UTS UNIVERSITY OF TECHNOLOGY SYDNEY

# Clinical impact of medication reviews with follow-up in cardiovascular older adult patients

**Thesis**

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Doctor of Philosophy
Graduate School of Health, Discipline of Pharmacy:
University of Technology Sydney

**CERTIFICATE OF ORIGINAL AUTHORSHIP**

I, Francisco Martinez Mardones, declare that this thesis is submitted in fulfilment of the requirements for the award of Doctor of Philosophy in the Graduate School of Health at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

This document has not been submitted for qualifications at any other academic institution.

This research is supported by the Australian Government Research Training Program.

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# Abstract

**Background:** In Chile, cardiovascular disease (CVD) risk factors are controlled in as few as 30% of cases. Pharmacist-led medication reviews with follow up (MRF) have shown effectiveness under these conditions. We postulate that providing MRF in primary care in Chile could improve the control of CVD.

**Objectives:** To evaluate the effect of MRF on CVD in primary care by assessing the clinical effect of MRF on older patients with CVD risk in primary care in Chile.

**Methodology:** A systematic literature search was conducted to explore literature on the effect of MR on ambulatory CVD risk patients, including randomised and cluster randomised trials (c-RCT). Meta-analyses used the odds ratio (OR) for therapeutic goals and raw differences for continuous data, with 95% prediction intervals (PI) to account for heterogeneity.

A c-RCT was then conducted in primary care centres in a metropolitan region of Chile. Older patients with moderate to high CVD risk and five or more medications were recruited from a CVD risk program and received either pharmacist-led MRF or usual care for a year. Generalised estimating equations adjusted for covariates were used for analysis during each visit. A sub-analysis of patients with chronic kidney disease (CKD) was conducted.

**Results:** The meta-analyses included 69 studies with a total of 11 644 patients. Demographic characteristics were similar between studies. MRF increased the control of hypertension (OR 2.73 [95% PI 1.05, 7.08]), type 2 diabetes mellitus (OR 3.11 [95% PI 1.17, 5.88]) and cholesterol (OR 1.91 [95% PI 1.05, 3.46]).

In the Polaris trial, 324 patients from 12 primary care centres (174 in the MRF group and 150 in the usual care group, 6 centres each) received, on average, four visits by pharmacists in one year. Significant effects were found for the control of hypertension (OR 4.37 [2.54–7.51]), cholesterol (OR

3.67 [2.13–6.33]), type 2 diabetes (6.97 [3.69–13.2]) and medication adherence (OR 6.60 [1.36–31.9]) as well as for the number of medications (-0.86 [-1.14 to -0.58]) and CVD risk (-2.27 [-2.84 to -1.69]). In total, 159 patients had CKD (71 in the usual care group and 88 in the MRF group). The OR for hypertension control was 8.41 (3.46–20.4), with reductions in systolic blood pressure (-15.3 mmHg [-20.3 to -10.3]), serum potassium (-0.50 mEq/L [-0.65 to -0.35]), the albumin-to-creatinine ratio (-53.1 mg/g [-92.3 to -13.9]) and LDL cholesterol (-27.8 mg/dL [-37.6 to -17.9]).

**Conclusion:** This work provides local evidence to support the implementation of MRF in primary care in Chile. Including pharmacists in programs for CVD could improve the quality of care for older adults with polypharmacy.

# Dissemination of Research

## Peer-reviewed publications

1. **SYSTEMATIC REVIEW AND META-ANALYSIS OF MEDICATION REVIEWS CONDUCTED BY PHARMACISTS ON CARDIOVASCULAR DISEASES RISK FACTORS IN AMBULATORY CARE.**

   **Francisco Martínez-Mardones**, Fernando Fernandez-Llimos, Shalom I. Benrimoj, Antonio Ahumada-Canale, José Cristian Plaza-Plaza, Fernanda S. Tonin, Victoria Garcia-Cardenas.

   Journal of the American Heart Association (JAHA). 2019;8: e013627. DOI: https://doi.org/10.1161/JAHA.119.013627

2. **STANDARDS IN MEDICATION REVIEW: AN INTERNATIONAL PERSPECTIVE.**

   Rose, O., Cheong, V.-L., Dhaliwall, S., Eislage, K., Erzkamp, S., Jorgenson, D, **Martínez-Mardones, F**, Luetsch, K. (2020). *Canadian Pharmacists Journal / Revue Des Pharmaciens Du Canada*, *153*(4), 215–223. https://doi.org/10.1177/1715163520929665

3. **PRIMARY HEALTH CARE PHARMACISTS AND VISION FOR COMMUNITY PHARMACY AND PHARMACISTS IN CHILE**.

   **Martinez-Mardones F**, Ahumada-Canale A, Gonzalez-Machuca L, Plaza-Plaza JC.

   Pharm Pract (Granada) [Internet]. 2020 Aug.28 [cited 2020Aug.31];18(3):2142.

