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First Cannulation Should Be More Than 3 Weeks after Creation of a Radial-Cephalic Arterio-Venous Fistula

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Abstract

Background: The KDOQI (Kidney Disease Outcomes Quality Initiative) recommends not using Arterio-Venous-Fistulas (AVFs) for Hemodialysis treatment (HD) within 1-month after creation because earlier cannulation (≤ 14 days) leads to reduced fistula survival.

Methods: This retrospective cohort study was conducted in 205 patients, who started maintenance HD with a Radial-Cephalic-AVF (RC-AVF) based on institutional guidelines similar to the KDOQI recommendations. Configuration of the RC-AVF was standardized. Postoperative day from creation to first RC-AVF cannulation was abbreviated as POD. The primary endpoint was the first occurrence of a Vascular Access (VA) event (thrombectomy, surgical revision, or percutaneous transluminal angioplasty). Hazard ratios and 95% confidence intervals for the primary endpoint were determined. The cut-off POD for a VA event was calculated using the Receiver-Operating Characteristic curve and a Diagnostic Performance plot.

Results: The primary endpoint occurred in 85 patients (41%) during 52 months (median). The cutoff POD to predict a VA event was <22 days. Cumulative incidence rates of VA endpoints were 53% and 31% for PODs ≤ 21 and >21 days, respectively (p=0.0008). A POD ≥ 22 days reduced the risk of a VA event by 52% compared with a POD <22 days. No significant difference in a VA event was seen for a POD ≤ 14 and a POD 15-21 days. A POD ≥ 22 days exerted a 60% reduction in a VA event compared with a POD ≤ 14 days.

Discussion: The time from creation until the first cannulation of a RC-AVF should be set at more than 3 weeks. This finding provides a good example of the KDOQI recommendations.

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Introduction

Among the types of Vascular Access (VA) for Hemodialysis treatment (HD), an autologous Arteriovenous Fistula (AVF) is the primary preferred type of access, because it has the advantages of a longer patency and a lower risk of infection [1-3]. A potential disadvantage is the need for a longer maturation time from fistula creation to first cannulation. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guideline recommends not cannulating AVF within 1-month after creation [4]. The recommendation was based on the Dialysis Outcomes and Practice Patterns Study (DOPPS) [5] indicating that cannulation within 14 days of fistula creation was associated with reduced long-term fistula survival. The Japanese Society for Dialysis Therapy guideline also recommends that an AVF should be created at least 2 to 4 weeks before the initial cannulation [6]. These recommendations suggest to clinical practitioners

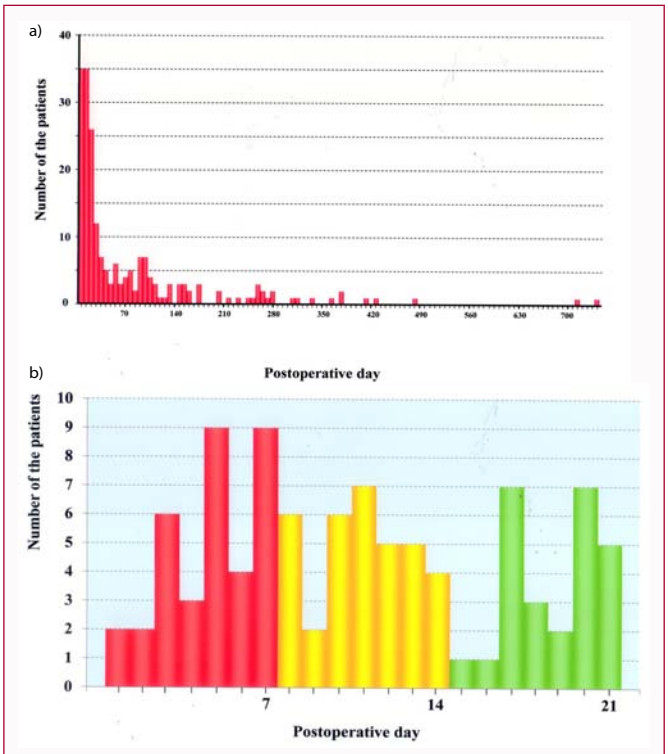


Figure 1: Number of patients who experienced the first AVF cannulation on each postoperative day (POD).
(a) All the 205 patients; (b) 96 patients with POD <22 days
Figure 1b exhibited that in patients with POD <22 days, the POD was distributed more evenly over time.

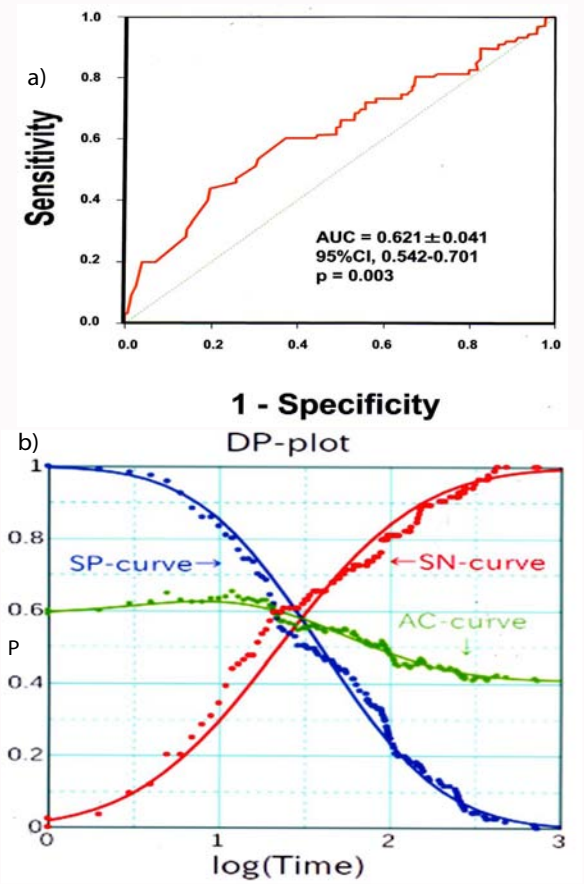


Figure 2: (a): Receiver-Operating Characteristic (ROC) curves for postoperative day (POD). ROC curve analysis identified the best POD cutoff value for predicting the vascular access end-point as 21.5 days. POD, Postoperative day; defined as time from construction to the first cannulation of the Arterio-venous fistula. **(b):** DP-plot (Diagnostic Performance plot) to determine the cutoff point. Recently, DP-plot was developed to determine the cutoff point (ref 8). Regarding cutoff values as flexible values, the DP-plot draws the Sensitivity curve (SN-curve), specificity curve (SP-curve), and accuracy curve (AC-curve).When the cutoff point at the intersection of SP-curve with SN-curve, [(sensitivity and specificity)/2] becomes maximum value, the cutoff value of POD was 20-21 days.

