Factors Influencing the Decline in Stroke Mortality

A Statement From the American Heart Association/American Stroke Association

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Background and Purpose—Stroke mortality has been declining since the early 20th century. The reasons for this are not completely understood, although the decline is welcome. As a result of recent striking and more accelerated decreases in stroke mortality, stroke has fallen from the third to the fourth leading cause of death in the United States. This has prompted a detailed assessment of the factors associated with the change in stroke risk and mortality. This statement considers the evidence for factors that have contributed to the decline and how they can be used in the design of future interventions for this major public health burden.

Methods—Writing group members were nominated by the committee chair and co-chair on the basis of their previous work in relevant topic areas and were approved by the American Heart Association Stroke Council’s Scientific Statements Oversight Committee and the American Heart Association Manuscript Oversight Committee. The writers used systematic literature reviews, references to published clinical and epidemiological studies, morbidity and mortality reports, clinical and public health guidelines, authoritative statements, personal files, and expert opinion to summarize evidence and to indicate gaps in current knowledge. All members of the writing group had the opportunity to comment on this document and approved the final version. The document underwent extensive American Heart Association internal peer review, Stroke Council leadership review, and Scientific Statements Oversight Committee review before consideration and approval by the American Heart Association Science Advisory and Coordinating Committee.

Results—The decline in stroke mortality over the past decades represents a major improvement in population health and is observed for both sexes and for all racial/ethnic and age groups. In addition to the overall impact on fewer lives lost to stroke, the major decline in stroke mortality seen among people <65 years of age represents a reduction in years of potential life lost. The decline in mortality results from reduced incidence of stroke and lower case-fatality rates. These significant improvements in stroke outcomes are concurrent with cardiovascular risk factor control interventions. Although

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it is difficult to calculate specific attributable risk estimates, efforts in hypertension control initiated in the 1970s appear to have had the most substantial influence on the accelerated decline in stroke mortality. Although implemented later, diabetes mellitus and dyslipidemia control and smoking cessation programs, particularly in combination with treatment of hypertension, also appear to have contributed to the decline in stroke mortality. The potential effects of telemedicine and stroke systems of care appear to be strong but have not been in place long enough to indicate their influence on the decline. Other factors had probable effects, but additional studies are needed to determine their contributions.

**Conclusions**—The decline in stroke mortality is real and represents a major public health and clinical medicine success story. The repositioning of stroke from third to fourth leading cause of death is the result of true mortality decline and not an increase in mortality from chronic lung disease, which is now the third leading cause of death in the United States. There is strong evidence that the decline can be attributed to a combination of interventions and programs based on scientific findings and implemented with the purpose of reducing stroke risks, the most likely being improved control of hypertension. Thus, research studies and the application of their findings in developing intervention programs have improved the health of the population. The continued application of aggressive evidence-based public health programs and clinical interventions is expected to result in further declines in stroke mortality. *(Stroke. 2014;45:00-00.)*

**Key Words:** AHA Scientific Statements ■ diabetes mellitus ■ hyperlipidemias ■ hypertension ■ risk factors ■ stroke

The remarkable decline in stroke mortality was acknowledged as one of the 10 great public health achievements for the United States in the 20th century. Along with the associated decline in ischemic heart disease mortality, stroke was one of the few diseases explicitly identified.1 This decline has continued over the past decade, and dropping stroke mortality was again identified as one of the 10 great public health achievements for the decade from 2001 to 2010.3 Stroke has now fallen from the third to the fourth leading cause of death in the United States.3–6

Although both stroke mortality and ischemic heart disease mortality have declined substantially, the patterns of their decline stand in stark contrast (Figure 1). In 1900, the numbers of deaths resulting from stroke and from diseases of the heart were approximately equal.5 Between 1900 and 1968, deaths resulting from stroke have shown a steady and (nearly) monotonic decrease, falling from >150 per 100000 to =50 per 100000. Stroke mortality declined slowly throughout most of the 20th century, at a rate of =0.5% per year. Then, in the 1970s, the rate of decline accelerated to =5% per year. This is in contrast to deaths resulting from diseases of the heart, in which there was a steady increase between 1900 and 1968, with the striking decline only since that time. Improvements in the International Classification of Diseases (ICD) coding system allowed the identification and reporting of deaths resulting from coronary heart disease starting in the mid-1950s. The differences in these patterns suggest that either shifts in the underlying risk factors with a differential impact on heart disease and stroke (eg, blood pressure [or atrial fibrillation (AF)], with a larger and more immediate impact on stroke than heart disease, to lipids with a larger impact on heart disease than stroke) or coding of deaths resulting from these diseases was changing over time.

Studies have suggested differential rates of decline in stroke mortality by race/ethnicity and sex. A study of race/ethnicity-specific trends in organ- and disease-specific mortality rates in the United States from 1996 to 2005 revealed that despite a 23% decline in age-adjusted stroke death rates, stroke remained the second leading cause of death in blacks.8 Among whites, however, the 26% decline in stroke age-adjusted death rates resulted in stroke moving from the second to the fourth leading cause of death after ischemic heart disease, lung cancer, and chronic lower respiratory disease (CLRD). Sex differences were also noted in that study. In men, stroke age-adjusted death rates fell by 28%, and stroke dropped from the third to the fifth leading cause of death after ischemic heart disease, lung cancer, accidents, and CLRD. Among women, although stroke age-adjusted death rates declined by 24%, stroke remained the second leading cause of death. In addition to disparities in rates of decline, the differences in rankings by sex and race/ethnicity were also attributable to differences in starting points, that is, the absolute rates, as well as competing causes of mortality. Gillum et al9 noted geographic differences in race/ethnicity-specific stroke mortality rates from 1999 to 2007, although overall rates declined in both blacks and non-Hispanic whites.

The Centers for Disease Control and Prevention WONDER (Wide-ranging Online Data for Epidemiologic Research) system1 and historical reports from the National Vital Statistics System (NVSS)3 can be used to describe these patterns of change in rates of death resulting from stroke. Figure 2 illustrates cerebrovascular mortality by mutually exclusive racial/ethnic groups between 1999 and 2010, showing that this decline in mortality continues to be shared by all in the United States (although potentially to different extents), as noted by Gillum et al.9 When data are available on temporal patterns in incidence10,11 and hospitalization rates,12 the data seem to reflect that these mortality declines are at least partly associated with the declining incidence of stroke.13 Thus, the trends in stroke mortality are influenced by the lower stroke incidence and improved case-fatality rates.

These remarkable declines in the United States must also be interpreted in the context of an associated worldwide decline in stroke documented primarily in Western countries.14–26 This statement assesses factors and interventions that have been
proposed to affect stroke mortality. The influence attributed to the different factors is described, and the potential contributions are quantified when possible.

Use and Limitations of Stroke Mortality and Ranking as an Indicator of Population Health and Risk

Mortality statistics commonly rely on sources such as the Compressed Mortality Files compiled by the National Center for Health Statistics and death certificate information on the underlying or single condition that is the most relevant cause of death. In assessing stroke mortality over time, it is important to note changes in the definition of stroke that might affect classification, advances in technology (such as the advent of imaging) that may affect diagnosis, revisions to the ICD, modification of the coding instructions within the ICD system, recognition of other competing causes of death, and changes in instructions on vital statistics coding from death certificates.

The NVSS is the most commonly used source for geographic and demographic mortality data in the United States. The classification and coding of cause of death listed on death certificates, including selection of the underlying cause of death, are based on the ICD. New versions of the ICD have been implemented nearly every decade since 1900 as medical knowledge has increased. Reclassification allows refinements to the coding system that account for advances in medical science and the discovery of new diseases. From 1968 to 1979, ICD, 8th Revision (ICD-8) was used; from 1979 to 1998, ICD, 9th Revision (ICD-9); and since 1999, ICD, 10th Revision (ICD-10). Changes in versions of the ICD can affect the interpretation of mortality trends over time.

The National Center for Health Statistics has produced reports documenting the comparability of different versions of the ICD for major disease categories. Comparability ratios can be applied to assess trends in mortality for a disease. This provides a more accurate assessment of the actual trend over time and corrects for changes in ICD versions. A comparability ratio of 1 for ICD-9 to ICD-10 for a disease would reflect that the change resulted in no increase or decrease of cases in the definition for that disease. A comparability ratio of >1 would imply that a coding change from ICD-9 to ICD-10 resulted in more cases of a particular disease attributable to the coding change alone in ICD-10 compared with ICD-9. The comparability ratio from ICD-8 to ICD-9 was 1.0049 for
cerebrovascular disease (ICD-8 and ICD-9 codes 430–438); the ratio from ICD-9 to ICD-10 was 1.0588 (ICD-9 codes 430–438 and ICD-10 codes I60–I69). According to the National Center for Health Statistics, this nearly 6% increase for cerebrovascular disease was due primarily to a coding rule change that moved many cases that would have been classified as pneumonia as the underlying cause of death in ICD-9 to cerebrovascular disease as the underlying cause of death in ICD-10.

One limitation of the use of NVSS data is the lack of detailed information in recording cause of death. For example, in 2008, of the 131 079 deaths resulting from cerebrovascular disease (I60–I69), 70 114 (53%) were coded as “stroke, not specified as infarction or hemorrhage” (I64), whereas only 6440 (5%) were identified as “cerebral infarction” (I63). Even among the 6440 deaths coded as “cerebral infarction” (I63), 3526 (55%) were coded as “cerebral infarction, unspecified” (I63.9), whereas only 912 (14%) were coded as “cerebral infarction due to thrombosis of cerebral arteries” (I63.3) and 895 (14%) were coded as “cerebral infarction due to embolism of cerebral arteries” (I63.4). This substantial lack of specificity implies that responsible reporting of stroke mortality statistics based on NVSS data must be limited largely to “cerebrovascular disease” (I60–I69), which not only will include deaths resulting from secondary causes associated with stroke but also limits the ability to assess whether changes in mortality are equally affecting deaths resulting from infarction versus hemorrhagic stroke. Similarly, changes in diagnostic technology and neuroimaging can affect stroke diagnosis, for example, the number of transient ischemic attacks (TIAs) that would be classified as minor strokes if all people with a TIA underwent neuroimaging as part of their workup.

In addition, a high error rate in the certification of cause of death on death certificates is well known. In the Reasons for Geographic and Racial Differences in Stroke Study (REGARDS), a comparison of cause of death in a cohort ≥45 years of age at baseline showed that stroke death based on death certificate and compared with physician adjudication had a sensitivity of 52% and a specificity of 99%. Similar work in the Cardiovascular Health Study (CHS) performed in an older cohort (all ≥65 years of age at baseline) showed that the sensitivity of nosologist-coded stroke with physician adjudication was 68%, whereas the specificity was 95%. With such a high specificity and lower sensitivity, it is possible that the number of deaths resulting from stroke may be systematically underreported. The reliability of vital statistics data depends on the accuracy of the death certificate, and inaccuracies are more likely to result from insufficient knowledge of the person’s medical history rather than from problems with the vital statistics coding system. However, whether there have been temporal changes in the coding of stroke is key to the interpretation of secular trends. To the best of our knowledge, the possibility of such a temporal change in the coding of deaths resulting from stroke has not been investigated except in a more recent period; however, it has been suggested that such changes are not present for coronary diseases.

Others, however, have raised the concern that such a temporal change in cause-of-death and hospital discharge coding may weaken efforts to accurately assess secular changes in causes of death.

Mortality rates are typically reported as age-adjusted death rates. The standard population for age adjustment from 1940 to 1999 was the 1940 standard population. Beginning in 1999, the standard population for age adjustment was the 2000 standard population. The population shift between 1940 and 2000 to a distribution with a greater proportion of elderly people in the population can produce very different results for mortality rates for cerebrovascular disease for identical years. In particular, the age-adjusted death rate for diseases associated with more deaths at advanced ages (eg, ischemic stroke) will tend to be substantially higher when standardized to the year 2000 population standard, which is used in this report. For example, the age-adjusted stroke death rate is 26.7 deaths per 100,000 standard population when the 1940 standard is used, but it is 63.9 when the year 2000 standard is used, which corresponds to a 2.4-fold difference.

Figure 3 includes similar stroke mortality trends with a different scale to clearly present the changes between years and time periods. In assessing the trend in stroke mortality, there has been an overall decline in stroke mortality from 1968 through 2010. The slight increase from 1998 to 1999 is reflective of the change from ICD-9 to ICD-10, but there has been a continued downward trend from 1999 through 2009. The changes from ICD-9 to ICD-10 have been modest compared
with the overall 50-year trend. In summary, a change in the ranking of a specific cause of death such as cerebrovascular disease over time is influenced by the comparability ratios for other diseases, the comparability ratio for cerebrovascular disease, and changes in classification and coding of other diseases over time. In addition, it is not clear to what extent increases in stroke mortality reflect poor quality of care or an increased appreciation for the role of patient preference in end-of-life decision making. Thus, it is possible that a steeper-than-appreciated decline in mortality is actually attenuated by an increasing trend toward palliative care in patients with severely disabling strokes.

**Recurrent and Incident Strokes as a Factor in the Decline of Stroke Mortality**

**Overview of Recurrence Rates**

Recurrent strokes represent 23% of the 800,000 strokes that occur each year in the United States and are associated with higher mortality rates, greater levels of disability, and increased costs compared with first stroke events. Recurrent stroke rates within the first year have been shown to range from 5% to 15%. The 30-day case-fatality rate is almost double for a recurrent stroke compared with the index stroke. Population-based epidemiological studies found that early mortality is more commonly related to the index or recurrent stroke, whereas later mortality is generally related to cardiovascular causes. Age appears to play a significant role in the cause of death after a recurrent stroke, with a greater proportionate mortality attributable to recurrent stroke rather than cardiac causes of death. This may be enhanced by the greater mean age; that is, older people are more likely to die as a result of the event than younger people are. The impact of index stroke on future events has led to the recommendation that ischemic stroke be included in cardiac risk assessment models and instruments because stroke survivors are at increased risk and are more likely to die of a cardiovascular event. It is important to note that the assessment of stroke mortality includes a mix of case fatality, in-hospital mortality, 30-day mortality, 1-year mortality, and other categories, with the definitions of mortality often varying across studies. Likewise, it should be noted the indicator of stroke occurrence as incidence, recurrence, and prevalence should be considered when assessing disease rates.

**Trends in Recurrence and Incidence Rates**

Recurrent stroke rates have been decreasing over time. Hong et al. using a novel approach to identify trends in recurrent stroke in the United States, found that recurrent stroke has declined substantially over the past 5 decades. Looking at the control arms of randomized, controlled trials of secondary stroke prevention interventions, they found that event rates for recurrent stroke and fatal stroke declined each decade from 1960 to 2009, with an almost 50% reduction in recurrent stroke rates in the 1990s and 2000s compared with the 1960s. A systematic review of 13 studies from hospital- or community-based stroke registries found a temporal reduction in 5-year risk of stroke recurrence from 32% to 16.2% but reported substantial differences across studies in terms of case mix and definition of stroke recurrence. Studies examining temporal trends in recurrent events are limited but also report decreases in recurrent events over time. Data from the initial cohort from the Framingham Heart Study (FHS) beginning in 1949 and followed up for 26 years showed a recurrent stroke rate of 28% among survivors, including second and third strokes. The 5-year cumulative recurrence rate was 42% for men and 24% for women. Results from epidemiological studies have shown a decline in first-ever stroke rates, with 20% to 40% of the decline attributed to the improvement of risk factor control. Similar and even greater reductions are associated with recurrent stroke rates. As with first strokes, the risk of recurrent stroke is affected by differences in geography, race/ethnicity, socioeconomic status, and type of care.

