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Early Ultrasound Surveillance of Newly-Created Hemodialysis Arteriovenous Fistula

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Introduction: We assess if ultrasound surveillance of newly-created arteriovenous fistulas (AVFs) can predict nonmaturation sufficiently reliably to justify randomized controlled trial (RCT) evaluation of ultrasound-directed salvage intervention.

Methods: Consenting adults underwent blinded fortnightly ultrasound scanning of their AVF after creation, with scan characteristics that predicted AVF nonmaturation identified by logistic regression modeling.

Results: Of 333 AVFs created, 65.8% matured by 10 weeks. Serial scanning revealed that maturation occurred rapidly, whereas consistently lower fistula flow rates and venous diameters were observed in those that did not mature. Wrist and elbow AVF nonmaturation could be optimally modeled from week 4 ultrasound parameters alone, but with only moderate positive predictive values (PPVs) (wrist, 60.6% [95% confidence interval, CI: 43.9–77.3]; elbow, 66.7% [48.9–84.4]). Moreover, 40 (70.2%) of the 57 AVFs that thrombosed by week 10 had already failed by the week 4 scan, thus limiting the potential of salvage procedures initiated by that scan's findings to alter overall maturation rates. Modeling of the early ultrasound characteristics could also predict primary patency failure at 6 months; however, that model performed poorly at predicting assisted primary failure (those AVFs that failed despite a salvage attempt), partly because patency of at-risk AVFs was maintained by successful salvage performed without recourse to the early scan data.

Conclusion: Early ultrasound surveillance may predict fistula maturation, but is likely, at best, to result in only very modest improvements in fistula patency. Power calculations suggest that an impractically large number of participants (>1700) would be required for formal RCT evaluation.

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For most individuals with end-stage renal disease, AVFs are the preferred modality for providing hemodialysis. Compared to dialysis via a central venous catheter, AVF use is associated with decreased hospitalization from bloodstream infections,[1-5] thereby offering substantial cost savings,[6,7] and a 40% reduction in

mortality.[8] Despite this, as many as two-thirds of those commencing hemodialysis in the United Kingdom do so via a central venous catheter.[9] This partly reflects that, once created, AVFs must "mature" over several weeks before they can be used for dialysis, with approximately 30% of fistulas failing to do so.[10–15] These failures necessitate either salvage interventions or creation of a new fistula, thus potentially prolonging the requirement for dialysis via a central venous catheter. Maturation failure and early thrombosis may, moreover, limit options for future AVF creation, by precluding reuse of the entire draining fistula vein.

AVF maturation is characterized by massive increases in blood flow through the AVF and marked expansion in the fistula vein diameter, with compensatory thickening or "arterialization" of the vein wall. Doppler ultrasound surveillance of AVFs immediately after their creation may therefore identify early flow characteristics or anatomical features (such as the development of juxta-anastomotic ["swing-segment"] stenosis[16]), that predict subsequent maturation failure. By providing an opportunity for successful radiological or surgical salvage, potentially before terminal thrombosis of the AVF, such early identification may improve overall AVF patency and lessen the requirement for dialysis via a central venous catheter. This, however, remains largely untested. One RCT[13] has evaluated routine early ultrasound and reported a 13.6% fistula failure in the surveillance group, compared to 25.4% in the control group (ultrasound performed selectively, according to clinical indication), but the study was powered for a relatively large (20%) effect size, and the difference in maturation rates in the 2 groups did not reach statistical significance.

For early ultrasound surveillance to improve AVF outcomes, the following 2 conditions must be met: (i) that ultrasound can reliably identify those fistulas that are either not going to mature or will fail early and (ii) that the salvage interventions triggered by the ultrasound findings make a lasting improvement in fistula patency. Here, we report the findings of the SONAR study, a prospective multicenter study involving several hundred patients that assessed whether ultrasound surveillance could reliably identify those AVFs that would either not mature or fail early, and if so, whether, within the constraints of standard United Kingdom vascular access provision, formal RCT evaluation of early ultrasound-directed salvage intervention was feasible.

METHODS

A prospective multicenter observational cohort study of adult patients undergoing formation of AVF for hemodialysis was performed, according to the previously published protocol.[17] Adults (aged 16 or over) with end-stage renal disease and due for creation of an AVF (with a minimum venous diameter of 2 mm at chosen site for fistula creation) were eligible for inclusion; those with known central venous stenosis or those unable to provide full informed consent were excluded. Standard wrist or elbow AVFs were performed under local, regional, or general anesthetic according to unit and individual surgeon preference. Participants underwent Doppler ultrasound of their AVF at weeks 2, 4, and 6 after its creation, with AVF flow (brachial artery blood flow), venous diameter, and resistance index recorded, performed by the trial vascular scientists at each center, according to a standardized study protocol (Supplementary Methods), and with clinical teams blinded to the ultrasound findings, unless a scan was simultaneously requested on clinical grounds, or the scan confirmed thrombosis of the fistula. The primary outcome, fistula maturation, was assessed by ultrasound at week 10, according to established surrogate ultrasound parameters[18] (wrist fistula: representative venous diameter $\geq$4 mm, with flow >400 ml/min; elbow fistula: representative venous fistula diameter $\geq$5 mm, with flow >500 ml/min). Nonmaturation of the AVF at 10 weeks was defined as AVF occlusion/thrombosis or abandonment within the study period (76 days post AVF creation), or failure to achieve (either reported at the week 10 scan or imputed) maturation. The 10-week timepoint for assessment of fistula maturity was chosen to provide sufficient time to capture all fistulas that were likely to mature spontaneously, in recognition that fistula maturation continues beyond 6 weeks.[19,20]

Assuming that early ultrasound surveillance predicts failure in 25% of AVFs, a total of 347 AVFs were required to achieve precision of $\pm$ 10% for an estimated 72% PPV, allowing for 10% dropout.

Mixed multivariable logistic regression (binary-data population average model with exchangeable correlation structure) of the early ultrasound scan data was then used to build separate models for wrist and elbow AVFs that contained the minimum number of measurements required to predict AVF nonmaturation by 10 weeks. The following candidate variables were considered for model inclusion: preoperative vein diameter, quality of artery (healthy or mildly, moderately, or severely diseased) at the time of surgery, quality of vein (healthy or diseased but distensible, or not distensible) at the time of surgery, clinical prediction of fistula maturity, average resistance index at scan time-point(s), representative venous diameter at scan time-point(s), average flow at scan time-point(s),

patient's biological sex, patient's age, and history of diabetes. Cases with scan data missing from all time points or with fistula failure prior to the time point being considered in the model were excluded. A purposeful variable selection approach was followed as recommended by Hosmer *et al*.[21] Evidence of nonlinearity in continuous variables was visually explored using univariable LOWESS smoothing and statistically assessed using quadratic and logarithmic univariable fractional polynomials. Receiver operating characteristic curves were used to assist decisions regarding the cut-off value to classify a fistula as a failure and to determine when surgical or radiological intervention on the developing AVF could be considered. The PPV and negative predictive value (the probability of AVF maturation given that the model predicts maturation) were calculated alongside a 95% CI for the chosen risk-score cut-off, and these parameters together with the number of patients who could benefit from a salvage intervention in a future RCT, informed the clinical selection of the optimum models. Diagnostic tests for model fit and influential observations analysis performed on the optimum models revealed good model fit. All statistical analyses were carried out using Base SAS version 9.4 (SAS Institute Inc., Cary, NC).

