A "Poly-Portfolio" for Secondary Prevention: A Strategy to Reduce Subsequent Events By Up to 97% Over Five Years

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A "polypill" for the primary prevention of cardiovascular disease has been proposed. We estimated the projected benefit of a secondary prevention "poly-portfolio" strategy, including pharmacologic and lifestyle approaches for those with coronary heart disease (CHD) or stroke. Based on recent clinical trial results and clinical guidelines, combinations of a high-dose statin, low to standard doses of antihypertensive therapy, aspirin, omega-3 fish oil, cardiac rehabilitation, and diet were evaluated. Patients with CHD, post–myocardial infarction (MI), or stroke were projected to experience 84%, 91%, and 77% reductions, respectively, in CHD events from a pharmacologic approach. Numbers of those needed to treat (NNT) for 5 years were 9 to 11 to prevent 1 CHD event, and 21 to prevent 1 stroke. Post-MI patients were projected to experience a 93% reduction in the risk of CHD death (NNT 16) from a pharmacologic approach and a 97% reduction in the risk of CHD death (NNT 15) with the addition of lifestyle changes. A secondary prevention polyportfolio holds great promise for reducing the burden of cardiovascular disease in the highest risk patients. ©2005 by Excerpta Medica Inc.

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A "polypill" has been proposed for the primary prevention of coronary heart disease (CHD) and stroke.[1] This formulation would contain a statin to lower low-density lipoprotein (LDL) cholesterol by approximately 35%, 3 half-dose antihypertensive agents, aspirin (75 mg), and folic acid (0.8 mg). If taken by everyone aged ≥55 years, this strategy is projected to reduce lifetime CHD events by 88% and stroke by 80%, gaining on average 11 years free of CHD and stroke. A strategy focusing on the highest risk patients, however, would result in two- to threefold greater absolute reductions over just 5 years of treatment than one focused on low-risk patients.[2] We describe a poly-portfolio strategy that includes pharmacologic and lifestyle approaches for the prevention of CHD and stroke in patients at high risk of cardiovascular disease based on similar principles of (1) intervention on multiple risk factors at once, (2) maximal treatment of risk factors, (3) minimization of adverse effects, and (4) a simple dosing regimen.

Preventive regimens were identified from the most recent United States recommendations for the prevention of CHD and stroke by the American Heart Association, American College of Cardiology, American Stroke Association, National Cholesterol Education Program Adult Treatment Panel, Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, and the American Diabetes Association.[3–13] Recommendations for patients with congestive heart failure, patients with diabetes mellitus, or multiple risk factors and a >20% 10-year CHD risk, but free of known cardiovascular disease, are not included in this analysis because fewer clinical trial data are available for these populations. Although folic acid supplementation was included in the primary prevention polypill analysis, it was not included in this analysis due to lack of short-term benefit in a clinical trial of cardiovascular risk reduction.[14]

Estimates of treatment benefit were derived from the guidelines, meta-analyses, and randomized, controlled clinical trials. Stroke survivors receiving statin therapy appear to experience similar reductions in CHD risk as patients with CHD.[15] Reductions in blood pressure and serum cholesterol have been shown to produce constant proportional reduction in risk across the range of risk factor levels.[11,16] Event rates in clinical trials of <5 years were extrapolated from the visual inspection of the Kaplan-Meier survival curves for nonfatal myocardial infarction (MI) plus coronary death and for fatal and nonfatal stroke. The effects of LDL, blood pressure lowering, aspirin, β blockers, angiotensin-converting enzyme inhibitors, and omega-3 fish oil after MI appear to be additive.[1,11,16–24] Therefore, we calculated the benefit of combined treatment by multiplying the relative risks associated with each treatment.[1] The numbers needed to treat and prevent 1 event were based on the relatively contemporary and undertreated Heart Protection Study population placebo group of 10,237 adults aged 40 to 80 years with total cholesterol levels ≥135 mg/dl.[25]

Table 1 lists the recommended preventive therapies for high-risk persons and the relative risk reduction expected for a change in risk factor level. To estimate the benefit of aggressive cholesterol lowering, the

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TABLE 1 Recommended Therapies for Prevention of Coronary Heart Disease (CHD) and Stroke Risk and Estimated Risk Reduction Benefits in Patients With Cardiovascular Disease Over Approximately Five Years