Clinical trials completed over the past 5 decades have demonstrated the benefit of secondary stroke prevention therapies. Evidence from these trials has demonstrated secondary stroke prevention benefits from vascular prevention therapies, including antihypertensive therapy, statins, and aspirin. The decrease in recurrent stroke through improved blood pressure control, increased use of antplatelet and anticoagulant medications and statins, and decreased smoking rates has been found by others to be associated with a decrease in coronary heart disease during the period from 1980 to 2000. Because people participating in clinical trials may not be representative of the general population, some caution should be urged in the generalization of these findings to the broader population. Further improvements in secondary prevention could reduce recurrent vascular events in stroke patients by as much as 80%. These findings suggest that a significant proportion of recurrent strokes can be prevented. It is important to recognize stroke in secondary prevention as a manifestation of multiple heterogeneous disorders, including cardioembolism, small-vessel disease, and large-artery atherosclerosis. Clinical trial evidence from Stenting Versus Aggressive Medical Therapy for Intracranial Arterial Stenosis (SAMMPRIS) compared with the Warfarin-Aspirin Symptomatic Intracranial Disease Trial (WASID) indicated a reduction of secondary stroke risk with aggressive medical management in patients with intracranial atherosclerotic stenosis. Results from the Secondary Prevention of Small Subcortical Strokes (SPS3) study identified a declining risk of recurrence of small-vessel disease compared with expected rates estimated from natural history studies, and findings from the prospective Oxford Vascular Study demonstrated declining risk of stroke caused by carotid stenosis. These decreases in secondary stroke would likely contribute to the decline in stroke mortality.

A systematic review of worldwide stroke incidence studies from the 1970s through 2008 found that the age-adjusted stroke incidence rates in high-income countries declined 42% overall with declines in each subsequent decade of the study. These trends were found across age groups, with a greater decline in those ≥75 years of age. They also noted that the early (up to 1 month) case-fatality rate declined in high-income countries, but incidence and case fatality increased in low- to middle-income countries. Data from the FHS showed significant declines in stroke incidence in both men and women when 3 time periods were compared (1950–1977, 1978–1989,
and 1990–2004). It was also noted that 30-day case fatality declined significantly in men but not women. The Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS) reported that the annual incidence of strokes declined in 2005 compared with 1993 to 1994 and 1999 among whites but not blacks. The GCNKSS also found no change in the incidence of intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) or in case-fatality rates across the study periods.13

Stroke incidence rates over time are subject to changes in the clinical definition of stroke and influenced by changes in technology that refine the diagnosis of stroke. Leary and Saver44 estimate that in 1998, ≈770,000 people experienced a symptomatic stroke and 11 million experienced an asymptomatic stroke. These changes would also affect rates of recurrent stroke over time, but the effect of that bias is unclear. Likewise, it is important to recognize the impact of silent stroke, which is estimated to be between 5% and 28% on the basis of magnetic resonance imaging scans.85,86 The rates of silent stroke vary by hypertension and smoking status, with highest rates in the older population.87 Similarly, diffuse white matter disease affects a high proportion of the elderly with a mix of vascular and Alzheimer pathology.88 It is thus important to recognize that silent stroke and diffuse white matter disease are aspects of cerebrovascular disease with major effects on risk of cognitive impairment and dementia contributing to mortality in the aging population. Stroke severity is an important influence on stroke mortality and, with occurrence, affects overall rates. The different risk factors associated with stroke mortality reduce stroke occurrence separately from those factors that influence mortality once a stroke has occurred.89 Thus, factors can be categorized in reducing stroke occurrence, stroke severity, or both, with different effects on mortality. For example, antplatelet therapy and antihypertension therapy have different impacts on reducing stroke occurrence and stroke severity.90

Increased application of advanced neuroimaging such as magnetic resonance imaging might improve the diagnosis of milder, less fatal strokes over time. This would result in an apparent decline in the stroke case-fatality rate, solely as a result of improved detection. However, this should not result in a change in stroke mortality over time unless technological advances improve the diagnosis of more severe, fatal strokes also, which seems unlikely. Likewise, stroke subtype is a major consideration. For example, the incidence of ICH increases with age and did not decrease between 1980 and 2006.91,92 Thus, future studies should include and address the different subtypes of stroke and corresponding stroke severity.

In summary, the evidence suggests that there has been a decline in recurrent stroke and a possible decline in stroke incidence. This may be more pronounced by sex and in certain racial/ethnic groups. The trends in the declining rate of recurrent stroke and stroke mortality seem to follow similar timelines, suggesting that secondary stroke prevention strategies may have impacted overall stroke mortality rates for both outcomes. The exact proportion of the stroke mortality decline that can be attributed to recurrent stroke is unclear and requires additional studies and trials specific to recurrent stroke. Although stroke systems of care have improved the initiation of medications for secondary stroke prevention during hospitalization, there are currently no nationwide systematic efforts aimed at ensuring control of risk factors after stroke.

### Changes in Pulmonary and Lung Disease on the Assessment of Stroke Mortality

#### Trends and Ranking

From 1979 to 1999, the mortality rate for CLRD increased at a slow but steady rate and then showed a minimal decline from 2000 to 2008.93,94 Mortality rates for CLRD again declined in 2009 and in the preliminary mortality data for 2010.94,95 In contrast, stroke mortality rates have declined steadily over the past 100 years, particularly in the past 50 years, and at a much faster rate than for CLRD mortality (Figure 4). These mortality trends for CLRD and stroke resulted in a change in the ranking of causes of death. Stroke, which had been the third ranking cause of death, fell to the fourth ranking cause of death, whereas CLRD rose from the fourth to the third ranking cause of death. It should be noted that coding changes in both stroke and CLRD played a small role in the shift in causes of death. In 2008, there was a coding change that moved many cases not previously classified as CLRD into the CLRD classification. CLRD includes ICD-10 codes J40 through J47. The following conditions were re-coded to J44.0 (chronic obstructive pulmonary disease with acute lower respiratory infection).

![Figure 4. Age-adjusted death rates for cerebrovascular disease and chronic lower respiratory disease by year: United States, 1979 to 2010.](https://stroke.ahajournals.org/doi/10.1161/01.STR.0000465337.94324.4a)
in 2008: pneumonia (J12–J16, J18), other acute lower respiratory infections (J20–J22), and unspecified chronic obstructive pulmonary disease (J44.9). Therefore, the mortality rates for CLRD through 2007 may not be comparable with rates from 2008 and beyond. According to the NVSS, stroke mortality rates declined 3.6% from 2007 to 2008, whereas mortality from CLRD increased 7.8%. The mortality rates for both stroke and CLRD declined from 2008 to 2009 and from 2009 to 2010 (preliminary data), with slightly greater declines in stroke than in CLRD. Also in 2008, a coding change resulted in some deaths that would have previously been coded as SAH (ICD-10 I60) reassigned to vascular dementia (ICD-10 F01). The age-adjusted mortality rate for SAH declined from 1.81 in 2007 to 1.73 in 2008 and 1.68 in 2009. The mortality changes resulting from ICD-10 coding changes in 2008 were followed by similar declines in both CLRD and stroke mortality based on mortality data for 2009. Despite an aging population, the actual numbers of stroke deaths have declined each year since 2000, whereas the numbers of actual deaths resulting from CLRD fluctuated during this time. Mortality data showed a similar decline in total deaths resulting from stroke and CLRD from 2008 to 2009. These more recent changes in the ranking causes of death for stroke and CLRD may be because the current rate of decline in stroke mortality has slowed over the previous 5 years and the mortality rate from CLRD has shown little decline since 2000. Both conditions are sensitive to tobacco use, which is discussed in another section of this review.

A recent study assessed whether there had been changes in mortality attribution methods over time that might explain the recent change in ranking of causes of death for stroke and CLRD when data from the death certificates were used. Determinations of disease-specific mortality rely on a complex and annually reevaluated algorithm to select the “underlying cause of death” from the up to 20 causes listed on a death certificate. Therefore, systematic changes in the classification of stroke as the underlying cause of death could occur through changes in the underlying algorithms or changes in death certificate completion patterns. In an analysis by Burke et al., mortality data from 2000 to 2008 were used to compare changes in reporting of stroke as the underlying cause of death with changes in death certificates reporting any mention of stroke. Similar comparisons were also made for the 6 leading organ- and disease-specific causes of death, including CRLD. If stroke mortality were underestimated by the system of mortality attribution, a greater decline in stroke as an underlying cause of death relative to any mention of stroke on the death certificate would have occurred. The authors found that age-adjusted death rates both for stroke as an underlying cause of death and for stroke mentioned anywhere on the death certificate declined by 33% from 2000 to 2008 and that the ratio of these death rates for stroke did not change over time (0.595 in 2000 versus 0.598 in 2008). Changes in the same ratio for CRLD were too small (from 0.49 to 0.52) to explain the decline in the ranking of stroke as the third leading cause of death. The authors concluded that, based on the data, changes in mortality attribution methodology are likely not responsible for the decline.

In summary, there have been significant changes in chronic obstructive pulmonary disease risks during the study period. However, these changes in lung disease do not offset or diminish the decline in stroke mortality. It will remain important to consider the epidemiology of chronic obstructive pulmonary disease in future research and surveillance studies.

Hypertension as a Factor in the Decline in Stroke Mortality

The association of blood pressure levels and risk of stroke was first recognized by the Society of Actuaries in the 1920s. In 1960, early clinical studies identified clear benefits of lowering blood pressure on reducing stroke deaths. In the Veterans Administration clinical trials for those with severe hypertension (diastolic blood pressure [DBP] 115–129 mmHg), the effect was dramatic. After just 18 months, those who received placebo were having strokes at such an increased rate that the trial was stopped and all participants were given antihypertensive drugs. The results of other blood pressure–lowering clinical trials were published, showing a consistent pattern of benefit (section on clinical trials). The evidence for the benefits of lower blood pressures and reduced stroke risks is strong, continuous, graded, consistent, independent, predictive, and pathogenically significant for those with and without coronary heart disease. This information was used to launch and then implement on a long-term basis the National High Blood Pressure Education Program (NHBPEP) about the benefits of treating hypertension among the public, patients, and physicians. The messages were heard; hypertension screenings increased and physicians began treating patients. Hypertension has become the most common primary diagnosis in America, and antihypertensive medications are among the most commonly prescribed. Thus, the lowering of high blood pressure (HBP) is proposed as a major factor for the reduction in stroke death rates during the last half of the 20th century and the early part of the 21st century. Specifically, the US age-adjusted stroke mortality rate reduction from 88 per 100,000 in 1950 to 23 per 100,000 in 2010, with consistent reductions in mortality rates for all age, racial/ethnic, and sex groups in the United States, as well as other countries, is consistent with HBP recognition and reduction campaigns initiated during the same period. These blood pressure reduction strategies included clinical interventions for hypertension and public health efforts focused on lifestyle for the shifting of blood pressure distributions. Although the decline in stroke mortality in the United States started at the beginning of the 20th century, decades before hypertension treatment, the slope of the decline in mortality accelerated significantly after the introduction of tolerable antihypertensive drug therapy in the 1960s. It has been suggested that the slight decline in stroke mortality in the first half of the 20th century is a statistical aberration, perhaps associated with classification and attribution methodology.

Epidemiological studies have shown that elevated blood pressure is the most important determinant of the risk of stroke. The risk is almost linear, beginning at relatively low levels of systolic blood pressure (SBP) and DBP. Risk factors for HBP such as obesity, increased waist circumference, higher
alcohol intake, and greater sodium intake are also associated with increased risks for stroke. It is estimated that the overwhelming majority of strokes each year could be prevented through awareness, optimal management of hypertension, and lifestyle changes to healthier diet, greater physical activity, and smoking cessation. These factors plus waist-to-hip ratio account for 82% and 90% of the population-attributable risk for ischemic stroke and hemorrhagic stroke, respectively.

Prevalence of HBP and Blood Pressure Distribution

Most recent estimates from the National Health and Nutrition Examination Survey (NHANES) identify ≥68 million Americans with HBP who warrant some form of monitoring or treatment. Global hypertension prevalence estimates of 1 billion people with an estimated 7.1 million deaths per year may be attributable to hypertension. As the population ages, the number of people with elevated blood pressure increases. The substantial and increasing prevalence of elevated blood pressure, combined with the evidence-based benefit of hypertension treatment, has led to the prioritization of prevention and control programs among federal, professional, and voluntary agencies. In the past, considerable success has been achieved in meeting the goals of these programs. The percentage of patients with hypertension receiving treatment has increased to the point where >90% of the population know the relationship between HBP and stroke, nearly 70% of the adult hypertensive population are receiving treatment, and 46% of those treated have their blood pressure controlled to <140/90 mm Hg. The mean SBP for the US adult population declined from 131 mm Hg in 1960 to 122 mm Hg in 2008. (Table). Figure 5 presents the smooth weighted frequency distributions of SBP from national population-based surveys, including the National Health Examination Surveys and NHANES I, II, III, and 1999 to 2010. Between 1959 and 2010, the median and 90th percentile SBP declined by 16 mm Hg. This declining shift in blood pressure distributions was consistent for different age groups, including age 18 to 29, 30 to 59, and 60 to 74 years (Figure 5). These population-wide changes in reduced blood pressures seen within the past 5 decades have been associated with the large accelerated reductions in stroke mortality. The shift in mean arterial blood pressure is more pronounced in older Americans, who have a greater prevalence, who are more likely to visit their physician, and who are receiving blood pressure treatment, than in younger people, although they may be less likely to achieve their goal blood pressure. This suggests that there is an opportunity to reduce stroke rates even further. Goff et al described a gradual downward shift of the entire distribution of blood pressure levels in the general population, going back to the early 1900s, suggesting one of the few risk factors for which documentation of such a long-term change could contribute to the beginning of the decline in stroke mortality over the same century. The identification and recognition of elevated blood pressure as a risk factor appears to have affected blood pressure levels and subsequent stroke mortality risks. Although the decline in stroke mortality and lowering blood pressure may have appeared to be evident before the recognition and treatment of hypertension, the effects of lowered blood pressure are most evident after the population-based campaigns. Hypertension treatment and control rates have consistently increased since the early 1970s. Although there are age, race/ethnicity, and sex disparities, this improvement is seen in all subsets of the population. Further demonstrating the impact of treatment, SBP is lower in people with treated hypertension than in those with untreated hypertension for all groups. All populations have shown significant improvements during the period. Likewise, a reduction in mean SBP has been observed for all age, race/ethnicity, and sex groups. Ninetieth percentile SBP levels have been lowered over the past decades, suggesting a significant impact of hypertension treatment and control. Similarly, the 10th percentiles have also been lower through the past years (Figure 5). The reduction in these blood pressure levels is most likely the result of lifestyle and nonpharmacological interventions and public health activities.

Although pharmacological treatment of blood pressure focuses on people with hypertension, currently defined as blood pressure >140/90 mm Hg, epidemiological data demonstrate that the risk of stroke begins at blood pressure levels <140/90 mm Hg. In a meta-analysis of 61 prospective, observational studies conducted by Lewington et al that involved 1 million adults with no previous vascular disease at baseline, researchers found that in people between the ages of 40 and 69 years, beginning with SBP of 115 mm Hg and DBP of 75 mm Hg, each incremental rise of 20 mm Hg in SBP and 10 mm Hg in DBP was associated with a 2-fold increase in death rates from stroke. This effect is seen in all decades of life.

