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The CNIC-Polypill reduces recurrent major cardiovascular events in real-life secondary prevention patients in Spain: The NEPTUNO study

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ABSTRACT

Background: 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.

Methods: Retrospective, observational study using data from electronic-health records. Patients were distributed into 4 different cohorts: CNIC-Polypill (case cohort) *vs* 3 control cohorts: same monocomponents taken separately (Monocomponents), equipotent drugs (Equipotent) and other drugs not included in the previous cohorts (Other therapies). Patients were followed for 2 years or until MACE or death.

Results: After propensity score matching, a total of 6456 patients (1614 patients per cohort) were analysed. After 2 years, the risk of recurrent MACE was lower in the CNIC-Polypill cohort compared to the control groups (22%; $p = 0.017$, 25%; $p = 0.002$, 27%; $p = 0.001$, higher in the Monocomponents, Equipotent and Other therapies cohorts, respectively). The incremental proportion of patients who achieved blood pressure (BP) and low-density lipoprotein cholesterol (LDLc) control from baseline was higher in the CNIC-Polypill cohort *vs* control cohorts (BP controlled patients: +12.5% *vs* + 6.3%; $p < 0.05$, +2.2%; $p < 0.01$, +2.4%; $p < 0.01$, LDLc controlled patients: +10.3% *vs* + 4.9%; $p < 0.001$, +5.7%; $p < 0.001$, +4.9%; $p < 0.001$, respectively). Medication persistence was higher in patients treated with the CNIC-Polypill (72.1% *vs* 62.2%, 60.0% and 54.2%, respectively; $p < 0.001$) at study end.

Conclusions: In secondary prevention patients, compared with control groups, treatment with the CNIC-Polypill was associated with significant reductions in the accumulated incidence of recurrent MACE, improved BP and LDLc control rates, and increased medication persistence.

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1. Background

Patients with prior atherosclerotic cardiovascular disease (ASCVD) have a high risk of recurrent Major Acute Cardiovascular Events (MACE). It has been estimated that up to 50–75% of patients with previous myocardial infarction will have a recurrent CV event within 1–3 years after the acute cardiac event. Therefore, the long-term prognosis among patients with a previous cardiovascular event remains poor [1–3].

Atherosclerosis, the main underlying cause of cardiovascular disease, has a multifactorial origin, including non-modifiable cardiovascular risk factors, and others like hypertension, dyslipidaemia, diabetes or prothrombotic state, that might be modified by lifestyle changes and appropriate pharmacologic treatment [4]. As these cardiovascular risk factors cluster in a high proportion of patients with established ASCVD, they usually need therapies that target the different cardiovascular risk factors. Low-dose acetyl salicylic acid (ASA), angiotensin-converting enzyme inhibitors (ACEI), and statins are recommended in guidelines to reduce MACE in patients with established ASCVD [4–6].

The concept of cardiovascular polypills, aimed at targeting several risk factors at the same time with a single pill including various drugs, was first proposed in 2003 [7]. Since then, a number of clinical trials with different cardiovascular polypills have demonstrated improved adherence and risk factor control compared to usual care [8–12]. A limited number of clinical trials have shown benefits in terms of preventing MACE in primary and secondary prevention patients [9,13,14].

The CNIC-Polypill, designed by the Spanish National Centre for Cardiovascular Diseases (CNIC), contains ASA 100 mg, atorvastatin 20/40 mg and ramipril 2.5/5/10 mg [15]. The CNIC-Polypill is approved for use in secondary prevention of cardiovascular events as substitution therapy in adult patients adequately controlled with the monocomponents given concomitantly at equivalent therapeutic doses [15]. Clinical data to date with the CNIC-Polypill include a prospective randomized clinical trial which showed a significant improvement in adherence, as well as various real world studies which demonstrated significant risk factor control [10,12,16–20]. In addition, a pharmacodynamic study has shown that there might be a synergistic effect between ramipril and atorvastatin in the CNIC-Polypill as there is an additional 7% decrease in low-density lipoprotein cholesterol (LDLc) levels compared to atorvastatin alone [18]. Although a long-term prospective randomized clinical trial, the SECURE study (Secondary prevention of cardiovascular disease in the elderly) it is currently ongoing, for the time being, data about the efficacy of the CNIC-Polypill on MACE in secondary prevention patients are lacking.

The NEPTUNO study aimed to evaluate the effectiveness of the CNIC-Polypill on the incidence of recurrent MACE compared to three other therapeutic options in patients with ASCVD treated according to clinical practice. Secondary objectives included the effect of the CNIC-Polypill on cardiovascular risk factor control and on persistence to treatment.

