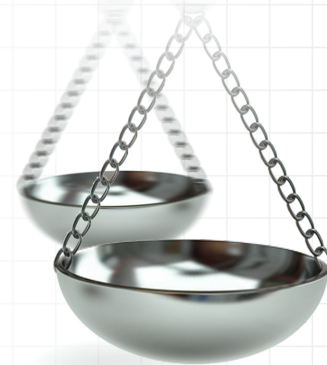




Evaluating patients' satisfaction and preferences with a secondary prevention cardiovascular polypill: the Aurora Study

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Aim: To evaluate the satisfaction, preferences and adherence of patients in secondary cardiovascular prevention treated with the Spanish National Cardiovascular Research Centre cardiovascular polypill compared with patients treated with the separate monocomponents. **Methods:** Observational, cross-sectional and multicenter study. Satisfaction was evaluated by the Treatment Satisfaction Questionnaire for Medication 9 items, adherence by the Morisky-Green questionnaire and *ad-hoc* questions were asked regarding patient preferences. **Results:** Polypill patients reported higher satisfaction than patients treated with the monocomponents (77.3 vs 71.2%; $p < 0.0001$). 72.8% of patients treated with the monocomponents would prefer to change to the polypill. Patients treated with the polypill had significantly higher adherence than patients treated with the monocomponents (57.7 vs 41.1%; $p = 0.0027$). **Conclusion:** Polypill patients show higher satisfaction and better adherence. Most patients receiving the monocomponents would prefer a polypill regime.

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Secondary prevention is key to reduce recurrent events in cardiovascular disease (CVD) patients. The European Society of Cardiology (ESC) Committee for Practice Guidelines and the American College of Cardiology/American Heart Association Task Force recommend statins, angiotensin-converting enzyme inhibitors (ACEi) and low-dose acetylsalicylic acid (ASA) among the most effective drugs to reduce repeated events in this very high-risk patient group [1,2]. As this is a lifelong indication, patients must persist on these treatments for several years. Unfortunately, a high proportion of these patients abandon their treatments soon after hospital discharge [3,4].

During the last 15 years, the concept of a CV polypill, a therapeutic strategy based on a single pill containing more than one medication with proven benefit for CV prevention and targeting more than one modifiable CV risk factors, has emerged as one of the most scalable strategies to reduce CVD burden [5]. Through an improvement in adherence and persistence, CV polypills have demonstrated to improve blood pressure or LDL cholesterol control [6] and more importantly, to reduce the incidence of CV events [7]. In particular, the Spanish National Cardiovascular Research Centre (CNIC) polypill was specifically developed for a secondary CV prevention and comprises ASA, an ACEi (ramipril) and a statin (atorvastatin), three of the most effective drug classes after a CV event that tackles three different modifiable risk factors [5]. Additional medication can be added on top of the polypill for a further fine-tuned risk factor control. Therefore, a CV polypill might be considered as a baseline treatment to optimize the CV risk in very-high risk patients [8]. Indeed, ESC guidelines on cardiovascular prevention stated that a CV

polypill should be considered as an integral part of a comprehensive CVD prevention strategy, together with lifestyle changes, to improve CV risk factor control [9,10].

One potential additional strength of CV polypills is to improve health-related quality of life (HRQoL) [11]. To improve the HRQoL of patients, doctors should understand what patients' need and how they feel [12]. Patients need, not only to be comprehensively informed about different treatment options, but also to express their preferences. Indeed, well informed patients and whose preferences have been taken into account, will adhere better to recommended life changes and pharmacological treatments [13].

Thus, the aim of the present study was to explore patients' preferences and satisfaction on being treated with the individual tablets or using the CNIC polypill in a secondary prevention setting as well as to evaluate treatment adherence with both regimes in routine clinical practice in Spain and Belgium. To the best of our knowledge, this is the first study to analyze patients' preferences and satisfaction with a CV polypill in real-world settings in Europe.

Methods

This was an observational, cross-sectional, multi-centric, two-cohort study with the participation of 32 investigator sites in Spain and four investigator sites in Belgium, conducted between July 2016 and September 2018. Each investigator site included consecutive patients in accordance with the selection criteria. Each investigator had to include 12 patients, 6 patients in each study cohort. However, due to the slow recruitment, inclusion became competitive. There were no interventions involving ongoing medications and/or decisions of the physicians. The registry was carried out following the current clinical guidelines and according to current clinical practice and was approved by the Spanish Agency of Medicines and Medical Devices and by the Independent Ethics Committee of the different hospitals involved in both countries.

