A multicenter randomized controlled trial indicates that paclitaxel-coated balloons provide no benefit for arteriovenous fistulas

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The role of paclitaxel-coated balloons has been established in the coronary and peripheral arterial circulations with recent interest in the use of paclitaxel-coated balloons to improve patency rates following angioplasty of arteriovenous fistulas. To assess the efficacy of paclitaxel-coated angioplasty balloons to prolong the survival time of target lesion primary patency in arteriovenous fistulas, we designed an investigator-led multi-center randomized controlled trial with follow up time variable for a minimum of one year. Patients with an arteriovenous fistula who were undergoing an angioplasty for a clinical indication were included but patients with one or more lesions outside the treatment segment were excluded. Following successful treatment with a high-pressure balloon, 212 patients were randomized. In the intervention arm, the second component was insertion of a paclitaxel-coated balloon. In the control arm, an identical procedure was followed, but using a standard balloon. The primary endpoint was time to loss of clinically driven target lesion primary patency. Primary analysis showed no significant evidence for a difference in time to end of target lesion primary patency between groups: hazard ratio 1.18 with a 95% confidence interval of 0.78 to 1.79. There were no significant differences for any secondary outcomes, including patency outcomes and adverse events. Thus, our study demonstrated no evidence that paclitaxel-coated balloons provide benefit, following standard care high-pressure balloon angioplasty, in the treatment of arteriovenous fistulas. Hence, in view of the benefit suggested by other trials, the role of paclitaxel-coated angioplasty balloons remains uncertain.

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C omplications of vascular access are an important cause of morbidity and mortality in hemodialysis patients.[1] It is widely accepted that an arteriovenous fistula (AVF) is the optimal form of vascular access, with better patency and lower infection rates than arteriovenous grafts and central

venous catheters.[2] The initial therapy for a stenosis in an AVF is balloon angioplasty with high pressure, as needed.[3] A major concern, however, is the longevity of this effect. Retrospective studies have reported postintervention primary patency rates of around 60% to 70% at 6 months and 40% to 50% at 1 year.[4–10] Hence, more durable interventions are required to reduce restenosis rates.

There has been recent interest in the use of paclitaxel-coated balloons to improve patency rates following angioplasty of AVFs. The role of paclitaxel-coated balloons has been established in the coronary and peripheral arterial circulations.[11,12] A number of small studies have explored the potential in AVFs.[13–17] These included studies with arteriovenous grafts in addition to AVFs[16,17] and a study in central venous stenosis.[13] Two larger randomized controlled trials in AVFs have been performed. One of these included 148 lesions and had an angiographic rather than clinical primary endpoint.[18] The other randomized 132 lesions and had an ultrasonographic endpoint.[19] In this second study, 48% of lesions contained an endovascular stent, which complicates interpretation of the results. In both of these studies, >1 lesion per participant was included in the trial in some cases, which means that the observations were not independent.

Two large industry-sponsored randomized controlled trials have been performed, and these provide the highest-quality evidence to date. The first, by Trerotola et al., enrolled 285 patients with AVFs from 23 centers.[20,21] There was no evidence that paclitaxel-coated balloon–assisted angioplasty was more effective at the primary end point, patency survival at 180 days, compared with conventional angioplasty. A second industry-sponsored study, by Lookstein et al., enrolled 330 patients from 29 sites.[22] The results showed that the primary endpoint of target lesion primary patency (TLPP) at 6 months was significantly greater in those treated with paclitaxel-coated balloons (82.2% vs. 59.5%). The Paclitaxel-assisted balloon Angioplasty of Venous stenosis in hEmodialysis access (PAVE) trial is the first investigator-led, large-scale randomized controlled trial designed to test the efficacy of paclitaxel-coated balloons in AVFs.

METHODS
Patients and trial design
We performed a randomized controlled trial and aimed to recruit 211 patients (aged ≥18 years), referred with a clinical indication for angioplasty of an AVF, from 20 UK centers. Eligible patients were randomized (1:1) postfistuloplasty to inflation of a second low-pressure balloon, which was either paclitaxel coated or standard (noncoated), by the King's Clinical Trials Unit using a web-based system. Randomization was minimized according to the interventional radiologist performing the procedure and 2 binary factors: previous radiological intervention (yes/no); and patient on hemodialysis at study entry (yes/no). The allocation was masked from patients, the clinicians responsible for referral to interventional radiology, and the research team, including trial statisticians. The treating radiologist could not be masked to treatment allocation because of the appearance of the paclitaxel-coated balloon.

If the access circuit contained synthetic graft material or stents, synchronous lesion(s) outside the treatment segment, thrombosis, central vein stenosis, or residual stenosis >30% after high-pressure balloon fistuloplasty, the patient was excluded.[23] Protocol changes in March 2016 and July 2016 broadened the eligibility criteria to include, in turn, patients who had not yet started hemodialysis and patients with a treatment segment containing ≥1 lesions that could be treated with a single drug-coated balloon up to 120 mm in length. These changes were made to aid recruitment, whilst maintaining the requirement for an absence of lesions outside the treatment segment, which was a unique feature of the trial. A log of changes to inclusion and exclusion criteria is available in Supplementary Material S1, with trial oversight detailed in Supplementary Material S2. Full details of inclusion and exclusion criteria are also in the original and final protocols (Supplementary Material S7). Patients were followed up for a minimum of 1 year, and all patients continued in the study until the last patient had completed 1 year of follow-up. All patients gave informed consent, and the trial was approved by the London-Chelsea Research Ethics Committee 15/LO/0638.

