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RESEARCH ARTICLE

An Educational Intervention to Improve Statin Use: Cluster RCT at the Primary Care Level in Argentina

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Introduction: Statins are essential drugs for high cardiovascular disease (CVD) risk management; however, there is still low adherence to good clinical practice guidelines for statin use at the primary care level in low- and middle-income countries. This study aimed to test whether a complex intervention targeting physicians improves treatment and control of hypercholesterolemia among patients with moderate to high CVD risk in Argentina.

Study design: Cluster RCT.

Setting/participants: Ten primary care centers from the public healthcare system of Argentina.

Intervention: Primary care physicians in the intervention group received an educational program with three main components: (1) an intensive 2-day training workshop; (2) educational outreach visits; and (3) a mobile health application installed on the physician's smartphones.

Main outcome measures: Reduction in mean low-density lipoprotein cholesterol level, reduction in mean Framingham risk score, proportion of patients receiving an appropriate statin dose, and mean annual number of primary care center visits.

Results: Data were analyzed in 2017−2018. Between April 2015 and April 2016, a total of 357 participants were enrolled (179 patients in the intervention group and 178 in the control group). The global follow-up rate was 97.2%. At the end of the follow-up period, there was no difference in low-density lipoprotein cholesterol levels in any of the follow-up points among the groups. Mean CVD risk had a significant net difference in the first 6 months in the intervention group versus the control group (−4.0, 95% CI = −6.5, −1.5). At the end of follow-up, there was an absolute 41.5% higher rate of participants receiving an appropriate statin dose in the intervention group versus the control group.

Conclusions: Although the intervention did not reach a reduction in cholesterol levels, it had a significant positive impact on the promotion of adequate use of clinical practice guidelines.

Trial registration: This study is registered at www.clinicaltrials.gov NCT02380911.

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INTRODUCTION

Statin utilization is the cornerstone of high cardiovascular disease (CVD) risk management. The robust evidence showing a reduction of CV events, and in some studies, CV mortality, has made statins essential in a variety of clinical conditions with elevated CV risk.[1]

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Despite this substantial evidence, even in developed countries and in coronary patients, a large proportion of patients do not achieve guideline standards.[2–4] In a recent study, the use of statins was significantly higher in high-income countries (66.5%) than in low-income countries (3.3%), and decreased in line with reduction of country economic status.[5] Moreover, a very low achievement of low-density lipoprotein cholesterol (LDL-c) goals was observed, even in high–CVD risk patients.[5] Low utilization of statins decreases potential population benefits both in primary and secondary prevention[1,6] and makes it necessary to implement multiple approaches to improve the long-term use of basic, inexpensive, and effective drugs.[5] In addition, the level of optimal adherence confers a significant inverse association with subsequent adverse outcomes,[7] and adherence drastically decreases during the first year of treatment.[8,9] Thus, the effectiveness of statins may be considerably affected given that a substantial proportion of people have suboptimal adherence.[10,11]

The 2013 American College of Cardiology and American Heart Association (ACC/AHA) guidelines made an abrupt change of goals for statin doses in four groups of specific patients, defined in the guidelines, in accordance to the trials reviewed by ACC/AHA.[12] One of the aims was to simplify statin prescription and increase statin utilization with a focus on general practitioners.

In Argentina, the National Essential Drugs Program called "Remediar"[13] provides free-of-charge ambulatory drugs to public primary care centers (PCCs) based on the WHO package of essential drugs for prevention and management of CV risk (such as antihypertensive, antidiabetic drugs, and low-dose aspirin). Statins (simvastatin 20 mg) were recently added to the National Essential Drugs Program in 2014, for patients with high cholesterol, increased CVD risk, or both. Despite the availability of evidence-based practice guidelines, multiple barriers hinder the appropriate management of hypercholesterolemia in primary care settings. These barriers include organizational hurdles within PCCs, confusing and conflicting guidelines from external sources, errors and omissions by primary care doctors, communication problems at the interface between secondary and primary care, multiple competing demands on physicians' time, and lack of reimbursement for preventive counseling. Some interventions that have been effective in dealing with barriers related to clinical practice include multifaceted educational outreach visits and audits and feedback.[14–16] In this sense, education and incentives to physicians and other health professionals have been shown to be important in increasing the proportion of patients treated and the average prescribed drug dose.[7] The promotion of adequate use of clinical practice guidelines (CPGs) leads to the reduction of inappropriate variability in clinical practice.[17] Therefore, the goal of this study was to test whether a complex intervention targeting physicians improves treatment and control of hypercholesterolemia among patients with moderate to high CVD risk in Argentina.

