Chapter 20

Stroke and Diabetes

Lewis H. Kuller, MD, DrPH

SUMMARY

Stroke death rates have declined substantially in the U.S. population and in populations of other countries during the past 40-50 years. This decline has accelerated in the past 20 years. Diabetes is an important cause of stroke. Diabetes is more common in the African-American population than in the white population in the United States and contributes to the increased risk of stroke among African Americans. Persons with diabetes may have a worse prognosis after a stroke.

Elevated blood pressure is the major risk factor for stroke. Other risk factors for stroke, besides diabetes, include cigarette smoking and a high level of low-density lipoprotein (LDL) cholesterol. Stroke is substantially increased in individuals who have other vascular diseases, especially coronary heart disease, left ventricular hypertrophy, atrial fibrillation, and peripheral vascular disease.

Preventing stroke in people with diabetes is feasible through identifying and treating risk factors, especially hypertension, cigarette smoking, and high LDL cholesterol. It is unknown whether reduction of blood glucose levels by either pharmacological or nonpharmacological methods will reduce the risk of stroke. Planned clinical trials may answer this question. It is also possible to identify individuals with atherosclerosis in other vascular beds and to more aggressively intervene to reduce the risk of stroke by a combination of surgical, pharmacological, and nonpharmacological therapies.

• • • • • • •

STROKE IN THE U.S. POPULATION

In 1992, cerebrovascular disease (stroke) was the third leading cause of death in the United States. There were 143,640 deaths with stroke listed as the underlying cause of death, of which ~100,000 (70%) occurred in people age >75 years[1]. Stroke death rates are higher in African Americans than in whites[2], but the age-adjusted stroke death rates for Asian-Pacific Islanders, Native Americans, and Hispanics are lower than for whites (Table 20.1)[3]. The lower death rates for Native Americans and Hispanics are somewhat unusual, given the high prevalence of diabetes in these two populations. Stroke death rates are highest in the southeastern United States, the so-called "stroke belt"[2].

The death rate due to stroke has declined in the United States as well as in other countries. The decline in stroke mortality in the United States began in the 1930s and has continued. Stroke death rates declined 32.7% during 1979-89[2]; this was the greatest decrease of any of the major causes of death (Figure 20.1). Stroke death rates have been declining ~5%-6% per year in all age, race, and sex groups. The reasons for the substantial decrease in stroke mortality are not completely determined. The decline, however, is clearly related to improved recognition and treatment of hypertension, decreased cigarette smoking, and improved treatment of stroke patients. It is not known whether the decline in stroke mortality has been simi-

Table 20.1
Mortality from Stroke in the U.S. Population, Age ≥45 Years, 1988-90

	Men	Women
White	103	88
Black	200	155
Asian/Pacific Islander	97	81
Native American	80	63
Hispanic	84	69

Mortality rates are age-adjusted number per 100,000 population.

Source: Reference 3

Figure 20.1
Age-Adjusted Death Rates for Stroke, 1950-89

Source: Reference 2

lar for diabetic and nondiabetic patients.

The decrease in stroke mortality has not been paralleled by a similar decline in hospitalizations for stroke[4]. In 1990, there were 812,000 hospital discharges in which stroke was the first-listed diagnosis, an increase from the estimated 519,000 discharges in 1970. The discharge rate with a first-listed diagnosis of stroke in 1990 was 3.3 per 1,000 population, varying from 0.2 per 1,000 for persons age <45 years to 42.3 per 1,000 for those age ≥85 years.

Based on the 1990-92 National Health Interview Surveys (NHIS), the prevalence of persons in the U.S. population who report a medical history of stroke increases with age, from 1.7% of those age 45-64 years to 8.1% of those age ≥75 years[5-7].

RELATIONSHIP OF STROKE AND DIABETES

The first edition of *Diabetes in America* documented the strong association of diabetes with risk of stroke, especially strokes due to vascular disease and infarction[8]. The relationship between transient cerebral ischemia and stroke was less consistent than that for completed stroke. Subsequently, the relationship between diabetes and stroke has been substantiated further in various racial and ethnic groups and among women and older individuals. Studies have also shown a strong relationship between subclinical vascular disease, both in the carotid and lower extremities and diabetes, and higher risks of stroke.

