AHA/ASA Scientific Statement

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; Amytis 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

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

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on July 3, 2013. A copy of the document is available at http://my.americanheart.org/statements by selecting either the “By Topic” link or the “By Publication Date” link. To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.


Expert peer review of AHA Scientific Statements is conducted by the AHA Office of Science Operations. For more on AHA statements and guidelines development, visit http://my.americanheart.org/statements and select the “Policies and Development” link.

Permissions: Multiple copies, modification, alteration, enhancement, and/or distribution of this document are not permitted without the express permission of the American Heart Association. Instructions for obtaining permission are located at http://www.heart.org/HEARTORG/General/Copyright-Permission-Guidelines_UCM_300404_Article.jsp. A link to the “Copyright Permissions Request Form” appears on the right side of the page.

© 2013 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/01.str.0000437068.30550.cf

Downloaded from http://stroke.ahajournals.org/ by guest on December 6, 2013
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. 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. Stroke has now fallen from the third to the fourth leading cause of death in the United States.

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. Between 1900 and 1968, deaths resulting from stroke have shown a steady and (nearly) monotonic decrease, falling from >150 per 100,000 to ≈50 per 100,000. 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. 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 al 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) system and historical reports from the National Vital Statistics System (NVSS) 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. When data are available on temporal patterns in incidence and hospitalization rates, the data seem to reflect that these mortality declines are at least partly associated with the declining incidence of stroke. 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. 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).31 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-10.31

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 6,440 (5%) were identified as “cerebral infarction” (I63).4 Even among the 6,440 deaths coded as “cerebral infarction” (I63), 3,526 (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).4 This substantial lack of specificity implies that the sensitivity of nosologist-coded stroke with physician adjudication was 68%, whereas the specificity was 95%.34 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.35 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.36,37 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.38

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 shifted between 1940 and 2000 to a distribution with a greater proportion of elderly people in the population that 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 (e.g., 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.39

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%.33 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%.34 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.35 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.36,37 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.38

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 that 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 (e.g., 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.39

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 2009.40 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.

Recurrence 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.83 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 Saver84 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, antiplatelet 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. This scientific evidence is essential to carefully and quickly identify the most effective and appropriate treatments for stroke patients.

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 recoded 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 2010.7 Per 100,000 population, standardized to the US 2000 standard population. Diseases were classified according to the International Classification of Disease codes in use at the time the deaths were reported. *Data for 2010 are preliminary.
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 mm Hg), 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.\textsuperscript{111} 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.\textsuperscript{112}

**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.\textsuperscript{113–115} Global hypertension prevalence estimates of 1 billion people with an estimated 7.1 million deaths per year may be attributable to hypertension.\textsuperscript{116} As the population ages, the number of people with elevated blood pressure increases.\textsuperscript{113,117,118} 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\textsubscript{Hg}.\textsuperscript{115,119} The mean SBP for the US adult population declined from 131 mm\textsubscript{Hg} in 1960 to 122 mm\textsubscript{Hg} in 2008\textsuperscript{113,120,121} (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\textsubscript{Hg}. This declining shift in blood pressure distributions was consistent for different age groups, including age 18 to 29, 30 to 59, 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\textsuperscript{122} 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.\textsuperscript{118} 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\textsubscript{Hg},\textsuperscript{110,123} epidemiological data demonstrate that the risk of stroke begins at blood pressure levels ≤140/90 mm\textsubscript{Hg}. In a meta-analysis of 61 prospective, observational studies conducted by Lewington et al\textsuperscript{110} 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\textsubscript{Hg} and DBP of 75 mm\textsubscript{Hg}, each incremental rise of 20 mm\textsubscript{Hg} in SBP and 10 mm\textsubscript{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.\textsuperscript{124} 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.\textsuperscript{125} 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.\textsuperscript{125} Such lifetime risk estimates can be used in calculating the impact of blood pressure reduction for stroke mortality declines.\textsuperscript{118} 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\textsubscript{Hg} range and 26\% for those with blood pressure of 120/80 to 129/84 mm\textsubscript{Hg}.\textsuperscript{127}

**Table. Mean Systolic Blood Pressure by Time Period**

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Systolic Blood Pressure, mm\textsubscript{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>
</tr>
<tr>
<td>1988–1991</td>
<td>119</td>
</tr>
<tr>
<td>1988–1994</td>
<td>121</td>
</tr>
<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.
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.

