Special Report

Stroke in Women
The 1997 Paul Dudley White International Lecture
Marie-Germaine Bousser, MD

Mister chairman, members and guests of this annual meeting, dear colleagues, ladies and gentlemen, it is a great honor and privilege for me to present the Paul Dudley White International Lecture during this 70th Scientific Session of the American Heart Association. I have chosen to talk about “Stroke in Women” not so much because I am one of the few representatives of this (up to now) rare species of female neurologists, but because stroke in women is a major health issue that has been somewhat neglected in the past but is now attracting more and more attention, as illustrated by the creation of the AHA Web site “Take Wellness to Heart.”

Although many aspects of stroke, particularly with regard to clinical presentation, neuroimaging, and management, are similar in both sexes, there are also some differences and specificities that I would like to highlight in considering the following 4 main issues: (1) the burden of stroke, which is increasing more rapidly in women than in men; (2) stroke prevention and the role of postmenopausal hormone replacement therapy (HRT); (3) pregnancy and stroke; and (4) stroke in young women.

The Burden of Stroke in Women

Misperceptions still exist that cardiovascular disease is not a real problem for women, who are far more fearful of breast or ovarian cancers than of stroke or myocardial infarction. Yet it is estimated that 1 in 3 women will die of heart disease and 1 in 6 of stroke, whereas 1 in 9 will develop breast carcinoma at any time during adult life and 1 in 25 will eventually die of it. The Global Burden of Disease Study has shown that ischemic heart disease and cerebrovascular disease are, respectively, the first and second causes of death worldwide, and all projections, whether pessimistic or optimistic, indicate that they will remain first and second in the year 2020. This applies to both sexes, but stroke is an even greater killer in women than in men, since over an entire lifetime, about 16% of women but only 8% of men will die of stroke.

Thus, stroke kills; but not only does it kill (roughly one third of its victims in the following 6 months), it also leaves a residual disability in about two thirds of the survivors. In a recent Italian population survey, nearly half of stroke patients had a severe disability in domestic care activities (OR of 7.5). Again, this is true for both sexes, but the burden is higher in women. Moreover, depression occurs in 11% to 68% of stroke patients (and major depression in 10% to 27%), with an increased risk in women in some studies. Second cause of death, first cause of disability, frequent cause of depression, stroke is also the second leading cause of dementia after Alzheimer’s disease in both sexes. However, whereas in the very old, it remains second in men, it ranks first in women.

Why is it then that more women than men die of a stroke, are incapacitated after a stroke, and are demented because of stroke? It is obviously not because of a higher incidence of stroke in women, since in all studies and in all countries, men have higher annual incidence rates of stroke than women (between 3 and 7 per 1000 in men, between 1.5 and 5 per 1000 in women). It is also not due to a lower age of onset of stroke in women, since in both sexes equally, the annual incidence of stroke rises exponentially with age, from <1/1000 below 50 years of age to 20/1000 after 80, so that three fourths of all new strokes occur in people aged 65 years and older.

The main reason the burden of stroke is heavier in women is simply that they live about 10 years longer than men. According to the Global Burden of Disease Study, this is presently true for all parts of the world except India, and projections indicate that life expectancy will increase even more in women than in men, reaching by the year 2020 a mean of 85 to 90 years in established market economies, 75 to 80 in China and Latin America, 65 to 70 years in India, and 60 to 65 years in sub-Saharan Africa. Because of this aging of the female population, stroke will become a real epidemic worldwide in the coming years. Age, however, does not explain everything. It is worrisome to see that stroke incidence, which had been steadily decreasing since World War II, is rising again, particularly in young women, which raises the question of new environmental risk factors.

Prevention

What can we do to try to prevent this epidemic of stroke in women? Stroke prevention is essentially based on the identification and treatment of risk factors and on the use of antithrombotic drugs, basically antiplatelet drugs to prevent atherothrombotic brain infarction and anticoagulants to pre-
vent emboli from the heart. To this basic treatment, which applies to all patients, one should add carotid surgery in selected cases.

