

Recurrent Ischemic Stroke Characteristics and Assessment of Sufficiency of Secondary Stroke Prevention

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ABSTRACT

Introduction: Disabilities due to stroke lead to a serious individual and socioeconomic burden. In this presented hospital-based study, we aimed to evaluate recurrent ischemic stroke (RIS) characteristics and the sufficiency of secondary prevention regarding the most common modifiable risk factors.

Methods: The records of patients with a diagnosis of ischemic stroke between November 2009 and November 2011 in our unit were retrospectively investigated.

Results: Ninety-one (18%) out of 500 patients with ischemic stroke had RIS. Hypertension, diabetes mellitus, ischemic heart disease, hyperlipidemia, atrial fibrillation, and smoking were found in 88%, 43%, 36%, 30%, 11%, and 14% of the patients, respectively. Thirty-eight percent of the patients had more than two risk factors. While 14% of the hypertensive patients did not use antihypertensive medications, antihypertensive treatment was insufficient in 39% of those who already

used antihypertensive medications. Twenty-three percent of the patients received no prophylactic agents. Sixty percent of the patients with a history of atrial fibrillation were on oral anticoagulant therapy (warfarin), and the international normalized ratio was <2.0 in 73% of them. Of the diabetic patients, 87% had an HgbA1C level above 6%. The LDL level was higher than 100 mg/dL in 72% of the patients.

Conclusion: The incidence of RIS and risk factors in our retrospective study was compatible with the results of those in literature. Secondary prophylactic treatment and modification of risk factors in the stroke patients were not satisfactory. The improvement of the patients' adherence to treatment is also very important in addition to the optimal treatment and follow-up strategy for decreasing the incidence of RIS. A multidisciplinary outpatient model of stroke care may be beneficial for decreasing the incidence of RIS.

Keywords: Recurrent stroke, risk factors, secondary prevention

INTRODUCTION

Cerebrovascular disease (CVD) is the most common disease group among all neurological diseases. Stroke-induced mortality is the third most common cause of death in developed countries, and disabilities related to stroke lead to a serious individual and socioeconomic burden. The incidence of stroke recurrence is high despite developments in primary and secondary preventive treatment. The first 5-year cumulative incidence of stroke recurrence varies between 16 and 30% in Western countries (1,2,3,4,5). The incidence of stroke recurrence is closely and significantly related to increased mortality and morbidity (6,7). The recurrence risk varies depending on CVD type and risk factors. The standard approach in preventing recurrence is by determining etiology and treating patients using pharmacological methods, such as antithrombotic and anticoagulant medications, and non-pharmacological methods, such as carotid endarterectomy and stenting procedures for occlusive vascular lesions. However, the effective treatment of the identified modifiable risk factors is another important factor in addition to the specific treatment methods. Although risk factors are very well identified, the extent of control for modifiable risk factors by secondary treatment and the success rate of secondary treatment for the prevention of recurrent stroke have not been sufficiently investigated in our country.

In this presented hospital-based study, we aimed to evaluate the characteristics of recurrent ischemic stroke (RIS) and the effectiveness of secondary prevention treatment with respect to the most common modifiable risk factors.

METHODS

The records of patients admitted to our neurology clinic with the diagnosis of CVD between November 2009 and November 2011 were retrospectively investigated. The data related to RIS was determined. The local research ethics committee approved this study.

The demographic data, risk factors, and ongoing medical treatment at RIS onset were recorded. "Trial of Org 10172 in Acute Stroke Treatment" (TOAST) (8) was used for the etiological classification. According to this classification, etiologies were accepted as



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- 1) Large artery atherosclerosis (thrombosis or embolism),
- 2) Cardioembolism,
- 3) Small vessel disease (lacunar),
- 4) Other identified etiologies,
- 5) Undetermined origin.

Bamford Criteria were used for clinical classification (9). According to this classification, clinical symptoms were accepted as

- a) Total anterior circulation infarction (TACI),
- b) Partial anterior circulation infarction (PACI),
- c) Lacunar infarcts (LACI),
- d) Posterior circulation infarction (POCI).

