Title

An Educational Intervention to Improve Effectiveness in the Detection, Treatment and Control of patients with high cardiovascular risk in low-resource settings in Argentina: Rationale and Study Design of a cluster randomized controlled trial.

Structured Abstract (250 words)

Purpose: The goal of this study is to test whether a multifaceted educational intervention targeting physicians and pharmacist assistants, improves detection, treatment and control of hypercholesterolemia among uninsured patients with moderate to high cardiovascular risk in Argentina.

Scope: Hypercholesterolemia, a major cause of disease burden in both the developed and developing world, is estimated to cause 2.6 million deaths annually. In Argentina, the prevalence of hypercholesterolemia increased between 2005 and 2013 from 27.9% to 29.8%, whereas the rate of non-optimal LDL-C, was 28.0%. The rate of high cholesterol awareness was 37.3 % and only one out of four subjects with a self-reported diagnosis of coronary heart disease (CHD) is taking statins. Although other antihypertensive, antidiabetic and low-dose aspirin were available free-of-charge at the primary care clinics of the public sector, statins had not been included until recently. As of 2014, statins (simvastatin 20mg) were incorporated into the package of drugs provided free-of-charge for patients with high cholesterol, according to CVD risk stratification.

Methods: This randomized cluster trial will enroll 350 patients from 10 public primary care clinics who will be assigned to receive either the intervention or the usual care. This study is timely and will generate urgently needed data on effective and practical intervention programs aimed at the prevention and control of CVD risk that can be directly used in LMICs.

Results:

Key Words: Cariovascular prevention, Statins, Educational interventions

2. Purpose

Study objectives

The overarching goal of this study is to test whether a multifaceted educational intervention targeted to physicians and pharmacist assistants at primary care clinics located in low-income settings improves treatment and control of hypercholesterolaemia among mostly uninsured patients with moderate-to-high cardiovascular risk in Argentina. The intervention will focus on the public primary care system through healthcare provider education, audit and feedback on the implementation of a CPG to improve management of statins and global CVD risk in these patients. The specific aims of this cluster randomized trial are:

1. to test whether a multifaceted educational intervention program lowers LDL-C levels and CVD risk in patients with moderate-to-high cardiovascular risk;
2. to test whether this intervention program improves physician compliance with clinical practice guidelines;
3. to test whether this intervention program improves patient care management and adherence to medication;
4. to estimate the cost-effectiveness of this comprehensive intervention program as compared with usual standard of care.

3. Scope

3.1 Hypercholesterolemia a major global public health challenge

Hypercholesterolemia, a major cause of disease burden in both the developed and developing world, is estimated to cause 2.6 million deaths annually (4.5% of all deaths) and one third of ischemic heart diseases.[1] Globally, mean total cholesterol levels changed little between 1980 and 2008, falling by less than 0.1 mmol/L per decade for both men and women. In 2008, the global prevalence of elevated total cholesterol among adults was 39% (37% for males and 40% for females).[2]

Observational studies show that there is a continuous positive relationship between coronary heart disease (CHD) and blood cholesterol concentrations.[3] The Cholesterol Treatment Trialists'

(CTT) Collaboration reported a meta-analysis[4] of individual data from 90,000 individuals in 14 randomized trials of statin therapy versus control. Statin regimens resulted in a mean difference of about 1.0 mmol/L in LDL-C and a proportional reduction of 20% in major vascular events (defined as coronary death, non-fatal myocardial infarction, coronary revascularization, or stroke). A recent meta-analysis showed that trials comparing less intensive vs. more intensive statin regimens produced further reductions in major vascular events. [5-8]

Although higher serum lipids level seems to be an inevitable consequence of economic development, urbanization, westernization, and nutritional transition, these determinants can be offset through healthier diets and pharmacological interventions. Consequently, statins and other lipid-lowering drugs are increasingly used in high-income countries; [9,10] however there is still low coverage of screening and treatment in low and middle-income countries.[11-16]

In Argentina, the National Risk Factor Surveys conducted by the Ministry of Health indicates that between 2005 and 2013[17] self-reported prevalence of hypercholesterolemia rose from 27.9% to 29.8%. Of these, only 54.8% received some treatment and of whom only 56.3% were prescribed lipid-lowering drugs (the rate of those receiving treatment was less than 20% among uninsured subjects, including subjects with more than 3 risk factors).[18] Recent baseline results are available with blood samples from the CESCAS I study, which is a population-based prospective cohort study for detection and follow-up of cardiovascular disease (CVD) and risk factors in 8,000 adults from four cities in Argentina, Chile and Uruguay.[19,20] This study, found that the prevalence of hypercholesterolemia in Argentina was 23.1% in men and 25.6% in women, and according to the Framingham heart study risk equation, the prevalence of non-optimal LDL-C is 28.0%.

