Combining Multiple Approaches for the Secondary Prevention of Vascular Events After Stroke
A Quantitative Modeling Study

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Background and Purpose—Numerous effective strategies for the secondary prevention of cardiovascular events in high-risk patients have now been established. We sought to calculate the cumulative benefit of combining multiple strategies for preventing recurrent events in patients with a history of ischemic stroke or transient ischemic attack.

Methods—A comprehensive literature search was undertaken to identify meta-analyses of randomized controlled trials reporting on the efficacy of secondary prevention strategies. The baseline incidence of vascular events was modeled from the Life Long After Cerebral Ischemia study. Strategies were combined on a multiplicative scale and cumulative risk reductions were computed over a 5-year interval.

Results—The combination of 5 proven strategies applied to survivors of an initial stroke or transient ischemic attack—dietary modification, exercise, aspirin, a statin, and an antihypertensive agent—could result in a cumulative relative risk reduction of 80%. Given a 5-year major cardiovascular event rate of 24%, this translates to a number needed to treat of about 5. Further gains would result from applying multimodality therapy over longer intervals and enriching the base strategy with dual antiplatelet therapy, high-dose statins, and more intensive blood pressure-lowering. Even more benefit would be present in high-risk subgroups with the addition, where appropriate, of carotid endarterectomy, moderate intensity oral anticoagulants, glycemic control, and smoking cessation.

Conclusions—At least four-fifths of recurrent vascular events in patients with cerebrovascular disease might be prevented by application of a comprehensive, multifactorial approach. (Stroke. 2007;38:1881-1885.)

Key Words: cerebrovascular disease ■ medical Rx ■ prevention ■ risk factor modification ■ secondary prevention ■ statistical models ■ stroke ■ systematic review

Despite major advances, cardiovascular disease remains the leading cause of mortality worldwide; atherosclerosis accounts for the majority of cases. Patients who survive a stroke or transient ischemic attack (TIA) are at particularly high risk for subsequent cardiovascular events, including recurrent stroke, myocardial infarction and death from vascular causes. Although population-based approaches to preventing vascular disease are valuable and necessary (that is, favorably shifting the distribution of risk factors in large groups over sustained intervals), such strategies do not address the high risk of patients with established vascular disease (including those with a prior stroke or TIA). Thus, high-risk, patient-specific approaches are still needed.

Clinical practice guidelines for treating patients with cerebrovascular disease are generally based on randomized trials or meta-analyses which evaluate 1 or at most 2 therapeutic strategies per study; such information does not shed light on the potential effects of combining multiple therapeutic strategies for secondary prevention. Because most of these strategies appear to be additive and independent in lowering cardiovascular risk (ie, efficacy is present on top of other established medical therapies), an incremental statistical model can be used to evaluate the cumulative risk reduction of all such strategies. Herein we model the estimated relative and absolute risk reductions that could be obtained by combining multiple approaches for the secondary prevention of vascular events in patients with stroke or TIA.

Data Sources
To ascertain the efficacy of secondary prevention strategies, we searched the literature for meta-analyses that quantified the benefits of therapies reported in randomized controlled trials. Meta-analyses of patients with stroke or TIA were preferred, but where such analyses were unavailable, meta-analyses of other secondary prevention (or high-risk primary prevention) populations were selected. We
Meta-Analyses of Strategies

