CHAPTER 19

STROKE AND DIABETES

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SUMMARY

In the total population, stroke is the fifth most common cause of death and the leading neurological cause of long-term disability in the United States, accounting in 2011 for $34 billion in health care costs. With the advent of sensitive brain imaging techniques, it is common to observe magnetic resonance imaging evidence of subclinical vascular brain injury, such as covert brain infarcts (CBI) and white matter hyperintensities (WMH). In an unselected sample of persons age >65 years without a history of clinical events, 10%–15% had CBI and 95% had WMH. The subclinical findings do not cause abrupt clinical symptoms but are often associated with cognitive decline and with an increased risk of subsequent stroke. Therefore, the clinical and public health burden of cerebrovascular disease is far greater than that of overt clinical disease. This burden is higher in persons with diabetes. Diabetes, a risk equivalent for cardiovascular disease, has been recognized as one of the major risk factors for stroke and subclinical vascular brain injury, such as CBI, WMH, and vascular cognitive impairment.

Stroke is clinically defined as an acute-onset focal neurological deficit persisting for more than 24 hours. About 85% of all strokes are ischemic, and the other 15% are hemorrhagic. Ischemic stroke is caused by an abrupt blockage of the artery, either by an embolus from the heart or from a more proximal artery, or from an *in situ* thrombus growing to occlude a cerebral artery affected by an atherosclerotic plaque, leading to an acute blockage of blood supply to the brain. Hemorrhagic stroke can result in accumulation of blood in the substrate of the brain, which is called intracerebral hemorrhage, in the cerebrospinal fluid around the brain, or in the cerebrospinal fluid spaces within the brain.

The etiology of stroke in persons with diabetes is comparable to the etiologies in other populations. However, multiple underlying pathophysiological processes in diabetes lead to a high prevalence of small vessel and/or large vessel atherosclerosis in persons with diabetes. Persons with diabetes have about twice the risk for stroke, particularly of ischemic stroke. Diabetic individuals after stroke have about a 25% reduction in a favorable outcome, such as being able to function independently in activities of daily living, and are more likely to die from the stroke. Those who survive are more likely to have recurrent strokes and to develop vascular cognitive impairment than persons without diabetes.

Diabetes is more common in nonwhite populations, and stroke risk has been assessed in various racial/ethnic subgroups. Diabetes is at least as important a risk factor for stroke in blacks, Japanese Americans, and Native Americans as it is in whites, with a 40%–100% higher risk in racial/ethnic minorities.

Coexistence of various risk factors, such as hypertension and hyperlipidemia, and concomitant coronary or peripheral vascular disease are common problems in persons with type 2 diabetes and are also independent risk factors for stroke and its serious complications. Impaired glucose tolerance and the metabolic syndrome, as well as microalbuminuria, are other stroke risk factors in persons with diabetes, with the metabolic syndrome increasing risk by 20%–40% and microalbuminuria increasing risk by approximately 80%.

Strict control of hyperglycemia has not been shown to reduce stroke incidence in persons with diabetes. Vigorous management of primary disease (diabetes) and careful identification and treatment of the concomitant vascular risk factors, especially hypertension, along with lifestyle modifications remain the fundamental approach for stroke prevention in this vulnerable population. Statins and low-dose aspirin may also be beneficial in preventing stroke or attenuating its adverse impact. Studies of oral hypoglycemic drugs and peroxisome proliferator-activated receptor-gamma (PPAR-γ) inhibitors have not, so far, shown a convincing effect on altering stroke risk among persons with diabetes.

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INTRODUCTION

In the total population, stroke is the fifth most common cause of death and the leading neurological cause of long-term disability in the United States, accounting in 2011 for $34 billion in health care costs; the mean lifetime cost to care for a single patient with an ischemic stroke was estimated at $140,048 (1). In 2014, there were an estimated 795,000 strokes, approximately 610,000 being new or incident strokes and around 185,000 being recurrent strokes (1).

Persons with diabetes have about twice the risk for stroke compared to those without diabetes, particularly for ischemic stroke. Yet, the etiology of stroke in persons with diabetes is comparable to etiologies in nondiabetic populations. Multiple underlying pathophysiological processes in diabetes, however, lead to a high prevalence of small vessel and/or large vessel atherosclerosis in individuals with diabetes.

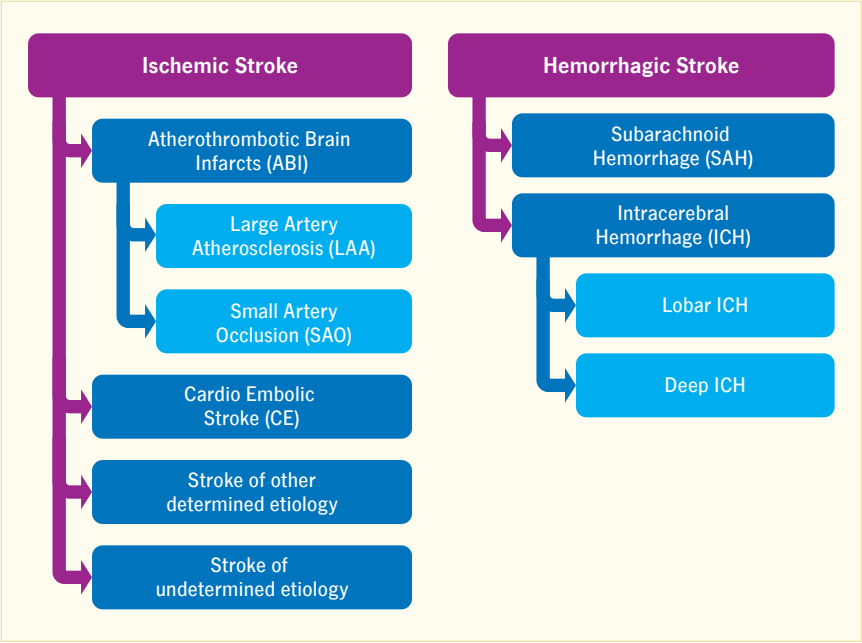
This chapter describes the measurement and classification of stroke and stroke subtypes, and in persons with diabetes, the pathophysiology of stroke, the epidemiology of stroke, predictors of stroke risk, control of risk factors for stroke, and the disease course and prognosis after a stroke.

DESCRIPTION, MEASUREMENTS, AND CLASSIFICATION OF STROKE IN DIABETES

DEFINITIONS, MEASUREMENTS, AND CLASSIFICATIONS

Traditionally, stroke is defined as an acute-onset focal neurological deficit persisting for more than 24 hours. Ischemic stroke (due to insufficient blood supply to a portion of the brain) accounts for approximately 85% of all strokes, and the other 15% are of hemorrhagic type (Figure 19.1) (2,3). Ischemic strokes are classified further based on presumed etiology; a commonly utilized classification of stroke subtypes is the TOAST classification, named for the Trial of Org 10172 in Acute Stroke Treatment, the clinical trial in which this system was initially developed (3). An alternative, more automated system used in genetic analyses is the Causative Classification of Stroke System (4). In these classification systems, ischemic strokes are subdivided into five categories as being due to: (1) large artery atherosclerosis, (2) cardioembolism, (3) small artery occlusion (or lacunar strokes), (4) stroke of other determined etiology, and (5) stroke of undetermined etiology. Hemorrhagic strokes are categorized as subarachnoid or intracerebral hemorrhages. Subarachnoid hemorrhages are due to rupture of an aneurysm, typically in the large intracranial arteries, into the subarachnoid space. Intracerebral hemorrhages are further categorized as lobar (in the cerebral hemispheres) or deep (in the basal ganglia, thalami, brainstem, or cerebellum).

FIGURE 19.1. Stroke Types



SOURCE: Original figure constructed by A. Pikula.

A transient ischemic attack (TIA) is a brief episode of neurologic dysfunction lasting <24 hours, resulting from focal but transient brain ischemia without acute infarction on brain imaging. TIA is a risk factor for subsequent stroke. The 90-day risk of stroke after a TIA is as high as 17%, with the greatest risk apparent in the first week. Whereas the common clinical definitions of stroke and TIA are based on the clinical presentation, a diagnosis of stroke and TIA can be confirmed with brain imaging techniques. Non-contrast computed tomography (CT) detects most hemorrhagic and some ischemic strokes, and brain magnetic resonance imaging (MRI) utilizes a sophisticated diffuse weighted imaging (DWI) technique for sensitive detection of acute ischemic brain injury in both TIAs and stroke (5).

Approximately 30%–50% of persons presenting with a TIA episode, with clinical symptoms lasting <24 hours, have abnormalities on DWI suggesting acute brain infarction; thus, a new tissue-based TIA definition has been proposed to differentiate TIA episodes with and without positive imaging (6). Pending further study, the short- and long-term management of individuals with clinical TIA remains unchanged by whether or not they have concomitant MRI DWI abnormalities (5).

Covert brain infarcts (CBI) and white matter hyperintensities (WMH) are subclinical lesions identified only by brain

imaging (CT or MRI) (5), and this has been an area of growing research interest, as the morbidity associated with these lesions is increasingly recognized (7,8).

This chapter focuses largely on clinical ischemic stroke in persons with diabetes. The frequency of hemorrhagic stroke in person with diabetes is the same as that in the general population (about 15%) (2,3,9), but this chapter does not consider hemorrhagic strokes in detail. Unless otherwise noted, diabetes refers to type 2 diabetes.

CLINICAL PRESENTATIONS AND STROKE TOPOGRAPHY

Most ischemic strokes present with symptoms of (a) an anterior cerebral circulation (carotid artery territory) involvement, such as an acute loss of motor power and sensory deficits on one side of the body (face, arm, and leg), associated with aphasia, visual deficits, or sensory neglect or (b) a posterior cerebral circulation (vertebrobasilar) involvement with presenting symptoms of dizziness or vertigo, double vision, balance, gait dysfunction or weakness, and sensory deficits (2). CBI or WMH lesions are not accompanied by obvious clinical symptoms, but their accumulation over time is associated with motor and/or cognitive impairment and with increased risk for subsequent clinical stroke and vascular dementia (10).

PATHOPHYSIOLOGY OF STROKE IN DIABETES

Diabetes adversely affects the extracranial and intracranial arterial circulation, including small perforating vessels within deep brain structures. Several possible mechanisms underlying the acceleration of macrovascular and microvascular injury in persons with diabetes could contribute to the development of cerebrovascular disease (11). One postulated mechanism is that atherosclerosis is the result of the oxidative modification of low-density lipoproteins (LDLs) by reactive oxygen species (ROS), which triggers a cascade of atherosclerotic processes within the arterial wall. Diabetes itself increases the production of free ROS, which in turn is thought to promote endothelial dysfunction, arteriosclerosis/lipohyalinosis of penetrating end-arteries, and accelerated atherosclerosis of large arteries, explaining higher prevalence of small and large vessel disease stroke types among persons with diabetes. Additionally, hyperglycemia independently promotes proinflammatory processes, smooth muscle cell dysfunction, overproduction of growth factors, and activation of protein kinase C pathways, which may influence overall fibrinolytic capacities; all of these processes lead to an increased risk of thrombus formation, atherosclerosis progression, and plaque rupture (11). Diabetes is also an acknowledged risk factor for coronary heart disease, atrial fibrillation, and heart failure, each of which predisposes to cardioembolic stroke. Finally, diabetes is associated with increased rates of hypertension, which contributes to stroke risk.

