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ORIGINAL INVESTIGATIONS

A Polypill Strategy to Improve Adherence

Results From the FOCUS Project

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CME Objective for This Article: After reading this article the reader should be able to explain: 1) the prevalence and significance of medication nonadherence; 2) the factors associated with medication nonadherence; and 3) the efficacy, safety, and tolerability of a fixed-dose combination polypill to improve medication adherence.

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A Polypill Strategy to Improve Adherence

Results From the FOCUS Project

ABSTRACT

BACKGROUND Adherence to evidence-based cardiovascular (CV) medications after an acute myocardial infarction (MI) is low after the first 6 months. The use of fixed-dose combinations (FDC) has been shown to improve treatment adherence and risk factor control. However, no previous randomized trial has analyzed the impact of a polypill strategy on adherence in post-MI patients.

OBJECTIVES The cross-sectional FOCUS (Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention) study (Phase 1) aimed to elucidate factors that interfere with appropriate adherence to CV medications for secondary prevention after an acute MI. Additionally, 695 patients from Phase 1 were randomized into a controlled trial (Phase 2) to test the effect of a polypill (containing aspirin 100 mg, simvastatin 40 mg, and ramipril 2.5, 5, or 10 mg) compared with the 3 drugs given separately on adherence, blood pressure, and low-density lipoprotein cholesterol, as well as safety and tolerability over a period of 9 months of follow-up.

METHODS In Phase 1, a 5-country cohort of 2,118 patients was analyzed. Patients were randomized to either the polypill or 3 drugs separately for Phase 2. Primary endpoint was adherence to the treatment measured at the final visit by the self-reported Morisky-Green questionnaire (MAQ) and pill count (patients had to meet both criteria for adherence at the in-person visit to be considered adherent).

RESULTS In Phase 1, overall CV medication adherence, defined as an MAQ score of 20, was 45.5%. In a multivariable regression model, the risk of being nonadherent (MAQ <20) was associated with younger age, depression, being on a complex medication regimen, poorer health insurance coverage, and a lower level of social support, with consistent findings across countries.

In Phase 2, the polypill group showed improved adherence compared with the group receiving separate medications after 9 months of follow-up: 50.8% versus 41% ($p = 0.019$; intention-to-treat population) and 65.7% versus 55.7% ($p = 0.012$; per protocol population) when using the primary endpoint, attending the final visit with MAQ $= 20$ and high pill count (80% to 110%) combined, to assess adherence. Adherence also was higher in the FDC group when measured by MAQ alone (68% vs. 59%, $p = 0.049$). No treatment difference was found at follow-up in mean systolic blood pressure (129.6 mm Hg vs. 128.6 mm Hg), mean low-density lipoprotein cholesterol levels (89.9 mg/dl vs. 91.7 mg/dl), serious adverse events (23 vs. 21), or death (1, 0.3% in each group).

CONCLUSIONS For secondary prevention following acute MI, younger age, depression, and a complex drug treatment plan are associated with lower medication adherence. Meanwhile, adherence is increased in patients with higher insurance coverage levels and social support. Compared with the 3 drugs given separately, the use of a polypill strategy met the primary endpoint for adherence for secondary prevention following an acute MI. (Fixed Dose Combination Drug [Polypill] for Secondary Cardiovascular Prevention [FOCUS]; NCT01321255) (J Am Coll Cardiol 2014;64:2071–82)

Mortality due to cardiovascular diseases (CVDs) is still rising in low- and middle-income countries (LMIC), and is expected to surpass communicable diseases as the leading cause of death by 2030 (1). In high-income countries, however, CVD mortality rates are stable or even decreasing, mainly due to the appropriate administration of evidence-based drug treatments (e.g., statins, antihypertensive and antithrombotic agents) in patients at high risk, particularly those recovering from an acute coronary event (2). It has been estimated that one-half of the overall reduction in CVD mortality observed over the past 20 years in western countries could be attributed to appropriate use of cardiovascular (CV) medications for secondary prevention (3).

Despite these advances, significant evidence highlights the existence of a gap in drug treatment and

room for improvement in secondary prevention. On a global scale, data from the PURE (Prospective Urban Rural Epidemiology) study showed that among participants with a history of coronary heart disease or stroke, only 25% were taking antiplatelet drugs, 17% were taking beta-blockers, 20% were taking angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-II receptor blockers (ARBs), and 15% were taking statins 5 years post-event. Considering only LMIC, the use of these drugs was found to be as low as 3% in the same study (4). In developed countries, the situation, although better, is still worrisome. For instance, in Europe, the EUROASPIRE study, a survey of coronary patients in 22 countries, showed that among participants with prior coronary artery disease (68% with myocardial infarction [MI], all comers), in spite of appropriate prescription of secondary CV medication, 56% of patients persisted with hypertension and 51% with hypercholesterolemia (5).

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Lack of compliance with prescribed lifestyle modification and lack of medication adherence, defined as the extent to which patients follow the instructions they are given for prescribed treatments, are also fundamental factors affecting the strategies for CVD secondary prevention. It has been estimated that adherence to CV medications is about 57% after a median of 2 years (6). It is generally recognized that adherence is determined by the interplay of 5 "dimensions": socioeconomic, medication-related, condition-related, health system-related, and patient-related factors (7). Among the number of factors associated with these dimensions, poor availability and affordability of medication are considered critical in emerging countries (8), but overall, the complexity of treatment and the daily number of prescribed pills have been repeatedly recognized as the most important factors responsible for lack of adherence to treatment (9,10).

To address these determinants of poor adherence, a strategy based on the use of a fixed-dose combination (FDC) or polypill, including key medications to reduce CV risk as a once daily dose pill, has been recently introduced. Several trials have tested the effect of such an approach on adherence (measured in various self-reported ways) in high-risk patients including those with established CV disease with promising results (11–13). To date, however, no trial has studied the effect of an FDC strategy on adherence in secondary prevention using direct measures in addition to self-report. The FOCUS (Fixed Dose Combination Drug for Secondary Cardiovascular Prevention) project was designed, using an appropriate conceptual framework, to better understand the adherence to medication in the post-MI setting, the factors that influence the lack of adherence, and the effect of an FDC on adherence in this high-risk population.