The strategies adopted for dealing with missing data are listed in the Supplementary Methods.

Additional modeling was then performed on a subset ($n = 192$) of the original SONAR cohort available for follow-up, to assess whether fistula failure at 6 and 12 months could be identified by analysis of early ultrasound characteristics. The primary outcome measure for the longer term follow-up was primary fistula patency at 6 months, defined as, "the interval between access creation to the earliest of fistula thrombosis, abandonment (except abandonment because of steal), intervention on the fistula (to reestablish or maintain patency), or the time of measurement of patency." Secondary outcome measures included assisted primary patency (the interval from access creation until access thrombosis or the time of measurement of patency, including any interventions to maintain patency) and secondary patency (the interval from access creation to time of measurement of patency or to abandonment of the fistula). Similar binary-data population-average modeling was performed as for predicting 10 week nonmaturation, aiming to build parsimonious models that contained the minimum number of variables from 1 scan time point (either at week 4 or week 6) to effectively predict primary fistula nonpatency at 6 months.

This study is in accordance with the Declaration of Istanbul, the ethical standards of our institution, and the 1964 Declaration of Helsinki. Informed consent was obtained from all participants involved in the study. The study was approved by the Cambridgeshire and Hertfordshire Research Ethics Committee and by the Health Research Authority (REC 18/EE/0234) and assigned ISRCTN 36033877.

RESULTS

Study Participants and AVF Surgery Outcomes

Between September 1, 2018 and November 11, 2019, 682 approaches at 17 United Kingdom hemodialysis sites were done, resulting in 347 consents to participate in the SONAR study (corresponding to 332 different participants; Supplementary Figure S1). The demographics of the enrolments are provided in Table 1, and in general, mirrored contemporaneous United Kingdom experience,[9] with the majority being elderly and male; over 40% were diabetic. At enrolment, 191 (55.0%) cases were predialysis, and a further 8 (2.3%) had received a previous transplant that was now failing.

Of those enrolled, 333 AVFs were created (on 318 different participants) (Table 2), with slightly more elbow (52.3%) than wrist fistulas fashioned; 240 (72.1%) had formal preoperative venous and arterial ultrasound mapping before surgery. Participants underwent Doppler ultrasound of their AVF at weeks 2, 4, and 6 after its creation; and fistula maturation was assessed at week 10, according to accepted surrogate ultrasound parameters.

By week 10, 219 (65.8%) of the 333 AVFs had reached maturity, with 67.2% of elbow and 60.4% of wrist AVFs maturing (Table 3). Fifty-seven (17.1%) had failed (either thrombosed or had been abandoned), but with 37 of the failures (64.9%) occurring before the first scan at 2 weeks, and 40 in total (70.2%) by the second scan at 4 weeks (Supplementary Table S1). A relatively small number of AVFs remained patent, but not mature, at week 10 ($n = 29$, 8.7%), and the outcome of the remainder ($n = 28$, 8.4%) not known and not imputable, because of nonattendance for ultrasound scanning.

Univariate analysis was performed to identify patient and preoperative anatomical factors associated with fistula nonmaturation at week 10. Candidate factors included preoperative vein diameter, quality of artery at the time of surgery, quality of vein at the time of surgery, clinical prediction of fistula maturity, patient's sex, patient's age, and history of diabetes. Preoperative vein diameter was excluded in the wrist model due to missing values. Out of those factors known at baseline, only sex was univariately

Table 1. Baseline characteristics of SONAR participants-stratified by fistula maturity

Participant characteristics	No AVF created	Primary fistula maturity by week 10	Primary fistula nonmaturity by week 10	Overall
Number of enrolments[a]	14 (4.0)	213 (61.4)	120 (34.6)	347
Age (yr)[b]	62 (51–69)	66 (52–74)	62 (51.5–74.5)	65 (52–74)
Sex				
Female	3 (2.4)	67 (55.0)	52 (42.6)	122
Male	11 (4.9)	146 (64.9)	68 (30.2)	225
Cause of renal failure				
Glomerulonephritis	0 (0.0)	13 (59.1)	9 (40.9)	22
Polycystic	1 (5.3)	11 (57.9)	7 (36.8)	19
Hypertension	1 (2.5)	29 (72.5)	10 (25.0)	40
Diabetic	7 (6.5)	57 (52.8)	44 (40.7)	108
Renovascular disease	0 (0.0)	9 (69.2)	4 (30.8)	13
Unknown	1 (2.3)	29 (65.9)	14 (31.8)	44
Other	4 (4.0)	64 (64.0)	32 (32.0)	100
Hypertension				
No	3 (4.7)	39 (62.0)	21 (33.3)	63
Yes	11 (3.9)	174 (61.3)	99 (34.9)	284
Diabetes				
No	4 (2.0)	126 (64.0)	67 (34.0)	197
Yes - insulin dependent	7 (7.9)	48 (53.9)	34 (38.2)	89
Yes - noninsulin dependent	3 (4.9)	39 (63.9)	19 (31.1)	61
IHD/CVA/PVD				
No	13 (5.0)	159 (61.4)	87 (33.6)	259
Yes	1 (1.1)	53 (60.9)	33 (37.9)	87
Dialysis status at enrolment				
Predialysis	9 (4.7)	124 (64.9)	58 (30.4)	191
Hemodialysis	5 (3.5)	79 (56.0)	57 (40.4)	141
Peritoneal	7 (2.0)	4 (57.1)	3 (42.9)	7
Failing transplant	8 (2.3)	6 (75.0)	2 (25.0)	8
Current vascular access for hemodialysis				
Fistula	0 (0.0)	0 (00.0)	3 (100.0)	3
Graft	0 (0.0)	0 (0.0)	0 (0.0)	0
Line	5 (3.6)	79 (57.2)	54 (39.1)	138
Number of previous fistulas				
0	10 (3.7)	177 (64.8)	86 (31.5)	273
1	3 (7.0)	24 (55.8)	16 (37.2)	43
2	1 (4.3)	9 (39.1)	13 (56.5)	23
>2	0 (0.0)	3 (37.5)	5 (62.5)	8
Number of patients re-entering the study[c]				
With AVF surgery	0	5	9	14
Without AVF surgery	0	0	0	0

AVF, arteriovenous fistula; CVA, cerebrovascular accident; IHD, ischemic heart disease; PVD, peripheral vascular disease.
[a]From 332 participants, reflecting re-entry into the study upon failure of first study AVF and creation of another.
[b]Data are median (IQR) for continuous variables and N (row %) for categorical variables.
[c]Of 332 participants enrolled, 318 had an AVF created. There were 333 AVFs created in total on these 318 participants; 318 first-time SONAR fistulas, 14 second-time, and 1 third-time. There were 14 participants enrolled; 13 of them reenrolled once, 1 of them twice, totaling 15 reenrollments on 14 different participants; all 14 participants underwent AVF surgery.
Summary of missing data: cause of renal failure and IHD/CVA/PVD are each missing for 1 observation.

significant at the 5% level, and for wrist fistulas only. For elbow fistulas, no baseline factor was significant at the 5% level; preoperative vein diameter, identified previously as an important predictive factor in AVF maturation,[22-24] was not statistically significant.

