Risk Factors, Vascular Lesion Distribution, Outcome and Recurrence of Strokes Due to Intracranial Atherosclerosis: One Year Data from Hyderabad Stroke Registry

Raghu Ram, Subhash Kaul, Suvarna Alladi, Jabeen S. Afshan, T. Surya Prabha, Abhijeet Kohat, Swetha Tandra, Jyotsna Y. Rani[1]

Departments of Neurology and [1]Radiology, Nizams Institute of Medical Sciences, Hyderabad, Telangana, India

Abstract

Background: Intracranial atherosclerotic stenosis (ICAS) is a common cause of ischemic stroke in Asian countries and probably in India. **Aim:** The aim of this study was to describe the risk factors, distribution of vascular lesions, recurrence and outcome of stroke due to ICAS. **Methodology:** A total of 100 consecutive patients of ischemic stroke due to ICAS were enrolled prospectively from January 1, 2015, to December 31, 2015, and followed for 1 year for treatment compliance and recurrence. The details about demographics, risk factors, and vascular lesions were noted. **Results:** There were 68 males and 32 females. Hypertension (HTN), diabetes, alcohol, smoking, hyperlipidemia, and hyperhomocysteinemia was present in 82%, 52%, 34%, 33%, 28%, and 23%, respectively. The number of arteries involved were middle cerebral artery, 53 (37.3%); posterior cerebral artery, 24 (16.9%); internal cerebral artery, 21 (14.8%); vertebral artery, 18 (12.7%); basilar artery, 6 (4.2%); and anterior cerebral artery, 6 (4.2%). Seventeen (17%) patients had a recurrent stroke during 1 year follow-up. The presence of uncontrolled HTN and diabetes mellitus after discharge were significantly associated with stroke recurrence ($P < 0.05$). The use of dual antiplatelet agents and statins was found to have a significant effect in the prevention of recurrent stroke ($P < 0.05$). Severe stroke at presentation and presence of hemiparesis were the predictors for unfavorable outcome at 3 months ($P < 0.05$). **Conclusion:** Risk factors, distribution of vascular lesions and high recurrence of stroke due to ICAS in this study is similar to that reported from other Asian countries. Aggressive medical management and risk factor control remains the best strategy for preventing recurrence.

Keywords: India, intracranial atherosclerosis, stroke

INTRODUCTION

Ischemic stroke is a clinical syndrome caused by various mechanisms of cerebrovascular disease. The risk of intracranial atherosclerotic stenosis (ICAS) is higher in patients of Asian, African, and Hispanic ethnicity compared to Caucasians.[1] It accounts for about 33%–50% of ischemic strokes and >50% of transient ischemic attacks (TIAs) in these populations. We have previously reported asymptomatic middle cerebral artery stenosis in 7.2% of patients above 40 years of age having at least two risk factors.[2] Intracranial stenosis was the most common stroke mechanism in the Hyderabad Stroke Registry reported by us.[3] As the majority of the world's population is represented by Asians, ICAS is the most common vascular lesion in stroke patients worldwide.[4]

Large vessel ICAS which includes intracranial internal carotid artery, middle cerebral artery, posterior cerebral artery (PCA), vertebral artery (VA), and basilar artery (BA) represents a more advanced stage of intracranial atherosclerotic disease, in which the vessel lumen has narrowed. In clinical practice as well as for research purpose, a diameter stenosis of 50%–99% is taken to qualify for symptomatic ICAS.[5] However, the atherosclerotic disease process can lead to complete occlusion of the intracranial vessel when it must be differentiated from the embolic occlusion from a proximal source. The estimated prevalence of symptomatic ICAS in more recent literature ranges from 20% to 53%, depending on the study population, race, and imaging method.[6] High rates of recurrent ischemic stroke in symptomatic ICAS mandate early diagnosis and treatment.

Address for correspondence: Dr. Subhash Kaul,
Department of Neurology, Millenium Block, Nizams Institute of
Medical Sciences, Panjagutta, Hyderabad - 500 083, Telangana, India.
E-mail: subashkaul@hotmail.com

Access this article online

Quick Response Code:

Website:
www.annalsofian.org

DOI:
10.4103/aian.AIAN_227_17

Aims and objectives

To assess the risk factors, vascular lesion distribution, outcome and recurrence of strokes due to ICAS.

