Persistence with Antihypertensive Agents for 12 Months After Ischemic Stroke Reduces the Rates of Death and Dependency

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Received 22 October 2012; revision 11

November 2012; accepted 12 November 2012.

doi: 10.1111/cns.12048

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High adherence to antihypertensive therapy, and the associated blood pressure control, reduces the risk of initial stroke when used as primary prevention [1–3]. Kettani et al. [1] found that patients with high adherence to antihypertensive therapy ($\geq 80\%$ calculated using the medication possession ratio) had a significantly lower risk of cerebrovascular disease, compared with patients with lower adherence. However, to our knowledge, the relationship between adherence to antihypertensive therapy after stroke and clinical outcomes has not been studied. The aim of this study was to assess the relationship between persistence with antihypertensive therapy after ischemic stroke and rates of death and dependency in patients with hypertension.

Data were obtained from the China National Stroke Registry (CNSR) [4], a nationwide, prospective, hospital-based registry of consecutive stroke patients (≥ 18 years) within 14 days after stroke onset who were admitted to 1 of 132 participating hospitals between September 2007 and August 2008 in China. The ethics committees at the 132 participating hospitals approved the procedures, and all patients or their designated relatives provided informed consent.

This observational analysis included patients in the CNSR who had been diagnosed with ischemic stroke according to the World Health Organization criteria [5]. Hypertension was defined with the composite of a self-reported physician diagnosis of hypertension and use of antihypertensive drugs before the onset of stroke, or with a final diagnosis of hypertension at discharge (International Classification of Diseases, 9th revision, [ICD-9] code: 401). Information about the use of antihypertensive medication at 3, 6, and 12 months was obtained by telephone interview with patients or their designated relatives.

Classes of antihypertensive medication included angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics, and β -blockers. Persistence was calculated as the cumulative duration of antihypertensive medication divided by the length of the follow-up period (12 months). Persistence of $\geq 75\%$ was defined as high. Persistence $<75\%$ was defined as low. Patients who did not take any antihypertensive therapy during the 12-month follow-up period were defined as untreated. Death during follow-up was considered as the end of the study, and persistence was calculated for the period before death. At 3, 6, and 12 months after stroke onset, the outcomes of all patients were assessed through telephone follow-up, including death and dependency. Dependency was assessed with the modified Rankin Scale (mRS), which was recorded for all patients in the CNSR database. Functionally, dependent was defined as an mRS score of 3, 4, or 5.

Logistic regression model was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the relationship between persistence and clinical outcomes at 12 months, after adjusting for potential confounders selected from baseline characteristics with a significant difference among groups $P < 0.05$ (Table 1). Data were analyzed with SAS version 9.1.3 statistical software (SAS Institute Inc., Cary, NC, USA).

The CNSR recruited a total of 22,216 patients, there were 11,208 patients diagnosed with ischemic stroke and of these, 8409 (75.0%) were considered to have hypertension. Of the 8409 patients in the study, 40% were female and the mean age at study entry was 66.1 years. Persistence with antihypertensive therapy varied among patients, with many patients having no ($n = 1603$; 19.1%) or low ($n = 4147$; 49.3%) persistence with

Table 1 Baseline characteristics of patients, *n* (%).

	Persistence levels*			
Characteristics	Untreated (<i>n</i> = 1603)	Low (<i>n</i> = 4147)	High (<i>n</i> = 2659)	<i>P</i> value [†]
<i>Demographics variables</i>				
Female	658 (41.0%)	1647 (39.7%)	1059 (39.8%)	0.636
Age (mean ± SD)	67.6 ± 11.4	66.3 ± 11.7	64.5 ± 12.1	<0.0001
<i>Monthly household income, yuan</i>				
≤ 1000	495 (30.8%)	1391 (33.5%)	925 (34.8%)	<0.0001
1001–3000	492 (30.7%)	1473 (35.5%)	971 (36.5%)	
≥ 3000	91 (5.7%)	290 (7.0%)	203 (7.6%)	
Unknown	525 (32.8%)	993 (23.9%)	560 (21.1%)	
<i>Types of health insurance</i>				
Urban employee	1008 (62.9%)	2613 (63.0%)	1727 (64.9%)	0.548
Rural Cooperative	257 (16.0%)	625 (15.1%)	396 (14.9%)	
Commercial	48 (3.0%)	140 (3.4%)	76 (2.9%)	
Own expense	290 (18.1%)	769 (18.5%)	460 (17.3%)	
<i>Level of education</i>				
Elementary or below	835 (52.1%)	1949 (47.0%)	1067 (40.1%)	<0.0001
Middle school	372 (23.2%)	1068 (25.8%)	725 (27.3%)	
High school or above	396 (24.7%)	1130 (27.2%)	867 (32.6%)	
Married	1403 (87.5%)	3710 (89.5%)	2415 (90.8%)	0.011
Live alone	68 (4.2%)	134 (3.2%)	81 (3.0%)	0.089
<i>Vascular risk factors</i>				
History of stroke	670 (41.8%)	1557 (37.5%)	946 (35.6%)	0.0003
History of CHD	261 (16.3%)	686 (16.5%)	444 (16.7%)	0.939
History of AF	225 (14.0%)	456 (11.0%)	194 (7.3%)	<0.0001
History of DM	463 (28.9%)	1339 (32.3%)	803 (30.2%)	0.025
History of dyslipidemia	798 (49.8%)	2395 (57.8%)	1660 (62.4%)	<0.0001
History of smoking	603 (37.6%)	1579 (38.1%)	1051 (39.5%)	0.368
History of drinking	147 (9.2%)	380 (9.2%)	229 (8.6%)	0.712
<i>Other clinical features</i>				
Pre-stroke dependency [‡]	220 (13.7%)	434 (10.5%)	209 (7.9%)	<0.0001
<i>NIHSS scores at admission</i>				
0–4	644 (40.2%)	2114 (51.0%)	1474 (55.4%)	<0.0001
5–14	606 (37.8%)	1543 (37.2%)	1019 (38.3%)	
≥ 15	353 (22.0%)	490 (11.8%)	166 (6.2%)	
<i>Class of initially prescribed antihypertensive drugs</i>				
Diuretics	64 (4.0%)	93 (2.2%)	48 (1.8%)	<0.0001
ARB	19 (1.2%)	97 (2.3%)	98 (3.7%)	
ACEI	316 (19.7%)	883 (21.3%)	614 (23.1%)	
CCB	894 (55.8%)	2364 (57.0%)	1545 (58.1%)	
Beta-blockers	63 (3.9%)	137 (3.3%)	72 (2.7%)	
More than one AH drug class	247 (15.4%)	572 (13.8%)	282 (10.6%)	
Discharge with antiplatelet or anticoagulation agents	899 (56.1%)	2877 (69.4%)	2084 (78.4%)	<0.0001
Discharge with lipid lowering agents	494 (30.8%)	1604 (38.7%)	1194 (44.9%)	<0.0001

