ORIGINAL ARTICLE

Drug-Coated Balloons for Dysfunctional Dialysis Arteriovenous Fistulas

Robert A. Lookstein, M.D., M.H.C.D.L., Hiroaki Haruguchi, M.D., Kenneth Ouriel, M.D., M.B.A., Ido Weinberg, M.D., Lanyu Lei, Ph.D., Stephanie Cihlar, B.S., and Andrew Holden, M.B., Ch.B., for the IN.PACT AV Access Investigators*

ABSTRACT

BACKGROUND

Standard percutaneous transluminal angioplasty is the current recommended treatment for dysfunctional hemodialysis fistulas, yet long-term outcomes of this treatment are poor. Drug-coated balloons delivering the antirestenotic agent paclitaxel may improve outcomes.

METHODS

In this prospective, single-blinded, 1:1 randomized trial, we enrolled 330 participants at 29 international sites. Patients with new or restenotic lesions in native upper-extremity arteriovenous fistulas were eligible for participation. After successful high-pressure percutaneous transluminal angioplasty, participants were randomly assigned to receive treatment with a drug-coated balloon or a standard balloon. The primary effectiveness end point was target-lesion primary patency, defined as freedom from clinically driven target-lesion revascularization or access-circuit thrombosis during the 6 months after the index procedure. The primary safety end point, serious adverse events involving the arteriovenous access circuit within 30 days, was assessed in a noninferiority analysis (margin of noninferiority, 7.5 percentage points). The primary analyses included all participants with available end-point data. Additional sensitivity analyses were performed to assess the effect of missing data.

RESULTS

A total of 330 participants underwent randomization; 170 were assigned to receive treatment with a drug-coated balloon, and 160 were assigned to receive treatment with a standard balloon. During the 6 months after the index procedure, target-lesion primary patency was maintained more often in participants who had been treated with a drug-coated balloon than in those who had been treated with a standard balloon (82.2% [125 of 152] vs. 59.5% [88 of 148]; difference in risk, 22.8 percentage points; 95% confidence interval [CI], 12.8 to 32.8; P<0.001). Drug-coated balloons were noninferior to standard balloons with respect to the primary safety end point (4.2% [7 of 166] and 4.4% [7 of 158], respectively; difference in risk, −0.2 percentage points; 95% CI, −5.5 to 5.0; P=0.002 for noninferiority). Sensitivity analyses confirmed the results of the primary analyses.

CONCLUSIONS

Drug-coated balloon angioplasty was superior to standard angioplasty for the treatment of stenotic lesions in dysfunctional hemodialysis arteriovenous fistulas during the 6 months after the procedure and was noninferior with respect to access circuit–related serious adverse events within 30 days. (Funded by Medtronic; IN.PACT AV Access Study ClinicalTrials.gov number, NCT03041467.)

From Icahn School of Medicine at Mount Sinai (R.A.L.) and Syntactx (K.O.), New York; Haruguchi Vascular Access Clinic, Tokyo (H.H.); VasCore, Massachusetts General Hospital, Boston (I.W.); Medtronic, Plymouth, MN (L.L., S.C.); and the Department of Radiology, Auckland Hospital, Auckland, New Zealand (A.H.). Address reprint requests to Dr. Lookstein at the Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Pl., Box 1234, New York, NY 10029-6574, or at robert.lookstein@mountsinai.org.

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

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Approximately 850 million persons worldwide have chronic kidney disease, and almost 4 million receive renal replacement therapy.[1] Among these 4 million, more than 520,000 Americans are undergoing dialysis, and fewer than 225,000 have a functioning kidney transplant.[2] To improve treatment and outcomes for these patients undergoing dialysis, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) is moving toward development of an individualized, patient-driven life plan addressing disease progression.[3] However, in most patients, preference is given to arteriovenous fistulas or grafts, given that the risk of infection associated with these treatment methods is lower than that associated with the use of a central venous hemodialysis catheter.

One limitation to the wide adoption of continuous hemodialysis through autologous arteriovenous fistulas is the high incidence of dysfunction caused by vascular stenosis within the fistula circuit, leading to inadequate hemodialysis. Unfortunately, despite many attempts to address stenoses in arteriovenous access circuits through endovascular approaches, the percentage of patients who undergo repeat intervention within 6 months has been estimated in systematic reviews and meta-analyses to be approximately 50%.[4-7] Angioplasty balloons coated with the antiproliferative agent paclitaxel have been shown to be safe and effective in the femoral artery, reducing neointimal hyperplasia–causing restenosis and thereby both improving primary patency and reducing the need for clinically driven target-lesion revascularization.[8] Numerous small single-center studies without independent adjudication have shown the feasibility of using drug-coated balloons to improve outcomes as compared with standard balloon angioplasty in arteriovenous fistulas.[9-13] One investigational-device-exemption trial showed similar patency between drug-coated balloons and standard balloons during the 6 months after the procedure.[14]

In the IN.PACT AV Access Study, an investigational-device-exemption randomized, controlled trial of a different drug-coated balloon with a different excipient and drug dose than was used in the previous investigational-device-exemption trial, we aimed to investigate whether this balloon could improve outcomes in patients with dysfunctional fistulas. Improvements in patency could potentially have significant benefits for patients, leading to longer periods of successful and uninterrupted dialysis, as well as reducing the use of catheter-based dialysis and the substantial incidence of adverse events associated with this type of dialysis.

