Declining Stroke and Vascular Event Recurrence Rates in Secondary Prevention Trials Over the Past 50 Years and Consequences for Current Trial Design

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Background—It is widely supposed, but not well-demonstrated, that cumulative advances in standard care have reduced recurrent stroke and cardiovascular events in secondary prevention trials.

Methods and Results—Systematic search identified all randomized, controlled trials of medical secondary stroke prevention therapies published from 1960 to 2009. Randomized, controlled trials narrowly focused on single stroke mechanisms, including atrial fibrillation, cervical carotid stenosis, and intracranial stenosis, were excluded. From control arms of individual trials, we extracted data for baseline characteristics and annual event rates for recurrent stroke, fatal stroke, and major vascular events and analyzed trends over time. Fifty-nine randomized controlled trials were identified, enrolling 66 157 patients in control arms. Over the 5 decade periods, annual event rates declined, per decade, for recurrent stroke by 0.996% (P=0.001), fatal stroke by 0.282% (P=0.003), and major vascular events by 1.331% (P=0.001). Multiple regression analyses identified increasing antithrombotic use and lower blood pressures as major contributors to the decline in recurrent stroke. For recurrent stroke, annual rates fell from 8.71% in trials launched in the 1960s to 6.10% in the 1970s, 5.41% in the 1980s, 4.04% in the 1990s, and 4.98% in the 2000s. The sample size required for a trial to have adequate power to detect a 20% reduction in recurrent stroke increased 2.2-fold during this period.

Conclusions—Recurrent stroke and vascular event rates have declined substantially over the last 5 decades, with improved blood pressure control and more frequent use of antiplatelet therapy as the leading causes. Considerably larger sample sizes are now needed to demonstrate incremental improvements in medical secondary prevention.

Key Words: randomized controlled trial • recurrent stroke • secondary stroke prevention • systematic review • vascular event rate

Over the last 50 years, successful clinical trials have led to the introduction into routine clinical practice of successive waves of secondary vascular prevention therapies with proven efficacy, including antihypertensive therapy, aspirin, thienopyridines and phosphodiesterase inhibitor antiplatelet therapy, warfarin for atrial fibrillation (AF), carotid endarterectomy and carotid stenting, and statins. Further progress is imperative. Despite advances in prevention practices, there were 15.3 million strokes and 5.7 million stroke deaths worldwide in 2002. Among the estimated 795 000 people with stroke in the United State each year, 185 000 are recurrent strokes. Recurrent strokes frequently lead to additional mortality or disability, and also contribute to greater cognitive decline.

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It is ironic that further advances in developing stroke prevention interventions can be hindered by past successes. If event rates in control arms of trials decline as a result of incorporating more and more proven therapies into standard care, greater sample sizes will be needed to test additional promising interventions, and trials will need to be larger and more expensive to be adequately powered. Epidemiological studies have demonstrated that first-ever stroke rates have declined by 20% to 40% with the improvement of risk factor control. It is widely supposed that similar or greater reductions have occurred in recurrent stroke rates, but salient studies are sparse, and the effect of event rate reductions on planning new secondary prevention trials has not been quantified.

This study seeks to quantify trends in recurrent stroke and vascular event rates in medical secondary stroke prevention trials over the last 50 years and assess their impact on designing future secondary stroke prevention trials. We also explored the influence of changes in frequency and control of vascular risk factors on the secular trends of vascular event rates.
Methods

Search and Inclusion Criteria

We performed a systematic search of the medical literature to identify medical secondary stroke prevention trials published until April 2009. The search was restricted to articles published in English appearing in journals listed in MEDLINE. We also reviewed the introduction and discussion sections of retrieved trials and of related meta-analyses to identify additional trials.

To promote homogeneity of populations compared across trials, this systematic review was confined to medical secondary prevention trials with broad subtype entry criteria, enrolling diverse ischemic stroke or noncardioembolic ischemic stroke patients. Trials enrolling only more narrowly defined, distinctive stroke subtypes were excluded, including studies of secondary prevention of stroke due to AF, cervical carotid stenosis, or intracranial stenosis.

Inclusion criteria were as follows: (1) randomized, controlled trial; (2) majority of qualifying events were ischemic stroke or transient ischemic attack (TIA); (3) intervention was a medical treatment; and (4) >6-month follow-up. Stroke and TIA qualifying event subgroup data were used from trials that enrolled patients with multiple types of qualifying events, not restricted to cerebral ischemic events, if detailed information about the event rates and baseline characteristics of the cerebral ischemic event subgroup was provided separately.

Exclusion criteria were as follows: (1) trials confined to patients with AF, cervical carotid stenosis, or intracranial stenosis; (2) surgical or endovascular trials; (3) outcome event rate data not reported; (4) results reported only in abstract form; (5) inappropriate randomization method, such as allocation based on birth date; and (6) trial reported in non-English language.