According to the Framingham heart study risk equation, the prevalence of non-optimal LDL-C was 28.0%. On the other hand, the percentageof subjects with hypercholesterolaemia who were aware of their condition was 37.3% (95% CI 32.8 to 41.9), and the percentage of aware patients under pharmacological treatment was dismally low: only 11.1%. Furthermore, only one in every four subjects with a self-reported diagnosis of CHD is taking statins, and most of those with CHD who are on statins have suboptimal LDL-C levels (Rubinstein et al. Personal communication. Data not yet published). This is especially relevant because

hypercholesterolaemia accounts for 25% of the burden of CHD in Argentina, as shown in another study.[21]

3.2 Use of Evidence-based Clinical Practice Guidelines (CPG) to improve effectiveness and quality of treatment for patients with dyslipidemia

Because CHD is highly prevalent and lipid-lowering drugs, particularly statins, are among the most frequently prescribed drugs, lipid treatment guidelines have important implications both for population health and for use of health care resources.[22] The International Atherosclerotic Society (IAS) has recently issued a CPG for the management of sub-optimal LDL-C, recommending statins as first-line therapy, choosing the type of statin based on availability and costs, and adjusting the dose according to patient's CVD risk.[23] More recently, the 2013 ACC/AHA panels have updated their blood cholesterol guidelines, recommending the prescription of high-intensity statin therapy (lowering LDL–C ≥50%) or moderate-intensity therapy (lowering LDL–C by approximately 30% to <50%), based on the presence of prior CVD, LDL-C levels, type 2 diabetes, age, and the estimated 10-year risk of CVD according to the risk estimates of pooled cohort equation[5]. Because of a lack of evidence from randomized controlled trials regarding the efficacy of titrating statins to reduce CVD, the guidelines no longer recommend statin treatment to meet specific LDL-C or non-HDL-C goals.[5] However, the publication of a CPG does not ensure its application in clinical practice, and therefore effective implementation plans that are tailored for the organizational context for which the CPG is intended, must be designed.

3.2 Interventions to improve CPG implementation

Despite the availability of evidence-based practice guidelines, multiple barriers hinder the appropriate management of hypercholesterolemia in the primary care setting. These barriers can be organizational within primary care clinics; confusing and conflicting guidelines from external sources; errors and omissions by primary care doctors; communication problems at the interface between secondary and primary care[24], multiple competing demands on physicians' time, and lack of reimbursement for preventive counseling.[25] Other barriers are

related to: (1) the health care system such as lack of access, medication cost, and poor insurance coverage; (2) the health care providers, such as lack of adherence to guidelines, willingness to accept elevated high cholesterol as a risk factor, and failure to prioritize this issue among multiple chronic medical issues; and (3) the patients, such as reluctance to take medication.[24]

Among the interventions that have been effective in dealing with barriers related to clinical practice are multifaceted educational outreach visits (EOVs)[26,27], and audit and feed-back.[27,28] EOVs have the potential to change health professional practice, particularly the prescribing patterns of physicians. The term EOV or "academic detailing" is used to describe a personal visit by a trained person to health professionals in their own settings. A recent systematic review, on interventions to improve adherence to cardiovascular disease guidelines, showed a positive impact of academic detailing on adherence to CPGs [OR: 1.32, 95% CI 0.83 – 1.70][27]. Some key principles of this approach include surveys of practitioners to determine barriers for appropriate practice and the subsequent development of an intervention tailored to address those barriers using simple messages; targeting of practitioners with low compliance; and the delivery of the intervention by a respected person. The intervention often includes feedback on existing practices.[29] EOVs with or without the addition of other interventions has been effective in improving practice in the majority of circumstances; in studies with dichotomous health professional outcomes, such as proportion of patients treated in accordance with the guideline, the improvement was 5.6% and for studies with continuous outcomes, such as mean number of prescriptions, it was at least 20%.[26] A recent Cochrane review indicates that patient re-enforcement and reminders seem to be the most promising interventions to increase adherence to lipid-lowering drugs. Other interventions associated with increased adherence were simplification of the drug regimen and patient information and education. [30]

3.3 Challenges and Opportunities for the implementation of interventions to prevent and control CVD in low resource settings in Argentina

The prevalence of CVD and risk factors in Argentina are high; however, awareness, treatment, and control, particularly for hypercholesterolemia are very low. Remediar program is a program of the National MoH that provides free ambulatory drugs at the point of care to vulnerable

people without health insurance who attend public primary care centers (PCCs) in Argentina.[31] The program uses the WHO package for the assessment and management of cardiovascular risk in low-resource settings.[32]

Interventions delivered by the program included: 1) identification and enrollment of the uninsured population in the catchment area served by PCCs; 2) screening to identify persons at risk of CVD in order to refer them to a PCC; 3) CVD risk stratification and classification of subjects by primary care physicians, including lab and other ancillary tests; 4) treatment with generic drugs as needed for hypertension, diabetes or for subjects with moderate-high CVD risk (10 year risk ,≥10%); and 5) regular follow-up for patients with moderate and high CVD risk. To date, Remediar has provided drugs for the treatment of different cardiovascular risk factors such as antihypertensive, antidiabetics, and low-dose aspirin. Recently, in mid-2014, statins (simvastatin 20mg) were incorporated into the package of drugs delivered free-of-charge for patients with high cholesterol and/or CVD risk, according to CVD risk stratification.

Although inclusion of statins is a critical step to reduce CVD in vulnerable, uninsured subjects with high cholesterol and moderate-to-high risk, a recent study that analyzed prescriptions to hypertensive patients seen in public clinics in Argentina reported that only 57% of hypertensive patients covered by Remediar were treated. Of those who were treated, almost 75% of patients received medication for less than 4 months/year and only 12% received it for ≥9 months/year.[33] Thus, a comprehensive intervention aimed to change practice styles in professionals and improve adherence to drugs in patients, is key to achieve the expected goal of reducing CVD through lowering cholesterol levels.