Patients were enrolled in two different cohorts according to whether they were treated: with the CNIC polypill [5] (cohort A) or with the three monocomponents separately (ASA, a statin and an ACE inhibitor; cohort B). Patients in cohort A had to have been treated with the separate monocomponents before receiving the polypill. Enrollees had to be on their current treatment for at least 3 months prior to enrolment in the study, to prevent from induction to prescription, and to ensure that the patient had been treated for long time enough to have a valid opinion. Patients had to meet the following criteria: age over 18 years, history of cardiovascular disease (CVD) with the last CV event happening >1 year before enrollment, being on preventive treatment for CVD with the CNIC polypill or the three separately monocomponents (ASA, a statin and an ACE inhibitor) for at least 3 months and having signed the informed consent. To ensure comparability across study cohorts and minimize bias, patients from both cohorts were paired based on gender and age (± 5 years).

Data collected from the medical record and at the study visit were sociodemographic, anthropometric and clinical characteristics. At the study visit patients were asked to complete two specific and validated questionnaires and one *ad-hoc* questionnaire. The Treatment Satisfaction Questionnaire for Medication (TSQM-9) [14] evaluated patients' satisfaction with treatment in three domains (effectiveness, convenience and global satisfaction) scored from 0 to 100. The Morisky Medication-Taking Adherence Scale (MMAS-4) [15] (used under permission by Donald E Morisky, ScD, ScM, MSPH) assessed adherence to treatment in a score ranging from 0 to 4, with three levels of medication compliance: highly compliant, moderately compliant and noncompliant with 0, 1–2 and 3–4 points, respectively [16]. The MMAS4 was selected because it is a convenient and easy to use self-reporting questionnaire that has demonstrated reasonable internal consistency and sensitivity and has been validated in different languages, including Spanish and French. In addition, the objective was to measure adherence and not to measure the causes for nonadherence, which case would have justified the need for a more sophisticated questionnaire. An *ad-hoc* questionnaire was designed to determine patients' preferences with different questions per cohort:

- Cohort A: Patients were asked to provide information about their preferences regarding the use of the CV polypill and the previous treatment with the monocomponents (Figure 1A);
- Cohort B: Patients were explained the concept of the polypill and were asked about their preferences regarding their current treatment with the separate components or the polypill concept (Figure 1B).

All data were collected in an electronic case report form designed for the study.