Data Collection

From the control arm of each trial, we extracted data for annual event rates of recurrent stroke (ischemic or hemorrhagic), fatal stroke, and the composite of nonfatal stroke, nonfatal myocardial infarction, and vascular death (major vascular events). We also extracted data for the following control group baseline characteristics: age, sex, systolic blood pressure (SBP) and diastolic blood pressure (DBP) at entry, history of hypertension, diabetes mellitus, hyperlipidemia, current smoking, coronary heart disease, peripheral arterial disease, TIA proportion as a qualifying event, maximum allowed interval from the qualifying event to enrollment, bleeding, and frequency of concomitant use of antithrombotics, antihypertensives, and lipid-lowering agents during the trial.

Annual event rates were abstracted if directly stated and otherwise derived from the reported number of events and person-years of follow-up. Person-years were derived in the following hierarchical order on the basis of the available data: (1) person-years directly stated (13 trials); (2) derivation from displayed number of patients at risk in survival curves or life tables (17 trials); and (3) number of patients multiplied by mean or median duration of follow-up (29 trials). To analyze trends across trials over time, year of enrollment start and year of follow-up end were extracted from each trial. For 3 trials in which the year of enrollment start was not stated, we estimated it from the trial duration and publication year using the following formula: year of enrollment start = publication year – duration – 1 year.

For placebo-controlled trials, the placebo arm was considered the control arm. For trials comparing 2 active interventions, the arm with the more well-established therapy was considered the control arm (eg, in clopidogrel versus aspirin, aspirin was the control arm). For trials of the same agent, the lower-dose arm was considered the control arm except for the Dutch TIA aspirin trial, which compared the 30-mg arm versus the 283-mg arm.

As long as trials did not specifically state the inclusion of all recurrent events as their composite outcome end point, we assumed that only the first events were counted for the composite end point. When multiple counting of event numbers was considered on the basis of the observation of individual event numbers (eg, total sum of nonfatal stroke, myocardial infarction [MI], and vascular death events was higher than the composite event number), to avoid multiple counting of events, we first abstracted the numbers of all stroke (or all MI) and fatal stroke (or fatal MI) and then recalculated nonfatal stroke (or nonfatal MI). If the event rate for vascular death rate was not reported separately, we analyzed the all-cause mortality rate. Data extractions were based on the intention-to-treat populations.

We also abstracted, when reported, the expected event rate and treatment effect size used in trial sample size projections and assessed discrepancies between the predicted and the observed values for event rates and relative risk reductions (RRRs) for primary end points of the individual trials. These analyses focused on whatever end point was selected as the primary outcome for the trial, which was variable across the trials and included recurrent stroke, recurrent stroke or death, or composite of nonfatal stroke, nonfatal MI, and vascular death (or all-cause death). The discrepancy ratio [(predicted value – observed value)/(predicted value)×100, %] was analyzed for trends over time and compared between positive and negative trials.

Data abstraction was performed in parallel by 3 investigators (S.Y., M.L., K.H.). Discrepancies were resolved by discussion.

Statistical Analyses

This was a study-level rather than an individual, patient-level systematic review, and each study was treated as a unit. Trends over time of annual event rates and the association of individual clinical characteristics with annual event rates were analyzed by restricted maximum likelihood fitting of univariable linear mixed meta-regression models for reported event rates. In these models, the effects of predictors were considered as fixed, studies varied additionally by normally distributed random effects, and event rates were weighted inversely to their estimated variances assuming that the numbers of events followed Poisson distributions. For multivariable random-effects meta-regression analyses to explore the influence of changes in clinical characteristics on the secular trends of annual recurrent stroke rates, we selected variables (1) that were associated with a decrease of recurrent stroke rate in univariable meta-regression analyses and (2) that showed a significant trend over time on Spearman’s correlation analyses.

In the primary analysis, each trial was time ranked on the basis of the year of starting enrollment. In sensitivity analyses, trials were time ranked on the basis of (1) year of end of follow-up and (2) midpoint year between enrollment start and follow-up end.

To determine the impact of event rate trends on sample sizes for adequately powered secondary prevention trials, we calculated for each decade the sample size required for a hypothetical trial designed to detect a 20% RRR in the frequency of recurrent stroke with 2 years of follow-up, 80% power, and 5% α error. Whereas a random-effects meta-regression model was used to identify trends of annual event rates over time as well as associations of clinical characteristics with event rates, the presented individual values of annual event rates and characteristics for variable periods and conditions were obtained from a simple average without sample-size weighting. Then the Mann-Whitney U test was employed for the comparison of these values between dichotomized conditions. All the analyses were performed with the use of SPSS (version 12.0; Chicago, IL) except for the meta-regression analyses, for which a “metareg” command in STATA (version 11.0; College Station, TX) was used. Statistical significance level was set at P<0.05.