Prolonged hyperglycemia may result in renal dysfunction. Microalbuminuria, an early clinical sign of diabetic nephropathy, is a risk marker for vascular disease in both persons with and without diabetes (12,13). When present at the time of diagnosis of type 2 diabetes, microalbuminuria may reflect the burden of underlying vascular risk factors and indicate the presence of cardiovascular disease (CVD) (14). If not effectively treated, microalbuminuria is followed by slowly progressive decline in renal function manifesting as macroalbuminuria or decreases in estimated glomerular filtration rate (eGFR) (15). A meta-analysis of 12 studies, with a total of 48,596 participants and 1,263 stroke events in an analysis adjusted for established cardiovascular risk factors, confirmed that presence of microalbuminuria was associated with greater stroke risk (relative risk [RR] 1.92, 95% confidence interval [CI] 1.61–2.28, p<0.001) (12). A similar trend was seen in studies (n=5) including only persons with type 2 diabetes (RR 1.70, 95% CI 1.43–2.04), but this did not reach statistical significance (p=0.26). However, the microalbuminuria definition was different in all five studies, including a urine albumin-to-creatinine ratio (UACR) of >2.5 mg/mmol (>22.1 mg/g) or ≥3.0 mg/mmol (≥26.5 mg/g) or a spot urine albumin concentration (UAC) of 150–299 mg/L (15–29.9 mg/dL) or 30–299 mg/L (3–29.9 mg/dL) (12). Among 1,181 stroke-free community subjects with type 2 diabetes, microalbuminuria was found to be an independent predictor of stroke (RR 1.83, 95% CI 1.16–2.87, p=0.09) (16). Another meta-analysis derived from 33 prospective studies, with more than 280,000 people, of whom 8,000 had stroke, demonstrated that persons with an eGFR <60 mL/min/1.73 m^2 had a 43% greater risk of having another stroke than persons with a normal baseline eGFR (RR 1.43, 95% CI 1.31–1.57, p<0.001) (17). This observation was true for persons with or without vascular risk factors, including diabetes, across all racial groups.

Over the course of the disease, a large number of persons with diabetes develop diabetic autonomic neuropathy (DAN), an independent risk factor for stroke (18). The underlying mechanisms by which autonomic nerve pathology contributes to the pathophysiology of stroke are largely unknown. Accelerated cerebral vascular damage and alterations in the regulation of cerebral blood flow in diabetic persons with DAN may increase the risk of stroke. Experimental studies demonstrate that stimulation of perivascular nitrergic nerves (cholinergic nerves releasing nitric oxide [NO]) may relax the cerebral arteries by the actions of NO and, thus, increase cortical blood flow. In DAN, nitrergic nerve degeneration may result in severe deficiency of NO and impaired vasodilation response to both nerve stimulation and shear stress in cerebral arteries, thus increasing susceptibility to strokes in diabetic rats (18,19).

EPIDEMIOLOGY OF STROKE IN DIABETES

The prevalence of self-reported stroke by age and sex in the general population based on data from the National Health and Nutrition Examination Surveys (NHANES) 2007–2010 is shown in Figure 19.2 (20). Prevalence was rare in young ages but rose to about 6%–7% in persons age 60–79 years and to about 14% in those age ≥80 years. Prevalence was similar by sex. Based on data from the Framingham Heart Study (FHS), however, women have a somewhat higher lifetime risk of stroke (20%–21%) compared to men (14%–17%) (21).

Incidence of first stroke in the general population is shown by race and year in Figure 19.3, based on data from the Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS) population (20). Incidence was 1.5–2 times higher in blacks than whites, regardless of type of stroke (ischemic, intracerebral hemorrhage, or subarachnoid hemorrhage), and was stable over time. The vast majority of stroke incidence was due to ischemia.

Prospective epidemiologic studies have confirmed diabetes to be an independent risk factor for ischemic stroke. The relative risk of stroke in persons with diabetes ranged from 1.8 to 6.0 (22). Whereas death rates among U.S. men and women with diabetes declined by almost 40% between 1997 and 2006 (23), the prevalence of diabetes actually increased, resulting in a parallel increase in the absolute number of vascular events in persons with diabetes (22).

FIGURE 19.2. Prevalence of Stroke, by Age and Sex, U.S., 2007–2010

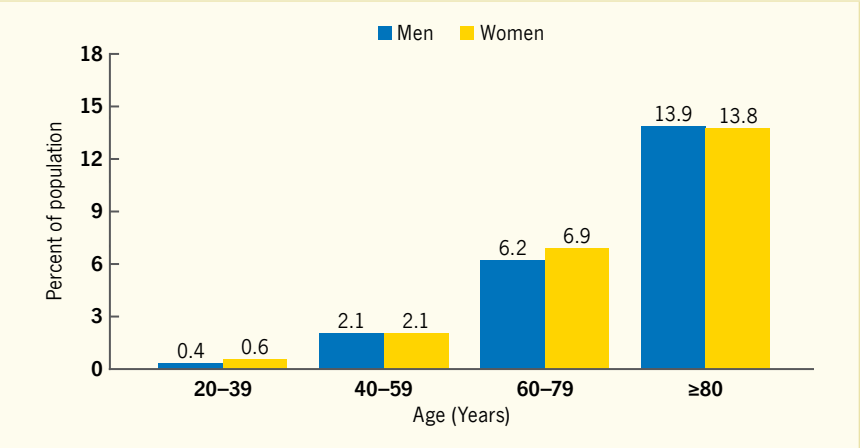


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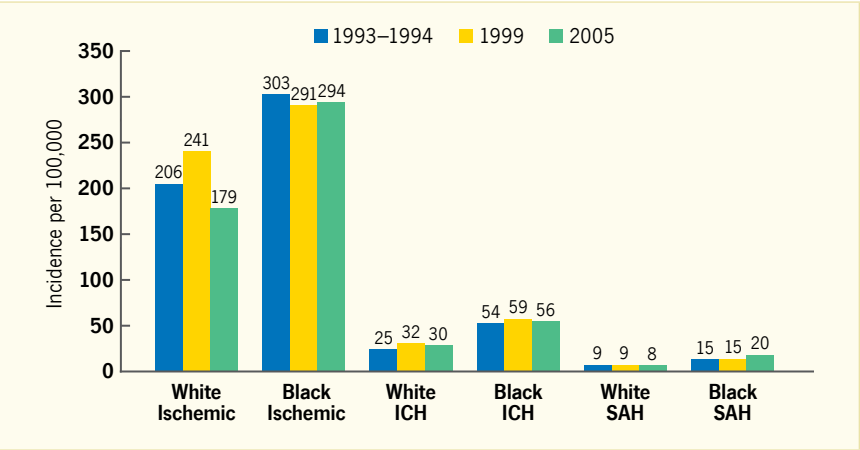
FIGURE 19.3. Annual Age-Adjusted Incidence of First-Ever Stroke, by Race and Stroke Type, Greater Cincinnati/Northern Kentucky Stroke Study, 1993–1994, 1999, and 2005



Data represent hospital and out-of-hospital ascertainment. ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage.

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INCIDENCE AND PREVALENCE OF STROKE IN DIABETES

Type 1 Diabetes

In the Pittsburgh Epidemiology of Diabetes Complications study, among 658 participants with childhood-onset type 1 diabetes followed for a mean duration of 15.4 years, 31 participants (mean age 40.2 years) experienced a stroke. Participants with stroke were older and had a longer duration of type 1 diabetes (mean duration 25 years) than persons without stroke. There was no difference in stroke risk based on sex or race. Participants who developed a stroke, either ischemic or hemorrhagic, were more likely to have albuminuria and to have a higher burden of concomitant vascular risk factors. Although the number of stroke events was small, the overall survival rates regardless of stroke type were 80.6%, 45.2%, and 9.6% at 1, 5, and 10 years, respectively, and were significantly worse after hemorrhagic than ischemic stroke (at 1 year, 95.2% vs. 50.0%, p=0.03) (24).

Over a follow-up period of 6 years, approximately 3% of a cohort of African American persons with type 1 diabetes, assembled at discharge from hospital, developed a stroke (25). Significant limitations of this study were the hospital-based nature of the cohort and the lack of nondiabetic and white comparison groups (26). Prior studies in whites with type 1 diabetes demonstrated a 6% stroke incidence over a much longer follow-up period of 20 years, suggesting that the relative risk of stroke may be higher in blacks with type 1 diabetes.

The Nurses' Health Study (NHS) evaluated the risk of stroke in women with type 1 or type 2 diabetes (26). The study utilized biennially mailed questionnaires to evaluate participants' medical status. During 24 years of follow-up, 2,719 first strokes were reported among 116,316

participants. Participants were categorized as having type 1 diabetes if they were diagnosed with diabetes before age 30 years and reported use of insulin or a history of ketosis. All others were categorized as having type 2 diabetes. Over a period of 24 years, women with type 1 diabetes were six times more likely to have a stroke than those without diabetes. In comparison, those with type 2 diabetes had a twofold increase in stroke risk compared to women without diabetes. Limitations of this important analysis were the use of mailed questionnaires to establish interval history and the fact that less than three-fourths of all historical stroke events could be confirmed on record review. This study emphasizes the importance of distinguishing the type of diabetes when estimating the risk of stroke (26). However, the majority of studies evaluating the risk of stroke among populations with diabetes have involved only persons with type 2 diabetes.

Population Data on Stroke in Type 2 Diabetes

As illustrated in Table 19.1, National Health Interview Survey (NHIS) 2009–2010 data on self-reported stroke among adults age ≥55 years with and without diabetes were analyzed for *Diabetes in America, 3rd edition*. The prevalence of stroke in persons with diabetes was 11.6% compared to 5.1% in persons without diabetes and was higher in diabetic individuals across all subgroups. Regardless of diabetes status, prevalence was similar for women and men, highest for non-Hispanic blacks, and lowest for Hispanic groups and non-Hispanic Asians.