Treatments
Following the preprocedure fistulogram, the operating radiologist assessed if the patient remained eligible. For all patients, the treatment had 2 components. First, the fistuloplasty procedure was performed with a high-pressure balloon (Bard Dorado), with inflation up to 24 atmospheres to ensure obliteration of the lesion waist, according to the study protocol. Following this, inclusion and exclusion criteria were rereviewed before randomization. In the intervention arm, the second component was insertion of a paclitaxel-coated balloon (Bard Lutonix); and in the control arm, an identical procedure was followed, but using a standard balloon (Bard Ultraverse).

Outcomes
The primary endpoint was time (days) to loss of TLPP. This was defined as patency with no reintervention to the area 5 mm proximal to, within, and 5 mm distal to the index treatment segment. TLPP ended when any of the following occurred: (i) clinically driven reintervention to the treatment segment; (ii) thrombotic occlusion that includes the treatment segment; (iii) surgical intervention that excludes the treatment segment from the access circuit; or (iv) abandonment of the AVF due to an inability to retreat the treatment segment. To minimize bias, a different interventional radiologist to the one who performed the index procedure performed repeated procedures whenever possible. Secondary patency endpoints were time to loss of access circuit primary patency and time to loss of access circuit cumulative patency. Access circuit primary patency ended when any of the following occurred: (i) access circuit thrombosis, (ii) an intervention (either radiological or surgical) anywhere in the access circuit, or (iii) the access circuit is abandoned due to an inability to treat any lesion. Access circuit cumulative patency ends when the AVF is abandoned, regardless of radiological or surgical intervention, with or without a thrombosis event. Multiple/repetitive treatments for stenoses that restore patency were compatible with cumulative patency. Other prespecified secondary endpoints were as follows: angiographically determined late lumen loss (mm), rate of binary angiographic restenosis (%), procedural success (stenosis ≤30% at completion fistulogram II), number of thrombosis events, fistula interventions, adverse events during follow-up, and patient quality of life, assessed using Palliative Care Outcome Scale (POS)–S renal scores and EQ-5D-5L scales at 6 and 12 months postrandomisation. Further details on the primary and
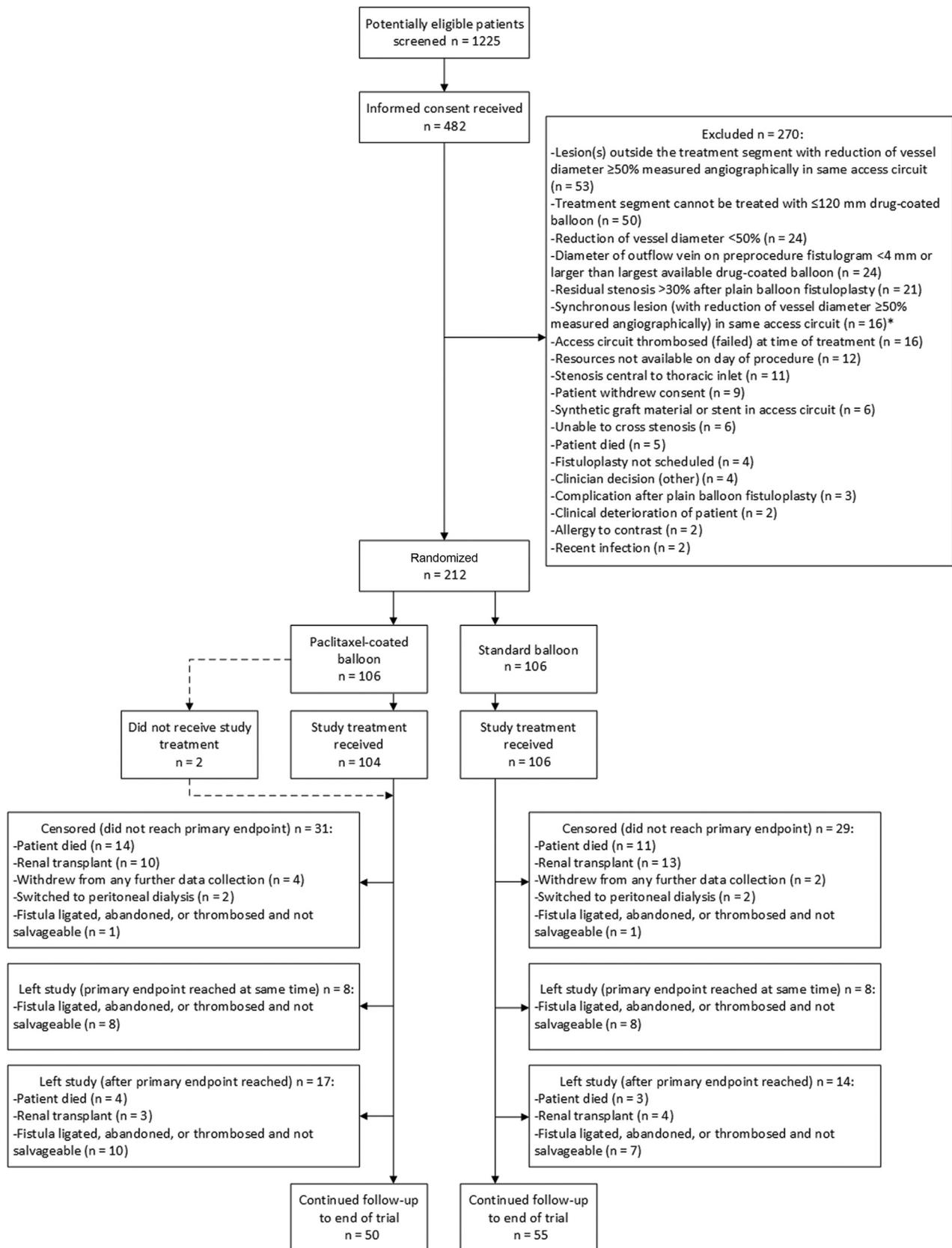
Figure 1 | Consolidated Standards of Reporting Trials (CONSORT) diagram. *These exclusion criteria were amended during the trial (see Supplementary Material S1).

