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CARDIOLOGY UPDATE 2016

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CHAPTER 4



Santanu Guha, Siddhartha Mani

Heart Outcomes Prevention Evaluation-3 Trial: Implications in Primary Prevention in India

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INTRODUCTION

Statins and blood pressure (BP) lowering agents are expected to cause large reductions in major CV events substantially and safely when used alone or in combination. However till date, most evidence comes from studies in high-risk individuals with established CVD or diabetes or substantially elevated LDL-C or high BP levels, thus confirming the efficacy and safety of these drugs in high-risk populations.[1,2]

ANALYSIS OF THE TRIAL

Based on these considerations, the heart outcomes prevention evaluation (HOPE)-3 trial was initiated in 2007 to evaluate the effects of a low-dose potent statin to lower LDL-C, a low-dose fixed combination of an angiotensin-receptor blocker (ARB) plus diuretic, and their combination to prevent major CV events in a large number of individuals who are at intermediate risk and had no previous CVD. There was no strictly defined cholesterol or BP levels in the inclusion criteria and were all receiving lifestyle modification. This trial, designed to focus on preventing cardiovascular disease before it starts, is an international randomized trial conducted in 21 countries; China, India, Colombia, Argentina, and Canada contributed the most participants. The trial included 12,705 people (age, ≥65 for women, and ≥55 for men) without known cardiovascular (CV) disease who were considered to be at intermediate risk by virtue of meeting at least one inclusion criterion: Elevated waist–hip ratio, HDL cholesterol level <39 mg/dL (men) or <50 mg/dL (women), current or recent smoking, pre-diabetes or diet-controlled diabetes, premature coronary disease in first-degree relatives, or early renal dysfunction. Most participants had at least two risk factors.

In a 2 × 2 factorial design, participants were randomly assigned to one of four groups: rosuvastatin 10 mg plus a combination pill of candesartan 16 mg and hydrochlorothiazide 12.5 mg daily, rosuvastatin 10 mg plus a placebo daily, a placebo plus the combination pill daily, or two placebo pills daily. At baseline, mean LDL cholesterol level was 128 mg/dL and mean blood pressure (BP) was 138/82 mm Hg. During median follow-up of 5.6 years, key findings were as follows:

- Compared with placebo, rosuvastatin reduced mean LDL cholesterol level by 35 mg/dL, and the antihypertensive drugs lowered mean systolic/diastolic BP by 6/3 mm Hg.
- The first co-primary outcome [CV-related death, nonfatal stroke, or nonfatal myocardial infarction (MI)] occurred significantly less frequently with rosuvastatin than with placebo (3.7% vs. 4.8%); absolute reductions were 0.3%, 0.4%, and 0.5% for CV-related death, MI, and stroke, respectively.
- Overall, candesartan/hydrochlorothiazide did not significantly lower the incidence of the first co-primary outcome compared with placebo (4.1% vs. 4.4%); however, it did lower the incidence in a subgroup with highest baseline systolic BP (>143 mm Hg; 4.8% vs 6.5%).
- Overall, outcomes with rosuvastatin plus candesartan/hydrochlorothiazide were not significantly better than outcomes with rosuvastatin alone.

- All cause mortality was not lowered by active therapies compared with placebo.
- Neither treatment increased risk for diabetes; a small excess of muscle pain was noted with rosuvastatin and dizziness with candesartan/hydrochlorothiazide.

A second analysis of HOPE-3 trial led by Bosch et al., focused only on the use of statins and found that 3.7% of those taking a statin experienced the first co-primary endpoint—a composite of cardiovascular deaths, myocardial infarction and stroke – compared with 4.8% of patients taking a placebo. Additionally, 4.4% of the statin group experienced the second co-primary endpoint—a composite of the events in the first co-primary endpoint plus heart failure, resuscitated cardiac arrest and revascularization procedures—compared with 5.7% of the placebo group. After 12 months, patients taking statins experienced, on average, a 25% reduction in low-density lipoprotein cholesterol. The benefits of statins, on the other hand, did not vary by LDL level or level of risk.

Participants will be tracked for an additional three to five years. The researchers will continue to conduct additional analyses examining the effects on cognitive decline, erectile dysfunction and vision, along with detailed analyses of potential differences among ethnic groups and geographic regions.

IMPLICATIONS OF THE RESULTS

The results point to a more simple approach, placing more emphasis on statins in the general population and indicates role of low doses of combination BP medications to the statins in patients with mild hypertension. However, this trial does not support the case for universal primary prevention, or widespread use of a polypill.

