

Economic Burden Associated with the Treatment with a Cardiovascular Polypill in Secondary Prevention in Spain: Cost-Effectiveness Results of the NEPTUNO Study

Alberto Cordero^{1,2}, Regina Dalmau González-Gallarza³, Lluís Masana⁴⁻⁶, Valentín Fuster^{7,8}, Jose M^a Castellano^{7,9,10}, José Emilio Ruiz Olivar¹¹, Ilonka Zsolt¹¹, Antoni Sicras-Mainar¹², Jose Ramón González Juanatey^{2,13,14}

¹Cardiology Service, San Juan University Hospital, Alicante, Spain; ²Cardiovascular Diseases Network Research Center (CIBERCV), Madrid, Spain; ³Cardiology Service, La Paz University Hospital, Madrid, Spain; ⁴Sant Joan University Hospital, Vascular Medicine and Metabolism Unit, Reus, Spain; ⁵Pere Virgili Institute of Health Research (IISPV), Reus, Spain; ⁶Center for Biomedical Research Network on Diabetes and Associated Metabolic Diseases (CIBERDEM), Reus, Spain; ⁷National Center for Cardiovascular Research (CNIC), Carlos III Health Institute, Madrid, Spain; ⁸Mount Sinai Medical Center, New York, NY, USA; ⁹Integral Center for Cardiovascular Diseases (CIEC), Montepíncipe University Hospital, HM Hospitales Group, Madrid, Spain; ¹⁰School of Medicine, CEU San Pablo University, Madrid, Spain; ¹¹Corporate Medical Affairs, Ferrer, Barcelona, Spain; ¹²Health Economics and Outcomes Research Department, Atrys Health, Madrid, Spain; ¹³Cardiology Service, University Hospital of Santiago de Compostela, Santiago de Compostela, Spain; ¹⁴Santiago de Compostela Health Research Institute (IDIS), Santiago de Compostela, Spain

Correspondence: Antoni Sicras-Mainar, Atrys Health SA, Calle Príncipe de Vergara, 132, planta 1, Madrid, 28002, Spain, Tel +34 917 819 465, Fax +34 915 776 744, Email ihernandez@atryshhealth.com

Purpose: The aim of this study was to estimate health-care resources utilization, costs and cost-effectiveness associated with the treatment with CNIC-Polypill as secondary prevention of atherosclerotic cardiovascular disease (ASCVD) compared to other treatments, in clinical practice in Spain.

Patients and Methods: An observational, retrospective study was performed using medical records (economic results [health-care perspective], NEPTUNO-study; BIG-PAC-database) of patients who initiated secondary prevention between 2015 and 2018. Patients were followed up to 2 years (maximum). Four cohorts were balanced with a propensity-score-matching (PSM): 1) CNIC-Polypill (aspirin+atorvastatin+ramipril), 2) Monocomponents (same separate drugs), 3) Equipotent (equipotent drugs) and 4) Other therapies ([OT], other cardiovascular drugs). Incidence of cardiovascular events, health-care resources utilization and healthcare and non-healthcare costs (2020 Euros) were compared. Incremental cost-effectiveness ratios per cardiovascular event avoided were estimated.

Results: After PSM, 1614 patients were recruited in each study cohort. The accumulated incidence of cardiovascular events during the 24-month follow-up was lower in the CNIC-Polypill cohort vs the other cohorts (19.8% vs Monocomponents: 23.3%, Equipotent: 25.5% and OT: 26.8%; $p < 0.01$). During the follow-up period, the CNIC-Polypill cohort also reduced the health-care resources utilization per patient compared to the other cohorts, particularly primary care visits (16.6 vs Monocomponents: 18.7, Equipotent: 18.9 and OT: 21.0; $p < 0.001$) and hospitalization days (2.3 vs Monocomponents: 3.4, Equipotent: 3.7 and OT: 4.0; $p < 0.001$). The treatment cost in the CNIC-Polypill cohort was lower than that in the other cohorts (€4668 vs Monocomponents: €5587; Equipotent: €5682 and OT: €6016; $p < 0.001$) (Difference: -€919, -€1014 and -€1348, respectively). Due to the reduction of cardiovascular events and costs, the CNIC-Polypill is a dominant alternative compared to the other treatments.

Conclusion: CNIC-Polypill reduces recurrent major cardiovascular events and costs, being a cost-saving strategy as secondary prevention of ASCVD.

Keywords: secondary prevention, cardiovascular events, use of healthcare resources, healthcare costs, Spain, CNIC-polypill

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is initiated by the atheromatous plaque, which is due to the retention and accumulation of cholesterol-rich apoB-containing lipoproteins within the arterial intima.^{1,2} Their clinical manifestations, like myocardial infarction and ischemic stroke, are the leading causes of morbidity and mortality worldwide, resulting in a high use of health-care resources and costs.¹⁻⁴ In Spain, the incidence of cardiovascular diseases is rising and they cause more than 260 deaths per 100,000 inhabitants, approximately 30% of all deaths (year 2014).⁵⁻⁷ The annual management of cardiovascular diseases costs around €9.2 billion (9% of the total healthcare expenditure) in our country (year 2015).⁴

Although the origin of cardiovascular diseases is multifactorial, they are mainly caused by cardiovascular risk factors (CVRFs), such as high blood pressure (BP), high cholesterol levels, diabetes, inactivity, smoking and obesity.⁸ The prevention and treatment of CVRFs have become key objectives for health-care systems,^{8,9} specifically in patients with established cardiovascular disease (secondary prevention).^{1,10} Preventive strategies in patients with ASCVD should be multidisciplinary, based on lifestyle measures and the administration of pharmacologic therapies,^{1,3,11,12} such as lipid modifying agents (statins alone or in combination with ezetimibe or proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors), antihypertensive agents (angiotensin-converting enzyme inhibitors [ACEIs] or angiotensin receptor blockers [ARBs]) and antiplatelet therapy to prevent thrombosis.^{1,2,11-13} Secondary prevention has been shown to reduce mortality and cardiovascular events in randomized trials and real-life studies.^{8,10,14} However, research has pointed out poor adherence to guidelines in our country, and medication underuse, with a consequent rise in mortality.^{15,16} In the consulted bibliography, the rates of therapeutic adherence to cardiovascular medication are low, around 45%-60%.^{11,17-20}