Diabetes in America analysis of data from the National Hospital Discharge Survey 2010 using International Classification of Diseases, Ninth Revision, codes for stroke (430–438) estimated that the prevalence of stroke (based on hospital discharges) among persons with diabetes (Table 19.2) was very similar to the NHIS estimates (based on self-reported stroke in persons with diabetes). For adults age ≥55 years who were hospitalized in 2010, the percentage of hospital discharges listing stroke among adults with diabetes was 10.1% compared to 8.4% in adults without diabetes. Because of the self-reporting of events and the substantial mortality associated with stroke, prevalence data may underestimate the burden of stroke in any sample.

TABLE 19.1. Prevalence of History of Stroke Among Adults Age ≥55 Years, by Diabetes Status, Age, Sex, and Race/Ethnicity, U.S., 2009–2010

CHARACTERISTICS	PERCENT (STANDARD ERROR)	
	Diabetes	No Diabetes
Total	11.6 (0.63)	5.1 (0.22)
Age (years)		
55–64	9.6 (0.89)	2.7 (0.21)
65–74	9.1 (0.95)	5.5 (0.43)
75–84	18.4 (1.62)	8.5 (0.68)
≥85	16.3 (3.02)	12.8 (1.31)
Sex		
Men	11.6 (0.96)	5.3 (0.34)
Women	11.6 (0.84)	5.0 (0.27)
Race/ethnicity		
Non-Hispanic white	11.8 (0.82)	5.2 (0.26)
Non-Hispanic black	15.2 (1.35)	6.2 (0.59)
Hispanic	9.5 (1.47)	3.7 (0.52)
Mexican American	9.2 (1.85)	4.3 (0.79)
Other Hispanic	9.8 (2.41)	3.1 (0.59)
Non-Hispanic Asian	5.5 (1.73)[1]	3.3 (0.69)

Stroke and diabetes status are self-reported.
[1] Relative standard error >30%–40%

SOURCE: National Health Interview Surveys 2009–2010

TABLE 19.2. Percent of Hospital Discharges Listing Stroke Among Adults Age ≥55 Years With and Without an Additional Diagnosis of Diabetes, by Age, Sex, and Race/Ethnicity, U.S., 2010

CHARACTERISTICS	PERCENT (STANDARD ERROR)	
	Diabetes	No Diabetes
Total	10.1 (0.37)	8.4 (0.22)
Age (years)		
55–64	7.4 (0.51)	5.9 (0.33)
65–74	10.5 (0.65)	8.3 (0.39)
75–84	11.9 (0.75)	10.8 (0.42)
≥85	14.2 (2.89)	10.2 (1.29)
Sex		
Men	10.1 (0.52)	9.1 (0.33)
Women	10.0 (0.53)	7.8 (0.29)
Race/ethnicity		
White	9.6 (0.45)	8.2 (0.26)
Black	13.5 (1.05)	10.1 (0.67)
All other	7.6 (1.02)	8.3 (0.98)
Not stated	9.3 (1.00)	8.2 (0.56)

Standard errors were most likely underestimated because the National Hospital Discharge Survey sampling variables were not available, and consequently, it was not possible to take into account the complex sampling design. ICD-9 codes for stroke include: 430–438. ICD-9 codes for diabetes include: 250, 357.2, 362.0, 366.41, 648.0, and 775.1. ICD-9, International Classification of Diseases, Ninth Revision.

SOURCE: National Hospital Discharge Survey 2010

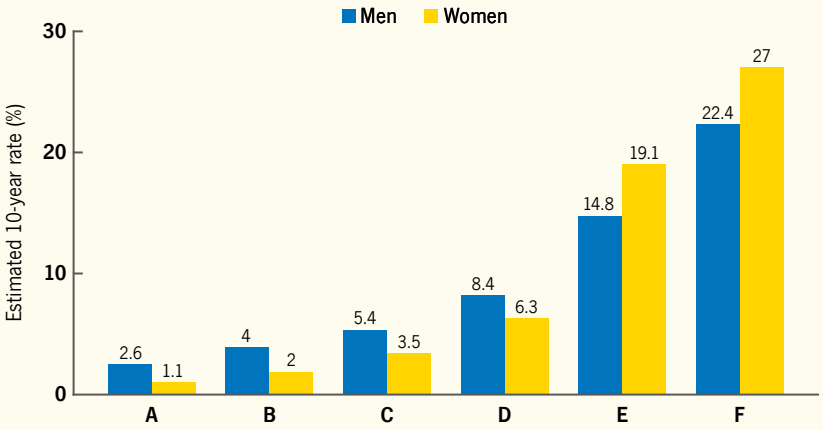
Age and Sex Differences in Stroke Risk in Diabetes

Data collected during a 10-year follow-up period between the ninth and fourteenth biennial exams of the largely white FHS were used to compute sex-specific 10-year probabilities for risk of incident stroke. Computations were based on the levels of baseline vascular risk factors.

A 10-year stroke risk was estimated for adults age 55–84 years (Figure 19.4) (27), and the probability of stroke was provided for both men (Figure 19.5) and women (Figure 19.6), depending on level of risk factors (28). Among 5,734 participants (58% female, mean age 66 years), there were 472 stroke events, and approximately 8% of female and 11% of male participants with a diagnosis of diabetes developed stroke (28). The estimated probability of stroke increased in relation to an individual's number of vascular risk factors, and the risk of stroke related to diabetes alone in both women and men was dramatic, with relative risks of 1.40 for women and 1.70 for men (28).

In the community of Rancho Bernardo, California, among 3,778 predominantly white men and women (age 50–79 years), 232 stroke cases occurred during a 12-year follow-up period. As in the Framingham cohort, the risk of stroke was higher among participants with diabetes compared

FIGURE 19.4. Estimated 10-Year Stroke Risk Among Adults Age 55–84 Years, by Sex and Risk Factors, Framingham Heart Study



	A	B	C	D	E	F
Blood pressure*	95–105	138–148	138–148	138–148	138–148	138–148
Diabetes	No	No	Yes	Yes	Yes	Yes
Cigarette smoking	No	No	No	Yes	Yes	Yes
Prior AF	No	No	No	No	Yes	Yes
Prior CVD	No	No	No	No	No	Yes

Data are based on 472 stroke events occurring during 10 years of follow-up from biennial examinations 9 and 14. AF, atrial fibrillation; CVD, cardiovascular disease.

* Systolic blood pressure (mmHg). Closest ranges for women are 95–104 and 135–144.

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FIGURE 19.5. Probability of Stroke in Men Age 55–84 Years and Free of Previous Stroke, Framingham Stroke Risk Estimator

	POINTS										
RISK FACTOR	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Age (yr)	54–56	57–59	60–62	63–65	66–68	69–71	72–74	75–77	78–80	81–83	84–86
SBP (mmHg)	95–105	106–116	117–126	127–137	138–148	149–159	160–170	171–181	182–191	192–202	203–213
Hyp Rx	No		Yes								
DM	No		Yes								
Cigs	No			Yes							
CVD	No			Yes							
AF	No				Yes						
LVH	No						Yes				

Points	10-yr Probability	Points	10-yr Probability	Points	10-yr Probability
1	2.6%	11	11.2%	21	41.7%
2	3.0%	12	12.9%	22	46.6%
3	3.5%	13	14.8%	23	51.8%
4	4.0%	14	17.0%	24	57.3%
5	4.7%	15	19.5%	25	62.8%
6	5.4%	16	22.4%	26	68.4%
7	6.3%	17	25.5%	27	73.8%
8	7.3%	18	29.0%	28	79.0%
9	8.4%	19	32.9%	29	83.7%
10	9.7%	20	37.1%	30	87.9%

Data are based on 472 stroke events occurring during 10 years of follow-up from biennial examinations 9 and 14 in the Framingham Heart Study. AF, history of atrial fibrillation; Cigs, smokes cigarettes; CVD, history of intermittent claudication or congestive heart failure; DM, history of diabetes mellitus; Hyp Rx, under antihypertensive therapy; LVH, left ventricular hypertrophy on electrocardiogram; SBP, systolic blood pressure.

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to those without diabetes. In addition, the age-adjusted stroke mortality and morbidity rate among female participants with both diabetes and a concomitant diagnosis of hypertension (defined as >160 mmHg systolic or >90 mmHg diastolic) was nearly double the rate in women with diabetes alone (17.8% vs. 8.9%, p=0.02). This finding suggests that some of the increased risk of stroke among persons with diabetes is attributable to the increased prevalence of hypertension (29).

In the NHS, 116,177 women without CVD (age 30–55 years) were followed for 8 years. After adjusting for other known vascular risk factors, such as blood pressure and smoking, the relative risk of stroke among women with diabetes compared to women without diabetes was 3.0 (95% CI 1.6–5.7) (30).

Racial and Ethnic Differences in Stroke Risk in Diabetes

Several population studies have provided insights into the racial and ethnic differences in stroke risk (22,31,32,33). The overall findings suggest an excess stroke risk among black and Hispanic populations compared to the white population. In the Atherosclerosis Risk in Communities (ARIC) study, a black-to-white age-adjusted incidence ratio for stroke of 2.41 was observed. The Northern Manhattan Study (NOMAS) showed a Hispanic-to-white incidence ratio of 1.69. The age-adjusted incidence of first ischemic stroke per 1,000 was 0.88 in whites, 1.91 in blacks, and 1.49 in Hispanics, according to data from the NOMAS (34).

Assuming that stroke case-fatality rates are similar across the United States, studies have used stroke mortality rates to estimate geographic variations in stroke incidence. The Centers for Disease Control and Prevention showed 20% and 40% higher stroke mortality rates in the "stroke belt" (Alabama, Arkansas, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, and Tennessee) and the "stroke buckle" (region along the coastal plain of North Carolina, South Carolina, and Georgia), respectively, than in the remaining states (22).

The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study is a longitudinal, population-based cohort study designed to investigate factors associated with excess stroke mortality among blacks and residents of the stroke belt region (33). Among 27,744 men and women age ≥45 years without prevalent stroke (40.4% black), 460 incident strokes were identified over 113,469 person-years

FIGURE 19.6. Probability of Stroke in Women Age 55–84 Years and Free of Previous Stroke, Framingham Stroke Risk Estimator

	POINTS										
RISK FACTOR	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Age (yr)	54–56	57–59	60–62	63–65	66–68	69–71	72–74	75–77	78–80	81–83	84–86
SBP (mmHg)	95–104	105–114	115–124	125–134	135–144	145–154	155–164	165–174	175–184	185–194	195–204
Hyp Rx	No, if yes, see below										
DM	No			Yes							
Cigs	No			Yes							
CVD	No		Yes								
AF	No						Yes				
LVH	No				Yes						

If currently under antihypertensive therapy, add points depending on SBP:

	SBP (mmHg)										
	95–104	**105–114**	**115–124**	**125–134**	**135–144**	**145–154**	**155–164**	**165–174**	**175–184**	**185–194**	**195–204**
Points	6	5	5	4	3	3	2	1	1	0	0

Points	10-yr Probability	Points	10-yr Probability	Points	10-yr Probability
1	1.1%	10	6.3%	19	31.9%
2	1.3%	11	7.6%	20	37.3%
3	1.6%	12	9.2%	21	43.4%
4	2.0%	13	11.1%	22	50.0%
5	2.4%	14	13.3%	23	57.0%
6	2.9%	15	16.0%	24	64.2%
7	3.5%	16	19.1%	25	71.4%
8	4.3%	17	22.8%	26	78.2%
9	5.2%	18	27.0%	27	84.4%

Data are based on 472 stroke events occurring during 10 years of follow-up from biennial examinations 9 and 14 in the Framingham Heart Study. AF, history of atrial fibrillation; Cigs, smokes cigarettes; CVD, history of intermittent claudication or congestive heart failure; DM, history of diabetes mellitus; Hyp Rx, under antihypertensive therapy; LVH, left ventricular hypertrophy on electrocardiogram; SBP, systolic blood pressure.

