Facilitated Prescription of Antihypertensive Drugs and Decreased Premature Death from Stroke

Prescripción facilitada de drogas antihipertensivas y disminución de la muerte prematura por accidente cerebrovascular

JAVIER MARIANI [MTSAC, 1], MARINA RIDAO[2], GABRIEL GONZÁLEZ VILLAMONTE[2,MTSAC], MAURICIO MONSALVO[3], ALEJANDRO MACCHIA[1]

ABSTRACT

Background: Since 2003, the Remediar (+Redes) program supplies free anti-hypertensive medication. During this period, mortality from stroke has decreased, albeit with inequalities between socioeconomic groups.
Objectives: The aim of this study was to assess the association between stroke mortality and the provision of antihypertensive drugs and to study the possible interaction between antihypertensive effects on mortality and socioeconomic status.
Methods: An ecological panel data study was performed. Mortality was expressed as standardized rates. Antihypertensive drugs were adjusted among the population to whom they were provided and expressed in dispensing quartiles. Socioeconomic status was measured by unmet basic needs.
Results: Since the program's initiation in 2003, the distribution of antihypertensive drugs increased significantly, especially in the less affluent groups (p<0.001). There was no statistically significant association between antihypertensive drug dispensing rate and overall stroke mortality. However, the interaction analyses showed that in quintiles 3 to 5 of unsatisfied basic needs (less affluent), the quartiles in which more antihypertensive drugs were distributed, had significantly lower mortality from stroke (p=0.004, p=0.015 and p=0.017, respectively).
Conclusions: The results of this analysis indicate no antihypertensive drug dispensing overall effect on stroke mortality. However, data suggest that among the most disadvantaged groups, the distribution of antihypertensive drugs was associated with a reduction in mortality from this cause.

Key words: Stroke/mortality; hypertension; ecological study; treatment; mortality.

RESUMEN

Introducción: Desde 2003, el programa Remediar (+Redes) distribuye gratuitamente medicación antihipertensiva. Durante este periodo, la mortalidad por accidente cerebrovascular disminuyó, aunque con inequidades entre grupos socioeconómicos.
Objetivo: Evaluar la asociación entre la mortalidad por accidente cerebrovascular y la provisión de fármacos antihipertensivos. Estudiar la posible interacción entre los efectos de los antihipertensivos sobre la mortalidad y el nivel socioeconómico.
Material y métodos: Se realizó un estudio ecológico para datos de panel. La mortalidad fue expresada como tasas estandarizadas. Los fármacos antihipertensivos están ajustados a la población entre la que fueron distribuidos y expresados en cuartiles de dispensación. El nivel socioeconómico fue medido mediante las necesidades básicas insatisfechas.
Resultados: Desde el inicio del programa en 2003, la distribución de antihipertensivos aumentó significativamente, sobre todo en los grupos menos afluentes (p<0,001). No hubo una asociación estadísticamente significativa entre la tasa de dispensación de antihipertensivos y la mortalidad por accidente cerebrovascular globalmente. Sin embargo, en los análisis de interacción se observó que en los quintilos 3 a 5 de necesidades básicas insatisfechas (menos afluentes), los cuartiles en los que se distribuyeron más antihipertensivos, tuvieron significativamente menor mortalidad por accidente cerebrovascular (p=0,004, p=0,015 y p=0,017, para los quintilos 3 a 5 de nivel socioeconómico).
Conclusiones: Los resultados del presente análisis sugieren la ausencia de efectos globales de la provisión de antihipertensivos sobre la mortalidad por accidente cerebrovascular. Sin embargo, los datos sugieren que entre los grupos más desfavorecidos, la distribución de antihipertensivos sí estuvo asociado a una reducción de la mortalidad por esta causa.

