RESEARCH ARTICLE

Patients prefer a polypill rather than the separate monocomponents for secondary cardiovascular prevention - Aurora: A real-world multicenter non-interventional study

Cosin-Sales Juan[1], Murcia-Zaragoza Jose[2], Pereyra-Rico Hector[3], de la Guía-Galipienso Fernando[4], Hermans Kurt[5], Rubio Gabriel[6]

Citation: Juan S, Jose M, Hector P, et al. Patients prefer a polypill rather than the separate monocomponents for secondary cardiovascular prevention - Aurora: A real-world multicenter non-interventional study. Clin Cardiol J 2020; 4(3):1-7.

OBJECTIVES: To evaluate the satisfaction, preferences and adherence of patients treated with the Spanish National Cardiovascular Research Centre (CNIC) polypill containing acetylsalicylic acid (ASA) 100 mg, atorvastatin 20 mg and ramipril 2.5;5;10 mg compared with patients with ASA, a statin and an angiotensin converting enzyme (ACE) inhibitor separately, for secondary prevention of cardiovascular disease (CVD).

DESIGN: An observational, cross-sectional, cohort, multicenter study was conducted in Spain and Belgium. Two cohorts were included: patients treated with CNIC polypill or trated with the monocomponents separately. Patients had to have a history of CVD (>1 year from the last CV event) and had to be treated with the current treatment for a minimum of 3 months prior to enrolment. Patients from both cohorts were paired based on gender and age.

METHODS: Satisfaction was evaluated by the TSQM-9, adherence by the Morisky-Green questionnaire and ad hoc questions were asked to determine patient preferences.

RESULTS: 366 patients were included and 335 were analyzed. Patients treated with the CNIC polypill reported higher level of 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: Patients treated with the CNIC polypill showed a significantly higher degree of satisfaction and better adherence, whereas most patients receiving the monocomponents would prefer to be treated with a polypill regime.

Key Words: *Cardiovascular; Polypill; Prevention; Satisfaction; Preferences; Adherence*

INTRODUCTION

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 medications with proven benefit for CV prevention, has emerged as one of the most scalable strategies to reduce CVD burden [5]. 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 several studies. 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 tackle three different non-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 life style 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 sites in Spain and 4 sites in Belgium. The study 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 three 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 were selected consecutively and had to meet the following criteria: age over 18 years, history of cardiovascular disease (CVD) with the last CV event

[1]*Hospital Arnau de Vilanova, Valencia Hi, Spain,* [2]*Hospital Vega Baja, Orihuela, Spain,*[3]*Hospital Comarcal La Línea de la Concepción, La Línea de laConcepción, Spain,* [4]*Hospital Marina Baixa, La Vila Joiosa, Spain,* [5]*AZ St. Lucas, Ghent, Belgium,* [6]*Ferrer International, Barcelona, Spain*

Correspondence: Rubio Gabriel, Ferrer International, Barcelona, Spain, Telephone: +34 619962605.; e-mail: grubio@ferrer.com

Received: October 02, 2020, Accepted: November 06, 2020, Published: November 13, 2020

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. 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: a) the Treatment Satisfaction Questionnaire for Medication (TSQM-9) [14] evaluated patients' satisfaction with treatment in 3 domains (effectiveness, convenience and global satisfaction) scored from 0 to 100; b) 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 non-compliant with 0, 1–2, and 3–4 points, respectively [16]; c) 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 cardiovascular 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 or the polypill concept (Figure 1B).

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 non-parametric 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.

Patient 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 (CNIC 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 where 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≤BMI<30) and 27.4% obesity (BMI ≥30), and although not statistically different, a 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 (≥140/≥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 patients treated with the monocomponents presented a family background of CV events compared to polypill patients (36.1% vs. 24.4%; p-value 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 (IQ)] 1.5; 7.2) while median time since the start of the initial CV prevention treatment was 3.1 years ([IQ] 1.4; 7.1), being significantly shorter (p=0,0383) for patients in polypill (2.7 years; [interquartile range (IQ)] 1.3; 6.8) compared to patients with the monocomponents (3.6 years; [interquartile range (IQ)] 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%).

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).

Treatments 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) that 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 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% vs. 71.2% in the polypill cohort and monocomponents cohort, respectively (p<0.0001).