that 2 weeks is enough time to wait for the first cannulation after AVF creation. The DOPPS study [5] used the study-entry-date, which was within 14 days of the first actual cannulation date, as a substitute for the first actual cannulation date. However, the actual days must be used as a primary measurement, when studying how long the waiting time, in units of a week, is sufficient to improve AVF patency. Since the treatment duration on maintenance HD treatment is longer in Japan [7,8] long-term AVF patency can be evaluated. In addition, our institution has adopted a uniform policy of 1) AVF is the preferred VA, and 2) do not cannulate the AVF until 3-4 weeks after its creation, which is similar to the KDOQI recommendation. Therefore, we investigated the effect of accurate time from creation to first cannulation on VA event and a Radial-Cephalic AVF (RC-AVF) patency as a good example to verify the KDOQI recommendations.

Methods

Study design and participants

This retrospective cohort study evaluated the effect of postoperative day from a RC-AVF creation to first cannulation (herein after abbreviated as POD) on the RC-AVF outcome in patients with maintenance HD treatment. Patients had to satisfy the following enrollment criteria: 1) started maintenance HD using a forearm autogenous RC-AVF during 1997-2008 at Nagoya City University Hospital, 2) the RC-AVF was created as the patient's initial VA at Nagoya City University Hospital, and 3) age ≥ 20 years at initiation of HD, regardless of gender. Therefore, the patients, who started HD using either a central venous catheter (CVC) [for either the treatment of acute kidney injuries or rapidly progressive glomerulonephritis and serious systemic diseases (unstable hemodynamics due to septic shock, disseminated intravascular coagulation, hepatic failure, or terminal stage of malignant diseases)], an anatomical snuff box AVF, prosthetic Arteriovenous Graft (AVG), or silastic cannula external arteriovenous shunt were not included in the study. The study was approved by the ethics review committee of Nagoya City University Graduate School of Medical Sciences (no. 974, UMIN000029819), and was conducted in accordance with the Declaration of Helsinki. The ethics review committee determined that, based on the nature of the study, informed consent was not required. Our institutional homepage provided patients with a means to opt-out.

Institutional policy

A dialysis center was open in 1979 for our institutes. VA surgery, the decision of whether the AVF was matures enough for cannulation, and the implementation of VA cannulation were the responsibility of experienced nephrologists. During the study period, we consistently choose autogenous AVFs as the preferred type of access in all new patients electing to undergo HD as renal replacement therapy (i.e., Fistula First initiative). We avoided venipuncture or continuous infusion in the forearm and upper-arm veins as well as the use of subclavian catheters to preserve veins suitable for VA in patients with chronic kidney disease. Preoperatively, we evaluated whether

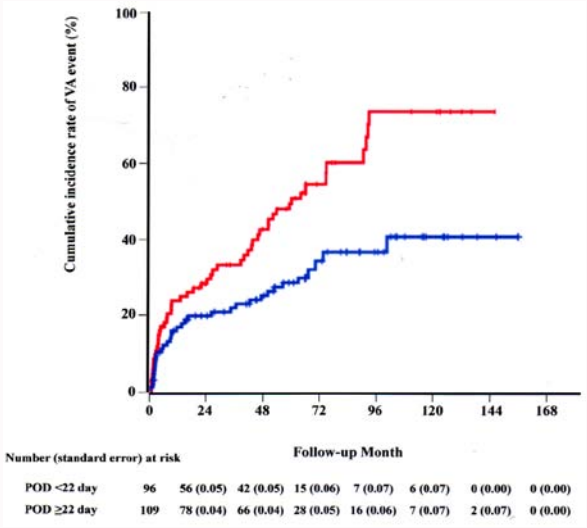


Figure 3: Cumulative incidence rates of Vascular Access (VA) events with postoperative day (POD) < 22 and ≥ 22 days. The cumulative rates of the VA end-points during the study period were 53% and 31% for POD ≤ 21 and >21 days, respectively (p=0.0008).

the forearm cephalic vein could be completely dilated with the use of a tourniquet and whether the radial artery was palpable with pulsation. Duplex scanning was not routinely performed in this series of patients. The RC-AVF was created with a side-to-side "terminally truncated cephalic vein"-to-radial artery anastomosis (Figure S1). A 2.0 mm diameter tube was used to confirm vessel-size and patency, and a vein was considered useable if it was 2 mm or larger. In principle, initiation of the fistula cannulation was avoided earlier than 3-4 weeks after creation. When a patient required HD, experienced nephrologists determined whether the RC-AVF had matured sufficiently for cannulation based on physical examination (Table S1) and the nephrologist performed all the AVF cannulation. We used 16-17G needles and avoided repetitive cannulation of the AVF at the same site. The cannulation methods are described in Figure S2. The prescribed Blood Flow Rate (BFR) for dialysis circuit was 150 mL/min for first three times, and 200 mL/min thereafter.