METHODS

The design and protocol details of this study have been published previously.[18] Briefly, this study was a cluster RCT conducted among ten PCCs from the public healthcare system of Argentina. All centers received statins free of charge through the National Essential Drugs Program in Argentina.[13] Four centers were selected from the province of Chubut (South region); four from the province of Corrientes (North region); and two from the province of La Rioja (West region). Randomization was stratified by province and was conducted at the data management center at the Institute for Clinical Effectiveness and Health Policy. Five centers were randomized to receive the intervention program and five centers to continue with usual care (control group). The study was approved by an independent Ethics Committee at Hospital Italiano of Buenos Aires. All participants signed an informed consent form during screening.

Study Population

All the included PCCs were located in urban settings and provided free health care and medication to uninsured patients. Patients were eligible if they were aged 40–74 years, were receiving care at participating PCCs, and met at least one of the following criteria: medical history of arteriosclerotic CVD (defined as acute coronary syndrome, history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack presumed to be of atherosclerotic origin or revascularization); high CVD risk according to the WHO charts adapted by the National Ministry of Health (estimated 10-year CVD risk ≥20%)[19]; LDL-c level ≥190 mg/dL; or Type 2 diabetes. Patients were excluded if at least one of the following conditions were present: statin treatment, pregnancy, bed-bound patient, inability to give informed consent, history of end-stage chronic kidney disease treated with dialysis, HIV/AIDS, alcohol or drug abuse, or active tuberculosis.

Measures

Physicians belonging to the intervention group received an educational program that was accompanied by support tools. As published previously,[18] the intervention included three main components: (1) an intensive 2-day training workshop followed by certification at the outset; followed by (2) three quarterly educational outreach visits (EOVs); and (3) a mobile health (mHealth) application installed on the physician's smartphones to facilitate evidence-based and guideline-driven decision aids to improve patient management.

The 2-day workshop was held at the Institute for Clinical Effectiveness and Health Policy and conducted by a cardiologist and an internal medicine specialist. The training curriculum was based on the CV risk clinical guideline promoted by the National Ministry of Health,[19] ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults,[12] and the chronic care model promoted by the National Ministry of Health.[20,21] The topics included in the training sessions were global CV risk assessment and management; diagnosis,

treatment, and monitoring of patients with dyslipidemia; the chronic care model components; and management of adherence issues in patients with chronic diseases. The EOVs were also performed by cardiologists and internal medicine specialists, and consisted of onsite face-to-face encounters with local physicians. Based on data from local practice and CPG practical exercises, the specialists gave individual feedback, assisted with the possible needs of practitioners at the clinics, and identified barriers that prevented appropriate prescription (e.g., side effects of statins, barriers for chronic treatment adherence). All physicians had the mHealth application installed in their phones during the study, which were used during the EOVs. It included evidence-based statin use recommendations shown on screen after completing information for CVD risk estimation. The application was developed by an IT team using the SANA framework (http://sana.mit.edu), a highly customizable, open-source, android-based mHealth information system.

During the intervention, the statin therapy algorithm was adapted from the 2013 ACC/AHA Guideline[12] and WHO CVD risk charts.[19] Physicians from both groups of clinics had already received training on global CV risk management, given previously by the Ministry of Health. Moreover, written material including charts with the CPG on the management of statins was delivered at all PCCs.

In addition, the following support tools were used in the intervention group: (1) a web-based platform designed to send weekly SMS messages to promote healthy lifestyles, regular visits to the clinic, and to improve medication adherence for study patients; and (2) onsite training to pharmacist assistants given at the first EOV in each intervention clinic, focused on patient counseling on medication adherence. Additionally, educational flyers were distributed to be displayed in the pharmacy room.

Study physicians, pharmacist assistants, and participants were not blinded to the intervention assignment. However, study outcomes were collected by nurses who were not involved in the intervention.

The primary outcome was net change in LDL-c levels from baseline to 12 months in the intervention group versus the control group. Secondary outcomes evaluated proportion of patients with high CVD risk who were on statins and receiving an appropriate dose according to the CPG, net change in 10-year CVD Framingham risk score before and after program implementation, mean annual number of follow-up visits to the PCC for high CVD risk, and patients' level of treatment adherence evaluated through a questionnaire among treated patients. Subgroup analyses on primary and secondary outcomes by diabetes status and level of CVD risk were included.

