Impact of Secondary Prevention on Mortality after a First Ischemic Stroke in Puerto Rico

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Objective: The objective of this study was to evaluate the impact of the prescription of secondary prevention therapies on mortality in Puerto Rican patients hospitalized with a first ischemic stroke.

Methods: This was a retrospective secondary data analysis of the 2007 and 2009 Puerto Rico Stroke Registry electronic database. Information was obtained from the medical charts of patients discharged with ICD-9 codes 434 and 436 from 20 hospitals located in Puerto Rico. Descriptive analyses were conducted for demographics and comorbidities. Chi2 statistics compared the proportion of patients prescribed secondary prevention therapy and the proportion of patients not prescribed secondary prevention therapy. Lastly, survival rates were calculated from 2007 up to and including December 2010.

Results: The mean age of the 3,965 patients was 70 (±14) years. Secondary prevention therapy was prescribed to only 1% of the patients. The most frequent comorbidities were hypertension (85%), diabetes (52%), and hyperlipidemia (25%). The case fatality rate for patients prescribed secondary prevention therapy was 16%, compared to 26% for patients not prescribed secondary prevention therapy (p <0.01). The mean survival for stroke patients prescribed secondary preventions was 450 days (95% CI;182–718), compared to 266 days (95% CI; 244–287) for those not prescribed secondary prevention therapy (p = 0.175).

Conclusion: A low percentage of patients with a first ischemic stroke were prescribed secondary prevention therapy. While not statistically significant, survival analysis suggests that secondary prevention therapy decreased mortality in patients with a stroke. [*P R Health Sci J 2017;36:11-16*]

Key words: First ischemic stroke, Secondary prevention therapy, Cerebrovascular disease, Acute ischemic stroke, Mortality

Globally, ischemic stroke is the second leading cause of death, causing nearly 5.5 million deaths annually (9.7% of deaths) (1). Stroke is a major public health challenge and presents a major financial burden, especially in Latin American countries (2, 3). About 80% of strokes can be prevented (4). However, without effective prevention strategies, the total cost for strokes through 2050 in the United States is projected to be $313 billion for Hispanics and $379 billion for blacks; in 2005 alone, strokes were responsible for 143,579 deaths in the United States (5).

Each year more than 795,000 strokes are first attacks and 185,000 are recurrent attacks (6, 7). The incidence rate of first ischemic stroke, mainly in Caribbean Hispanics, is estimated to be 149 per 100,000. By the year 2030, it is expected that the prevalence will increase 25%. Furthermore, stroke is the leading cause of severe, long-term disability, which exponentially increases health care costs. About 15% to 30% of stroke survivors are disabled, and there are more than 1 million American families affected by stroke (5,8,9). Currently, stroke costs over $70 billion in lost productivity and health care costs, including $12 billion in nursing-home expenditures (10). In Puerto Rico (PR) strokes caused 1,525 deaths in 2005 and have been the leading cause of severe, long-term disability for several decades (11). For these reasons, the implementation of evidence-based secondary prevention therapy is crucial for the prevention of recurrent stroke and can substantially reduce morbidity and the loss of gross domestic product in the future.

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Much of the morbidity and mortality is the result of recurrent attacks rather than the initial attack (6, 12). Since the risk of recurrent ischemic stroke is highest in the first 6 months after the initial stroke, the prompt initiation of appropriate secondary therapy is crucial to decrease morbidity and mortality (13).

Evidence has shown that secondary prevention therapies for the treatment of acute ischemic stroke patients decrease complications, prevent recurrence, and decrease the risk of death. For example, lowering blood pressure with an angiotensin-converting-enzyme inhibitor (ACEI) alone or in combination with a thiazide diuretic can reduce the risk of recurrent stroke by 28% and the risk of disability from recurrent stroke by 36% (14). Similarly, use of a thiazide diuretic reduces the risk of stroke by 34% (15, 16). Aspirin alone or in combination with dipyridamole reduces the recurrence of stroke by 18% and 37%, respectively (17). Though studies on lifestyle modifications are limited, there is evidence that exercise may reduce the risk of stroke by 20% for patients exercising rigorously once a week and by 26% for patients engaging in rigorous physical activity more than 5 times a week (18, 19). The American Heart Association and the American Stroke Association have compiled this evidence and developed clinical practice guidelines for physicians to guide them in prescribing secondary prevention therapy to reduce morbidity and mortality from stroke (18). The aim of this study was to evaluate the impact of secondary prevention therapy on mortality in patients discharged after having had a first ischemic stroke.