Early Ultrasound Surveillance

Analysis of the early ultrasound findings revealed that the increases in AVF blood flow and venous diameter that characterize AVF maturation occur surprisingly rapidly (Figure 1a–d, Supplementary Table S2). For example, by week 2, a median AVF blood flow of 770 ml/min and a median venous diameter of 5.2 mm were achieved, excluding those AVFs that had already thrombosed. Therefore, of those with scan data at week 2, 61.5% of wrist, and 62.0% of elbow, AVFs had reached maturation (Figure 1e and f). The proportion of wrist and elbow AVFs that were mature at the subsequent weeks 4, 6, and 10 scans remained relatively constant, because although AVF maturation did occur beyond week 2, small numbers of AVFs either regressed to an immature state or had thrombosed on subsequent scanning (Figure 1g and h). The proportion

Table 2. AVF surgery details of SONAR enrolments - stratified by fistula maturity[a]

AVF surgical details	Primary fistula maturity by week 10	Primary fistula nonmaturity by week 10	Overall
Number of fistula operations performed[b]	213 (64.0)	120 (36.0)	333
Preoperative mapping ultrasound performed			
No	56 (60.2)	37 (39.8)	93
Yes	157 (65.4)	83 (34.6)	240
Anesthesia[c]			
Local anesthesia	179 (63.0)	105 (37.0)	284
Regional block	26 (72.2)	10 (27.8)	36
General anesthetic	7 (58.3)	5 (41.7)	12
Side and site of fistula			
Left Wrist	74 (63.8)	42 (36.2)	116
Left - Radiocephalic	74	41	115
Left - Ulnobasilic	0	1	1
Left Elbow	94 (70.1)	40 (29.9)	134
Left - Brachiocephalic	77	32	109
Left - Brachiobasilic	17	8	25
Right Wrist	22 (51.2)	21 (48.8)	43
Right - Radiocephalic	22	21	43
Right - Ulnobasilic	0	0	0
Right Elbow	23 (57.5)	17 (42.5)	40
Right - Brachiocephalic	20	13	33
Right - Brachiobasilic	3	4	7

[a]Data are *n* (row %).
[b]Number of enrolments that did not undergo surgery is 14.
[c]Anesthesia for 1 enrolment was reported as 'Other – axillary nerve block and general anesthetic.'

of AVFs that were immature gradually decreased at each subsequent scan, either because they had matured or because they had thrombosed or had been abandoned (Figure 1g and h).

As shown in Figure 1a to d, analysis of the early ultrasound data revealed marked differences in recorded fistula vein diameter and fistula blood flow in those AVFs that reached maturity by week 10, compared to those that remained immature. For example, in those AVFs that reached maturity by week 10, median blood flow through the AVF on the week 2 scan was 1135.5 and 691.0 ml/min for elbow and wrist AVF, respectively; whereas corresponding figures for elbow and wrist AVFs that remained immature were 349 and 395.5 ml/min. Scatter plot diagrams of average fistula flow against fistula vein diameter for the week 2, 4, and 6 scan data (Figures 2a–c), highlight the different patterns of fistula development in those that will mature by week 10 compared to those that remain immature.

Table 3. Primary outcome by week 10 following AVF creation

	All fistulas[a]		Elbows		Wrists	
Fistula status	*n/N*	%	*n/N*	%	*n/N*	%
Mature	219/333	65.8%	117/174	67.2%	96/159	60.4%
Patent but nonmature	29/333	8.7%	19/174	10.9%	16/159	10.1%
Failed[b]	57/333	17.1%	18/174	10.3%	39/159	24.5%
Unknown	28/333	8.4%	20/174	11.5%	8/159	5.0%

AVF, arteriovenous fistula.
[a]"All fistula" criteria for maturity; representative venous diameter ≥4 mm and average volume flow >400 ml/min.
[b]Failed means the fistula occluded/thrombosed or the fistula was abandoned due to failure to mature or due to thrombosis/occlusion.

Logistic Regression Modeling of Nonmaturation From Early Ultrasound Characteristics

The above data suggest that the early scan data could be used to identify those AVFs that will not reach maturity by week 10. If so, this identification may improve overall AVF patency, because it informs early radiological or surgical interventions that more successfully salvage the at-risk AVF than if delayed until initiated upon clinical grounds. Logistic regression was therefore used to construct models that incorporated the minimal number of variables from the preoperative clinical and anatomical details and from the early scan data (preferably from an ultrasound scan at only 1 time-point) to effectively predict fistula nonmaturation at 10 weeks. Missing data were imputed where possible, as detailed in supplementary data.

The optimum models considered elbow and wrist AVFs separately and could be constructed from week 4 scan data only, including data from the earlier or later scans did not improve performance (Table 4 and Figure 3). Therefore, for elbow AVFs, an algorithm that included the week 4 average resistance index and fistula blood flow predicted nonmaturation at week 10 in 27 cases, and correctly so in 18 of these (true positives), giving a PPV of 66.7% (95% CI: 48.9–84.4). The equivalent model for wrist AVFs incorporated week 4 fistula venous diameter and fistula blood flow, and predicted fistula nonmaturation in 33 cases, with 20 of these true positives (PPV 60.6% [95% CI: 43.9–77.3%]). Diagnostic tests for model fit confirmed that both models performed well, with area under the curve values of at least 0.9 (Figure 3). Interestingly, although the focus was on identifying on early surveillance ultrasound those AVFs that were not going to mature, the negative predictive value—that is, the identification of those fistulas that were going to be mature at week 10—was extremely high for both models (95.4% [91.0–99.8] for wrist and 95.6% [91.8–99.4] for elbow). In Figure 4, we provide a summary of the modeling of the week 4 ultrasound data in predicting week 10 AVF status. The models performed very similarly when only reported data was considered and imputed outcome data excluded (not shown).

Cohort 1 Year Follow-Up

The justification for early salvage intervention is not simply that it would improve 10 week maturation, but