Risk Factor and Goal	Recommended Agent(s)	Change in Risk Factor	Relative Risk Reduction (Major CHD events)**	Relative Risk Reduction (stroke)	Source of Recommendation or Evidence
LDL cholesterol <70 mg/dl	High-dose statin + diet	≥ ↓ 50%	48%	38%	References[11,20,30]
Blood pressure <140/90 mm Hg except <130/80 mm Hg with diabetes	3-drug combination: diuretic (1/2 dose), β blocker, ACE inhibitor or calcium channel blocker	Systolic ↓ 20 mm Hg or diastolic ↓ 10 mm Hg	46%–49%*	63%–66%*	References[19,30]
Platelet function	Aspirin 75–81 mg/d		CHD pts. 42% Stroke pts. 17%	CHD pts. 25% Stroke pts. 19%	Reference[1]
β blocker post-MI	Noncardioselective; no intrinsic sympathomimetic activity		23% CHD death†		Reference[32]
ACE inhibitor post-MI			20%‡	32%‡	References[33,64]
Sudden death post-MI	Omega-3 fish oil 1,000 mg/d		30%§ 30% CHD death		References[8,61]
Cardiac rehabilitation	Individual prescription	↑ Moderate acrobic physical activity	26% CHD death§		Reference[65]
Diet	Mediterranean	↑ Fruits, vegetables, legumes, nuts, whole grains, fish, monounsaturated oils	52%–72%‖ 33% CHD death (25% total mortality)		References[66–68]

*Based primarily on trials in patients without cardiovascular disease; 3 drugs at half dose is lower estimate and 3 drugs at full dose the higher estimate.
†Mean study follow-up 6 to 48 months; risk reduction independent of length of follow-up.
‡Mean study follow-up 4 years.
§Independent of duration of follow-up; mean study follow-up 3.5 years.
‖Approximately 2-year intervention.
**Nonfatal MI and CHD death.
ACE = angiotens-converting-enzyme; pts = patients; ↓ = decreased; ↑ = increased.

results of the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 (PROVE-IT-TIMI 22) trial showed that atorvastatin 80 mg (mean LDL 62 mg/dl, expected LDL reduction 46% to 52%[26,27]) resulted in an additional 18% reduction in nonfatal MI and CHD death beyond treatment with pravastatin 40 mg (mean LDL 95 mg/dl, expected LDL reduction 25% to 28%[28,29]) over 24 months of treatment.[30] Extrapolation of the event rate after 12 months of treatment yielded an approximate additional 22% reduction in major CHD events in the atorvastatin group at 5 years. Based on clinical trials of >4 years of pravastatin therapy (CHD relative risk reduction 24%[28,29]), the expected relative risk reduction for atorvastatin 80-mg therapy would therefore be expected to be approximately 46%. Stroke was infrequent in the PROVE-IT TIMI 22 trial, so similar calculations could not be performed. Because pravastatin therapy reduces stroke risk by 19%,[29] and atorvastatin 80 mg would be expected to reduce stroke risk by approximately 19% beyond that expected for pravastatin 40 mg/day, the expected relative risk reduction in stroke would therefore be 38% for atorvastatin 80 mg.

The effects of antihypertensive drugs on blood pressure appear to be additive.[16] To minimize the side effect profile, half doses of antihypertensive therapy were proposed for the primary prevention polypill. Based on the available clinical trial evidence, half doses would also be appropriate for survivors of stroke and patients with CHD without acute MI. However, for patients with acute MI, standard doses rather than half doses[31] were chosen for β blockers and angiotensin-converting enzyme inhibitors because these were the doses used in trials after MI.[32] The benefits of β blockers and angiotensin-converting enzyme inhibitors after MI appear to be additive and independent of blood pressure lowering.[32,33] The benefits of physical activity and diet were not available from non–post-MI populations; thus, these estimates were not included for those with stable CHD or stroke.

According to this analysis, a secondary prevention poly-portfolio strategy would prevent most new events in patients with cardiovascular disease, with a compelling suggestion of almost complete elimination of the risk of CHD death in post-MI patients with a combination of drug and lifestyle therapy over 5 years (Table 2). Treatment with a polypill combination of a high-dose statin, 3 antihypertensive medications (the doses of which vary depending on whether the patient is post-MI), aspirin, and omega-3 fish oil is projected to result in a 77% to 91% reduction in susequent CHD events, a 93% reduction in CHD death after MI, and an 83% reduction in stroke. In patients with CHD, the addition of lifestyle therapy would further reduce the

