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Cost-utility analysis of medication review with follow-up for cardiovascular outcomes: A microsimulation model

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ABSTRACT

Background: Cardiovascular diseases are the leading cause of death. Pharmacist-led medication review with follow-up might be cost-effective preventing cardiovascular diseases.
Objective: To undertake a cost–utility analysis of the addition of pharmacist-led medication review with follow-up to usual care compared to usual care alone for cardiovascular outpatients.
Materials and methods: A state-transition microsimulation model was built to project outcomes over a lifetime time horizon. Inputs from a cluster randomized controlled trial conducted in primary health care centers in Chile with full-time pharmacists were used. Probabilities were estimated using patient-level data. Utilities and costs associated with each health state were obtained from the literature, whereas the intervention costs were retrieved from the trial. The public third-party payer perspective was used. Uncertainty was evaluated through one-way and probabilistic sensitivity analyses.
Results: For the base case analysis, an incremental cost-effectiveness ratio of $963 per quality-adjusted life-year was observed which was considered cost-effective. The results were robust to sensitivity analyses and were driven by decreased cardiovascular events resulting in lower mortality.
Conclusions: Medication review with follow-up was deemed a cost-effective addition to usual care with low uncertainty.

1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of death worldwide, with ischemic heart disease and stroke accounting for 26.8% of global deaths [1]. These events cause deterioration of health-related quality of life and long-term disability [2]. Health care costs related to CVDs are expected to have a global burden of $1000 billion by 2030 [3]. Consequently, evidence-based guidelines have been developed to prevent CVDs and manage risk factors such as hypertension (HTN), dyslipidemia (DLP), and type 2 diabetes mellitus (T2DM) [4–7]. Despite the availability and implementation of these guidelines, there is evidence that in South American countries such as Argentina, Uruguay, and Chile, 43.3% of patients suffering from HTN treated with medications still have their blood pressure above therapeutic objectives [8].

In 2016, the Chilean Ministry of Health reported that CVDs accounted for the highest mortality rate, with 26.7% of deaths [9]. The main contributors were myocardial infarction (MI) with 7.8% and stroke with 8.1% [9]. In addition, 8.0% of hospitalizations were caused by CVDs, increasing in the elderly to 19.6% [10]. In terms of CVD risk factors, the latest health survey found that 27.6% of the population had HTN, 12.3% had T2DM, and 27.8% had DLP [11,12]. These risk factors play a significant role in determining the 10-year CVD risk, which was high for 25.5% and moderate for 26.0% of the population [12]. Hence, it is expected that this increased risk would affect the country's health care budget, which is the lowest among the countries belonging to the Organization for Economic Co-operation and Development [13].

In 2014, the pharmacy fund for noncommunicable diseases was established by the government as one of the strategies to improve

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CVD prevention. Targeting treatments for HTN, DLP, and T2DM, the fund aimed to ensure timely and free access to medications for patients who receive care through the public primary health care system [14]. This initiative involved the employment of pharmacists to ensure the management of these medications. Pharmacists were also included in an existing CVD prevention program. This program includes consultations with physicians, registered nurses (RNs), and dietitians to address CVD risk through interdisciplinary work to reduce morbidity and mortality [15]. According to the guidelines, pharmacists could provide three services: (i) reconciliation of medications, (ii) prescription training for physicians, and (iii) pharmacist-led medication review with follow-up (MRF) [15]. Nonetheless, these services are being implemented at the discretion of each center.

MRF is defined as "a structured evaluation of a patient's medicines to optimize medicines use and improve health outcomes. This entails detecting drug-related problems and recommending interventions" [16]. This professional pharmacy service has previously shown its effectiveness in a meta-analysis that reported increased attainment of therapeutic goals compared to usual care in HTN (odds ratio [OR] = 2.73 95% prediction interval [PI] 1.05–7.08), T2DM (OR 3.11 95% PI 1.17–5.88), and DLP (OR 1.91 95% PI 1.05–3.46) [17]. It is expected that the achievement of these objectives translates into lower morbidity and mortality due to CVDs [4–7].

MRF demand would increase professional resource use, which is likely to be associated with higher costs mainly derived from additional human capital. Thus, assessing the opportunity cost in a scenario where resources are scarce is critical to ensure efficiency in allocating public resources and value for money. This issue can be addressed by conducting an economic evaluation of relevant competing interventions in a health problem to assess whether the additional benefits are worth the additional cost, given additional resources [18]. In this context, previous economic evaluations have modeled the comparison of MRF to usual care in outpatients with CVDs. Studies have used the cost–utility approach, and most found the intervention to be dominant (improved benefits at lower cost), whereas others demonstrated the cost-effectiveness of the service [19–24]. Cost–utility analysis is adequate to evaluate CVDs, as it is useful in comparing interventions in other disease groups, thereby facilitating decisions concerning the allocation of resources [18]. In addition, not only can CVDs shorten life expectancy because of acute events, but they can also cause disability and, therefore, decrease the quality of life in the long term. Both aspects are captured in cost–utility analysis [18].

