Long-term Adherence to National Guidelines for Secondary Prevention of Ischemic Stroke: A Prospective Cohort Study in a Public Hospital in Chile

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Background: Clinical guidelines for the secondary prevention of ischemic stroke have been developed, but their publication is insufficient to make them effective. Our aim was to investigate adherence to Chilean guidelines, its associated variables, and to determine prognosis at follow-up. *Methods:* We prospectively included all consecutive patients discharged with a diagnosis of ischemic stroke from Valparaíso Regional Hospital between July 15, 2007 and January 15, 2008. Patient follow-up was performed at 5, 10, and 15 months using a standardized questionnaire. We used the Chi-square and Fisher exact tests to compare discrete variables and multivariate logistic regression analysis to adjust for potential confounding factors. A Cox regression model was fitted. *Results:* We included 156 patients; 128 patients (82%) completed follow-up. Adherence to oral anticoagulation decreased significantly compared to all other medications during follow-up ($P = .004$). This was not associated with any of the studied variables. Adherence to antihypertensives, statins, and hypoglycemic medications remained >65% without a significant variation. Patients with cardioembolic stroke had greater mortality ($P = .003$) and recurrence rates. *Conclusions:* The observed significant decrease in adherence to oral anticoagulation in patients with cardioembolic stroke suggests a need for the implementation of specific strategies to achieve the desired secondary prevention goals in these patients. Future research into the evaluation of other factors that could be associated with the lack of adherence to these guidelines, measurements of therapeutic goals, and new therapeutic strategies that are easier to use and that are associated with less risk could improve the prognosis of these patients. **Key Words:** Cerebrovascular disease—secondary prevention—stroke.

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Patients with ischemic stroke (IS) have a 4% to 20% annual recurrence rate, and IS can be disabling or fatal.[1,2] Secondary prevention has proven to be effective in decreasing recurrences in these patients.[3] International and national clinical guidelines based on the best evidence for effective secondary prevention have been published.[4-7] However, it is known that the publication of these guidelines is not enough to produce a change in medical practice or patient treatment.[8]

The adherence to secondary prevention recommendations is highly variable among populations and usually decreases with time after the primary event. Most studies have been conducted in high-income countries.[6,9-12] One large prospective study performed in low- and medium-income countries found important differences in the adherence to secondary prevention: aspirin was prescribed to 79.6% of patients, whereas statins were only prescribed to 19.6% of patients.[3]

In Chile, few investigations have looked at the long-term outcome and adherence to secondary prevention. The prognosis of ischemic stroke subtypes in a predominantly Hispanic-Mestizo population in Iquique, Chile (PISCIS) project, a population-based stroke incidence study, reported on functional outcome and death at 6 months of follow-up.[13] A recently published cohort study only looked at prognosis of cryptogenic strokes but not adherence to secondary prescriptions.[14]

Our primary goal was to prospectively evaluate local adherence to secondary prevention indications as well as prognosis and recurrence at the end of the follow-up period in a hospital-based sample of patients with IS.

Methods

Date and Participants

We prospectively included all consecutive patients with a diagnosis of IS (cerebral infarct or transient ischemic attack [TIA]) who were discharged from Valparaíso Regional Hospital, Chile, between July 15, 2007 and January 15, 2008.

Context

Valparaíso Regional Hospital is a tertiary level university medical center located in the third most populated region of Chile, which is primarily urban (92%). This 540-bed hospital is the primary center providing health care services to 466,143 inhabitants and is one of the teaching campuses for the medical and health professionals studying at the Valparaíso University. Seventy-seven percent of the population uses the public health care system, and 15.3% are under the poverty line. The average level of education is 11 years. Sixteen percent of the population is >60 years of age.[15,16]

Case Definition

We defined IS based on the definition of the World Health Organization as patients who were admitted with rapid-onset focal neurologic symptoms suggestive of an acute stroke and had a computed tomographic (CT) scan that ruled out intracranial hemorrhage or other nonvascular causes of these symptoms. The event was considered a TIA when the symptoms resolved within 24 hours, and as a cerebral infarct if they persisted after 1 day.