Outcome measures

The primary endpoint was the first occurrence of a VA event, defined as the composite of thrombectomy, surgical revision, or Percutaneous Transluminal Angioplasty (PTA). Table S2 shows the choice of interventions for RC-AVF. Only the first event in an individual patient was counted in the analysis of the primary endpoint. The POD was defined as the time from creation to first cannulation of a RC-AVF, and the dates (year, month and date) were confirmed by the medical records. Hypertension was defined as either office blood pressure >140/90 mmHg or the use of antihypertensive medication. Diabetes Mellitus (DM) was defined as reported diabetes and use of antidiabetic treatment. Coronary heart disease included angina pectoris, myocardial infarction, and a history of percutaneous coronary intervention or coronary artery bypass graft surgery. Cerebrovascular disease included hemorrhagic or ischemic stroke or a transit ischemic attack. Peripheral vascular disease was defined when the patient was diagnosed as having blood vessel diseases outside of the heart and brain (e.g., arteriosclerosis obliterans and carotid artery disease) or underwent percutaneous transluminal angioplasty of either peripheral arteries or carotid endarterectomy. Early referral to a nephrologist was defined if the patient was treated by a nephrologist

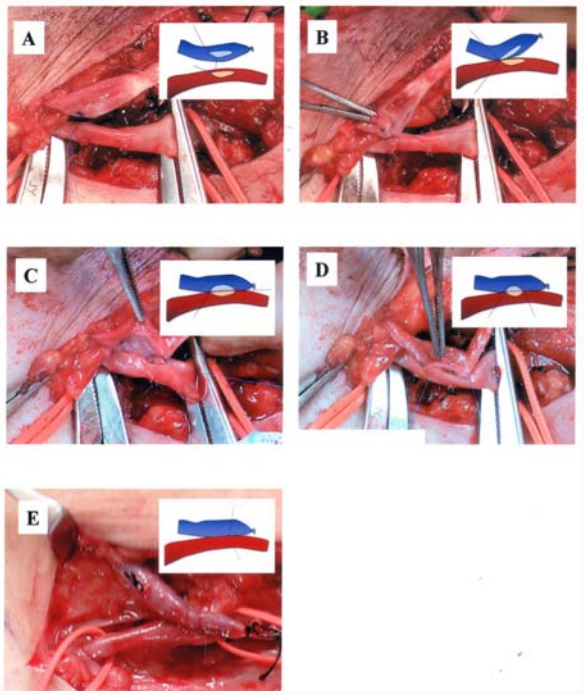


Figure S1: Side-to-side Arterio-venous anastomosis with distal vein closure. Ligate and dissect the peripheral vein distal to predetermined site of anastomosis; set the anastomosis at the inferior wall of the vein and upper wall of the artery (**A**); place a stitch at the heel and leave the toe free (**B**); running-suture on the far side of the vessel walls [arterial wall inside-out and venous wall outside-in using 7/0 polypropylene running suture] (**C**); turn down the running suture at the toe end {suture back from the toe} and put 4 stitches from the toe (**D**); start another running suture on the near side from the heel toward the toe, and then tie to the previously retained threads (**E**). This method allows direct viewing of the heel of the anastomosis. The suturing of the heel of the anastomosis should be carefully performed.

at ≥ 3 months before the AVF creation. Smoking habit was defined as when the patient smoked at the time of the AVF creation.

Statistical analysis

Results are expressed as either mean ± SD or median (interquartile range, IQR) according to the data distribution validated by the Kolmogorov-Smirnov test. Comparisons between the POD groups for categorical data were evaluated with the χ^2 test. Comparisons of continuous variables among the POD groups were evaluated with either the Student's t-test or one-way ANOVA (analysis of variance) for normally distributed variables, and with either the Mann-Whitney's U test or Kruskal-Wallis test for not-normally distributed variables. We calculated the cut-off point of the POD for a VA event using the Receiver-Operating Characteristic (ROC) curve ([1-specificity] on the x-axis and sensitivity on the y-axis). The cut-off point was also calculated using the DP-plot (Diagnostic Performance plot) [9]. The Kaplan-Meier method was used to construct the cumulative incidence curve for the POD groups, and the main comparison was based on a log-rank test. Univariate Cox regression was used to estimate Hazard Ratios (HRs) for the primary endpoint and its 95 percent Confidence Intervals (95% CIs) of baseline demographics. The multivariable Cox proportional hazards model, including the POD as a primary measurement and baseline demographics as a covariate, was used to determine the HRs for the primary endpoint and the 95% CI between the different POD groups. The covariates to adjust the risk of a VA event included baseline demographics, such as age, gender, body mass index, hypertension, DM, coronary heart

Table 1: The risk (HR) for a VA event of baseline demographics of the participants.

		Unadjusted HR	95% CI	p
Age, years	64 (53-72)	0.99	0.98-1.01	0.7
Gender, male	140 (68)	0.98	0.62-1.55	0.9
Body mass index, kg/m^2 [a]	22 (20-24)	0.98	0.91-1.05	0.6
Hypertension	189 (92)	0.86	0.41-1.78	0.7
Diabetes mellitus	94 (46)	1.25	0.81-1.91	0.3
Coronary heart disease	40 (20)	1.28	0.77-2.14	0.3
Cerebrovascular disease	26 (13)	0.61	0.27-1.40	0.2
Peripheral vascular disease	10 (5)	1.67	0.61-4.59	0.3
Early referral to a nephrologist	147 (72)	1.05	0.65-1.71	0.8
Smoking habit	96 (47)	0.98	0.64-1.50	0.9

Data are number (%) or median (Interquartile Range).
VA (Vascular Access) event was defined as the composite of thrombectomy, surgical revision, or percutaneous transluminal angioplasty. Early referral to a nephrologist was defined if the patient was treated by a nephrologist ≥ 3 months before creation of the Arterio-Venous Fistula (AVF). Smoking habit was defined when the patient smoked at the time of the AVF construction.
[a]The numbers of the patients with non-obese, pre-obese (BMI ≥ 25), obese class I (BMI ≥ 30), obese class II (BMI ≥ 35), and obese class III (BMI ≥ 40), were 166, 34, 4, 1 and 0, respectively. The risk of BMI ≥ 25 (vs. BMI <25) was 0.94 (95% CI, 0.55-1.62, p=0.8).
HR: Hazard Ratio; 95% CI: 95% Confidence Interval

Table 2: Clinical variables between POD < 22 vs. ≥ 22 days.