As there is evidence that MRF has a positive clinical and economic impact internationally, a trial named "Polaris" was undertaken to study the effect of adding pharmacist-led MRF to usual care in the Chilean public primary health care setting. To be aligned with governmental initiatives to prevent CVDs, MRF was undertaken in patients with HTN, T2DM, and DLP in this study. The purpose of this study was to perform a cost–utility analysis comparing the addition of MRF to usual care with usual care alone, from the public third-party payer perspective, considering a lifetime time horizon.

2. Materials and methods

This economic evaluation was mainly based on a cluster randomized controlled trial conducted in public primary health care centers. Details of the trial can be found in clinicaltrials.gov (NCT03502109). In brief, the trial followed up patients for 12 months from January 2018 to July 2019. A total of 283 patients from 12 primary care centers completed the study (146 patients who received MRF throughout seven centers and 137 patients who received usual care throughout six centers).

2.1. Target population

Patients were included if they were at least 65 years old, with five or more prescription medicines, were independent [25], were enrolled in the CVD prevention program [15], and had moderate (5–10%) or high (>10%) 10-year CVD risk according to the Framingham risk charts adapted to the Chilean population [26].

2.2. Intervention: MRF

The complete intervention is described in detail according to the template for intervention description and replication (TIDieR) methods (Appendix 1) [27]. However, the three main components are as follows:

1. Pharmacists training. Pharmacists were trained in an MRF method adapted to the local context [28], CVD prevention pharmacotherapy for the elderly, interview skills, health education, and interprofessional collaboration.
2. The service was delivered in a stepwise approach, starting with reviewing the patient's medical and pharmacy dispensing records. Then, in the first interview, a review of medications, including prescription and over-the-counter, was performed. Following this, an assessment concerning the knowledge of each medication, adherence, comorbidities, clinical therapy outcomes , and signs or symptoms of adverse drug reactions was performed. If required, laboratory examinations were requested from the clinical team caring for the patient [15]. With the information gathered from the interview and other sources, the pharmacists evaluated drug-related problems and developed a care plan. The plan was tailored to the patient's needs, adapting educational interventions, or implementing changes in the therapy agreed upon with the physician. Recommendations were prioritized, starting with medication adherence and educational needs if these were an issue. Then, if therapeutic objectives were not met, changes to therapy were suggested to the physician. Prioritization was not intended to replace clinical judgment, such as where other urgent issues required treatment. Each pharmacist had to interview the patient at least four times during the study period.
3. To aid in MRF provision, a trained practice change facilitator with experience in MRF and primary health care visited the pharmacists periodically. The visits' main objective was to conduct a fidelity assessment of the intervention delivery and a systematic evaluation of MRF provision barriers and facilitators [29]. Actions recommended by the facilitator were discussed with the pharmacist, the center manager, or both.

2.3. Comparator: usual care

The control group received four abbreviated interviews (15 min) to register study parameters and answer patients' questions as would occur in usual care. Both MRF and control patients had consultations with physicians, RNs, and dietitians every three to six months, depending on the individual 10-year CVD risk [15].

2.4. Outcomes

The primary outcomes were quality-adjusted life-years (QALY) and costs generated during a lifetime time horizon. Results are presented as an incremental cost-effectiveness ratio (ICER). A discount rate of 3% for QALY and costs was applied.

2.5. Decision-analytic model

A trial-based cost–utility analysis was conducted using a decision-analytic model, following the local economic evaluation

