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**ORIGINAL ARTICLE**
*Coronary artery disease*

# The CNIC-polypill (acetylsalicylic acid, atorvastatin, and ramipril), an effective and cost-saving secondary prevention strategy compared with other therapeutic options in patients with ischaemic heart disease

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**Aims** The retrospective NEPTUNO study evaluated the effectiveness of the Centro Nacional de Investigaciones Cardiovasculares (CNIC)-polypill (including acetylsalicylic acid, ramipril, and atorvastatin) vs. other therapeutic approaches in secondary prevention for cardiovascular (CV) disease. In this substudy, the focus was on the subgroup of patients with ischaemic heart disease (IHD).

**Methods and results** Patients on four strategies: CNIC-polypill, its monocomponents as loose medications, equipotent medications, and other therapies. The primary endpoint was the incidence of recurrent major adverse CV events (MACEs) after 2 years. After matching, 1080 patients were included in each cohort. The CNIC-polypill cohort had a significantly lower incidence of recurrent MACE compared with monocomponents, equipotent drugs, and other therapies cohorts (16.1 vs. 24, 24.4, and 24.3%, respectively; $P < 0.001$). The hazard ratios (HRs) for recurrent MACE were higher in monocomponents (HR = 1.12; $P = 0.042$), equipotent drugs (HR = 1.14; $P = 0.031$), and other therapies cohorts (HR = 1.17; $P = 0.016$) compared with the CNIC-polypill, with a number needed to treat of 12 patients to prevent a MACE. The CNIC-polypill demonstrated a greater reduction in LDL cholesterol (LDL-c; −56.1 vs. −43.6, −33.3, and −33.2% in the monocomponents, equipotent drugs, and other therapies, respectively; $P < 0.001$) and systolic blood pressure (−13.7 vs. −11.5, −10.6, and −9.1% in the CNIC-polypill, monocomponents, equipotent drugs, and other therapies, respectively; $P < 0.001$) compared with other cohorts. The CNIC-polypill intervention was less costly and more effective than any other therapeutic option, with €2317–€2407 cost savings per event prevented.

**Conclusion** In IHD, the CNIC-polypill exemplifies a guideline-recommended secondary prevention treatment linked to better outcomes and cost saving compared with other therapeutic options.

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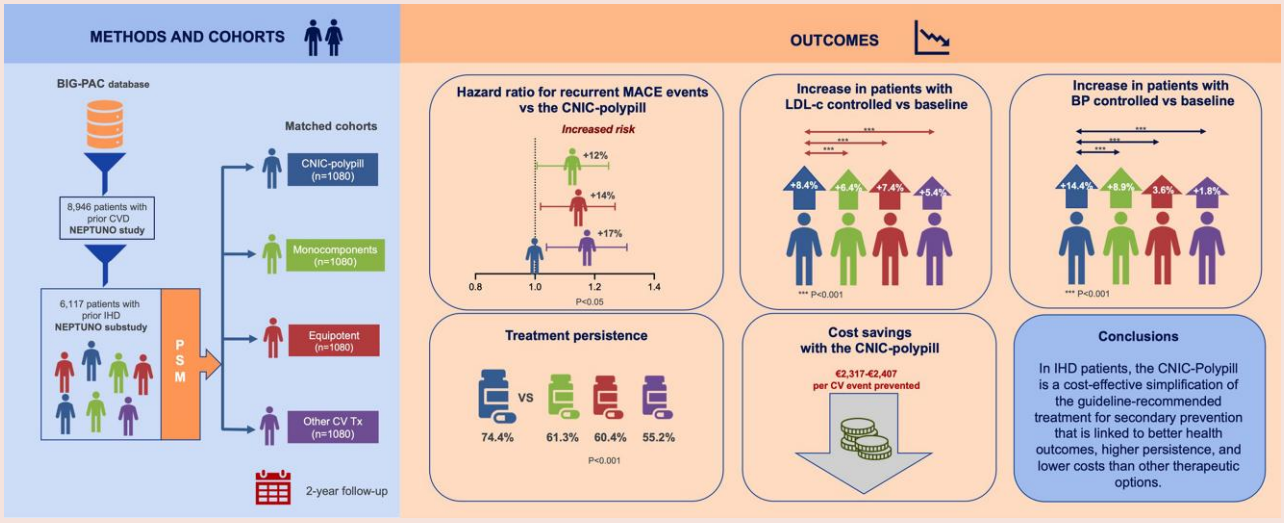
## Graphical Abstract




**Keywords** Secondary prevention • Ischaemic heart disease • Cardiovascular events • MACE • Healthcare costs • CNIC-polypill

# Introduction

The major components of cardiovascular diseases (CVDs) encompass ischaemic heart disease (IHD), ischaemic cerebrovascular disease, and peripheral arterial disease (PAD). Survivors of each cardiovascular (CV) event face a significantly heightened risk of subsequent ischaemic events, CV death, or hospitalization.[1,2] Although recurrent CV events typically occur within the same disease category as the first event,[3–5] patients with IHD have the highest incidence of non-fatal myocardial infarction (MI), whereas those with cerebrovascular disease show the highest non-fatal stroke rates.[2] Shared vascular risk factors vary among CVD categories, with diabetes mellitus, hypercholesterolaemia, and male sex showing stronger associations with MI, while hypertension is more strongly linked to stroke,[6] and smoking emerges as the most influential risk factor for PAD.[7] Lastly, the financial impact of non-fatal CV events differs by disease category, with patients experiencing acute coronary syndrome (ACS) being more frequently readmitted to the hospital following the initial CV event compared with stroke patients.[8]

The pharmacological treatments recommended by the guidelines for very high-risk patients with established CVD include lipid-lowering drugs, antihypertensive agents, and antiplatelet therapy (and other drugs depending on the associated comorbidities).[9–11] In this context, the CV polypill strategy, combining generic pharmaceutical components to simultaneously target major CV risk factors, was initially proposed for primary and secondary CVD prevention.[12] The first commercially available polypill for secondary CV prevention in Europe, known as the Centro Nacional de Investigaciones Cardiovasculares (CNIC)-polypill, consists of 100 mg of acetylsalicylic acid (ASA), 20 or 40 mg of atorvastatin, and 2.5, 5, or 10 mg of ramipril.[13,14] The inclusion of ASA in the pill aligns with established guidelines recommending antiplatelet therapy in patients with a history of CV events. Therefore, the CNIC-polypill is specifically indicated for secondary prevention of CVD in adult patients who are already well-controlled on concomitantly administered monocomponents at therapeutically equivalent doses.[13,14]

In real-world clinical practice for secondary prevention of CVD, the CNIC-polypill has demonstrated efficacy in reducing and controlling blood pressure (BP) and LDL-c, improving the overall lipid profile.[15–18] The SECURE randomized clinical trial showed that the CNIC-polypill strategy in post-acute MI patients was associated with a significant reduction in major CV events, driven by a significant 33% reduction in CV mortality.[18] For that reason, the polypill containing ASA, atorvastatin and ramipril are recommended in the 2023 European Society of Cardiology (ESC) guidelines for the management of ACS,[19] the 2023 European Society of Hypertension guidelines for the management of hypertension in patients in secondary prevention,[20] and has been included in the WHO essential medicines list.[21] A retrospective observational study conducted in subjects with an established CVD (NEPTUNO study) reported that the CNIC-polypill significantly reduced the cumulative incidence of recurrent major adverse CV event (MACE) compared with three alternative options: separate administration of the same individual monocomponents, equipotent drugs, and other medications not included in the other cohorts.[22] Additionally, health economic assessments conducted in the MERCURY cost-effectiveness analysis (CEA) and model-based CEAs based on NEPTUNO effectiveness data concluded that the CNIC-polypill is a cost-effective therapeutic strategy compared with other approaches.[23–25] These findings underscore the growing body of evidence advocating for the incorporation of polypills in CV care.[26–28]