Data associated with risk factors, such as hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HL), atrial fibrillation (AF), ischemic heart disease, and smoking, were assessed. The adequacy for the treatment of HT (blood pressure \geq 130/85 mmHg) and HL (LDL cholesterol $>$ 130 mg/dL) was evaluated according to the Adult Treatment Panel III (ATP III) (10). A fasting plasma glucose level \geq 126 mg/dL (7.0 mmol/L) or HgbA1C \geq 6.5% or a casual plasma glucose $>$ 200 mg/dL (11.1 mmol/L) in the setting of symptoms attributable to hyperglycemia meets the threshold for the diagnosis of diabetes according to the American Diabetes Association criteria (11). Anticoagulant therapy and international normalized ratio (INR) status for the patients with AF and antiaggregant therapy for the patients with ischemic heart disease were evaluated. "The National Institute of Health Stroke Scale (NIHSS)" was used in the assessment of stroke severity (12).

Statistical Analysis

Data analyses were performed using Statistical Package for the Social Sciences software (SPSS 16, Chicago, IL, USA). Descriptive statistical analysis was used to describe the basic features of the data. The numerical descriptors including mean and standard deviation were used to describe continuous data. The descriptors including frequency and percentages were used to describe categorical data.

RESULTS

A total number of 500 patients were recruited for the study. It was found that 91 (18%) out of the 500 patients with ischemic stroke followed-up in our clinic had RIS. Of the patients who had RIS, 50 (55%) were male and 41 (45%) were female. The mean age of the patients with RIS was 71.55 ± 10.40 years.

The parameters regarding TOAST and Bamford Criteria and risk factors are depicted in Tables 1, 2, and 3.

The mean NIHSS score was calculated as 8 ± 6 at the time of admission to the hospital.

On admission, the mean arterial systolic and diastolic blood pressures were 142.09 ± 29.14 mmHg and 81.48 ± 11.73 mmHg, respectively. Seventy-six percent (69/91) of the patients were using an antihypertensive medication. The proportion of the patients who did not use an antihypertensive medication despite having HT was 14% (11/80). Antihypertensive medications were changed because of insufficient control of HT during the service follow-up in 38% (26/69) of the patients who already were on antihypertensive treatment.

The mean fasting blood glucose (FBG) level of the patients with RIS was 139 ± 67 mg/dL. Of the patients with RS, 61% had FBG \geq 110 mg/dL, and the mean HgbA1C level was $6.80 \pm 1.59\%$. Of the diabetic patients (39/91, 43%), 30 had recorded their HgbA1C level, and the mean HgbA1C level of these diabetic patients was $7.94 \pm 1.85\%$.

Table 1. Risk factors data of 91 patients with recurrent stroke

	n (91)	(%)
Hypertension	80	88
Diabetes mellitus	39	43
Cardiac disease	33	36
Atrial fibrillation	10	11
Hyperlipidemia	27	30
Current smokers	13	14
>2 risk factors	35	38

Table 2. The etiological classification of 91 patients with recurrent ischemic stroke

Toast*	n (91)	(%)
Large artery atherosclerosis	31	34
Cardioembolism	30	33
Small vessel disease	3	3
Other identified etiologies	-	
Undetermined origin	22	24
Transient ischemic attack	5	6

*Trial of Org 10172 in acute stroke treatment

Table 3. The clinical classification of 91 patients with recurrent ischemic stroke

Bamford*	n (91)	(%)
Total anterior circulation infarction	8	8
Partial anterior circulation infarction	55	60
Lacunar infarcts	5	6
Posterior circulation infarction	18	20

*Bamford Classification

The mean LDL cholesterol level was 119.89 ± 37.54 mg/dL. Of the patients, 72% had LDL levels \geq 100 mg/dL. Ninety-two percent (58/63) of those patients who had LDL levels \geq 100 mg/dL were not receiving antihyperlipidemic medication. Only 52% (14/27) of the patients who reported HL in their medical history were using antihyperlipidemic medication.

When the secondary prophylactic treatments before RIS were investigated, 52% (47/91), 10% (9/91), 6% (6/91), and 9% (8/91) of the patients were using acetylsalicylic acid (ASA), warfarin, ASA+warfarin, and ASA+clopidogrel, respectively. Twenty-three percent (21/91) of the patients were receiving neither the antiaggregant nor the anticoagulant prophylactic treatment. Of the patients with AF, 60% were using warfarin, whereas 20% were using only ASA, and 10% were using ASA+clopidogrel; 10% of patients with AF were receiving neither anticoagulant nor antiaggregant treatment. The INR value was $<$ 2 in 73% (11/15) of the patients who used warfarin.