In addition, an age-related rise in SBP is primarily responsible for an increase in both the incidence and prevalence of hypertension. Furthermore, FHS investigators reported the lifetime risk of hypertension to be ≥90% for men and women who were nonhypertensive at age 55 or 65 years and survived to age 80 to 85 years. Thus, if people live long enough, virtually all will become hypertensive. Even after adjustment for competing mortality, that is, death resulting from other causes that would preclude death resulting from hypertension, the remaining lifetime risks of hypertension were 86% to 90% in women and 81% to 83% in men. Such lifetime risk estimates can be used in calculating the impact of blood pressure reduction for stroke mortality declines. The increase in blood pressure to hypertensive levels with age is evident from patterns and trends indicating that the 4-year rates of progression to hypertension are 50% for those ≥65 years of age with blood pressure in the 130/85 to 139/89 mm Hg range and 26% for those with blood pressure of 120/80 to 129/84 mm Hg.

Table. Mean Systolic Blood Pressure by Time Period

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Systolic Blood Pressure, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960–1962</td>
<td>131</td>
</tr>
<tr>
<td>1971–1974</td>
<td>129</td>
</tr>
<tr>
<td>1976–1981</td>
<td>126</td>
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<td>1988–1991</td>
<td>119</td>
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<td>1988–1994</td>
<td>121</td>
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<tr>
<td>1999–2004</td>
<td>123</td>
</tr>
<tr>
<td>2001–2008</td>
<td>122</td>
</tr>
</tbody>
</table>

Source: National Health and Nutrition Examination Surveys I through IV.
Figure 5. Smoothed weighted frequency distribution, median, and 90th percentile of systolic blood pressure: United States, 1959 to 2010. A, Age 18 to 29 years. B, Age 18 to 59 years. C, Age 30-59 years. D, Age 60-74 years. NHANES indicates National Health and Nutrition Examination Survey; and NHES, National Health Examination Surveys.
As indicated, the reduced stroke mortality rates are evident in all categories of hypertension and blood pressure levels. Great benefits of blood pressure reduction are evident in the malignant or severe category of elevated blood pressure levels. These extreme blood pressure levels are more prevalent among the high-stroke-risk populations, especially blacks, but the values have been reduced with treatment with corresponding risk reduction. However, hypertension emergencies, crises, and malignant hypertension represent a small percentage of the population with HBP. Up to 2% of patients with hypertension develop a hypertensive crisis at some point in their lifetime. Thus, the lowering of these extreme HBP levels has an impact on the decline of stroke mortality but should be considered less of a contributor to overall stroke mortality decline because there are relatively fewer patients with this condition.

Observational Studies
CoHORT studies have demonstrated increased attributable risks associated with elevated blood pressure levels. HBP was identified as being responsible for the largest number of cardiovascular and stroke deaths in the United States. The INTERSTROKE study concluded that the contribution of various risk factors to the burden of stroke worldwide was 34.6% for hypertension (95% confidence interval [CI], 30.4–39.1). In addition, it was estimated that among people with treated hypertension, 45% of all strokes might be attributed to uncontrolled blood pressure. Such risk estimates are consistent for all components of the population with significant population-attributable risk for elevated blood pressure and stroke mortality. The relationship between blood pressure and risk of cardiovascular disease (CVD) events is demonstrated over time, continuous, consistent, and independent of other risk factors. The linear relationship holds true for all demographics, indicating that the higher the blood pressure, the greater the risk of stroke mortality.

Clinical Trials
The benefit of hypertension treatment to reduce stroke risks is evident with the effective number-needed-to-treat estimates. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) states:

In clinical trials, antihypertensive therapy has been associated with reductions in stroke incidence averaging 35–40 percent; myocardial infarction, 20–25 percent; and heart failure, more than 50 percent. It is estimated that among patients with stage 1 hypertension (SBP 140–159 mmHg and/or DBP 90–99 mmHg) and additional cardiovascular risk factors, achieving a sustained 12 mmHg reduction in SBP over 10 years will prevent 1 cardiovascular event for every 11 patients treated. In the presence of CVD or target organ damage, only 9 patients would require such BP reductions to prevent a death.

Clinical trials have demonstrated that control of isolated systolic hypertension reduces total and stroke mortality. Reducing SBP even if blood pressure control levels are not achieved improves risk and outcomes. In the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) Trial and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), DBP control rates exceeded 90%, but SBP control rates were considerably less (60%–70%).

Data from the Hypertension Detection and Follow-up Program showed that declines of 4.7 mmHg reduced stroke mortality by 17.6%. Numerous other trials have provided evidence of hypertension treatment with blood pressure reduction and subsequent reduced stroke risks. The trials included placebo, comparison, and efficacy designs, with similar results indicating a benefit of blood pressure reduction and stroke risks. The studies also included different ages and races/ethnicities and both sexes, as well as different time periods, with consistent findings of stroke risk reduction with hypertension treatment. Furthermore, a recent meta-analysis of 32 randomized trials confirmed treatment of hypertension in reducing stroke risks. Another meta-analysis reported substantial stroke risk reduction with tight blood pressure control and lowered blood pressure levels. Likewise, a meta-analysis of 147 trials determined a 41% reduction in stroke risks with SBP reductions of 10 mmHg. Another overview of evidence from observational epidemiological studies and randomized, controlled trials determined that an average reduction of 12 to 13 mmHg in SBP over 4 years of follow-up was associated with a 37% reduction in stroke mortality. Although there remain some questions about the specific blood pressure treatment levels for stroke reduction because of trial design and study sample size, the clinical trial results are clear with regard to the benefit of blood pressure reduction and stroke risks. Without exception, every large-scale, well-conducted clinical trial of blood pressure lowering has shown the clear benefits of this maneuver. The decrease in blood pressure with drug therapy as assessed in clinical trials appears to be the major determinant of reduction in the risk of stroke and stroke deaths. Nonetheless, specific blood pressure reduction target goals <140/90 mmHg remain somewhat unclear. Further studies are required to determine the optimal blood pressure goal and timing of achieving this goal after a stroke.

Several studies focused on secondary prevention, including an early study of US veterans. The Dutch TIA Trial Study and other major trials have shown significant lower rates of recurrent stroke with lower blood pressures. Most recently, the blood pressure reduction component of the SPS3 trial showed that targeting SBP of <130 mmHg is likely to reduce recurrent stroke by 20% (P=0.08) and significantly reduces ICH by two thirds. The ongoing Systolic Blood Pressure Intervention Trial (SPRINT) is a 2-arm, multicenter, randomized clinical trial designed to test whether a treatment program aimed at reducing SBP to a lower goal than currently recommended will reduce CVD and stroke risk, as well as improve cognitive function.

Hypertension Treatment Guidelines
Since 1977, the JNC has recognized the high impact of elevated blood pressures and published guidelines on the diagnosis, prevention, and management of hypertension.
The treatment guidelines have included recommendations focused on the reduction of hypertension-related conditions, including stroke. The guidelines have evolved as evidence about the benefits of treatment to lower blood pressure levels becomes available, along with study results that differentiate the effectiveness of the different classes of treatment. A major contribution of the JNC guidelines remains the definition of hypertension and blood pressure treatment goals. With each set of JNC guidelines, the blood pressure level for treatment and goals has typically been lowered. Specifically, the JNC 7 report has recognized and then emphasized the need to treat SBP, especially in older people. These recommendations may have an impact on population blood pressure levels because SBPs have been lower with the evolving guidelines (Table). These guideline recommendations for clinical management are also used for public health hypertension control efforts. The implementation of the guidelines to address the populations at risk is designed to impact the disease risk, including stroke mortality. A recent article identified the potentially high impact of hypertension guidelines on the high-risk population with HBP.178

**Structured Programs**

The impact of elevated blood pressure on the population has led to the establishment of strategies for the prevention and management of hypertension as major public health objectives.179–181 The premise is that if the elevation of blood pressure with age can be prevented or reduced, then stroke and stroke mortality will be affected. This concept has led to the implementation of public health strategies and programs to reduce blood pressure in the population as an effort to lower stroke risks. Risk factors of interest include excess body weight; excess dietary sodium intake; suboptimal level of physical activity; inadequate intake of fruits, vegetables, and potassium; and excess intake of alcohol.182,183 These programs are aimed at working with manufacturers and restaurants, as well as developing food procurement policies to reduce salt in prepared and processed food; encouraging consumption of more fresh fruits and vegetables; increasing community participation in physical activity; and detecting and tracking HBP where people gather, for example, at churches, worksites, and community events, and through public education campaigns.184–187

This population-based approach uses a public health strategy that complements clinical hypertension treatment and management. Primary prevention strategies are implemented to reduce blood pressure levels in the population, particularly in people with prehypertension (<140/90 mm Hg). This approach serves to decrease blood pressure levels in the general population by relatively modest amounts but in large populations has the potential to substantially reduce stroke morbidity and mortality and delay the onset of hypertension.188 Stamler189 estimated 2 decades ago that a 5-mm Hg reduction of SBP in the adult population would result in a 14% overall reduction in mortality caused by stroke. As presented in Figures 1 and 2 and the Table, the reduction in SBP is consistent with the decline in stroke mortality and corresponds to the predicted lower stroke mortality rates.

In the 1970s, as a strategy to increase public knowledge about and screening for HBP, the National Heart, Lung, and Blood Institute provided funding and technical assistance to develop state hypertension education and control programs. States and territories organized hypertension coalitions composed of voluntary agencies such as the American Heart Association (AHA), the American Red Cross, and local medical and nursing societies and representatives from nearby hospitals. More than 2000 community groups and coalitions were developed and began hypertension screening and education programs. Programs developed patient tracking systems to determine what became of those who were screened. These efforts demonstrated a sharp increase in hypertension control rates and a marked decline in stroke mortality.190–194 This was later corroborated by data from the US Department of Veterans Affairs.195

As state health department epidemiologists began assembling hypertension prevalence rates from data collected during the screenings, it became apparent that some states, particularly those in the Southeast, had greater hypertension prevalence and more severe hypertension than others. These data prompted the examination of the NHANES blood pressure regional data and stroke mortality, and subsequently 2 landmark studies were published, identifying 11 contiguous states in the Southeast that had higher stroke mortality than the rest of the nation. These states were identified as the “Stroke Belt.”196,197

Subsequently, the National Heart, Lung, and Blood Institute and its partners developed structured education efforts in the Southeast. Contracts were issued to state health departments in the Stroke Belt to increase the intensity of education activities.198 Blood pressure screening programs were conducted using models from activities in barbershops. Mass media campaigns increased; encouraging people to know their numbers, visit their doctor, reduce salt consumption, and increase physical activity. Two professional and advocacy societies were established: the Consortium for Southeastern Hypertension Control and the International Society on Hypertension in Blacks. Both focused their efforts on continuing medical education and community outreach. In addition, the Southern Medical Society increased its continuing medical education programs to focus on hypertension. Likewise, the American Society of Hypertension organized regional chapters, including the Carolinas-Georgia-Florida chapter, to address specific regional risks.199–201 The pharmaceutical industry assisted by reprinting program materials or providing unrestricted education grants for regional continuing education conferences. Workshops were conducted to determine why the Southeastern United States had a higher stroke mortality rate than the rest of the nation.202

This compendium of structured community and professional activities was associated with a reduction in stroke mortality in the Southeast. Other structured programs such as those at worksites203,204 and subsequently the US Department of Health and Human Services Million Hearts initiative, the AHA's Get With The Guidelines programs, and the Citizens for the Treatment of High Blood Pressure were developed and maintained under the premise of prevention, treatment, and control of HBP as
Hypertension Research Gaps and Considerations

Although the evidence for hypertension management and stroke risks is strong, several research gaps should be addressed for the development of the most effective primary, secondary, and tertiary prevention interventions. For example, a substantial fall in hypertension-associated ICH over the past 25 years has been well documented, but not in the overall number of cases of ICH in older age groups, partly as a result of an increase in the use of antithrombotic agents. With an expected increase in prevalence of amyloid angiopathy among the aging population, an increase in the number of cases of ICH might be projected. Likewise, the study of cerebral microbleeds and hypertension with increased stroke risks has a potentially high impact as an important emerging imaging biomarker with the potential to provide insights into the pathophysiology, prognosis, and disease progression of ICH, as well as therapeutic strategies for its treatment. Such studies also demonstrate disparities as significant racial differences in cerebral microbleed prevalence in ICH. Although the benefit of blood pressure reduction is well documented, the management of hypertension is complicated, with several clinical questions remaining. Blood pressure management in acute ischemic stroke (AIS) also remains problematic, with questions such as when to initiate antihypertensive agents, to what level of blood pressure reduction, and which class of agents should be used.

In summary, multiple sources of evidence identify the impact of blood pressure reduction on the decline in stroke mortality. Epidemiological and observational studies over the past 5 decades consistently identify a significant association of blood pressure level and stroke mortality for both sexes and all races/ethnicities and cultures, as well as all age groups. Higher blood pressure equals greater risk for stroke. Clinical trials have confirmed the consistent findings of reduced blood pressure and lower stroke mortality rates. The trends in stroke risks with blood pressure level identified from the observational epidemiological studies are consistent with the evidence for levels of blood pressure reduction from clinical trials. The strength of the evidence is such that clinical guidelines and intervention programs focus on blood pressure management and lower blood pressure levels for primary and secondary stroke prevention. These comprehensive components of population risk reduction are ideal models for the clinical medicine and population health partnership. The accelerated decline in stroke mortality that began in the 1970s is consistent with the aggressive hypertension treatment and control strategies implemented in that period. In addition, with an aging and heavier population, the pool of people at risk has increased substantially during this time. Yet, stroke mortality rates continued to decline, which is consistent with the improved hypertension prevention and control rates and declines in mean arterial blood pressure rates in populations. The decrease in blood pressure with drug therapy as assessed in clinical settings and widespread public health interventions in the general population appears to be the major determinant for reduction in the risk of stroke and stroke deaths.

Contribution of Diabetes Mellitus Treatment and Control to Decline in Stroke Mortality

Diabetes mellitus is a risk factor for stroke and stroke mortality. The prevalence of diabetes mellitus has been steadily increasing in the United States and throughout the world. Sparse data are available on trends in population prevalence of diabetes mellitus treatment or treatment intensity. Therefore, the temporal effect of changes in diabetes mellitus treatment on risk of stroke death cannot be determined.

Although the incidence of ischemic stroke has been declining in the United States in recent years, the proportion of people with ischemic stroke with comorbid diabetes mellitus has increased. A recent analysis of nationwide trends in AIS hospitalizations in the United States from 1997 to 2006 revealed that the absolute number of AIS hospitalizations declined by 17% (from 489,766 in 1997 to 408,378 in 2006); however, the absolute number of AIS hospitalizations with comorbid type 2 diabetes mellitus rose by 27% (from 97,577 [20%] in 1997 to 124,244 [30%] in 2006; P<0.001). The rise in comorbid diabetes mellitus over time was more pronounced in patients who were relatively younger, of black or “other” race, on Medicaid, or admitted to hospitals located in the South. Factors independently associated with higher odds of diabetes mellitus in AIS patients were black or “other” race versus white race, congestive heart failure, peripheral vascular disease, history of myocardial infarction, renal disease, and hypertension.

