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Original Investigation

Cost-effectiveness Analysis of Vascular Access Referral Policies in CKD

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Background: The optimal timing of vascular access referral for patients with chronic kidney disease who may need hemodialysis (HD) is a pressing question in nephrology. Current referral policies have not been rigorously compared with respect to costs and benefits and do not consider patient-specific factors such as age.

Study Design: Monte Carlo simulation model.

Setting & Population: Patients with chronic kidney disease, referred to a multidisciplinary kidney clinic in a universal health care system.

Model, Perspective, & Timeframe: Cost-effectiveness analysis, payer perspective, lifetime horizon.

Intervention: The following vascular access referral policies are considered: central venous catheter (CVC) only, arteriovenous fistula (AVF) or graft (AVG) referral upon HD initiation, AVF (or AVG) referral when HD is forecast to begin within 12 (or 3 for AVG) months, AVF (or AVG) referral when estimated glomerular filtration rate is <15 (or <10 for AVG) mL/min/1.73 m^2.

Outcomes: Incremental cost-effectiveness ratios (ICERs, in 2014 US dollars per quality-adjusted life-year [QALY] gained).

Results: The ICER of AVF (AVG) referral within 12 (3) months of forecasted HD initiation, compared to using only a CVC, is ~$105k/QALY ($101k/QALY) at a population level (HD costs included). Pre-HD AVF or AVG referral dominates delaying referral until HD initiation. The ICER of pre-HD referral increases with patient age. Results are most sensitive to erythropoietin costs, ongoing HD costs, and patients' utilities for HD. When ongoing HD costs are excluded from the analysis, pre-HD AVF dominates both pre-HD AVG and CVC-only policies.

Limitations: Literature-based estimates for HD, AVF, and AVG utilities are limited.

Conclusions: The cost-effectiveness of vascular access referral is largely driven by the annual costs of HD, erythropoietin costs, and access-specific utilities. Further research is needed in the field of dialysis-related quality of life to inform decision making regarding vascular access referral.

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INDEX WORDS: Vascular access; arteriovenous fistula (AVF); arteriovenous graft (AVG); central venous catheter (CVC); hemodialysis; vascular access referral; chronic kidney disease (CKD); predialysis care; cost-effectiveness; health care costs; end-stage renal disease (ESRD).

An arteriovenous fistula (AVF) is often considered the gold standard of vascular access for hemodialysis (HD).[1] HD through an AVF is associated with lower mortality and morbidity and higher quality of life compared to that through an arteriovenous graft (AVG) or central venous catheter (CVC).[2-6]

Although an AVF may be a superior access for HD delivery, there has been increasing debate regarding whether or when patients with chronic kidney disease (CKD) should be referred for an AVF.[7-9] The debate arises because AVFs are not immediately ready for use, a high percentage of AVFs fail to mature successfully, an AVF creation is a more invasive surgical procedure compared to a CVC insertion, and patients may die before ever needing HD.[9-11] These last issues are of particular concern for elderly patients.[12-14] An AVG can be placed closer to the time of HD initiation; however, long-term failure and intervention rates are higher compared with those of an established AVF.[15] It has been suggested that patient-specific factors such as expected remaining lifetime and quality of life should be considered when making vascular access referral decisions.[14,16-18] From a system perspective, it is also important to consider the costs of various referral policies so that governmental health care budgets can be managed effectively.

Current vascular access referral guidelines[19-21] for patients with CKD not yet receiving dialysis (non−dialysis-dependent CKD) have not been evaluated using cost-effectiveness analysis. We developed

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a data-driven simulation model of the vascular access decision process, which is ideally suited for capturing the complexities and uncertain nature of CKD progression, effects of receiving HD, and ultimately the costs and benefits arising from different referral policies. In addition, we evaluated the cost-effectiveness of referral policies for different age groups, given the uncertainties regarding vascular access referral in elderly people in particular.

METHODS

Study Design

We developed a Monte Carlo simulation model using the computer programming language C++. We used the cost and utility information from Xue et al,[22] combined with our previously published decision analytic model comparing total lifetimes for different AVF referral policies in non−dialysis-dependent CKD,[23] to estimate the average cost and quality-adjusted life expectancy of various AVF and AVG referral policies for patients being followed up in a CKD clinic before HD initiation.

Our cost-effectiveness analysis covers the time from the first visit of a patient with CKD to a multidisciplinary kidney clinic until death, in monthly time steps. Each referral policy is replicated 10,000 times. Total costs and quality-adjusted lifetime directly attributable to the patient over his or her lifetime are discounted at an annual rate of 3%.[24] We do not consider societal costs and consequences, such as those attributable to caregiver or family support. All costs are paid by the Canadian health care system and given in 2014 US dollars. When possible, we follow the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines for conducting a cost-effectiveness analysis.[25] This study was approved by our institution's ethical review board (UBC REB H11-03068), and the need for informed consent was waived.

CKD Progression

Data-driven regression models of estimated glomerular filtration rate (eGFR) progression are used to simulate periodic measurements of a patient's eGFR before initiating HD. The simulated progressions reflect a variety of trajectories from patients enrolled in a multidisciplinary CKD clinic at Vancouver General Hospital, Vancouver, Canada. Cohort demographics are as follows: 63% men, 40% white, 46% Asian, mean age of 66.9 years, 41% with diabetes mellitus, and mean initial eGFR of 30.8 mL/min/1.73 m^2.[23]

Survival curves are used to simulate patient lifetimes pre-HD according to age and sex. If a patient survives until HD initiation, a vascular access–based on-HD survival time is generated.[23] We assume that HD initiation is when a patient's eGFR decreases to ≤7 mL/min/1.73 m^2.[26]

Vascular Access Referral Policies

The simulated eGFRs combined with the vascular access referral policy being evaluated determine whether or when a patient is referred for AVF or AVG creation. We compare 2 types of referral policies discussed in recent clinical practice guidelines[19-21]: a "time window" policy and an "eGFR threshold" policy.