METHODOLOGY

The study was planned to be a prospective study to enroll 100 consecutive patients of stroke due to intracranial stenosis, admitted in Nizam's Institute of Medical Sciences, a major University hospital in the south Indian state of Telangana, from January 1, 2015, to December 31, 2015. The diagnosis of ischemic stroke due to large artery intracranial atherosclerosis was made as per the TOAST (trial of ORG 10172 in acute stroke treatment) classification.[7] Following data were recorded in all patients: demographic data; detailed history of present and preceding (if any) illness with a special emphasis on vascular risk factors; physical as well as neurological examination details; disease duration; laboratory characteristics; any complications; and treatment received. The data were captured in predesigned case record forms.

Magnetic resonance angiography (MRA) (GE Systems 1.5 T) was done in all patients. Stenosis (segmental flow gap or luminal stenosis >50%) or occlusion (nonvisualized vessel segment with absent distal flow) was assessed in proximal middle cerebral arteries, proximal anterior cerebral arteries, intracranial internal carotid arteries, proximal posterior cerebral arteries, VAs, and the BA. The distribution of stenotic and occlusive lesions was noted. Patients were put on treatment with antiplatelet drugs in addition to other required medications.

Patients were contacted at a regular basis in person, by proxy or on telephone. The patient's adherence to treatment, the disability scores by modified Rankin Scale (mRS) and the recurrence of the stroke was assessed during a hospital stay, at 3 months and 1 year. Unfavorable outcomes were defined as mRS ≥3 or death due to any event at 3 months.

Diagnostic criteria for risk factors

Hypertension (HTN): history of HTN in the past, systolic blood pressure (SBP) ≥140 mmHg, and or diastolic blood pressure ≥90 mm hg.[8] Diabetes: history of diabetes; fasting blood glucose >126 mg/dl or 2-h postprandial blood glucose >200 mg/dl, HbA1C >6.5.[8] Hyperhomocysteinemia: Elevated levels of serum homocysteine more than 20 μmoles/L.[8] Hyperlipidemia: history of dyslipidemia, cholesterol >200 mg/dL, low-density lipoprotein >100 mg/dl (or) triglycerides >150 mg/dL.[9] Smoking: if the patient was a current smoker or had quit smoking in the past 6 months.[10] Alcohol: the history of drinking is defined as the average daily alcohol consumption of patients with >50 g for >1 year.[11]

Definition of symptomatic and asymptomatic occlusion/stenosis

Arterial lesions corresponding to the location/territory of the recent infarct on diffusion weighted imaging were considered symptomatic. Asymptomatic lesion was defined as stenosis or occlusion not related to the current neurologic signs and with no old infarction visible in neuroimaging in its respective vascular territory.

Inclusion criteria

1. Stroke was defined as focal/global symptoms lasting >24 h and associated with imaging evidence of acute ischemia in the distribution of the stenotic vessel on computed tomography or magnetic resonance imaging
2. Intracranial atherosclerotic disease comprised the involvement of the intracranial carotid, middle cerebral, posterior cerebral, intracranial VA or BAs
3. Patients should have given informed consent for participation in the study.

Exclusion criteria

1. Other cause for stroke: atrial fibrillation, acute anterior wall ST-elevation myocardial infarction <30 days, mitral stenosis, mechanical valve, intracardiac thrombus or vegetation, dilated cardiomyopathy or ejection fraction <30%, proximal extracranial carotid or vertebral stenosis >50%, intracranial tumors, arteriovenous malformations, moyamoya disease, arteritis, and other clear cause of stroke
2. Unable to obtain informed consent by patient or authorized representative
3. If patient was unlikely to return for follow-up/noncontactable for telephonic interview.

