

Barriers to adherence to secondary prevention therapy in patients with ischemic heart disease: A cross- sectional study of a Mexican reference center

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Abstract

Background and objectives: Inadequate adherence has been recognized as a constant determinant in the overall burden of ischemic heart disease, particularly in countries with higher income-health inequalities, such as Mexico. The overall impression is that the lack of population-based epidemiological data and low public awareness may account for this problem. This study aimed to determine the level of adherence to secondary cardiovascular prevention therapy in a tertiary hospital in Mexico City and identify the barriers contributing to medication nonadherence. **Methods:** A cross-sectional study was conducted in the cardiology outpatient department between August 2018 and February 2020. Participants were asked about socio-demographic data, the MMAS-4, and an interview regarding reasons for nonadherence. **Results:** A total of 991 patients were included, with a median age of 65 (58,72) years old. Inadequate adherence to treatment was reported by 70.3%, with forgetfulness as the most frequent cause (55.4%). Patients on combined pharmacological therapy with PCI or CABG were more adherent than those on optimal medical therapy alone. A higher proportion of patients in the inadequate group were in NYHA classes II and III. Low educational level and the use of optimal medical treatment alone were predictors for poor adherence. **Conclusion:** These findings provide an initial framework of the current situation of adherence to secondary prevention therapy in Mexico, highlighting the value of promoting national consensus on medication adherence to move towards a population-based strategy to reduce cardiovascular disease burden.

1. Introduction

Advances in diagnostic and therapeutic strategies have improved ischemic heart disease (IHD) outcomes over the last decades.¹ Particularly, the use of evidence-based pharmacological therapy (β blockers, renin-angiotensin-aldosterone system blockers, statins, and antiplatelet drugs) has been demonstrated to improve long-term prognosis by reducing mortality by up to 40%, stabilizing disease progression, reducing the risk of recurrence, and enhancing functional capacity.^{2,3} Nonetheless, despite these advancements, IHD remains the leading cause of morbidity and mortality in countries of all income groups,⁴ reflecting the suboptimal implementation of secondary prevention strategies and subsequent burden on global healthcare services. Likewise, the use of such medications is still low, with a nonadherence prevalence ranging from 40 to 80%,⁵ exhibiting health disparities among countries and socioeconomic status.⁴ In this context, most available data on medication adherence proceeds from developed countries and clinical trials,⁶ which may not reflect the actual situation of developing countries, especially in those with higher income-health inequalities. Thus, medication-taking behavior may require national consensus and individualized tools to address the problem in a population-based manner to overcome socioeconomic, cultural, and ethnic barriers. Although data exist on medication adherence for secondary prevention of cardiovascular disease (CVD) in developing countries,

to the best of our knowledge, no study has explored potential reasons for nonadherence in Mexico. This study aimed to determine the level of adherence to secondary prevention therapy in patients with IHD and dyslipidemia in the National Institute of Cardiology "Ignacio Chávez" and identify the key barriers contributing to medication nonadherence.

2. Materials and methods

2.1. Study design and setting

A single-center prospective cross-sectional study was conducted between August 1st, 2018, and February 28th, 2020 in the cardiology outpatient department of the National Institute of Cardiology "Ignacio Chávez" a tertiary hospital in Mexico City that provides high specialty cardiovascular care to uninsured population. This study complied with the edicts of the Declaration of Helsinki and was approved by the Institutional Ethics Board (REF. INCAR-DG-DI-CI-003-2022). Informed consent was obtained from all patients. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions

2.2. Study population and variables

The inclusion criteria for participating in the study were patients between 18 and 90 years old with a diagnosis of IHD and/or dyslipidemia on pharmacological treatment for secondary CVD prevention. IHD was established by the presence of at least one imaging study (Echocardiography, computed tomography, coronary angiography, magnetic resonance imaging, SPECT or PET) performed at the institution confirming the presence of coronary atherosclerotic disease and/or history of acute myocardial infarction documented in the institution's electronic or physical medical records.