Multiple logistic regression adjusted by center showed that: 1) 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; 2) a younger age and receiving the polypill were related to greater satisfaction with treatment convenience; and 3) 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 (Figures 1A and 1B). In cohort B, 72.8% of patients treated with the 3 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 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 where 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 non-compliant patients (23.4% vs. 50.0%).

DISCUSSION

The present study evaluated the treatment satisfaction, preferences and drug adherence of patients treated with the CNIC polypill compared to patients receiving the three monocomponents separately, in a secondary prevention setting.

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 to the polypill arm. 35.5% and 23.9% were treated with atorvastatin 40 mg and 80 mg respectively, compared to 10.3% with 20 mg. At the time of the study, the CNIC polypill was

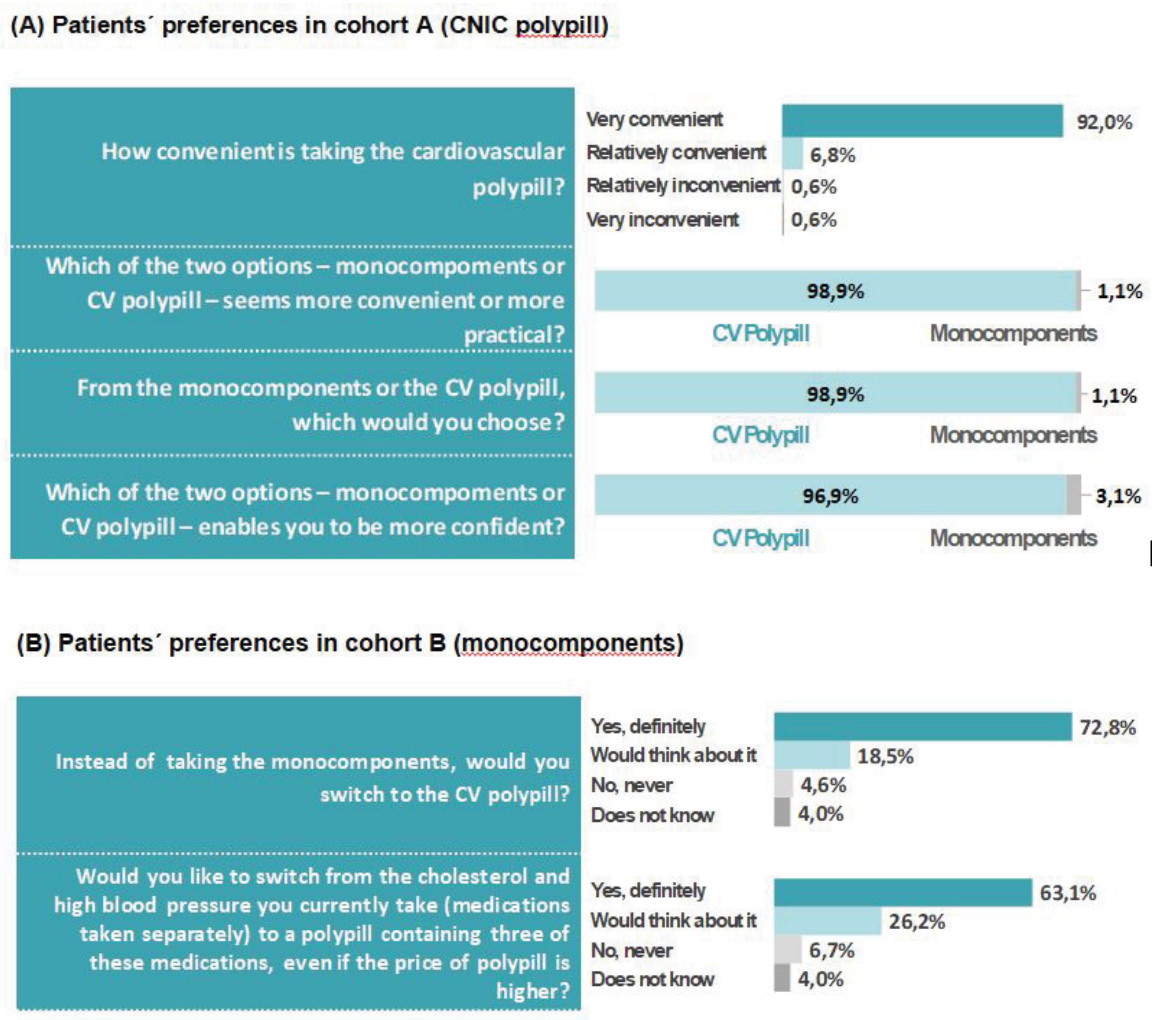
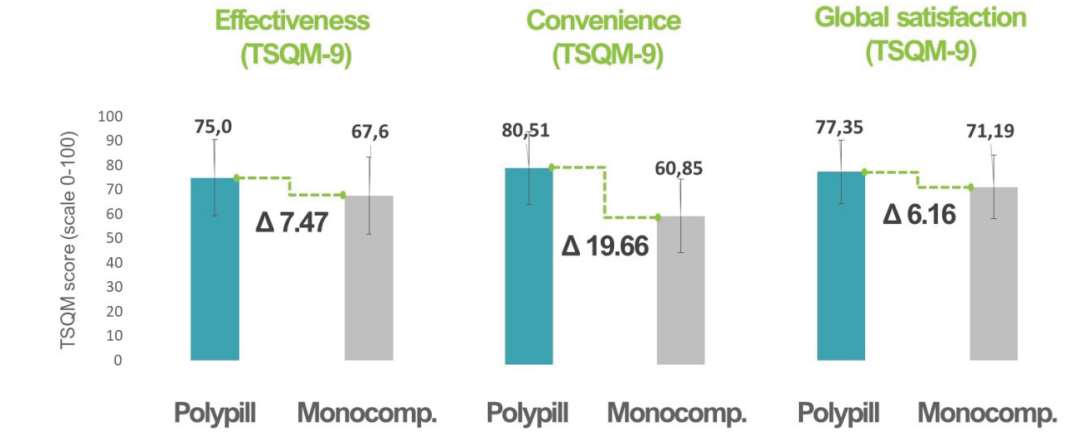