Several studies have shown that polypills improve the control of CVRFs,^{8,21} while reducing the incidence of cardiovascular events.²²⁻²⁴ In Spain, a polypill designed by Dr. Valentin Fuster (Spanish National Center for Cardiovascular Diseases, CNIC) and marketed by Ferrer, is administered in capsules once daily, and combines 100 mg aspirin, 20 or 40 mg atorvastatin and 2.5, 5 or 10 mg ramipril.^{23,25-28} Recent results suggest a synergic effect among the components of this polypill that implies a higher decrease in low-density lipoprotein cholesterol (LDL) levels in comparison to atorvastatin alone.²⁹ This CNIC-Polypill is authorized for secondary prevention in Spain, as a substitute treatment in adult patients adequately controlled with the monocomponents given concomitantly at therapeutically equivalent doses.³⁰⁻³³ In this sense, the available evidence also associates high therapeutic adherence with better control of CVRFs, resulting in lower ASCVD rates.^{14,17,18} In several countries, polypills reduce the use of health-care resources, and are considered cost-effective, compared to the separate administration of the monocomponents.³⁴⁻³⁸ In Spain, a simulation model carried out by Barrios et al showed that the CNIC-Polypill would avoid 46 non-fatal and 11 fatal cardiovascular events (per 1000 patients treated), being dominant (less costly and more effective) for secondary prevention of cardiovascular events in the Spanish National Health System (SNHS).³⁴ However, the cost-effectiveness of this polypill in a real-life setting still has not been assessed in our country. Therefore, this study aimed to estimate the use of health-care resources, costs, and cost-effectiveness associated with the treatment with the CNIC-Polypill as secondary prevention for ASCVD in clinical practice in Spain.

Materials and Methods

The NEPTUNO study is an observational, multicenter, and retrospective study carried out through the review of electronic medical records (EMR)³⁹ from the BIG-PAC[®] database. It gathers data from the records of health providers from primary and hospital centers in Spain (approximately 1.81 million people),^{40,41} and it is representative of the Spanish population.⁴¹ The original study was approved by the Ethics Committee (EC) of the Hospital Consorci Sanitari de Terrassa. As the proposed analysis of pharmacoeconomic variables does not modify the objective of the study nor does it require modification of the same, the resubmission of the project as an amendment to the EC was not required.

Patients

The study included patients who initiated a secondary prevention treatment for ASCV between 01/01/2015 and 31/12/2018 due to a cardiovascular event. The diagnosis of cardiovascular events was obtained from the International

Classification of Diseases, 9th edition, Clinical Modification (ICD-09-CM),⁴² including: 1) coronary heart disease (acute myocardial infarction, stable or unstable angina pectoris), 2) cerebrovascular disease (ischemic stroke, transient ischemic attack) and 3) peripheral artery disease. The inclusion and exclusion criteria were previously reported.³⁹ Patients ≥ 18 years of age were included.

Four cohorts of patients were considered: 1) CNIC-Polypill: patients receiving the CNIC-Polypill, a fixed-dose combination of aspirin/atorvastatin/ramipril in dosages of 100/20/2.5, 5 or 10 mg and 100/40/2.5, 5 or 10 mg, respectively (Case Cohort); 2) Monocomponents: patients receiving separately aspirin + atorvastatin + ramipril in dosages of 100/20/2.5, 5 or 10 mg and 100/40/2.5, 5 or 10 mg, respectively; 3) Equipotent: patients receiving equipotent antihypertensive⁴³ and lipid modifying agents⁴⁴ (aspirin + simvastatin or rosuvastatin + enalapril or valsartan) separately (Table S1); 4) Other therapies: patients receiving any other cardiovascular treatment not described in the prior cohorts (2,3 and 4, Control cohorts). This study compared patients receiving the CNIC-Polypill vs the three control cohorts. All treatments were administered once daily.

The follow-up period was 2 years from the index date, or until the development of a recurrent cardiovascular event or death, whichever occurred first. The index date for the CNIC-Polypill cohort was defined as the date of the first dispensation of the CNIC-Polypill at the pharmacy after the cardiovascular event that implied the inclusion. In all cohorts except the CNIC-Polypill cohort, the index date was that of the first dispensation of the last drug prescribed (aspirin, lipid modifying, or antihypertensive agents).

Characteristics of the Study Population

The demographic characteristics and comorbidities of the study population were collected. The Charlson comorbidity index⁴⁵ was used as a summary variable of general comorbidity.³⁹ These data were collected at the index date, as the baseline characteristics of the patient.

Treatments

Drugs were obtained from records of drug prescriptions and were associated with the Anatomical Chemical Therapeutic Classification System (ATC).⁴⁶ The drugs were lipid modifying agents (C10), agents acting on the renin-angiotensin system (C09), antithrombotic agents (B01), antihypertensives (C02), diuretics (C03), beta blocking agents (C07), calcium channel blockers (C08), cardiac therapy (C01), insulins and analogues (A10A), and blood glucose lowering drugs, excluding insulins (A10B). The number of drugs prescribed was also collected, along with the medical specialty that firstly prescribed the CNIC-Polypill (general practitioner or specialist).

The persistence/duration of the treatment was defined as the period from the index date to the discontinuation date. This was defined as the average period that the patients did not withdraw or change the initial treatment in the first 30 days after the first prescription. The discontinuation date was defined as the end of the follow-up period, the development of a new cardiovascular event, or cardiovascular-related death, the change to a lipid modifying, antihypertensive or antiplatelet treatment different to the inclusion medication and/or the interruption or abandonment of treatment (≥ 60 days without renewing the medication and/or ≥ 2 prescriptions), whichever occurred first. In the CNIC-Polypill cohort, it was considered that the interruption of initial treatment took place when there was a change or an interruption in the dispensation of the CNIC-Polypill, while in the other cohorts, it was considered when any of the drugs (aspirin, lipid modifying and/or antihypertensive agents) in the treatment was changed or interrupted (dosage changes of the same drug were not considered treatment interruptions). The persistence to the treatment was measured 2 years after the index date.

Healthcare Resources Utilization and Costs

Health-care and non-healthcare (indirect) costs were considered during the follow-up period. Health-care costs were those related to healthcare activity (primary care visits, emergency visits, days of hospitalization, specialized care visits, diagnostic and laboratory tests, therapeutic requests [including drugs, radiodiagnostic, rehabilitation], and surgical procedures), while non-healthcare costs were those associated to lost productivity (days of sick leave due to temporary or permanent disability) in the population under 65 years, which is the retirement age in Spain.

Table 1 Unit Costs and Work Disability (€, 2020)

Health and Non-Health Resources	Unit Costs (€)
Medical visits	
Primary care medical visit	23.19
Emergency medical visit	117.53
Hospitalization (one day)	420.90
Specialized care medical visit*	92.00
Complementary tests	
Laboratory tests	22.30
Conventional radiology	18.50
Other diagnostic/therapeutic tests	37.12
Computed tomography	96.00
Magnetic nuclear resonance	177.00
Pharmaceutical prescription	Retail price
Work disability - Indirect costs (source: BIG-PAC)	
Cost per day not worked	101.20

Notes: *Includes rehabilitation session. Sources: Own analytical accounting and INE (25,165.51 EUR).⁴⁸

Costs were expressed in 2020 Euros. Health-care costs were calculated by multiplying the frequency of use during follow-up by the unit cost of each healthcare resource (own analytical accounting, Table 1). Drug costs were quantified using the retail price per pack (VAT included) at the time of dispensing from the community pharmacy.⁴⁷ To estimate the productivity loss (source: BI-PAC database), the number of days of sick leave is considered, as well as the average professional salary for the Spanish population⁴⁸ (Table 1). A sub-analysis was carried out to estimate the costs of the treatment considering the cardiovascular event before the index date in each cohort of patients.