The NEPTUNO study included the following categories of CVD: IHD (acute MI and stable/unstable angina), ischaemic cerebrovascular disease [ischaemic stroke and transient ischaemic attack (TIA)], and PAD (intermittent claudication, ischaemia, and amputation). Given the potential variations in CV risk factors, prevalence, therapeutic management, prognosis, and financial costs associated with recurrent CV events among different categories of CVD, our objective was to assess the effectiveness of the CNIC-polypill specifically in a subgroup of patients with IHD, which represents the most prevalent form of CVD.[29] For this, we extracted data pertaining to this specific subgroup from the NEPTUNO primary study. Our evaluation encompassed the 2-year cumulative incidence and risk of recurrent MACE, clinical

effectiveness in controlling CV risk factors, medication persistence, and utilization of healthcare resources and costs, comparing these outcomes with other therapeutic strategies.

# Methods

## Study design and patients

This subanalysis was conducted within the framework of the primary retrospective, non-interventional, multicentre NEPTUNO study, with the detailed methodology having been previously published.[22] In summary, the primary study used clinical data extracted from anonymized medical records in the BIG-PAC® administrative database spanning the period between 2015 and 2018. The current study focused on patients with prior CV events, including IHD encompassing acute or old MI or stable/unstable angina, cerebrovascular disease involving ischaemic stroke or transient TIA, and PAD involving intermittent claudication, ischaemia, or amputation, all within the context of secondary prevention. For this *post hoc* analysis, only patients with International Statistical Classification of Diseases and Related Health Problems Ninth Revision, Clinical Modification (ICD-9-CM) codes corresponding to acute or old MI (Codes 410 and 412) or stable/unstable angina pectoris (Codes 411 and 413) were included. The original study received approval from the Ethics Committee (EC) of the Hospital Consorci Sanitari de Terrassa. Since the proposed subanalysis does not alter the study's objectives, there was no requirement for resubmission of the project as an amendment to the EC.

## Study cohorts

As previously described,[22] patients were subdivided into four different cohorts based on the therapy received: Cohort 1 (see Supplementary material online, *Table S1*): CNIC-polypill (case–cohort), patients treated with the CNIC-polypill containing 100 mg aspirin, 20 or 40 mg atorvastatin and 2.5, 5, or 10 mg ramipril; Cohort 2: Monocomponents: identical monocomponents, but taken as loose medications; Cohort 3: Equipotent medication: patients treated with ASA, a statin (simvastatin or rosuvastatin) and angiotensin-converting-enzyme inhibitors (ACEi) or an angiotensin receptor blocker (ARB) (enalapril or valsartan, respectively); and 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.

## Study variables and outcomes

The primary objective of this study was the cumulative incidence of recurrent MACE (IHD, PAD, ischaemic cerebrovascular disease, or CV death) over a 2-year follow-up period across all cohorts. Secondary endpoints included the time to the occurrence of the first recurrent CV event or CV death, control of BP and LDL-c levels, and therapeutic persistence. Therapeutic persistence was defined as the duration, measured in days, during which patients did not discontinue the initial treatment or switch to another medication for at least 30 days following the initial prescription. Dose adjustments were not considered indicative of a lack of therapeutic persistence.

For the economic analysis, we conducted a deterministic cost-effectiveness analysis from a societal perspective with a 2-year time horizon. Direct healthcare costs were estimated as the products of healthcare resource utilization (HCRU; including inpatient and outpatient care) during the follow-up period multiplied by the corresponding unit cost (see Supplementary material online, *Table S2*).[30] Medication costs were calculated as the costs for prescribed drugs according to the pharmacy sales price at the prescription date in the BOT PLUS drugs database.[31] Non-healthcare (indirect) costs were estimated based on the number of sick leave days due to temporary or permanent disability and calculated by multiplying the number of sick leave days by the mean daily loss of productivity for a working person in Spain in the related calendar year.[32] All costs were expressed in euros at 2020 rates.

## Statistical analysis

Stratified propensity score matching (PSM) technique was performed to match the four cohorts 1:1 with baseline variables as covariates (see Supplementary material online, *Table S3*). 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). Absolute and relative frequencies were calculated for qualitative variables, and the mean, standard deviation (SD), median, and percentiles were calculated for quantitative variables. The incidence of MACE was assessed using Kaplan–Meier survival curves. The incidence among the groups was compared using a Cox proportional risk regression model, estimated as the hazard ratio and 95% confidence interval (CI). The persistence/duration of treatment was analysed using Kaplan–Meier survival analysis (log-rank test procedure). Quantitative variables were compared among the groups using analysis of variance (ANOVA) and $\chi^2$ tests for quantitative and qualitative variables, respectively. Student's *t*-tests and McNemar's tests were used for paired samples or repeated measurements. A generalized linear model analysis of covariance (ANCOVA) was developed to correct costs, considering age, sex, and Charlson comorbidity index scores as covariates by estimating the marginal average with Bonferroni adjustment.

The incremental cost-effectiveness ratio per CV event prevented was estimated as $(C_1 - C_0)/(E_1 - E_0)$, where $C_1$ is the total cost in the CNIC-polypill group, $C_0$ the cost in the control cohorts (monocomponents, equipotent or other therapies groups), $E_1$ is the effectiveness (estimated as the percentage of patients without CV events) in the CNIC-polypill group, and $E_0$ is the effectiveness in the control cohorts (monocomponents, equipotent, or other therapies groups).

A two-sided significance level of 0.05 was set in all statistical tests. The data were analysed using the SPSS (v27.0) statistical package (SPSS Inc., Chicago, IL, USA).

# Results

From 8946 subjects with established CVD in the main NEPTUNO study, 6117 (68.4%) were diagnosed with IHD and were used for the PSM technique (see Supplementary material online, *Figure S1*). After matching, 1080 patients remained in each cohort (i.e. CNIC-polypill, monocomponents, equipotent, and other therapies). The mean overall age was 62.9 years, and there was a preponderance of male patients (61.3%). The matched cohorts were well-balanced for most demographic characteristics, baseline comorbidities, and CV risk factors (*Table 1*). Approximately half of the patients across the cohorts were on more than four medications at baseline (*Table 1*). Almost all patients received ASA and statins, and approximately 53% antihypertensives (in nearly all cases, renin-angiotensin-aldosterone system [RAA] inhibitors).

## Cumulative incidence and risk of recurrent major adverse cardiovascular event

During the 2-year follow-up, MACE occurred in 22.2% of all patients, and the most frequent subsequent CV event observed across cohorts was another IHD (58.6%), followed by PAD (23.1%) and ischaemic cerebrovascular disease (18.3%; see Supplementary material online, *Figure S2*). The recurrent MACE incidence was significantly lower in patients treated with the CNIC-polypill than in all other cohorts [16.1% (95% CI = 13.9–18.3) vs. 24.0% (21.5–26.5) in those on monocomponents, 24.4% (21.8–27.0) among those on equipotent drugs, and 24.2% (21.7–26.9) in those on other therapies; $P < 0.001$; *Figure 1A*]. Compared with patients in the CNIC-polypill cohort, all other treatment groups had a greater risk of recurrent MACE (12, 14, and 17% increased risk among monocomponents, equipotent, or other therapies cohorts, respectively; $P < 0.05$; *Figure 1B*), with a calculated number needed to treat of 12 patients to prevent a recurrent event. The median time to the recurrent MACE was significantly longer among patients in the CNIC-polypill (229 vs. 228–168 days across the control cohorts; $P = 0.004$; *Table 2*).