4. Methods

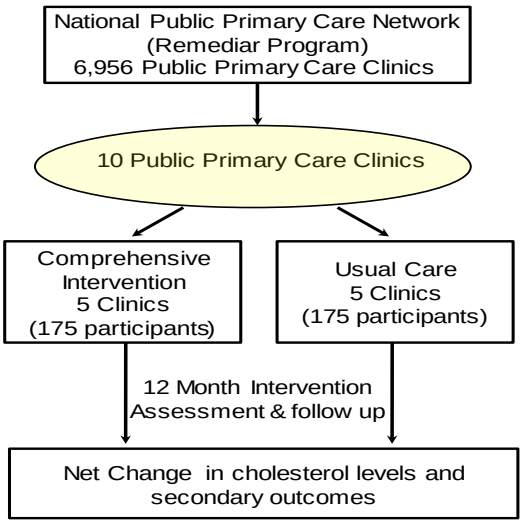
4.1 Study Design and Methods

Overview of Study design

The present study is a cluster randomized controlled trial. 357 patients with high cholesterol and moderate to high CVD risk were recruited among 10 public PCCs in Argentina; 5 clinics were randomized to receive the intervention program and 5 clinics to receive usual care (Figure 1[34]).

It is important to highlight that all clinics will provide statins as prescribed. The intervention consisted in an educational program focused on the implementation of a CPG to improve management of statins in moderate-to-high CVD risk patients. The program included innovative tools as mobile phone (mHealth) applications to provide decision aids to physicians and a web-based platform to send tailored SMS messages to patients. Eligible patients were enrolled and had 12 months of follow-up after randomization.

Figure 1: Study Design



Rationale for using a cluster randomized controlled trial design

Cluster trials are an important method for evaluating educational outreach and related interventions. Randomization by clinic is preferable because it avoids the potential contamination that could occur if randomization were to be done at individual level (e.g. the cholesterol treatments and CVD management for patients in one clinic are more similar to each other than to patients from another clinic). In addition, the effect of the intervention can be assessed in the natural practice environment[35].

Study population

Ten PCCs from the provinces of Chubut (4 clinics), Corrientes (4 clinics) and La Rioja (2 clinics) were selected for this trial from a national public primary care network. The eligibility criteria for PCCs and patients are presented in **Table 1**. Study participants were recruited from the participating PCCs with minimum eligibility criteria so that the intervention can be tested in "real-world" clinical settings. All the selected PCCs staffs (physicians, nurses, and pharmacist assistants) work closely with the study team in order to optimize the referral of potential eligible patients to our study nurses.

TABLE 1. Eligibility criteria for study clinics and participants

Eligibility criteria for study clinics (PCCs)

- The clinic is affiliated with the Remediar program.
- The clinic is located in a poor urban area according to 2010 census data.
- The clinic has ≥800 outpatient adult visits each month (to ensure recruitment of enough participants).
- Physician visits and statins are available free of charge to patients at the point of care.
- The minimum distance between PCCs is 10 kilometers (different catchment area) and they do not share health professionals (to minimize intervention bias).
- Good performance of the PCCs (and their pharmacy) according to the reports of Remediar program.

Eligibility criteria for study participants

Inclusion criteria

Patients aged ≥40 years and < 75 years who received primary care at participating PCCs with at least one of the following criteria:

- Arteriosclerotic cardiovascular disease (ASCVD): 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 MoH (estimated 10-year CVD risk ≥ 20%)[36]
- LDL-C level ≥ 190 mg/dL
- Type 2 diabetes

Exclusion criteria

- Statin treatment
- Pregnant women
- Bed-bound patients
- Patients who cannot give informed consent
- History of end-stage Chronic Kidney Disease treated with dialysis, HIV/AIDS, alcohol or drug abuse or active tuberculosis.

Randomization

The 10 selected PCCs fulfilling the inclusion criteria were randomized to either the intervention or the control group: 5 PCCs to the intervention and 5 to the control group. Randomization was conducted at the data management center at the Institute for Clinical Effectiveness and Health Policy (IECS).

4.2 Intervention program

The physician education program consisted of 1) an on-site intensive training and certification workshop at the outset, followed by 2) EOVs after the workshop tailored to the needs of individual practitioners at the clinics as well as to identify barriers that prevent appropriate prescribing (e.g., side effects of statins, barriers on chronic treatment adherence). The EOVs include CPG practice exercises; prescribing audit and feedback using selected charts from high CVD risk patients; and suggested changes for improving practice administration/procedures such as support for systematic case identification, particularly for complex patients with low adherence. Reinforcement through subsequent visits to the clinic is provided at 3, 6 and 9 months from enrollment of the clinic. Finally, 3) an mHealth application installed in the physician's smartphones was used to facilitate evidence-based and guideline-driven decision aids to improve patient management. SANA framework (http://sana.mit.edu), a highly customizable, open-source, android-based mHealth information system, was used to develop this application

Irrespective of the assignment of the clinic to the intervention or control group, all physicians from participating PCCs had already received previous training on global cardiovascular risk management, given by the Ministry of Health. In addition, all clinics were provided with educational flyers and written materials to be displayed at the PCCs, including charts with the CPG on management of statins.