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. 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. 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.

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.

Stamler 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, 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. This was later corroborated by data from the US Department of Veterans Affairs.

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.”

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. 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.

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.

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 worksites 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...
a means to reduce stroke mortality risk. These programs addressed the clinical and public health efforts and demonstrated an essential partnership to reduce the population burden from stroke.

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 typically 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.\textsuperscript{221} 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.\textsuperscript{222}

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 substudy of ACCORD, patients with type 2 diabetes mellitus were found to have a reduced risk for stroke if blood pressure was tightly controlled\textsuperscript{227}; this same effect was also seen in the UK Prospective Diabetes Study (UKPDS).\textsuperscript{224} 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.\textsuperscript{225,226} 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 $\leq 150$ 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])\textsuperscript{227} 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\textsuperscript{228-230} 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,\textsuperscript{231} although a meta-analysis of all intensive care unit–based glucose management trials did not find a similar benefit.\textsuperscript{232} 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.\textsuperscript{233}

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.\textsuperscript{234}

**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.\textsuperscript{235} 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.\textsuperscript{236}

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.\textsuperscript{237} 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.\textsuperscript{236,237}

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 569,883 ischemic stroke admissions to Get With The Guidelines–Stroke 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 stroke mortality rates in the population, 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/m².239 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.256–261 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 ICH254,257; however, 1 study did not show an independent association.253 The lipid fractions responsible for the association with ICH risk are unclear,253,260,262,269 but low LDL cholesterol270 and triglyceride levels260,270 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 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.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.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.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.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.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).288 A subsequent retrospective cohort study found no association between statin use and subsequent ICH among people with previous ischemic stroke.289

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.290 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).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).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 coronary disease treated with a statin.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).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 antiplatelets 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)294 or for secondary prevention after other major vascular events (ORs, 0.62–0.73; all P<0.05).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).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.296 The risk of fatal stroke was nonsignificantly increased (OR, 1.21; 95% CI, 0.84–1.74).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 and 1980s, 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 the choice 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 39% in 1971 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 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 2007 and 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.\textsuperscript{317}

The use of aspirin has a substantial global impact as well, with differing specific high risks in developing countries.\textsuperscript{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.\textsuperscript{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 Schmidt\textsuperscript{19} 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.\textsuperscript{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.\textsuperscript{321}

Doppler ultrasonography was introduced in the 1960s.\textsuperscript{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.\textsuperscript{323} The procedures have been developed into practice protocols in an effort to prevent stroke risks.\textsuperscript{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.\textsuperscript{325} With the approval of intravenous thrombolysis and catheter-based embololysis devices as critical stroke therapies, computed tomography has become an essential component of all acute treatment protocols.\textsuperscript{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.

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.\textsuperscript{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%; \(P=0.68\)). 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. Endovascular therapies are used in <1% of AIS patients 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; \(P=0.001\)).

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 those in noncertified hospitals (10.7±1.7% versus 11.0±1.7%), although the differences were small. Almost half of JNC-certified PSC hospitals had risk-standardized mortality rates lower than the national average compared with 19% of noncertified hospitals.

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. However, a retrospective analysis of 2002 data showed that JNC PSC–certified hospitals had better outcomes than noncertified hospitals even before the program began. 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 al 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.

More recently, Langhorne et al 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.

