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ORIGINAL ARTICLE

BC Clinical impact of medication reviews with follow-up in cardiovascular older patients in primary care: A cluster-randomized controlled trial

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Aims: Cardiovascular diseases (CVD) are the primary cause of death in Chile. Pharmacist-led medication review with follow-up (MRF) has improved CVD risk factors control in Europe and North America. However, their healthcare systems differ from Chile's, precluding generalizability. This trial aimed to determine the effect of MRF on CVD risk factor control among older patients with polypharmacy attending public primary care centres in Chile.

Methods: A cluster-randomized controlled trial was conducted in 24 centres. Patients older than 65 years with moderate-to-high CVD risk, five or more medications, hypertension, type 2 diabetes or dyslipidaemia, received MRF in addition to usual care or usual care alone for 12 months. Primary outcome measures were clinical goal achievement for hypertension, type 2 diabetes and dyslipidaemia, as well as medication adherence, medication number and CVD risk score. Adjusted generalized estimating equations were used, with odds ratios (ORs) for binary measures and mean differences for continuous measures.

Results: In total, 324 patients from 12 centres (174 MRF group, 150 usual care group, six centres each) received four pharmacist visits. Significant improvements were found for goal achievement in hypertension (OR 4.37, 95% confidence interval [CI] 2.54 to 7.51, $P = .001$), LDL cholesterol (OR 3.67, 95% CI 2.13 to 6.33, $P = .001$), type 2 diabetes (OR 6.97, 95% CI 3.69 to 13.2, $P = .001$), medication adherence (OR 6.60, 95% CI 1.36 to 31.9, $P = .022$), medications number (−0.86, 95% CI −1.14 to −0.58, $P < .001$) and CVD risk score (−2.27, 95% CI −2.84 to −1.69, $P < .001$).

Conclusion: Pharmacist-led medication review with follow-up improved cardiovascular disease risk factor control and medication adherence. This study supports pharmacists' inclusion in primary care teams.

The authors confirm that the principal investigator for this paper is Jose C. Plaza-Plaza and that he had direct clinical responsibility for patients.

KEYWORDS
cardiovascular risk, hypertension, medication reviews, pharmacist care, primary care, type 2 diabetes

1 | INTRODUCTION

More than 25% of total deaths are attributable to stroke and ischemic heart disease in Chile.[1] Risk factors for cardiovascular diseases (CVD) such as dyslipidaemia (DLP), hypertension (HT) and type 2 diabetes mellitus (T2DM) are prevalent in the Chilean adult population (37%, 28% and 12%, respectively).[1] Adults older than 65 years are at higher risk of CVD due to a greater prevalence of risk factors. This group is expected to account for more than 20% of the Chilean population by 2025.[2]

A national cardiovascular primary care program (NCCP) was introduced in 2003 by the Chilean Ministry of Health to improve the control of HT, T2DM and DLP by increasing general practitioner (GP) check-ups and further involving nurses and dietitians.[2] The results of this program have been modest. By 2017, one-third of patients with HT had blood pressure (BP) levels lower than 140/90 mmHg and 34.3% of patients with T2DM had glycated haemoglobin (HbA1c) lower than 7%.[2,3]

The Pharmacy Fund program (Fondo de Farmacia or FOFAR) was established in 2014 by the government. It assured free medications by improving access in primary care for patients with HT, T2DM and DLP.[4] The program also provided funding for employing pharmacists in larger centres to manage pharmacies. A primary care centre cares for patients from a geographically defined area. The interdisciplinary group of health professionals located in such centres comprises GPs, nurses, dietitians, psychologists, physiotherapists, dentists and pharmacists.[1,2] Pharmacists typically are in charge of managing the centres' pharmacies and providing therapy advice if requested by patients. Government guidelines suggest that pharmacists can be further involved in the clinical care of CVD management by delivering pharmaceutical services such as medication review with follow-up (MRF).[4] However, there is no local evidence to support this recommendation.

MRF is a comprehensive method for evaluating and optimizing patients' pharmacotherapy to improve health outcome measures.[5] This service has shown positive results in managing chronic conditions, particularly in controlling CVD risk factors.[6] A meta-analysis showed that pharmacists improved control of HT (OR 2.73, 95% prediction interval [PI] 1.05, 7.08), T2DM (OR 3.11, 95% PI 1.17, 5.88) and elevated cholesterol (OR 2.52, 95% PI 1.06, 5.34) accounting for high heterogeneity.[7] However, none of the studies were undertaken in Chile and most did not report detailed intervention components allowing replication of the interventions, limiting the findings' generalizability.[7]

To fill this evidence gap, a cluster-randomized controlled trial (c-RCT), the Polaris study, was conducted to assess the impact of pharmacist-led MRF on adults older than 65 years with moderate-high CVD risk who used five or more medications. The main objective was to determine the clinical impact on the control of HT, T2DM and DLP, as well as the impact on CVD risk scores and medication adherence.

What is already know about this subject

- Cardiovascular diseases are the primary cause of death in Chile.
- Internationally, pharmacist-led medication reviews have shown improvement in managing cardiovascular diseases.
- Evidence for medication reviews from South America, particularly Chile, is lacking.

What this study adds

- This study showed that pharmacist-led medication reviews improved the number of patients achieving their therapeutic goals for hypertension, type 2 diabetes mellitus and dyslipidaemia.
- Pharmacist-led medication reviews could be considered for implementation in Chilean primary care setting to improve cardiovascular prevention.

2 | METHODS

The CONSORT statements for c-RCT and nonpharmacological interventions, as well as the Template for Intervention Description and Replication (TIDieR) guidelines were used for reporting.[8–10]

A pilot study was conducted between March and July 2017 in two municipalities (Puente Alto and La Granja) in the south-eastern metropolitan region of Santiago to test service feasibility and estimate an effect size for sample size calculations.[11] The results of the main c-RCT are reported in this article. The c-RCT was conducted between January 2018 and May 2019 (https://clinicaltrials.gov/ct2/show/NCT03502109). A cluster design was used to account for high variability in Chilean public primary care centres regarding size and location, and to avoid patient cross-contamination.[11] All six National System of Health Services (NSHSs) in Santiago were contacted. NSHSs that agreed to participate suggested municipalities to include in the study, as not all centres have pharmacists. Clusters included 24 centres in seven municipalities in the Santiago metropolitan region. These were stratified by patient number. Large was defined as more

than 50 000 patients, medium centres cared for 30 000–50 000 patients, and small centres had fewer than 30 000 patients. Health authorities requested prioritizing larger centres.