Variables	All	< 22	≥ 22	p value
	(n=205)	(n = 96)	(n = 109)	
Age, years	64(53-72)	63(52-57)	65(56-72)	0.3
Gender, male	140 (68)	67 (70)	73 (67)	0.8
Body mass index, kg/m^2	22(20-24)	21(19-24)	22(21-25)	0.01
Hypertension	189 (92)	87 (91)	102 (94)	0.6
Diabetes mellitus	94 (46)	48 (50)	46 (42)	0.3
Coronary heart disease	40 (20)	18 (19)	22 (20)	0.9
Cerebrovascular disease	26 (13)	9 (9)	17 (16)	0.3
Peripheral vascular disease	10 (5)	5 (5)	5 (5)	0.9
Early referral to a nephrologist	147 (72)	65 (68)	82 (75)	0.3
Smoking habit	96 (47)	44 (46)	52 (48)	0.9

Data are number (%) or median (Interquartile Range).
Early referral to a nephrologist was defined if the patient was treated by a nephrologist ≥ 3 months before creation of the Arterio-Venous Fistula (AVF). Smoking habit was defined when the patient smoked at the time of the AVF construction. POD, post operative day from creation to first cannulation of an AVF. For example, the risk of presence of DM for the composite AVF outcome compared with absence of DM was 1.23 (95% CI, 0.79-1.93; p=0.4) even after adjustment for age, gender, BMI, cardiovascular, cerebrovascular or peripheral vascular disease, hypertension, smoking, and early referral to a nephrologist.

disease, cerebrovascular disease, peripheral vascular disease, early referral to a nephrologist, and smoking. The risk was also adjusted for cannulation-related complications at the beginning of HD treatment (three serial treatments). The risk reduction was calculated as 100 percent X (1-HR). In the analyses of the primary endpoints, data for the patients who had died with no VA event were considered to have been censored. A value of $p<0.05$ was considered to be significant. Statistical analyses were performed using SPSS Statistics 22 and SPSS

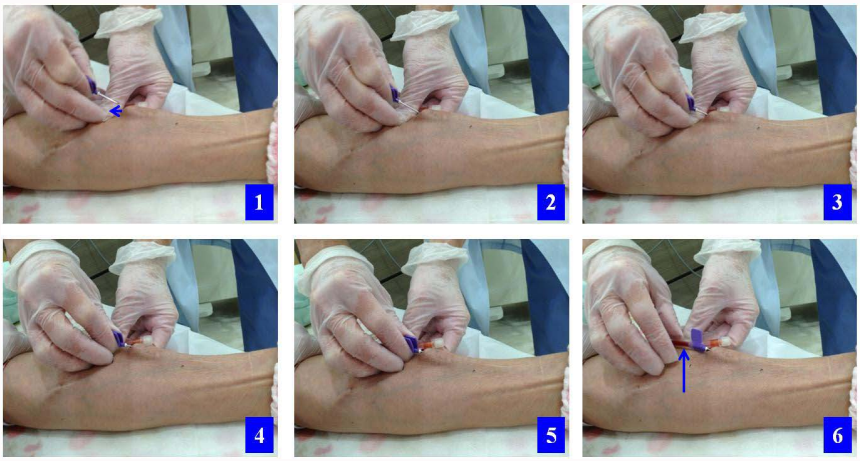


Figure S2 (a): Cannulation procedures using Dialysis Needle.
I. To make sure the center and margin of the vein and whether the vein dilate well.
- Nephrologist put the index finger of the non-dominant hand, and then, the dialysis center nurse compresses the patient's arm at the cubital fossa by manual pressure.
- Nephrologist determines the puncture site and needle size based on the inspection and palpation.

II. Wear mask and gloves and sterilize the forearm of the patient with chlorhexidine–alcohol.
III. The nurse compresses the patient's arm at the cubital fossa again, and the nephrologist performs the cannulation.
IV. Hold the vein at the upstream of the puncture site to immobilize the vein and to provide counter-traction (1, arrow).
- The counter-traction facilitates the skin incision by the needle.

V. Insertion angle of the needle are <30° regularly.
- Fasten the lure cap to close the needle tube, and grasp the needle wings with beval facing up.
- The steeper angle (2) is required at the moment of skin incision for patients, whose vein is prone to move under the skin.
- Take meticulous attention to avoid backwall or posterior wall infiltration (needle tip punctures the bottom of the fistula), when steeper angle is needed.

VI. Watch the blood pulsation within the tube (6, arrow). Blood flow indicates the presence of the needle tip within the vessel lumen.
- If the pulsation of the blood within the dialysis-needle-tube stop, it indicates that needle tip attach the vessel wall or an infiltration occurs.

VII. Once the blood pulsation is observed, flatten the insertion angle and advance the needle.
- During the advancement of the needle, feel the smooth texture to sense passage of the needle within the venous lumen (3,4,5).
- If the resistance is felt, attach a 20-mL syringe to confirm whether the blood can be drawn easily by the syringe and whether the saline infusion pressure is low.

VIII. When the needle is inserted enough, connect the needle tube to the hemodialysis circuit via lure connector.

Sample power (IBM Corp., NY).