During the past 2 decades, the main thrust of diabetes mellitus treatment research has been to investigate whether tight glucose control improves long-term outcomes, especially related to the development of both microvascular and macrovascular complications. Microvascular complications include retinopathy, nephropathy, and neuropathy (peripheral and autonomic), whereas macrovascular outcomes include cardiovascular events and cerebrovascular events.

Regarding tight glucose control in the outpatient setting, observational studies have shown a positive correlation between measures of glycemic control and reduced rates of developing microvascular and macrovascular outcomes. The current guidelines for the management of diabetes mellitus emphasize patient-tailored goals for patients with diabetes mellitus and related comorbid conditions.

For patients with type 1 diabetes mellitus, the Diabetes Control and Complications Trial (DCCT) tested intensive glucose control versus standard care among typically young patients with type 1 diabetes mellitus (mean age, 27 years at trial enrollment). Patients were treated for a mean of 6.5 years between 1983 and 1993, and a substantial benefit was seen in reducing microvascular complications. The number of macrovascular events was very small, as might be expected for typical young patients with type 1 diabetes mellitus. A follow-up study tracked patients to 11 years after enrollment and found a significant reduction in macrovascular events for subjects in the intensive treatment arm.

A recent meta-analysis of 5 interventional trials in both type 1 and type 2 diabetes mellitus examined the effect of...
tight glucose control on reducing macrovascular events and all-cause mortality, and found that tight glucose control does provide benefit for reducing myocardial infarction and coronary heart disease events. No consistent effect was found for stroke; tight glucose control was neither beneficial nor harmful. There was a suggestion that mortality may be increased with tight glucose control, driven primarily by the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial results.

With any strategy of glucose lowering (short-term/intensive versus long-term), there is a risk of symptomatic hypoglycemia and other adverse effects, and thus it is imperative that a benefit for such strategies be robust. The ACCORD study is worth discussing because it is one of the most recent glucose management trials in the outpatient setting and also one of the largest.

Blood pressure reduction and modification of other risk factors have been shown to be beneficial for stroke reduction in patients with type 2 diabetes mellitus. In a preplanned sub-study of ACCORD, patients with type 2 diabetes mellitus were found to have a reduced risk for stroke if blood pressure was tightly controlled; this same effect was also seen in the UK Prospective Diabetes Study (UKPDS). Patients with type 2 diabetes mellitus and chronic kidney disease are among those with the greatest risk for stroke. In the Steno-2 study, these patients had reduced all-cause mortality and stroke incidence in both the short and long term when randomly assigned to a comprehensive interventional health program compared with usual care. This program involved a regimented plan for managing diabetes mellitus, as well as HBP and high cholesterol, and included wellness programs in exercise, smoking cessation, and dietary intervention. Collectively, these studies suggest that multifactorial risk factor intervention, especially tight blood pressure control, lowers risk for macrovascular events, including stroke, in patients with diabetes mellitus. An increasing obese population will present with increasing diabetes mellitus, further driving up blood pressure prevalence and increasing stroke mortality. Preventing and controlling hypertension and diabetes mellitus, particularly in this population, mitigates stroke risk.

An additional line of research is whether intensive glucose control (typically defined as a glucose goal ≤150 mg/dL obtained with an insulin infusion during part or all of the intensive care unit stay) during the acute stroke hospitalization improves outcomes and mortality. For this question, research is inconclusive and ongoing in a large phase III clinical trial (Stroke Hyperglycemia Insulin Network Effort [SHINE]) in relation to stroke mortality, with a glucose goal of 80 to 130 mg/dL in the intensive arm. Prior studies did not show a benefit for poststroke mortality, but either were pilot/safety studies or were underpowered because of difficulties with recruitment. This line of research is supported by trials of acute intensive glucose management that showed a reduced intensive care unit mortality and length of stay, although a meta-analysis of all intensive care unit–based glucose management trials did not find a similar benefit. The Insulin Resistance Intervention After Stroke (IRIS) trial is a randomized, double-blind, placebo-controlled study that is seeking to test the effectiveness of pioglitazone for lowering risk for stroke after ischemic stroke or TIA. Because insulin resistance is estimated to affect 50% of stroke patients, these results may have an impact on secondary stroke prevention.

In summary, research on the benefit of intensive glucose lowering in the setting of acute stroke hospitalization continues. At this time, there is insufficient evidence to know if this treatment is beneficial for reducing mortality or improving outcome, and more data are needed. Tight glucose control did reduce stroke incidence for patients with type 1 diabetes mellitus in 1 randomized, controlled trial; however, the impact on overall stroke mortality in the population would be small, given that type 1 diabetes mellitus is much less prevalent than type 2 diabetes mellitus and thus may have a relatively small impact on stroke mortality. Tight glucose control for patients with type 2 diabetes mellitus has not been shown to reduce mortality from stroke (based on a meta-analysis) and in fact led to higher mortality in 1 large, randomized, controlled trial. Multifactorial risk factor intervention in patients with diabetes mellitus, especially blood pressure control, has been shown to reduce mortality and macrovascular events, including stroke, in multiple randomized, controlled trials. Data on the prevalence of diabetes mellitus over the past century are sparse.

**Contribution of AF Treatment and Control to Decline in Stroke Mortality**

AF is a significant risk factor for stroke, with an attributable risk of 1.5% for people 50 to 59 years of age and 23.5% for people 80 to 89 years of age. Data on secular trends in age-adjusted prevalence of AF are limited. Trends based on hospital discharge data are limited by ascertainment bias because telemetry and serial ECGs have become more common in hospitals over time. Results from a community-based study in Rochester, MN, showed a significant secular trend of increased prevalence of AF from 1960 to 1989 among both stroke cases and controls of both sexes, but it was not possible to quantify the contribution of ascertainment bias to the observed trends.

In the FHS, it was possible to identify secular trends based on biennial clinic examinations alone and based on all sources, including biennial examinations, private physician records, and interim hospitalizations. Among men 65 to 84 years of age, the age-adjusted prevalence of AF at the biennial examination suggested an increase from 2% in 1968 to 1970 to 5.3% in 1987 to 1989 (P=0.08). No secular trend for an increased prevalence of AF was identified among women. Results based on AF detected from all sources showed an increase among men from 3.2% in 1968 to 1970 to 9.1% in 1987 to 1989 (P=0.0002), but again there was no trend among women. Thus, limited available evidence suggests that age-adjusted AF rates are not decreasing over time and may be increasing among men. In part, this may be attributable to better survival of cardiac conditions, including myocardial infarction.

Randomized, clinical, controlled trials comparing warfarin with aspirin in nonvalvular AF were not powered to detect differences in stroke mortality. Even a meta-analysis of available data published before 1999 was underpowered for this end point; the pooled estimate of the effect of warfarin on stroke
mortality for 6 trials was 0.74 (95% CI, 0.39–1.40). A subsequent trial conducted among people with AF who were ≥75 years of age also showed a trend toward decreased stroke mortality for patients treated with warfarin (relative risk [RR], 0.59; 95% CI, 0.27–1.24).

Data from a large administrative data set show a significant reduction in the composite end point of stroke or mortality for patients on warfarin with a CHADS2 score ≥1. The clinical prediction rule for estimating the risk of stroke in patients with nonrheumatic AF includes C (congestive heart failure=1), H (hypertension: blood pressure consistently >140/90 mm Hg/or treated hypertension on medication=1), A (age ≥75 years=1), D (diabetes mellitus=1), and S (prior stroke or TIA or thromboembolism=2). However, it should be noted that observational data of this type are subject to the potential bias that warfarin might be prescribed to healthier patients and aspirin to sicker patients.

The evidence is very strong that anticoagulation with warfarin for patients with AF reduces fatal and nonfatal stroke by ≥50%. There is a reduction in case-fatality rates in patients taking warfarin compared with those not taking it.

Since 1989, numerous trials have shown a benefit of warfarin treatment over antiplatelet therapy among patients with AF. Available evidence supports an increase in the use of anticoagulation therapy for treatment of AF since the publication of these trials. A study of Medicare patients with AF from 1992 to 2002 showed that use of warfarin increased significantly for each year examined, from 24.5% to 56.3%. A comparison of treatment trends among 569 hospitals between 2003 and 2009 showed that the percentage of stroke patients with AF treated with anticoagulation increased from 28% to 69% and that the percentage of stroke patients with a contraindication to anticoagulation declined from 58% to 27%

In summary, there is evidence from observational studies that treatment of AF with warfarin has increased during the past 40 years, especially within the past 2 decades. Although data from randomized clinical trials show a reduction of stroke mortality of 26% to 41% with warfarin, the estimated effect is not statistically significant because of the relatively small numbers of fatal stroke events. However, there are strong data indicating that incident stroke, which does impact small numbers of fatal stroke events. However, there are strong data indicating that incident stroke, which does impact small numbers of fatal stroke events, has been reduced. More important, there is evidence from a single observational study suggesting that the age-adjusted prevalence of AF may be increasing.

There is a need for further data on temporal trends in age-adjusted prevalence of AF. In addition, it will be important for postmarketing surveillance to monitor the prevalence of use and clinical outcomes of the newer oral anticoagulants because available data suggest that they will have an even stronger effect than warfarin on reducing stroke mortality in AF. Thus, it is unclear whether changes in prevalence or management of AF have contributed to changes in stroke mortality because of the competing effects of increasing prevalence of AF, improved treatment of AF, and the fact that warfarin was not actively used as a routine treatment for AF until the past decade.

**Contribution of Hyperlipidemia Treatment and Control to Decline in Stroke Mortality**

**Recent Trends in Prevalence of Dyslipidemia in the United States**

Over the past 30 years, there have been improvements in awareness, treatment, and control of dyslipidemia; however, dyslipidemia remains highly prevalent in the United States. Data from the NHANES cross-sectional samples of the US population showed a decrease in the proportion of people with total cholesterol ≥240 mg/dL from 20.5% in 1988 to 1994 to 14.2% in 2005 to 2010. Age-adjusted mean total cholesterol levels decreased from 210 mg/dL in 1976 to 1980 to 200 mg/dL in 1999 to 2006, and mean low-density lipoprotein (LDL) cholesterol levels declined from 134 to 119 mg/dL during the same time. On the other hand, the prevalence of adults with untreated desirable total cholesterol levels (<200 mg/dL) remained unchanged from 1988 to 2010 (46.8% in 1988 to 1994 to 46.0% in 2005 to 2010), and an estimated 33.5 million US adults >20 years of age currently have total serum cholesterol levels ≥240 mg/dL.

The mild improvements in total cholesterol and LDL cholesterol levels have likely been because of population-wide behavioral and environmental factors, in addition to an increase in dyslipidemia awareness and medication use. An analysis of the distribution of total cholesterol levels across US birth cohorts from 1959 to 1994 revealed that the entire distribution of total cholesterol concentrations shifted to lower levels in the United States. The shift was more pronounced in the upper range of the distribution, likely reflecting changes in treatment and control of hypercholesterolemia. The decrease in the lower end of the distribution was likely attributable to population influences such as reduced consumption of dietary saturated fatty acid and cholesterol intake. Studies have shown improvements in awareness and control of hypercholesterolemia in the United States. The self-reported history of “high cholesterol” increased from 17% in 1988 to 27% in 1999 to 2006; self-reported lipid medication use by those with high cholesterol increased from 16% to 38% and control of LDL cholesterol increased from 4.0% in 1988 to 1994 to 25.1% in 1999 to 2004 among those with high LDL cholesterol. More recent data show that treatment of high LDL cholesterol increased to 48% and control of LDL cholesterol among those with high LDL cholesterol was 33.2% in 2005 to 2008.

Improvements in dyslipidemia control have not been uniform across demographic strata. Rates of LDL cholesterol control were lower among adults 20 to 49 years of age compared with those ≥65 years of age (13.9% versus 30.3%), non-Hispanic blacks and Mexican Americans compared with non-Hispanic whites (17.2% and 16.5% versus 26.9%), and men compared with women (22.6% versus 28.0%). In addition, in the FHS, the proportion of those treated for high LDL cholesterol was 41% in insured men but only 7% in uninsured men (odds ratio [OR] of treatment, 0.12; P<0.001). Control of LDL cholesterol was achieved in only 7% of uninsured men with elevated LDL cholesterol versus 31% in insured men (OR of control, 0.17; P=0.004).

High-density lipoprotein (HDL) cholesterol and triglyceride levels—components of the metabolic syndrome—have not
shown clear improvements over the past 30 years. Mean HDL cholesterol increased from 50 mg/dL in 1976 to 1980 to 53 mg/dL in 1999 to 2006, but this change was likely because of alterations in measurement method. Mean triglyceride levels worsened from 130 to 146 mg/dL over the same time, coincident with an increase in mean body mass index (BMI) from 26 to 29 kg/m².260 Obese people were nearly 4 times as likely (OR, 3.7; 95% CI, 3.4–4.0) and overweight people were >2 times as likely (OR, 2.4; 95% CI, 2.2–2.6) to have elevated triglycerides as those with a BMI <25 kg/m² after adjustment for numerous variables.

Association Between Dyslipidemia and Stroke Incidence
Although high LDL cholesterol and low HDL cholesterol levels are clearly established risk factors for coronary artery disease, there is a less consistent association between dyslipidemia and stroke risk.253–255 The lack of an overall association likely conceals a positive association with ischemic stroke and a negative association with hemorrhagic stroke.251 In addition, there is an unclear association between dyslipidemia and ischemic stroke risk, likely because of the heterogeneity of ischemic stroke mechanisms.

Some cohort and case-control studies have found an association between high total cholesterol, high LDL cholesterol levels, high triglyceride levels, and low HDL cholesterol levels and ischemic stroke,256–258 whereas others have shown weak or inconsistent associations.254,255,262,263 Grouping all ischemic strokes together may conceal valuable information about the association between dyslipidemia and stroke subtypes: Dyslipidemia is a risk factor for large-vessel intracranial and extracranial atherosclerosis258,263–266 and lacunar stroke258 but is not an established risk factor for cardioembolic stroke.

Case-control and cohort studies have shown that serum total cholesterol levels are inversely related to ICH260,267; however, 1 study did not show an independent association.281 The lipid fractions responsible for the association with ICH risk are unclear,255,260,262,263 but low LDL cholesterol270 and triglyceride levels260,270,271 may drive the increased risk of ICH.

