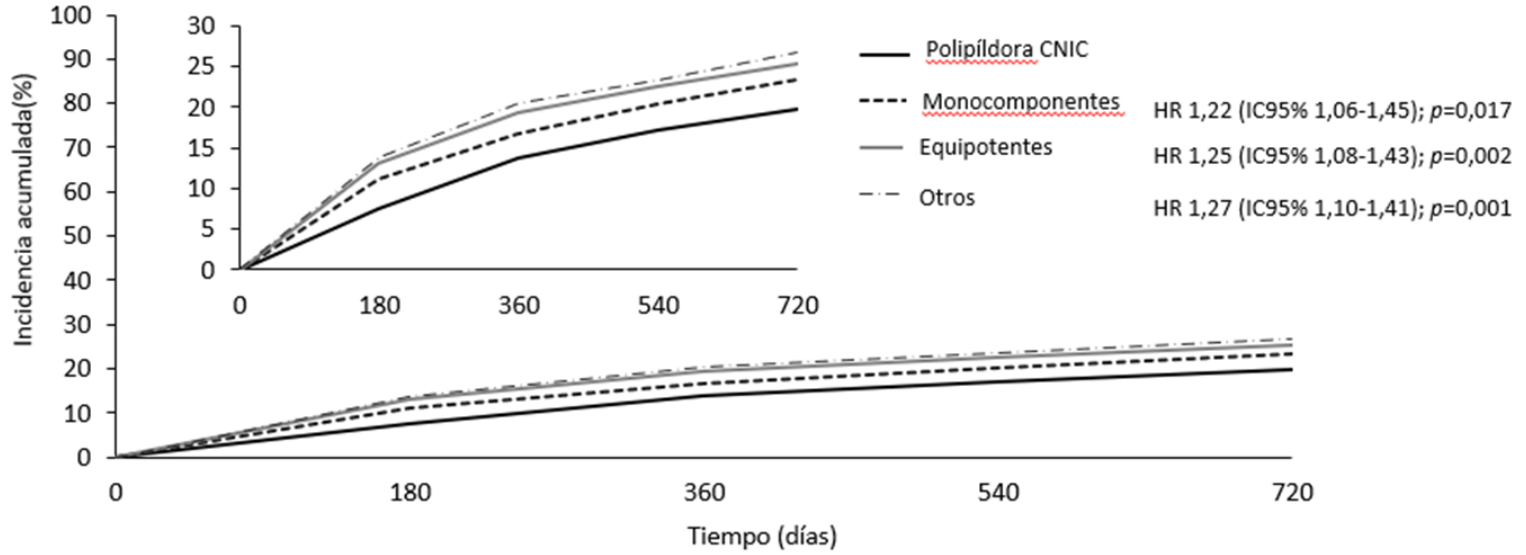


Bansilal S, Castellano JM, Fuster V et al, . *J Am Coll Cardiol*. 2016 Aug 23;68(8):789-801

Results in Context | Reductions in MACE

Effectiveness of the CNIC Polypill in patients with previous cardiovascular events in hospitals and primary care centers in Spain: NEPTUNO study

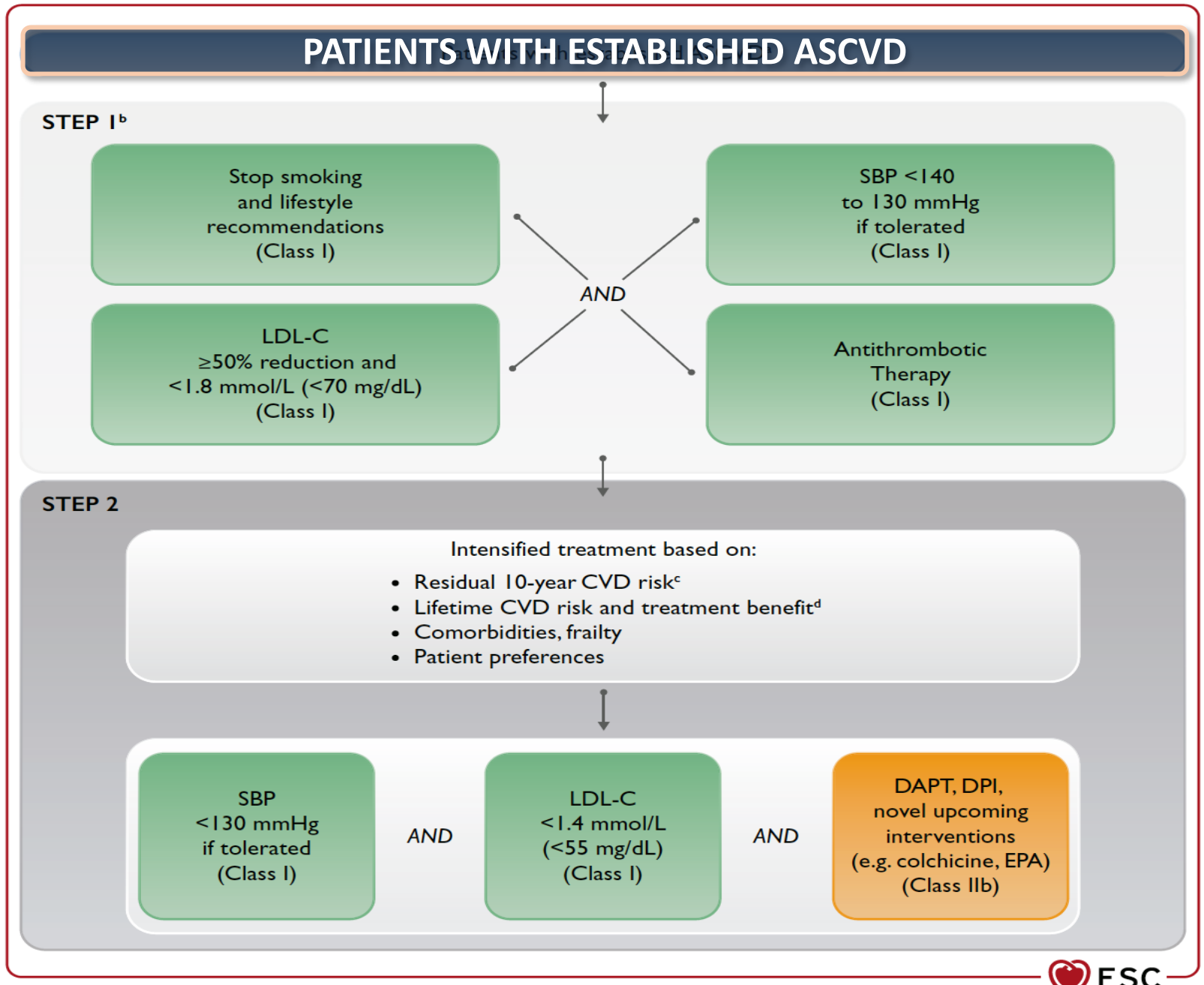
Cumulative Incidence of MACE after 2 year follow up



