Risk factors for Stroke

BACKGROUND: Stroke is the second leading cause of death in the world. An absence of a definite treatment for stroke further emphasizes the importance of its prevention. This has led to a tremendous amount of research on the identification of the risk factors for stroke. Because of the publication of an enormous number of articles on this subject, a periodic review is always needed. This review has been conducted with similar objectives.

METHODS: An effort has been made to review the results of all major large scale studies which have been previously published on the identification of risk factors for stroke. We have also searched for the studies that have identified new risk factors for stroke.

RESULTS: The risk factors for stroke identified in previous studies are hypertension, cigarette smoking, diabetes mellitus, atrial fibrillation, a history of myocardial infarction, asymptomatic carotid stenosis, transient ischemic attack, race, ethnicity, geographical location, and physical inactivity. The role of increased cholesterol as a risk factor for stroke could not be established. Though both light and heavy alcohol drinking were found to be associated with an increased incidence of hemorrhagic stroke, a J-shaped relationship was observed regarding ischemic stroke, with a somewhat protective effect of alcohol in light drinkers to an elevated risk in heavy drinkers. Increased levels of homocysteine in blood, cocaine use, obesity and sleep apnea were the other recently identified risk factors, though more studies are needed to confirm their role.

CONCLUSION: The need for continuous identification and modification of risk factors for stroke is always going to be present. With the modification of the already identified risk factors, stroke incidence has seen a decline all over the world.

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INTRODUCTION

Stroke is the second leading cause of death world wide with around 4.6 million deaths annually [1]. Out of these, one third of the stroke related deaths occur in the developed countries and the rest in the developing countries [5]. Whereas stroke is currently ranked as the sixth leading cause of disability-adjusted life years (DALYs; one DALY is one lost year of healthy life) in 1990, it is projected to rank fourth by the year 2020 [3]. In the United States, it ranks as the third leading cause of death behind heart disease and cancer [4]. Every year, there are 600,000 cases of stroke. Among these cases, 500,000 are new

and 100,000 are recurrent cases of stroke. 83% of the strokes are ischemic, 10% are intracerebral hemorrhage and 7% are subarachnoid hemorrhage. Overall, 15 to 30% of the cases become permanently disabled and death results in 23% of the cases [1]. Almost half of the stroke cases can be prevented, by modifying the risk factors. Due to large scale studies such as WHO Monica project, Framingham Heart study, Swedish Trial in Old Patients with Hypertension STOP Hyperten-sion, NHANES, Northern Manhattan Stroke Study (NOMASS), Systolic Hyperten-sion in the Elderly Program SHEP Cooperative Research Group, The Honolulu Heart Program, SPRINT Study Group, The Greater Cincin-

nati/Northern Kentucky Stroke Study, many of the risk factors of stroke have been identified. These riskfactors are discussed below.
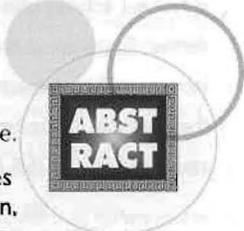
AGE & SEX

A total of 28% of the cases of stroke are below 65 years of age. Incidence of stroke doubles with each decade over age 55. In both sexes, the chances of having a stroke before the age of 70 years is 1 in 20[1]. The incidence and prevalence of stroke is shared equally between both sexes. However, the stroke mortality is more in women than men [1].

ETHNICITY AND GEOGRAPHIC DISTRIBUTION

The incidence of stroke varies in different geographical locations as well as ethnic groups. The largest study in this regard is the WHO Monica project that has been done in 17 stroke centers in 10 different countries. The countries included China, Finland, Russia, Yugoslavia, Italy, Germany, Poland, Denmark Lithuania and Sweden. The incidence of stroke, in general, is found to be higher among populations in eastern than in Western Europe with the highest incidence in Russia. In addition, stroke is relatively high in the Chinese population [6]. In the United States, African-Americans have about twice the risk of stroke than white Americans [1]. This is partly due to a higher incidence of diabetes and hypertension in African-Americans. The increase in stroke mortality is greatest in the southeastern portion of the United States (the "Stroke Belt") for both blacks and whites. In the Northern Manhattan Stroke Study, blacks had a 2.4-fold and Hispanics a two-fold increase in stroke incidence over whites [7]. In the United States, although stroke mortality may have declined, at least in the early 1980s owing to better control of hypertension, more recent data shows a slight increase [8].