Results

Patients

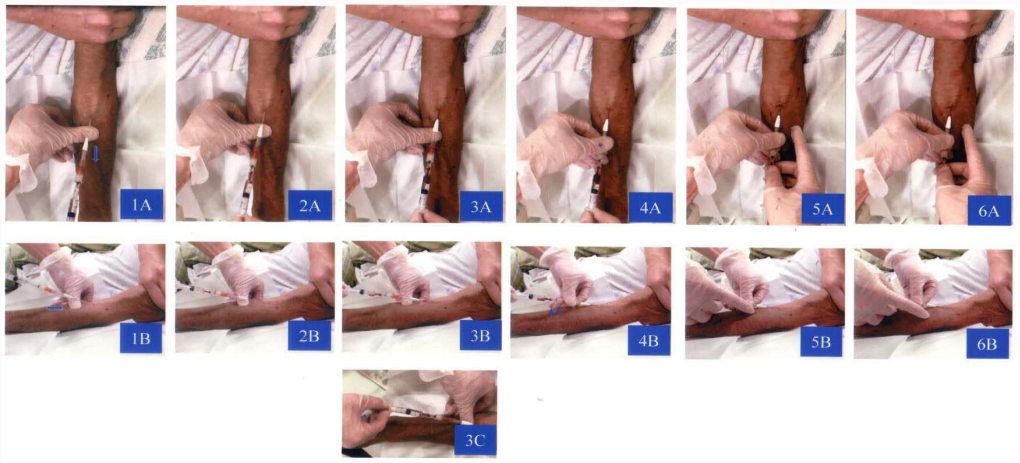
From January 1997 through December 2008, 335 patients began chronic dialysis therapy at Nagoya City University Hospital. Their initial VAs for hemodialysis were as follows: radial-cephalic AVF (n=208, 62.1%), anatomical snuff box AVF (n=2, 0.6%), AVG (n=53, 15.8%), silastic cannula external arteriovenous shunt (i.e., classical forearm external arteriovenous cannulas) (n=21, 6.3%), and temporary CVC (n=51, 15.2%). The surgeries to create either the AVF or AVG and placement of the CVC were all performed by nephrologists. Thus, 208 patients were eligible for the study. None of the 208 patients in the study group required ligation of collaterals due to insufficient inflow after surgical creation of the AVF. Of the 208 patients, 3 (1.4%) patients were lost to follow-up because the maintenance dialysis center lost their medical records, and thus these patients were removed from the study. Accordingly, 205 patients [140 males and 65 females; 64 (IQR, 53-72) years)] enrolled in the study. The original end-stage renal disease in this cohort included glomerulonephritis in 57 patients (27.8%), nephrosclerosis in 50 (24.4%), DM in 83 (40.4%), tubulo-interstitial nephritis in 7 (3.4%), polycystic kidney disease in 4 (2.0%), and vesicoureteral reflux in 4 (2.0%). All of the 205 RC-AVFs were able to achieve the prescribed BFR during the beginning period of HD (150 mL/min for first three times and 200 mL/min for following, at least, two times).

The median time from when the AVF was created until when the AVF was first cannulated (POD) was 23 (IQR, 11-96) days (Figure 1a). As mentioned above, we preferably performed the first AVF cannulation at 3-4 weeks after its creation. However, a first cannulation was performed at <22 days in 96 of the 205 patients (47%) (Figure 1b). In these patients, our institutional policy was violated because the attending physician chose AVF puncture rather than CVC insertion.

Table 1 lists the baseline demographics of the patients at initiation of the HD, when their VA was cannulated for the first time. Of the 94 patients with DM, their original disease of end stage renal disease was DM in 82 patients, nephrosclerosis in 5 and glomerulonephritis in 7.

Outcomes

The median follow-up period was 52 (IQR, 13-65; min 0.25, max 155) months (791 patient-years). One hundred and twenty patients



I. To make sure the center and margin of the vein and whether the vein dilate well.
- Nephrologist put the index finger of the non-dominant hand, and then, the dialysis center nurse compresses the patient's arm at the cubital fossa with a tourniquet or by manual pressure.

II. Wear mask and gloves and sterilize the forearm of the patient with chlorhexidine–alcohol.
III. The nurse compresses the patient's arm at the cubital fossa again, and the nephrologist performs the cannulation.
- Attach catheter-over-needle device to a 2.5-mLsyringe filled with 1.0 mL of normal saline solution.
- Purge air of the needle by flushing the saline using a syringe.

IV. Hold the vein at the upstream of the puncture site to immobilize the vein and to provide counter-traction (1A,B, arrow).
- The counter-traction facilitates the skin incision by the needle.

V. Insertion angle of the needle are <30° regularly.
- The steeper angle is required at the moment of skin incision for patients, whose vein is prone to move under the skin (1B).
- Take meticulous attention to avoid backwall or posterior wall infiltration (needle tip punctures the bottom of the fistula), when steeper angle is needed.

VI. Watch the blood flow into the syringe. Blood flow in the syringe indicates the presence of the needle tip within the vessel lumen (2A,B).
- Of note, this does not indicate that cannula tip is within the lumen, because we use the catheter-over-needle device, of which the internal needle is longer than the cannula by 5mm in length.

VII. Once the catheter-over-needle device advances in length enough that cannula itself is within the lumen, flatten the insertion angle maintaining gentle negative pressure to confirm the blood backflow into the syringe (3A,B).
- In this process, placement of the 4th and 5th fingers of the dominant hand of the nephrologist on the patient's skin is helpful to keep the insertion angle and the depth of the cannulation (3C, asterisk).
- Repeat "advancing the device <1.0mm" and "flattening the insertion angle" carefully.
- When advance the device, feel the smooth texture to sense passage of the needle within the venous lumen.
- If the resistance is felt, re-confirm whether the blood can be drawn easily by the syringe.

VIII. Then, grasp the syringe by the 1st and 3rd finger (4A, asterisk) and place the 4th and 5th fingers of the of non-dominant hand (4B, arrow head) to further keep the insertion angle and the depth of the cannulation in each moment.
- Cannula can pass the venous valve easily with the screw-like advance driven by the 1st and 2nd finger of the non-dominant hand (4A,5A,6A).

IX. When the cannula is inserted enough, hold the cannula with non-dominant hand and remove the internal needle with the dominant hand.
X. Re-confirm the blood backflow and then, flush the cannula with saline before the connecting cannula to hemodialysis circuit.

Table 3: Risk of a vascular event in postoperative ≥ 22 days (vs. <22 days).