Trained and certified research nurses who did not participate in the intervention collected all study data at baseline, 6 months, and 12 months of follow-up in PCCs using standard questionnaires and measurement methods, as described previously.[18] Ten-year CVD risk was estimated using the Framingham Risk Score.[22] The dose of statins indicated by physicians was considered appropriate if it followed the recommendation promoted by the study algorithm (Appendix Figure 1, available online), which was adapted from the new ACC/AHA Guideline[12] and WHO CVD risk charts[19] promoted by the Ministry of Health. Adherence to chronic medications was assessed with the Morisky–Green questionnaire,[23–25] and high adherence to medication was defined as a total score of 8.

For biochemical measures, each PCC was provided with a Cholestech LDX and LDX Capillary Plungers (Alere Cholestech LDX® Analyzer) to measure total cholesterol; calculated LDL-c; high-density lipoprotein cholesterol; triglycerides; and glucose from a fasting capillary blood sample obtained by finger stick at the baseline and follow-up visits.[26–29]

Statistical Analysis

The study was designed to provide 90% statistical power to detect a 0.7-mmol/L (27-mg/dL) reduction in LDL-c level at a significance level of 0.05 using a two-tailed test, assuming an intra-cluster correlation coefficient of 0.06. The cluster design effect was taken into account in the power calculations using the formula developed by Donner and Klar[30,31] and was implemented in PASS 2008 software. Assuming an 85% follow-up rate, and considering a total of ten clusters (five per group), the estimated sample size for each cluster (PCC) was 35, accounting for 175 participants in each group.

Data were analyzed in 2017–2018. Baseline patient characteristics were compared between the intervention and control groups considering clustering. Statistical analyses were based on the intention-to-treat principle. The primary research hypothesis that there was a greater reduction in mean LDL-c levels from baseline to 12 months in the intervention group was tested using generalized estimating equation regression models with normal distribution, the identity link function, and compound symmetry working covariance structure to account for cluster effect. For other continuous outcomes, generalized estimating equation models were also used. For binary outcomes, binomial distribution was assumed for the variance function and logit link. For the outcome annual number of visits, Poisson distribution was used for the variance function and log link. Cluster effects were accounted for by assuming a compound symmetry covariance structure. Additional subgroup analyses by sex, diabetes condition, and CVD risk results are presented following the same analysis strategies. All analyses were performed with SAS, version 9.3, and the models were estimated using the GENMOD procedure.

RESULTS

Between April 2015 and April 2016, a total of 697 patients from the study's participating PCCs were prescreened for eligibility. Among those patients, 434 attended a screening visit for eligibility assessment. Of those, 357 met eligibility criteria and were enrolled in the study: 179 patients in the intervention group and 178 in the control group (Figure 1). Globally, the follow-up rate was 97.2% (98.3% in the intervention group and 96.1% in the control group).

Baseline characteristic distribution between the intervention and control groups are presented in Table 1. All analyzed variables were balanced except for the mean diastolic blood pressure, which was higher in the control group.

Table 2 shows the primary and secondary outcomes at baseline, 6 months, and 12 months. The mean differences are compared to baseline, and a separate adjusted