Analyses of the association between lipid levels and stroke risk should take into account the use of cholesterol-lowering medications, changes in lipid levels, and time from laboratory testing until event. An analysis of 2940 people from the population-based, prospective cohort Northern Manhattan Study (NOMAS) revealed that high LDL cholesterol and non–HDL cholesterol levels were paradoxically associated with lower stroke risk.272 This paradoxical effect was likely attributable to the fact that treatment with cholesterol-lowering medications modified the effect of elevated LDL cholesterol levels on stroke. After people taking cholesterol-lowering medications were excluded, the paradoxical effect disappeared, and there was a trend toward an increased risk of ischemic stroke with an LDL cholesterol level >130 mg/dL.272

Association Between Dyslipidemia and Stroke Severity and Mortality
Dyslipidemia has been associated with lower mortality after ischemic stroke.273,274 In a recent study of 274,988 ischemic stroke patients admitted to 1036 hospitals participating in the Get With The Guidelines–Stroke Program, a history of dyslipidemia was associated with lower risk of in-hospital mortality (OR, 0.68; 95% CI, 0.64–0.71).273 This inverse association with stroke mortality could be attributable to the fact that dyslipidemia is associated with noncardioembolic strokes, which are less severe and have a better prognosis than cardioembolic strokes.273–275 Supporting this theory, the Copenhagen Stroke Study revealed an inverse and almost linear independent association between concentrations of total serum cholesterol and stroke severity. Smaller infarcts were associated with lower stroke severity. An increase of 1 mmol/L in cholesterol resulted in lower mortality (hazard ratio [HR], 0.89; 95% CI, 0.82–0.97).274 An alternative explanation is that a history of dyslipidemia is associated with use of medications such as statins, which may impact the severity or prognosis of stroke.273

Low total cholesterol, triglyceride, and LDL cholesterol levels are also associated with a higher risk of death after ICH.276–278 This may be attributable to the protective effect of cholesterol against hematoma growth279 or its importance for maintaining vessel integrity and resistance to rupture.280

On the other hand, 1 study revealed higher stroke mortality rates among those with dyslipidemia. Among people with diabetes mellitus who participated in NHANES, those with higher serum levels of non–HDL cholesterol [composite marker of several atherogenic lipoproteins, including LDL, very-low-density lipoprotein, intermediate-density lipoprotein, and lipoprotein(a)] had a higher risk of death resulting from stroke (RR, 3.37; 95% CI, 0.95–11.90; and RR, 5.81; 95% CI, 1.96–17.25) for non–HDL cholesterol concentrations of 130 to 189 mg/dL and 190 to 403 mg/dL, respectively (P=0.001 for linear trend), compared with participants with serum non–HDL cholesterol concentrations of 35 to 129 mg/dL after adjustment for demographic characteristics and selected risk factors.281

Effects of Lipid-Lowering Therapy on Stroke Incidence and Mortality
An estimated 24 million adults were taking statins in 2003 to 2004, representing a steady increase in use from previous decades.282 Lipid-lowering therapy with statins reduces ischemic stroke incidence; however, the benefit is less robust among people with established cerebrovascular disease and may be counterbalanced by higher rates of ICH in statin users. A 2008 systematic review of studies investigating the effect of statins in 8832 patients with a history of cerebrovascular disease showed a pooled RR of ischemic stroke of 0.80 (95% CI, 0.70–0.92) and hemorrhagic stroke of 1.73 (95% CI, 1.19–2.50), suggesting that the beneficial impact of statins on ischemic stroke might be partially offset by the increased risk of hemorrhagic stroke.283 In addition, a 2009 Cochrane review reported a marginal benefit in reducing subsequent cerebrovascular events in those with a previous history of stroke or TIA (OR, 0.88; 95% CI, 0.77–1.00) and a lack of association with all-cause mortality or sudden death (OR, 1.00; 95% CI, 0.83–1.20).284 There was an increase in the odds of hemorrhagic stroke with statin therapy (OR, 1.72; 95% CI, 1.20–2.46); however, only 2 trials in the review specifically assessed
the risk of hemorrhagic stroke.\textsuperscript{284} One, Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL), randomly assigned 4731 people with recent stroke or TIA to high-dose atorvastatin versus placebo and showed a 5-year absolute reduction in risk of stroke of 2.2\% (adjusted HR, 0.84; 95\% CI, 0.7–0.99; \(P=0.03\); unadjusted, \(P=0.05\)). This result included a reduction in ischemic stroke but an excess of hemorrhagic stroke. The overall mortality rate was similar.\textsuperscript{286} A post hoc analysis of the trial found that treatment with atorvastatin was independently associated with an increased risk of hemorrhagic stroke (HR, 1.68; 95\% CI, 1.09–2.59). Subjects enrolled with an index hemorrhagic stroke had a \(>5\)-fold increase in risk of recurrent hemorrhage.\textsuperscript{286}

The association between statin therapy and ICH, however, is not consistent. A 2012 meta-analysis of 31 randomized controlled trials of statin therapy (91,588 subjects in the active group and 91,215 in the control group) revealed no significant difference in incidence of ICH observed in the active treatment group versus control (OR, 1.08; 95\% CI, 0.88–1.32); however, the meta-analysis included only 2 secondary stroke prevention trials.\textsuperscript{287} Total stroke (OR, 0.84; 95\% CI, 0.78–0.91) and all-cause mortality (OR, 0.92; CI, 0.87–0.96) were reduced in the active therapy group.\textsuperscript{287} In addition, a 2011 systematic review and meta-analysis of 23 randomized trials and 19 observational studies (248,391 patients) revealed that statins were not associated with an increased risk of ICH in randomized trials (RR, 1.10; 95\% CI, 0.86–1.41), cohort studies (RR, 0.94; 95\% CI, 0.81–1.10), or case-control studies (RR, 0.60; 95\% CI, 0.41–0.88).\textsuperscript{288} A subsequent retrospective cohort study found no association between statin use and subsequent ICH among people with previous ischemic stroke.\textsuperscript{288}

In a meta-analysis of 5 trials of more versus less intense therapy with statins (39,612 people; median follow-up, 5.1 years) and 21 trials of statin versus control (129,526 people; median follow-up, 4.8 years), all-cause mortality was reduced by 10\% per 1-mmol/L reduction in LDL (RR, 0.90; 95\% CI, 0.87–0.93), largely reflecting significant reductions in deaths resulting from coronary heart disease and other cardiac causes, with no significant effect on deaths caused by stroke or other vascular causes.\textsuperscript{289} Specifically, there were no significant effects on mortality from first stroke, mortality from first ischemic or first hemorrhagic stroke, or incidence of first nonfatal hemorrhagic stroke. There was, however, a significant reduction in first nonfatal ischemic stroke, corresponding to a 23\% (99\% CI, 15–30) reduction per 1.0-mmol/L reduction in LDL cholesterol. Compared with the less intensive regimens, more intensive regimens produced a 16\% further reduction in ischemic stroke (RR, 0.84; 99\% CI, 0.71–0.99) and nonsignificant increase in risk of hemorrhagic stroke (RR, 1.21; 99\% CI, 0.76–1.91).\textsuperscript{290}

Statin therapy in the acute setting after stroke may have a beneficial impact on survival. A population-based, prospective cohort study found that new poststroke statin therapy was associated with both early and late survival compared with no statin treatment (OR for death, 0.12; 95\% CI, 0.03–0.54 at 7 days; OR, 0.19; 95\% CI, 0.07–0.48 at 90 days; OR, 0.26; 95\% CI, 0.12–0.55 at 1 year) after adjustment for age, pre-stroke disability, National Institutes of Health Stroke Scale score, hypertension, and aspirin use. Similar findings were seen for statin therapy before stroke onset (adjusted OR for death compared with patients not treated with statins, 0.04; 95\% CI, 0.00–0.33 at 7 days; OR, 0.23; 95\% CI, 0.09–0.58 at 90 days; OR, 0.48; 95\% CI, 0.23–1.01 at 1 year).\textsuperscript{291} A meta-analysis of 15 randomized, placebo-controlled trials using various statins assessed the risk of strokes for patients with a history of coronary disease identifying significantly reduced recurrent ischemic stroke risk (RR, 0.74; 95\% CI, 0.64–0.86) with 1 recurrence of ischemic stroke prevented for every 110 patients with coriary disease treated with a statin.\textsuperscript{292}

The effect of fibrate therapy on stroke incidence and mortality is unclear, but a recent meta-analysis revealed a reduction in risk of vascular events among people with high triglycerides and/or low HDL cholesterol treated with fibrates. Compared with placebo, fibrate therapy reduced the risk of vascular events in 7389 subjects with high triglycerides (RR, 0.75; 95\% CI, 0.65–0.86), in 5068 subjects with both high triglycerides and low HDL cholesterol (RR, 0.71; 95\% CI, 0.62–0.82), and in 15,303 subjects with low HDL cholesterol (RR, 0.84; 95\% CI, 0.77–0.91).\textsuperscript{293}

In summary, over the past 30 years, there have been improvements in awareness, treatment, and control of dyslipidemia; however, dyslipidemia remains highly prevalent, and levels of control remain suboptimal. Declines in stroke were underway for more than a half century before documentation of the potent role of blood lipids in heart disease (and potentially stroke) risk. The relationships between dyslipidemia and stroke risk and mortality remain equivocal, likely because of the differential impact of various lipid fractions on ischemic and hemorrhagic stroke risk. In addition, the heterogeneity of ischemic stroke mechanisms further complicates the picture. Currently, there is unclear evidence that dyslipidemia treatment and control have contributed to the decline in stroke mortality. Further randomized, controlled trials are needed to assess the impact of treatment of dyslipidemia on stroke incidence, outcomes, and mortality, stratified by stroke subtype.

**Contribution of Aspirin and Other Antiplatelet Drugs to Decline in Stroke Mortality**

Aspirin and other antithrombotics reduce stroke mortality by preventing thrombotic ischemic strokes and by reducing the case-fatality rate when started after AIS.

A systematic review and meta-analysis of randomized, controlled trials showed that aspirin reduced the risk of incident stroke when used for secondary prevention after previous ischemic stroke (OR, 0.77; 95\% CI, 0.69–0.85)\textsuperscript{294} or for secondary prevention after other major vascular events (ORs, 0.62–0.73; all \(P<0.05\)).\textsuperscript{294} By contrast, when used in men and women for primary prevention, aspirin did not reduce the overall stroke incidence (OR, 0.95; 95\% CI, 0.85–1.06).\textsuperscript{295} The reason was that a significant reduction in incident ischemic stroke (OR, 0.86; 95\% CI, 0.74–1.00) was offset by an increased incidence of hemorrhagic stroke (OR, 1.32; 95\% CI, 1.00–1.75), with no difference in the risk of stroke of unknown type, which accounted for approximately one third of stroke events in the randomized trials.\textsuperscript{296} The risk of fatal stroke was nonsignificantly increased (OR, 1.21; 95\% CI, 0.84–1.74).\textsuperscript{297} There is evidence that these effects differ by sex, however, with women...
experiencing more benefit than men. In a systematic review and meta-analysis of clinical trials of aspirin for primary stroke prevention in women, aspirin for primary prevention reduced the overall incidence of stroke (OR, 0.83; 95% CI, 0.70–0.97), driven by a reduction in ischemic stroke (OR, 0.76; 95% CI, 0.63–0.93) that outweighed a nonsignificant increase in hemorrhagic stroke (OR, 1.07; 95% CI, 0.42–2.69) in the study sample. However, the largest randomized, controlled trial in women found a nonsignificant increase in fatal stroke (OR, 1.04; 95% CI, 0.58–1.86) despite a reduction in overall (fatal and nonfatal) stroke incidence (OR, 0.83; 95% CI, 0.69–0.99), probably because hemorrhagic stroke, which was more frequent in aspirin users compared with those taking placebo, had a higher case-fatality rate than ischemic stroke, which was less frequent in aspirin users compared with those taking placebo. Therefore, aspirin does not appear to reduce fatal stroke in either men or women when used for primary prevention.

When started within 48 hours of AIS, aspirin may reduce the risk of all-cause death at 1 to 3 months (OR, 0.93; 95% CI, 0.86–1.01) compared with placebo, according to a Cochrane systematic review and meta-analysis. The use of regular daily aspirin increased from the 1970s to 2003. In 1980, after the seminal randomized, controlled trials in the 1970s, aspirin was approved by the US Food and Drug Administration for secondary prevention of stroke after TIA. It was recommended by professional guidelines for prevention of stroke in 1994 and recommended for primary prevention of stroke in women and men at high risk by the US Preventive Services Task Force in 2002 and 2009. Longitudinal, nationally representative data on changing use of aspirin over time are available but are limited by differences in sampling and in ascertainment of aspirin use. Survey data from NHANES I indicate that aspirin use for analgesic purposes was common and increased from 35% in 1971 to 1975 to 78% in 1976 to 1980; however, the majority of use was intermittent, and the frequency of daily use was not determined. In 1998 and 1999, aspirin was used frequently, either daily or within with past week, by 18% to 30% of the US population. The growth of daily or every-other-day use of aspirin in adults with stroke or CVD has been even higher. According to data from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey in outpatients with CVD, initiation or continuation of aspirin use was recommended in 5% of outpatient visits in 1980, 26% of outpatient visits in 1996, 33% of outpatient visits in 2003, and 47% of outpatient visits in 2007and 2008. However, the true prevalence of aspirin use in patients might be underestimated from these physician surveys because patients may be taking aspirin without the recommendation or knowledge of the physician. Indeed, data from the Behavioral Risk Factor Surveillance System (BRFSS) surveys show that the prevalence of frequent aspirin use among people with known stroke or CVD is much higher: 61% in 1999 and 69% in 2003.

A growing number of antithrombotic alternatives to aspirin are available. Ticlopidine reduced the risk of major vascular events compared with aspirin but was never widely used because of safety concerns. Clopidogrel reduced the risk of incident stroke in patients with CVD or stroke compared with aspirin (RR, 0.93; 95% CI, 0.81–1.06) in 1 study sample; this reduction was similar to that observed in the trial for all major vascular events (RR, 0.91) but was not statistically significant because of the small number of incident strokes. Likewise, the reduction in vascular deaths was similar (RR, 0.92; 95% CI, 0.80–1.07) but also not significant because of few deaths. One randomized, controlled trial suggested that the combination of aspirin and sustained-release dipyridamole reduced the risk of recurrent ischemic stroke compared with aspirin alone when used for secondary prevention of stroke (RR, 0.77; 95% CI, 0.64–0.91) but another similar-sized randomized, controlled trial found a nonsignificant reduction in risk (HR, 0.84; 95% CI, 0.64–1.10) with neither trial finding that aspirin and dipyridamole reduced the risk of vascular or all-cause death compared with aspirin. In a subsequent randomized, controlled trial, aspirin and sustained-release dipyridamole were not superior to clopidogrel for secondary prevention of recurrent ischemic stroke, with higher risk of intracranial hemorrhage. A meta-analysis showed that the combination of aspirin and clopidogrel reduced the risk of stroke compared with aspirin alone in patients with CVD (RR, 0.84; 95% CI, 0.72–0.96). However, the combination of aspirin and clopidogrel increased the risk of major bleeding and did not reduce all-cause mortality; fatal strokes were not reported separately. A randomized, controlled trial of aspirin and clopidogrel to prevent recurrent stroke in patients with ischemic stroke showed no benefit compared with clopidogrel alone. Integrating all the evidence, current professional guidelines from the AHA/American Stroke Association suggest that either aspirin, clopidogrel, or the combination of aspirin and sustained-release dipyridamole are reasonable alternatives for secondary prevention of ischemic stroke, although aspirin has the highest-rated supporting evidence; the guidelines recommended against the use of the combination of aspirin and clopidogrel. Nationally representative data on the choice of aspirin, clopidogrel, or the combination of aspirin and clopidogrel for secondary prevention of stroke are not available, nor are data on longitudinal changes over time. Data from a large hospital registry from 2003 to 2008 showed that aspirin monotherapy remains the most common choice for patients discharged after admission for ischemic stroke, possibly based on its good adverse-effect profile and low cost.