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Meta-Analysis</th>
<th>Relative risk</th>
<th>Trials, n</th>
<th>Patients, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary modification</td>
<td>Iestra et al\textsuperscript{14}</td>
<td>0.56 (0.42 to 0.74)</td>
<td>3</td>
<td>2011</td>
</tr>
<tr>
<td>Exercise</td>
<td>Clark et al\textsuperscript{11}</td>
<td>0.72 (0.54 to 0.95)</td>
<td>11</td>
<td>2285</td>
</tr>
<tr>
<td>Aspirin</td>
<td>ATC-3\textsuperscript{8}</td>
<td>0.78 (0.71 to 0.85)</td>
<td>21</td>
<td>18 270</td>
</tr>
<tr>
<td>Statins</td>
<td>CTT\textsuperscript{7}</td>
<td>0.79 (0.77 to 0.81)</td>
<td>14</td>
<td>90 056</td>
</tr>
<tr>
<td>Antithromboprophylaxis</td>
<td>Rashid et al\textsuperscript{15}</td>
<td>0.79 (0.66 to 0.95)</td>
<td>7</td>
<td>15 527</td>
</tr>
<tr>
<td>Aspirin/dipryramide</td>
<td>Halpke et al\textsuperscript{13}</td>
<td>0.82 (0.74 to 0.91)*</td>
<td>6</td>
<td>7 795</td>
</tr>
<tr>
<td>Intensified statins</td>
<td>BPLTTC-2\textsuperscript{19}</td>
<td>0.85 (0.76 to 0.95)†</td>
<td>5</td>
<td>21 982</td>
</tr>
<tr>
<td>Intensified statins</td>
<td>Cannon et al\textsuperscript{10}</td>
<td>0.84 (0.80 to 0.89)§</td>
<td>4</td>
<td>27 548</td>
</tr>
<tr>
<td>Carotid endarterectomy</td>
<td>Rothwell et al\textsuperscript{16}</td>
<td>0.52 (0.40 to 0.64)§</td>
<td>3</td>
<td>6 092</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>Saxena et al\textsuperscript{17}</td>
<td>0.55 (0.37 to 0.82)</td>
<td>2</td>
<td>485</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>Critchley et al\textsuperscript{12}</td>
<td>0.64 (0.58 to 0.71)</td>
<td>20</td>
<td>12 603</td>
</tr>
<tr>
<td>Glycemic control</td>
<td>Stettler et al\textsuperscript{18}</td>
<td>0.81 (0.73 to 0.91)</td>
<td>10</td>
<td>6 272</td>
</tr>
</tbody>
</table>

\textsuperscript{*vs aspirin alone; †vs conventional antihypertensive strategy; §vs conventional statin strategy; §in patients with symptomatic internal carotid artery stenosis (70%–99%).}

Data Extraction

For the individual relative risk reductions conferred by various strategies, we extracted the pooled risk reductions reported in the meta-analyses. Most meta-analyses reported relative risks, but where odds ratios were reported, we assumed equivalence to relative risk, which is likely because most event rates were relatively infrequent in the meta-analyses (<10%).\textsuperscript{21} We used the point estimate for major cardiovascular events (nonfatal stroke, nonfatal myocardial infarction, and vascular death). In 4 meta-analyses, risk reductions for mortality\textsuperscript{11,12,14,15} or stroke and mortality\textsuperscript{16} were reported instead of cardiovascular events, and hence these risk ratios were used as an approximation of efficacy for major vascular events. All estimates were recorded on a standardized pilot-tested data collection form and any disagreement between investigators was resolved by consensus.

Calculations

We used the method of Yusuf\textsuperscript{22} to calculate the cumulative relative risk reduction by assuming a multiplicative scale. This assumption is founded on evidence that for each therapy, effect estimates were independent of the presence or absence of other therapies in large randomized trials and in pooled analyses of trials.\textsuperscript{5–6} The formula for calculating the cumulative relative risk reduction (RRR) was: RRR\textsuperscript{1} = \[\frac{[1-(RR_1 \times RR_2 \times RR_3 \times \ldots \times RR_n)]}{1}]\times 100,\] where RR\textsubscript{1} represents the relative risk for therapy, and so forth. The absolute risk reduction (ARR) over 5 years and the number needed to treat (NNT) to prevent 1 event were calculated by convention as: ARR = RRR \times baseline risk and NNT = \frac{100}{ARR}.\textsuperscript{1} We also calculated the risk remaining after treatment as: (baseline risk \times RRR) – baseline risk. We used a 5-year interval to reflect the average duration of most trials included in the meta-analyses.

Base Analysis

The 5 risk-reducing strategies with broadest applicability to patients with stroke/TIA were: comprehensive dietary modification, exercise, aspirin, hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), and antithromboprophylaxis therapy.\textsuperscript{6,9,11,14,15} The extracted pooled risk ratios corresponding to these 5 approaches, together with the 5-year rate of secondary cardiovascular events in stroke/TIA patients, formed the inputs for the base analysis.

Sensitivity Analyses

We also considered a number of modifications to this analysis. First, we lengthened the exposure window in the primary analysis to 10 years, given that most secondary prevention therapies are applied indefinitely in most patients. We also considered 10-year therapy estimates in TIA patients alone, given that they were separately available in LiLAC. Second, we recognized that clinicians often select an even more intensive strategy for patients at exceptionally high risk for recurrent cardiovascular events.\textsuperscript{23} For this approach we supplemented the base strategy with dual antiplatelet therapy (in the form of combination aspirin-dipyridamole), intensified antithromboprophylactic therapy, and intensive cholesterol-lowering with high dose statins.\textsuperscript{10,13,19} The remaining components (exercise and diet) were kept constant. We also calculated the efficacy of this approach for the 10-year observation interval.