METHODS

The protocol for the FOCUS study, which was funded by the 7th Framework Programme of the European Commission, has been previously described (14). FOCUS consists of 2 concurrent but sequential phases. Phase 1 is a multicountry comprehensive analysis of factors that determine the appropriate use of CV prevention interventions, particularly socioeconomic and comorbid factors. Phase 2 is a randomized, controlled clinical trial testing the effect of an FDC, the CNIC-FS-FERRER polypill containing acetylsalicylic acid (ASA) 100 mg, simvastatin 40 mg, and ramipril 2.5, 5, or 10 mg, on adherence and control of CV risk factors. The local ethical committees and the health authorities in the participating countries approved the protocol.

PHASE 1. Rationale. FOCUS Phase 1 was designed as an observational, prospective, cross-sectional study to assess the relationship of a variety of factors—including socioeconomic, clinical, and psychosocial factors—to patients' adherence to treatment in 5 different countries (Argentina, Brazil, Italy, Paraguay, and Spain). In addition to patients' information, data regarding the national health systems and various economic indicators for each country were also registered, including accessibility, cost, and affordability of the standard drugs for secondary CV prevention (ASA, statin, ACEI, and beta-blocker). Data at the national level on economic development were obtained from the World Bank as well as from the Panamerican Health Organization (a yearly updated database on health-related data), which included gross internal product as well as other indicators such as literacy rate, gross national income adjusted for international dollars, percent of population under national and international poverty line, percent of unemployment on a given year, and inflation rate (Online Appendix, Annex 1).

A research network linking 3 institutions was established to carry out the study: the Istituto di Ricerche Farmacologiche "Mario Negri" (IRFMN) in Milan (Italy), the Instituto Damic in Buenos Aires (Argentina), and the Fundació Clinic per la Recerca Biomèdica in Barcelona (Spain). These institutions

ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitor

ARB = angiotensin-II receptor blocker

ASA = acetylsalicylic acid

BP = blood pressure

CV = cardiovascular

LDL-C = low-density lipoprotein cholesterol

LMIC = low- and middle-income countries

MAQ = Morisky-Green medication adherence questionnaire

MI = myocardial infarction

coordinated 26 outpatient clinics in Argentina, Brazil, and Paraguay and another 38 in Italy and Spain (Online Appendix, FOCUS Investigators). Sites were selected so as to include patients from widely differing socioeconomic strata. The Centro Nacional de Invetigaciones Cardiovasculares (CNIC) in Madrid (Spain) functioned as the coordinating center for the overall study.

Sample size. A total of 2,000 subjects had to be included in the study, 1,000 in Europe and 1,000 in South America. With this sample size, a 2-sided 95% confidence interval for a single proportion using the large sample normal approximation would extend 1.5% from the observed proportion for an expected proportion of 50%.

Patient selection. The study population included men and women age ≥40 years with a history of acute MI within the last 2 years. After signing the informed consent, data was recorded in appropriate, specifically-designed forms derived from the manual developed by the World Health Organization/Health Action International for the Medicine Prices survey (15). All variables were collected in a single visit. Due to slow recruitment, after the initial 591 participants had been included, an amendment to the initial protocol was approved to allow for the inclusion of patients with any past history of an acute MI, regardless of duration from enrollment. Exclusion criteria were as follows: contraindication for any of the FDC components, residence in a nursing home, or having a mental illness that limits the capacity for self-care.

Primary endpoint. FOCUS Phase I included 3 primary outcomes: 1) to assess the proportion of patients with no contraindications who were prescribed aspirin, ACEIs, beta-blockers, and statins; 2) to calculate adherence to those medications using the Morisky-Green medication adherence questionnaire (MAQ); and 3) to identify factors contributing to inadequate adherence to treatment.

Estimation of adherence. The MAQ is a self-reported questionnaire with 4 questions:

1. Some people forget to take their medications. How often does this happen to you?
2. Some people miss out a dose of their medication or adjust it to suit their own needs. How often do you do this?
3. Some people stop taking their medication when they feel better. How often do you do this?
4. Some people stop taking their medication when they feel worse. How often do you do this?

Each question is scored 1 to 5 according to the possible answers (always, very frequently, frequently, not very frequently, or never). Total score number may range from 4 to 20 with higher scores indicating higher levels of reported adherence. Although it is generally accepted that a MAQ score ≥16 identifies good adherence (16), (initially planned in the protocol), most previous studies have used a single yes/no answer to each question on self-reported use of medications to evaluated adherence (11–13), a method that might be better and is comparable to the MAQ score of 20 used in our study.

Accessibility and affordability of medication. Availability was defined as "percentage of facilities (hospitals, pharmacy offices) in which the medicines were available at the time of survey." To calculate availability, a telephone survey was carried out in 146 pharmacies located within 500 m of each participating site (49 in Argentina, 40 in Italy, 31 in Spain, 20 in Brazil, and 6 in Paraguay). Affordability was calculated as the number of days' wages the lowest-paid government worker would be required to pay for purchasing from the private sector a 1-month course of medication.

PHASE 2. Phase 2 was designed as a randomized, open-label, active-controlled, piggyback, 2-group parallel trial. The overall aim of Phase 2 was to assess the efficacy, safety, and efficiency of the CNIC-FS-Ferrer polypill, an FDC pill containing ASA (100 mg), simvastatin (40 mg), and Ramipril at 3 different doses (2.5, 5, or 10 mg, which allowed for up-titration at the discretion of the physician), on increasing adherence, as well as reducing blood pressure (BP) and low-density lipoprotein cholesterol (LDL-C) after 9 months of follow-up.

Sample size for Phase 2. To detect a 14% improvement in adherence compared with the standard control group (expected around 50%), with type I error of 0.025 and 80% power, 251 patients in

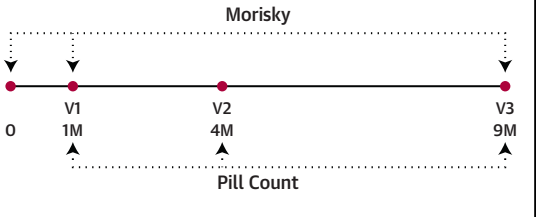

FIGURE 1 Visiting Schema Phase 2

The FOCUS trial included various visits during the 9-month follow-up period in which adherence was measured using Morisky Green Adherence Questionnaire and pill count.

each group were needed. This was increased to 335 per group to allow for a drop-out rate of 25%.