Results

Fifty-nine trials met study entry criteria, enrolling a total of 66 157 patients in control arms. Characteristics of individual trials and all trials combined are summarized in Table 1. Citations and full study names, in addition to acronyms for each trial, are listed in the online-only Data Supplement. By decades, 5 trials began enrollment in the 1960s, 11 in the 1970s, 13 in the 1980s, 24 in the 1990s, and 6 in the 2000s. There were 51 double-blind and 8 open-label trials; 37 trials tested antithrombotic agents (62.7%), 11 antihypertensives
Table 1. Characteristics of Individual Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Years of Enrollment Start/End</th>
<th>Intervention, Active/Control Groups</th>
<th>Randomized Patients, No. in Active/Control Groups</th>
<th>Mean Follow-Up, Mean Age, y</th>
<th>Female, %</th>
<th>Allowed Interval, d</th>
<th>Recurrent Stroke, %/y</th>
<th>Fatal Stroke, %/y</th>
<th>CV Event, %/y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acheson</td>
<td>1962/1969</td>
<td>Clofibrate/placebo</td>
<td>47/48</td>
<td>5.5</td>
<td>31.6</td>
<td>1460</td>
<td>8.33</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Carter</td>
<td>1964/1967</td>
<td>Thiazide/H11006 methyldopa/placebo</td>
<td>49/48</td>
<td>3.5</td>
<td>63.8</td>
<td>1825</td>
<td>12.50</td>
<td>5.95</td>
<td>NR</td>
</tr>
<tr>
<td>Acheson</td>
<td>1966/1969</td>
<td>Dipyridamole/placebo</td>
<td>85/84</td>
<td>2.1</td>
<td>57.5</td>
<td>1825</td>
<td>9.28</td>
<td>1.99</td>
<td>13.26†</td>
</tr>
<tr>
<td>HSCSG</td>
<td>1966/1972</td>
<td>Deserpine + thiazide/placebo</td>
<td>233/219</td>
<td>3.0</td>
<td>59.0</td>
<td>365</td>
<td>8.60</td>
<td>2.05</td>
<td>10.64</td>
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<tr>
<td>VACSG</td>
<td>1966/1972</td>
<td>Clofibrate/placebo</td>
<td>268/264</td>
<td>1.8</td>
<td>NR</td>
<td>365</td>
<td>4.83</td>
<td>1.47</td>
<td>8.82</td>
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<td>CSG</td>
<td>1971/1977</td>
<td>Sulfonpyrazone/aspirin/placebo</td>
<td>446/139</td>
<td>2.2</td>
<td>34.5</td>
<td>90</td>
<td>6.63</td>
<td>0.99</td>
<td>9.28</td>
</tr>
<tr>
<td>ATIA</td>
<td>1972/1975</td>
<td>Aspirin/placebo</td>
<td>88/90</td>
<td>2.0</td>
<td>62.2</td>
<td>90</td>
<td>11.40</td>
<td>2.29</td>
<td>13.60</td>
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<tr>
<td>AICLA</td>
<td>1975/1981</td>
<td>Aspirin, dipyridamole-aspirin/placebo</td>
<td>400/204</td>
<td>3.0</td>
<td>64.0</td>
<td>365</td>
<td>5.39</td>
<td>0.33</td>
<td>7.19</td>
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<td>ATIAIS</td>
<td>1976/1979</td>
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<td>61/63</td>
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<td>53.3</td>
<td>90</td>
<td>3.41</td>
<td>0.00</td>
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<td>DCS</td>
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<td>Aspirin/placebo</td>
<td>101/102</td>
<td>2.1</td>
<td>59.0</td>
<td>30</td>
<td>5.18</td>
<td>0.47</td>
<td>11.78</td>
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<td>Garde</td>
<td>1976/1980</td>
<td>Warfarin/aspirin</td>
<td>114/127</td>
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<td>59.7</td>
<td>14</td>
<td>3.37</td>
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<td>5.90</td>
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<td>9.05</td>
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<td>253/252</td>
<td>2.0</td>
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<td>21</td>
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<td>12.70</td>
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<td>63.8</td>
<td>90</td>
<td>7.36</td>
<td>1.76</td>
<td>11.08</td>
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<tr>
<td>Gent</td>
<td>1979/1983</td>
<td>Sulcotril/placebo</td>
<td>218/220</td>
<td>1.7</td>
<td>68.0</td>
<td>120</td>
<td>8.71</td>
<td>1.63</td>
<td>14.43</td>
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<tr>