CIGARETTE SMOKING

Cigarette smoking is one of the most important and modifiable risk factor in the prevention of morbidity and early death from stroke. Cigarette smoking is responsible for 1 in every 5 deaths occurring in United States. Presently 28.5% adults are smokers (28% men and 23% women). Its prevalence in the younger age group has alarmingly increased from 21% in 1991 to 27% in 1997 (in high school students). Smoking results in a 2 fold higher incidence of stroke as compared to non-smokers. Though many studies have suggested that cessation of smoking results in almost a complete disappearance of risk after 4 [10] to 15 years of quitting smoking [1, 3], a recent study showed that the progression of atherosclerosis over a 3 year period was found to be 25% more in past smokers and 50% more in current smokers as compared to the non-smokers. This suggests that some adverse effects of smoking may be cumulative, and irreversible [11]. Risk of stroke, of past smokers remains intermediate between the smokers and non-smokers[10]. Further studies are needed on this aspect. Overall, smokers die 5-8 years earlier than the nonsmokers. It has been calculated that women smokers who quit smoking by age 35 add 3 years and men 2 years to their lives. As for passive smoking, it has been estimated that of the 450,000 smoking related deaths in USA, 53,000 are attributable to passive smoking [42].

HYPERTENSION

Over 50 million adults in USA have hypertension. Hypertension is the most important risk factor in stroke. This is also the most prevalent (one in 5 persons) and modifiable risk factor. Hypertensive patients have a two to three fold higher risk of stroke as compared to the normotensive patients between both sexes and all ages [12]. Treatment of hypertension significantly decreases the risk of stroke. A series of trials in hypertensive individuals under 65 years of age, indicate that antihypertensive therapy reduces the risk for stroke by about 42%. In elderly patients with severe hypertension (180/110 mm Hg) who participated in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension), the figure was even better with a 47% relative risk reduction in all strokes [15]. Another trial, the Systolic Hypertension in the Elderly Program (SHEP) study, also showed a dramatic reduction (36%) in stroke rates among treated persons over 60 years with isolated systolic hypertension [16]. The degree of hypertension, particularly systolic blood pressure is closely associated with an increase in incidence of stroke [13]. Recent studies identify both systolic and diastolic blood pressures as equally important factors in stroke [3].

According to a study from the Department of Healthy Hypertension Care Computer Project, the blood pressures associated with the lowest overall mortality were within the range (<142/ 95 mm Hg) [17]. Therefore, the goal of antihypertensive therapy for stroke prevention is to normalize rather than simply to reduce blood pressure. The primary prevention of hypertension should be targeted at both the general population as well as the high-risk population such as those with a family history, high salt intake, sedentary life style and obesity. A major cause of the decline in stroke worldwide has been the improved diagnosis and management of hypertension.

PHYSICAL INACTIVITY

There is a negative correlation between physical activity and stroke risk. In the Framingham study, men who maintained moderate or high levels of physical activity had a lower stroke risk than those who were inactive; no benefit was seen in women [18]. The evidence from the first large National Health and Nutrition Examination Survey (NHANES I) suggested that for both men and women even a modest degree of physical activity (e.g., maintain target pulse rate for 20 minutes three times weekly) may be beneficial for the prevention of stroke[19]. Similarly, some more data from the Northern Manhattan Stroke Study (NOMASS) shows a graded reduction in stroke rate with increasing activity levels in all age groups and both sexes of the white, black and Hispanic populations [20].

IS CHOLESTEROL A RISK FACTOR?

Though a well-documented risk factor in heart disease, its role in stroke is still not completely clear as the studies have given conflicting results. Review of 45 prospective clinical observational studies involving 450,000 individuals show no relationship between stroke risk and hypercholesterolemia[21]. Renfrew/Paisley study conducted in Scotland