4. **ECONOMIC EVALUATIONS OF PHARMACIST-LED MEDICATION REVIEW IN OUTPATIENTS WITH HYPERTENSION, TYPE 2 DIABETES MELLITUS, AND DYSLIPIDAEMIA: A SYSTEMATIC REVIEW.**

   Ahumada-Canale, A., Quirland, C., **Martínez-Mardones, F.J.** et al. Eur J Health Econ (2019) 20: 1103.

5. **SUBMITTED - CLINICAL IMPACT OF MEDICATION REVIEWS WITH FOLLOW-UP IN CARDIOVASCULAR OLDER PATIENTS IN PRIMARY CARE: THE POLARIS TRIAL, A CLUSTER-RANDOMIZED CONTROLLED TRIAL (**CIRC CARDIOVASC QUAL OUTCOME (**CIRCCQO/2020/006575)).**

**Francisco Martínez-Mardones**, Shalom I. Benrimoj, Antonio Ahumada-Canale, José Cristian Plaza-Plaza, Victoria Garcia-Cardenas.

6. **SUBMITTED - MEDICATION REVIEWS WITH FOLLOW UP ON OLDER PATIENTS WITH CHRONIC KIDNEY DISEASE AND CARDIOVASCULAR RISK FACTORS: A CLUSTER RANDOMIZED CONTROLLED TRIAL (**EUR HEART J **(EURHEARTJ-D-20-00680))**

   **Francisco Martínez-Mardones**, Shalom I. Benrimoj, Antonio Ahumada-Canale, José Cristian Plaza-Plaza, Pía Venegas-Araneda, Victoria Garcia-Cardenas.

7. **SUBMITTED - COST-UTILITY ANALYSIS OF A MEDICATION REVIEW FOR CARDIOVASCULAR OUTCOMES: A MICROSIMULATION MODEL.**

   Ahumada-Canale A, Vargas C., **Martinez-Mardones FJ**, Plaza-Plaza JC, Benrimoj S, Garcia-Cardenas V.

8. **SUBMITTED - MEDICATION REVIEW WITH FOLLOW-UP FOR CARDIOVASCULAR OUTCOMES: A TRIAL-BASED COST-UTILITY ANALYSIS.**

   Ahumada-Canale A, Vargas C., Balmaceda C. **Martinez-Mardones FJ**, Plaza-Plaza JC, Benrimoj S, Garcia-Cardenas V.

## Authorship on national clinical guidelines

1. **2017-2018 TECHNICAL GUIDELINES FOR THE NATIONAL CARDIOVASCULAR PROGRAM.** Ministry of Health, Chile. Web resource: http://www.repositoriodigital.minsal.cl/bitstream/handle/2015/862/OT-PROGRAMA-DE-SALUD-CARDIOVASCULAR_05.pdf
2. **2017-2018 CLINICAL GUIDELINES FOR THE PHARMACOLOGICAL TREATMENT OF TYPE-2 DIABETES MELLITUS.** Ministry of Health, Chile. Web resource: https://diprece.minsal.cl/wrdprss_minsal/wp-content/uploads/2018/01/DIABETES-MELLITUS-TIPO-2-1.pdf

3. **2018-2019 CLINICAL GUIDELINES FOR THE PHARMACOLOGICAL TREATMENT OF HYPERTENSION.** Ministry of Health, Chile. Web resource: https://diprece.minsal.cl/garantias-explicitas-en-salud-auge-o-ges/guias-de-practica-clinica/hipertension-arterial-primaria-o-esencial-en-personas-de-15-anos-y-mas/recomendaciones/
4. **2018 TECHNICAL GUIDELINES FOR THE IMPLEMENTATION OF MEDICATION REVIEWS IN PRIMARY CARE**. Ministry of Health, Chile. Web resource: https://www.sscoquimbo.cl%2Fgob-cl%2Fdocumentos%2Ffiles%2Finred%2Ffarmacia%2F28-05-2018%2FAtencion%2520Farmaceutica%2520y%2520SFT%2520en%2520APS%25202018.pdf&usg=AOvVaw1TAA8qfegTMfI0vakLIznd
5. **2019 CLINICAL GUIDELINES FOR THE MANAGEMENT OF CONSERVATIVE (NON-DIALYTIC) TREATMENT IN PATIENTS WITH SEVERE CHRONIC KIDNEY DISEASE**. Ministry of Health, Chile. Web resource: https://diprece.minsal.cl/garantias-explicitas-en-salud-auge-o-ges/guias-de-practica-clinica/tratamiento-conservador-no-dialitico-de-la-enfermedad-renal-cronica/recomendaciones/
6. **2019-2020 DEFINITIONS FOR PHARMACEUTICAL SERVICES IN PRIMARY AND SECONDARY CARE, STATISTICAL REGISTRY MANUAL**. Ministry of Health, Chile. Web resource: http://estadisticas.ssosorno.cl/estadisticas/2019/manuales/Manual%20Series%20REM%20V1.0%202019.pdf
7. **2019 MANUAL FOR CONDUCTING MEDICATION REVIEWS WITH FOLLOW-UP IN PRIMARY CARE CENTERS**. Ministry of Health, Chile. Web resource: http://quimica.uc.cl/images/noticias/2019/2019_07_12_MANUAL-SEGUIMIENTO-FARMACO-TERAPEUTICO1_compressed.pdf
8. **2020 STRATEGY FOR PATIENT-CENTERED SEAMLESS CARE TO PROMOTE, PREVENT AND MANAGE CHRONIC CONDITIONS IN MULTIMORBIDITY.** Ministry of Health, Chile.