Cardiovascular death occurred in 8.1% of overall patients, but the incidence and the time to CV death were similar among cohorts ($P =$

**Table 1** Baseline characteristics of the studied cohorts after propensity score matching

| Characteristic | CNIC-polypill ($n = 1080$) | Monocomponents ($n = 1080$) | Equipotent ($n = 1080$) | Other therapies ($n = 1080$) | *P*-value | Standardized coefficient |
|---|---|---|---|---|---|---|
| Age, years, mean (SD) | 63.2 (11.4) | 62.7 (11.9) | 63.4 (12.9) | 62.6 (13.6) | 0.369 | 0.038 |
| Sex, male (%) | 61.2 | 61.2 | 61.9 | 60.8 | 0.961 | 0.014 |
| Comorbidities, % | | | | | | |
| Hypercholesterolaemia | 63.2 | 62.7 | 64.0 | 63.5 | 0.852 | 0.026 |
| Hypertension | 63.2 | 63.6 | 63.3 | 63.3 | 0.998 | 0.008 |
| Diabetes mellitus | 26.6 | 27.2 | 26.1 | 26.4 | 0.946 | 0.014 |
| Obesity | 15.6 | 15.6 | 15.1 | 15.0 | 0.967 | 0.000 |
| Chronic kidney disease | 12.2 | 11.5 | 12.4 | 12.3 | 0.909 | 0.006 |
| Heart failure | 11.9 | 11.9 | 11.5 | 11.1 | 0.916 | 0.000 |
| Thromboembolism | 2.7 | 2.0 | 2.7 | 2.5 | 0.740 | 0.000 |
| CV risk factors | | | | | | |
| Current smoker, % | 13.6 | 13.9 | 13.2 | 13.9 | 0.968 | 0.009 |
| BMI, kg/m$^2$, mean (SD) | 28.4 (4.2) | 29 (4.3) | 28.9 (4.3) | 29 (4.3) | 0.005 | |
| HbA1c, % (SD) | 8.1 (1.4) | 8.1 (1.5) | 8.1 (1.6) | 8.1 (1.5) | 0.985 | |
| Lipid profile, mg/dL, mean (SD) | | | | | | |
| Total cholesterol | 227.7 (50.7) | 229 (52.2) | 229.8 (48.7) | 229.7 (47) | 0.757 | |
| LDL-c | 126.8 (42.8) | 127.7 (43.7) | 127.8 (41.8) | 127.7 (40.1) | 0.948 | |
| LDL-c <55, % | 1.2 | 3.2 | 2.6 | 2.6 | 0.017 | |
| LDL-c <70, % | 7.9 | 8.0 | 7.9 | 7.1 | 0.875 | |
| LDL-c <100, % | 26.4 | 26.6 | 26.1 | 26.4 | 0.996 | |
| HDL-c | 48.4 (11.9) | 47.6 (11.8) | 48.4 (13.3) | 48.5 (13.3) | 0.375 | |
| Triglycerides | 238.2 (90.8) | 239.9 (93.1) | 239.7 (91.9) | 238.2 (89.9) | 0.954 | |
| Triglycerides <150, % | 12.2 | 12.0 | 13.9 | 13.4 | 0.500 | |
| Triglycerides <200, % | 41.8 | 40.6 | 41.5 | 41.3 | 0.960 | |
| Blood pressure, mm Hg, mean (SD) | | | | | | |
| SBP | 139.5 (21.1) | 138.6 (21.8) | 139.2 (21.7) | 139.4 (22.6) | 0.779 | |
| DBP | 81.7 (13) | 81.9 (12.5) | 82.4 (13) | 82.1 (12.8) | 0.549 | |
| SBP/DBP <130/80, % | 31.5 | 29.6 | 32.7 | 29.6 | 0.332 | |
| Charlson comorbidity index, mean (SD) | 2.1 (1) | 2.1 (1) | 2.1 (1) | 2.1 (1) | 0.771 | 0.014 |
| Charlson comorbidity index, score, % | | | | | | |
| 1 | 35.3 | 32.7 | 33.1 | 30.4 | | −0.055 |
| 2 | 32.9 | 36.0 | 35.6 | 36.5 | | 0.065 |
| ≥3 | 31.9 | 31.3 | 31.3 | 33.1 | 0.402 | 0.026 |
| Prior CV events | | | | | | |
| Event category, *n* (%) | | | | | | |
| IHD | 1080 (100%) | 1080 (100%) | 1080 (100%) | 1080 (100%) | | — |

*Continued*

**Table 1** *Continued*

| Characteristic | CNIC-polypill (*n* = 1080) | Monocomponents (*n* = 1080) | Equipotent (*n* = 1080) | Other therapies (*n* = 1080) | *P*-value | Standardized coefficient |
|---|---|---|---|---|---|---|
| Acute myocardial infarction | 449 (41.6) | 456 (42.2) | 444 (41.1) | 435 (40.3) | 0.369 | 0.012 |
| Stable Angina | 476 (44.1) | 471 (43.6) | 468 (43.3) | 465 (43.0) | 0.815 | −0.010 |
| Unstable angina | 155 (14.3) | 153 (14.2) | 168 (15.6) | 180 (16.7) | 0.108 | 0.064 |
| Number of previous events, mean (SD) | 1.1 (0.3) | 1.1 (0.3) | 1.2 (0.4) | 1.1 (0.3) | <0.001 | 0.231 |
| 1 event (%) | 88.9 | 88.4 | 81.4 | 90.0 | | 0.036 |
| 2 events (%) | 11.0 | 11.4 | 17.9 | 9.8 | | 0.197 |
| 3 events (%) | 0.1 | 0.2 | 0.7 | 0.2 | <0.001 | 0.095 |
| Time from diagnosis to the index date, days, mean (SD) | 262.8 (187.2) | 259.1 (189.9) | 232.5 (202.4) | 208 (171.7) | 0.004 | 0.205 |
| Time from diagnosis to the index date, days, median (P25–P75) | 229 (107.5–394.8) | 228 (104–370) | 189 (54–351) | 168 (62.3–308.8) | | |
| **Pharmacological treatment** | | | | | | |
| Number of drugs, mean (SD) | 4.7 (1.2) | 4.8 (1.3) | 4.7 (1.3) | 4.7 (1.4) | 0.134 | 0.028 |
| Number of drugs, *n* (%) | | | | | | |
| ≤2 | 0.0 | 0.0 | 0.0 | 4.4 | | 0.303 |
| 3 | 17.3 | 16.5 | 17.3 | 17.4 | | 0.003 |
| 4 | 32.7 | 31.8 | 30.9 | 26.3 | | −0.019 |
| ≥5 | 50.0 | 51.8 | 51.8 | 51.9 | <0.001 | 0.038 |
| Antithrombotic therapy, % | 100.0 | 100.0 | 100.0 | 93.9 | <0.001 | — |
| Lipid-lowering drugs, % | 100.0 | 100.0 | 100.0 | 93.5 | <0.001 | — |
| Antihypertensive drugs, % | 53.2 | 52.3 | 53.1 | 53.0 | 0.976 | −0.002 |
| Renin–angiotensin–aldosterone inhibitors | 100.0 | 100.0 | 100.0 | 89.4 | <0.001 | — |
| Beta-blockers/calcium channel blockers | 58.6 | 59.0 | 57.6 | 57.3 | 0.838 | 0.008 |
| Diuretics | 19.4 | 20.7 | 19.9 | 20.0 | 0.900 | 0.032 |
| Cardiac therapy, %[a] | 10.6 | 10.8 | 11.4 | 11.0 | 0.939 | 0.026 |
| Antidiabetic drugs, % | 24.5 | 25.3 | 25.5 | 24.8 | 0.958 | 0.023 |
| Insulin, % | 5.2 | 5.9 | 5.5 | 5.4 | 0.892 | 0.031 |

