Use of Aspirin in the Public Primary Care Level. Experience of the Remediar Program, Argentina.

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SUMMARY

Background
Cardiovascular diseases cause 32% of deaths in Argentina. Aspirin produces a 12% reduction in the incidence of events and is indicated when cardiovascular risk at 10 years is above 10%. The Remediar Program provides aspirin to patients without medical coverage in the public primary care level.

Objective
To analyze the use of aspirin and estimate its indication.

Material and Methods
The present study has three designs: 1. Ecological study with cross comparisons of aspirin prescriptions, diagnoses and beneficiaries, by province, of the prescriptions of the Remediar Program. Sources: prescriptions from 6000 health care centers from March 2005 to February 2006. 2. Evaluation of a counterfactual approach. 3. Estimate of medication costs based on results.

Results
The Remediar Program identified 708,470 beneficiaries >50 years with increased cardiovascular risk. Aspirin was prescribed to 60,408 beneficiaries, with a mean of 2.0 treatments per month/year despite drug availability. The Program provided national coverage for 6.8% of the target population of 882,205 people, with an important variability among provinces. The evaluation of the potential impact of aspirin prescription in three counterfactual scenarios shows that 725 to 21,173 events could have been prevented, and that the cost of the Remediar Program to prevent one event would be of USD 3111 to 6222 during 10 years.

Conclusions
Underprescription of aspirin, failure to provide a minimum annual number of effective treatments and access issues might limit the impact on health care.


Key words
Aspirin - Primary Health Care Level- Impacts on Health- Public Health

Abbreviations
S Stroke
PHCC Primary Health Care Center
CVD Cardiovascular disease
NSRF First National Survey of Risk Factors
EPH-INDEC Encuesta Permanente de Hogares - Instituto Nacional de Estadística y Censos (Permanent Household Survey - National Institute of Statistics and Censuses)
HT Hypertension
MI Myocardial infarction
WHO World Health Organization
PCL Primary care level
CVR Cardiovascular risk

BACKGROUND

In Argentina, the prevalence of cardiovascular disease (CVD) – myocardial infarction (MI), stroke (S), peripheral vascular disease (PVD) – is very high and is responsible for 32% of deaths. (1) Cardiovascular disease is more frequent in older people, with known risk factors, such as sedentary life, hypertension, hypercholesterolemia, obesity, diabetes or history of smoking habits. (2) The Framingham risk equation is useful to evaluate the risk of developing a “hard” coronary event, such as myocardial infarction or death due to coronary artery disease – cardiovascular risk (CVR). (3) Lifelong low-dose aspirin therapy might be very effective for primary and secondary prevention of CVD. A meta-analysis that included five randomized trials (more than 55,000 patients), examined the

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effects of aspirin taken every day during 4 to 7 years, and concluded that aspirin reduces the risk of MI and mortality due to coronary artery disease by 28%, and the risk of other CVDs by 15%. (4) The effectiveness of aspirin for primary prevention of CVD far exceeds the risks of adverse effects when the overall risk of coronary artery disease at 5 years is > 3%. In patients with such CVR it is necessary to treat 1000 subjects with aspirin to prevent 4 to 12 MIs, while 0 to 1 hemorrhagic strokes and 2 to 4 episodes of gastrointestinal bleeding may occur at 5 years. When CVR is 5%, 6 to 20 MIs are prevented with a similar risk of adverse effects. In 2005, new evidence provided information about the effects of aspirin in women, (5) confirming that aspirin reduces the risk of CVD in adults - MI in men and ischemic stroke in women -without previous CVD. (6) Sixty percent of diabetics die due to CVD. However, the use of aspirin for primary prevention of CVD in that population is controversial despite the pharmacological targets of the current guidelines. (7) A study performed in Japan reported that low-dose aspirin in patients with type 2 diabetes did not produce significant outcomes, just a slight (not significant) reduction in the risk of coronary artery events, cerebrovascular events and peripheral events in the population, and a significant reduction in the incidence of fatal coronary and cerebrovascular events. (8) A recent meta-analysis published in the Lancet, (9) intended to compare the impact of aspirin in primary prevention versus secondary prevention, concluded that the proportional reductions of major coronary events and ischemic stroke was similar in both primary and secondary prevention trials, yet the reduction in cardiovascular mortality was not significant in primary prevention trials. The US Preventive Services Task Force (USPSTF) (10) stands by its seemingly broad recommendations for aspirin to prevent a first MI in men and stroke in women. However, a steady stream of studies have warned against aspirin use in some of the key primary-prevention populations; among these, the meta-analysis published in the Lancet (9) found that while aspirin, used for primary prevention, may reduce the risk of nonfatal ischemic events, these benefits are offset by higher bleeding, leaving no net effect on vascular mortality.