Table 1 | Baseline demographic, clinical, and treatment characteristics of the intention-to-treat population

Characteristics		Paclitaxel-coated balloon (n = 106)	Standard balloon (n = 106)
Age, yr	Mean (SD)	66.9 (12.7)	64.1 (13.3)
Sex	Male	67 (63.2)	61 (57.5)
Ethnicity	White	82 (77.4)	72 (67.9)
	Black	9 (8.5)	16 (15.1)
	Asian	11 (10.4)	14 (13.2)
	Mixed/other	4 (3.8)	4 (3.8)
Current diabetes diagnosis	Yes	58 (54.7)	46 (43.4)
Coronary artery disease	Yes	25 (23.6)	30 (28.3)
Peripheral vascular disease	Yes	13 (12.3)	18 (17.0)
Currently on hemodialysis[a]	Yes	94 (88.7)	97 (91.5)
Location of fistula (arm)	Left	84 (79.2)	72 (67.9)
Type of native fistula	Radiocephalic	43 (40.6)	39 (36.8)
	Brachiocephalic	52 (49.1)	55 (51.9)
	Basilic vein transposition	10 (9.4)	12 (11.3)
	Radial ulna loop	1 (0.9)	NA
Time since fistula formed, mo (n = 210)	Median (IQR)	23 (8–40)	16 (7.5–40.5)
Fistula been used at least once	Yes	84 (79.2)	82 (77.4)
Time since fistula was first used, mo (n = 166)[b]	Median (IQR)	21 (7–41)	15 (5–36)
Current access circuit previously had a thrombosis	Yes	7 (6.6)	3 (2.8)
Previous surgical interventions to the current access circuit	Yes	20 (18.9)	24 (22.6)
Previous radiological intervention in access circuit[a]	Yes	35 (33.0)	38 (35.8)
Location of stenosis	Juxta-anastomotic	51 (48.1)	43 (40.6)
	Venous segment[c]	40 (37.7)	51 (48.1)
	Cephalic arch	15 (14.2)	10 (9.4)
	From cephalic arch to thoracic inlet	—	2 (1.9)
Primary indication for the index procedure	Inadequate dialysis	12 (11.3)	6 (5.7)
	Poor blood flow	37 (34.9)	37 (34.9)
	Prolonged bleeding	5 (4.7)	9 (8.5)
	High venous pressure	9 (8.5)	11 (10.4)
	Low arterial pressure	—	1 (0.9)
	Difficulty needling	25 (23.6)	20 (18.9)
	Immature fistula	5 (4.7)	6 (5.7)
	Not specified	11 (10.4)	13 (12.3)
	Other	2 (1.9)	3 (2.8)
High-pressure balloon type, as per protocol	Yes	87 (82.1)	85 (80.2)
High-pressure balloon length, cm	Mean (SD)	4.6 (1.7)	4.6 (1.8)
Treatment balloon length, cm	Mean (SD)	6.8 (2.0)	6.6 (1.9)
Treatment balloon inflation time >1 min	Yes	104 of 104 (100)	100 of 106 (94)

IQR, interquartile range.
Data are given as n (%), unless otherwise indicated.
[a]Minimization factor.
[b]If used at least once before randomization.
[c]Draining vein (not just the cannulation segment).

secondary endpoint definitions are in the original and final protocols (Supplementary Material S7). Angiographic secondary endpoint core laboratory analysis was performed by the Cardiovascular European Research Centre (Massy, France).