Statistical analysis

All data were entered into the Microsoft Excel file, and the analysis was performed in SAS software (version 9.2 for Windows). Mean, standard deviation, and Student's *t*-test was performed for quantitative variables. Frequency, percentage, and Chi-square tests were performed for qualitative variables. Two-sided statistical significance was considered at 5% level of significance (LOS). Univariate Logistic Regression analysis was performed on dependent variable outcome event (based on mRS at 3 months), and multivariate regression analysis was performed to find out the significant predictors for the dependent variable. COX-Proportional Hazard Ratio Analysis was performed on "Recurrence" as dependent variable and "Recurrence Event at Months" as a Time variable to find out the significant predictors (independent variables) to the dependent variable. Variables were identified as significant at 5% LOS (i.e., variable are significant if respective $P < 0.05$). Uncontrolled risk factors and treatment effect on recurrence was tested on null hypothesis using Chi-square test with $P < 0.05$ as significant.

RESULTS

A total of 100 consecutive patients of ischemic stroke due to ICAS were included in the study with mean age of 55.2 ± 11.8 years among whom 68 were males. Out of all vascular risk factors, HTN ($n = 82$, 82%) was found to be the most common risk factor, followed by diabetes mellitus (DM) in 52 (52%) patients [Table 1]. A total of 142 arteries fulfilled

the criteria of symptomatic ICAS. MCA lesions were common in anterior circulation (53/142, 37.3%) followed by ICA (21/142, 14.8%) and ACA (6/142, 4.2%). In posterior circulation PCA (24/142, 16.9%) was frequently involved followed by VA (18/142, 12.7%) and BA (6/142, 4.2%). Mixed arterial lesions were noted in 14/142 patients [Table 2]. Cortical distribution of infarcts was found in 26/100 (26%) of patients followed by subcortical (24/100, 24%) and mixed cortical and subcortical infarcts in (24/100, 24%). Cerebellar and brainstem infarcts were observed in (12/100) 12% and (7/100) 7% of patients, respectively [Table 3].

Logistic regression analysis showed that age, gender, presence of individual risk factors, multiple lesions on MRA and severity of stroke (National Institutes of Health Stroke Scale [NIHSS]) had no predictive value for recurrence, but the presence of ≥ 3 risk factors was significantly associated with recurrence up to 1 year ($P = 0.0351$) [Table 4]. The presence of uncontrolled HTN, DM at 3-month follow-up were significantly associated with recurrence of stroke ($P < 0.05$), whereas uncontrolled hyperlipidemia was not significantly associated with recurrence [Table 5]. The use of dual antiplatelet agents and statins was found to have a significant effect in the prevention of recurrent stroke ($P < 0.05$). Patients on single antiplatelet agents were found to have a high chance of recurrent strokes compared to those on dual antiplatelets ($P = 0.004$) [Table 5].

Functional outcome was analyzed at 3 months. Two patients died during a hospital stay due to pneumonia and sepsis. At 3 months the mean age of patients with favorable ($n = 56$) and unfavorable ($n = 44$) outcome was 55.25 ± 10.9 and 55.20 ± 13.1 years, respectively. On univariate analysis, the absence of hemiparesis and low NIHSS 9.07 ± 3.5 determined the favorable group versus 13.23 ± 4.3 in the unfavorable group, which was found statistical significance ($P < 0.05$). Among the risk factors, persistent smoking (odds ratio 0.2666, $P = 0.0047$) was significantly associated with unfavorable outcome.

DISCUSSION

The focus on intracranial atherosclerotic disease has dramatically increased over the last two decades, and it is now agreed that ICAS is the leading cause of ischemic stroke and TIA worldwide.[4] Previous studies from India including the one from our center[3,12,13] have shown that ICAS was the most frequent ischemic stroke subtype.

Risk factors

The risk factors for ICAS found in our study [Table 1] are in agreement with the prior studies done in other parts of the world.[14-16] HTN was identified as the most common risk factor among 82% of the patients in our study, as also found in the previous studies.[17] Majority of hypertensives were also found to be have diabetes in the study population indicating the complex interplay between vascular risk factors. Alcohol and smoking were found more commonly in males probably due to local socio economic and cultural influences.