HOPE-3 differs significantly from previous statin and BP-lowering trials in primary prevention. The Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), published after the initiation of HOPE-3, evaluated treatment with rosuvastatin 20 mg/d in a highly selective population of largely white men and women with increased high-sensitivity C-reactive protein levels and reported a 44% reduction in major CV events after a median of 1.9 years of follow-up.[3] However, because of the trial's restrictive eligibility criteria (only 20% of participants screened were eligible), it is unclear whether these findings can be generalized to the entire population. Other trials of statin drugs in primary prevention also used restrictive eligibility criterias. Different trials were conducted in various clinical settings, e.g. in middle-aged Scottish men with hypercholesterolemia,[4] individuals with high LDL-C and low HDL-C,[5] Japanese individuals with hypercholesterolemia,[6] patients with hypertension and additional CV risk factors,[7] and individuals with diabetes.[8,9] Two trials included individuals targeted for both primary and secondary prevention, although study participants without previous CV events had high-risk profiles.[10,11] Compared with these trials, HOPE-3 uses wider eligibility criteria, a longer duration of follow-up, wider ethnic diversity, and simpler monitoring procedures. The Cholesterol Treatment Trialists' (CTT) meta-analysis reported large relative risk reductions (RRRs) in major CVD events in low- and intermediate-risk groups.[12] However, in this meta-analysis, data in the lowest-risk group (major yearly CV event rate of >1%) were provided by the aforementioned trials, which used narrow eligibility criteria. Moreover, these data are based on a modest number of events: only 71 vascular deaths among those without CVD, 138 major coronary events, 161strokes, 208 revascularizations, and a total of 377 major CV events. The HOPE-3 trial is expected to accrue almost twice as many events, and will thus add substantially to the available information in this population. Similarly, BP-lowering trials published before and after the start of HOPE-3 were conducted in individuals with hypertension defined as BP >160/100 mm Hg or with pre-existing CVD, diabetes, or renal disease, or a combination.[13] Whether BP-lowering drugs will benefit a wider range of individuals without CVD, including those with "normal" entry BP levels, remains uncertain. Recent critical appraisals of the available data suggest than even for patients with "mild" hypertension (systolic BP of 140–160 mm Hg), the evidence for benefit with BP-lowering drugs is not robust. Some of these unresolved issues in BP management in primary prevention in the absence of end-organ damage are addressed in HOPE-3.[14]

INDIAN PERSPECTIVE

Cardiovascular disease (CVD) is globally considered as the leading cause of death with approx. 80% of CVD related deaths being reported from low and middle income countries like India. The relatively early onset age of CVD in India in comparison to Western countries also implies that most productive ages of the patient's life are lost from the ailments. Conventional cardiovascular risk is attributed to lifestyle changes and altered metabolic activity.

A substantial proportion of these CVD events occur in average-risk populations with no known vascular disease and often without major elevations in cardiovascular (CV) risk factors. Prevention in such populations may have a bigger impact, a concept known as the "prevention paradox." Moreover, "mildly" abnormal CV risk factor levels are common. In the Framingham study, fewer than 5% of participants had optimal CV risk factor levels. In the

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US National Health and Nutrition Examination Surveys I, II, and III, the prevalence of low CV risk factors was only 4.4% during 1971–1975, 10.5% during 1988-1994, and 7.5% during 1999-2004, and in the INTERHEART study, 99% of control participants had at least 1 abnormal CV risk factor. Therefore, to substantially reduce the population burden of CVD, the majority of individuals in most urban populations may require modification of their risk factors.

An important barrier to reducing the population burden of CVD is the lack of simple and widely applicable approaches to prevention. Guidelines for primary prevention vary by region, change very often, extrapolate far beyond data available from randomized trials, and frequently involve complex algorithms for selecting individuals requiring drug therapies to reduce risk factor levels, such as cholesterol and BP, and for administering and monitoring the effects of therapy. These factors may contribute to the low rates of adoption of cholesterol- and BP lowering strategies. Simplifying the selection of individuals who should receive preventive interventions using simple risk criteria instead of strict lipid or BP thresholds, generating evidence globally in multiple ethnic groups, avoiding rigid "targets," and using less frequent monitoring may reduce the complexity and cost of primary prevention and increase its uptake. In HOPE-3 trial, the intermediate risk was stratified based on simple clinical criteria but no standardized risk calculation tool or algorithm was used. Moreover, we Indians do not have a standardized risk calculator for our own population which could stratify future CVD risk and thus determine our eligibility for primary prevention. Asian Indian pedigree constitute over one-fifth of the world population. Asian Indian phenotype is marked by combination of clinical (larger waist-to-hip and waist-to-height ratios signaling excess visceral adiposity), biochemical [insulin resistance, lower adiponectin and higher C-reactive protein (CRP) levels], and metabolic alterations [raised triglycerides, low high-density lipoprotein cholesterol (HDL-C)].[15] Over last 30 years, the rate of CHD-related incidence has increased from 2% to 6% in rural population and from 4 to 12% in urban population.[16] The prevalence of so called Asian Indian phenotype in South Asians has led to their excessive vulnerability to diabetes and premature CHD.[17] Presence of high lipoprotein (Lp) (a), environmental and lifestyle risk factors explain the growing prevalence of heart diseases in India[16,17] Higher predisposition to metabolic syndrome characterized by insulin resistance, hyperinsulinemia, type 2 diabetes, impaired glucose tolerance, central obesity, hypertension and dyslipidemia (high triglyceride and low high density lipoprotein levels) is another important reason for increased CVD incidence in Indian population. In a study in Indian population, out of the total respondents 67.7% had normal BMI 5.82% participants had BMI in the overweight range and only 2.12% were obese with BMI>30 kg/m. Almost similar findings were observed by the measurements of waist circumference. But the percentage of overweight and obese raised to almost four times, i.e. 23.28% and 7.94% respectively when classified as per waist-hip ratio.[18] In Tamil Nadu, Maharashtra, Jharkhand, and Chandigarh, the prevalences of prediabetes (impaired fasting glucose and/or impaired glucose tolerance) were 8.3%, 12.8%, 8.1% and 14.6% respectively.[19] Global Adult Tobacco Survey (GATS) conducted by International Institute of Population Sciences, Mumbai, found overall tobacco use in India in 25.3% in urban setting and 38.4% in rural setting. In another study using Framingham Risk Score, out of 2483 individuals, 65.4% had low risk of CVD event followed by 21.95% having intermediate and 12.65% showing high risk. The low level of HDL-C in 85.03%, hypertension in 63.69%, elevated TC in 60.83% and LDL-C in 60.83% were found to be the main contributors for CVD risk. In high-risk males, the levels of TC (58.45%) and LDL-C (58.1%) were significantly elevated ($p<0.0001$), whereas levels of HDL-C (92.25%) markedly low in this subset of population, whereas in females hypertension (100%) and abnormalities of lipids (TC–83.33%, LDL-C–86.67%) were the contributors.[20]

