Evaluation of Antihypertensive Therapy Among Ischemic Stroke Survivors: Impact of Ischemic Heart Disease

Yahaya Hassan, Noorizan Abd Aziz, Samah W. Al-Jabi, Irene Looi and Sa'ed H. Zyoud

*J CARDIOVASC PHARMACOL THER* 2010 15: 282 originally published online 14 May 2010

DOI: 10.1177/1074248410368049

The online version of this article can be found at:
http://cpt.sagepub.com/content/15/3/282
Evaluation of Antihypertensive Therapy Among Ischemic Stroke Survivors: Impact of Ischemic Heart Disease

Yahaya Hassan, PharmD¹, Noorizan Abd Aziz, PharmD¹, Samah W. Al-Jabi, MSc¹,², Irene Looi, MBBS, MRCP³, and Sa’ed H. Zyoud, MSc²,⁴

Abstract

Background: Hypertension and ischemic heart disease (IHD) are among the most prevalent modifiable risk factors for stroke. Clinical trial evidence suggests that antihypertensive medications are recommended for prevention of recurrent ischemic stroke in hypertensive and normotensive patients. Objectives: The objectives of this study were to analyze and evaluate the utilization of antihypertensive medication for acute ischemic stroke (AIS) or transient ischemic attack (TIA) survivors in relation to recent recommendations and guidelines and to compare their use among patients with or without IHD. Methods: This was a retrospective cohort study of all patients with AIS/TIA attending the hospital from July 1, 2008 to December 31, 2008. Demographic data, clinical characteristics, different classes of antihypertensive medications, and different antihypertensive combinations prescribed to AIS/TIA survivors were analyzed among patients with and without IHD. Statistical Package for Social Sciences (SPSS) program version 15 was used for data analysis. Results: In all, 383 AIS/TIA survivors were studied, of which 66 (19.5%) had a documented history of IHD. Three quarters (n = 260; 76.9%) of AIS or TIA survivors received antihypertensive medication, mostly as monotherapy, at discharge. The majority of patients (n = 201, 59.5%) were prescribed angiotensin-converting enzyme inhibitors (ACEIs). Patients with IHD were significantly prescribed more β-blockers than patients without IHD (P = .003). A history of hypertension, a history of diabetes mellitus, and age were significantly associated with prescription of antihypertensive medications at discharge (P < .001, P < .001, and P < .001, respectively). Conclusion: Patterns of antihypertensive therapy were commonly but not adequately consistent with international guidelines. Screening stroke survivors for blood pressure control, initiating appropriate antihypertensive medications, and decreasing the number of untreated patients might help reduce the risk of recurrent strokes and increase survival.

Keywords
antihypertensive medications, hypertension, ischemic heart disease, ischemic stroke

Introduction

Stroke is one of the leading causes of significant disability and mortality worldwide and occurs with greater frequency in patients with hypertension and ischemic heart disease (IHD).¹ Hypertension and IHD are among the most prevalent modifiable risk factors for stroke.² Large-scale observational studies have shown that blood pressure is positively and continuously associated with the risk of stroke and IHD in a log-linear way.³,⁴ Furthermore, over the range of 115/75 to 185/115 mm Hg, each 20-mm Hg elevation in systolic blood pressure (or 10-mm Hg elevation in diastolic blood pressure) roughly doubled the risk of death from IHD or stroke.³

The new statement from the American Stroke Association recommended the use of antihypertensive therapy for all hypertensive and normotensive ischemic stroke survivors.² There are a growing number of pharmacological treatment choices for patients with hypertension. However, the choice of a certain antihypertensive drug class is affected by many factors including the presence of comorbid condition.³ The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of high blood pressure (JNC-7) has recommended the use of angiotensin-converting enzyme inhibitors (ACEIs) plus thiazide diuretics for reducing blood pressure among patients with
ischemic stroke to prevent recurrent attack. Furthermore, in the PROGRESS trial of post-stroke patients, therapy with ACEIs and a diuretic that lowered blood pressure by 12/5 mm Hg reduced the recurrence of stroke by 43%. Because recent studies have shown that the presence of hypertension or IHD at the time of hospital discharge are considered predictors of high early risk of secondary stroke, there is a need to improve antihypertensive treatment among ischemic stroke and IHD survivors.

To improve our knowledge about the patterns of antihypertensive prescription at discharge for patients with acute ischemic stroke (AIS) or transient ischemic attack (TIA), we carried out this hospital-based study with the following objectives: (1) to analyze the use of antihypertensive medication for AIS/TIA survivors, (2) to evaluate and compare the use of antihypertensive medication among those patients with ischemic stroke, with or without IHD in relation to recent recommendations and guidelines.