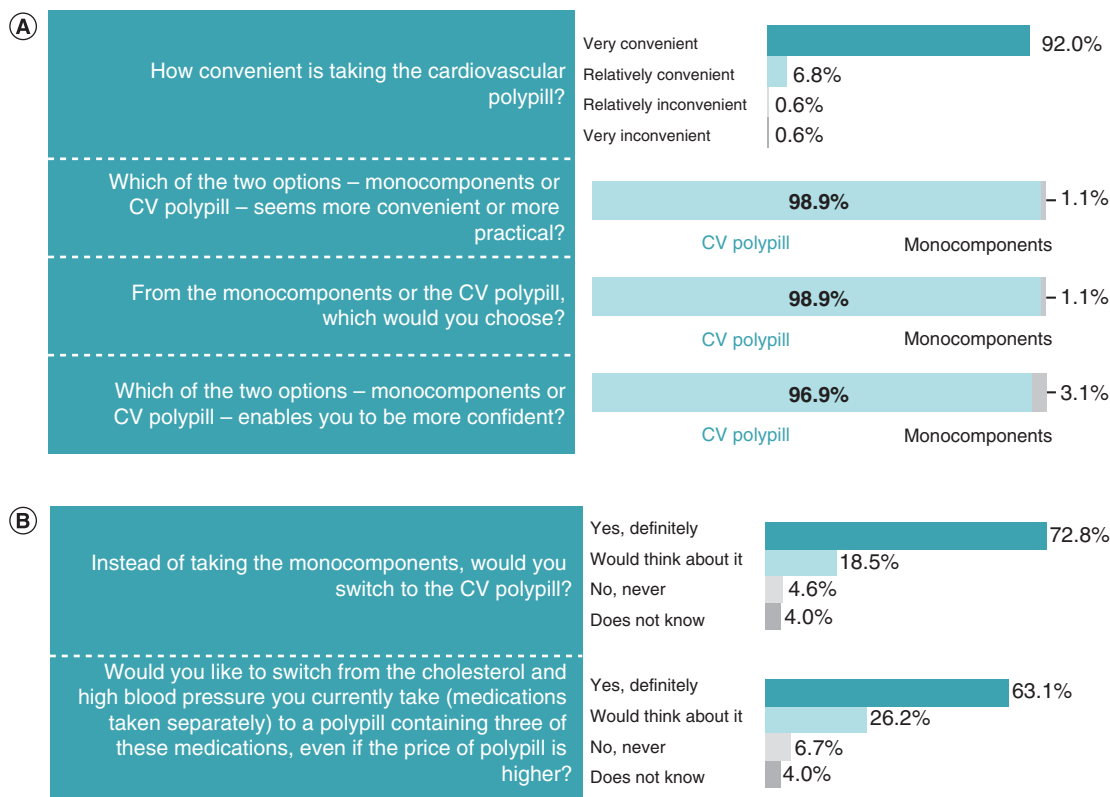


Figure 1. Results of the preferences *ad-hoc* questionnaire. Responses of the *ad-hoc* questionnaire exploring patients' satisfaction **(A)** in cohort A (polypill) and **(B)** in cohort B (monocomponents). CV: Cardiovascular.

Statistical analysis

Descriptive statistics were used to evaluate sociodemographic and clinical variables at the study visit, stratified by cohort. The chi-square test was used to compare the categorical variables between the different study cohorts, and Student's t-test or its nonparametric equivalent, Mann–Whitney U-test, for the continuous variables. Continuous variables were described by mean, standard deviation, minimum, median and maximum; categorical variables will be described by number and percentage of patients per response category.

Patients' satisfaction with the treatment was analyzed by means of the TSQM-9 scores. The result was presented globally and by study cohort. Adherence, assessed by the MMAS questionnaire, was analyzed as an ordinal variable and described globally and by study cohort. For each of the *ad-hoc* questions, the number and percentage of patient responses was described. There was no imputation of missing data; only the available data were analyzed. The number and percentage of missing values for each variable was recorded in all descriptive analyses. Two-tailed alpha of 0.05 was used in all statistical tests.

Database management and data analysis were performed using SAS® 9.4.

Results

Patient population

A total of 366 patients were included: 345 in Spain and 21 in Belgium, 335 of whom were evaluable: 5 patients did not complete the questionnaires, 1 retired the consent and 25 patients were not treated with the 3 monocomponents separately.

Table 1 shows the demographic characteristics of patients receiving preventive treatment for CVD in cohorts A (polypill) and B (monocomponents) and total; with no significant differences between cohorts. Mean (SD) age was 69.4 ± 11.2 years, 77.0% of patients included were male and the majority were Caucasian (92.2%). 11.7% were active smokers and 44.1% ex-smokers with an average of 11.5 ± 10.8 years since quitting. 50.2% of patients presented overweight ($25 \leq \text{BMI} < 30$) and 27.4% obesity ($\text{BMI} \geq 30$), and although not statistically different, a

Table 1. Sociodemographic and clinical characteristics of the population included in the study.