Definition of Variables

Adherence to secondary prevention was estimated according to current national recommendations.[7] It was defined as the proportion of patients who continued taking the prescribed medications compared to those who had an indication to continue taking them according to the guidelines.[7] Based on this, we determined that all patients with noncardioembolic stroke should take antiplatelet medications and those with cardioembolic strokes who are not taking oral anticoagulation medications. All patients in these groups should be taking antihypertensive agents and statins; all cardioembolic IS patients should be taking oral anticoagulation therapy unless they are taking antiplatelet medications, and all diabetic patients should be taking hypoglycemic drugs. We considered all new cerebral infarcts or TIAs to be recurrences.

Functional outcome was defined according to the modified Rankin Scale (mRS) score. Patients with a mRs score of 0 to 2 were considered independent; those with mRS scores of 3 to 5 were considered dependent.[13]

We assigned patients with IS to 1 of 5 etiologic subgroups based on a modified TOAST classification, considering clinical presentation, neuroimaging results, and risk factors.[13,17]

Case Ascertainment

In order to ascertain all possible cases, 2 sources of patients were checked prospectively. The weekly list of patients added to the IS database is generated in the emergency department or during hospitalization for all patients presenting with IS at admission or during hospitalization. Since the implementation of a national plan for the management of stroke,[7] this database is required and must be filled with the information of all IS patients. On a biweekly basis, we also reviewed the list of patients who were admitted and discharged from the hospital with a diagnosis of stroke. We obtained demographic data (e.g., age, sex, contact telephone number, and address), cardiovascular risk factors (e.g., hypertension, diabetes mellitus, alcohol and tobacco use, previous stroke, coronary heart disease, and arrhythmias), biochemical and hematologic results, cardiac studies and vascular imaging, discharge notes, and prescriptions from the patients' medical records.

Follow-up

Follow-up was performed via telephone at 5, 10, and 15 months postdischarge. All sessions were conducted

by the same investigator (P.M.V.) using a standardized questionnaire applied to patients and family members or caregivers after consent was obtained. The questionnaire included vital status, stroke recurrence, medications currently in use, and place of outpatient visit. The survey at 15 months also included the degree of disability based on the mRS score.[18] To verify the data obtained for vital status and recurrences, we reviewed the medical records of all patients at the end of the study, including those lost to follow-up. Moreover, the National Death Registry was also reviewed to verify vital status for lost patients.

Data Analysis

We used the Chi-square and Fisher exact tests to compare discrete variables and multivariate logistic regression analysis to adjust for potential confounding factors. A Cox regression model was fitted to evaluate the association between adherence to oral anticoagulation medications and demographic characteristics, risk factors, and place of outpatient visit. A 2-tailed $P < .05$ was considered statistically significant. We used SPSS software (SPSS Inc., Chicago, IL).

This study was approved by the hospital institutional review board. We obtained verbal informed consent from all of the patients or caregivers. The informed consent process met all the requirements of the institutional review board.

Results

During the study period, 156 patients with a diagnosis of IS were discharged from the hospital; 137 (88%) had a cerebral infarction and 19 (12%) had a TIA. This cohort was followed and surveyed at 5, 10, and 15 months. One hundred twenty-eight patients (82%) completed the follow-up (mean ± SD 381 ± 148 days). Of those who did not complete the follow-up, 24 (15%) could not be contacted and 4 (3%) patients refused to answer the telephone survey. Thirty patients (19%) died during the study. Figure 1 describes the flow of patients at each stage of follow-up.

The cohort included 80 (51%) males. The average age was 69.2 years (SD 11.3 years). The demographic and clinical characteristics of all patients are shown in Table 1.

A brain CT scan was obtained in all patients. An electrocardiogram was performed in 126 patients (81%), a lipid profile in 94 (60%), a duplex ultrasound of the neck vessels in 47 (30%), other vessel studies in 3 patients (magnetic resonance angiography and conventional angiography), transthoracic echocardiography in 34 (22%), transesophageal echocardiography in 2 (1%), 24-hour Holter monitoring in 29 (19%), and a magnetic resonance imaging scan of the brain in 12 (8%) patients. Hematocrit, hemoglobin, white blood cell count, blood glucose, creatinine, blood urea nitrogen, electrolytes, prothrombin time, and activated partial thromboplastin time laboratory values were measured for all patients during hospitalization or at follow-up.