Statistics and analysis

The sample size and power calculations have been described fully in the published protocol[23] and in the statistical analysis plan, which was signed off before database lock. To test the superiority of the paclitaxel-coated balloon compared with the standard balloon in time to loss of TLPP, Cox proportional-hazards regression was used with treatment group and the 2 binary minimization factors as covariates. The third minimization factor, interventional radiologist performing the study procedure, was not adjusted for as this would not allow enough degrees of freedom. Analysis was by intention to treat. Patients were censored if: they had TLPP survival at the end of follow-up; or received a renal transplant, switched to peritoneal dialysis, died, or withdrew from further data collection before reaching the primary endpoint, before the study end. Schoenfeld

residuals were assessed to test whether the proportional-hazards assumption was violated; and an interaction term between treatment group and (log)time was considered to allow for variable follow-up time effects, if they existed. Multiple imputation was considered if numbers of patients noncompliant with study treatment or lost to follow-up were notable or uneven across treatment groups

Planned secondary and sensitivity analyses included: an adjusted analysis of the primary outcome to evaluate the impact of pre-specified baseline covariates on the estimated treatment effect; and an analysis using deaths (not relevant to primary endpoint) and transplantation as competing risks rather than censored events to evaluate the influence of the competing events from preventing the primary endpoint being observed. For the former, the baseline variables were: ethnicity; age; diabetes diagnosis; smoking history; total time (quartiles) on hemodialysis; type of native fistula (where the one patient with radial ulna loop was excluded); previous surgical intervention to the access circuit; and location of stenosis (where the smallest 2 categories, cephalic arch and after cephalic arch but not

beyond the thoracic inlet, were merged because of low subgroup numbers).

Time to event secondary outcomes were analysed using the same Cox proportional-hazards regression. Continuous outcomes employed multiple linear regression, again adjusting for the 2 binary minimization factors, as well as baseline measures of the outcome, if relevant. Count outcomes (checked for overdispersion) were analyzed using negative binomial regression, with time in trial set as the exposure period. Results are reported as hazard ratios (HRs), regression coefficients, odds ratios, or incidence rate ratios, with 95% confidence intervals (CIs), where appropriate. Kaplan-Meier survival curves were constructed by treatment group to illustrate the time to loss of the 3 patency endpoints. Adverse events were categorized into relevant types for this patient population (e.g., access related or not), and a stacked bar chart of maximum severity was used to visually compare treatment groups where patients had reported at least one event.

Analysis was done using Stata version 16.0 (StataCorp, College Station, TX).

RESULTS
Patients
Between November 16, 2015, and October 4, 2018, 212 patients from 20 UK centers (Supplementary Material S3) were randomized into the trial (106 paclitaxel-coated balloon and 106 standard balloon) (Figure 1). The trial ended on October 4, 2019, when all patients had completed at least 1 year of follow-up. Baseline patient demographics and medical history are reported in Table 1 and Supplementary Material S4 and S5 (smoking, renal replacement therapy history, and quality of life). The respective proportions of patients in both the paclitaxel-coated and standard balloon groups who were male (63.2% and 57.5%), white (77.4% and 67.9%), had diabetes (54.7% and 43.3%), or had coronary artery disease (23.6% and 28.3%) reflect the population receiving hemodialysis in the United Kingdom, as does the mean age (66.9 and 64.1 years). Although we included patients who had not yet started dialysis, the large majority (88.7% and 91.5%) were receiving hemodialysis. In 79.2% and 77.4% of cases, the fistula had been used. In the remainder, the intervention was performed to aid fistula maturation or blood flow before use for hemodialysis. There was a range of indications for intervention that are in keeping with clinical experience (Table 1). All characteristics, including fistula type and lesion location, appeared balanced between the groups. A specific high-pressure balloon (Bard Dorado) is named in the protocol. There were no differences in frequency of its use or in the lengths of the high-pressure and treatment balloons used. Two patients did not receive their allocated treatment (paclitaxel-coated balloon) because they were ineligible after randomization, but they were both included in the intention-to-treat analysis (denoted by dashed lines in Figure 1). The inflation time of the treatment balloon was as specified in the protocol in 100% and 94% of cases in the paclitaxel-coated and standard balloon groups, respectively. There were no other major protocol deviations. Six patients withdrew from further data collection during follow-up and were censored in the primary analysis; no patients were lost to follow-up. Multiple imputation was not necessary.