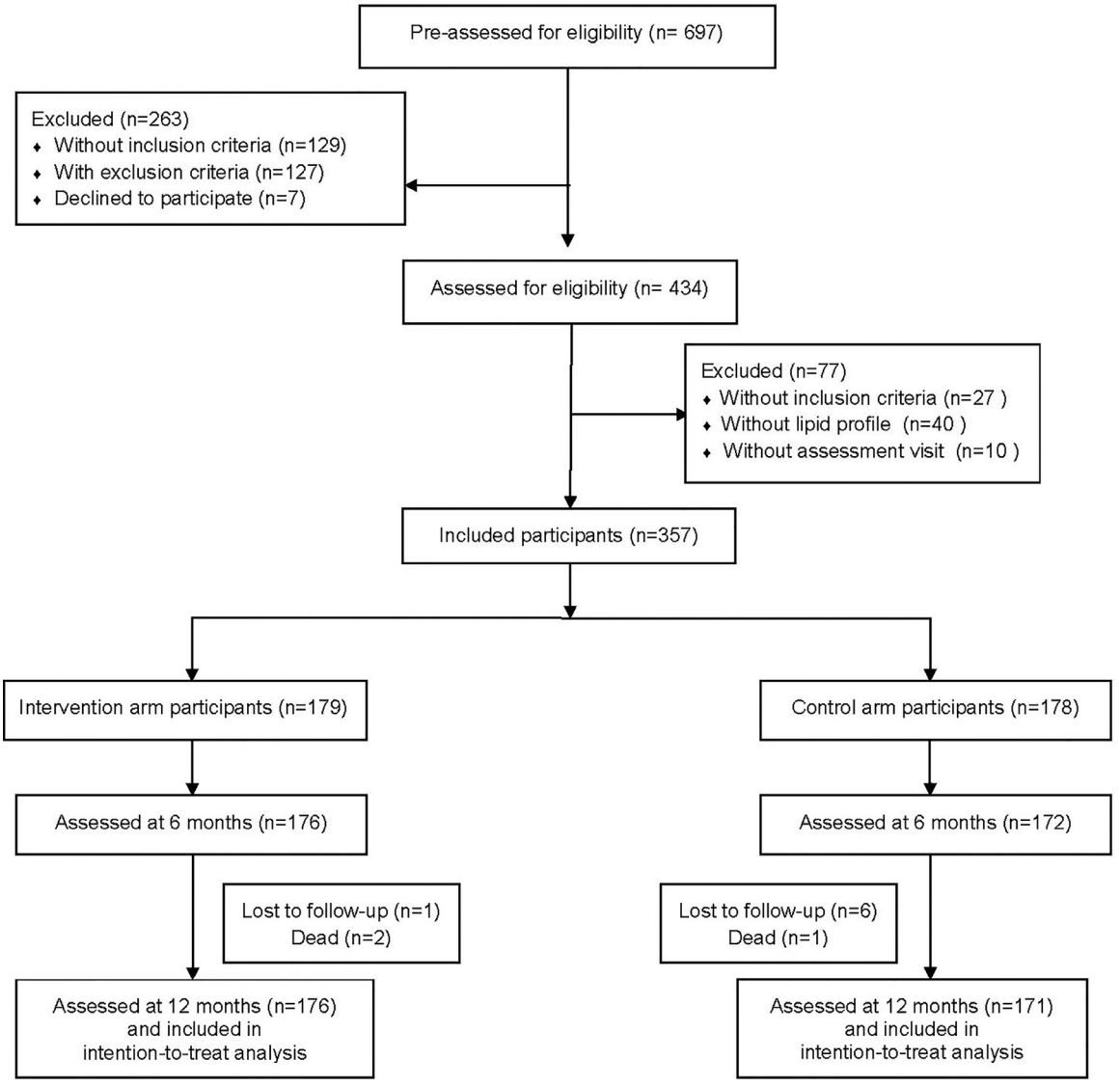

Figure 1. Study participants and follow-up.

analysis is presented. In relation to the primary outcome, there was no difference in LDL-c levels in any of the follow-up points among the groups. For the Framingham risk analysis, a statistically significant reduction in mean CVD risk was observed after the first 6 months in the intervention group versus the control group; this difference was not maintained at the end of follow-up. Regarding statin prescription, a significantly higher proportion of participants in the intervention group received statins at an appropriate dose. This difference was significant not only at 6 months of follow-up (44.4% vs 7.3%) but also at the 12-month follow-up (49.1% vs 7.7%). For the secondary outcomes related to patient care management and adherence to medication, a higher, but not significant, mean annual number of PCC visits was observed in the intervention group (4.2 visits) versus that observed in the control group (2.7 visits, p=0.1231). No differences were observed in the proportion of participants with high adherence to statins after 6 or 12 months of follow-up. Primary and secondary outcomes analyzed by gender are presented in Appendix Table 1 (available online). Briefly, mean CVD risk reduction was significant at 6 and 12 months of follow-up and, among men, the annual number of PCC visits increased significantly.

Table 3 includes study outcomes analyzed by diabetes condition. The diabetes group had a higher reduction in the mean Framingham Risk Score at 6-month follow-up, which was not significant at the end of the follow-up (−2.7%, 95% CI= −6.2%, 0.7%); this was not observed