The incremental cost-effectiveness ratio (ICER) per cardiovascular event avoided was estimated as $(C1-C0)/(E1-E0)$, being C1 the total cost in the case cohort (CNIC-Polypill group), C0 the cost in the control cohorts (Monocomponents, Equipotent or Other therapies groups), E1 the effectiveness in the case cohort (CNIC-Polypill group) and E0 the effectiveness in the control cohorts (Monocomponents, Equipotent or Other therapies groups).

Confidentiality of Information/Ethical Aspects

The confidentiality of EMR (anonymous and dissociated) was respected according to the Law of Protection of Personal Data, Regulation (EU) 2016/679 of the European Parliament⁴⁹ and Organic Law 3/2018 of December 5 on the Protection of Personal Data and guarantee of digital rights.⁵⁰ This study was approved by the Research Ethics Committee of the Hospital de Terrassa, Barcelona, Spain.

Statistical Analysis

Data collected from the BIG-PAC[®] database were validated using computer sentences (specific SQL scripts) and reviewed using exploratory analysis. Frequency distributions were explored, searching for possible registration or coding errors. A quality process was followed to assure the quality of the results.

To minimize possible confounding variables and improve the comparability of the study cohorts, a propensity score matching (PSM) was carried out, with three 1:1 pairing: ie, for each case patient receiving the CNIC-Polypill, a matching

patient was obtained in each one of the other three cohorts. The methodology used to conduct propensity score matching was described in a previous study.³⁹

Descriptive univariate statistical analyses were conducted, and absolute and relative frequencies were calculated for qualitative data. Quantitative data were expressed using means, standard deviations (SD), medians, and the 25th and 75th percentiles of the distribution (interquartile ranges, IQR). The 95% confidence intervals (CI) were used to estimate the study population parameters.

Bivariant statistical analyses were carried out using the analysis of variance (ANOVA) and chi-squared tests for independent groups and t-student and McNemar's tests for paired groups. A Kaplan–Meier survival analysis (Log rank tests) was performed to estimate the persistence/duration of treatment. A covariance analysis was developed to correct costs (analysis of covariance [ANCOVA], generalized linear model), considering age, gender, and Charlson index scores as covariates (procedure: estimation of marginal average; Bonferroni adjustment). The analyses were made using the statistical software IBM/SPSS. Statistical significance was set at $p < 0.05$.

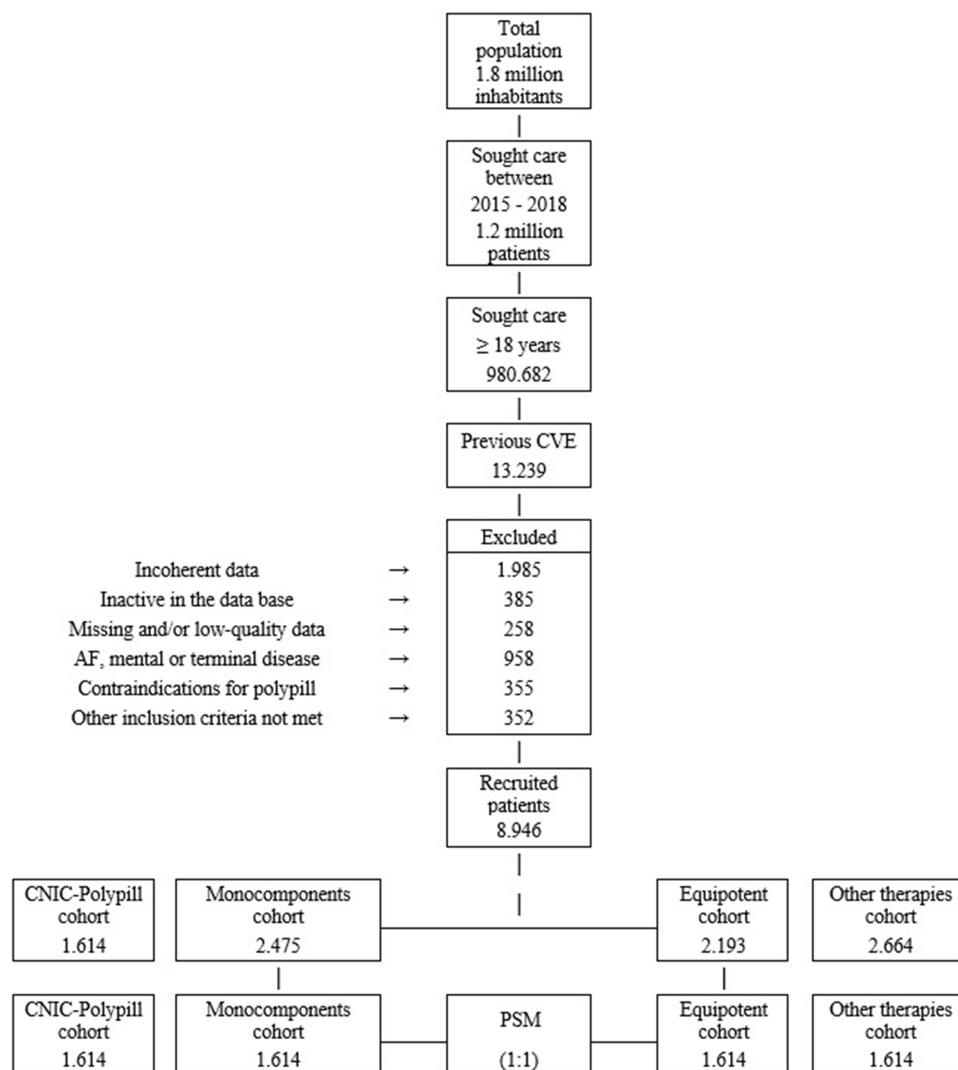


Figure 1 Study flow diagram.

Abbreviations: AF, auricular fibrillation; CVE, cardiovascular event; PSM, propensity score matching.

Results

Out of 980,682 patients who were at least 18 years of age, 8946 patients met the criteria to be included into the study and were divided into cohorts: CNIC-Polypill (n=1614); Monocomponents (n=2475); Equipotent (n=2193) and Other therapies (n=2664) (Figure 1). After PSM, each study group was made up of 1614 patients (N total: 6456).

