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Drouven, Johannes W; de Bruin, Cor; van Roon, Arie M; Bokkers, Reinoud P H; El Moumni, Mostafa; Zeebregts, Clark J

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Vascular access creation in octogenarians: The effect of



age on outcomes

Johannes W. Drouven, MD,^a Cor de Bruin,^a Arie M. van Roon,^b Reinoud P. H. Bokkers, MD, PhD,^c Mostafa El Moumni, MD, PhD,^a and Clark J. Zeebregts, MD, PhD,^a *Groningen, The Netherlands*

ABSTRACT

Background: The prevalence of end-stage renal disease is accelerating among older age groups. Patient-specific factors in the elderly patient group might advocate for a different vascular access creation approach, in which patency, risk of nonmaturation, and time to cannulation with accompanied prolonged catheter use should be of primary importance. The aim of this study was to determine which vascular access has the best outcomes and to determine whether age is associated with different outcomes after vascular access surgery.

Methods: Data were obtained from a prospectively maintained database of patients treated between November 2004 and December 2017. Two different patient groups were identified: the octogenarian group, consisting of patients aged \geq 80 years; and the control group, consisting of all the other patients. A total of 694 vascular access procedures were included in this study, 65 in the octogenarian group and 629 in the control group. Primary assisted, and secondary patency rates were calculated and compared between groups and vascular accesses. Multivariable analysis was used to determine whether age is an effect modifier in the association between type of vascular access and different patency outcomes.

Results: Mean follow-up was 23.2 months in the octogenarian group and 21.2 months in the control group (P = .210). No significant differences were found in patient survival, with a 5-year survival rate of 63.8% (±5.9%) in the octogenarian group and 57.2% (±2.2%) in the control group (P = .866). Within the octogenarian group, primary failure rate was highest in the radiocephalic arteriovenous fistula (AVF) patients, 42.1% (P = .006). Brachiocephalic AVF had significantly improved assisted patency compared with the other vascular accesses among the octogenarians (P = .016). Age was not an effect modifier in the association between type of vascular access and different patency outcomes. The adjusted analysis, corrected for octogenarian age, diabetes mellitus, hypertension, and sex, showed that brachiocephalic AVF was significantly associated with an increase in primary patency (hazard ratio, 0.70; 95% confidence interval, 0.54-0.90; P = .006) and primary assisted patency (hazard ratio, 0.58; 95% confidence interval, 0.39-0.86; P = .006) compared with other vascular accesses.

Conclusions: The results of our study support primary placement of a brachiocephalic AVF in the octogenarian patient. A low primary failure rate was achieved with significant improved patency rates compared with the other vascular accesses. (J Vasc Surg 2020;72:171-9.)

Keywords: Vascular access; Octogenarian; Elderly; Outcomes

The number of patients with end-stage renal disease (ESRD) requiring intermittent hemodialysis is rising worldwide, with the highest increase in prevalence among patients older than 65 years.^{1,2} According to the latest U.S. Renal Data System report, almost 47% of the patients with ESRD on hemodialysis were older than 65 years.² Current guidelines advocate a fistula-first approach for all patients, and treatment is started as distally as possible.³ The rationale of this fistula-first

Author conflict of interest: none.

approach is to preserve the more proximal vessels for future vascular access creation. There is, however, growing evidence that this approach might not be beneficial in elderly patients. A significantly higher mortality and an increased incidence of comorbidities, such as diabetes mellitus, hypertension, and peripheral vascular disease, are reported in the elderly population.^{2,4,5} Nonmaturation also plays an important role as patients older than 65 years seem to have twice the failure rate

From the Division of Vascular Surgery, Department of Surgery,^a Division of Vascular Medicine, Department of Internal Medicine,^b and Department of Radiology, Medical Imaging Center,^c University Medical Center Groningen, University of Groningen.

Correspondence: Johannes W. Drouven, MD, Division of Vascular Surgery, Department of Surgery, University Medical Center Groningen, University of Groningen, P.O. Box 30 001, 9700 RB Groningen, The Netherlands (e-mail: vj.w.drouven@umcg.nl).