<td>UK-TIA</td>
<td>1979/1986</td>
<td>Aspirin/placebo</td>
<td>1621/814</td>
<td>4.0</td>
<td>59.5</td>
<td>90</td>
<td>3.38</td>
<td>0.48</td>
<td>5.80</td>
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<tr>
<td>Boysen</td>
<td>1982/1986</td>
<td>Aspirin/placebo</td>
<td>150/151</td>
<td>2.1</td>
<td>59.1</td>
<td>90</td>
<td>3.47</td>
<td>0.00</td>
<td>5.99</td>
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<tr>
<td>TASS</td>
<td>1982/1987</td>
<td>Ticlopidine/aspirin</td>
<td>1529/1540</td>
<td>3.3</td>
<td>63.2</td>
<td>90</td>
<td>4.43</td>
<td>0.59</td>
<td>7.30†</td>
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<td>CATS</td>
<td>1984/1987</td>
<td>Ticlopidine/placebo</td>
<td>525/528</td>
<td>2.0</td>
<td>65.0</td>
<td>120</td>
<td>12.68</td>
<td>NR</td>
<td>17.34</td>
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<tr>
<td>SALT</td>
<td>1984/1990</td>
<td>Aspirin/placebo</td>
<td>670/684</td>
<td>2.7</td>
<td>66.8</td>
<td>90</td>
<td>5.72</td>
<td>0.51</td>
<td>9.81</td>
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<td>Dutch TIA-aspirin</td>
<td>1986/1990</td>
<td>Aspirin/placebo</td>
<td>1555/1576</td>
<td>2.8</td>
<td>NR</td>
<td>90</td>
<td>3.96</td>
<td>NR</td>
<td>6.30</td>
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<td>Dutch TIA-atenolol</td>
<td>1986/1990</td>
<td>Atenolol/placebo</td>
<td>732/741</td>
<td>2.8</td>
<td>NR</td>
<td>90</td>
<td>3.35</td>
<td>0.43</td>
<td>5.13</td>
</tr>
<tr>
<td>Forconia</td>
<td>1988/1991</td>
<td>Mesoglycan/aspirin</td>
<td>701/697</td>
<td>1.5</td>
<td>65.1</td>
<td>90</td>
<td>4.30</td>
<td>1.72</td>
<td>6.50</td>
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<tr>
<td>Marti*</td>
<td>1990 published</td>
<td>Nicardipine + aspirin/aspirin</td>
<td>170/94</td>
<td>1.0</td>
<td>59.0</td>
<td>365</td>
<td>6.38</td>
<td>1.06</td>
<td>8.51</td>
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<td>TEST</td>
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<td>Atenolol/placebo</td>
<td>372/348</td>
<td>2.6</td>
<td>70.1</td>
<td>21</td>
<td>9.23</td>
<td>2.09</td>
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<td>CARE</td>
<td>1989/1996</td>
<td>Pravastatin/placebo</td>
<td>111/100</td>
<td>5.0</td>
<td>NR</td>
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<td>2.40</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>ESPS II</td>
<td>1989/1995</td>
<td>Dipyridamole-aspirin, dipyridamole, aspirin/placebo</td>
<td>4953/1649</td>
<td>2.0</td>
<td>66.6</td>
<td>90</td>
<td>7.58</td>
<td>0.67</td>
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<td>PATS</td>
<td>1989/1995</td>
<td>Indapamide/placebo</td>
<td>2841/2824</td>
<td>2.0</td>
<td>60.0</td>
<td>840</td>
<td>4.21</td>
<td>1.49</td>
<td>4.79</td>
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<td>TISS</td>
<td>1989/1993</td>
<td>Ticlopidine/indobufen</td>
<td>821/811</td>
<td>1.0</td>
<td>65.7</td>
<td>30</td>
<td>2.68</td>
<td>NR</td>
<td>NR</td>
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<td>LIPID</td>
<td>1990/1997</td>
<td>Pravastatin/placebo</td>
<td>327/374</td>
<td>6.1</td>
<td>NR</td>
<td>1825</td>
<td>1.67</td>
<td>NR</td>
<td>NR</td>
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<td>CAPRIE</td>
<td>1992/1996</td>
<td>Clopidogrel/aspirin</td>
<td>3233/3198</td>
<td>1.9</td>
<td>64.7</td>
<td>180</td>
<td>5.65</td>
<td>0.27</td>
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<td>CSPS</td>
<td>1992/1997</td>
<td>Clofostazol/placebo</td>
<td>526/526</td>
<td>3.3</td>
<td>65.1</td>
<td>180</td>
<td>6.49</td>
<td>0.30</td>
<td>6.80</td>
</tr>
<tr>
<td>Lee</td>
<td>1992/1995</td>
<td>Aspirin/placebo</td>
<td>222/244</td>
<td>1.7</td>
<td>62.9</td>
<td>42</td>
<td>7.66</td>
<td>0.48</td>
<td>8.86</td>
</tr>
<tr>
<td>Steiner*</td>
<td>1990 published</td>
<td>Vitamin E + aspirin/aspirin</td>
<td>52/48</td>
<td>2.0</td>
<td>71.4</td>
<td>56</td>
<td>6.25</td>
<td>NR</td>
<td>8.33</td>
</tr>
</tbody>
</table>