	Cohort A (polypill) (n = 180)	Cohort B (monocomponents) (n = 155)	Total (n = 335)	p-value
Age (mean [SD])	69.8 (11.1)	68.9 (11.4)	69.4 (11.2)	0.65
Male	141 (78.3%)	117 (75.5%)	258 (77.0%)	0.53
Caucasian	165 (92.2%)	143 (92.3%)	308 (92.2%)	0.47
Education: with university studies	9 (5.7%)	6 (4.3%)	15 (5.1%)	0.90
Occupational status: retired	115 (69.3%)	91 (64.1%)	206 (66.9%)	0.78
Civil status: married/with partner	117 (74.5%)	110 (77.5%)	227 (75.9%)	0.76
Ex-smokers	74 (43.0%)	69 (45.4%)	143 (44.1%)	0.22
• Years since quitting (mean [SD])	11.4 (11.6)	11.5 (10.0)	11.5 (10.8)	
Smokers	16 (9.3%)	22 (14.5%)	38 (11.7%)	0.64
• Number of cigarettes/day (mean [SD])	19.5 (9.7)	18.6 (8.9)	19.1 (9.3)	
Family background of CV events	44 (24.4%)	56 (36.1%)	100 (29.9%)	0.01
BMI (mean [SD])	27.7 (3.9%)	25.9 (3.6%)	27.56 (3.99)	0.21
Overweight (BMI ≥ 25)	63 (45.7%)	69 (55.2%)	132 (50.2%)	0.13
Obesity (BMI ≥ 30)	46 (33.3%)	26 (20.8%)	72 (27.4%)	
Blood pressure, mmHg:				0.91
• Normal: 120–129/80–84 mmHg or less	95 (54.3%)	74 (48.4%)	169 (51.5%)	
• Normal-high: 130–139/85–89 mmHg	12 (6.9%)	27 (17.6%)	39 (11.9%)	
• High: $\geq 140/\geq 90$ mmHg	68 (38.9%)	52 (34.0%)	120 (36.6%)	
Total cholesterol (mean [SD]), mg/dl	153.1 (34.0)	149.6 (32.4)	151.8 (33.2)	0.59
On target level (<200 mg/dl)	143 (89.9%)	139 (93.9%)	282 (91.9%)	0.2024
Hypercholesterolemia (≥ 200 mg/ml)	16 (10.1%)	9 (6.1%)	25 (8.1%)	
High-density lipoprotein cholesterol (mean [SD]), mg/dl	45.0 (13.03)	44.9 (14.8)	45.0 (13.90)	0.76
On target level (<70 mg/dl)	49 (33.6%)	50 (37.9%)	99 (35.6%)	0.4529
Not on target level (≥ 700 mg/dl)	97 (66.4%)	82 (62.1%)	179 (64.4%)	
Low-density lipoprotein cholesterol (mean [SD]), mg/dl	84.3 (30.0)	79.5 (27.2)	82.0 (28.7)	0.34
On target level (<35 mg/dl in men and <40 mg/dl in women)	104 (73.2%)	94 (72.3%)	198 (72.8%)	0.8631
Altered (≥ 35 mg/dl in men and ≥ 40 mg/dl in women)	38 (26.8%)	36 (27.7%)	74 (27.2%)	
Triglycerides (mean [SD]), mg/dl	132.2 (62.7)	131.9 (69.2)	132.0 (65.8)	0.45
Normal (<150 mg/dl)	106 (69.7%)	99 (68.8%)	205 (69.3%)	0.8599
Normal-High (150–200 mg/dl)	26 (17.1%)	23 (16.0%)	49 (16.6%)	
Moderate hypertriglyceridemia (200–500 mg/dl)	20 (13.2%)	22 (15.3%)	42 (14.2%)	
Presence of concomitant conditions:	153 (85.0%)	137 (88.4%)	290 (86.6%)	0.36
• Hypertension	135 (88.2%)	120 (87.6%)	255 (87.9%)	
• hypercholesterolemia	110 (71.9%)	120 (87.6%)	230 (79.3%)	
• Type I/II diabetes	76 (49.7%)	63 (46.0%)	139 (47.9%)	
• COPD	20 (13.1%)	27 (19.7%)	47 (16.2%)	

Data are expressed as number of patients (%), with the exception of age, years since quitting, N° cigarettes/day; total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides, which are expressed as mean absolute (SD). The chi-square test was used to compare the categorical variables between the different study cohorts, and Student's t-test or its non-parametric equivalent, Mann-Whitney U-test, for the continuous variables.

BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CV: Cardiovascular; SD: Standard deviation.

higher percentage of obese patients was found in the polypill cohort (33.3 vs 20.8% in the monocomponents cohort, $p = 0.1325$). At the study visit, 120 patients (36.6%) had high blood pressure ($\geq 140/\geq 90$ mmHg), while 25 (8.1%) and 179 (64.4%) had high total (≥ 200 mg/dl) and low density (≥ 70 mg/dl) cholesterol levels, respectively. A significantly higher proportion of patients treated with the monocomponents presented a family background of CV events compared with polypill patients (36.1 vs 24.4%; $p 0.0198$).

Table 2 describes time since last CV event and time with the current study treatment for both cohorts. Median time since the last CV event to the study visit was 3.0 years ([interquartile range (IQR)] 1.5; 7.2) while median time since the start of the initial CV prevention treatment was 3.1 years ([IQR] 1.4; 7.1), being significantly shorter ($p = 0.0383$) for patients in polypill (2.7 years; [IQR] 1.3; 6.8) compared with patients with the monocomponents (3.6 years; [IQR] 1.7; 7.9). The most frequent previous CV events reported were coronary artery disease (80.3%) followed by cerebrovascular disease (14.0%). Hypertension was the most frequent risk factor described (87.9%) followed by hypercholesterolemia (79.3%).