Palabras clave: Accidente Cerebrovascular/mortalidad - Hipertensión / tratamiento farmacológico

Abbreviations

HTN	Hypertension		**IRR**	Incidence rate ratio
UBN	Unmet basic needs			

Address for reprints: Javier Mariani - Fundación GESICA - Av. Rivadavia 2358- (C1034ACP) CABA, Argentina – Tel: 54(11)4953-9604
e-mail: ja_mariani@hotmail.com / javier.mariani@fundaciongesica.org

[MTSAC] Full Member of the Argentine Society of Cardiology
[1] GESICA Foundation, Buenos Aires, Argentina.
[2] REDES Program, National Ministry of Health, Argentina
[3] Remediar Program, National Ministry of Health, Argentin

INTRODUCTION

An accompanying article in the *Journal* presents the time evolution of stroke mortality between 2000 and 2011, and its relationship with socioeconomic status. (1) This article reports the progressive reduction in mortality and the persistent gap between groups defined by socioeconomic status quintiles.

Hypertension (HTN) is the main risk factor for stroke, (2) and pharmacological control of blood pressure is one of the fundamental strategies for its primary prevention. (3, 4) In addition, several studies have shown an inverse relationship between the prevalence of the most relevant risk factors and socioeconomic status. (5-7) In Argentina, the National Risk Factor Survey has reported a stable prevalence of HTN (34%) since 2005 and an inverse relationship with the socioeconomic status measured by level of education and income. (8) These inequities in the distribution of risk factors might contribute to the differences observed in stroke mortality. (1, 2, 5)

Since 2002, the National Ministry of Health has launched the Remediar (+Redes) Program, designed to ensure essential drugs to patients without health insurance coverage (exclusive public coverage), including five antihypertensive drugs. (9) Since HTN is the main risk factor, the provision of this type of drugs to the most vulnerable population groups could contribute to reduce inequality in stroke mortality.

Our purpose was to evaluate the association between stroke mortality and the provision of antihypertensive drugs in Argentina between 2003 and 2011. The study hypothesis was that there could be an interaction between socioeconomic status and the effects of antihypertensive drug provision on stroke mortality.

METHODS

A longitudinal panel study combining an ecological design with a time series analysis evaluated the association between the provision of antihypertensive drugs in the Remediar (+Redes) program, socioeconomic status and standardized stroke mortality in Argentina between 2000 and 2011. The analysis unit was the departments.

Mortality

As described in the accompanying article, the data on the number of deaths in each age and sex group for each department and year of the study period were obtained from the Bureau of Vital Statistics and Health Information (DEIS) of the National Ministry of Health. Data originates from the processing of death certificates coded according to the International Statistical Classification of Diseases, 10th Revision (ICD-10). (10) Stroke deaths were identified as those corresponding to the codes I60-I69, which include both ischemic and hemorrhagic stroke. (10)

The denominators for the calculation of annual death rates in each department were obtained from the 2000 and 2010 censuses; for the years between censuses, the population was estimated by the cohort-component method. (11)

Socioeconomic level

The socioeconomic status was characterized by the percentage of households within each department with unsatisfied basic needs (UBN), measured in 2003. This indicator includes the following domains: income, level of educational attainment, housing conditions, overcrowding and sanitary conditions (12). The departments were then divided into quintiles of UBN, with the first quintile indicating the best socioeconomic status and the fifth quintile the worst (highest level of UBN).

Antihypertensive drugs

Since the end of 2002, the National Ministry of Health implemented the Remediar program, which provides free essential drugs through primary care centers (PCCs). In 2009, the program was expanded (Remediar + Redes) with the aim of strengthening provincial and local participating projects. Today, the program is estimated to cover the provision of drugs to approximately 15 million people with exclusive public health care (9). Although five antihypertensive agents (atenolol, hydrochlorothiazide, enalapril, amlodipine and losartan) are currently provided, during the analysis period the program did not include losartan and amlodipine, so the analyses were limited to the first three drugs. Furosemide, a drug distributed by the program, was considered as antihypertensive drug for the study purposes, and since in the sensitivity analysis its exclusion did not significantly affect the results, it was included in the reported data. For analytical purposes, the equivalent of a monthly treatment with each drug was considered as unit (for example, in the case of hydrochlorothiazide, a box of 30 tablets was one unit). All units distributed within each department since 2003 were added (because as the program began in October 2002, the following year was taken for the estimation of the doses dispensed). The annual rates of doses dispensed (expressed as doses per 1000 inhabitants per year) were then estimated, adjusting in this way the number of prescriptions to the size of the department's population. Finally, the departments were divided into quartiles according to the annual rate of antihypertensive treatment provided each year, so the first quartile corresponded to the departments with lower dispensing rate and the fourth to the highest.

