Part I

Overview Topics

1 Stroke Epidemiology

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EXAMPLE CASE

A 45-year-old right-handed African-American man residing in central North Carolina has a history of hypertension and presents with right-sided weakness without a language impairment and visual or sensory deficits. He also has a 50-pack-year history of cigarette smoking. His examination revels a body mass index (BMI) of 35, a blood pressure of 180/95 mm Hg, a regular pulse, no cervical bruits, and no cardiac murmur. His neurological examination is notable only for a right upper-motor neuron pattern facial paresis and 3/5 strength in his right arm and leg with depressed right-sided deep tendon reflexes and a right plantar-extensor response. A brain CT scan obtained 4 hours after symptom onset was normal. An EKG followed by a transthoracic echocardiogram showed left ventricular hypertrophy (LVH).

MAJOR POINTS

- Although overall stroke mortality rates have been rapidly declining, consistently higher rates remain among African-Americans (particularly between ages 45 and 65) and Southerners.
- Risk factors influencing stroke incidence can be stratified into two tiers:
  - Tier 1. Risk factors consistently identified as playing a major role
    - The "big three" risk factors contributing over half of the population attributable risk: hypertension, diabetes, and smoking
    - Others: left ventricular hypertrophy, atrial fibrillation, and heart disease
  - Tier 2. Risk factors likely playing a role
    - Risk factors for risk factors: obesity, fat distribution, and physical activities may have minor direct impact but play a major role by increasing the risk for hypertension and diabetes (tier 1 factors)
    - Risk factors important to control regardless of direct stroke risk: dyslipidemia and metabolic syndrome
    - Risk factors playing an important role in special populations: asymptomatic carotid stenosis, postmenopausal hormone therapy, and sickle-cell disease
    - Risk factors likely playing a smaller or questionable role.
- The "graying of America" is likely to have a major impact on the absolute number of stroke events in the next half-century, with an anticipated dramatic increase in the number of stroke events particularly among elderly women.

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Stroke mortality and its disparities

There are few US national data describing stroke incidence, and as a result, most of what is known about stroke epidemiology focuses on mortality rates. The age–sex-adjusted stroke mortality rates by race-ethnic group for the United States between 1979 and 2005 are shown in Figure 1.1. This figure reflects the remarkable successes and failures in stroke. During this brief 26-year period, stroke mortality has declined by 48.4% for African-Americans, by 52.9% for whites, and by 45.5% for other races [1] – a decline in a chronic disease that is simply striking. Along with similar reductions in heart disease mortality, this decline was acknowledged as one of the "Ten Great Public Health Achievements" of the 20th century (the only two achievements that were listed for a specific disease) [2].

This same figure, however, underscores one of the great failures in the 20th century – striking disparities by race. Using the year 2000 age standard, in 1979, African-Americans had an age-adjusted stroke mortality rate that was 30.8% higher than whites, whereas other races had a rate that was 26.7% below whites. This is in contrast to 2005, when African-Americans had stroke mortality rates 43.0% higher than whites, a relative *increase* of 39.6% ([43.0–30.8]/30.8) in the magnitude of the racial disparity in stroke deaths. This increase in stroke mortality among African-Americans persists despite the Healthy Persons 2010 goals (one of the guiding documents for the entire Department of Health and Human Services) having as one of its two primary aims "to eliminate health disparities among segments of the population, including differences that occur by gender, race or ethnicity, education or income, disability, geographic location, or sexual orientation" [3].

This figure obscures another disturbing pattern. The African-American–white differences in stroke mortality rates are three to four times (300–400%) higher between the ages of 40 and 60. These are attenuated with increasing age to become approximately equivalent above age 85 (see Figure 1.2) [4]. Data from the Greater Cincinnati/Northern Kentucky Stroke Study suggest that this excess burden of stroke mortality is primarily attributable to higher stroke incidence rates in African-Americans (rather than case fatality), and is uniformly shared between first and recurrent stroke, as well as between ischemic and hemorrhagic (both intracerebral and subarachnoid) stroke subtypes; all have incidence race ratios between 1.8 and 2.0 [5,6].

