Hypertension

BLOOD PRESSURE LOWERING TRIALS

# Applicability of Blood Pressure–Lowering Drug Trials to Real-World Patients With Cardiovascular Disease

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**ABSTRACT:** This study aimed to assess applicability of blood pressure–lowering drug trials to real-world secondary preventive care. We applied the eligibility criteria of the landmark blood pressure–lowering drug trials (EUROPA, PEACE, HOPE-peripheral arterial disease [PAD], PRoFESS, and PROGRESS) to patients with coronary artery disease (CAD; n=5155), peripheral arterial disease (PAD; n=1487), and cerebrovascular disease (n=2515) participating in the UCC-SMART cohort. Baseline differences according to trial eligibility were assessed. Differences in risk of all-cause mortality and a composite of cardiovascular death, myocardial infarction, and stroke (major adverse cardiovascular event) were calculated using Cox proportional hazard models, adjusted for age, sex, and cardiovascular risk factors. Seventy-five percent of UCC-SMART patients with CAD would have been eligible for EUROPA, 84% for PEACE, 59% of patients with PAD for HOPE-PAD, 17% of patients with cerebrovascular disease for PRoFESS, and 100% for PROGRESS. Eligible patients were older (average difference ranging 1.4–14.6 years across trials). Eligible patients with CAD were at lower risk of major adverse cardiovascular event after adjustment for age, sex, and cardiovascular risk factors in PEACE (hazard ratio, 0.65 [95% CI, 0.53–0.79]) and of mortality in both EUROPA (hazard ratio, 0.72 [95% CI, 0.62–0.82]) and PEACE (0.63 [95% CI, 0.51–0.78]). Adjusted mortality and major adverse cardiovascular event risks were not different between eligible and ineligible patients with PAD and cerebrovascular disease in HOPE-PAD, PRoFESS, and PROGRESS. The majority of real-world patients with CAD, PAD, or cerebrovascular disease would be eligible for landmark trials on blood pressure–lowering drugs. Patients with CAD ineligible for the EUROPA and PEACE trials are at higher adjusted mortality and major adverse cardiovascular event risks, which may limit applicability of their results to ineligible patients.
**(*Hypertension*. 2021;77:357–366. DOI: 10.1161/HYPERTENSIONAHA.120.15965.)** • **Data Supplement**

**Key Words:** blood pressure ■ cardiovascular disease ■ myocardial infarction ■ peripheral arterial disease ■ stroke



Cardiovascular disease is the leading cause of morbidity and mortality worldwide.[1,2] Advances in management of acute cardiovascular events, such as acute myocardial infarction and stroke, have contributed to a nearly 30% decline in cardiovascular mortality rates over the last 3 decades.[2,3] Together with the increasing age of the general population, this has resulted in an increased number of patients with stable cardiovascular disease. Secondary preventive interventions are crucial for these patients at high risk of recurrent events.[4]

Blood pressure lowering is one of the mainstays of secondary preventive care and has been proven effective in reducing the risk of fatal and nonfatal cardiovascular outcomes and in reducing all-cause mortality.[5–11] International guidelines for secondary prevention in stable coronary artery disease (CAD), peripheral artery disease (PAD), and cerebrovascular disease (CeVD) recommend blood pressure management[12–17] with some expressing a preference for the use of ACE (angiotensin-converting enzyme) inhibitors or angiotensin II receptor blockers based on the available trials.[12–15]

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For Sources of Funding and Disclosures, see page 365.
The Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/HYPERTENSIONAHA.120.15965.

*Hypertension* is available at www.ahajournals.org/journal/hyp

## Novelty and Significance

### What Is New?

- Broad application of trial eligibility criteria to a real-world cohort with long follow-up allowing for assessment of differences in prognosis of would be trial-eligible and ineligible patients.

### What Is Relevant?

- Landmark trials inform clinical blood pressure–lowering treatment decisions for patients who may not have been eligible for the trial.

### Summary

Most cardiovascular patients would have been eligible for major blood pressure–lowering drug trials, suggesting broad applicability of the results. Would be ineligible patients with coronary artery disease are at higher adjusted risk of mortality and major adverse cardiovascular event, potentially limiting applicability of trial results to these patients.

## Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **ACE** | angiotensin-converting enzyme |
| **CAD** | coronary artery disease |
| **CeVD** | cerebrovascular disease |
| **CVOT** | cardiovascular outcome trial |
| **HR** | hazard ratio |
| **MACE** | major adverse cardiovascular event |
| **PAD** | peripheral arterial disease |
| **RCT** | randomized controlled trial |
| **SMART** | Second Manifestations of Arterial Disease |

International guidelines are based on (meta-analyses of) randomized controlled trials (RCTs) and by applying their results to the individual patient, it is implicitly assumed that treatment effects will be similar in a real-world setting. However, there are concerns that clinical trials employ overly strict eligibility criteria to ensure a clearly demarcated study population and internal validity. In the field of cardiovascular medicine, external applicability has previously been assessed for RCTs on antithrombotic therapy and coronary reperfusion interventions.[18–20] These studies found that approximately half of the patients seen in clinical practice would not have been eligible for participation in the studied RCTs. Stringent patient selection may limit applicability of trial results to a real-world patient if the trial and patient populations differ to an extent that variances in the investigated effect size might be expected.[21–23] Real-world patient eligibility for landmark RCTs on blood pressure–lowering medication has not been previously studied.

The objective of this article was to assess the applicability of guideline-informing trials of blood pressure–lowering medication to a real-world patient cohort consisting of patients with a history of CAD, PAD, or CeVD.

# METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Study Population

Data were obtained from patients enrolled in the SMART (Second Manifestations of Arterial Disease) study, an ongoing single-center prospective cohort study. From September 1996 onward, patients referred to the University Medical Center Utrecht with clinically manifest cardiovascular disease or cardiovascular risk factors were asked to participate. All subjects gave informed consent and the study was approved by the local Medical Ethics Committee. A detailed description of the study design has been published previously.[24]

For the present study, data were used from 8434 patients included between September 1996 and February 2018, with established coronary, peripheral artery, or cerebrovascular disease at inclusion in the cohort. Patients were divided into 3 nonmutually exclusive groups as patients could have >1 clinical manifestation of vascular disease. The first, SMART-CAD, comprised 5165 patients with stable CAD (angina pectoris, myocardial infarction, and/or coronary revascularization intervention); the second, SMART-PAD, included all patients with symptomatic PAD, vascular interventions, or limb amputations for PAD (n=1487) and the third, SMART-CeVD, consisted of 2518 patients with a history of CeVD (transient ischemic attack, ischemic or hemorrhagic stroke, amaurosis fugax, or retinal infarction).

## Baseline Data Collection and Outcome Assessment

After inclusion in the SMART cohort, all patients were screened for vascular health according to a standardized protocol consisting of a health questionnaire, physical examination, and laboratory testing. Cardiovascular history at baseline was determined based on referral diagnosis or self-reported data from the questionnaire. Participants were followed up with twice yearly questionnaires. When a potential event was reported, additional information such as hospital discharge letters and radiology examinations were obtained. Each event was assessed and categorized by 3 members of the SMART end point committee according to previously published definitions.[24]

The primary outcomes of this study were all-cause mortality and a composite of major adverse cardiovascular events (MACEs): cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. The individual components of the MACE composite were assessed as secondary outcomes.

## Trial Selection and Eligibility

RCTs underpinning the recommendations on the use of blood pressure–lowering medication for secondary prevention in the latest European and American guidelines on stable CAD,[12,13] PAD,[14,15] and CeVD[16,17] were selected. If the recommendations were based on multiple studies, the 2 largest randomized controlled cardiovascular outcome trials (CVOTs) in a strictly dedicated population (CAD, PAD, or CeVD) were included in the analysis. If the recommendation was based on meta-analyses, the largest dedicated CVOTs included in the meta-analyses were selected. This resulted in the selection of the EUROPA (n=12 218)[25] and PEACE trials (n=8290)[26] for the CAD population, a single dedicated PAD publication by Ostergren et al,[27] based on a subgroup analysis of 3843 PAD patients in the HOPE trial[28] and the PRoFESS (n=20 332)[29] and PROGRESS trials (n=9297)[30] for the CeVD population.

CVOT eligibility criteria were collected from the reporting articles and additional publications (eg, study design publications) and applied to the 3 SMART subcohorts. Criteria on the use of trial medication were disregarded as the observational design of the SMART cohort prohibited assessment of true indications for these medications and potential wash-out periods. Table S1 in the Data Supplement provides an overview of the included trials' eligibility criteria and their application to the SMART cohort.

## Statistical Analysis

Baseline characteristics were described for trial-eligible and -ineligible patients. Continuous data are presented as mean±SD or as median with interquartile range for normally and unevenly distributed data, respectively. Differences between patients at baseline were attested with a *t*-test for normally distributed variables and the Kruskal-Wallis test in case of a skewed distribution. Baseline differences in categorical variables were evaluated using Pearson $\chi^2$-test.

The relationship between trial eligibility status and (cardiovascular) events was assessed by fitting Kaplan-Meier curves and testing for differences using a log-rank test. Multiple Cox proportional hazard models were used to quantify the relationship. The proportional hazard assumption was tested by visual inspection of Schoenfeld residuals. In the first Cox model, unadjusted hazard ratios (HRs) and 95% CIs were calculated for all outcomes. In the second model, adjustments were made for age and sex. In the third model, additional adjustment for cardiovascular risk factors at baseline (systolic blood pressure, body mass index, low-density lipoprotein cholesterol (mmol/l), current smoking, and glomerular filtration rate) were added.

To improve statistical accuracy, the presumed randomly missing values for baseline variables were completed by single imputation using predictive mean matching (aReg-Impute function). A *P* value of <0.05 was considered statistically significant. All analyses were performed using R statistical software, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

## Sensitivity Analyses

To assess the impact of use of trial medication at baseline, subgroup analyses were performed in patients not using ACE inhibitors or angiotensin II receptor blocker. All previously described analyses were performed for these subgroups. To account for potential bias introduced by competing risks, a Fine-Gray model was used to calculate subdistribution hazard ratios for MACE. The model was adjusted for age, sex, and cardiovascular risk factors, in accordance with the adjustments in the primary analysis.

# RESULTS

## Trial Eligibility

Patients' eligibility for the included CVOTs is presented in Figure 1. The majority of patients with SMART-CAD would have been eligible for EUROPA (75%) or PEACE (84%). In the SMART-PAD cohort, 59% met the eligibility criteria for the HOPE-PAD trial. The main reason for exclusion of patients with PAD was age younger than 55 years. In the SMART-CeVD subcohort, all patients would have been eligible for the PROGRESS trial, while only 17% met the eligibility criteria for the PRoFESS trial. The majority of SMART-CeVD patients was deemed ineligible for PRoFESS on account of the timing of their cerebrovascular event (ie, ischemic stroke did not occur within 120 days before inclusion in SMART). If this criterion was not applied to the cohort, 60.4% of SMART-CeVD would have met de eligibility criteria.