	HR	95% CI	p value
model 1	0.48	0.31-0.75	0.001
model 2	0.48	0.31-0.75	0.001
model 3	0.48	0.31-0.76	0.002
model 4	0.48	0.30-0.76	0.002

HR: Hazard Ratio; 95% CI: 95% Confidence Interval
HRs are shown in model 1 (unadjusted); model 2 (adjusted with age, gender and body mass index at baseline), model 3 (adjusted with model 2 + hypertension, diabetes mellitus, coronary heart disease, cerebrovascular disease, and peripheral artery disease), and model 4 (adjusted with model 3 + early referral to a nephrologist, and smoking habit).

Table 4: Baseline demographics in patients with postoperative ≤ 14, 15-21 and ≥ 22 days.

	Postoperative day			
	≤14 (n = 70)	15-21 (n=26)	≥ 22 (n = 109)	p value
Age, years	63(53-73)	58(50-70)	65(56-72)	0.4
Gender, male	51 (73)	16 (62)	73 (67)	0.5
Body mass index, kg/m^2	21(19-23)	22(19-24)	22(21-25)	0.03
Hypertension	66 (94)	21 (81)	102 (94)	0.07
Diabetes	37 (53)	11 (42)	46 (42)	0.3
Coronary heart disease	13 (19)	5 (19)	22 (20)	0.9
Cerebrovascular disease	7 (10)	2 (8)	17 (16)	0.4
Peripheral vascular disease	4 (6)	1 (4)	5 (5)	0.9
Early referral to a nephrologist	44 (63)	21 (81)	82 (75)	0.1
Smoking habit	29 (41)	15 (58)	52 (48)	0.4

Data are number (%) or median (Interquartile Range).
Early referral to a nephrologist was defined if the patient was treated by a nephrologist ≥ 3 months before Arterio-Venous Fistulae (AVF) construction. Smoking habit was defined when the patient smoked at the time of the AVF construction. The postoperative day was defined as the time from creation to first cannulation of an AVF.

Table 5: Risk of a vascular event in postoperative ≤ 14, 15-21 and ≥ 22 days.

	Postoperative day								
	≤ 14 (n = 70)			15-21 (n=26)			≥ 22 (n = 109)		
model	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
model 1	1	(ref)	-	0.69	0.36-1.32	0.3	0.44	0.27-0.69	0.0004
model 2	1	(ref)	-	0.68	0.35-1.31	0.3	0.43	0.27-0.69	0.0005
model 3	1	(ref)	-	0.63	0.32-1.23	0.2	0.42	0.26-0.69	0.0006
model 4	1	(ref)	-	0.56	0.28-1.12	0.1	0.39	0.24-0.65	0.0003

HR: Hazard Ratio; CI: Confidence Interval
HRs are shown in model 1 (unadjusted); model 2 (adjusted with age, gender, and body mass index at baseline), model 3 (adjusted with model 2 + hypertension, diabetes mellitus, coronary heart disease, cerebrovascular disease, and peripheral vascular disease), and model 4 (adjusted with model 3 + early referral to a nephrologist, and smoking habit).

(59%) did not experience a VA event at any time after the first AVF cannulation. Among them, 3 underwent renal transplantation and 21 died with no VA events after the first AVF cannulation. Eighty-five patients (41%) experienced the primary endpoint. None of these patients experienced thrombosis accompanied by Hb>15 g/dL or excess blood pressure reduction in the absence of a stenosis in their AVF. The 1-, 5-, and 10-year functional primary patency (from the first cannulation until the first VA event) was 80, 64, and 59%, respectively. The 1-, 5-, and 10-year primary patency (from the access creation until the first VA event) was 82, 64, and 59 %, respectively. The median (IQR) time from the first cannulation to a VA event was 14 (3-49) months. The VA events included 46 PTAs and 39 surgical revisions of the AVF. Five of these 39 surgical revisions were accompanied with thrombectomy.

Supplemental Table 1: Physical examination of arterio-venous fistula (AVF).

	Favorable signs	Warning signs
On inspection	1) Larger appearance without a tourniquet. 2) Dilate well[a] when we compress the patient's arm above the cubital fossa with a tourniquet or by manual pressure. 3) Outflow vein in the puncture area was straight and large enough for placement of 2 needles.	1) AVF with upstream stenosis may fail to dilate with manual pressure on the downstream vessel. 2) Downstream stenosis produces either a segmental dilation of the vein or an aneurysmal appearance. 3) Venous hypertension (e.g., caused by central vein stenosis) may cause swelling in the forearm and/or upper arm.
On palpation	1) AVF with no downstream stenosis demonstrates continuous thrill and a soft tactual sense, and can be easily compressed. 2) Easily palpable, superficial, and sufficient-diameter vein is acceptable for cannulation.	1) AVF with stenosis demonstrates hard pulsation rather than thrill at a site peripheral to the stenotic lesion.
On auscultation	1) Low-pitch and systolic-diastolic continuous sound can be audible in an AVF with both sufficient inflow and outflow.	1) An intensification of systolic high-pitch bruit suggests stenosis.

Whether the AVF had matured sufficiently to cannulate for hemodialysis treatment was determined based on physical examination, including inspection, palpation and auscultation. [a]Vein can be dilated enough to puncture (approximately >4 mm in width between 2 lateral borders of the fistula with manual compression). When a patient need the initiation of HD, experienced nephrologists determined whether the AVF had matured sufficiently to cannulate based on physical examination shown in this Table, and the nephrologist implemented all the AVF cannulation.

The risks of baseline characteristics for contributing to VA events are shown in Table 1. Univariate analysis showed that none of the baseline characteristics contributed to a higher HR for VA events.