Statistical analysis

Mortality is expressed as standardized rates by age and sex per 100,000 persons. The Argentine population distribution in 2010 was used as standard population. (13)

The distribution of antihypertensive drugs was described as annual rates (per 1,000 persons) for each department, and expressed as means with their corresponding 95% confidence intervals (95% CI).

To analyze the temporal evolution of drug dispensing in each of the UBN quintiles, panel data were fitted to a conditional multivariate Poisson regression model. (14) Panel data arose from the same experimental observation units over time. (15) In case the units observed are always the same, they are balanced panels (this is the case of the data presented) and can be measured at regular or irregular intervals (in this case they were regular yearly intervals). Poisson regression is used in regression models in which the dependent variable is calculated (number of monthly treatments dispensed in a year or rate). (14). Model specification included a randomized "y" intercept -random effects model- since the effects not measured within the experimental units did not have a significant effect, as evaluated by the Hausman test (p=0.287). (16) In these cases, the random effects model is more efficient. (16)

To evaluate the effects of free antihypertensive drugs dispensing on stroke mortality, data were fitted to a multivariate Poisson regression model using the quartiles (rates) of antihypertensive drugs as independent variable, modeled as a time-changing variable (as quartiles were calculated for each year). Furthermore, the exposure effect was evaluated a year later (lag 1), i.e. the effects of belonging to a particular quartile of antihypertensive drugs divided by the standardized rate of death from stroke was evaluated dividing by the rate of the following year. In this way it allowed the model to contemplate the delay that may exist between the beginning of the exposure to the drug and its influence on the outcome, and some reverse causality (higher dispensing in departments with the highest mortality from stroke) could be avoided.

To assess the hypothesis of interaction between the UBN quintile and the antihypertensive quartile on mortality, another multivariate Poisson regression model was used, where UBN quintiles, antihypertensive drugs dispensed and an interaction term between both were included. The UBN quintiles were modeled as time-invariant.

Results are expressed as incidence rate ratio (IRR), whose interpretation is that of relative risk, with its corresponding 95% confidence interval. (14) A p value <0.05 was considered statistically significant. All confidence intervals were estimated using 100 bootstrap samples.

All analyses were performed using R version 3.2.3 for OSX statistical package. (17) The "pglm" (18) package was used for regression models.

Ethical considerations
As the data analyzed are anonymous and public, the approval of an Ethics Committee was not necessary to perform the study.

RESULTS
During the study period, the standardized rate of death from stroke was significantly reduced in Argentina from 31.3 (95% CI 29.5 to 33.1) to 20.6 (95% CI 19.3 to 21.9) per 100,000 people. The significant reduction was recorded in each UBN quintile, in which reductions between 32.0% and 34.5% in mortality due to this cause were recorded (1).

Since the beginning of the Remediar (+ Redes) Program, the number of monthly antihypertensive treatments across Argentina increased significantly, especially at the expense of the first four years of the program (from 1,157,741 in 2003 to 3,140,165 in 2006) (Table 1). However, from the socioeconomic point of view the increase was more pronounced during the entire period in the poorest quintiles (Table 1 and Figure 1A). Table 2 shows that the antihypertensive rates increased in the first two UBN quintiles in the first half of the period, whereas in the last three quintiles there was a steady increase and of greater magnitude the higher the quintile. The increase within each UBN group was statistically significant, as well as the comparison between quintiles (IRR 1.25, 1.91, 2.21 and 2.70, for the second, third, fourth and fifth quintile compared with the first, respectively; p<0.001 for the four comparisons) (Table 2 and Figure 1B).