2. Methods

2.1. Study design

NEPTUNO is a retrospective and non-interventional analysis of an anonymized medical history dataset covering patients contained in the BIG-PAC® administrative database during the years 2015–2018. The validity and the representativeness of this database have been demonstrated previously [21,22].

The study included adults with a diagnosis of ASCVD, defined as coronary heart disease (acute myocardial infarction, stable/unstable angina), cerebrovascular disease (ischaemic stroke, transient ischaemic attack), or peripheral artery disease (intermittent claudication, ischaemia, amputation), who initiated treatment for secondary prevention between January 1st 2015 and December 31st 2018 (index date).

Included patients were required to have available data from 1 year before and 2 years after the index date. By contrast, patients with any contraindication for use of any of the components of the CNIC-Polypill (haemodialysis, severe renal or hepatic impairment, gastrointestinal bleeding, peptic ulcer, cerebrovascular haemorrhage, history of angioedema, atrial fibrillation, severe mental disorders, or end-stage kidney disease) were excluded from the study.

2.2. Study cohorts

Patients were allocated into 4 different cohorts according to their therapy: **Cohort 1: CNIC-Polypill** (case cohort); patients treated with the CNIC-Polypill. The index date was the date of the first prescription of the CNIC-Polypill after a cardiovascular event between 2015 and 2018. **Cohort 2: Monocomponents**: identical monocomponents, but taken as loose medications. **Cohort 3: Equipotent medication**: patients treated with ASA, a statin (simvastatin or rosuvastatin) and an ACEI or an angiotensin II receptor blocker (ARB) (Enalapril or Valsartan, respectively). Supplementary Table 1 reports the equipotent doses of these drugs. The index date for cohorts 2 and 3 was the date of the first prescription of the last of the three drug classes. **Cohort 4: Other therapies**: patients treated with different drug combinations to those described in the prior cohorts or not receiving all three drug classes concomitantly. In this cohort, the date of the first dispensation of the last of the prescribed drug classes (some patients could receive only one or two drug classes) was considered as the index date (Supplementary Fig. 1). Patients were followed for 2 years from the index date or until the development of recurrent MACE or death (maximum follow-up until 31 December 2020). Cohorts 2, 3 and 4 were considered control cohorts.

2.3. Variables estimated at baseline

At baseline, biodemographic and comorbidity data, including age, gender, Charlson comorbidity index (high risk >3 points) [23], hypertension, diabetes, obesity, smoking status, renal impairment, heart failure, thromboembolism and HbA1c levels, as well as data from physical examination (body mass index [kg/m^2]), were collected.

Previous CV events (including coronary heart disease [acute myocardial infarction, stable/unstable angina], cerebrovascular disease [ischaemic stroke, transient ischaemic attack], peripheral artery disease [intermittent claudication, ischaemia, amputation]) were retrieved based on ICD-9 codes (https://eciemaps.mscbs.gob.es) (Supplementary Table 2). Additionally, cardiovascular risk factors (blood pressure, lipid profile [total cholesterol, LDLc, high-density lipoprotein cholesterol (HDLc) and triglycerides] recorded at baseline, defined as the last available data in the database before the index date, were included. Furthermore, concomitant treatments at baseline were also collected from the registries of dispensed medicines, according to the Anatomical Therapeutic Chemical Classification System [24].

2.4. Evaluation of variables during follow-up

The primary endpoint of the study was the accumulated incidence of recurrent MACE during 2 years of follow-up in all cohorts. Secondary endpoints were time to first recurrent cardiovascular event or death, blood pressure and LDLc control and persistence to therapy.

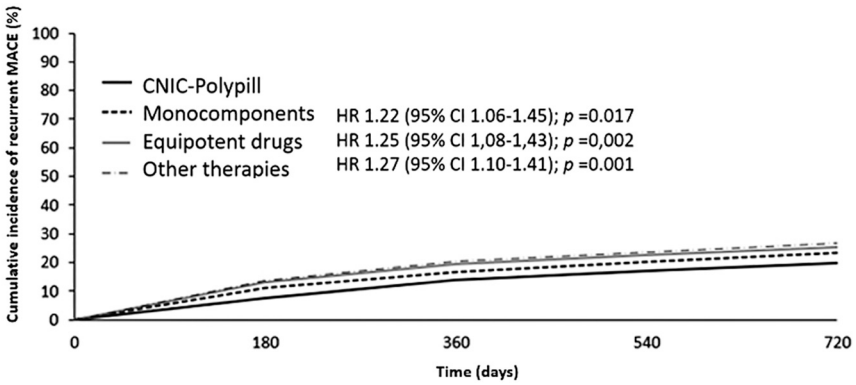
Changes in systolic/diastolic blood pressure and lipid variables from baseline until the last data available in the database were analysed. Additionally, the proportion of patients attaining the blood pressure goal of <130/80 mmHg, the LDLc target of <70 mg/dL (the target recommended by the guidelines at the time when the study was conducted) and the triglycerides goal of <150 mg/dL, were also estimated [25].