Methods

This was a secondary database analysis of data from the Puerto Rico Cardiovascular Disease and Stroke Registry, a registry containing information on the stroke patients admitted to 20 medical centers in PR.

Study population

The study population for the registry consisted of 3,965 hospitalized patients with a first acute stroke. The study years were 2007 and 2009. Inclusion criteria were being an adult over 18 years of age, having suffered a first ischemic stroke, and having been discharged with ICD-9 codes 434.00 to 434.91 and 436. Missing data were eliminated. Excluded from the study were all recurrent cases of stroke, hemorrhagic stroke, fatal stroke, and transient ischemic stroke.

Mortality data

Dates of death were obtained from the National Death Index and the Puerto Rico Department of Health. The dates of death were linked to the study subjects' identification code numbers. Survival until December 2010 was calculated for 3,945 patients.

Variable definition

Based on the guidelines of the American Heart Association and American Stroke Association (18), patients were considered to have adequate secondary prevention therapy only if they received the following:

Patients with atrial fibrillation needed to receive warfarin during the first 24 hours after admission and at hospital discharge. Patients with non-cardioembolic stroke needed to receive one of the following antiplatelet therapies (Aspirin, clopidogrel, aspirin/dipyridamole, or dipyridamole) during the first 24 hours after admission and at hospital discharge. At hospital discharge all patients needed to receive an antihypertensive (diuretic, ACEI, ARB, beta-blocker, or calcium channel blocker), a lipid-lowering agent (statin or non-statin), and counseling about lifestyle modifications (stroke education, increased activity, weight reduction).

Statistical analyses

A combination of descriptive and inferential statistics was used to evaluate the proportions of patients prescribed secondary prevention therapy versus patients not prescribed secondary prevention therapy during the first 24 hours of hospitalization and at discharge. A Kaplan–Meier analysis was used to estimate survival ratios. The log-rank statistic was used to test significance in the survival analysis. Multiple logistic regression models of the association between secondary prevention therapy and mortality were performed. For all analyses, a p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using Stata v11. This study was approved by the Institutional Review Board of the University of Puerto Rico.

Results

Demographics

The mean age of the 3,965 patients was 70 (± 14) years. The most frequent comorbidities were hypertension (85%), diabetes (52%), and hyperlipidemia (25%). A total of 222 (6.5%) patients had atrial fibrillation. The patients were followed for 1,250 days or until the time of death. See Table 1 for the baseline demographics of the subjects.

Secondary prevention therapy

Twenty percent (672) of the patients were not prescribed any medication after discharge. Only 41 (1%) of patients were prescribed *adequate* (per our definition) secondary prevention therapy following hospital discharge. Atrial fibrillation was most prevalent in the elderly and increased with age, with 22% in the 65 to 74 years age range, 38% in the 75 to 84 years age range, and 29% in the over 84 years age group (see Figure 1). About 75% of the patients with hypertension were not prescribed antihypertensives, 56% of the patients with hyperlipidemia were not prescribed a lipid-lowering agent, and 67% of the patients with atrial fibrillation were not prescribed warfarin at discharge (see Table 2). The prescribing of secondary prevention therapies varied with the age group and type of medication. Prescriptions of lipid-lowering agents were fewer in the under 55 and over 84