Several hospitals described the implementation of acute stroke teams but provided few comparisons of patient outcomes before and after implementation. In Australia, Hamidon and Dewey 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 al 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. Experts strongly believe that an organized system for stroke care is necessary to deliver high-quality stroke care. Several teams have described their experiences implementing use of stroke centers and systems; 2 teams reported increased...
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 in meta-analyses pooling results across studies. Among current smokers, there is a dose-response relation between the number of cigarettes smoked and stroke risk. Smoking cessation results in a reduction in stroke risk. Data from the FHS demonstrated that among former smokers, stroke risk decreased by 2 years after smoking cessation and was at the level of nonsmokers by 5 years after cessation. Similar to studies of incidence, studies focused on stroke mortality have demonstrated associations with smoking. In the Multiple Risk Factor Intervention Trial (MRFIT), after 10 years of follow-up, the RR of stroke mortality associated with current smoking was 2.5. In the Cancer Prevention Study II (CPS II), risk of stroke mortality for current smokers versus never smokers was 1.7 in men and 2.2 in women after accounting for demographics and additional risk factors in a multivariable model. In addition, abstention from smoking after stroke is associated with better outcomes. A retrospective analysis of people who participated in NHANES from 1988 to 1994 with mortality assessment through 2000 revealed that among people with a history of stroke, abstaining from smoking was associated with lower all-cause mortality after adjustment for demographic factors, medical comorbidities, and lifestyle habits (HR, 0.57; 95% CI, 0.34–0.98).

Although studies directly assessing the role of cigarette smoking in declining stroke mortality rates are lacking, assuming that the stroke mortality risk associated with cigarette smoking has remained constant over time, any decline in the prevalence of smoking would contribute to the decline in stroke mortality. The prevalence of cigarette smoking in US adults has declined substantially over time from 42% in 1965 to 19% in 2010. More recently, declines in the prevalence of smoking have slowed, with a 24% relative change in current cigarette smoking for the period 1995 through 2010 and an 8% relative change for the period 2005 to 2010. In addition, smoking intensity or the number of cigarettes smoked per day among smokers has decreased over time.

Stroke deaths attributable to smoking for successive years can be determined by using estimates of prevalence of current smoking over time, the confounder-adjusted HRs for 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 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 Thus, any reduction in the occurrence of poststroke pneumonia or in its impact on case fatality over time would translate into improvements in stroke mortality. The incidence of poststroke pneumonia and its impact on case fatality have likely improved over time as a result of earlier detection and treatment among stroke patients, as well as the availability and increased uptake of pneumococcal vaccines, particularly among the elderly.380 A recent analysis of stroke admissions identified from the Nationwide Inpatient Sample suggested no change in the percentage of in-hospital cases of pneumonia for the relatively short period from 1997 and 1998 to 2005 and 2006381; however, longer-term temporal trend data are not available. Similarly, data on changes in the impact of pneumonia on stroke case fatality over time are not available.

Sleep-disordered breathing is common in the United States both in the general population and in stroke patients. Obstructive sleep apnea (OSA), one form of sleep disordered breathing, is increasingly prevalent in the United States and has been identified as an independent risk factor for ischemic stroke and for the combined end point of stroke and death in prospective studies.382,383 In the Sleep Heart Health Study, OSA measured by the apnea-hypopnea index was associated with risk of incident ischemic stroke in men after multivariable adjustment for confounders (P=0.016 for linear trend associated with quartiles of the apnea-hypopnea index). Compared with men in the lowest quartile of the apnea-hypopnea index, men in the highest quartile had an adjusted HR of 2.86 (95% CI, 1.1–7.4). A similar dose-response pattern was not observed in women.382 OSA is also associated with poststroke mortality.384–386 The prevalence of OSA among middle-aged adults has been estimated to be 4% for men and 2% for women (measured as an apnea-hypopnea index >5 and sleepiness) or 24% in men and 9% in women based on the apnea-hypopnea index alone.387 The prevalence of OSA has likely increased over time because of the increasing prevalence of obesity388; however, long-term trend data are not available. An analysis from the National Ambulatory Medical Care Survey reported a 12-fold increase in the diagnosis of sleep apnea in outpatients between 1990 and 1998.389 Countering the increase in prevalence in 1981, treatment for OSA with continuous positive air pressure became available.390,391 Treatment with continuous positive airway pressure reduces cardiovascular events and thus could affect stroke risk.392 However, OSA is underdiagnosed393 and compliance with continuous positive airway pressure treatment, particularly among stroke patients, is suboptimal,394,395 making it difficult to assess the potential impact of OSA and its treatment on stroke mortality trends.