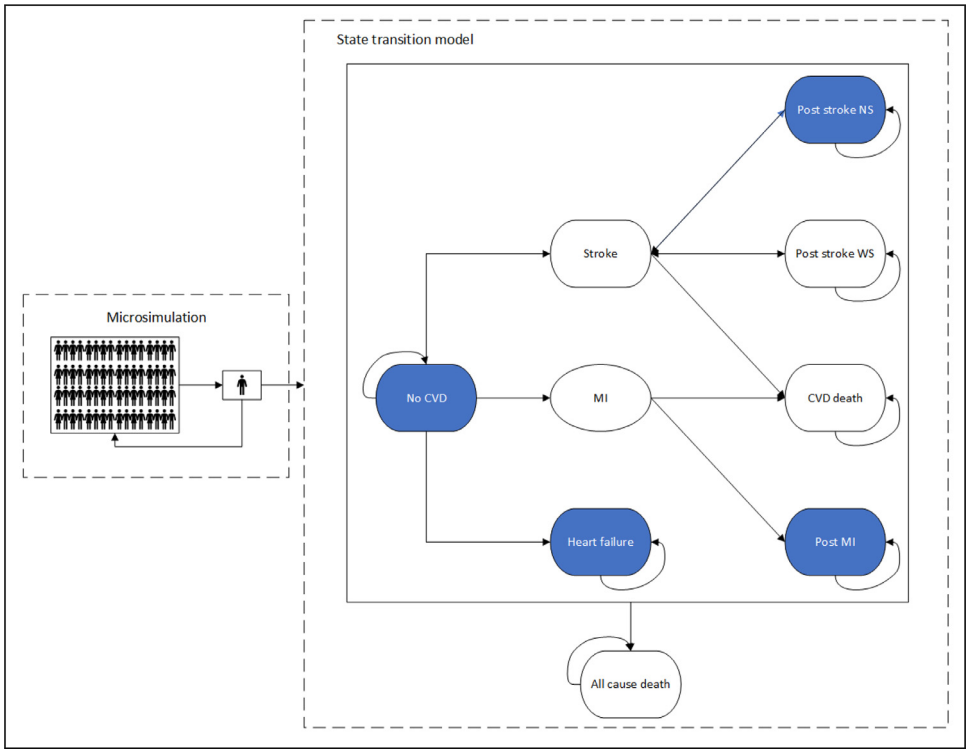

Fig. 1. Decision-analytic model.
A Monte Carlo simulation using a uniform distribution was used on the microsimulation phase to select patient-level data. Once in the state-transition model, a patient could start in one of the colored states according to their individual clinical history (a previous stroke or myocardial infarction or history of heart failure). MI indicates myocardial infarction; No CVD, no history of cardiovascular diseases (stroke, myocardial infarction or heart failure); NS, no sequelae; WS, with sequelae.

guideline [30]. Recommendations from the Second Panel on Cost-Effectiveness in Health and Medicine and the Consolidated Health Economic Evaluation Reporting Standards were used for reporting [31,32]. Also, clinical experts' inputs from the Department of Non-communicable Diseases of the Chilean Ministry of Health were obtained to support the model structure, assumptions, and inputs to ensure face validity. TreeAge Pro (v2021 R1.1) was used to perform calculations.

2.5.1. Model structure and assumptions

The structure was conceptualized based on inputs from a systematic review using the Cochrane methods [33]. The results are provided in Appendix 2 [19–23,34]. Inclusion criteria involved economic models of pharmacist-led interventions in CVD prevention.

The model was structured as a state-transition microsimulation with nine health states (Fig. 1). The selection of health states was informed by the articles identified in the systematic review (Appendix 2) and then adapted to incorporate CVD risk equations' events (see 2.5.2). Microsimulation was selected for two main reasons: to account for heterogeneity (different baseline characteristics) and to add memory to the model limiting the number of health states allowing for multiple events to occur (e.g. MI or stroke) and avoiding the modeling of several subgroups of varying sizes [35]. One of the trial's inclusion criteria was previous enrollment in the CVD prevention program. Being a program member implies that a patient may have one or more of the following conditions: previous CVD history, HTN, T2DM, DLP, or smoking history [15]. Each of these comorbidities modifies CVD risk leading to different outcomes, and are expected to be non-linear, therefore, the modeling approach was considered appropriate. In this context, each patient with its CVD risk factors (descriptive statistics are presented in Appendix 4) was resampled using a first-order Monte Carlo microsimulation. The microsimulation was performed using uniform distribution to produce 100,000 simulated patients. This approach allows the use of patient's unique history and events to be accordingly recorded. Stability was determined when the variance was ten times lower than the smallest difference between the groups [35].