Persistence to treatment during the study was defined as the time, measured in days, without abandonment of initial treatment or without change to another medication at least 30 days after the initial

Table 1
Baseline data after propensity score matching (PSM).

	CNIC-Polypill cohort (N = 1614)	Monocomponents cohort (N = 1614)	Equipotent cohort (N = 1614)	Other therapies cohort (N = 1614)	p	SC
Biodemographic data and comorbidities						
Age, years, mean (SD)	63.5 (11.2)	63.1 (12.0)	63.5 (13.1)	63.0 (13.9)	0.550	0.036
≥75 years (%)	17.7	17.3	19.7	18.0	0.119	0.040
Gender, male (%)	60.5	60.3	60.3	60.6	0.998	0.002
Hypertension (%)	64.1	64.9	64.6	64.1	0.951	0.007
Diabetes mellitus (%)	26.8	26.3	26.5	26.1	0.982	0.005
Obesity (%)	16.5	16.1	16.5	16.1	0.974	0.006
Current smoker (%)	15.4	15.8	15.4	15.6	0.983	0.005
Charlson index, mean (SD)	2.1 (1.0)	2.1 (1)	2.1 (1)	2.1 (1)	0.875	0.007
Heart failure (%)	10.4	10.8	10.7	10.2	0.935	0.008
Renal impairment (%)	12.6	12.6	11.8	12.0	0.847	0.009
Thromboembolism (%)	2.5	2.5	2.4	2.5	0.999	0.002
HbA1c, % (SD)	8.1 (1.5)	8.0 (1.5)	8.3 (1.6)	8.4 (1.5)	<0.001	0.234
Physical examination						
Body mass index, kg/m^2(SD)	28.6 (4.4)	28.8 (4.4)	28.8 (4.3)	28.8 (4.4)	0.294	0.087
Prior cardiovascular events						
Cardiovascular events (%)						
Ischaemic heart disease	69.5	66.9	68.3	69.1	0.088	0.091
Cerebrovascular disease	21.9	23.9	21.7	20.7	0.064	0.055
Peripheral artery disease	8.6	9.2	10	10.2	0.115	0.031
Number of previous events, mean (SD)	1.1 (0.3)	1.1 (0.3)	1.1 (0.4)	1.1 (0.3)	0.264	0.082
1 event (%)	88.5	87.9	85.4	87.6		
2 events (%)	11.4	11.8	14	12.2	0.091	0.074
3 events (%)	0.1	0.3	0.6	0.2		
Time from diagnosis, days, mean (SD)	324.1 (176)	258.6 (127.2)	269.5 (119.9)	274.2 (161)	<0.001	0.257
Median (P25 – P75)	297 (181–430)	255 (151-369)	268 (166-374)	271 (130-417)		
Treatments						
Number of drugs, mean (SD)	4.6 (1.2)	4.6 (1.3)	4.6 (1.2)	4.5 (1.4)	0.255	0.057
Antithrombotic therapy (%)	100	100	100	92.6	<0.001	0.238
Lipid-lowering drugs (%)	100	100	100	93.1	<0.001	0.230
Renin-angiotensin-aldosterone (%)	100	100	100	87.7	<0.001	0.309
Insulin (%)	5.7	5.6	5.6	5.3	0.957	0.007
Antidiabetic (%)	23.6	24.5	24.0	23.7	0.935	0.008
Cardiac therapy (%)	8.8	9.4	9.1	9.2	0.944	0.008
Antihypertensive drugs (%)	51.2	51.1	51.7	51.5	0.986	0.005
Diuretic (%)	19.4	18.9	18.6	18.5	0.909	0.009
Beta blockers/calcium channel blockers (%)	51.6	50.7	51.7	51.7	0.935	0.008

p: statistical significance; SC: standardized coefficient; SD: standard deviation. P: percentile.