Methods

Trial Design

We conducted the present trial as a prospective, global, multicenter, single-blind, 1:1 randomized clinical trial evaluating the IN.PACT AV drug-coated balloon (Medtronic) as compared with standard (non–drug-coated) balloon angioplasty for the treatment of new (i.e., not previously treated) or nonstented restenotic lesions up to 100 mm in length in arteriovenous dialysis fistulas. The trial was conducted at sites (29 in total) in the United States, Japan, and New Zealand (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). All the data used for the analyses of the primary end points were adjudicated by an independent clinical events committee (Syntactx), the members of which were unaware of the treatment assignments, and a data and safety monitoring board was used (Syntactx). Independent core laboratories analyzed duplex ultrasonographic images (VasCore, Massachusetts General Hospital) and angiographic images (Syntactx).

The trial was conducted under a Food and Drug Administration (FDA) investigational device exemption in compliance with the laws and regulations of the countries where the trial was being conducted and in accordance with the Declaration of Helsinki. The trial protocol and amendments, available at NEJM.org, were reviewed and approved by the ethics committee or institutional review board at each site, and all participants provided written informed consent before undergoing any trial-specific procedures. Medtronic sponsored the trial and owns the data. Data analyses were performed by Medtronic and the Baim Institute for Clinical Research (formerly the Harvard Clinical Research Institute). The authors had unrestricted access to the data; one academic author not employed by the sponsor and two authors employed by the sponsor wrote the manuscript that was submitted, and all the authors reviewed and approved the manuscript and vouch for the accuracy and com-

pleteness of the data and for the fidelity of the trial to the protocol.

TRIAL END POINTS

The primary effectiveness end point was target-lesion primary patency, defined as freedom from clinically driven target-lesion revascularization or access-circuit thrombosis measured during the 6 months after the index procedure. An event was adjudicated as clinically driven target-lesion revascularization if the target lesion either had stenosis of at least 50% of the diameter of the vessel (per angiographic core laboratory assessment) in the presence of clinical or physiological abnormalities that indicated dialysis access dysfunction or had at least 70% stenosis in the absence of abnormalities that indicated dysfunction. For the end point of 6-month target-lesion primary patency, the upper limit of the follow-up window was 210 days after the index procedure to maximize the number of participants with complete follow-up data that could be included in the calculation of the end point.

The primary safety end point was defined as serious adverse events involving the arteriovenous access circuit within 30 days after the procedure, in accordance with the ISO14155 criteria.[15] The results for the primary end point are reported exclusively on the basis of adjudicated data from the independent clinical events committee, the members of which were unaware of the treatment-group assignments. Participants who died before data on the primary end point were collected were excluded from the primary analysis.

TRIAL DEVICE

The drug-coated balloon carries a paclitaxel dose of 3.5 μg per square millimeter with a urea excipient. It is a 0.035-in. guidewire-compatible device, and the sizes used in the trial included balloon diameters of 4 to 12 mm, balloon lengths of 40 to 150 mm, and shaft lengths of 40 to 80 cm.

TRIAL POPULATION

Participants were eligible for enrollment if they were at least 21 years of age and presented with a new or nonstented restenotic native arteriovenous dialysis fistula that had at least 50% stenosis (criteria are listed in Table S2 in the Supplementary Appendix). Key inclusion criteria included a native arteriovenous fistula created at least 60 days before the index procedure that had been used for dialysis for at least 8 of 12 sessions during a 4-week period, ensuring fistula maturity. Exclusion criteria included any history of or current access-circuit thrombosis or a previous stent in the access circuit. The arteriovenous access circuit was defined as the arteriovenous anastomosis (extending up to 2 cm into the inflow artery) through the axillosubclavian venous junction (extending up to 2 cm into the subclavian vein).

TRIAL PROCEDURE

Participants, core laboratories, and the clinical events committee were unaware of the treatment assignments. Because of the macroscopic differences between the drug-coated balloon and standard balloons, investigators and research coordinators were aware of the treatment assignments and were trained to conceal the assignment from each participant.