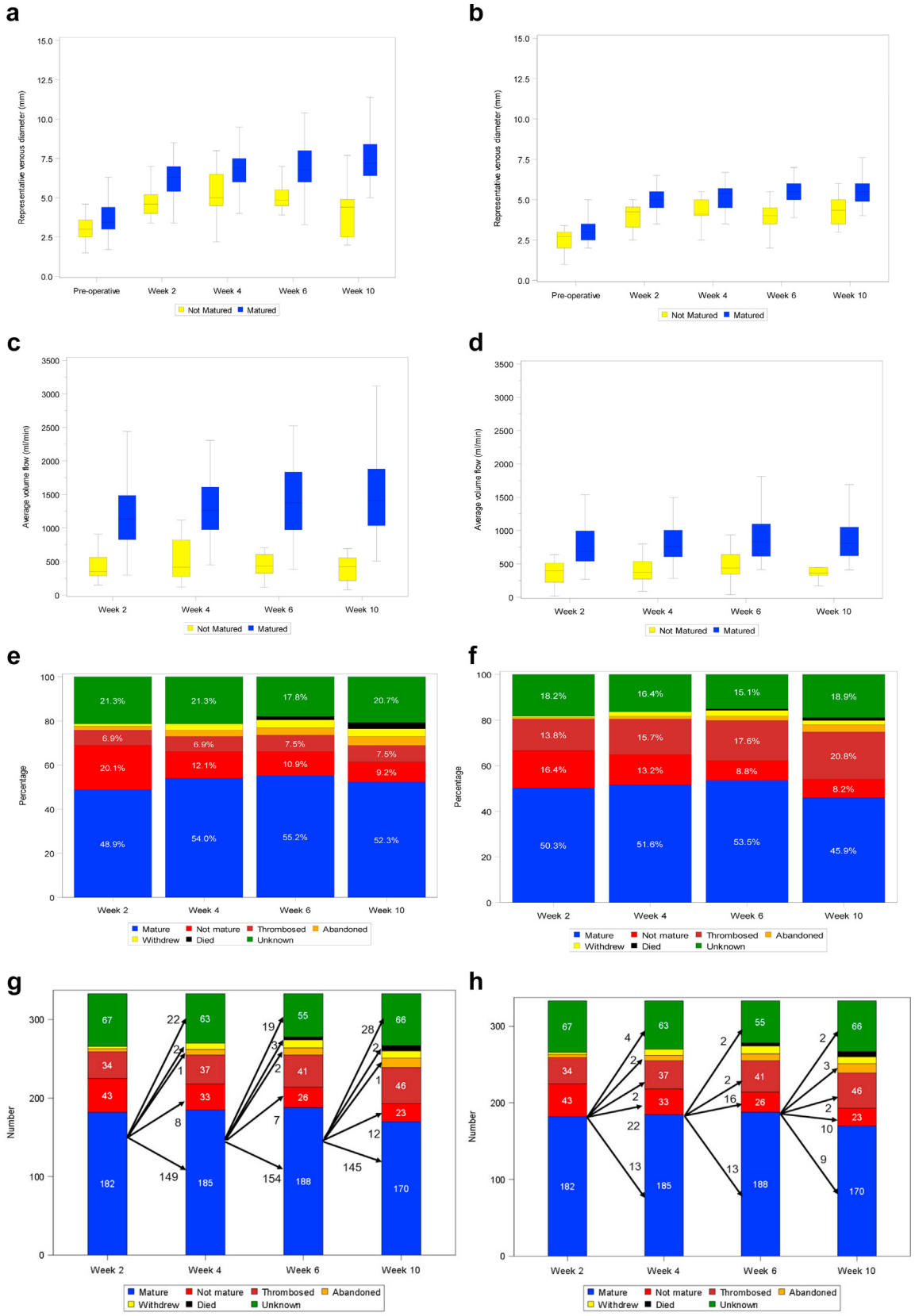

Figure 1. Representative fistula venous diameter (a and b) and fistula volume flow rate (c and d) for elbow (a and c) and wrist (b and d) according to maturation status at week 10. Box and whisker plot shows minimum value (after excluding outliers), 25th centile, median, 75th centile and maximum value (after excluding outliers) without imputation of primary outcome. Fistulas that failed before week 10 (thrombosis or abandonment after a failure) were excluded from the analysis.

Stacked 100% bar charts showing the proportion of (e) elbow and (f) wrist fistulas, with the following outcomes at each of weeks 2, 4, 6, and 10: died, withdrawn, abandoned, thrombosed, mature by ultrasound parameters (at that scan), not mature by ultrasound parameters (continued)

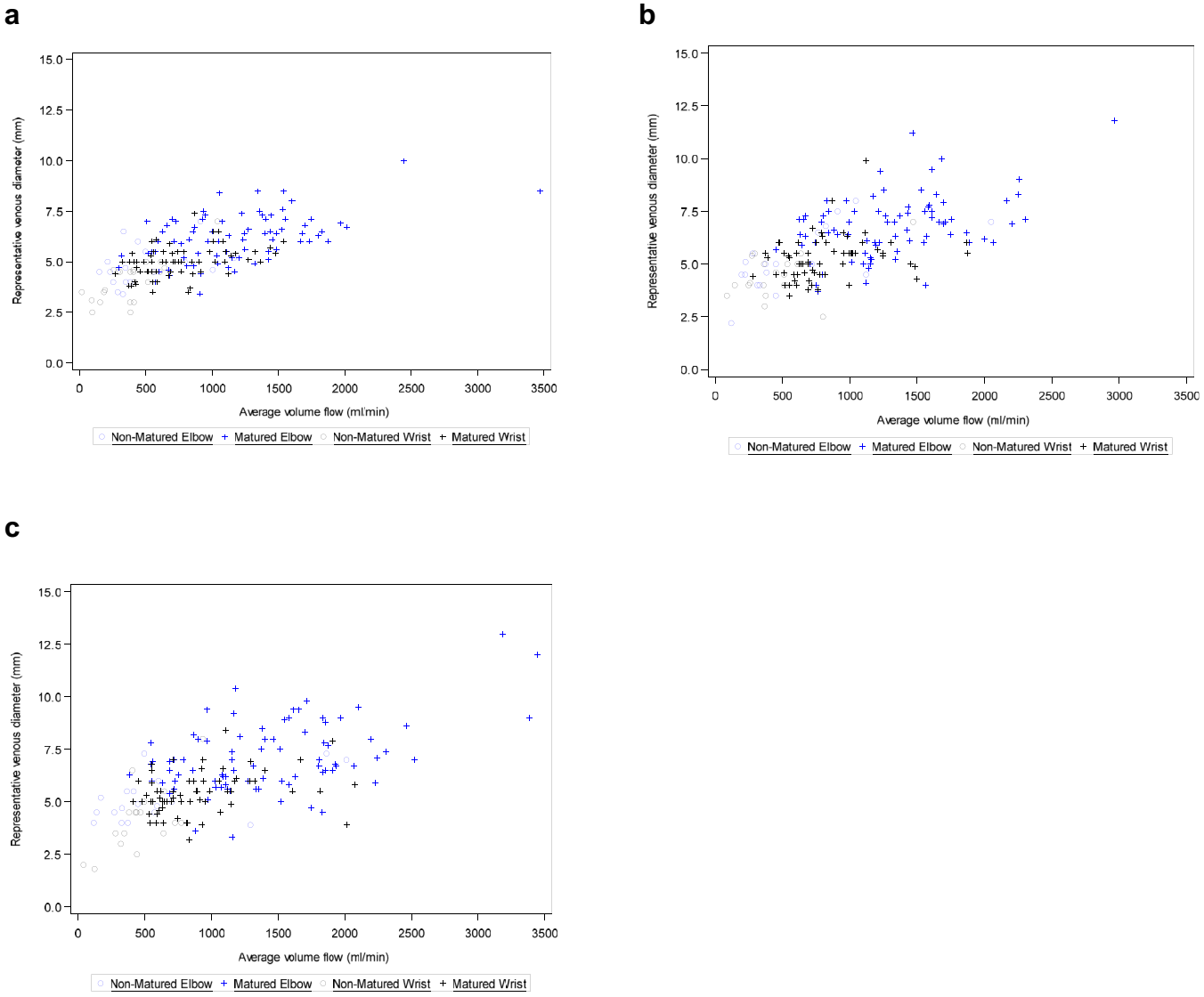

Figure 2. Scatter plot of representative venous diameter by average volume flow at 2, 4, and 6 weeks (a, b, and c, respectively) with different symbols for matured/not matured fistulas at week 10 (as per primary outcome with no imputation).

that this would translate to better longer term AVF patency. In this regard, it was notable that, of the 74 AVFs that were patent on the week 4 ultrasound scan but did not reach maturity, only 17 had thrombosed by the week 10 scan, raising the possibility that the remainder could still be successfully salvaged at a later stage without recourse to early ultrasound surveillance. The relationship between the early ultrasound findings and longer term AVF outcomes were therefore assessed on a subset (n = 192) of the original SONAR cohort available for follow-up. Participants were not required to attend any additional hospital appointments and primary patency at 6 months was reported in 99.0% of followed-up cases. Primary AVF patency at 6 months for all fistulas was 76.6% (69.9–82.4) and was higher at 6 months for elbow AVF than for wrist AVF (83.0% [73.8–89.9] vs. 70.4% [60.3–79.2]). This partly reflects the higher rate of early failure already noted for wrist AVFs; however, as shown in Figure 5, wrist AVF failure also occurred after week 10. Notably, of the 42 elbow and wrist AVFs patent, but still immature, at 10 weeks, the majority (29 (69.0%)) had failed by 6 months; only a relatively small number (13 [31.0%]) matured successfully beyond 10 weeks (Supplementary Figure S2).

