Prevalence of Concurrent Prescribing of ACE-Is and ARBs among Beneficiaries of Puerto Rico's Government-Sponsored Health Care Plan During 2012 and 2013

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Objective: Cardiovascular conditions are the second cause of death in Puerto Rico. The individual use of angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs) is considered the first-line therapy for the treatment of several cardiovascular-related medical conditions. However, the concurrent use of these 2 therapeutic classes of drugs is not supported by treatment guidelines. Studies have shown that their concurrent use represents a potential health risk. The research described in this paper aimed to determine the prevalence of the concurrent prescription of ACE-Is and ARBs, either separately or as a combination product, in a group of beneficiaries of the Puerto Rico Health Services Administration (ASES, by its initials in Spanish).

Methods: A 2-year cross-sectional study was conducted. All pharmacy claims from the years 2012 and 2013 were provided by ASES and subsequently evaluated by the investigators to identify those involving the prescription of an ACE-I, an ARB, or a combination of drugs belonging to both therapeutic classes. Each pharmacy claim was complemented with sociodemographic and clinical data. The final dataset was analyzed at the person-month level using frequency, cumulative frequency, percentage, and cumulative percentage.

Results: The final sample consisted of 361,841 beneficiaries. A total of 23,598 beneficiaries were excluded because of incomplete diagnostic information. Of the beneficiaries with complete information, 36,202 out of 338,243 (10.7%) had concurrent prescriptions for ACE-Is and ARBs during the study period. We excluded 1,124 beneficiaries who had a primary diagnosis of HF, resulting in a final pool of 35,078 beneficiaries (10.4%) who had prescriptions for combination products.

Conclusion: An unacceptable pattern of ACE-I and ARB co-prescribing during the years 2012 and 2013 was observed in patients with diagnoses for which the combination is not clinically indicated. [*P R Health Sci J 2017;36:71-76*]

Key words: ACE-Is, ARBs, Co-prescribing, Dual Renin-Angiotensin System Blocking, Pharmacy Claims, Puerto Rico

Cardiovascular diseases are the second leading cause of death in Puerto Rico (1). Current recommendations for the treatment of cardiovascular diseases include the use of medications with proven benefits in reducing morbidity and mortality. Because of their proven clinical benefits, drugs that act on the renin-angiotensin system (RAS) such as angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs) have become the first-line therapy for many patients with cardiovascular conditions. RAS plays an important role in the regulation of blood pressure, plasma volume, and sympathetic nervous system activity to maintain organ perfusion (2). Pharmacotherapy with ACE-Is or ARBs has been shown to reduce morbidity and mortality among patients with hypertension (HTN), heart failure (HF), or post-myocardial infarction (MI) and to halt the progression of chronic kidney disease (2, 3).

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ACE-Is inhibit the enzymatic conversion of angiotensin I to angiotensin II, which inhibition causes an initial reduction in AT-II levels. With the chronic use of ACE-Is, the levels of AT-II gradually increase to pretreatment values (4). This is caused by the production of AT-II by non-ACE pathways. This phenomenon, termed ACE escape, has led many scientists to believe that combining ACE-Is with ARBs to more completely block RAS would translate into better cardiovascular outcomes. Dual RAS blockage with ACE-Is and ARBs became a common medical practice despite the lack of evidence in cardiovascular end points (2–5). The benefits of dual RAS blockage have been documented for several CV and renal diseases, such as HTN, HF, post-MI LVD (left ventricle dystrophy), and chronic kidney disease with proteinuria.

Initial studies that evaluated the effects of the combination therapy in the treatment of HTN showed that this therapy had a modest additive effect on blood pressure, but the effects on cardiovascular outcomes were not evaluated (6–9). Some of the most compelling evidence of the effects of dual therapy in cardiovascular outcomes comes from the ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial) (10). In the ONTARGET study (the endpoint of which is a composite of CV death, MI, stroke or hospitalization for HF), no additional cardiovascular benefit was observed when combining an ACE-I and an ARB compared to when ACE-I monotherapy was implemented. A statistically significant increase in the incidence of renal failure, hyperkalemia, and hypotension was observed in the combination group, along with only a moderate decrease in blood pressure.