During the first three serial treatments of HD, the cannulation-related complications were infiltration alone (n=11), re-cannulation alone (n=6), and re-cannulation with concurrent infiltration (n=7). Between the patients, who experienced infiltration (n=18) and those without infiltration (n=187), there was no difference in baseline characteristics (age, gender, BMI, cardiovascular, cerebrovascular or peripheral vascular disease, hypertension, DM, smoking, and early referral to a nephrologist). There was no difference in POD between the patients with infiltration and those without infiltration [28(IQR, 14-154) *vs.* 23(IQR, 11-94) days, p=0.3]. Even after adjustment for the baseline characteristics, the risk of the occurrence of infiltration was not related to the risk for a VA event (HR, 0.72; 95% CI, 0.32-1.60, p=0.4). There was no difference in the baseline characteristics between the patients with re-cannulation (n=13) and those without re-cannulation (n=192). There was no difference in POD from creation to the first cannulation between the patients with re-cannulation and those without re-cannulation [20(IQR, 13-23) *vs.* 25(IQR, 11-97) days, p=0.5]. After adjustment for the baseline characteristics, the re-cannulation was not related to the risk for a VA event (HR, 0.89; 95% CI, 0.38-2.10, p=0.8).

Supplemental Table 2: Treatment Choice for the first VA events.

	Presence/absence of thrombosis		
	Established thrombosis[a]	AVF still has blood flow (not completely occluded)	
Preferred procedures[b]	Surgical Revision[c]	PTA[d]	Surgical Revision[d]
	• Surgical thrombectomy is performed by using a Fogarty thrombectomy catheter. • Jump-up anastomosis; create a new arterio-venous anastomosis at the more proximal site of the old anastomosis.	PTA is preferred rather than surgical revision if; • The patients need to start the HD treatment immediately (in unit of a minute). • The jump-up anastomosis reduces the length for cannulation site. 1. Main outflow vein places far away from the artery. 2. Inflow (arterial) stenosis was at forearm closed to elbow or upper arm. • Inflow (arterial) stenosis, which prevents the AVF from further maturation, is noted.	Surgical revision is preferred if; • The stenotic lesion is long (e.g., juxta-anastomotic stenosis), indicating the recurrence of the stenosis when we chose the PTA. • Severe stenosis of the AVF preventing the guide-wire from going through the stenotic site for PTA. • Occluded AVF with massive thrombus.

[a]Recently, we often use thrombus-aspiration-catheter. Therefore, the case, in which we do not need skin incision (surgical procedure), is increasing even in the case with established thrombosis. However, at the study period, we chose surgical revision rather than PTA as the indication for first VA event.
[b]Prior to the start of procedures, review the medical record of previous dialysis treatment regarding physical examination of the arterio-venous fistula, blood flow rate, venous pressure and re-circulation. Insufficient blood flow rate indicates stenosis in the AVF upstream of the puncture site (including the feeding artery). Elevated venous pressure indicates stenosis in the downstream of the puncture site (including the central vein). Recirculation can be caused by upstream stenosis, downstream stenosis or both. Need for fistulography should be considered before the treatment when thrombosis is not established.
[c]Surgical thrombectomy is performed by using a Fogarty thrombectomy catheter.
[d]We chose PTA rather than revision because the time "from when the event occur to when the operation room have prepared" is shorter for PTA. On occasion, when both the artery and vein are thrombosed. Recently, we can choose combination treatment of surgical thrombectomy followed by PTA. However, during the study period, the combination procedures was not performed.
PTA, percutaneous transluminal angioplasty; AVF, arterio-venous-fistula.
In summary, when the thrombosis was established in the AVF, we chose surgical revision (thrombectomy and creation of a new anastomosis at the more proximal site of the old anastomosis). When the AVF had not completely occluded by the thrombus, we chose surgical revision or PTA due to the urgency of treatment and the stenotic site of the AVF.

Figure 2a shows the ROC curves for POD (AUC 0.621 ± 0.041, 95% CI 0.542-0.701, p=0.003). The ROC curve analysis revealed that the best cutoff value of POD for predicting a VA event was 21.5 days. Generally, an AUC ≥ 0.7 is considered acceptable, but DP-plot methods also demonstrated that the cutoff value of the POD was 20-21 days (Figure 2b). Patients with a POD<22 days (n=96) and ≥ 22 days (n=109) had similar baseline characteristics except for a lower BMI in patients with a POD <22 days (Table 2). Figure 3 shows the Kaplan–Meier curves with this POD cutoff value. The cumulative incidence rates of a VA event during the study period were 53% and 31% for those above and below the cutoff, respectively (p=0.0008). At the follow-up periods of 24, 48, 72, 96, 120, and 150 months, the AVF survival rates in POD<22 days *vs.* ≥ 22 days were 72% *vs.* 81%, 61% *vs.* 76%, 53% *vs.* 71%, 47% *vs.* 70%, 47% *vs.* 69%, and 47% *vs.* 69%, respectively. The predictive accuracies of the cut-off values (POD<22 days *vs.* ≥ 22 days) as an indicator of a VA event were as follows: sensitivity, specificity, positive predictive accuracy, negative predictive accuracy, and the overall accuracies were 60, 63, 53, 69, and 61%, respectively. In the Cox regression analysis, a POD ≥ 22 days reduced the risk of a VA event by 52% compared with that of a POD<22 days (Table 3). Based on the cumulative rates of primary endpoints of 53% *vs.* 31% and the sample size of 205 patients, the statistical power of our study was 89% [α=0.05 (two-sided), β=0.11]. We were unable to achieve >80% statistical power when investigating the risk for a VA event when surgical revision and PTA were analyzed separately.

As mentioned above, the practice of initial puncture of an AVF on POD 14 days deserves attention [5,6] but our study found that the initial puncture of the fistula on POD ≥ 22 days reduced the risk of a VA event. We thus, compared the risk for a VA event for an initial puncture on POD ≤ 14 days and on POD 15-21 days. Patients with a POD ≤ 14 days (n=70), 15-21 days (n=26), and ≥ 22 days (n=109) had similar baseline characteristics except for a lower BMI in patients with a POD ≤ 14 days (Table 4). No significant difference in a VA event was seen for fistulae cannulated in ≤ 14 days compared with that of a POD 15-21 days. The practice of initial puncture of a RC-AVF on POD ≥ 22 days yielded approximately a 60% reduction in a VA event compared with that of a POD ≤ 14 days (p=0.0003, Table 5).