Table 1. Baseline Characteristics of Study Subjects

Characteristics	Intervention (*n*=179)	Control (*n*=178)	*p*-value
Sociodemographic variables			
Age, years, M (SD)	56.8 (8.4)	56.0 (8.0)	0.5640
Male, *n* (%)	75 (41.9)	55 (30.9)	0.1063
Less than high school, *n* (%)	105 (58.7)	129 (72.5)	0.2855
Living alone, *n* (%)	68 (38.0)	69 (38.8)	0.8881
CVD risk factors, *n* (%)			
Diabetes	144 (80.4)	123 (69.1)	0.3062
Current cigarette smoking	25 (14.0)	33 (18.5)	0.7728
Low physical activity[a]	119 (66.5)	141 (79.2)	0.2538
Low fruit and vegetable intake[b]	174 (97.2)	175 (98.3)	0.7794
Biochemical measures, mg/dL, M (SD)			
Total cholesterol	193.3 (41.3)	192.2 (42.8)	0.8845
LDL cholesterol	114.0 (36.5)	113.5 (36.1)	0.8963
HDL cholesterol	42.5 (13.4)	40.9 (12.8)	0.5943
Triglyceride	184.2 (79.9)	189.4 (86.5)	0.6136
Fasting plasma glucose	150.2 (67.7)	147.3 (65.2)	0.9169
Physical measures, M (SD)			
Systolic blood pressure, mmHg	142.6 (19.5)	139.8 (21.0)	0.4070
Diastolic blood pressure, mmHg	84.2 (10.4)	81.8 (11.0)	0.0305
BMI	33.5 (6.9)	34.3 (8.3)	0.4927
Waist circumference, cm	106.1 (15.0)	110.3 (17.7)	0.0535
CVD risk, *n* (%)			
History of CVD	46 (25.7)	66 (37.1)	0.5458
Moderate CVD risk[c]	58 (32.4)	54 (30.3)	0.9728
High CVD risk[d]	75 (41.9)	58 (32.6)	0.9728

Note: Boldface indicates statistical significance ($p<0.05$).
[a]Low physical activity was defined as <600 MET-minutes/week.
[b]Low fruit and vegetable intake was defined as <5 servings per day.
[c]Moderate CVD risk was defined as diabetics and/or 10%–20% Framingham 10-year CVD risk score.
[d]High CVD risk was defined >20% Framingham 10-year CVD risk score.
CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

in the non-diabetes group. The proportion of patients that received statin treatment in an appropriate dose was significantly higher in the intervention group compared with the control group, throughout the follow-up period and regardless of diabetes status. The mean annual number of PCC visits was higher in the intervention group but statistically significant only in the non-diabetes subgroup.

Table 3 also includes an analysis by CVD risk strata. There was no significant difference observed in the main outcome in any of the analyzed risk strata. In the moderate-risk stratum, there was an initial higher and significant net difference in mean CVD risk (−1.8, 95% CI= −3.4, −0.2) in the intervention group versus the control group, which persisted at the end of follow-up (−0.6, 95% CI= −1.1, −0.2). In the high CVD stratum, there was a drop in mean CVD risk at 6 months of follow-up that did not persist at the end of the study. Again, the proportion of patients treated with an appropriate statin dose was significantly higher in all risk strata. Mean annual number of PCC visits was consistently higher in the intervention group but only statistically significant in the group of patients with high CVD risk.

DISCUSSION

Adequate management of hypercholesterolemia and elevated CVD risk imposes important clinical as well as economic consequences for the healthcare system. Argentina has a worryingly high prevalence of undiagnosed and uncontrolled patients with dyslipidemia and elevated CVD risk, which is similar to other developing countries.[32–34] This paper presents the results of a "proof-of-concept" trial designed with an implementation focus. To the authors' knowledge, this is the first trial of an educational intervention to reduce CVD risk, designed for primary care physicians in Latin America.[35]

Table 2. Primary and Secondary Outcomes at 6 and 12 Months

Variable	Mean or proportion (95% CI)		Net differences: Intervention group versus control group (95% CI)	*p*-value	Adjusted[a] net differences: Intervention group versus control group (95% CI)	*p*-value
	Intervention	Control				
LDL cholesterol, mg/dL (mean difference from baseline)						
At 6 months	−16.0 (−23.9, −8.0)	−9.1 (−17.8, −0.5)	−6.8 (−18.5, 4.9)	0.2552	−6.0 (−15.6, 3.6)	0.2224
At 12 months	−8.7 (−24.3, 6.8)	−8.0 (−15.9, −0.2)	−0.7 (−18.1, 16.7)	0.9366	−0.8 (−15.6, 14.1)	0.9207
Framingham Risk Score (mean difference from baseline)						
At 6 months	−5.3 (−7.9, −2.7)	−1.1 (−1.9, −0.4)	−4.2 (−6.9, −1.4)	**0.0029**	−4.0 (−6.5, −1.5)	**0.0019**
At 12 months	−3.8 (−6.8, −0.8)	−2.0 (−2.5, −1.5)	−1.8 (−4.8, 1.2)	0.2435	−1.5 (−4.3, 1.2)	0.2802
Proportion of patients who are on statins and are receiving an appropriate dose (%)						
At 6 months	44.4 (22.9, 68.1)	7.3 (3.1, 16.5)	37.1 (12.0, 62.2)	**0.0007**	28.8 (3.0, 54.6)	**0.0031**
At 12 months	49.1 (27.9, 70.7)	7.7 (4.2, 13.6)	41.5 (18.1, 64.8)	**0.0001**	38.5 13.2, 63.9)	**<0.0001**
High adherence to medication[b] (%)						
At 6 months	30.3 (17.0, 48.1)	27.8 (15.0, 45.5)	2.6 (−19.7, 24.9)	0.8209	4.6 (−16.9, 26.1)	0.6701
At 12 months	30.3 (16.1, 49.6)	38.6 (26.2, 52.7)	−8.3 (−30.2, 13.6)	0.4665	−10.6 (−37.5, 16.3)	0.4405
Annual number of visits to the PCC (mean)	4.2 (2.5, 7.1)	2.7 (2.2, 3.3)	1.5 (−0.8, 3.8)	0.1216	1.4 (−0.9, 3.7)	0.1231