Nr. at risk	Day 0	Day 180	Day 360	Day 540	Day 720
CNIC-Polypill	1614	1491	1393	1336	1294
Monocomponents	1614	1434	1344	1285	1236
Equipotent drugs	1614	1404	1302	1251	1203
Other therapies	1614	1391	1282	1236	1182

Fig. 1. Cumulative incidence of recurrent MACE after 2 years of follow up in patients with established ASCVD treated with CNIC-Polypill and three other active treatment cohorts.
The figure shows the cumulative incidence of a first recurrent outcome event (death from cardiovascular causes, myocardial infarction, angina, ischaemic stroke, transient ischaemic attack or peripheral artery disease) for the comparison of the CNIC-Polypill with three active medication control cohorts (Monocomponents, Equipotents and Other therapies).
ASCVD: atherosclerotic cardiovascular disease; CI: confidence interval; MACE: major adverse cardiovascular event; HR: Hazard Ratio.

prescription.

2.5. Study approval and consent

The study was approved by the Ethics Committee of Research of the Consorci Sanitari de Terrassa. As data were completely anonymized, which was in accordance with local applicable legal requirements, informed consent from patients was not required.

2.6. Statistical analysis

As this was a descriptive study, data for all patients available in the database that met the inclusion/exclusion criteria were collected. Propensity score matching (PSM) was performed to minimize possible confounding variables and to allow comparability of the study cohorts. A 1:1 pairing was performed, *i.e.* for each case (CNIC-Polypill cohort), one control was obtained (matching) in each of the three control cohorts according to 23 prespecified variables (Supplementary Table 3). As a result, three PSM procedures were performed (cohort 1 *vs* cohorts 2, 3 and 4, respectively). The PSM was developed according to the greedy nearest neighbour algorithm, with replacement (substitution) and accepting a calliper (tolerance) of 0.20. Exact matches were prioritized (randomly). The homogeneity of the cohorts was tested using a logistic regression model. After conducting the PSM procedure, standardized coefficients (standardized differences) were provided in subsequent comparisons.

A univariate-descriptive analysis was performed. For qualitative data, absolute and relative frequencies were calculated and, for quantitative date, mean, standard deviation (SD), median and percentiles were provided. The 95% CI was calculated to estimate population parameters.

Bivariate analysis (comparison between cohorts), ANOVA (quantitative variables) and Chi-square test (qualitative variables) were used for independent groups. In addition, the Student's *t*-test and McNemar tests were used for paired samples or repeated measurements.

The raw incidence of MACE is presented in Kaplan-Meier survival curves. A Cox proportional risk regression model was performed to compare the incidence of recurrent MACE during the 2-year follow-up period. The risk of MACE was estimated as the hazard ratio [HR] and 95% confidence interval [CI]. Additionally, a bivariate regression analysis (successive steps procedure; Wald test) was performed to determine which variables recorded at baseline (independent variables), such as demographic variables, comorbidities, time from diagnosis and concomitant medications, were associated with the development of MACE during the follow-up period (dependent variable). The persistence/duration of treatment was analysed using a Kaplan-Meier survival analysis (procedure: log-rank test). A 0.05 level of statistical significance was applied in all statistical tests. Data were analysed using the SPSS (v27.0) statistical package (SPSS Inc., Chicago, Illinois, USA).

3. Results

3.1. Flow chart of patients

Out of 1.8 million people included in the BIG-PAC® database in 2015, 1.2 million sought medical attention during the 2015–2018 period and had data registered, of whom 980,682 were aged ≥18 years. Of these, 13,239 had a previous cardiovascular event. Overall, 4293 patients were excluded due to different reasons (*i.e.* inconsistent data, inactive in the database, follow-up not guaranteed, mental/terminal disease, atrial fibrillation, contraindications for the CNIC-polypill), with 8946 patients being enrolled in the study (1614 in the CNIC-Polypill cohort; 2475 in the Monocomponents cohort; 2193 in the Equipotent cohort; and 2664 in the Other therapies cohort). As these cohorts were not homogeneous (Supplementary Tables 4 and 5), PSM was performed. After PSM, a total of 6456 patients (1614 patients in each cohort) were finally analysed (Supplementary Fig. 2).

3.2. Baseline characteristics

After PSM, all cohorts were comparable in relation to baseline clinical characteristics. Approximately 60% of patients were male, nearly two-thirds had hypertension, 26% diabetes, 16% obesity, and 12% renal impairment. Nearly 70% of patients had ischaemic heart disease and the majority of patients had had only one cardiovascular event (Table 1).