Discussion

Our study demonstrated that we should refrain from performing the first cannulation until 21 days has elapsed after a RC-AVF creation. This timing differs from the aforementioned DOPPS results showing that 2 weeks should elapse before first AVF cannulation [5]. We felt by experience that a 2-week waiting time was too short for maturation of an AVF, and therefore conducted this retrospective study. DOPPS [5] used study-entry-date, which was within 14 days of the first cannulation date, as a substitute for the exact first cannulation date. We used the actual number of days postoperatively when the fistula was first cannulated which is a more accurate assessment of the degree of fistula maturation. Rayners' study [5] was based on data derived from France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States. The proportion of patients starting HD via AVF, AVG or CVC and BFR during HD varied greatly between these countries. The study results regarding AVF patency can be affected by these variables. In our study, AVFs were created and maintenance HD was initiated at a single-center, where the institutional policy was for the first cannulation to be performed at 3-4 weeks after AVF creation. The prescribed BFR during the HD procedure was predetermined. A computational fluid dynamics models of AVF demonstrated that1) end-to-side anastomosis can resist reversed arterial outflow to prevent a steal phenomenon, 2) side-to-side anastomosis with a non-occluded distal vein can achieve the highest venous outflow, and 3) side-to-side anastomosis with the ligated distal vein closer to the anastomosis (same as ours) can produce uniform vessel wall shear stress to avert intimal hyperplasia [10]. In our study, configuration of arterio-venous anastomoses was also standardized (Figure S1). Saran and colleagues [11] reported that earlier cannulation of a newly created AVF did not increase the risk

for VA failure. Their study was based on a facility-level analysis and was examined based on a unit of a month, whereas our study was a patient-level analysis and was examined in a unit of a day. These differences can explain the discrepancy between their study and ours.

The treatment duration for patients on maintenance HD is longer in Japan [7,8] and thus Japan has a better population for evaluating long-term AVF patency. The longer HD treatment duration in Japan seems to be attributed not only to the longer life expectancy of HD patients, but also to the lower availability of renal transplantation.

The North American Vascular Access Consortium (NAVAC) [12] and Society of Vascular Surgery (SVS) [13] defined primary patency as the interval from access construction until first access thrombosis or any intervention to maintain or restore blood flow. Functional primary patency was defined as the time from the first successful 2-needle cannulation until first intervention or access failure. The latter was our study measurement described as a POD. A recent systematic review and meta-analysis [14] found that the values for functional primary patency at 1 and 2 years were 60% and 51%, respectively, and concluded that AVFs had a high rate of primary failure [14]. However, these values for patency were 82% and 77% in our study, respectively. The discrepancy between the findings in the USA and in Japan may relate to HD treatment differences. The POD from creation to the first cannulation of the AVF was recommended as 6-8 weeks in the USA [4] and as 2-3 weeks in Japan [6]. Furthermore, the proportion of AVFs out of VAs also differed between the USA and Japan as follows: 24 % *vs.* 93% in 1996-2001, 31% *vs.* 91% in 2002-2004, and 47 % *vs.* 91% in 2005-2007. The prescribed BFR during HD treatment was higher in the USA (350-450 mL/min) than that in Japan (150-250 mL/min). The difference might be, in part, attributable to the systemic blood volume. The higher prescribed BFR may lower the threshold for detection of VA dysfunction. In the USA, a longer POD is recommended as compared with that in Japan. This may decrease the choice for AVF especially in patients who have little time based on the anticipated need for HD. Once a longer time from creation to first cannulation of AVF is attained, a higher BFR is attained for the initial HD treatment.

Limitations

Our study has several limitations. First, the non-randomized nature of the study with the possibility of residual confounding is a limitation. Even with an institutional policy of not cannulating an AVF within 3-4 weeks after creation, the first cannulation was performed at <22 days in 47% of the patients. Our institutional policy might be violated based on a balance between the potential benefits (avoidance of the risk of CVC insertion) and risks of early cannulation (impairment of AVF patency). In this way, physicians are inclined to perform the first AVF cannulation earlier than the POD recommended in guidelines, and it has become customary for physicians to use this approach. Therefore, our study is a good example of verification of the effect of the KDOQI recommendation of not cannulating an AVF within 3-4 weeks after its creation in clinical practice. Second, our institutional policy might be violated based on the appearance of the vein. Even if the vein seems to be thick enough, the venous wall may not be mature (arterialization). Cannulation of an immature AVF predisposes vessel compression by an infiltrated hematoma [15] and can lead to stenosis of the AVF. When a non-arterized vein is cannulated, the puncture site is liable to have intimal hyperplasia and fibrosis which prevents vessel dilation to cause cicatricial stenosis. Stenosis of the AVF can occur naturally due to intimal hyperplasia [16-18] or a surgical procedure (juxto-anastomosis lesion) [19-22] independent of early cannulation. Fibrosis can originate due to co-ordinated processes involving inflammation, uremia, hypoxia, sheer stress, and increased thrombogenicity [23]. Our study failed to evaluate whether the vessel wall requiring VA intervention was at the same site as the puncture zone during the initial period of HD in each patients. We could not investigate the histopathology of vessels of AVF in patients with VA events. Third, it was recommended that an AVF usable for HD treatment meet following criteria; blood flow >600 mL/min, a diameter >0.6 cm, and a depth <0.6 cm from the skin surface (the Rule of 6s) [2]. A lower volume of a brachial artery blood flow measured by sonography at 1 day and 14 day after AVF creation can also predict AVF failure [24]. However, during 1997-2008, we did not use ultrasound examination of the AVF before the first cannulation.

Conclusion

The time from creation until the first cannulation of a RC-AVF should be set at more than 3 weeks. This finding provides a good example of the KDOQI recommendations.

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