Table 2. Description of time since last cardiovascular event, time with secondary preventive treatment and time with the treatment at the time of study visit.

Variable	Cohort A (polypill) (n = 180)	Cohort B (monocomponents) (n = 155)	Total (n = 335)	p-value [‡]
Time since last CV event (years) [†]				
– N valid	168	137	305	0.3904
– Mean (SD)	5.05 (5.4)	5.11 (5.0)	5.08 (5.2)	
– Median	2.7	3.2	3.0	
– P25; P75	1.4; 7.3	(1.6; 7.1)	(1.5; 7.2)	
– Min; Max	0.2; 29.8	(0.0; 27.5)	(0.0; 29.8)	
– N missing	12	18	30	
Time since first treatment for secondary prevention (years)				
– N valid	155	136	291	0.0383
– Mean (SD)	4.55 (4.6)	5.54 (5.4)	5.01 (5.0)	
– Median	2.7	3.6	3.1	
– P25; P75	1.3; 6.8	1.7; 7.9	1.4; 7.1	
– Min; Max	0.2; 22.6	0.3; 33.1	0.2; 33.1	
– N missing	25	19	44	
Time with current drug treatment at study visit (months)				
– N valid	180	153	333	<0.0001
– Mean (SD)	10.59 (6.7)	45.76 (43.7)	26.75 (34.7)	
– Median	9.8	26.1	13.8	
– P25; P75	4.5; 14.1	14.9; 68.8	7.8; 25.4	
– Min; Max	3.0; 35.8	3.0; 252.3	3.0; 252.3	
– N missing	0	2	2	

[†] 31 patients with a CV event <1 years since study visit were included.
[‡] Wilcoxon-Mann-Whitney test.
Two-tailed alpha of 0.05 was used to determine statistical significance.
CV: Cardiovascular.

Significant differences were observed between both cohorts when comparing time in treatment with current study drug ($p < 0.0001$): patients in the polypill group were receiving this treatment for a shorter period 9.8 months ([IQR] 4.5; 14.1) than patients with the three monocomponents, 26.1 months ([IQR] 14.9; 68.8).

Treatment at study visit

A total of 180 patients were receiving treatment with the polypill (cohort A) and 155 patients the three monocomponents separately (cohort B). Ramipril 5 mg was the dose most frequently reported in the polypill cohort (50%; Table 3). Patients receiving the polypill reported fewer concomitant medications prescribed at the study visit (6.13 ± 2.88) than those in cohort B (8.12 ± 3.18 ; $p < 0.0001$).

Treatment satisfaction

The level of satisfaction with treatment in both cohorts was evaluated at the unique study visit according to the scores obtained in the three TSQM-9 domains. A total of 329 patients completed the TSQM-9 questionnaire: 178 patients in cohort A and 151 in cohort B. As shown in Figure 2, patients treated with the CV polypill showed significantly higher scores in the two specific domains of TSQM-9 and in the global satisfaction domain, with a score of 77.3 versus 71.2% in the polypill cohort and monocomponents cohort, respectively ($p < 0.0001$).

Multiple logistic regression adjusted by center showed that: a lower number of concomitant medications, LDL level at therapeutic goal (<70 mg/dl) and receiving the polypill were related to greater satisfaction with the effectiveness of the treatment; a younger age and receiving the polypill were related to greater satisfaction with treatment convenience; and receiving the polypill was related to greater overall satisfaction with the treatment.

Patients' preferences

Patients' preferences were analyzed by an *ad-hoc* questionnaire created for this study for each cohort. In cohort A, 92% patients treated with the CNIC polypill declared that it was very easy to take, and compared with the monocomponents, 98% would choose the polypill, and 98.8 and 96.9% considered the polypill more practical and more trustable than the monocomponents, respectively (Figure 1A).

In cohort B, 72.8% of patients treated with the three monocomponents reported they would switch to the CNIC polypill. 62.5% would still change the three monocomponents for a polypill even if the price of the polypill

Table 3. Description of treatment at study visit.