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of the younger population.⁶ These patient-specific factors in the elderly patient group might advocate for a different vascular access creation approach, in which the patency outcomes, the risk of nonmaturation, and the time to cannulation with accompanied prolonged catheter use should be of primary importance.⁷⁻¹⁰ Hence, a more proximal arteriovenous fistula (AVF) or even an arteriovenous graft (AVG) could be the primary vascular access of choice for these patients.^{9,11-14}

The aim of this study was to determine which vascular access has the best outcomes in patients on intermittent hemodialysis and to determine whether age is associated with different outcomes after vascular access surgery. The outcomes of this study might aid physicians in future vascular access planning for the frail octogenarian patient.

METHODS

Study design. This is a retrospective cohort study of patients with chronic renal dysfunction requiring hemodialysis who are being treated in a single-center tertiary referral center. Data were obtained from a prospectively maintained database of patients treated between November 2004 and December 2017. During this period, a total of 599 patients underwent 694 vascular access creations at our center and were included in our study. Approval of the Institutional Review Board was obtained (METc 2018/015). Retrospective research of patient files does not fall under the scope of the Dutch Medical Research Involving Human Beings Act (WMO), and therefore patient informed consent was not required. Patient-related data were analyzed anonymously.

Preoperative assessment. Physical examination of both arms was routinely performed. Duplex ultrasound examination was performed in all patients to measure the course, depth, and diameter of arteries and suitable veins, including assessment of possible central venous obstructions.¹⁵ Vein diameter measurements were performed with an inflated cuff to 50 mm Hg at the level of the proximal upper arm. Doppler spectral analysis combined with pressure measurements of the arm and hand was performed. For patients in predialysis, vascular access creation was scheduled approximately 3 months before the expected start of hemodialysis in patients receiving an AVF. For AVG, patients were scheduled for creation 4 to 6 weeks before the expected start of hemodialysis. Following the Kidney Disease Outcomes Quality Initiative (KDOQI) and national guidelines, a fistula-first approach was used in vascular access creation, starting as distally as possible.³ The nondominant arm was preferred to create the vascular access. In patients with previous maturation problems or with a subacute indication for dialysis (ie, <4 weeks), an AVG was considered instead of the fistula-first approach.^{10,16}

cording to the KDOQI clinical practice guidelines,

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center, retrospective cohort study
- **Key Findings:** Brachiocephalic arteriovenous fistula showed improved patency in 65 octogenarians compared with other vascular accesses. Age was not an effect modifier in the relationship between the type of vascular access and the different patency outcomes.
- Take Home Message: In octogenarians, primary placement of a brachiocephalic arteriovenous fistula might be considered.

first-time cannulation was allowed after a 6-week maturation period in patients with an AVF. In patients with an AVG, first-time cannulation was allowed within 3 to 4 weeks after surgery when a standard wall polytetrafluoroethylene graft was used.³

Patients' demographics and characteristics, including the use of anticoagulant medication, catheter use (tunneled or nontunneled), comorbidity, type of vascular access, and intraoperative details, were obtained from the database. Types of vascular access were categorized into radiocephalic AVF, brachiocephalic AVF, AVG, and basilic vein transpositions.

Operative techniques. All procedures were performed under regional or general anesthesia. In case of the creation of an AVG, patients received prophylactic antibiotic therapy according to our hospital standard. For the creation of a radiocephalic AVF, cephalic vein diameter of 2 mm and radial artery diameter of 3 mm were considered appropriate for fistula creation. For the creation of brachiocephalic AVF and basilic vein transposition, vein diameters of 3 mm and brachial artery diameters of 3 mm were considered appropriate for fistula creation. All basilic vein transpositions were performed in a one-stage procedure. For AVG creation, a standard wall polytetrafluoroethylene graft (Gore-Tex; W. L. Gore & Associates, Flagstaff, Ariz) with 6-mm diameter and 0.5-mm wall thickness was used in a forearm loop or upper arm straight configuration. All anastomoses were created with a running polypropylene 6-0 suture (Prolene; Ethicon Inc, Somerville, NJ). Low-dose acetylsalicylic acid was started in patients who did not receive antiplatelet or antithrombotic drugs preoperatively.