Baseline treatments after PSM showed that whereas in the CNIC-Polypill, Monocomponents and Equipotent cohorts, all patients were receiving ASA 100 mg, a statin and an ACEI/ARB, in the Other therapies' cohort, only 86.1% were taking antiplatelet agents, 70.7% statins, and 87.7% ACEI/ARBs. Further information about the specific prescribed

Table 2
Proportion of patients with cardiovascular events or death and time to events after 2 years of follow up (post-PSM cohorts).

Total events	CNIC-Polypill cohort (N = 1614)	Monocomponents cohort (N = 1614)	Equipotent cohort (N = 1614)	Other therapies cohort (N = 1614)	*p*
Patients with recurrent MACE, % (95% CI)	19.8 (17.9–21.7)	23.3 (21.2–25.4)	25.5 (23.4–27.6)	26.8 (24.4–28.8)	<0.001
Mean number of cardiovascular events (SD) *	0.2 (0.4)	0.2 (0.5)	0.3 (0.5)	0.3 (0.5)	<0.001
0 events, %	80.2	76.7	74.5	73.2	
1 event, %	18.3	21.7	23.6	24.7	<0.001
≥2 events, %	1.5	1.5	1.9	2.1	
Time to CV event, days, mean (SD)	274.8 (195.5)	249.2 (201.5)	226.4 (203.4)	217.8 (184.5)	<0.001
Median (P25 - P75)	236 (107–413)	204 (76–373)	160 (50–351)	173 (57–337)	
Type of recurrent MACE, %					
Ischaemic heart disease	8.7	10.7	12	12.9	0.001
Cerebrovascular disease	5.6	6.9	6.7	7.9	0.08
Peripheral artery disease	7	7.2	8.7	8	0.256
Death, % (95% CI)	8.1 (6.8–9.4)	8.1 (6.8–9.4)	8.9 (7.5–10.3)	9.2 (7.8–10.6)	
Time to death, days, mean (SD)	406.3 (183)	395.6 (203.6)	387.2 (205.1)	386.6 (196.1)	0.357
Median (P25 - P75)	**392 (246–568)**	**322 (222–472)**	**333 (188–461)**	**367 (225–452)**	0.828

CI: confidence interval; CV: cardiovascular; MACE: major acute CV event. *p*: statistical significance; SD: standard deviation. P: Percentile *Categorized variable within the multivariate model.

drugs from the three therapeutic classes (antithrombotic agents, statins and ACEI/ARBs) is presented in Supplementary Table 6 and Supplementary Fig. 3.

3.3. Results after 2 years of follow up

3.3.1. Recurrent MACE

After 2 years of follow up, the incidence of recurrent MACE was lower in the CNIC-Polypill cohort *vs* the three control cohorts (19.8% *vs* 23.3%, 25.5% and 26.8%; $p < 0.001$). The risk of experiencing recurrent MACE was 22%, 25% and 27% higher in the Monocomponents, Equipotent and Other therapies cohorts compared with the CNIC-Polypill cohort (Monocomponents: HR 1.22; 95% CI 1.06–1.45; $p = 0.017$; Equipotent: HR 1.25; 95% CI 1.08–1.43; $p = 0.002$; and Other therapies: HR 1.27; 95% CI 1.10–1.41; $p = 0.001$) (Fig. 1).The most common type of cardiovascular event was ischaemic heart disease (44%), followed by peripheral artery disease (30%) and cerebrovascular disease (26%) (Table 2).

Bivariate logistic regression showed that age (odds ratio [OR] 1.03, 95% CI 1.02–1.04), more than one previous cardiovascular event (OR 1.32, 95% CI 1.21–1.44), and diabetes (OR 1.21, 95% CI 1.05–1.39) were independent predictors of experiencing subsequent cardiovascular events during the follow-up period. Among patients included in the CNIC-Polypill cohort, the independent variables of recurrent MACE were male sex (OR 1.54, 95% CI 1.15–2.1), more than one previous cardiovascular event (OR 1.28, 95%CI 1.05–2.07), and persistence with treatment (OR 1.71, 95% CI 1.31–2.23).

In addition, mean time to recurrent MACE was longer in the CNIC-Polypill cohort compared to control cohorts (Table 2 and Fig. 1). No significant differences were observed regarding death rates or time to death between cohorts (Table 2).