Study protocol. Patients previously included in Phase 1 and without exclusion criteria were invited to participate in Phase 2. Exclusion criteria for Phase 2 were: secondary dyslipidemia, contraindication to any of the components of the polypill, participation in another trial, previous percutaneous transluminal coronary angioplasty with a drug-eluting stent within the previous year, severe congestive heart failure (New York Heart Association functional class III to IV), serum creatinine >2 mg/dl, any condition limiting life expectancy <2 years, and pregnancy or pre-menopause. After signing the informed consent, a central electronic randomization service assigned participants to 1 of 2 arms: the FDC polypill, or the 3 drugs (ASA, ramipril, and simvastatin) separately. Both the FDC pill and the conventional treatment were provided freely for the study. The FDC polypill was administered once daily, as were the 3 active substances given separately. After the first visit (inclusion/randomization), patients were followed at 1, 4, and 9 months to assess clinical status, detect potential adverse events, titrate ramipril dosage, count number of pills, and provide medication (**Figure 1**). The number of pills provided at each visit varied randomly to avoid patients' manipulation and to optimize adherence assessment. A total of 38 sites in 2 countries in Europe (Italy and Spain) and 25 sites in 2 countries in South America (Argentina and Paraguay) participated in FOCUS phase 2 (Online Appendix, Annex 2).

The study was conducted in accordance with Good Clinical Practice. All appropriate national regulatory authorities and ethics committees of the participating sites approved the study. All patients participated voluntarily in the study after signing informed consent.

Estimation of adherence. Similar to Phase 1, FOCUS Phase 2 used the indirect self-reported MAQ to estimate adherence, but also used pill count as a direct measurement of adherence. All medication boxes were labeled and numbered to facilitate auditing of dispensed and returned medication. Each patient received a quantity of pills exceeding the number required before the next visit. Patients were instructed to return all boxes and surplus medication. Pill count was calculated as: (no. of pills dispensed − no. of pills returned)/number of pills prescribed × 100. A pill count between 80% and 110% was considered good adherence. For statistical analysis, adherence was considered as a dichotomous variable. Patients were considered to be "adherent" if they achieved good adherence scores with both methods—pill count and MAQ.

Endpoints and outcomes. The Phase 2 primary outcome was percentage of patients taking medication adequately at 9 months in each arm assessed by attendance at the final 9-month visit and the MAQ and pill count methods, simultaneously. Patients lost for follow-up and those discontinuing medication due to adverse effects were also considered to be nonadherent for this analysis.

Secondary outcomes of Phase 2 included: risk factor control in each study arm (BP and lipid LDL-C levels at months 1 and 9), incidence of adverse events (including death, reinfarction, and rehospitalization for any CV cause), rate of treatment withdrawal, tolerability, and quality of life, as well as economic endpoints (medical and nonmedical costs, data not shown).

STATISTICAL ANALYSIS. Phase 1 descriptive analyses are based on means and SDs for continuous variables and counts and proportions for categorical variables. Differences between groups were tested by t-tests for continuous variables or chi-square for binary variables. A model for the determinants of adherence used a binary outcome (MAQ score 20 yes/no) and forward stepwise regression forcing country into the model.

For Phase 2, country-adjusted logistic models were used to study adherence to treatment following intention-to-treat assumptions. Furthermore, a sensitivity analysis was carried out using 458 patients with complete data at every visit. For the study of systolic/diastolic BP and LDL-C, analysis of covariance models were fitted using baseline values as a covariate. Statistical analyses were conducted using STATA version 12 (Stata Corp. 2011, College Station, Texas). Differences were considered statistically significant at a 2-sided p value <0.05.

RESULTS

PHASE 1. Baseline characteristics of participants. A total of 2,118 patients with a history of MI who met the inclusion and exclusion criteria were enrolled between January 2011 and January 2014 (761 in Spain, 654 in Italy, 528 in Argentina, 113 in Brazil, and 62 in Paraguay). Patient baseline characteristics by country and overall are shown in **Table 1**. Baseline patient characteristics categorized by adherence levels (using MAQ = 20) are shown in Online Table 1. Mean age at enrollment was 64.1 years and mean time from the index MI was 3.5 years.

Proportion of post-MI patients receiving appropriate secondary prevention. **Table 2** shows reported use of

TABLE 1 Baseline Characteristics of Patients Included in Phase 1, By Country and Overall