## Baseline Characteristics

Table 1 shows the differences in baseline characteristics between eligible and ineligible SMART patients. Eligible patients' mean age was significantly higher compared with ineligible patients (range, +1.4 to +14.6 years). For the EUROPA trial, eligible patients had fewer cardiovascular comorbidities than ineligible patients. Conversely, patients eligible for the HOPE-PAD trial had more comorbidities and a higher predicted 10-year risk of MACE. Other baseline differences reflected trial eligibility criteria. Table S2 provides an overview of the baseline characteristics of eligible and ineligible patients.

## Difference Between Trial-Eligible and -Ineligible Patients in Risk of MACE and Mortality

Median follow-up in the SMART cohort was 8.6 years (interquartile range, 4.7–12.8). During follow-up, MACE occurred 994 times in the CAD population, 402 times in the PAD population, and 529 times in the CeVD population. All-cause mortality occurred 1058 times in the CAD population, 583 times in the PAD population, and 653 times in the CeVD population. Event rates for MACE ranged from 2.1 to 3.8 events per 100 person-years and event rates for all-cause mortality ranged from 1.5 to 5.4 events per 100 person-years (Figures 2 and 3).

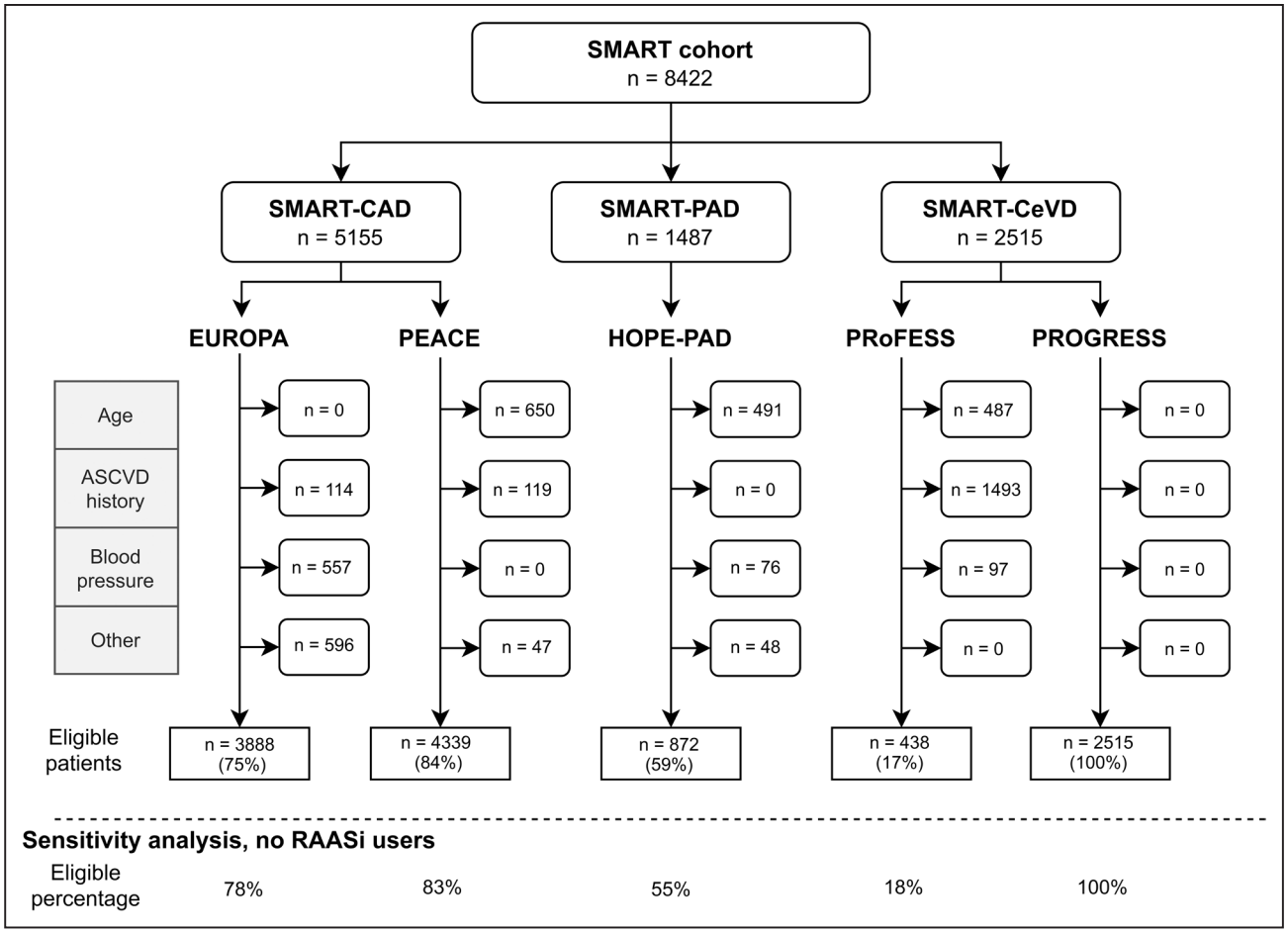


**Figure 1. Application of trial selection criteria to the SMART (Second Manifestations of Arterial Disease)-cohort.**
*Other reasons for exclusion were the following: EUROPA: women of childbearing potential, history of alcohol abuse, serum creatinine >150 µmol/L; PEACE: women of childbearing potential, serum creatinine >177 µmol/L, and HOPE-peripheral artery disease (PAD): overt nephropathy. ASCVD indicates atherosclerotic cardiovascular disease; CAD, coronary artery disease; CeVD, cerebrovascular disease; EUROPA, EUropean trial on Reduction Of cardiac events in patients with stable coronary Artery disease[25]; HOPE, Heart Outcomes Prevention Evaluation[27,28]; PEACE, Prevention of Events with Angiotensin Converting Enzyme[26]; PRoFESS, Prevention Regimen for Effectively Avoiding Second Strokes[29]; PROGRESS, Perindopril protection against recurrent stroke study[30]; and RAASi, renin-angiotensin-aldosterone system inhibitor.