Another great disparity in stroke mortality is the "stroke belt" – a region in the southeastern United States with high stroke mortality that has persisted since at least 1940 (see Figure 1.3 [7]). Whereas the overall magnitude of geographic disparity is between

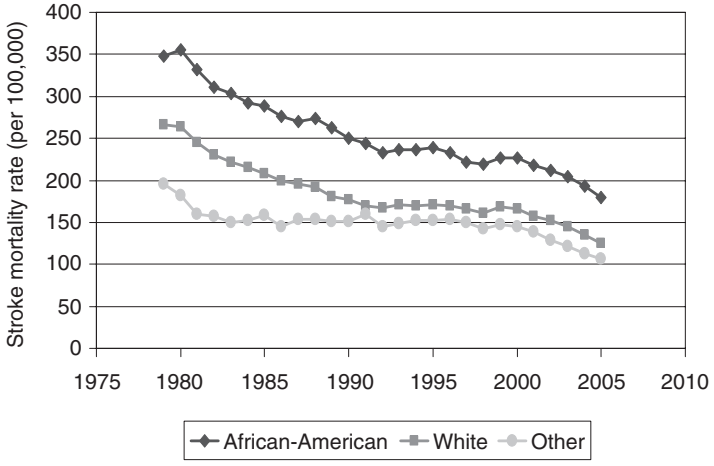

Fig. 1.1 Age-adjusted (2000 standard) stroke mortality rates for ages 45 and older, shown for African-American, white, and all other races. Data were retrieved from the Centers for Disease Control Wonder System [1], with ICD-9 codes 430–438 for years 1979–1998, and ICD-10 codes I60 to I69 for years 1999–2005.

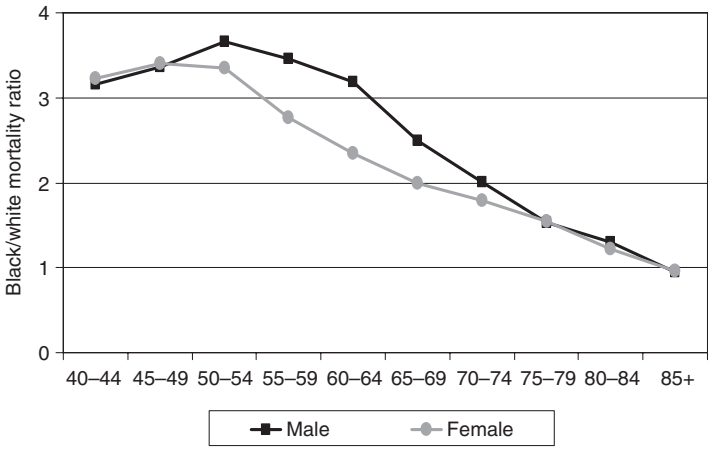

Fig. 1.2 African-American-to-white age-specific stroke mortality ratio for 2005 for the United States [4].