Eligible participants underwent predilation with a high-pressure balloon matching the reference-vessel diameter (1:1 sizing); inflation time was left to the discretion of the interventionalist. Successful predilation was judged by the interventionalists at the time of the procedure and was defined as a residual stenosis of no more than 30% of the vessel diameter and an absence of perforation or flow-limiting dissection of grade C or higher.[16] After successful predilation with the high-pressure balloon and crossing of the lesion with the guidewire, participants were enrolled and randomly assigned to treatment with the drug-coated balloon or a standard balloon (not a high-pressure balloon) in a 1:1 ratio and stratified according to lesion status (new or restenotic) and with prespecified block sizes within trial sites.

Whether participants were treated with a drug-coated balloon or a standard balloon after randomization, the angioplasty balloon diameter was identical to the high-pressure predilation balloon. In the drug-coated–balloon group, balloon length was selected to exceed the target lesion by approximately 10 mm at either end to ensure full coverage and prevent geographic miss (i.e., balloon dilation or stent placement at an unintended area of the vessel wall). If more than one balloon was used, approximately 10 mm of overlap was required. In the standard-balloon group, interventionalists were instructed to fol-

low the individual device instructions for use. If a residual stenosis of more than 30% or a flow-limiting dissection was present, additional dilation with a standard balloon was performed.

FOLLOW-UP

The protocol specifies that participants in the trial be followed up for as long as 5 years after the index procedure. Follow-up assessments for this report occurred at 30 days, 3 months, and 6 months after the index procedure. Duplex ultrasonography was required at 30 days and 6 months, and angiographic follow-up was performed as clinically indicated in accordance with the protocol. Unscheduled visits, including repeat interventions, were captured throughout the trial and were performed in accordance with the treating investigator's standard of care.

STATISTICAL ANALYSIS

We calculated that the planned enrollment of 330 participants would provide at least 92% power for showing superiority of the drug-coated balloon to the standard balloon for the primary effectiveness end point, with a one-sided z test and an alpha level of 2.5%, under the assumption that 60% in the drug-coated–balloon group and 40% in the standard-balloon group would meet the primary effectiveness end point and that there would be 15% attrition within 6 months. Simultaneously, it would provide 80% power to show noninferiority for the primary safety end point with the Farrington–Manning test, a noninferiority margin of 7.5 percentage points, and an alpha level of 2.5%, under the assumption that 5% of participants in each group would have a serious adverse event and that there would be 2% attrition within 30 days. Participants with data that could be evaluated were included in the primary and secondary analyses according to their randomization assignment. Participants with missing data for an end point were excluded from the analysis of that end point. Prespecified sensitivity analyses, including multiple imputation with logistic regression for the primary effectiveness end point and worst-case analysis for both primary end points, were performed to assess the effect of missing data.

To maintain familywise type I error at 2.5%, after the hypothesis tests succeeded for both primary end points, four of the secondary end points and the primary safety end point were tested in a prespecified order for superiority of the drug-coated balloon to the standard balloon with the use of a fixed-sequence procedure[17-19] with a one-sided test. The test procedure was stopped at the first end point that showed nonsignificance at the one-sided 2.5% level. The between-group differences for these five end points were assessed by chi-square test or Fisher's exact test for binary variables and by t-test or Wilcoxon rank-sum test for continuous variables. No P values are provided for other outcomes. For all outcomes, 95% confidence intervals are provided as applicable and have not been adjusted for multiple comparisons.[17] For 30-day end points expressed as percentages of participants, the number of participants with an event within 30 days is the numerator and the total number of participants who had an event or had at least 23 days of clinical follow-up is the denominator. For 6-month end points expressed as percentages of participants, the number of participants with an event within 6 months is the numerator, and all participants who had an event or who had at least 150 days of clinical follow-up is the denominator. Time-to-event analyses were conducted with the use of the Kaplan–Meier method and supplement the primary analysis. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute).

RESULTS

PARTICIPANTS

Of the 330 participants who underwent randomization, 170 were assigned to receive treatment with a drug-coated balloon and 160 were assigned to receive treatment with a standard balloon (Fig. 1). A total of 204 participants were treated in the United States, 112 in Japan, and 14 in New Zealand. The baseline demographic characteristics were similar in the two treatment groups (Table 1), with the expected high percentages of participants with diabetes, hypertension, and cardiovascular disease. There was an even distribution between forearm (radiocephalic) and upper-arm (brachiocephalic and brachiobasilic) arteriovenous access lesions treated (Table S3). Decreased blood flow and elevated venous pressure were common presenting clinical symptoms of arteriovenous fistula dysfunction. The target lesions in most of the participants were in the venous outflow, including the cephalic arch,