Follow-up. All patients were monitored in the postprocedural period. Patients were generally discharged the day after the procedure. After discharge, routine physical examination, duplex ultrasound, and ultrasound dilution flow measurements were performed with either a Transonic HD01 Plus Hemodialysis Monitor (Transonic Systems

Table I. Causes of renal failure

	Octogenarians	Controls
Chronic renal failure, cause unknown	7 (10.8)	59 (9.4)
Cystic kidney diseases	2 (3.1)	62 (9.9)
Diabetes mellitus	8 (12.3)	114 (18.1)
Interstitial nephritis, pyelonephritis, drug induced, nephrolithiasis	4 (6.2)	48 (7.6)
Not specified	3 (4.6)	28 (4.5)
Other congenital diseases or hereditary kidney diseases	O (O)	9 (1.4)
Other multisystem diseases	2 (3.1)	44 (7.0)
Primary glomerular diseases	3 (4.6)	60 (9.5)
Renal vascular disease, excluding vasculitis	36 (55.4)	120 (19.1)
Transplant failure	O (O)	85 (13.5)
Data are presented as number (%).		

Table II. Patients' characteristics

	Octogenarians	Controls	P value				
No. of cases	65	629					
Age at surgery, years	82.1 (2.6)	61.7 (13.5)	<.001ª				
Sex							
Male	41 (63.1)	371 (59.0)	.522				
Female	24 (36.9)	258 (41.0)					
BMI, kg/m ²	25.3 (4.9)	26.1 (7.4)	.304				
Diabetes mellitus	15 (23.1)	206 (32.8)	.111				
Hypertension	52 (80)	516 (82.0)	.685				
Predialysis	37 (56.9)	248 (39.4)	.008 ^ª				
Catheter use in predialysis patients	1 (2.7)	15 (6.0)	.154				
Overall catheter use	27 (41.5)	372 (59.1)	.005ª				
Primary vascular access	54 (83.1)	454 (72.2)	.061				
Access type			.051				
Radiocephalic AVF	19 (29.2)	203 (32.3)					
Brachiocephalic AVF	36 (55.4)	248 (39.4)					
AVG	8 (12.3)	124 (19.7)					
Basilic vein transposition	2 (3.1)	54 (8.6)					
Follow-up time, months	23.1 (48)	21.2 (37.5)	.210				
AVF, Arteriovenous fistula; AVC, arteriovenous graft; BMI, body mass index.							

AVF, Arteriovenous fistula; AVG, arteriovenous graft; BMI, body mass inde. Data are presented as number (%) or median (interquartile range).

Inc, Ithaca, NY) or Fresenius 5008S CorDiax dialysis machine (Fresenius Medical Care, Bad Homburg, Germany). Indications for postsurgical interventions were standardized; in patients with an AVF with flow rates <500 mL/min, an AVG with flow rates <600 mL/min, or a consistent monthly decrease of 25% or more with a flow rate <1000 mL/min, angiography was scheduled and percutaneous transluminal angioplasty performed in case of stenosis.³ Complications, interventions, and patency rates were registered and alculated. **Definitions.** Primary failure was defined as occlusion or if cannulation was not possible after the regular maturation period; this includes inadequate maturation and other complications, such as ischemia or infection.¹⁷ Adequate fistula maturation was defined as a fistula with a vein diameter >4 mm, a flow >500 mL/min, and a puncture track length >10 cm.^{18,19} Primary patency was defined as the interval from the time of access placement until any intervention designed to maintain or to re-establish patency, access thrombosis, or the time of

 $^{^{}a}P < .05$.