Bell[9] has reviewed the literature describing the relationship between diabetes and stroke. Most ischemic strokes in diabetic patients are due to occlusion of small paramedial penetrating arteries. The occlusions cause small infarcts within the white matter of the brain. Diabetic autonomic neuropathy may contribute to the development of cerebrovascular disease in people with diabetes.

The improved clinical diagnosis of stroke by computerized tomography and magnetic resonance imaging has probably increased the measured incidence of stroke in the population, especially among older individuals who receive more frequent and intensive medical care. Further, there is probably a very high prevalence of "silent" cerebral infarction that can be documented by these new noninvasive techniques. The incidence and prevalence of stroke among diabetic patients may, therefore, be higher now than was suggested in the past.

There is a high prevalence of undetected diabetes in the U.S. population, especially among older individuals[10,11]. The incidence of stroke also increases with increasing age. Thus, many stroke patients may have undetected diabetes at the time of the stroke; subsequent examination in the hospital or following treatment for stroke may identify the previously undetected diabetes. The reported prevalence of diabetes among stroke patients as compared with those without a stroke may therefore be inflated by differences in ascertainment.

PREVALENCE OF A MEDICAL HISTORY OF STROKE

It should be noted that, because of the substantial mortality in patients with stroke, prevalence data do not adequately represent the magnitude of stroke in the population.

In the 1989 NHIS Diabetes Supplement, 9.3% of all individuals reporting a medical history of physician-diagnosed diabetes also reported a medical history of stroke (Table 20.2). The percentage increased from 2.0% for those age 18-44 years to 12.7% for those age ≥65 years.

Table 20.2
Prevalence of a Medical History of Stroke in Diagnosed Diabetes, U.S., 1989

Age (years)	No. subjects studied	Percent with stroke
18-44	353	2.0
45-64	970	8.4
≥65	1,056	12.7
≥18	2,379	9.3

Source: 1989 National Health Interview Survey Diabetes Supplement

Table 20.3
Average Annual Number of Hospital Discharges for Stroke that Included a Diabetes Diagnosis, U.S., 1989-91

Stroke diagnosis	Number
Subarachnoid hemorrhage	1,631
Intracerebral hemorrhage	8,373
Intracranial hemorrhage	2,167
Precerebral occlusion	39,505
Cerebral artery occlusion	76,218
Transient cerebral ischemia	38,541
Cardiovascular accident	46,483
Other cerebrovascular disease	35,050
Late effects of cerebrovascular disease	79,779
Total	327,746
All stroke discharges, percent with diabetes diagnosis	19.8%
All diabetes discharges, percent with a stroke diagnosis	11.2%

Table includes all hospitalizations in which stroke (ICD9CM 430-438) and diabetes (ICD9CM 250, 251.3, 357.2, 362.0, 366.41, 648.0, and 775.1) were both listed as a discharge diagnosis.

Source: 1989-91 National Hospital Discharge Surveys

Based on the National Ambulatory Medical Care Survey, in the United States during 1990-91 there was an annual average of 3.43 million physician visits in which cerebrovascular disease (ICD 430-438) was listed as a diagnosis. In 10.2% of these (350,000), the stroke patient was also listed as having a history of diabetes.

Based on the National Hospital Discharge Survey, in the United States during 1989-91 there was an annual average of 327,746 hospitalizations that listed both diabetes and stroke as a discharge diagnosis (Table 20.3). These represented 11.2% of all hospital discharges in which diabetes was listed. In addition, 19.8% of all hospitalizations that listed stroke as a discharge diagnosis also listed a diabetes discharge diagnosis (Table 20.3).