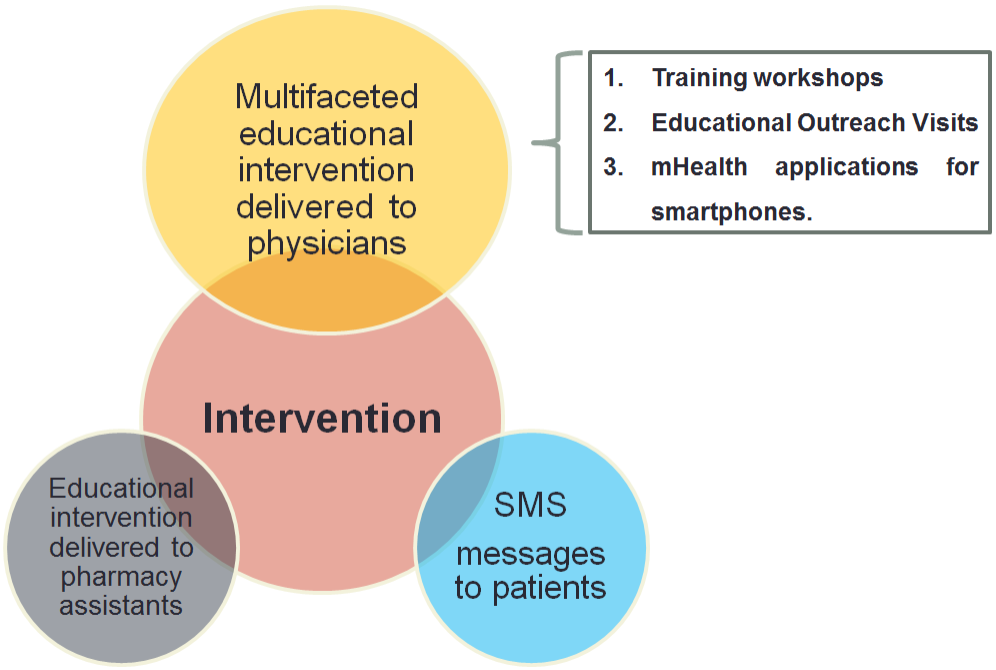
Physicians belonging to the PCC randomized to the intervention group received a 3-component intervention: training workshop, educational Outreach Visits (EOV's) and a mHealth application uploaded in their smartphones. **(Figure 2)**

In addition to the 2 main educational components aimed at primary care physicians, two intervention support tools were used:

1. A web-based platform tailored to send SMS messages to promote healthy lifestyles, and prompts to regular visits for clinic visits and to improve medication adherence for participating patients at the intervention clinics.

2. On-site training to pharmacist assistants was given at the first EOV in each intervention clinic, focused on counseling to improve medication adherence among patients initiating statin therapy and at each patient visit to the clinic to refill drug prescriptions. Additionally, pharmacist assistants received educational flyers to be placed at the pharmacy.

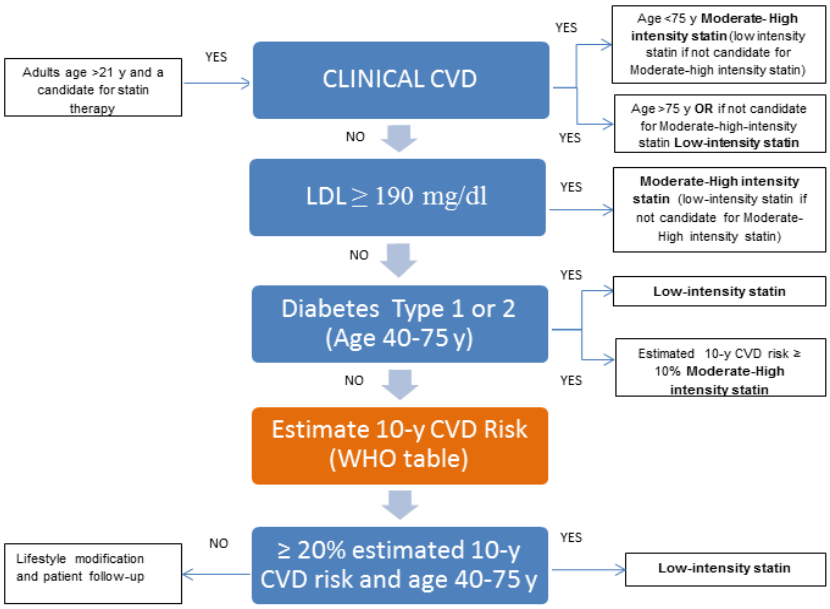
Figure 2: Intervention components



Treatment algorithm

The algorithm for the use of statins in the treatment of high cholesterol according to CVD risk was adapted from the new ACC/AHA Guideline on the Treatment of Blood Cholesterol to reduce Atherosclerotic Cardiovascular Risk in Adults[5] and the WHO CVD risk charts.[36] Physicians will prescribe statins in moderate-high intensity (simvastatin 40 mg) or low intensity (simvastatin 20 mg) doses. **(Figure 3)**

Figure 3. Treatment algorithm



Low intensity: simvastatin 20 mg
Moderate-high intensity: simvastatin 40mg.

4.3 Study Outcomes

The primary outcome is net change in LDL-C levels from baseline to month 12, between intervention and control groups among all study participants. Secondary outcomes are: net change in 10-year-CVD Framingham risk score before and after the implementation of the program; proportion of patients with moderate and high CVD risk who have reduced 30% and 50% of their LDL-C, respectively; proportion of patients with high CVD risk who are on statins,

and are receiving an appropriate dose according to the CPG; annual number of follow-up visits to the PCC for high CVD risk patients, annual rate of prescription refills at the clinic pharmacy among treated patients, and cost-effectiveness of the intervention program **(Table 2)**

Table 2: Study outcomes		
Specific aim 1	• Net change in LDL-C levels from baseline to month 12 in the intervention group vs the control group	Primary outcome
Specific aim 1	• Proportion of patients with moderate and high CVD risk who have reduced their LDL-C by 30% and 50%, respectively	Secondary outcomes
Specific aim 2	• Proportion of patients with high CVD risk who are on statins and are receiving an appropriate dose according to the CPG	
Specific aim 3	• Net change in 10-year-CVD Framingham risk score before and after program implementation • Annual number of follow-up visits to the PCC for high CVD risk patients' level of treatment adherence evaluated through questionnaire among treated patients	
Specific aim 4	• Incremental cost-effectiveness ratio (ICER) as cost per mg/dl of change in LDL-C, per treated case, per case receiving an appropriate dose according to the CPG, and per QALY using the Argentina EuroQol EQ-5D.	