Dyslipidemia was determined by at least one laboratory documenting total cholesterol levels > 200 mg/dl or triglyceride levels > 150 mg/dl. While pharmacological treatment for secondary CVD prevention was defined by the use of at least one of the following drugs: a) angiotensin-converting enzyme inhibitors: captopril, enalapril, ramipril, or lisinopril; b) angiotensin II receptor inhibitors: candesartan, losartan, irbesartan, telmisartan, valsartan, or olmesartan; in addition to at least one HMG-CoA reductase inhibitor (statins): pravastatin, atorvastatin, rosuvastatin or simvastatin.

Patients were excluded if they were pregnant, had a diagnosis of major depression, psychosis, dementia, or other mental illnesses, or were from other institutions.

2.3. Screening study and data collection

Screening followed a two-phase strategy to gather data on medication adherence. First, patients were asked to self-complete a questionnaire designed by the research team. This survey consisted of the Morisky Medication- Taking Adherence Scale (MMAS-4)³⁴ and questions regarding demographic and identification data including age, ID number, sex, education level, place of residence (rural or urban), and body mass index. MMAS-4 license was obtained. Instructions on its filling were provided by a trained medical undergraduate. After questionnaire completion, a directed interview was conducted by the cardiology attending physician or resident of the institution in the office during the medical consultation to discern reasons for nonadherence. New York Heart Association (NYHA) Functional Classification was also determined at this point. Once the interview was completed, electronic medical records were reviewed to complete information on reperfusion therapy, the number of emergency visits and major cardiovascular events (MACE) in the last two years, along with the most recent laboratory findings including hemoglobin, creatinine, total cholesterol, triglycerides, and HbA1c levels.

Patients were randomly selected prior to appointments from the attending physician's agenda to address potential bias. Electronic medical records were reviewed afterward to validate inclusion criteria fulfillment.

All data were recorded in predesigned files for data management and analysis by a research team member. Databases were encrypted in password-protected files, limiting their access to research staff only.

2.4. Inadequate adherence cause

Patients' reasons for inadequate adherence were classified into one or more of the following categories: economic (nonadherence due to lack of financial resources that prevented medication purchase or follow-up by the patient); forgetfulness (failure to remember medication taking, as well as complex medication schedules); prescription loss (paper medical prescription mislead granted by an institution provider), physician-related (lack of therapy regimen explanation or inadequate information regarding treatment importance); prescription misunderstanding (patient was aware of the established medications and their importance but changed schedules, dosages, medications, or did not follow prescription by removing or adding other medications); and patient preference (inadequate adherence was the result of their decision despite having knowledge of its importance and that the physician made an adequate explanation of their treatment).

2.5. Statistical analysis

In the present study to determine inadequate adherence level in our institution, a sample size of at least 940 patients was calculated based on an expected inadequate adherence level of 55% with a power of 80% and a two-tailed 5% significance level, considering a 20% anticipated patient dropout. Initially, a 24-month inclusion period was anticipated. However, enrollment concluded in February 2020 when the calculated sample size was reached.

Categorical variables are expressed as frequency and percentages, whereas continuous variables are reported as mean and standard deviation (SD), or median and quartiles 1 and 3 according to their distribution. Continuous variable distribution was determined using the Kolmogorov-Smirnoff test.

According to the results of the MMAS-4, patients were classified into two groups: adequate and inadequate adherence to treatment for statistical analysis. Bivariable analysis was initially performed using the chi-squared test or Fisher's exact test for categorical variables and Student t or Mann Whitney U for continuous variables to generate unadjusted 2-sided p values. Multivariable analysis was then conducted using logistic regression, including all statistically significant variables obtained from the bivariate analysis. A two-tailed $p < 0.05$ was considered significant. The IBM-SPSS Statistics package v. 25 was used for statistical analysis.