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.397 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 because of their potential to cause harm to humans.398 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.398 The first standards for this pollutant were based on total suspended particles, with a revision in 1987 to focus the standards on 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$_{2.5}$ 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.399 There was a subsequent leveling off of emission levels in the 1990s.400 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).401 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 AHA402 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.403 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.404–406 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.407,408 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.409 As described in the AHA report, there is also supporting evidence of the PM-stroke association from outside the United States.410

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$_{2.5}$ after accounting for confounding factors,410 but similar results were not found in CPS II or the Health Professionals Follow-up Study.411,412 In the latter, associations were also not found between PM$_{10}$ and stroke mortality.411 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.413 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 al414 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 mortality415,416 and CVD mortality417–419 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 al420 analyzed data from the Nurses’ Health Study, which followed up 72488 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. RR's 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, 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, Williams 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-Trondelag Health Survey in Norway, Ellekjaer et al.423 reported that physical activity was lower risk than those who ran ≥2 km/d (<60%). 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 lower risk than those who ran ≤2 km/d (exceeding the

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. 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.427

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.428 Although increased body weight is an established risk factor for primary stroke, 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, 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 212000 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.484 BMI was linearly related to increased stroke mortality in a prospective study of 154736 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 3321 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.484 In a prospective cohort of 43913 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 104928 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 21414 US male physicians.429

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, subcapular skinfold thickness, a measure of subcutaneous trunk fat, and subcapular-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 21884 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 2785 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=15299) with previous stroke (n=649) followed up from survey participation (1988–1994) to mortality assessment (2000), the relations between 5 factors (eating ≥25 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.435 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.99,100,448 Armed with this information, Elliot Richardson, Secretary of the US Department of Health, Education, and Welfare, created the NHBPEP.119 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.119 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.119–121

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 2002.119

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 risks449 and likewise the variation in stroke mortality by geographic area, with particular emphasis in the Stroke Belt.492,493 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 risks449 and likewise the variation in stroke mortality by geographic area, with particular emphasis in the Stroke Belt.492,493

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.459–461

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.

**Acknowledgments**

We appreciate the contribution of Figure 5 provided by Cathleen Gillespie, MS, Division for Heart Disease and Stroke Prevention, Centers for Disease Control and Prevention; Connie Land and Anne Leonard, AHA; and several thoughtful anonymous reviewers.
## Disclosures

The table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be “significant” if (a) the person receives $10,000 or more during any 12-month period, or 5% or more of the person’s gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10,000 or more of the fair market value of the entity. A relationship is considered to be “modest” if it is less than “significant” under the preceding definition.

*Modest.
†Significant.
This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be “significant” if (a) the person receives $10,000 or more during any 12-month period, or 5% or more of the person’s gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10,000 or more of the fair market value of the entity. A relationship is considered to be “modest” if it is less than “significant” under the preceding definition.

### References


69. Lackland et al. Decline in Stroke Mortality 29

professionals from the American Heart Association/American Stroke Outcomes Research. Guidelines for the prevention of stroke in patients

2003;34:122–126.


Effects of treatment on morbidity in hypertension, II: results in patients with diastolic blood pressure averaging 90 through 114 mmHg. JAMA. 1970;213:1143–1152.


238. Taylor FC, Cohen H, Ebrahim S. Systematic review of long term antico-


thrombotic treatment and stroke severity in patients with atrial fibrilla-


250. Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general popu-


253. Arnett DK, Jacobs DR Jr, Tracy RP, Orchard T, Fried LP, Lumbey T, Robbins J, Burke G, Newman AB, Furberg CD. The association between lipid levels and the risks of incident myocardial infarc-


255. Fine-Edelstein JS, Wolf PA, O’Dwyer DH, Poehlman E, Belanger AJ, Kase CS, D’Agostino RB. Precursors of extracranial carotid atheroscle-


257. Sacco RL, Kargman DE, Gu Q, Zamanillo MC. Race-ethnicity and deter-


259. Sah J, Lee SH, Kim HC, Nam CM, Kim IS, Appel LJ. Low serum cho-


261. Sturgeon JD, Folsom AR, Longstreth WT Jr, Shahar E, Rosamond WD, Cushman M. Risk factors for intracerebral hemorrhage in a pooled pro-


266. Kolominsky-Rabas PL, Weber M, Gefeller O, Neuendorffer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term...


365. Lackland et al. Decline in Stroke Mortality 37


385. Lackland et al. Decline in Stroke Mortality 37