Finally, in light of the well-known heterogeneous etiology of stroke, we considered 4 additional scenarios of patients with cerebrovascular disease: namely, patients with symptomatic high-grade carotid artery stenosis (70% to 99%); atrial fibrillation; smokers; and patients with type 2 diabetes. The additional therapies considered in these situations were carotid endarterectomy, moderate intensity oral anticoagulation, smoking cessation, and pharmacological glycomic control, respectively.\textsuperscript{12,16–18} The efficacy of these therapies was again drawn from published meta-analyses of randomized trials, with the sole exception of smoking cessation, for which a meta-analysis of prospective cohort studies with long-term follow-up was used.\textsuperscript{12} Five-year cardiovascular event rates specific to all these conditions were calculated from published data.\textsuperscript{20,24,25}

Results

Data Sources

We found 12 recent meta-analyses reporting risk ratios for various strategies for secondary (n = 11)\textsuperscript{8–18} or mixed secondary/high-risk primary prevention (n = 1).\textsuperscript{19} Most reports dated from 2003 to 2006 with no publication older than 2002. In aggregate, the meta-analyses encompassed a total of 106 studies and 210 926 patients (Table). The average meta-
analysis combined data on 9 trials with 17,577 patients and provided a relative risk of 0.79.

**Base and 10-Year Analyses**

The calculated cumulative risk reduction for implementing diet, exercise, aspirin, statins, and antihypertensive therapy (the 5 most broadly applicable strategies) was 80%. Given a 5-year major vascular event rate of 24.4% in patients with an initial cerebrovascular event (as seen in LiLAC), the ARR conferred combination therapy was 20%, equivalent to an NNT of 5. The residual 5-year risk of major cardiovascular events after treatment was 5%. The cumulative relative and absolute risk reductions modeled from the upper limit of the confidence intervals for the meta-analyses were 54% and 13%, with an NNT of 8; based on the lower limits, the corresponding RRR, ARR and NNT were 92%, 22%, and 4, respectively.

In the LiLAC study, the 10-year major vascular event rate was 44.1%. The corresponding ARR, NNT, and residual risk for treatment applied for a decade were therefore 35%, 3, and 9%, respectively. Patients with TIA had a significantly lower 10-year major vascular event rate of 35.8%; among such patients, the ARR, NNT, and residual risk were 29%, 3, and 7%, respectively.

**Intensified Strategy**

The intensive approach consisted of diet, exercise, modified release aspirin/dipyridamole, high dose statins, and aggressive blood pressure-lowering. The RRR, ARR, NNT, and residual risk for this approach applied over 5 years were 90%, 22%, 5, and 3%, respectively. Hence, the intensified strategy nearly halved the residual risk remaining after the base strategy (from 4.8% to 2.8%). Applied over a 10-year time frame, the intensified strategy resulted in an ARR and residual risk of 39% and 5%, respectively, with an NNT of only 3.

**Other Sensitivity Analyses**

Patients with symptomatic high-grade carotid stenosis have a particularly high risk of major vascular events (45% at 5 years); such patients benefit from carotid endarterectomy in addition to medical therapy (Figure). The estimated cumulative RRR from adding endarterectomy to the base strategy is 90%; used in combination with intensive medical therapy, the total RRR is 94%. Similarly, patients with atrial fibrilla-
tion and a previous stroke or TIA are at exceptionally high risk for future vascular events (Figure). These patients benefit substantially from moderate intensity oral anticoagulation, which in combination with the other primary risk-lowering strategies, yields a cumulative RRR of 86%. The intensive strategy for such patients yields a RRR of 90%.

Finally, patients with cerebrovascular disease who smoke or have diabetes may benefit from smoking cessation (individual RR 0.64) and glycemic control (individual RR 0.81), respectively.27,30 Such patients are also at higher risk for cardiovascular events (Figure). In concert with other medical therapies, the estimated cumulative RRR for adding smoking cessation and glycemic control to the base package is 87% and 84%, respectively. Added to the intensive package, the RRR for these strategies is 93% and 91%, respectively.

Discussion
Our main finding is that a combination of 5 key strategies reduces the risk of recurrent vascular events by >80% in patients with a history of stroke or TIA. Furthermore, because the risk of future events is so high in patients with established cerebrovascular disease, only 5 patients need to be treated with this approach to prevent 1 major vascular recurrence over 5 years.