3.3.2. Cardiovascular risk factors

After 2 years of follow up, systolic and diastolic blood pressure decreased from baseline in all four cohorts, but this decrease was significantly higher in the CNIC-Polypill cohort compared to the control cohorts (systolic blood pressure: −14.1 *vs* − 11.7; −10.4; and −10.4 mmHg; [$p < 0.001$] and diastolic blood pressure: −4.5 *vs* − 2.5, −2.1 and −1.2 mmHg; [$p < 0.001$]) and also in the one-to-one comparison with each of the control cohorts (Table 3 and Supplementary Fig. 4). The proportion of patients achieving the blood pressure control goal of <130/80 mmHg increased significantly from baseline in the CNIC-Polypill and monocomponents cohorts, but was not significant in the other two cohorts. The incremental proportion of patients with controlled blood pressure after 2 years of therapy was significantly higher in the CNIC-Polypill cohort compared to each of the other cohorts [SBP/DBP <130/80mmHg: 44.1% vs 37.9 % ($p<0.05$); 34.6% ($p< 0.01$) and 32.4% ($p<0.01$) in the CNIC-Polypill cohort compared to monocomponents, equipotents and other therapies, respectively.] (Supplementary Table 7 and Supplementary Fig. 5).

In relation to the lipid profile, there was a significant reduction from baseline in total cholesterol, LDLc and triglycerides in all cohorts and this decrease was significantly higher in the CNIC-Polypill cohort when compared to the control cohorts (total cholesterol: −54.9 *vs* − 42.8, −31.7 and − 31.7 mg/dL [$p < 0.001$]; LDLc: −19.6 *vs* − 12.9, −12.3 and − 9.1 [$p < 0.001$]; triglycerides: −67.5 *vs* − 59.9, −56,1 and − 54.4 mg/dL [$p < 0.001$]), and also in the one-to-one comparison with each of the control cohorts (Table 3 and Supplementary Fig. 6). HDLc increased significantly from baseline in the CNIC-Polypill cohort when compared to the control cohorts (HDLc: 6.5 *vs* 4.6, 3.8 and 2.8 mg/dL; [$p < 0.001$] and when compared to each of the control cohorts (Table 3 and Supplementary Fig. 6). The proportion of patients achieving the LDLc goal of <70 mg/dL increased significantly from baseline in all four cohorts. The incremental proportion of patients with controlled LDLc after 2 years of therapy was significantly higher in the CNIC-Polypill cohort compared to each of the other cohorts [LDLc <70mg/dL: 15.4% vs 12.5 % ($p<0.001$);

Table 3
Evolution of blood pressure and lipid parameters after 2 years of follow-up (post-PSM cohorts).

	CNIC-Polypill ($n = 1614$)			Monocomponents ($n = 1614$)			Equipotents ($n = 1614$)			Other Therapies (n = 1614)		
Parameters	Baseline	Final	Difference	Baseline	Final	Difference	Baseline	Final	Difference	Baseline	Final	Difference
SBP, mmHg, mean (SD)	140.7 (21.0)	126.5 (20.8)	−14.1 (24.8)*	139.9 (21.3)	128.3 (20.9)	−11.7 (23.9)* ‡	139.4 (21.5)	129.1 (21.4)	−10.4 (24.3)* †	140.6 (22.4)	130.1 (21.6)	−10.4 (23.6)* †
DBP, mmHg, mean (SD)	81.8 (12.7)	77.3 (12.0)	−4.5 (13.3)*	82.1 (12.3)	79.5 (12.2)	−2.5 (12.0)* †	82.5 (12.5)	80.4 (12.0)	−2.1 (12.4)* †	82.3 (12.5)	81.1 (12.4)	−1.2 (12.7)* †
Total cholesterol, mg/dL, mean (SD)	229.4 (48.9)	174.6 (50.6)	−54.9 (43.2)*	230 (51.6)	187.2 (51.9)	−42.8 (45.2)* †	229.7 (46.9)	198.0 (48.0)	−31.7 (43.3)* †	229.8 (46.9)	198.1 (47.2)	−31.7 (42.4)* †
LDL cholesterol, mg/dL, mean (SD)	128.1 (41.1)	108.3 (40.3)	−19.6 (38.2)*	128.9 (43.6)	115.9 (43.0)	−12.9 (42.2)* ‡	130.1 (40.3)	117.4 (41.5)	−12.3 (39.7)* †	128.6 (40.0)	119.2 (41.5)	−9.1 (41.2)* †
HDL cholesterol, mg/dL, mean (SD)	48.9 (12.0)	55.4 (12.2)	6.5 (10.2)*	48.5 (12.3)	53.0 (12.5)	4.6 (10.5)*†	49.2 (13.6)	53.0 (13.5)	3.8 (11)*‡	48.9 (13.4)	51.8 (13.5)	2.8 (11.0)* †
Triglycerides, mg/dL, mean (SD)	235.8 (104.8)	168.3 (95.6)	−67.5 (98.7)*	236.8 (103.7)	176.9 (81.4)	−59.9 (80.3)* ‡	236.1 (93.2)	180.1 (86.3)	−56.1 (77.1)* †	236.2 (96.7)	181.7 (80.9)	−54.4 (79.5)* †