(Continued)
(18.6%), 5 statins (8.5%), and 6 other interventions (10.2%: 2 clofibrate, 3 vitamins, and 1 estrogen). Among the 59 trials, 24 trials (40.7%) found positive results for treatment efficacy for the primary end point. Of note, all of the trials initiated in the 2000s have failed to prove their treatment efficacy. The median (interquartile range) sample size in person-years in control groups was 1046 (418 to 3298), increasing from 264 (160 to 483) in the 1960s to 367 (207 to 1017) in the 1970s, 1046 (637 to 3554) in the 1980s, 1682 (836 to 3179) in the 1990s, and 4632 (988 to 24 270) in the 2000s.

The annual recurrent stroke rate declined substantially over time (β-coefficient [SE] = -0.0996 [0.0280]; P=0.001) (Figure), falling 0.996% per decade, from 8.71 ± 1.22%/y (mean ± SE) in trials launched in the 1960s to 4.98 ± 0.52%/y in 2010.
the 2000s (Table 2). Annual event rates also declined for fatal stroke ($\beta$-coefficient [SE] = -0.0282 [0.0088]; $P = 0.003$) and for major vascular events ($\beta$-coefficient [SE] = -0.1331 [0.0380]; $P = 0.001$) (Figure). Annual event rates for fatal stroke fell by 0.282% per decade, from 2.87%/y in the 1960s to 0.36%/y in the 2000s. Annual event rates for major vascular events fell by 1.331% per decade, from 10.91%/y in the 1960s to 6.29%/y in the 2000s (Table 2). In sensitivity analyses, these rates of change over time were essentially unchanged when each trial was time ranked on the basis of the year of follow-up end and midpoint year between enrollment start and follow-up end rather than year of enrollment start.

When the study periods were dichotomized into the era before and after 1990, the annual event rates (obtained from the simple average without sample-size weighting) declined from 6.24%/y to 4.21%/y for recurrent stroke, from 1.31%/y to 0.39%/y for fatal stroke, and from 9.39%/y to 6.65%/y for major vascular events ($P < 0.05$ for all).

In univariate meta-regression analyses, the annual recurrent stroke rate was positively associated with proportion of patients with a history of hypertension and was negatively associated with increasing proportion of patients on anti-thrombotic agents, TIA as a qualifying event, and increase of maximum allowed delay from onset. When the event rates were compared between double-blind and open-label trials, no significant differences were found for annual recurrent stroke (5.34%/y [n = 49 included trials] versus 4.68%/y [n = 8]; $P = 0.224$), fatal stroke (0.85%/y [n = 31] versus 1.96%/y [n = 5]; $P = 0.147$), and major vascular events (8.15%/y [n = 44] versus 6.63%/y [n = 5]; $P = 0.308$).

As shown in Table 3, substantial changes over time were noted in the frequencies of several vascular risk factors in the control arms. The proportions of patients with histories of hypertension, diabetes mellitus, hyperlipidemia, and concomitant antithrombotic use have increased, whereas SBP values, DBP values, smoking, and proportion with TIA as a qualify-

<table>
<thead>
<tr>
<th>Table 2. Annual Event Rates by Decades</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recurrent Stroke</strong></td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>1960s</td>
</tr>
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<td>1970s</td>
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<td>1980s</td>
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<tr>
<td>1990s</td>
</tr>
<tr>
<td>2000s</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Values are expressed as percentage per year. n indicates included trials.
ing event have decreased. Data for frequencies of antihypertensive agent and statin use were too scarce to allow adequate analyses. When compared between the eras before and after 1990, antithrombotic use rose from 39.8% to 88.9%, hypertension from 54.1% to 66.3%, diabetes mellitus from 15.4% to 26.9%, and hyperlipidemia from 33.9% to 43.9%. In contrast, the average SBP/DBP at enrollment declined from 154.9/90.5 to 144.5/83.8 mm Hg, current smoking declined from 43.5% to 26.2%, and TIA proportion declined from 39.7% to 16.0% (P < 0.05 for all).

To define the factors underlying the decline in the annual recurrent stroke rate over time, we performed multivariable random-effects meta-regression analyses. When antithrombotic use, SBP, or DBP was included in the multivariable meta-regression models, the year of study initiation dropped out as an independent predictor of the annual recurrent stroke rate. However, putting the variables of current smoking, TIA proportion, or maximum allowed delay into the model did not change the statistical significance (Table 4).