The anticoagulant treatment was initiated in 12 of 91 patients with RIS. Of those patients who started anticoagulant treatment, two were neither using antiaggregant nor anticoagulant, one was using double antiaggregant (ASA+clopidogrel), and the remaining nine patients were using only ASA. A second antiaggregant was added to the treatment of 23 patients. Four

patients underwent carotid stenting/angioplasty, whereas 2 underwent carotid endarterectomy.

DISCUSSION

Concordant with increased mean human survival, recurrent stroke with high mortality and morbidity has become an important public health problem for the whole world. Although there are various studies including different outcomes related to the clinical and topographical characteristics of recurrent stroke in literature, there are only a limited number of studies that have evaluated the sufficiency of secondary prophylactic treatment.

In our cross-sectional retrospective study, the incidence of ischemic recurrent stroke was 18%, which was compatible with the reported rates in the Western population (1,2,3,4,5). Age is the most important unmodifiable risk factor for all stroke types and is also one of the significant independent predictors of recurrent stroke (13,14,15). The rate of stroke increases more than twice in both men and women for each successive 10 years after the age of 55 years (14). In literature, it is indicated that 65% of all strokes occur in individuals over the age of 65 years (14,16). The mean age of ≥ 74 years was found to be important determining factor related to stroke recurrence (15,17). In our study, the mean age (71.55 ± 10.40 years) and gender distribution (55% male, 45% female) was found to be in accordance with those in literature.

In our study, the most common etiology for RIS was large-artery atherosclerosis (34%), and the other factors were cardioembolism (33%), undetermined origin (24%), and small vessel disease (3%) according to the TOAST classification. The ranking of the etiologic groups demonstrates different data in the studies that were conducted in different countries. In the RESQUE study that evaluated 889 patients with RIS, small vessel disease was the most common etiological factor and was followed by large artery atherosclerosis and cardioembolism (18). In another study conducted by Petty et al. (2), cardioembolic strokes were the most common cause followed by strokes with an undetermined etiology. The strokes due to undetermined etiologies and cardioembolic strokes were the most common causes with similar frequencies in the study that Sumer et al. (19) conducted in Turkey. In the study conducted by Kolominsky et al. (1) in Europe, cardioembolic strokes ranked first and strokes due to large vessel atherosclerosis ranked second in the disease group. No association was found between RS and any etiological subtype in the study by Laloux et al. (3,20). We assessed these differences regarding the etiology of RIS as a result of different prevalences of RIS inducing etiological factors, quality of preventive treatments for RIS, and methodological variations between studies. The inclusion of only ischemic strokes and exclusion of the patients with hemorrhagic strokes and subarachnoid hemorrhage may have an additional discrepant effect on the results of our study.

The most common clinical subtype of RIS in our study was PACI (60%) followed by POCI (20%), TACI (8%), and LACI (6%). Although this finding was compatible with some studies reported in literature, there are also studies that reported different outcomes (9,21). In the NEMESIS-Study, 1316 patients with the first episode of stroke were recruited into the study over 3 years. A total of 103 first recurrent stroke events (fatal or nonfatal) occurred among those with a first-ever ischemic stroke or intracerebral hemorrhage during the 2-year follow-up period. The subtype for the first episode of stroke and RIS was different in most of the patients (78%). The highest and lowest recurrence rates were found in the PACI (13%) and TACI groups, respectively (22). The lower recurrence rate in the TACI group may be because of a higher mortality rate in the early stage of stroke. This situation may be associated with the presence of active embolic focus. In our study, no comparison could be performed

between first-ever strokes and RS with respect to clinical and etiological subtypes because the records related with the first-ever strokes of the patients were insufficient.