Table 1: Demography and risk factors in the study population (*n*=100)

Variable	*n* (%)
Age (mean±SD)	55.2±11.8
Male	68 (68)
Female	32 (32)
Alcohol	34 (34)
Homocysteine	23 (23)
HTN	82 (82)
Diabetes	52 (52)
Hyperlipidemia	28 (28)
Smoking	33 (33)
HTN + diabetes	46 (46)
HTN + diabetes + hyperlipidemia	16 (16)
HTN + diabetes + hyperlipidemia + smoking + alcohol	5 (5)
Others	10 (10)

SD=Standard deviation, HTN=Hypertension

Table 2: Distribution of atherosclerotic lesions (stenosis or occlusion) in various arteries

Artery	Frequency of lesions (*n*=142)	Percentage distribution of lesions
MCA	53	37.3
ICA	21	14.8
ACA	6	4.2
VA	18	12.7
BA	6	4.2
PCA	24	16.9
MCA + ICA	4	2.8
ICA + MCA + ACA	4	2.8
BA + PCA	4	2.8
VA + BA	2	1.4

ICA=Internal carotid artery, MCA=Middle cerebral artery, ACA=Anterior carotid artery, VA=Vertebral artery, BA=Basilar artery, PCA=Posterior cerebral artery

Table 3: Topographical distribution of infarcts

Distribution	Frequency (%)
Cortical	26
Subcortical	24
Cortical and subcortical	24
Brain stem	7
Cerebellum	12
Others	7

Homocysteine in our study has emerged as the sixth common risk factor after HTN, diabetes, alcohol, smoking, and hyperlipidemia. Many other studies have also found it as a risk factor for cerebral atherosclerosis with a higher prevalence in males,[18] although we did not find this gender association. In India, common associations of high homocysteine levels have been found with vegetarian diet due to deficiency of Vitamin B12.[19] There is 54.5% prevalence of MTHFR polymorphism in Indian population.[20] These may be the possible reasons for high prevalence of hyperhomocysteinemia

Table 4: Predictors of recurrence within 1 year

	No recurrence (*n*=83), *n* (%)	Recurrence (*n*=17), *n* (%)	Hazard ratio	*P*
Age	54.93±11.3	56.71±14.2	1.078	0.5075
Gender	55 (66.3)	13 (76.5)	0.759	0.9048
Hypertension	68 (81.9)	14 (82.4)	0.550	0.8359
Diabetes	41 (49.4)	11 (64.7)	7.347	0.6757
Hyperlipidemia	20 (24.1)	8 (47.1)	0.044	0.0533
Alcohol	25 (30.1)	9 (52.9)	0.582	0.7582
Smoking	26 (31.3)	7 (41.2)	0.217	0.5391
Homocysteine	19 (22.9)	4 (23.5)	2.994	0.7390
Multiple lesions (>3)	32 (38.6)	7 (41.2)	8.753	0.4689
NIHSS	10.64±4.3	12.18±4.6	1.076	0.5614
Risk factors ≥3	36 (43.4)	14 (82.4)	218.294	0.0351

NIHSS=National Institutes of Health Stroke Scale

Table 5: Effect of uncontrolled risk factors and treatment on recurrence

Parameter	No recurrence (*n*=83), *n* (%)	Recurrence (*n*=17), *n* (%)	*P*
Drug compliance to anti-platelets	75/83 (90)	13/17 (76)	0.10
Dual antiplatelet	70/83 (84)	6 (35)	<0.05
Single antiplatelet	5 (6)	7 (41)	0.004
Statins	70 (84)	10 (59)	0.016
Hypertension controlled	60/68 (88)	5/14 (35)	<0.05
Diabetes controlled	35/41 (85)	7/11 (64)	<0.05
Hyperlipidemia controlled	15/20 (75)	5/8 (63)	0.50

in the Indian population, although we did not do any genetic study to study this polymorphism.

These vascular risk factors, either alone or in combination, contributed to ICAS-related stroke.

Distribution of atherosclerotic lesions

It is well known that atherosclerosis of the intracranial arteries is more common in nonCaucasians compared to Caucasians.[21,22] MCA was the most commonly involved vessel in our study [Figure 1] followed by ICA [Table 2] which is consistent with previous studies in Asian populations.[23,24] Compared to extracranial ICA disease, intracranial ICA occlusive disease is less recognized site of atherosclerosis.[25,26] However, the thrombus in intracranial ICA may extend distally causing MCA and ACA territory infarcts [Figure 2]. ACA was the least involved vessel (4.2%) in our study. Intrinsic atherostenotic lesions of the ACA are unusual and often remain silent in the presence of the anterior communicating artery.[27] In our study, posterior circulation lesions commonly involved the PCA (16.9%). Other studies have not reported atherosclerotic PCA involvement as commonly as the VA and BA.[28] Most of the PCA lesions reported have been accompanied by coexistent lesions of the VA and BA[29] [Figure 3]. However, we found more frequent involvement of isolated PCA.