Patients entered the model through a no CVD state, post-MI state, post-stroke with no sequelae state, or heart failure (HF) state depending on their individual clinical history (Table 1). Those who did not have any history of MI, stroke, or HF entered the model in the no CVD state. In each cycle, a patient could suffer either a stroke or an MI, be diagnosed with HF, die because of other causes, or survive without having any event. If patients suffered a stroke or an MI, they could die because of the event, die because of another cause, or survive. Those who survived a CVD event (stroke or MI) could have a recurrent event or survive until death from other causes. Other model assumptions are as follows:

- A one-year cycle length was used. This was chosen as the yearly CVD risk observed in the trial was 1.1%. In addition, five out of six models in the systematic review (Appendix 2) used a one-year cycle length.
- Delivery four times annually of the MRF intervention with its associated cost were assumed to be constant over the time horizon until death. This approach was used because the CVD prevention program includes yearly consultations with physicians, RNs, and dietitians throughout patients' lifetime [15].
- A patient who suffers a stroke may develop long-term sequelae, which affects the quality of life and cost.
- Because ischemic stroke is more frequent than other types of strokes (e.g., hemorrhagic stroke), it was assumed that all patients would suffer this type of event [36,37].
- Patients with HF were assumed to be in states I or II, according to New York Heart Association (NYHA) [38]. This was decided

Table 1
Model parameters.

Probabilities		
Probabilities	Point estimate [source]	Observations
Patient with no CVD history suffers a stroke	Calculated with Framingham equations and calibration coefficients [40]	
Patients with no CVD history suffer an MI	Calculated with Framingham equations for hard CHD events [41] discounting coronary death	Hard CHD events are defined as MI and coronary death
Patient with no CVD history is diagnosed with HF	Calculated with Framingham equations and calibration coefficients [40]	
Patient dies from a non-CVD related cause	According to sex and age extracting CVD death [46]	Appendix 4
Dies from MI	Calculated with mortality and hospitalization data according to sex and age [10,47]	Appendix 4
Survives stroke with sequelae (SE)	M: 0.24 (0.042) F: 0.38 (0.053) [36]	
Dies from stroke	Calculated with mortality and hospitalization data according to sex and age [10,47]	Appendix 4
Recurrent MI or stroke	Calculated with international equations for recurrent CVD [42]	
Utilities [44]		
Health state	Utilities (SE)	Observations
No CVD	0.86 (0.02)	Hypertension
MI	0.69 (0.036)	
Stroke	0.62 (0.068)	
HF	0.64 (0.056)	
Post MI	0.78 (0.015)	
Post stroke NS	0.68 (0.025)	
Post stroke WS	0.68 (0.025)	
Costs [46,47]		
Health state	Costs (SE)	Observations
No CVD	$102.79 (15.73)	Hypertension
MI	$1209.11 (185.07)	
Stroke	$2136.95 (327.08)	Hemorrhagic stroke costs were included in one-way sensitivity analyses [36]
HF diagnosis	$240.99 (36.89)	
HF follow-up	$114.40 (17.51)	
Post-MI	$268.07 (41.03)	
Post-stroke NS	$434.75 (66.54)	Hemorrhagic stroke costs were included in one-way sensitivity analyses [36]
Post-stroke WS 1st year	$1183.76 (343.53)	Hemorrhagic stroke costs were included in one-way sensitivity analyses [36]
Post-stroke WS	$434.75 (66.54)	Hemorrhagic stroke costs were included in one-way sensitivity analyses [36]
Trial cost data		
Medication review with follow-up [a]	$69.26 (2.65)	Local high and low-end salaries according to local regulations were included in the one-way sensitivity analysis [45]
Practice change facilitator [a]	$3.70 (0.57)	A scenario analysis was performed using these costs only the first year
Training [a]	$2.86 (0.44)	Cost accrued only in year one
Number of trial patients per starting health state		
Health state	MRF	Usual care
No CVD	117	113
MI	14	4
Stroke	7	11
HF	8	9

Notes: F indicates female; HF, heart failure; M, male; CHD. Coronary heart disease; MI, myocardial infarction; No CVD, No history of cardiovascular diseases (stroke, myocardial infarction or heart failure); NS, no sequelae; SE, standard error; WS, with sequelae. [a] Cost added only to the intervention group.

because patients in states III or IV are treated in secondary care [39].
- Patients with HF stayed in that state until they died from other causes.
- If patients suffered a CVD event (stroke or MI), they stayed in that state for one cycle.
- Half-cycle correction was used.

2.5.2. Probabilities

The relative effect of MRF was measured as changes in CVD risk factors, such as blood pressure, LDL, HDL and total cholesterol, among others. Additionally, baseline characteristics that modify CVD risk were also used, such as T2DM, smoking, HF, and previous CVD. A summary of the patient's baseline characteristics and comparative effectiveness of MRF to usual care is presented in Appendix 3. These individual risk factors were used to calculate the CVD risk probability of each patient. The equations for different types of patients were sourced from the systematic literature review (Appendix 2) and are described in Appendix 4. The Framingham equations were used to determine the chance of suffering an MI, stroke, or HF in patients with no CVD history [40,41]. If a patient had a history of CVD events, equations adjusted to this population were used [42]. After each cycle (one year), the probability of having an event was recalculated, adjusting for the patient's age and events accrued in the model. As the Framingham equations estimate the 10-year CVD risk, whereas recurrent CVD equations calculate it for two years [40–42], each probability was transformed into one-year values. Other transition probabilities were obtained from the literature and are described in Table 1 [43]. Calculations of probabilities other than CVD risk are explained and described in Appendix 4.