Sociodemographic Characteristics, Comorbidities and Treatments

The average age in the study population was 63.0 years (SD: 13.0) and most of the patients were men (61.3%). The most frequent comorbidities were arterial hypertension (65.7%) and diabetes (27.2%). Patients in the study groups differed mainly in age, lipid profile, time from diagnosis, previous cardiovascular events, and drugs administered at the index date (Table S2). Due to this heterogeneity, a PSM was carried out. Patients receiving CNIC-Polypill were paired with those in the Monocomponents, Equipotent, and Other therapies cohorts; there were 1614 patients in each cohort (Figure 1). Therefore, the patients' characteristics were balanced among the study groups, with an average age of 63.0 years (SD: 13.9) and a male proportion of 60.6%³⁹ (Table S3). The study population had had an average of one cardiovascular event before the index date, with coronary heart diseases being the most frequent. The median time from index date to recurrent cardiovascular event was between 255 and 297 days³⁹ (Table S4).

Effectiveness

The accumulated incidence of cardiovascular events during the follow-up period was lower in the CNIC-Polypill cohort (19.8% [95% CI: 17.9–21.7%]) in comparison to the other cohorts (Monocomponents: 23.3% [95% CI: 21.2–25.4%]; Equipotent: 25.5% [95% CI: 23.4–27.6%] and Other therapies: 26.8% [95% CI: 24.4–28.8%], $p < 0.01$ for all comparisons). In addition, the time to the first recurrent cardiovascular event was longer in patients on treatment with the CNIC-Polypill (236 days), compared to the other cohorts (Monocomponents: 204 days; Equipotent: 160 days and Other therapies: 173 days, $p < 0.01$). Furthermore, although there were no statistical differences in the time to death, it was longer in patients receiving the CNIC-Polypill compared to those in the other study groups³⁹ (Table S5). It was also shown that lipid profiles (total cholesterol, LDL and triglyceride levels) and BP control were significantly improved in the CNIC-Polypill cohort compared to the control cohorts, as was the persistence to therapy.³⁹

Use of Healthcare Resources and Costs

During the follow-up period, CNIC-Polypill patients showed a lower use of resources compared to the other cohorts, particularly primary care visits (16.6 visits vs Monocomponents: 18.7 visits, Equipotent: 18.9 visits and Other therapies: 21.0 visits; $p < 0.001$) and hospitalization days (2.3 days vs Monocomponents: 3.4 days, Equipotent: 3.7 days and Other

Table 2 Use of Healthcare Resources (SD) per Patient During the Follow-Up Period

Number of patients	CNIC-Polypill	Monocomponents	Equipotent	Other Therapies	p
	1614	1614	1614	1614	
Primary care medical visits	16.6 (12.2)	18.7 (14.7)	18.9 (13.9)	21.0 (13.4)	<0.001
Specialized care medical visit	5.0 (4.7)	6.2 (5.7)	6.5 (6.9)	7.3 (7.1)	<0.001
Emergency medical visit	1.0 (3.0)	1.8 (2.6)	1.9 (2.8)	2.5 (3.1)	<0.001
Rehabilitation session	0.7 (3.1)	1.1 (3.2)	1.0 (2.9)	1.1 (2.8)	<0.001
Hospitalization, %	16.5%	19.8%	21.9%	24.0%	<0.001
Hospitalization days	2.3 (6.0)	3.4 (8.2)	3.7 (8.3)	4 (8.1)	<0.001
Laboratory tests	3.2 (3.4)	3.0 (3.2)	2.8 (2.9)	3.2 (3)	<0.001

(Continued)

Table 2 (Continued).

Number of patients	CNIC-Polypill	Monocomponents	Equipotent	Other Therapies	p
	1614	1614	1614	1614	
Conventional radiology	1.8 (1.6)	2.2 (1.7)	2.2 (1.7)	2 (1.7)	<0.001
Computed tomography	0.4 (0.8)	0.4 (0.8)	0.5 (0.8)	0.5 (0.9)	<0.001
Magnetic nuclear resonance	0.1 (0.4)	0.3 (0.6)	0.3 (0.6)	0.5 (0.8)	<0.001
Other diagnostic/therapeutic tests	0.4 (0.8)	0.5 (0.8)	0.5 (0.9)	0.8 (1.1)	<0.001
Patients on sick leave, %	11.5%	14.7%	15.2%	15.6%	0.003
Sick leave days	6.4 (22.3)	8.4 (28.4)	8.3 (28.2)	7.9 (24.8)	<0.001

Notes: The use of healthcare care resources are indicated as the average number of resources (SD) (unless otherwise stated) required per patient during the follow-up period (two years from the index date, or until the development of a cardiovascular event or death, whichever occurred first). p statistical significance.

Abbreviation: SD, standard deviation.

therapies: 4.0 days; $p < 0.001$). Productivity losses were also lower in patients receiving the CNIC-Polypill, in comparison to the other cohorts, not just in terms of the number of patients who took sick leave (11.5% vs Monocomponents: 14.7%, Equipotent: 15.2% and Other therapies: 15.6%; $p < 0.003$), but also regarding the number of sick leave days during the follow-up period (6.4 days vs Monocomponents: 8.4 days, Equipotent: 8.3 days and Other therapies: 7.9 days; $p < 0.001$) (Table 2).

Table 3 Costs per Patient (€, 2020) During the Follow-Up Period

Number of patients	CNIC-Polypill	Monocomponents	Equipotent	Other Therapies	p
	1614	1614	1614	1614	
Costs, € (SD)					
Primary care medical visits	384 (284)	434 (341)	437 (322)	486 (311)	<0.001
Specialized care medical visit	462 (434)	573 (522)	600 (632)	673 (653)	<0.001
Emergency medical visit	117 (358)	207 (308)	228 (334)	297 (359)	<0.001
Rehabilitation session	67 (282)	100 (295)	93 (265)	106 (262)	<0.001
Hospitalization	963 (2537)	1414 (3453)	1571 (3485)	1669 (3391)	<0.001
Laboratory tests	72 (76)	68 (72)	62 (64)	72 (66)	<0.001
Conventional radiology	33 (30)	40 (31)	41 (32)	38 (31)	<0.001
Computed tomography	36 (75)	43 (80)	45 (81)	47 (83)	<0.001
Magnetic nuclear resonance	26 (64)	50 (107)	55 (111)	88 (135)	<0.001
Other diagnostic/therapeutic tests	15 (30)	17 (31)	19 (33)	31 (41)	<0.001
Drugs	1860 (969)	1780 (1162)	1698 (948)	1632 (1060)	<0.001
Healthcare cost	4036 (3432)	4725 (4456)	4849 (4548)	5139 (4647)	<0.001
Non-healthcare cost (productivity loss)	645 (2259)	854 (2876)	841 (2853)	804 (2506)	0.090
Total cost	4681 (4268)	5578 (5484)	5691 (5574)	5943 (5406)	<0.001

(Continued)