Table 1. Baseline patient demographic characteristics

	Male n (%)	Female n (%)	Total Population n (%)
Stroke patients	1882 (47.5)	2083 (52.5)	3965 (100)
Mean age: Years (± SD)	68 (±14)	72 (±14)	70 (±14)
Age groups (years)			
<55	273 (52)	255 (48)	528 (13)
55 – 64	427 (59)	297 (41)	724 (18)
65 – 74	518 (50)	513 (50)	1,031 (26)
75 – 84	445 (41)	632 (59)	1,077 (27)
>84	213 (36)	380 (64)	593 (15)
Total	1,876 (48)	2,077 (53)	3,953 (100)
Cardiovascular risk factors^			
Hyperlipidemia	377 (46)	448 (54)	825 (26)
Hypertension	1,457 (46)	1,689 (54)	3,146 (85)
Diabetes	838 (46)	993 (54)	1,831 (52)
Current smoker	226 (66)	116 (34)	342 (10)
Atrial fibrillation	98 (44)	124 (56)	222 (7)
Secondary Prevention Therapy			
Total (Per our definition)€	25 (1.3)	16 (0.77)	41 (1.0)

Age calculated for 3,953 patients. Calculated for 3,965 patients. ^Unrecorded data were eliminated. €Per definition: stroke patients were prescribed antithrombotics (antiplatelets for non-cardioembolic stroke and warfarin for stroke from cardiac-origin atrial fibrillation) during the first 24 hrs and at hospital discharge; antihypertensives, lipid-lowering agents, and lifestyle modifications at discharge.

age groups (12% for both groups) than they were in the 55 to 84 age group (varying from 22% to 25%) (see Figure 2).

Lifestyle modifications, as defined previously, were prescribed at discharge to 87% of the patients with atrial fibrillation. Warfarin was prescribed to 28% of the patients with atrial fibrillation during the first 24 hours and to 32% at discharge. Antiplatelets were prescribed during the first 24 hours and at discharge to 51% and 44% of the patients, respectively (see Table 3).

Survival and logistic regression analyses

For the first 200 days, post-stroke, survival was the same for the secondary prevention therapy group and for those not prescribed secondary prevention therapy (p = 0.175) (see Figure 3). The mean survival was 450 days (95% CI: 182–718) for stroke patients prescribed secondary prevention therapy and 266 days (95% CI; 244–287) for those who were not prescribed secondary prevention therapy. The median survival time was 230 days (95% CI: 0–575.5) for patients prescribed secondary prevention therapy and 97 days (95% CI: 76–117) for those not prescribed secondary prevention (see Figure 3).

The risk of mortality increased about 3-fold (OR 2.8, 95% CI: 1.17–6.5; p = 0.02) and about 2-fold (OR: 1.9; 95% CI: 1.64–2.32; p<0.001), respectively, for patients who were not prescribed lipid lowering agents and lifestyle modifications after discharge (n = 3,945). The case fatality rate for patients prescribed secondary prevention therapy was 16% compared to 26% for patients not prescribed secondary prevention therapy (p<0.01). Complete results of the logistic regression analyses for associations of secondary prevention therapies to mortality are shown in Table 4.

Discussion

We found that a very low percentage of first ischemic stroke patients were being prescribed the secondary prevention therapy that is recommended by the American Heart Association and American Stroke Association, regardless of the cardiovascular risk factors of those patients. For example, although hypertension, which is the most significant risk factor for stroke (7, 20), was present in 85% of the stroke patients in our study, only one fourth of these patients were prescribed antihypertensives at discharge. Previous studies in PR have shown a high prevalence of hypertension and diabetes, thus increasing the risk for ischemic stroke in this population. The study by Monsanto et al. found that 72% (n = 303) of patients had hypertension, 38% had dyslipidemia, and 38% had diabetes (21). In a survey of the Puerto Rican population (n = 840), Perez et al. found hypertension in 19% of people with normal

