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A double-blind, randomized, placebo-controlled pilot trial to evaluate safety and efficacy of vorapaxar on arteriovenous fistula maturation

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Abstract

Background: Protease-activated receptor-1 antagonism by vorapaxar could facilitate arteriovenous fistula maturation but may increase bleeding risk.

Objective: The primary objective of the Vorapaxar Study for Maturation of arteriovenous fistula for Hemodialysis Access (VorapAccess) was to determine if vorapaxar improves arteriovenous fistula functional maturation in patients with end-stage renal disease.

Methods: VorapAccess was a randomized, placebo-controlled, double-blind pilot trial comparing 2.5 mg vorapaxar per day with placebo for twelve weeks starting on day two after arteriovenous fistula creation. The primary outcome was time to functional maturation defined as successful cannulation for six hemodialysis sessions within three weeks. The planned sample size was 50 participants. The study was terminated early after withdrawal of planned financial support. Given the small number of randomized patients, we performed descriptive analyses without inference testing.

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Declaration of conflicting interests

The remaining authors had no conflicts to declare.

Trial registration

ClinicalTrials.gov Identifier: NCT02475837.

Supplemental material

Supplemental material for this article is available online.

Results: A total of 13 participants were randomly allocated study drug (six vorapaxar and seven placebo). The median age was 56 years and seven participants (54%) were female. The median (minimum–maximum) days to functional maturation were 169 (77–287) days in the vorapaxar group and 145 (48–198) days in the placebo group. Six of the 13 (46%) participants had arteriovenous fistula functional maturation within 180 days; two of six (33%) in the vorapaxar group and four of seven (57%) in the placebo group. There was one bleeding event in the placebo group.

Conclusion: Fewer than half of participants had functional maturation within 180 days after surgery, suggesting a major need for agents or strategies that enhance arteriovenous fistula maturation.

Keywords

Arteriovenous fistula; dialysis; vorapaxar; thrombin; VorapAccess; clinical trial

Introduction

Arteriovenous fistula (AVF) is the recommended vascular access for maintenance hemodialysis.[1] For patients who undergo AVF creation, either in advance of, or after starting, hemodialysis, 20%–60% of AVF never mature sufficiently to be used for hemodialysis.[2–5]

Studies have attempted to improve short- and long-term functions of AVF with a variety of therapeutic agents, including warfarin, acetylsalicylic acid (ASA), and $P2Y_{12}$-antagonists.[6–10]

To address the need for improved outcomes, the National Institutes of Health (NIH) National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) assembled the Dialysis Access Consortium (DAC).[11] The DAC investigators conducted a randomized, placebo-controlled trial of clopidogrel in patients receiving AVF.[2] Clopidogrel significantly enhanced short-term patency of AVF but failed to improve AVF maturation sufficient for serial cannulation: 61% of the patients failed to have a usable AVF at three to four months,[2] highlighting the need for more effective therapy.

The inhibition of protease-activated receptor (PAR)-1 represents an alternative approach in antiplatelet strategies—independent of ASA or $P2Y_{12}$-antagonists targeted pathways.[12] Vorapaxar competitively inhibits PAR-1 and has been shown in preclinical studies to inhibit platelet aggregation[13] and thrombosis.[14] Besides on platelets, PAR-1 is found on endothelial cells, smooth muscle cells, and monocytes regulating vascular integrity and inflammation, for example, through cytokine release.[15–18]

PAR-1 inhibition reduces activation of the endothelium and inflammation, suggesting important roles in tissue response to injury.[19] Thus, the effects of vorapaxar on factors relevant to AVF maturation[20] above and beyond those related to platelet inhibition itself provides a rationale for testing vorapaxar with the goal of facilitating maturation of AVF for hemodialysis.

The primary objective of the Vorapaxar Study for Maturation of Arteriovenous Fistulae for Hemodialysis Access (VorapAccess) was to determine if 2.5 mg vorapaxar daily safely improves AVF functional maturation when administered in the first twelve weeks after AVF creation. Secondary objectives were to determine if vorapaxar safely improves AVF patency and to analyze the safety profile of vorapaxar for patients with advanced chronic kidney disease (CKD) and end-stage renal disease (ESRD).