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of follow-up. Incident stroke was defined as first occurrence of stroke over 4.4 years of follow-up. Incidence rate ratios of stroke in the southeastern stroke belt and stroke buckle were 1.06 (95% CI 0.87–1.29) and 1.19 (95% CI 0.96–1.47), respectively. The overall age-sex-adjusted black/white incidence rate ratio was 1.51 (95% CI 1.26–1.81), but for persons age 45–54 years, the black/white incidence rate ratio was 4.02 (95% CI 1.23–13.11), and for those age ≥85 years, it was 0.86 (95% CI 0.33–2.20) (31). In a separate analysis of REGARDS data, 427 stroke events were detected over a median follow-up of 4.4 years among 25,714 black and white individuals age ≥45 years who were stroke free at baseline. Of the various vascular risk factors, hypertension and diabetes were the largest contributors to racial disparities, accounting for one-half and one-third of the joint mediating effect of all risk factors combined, respectively. In addition, blacks with stroke were twice as likely to have diabetes compared to whites (33).

The GCNKSS was the first to estimate diabetes-specific incidence rates, case-fatality rates, and population attributable risks of ischemic stroke in black and white persons with diabetes within the same population. The study demonstrated a race-specific effect, with a higher risk for stroke in African Americans with diabetes compared to whites, and an age effect, with substantially increased risk for diabetic persons age <65 years compared with individuals without diabetes. The maximum risk ratios of 9.9 in those age 35–44 years for black persons with diabetes compared to nondiabetic black subjects declined gradually with age to a risk ratio of 0.8 in those age ≥85 years. The risk ratio estimates for the white diabetic versus nondiabetic populations were less dramatic but followed a similar pattern, with a risk ratio of 5.3 in persons age 45–54 years, declining to 2.3 in those age ≥85 years. These findings indicate that the risk of stroke in diabetes is somewhat higher in older white than black adults. The greatest increase in risk was seen in younger African Americans (age 35–44 years), who had a substantially higher risk than whites of the same age. The overall population attributable risk of diabetes for stroke was 5.6% in African Americans and 5.2% in whites; when combined with hypertension, the population attributable risk was 20%–21% in both races. Interestingly, the case-fatality after ischemic stroke in this study was not found to be higher in persons with diabetes. The definition of "diabetics with stroke" in the GCNKSS was based on prior diagnosis of diabetes, excluding persons who had not been diagnosed with diabetes at the time of their ischemic stroke. Therefore, the incidence rates, relative risks, and population attributable risks in this study could be underestimated (35).

In the NHANES 1971–1975, during an 8-year follow-up, a 2.5-fold higher risk of stroke was observed among persons with diabetes compared to those without; this risk was similar for black and white women and men with diabetes (36).

In the Strong Heart Study, a population-based study of 4,507 American Indian participants (mean age 59.5 years) who were free of prevalent stroke at baseline, 306 (6.8%) had a first stroke over a 12–15-year follow-up period. The hazard ratio (HR) for diabetes and impaired glucose tolerance was 2.05, where impaired glucose intolerance was defined as fasting glucose <126 mg/dL (<6.99 mmol/L) with postchallenge glucose between 140 and 199.9 mg/dL (7.77–11.09 mmol/L) (37). Overall age-adjusted incidence and case-fatality rates for stroke in American Indians were higher than those published for white or black populations in the United States.

In the Honolulu Heart Program, 8,006 Japanese American men (mean age 55 years) were followed for 12 years. Incident stroke was observed in 62.3 per 1,000 diabetic men and 32.7 per 1,000 nondiabetic men. The estimated relative risk of stroke for those with diabetes compared with those without diabetes was 2.0 (95% CI 1.4–3.0) for ischemic stroke (38).

Stroke in Young Persons With Diabetes

High-risk young men (age 35–57 years) in the Multiple Risk Factor Intervention Trial (MRFIT) were followed for 12 years. The relative risk of stroke-related mortality among participants with diabetes (N=5,163) was 2.8-fold higher compared to nondiabetic men (N=342,815). The risk was even higher among persons with diabetes who also had prevalent hypertension or dyslipidemia or were current smokers (39).

In 1,220 young participants (age 18–44 years) in the Baltimore-Washington Cooperative Young Stroke Study, the risk of ischemic stroke in persons with diabetes was high. The population attributable risk percent for a history of diabetes (not precisely defined as type 1 or type 2 diabetes) was high for all sex and race groups (for white men 19.0%, 95% CI 8.2%–28.5%; white women 15.8%, 95% CI 3.8%–26.3%; black men 13.2%, 95% CI 5.3%–20.4%), but highest for young black women at 22.1% (95% CI 12.5%–30.7%) (40). Population attributable risks for hypertension and smoking were also high in this cohort.

STROKE RISK IN DIABETES BY STROKE SUBTYPES

The prevalence of stroke subtypes in the diabetic population appears to be similar to that in persons without diabetes (26). A common stroke subtype in persons with diabetes is lacunar stroke. The prevalence of diabetes in persons with lacunar stroke is 28%–43%. In the NOMAS, a comparison was made between the relative risks of lacunar infarcts and deep intracerebral hemorrhages, both stroke types occurring as a result of small vessel disease within the deep brain structures, in persons with diabetes. The presence of diabetes conferred a threefold higher chance for having a lacunar stroke over a deep intracerebral hemorrhage (41). In the Cardiovascular Health Study, among 3,660 participants (age >65 years) who underwent brain MRI imaging, diabetes was an independent risk predictor of lacunar infarcts (42).

Most studies have shown that diabetes is an important risk factor for ischemic stroke, while the incidence of hemorrhagic stroke in individuals with diabetes may be the same as in persons without diabetes (9). In the Honolulu Heart Program, the risk for hemorrhagic stroke in Japanese American men with diabetes was not higher than in persons without diabetes (38). In the NHS, the risk of hemorrhagic stroke in persons with type 1 diabetes was higher (RR 3.8, 95% CI 1.2–11.8) than in persons without diabetes, but this was not true for persons with type 2 diabetes (26).

Diabetes is a risk factor for extracranial and intracranial cerebral atherosclerosis and for stroke in persons with carotid atherosclerosis (43,44,45). In the FHS, the 2-year age-adjusted incidence of stroke was fivefold higher for women with both carotid bruits and diabetes compared to women without diabetes and the carotid bruit (5.0/100 vs. 1.1/100, respectively) and was greater than the sum of the individual risks, suggesting some synergistic interaction between the two risk factors (46).

PREDICTORS OF STROKE RISK IN PERSONS WITH DIABETES

Vascular risk factors may modify the risk of stroke among subjects with diabetes just as they alter stroke risk among those without diabetes (2,4,34,38). These risk factors include hypertension, smoking, hyperlipidemia, and atrial fibrillation. Hypertension is the most important of these comorbidities: the single most effective strategy to prevent stroke among persons with diabetes is to ensure optimal blood pressure control. Attention has shifted to the evaluation of diabetes-specific risk factors in modifying stroke risk among persons with diabetes (47).

HYPERGLYCEMIA AS A STROKE RISK FACTOR

Hyperglycemia is an independent risk factor for stroke and stroke-related mortality. Boden-Albala et al. evaluated the effect of glycemic control in subjects with diabetes on stroke risk over 6 years of follow-up in the NOMAS (48). Of 3,298 participants, approximately 18% had diabetes and were being treated with diet control, oral medications, or insulin therapies. More than half of all persons with diabetes did not achieve adequate glycemic control (defined as blood glucose ≤126 mg/dL). Persons with elevated fasting blood glucose levels had a higher risk of stroke than those with a fasting blood glucose value within the target range (HR 2.7, 95% CI 2.0–3.8) (48). In adjusted analyses, however, when controlled for age, race/ethnicity, sex, insurance status, education, hypertension, coronary artery disease, lipids, obesity, physical activity, alcohol intake, and smoking, this association was not statistically significant. In addition, the authors failed to observe any dose-response effect among persons with hyperglycemia; the risk of developing an ischemic stroke was not significantly different in persons with blood glucose level <150 mg/dL (<8.33 mmol/L) compared to subjects with blood glucose level ≥150 mg/dL.

In a systematic review, higher blood glucose levels in the first 12–48 hours after an acute stroke predicted poorer stroke outcomes. Even in persons without a prior diagnosis of diabetes, an admission glucose level of 121–144 mg/dL (6.72–7.99 mmol/L) was associated with a greater risk of poor functional recovery (RR 1.41, 95% CI 1.16–1.73) after stroke compared to persons with lower glucose levels (49). The most common explanation is that persons with large stroke could develop so-called "stress" hyperglycemia, unmasking an underlying propensity to diabetes. Hyperglycemia per se has a neurotoxic effect on brain cells that causes cellular acidosis in the ischemic penumbra. This acidosis results in a greater infarct volume and/or makes the infarcted tissue more susceptible to hemorrhagic conversion, each of which leads to poorer motor and cognitive outcomes and higher rates of stroke-related morbidity and mortality. This effect was demonstrated in the European Cooperative Acute Stroke Study (ECASS)-II trial, in which hyperglycemia at 24 hours after stroke onset (but not baseline hyperglycemia) increased the risk of death sixfold among 748 participants (50). Since the degree of hyperglycemia is strongly correlated with diabetes duration, the observed relation between diabetes control and stroke risk could be confounded by duration, which is not generally controlled in analyses. While intensive insulin therapy appears to safely reduce blood glucose levels in persons with acute stroke, the effect of such intervention on mortality and functional outcomes remains uncertain (51).