also shows no association between the two [3]. Similarly, results of the Framingham Study and the Cardiovascular Health Study, each of which enrolled over 5,000 individuals, show no increase in stroke incidence with increasing total cholesterol levels. The Atherosclerosis Risk in Communities (ARIC) study indicates a relationship between total cholesterol and stroke only in black women. On the other hand, incidence of stroke determined from death certificates during 6 years of follow-up on nearly 351,000 men who were screened for the multiple risk factor intervention trial indicated a positive relationship between total serum cholesterol and death from ischemic stroke [22]. Similarly, the Honolulu Heart Study indicates that elevated serum cholesterol predicts a higher stroke rate when stroke rate is assessed 15 years after the cholesterol measurements [23]. Because each of these major studies revealed a strong relationship between serum cholesterol and myocardial infarction, but only weak or absent links between cholesterol and stroke, it was a great surprise when statin cholesterol-lowering agents sharply reduced stroke rates in clinical trials [24-26]. There was a 62% reduction in both fatal and non-fatal strokes. One hypothesis to explain this apparent paradox is that other effects of the statin drugs, such as reduction in smooth muscle proliferation, reduction in inflammation, and restoration of impaired endothelial function, may be responsible for the reduced rate of stroke [26]. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study shows a striking reduction in any stroke (19%) a more than 20% risk reduction in persons with coronary heart disease (CHD) and normal or elevated cholesterol levels [27]. Further studies are needed to ascertain the relationship between stroke and cholesterol.

DIABETES MELLITUS

Diabetes is a well established risk factor for stroke as identified in the Framingham study [35]. The role of blood sugar in stroke risk was examined recently in the Honolulu Heart Study. The risk for thromboembolic stroke was lowest in persons with low-normal fasting blood glucose and increased incrementally with high-normal fasting blood glucose, asymptomatic high blood glucose, and diabetes. [32]

HEART DISEASE

MI (Myocardial Infarction) and AF (atrial fibrillation) are well known risk factors in stroke. The incidence of ischemic stroke is approximately 1% to 2% per year after MI . This risk is particularly high during the first month following an MI [33]. Nonvalvular atrial fibrillation (NVAF) is an important risk factor for stroke. It increases the risk of stroke by approximately 5 fold [34]. More than 2 million adults in the United States have NVAF, and about 36% of strokes in patients between the ages of 80 and 89 years are attributed to this condition. Most stroke patients in the Framingham study also have some cardiac co-morbidity, such as heart failure (CHF), coronary artery disease (CAD), or AF. AF is probably the most significant of these conditions for stroke, particularly in elderly populations, in whom AF is most prevalent.

TRANSIENT ISCHEMIC ATTACK

Transient ischemic attack (TIA) is a very important risk factor as a person having had one or more TIA is 10 times more likely to have stroke than a person who has not had a single episode. Any person with TIA should have an extensive work-up for other modifiable risk factors for stroke.

ASYMPTOMATIC CAROTID ARTERY DISEASE

Atherosclerotic carotid artery disease is an important stroke risk factor. The risk of clinical symptoms increases with the degree of stenosis. With stenosis greater than 75%, combined transient ischemic attack and stroke rate is 10.5% per year, with 75% of events ipsilateral to the stenosed artery [36].

ALCOHOL

The role of alcohol as a risk factor for stroke is not very clear. While both light and heavy drinkers had a 2 and 3 fold increase in hemorrhagic strokes as reported in 1985 by the Honolulu heart study, a J-shaped relationship has been proposed for ischemic stroke, with a somewhat protective effect of alcohol in light drinkers to an elevated stroke risk in heavy drinkers [38].

HOMOCYSTINEMIA

Though many case control studies have suggested increased serum levels of homocysteine as a risk factor for stroke, very few prospective studies have confirmed it. Data from the third NHANES survey and case control studies are however very suggestive of a likely association [29]. The Vitamins in Stroke Prevention (VISP) trial was recently initiated to examine the effects of treatment with vitamins B6, B12, and folic acid on serum homocysteine and stroke incidence.

CONCLUSION

Besides the above identified risk factors for stroke, there are other factors like a low socio-economic status, cocaine use, sleep apnea, obesity which have also been associated with stroke. Stroke risk varies widely from one person to another, from very low to very high, depending on the number of risk factors possessed by the individual and the relative risk for stroke associated with each. A risk profile, which has been developed from the Framingham study data, illustrates this point. For example, a person with a systolic BP of 180 mm Hg but no other risk factors is at a lower risk for stroke than a person with systolic BP of 120 mm Hg who has AF and diabetes and who also smokes. Now that many of the risk factors for stroke have been identified and found to be modifiable, persons at high risk for stroke can be identified and their first stroke can be avoided [39]. A recent projection from epidemiologic data suggests that adequate BP control, warfarin treatment for AF, and cessation of smoking in all affected persons could prevent more than half of the estimated 731,000 strokes that occur in the United States each year. [9, 41]

BIBLIOGRAPHY:

1. American Heart Association. 2001 heart and stroke statistical update. http://www.americanheart.org/statistics/.

2. World Health Organization (WHO). The World Health Report 1997. Conquering suffering, enriching humanity. Geneva: WHO, 1997:1-162.