Hypertension is the most prevalent and important modifiable risk factor among all stroke factors within the population (18,23,24,25). According to the outcomes of a meta-analysis including 17 different studies, a reduction of 38% in the total stroke risk may be provided by controlling HT (26). It was reported in literature that stroke recurrence increases 4-fold in the presence of HT, and approximately 60–75% of the strokes occur in the presence of HT (27). A meta-analysis of seven randomized controlled trials including the PATS (indapamide, a diuretic), HOPE (ramipril), and PROGRESS (perindopril, with or without indapamide) studies showed that antihypertensive drugs reduce stroke recurrence after stroke or TIA (RR 0.76; 95% CI 0.63–0.92) (28,29,30,31,32). It was demonstrated in various meta-analyses that an effective antihypertensive treatment reduces stroke recurrence rate by 30–40% (28,33,34). It was also reported in another study that an effective antihypertensive treatment reduces the stroke recurrence rate by 50% (35). The American Heart Association/American Stroke Association (AHA/ASA) 2011 guideline and The European Stroke Organization (ESO) Executive Committee and the ESO Writing Committee recommended that the prevention of recurrent stroke is closely related to the aggressive treatment of HT (Class I, Level of Evidence A), and in spite of the unclear definition of absolute target of blood pressure, a benefit has been associated with an average reduction of 10/5 mmHg, and normal blood pressure levels have been defined as $< 120/80$ mmHg by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (Class II, Level of Evidence B) (36,37,38). HT was the most common risk factor in our trial group (85% of the patients). The proportion of patients with HT who did not use antihypertensive medication in the cohort was 14%. In addition, the proportion of patients whose medications were changed because of insufficient efficacy observed during the follow-up period in our cohort was 39%. The proportion of patients with recurrent stroke who received insufficient antihypertensive medication was found to be 39% in the study by Laloux et al. (20). These proportions were evaluated to be remarkably high and showed HT as an important modifiable risk factor for the prevention of stroke recurrence in our patient cohort.

Stroke incidence increases 2-fold in the presence of DM in patients with atherosclerotic disease (39). In our study, DM was found to be the second most common risk factor for RIS. DM was the fifth most common disease with a rate of 24% in the RESQUE trial (17). It was also determined that 59% of the patients had insufficient medication (19). An insufficient medication rate was also high in our patients, which depended on a mean Hg-bA1C level of $6.80 \pm 1.59\%$ in all patients and $7.94 \pm 1.85\%$ in the diabetic group. This data was very closely related with the poor control of DM and implied the potential of uncontrolled DM for RS.

While a directly proportional elevation was found between the total cholesterol/HDL cholesterol ratio and myocardial infarction, similar rates were also found valid for atherothrombotic brain ischemia (40). HL was the second ranked etiological factor for recurrent stroke with a rate of 56% in the RESQUE trial (17). It was found in the study by Laloux et al. (20) that HL is the second most common disease (43%) and that treatment was insufficient in 42% of the patients. According to the AHA/ASA 2011 guideline, statin treatment with intensive lipid-lowering effects is recommended to reduce the risk of stroke and cardiovascular events for patients with ischemic stroke or TIA, evidence of atherosclerosis, an LDL-C level ≥ 100 mg/dL, and without known coronary artery disease. In these patients, a target reduction of

at least 50% in LDL-C or a target LDL-C level <70 mg/dL is recommended (36,41,42). The medical history of HL was known in 23% of our patients, and only 32% of these patients were receiving antihyperlipidemic treatment. The fact that the mean LDL cholesterol level was 119 ± 37.54 mg/dL in all patients including treated and non-treated ones and that 73% of those have LDL level higher than 100 mg/dL was interpreted in favor of insufficiency in the treatment of patients.

Atrial fibrillation accompanied with rheumatic heart disease and mitral stenosis is an important predisposing factor for stroke (43). AF is a very important risk factor for both first-ever stroke and recurrent stroke (44). Warfarin treatment provides 64% relative risk reduction in the prevention of stroke (45). The percentages of ischemic heart disease and AF were 37% and 29%, respectively, in the RESQUE trial (17). Correspondingly, the rates of ischemic heart disease and AF were 36% and 11%, respectively, in our study. Patients with ischemic stroke or TIA with permanent or paroxysmal (intermittent) nonvalvular AF should receive anticoagulation with a vitamin K antagonist or new oral anticoagulant agents (target INR 2.5, range 2–3) (36,46). Thirty percent of the patients with cardioembolic stroke were receiving anticoagulant treatment in our cohort compared with the rate of 21% in the RESQUE trial (17). In the study conducted by Laloux et al. (20), only 34% of the patients with a determined AF had anticoagulant treatment, and 71% of those had an INR value <2. Of our patients with AF, 60% were using warfarin, and the INR value was <2 in 73% of the patients who used warfarin. This result was consistent with the undertreatment of AF and increased tendency of this subgroup to RIS in our patient cohort.