2.1 | Eligibility criteria

Each centre employed one pharmacist, meaning the number of centres and pharmacists was equal. Inclusion and exclusion criteria for centres and patients are presented in Table 1.

2.2 | Sample size

The sample size was calculated using data from the pilot study that showed a significant decrease in BP (systolic BP −11.2 ± 15.4 mmHg, $P = .006$; diastolic BP −6.49 ± 10.5, $P = .01$) and LDL cholesterol levels (−36.1 ± 34.2 mg/dL, $P = .002$) after 3 months of intervention (https://clinicaltrials.gov/ct2/show/NCT03502109). The standardized effect size (0.324) was estimated conservatively by reducing CVD risk scores (−1.94 ± 4.17, $P = .042$) as it generally requires a larger number of patients to detect changes and is the main focus of the NCCP.[2,13] We used a balanced control-intervention relationship of 1:1 with 80% statistical power and a P value of <.05. The intraclass correlation coefficient (ICC) was 0.03, with 24 centres available. The resulting cluster size was 20 patients (design effect 1.57). The total sample size was 576 patients, with 288 in each group and 20% attrition.[14,15]

TABLE 1 Eligibility criteria.

Eligibility criteria	Primary care centres	Patients
Inclusion criteria	Primary care centres with at least one full-time pharmacist	Individuals older than 65 years who sign the informed consent form
	Pharmacists able to request laboratory examinations for cardiovascular parameters such as HbA1c and lipid levels	Individuals included in the NCCP with diagnoses of HT, T2DM or DLP[2]
	Pharmacists able to add findings in official clinical records	Individuals classified as independent based on the Barthel index for activities of daily living[2]
	Pharmacists able to devote at least 5 h a week (10 h in the intervention group) to participation in the study	Individuals with moderate or high CVD risk by the Chilean adaptation of Framingham's risk charts[12]
		Individuals who take five or more daily medications
Exclusion criteria	Primary care centres attached to a hospital	Participants in the pilot study
	Private primary care centres	Individuals with low CVD risk bases on the Chilean adaptation of Framingham's risk charts[12]

Abbreviations: CVD, cardiovascular disease; DLP, dyslipidaemia; HT, hypertension; NCCP, national cardiovascular care program; T2DM, type 2 diabetes mellitus.

2.3 | Randomization and recruitment

Randomization was undertaken after receiving ethics approval and written, nonlegally binding formal commitment from centres agreeing to participate.[11] Simple randomization was undertaken with the MS Excel random function, using centres as the unit of randomization. Randomization was conducted with at least one representative from each municipality acting as a witness, as required by ethics committees. To reduce the risk of imbalances between groups in cluster randomized trials, matching clusters is a common practice as these imbalances could compromise the study's internal and external validity.[11,12] We used the total number of patients and patients belonging to the NCCP in each centre to match the larger and smaller centres, and these matches were randomized between groups.[11,15] The number of patients each centre recruited was determined by the number of patients in the NCCP, as informed by the Ministry of Health.[2,11] Smaller centres had to recruit between 24 and 35 patients, and larger centres between 42 and 60 patients. A centre contributing more than 40% of the study population was matched with the second- and third-largest centres (adding 43% of the population) to prevent further imbalances between samples (Figure 1).[11,15]

Patient recruitment was not random. Pharmacists recruited patients at the pharmacy or by referral from GPs and nurses until the required number was achieved. GP and nurse referrals to the MRF service were encouraged to reduce the risk of selection bias. However, both methods were used due to high staff workload and patients being not aware of pharmacists' involvement in the national CV program.[2,3] Selection bias, specifically sampling bias, can reduce the external validity of a sample because of the risk of recruiting patients by prognostic factors.[9–11] To account for this risk of bias, baseline characteristics were compared between control and intervention groups.[10]

Patients were not aware of their study group. As the intervention was randomized by centre and given the nature of the MRF service, pharmacists and clinical teams were aware of their group allocation.

2.4 | Intervention

A TIDieR checklist with a detailed description of the intervention and its components, pharmacist training, materials used, procedures and flowcharts is provided in Supporting Information Table S1 and Figures S1 to S6.[10]