BMI, body mass index; HbA1c, haemoglobin A1c; CNIC-polypill, acetylsalicylic acid 100 mg, atorvastatin 20/40 mg, and ramipril 2.5/5.0/10 mg; CV, cardiovascular; DBP, diastolic blood pressure; HDL-c, HDL cholesterol; IHD, ischaemic heart disease; LDL-c, LDL cholesterol; P25–P75, 25th percentile–75th percentile; PAD, peripheral artery disease; SBP, systolic blood pressure; SD, standard deviation.

[a]Includes cardiac glycosides, antiarrhythmics (Classes I and III), cardiac stimulants excluding cardiac glycosides, vasodilators used in cardiac diseases, and other cardiac preparations.

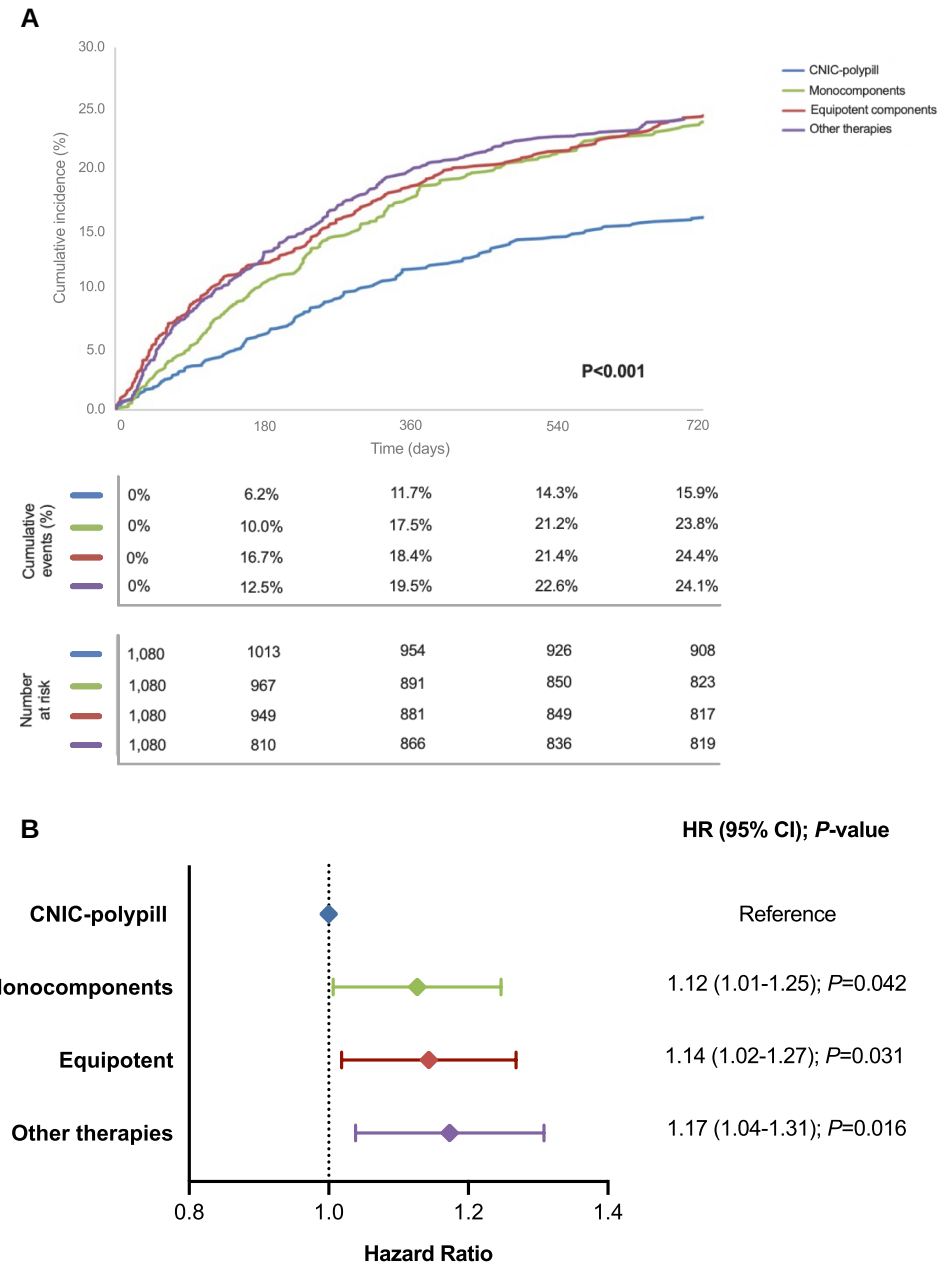



**Figure 1** Cumulative incidence of major adverse cardiovascular event of individuals evaluated at 2 years (*A*) and risk of major adverse cardiovascular event (*B*) among the different treatment cohorts. CI, confidence interval; CNIC-polypill, acetylsalicylic acid 100 mg, atorvastatin 20/40 mg, and ramipril 2.5/5.0/10 mg; HR, hazard ratio.

0.936 and $P = 0.489$, respectively; *Table 2* and Supplementary material online, *Figure S2*).

## Cardiovascular risk factors evolution and control

After 2 years, the lipid profile improved from baseline in all treatment cohorts ($P < 0.001$), but the magnitude of the observed change was significantly greater among patients in the CNIC-polypill and greater than that of each of the three control cohorts for all the assessed parameters (all $P < 0.001$; *Figure 2A–D*). The proportion of patients achieving an LDL-c goal of <55 or <70 mg/dL at the end of the study was not significantly different between cohorts; however, the increase from baseline in the number of controlled patients was significantly greater in the CNIC-polypill cohort than in each of the control cohorts (all $P < 0.001$; Supplementary material online, *Figure S3*). Conversely, the least strict LDL-c goal of <100 mg/dL was achieved in a significantly greater proportion of patients in the CNIC-polypill cohort (52.6 vs. 36.4–43.8% across the control cohorts; $P < 0.001$), and the number of controlled patients was also greater in the CNIC-polypill cohort than in each of the control cohorts (all $P < 0.001$). This pattern was also observed when assessing the proportion of patients achieving triglycerides levels