I'll be brief on risk factors, since there are only a few, minor gender differences with regard to the relative risk (RR) they carry as well as the benefit of their treatment. Hypertension is the leading risk factor in both sexes, with an RR of 4 and a 46% increase in stroke risk for every 7.5 mm Hg increase in diastolic blood pressure. The evidence for the benefit of hypertension treatment for primary stroke prevention is overwhelming, but some early studies suggested that this benefit was lower in women than in men. This was not confirmed in recent studies or in a convincing meta-analysis that found no major sex differences with regard to the effect of antihypertensive treatment on the absolute risk of stroke. Concerning other major risk factors, results from the Framingham Study indicate an RR of stroke in diabetics that is slightly higher in women (1.7) than in men (1.4) and a risk of stroke associated with atrial fibrillation that is twice as great in women as in men (RR 3.16 versus 1.83). Transient ischemic attacks are, in both sexes, the best predictors of stroke, with an RR of 14 during the first year; in the Rochester study, the risk of stroke in women was more than twice that of men in all age groups. These gender differences, however, are marginal, and basically, for the majority of strokes (except those occurring in the young), risk factors are similar in men and women.

Among antithrombotic drugs, there is thus far no established gender difference, but some of you might remember that 20 years ago, aspirin was thought to be effective in secondary stroke prevention only in men. Five years later, we showed that it was equally effective in women and in men, but for some years there was still quite a strong debate about the presumed sex difference in aspirin efficacy. This controversy is now over, but there remains a sex difference about aspirin, which pertains to primary cardiovascular prevention, that has been studied only in men. Thus, we do not know if the remarkable 47% decrease in the risk of myocardial infarction observed in men in the Physicians' Health Study applies equally to women. This lack of information, which is also found in other aspects of cardiovascular diseases in women, is illustrative of the far less frequent participation of women in studies devoted to a field traditionally perceived as a predominantly male health issue.

There are thus no consistent major gender differences with regard to the efficacy of antithrombotic treatments or the management of risk factors. This might not be the case for carotid surgery. It is crucial to remember that whereas the benefit of surgery is impressive in symptomatic stenosis ≥70% in both sexes (although more marked in men than in women), it is not demonstrated thus far in women with asymptomatic carotid stenosis. In the Asymptomatic Carotid Atherosclerosis Study (ACAS), the estimated RR reduction for ipsilateral stroke 5 years after surgery was 66% in men but only 17% in women. Although the difference between genders was not statistically significant, the risk reduction was significant in men but not in women. This gender difference could just be a statistical artifact as a result of the small number of women (as was initially the case for aspirin), but this seems unlikely since in ACAS, as well as in other studies, the risk of carotid surgery in women is twice that of men. Furthermore, in ACAS, the stroke risk in the nonoperated group was lower in women than in men. Thus, there is presently no evidence that carotid surgery is beneficial in women with asymptomatic carotid stenosis, and the results of the ongoing European trial will be crucial in that respect. This important gender difference should be kept in mind when one is dealing with asymptomatic patients or thinking about studies devoted to other treatment modalities, such as angioplasty and stenting.

Since the vast majority of strokes in women occur after menopause, there has been much hope that HRT would alleviate the burden of stroke, as it seems to do for myocardial infarction. Many studies have been devoted to the relationships between HRT and stroke, but they are fraught with difficulties and biases: data derive from case-control and cohort observational studies but not from randomized trials; different estrogens, different progestogens, different combinations of the 2, and different doses have been used; some studies compare current use with past use and no use, whereas others compare “ever use” to “never use”; some studies relate to stroke in general and others to various subtypes, such as cerebral infarction, intracerebral hemorrhage, or subarachnoid hemorrhage; and there are many confounding associated risk factors.

Data on HRT and nonfatal stroke in general are somewhat conflicting, with RRs ranging from 0.40 in the Walnut Creek study to 2.27 in Framingham but with a majority of studies showing no or very little beneficial effect. There seems to be really no effect on subarachnoid and intracerebral hemorrhage, but results with ischemic stroke are more conflicting, with a tendency to an increased risk, which was actually found to be significant only in the most recent analysis of the Nurses' Health Study (adjusted RR for ischemic stroke 1.40; 95% CI, 1.02 to 1.92). By contrast, and for unclear reasons, the risk of fatal stroke was consistently found to be decreased.