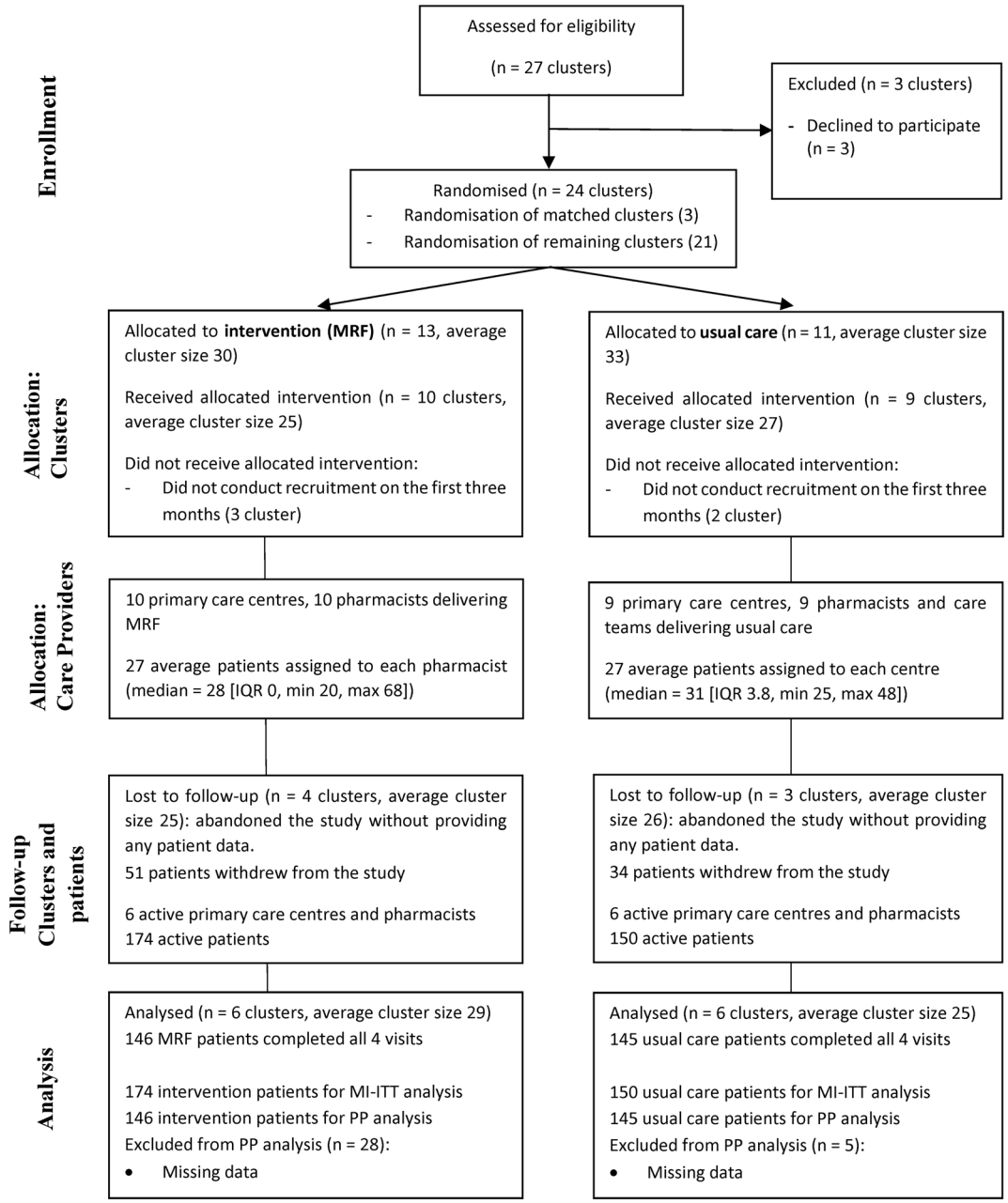

FIGURE 1 CONSORT flowchart for the Polaris study. IQR, interquartile range; MI-ITT, multiple imputation intention-to-treat; MRF, medication review with follow-up; PP, per-protocol.

In the intervention centres, MRF was performed by pharmacists using the Polaris method in four face-to-face visits over 12 months. This method is mainly based on Dader's MRF method. However, it also includes other methods' components, such as the pharmacotherapy workup, medication therapy management and polypharmacy guidelines from the United Kingdom.[16–19] Flowcharts with detailed and comprehensive pharmacotherapy evaluations were developed to explore drug necessity, safety, effectiveness and medication adherence (Supporting Information Figures S1 to S6). These tools supported pharmacists in detecting and resolving drug-related problems (DRPs). DRPs are "events or circumstances involving drug therapy that actually or potentially interfere with desired health outcome measures".[20] The intervention also included practice change facilitators (PCFs). PCFs were experienced pharmacists trained by the research team in process evaluation and chronic disease management to guide and support pharmacists. Intervention group pharmacists were trained in the Polaris MRF method and disease management by the PCFs. A nurse trained them to deliver health information and assess vitals effectively. Pharmacists could access patients' clinical and pharmacy records and request pathology tests when needed.

Patients were invited to a consultation room. This room was shared by different clinicians and used as required to interview or

examine patients. The initial visit (30 min) allowed pharmacists to gather information to complement clinical records, detect self-medication and nonadherence behaviours, and establish individual goals with patients. After this visit, pharmacists reviewed patients' status using clinical and pharmacy records, and information collected in the initial visit to develop interventions to resolve DRPs. These interventions included drug therapy or disease management advice, interventions to improve medication adherence or treatment changes. Pharmacists met face-to-face with GPs to suggest changes when treatment changes were deemed necessary. GPs then decided if suggestions would be implemented. Educational interventions were not discussed with GPs. Patients decided in follow-up visits (20 min) if they wanted to follow the pharmacists' and GPs' recommendations. All interventions were implemented only with patients' approval. During each visit, pharmacists measured patients' vitals and medication adherence. Using this information in addition to pathology test results, pharmacists evaluated the effect of implemented interventions. After the 12-month study period, patients could continue the MRF service if needed, but data were no longer collected.

Usual care entailed care from GPs, nurses and dietitians, as per the NCCP guidelines[2,3]:

- Patients with high CVD risk received at least two physician check-ups, one nurse check-up and one dietitian check-up in a year.
- Patients with moderate CVD risk received at least one physician check-up, one nurse check-up and one dietitian check-up in a year.

Additionally, pharmacists were available on request when dispensing in the centre's pharmacy. Patients in the usual care group also had pharmacists collecting data in short interviews. MRF was provided in addition to usual care in the intervention group.

2.5 | Outcome measures

The primary binary outcome measures were the achievement of therapeutic goals for HT, T2DM and LDL cholesterol, as well as medication adherence according to the validated medication adherence questionnaire provided by the Chilean Ministry of Health (Chilean MAQ).[2] Therapeutic goals from the Chilean CVD guidelines were used. These were systolic blood pressure (SBP) lower than 140 mmHg and diastolic blood pressure (DBP) lower than 90 mmHg for HT, HbA1c lower than 7% (8% for ≥80 years of age) for T2DM and LDL cholesterol levels lower than 100 mg/dL for patients with moderate CVD risk and lower than 70 mg/dL for high-risk patients or patients with T2DM or a previous CVD.[2] Primary continuous outcome measures were the number of prescribed medications and CVD risk scores. CVD risk scores were determined using Framingham's risk charts adapted to the Chilean population.[2,12]

Secondary outcome measures were SBP and DBP, total, low and high-density lipoprotein cholesterol (TC, LDL and HDL), triglycerides (TGs) and fasting glucose (FG). HbA1c was used in patients with T2DM. Subgroup analyses of patients with T2DM were conducted on all primary outcome measures to further explore the MRF effect on this population.

