



The online version of this article, along with access to discussion threads on NATF's eForum, is available at: www.NATFonline.org/ethrombosis.php (January, 2009)

Preventing First-Ever Stroke

Farzaneh Sorond, MD, PhD, Associate Neurologist; Brigham and Women's Hospital, Boston, Massachusetts, USA

As the second leading cause of death, stroke is a significant healthcare problem in the world [1]. Worldwide, about 15 million people suffer from stroke every year with 5 million dying and another 5 million living with permanent disability [2, 3]. By 2015 there will be approximately 18 million first-ever strokes and 6.5 million deaths from stroke for all ages [1]. In the United States, stroke is the third leading cause of death. There are more than 700,000 strokes in the United States each year, resulting in more than 160,000 deaths annually, with 4.8 million stroke survivors alive today [4]. On the average, someone in the United States suffers a stroke every 45 seconds and every 3 to 4 minutes someone dies of a stroke [5, 6]. Stroke is also a leading cause of disability, with 20% of survivors requiring institutional care after 3 months and 15% to 30% being permanently disabled [4].

While these numbers may seem astonishingly large, they are estimates of strokes based on the clinical event only and do not account for silent strokes. As such they significantly underestimate the true prevalence of this disease. Silent cerebral infarctions, which were first described by Fisher [7], have been associated with an increased risk of incident stroke and cognitive impairment [8]. With the recent advent of neuroimaging, we now know that up to one-third of patients with transient ischemic attacks (TIA) and no physical examination changes have infarcts on scans [9]. More recent imaging studies have reported the prevalence of 5.84% to 28% for these lesions by MRI [10-12]. Recent data from the Framingham Offspring Study shows a prevalence of 10.7% among more than 2000 mid-life (mean age, 61 years), community-dwelling people who were clinically stroke-free [10]. Risk factors associated with clinical stroke such as age, sex, diabetes mellitus, atrial fibrillation, hypertension, carotid artery disease and cigarette smoking have also been associated with these silent strokes [9, 12-17]. The association of these clinical stroke risk factors with silent stroke reinforces the importance of early detection and treatment of risk factors in mid-life.

Indeed, the greatest impact on stroke as a public health issue is via preventive measures. Stroke prevention is two tiered, primary and secondary. Primary prevention targets recognized risk factors with the aim of reducing the incidence of first-ever-stroke. Secondary prevention aims to reduce recurrent stroke in those who have suffered a TIA or stroke. While secondary prevention and acute management of stroke have been studied using the standardized clinical trials and the findings emphasized in clinical practice guidelines (for detailed review see [18, 19]), given that almost 70% of strokes are first-ever-strokes, until recently, primary stroke prevention has not received proportional public health attention. In



The online version of this article, along with access to discussion threads on NATF's eForum, is available at: www.NATFonline.org/ethrombosis.php (January, 2009)

2004, the "Stroke Risk Assessment and Future Stroke Primary Prevention Trials" workshop was sponsored by the NINDS to discuss and identify the challenges that have delayed primary stroke prevention trials [20]. The report of this workshop was published in 2005 [21] and in 2006 the AHA/ASA issued its first guidelines on primary stroke prevention [4]. Some specific challenges identified in this workshop included the [20]:

- 1) definition of an at-risk population
- 2) choice of treatment and likelihood of adoption
- 3) inclusion of the elderly who may be at the highest risk, but face the issues of attrition and compliance
- 4) choice of surrogate markers
- 5) issue of subclinical disease and silent strokes

Despite these challenges, the ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events; <http://clinicaltrials.gov>) trial was started in 2007. ARRIVE is a randomized, double-blind, placebo-controlled clinical trial assessing the efficacy and safety of daily 100mg enteric-coated Aspirin in preventing a first stroke or heart attack in patients at moderate risk. Moderate risk is defined as approximately 30% 10-year cardiovascular disease event risk; or 10-20%, 10-year coronary heart disease event risk. Approximately 12,000 patients will be enrolled in five countries (Germany, Italy, Spain, the United Kingdom, and the United States) with 400 study sites participating. It is estimated that the trial will take approximately 5 years to reach the primary endpoint of an adequate number of events associated with cardiovascular disease for analysis.