A time window policy is when AVF (or AVG) referral occurs when HD is anticipated to be initiated within a 12-month (or 3-month for AVG) time window (we label these as AVFTW12 and AVGTW3, respectively).[19] We estimate the time until HD is needed based on when a patient's eGFR is forecast to decrease to 7 mL/min/1.73 m^2. Due to forecast errors, it is possible that a patient may initiate HD (with a CVC) before being referred for an AVF or AVG. If this happens, we assume the patient is referred for an AVF (or AVG) when HD is initiated.

An eGFR threshold policy is when AVF (or AVG) referral occurs when a patient's eGFR decreases below a threshold of 15 (or 10 for AVG) mL/min/1.73 m^2 (AVFTH15 and AVGTH10, respectively).[21]

The shorter time window and lower eGFR threshold for the AVG referral policies were chosen to reflect the short time from creation to use for an AVG compared to for an AVF.

We also consider 2 other types of referral policies. The first refers patients for an AVF (or AVG) only if and when HD is initiated (with a CVC). In other words, there is no pre-HD referral. This includes a policy that begins with referral for an AVF at HD initiation and then refers patients for an AVG after 3 failed AVFs. The other policy, ONLYCVC, never refers a patient for an AVF or AVG and assumes that a CVC is used exclusively. We let this be the baseline policy for calculating incremental cost-effectiveness ratios (ICERs) because it yields the lowest costs and quality-adjusted life-years (QALYs) of any of the referral policies.

Vascular Access Outcomes

If a patient is referred for an AVF, we simulate the time it takes to see a vascular surgeon, the time it takes for the AVF to mature, whether the AVF is functional, and the useful lifetime of the AVF (Table 1). We assume that 15% of AVFs fail within 6 weeks of surgery,[27] then 53% subsequently fail to mature if the patient has a history of CVC use, whereas 29% fail if the patient has never used a CVC[10] (this gives an overall AVF maturation failure rate of 60% with history of CVC and 40% without history of CVC). Based on data from AVF creations from 2009 to 2012 at Vancouver General Hospital, we estimate 0.6 percutaneous intervention per AVF that eventually matures and 1.1 percutaneous intervention per AVF that fails to mature.

The probability that a functional AVF used for HD becomes dysfunctional and requires an intervention decreases with the time since the AVF was established.[15] We assume that 10% of these cannot be salvaged and therefore fail; AVFs that are eligible will have a percutaneous intervention that has a 0.11 probability of failing.[22] We assume that failure of an AVF results in referral for another AVF creation (up to a maximum of 3 AVF attempts, with no more than 2 occurring in the pre-HD period). We assume that a mature AVF that is ready for use before HD initiation has a yearly failure probability that is half the failure probability of an on-HD functional AVF failing.[23] See Fig S1, provided as online supplementary material, for further details.

The model of AVG dynamics and outcomes follows the same process as for an AVF, but with different parameters for mortality, probability of infection and percutaneous intervention, costs, and utilities (Tables 1-3). In addition, we assume that on average, an AVG can be used in 3.5 weeks, and an AVF, in 3 months.

A CVC is placed when a patient initiates HD without a functional permanent access or when an access fails after a patient has initiated HD. Replacement of CVCs is required at a rate that decreases with the time since the CVC was established.[15]

We model vascular access–related infections based on vascular access type and the time since the vascular access was established.[15] Infections lead to treatment (either outpatient or in hospital), possible removal of the current vascular access and creation of a new one, or death.

Patient Outcomes

We simulate patient survival based on age, sex, HD status, and vascular access (if the patient is receiving HD).[23] We model an increased risk for death during infection using hazard ratios associated with infected HD patients[23] (Table 1; Fig S2).

Table 1. Event Probabilities

Description	Baseline Value
Monthly probability of infection with AVF	See Table S1
Monthly probability of infection with AVG	See Table S1
Monthly probability of infection with CVC	See Table S1
Probability of hospitalization given an infection	0.6 (from[22])
HR of death from hospitalized infection	2.52 (from[40])
HR of death from outpatient infection	1.51 (from[40])
Probability of AVF failing to mature, without history of CVC use	0.4 (from[23])
Probability of AVF failing to mature, with history of CVC use	0.6 (from[23])
Percutaneous interventions per successful AVF maturation	0.6 (VGH data[a])
Percutaneous interventions per unsuccessful AVF maturation	1.1 (VGH data[a])
Probability of AVF surgery failure	0.15 (from[27])
Probability of AVG surgery failure	0.06 (NZ[b])
Probability of a functional AVF needing a percutaneous intervention if used for HD	See Table S1
Probability of a functional AVF failure if not used for HD	See Table S1
Probability of a functional AVG needing a percutaneous intervention if used for HD	See Table S1
Probability of a functional AVG failure if not used for HD	See Table S1
Probability that a patient is ineligible for a percutaneous intervention	0.10 (NZ[b])
Probability of percutaneous intervention failure for AVF	0.11 (from[22])
Probability of percutaneous intervention failure for AVG	0.068 (from[22])
Probability of a CVC failing	See Table S1
Relative risk for mortality on CVC vs AVF	1.53 (from[23])
Relative risk for mortality on CVC vs AVG	1.18 (from[23])
Maximum AVF or AVG placement attempts pre-HD	2 (NZ[b])
Maximum AVF or AVG placement attempts	3 (NZ[b])

Note: Shown are the transition probabilities used in baseline run.

Abbreviations: AVF, arteriovenous fistula; AVG, arteriovenous graft; CVC, cerebrovascular catheter; HD, hemodialysis; HR, hazard ratio.

[a]Vancouver General Hospital.

[b]Author's expert opinion.