3. Results

3.1. General characteristics of study patients

A total of 991 patients were included in the present study, with a median age of 65 (58,72) years old. Study participants were 76.1% male, and 26.7% lived in a rural area. As the highest level of education completed, elementary school accounted for the most frequent in 36.2% of the participants. Of the total respondents, 79% had a diagnosis of IHD and dyslipidemia, 88.5% were in NYHA functional class I, and 56.6% were on optimal medical therapy after percutaneous coronary intervention. Inadequate adherence to treatment was reported by 70.3%, with forgetfulness as the most frequent cause mentioned in 55.4% of the cases. Complete general characteristics of study participants are summarized in Table 1.

3.2. Comparison between patients with adequate and inadequate adherence

Bivariate analysis showed that patients with inadequate adherence were older ($p = 0.010$), a more extensive proportion lived in rural areas ($p = 0.005$), and had higher total cholesterol ($p < 0.0001$) and triglycerides levels ($p = 0.003$) compared with their adherent counterparts. Moreover, participants with a low educational level, including those with middle school or less as the highest level of education completed, showed inadequate adherence patterns to treatment contrasted with those with high school or a college degree ($p < 0.0001$). Finally, patients on a combined pharmacological therapy with either PCI or CABG were more adherent than those on optimal medical therapy alone ($p = 0.004$). Likewise, a higher proportion of patients in the inadequate group were in NYHA classes II and III ($p < 0.0001$), as shown in Table 2.

3.3. Key barriers and predictors for inadequate adherence to treatment

Forgetfulness, economic reasons, and patient preference are the leading causes for inadequate adherence

among patients on secondary prevention therapy for CVD in this institution ($p < 0.0001$), as displayed in Table 3. Furthermore, low educational level (OR 1.68, 95% CI 1.23–2.3, $P = 0.001$) and the use of optimal medical treatment alone (OR 1.52, 95% CI 1.11–2.07, $P = 0.007$) are correlated with inadequate adherence, performing as predictors for poor adherence as demonstrated in the multivariate analysis (Table 4).

4. Discussion

The present study has highlighted that 70% of the patients on secondary prevention therapy for CVD have an inadequate adherence in the National Institute of Cardiology "Ignacio Chávez" in Mexico City. In agreement with this finding, a population-based study in Taiwan reported statin discontinuation of 68% at five years.⁷ These results contrast with previously reported in the United States, where adherence ranged between 50%⁸ and 87%⁹ within the first year of treatment initiation, declining up to 45%⁷ in the second. Although our study did not intend to assess adherence over time, our adherence rate may be one of the lowest reported, reflecting the discrepancies observed across countries and ethnic groups.

According to the WHO, nonadherence arises from the interplay between patient-related barriers and socioeconomic, health care system, disease, and therapy-related factors.¹⁰ In patients under statin therapy, adverse effects were the leading cause for statin discontinuation in a previous study, reporting that 25% of statin users believed statins cause memory loss,¹¹ a rare and inconsistent finding in the literature.^{12,13} Furthermore, Ahmed ST et al. reported that physicians preferred to avoid explaining all potential adverse effects to patients as it could influence their medication-taking behavior.¹⁴ Conversely, Rodriguez F et al. observed that patient preference was a higher determinant for statin withdrawal than adverse effects.⁹ This result does parallel with ours, leading to the suggestion that suboptimal health literacy may account for a significant proportion of nonadherence, reflecting an inadequate doctor-patient relationship. In this regard, a study found statin safety and risks concerns were the main reason for withdrawal, and those nonadherent were more skeptical of having a higher risk of myocardial infarction and stroke with high cholesterol levels than their adherent counterparts.¹¹ Thus, effective communication and education on the natural history of disease and treatment characteristics might be needed to clarify patients' concerns and demystify statin impact on CVD. Moreover, clinicians should promote adherence by encouraging a higher patient-physician involvement, potentially ameliorating therapy misconceptions, and decreasing patient misinterpretations about their condition, henceforth decreasing nonadherence. In this framework, a significant trend toward statin treatment reinitiation willingness (59.7%) was observed in those patients who discontinued statins after dialogue with their doctor.¹¹