Methods

Patient population

Participants were eligible for participation if they were older than 18 years, able to sign informed consent, receiving or planning to receive maintenance hemodialysis, and with a ⩾3 mm venous diameter within recipient vein. Exclusion criteria were a history of stroke, transient ischemic attack or intracranial hemorrhage; severe arterial insufficiency of the hand; indication for or ongoing therapy with other antiplatelet agents other than ASA 81 mg daily; or indication for or ongoing therapy with anticoagulants, including warfarin, low molecular weight heparin, factor Xa inhibitors, or direct thrombin and other inhibitors. Pre-operative mapping, selection of AVF location, and surgery were performed by board-certified vascular surgeons at Stanford University School of Medicine (Stanford, California, USA).

Study design and procedures

This was a randomized, placebo-controlled, double-blind pilot trial comparing 2.5 mg vorapaxar daily with placebo following AVF creation. Informed consent was obtained before study procedures. Participants were assigned to receive the study drug (vorapaxar 2.5 mg daily) or a look-alike placebo with a 1:1 stratified randomization in blocks of four. We stratified participants by AVF location (lower arm or upper arm). We instructed participants to take the study medication for twelve weeks starting on the second day after surgery. We performed data collection at baseline, six weeks, three months (phone call), four months (phone call), and a final visit at six months. We tracked patients for the occurrence of efficacy and safety outcomes until 180 days ± 4 weeks. Supplemental Figure S1 illustrates the study design.

This study was carried out in accordance with the Declaration of Helsinki and was approved by the Stanford Institutional Review Board (IRB; #33763) on 15 July 2015. Due to a lower-than-expected recruitment rate, the study protocol was amended, and sample size decreased from 128 to 50, another site was added, and duration was extended from 24 to 30 months. The amended protocol was approved by the IRB on 14 December 2016. On 15 May 2017, the grantor withdrew planned financial support and the trial was terminated.

End points

The primary end point was the time to AVF functional maturation defined as successful cannulation of the AVF for six hemodialysis sessions within three weeks. We calculated time to AVF maturation as the number of days from surgery until first successful use of AVF for

participants who had functional maturation; participants without functional maturation were censored at their six-month follow-up visit date.

Secondary efficacy end points were the following: (1) any AVF use within 180 days of surgery; (2) AVF patency at 150–180 days, with at least 50% increase in vein diameter by ultrasound compared with preoperative vein diameter; and (3) AVF maturation defined as a composite of functional or anatomical maturation within 180 days of surgery and was determined by the principal investigator (M.W.M.) blinded to treatment per clinical judgment. This third secondary end point was added in an amendment to the protocol which was approved by the IRB on 30 June 2018. Key safety outcomes included bleeding events defined by the Bleeding Academic Research Consortium (BARC)[21] and the Global Use of Strategies to Open Occluded Arteries (GUSTO) criteria.[22]

Statistical considerations

The planned primary analysis was based on the intentionto-treat principle. Participants were to be analyzed according to their randomized treatment assignment even if they were lost to follow-up or died before the end of their observation period. We had planned a log-rank test stratified by location of fistula to assess whether time to maturation of AVF differed between treatment arms (vorapaxar vs placebo). All tests were to be two-sided and conducted at the 0.05 level of significance. Due to low enrollment and early termination of the study, the planned analyses were not conducted. We present descriptive analyses of enrolled participants and outcomes of interest.

Based on the planned sample size of 25 participants per group, there was approximately 70% power to detect a hazard ratio of 2.05 between treatment arms, assuming that only 50% of participants would experience maturation by six months after randomization in the placebo group. If we assume that only 40% of participants experienced maturation by six months after randomization, there was over 70% power to detect a hazard ratio of 2.15.