A study reported that dual RAS blockage decreases proteinuria to a greater extent than ACE-I monotherapy does. However, this decrease in proteinuria didn't translate into a decrease in the progression to end-stage renal disease and dialysis. Therefore, the decrease in the surrogate endpoint didn't translate into better cardiovascular and renal outcomes (2). The VA-NEPHRON-D study, a large-scale clinical trial evaluating the effect of dual RAS blockades in patients with diabetic nephropathy, had to be stopped early because of a high incidence of acute kidney injury and hyperkalemia and no additional benefit in the combination group (11). The lack of clinical benefit of the dual therapy has also been proven in nephropathy not related to DM. The HALT-PKD trials failed to demonstrate the clinical superiority of dual therapy compared to ACE-I monotherapy among patients with hypertensive ADPKD (autosomal dominant polycystic kidney disease) (12–14).

Although both ACE-Is and ARBs have demonstrated benefits as monotherapies in preventing cardiac remodeling after myocardial infarction, their combination hasn't proved to provide such benefits (15). The Valsartan in Acute Myocardial Infarction Trial (VALIANT) evaluated the efficacy and safety of the ACE-I and ARB combination in patients with post-MI LVD. In this study, combination therapy didn't improve survival over monotherapy with either an ACE-I or an ARB, and discontinuation rates associated with adverse events such as hyperkalemia and renal dysfunction were higher in the dual-therapy group (16).

Due to the lack of benefits and increased risks associated with the concurrent therapy composed of an ACE-I and an ARB, this approach cannot be recommended for any CV-related condition at present, with the exception of HF, and that in only select patients.

According to ACCF/AHA treatment guidelines published in 2013, combining an ACE-I and an ARB may be an alternative for patients with reduced ejection fraction and classified as AHA (American Heart Association) stage C or stage D who remain symptomatic after an adequate dose of an ACE-I and a beta-blocker (unless contraindicated) and who cannot tolerate an aldosterone receptor antagonist or in whom such an antagonist is contraindicated (17). The more recently published European guidelines also addressed the combination of ACE-Is and ARBs in the treatment of HF. According to the guidelines, the combination of ACE-Is and ARBs should be used under strict medical supervision and restricted to patients with reduced ejection fraction who remain symptomatic with a beta-blocker and who are unable to tolerate a mineralocorticoid receptor antagonist (18, 19). Although the combination has not consistently proved to decrease mortality in such patients, a decrease in hospitalizations due to HF has been reported in some clinical trials (18, 20).

The purpose of this study was to estimate the prevalence of the concurrent prescribing of ACE-Is and ARBs, alone or as a combination product, among beneficiaries of the Puerto Rico Health Insurance Administration during the years of 2012 and 2013. Although major pertinent clinical guidelines for the treatment of heart failure and hypertension were published after this study was conducted (17, 21), compelling evidence of the potential risks of the combination was published since the large scale ONTARGET trial in 2008 (10). Clinicians should be aware of the impact of evidence-based medicine and should not rely solely on published treatment guidelines, as they may not always reflect the most recent research findings.

Methods

This 2-year study followed a cross-sectional design. All pharmacy claims during the years 2012 and 2013 involving an ACE-I, an ARB, or a combination product containing either of these 2 therapeutic classes of drugs were provided by ASES. Each pharmacy claim number was complemented with the following variables: 1) a unique scrambled identifier for the beneficiary who generated the claim; 2) the year and month the claim was generated; 3) the name of the drug product associated with the claim; 4) the National Drug Code of the drug product associated with the claim; 5) the major drug classification of the drug product associated with the claim; and 6) the therapeutic class of the drug product associated with the claim. The resulting dataset was named *pharmacy claims*

dataset and was sorted by the beneficiary number and the year and month in which each claim was generated. The months of January to December 2012 were numbered from 1 to 12, and the months of January to December 2013 were numbered from 13 to 24. Each of the 24 periods was analyzed for each beneficiary to find duplicate therapies and, thereby, identify the most prevalent combinations of such therapies. Duplicate therapy was defined as having more than 1 pharmacy claim for an ACE-I, an ARB, a combination product, or any combination of these 3 groups in a single month for at least 2 consecutive months. The 2-consecutive-months rule was used to minimize the probability of capturing transitions from one therapy to another, instead of real duplicate therapies. The prevalence of the occurrence of at least 2 concurrent claims for an ACE-I, an ARB, and/or a combination product for the same beneficiary during 2 consecutive months was calculated.