## Conferences and poster presentations

1. Patient Centered Meeting (PCM) on Diabetes, Dyslipidemia and Hypertension. 17 CME credits. October 31 to November 3, 2019, Vienna, Austria. E-Poster:

   **PHARMACIST LED MEDICATION REVIEWS WITH FOLLOW-UP IN OLDER ADULTS ATTENDING PUBLIC PRIMARY HEALTH CARE CLINICS IN CHILE (POLARIS study preliminary results)**

   **Francisco Martínez-Mardones**, Shalom I. Benrimoj, Antonio Ahumada-Canale, José Plaza-Plaza, Victoria García-Cárdenas.

2. 2º *Simpodader Internacional*. June 29 – 30, 2018, Granada, Spain. Poster:

   **A SYSTEMATIC REVIEW AND META-ANALYSIS OF PHARMACISTS CONDUCTED MEDICATION REVIEWS ON CARDIOVASCULAR DISEASES RISK FACTORS IN THREE AMBULATORY CARE SETTINGS**

   **Martínez Mardones, Francisco**; Ahumada, Antonio; Garcia-Cardenas, Victoria; Benrimoj, Shalom; Plaza-Plaza, Cristian.

3. 2º *Simpodader Internacional*. June 29 – 30, 2018, Granada, Spain. Poster:

   **ECONOMIC EVALUATIONS OF PHARMACIST-LED MEDICATION REVIEW IN CARDIOVASCULAR DISEASES RISK FACTORS: SYSTEMATIC REVIEW**

   Ahumada, Antonio; **Martínez Mardones, Francisco**; Garcia-Cardenas, Victoria; Benrimoj, Shalom; Plaza-Plaza, Cristian.

4. 1st International Conference Pharmacy practice research: postgraduate students, postdoctoral fellows and supervisor's symposium conference organised by the FIP special interest group on pharmacy practice research. June 25 – 27, 2018, Lisbon, Portugal.

   **PHARMACIST-LED MEDICATION REVIEW WITH FOLLOW-UP ON PRIMARY CARE CARDIOVASCULAR OLDER ADULT PATIENTS (POLARIS study trial design)**

   **Martínez Mardones, Francisco**; Ahumada, Antonio; Garcia-Cardenas, Victoria; Benrimoj, Shalom; Plaza-Plaza, Cristian.

5. 1º *Simpodader Internacional*. June 24 – 26, 2016, Granada, Spain. Poster:

   *DESARROLLO E IMPLEMENTACIÓN DE UN PROGRAMA DE SEGUIMIENTO FARMACOTERAPÉUTICO EN USUARIOS ADULTOS MAYORES POLIMEDICADOS DE UN CENTRO DE ATENCIÓN PRIMARIA DE SALUD* / **DEVELOPMENT AND IMPLEMENTATION OF A MEDICATION REVIEW WITH FOLLOW-UP PROGRAM IN POLYMEDICATED OLDER ADULT PATIENTS IN A PRIMARY CARE CENTER.**

   **Martínez Mardones, Francisco**; Plaza-Plaza, Cristian; Palma, Lorena.

## Invited presentations

1. **MEDICATION ADHERENCE AND THE COVID-19 PANDEMIC.** Cardiovascular Webinar, Chilean Heart Month, 26 August 2020. Ministry of Health.
2. **CLINICAL PHARMACISTS IN PRIMARY HEALTH CARE: OFFICIAL POSITION OF THE MINISTRY OF HEALTH**. Primary care pharmacy meeting, 4–5 October 2018, La Frontera University and South-Araurania Health Service Coordinator, Temuco, 9th region, Chile.
3. **PROPOSED ROLE FOR PHARMACISTS IN THE NATIONAL CARDIOVASCULAR CARE PROGRAM**. Yearly national meeting of the Ministry of Health for the cardiovascular care program, 3–6 June 2018, Santiago, Chile.
4. **IMPLEMENTING MEDICATION REVIEWS WITH FOLLOW-UP IN PRIMARY HEALTH CARE**. Pharmaceutical meeting of South-Eastern Metropolitan Health Service Coordinator, 15 July 2017, Santiago, Chile.
5. **PHARMACOTHERAPY FOR CARDIOVASCULAR DISEASES: ROLE OF THE PRIMARY CARE PHARMACIST**. Pharmaceutical meeting of Viña del Mar-Quillota Health Service Coordinator, 21 April 2017, Villa Alemana, 5th region, Chile.

