Future of Prevention

What Is the Future of Stroke Prevention?
Debate: Polypill Versus Personalized Risk Factor Modification

Walter N. Kernan, MD; Lenore J. Launer, PhD; Larry B. Goldstein, MD, FAAN, FAHA

Background and Purpose—The control of stroke risk factors remains challenging. The “polypill” concept represents a novel approach for reducing stroke and cardiovascular risk factors in the entire population. The polypill would include several components and be provided without prescription to all adults of a certain age.

Results—A polypill aimed at lowering blood pressure and cholesterol levels is estimated to potentially reduce the risk of a first ischemic stroke by 53%; this would translate to about 400 000 fewer strokes each year in the United States alone. Recommending a polypill for the entire older adult population would, however, include many individuals without the multiple risk factors targeted by its components, putting them at risk for drug-related side effects and responsible for the costs of a medication from which they would not derive benefit. Additional arguments for and against the polypill approach are discussed.

Conclusions—Only clinical trials can provide the evidence needed to determine the usefulness of the polypill approach. Issues related to defining the components of the polypill, evaluating the pharmacodynamics and pharmacokinetics of a multiple-component formulation, and establishing safety and cost-effectiveness when given to large populations, however, are not trivial. (Stroke. 2010;41[suppl 1]:S35-S38.)

Key Words: cerebrovascular disorders ■ primary prevention

Stroke mortality rates in the United States fell by 33.5% between 1996 and 2006 with the actual number of stroke deaths declining by 18.4%.1 Arguably, most of this benefit can be attributed to more effective prevention. Primary prevention is particularly important, because 610 000 of the 795 000 strokes occurring in the United States each year are first events.1

There are 2 broad approaches to primary prevention. The “population” (also known as the “mass”) approach aims at reducing the distribution of risk factors in the entire population.2 This is in contrast to the “high risk” (also known as the “personalized”) approach, in which an individual’s risk factors are identified through screening and then addressed with targeted interventions. The population approach has traditionally focused on lifestyle modification through health education, societal, and economic measures to reduce exposures and encourage “healthy” behaviors.2 Based on a combination of an analysis of the distribution of risk factors in the general population, the results of meta-analyses of randomized trials, and extrapolation from case-control and cohort studies, a novel strategy for population prevention of cardiovascular disease was proposed—pharmacotherapy with a combination of drugs combined in a single preparation, the “polypill.”3 As originally described, the polypill contained 3 antihypertensive drugs (each at half-standard dose), low-moderate dose statin, folic acid, and low-dose aspirin. The recommendation was for the polypill to be taken by everyone older than age 55 years and anyone with cardiovascular disease, regardless of their individual risk factor profile. If adopted, the polypill approach was estimated to reduce the risk of ischemic heart disease events by 88% (95% CI, 84% to 91%) and stroke by 80% (95% CI, 71% to 87%).3 The proposal met with strong reactions from the clinical and public health communities, ranging from “evangelical support for the principle to outright condemnation.”4 The polypill approach remains controversial.

Arguments for the Polypill Approach
The current approaches to primary stroke prevention include public health advice and treatment of an individual’s risk factors by healthcare providers. These approaches can have considerable limitations. Public health advice to exercise, eat healthier, and stop smoking largely has been ineffective, with the possible exception of smoking cessation (smoking rates among adults have declined by almost 50% over the past 40 years).5 Changing smoking behaviors required a multifaceted approach including regulation of access, advertising restrictions, and tax policy. Personalized care does not reach everyone, especially in the disorganized primary care environment of some developed countries. Furthermore, considerable vascular damage can occur before risk factors are...
identified and treated. New approaches are needed to reach more people earlier in the course of vascular disease. The polypill is one such approach. It is intended to be a population-based intervention aimed at preventing vascular disease, including stroke and myocardial infarction. To reduce barriers to access, it is envisioned to be made available without a physician’s prescription.

The argument for the polypill in prevention of ischemic stroke is based on 6 facts (Table 1). First, ischemic stroke is substantially preventable by reducing blood pressure and LDL-cholesterol, achieving smoking cessation, and treating atrial fibrillation. The polypill concept focuses on blood pressure reduction and lowering cholesterol levels. Second, the association between risk factors (ie, blood pressure, cholesterol) and stroke is linear over most of their ranges, meaning that the benefits of treatment may be proportionally similar at high and low values. Third, most ischemic strokes occur in persons with only a mild burden of known risk factors. Fourth, many persons with clinically defined hypertension or dyslipidemia do not know they have these conditions (treatment everyone will minimize the under-treatment of populations). Fifth, preventing risk factors from emerging is probably more effective than treating them once they emerge. Sixth, adherence is improved with simple, once daily regimens.

Blood pressure reduction is 1 of the 2 primary targets of the polypill. It is well established that stroke risk increases by one-third for every 10 mm Hg increase in systolic blood pressure above about 115 mm Hg. The treatment implications of this association are demonstrated by studies showing one-third for every 10 mm Hg increase in systolic blood pressure above about 115 mm Hg.7,8 The treatment implications of this association are demonstrated by studies showing that lowering blood pressure by this amount from any starting value provides similar relative risk reductions.9 Therefore, the notion that blood pressure is only damaging when it reaches a specific threshold must be questioned.