The rural-urban differences, public-private health care, low awareness across the region, long-term and asymptomatic nature of noncommunicable risk factors and disease delays diagnosis of CVD and serve as a roadblock to seek care and self-management of risk factors. The genetic and environmental factors act as the important etiological clues to diversity in terms of disease presentation, therapeutic needs and responses to treatment. Hence, ethnicity is regarded as a probable independent risk factor that could help in recognizing treatment goals and the choice of therapy in particular population or race.[21,22]

Over 300 existing risk factors for CVDs have been discovered which mostly fall into two broad categories: (1) modifiable and (2) nonmodifiable. Though existing risk factors such as smoking, dyslipidemia, hypertension, diabetes and obesity have been considered while calculating the risk among various ethnic groups, they could not fully explain excess risk in Indians and other ethnic groups, indicating a search for alternative risk factors. About 30-50% of coronary disease patients have been reported asymptomatic with absence of any conventional risk factor. In United States, adults with no history of CVD have been identified to possess intermediate risk and 10-year CVD risk of 10-20%. In the wake of increasing incidences of cardiovascular events in people who were apparently healthy and asymptomatic, both

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the American Heart Association and National Cholesterol Education Program Adult Treatment Panel-III (NCEP-ATP III) issued directives to identify these individuals who may be sufficiently at high risk of coronary event in the future and justified efforts directed at aggressive risk reduction. It was also reported that even the modest elevation in blood pressure, cholesterol and glucose levels would predispose an individual at a CVD risk.[23]

These data prove that a substantial population of our country would fall into the category of patients eligible for primary prevention. But before implementing such universal strategy of giving statins and/or BP lowering agents to normal population with no documented CVD, we need to formulate our own risk stratification algorithm. Large scale trials in our indigenous population are also necessary before the final verdict. Hence such therapeutic strategy can be practiced on an individual basis with patient preferences obviously playing an important role to guide these decisions, but incorporating into guidelines for our country may be premature as of now.

Moreover in HOPE-3 for the cholesterol-lowering arm, the 1% point difference in CV-related death, MI, or stroke that favored rosuvastatin (vs. placebo) means that about 100 people were treated for 5 years to benefit 1 person. In the US, the retail cost of rosuvastatin (Crestor)—for which a generic form is not available—is about US$ 3,600 annually. This huge financial burden will be another hindrance to large scale implication of such strategy in our country's health care policy.

Concept of polypill can be often detrimental particularly in our country's scenario. Dose titration of individual components is not possible in a polypill. Combination of diuretics in a polypill may lead to dyselectrolytemia and its consequences.

Thus, HOPE-3 is a step forward in primary prevention of CVD globally. But how far it can be implemented in a developing country like ours with a huge population and financial constraints is a matter of concern. We need our own risk algorithms and long term data considering Asian Indian phenotype. Since South Asians display considerable heterogeneity in risk factors as compared to developed countries, there is a need to identify newer risk factors which would not only help in primary prevention but also prevent their recurrence.

CONCLUSION

So to summarize the implications derived from HOPE-3 trial, we can clearly say that low dose statins are beneficial in intermediate risk population and in addition to reducing LDL-C level further, it also reduces CV events and target end points. Combination of low dose antihypertensives including diuretics and ARB is ineffective among normotensives in reducing CV events. Concept of polypill is not advocable for universal and widespread use in general population.

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