Cohort A (polypill)		Dosage	N = 180
ASA doses in the CV polypill		100 mg	180 (100.0%)
Atorvastatin doses in the CV polypill		20 mg	180 (100.0%)
Ramipril doses in the CV polypill		2.5 mg	52 (28.9%)
		5 mg	90 (50.0%)
		10 mg	38 (21.1%)
Cohort B (monocomponents)		Drug/dosage	N = 155
Doses ASA		ASA 80 mg	10 (6.5%)
		ASA-100 mg	133 (86.9%)
		ASA-150 mg	8 (5.2%)
		ASA300 mg	2 (1.3%)
Statin		Atorvastatin	116 (74.8%)
		Simvastatin	26 (16.8%)
Statin doses		Atorvastatin-40 mg	55 (35.5%)
		Atorvastatin-80 mg	37 (23.9%)
		Atorvastatin-20 mg	16 (10.3%)
		Simvastatin-20 mg	13 (8.4%)
		Simvastatin-40 mg	11 (7.1%)
ACE-i		Ramipril	72 (46.5%)
		Enalapril	69 (44.5%)
Doses ACE-i		Ramipril-5 mg	44 (28.4%)
		Enalapril-10 mg	17 (11.0%)
		Enalapril-20 mg	35 (22.6%)
		Enalapril-5 mg	16 (10.3%)

Results are expressed as number of patients (% over total).
ACE-i: Angiotensin converting enzyme inhibitor; ASA: Acetylsalicylic acid; CV: Cardiovascular.

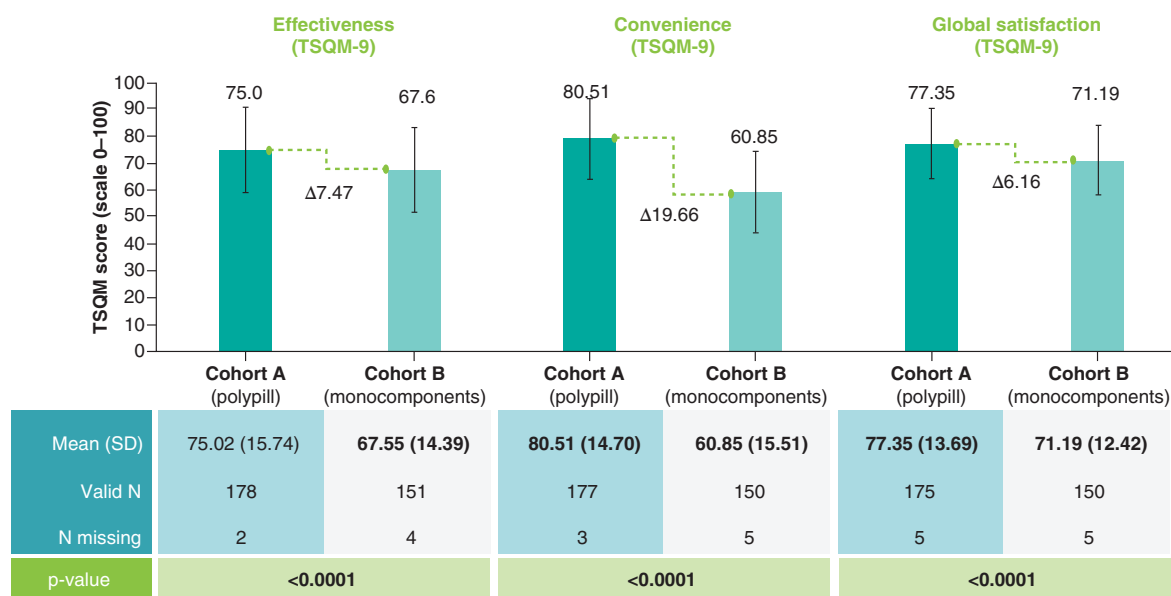


Figure 2. Treatment Satisfaction Questionnaire for Medication (TSQM-9) scores in the three-dimensions of the questionnaire: 'Effectiveness', 'Convenience' and 'Global satisfaction' for cohort A (polypill) and cohort B (monocomponents). Two-tailed alpha of 0.05 was used to determine statistical significance. SD: Standard deviation.

Table 4. Assessment of medication adherence in patients with secondary prevention by MMAS-4 questionnaire.

