ORIGINAL ARTICLE

Mortality with Paclitaxel-Coated Devices in Peripheral Artery Disease

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ABSTRACT

BACKGROUND

The results of a recent meta-analysis aroused concern about an increased risk of death associated with the use of paclitaxel-coated angioplasty balloons and stents in lower-limb endovascular interventions for symptomatic peripheral artery disease.

METHODS

We conducted an unplanned interim analysis of data from a multicenter, randomized, open-label, registry-based clinical trial. At the time of the analysis, 2289 patients had been randomly assigned to treatment with drug-coated devices (the drug-coated–device group, 1149 patients) or treatment with uncoated devices (the uncoated-device group, 1140 patients). Randomization was stratified according to disease severity on the basis of whether patients had chronic limb-threatening ischemia (1480 patients) or intermittent claudication (809 patients). The single end point for this interim analysis was all-cause mortality.

RESULTS

No patients were lost to follow-up. Paclitaxel was used as the coating agent for all the drug-coated devices. During a mean follow-up of 2.49 years, 574 patients died, including 293 patients (25.5%) in the drug-coated–device group and 281 patients (24.6%) in the uncoated-device group (hazard ratio, 1.06; 95% confidence interval, 0.92 to 1.22). At 1 year, all-cause mortality was 10.2% (117 patients) in the drug-coated–device group and 9.9% (113 patients) in the uncoated-device group. During the entire follow-up period, there was no significant difference in the incidence of death between the treatment groups among patients with chronic limb-threatening ischemia (33.4% [249 patients] in the drug-coated–device group and 33.1% [243 patients] in the uncoated-device group) or among those with intermittent claudication (10.9% [44 patients] and 9.4% [38 patients], respectively).

CONCLUSIONS

In this randomized trial in which patients with peripheral artery disease received treatment with paclitaxel-coated or uncoated endovascular devices, the results of an unplanned interim analysis of all-cause mortality did not show a difference between the groups in the incidence of death during 1 to 4 years of follow-up. (Funded by the Swedish Research Council and others; ClinicalTrials.gov number, NCT02051088.)

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A list of investigators in this trial is provided in the Supplementary Appendix, available at NEJM.org.

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Peripheral artery disease is a worldwide health problem characterized by reduced blood flow to the lower limbs due to obstructive atherosclerosis.[1] Endovascular interventions are often indicated to prevent amputations and alleviate symptoms, but they are associated with a tangible risk of postprocedural restenosis that in turn jeopardizes the long-term patency of the intervention.[2,3]

Paclitaxel, a hydrophobic natural diterpenoid originally isolated from the tree *Taxus brevifolia*, is an antiproliferative agent that is used for all drug-coated balloons and drug-coated stents that have been approved in the European Union (where it received a European Certificate of Conformity, known as the CE mark) and the United States (where it received Food and Drug Administration [FDA] approval) for peripheral artery disease interventions.[4] Drug-coated devices reduce the risk of restenosis and the likelihood of repeat interventions and have been widely adopted, but their effects on patient-oriented clinical end points such as amputation rate and quality of life have not yet been shown.[5-7] The Swedish Drug Elution Trial in Peripheral Arterial Disease (SWEDEPAD) is a multicenter, randomized, open-label, registry-based trial that aims to determine whether drug-elution technology favorably affects the incidence of amputation among patients with chronic limb-threatening ischemia and health-related quality of life among patients with intermittent claudication.

A recent meta-analysis showed a signal of an increased late risk of death associated with the use of paclitaxel-coated devices.[8] This finding caused substantial concern and controversy regarding long-term safety.[9-13] As a result, patient recruitment in the SWEDEPAD trial was temporarily halted on December 10, 2018. Owing to the worldwide public health concern related to the safety of paclitaxel-coated devices in peripheral interventions, the data and safety monitoring committee of the trial recommended an unplanned interim analysis of all-cause mortality after a prolonged period of follow-up.

Methods

Trial Design, Oversight, and Funding

The SWEDEPAD trial is a pragmatic, multicenter, randomized, parallel-group, open-label, single-blind, registry-based clinical trial. A complete list of the trial personnel is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. In total, 22 of the 28 vascular centers in Sweden are participating in the trial. Screening, enrollment, randomization, and follow-up of the patients in the trial are being performed with the use of the National Quality Registry for Vascular Surgery (Swedvasc) (details are provided in the Supplementary Appendix).[14,15] The registry is maintained by the Uppsala Clinical Research Center at Uppsala University.