2.5.3. Utilities

Utility values were obtained from a systematic review of EQ-5D scores [44]. The average utility value was used for all given health states. For the no CVD health state, HTN values were used as a proxy. This was chosen because every patient in the trial had this risk factor. The values are presented in Table 1.

2.5.4. Costs

Costs were estimated from the public third-party payer perspective. MRF costs were obtained directly from the trial, including the time spent by pharmacists, physicians, and practice change facilitators [45]. Training costs were accounted for only in the first year. Trial costs details can be found in Appendix 5.

The costs associated with each health state were obtained from local sources [46,47]. For the no CVD state, HTN costs were assumed as a proxy on the same grounds as explained previously. Because HF costs were not reported in the data sources, resources were identified and measured from current clinical guidelines and valued using local price weights (Appendix 6) [39,46,47]. Costs per health state are presented in Table 1.

2.5.5. Currency, price date, and conversion

Results are reported in 2019 US dollars. For conversion from the original currency and update to 2019, the online tool developed by the Cochrane Economics Methods Group and the Evidence of Policy and Practice Information and Co-ordinating center was used [48]. Purchasing power parity values available from the International Monetary Fund were used [49].

2.5.6. Sensitivity analysis

One-way sensitivity analysis was performed for each fixed model parameter to assess the results' robustness (Table 1). In addition, time horizons of two and 20 years and discount rates

Table 2
Base case microsimulation outcomes per state.

Health state	QALY*		Costs[a]	
	MRF	Usual care	MRF	Usual care
No CVD	7.11	6.28	$1454	$751
MI	0.09	0.12	$167	$206
Stroke	0.05	0.07	$187	$254
HF	0.41	0.057	$126	$112
Post MI	0.94	0.57	$409	$195
Post stroke NS	0.05	0.07	$239	$57
Post stroke WS	0.32	0.55	$44	$352
All cause death	0	0	0	0
CVD death	0	0	0	0
Total	8.97	8.24	$2626	$1926
Incremental	0.73		$699	
ICER	$963 per QALY			

Notes: HF indicates heart failure; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction; MRF, medication review with follow-up; No CVD, No history of cardiovascular diseases (stroke, myocardial infarction or heart failure); NS, no sequelae; QALY, quality-adjusted life-year; WS, with sequelae.
[a] Total costs and QALYs were estimated and divided per 100,000 for better interpretability.

of 0% and 6% were analyzed [30]. Also, a scenario where practice change facilitator costs were accrued only in the first year was tried. This scenario was analyzed, as it has been described that pharmacists' learning curve requires this intervention for a finite amount of time [50]. In addition, a scenario where hemorrhagic stroke costs were also taken into account was performed (Appendix 7).

Probabilistic sensitivity analysis (PSA) was also conducted to assess joint parameter uncertainty using a second-order Monte Carlo simulation with 1000 iterations. Parameters included in the PSA were costs, utilities, and probabilities not recalculated in each microsimulation (non CVD death, MI death, stroke death, stroke sequelae). Beta distribution was used for utilities and probabilities, and gamma distribution for costs. A cost-effectiveness threshold of one gross domestic product per capita was used, as suggested by the local guideline [30], which according to the World Bank, was $15,923 in 2018 ($16,207 updated to 2019) [51].

3. Results

Base case analysis results are presented in Table 2. MRF was associated with more benefits compared to usual care (8.97 vs. 8.24 QALYs, respectively), as well as more cost ($2626 vs. $1926, respectively). These values translate into a gain of 0.73 QALYs and an additional cost of $699, leading to an ICER of $963 per QALY. Therefore, the ICER is below the cost-effectiveness threshold of $16,207 per QALY, and hence MRF is considered cost-effective compared to usual care.