Figures 2 and 3 show Kaplan-Meier curves for MACE and all-cause mortality stratified by trial eligibility, and Table 2 provides the corresponding hazard ratios. With the exception of the EUROPA trial, would-be eligible patients had higher incidence rates of MACE and all-cause mortality compared with ineligible patients. In the unadjusted analysis, EUROPA eligible patients had a lower risk of all-cause mortality (HR, 0.73 [95% CI, 0.64–0.83]). In the PEACE, HOPE, and PRoFESS trials, risks of MACE and all-cause mortality were higher for eligible patients. All SMART-CeVD patients would have been eligible for the PROGRESS trial, so HRs could not be calculated. After adjustment for age, sex, and cardiovascular risk factors, no statistically significant differences in MACE and all-cause mortality risk were observed for HOPE-PAD and PRoFESS. For the EUROPA and PEACE trials, age- and sex-adjusted HRs were 0.88 (95% CI, 0.76–1.01) and 0.56 (95% CI, 0.46–0.69), respectively for MACE and 0.68 (95% CI, 0.59–0.77) and 0.52 (95% CI, 0.43–0.64) for all-cause mortality. Additional adjustments for age, sex, and cardiovascular risk factors resulted in unchanged HRs compared with the first adjusted model. Kaplan-Meier curves and hazard ratios for the individual MACE components are provided in Figures S1 through S3 and Table S3.

## Sensitivity Analysis

In subgroup analyses of the 3 cohorts after exclusion of patients using ACE inhibitors or angiotensin II receptor blockers, eligibility rates were similar to those found in the full analysis (Figure 1). The calculated hazard ratios closely resembled those found in the primary analysis (Table S4). Adjustments for competing risks did not result in significant changes in risk of MACE for trial-eligible patients compared with ineligible patients. The calculated subdistribution hazard ratios were similar in size and direction to the hazard ratios from the base analysis (Table S5).

**Table 1. Baseline Differences Between Trial-Eligible and -Ineligible SMART Participants**

| Δ Eligible–ineligible (95% CI) | | | | | |
|---|---|---|---|---|---|
| **Characteristics** | **EUROPA** | **PEACE** | **HOPE-PAD** | **PRoFESS** | **PROGRESS** |
| Patient characteristics | | | | | |
| Age, y | 1.4* (0.8 to 2.0) | 14.6 (13.8 to 15.3) | 13.2 (12.3 to 14.1) | 5.7 (4.9 to 6.6) | N/A |
| Male, % | 3.6* (1.0 to 6.2) | −0.3 (−3.3 to 2.7) | 3.8 (−1.2 to 8.8) | 10.6 (5.7 to 15.4) | N/A |
| History | | | | | |
| Coronary disease, % | | | 12.9* (8.3 to 17.5) | −4.3* (−8.2 to −0.3) | N/A |
| Cerebrovascular disease, % | −2.7* (−4.7 to −0.7) | −0.3 (−2.6 to 2.0) | 7.7* (4.2 to 11.2) | | N/A |
| Peripheral artery disease, % | −3.9* (−5.9 to −2.0) | −0.6 (−2.7 to 1.6) | | 0.3 (−2.6 to 3.3) | N/A |
| AAA, % | −2.8* (−4.5 to −1.1) | 0.7 (−1.1 to 2.4) | 2.9 (−0.1 to 5.8) | −0.6 (−2.7 to 1.5) | N/A |
| Diabetes, % | 1.8 (−0.7 to 4.3) | 5.4* (2.6 to 8.1) | 6.8* (2.6 to 11.0) | 3.4 (−0.7 to 7.5) | N/A |
| Cardiovascular risk factors | | | | | |
| Systolic BP, mm Hg | −4.5* (−6.2 to −2.8) | 4.9* (3.5 to 6.4) | −1.0 (−3.4 to 1.3) | 3.1* (1.4 to 4.8) | N/A |
| Diastolic BP, mm Hg | −3.2* (−4.1 to −2.3) | −1.0* (−1.8 to −0.2) | −3.7* (−4.9 to −2.5) | −1.0 (−2.0 to 0.1) | N/A |
| Body mass index, kg/m$^2$ | 0.2 (−0.1 to 0.4) | −0.3* (−0.7 to 0.0) | 0.0 (−0.5 to 0.4) | −0.2 (−0.6 to 0.1) | N/A |
| Current smoker, % | −3.3* (−6.1 to −0.5) | −16.0* (−19.6 to −12.4) | −18.6* (−23.8 to −13.4) | −1.7 (−6.6 to 3.2) | N/A |
| SMART risk score | −4.2* (−5.4 to −2.9) | 5.0* (3.7 to 6.4) | 10.7* (8.6 to 12.8) | 4.2* (2.2 to 6.1) | N/A |
| Laboratory findings | | | | | |
| eGFR (CKD-EPI), % | 2.8* (1.5 to 4.1) | −9.5* (−11.2 to −7.9) | −8.9* (−11.0 to −6.8) | −4.7* (−6.4 to −2.9) | N/A |
| Albuminuria | | | | | |
| ACR 3–30 mg/mmol, % | −5.9* (−8.2 to −3.7) | 1.8 (−0.4 to 4.1) | 5.6* (1.7 to 9.5) | −0.5 (−4.0 to 3.1) | N/A |
| ACR ≥30 mg/mmol, % | −2.7* (−3.8 to −1.5) | −1.5* (−2.8 to −0.2) | −8.1* (−10.4 to −5.8) | −0.8 (−2.1 to 0.5) | N/A |
| Total cholesterol, mmol/L | −0.2* (−0.2 to −0.1) | −0.2* (−0.3 to −0.1) | −0.1 (−0.2 to 0.0) | −0.1 (−0.2 to 0.0) | N/A |
| Triglycerides, mmol/L | −0.1 (−0.1 to 0.0) | −0.3* (−0.4 to −0.1) | −0.2* (−0.3 to −0.1) | 0.0 (−0.1 to 0.1) | N/A |
| HDL-C, mmol/L | 0.0* (−0.1 to 0.0) | 0.0* (0.0 to 0.1) | 0.1* (0.0 to 0.1) | 0.0 (−0.1 to 0.0) | N/A |
| LDL-C, mmol/L | −0.1* (−0.1 to 0.0) | −0.1* (−0.2 to 0.0) | −0.1 (−0.2 to 0.0) | −0.1 (−0.2 to 0.0) | N/A |
| Medication | | | | | |
| Antihypertensive therapy, % | 0.2 (−1.8 to 2.2) | 7.2* (4.4 to 10.0) | 15.7* (10.5 to 20.9) | −0.2 (−5.4 to 5.0) | N/A |
| β-blocker, % | 2.8 (0.0 to 5.7) | 8.4* (4.9 to 12.0) | 10.6* (5.9 to 15.3) | −2.4 (−7.3 to 2.4) | N/A |
| Calcium channel blocker, % | −0.4 (−3.2 to 2.4) | 3.4* (0.2 to 6.6) | 8.7* (4.6 to 12.8) | −2.3 (−6.2 to 1.6) | N/A |
| Diuretic, % | −9.8* (−12.7 to −7.0) | 4.7* (1.7 to 7.7) | 9.5* (5.4 to 13.5) | −3.7 (−8.0 to 0.7) | N/A |
| Lipid-lowering therapy, % | 4.2* (1.6 to 6.8) | 3.8* (0.7 to 6.9) | 6.2* (0.9 to 11.4) | 9.2* (4.2 to 14.2) | N/A |
| Antithrombotic therapy, % | 2.7* (0.9 to 4.5) | 6.7* (4.2 to 9.2) | 11.1* (6.2 to 16.1) | 12.7* (9.3 to 16.0) | N/A |