Pharmacist intervention acceptance rates by GPs and patients were used as process indicators, along with detected and solved DRPs.[6,7]

2.6 | Data collection

Pharmacists in the intervention group collected data from each visit by assessing vitals and medication adherence, and by reviewing medications brought by the patient. Vitals, such as BP, were collected by nurse technicians before each interview to avoid bias. Pharmacists also registered results from pathology tests and official pharmacy and medical records. A codified MS Excel file without patient identification data was sent to the research team for all four visits (Supporting Information Figure S7). The research team estimated CVD risk scores using SBP, TC, age, TG, presence of T2DM and smoking habit.[12]

2.7 | Statistical analysis

Individual generalized estimating equation (GEE) models were used to determine outcome measures, adjusting for age, gender, CVD event history, high baseline CVD risk score (≥10), T2DM, educational level by years of study (no formal education, at least 8 years, at least 12 years or >12 years), civil status (married, single, widowed), more than nine prescribed daily medications, baseline medication adherence, body mass index (BMI) higher than 32 kg/m^2 and baseline values for each analysed variable. Model-based estimators and an exchangeable working correlation matrix were used to account for clustering.[15,21,22]

Changes in binary outcome measures between groups, such as medication adherence and goal achievement, were analysed using the χ^2 test odds ratio (OR) with 95% confidence interval [CI] and a *P* value lower than .05. For continuous outcome measures, the mean difference between groups was calculated for each visit with 95% CI and a *P* value of <.05.

The primary analysis was a partial intention-to-treat (ITT) GEE analyses conducted on imputed data and pooled outcome measures as previously determined and published in clinicaltrials.gov. These analyses excluded clusters lost to follow-up at either the allocation stage or the follow-up stage (Figure 1), which did not provide analysable data as patients were not recruited or not interviewed, precluding a full ITT analysis. All outcome measures for patients included in the study had a normal distribution and less than 13% missing values (missing values for each visit were 7%, 9%, 10% and 12% for the intervention group and 6%, 10%, 11% and 12% for the control group). Patterns of missing data were explored for patients with at least one visit, and they appeared to be missing at random. Then, a five-imputations multiple imputation (MI) model using the Markov Chain Monte Carlo approach with 20 000 iterations (one imputation every 4000 iterations) was applied, accounting for patient covariates and

reported outcome measures, and with binary variables restrained between 0 and 1.[15,21,22] Additionally, per-protocol (PP) GEE analyses were conducted on patients who completed all four visits.[21] This analysis was compared with the partial ITT analysis.[22] Subanalyses of primary and secondary outcome measures in patients with T2DM were conducted. IBM SPPS 25 software was used.

2.8 | Ethics approval

The University of Technology Sydney (UTS) human research ethics committee in Sydney, Australia approved this study (UTS HREC Ref no. ETH17-1346). This was endorsed by each NSHS (south, south-eastern, eastern and western metropolitan health services ethics committees). Each participating pharmacist and patient signed an informed consent form before enrolling. Pharmacists reinforced to patients that their participation was voluntary and that they could withdraw at any time.

3 | RESULTS

In total, 324 patients were recruited in 24 primary care centres (174 in the MRF group and 150 in the usual care group). Five centres dropped out within the first 3 months, recruiting no patients. Seven additional centres were lost, with pharmacists not conducting any patient visits or collecting data after recruitment due to inability to allocate time for the trial (Figure 1).

Most baseline characteristics were similar between groups. However, significant baseline differences were observed in the number of health problems and medication adherence (Table 2). Recruited patients' dropout rate was at the expected level and balanced between groups (20% for the MRF group and 18% for the usual care group). Overall, 85% of patients in the MRF group and 94% in the usual care group completed all four visits.

3.1 | Clinical outcome measures

There were significant differences between groups at the final visit for the achievement of therapeutic goals for BP (OR 4.37, 95% CI 2.54 to 7.51, $P = .001$) and LDL cholesterol (OR 3.67, 95% CI 2.13 to 6.33, $P = .001$). There were also significant differences for medication adherence (OR 6.60, 95% CI 1.36 to 31.9, $P = .001$), CVD risk score (-2.27, 95% CI -2.84 to -1.69, $P < .001$), number of medications (-0.86, -1.14 to -0.58, $P < .001$) and all secondary outcome measures in both the PP and ITT analyses (Table 3, Supporting Information Tables S2–S5 and Figures 2–3). As the difference in baseline medication adherence was significant, the GEE models were adjusted using the adherence-by-visit interaction.[23] Single-slope analysis assuming that both groups had the same baseline medication adherence, commonly used in the literature to explore the risk of selection bias, showed significant differences in medication adherence at the final visit even after this adjustment.[15,21]

3.2 | Process indicators

Pharmacists in the MRF group performed 542 interventions to address 511 DRPs. The most common interventions were stopping unnecessary or unsafe drugs (32.7%), changing a drug for a safer or more effective alternative (18.6%), intervening in medication adherence (16.4%), decreasing dosage to prevent adverse drug events (11.8%) and increasing dosage to improve effectiveness (10.3%). Pharmacists reported and intervened in 54 adverse drug reactions, with drowsiness (13.5%), ankle oedema (13.5%), gastrointestinal pain (11.5%) and hypoglycaemia (9.6%) being the most common. Of the 511 DRPs, 472 were solved entirely during the follow-up period, 21 were partially solved and 18 were not solved. The GP intervention acceptance rate was 92.9% (83.3-97.8%), whereas for patients it was 99.2% (97.5-100%).