The trial is led by an executive committee with national representation. An independent data and safety monitoring committee periodically evaluates blinded event-rate data and the overall safety of the investigational treatment. The trial protocol (available at NEJM.org) was approved by the Central Ethical Review Authority in Sweden. The trial sponsor is the Institute of Clinical Sciences at the Sahlgrenska Academy, University of Gothenburg, Sweden. Trial management and statistical analyses are performed at the Uppsala Clinical Research Center at Uppsala University.

The trial is funded by grants from the Swedish Research Council, the Swedish Heart–Lung Foundation, and Region Västra Götaland. In addition, all the companies that provide drug-coated balloons and drug-coated stents for patients in Sweden with peripheral artery disease are supporting the trial by providing price discounts on their devices. Neither the trial sponsor nor any of the funding bodies had any influence on the trial design; the preparation of the protocol or statistical analysis plan; the selection of sites or patients; patient enrollment, evaluation, or follow-up; site monitoring or supervision; the collection or storage of the data; the decision to suspend enrollment for this analysis; the analysis or interpretation of the data; the preparation of the manuscript; or the decision to submit the manuscript for publication. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol, with the exception of the decision to perform this unplanned interim analysis, as noted previously.

Patients

The target population consists of adults with confirmed symptomatic peripheral artery disease that is caused by a new or recurrent flow-limiting stenosis (defined as a loss of >50% of the cross-sectional diameter) or occlusion in infrainguinal arteries and that is eligible for endovascular treat-

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ment according to established indications. The trial includes two cohorts of patients who undergo randomization separately: patients with chronic limb-threatening ischemia and patients with intermittent claudication. Exclusion criteria are acute lower-limb ischemia, infrainguinal aneurysmal disease, and either previous participation in the trial or concurrent participation in another interventional trial involving infrainguinal arterial lesions. Patients without a Swedish personal identification number are also excluded. All the patients provide written informed consent.

TRIAL PROCEDURES

A summary of the trial design and trial procedures is provided in Figure S1 in the Supplementary Appendix. After patients are admitted to the hospital for the scheduled procedure, informed consent is obtained. Randomization occurs during the intervention procedure, after a guide wire has crossed the lesion but before any dilation has been performed. At each trial center, patients are randomly assigned to treatment with either a drug-coated device or an uncoated device. Randomization is performed online with the Swedvasc Web-based platform and a dedicated computerized randomization module that has been introduced in the registry. Randomization is stratified according to disease severity (chronic limb-threatening ischemia or intermittent claudication) and center. To activate the randomization function, information regarding disease severity, the vascular segment to be treated (femoropopliteal, infrapopliteal, or both), and the planned revascularization technique (primary balloon angioplasty or primary stenting) must first be recorded.

All devices with European Union approval (i.e., those that have received the CE mark) for peripheral artery disease interventions are allowed. In case of target lesions in multiple vessel segments, the treatment assignment applies to all the treated lesions. The patient and the ultrasonographer who performs duplex ultrasonography on follow-up are unaware of the treatment assignment, whereas the operator for the revascularization procedure is aware of the treatment assignment. Details of the interventional procedure and the associated antithrombotic treatment are provided in the Supplementary Appendix.

Patients in the trial are followed according to the Swedvasc follow-up procedures, which include patient visits to the center at 30 days and 1 year after the revascularization procedure (details are provided in the Supplementary Appendix). All reinterventions as well as any additional procedures with paclitaxel-coated devices other than the index revascularization are recorded in Swedvasc. Swedvasc is interlinked with the Swedish national population registry, enabling continuous updates regarding all-cause mortality to be made to the trial database. Therefore, the vital status of each patient is known and regularly updated during long-term follow-up.

TRIAL OUTCOMES

The end point for this unplanned interim analysis was all-cause mortality. The prespecified primary efficacy end points in the overall trial differ for the two trial cohorts. For the cohort of patients with chronic limb-threatening ischemia, the primary efficacy end point is the incidence of major amputations during follow-up, which is planned to be analyzed when all the patients in that cohort have been followed for at least 1 year. For the cohort of patients with intermittent claudication, the primary efficacy end point is health-related quality of life after 1 year, which is assessed with the use of the Vascular Quality of Life Questionnaire-6. All-cause mortality is a prespecified secondary end point in the trial protocol for both cohorts. A complete list of the trial end points is provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

Baseline characteristics are presented as means and standard deviations or as medians and interquartile ranges for continuous variables and as absolute and relative percentages for categorical variables. A detailed description of the original sample size estimation for the trial is provided in the Supplementary Appendix. In this interim analysis, only the single end point of all-cause mortality was analyzed. The analysis was based on the intention-to-treat population, which included all the patients who underwent randomization, irrespective of their adherence to the protocol and their continued participation in the trial. Comparisons of all-cause mortality between the drug-coated–device group and the uncoated-device group were performed with the use of a Cox proportional hazards model; hazard ratios and 95% confidence intervals were estimated for the overall trial population as well as separately for patients with chronic limb-threatening ischemia

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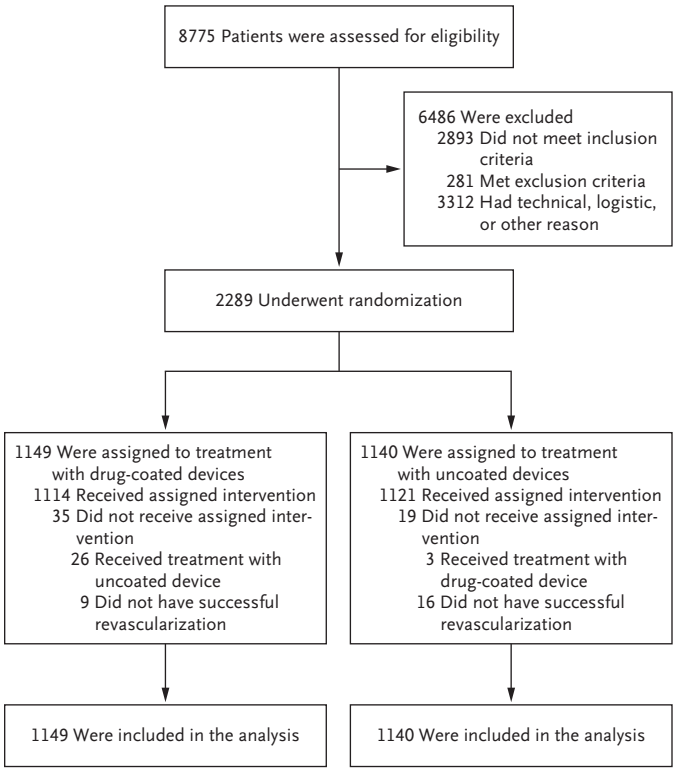

Figure 1. Enrollment, Randomization, and Interim Follow-up for Analysis of All-Cause Mortality.

Additional detailed information regarding the reasons for exclusion of patients after they had been assessed for eligibility are provided in Table S1.

and those with intermittent claudication. The hazard ratios and confidence intervals have been adjusted to account for center effects. The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects. A Kaplan–Meier analysis was used to estimate the cumulative probability of death from any cause in each treatment group during follow-up. All the analyses were performed with the use of R software, version 3.6.[16]

RESULTS

PATIENT POPULATION

From November 5, 2014 until December 10, 2018, a total of 8775 patients were assessed for trial eligibility (Fig. 1). Of these patients, 6486 were excluded for the reasons listed in Table S1. The remaining 2289 patients (of 3733 planned for the final efficacy assessment) underwent randomization: 1149 to treatment with drug-coated devices (the drug-coated–device group) and 1140 to treatment with uncoated devices (the uncoated-device group). In total, 1480 patients had chronic limb-threatening ischemia and 809 had intermittent claudication.

Table 1 shows demographic data and coexisting conditions at baseline in the overall trial population and in the cohorts of patients with chronic limb-threatening ischemia and with intermittent claudication. The mean (±SD) age was 76.8±9.3 years among patients with chronic limb-threatening ischemia and 72.7±7.6 years among those with intermittent claudication. Overall, 815 (55.1%) of the patients with chronic limb-threatening ischemia and 439 (54.3%) of the patients with intermittent claudication were men. Among the patients with available data, 811 of 1227 (66.1%) with chronic limb-threatening ischemia and 620 of 745 (83.2%) with intermittent claudication were current or former smokers, and 1079 of 1434 (75.2%) with chronic limb-threatening ischemia and 697 of 792 (88.0%) with intermittent claudication were receiving statin treatment.

PROCEDURES AND FOLLOW-UP

Paclitaxel was used as the coating agent in all the drug-coated devices. The manufacturers and brands of the drug-coated devices used in the trial are listed in Table S2. There were a total of 175 operators (vascular surgeons and interventional radiologists) for the drug-coated–device group and 171 operators for the uncoated-device group. Data on additional lower-limb interventions with paclitaxel-coated devices undertaken before and after the index revascularization are available from May 2008, when this variable was first introduced into Swedvasc, through March 2020. In total, 23 patients (2.0%) in the drug-coated–device group and 25 patients (2.2%) in the uncoated-device group had had an additional intervention with paclitaxel-coated devices before the index revascularization, and 89 patients (7.7%) and 85 patients (7.5%), respectively, had additional interventions after the index revascularization (Table 1). With the exception of 14 hybrid procedures, in which both open and endovascular techniques were used, all the procedures were percutaneous endovascular interventions.

The date of database lock for deaths in this interim analysis was March 16, 2020. At that time, the mean follow-up was 2.49 years in the overall population and 2.34 and 2.77 years among

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Overall Population (N=2289)		Patients with Chronic Limb-Threatening Ischemia (N=1480)		Patients with Intermittent Claudication (N=809)	
	Drug-Coated Device (N=1149)	Uncoated Device (N=1140)	Drug-Coated Device (N=745)	Uncoated Device (N=735)	Drug-Coated Device (N=404)	Uncoated Device (N=405)
Age — yr						
No.	1149	1140	745	735	404	405
Median (IQR)	75.4 (70.0–82.1)	75.6 (69.9–81.6)	77.2 (71.5–84.0)	77.6 (71.1–83.5)	72.8 (68.1–77.7)	73.2 (68.6–77.8)
Male sex — no./total no. (%)	626/1149 (54.5)	628/1140 (55.1)	409/745 (54.9)	406/735 (55.2)	217/404 (53.7)	222/405 (54.8)
Smoking status — no./total no. (%)						
Never	274/982 (27.9)	267/990 (27.0)	208/612 (34.0)	208/615 (33.8)	66/370 (17.8)	59/375 (15.7)
Previous	569/982 (57.9)	592/990 (59.8)	294/612 (48.0)	306/615 (49.8)	275/370 (74.3)	286/375 (76.3)
Current	139/982 (14.2)	131/990 (13.2)	110/612 (18.0)	101/615 (16.4)	29/370 (7.8)	30/375 (8.0)
Hypertension — no./total no. (%)	921/1115 (82.6)	914/1115 (82.0)	603/718 (84.0)	590/718 (82.2)	318/397 (80.1)	324/397 (81.6)
Diabetes mellitus — no./total no. (%)	519/1124 (46.2)	508/1126 (45.1)	386/727 (53.1)	371/726 (51.1)	133/397 (33.5)	137/390 (35.1)
Previous cardiovascular disease — no./total no. (%)	521/1114 (46.8)	487/1112 (43.8)	379/719 (52.7)	342/714 (47.9)	142/395 (35.9)	145/398 (36.4)
Pulmonary disease — no./total no. (%)	169/1114 (15.2)	166/1108 (15.0)	121/719 (16.8)	107/709 (15.1)	48/395 (12.2)	59/399 (14.8)
Cerebrovascular disease — no./total no. (%)	161/1111 (14.5)	152/1105 (13.8)	120/717 (16.7)	102/705 (14.5)	41/394 (10.4)	50/400 (12.5)
Medication at admission — no./total no. (%)						
Statin	901/1113 (81.0)	875/1113 (78.6)	557/720 (77.4)	522/714 (73.1)	344/393 (87.5)	353/399 (88.5)
Anticoagulant agent	233/1119 (20.8)	265/1115 (23.8)	186/725 (25.7)	210/717 (29.3)	47/394 (11.9)	55/398 (13.8)
Platelet inhibitor	907/1121 (80.9)	854/1118 (76.4)	562/725 (77.5)	508/719 (70.7)	345/396 (87.1)	346/399 (86.7)
Ankle–brachial index						
No.	945	961	594	590	351	371
Median (IQR)	0.6 (0.4–0.7)	0.6 (0.4–0.7)	0.5 (0.4–0.7)	0.5 (0.4–0.7)	0.6 (0.5–0.7)	0.6 (0.5–0.7)
Renal insufficiency without dialysis — no./total no. (%)	215/1085 (19.8)	220/1086 (20.3)	170/692 (24.6)	162/688 (23.5)	45/393 (11.5)	58/398 (14.6)
Dialysis — no./total no. (%)	38/1124 (3.4)	40/1128 (3.5)	35/728 (4.8)	37/725 (5.1)	3/396 (0.8)	3/402 (0.7)
Femoropopliteal target lesion — no./total no. (%)	921/1117 (82.5)	947/1118 (84.7)	545/724 (75.3)	568/722 (78.7)	376/393 (95.7)	379/396 (95.7)
Infrapopliteal target lesion — no./total no. (%)	338/1117 (30.3)	350/1118 (31.3)	308/724 (42.5)	317/722 (43.9)	30/393 (7.6)	33/396 (8.3)
Paclitaxel-coated device before index procedure — no./total no. (%)	23/1149 (2.0)	25/1140 (2.2)	13/745 (1.7)	17/735 (2.3)	10/404 (2.5)	8/405 (2.0)
Paclitaxel-coated device after index procedure — no./total no. (%)	89/1149 (7.7)	85/1140 (7.5)	60/745 (8.1)	52/735 (7.1)	29/404 (7.2)	33/405 (8.1)

* IQR denotes interquartile range.

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Table 2. All-Cause Mortality during Entire Follow-up Period and during First Postprocedural Year.

Variable	Drug-Coated Device (N=1149)	Uncoated Device (N=1140)	Hazard Ratio (95% CI)*
	no./total no. (%)		
Deaths at 1 yr of follow-up			
Overall population	117/1149 (10.2)	113/1140 (9.9)	1.03 (0.77–1.37)
Patients with chronic limb-threatening ischemia	107/745 (14.4)	105/735 (14.3)	1.00 (0.75–1.35)
Patients with intermittent claudication	10/404 (2.5)	8/405 (2.0)	1.26 (0.49–3.24)
Deaths during entire follow-up period			
Overall population	293/1149 (25.5)	281/1140 (24.6)	1.06 (0.92–1.22)
Patients with chronic limb-threatening ischemia	249/745 (33.4)	243/735 (33.1)	1.04 (0.90–1.21)
Patients with intermittent claudication	44/404 (10.9)	38/405 (9.4)	1.18 (0.72–1.93)

* The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

patients with chronic limb-threatening ischemia and patients with intermittent claudication, respectively.

ALL-CAUSE MORTALITY

No patient was lost to follow-up. During the mean follow-up period of 2.49 years, 574 patients (25.1%) died, including 293 of 1149 patients (25.5%) who were assigned to receive drug-coated devices and 281 of 1140 patients (24.6%) who were assigned to receive uncoated devices (hazard ratio, 1.06; 95% confidence interval [CI], 0.92 to 1.22) (Table 2). The treatment effect varied among the centers (Fig. S2). The incidence of death at 1 year of follow-up did not differ significantly between the groups. During the entire follow-up period, no significant difference in the incidence of death was observed between the treatment groups among the patients with chronic limb-threatening ischemia (33.4% [249 patients] in the drug-coated–device group and 33.1% [243 patients] in the uncoated-device group; hazard ratio, 1.04; 95% CI, 0.90 to 1.21) or among those with intermittent claudication (10.9% [44 patients] and 9.4% [38 patients], respectively; hazard ratio, 1.18; 95% CI, 0.72 to 1.93) (Table 2). There was also no significant difference in the incidence of death between the treatment groups at 1 year of follow-up among patients with either chronic limb-threatening ischemia or intermittent claudication. As shown in the Kaplan–Meier analysis, deaths occurred at a continuous rate during the entire follow-up period in the overall population (Fig. 2A) and in the cohort of patients with chronic limb-threatening ischemia (Fig. 2B), but the event rate was higher during the later 2 years of the trial than during the earlier 2 years in the cohort of patients with intermittent claudication, the group with the lower overall risk of death (Fig. 2C). In the overall population, the mortality rate per 100 patient-years was 10.4% among patients who received treatment with drug-coated devices and 9.8% among those who received treatment with uncoated devices.

DISCUSSION

In this randomized trial in which the use of paclitaxel-coated devices is being compared with uncoated devices for the endovascular treatment of peripheral artery disease, an unplanned interim analysis did not show a significantly higher mortality rate with paclitaxel-coated devices. The rationale for publishing these total mortality data ahead of completion of the trial is twofold. First, we sought to reduce patients' and physicians' concerns regarding the safety of paclitaxel-coated devices, and second, we considered the data to be important to support completion of ongoing trials investigating the efficacy of such devices in peripheral artery disease.

Since December 2018, concerns regarding the safety of paclitaxel-coated devices in peripheral artery disease have led to a scientific and clinical deadlock. An increased late mortality signal was first reported in a meta-analysis of randomized trials by Katsanos et al.[8] and later repeated by both the FDA and an independent physician group (Vas-

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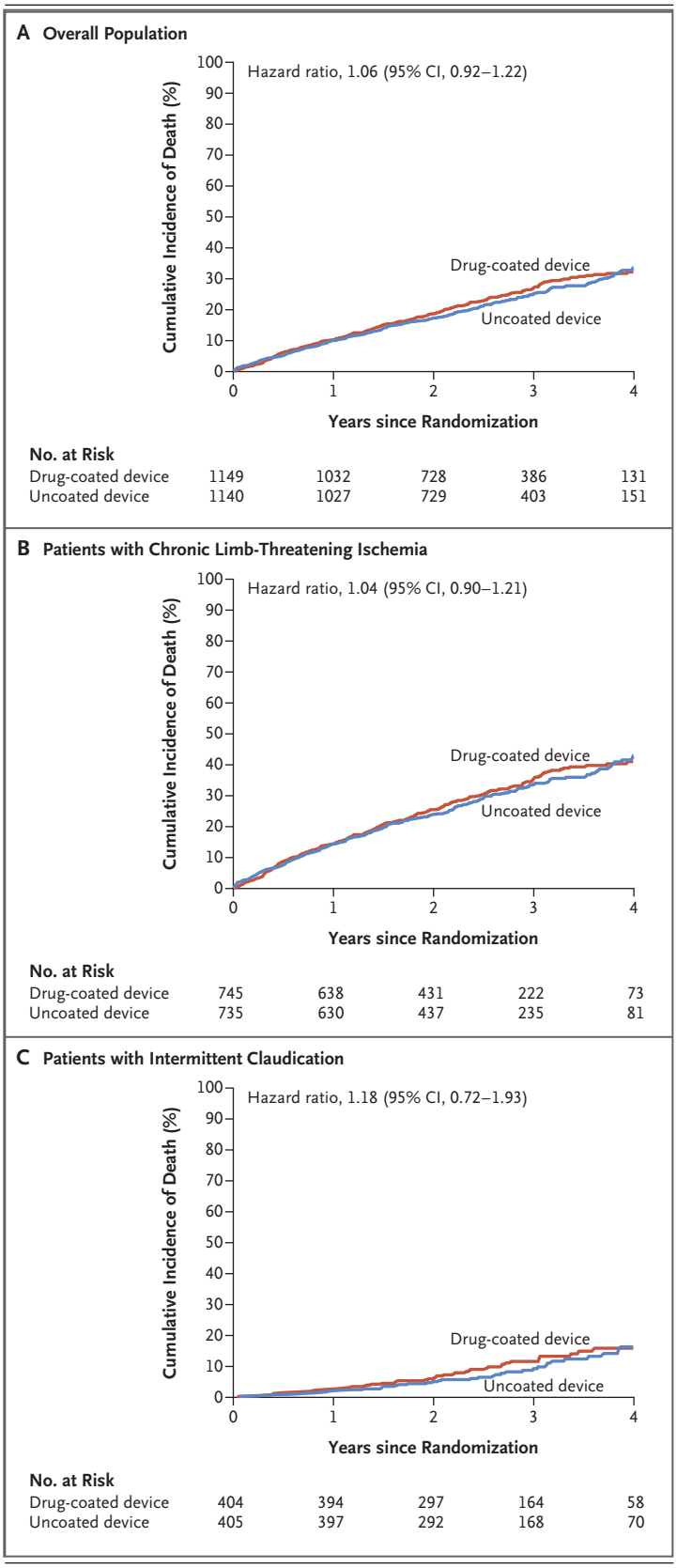
Figure 2. Kaplan–Meier Estimates of All-Cause Mortality.
Shown are Kaplan–Meier estimates of all-cause mortality during the entire follow-up period in the overall population (Panel A), in the cohort of patients with chronic limb-threatening ischemia (Panel B), and in the cohort of patients with intermittent claudication (Panel C). Formal testing showed that the assumptions of proportional hazards were not violated. The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.



cular Interventional Advances) with the use of patient-level data from the same trials.[12,17] Other meta-analyses reached diverging conclusions, despite the fact that they were based on similar target populations and vessel segments.[9,11,18] Observational studies have not replicated the signal, even after efforts were made to adjust for confounders and data imbalances.[19-21]

No plausible mechanism for higher mortality has been identified. The doses of paclitaxel that are delivered by drug-coated devices are very small as compared with doses used in other applications, such as cancer treatment.[22,23] Some authors have suggested that the extended half-life of the crystalline paclitaxel formulation used for coating balloons and stents may exert negative long-term effects[8,24,25] and that an unknown amount of the compound may embolize downstream of the target lesion.[11,26] Others have suggested that the prevention of restenosis by the use of drug-coated devices may lead to infrequent contact between patients and health care personnel during follow-up, possibly resulting in suboptimal secondary prevention pharmacotherapy and thereby an increased risk of death.[13] Finally, given that none of the previously published randomized trials on this topic were designed or powered to investigate long-term safety, the reported mortality signal may have been caused by attrition bias that was potentiated in the meta-analysis or may even have been the result of chance.

The demographic data, coexisting conditions, and incidence of death during follow-up in this trial population are consistent with data from the complete Swedish national database on revascularizations for peripheral artery disease.[27] The aggregate number of deaths in this interim analysis was 574, which is more than the combined total number of unique deaths reported in 36 previously published randomized trials.[8,11,28] Among

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these trials, the largest number of deaths reported in a single trial was 119.[28] The total duration of follow-up in our trial (up to 4 years) was longer than that of most trials, with no signs of diverging event-rate curves over time, and no patients were lost to follow-up. The number of protocol violations related to the initial treatment assignments is also low in this trial.

Still, this trial has limitations. First, the open-label design could have the potential to introduce bias. However, the end point of all-cause mortality reported herein is less sensitive to this particular limitation than more subjective outcomes. Second, this interim analysis was not a prespecified part of the trial protocol. However, this analysis was recommended by an independent data and safety monitoring committee in order to alleviate patients' and physicians' concerns after the publishing of the meta-analysis that brought into question the safety of paclitaxel-coated devices.[8] Third, because there were few deaths among patients with intermittent claudication, the confidence interval for that particular group of patients was wide (ranging from 0.72 to 1.93), and therefore, we cannot completely exclude the possibility of a difference in mortality in this subgroup. Fourth, the use of "low-dose" (rather than "high-dose") paclitaxel-coated devices was relatively common in the trial, and this may have influenced our results. Fifth, there was variation in the treatment effect among the centers, although it seems likely that this variation is due to chance rather than to variation in center characteristics. Finally, no analysis of the efficacy of paclitaxel-coated devices is included in this interim report; these data are planned to be provided in the final clinical trial report after formal completion of the trial.

The SWEDEPAD trial was not primarily intended for analysis of total mortality. The main purpose was to determine whether drug-coating technology ultimately improves the lives of patients with symptomatic peripheral artery disease by preventing amputations and improving health-related quality of life. Because this interim analysis does not show a significantly higher incidence of death resulting from the use of paclitaxel-coated devices than from the use of uncoated devices, we believe that equipoise remains, and recruitment has recently resumed, with enrollment of patients in both the chronic limb-threatening ischemia cohort and the intermittent claudication cohort.

In this randomized trial in which the use of paclitaxel-coated devices is being compared with uncoated devices for the endovascular treatment of peripheral artery disease, an unplanned interim analysis did not show a significantly higher all-cause mortality rate with paclitaxel-coated devices during 1 to 4 years of follow-up.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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