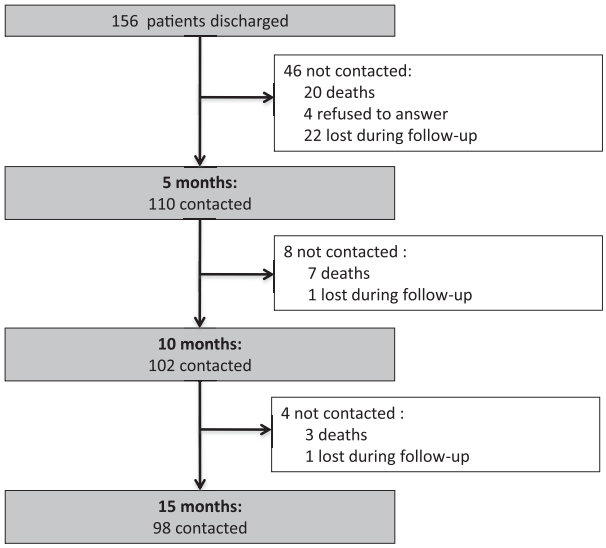

Figure 1. *Flowchart of patients participating in the study.*

The adherence to guidelines for antithrombotic therapy decreased significantly during follow-up, mainly as a result of low adherence to oral anticoagulation therapy ($P = .004$), which decreased from 64% (95% confidence interval 39%-79%) at discharge to 7% (95% confidence interval 0%-32%) at the end of the study. The only anticoagulant used was a vitamin K antagonist

Table 1. *Characteristics of the study patients*

	Total (n = 156)	Percent (95% CI)
Demographic characteristics		
Men	80	51 (44-59)
Average age, y (SD)	69.2 (11.3)	—
Risk factors		
Arterial hypertension	129	83 (77-89)
Diabetes mellitus	43	28 (21-35)
Dyslipidemia	20	13 (8-18)
Atrial fibrillation	31	20 (14-26)
Coronary disease	22	14 (9-20)
Tobacco use	34	22 (15-28)
Ischemic stroke subtype		
Undetermined	54	35 (27-42)
Small vessel	41	26 (19-33)
Cardioembolic	32	21 (14-27)
Transient ischemic attack	19	12 (7-17)
Atherothrombotic	8	5 (2-9)
Other	2	1 (0-3)
Location of outpatient visit*		
Primary care center	80	88 (81-95)
Hospital	11	12 (5-19)

Abbreviations: CI, confidence interval; SD, standard deviation.
*Information regarding the location of the outpatient visit was obtained for 91 patients.

(acenocoumarol). No patient received warfarin or any of the newer oral anticoagulants because they were not available in the public health system in Chile. Adherence to antihypertensive agents, statins, and hypoglycemic drugs did not show any significant variation (Fig 2). None of the studied variables were associated with lack of adherence to oral anticoagulation treatment after adjustments in the Cox regression.

Prognosis at 15 months by IS subtype is shown in Figure 3. Patients with cardioembolic stroke had a significantly higher mortality ($P = .003$). Among patients with cardioembolic strokes, no mortality difference was found between those who were adherent or nonadherent to the anticoagulant regimen. Regarding the patients with cerebral infarctions, those with small vessel stroke were significantly more likely to be independent at 15 months (mRS score 0-2; $P = .002$). There was no significant difference in the number of dependent patients between subgroups.

Twenty-three (15%) patients presented with at least 1 stroke recurrence episode, of whom 8 (35%) had a fatal stroke. Recurrences were observed in 9 patients with cardioembolic stroke, of which 5 were fatal. The remaining cases were distributed as follows: 6 patients with small vessel infarction, 5 undetermined strokes, 2 TIAs, and 1 with large artery atherothrombotic infarction. There were no significant differences in fatal or nonfatal recurrences between groups.

Discussion

In the present study, we found that adherence to guidelines for the secondary prevention of ischemic stroke is lower than it should be and that it varies significantly depending on the prescription. The most notable finding was the significant decrease of adherence to oral anticoagulant therapy in patients with cardioembolic stroke, which was as low as 7% at the end of the follow-up period. This group of patients had the highest mortality and recurrence of cerebrovascular events. Adherence to other prevention interventions remained stable (>65%).