Role of the grantor

Merck provided an investigator-initiated study grant for the conduct of the study and the study drug with matching placebo in study kits. On 15 May 2017 after discussions about enrollment potential and funding, Merck withdrew planned financial support of the study, recruitment ceased, and follow-up visits of the enrolled participants were completed.

Results

From August 2015 through May 2017, we screened 69 participants for eligibility (cumulative screening and enrollment shown in Supplemental Figure S2). We consented 17 participants and 13 were randomized (26% of the planned sample size of 50 participants) to either 2.5 mg vorapaxar (six participants) or placebo (seven participants). Figure 1 shows the study flow chart. In three participants, the end-of-study visit occurred after 180 days ± 4 weeks.

Patients

Baseline characteristics of the participants are shown in Table 1 (for individual characteristics see Supplemental Table S1). The median age was 56 (IQR 45–66) years and seven participants (54%) were female; nine participants (69%) were on hemodialysis at the time of inclusion. Nine (69%) participants had diabetes mellitus and twelve (92%) had hypertension. Six (46%) participants had concomitant 81 mg aspirin. In four (31%) participants, AVF was placed in the lower arm and in nine (69%) in the upper arm.

Efficacy

The median (minimum–maximum) number of days to functional maturation was 169 (48–287) days. Six of the 13 participants (46%) had AVF functional maturation within 180 days after surgery (none of four participants with lower arm AVF and six of nine participants with upper arm AVF).

The median (minimum–maximum) days to functional maturation were 169 (77–287) days in the vorapaxar group and 145 (48–198) days in the placebo group (Figure 2). AVF functional maturation within 180 days after surgery was found in two of six participants (33%; at 77 and 96 days after randomization, respectively) in the vorapaxar group and in four of seven participants (57%; at 48, 76, 84, and 145 days after randomization, respectively) in the placebo group. Secondary outcomes are summarized in Table 2.

Six of the 13 participants (46%) had a patent AVF with an increase in vein diameter of at least 50% at 180 days after surgery compared with baseline measurement (one of six [17%] in the vorapaxar group and five of seven [71%] in the placebo group). Three participants in the vorapaxar group received the ultrasound examination out of window and their AVF was assessed to be patent with an increase in vein diameter of at least 50% at 225, 287, and 295 days after randomization. Seven of the 13 participants (54%) had functional or anatomic maturation at 180 days ± 4 weeks after surgery (two of six [33%] in the vorapaxar group and five of seven [71%] in the placebo group). However, in two participants, the visit occurred out of window and their AVF were found to be anatomically mature at 287 and 324 days after randomization, respectively.

Ultrasound parameters at 180 days ± 4 weeks after surgery were available in seven participants (one of the vorapaxar group and six of the placebo group). The AVF of the patient of the vorapaxar group showed a diameter of 13.0 mm and the median diameter (IQR) of the AVFs of the participants treated with placebo was 5.9 (5.5–8.4) mm.

Safety

Three (50%) participants in the vorapaxar group and three (43%) participants in the placebo group experienced at least one serious adverse event (see Table 3 and Supplemental Table S2 for detailed information). A total of 14 serious adverse events occurred (six in the vorapaxar group and eight in the placebo group). There were no bleeding events in the vorapaxar group and one bleeding event in the placebo group. This bleeding event was an upper gastrointestinal hemorrhage classified as BARC Type 2 and GUSTO mild and occurred 39 days after surgery.

Discussion

The VorapAccess trial was designed to determine whether vorapaxar safely facilitates AVF functional maturation when administered for twelve weeks following AVF creation. While the trial was terminated early, we found in the 13 randomized participants that (1) the rate of functional maturation rate at 180 days was low and (2) no bleeding occurred in the six patients randomized to vorapaxar.

Despite the small number of participants, the overall proportion of participants with functional maturation at 180 days ± 4 weeks after surgery was 46% and is similar to other trials or registries (~45%–60%).[2,23,24] In the US Renal Data System,[25] the median time to first use of matured AVF is 108 days—similar to our results of the six participants with functional AVF maturation within 180 days at 48, 76, 77, 84, 96, and 145 days.