**Methods and Materials**

**Settings and Study Design**

This was an observational retrospective cohort study of all patients diagnosed with AIS or TIA admitted to a 1200-bed hospital located in the Northern region of Malaysia. The hospital provides health care and emergency treatment for all illnesses and accidents. All aspects of the study protocol, including access to and use of the patient clinical information, were authorized by the local health authorities before initiation of this study.

**Participants and Data Collection**

Data were collected for the period between July 1, 2008 and December 31, 2008. A computer-generated list was obtained from the Hospital Record Office. We identified our cases from the Hospital Record Office. We identified our cases based on the World Health Organization definition of stroke (tenth revision [ICD-10]). Patients with diagnostic codes I63.0-I63.9 (AIS) and G45.0-G45.9 (TIA) were included in the study. Patients’ records were traced according to their identification numbers and hospital registration numbers. These cases were identified according to the discharge diagnosis documented in their medical records. The diagnosis of AIS and TIA was based on the World Health Organization definition of stroke and the computerized tomography (CT) scan or magnetic resonance imaging (MRI) results.

However, patients who died during hospitalization, who were discharged against medical advice, or who were discharged to another hospital were excluded from the study.

Specially designed data-collection forms were used to collect data from the medical records which included demographic information, diagnostic information, risk factors, vital signs, and prescription drug use. The main risk factors that were considered in this study were hypertension, diabetes mellitus (DM), IHD, previous stroke, dyslipidemia, atrial fibrillation (AF), and valvular heart disease. Hypertension was defined as systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, a physician diagnosis of hypertension or a patient’s self-report of a history of hypertension or antihypertensive use. Diabetes mellitus was diagnosed based on a history of fasting blood glucose levels >7 mmol/L from medical records of either diet-controlled, oral hypoglycemic-treated, or insulin-treated disease. Patients with a history of angina or myocardial infarction or any diagnosis of coronary artery disease were considered to have IHD. Recurrent stroke was defined as a previous history of ischemic attacks. Dyslipidemia was defined by the presence of one or more than 1 abnormal serum lipid concentration. A previous history of AF was noted in addition to a screen for AF by the hospital physician from an ECG performed either during the patient’s hospital stay or from previous history for community-treated patients. Valvular heart disease is any disease process involving one or more of the valves of the heart.

To better study the use of ACEI or angiotensin receptor blockers (ARB) specifically for AIS, patients with a diagnosis of chronic heart failure (CHF) were excluded.

**Outcome Measures**

Antihypertensive drug classes (ACEI/ARB, β-blockers [BBs], calcium channel blockers [CCBs], diuretics and α-blockers) were recorded. The number of antihypertensive drugs being prescribed was tabulated. Because only 5 patients were prescribed ARB, we considered patients on ACEI or ARB prescription as ACEI users. In addition, we classified patients with any prescriptions of thiazide or loop diuretic or potassium sparing diuretic as diuretic users. We then examined and analyzed the use of different classes of antihypertensive medications among patients with and without IHD.

The proportion of use of these antihypertensive drug classes among patients with 1, 2, 3, 4, or more drugs was tabulated for all patients. We present the patterns of use of antihypertensive drugs among all patients overall, and in subgroups of patients on 1, 2, 3, 4, or more drugs. We compared the proportions of drug class use among patients with and without IHD.

**Statistical Analysis**

Data were entered and analyzed using Statistical Package for Social Sciences program version 15 (SPSS). Data were expressed as frequency (%) for categorical variables and as mean ± SD for continuous variables. Chi-square or Fischer exact test, whichever appropriate, was used to test significance between categorical variables. Independent student t test was used to compare means of continuous variables. Variables that were not normally distributed were expressed as median (lower–upper quartiles). Variables were tested for normality using the Kolmogorov-Smirnov test. Mann-Whitney U test was used to test the differences between groups, if the data were not normally distributed. A P value < .05 was considered statistically significant.
Results

During the study period, 414 patients with a diagnosis of AIS or TIA were admitted to the hospital. Of these, 76 patients were excluded. In all, 52 patients died during hospitalization, 6 patients had CHF, 7 were discharged against medical advice, and 11 were discharged to another hospital, therefore, the study population consisted of 338 patients.

The average age of the survivors was 62.8 ± 12.8 years (range: 23.9-92.1). The majority 212 (62.7%) were male, giving a male:female ratio of 1.68:1. Chinese patients represented 182 (53.8%) of the study population, followed by Malays 96 (28.4%) and Indians 54 (16.0%). Other ethnic groups consisted of foreigners from other neighboring Asian countries. The median (interquartile range) of the number of chronic diseases present among the study patients was 2 (1-3). A total of 66 (19.5%) patients had a history of IHD, while 272 (80.5%) did not (Table 1).