6. **PHARMACEUTICAL SERVICES IN PRIMARY CARE: HOW TO INITIATE CONTACT WITH PATIENTS**. Pharmaceutical meeting of Chile's Health Service Coordinator, 30–31 October 2016, Castro, 10th region, Chile.

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The Polaris trial was supported by the Chilean Ministry of Health and the South-Eastern, South and Occidental Metropolitan Health Services coordinators. This project was only possible with the participation of several municipalities: La Granja, Puente Alto, Pudahuel and San Bernardo. They allowed their pharmacists to participate in the training and perform the intervention while providing resources such as laboratory tests, time with physicians and private attention zones.

I would like to thank Karina Castillo and Melanie Paccot for their role in the support of the Ministry of Health and the dissemination of this work as well as Lorena Palma and Daniela Núñez for supporting this research since my bachelor's thesis on the Municipality of Puente Alto. I would also like to thank all pharmacists that participated in the Polaris trial, especially my classmates and friends, Felipe and Nadia.

Lastly, thanks to my family for all their support, even in difficult times. To my partner in life, Cristina, thank you for your everlasting support and for joining me in this foreign country.

# Preface

This thesis is presented in fulfilment of the doctoral degree (Doctor of Philosophy) requirements of the Graduate School of Health, University of Technology Sydney, Australia.

This document was structured as a thesis by compilation. Chapter 1 presents a synopsis of the general approach of this thesis and research. Chapter 2 provides a background for cardiovascular diseases and contains the published systematic review and meta-analysis of pharmacist-led medication reviews and interventions, which analyse the international literature and contextualise the research. Chapter 3 contains information related to the burden of cardiovascular diseases in Chile and the role of pharmacists in the health system. Chapter 4 presents the methods and rationale for the Polaris trial, a cluster-randomised controlled study on medication reviews with follow-up in older adults with cardiovascular diseases. It was conducted in Chile as a collaborative effort between UTS and the Pontifical Catholic University of Chile. Chapters 5 and 6 contain papers on the clinical outcomes of the Polaris trial that were submitted to journals. Chapter 7 discusses the results and limitations. Chapter 8 presents the conclusions that arise from this research.

Francisco Martinez Mardones is the primary author of the publications. Co-authors contributed to the conception or design of the work, data collection, data analysis and interpretation, and/or revision of the manuscripts.

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# Abbreviations

ACR: albumin-to-creatinine ratio

ADR: adverse drug reaction

AF: atrial fibrillation

BMI: body mass index

BP: blood pressure

CESFAM: family health centre (*centro de salud familiar*)

CKD: chronic kidney disease

CI: confidence interval

c-RCT: cluster-randomised control trial

CVD: cardiovascular disease

DALY: disability-adjusted life year

DBP: diastolic blood pressure

DLP: dyslipidaemia

DRP: drug-related problem

eGFR: estimated glomerular filtration rate

FG: fasting glucose

FONASA: national health insurance (*fondo nacional de salud*)

GEE: generalised estimating equation

GFR: glomerular filtration rate

GP: general practice

HbA1c: glycated haemoglobin

HDL: high-density lipoprotein cholesterol

HF: heart failure

HR: hazard ratio

HT: hypertension

ICC: intracluster correlation coefficient

ISAPRE: social security health institution (*instituciones de salud previsional*)

ITT: intention to treat

K: potassium serum level

LDL: low-density lipoprotein cholesterol

MAR: missing at random

mEq/L: milliequivalents per litre

mg/dL: milligrams per decilitre

mg/g: milligrams per gram

MHSC: Metropolitan Health Services Coordinator

MI: myocardial infarction

mL/min/1.73 $m^2$: millilitres per min per 1.73 square meters

mmHg: millimetres of mercury

MR: medication reviews

MRF: medication review with follow-up

Na: sodium serum levels

NCCP: national cardiovascular care program

NCD: non-communicable diseases

NHSC: National Health Services coordinator

OR: odds ratio

OECD: Organisation for Economic Co-operation and Development

PCNE: Pharmaceutical Care Network Europe

PPS: professional pharmacy service

PI: prediction interval

PP: per protocol

SBP: systolic blood pressure

T2DM: type 2 diabetes mellitus

TC: total cholesterol

TG: triglyceride

TIDieR: Template for Intervention Description and Replication

USD: United States dollars

WHO: World Health Organization