Note: Boldface indicates statistical significance ($p < 0.05$).
[a]Adjusted by age, male, less than high school, current smoker, diastolic blood pressure, diabetes, and history of CVD; except for Framingham Risk Score outcome: adjusted by less than high school, current smoker, and diastolic blood pressure.
[b]High adherence was defined as a Morisky-Green total score of 8 among participants under statin treatment.
CVD, cardiovascular disease; LDL, low-density lipoprotein; PCC, primary care center.

Continuing education training in the form of "face-to-face" outreach visits can improve physician- and patient-related outcomes.[16,36] This study found positive and significant impacts on two secondary outcomes related to the management of patients with elevated cardiovascular risk: (1) a consistent and significantly increased proportion of participants correctly treated with statins; and (2) a higher mean annual number of PCC visits. However, after 12 months of follow-up, no differences were observed in either mean LDL-c values or CVD risk between groups.

The lack of positive results in the primary outcome could be explained primarily by the low medication adherence rate observed in both groups. Several studies have reported that during the first year of treatment, most patients stop statin treatment.[8,9,37–39] Poor adherence to statins has been found to be related with increased rates of adverse CV outcomes[38,40–42] and has been associated with several conditions such as age, gender, patients' beliefs about disease and medication, the nocebo effect, number of medications, adequate patient follow-up, comorbidities, and other factors.[9,43–46] In the present study, the implemented intervention was highly directed to physician's adherence to CPGs whereas the support components (text messages to promote healthy lifestyles and counseling of pharmacist assistants) seem to have been insufficient to improve medication adherence in the intervention arm, suggesting that more intense and specific interventions oriented to improve patient's adherence should be included in this type of

Table 3. Primary and Secondary Outcomes at 6 and 12 Months Stratified by Diabetes and Cardiovascular Disease (CVD) Risk

Variable	Mean or proportion (95% CI)		Net differences: Intervention group versus control group (95% CI)	*p*-value
	Intervention	Control		
Stratified by diabetes				
LDL cholesterol, mg/dL (mean difference from baseline)				
With diabetes				
At 6 months	−14.8 (−22.9, −6.8)	−8.3 (−18.7, 2.2)	−6.6 (−19.7, 6.6)	0.3275
At 12 months	−9.3 (−24.6, 6.0)	−8.5 (−15.7, −1.2)	−0.8 (−17.8, 16.1)	0.9231
Without diabetes				
At 6 months	−20.3 (−35.6, −5.0)	−10.2 (−15.1, −5.3)	−10.1 (−26.2, 5.9)	0.2173
At 12 months	−6.6 (−26.5, 13.2)	−7.4 (−17.4, 2.5)	0.8 (−21.4, 23.0)	0.9428
Framingham Risk Score (mean difference from baseline)				
With diabetes				
At 6 months	−4.9 (−8.0, −1.9)	−0.2 (−1.4, 1.1)	−4.8 (−8.1, −1.5)	**0.0047**
At 12 months	−3.6 (−6.9, −0.3)	−0.9 (−1.9, 0.2)	−2.7 (−6.2, 0.7)	0.1244
Without diabetes				
At 6 months	−7.8 (−9.3, −6.3)	−5.6 (−8.1, −3.2)	−2.2 (−5.1, 0.7)	0.1344
At 12 months	−5.7 (−7.8, −3.5)	−8.5 (−10.8, −6.1)	2.8 (−0.4, 6.0)	0.0865
Proportion of patients who are on statins and are receiving an appropriate dose (%)				
With diabetes				
At 6 months	42.2 (21.2, 66.4)	8.5 (3.6, 18.7)	33.7 (8.4, 59.0)	**0.0027**
At 12 months	46.6 (26.5, 67.8)	8.3 (4.2, 15.8)	38.3 (15.7, 60.9)	**0.0001**
Without diabetes				
At 6 months	55.6 (27.3, 80.6)	2.2 (0.4, 12.1)	53.4 (23.5, 83.3)	**0.0003**
At 12 months	61.6 (28.2, 86.7)	4.6 (1.5, 13.4)	56.9 (23.3, 90.6)	**0.0002**
High adherence to medication[c] (%)				
With diabetes				
At 6 months	28.8 (15.6, 47.0)	23.1 (12.7, 38.4)	5.7 (−15, 26.4)	0.5874
At 12 months	32.4 (19.2, 49.2)	42.3 (27.8, 58.4)	−10.0 (−32, 12.1)	0.3813
Without diabetes				
At 6 months	38.2 (24.0, 54.7)	46.8 (20.7, 74.7)	−8.6 (−42.7, 25.5)	0.6172
At 12 months	29.3 (10.4, 59.5)	38.2 (18.2, 63.2)	−8.9 (−44.6, 26.7)	0.6290
Annual number of visits to the PCC (mean)				
With diabetes	4.3 (2.5, 7.4)	2.7 (2.2, 3.3)	1.5 (−0.8, 3.8)	0.1184