The sample size planning assumptions regarding control arm event rates and treatment effect magnitude were stated for 41 and 42 trials, respectively. Predicted control arm event rates tended to be higher than actual observed rates by 10.1% (95% confidence interval, −0.2 to 20.3). Predicted treatment effect RRRs were higher than actual observed RRRs by 60.6% (95% confidence interval, 26.8 to 94.4). These discrepancies did not change over time (event rates: r = 0.051, \( P = 0.753 \); RRRs: r = 0.083, \( P = 0.602 \)). For control arm event rates, 18 trials (43.9%) overestimated actual observed rates by >20%. The proportion of trials with >20% overestimation was similar between positive and negative trials (47.1% versus 41.7%; \( P = 0.760 \)). For treatment effect RRRs, 30 trials (71.9%) overestimated actual RRRs by >20%.

The impact of recurrent stroke rate trends on the sample sizes required for adequately powering trials to test new interventions was substantial. The projected control group sample sizes for a secondary stroke prevention trial with 2 years of follow-up to detect a 20% RRR of a new medical intervention with 80% power and 5% error increase from 4674 in the 1960s to 5379 in the 1970s, 6354 in the 1980s, 7773 in the 1990s, and 10 089 in the 2000s. For the 2010s, the annual stroke recurrent rate in trial control arms, if a continued linear decline is assumed, is predicted to be 2.25% [from the following formula: event rate = (−0.997) \times (rank of decade) + 8.225]. Consequently, control group sample size requirements would increase to 15 983 patients for the same projected treatment effect.

This study-level systematic review demonstrates that rates of recurrent stroke and major vascular events have declined substantially in the control arms of secondary stroke prevention trials over the last 5 decades. The average annual recurrent stroke rate in the 1990s and 2000s was approximately half that in the 1960s. Consonant with their known powerful effects in reducing global vascular risk, increased use of antithrombotics and decreased SBP or DBP were each individually sufficient, in multiple meta-regression models, to account for the statistically significant secular decline in the recurrent stroke rate.

The medical treatment of atherosclerotic disease has evolved dramatically over the last 50 years. Successive waves of treatments moved from being of uncertain efficacy and
to declining event rates to change study entry criteria to require the presence of more vascular risk factors in order to enrich trial populations with patients with at least moderate risk for events.

Our results are in accord with multiple epidemiological studies that have demonstrated a decline in first stroke rates over this half-century period. Our findings regarding trends in risk factor frequencies also are concordant with the results of a population-based epidemiological study, in which age-adjusted stroke incidence and stroke mortality decreased in concert with an improvement of blood pressure control and smoking cessation and despite an increase in diabetes mellitus and hyperlipidemia prevalence. Several recent studies of stroke rate in asymptomatic carotid stenosis also support our observations. A systematic review demonstrated that the annual stroke rate of patients with asymptomatic carotid stenosis on medical treatment has significantly declined over the last 25 years, which is likely attributed to the improved risk factor controls.

Our findings contrast with a recent study of event rates in stroke clinical trials that analyzed a more restricted group of trials. That analysis examined the rate of major vascular events in the aspirin arms of 34 antiplatelet trials and found no major decline over time. The different findings of our study likely reflect several factors, including the following: (1) broader study selection criteria yielding a larger corpus of trials covering a broader time period with increased statistical power; (2) analysis of a wider set of outcomes, including all stroke alone and fatal stroke alone, in addition to the composite of stroke, MI, and vascular death; and (3) inclusion of older trials using no aspirin in the control arm and of later trials using newer antiplatelet agents more effective than aspirin in the control arm.

Our study demonstrated that, throughout the past 50 years, there have been great discrepancies between the actual sample sizes used in clinical trials and the sample sizes that would have been required for adequately powered trials on the basis of actual observed event rates. The ratios of adequately powered sample sizes to the actual median values of trials were 35.4 in the 1960s, 29.3 in the 1970s, 12.5 in the 1980s, 9.2 in the 1990s, and 4.4 in the 2000s. This improving trend indicates clinical trialists’ increasing awareness of and attention to the problem of underpowered trials. However, although the degree of insufficient power in trials used to be even more severe than at present, the problem of needing very large sample sizes to adequately power trials is greater now than ever. More accurate prediction of vascular event rates in control arms is accordingly urgently needed.