Differences were found between the intervention and the comparator in terms of mortality. A graphical representation is provided in Appendix 8. In the MRF arm, the model predicted that 15.5% died because of CVDs, which increased to 20.4% in the comparator arm. Regarding the incidence of events, fewer patients suffered MI in the MRF arm than the comparator arm (17,561 and 22,274, respectively). The incidence of stroke was lower, but it followed a similar trend (11,344 in the MRF group and 15,573 for usual care). These differences in CVD mortality and events translate into changes in QALYs and costs. In terms of total QALYs, most were generated by patients who did not suffer a CVD event (79.3% for MRF and 76.2% for usual care), followed by those who survived an MI event 10.4% for MRF and 6.9% for usual care. In terms of costs, 55.4% ($1454) of costs in the MRF group were generated in the no CVD state, whereas in the control group it was 39.0% ($751).

3.1. Sensitivity analysis

One-way sensitivity analysis using a tornado diagram is illustrated in Appendix 9. Overall, no parameter was sensitive enough to deem the intervention as dominant or above the cost-effectiveness threshold. The ICER was reasonably sensitive to the effect of changes in pharmacist-physician salaries. Low-end salaries decreased the ICER by 55.5% ($534 per QALY), and high-end salaries increased it by 34.3% ($1293 per QALY). When hemorrhagic stroke costs were considered, the ICER decreased to $722 per QALY. In addition, when facilitator's costs were considered only in the first year, the ICER was similar to the base case ($910 per QALY). Evaluating shorter time horizons considerably changed the ICER. Particularly in the two year time horizon an ICER of $7009 per QALY was observed.

3.2. Probabilistic sensitivity analysis

The cost-effectiveness plane shows a graphical representation of 1000 iterations (Appendix 10). All the estimated ICERs lay in the northeast quadrant of the plane and below the cost-effectiveness threshold. This means that the intervention had a higher associated cost and increased health benefits compared to usual care considering parameter uncertainty. In addition, Fig. 2 provides the cost-effectiveness acceptability curve where the probability of MRF being cost-effective reached 100% using a cost-effectiveness threshold of $1290 per QALY, below the suggested setting's threshold of one gross domestic product per capita.

4. Discussion

Consistent with international evidence, our study showed that adding pharmacist-led MRF to usual care to prevent CVDs in primary health care patients from the public third-party payer perspective was cost-effective compared to usual care alone. MRF was associated with gains in QALYs at increased costs, mainly driven by fewer CVD events. With these results, the base case yielded an ICER of $963 per QALY, below the setting's cost-effectiveness threshold. Furthermore, the results were robust to one-way sensitivity analysis, scenario analysis, and PSA. One-way sensitivity analysis showed the model was sensitive to shorter time horizons but maintaining the cost-effectiveness of MRF over usual care alone. Consequently, allocating public resources to implement MRF represents value for money in a setting where CVDs are the leading cause of mortality.

To the best of our knowledge, this is the first published state-transition microsimulation model of professional pharmacy services in CVD outcomes [52–55]. We decided to use this approach to account for the heterogeneous population of the CVD program that included patients with primary and secondary prevention, with or without T2DM, among other characteristics that might impact CVD risk. For each patient, probabilities were re-estimated in each cycle according to CVD history, clinical parameters, and the model's events. Adding memory to the model is also relevant to evaluate CVDs as patients might have multiple events. Moreover, the model showed face validity in terms of mortality. In 2016, CVD deaths accounted for 17.6% of deaths in older adults, similar to that observed in the base case for the control groups (20.4%) [9]. The model prediction might be slightly higher as the equations used were calibrated for a Caucasian population [26]. The model was also conceptualized with inputs of a systematic review and the Department of Noncommunicable Diseases of the Ministry of Health. As a result, we modeled characteristics such as patients developing impairing sequelae after a stroke, which is relevant as the quality of life is dramatically affected in this population [44]. Stroke