MMAS-4 items	Percentage of patients who answered 'no' (%)		
	Cohort A (polypill) (n = 175)	Cohort B (monocomponents) (n = 151)	p-value
Item 1. Have you ever forgotten to take your medicine?	132 (75.0%)	74 (49.0%)	<0.0001
Item 2. Do you take your medicine at the indicated times?	11 (6.6%)	25 (17.9%)	0.0024
Item 3. When you are feeling well, do you sometimes stop taking your medicine? (for Spain)	165 (93.8%)	129 (85.4%)	0.0128
Item 3. Are you sometimes a little careless when taking your medications? (for Belgium)	10 (100.0%)	11 (100.0%)	NA
Item 4. If they ever make you feel unwell, do you stop taking your medicine?	137 (78.3%)	110 (73.3%)	0.2973
Highly compliant (0 points in MAAS-4)	101 (57.7%)	62 (41.3%)	<0.0001
Moderately compliant (1–2 points in MAAS-4)	33 (18.9%)	13 (8.7%)	
Noncompliant (3–4 points in MAAS-4)	41 (23.4%)	75 (50.0%)	

MAAS-4: Morisky Medication-Taking Adherence Scale.
Results are expressed in number of patients (% over total). Two-tailed alpha of 0.05 was used to determine statistical significance.

was higher than the monocomponents, while 25.4% would have to think about the switch and 6.7% would not consider changing (Figure 1B).

Adherence

Adherence to secondary prevention treatment was analyzed using the MMAS-4 and revealed statistically significant differences between cohorts. Patients with the CV polypill were significantly ($p = 0.0027$) more compliant (57.7%) than patients taking the monocomponents separately (41.3%; Table 4). There were also significant differences between cohort in moderately compliant patients (18.9 vs 8.7%) and noncompliant patients (23.4 vs 50.0%).

Discussion

The study showed higher satisfaction assessed by the TSQM-9 questionnaire and higher adherence measured using the MMAS-4 in patients receiving the CNIC polypill. In addition, the CNIC polypill was the preferred treatment option for most patients.

The two cohorts of patients were well balanced as shown in Table 1. Sociodemographic and clinical characteristics were similar between both cohorts and with those reported in literature for patients in secondary CV prevention [17]: elderly patients, mainly males, smokers or ex-smokers with an important degree of obesity and with concomitant pathologies. Treatment in cohort B was mainly ASA 100 mg, atorvastatin as the main statin, and ramipril or enalapril as ACEi. Statin strengths were higher in the monocomponents arm compared with the polypill arm. 35.5 and 23.9% were treated with atorvastatin 40 and 80 mg, respectively, compared with 10.3% with 20 mg. At the time of the study, the CNIC polypill was available in the 20 mg atorvastatin strength, although since 2017 the 40 mg atorvastatin strength has also been available.

Regarding the primary aim of the study, patients' satisfaction (as the perception of an individual's experience compared with their expectations), our results showed that secondary prevention patients treated with the CNIC polypill were more satisfied than those patients treated with monocomponents separately, with a significantly higher score in each of the three scales in the TSQM-9 questionnaire: 'effectiveness', 'convenience' and 'global satisfaction'. In this regard, a factor that can contribute to a higher satisfaction is the number of prescribed drugs. In our study, patients treated with the polypill took a smaller number of concomitant drugs than patients treated with the monocomponents (6.1 ± 2.9 vs 8.1 ± 3.2 , $p < 0.0001$) which may explain, at least in part, the results on satisfaction. It is also important to notice that the perception of 'effectiveness' increased with the polypill, even though patients in cohort A were treated with higher statin strengths. It could be argued that higher satisfaction would be indirectly related with a higher degree of treatment adherence, which may result in a better CV risk factors control. In fact, recent data from two different observational studies in a real-life clinical settings in Mexico [18,19] shed some light into this hypothesis, showing that patients treated with a version of the CNIC polypill containing simvastatin instead of atorvastatin improved their blood pressure and lipid levels, and showed a significant reduction Framingham risk score compared with their previous treatment.

Our results on satisfaction were also consistent with results of another study that compared satisfaction of an antihypertensive fixed dose combination versus separate pills. A high percentage of patients were more satisfied with the antihypertensive polypill therapy, stating that 'effectiveness' and 'convenience' of the treatment were the most important factors for patients [20].

In terms of patients' preferences, an *ad-hoc* questionnaire was developed to evaluate this item. Questionnaire results for cohort A revealed that the polypill strategy was relevant for nearly all our studied population (98.9%) who stated to prefer the polypill rather than the monocomponents separately. This could be explained as patients' expectations with the polypill have been satisfied also in improving patient's quality of life, willing to keep the polypill treatment as a long-term option. Most patients also stated that the polypill was easier to take and more trustful than the monocomponents, which could reinforce a better adherence, and ultimately, a better CV risk control.

Conversely, 72.8% of the patients treated in cohort B declared they would switch to the CV polypill while 4.6% answered that they would not consider it. These findings are aligned with published literature which also reflects that the a polypill treatment is an attractive option to patients, who see advantages over their current treatment [21], and highlight the need to ask patients about their preferences. In addition, in our study 63.1% of all the patients reaffirmed their will to switch to the CV polypill even if the out of pocket cost was higher. Previous research supports an increased willingness to pay from patients in order to reduce the pill burden [22].