TABLE 2 Estimated Reductions in the Risk of Major Coronary Heart Disease (CHD) Events and Stroke in Patients With Any CHD, Post-myocardial Infarction (MI), and Stroke from Five Years of Treatment With Combined Statins, Antihypertensive, Aspirin, and Omega-3 Therapies and With and Without Lifestyle Therapies

Estimated Reduction in Relative Risk of Event Over 5 yrs	Type of Patient		
	Any CHD	Post-MI	Stroke
Major CHD events with combined drug therapy	84% NNT = 10	91% NNT = 9	77% NNT = 11
Major CHD events with addition of lifestyle therapy	92% NNT = 9	96% NNT = 9	
CHD death with combined drug therapy		93% NNT = 16	
CHD death with addition of lifestyle therapy		97% NNT = 15	
Stroke with combined drug therapy	83% NNT = 21		

Major CHD events = nonfatal MI and CHD death.
NNT = number of patients treated to prevent 1 event (nonfatal MI or CHD death, CHD death, or stroke) over 5 years.

risk of CHD by 92%, and in post-MI patients the risk of CHD death would be reduced by 97%. In contrast to a primary prevention, a secondary prevention polypill would accrue similar or greater risk reductions over 5 years rather than a lifetime of treatment. Between 9 and 11 patients with CHD or stroke would need to be treated for 5 years to prevent 1 CHD event or stroke versus the 13 to 33 primary prevention patients who would need to be treated for 10 years.[1]

A polypill could help bridge the treatment gap in secondary prevention. In a survey of patients enrolled in a large acute coronary syndrome registry through 2003, 90% were discharged on aspirin, 56% on β blockers, 17% on angiotensin-converting enzyme inhibitors, and 46% on statins.[36] Utilization rates are even lower in patients aged $>$ 65 years.[37] Substantial progress toward reducing the burden of cardiovascular disease in high-risk patients could be made if secondary prevention polypill utilization rates approached the level of aspirin. Additional benefits of a secondary prevention polypill strategy would include a $\geq$50% reduction in congestive heart failure with treatment of cholesterol and blood pressure.[38,39]

As with the primary prevention polypill, statin therapy drives the risk reduction estimates, and the risk reduction from the addition of a third or subsequent agent is substantially less than when the agent is given alone.[1] Although the additive benefits of statin therapy in addition to antihypertensive therapy[21] and 2 drug antihypertensive regimens[31] have been established, the degree of additivity of multiple drug and lifestyle therapies has not been determined in clinical trials. Therefore, estimates of benefit for primary and secondary prevention polypills and lifestyle therapy may be lower than expected, especially in populations with other risk factors, such as smoking or metabolic syndrome.[40,41] Overestimation of risk reductions may be counterbalanced by the likelihood that numbers needed to treat are overestimated in this analysis. In the study used to estimate the numbers needed to treat, 25% of participants received secondary prevention medications at baseline.[25] Event rates based on untreated risk factor levels would result in approximately 20% fewer numbers needed to treat for this analysis.

The risk reduction benefit from more aggressive LDL reduction ($\geq$50%) was based on an extrapolation of benefit from just 1 small clinical trial of atorvastatin 80 mg in patients with acute coronary syndromes. However, the projected risk reduction from this study is similar to that seen in the larger, long-term statin trials, which have consistently shown a 1:1 relation between LDL reduction and CHD risk reduction in patients with stable CHD and stroke.[11] Just completed or ongoing clinical trials will provide more accurate estimates of the benefit of aggressive LDL reduction in patients with stable CHD or stroke.[42,43]

No morbidity or mortality clinical trial data and much less long-term safety data are available for the other agents that lower LDL by 50% to 60% (rosuvastatin 20 to 40 mg and combinations of simvastatin/ezitimibe).[44–47] Use of simvastatin 40 mg and a 30% reduction in LDL, on the basis of evidence from the Heart Protection Study,[25] would result in projected 77% to 79% and 66% relative risk reductions for CHD and stroke, respectively, in patients with CHD (compared with 84% to 91% and 77% for atorvastatin 80 mg).