4.4 Data Collection

All questionnaires and measurements are performed by trained nurses not participating in the study intervention. After identifying each potentially eligible participant, a research physician/nurse explains the goals and scope of the study, and invites her/him to participate, and sign a written inform consent form. The study has been approved by an independent Internal Review Board (IRB) at Hospital Italiano of Buenos Aires. A research nurse administers a questionnaire and performs the physical and biochemical measurements at baseline, 6 and 12 months of follow-up **(Table 3).**

Table 3. Data collection schedule

Measures	Baseline Visits	6-month follow up visit	12-month termination visit
Informed Consent	X		
Medical history and questionnaires	X	X	X
Physical measurements	X	X	X
Delivery of statins	X	X	X
Biochemical measurements	X	X	X
Statins adherence questionnaire		X	X
Assessment of outcomes		X	X

The study forms included questions on history of CVD and risk factors, health behaviors (e.g., smoking, diet, and physical activity) and health services utilization patterns. Adherence to chronic medications are assessed with the Morisky Green questionnaire.[37]

The average value of two blood pressure (BP) measurements was obtained at each visit using an automatic device (OMRON HEM-7200)[38]. At the clinic visit, anthropometric measurements were taken on individuals in light clothing without shoes using a standard protocol. *Body weight* was measured to the nearest 0.1 kg on a dedicated scale; *Body height* is measured to the nearest 0.1 cm with a free-standing stadiometer; *Body mass index* was calculated as an index for overall obesity; *Waist circumference* was measured (at the smallest circumference between the ribs and iliac crest) in centimeters to the nearest 0.1 cm. To minimize measurement error, the Gulick II tape measure (Gays Mills, WI) with a no-stretch, retractable tape and tensioning device was used. Each PCC participating in the intervention arm of the trial was provided with a Cholestech LDX and LDX Capillary Plungers (*Alere Cholestech LDX*® Analyzer) to measure: total cholesterol (TC), calculated LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and glucose. Point of care testing with this device has been validated in several studies.[39-42] Fasting capillary blood sample is obtained by finger stick at the baseline and follow-up visits with a Cholestech LDX analyzer.

Follow-up visits are scheduled at 6 and 12 months (termination visit) from the baseline visit. These visits are coordinated with patients' regular clinic visits in order to reduce time burden for patients. BP, anthropometrics measures, biochemical measures and updated information on the use of medications, cigarette smoking, alcohol drinking, diet, physical activity, and costs of treatment are also obtained.

4.5 Statistical analysis

Sample Size

The study was designed to provide 90% statistical power to detect a 27 mg/dl reduction in LDL cholesterol level at a significance level of 0.05 using a 2-tailed test, assuming an intra-cluster correlation coefficient (ICC) of 0.06. The cluster design effect has been taken into consideration in the power calculations by using the formula developed by Donner and Klar[43,44] and was implemented in the Power Analysis and Sample Size (PASS 2008) software (NCSS, Kaysville, UT). An 85% follow-up rate is assumed. Considering 10 clusters, the estimated sample size for each cluster (PCC) is 35, and totals 175 for each group based on these assumptions. This sample size ensures adequate power for testing our secondary outcomes as well.

Analytical Planning

We tested the primary research hypothesis that there is a greater reduction in mean LDL-C levels from baseline to month 12 between intervention and usual care groups, using mixed-effects regression analysis with participants and clinics included as random effects, and group, time and group-by-time interaction as estimable fixed effects.

Intention-to-treat analyses will be conducted. In order to assess comparability between arms, baseline characteristics of patients (demographics, clinical variables, lifestyle factors, anthropometrics measures and laboratory measurements) were compared between the intervention and control groups using one-way ANOVA or Chi 2 tests. In addition sub-group analysis on primary and secondary outcomes by diabetes status and level of CVD risk will also be performed.

An economic evaluation component based on patient-level trial data will be complemented with a model-based component for long-term costs and effects extrapolation. Trial-based primary economic evaluation will use patient-level data collected from the proposed study. We will document all resources involved in conducting this comprehensive intervention program, as well as all patient-level costs, in 2017 Argentinean Pesos adjusted by Argentina consumer price index (CPI) and then converted into International Dollars (Int$). Primary incremental cost effectiveness ratio (ICER) measure will be cost per mg/dl of change in LDL-C. Secondary measures will be cost per additional case of reduction of LDL-C by 30-50% in moderate-high CVD risk patients, and per QALY using the Argentina Euroqol EQ-5D developed by our group.[45]

5. Results.

5.1 Study participants and follow-up

From April 2015 to April 2016, a total of 697 patients from the study clinics were pre-screened for eligibility. From that number, 434 attended to the screening visit and finally 357 who met eligibility criteria were enrolled in the study (**Figure 3).** Of them, 179 patients were recruited by the clinics assigned to the intervention branch and 178 belonged to the control clinics. Globally, the follow-up rate was 97.2% (98.3% on the intervention group and 96.1% in the control group). On **Table 4** presents how baseline characteristics were distributed between intervention and control group. Most of the analyzed variables are balanced between groups except the proportion of participants with less than high school educational level, proportion of participant with low physical activity, proportion of participant with history of CVD and mean of waist circumference that were higher at the control group and proportion of male, proportion of diabetes and mean diastolic blood pressure that were higher at the intervention group.