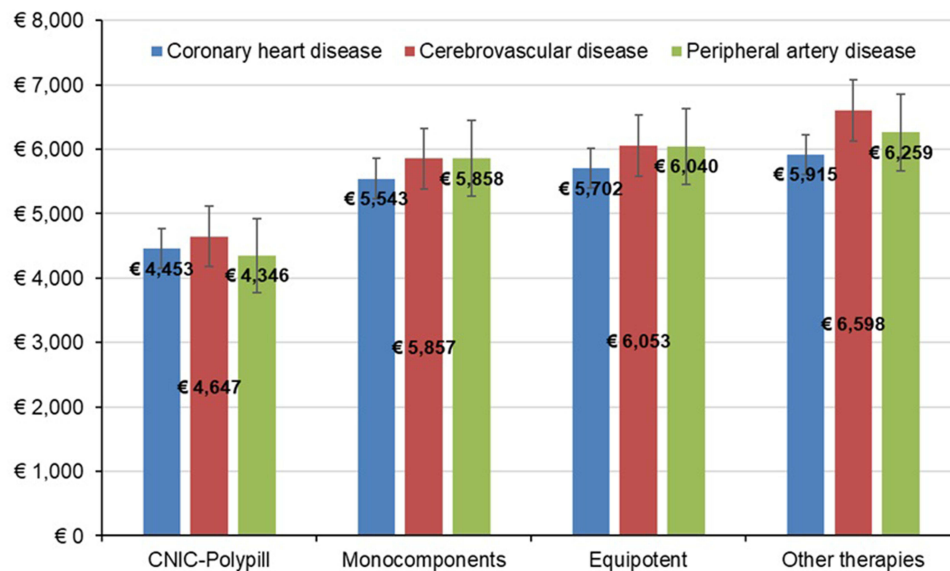
Table 3 (Continued).

Number of patients	CNIC-Polypill	Monocomponents	Equipotent	Other Therapies	p
	1614	1614	1614	1614	
Adjusted model (ANCOVA)*					
Healthcare cost, €	4012	4740 [‡]	4830 [‡]	5204 [‡]	<0.001
– 95% CI	3808–4216	4537–4945	4626–5034	5000–5409	
Non-healthcare cost (productivity loss), €	656	847	852	812	0.114
– 95% CI	528–784	719–975	724–980	684–941	
Total cost, €	4668	5587 [‡]	5682 [‡]	6016 [‡]	<0.001
– 95% CI	4411–4926	5331–5845	5425–5940	5759–6274	

Notes: Costs were estimated as mean costs (SD) per patient (in euros 2020) during the follow-up period (two years from the index date, or until the development of a cardiovascular event or death, whichever occurred first). p statistical significance. *Contrasts are based on paired comparisons between estimated marginal means; covariates: age, gender, and Charlson index. [‡]p <0.001; reference cohort: polypill.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence intervals; SD, standard deviation.

In line with these results, the average cost of the treatment per patient during the follow-up period in the CNIC-Polypill cohort was lower than those in the other cohorts (€4668 vs Monocomponents: €5587, Equipotent: €5682 and Other therapies: €6016; p<0.001), being the difference: -€919, -€1014 and -€1348, respectively. The costs of lost labor productivity in the CNIC-Polypill cohort were lower, although not reaching statistical significance (p=0.114) (Table 3). The main healthcare cost categories were hospitalizations (28.0%) and drugs (27.5%). Figure 2 shows the costs of the treatment for each of the four cohorts according to the previous events. As can be seen, in most of the study groups the costs associated with the management of patients who had suffered cerebrovascular disease were higher in comparison to the other cardiovascular events.

**Figure 2** Cost of the treatment per patient during the follow-up period, according to the previous event.

Note: Results expressed as average.

Table 4 Cost-Effectiveness Results

	Cost*	Incremental Cost	Effectiveness**	Incremental Effectiveness	ICER	Cost per Event Avoided	Difference
CNIC-Polypill	4668	-919	80.2	-3.5	Dominant	5820	-1464
Monocomponents	5587	-	76.7	-	-	7284	-
CNIC-Polypill	4668	-1014	80.2	-5.7	Dominant	5820	-1806
Equipotent	5682	-	74.5	-	-	7627	-
CNIC-Polypill	4668	-1348	80.2	-7.0	Dominant	5820	-2398
Other therapies	6016	-	73.2	-	-	8219	-

Notes: *Adjusted total cost. **Estimated as the percentage of patients without cardiovascular events.

Abbreviation: ICER, incremental cost-effectiveness ratio.

Cost-Effectiveness Results

Compared to the CNIC-Polypill group, the percentage of patients suffering cardiovascular events was greater in the other groups (3.5%, 5.7% and 7.0%, in the Monocomponents, Equipotent and Other therapies groups, respectively). On the other hand, the cost of the administration of the CNIC-Polypill was lower in comparison to the other groups (-€919, -€1014, and -€1348 in the Monocomponents, Equipotent and Other therapies groups, respectively). Therefore, due to the improvement in the clinical effectiveness and cost savings, the CNIC-Polypill was considered cost-effective and dominant in comparison to the other treatments (Table 4).

Discussion

This study found that treatment with CNIC-Polypill for secondary prevention of ASCVD reduced the incidence of recurrent cardiovascular events ($p < 0.01$), improved CVRF control (lipid profile and BP) and led to a significantly higher persistence to therapy,³⁹ leading to a decrease in the use of health-care resources, particularly primary care visits ($p < 0.001$) and hospitalization days ($p < 0.001$). Consequently, all the previously mentioned factors implied a reduction of patients on sick leave and sick leave days in the CNIC-Polypill group in comparison to patients on treatment with the other alternatives. Therefore, the cost of the treatment during the follow-up in the CNIC-Polypill cohort was lower than those in the other cohorts (€4668 vs Monocomponents: €5587; Equipotent: €5682 and Other therapies: €6016; $p < 0.001$). The difference among the groups in the study varied between €919 to €1348 per patient, during the 24-month follow-up. Consequently, our results showed that the CNIC-Polypill provided cost savings of between €17,790 to €26,257 per patient without cardiovascular events, compared to the other alternatives. The decrease of recurrent MACE with the CNIC-Polypill strategy compared to usual care has been confirmed in a prospective RCT recently published in the NEJM (SECURE study).⁵¹

The cost-effectiveness of polypills as a secondary preventive treatment for ASCVD has been widely estimated.^{34–36} A systematic review of cost-effectiveness analyses carried out by Marquina et al observed that most of the studies considered polypills to be cost-effective, compared to the standard of care, according to the pricing and willingness-to-pay thresholds at the time of each study.³⁵ In addition, several European countries analyzed the cost-effectiveness of the CNIC-Polypill for secondary prevention of ASCVD. In the UK, a Markov-model cost-effectiveness analysis developed by Becerra et al showed that over 10 years, this polypill would prevent around 15% of fatal and non-fatal recurrent cardiovascular events. They concluded that CNIC-Polypill could prevent 3260 recurrent cardiovascular events and 590 cardiovascular-related deaths over a decade, being a cost-effective strategy.³⁸ Another recent cost-effectiveness analysis carried out in Greece showed that the ICER of the CNIC-Polypill was -€2926 per QALY gained in comparison to the monocomponents. Therefore, it was considered a dominant alternative compared to the medicines administered separately.³⁶ Recently, a cost-effectiveness analysis based on real-life data based on CVRF improvement (LDL and