	Overall	Argentina	Brazil	Paraguay	Italy	Spain
n	(%) 2,118	528 (24.93)	113 (5.34)	62 (2.93)	654 (30.9)	761 (35.93)
Characteristics						
Male	1,700 (80.26)	437 (82.8)	81 (71.7)	49 (79.0)	491 (75.1)	642 (84.4)
Age, yrs	64.01 ± 11.28	60.4 ± 10.3	62.3 ± 10.4	61.5 ± 9.08	67.2 ± 11.4	64.2 ± 11.4
≤50	262 ± 12.37	93 ± 17.9	13 ± 11.5	8 ± 12.9	50 ± 7.66	98 ± 13.1
51–70	1,220 ± 57.6	342 ± 65.6	72 ± 63.7	43 ± 69.4	341 ± 52.2	422 ± 56.4
>70	615 ± 29.04	86 ± 16.5	28 ± 24.8	11 ± 17.7	262 ± 40.1	228 ± 30.5
Clinical						
Age at date of AMI	60.45 ± 11.27	57.7 ± 10	61.2 ± 10.6	61.3 ± 9.05	63.3 ± 11.5	59.6 ± 11.6
Previous AMI history	281 (13.27)	67 (12.8)	22 (19.5)	14 (22.6)	96 (14.7)	82 (12.1)
Previous angina history	612 (28.9)	205 (39.1)	33 (29.2)	35 (56.5)	206 (31.5)	133 (19.6)
Previous syncope history	94 (4.44)	13 (2.49)	8 (7.08)	0 (0)	55 (8.41)	18 (2.65)
Previous ventricular tachycardia	94 (4.44)	17 (3.24)	5 (4.42)	2 (3.23)	44 (6.73)	26 (3.82)
Previous pacemaker	46 (2.17)	6 (1.15)	0 (0)	0 (0)	28 (4.28)	12 (1.76)
Previous ICD	46 (2.17)	9 (1.72)	1 (0.885)	0 (0)	20 (3.06)	16 (2.38)
Previous hypertension history	1,328 (62.7)	364 (69.5)	84 (74.3)	44 (71)	410 (62.7)	426 (60.9)
Previous dyslipidemia history	1,249 (58.97)	319 (60.9)	74 (65.5)	30 (48.4)	385 (58.9)	441 (63.0)
Previous diabetes history	554 (26.16)	119 (22.8)	35 (31.0)	19 (30.6)	159 (24.3)	222 (31.8)
Previous SBP, mm Hg	129.05 ± 18.39	125 ± 17.1	129 ± 21.9	110 ± 15.8	131 ± 16.3	131 ± 19.4
Previous DBP, mm Hg	75.93 ± 10.04	75.6 ± 9.86	77 ± 12.7	67.9 ± 8.71	78.5 ± 8.37	74.3 ± 10.6
Normal <120 or <80 mm Hg	464 ± 21.91	144 ± 27.5	34 ± 30.1	39 ± 62.9	86 ± 13.3	161 ± 22.7
Pre-hypertension 120–139 or 80–89 mm Hg	991 ± 46.79	265 ± 50.6	45 ± 39.8	17 ± 27.4	349 ± 53.8	315 ± 44.4
Hypertension	602 ± 28.42	115 ± 21.9	34 ± 30.1	6 ± 9.68	214 ± 33	233 ± 32.9
BMI, kg/m^2	27.51 ± 4.57	28 ± 5.05	27.5 ± 4.65	27.8 ± 4.18	27 ± 4.34	27.6 ± 4.36
Normal (healthy weight) <25 kg/m^2	618 ± 29.18	149 ± 28.7	40 ± 35.4	15 ± 24.2	235 ± 36	179 ± 27.2
Overweight from 25 to 30 kg/m^2	890 ± 42.02	211 ± 40.6	44 ± 38.9	34 ± 54.8	285 ± 43.6	316 ± 48.1
Obese >30 kg/m^2	497 ± 23.47	160 ± 30.8	29 ± 25.7	13 ± 21	133 ± 20.4	162 ± 24.7
s3	23 (1.09)	5 (0.954)	1 (0.885)	2 (3.23)	10 (1.53)	5 (0.711)
History of pulmonary disease	28 (1.32)	5 (0.954)	1 (0.885)	4 (6.45)	13 (1.99)	5 (0.711)
History of chronic disease	125 (5.9)	19 (3.63)	3 (2.65)	2 (3.23)	59 (9.02)	42 (5.96)
History of renal disease	102 (4.82)	19 (3.63)	6 (5.31)	2 (3.23)	47 (7.19)	28 (3.97)
History of cancer	78 (3.68)	7 (1.34)	2 (1.77)	0 (0)	27 (4.13)	42 (5.96)
Comorbidity	342 (16.15)	50 (9.47)	12 (10.6)	8 (12.9)	120 (18.3)	152 (20.0)
Socioeconomic						
Distance to the nearest medical center, km	5.9 ± 21.7	10.4 ± 37.4	3.8 ± 6.8	5.5 ± 8.8	6.7 ± 14.1	1.5 ± 4.5
≤10 km	1,656 ± 78.19	441 ± 84.5	100 ± 88.5	49 ± 79	520 ± 80	546 ± 97.2
>10 km	253 ± 11.95	81 ± 15.5	13 ± 11.5	13 ± 21	130 ± 20	16 ± 2.85
% Insurance coverage	87.3 (30.71)	63.2 (46.9)	96.9 (13.8)	85.5 (35.5)	93.5 (17.2)	99.5 (6.7)
<50%	197 (9.3)	181 (34.9)	1 (0.885)	9 (14.5)	3 (0.459)	3 (0.45)
≥50%	1,815 (85.69)	337 (65.1)	112 (99.1)	53 (85.5)	650 (99.5)	663 (99.5)
Educational level						
Illiterate	59 (2.79)	5 (0.958)	5 (4.42)	0 (0)	18 (2.75)	31 (4.54)
Others	1,975 (93.25)	517 (99)	108 (95.6)	62 (100.0)	636 (97.2)	652 (95.5)
Occupation						
Professionals	440 (20.77)	86 (16.4)	4 (3.57)	8 (12.9)	104 (15.9)	238 (34.7)
Others	1,597 (75.4)	438 (83.6)	108 (96.4)	54 (87.1)	549 (84.1)	448 (65.3)

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ASA, beta-blockers, statins, ACEIs, and ARBs both overall and by country, and reveals high rates of adequate prescription in a post-MI population according to current guidelines.

Estimation of baseline adherence. The degree of adherence to prescribed medications was calculated using the MAQ. Baseline adherence of the entire population and by country is shown in Online Table 2. When good adherence was defined as an MAQ score >16, >90% of patients were included in this category, suggesting that this score overestimates adherence in our population. Using 20 as the cut-off point to define adherence, we found average baseline adherence levels of 45.5%, in concordance with most published