Clinical features

Hemiparesis was the predominant symptom (58%) in our study due to the maximum distribution of the infarcts in cortical and subcortical areas [Table 4]. Ataxia, giddiness, hemianopia, headache, cranial nerves such as lower motor neuron facial
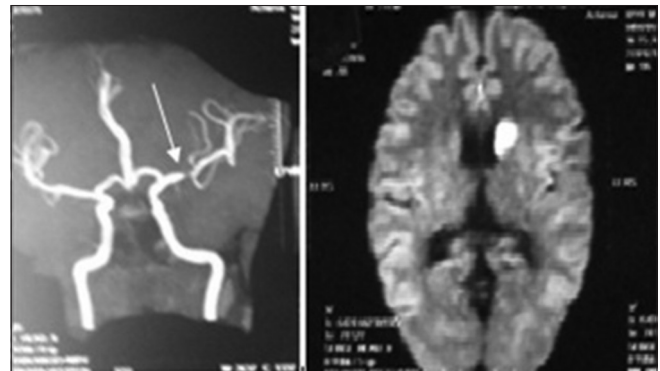

Figure 1: Left middle cerebral artery stenosis with diffusion weighted imaging showing subcortical infarct

palsy, diplopia, dysarthria, and alteration in consciousness were frequently observed in strokes with lesions involving posterior circulation than anterior circulation as reported in other posterior circulation registries.[28,30] Previous studies have shown that strokes with MCA stenosis can manifest as large artery infarcts with or without perforator artery infarcts, occurring singly or in addition to pial or border zone infarcts.[31,32] In short, there is nothing specific about the clinical presentation of strokes due to ICAS, which therefore needs to be excluded in all patients with ischemic strokes.

Recurrence

In our study, 17 patients (17%) had recurrent ischemic events over 1 year as observed in other studies (SAMMPRIS: 12.2%, WASID: 23%, CICAS: up to 19%).[33-36] Most of the recurrent
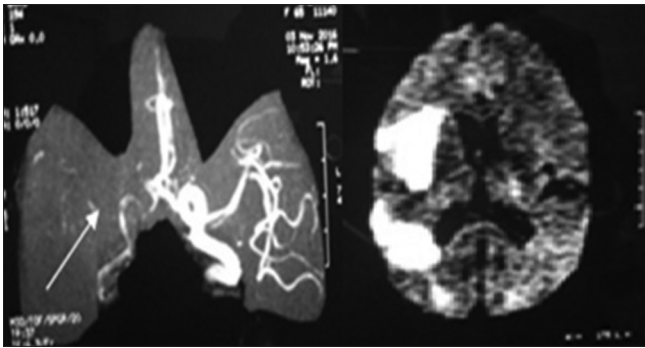
Figure 2: Right middle cerebral artery/internal carotid artery occlusion with diffusion weighted imaging showing corresponding infarct

Figure 3: Basilar artery stenosis, right superior cerebellar, and right posterior cerebral artery not visualized with diffusion weighted imaging showing infarct in the midbrain and occipital cortex

events were observed in the first 3 months (12 of 17 individuals) which is in line with data from previous observational and randomized studies.[37] Symptomatic lesions are more prone for further events than asymptomatic lesions.[38] In the present study, the recurrent events were observed in the same symptomatic territory as the initial stroke in 16 of 17 patients.