(*continued on next page*)

Table 3. Primary and Secondary Outcomes at 6 and 12 Months Stratified by Diabetes and Cardiovascular Disease (CVD) Risk (*continued*)

Variable	Mean or proportion (95% CI)		Net differences: Intervention group versus control group (95% CI)	*p*-value
	Intervention	Control		
Without diabetes	4.5 (2.9, 6.8)	2.7 (2.1, 3.3)	1.8 (0, 3.8)	**0.0325**
Stratified by cardiovascular risk				
LDL cholesterol, mg/dL (mean difference from baseline)				
Moderate CVD risk[a]				
At 6 months–	−18.8 (−27.8, −9.8)	−10.4 (−21.5, 0.6)	−8.4 (−22.6, 5.9)	0.2498
At 12 months	−11.4 (−17.7, −5.2)	−7.8 (−15.5, −0.1)	−3.6 (−13.5, 6.3)	0.4769
High CVD risk[b]				
At 6 months	−24.0 (−28.1, −19.9)	−18.7 (−25.4, −12.1)	−5.2 (−13.1, 2.6)	0.1895
At 12 months	−17.0 (−33.3, −0.6)	−9.3 (−17.2, −1.4)	−7.7 (−25.8, 10.5)	0.4079
History of CVD				
At 6 months	2.8 (−3.4, 8.9)	−4.9 (−12.4, 2.7)	7.6 (−2.1, 17.3)	0.1234
At 12 months	6.2 (−11.1, 23.5)	−0.5 (−15.2, 14.2)	6.7 (−16, 29.4)	0.5647
Framingham Risk Score (mean difference from baseline)				
Moderate CVD risk[a]				
At 6 months	−2.1 (−2.5, −1.6)	−0.3 (−1.9, 1.3)	−1.8 (−3.4, −0.2)	**0.0322**
At 12 months	−0.5 (−1.0, −0.1)	0.1 (0.1, 0.1)	−0.6 (−1.1, −0.2)	**0.0083**
High CVD risk[b]				
At 6 months	−7.6 (−11.4, −3.9)	−2.0 (−3.9, −0.1)	−5.6 (−9.8, −1.4)	**0.0091**
At 12 months	−6.0 (−10.3, −1.6)	−4.2 (−5.0, −3.4)	−1.8 (−6.3, 2.6)	0.4190
Proportion of patients who are on statins and are receiving an appropriate dose (%)				
Moderate CVD risk[a]				
At 6 months	54.8 (32.5, 75.4)	17.6 (6.1, 41.2)	37.2 (8.5, 65.9)	**0.0238**
At 12 months	54.7 (39.8, 68.8)	17.4 (8.3, 32.9)	37.4 (18.1, 56.6)	**0.001**
High CVD risk[b]				
At 6 months	51.3 (31.5, 70.6)	5.9 (2.5, 13.5)	45.3 (24.1, 66.5)	**0.0001**
At 12 months	61.0 (42.2, 77)	7.7 (5.1, 11.4)	53.3 (35, 71.7)	**<0.0001**
History of CVD				
At 6 months	20.0 (8.0, 31.1)	0.0	—	—
At 12 months	21.7 (9.8, 33.7)	0.0	—	—
High adherence to medication[c] (%)				
Moderate CVD risk[a]				