The prediction of vascular event rates in trial control arms is critical in designing clinical trials. More than 4 of every 10 secondary prevention trials overestimated primary end point event rates by >20%. Selection of correct sample size for trials may be more likely if projections do not simply reflect event rates observed in earlier completed trials, but also incorporate the observation that recurrent event rates have historically declined per decade by ~1.0% for recurrent stroke and 1.3% for major vascular events that might be attributed to improved vascular prevention therapies. Of course, in the coming years, the pace of event rate decline

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**Table 4. Factors Determining the Decline in Annual Recurrent Stroke Rate**

<table>
<thead>
<tr>
<th>Multivariate Analyses</th>
<th>Adjusted Model</th>
<th>Included Covariates</th>
<th>β-Coefficient (SE)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1</strong> (n=45)</td>
<td>0.285</td>
<td>Year of study initiation</td>
<td>0.088 (0.037)</td>
<td>0.813</td>
</tr>
<tr>
<td><strong>Model 2</strong> (n=24)</td>
<td>0.082</td>
<td>Year of study initiation</td>
<td>-0.025 (0.0075)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Model 3</strong> (n=24)</td>
<td>0.066</td>
<td>SBP</td>
<td>-0.090 (0.053)</td>
<td>0.108</td>
</tr>
<tr>
<td><strong>Model 4</strong> (n=37)</td>
<td>0.188</td>
<td>Year of study initiation</td>
<td>-0.083 (0.057)</td>
<td>0.158</td>
</tr>
<tr>
<td><strong>Model 5</strong> (n=54)</td>
<td>0.468</td>
<td>DBP</td>
<td>-0.024 (0.11)</td>
<td>0.670</td>
</tr>
<tr>
<td><strong>Model 6</strong> (n=57)</td>
<td>0.374</td>
<td>Year of study initiation</td>
<td>-0.168 (0.061)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

- **SBP** indicates systolic blood pressure; **DBP**, diastolic blood pressure; and **TIA**, transient ischemic attack.
may vary from the historical norm. If so, event rate changes among more recent, larger trials may provide better future guidance than trends influenced by data from older and smaller studies. Our findings also underscore the dangers of using historical controls to support the efficacy of interventions, which is a current problem for single-arm device studies in particular.

The present study could not directly demonstrate an increasing use of antihypertensive therapy among stroke patients because information on the rate of antihypertensive use was missing from many trial reports. However, throughout the study period, whereas the proportion of patients with a history of hypertension enrolled in trials increased, the measured SBP and DBP at trial entry decreased. This finding strongly suggests that more aggressive and successful deployment of antihypertensives has occurred among stroke patients.13

This study has limitations. The entry criteria excluded trials solely targeted at patients with specific vascular conditions, such as AF or cervical carotid stenosis. This enhanced the comparability of analyzed trials but limited the breadth of the analysis. Analyses of event rates in control arms of these more focused stroke subtype trials would be of interest as topics of future investigations. A portion of the decline in stroke event rates we observed may have been due to increasing exclusions over time from general prevention trials of patients with specific, high-risk causes, such as AF and cervical carotid stenosis. For AF, however, such a trend does not appear to have been a major factor. The proportion of patients with AF at enrollment did not show a statistically significant decline over time. For severe carotid stenosis, the frequency of this condition in trial populations was not reported frequently enough to allow detailed analysis of potential confounding. However, because symptomatic cervical carotid stenosis is present in only 11.5% of all patients with ischemic stroke,14 it is also unlikely to have exerted a major confounding effect. The declining event rates primarily reflect genuine advances in primary and secondary prevention rather than solely a differing selection of patients.

Diagnostic technologies have evolved dramatically over the last 50 years, altering event definitions for both study entry and study end point. We were not able to analyze precisely the effect of the incorporation of these technologies in study design; many trials did not provide details of event adjudication processes, and any diagnostic testing variable analysis would be time confounded because advanced techniques were never used in very early trials and universally used in very recent trials. Epidemiological studies indicate that the introduction of sensitive serum tests for cardiac proteins dramatically increased the frequency of diagnosis of MI, and the development of computed tomography and magnetic resonance neuroimaging modestly increased the frequency of diagnosis of stroke.15 Accordingly, we speculate that the decline in event rates we observed would have been even more pronounced had outcome event adjudications been stable in trials across decades, but we could not directly test this hypothesis.

This study was a trial-level meta-analysis rather than an individual, patient-level pooled analysis. Using trials as the primary unit of analysis is appropriate for the primary purpose of this study: to characterize changes in event rates in trials over time. However, a patient-level analysis would better be able to indicate the impact of changes in risk factors and their treatment on changes in vascular event rates. Our systematic literature search was confined to English-language articles, and this study may not have identified relevant trials published in other languages.

In conclusion, formal analysis of secondary prevention trials over the last 5 decades confirms that stroke investigators must cope with the paradox of progress. Our efforts to identify beneficial therapies have been notably successful, resulting in a substantial decline in the rate of recurrent vascular events in the control arms of secondary stroke prevention trials. As a result, however, trials of new therapies are more arduous, requiring ever larger sample sizes to confirm treatment efficacy. This systematic review can inform the design of future stroke trials.

Sources of Funding
This work was supported by a grant (A060171) of the Korea Health 21 R&D project, Ministry of Health, Welfare, and Family Affairs, Republic of Korea (K.H., J.L.); a grant from CMRPG (660311), Taiwan (M.L.); National Institutes of Health/National Institute of Neurological Disorders and Stroke award P50 NS044378 (J.L.S.); and an American Heart Association Pharmaceutical Roundtable Outcomes Research Center Award (J.L.S.).