The low adherence to oral anticoagulation in the cardioembolic stroke patient group may be related to several factors. It could be related to failure of prescription by the attending physician, discontinuation by the primary care physician because of a lack of knowledge regarding its use, lack of access to an adequate anticoagulation program, or discontinuation of use by the patients because of practical or financial reasons.[19] We did not find that demographic variables, cardiovascular risk factors, or site of outpatient care were associated with adherence. Improved medication adherence can be attained using a number of strategies. Case management or enhanced multidisciplinary team work focusing on particular risk factors or functional difficulties in patients with comorbid conditions or multimorbidity could improve long-term medication adherence and outcome.[20]

Adherence to antiplatelet and hypoglycemic medications was found to be >75% during the study period. This higher adherence may be associated in part to physician experience and confidence in their use, low cost, and the existence of specific primary care programs for diabetic patients.

The low prescription rate of antihypertensives agents, for which we observed an adherence that varied between 69% and 78% during follow-up, is also noteworthy. The use of antihypertensive medications in secondary prevention achieves a reduction of 43% in stroke recurrence in both hypertensive and nonhypertensive patients, independent of the medication used.[21,22] Accordingly, their use is recommended for all patients after stroke. Similarly, only 65% to 75% of patients were taking statins, despite the fact that it has been shown that their use significantly reduces coronary and cerebral vascular recurrences in patients with noncardioembolic stroke with an low-density lipoprotein level >100 mg/dL.[23,24]

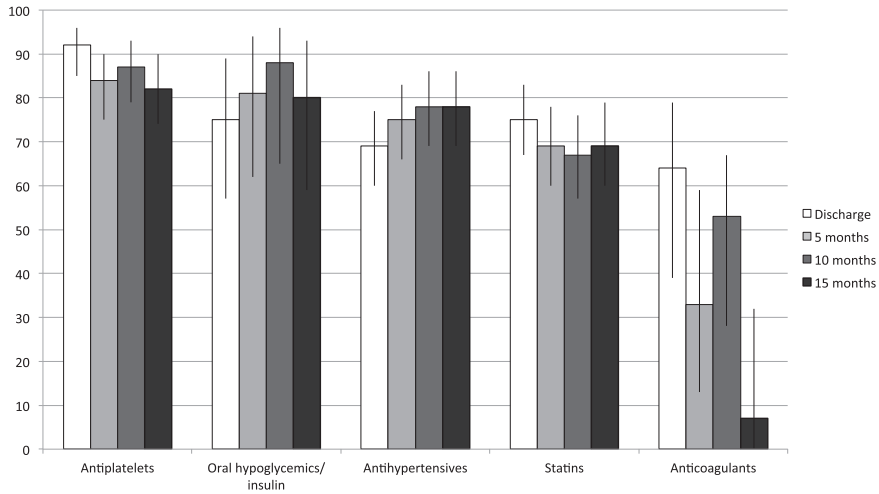

Figure 2. *Percentage of patients who received prescriptions at the time of discharge and adherence to pharmaceutical guidelines during follow-up.*

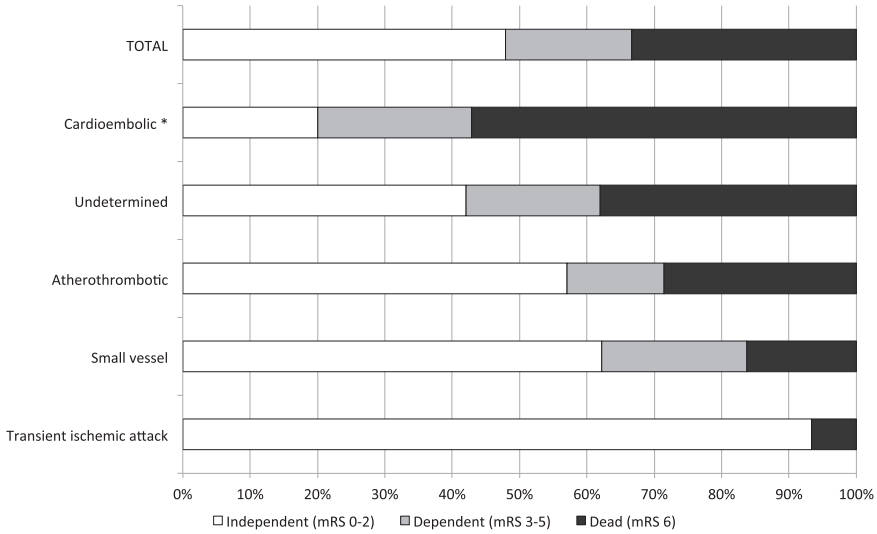

Figure 3. *Dependence and mortality based on the modified Rankin Scale at the 15 month follow-up by stroke type.* *P $<$ .005.