**Table 2 Time to recurrent major adverse cardiovascular event and cardiovascular death at 2 years follow-up**

| Event | CNIC-polypill (*n* = 1080) | Monocomponents (*n* = 1080) | Equipotent (*n* = 1080) | Other therapies (*n* = 1080) | *P*-value |
|---|---|---|---|---|---|
| CV events, *n* (%) | 174 (16.1) | 259 (24.0%)* | 263 (24.4%)** | 262 (24.3%)** | <0.001 |
| Time to MACE, days | | | | | |
| Mean (SD) | 262.8 (187.2) | 259.1 (189.9) | 232.5 (202.4) | 208 (171.7) | 0.004 |
| Median (P25–P75) | 229 (107.5–394.8) | 228 (104–370) | 189 (54–351) | 168 (62.3–308.8) | |
| CV deaths | 87 (8.1) | 86 (8.0) | 93 (8.6) | 86 (8.0) | 0.936 |
| Time to CV death, days | | | | | |
| Mean (SD) | 406.1 (188.1) | 384.7 (205.2) | 363.1 (204.6) | 370 (196.8) | 0.489 |
| Median (P25–P75) | 389 (246–574) | 402 (208.5–564) | 358 (179–536) | 351.5 (226–520.3) | |

CV, cardiovascular; P25–P75, 25th percentile–75th percentile; MACE, major adverse cardiovascular event; SD, standard deviation.
*$P < 0.01$; **$P < 0.001$; reference cohort: CNIC-polypill (acetylsalicylic acid 100 mg, atorvastatin 20/40 mg, and ramipril 2.5/5.0/10 mg).

<150 and <200 mg/dL at the end of the study, with more patients in the CNIC-polypill able to achieve either goal ($P < 0.001$) and showing a significantly greater change in the proportion of patients at these goals compared with each of the control groups (all $P < 0.001$; Supplementary material online, *Figure S4*).

There was a significant decrease from baseline in both systolic BP and diastolic BP in all cohorts ($P < 0.001$), although the greatest reductions were observed among patients in the CNIC-polypill cohort and were greater than those observed in each of the control cohorts ($P < 0.001$; *Figure 2E and F*). As for BP control, the proportion of patients reaching <130/80 mmHg was greater among patients in the CNIC-polypill cohort (14.4 vs. 1.8–8.9% across control cohorts; $P < 0.001$), and the magnitude of the change was also greater in the CNIC-polypill compared with each of the other control groups (all $P < 0.001$; Supplementary material online, *Figure S5*).

## Treatment persistence and concomitant treatments

Persistence at 1 and 2 years was significantly higher in patients treated with the CNIC-polypill than in the control cohorts (87.3 vs. 79.0–81.9%, $P < 0.001$; and 74.4 vs. 55.2–61.3%, $P < 0.001$, respectively; Supplementary material online, *Figure S6*). Moreover, the number of patients who abandoned the treatment during the 2-year follow-up was significantly lower among those prescribed the CNIC-polypill than in the other cohorts (25.6 vs. 38., 39.6, and 44.8% in the monocomponents, equipotent, and other therapies, respectively; $P < 0.001$).

The number of patients needed five or more drugs slightly increased from baseline in all cohorts (from 51.4 to 58.6%), but the smallest increase was observed in the CNIC-polypill group (55.3 vs. 57.7–61.2% across other cohorts; $P < 0.001$; Supplementary material online, *Table S4*). In the case of antihypertensives, the proportion of subjects requiring additional drugs increased (52.9% at baseline and 57.9% at 2 years) but was lower among CNIC-polypill users than in the other treatment groups (54.3 vs. 58.6–59.9%; $P = 0.04$). Lastly, the percentages of patients requiring additional medications besides their CV preventive treatment, such as insulin, non-insulin antidiabetic drugs, cardiac therapy, or other antihypertensives such as beta-blockers (BBs), calcium channel blockers (CCBs), or diuretics, was slightly higher at the end of the study compared with baseline in all cohorts (see Supplementary material online, *Table S4*). However, this increase was non-significant across cohorts for diuretics and insulin, whereas it was significantly lower among CNIC-polypill users than in any of the other cohorts regarding BB/CCB, cardiac therapy, and antidiabetic drugs.

## Healthcare resource utilization and costs

Overall, primary care visits and productivity losses were the largest components of the overall resource use across cohorts. The average per-patient HCRU was significantly lower among CNIC-polypill patients than in the other cohorts for all assessed resources except laboratory tests (*Table 3*). For instance, the average proportion of CNIC-polypill patients requiring hospitalization was lower and was associated with fewer inpatient days ($P < 0.001$). Similarly, fewer CNIC-polypill patients were on sick leave than in the other cohorts ($P < 0.001$), and the average duration of the sick leave was significantly shorter ($P = 0.021$).

The adjusted average total (direct and indirect) cost per patient during the follow-up was lower among patients on the CNIC-polypill compared with each of the other cohorts (€4485 vs. monocomponents: €5824, equipotent: €5805 and other therapies: €5869; all $P < 0.001$; *Figure 3*). Direct costs (HCRU-associated costs and medication costs) represented 86.6% of the total costs, and in terms of cost components, the highest contributors were pharmacy and inpatient stays (see Supplementary material online, *Table S5*). In addition, direct cost components in the CNIC-polypill cohort were significantly lower than those in the other cohorts.

## Cost-effectiveness

After 2 years of follow-up, the mean average cost of the CNIC-polypill intervention per patient was lower than that of other therapeutic options (−€1339, −€1320, and −€1384 difference with respect to the monocomponents, equipotent, and other therapies, respectively; Supplementary material online, *Table S6*). Moreover, the proportion of patients experiencing a recurrent MACE was lower in the CNIC-polypill strategy (−7.9, −8.3, and −8.2% difference with respect to the monocomponents, equipotent, and other therapies, respectively). Therefore, the CNIC-polypill strategy was considered an economically dominant strategy, that is, it avoided more recurrent CV events and was less costly than any other therapeutic option, with savings exceeding €2000 per event prevented compared with other options (difference −€2317 to −€2407 across groups).

# Discussion

Compared with other therapeutic strategies, patients with IHD treated with the CNIC-polypill had a reduced incidence, risk, and time to a subsequent MACE. Moreover, it provided better control of preventable CV risk factors (i.e. BP and lipid profile), was associated with greater medication persistence, and was a cost-effective strategy.