Data are presented as difference in proportion for categorical variable and difference in mean for continuous variables. AAA indicates abdominal aortic aneurysm; ACR, urine albumin to creatinine ratio; BP, blood pressure; CKD-EPI, chronic kidney disease epidemiology collaboration formula; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; N/A, not applicable; and SMART, Second Manifestations of Arterial Disease.

*Data represent a statistically significant difference between trial-eligible and -ineligible patients ($P<0.05$).

## DISCUSSION

Real-world patient eligibility for major blood pressure–lowering drug trials ranged from 17% to 100%. Compared with ineligible patients, eligible patients with CAD had a lower adjusted risk for MACE (PEACE) and all-cause mortality (EUROPA, PEACE). These findings suggest that both EUROPA and PEACE inadvertently selected lower risk patients. Patients with PAD eligible for HOPE participation had a comparable adjusted risk for both MACE (HR, 0.88 [95% CI, 0.68–1.14]) and all-cause mortality (HR, 0.93 [95% CI, 0.74–1.16]) compared with ineligible patients. All SMART-CeVD patients met the eligibility criteria for the PROGRESS trial. The PRoFESS trial applied the most stringent selection criteria, resulting in only 17% of SMART-CeVD patients being eligible. However, after adjusting for age, sex, and cardiovascular risk factors, the risk for both MACE and mortality was similar irrespective of patients' PRoFESS eligibility. The present study shows that applying CVOT selection criteria to real-world patients yields comparable adjusted risks for MACE and mortality in patients with PAD or CeVD, but eligibility for CAD trials was associated with a reduced adjusted risk.

A majority of patients with CAD would have been eligible for participation in EUROPA and PEACE. The main reasons for exclusion of these patients were the character of their CAD (ie, no myocardial infarction), an