Until the results of the ARRIVE trial are available and more future novel primary prevention trials have been launched, we have some important measures that we can implement. Extensive evidence is available identifying a variety of specific factors that increase the risk of a first-ever-stroke; hence providing us with strategies for reducing that risk. The risk factors for all stroke subtypes can be divided into, non-modifiable, modifiable or potentially modifiable. The non-modifiable risk factors are age, gender, race and family history. The modifiable risk factors are hypertension, heart disease, atrial fibrillation, diabetes, hypercholesterolemia, carotid stenosis and prior strokes or TIAs. Risk factors that are modified by behavioral changes include smoking, alcohol, diet and exercise for reducing obesity & waist-hip ratio and stress reduction. Here is a brief summary of what the AHA/ASA recommended in 2006 [4]:

- 1) Each patient should have their stroke risk assessed. This can be achieved through risk-assessment tools such as the Framingham Stroke Profile.
- 2) Each patient should have regular screening for hypertension (at least every 2 years in adults and more frequently in minority populations and the elderly). Diet and lifestyle changes should be implemented and medications started.



The online version of this article, along with access to discussion threads on NATF's eForum, is available at: www.NATFonline.org/ethrombosis.php (January, 2009)

- 3) In patients with diabetes, hypertension should be tightly controlled, possibly with an ACE inhibitor or an ARB. Also, a statin should be considered to lower the risk of a first stroke is recommended.
- 4) Patients with atrial fibrillation who have valvular heart disease (particularly those with mechanical heart valves) should be anticoagulated. Specific strategies are also recommended to manage a number of other cardiac conditions such as MI, heart failure and others.
- 5) Individuals with elevated total cholesterol, or with elevated non-HDL cholesterol in the presence of hypertriglyceridemia should be treated.
- 6) Patients with asymptomatic carotid artery stenosis should be screened for other treatable causes of stroke. All identified stroke risk factors should be treated. Aspirin and carotid revascularization should be considered in appropriate patients.
- 7) Children with sickle cell disease should be screened with transcranial Doppler ultrasound starting at 2 years of age and transfusion therapy should be considered for those at elevated stroke risk.
- 8) Postmenopausal hormone therapy should not be used for primary prevention of stroke.
- 9) Diet and nutrition are major components of risk reduction. Reduced sodium and increased potassium intake is recommended to lower blood pressure in persons with hypertension. A diet, which is rich in fruit and vegetables, and low-fat dairy products and is reduced in saturated and total fat (such as the DASH diet) should be considered.
- 10) Physical activity should be increased. The CDC and the National Institutes of Health recommend at least 30 minutes of moderate intensity activity daily.
- 11) Weight reduction is recommended because it lowers blood pressure.
- 12) Heavy drinkers should reduce their alcohol consumption. For those who consume alcohol, no more than 2 drinks per day for men and 1 drink per day for nonpregnant women, is recommended.
- 13) Drug abuse should be identified and managed through counseling.
- 14) Oral contraceptives should be discouraged in women with additional risk factors such as cigarette smoking or prior thromboembolic events
- 15) Sleep-Disordered Breathing should be identified and treated especially in the setting of drug-resistant hypertension.

There are also a number of risk factors that may be potentially modifiable, but we just don't have conclusive data on them. These include hyperhomocysteinemia, elevated lipoprotein a (LP(a)) levels, prothrombotic states, inflammation, patent foramen ovale, and migraine.

Given that the highest stroke burden is in the low and middle income regions for the world, the largest impact will come from primary prevention [1]. Over 60% of stroke mortality is attributable to a few modifiable risks such tobacco use, raised blood pressure, and poor diet [1]. The impact of a combination of healthy life style factors on primary stroke prevention was



The online version of this article, along with access to discussion threads on NATF's eForum, is available at: www.NATFonline.org/ethrombosis.php (January, 2009)

recently studied in more than 114,000 primarily white participants of the Nurses Health Study and Health Professionals Follow-up Study. The results showed that a low-risk life style (not smoking, diet, exercise, optimal body weight and low alcohol consumption) was associated with a substantial reduction (about 70-80%) of stroke, especially ischemic stroke [22]. Therefore, more aggressive primary stroke prevention will have a significant impact on lowering the personal, social and economic burden of this disabling disease. The challenge is to veer off the many temptations of the unhealthy life style choices and promote sustainable low-risk life style changes across all communities, especially the low and middle-income regions of the world who are most at risk.