5.2 Intervention implementation

During the 12-month intervention period, 100% (15/15) of the EOV`s were completed in the three provinces as it was planned. Globally, there was a 90% of attendance by the participating physicians. 100% of the physicians had the mHealth application installed in their smartphone

for cardiovascular risk assessment with evidence-based and guideline-driven decision aids. And 100% of the pharmacists assistant received their training and educational material about statin use.

In relation to the SMS messages delivered to the participants: 84.3% of the intervention group participants said that they are receiving the messages. Among this participants: 46.9% strongly agree, 43.4% agree, 7.6% neither agree nor disagree and 2.1% disagree on that the reception of these type of messages help to improve their health.

5.3 Principal findings and outcomes

Table 5 presents the results for the primary and secondary outcomes at baseline, 6 and 12 months. The mean differences are compared to baseline and a separate adjusted analysis is presented. In relation to the primary outcome, there was none difference on the LDL-c levels in any of the follow-up points none of the two groups.

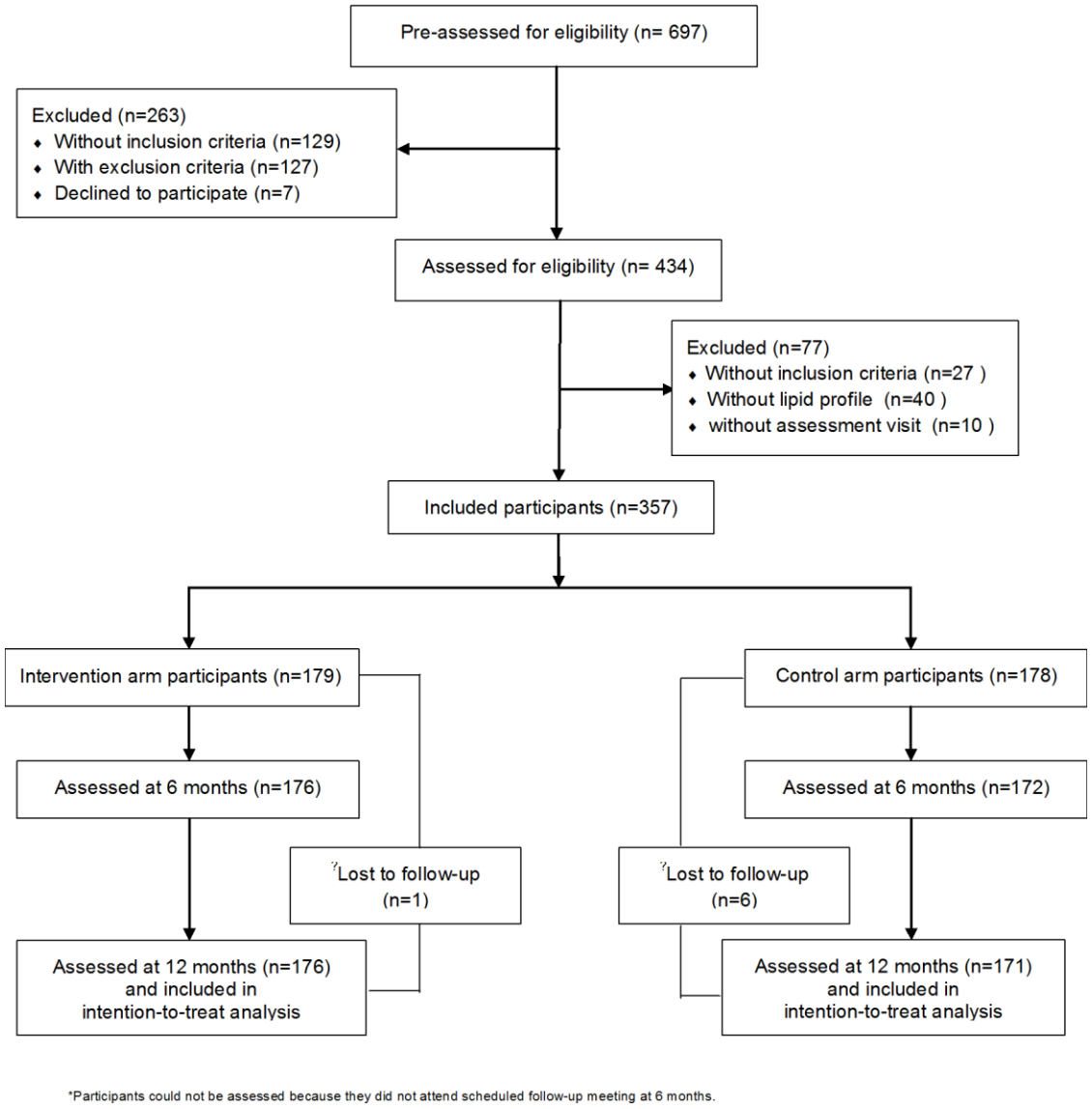
It was observed a significant reduction of the Frahmingam Risk Score on the first 6-months at the intervention groups vs the control group. That difference was not observed at the end of the follow-up.

In relation to the statins prescription, there was a significant higher proportion of participant receiving statins and receiving an appropriate doses. This difference was significant not only at 6 months of follow-up (43% vs 7.3%) but also was observed at the end of the trial (48% vs 7.3%).

Moreover, participants in the intervention group attended to a higher mean of follow-up visits to their PCC (6.9) vs the mean observed at the control group (4.5).

Table 6 includes the same set of outcomes analyzed by diabetes condition. In the diabetes group, there was a significant difference of the mean of the Framingham Risk Score at the end of the follow-up (3.6, IC95% 0.8 - 6.3). The proportion of correctly treated patients and the mean of follow-up visits to the PCC were significantly higher in the intervention group in both subgroups.

