The HOPE-3 (Heart Outcomes Prevention Evaluation-3) trial was an international primary cardiovascular disease prevention trial with a randomized $2 \times 2$ factorial design that tested the effect of cholesterol lowering with rosuvastatin 10 mg/day and blood pressure lowering with candesartan/hydrochlorothiazide 16/12.5 mg/day individually or combined (1–3). Men $\geq 55$ years of age and women $\geq 65$ years of age without known atherosclerotic cardiovascular disease (ASCVD) were eligible for the trial if they had at least 1 (or in women $\geq 60$ to 65 years of age at least 2) of the following categorical risk factors: elevated waist-to-hip ratio, low high-density lipoprotein cholesterol, smoking, family history of premature coronary heart disease (CHD), dysglycemia, or mild renal dysfunction. HOPE-3 was a pragmatic trial using simple and widely applicable selection criteria, moderate-intensity drug therapy, no treatment targets, and minimal monitoring of treatment. However, despite the intention of documenting the efficacy and safety of treatment in a global population, the results may not automatically be uniformly applicable to everyone meeting the broad inclusion criteria used in the HOPE-3 trial, as discussed here focusing on the statin-only arm of HOPE-3 (1).

### Relative Risk Reduction

The relative risk reduction with statin therapy was substantial (24% for first coprimary outcome) and consistent across a broad variety of subgroups, including those defined by sex, age, race, and ethnicity (1). However, the net benefit of statin therapy is critically dependent on an individual’s absolute risk for ASCVD: the higher the absolute risk, the larger the absolute risk reduction with statin therapy and the fewer people who need to be treated to prevent 1 ASCVD event.

### Absolute Risk Reduction

The absolute risk in the placebo group over a median follow-up of 5.6 years was 4.8% for the first coprimary outcome, giving an absolute risk reduction with statin therapy of only 1.1% (1) and a 5-year number needed to treat (NNT) to prevent 1 event $>100$. This is 1 of the highest NNT to prevent 1 major cardiovascular event in a randomized statin trial (4,5). Although rosuvastatin 10 mg/day was safe in those who passed the 4-week run-in phase, it makes sense to identify those at lowest and highest absolute risk in the HOPE-3 trial to optimize the trade-off between efficacy and safety (benefits vs. risks) of treatment (6). The absolute risk reduction and net benefit of statin therapy depend critically on the background population risk (7,8), defined here as the inherent ASCVD risk of a population that is not explained by the traditional risk factors.

### Background Population Risk

The nonuniform background risk of the diverse HOPE-3 population complicates the translation of the overall trial results to a specific target population (9). The importance of background population risk in absolute risk assessment is recognized by current guidelines (4,10,11), including those issued by the World Health Organization (12), in which it is stressed that a risk score used for primary ASCVD prevention...
needs to be well calibrated to the target population to ensure optimal treatment. For example, the International Atherosclerosis Society recently published a list of recalibration coefficients to guide adjustment of the Framingham CHD risk score for international use, ranging from 0.36 for China (to avoid over-treatment) to 1.81 for urban India (to avoid under-treatment) (13). Consequently, for persons with similar risk factor profile, the NNT to prevent 1 ASCVD event is much higher in China than urban India.

The HOPE-3 participants were recruited from countries in which the background population risk and burden of ASCVD are known to differ markedly (Figure 1). Further, despite the title of the HOPE-3 paper (1), HOPE-3 did not exclusively enroll “intermediate-risk” persons, although the average risk of the overall study population might have been “intermediate.” Indicators of high risk, such as hypertension, smoking, and family history of premature CHD, were common, and 70% of study participants had 2 or more risk factors. If the average person enrolled in HOPE-3 had an “intermediate” risk, then the absolute risk of a person with just 1 HOPE-defined risk factor from a population with a low background risk would be substantially below average, where the net benefit of statin therapy might be questionable. In contrast, the net benefit of statin therapy would be higher and initiation of statin therapy more important for a person with multiple HOPE-defined risk factors from a population with a high background risk.