BP) was carried out in Portugal. The incremental cost–utility ratio was €2328 per QALY in patients with coronary heart disease and €553/QALY in those with a previous stroke, being cost-effective for a threshold of €30,000/QALY.³⁷

In Spain, the study carried out by Barrios et al showed that CNIC-Polypill was cost-effective, based on efficacy outcomes from a previous meta-analysis. Their results showed that this CNIC-Polypill implied lower costs (drugs and management of acute and chronic recurrent cardiovascular events) based on improvement in the adherence to medication rate, in comparison to the monocomponents, leading to cost savings of €509,861.64 per 1000 patients in 10 years of follow-up. Besides, the CNIC-Polypill improved life expectancy by 51.06 life-year gained and patients' quality of life by 48.34 QALY in the study population, being the dominant alternative over the multiple monotherapies.³⁴ Our results are in line with this study, as we estimated that the CNIC-Polypill reduced the incidence of recurrent cardiovascular events and costs, in comparison to other alternatives. Therefore, the improvement of the patients' health status and the decrease in costs showed that the CNIC-Polypill is cost-effective and dominant over the other alternatives.²⁴

One of the most important contributions of our study was the inclusion of patients who are on treatment with other preventive strategies such as equivalent doses of antihypertensive and lipid modifying agents (enalapril or valsartan, instead of ramipril and simvastatin or rosuvastatin instead of atorvastatin) and other alternatives used in clinical practice. This design allowed us to describe the management of patients with ASCVD who received secondary preventive treatments in a real-life setting. Our results also complement those previously published,³⁹ which evidenced that CNIC-Polypill increased adherence to secondary prevention medication in comparison to drugs administered separately, and consequently improving lipid profile and BP control. As could be expected, the improvement in clinical outcomes was associated with a reduction in the number of sick leave days and patients on sick leave, which decreased the costs associated with productivity losses in these patients.

The limitations of this study were those inherent to retrospective studies, such as under-recording (missing data) or possible intrinsic variations in physicians and patients due to observational design, measurement methods, or possible classification/selection bias. Likewise, possible inaccuracies in the diagnostic coding could have influenced the results, such as the socioeconomic level of patients or changes in the prescribed pharmacological dose. Patients with missing/inconsistent data were excluded from the analysis, so they could cause potential bias in the study; however, because they were a low number of subjects, we consider it would not interfere with the results of the study. Finally, although our study did not estimate the quality of life associated with the treatment of these patients, it is expected that the CNIC-Polypill would improve the quality of life of these patients, considering the improvements in the control of CVRF. In addition, to facilitate the understanding of the economic results, they should have been provided on an annualized basis. Due to the complexity of the study, we were unable to provide this information. Although the patients with loss of job productivity were few (range: 11–16% according to the study cohorts), it has not been possible for us to provide these results broken down by age and sex, due to their technical difficulty.

It would have been of great interest to know the prevalence of the use of the CV polypill in our country (despite its potential advantages), although it is presumably low; possibly due to resistance to change from health professionals and a lack of flexibility in its components and doses, among other factors.

It is important to highlight the significant increase in treatment persistence in the CNIC-Polypill cohort compared to the other three cohorts. In this sense, a greater persistence to treatment was associated with an improvement in CVRFs, a circumstance that can lead to a reduction in cardiovascular events, with repercussions in lower use of health resources and costs for the National Health System. Our results seem consistent with the consulted bibliography.^{14,18,30}

Conclusion

Treatment with the CNIC-Polypill in secondary cardiovascular prevention decreased the incidence of recurrent cardiovascular events, reducing the use of health-care resources and costs in a real-life setting. Therefore, CNIC-Polypill is cost-effective and dominant, compared to other alternatives, such as the administration of the monocomponents of the CNIC-Polypill separately, equipotent drugs and other medicines. Taking into account these results, the CNIC-Polypill strategy could be considered as baseline therapy after a CV event as it provides better health outcomes together with lower costs in the secondary prevention population.

Data Sharing Statement

The datasets generated during the current study are available from the corresponding author on reasonable request. All analyzed data are included in this article and its supplementary files.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Hospital of Terrassa (Barcelona). Patient consent was not necessary, according to the Article 5 of Royal Decree 957/2020, of November 3, which regulates observational studies with medicines for human use.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was funded by Ferrer.

Disclosure

AC reports a) honoraria for lectures from AstraZeneca, Bristol-Myers Squibb, Ferrer, Boehringer Ingelheim, MSD, and Amgen; b) consulting fees from AstraZeneca, Ferrer and Amgen. RDGG has received consulting fees from Ferrer International. LM has received honoraria for lectures and/or consulting work from Amgen, Sanofi, Novartis, Ferrer, Servier, Daiichi-Sankyo, Amarin and Amryt.

VF reports grants from H2020 related to conducting the ongoing SECURE trial. JMC reports grants from H2020 related to conducting the ongoing SECURE trial as well as receiving honoraria and reimbursement for travel expenses from Ferrer, Pfizer, Bayer, and Servier. JERO and IZ are currently working at Ferrer International. ASM was an employee of Atrys Health when the study was developed. Atrys Health is a contract research organization that received funds from Ferrer International to conduct this study. JRGJ has received honoraria for consulting and lectures from Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, MSD, Daiichi-Sankyo, Ferrer International, Novartis, Lilly, Sanofi and Servier. The authors report no other conflicts of interest in this work.