		Octogenarians				
	Radiocephalic AVF	Brachiocephalic AVF	AVG	Basilic vein transposition	P value	
Time to cannulation, days	103 (99)	61 (34)	33 (23)	80 (53)	.026	
Primary failure	8 (42.1)	2 (5.6)	1 (12.5)	0 (0.0)	.006	
Endovascular interventions	0.45 PY ⁻¹	0.74 PY ⁻¹	1.62 PY ⁻¹	0.98 PY ⁻¹	.130	
Surgical revisions	0.07 PY ⁻¹	0.06 PY ⁻¹	0.23 PY ⁻¹	0.08 PY ⁻¹	.660	
AVF, Arteriovenous fistula; AVG, arteriovenous graft; PY, patient-year.						

Table III. Vascular access characteristics

measurement of patency. Primary assisted patency was defined as the interval from the time of access placement until access thrombosis or the time of measurement of patency, including intervening manipulations designed to maintain the functionality of a patent access. Secondary patency was defined as the interval from the time after creation until access abandonment, thrombosis, or the time of patency measurement including intervening manipulations designed to reestablish functionality in thrombosed access. Stenosis was defined as the presence of a peak systolic velocity >310 cm/s in AVG and >375 cm/s in AVF, with a vessel diameter <2.0 mm.²⁰

Statistical analysis. Data are presented as medians including interguartile range or numbers including percentages. Differences in incidence rates between groups were calculated with the Pearson χ^2 test or Fisher exact test. Two different patient groups were identified: the octogenarian group, consisting of patients with an age \geq 80 years; and the control group, consisting of all the other patients. Of note, one 91-year-old patient was included in the octogenarian group. Differences within the groups were calculated with the Mann-Whitney U test because data were skewed. Kaplan-Meier survival analysis and the life-table method were used to calculate survival and patency rates. The log-rank test was used to compare patencies between the patient groups and to determine significant factors influential to patency outcomes. Multivariable Cox regression analysis was performed to define predictors for failure. Radiocephalic AVF was indicated as the index group, and outcomes of other vascular access types were compared with the outcomes of the index group. To answer whether there is an association between the type of vascular access and the decrease in patency outcomes, the analysis was adjusted for age, body mass index, diabetes mellitus, hypertension, and sex. To investigate whether the association between the type of vascular access and the different patency outcomes changed by age, the interaction term age*vascular access type was included.

The incidence of complications and reinterventions was defined per patient-year: the total number of complicans and reinterventions was divided by the cumulative follow-up time of all patients in years.²¹ Differences were calculated with the Mann-Whitney U test. P values of <.05 were considered statistically significant. SPSS 24 (IBM Corp, Armonk, NY) was used for analysis.

RESULTS

Characteristics. A total of 694 vascular access procedures were included in this study, 65 in the octogenarian group and 629 in the control group. The causes of renal failure are listed in Table I.²² Renal vascular disease and diabetes mellitus were the major underlying causes of renal failure in both groups. There were no significant differences in the underlying diseases between the groups (P = .07). Patients' characteristics are listed in Table II. Overall catheter use was significantly different between groups, 41.5% in the octogenarian group and 59.1% in the control group (P = .005). The percentage of predialysis patients was significantly different between groups, 56.9% in the octogenarian group and 39.4% in the control group (P = .008). Catheter use in predialysis patients was low in both groups, with a single case in the octogenarian group and 15 cases in the control group (P = .154). No significant differences in catheter days were found between the various vascular access types (P = .471).

Patient survival. Patient survival was comparable between the octogenarian and control groups, with a 1year survival of 80% (\pm 5.0%) vs 84.9% (\pm 1.4%), a 3-year survival of 74.1% (\pm 5.1%) vs 72.4% (\pm 1.8%), and a 5-year survival of 63.8% (\pm 5.9%) vs 57.2% (\pm 2.2%), respectively (P = .866).

Access failure and reinterventions. Differences were calculated within groups. Time to cannulation, incidence of primary failure, and number of reinterventions are shown in Table III. In the octogenarian group, time to cannulation was significantly different between the various vascular accesses (P < .001). The shortest time to cannulation was observed in the AVG patients at 33 days. The primary failure rate was significantly different in the octogenarian group, with 42.1% for radiocephalic AVF patients (P = .006). In the control group, the shortest time to cannulation was seen in AVG patients at 34 days (P < .001).

Table III. Continued.