TABLE 1 Continued

	Overall	Argentina	Brazil	Paraguay	Italy	Spain
Risk factors						
Smoker	319 (15.06)	103 (19.9)	17 (15.0)	17 (27.4)	85 (13.0)	97 (14.0)
Former smoker	855 (40.37)	184 (35.5)	66 (58.4)	21 (33.9)	278 (42.6)	306 (44.1)
Family history of CV diseases	641 (30.26)	160 (30.5)	53 (46.9)	28 (45.2)	245 (37.5)	155 (22.3)
Sedentary	905 (42.73)	323 (61.6)	65 (57.5)	40 (64.5)	278 (42.5)	199 (28.6)
Alcohol	646 (30.5)	97 (18.6)	30 (26.5)	20 (32.3)	299 (45.7)	200 (28.7)
Baseline treatment						
Aspirin	1,917 (90.51)	480 (97.2)	111 (99.1)	60 (100.0)	606 (92.9)	660 (95.4)
Antiplatelets	959 (45.28)	277 (56.0)	55 (49.1)	53 (88.3)	294 (45.1)	280 (40.1)
Statin	1,934 (91.31)	475 (96.5)	111 (99.1)	60 (100)	614 (94.3)	674 (97.1)
Beta-blocker	1,740 (82.15)	454 (92.1)	105 (93.8)	57 (96.6)	546 (83.9)	578 (84.4)
ACEI	1,370 (64.68)	370 (75.1)	78 (69.6)	46 (78.0)	469 (72.0)	407 (60.6)
ARB	337 (15.91)	87 (18.1)	29 (26.1)	8 (13.6)	93 (14.3)	120 (19.1)
Total number of pills (and others)/day	7.25 ± 2.85	6.89 ± 2.15	8.95 ± 2.68	8.87 ± 1.72	6.55 ± 2.52	7.73 ± 3.38
Depression						
PHQ-9 score 5–9 minimal symptoms	661 (31.21)	0 (0)	0 (0)	0 (30.6)	311 (48.5)	350 (48.4)
PHQ-9 score 10–14 minor depression	936 (44.19)	215 (41)	41 (36.3)	19 (30.6)	311 (48.5)	350 (48.4)
PHQ-9 score 15–19 major depression, moderately severe	693 (32.72)	194 (37)	31 (27.4)	22 (35.5)	208 (32.4)	238 (32.9)
PHQ-9 score ≥20 major depression, severe	435 (20.54)	116 (22.1)	41 (36.3)	21 (33.9)	122 (19.0)	135 (18.7)
Stress, yes	1,583 (74.74)	403 (76.5)	70 (61.9)	44 (71.0)	457 (70.1)	609 (81.6)
Center private	514 (24.27)	402 (81.2)	112 (100.0)	0 (0)	0 (0)	0 (0)
Center public	1,503 (70.96)	93 (18.8)	0 (0)	60 (100.0)	652 (100.0)	698 (100.0)
Cardiologist	1,663 (78.52)	495 (100.0)	0 (0)	60 (100.0)	652 (100.0)	456 (65.3)
General treatment	354 (16.71)	0 (0)	112 (100.0)	0 (0)	0 (0)	242 (34.7)
<4 pills	68 (3.21)	12 (2.42)	0 (0)	0 (0)	29 (4.45)	27 (3.87)
≥4–9 pills	1,181 (55.76)	324 (65.5)	37 (33.0)	14 (23.3)	442 (67.9)	364 (52.1)
≥10 pills	767 (36.21)	159 (32.1)	75 (67.0)	46 (76.7)	180 (27.6)	307 (44.0)
Complex treatment, yes	208 (9.82)	34 (6.87)	4 (3.57)	15 (25.0)	64 (9.82)	91 (13)
Time from AMI, months	42.96 ± 66.93	33.8 ± 63.9	15.5 ± 16	2.17 ± 4	45.9 ± 68	54.9 ± 72.4
<6 months	595 (28.09)	222 (50.2)	14 (12.8)	52 (88.1)	149 (26.3)	158 (28.0)
6 months to 1 yr	239 (11.28)	59 (13.3)	30 (27.5)	5 (8.47)	59 (10.4)	86 (15.2)
1–2 yrs	446 (21.06)	68 (15.4)	57 (52.3)	2 (3.39)	216 (38.1)	103 (18.2)
>2 yrs	462 (21.81)	93 (21.0)	8 (7.34)	0 (0)	143 (25.2)	218 (38.6)

Values are n (%) or mean ± SD.

ACEI = angiotensin-converting enzyme inhibitors; AMI = acute myocardial infarction; ARB = angiotensin-II receptor blockers; BMI = body mass index; CV = cardiovascular; DBP = diastolic blood pressure; ICD = implantable cardioverter-defibrillator; PHQ-9 = Patient Health Questionnaire-9; SBP = systolic blood pressure.

data. We used this cut-off point for the main analyses in both FOCUS Phase 1 and 2.

Accessibility and affordability. All facilities in all countries had all 4 study drugs available at the time of enquiry. Affordability ranged from 16.96 days mean wages in Argentina to 0.65 in Spain (Paraguay 5.7, Brazil 4.4, and Italy 0.72 days).

Factors that contribute to inadequate patient adherence to treatment. Online Appendix Annex 1 and Online Table 3 summarize the variables included in the study and their association with adherence. Patients younger than 50 years of age, those taking more than 10 pills, those following a complex regimen (e.g., those taking medications other than orally), current smokers, and those with sedentary lifestyles were significantly more nonadherent. Importantly, there was a significant trend toward more nonadherence with a higher score of depression (as measured by the Patient Health Questionnaire-9). Of the sociodemographic variables, illiteracy level, lower social support, and lower percentage of insurance coverage showed significantly lower levels of adherence. Lower levels of adherence were also noted for those patients being treated by general practitioners (as opposed to cardiologists) and those being treated in a private center (as opposed to a public health center).

To identify which were the key independent predictors of nonadherence, a forward stepwise regression procedure was used with country forced into the

TABLE 2 Percentages of Patients Receiving Secondary Prevention Medication, by Country and Overall, in Phase 1

	Patients Included in Phase 1	ASA	Statin	BB	ACEI	ARB
Argentina	528	486 (97.2)	481 (96.6)	460 (92.2)	376 (75.4)	88 (18.1)
Brazil	113	46 (100.0)	45 (97.8)	43 (93.5)	33 (71.7)	10 (21.7)
Paraguay	62	60 (100.0)	60 (100.0)	57 (96.6)	46 (78.0)	8 (13.6)
Italy	654	614 (91.6)	622 (93.0)	555 (83.0)	472 (70.6)	99 (14.8)
Spain	761	633 (94.9)	648 (96.9)	558 (84.5)	402 (62.2)	105 (17.6)
Overall	2,118	1,953 (94.9)	1,972 (95.8)	1,777 (86.7)	1,392 (68.4)	348 (17.7)

Values are n (%).
ASA = acetyl salicylic acid; BB = beta-blocker; other abbreviations as in Table 1.

model (Table 3).The risk of being nonadherent was independently associated with younger age (younger than age 50 years), scoring high on the depression scale, and following a complex (administrations other than oral) treatment. However, the odds of being adherent increased with higher percentage of health insurance coverage and with optimal levels of social support.