We obtain patient quality-adjusted lifetimes using the access-based utility weights of Table 2. Based on survey instruments used in[4] and[5], we weight survival on HD via CVC by a utility of 0.54 and increase this weight for patients living on HD via AVF (or AVG) to 0.61 (or 0.57 for AVG; for details, see Item S1). We also assumed a small quality-of-life reduction for patients with CKD who live with an AVF or AVG pre-HD; we multiply the pre-HD AVF or AVG duration by −0.01.

Costs

Key costs are outlined in Table 3. There has been debate as to whether to include ongoing dialysis costs in a cost-effectiveness analysis comparing treatments that affect survival on dialysis without affecting the need for dialysis.[28] The cost-effectiveness analysis literature suggests including all future costs because this represents the true impact to society.[29] We present results with and without yearly HD delivery costs included.

Table 2. Utilities

Description	Baseline Value
CVC on-HD utility	0.54 (from[4])
AVF on-HD utility	0.61 (from[4,5,41])
AVG on-HD utility	0.57 (from[4,5,41])
AVF pre-HD disutility	−0.01 (NZ[a])
AVG pre-HD disutility	−0.01 (NZ[a])

Note: Shown are utilities used in baseline run. All utilities shown are multiplied by the time spent in each of the states for the quality-adjusted lifetime calculation.

Abbreviations: AVF, arteriovenous fistula; AVG, arteriovenous graft; CVC, cerebrovascular catheter; HD, hemodialysis.

[a]Author's expert opinion.

Sensitivity Analysis

In 1-way sensitivity analysis, we varied each of the parameters in Tables 1 to 3 by ±25% of the baseline value. For several parameters and dynamics of interest, we performed extra sensitivity analysis beyond the bounds of the ±25% range (pre-HD disutility, number of percutaneous interventions required for maturing AVFs, cost of percutaneous intervention, survival benefit of AVF vs CVC, and utility of HD by AVF vs CVC). In addition, in the base case, we assume that interventions to achieve AVF or AVG functional patency are always percutaneous. In reality, surgical revisions (which are more expensive) are sometimes required. To account for this, we varied the cost of percutaneous intervention in the sensitivity analysis up to the point at which the cost is equivalent to a surgical intervention.

In a probabilistic sensitivity analysis, we compared AVFTW12 to ONLYCVC by sampling each parameter from a uniform distribution between ±25% of baseline values. To facilitate probabilistic sensitivity analysis comparison across referral policies, we use the net monetary benefit (NMB) approach, in which we consider different maximum willingness-to-pay levels, λ, for a gain of 1 QALY.[30,31] We evaluate λ values from $0 to $200k. We sampled 1,000 versions of Tables 1 to 3, and for each, we calculated the average NMB (based on 1,000 replications) of each policy as $NMB_\pi = \lambda Q_\pi - C_\pi$, where π represents the policy evaluated (AVFTW12 or ONLYCVC), Q_π is the average net present QALYs of policy π, and C_π is the average net present cost of policy π. We recorded the proportion of times each policy yields the greatest average NMB across the 1,000 sets of sampled parameters (similar to[32]).

Table 3. Costs

Description	Baseline Value
Annual HD	$90,186 (from[42])
AVF creation	$888 (from[22])
CVC creation	$319 (from[22])
CVC removal	$154 (from[22])
AVG creation	$643 (from[22])
AVF erythropoietin per mo	$680 (from[22])
CVC erythropoietin per mo	$831 (from[22])
AVG erythropoietin per mo	$725 (from[22])
Outpatient infection treatment	$177 (from[22])
Hospitalized infection treatment	$23,138 (from[22])
Percutaneous intervention	$508 (from[22])

Note: The table shows costs used in baseline run.

Abbreviations: AVF, arteriovenous fistula; AVG, arteriovenous graft; CVC, cerebrovascular catheter; HD, hemodialysis.

RESULTS

Base Case

Table 4 compares AVF referral policies (AVFTW12 [AVF referral with anticipated HD initiation within a 12-month time window] and AVFTH15 [AVG referral with anticipated HD initiation within a 3-month time window], respectively) to ONLYCVC (no referral for access creation; exclusive use of a CVC) for the population as a whole and by age categories (50-59, 60-69, 70-79, and 80-89 years). Both population-level ICERs are similar, at ∼$105k/QALY. Table 4 also compares AVG referral policies to the exclusive CVC approach. These ICERs are slightly lower, at ∼$100k/QALY. The ICERs of pre-HD AVF and AVG referral policies generally increase with age cohort. Policies of delaying AVF or AVG referral until HD initiation were dominated by pre-HD referral policies.

Table 4 shows results for the same referral policies, but with HD costs excluded. Here, pre-HD AVF (or AVG) referral policies dominate an exclusive CVC policy, except for the oldest cohort aged 80 to 89 years, because the cost of ongoing HD no longer penalizes the survival benefit of AVF or AVG over CVC. Even for the oldest cohort, pre-HD referral is cost-effective, ranging from $3k to $8k/QALY. Moreover, the AVF referral policies dominate the AVG policies for every age group except 80 to 89 years (for which AVF is still cost-effective compared to AVG). This is attributable to the better survival, lower infection rate, and lower monthly erythropoietin cost of AVF compared to AVG.

Sensitivity Analysis

One-Way Sensitivity Analysis

Figure 1 shows a tornado diagram of 1-way sensitivity analyses for both AVFTW12 and AVGTW3 versus ONLYCVC (HD costs included). The ICERs are most sensitive to monthly erythropoietin costs, ongoing HD costs, and patient utilities. Importantly, patients' utilities for AVF versus AVG can make the difference between AVF versus AVG appearing more cost-effective.