References

1. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European atherosclerosis society consensus panel. *Eur Heart J.* 2017;38(32):2459–2472. doi:10.1093/eurheartj/ehx144
2. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. *Circulation.* 2019;140(11):e596–e646. doi:10.1161/CIR.0000000000000678
3. Turk-Adawi K, Sarrafzadegan N, Fadhil I, et al. Cardiovascular disease in the eastern Mediterranean region: epidemiology and risk factor burden. *Nat Rev Cardiol.* 2018;15(2):106–119. doi:10.1038/nrcardio.2017.138
4. Wilkins E, Wickramasinghe K, Leal J, et al. *European Cardiovascular Disease Statistics 2017*. European Heart Network; 2017.
5. Bernick A, Davis C. Coste económico de las enfermedades cardiovasculares desde 2014 a 2020 en seis países europeos [Economic cost of cardiovascular diseases from 2014 to 2020 in six European countries]. *Acta Sanitaria.* 2014;2014:1.
6. Soriano JB, Rojas-Rueda D, Alonso J, et al. La carga de enfermedad en España: resultados del Estudio de la Carga Global de las Enfermedades 2016 [The burden of disease in Spain: results from the Global Burden of Disease Study 2016]. *Med Clin.* 2018;151(5):171–190. doi:10.1016/j.medcli.2018.05.011
7. Ministerio de Sanidad, Consumo y Bienestar Social. Informe anual del Sistema Nacional de Salud 2019. Aspectos destacados [The burden of disease in Spain: results from the Global Burden of Disease Study 2016; 2021]; 2021. Available from: https://www.msbs.gob.es/estadEstudios/estadisticas/sisInfSanSNS/tablasEstadisticas/InfAnualSNS2019/Informe_SNS_2019.pdf. Accessed May 24, 2023.
8. Piepoli MF, Hoes AW, Agewall S, et al. 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. *Eur Heart J.* 2016;37(29):2315–2381. doi:10.1093/eurheartj/ehw106
9. World Health Organization. Prevention of cardiovascular disease. Guidelines for assessment and management of cardiovascular risk; 2007. Available from: https://www.who.int/cardiovascular_diseases/guidelines/Ful%20text.pdf. Accessed June 21, 2021.

10. Fitzsimons D, Stepińska J, Kerins M, et al. Secondary prevention and cardiovascular care across Europe: a survey of European society of cardiology members' views. *Eur J Cardiovasc Nurs.* 2020;19(3):201–211. doi:10.1177/1474515119877999
11. Coca A, Agabiti-Rosei E, Cifkova R, Manolis AJ, Redón J, Mancia G. The polypill in cardiovascular prevention: evidence, limitations and perspective – position paper of the European society of hypertension. *J Hypertens.* 2017;35(8):1546–1553. doi:10.1097/HJH.0000000000001390
12. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice: developed by the task force for cardiovascular disease prevention in clinical practice with representatives of the European society of cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). *Eur Heart J.* 2021;ehab484. doi:10.1093/eurheartj/ehab484
13. Coll PP, Roche V, Olsen JS, Voit JH, Bowen E, Kumar M. The prevention of cardiovascular disease in older adults. *J Am Geriatr Soc.* 2020;68(5):1098–1106. doi:10.1111/jgs.16353
14. Solomon MD, Leong TK, Levin E, et al. Cumulative adherence to secondary prevention guidelines and mortality after acute myocardial infarction. *J Am Heart Assoc.* 2020;9(6):e014415. doi:10.1161/JAHA.119.014415
15. Redón J, Usó R, Trillo JL, et al. Number of drugs used in secondary cardiovascular prevention and late survival in the population of Valencia Community, Spain. *Int J Cardiol.* 2019;293:260–265. doi:10.1016/j.ijcard.2019.05.071
16. Kotseva K, De Backer G, De Bacquer D, et al. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: results from the European society of cardiology ESC-EORP EUROASPIRE V registry. *Eur J Prev Cardiol.* 2019;26(8):824–835. doi:10.1177/2047487318825350
17. Fuster V. An alarming threat to secondary prevention: low compliance (lifestyle) and poor adherence (drugs). *Rev Esp Cardiol.* 2012;65(Suppl 2):10–16. doi:10.1016/j.recesp.2012.07.005
18. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation.* 2009;119(23):3028–3035. doi:10.1161/CIRCULATIONAHA.108.768986
19. Mahtta D, Rodriguez F, Jneid H, Levine GN, Virani SS. Improving adherence to cardiovascular guidelines: realistic transition from paper to patient. *Expert Rev Cardiovasc Ther.* 2020;18(1):41–51. doi:10.1080/14779072.2020.1717335
20. Bansilal S, Castellano JM, Fuster V. Global burden of CVD: focus on secondary prevention of cardiovascular disease. *Int J Cardiol.* 2015;201:S1–S7. doi:10.1016/S0167-5273(15)31026-3
21. Webster R, Patel A, Selak V, et al. Effectiveness of fixed dose combination medication ('polypills') compared with usual care in patients with cardiovascular disease or at high risk: a prospective, individual patient data meta-analysis of 3140 patients in six countries. *Int J Cardiol.* 2016;205:147–156. doi:10.1016/j.ijcard.2015.12.015
22. Roshandel G, Khoshnia M, Poustchi H, et al. Effectiveness of polypill for primary and secondary prevention of cardiovascular diseases (POLYIRAN): a pragmatic, cluster-randomised trial. *Lancet.* 2019;394(10199):672–683. doi:10.1016/S0140-6736(19)31791-X
23. Castellano JM, Verdejo J, Ocampo S, et al. Clinical effectiveness of the cardiovascular polypill in a real-life setting in patients with cardiovascular risk: the SORS study. *Arch Med Res.* 2019;50(1):31–40. doi:10.1016/j.arcmed.2019.04.001
24. Wilke T, Weisser B, Predel HG, et al. Effects of single pill combinations compared to identical multi pill therapy on outcomes in hypertension, dyslipidemia and secondary cardiovascular prevention: the START-study. *IBPC.* 2022;15:11–21. doi:10.2147/IBPC.S336324
25. Fuster V, Gambús F, Patriciello A, Hamrin M, Grobbee DE. The polypill approach - an innovative strategy to improve cardiovascular health in Europe. *BMC Pharmacol Toxicol.* 2017;18(1):10. doi:10.1186/s40360-016-0102-9
26. Ibañez B, Castellano JM, Fuster V. Polypill strategy at the heart of cardiovascular secondary prevention. *Heart.* 2019;105(1):9–10. doi:10.1136/heartjnl-2018-313464
27. Gómez-álvarez E, Verdejo J, Ocampo S, Ruiz E, Martínez-Rios MA. Reaching blood pressure guideline targets with the CNIC polypill in patients with a previous cardiovascular event in Mexico: a post hoc analysis of the SORS study. *Future Cardiol.* 2020;16(1):53–60. doi:10.2217/fca-2019-0075
28. Tamargo J, Castellano JM, Fuster V. The Fuster-CNIC-Ferrer Cardiovascular Polypill: a polypill for secondary cardiovascular prevention. *Int J Cardiol.* 2015;201(Suppl 1):S15–S22. doi:10.1016/S0167-5273(15)31028-7
29. González-Juanatey JR, Tamargo J, Torres F, Weisser B, Oudovenko N. Pharmacodynamic study of the cardiovascular polypill. Is there any interaction among the monocomponents? *Rev Esp Cardiol.* 2021;74(1):51–58. doi:10.1016/j.rec.2019.11.008
30. Castellano JM, Sanz G, Peñalvo JL, et al. A polypill strategy to improve adherence: results from the FOCUS project. *J Am Coll Cardiol.* 2014;64(20):2071–2082. doi:10.1016/j.jacc.2014.08.021
31. González-Juanatey JR, Mostaza JM, Lobos JM, et al. Consensus document for the use of the polypill in the secondary prevention of cardiovascular disease. *Med Clin.* 2017;148(3):139.e1–139.e15. doi:10.1016/j.medcle.2016.10.047
32. Agencia Española de Medicamentos y Productos Sanitarios. Ficha técnica. Trinomia 100 mg/40 mg/10 mg cápsulas duras [Spanish Agency of Medicines and Health Products. Technical Data Sheet. Trinomia 100 mg/40 mg/10 mg cápsulas duras]; 2021. Available from: https://cima.aemps.es/cima/dohtml/ft/81774/FT_81774.html. Accessed February 28, 2022.
33. Agencia Española de Medicamentos y Productos Sanitarios. Ficha técnica. Trinomia 100 mg/20 mg/5 mg cápsulas duras [Spanish Agency of Medicines and Health Products. Technical Data Sheet. Trinomia 100 mg/20 mg/5 mg cápsulas duras]; 2021. Available from: https://cima.aemps.es/cima/pdfs/es/ft/78575/78575_ft.pdf. Accessed February 28, 2022.
34. Barrios V, Kaskens L, Castellano JM, et al. Usefulness of a cardiovascular polypill in the treatment of secondary prevention patients in Spain: a cost-effectiveness study. *Rev Esp Cardiol.* 2017;70(1):42–49. doi:10.1016/j.rec.2016.05.009
35. Marquina C, Zomer E, Vargas-Torres S, et al. Novel treatment strategies for secondary prevention of cardiovascular disease: a systematic review of cost-effectiveness. *Pharmacoeconomics.* 2020;38(10):1095–1113. doi:10.1007/s40273-020-00936-0
36. Ntaios G, Vemmos K, Papapetrou P, Zafeiri S, Rubio G. PCV53 cost-effectiveness of the CNIC polypill - fixed dose combination of acetylsalicylic acid, ramipril and atorvastatin - for the secondary prevention of cardiovascular disease in Greece. *Value Health.* 2019;22:S550. doi:10.1016/j.jval.2019.09.778
37. Aguiar C, Araujo F, Rubio-Mercade G, et al. Cost-effectiveness of the CNIC-polypill strategy compared with separate monocomponents in secondary prevention of cardiovascular and cerebrovascular disease in Portugal: the MERCURY study. *J Health Econ Outcomes Res.* 2022;9(2):134–146. doi:10.36469/001c.39768
38. Becerra V, Gracia A, Desai K, et al. Cost-effectiveness and public health benefit of secondary cardiovascular disease prevention from improved adherence using a polypill in the UK. *BMJ Open.* 2015;5(5):e007111. doi:10.1136/bmjopen-2014-007111