Controls						
Radiocephalic AVF	Brachiocephalic AVF	AVG	Basilic vein transposition	P value		
69 (104)	62 (48)	34 (20)	54 (28)	<.001		
62 (30.5)	48 (19.4)	31 (25.0)	14 (25.9)	.06		
0.25 PY ⁻¹	0.52 PY ⁻¹	1.40 PY ⁻¹	2.07 PY ⁻¹	<.001		
0.03 PY ⁻¹	0.08 PY ⁻¹	0.07 PY ⁻¹	0.01 PY ⁻¹	<.001		

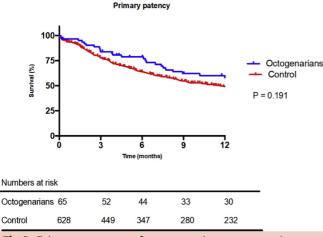


Fig 1. Primary patency of octogenarians vs control population. Time points after 12 months were censored when the standard error approximately reached 10%.

Patency. Primary, primary assisted, and secondary patencies of octogenarian and control patients are shown in Figs 1 to 3. Primary assisted and secondary patencies are significantly longer in the octogenarians than in the control group (P = .008 and P = .047, respectively). Primary, primary assisted, and secondary patency rates of radiocephalic AVF, brachiocephalic AVF, and AVG in octogenarians are shown in Fig 4. Basilic vein transposition was not included in this analysis because of the small number of patients. In the octogenarian patient group, primary assisted patency of brachiocephalic AVF was significantly longer compared with the other vascular accesses (P = .016).

The results of the Cox regression analysis are shown in Table IV. Radiocephalic AVF was indicated as the index group; outcomes of other vascular access types were compared with the outcomes of the index group. Raw analysis showed brachiocephalic AVF as having a significantly increased primary and primary assisted patency rate compared with radiocephalic AVF; AVG showed a significantly decreased primary, primary assisted, and secondary patency compared with radiocephalic AVF. The adjusted analysis, corrected for octogenarian age, diabetes mellitus, hypertension, and sex, showed that rachiocephalic AVF was a significant factor associated

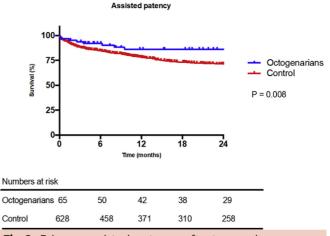
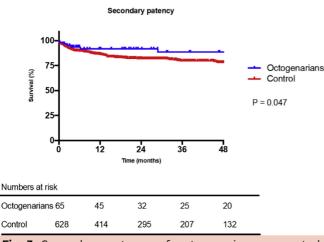


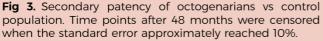
Fig 2. Primary assisted patency of octogenarians vs control population. Time points after 24 months were censored when the standard error approximately reached 10%.

with the increase in primary patency (hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.54-0.90; P = .006) and primary assisted patency (HR, 0.58; 95% CI, 0.39-0.86; P = .006). In addition, AVG was a significant factor associated with the decrease in primary patency (HR, 1.64; 95% CI, 1.25-2.16; P < .001), primary assisted patency (HR, 1.95; 95% CI, 1.36-2.81; P < .001), and secondary patency (HR, 1.61; 95% CI, 1.00-2.58; P = .050). Age did not change the association between type of vascular access and the primary patency (HR, 1.007; 95% CI, 0.56-1.82; P = .982), primary assisted patency (HR, 0.80; 95% CI, 0.32-2.00; P = .630), and secondary patency outcomes (HR, 1.05; 95% CI, 0.37-294; P = .927).

DISCUSSION

In this study, we investigated the outcomes of vascular access creation in octogenarian patients. The highest primary failure rate was observed in radiocephalic AVF patients, with up to 42.1% in the octogenarian group. In terms of patency, brachiocephalic AVF showed improved primary and primary assisted patency. As for octogenarians, patency rates were not decreased compared with the controls. Brachiocephalic AVF showed improved primary assisted patency compared





with the other vascular accesses in octogenarians. In both patient groups, grafts were associated with higher endovascular and surgical reintervention rates compared with other vascular accesses.