3. Hart CL, Hole DJ, Smith GD. Comparison of risk factors for stroke incidence and stroke mortality in 20 years of follow-up in men and women in the Renfrew/Paisley Study in Scotland. *Stroke*. 2000;31:1893-1896.

4. American Heart Association. 1999 heart and stroke statistical update. http://www.americanheart.org/statistics/.

5. Murray CJL, Lopez AD. Mortality by cause for eight regions of the world: global burden of disease study. *Lancet*. 1997;349:1269-1276.

6. Thorvaldsen P, Kuulasmaa K, Rajakangas AM, Rastenyte D, Sarti C, Wilhelmsen L. Stroke trends in the WHO MONICA project. *Stroke*. 1997;28:500.

7. Massing MW, Rywik SL, Jasinski B, Manolio TA, Williams OD, Tyroler HA. Opposing national stroke mortality trends in Poland and for African Americans and whites in the United States, 1968 to 1994. *Stroke*. 1998;29:1366-1372.

8. Gillum RF, Sempos CT. The end of the long-term decline in stroke mortality in the United States? *Stroke*. 1997;28:1527-1529.

9. Sacco RL, Wolf PA, Gorelick PB. Risk factors and their management for stroke prevention: outlook for 1999 and beyond. *Neurology*. 1999;53(7 Suppl 4):S15-24.

10. Kawachi I, Colditz GA, Stampfer MJ, Willett WC, Manson JE, Rosner B, Speizer FE, Hennekens CH. Smoking cessation and decreased risk of stroke in women. *JAMA*. 1993;269:232-236.

11. Howard G, Wagenknecht LE, BurkeGL, Diez-Roux A, Evans GW, McGovern P, Nieto FJ, Tell GS. Cigarette smoking and the progression of atherosclerosis. The Atherosclerosis Risk in Communities (ARIC) Study. *JAMA*. 1998;279:119-124.

12. Wolf PA, D'Agostino RB. Epidemiology of stroke. In: Barnett HJM, Mohr JP, Stein BM, Yatsu FM, eds. Stroke: pathophysiology, diagnosis, and management. Philadelphia: Churchill Livingstone, 1998:3-28.

13. Nielsen WB, Vestbo J, Jensen GB. Isolated systolic hypertension as a major risk factor for stroke and myocardial infarction and an unexploited source of cardiovascular prevention: a prospective population-based study. *Journal of Hum Hypertens*. 1995;9:175-80.

14. MacMahon S, Rodgers A. The epidemiological association between blood pressure and stroke: implications for primary and secondary prevention. *Hypertens Res*. 1994;17(suppl I):S23-32.

15. Dahlof B, Hansson L, Lindholm LH, Schersten B, Ekbom T, Wester PO. Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) analyses performed up to 1992. *Clin Exp Hypertens*. 1993;15:925-939.

16. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA*. 1991;265:3255-3264.

17. Bulpitt CJ, Palmer AJ, Fletcher AE, Beevers DG, Coles EC, Ledingham JG, O'Riordan PW, Petrie JC, Rajagopalan BE, Webster,J.

Optimal blood pressure control in treated hypertensive patients. Report from the Department of Health Hypertension Care Computing Project (DHCCP). *Circulation*. 1994;90:225-233.

18. Kiely DK, Wolf PA, Cupples LA, Beiser AS, Kannel WB. Physical activity and stroke risk: the Framingham Study. *Am J Epidemiol*. 1994;140:608-620.

19. Gillum RF, Mussolino ME, Ingram DD. Physical activity and stroke incidence in women and men: the NHANES I Epidemiologic Follow-up Study. *Am J Epidemiol*. 1996;143:860-869.

20. Sacco RL, Gan R, Boden-Albala B, Lin IF, Kargman DE, Hauser WA, Shea S, Paik MC. Leisure-time physical activity and ischemic stroke risk: the Northern Manhattan Stroke Study. *Stroke*. 1998;29:380-387.