Figure 1) *Patients prefer the polypill strategy.* (A) *Responses of the ad-hoc questionnaire exploring patients' preferences in cohort A (CNIC polypill) reveal the polypill as a very convenient strategy in the eyes of patients, and when compared to monocomponents it seems more convenient, more trustful and most patients prefer this treatment option.* (B) *Responses for the preferences questionnaire in cohort B (monocomponents) reveal that a majority of patients would switch or would consider switching their current treatment to a polypill strategy, even when considering superior cost, while very few would not think about it.*



	Effectiveness (TSQM-9)		Convenience (TSQM-9)		Global satisfaction (TSQM-9)	
Mean (SD)	75.02 (15.74)	67.55 (14.39)	80.51 (14.70)	60.85 (15.51)	77.35 (13.69)	71.19 (12.42)
Valid N	178	151	177	150	175	150
N missing	2	4	3	5	5	5
p value	<0.0001		<0.0001		<0.0001	

Figure 2) *Patients show higher satisfaction with the polypill strategy over the monocomponents. Treatment Satisfaction Questionnaire for Medication (TSQM-9) three-dimension score depict significantly higher scores in each of the three dimensions of the questionnaire "Effectiveness", "Convenience" and "Global satisfaction". Median (Standard Deviation, SD) score in each scale of the TSQM-9. Two-tailed alpha of 0.05 was used to determine statistical significance.*

TABLE 1

Socio-demographic and clinical characteristics of the population included in the study.

Variables	Cohort A	Cohort B	Total	P value
	(n=180)	(n=155)	(n=335)	
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%)	0.9
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
· Nº 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, mm Hg:				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: ≥140/≥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)				
Not on target level (≥700 mg/dL)	49 (33,6%)	50 (37,9%)	99 (35,6%)	0.4529
	97 (66,4%)	82 (62,1%)	179 (64,4%)	
Low-density lipoprotein cholesterol (mean (SD)), mg/dL (SD)	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)				
Altered (≥35 mg/dL in men and ≥40 mg/dL in women)	104 (73,2%)	94 (72,3%)	198 (72,8%)	0.8631
	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%)	

SD: Standard Deviation. CV: Cardiovascular. BMI: Body Mass Index. COPD: Chronic Obstrictive Pulmonary Disease.
Data are expressed as number of patients (%), with the exception of age, years since quitting, Nº cigarretes/day; total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglicerides, 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.