Because AVFs are more commonly used as permanent vascular access than AVGs, we focused on AVF policies for the extended sensitivity analyses and probabilistic sensitivity analysis. Varying the pre-HD disutility and number of percutaneous interventions for maturing AVFs by ±100% and increasing percutaneous intervention costs by 75% (to test the extreme case in which all AVF interventions are surgical) did not alter the baseline ICER of AVFTW12 versus ONLYCVC by >3%. When we reduced the survival benefit of AVF over CVC by half, the ICER decreased to $97k/QALY. The direction of change is a reduction in the ICER, rather than an increase, because lower survival means lower total HD costs. Eliminating the survival benefit of AVF over CVC makes AVFTW12 dominate ONLYCVC (due to fewer infection treatments with AVF and lower erythropoietin costs combined with a higher utility of HD via AVF vs CVC). When we also eliminate the utility benefit of AVF, the AVFTW12 policy becomes less costly but also provides fewer QALYs than ONLYCVC (ICER of ∼$260k/QALY). Eliminating the utility benefit while keeping the baseline survival benefit of AVF versus CVC increased the ICER to $168k/QALY.

We also performed 1-way sensitivity analysis of advanced referral policy with HD costs excluded. In every case, AVFTW12 still dominated ONLYCVC. AVGTW3 dominated ONLYCVC in every case except when we varied erythropoietin costs. When the erythropoietin cost of AVG increased by 25% relative to CVC, the ICER increased to ∼$25k/QALY.

Probabilistic Sensitivity Analysis

Figure 2 shows results of the population-based analysis of AVFTW12 versus ONLYCVC policies (HD costs included). ONLYCVC has a higher probability of yielding the greatest NMB for willingness-to-pay levels $\lambda <$ $105k/QALY, whereas AVFTW12 has the greater probability of being the most cost-effective policy for larger λ. Also, as expected, the range of λ for which the exclusive CVC policy appears best increases for older patients, although moderately. For 50- to 60-year-old patients, ONLYCVC appears best for λ up to $105k/QALY, and for 80- to 90-year-old patients, ONLYCVC appears best for λ up to $135k/QALY (with AVFTW12 having a greater probability of being the most cost-effective policy for larger λ values in each case).

DISCUSSION

We performed a cost-effectiveness analysis comparing various vascular access referral policies for individuals with non−dialysis-dependent CKD followed up in a multidisciplinary kidney clinic. Overall, the ICER of the AVFTW12 policy compared to the ONLYCVC policy yields approximately 90 extra quality-adjusted life-days at a cost of $26,600 per patient, for an overall ICER of ∼$105k/QALY at a population level. The cost-effectiveness of this policy decreased with advancing age, to $132k/QALY for 80 to 90 year olds. Results were very similar for the eGFR threshold policy of AVFTH15. For the AVG policies, AVGTH10 was the most cost-effective, with an overall ICER of $98k/QALY at a population level.

Reassuringly, our probabilistic sensitivity analysis suggests that the ICERs of our baseline analysis are

Table 4. Cost and QALE for AVF and AVG Referral Policies, With and Without HD Costs

	All				Age 50-59 y				Age 60-69 y				Age 70-79 y				Age 80-89 y			
	Policy	Cost	QALE	ICER	Policy	Cost	QALE	ICER	Policy	Cost	QALE	ICER	Policy	Cost	QALE	ICER	Policy	Cost	QALE	ICER
HD Cost Included																				
Time window AVF	ONLYCVC	186,697	1,415	—	ONLYCVC	289,653	1,807	—	ONLYCVC	181,905	1,634	—	ONLYCVC	104,495	1,070	—	ONLYCVC	42,415	729	—
	AVFTW12	213,357	1,508	105,053	AVFTW12	332,541	1,955	105,641	AVFTW12	209,019	1,728	105,087	AVFTW12	123,619	1,131	113,787	AVFTW12	53,964	761	132,328
eGFR threshold AVF	ONLYCVC	186,697	1,415	—	ONLYCVC	289,653	1,807	—	ONLYCVC	181,905	1,634	—	ONLYCVC	104,495	1,070	—	ONLYCVC	42,415	72	—
	AVFTH15	213,305	1,507	105,764	AVFTH15	332,931	1,956	106,206	AVFTH15	208,999	1,727	105,584	AVFTH15	123,594	1,132	112,559	AVFTH15	53,749	760	133,264
Time window AVG	ONLYCVC	186,697	1,415	—	ONLYCVC	289,653	1,807	—	ONLYCVC	181,905	1,634	—	ONLYCVC	104,495	1,070	—	ONLYCVC	42,415	729	—
	AVGTW3	197,077	1,453	100,812	AVGTW3	304,481	1,863	95,987	AVGTW3	192,465	1,674	96,699	AVGTW3	113,191	1,098	113,694	AVGTW3	48,546	745	136,705
eGFR threshold AVG	ONLYCVC	186,697	1,415	—	ONLYCVC	289,653	1,807	—	ONLYCVC	181,905	1,634	—	ONLYCVC	104,495	1,070	—	ONLYCVC	42,415	729	—
	AVGTH10	196,837	1,453	98,103	AVGTH10	305,428	1,867	96,220	AVGTH10	191,821	1,672	94,164	AVGTH10	112,799	1,097	111,109	AVGTH10	48,438	746	129,894
HD Cost Excluded																				
Time window AVF	AVFTW12	25,799	1,508	—	AVFTW12	39,787	1,955	—	AVFTW12	25,144.9	1,728	—	AVFTW12	15,394	1,131	—	ONLYCVC	6,996	729	—
	ONLYCVC	27,340	1,415	Dom	ONLYCVC	42,106	1,807	Dom	ONLYCVC	26,719	1,634	Dom	ONLYCVC	15,856	1,070	Dom	AVFTW12	7,527	761	6,078
eGFR threshold AVF	AVFTH15	25,786	1,507	—	AVFTH15	39,518	1,956	—	AVFTH15	25,018	1,727	—	AVFTH15	15,436	1,132	—	ONLYCVC	6,996	729	—
	ONLYCVC	27,340	1,415	Dom	ONLYCVC	42,106	1,807	Dom	ONLYCVC	26,719	1,634	Dom	ONLYCVC	15,856	1,070	Dom	AVFTH15	7,599	760	7,082
Time window AVG	AVGTW3	26,858	1,453	—	AVGTW3	41,107	1,863	—	AVGTW3	26,153	1,674	—	AVGTW3	15,840	1,098	—	ONLYCVC	6,996	729	—
	ONLYCVC	27,340	1,415	Dom	ONLYCVC	42,106	1,807	Dom	ONLYCVC	26,719	1,634	Dom	ONLYCVC	15,856	1,070	Dom	AVGTW3	7,359	745	8,076
eGFR threshold AVG	AVGTH10	26,393	1,453	—	AVGTH10	40,476	1,867	—	AVGTH10	25,540	1,672	—	AVGTH10	15,405	1,097	—	AVGTH10	6,996	729	—
	ONLYCVC	27,340	1,415	Dom	ONLYCVC	42,106	1,807	Dom	ONLYCVC	26,719	1,634	Dom	ONLYCVC	15,856	1,070	Dom	ONLYCVC	7,175	746	3,858