Outcomes
Only 1 (of a possible 3) interim analysis was conducted during the trial, when number of primary endpoint events had reached 27 and recruitment was still ongoing. The independent data monitoring and ethics committee reviewed partially masked results and recommended the continuation of the trial as the prespecified futility and efficacy boundaries had not been met. At the end of the study, 89 patients had reached the primary endpoint, loss of TLPP over the trial period, with similar numbers in each treatment group: 44 in the paclitaxel-coated balloon group and 45 in the standard balloon group (Table 2 and Figure 2a). For those who lost TLPP, the median (interquartile range) times to event were similar at 159 (102–234) and 215 (145–340) days. There was no evidence of a difference in time to loss of TLPP in the paclitaxel-coated balloon group compared with the standard balloon using Cox proportional-hazards regression (HR, 1.18; 95% CI, 0.78, 1.79; $P = 0.440$; Table 2), and there was no suggestion that variable follow-up time effects needed to be adjusted for. The results were not appreciably different in the secondary adjusted analysis, including baseline covariates (HR [95% CI], 1.11 [0.69, 1.78]; $P = 0.664$), or in the competing risks sensitivity analysis (sub-HR [95% CI], 1.06 [0.67, 1.67]; $P = 0.805$). All patients randomized in the current trial were included in the final intention-to-treat survival analysis, and no patients were lost to follow-up, so there were no missing primary outcome data.

At 6 months, the TLPP was 71.7% (66 of 92 patients) in the paclitaxel-coated balloon group, compared with 84.5% (82 of 97 patients) in the standard balloon group. By 12 months, these figures were 52.5% (44 of 81) and 58.8% (50 of 85), respectively. Radiological reintervention was the reason for meeting the primary endpoint in 31 (70.5%) and 34 (75.6%) of the paclitaxel-coated and standard balloon groups, respectively. In only one-quarter (17 of 65) of cases was the primary endpoint met because of reintervention by the interventional radiologist who performed the index procedure, which was evenly split across treatment groups (8 paclitaxel-coated and 9 standard balloons). Otherwise, the primary endpoint was reached because of: thrombosis (3 [6.8%] and 5 [11.1%]); surgical intervention (5 [11.4%] and 1 [2.2%]); or a decision to abandon the fistula (5 [11.4%] and 5 [11.1%]) of paclitaxel-coated and standard balloon groups, respectively. Of 46 fistulas that had not yet been used for dialysis, only 10 (21.7%) of these were abandoned (having reached the end of access circuit cumulative patency) during follow-up.

For the 2 time to event secondary outcomes of loss of access circuit primary and cumulative patency, there was again no evidence for a difference between the treatment groups (HR [95% CI], 1.06 [0.71, 1.59] [$P = 0.764$]; and HR [95% CI], 1.30 [0.67, 2.55] [$P = 0.438$], respectively) (Table 2 and Figure 2b and c). None of the other secondary outcomes demonstrated a treatment effect of paclitaxel-coated balloon compared with standard balloon (Table 2): mean late lumen loss was 1.49 and 1.48 mm; binary restenosis at 6 months

Table 2 | Descriptive summaries and formal between-group comparisons of the primary and secondary outcome measures

Outcomes		Paclitaxel-coated balloon (n = 106)	Standard balloon (n = 106)	Estimated treatment group difference (95% CI)	P value
Primary outcome					
Time to loss of target lesion primary patency	Endpoint reached	44 (41.5)	45 (42.5)	HR, 1.18 (0.78, 1.79)	0.440
	Median (IQR), d	159 (102–234)	215 (145–340)		
Secondary outcomes					
Time to loss of access circuit primary patency	Endpoint reached	47 (44.3)	51 (48.1)	HR, 1.06 (0.71, 1.59)	0.764
	Median (IQR), d	160 (94–268)	203 (139–324)		
Time to loss of access circuit cumulative patency	Endpoint reached	19 (17.9)	16 (15.1)	HR, 1.30 (0.67, 2.55)	0.438
	Median (IQR), d	201 (85–359)	270.5 (173.5–383.5)		
Angiographically determined late lumen loss, mm[a]	Mean (SD)	1.49 (1.55) (n = 55)	1.48 (1.68) (n = 50)	0.17 (–0.38, 0.72)	0.541
Angiographic restenosis (≥50%)[a]	Yes	35 (62.5) (n = 56)	30 (57.7) (n = 52)	OR, 1.23 (0.56, 2.71)	0.600
Procedural success	Yes	102 (98.1) (n = 104)	98 (92.5) (n = 106)	OR, 4.16 (0.85, 20.37)	0.079
No. of thrombosis events	0	87 (82.1)	91 (85.8)	IRR, 1.58 (0.70, 3.58)	0.273
	1	16 (15.1)	10 (9.4)		
	>1	3 (2.8)	5 (4.7)		
No. of fistula interventions	0	55 (51.9)	53 (50.)	IRR, 1.26 (0.85, 1.87)	0.245
	1	25 (23.6)	32 (30.2)		
	>1	26 (24.5)	21 (19.8)		
No. of adverse events	Median (IQR)	0 (1–2)	0 (0–2)	IRR, 1.26 (0.78, 2.04)	0.338
Health today (EQ-5D-5L VAS) at 6 mo	Mean (SD)	64.4 (21.0) (n = 68)	63.9 (20.5) (n = 74)	0.32 (–5.25, 5.89)	0.909
Health today (EQ-5D-5L VAS) at 12 mo	Mean (SD)	65.9 (20.2) (n = 48)	66.0 (22.2) (n = 47)	–1.79 (–9.40, 5.81)	0.640
POS-S renal at 6 mo	Mean (SD)	13.6 (10.8) (n = 68)	13.6 (8.6) (n = 72)	1.01 (–1.59, 3.60)	0.443
POS-S renal at 12 mo	Mean (SD)	13.9 (10.5) (n = 48)	13.6 (8.1) (n = 47)	2.07 (–0.49, 4.62)	0.111