Combination of >3 risk factors was found to be an independent predictor for recurrence than the presence of individual risk factors such as HTN, diabetes, or smoking in our study [Table 3]. However, uncontrolled HTN or uncontrolled diabetes at 3 months follow-up were predictors of recurrence even in isolation ($P < 0.05$). The presence of elevated SBP at the time of hospital discharge after a stroke is a strong predictor of early recurrence.[39] Uncontrolled DM has also been shown to be significantly associated with stroke recurrence in WASID study.[34] Although the presence of hyperlipidemia reached modest significance for recurrence in our study, its control was not significantly associated with a reduction of recurrence. However, the patients who were on statins showed significantly lower recurrence ($P < 0.05$), [Table 5]. Dual antiplatelet therapy has been strongly recommended as the first-line treatment in the secondary prevention of stroke due to intracranial stenotic lesions.[40,41] In our study also, recurrent stroke was significantly less in patients on double antiplatelets.

Outcome

A host of prestroke comorbid conditions, specific neurodeficits, location and size of infarct[42] have been shown to be associated with poor outcome following ischemic stroke, but the major predictors are the severity of stroke on neurologic examination (NIHSS) and age.[43] As in a previous study,[37] we used a composite definition for outcome assessment which included functional disability as measured by mRS ≥3, and death of any cause. We did not find age, gender, HTN, DM, and location of the stroke (Anterior and Posterior) as the predictors for poor outcome for 3 months after stroke. However, the presence of smoking was significantly associated with unfavorable functional outcome at 3 months. The return of arm and hand function after stroke is particularly important to a good functional recovery, hence, the presence of hemiparesis is associated with poor functional outcome, as observed in this study at 3 months analysis after stroke.
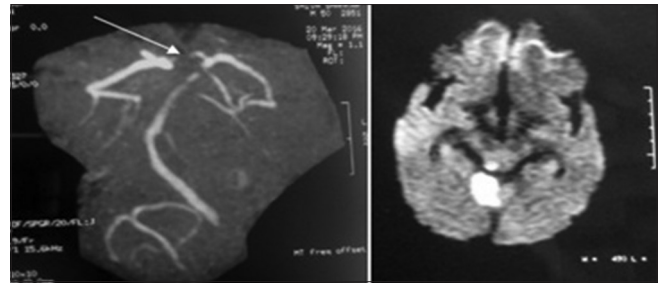
Limitations

This is a study with a modest sample size. MRA offers good equivalency with digital subtraction aortogram for detection of 50% stenosis,[44] albeit the latter is gold standard for detecting ICAS. Three-dimensional MRA time-of-flight images might have suffered from blood-flow artifacts that mimic stenosis. The degree of stenosis beyond 50% was not studied which could have affected the recurrence and outcome analysis. Although we excluded patients with presumed cardioembolism, 24-h Holter monitoring, and other investigations were not done in all patients.

Conclusions

Common modifiable risk factors of ICAS in this study were HTN, diabetes mellitus, alcoholism, smoking, hyperlipidemia, and hyperhomocysteinemia. The incidence of ICAS in anterior circulation stenosis was found to be higher than that in posterior circulation. MCA was the most commonly affected artery. Severity of the stroke at presentation as measured with NIHSS and presence of hemiparesis along with continued smoking were the predictors for unfavorable outcome at 3 months. Patients on single antiplatelet therapy, uncontrolled HTN, and DM were at high risk for recurrence. The recurrence risk was reduced by treatment with dual antiplatelets, statins, and strict control of HTN and diabetes. The aforesaid facts highlight the importance of early diagnosis and aggressive medical treatment with risk factor control.

Conflicts of interest
There are no conflicts of interest.

References

1. Huang YN, Gao S, Li SW, Huang Y, Li JF, Wong KS, *et al.* Vascular lesions in Chinese patients with transient ischemic attacks. Neurology 1997;48:524-5.
2. Sada S, Reddy Y, Rao S, Alladi S, Kaul S. Prevalence of middle cerebral artery stenosis in asymptomatic subjects of more than 40 years age group: A transcranial Doppler study. Neurol India 2014;62:510-5.
3. Kaul S, Sunitha P, Suvarna A, Meena AK, Uma M, Reddy JM. Subtypes of ischemic stroke in a metropolitan city of South India (one year data from a hospital based stroke registry). Neurol India 2002;50:S8-14.

4. Gorelick PB, Wong KS, Bae HJ, Pandey DK. Large artery intracranial occlusive disease: A large worldwide burden but a relatively neglected frontier. Stroke 2008;39:2396-9.