Evidence-based recommendations (10-13) about low-dose aspirin therapy in subjects with CVR of ≥ 5% at 5 years or 10% at 10 years without increased risk of bleeding are still valid in the primary care level in Argentina.

In 2002, The Ministry of Health implemented the Remediar Program to supply free essential medications, including tablets containing 100 mg of aspirin, to people with lack of medical coverage directly from the Primary Health Care Centers (PCCCs). (14) The Remediar Program was evaluated by the Sistema de Información, Monitoreo y Evaluación de Programas (SIEMPRO, Program Evaluation and Monitoring System), which revealed that 71% of beneficiaries were destitute, 20% were non-destitute poor and 84% lacked medical coverage. (15) In order to obtain the medications, patients had to fill some forms regarding medical diagnoses, prescriptions and demographic data in order to allow the construction of an important database.

The goal of this investigation is to analyze the use of aspirin in the public primary care level (PCL) in Argentina, and to estimate its effectiveness. The information available allows exploring the frequency of prescriptions separated by province and beneficiaries, discussing the adherence to treatment, generating hypotheses about limiting factors against the best impact on health care, and quantifying the costs of treatment with aspirin by person and effect unit.

**MATERIAL AND METHODS**

The present study about the use of medications has three designs. The first design corresponds to an ecological or cluster study –the unit of analysis is the country or regions, but not the persons. This design studies populations (clusters of prescriptions) without evaluating patients or clinical histories, – with cross comparisons of diagnoses and prescriptions by province in the public PCL in Argentina. (16) The secondary sources of information come from the Remediar Program Forms (Table 1).

The units of analysis are the fields of the R-Forms or prescriptions of aspirin made from March 2005 to February 2006 in almost 6000 PHCCs nationwide. The R-Form allows delivery of the medication included in the Remediar kit to the patient, which prescribed during medical consultation. All aspirin prescriptions are included. The diagnoses were classified using the Coding Manual CEPS-AP, first edition, which was in force when the prescriptions were made. (17) The beneficiaries were unequivocally individualized by means of a verification procedure implemented by the Sistema de Identificación Nacional Tributario y Social (SINTyS, National System for Social and Tax Identification).

Each month, the PHCC provides the Remediar Program with a B-Form that has information consolidated about pharmaceuticals’ consumption and medical consultations. Data from the number of beneficiaries of the Remediar Program were crossed with the projected target population of the First National Survey of Risk Factors (NSRF). (18) Similar to the ATP III (19), the NSRF allows the possibility of classifying the Argentine population exclusively under public medical coverage, according to the number of risk factors, in: low CVR (0 to 1 RF; < 10% risk of events at 10 years); moderate CVR (2 RF; 10-20%); high CVR (= or more than 3; > 20%).

Coverage was calculated as the ratio between:

\[
\text{Cases of beneficiaries with aspirin prescriptions by province} \times 100
\]

Cases with CVR >10% exclusively under public medical coverage by province according to the NSRF.
Effective treatment was defined as the monthly delivery of 30 doses of aspirin per patient, and treatment persistence compliance was evaluated analyzing the number of months per year that each patient required the treatment during 1 year.

Availability of aspirin was analyzed at the beginning of the studied period and defined as the months of use covered by the stocks of medicine left at the each center if the rate of use did not vary.