Surgical (n = 23) or radiological (n = 20) "salvage" procedures were attempted on 43 occasions on 38 AVFs in the first year after transplantation to either maintain

Figure 1. (continued) (at that scan), unknown (did not attend scan or where missing data from the scan prevented determination of maturity). (g) and (h): as for (e) and (f) but for all fistulas, presented as numbers and including arrows depicting status at next scan of those fistulas mature (g) or immature (h) at previous scan.

Table 4. Optimum models for predicting primary fistula nonmaturation by week 10

Week 4 factors included in model[a]	Elbow (n = 140) odds ratio (95% CI)	Wrist (n = 120) odds ratio (95% CI)
Average resistance index (0.1 unit change from mean)	5.9 (2.6–13.3) $P < 0.0001$	NS
Average volume flow (100 unit change from mean)	0.8 (0.6–1.0) $P = 0.0224$	2.2 (1.2–4.0) $P = 0.0080$
Representative venous diameter (1 unit change from mean)	NS	0.5 (0.3–0.7) $P = 0.0006$
Log of average volume flow at week 4 scan (1 unit change from mean)	NS	<0.001 (<0.001–0.019) $P = 0.0005$
Model performance		
Area under the curve value	0.92	0.90
Threshold (Youden index)	0.27	0.17
PPV for threshold (95% CI)	66.7% (48.9–84.4)	60.6% (43.9–77.3)
NPV for threshold (95% CI)	95.6% (91.8–99.4)	95.4% (91.0–99.8)
Number of predicted failures vs. actual failures	27 vs. 23	33 vs. 24
Number of correctly predicted failures	18	20

CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.
[a]Variables considered for inclusion in the models were: preoperative vein diameter,[b,d] quality of artery at the time of surgery,[b,c] quality of vein at the time of surgery,[b,e] clinical prediction of fistula maturity,[b,c] average resistance index at week 4,[c] representative venous diameter at week 4,[b] average flow at week 4, patient sex,[b,c] patient's age,[b,c] and history of diabetes.[c,f] In addition, the wrist model considered the interaction between representative venous diameter and average volume flow.[e]
[b]Factor not included in the week 4 elbow model of primary fistula nonmaturation by week 10. Nonstatistically significant (NS) factor, at the 5% significance level.
[c]Factor not included in the week 4 wrist model of primary fistula nonmaturation by week 10. NS factor.
[d]Factor not considered in the candidate set of variables for the wrist model due to presence of missing data above the predetermined cut-off of up to 30% data missing.
[e,f]Statistically significant factor, at the 5% level in the multi-variable wrist[e] or elbow[f] model, but not included in the final model. Statistical significance was not the only criterion used to select variables for model building. Other criteria, such as the Hosmer *et al.*[21] delta-beta-hat-percent measure, as well as clinical relevance and parsimony, were also used.

or restore fistula patency. These interventions were successful in 79.1% of the procedures, and the assisted primary and secondary patency rates at 6 months (80.7% and 83.3%, respectively) and 12 months (74.1% and 79.5%, respectively) were therefore notably higher than the primary patency rates (Figure 5). Only 5 of these interventions (11.6%) occurred within 10 weeks of fistula creation, and these early interventions were prompted by notification from the vascular scientists that the fistula had thrombosed; the clinical teams were otherwise blinded to the scan results.

Logistic regression modeling was then performed to assess whether early ultrasound surveillance could predict primary fistula failure at 6 months (Table 5). As with the modeling for 10 week nonmaturation, optimum models could be developed using ultrasound data from a single week, but separate models for predicting nonpatency at 6 months for wrists and elbow AVFs performed superiorly and relied on a different week's scan data. Therefore, for elbow AVFs, an algorithm that included preoperative vein diameter, week 4 average resistance index, and fistula blood flow, predicted 6-month nonpatency in 7 cases,

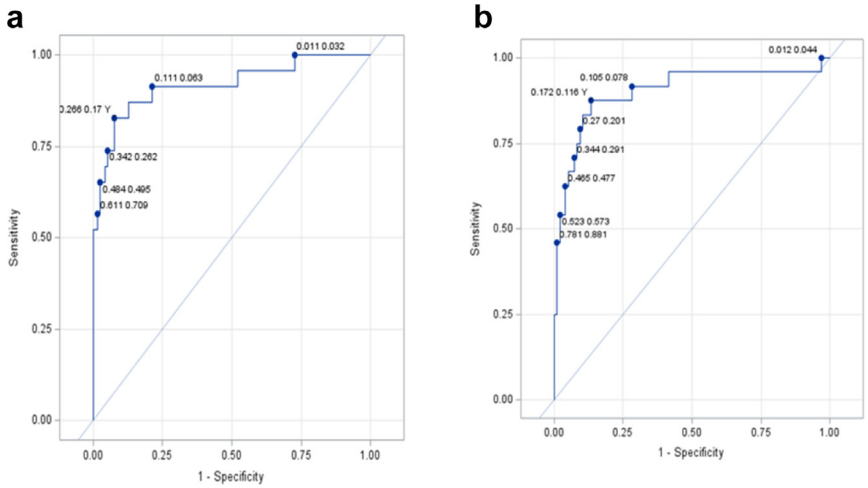

Figure 3. Standard receiver operating characteristic curves for the optimum models established for predicting week 10 fistula nonmaturation from week 4 ultrasound findings for (a) elbow, and (b) wrist fistulas, with 1-specificity (x-axis) plotted against sensitivity (y-axis), and each point on the graph generated by using a different threshold point. The optimal threshold point chosen in our study is shown in the plot (Youden index, symbol "Y"); the threshold value is the number on the far left to the "Y".