(*continued on next page*)

Table 3. Primary and Secondary Outcomes at 6 and 12 Months Stratified by Diabetes and Cardiovascular Disease (CVD) Risk (*continued*)

Variable	Mean or proportion (95% CI)		Net differences: Intervention group versus control group (95% CI)	*p*-value
	Intervention	Control		
At 6 months	35.4 (24.7, 47.9)	19.6 (7.1, 43.6)	15.9 (−5.8, 37.6)	0.2086
At 12 months	46.9 (32.5, 61.9)	50.1 (31.5, 68.7)	−3.2 (−27.9, 21.5)	0.7994
High CVD risk[b]				
At 6 months	36.5 (18.8, 58.9)	18.6 (6.7, 42.3)	17.9 (−9.6, 45.5)	0.2218
At 12 months	30.3 (17.0, 48.1)	45.8 (26.0, 67.1)	−15.5 (−42.6, 11.6)	0.2616
History of CVD				
At 6 months	23.6 (6.7, 57.3)	36.5 (17.4, 61.1)	−12.9 (−48.1, 22.4)	0.4943
At 12 months	25.7 (7.9, 58.2)	21.2 (6.8, 49.7)	4.5 (−29.8, 38.8)	0.7967
Annual number of visits to the PCC (mean)				
Moderate CVD risk	4.3 (2.4, 7.6)	2.9 (2.2, 3.6)	1.4 (−1.1, 3.9)	0.2049
High CVD risk	4.3 (2.5, 7.4)	2.2 (1.9, 2.7)	2.0 (−0.3, 4.4)	**0.0277**
History of CVD	4.5 (3.0, 6.6)	3.1 (2.3, 4.4)	1.3 (−0.7, 3.3)	0.1801

Note: Boldface indicates statistical significance ($p < 0.05$).
[a]Moderate CVD risk was defined as having diabetes and/or 10%–20% Framingham 10-year CVD risk score.
[b]High CVD risk was defined >20% Framingham 10-year CVD risk score.
[c]High adherence was defined as Morisky-Green total score of 8 among participants under statin treatment.
LDL, low-density lipoprotein; PCC, primary care center.

intervention. Although this study could not reach a reduction of cholesterol levels in the intervention group, it found an improvement in the adequate use of CPGs, which is a key aspect related to the reduction of inappropriate clinical practice variability and therefore better control of chronic patients.[17,20] These results support previous observations that evidence-based EOVs can lead to improvements in adequate physicians' prescriptions.[16,47–49,50] However, further research should be conducted to assess how this type of interventions may also lead to effective and sustainable positive change in patients' adherence to medication.[51]

Limitations

This study has several important strengths. The study was implemented soon after the introduction of statins to the national list of ambulatory drugs provided free of charge in public PCCs in Argentina; this was an opportunity window to explore clinical practice changes at the primary care level. The study utilized a point of care device that facilitated the measurement of lipid profiles in "real-world conditions," where patients received medical care at their PCC. It included innovative components in the intervention package, such as the mHealth application to help primary care physicians make decisions about statins use, as well as the use of a web-based platform to send text messages promoting healthy behavioral changes. Finally, PCCs were included from three different regions of Argentina, the South, North, and West, which make the results more generalizable to a broader spectrum of clinical settings. The following limitations should be considered: (1) cluster trial designs could lead to potential imbalances between study groups; however, to avoid potential confounders, the analysis was adjusted for relevant covariables; and (2) baseline mean LDL-c levels were lower than those observed in the general population of the region[52]; this may have played a potential "floor effect" role. However, baseline lipid profiles and fasting glucose levels were similar in both groups.

Concepts from the WHO chronic care model highlight several relevant dimensions, such as improvement in physicians' decision making, patient self-management (such as improvement in medication adherence); adequate medical record systems; and adequate health system organization.[20] This study showed positive results linked

to the implementation of a GCP guideline to improve statin use by primary care physicians but could not achieve changes in LDL-c levels. This study offers information generated in PCCs that would be useful for decision makers involved in the implementation of complex interventions in low- and- middle-income countries. Such data are urgently needed to build more effective, practical, and sustainable interventions with the purpose of improving CVD prevention and control.

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SUPPLEMENTAL MATERIAL

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