RISK OF STROKE IN DIABETIC PATIENTS

In the Multiple Risk Factor Intervention Trial (MRFIT) in 1973-75, 12-year mortality was determined for 5,163 men age 35-57 years who reported taking medication for diabetes and 324,815 men without a history of diabetes[12]. The risk of mortality from stroke was increased 2.8-fold (95% confidence interval (CI) 2.0-3.7) among those with diabetes, even after adjusting for age, race, income, and cardiovascular risk factors (Table 20.4). The risk of stroke mortality was greatest for nonhemorrhagic stroke (relative risk 3.8) than for subarachnoid (1.1) or intracranial hemorrhage (1.5)[13].

The risk of cardiovascular disease, including stroke, increased among both diabetic and nondiabetic men with increasing blood pressure levels (systolic and diastolic), blood cholesterol level, and number of cigarettes smoked[12]. An analysis limited only to stroke deaths was not included in the reports. The results are consistent with the hypothesis that among diabetic persons, the risk of stroke is directly related to other risk factors, especially smoking, blood pressure, and lipoprotein levels.

In the Nurses Health Study, the risk of stroke and cardiovascular disease was determined in 116,177 female registered nurses who were free of coronary heart disease, stroke, and cancer at baseline[14]. There was an 8-year followup during 1976-84. Sixteen nonfatal and eight fatal stroke cases were reported in the 1,483 women with diabetes, and 167 and 68 cases, respectively, among the nondiabetic women. The age-adjusted risk of stroke for diabetic versus nondiabetic

Table 20.4
Mortality from Stroke by Diabetes Status in MRFIT Screenees

Cause of death (ICD9 code)	Men with diabetes		Men without diabetes		Adjusted relative risk, diabetic versus nondiabetic (95% CI)
	No. of deaths	Rate per 10,000 person-years	No. of deaths	Rate per 10,000 person-years	
CVD (390-459)	603	85.13	8,965	22.88	3.0 (2.8-3.3)
CHD (410-414,429.2)	469	65.91	6,681	17.05	3.2 (2.9-3.5)
Stroke (430-438)	48	6.72	685	1.75	2.8 (2.0-3.7)
Other CVD	86	12.49	1,599	4.08	2.3 (1.8-2.9)
All deaths	1,092	160.13	20,867	53.20	2.5 (2.4-2.7)

Relative risk is adjusted for age, race, income, serum cholesterol level, systolic blood pressure, and number of cigarettes per day. MRFIT, Multiple Risk Factor Intervention Trial; CI, confidence interval; diabetes status was ascertained at initial screening; n=5,163 (diabetes), n=342,815 (no diabetes).

Source: Reference 12

Table 20.5

Age-Adjusted Percent Developing Stroke by Sex and Diabetes Status, Rancho Bernardo, CA 1972-85

	Nondiabetic subjects, by SBP			Diabetic subjects, by SBP			p value
	<160	≥160	All	<160	≥160	All	
All subjects							
Men							
Number of subjects	1,178	357	1,535	139	55	194	
Stroke deaths (%)	3.0	5.1	3.7	3.1	9.5	5.2	0.45
Stroke deaths and new cases (%)	5.6	8.6	6.3	6.6	14.7	9.4	0.17
Women							
Number of subjects	1,577	346	1,923	92	34	126	
Stroke deaths (%)	2.5	5.3	3.2	7.1	11.2	7.4	0.03
Stroke deaths and new cases (%)	4.5	8.6	5.3	8.9	17.8	10.5	0.02
Excluding all persons with history of CHD							
Men							
Number of subjects	1,027	296	1,323	114	47	161	
Stroke deaths (%)	2.6	6.4	3.9	2.7	9.7	5.0	0.21
Stroke deaths and new cases (%)	4.5	8.1	4.7	6.0	11.6	8.1	0.09
Women							
Number of subjects	1,496	314	1,810	82	28	110	
Stroke deaths (%)	2.4	3.9	2.7	8.5	6.8	7.0	0.03
Stroke deaths and new cases (%)	3.8	6.6	4.4	9.5	14.1	9.8	0.02

SBP, systolic blood pressure in mmHg; CHD, coronary heart disease; p value is for comparison between diabetic and nondiabetic persons; diabetes was determined in 1972-74 from medical history or fasting plasma glucose ≥140 mg/dl; stroke was ascertained by death certificate, self-report, and medical record review.