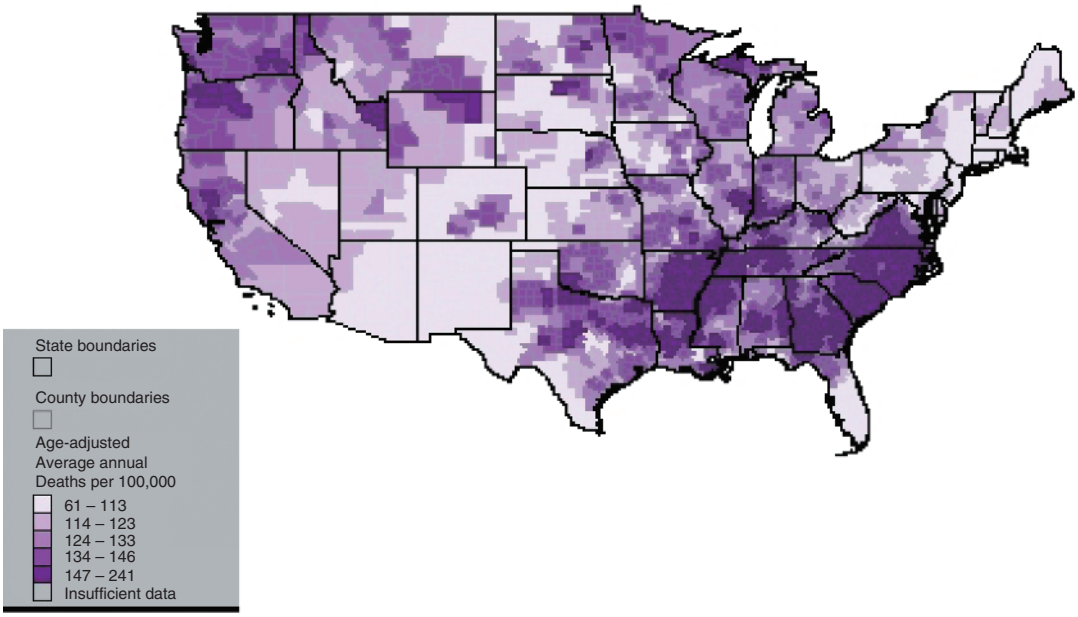

Fig. 1.3 Geographic pattern of stroke mortality rates between 1991 and 1998 for US residents aged 35 and older. Centers for Disease Control and Prevention, Stroke Atlas. www.cdc.gov/DHDSP/library/maps/strokeatlas/index.htm.

30% and 50%, this map shows that specific regions (such as the "buckle" region of the stroke belt along the coastal plain of North Carolina, South Carolina, and Georgia) have stroke mortality rates well over twice those of other regions. There are as many as 10 published hypothesized causes of this geographic disparity [8,9], but the reason for its existence remains uncertain. Finally, depending on sex and age strata, the magnitude of the southern excess stroke mortality is between 6% and 21% greater for African-Americans than for whites [10]. The example patient is at a higher risk of stroke and stroke mortality compared with Americans of other race-ethnic groups because he is an African-American and because he resides within the stroke-belt region of the country.

Stroke risk factors

The current American Heart Association/American Stroke Association Primary Stroke Prevention Guidelines provides a comprehensive review of

potential stroke risk factors with an extensive listing of references (offering a total of 572) [11]. A list of more than 30 separate risk factors and conditions reviewed in these guidelines is summarized in Table 1.1, along with classifications on the support for treatment and the level of evidence regarding the role of the factor in modifying stroke risk. Although the table is comprehensive, the goal of this section is to provide a more focused discussion within a framework that may be quickly considered by practicing clinicians. Any attempt to reorganize the listing provided in the guidelines should not be interpreted as minimizing the importance of any factor in an individual patient, but rather as helping to set priorities in a resource-limited environment.

The foundation of the approach to organize risk factors is to consider efforts to establish "risk functions" for stroke in which the factors are considered as independent predictors of stroke risk taken from the more comprehensive list. Although reported over 15 years ago, the most well known of these risk assessments is from the Framingham Study cohort in which independent stroke predictors included age, systolic blood pressure, use of antihypertensive medications, diabetes mellitus, current smoking, established coronary disease (any one of myocardial

Table 1.1 Summary of recommendations from the American Heart Association Guidelines for primary stroke prevention

Nonmodifiable

1 Age
2 Sex
3 Low birth weight
4 Race ethnicity
5 Genetic factors (IIb, C)

Well-documented and modifiable risk factors

1 Hypertension (I, A)
2 Cigarette smoking (I, B)
3 Diabetes (I, A)
4 Atrial fibrillation (I, A)
5 Other cardiac conditions
- Left ventricular hypertrophy (IIa, A)
- Heart failure (IIb, C)

6 Dyslipidemia (I, A)
7 Asymptomatic carotid stenosis (I, C)
8 Sickle-cell disease (I, B)
9 Postmenopausal hormone therapy (III, A)
10 Diet and nutrition
- Sodium intake (I, A)
- Healthy diet (DASH) (I, A)
- Fruit and vegetable diet (IIb, C)