The second design is an evaluation of the counterfactual approach of the impact the proper use of aspirin might have for the prevention of CVD. This design is used in health assessment when the results of the interventions cannot be compared with control groups. A counterfactual event is a consequence or condition that cannot be observed by human investigation but could have happened.

The PICO method is useful to build clinical questions (20): Patient or Population, Intervention, Comparison and Outcome.

The impact of the use of aspirin is based on the evidence showing that aspirin reduces the risk of CVD by 25%. (21) However, for the purposes of this analysis, we considered that the potential impact of aspirin provided by the Remediar Program in the target population was a reduction of CVD risk by 12% (RR = 0.88, 0.82 - 0.94), a conservative approach based on findings of the most recent meta analyses. (9) Three possible scenarios were considered depending on the population considered. A minimal risk of events of 10% and a maximal risk of 20% were considered at 10 years.

Population: subjects > 50 years (an arbitrary cut-off value, between 45 years in men and 55 years in women, according to the Framingham study), high CVR and exclusive public medical coverage: Scenario 1.

Beneficiaries of the Remediar Program with prescriptions of aspirin: Scenario 2. Beneficiaries of the Remediar Program with high CVR (with HT and/or diabetes) with or without prescription of aspirin: Scenario 3. Population with high CVR, according to the NRFS.

– Intervention: prescription and daily use of aspirin in the populations described.
– Comparison: the same populations that were not using aspirin or with insufficient medication.
– Outcome or impact: number of events prevented.

The third design is a calculation of medication costs by beneficiary with high CVR and by event prevented (effect unit) after 10 years of therapy. Costs were calculated in United States Dollars (USD) according to: 1) Remediar Program purchase price plus management and distribution costs. (22) 2) Aspirin retail price. (23) The costs of medical visits and laboratory tests were not considered. The economic impact of treatment costs by beneficiary on mean households’ income is evaluated.

RESULTS

From a total of 15,001,041 prescriptions recorded during the year of the study, 225,411 corresponded to aspirin prescriptions, frequency 1.5%. Among 96,755 prescriptions in patients > 50 years with high CVR, 60 408 beneficiaries were identified. Figure 1 shows the distribution of aspirin use by age. In patients < 16 years (12.8% of prescriptions) the most frequent diagnoses were pharyngitis, fever, cold and pain. In subjects < 50 years (64.5% of prescriptions), the diagnoses were hypertension (60.1%), other cardiovascular diseases (8%), diabetes (7.4%), pain (6.5%), heart failure (5.8%), ischemic heart disease (4.5%), cerebrovascular disease (0.4%), and other diagnoses (26.7%). Among aspirin prescriptions, 61.22% corresponded to women and 38.78% to men; this distribution was similar to that of general medical consultations in the PCL.

Aspirin was prescribed due to the following conditions: HT (7.1%), type 2 diabetes (2.9%), heart...
failure (27.7%) and other heart diseases (20.4%).

Median availability of aspirin nationwide was 9.1 months (percentiles 25-75: 2.8 - 32) (Figure 2). The high availability was constant during 2005; yet there was great variability among the different provinces and inside a same province.

A total of 60408 beneficiaries with aspirin prescriptions were identified nationwide; mean treatment was 2.0 months per year (table 2); 92.3% , 6.3% and 1.4% of beneficiaries received treatment for 4, 5 to 8 and 9 months per year or greater, respectively. The number of beneficiaries > 50 years with cardiovascular disease (including HT) and/or diabetes was 708470; aspirin was prescribed to 8.5% of them (60,408 beneficiaries). Analysis of the cross-over information provided by the Remediar Program and the NSRF shows that the population > 50 years with high CVR and exclusive public medical coverage consists of 882,205 persons; the Remediar Program covers 6.8% of this population. Figure 3 describes the information separated by province.

The potential impact of aspirin after 10 years was evaluated in three counterfactual scenarios (Table 3). In scenario 1, 725 to 1450 events could be prevented with proper compliance of aspirin prescription - 12 months per year. In scenario 2, 8503 to 17003 events could be prevented if aspirin was prescribed to the population with CVR identified by the program. In scenario 3, 10586 to 21173 events could be prevented if aspirin was prescribed to all patients under exclusive public coverage and high CVR.