PHASE 2. In Phase 2, a total of 695 patients were enrolled from 4 countries during January 2011 to September 2013. They were followed for 9 months. Figure 2 shows the study flow chart. In Phase 2, 695 patients were randomized: 345 to the control group and 350 to the polypill. In the control group, 35 patients missed their 9-month visit (10.1%) versus 43 patients in the polypill arm (12.3%). All 695 patients were included for the primary endpoint analysis (percentage of patients taking medication adequately at 9 months) in the intention-to-treat analysis. In addition, the 458 patients attending all visits and completing all data on adherence were analyzed in a per-protocol analysis.

Effects on adherence. Intention-to-treat analysis showed that after 9 months, 41% in the usual care group and 50.8% in the polypill group were taking the medication adequately ($p = 0.019$). This difference persisted after adjusting for the covariates showing association with patients' adherence in Phase 1. For the 458 patients with complete data (per-protocol analysis) 55.7% in the control group and 65.7% in the polypill group were taking medication adequately ($p = 0.012$). The Central Illustration and Table 4 show various measures of the patients' adherence to treatment in the study.

Effect of the polypill on BP and LDL-C. There were no differences in BP and cholesterol levels between the control and FDC polypill groups at the end of trial (Table 5).

Safety and tolerability of the polypill. There were no significant differences in adverse events in both groups. A total of 32% of patients in the control group and 35% in the polypill group suffered an adverse event. In 6.6% of the control group and 6% of the FDC group, the adverse effect was considered severe. Treatment was discontinued in 4% of patients in each group (Table 6).

TABLE 3 Multivariable Analysis of Variables That Independently Contribute to Adherence, Phase 1

	Odds Ratio	95% Confidence Interval	p Value
Age <50 yrs	1.50	1.08-2.09	0.015
Score depression	1.07	1.04-1.09	<0.001
Score social support	0.94	0.92-0.96	<0.001
% insurance coverage	1.00	0.99-1.00	0.025
Complexity of treatment	1.42	1.00-2.02	0.047

DISCUSSION

To the best of our knowledge, this is the first study to carry out an in-depth assessment of the factors that contribute to nonadherence to evidence-based CV medications in a post-MI cohort from various socioeconomic and demographic backgrounds. Moreover, the FOCUS trial has used validated, direct, and indirect measures of adherence to assess the impact of a polypill strategy in secondary prevention.

Our study shows that adherence to CV medications is a complex problem, and many different factors influence adherence in various ways. The single most important factor associated with poor adherence was depression; but, lack of social support and complexity of treatment also contributed significantly to poor adherence. The results also demonstrate that access to polypill in patients with CVD improved adherence significantly by 22% (41% vs. 50.1% in control and polypill groups, respectively) after a 9-month follow-up. The difference persisted in the per-protocol analysis and after adjusting for variables identified in Phase 1 as independent predictors of patients' adherence to treatment. There were no differences in BP and LDL-C profile between the polypill and control groups. Finally, the number of severe adverse effects was low and similar in both groups of treatment.

ASSESSMENT OF ADHERENCE TO PRESCRIBED MEDICATIONS: AN UNRESOLVED ISSUE. There are several issues that need to be considered when interpreting results from adherence trials, particularly the lack of a gold standard for measuring adherence and the enormous amount of factors that have been shown to play a role in patients' adherence

(9). There are a number of self-reported instruments that have been developed to measure medication adherence. The main advantage of these instruments is that they are generally brief and inexpensive, they provide immediate feedback to the clinician or researcher, and the responses may help identify some correctable misperceptions about adherence to medications. However, despite their relative simplicity, these scales are at best moderately related to objective measures of adherence and are limited by social desirability and other recall biases. These biases lead the instruments to overestimate how well patients adhere by approximately 20% as compared with objective measures.

The results of FOCUS Phase 1 demonstrated that the MAQ score can overestimate adherence when a cut-off of 16 is used, probably because in addition to the patient overestimation, the physician quantification (evaluation) introduces a second source of overestimation. Therefore, we used a cut-off of 20. A score of 20 identifies good adherers and scoring below 20 identifies patients that are at some level non-adherent to medication. This way to measure adherence is similar to the first option described in the previous text, but due to the fact that it identifies perfect adherent behavior, it probably counterbalances for some of the indirect overestimation inherent to the methodology.

FACTORS THAT DETERMINE ADHERENCE. The results from our study describe a very clear picture of how these variables influence adherence and are in agreement with previous findings. The single most important factor that associates with poor adherence is depression, which has repeatedly been identified in the literature with low levels of patient adherence (17–19).

Recent evidence shows that adherence to treatment for certain chronic diseases decreases significantly during the first 6 months after the prescription (20). Contrary to these data, our study found reasonable levels of adherence at baseline. We believe that this is the consequence of an inclusion bias secondary to the amendment that allowed the inclusion of patients with any time from the original MI. By extending the inclusion of patients based on the time from the event, inclusion was biased toward patients who were alive (due in part to being adherent to medications), as well as compliance with the visit schedule at the recruiting center (and therefore, in turn, more likely to be adherent as well).

Although our results are in line with most of the available data, including the critical role of depression and social support on patients' adherence, the fact that "number of pills" was not selected by the