There has been much debate about unopposed and opposed estrogens. Recent studies indicate that the adjunction of progestosterone to estrogens does not increase the thrombotic risk. If anything, it decreases the RR for cardiovascular events (from 1.27 to 1.09 for stroke and from 0.60 to 0.39 for major coronary disease). There remain many unanswered questions concerning HRT and stroke, particularly with regard to the following: primary versus secondary prevention; the type, dose, and treatment duration of estrogens and progestogens; the possibility of a major bias due to the fact that women who take HRT tend to be healthier than those who do not (“the healthy women bias”); and the benefit-risk ratio of HRT itself, which remains difficult to establish, taking into account the benefits on osteoporosis, mortality, heart disease, and possibly Alzheimer's disease, the seemingly absent benefit on nonfatal stroke, and the increased risk of breast or ovarian cancer.

Ongoing randomized studies aim to answer these questions, both in primary prevention (Heart and Estrogen/Progestin Replacement study [HERS], to be reported about the year 2000, and the Women’s Health Initiative, to be
Stroke in Young Women: Pregnancy

Let us now turn to women younger than 50 years of age. Although stroke is rare in this age group (<5% of all stroke in women), there are some specific causes, and the long-term disability is of even greater consequence. Furthermore, it is an important target group for the modification of risk factors.

There are in this age group important gender differences with regard to underlying conditions, causes, and risk factors. Atherosclerosis, for instance, is much less frequent in women <50 years of age than in men, whereas the opposite is true for conditions such as fibromuscular dysplasia, antiphospholipid antibodies syndrome, Takayasu arteritis, and SICRET (Small Infarcts of the Cochlear, Retinal, and Encephalic Tissues) syndrome. Time does not permit me to go into the details, and I would just like to say a few words about stroke in pregnancy and about some risk factors that might play an important role in young women.

Pregnancy has long been thought to carry a high risk of stroke, and this is unfortunately still the case in many poor countries, mostly because of multiple pregnancies and because of eclampsia, which still occurs in up to 2% of pregnancies and represents the first cause of cerebral infarction, cerebral hemorrhage, and death during pregnancy. In countries like the United States, eclampsia is still found in 24% of pregnant women with cerebral infarction and in 14% of those with intracerebral hemorrhage, and in France the respective figures are 47% and 44%. Patients present with headache, seizures, visual signs, or stupor; MRI shows (on T2-weighted imaging) a diffuse white matter increased signal that resolves after successful treatment. Other pregnancy-specific causes, such as choriocarcinoma, amniotic fluid embolism, or peripartum cardiomyopathy, are extremely rare.

On the whole, recent studies in developed countries did not show an increased risk of stroke during pregnancy (RR = 1.1). There might be a slight increase in the risk of intracerebral hemorrhage (RR = 2.5) but possibly a slight decrease in that of cerebral infarction (RR = 0.7; 95% CI, 0.3 to 1.06). In clinical practice, it should be kept in mind that all causes of stroke in the young can occur during pregnancy or delivery, such as rupture of a vascular malformation as a cause of hemorrhage, or cardiac emboli or cervical artery dissections as causes of cerebral infarction. The etiologic workup should therefore encompass all these causes together with the pregnancy-related ones.

By contrast, the risk of both ischemic and hemorrhagic stroke is markedly increased during the postpartum period, with an RR of 5.4 (95% CI, 2.9 to 10) for cerebral infarction, 18.2 (95% CI, 8.7 to 38.1) for intracerebral hemorrhage, and 7.9 (95% CI, 5 to 12.7) for all strokes. A rare type of stroke that should always be kept in mind during puerperium is cerebral venous thrombosis (CVT). In our series of 145 CVTs, 4 occurred during pregnancy and 13 during the postpartum period. When a woman complains of headache, seizures, or focal deficits a few days after delivery, it should immediately raise suspicion of CVT, prompting appropriate investigations and initiation of treatment with heparin, which can be lifesaving. MRI is at present the best diagnostic tool: it shows the signal of the thrombosed sinus, most commonly the superior sagittal sinus, which contrasts with its nonvisualization at magnetic resonance angiography.

Another condition that occurs preferentially after delivery is postpartum cerebral angiopathy. It is a rare condition characterized by headaches, seizures, and focal deficits with multiple segmental arterial narrowing at angiography. The roles of eclampsia, ergot derivatives, bromocriptine, and migraine have been discussed, but the pathogenesis remains unknown, the important thing being that it is spontaneously reversible within a few weeks. Although more frequent during the postpartum period, this syndrome is not specific and seems to be a variant of the syndrome reported as isolated benign vasculitis.