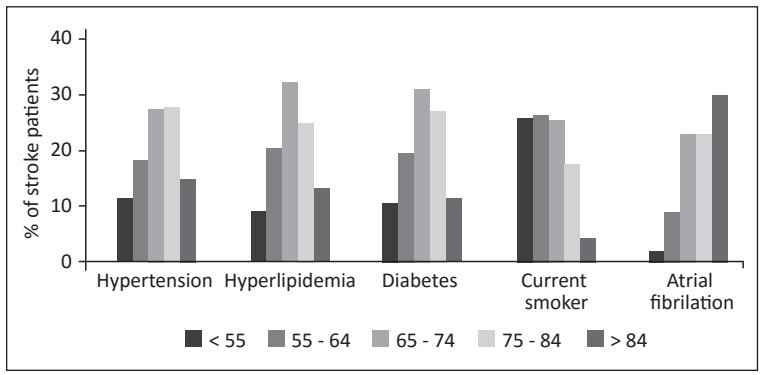

Figure 1. Cardiovascular risk factors increased by age group. Atrial fibrillation increased with age, with 22% in the 65 to 74 years age range, 38% in the 75 to 84 years age range, and 29% in the over 84 years age group. Lipid-lowering agents (27%), antihypertensives (28%), and antiplatelets (27%) were higher in the over 65 and under 75 years age group.

Table 2. Cardiovascular risk factors and prescribing secondary prevention therapy at discharge

Risk Factors£	Antiplatelets n (%)	Anticoagulants* n (%)	Antihypertensives n (%)	Lipid Lowering Agents n (%)
Hyperlipidemia	469 (57)	1,468 (47)	886 (48)	178 (52)
Hypertension	41 (19)	72 (9)	210 (7)	126 (7)
Diabetes	16 (5)	72 (32)	250 (30)	814 (26)
Current smoker	440 (24)	67 (20)	56 (25)	362 (44)
Atrial fibrillation	870 (28)	523 (29)	117 (34)	41 (19)

*warfarin. £Patients had concurrent comorbidities.

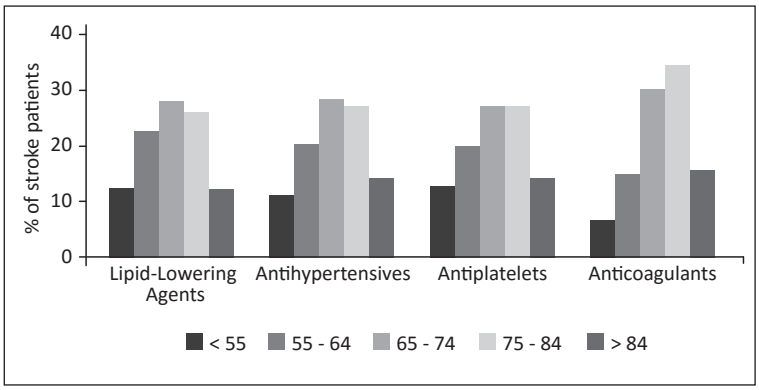

Figure 2. Prescriptions of secondary preventio therapy at discharge by age group. Prescriptions of lipid-lowering agents (27%), antihypertensives (28%), antiplatelets (27%), and anticoagulants (30%) were more frequent in the over 65 and under 75 years age group. Prescriptions of anticoagulants (warfarin) were more frequent (34%) in the over 75 and under 85 years age group.

Table 3. Secondary prevention therapy prescribed during the first 24 hrs and at hospital discharge

Secondary prevention therapy prescribed	First 24 hrs in hospital n (%)	At hospital discharge n (%)
Warfarin-AF*	61 (28)	72 (32)
Antiplatelets	2,033 (51)	1,728 (44)
Antihypertensives	–	873 (22)
Lipid lowering agents	–	1,021 (26)
Lifestyle modifications	–	2,692 (68)

Unrecorded data were eliminated. *AF = atrial fibrillation (n = 222)

weight, 41% of overweight persons, and 49% of obese people (22).

In our study, half of the population had diabetes, which is consistent with the findings from a recent study by Zevallos et al. that found a high prevalence of hypertension (>85%) and diabetes (>54%) in the Puerto Rican population (n = 5005) (23).

