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EDITORIAL

The legacy of HOPE-3

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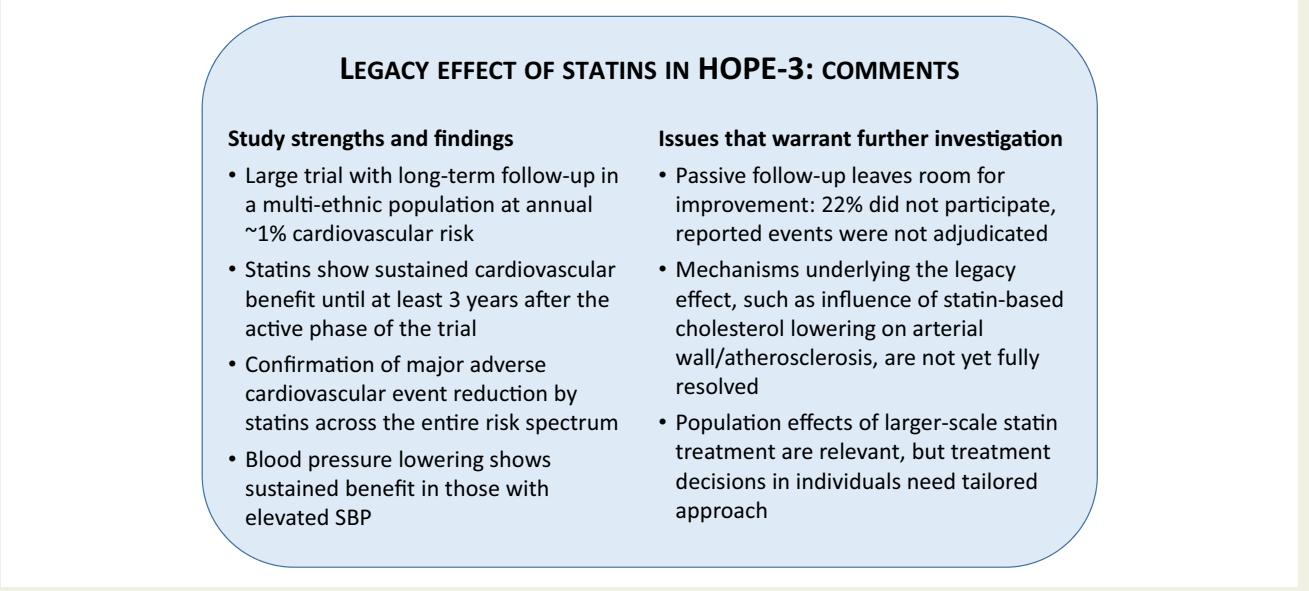
This editorial refers to 'Lowering cholesterol, blood pressure, or both to prevent cardiovascular events: results of 8.7 years of follow-up of Heart Outcomes Evaluation Prevention (HOPE)-3 study participants' by J. Bosch *et al.*, doi:10.1093/eurheartj/ehab225.



Grahical abstract Overview of strengths and findings of HOPE-3, and issues that warrant further investigation.

In the current issue of the *European Heart Journal*, the HOPE-3 investigators present the long-term results of their randomized clinical trial on the lowering of cholesterol, blood pressure, or both to prevent cardiovascular (CV) events in persons without clinically established CV disease (CVD).[1] The investigators aimed at a population with an ~1% annual risk of major adverse cardiac events (MACE), including CV death, myocardial infarction, and stroke. They enrolled men aged ≥55 years and women ≥65 years who had one CV risk factor, as well as women aged ≥60 to 65 years who had two CV risk factors. A total of 12 705 participants were randomized to receive rosuvastatin 10 mg/day or placebo, and a combination of candesartan 16 mg/day plus hydrochlorothiazide 12.5 mg/day or placebo, in a 2 × 2 factorial design. After a median active treatment period of 5.6 years, participants randomized to rosuvastatin showed a 0.90 mmol/L reduction in LDL cholesterol (baseline 3.31 mmol/L), which was accompanied by a 24% reduction in MACE compared