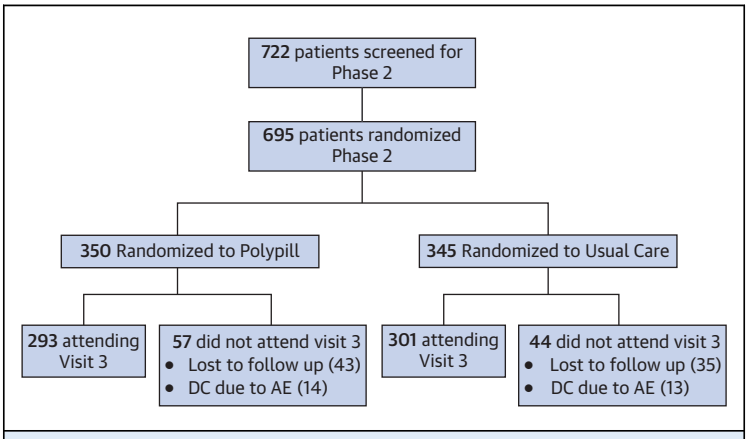
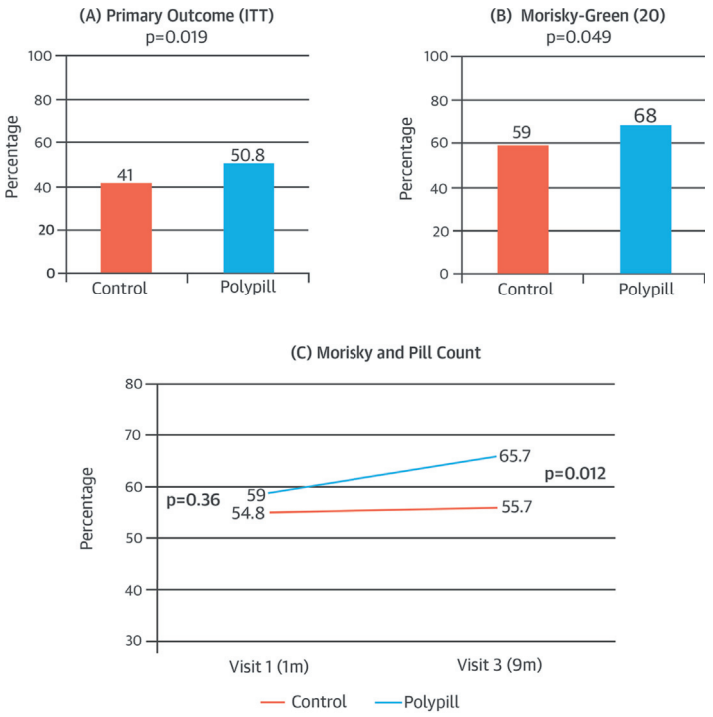


FIGURE 2 Study Flow Chart in Phase 2

AE = adverse effect(s); DC = discontinued.



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CENTRAL ILLUSTRATION Effect of a Polypill Strategy on Adherence in Secondary Cardiovascular Prevention

Adherence to treatment in post-myocardial infarction patients receiving a fixed-dose combination polypill versus those with conventional treatment (3 drugs given separately) in Phase 2: **(A)** primary outcome measure (Visit + Morisky-Green questionnaire [MAQ] = 20 + pill count >80% to 110%); **(B)** using MAQ; and **(C)** adherence to treatment using MAQ and pill count. ITI = intention-to-treat.

TABLE 4 Differences in Adherence Using MAQ and Pill Count, Primary Endpoint in Phase 2

	Control	Polypill	p Value
Intention-to-treat			
9-month visit + pill count (80%–110%) + Morisky = 20	n = 345	n =350	
Adherence	141 (41%)	178 (50.8%)	0.019
Per protocol			
All visits + pill count (80%–110%) + Morisky = 20	n = 219	n = 239	
Adherence	122 (55.7%)	157 (65.7%)	0.012

MAQ = Morisky-Green questionnaire.

multivariable analysis needs further exploration. Several explanations have been considered: First, the number of pills that FOCUS patients were taking is very high, with a mean >7 and with 767 patients taking more than 10 pills/day. Extremely high values have been detected, with a considerable number of patients taking up to 20 and 30 pills/day. Second, the number of pills that the patients take daily is not uniform and varies among countries. Most of these extreme cases are patients recruited in Spain. Third, the information provided by "number of pills" may be provided also by other variables such as complexity of treatment. In addition, we found that there was an interaction between depression status and number of pills. The relationship between number of pills and poor adherence is evident only in patients without depression.

IMPACT OF THE FDC ON ADHERENCE. The results of FOCUS Phase 2 show that a polypill strategy in secondary prevention significantly increased adherence compared with the control group even in a highly-adherent population at baseline. These results should be considered in the context of previous trials showing that FDCs improve adherence (11–13), which found baseline adherence rates of 46% to 60% and improvements in adherence after randomization to polypill to 70% to 85%. The FOCUS trial found adherence levels at baseline of 59% (measured by MAQ) and 59% (measured by MAQ and pill count combined) with significant increases at the end of the study measured by MAQ alone and both MAQ and pill count combined (68% and 65.7%, respectively). There are various factors that potentially explain the differences in magnitude of improved adherence. First, the FOCUS trial had a shorter follow-up period than other trials exploring the effect of a polypill strategy on adherence, which had follow-up periods of 12 to 18 months. This is an important issue, as our results show that, using the MAQ, the difference in adherence on both groups seems to diverge the more time goes by. Second, the different methods of measuring adherence play a significant role in the observed results.

TABLE 5 Changes in Mean BP and Mean LDL-C Over 9 Months for Polypill Treatment and Control Groups, Phase 2

	Control	Polypill	p Value
Intention-to-treat			
ΔSBP, mm Hg	0.88 (−0.76 to 2.53)	−0.32 (−2.02 to 1.38)	0.32
ΔDBP, mm Hg	0.38 (−0.69 to 1.46)	−0.11 (−1.13 to 0.90)	0.51
ΔLDL-C, mg/dl	2.17 (−0.96 to 5.29)	5.27 (−0.31 to 10.86)	0.34
Per-protocol			
ΔSBP, mm Hg	0.63 (−1.47 to 2.74)	−0.97 (−3.15 to 1.21)	0.30
ΔDBP, mm Hg	0.49 (−0.86 to 1.85)	−0.58 (−1.91 to 0.74)	0.27
ΔLDL-C, mg/dl	2.90 (−1.15 to 6.95)	5.13 (−2.97 to 13.24)	0.64

Values are change in BP and LDL cholesterol, given in mm Hg and mg/dl.
BP = blood pressure; LDL = low density lipoprotein; other abbreviations as in Table 1.

The FOCUS trial used more robust methods of adherence (measurements in previous studies were based on a single question on either whether the patient could remember the name and dosage of treatment to be classified as adherent—IMPACT (IMProving Adherence using Combination Therapy) [13]—or whether the patient had forgotten to take any of the medication the week before—UMPIRE (Use of a Multidrug Pill in Reducing cardiovascular Events) [11] and KANYINI GAP (guidelines adherence with the polypill) [12]). Even with seemingly simple methods such as pill counts, adherence measurement is complex, with issues concerning how to handle visits when pills are not returned, apparent "over-adherence" (>100% of expected pills for the interval between visits), missed visits (when product is thus not dispensed for a period), and protocol-specified time off treatment. Moreover, pill count as a measure of adherence has been shown to change pill taking behavior and positively impact adherence itself, the so called "pill count effect." To this effect, a recent study found a positive correlation between the number of clinician pill counts and adherence. Patients were divided into 3 groups (0 counts, 1 to 3 counts, and 4 to 7 counts) and exhibited adherence of 76%, 84%, and 92%, respectively (p = 0.004) (21). Therefore, direct measures of adherence (such as pill count) should be taken with caution as they can affect adherence itself. In our study, the pill count was performed for both the group treated with polypill and the control group. By performing pill count with 3 different drugs, it is reasonable to expect a larger effect of the overestimation of pill counting on the control group.

