Canadian Journal of Cardiology 32 (2016) 311–318

Clinical Research

Novel Approaches in Primary Cardiovascular Disease Prevention: The HOPE-3 Trial Rationale, Design, and Participants' Baseline Characteristics

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See editorial by Waters and Chau, pages 275-277 of this issue.

ABSTRACT

Background: Cholesterol and blood pressure (BP) can be effectively and safely lowered with statin drugs and BP-lowering drugs, reducing major cardiovascular (CV) events by 20%-30% within 5 years in high-risk individuals. However, there are limited data in lower-risk pop-

RÉSUMÉ

Introduction : Il est possible de faire baisser efficacement et en toute sécurité le cholestérol et la pression artérielle (PA) avec les statines et les antihypertenseurs tout en réduisant de 20 à 30 % les manifestations cardiovasculaires majeures en l'espace de cinq ans chez les

Cardiovascular disease (CVD) is a major cause of mortality, morbidity, and health care expenditures worldwide and affects > 50% of men and 40% of women over their lifetimes.[1,2] Current primary prevention strategies are suboptimal. The **H**eart **O**utcomes **P**revention **E**valuation-3 (HOPE-3) trial is testing novel approaches to primary prevention. This article

Received for publication June 24, 2015. Accepted July 1, 2015.

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See page 316 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2015.07.001

ulations. The Heart Outcomes Prevention Evaluation-3 (HOPE-3) trial is evaluating whether cholesterol lowering with a statin drug, BP lowering with low doses of 2 antihypertensive agents, and their combination safely reduce major CV events in individuals at intermediate risk who have had no previous vascular events and have average cholesterol and BP levels.

Methods: A total of 12,705 women 65 years or older and men 55 years or older with at least 1 CV risk factor, no known CV disease, and without any clear indication or contraindication to the study drugs were randomized to rosuvastatin 10 mg/d or placebo and to candesartan/hydrochlorothiazide 16/12.5 mg/d or placebo (2 × 2 factorial design) and will be followed for a mean of 5.8 years. The coprimary study outcomes are the composite of CV death, nonfatal myocardial infarction (MI), and nonfatal stroke and the composite of CV death, nonfatal MI, nonfatal stroke, resuscitated cardiac arrest, heart failure, and arterial revascularization.

Results: Participants were recruited from 21 countries in North America, South America, Europe, Asia, and Australia. Mean age at randomization was 66 years and 46% were women.

Conclusions: The HOPE-3 trial will provide new information on cholesterol and BP lowering in intermediate-risk populations with average cholesterol and BP levels and is expected to inform approaches to primary prevention worldwide (HOPE-3 ClinicalTrials.gov NCT00468923).

personnes à risque élevé. Les données obtenues dans les populations exposées à un risque plus faible sont néanmoins limitées. L'essai HOPE-3 (*Heart Outcomes Prevention Evaluation-3*) tâche de déterminer si l'abaissement du cholestérol à l'aide d'une statine, l'abaissement de la pression artérielle à l'aide de deux agents antihypertenseurs administrés à raison d'une faible dose et leur association permettent de réduire en toute sécurité les manifestations cardiovasculaires majeures chez les personnes exposées à un risque intermédiaire qui n'ont pas d'antécédents d'événements vasculaires et dont le taux de cholestérol et la PA se situent dans la moyenne.

Méthodes : Au total, 12 705 femmes et hommes, les unes âgées de 65 ans et plus et les autres de 55 ans et plus, qui présentent au moins un facteur de risque cardiovasculaire et qui n'ont pas de maladie cardiovasculaire connue ni aucune indication ou contre-indication claires aux médicaments à l'étude, ont été répartis aléatoirement pour recevoir de la rosuvastatine à raison de 10 mg par jour ou un placebo et l'association candésartan/hydrochlorothiazide à raison de 16/12,5 mg par jour ou un placebo (plan factoriel 2 × 2). Ces patients seront suivis pendant une moyenne de 5,8 ans. Les principaux paramètres d'évaluation de l'étude combinent le décès d'origine cardiovasculaire, l'infarctus du myocarde non mortel et l'AVC non mortel d'une part, et le décès d'origine cardiovasculaire, l'infarctus du myocarde non mortel, l'AVC non mortel, la réanimation après arrêt cardiaque, l'insuffisance cardiaque et la revascularisation artérielle d'autre part.

Résultats : Les participants ont été recrutés dans 21 pays situés en Amérique du Nord, en Amérique du Sud, en Europe, en Asie et en Australie. L'âge moyen au moment de la répartition aléatoire était de 66 ans, et 46 % des sujets étaient des femmes.

Conclusions : L'essai HOPE-3 fournira de nouveaux renseignements sur l'abaissement du taux de cholestérol et de la PA dans des populations exposées à un risque intermédiaire dont le taux de cholestérol et la PA se situent dans la moyenne. Il devrait également fournir des données à l'appui des stratégies de prévention primaire mises en place partout dans le monde (HOPE-3 ClinicalTrials.gov NCT00468923).

summarizes the trial rationale and design and the baseline characteristics of the study population.

A substantial proportion of CVD events occur in average-risk populations with no previous vascular disease and often without major elevations in cardiovascular (CV) risk factors. Prevention in such populations may have a big impact, a concept known as the "prevention paradox."[3] Moreover, "mildly" abnormal CV risk factor levels are common. In the Framingham study, fewer than 5% of participants had optimal CV risk factor levels.[2] In the 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,[4] and in the INTERHEART study, 99% of control participants had at least 1 abnormal CV risk factor.[5] 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 often, extrapolate beyond data available from randomized trials, and frequently involve complex algorithms for selection of 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.[6-9] 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.

Lifestyle interventions are considered to be the preferred approach in primary prevention because of perceived low cost, apparent simplicity, and safety. However, most lifestyle intervention trials have failed to show reductions in CV events, largely because substantial lifestyle changes are difficult to achieve and sustain long-term.[10-12] Although specific risk factors were lowered in studies involving intensive and costly lifestyle interventions in selected groups (such as preventing diabetes in individuals with impaired glucose tolerance through exercise and diet or lowering BP by strict dietary changes in short-term trials),[13,14] these approaches are neither widely applicable to populations or affordable.[15] A Mediterranean diet reduced CV events,[16] but it is costly and cannot be easily implemented in many parts of the world. A complementary approach may be the use of inexpensive drugs that