DBP: diastolic blood pressure; HDL: high-density lipoprotein: LDL: low-density lipoprotein; SBP: systolic blood pressure; SD: standard deviation.
*$p < 0.001$ *vs* baseline; †$p < 0.001$ and ‡$p < 0.01$ *vs* reference cohort: CNIC-Polypill.

12.8% (p< 0.001) and 11.6% (p<0.001) in the CNIC-Polypill cohort compared to monocomponents, equipotents and other therapies, respectively.] (Supplementary Table 7 and Supplementary Fig. 7). Similar results were obtained for triglycerides and HDLc (Table 3, Supplementary Table 7 and Supplementary Figs. 6 and 8).

3.3.3. Treatment persistence

More patients in the CNIC-polypill cohort remained on treatment compared with all other cohorts (72.1% *vs* 62.2%, 60,0% and 54,2%, respectively; $p < 0.001$) after 2 years of follow up. Consequently, treatment duration was significantly longer in the CNIC-Polypill cohort [627 *vs* 596.2, 590.2 and 573.3 days, respectively; $p < 0.001$] (Supplementary Table 10).

All patients in the four cohorts were also taking additional medications, such as ezetimibe, fibrates or other blood pressure-lowering agents from other therapeutic classes, with no differences at baseline. After 2 years of follow up, concomitant therapy was intensified in all cohorts similarly, with higher use of calcium channel blockers in the Other therapies cohort. There was not a use of a higher amount of medication in the CNIC-Polypill cohort. The total mean number of treatments by the end of follow-up was significantly lower in the CNIC-Polypill cohort compared to the control cohorts (4.7 *vs* 4.8, 4.9 and 4.8. [$p = 0.042$]) (Supplementary Table 8). Further information about the specific prescribed drugs and doses from the different therapeutic classes can be found in Supplementary Fig. 9 and Supplementary Table 9.

4. Discussion

The NEPTUNO study is, to our knowledge, the first study that has shown that the use of the CNIC- Polypill is associated with a significant reduction in the incidence of recurrent MACE, together with a delay to time to event, in a large sample of real-world patients with a history of ASCVD compared with three different active treatment control groups (Monocomponents, Equipotent and Other therapies). In addition, the CNIC-Polypill provides greater blood pressure and lipid control rates, as well as higher medication persistence. These results may reinforce the utility of these strategy for secondary CV prevention in clinical practice.

Results in reduction in MACE following a therapeutic approach with a polypill strategy have been recently published [9] but this was a meta-analysis conducted in primary prevention population and the control cohorts were placebo or a non-pharmacologic intervention, thus the results are not comparable.

Baseline clinical characteristics and the prevalence of established cardiovascular disease (cardiovascular, cerebrovascular or peripheral artery disease) were in line with other published studies that included patients with established ASCVD [26,27]. Of note, in our study time from diagnosis was different after PMS between cohorts. But it should be taken into account that the CNIC-Polypill was launched on 2015 in Spain and its regular use in clinical practice started later.

The improvement in CV risk factors (BP and lipid profile) with the CNIC-Polypill compared with prior therapy had already been documented in a real-world study carried out in Mexico where marked reductions in blood pressure (from 147/89 mmHg to 128/80 mmHg; $p < 0.001$) and LDLc levels (from 132 mg/dL to 108 mg/dL; $p < 0.001$) after 1 year of treatment with the CNIC-Polypill were shown [12,16]. Remarkably, in the case of the Neptuno study, the significant improvement took place compared to the treatment with the identical monocomponents or equipotent drugs after 2 years of follow up.