In this sample, baseline low-density lipoprotein cholesterol values were not available, which prevented us from being more precise when defining the group of patients with indications for statin use.[7,23] This observed lower than expected prescription of antihypertensives and statins at discharge emphasizes the need to have continuous monitoring of guideline adhesion.[8]

Adherence to antiplatelet, statin, or hypoglycemic agents in our study is similar to that described by studies conducted in high-income nations.[11,12] However, we found adherence to antihypertensive and oral anticoagulation medications to be lower compared to the rates described in high-income populations, which have reported adherence rates of 91% to antihypertensives and between 77% to 79% to oral anticoagulation at 1-year follow-up.[11,12] When comparing our results with those found in middle- and low-income nations, our sample has higher adherence to all of the medications analyzed.[3]

Cardioembolic stroke patients had a significantly higher mortality (57%) at the end of the study. This group also had a higher rate of recurrence. We found no significant differences in the demographic characteristics between patients with different types of stroke that could account for this result. Interestingly, this difference has also been observed in previous studies.[13,25-27] We stress the importance of anticoagulation adjusted by INR in the group of patients with permanent or paroxysmal atrial fibrillation, which has shown to reduce the absolute risk of stroke from 4.5% to 1.4% yearly, with a relative risk reduction of 68%.[28] Moreover, INR levels were not known, so our result could have overestimated the treatment effect.

By the same means, emphasis should also be placed at the low rate of examinations performed on patients in this cohort, which is similar to the findings of an epidemiologic study conducted in a northern city in Chile.[13] In addition, it is highly possible that some cardioembolic causes of stroke were left undiagnosed, widening the gap to an ideal treatment, making the lack of oral anticoagulation even a bigger public health problem in communities such as this one.

In our knowledge, this is the first prospective study on Chilean patients suffering IS with such a long follow-up period. The study was conducted after the implementation of the national plan for the management of stroke, allowing us to compare the results with the guidelines recommendations.[29] External validity seems appropriate, reflecting the reality of most of the population of Valparaíso, given that all patients served by the national public health service were included and the results of the etiologic classification of stroke were in agreement with those obtained in a previous Chilean population study.[13,24] Among the weaknesses of this study is possible adherence overestimation related to selection bias because of telephonic follow-up. The number of patients lost to follow-up could bias our results, and we did not perform a sensitivity analysis. Even though we reviewed hospital records in only one hospital (Valparaíso), it is unlikely that patients with recurrences were admitted to another hospital, because this is the main public hospital of the area and the only one with a Neurology Service. In addition, in the event that a patient was admitted to another health facility, they might be referred to the aforementioned hospital. Patients using the public system of health usually do not have access to private medicine. Socioeconomic variables were not available, so we could not investigate their association with adherence. Other possible confounders, such as stroke severity, could be associated with prognosis and the prescription of secondary prevention. The low statistical power for the analysis of the association between adherence and prognosis (including recurrences) could also have influenced the results.

The poor adherence to the national recommendations for the secondary prevention of cardioembolic stroke in a group with high risk of mortality, disability, and recurrence suggests a need for the implementation of specific strategies to achieve an adequate prescription of oral anticoagulants and increased study efforts in cases classified as undetermined but of high risk of being cardioembolic. Future research into the evaluation of other factors that could be associated with the lack of adherence to these guidelines, measurements of therapeutic goals, and new therapeutic strategies that are easier to use and that are associated with less risk could improve the prognosis of these patients.