This analysis has a number of limitations. First, proof for the overall approach would require a randomized trial comparing the combination of all 5 approaches with no therapy, which would be unethical. However, in an active comparator study, Gaede et al demonstrated that multifactorial treatment of high-risk patients with diabetes—involving intensive behavioral modification and risk factor control—reduced the risk of major vascular complications by 53% and the risk of microvascular complications by about 60% in comparison with a strategy of conventional guideline-based active therapy.26 Second, the overall approach assumes that each strategy is independent and additive to all other strategies; in other words, no interaction between therapies occurs. Although this has been shown for antiplatelet agents, statins, antihypertensive drugs, and carotid endarterectomy, it is unknown to what extent lifestyle modification (diet, exercise, and smoking cessation) exerts benefit on top of optimal medical therapy.3–7

A third limitation is that some of the meta-analyses studied patients with other forms of vascular disease (rather than focusing strictly on patients with stroke or TIA); moreover, 3 of the meta-analyses reported on total mortality rather than total vascular events.11,14,16 However, if anything, the latter probably led to an underestimate of efficacy because all-cause mortality is diluted by nonvascular causes which are generally not affected by cardiovascular therapies. In addition, each of the 3 meta-analyses reported risk reductions for myocardial infarction which were similar to the primary estimates for mortality.11,14,16 A fourth limitation is that most participants in source clinical trials were whites of North American or European origin which raises questions of applicability to other ethnic groups, although some evidence suggests that the therapies discussed here are broadly effective in other populations.27–30 Finally, the statistical approach we have taken for combining the relative risk reductions of individual therapies may not fully reflect such nuances as poor adherence, adverse drug reactions, and lack of titration by providers to the target doses used in clinical trials.

An assumption of our study is that the baseline rates of recurrent events from LiLAC are generalizable to other stroke or TIA patients typically seen in secondary prevention. Yet as noted by the LiLAC authors, such rates may have underestimated true community risk for several reasons, including loss to follow-up of a small number of patients (which may have occurred because of fatal or severe nonfatal events), selection bias attributable to consent for participation in a related clinical trial, and lack of very early events (only 22% of the cohort were included within 1 week of the index event). Nonetheless, LiLAC has been referred to by at least 1 editorialist as an “almost ideal prognostic study”, given that it meets many of the criteria for gold standard research into prognosis.31

Our analysis of combinatorial approaches to vascular risk reduction yielded estimates similar to those of Wald and Law’s proposed “polypill” approach to vascular prevention.32 However, several differences exist. The polypill incorporates 3 low-dose antihypertensive agents (thiazide diuretic, β blocker, and angiotensin-converting enzyme inhibitor), aspirin, folic acid, and a statin (and ignores lifestyle change), whereas our base strategy uses aspirin, 1 full dose antihypertensive agent, a statin, exercise, and dietary change. A further difference is that the polypill may not be fully adequate for high-risk secondary prevention settings such as survivors of stroke or TIA.33 Our proposed approach is particularly adaptable to patients with cerebrovascular disease (suggesting incremental benefits of carotid endarterectomy and oral anticoagulants) and the model expands to encompass smoking cessation and glycemic control where appropriate (both of which prevent vascular events and death).11,18 There is virtually no evidence that β blockers, low-dose angiotensin-converting enzyme inhibitors, or folic acid prevent recurrent events in patients with cerebrovascular disease, although evidence on B-vitamin therapy for total homocysteine is not yet complete.34

Several other intriguing findings emerge from our model. Intensified management, which supplements the base strategy with combination aspirin-dipyridamole,13 intensive blood pressure-lowering,19 and high-dose statins,10 yields a net efficacy estimate of nearly 90%; in combination with carotid endarterectomy16 the relative risk reduction is 94%, suggesting that nearly all recurrent events in high-risk patients with symptomatic carotid stenosis could be prevented. In addition, extending the timeline to 10 years, which may be an accurate reflection of an elderly stroke survivor’s duration of “life-long” treatment, nearly doubles the absolute risk reduction from treatment. Indeed, our estimates of efficacy are probably underestimates because they ignore the effects of continued therapy on preventing second or third events (trials uniformly focus only on the first event during follow-up); furthermore, they reflect intent-to-treat analyses which are invariably diluted by crossover between groups as well as nonadherence; and finally, the baseline estimates of pretreatment risk reflect event rates partially contaminated by pre-existing treatment (thus underestimating the absolute risk reduction in truly untreated patients).20,24,25
Summary
A strategy combining 3 medications with diet and exercise might reduce recurrent cardiovascular events by four-fifths in patients with cerebrovascular disease. Our analysis, therefore, lends some support to a comprehensive, multifactorial approach to the long-term management of vascular risk after stroke or TIA. Far from being pessimistic regarding long-term prospects, physicians might expect major gains from instituting and combining multiple effective approaches for patients who survive an initial cerebrovascular event.

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References
32. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ. 2003;326:1419.
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