Our study demonstrates improved primary and primary assisted patency in brachiocephalic AVF compared with radiocephalic AVF. The aim of this study was to determine which vascular access in patients on hemodialysis has the best outcomes. The results of our study support the primary placement of a brachiocephalic AVF in octogenarians, discarding radiocephalic AVF as the primary vascular access in this patient group. These results were not influenced by the suitability of vessels for the chosen vascular access because all vascular accesses were planned according to the minimum diameters as stated in the guidelines.³ Interestingly, age does not influence vascular access patency significantly in our population. Overall primary patency was not significantly different between the octogenarians and controls either. These results signify that octogenarians should not be withheld from vascular access creation on the basis of their age status alone. Octogenarian patients who are considered fit for surgery can achieve acceptable results after vascular access creation, especially of a brachiocephalic AVF. Because of our early referral policy, catheter use is low in predialysis patients. Moreover, the majority of octogenarians who survived 3 years after surgery (74.1%) also survived for 5 years (63.8%). In our control group, 261 patients (41.5%) were aged between 65 and 80 years; therefore, comparing the octogenarians with the control group was still a comparison between mostly older patients.

Vascular access planning in the elderly remains a topic of discussion. KDOQI guidelines advocate a fistula-first approach for all patients, starting as distally as possible. "he goal of this fistula-first approach is to preserve the

e proximal vessels for future vascular access

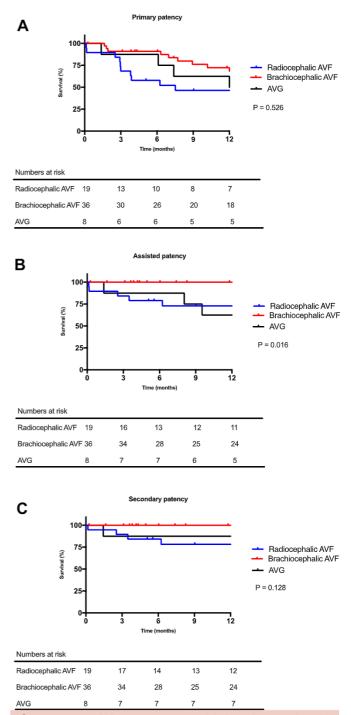


Fig 4. Primary **(A)**, primary assisted **(B)**, and secondary **(C)** patency rates of radiocehaplic arteriovenous fistula (*AVF*), brachiocephalic AVF, and arteriovenous graft (*AVG*) in octogenarians. Time points after 12 months were censored when the standard error approximately reached 10%.

creation.³ Because of patient-specific factors in the elderly, several other studies propose a different vascular access planning strategy for this population.^{10,23-25} Arguments for a modified strategy are reduced life expectancy and increased rates of primary failure in elderly

Table IV. Cox regression analysis

	Loss of primary patency			Loss of primary assisted patency			Loss of secondary patency		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Radiocephalic AVF ^a									
Brachiocephalic AVF ^a	0.76	0.60-0.97	.025	0.55	0.38-0.80	.002	0.69	0.44-1.08	.101
AVGª	1.74	1.35-2.25	<.001	2.08	1.49-2.92	<.001	1.66	1.07-2.59	.025
Basilic vein transposition ^a	1.33	0.93-1.90	.116	0.96	0.56-1.65	.876	1.21	0.64-2.30	.558
Radiocephalic AVF ^b									
Brachiocephalic AVF ^b	0.70	0.54-0.90	.006	0.58	0.39-0.86	.006	0.73	0.46-1.18	.199
AVG ^b	1.64	1.25-2.16	<.001	1.95	1.36-2.81	<.001	1.61	1.00-2.58	.050
Basilic vein transposition ^b	1.29	0.89-1.87	.176	0.94	0.54-1.64	.836	1.23	0.64-2.36	.536

AVF, Arteriovenous fistula; AVG, arteriovenous graft; CI, confidence interval; HR, hazard ratio.

Radiocephalic AVF was used as indicator; outcome measures were predictors for failure.