Table 1 also compares the clinical and demographic characteristics of patients with and without IHD. Patients with IHD had a significantly higher median of total number of chronic diseases than patients without IHD (3 [3-4] versus 2 [1-3], P < .001). The only significant risk factors between the 2 groups were the presence of a history of hypertension and a history of DM (P = .03 and P = .009, respectively).

Approximately three quarters (n = 260; 76.9%) of AIS or TIA survivors received antihypertensive therapy at discharge, whereas 78 (23.1%) were solely on nonpharmacological interventions (Figure 1 and Table 2). The majority of patients (n = 201, 59.5%) were prescribed ACEI/ARB, followed by BBs (n = 145, 42.9%), CCBs (n = 53, 15.7%), diuretics (n = 34,
medications were prescribed, a median (interquartile range) of 1 (1-2) medications per patient. A total of 66 (24.3\%) of these patients had no history of hypertension. Among most of the tested factors, a history of hypertension, a history of DM, and female gender were significantly associated with the prescribing of antihypertensive medications at discharge \((P < .001, P < .001, and P < .001\), respectively).

Moreover, a history of hypertension, a history of DM, and older age were significantly associated with the prescribing of antihypertensive medications at discharge \((P < .001, P < .001, and P < .001\), respectively). The median (interquartile range) number of antihypertensive medications prescribed for the patients was 1 (1-2) and was positively correlated with the number of chronic diseases \((P < .001\), and significantly associated with a history of hypertension \((P < .001\), a history of dyslipidemia \((P = .048\), and female gender \((P = .028\).

**Discussion**

This study is the first of its kind to obtain an initial data to evaluate the patterns of antihypertensive drug therapy in patients with and without IHD. Patients with IHD were prescribed significantly more BBs and diuretics than patients without IHD \((P = .003\) and \(P = .001\), respectively; Figure 1).

Within the ACEI drug class, perindopril (185 of 201, 92\%) was most commonly prescribed. The most common BB was metoprolol (124 of 145, 85.5\%). The CCB that was most used was nifedipine (26 of 53, 49\%). Within the diuretics, thiazide (23 of 34, 67.6\%) was the most commonly used. Prazosin (5 of 6, 83.3\%) was the most prescribed agent among \(\alpha\)-blockers.

Overall, monotherapy was prescribed for 133 (39.3\%) patients and combination therapy for 127 (37.6\%) patients; of these, a 2-drug regimen was prescribed for 90 (26.6\%) patients, a 3-drug regimen for 26 (7.7\%), and a 4-drug regimen for 11 (3.3\%) patients (Table 2).

Patients with IHD were prescribed a total of 103 antihypertensive medications, a median (interquartile range) of 1(1-2) medications per patient. A total of 12 (18.2\%) patients were on nonpharmacological therapy, 24 (36.4\%) on monotherapy, and 30 (45.4\%) were on combination therapy. \(\beta\)-Blockers were the most commonly prescribed (19.7\%) drug class for monotherapy in this group of patients. Angiotensin-converting enzyme inhibitors with BBs followed by ACEI with diuretics were the most commonly prescribed drugs for the 2-drug combination therapy among these patients (Table 2).

In patients without IHD, a total of 338 antihypertensive medications were prescribed, a median (interquartile range) of 1(1-2) medications per patient. A total of 109 (40.0\%) patients were on nonpharmacological therapy, 109 (40.0\%) patients were on monotherapy and 97 (35.7\%) were on drug combination therapy. Angiotensin-converting enzyme inhibitors (29.8\%) was the most commonly prescribed monotherapy drug for patients in this group. Angiotensin-converting enzyme inhibitors with BBs followed by BBs with CCBs were the most commonly used drugs for the 2-drug combination therapy among these patients (Table 2).
with AIS and TIA, with and without IHD. This study showed that patients with AIS and TIA have relatively high proportions of risk factors, mainly hypertension, DM, and dyslipidemia. This suggests that screening and preventive therapies for such risk factors are important to decrease morbidity and mortality among this category of patients.

This study showed that approximately 1 of every 4 AIS and TIA survivors was discharged on no antihypertensive therapy. However, there is strong evidence that lowering blood pressure reduces the risk of strokes in hypertensive patients and in those whose blood pressure is considered normal but who are at high risk of developing stroke. Furthermore, the study showed that the majority of patients who were on antihypertensive medications at discharge were on monotherapy, and only 37.6% of the survivors were discharged on combination antihypertensive regimens. There was also evidence that a high number of hypertensive stroke survivors remain poorly controlled, and recent American guidelines call for antihypertensive combination therapy to stroke survivors.

The majority of patients were prescribed ACEI/ARB, followed by BBs, CCBs, diuretics, and α-blockers. These findings are consistent with other studies from different countries.