A second dataset was provided by ASES. This dataset contained information on sociodemographics and primary diagnoses for the beneficiaries in the pharmacy claims dataset. The main purpose of creating this dataset was to be able to identify beneficiaries in the pharmacy claims dataset where the duplicate therapy was possibly indicated, which beneficiaries would be, for example, those who had suffered from heart failure. The resulting data repository was named the sociodemographics and primary diagnosis dataset. This data was merged with the pharmacy claims dataset by the unique beneficiary identification number. Beneficiaries whose data were not present in both datasets were excluded from the analysis, stratifying by primary diagnosis. The final dataset was analyzed at the person-month level using frequency, cumulative frequency, percentage, and cumulative percentage. This research was submitted to and approved by the University of Puerto Rico Medical Sciences Campus Institutional Review Board.

Results

The pharmacy claims dataset contained a total of 4,042,823 claims for ACE-Is, ARBs, or combination products containing any of the drugs in these 2 therapeutic classes, which claims were generated by 361,841 unique beneficiaries (Table 1). After sorting by the beneficiary number and by the year and month in which each claim was generated, a total of 150,264 (3.72%) pharmacy claims generated by 37,120 (10.26%) beneficiaries were associated with 2 or more prescriptions (per month) for ACE-Is, ARBs, or combination products for the same beneficiary for 2 consecutive months. This prevalence does not exclude cases in which duplicate therapy may be indicated, such as those cases in which the beneficiary was diagnosed with heart failure. To capture cases where duplicate therapy may be indicated, a secondary analysis was conducted in which the pharmacy claims were merged with sociodemographic and primary diagnosis information.

In the sociodemographics and primary diagnosis claims dataset, a total of 23,598 (6.5%) beneficiaries without primary diagnosis information were excluded, leaving a final pool of 338,243 beneficiaries with at least 1 pharmacy claim for an ACE-I, an ARB, or a combination product containing any of the drugs in either of these 2 therapeutic classes (Table 2). The mean age of these beneficiaries was 61 years, and more than half were female (58.51%). A total of 36,202 (10.7%) beneficiaries had 2 or more claims for an ACE-I, an ARB, or combination products in a single month, for 2 consecutive months.

Table 1. Distribution of claims for ACE-Is, ARBs, or antihypertensive combinations of the 2 (n = 4,042,823).

Therapeutic Class	Frequency	Percent
ACE-I*	2567085	63.50
ARB†	951068	23.52
Antihypertensive combinations	524670	12.98

*Angiotensin-converting enzyme inhibitor; †Angiotensin II receptor blocker

Table 2. Sociodemographics and primary diagnosis claims distribution for beneficiaries with at least 1 pharmacy claim for an ACE-I, an ARB, or a combination product (n = 338,243).

	Frequency	Percent
Gender		
Female	197908	58.51
Male	140335	41.49
ASES* region		
East	55697	16.47
Metro-North	49646	14.68
North	52216	15.44
Northeast	33243	9.83
San Juan	20376	6.02
Southeast	38292	11.32
Southwest	32017	9.47
Special	22	0.01
West	56734	16.77
Primary diagnosis		
Diabetes	144619	42.76
Hypertension	185570	54.86
Coronary artery disease	1296	0.38
Congestive heart failure	6742	1.99
Chronic kidney disease	16	0.00
Number of claims in the same month		
1	302041	89.30
2	34795	10.29
3	1384	0.41
4	23	0.01

*The Puerto Rico Health Services Administration (by its initials in Spanish)

The most prevalent duplicate therapy combination consisted of ACE-Is and ARBs (49.3%), followed by ACE-Is or ARBs and a combination product (21.3% and 13.9%, respectively) (Table 3). Combinations of 2 ACE-Is or 2 ARBs, rare duplicate combinations, and multiple (>2) drug therapy combinations were also observed. The highest prevalence of duplicate therapy was observed in the western and eastern regions of the ASES coverage area, and the primary diagnoses most commonly associated with these claims were diabetes mellitus

and hypertension. A primary diagnosis of HF was identified in 1,124 (3.10%) of the beneficiaries (Table 3). Excluding these beneficiaries, a total of 35,078 beneficiaries were co-prescribed any combination of ACE-Is and ARBs during 2012 and 2013 for a primary diagnosis other than heart failure. They represented 10.4% of all the beneficiaries who were prescribed at least 1 ACE-I, 1 ARB, or a combination product during the study period (Table 4).

Table 3. Primary diagnosis and co-prescribing distribution of ACE-I, ARBs, and/or combination products in a single month for a single beneficiary (for at least 2 consecutive months) (n = 36,202).