The relationship between antihypertensive drug provision and standardized stroke mortality evaluation suggested a positive and statistically significant association between the two; however, the magnitude of the association was attenuated and no longer significant after controlling for socioeconomic status (Table 3). Despite the overall lack of association in the adjusted analysis, within each UBN quintile, the effects of the amount of antihypertensive drugs dispensed were not homogeneous, but dependent on the socioeconomic status of the target population (interaction). Thus, an inverse association was observed between standardized mortality from stroke and quartiles of antihypertensive drugs dispensed starting from the third quintile of UBN, and this association was statistically significant only for the highest quartile of antihypertensive drug dispensing. Figure 2 shows the stroke mortality curves estimated by the regression model, where the curve slopes for UBN quintiles 3 to 5 (Figure 2C to 2E) are more pronounced for the fourth

Table 1. Number of monthly antihypertensive drug treatments dispensed since the beginning of the Remediar (+Redes)* program.

| Year | All | UBN Quintiles | | | | |
		1	2	3	4	5
2003	1,157,741	188,380	377,385	374,612	140,696	76,668
2004	1,700,377	246,408	498,984	535,540	243,056	176,389
2005	2,082,904	284,526	591,427	666,794	318,411	221,747
2006	3,140,165	445,410	901,811	969,950	493,546	329,450
2007	2,778,185	366,832	742,068	874,662	451,613	343,011
2008	2,663,589	344,085	697,751	845,227	439,181	337,346
2009	3,149,532	394,155	844,073	845,226	529,405	395,085
2010	3,226,532	386,284	874,084	996,242	559,678	410,245
2011	2,979,647	355,682	809,873	924,410	522,246	367,437
p value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

* Drugs include enalapril, atenolol, hydrochlorothiazide and furosemide. UBN: Unmet basic needs.

quartile of antihypertensive drugs (solid lines), while in the first two UBN quintiles there was no association between the amount of dispensed antihypertensive drugs and estimated stroke mortality rate (Figure 2A and 2B).

DISCUSSION

Data from this study show that from the onset, the Remediar (+Redes) program gradually increased the amount of antihypertensive drug doses dispensed, consistent with the objectives of the program (aimed at people with exclusive public coverage) to benefit groups with lower socioeconomic status. Furthermore, the results suggest a significant interaction of antihypertensive drug dispensing effect on standardized stroke mortality, depending on the socioeconomic status of the department. Thus, the effects were only significant for the groups with higher dispensing of antihypertensive drugs in the three quintiles of lower socioeconomic status.

These results are consistent with the importance of HTN as a risk factor for stroke and the evidence of the clinical effectiveness of antihypertensive treatment to reduce its incidence and cardiovascular mortality (2, 3, 19).

Because most of the temporal reduction in the incidence of non-fatal cardiovascular events and cardiovascular mortality observed in other studies has been attributed to the prevention treatments available, the interaction observed between socioeconomic sta-
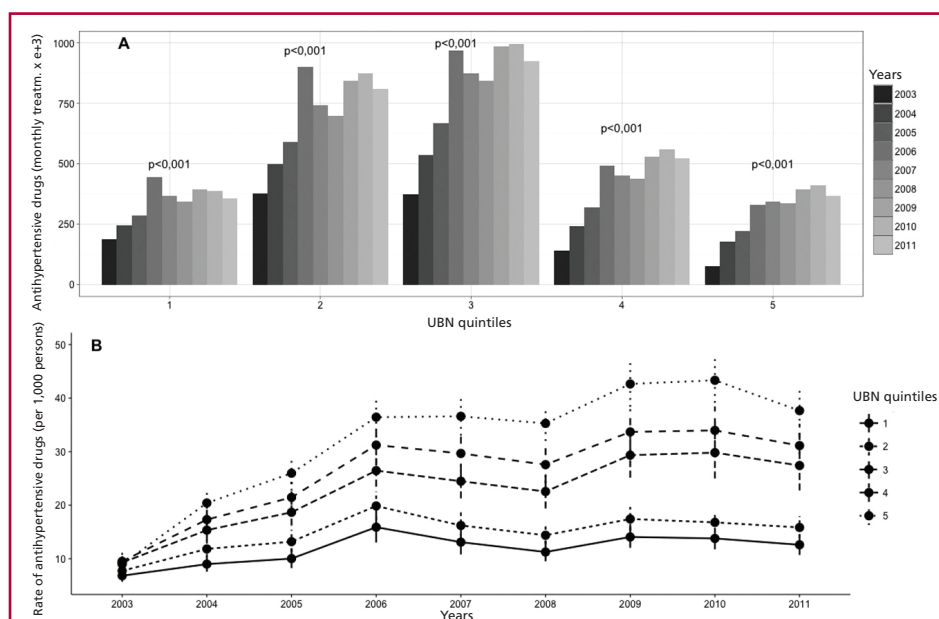