5. Qureshi AI, Feldmann E, Gomez CR, Johnston SC, Kasner SE, Quick DC, *et al.* Intracranial atherosclerotic disease: An update. Ann Neurol 2009;66:730-8.

6. Ritz K, Denswil NP, Stam OC, van Lieshout JJ, Daemen MJ. Cause and mechanisms of intracranial atherosclerosis. Circulation 2014;130:1407-14.

7. Adams HP Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, *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.

8. Kernan WN. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:2160-236.

9. Amarenco P, Goldstein LB, Szarek M, Sillesen H, Rudolph AE, Callahan A 3rd, *et al.* Effects of intense low-density lipoprotein cholesterol reduction in patients with stroke or transient ischemic attack: The stroke prevention by aggressive reduction in cholesterol levels (SPARCL) trial. Stroke 2007;38:3198-204.

10. Agency for Healthcare Research and Quality. Clinical Guidelines for Prescribing Pharmacotherapy for Smoking Cessation. Rockville, MD: Agency for Healthcare Research and Quality; 2012.

11. Briasoulis A, Agarwal V, Messerli FH. Alcohol consumption and the risk of hypertension in men and women: A systematic review and meta-analysis. J Clin Hypertens (Greenwich) 2012;14:792-8.

12. Padma MV, Gaikwad S, Jain S, Maheshwari MC, Misra NK. Distribution of vascular lesions in ischaemic stroke: A magnetic resonance angiographic study. Natl Med J India 1997;10:217-20.

13. Dalal PM, Shah PM, Aiyar RR, Kikani BJ. Cerebrovascular diseases in west central India. A report on angiographic findings from a prospective study. Br Med J 1968;3:769-74.

14. Wityk RJ, Lehman D, Klag M, Coresh J, Ahn H, Litt B, *et al.* Race and sex differences in the distribution of cerebral atherosclerosis. Stroke 1996;27:1974-80.

15. Leoo T, Lindgren A, Petersson J, von Arbin M. Risk factors and treatment at recurrent stroke onset: Results from the Recurrent Stroke Quality and Epidemiology (RESQUE) study. Cerebrovasc Dis 2008;25:254-60.

16. Rincon F, Sacco RL, Kranwinkel G, Xu Q, Paik MC, Boden-Albala B, *et al.* Incidence and risk factors of intracranial atherosclerotic stroke: The Northern Manhattan Stroke Study. Cerebrovasc Dis 2009;28:65-71.

17. Chaturvedi S, Turan TN, Lynn MJ, Kasner SE, Romano J, Cotsonis G, *et al.* Risk factor status and vascular events in patients with symptomatic intracranial stenosis. Neurology 2007;69:2063-8.

18. Zhang W, Sun K, Chen J, Liao Y, Qin Q, Ma A, *et al.* High plasma homocysteine levels contribute to the risk of stroke recurrence and all-cause mortality in a large prospective stroke population. Clin Sci (Lond) 2009;118:187-94.

19. Shridhar K, Dhillon PK, Bowen L, Kinra S, Bharathi AV, Prabhakaran D, *et al.* Nutritional profile of Indian vegetarian diets – The Indian Migration Study (IMS). Nutr J 2014;13:55.

20. Nair KG, Nair SR, Ashavaid TF, Dalal JJ, Eghlim FF. Methylenetetrahydrofolate reductase gene mutation and hyperhomocysteinemia as a risk factor for coronary heart disease in the Indian population. J Assoc Physicians India 2002;50:9-15.

21. Wong KS, Huang YN, Gao S, Lam WW, Chan YL, Kay R, *et al.* Intracranial stenosis in chinese patients with acute stroke. Neurology 1998;50:812-3.

22. Caplan LR, Gorelick PB, Hier DB. Race, sex and occlusive cerebrovascular disease: A review. Stroke 1986;17:648-55.

23. Tomita T, Mihara H. Cerebral angiographic study on C.V.D. In Japan. Angiology 1972;23:228-39.

24. Suh DC, Lee SH, Kim KR, Park ST, Lim SM, Kim SJ, *et al.* Pattern of atherosclerotic carotid stenosis in Korean patients with stroke: Different involvement of intracranial versus extracranial vessels. AJNR Am J Neuroradiol 2003;24:239-44.