In the current study, 59.5% of patients with ischemic stroke were prescribed ACEI at discharge, which is generally but not adequately in accordance with the recommended guidelines for using ACEI in the management of hypertension among patients with stroke. Besides their blood pressure-lowering properties, evidence from a recent study has demonstrated that inhibition of the renin–angiotensin system attenuates periadventitial inflammation and reduces atherosclerotic lesion formation. In the LIFE study, there were fewer strokes in the losartan-treated group than in the group treated with atenolol. Moreover, results from previous studies showed that prestroke use of ACEI was associated with a reduced risk of severe stroke and improvement of stroke outcome. For monotherapy, patients with IHD were prescribed significantly more BBs than patients without IHD. The underutilization of ACEI in this group may be explained by physicians focusing on the presence of IHD and giving less attention to the ischemic stroke condition, or it could be attributed to intolerance or adverse effects of ACEI. In a previous study, the UKPDS group noted that 4% of patients receiving captopril discontinued therapy due to dry cough. Angiotensin receptor blockers are considered appropriate agents if patients cannot tolerate an ACEI. However, ARB was rarely prescribed in the current study.

In the current study, the underutilization of valuable, efficacious, and cost-effective thiazide diuretics is unjustifiable. Guidelines recommend thiazide diuretics in treating most patients with ischemic stroke hypertension either alone or combined with drugs from other classes. Thiazide diuretics are of proven benefit in the primary and secondary prevention of stroke, particularly when used in combination with an ACEI.
Interestingly, we observed that more than one quarter of patients discharged on antihypertensive medications had no history of hypertension. However, this result may reflect the influence of clinical trials that suggested stroke survivors with normal blood pressures may benefit from antihypertensive treatment, or these agents may have been prescribed for other therapeutic reasons such as BBs and CCBs used for IHD or cardiac rate control.

It is recommended that BBs and CCBs are prescribed for patients with IHD. Among those patients, pharmacological therapy should be initiated with a BB, unless contraindicated. β-Blockers can lower blood pressure, reduce symptoms of angina, decrease mortality, and reduce cardiac output, heart rate, and AV conduction.

In the current study, BB was prescribed significantly more among patients with IHD than those without IHD. In addition, patients with IHD were prescribed a significantly higher percentage of diuretics than patients without IHD. This result may be because thiazide diuretics are highly recommended for patients with ischemic stroke. In this study, older age, a history of hypertension, and a history of DM were significantly associated with antihypertensive prescription at discharge. These findings are consistent with a previous study done in 11 hospitals in the state of California, but are not consistent with a study done in Palestine, in which the history of DM was not significantly associated with antihypertensive prescription. However, it is noted that previous stroke or TIA was not significantly associated with antihypertensive prescription at discharge. This finding was observed regardless of the recent guidelines and a secondary stroke prevention trial that showed the benefit of antihypertensive medication for preventing secondary stroke even among those with relatively normal blood pressure. Similar to a previous study evaluating antihypertensive therapy in diabetic hypertensive patients, the median number of antihypertensive medications prescribed for the patients was positively correlated with the number of chronic diseases. Furthermore, the median number of antihypertensive medications was significantly associated with female gender. This was because in the current study the prevalence of hypertension among female patients was considerably higher than that among males.

The method of using blood pressure measurement as the sole determinant in the judgment whether to initiate antihypertensive therapy for AIS or TIA patients may not be as relevant as previously thought because the key to the efficacy of antihypertensive treatment in stroke prevention may lie in blood pressure reduction, and perhaps in other mechanisms, but not just treatment of diagnosed hypertension.

Although this study is the first one of its type in Malaysia, our study was a retrospective analysis of medical records with inherent limitations. Reliance on the accuracy and completeness of documentation in hospital medical records should be viewed cautiously. However, regardless of its nature as a retrospective study, the findings are widely applicable and comparable to previous studies. In addition, the study was conducted in one hospital, but may reflect the practice in other centers and by other physicians.

**Conclusion**

In general, there was a suboptimum use of combination therapy among patients with AIS/TIA hypertension. Moreover, patterns of antihypertensive therapy were commonly but not adequately consistent with the international guidelines.

Because hypertension and IHD are 2 of the most important risk factors for stroke, better control of blood pressure is needed to minimize the risk of stroke. Furthermore, screening stroke survivors for blood pressure control, initiating appropriate antihypertensive medications, and decreasing the number of untreated patients should help reduce the risk of recurrent strokes and increase survival. Finally, better drug education for health care providers regarding appropriate and international guidelines for patients with ischemic stroke, improving the practice with regard to antihypertensive combination therapy and better follow-up for blood pressure control are required.

**Acknowledgments**

The authors would like to thank the Universiti Sains Malaysia (USM) for the financial support provided for their research. The assistance of the medical and record office staff is gratefully acknowledged.

**Declaration of Conflicting Interests**

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

**Financial Disclosure/Funding**

The authors received no financial support for the research and/or authorship of this article.

**References**