Source: Reference 15

women was 4.1 (95% CI 2.8-6.1). The risk was similar for fatal (5.0) and nonfatal (3.8) strokes.

In the community of Rancho Bernardo, CA, 3,778 men and women who were age 50-79 years in 1972-74 were evaluated during the next 12 years for fatal and nonfatal stroke[15]. The risk of stroke was significantly higher among diabetic men and women compared with those without diabetes (Table 20.5). The risk of stroke among both diabetic and nondiabetic individuals increased substantially with higher systolic blood pressure. For diabetic men and women, the risk of stroke among those with systolic blood pressure ≥160 was about two times that of those with systolic blood pressure <160 (Table 20.5).

The followup of the 1971-75 National Health and Nutrition Examination Survey included 1,298 African Americans and 7,814 whites age 35-74 years[16]. For all subjects, African Americans had a higher stroke incidence than whites during the 8-year followup. The relative risk of stroke among those with a medical history of diabetes at baseline compared with nondiabetic persons was about 2.5 and was similar for the four race/sex groups (Table 20.6).

Table 20.6

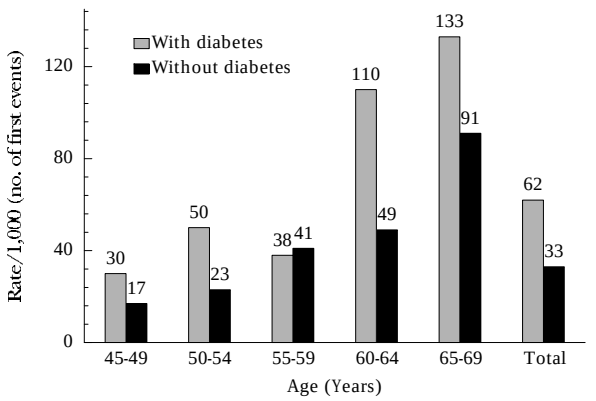
Diabetes as a Risk Factor for Stroke, NHANES I Followup, 1971-84

	Relative risk, diabetes/no diabetes	95% confidence interval
Black men	2.5	1.6-4.0
Black women	2.4	1.7-3.4
White men	2.5	2.0-3.1
White women	2.5	2.0-3.1

Source: Reference 16

Figure 20.2

Twelve-Year Incidence of Stroke for Men With and Without Diabetes, Honolulu Heart Program



Incidence rates increased significantly with age ($p<0.05$) except for thromboembolic strokes in diabetic subjects.

Source: Reference 17

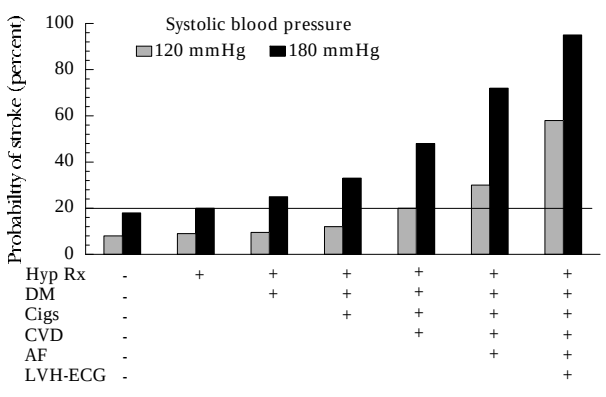
In the 12-year followup of Japanese men in the Honolulu Heart Program, the risk of stroke increased with age for both diabetic and nondiabetic subjects[17]. The risk was substantially higher among diabetic compared with nondiabetic individuals at almost all ages (Figure 20.2).

Wolf described a "health risk appraisal function" for the prediction of stroke based on the Framingham cohort study[18]. During a 10-year followup between examinations 9 and 14 in the Framingham Study for individuals age 55-84 years, there were 472 stroke events among 2,372 men and 3,362 women. Approximately 11% of men and 8% of women had diabetes. The risk of stroke was adversely related to a history of diabetes in both men (relative risk 1.40) and women (relative risk 1.70). The estimated probability of stroke increased dramatically in relation to the number of risk factors for stroke (Figure 20.3).