CI, confidence interval; EQ-5D-5L VAS, EuroQol-5 dimension-5 level visual analogue scale; HR, hazard ratio; IQR, interquartile range; IRR, incidence rate ratio; OR, odds ratio; POS-S, palliative outcome scale-symptom.
[a]For those who required an intervention before 6 months, mean days to intervention were 125.1 in the paclitaxel-coated balloon group (n = 23) and 149.6 in the standard balloon group (n = 17).
Data are given as n (%), unless otherwise indicated.

occurred in 62.5% and 57.7%; and procedural success (residual stenosis <30% after treatment with paclitaxel-coated or standard balloon) occurred in 98.1% and 92.5%. Data for the number of thrombosis events, fistula interventions, adverse events, and quality of life at 6 and 12 months are also given in Table 2 and were similar in both groups. Further data on quality of life at 6 and 12 months are given in Supplementary Material S5 with a list of adverse events in Supplementary Material S6. All relevant model assumptions were checked and considered compliant. Finally, Figure 3 illustrates the maximum severity for reported adverse events, where a patient had at least one event for each respective category. In total, 216 events were reported during the study (113 paclitaxel-coated balloon vs. 103 standard balloon), including 32 deaths (18 vs. 14) and 59 access-related events (36 vs. 23).

DISCUSSION

The aim of the PAVE trial was to assess the efficacy of paclitaxel-coated balloons in the treatment of AVFs used to deliver hemodialysis. Although a number of earlier studies have suggested a possible benefit,[13–19] there are only 2 previous large randomized trials, with clinical endpoints, addressing this question.[20,22] The first published large-scale trial by Trerotola *et al.*, using the same paclitaxel-coated balloon as the current trial, also failed to demonstrate a difference between arms in their prespecified primary endpoint, TLPP at 180 days,[20] but there was a significant difference at 210 days in an exploratory analysis. A later publication from this same study showed a significant difference at 9 and 12 months but not at 18 or 24 months.[21] Therefore, uncertainty remained regarding the efficacy of paclitaxel-coated balloons for this indication.