The cost of aspirin per unit for the Remediar Program was USD 0.02, and the retail price during the same period was USD 0.19. The cost of treatment with aspirin for ten years and per beneficiary is USD 74.67 in the Remediar Program and USD 710.02 according to retail prices. According to CVR (Table 3) the cost of the Remediar Program to prevent one event would be of USD 3111 and 6222 during 10 years for CVR of 20% and 10%, respectively (Table 4).

Fig. 1. Distribution of the population under aspirin per age (years) ( %). Source: R-Forms. Total Nationwide. Remediar Program.

Fig. 2. Availability of aspirin (months): median and percentiles 25 and 75. First trimester 2005. Source: B-Forms. PROAPS-REMEDIAR.
Free provision of aspirin reduces not only CVR and but also expenses in low-income households. Average destitute household income was USD 83.3 during the second semester of 2005 (EPH-INDEC); thus, free provision of aspirin per month means that destitutes may save 7% of their income (speaking of retail prices). For non-destitute poor households with an income of USD 163.3, savings represent 3.6% per month.

DISCUSSION

The Remediar Program supplied aspirin to reduce morbidity and mortality due to CVD. Primary prevention of CVD with aspirin should complement population-based strategies focused on health promotion and changing behaviors. (24) The analysis of the database generated by the Program has allowed making some inferences about physicians’ prescription patterns and the scope of the Remediar Program on the population with high CVR and lack of medical coverage.

Preliminary investigations have detected over-prescription of aspirin in the Argentine PCL in the population under 16 years despite contraindicated due to the risk of Reye syndrome, and under-prescription in patients with HT or diabetes. (25) Under-prescription of aspirin was noted in patients with HT or diabetes, despite greater CVR. According to the pharmacological targets recommended by current guidelines, aspirin should have been prescribed to most of these patients (7, 26) as it may reduce events by 25%. (19, 21)

**Table 2.** Analysis of the Argentine population > 50 years with high CVR under aspirin therapy, separated by province.

<table>
<thead>
<tr>
<th>Province Name</th>
<th>Total treatments provided</th>
<th>Patients with aspirin prescription, &gt; 50 years and circulatory disease and/or diabetes</th>
<th>Average treatments per patient Aspirin</th>
<th>Covered by Remediar</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL NATIONWIDE</td>
<td>882,205</td>
<td>121,850</td>
<td>60,408</td>
<td>2.0</td>
</tr>
</tbody>
</table>


Source: Beneficiaries of the Remediar Program identified in the R Forms of the Program. n = 15 million people.

**Table 3.** Counterfactual approach. Number of events to be prevented by aspirin use in three scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Population with high CVR</th>
<th>Events to be prevented</th>
<th>Risk 10%</th>
<th>Risk 26%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt; 50 years with CVD and/or diabetes receiving aspirin from the Remediar Program (*)</td>
<td>60,408</td>
<td>725</td>
<td>1.450</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[362-1,087]</td>
<td>[725-2,175]</td>
</tr>
<tr>
<td>2</td>
<td>Beneficiaries of the Remediar Program &gt; 50 years with CVD and/or diabetes (*)</td>
<td>708,470</td>
<td>8,502</td>
<td>17.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[4,251-12,752]</td>
<td>[8,502-25,505]</td>
</tr>
<tr>
<td>3</td>
<td>Population with high CVR, &gt; 50 years, under exclusive public medical coverage (**)</td>
<td>882,205</td>
<td>10,586</td>
<td>21.173</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[5,293-15,880]</td>
<td>[10,586-31,759]</td>
</tr>
</tbody>
</table>

CVR: Cardiovascular risk. CVD: Cardiovascular disease.

prescription of aspirin cannot be attributed to lack of medication, as the PHCCs had acceptable stocks of aspirin during the studied period with important variability among the different provinces and inside a same province.

