EDITORIALS

More HOPE for Prevention with Statins

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In view of the worldwide burden of cardiovascular disease and the high cost of and poor adherence to medication regimens for the prevention of cardiovascular disease, the concept of a "polypill" — a single pill that combines several medications — is an attractive public health approach. However, evidence that each component of a polypill would independently reduce the risk of cardiovascular events and that the combination of agents would be safe is lacking. The primary results of the Heart Outcomes Prevention Evaluation (HOPE)–3 trial are now reported in three articles in the *Journal*.[1-3] HOPE-3 was a double-blind, randomized, placebo-controlled trial with a 2-by-2 factorial design, in which 12,705 intermediate-risk men (≥55 years of age) and women (≥60 years of age) who did not have cardiovascular disease were randomly assigned to receive cholesterol-lowering treatment with rosuvastatin at a dose of 10 mg per day or placebo and were also randomly assigned to receive blood-pressure–lowering treatment with candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day or placebo for a median of 5.6 years. Treatment with rosuvastatin resulted in a 24% lower risk of cardiovascular events than that with placebo (absolute difference, 1.1 percentage points), but the antihypertensive therapy did not result in a significantly lower risk of cardiovascular events. The HOPE-3 trial provides evidence to reinforce some current guideline recommendations and to influence future guidelines.

The cholesterol-lowering component of the trial[1] produced results consistent with a meta-analysis of randomized trials of statin therapy, which showed that a reduction of 1 mmol per liter in the low-density lipoprotein (LDL) cholesterol level was associated with a 25% lower risk of cardiovascular events in a primary-prevention population.[4] Furthermore, the rate of cardiovascular events that was observed in the placebo group (4.8% over a period of 5.6 years) was within the range of the rates that were observed among the lowest-risk groups shown to have a benefit from statin therapy in the meta-analysis. The trial participants who had high-sensitivity C-reactive protein (CRP) levels higher than 2 mg per deciliter and those who had levels lower than 2 mg per deciliter had similar rates of cardiovascular events and a similar benefit from rosuvastatin. Hence, these results support a risk-based approach to statin use, which has been recommended in recent guidelines,[5] rather than an approach that is based primarily on LDL cholesterol levels, and the results add to the evidence supporting statin use for primary prevention.

The blood-pressure–lowering component of the trial[2] showed no significant benefit of antihypertensive therapy in reducing the risk of cardiovascular events. The observed difference between the active-treatment group and the placebo group in the decrease in blood pressure over the course of the trial (6.0/3.0 mm Hg) was small, and the 95% confidence interval for the estimated hazard ratio did not exclude the benefit one might expect (on the basis of the results from the meta-analysis) from this degree of blood-pressure lowering.[6] Neither of the drugs for blood-pressure lowering that were used in the trial have been shown to reduce the risk of cardiovascular events at such low doses. If higher doses had been used, the risk of cardiovascular events might have been significantly reduced,

whether from greater blood-pressure lowering, additional effects of the antihypertensive drugs, or both. Hydrochlorothiazide, even at a dose of 25 mg per day, has been less effective in reducing the risk of cardiovascular events than has a full dose of amlodipine,[7] whereas chlorthalidone at a dose of 25 mg per day has been effective in reducing the risk of cardiovascular events in a placebo-controlled trial[8] and has been at least as effective as amlodipine.[9] These observations suggest that the use of chlorthalidone could have been more effective than the use of hydrochlorothiazide in HOPE-3.

The trial population was at a lower cardiovascular risk than the populations in previous hypertension trials. The observed rate of cardiovascular events in the dual-placebo group was 5.0% over a period of 5.6 years. Since most previous trials of blood-pressure lowering have used inclusion criteria that are designed to increase the level of cardiovascular risk in order to increase trial efficiency, those trials have included few low-risk adults. Meta-analyses of such trials provide evidence of cardiovascular benefit from the use of blood-pressure–lowering medications in adults with an average systolic blood pressure higher than 130 mm Hg and either clinical cardiovascular disease or a high cardiovascular risk (defined as a 5-year risk of cardiovascular events of ≥6.5%).[6] In addition, the Systolic Blood Pressure Intervention Trial (SPRINT) provides support for the use of blood-pressure–lowering medications in patients who do not have cardiovascular disease but who have a systolic blood pressure higher than 130 mm Hg; in SPRINT, the risks of cardiovascular events and death from any cause were significantly reduced with the use of regimens for blood-pressure lowering that were more intensive than the regimen used in this trial.[10] However, the SPRINT participants who did not have clinical cardiovascular disease at baseline were required to have subclinical cardiovascular disease or a 10-year cardiovascular risk (on the basis of the Framingham risk score) that was higher than 15%. The difference in systolic blood pressure between the active-treatment and control groups that was seen in SPRINT was twice the difference seen in HOPE-3 because the treatment regimen was more intensive.