Disclosures
Dr Hong is a site investigator in multicenter clinical trials sponsored by Kureha Otsuka, Norvatis Korea, and Boryung and received lecture honoraria from Sanofi-aventis (modest). Dr Saver is an employee of the University of California, which holds a patent on retriever devices for stroke; is a scientific consultant regarding trial design and conduct to AGA Medical (modest); has received lecture honoraria from Boehringer Ingelheim (modest); received devices for use in a National Institutes of Health multicenter clinical trial from Concentric Medical (modest); is a site investigator in a multicenter trial sponsored by AGA Medical, for which the University of California Regents received payments based on the clinical trial contracts for the number of subjects enrolled; is a site investigator in the National Institutes of Health IRIS, COSS, and SAMMPRIS multicenter clinical trials, for which the University of California Regents receive payments based on the clinical trial contracts for the number of subjects enrolled; and is funded by National Institutes of Health/National Institute of Neurological Disorders and Stroke award P50. The other authors report no conflicts of interest.

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CLINICAL PERSPECTIVE

Formal analysis of secondary stroke prevention trials over the last 5 decades confirms that vascular event rates in control arms have declined substantially. Annual recurrent stroke rates in control arms fell from 8.71% in trials launched in the 1960s to 6.10% in the 1970s, 5.41% in the 1980s, 4.04% in the 1990s, and 4.98% in the 2000s. Annual event rates for fatal stroke decreased from 2.87/1000 in the 1960s to 0.36/1000 in the 2000s, and those for major vascular events declined from 10.91/1000 in the 1960s to 6.29/1000 in the 2000s. Multivariate analysis suggests that increasing antithrombotic use and lower blood pressures were the most important drivers of vascular event rate reduction. The sample size required for adequately powered trials more than doubled during the study period. If a continued linear decline is assumed, the annual recurrent stroke rate in trial control arms in the coming decade is projected to be 2.25%, and control group sample size requirements would increase to 15,983 patients for a trial designed to detect a 20% relative risk reduction in the frequency of recurrent stroke, with 2 years of follow-up, 80% power, and 5% α error. The introduction into clinical practice of successive waves of therapies with proven efficacy in stroke prevention has been notably successful, resulting in a substantial decline in the rate of recurrent vascular events in the control arms of secondary stroke prevention trials. Consequently, trials of new therapies are more arduous, requiring ever larger sample sizes to confirm treatment efficacy, and clinical investigators must cope with the paradox of progress.

Go to http://cme.ahajournals.org to take the CME quiz for this article.
Trials listed by the acronym

Prevention Study,\textsuperscript{33} TACIP: Triflusal vs. Acetylsalicylic Acid in Secondary Prevention of Cerebral Infarction,\textsuperscript{34} TAPIRSS: Triflusal vs. Aspirin for the Prevention of Infarction, Randomized Stroke Study,\textsuperscript{35} VISP: Vitamin Intervention for Stroke Prevention,\textsuperscript{36} ESPRIT: European / Australasian Stroke Prevention in Reversible Ischaemia Trial,\textsuperscript{37} MOSES: Morbidity and Mortality After Stroke - Eprosartan vs. Nitrendipine for Secondary Prevention,\textsuperscript{38} TNT: Treating New Target study,\textsuperscript{39} SPARCL: Stroke Prevention by Aggressive Reduction in Cholesterol Levels,\textsuperscript{40} BRAVO: Blockage of the Glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion,\textsuperscript{41} HOPE-2: The Heart Outcomes Prevention Evaluation 2,\textsuperscript{42} MATCH: Management of ATherothrombosis with Clopidogrel in High-risk patients,\textsuperscript{43} S-ACCESS: Sarpogrelate Used as Preventive Therapy Against Recurrent Ischemic Events,\textsuperscript{44} CHARISMA: Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance,\textsuperscript{45} PROFESS-DP: Prevention Regimen For Effectively avoiding Second Strokes-Dipyridamole trial,\textsuperscript{46} PROFESS-T: Prevention Regimen For Effectively avoiding Second Strokes-Telmisartan trial,\textsuperscript{47} CASISP: Cilostazol versus Aspirin for Secondary Ischaemic Stroke Prevention.\textsuperscript{48}

Trials listed by the first author

Acheson,\textsuperscript{49, 50} Carter,\textsuperscript{51} Garde,\textsuperscript{52} Gent,\textsuperscript{53} Boysen,\textsuperscript{54} Forconia,\textsuperscript{55} Marti,\textsuperscript{56} Lee,\textsuperscript{57} Steiner,\textsuperscript{58} Grotemeyer\textsuperscript{59}
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