Fifure 1: Study participants and follow-up



*Participants could not be assessed because they did not attend scheduled follow-up meeting at 6 months.

Table 4. Baseline characteristics of study subjects

Characteristics		Intervention N = 179	Control N = 178	p-value
Socio-demographic variables				
Age ,years	Mean (SD)	56.8 (8.4)	56.0 (8.0)	0.3784
Male		75 (41.9%)	55 (30.9%)	0.0326
Less than high school		105 (58.7%)	129 (72.5%)	0.0058
Living alone		68 (38.0%)	69 (38.8%)	0.8803
CVD risk factors				
Diabetes		144 (80.4%)	123 (69.1%)	0.0133
Current cigarette smoking		25 (14.0%)	33 (18.5%)	0.2416
Low physical activity		119 (66.5%)	141 (79.2%)	0.0066
Low fruits and vegetables intake		174 (97.2%)	175 (98.3%)	0.4793
Biochemical measures				
Total cholesterol, mg/dL	Mean (SD)	193.3 (41.3)	192.2 (42.8)	0.8105
LDL cholesterol, mg/dL	Mean (SD)	114.0 (36.5)	113.5 (36.1)	0.9043
HDL cholesterol, mg/dL	Mean (SD)	42.5 (13.4)	40.9 (12.8)	0.2422
Triglyceride, mg/dL	Mean (SD)	184.2 (79.9)	189.4 (86.5)	0.5598
Fasting plasma glucose, mg/dL	Mean (SD)	150.2 (67.7)	147.3 (65.2)	0.6798
Physical measures				
Systolic blood pressure (mmHg)	Mean (SD)	142.6 (19.5)	139.8 (21.0)	0.1879
Diastolic blood pressure (mmHg)	Mean (SD)	84.2 (10.4)	81.8 (11.0)	0.0341
Body-mass index (kg/m^2)	Mean (SD)	33.5 (6.9)	34.3 (8.3)	0.3241
Waist circumference (cm)	Mean (SD)	106.1 (15.0)	110.3 (17.7)	0.0144
Cardiovascular risk				
History of CVD		46 (25.7%)	66 (37.1%)	0.0202
Framingham risk	≤ 10%	15 (11.3%)	20 (17.9%)	0.2330
	10-12%	43 (32.3%)	34 (30.4%)	
	> 20 %	75 (56.4%)	58 (51.8%)	

†<Low physical activity was defined as <600 MET-minutes/per week and low fruit and vegetable intake was defined as <5 servings per day

Table 5: Primary and secondary outcomes at baseline, 6 and 12 months

	Mean or proportion (95% CI)		Net differences Intervention group vs control group (95% CI)	*P* Value	Adjusted[¥] net Differences Intervention group vs control group (95% CI)	*P* Value
	Intervention	Control				
LDL Cholesterol, mg/dL (mean difference compared to baseline)						
At 6 month	15.9 (10.0, 21.8)	9.6 (4.7, 14.4)	6.4 (-1.3, 14.0)	0.1018	4.6 (-3.2, 12.5)	0.2447
At 12 month	8.6 (2.6, 14.7)	8.7 (3.7, 13.7)	-0.0 (-7.9, 7.8)	0.9909	-2.0 (-10.2, 6.1)	0.6208
Framingham Risk Score (mean difference compared to baseline)						
At 6 month	5.1 (3.3, 6.9)	1.2 (-0.5, 2.9)	4.0 (1.5, 6.4)	0.0016	4.0 (1.6, 6.4)[£]	0.0012
At 12 month	3.9 (2.1, 5.7)	1.8 (-0.1, 3.7)	2.1 (-0.5, 4.7)	0.1081	2.4 (-0.2, 5.1)[£]	0.0714
Proportion of patients who are on statins and are receiving an appropriate dose (%)						
At 6 month	43.0 (35.8, 50.3)	7.3 (3.5, 11.1)	35.7 (27.5, 43.9)	0.0000	36.0 (27.6, 44.5)	0.0000
At 12 month	48.0 (40.7, 55.4)	7.3 (3.5, 11.1)	40.7 (32.5, 49.0)	0.0000	40.2 (31.8, 48.6)	0.0000
Annual number of follow-up visits to the PCC (mean)						
	6.9 (6.3, 7.6)	4.5 (4.1, 5.0)	2.4 (1.6, 3.2)	0.0000	2.5 (1.6, 3.3)	0.0000

[¥]Adjusted by age, male, less than high school, low physical activity, diastolic blood pressure, waist circumference, diabetes and history of CVD

[£] Adjusted by less than high school, low physical activity, diastolic blood pressure and waist circumference.