The Copenhagen City Heart Study evaluated 3,015 men and 3,501 women age 55-84 years[19]. There were 474 strokes over a 10-year period. Only 3% of men and 2% of women had a history of diabetes. The risk of stroke was greater for diabetes in the Copenhagen study than in the Framingham study, probably due to the restriction of diagnosis of diabetes to those with a reported clinical history, whereas the Framingham study included a casual blood glucose >150 mg/dl as part of the diagnosis for diabetes.

Peripheral vascular disease is much more common among diabetic than nondiabetic individuals. In the Framingham Study, the 2-year incidence of carotid or femoral bruits or nonpalpable pedal pulses was higher among diabetic than nondiabetic subjects[20]. The 2-year incidence of stroke was highest for women with both carotid bruits and diabetes, about a fivefold difference compared with women with neither diabetes nor bruits. The results for men were similar, with a relative risk of ~2.5 (Figure 20.4). The presence of a nonpalpable pedal pulse or femoral bruit and diabetes was also associated with a substantially increased risk of stroke among women.

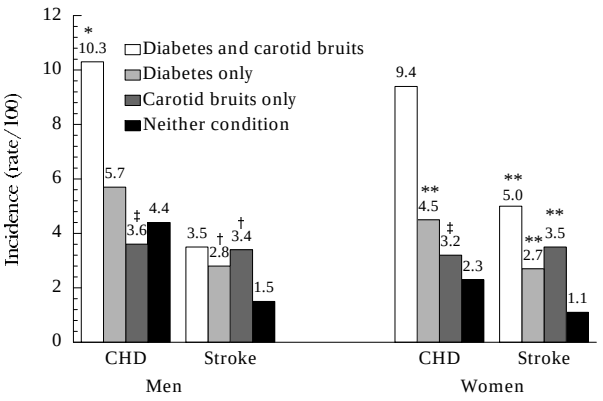
Figure 20.3
Ten-Year Probability of Stroke in Men Age 70 Years by Risk Factors, Framingham, MA



Hyp Rx, antihypertensive therapy; DM, diabetes mellitus; Cigs, cigarette smoking; CVD, previously diagnosed coronary heart disease, cardiac failure, or intermittent claudication; AF, atrial fibrillation; LVH-ECG, left ventricular hypertrophy by electrocardiogram; the horizontal line indicates average risk for stroke.

Source: Reference 18

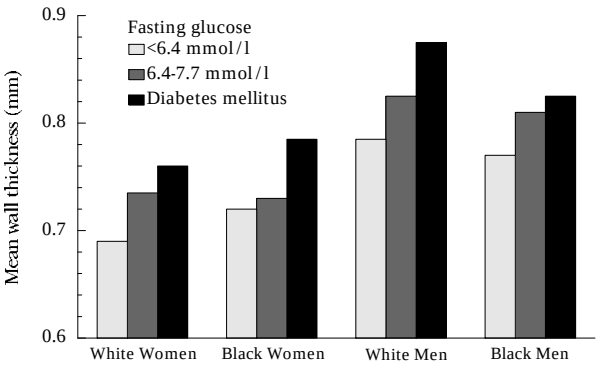
Figure 20.4
Incidence of CHD and Stroke by Diabetes and Carotid Bruits Status



*p<0.005, **p<0.01, †p<0.001, significant excess compared to subjects with neither condition; ‡p<0.05, significant difference compared to subjects with both diabetes and carotid bruits; data are 2-year age-adjusted rates per 100 subjects; CHD, coronary heart disease.