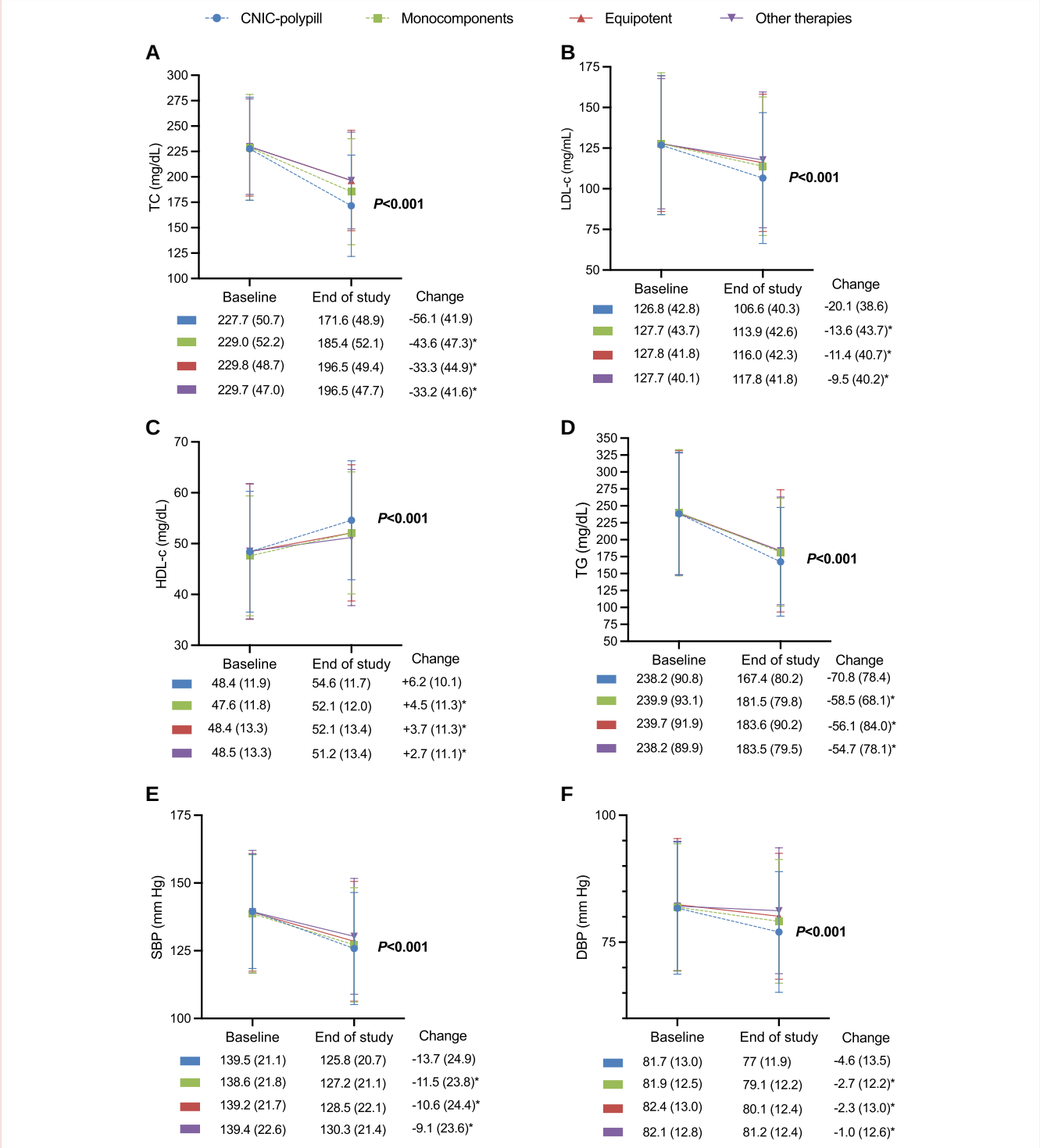



**Figure 2** Evolution of cardiovascular risk factors from baseline for lipid parameters (*A*–*D*) and blood pressure (*E*, *F*) by treatment cohort. *$P < 0.001$, with the CNIC-polypill (acetylsalicylic acid 100 mg, atorvastatin 20/40 mg, and ramipril 2.5/5.0/10 mg) as the reference cohort. CV, cardiovascular; DBP, diastolic blood pressure; HDL-c, HDL cholesterol; LDL-c, LDL cholesterol; SBP, systolic blood pressure; SD, standard deviation.

In agreement with the results of the NEPTUNO primary study, the rate, risk, and time to subsequent MACE in patients with IHD were significantly lower in the CNIC-polypill cohort compared with the three other strategies.[22] Moreover, the recent results of the prospective, randomized SECURE trial conducted in 2499 post-MI patients over 65 years followed for a median of 3 years confirmed that there was a 24% risk reduction in recurrent MACE with the CNIC-polypill strategy compared with usual care, mainly driven by a 33% risk reduction in CV death.[18] The observed significant reduction in MACE in the polypill group compared with patients on loose medications may be attributed to enhanced treatment

**Table 3 Average number per-patient health care resource utilization in the different treatment cohorts during the 2year follow-up**

| Resource | CNIC-polypill (*n* = 1080) | Monocomponents (*n* = 1080) | Equipotent (*n* = 1080) | Other therapies (*n* = 1080) | *P*-value |
|---|---|---|---|---|---|
| Medical visits, average (SD) | | | | | |
| Primary care | 16.3 (12.2) | 18.5 (14.4) | 19.9 (14.1) | 21.2 (13.3) | <0.001 |
| Specialized | 5.8 (4.7) | 7.3 (5.8) | 7.5 (7.4) | 7.9 (7.4) | <0.001 |
| Emergency department | 0.9 (2.9) | 1.8 (2.7) | 2.0 (3) | 2.4 (3.1) | <0.001 |
| Inpatient stays, % | 13.6% | 19.2% | 21.7% | 20.2% | <0.001 |
| Inpatient days | 1.9 (5.6) | 3.2 (8.1) | 3.8 (8.3) | 3.2 (7.4) | <0.001 |
| Rehabilitation sessions | 0.6 (2.9) | 1.1 (3.2) | 1.0 (3) | 1.0 (2.9) | 0.002 |
| Non-invasive diagnostic procedures, average (SD) | | | | | |
| Laboratory tests | 3.2 (3.5) | 2.9 (3.1) | 2.8 (2.9) | 3.2 (3.1) | 0.006 |
| Conventional radiology | 1.8 (1.6) | 2.2 (1.7) | 2.2 (1.7) | 2.0 (1.7) | <0.001 |
| Computed tomography | 0.3 (0.7) | 0.4 (0.8) | 0.5 (0.8) | 0.4 (0.8) | <0.001 |
| Magnetic nuclear resonance | 0.1 (0.3) | 0.3 (0.6) | 0.3 (0.6) | 0.4 (0.7) | <0.001 |
| Other diagnostic/therapeutic tests | 0.3 (0.7) | 0.4 (0.8) | 0.5 (0.9) | 0.7 (1) | <0.001 |
| Patients on sick leave, % | 10.2% | 15.3% | 14.8% | 16.1% | <0.001 |
| Sick leave days | 5.9 (22.7) | 9.4 (31.8) | 7.9 (26.9) | 8.5 (27.2) | 0.021 |

CNIC-polypill, acetylsalicylic acid 100 mg, atorvastatin 20/40 mg, and ramipril 2.5/5.0/10 mg; HCRU, health care resource utilization; SD, standard deviation.

persistence. Indeed, adherence to vascular medications is crucial in preventing CVD, with approximately 9% of CVD events in Europe attributed to poor medication adherence.[33] Additionally, optimal adherence significantly reduces adverse outcomes, as seen in a post-MI cohort where fully adherent individuals had a 27% lower risk of MACE compared with non-adherent individuals.[34] However, beyond increased adherence, other non-mutually exclusive mechanisms could contribute to the observed lower risk of MACE in patients receiving the CNIC-polypill. The GREACE study demonstrated that combined treatment with a statin and an ACEi significantly reduced CV events more effectively than each drug alone or neither drug, particularly in high-risk dyslipidaemic coronary heart disease (CHD) patients.[35] Building on these observations, a recent pharmacodynamic trial comparing the CNIC-polypill with atorvastatin and ramipril taken separately showed that the polypill group had greater reductions in LDL-c levels.[36] Notably, in this Phase I study adherence was 100% in both groups, suggesting a potential synergistic effect of the polypill components. Collectively, these studies contribute to our evolving understanding of potential synergies between statins and BP-lowering agents in CV risk reduction.