21. Prospective Studies Collaboration. Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. *Lancet*. 1995;346:1647-1653.

22. Iso H, Jacobs DRJ, Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. *N Engl J Med*. 1989;320:904-910.

23. Benfante R, Yano K, Hwang LJ, Curb JD, Kagan A, Ross W. Elevated serum cholesterol is a risk factor for both coronary heart disease and thromboembolic stroke in Hawaiian Japanese men: implications of shared risk. *Stroke*. 1994;25:814-820.

24. Byington RP, Jukema JW, Salonen JT, Pitt B, Bruschke AV, Hoen H, Furberg CD, Mancini GB. Reduction in cardiovascular events during pravastatin therapy: pooled analysis of clinical events of the Pravastatin Atherosclerosis Intervention Program. *Circulation*. 1995;92:2419-2425.

25. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383-1389.

26. Hebert PR, Gaziano JM, Chan KS, Hennekens CH. Cholesterol lowering with statin drugs, risk of stroke, and total mortality: an overview of randomized trials. *JAMA*. 1997;278:313-321.

27. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349-1357.

28. Vaughan CJ, Murphy MB, Buckley BM. Statins do more than just lower cholesterol. *Lancet*. 1996;348:1079-1082.

29. Giles WH, Croft JB, Greenlund KJ, Ford ES, Kittner SJ. Total homocyst(e)ine concentration and the likelihood of nonfatal stroke: results from the Third National Health and Nutrition Examination Survey, 1988-1994. *Stroke*. 1998;29:2473-2477.

30. Boushey CJ, Beresford SAA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. *JAMA*. 1995;274:1049-1057.

31. Wolf PA. Epidemiology and risk factor management. In: Welch KMA, Caplan LR, Reis DJ, Siesjo BK, Weir B, eds. Primer on cerebrovascular diseases. San Diego: Academic Press, 1997:751-757.

32. Burchfiel CM, Curb JD, Rodrigues BL, Abbott RD, Chiu D, Yano K. Glucose intolerance and 22-year stroke incidence: the Honolulu Heart Program. *Stroke*. 1994;25:951-957.

33. Tanne D, Goldbourt U, Zion M, Reicher-Reiss H, Kaplinsky E, Behar S, for The SPRINT Study Group. Frequency and prognosis of stroke/TIA among 4808 survivors of acute myocardial infarction. *Stroke*. 1993;24:1490-1495.

34. Wolf PA, Dawber TR, Thomas HEJ, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham Study. *Neurology*. 1978;28:973-977.

35. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke*. 1991;22:312-318.

36. Norris JW, Zhu CZ, Bornstein NM, Chambers BR. Vascular risks of asymptomatic carotid stenosis. *Stroke*. 1991;22:485-1490.

37. Donahue RP, Abbott RD, Reed DM, Yano K. Alcohol and hemorrhagic stroke: The Honolulu Heart Program. *JAMA*. 1986;255:2311-2314.

38. Gill JS, Zezulka AV, Shipley MJ, Gill SK, Beevers DG. Stroke and alcohol consumption. *N Engl J Med*. 1986;315:1041-1046.

39. Gorelick PB, Sacco RL, Smith DB, Alberts M, Mustone-Alexander L, Rader D, Ross JL, Raps E, Ozer MN, Brass LM, Malone ME, Goldberg S, Booss J, Hanley DF, Toole JF, Greengold NL, Rhew DC. Prevention of a first stroke: a review of guidelines and a multidisciplinary consensus statement from the National Stroke Association. *JAMA*. 1998;281:1112-1120.

40. Broderick J, Brott T, Kothari R, Miller R, Khoury J, Pancioli A, Gebel J, Mills D, Minneci L, Shukla R. The Greater Cincinnati/Northern Kentucky Stroke Study: preliminary first-ever and total incidence rates of stroke among blacks. *Stroke*. 1998;29:415-421.

41. Gorelick PB. Stroke prevention: an opportunity for efficient utilization of health care resources during the coming decade. *Stroke*. 1994;25:220-224.

42. JAMA patient page: secondhand smoke. *JAMA*. 1998;280:1968.

43. Kawachi I, Colditz GA, Stampfer MJ, Willett WC, Manson JE, Rosner B, Speizer FE, Hennekens, CH. Smoking cessation and decreased risk of stroke in women. *JAMA*. 1993;269:232-236.