3.3 | Patients with T2DM

A planned subgroup analysis was conducted on patients with T2DM ($n = 179$: 89 intervention, 90 control). There were significant differences between groups in the achievement of T2DM goal (OR 6.97, 95% CI 3.69 to 13.2, $P = .001$), HbA1c (-1.27%, 95% CI -1.56 to -0.99, $P = .001$) and all other outcome measures (Table 4 and Supporting Information Table S5).

Pharmacists in the MRF group suggested the initiation or an increasing dose of insulin in 16% of patients. These adjustments were observed twice as much in the intervention group compared with the usual care group. Insulin administration advice was provided to 92% of insulin users in the intervention group. Pharmacists in this group also suggested changing glibenclamide prescription in 84% of patients to high metformin doses (68%) and initiating insulin (26%). This resolved six cases of confirmed hypoglycaemia with glyburide.

4 | DISCUSSION

To our knowledge, this is the first c-RCT to explore the impact of pharmacist interventions in public primary care centres in Latin America. The study provides insights for future research, as the local health system in Chile diverges greatly from Europe and North America, where most trials have been conducted.[6,7]

MRF effects on achieving therapeutic goals for HT, DLP and T2DM directly impact CVD risk, particularly as high BP and high LDL cholesterol levels are the leading causes of CVD. Our analysis showed a 2% reduction in the 10-year CVD risk (from 9.64 ± 3.24 to 7.37 ± 3.93), providing a great improvement opportunity for the national

TABLE 2 Baseline patient characteristics.

Characteristic	Total (12 cluster, 324 patients)	Control group (six clusters, 150 patients)	Intervention group (six clusters, 174 patients)
Age, mean (SD), year	73.6 (5.91)	74.1 (5.99)	73.2 (5.82)
65–74 years, n (%)	190 (58.6)	82 (54.7)	108 (62.1)
≥75 years, n (%)	134 (41.4)	68 (45.3)	66 (37.9)
Gender, n (%)			
Male	91 (28.1)	43 (28.6)	48 (27.5)
Female	233 (71.9)	107 (71.4)	126 (72.5)
Educational level, n (%)			
No studies (<8 years)	150 (46.3)	71 (47.4)	79 (45.4)
Primary (8–11 years)	114 (35.2)	57 (38.0)	57 (32.8)
Secondary (12 years)	53 (16.4)	20 (13.3)	33 (19.0)
Tertiary (>12 years)	7 (2.1)	2 (1.3)	5 (2.8)
Civil status, n (%)			
With partner	189 (58.3)	86 (57.3)	103 (59.2)
Without partner	135 (41.7)	64 (42.7)	71 (40.8)
Number of medications, mean (SD)	8.11 (2.40)	7.86 (2.27)	8.31 (2.48)
5–9 medications, n (%)	245 (75.6)	117 (78.0)	128 (73.6)
>9 medications, n (%)	79 (24.4)	33 (22.0)	46 (26.4)
Health problems, mean (SD)	3.90 (1.45)	3.56 (1.55)	4.17 (1.39)
Patients with T2DM, n (%)	200 (61.7)	93 (62.0)	107 (61.5)
BMI, mean (SD), kg/m^2	31.0 (5.22)	30.9 (4.60)	31.4 (5.71)
Normal/overweight, n (%)	200 (61.7)	102 (68.0)	98 (56.3)
Obese, n (%)	124 (38.3)	48 (32.0)	76 (43.7)
Smoker, n (%)	43 (13.3)	18 (12.0)	25 (14.3)
CVD history, n (%)	55 (17.0)	22 (14.7)	33 (18.9)
CVD risk score, mean (SD)[a]	9.44 (3.20)	9.20 (3.16)	9.64 (3.24)
Moderate (5–9), n (%)	157 (58.4)	73 (57.1)	84 (59.6)
High (≥10), n (%)	112 (41.6)	55 (42.9)	57 (40.4)
BP control, n (%)	125 (38.6)	51 (34.1)	74 (42.5)
SBP, mean (SD), mmHg	138 (17.2)	139 (12.5)	137 (16.2)
DBP, mean (SD), mmHg	75.0 (11.8)	74.8 (10.0)	75.0 (10.8)
T2DM control, n (%)[b]	107 (54.0)	52 (57.1)	55 (51.4)
HbA1c, mean (SD), %[b]	7.34 (1.45)	7.19 (1.05)	7.49 (1.27)
FG, mean (SD), mg/dL	116 (32.0)	115 (22.5)	118 (29.6)
LDL control, n (%)	102 (31.5)	45 (30.0)	57 (32.8)
LDL, mean (SD), mg/dL	99.4 (38.6)	98.5 (30.0)	99.4 (35.7)
TC, mean (SD), mg/dL	179 (45.2)	175 (36.9)	181 (40.4)
HDL, mean (SD), mg/dL	45.7 (11.4)	45.5 (10.0)	45.7 (10.1)
TG, mean (SD), mg/dL	173 (82.5)	174 (60.6)	172 (78.1)
Medication adherence, n (%)	129 (39.8)	48 (32.1)	81 (46.4)

Abbreviations: BMI, body-mass index; BP, blood pressure; CVD, cardiovascular disease; FG, fasting glycaemia; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; mg/dL, milligrams per decilitre; mmHg, millimetres of mercury; SD, standard deviation; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglycerides.

[a]128 control patients, 141 intervention patients with CVD risk score.

[b]93 control patients, 107 intervention patients with T2DM.

TABLE 3 Primary outcome measures adjusted GEE analyses.