Results from the SPS3 trial indicated that a combination of clopidogrel plus aspirin in patients with small-vessel stroke led to reduction in stroke but was not significantly better than aspirin alone, and there was an increase in hemorrhagic complications. These findings were consistent for the risk of recurrent stroke, dual antiplatelet therapy (2.5% per year) versus aspirin alone (2.7% per year) (HR, 0.92; 95% CI, 0.72–1.16), as well as the risk of recurrent ischemic stroke (HR, 0.82; 95% CI, 0.63–1.09) and disabling/or fatal stroke (HR, 1.06; 95% CI, 0.69–1.64). In addition, 2 ongoing trials may provide additional evidence on the benefit of aspirin and antithrombotic therapy. The Clopidogrel in High-Risk Patients With Acute Non-disabling Cerebrovascular Events (CHANCE) trial was designed to assess the effects of a 3-month regimen of clopidogrel versus a 3-month regimen of aspirin alone on reducing the 3-month risk of any stroke in high-risk patients with TIA or minor stroke in China. In addition, the Platelet-Oriented...
Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial is a randomized, double-blind trial to determine whether clopidogrel is effective in improving survival free from major ischemic vascular events.317

The use of aspirin has a substantial global impact as well, with differing specific high risks in developing countries.82 In addition to risk levels, stroke type varies, as well as the prevalence of comorbid conditions, representing a significant future study need.

In summary, increased use of aspirin for secondary prevention of ischemic stroke in people with a history of ischemic stroke or ischemic heart disease has probably had a moderate impact on reducing stroke mortality, mediated by a reduction in the incidence of both fatal and nonfatal recurrent strokes. However, increased use of aspirin in people without known CVD has probably had no effect on stroke mortality because reductions in first-ever fatal ischemic stroke are balanced by increases in fatal hemorrhagic stroke, with overall no net reduction in fatal stroke. Increased use of aspirin for AIS is expected to have had a mild impact on stroke mortality by reducing the stroke case fatality rate. The increased use of alternatives to aspirin such as clopidogrel or the combination of aspirin and sustained-release dipyridamole has probably had no impact on reducing stroke mortality because the effects of these on fatal stroke are so similar to the effects of aspirin. In contemporary practice, the use of aspirin in acutely hospitalized ischemic stroke patients is widespread without much opportunity for further improvement; however, in the outpatient setting, a substantial portion of patients with known CVD are not taking aspirin, although they probably should.

**Contribution of Neurological and Technical Advances in Stroke Treatment to Decline in Stroke Mortality**

Advances in the technological and medical treatment of stroke, as well as the systems for delivering care, have affected stroke mortality rates. Although these advances are addressed in the individual sections of this report, the history and timing of the specific developments are important when considering the potential impact on the decline in stroke mortality.

One of the first major advances in stroke diagnosis occurred during the 1920s and 1930s and involved the development of contrast angiography. The technique provided contrasted x-ray cerebral angiography for the diagnosis of stroke and distinction from other neurological conditions. Cerebral angiography was enhanced with the Seldinger technique, which provides a safer procedure for access with less potential damage.318 Since its development, angiography technology has become a critical component in the diagnosis and management of stroke.

The measurement and assessment of cerebral flow metabolism developed in the 1940s and 1950s represent a significant advancement in the treatment of stroke. This assessment represents a minimal risk and cost-effective resource easily used in the clinical setting. The first well-recognized studies performed by Kety and Schmidt319 in the 1940s used nitrous oxide gas, resulting in the development of rate equations for blood flow and the elucidation of the physiological relationships between cerebral blood flow, blood pressure, and blood volume. Several recently completed trials in acute stroke have used the principles of mismatch between blood flow and tissue injury (diffusion-perfusion mismatch) to identify patients with territory at risk who might benefit from reperfusion therapies.

In the 1950s, carotid endarterectomy was developed and introduced as a procedure that reduced the incidence of stroke from carotid stenosis. It was proven beneficial in randomized clinical trials among patients with symptomatic and asymptomatic carotid artery stenosis, leading to inclusion of the procedure in randomized clinical trials.320 These trial results have led to the development of protocols for selection of the procedure for maximum benefits. Also in the 1950s, prosthetic heart valves were implanted in patients with rheumatic heart disease to reduce the risk for embolic stroke.321

Doppler ultrasonography was introduced in the 1960s.322 This technology was substantially enhanced during the 1980s to effectively assess blood flow velocity and to routinely screen for and follow carotid artery stenosis. Further enhancements that permitted the use of transcranial sonography permit insonation of intracranial vessels and have proved useful in stroke prevention among patients with sickle cell disease.323 The procedures have been developed into practice protocols in an effort to prevent stroke risks.324 During the 1970s, computed tomography was introduced and has become the main diagnostic tool available for the evaluation of brain injury and the identification of AIS used in the assessment of stroke and stroke risks.325 With the approval of intravenous thrombolysis and catheter-based embolectomy devices as critical stroke therapies, computed tomography has become an essential component of all acute treatment protocols.326 Although magnetic resonance imaging has improved the accuracy of stroke diagnosis, there is insufficient evidence as to whether or not it has any relationship to stroke mortality.

During the 1990s, the US Food and Drug Administration approved the use of tissue-type plasminogen activator (tPA) to treat stroke in the first 3 hours after symptom onset. As discussed in another section of this statement, although use of intravenous tPA has demonstrated time-dependent improvements in functional independence at 3 months and 1 year after stroke, it has not yet convincingly shown a reduction in stroke mortality. Likewise, 3 trials determined that endovascular therapy has not been found to reduce mortality from stroke.327–329

In summary, the numerous advancements in diagnosis, management, and prevention strategies have the potential for significant impact on stroke mortality. On the basis of the time frame for implementation into practice, it seems reasonable that in the most recent decades, changes in the organization of stroke care delivery may have the greatest impact on the decline in stroke mortality.

**Contribution of tPA to Decline in Stroke Mortality**

The increasing use of intravenous tPA for AIS since 1996 is unlikely to have contributed to the overall decline in stroke mortality. Randomized, controlled trials have not shown that treatment with intravenous tPA prevents poststroke death, although it does prevent poststroke disability.330,331 In a pooled
analysis of patients treated within 4.5 hours of symptom onset, there was a slight nonsignificant excess of deaths at 90 days in the tPA-treated group (170 of 1273, 13.3%) compared with those treated with placebo (162 of 1277, 12.7%; P=0.68).332 Additionally, only a small proportion of ischemic stroke patients are treated with tPA. Administrative data suggest that treatment rates are low but have increased modestly from 1.1% in 2004 to 2005 to 3.4% in 2009.333,334 Endovascular therapies are used in <1% of AIS patients335 and are also unlikely to have reduced ischemic stroke mortality.

In summary, evidence from randomized, controlled trials suggests that increasing use of tPA cannot account for reductions in ischemic stroke mortality.

Contribution of Stroke Systems of Care (Telemedicine, Stroke Units/Teams, Primary and Secondary Stroke Centers) to Decline in Stroke Mortality

A Cochrane systematic review of 26 trials showed that compared with alternative services, stroke unit care reduced the odds of death recorded at final (median, 1 year) follow-up (OR, 0.86; 95% CI, 0.76–0.98; P=0.02), the odds of death or institutionalized care (OR, 0.82; 95% CI, 0.73–0.92; P=0.0006), and death or dependency (OR, 0.82; 95% CI, 0.73–0.82; P=0.001).336 Outcomes were independent of patient age, sex, and stroke severity. A nationwide population-based cohort study found no association between mortality and the number of stroke patients treated, despite a higher quality of early stroke care and fewer days in the hospital compared with patients in low-volume units.337 The results from data analyses indicate a positive impact of a policy of stroke unit care on case-fatality rates.338 The positive stroke outcomes are part of the interactions of stroke systems of care, stroke units, and telemedicine.

Primary or Comprehensive Stroke Centers and Stroke Systems of Care

More recent US data suggest that primary stroke center (PSC) hospitals may have lower rates of mortality at discharge or beyond compared with nonstroke centers. A study of Medicare beneficiaries discharged with a primary diagnosis of ischemic stroke in 2006 evaluated risk-standardized mortality rates in stroke discharges from 315 Joint Commission–certified PSCs and 4231 noncertified hospitals. Mean overall 30-day risk-standardized mortality rates were 10.9±1.7%. The risk-standardized mortality rates of JNC-certified PSCs were lower than the national average compared with 19% of noncertified hospitals.339 The same analysis technique applied to hemorrhagic strokes in 2006 revealed that unadjusted in-hospital mortality (SAH, 27.5% versus 33.2%, P<0.0001; ICH, 27.9% versus 29.6%, P=0.003) and 30-day mortality (SAH, 35.1% versus 44.0%, P<0.0001; ICH, 39.8% versus 42.4%, P<0.0001) were lower in JNC PSC hospitals. Risk-adjusted 30-day mortality was 34% lower (OR, 0.66; 95% CI, 0.58–0.76) after SAH and 14% lower (OR, 0.86; 95% CI, 0.80–0.92) after ICH for patients discharged from JNC PSC–certified hospitals.340 However, a retrospective analysis of 2002 data showed that JNC PSC–certified hospitals had better outcomes than noncertified hospitals even before the program began.341 In summary, the evidence that certification itself produced these mortality reductions remains inconclusive.

Using data from 34 academic medical centers in the United States, Douglas et al342 examined the 11 major criteria for establishing PSCs and found 4 of the criteria (written care protocols, integrated emergency medical services, organized emergency departments, and continuing medical/public education in stroke) were associated with increased use of tPA and that hospitals with additional criteria (acute stroke team, a stroke unit, or rapid neuroimaging) tended to have higher use of tPA. However, none of the 11 criteria were associated with changes in stroke mortality.

Stroke Units/Stroke Teams

In a systematic review examining the impact of acute stroke units, 13 of 14 studies found that the percentage of patients with stroke who died was lower when patients were treated in stroke units, and the effect was primarily during the first 1 to 4 weeks after the index stroke.343 More recently, Langhorne et al344 used a national comprehensive data set from Scotland to examine the 6-month mortality rate for patients treated in organized inpatient stroke units versus those not treated in an organized stroke unit and found that the impact of the stroke unit was an absolute risk reduction in case fatality of 3%. It is important to note that the organized stroke unit is a heterogeneous “intervention” and that many of these studies are based in Europe and Canada, where the health systems are organized differently than in the United States. In the United States, 1 academic medical center implemented a multidisciplinary stroke team care consultation service. After implementation of stroke team involvement, median length of stay decreased, and there were fewer urinary tract infections. However, there was no change in the rate of aspiration pneumonia, and mortality did not change.345 Several hospitals described the implementation of acute stroke teams but provided few comparisons of patient outcomes before and after implementation.345,346 In Australia, Hamidon and Dewey347 reported that implementation of an acute stroke team led to reduced time from door to computed tomography scan and reduced length of stay but no significant change in mortality. Xian et al348 used data from the New York Statewide Planning and Research Cooperative System and found that among 30,947 patients with AIS, 15,297 (49.4%) were admitted to designated stroke centers. Treatment in a designated stroke center, using the instrumental variable analysis, was associated with lower 30-day all-cause mortality (10.1% versus 12.5%). Differences in mortality also were observed at 1-day, 7-day, and 1-year follow-ups.

Although the above description of future systems of care is promising, there are few articles and empirical data examining the impact of stroke systems of care.339–341,348 Experts strongly believe that an organized system for stroke care is necessary to deliver high-quality stroke care.349,351 Several teams352 have described their experiences implementing use of stroke centers and systems; 2 teams reported increased

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use of tPA for thrombolysis; only 1 study from Europe reported patient outcomes.

Telemedicine

One barrier to effective stroke care has been the limited availability of stroke specialists on a 24/7 basis in all geographic regions. Telemedicine enables remote assessment of people presenting with acute stroke by a stroke specialist. Use of telemedicine during the hyperacute/emergency, acute care, and subacute phases of care is a strategy that could increase the number of patients who can be assessed and treated by stroke specialists. In 2009, Schwamm et al reviewed the evidence for use of telemedicine for stroke care, including whether telemedicine was effective and a feasible alternative to bedside care when stroke specialists are not available. They concluded that (1) high-quality video teleconferencing is reasonable for performing a general neurological examination and a nonacute National Institutes of Health Stroke Scale assessment, (2) US Food and Drug Administration–approved teleradiology systems are recommended for timely review of computed tomography scans, and (3) high-quality video teleconferencing can facilitate appropriate use of intravenous tPA if a stroke specialist is not immediately available. In the acute setting, high-quality video teleconferencing is recommended if a stroke specialist is not immediately available. There is a need for future research focused on telemedicine and primary prevention of stroke.

In summary, given that stroke systems of care have only recently been developed, the impact of these systems on reductions of stroke mortality before 2010 is unknown but likely small.

Contribution of Smoking and Other Respiratory Conditions to Decline in Stroke Mortality

The effect of cigarette smoking on stroke risk and mortality is well known and has been previously summarized. Cigarette smoking is an established independent risk factor for stroke. The estimated RR of stroke associated with current cigarette smoking (versus nonsmokers) varies across epidemiological studies and also by stroke type (ischemic, ICH, SAH) but has been estimated to be 1.5 for total stroke mortality comparing current versus never smokers from the CPS-II, and the number of stroke deaths resulting from the National Center for Health Statistics. These data show that from 2000 to 2009 the number of stroke deaths attributed to smoking clearly declined, with notable differences across age and sex subgroups. The numbers of stroke deaths attributable to smoking would have been considerably greater for the time from 1965 through the late 1980s, when smoking prevalence ranged from 30% to 40%.

It seems logical to assume that the decline in smoking from ≈4500 cigarettes per capita in 1965 to ≈2000 cigarettes per capita in 2000 is a substantial contributor to declining stroke mortality rates for this period. However, stroke mortality was also steadily declining between 1900 and 1965 (Figures 1 and 2), the same period when per capita consumption of cigarettes increased from nearly nonexistent to the 4500 noted previously. In addition, smoking prevalence has been relatively constant since 2000, a period in which stroke mortality has continued to decline. Therefore, the longer-term patterns in tobacco use do not fully correlate with the pattern of declining stroke mortality in the first half of the 20th century. This discordance is in contrast to the patterns for heart disease, which seem to better align with the trends in tobacco use, perhaps because of the differing ages of onset for these 2 diseases.

Aside from active cigarette smoking, recent decades have seen an increase in research investigating the association of exposure to secondhand smoke (also called passive smoking and environmental tobacco smoke) and stroke risk. Two meta-analyses on this topic have been published. In 2006, Lee and Blair reported a pooled RR of 1.25 (95% CI, 1.16–1.36) for exposure to spousal smoking (or nearest equivalent) and risk of stroke. In a subsequent meta-analysis published in 2011, which included several new studies, the pooled RR was the same. Both reports also supported a dose-response relation between exposure to secondhand smoke and stroke risk. These results suggest that exposure to secondhand smoke
may be a risk factor for stroke and therefore for stroke mortality, but because most studies relied on self-reported exposure, recall bias is a concern, as is publication bias. Of note, prospective studies using cotinine-assessed exposure to secondhand smoke have not reported positive associations with stroke risk.370,371

Similar to the prevalence of active smoking, exposure to secondhand smoke has declined substantially over time, suggesting a possible role in the decline in stroke mortality. Data from NHANES suggest that the proportion of nonsmokers exposed to secondhand smoke decreased from 88% in 1988 to 1991 to 43% in 2001 to 2002.372,373 This decline in exposure to secondhand smoke is likely a combination of the decline in active smoking among the population described earlier and an increase in the enactment of smoke-free policies in work and public settings. Some ecological work has been done to investigate the impact of smoke-free policies on stroke.374–376 Some374,376 but not all375 of these studies have suggested an association between implementation of smoking bans and stroke hospital admissions, but more definitive studies that account for individual-level confounding factors and assess incident stroke or stroke mortality as the end point are lacking.