Note: The table shows average total cost and QALE (measured in days) for various referral policies, both for entire population and by age category. ICERs are given in dollars per quality-adjusted life-year. We performed 10,000 replications of each policy to attain 95% confidence interval half-widths on cost and QALEs that were <0.06% of average in each case.

Abbreviations and definitions: AVF, arteriovenous fistula; AVFTH15, policy that AVF referral occurs when a patient's eGFR decreases below a threshold of 15 mL/min/1.73 m^2; AVFTW12, policy that AVF referral occurs when HD is anticipated to be initiated within a 12-mo time window; AVGTH10, policy that AVG referral occurs when a patient's eGFR decreases below a threshold of 10 mL/min/1.73 m^2; AVGTW3, policy that AVG referral occurs when HD is anticipated to be initiated within a 3-month time window; AVG, arteriovenous graft; CVC, central vascular catheter; Dom, dominant; eGFR, estimated glomerular filtration rate; HD, hemodialysis; ICER, incremental cost-effectiveness ratio; ONLYCVC, policy when a patient is never referred for AVF or AVG and assumes a CVC is used exclusively; QALE, quality-adjusted life expectancy.

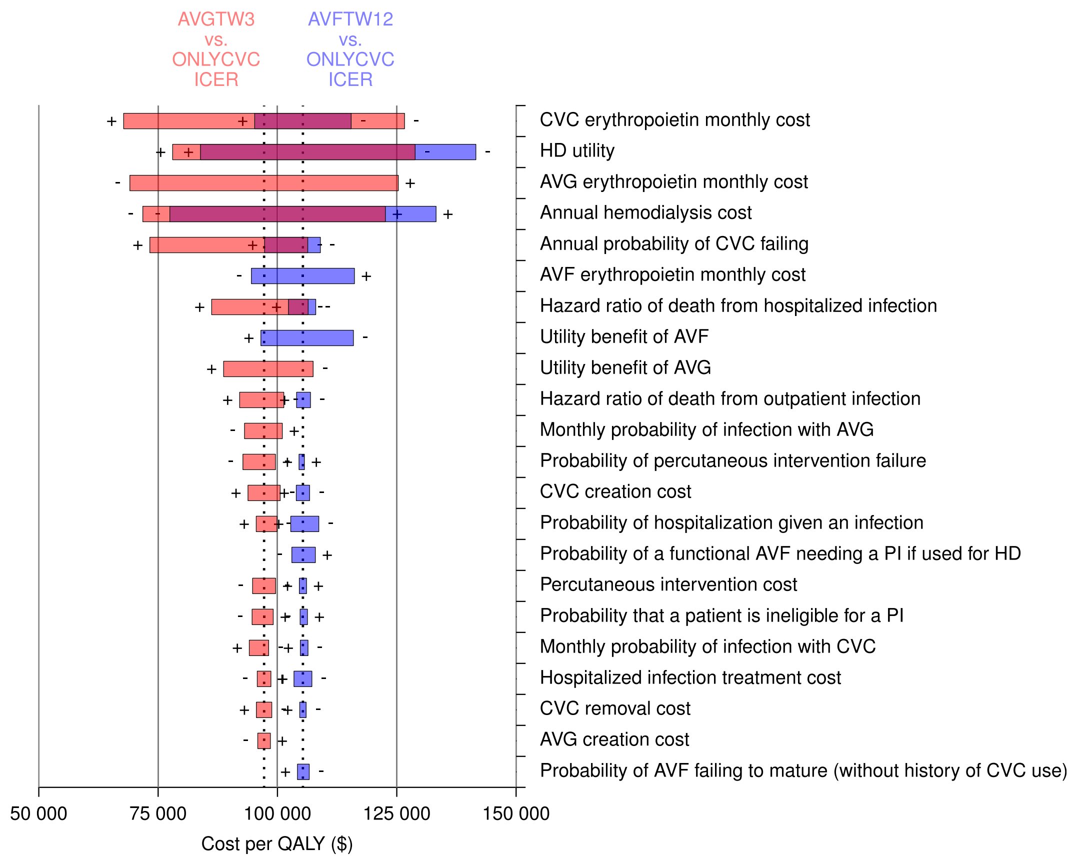

Figure 1. Tornado diagram for 1-way sensitivity analysis. Each parameter in Tables 1 to 3 was varied by ±25% and the resulting AVFTW12 and AVGTW3 versus ONLYCVC ICER is shown compared with the respective baseline ICERs (1,000 replications each). The vertical dotted line to the left shows the baseline ICER of AVGTW3 vs ONLYCVC, and the vertical dotted line to the right shows the baseline ICER of AVFTW12 vs ONLYCVC. The "+" ("-") on one side of a bar indicates the ICER corresponding to increasing (decreasing) that parameter by 25%. Instead of varying the AVF, AVG, and CVC on-HD utilities individually, we varied them by ±25% together ("HD utility" row) and by their ratios (the 13% "Utility benefit of AVF" over CVC and the 6% "Utility benefit of AVG" over CVC). Abbreviations and definitions: AVF, arteriovenous fistula; AVFTW12, policy that AVF referral occurs when HD is anticipated to be initiated within a 12-mo time window; AVGTW3, policy that AVG referral occurs when HD is anticipated to be initiated within a 3-month time window; AVG, arteriovenous graft; CVC, central vascular catheter; eGFR, estimated glomerular filtration rate; HD, hemodialysis; ICER, incremental cost-effectiveness ratio; ONLYCVC, policy that a patient is never referred for AVF or AVG and assumes a CVC is used exclusively; PI, percutaneous intervention.