Outcome	Visit	ITT with multiple imputation (150 control, 174 intervention) OR/mean difference (95% CI)	*P* value
BP at goal	1	1.53 (0.96 to 2.43)	.074
	2	1.12 (0.67 to 1.86)	.659
	3	1.65 (0.95 to 2.86)	.038
	4	**4.37 (2.54 to 7.51)** *	**.001**
LDL at goal	1	1.14 (0.70 to 1.87)	.600
	2	0.98 (0.59 to 1.63)	.926
	3	1.69 (0.98 to 2.93)	.060
	4	**3.67 (2.13 to 6.33)** *	**.001**
Medication adherence[a]	1	1.35 (0.39 to 4.70)	.625
	2	1.27 (0.30 to 5.41)	.732
	3	3.31 (0.90 to 12.3)	.071
	4	**6.60 (1.36 to 31.9)** *	**.022**
CVD risk score (%)[b]	1	0.24 (−0.36 to 0.83)	.442
	2	−0.10 (−0.64 to 0.44)	.726
	3	**−1.34 (−1.92 to −0.75)** *	**<.001**
	4	**−2.27 (−2.84 to −1.69)** *	**<.001**
Number of medications	1	0.27 (−0.09 to 0.62)	.142
	2	−0.23 (−0.50 to 0.04)	.100
	3	**−0.50 (−0.79 to −0.22)** *	**.001**
	4	**−0.86 (−1.14 to −0.58)** *	**<.001**

Note: Values in bold indicate statistical significance.
Abbreviations: BP, blood pressure; CI, confidence interval; CVD, cardiovascular diseases; GEE, individual generalized standardized equation; ITT, intention-to-treat analysis; LDL, low-density lipoprotein cholesterol; OR, odds ratio.
*Statistical significance.
[a]Model adjusted by significant baseline differences in medication adherence using the baseline adherence-by-visit interaction.
[b]124 control patients, 148 intervention patients.

cardiovascular program.[2,12] These effects were observed together with a significant reduction in the number of medications (−0.86, 95% CI −1.14 to −0.58). This shows that improved clinical outcome measures of MRF were not achieved by simply adding more medications, as has been previously reported.[6,7]

Medication adherence was increased, which has been observed in other MRF experiences.[6,7] In observational studies, improved medication adherence has been shown to decrease all-cause mortality (OR 0.56, 95% CI 0.43 to 0.74).[13,24,25] Conversely, nonadherence is associated with an increased risk of CV mortality (hazard ratio 1.18, 95% CI 1.11, to 1.25).[13,24,25] Better clinical outcome measures from this study could be related to greater medication adherence and reductions in treatment complexity by decreasing the number of medications and simplifying dosing regimens.[24]

T2DM is considered an independent indicator of high CVD risk.[1,2,26] Patients with T2DM have two to four times more risk of having a CVD or dying because of it than the normal population.[1,26] Our subgroup analysis showed that MRF was effective for this population. We found significant effects, including a reduction in HbA1c and an increase in the proportion of patients who reached therapeutic goals. This effect could be explained by pharmacists suggesting initiation or increasing the insulin dose on more patients (double the rate compared to the usual care group) and by deprescribing glibenclamide. Glibenclamide is not recommended in older adults because of its high hypoglycaemia risk and low effectiveness.[2] Pharmacists recommended changing glibenclamide to high-dose metformin or initiating or modifying insulin regimes. This improved treatment safety and lowered clinical inertia. In diabetes, clinical inertia is defined as not initiating or failing to intensify therapy when clinically required. This further increases CVD risk and other negative outcomes. This phenomenon is increasingly targeted as a main contributor to diabetes morbidity and mortality.[27] Our results also showed benefits in HbA1c reduction. Studies have suggested that a 1% reduction in HbA1c could prevent 21.6% of fatal and nonfatal myocardial infarctions, therefore the clinical benefit of MRF for CVD prevention could be substantial.[27,28]

Pharmacists resolved most DRPs, with high acceptance rates by GPs and patients. Interestingly, GP acceptance rates above 90% are not typical in studies on pharmaceutical services. Often, they are between 40% and 80%.[6,7,29–31] Previous contact with GPs and sharing the workplace in a primary care setting could favour collaboration

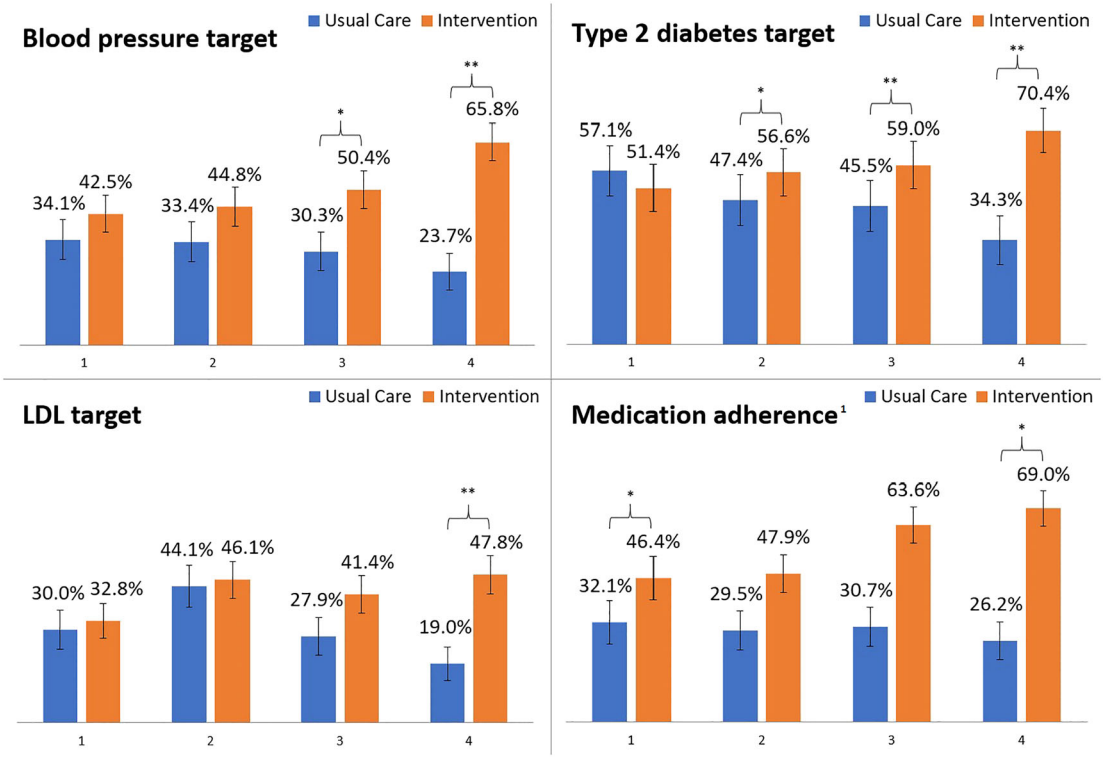

FIGURE 2 Control of health conditions and medication adherence per visit. LDL, low-density lipoprotein cholesterol. Bars presented as group mean percentages per visit with 95% confidence intervals. *$P < .05$, **$P < .01$. [1]Model adjusted by significant baseline differences in medication adherence using the baseline adherence-by-visit interaction.