In line with the results of the original NEPTUNO study,[22] treatment with CNIC-polypill improved the lipid profile and BP control rates in the subgroup of patients with IHD compared with other therapeutic strategies. However, no substantial differences in LDL-c or BP were observed between the CNIC-polypill and the usual care group of the SECURE trial.[18] A possible explanation for this discrepancy may be related to the different designs. Indeed, the NEPTUNO study was retrospective and observational, whereas the SECURE trial was a Phase 3, randomized, controlled clinical trial. Although in both studies the increase in adherence/persistence was around 10%,[18,22] in prospective studies, patients may have enhanced adherence around the days of the scheduled study visits. In contrast, patients are unaware that they will be studied retrospectively. Moreover, patients in the real-world NEPTUNO study were much less well-controlled at baseline than those in the SECURE trial, so they had a much greater chance of improvement with similar treatment. Finally, more than 40% of the patients in the usual care arm of the SECURE trial were on statins with an intensity higher than the 20/40 mg of atorvastatin contained in the CNIC-polypill (e.g. atorvastatin 80 mg or rosuvastatin 10 mg), showing that, at lower doses, the polypill produces similar outcomes.

In the current study, it was quite striking that, despite the high prescription rate of recommended drugs in all cohorts, the proportion of patients with inadequate BP and LDL-c was still high at the end of the study. It is worth noting that the study period, spanning 2015–2018, coincided with ESC and the European Atherosclerosis Society (ESC/EAS) guidelines recommending an LDL-c target of <70 mg/dL (<1.8 mmol/L),[37] whereas this goal was subsequently revised to <55 mg/mL (<1.4 mmol/L) in the ESC/EAS 2019 update.[38] Despite this, the proportion of patients with LDL-c < 70 mg/dL (<1.8 mmol/L) remained lower in our IHD population (16.3% in the best cohort, that is, the CNIC-polypill) compared with the EUROASPIRE V survey (32% in patients using lipid-lowering drugs) and other international studies conducted before 2019 (43–61%).[39–41] As for the recent stricter goal of <55 mg/dL (<1.4 mmol/L), it was anticipated that the proportion of patients meeting this goal target would be markedly lower (4.6% in the CNIC-polypill cohort). However, this figure is much lower than the 20% reported among patients at high and very high-risk across Europe,[42] and it lags behind the results observed in other international studies conducted before 2019 (13.4–23.4%).[41,43] This low target achievement is of concern considering that the 1-year risk of subsequent CV events is inversely related to risk factor control[44] and that the rate of a subsequent CV event or death significantly increases with underuse and poor statins adherence.[45–47] However, treatment persistence at the conclusion of our study remained notably high in the CNIC-polypill cohort (74.4 vs. 55.2–61.3% across other cohorts), exceeding the 60% adherence to CV medications in patients with CVD reported in a meta-analysis.[33] Despite the high persistence observed after 2 years of treatment, our study showed a reduction in therapy adherence over time, a trend evident even within the CNIC-polypill group. This observation underscores the imperative for continuous patient monitoring and emphasizes the challenges associated with maintaining therapy adherence over the long term.[48] Additionally, our results highlight the importance of adopting comprehensive, long-term approaches that prioritize consistent lipid management to meet therapeutic goals.

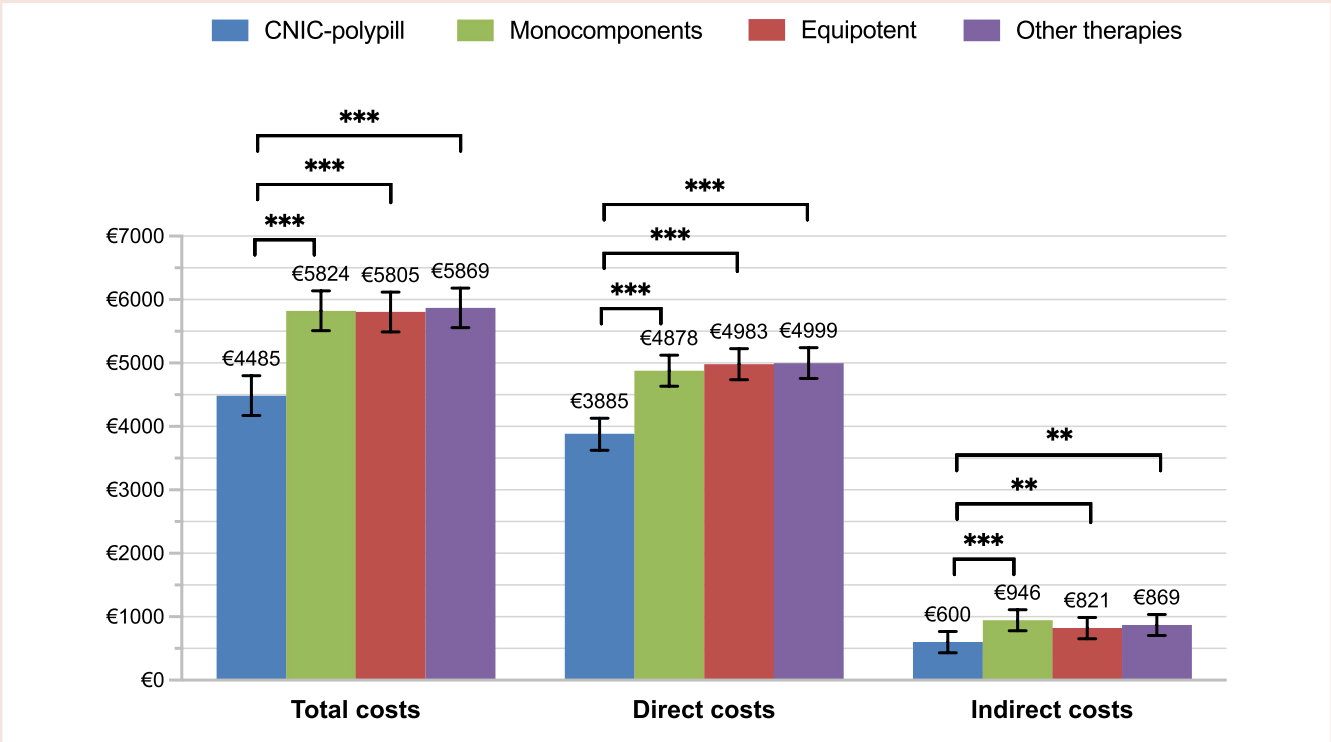



**Figure 3** Adjusted average costs* per patient during the follow-up by treatment cohort. *Models corrected for age, sex, and Charlson comorbidity index. **$P < 0.01$, with the CNIC-polypill (acetylsalicylic acid 100 mg, atorvastatin 20/40 mg, and ramipril 2.5/5.0/10 mg) as the reference cohort. ***$P < 0.001$, with the CNIC-polypill (acetylsalicylic acid 100 mg, atorvastatin 20/40 mg, and ramipril 2.5/5.0/10 mg) as the reference cohort.