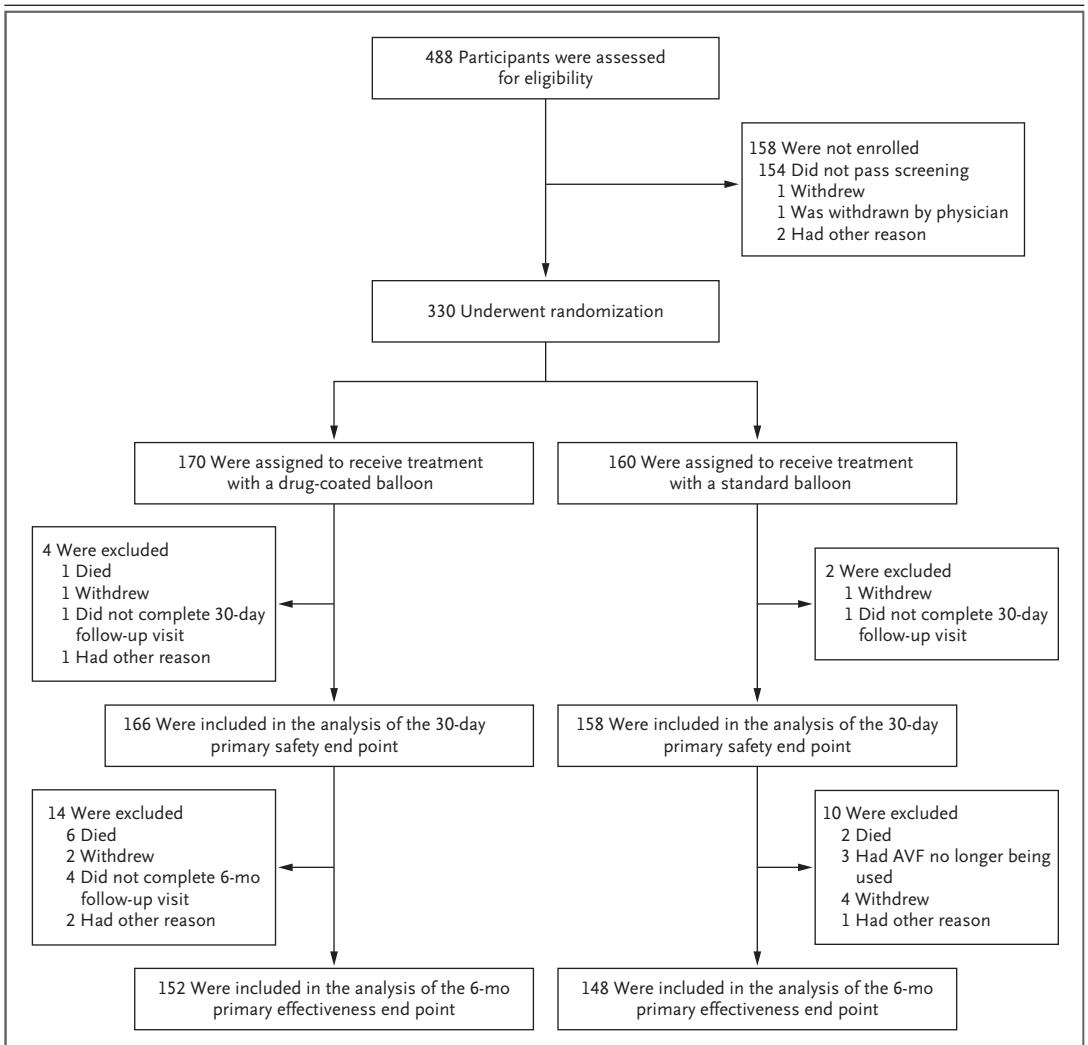

Figure 1. Enrollment, Randomization, and Follow-up.

In total, 330 participants were randomly assigned (1:1) to receive percutaneous transluminal angioplasty with a drug-coated balloon or a standard balloon. AVF denotes arteriovenous fistula.

with the lesion in 25.5% of participants (84 of 330) located at the arteriovenous anastomosis (Table S4).

Procedural characteristics are shown in Table S5; the mean (±SD) length of the balloons used during the index procedure was greater in the drug-coated–balloon group (59.0±23.3 mm) than in the standard-balloon group (47.4±15.7 mm). The final mean percent diameter stenosis was similar in the two treatment groups (drug-coated balloon, 26.3%±10.5%; standard balloon, 25.8%±10.7%). Antiplatelet therapy use after the procedure was similar in the two treatment groups (Table S6).