FIGURE 3 Mean values of CVD risk scores (A) and number of medications (B) per visit. Points presented as group means per visit with 95% confidence intervals and linear trends. CVD, cardiovascular disease; MRF, medication review with follow-up; UC, usual care.

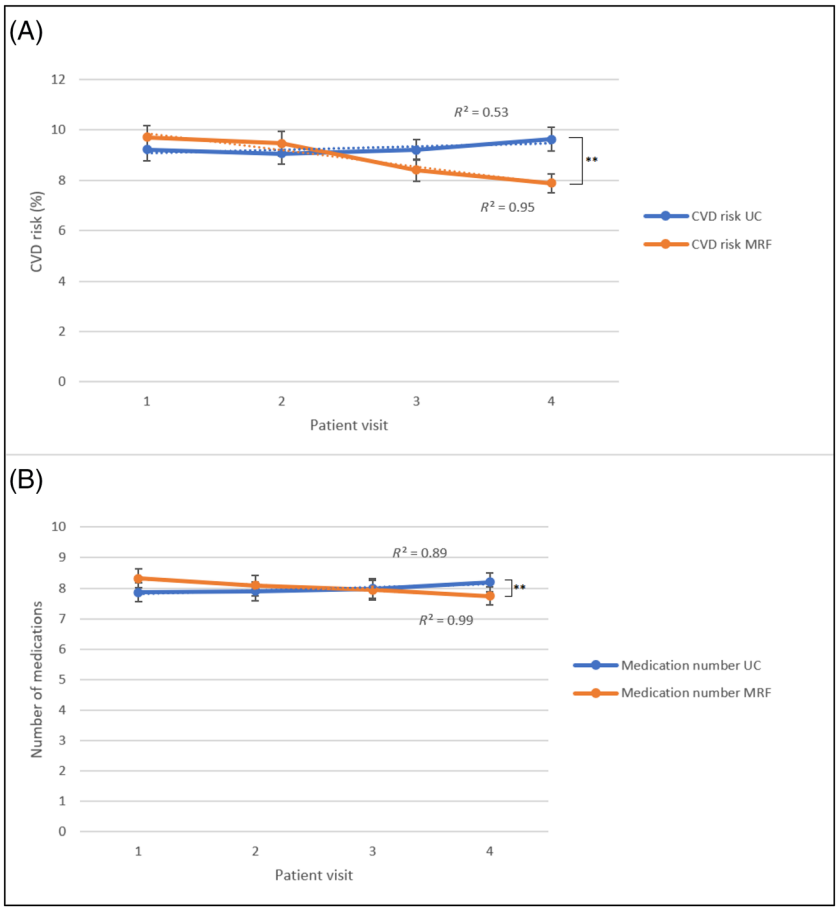

TABLE 4 Outcome measures for patients with type 2 diabetes mellitus.

Outcome	Visit	ITT with multiple imputations (91 control, 107 intervention) OR/mean difference (95% CI)	*P* value
HbA1c at goal (OR)	1	1.08 (0.58 to 2.00)	.814
	2	**2.07 (1.14 to 3.74)** *	**.017**
	3	**2.45 (1.31 to 4.56)** *	**.005**
	4	**6.97 (3.69 to 13.2)** *	**.001**
BP at goal (OR)	1	0.97 (0.54 to 1.75)	.926
	2	1.70 (0.88 to 3.29)	.117
	3	2.71 (0.72 to 9.60)	.060
	4	**7.90 (1.34 to 5.50)** *	**.001**
LDL at goal (OR)	1	1.39 (0.70 to 2.70)	.337
	2	0.97 (0.50 to 1.90)	.935
	3	1.18 (0.58 to 2.41)	.648
	4	**4.94 (2.05 to 11.9)** *	**.001**
Medication adherence (OR)	1	0.96 (0.53 to 1.75)	.905
	2	**1.96 (1.04 to 3.69)** *	**.037**
	3	**4.93 (2.47 to 9.87)** *	**.001**
	4	**7.20 (3.56 to 14.6)** *	**.001**
CVDR score (%)	1	0.30 (−0.57 to 1.17)	.501
	2	−0.09 (−0.76 to 0.58)	.790
	3	**−1.35 (−2.06 to −0.65)** *	**.001**
	4	**−2.51 (−3.29 to −1.73)** *	**.001**
Number of medications	1	0.41 (−0.04 to 0.86)	.074
	2	−0.33 (−0.68 to 0.02)	.064
	3	**−0.58 (−0.93 to −0.23)**	**.001**
	4	**−1.13 (−1.50 to −0.76)**	**.001**
HbA1c (%)	1	0.10 (−0.29 to 0.49)	.623
	2	**−0.47 (−0.82 to −0.13)** *	**.007**
	3	**−0.40 (−0.72 to −0.08)** *	**.014**
	4	**−1.17 (−1.51 to −0.82)** *	**.001**
SBP (mmHg)	1	−3.14 (−7.47 to 1.20)	.156
	2	−0.31 (−4.10 to 3.49)	.875
	3	**−5.38 (−9.21 to −1.55)** *	**.006**
	4	**−11.3 (−15.6 to −6.90)** *	**.001**
DBP (mmHg)	1	0.50 (−2.44 to 3.44)	.738
	2	−0.55 (−3.25 to 2.15)	.689
	3	**−4.01 (−6.76 to −1.26)** *	**.004**
	4	**−7.65 (−10.6 to −4.74)** *	**.001**
LDL (mg/dL)	1	−3.39 (−13.1 to 6.29)	.492
	2	3.53 (−4.54 to 11.6)	.391
	3	**−9.42 (−17.6 to −1.23)** *	**.024**
	4	**−24.8 (−33.3 to −16.2)** *	**.001**

Note: Values in bold indicate statistical significance.