25. Hass WK, Fields WS, North RR, Kircheff II, Chase NE, Bauer RB, *et al.* Joint study of extracranial arterial occlusion. II. Arteriography, techniques, sites, and complications. JAMA 1968;203:961-8.

26. Kim Jong S. Anterior circulation disorders. In: Kim Jong S, Caplan Louis R, Lawrence WK, editors. Intracranial Atherosclerosis. Oxford: Wiley-Blackwell; 2008. p. 69-82.

27. Radwan ME, Aboshaera KO. Magnetic resonance angiography in evaluation of acute intracranial steno-occlusive arterial disease. Egypt J Radiol Nucl Med 2016;47:903-8.

28. Caplan LR, Wityk RJ, Glass TA, Tapia J, Pazdera L, Chang HM, *et al.* New England medical center posterior circulation registry. Ann Neurol 2004;56:389-98.

29. Castaigne P, Lhermitte F, Gautier JC, Escourolle R, Derouesne C, Der Agopian P, *et al.* Arterial occlusions in the vertebrobasilar system. A study of 44 patients with postmortem data. Brain 1973;96:133-54.

30. Tao WD, Liu M, Fisher M, Wang DR, Li J, Furie KL, *et al.* Posterior versus anterior circulation infarction: How different are the neurological deficits? Stroke 2012;43:2060-5.

31. Lee PH, Oh SH, Bang OY, Joo SY, Joo IS, Huh K, *et al.* Infarct patterns in atherosclerotic middle cerebral artery versus internal carotid artery disease. Neurology 2004;62:1291-6.

32. Kim JM, Jung KH, Sohn CH, Moon J, Han MH, Roh JK, *et al.* Middle cerebral artery plaque and prediction of the infarction pattern. Arch Neurol 2012;69:1470-5.

33. Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, *et al.* Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med 2011;365:993-1003.

34. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, *et al.* Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis (WASID). N Engl J Med 2005;352:1305-16.

35. Wang Y, Zhao X, Liu L, Soo YO, Pu Y, Pan Y, *et al.* Prevalence and outcomes of symptomatic intracranial large artery stenoses and occlusions in China: The Chinese Intracranial Atherosclerosis (CICAS) Study. Stroke 2014;45:663-9.

36. Samaniego EA, Hetzel S, Thirunarayanan S, Aagaard-Kienitz B, Turk AS, Levine R, *et al.* Outcome of symptomatic intracranial atherosclerotic disease. Stroke 2009;40:2983-7.

37. Kate M, Sylaja PN, Kesavadas C, Thomas B. Imaging and clinical predictors of unfavorable outcome in medically treated symptomatic intracranial atherosclerotic disease. J Stroke Cerebrovasc Dis 2014;23:973-8.

38. Gouveia A, Sargento-Freitas J, Penetra J, Silva F, Machado C, Cordeiro G, *et al.* Recurrence in intracranial atherosclerotic disease: A stenosis-based analysis. J Stroke Cerebrovasc Dis 2014;23:2080-4.

39. Lawes CM, Bennett DA, Feigin VL, Rodgers A. Blood pressure and stroke: An overview of published reviews. Stroke 2004;35:1024.

40. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86.

41. European Stroke Organisation (ESO) Executive Committee, ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis 2008;25:457-507.

42. Schiemanck SK, Kwakkel G, Post MW, Prevo AJ. Predictive value of ischemic lesion volume assessed with magnetic resonance imaging for neurological deficits and functional outcome poststroke: A critical review of the literature. Neurorehabil Neural Repair 2006;20:492-502.

43. Saver JL, Altman H. Relationship between neurologic deficit severity and final functional outcome shifts and strengthens during first hours after onset. Stroke 2012;43:1537-41.

44. Hirai T, Korogi Y, Ono K, Nagano M, Maruoka K, Uemura S, *et al.* Prospective evaluation of suspected stenoocclusive disease of the intracranial artery: Combined MR angiography and CT angiography compared with digital subtraction angiography. AJNR Am J Neuroradiol 2002;23:93-101.