End point selection in AVF trials is challenging. AVF development is categorized in four stages: creation; maturation; clinical use, initial; and clinical use, sustained.[26] While the clinical significance increases along these stages, every stage comes with challenges in trial design. Several prior trials chose the occurrence of thrombotic complications at six or twelve weeks as primary outcome measures.[11,27] In the recent PATENCY trial,[28] treatment with vonapanitase did not significantly improve primary patency but was associated with increased secondary patency and use for hemodialysis. The reduction of early thrombosis, however, does not necessarily result in improved maturation at later time points.[2] Thus, the primary outcome measure of VorapAccess was time to AVF functional maturation which is similar to a recently published recommendation by the Kidney Health Initiative.[26] Nearly a third (four [31%] of the 13 participants, however, did not undergo hemodialysis during the trial. These participants therefore did not qualify for the selected primary outcome measure. Clinical practice guidelines recommend pre-emptive creation of an AVF in patients destined to require renal replacement therapy, who have selected hemodialysis (rather than peritoneal dialysis) and do not have an imminently scheduled living donor kidney transplant. Thus, future trials should carefully consider the clinical significance of an end point and the need for number of events for sufficient power.

Safety

Vorapaxar has been studied in two large cardiovascular outcome trials in participants with chronic stable coronary artery disease and after acute coronary syndrome.[29,30] In both trials, vorapaxar reduced the composite of cardiovascular death, myocardial infarction, and stroke with an excess in bleeding.[29,30] However, vorapaxar was tested on top of concomitant antiplatelet therapy—in most cases, ASA plus a thienopyridine. Only one of the 13 participants in VorapAccess had a bleeding event that was mild by the GUSTO criteria, and this event occurred in a participant assigned to placebo and who was taking ASA. None of the participants randomized to vorapaxar had any bleeding. Four of these participants were treated with additional ASA and two had no additional platelet inhibitors. While reassuring, the small number of participants limits any real conclusions about safety of vorapaxar in participants with ESRD and AVF.

Challenges and limitations

We experienced challenges during the conduct of the trial. First, the local referral patterns for vascular surgery consults at Stanford for AVF consideration changed during the trial conduct and enrollment was lower than anticipated. Screening efforts were increased with additional resources; screening of clinical databases and operating room schedule, and an additional local hospital was identified as clinical site but never enrolled a participant. These measures resulted in boost in screening (see Supplemental Figure S2). Unfortunately, during the conduct of the study the granting pharmaceutical company sold the rights of the drug to another company. This limited drug supply that was being provided at no cost to the investigators. In addition, the grantor did not have confidence that overall enrollment targets would be met despite the improvement in recruitment. The grantor, therefore, chose to withdraw the funding that had been planned and only support close out activities. We did not meet the target sample size and thus, we were unable to make quantitative comparisons between randomized groups. However, results from all clinical trials should be reported in compliance with the Declaration of Helsinki, whether or not the intervention is successful, and whether or not the trial itself proved feasible. Unpublished trials fail to inform the field.