Abbreviations: BP, blood pressure; CI, confidence interval; CVDR, cardiovascular disease risk; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; ITT, intention-to-treat analysis; LDL, low-density lipoprotein cholesterol; mg/dL, milligrams per decilitre; mmHg, millimetres of mercury; OR, odds ratio; SBP, systolic blood pressure.

*Statistical significance.

between GPs and pharmacists, increasing trust and confidence in pharmacist interventions.[25–27] In our study, most interventions involved stopping, changing or modifying medication dosage, which requires interaction with GPs. Conversely, previous studies reported a higher proportion of educational interventions to increase patient adherence or knowledge of chronic diseases.[5–7] This difference in pharmacist focus for interventions could explain the larger improvement in outcomes as compared to previous studies, as type 3 medication reviews have been shown to provide better clinical outcomes in the literature than type 2 or 1 because as clinical inertia in hypertension and diabetes is one of the main causes of CVD.[5–7]

Many DRPs were related to inappropriate prescriptions or undertreated diseases, showing that pharmacists had a clear role in pharmacotherapy optimization. However, pharmacists' and GPs' time to suggest and agree on therapy modifications was described as a barrier to the MRF service, which additionally represents an increased cost to the intervention. A possible solution to this issue is to authorize pharmacists to prescribe.[12,25–27] Providing prescription authority to trained pharmacists on chronic disease management or allowing them to use mutually agreed protocols to treat CVD risk conditions could be the next step for the Chilean cardiovascular program. This is the case in the UK with general practice pharmacists.[32,33] However, evidence is still required to show the effect of prescribing pharmacists in Chile.

A critical issue observed in our study of implementing MRF was the time allocated to the intervention. Pharmacists providing the service had to continue to manage the centre's pharmacy. Pharmacists who abandoned the study expressed frustration due to time constraints and the inability to use consultation rooms in their centres, which are common issues in Chile's public primary care system and need to be considered for future implementation.[2,3] PCFs attempted to resolve these problems by contacting the centre's directors and assisting pharmacists in organizing their time. Although this indeed worked for centres that completed the study, it was not the case for all of them. Key factors for success were identified in successful centres: pharmacists having specific times to provide the MRF service and available consultation rooms for patient interviews. These implementation factors have been described and ideally should be addressed previously to implement an intervention such as MRF.[29–34]

Finally, this study found that pharmacists' interventions benefited the control of HT, T2DM and DLP without increasing the number of medications, resolving most DRPs encountered in the intervention group. Fully integrating pharmacists into primary care teams for older adults with CVD risk conditions could represent an opportunity to improve the control of these diseases. Several countries have already implemented the MRF service in ambulatory clinics or community pharmacies, with beneficial clinical and economic results.[6,7,29–32,35]

This study has some methodological limitations. Centre dropout was high (50%), which led to not achieving the initial required sample size. This issue could impact the trial's generalizability due to random error. However, the risk of not having enough statistical power was low as the observed ICC was much lower than initially estimated (0.0028 *vs* 0.03) for primary outcome measures, and the average cluster size was higher than the previously determined value of 20,[2,15] therefore the initial sample size was likely overestimated, which is a problem commonly reported in cluster trials.[15,21,22] In addition, lost centres did not provide any patient baseline data, potentially compromising inference. This is a common phenomenon in c-RCT and has previously been described as "non-analysable data".[36] Statistical treatment has been proposed to address lost centres, but statistical analysis with available data could be acceptable if the planned analysis does not consider all clusters.[36] Ideally, a second set of centres would have been randomized by amending the protocol, but no more centres were eligible or willing to participate due to not having a pharmacist or insufficient pharmacist time to allocate to the study.

Pharmacists in the MRF group performed patient recruitment, interventions and data collection, which could be a possible source of bias. We tried to lower this effect by encouraging GPs and nurses to directly refer patients to the service if they fulfilled the eligibility criteria (at least 52% of patients were not recruited by pharmacists) and by requesting independent vitals assessment, such as BP measurement by nurse technicians. We believe this risk is low as usual care and MRF patients had similar baseline characteristics.[15] Due to the MRF service nature, providers and recruiters could not be blinded to their randomized group, which might introduce bias. However, patients did not know their study group, as data collection from usual care was performed in similar visits and cluster-level randomization prevented cross-contamination.[14] A statistically significant difference in baseline medication adherence was present, which could affect disease control and other outcome measures. All GEE models were adjusted with the baseline-adherence-by-visit interaction to account for the issue, and it was found that this factor was not associated with the outcome measures.

This is the first trial assessing the effect of pharmacist-led MRF in primary care centres in Latin America. Despite the healthcare system differences between Chile and the United States and Europe, similar results were obtained in our study. Statistically significant differences were found in all primary and secondary outcome measures when pharmacists applied the Polaris MRF method. These findings support the Chilean government to employ pharmacists in primary healthcare centres and consider directly including them in the cardiovascular program care teams. Due to the high recommendations acceptance rate, it seems a natural step for pharmacists to be formally incorporated into primary care teams. Including pharmacists could enhance the current outcome measures of the government-funded cardiovascular program. To enhance MRF implementation, pharmacists should be given enough time and consultation rooms to provide the service.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the trial. All authors contributed to the work's acquisition, analysis or interpretation of data. Francisco Martínez-Mardones drafted the manuscript. Everyone critically revised the manuscript. Everyone gave final approval and agreed to be accountable for all aspects of work, ensuring integrity and accuracy.

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COMPETING INTEREST

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data supporting this study's findings are available from the corresponding author upon reasonable request.

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