Source: Reference 20

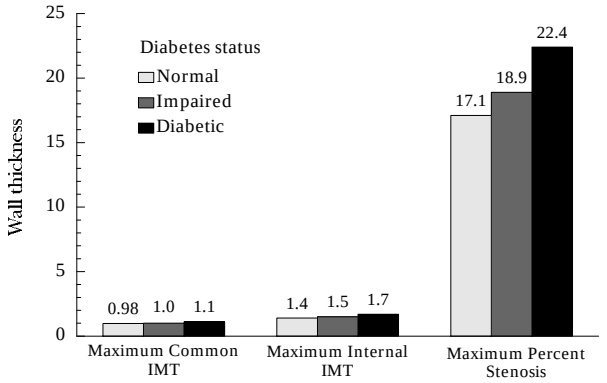
Figure 20.5
Average Carotid Artery Intimal-Medial Wall Thickness by FPG and Diabetes Status, ARIC Study, 1987-89



FPG, fasting plasma glucose; ARIC, Atherosclerosis Risk in Communities.

Source: Reference 21

Figure 20.6
Intimal-Medial Wall Thickness and Percent Stenosis of Carotid Arteries by Diabetes Status



IMT, mean maximum intimal-medial thickness, near and far wall, right and left carotid arteries; data are from the Cardiovascular Health Study.

Source: Reference 22

An increase in carotid artery intima medial wall thickness, or carotid stenosis, has been associated with an increased risk of stroke. In the Atherosclerosis Risk in Communities Study, the carotid artery medial wall thickness increased with age and was greater in men than in women. There was a direct relationship of carotid artery wall thickness with both blood glucose levels and diagnosed diabetes, for both African-American and white men and women (Figure 20.5)[21].

In the Cardiovascular Health Study of ~5,000 individuals age ≥65 years, the maximum internal and common carotid artery wall thickness (as well as the extent of carotid artery stenosis) was higher among diabetic than nondiabetic subjects (Figure 20.6)[22].

RELATIONSHIP OF HYPERGLYCEMIA AND STROKE

The relationship between blood glucose levels and risk of stroke is less certain than the strong relationship between diabetes and stroke. In the 12-year followup of the Honolulu Heart Program, the risk of stroke was elevated for nondiabetic persons with blood glucose in the 80th versus the 20th percentile (199 mg/dl versus 115 mg/dl)[17]. The blood glucose measurements, however, were nonfasting. In the 6-year followup of this study, the incidence of stroke was lowest among individuals in the lowest quartile of blood glucose (<122 mg/dl) 1 hour after a 50-g glucose load.

Stroke death rates are highest in the southeastern United States[2]. In the Three Area Study conducted in the early 1970s, both fasting and 2-hour blood glucose levels were higher in Savannah, GA, which had high stroke death rates, than in Hagerstown, MD and Pueblo, CO, which had low death rates[23]. Blood glucose levels were also higher in blacks than whites, consistent with the higher stroke rates in African Americans. Elevated blood glucose was the only risk factor that correlated with both the geographic variations and the race-sex differences in stroke incidence and mortality.

The 30-year followup of the Framingham Study found that blood glucose level was an independent risk factor for stroke in multiple logistic regression analysis among women but not men. The risk of stroke was increased for both diabetic men and women[24].

In the MRFIT, there were 43 stroke deaths during the first 10.5 years of followup. In multiple logistic regression analysis, fasting blood glucose level was an independent predictor of stroke mortality[13]. This association, however, was found in cigarette smokers only.

McCall[25] has noted that a higher blood glucose level at hospital admission predicts a poorer prognosis after a stroke, irrespective of whether the patient is diabetic or not. Also, the degree of disability after the stroke may be worse among individuals with elevated blood glucose at the time of the stroke. Animal models showed that hyperglycemia alone worsens the ischemic brain damage from a stroke.