References

1. Burn J, Dennis M, Bamford J, et al. Long-term risk of recurrent stroke after a first-ever stroke. The Oxfordshire Community Stroke Project. Stroke 1994;25:333-337.
2. Hardie K, Hankey GJ, Jamrozik K, et al. Ten-year risk of first recurrent stroke and disability after first-ever stroke in the Perth Community Stroke Study. Stroke 2004; 35:731-735.
3. Mendis S, Abegunde D, Yusuf S, et al. WHO study on Prevention of REcurrences of Myocardial Infarction and StrokE (WHO-PREMISE). Bull World Health Organ 2005;83:820-829.
4. Furie KL, Kasner SE, Adams RJ, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011;42:227-276.
5. Scottish Intercollegiate Guidelines Network. Management of patients with stroke: Rehabilitation, prevention and management of complications, and discharge planning. A national clinical guideline. Scottish Intercollegiate Guidelines Network (SIGN), Edinburgh (Scotland) 2010. Available from http://guideline.gov/content.aspx?id=23849. Accessed December 22, 2012.
6. Hamann GF, Weimar C, Glahn J, et al. Adherence to secondary stroke prevention strategies—Results from the German Stroke Data Bank. Cerebrovasc Dis 2003;15: 282-288.
7. República de Chile, Ministerio de Salud. Guía Clínica Ataque Cerebrovascular Isquémico del Adulto. Septiembre 2007. Available from www.redsalud.gov.cl/archivos/guiasges/isquemico.pdf. Accessed December 22, 2012.
8. Dippel DW, Simoons ML. Improving adherence to guidelines for acute stroke management. Circulation 2009; 119:16-18.
9. Ovbiagele B, Kidwell CS, Selco S, et al. Treatment adherence rates one year after initiation of a systematic hospital-based stroke prevention program. Cerebrovasc Dis 2005;20:280-282.
10. Ovbiagele B, Saver JL, Fredieu A, et al. In-hospital initiation of secondary stroke prevention therapies yields high rates of adherence at follow-up. Stroke 2004;35:2879-2883.
11. Sappok T, Faulstich A, Stuckert E, et al. Compliance with secondary prevention of ischemic stroke: A prospective evaluation. Stroke 2001;32:1884-1889.
12. De Schryver EL, van Gijn J, Kappelle LJ, et al. Non-adherence to aspirin or oral anticoagulants in secondary prevention after ischaemic stroke. J Neurol 2005;252: 1316-1321.
13. Lavados PM, Sacks C, Prina L, et al. Incidence, case-fatality rate, and prognosis of ischaemic stroke subtypes in a predominantly Hispanic-Mestizo population in Iquique, Chile (PISCIS project): A community-based incidence study. Lancet Neurol 2007;6:140-148.
14. Vallejos J, Jaramillo A, Reyes A, et al. Prognosis of cryptogenic ischemic stroke: A prospective single-center study in Chile. J Stroke Cerebrovasc Dis 2012; 21:621-628.
15. Ministerio de Planificación, Gobierno de Chile. La Encuesta de Caracterización Socioeconómica Nacional CASEN 2006. Available from http://www.ministeriodesarrollosocial.gob.cl/casen/publicaciones/2006/Pobreza.pdf. Accessed December 22, 2012.
16. Instituto Nacional de Estadística INE Chile, CENSO 2002. Available from www.ine.cl/cd2002/index.php. Accessed December 22 2012.
17. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993; 24:35-41.
18. Merino JG, Lattimore SU, Warach S. Telephone assessment of stroke outcome is reliable. Stroke 2005;36: 232-233.
19. Baroletti S, Dell'Orfano H. Medication adherence in cardiovascular disease. Circulation 2010;121:1455-1458.
20. Smith SM, Soubhi H, Fortin M, et al. Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. Cochrane Database Syst Rev 2012;4:CD006560.
21. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 2001;358:1033-1041.
22. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: Meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;338:b1665.
23. Amarenco P, Bogousslavsky J, Callahan A 3rd, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006;355:549-559.
24. Amarenco P, Benavente O, Goldstein LB, et al. Results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial by stroke subtypes. Stroke 2009;40:1405-1409.
25. Lavados PM, Sacks C, Prina L, et al. Incidence, 30-day case-fatality rate, and prognosis of stroke in Iquique, Chile: A 2-year community-based prospective study (PISCIS project). Lancet 2005;365:2206-2215.
26. Kolominsky-Rabas PL, Weber M, Gefeller O, et al. Epidemiology of ischemic stroke subtypes according to TOAST criteria: Incidence, recurrence, and long-term survival in ischemic stroke subtypes: A population-based study. Stroke 2001;32:2735-2740.
27. Petty GW, Brown RD Jr, Whisnant JP, et al. Ischemic stroke subtypes: A population-based study of functional outcome, survival, and recurrence. Stroke 2000;31: 1062-1068.
28. Atrial-Fibrillation-Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med 1994;154:1449-1457.
29. Lavados PM, Salinas R, Maturana R. Government programs for treating stroke in Chile. Int J Stroke 2007; 2:51-52.