Conclusion

This pilot study was designed to determine whether vorapaxar safely facilitates AVF functional maturation when administered for twelve weeks following AVF creation but was terminated early. The small number of participants did not allow for quantitative treatment comparisons. Overall, fewer than half of participants had AVF functional maturation within 180 days after surgery, suggesting that there remains a major need for agents or strategies that can enhance maturation of AVF for use in maintenance hemodialysis. None of the participants randomized to vorapaxar had any bleeding. While reassuring, the small number of participants limits any real conclusions about safety of vorapaxar in participants with ESRD or near ESRD and AVF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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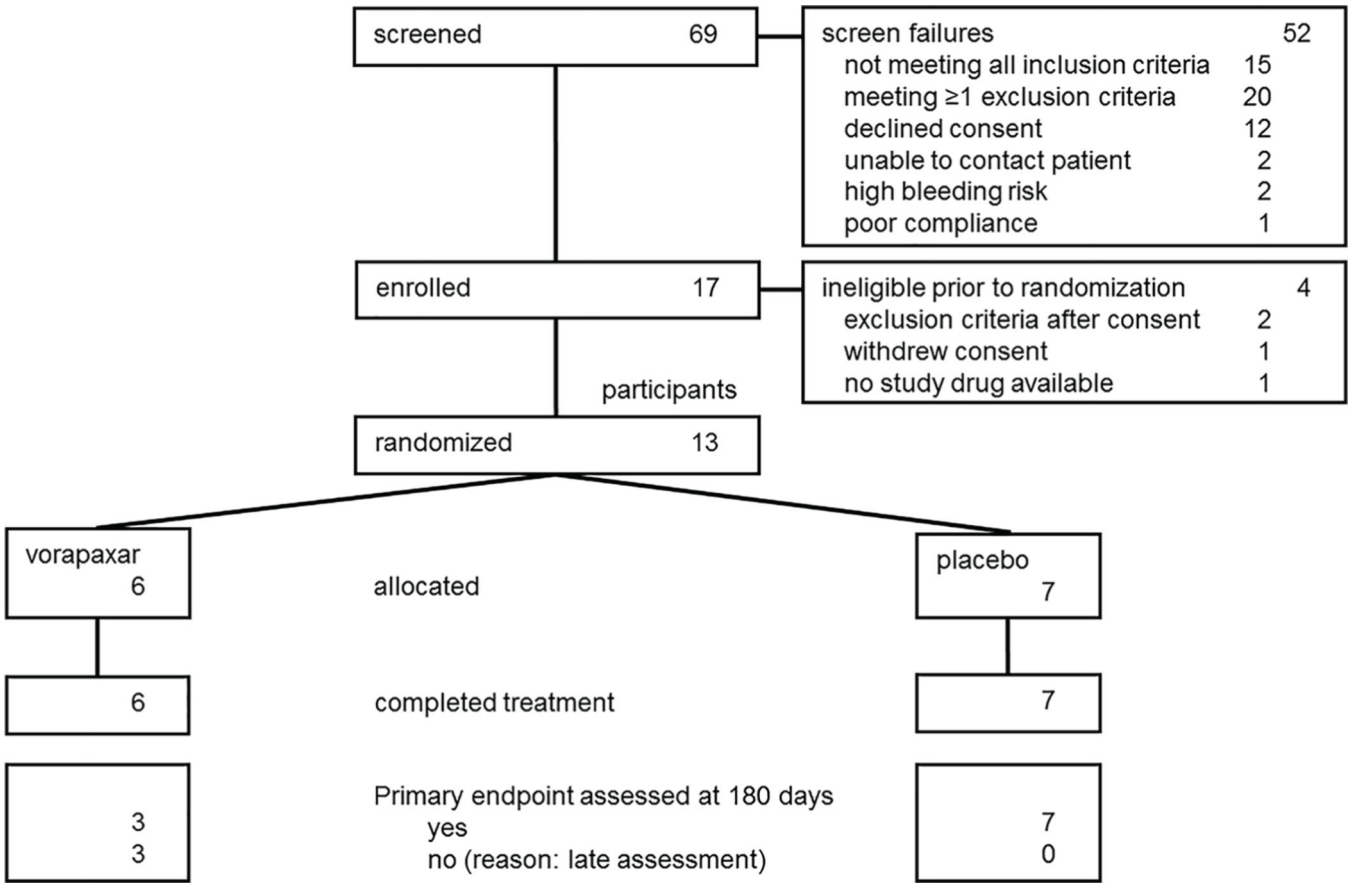

Figure 1. Study flow chart.

Thirteen participants were assigned to receive the vorapaxar 2.5 mg daily or a look-alike placebo with a 1:1 randomization in blocks of four. Participants were stratified based on fistula location (lower arm or upper arm) and instructed to take the study medication for twelve weeks starting on day two after surgery.