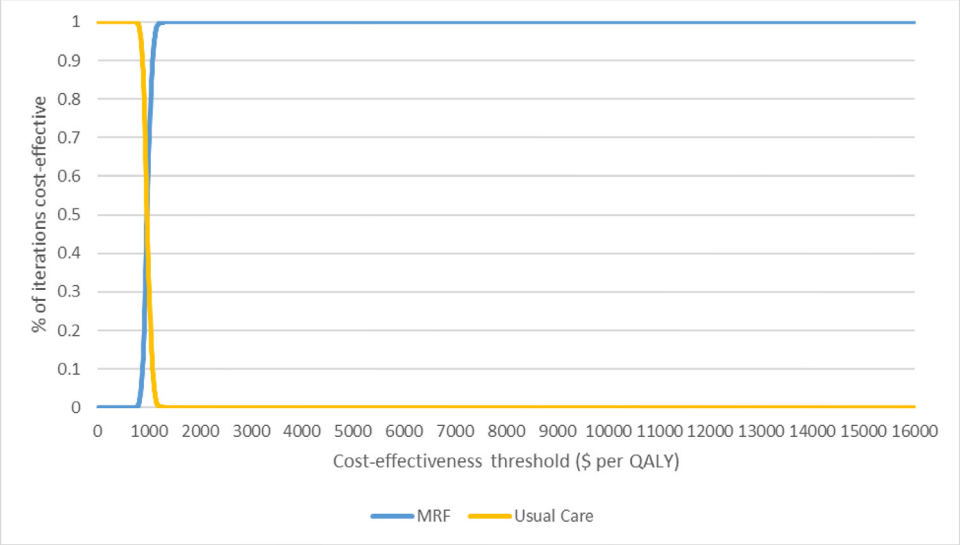

Fig. 2. Cost-effectiveness acceptability curve.
QALY indicates quality-adjusted life-year.

with sequelae has traditionally not been considered in other models [54,55].

In terms of perspective, the model adopted the third-party payer perspective instead of societal, as recommended by the local guideline [30]. Despite this, we believe that the inclusion criteria and study setting addressed this issue. It is not expected that productivity losses would significantly impact the overall estimated costs as patients included were at least 65 years old, therefore not in employment. The same can be assumed for carer costs as patients were independent. Also, the public sector provides health care at no cost for these patients. This includes consultations with different health care professionals, pathology examinations, and different treatments such as medications. Therefore, out-of-pocket expenditure was not expected to be significant either.

Other authors have used Markov models to evaluate the cost-effectiveness of these services. Markov models are a state-transition model that uses cohorts instead of patient-level data to perform projections over longer time horizons. Some of them have deemed the intervention cost-effective [19], whereas others as dominant [20–24]. This difference might be explained by MRF variations, particularly including complimentary prescribing. This addition makes the intervention more efficient, removing physician time constraints [20,22–24]. Marra et al. explored the cost-effectiveness of "full-scope" and "partial-scope" pharmacist intervention in blood pressure control [22]. The full-scope intervention included a patient visit to the pharmacy, MRF, and prescribing, whereas partial-scope intervention excluded prescribing. The primary cost-effectiveness driver was the change in blood pressure (18.3 mmHg "full-scope" vs. 7.6 mmHg "partial-scope"), which resulted in the full-scope intervention being dominant in 100% of the PSA iterations. On the other hand, in the partial-scope intervention, cost savings were not observed, although it achieved cost-effectiveness in 100% of the iterations [22]. Apart from that, including only patients with increased CVD risk, such as those on secondary CVD prevention, might determine the difference between dominance and cost-effectiveness of MRF. An example is an intervention in the Netherlands focused on lipid-lowering medications [21]. The researchers found that MRF was dominant for secondary prevention, and despite maintaining higher incremental effects for primary prevention, this was achieved at an increased cost. When primary prevention patients were evaluated, an ICER of €4585 per QALY was observed, having 91.7% of the PSA iterations under a cost-effectiveness threshold of €20,000 per QALY. Similar results to the Dutch study were observed in a Markov model based on a trial that included patients with more than 20% 10-year CVD risk, yielding dominance across all scenarios, generating more QALYs (0.18) at lower costs (4770 Canadian dollars) [23,24]. Another economic evaluation examined the effect of MRF in improving blood pressure in different risk scenarios based on T2DM status, smoking history, and cholesterol/body mass index profile of patients [19]. Using a Markov model, they found that the highest risk group had the lowest ICER ($13,418 per QALY), whereas the low-risk group was not cost-effective ($68,298 per QALY) using a cost-effectiveness threshold of $50,000 per QALY. These factors might explain our evaluation results where dominance was not achieved, as independent prescribing was not included, and they were based mainly on primary prevention patients (82.0%), including patients with moderate (5–10%) 10-year CVD risk.

As data was sourced from a single country, there are generalizability issues to other settings that need to be noted. First, differences of usual care between settings have been described as an issue by a systematic review of MRF economic evaluations hindering generalizability [52]. While usual care in our study comprised consultations with physicians, dietitians, and RNs, another study reported using a home blood pressure monitor and different medication administration aids, stressing the importance of usual care description and assessment for appropriate comparison and transferability of the results [56,57]. Second, patients included in our trial were users of the public health care system with limited access to treatments and medications [58]. Therefore, comparisons with other countries where this is not an issue (particularly in terms of resource use) should be considered. Third, the Chilean health care system segregates patients by age and income, resulting in public patients being older and from low socioeconomic status [59,60]. On our cluster randomized controlled trial, 33% of the study population had completed primary studies, and 45% did not have any kind of formal studies. As evidence has shown that socioeconomic status might be linked to stroke, MI, and poor medication adherence, we believe that these issues, might in part, lead to the results observed in this trial, particularly in terms of incremental QALYs as interventions for these patients might have more significant benefits [61,62].