Furthermore, our findings are consistent with those of previous studies that also found that prescribing secondary prevention therapy for stroke was occurring at a suboptimal rate. Studies in the United States (24) and France (25) showed that only 80% and 50% of stroke patients, respectively, were prescribed antihypertensives. Other studies showed that about 50% of patients with hyperlipidemia were not managed adequately (26) and that about 50% of patients with atrial fibrillation were not prescribed oral anticoagulants (27). The Paul Coverdell National Acute Stroke Registry (PCNASR) showed that in spite of an increase in secondary-prevention prescribing from 2005 to 2009, a large number of acute stroke patients still were not prescribed adequate secondary prevention, according to the guidelines in the United States (28). According to a study done in England (Shakur et al.), about 30% of the patients with cardiovascular risk factors did not receive the guideline-mandated statins at hospital discharge; the most overlooked indication was cerebral vascular accident (29). The authors speculated that the lack of secondary-prevention prescribing was mainly due to physician oversight. To assist with this issue, they suggested using a prescription-chart checking system to help pharmacists as well as physicians increase secondary prevention (29).

Atrial fibrillation increases the risk of acute stroke about 5 times and is considered to be a major cause of ischemic stroke (7). Although we found that atrial fibrillation increased with age, patients older than 84 years were less likely to be prescribed secondary prevention therapy. Its findings similar to our own, a study in Sweden showed that, following an acute stroke, patients older than 85 years of age were less likely to be prescribed secondary prevention therapy at discharge, despite the fact

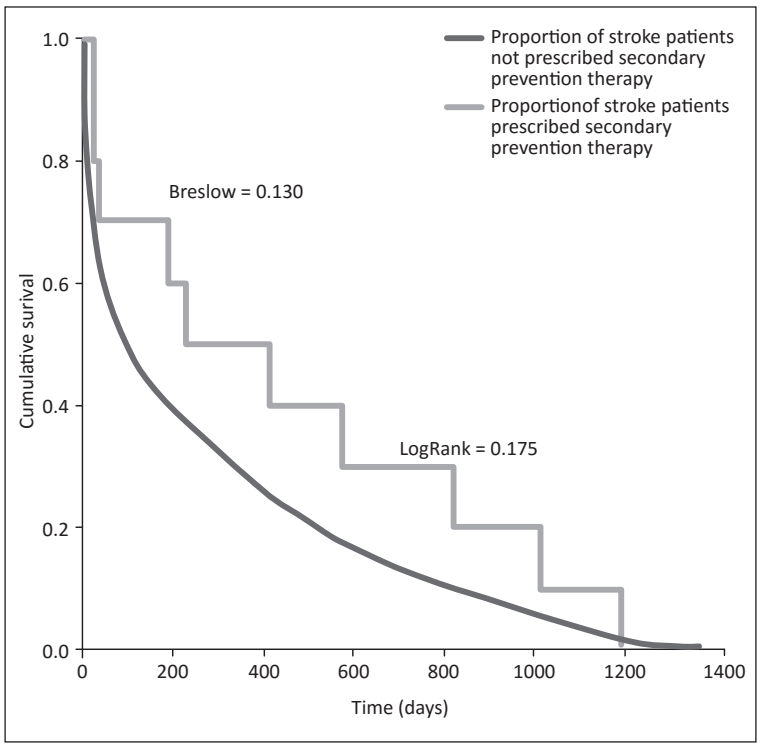

Figure 3. Survival curves for stroke patients prescribed secondary prevention therapy and not prescribed secondary prevention therapy. For the first 200 days, post-stroke, survival was the same for the secondary prevention therapy group and for those not prescribed secondary prevention therapies. Patients were followed for 1,250 days or until the time of death.