Other reasons for not achieving the goals in CV risk factor control, as mentioned in the EUROSPIRE registry, include that lipid-lowering treatment is not used to its full potential, with statin dosages not maximized (moderate intensity), infrequent up-titration of doses following treatment initiation, and scarce use of combination therapies.[39] In our study, only about half of the patients used high-intensity statins, which agrees with the 50% reported in the EUROSPIRE V survey and the 42.8% reported in Spanish registries of patients with stable IHD.[39,49] In keeping with this, a simulation in patients with a recent MI estimated that the <55 mg/dL goal could be reached in approximately 20% of patients using high-intensity statin monotherapy and in another 30% by adding ezetimibe, while half of the patients would still be eligible for treatment with PCSK9 inhibitors if the target was not reached.[43] Additionally, a recent study assessing the upfront combination therapy of a statin and ezetimibe in patients with ACS showed that the risk of all-cause mortality was significantly reduced compared with statin monotherapy through a 3-year follow-up period.[50] Although inappropriate therapeutic management was apparent across all four treatment cohorts, the CNIC-polypill strategy exhibited superiority in reducing recurrent MACE. Consequently, we advocate for considering the polypill as the baseline therapy while customizing additional interventions based on specific patient requirements. For instance, to attain LDL-c goals, a combinatory approach like polypill + ezetimibe ± PCSK9 inhibitor, as needed, could be contemplated.[51–53] Similarly, for hypertension management, a regimen involving polypill + a beta-blocker ± a calcium channel blocker ± a diuretic tailored to individual needs may prove beneficial.[51–53] Lastly, while our study primarily reflects the current guideline-recommended use of aspirin in polypill strategies, it is noteworthy that ongoing discussions, supported by a meta-analysis,[54] suggest the potential benefits of $P2Y_{12}$ inhibitors for long-term secondary prevention in patients with coronary artery disease (CAD). The consideration of future polypill formulations may need to account for evolving evidence and specific patient populations, such as those with a history of gastrointestinal bleeding or predisposing factors.[55]

The fact that primary care visits and productivity losses were the largest components of resource use in all cohorts is in line with a real-world study conducted in Spain on patients with recent MI.[56] Moreover, the largest contributors to overall costs were direct costs, with hospitalization and medication as the main drivers, which is in line with the 2017 analysis of the European Heart Network.[57] In our study, patients treated with the CNIC-polypill incurred significantly less HCRU and lower adjusted healthcare and non-healthcare costs than those in the other cohorts. This is in line with the primary NEPTUNO trial, which included other CVD (i.e. cerebrovascular diseases and PDA), except that lost work productivity (sick leave) costs were similar between treatment cohorts.[24] The reason for this difference could be related to the differential proportion of patients with productivity losses due to morbidity between CVD categories, which in Europe is higher among patients with stroke than IHD,[58] and in Spain represents 27 and 16% of all non-healthcare costs, respectively.[57] Finally, our study found that the CNIC-polypill was a dominant strategy (i.e. a more effective and cost-saving approach than the other regimens) in patients with IHD in secondary prevention. This result is in line with the results of the MERCURY cost-effectiveness analysis, where the CNIC-polypill strategy was cost-effective compared with monocomponents from the perspective of the National Health System in Portugal in patients who have suffered a CHD event or a stroke.[23] This is also in line with the conclusions of a recent systematic literature review where the CV polypill (consisting of ASA, a lipid-lowering agent, and at least one antihypertensive drug) was cost-effective compared with the standard treatment for secondary prevention in patients with at least one non-fatal coronary heart event.[59]

Although a retrospective database study design might be generally considered a limitation, the fact that there is no influence on patients' adherence to

medication reflects real-world scenarios and current clinical practice in secondary prevention populations with patients from different geographical regions and age groups. Most notably, the comparators included a range of therapeutic options, from monocomponents to equipotent components and other therapies, to minimize the risk of potentially attributing a differential effect of the CNIC-polypill driven by less potent or suboptimal therapeutic regimens. However, this study has several limitations that need to be acknowledged. Firstly, the retrospective design has inherent drawbacks, such as coding errors or data omissions. Secondly, although we conducted a PSM technique to correct baseline imbalances and approximate a completely randomized experiment, we cannot discard additional potential confounders, such as statin dose or disease duration.[60] Thirdly, a potential limitation is selection bias if patients were given a particular treatment approach based on patient and investigator preferences or perceptions (e.g. age, severity, perceived poor prognosis, or comorbidities). Fourthly, the investigation, conducted between 2015 and 2018, corresponds with a phase in which the ESC/EAS guidelines recommended an LDL-c target of <70 mg/dL. However, these guidelines were subsequently updated in 2019, introducing a more stringent target of <55 mg/dL. This shift in recommended LDL-c targets poses a limitation as our study predominantly reflects the clinical practices and outcomes during the earlier guideline period. Fifthly, since the time from the diagnosis of the first CV event to the index date was longer in the CNIC-polypill and monocomponents cohorts, we cannot discard the possibility that this somehow influenced the results regarding the time to subsequent MACE. However, in all the cohorts, the median time was <1 year, when the main incidence of recurrent events after acute MI is described to occur.[2] Another limitation of our study is the absence of detailed information on other adverse events beyond major clinical outcomes. The BIG-PAC® database, from which our data is derived, primarily emphasizes clinical outcomes, and thus, the lack of comprehensive data on adverse events (AE) restricts our capacity to offer an exhaustive safety profile for the various regimens investigated in this study. Lastly, we only estimated production losses due to morbidity, whereas production losses due to mortality and informal care may represent up to 21 and 63% of all non-healthcare costs, respectively, in patients with IHD.[57]

# Conclusions

Using the CNIC-polypill strategy as baseline therapy in patients in secondary prevention following IHD was advantageous compared with other treatment options in terms of the incidence of recurrent MACE, improvement of CV risk factors, and cost-effectiveness. The CNIC-polypill (ASA, atorvastatin, and ramipril) exemplifies a cost-effective simplification of the guideline-recommended treatment linked to better health outcomes and higher persistence to therapy.

# Lead author biography

Regina Dalmau is a MD at the University Hospital la Paz in Madrid, Spain, and a PhD candidate at the Autonomous University of Madrid. She obtained a Master's Degree in Cardiology and in Management of Clinical Units. Her areas of expertise are cardiovascular prevention and cardiac imaging. She has been the Spanish National Coordinator of cardiovascular prevention at the ESC from 2014 to 2021 and has been actively involved in registries such as EUROASPIRE IV and V, SURF 2, and ESC-EORP-HFA Heart Failure Long-Term Registry. She has collaborated as investigator in many clinical trials related to ischaemic heart disease.

## Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

# Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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**Conflict of interest:** R.D. reports consulting fees from Ferrer International, Amarin Sanofi, and Amgen; payment or honoraria for lectures from Novo Nordisk, Novartis, Ferrer, Amarin, Sanofi, Daiichi Sankio, and AMGEN; support for attending meetings and/or travel from Ferrer International, Novartis, Sanofi, Amarin, and Daiichi Sankio; has participated on Data Safety Monitoring Board or Advisory Board for Sanofi, and holds leadership or fiduciary roles in the World Heart Federation. A.C. reports honoraria consulting fees from AstraZeneca, Ferrer, Sanofi, AMGEN, Novartis, Lilly, Novo Nordisk, and Amarin; payment or honoraria for lectures from AstraZeneca, Ferrer, Sanofi, AMGEN, Novartis, Lilly, Novo Nordisk, and Amarin; and support for attending meetings and/or travel from Ferrer, Sanofi, AMGEN, Daiichi Sankio, Novartis, Novo Nordisk, and Amarin. L.M. reports honoraria consulting fees and payment or honoraria for lectures from Amgen, Sanofi, Novartis, Ferrer International, Servier, Daiichi Sankyo, Amarin, and Amryt. E.R. is a current worker at Ferrer International. A.S.-M. was working at Atrys Health at the time of the study. J.R.G.-J. reports honoraria for consulting and lectures from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, MSD, Daichi Sankyo, Ferrer International, Novartis, Lilly, Sanofi, and Servier.

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