Fig.1. Number of antihypertensive drugs dispensed (**A**) and annual rate per each quintile of unmet basic needs (UBN) (in monthly treatments) (**B**).

Table 2. Rate of antihypertensive drugs dispensed per 1,000 persons.

| Quintiles	2003 Mean (95%CI)	Years 2007 Mean (95%CI)	2011 Mean (95%CI)	IRR (95%CI)	p value*
1	6.8 (5.6 to 8.3)	13.1 (10.7 to 15.7)	12.6 (10.8 to 14.7)	-	
2	7.7 (6.3 to 8.7)	16.2 (14.2 to 18.4)	15.8 (13.9 to 18.1)	1.25 (1.22 to 1.28)	<0.001
3	9.3 (8.2 to 10.5)	24.5 (21.3 to 27.9)	27.4 (22.4 to 334)	1.91 (1.87 to 1.95)	<0.001
4	9.5 (8.1 to 11.1)	29.7 (26.1 to 33.3)	31.1 (27.2 to 35.3)	2.21 (2.16 to 2.26)	<0.001
5	9.0 (7.8 to 10.2)	36.6 (33.2 to 40.2)	37.7 (33.3 to 41.9)	2.70 (2.64 to 2.76)	<0.001

*Evaluation of time trends within each quintile showed a statistically significant increase in the rate of antihypertensive drugs (p<0.001 for each of the five models corresponding to the quintiles).

Table 3. Non-adjusted and adjusted association by socioeconomic status between antihypertensive drugs dispensed and standardized stroke mortality.

Antihypertensive quartiles	Incidence rate ratios (95%CI) Non adjusted	p value	Adjusted by UBN	p value
1	Ref.	-	Ref.	-
2	1.03 (0.97 to 1.08)	0.330	1.01 (0.96 to 1.07)	0.604
3	1.07 (1.01 to 1.13)	0.021	1.04 (0.99 to 1.10)	0.136
4	1.08 (1.02 to 1.14)	0.008	1.04 (0.98 to 1.10)	0.160