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with placebo (3.7% vs. 4.8%).[2] Participants randomized to cardesartan/hydrochlorothiazide showed a 6.0/3.0 mmHg blood pressure reduction (baseline 138.1/81.9 mmHg). This effect, however, did not translate into a significant reduction in MACE, except in those with a baseline systolic blood pressure in the upper tertile (>143 mmHg).[3]

The current report presents findings after a median of 3.1 additional years of observation in 9326 (78%) HOPE-3 survivors, during which participants who were previously receiving the study drugs no longer did so. During this so-called 'passive follow-up', those originally randomized to rosuvastatin had a further 20% reduction in MACE compared with placebo (3.1% vs. 3.9%), which the investigators interpret as a 'legacy effect'.[1] Over the entire 8.7-year follow-up period, a 21% reduction in MACE was reported in favour of rosuvastatin. Furthermore, the investigators found a non-significant 17% lower incidence of MACE in the participants originally randomized to candesartan/hydrochlorothiazide and who had a baseline systolic blood pressure in the upper tertile compared with placebo (3.9% vs. 4.7%). The MACE reduction over the full follow-up period was estimated at 24% in this blood pressure stratum.

The HOPE-3 investigators are to be lauded for conducting an extended follow-up. The effort to achieve the extra data, which must not be underestimated, resulted in an additional valuable ~29 000 person-years of observation (9326 subjects × 3.1 years of follow-up, swapping the mean for the median). The quality of the newly added information is probably somewhat lower than in the original study, as reported events were not adjudicated. Furthermore, follow-up data were not available in all alive patients, although we agree with the investigators that selection bias is unlikely, because lack of participation was mostly due to the fact that centres withdrew entirely (rather than individual participants withdrawing). Nevertheless, although indeed there seems to be a persisting treatment benefit, the absence of 'passive follow-up' data on 22% of eligible participants complicates the interpretation of incidence estimates of adverse events during the entire follow-up period. The interpretation is further complicated by the fact that MACE occurring during passive follow-up might have been repeat events in participants who had had a non-fatal event during active treatment. Finally, we must not overlook the fact that the original randomization is no longer maintained in the 5.6-year survivors. The current findings must be interpreted with some caution against the background of these limitations. That being said, we concur with the conclusion by the investigators that the initial beneficial effects of rosuvastatin treatment were at least maintained for another ~3 years.

Evidence for a legacy effect

In their meta-analysis, the Cholesterol Treatment Trialists report a 22% proportional reduction in major vascular events per 1 mmol/L reduction in LDL cholesterol.[4] The original HOPE-3 results (0.90 mmol/L reduction; 24% MACE reduction during active treatment with rosuvastatin) are well in agreement with this estimate. Now, based on their current findings, the HOPE-3 investigators conclude that benefits of rosuvastatin were sustained, and were perhaps even enhanced, after study termination,[1] which they state is in line with known effects of statin-based cholesterol lowering on the structure of the arterial wall and plaque morphology and composition.[5]

Indeed already back in 1994, in a randomized trial, the MAAS investigators demonstrated that simvastatin 20 mg/day over 4 years slowed angiographic progression of coronary atherosclerosis compared with placebo.[6] A meta-analysis of nine observational studies utilizing intravascular ultrasound provided evidence for reduced plaque volume in patients with established CVD during 6–24 months of high-intensity statin use.[7] It should be noted that effects were less pronounced after low- to moderate-intensity treatment, including the 10 mg/day rosuvastatin regime. Furthermore, the necrotic core remained unchanged, whereas, remarkably, the reduction in plaque volume was not associated with LDL cholesterol reductions. These observations are in agreement with another meta-analysis of 17 intravascular imaging studies,[8] as well as with IBIS-3, IBIS-4, and SATURN.[9–11] The IBIS-4 investigators refer to the regression to the mean phenomenon as a partial explanation of temporal changes in coronary plaque characteristics in observational studies.[9] In spite of these side notes, altogether, these studies do point towards a beneficial role for statins in the process of atherosclerosis, and further studies in this field are warranted.