Our model results suggest that MRF is a feasible and efficient addition to usual care to prevent CVDs in primary care. Currently, the leading mortality cause are CVDs, particularly MI and stroke, generating an estimated economic toll of 1.5–1.8% of the gross do-

mestic product [11,12,14]. Therefore, adding cost-effective interventions to prevent CVDs is critical for evidence-based health policy development, suggesting that Chilean policymakers should consider MRF. To estimate eligible patients at a national level, data of nine out of 12 recruited primary care centers was available, where 26,755 patients were identified as eligible for the trial. These patients represented 39.5% of the total patients enrolled in the CVD prevention program in those centers. Extrapolating these numbers nationwide translates into an estimated total of 928,696 patients that would be eligible at a national level [63]. Additionally, this service encourages interprofessional collaboration and patient involvement in treatment decisions to improve patients' quality of life and prevent long-term disability and mortality. These factors align with the Chilean CVD prevention program and the family medicine model recommended by the World Health Organization (WHO), making MRF fit the setting's requirements [15,56]. Moreover, the WHO statement about pharmacy services for primary care recommends MRF as one of pharmacists' main interventions [64].

As models are a simplification of reality, this study was not exempt from limitations: Trial hospitalizations were only partially registered precluding their use in the model for costing purposes and CVD risk estimation. Furthermore, the equations used to calculate CVD event probabilities were not calibrated to the Chilean population. Even though calibrated Framingham equations are available, they do not capture events such as stroke and HF, limiting their applicability to the model [26]. In addition, a sensitivity analysis of the estimated CVD risk was not performed, as this parameter was calculated in each microsimulation according to age, trial recorded clinical history and CVD events occurring in the modelled time horizon. The model also assumed that patients diagnosed with HF were classified as I or II according to the NYHA classification. However, it was possible that patients with decreased functional status could also be treated in the study setting, which would result in an underestimation of the cost associated with experiencing HF. In terms of data availability, complications associated with T2DM or renal disease could not be included as local data is lacking. Moreover, the model used fixed parameters, such as all-cause mortality, which for people aged 85 years and older it was only available as a combined parameter. As per utilities, local estimates were not available. Instead, an international catalog was used, introducing uncertainty to these parameters as utilities differ between countries and settings [44]. Regardless, the sensitivity analysis showed that the results were robust to changes in utilities. In terms of the control group, patients could ask the pharmacist treatment-related questions as an on-demand service reflecting usual care practice. Although this might impact the control group homogeneity, it represents the setting's standard practice enhancing external validity. Finally, the estimated costs of each health state might be underestimated, as prices established by the Chilean government have been described as undervalued. In 2014, a study showed that these prices covered the actual billing costs by 56% [65]. Nonetheless, this assumption is conservative as higher costs per health state would offset MRF costs minimizing its impact on the results.

5. Conclusions

This economic evaluation deemed MRF as a cost-effective intervention preventing CVD events compared to usual care in the Chilean primary health care setting from the public third-party payer perspective. The model showed that MRF decreased CVD events such as MI and stroke, resulting in lower mortality and accruing more QALYs at higher costs compared to usual care, yielding a robust ICER below the suggested cost-effectiveness threshold. Based on these results, MRF is considered value for money and hence, recommended for future funding of new health technologies.

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Submission declaration

Each author states that this manuscript is not currently under consideration by any other journal and have approved its contents.

Ethics approval

This study was approved by the ethics committee of each Health Service Administration and by the University of Technology Sydney Human Research Ethics Committee (ETH17–1346).

Others

The original trial is registered in clinicaltrials.gov (NCT03502109).

Declaration of Competing Interest

None.

CRediT authorship contribution statement

Antonio Ahumada-Canale: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft. **Constanza Vargas:** Conceptualization, Methodology, Validation, Writing – review & editing. **Francisco Martinez-Mardones:** Conceptualization, Data curation, Investigation, Project administration, Writing – review & editing. **José Cristian Plaza-Plaza:** Conceptualization, Resources, Supervision, Writing – review & editing. **Shalom Benrimoj:** Conceptualization, Methodology, Resources, Supervision, Validation, Writing – review & editing. **Victoria Garcia-Cardenas:** Conceptualization, Resources, Supervision, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found in the online version, at doi:10.1016/j.healthpol.2021.09.004.

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