Lowering cholesterol levels is the second primary target of the polypill approach. Reduction of cholesterol levels with statin therapy reduces stroke risk in a linear fashion, even among those with minimally elevated baseline values. For example, among nondiabetic patients with hypertension enrolled in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA), treatment with a statin reduced stroke risk by 27% (relative risk 0.73; 95% CI, 0.56 to 0.96; \( P = 0.024 \)).

What could be expected from a polypill that effectively reduced blood pressure and cholesterol? A 1 mmol/L reduction in LDL-cholesterol results in about a 20% reduction in stroke risk, and a 10 mm Hg reduction in blood pressure reduces stroke risk about 40%.

Table 1. Six Facts Underlying the Polypill Concept

<table>
<thead>
<tr>
<th>Fact</th>
<th>Description</th>
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<tbody>
<tr>
<td>1.</td>
<td>Ischemic stroke is substantially preventable</td>
</tr>
<tr>
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<tr>
<td>3.</td>
<td>Most ischemic strokes occur in persons with a mild burden of known risk factors</td>
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</tr>
<tr>
<td>5.</td>
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</tr>
<tr>
<td>6.</td>
<td>Adherence is improved with simple, once daily regimens</td>
</tr>
</tbody>
</table>

Table 2. Possible Formulations for a Polypill for Primary Stroke Prevention

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Formulation</th>
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<tbody>
<tr>
<td>&lt;55 yr, no coronary artery disease</td>
<td><strong>For persons over age 55 without coronary artery disease</strong>&lt;br&gt;• Pravastatin 20 mg&lt;br&gt;• Amlodipine 5 mg&lt;br&gt;• Valsartan 80 mg†&lt;br&gt;<strong>For persons with coronary artery disease</strong>&lt;br&gt;• Aspirin 80 mg&lt;br&gt;• Amlodipine 5 mg&lt;br&gt;• Valsartan 80 mg†</td>
</tr>
</tbody>
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†Could be atorvastatin or rosuvastatin if cost can be contained.

Based on many of these concepts, in 1993 Nicholas Wald and Malcolm Law proposed giving a polypill to everyone over age 55 years and everyone with existing cardiovascular disease. They originally suggested that the polypill include 3 blood pressure–lowering drugs at half standard dose, a statin, folic acid, and aspirin. It has since been learned that folic acid is probably not effective in preventing stroke and that calcium channel blockers and angiotensin enzyme inhibitors may be more effective than \( \beta \) blockers or thiazide diuretics in preventing vascular disease in most patients. Although beneficial for secondary prevention of stroke and cardiovascular disease, it has also become clear that aspirin is not very effective for primary prevention of stroke, and that its use can be associated with a meaningful increase in bleeding complications. Even Dr Wald agrees that a polypill used for primary prevention should not include aspirin. Based on the available data, it could be proposed that the polypill for primary stroke prevention in persons without known coronary artery disease should probably include amiodipine, a statin, and an angiotensin-converting enzyme inhibitor (Table 2). For patients with known cardiovascular disease, the polypill should also include a \( \beta \) blocker and aspirin. Costs would be low because generic versions of each are available. At least partial versions of the polypill are already available and approved by regulatory agencies in the form of preparations combining a calcium channel antagonist and a statin.

The requirements for a successful polypill would be that it be both safe and cost-effective for a clearly defined popula-
tion. The only way this can be assessed is through research. A phase II study of a polypill was completed in India.\textsuperscript{18} The formulation included a thiazide, atenolol, ramipril, simvastatin, and aspirin. Compared to placebo, the polypill reduced systolic blood pressure by 7.4 mm Hg and LDL-cholesterol by 0.70 mmol/L. Cholesterol reduction, however, was not as great with the polypill compared with simvastatin alone, suggesting that the statin included in the combination pill was not bioequivalent to the single drug formulation. Rates of drug discontinuation were similar for the polypill and placebo, and no significant safety concerns were identified. Thus, the safety data are encouraging, at least for this preparation.

The concept of general pharmacological treatment of the US population is not new. Fluoride has been added to public water supplies for 65 years; iodine is added to salt and folic acid to enriched breads, pasta, and cereals. There is much to gain and little to lose in testing a polypill for primary stroke prevention in the United States and elsewhere. If the polypill is to be used in large populations, 5 conditions must be met. First, it must be proven safe and effective in high quality clinical trials to achieve broad acceptance among scientists, clinicians, and citizens.\textsuperscript{19} Second, a far-reaching, long-term campaign by public health agencies would be required for effective dissemination of the concept. Third, it must be easily available at a minimal cost. Fourth, it should be marketed as a foundation therapy; clinicians could add other agents as necessary to achieve risk factor control. Fifth, regulatory authorities must be willing to accommodate practices for polypill drug formulation and distribution. It is now time to undertake the necessary research to prove the value of the polypill approach.