	Frequency	Percent
Primary diagnosis		
Diabetes	16176	44.68
Hypertension	18678	51.59
Coronary artery disease	220	0.61
Congestive heart failure	1124	3.10
Chronic kidney disease	4	0.01
CO-PRESCRIBING		
ACE-I* + ARB†	17859	49.33
ACE-I + COMBO††	7726	21.34
ARB + COMBO	5041	13.92
OTHER COMBINATIONS‡	5576	15.40

*Angiotensin-converting enzyme inhibitor; †Angiotensin II receptor blocker; ††Combination therapy that includes an ACE-I or ARB; ‡Multiple (>2) drug therapy combinations.

Table 4. Distribution of beneficiaries who, based on current guidelines, incorrectly received 2 or more prescriptions for an ACE-I, ARB, or combination therapy in a single month (for at least 2 consecutive months) (n = 35,078).

	Frequency	Percent
Gender		
Female	20887	59.54
Male	14191	40.46
ASES* Region		
East	5862	16.71
Metro-North	5117	14.59
North	5388	15.36
Northeast	3641	10.38
San Juan	1888	5.38
Southeast	3882	11.07
Southwest	2929	8.35
West	6371	18.16
Number of claims in the same month		
2	33727	96.15
3	1328	3.79
4	23	0.07
CO-PRESCRIBING		
ACE-I** + ARB†	17211	49.06
ACE-I + COMBO	7556	21.54
ARB + COMBO††	4927	14.05
OTHER COMBINATIONS‡	5384	15.35

*The Puerto Rico Health Services Administration (by its initials in Spanish); **Angiotensin-Converting enzyme inhibitor; †Angiotensin II receptor blocker; ††Combination therapy that includes an ACE-I or ARB; ‡Multiple (>2) drug therapy combinations.

Discussion

ACE-I and ARB pharmacotherapies are frequently prescribed to beneficiaries of Puerto Rico's government-sponsored health care plan. This study identified more than 4 million pharmacy claims (made within the 2-year study period) for these pharmacological products. Interestingly, 10.26% of all the beneficiaries who received at least 1 ACE-I, ARB, or combination product, were receiving a dual RAS blockade with ACE-Is, ARBs, or combination products.

To the best of our knowledge, this is the first study to measure the prevalence of the concurrent prescribing of ACE-Is and ARBs in the United States. A similar study evaluated the trends of the co-prescription of ACE-Is and ARBs in Ireland from 2000 to 2009 (20). The authors reported that 0.3% of the Irish population were receiving a dual RAS blockade over the study period. The Irish study had a population distribution and a prevalence of cardiovascular disease similar to those reported in this study. However, their study was performed over a longer period of time (9 years) and during years in which conflictive evidence of the combination was being published. Although a higher concurrent prescribing of dual RAS blockade therapies was to be expected in the Irish study, the study described herein revealed a higher prevalence in a more recent and shorter time frame.

The concurrent prescribing of ACE-Is and ARBs for 2 consecutive months was present in a range of 2 to 8 claims per patient-month, with the majority of beneficiaries being on duplicate therapy. Having 2 or more claims could be explained by the following: It is possible that the prescribers believed that an additional benefit would accrue from using the combination; there may have been different prescribers for the same patient; there may have been a lack of communication between a given patient and his or her healthcare professionals (including doctors and pharmacists) and/or between those professionals assisting that patient. Another possibility that must be considered is that such dual prescribing might have been caused by the flaws in the current health care plan and the system that regulates it. The concurrent prescribing of more than 3 dual RAS blockade therapies represented less than 1% of the final dataset.

After evaluating each beneficiary's sociodemographic information and primary diagnosis, and excluding those beneficiaries with incomplete information, it was found that a total of 10.7% of the remaining beneficiaries had 2 or more concurrent pharmacy claims for dual RAS blockade in a single month, for 2 consecutive months. The most prevalent combination was at least 1 ACE-I together with at least 1 ARB.

Although a dual RAS blockade was initially thought to be useful in many CV and renal conditions, the current clinical literature recommends its use only in select patients with HF (17). In this study, the primary diagnoses associated with dual RAS blockage were hypertension and diabetes, which are also the main comorbidities in the Puerto Rican population (22). Only 3.10% of the beneficiaries with concurrent dual RAS blockade therapies had a primary diagnosis of HF, which means

that 10.4% of the beneficiaries were prescribed a combination therapy without there being a diagnostic indication (per current treatment guidelines) of its necessity. It is important to note that in both the 2012 and 2013 ADA (American Diabetes Association) treatment guidelines, a regimen that includes an ACE-I or an ARB was recommended as the first-line treatment for patients with hypertension and diabetes. Those guidelines do not directly assess combination therapy, but instead recommend using one class of drug or the other (23, 24). Similarly, the guidelines for hypertension in the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7), which were published in 2003 and updated in 2013, didn't directly address the combination of an ACE-I and an ARB for the treatment of hypertension, either alone or with any other compelling indications (25).