The overall null results of the blood-pressure–lowering component of HOPE-3 could be due to insufficient dosing of antihypertensive medications, treatment of a relatively low-risk group, or chance. Setting aside the play of chance, we may take from these results new insight regarding the initiation threshold and treatment targets for blood-pressure–lowering medications. Although no benefit of blood-pressure lowering was observed overall, a prespecified subgroup analysis showed a 27% lower risk of cardiovascular events with blood-pressure–lowering therapy in the subgroup of participants who were in the upper third of systolic blood pressure levels (>143.5 mm Hg). Among the patients in that subgroup who received placebo, the rate of cardiovascular events was 6.5% over a period of 5.6 years. This rate is within the range of rates reported in the previously mentioned meta-analysis. However, the rates of cardiovascular events in the subgroups of participants in the lower and middle thirds of systolic blood pressure levels who received placebo were lower than the rates among the lowest-risk groups shown to have benefit from blood-pressure lowering in previous trials. Blood-pressure–lowering treatment with low doses of the two drugs used in HOPE-3 may not be effective over the period studied in this trial among patients with low levels of systolic blood pressure and low levels of cardiovascular risk. These results may help to define the combined threshold of systolic blood pressure (<140 mm Hg) and cardiovascular risk (<5.0%) below which the use of blood-pressure–lowering medications may not be useful in the short term. However, these results do not rule out the possibility of a benefit with longer-term treatment in a portion of this relatively low-risk population.

The results of the comparison of the effects of the combined intervention (rosuvastatin and candesartan plus hydrochlorothiazide) with placebo[3] generally agreed with the results for the separate interventions. There was no evidence of harm or synergy between the two interventions. Although the addition of blood-pressure lowering to rosuvastatin therapy appeared to provide more benefit than that observed with rosuvastatin alone in the subgroup of participants who were in the upper third of systolic blood pressure levels, the P value for interaction was not significant.

The results of the HOPE-3 trial suggest that rosuvastatin at a dose of 10 mg per day is more effective in preventing cardiovascular events than

is candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day in this relatively low-risk population. Although these results do not exclude the possibility that more effective therapy for blood-pressure lowering might be beneficial in a relatively low-risk, older population, they provide support for the use of statins as a safe and effective intervention to prevent cardiovascular events in such patients.

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Hemophilia Therapy — Navigating Speed Bumps on the Innovation Highway

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Hemophilia A is an X-linked hemorrhagic disorder characterized by a congenital absence or decrease in plasma clotting factor VIII, a procoagulation cofactor and potent generator of thrombin when bound to activated factor IX and factor X. Unprecedented biotechnological progress has increased life expectancy for patients across the range of disease severity through an expanding menu of highly safe and effective recombinant factor VIII and plasma-derived factor VIII concentrates for bleeding treatment and prophylaxis.[1] Widespread adoption of primary strategies of bleeding prophylaxis (before the onset of arthropathy in children) has unequivocally minimized orthopedic morbidity, which has long been the hallmark of hemophilia.[2]

But even as benefit far exceeds risk, and healthy outcomes are assured for 80% of those affected in resource-rich countries, economic and practical burdens of therapy still impede access and adherence. Multiple intravenous infusions of factor VIII per week are required for healthy joints and present a particular challenge for children; protein modifications intended to delay recombinant factor VIII clearance and reduce infusion frequency have been only moderately successful to date.[1] Furthermore, early development (median age, 15.5 months) of polyclonal neutralizing IgG4 antidrug antibodies (inhibitors) to factor VIII replacement threatens healthy outcomes in 32% of the severely affected (factor VIII activity <1 IU per deciliter).[3] Once high-titer inhibitors develop, eradication is laborious and not ensured.[4] Effective therapeutic options are limit-