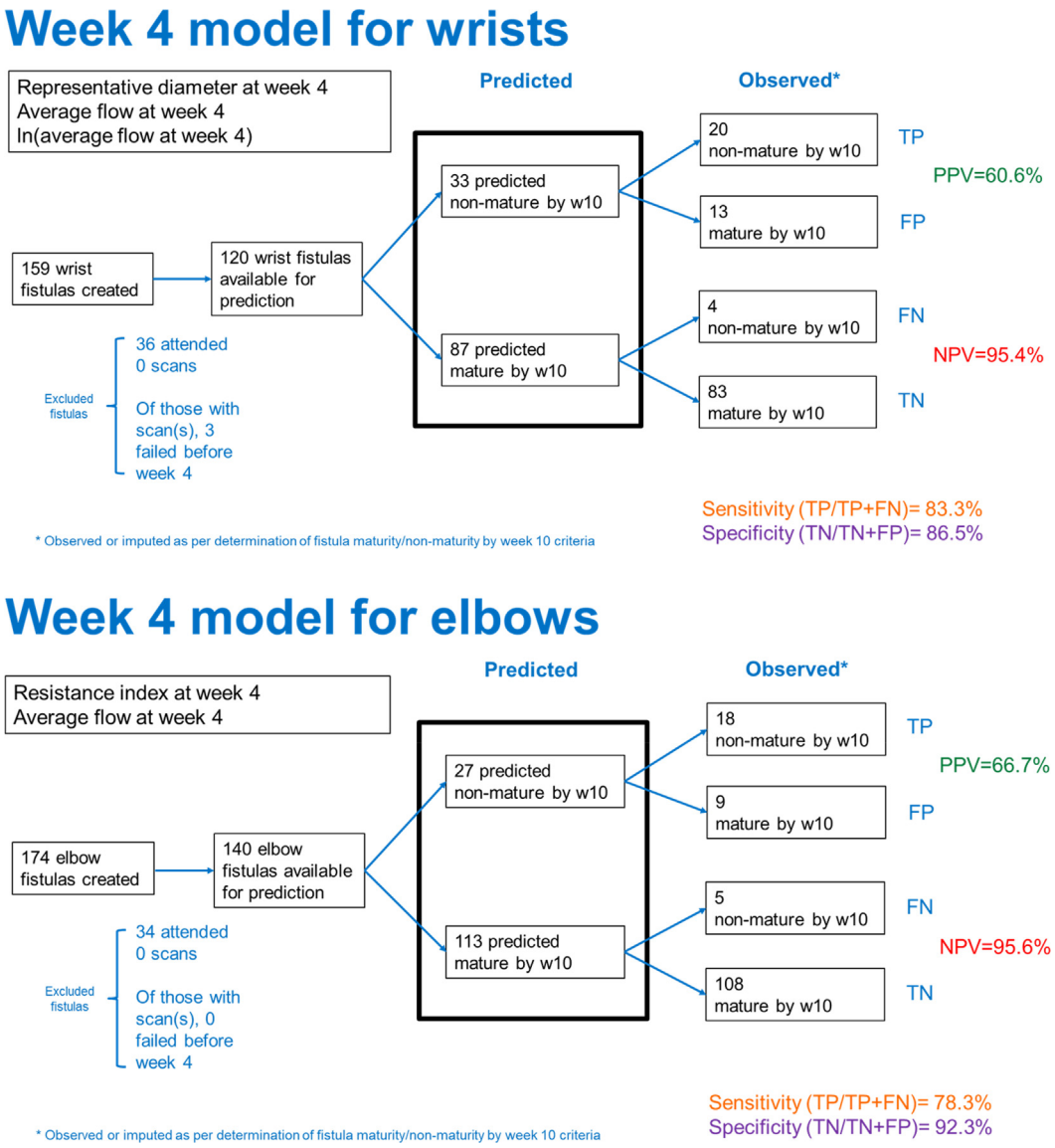

Figure 4. Summary of week 4 ultrasound modeling on identifying 10-week fistula status.

and correctly so (true positives) in 4 of these, giving a PPV of 57.1% (20.5–93.8). A similar model could be developed for wrist fistulas, based on the week 6 scan data, and incorporated fistula venous diameter, fistula blood flow, and average resistance index, with an additional interaction between sex of the participant and fistula venous diameter. This predicted nonpatency in 11 cases, with 8 true positives, giving a PPV of 72.7% (46.4–99.0). Both models performed moderately well (Figure 6). As with the modeling for maturation status at 10 weeks, the models for 6 month patency were remarkably effective at identifying those fistulas that would be patent, with negative predictive values of 88.2% (80.9–95.4) and 91.3% (84.7–98.0) for elbow and wrist fistula, respectively.

Transferability of Selected Models

Given the likelihood that similar early ultrasound characteristics would predict 10 week nonmaturation and longer term AVF failure, one would perhaps anticipate that the optimum models for predicting wrist and elbow AVF 10 week nonmaturation would perform well when tested for their ability to predict 6 month primary failure, and vice versa. However, as detailed in Table 6, this is not the case; when the model for 10-week fistula maturation is applied to the 1-year follow-up cohort to predict 6-month primary fistula failure, the PPV falls to 31.8% and 22.2% for wrist and elbow fistulas, respectively. Similarly, neither the 10-week maturation nor the 6-month patency models could reliably predict assisted primary failure at 6 months; those AVFs that fail even after salvage intervention (Table 6).

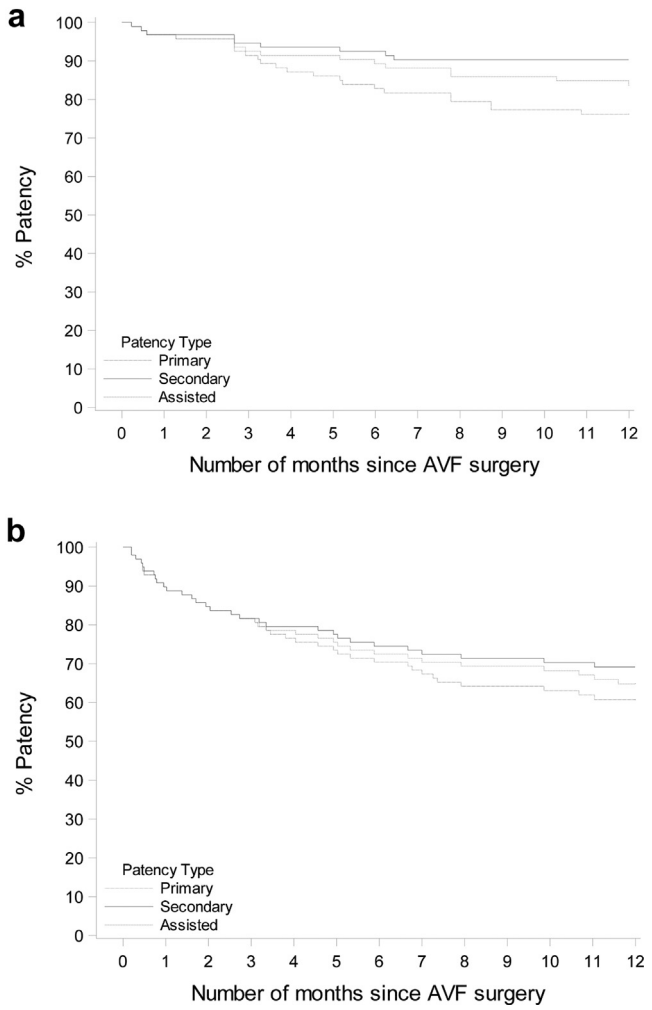

Figure 5. Kaplan Meier analysis of primary, assisted primary, and secondary patency rates to 12 months for (a) elbow and (b) wrist AVFs. Numbers in brackets represent 12 month (+ 95% confidence interval) patency rates.

