Progressive reduction in stroke deaths over the last few decades has resulted in the recent preliminary announcement that stroke has declined from the third to the fourth-leading cause of death in the United States. Moreover, the 2010 American Heart Association goal of reducing coronary heart disease and stroke mortality by 25% in the first decade of this century was achieved early, with a 30.7% reduction in CHD mortality and a 29.2% reduction in stroke mortality from 1999 to 2008.

Article see p 2111

Stroke incidence also appears to be declining. Two population-based studies in the United States and United Kingdom have demonstrated an age-adjusted decrease in stroke incidence. The rise in the number of primary and comprehensive stroke centers in the United States, increasing use of acute stroke therapies, and greater availability of evidence-based approaches to prevent and treat stroke have undoubtedly had a favorable impact on these improving trends.

Less is known about temporal trends in recurrent stroke risks. Of the estimated 795,000 annual strokes in the United States, 23% are recurrent events. In this issue of *Circulation*, Hong et al have provided important data on trends in the risk of recurrent stroke over the last 50 years. They performed a study-level systematic review of the control arms of secondary stroke prevention randomized, controlled trials with broad inclusion criteria, excluding trials that tested interventions directed at specific stroke mechanisms, such as atrial fibrillation or carotid or intracranial stenoses. In total, 59 trials and 66,157 patients in control arms were analyzed. Significant absolute average declines of 1% per decade for annual rate of recurrent stroke, 0.3% for fatal recurrent stroke, and 1.3% for major vascular events were estimated.

Other studies have also reported decreases in stroke recurrence in population-based samples. Among more than 2.5 million US Medicare beneficiaries, the 1-year recurrent ischemic stroke rate decreased by 4.5% from 13.2 per 100,000 in 1994–1996 to 12.6 per 100,000 in 2000–2002. The Perth Community Stroke Study in Australia observed a reduction in the 5-year cumulative risk of recurrent stroke from 32% to 23% between the 1989–1990 and 1995–1996 cohorts. In Scotland, the adjusted risk of recurrent stroke hospitalization decreased by 27% over 15 years. Another systematic review of more than 23,000 patients treated with aspirin in various studies observed a nonsignificant 0.9% annual relative risk reduction in stroke recurrence over time; however, that study did not include older studies without an aspirin arm, as did the present report. Lemmens et al reported on only 35% of the patients in trials that averaged a 22% lower mean follow-up than the present study, which could easily explain the absence of statistical significance in their logistic model. These reports should thus not be viewed as discrepant.

The meta-regression analyses in the present study by Hong et al showed temporal decreases in blood pressure and tobacco smoking and increased use of antithrombotic agents. In 1-by-1 adjustments of the temporal trends in recurrent stroke risk for each of these possibly contributing factors, the antithrombotic benefit was statistically significant, and effectively accounted for the time trend. Systolic and diastolic blood pressures and smoking altered standardized regression coefficients with time only modestly, and did not achieve statistical significance themselves. That the study-level results reported by Hong et al are consistent with a population-level benefit of antithrombotics but ambiguous for other risk factors should neither overly excite nor disturb us. Evidence from patient-level studies on the importance of antithrombotics and on the control of multiple vascular risk factors in prevention of first and recurrent stroke is substantial, and has been the foundation of our American Heart Association/American Stroke Association guidelines.

Contributors to temporal trends are notoriously difficult to disentangle, because concurrent trends in multiple causal and noncausal factors can confound one another’s effects. Thus, in principle, a secularly changing variable unrelated to disease, such as automotive deaths per 100 million vehicle miles, as an extreme example, could statistically behave similarly to antithrombotic use in analyses such as that by Hong et al. Moreover, study-level meta-regression analyses are subject to ecological fallacy, which compounds the interpretive problem. Inadequate data collection on potentially important contributing factors can also be a limitation. Here, antihypertensive use was not reported consistently, particularly in earlier studies, whereas blood pressure and tobacco smoking data for adjusted analyses were available for only 41% and 64% of studies, respectively, which reduced the precision and power of these analyses to detect possible meaningful effects. Unaccounted diet and exercise trends could also play potential roles. Concurrent temporal improvements in imaging and diagnostic sensitivity also likely led to recent trials enrolling higher percentages of patients with small-vessel disease–related infarcts and lower risk of symptomatic stroke recurrence. The findings by Hong et al are
suggestive, but multifactorial patient-level cohort analyses and mechanistic experimentation are far better for parsing the contributions of multiple risk factors and interventions.

Hong et al observe, importantly, that secondary stroke prevention trials have historically been substantially under-powered, and that continued declines in stroke recurrence will increase the required sample sizes and the costs of future randomized trials to detect a fixed relative risk reduction. Indeed, recent large secondary stroke prevention trials have reported a lower recurrence rate than anticipated in their original study designs, and had to increase their recruitment goals, prolong follow-up, revise inclusion criteria, and alter their projected timelines. We will need more innovative designs to test secondary prevention therapies with more efficient and cost-effective approaches. However, the projections made by Hong et al presume studies should continue to be powered against a 20% relative risk reduction. Perhaps we might wish this, but as baseline risk declines, a 20% relative risk reduction yields proportionately diminishing absolute risk reductions and proportionately increasing numbers needed to treat. Trialists need to consider whether powering studies against smaller and smaller absolute benefits is appropriate. In any case, this approach seems unsustainable because of predictable increases in postapproval risk-benefit and cost-benefit ratios of new treatments that deliver diminishing incremental gains, even if the increasing development costs caused by trial sample sizes are disregarded.

Despite declines in stroke mortality, incidence, and recurrence risk, there is cause for significant concern in the decades to come. The aging of the population will have a definite impact on the future public health burden due to stroke, which remains the leading cause of adult disability. It is projected that the US population ≥65 years of age will double by 2040. Obesity, physical inactivity, and diabetes are increasing alarmingly, particularly in children and in the middle-aged segment of our population. These factors are anticipated to greatly impact the future occurrence of vascular diseases, with an anticipated large increase in the number of annual strokes. Some recent studies have already demonstrated 3-fold increases in the prevalence of stroke among women 35 to 54 years of age from 1999 to 2004 compared with 1988 to 1994. By 2030, stroke prevalence is expected to increase by 25% from 3.2% to 4.0%, with a projected increase by 238% in direct annual medical costs to $95.6 million. In fact, Tables 1 and 2 and Figure 1 of the study by Hong et al suggest a slowing in the declines in all 3 outcome variables for trials that began enrollment in 2000 to 2009 compared with the previous decade, with all 21st century trials reporting recurrent and fatal recurrent stroke risks falling on or above the overall trend lines. The recent decline in recurrent stroke risk, in a period when secondary anti-thrombotic prophylaxis in trials is virtually universal, may be close to the smaller 0.9% annual relative risk reduction estimated by Lemmens et al. Models such as those by Hong et al are empirical summaries of the past rather than principle-based projections into the future. They provide encouragement that efforts at primary and secondary stroke and vascular prevention strategies may be working, but there is ample reason for concern and no time for complacency. We need to do everything we can to help the American Heart Association and American Stroke Association achieve the new goal of improving the cardiovascular health of all Americans by 20% while reducing deaths due to cardiovascular diseases and stroke by 20% by 2020. An invigorated focus on improving cardiovascular health across the lifespan should not only reduce the risk of a first stroke, but also the risk of a recurrence among our growing number of stroke survivors.

Disclosures

None.

References


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Further Good News on Stroke, but No Time for Rest
Jose G. Romano, Peter B. Imrey and Ralph L. Sacco

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