In the current study, forgetfulness accounted for the most prevalent cause of nonadherence (53.5%), likely exposing underlying prescription complexities beyond medication-taking behavior such as multi-drug regimen, different dosing times, blood pressure, and glucose self-tracking, and lifestyle modifications.¹⁵ In this sense, polypill implementation could offer potential advantages over conventional pharmacotherapy as it provides an easy-to-remember monotherapy regimen. Multiple studies have reported the cost-effectiveness of a polypill strategy for secondary prevention of CVD, observing an increase in adherence rate, reduction in CVD burden,^{16–18} and dose titration.¹⁹ Nonetheless, their clinical employment in diverse populations might be hampered by healthcare systems and socioeconomic disparities across countries. Although some randomized clinical trials in developing countries^{17,20} and underserved populations in the United States¹⁶ demonstrated its cost-efficacy, drug prices need to be reduced to improve access, availability, and affordability in these countries.^{21,22} Hence, polypill strategy might be challenging in low- and middle-income countries owing to higher out-of-pocket costs than conventional pills. In this context, limited access to care, medication costs, and low socioeconomic status might account for poor adherence in low- and middle-income countries, as observed in this study, where 24% of the patients reported drug discontinuation for economic factors. Likewise, although forgetfulness might play a role in some patients, particularly in those with mild cognitive impairment and aging patients, underlying causes such as personal indifference to well-being, low self-esteem, suboptimal health literacy, age misconception, absence of family support, polypharmacy, and depression should also be considered as they may contribute to this phenomenon as well. Early decline and suboptimal adherence in such patients could be prevented by frequent communication and assessment

of patients' environment and psychosocial and cognitive status, particularly in patients with clinical and subclinical depression.

Even though physician-related barriers were the less prevalent (1.2%) in our study, lipid-lowering guidelines' misunderstanding might also account for poor adherence, leading to suboptimal risk reduction in those who may benefit from high-intensity therapy.²³ A previous study observed higher adherence patterns in patients taking moderate-intensity statin therapy than patients on low-intensity or high-intensity statin regimens.⁹ While, Khunti K et al. found that patients receiving high-intensity therapy were the more adherent group.²⁴ According to a study, stable LDL-C levels or at goal was the most prevalent cause reported by 42% of physicians for treating patients with a lower statin intensity than recommended.²⁵ Consistently, statin therapy discontinuation by physicians was observed in a large proportion of patients with adverse effects after the index event, receiving a lipid-lowering drug alternative in only 2.6% of the cases.²⁵ Moreover, high to moderate adherence has shown to lead to more significant reductions in total cholesterol and LDL-C levels than statin discontinuation and/ or withdrawal.²⁶ These findings could explain our observations as higher cholesterol, triglycerides, and hemoglobin A1c levels were found in those patients with inadequate adherence. In such patients, physicians might seek to maintain a high to moderate statin regimen in order to reduce overall atherosclerotic cardiovascular disease (ASCVD) risk and improve medication-taking behavior, as patients seem to be more conscious of the importance of medication adherence and disease control.

Furthermore, the number of consultations and the level of care might also impact secondary prevention therapy adherence. In a study performed at the Veterans Affairs system, a higher adherence was observed in those with regular primary care physician (PCP) control, reporting adherence improvement in those patients with at least one visit compared to those without any consultation.²⁷ Rehman H et al. found that patients under cardiology control had 9% higher odds of being more adherent in comparison with those under primary care management.²⁸ This finding seems to differ markedly from ours as the National Institute of Cardiology "Ignacio Chávez" is one of the highest accredited healthcare organizations in Cardiology in Mexico. However, it is worth mentioning that most of the patients do not have any further medical control and depend solely on their annual Cardiology consultation at the institute. In this understanding, the low adherence found in the institute could portray the country's health care scenario. Therefore, it could be hypothesized that adherence to statins and renin-angiotensin-aldosterone system blockers, and potentially other medications, might be more severe in other country institutions.