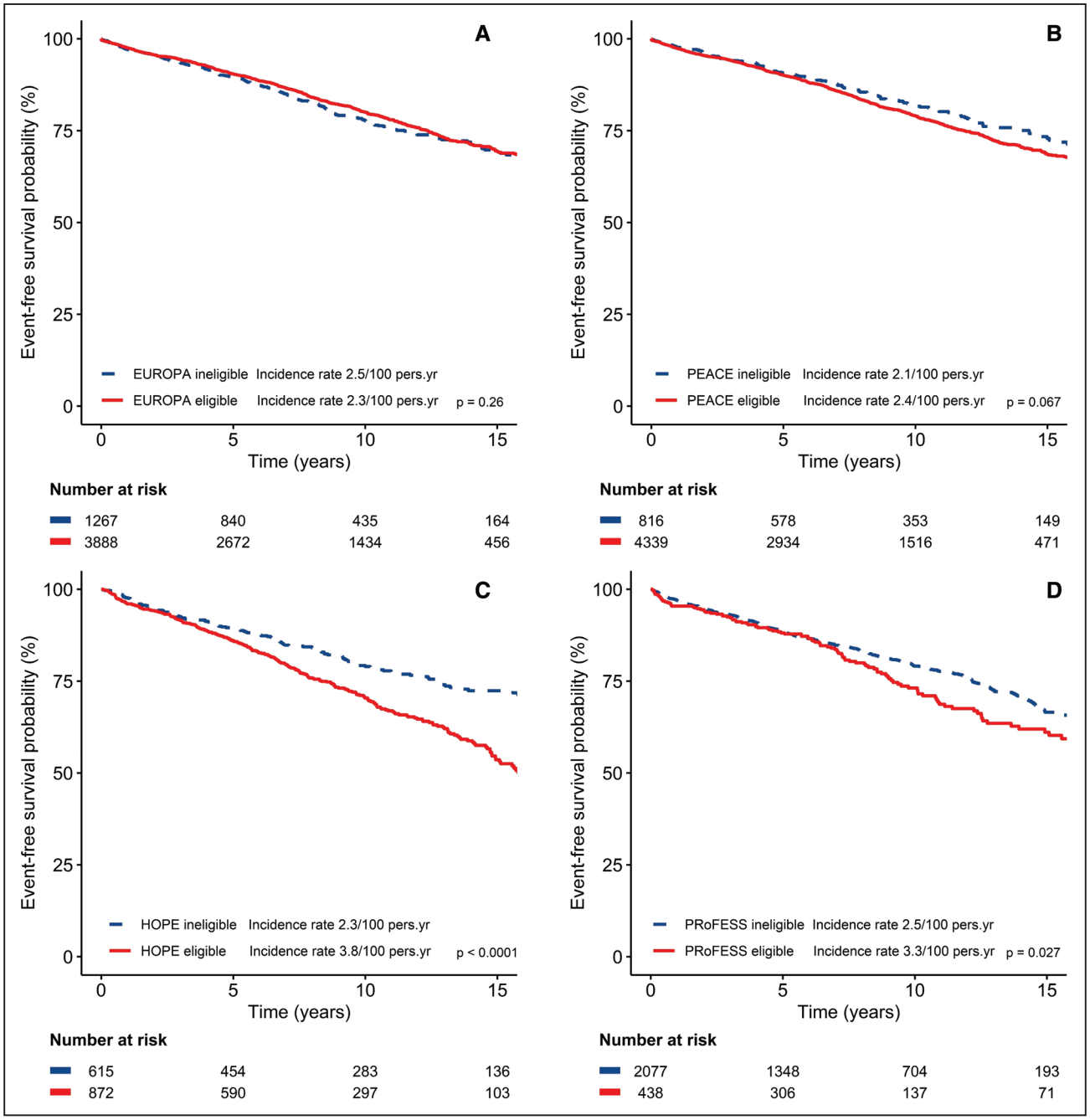


**Figure 2. Kaplan-Meier curves for major cardiovascular events, stratified by trial eligibility.**
**A**, SMART (Second Manifestations of Arterial Disease)-coronary artery disease (CAD) cohort stratified by EUROPA eligibility, (**B**) SMART-CAD cohort stratified by PEACE eligibility, (**C**) SMART-PAD cohort stratified by HOPE eligibility, and (**D**) SMART-cerebrovascular disease cohort stratified by PRoFESS eligibility. *P* values were calculated using a log-rank test.

extremely low or high blood pressure or, for the PEACE trial, age under 50 years. Would be ineligible HOPE-PAD patients were mainly excludes on account of age under 55 years. The PROGRESS trial employed unrestrictive criteria, resulting in 100% eligibility of SMART-CeVD patients. By contrast, only 17% of the SMART-CeVD patients was eligible for the ProFESS trial. This relatively low number can be explained because PRoFESS only included patients with recent CeVD (<120 days before enrollment), whereas the SMART-CeVD cohort primarily consists of patients with stable and asymptomatic CeVD.

The high eligibility rate for the EUROPA and PEACE trials suggests that their results are broadly applicable. However, after adjusting for age, sex, and cardiovascular risk factors, trial-eligible patients were at lower risk of MACE (in PEACE) and mortality (in both EUROPA and PEACE). This suggests that these trials selected healthier