PRIMARY EFFECTIVENESS END POINT

The percentage of participants with target-lesion primary patency during the 6 months after the index procedure was 82.2% (125 of 152) in the drug-coated–balloon group and 59.5% (88 of 148) in the standard-balloon group (risk difference, 22.8 percentage points; 95% confidence interval [CI], 12.8 to 32.8; P<0.001) (Table 2). When the effect of missing data was evaluated in sensitivity analyses, the conclusions were consistent with those of the primary analysis (Table 3). The percentage of participants with clinically driven target-lesion revascularization was 16.4% (25 of 152) in the drug-coated–balloon group and 38.5%

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Drug-Coated Balloon (N=170)	Standard Balloon (N=160)	Overall (N=330)
Age — yr	65.8±13.1	65.5±13.4	65.6±13.3
Male sex — no. (%)	112 (65.9)	101 (63.1)	213 (64.5)
Hispanic or Latino ethnic group — no./total no. (%)†	15/167 (9.0)	14/157 (8.9)	29/324 (9.0)
Race or ethnic group — no. (%)†			
White	42 (24.7)	46 (28.8)	88 (26.7)
Black	54 (31.8)	48 (30.0)	102 (30.9)
Asian	63 (37.1)	57 (35.6)	120 (36.4)
Native Hawaiian or other Pacific Islander	6 (3.5)	4 (2.5)	10 (3.0)
American Indian or Alaska Native	0	0	0
Other	5 (2.9)	5 (3.1)	10 (3.0)
Medical conditions — no./total no. (%)			
Hypertension	155/170 (91.2)	151/160 (94.4)	306/330 (92.7)
Hyperlipidemia	92/170 (54.1)	84/160 (52.5)	176/330 (53.3)
Diabetes mellitus	107/170 (62.9)	110/160 (68.8)	217/330 (65.8)
Renal insufficiency	170/170 (100)	160/160 (100)	330/330 (100)
Carotid artery disease	7/170 (4.1)	14/160 (8.8)	21/330 (6.4)
Congestive heart failure	39/170 (22.9)	39/160 (24.4)	78/330 (23.6)
Coronary heart disease	61/170 (35.9)	62/160 (38.8)	123/330 (37.3)
Peripheral artery disease	33/170 (19.4)	24/159 (15.1)	57/329 (17.3)
Smoking status — no. (%)			
Current smoker	19 (11.2)	26 (16.2)	45 (13.6)
Former smoker	64 (37.6)	45 (28.1)	109 (33.0)

* Plus–minus values are means ±SD.
† Race and ethnic group were reported by the site investigators, who obtained the information from the participants' charts.

(57 of 148) in the standard-balloon group (risk difference, –22.1 percentage points; 95% CI, –31.9 to –12.3). There was no significant difference in the risk of access-circuit thromboses between the treatment groups (2.0% [3 of 151] and 3.4% [5 of 146]; risk difference, –1.4%; 95% CI, –5.1 to 2.3). The percentage of participants with target-lesion primary patency through the end of the follow-up window, calculated in a Kaplan–Meier analysis, was 81.4% in the drug-coated–balloon group and 59.0% in the standard-balloon group (hazard ratio, 0.39; 95% CI, 0.24 to 0.61) (Fig. 2A).

PRIMARY SAFETY END POINT

In the analysis of the percentage of participants with a serious adverse event involving the arteriovenous access circuit within 30 days, the drug-coated balloon was found to be noninferior to the standard balloon (4.2% [7 of 166] and 4.4% [7 of 158], respectively; risk difference, –0.2 percentage points; 95% CI, –5.5 to 5.0; with a noninferiority margin of 7.5 percentage points, P=0.002 for noninferiority) (Table 2). When the effect of the missing data was evaluated in sensitivity analyses, the conclusions were consistent with those of the primary analysis (Table 3). Serious adverse events through 12 months are listed in Table S7.

KEY SECONDARY END POINTS

After the hypothesis tests for both primary end points were successful, four key secondary end points were found to pass the sequential superiority hypothesis test, all at a one-sided 2.5% level until the first failure of null-hypothesis rejection; the fifth test (a superiority test of the primary safety end point) was not successful at the 2.5% level (the fixed-sequence test procedure preserved the familywise type I error). The per-