Further analysis observed that low school level and optimal medical therapy (OMT) without revascularization were independent predictors for nonadherence. In such patients, an invasive approach by revascularization or coronary artery bypass graft surgery (CABG) may account for a proper adherence pattern, likely behaving as a placebo. Likewise, these patients may be more knowledgeable about their disease and nonadherence potential consequences as opposed to those under OMT alone, exhibiting more adequate adherence patterns. This discrepancy could be attributed to patient misconception on their condition and medication unawareness due to chronic diseases' asymptomatic and slowly progressive nature and the lack of short-term clinical evidence of medication administration benefits. From this perspective, nonadherence may arise from ineffective implementation tools of intensive pharmacologic and lifestyle intervention, disclosing current approach failure and the need for strategies reassessment to impel more valuable and efficient enforcement methods. In this sense, whether the initial strategy should be conservative or interventional is still a matter of open-ended debate. Although multiple trials have been conducted to compare the effectiveness of OMT with and without percutaneous coronary intervention (PCI) on cardiovascular mortality, nonfatal MI, and all-cause mortality reduction, none has shown a difference between groups.^{29,30} In contrast with these conclusions, observational studies have reported lower mortality and cardiac deaths in the PCI arm.³¹ This disagreement could be attributed to the closed control observed in randomized clinical trials, potentially conferring a predictive model with ideal characteristics which might not represent a real-world setting. Therefore, when superimposed these observations with our findings, it could be hypothesized that observational studies demonstrated better outcomes with invasive strategies by better reflecting real-world variabilities such as medication adherence. Henceforth in order for the OMT to achieve the results observed in clinical trials, it might be necessary to generate effective patient-based adherence strategies.

On the other hand, low school level was the most important predictor for nonadherence. The odds of nonadherence were 2.37 times higher in those patients with elementary school or less, finding similar results to previously documented in a former study.²³ This finding could potentially explain adherence rate discrepancies observed with high-income countries, and it could be extrapolated to other low- and middle-income countries as well, reflecting the complex interrelation of economic burden and medication-taking behavior. Hence, medication nonadherence may compel all institutions to develop population-based adherence instruments to address the problem in an integral manner since the spectrum of adherence seems to overcome cultural and ethnic barriers. Besides, adherence might differ among institutions. Measuring adherence data as a quantitative analysis could probably be of limited value. Thus, a new method should be implemented to measure this complex parameter, in which case screening tools could be used to identify high-risk persons on the basis of all five nonadherence-related factors and clinical prediction algorithms. Nonetheless, more data is needed to evaluate these hypotheses, and a properly designed multicenter registry study must be conducted to complement these results with a representative sample of Mexico.

In this area of high unmet medical need, these findings should raise concern among physicians as nonadherence can lead to suboptimal risk reduction in high-risk populations, negatively impacting not only patients' quality of life and survival rate but also increasing direct and indirect health care system costs. Consistently, these findings could provide incremental value to promote interdisciplinary units and develop patient-centered health policies to improve patients' quality of life and survival rate in high-risk populations to attenuate the CVD burden. Thus, new and targeted specific population-based strategies are needed to improve the current adherence situation in the country.

5. Conclusion

The present study provides an introductory framework of the current situation of adherence to secondary prevention therapy in Mexico, highlighting the value of promoting national consensus on medication adherence to move towards a population-based strategy to reduce CVD burden. Thus, understanding the underlying motives for poor medication-taking behavior is of particular concern given the lack of information in the country.

6. Limitations

We recognize limitations in our study, particularly its observational and single-centered nature, as well as the lack of epidemiological data on adherence prevalence in the country. In this regard, due to the need for a properly designed multicenter registry study, no global conclusions can be made based on its results as it is a hypothesis generator.

Declaration of interest

None.

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