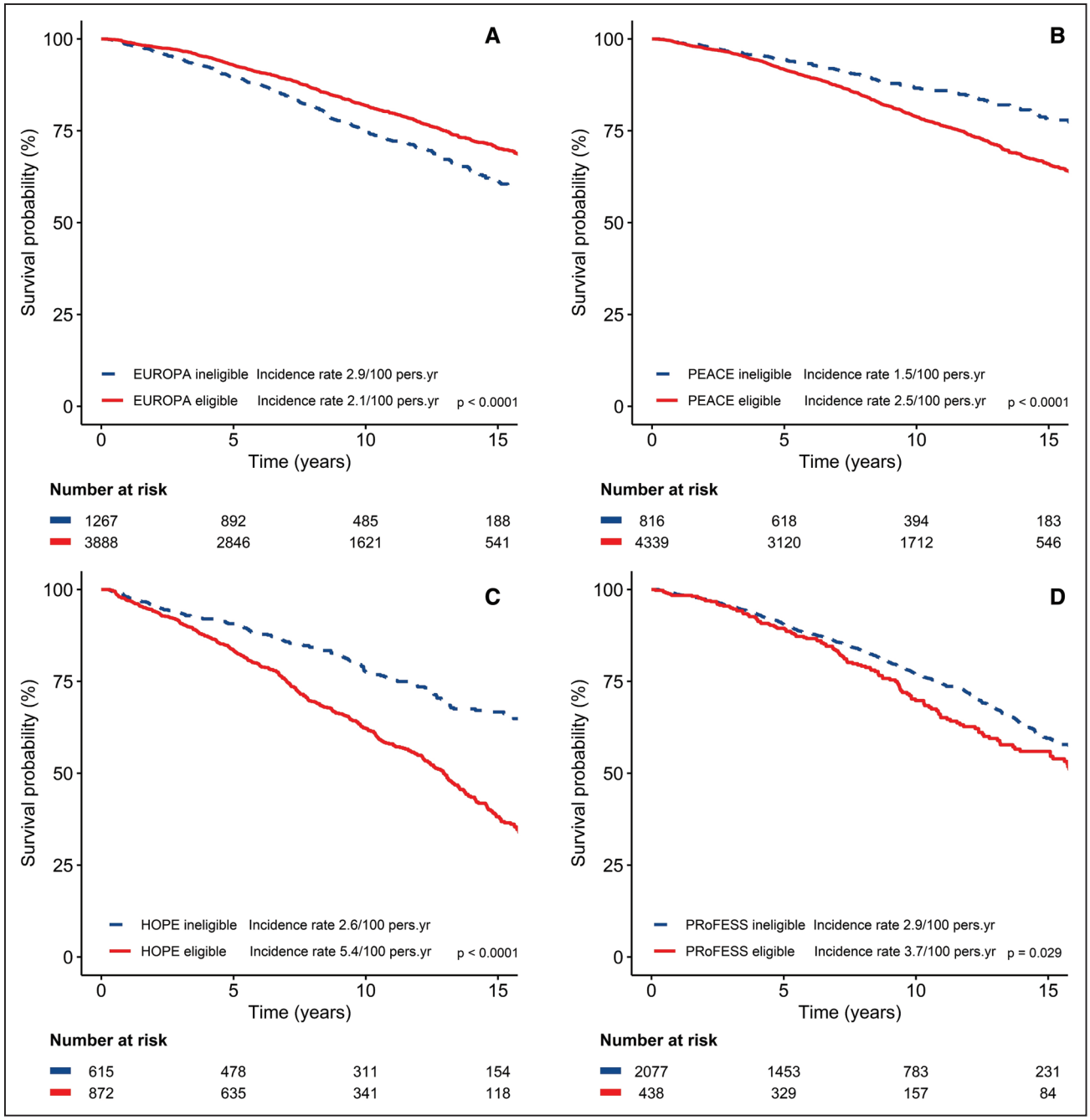


**Figure 3. Kaplan-Meier curves for all-cause mortality, stratified by trial eligibility.**
**A**, SMART (Second Manifestations of Arterial Disease)-coronary artery disease (CAD) stratified by EUROPA eligibility, (**B**) SMART-CAD stratified by PEACE eligibility, (**C**) SMART-peripheral artery disease stratified by HOPE eligibility, (**D**) SMART-CeVD stratified by PRoFESS eligibility. *P* values were calculated using a log-rank test.

patients, independent of recorded patient characteristics. Differences in baseline characteristics between the groups could not explain the relatively favorable prognosis of these eligible patients with CAD. Some cardiovascular risk factors such as advanced age and diabetes were more prevalent in eligible patients, whereas others such as cardiovascular history and current smoking status occurred more frequently in the ineligible patient group. Overall, there appears to be no factor tipping the balance of the cardiovascular risk profile to either group. Importantly, because the differences in prognosis are not readily explained, extrapolating the results of the EUROPA and PEACE trials to ineligible patients with CAD warrants caution. The relatively poor prognosis of ineligible patients could be caused by an unobserved confounding factor linked to the trial's eligibility criteria. If related to the treatment mechanism, this factor may cause ineligible patients to respond differently to antihypertensive treatment.

**Table 2. Hazard Ratios for Major Cardiovascular Events and All-Cause Mortality, Trial Eligible vs Ineligible Patients**

| | SMART-CAD | SMART-PAD | | SMART-CeVD | |
|---|---|---|---|---|---|
| Outcome | EUROPA | PEACE | HOPE-PAD | PRoFESS | PROGRESS |
| N (eligible \| ineligible) | 3888 \| 1267 | 4339 \| 816 | 872 \| 615 | 438 \| 2077 | 2515 \| 0 |
| Major cardiovascular events | | | | | |
| Number of events (%), eligible \| ineligible | 738 (19) \| 256 (20) | 839 (19) \| 155 (19) | 267 (31) \| 135 (22) | 120 (27) \| 409 (20) | 529 (21) |
| Model 1 | 0.92 (0.80–1.06) | 1.17 (0.99–1.39) | 1.73* (1.40–2.13) | 1.26* (1.03–1.55) | N/A |
| Model 2 | 0.88 (0.76–1.01) | 0.56* (0.46–0.69) | 0.76* (0.59–0.97) | 1.00 (0.81–1.22) | N/A |
| Model 3 | 0.94 (0.81–1.09) | 0.65* (0.53–0.79) | 0.88 (0.68–1.14) | 0.99 (0.80–1.21) | N/A |
| All-cause mortality | | | | | |
| Number of events (%), eligible \| ineligible | 738 (19) \| 320 (25) | 938 (22) \| 120 (15) | 416 (48) \| 167 (27) | 149 (34) \|504 (24) | 653 (26) |
| Model 1 | 0.73* (0.64–0.83) | 1.79* (1.48–2.16) | 2.22* (1.86–2.67) | 1.23* (1.02–1.47) | N/A |
| Model 2 | 0.68* (0.59–0.77) | 0.52* (0.43–0.64) | 0.87 (0.71–1.07) | 0.94 (0.78–1.13) | N/A |
| Model 3 | 0.72* (0.62–0.82) | 0.63* (0.51–0.78) | 0.93 (0.74–1.16) | 0.93 (0.77–1.12) | N/A |

Data are reported as hazard ratios (95% CIs) for trial-eligible SMART patients compared with trial-ineligible SMART patients. Model 1: crude analysis, Model 2: adjusted for age and sex, Model 3: Model 2+systolic blood pressure, body mass index, low-density lipoprotein cholesterol, eGFR, diabetes, and current smoker. CAD indicates coronary artery disease; CeVD, cerebrovascular disease; eGFR, estimated glomerular filtration rate; N/A, not applicable; PAD, peripheral arterial disease; and SMART, Second Manifestations of Arterial Disease.