Table 2. Principal Effectiveness and Safety End Points within 6 Months.*

End Point	Drug-Coated Balloon (N=170)	Standard Balloon (N=160)	Difference (95% CI)†	P Value‡
Primary effectiveness end point				
Target-lesion primary patency over 6 mo — no./total no. (%)§¶	125/152 (82.2)	88/148 (59.5)	22.8 (12.8 to 32.8)	<0.001
Clinically driven target-lesion revascularization	25/152 (16.4)	57/148 (38.5)	−22.1 (−31.9 to −12.3)	
Access-circuit thrombosis	3/151 (2.0)	5/146 (3.4)	−1.4 (−5.1 to 2.3)	
Primary safety end point‖				
Serious adverse events involving the arteriovenous access circuit within 30 days — no./total no. (%)**	7/166 (4.2)	7/158 (4.4)	−0.2 (−5.5 to 5.0)	0.002
Arteriovenous fistula occlusion	1/166 (0.6)	0/158		
Arteriovenous fistula site complication	5/166 (3.0)	4/158 (2.5)		
Arteriovenous fistula thrombosis	1/166 (0.6)	1/158 (0.6)		
Hemodialysis complication	1/166 (0.6)	0/158		
Vasospasm	0/166	1/158 (0.6)		
Vessel puncture–site hematoma	0/166	1/158 (0.6)		
Key secondary end points within 6 months¶				
Any target-lesion revascularization within 180 days — no./total no. (%)	25/153 (16.3)	59/148 (39.9)	−23.5 (−33.4 to −13.7)	<0.001
No. of interventions performed to maintain target-lesion primary patency††	0.2±0.6	0.6±0.7	−0.3 (−0.5 to −0.2)	<0.001
No. of interventions (no. of participants)	40 (31)	91 (70)	56.0	
No. of interventions performed to maintain access-circuit primary patency‡‡	0.3±0.7	0.6±0.8	−0.3 (−0.5 to −0.2)	<0.001
No. of interventions (no. of participants)	54 (39)	103 (75)	47.6	
Access-circuit primary patency — no./total no. (%)§§	112/153 (73.2)	71/148 (48.0)	25.2 (14.6 to 35.9)	<0.001
Repeat intervention in access circuit	39/153 (25.5)	75/148 (50.7)	−25.2 (−35.8 to −14.6)	
Access-circuit thrombosis	3/151 (2.0)	5/146 (3.4)	−1.4 (−5.1 to 2.3)	

* Plus–minus values are means ±SD. The 95% confidence intervals were not adjusted for multiple comparisons. All events reported in the primary and key secondary end points were adjudicated by the independent clinical events committee, the members of which were unaware of the treatment assignments; all duplex ultrasonographic and angiographic measures were made by the independent core laboratories, and all other data were reported by investigators at the trial site.

† For end points expressed as number/total number (%), differences are given in percentage points (drug-coated balloon minus standard balloon). For end points expressed as the mean number of interventions, differences are the difference between the means (drug-coated balloon minus standard balloon). For end points expressed as number of interventions (number of participants), the difference is the percentage by which the number of interventions in the drug-coated–balloon group is lower than that in the standard-balloon group (i.e., the relative difference).

‡ P values for the primary effectiveness end point and binary key secondary end points were based on one-sided z tests; the P value for noninferiority for the primary safety end point was based on the Farrington–Manning noninferiority test with a margin of 7.5 percentage points. P values for the end points on number of interventions performed were based on one-sided Wilcoxon rank-sum tests. P values for the other end points were based on one-sided chi-square tests. The significance level was at 2.5%.

§ Target-lesion primary patency was defined as freedom from clinically driven target-lesion revascularization or access-circuit thrombosis after the index procedure. For this end point and its components, the difference between the groups is expressed in percentage points.

¶ For 6-month end points, all participants who had had an event — or who had not had an event but had at least 150 days of clinical follow-up — were counted as participants who could be evaluated. If a participant had not had an event and the arteriovenous access circuit had been abandoned (i.e., was no longer being used for dialysis) within 150 days, the participant was considered not able to be evaluated for 6-month effectiveness end points. The 6-month period of evaluation was 210 days for the patency-related end points and their components, including target-lesion primary patency, clinically driven target-lesion revascularization, access-circuit thrombosis, access-circuit primary patency, and repeat intervention in the access circuit; 180 days was used for all the other 6-month end points.

‖ Results shown here are for the test of noninferiority; the prespecified sequential superiority test of this end point (the fifth test in the sequence) did not succeed at the 2.5% level.

** For the 30-day end point, all participants who had an event and participants who did not have an event but had at least 23 days of clinical follow-up were counted as participants who could be evaluated. The difference between the groups is expressed in percentage points.

†† The number of interventions performed to maintain target-lesion primary patency was defined as the number of target-lesion revascularization procedures performed after the index procedure.

‡‡ The number of interventions performed to maintain access-circuit primary patency was defined as the number of repeat interventions in the target lesion or the access circuit after the index procedure.

§§ Access-circuit primary patency was defined as freedom from repeat intervention in the access circuit or access-circuit thrombosis after the index procedure.

Table 3. Sensitivity Analysis of the Effectiveness and Safety End Points within 6 Months.

End Point	Drug-Coated Balloon (N=170)	Standard Balloon (N=160)	Difference (95% CI)*	P Value†
Primary effectiveness end point: target-lesion primary patency over 6 mo				
Primary analysis — no./total no. (%)‡	125/152 (82.2)	88/148 (59.5)	22.8 (12.8 to 32.8)	<0.001
Multiple imputation — %§	81.3	58.4	22.9 (12.8 to 33.0)	<0.001
Worst-case analysis — no. (%)¶	125 (73.5)	100 (62.5)	11.0 (1.0 to 21.0)	0.02
Primary safety end point: serious adverse events involving the arteriovenous access circuit within 30 days				
Primary analysis — no./total no. (%)‡	7/166 (4.2)	7/158 (4.4)	−0.2 (−5.5 to 5.0)	0.002
Worst-case analysis — no. (%)¶	11 (6.5)	7 (4.4)	2.1 (−3.2 to 7.4)	0.02