The question of whether or not there is a beneficial legacy effect of statins is intriguing and might stimulate future research. For now, we agree with the HOPE-3 investigators that their data should not be interpreted as an argument to discontinue statins after several years of treatment.[1] Lifelong statin treatment is indicated in patients with clinically established CVD as well as in persons with seriously elevated CVD risk. Still, the legacy issue is not entirely an academic question. Especially in the elderly, polypharmacy is of concern. The percentage of elderly above the age of 75 years that use a combination of at least five different drugs is reported to be as high as 37%.[12] Evidence exists that such polypharmacy is associated with non-adherence, adverse drug reactions, and drug–drug interactions.[12] Statins are among the most commonly used drugs in the elderly.[12] Hence, in the quest for a balance between 'adding years to life' and 'adding life to years' (https://www.ageing-better.org.uk/news/adding-life-years), any legacy effect of these drugs might give sufficient comfort to terminate their use in the very elderly.

Expanding indications for statins?

From the presented results, we estimate that in HOPE-3, the average incidence of (first) MACE during the active treatment period was ~0.86 per 100 person-years in participants randomized to placebo, whereas the average incidence of CV death was ~0.48 per 100 person-years (304 MACE and 171 CV deaths in 6344 subjects × 5.6 years of follow-up, swapping the mean for the median). These are risks that were actually observed. From a European Society of Cardiology (ESC) perspective, persons with an estimated 10-year CV death risk <5% [based on the Systematic Coronary Risk Estimation (SCORE) model] can be considered as low to moderate risk.[13] The ESC does not recommend drug treatment for this population as a whole.[13] In that respect, although the HOPE-3 investigators describe it as surprising, it may not have been fully unexpected that 1 year after the end of the active phase only 37% of participants were prescribed a statin.

We do concur that advice on a healthy lifestyle—which was offered to the HOPE-3 participants at each study visit—will not be followed by each and every low- to moderate-risk person. Also, even if such advice is taken seriously, it cannot eliminate CVD risk entirely. Hence, CVD medication, including statins, should be considered. However, in HOPE-3, for an individual, the probability of being MACE free during at least 5.6 years without using rosuvastatin was as high as 95.2% (100 – 4.8% subjects in the placebo arm who experienced MACE). Although this figure was improved to 96.3% by daily rosuvastatin use (100 – 3.7% subjects in the rosuvastatin 10 mg/day arm who experienced MACE), the individuals concerned might not be impressed by this difference. Furthermore, on a study level, ∼91 participants needed to be treated for 5.6 years in order to prevent one MACE event, which is a substantial number. The average incidence of (first) MACE was increased to ∼1.26 per 100 person-years in the passive follow-up period (181 MACE in 4630 subjects × 3.1 years of follow-up, swapping the mean for the median). Still, over the entire 8.7-year period, the (first) MACE incidence as reported by the investigators remained below 1 per 100 person-years, and, consequently, so did the incidence of CV death. Indeed, 'additional strategies to overcome healthcare barriers' in order to improve the adoption of statins, as the investigators suggested,[1] might reduce the burden of CVD on a population level. However, in view of the currently presented data and aforementioned considerations, we can imagine that a tailored approach is likely to be implemented for individuals that belong to the population from which HOPE-3 participants were sampled.

We conclude that the initial beneficial effect of rosuvastatin treatment that was observed in the HOPE-3 trial persisted for at least 3 years after termination of the study. For now, the effective use of such agents by individuals without clinically established disease, and at low CV risk in spite of the presence of a risk factor, seems to remain a matter of shared decision-making by these individuals and their physicians, which includes a well-informed weighing of pros and cons (*Graphical abstract*).[14,15]

Conflict of interest: none declared.

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