Smoking increases the risk of CVD. This increased risk is more remarkable in the patients associated with HT and/or DM (47). However, the effect of smoking on the increased risk of RS is not entirely clear in literature. The studies that explored a link between smoking and RS show discrepant results (3,48,49,50). In our study that involved a retrospective evaluation, 14% of the patients (13/91) were currently smoking at the time of RS. That rate was 25% in the study by Laloux et al. (20) and 30% in the RESQUE trial (17). The smoking rate of our patients was determined to be lower when compared with that in literature. In the prospective study by Bak et al that involved patients who had the first-ever stroke in their lifetime and that evaluated smoking habits in a 6 month-follow-up period, smoking cessation rate of the patients was 21.7% (49). The patients with RS were excluded from this study. Hornnes et al. (50) found at the end of the 1-year follow-up period of the patients who recently had stroke that 47% of the smokers continued smoking. When viewed from this perspective, it is noticeable that the smoking cessation rate is significantly low particularly in patients who experienced stroke. This finding creates a wide area for clinicians to implement preventive medicine, such as including the patients into a smoking cessation program, about smoking.

Of our patients, 38% (35/91) were carrying more than two risk factors, whereas 51% of the patients with ischemic recurrent stroke were carrying three or more risk factors in RESQUE trial (17). In the study by Laloux et al. (20), 84% of the patients were carrying more than one risk factor. This data showed that the impact of solitary risk factors are more important than those of combined risk factors for recurrent stroke and based on better drug compliance, prophylactic treatment, which requires approval by further studies, may be more fruitful in our country.

When secondary prophylactic treatments prior to recurrent stroke were investigated, 67% (61/91), 16% (15/91), 6% (6/91), and 9% (8/91) were using ASA, warfarin, ASA+warfarin, and ASA+clopidogrel, respectively,

Twenty-three percent (21/91) of the patients were using none of these treatments. In the study by Laloux et al. (20), the proportion of the patients who used no antithrombotic agent although they had a previous stroke or TIA was 15%. This proportion was 16% in our study. The proportions of the patients who used warfarin because of AF in our and Laloux et al.'s (20) study were 60% and 34%, respectively. The proportion of treatment insufficiency determined by an INR value <2 in our study was 73% compared with that of Laloux et al.'s study as 71% (19).

The improvement of patients' adherence to the treatment is also very important in addition to the optimal treatment and follow-up strategy for decreasing the incidence of RIS. Coordinated multidisciplinary inpatient stroke care has been shown to improve mortality and functional recovery post stroke (51,52). Although post-stroke outpatient clinics have been described in literature (53,54,55,56), there are insufficient data about the use or effectiveness of a multidisciplinary approach to stroke care in the outpatient setting. It is reported that an initial post-stroke home assessment and team-based approach result in improvements for neuromotor function, severe complications, quality of life, management of risk for common post-stroke complications and recurrent stroke, and stroke knowledge (57). Schmid et al. (58) also found supportive data for the effectiveness of a multidisciplinary outpatient model of stroke care for improving the care and outcomes of patients with cerebrovascular disease and risk factors in a veteran clinical setting. Improvements in care may be related to the implementation of standard screening procedures that efficiently identify potential problems for patients (58).

Our study has two limitations. First, the size of the study population with RIS was small. Second, the records of some patients regarding the etiology and detailed treatment at the first episode of stroke were missing. Because the records related to the first-ever strokes of the patients were insufficient, no comparison could be made between first-ever strokes and RIS with respect to the clinical and etiological subtypes.

In conclusion, it is clear that secondary prophylactic treatment and a modification of risk factors in stroke patients are not satisfactory in clinical practice worldwide as well as in our population. The improvement of patients' adherence to the treatment is also very important in addition to the optimal treatment and follow-up strategy for decreasing the incidence of RIS. A multidisciplinary outpatient model for stroke care may be beneficial for decreasing the incidence of RIS.

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