Table 3: Primary and secondary outcomes at baseline, 6 and 12 months by diabetes

	Mean or proportion (95% CI)		Net differences Intervention group vs control group (95% CI)	*P* Value	Adjusted[¥] net Differences Intervention group vs control group (95% CI)	*P* Value
	Intervention	Control				
LDL Cholesterol, mg/dL (mean difference compared to baseline)						
Diabetics						
At 6 month	9.3 (3.2, 15.3)	14.8 (8.3, 21.3)	5.5 (-3.4, 14.4)	0.2239	4.2 (-4.8, 13.2)	0.3644
At 12 month	8.8 (2.8, 14.9)	9.3 (2.6, 16.0)	0.5 (-8.5, 9.5)	0.9154	-0.5 (-9.6, 8.6)	0.9189
Nondiabetics						
At 6 month	10.2 (2.2, 18.2)	20.4 (6.7, 34.1)	10.2 (-5.6, 26.0)	0.2057	7.2 (-10.4, 24.7)	0.4206
At 12 month	8.4 (-0.7, 17.5)	6.0 (-8.4, 20.4)	-2.4 (-19.5, 14.6)	0.7808	-8.5 (-26.0, 9.1)	0.3425
Framingham Risk Score (mean difference compared to baseline)						
Diabetics						
At 6 month	0.3 (-1.5, 2.2)	4.8 (2.8, 6.8)	4.5 (1.8, 7.2)	0.0013	4.4 (1.7, 7.0)	0.0011
At 12 month	0.6 (-1.3, 2.5)	3.7 (1.8, 5.6)	3.1 (0.4, 5.8)	0.0243	3.6 (0.8, 6.3)	0.0112
Nondiabetics						
At 6 month	5.9 (2.5, 9.4)	7.8 (4.6, 11.1)	1.9 (-2.8, 6.7)	0.4212	2.5 (-2.6, 7.7)	0.3258
At 12 month	8.4 (2.7, 14.2)	5.5 (0.8, 10.1)	-3.0 (-10.4, 4.4)	0.4235	-3.0 (-9.6, 3.6)	0.3614
Proportion of patients who are on statins and are receiving an appropriate dose (%)						
Diabetics						
At 6 month	40.3 (32.2, 48.3)	9.8 (4.5, 15.0)	30.5 (20.9, 40.1)	0.0000	31.9 (22.2, 41.5)	0.0000
At 12 month	45.1 (37.0, 53.3)	8.9 (3.9, 14.0)	36.2 (26.6, 45.8)	0.0000	36.6 (27.1, 46.1)	0.0000
Nondiabetics						
At 6 month	54.3 (37.7, 70.9)	1.8 (0.0, 5.4)	52.5 (35.5, 69.5)	0.0000	51.0 (34.2, 67.8)	0.0000

At 12 month	60.0 (43.7, 76.3)	3.6 (0.0, 8.6)	56.4 (39.3, 73.4)	0.0000	54.2 (37.2, 71.1)	0.0000
Annual number of follow-up visits to the PCC (mean)						
Diabetics						
	6.8 (6.1, 7.6)	4.4 (3.9, 5)	2.4 (1.5, 3.3)	0.0000	2.3 (1.4, 3.3)	0.0000
Nondiabetics						
	7.4 (6.1, 8.7)	4.8 (3.9, 5.6)	2.6 (1.1, 4.2)	0.0000	2.6 (1.1, 4.1)	0.0000

[¥]Adjusted by age, male, less than high school, low physical activity, diastolic blood pressure, waist circumference, diabetes and history of CVD

[£] Adjusted by less than high school, low physical activity, diastolic blood pressure and waist circumference.

5.4 Significance and implications

Conclusions and policy implications

Hypercholesterolemia imposes not only clinical but also economic consequences to an already overburdened health care system in Argentina. This "proof-of-concept" trial is designed with an implementation focus and has several distinctive aspects: There is a high prevalence of undiagnosed and uncontrolled population with dyslipidemia and high CVD risk in our country similar to other developing countries[13,14,16]. To our knowledge, this is the first trial of an educational intervention to reduce CVD risk, targeted to primary care physicians in Latin America[27] . This study is very timely not only because statins were recently introduced in 2014 into the national list of ambulatory drugs to be provided free-of-charge at public primary care clinics in Argentina, but also because there is no clinical practice guidelines in place in public PCCs aimed at specifically addressing the management of dyslipidemia and statins by health providers.

After the 12 months of follow-up there was no difference in the main outcome of this study. However, positive results were observed in relation to the clinical practice as the proportion of patients who are on statins and are receiving an appropriate dose and the number of follow-up visits to the primary care center. In addition, in the subgroup analysis we found that at the end of the follow-up the control group had higher cardiovascular risk than the intervention group.

This study mainly focused the intervention on physicians an almost none intervention was delivered to patients. Having said this, we consider that our intervention plan had an important success in increasing the physicians adherence to the intervention recommendations based on the good clinical practice guidelines. However, the lack of impact on the cholesterol values at the end of the follow-up suggests that there were inadequate levels of medication adherence in both groups.

It has been previously published that during the first year of treatment, most of the patients stop the treatment[46,47]. In our study medication adherence level, not only was low but also similar in the two groups.

However, the two outcomes that reflect a better adherence to statins good clinical practice guidelines by physicians and a more frequent attendance to primary care physicians showed significant positive results in the intervention group. Especially the higher mean of follow-up visits to the PCC could explain a better cardiovascular risk result at the end of the follow-up.

Although we couldn´t reach a reduction of the cholesterol levels at the intervention group, the promotion of adequate use of CPG led to a higher proportion of patients treated with adequate doses of statins and also we observed a more frequent rate of clinical visits in the intervention group. This two findings are related with the reduction in the inappropriate clinical practice variability and better control of chronic patients[48,49].

This type of study interventions targeting uninsured population living in low-income settings, can have an immediate impact in the real world through the dissemination and scale-up of the intervention program to the entire national public primary care network in Argentina, thereby reducing health disparities in CVD risk management and control. This study has contributed wit data on an effective, practical and sustainable intervention programs aimed at the prevention and control of CVD risk that can be directly used in other primary care settings and health care systems in LMICs.

6. List of Publications and Products

Gulayin P, Irazola V, Lozada A, et al. Educational intervention to improve effectiveness in treatment and control of patients with high cardiovascular risk in low-resource settings in Argentina: study protocol of a cluster randomised controlled trial. BMJ open. Jan 31 2017;7(1):e014420.

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