*Data represents a statistically significant result ($P<0.05$).

Applicability in patients with CeVD has been investigated before in a study that compared the baseline characteristics of the PROGRESS trial to a primary care population with stroke. It was found that the real-world population was older (76±10 versus 64±10years) and more frequently female (54% versus 30%),[31] leading the authors to conclude that the applicability of the PROGRESS trial is uncertain. This conclusion contrasts starkly with our findings of nonrestrictive selection criteria and 100% eligibility for the PROGRESS trial. This can most likely be explained by differences in care setting (primary versus tertiary) and study design.

The present study shows that results from landmark blood pressure–lowering trials in patients with PAD (HOPE-PAD) and CeVD (PRoFESS and PROGRESS) can be broadly applied to real-world patients. Although patients who do not meet trials' selection criteria are at higher risk of mortality and MACE, this difference no longer persists after adjusting for age, sex, and cardiovascular risk factors. Although there are no reasons to suspect that the relative treatment effect size differs between eligible and ineligible patients, it is important to note that the absolute treatment effect may vary. Risk of all-cause mortality and MACE was lower among ineligible patients, who therefore stand to gain a smaller absolute risk reduction from treatment and consequently require higher numbers needed to treat.

Although large percentages of real-life patients would be included in trials, the inclusion and exclusion criteria may inadvertently select patients with a lower risk for MACE or mortality such as in the CAD trials we investigated here. Using the data from the PEACE or EUROPA trials for development or validation of cardiovascular risk models for real-life patients may therefore not be appropriate and a similar caveat should be considered when developing these models.[32]

Study strengths and limitations need to be considered. Although the SMART study is no true reflection of all real-world patients with manifest cardiovascular disease, it provides a large and representative cohort of patients as seen in clinical practice in a tertiary center, potentially limited by selection bias for patients willing to participate. Long follow-up allowed for assessment of long-term risk differences between trial-eligible and -ineligible patients, powered by a large number of cardiovascular events and completeness of the data are further strengths. Sensitivity analyses showed that potential bias introduced by competing risks during the long follow-up had no significant effect on the observed differences in risks for eligible and ineligible patients. A limitation of the study is that not all eligibility criteria could be applied since the required data were not collected in the SMART cohort. This may have resulted in an overestimation of real-world eligibility, but the effect is likely to be small as the unavailable data mostly concerned relatively uncommon baseline characteristics, such as laboratory abnormalities. Moreover, the baseline characteristics and cardiovascular risk profiles reported for the original CVOT participants were similar to those of eligible SMART patients, which supports the notion that the most relevant eligibility criteria were applied. Because of the observational design of the SMART cohort versus the experimental designs of the studied RCTs, criteria concerning run-in periods, discontinuation, or adverse reactions to the trial medication could not be applied and were dropped. However, sensitivity analysis in a subgroup of SMART patients who did not use the studied trial medication showed that the eligibility rates and HRs were nearly identical compared with the full analysis. This study focuses on patient selection in

RCTs as a potential restrictive factor for applicability of the results to a broader population. However, other factors in a study design should also be considered when drawing conclusions on applicability of the results to clinical practice, such as a trial's setting (population, hospital, and clinical relevance of the reported outcome measures).[21,23] In the current study, it was not possible to assess applicability in elderly populations because they were not originally included in the SMART cohort. Further research in elderly populations could provide relevant new insights, as it has been shown that real-world elderly patients have higher rates of adverse events than those included in trials.[33]

## PERSPECTIVES

The majority of real-world patients would be eligible for major guideline-informing trials on blood pressure–lowering medication. The results from trials performed in a PAD or CeVD population can be broadly applied to clinical patients as the prognosis for eligible and ineligible patients does not significantly differ. However, ineligible real-world CAD patients have a relatively unfavorable prognosis without a satisfactory explanation. Based on these findings, we conclude that the HOPE-PAD, PRoFESS, and PROGRESS trials provide a strong foundation for the guidelines of secondary preventive care in PAD and CeVD. The EUROPA and PEACE trials can be applied to a large majority of patients with CAD, but caution is warranted in extending the results to patients who do not meet the eligibility criteria, such as younger patients with CAD. In the design of future cardiovascular outcome research, care should be taken to represent the target population as closely as possible to ensure applicability of the results.

## ARTICLE INFORMATION

Received July 12, 2020; accepted November 11, 2020.

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### Acknowledgments

We gratefully acknowledge the contribution of the research nurses; R. van Petersen (data-manager); B. van Dinther (study manager), and the Members of the Utrecht Cardiovascular Cohort (UCC)-SMART (Second Manifestations of Arterial Disease) Study group: F.W. Asselbergs and H.M. Nathoe, Department of Cardiology; G.J. de Borst, Department of Vascular Surgery; M.L. Bots and M.I. Geerlings, Julius Center for health Sciences and Primary Care; M.H. Emmelot, Department of Geriatrics; P.A. de Jong and T. Leiner, Department of Radiology; A.T. Lely, Department of Obstetrics & Gynecology; N.P. van der Kaaij, Department of Cardiothoracic Surgery; L.J. Kappelle and Y.M. Ruigrok, Department of Neurology; M.C. Verhaar, Department of Nephrology, F.L.J. Visseren (chair) and J. Westerink, Department of Vascular Medicine, University Medical Center Utrecht and Utrecht University.

### Sources of Funding

The SMART (Second Manifestations of Arterial Disease) study was financially supported by a grant of the University Medical Center Utrecht. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

### Disclosures

None.

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