**HOPE IN EUROPE**

The diversity among the 8 European HOPE-3 countries regarding background population risk, burden of cardiovascular disease, and economic wealth is as extreme as that seen in the whole HOPE-3 study population (Figure 1). Among all countries participating in the HOPE-3 trial, ≥2 and possibly 4 European countries are known to have the highest CHD mortality (Ukraine, Russia, Hungary, and Slovakia), and Ukraine is among the poorest HOPE-3 countries. In contrast, the Netherlands, Sweden, and United Kingdom belong to the HOPE-3 countries with the lowest CHD mortality and are among the richest countries. The conceptual relationship between NNT to prevent 1 ASCVD event and background population risk in the European HOPE-3 countries is shown in Figure 2.
For a strong statin-modifiable outcome such as CHD, the age-adjusted mortality is more than 10× higher in Ukraine (337 per 100,000) than the Netherlands (25 per 100,000) (Figure 1), which is at least partly explained by the higher background population risk in Ukraine. Clinically, the net benefit of statin therapy in preventing a first event in Ukraine (primary prevention) may rival that of preventing a recurrent event in the Netherlands (secondary prevention). For persons with similar risk factor profile, the NNT to prevent 1 ASCVD event is much lower in Ukraine and most other Eastern European countries than in the Netherlands and most other Western European countries (Figure 2). Although both the relatively poor Ukraine and the much wealthier Netherlands participated in the HOPE-3 trial, the clinical implications of the overall findings in HOPE-3 will necessarily differ not only between Ukraine and the Netherlands, but also across Europe and worldwide. The challenge is to extrapolate the findings obtained in the worldwide HOPE-3 population to a more meaningful, personalized treatment strategy in the target population of interest.

European guidelines disagree on the preferred ASCVD risk model and the level of risk at which primary prevention with statins should be initiated. While the HOPE-3 trial was ongoing, the 2014 UK-NICE (National Institute for Health and Care Excellence) guidelines (10) lowered the 10-year risk threshold for primary prevention with statins from 20% to 10% as estimated by the ethnic-specific QRISK prediction model, thereby substantially expanding primary prevention with statins (similar to what happened in the United States with the 2013 American College of Cardiology/American Heart Association guideline [4]). In populations in which the 2014 UK-NICE (or 2013 American College of Cardiology/ American Heart Association) guidelines are followed, the effect of HOPE-3 may be limited. In contrast, the 2016 European guidelines (11) indirectly restricted the use of statins in countries with declining ASCVD mortality by preserving the 5% high-risk threshold estimated by SCORE (Systematic COronary Risk Evaluation), which depends solely on the risk of dying from ASCVD. Hence, in countries where the 2016 European guidelines are followed, HOPE-3 may provide hope—a trial-based escape possibility—for health care providers who disagree with the guideline-recommended conservative approach to prophylactic statin therapy. Further, considering that SCORE is applicable only in people age 40 to 65 years, the HOPE-3 trial provides evidence for statin therapy beyond age 65 years.

Sensible local and national implementation of the results of the statin arm of HOPE-3 requires attention to country-specific background risk, net benefit of treatment, culture and lifestyle, and available resources, including the ability and willingness to pay for prophylactic medical therapy. Given that inexpensive generic statins are now widely available, the pragmatic approach tested in HOPE-3 is practicable and affordable for many less wealthy countries worldwide, representing a major step forward in the global prevention of ASCVD. The HOPE-3 results may help guide treatment decisions in populations where appropriately calibrated risk scores are unavailable, including in immigrants and ethnic minorities. However, the traditional risk-based approach recommended by many medical societies, in which treatment is targeted to those who are at the highest absolute risk, may be more efficient if feasible (17,18).

**FIGURE 2 Conceptual Relationship Between Benefit of Treatment and Background Population Risk**

Because the relative risk reduction with a fixed dose of a statin seems to be consistent across Europe, the absolute risk reduction (ARR) and the number needed to treat (NNT) to prevent 1 atherosclerotic cardiovascular disease (ASCVD) event (1/ARR) over a certain period of time depends on the absolute risk for ASCVD when treatment is initiated. For average "intermediate-risk" Europeans in the HOPE-3 trial, the NNT is much higher and net benefit of treatment much smaller in the Netherlands than Ukraine because of the higher background population risk in Ukraine (7). The order of background risk is taken from Figure 1.
REFERENCES