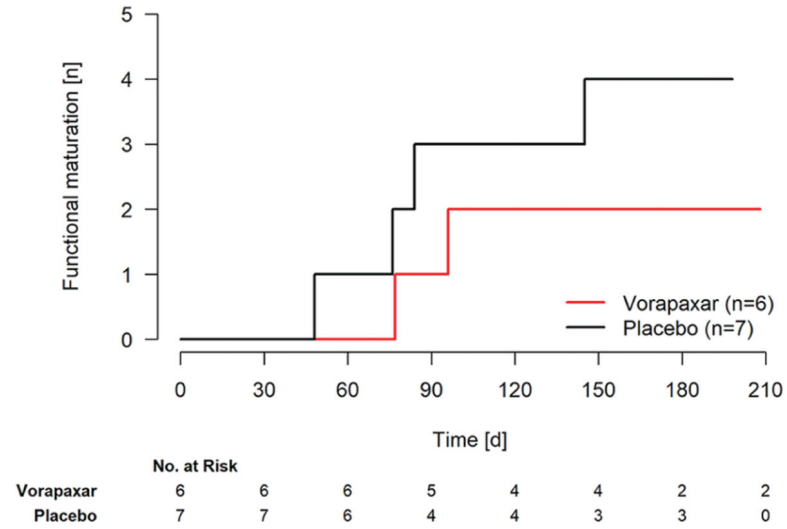

Figure 2. Primary end point: time to functional maturation.

The median (minimum–maximum) days to functional maturation were 169 (77–287) days in the vorapaxar group and 145 (48–198) days in the placebo group. Six of the 13 participants (46%) had AVF functional maturation within 180 days after surgery; two of six (33%; at 77 and 96 days after randomization, respectively) in the vorapaxar group and four of seven (57%; at 48, 76, 84, and 145 days after randomization, respectively) in the placebo group.

Table 1.

Baseline Characteristics.

Characteristic	Overall N = 13		Vorapaxar N = 6		Placebo N = 7	
Demographics						
Age, (y)	56	(45–66)	50	(45–66)	62	(46–66)
Female	7	(54)	3	(50)	4	(57)
Race						
White	2	(15)	2	(33)	0	
Black	3	(23)	1	(17)	2	(29)
Asian	2	(15)	1	(17)	1	(14)
American Indian/Alaska Native	1	(8)	0	(33)	1	(14)
Other	5	(38)	2		3	
Hispanic or Latino	5	(38)	3	(50)	2	(29)
Comorbidities and conditions						
Previous hemodialysis access surgery	9	(69)	4	(67)	5	(71)
Hemodialysis (at time of inclusion)	9	(69)	4	(67)	5	(71)
Diabetes mellitus	9	(69)	3	(50)	6	(86)
Coronary artery disease	1	(8)	0		1	(14)
Congestive heart failure	2	(15)	0		2	(29)
Peripheral artery disease	0		0		0	
Hypertension	12	(92)	5	(83)	7	(100)
Cancer	4	(31)	3	(50)	1	(14)
Peptic ulcer disease	1	(8)	1	(17)	0	
Ejection fraction performed	7	(54)	3	(50)	4	(57)
Ejection fraction (%)	58	(50–63)	55	(50–63)	59	(48–63)
Systolic blood pressure (mmHg)	133	(125–152)	136	(115–144)	132	(125–157)
Diastolic blood pressure (mmHg)	81	(77–86)	84	(79–86)	81	(77–86)
Heart rate (beats/min)	81	(78–83)	86	(81–100)	78	(73–81)
Body weight (kg)	82	(67–95)	86	(67–93)	82	(62–97)
Body mass index (kg/m^2)	28	(27–40)	32	(27–40)	27	(22–40)
Comedication						