Aside from smoking, other respiratory-related conditions may have contributed to declining stroke mortality over time, although there are more limited data to inform these hypotheses. Pneumonia is common after stroke. A recent meta-analysis of 87 studies estimated the rate of pneumonia in stroke patients to be 10%.377 In studies conducted in the United States, pneumonia is associated with increased stroke case fatality, with estimates of a 2- to 3-fold increased risk.378,379 This decline in exposure to secondhand smoke is likely a combination of the decline in active smoking among the population described earlier and an increase in the enactment of smoke-free policies in work and public settings. Some ecological work has been done to investigate the impact of smoke-free policies on stroke.374–376 Some374,376 but not all375 of these studies have suggested an association between implementation of smoking bans and stroke hospital admissions, but more definitive studies that account for individual-level confounding factors and assess incident stroke or stroke mortality as the end point are lacking.

In summary, given the known link between cigarette smoking and stroke mortality from prospective cohort studies, the large decrease in the prevalence of active smoking in the United States in the second half of the 20th century likely contributed to the decline in stroke mortality during this period, although this hypothesis has not been formally tested. The data presented show that smoking-related stroke deaths decreased from 2000 to 2009 as a result of the declining prevalence of smoking for this period, with declines undoubtedly larger in previous decades when an even greater falloff in smoking prevalence was achieved, suggesting a moderate impact of smoking on the overall decline in stroke mortality. However, a paradox in the relation of smoking with the decline in stroke mortality is the period up to the mid-1960s, during which smoking rates were dramatically increasing whereas stroke mortality was rapidly declining. The role of secondhand smoke in declining stroke mortality remains unclear because of the inconclusive evidence for a causal effect of secondhand smoke on stroke mortality. Other respiratory-related conditions, including pneumonia and OSA, may have had an impact on the decline in stroke mortality, given their associations with stroke risk and/or poststroke mortality, but epidemiological data are not sufficient to determine their impact.

## Contribution of Air Pollution and Environmental Factors to Decline in Stroke Mortality

As a result of the Clean Air Act and the implementation and periodic revision of clean air standards, air pollution levels in the United States have decreased considerably over time.396 Declines have been substantial for particulate matter (PM), a pollutant with known links to CVD (below); thus, this section focuses on the impact of PM on declining stroke mortality. PM is a “complex mixture of extremely small particles and liquid droplets.”397 Particles are measured by their size in micrometers, and this size is related to their potential to cause health problems.398 Both PM_{10} (particles 10 μm in diameter) and PM_{2.5} (particles 2.5 μm in diameter) are criteria pollutants, meaning that they are regulated by the US Environmental Protection Agency.
There have been several revisions to the standards for PM in the past 40 years based on mounting epidemiological evidence linking exposure to PM to morbidity and mortality. The first standards for this pollutant were based on total suspended particles, with a revision in 1987 to focus on the standards for PM$_{10}$. Standards for PM$_{2.5}$ were added in 1997 with an update to reflect stricter allowable levels for this pollutant (for a 24-hour period) in 2006. A national monitoring network for PM$_{10}$ began in 1999 and was fully implemented in 2000.

In terms of temporal trends, in the United States, PM$_{10}$ emission levels (the amount of pollutant released into the atmosphere) peaked in 1950, with a sharp decline beginning in 1970, when the US Environmental Protection Agency was established and clean air standards were initiated. There was a subsequent leveling off of emission levels in the 1990s. Concentrations of PM in the air are affected by emission levels and weather; thus, the declining emissions have translated into declining PM concentrations. From 1990 through 2010, there was a 38% decrease in the national average of PM$_{10}$ concentrations (based on annual second maximum 24-hour average), and from 2000 through 2010, there was a 27% decrease in the national average of PM$_{2.5}$ concentrations (based on seasonally weighted annual averages). Although monitoring data are not available, declines in PM concentrations were undoubtedly larger before 1990, given the large declines in emission levels.

The influence of air pollution on CVD was summarized in a 2004 scientific statement published by the AHA with an updated statement focused specifically on PM published in 2010, given the growing body of literature for this pollutant published after the 2004 report. As summarized in the 2010 report, there is evidence from epidemiological studies of both short- and long-term effects of exposure to PM on stroke risk and mortality. Briefly, time-series studies conducted in the United States, where levels are lower than those seen in many other parts of the world, have demonstrated significant associations between acute exposure to PM$_{10}$ and stroke hospital admissions. Similarly, results from a time-series study and a case-crossover study in the United States have demonstrated significant associations between short-term exposure to PM$_{2.5}$ and stroke risk and mortality. Importantly, the case-crossover approach controls for potential confounders of the PM-stroke association, which is a limitation of most time-series studies; however, this case-crossover study was limited to 1 geographic area. As described in the AHA report, there is also supporting evidence of the PM-stroke association from outside the United States.

With regard to long-term effects, there is less published information, although this area of research is growing. Investigators from the Women’s Health Initiative (WHI) found an increased risk of both fatal (HR, 1.83; 95% CI, 1.11–3.00) cerebrovascular disease and nonfatal (HR, 1.28; 95% CI, 1.02–1.61) stroke with increasing exposure to PM$_{10}$ after accounting for confounding factors, but similar results were not found in CPS II or the Health Professionals Follow-up Study. In the latter, associations were also not found between PM$_{10}$ and stroke mortality. In the California Teachers Study, a large prospective study of women, PM$_{10}$ (HR, 1.06; 95% CI, 1.00–1.13) was associated with incident stroke. A borderline association of PM$_{2.5}$ (HR, 1.14; 95% CI, 0.99–1.32) with incident stroke was identified in the entire cohort, with a significant association noted among the subset of postmenopausal women. Associations with stroke mortality, however, were not found. Note that these studies varied in their exposure ascertainment, study populations, and adjustment for confounding factors, making comparisons across the studies challenging.

Although not specific to stroke mortality, Laden et al considered whether declines in PM over time have contributed to declines in cardiovascular mortality. In this follow-up study of the Harvard Six Cities Study, PM$_{2.5}$ concentrations and cardiovascular mortality were ascertained for 2 time periods, 1974 to 1989 (period 1) and 1990 to 1998 (period 2). The study found that PM$_{2.5}$ exposure was associated with cardiovascular mortality to a similar extent for the 2 periods and that improved cardiovascular mortality over time was associated with decreased mean concentrations of PM$_{2.5}$ between the 2 periods after accounting for confounding factors. Specifically, controlling for PM$_{2.5}$ in period 1, each 10 μg/m$^3$ reduction in mean PM$_{2.5}$ concentrations in period 2 was associated with a reduction in cardiovascular mortality risk (RR, 0.73; 95% CI, 0.57–0.95). If PM is linked to stroke mortality, it can be conjectured that decreasing concentration levels have also contributed to declining stroke mortality rates over time, although this has not been formally evaluated.

In summary, although large decreases in PM concentrations in the United States have occurred in recent years, the role of PM air pollution in declining stroke mortality remains unclear because of inconclusive epidemiological evidence of a causal effect of PM on stroke mortality. This association is made more complex by the period from the beginning of the 1900s to the 1970s, during which pollution levels were increasing whereas stroke mortality was declining. Although studies conducted in the United States have demonstrated associations between short-term PM exposures and stroke risk and mortality, almost all have been ecological in nature, leaving open the potential for confounding by individual-level factors. Studies of long-term PM exposures conducted in the United States have not been consistent with respect to an association with stroke risk, mortality, or both.

**Contribution of Exercise to Decline in Stroke Mortality**

Associations between higher levels of physical activity and reduced all-cause mortality and CVD mortality have been found in large prospective cohort studies and reported in meta-analyses. Fewer studies have examined the role of physical activity and stroke mortality. This section reviews the literature focused on the potential impact of physical activity and cardiorespiratory fitness on stroke incidence and mortality.

Hu et al analyzed data from the Nurses’ Health Study, which followed up 72,488 female nurses for 8 years and collected physical activity levels 3 times during the study period. Physical activity, including moderate-intensity exercise (ie, walking), was associated with a substantial reduction in the
risk of incident total stroke and ischemic stroke in a dose-response relation. RRs for experiencing a stroke in the lowest to highest metabolic equivalent tasks quintiles were 1.00, 0.98, 0.82, 0.74, and 0.66 (P for trend=0.005). As part of the Women’s Health Study, a cohort of 37,636 women were followed up for 10 years,426 and healthy lifestyle self-reported data (abstinence from smoking, low BMI, moderate alcohol consumption, regular exercise, and healthy diet) were collected. The overall healthy lifestyle index, derived from self-reported data, was associated with a significantly reduced risk of incident total and ischemic stroke but not hemorrhagic stroke. In the National Runners’ Health Study, Williams422 reported that the risk for having a stroke was substantially reduced for men and women who reported vigorous physical activity. Men and women who ran ≥2 km/d (exceeding the guideline physical activity level) had significantly lower risk than those who ran less (P=0.05), and those who ran ≥4 km/d had significantly lower risk than those who ran 2 to 3.9 km/d (P=0.02). Men and women who ran ≥8 km/d were at 60% lower risk than those who ran <2 km/d (P<0.01).

Several studies examined physical activity or fitness and stroke mortality. In the Nord-Trøndelag Health Survey in Norway, Ellekjaer et al423 reported that physical activity was associated with reduced risk of death resulting from stroke among women ≥50 years of age (n=14,101) who were followed up for 10 years. For all women, the adjusted RR of risk of stroke death was 0.77 (95% CI, 0.61–0.98) for medium levels of physical activity and 0.52 (95% CI, 0.38–0.72) for high levels of physical activity. When data were stratified by age group, women 50 to 69 years of age had reduced risk of stroke for medium and high levels of physical activity, and women 70 to 79 years of age had a reduced risk of stroke death for high levels of physical activity. Another cohort study followed up 31,023 men and 42,242 women in Japan 40 to 79 years of age for 10 years after completion of a physical activity survey. The multivariate-adjusted HR for the highest versus the second lowest categories of walking or sports participation was 0.71 (95% CI, 0.54–0.94) for ischemic stroke death. When data were stratified by sex, the inverse relationship remained, but the results were not statistically significant.424

Lee and Blair426 used data from the Aerobics Center Longitudinal Study, a US-based prospective cohort study of 16,878 men who were followed up for an average of 10 years. Moderate and high levels of cardiorespiratory fitness were associated with lower risk of stroke mortality in this sample. Highly fit men had a 68% (95% CI, 0.12–0.82) lower risk of stroke mortality and moderately fit men had a 63% (95% CI, 0.17–0.83) lower risk of stroke mortality compared with men with low levels of fitness. The cohort study reported by Hooker et al425 included 46,405 men and 15,282 women who completed a maximal treadmill exercise test between 1970 and 2001. Cardiorespiratory fitness was grouped as quartiles of the sex-specific distribution of maximal metabolic equivalents achieved. Mortality follow-up based on the National Death Index was conducted through December 31, 2003, and data on nonfatal stroke, defined as physician-diagnosed stroke, were obtained from surveys through 2004. Significant inverse associations between cardiorespiratory fitness and age-adjusted fatal, nonfatal, and total stroke rates were found for women and men.

For stroke survivors who have functional limitations, reduced physical activity after stroke may lead to an increased risk of mortality. For example, among a nationally representative sample of the US population with previous stroke who were followed up for 6 to 12 years, regular exercise was associated with reduced all-cause mortality (HR, 0.66; 95% CI, 0.44–0.99).435

The prospective cohort studies described above suggest that higher levels of physical activity could reduce stroke mortality. The question of whether physical activity is a factor that contributed to the observed decline in stroke mortality between 1970 and 2010 requires data showing that physical activity among the US population increased during that time. According to the Centers for Disease Control and Prevention, the proportion of the US population who reported no leisure-time physical activity decreased from ≥31% in 1988 to 28% in 1998 and 25% in 2008.427 More detailed data from the BRFSS surveys showed that the percentage of people who engaged in recommended levels of activity increased slightly from 24% in 1990 to 25% in 1998. The percentage of those reporting insufficient activity increased from 45% in 1990 to 46% in 1998, and those reporting no physical activity decreased from 31% in 1990 to 29% in 1998.428 The reduction in physical activity during the past 50 years has been tied to workplace technological changes leading to a decline of physically active occupations, changes in the home with the increased availability and use of labor-saving devices, and changes in transportation systems with widespread use of automobiles.429

In summary, the available data suggest small increases in the amount of physical activity in the past 20 years, and thus the effect of physical activity on the decline in stroke mortality may be minimal.

Effect of Obesity and Body Mass Patterns on Decline in Stroke Mortality

Obesity prevalence rates are rising in the United States. It is estimated that 36% of US adults are obese and 33% are overweight.430 Although increased body weight is an established risk factor for primary stroke,429–431 the relation of body size and obesity, defined as a BMI >30 kg/m², with stroke mortality is more complex. A large prospective study of 18,403 middle-aged London-based male government employees reported that compared with normal-weight subjects, overweight or obese men who were free of coronary heart disease at initiation of the study had an increased risk of mortality, including stroke mortality (OR, 1.64; 95% CI, 1.17–2.28).432 The association between increased weight and mortality was mediated largely through risk factors such as blood pressure and plasma levels of cholesterol and glucose.432 Several large studies in the general US population have consistently identified a link between obesity and increased CVD mortality,433,434 but few have investigated stroke mortality specifically. In a collaborative meta-analysis of 57 prospective studies with 894,576 participants,
mostly in western Europe and North America (61% male; mean recruitment age, 46 years), there was no evidence of an association between BMI and stroke mortality in the lower BMI range (15–25 kg/m²). However, in the upper BMI range (25–50 kg/m²), each 5-kg/m²-greater BMI was associated with 40% higher stroke mortality, regardless of stroke subtype. This association was mostly accounted for by the effects of BMI on blood pressure and was much stronger in middle than in old age.435 Similarly, risk is increased with the association of body mass and increased metabolic risk factors, indicating the benefit of lifestyle modification.136

Most studies examining the association of BMI with stroke mortality have been conducted in Asian populations, where BMI tends to be lower and stroke incidence higher than in the United States. In a prospective study of 212,000 Chinese men 40 to 79 years of age with no history of CVD, there was a significant excess risk of stroke deaths among those with a BMI ≥25 kg/m². This association was largely accounted for by higher blood pressure in these subjects and did not differ by major stroke subtypes.486 BMI was linearly related to increased stroke mortality in a prospective study of 154,736 Chinese men and women ≥40 years of age. In this study, the relation between BMI and stroke mortality was stronger among participants ≤60 years of age.437 In a prospective cohort of 3,321 Korean postmenopausal women, obesity was associated with an increased risk of total stroke mortality and hemorrhagic stroke mortality and with an increased risk of ischemic stroke mortality among ever-smokers but not never-smokers.488 In a prospective cohort of 43,913 Japanese adults 40 to 79 years of age with no history of cancer, stroke, and ischemic heart disease, both obesity, defined as self-reported BMI ≥27.5 kg/m², and underweight, defined as self-reported BMI <18.5 kg/m², were associated with all stroke mortality. A trend for a U-shaped association was observed for both hemorrhagic and ischemic stroke mortality, but only associations between increased hemorrhagic mortality and lower BMI and between increased ischemic stroke mortality and higher BMI were statistically significant.439 An association of total and hemorrhagic stroke mortality with underweight has also been reported in a study of 104,928 Japanese adults 40 to 79 years of age who were free of stroke, coronary heart disease, and cancer at enrollment.440 Fatal hemorrhagic stroke was also more frequent in lean men than in overweight and obese men in the Physicians’ Health Study of 21,414 US male physicians.450

The association of body fat distribution with stroke mortality has not been widely addressed. In a study of middle-aged male civil servants free of CVD in Israel, subcapsular skinfold thickness, a measure of subcutaneous trunk fat, and subcapsular-to-triceps skinfold thickness, a measure of trunk versus peripheral body fat distribution, were associated with increased long-term stroke mortality. The association between central adiposity and stroke mortality was independent of BMI but was at least partially mediated by blood pressure.441

The complex relation between body weight and stroke mortality is also manifest in patients with established stroke. Mounting evidence suggests that overweight and obese patients with established CVD have a more favorable prognosis than leaner patients.442 In a Danish stroke registry of 21,884 hospitalized stroke patients with BMI data (mean age, 72.3 years), total poststroke mortality was inversely related to BMI even after accounting for CVD risk factors.443 Overweight and obese patients had 27% and 16% lower mortality rates, respectively, than normal-weight patients, whereas underweight patients had the highest mortality rate. This association was independent of age and smoking status and was similar for hemorrhagic and ischemic stroke patients. A study of the association between BMI category and all-cause mortality in 644 stroke survivors from NHANES III, a nationally representative survey of the noninstitutionalized civilian US population ≥25 years of age, showed that after multivariable analysis, overall risk for all-cause mortality increased per kilogram per square meter higher BMI (P=0.030), but an interaction between age and BMI (P=0.009) revealed that the association of higher BMI with mortality risk was strongest in younger people and declined linearly with increasing age such that, in the elderly, overweight and obesity had a protective effect. The results were similar for the cardiovascular mortality outcome. Obese/overweight people <70 years of age were more likely to die as a result of cardiovascular or all causes than their normal-weight counterparts. However, elderly stroke patients who were overweight or obese had a decreased rate of all-cause and cardiovascular mortality compared with normal-weight people of the same age.444 Similar findings of a protective effect of overweight/obesity on all-cause mortality after stroke have been reported in 2,785 first-ever acute stroke patients from Greece.445 The risk of 10-year total mortality was lower by 18% and 29% in overweight and obese patients, respectively, compared with those with normal BMI. Overweight and obese patients also had better early (1 week) survival rates.