The adherence to the treatment as measured by the MMAS-4 was higher in the CV polypill group (57.7 vs 41.1% $p = 0.0027$) when considering highly compliant patients and the adherence difference between groups increased when also considering moderately compliant patients (76.6 vs 50.0% $p < 0.0001$). It is important to notice that 50.0% of patients treated with the monocomponents were considered non-adherent to treatment, and 49.7% answered 'no' to all MMAS-4 items compared with the 23.4% of patients in cohort A. The increased number of drugs could be one of the reasons for the higher non-adherence in the monocomponents cohort of our study. There is also evidence that adherence in chronic diseases is influenced by medication complexity: the simplest the regimen the greater patient adherence is. Our results on adherence are in line with previous studies with several polypills [23,24].

Although the increase in adherence is followed by an increase in CV risk factors control and in a lower incidence of CV events, as recently shown in the PolyIran study [7], a recent study has also shown a synergistic effect within the components of the present CV polypill, in terms of a higher LDL-c reduction, which also may contribute to a better risk factors control [25].

This research, however, is subject to several limitations. One of them is the cross sectional study design, with no longitudinal data obtained. Another limitation is the criteria about time since the event, which was defined once the study was active, and 30 patients who had the last CV event <1 year since study visit were included in the total analyzed population. It must be pointed out that patients in cohort B had a significantly longer median duration of treatment at the time of study compared with those patients in cohort A, potentially having an effect in the comparability of the data between the two cohorts. The impact on comparability can be more significant in the adherence end point as it has been demonstrated that adherence to treatment tends to decrease over time. However, research shows that the decrease in treatment adherence occurs during the first 18 months of treatment, plateauing at a later stage [26]. Finally, the self-reported nature of the three questionnaires employed have intrinsic limitations such as a social desirability bias or the absence of introspective ability. In particular, the use of the MMAS-4 may limit comparability to other adherence studies. MMAS-4 was selected as a self-reported, easy to use and validated instrument for adherence measurement that enabled the comparison between two groups. However, its simplistic nature has been suggested to affect its acceptability and internal consistency, and comparisons with more sophisticated instruments or direct adherence observation must be made with caution.

Conclusion

According to results, we can conclude that secondary prevention patients treated with a CV polypill showed a significantly higher degree of satisfaction and significantly higher medication adherence compared with patients that were treated with the monocomponents separately. Patients treated with the polypill strategy stated their perception of the polypill strategy as a convenient treatment enabling a high degree of confidence, preferring it over being treated with the separate monocomponents. A majority of patients treated with separate monocomponents expressed preference toward the polypill strategy when explained the concept.

By asking the patient about its preferences the patient becomes judgmental of the posed treatment options and may become more involved, committed and satisfied with the received treatment positively impacting persistence and adherence to treatment which in turn could lead to improved treatment outcomes. Therefore, patient preferences should be considered, especially when establishing chronic treatments.

Our work settles the ground for further research in this area, aiming to clarify the long-term relationship between patient satisfaction to the treatment with increased adherence and treatment outcomes. Nonetheless, considering the relevant burden of CV disease and the treatment gaps in cardiovascular prevention, the implications of our findings become relevant providing further evidence of the potential role polypill strategies can play in cardiovascular prevention.

Summary points

- Patients' preferences are gaining importance and they should be considered when establishing chronic treatments.
- This paper explored patients' satisfaction, preferences and adherence of a cardiovascular (CV) polypill compared with the individual monocomponents.
- Patients treated with the CV polypill showed a significantly higher degree of satisfaction and better adherence compared with those who were treated with the monocomponents.
- A majority of patients treated with the CV polypill asserted their preference for this treatment.
- A significant proportion of patients receiving the monocomponents declared that they would like to switch their regime when they were explained the concept of the CV polypill.
- CV polypills offer a simplified pill burden that may be preferred by certain patients.
- It has been suggested that patients that are satisfied with their treatment are more likely to have long term compliance and may experience better treatment outcomes.

Author contributions

All authors have contributed to the conception, design and acquisition of this article. Additionally, they have drafted and critically revised this manuscript. They all agree to be accountable for all aspects of work ensuring integrity and accuracy, as well as its final approval.

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Data sharing statement

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

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