^aShows the raw analysis outcomes.

^bShows the multivariable regression results adjusted for age, body mass index, diabetes mellitus, hypertension, and sex.

patients with an AVF. Older patients might simply not benefit from the fistula-first strategy as increased mortality rates have been reported after initiation of dialysis in the elderly.^{2,14} Hence, simple application of the fistulafirst strategy, by placing a radiocephalic AVF in the elderly, does not seem beneficial.²⁶ Moreover, radiocephalic AVF is associated with poor patency outcomes and increased failure rates compared with other vascular accesses in the elderly.^{11,14} For this reason, the primary placement of a brachiocephalic AVF is often suggested in the elderly population.^{10,11,14,23,24} Varying age groups are used to define the elderly in these studies. An age >65 years is frequently used.^{11,14} According to the U.S. Renal Data System 2017 annual report, about 39% of the population with ESRD is at least 65 years old, so a large part of the population is still included when the elderly are defined as 65 years of age or older.²

Numerous articles have outcomes for octogenarians, in terms of patency, survival, and complications, with varying outcomes.²⁷⁻³⁴ Nadeau-Fredette et al²⁸ compared the outcomes of 26 octogenarians with a control group of 41 patients aged 50 to 60 years; 22 of 26 patients had brachiocephalic AVF in the octogenarian group and 33 of 41 in the control group. Primary failure was significantly higher in the octogenarian group (40% vs 17%; P = .04). Our study showed improved primary failure rates compared with their findings (5.6% for the brachiocephalic AVF in octogenarian patients). Only secondary patency duration was significantly longer in the younger group. No comparison was made between the different vascular accesses in the octogenarian population; results of grafts and fistulas were pooled as primary failure rates, and patency rates were comparable. They concluded that patency seems to decline in older patient groups, although age should not be considered a contraindication to AVF creation, which is in line with our conclusion.

Diandra et al³² described the outcomes of AVF creation in 47 octogenarians. Because of a 72% primary failure rate in 47 AVFs in their octogenarian population, primary catheter use is suggested as a viable option for octogenarians. We did not find these high primary failure rates; moreover, catheter use in our predialysis patients was much lower. This might be addressed to our early referral policy. Olsha et al³¹ found that octogenarians should still be included in the fistula-first initiative as similar patency rates to radiocephalic AVF were achieved in their population of 134 octogenarians compared with the younger population in the literature. Their results were in line with our findings; patency rates of octogenarians and controls were comparable in our study.

Similar results are presented by Misskey et al,³⁴ who compared the outcomes of AVFs in 941 patients of different age groups, including an octogenarian group consisting of 152 patients. In contrast to our findings, they found overall patency to be significantly worse in the elderly patient group than in patients younger than 65 years. Especially outcomes in elderly patients with radiocephalic AVF were significantly worse compared with brachiocephalic AVF. Our results also showed an increased patency in brachiocephalic AVF patients. No patients with AVGs were included in this study.

The strengths of this study are that we provided detailed information about the outcomes of vascular access creation in the octogenarian and control patients for relatively large groups of patients. Patency rates were also compared, and multivariable Cox regression was used to determine whether age alone is associated with differences in patency outcomes.

Weaknesses of this study are its retrospective nature and that the choice of vascular access was nonrandomized. The sample size in the octogenarian AVG and basilic vein transposition groups is small, and no information about elderly patients who were not considered eligible for vascular access creation is available.

CONCLUSIONS

The results of our study support the primary placement of a brachiocephalic AVF in the octogenarian patient. An acceptable time to cannulation and a low primary failure rate were achieved, with significantly improved patency rates compared with the other vascular accesses.

AUTHOR CONTRIBUTIONS

Conception and design: JD, CZ Analysis and interpretation: JD, MM Data collection: CB, AR, RB, MM, CZ Writing the article: JD Critical revision of the article: JD, CB, AR, RB, MM, CZ Final approval of the article: JD, CB, AR, RB, MM, CZ Statistical analysis: JD, AR, MM Obtained funding: Not applicable Overall responsibility: JD

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