The effect of weight change on cardiovascular mortality in obese/overweight people with CVD and/or diabetes mellitus has been recently reported in the Sibutramine Cardiovascular Outcomes (SCOUT) trial, which assessed the effects of weight loss by lifestyle intervention and pharmacotherapy on cardiovascular morbidity and mortality, including stroke.446 Modest weight loss over short-term (6 weeks) and longer-term (up to 12 months) periods was associated with a lower cardiovascular mortality. In those with severe CVD, there was a U-shaped association between cardiovascular mortality and weight change.

There are data to suggest that adhering to a combination of healthy lifestyle practices in consideration of body size can lower both stroke incidence421,447 and mortality after stroke.435 In a nationally representative sample of the US population (n=15,299) with previous stroke (n=649) followed up from survey participation (1988–1994) to mortality assessment (2000), the relations between 5 factors (eating ≥5 servings of fruits and vegetables per day, exercising ≥12 times a month, having a BMI of 18.5–29.9 kg/m², having a moderate alcohol intake [1 drink per day for women and 2 drinks per day for men], and not smoking) and all-cause and cardiovascular mortality were assessed.436 Combinations of healthy lifestyle factors were associated with lower all-cause and cardiovascular
mortality in a dose-dependent fashion. All-cause mortality decreased with higher numbers of healthy behaviors (1 to 3 factors versus none: HR, 0.12; 95% CI, 0.03–0.47; 4 to 5 factors versus none: HR, 0.04; 95% CI, 0.01–0.20; 4 to 5 factors versus 1 to 3 factors: HR, 0.38; 95% CI, 0.22–0.66; P for trend=0.04). Similar effects were observed for cardiovascular mortality (4 to 5 factors versus none: HR, 0.08; 95% CI, 0.01–0.66; 1 to 3 factors versus none: HR, 0.15; 95% CI, 0.02–1.15; 4 to 5 factors versus 1 to 3 factors: HR, 0.53; 95% CI, 0.28–0.98; P for trend=0.18).

In summary, the impact of obesity and body mass patterns on stroke mortality likely differs in the contexts of health or preexisting stroke or CVD, stroke subtypes, age, and other risk factors. The pathophysiological mechanisms underlying these complex relationships are incompletely understood and highlight the need for well-designed prospective and interventional studies to clarify the role of body size and composition, nutritional status, and their change over time on stroke mortality and outcome. Although obesity is associated with increasing prevalence of hypertension and diabetes mellitus, the increase in prevalence of obesity does not appear to influence the decline in stroke mortality rates. This most likely is attributable to treatment effects of hypertension and diabetes mellitus.

Impact of Research and Program Funding on Decline in Stroke Mortality: A Case Study

The 1965 Report of the Commission on Heart Disease, Cancer, and Stroke called for a nationwide increase in screening and treatment of hypertension. Although actuarial studies showed a clear relation between rising blood pressure and increased risk of death and epidemiological studies showed a high prevalence of hypertension, no public health initiative was created. At that time, there was no clear evidence of the benefit of lowering blood pressure. The evidence became available with the publication of the 1967 and 1969 Veterans Administration Cooperative Study on the Treatment of Hypertension. Armed with this information, Elliot Richardson, Secretary of the US Department of Health, Education, and Welfare, created the NHBPEP. The NHBPEP was designed to raise public awareness and to stimulate screening and treatment throughout the nation. The NHBPEP included the 50 state health departments, 2000 community groups, 7 federal agencies, and a coordinating committee composed of 45 national voluntary health organizations and professional societies. In addition, throughout the 1970s, 1980s, and beyond, several national professional associations such as the American Society of Hypertension, International Society on Hypertension in Blacks, AHA Council for High Blood Pressure Research, American Stroke Association, Consortium for Southeastern Hypertension Control, National Hypertension Association, and National Stroke Association, along with AHA programs such as Get With The Guidelines, Million Hearts (in partnership with the US Department of Health and Human Services), Power to End Stroke, assorted stroke prevention guidelines, and other professional medical and nursing societies, began to increase activities in hypertension research service and education. These NHBPEP partners used mass media campaigns, conducted patient education programs, developed clinical guidelines, held national and regional conferences on the detection and management of hypertension, and stimulated development of hypertension detection and control programs at the local level. Hypertension quickly became fashionable and in the public eye. Within 1 decade, the percentage of people aware of their hypertension substantially increased, treatment rates doubled, and control rates increased to over half within the past 4 decades.

Concomitantly, mean arterial blood pressures have fallen precipitously (Figure 5). In addition to increasing public awareness about hypertension, the NHBPEP appears to have interested scientists and clinical investigators in seeking more information about the condition. The number of citations from the National Library of Medicine PubMed database accessed by using the search terms hypertension and clinical trials increased from <50 in 1972 to 1200 per year in 2002. The decline of stroke mortality represents an indicator of success and a metric for programs and strategies specifically designed and implemented to reduce risks. Stroke mortality has been recognized for decades as an outcome with significant racial disparities, with particular high risk among blacks. The decline in stroke mortality for all racial/ethnic groups has reduced the magnitude of the racial/ethnic gap in stroke mortality risks and likewise the variation in stroke mortality by geographic area, with particular emphasis in the Stroke Belt. Although the racial/ethnic and geographic stroke risk disparities are evident, the factors associated with the patterns appear to originate in early life. These disparities and excess disease risks have been the stimulus for research and intervention programs focused on the identification of factors associated with these disparities. Included in these decades of funded efforts is the REGARDS study, which is focused on the identification of factors associated with racial and geographic differences in stroke risks.

This large cohort has confirmed many of the parameters for the differences in stroke risks, including elevated blood pressure and diabetes mellitus, and has identified additional factors. These epidemiological studies have contributed to the effective intervention programs for reducing the disparity gaps in stroke risks.

In summary, driven by solid research findings on stroke risk and prevention, funding of studies and intervention programs has made a significant contribution to the reduction in stroke mortality, as well as the narrowing of the racial/ethnic and geographic disparities in risks. For the nation as a whole, control rates for hypertension have improved 6-fold during the past 4 decades, driven by an increase in public awareness and treatment. The campaign has stimulated scientists to identify more refined contributing factors of stroke and high-impact intervention programs.

Other Factors

The factors and parameters associated with the decline in stroke mortality previously described represent the traditional influences with the highest evidence and studies. Other conditions also could contribute to the decline in stroke and serve...
as mediating factors that reduce stroke risk and stroke risk factors.

Sickle cell disease has long been recognized as associated with increased risk of stroke among young blacks. Treatment guidelines and protocols have been implemented over the past 2 decades, including use of transcranial Doppler and transfusion therapy, and have significantly reduced the stroke risks for this population. Nonetheless, these interventions among patients with sickle cell disease affect a relatively low number of people and probably have minimal impact on the overall historical and large stroke declines.

Salt intake is a cardiovascular risk factor, with reduced sodium intake associated with reduced stroke rates, which is independent of other risk factors such as hypertension. The potential impact of sodium reduction is reported on the individual and population levels. Good measures of population-wide consumption of sodium over long periods are needed to determine the contribution of sodium reduction to long-term stroke mortality trend data. Reducing sodium consumption, however, can reduce blood pressure levels and is adjunctive therapy for most and definitive therapy for some patients with hypertension.

Adherence to medical regimens has served as a mediating factor in the decline in stroke mortality rates. The impact is seen through the reduction in stroke risk factors. Within the past few decades, hypertension control rates and smoking cessation rates have substantially improved, suggesting that patients are adhering more to their medical regimens.

Diet is also a mediating factor in the decline of stroke mortality. The Dietary Approaches to Stop Hypertension eating plan, which uses a diet that is low in sodium and rich in potassium and calcium, has been shown to reduce blood pressure levels. Higher dietary potassium intake and magnesium intake are associated with lower rates of stroke, particularly among hypertensive women. The impact on steady long-term decline in stroke mortality requires more data.

In summary, these parameters are reasonable considerations as factors influencing the decline in stroke mortality and represent very important components of stroke prevention. The factors are strongly associated with other risk variables for stroke. More research is needed to quantify their direct effect and influence on stroke mortality.

Conclusion and Discussion

Stroke has now moved from the third to the fourth leading cause of death in the United States. Within the past 5 decades, the decline in stroke mortality represents a major success for public health and clinical medicine. The decline is seen among both sexes and all racial/ethnic and age groups. In addition to reduced overall risks, the reduced mortality for people <65 years of age contributes significantly to the improved reduced years of potential life lost. The decline is considered valid and real and not an artifact of competing conditions as cause of death or recurrent stroke rates or a marked increase in death rates from respiratory disease. Although the precise attribution of specific factors is not possible, the writing panel was able to assess multiple factors and interventions associated with the decline. Most likely, the combination of the different parameters and programs contributes to the significant decline. However, the available evidence indicates that some factors have a greater impact. Clinical trial evidence demonstrates that lowering blood pressure reduces strokes and stroke deaths. Observational and epidemiological studies demonstrate that blood pressure levels are associated with risk of stroke mortality, that is, the higher the blood pressure, the greater the risk for stroke. National probability survey data have shown a significant improvement in blood pressure control and reduction in population systolic pressures. These factors are associated with a very significant and accelerated decline in stroke deaths. Treatment and control of diabetes mellitus and hyperlipidemia have contributed to the stroke mortality declines; however, the onset of these interventions is more recent, and thus their impact is less clear. Systems of care, use of tPA, smoking cessation, air pollution, exercise, AF, and other factors may play a role, but additional studies are needed to determine their impact on population stroke deaths.

The decline in stroke mortality is one of the major public health successes of the past 50 years. With the implementation of evidence-based primary, secondary, and tertiary stroke prevention strategies, these trends should continue.

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### Disclosures

#### Writing Group Disclosures

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*Modest.
†Significant.
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影响脑卒中死亡率下降的因素

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Factors Influencing the Decline in Stroke Mortality
A Statement From the American Heart Association/American Stroke Association

Daniel T. Lackland, DrPH, FAHA, Chair; Edward J. Roccella, PhD, MPH, Co-Chair; Anne F. Deutsch, RN, PhD, CRRN; Myriam Fornage, PhD, FAHA; Mary G. George, MD, MSPH, FAHA; George Howard, DrPH, FAHA; Brett M. Kissela, MD, MS; Steven J. Kittner, MD, MPH, FAHA; Judith H. Lichtman, PhD, MPH; Lynda D. Lisabeth, PhD, MPH, FAHA; Lee H. Schwamm, MD, FAHA; Eric E. Smith, MD, MPH, FAHA; Amyitis Towfighi, MD;
on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Quality of Care and Outcomes Research, and Council on Functional Genomics and Translational Biology

背景和目的: 卒中死亡率从二十世纪早期一直不断下降。尽管这一下降令人可喜，但引起下降的原因尚未完全清楚。在美国，最近脑卒中死亡率显著快速地下降，使得脑卒中从第三位死因下降到第四位，这引发了人们详细评估“造成卒中风险与死亡率变化的相关因素”。本声明列举了促进死亡率下降相关因素的证据，并思考了如何利用这些证据用于未来制定对主要公众健康负担的疾病干预计划。

方法: 撰写组成员是由相关领域的委员会主席和副主席任命，并获得美国心脏协会(AHA)卒中委员会科学声明监督委员会及AHA初稿监督委员会批准。写作者应用系统文献回顾，参考已发表的临床和流行病学研究、发病率和死亡率报告、临床和公共健康指南、权威声明、个人卷宗，以及专家意见来总结证据，表明当前的学术分歧。在美国心脏协会科学咨询和协调委员会审议和批准之前，文献经历了广泛的美国心脏协会内部同行评审，卒中委员会领导审核以及科学声明监督委员会审核。

结果: 在过去几十年里，卒中死亡率下降是公共健康的一项重大进步，不论男女、种族、各年龄组均可观察到这种下降。不考虑少数卒中死亡病例对总体的影响，卒中死亡率的主要下降是在<65岁的人群中，这意味着潜在生命年丧失的减少。卒中发生率的降低及较低的病死率导致了卒中死亡率的下降。脑卒中结局的这种显著进步与心血管危险因素控制干预结果一致。虽然很难计算出具体归因危险因素的评估，然而从1970年开始的对高血压的控制似乎对脑卒中的快速下降呈现了最为显著的影响。后来实施的糖尿病和血脂异常控制以及戒烟计划，尤其联合高血压控制，都有助于脑卒中死亡率的下降。远程医疗和脑卒中管理体系所起的潜在影响似乎非常大，但尚无足够长时间来表明它们对脑卒中死亡率下降的影响。其他因素也可能有作用，但还需更多研究以确定他们的作用。

结论: 脑卒中死亡率的下降是真实的并且代表了公共健康和临床医学的重大成功。脑卒中从第三位死因下降到第四位，是真正意义上的死亡率下降，而非由于慢性肺疾病死亡率上升，肺疾病在美国现在是第三位死因。强有力的证据表明卒中死亡率的下降是由于采取的干预措施和实施的项目导致的，这些项目是基于循证科学研究，并以减少脑卒中风险为目的，最有可能是减少高血压控制上的进步。因此，医学研究和研究发现在干预项目上的应用提高了人口健康状况。积极的以循证为基础的公共卫生项目和临床干预措施的持续应用将导致脑卒中死亡率的进一步下降。

关键词: AHA 科学声明, 糖尿病, 高脂血症, 高血压, 危险因素, 脑卒中

(Stroke. 2014;45:315 - 353. 首都医科大学附属北京天坛医院 窦鑫 陈瑶枝 译；刘丽萍 校)