PREVENTION OF STROKE

There are several approaches that can reduce the risk of stroke[26]. Treatment of hypertension is effective in decreasing stroke incidence and mortality. There is no evidence that the treatment of hypertension is less effective among patients with diabetes[27]. Hypertension is a key risk factor for stroke among both diabetic and nondiabetic individuals. Clinical trials have documented that lowering blood pressure substantially reduces the risk of stroke, especially among older individuals[28]. The number of subjects with diabetes in most of these trials has been small, however, so the ability to specifically compare diabetic and nondiabetic individuals is difficult. In the Systolic Hypertension in the Elderly trial, the treatment effect (reduced risk of stroke) in the intervention compared to the control group was similar for diabetic and nondiabetic subjects. Complications of treatment also did not appear to vary between diabetic and nondiabetic individuals. The American Diabetes Association[29] and the National High Blood Pressure Education Program Working

Group [30,31] have presented recommendations for the treatment of hypertension among patients with diabetes.

Antiplatelet aggregating agents such as aspirin are effective in decreasing the incidence of stroke, especially among individuals with existing cardiovascular disease or transient ischemic attack[32]. At least one study has shown beneficial effects in both diabetic and nondiabetic individuals. Smoking cessation will also decrease the risk of stroke.

Surgical therapy for carotid artery stenosis ≥70% will reduce the risk of stroke. There is no evidence that the surgical therapy is better or worse among patients with diabetes.

An important unanswered question is whether reduction of blood glucose levels in either insulin-dependent diabetes mellitus (IDDM) or non-insulin-dependent diabetes mellitus (NIDDM) will reduce the risk of stroke. The increase of older individuals in the U.S. population, as well as the prolonged survival of both diabetic patients with cardiovascular disease and of stroke patients, will result in a higher prevalence of diabetic patients who have experienced a stroke and associated disability and comorbidity in the community.

It is possible to reduce the risk of stroke among people with diabetes. Both the systolic and diastolic blood pressure should be monitored based on the recommendations of the National High Blood Pressure Education Working Group[30]. Blood lipoprotein levels should be monitored and LDL cholesterol lowered to at least 130 mg/dl and probably to 100 mg/dl in most diabetic subjects by diet or drug therapy. An attempt to raise HDL cholesterol by increasing exercise and/or weight reduction should be considered. Smoking cessation must be achieved. Careful evaluation of asymptomatic vascular disease and symptomatology, especially transient cerebral ischemia, atrial fibrillation, and peripheral vascular disease, should be encouraged. The view that stroke is an inevitable consequence of diabetes and aging should be replaced by aggressive efforts to prevent stroke.

Dr. Lewis H. Kuller is Professor and Chair, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA.