INSULIN RESISTANCE AND STROKE RISK

Insulin resistance, a metabolic condition that is characterized by reduced peripheral response to insulin, is a major determinant of type 2 diabetes and is present in most diabetic persons. Insulin resistance is associated with dyslipidemia, endothelial dysfunction, a proinflammatory state, and hypertension, all known vascular risk factors. Whereas insulin resistance can be assessed by several methods and fasting insulin is a reasonable reflection of insulin resistance in persons without diabetes, the homeostasis model assessment of insulin resistance (HOMA-IR) is the most commonly used measure of insulin resistance in epidemiologic studies (52); however, fasting insulin and HOMA-IR are not reliable reflections of insulin resistance in persons with diabetes compared to persons without diabetes.

In the Third NHANES (1988–1994), after adjusting for age, hypertension, myocardial infarction, claudication, physical activity, and glycosylated hemoglobin (A1c) values, higher HOMA-IR levels in persons without diabetes were independently associated with increased risk of stroke (odds ratio [OR] 1.06, 95% CI 1.01–1.12, for each HOMA-IR unit) (53). Among 1,509 nondiabetic, mostly Hispanic NOMAS participants mean

age±standard deviation 68±10 years; 64% women), those in the top quartile of HOMA-IR values had a higher risk for ischemic stroke (adjusted HR 2.83, 95% CI 1.34–5.99) than those in the lowest quartiles during a mean follow-up of 8.5 years. This effect was independent of sex, race/ethnicity, and traditional vascular risk factors, as well as the metabolic syndrome and its components (54).

THE METABOLIC SYNDROME AND STROKE RISK

The metabolic syndrome may increase the risk of stroke even in euglycemic persons (55). The metabolic syndrome is a constellation of clinical and metabolic components that are typically a reflection of insulin resistance, including elevated blood pressure and blood glucose, low high-density lipoprotein (HDL) cholesterol, and high triglycerides as separate components, and abdominal obesity (52). Each component of the metabolic syndrome is individually recognized as a risk factor for stroke, but due to a synergistic relationship among these components, the collective entity of the metabolic syndrome provides better stroke risk estimates (56).

Among 15,792 middle-aged and elderly ARIC participants, the adjusted incidence rate of ischemic stroke was higher in participants with the metabolic syndrome compared to those without the metabolic syndrome (HR 1.42, 95% CI 0.96–2.11 in men, and HR 1.96, 95% CI 1.28–3.00 in women) (57). In the NOMAS, 44% of 3,300 subjects met criteria for the metabolic syndrome, and women with the metabolic syndrome had a twofold increase in ischemic stroke risk compared to those without the metabolic syndrome, while the metabolic syndrome did not have an effect on risk of stroke in men (58). The metabolic syndrome is also a significant predictor of carotid atherosclerosis, with a 36% higher prevalence of internal carotid artery plaque among subjects with the metabolic syndrome (59).

Elevated blood glucose is a component of the metabolic syndrome; although the metabolic syndrome was defined for use in persons without diabetes, it is sometimes used in persons with diabetes. Several studies have examined whether persons with both diabetes and the metabolic syndrome are at higher risk of stroke than those with diabetes but no other metabolic features of the metabolic syndrome (55). In the United Kingdom Prospective Diabetes Study (UKPDS), 14% (480) of 3,367 subjects with diabetes and baseline data available met diagnostic criteria for the metabolic syndrome. Over a median 10-year follow-up, participants with both diabetes and the metabolic syndrome had a higher risk of incident stroke compared to those without the metabolic syndrome, with the relative risk ranging from 1.2 to 1.4, depending on what definition of the metabolic syndrome was applied in the analysis (60).

Among 2,097 participants of the Framingham Offspring Study who were age 50–81 years and free of stroke, age-adjusted risk ratios, 10-year incidence, and population attributable risks of stroke were estimated for men and women with the metabolic syndrome alone, diabetes alone, and both. In persons with both diabetes and the metabolic syndrome, risk of stroke was higher than that for either condition alone (diabetes and the metabolic syndrome, RR 3.28, 95% CI 1.82–5.92; the metabolic syndrome alone, RR 2.10, 95% CI 1.37–3.22; diabetes alone, RR 2.47, 95% CI 1.31–4.65). The population attributable risk of stroke was greater for the metabolic syndrome alone than for diabetes alone (19% vs. 7%), likely due to the higher prevalence of the metabolic syndrome in this population (22% of all participants had the metabolic syndrome alone vs. 5% with diabetes) (61).

ALBUMINURIA AND STROKE RISK

Hitman *et al*. evaluated the impact of diabetes-specific factors—microalbuminuria and glycemic control—on the risk of stroke or TIA among 2,838 participants in the Collaborative Atorvastatin Diabetes Study (CARDS), a placebo-controlled randomized trial evaluating atorvastatin therapy in diabetic subjects free of macrovascular disease (47). Over a follow-up period of nearly 4 years, 60 incident cerebrovascular events were observed. Subjects with A1c >10% (>86 mmol/mol) had more than double the odds of stroke compared to those with lower A1c levels. Microalbuminuria was measured using UACR (the normal range for this measure is 1–2.5 mg/mmol). A level of >2.5 mg/mmol conferred twice the risk of a stroke compared to a lower UACR level (47). This finding was also true for a general population sample in the FHS, in which higher UACR levels were associated with an increased risk of stroke and TIA among middle-aged, stroke-free participants (13).

OTHER MARKERS OF STROKE RISK

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is an independent risk factor, doubling the risk of stroke (22,62). Almost 50% of persons with type 2 diabetes have OSA, including close to 90% of obese persons with type 2 diabetes (63,64). Among 128 persons with stroke and TIA, a higher frequency of OSA (62.5%) was observed in persons with higher body mass index (BMI) and type 2 diabetes (65).

Inflammation

High sensitivity C-reactive protein (hsCRP), a marker of systemic inflammation, is a risk factor for stroke (22). Among FHS participants, high CRP was found to be an independent predictor of stroke. Men in the highest CRP quartile had two times the risk of ischemic stroke/TIA (RR 2.0, 95% CI 1.10–3.79, p=0.027), and women had almost three times the risk (RR 2.7, 95% CI 1.59–4.79, p=0.0003), compared with those in the lowest quartile (66).

While elevated levels of hsCRP predict CVD, hsCRP is also a risk marker for the development of type 2 diabetes; persons with hsCRP levels >3 mg/L have a fourfold to sixfold higher risk of getting diabetes than those with lower levels. Thus, the link between diabetes and stroke risk might be partially mediated via inflammation (67).

Receptor for Advanced Glycation Endproducts

Advanced glycation endproducts (AGEs) and their receptors are strongly implicated in the development of diabetes

complications (68). The most widely studied AGE receptor is the receptor for AGEs (RAGE), which is expressed in the vasculature and other organs (69). Several studies demonstrated an association between low serum soluble RAGE (sRAGE) and coronary heart disease (70) and carotid atherosclerosis (71). The ARIC study measured sRAGE in 1,201 participants with normal kidney function and free of CVD (age 47–68 years). In cross-sectional analyses, male sex, black race, higher BMI, and hsCRP levels were independently associated with low sRAGE. During approximately 18 years of follow-up, there were 192 incident coronary heart disease events, 53 ischemic strokes, 213 deaths, and 253 cases of type 2 diabetes (among 1,057 persons without type 2 diabetes at baseline). In multivariable Cox models comparing risk in the first quartile versus the fourth quartile of baseline sRAGE, low levels of sRAGE were significantly associated with risk of type 2 diabetes (HR 1.64, 95% CI 1.10–2.44), coronary heart disease (HR 1.82, 95% CI 1.17–2.84), and mortality (HR 1.72, 95% CI 1.11–2.64), but not ischemic stroke (HR 0.78, 95% CI 0.34–1.79) (72). However, the study was underpowered with a small number of stroke events.

Hypercoagulability

Hypercoagulable state has been linked to cerebrovascular disease. Of all persons with type 2 diabetes, 80% would die from atherosclerotic disease; 75% of these deaths result from cardiovascular events and 5% as complications of peripheral vascular and cerebrovascular disease (73). Diabetes is associated with the development of endothelial dysfunction and enhanced platelet aggregation and activation. Plasma levels of many clotting factors, including fibrinogen and factors VII, VIII, XII, and XIII b-subunit, are elevated, while natural anticoagulants and fibrinolytic factors are relatively inhibited as a consequence of an increase in plasminogen activator inhibitor type-1 levels (74).

Insulin-Like Growth Factor 1

Insulin-like growth factor 1 (IGF-1) levels are measured in the blood and may decrease with age, but also with decline in physical functioning, atherosclerosis, and type 2 diabetes (75). Several epidemiologic studies revealed an inverse relationship between plasma IGF-1 levels and risk of stroke, but it remains uncertain whether this risk is different among patients with type 2 diabetes (76,77,78). Other experimental and clinical studies suggest that IGF-1 and IGF-binding protein 1 (IGFBP-1) could be important determinants of glucose homeostasis (79). High circulating concentrations of highly phosphorylated IGFBP-1 may protect against the development of hypertension and CVD by reducing the mitogenic potential of IGFs on the vasculature. Heald *et al*. demonstrated that for every increase of 2.73 µg/L in IGFBP-1 concentration, there was a 43% decrease in the odds of a subject having macrovascular disease (OR 0.57, 95% CI 0.40–0.83, p=0.001) (80). Macrovascular disease was defined as a history of any of the following: ischemic heart disease (myocardial infarction and congestive heart failure), peripheral vascular disease (intermittent claudication or unilateral/bilateral absence of foot pulses), cerebrovascular accident (stroke and TIA), or systolic blood pressure (SBP) ≥170 mmHg. Interestingly, total IGFBP-1 was markedly reduced in subjects (n=40) with known macrovascular disease (geometric mean 48.7 µg/L, 95% CI 33.7–63.6) compared with patients (n=120) with no manifest macrovascular pathology (80.0 µg/L, 95% CI 52.2–107, F=5.4, p=0.01), but there was no difference among subjects for IGF-1 levels (80). Thus, more clinical studies are expected in this important area of research.

Autonomic Neuropathy

In 950 normotensive and hypertensive type 2 diabetic persons enrolled in the Appropriate Blood Pressure Control in Diabetes trial on the incidence of stroke, DAN was found to be an independent risk factor for stroke (OR 2.2, 95% CI 1.10–4.44) (18).

CONTROL OF STROKE RISK FACTORS IN DIABETES

The risk of stroke in persons with diabetes can be estimated based on their vascular risk factor profiles; the algorithm is similar to those used for a general population sample. In 2008, the UKPDS published a risk estimation model that can be used to predict 10-year stroke risk in persons with type 2 diabetes, based on age, presence or absence of hyperglycemia (A1c >6.3% [>45 mmol/mol] and fasting plasma insulin >9.8 µIU/mL [>58.8 pmol/L]), presence of elevated blood pressure (SBP >140 mmHg, diastolic blood pressure >80 mmHg), dyslipidemia, and history of smoking (81). The UKPDS developed a model for cardiovascular risk assessment. The UKPDS Risk Engine provides risk estimates for nonfatal and fatal stroke in individuals with type 2 diabetes. These estimates can be calculated for any given duration of type 2 diabetes based on current age, sex, ethnicity, smoking status, presence or absence of atrial fibrillation and levels of A1c, SBP, total cholesterol, and HDL cholesterol (81,82).