A recent study by Lookstein *et al.* that also used a binary primary endpoint of TLPP at 6 months did find evidence of a benefit for paclitaxel-coated balloons.[22] One possible explanation for the contrasting result in this and the current study is the use of a different treatment balloon. The Lutonix balloon used in the current study used a coating of paclitaxel, sorbitol, and polysorbate with a drug dose density of 2 µg/mm^2. In contrast, the IN.PACT balloon used by Lookstein *et al.* is loaded with a higher concentration of paclitaxel (3.5
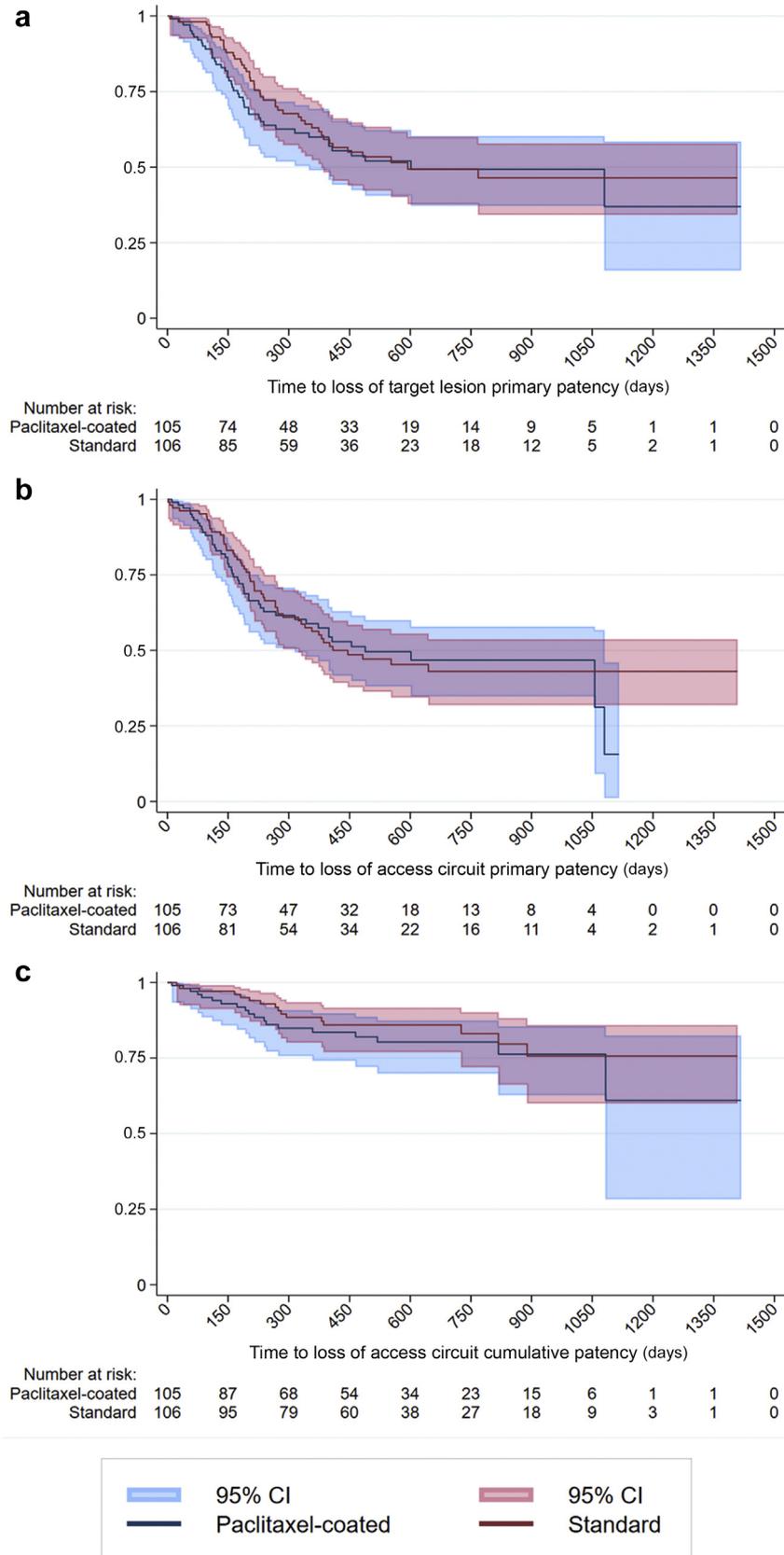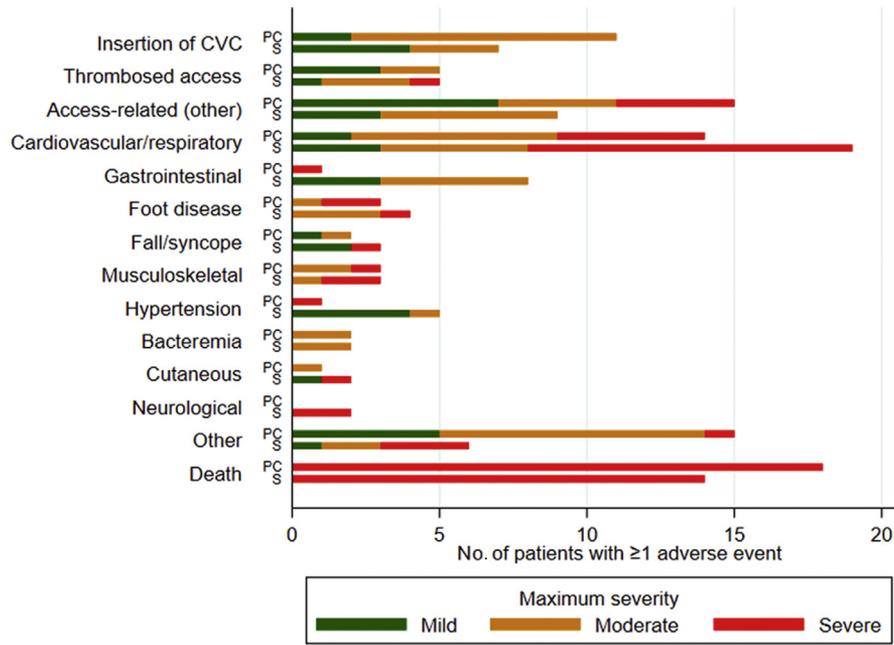
Figure 2 | Kaplan-Meier survival curves by treatment group for the loss of patency outcomes. CI, confidence interval.

Figure 3 | Severity and type of adverse event by treatment group. This bar chart illustrates the main types of adverse events that were reported by patients during follow-up, by treatment group and maximum severity. Patients can be included in >1 type of event, but if they experienced a certain event type more than once, then they have only been counted once for that event, and the maximum severity that they reported for that type of event has been used. Please note: this graph does not include deaths that occurred after patients formally withdrew from the trial. CVC, central venous catheter; PC, paclitaxel-coated balloon group; S, standard balloon group.

$\mu g/mm^2$) and uses a urea-based excipient. These devices were compared in a pig femoral artery angioplasty model.[24] There was no comparison of the amount of drug delivered to the artery. However, there was a higher paclitaxel content in nontarget tissues and evidence of downstream embolic crystalline material with the IN.PACT balloon. Another study showed greater drug loss from the IN.PACT balloon than from the Lutonix balloon with dry handling or inflation.[25] Therefore, the higher drug dose density on the IN.PACT balloon does not necessarily result in a higher drug dose being delivered to the target lesion because a higher proportion may be lost before insertion or deposited in nontarget tissues.