Arguments for Personalized Risk Factor Modification

Personalized medicine can be viewed from several perspectives, including designing prevention and treatment approaches based on an individual’s risk profile. There are several reasons for taking an individual approach rather than a strategy of providing a multicomponent polypill for everyone above a certain age (usually 50 or 60 years) regardless of their individual risk profile. These include the relatively low prevalence of risk factor clustering in normal and overweight subjects, the unintended pleitropy of medications, the risk of drug-drug interactions, and cost.

The National Health and Nutrition Examination Survey (NHANES) 1999 to 2004 found that 30.1%, 51.2%, and 70.8% of normal, overweight, and obese adult men, and 21.1%, 43.0%, and 64.6% of adult women respectively, had 2 or more cardiometabolic abnormalities.\textsuperscript{20} Recommending a polypill for the entire older adult population would, therefore, include many individuals without the multiple risk factors targeted by the several polypill components. Additionally, there is a risk of delaying intervention to the older population. For example, using criteria for adults, the prevalence of the metabolic syndrome is 1.1% in normal, 5.8% in at risk, and 26.2% in overweight teens.\textsuperscript{21} Clearly, a strategy of delaying provision of a polypill to persons aged 50 or 60 years old may be too late.

Another problem of the polypill approach is the risk of adverse events when an intervention is used without medical supervision by large proportions of the general population. Recognition of low-frequency events may not be apparent for many years, by which time many persons could have been unknowingly harmed. For example, the adverse coronary side effects of Cox-2 inhibitors only became evident years after the drug class was introduced,\textsuperscript{22} and hormone therapy in women was shown to adversely affect health in a clinical trial that was on-going at the height of estrogen replacement therapy use by peri- and postmenopausal women.\textsuperscript{23} Other drugs, such as statins, modulate several different pathways, some of which may not be beneficial. In addition, the possibly harmful side effects that can occur when multiple drugs are taken in combination cannot be dismissed.

Several studies indicate that using multiple medications to control risk factors may change the risk factors’ levels, but do not reduce clinical events. For example, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) treatment trials were designed to test the effect of intensive as compared to standard treatment strategies to lower glycohemoglobin levels (a marker of glucose dysregulation) on cardiovascular outcomes.\textsuperscript{24,25} Despite achieving the targeted glycohemoglobin levels with treatment, the trials were negative, and there was a suggestion of harm. An accompanying editorial noted that, in addition to the target risk factor reduction goals, the strategy itself needs to be reconsidered.\textsuperscript{26}

If a polypill given to all middle age and older persons is not the ‘solution’ to prevention, what alternative strategies can be used to prevent stroke and cardiovascular events? Healthy lifestyle choices should form a critical component of the strategy. The Health Professionals Study found that persons following a low risk lifestyle (no smoking, BMI <25, engaging in ≥30 minutes exercise, each day, having modest alcohol intake and following a healthy diet) had an 80% lower risk for ischemic stroke compared with men who had none of these factors (relative risk 0.20; 95% CI, 0.1 to 0.42).\textsuperscript{27} Similarly, women in the Nurses Health Study who followed similar lifestyles had an 81% lower stroke risk (relative risk 0.19; 95% CI, 0.09 to 0.40).\textsuperscript{27} The Diabetes Prevention Program Outcomes Study (DPP) further suggested that lifestyle interventions may be even more efficacious than a drug approach to reduce clinical events. As compared to treatment with metformin, the DPP found weight loss and physical activity was 12% more effective in reducing the development of diabetes in those with prediabetes (34% reduction in diabetes in the lifestyle group versus 18% in the metformin group), a difference that persisted 10 years after the intervention.\textsuperscript{28}

A European study estimated that to be cost-effective, assuming a €20 000/yr of life saved threshold, among those with a 10 year coronary heart disease risk over 20%, the annual cost of the polypill should be no more than €302 or €410 for men at age 50 and 60 years, respectively (and 2 to 3 times lower for a risk between 10% and 20%).\textsuperscript{29} It was concluded that even if provided free, the polypill strategy would result in no cost savings in moderate risk populations or in the total population if given irrespective of risk levels. In the United States, considering the costs of interventions, healthcare delivery and utilization, tests and treatment, adherence and clinical events, the greatest benefits to the US population would
come from behavioral changes including weight reduction and smoking cessation and targeted monotherapy to specific high risk groups. The polypill strategy, although attractive, is not the answer to population-based stroke prevention.

Implications and Future Directions

The debate highlights arguments for and against the polypill approach. Provocative since the concept’s first introduction, trials proving or disproving the strategy remain to be conducted. Preliminary work suggests that it might be a viable alternative. Only clinical trials can provide the evidence needed to determine its usefulness. Prerequisites for such trials including addressing issues related to defining the components of the polypill and evaluating the pharmacodynamics and pharmacokinetics of a multiple-component formulation are not trivial.

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References


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