Finally, most notably, FOCUS, unlike other trials, provided both the polypill group and the control group with free medications and an identical visit

TABLE 6 AEs Reported in Fixed-Dose Combination and Usual Care Groups During the Trial, Phase 2

	Control	Polypill
Reported AE	112 (32.5)	124 (35.4)
Reported SAE	23 (6.6)	21 (6.0)
Patients interrupting treatment because of AE	13 (3.7)	14 (4.0)
Death*	1 (0.3)	1 (0.3)
Reinfarction	2 (0.6)	2 (0.6)
Hospitalization	23 (6.7)	21 (6.0)
Hematological AE	6 (1.7)	5 (1.4)
Other cardiac AE†	4 (1.1)	10 (2.8)
Musculoskeletal AE	10 (3.8)	5 (1.4)
Cough	6 (1.7)	5 (1.4)
Dizziness	2 (0.6)	2 (0.6)
Hypotension	7 (0.2)	0 (0.0)

Values are n (%). *Control (cancer); polypill (traffic accident). †Other cardiac AE: for example, nonspecific angina.

AE = adverse event(s).

plan, so that the adherent behavior in the control group was improved.

STUDY LIMITATIONS. This study had additional limitations, as trials that are unavoidably unblinded can have unintended differences between groups in diagnostic and therapeutic intensity that are difficult to measure. To overcome the possibility of differential intensity of treatment, diagnosis, or adverse event reporting between groups, pill count enabled a more objective assessment of adherence during the trial.

There are several mechanisms whereby a polypill strategy may enhance adherence, which include ease of prescription, packaged delivery, ease of taking, and patient acceptability. This shows that physicians from 5 different countries are willing to prescribe a polypill to a post-MI population by involving them in the trial, and at the end of the study, more patients were taking the combination treatment than the medications given separately.

The trial included patients with different socioeconomic background. It is noteworthy to mention that in the case of Paraguay, most of the population enrolled in the study was of the indigenous Guaranis, with an underprivileged background. In this setting, baseline adherence levels were extremely low (17% at baseline), which is in line with previous findings (4). As suggested by these results, it is in the setting of LMIC in populations with lower use of indicated medications that the effect of the FDC strategy could have the most impact, due to lack of adherence, accessibility, and affordability of CV medications.

IMPACT OF POLYPILL ON BP AND LDL-C. There were no significant differences between randomized groups for changes in systolic BP or LDL-C, in line with other previous reports. The main reason for that is the added benefit of an increase in adherence in the polypill group was effectively counter-balanced by the use of other lipid-lowering and antihypertensive drugs in the control group.

IMPLICATIONS OF FINDINGS AND FUTURE RESEARCH. The FOCUS trial had several strengths in terms of identifying the factors that impede adherence to CV medications in secondary prevention, assessing adherence with different methods, and dispensing both the FDC and the 3 drugs given separately for free. Our results support the potential usefulness of a polypill-based care in secondary prevention, particularly in patients with a previous MI. Complexity of treatment and number of pills, as well as depression, all of which tend to coexist in this patient population, impede adequate adherence to guideline-recommended, effective CV pharmacotherapy. In the past 2 decades, the responsibility has shifted from caregivers (as seen by the nearly universal prescription rates at discharge) to patients taking the prescribed medications. The reasons for nonadherence are complex and fall into different categories as proposed by the World Health Organization (socioeconomic, medication-related, condition-related, health system-related, and patient-related factors) (22). The reality is that nonadherence to secondary CV medication has tremendous health impact and economic costs. In fact, 37% of all MIs in the United States in 2013 were recurrences, and, with this understanding, strategies that improve adherence will have an important effect on mitigating, at least in part, the CVD burden.

We believe the FOCUS trial has included the use of validated, direct, and indirect measures of adherence that go beyond previous trials. Furthermore, FOCUS has successfully identified the factors that weigh into being nonadherent, mainly the level of depression, complexity of treatment, and number of medications. In the light of these results, these factors need to be addressed by the different stakeholders in order to provide effective strategies that improve medication nonadherence.

The use of medications based on solid clinical evidence has contributed substantially to reductions in CV morbidity and mortality. Current guidelines recommend concomitant use of aspirin, statin, and BP-lowering agents in patients with a history of coronary heart disease; yet, available data have continuously shown that many patients in high-income countries, and most in low-income countries, do not receive such treatment long term. The results from the FOCUS trial effectively show that FDC-based care

achieves significantly better rates of adherence than when 3 drugs are given separately. The use of FDC demonstrated good short-term safety and tolerability and short-term risk factor reductions that were of approximately the size expected from the additive effects of the individual agents.

Larger, longer-term pragmatic trials assessing the effect of an FDC strategy on clinical CV outcomes are needed.

CONCLUSIONS

Compared with the 3 drugs given separately, the use of a polypill strategy significantly increases self-reported and directly-measured medication adherence for secondary prevention following an acute MI.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Lack of adherence to guideline-recommended, efficacy-proven CV medications after an acute MI is, in part, responsible for the gap in secondary prevention.

COMPETENCY IN PATIENT CARE: In secondary prevention following an acute MI, younger age, depression, and following a complex drug treatment are associated with a lower medication adherence, whereas adherence is increased in patients with higher levels of insurance coverage and social support. In patients following an acute MI, a polypill strategy significantly increases adherence to medication.

TRANSLATIONAL OUTLOOK: Although this is a short-term study, long-term evaluation of the polypill strategy is necessary for a confirmation of adherence and clinical endpoints.

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KEY WORDS adherence, polypill, secondary prevention

APPENDIX For Annexes 1 and 2, supplemental tables, and a list of FOCUS investigators, please see the online version of this article.

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