LIFESTYLE INTERVENTIONS

All persons with or without diabetes should be routinely counseled on the importance of lifestyle modifications, such as healthy dietary habits, smoking cessation, moderate alcohol consumption, and regular exercise, for primary and secondary stroke prevention. As a part of the lifestyle changes and risk factor intervention, a weight loss program should be included to help reduce the risk associated with the metabolic syndrome and obesity. The 2011 American Heart Association (AHA) guidelines advise all persons to participate in moderate physical activity for at least 30 minutes at least three times per week (5,83).

HYPERTENSION AND SYSTOLIC BLOOD PRESSURE

Hypertension is the major risk factor for ischemic stroke in persons with diabetes and the most frequently targeted modifiable factor for stroke prevention in this population. In the Systolic Hypertension

in the Elderly Program Cooperative Research Group (SHEP) trial, elderly persons with diabetes had >20% reduction of stroke events with control of isolated systolic hypertension (84). In the UKPDS, every 10 mmHg reduction in SBP in persons with type 2 diabetes decreased the risk of ischemic stroke by 19% (85). Although blood pressure control that is overly stringent in persons with diabetes could also be associated with adverse events (postural hypotension, dehydration, and hypo- or hyperkalemia related to medication use), such intervention is a well-established approach for prevention of cerebrovascular events in all persons (86). Based on the Eighth Joint National Committee (JNC 8) and 2016 American Diabetes Association (ADA) guidelines, a blood pressure of <140/90 mmHg for persons with type 2 diabetes is considered optimal (87,88).

Blood Pressure Management

A range of antihypertensive therapies is effective in reducing cardiovascular events, and the choice of such therapies depends on associated comorbidities in persons with diabetes. Based on experimental and clinical evidence suggestive of an effect of angiotensin-converting enzyme inhibitors (ACEI) and an angiotensin receptor blocker (ARB) on endothelial and renal function, the AHA recommends that hypertensive persons with diabetes be treated with ACEIs and ARBs to slow progression of diabetic nephropathy (83). In the subset of the Heart Outcomes Prevention Evaluation (MICRO-HOPE) study of 3,577 persons with diabetes and prevalent CVD events or additional cardiovascular risk factors, researchers compared the addition of an ACEI (ramipril) to the current medical regimen in this high-risk population. The results showed a 25% reduction (95% CI 12%–36%, p=0.0004) in the primary combined outcomes (myocardial infarction, stroke, and cardiovascular death) and a 33% reduction (95% CI 10%–50%, p=0.0074) in stroke. In addition, the number of diabetic complications, such as overt nephropathy, need for dialysis, or need for laser retinal therapy, was lower in persons on ramipril (89). The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) diabetes substudy of 11,935 persons with diabetes, hypertension (160–200/95–115 mmHg), and left ventricular hypertrophy compared an ARB (losartan) to a beta blocker (atenolol). After 4 years of follow-up, the effect on blood pressure reduction was similar between losartan and atenolol. In addition, there was a 24% reduction of major vascular events with losartan, while the reduction of stroke alone (21%) was nonsignificant (90). The effect of combination of an ACEI (perindopril) and thiazide diuretic (indapamide) versus placebo for prevention of microvascular and macrovascular outcomes, defined as a composite outcome of cardiovascular death, nonfatal stroke or myocardial infarction, and new or worsening renal disease or diabetic retinal disease in 11,140 persons with type 2 diabetes was assessed in the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial. After a mean of 4.3 years of follow-up, the relative risk of microvascular and macrovascular events was reduced by 9% (HR 0.91, 95% CI 0.83–1.00, p=0.04), but the relative reductions for macrovascular outcomes alone were nonsignificant, including the risk of stroke (91).

2016 ADA hypertensive therapy guidelines for persons with diabetes recommend a blood pressure target <140/90 mmHg, and antihypertensive agents of choice are ACEIs or ARBs, if there are no contraindications (88). Diabetic persons with documented albuminuria are also recommended to start ACEIs or ARBs. Once renin-angiotensin system modulators are initiated, close follow-up of renal functions and potassium levels is recommended (88).

DYSLIPIDEMIA

Dyslipidemia is a frequent comorbidity in persons with diabetes. Clinical evidence supports aggressive control of elevated plasma lipids in persons with diabetes to lower risk of all forms of CVD (83). No prospective, double-blind, placebo-controlled trials have specifically examined whether statin use might reduce the risk of recurrent stroke in persons with diabetes. However, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial found that persons with high risk for subsequent stroke, such as persons with prior stroke or any other risk factor (including diabetes), would benefit from initiation of high-dose statins at the time of discharge from the hospital (92).

Dyslipidemia Management

Based on strong clinical evidence, aggressive control of lipid levels and the use of statins in persons with diabetes are strongly recommended for primary prevention of CVD and stroke. CARDS enrolled 2,838 stroke- or CVD-free persons age 40–75 years with diabetes, LDL cholesterol ≤160 mg/dL (≤4.14 mmol/L), fasting triglycerides ≤600 mg/dL (≤6.78 mmol/L), and one additional vascular risk factor (retinopathy, albuminuria, current smoking, or hypertension), and randomized them to receive atorvastatin 10 mg per day or placebo. Stroke events occurred in 39 (2.8%) persons taking placebo and 21 (1.5%) taking atorvastatin (HR 0.52, 95% CI 0.31–0.89). There was a 48% reduction in stroke risk and a 27% reduction in mortality for atorvastatin compared to placebo. The authors concluded that persons with diabetes may be considered for treatment with statins to lower their risk of first stroke, even if their baseline LDL cholesterol was in the normal range (93).

A large meta-analysis of 14 randomized trials of statin use in the diabetic population, involving 1,466 subjects with type 1 diabetes and 17,220 subjects with type 2 diabetes, demonstrated a 21% reduction in stroke risk among diabetic persons on statins compared to persons not on statins (OR 0.79, 95% CI 0.67–0.93) (94). An exploratory analysis among subjects with diabetes (n=794) and the metabolic syndrome (n=642) from the SPARCL trial, which compared high-dose atorvastatin (80 mg/day) and placebo for secondary stroke prevention, found no difference in the effect of statin treatment in reducing vascular events in subjects with or without type 2 diabetes or the metabolic syndrome (95).

A 2013 report of the American College of Cardiology/AHA Blood Cholesterol guidelines advises high-intensity statin therapy for all persons with diabetes to achieve low LDL levels for primary and secondary prevention of all cardiovascular events (88,96,97); therefore, statin therapy is indicated for prevention of stroke in persons with diabetes.

GLYCEMIC CONTROL

Although tighter glycemic control may seem from observational data to be a reasonable approach for prevention of vascular events in persons with diabetes, several clinical trials have failed to demonstrate the effectiveness of tight glycemic control in preventing stroke. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial enrolled 10,251 persons with type 2 diabetes (mean age 62 years), with 10 years average duration of diabetes, and a mean A1c level of 8.1% (65 mmol/mol) at the start of the study. Participants were randomly assigned to two groups: intensive glucose control with A1c target levels of <6.0% (<42 mmol/mol) and standard glucose control with A1c target levels of 7.0%–7.9% (53–63 mmol/mol). The main objective was to determine by assessment of A1c levels the effect of intensive glucose-lowering strategies on cardiovascular outcomes in persons with type 2 diabetes. The study was halted in February 2008 due to an increased fatality rate in the intensive-control group. The data showed that after an average of 3.5 years of treatment (range 2–7 years), 229 of 460 total deaths were due to cardiovascular causes: 135 in the intensive-control group and 94 in the standard-control group. Approximately 10% of persons following the intensive regimen had experienced serious hypoglycemia that additionally explained the high rate of death due to CVD. Nevertheless, the intensive intervention regimen did not significantly reduce stroke risk, perhaps because of the small numbers (98).

The ADVANCE trial was launched in 2001 to evaluate the effect of lowering glucose to near-normal levels (comparing standard and intensive glucose-lowering targets) on microvascular and macrovascular outcomes, including stroke. A total of 11,140 participants with type 2 diabetes (mean age 66 years; mean duration of diabetes 8 years; mean A1c 7.2% [55 mmol/mol]) were randomized to two arms: a standard-control group with an A1c goal of 7.0% and an intensive-control group with an A1c goal of 6.3%. No significant difference was observed between the two arms with regard to macrovascular outcomes (including stroke) and all-cause mortality, but the intensive-control arm had more episodes of severe hypoglycemia (2.7% vs. 1.5%, p<0.001) (99).

In the Veterans Affairs Diabetes Trial (VADT), 1,791 military veterans (mean age 60.3 years) with poorly controlled type 2 diabetes and a mean A1c level of 9.5% (80 mmol/mol) at the start of the trial were randomly assigned to receive either intensive or standard glucose control. After a mean follow-up of 6.5 years, despite an average reduction in SBP and decrease in LDL, triglyceride, and A1c levels, no significant differences were found in the rates of major cardiovascular events (including stroke), death, or microvascular complications, with the exception of progression of albuminuria (p=0.01) (100).

The UKPDS is the largest primary prevention study in persons with newly diagnosed type 2 diabetes and the first study to design a model to estimate the risk of a first stroke in persons with diabetes. Among 4,549 participants, 188 persons experienced a stroke. Age, duration of diabetes, sex, smoking status, SBP, total cholesterol/HDL ratio, and presence of atrial fibrillation were the most frequent variables associated with the risk of stroke in this population (81). Intensive glucose control with sulfonylureas or insulin compared to diet therapy did not reduce the number of cardiovascular events in the same population (101). In the UKPDS substudy, despite equivalent glycemic control, fewer stroke events occurred in the metformin group compared to the sulfonylureas or insulin group (102).

The Diabetes Control and Complications Trial (DCCT) involved a young cohort (age 13–39 years) with type 1 diabetes and compared the effects of conventional treatment versus intensive blood glucose control on risk of diabetic complications over a mean follow-up of 6.5 years. The goal of intensive control was to attain and keep A1c levels at ≤6%. The A1c level achieved was 2% lower in the intensive-control group (average A1c 7.0% vs. 9.0% [53 vs. 75 mmol/mol]), but perhaps due to a small number of vascular events in this young cohort, no statistical difference was observed in stroke outcomes between the two groups during the randomized trial (103). The majority of persons in the DCCT were then followed for a mean of 17 years as part of an observational extension, the Epidemiology of Diabetes Interventions and Complications (EDIC) study. There were fewer vascular events (46 in the original DCCT intensive vs. 98 in the conventional treatment groups) and the risk of nonfatal myocardial infarction, stroke, and cardiovascular death was reduced by 57% in persons who received intensive glucose control during the DCCT (104).