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

TABLE 2

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

Variables		Cohort A	Cohort B	Total	p-value**
		(n=180)	(n=155)	(n=335)	
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	
	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; **test Wilcoxon-Mann-Whitney

CV: Cardiovascular
Two-tailed alpha of 0.05 was used to determine statistical significance.

TABLE 3

Description of treatment at study visit.

Cohort A	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	**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%)

CV: Cardiovascular; ASA: Acetylsalicylic Acid; ACE-I: Angiotensin Converting Enzyme Inhibitor
Results are expressed as number of patients (% over total).

TABLE 4

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

MMAS-4 items	Number of Patients who answered "No" (%)		
	Cohort A (n=175)	**Cohort B (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 4. Are you sometimes a little careless when taking your medications? (for Belgium)	10 (100.0%)	11 (100.0%)	NA
Item 5. 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%)	
Non-compliant (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.

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 to 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 than "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. In our study 72.8% of the patients treated with the separate monocomponents declared they would switch to the CV polypill while 4.6% answered that they would not consider it. 63.1% of all the patients reaffirmed their will to switch to the CV polypill even if the out of pocket cost was higher. These findings are aligned with published literature [21] as the strategy of polypill is an attractive option to patients, who see advantages over their current treatment, and highlight the need to ask patients about their preferences. As per cohort B the polypill strategy was relevant for nearly all our studied population treated with the polypill (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, keeping 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.

In this context, 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 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 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 than 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 [22,23]. 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 [24].

The study has some limitations that must be pointed out. One of them is the 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.

According to results, we can conclude that secondary prevention patients treated with a CV polypill showed a significantly higher degree of satisfaction, medication adherence and higher treatment preference compared with the monocomponents separately. Patients´ preferences are gaining importance and they should be considered when establishing chronic treatments.

CONFLICT OF INTEREST

JCS has received research grants and speaker honorarium from Ferrer Internacional. JMMZ, HOPR, FGG and KH have received research grants from Ferrer Internacional. GRM and NO are full-time employees in Ferrer Internacional. Otherwise the authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

ACKNOWLEDGEMENT

The authors wish to acknowledge all the cardiologist from the Aurora investigator group for their effective contribution in this study: Ana Peset (H. Catstellon); Victor J. Girbes (H. Lluis Alcanyis); Victor Ortiz (H. de Sagunto); Mariam Quintanilla (H. Gerenal Elche); Alejandra Tamayo (H. Elda); Nelson Leal (H. General de Catalunya); Marga Gimenez (H. Clinic de Barcelona); Monica Ribells (H. General de Granollers); Francisco J. Muñoz (H. de Mollet); Merce Borras (H. Arnau de Vilanova); Migueal A. Araujo (H. Severo Ochoa); Alejandro Curcio (H. de Fuenlabrada); Pedro P. Casado (H. la Princesa); Alejandro Villanueva (H. Universitario Rey Juan Carlos); Natalia Lorenzo (H. Infanta Cristina); Nuria Muñoz (H. Infanta Leonor); Diego Gudiño (H. Nuestra Señora de la Candelaria); Jose A. Alarcon (H. Universitario Donostia); Eva M. Pereira (H. Lucus Augusti); Carlos Peña (H. Clinico Santiago); Mario Gutierrez (Complejo H. Universitario Ourense); Alejandro Rodriguez (H. Arquitecto Macide); Javier Idoate (H. de Leon); Maximiliano Amado (H. General Segovia); Esteban Martin (H. Universitario Guadalajara); Juan L. Bardaji (H. Virgen de la Luz); Jose Lopez (H. Reina Sofia); Miriam Padilla (H. de Jaen); Pablo Santiafo (H. la Loja); Fernando Sabatel (H. Santa Ana); Bernard Cosyns (UZ Brussel) and Ruben Casado (Hôspital Erasme).

Thanks are also extended to Antonio Molina, Carlos Ruiz, Francisco Rodriguez, Jose Ferrer and Manuel Garcia for their great motivation and commitment with this project. Acknowledgment to Ferrer International for the support on this work. Writing assistance was provided by Anna del Prado, IQVIA, Madrid, Spain.