Fig. 2. Estimated stroke mortality rates per quartile of antihypertensive drugs dispensed in each socioeconomic status group (2A to 2E, 1st to 5th UBN quintile, respectively)
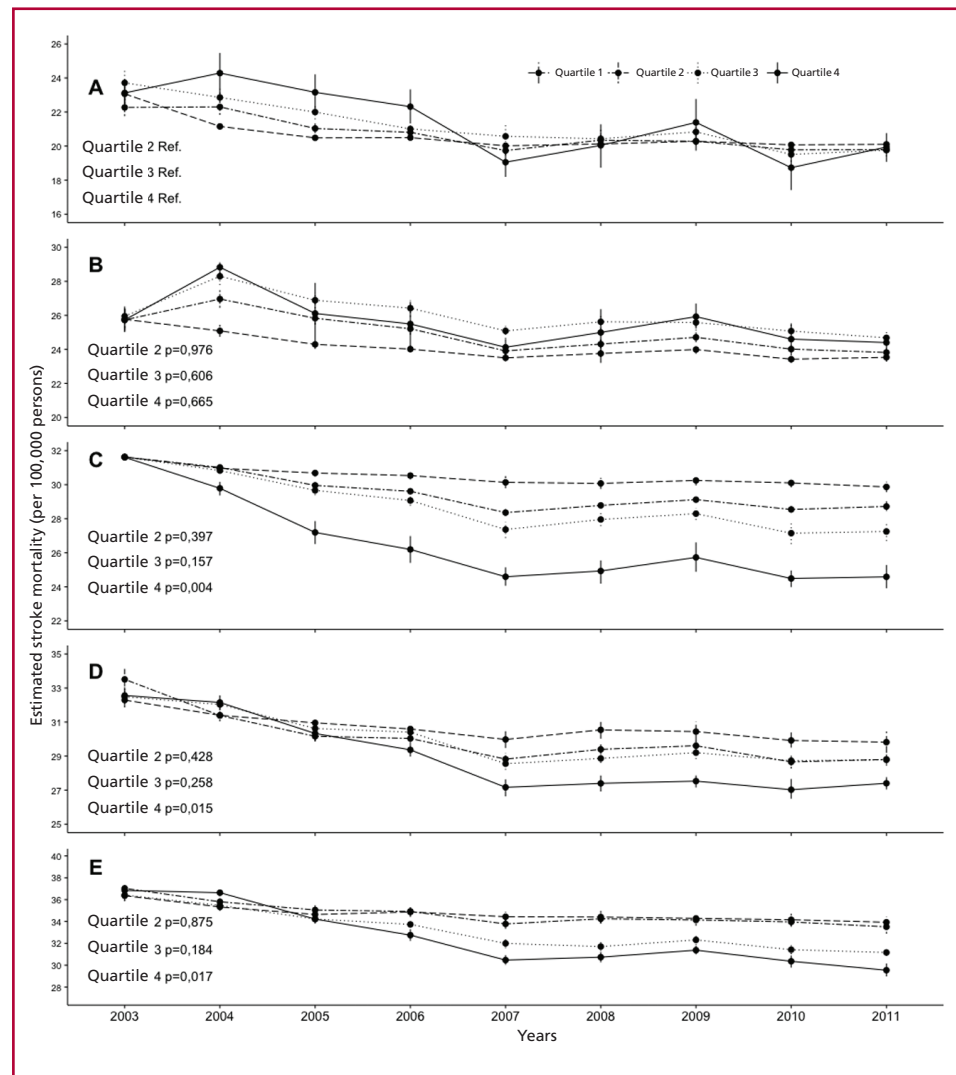
tus and the effects of antihypertensive drug provision could indicate that the relative importance of free antihypertensive drug distribution among the wealthiest departments is lower (due to less reliance on exclusive medical care), whereas its impact among the most disadvantaged departments is more pronounced (20). Thus, aggressive control of risk factors could mitigate identified inequities in mortality from cardiovascular disease in general and stroke in particular (1, 5, 7, 21)

Our study also demonstrates the feasibility of performing population intervention analyses in Argentina linking data from different sources, and the need and importance of optimizing the quality of the records to obtain reliable data. Such studies could become a useful tool for assessing interventions or programs at a population level as demonstrated in other settings. (22)

Our study has limitations that should be considered when interpreting the results. Since it is an ecological study, the associations that occur at departmental level should not be interpreted as occurring at the individual level (ecological fallacy). It should also

be considered, that since we do not have access to risk factor data, it was not possible to correct analyses by these potential confounders; however, the temporal evolution of the three National Risk Factor Surveys (2005, 2009 and 2013) suggests an adverse outcome for most stroke-associated factors. (8) In addition, socioeconomic status was evaluated at a point in time, and assumed for the analyses as an invariant variable, although it is possible that some departments may have changed their relative socioeconomic status over time. Because it evaluates a specific cause of death, the quality of mortality records may have affected the results, both globally and systematically (record bias). (23). Finally, due to the nature of the data, it was not possible to consider residential mobility from one department to another, with different exposure to antihypertensive drugs or socioeconomic status, which could have caused exposure misclassification; however, this phenomenon generally tends to attenuate the associations. (24)

Study results show growing antihypertensive drug dispensing through the Remediar (+Redes) Program

with a steady increase in the departments of lower socioeconomic status. They also suggest that in underprivileged socioeonomic departments, free delivery of antihypertensive drugs is associated with a reduction of stroke mortality.

Conflicts of interest

None declared. (See author´s conflicts of interest forms in the web / Supplementary Material)

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