39. González-Juanatey JR, Cordero A, Castellano JM, et al. The CNIC-polypill reduces recurrent major cardiovascular events in real-life secondary prevention patients in Spain: the NEPTUNO study. *Int J Cardiol.* 2022;361:116–123. doi:10.1016/j.ijcard.2022.05.015
40. European network of centres for pharmacoepidemiology and pharmacovigilance. BIG-PAC; 2021. Available from: <http://www.encepp.eu/encepp/viewResource.htm?id=29236>. Accessed April 13, 2021.
41. Sicras-Mainar A, Enriquez JL, Hernández I, Sicras-Navarro A, Aymerich T, Leon M. PMU146 validation and representativeness of the Spanish BIG-PAC database: integrated computerized medical records for research into epidemiology, medicines and health resource use (real world evidence). *Value Health.* 2019;22:S734. doi:10.1016/j.jval.2019.09.1764
42. Ministerio de Sanidad, Consumo y Bienestar Social. International classification of diseases (9th edition) clinical modification (ICD-09-CM) [Ministry of Health, Consumption and Social Welfare. International classification of diseases (9th edition) clinical modification (ICD-09-CM)]; 2021. Available from: https://eciemaps.mscbs.gob.es/ecieMaps/browser/index_9_mc.html. Accessed June 11, 2021.
43. Matchar DB, McCrory DC, Orlando LA, et al. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension. *Ann Intern Med.* 2008;148(1):16–29. doi:10.7326/0003-4819-148-1-200801010-00189
44. Riella LV, Gabardi S, Chandraker A. Dyslipidemia and its therapeutic challenges in renal transplantation. *Am J Transplant.* 2012;12(8):1975–1982. doi:10.1111/j.1600-6143.2012.04084.x
45. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373–383. doi:10.1016/0021-9681(87)90171-8
46. World Health Organization. The Anatomical Therapeutic Chemical Classification System with Defined Daily Doses (ATC/DDD). Available from: <https://www.who.int/standards/classifications/other-classifications/the-anatomical-therapeutic-chemical-classification-system-with-defined-daily-doses>. Accessed April 8, 2021.
47. Consejo General de Colegios Oficiales de Farmacéuticos. BOT plus 2. Base de Datos de Medicamentos [General Council of Official Associations of Pharmacists. BOT plus 2. Medicines Database]. Available from: <https://botplusweb.portalfarma.com/>. Accessed April 13, 2021.
48. Instituto Nacional de Estadística. Ganancia media laboral por edad y sexo [National Institute of Statistics. Average labor earnings by age and sex]. Available from: <https://www.ine.es/dynt3/inebase/index.htm?padre=4563&capsel=4563>. Accessed April 8, 2021.
49. Official Journal of the European Union. Regulation (EU) 2016/679 of the European parliament and of the council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing directive 95/46/EC (general data protection regulation). Vol L119/1; 2016. Available from: <https://eur-lex.europa.eu/eli/reg/2016/679/oj>. Accessed April 13, 2021.
50. Boletín Oficial del Estado. Ley Orgánica 3/2018, de 5 de Diciembre, de Protección de Datos Personales y Garantía de Los Derechos Digitales. Vol 294 [Official State Gazette. Organic Law 3/2018, of December 5, 2018, on the Protection of Personal Data and Guarantee of Digital Rights]; 2018:119788–119857. Available from: <https://www.boe.es/buscar/doc.php?id=BOE-A-2018-16673>. Accessed April 13, 2021.
51. Castellano JM, Pocock SJ, Bhatt DL, et al. Polypill Strategy in Secondary Cardiovascular Prevention. *N Engl J Med.* 2022;387(11):967–977. doi:10.1056/NEJMoa2208275

Publish your work in this journal

ClinicoEconomics and Outcomes Research is an international, peer-reviewed open-access journal focusing on Health Technology Assessment, Pharmacoeconomics and Outcomes Research in the areas of diagnosis, medical devices, and clinical, surgical and pharmacological intervention. The economic impact of health policy and health systems organization also constitute important areas of coverage. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/clinicoeconomics-and-outcomes-research-journal>