REFERENCES

1. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2019.

2. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2014;64:1929-49.

3. Chen ST, Huang ST, Shau WY, et al. Long-term statin adherence in patients after hospital discharge for new onset of atherosclerotic cardiovascular disease: A population-based study of real world prescriptions in Taiwan. BMC cardiovascular disorders. 2019;19:62.
4. Klimis H, Chow CK. Clinical consequences of poor adherence to lipid-lowering therapy in patients with cardiovascular disease: can we do better? Heart Asia. 2019;11:e011200.
5. Fuster V, Gambus F, Patriciello A, et al. The polypill approach - An innovative strategy to improve cardiovascular health in Europe. BMC pharmacology & toxicology. 2017;18:10.
6. Munoz D, Uzoije P, Reynolds C, et al. Polypill for cardiovascular disease prevention in an underserved population. New Eng J Med. 2019;381:1114-23.
7. Roshandel G, Khoshnia M, Poustchi H, et al. Effectiveness of polypill for primary and secondary prevention of cardiovascular diseases (PolyIran): a pragmatic, cluster-randomized trial. Lancet (London, England). 2019;394:672-83.
8. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ (Clinical research ed). 2003;326:1419.
9. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39:119-77.
10. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016;37:2315-2381.
11. Roy A, Naik N, Srinath RK. Strengths and Limitations of Using the Polypill in Cardiovascular Prevention. Current cardiology reports. 2017;19:45.
12. Say RE, Thomson R. The importance of patient preferences in treatment decisions--challenges for doctors. BMJ (Clinical research (ed). 2003;327:542-5.
13. Paterick TE, Patel N, Tajik AJ, et al. Improving health outcomes through patient education and partnerships with patients. Proceedings (Baylor University Medical Center). 2017;30:112-3.
14. Atkinson MJ, Sinha A, Hass SL, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health and quality of life outcomes. 2004;2:12.
15. Val JA, Amoros BG, Martinez VP, et al. [Descriptive study of patient compliance in pharmacologic antihypertensive treatment and validation of the Morisky and Green test]. Atencion primaria. 1992;10:767-70.
16. Koschack J, Marx G, Schnakenberg J, et al. Comparison of two self-rating instruments for medication adherence assessment in hypertension revealed insufficient psychometric properties. J Clin Epidemiol. 2010;63:299-306.
17. Kotseva K, De Backer G, De Bacquer D, et al. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: Results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. Eur J Prevent Cardiol. 2019;26:824-35.
18. Castellano JM, Verdejo J, Ocampo S, et al. Clinical Effectiveness of the Cardiovascular Polypill in a Real-Life Setting in Patients with Cardiovascular Risk: The SORS Study. Arch Med Res. 2019;50:31-40.
19. Mendez-Garcia LA, Gonzalez-Chavez A, Trejo-Millan F, et al. Six Month Polypill Therapy Improves Lipid Profile in Patients with Previous Acute Myocardial Infarction: The Heart-Mex Study. Arch Med Res. 2019;50:197-206.
20. Olszanecka-Glinianowicz M, Smertka M, Almgren-Rachtan A, et al. Ramipril/amlodipine single pill - effectiveness, tolerance and patient satisfaction with antihypertensive therapy in relation to nutritional status. Pharmacological reports : PR. 2014;66:1043-9.
21. Lafeber M, Grobbee DE, Schrover IM, et al. Comparison of a morning polypill, evening polypill and individual pills on LDL-cholesterol, ambulatory blood pressure and adherence in high-risk patients; a randomized crossover trial. Int J Cardiol. 2015;181:193-99.
22. Castellano JM, Sanz G, Penalvo JL, et al. A polypill strategy to improve adherence: Results from the FOCUS project. J Am Coll Cardiol. 2014;64:2071-82.
23. Thom S, Poulter N, Field J, et al. Effects of a fixed-dose combination strategy on adherence and risk factors in patients with or at high risk of CVD: the UMPIRE randomized clinical trial. Jama. 2013;310:918-29.
24. Gonzalez-Juanatey JR, Tamargo J, Torres F, et al. Pharmacodynamic study of the cardiovascular polypill. Is there any interaction among the monocomponents? Revista espanola de cardiologia (English ed). 2020.