11 Physical inactivity (I, B)
12 Obesity and body fat distribution (I, A)

Less well-documented or potentially modifiable risk factors

1 Metabolic syndrome (see individual components)
2 Alcohol abuse (IIb, B)
3 Drug abuse (IIb, C)
4 Oral contraceptive use (III, B/C)
5 Sleep-disordered breathing (IIb, C)
6 Migraine (ratings not provided, but considered "insufficient" to recommend a treatment approach)
7 Hyperhomocysteinemia (IIb, C)
8 Elevated lipoprotein (a) (IIb, C)
9 Elevated lipoprotein-associated phospholipase A_2 (absence of evidence)
10 Hypercoagulability (absence of evidence)
11 Inflammation (IIa, B)
12 Infection (absence of evidence)
13 Aspirin for primary stroke prevention (III, A)

DASH, Dietary Approaches to Stop Hypertension

Attempts were made to classify each potential risk factor on two scales (shown in the table as Roman numerals and letters). First, each was classified by the strength of evidence for a treatment approach into strata: I) conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective; IIa) conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment, but the weight of evidence or opinion is in favor of the procedure or treatment; IIb) conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment, and the usefulness/efficacy is less well established by evidence or opinion; and III) conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful. The second classification was on the level of evidence into strata: A) data derived from multiple randomized clinical trials; B) data derived from a single randomized trial or nonrandomized studies; or C) consensus opinion of experts.

infarction [MI], angina or coronary insufficiency, congestive heart failure, or intermittent claudication), atrial fibrillation, and LVH [12]. It is striking that this list of independent predictors was confirmed by perhaps the second best known of these risk functions, produced from the Cardiovascular Health Study, which included precisely the same list of risk factors (plus additional measures of frailty) [13]. Not accounting for age as a disease risk factor and considering systolic blood pressure and use of antihypertensive medications as one factor, that these two risk functions were concordant with the independent risk factors for stroke strongly suggests these six factors as "first-tier" risk factors for stroke (see Table 1.2). The example patient has a history of hypertension, an additional, modifiable, "first-tier" stroke risk factor.

The "population attributable risk" (the proportion of stroke events attributable to specific risk factors) is a product of both the magnitude of the impact of a risk factor and its prevalence in the at-risk population, and provides important insights to the contributions of these first-tier risk factors. The population attributable risk for major stroke types was recently reported from the Atherosclerosis Risk in Communities Study (Figure 1.4) [14] showing that the combination of hypertension, diabetes, and cigarette smoking contributes the great majority of

Table 1.2 A proposed structure for consideration for modifiable stroke risk factors

1 First-tier factors
- The "big three" factors (based on population attributable risk)
  a. Hypertension
  b. Diabetes
  c. Cigarette smoking
- Other first-tier factors
  a. Heart diseases
  b. Atrial fibrillation
  c. Left ventricular hypertrophy

2 Second-tier factors
- Risk factors for risk factors. Examples:
  a. Obesity and body fat distribution
  b. Physical inactivity
- Risk factors important to control (regardless of stroke risk). Examples:
  a. Dyslipidemia
  b. Metabolic syndrome
- Risk factors important in special populations
  a. Asymptomatic carotid stenosis
  b. Postmenopausal hormone therapy
  c. Sickle-cell condition
- Risk factors with a smaller effect or questionable effect (others)