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Characteristic	Overall N = 13		Vorapaxar N = 6		Placebo N = 7	
ASA 81 mg or less	6	(46)	4	(67)	2	(29)
ACE-inhibitor	3	(23)	2	(33)	1	(14)
Statins	5	(38)	2	(33)	3	(43)
Insulin	6	(46)	2	(33)	4	(57)
Oral diabetic medications	1	(8)	1	(17)	0	
ARBs	2	(15)	0		2	(29)
Other anti-hypertensive	6	(46)	3	(50)	3	(43)
Laboratory results						
Hemoglobin (g/dL), n = 11	12.0	(9.0–12.8)	12.0	(9.0–13.3)	12.2	(10.2–12.4)
Hematocrit (%), n = 11	38	(29–40)	39	(38–41)	33	(19–37)
Platelet count (1000/μL), n = 11	212	(177–234)	184	(164–212)	233	(232–269)
INR, n = 4	1.2	(1.1–1.3)	1.2	(1.1–1.2)	1.2	(1.1–1.3)
Potassium (mg/dL)						
On hemodialysis, n = 7	4.7	(4.3–4.8)	4.8	(4.3–4.9)	4.7	(3.9–4.8)
Not on hemodialysis, n = 3	4.4	(3.7–4.9)	4.7	(4.4–4.9)	3.7	
Creatinine (μmol/L)						
On hemodialysis, n = 7	8.1	(4.4–11.2)	8.6	(8.1–11.2)	5.4	(4.2–10.2)
Not on hemodialysis, n = 3	4.8	(4.7–9.5)	4.8	(4.7–4.8)	9.5	
Blood urea nitrogen (mg/dL)						
On hemodialysis, n = 7	52	(50–53)	52	(50–53)	52	(41–59)
Not on hemodialysis, n = 3	64	(59–86)	62	(59–64)	86	
Glucose (mg/dL)						
With diabetes, n = 6	130	(104–205)	106	(68–144)	161	(110–208)
Without diabetes, n = 3	111	(79–116)	114	(111–116)	79	
Procedural characteristics						
Study fistula location						
Forearm	4	(31)	2	(33)	2	(29)
Radiocephalic	4	(31)	2	(33)	2	(29)
Upper arm	9	(69)	4	(67)	5	(71)
Brachiocephalic	5	(38)	2	(33)	3	(43)
Brachiobasilic	4	(31)	2	(33)	2	(29)

Characteristic	Overall N = 13		Vorapaxar N = 6		Placebo N = 7	
Calcification of artery						
Normal	10	(77)	6	(100)	4	(57)
Mild	2	(15)	0		2	(29)
Moderate	1	(8)	0		1	(14)
Severe	0		0		0	
Palpable thrill at completion	13	(100)	6	(100)	7	(100)
Audible bruit at completion	7	(54)	2	(33)	5	(71)

Values are median (interquartile range) or n (%).

ASA: acetylsalicylic acid; ARB: angiotensin II receptor blocker; INR: international normalized ratio; ACE: angiotensin-converting enzyme.

Table 2.

Secondary and Exploratory End Points.

	Vorapaxar N = 6	Placebo N = 7
Secondary end points		
AVF use *	2 (33)	4 (57)
AVF patency, with at least 50% increase in vein diameter *[a]	1 (17)	5 (71)
AVF functional or anatomic maturation[b]	2 (33)	5 (71)
Exploratory end points *		
Diameter (mm), median (IQR)	N = 1 13.0	N = 6 5.9 (5.5–8.4)
Velocity (cm/s), median (IQR)	N = 1 269	N = 6 146 (90–156)

Values are median (interquartile range) or n (%).

AVF: arteriovenous fistula; IQR: interquartile range.

[a]Three participants in the vorapaxar group had AVF patency at 225, 287, and 295 days after randomization.

[b]Two participants in the vorapaxar group had AVF maturation at 287 and 324 days after randomization.

*Assessed at 180 days ± 4 weeks after surgery.

Table 3.

Safety Outcomes and Adverse events.

	Vorapaxar N = 6	**Placebo N = 7**
Any serious adverse event *	3 (50)	3 (43)
Bleeding	0	1 (14)
Death	0	0

* All serious adverse events were deemed unlikely to be related to the study drug.