In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive), the use of pioglitazone (a peroxisome proliferation-activated receptor [PPAR-γ] agonist) was evaluated in 5,238 persons with type 2 diabetes and macrovascular disease. No significant reduction was found in the primary endpoint of all-cause death or cardiovascular events (including ischemic stroke events) in persons randomly assigned to pioglitazone (HR 0.78, 95% CI 0.60–1.02) (105). However, in the subset of subjects with a history of prior stroke, pioglitazone was associated with a 47% relative risk reduction in the combined endpoint of recurrent fatal and nonfatal stroke (HR 0.53, 95% CI 0.34–0.85) with a 28% relative risk reduction in stroke, myocardial infarction, or vascular death (HR 0.72, 95% CI 0.53–1.00) (106).

The Insulin Resistance Intervention after Stroke (IRIS) trial examined the effectiveness of pioglitazone compared with placebo for prevention of recurrent stroke and heart attack among nondiabetic men and women with a recent ischemic stroke or TIA and insulin resistance. The trial found that pioglitazone reduced the risk of a stroke by 24% (107).

Based on the JNC 8, AHA, and ADA guidelines, recommendations for control of stroke risk factors for primary and secondary stroke prevention are presented in Table 19.3 (83,86,87,88,96). Clinical trial outcomes are summarized in Tables 19.4 (47,84,85,89,90,91,98,100, 101,103) and 19.5 (92,95,107).

ANTIPLATELET USE

In 2010, due to conflicting evidence about the efficacy of aspirin for primary prevention in people with diabetes, the ADA, AHA, and the American College of Cardiology Foundation (ACCF) changed their recommendations on antiplatelet use in persons with diabetes. It is now recommended that individuals with >10% 10-year risk of a cardiovascular event be offered aspirin for primary prevention. The ADA further specifies that this population includes the vast majority of men age >50 years and women age >60 years with one additional risk factor besides diabetes (88). However, in secondary stroke prevention, provided that no contraindication exists, all persons with diabetes and history of ischemic stroke should be taking an antithrombotic drug to reduce their risk of second stroke and other cardiovascular events (5,108).

TREATMENT OF CAROTID AND VERTEBRAL ARTERY DISEASE

Extracranial carotid and vertebral artery disease (ECVD) is common in persons with diabetes. In asymptomatic persons with carotid bruit, duplex ultrasonography is recommended as the initial test to detect hemodynamically significant carotid stenosis (109).

2011 AHA/American Stroke Association/ ACCF guidelines (109) on management of ECVD recommend diet, exercise, and antihypertensive, glucose-lowering, lipid-lowering, and antiplatelet agents as useful measures for persons with diabetes

TABLE 19.3. Risk Factor Management for Primary Prevention of Stroke in Persons With Diabetes

RISK FACTOR	RECOMMENDATIONS FOR THE GENERAL POPULATION	RECOMMENDATIONS FOR PERSONS WITH DIABETES
Hypertension	In addition to lifestyle changes, blood pressure goal is <140/90 mmHg (*Class I; Level of Evidence A*).	Based on the JNC 8: In the population age ≥18 years with diabetes and hypertension, initiate pharmacologic treatment to a goal SBP <140 mmHg and goal DBP <90 mmHg (*Expert Opinion*). Initial treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB) (*Moderate Recommendation*). In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB (*Weak Recommendation*). Based on AHA 2014 recommendations: A target of <140/90 mmHg is recommended in patients with type 1 or type 2 diabetes mellitus (*Class I; Level of Evidence A*). Based on ADA 2016 recommendations: Lower systolic targets, such as SBP <130 mmHg or DBP <80 mmHg, may be appropriate for certain individuals with diabetes, such as younger patients, those with albuminuria, and/or those with hypertension and one or more additional atherosclerotic cardiovascular disease risk factors, if they can be achieved without undue treatment burden.
Dyslipidemia	In addition to therapeutic lifestyle changes, treatment with an HMG coenzyme-A reductase inhibitor (statin) medication is recommended for primary prevention of ischemic stroke in patients estimated to have a high 10-year risk for cardiovascular events, as recommended in the 2013 "ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults" (*Class I; Level of Evidence A*).	Based on AHA/ASA 2014 recommendations: Treatment of adults with diabetes mellitus with a statin, especially those with additional risk factors, is recommended to lower the risk of first stroke (*Class I; Level of Evidence A*). Adding a fibrate to a statin in people with diabetes mellitus is not useful for decreasing stroke risk (*Class III; Level of Evidence B*). Based on ADA 2016 recommendations: For patients of all ages with diabetes and atherosclerotic cardiovascular disease, high-intensity statin therapy should be added to lifestyle therapy (*Level of Evidence A*). For patients with diabetes age 40–75 years without additional atherosclerotic cardiovascular disease risk factors, consider using moderate-intensity statin and lifestyle therapy (*Level of Evidence A*). The addition of ezetimibe to moderate-intensity statin therapy has been shown to provide additional cardiovascular benefit compared with moderate-intensity statin therapy alone and may be considered for patients with a recent acute coronary syndrome with LDL cholesterol ≥50 mg/dL (≥1.3 mmol/L) or for those patients who cannot tolerate high-intensity statin therapy.

Table 19.3 continues on the next page.

TABLE 19.3. (continued)

RISK FACTOR	RECOMMENDATIONS FOR THE GENERAL POPULATION	RECOMMENDATIONS FOR PERSONS WITH DIABETES
Atrial fibrillation	For patients with valvular AF at high risk for stroke, defined as a CHA_2DS_2-VASc score* of ≥2 and acceptably low risk for hemorrhagic complications, long-term oral anticoagulant therapy with warfarin at a target INR of 2.0–3.0 is recommended (*Class I; Level of Evidence A*). For patients with nonvalvular AF, a CHA_2DS_2-VASc score* of ≥2, and acceptably low risk for hemorrhagic complications, oral anticoagulants are recommended (*Class I*). Options include warfarin (INR 2.0–3.0) (*Level of Evidence A*), dabigatran (*Level of Evidence B*), apixaban (*Level of Evidence B*), and rivaroxaban (*Level of Evidence B*). The selection of antithrombotic agent should be individualized on the basis of patient risk factors (particularly risk for intracranial hemorrhage), cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including the time that the INR is in therapeutic range for patients taking warfarin.	Not different
Smoking	Counseling, in combination with drug therapy using nicotine replacement, bupropion, or varenicline, is recommended for active smokers to assist in quitting smoking (*Class I; Level of Evidence A*). Abstention from cigarette smoking is recommended for patients who have never smoked on the basis of epidemiologic studies showing a consistent and overwhelming relationship between smoking and both ischemic stroke and SAH (*Class I; Level of Evidence B*).	Not different
Obesity/diet	Among overweight (BMI 25–29 kg/m^2) and obese (BMI ≥30 kg/m^2) individuals, weight reduction is recommended for lowering blood pressure (*Class I; Level of Evidence A*). Among overweight (BMI 25–29 kg/m^2) and obese (BMI ≥30 kg/m^2) individuals, weight reduction is recommended for reducing the risk of stroke (*Class I; Level of Evidence B*).	Not different
Physical inactivity	Healthy adults should perform at least moderate- to vigorous-intensity aerobic physical activity at least 40 minutes per day, 3–4 days per week (*Class I; Level of Evidence B*).	Not different

Evidence class and level as defined by the American Heart Association: Class I, Evidence and/or general agreement that treatment is useful and effective; Class II, Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of treatment; Class IIa, Weight of evidence or opinion in favor of treatment; Class IIb, Usefulness/efficacy less well established by evidence or opinion; Class III, Evidence and/or general agreement that treatment is not useful/effective and may be harmful. Level A, Data from multiple randomized clinical trials; Level B, Data from a single randomized trial or nonrandomized studies; Level C, Expert opinion or case studies. ACC, American College of Cardiology; ADA, American Diabetes Association; AF, atrial fibrillation; AHA, American Heart Association; ASA; American Stroke Association; BMI, body mass index; CCB, calcium channel blocker; DBP, diastolic blood pressure; INR, international normalized ratio; JNC 8, Eighth Joint National Committee; LDL, low-density lipoprotein; SAH, subarachnoid hemorrhage; SBP, systolic blood pressure.

* $CHADS_2$ risk score assigns 1 point for **C**ongestive Heart Failure, **H**ypertension, **A**ge ≥75 years, and **D**iabetes Mellitus and assigns two points for a previous **S**troke or transient ischemic attack. CHA_2DS_2-VASc modifies $CHADS_2$ by adding an age category (1 point for age 65–74 years, 2 points for age ≥75 years) and adding 1 point each for diagnosis of vascular disease (such as peripheral artery disease, myocardial infarction, or aortic plaque) and for female sex.

SOURCE: References 83, 86, 87, 88, and 96

TABLE 19.4. Clinical Studies: Primary Stroke Prevention in Patients With Diabetes

STUDY, YEARS (REF.)	POPULATION	INTERVENTION	MAIN RESULTS
Blood pressure control studies			
Systolic Hypertension in the Elderly Program Cooperative Research Group Trial (SHEP), 1985–1991 (84)	Elderly population with type 2 diabetes and isolated hypertension	Low-dose diuretic with or without beta blocker or reserpine for CVD	20% reduction of stroke events with control of isolated systolic hypertension
United Kingdom Prospective Diabetes Study (UKPDS), 1977–1997 (85)	Newly diagnosed type 2 diabetes	Prospective observation	Every 10 mmHg reduction in systolic blood pressure reduced the risk of ischemic stroke by approximately 20%.
MICRO Heart Outcomes Prevention Evaluation Study (MICRO-HOPE), not reported (89)	High-risk patients with type 2 diabetes and coronary artery disease	Addition of an ACEI to any current medical therapy for CVD	Stroke reduction of 33%
Losartan Intervention for Endpoint Reduction in Hypertension Trial (LIFE), 1995–2001 (90)	High-risk patients with diabetes, severe hypertension, and left ventricular hypertrophy	Comparison of angiotensin receptor blocker (ARB) versus beta blocker on CVD	24% reduction of major vascular events with losartan; nonsignificant 20% reduction of stroke
Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation Trial (ADVANCE), 2001–2007 (91)	Type 2 diabetes	ACEI (perindopril) plus thiazide diuretic (indapamide) versus placebo for prevention of microvascular and macrovascular outcomes	9% of all vascular events; relative reductions for macrovascular outcomes alone, including the risk of stroke, were nonsignificant.

Table 19.4 continues on the next page.