Risk Factors for Stroke in Young Women

I’ll now turn to the last part of my talk, which will be devoted to risk factors for stroke in young women. These are absolutely crucial because first, they are the only etiologic factors found in >50% of ischemic strokes in young women; second, the duration of exposure is a major factor of the later risk; and third, their impact decreases with age, as illustrated for smoking in the Rochester study, in which the OR for the risk of stroke decreases from around 4 at the age of 50 to 0 at the age of 90. Last but not least, it is in this age group that risk factor modification should be started whenever possible.

Although the usual vascular risk factors, such as hypertension and diabetes, also play a major role in this age group, I would like to concentrate on 3 that are particularly frequent in young women or are specific to them: migraine, oral contraceptive use, and smoking.

Migraine is still debated as a risk factor for stroke in general, but our group has shown in 2 successive case-control studies that migraine is a risk factor for ischemic stroke in young women, with an OR of 3.5 for all types of migraine and of 6 for migraine with aura. This has been confirmed by subsequent studies from Denmark and Italy. The risk is further increased by smoking (RR = 10) and by oral contraceptive (OC) use (RR = 14). However, young migraineous women should not be frightened by these figures because despite this increase in RR, the absolute risk of stroke remains very low in this group. This is why we think that migraine in and of itself is not a contraindication to OC use, but we strongly advise our young female migraineous patients not to smoke and, if they use OCs, to choose pills with the lowest estrogen content.

Over 25 studies have been devoted to the association between OC use and stroke, but many of them are fraught with the same methodological problems as HRT studies. Recent studies have nevertheless convincingly shown that by
contrast to high doses, which more than triple the risk of stroke, low doses carry little risk (RR of cerebral ischemia from 1 to 3 and RR of cerebral hemorrhage <2), provided that there are no associated vascular risk factors and that blood pressure is checked before OC use is begun. In many studies, such as the Royal College of General Practitioners’ Study, the European part of the WHO study, and the California study, there was no significant increase in risk. By contrast, the risk was increased in Asia, Africa, and South America, where associated risk factors were present and blood pressure was not systematically checked. The presence of hypertension dramatically increases the risk in all studies and for all varieties of strokes, with OR reaching 10 to 14 in the WHO study in Europe and outside Europe.

The same applies to a lesser extent to smoking: when tobacco is present together with OC use, the risk increases to 4.7 for all strokes, 5 for cerebral infarction, and 3.5 for hemorrhage. Even without OC use, smoking is a major risk factor in young women, both for ischemic stroke, with an RR of 2.5, and for subarachnoid hemorrhage, with an RR of 5. The good news is that it is worth stopping smoking, since the risk of stroke decreases (but does not completely reverse) after smoking cessation; the bad news is first, that more and more women smoke and at an ever-younger age in all countries, and second, that for a similar number of pack-years, the vascular risk, at least for myocardial infarction, is consistently higher in women than in men, suggesting that women may be more sensitive than men to the harmful effects of smoking. Clearly, tobacco smoking, which has long been neglected in the stroke field but carries a considerable attributable risk, is the single most important modifiable risk factor for stroke in the young (in either sex). Strategies must be developed internationally to respond to this major health threat, which killed (also due to all its other deleterious effects) 3 million people in 1990 and will kill 8 million in 2020.

Among other lifestyle factors, the lack of physical activity was found to be a risk factor for stroke, but the protective effect of physical activity has received little attention in women; data from Framingham indicate a protective effect in men but not in women, whereas the Birmingham stroke project shows a protective effect in both sexes, with an OR between 0.2 and 0.6 for vigorous exercise in early adulthood, for lifelong continuation of exercise, and for recent vigorous exercise and regular walking. A similar beneficial effect was recently confirmed in both sexes in the Northern Manhattan Stroke Study.

In conclusion, stroke is a major threat to men and women, and it will become a real epidemic in women, essentially because of their longer life duration and their increasing exposure to tobacco smoking. Given the magnitude of this problem and the thus far limited efficacy of acute stroke treatment, major efforts should be made worldwide to increase public awareness of this condition and to launch effective programs of prevention.

References


**Key Words:** stroke ■ hemorrhage ■ contraceptives, oral ■ estrogen replacement therapy
Stroke in Women: The 1997 Paul Dudley White International Lecture
Marie-Germaine Bousser

_Circulation_. 1999;99:463-467
doi: 10.1161/01.CIR.99.4.463

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/99/4/463

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/