* The 95% confidence intervals were not adjusted for multiple comparisons.
† For target-lesion primary patency during the 6 months after the index procedure, P values were based on one-sided z tests. For serious adverse events involving the arteriovenous access circuit within 30 days, P values were based on the Farrington–Manning noninferiority test with a margin of 7.5 percentage points.
‡ The analyses were performed with all data that could be evaluated.
§ The baseline characteristics included in the imputation model were treatment group, geographic region (United States, Japan, or New Zealand), lesion type (new or restenotic), age, sex, arteriovenous fistula type, history of coronary artery disease, and history of peripheral artery disease. Multiple imputation was not planned for the primary safety end point because missing values were minimal. Denominators in the multiple imputation analysis were 170 in the drug-coated–balloon group and 160 in the standard-balloon group.
¶ For the worst-case analysis of the primary end point, all missing data in the drug-coated–balloon group were imputed as failures and all missing data in the standard-balloon group were imputed as successes.

centage of participants with any target-lesion revascularization in the drug-coated–balloon group during the 6 months after the index procedure was 16.3% (25 of 153), as compared with 39.9% (59 of 148) in the standard-balloon group (risk difference, −23.5 percentage points; 95% CI, −33.4 to −13.7; P<0.001). The mean number of repeat interventions performed to maintain target-lesion primary patency during the 6 months after the index procedure was 0.2±0.6 in the drug-coated–balloon group and 0.6±0.7 in the standard-balloon group (mean difference, −0.3; 95% CI, −0.5 to −0.2; P<0.001). The number of repeat interventions performed to maintain access-circuit primary patency during the 6 months after the index procedure was 0.3±0.7 in the drug-coated–balloon group and 0.6±0.8 in the standard-balloon group (mean difference, −0.3; 95% CI, −0.5 to −0.2; P<0.001). The percentage of participants with primary patency of the entire dialysis circuit from arterial inflow to venous outflow, inclusive of the target lesion, during the 6 months after the index procedure was 73.2% (112 of 153) in the drug-coated–balloon group and 48.0% (71 of 148) in the standard-balloon group (risk difference, 25.2 percentage points; 95% CI, 14.6 to 35.9; P<0.001) (Table 2; results of a Kaplan–Meier analysis are shown in Fig. 2B). Additional end points in prespecified subgroups are shown in Table S8. Over the course of 12 months, mortality was 9.4% (15 deaths) in the drug-coated–balloon group and 9.6% (14 deaths) in the standard-balloon group (P=0.93 by log-rank test) (Table S9).

DISCUSSION

The National Kidney Foundation KDOQI has led to a dramatic increase in the use of autologous fistulas for patients undergoing hemodialysis in the United States.[3] However, arteriovenous fistulas often develop stenoses because of the physiological nature of the circuit, which leads to endovascular intervention or surgical revision to restore function. Unfortunately, the percentage of patients who undergo repeat endovascular therapy within 6 months for the treatment of stenoses in arteriovenous fistulas is approximately 50%.[4-7] However, the previous independently adjudicated investigational-device-exemption trial of a drug-coated balloon did not meet the prespecified primary effectiveness end point.[14]

In the investigational-device-exemption trial reported here, we evaluated the effectiveness and safety of a distinct drug-coated balloon with a different paclitaxel dose and excipient to treat

stenoses within dysfunctional hemodialysis arteriovenous fistulas. The drug-coated balloon was superior to the standard balloon with respect to the percentage of participants with target-lesion primary patency during the 6 months after the index procedure (the primary effectiveness end point) and was noninferior with respect to the percentage of participants with serious adverse events involving the arteriovenous access circuit within 30 days (the primary safety end point). The results of sensitivity analyses performed to account for missing data were consistent with those of the primary analyses. The 6-month findings in this trial are promising and offer evidence of the short-term benefit and safety of this device.

A 2018 meta-analysis of paclitaxel-coated devices showed that the devices were associated with higher mortality than uncoated devices when used to treat atherosclerotic femoropopliteal lesions.[20] An FDA safety panel was convened in June 2019 to investigate these findings and noted that the benefit–risk profile may be different in patients with end-stage renal disease.[21] A meta-analysis published in 2019 showed no difference in mortality between patients with arteriovenous fistula lesions treated with drug-coated balloons and patients treated with standard balloons.[22] In the present trial, no significant difference in mortality was seen between the treatment groups during the 12 months after the index procedure, and in November 2019 the FDA approved this device to treat lesions in arteriovenous fistulas. Longer-term follow-up should provide further definition of the benefit–risk profile in this disease context.