TABLE 19.4. (continued)

STUDY, YEARS (REF.)	POPULATION	INTERVENTION	MAIN RESULTS
Lipid control study			
Collaborative Atorvastatin Diabetes Study (CARDS), 1997–2001 (47)	Type 2 diabetes, an LDL cholesterol level ≤160 mg/dL, plus one additional risk factor	Atorvastatin 10 mg/day or placebo for primary stroke prevention	48% reduction in stroke risk with atorvastatin
Glucose control studies			
Action to Control Cardiovascular Risk in Diabetes (ACCORD), 2001–2007 (98)	Type 2 diabetes, average duration 10 years, plus mean A1c 8.1%	Intensive glucose control with A1c target <6% versus standard glucose control with an A1c target 7.0%–7.9% for CVD and CVD mortality	No benefit of intensive glucose control was seen for stroke events. Trial was stopped due to increased mortality in the intensive arm.
Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), 2001–2007 (91)	Type 2 diabetes, average duration 8 years, plus mean A1c 7.2%	Intensive glucose control with an A1c target 6.3% versus standard glucose control with an A1c target 7.0% for microvascular and macrovascular outcomes	No difference was found between the two arms. Severe hypoglycemia was observed in the intensive arm.
Veterans Affairs Diabetes Trial (VADT), 2000–2008 (100)	Poorly controlled type 2 diabetes, plus mean A1c 9.5%	Intensive versus standard glucose control	No difference was found between the arms. Less progression to albuminuria was seen with intensive control.
United Kingdom Prospective Diabetes Study (UKPDS), 1977–1997 (101)	Newly diagnosed type 2 diabetes	Intensive glucose control with sulfonylureas or insulin versus diet therapy	Intensive blood glucose-lowering therapy reduced the risk of microvascular (retinal) disease but not of macrovascular disease, including overall stroke risk. The study did not separately assess the risks of small artery and large artery subtypes of stroke.
Diabetes Control and Complications Trial (DCCT), 1983–1993 (103)	Type 1 diabetes	Intensive glucose control with A1c ≤6.0% and glucose levels 70–120 mg/dL versus standard glucose control	No difference was found between the arms.

Conversions for A1c, cholesterol, and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; ACEI, angiotensin-converting enzyme inhibitor; CVD, cardiovascular disease; LDL, low-density lipoprotein.

SOURCE: References are listed within the table.

TABLE 19.5. Clinical Studies: Secondary Stroke Prevention in Patients With Diabetes

STUDY, YEARS (REF.)	POPULATION	INTERVENTION	MAIN RESULTS
Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial (SPARCL), 1998–2001 (92,95)	Patients with prior stroke and type 2 diabetes or the metabolic syndrome	Atorvastatin 80 mg/day or placebo for secondary stroke prevention	Atorvastatin did not show any effect on reduction of vascular events.
Insulin Resistance Intervention after Stroke trial (IRIS), 2005–2013 (107)	Patients with recent stroke/transient ischemic attack plus insulin resistance, but no diabetes	Pioglitazone 45 mg/day or placebo for secondary stroke prevention	Stroke reduction of 24%

SOURCE: References are listed within the table.

and *asymptomatic ECVD*. Whereas the efficacy of intensive glucose-lowering therapy to A1c <7.0% for reducing risk of stroke has not been established, aggressive management of elevated LDL cholesterol levels is recommended to lower risk of all CVD with the target LDL cholesterol ≤70 mg/dL (≤1.81 mmol/L) for persons with diabetes.

Selection of carotid revascularization via carotid endarterectomy (CEA) or carotid artery stenting (CAS) for asymptomatic and symptomatic carotid artery disease should be guided by the degree of stenosis, assessment of comorbid conditions, life expectancy, and individual surgical/procedural risk and should include a thorough discussion of the risks and benefits of the procedure and medical management with an understanding of patient preferences.

Asymptomatic carotid disease with <70% stenosis is uniformly treated with aggressive medical management and close surveillance with carotid ultrasound for disease progression. In selected patients with asymptomatic carotid disease with ≥70% stenosis and low perioperative risk for stroke, myocardial infarction, or death (<6%), CEA is readily offered, but mostly to patients with progression of carotid stenosis from mild-moderate to severe despite aggressive medical management. In the past

decade, this practice is becoming more controversial, and carotid revascularization in patients with asymptomatic high grade stenosis (>70%) is center-based and personalized based on response to aggressive medical management.

Persons who experience nondisabling ischemic stroke or TIA due to carotid artery disease are defined as symptomatic patients. Carotid revascularization is generally considered beneficial for symptomatic carotid disease with ≥70% artery stenosis as detected by carotid ultrasound or >50% as detected by catheter angiography. If perioperative risk for stroke, cardiac complications, and death is low (<6%), these patients should undergo CEA within 2–4 weeks of diagnosis, as most events occur early and the relative benefit from surgery continues to drop after this time. However, if the perioperative risk is high (≥6%), these patients should be considered for CAS.

Medical management and antiplatelet therapy are recommended before and after carotid recanalization. Noninvasive imaging at 1 month, 6 months, and annually to evaluate for restenosis is recommended for all patients who undergo CEA or CAS. Once patients are no longer candidates for revascularization, noninvasive surveillance of carotid artery can be terminated.

OTHER VASCULAR RISK FACTORS

Atrial fibrillation, peripheral vascular disease, and coronary artery disease are well-established risk factors for stroke in persons with and without diabetes, and each should be adequately treated (5,83).

DISEASE COURSE AND PROGNOSIS AFTER STROKE IN PERSONS WITH DIABETES

Diabetes is a common risk factor for incident stroke, as well as an independent risk factor for stroke recurrence. Diabetes adversely impacts stroke severity, survival (case-fatality) after stroke, cognitive function, and disability after stroke.

The Get With the Guidelines-Stroke program found a significant difference in stroke-related outcomes between persons with and without diabetes. Patients with diabetes had worse outcomes; they were less able to ambulate at discharge and were more likely to be discharged to a skilled nursing facility or an inpatient acute rehabilitation. The length of hospital stay for persons with diabetes was longer compared to patients without diabetes. The adjusted odds of in-hospital mortality were also elevated in persons with diabetes (OR 1.12, 95% CI 1.08–1.15). In a study of health-related quality of life, diabetes was found to be an independent risk factor for worse quality of life at 1-year post-stroke (110). Using data from the Vitamin Intervention in Stroke Prevention Study, Newman *et al*. evaluated >3,000 subjects over 1 year post-stroke; a sole diagnosis of diabetes was associated with worse outcomes on both the Mini Mental Status Examination (a measure of cognitive status) and modified Rankin Score (a measure of disability), suggesting that diabetes impacts cognitive and motor recovery in stroke survivors (111).

CONCLUSION

Diabetes is an independent risk factor for ischemic stroke. Persons with diabetes are equally at risk of having a small or large vessel ischemic stroke, and risks are higher among American Indian, black, and Hispanic persons compared to whites. Persons with diabetes who suffer a stroke have a higher risk of recurrent stroke and of mortality and morbidity. Stroke risk among persons with diabetes can be reduced through comprehensive control of cardiovascular risk factors and carefully monitored lifestyle interventions. Health care providers are encouraged to be vigilant in monitoring and treating elevated blood pressure and blood lipid levels. In addition, careful surveillance for asymptomatic vascular disease, such as carotid artery disease, coronary disease, and atrial fibrillation, and all well-established risk factors for stroke should be addressed promptly. All women age >60 years and men age >50 years with diabetes and an additional vascular risk factor should be offered antiplatelet therapy. Persons with diabetes who experience a stroke could benefit from targeted attention to ensure appropriate medical care and intense rehabilitation efforts to improve their outcomes following stroke.

Additional studies are needed to evaluate stroke risk in prediabetic states, to identify a biomarker profile that may predict stroke in persons with diabetes, and to examine new preventive and therapeutic interventions in these individuals.

LIST OF ABBREVIATIONS

A1c. . . . . .glycosylated hemoglobin
ACCF . . . . . .American College of Cardiology Foundation
ACEI. . . . . .angiotensin-converting enzyme inhibitor
ADA . . . . . .American Diabetes Association
ADVANCE . . . .Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial
AGE . . . . . .advanced glycation endproduct

LIST OF ABBREVIATIONS (continued)

AHA . . . . . American Heart Association
ARB . . . . . angiotensin receptor blocker
ARIC. . . . . Atherosclerosis Risk in Communities study
BMI . . . . . body mass index
CARDS. . . . . Collaborative Atorvastatin Diabetes Study
CAS . . . . . carotid artery stenting
CBI. . . . . covert brain infarct
CEA . . . . . carotid endarterectomy
CI . . . . . confidence interval
CRP . . . . . C-reactive protein
CT . . . . . computed tomography
CVD . . . . . cardiovascular disease
DAN . . . . . diabetic autonomic neuropathy
DCCT . . . . . Diabetes Control and Complications Trial
DWI . . . . . diffuse weighted imaging
ECVD . . . . . extracranial carotid and vertebral artery disease
eGFR . . . . . estimated glomerular filtration rate
FHS . . . . . Framingham Heart Study
GCNKSS . . . . . Greater Cincinnati/Northern Kentucky Stroke Study
HDL . . . . . high-density lipoprotein
HOMA-IR . . . . . homeostasis model assessment of insulin resistance
HR . . . . . hazard ratio
hsCRP . . . . . high sensitivity C-reactive protein
IGF-1 . . . . . insulin-like growth factor 1
IGFBP-1 . . . . . IGF binding protein 1
IRIS . . . . . Insulin Resistance Intervention after Stroke trial
JNC 8 . . . . . Eighth Joint National Committee
LDL . . . . . low-density lipoprotein
MRI . . . . . magnetic resonance imaging
NHANES . . . . . National Health and Nutrition Examination Survey
NHIS . . . . . National Health Interview Survey
NHS . . . . . Nurses' Health Study
NO . . . . . nitric oxide
NOMAS . . . . . Northern Manhattan Study
OR . . . . . odds ratio
OSA . . . . . obstructive sleep apnea
RAGE . . . . . receptor for advanced glycation endproduct
REGARDS . . . . Reasons for Geographic and Racial Differences in Stroke study
ROS . . . . . reactive oxygen species
RR . . . . . relative risk
SBP . . . . . systolic blood pressure
SPARCL. . . . . Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial
sRAGE . . . . . soluble RAGE
TIA . . . . . transient ischemic attack
UAC . . . . . urine albumin concentration
UACR . . . . . urine albumin-to-creatinine ratio
UKPDS. . . . . United Kingdom Prospective Diabetes Study
WMH . . . . . white matter hyperintensities

CONVERSIONS

Conversions for A1c, glucose, insulin, LDL cholesterol, and triglyceride values are provided in *Diabetes in America Appendix 1 Conversions.*

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