The NSRF estimates that 880,000 persons are under exclusive public medical coverage and have high CVR. The level of CVR at 10 years recommended to indicate aspirin is controversial -10% for the American Heart Association (27), and greater for the European Society of Cardiology and the WHO - as the disadvantages of the treatment might counteract the benefits when used in patients with this level of risk. (26, 29) The Remediar Program has recommended a level of risk of 10% on the basis of systematic reviews. (30)

About 700,000 beneficiaries of the Remediar Program were examined during that period and had diagnosis of CVD; yet, aspirin was prescribed to only 60,000. Despite aspirin could not have been recommended to all these patients (e.g., those with hemorrhagic diathesis), two problems were identified: 1) lack of access among the population with high CVR, and, 2) aspirin was prescribed to only 8.4% of the population undergoing medical care in which diagnosis of high CVR was made. Thus, the Program provided aspirin to 6.8% of the target population (see Table 3). In some provinces, as La Rioja, Formosa or Santiago del Estero, this coverage was greater compared to Buenos Aires and Neuquén and the city of Buenos Aires (Figure 3). Does this mean that the latter are less dependent on the medications supplied by the Remediar Program to treat their population without medical coverage in the PCL?

The request of supplies of aspirin according to CVR was persistently low; the median number of treatment prescriptions for each beneficiary was 2 months per year; only 1.4% received treatments for 9 months or greater. We know that treatment should be administered throughout the whole year and life to have an impact on health care. (4, 5) Patients might have purchased aspirin due to the low price of this medication, and subsequently, the Remediar Program was not able to estimate the real number of prescriptions. Yet, the low income level of the beneficiaries -total income of USD 83.3 and 163.3 for destitute and non-destitute poor households, respectively - makes us think that this low percentage reflects the reality. In the United States, only 16.3% of the population with intermediate CVR received aspirin. (31) In Switzerland, only 9% of persons with CVR of 20% at 10 years were treated with aspirin. (32) They estimated that a more appropriate aspirin use would reduce up to 2348/24310 CHD deaths (10%) expected over 10 years. Although there are no population-based studies in Latin American showing the use of aspirin in prevention of CVD, it is expected that this percentage will be even lower. The lack of adequate controls is a universal problem for therapy with antihypertensive agents, hypoglycemic drugs or lipid-lowering agents. (33-35)

The impact on health care was evaluated using the PICO method. (20) The population evaluated is that with CVR 10% - 20%. The effectiveness of the factual intervention - aspirin free provision and prescription - is minimal, due to persistence problems. The impact would be significant in the three counterfactual scenarios: 1. Treatment persistence or compliance: if the beneficiaries with aspirin prescription had received the medication for the whole year. 2. Rational prescription: if aspirin had been prescribed to all beneficiaries with CVD (including

<table>
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<tr>
<th>Table 4. Costs of treatment with aspirin per event prevented</th>
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<tr>
<td><strong>Costs of treatment with aspirin at 10 years</strong></td>
</tr>
<tr>
<td><strong>per event prevented</strong></td>
</tr>
<tr>
<td><strong>Price</strong></td>
</tr>
<tr>
<td><strong>10%</strong></td>
</tr>
<tr>
<td>Remediar Program</td>
</tr>
<tr>
<td>Retail price</td>
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</tbody>
</table>


Fig. 3. Patients receiving aspirin assisted at the PCL with medications supplied by the Remediar Program per 100 patients with high cardiovascular risk exclusively under public medical coverage. Source: Beneficiaries of the Remediar Program and National Survey of Risk Factors.
Het or diabetes. 3. **Access** of persons with high CVR under exclusive public medical coverage. Considering a context of high availability of medication, 725 (scenario 1) to 21173 (scenario 3) events might be prevented. Although most recent evidence has moderated the estimation of the impact of aspirin in primary prevention of cardiovascular events in high-risk population, (9) its use is still a priority according to recommendations. (36)