REFERENCES

1. Strong, K., C. Mathers, and R. Bonita, *Preventing stroke: saving lives around the world*. *Lancet Neurol*, 2007. **6**(2): p. 182-7.
2. *World Health Organization. World Health Report 2007: A safer future: global public health security in the 21st century*, in WHO. 2007: Geneva.
3. *International Cardiovascular Disease Statistics: 2007 Update*, in *American Heart Association*. 2007.
4. Sacco, R.L., et al., *Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline*. *Stroke*, 2006. **37**(2): p. 577-617.
5. *Stroke*. 2007, Centers for Disease Control and Prevention.
6. *Heart Disease and Stroke Statistics-2007 Update*. 2007, American Heart Association.
7. Fisher, C.M., *Lacunes: Small, Deep Cerebral Infarcts*. *Neurology*, 1965. **15**: p. 774-84.
8. Vermeer, S.E., N.D. Prins, T. den Heijer, A. Hofman, P.J. Koudstaal, and M.M. Breteler, *Silent brain infarcts and the risk of dementia and cognitive decline*. *N Engl J Med*, 2003. **348**(13): p. 1215-22.
9. Masuda, J., T. Nabika, and Y. Notsu, *Silent stroke: pathogenesis, genetic factors and clinical implications as a risk factor*. *Curr Opin Neurol*, 2001. **14**(1): p. 77-82.
10. Das, R.R., et al., *Prevalence and correlates of silent cerebral infarcts in the Framingham offspring study*. *Stroke*, 2008. **39**(11): p. 2929-35.
11. Lee, S.C., et al., *Prevalence and risk factors of silent cerebral infarction in apparently normal adults*. *Hypertension*, 2000. **36**(1): p. 73-7.
12. Price, T.R., et al., *Silent brain infarction on magnetic resonance imaging and neurological abnormalities in community-dwelling older adults. The Cardiovascular Health Study. CHS Collaborative Research Group*. *Stroke*, 1997. **28**(6): p. 1158-64.



The online version of this article, along with access to discussion threads on NATF's eForum, is available at: www.NATFonline.org/ethrombosis.php (January, 2009)

13. Ezekowitz, M.D., et al., *Silent cerebral infarction in patients with nonrheumatic atrial fibrillation. The Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators*. *Circulation*, 1995. **92**(8): p. 2178-82.
14. Howard, G., L.E. Wagenknecht, J. Cai, L. Cooper, M.A. Kraut, and J.F. Toole, *Cigarette smoking and other risk factors for silent cerebral infarction in the general population*. *Stroke*, 1998. **29**(5): p. 913-7.
15. van Dijk, E.J., N.D. Prins, S.E. Vermeer, P.J. Koudstaal, and M.M. Breteler, *Frequency of white matter lesions and silent lacunar infarcts*. *J Neural Transm Suppl*, 2002(62): p. 25-39.
16. Vermeer, S.E., P.J. Koudstaal, M. Oudkerk, A. Hofman, and M.M. Breteler, *Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study*. *Stroke*, 2002. **33**(1): p. 21-5.
17. Vermeer, S.E., W.T. Longstreth, Jr., and P.J. Koudstaal, *Silent brain infarcts: a systematic review*. *Lancet Neurol*, 2007. **6**(7): p. 611-9.
18. Donnan, G.A., M. Fisher, M. Macleod, and S.M. Davis, *Stroke*. *Lancet*, 2008. **371**(9624): p. 1612-23.
19. Romano, J.G. and R.L. Sacco, *Progress in secondary stroke prevention*. *Ann Neurol*, 2008. **63**(4): p. 418-27.
20. Gorelick, P.B., *Challenges of Designing Trials for the Primary Prevention of Stroke*. *Stroke*, 2008.
21. Radziszewska, B., R.G. Hart, P.A. Wolf, R.B. D'Agostino, Sr., and J.A. Cutler, *Clinical research in primary stroke prevention: needs, opportunities, and challenges*. *Neuroepidemiology*, 2005. **25**(2): p. 91-104.
22. Chiuve, S.E., K.M. Rexrode, D. Spiegelman, G. Logroscino, J.E. Manson, and E.B. Rimm, *Primary prevention of stroke by healthy lifestyle*. *Circulation*, 2008. **118**(9): p. 947-54.