robust. If the health system's willingness-to-pay for an extra QALY is <\$105k/QALY, the exclusive CVC policy is probabilistically better (and becomes even better as willingness-to-pay decreases to <\$105k/QALY), and if willingness-to-pay is >\$105k/QALY, AVF creation pre-HD becomes more favorable (and becomes even better as willingness-to-pay increases further). Hence, referral for AVF creation before HD initiation appears to be a reasonable strategy for many patients depending on the willingness-to-pay threshold, especially in younger age groups. However, because the survival advantage of AVF creation pre-HD (compared to dialysis with a CVC long term) decreases and the ICER of AVF referral increases with advancing age, a blanket AVFTW12 policy for all patients with progressive CKD is probably not appropriate. Different referral timing windows may be considered for different age groups, such as later referral (or perhaps in some cases, no referral) for the very elderly who are at higher risk for death before HD initiation and have limited survival on dialysis.

A key driver of ICERs was the provision of costly HD treatment. Results are in keeping with a recent cost-effectiveness analysis, which found that the ICER of dialysis compared to no dialysis was ∼\$110k/QALY.[33] The challenge of cost-effectiveness analyses in the HD population has been discussed recently by Grima et al,[28] who point out that inclusion of dialysis costs in cost-effectiveness analyses of interventions that extend the lives of HD patients but do not change the need for dialysis makes it nearly impossible to obtain a favorable cost-effectiveness ratio. When we removed ongoing HD costs from the analysis, the pre-HD AVF and AVG referral policies either dominated or were

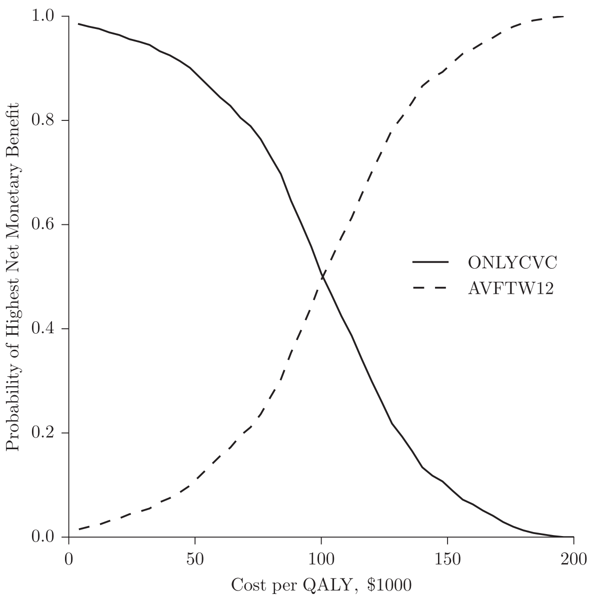

Figure 2. Probabilistic sensitivity analysis. Each parameter in Tables 1 to 3 was randomly sampled 1,000 times, uniformly over a range of ±25% of its baseline value. The ONLYCVC and AVFTW12 policies were then evaluated for each set of samples 1,000 times, and the average net monetary benefit of each policy was calculated. The estimated probability (based on the 1,000 random samples) that a policy has a higher net monetary benefit is plotted. Abbreviations and definitions: AVF, arteriovenous fistula; AVFTW12, policy that AVF referral occurs when HD is anticipated to be initiated within a 12-mo time window; AVGTW3, policy that AVG referral occurs when HD is anticipated to be initiated within a 3-month time window; CVC, central vascular catheter; HD, hemodialysis; ONLYCVC, policy that a patient is never referred for AVF or AVG and assumes a CVC is used exclusively; QALY, quality-adjusted life-year.

extremely cost-effective (in the case of the oldest age group, 80-89 years) compared to an exclusive CVC policy. Costs of HD are also relevant in the comparison of AVF and AVG policies, the latter of which appear to be more cost-effective until HD costs are removed, emphasizing that living longer on HD results in AVF policies appearing less cost-effective.

We considered a delayed referral policy, which refers patients for vascular access when, and only when, they initiate HD. This was ruled out of consideration due to dominance of pre-HD referral policies in comparison. In other words, the model favors AVF (or AVG) referral earlier because it maximizes the chance of attaining the survival benefit associated with AVF (or AVG) over CVC when HD is initiated. Our analyses indicate that it would take a disutility for living with an AVF pre-HD of ≥0.04 before a referral policy of waiting until HD initiation to compete with the other policies considered. That is to say, if a person would rather live 96 (or fewer) days without an AVF than 100 days with an AVF in place pre-HD, the policy of first referring patients for AVF (or AVG) only if and when HD is initiated may be viable. This degree of disutility (or higher) is plausible, especially in older age groups. Unfortunately, no estimates were available in the literature to inform this important aspect of the analysis.