REFERENCES

1. National Center for Health Statistics: Annual summary of births, marriages, divorces, and deaths: United States, 1992. *Monthly Vital Statistics Report* 41:1-36, 1993
2. Feinlieb M, Ingster L, Rosenberg H, Maurer J, Singh G, Kochanek K: Time trends, cohort effects, and geographic patterns in stroke mortality—United States. *Ann Epidemiol* 3:458-65, 1993
3. National Center for Health Statistics: *Health, United States, 1992 and Healthy People 2000*. Hyattsville, MD, U.S. Public Health Service, 1993
4. Kovar MG, Pokras R, Collins JG: Trends in medical care and survival from stroke. *Ann Epidemiol* 3:466-70, 1993
5. National Center for Health Statistics: Current estimates from the National Health Interview Survey, 1990. *Vital and Health Statistics*, Series 10, No. 181, 1991
6. National Center for Health Statistics: Current estimates from the National Health Interview Survey, 1991. *Vital and Health Statistics*, Series 10, No. 184, 1992
7. National Center for Health Statistics: Current estimates from the National Health Interview Survey, 1992. *Vital and Health Statistics*, Series 10, No. 189, 1994
8. Kuller LH, Dorman JS, Wolf PA: Cerebrovascular disease and diabetes. Chapter XVIII in *Diabetes in America*, Harris MI, Hamman RF, eds. NIH publ. no. 85-1468, 1985
9. Bell DSH: Stroke in the diabetic patient. *Diabetes Care* 17:213-19, 1994
10. Simon NR, Frishman WH: Diabetes mellitus in the aging: Epidemiologic and therapeutic considerations. *Am J Geriatr Cardiol* Sep-Oct:22-36, 1992
11. Harris MI: Epidemiology of diabetes mellitus among the elderly in the United States. *Clinics in Geriatric Medicine* 6:703-19, 1990
12. Stamler J, Vaccaro O, Neaton JD, Wentworth D, for the MRFIT Research Group: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16:434-44, 1993
13. Neaton JD, Wentworth DN, Cutler J, Stamler J, Kuller L, for the MRFIT Research Group: Risk factors for death from different types of stroke. *Ann Epidemiol* 3:493-99, 1993
14. Manson JE, Colditz GA, Stampfer MJ, Willett WC, Krolewski AS, Rosner B, Arky RA, Speizer FE, Hennekens CH: A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. *Arch Intern Med* 151:1141-47, 1991
15. Barrett-Connor E, Khaw K-T: Diabetes mellitus: An independent risk factor for stroke? *Am J Epidemiol* 128:116-23, 1988
16. Kittner SJ, White LR, Losonczy KG, Wolf PA, Hebel JR: Black-white differences in stroke incidence in a national sample. The contribution of hypertension and diabetes mellitus. *JAMA* 264:1267-70, 1990
17. Abbott RD, Donahue RP, MacMahon SW, Reed DM, Yano K: Diabetes and the risk of stroke. The Honolulu Heart Program. *JAMA* 257:949-52, 1987
18. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB: Probability of stroke: A risk profile from the Framingham Study. *Stroke* 22:312-18, 1991
19. Truelsen T, Lindenstrom E, Boysen G: Comparison of stroke between the Copenhagen City Heart study and the Framingham study. *Stroke* 25:802-07, 1994
20. Abbott RD, Brand FN, Kannel WB: Epidemiology of some peripheral arterial findings in diabetic men and women: Experiences from the Framingham Study. *Am J Med* 88:376-81, 1990
21. Folsom AR, Eckfeldt JH, Weitzman S, Ma J, Chambless LE, Barnes RW, Cram KB, Hutchinson RG, for the ARIC Study Investigators: Relation of carotid artery wall thickness to diabetes mellitus, fasting glucose and insulin, body size, and physical activity. *Stroke* 25:66-73, 1994
22. O'Leary DH, Polak JF, Kronmal RA, et al: Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. *Stroke* 23:1752-60, 1992
23. Stolley PD, Kuller LH, Nefzger MD, Tonascia S, Lillienfeld AM, Miller GD, Diamond EL: Three-area epidemiological study of geographic differences in stroke mortality. *Stroke* 8:551-57, 1977
24. Kannel WB, Wolf PA, Garrison RJ (eds): *The Framingham Study. An epidemiological investigation of cardiovascular disease*. U.S. Department of Health and Human Services, National Heart, Lung, and Blood Institute, NIH publ. no. 87-2703, 1987
25. McCall AL: The impact of diabetes on the CNS. *Diabetes* 41:557-70, 1992
26. Biller J, Love BB: Diabetes and stroke. *Med Clin North Am* 77:95-110, 1993
27. Davis BR, Vogt T, Frost PH, Burlando A, Cohen J, Wilson A, Brass L, Frishman W, Price T, Stamler J, for the SHEP Cooperative Research Group: Risk factors for cerebrovascular disease in persons with isolated systolic hypertension (abstract no. 0901). *Circulation* 88:1-169, 1993
28. National High Blood Pressure Education Program Working Group: National high blood pressure education program working group report on hypertension in the elderly. *Hypertension* 23:275-85, 1994
29. Consensus Development Conference: Treatment of hypertension in diabetes. *Diabetes Care* 16:1394-1401, 1993
30. National High Blood Pressure Education Program Working Group: National high blood pressure education program working group report on hypertension in diabetes. *Hypertension* 23:145-58, 1994
31. Re RN: The national high blood pressure education program working group report on hypertension in diabetes. *Hypertension* 23:159-60, 1994
32. Sivenius J, Laakso M, Riekkinen P Sr, Smets P, Lowenthal A: European stroke prevention study: Effectiveness of antiplatelet therapy in diabetic patients in secondary prevention of stroke. *Stroke* 23:851-54, 1992