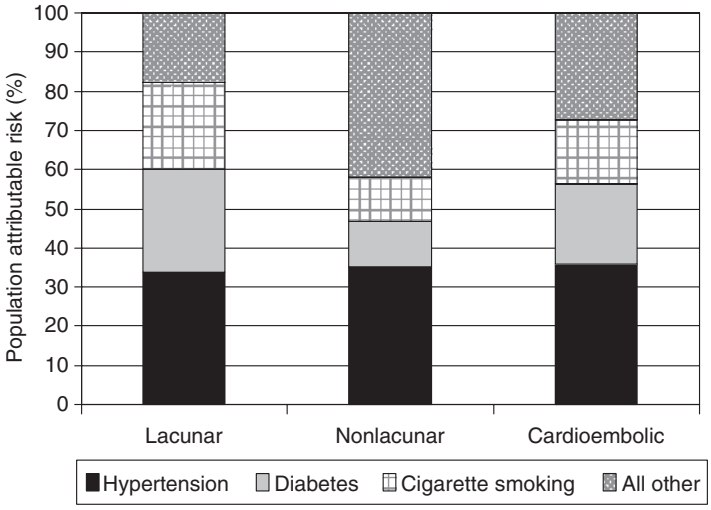

Fig. 1.4 Population attributable risk for major stroke subtypes of stroke from the Atherosclerosis Risk in Communities study for the "big three" risk factors and all others (including second-tier risk factors). Adapted from data available in Ohira *et al.* [14].

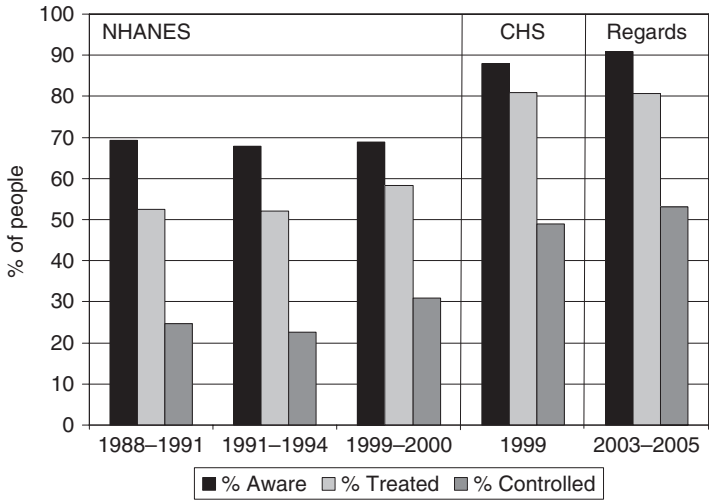

Fig. 1.5 Awareness, treatment, and control of blood pressure.
CHS, Cardiovascular Health Study; NHANES, National Health and Nutrition Examination Survey; REGARDS, Reasons for Geographic and Racial Differences in Stroke.

risk for lacunar (82%), nonlacunar (58%), and cardioembolic (73%) stroke. The substantial contribution of these three risk factors to stroke risk is underscored by the population attributable risk in the American Heart Association (AHA)/American Stroke Association (ASA) guidelines paper [11], which, while based on different studies, sums to more than 100% (i.e., more than 100% of the risk of stroke is attributed to different causes). The guidelines statement suggests that hypertension alone contributed between 30% and 40% of stroke risk, cigarette smoking between 12% and 18%, and diabetes between 5% and 27% [11]. Clearly, these three risk factors could be called "the big three" of the first tier. In addition to being an African-American residing in the stroke belt with a history of hypertension, the example patient smokes cigarettes, further increasing his stroke risk. His clinical syndrome is consistent with a "lacunar" syndrome.

As a clinician, it is not only important to treat specific risk factors in individual patients, but it is also important to think at the level of a group of patients (e.g., a practice) and allocate resources where they can have the greatest impact. Importantly, treatment approaches that will lead to substantial reductions in the overall burden of stroke would need to particularly target this "big three" cluster of risk factors. Although there have been some improvements in their management over time, the control of these risk factors remains suboptimal. For example, awareness, treatment, and control of high blood pressure in the National Health and Nutrition Examination Survey (NHANES) Study over the period 1988–1991 to 1999–2000, and from the Reasons for Geographic and Racial Differences in Stroke Study through 2003–2005, are shown in Figure 1.5 [15]. These data suggest that while there may have been an increase in awareness of hypertension from 70% to 90%, an increase in treatment from 52% to 80%, and an increase in control (to systolic blood pressure < 140 and diastolic blood pressure < 90) from 25% to 52%, approximately 50% of hypertensive individuals still fail to achieve control of their condition. Likewise, while there were substantial decreases in the prevalence of cigarette smoking from 1965 (with a prevalence of 51.2% in men and 33.7% in women) to 1990 (with a prevalence of 28.0% in men and 22.9% in women), the rate of decline substantially slowed in the 16 years between 1990 and 2005. The prevalence only decreased to 23.4% in men and to 18.3% in women – with one in every five adults remaining as active smokers [16]. We are also largely failing at adequate control of diabetes, for which between 35% and 50% of type 2 diabetics in the NHANES study had hemoglobin A1c values at or above 8% [17]. Although we know that impacting these "big three" risk factors would reduce stroke incidence by

more than 50%, interventions to manage these risk factors are not being optimally employed.