Our 1-way sensitivity analysis indicates that our results are most sensitive to HD costs, erythropoietin costs, and patient utilities for being on HD with an AVF versus AVG versus CVC. Although the cost estimates appear to be robust in the literature, data for utility parameters are limited. This effect is most dramatic for the HD utilities, for which varying the estimates by 25% from the baseline value resulted in a wide range of cost per QALY ($84k-$142k) when comparing AVFTW12 to ONLYCVC. The impact of HD and vascular access−specific utilities on the results highlights the urgent need for patient-centered research on the impact of vascular access and HD on quality of life to inform decision making in this important area of end-stage renal disease care. Considering this limitation and the need for further study, our results should not be taken as evidence against referral for permanent vascular access creation after HD initiation. In addition, our model was designed to assess decision making in non−dialysis-dependent CKD. It does not apply to the significant but heterogeneous group of patients who initiate HD via a CVC with little or no predialysis care.

Other publications have described cost-effectiveness analysis models of vascular access[22,34,35]; however, these studies have focused on comparing vascular access options for patients who have initiated HD with a CVC. One of these studies found that AVF referral at HD initiation was cost-effective when compared to referral for an AVG.[22] A unique feature of our model is that it considers patients with stages 4 and 5 non−dialysis-dependent CKD, whose nephrologists are considering whether to refer them for AVF or AVG creation. It mimics the dynamic forecasting faced by nephrologists following up individuals with CKD and implicitly factors in forecast errors in estimating the need for dialysis initiation.

The strengths of our study include use of a detailed dynamic simulation model, driven by literature-based estimates of probabilities, utilities, and costs. We also performed extensive sensitivity analyses and took the effect of age into account in our results. Given the debate about what ICERs should be considered "cost-effective,"[36,37] our probabilistic sensitivity analyses over a wide range of willingness-to-pay values allows policy makers to consider various perspectives.

Our study also has several limitations. First, by taking a payer rather than a societal perspective, we did not account for patient or family lost wages, which are likely greater for AVF/AVG surgery than CVC placement, at least initially. Including these initial extra costs would make AVF referral less cost-effective. Second, our estimates for vascular access−based survival come from publications based on observational data, which are likely confounded.[38,39] We do not consider the possibility that individuals dialyzing with a CVC could be heterogeneous with respect to their mortality risk, and we assume that individual patient survival probability changes as the vascular access type changes, which may be untrue. However, to investigate the effect of this on our results, we performed a sensitivity analysis that eliminated the survival benefit of AVF versus CVC. We found that predialysis AVF creation still appears to be advantageous because initiating HD with an AVF leads to fewer infections and less erythropoietin use and therefore lower overall costs compared to using a CVC. Even if we also remove the HD utility benefit of AVF versus CVC, the cost reduction of AVF versus CVC is relatively large in comparison to the QALY reduction. Third, there is a dearth of data for quality of life related to vascular access and to HD treatment itself, both of which have a major impact on results. However, we tested the effect of these variables in our sensitivity analysis. Fourth, our study takes place in a universal health care system; the results may not be valid in other models of health care delivery. We attempted to create a realistic simulation model, for example, by including multiple vascular access creation attempts and interventions to achieve and restore patency, and by varying survival during infection episodes. However, we acknowledge that our model is likely an oversimplification of a complex process. Ultimately, randomized controlled trials are needed for definitive answers in this field. Nonetheless, we believe that our results serve to highlight important questions in vascular access care.

In conclusion, the cost-effectiveness of vascular access referral is largely driven by access-based utilities and annual HD and erythropoietin costs and varies with age. Our results suggest that further research is needed in the field of vascular access and in HD-related quality of life to inform decision making regarding referral for vascular access creation.

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SUPPLEMENTARY MATERIAL

Table S1: Infection and failure probabilities.
Figure S1: Model of AVF outcomes.
Figure S2: Model of patient survival and infections.
Item S1: Supplementary methods.
Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2017.04.020) is available at www.ajkd.org

REFERENCES

1. Hemodialysis Adequacy 2006 Work Group. Clinical practice guidelines for vascular access. *Am J Kidney Dis*. 2006;48(suppl 1):S176-S247.

2. Dhingra R, Young E, Hulbert-Shearon T, Leavey S, Port F. Type of vascular access and mortality in U.S. hemodialysis patients. *Kidney Int*. 2001;60(4):1443-1451.

3. Perl J, Wald R, McFarlane P, et al. Hemodialysis vascular access modifies the association between dialysis modality and survival. *J Am Soc Nephrol*. 2011;22(6):1113-1121.

4. Gorodetskaya I, Zenios S, McCulloch CE, et al. Health-related quality of life and estimates of utility in chronic kidney disease. *Kidney Int*. 2005;68(6):2801-2808.

5. Wasse H, Kutner N, Zhang R, Huang Y. Association of initial hemodialysis vascular access with patient-reported health status and quality of life. *Clin J Am Soc Nephrol*. 2007;2(4):708-714.

6. Lopes A, Bragg-Gresham J, Goodkin D, et al. Factors associated with health-related quality of life among hemodialysis patients in the DOPPS. *Qual Life Res*. 2007;16(4):545-557.

7. Amerling R. Con: on cardiovascular outcomes and the arteriovenous fistula: lesser of evils. *Nephrol Dial Transplant*. 2012;27(10):3756-3757.

8. Basile C, Lomonte C. Pro: the arteriovenous fistula is a blessing of god. *Nephrol Dial Transplant*. 2012;27(10):3752-3756.

9. O'Hare A, Allon M, Kaufman J. Whether and when to refer patients for predialysis AVF fistula creation: complex decision making in the face of uncertainty. *Semin Dial*. 2010;23(5):452-455.

10. Feldman H, Joffe M, Rosas S, Burns E, Knauss J, Brayman K. Predictors of successful arteriovenous fistula maturation. *Am J Kidney Dis*. 2003;42(5):1000-1012.

11. Rayner H, Pisoni R, Gillespie B, et al. Creation, cannulation and survival of arteriovenous fistulae: data from the Dialysis Outcomes and Practice Patterns Study. *Kidney Int*. 2003;63(1):323-330.