Reasons that could explain this fact are, in the first place, the significant increase in treatment persistence in the CNIC-Polypill cohort compared to the other 3 cohorts. This is in line with other prior studies in which higher adherence to the CNIC-Polypill therapy was assessed [10,17]. The importance of full adherence to medication (≥80%) in post-MI patients was shown in another claim database study in over 4000 patients in which those patients who were fully adherent to their prescribed secondary prevention medications had significantly better event-free survival, with a 27% risk reduction of MACE [28]. In the second place, the patient's preferences could also be involved, as in a recent study, patients preferred the CNIC-Polypill compared to the same individual drugs, which translates into greater medication adherence rates [29]. Finally, a synergistic effect between the polypill components (ramipril and atorvastatin *vs* atorvastatin alone) that would increase the beneficial effect on LDLc reduction without increasing the adverse event rate has been suggested [18]. This is concordant with another study that also showed the synergistic effect of combining ACEI and statins in patients with coronary heart disease, resulting in a lower incidence of cardiovascular events in this subgroup [30]. In the Neptuno study, the improvement in CV risk factors cannot be attributed to a higher amount of concomitant medication in the CNIC-Polypill cohort, as the intensification in therapy was very similar in all four cohorts during the follow up of the study.

Although the LDLc and BP control rate achieved by the end of the two years of follow up in the Neptuno study was significantly higher in the CNIC-Polypill cohort compared to the other 3 cohorts, a great amount of patients in all the cohorts did not reach the treatment goals recommended by the guidelines and not even the 32% LDLc or 50% BP control rate observed in the EUROSPIRE V study [26]. Due to its retrospective design, the NEPTUNO study reflects the real-world clinical practice. The fact that patients still remain uncontrolled, even after the addition of supplementary medication in all cohorts indicates that in

Spain, intensification of therapies for CV prevention in these very high-risk patients is urgently warranted.

Thus, the CNIC-Polypill used as baseline therapy following the stepwise approach recommended by the 2021 CV prevention guidelines [4] could help in achieving CV risk factor goals, as there is the possibility of intensifying therapy by adding further antihypertensive drugs in single or double combination to attain blood pressure goals and/or adding ezetimibe alone, or in combination with atorvastatin or PCSK9 inhibitors, to obtain LDLc targets in a second step [4]. This strategy assures that patients take at least the three fundamental drugs once a day and provides additional flexibility to build the complete therapy for patients.

Our study might have some limitations. As this study had a retrospective design, with data collected from electronic health records, some diagnoses or treatments (*i.e.* dose modifications) may not have been recorded adequately. However, the retrospective analysis is the best design to determine the role of a therapeutic approach in current clinical practice, as no specific intervention was used in the study. Furthermore, the high number of included patients and the quality of the recorded data, may reduce any potential bias. In addition, the BIG-PAC® database has been validated in previous studies [21,22].Remarkably, the time from the previous event to the index date was not considered as matching variable. Although analysis of propensity matching by average treatment effect in the treated (ATT) could have added power by improving SE magnitudes [31], analysis by average treatment effect (ATE) was performed as it is also considered acceptable to show comparability between cohorts. On the other hand, all patients, except those that died, were followed during 2 years in all cohorts of the study. Persistence referred only to treatment, but the estimation of parameters was calculated at the end of the follow up (2 years). This was the same for all cohorts and no heterogeneity was observed between them. However, although PSM was performed to homogenize the cohorts, patients were not assigned randomly to different treatment arms. Consequently, only indirect causality may be suggested. In any case, specific prospective studies should be conducted to confirm the results obtained in our study. In this context, the SECURE trial (NCT02596126) is an ongoing prospective randomized trial to evaluate whether the CNIC-Polypill will reduce the rate of death from CV causes, nonfatal myocardial infarction, stroke, and hospitalization requiring revascularization, when compared to usual care among patients with type 1 myocardial infarction aged ≥65 years from seven European countries.

5. Conclusions

The NEPTUNO study has shown that, in patients with established ASCVD, the CNIC-Polypill (ASA 100 mg, atorvastatin 20/40 mg and ramipril 2.5/5/10 mg) is associated with significant reductions in recurrent MACE, improvements in blood pressure, lipids and medication persistence, reducing the total number of pills, compared with three control groups (Monocomponents, Equipotent or Other therapies). For that reason, these results reinforce the use of the CNIC-Polypill as a baseline treatment for patients with established ASCVD, contemplating the addition of other drugs to achieve CV risk factor control and consequently decrease the incidence of recurrent MACE.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

All authors have contributed significantly to the conception, design, or acquisition of data, or analysis and interpretation of data. All authors have participated in in drafting, reviewing, and/or revising the manuscript and have approved its submission.

Declaration of Competing Interest

José Ramón González-Juanatey has received honoraria for consulting and lectures from: Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, MSD, Daichii-Sankyo, Ferrer International, Novartis, Lilly, Sanofi y Servier.

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Appendix A. Supplementary data

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