The other three "first-tier" risk factors – history of heart diseases, atrial fibrillation, and LVH – are as important (or perhaps even more important) in individual patients with these prevalent conditions [12,13]. The population prevalence of each of these conditions is lower, thereby making their overall contributions smaller. Also, it is clear that effective treatments exist for high-risk patients with atrial fibrillation using warfarin [18–20], although the standard treatments for LVH and previous heart disease are more complex. Hence, it could be suggested that a primary care physician could have the largest impact intervening on the "big three," but the awareness and treatment of individual patients who have these "other first-tier" risk factors remain important. The example patient also had LVH, possibly related to his history of hypertension.

Although non-first-tier risk factors should not be thought of as being unimportant, it is useful to use a different framework for their consideration. This framework includes thinking about these "other" risk factors in three classes.

There are several risk factors that do not directly impact stroke risk, but rather act as risk factors for one or more of the first-tier risk factors. For example, obesity is largely absent or has a relatively minor role in multivariable stroke risk models. In the Framingham and other studies, obesity is a potent risk factor for diabetes and carries an odds ratio 2.5 times greater for incident diabetes among participants with a BMI of 30 or greater [21]. In the Incidence of Hypertension in a French Working Population (IHPAF) study, obesity was the single greatest predictor of incident hypertension; individuals with a BMI above 30 had an odds ratio for incident hypertension 5.5 times greater for men and 2.8 times greater for women [22]. With obesity playing such a major role on the risk for two of the three "first-tier" stroke risk factors (and also having a relationship with atrial fibrillation and LVH), its absence in the major risk models should not be interpreted as reflecting a lack of importance, but rather as identifying obesity prevention and treatment as a point of intervention to reduce the major risk factors for stroke. A similar argument could be made for other non-first-tier stroke risk factors, most notably physical inactivity. The example patient had a BMI in the obese range – a factor that increased his chances of developing hypertension.

There are other non-first-tier risk factors for which treatment is critical for reasons that extend quite beyond protection from stroke. Examples of this class include treatments for dyslipidemia. With statin treatment, patients with coronary heart disease or additional risk factors such as hypertension or diabetes not only have a reduction in their risk of coronary heart events, but also a reduction in the risk of a first stroke [11]. In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial that assessed statin treatment for secondary stroke prevention among stroke/transient ischemic attack patients with a low-density lipoprotein level between 100 and 190 mg/dL, there was a 48% reduction (hazard ratio [HR] of 0.58) for subsequent coronary events in addition to a 16% reduction (HR of 0.84) in stroke events [23]. While in SPARCL there were more stroke than MI events, in most populations, the incidence of MI overwhelms that of stroke, and the impact of statin treatment is more powerful for coronary event prevention – suggesting that individuals with elevated lipid levels should be treated with statins almost regardless of their stroke risk. The interpretation of the role of the metabolic syndrome, a clustering of other well-documented cardiovascular risk factors, may also fall to this consideration.

There are also risk factors in special populations. For example, it is clear that surgical treatment of individuals with asymptomatic carotid disease will reduce stroke risk if the operation is performed safely; however, it is not clear whether (a) this is a risk factor for stroke or part of the causal pathway (i.e., hypertension and diabetes cause advancement of atherosclerosis that in turn causes stroke) and (b) treatment is warranted given the relatively small absolute risk reduction [24]. This is reviewed in the chapter on carotid surgery. A similar "special population" is the use of postmenopausal hormone therapy, which has been shown in three randomized trials to be associated with higher cardiovascular risk (including stroke) [25–27]. In all three of these studies, however, the risk of placing women on hormone therapy appeared to be associated with an early higher risk of thrombotic events, raising the question of the optimal treatment for women already on such treatment (who have already passed this high-risk period).