12. Tamura M, Covinsky K, Chertow G, Yaffe K, Landefeld C, McCulloch C. Functional status of elderly adults before and after initiation of dialysis. *N Engl J Med*. 2009;361(16):1539-1547.

13. Vachharajani T, Moossavi S, Jordan J, Vachharajani V, Freedman B, Burkart J. Reevaluating the fistula first initiative in octogenarians on hemodialysis. *Clin J Am Soc Nephrol*. 2011;6(7):1663-1667.

14. Tamura M, Tan J, O'Hare A. Optimizing renal replacement therapy in older adults: a framework for making individualized decisions. *Kidney Int*. 2011;82(3):261-269.

15. Ravani P, Gillespie B, Quinn R, et al. Temporal risk profile for infectious and noninfectious complications of hemodialysis access. *J Am Soc Nephrol*. 2013;24(10):1668-1677.

16. Moist L, Lok C, Vachharajani T, et al. Optimal hemodialysis vascular access in the elderly patient. *Semin Dial*. 2012;25(6):640-648.

17. Kalloo S, Blake PG, Wish J. A patient-centered approach to hemodialysis vascular access in the era of fistula first. *Semin Dial*. 2016;29(2):148-157.

18. Murea M, Satko S. Looking beyond "Fistula First" in the elderly on hemodialysis. *Semin Dial*. 2016;29(5):396-402.

19. National Kidney Foundation. K/DOQI clinical practice guidelines for vascular access: update 2000. *Am J Kidney Dis*. 2000;37(suppl 1):S137-S181.

20. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease, classification and stratification. *Am J Kidney Dis*. 2002;39(suppl 2):S1-S266.

21. Jindal K, Chan C, Dezial C, et al. Hemodialysis clinical practice guidelines for the Canadian Society of Nephrology: vascular access. *J Am Soc Nephrol*. 2006;17(3)(suppl 1): S16-S23.

22. Xue H, Lacson E Jr, Wang W, Curhan GC, Brunelli SM. Choice of vascular access among incident hemodialysis patients: a decision and cost-utility analysis. *Clin J Am Soc Nephrol*. 2010;5(12):2289-2296.

23. Shechter S, Skandari M, Zalunardo N. Timing of arteriovenous fistula creation in patients with CKD: a decision analysis. *Am J Kidney Dis*. 2014;63(1):95-103.

24. Gold MR. *Cost-effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996.

25. Husereau D, Drummond M, Petrou S, et al; ISPOR Health Economic Evaluation Publication Guidelines-CHEERS Good Reporting Practices Task Force. Consolidated health economic evaluation reporting standards (CHEERS)–explanation and elaboration: a report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. *Value Health*. 2013;16(2):231-250.

26. Cooper BA, Branley P, Bulfone L, et al; IDEAL Study. A randomized, controlled trial of early versus late initiation of dialysis. *N Engl J Med*. 2010;363(7):609-619.

27. Dember LM, Beck GJ, Allon M. Effect of clopidogrel on early failure of arteriovenous fistulas for hemodialysis. *JAMA*. 2008;299(18):2164-2171.

28. Grima DT, Bernard LM, Dunn ES, McFarlane PA, Mendelssohn DC. Cost-effectiveness analysis of therapies for chronic kidney disease patients on dialysis. *Pharmacoeconomics*. 2012;30(11):981-989.

29. Meltzer D. Accounting for future costs in medical cost-effectiveness analysis. *J Health Econ*. 1997;16(1):33-64.

30. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ*. 2001;10:779-787.

31. Stinnett A, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Med Decis Making*. 1998;18(suppl):S68-S80.

32. Briggs A, Goeree R, Blackhouse G, O'Brien B. Probabilistic analysis of cost-effectiveness models: choosing between treatment strategies for gastroesophageal reflux disease. *Med Decis Making*. 2002;22(4):290-308.

33. Lee CP, Chertow GM, Zenios SA. An empiric estimate of the value of life: updating the renal dialysis cost-effectiveness standard. *Value Health*. 2009;12(1):80-87.

34. Leermakers J, Bode A, Vaidya A, van der Sande F, Evers S, Tordoir J. Cost-effectiveness of vascular access for haemodialysis: arteriovenous fistulas versus arteriovenous grafts. *Eur J Vasc Endovasc*. 2013;45(1):84-92.

35. Drew D, Lok C, Cohen J, Wagner M, Tangri N, Weiner D. Vascular access choice in incident hemodialysis patients: a decision analysis. *J Am Soc Nephrol*. 2014;26(1):183-191.

36. Neumann P, Cohen J, Weinstein M. Updating cost-effectiveness - the curious resilience of the $50,000-per-QALY threshold. *N Engl J Med*. 2014;371(9):796-797.

37. Braithwaite R, Meltzer D, King JJ, Leslie D, Roberts M. What does the value of modern medicine say about the $50,000 per quality-adjusted life-year decision rule? *Med Care*. 2008;46(4):349-356.

38. Brown R, Patibandla B, Goldfarb-Rumyantzev A. The survival benefit of "fistula first, catheter last" in hemodialysis is primarily due to patient factors. *J Am Soc Nephrol*. 2017;28(2): 645-652.

39. Quinn R, Oliver M, Devoe D, et al. The effect of predialysis fistula attempt on risk of all-cause and access-related death. *J Am Soc Nephrol*. 2017;28(2):613-620.

40. Ishani A, Collins AJ, Herzog CA, Foley RN. Septicemia, access and cardiovascular disease in dialysis patients: the USRDS Wave 2 Study. *Kidney Int*. 2005;68(1):311-318.

41. Sengupta N, Nichol MB. Mapping the SF-12 to the HUI3 and VAS in a managed care population. *Med Care*. 2004;42(9): 927-937.

42. Lee H, Manns B, Taub K, et al. Cost analysis of ongoing care of patients with end-stage renal disease: the impact of dialysis modality and dialysis access. *Am J Kidney Dis*. 2002;40(3):611-622.