One possible explanation why the model for 6 month primary fistula failure performs so poorly at predicting assisted primary failure is that those AVFs identified to be at risk of primary failure have their patency prolonged by successful salvage intervention. In support, predictive modeling of the 6 week ultrasound data identified 11 of 80 wrist AVFs at risk of primary failure at 6 months, and salvage interventions to maintain or restore patency were performed on 8 (72.7%) of these, whereas only 6 of the 69 fistulas (8.7%) predicted as patent at 6 months underwent interventions to maintain or restore patency (Fisher's exact test, $P < 0.0001$). Similarly, 3 of the 7 (42.8%) elbow AVFs identified on the modeling of the 4 week ultrasound data as at risk of primary failure at 6 months underwent an intervention, with only 11 of the 76 (14.5%) AVFs predicted as patent experiencing an intervention (Fisher's exact test, $P = 0.0896$). Therefore, it appears that even without knowing the early ultrasound findings (the clinical teams were blinded to this data), a similar cohort of at risk AVFs could be identified, and subject to successful salvage intervention, on the basis of the later clinical manifestations.

DISCUSSION

Despite current guidelines from the National Kidney Foundation recommending that there is insufficient evidence to support ultrasound surveillance of AVFs,[25] many centers have established protocols for performing routine Doppler ultrasound of AVFs that have matured and are being used for dialysis. Pick-up rates for these studies are low, because once mature, AVFs have generally favorable long-term patency. In contrast, the high rates of early failure following AVF creation, with as many as a third failing to mature, suggest that ultrasound surveillance of newly-formed AVFs has the potential to improve AVF patency rates more profoundly. This depends, however, not only upon successful identification of those AVFs that are likely to either fail early or not mature, but also on whether this informs timely salvage interventions that ultimately improve AVF maturation and patency rates. Thus, the SONAR study was designed to assess first, how reliably early ultrasound could identify those nascent AVFs at risk of failure or nonmaturation; and second, the feasibility of performing a prospective RCT that evaluates whether early surveillance, by directing timely and effective salvage intervention, leads to sustained improvements in fistula patency. In this latter objective, our study differs from the limited number of previous early ultrasound mapping studies, which have generally considered preoperative factors that predict maturation[26] or have focused on detailing the maturation process.[20,24,27]

Although there is a correlation between early ultrasound findings and subsequent AVF maturation or patency, we conclude that introduction of an early ultrasound surveillance program would, at best, make only minimal improvements in AVF maturation and patency rates; and furthermore, that impractically large numbers of participants would be required to assess this potential benefit by a formal RCT. This conclusion is based on several factors. First, the AVF 10-week maturation and 6-month primary patency rates achieved by the SONAR consortium (65.8% and 76.6%, respectively) were generally better than had been anticipated at initial study design. In addition, a high proportion of those AVFs that failed to mature had suffered early thrombosis. By week 2, 37 (11.1%) of AVFs had already failed (Supplementary Table S1), and their outcome is unlikely to be altered by a surveillance program, no matter how early its implementation. Indeed, the modeling identified the week 4 scan as the

Table 5. Optimum models for predicting primary fistula nonpatency at 6 months

Factors included in model[a]	Elbow (n = 83) odds ratio (95% CI)	Wrist (n = 80) odds ratio (95% CI)
Preoperative vein diameter (1 unit change from mean)	1.57 (0.91–2.72) $P = 0.1030$	n/a
Average resistance index[b] (0.1 unit change from mean)	1.65 (0.61–4.46) $P = 0.3146$	2.59 (1.46–4.58) $P = 0.0015$
Average volume flow[b] (100 unit change from mean)	0.93 (0.83–1.05) $P = 0.2471$	1.13 (1.06–1.20) $P = 0.0003$
Sex[c]	NS	$P = 0.0067$
Representative venous diameter[b,c]	NS	$P < 0.0001$
Interaction between sex and representative venous diameter[b]	n/a	$P = 0.0003$
1 unit change of representative diameter from mean for males		0.71 (0.53–0.95)
1 unit change of representative diameter from mean for females		0.09 (0.03–0.26)
Model performance		
Area under the curve value	0.71	0.81
Threshold (Youden index)	0.37	0.32
PPV for threshold (95% CI)	57.1% (20.5–93.8)	72.7% (46.4–99.0)
NPV for threshold (95% CI)	88.2% (80.9–95.4)	91.3% (84.7–98.0)
Number of predicted failures vs. actual failures	7 vs. 13	11 vs. 14
Number of correctly predicted failures[d]	4	8

CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.
[a]Variables considered for inclusion in the models were: preoperative vein diameter,[g] quality of artery at the time of surgery,[e,f] quality of vein at the time of surgery,[e,f] clinical prediction of fistula maturity,[e,f] average resistance index at scan timepoint,[b] representative venous diameter at scan timepoint,[b,e] average flow at scan timepoint,[b] patient sex,[e] patient's age,[e,f] and history of diabetes.[e,f] A significant *P*-value was not the only criterion used to select variables for model building. Other criteria, such as the Hosmer *et al.*[21] delta-beta-hat-percent measure, as well as clinical relevance, were also used.
[b]Week 4 scan data for elbow; week 6 scan data for wrist.
[c]Main effects odds ratio is not presented for the wrist model due to this factor's involvement in an interaction term.
[d]Failure is defined as abandonment due to failure to mature or due to thrombosis/occlusion or had an intervention following a thrombosis/occlusion or failure to mature/provide adequate access.
[e]Factor not included in the week 4 elbow model of primary fistula nonpatency by month 6. Nonstatistically significant (NS) factor, at the 5% significance level.
[f]Factor not included in the week 6 wrist model of primary fistula nonpatency by month 6. NS factor.
[g]Factor not considered in the candidate set of variables for the wrist model due to presence of missing data above the predetermined cut-off of up to 30% data missing.

most predictive for fistula nonmaturation at week 10; and of the 293 of the original 333 (88.0%) study fistulas that were still patent at 4 weeks, maturation rates of 74.7% (95% CI: 69.4–79.6) were achieved. Factoring in an overall sensitivity of 80.5% (postulated from our modeling exercises where all fistulas [elbows and wrists] were considered together) for identifying those AVFs that will not mature, week-4 ultrasound surveillance could therefore potentially prevent nonmaturation in 17.8% of AVFs created, but only if every at-risk AVF identified could then be successfully salvaged either surgically or radiologically. Thus, in powering for an RCT with 1:1 randomization to standard care or to the treatment arm (salvage intervention