In defining the benefits of this therapy, it is notable that dialysis circuit stenoses have indirect consequences that go far beyond local hemodynamic effects. If a patient has a dysfunctional arteriovenous fistula, placement of a central venous catheter is often used as an alternative form of dialysis. Clinical outcomes of this type of dialysis are poor; the use of a central venous catheter is associated with a higher risk of death from cardiovascular or infectious causes and of death from any cause than the use of an arteriovenous fistula for dialysis.[23] Therefore, any treatment method that has the potential to offer patients with end-stage renal disease uninterrupted hemodialysis can dramatically affect patients over the course of their lives.

This trial has certain limitations. The drug-coated balloon has a different appearance than a standard balloon, which made a double-blind trial design unfeasible, and the repeat interven-

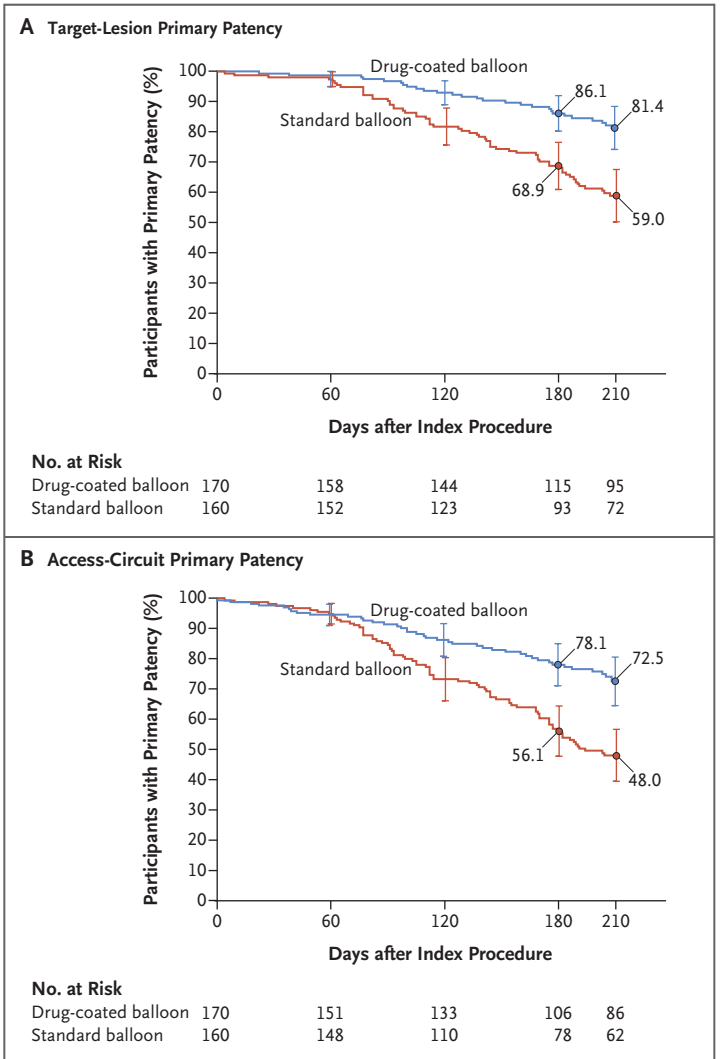

Figure 2. Kaplan–Meier Analyses of Primary Patency during the 6 Months after the Index Procedure.

Panel A shows the Kaplan–Meier analysis of target-lesion primary patency, which was defined as freedom from clinically driven target-lesion revascularization or access-circuit thrombosis measured during the 6 months after the index procedure. An event was adjudicated as a clinically driven target-lesion revascularization if the target lesion had stenosis of at least 50% of the diameter of the vessel (per angiographic core laboratory assessment) in the presence of clinical or physiological abnormalities that indicated dialysis access dysfunction or had at least 70% stenosis without the presence of clinical or physiological abnormalities indicating dialysis access dysfunction. Panel B shows the Kaplan–Meier analysis of access-circuit primary patency, which was defined as freedom from repeat intervention in the access circuit or access-circuit thrombosis during the 6 months after the index procedure. All events for both end points were adjudicated by the independent clinical events committee, the members of which were unaware of the treatment assignments. In both panels, I bars indicate 95% confidence intervals.

tion rates may be biased. This report also details only short-term outcomes. Between-group differences in the number of inflations and the maximum inflation pressures could be considered confounders. We investigated lesions in arteriovenous fistulas; further studies will be required to evaluate the safety and effectiveness of drug-coated balloons for the treatment of central vein obstruction, in-stent restenosis, or arteriovenous graft stenosis.

Treatment of dysfunctional native hemodialysis arteriovenous fistulas with a drug-coated balloon provided primary patency, including freedom from clinically driven target-lesion revascularization, that was superior to that provided by standard balloon angioplasty. The drug-coated balloon was noninferior to standard balloon angioplasty with respect to safety.

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