Pertinent clinical guidelines that explicitly addressed the combination of ACE-Is and ARBs (e.g., the ACC/AHA HF guidelines and the eighth Joint National Committee [JNC-8] hypertension guidelines) were updated in late 2013, at the end of our study period. Although the fact that the updated guidelines were released late in the "life" of our study may be seen as a potential limitation, it really emphasizes the importance of incorporating updated research clinical evidence into the medical practice. Clinical research is published constantly, and some of the findings of important clinical research end up changing the way medicine is practiced. Clinicians should keep reading medical literature in order to provide patients with the most recent and validated treatment recommendations. Treatment guidelines are only guidelines, and sometimes it takes time to update recommendations based on recent evidence. Ultimately, clinicians are responsible for their patients' clinical outcomes, no matter what the guidelines recommend—especially if outdated guidelines are used to make important clinical decisions.

One limitation of this study was that the database did not provide information about HF stage, making it impossible to determine whether there was really a possible indication for concomitant prescribing in these beneficiaries. Moreover, we could identify only the primary diagnosis of each of the beneficiaries. Other possible comorbidities not listed as primary, which may also include HF, couldn't be identified. This may have caused an overestimation of inappropriate co-prescribing in this study. Another limitation of this study was that the database is representative of only the medically indigent and elderly population enrolled in the government health care plan. In addition, the study was performed during a 2-year time frame, which makes it difficult to determine whether there has been an increasing or decreasing trend of concurrent prescribing.

Conclusion

To our knowledge this is the first study that reports the prevalence of the concurrent prescribing of ACE-Is and ARBs in the Puerto Rican population. An unacceptable pattern of ACE-I and ARB co-prescribing was observed among beneficiaries with diagnoses for which the combination is not supported by clinical evidence or current treatment guidelines. There is a need to develop education policies and strategies aimed at prescribers and health plans to ensure the safe and effective use of these pharmacotherapies. Such strategies could lead to reducing the concurrent prescribing of RAS blockade therapies and subsequently decreasing health care costs, and lead, as well, to the elimination of those risks associated with concurrent prescribing, which risks include hyperkalemia, hypotension, and acute renal failure. As a result, the successful implementation of these kinds of programs may further contribute to the reduction of morbidity and mortality associated with poor management in the treatment of cardiovascular diseases.

Resumen

Objetivo: Las enfermedades cardiovasculares son la segunda causa de muerte en Puerto Rico. Los inhibidores de la enzima convertidora de angiotensina (ACE-Is, por sus siglas en inglés) y los bloqueadores de los receptores de angiotensina (ARBs, por sus siglas en inglés) son considerados primera línea para el tratamiento de éstas condiciones. El uso concurrente de estos agentes no está sustentado por las guías de tratamiento. Estudios han reportado que más que un beneficio, su uso concurrente representa un riesgo potencial a la salud. Este trabajo determinó la prevalencia de prescripción concurrente de ACE-Is y ARBs en beneficiarios de la Administración de Servicios de Salud (ASES) de Puerto Rico. Metodología: Se realizó un estudio transversal de dos años. Las reclamaciones de farmacia durante los años 2012 y 2013 para ACE-Is, ARBs o combinaciones de estos fueron proporcionados por ASES. Cada reclamación de farmacia se complementó con información clínica y socio-demográfica. Los datos fueron analizados por persona-mes utilizando frecuencia, frecuencia cumulativa, porcentaje y porcentaje cumulativo. Resultados: La muestra final fue de 361,841 beneficiarios. De estos, 23,598 fueron excluidos, ya que no tenían información completa de diagnóstico. Entre los beneficiarios con información completa, un total de 36,202 de 338,243 (10.7%) tenían prescripción concurrente. Excluyendo 1,124 beneficiarios con un diagnóstico primario de insuficiencia cardiaca, se obtuvo un grupo final de 35,078 beneficiarios (10.4%) con la combinación de medicamentos. Conclusión: Durante los años 2012 y 2013 se encontró una alta proporción de beneficiarios con reclamaciones concurrentes de ACE-Is y ARBs. En la mayoría de los casos estas reclamaciones no eran clínicamente plausibles.

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