A number of other risk factors discussed in the AHA/ASA Primary Prevention Guideline have been documented in individual studies as potentially related to increased stroke risk [11]. Although their role in increasing stroke risk may be relatively smaller, and additional information may be needed to better understand their roles, the treating physician should be aware of each and consider them for treatment.

The projected future burden of stroke on the healthcare system

As noted earlier, the decline in stroke mortality, presumed to be at least partially attributable to declines in stroke incidence, has been a striking success [2]. Even assuming a continued decline in stroke incidence (perhaps a bold assumption), these declines are likely to be overwhelmed by the "graying of America" as reflected in the population pyramids shown in Figure 1.6. The year 2000 pyramid makes the "baby-boomer" bulge at approximately 45 years apparent – and it is noteworthy that this bulge is at the age when stroke risk is frequently considered to increase. Between 2000 and 2050, it is anticipated that the overall US population will grow by approximately 48% [28]. This "baby-boomer" bulge suggests that there will be a 109% growth among individuals aged 60–69, a 100% growth for individuals aged 70–79, a 196% growth for individuals aged 80–89, and a remarkable 569% growth for individuals over 90 [29]. With the risk of stroke approximately doubling with each increasing decade of age, these increases in the elderly population are likely to lead to more than a doubling in the number of stroke events before 2050 [30]. This increase in the number of persons having strokes, particularly among Hispanic and African-American populations, has been estimated to be associated with public health costs in excess of $2.2 trillion dollars over this period – $1.52 trillion for non-Hispanic whites, $313 billion for Hispanics, and $379 billion for African-Americans [30]. Unfortunately, the graying of America makes it likely that the absolute numbers of Americans having and being disabled by stroke will be increasing.

The example patient's stroke may have largely been preventable. Although he was an African-American residing in the stroke belt, lifestyle changes such as smoking cessation and weight loss would have lowered his risk. Effective control of his blood pressure would also be important as the stroke that occurred can be attributed to occlusion of a small intracranial artery, which is particularly sensitive to the effects of hypertension.

References available online at www.wiley.com/go/strokeguidelines.

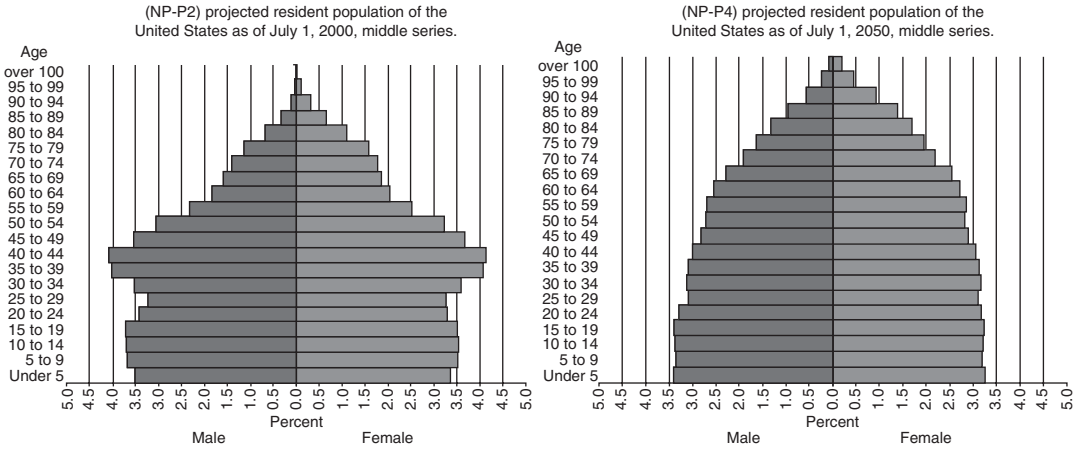

Fig. 1.6 Population pyramids for the United States in the year 2000 (left) and in the year 2050 (right).