Table 4. Odds ratios with 95% CIs for not prescribing secondary prevention therapy and mortality after discharge.

n = 3945	n	%	OR*	95% CI	P-Value
Anticoagulant-Warfarin-AF	72	32	0.81	0.61–1.06	0.128
Antiplatelets	1,728	44	2.26	0.94–5.43	0.068
Antihypertensives	873	22	0.76	0.31–1.87	0.555
Lipid lowering agents (Total)	1,021	26	2.76	1.17–6.50	0.02
Lifestyle modifications	2,692	68	1.95	1.64–2.32	<0.001
Age	–	–	1.05	1.04–1.06	<0.001
Gender	–	–	1.09	0.92–1.29	0.326

that prescribing statins and warfarin to this population was associated with lower mortality (30). Other studies, these in the United States, showed that the elderly were less likely to be prescribed antiplatelets and antihypertensives for secondary prevention therapy for stroke, despite the proven benefit (31, 32). Possible reasons why the elderly are prescribed secondary prevention therapy less frequently might include the expected life span of the members of this population, physician fear of complications, concurrent comorbidities (in a given patient), and the lack of specific evidence-based prescribing guidelines for this population (30, 31, 33).

In our study, there were no statistically significant differences in survival time in patients not prescribed adequate secondary prevention therapy and those who were prescribed adequate (per our definition) secondary prevention therapy. However, the small sample size of stroke patients who were prescribed secondary prevention, per our definition (n = 41), may be responsible for our not having detected a difference between the groups. In spite of this limitation, the odds of survival of patients with secondary prevention compared to patients without seemed to be more favorable, especially after 200 days. In the first 200 days, survival was the same for the 2 groups (p>0.05). The groups may be similar initially and diverge at later time points because the drugs take time to work, because patients not receiving the adequate secondary prevention were still taking some medications, or because the medications may primarily affect delayed stroke pathology (34–36).

Two of the limitations of our study are the small sample size and the retrospective analysis from a secondary database containing data from medical chart reviews, which analysis depended on the original physician's accurate documentation and did not establish causality. In addition, we did not assess whether the drugs were contraindicated for some patients. Another limitation of this study is that the only anticoagulant evaluated for atrial fibrillation was warfarin. In addition, the researchers were not able to assess the severity of the stroke upon hospital admission. Power calculations prior to the study were not performed.

Conclusions

A low percentage of patients with first ischemic stroke received secondary prevention therapy. Although there was no statistically significant difference, survival analyses suggest that secondary prevention therapy may decrease mortality in patients with stroke. The limited prescribing of secondary prevention therapy in PR suggests that there is a disparity in the implementing of guidelines by clinical practice. Perhaps, the national implementation of GWTG-Stroke in PR, as has occurred in the United States, could be an effective strategy to address the disparity in the use of secondary prevention therapy at Puerto Rican hospitals (37).

Resumen

Objetivo: Evaluar el impacto de prescribir terapias de prevención secundarias en la mortalidad en pacientes puertorriqueños hospitalizados con un primer accidente cerebrovascular isquémico. Métodos: Análisis retrospectivo de la base de datos electrónica del Registro de Ataques Cerebrales de Puerto Rico. Data obtenida de expedientes médicos de pacientes dados de alta con códigos ICD-9 434 y 436 de 20 hospitales de Puerto Rico de 2007 y 2009. Se hicieron análisis descriptivos de demografía y comorbilidades. El chi-cuadrado comparó la proporción de pacientes que se les prescribió terapia de prevención secundaria con la proporción de pacientes que no se les prescribió. Resultados: La edad promedio de los 3,965 pacientes fue 70 ±14 años. Se prescribió terapia de prevención secundaria a solo el 1% de los pacientes. Las comorbilidades frecuentes fueron hipertensión (85%), diabetes (52%) e hiperlipidemia (25%). La tasa de mortalidad para los pacientes que se les prescribió terapia de prevención secundaria fue un 16% en comparación con un 26% en pacientes que no se les prescribió (P< 0.01). La media de la supervivencia para los pacientes de accidente cerebrovascular que se les prescribió terapia de prevención secundaria fue 450 días (95% CI, 182-718) en comparación con 266 días (95% CI, 244-287) para los que no se les prescribió (p= 0.175). Conclusión: Un por ciento bajo de los pacientes con un primer accidente cerebrovascular isquémico recibió terapia de prevención secundaria. Aunque no fue estadísticamente significativo, el análisis de supervivencia sugiere que la terapia de prevención secundaria redujo la mortalidad en pacientes con un accidente cerebrovascular.

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