*Persistence of ≥ 75% was defined as high; persistence <75% was defined as low; Patients who did not take any antihypertensive therapy during the 12-month follow-up period were defined as untreated. [†]The *P* values are related to comparison between three groups. [‡]Prestroke dependency was defined as mRS 3–5. ACEI, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; AH, antihypertensive; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; CHD, coronary heart disease; DM, diabetes mellitus; NIHSS, National Institutes of Health Stroke Scale.

therapy. Only one-third of patients were considered to have high persistence with their antihypertensive therapy (*n* = 2659; 31.6%). The baseline characteristics of study population are presented in Table 1. Of the 8409 patients in the study, 1210 (14.4%) were dead 12 months after their initial stroke and 1696 (23.6%) were considered dependent (mRS 3–5). Compared with untreated patients, patients with either high (odds ratio, 0.38;

95% CI: 0.28–0.47) or low persistence (0.64, 0.55–0.79) had a significantly lower rate of death (Table 2). Compared with untreated patients, patients with high persistence (0.82, 0.67–0.96), but not low persistence (0.97, 0.87–1.23), also had a significantly lower rate of dependency (Table 2).

In conclusion, the results from our study show that high persistence with antihypertensive therapy reduces the rates of both

Table 2 Rates and Odds ratios (OR and 95% CI) of death and dependency at 12 months for patients with hypertension who have had an ischemic stroke

	Dependency		Death	
	Rate	Adjusted OR* (95% CI)	Rate	Adjusted OR* (95% CI)
Untreated group	308 (27.0%)	Reference	461 (28.8%)	Reference
Low persistence group	903 (25.4%)	0.97 (0.87–1.23)	595 (14.4%)	0.64 (0.55–0.79)
High persistence group	485 (19.4%)	0.82 (0.67–0.96)	154 (5.8%)	0.38 (0.28–0.47)

High persistence was defined as $\geq 75\%$, and low persistence was defined as $<75\%$. CI, confidence interval; OR, odds ratio. *Adjusted for: (1) age, (2) monthly household income, (3) level of education, (4) marital status, (5) history of stroke, (6) atrial fibrillation, (7) diabetes mellitus, (8) dyslipidemia, (9) prestroke dependency, (10) severity of stroke on admission, (11) classes of initially prescribed antihypertensive drugs, (12) discharge with antiplatelet or anticoagulation agents, and (13) discharge with lipid-lowering agents.

death and dependency in patients with hypertension who have had an ischemic stroke.

Apart from improved blood pressure control, a number of other reasons could be proposed to explain the association between high adherence to antihypertensive therapy and positive stroke outcomes. For example, patients who were at lower risk of death or dependency at 12 months may have had a milder initial stroke. In addition, it is possible that patients who report adherence to one medication may be more likely to adhere to other recommended treatments. In this study, patients with high adherence to antihypertensive therapy may have also adhered to other prescribed therapies, including antiplatelet and lipid-lowering agents. However, after adjustment for the effect of different severity of initial stroke and other secondary prevention medication in multivariable analysis model, significant positive associations between persistence with antihypertensive therapy and rates of death and dependency were still observed.

Our study has several limitations. Firstly, persistence was measured by patient self-report, which may have led to an over-estimation of adherence rates. However, we also note that this

method has been used for assessing medication adherence in several cardiac and stroke studies [6,7]. And adherence assessed by patient self-report has been shown to correlate well with adherence assessed by pill count or electronic medication monitors [8,9]. Secondly, our study is also limited by the fact that blood pressure data during follow-up were unavailable, negating our ability to assess the effectiveness of the antihypertensive therapy. In addition, depression, which is an important factor that influences adherence and clinical outcomes [10], was not assessed after discharge of patients in this study.

Acknowledgments

This study was funded by the Ministry of Science and Technology and the Ministry of Health of the People's Republic of China (grand no.: 2008ZX09312-008 and 2009CB521905). The current analysis of the CNSR data was supported by Beijing Novartis Pharma Co., Ltd, who did not impose any impediment, directly, or indirectly, on the publication of the study's results.

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