No. en riesgo	Día 0	Día 180	Día 360	Día 540	Día 720
Polipíldora CV	1614	1491	1393	1336	1294
Monocomponentes	1614	1434	1344	1285	1236
Equipotentes	1614	1404	1302	1285	1203
Otros	1614	1391	1282	1236	1182

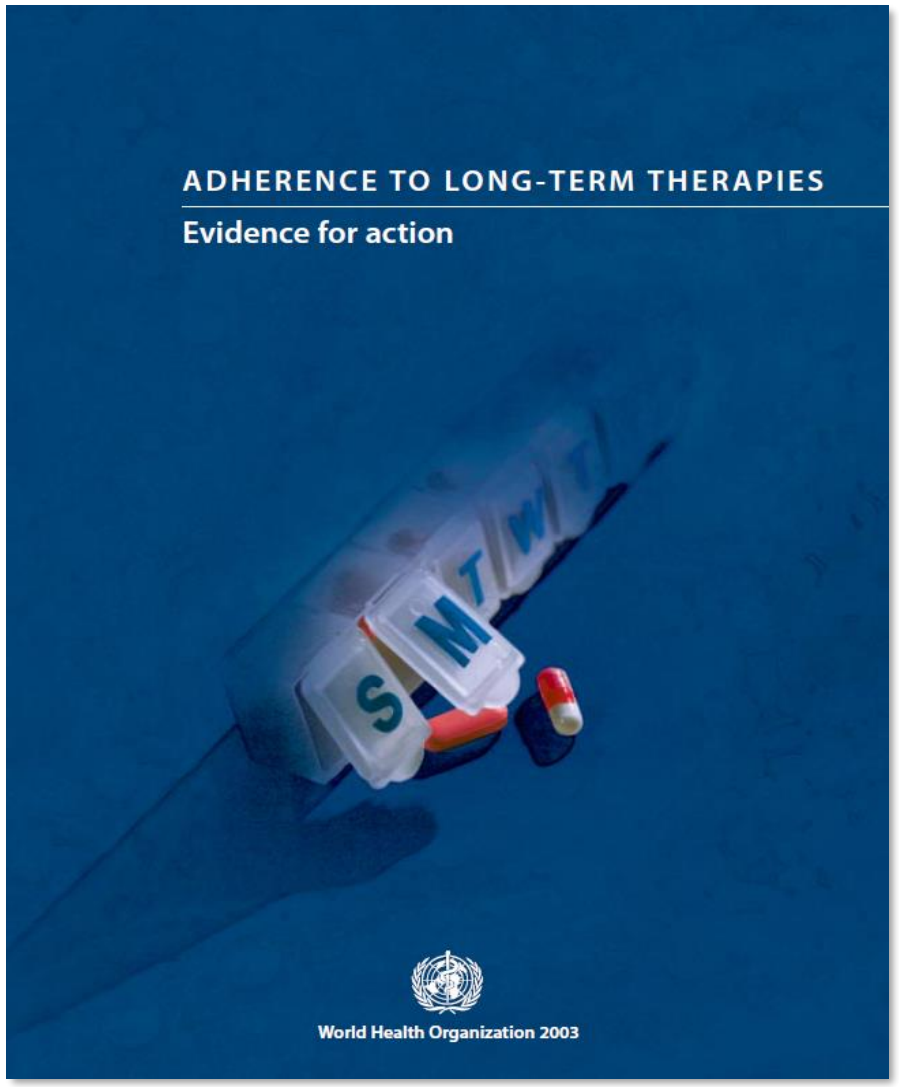
HR: Hazard Ratio. IC: intervalo de confianza. p: significación estadística

González Juanatey JR, Cordero A, Castellano JM, Masana L, Dalmau R, Ruiz E, Fuster V. Reduction of cardiovascular events in patients with cardiovascular disease with the CV-polypill: a retrospective and propensity score matching study. ESC 2021.



ESC 2021

Prevention Guidelines



"Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments"