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# Longitudinal Assessment of Safety of Femoropopliteal Endovascular Treatment With Paclitaxel-Coated Devices Among Medicare Beneficiaries
## The SAFE-PAD Study

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**IMPORTANCE** Paclitaxel-coated peripheral devices have been associated with increased mortality, yet this harm signal has not been replicated outside of meta-analyses of small trials.

**OBJECTIVE** To provide a longitudinal assessment of the safety of femoropopliteal endovascular treatment with peripheral drug-coated devices (DCDs) among Medicare beneficiaries.

**DESIGN, SETTING, AND PARTICIPANTS** SAFE-PAD (Safety Assessment of Femoropopliteal Endovascular Treatment With Paclitaxel-Coated Devices) was a retrospective cohort study designed with the US Food and Drug Administration to evaluate the noninferiority of mortality between DCDs and non–drug-coated devices (NDCDs) for femoropopliteal revascularization performed in 2978 inpatient and outpatient facilities in the US from April 1, 2015, through December 31, 2018. Evaluation of the primary outcome was assessed through May 31, 2020. Participants were Medicare fee-for-service beneficiaries 66 years and older with 1 or more years of enrollment prior to femoropopliteal revascularization. Prespecified subgroups included low-risk cohorts, procedure location, disease severity, and device type. Inverse probability weighting was used to account for imbalances of observed characteristics. Sensitivity analyses were used to evaluate the potential influence of unmeasured confounding.

**EXPOSURES** Treatment with DCDs vs NDCDs as determined by claims codes during the index procedure.

**MAIN OUTCOMES AND MEASURES** The primary outcome was all-cause mortality. Secondary outcomes included repeated hospitalization, repeated lower extremity revascularization, and lower extremity amputation. Falsification end points were acute myocardial infarction, congestive heart failure, and pneumonia.

**RESULTS** Of 168 553 patients, 70 584 (41.9%) were treated with a DCD. The mean (SD) age was 77.0 (7.6) years, 75 744 (44.9%) were female, 136 916 of 167 197 (81.9%) were White individuals, 85 880 of 168 553 (51.0%) had diabetes, 82 554 of 168 553 (49.0%) used tobacco, 78 665 of 168 553 (45.7%) had critical limb ischemia (CLI), and 13 296 of 168 553 (7.9%) had a prior amputation. Median follow-up was 2.72 years (interquartile range, 0.87-3.77; longest, 5.16 years). After weighting, the cumulative incidence of all-cause mortality was 53.8% with DCDs and 55.1% with NDCDs (hazard ratio [HR], 0.95; 95% CI, 0.94-0.97; noninferiority $P < .001$). Cox regression and instrumental variable analyses were consistent with the primary findings. No harm associated with DCDs was observed among subgroups, including those treated with stents (HR, 0.97; 95% CI, 0.95-1.00) or balloons (HR, 0.94; 95% CI, 0.92-0.96), with or without CLI (CLI: HR, 0.95; 95% CI, 0.93-0.97; non-CLI: HR, 0.97; 95% CI, 0.95-0.99), and those within the lowest quartile of total comorbidities (HR, 0.95; 95% CI, 0.92-0.99).

**CONCLUSIONS AND RELEVANCE** In this initial report from the SAFE-PAD cohort study, DCDs were found to be noninferior to NCDCs in respect to mortality through a median follow-up of 2.72 years. This finding remained robust in sensitivity analyses and was consistent across prespecified subgroups.

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Editorial
Supplemental content

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Medical and structured exercise therapies are the primary strategies for managing patients with symptomatic peripheral artery disease (PAD).[1] However, revascularization may be needed for select patients with life-limiting symptoms unresponsive to noninvasive treatments or critical limb ischemia (CLI). When femoropopliteal artery percutaneous revascularization is performed, drug-coated peripheral stents and balloons are frequently used to reduce the long-term risk of clinically driven target lesion revascularization[2-4] and are endorsed by societies as first-line therapies during femoropopliteal artery intervention.[5] In December 2018, a meta-analysis of randomized clinical trials involving paclitaxel drug-coated devices (DCDs) for the treatment of PAD involving the femoropopliteal artery found an association with higher mortality through 5 years compared with non-drug-coated devices (NDCDs).[6] The results of this study led to a number of changes affecting the care of patients with PAD, including halting of ongoing randomized clinical trials,[7] placement of restrictions on peripheral DCD use by medical centers,[8] and publication of a letter of caution to clinicians by the US Food and Drug Administration (FDA).[9] Subsequently, the signal of harm associated with DCDs was replicated in an internal meta-analysis by the FDA.[10] However, the limitations of the small randomized trials studied—in particular, the lack of comprehensive ascertainment of long-term survival and the prospect of substantial nonrandom loss to follow-up[11]—were recognized as potential sources of irreconcilable bias. Following an advisory committee meeting in June 2019,[12] the FDA allowed these devices to remain on the market, but with severe restrictions and a call for additional long-term safety data.[13]

Although prior cardiovascular device safety concerns have been addressed with large-scale randomized clinical trials,[14,15] a de novo trial powered to evaluate long-term mortality among a population of patients with PAD not previously exposed to paclitaxel was thought to be infeasible.[16] Aligned with the mission of the 21st Century Cures Act,[17] the FDA engaged academic partners to explore the utility of real-world claims and registry data to provide a longitudinal mechanism to evaluate the safety of these devices. Strengthened by the sample size and fidelity of ascertaining all-cause mortality, data from the Centers for Medicare & Medicaid Services (CMS) have emerged as a vital resource to address this safety concern.[12,18,19]

Designed with feedback from the FDA, the prespecified, multiyear Safety Assessment of Femoropopliteal Endovascular Treatment With Paclitaxel-Coated Devices (SAFE-PAD) study was created to provide an ongoing evaluation of the safety of DCDs for femoropopliteal artery revascularization using CMS claims data.[20] These data build off prior investigations using Medicare data by including both inpatient and outpatient procedures, extending survival follow-up time, investigating consistency of the harm signal among key patient subgroups, and sensitivity testing for the potential influence of model misspecification and unmeasured confounding.

### Key Points

**Question** Are drug-coated devices used during femoropopliteal artery endovascular treatment noninferior to non–drug-coated devices in respect to mortality among Medicare beneficiaries?

**Findings** In this cohort analysis of 168 553 Medicare fee-for-service beneficiaries who underwent femoropopliteal artery revascularization from 2015 through 2018, the weighted cumulative incidence of mortality at 5 years was 53.8% among those treated with drug-coated devices and 55.1% among those treated with non–drug-coated devices.

**Meaning** While this initial report demonstrated that peripheral drug-coated devices were noninferior for mortality to non–drug-coated devices, the ongoing study will provide a mechanism to continue the safety evaluation of these devices.

## Methods

### Data Source and Study Sample

The SAFE-PAD study (ClinicalTrials.gov identifier: NCT04496544) was conducted in accordance with a prespecified statistical analysis plan[20] designed by investigators from the Richard A. and Susan F. Smith Center for Outcomes Research in Cardiology at Beth Israel Deaconess Medical Center with feedback from members of the FDA's Center for Devices and Radiological Health and Office of Clinical Evidence and Analysis. The study was conducted in compliance with the data use agreement in place between CMS and Beth Israel Deaconess Medical Center. The study was approved by the institutional review board of Beth Israel Deaconess Medical Center, with a waiver of informed consent for retrospective data analysis. This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

The study cohort included procedures from April 1, 2015, through December 31, 2018, among Medicare fee-for-service beneficiaries 66 years and older with 1 or more years of enrollment prior to their index procedure. Procedures were required to have involved femoropopliteal artery revascularization with either a DCD (defined as a drug-eluting stent with or without a drug-coated balloon, a drug-coated balloon with a bare metal stent, or a drug-coated balloon alone) or an NDCD (bare metal stent with or without uncoated percutaneous transluminal angioplasty, or percutaneous transluminal angioplasty alone). Other exclusions were procedures with missing age or missing fee-for-service coverage in the past year (eFigure 1 in the Supplement).

### Treatment Exposure

Treatment with DCDs was determined using the first procedure recorded during the study period. The methods and claims codes used to identify device exposure are detailed in eMethods 1 and eTable 1 in the Supplement. A prior validation study of the coding scheme used to identify DCDs and NDCDs demonstrated high negative and positive predictive values.[20] For the subgroup analyses of stent implantation and

angioplasty, patients were included in a single subgroup. Treatment with DCDs superseded NDCDs for group assignment, and subsequently, stent implantation superseded balloon angioplasty.

### Patient, Procedural, and Hospital Characteristics

Baseline demographic characteristics were measured as of the index procedure date. Race/ethnicity was classified based on self-report using categories specified by Medicare at the time of Medicare enrollment. Race/ethnicity was included as a covariate in the analysis because it is associated with mortality.[21] Comorbidities were ascertained using the CMS Chronic Conditions Warehouse common chronic conditions.[22] In addition, *International Classification of Diseases, Ninth Revision, Clinical Modification* and *International Classification of Diseases, Tenth Revision, Clinical Modification* claims codes ascertained via a 1-year lookback period were used to identify current or prior tobacco use, CLI, and prior amputation (eTable 2 in the Supplement).

Procedural characteristics included adjunctive atherectomy, stent placement, and setting. Hospital characteristics were retrieved from the 2016 American Hospital Association Annual Survey File, which includes teaching status, region, and bed capacity.

Among patients with Part D pharmacy data, prescription data were ascertained at baseline and annually through 3 years. Patients were considered to be receiving therapy if they filled a prescription within their refill window (ie, 30 or 90 days) preceding each time point, with an additional 30-day grace period to allow for late refills.

### End Points

The primary end point was all-cause mortality, ascertained from the Vital Status file through May 31, 2020. Secondary end points included all-cause repeated hospitalization; repeated lower extremity endovascular or surgical revascularization; and lower extremity amputation (eTable 3 in the Supplement). Both repeated revascularization and amputations could occur to either the index or nonindex leg, as laterality cannot be determined using Current Procedural Terminology codes.

The primary study aim was to examine whether mortality associated with DCDs was noninferior to that observed with NDCDs. Because DCDs offer the benefit of having reduced rates of restenosis[3,4] and were not designed to reduce mortality, we selected a noninferiority design for this study. Our preliminary data set composed of 90 966 NDCD procedures suggested an annual total mortality rate of 18.7%. We considered a 5% relative increase in the mortality rate as the noninferiority margin. The null hypothesis for this analysis was that the hazard ratio (HR) of all-cause mortality of DCDs compared with NDCDs is 1.05 or greater, and the alternative hypothesis was that the HR of all-cause mortality of DCDs compared with NDCDs is less than 1.05. Because there will be 7 semiannual data updates over the course of SAFE-PAD, to control the family-wise type I error rate at 0.05, we applied the Bonferroni approach so that each individual test will be performed at the level of 0.007 (1-sided).

### Statistical Analysis

We used inverse probability weighting as the primary analytic tool for the end points to correct for potential confounding owing to imbalances in observed characteristics.[23,24] After computing the probability of being in the DCD group, we examined the overlap in the distributions of the propensity score of the 2 arms (eFigure 2 in the Supplement) and the balance of characteristics between groups after weighting (eFigure 3 in the Supplement). Standardized mean differences (SMDs) were calculated preweighting and postweighting, with an SMD greater than 0.1 considered significant.[25] The model created in this first step was done using a data set that did not include outcome data and was locked prior to moving on to the second step. In the second step, we fit a weighted Cox proportional hazards regression model with group membership as the only covariate. The Kaplan-Meier estimation of the cumulative incidence of mortality and log-rank test was computed. Statistical inference was performed using the bootstrap method.

We performed 4 sensitivity analyses to evaluate the influence of model misspecification or uncontrolled confounders. First, as the inverse probability weighting method could yield biased estimates if the propensity score model was misspecified, we used multivariable Cox regression as an alternative approach. The proportional hazards assumption was evaluated by plotting the HRs between DCDs and NDCDs with survival over time (eFigure 4 in the Supplement). Second, to examine the robustness of the inference with respect to uncontrolled confounding, we artificially created a confounder and reestimated the association between DCD exposure and mortality.[26] By gradually varying the prevalence of the uncontrolled confounder and increasing its strength as measured by the association with treatment exposure and the end point, we were able to assess how strong it had to be to reverse the conclusions of the primary analysis (eMethods 1 in the Supplement). Third, as an alternative strategy to address uncontrolled confounders arising from treatment selected bias, we performed an instrumental variable analysis. For this analysis, we used each institution's proportional use of DCDs as the instrument and 2-stage regression involving Cox models (eMethods 2 in the Supplement). Lastly, we used falsification end point testing to assess the presence of unmeasured confounding.[27] The prespecified falsification end points were (1) congestive heart failure requiring hospitalization, (2) acute myocardial infarction requiring hospitalization, and (3) pneumonia requiring hospitalization (eTable 4 in the Supplement).

We repeated the primary analysis among the following prespecified subgroups: (1) treatment with stents vs balloon angioplasty, (2) low-risk patients aged 66 to 70 years with 2 or fewer comorbidities and no history of CLI, (3) patients in the lowest quartile of total comorbidities, (4) index procedures performed in an inpatient vs outpatient setting, and (5) patients with or without a history of CLI.

A similar inverse probability weighting approach as described for the primary end point was used to analyze all secondary end points and subgroups. For each analysis, propensity scores were recalculated and used for weighting. To

deal with the competing risk of death, we estimated HRs from Cox models based on both the subdistribution framework and a cause-specific hazard.[28]

Data linkage and analyses were performed using SAS, version 9.4 (SAS Institute). A total of 4251 procedures had 1 or more missing characteristic values and were not included in the adjusted analysis.

## Results

### Study Cohort

A total of 287 866 femoropopliteal artery revascularization procedures were identified during the study period. Following exclusions, 168 553 Medicare fee-for-service patients treated at 2978 institutions were included in the analysis (eFigure 1 in the Supplement), and 70 584 (41.9%) were treated with a DCD during their index procedure. The mean (SD) age was 77.0 (7.6) years; 75 744 (44.9%) were female, and 136 916 (81.9%) were White (**Table 1**). Cardiovascular comorbidities included hypertension in 135 272 (80.3%), hyperlipidemia in 118 567 (70.3%), ischemic heart disease in 110 100 (65.3%), diabetes in 85 880 (51.0%), tobacco use in 82 554 (49.0%), congestive heart failure in 63 796 (37.9%), and acute myocardial infarction in 7748 (4.6%). With regard to PAD, 78 665 (46.7%) had a diagnosis of CLI, and 13 296 (7.9%) had a prior amputation. Procedurally, 80 228 (47.6%) procedures occurred in an inpatient setting, 67 689 (40.2%) involved stent placement, and 59 142 of 168 353 (35.1%) required adjunctive treatment with atherectomy.

Among the study cohort, 41 627 patients (24.7%) had a repeated femoropopliteal artery procedure during follow-up. Of the 97 969 patients (58.1%) initially treated with an NDCD, 8750 (8.9%) received subsequent treatment with a DCD.

### Characteristics Between Treatment Groups

Prior to weighting, sociodemographic and patient characteristics were generally balanced between groups (Table 1). Procedurally, patients treated with DCDs vs NDCDs were more likely to be treated with adjunctive atherectomy (42.5% vs 29.8%; SMD, 0.27) and less likely to be treated as an inpatient (41.4% vs 52.1%; SMD, 0.22). Patients treated with DCDs were more likely to be treated at centers with higher volumes of procedures during the study period (mean, 375.6 procedures vs 331.8 procedures; SMD, 0.15). These differences were no longer apparent after weighting (eFigure 3 in the Supplement).

### Medication Use

Among 130 919 patients (77.7%) with pharmacy data, baseline medication use was similar between groups (eTable 5 in the Supplement). At 1 year, patients who were treated with a DCD were more often receiving a P2Y12 inhibitor (56.6% vs 50.6% for NDCD; SMD, 0.12). This difference persisted at 2 and 3 years. No other differences in medication use were observed between groups at each time point.

### Primary Outcome

The median (interquartile range [IQR]) study follow-up was 2.72 (0.87-3.77) years, and longest follow-up was 5.16 years. Prior to weighting, DCDs were not associated with increased mortality compared with NDCDs (cumulative incidence of death: 51.6% vs 56.7%, respectively; HR, 0.84; 95% CI, 0.82-0.85; $P < .001$) (**Figure 1**A). After weighting, this association persisted, with no association between DCDs and increased mortality compared with NDCDs (cumulative incidence of death: 53.8% vs 55.1%; HR, 0.95; 95% CI, 0.94-0.97; noninferiority $P < .001$; Figure 1B).

### Sensitivity Analyses

The multivariable Cox regression analysis demonstrated similar findings as the primary analysis, with no association between DCDs and increased death compared with NDCDs (HR, 0.94; 95% CI, 0.93-0.96; noninferiority $P < .001$). For the missing confounder analysis, we considered a binary confounder with aggregate prevalence of 10%, 20%, and 50%, respectively (eMethods 1, eFigures 5-7 in the Supplement). **Figure 2** shows how measured covariates included in the statistical adjustment in this analysis compare with unmeasured confounder thresholds required to overturn the primary noninferiority results. No single measured covariate would have met the criterion to overturn the noninferiority result.

For the instrumental variable analysis, the median (IQR) proportion of DCD use among all femoropopliteal artery revascularization procedures was 40.9% (26.7%-54.4%) (eTable 6 and eFigure 8 in the Supplement). In the instrumental variable analysis, there was no association between DCD use and mortality at each time point (**Table 2**).

Of the falsification end points of acute myocardial infarction and congestive heart failure, the adjusted cumulative incidences were similar between patients treated with DCDs and NDCDs (eTable 7 and eFigures 9 and 10 in the Supplement). For pneumonia, the cumulative incidence of events was similar between treatment groups through 730 days (eFigure 11 in the Supplement). After 730 days, there was a greater increase in events among patients treated with NDCDs.

### Secondary Outcomes

Of the secondary outcomes, the adjusted cumulative incidence of all-cause hospitalization was modestly lower among patients treated with vs without DCDs (eTable 8 in the Supplement). The cumulative incidence of repeated endovascular femoropopliteal artery revascularization to either leg was modestly greater among patients treated with DCDs compared with NDCDs, while DCD treatment was associated with a lower use of surgical revascularization and amputation at all time points.

### Prespecified Subgroups

There was consistency of safety associated with DCDs across all prespecified subgroups (**Figure 3**; eFigures 12-19 and eTables 9-16 in the Supplement). In particular, of the total cohort, 67 689 (40.2%) were treated with a stent during their index procedure, 27 963 (41.3%) of whom received a drug-eluting stent. Following weighting, the HR comparing survival between drug-eluting stent and bare metal stent was 0.97

Table 1. Baseline Characteristics of Patients Undergoing Femoropopliteal Artery Revascularization, Stratified by Treatment With or Without Drug-Coated Devices

| | Unweighted | | | | Weighted | | |
|---|---|---|---|---|---|---|---|
| | No./No. (%) | | | | % | | |
| Characteristic | Overall (n = 168 553) | NDCDs (n = 97 969) | DCDs (n = 70 584) | SMD | NDCDs | DCDs | SMD |
| **Patient characteristics** | | | | | | | |
| Age, mean (SD), y | 77.02 (7.59) | 77.25 (7.70) | 76.71 (7.42) | 0.07 | 77.03 (7.08) | 77.04 (8.23) | 0.001 |
| Sex | | | | | | | |
| Female | 75 744/168 553 (44.9) | 44 205/97 969 (45.1) | 31 539/70 584 (44.7) | 0.01 | 44.97 | 45.01 | 0.001 |
| Male | 92 809/168 553 (55.1) | 53 764/97 969 (54.9) | 39 045/70 584 (55.3) | 0.01 | 55.04 | 55.01 | <0.001 |
| Race/ethnicity | | | | | | | |
| White | 136 916/167 197 (81.9) | 79 070/97 226 (81.3) | 57 846/69 971 (82.7) | 0.04 | 81.96 | 81.87 | 0.002 |
| Black | 21 590/167 197 (12.9) | 13 112/97 226 (13.5) | 8478/69 971 (12.1) | 0.04 | 12.90 | 12.98 | 0.002 |
| Asian | 1488/167 197 (0.9) | 913/97 226 (0.9) | 575/69 971 (0.8) | 0.01 | 0.89 | 0.90 | <0.001 |
| Hispanic | 4053/167 197 (2.4) | 2356/97 226 (2.4) | 1697/69 971 (2.4) | <0.001 | 2.39 | 2.39 | <0.001 |
| Native American | 1106/167 197 (0.7) | 591/97 226 (0.6) | 515/69 971 (0.7) | 0.02 | 0.66 | 0.66 | <0.001 |
| Other[a] | 2044/167 197 (1.2) | 1184/97 226 (1.2) | 860/69 971 (1.2) | 0.001 | 1.21 | 1.20 | <0.001 |
| Comorbidities | | | | | | | |
| Acquired hypothyroidism | 29 418/168 553 (17.5) | 17 139/97 969 (17.5) | 12 279/70 584 (17.4) | 0.003 | 17.43 | 17.43 | <0.001 |
| Acute myocardial infarction | 7748/168 553 (4.6) | 4778/97 969 (4.9) | 2970/70 584 (4.2) | 0.03 | 4.56 | 4.55 | <0.001 |
| Alzheimer disease | 7636/168 553 (4.5) | 4785/97 969 (4.9) | 2851/70 584 (4.0) | 0.04 | 4.55 | 4.60 | 0.003 |
| Alzheimer disease and related[b] | 28 904/168 553 (17.1) | 17 886/97 969 (18.3) | 11 018/70 584 (15.6) | 0.07 | 17.16 | 17.27 | 0.003 |
| Anemia | 77 592/168 553 (46.0) | 46 339/97 969 (47.3) | 31 253/70 584 (44.3) | 0.06 | 45.84 | 45.89 | 0.001 |
| Arthritis (RA/OA) | 66 730/168 553 (39.6) | 38 605/97 969 (39.4) | 28 125/70 584 (39.9) | 0.009 | 39.63 | 39.65 | 0.001 |
| Asthma | 9989/168 553 (5.9) | 5948/97 969 (6.1) | 4041/70 584 (5.7) | 0.02 | 5.90 | 5.90 | <0.001 |
| Atrial fibrillation | 31 051/168 553 (18.4) | 18 637/97 969 (19.0) | 12 414/70 584 (17.6) | 0.04 | 18.39 | 18.40 | <0.001 |
| Benign prostatic hyperplasia | 21 676/168 553 (12.9) | 12 717/97 969 (13.0) | 8959/70 584 (12.7) | 0.009 | 12.85 | 12.85 | <0.001 |
| Cancer | | | | | | | |
| Breast | 4264/168 553 (2.5) | 2547/97 969 (2.6) | 1717/70 584 (2.4) | 0.01 | 2.53 | 2.53 | <0.001 |
| Colorectal | 3294/168 553 (2.0) | 1975/97 969 (2.0) | 1319/70 584 (1.9) | 0.01 | 1.96 | 1.98 | <0.001 |
| Endometrial | 638/168 553 (0.4) | 377/97 969 (0.4) | 261/70 584 (0.4) | 0.003 | 0.38 | 0.38 | <0.001 |
| Lung | 3630/168 553 (2.2) | 2135/97 969 (2.2) | 1495/70 584 (2.1) | 0.004 | 2.15 | 2.15 | <0.001 |
| Prostate | 7625/168 553 (4.5) | 4441/97 969 (4.5) | 3184/70 584 (4.5) | 0.001 | 4.51 | 4.50 | <0.001 |
| Cataract | 23 563/168 553 (14.0) | 13 283/97 969 (13.6) | 10 280/70 584 (14.6) | 0.03 | 13.93 | 13.89 | 0.001 |
| Chronic kidney disease | 84 519/168 553 (50.1) | 49 289/97 969 (50.3) | 35 230/70 584 (49.9) | 0.008 | 50.00 | 50.03 | 0.001 |
| Congestive heart failure | 63 796/168 553 (37.9) | 38 191/97 969 (39.0) | 25 605/70 584 (36.3) | 0.06 | 37.73 | 37.76 | <0.001 |
| COPD/bronchiectasis | 49 949/168 553 (29.6) | 29 175/97 969 (29.8) | 20 774/70 584 (29.4) | 0.008 | 29.66 | 29.66 | <0.001 |
| Critical limb ischemia | 78 665/168 553 (46.7) | 46 390/97 969 (47.4) | 32 275/70 584 (45.7) | 0.03 | 46.81 | 47.10 | 0.006 |
| Depression | 36 501/168 553 (21.7) | 21 529/97 969 (22.0) | 14 972/70 584 (21.2) | 0.02 | 21.64 | 21.69 | 0.001 |
| Diabetes | 85 880/168 553 (51.0) | 49 416/97 969 (50.4) | 36 464/70 584 (51.7) | 0.02 | 50.85 | 50.92 | 0.001 |
| Glaucoma | 13 103/168 553 (7.8) | 7510/97 969 (7.7) | 5593/70 584 (7.9) | 0.01 | 7.76 | 7.76 | <0.001 |
| Hip/pelvic fracture | 2390/168 553 (1.4) | 1486/97 969 (1.5) | 904/70 584 (1.3) | 0.02 | 1.42 | 1.43 | <0.001 |
| Hyperlipidemia | 118 567/168 553 (70.3) | 67 475/97 969 (68.9) | 51 092/70 584 (72.4) | 0.08 | 70.30 | 70.26 | 0.001 |
| Hypertension | 135 272/168 553 (80.3) | 77 690/97 969 (79.3) | 57 582/70 584 (81.6) | 0.06 | 80.23 | 80.21 | <0.001 |
| Ischemic heart disease | 110 100/168 553 (65.3) | 63 233/97 969 (64.5) | 46 867/70 584 (66.4) | 0.04 | 65.21 | 65.18 | <0.001 |
| Osteoporosis | 12 524/168 553 (7.4) | 7474/97 969 (7.6) | 5050/70 584 (7.2) | 0.02 | 7.43 | 7.43 | <0.001 |
| Prior amputation | 13 296/168 553 (7.9) | 8211/97 969 (8.4) | 5085/70 584 (7.2) | 0.04 | 7.87 | 7.93 | 0.002 |
| Stroke/TIA | 15 715/168 553 (9.3) | 9508/97 969 (9.7) | 6207/70 584 (8.8) | 0.03 | 9.31 | 9.33 | <0.001 |
| Tobacco use | 82 554/168 553 (49.0) | 48 526/97 969 (49.5) | 34 028/70 584 (48.2) | 0.03 | 49.03 | 48.99 | <0.001 |

(continued)

Table 1. Baseline Characteristics of Patients Undergoing Femoropopliteal Artery Revascularization, Stratified by Treatment With or Without Drug-Coated Devices (continued)

| | Unweighted | | | | Weighted | | |
|---|---|---|---|---|---|---|---|
| | No./No. (%) | | | | % | | |
| Characteristic | Overall (n = 168 553) | NDCDs (n = 97 969) | DCDs (n = 70 584) | SMD | NDCDs | DCDs | SMD |
| **Procedure characteristics** | | | | | | | |
| Adjunctive atherectomy | 59 142/168 353 (35.1) | 29 167/97 824 (29.8) | 29 975/70 529 (42.5) | 0.27 | 35.16 | 35.15 | <0.001 |
| Inpatient procedure | 80 228/168 553 (47.6) | 51 031/97 969 (52.1) | 29 197/70 584 (41.4) | 0.22 | 47.70 | 47.82 | 0.002 |
| Stent placement | 67 689/168 553 (40.2) | 39 726/97 969 (40.6) | 27 963/70 584 (39.6) | 0.02 | 41.17 | 41.35 | 0.004 |
| **Hospital characteristics** | | | | | | | |
| Procedural volume, mean (SD)[c] | 350.18 (284.47) | 331.76 (267.60) | 375.64 (304.44) | 0.15 | 349.54 (266.33) | 348.66 (306.52) | 0.003 |
| Teaching hospital | 120 093/165 836 (72.4) | 69 752/96 233 (72.5) | 50 341/69 603 (72.3) | 0.004 | 72.35 | 72.28 | 0.002 |
| Region | | | | | | | |
| Northeast | 7117/165 836 (4.3) | 4185/96 233 (4.4) | 2932/69 603 (4.2) | 0.007 | 4.27 | 4.26 | 0.001 |
| Mid-Atlantic | 21 574/165 836 (13.0) | 12 479/96 233 (13.0) | 9095/69 603 (13.1) | 0.003 | 12.98 | 13.02 | 0.001 |
| Northeast Central | 28 852/165 836 (17.4) | 16 482/96 233 (17.1) | 12 370/69 603 (17.8) | 0.02 | 17.42 | 17.42 | <0.001 |
| Southeast Central | 13 213/165 836 (8.0) | 7869/96 233 (8.2) | 5344/69 603 (7.7) | 0.02 | 7.98 | 7.98 | <0.001 |
| Northwest Central | 12 770/165 836 (7.7) | 6762/96 233 (7.0) | 6008/69 603 (8.6) | 0.06 | 7.63 | 7.63 | <0.001 |
| Southwest Central | 22 767/165 836 (13.7) | 13 188/96 233 (13.7) | 9579/69 603 (13.8) | 0.002 | 13.83 | 13.83 | <0.001 |
| South Atlantic | 34 675/165 836 (20.9) | 20 897/96 233 (21.7) | 13 778/69 603 (19.8) | 0.05 | 20.92 | 20.92 | <0.001 |
| Mountain | 8346/165 836 (5.0) | 4594/96 233 (4.8) | 3752/69 603 (5.4) | 0.03 | 5.01 | 5.00 | <0.001 |
| Pacific | 15 776/165 836 (9.5) | 9164/96 233 (9.5) | 6612/69 603 (9.5) | 0.001 | 9.50 | 9.46 | 0.001 |
| Other | 746/165 836 (0.5) | 613/96 233 (0.6) | 133/69 603 (0.2) | 0.07 | 0.45 | 0.48 | 0.005 |
| Bed size | | | | | | | |
| 6-24 | 145/165 836 (0.1) | 82/96 233 (0.1) | 63/69 603 (0.1) | 0.002 | 0.09 | 0.09 | <0.001 |
| 25-49 | 1391/165 836 (0.8) | 872/96 233 (0.9) | 519/69 603 (0.8) | 0.02 | 0.83 | 0.84 | <0.001 |
| 50-99 | 6995/165 836 (4.2) | 3981/96 233 (4.1) | 3014/69 603 (4.3) | 0.01 | 4.21 | 4.23 | 0.001 |
| 100-199 | 26 715/165 836 (16.1) | 15 462/96 233 (16.1) | 11 253/69 603 (16.2) | 0.003 | 16.23 | 16.32 | 0.002 |
| 200-299 | 33 788/165 836 (20.4) | 19 360/96 233 (20.1) | 14 428/69 603 (20.7) | 0.02 | 20.38 | 20.44 | 0.002 |
| 300-399 | 30 963/165 836 (18.7) | 17 796/96 233 (18.5) | 13 167/69 603 (18.9) | 0.01 | 18.66 | 18.59 | 0.002 |
| 400-499 | 18 952/165 836 (11.4) | 11 354/96 233 (11.8) | 7598/69 603 (10.9) | 0.03 | 11.47 | 11.45 | <0.001 |
| ≥500 | 46 887/165 836 (28.3) | 27 326/96 233 (28.4) | 19 561/69 603 (28.1) | 0.007 | 28.13 | 28.03 | 0.002 |

Abbreviations: COPD, chronic obstructive pulmonary disease; DCD, drug-coated device; NDCD, non–drug-coated device; RA/OA, rheumatoid arthritis/osteoarthritis; SMD, standardized mean difference; TIA, transient ischemic attack.

[a] Specific categories included in "Other" were not provided in the Centers for Medicare & Medicaid Services data.

[b] Alzheimer disease and related disorders or senile dementia.

[c] Total femoropopliteal artery peripheral procedure volume during the study period.

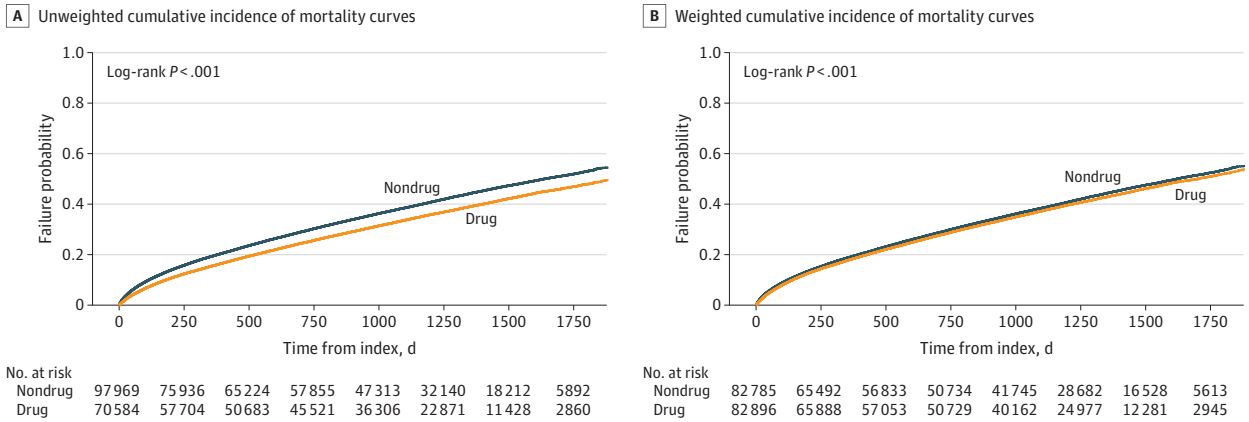
(95% CI, 0.95-1.00). In addition, 100 864 (59.8%) were treated with balloon angioplasty alone during the index procedure, of whom 42 621 (42.3%) were treated with a drug-coated balloon. Following weighting, the HR comparing survival between drug-coated and uncoated balloon angioplasty was 0.94 (95% CI, 0.92-0.96).

Furthermore, 78 665 (46.7%) had a diagnosis of CLI, and 89 888 (53.3%) had non-CLI PAD. Among both subgroups, there was no association between DCDs and increased mortality (CLI: HR, 0.95; 95% CI, 0.93-0.97; non-CLI: HR, 0.97; 95% CI, 0.95-0.99). Of patients in the low-risk subgroup (n = 4212) and those within the lowest quartile of total comorbidities (n = 50 869), there was similarly no harm associated with DCDs (low-risk subgroup: HR, 0.98; 95% CI, 0.84-1.13; lowest quartile of total comorbidities: HR, 0.95; 95% CI, 0.92-0.99).

## Discussion

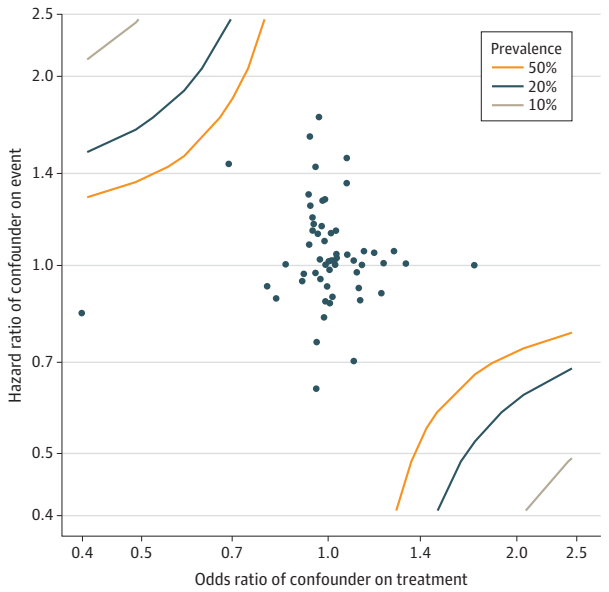
In this initial report from the prespecified SAFE-PAD study involving 168 553 Medicare beneficiaries who underwent femoropopliteal artery revascularization from 2015 through 2018, DCDs were found to be noninferior to NDCDs in respect to mortality through a median (IQR) follow-up of 2.72 (0.87-3.77) years (longest follow-up, 5.16 years). Sensitivity analyses to assess model misspecification and unmeasured confounding supported the robustness of the primary result. In addition, safety associated with DCDs was consistently found among all prespecified subgroups—in particular, those treated with stent implantation and those treated with balloon angioplasty alone.

Figure 1. Unweighted and Weighted Cumulative Incidence of Mortality Curves, Stratified by Treatment With or Without Drug-Coated Devices




Displayed are the unweighted (A) and weighted (B) cumulative incidence curves of mortality, stratified by treatment with a drug-coated or non–drug-coated device. Of the 168 553 Medicare beneficiaries studied, the median (interquartile range) follow-up was 993 (319-1377) days, and longest follow-up was 1883 days. At 1883 days, the crude cumulative incidence of mortality was 56.7% in the non–drug-coated device group and 51.6% in the drug-coated device group, with an unadjusted hazard ratio of 0.84 (95% CI, 0.82-0.85). After weighting, the cumulative incidence of mortality at 1883 days was 55.1% among those treated with non–drug-coated devices and 53.8% among those treated with drug-coated devices, with an adjusted hazard ratio of 0.95 (95% CI, 0.94-0.97). The 1-sided *P* value for the noninferiority test was <.001.

Figure 2. Simulation of a Hypothetical Uncontrolled Confounder and Association With Measured Covariates in SAFE-PAD




Displayed is the simulation of a hypothetical uncontrolled confounder or group of confounders with a prevalence of 50% (orange curves), 20% (blue curves), and 10% (gray curves). The black dots represent a scatterplot of the odds ratio of treatment vs hazard ratio of mortality for the covariates adjusted for in the primary analysis of SAFE-PAD. In the SAFE-PAD cohort, no single measured covariate would have met the criterion to overturn the noninferiority margin. SAFE-PAD indicates Safety Assessment of Femoropopliteal Endovascular Treatment With Paclitaxel-Coated Devices.

The peripheral paclitaxel device safety signal has created concerns for patients, clinicians, and regulators. Although harm was observed in the initial meta-analysis,[6] there has remained skepticism in regard to causality owing to the lack of a proposed mechanism, absence of a dose-mortality relationship, and attenuation of the risk estimate as loss to follow-up was decreased.[29,30] Nonetheless, as this safety signal has persisted in updated meta-analyses,[29] these devices remain restricted to patients at the highest risk of restenosis and with specific labeling addressing the concern over long-term harm.[13]

The 21st Century Cures Act[17] included specification on the use of real-world evidence to support regulatory decision-making, with the goal of leveraging alternative data sources other than traditional clinical trials to inform premarket and postmarket device evaluation.[31] Consistent with this mission, SAFE-PAD was designed to meet the rigorous standards typically used for regulatory safety and efficacy evaluations and to serve as a template for timely device safety assessments. The CMS data used in this study are uniquely qualified to study paclitaxel safety because missing data are minimal; the outcome (all-cause mortality) is ascertained with high fidelity and validation[32]; specific billing claims codes for the device exposure are available and tied to compensation, thus reducing the likelihood of misclassification; and key comorbidities are available for risk adjustment. In addition, because PAD is a condition that primarily affects the older population,[1] CMS beneficiaries represent the majority of patients with the condition of interest and overlap with the average patient enrolled in the pivotal clinical trials.[33-35] Lastly, these data are retrospective in regard to patient exposure, which is critical, as the types of patients treated after publication of the initial meta-analysis likely differ from those treated beforehand. SAFE-PAD was prespecified,[20] publicly registered, and involved critical feedback from the FDA to ensure it met criteria to be used for regulatory decision-making.

With this in mind, DCDs were not found to be associated with increased death when compared with NDCDs in this initial report from the SAFE-PAD study. As DCDs were not designed with intent to reduce survival, we used a noninferior-

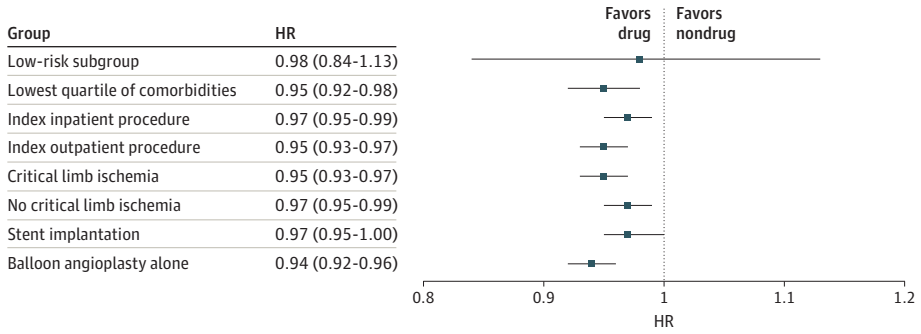
Table 2. Risk Differences in Mortality Between Treatment Groups in the Instrumental Variable Analysis

| Days from index procedure | No.[a] | Risk difference in mortality (SE) [95% CI] | Noninferiority | |
|---|---|---|---|---|
| | | | Margin[b] | *P* value |
| 365 | 121 974 | −0.00038 (0.0047) [−0.0096 to 0.0088] | 0.0085 | .03 |
| 730 | 104 214 | −0.00053 (0.0065) [−0.013 to 0.012] | 0.016 | .007 |
| 1095 | 72 146 | −0.00062 (0.0076) [−0.016 to 0.014] | 0.021 | .002 |
| 1460 | 33 821 | −0.00067 (0.0083) [−0.017 to 0.016] | 0.026 | <.001 |
| 1825 | 3855 | −0.00069 (0.0085) [−0.017 to 0.016] | 0.03 | <.001 |

[a] The instrumental variable analysis cohort excluded 3500 patients who underwent the procedure at a hospital with a femoropopliteal artery revascularization procedure volume <10 during the study period.

[b] The noninferiority margin is based on a 5% relative increase in the risk of mortality.

Figure 3. Adjusted Risks of All-Cause Mortality Between Drug-Coated and Non–Drug-Coated Devices Among Prespecified Subgroups




Displayed are the adjusted risks of mortality associated with drug-coated vs non–drug-coated devices across the different prespecified subgroups. Each subgroup underwent separate inverse probability weighting. No evidence of harm associated with drug-coated devices was observed across any of the subgroups. HR indicates hazard ratio.

ity approach. Although this required us to allow for a margin of harm with DCDs, which was conservatively set at a relative increase of death of 5% at 5 years, the upper bound of the CI surrounding our risk estimate did not exceed 1, suggesting the absence of harm with these devices at the 95% confidence level. In this analysis, both patients with and without CLI were included, which differs from the initial meta-analysis. However, more than half of the patients were without CLI, and the safety signal was preserved. Furthermore, although the cumulative incidence of death was high, which has raised question as to whether Medicare patients have competing mortality risks that may veil the harm associated with DCDs, safety was consistent among patients with lower risk profiles. In particular, we found no association between DCDs and mortality among low-risk patients (defined as aged 66-70 years with no CLI and ≤2 comorbidities) and those within the lowest quartile of total comorbidities.

Overall, these findings parallel the recently reported interim results from the Swedish Drug-Elution Trial in Peripheral Arterial Disease (SWEDEPAD) trial,[36] which also did not demonstrate harm associated with paclitaxel-coated devices through a median follow-up of 2.49 years. However, SWEDEPAD has limitations, including that it was not powered for mortality, it combined patients with either claudication or CLI to increase event rates, and it was prematurely halted over the DCD safety concerns. As such, SAFE-PAD will continue to be an important source of safety data for stakeholders, including patients, the clinical community, industry, and regulators.

Irrespective of the findings of this analysis, it is important to highlight the role of noninvasive therapies for managing PAD, in particular for those with claudication. The benefits of peripheral artery revascularization must be weighed against its risks, which include both periprocedural complications[37,38] and the need for additional revascularization procedures. For instance, in this analysis, approximately 25% of patients underwent a subsequent endovascular procedure and approximately 6% underwent surgical revascularization by 3 years. The risk-benefit trade-off becomes even more important to consider when there is a device safety concern, with potential harm as severe as death. As such, consistent with society guidelines,[1] every patient with claudication should undergo an aggressive attempt at lifestyle interventions and medical management prior to consideration of revascularization.[1]

## Limitations

The study results must be interpreted in the context of the study design. First, device exposure may have been misclassified; however, the influence of this is likely small, as appropriate billing is required for reimbursement, and a prior study supported the validity of these codes.[20] Second, CMS data do not include detailed procedural information, including lesion characteristics and device sizes. However, most predictors of long-term mortality have not included procedural characteristics, whereas patient comorbidities captured in this analysis have the strongest associations.[11,39] Third, the median length of follow-up was only 2.72 years, whereas the harm signal in the meta-analysis was most apparent at years 4 to 5. This shorter follow-up was in part due to the high incidence of death, and nearly 30 000 patients had follow-up data at 4 years. Fourth, cumulative paclitaxel dose exposure could not be calculated, the association of repeated paclitaxel exposure was not included in the primary analysis, and prior

paclitaxel exposure cannot be confirmed for all patients. Although repeated exposure was tracked, this was purposefully not modeled owing to the concern of introducing survivorship bias. Also, the degree of prior paclitaxel exposure was limited by the timing of the analysis, which began shortly after device approval of drug-coated balloons. Fifth, these data are limited in their ability to estimate effectiveness, as only *International Classification of Diseases, Tenth Revision, Procedure Coding System* codes include the laterality required to assess lesion-specific reintervention. Sixth, this study lacks a medical therapy arm, which can provide greater context of the long-term risks between those who did and did not undergo endovascular revascularization. Seventh, we prespecified a relative noninferiority margin of 5% for this study. However, it could be considered unacceptable for the device to be associated with any mortality increase whatsoever, considering that select patients can be treated conservatively without invasive management and that the primary benefits of DCDs are related to quality of life. Eighth, this study may not be generalizable to less-represented patients, including those of different racial/ethnic backgrounds. In addition, the mortality rates were high in this analysis, and competing causes of death in this age group may have obscured any mortality signals from these devices. Furthermore, these findings may not be generalizable to patients with lower risks of mortality. Lastly, this study was observational in design, and there remains the possibility of residual and unmeasured confounding.

## Conclusions

In this initial report from the SAFE-PAD study, DCDs were found to be noninferior to NDCDs in respect to mortality through a median follow-up of 2.72 years. These findings remained robust in sensitivity analyses and were consistent across all prespecified subgroups. SAFE-PAD will continue until the median follow-up of all patients surpasses 5 years and will provide the FDA a mechanism for the ongoing safety evaluation of these devices. Furthermore, SAFE-PAD may serve as a case example of how to leverage real-world evidence to provide timely device safety evaluations.

### ARTICLE INFORMATION

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**Author Contributions:** Drs Secemsky and Yeh had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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*Acquisition, analysis, or interpretation of data:* All authors.
*Drafting of the manuscript:* Secemsky, Shen.
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