The adverse effects of statins are dose-related. Myalgias occur in 5% to 7% of patients.[48,49] The risk of myopathy is uncommon ($\leq$1/1,000) for most statins, although it appears to be somewhat higher for simvastatin 80 mg/day.[49–51] Abnormal liver function tests $>$3 times the upper limit of normal on $\geq$2 consecutive occasions occur somewhat more frequently with atorvastatin 80 mg (2.3%) than with rosuvastatin 20 to 40 mg ($\leq$0.1%) and ezitimibe in combination with simvstatin 80 mg (1%).[47] A slightly greater frequency of dipstick-positive proteinuria and microscopic hematuria has been observed with rosuvastatin 40 mg than for lower doses or for other statins.[50] The clinical significance of this is unclear, because the proteinuria was mostly transient and tubular in origin, whereas creatinine clearance stayed the same or increased over time with continued therapy. Data suggest that persons aged $\geq$80 years at study entry experience similar relative risk reductions from statin therapy as younger persons.[15] Because long-term efficacy and safety data are not available for high-dose statins in the elderly, lower statin doses should be administered to persons $>$70 years old until such data become available. Although less aggressive LDL reduction will result in less reduction in relative risk, the reduction in absolute risk in this very high-risk population is still substantial.[52]

For aspirin used in high-risk populations, the benefit from reducing CHD and thrombotic stroke far exceeds the small risk of hemorrhagic complications.[1] On the basis of cost, aspirin is preferred over clopidogrel, despite clopidogrel's apparently greater benefit for CHD reduction. Aspirin and clopidogrel appear to be less effective in lowering cardiovascular risk in stroke patients.[53] Aspirin does not appear to appreciably diminish the cardioprotective benefits of angiotensin-converting enzyme inhibitors.[54]

Low-dose thiazide-type diuretics are inexpensive and superior to angiotensin-converting enzyme inhibitors and calcium channel blockers for preventing ≥1 major forms of cardiovascular disease.[12,55,56] Hydrochlorothaizide and chlorthalidone appear to be similarly efficacious.[57] Noncardioselective β blockers without intrinsic sympathomimetic activity are recommended for the secondary prevention of CHD,[5–7,33] but superiority in other populations has not been demonstrated.[58] Observational data suggest ramipril may result in greater survival benefits than other angiotensin-converting enzyme inhibitors,[59] although no head-to-head comparisons in clinical trials have been performed. Angiotensin-receptor antagonists also reduce cardiovascular events and may be superior to β blockers in patients with left ventricular hypertrophy but without known CHD.[58] Angiotensin-converting enzyme inhibitors may not be as effective in preventing stroke, although this may result from less effective blood pressure lowering in blacks and patients aged ≥65 years.[55] Dihyropyridine calcium channel blockers appear to be superior to nondihydrydropyridine calcium channel blockers for cardiovascular prevention.[60] Amlodipine does not appear to provide a similar degree of protection against congestive heart failure as diuretics or angiotensin-converting enzyme inhibitors, but does appear to reduce overall cardiovascular risk similar to angiotensin-converting enzyme inhibitors.[55]

Half-standard doses of antihypertensive agents result in 20% lower systolic and diastolic blood pressure reduction than standard doses with fewer adverse effects (0 to 5.5% vs 0 to 8.3% with full dose).[16,31] On the basis of efficacy and adverse effects, half doses of diuretics, β blockers, and angiotensin-converting enzyme inhibitors may be preferred in patients with stable CHD or stroke, and full-dose β blockers and angiotensin-converting enzyme inhibitors reserved for post-MI patients. In elderly patients, a lower dose, stepped approach to antihypertensive therapy, and then switching to a polypill formulation, would minimize the risk of orthostatic hypertension. Patients with uncontrolled hypertension should be controlled before starting a regimen containing aspirin.[12]

Both marine-derived omega-3 fatty acids (eicosapentaenoic and docosahexaenoic acids) and plant-derived omega-3 fatty acids (α-linolenic) reduce CHD risk.[61] Total marine omega-3 fatty acids (≈1,000 mg/day) is recommended on the basis of the largest trial.[8,23] Adverse effects include fishy eructation and gastrointestinal disturbance, which occurred in 4% of participants discontinuing their supplements in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto Miocardio (GISSI)-Prevention study.[23] Given the volume of fish oil required, it may be difficult to formulate a single tablet containing all 6 medications.

Although the morbidity and mortality benefit has not been quantified in long-term trials, data does suggest regular, aerobic physical activity is beneficial for patients with CHD without acute MI[62] and stroke patients.[63]

Observational data has shown that patients with acute coronary syndrome who received ≥4 secondary prevention medications experienced up to 87% lower mortality at 6 months.[24] Systematic efforts need to be undertaken to incorporate proven pharmacologic and lifestyle therapies into a comprehensive treatment strategy for each patient with cardiovascular disease. Such a poly-portfolio approach would substantially reduce the burden of cardiovascular disease and prolong life in the highest risk patients.

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