The problem is even greater due to higher morbidity and mortality from CVD in the population with lower income and lack of medical coverage, (37), the beneficiaries of the Remediar Program. (15) Free provision of aspirin allows destitute and non-destitute poor households save 7% and 3.6% of their monthly income, respectively; in addition, the Argentine State might spend between USD 3111 and 6222 in 10 years to prevent each event. Low costs are partially due to the fact that aspirin price in the Program is 9% lower compared to retail price. (22) Despite the Program uses resources to deliver medications, the economical value is not estimated as these resources were previously present in sub-national jurisdictions (sunk costs). If all costs were considered, they would probably be twice as high.* However, according to pharmacological and economical investigations, primary prevention in CVD is less expensive than the absence of treatment (cost-effective) when CVR is > 10% at 10 years. (38-40)

The availability of medications in medical facilities is an intermediate target of health care policies. Provision of supplies should be accompanied by permanent training in services, sensitization and information for prescribers and patients, in order to achieve the final target: improvement of quality and quality of life. These measures should focus on increasing the number of patients treated at the PCL and ensuring adequate risk stratification, aspirin prescription and follow-up of patients with high CVR.

Ecological studies are frequently biased. (16) For example, there is no information whether the medication has been provided by other source; however, personal communications with the responsible authorities of the jurisdictions may minimize this limitation. Another limitation is related with the quality of the records used. The construction of the counterfactual scenario limits the comparative evaluation of the impact. Estimating something that has not occurred is controversial; yet this approach is used to evaluate biological models as well as social and health care projects. (41) Costs of medications were considered but not those of medical visits or indirect costs (transportation, loss of profit, etc.)

These limitations should not be an excuse for the evaluation of health programs from an administrative and financial point of view and their impact in health care. The study provides interesting information that may be helpful to elaborate hypotheses and qualitative investigations about the reasons of the lack of access, prescription and persistence. Doesn’t the population have access to the PCL? If the population has access, do physicians work more with emergencies than in health promotion and prevention? In patients with high CVR, is aspirin under-prescription due to lack of training? If aspirin is prescribed, is the lack of treatment persistence due to the characteristics of the population, to the use of medications in chronic diseases or to doctors’ failure in communicating with patients?

**CONCLUSIONS**

In spite of the fact that the Program had sufficient stocks of aspirin, the positive impact on health care related to the supply of drugs was limited by the problems of access and under-prescription. Yet, the lack of treatment persistence is the major limitation. It is more important to ensure that treatment is delivered to the target population than to extend the prescription to a larger segment of the population (due to the risk of adverse events related with prevention in healthy populations). For this reason, it is necessary to develop programs focused on this issue and to strengthen health care networks. Aspirin provision, a cost-effective and affordable technique, could have had a greater impact in the prevention of CVD.

**RESUMEN**

**Uso de Aspirina en el Primer Nivel de Atención Pública. Experiencia del Programa Remediar, Argentina**

**Introducción**

La enfermedad cardiovascular causa el 32% de las muertes en la Argentina. La aspirina reduce un 12% los eventos y está indicada cuando el riesgo cardiovascular (RCV) a los 10 años supera el 10%. El Programa Remediar provee aspirina gratuitamente en el primer nivel de atención pública para la población sin cobertura.

**Objetivo**

Analizar el uso de la aspirina y estimar su efectividad.

**Material y métodos**


**Resultados**

A pesar de que el Programa contaba con disponibilidad, se
prescribió aspirina a 60.408 beneficiarios, con una media que recibe 2.0 tratamientos mensuales por año, sobre una población de 708.470 beneficiarios identificados por el Programa mayores de 50 años con RCV aumentado. La cobertura nacional alcanzó al 6.8% de la población objetivo de 882.205 personas, con una gran variabilidad interprovincial. La evaluación del impacto potencial de la prescripción de aspirina en tres escenarios contrafácticos muestra que podrían haberse evitado 725 a 21.173 eventos. El costo de evitar cada evento sería para el Programa Remediar de 3.111 a 6.222 dólares a lo largo de 10 años.

**Conclusions**

Se evidencia subprescripción de aspirina, falta de cumplimiento de un mínimo anual de tratamientos efectivos y problemas de acceso, lo cual limitaría el impacto sanitario.

**Palabras clave >** Aspirina - Atención primaria de salud - Evaluación de impacto - Salud pública

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