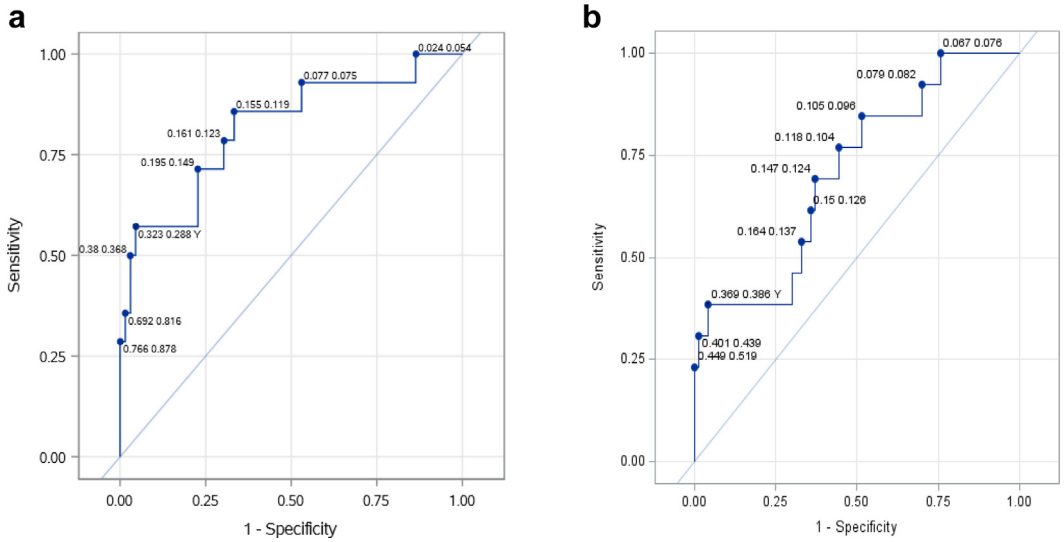

Figure 6. Standard receiver operating characteristic curve analysis for the optimum models established for predicting 6-month fistula nonpatency from (a) week 6 ultrasound findings for wrist and (b) week 4 ultrasound findings for elbow fistula, with 1-specificity (x-axis) plotted against sensitivity (y-axis), and each point on the graph generated by using a different threshold point. The optimal threshold point chosen in our study is shown in the plot (Youden index, symbol "Y"); the threshold value is the number on the far left to the "Y".

Table 6. Validation of optimum SONAR and SONAR 12M models against primary fistula failure and assisted primary fistula failure at 6 months

Predictive values for fistula models	SONAR models	SONAR-12M models
Against primary fistula failure at 6 months		
PPV for optimum wrist model (95% CI)	31.8% (18.1–45.6)	72.7% (46.4–99.0)
NPV for optimum wrist model (95% CI)	94.7% (87.6–100.0)	91.3% (84.7–98.0)
PPV for optimum elbow model (95% CI)	22.2% (6.5–37.9)	57.1% (20.5–93.8)
NPV for optimum elbow model (95% CI)	87.5% (78.8–96.2)	88.2% (80.9–95.4)
Against assisted primary fistula failure at 6 months		
PPV for optimum wrist model (95% CI)	31.6% (16.8–46.4)	29.3% (15.3–43.2)
NPV for optimum wrist model (95% CI)	95.5% (89.3–100.0)	100.0% (100.0–100.0)
PPV for optimum elbow model (95% CI)	14.3% (1.3–27.3)	17.9% (3.7–32.0)
NPV for optimum elbow model (95% CI)	94.5% (88.5–100.0)	96.4% (91.4–100.0)

CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

of the AVF based on results of a week 4 ultrasound scan), if one postulates a more conservative intervention effect of 8% (equating to an intervention success rate of 60%), then relative to an event rate in the control arm of 65%, 1720 participants would be required (allowing for drop-out). Of the 860 patients who would be randomized to the treatment group, estimates based on our optimum wrist week 4 model (the most conservative of our models) indicate that surveillance would result in 184 salvage interventions, with 72 of these unnecessary (the fistula would have matured successfully if managed conservatively); and of the 112 true positives, 78 interventions would be successful at restoring or maintaining patency. This would improve maturation rates from the postulated 65% to 73%, with surveillance missing a further 22 fistulas that fail to mature. Intervention success rates of 50% would theoretically improve AVF maturation from 65% to 71.5% (56/860), and that would require almost 2000 participants.

We therefore decided to examine whether early surveillance ultrasound could predict longer term outcomes (6 and 12 month AVF patency), with assisted primary patency as primary end point. However, the ability of the early ultrasound to model 6-month primary fistula failure was, if anything, poorer than for predicting 10-week maturation status, with only the wrist model worthy of consideration. It is perhaps surprising that the optimum models for predicting 10-week maturation and 6-month patency were not interchangeable, given that similar ultrasound features are considered in both. This possibly reflects that a similar cohort of fistulas to those identified as at risk on the early surveillance ultrasound are subject to late salvage intervention. These interventions were presumably initiated because of concerns relating to fistula maturation and patency (clinical teams were routinely blinded to the early scan results); and they were generally successful at maintaining or restoring patency. This raises doubts on the premise that, by avoiding thrombosis and loss of the draining fistula vein for further fistula creation, early identification and salvage of at-risk fistulas maximizes fistula patency. Rather, our results highlight that an observant approach, with interventions guided by the later clinical findings, achieves very respectable patency rates.

Finally, although not the main focus of our study, this ability to use early ultrasound to identify, with a high degree of certainty, those fistulas that will reach maturity and be patent at 6 months, is not without clinical relevance. Vascular access surgery is generally a tertiary specialty, and an early ultrasound scan that provides strong reassurance of short-term and medium-term fistula patency would potentially allow the patient to be discharged back to their referring center at an earlier stage, thereby rationalizing patient care while minimizing costs and travel times.

APPENDIX

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DISCLOSURE

All the authors declared no competing interests.

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We would like to acknowledge the Trial Steering Committee: Prof. Patrick Mark (chair), Dr Kate Steiner, Prof. Julie Brittenden, Mr. Andrew Norton, Mr. Laszlo Szabo; and the Independent Data Monitoring Committee: Dr Sian Griffin (Chair), Ms. Kerri Barber, and Ms. Helen Dixon. In addition, we would like to acknowledge the Addenbrooke's Kidney Patient Association for their financial support toward patients' travel expenses related to the study.

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DATA AVAILABILTY STATEMENT

The datasets generated and analyzed during the study will be available upon request from the corresponding author. Reasonable requests with an acceptable scientific case will be considered. Transfer of data will require a Data Transfer Agreement (DTA).

AUTHOR CONTRIBUTIONS

JR (Locum Consultant in NORS, HPB and Transplant Surgery) was involved in the conception and design of the study, patient recruitment and data acquisition, and drafting of the report. DS (Consultant Transplant and Vascular Access Surgeon) was involved in the conception and design of the study, data acquisition, and drafting of the report. AS (Trial Manager) was involved in the conception and design of the study and drafting of the report. EA (Trial Statistician) was involved in the conception and design of the study, analysis and interpretation of the data and drafting of the report. HT (Head of Clinical Trial Statistics) was involved in the conception and design of the study, analysis and interpretation of the data and drafting of the report. MAH (Consultant Transplant Surgeon) was involved in the conception and design of the study, data acquisition, and drafting of the report. SP (Senior Clinical Fellow in Transplant Surgery and Organ Retrieval) was involved in the conception and design of the study, data acquisition, and drafting of the report. MS (Vascular Scientist) was involved in the conception and design of the study, ultrasound data acquisition and drafting of the report. MB (Vascular Scientist) was involved in the conception and design of the study, ultrasound data acquisition and drafting of the report. RL (Renal and Vascular Access Nurse) was involved in the conception and design of the study, data acquisition, and drafting of the report. EL (Clinical Operations Manager) was involved in the conception and design of the study and drafting of the report. VH (Clinical Trial Coordinator) was involved in the conception and design of the study and drafting of the report. CF-C (Clinical Trial Administrator) was involved in the conception and design of the study and drafting of the report. CH (Trial Statistician) was involved in the conception and design of the study, analysis and interpretation of

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods. Missing data. Doppler ultrasound protocol.

Figure S1. Study CONSORT diagram.

Figure S2. Fistula status at key study time-points.

Table S1. Primary outcome following arteriovenous fistulas creation, considered at each scan time-point.

Table S2. Ultrasound scan data.

STROBE Statement.

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