When recruitment to the PAVE trial began in November 2015, the instructions for the paclitaxel-coated balloon recommended an inflation time of 30 seconds, and 60 seconds was stated in the protocol to ensure this was exceeded. Data collected during the trial included a question asking if an inflation time of >60 seconds was achieved (yes or no). From March 2018, when 75% of patients had been randomized, study sites were asked to inflate for a minimum of 120 seconds following a change in the manufacturer's instructions. The data in Table 1 showed good adherence to the protocol, with inflation recorded as >60 seconds in 97% of patients, with no evidence of a difference between groups. The manufacturer's recommendation for an increase in inflation time is based on preclinical data in a pig femoral artery angioplasty model, but there are no data given comparing 60 with 120 seconds.[25] The fact that the current study used the Lutonix balloon with a minimum inflation time of 60 seconds does not necessarily mean that a lower dose of paclitaxel was

delivered to the target lesion that occurred in the study by Lookstein *et al.* using the IN.PACT balloon.[22] However, we acknowledge that this is a possible explanation for the differing results.

A limitation of the PAVE trial is that it was not a fully blinded trial. It was impossible to ensure that treating radiologists were blinded to treatment allocation because of the appearance of the paclitaxel-coated balloon. However, all other investigators as well as the patients were blinded, and this minimized the chance of bias. Furthermore, it is more likely that any small introduction of bias would have led to a positive outcome, rather than the negative result that we found. Patients were invited to attend a 6-month protocol fistulogram. If clinically indicated imaging or intervention was planned, then the protocol fistulogram was not requested. Radiologists were instructed not to intervene if subclinical stenosis was detected at the protocol fistulogram, and this was adhered to in all cases. Therefore, the protocol fistulogram had no effect on the primary outcome measure of clinically driven TLPP.

A number of aspects in the design of the current trial further reduced the possibility of bias. Reintervention was only performed after referral for a clinical indication by a member of the clinical team blinded to the treatment allocation. Clinically driven radiological reintervention was the predominant reason for meeting the primary endpoint. Reintervention was performed by a different interventional radiologist whenever possible. Images from radiological interventions leading to loss of TLPP were reviewed by an interventional radiologist from a different study site or the core laboratory in all cases. In cases where the primary

endpoint was reached because of surgical intervention or a decision to abandon the fistula, the decision would not have been influenced by knowledge of treatment allocation.

The 6-month TLPP in the control group was 84.5% in the current trial, and this is higher than those reported in the other published trials[20,22] and most institutional case series.[4–10] The TLPP in the control arm of the study by Lookstein *et al.* was only 59.5% at 6 months.[22] This underlines the value of a good balloon fistuloplasty in maintaining patency. If a good result is achieved with a high-pressure plain balloon, then there may be little or no benefit in using an additional paclitaxel-coated balloon. This may be why paclitaxel-coated balloons were shown to improve the outcome in the study by Lookstein *et al.*,[22] but not in the current study. An increase in mortality has been linked with the use of paclitaxel-coated balloons in peripheral vascular disease.[26] An effect was seen after 2 years but not after 1 year, and the mechanism was not clear. Although we saw more deaths in patients treated with paclitaxel-coated balloons compared with the control group (Figure 3), the difference was small, and the numbers were too low to draw any conclusions.

In contrast to the previous trials,[20,22] only patients with a single lesion or tandem lesions that could be treated by a single drug-coated balloon were eligible in the current trial. This is unlikely to explain the lower event rate in the current trial because previous data suggest that post-intervention access circuit primary patency is similar in patients with multiple or single lesions.[7] However, stenoses at multiple sites in the access circuit are a common finding, and deciding which is clinically most significant can be subjective. We therefore only included patients with a stenosis at a single site in the circuit to be sure that this lesion was responsible for the clinical problem leading to intervention. To maintain recruitment of patients with a single treatment segment, we included fistulas that had not yet been used for dialysis. However, few of these were abandoned (having reached the end of access circuit cumulative patency) during follow-up. Therefore, a high rate of primary failure of fistula maturation was unlikely to affect the outcome. We consider the application of a drug-coated balloon to a single treatment segment to be a unique feature and a strength of the current study.[20,22] The aim was to investigate the efficacy of paclitaxel-coated balloons, and we believe that this increased the rigor with which we were able to address this aim.

In conclusion, the current results provide no evidence of an additional benefit from paclitaxel-coated balloons compared with standard balloons when used after a clinically driven high-pressure balloon angioplasty in AVFs. We did not observe any indication of an early treatment effect in the data, and all of the prespecified outcomes support the same conclusion.

DISCLOSURE

KS has performed consultancy work and sat on an advisory board for CR Bard (Becton Dickinson). All the other authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Section S1. Inclusion and exclusion criteria.
Section S2. Trial oversight.
Section S3. Sites.
Section S4. Baseline smoking and renal replacement therapy history.
Section S5. Health-related quality of life.
Section S6. List of adverse events.
Section S7. Protocols and statistical analysis plans: original protocol (version 2.0, approved before the first site opened), final protocol (version 9.0), version control document (summary of changes), original statistical analysis plan (version 1.0), and second and final statistical analysis plan (version 2.0, changes listed in section 1.6).

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