Temporal Risk Profile for Infectious and Noninfectious Complications of Hemodialysis Access

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ABSTRACT

Vascular access complications are a major cause of morbidity in patients undergoing hemodialysis, and determining how the risks of different complications vary over the life of an access may benefit the design of prevention strategies. We used data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) to assess the temporal profiles of risks for infectious and noninfectious complications of fistulas, grafts, and tunneled catheters in incident hemodialysis patients. We used longitudinal data to model time from access placement or successful treatment of a previous complication to subsequent complication and considered multiple accesses per patient and repeated access complications using baseline and time-varying covariates to obtain adjusted estimates. Of the 7769 incident patients identified, 7140 received at least one permanent access. During a median follow-up of 14 months (interquartile range, 7–22 months), 10,452 noninfectious and 1131 infectious events (including 551 hospitalizations for sepsis) occurred in 112,085 patient-months. The hazards for both complication types declined over time in all access types: They were 5–10 times greater in the first 3–6 months than in later periods after access placement or a remedial access-related procedure. The hazards declined more quickly with fistulas than with grafts and catheters ($P<0.001$; Weibull regression). These data indicate that risks for noninfectious and infectious complications of the hemodialysis access decline over time with all access types and suggest that prevention strategies should target the first 6 months after access placement or a remedial access-related procedure.

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Clinical practice guidelines recommend the arteriovenous fistula as the optimal vascular access for hemodialysis because mature fistulas have lower rates of thrombosis and infection compared with synthetic arteriovenous grafts or central venous catheters.[1–3] Given the mortality, morbidity, and costs associated with the use of grafts and catheters and low rates of fistula use in the United States in the mid-1990s,[4] national initiatives were created to increase the placement of fistulas.[5] These programs have had markedly increased fistula prevalence since their inception.[5] However, 20%–60% of patients treated with hemodialysis worldwide use grafts or catheters,[6,7] at least in part because their vessels are unsuitable for fistula creation.[8,9] Increasing fistula attempts in all patients may therefore be insufficient to improve access and patient outcomes. Considering the limited benefits of available pharmacologic interventions,[9–11] novel strategies are needed to improve access outcomes. A better

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understanding of the timing and risk of complications of each type of access would help to develop new therapies or approaches.[12,13]

There are limited data on the temporal profiles of risk for infectious and noninfectious complications in different forms of vascular access. The risk for noninfectious complications (*e.g.*, stenosis and thrombosis) declines over the life of the access in both fistulas and grafts. Data from centers where local policies favor fistula creation, early transition from catheters to arteriovenous accesses, and limited use of grafts indicate that the hazard for access failure due to noninfectious complication is initially higher with fistulas than grafts, declines more quickly with fistulas, and is lower with fistulas than grafts within 3–6 months of access creation.[14] This pattern is consistent with the known higher rates of primary failure in fistulas and inferior long-term outcomes in grafts,[15] although results from this study need to be confirmed in larger cohorts and different populations. No other risk patterns have been described, including the temporal profiles of risks for noninfectious complications with permanent catheters. Furthermore, the risk profile for infectious complications in any access type, including access infection and sepsis, remains uncharacterized. Knowledge about how these risks vary over time may be important for informing studies seeking to test the effectiveness of new interventions and for designing strategies that can improve access-related outcomes.

We sought to describe and compare the profile of the risks over time for infectious and noninfectious complications of each permanent access type (fistula, graft, and tunneled catheter), accounting for patient characteristics and considering multiple accesses per patient. To maximize the generalizability of the results, we used data from the Dialysis Outcomes and Practice Patterns Study (DOPPS), an ongoing large, international, prospective cohort study of dialysis practices and patient outcomes.

RESULTS

Participants

In DOPPS I–III, there were 27,129 prevalent patients with access data and 7140 incident patients who (*1*) were enrolled within 15 days of hemodialysis commencement, (*2*) were new to any renal replacement therapies, and (*3*) received at least one permanent access for hemodialysis (fistula, graft, or tunneled catheter, hereafter called *catheter*). We used the incident cohort for our main analyses and prevalent patients in sensitivity analyses for assessing generalizability of study findings. Baseline patient characteristics by initial access are reported in Table 1; patients who were excluded for missing data had characteristics similar to those included (Supplemental Table 1). Patients who received a fistula as first access tended to be younger, were more likely to be male, and were less likely to have diabetes or cardiovascular diseases. Typically, incident patients received their first permanent access near the time of hemodialysis initiation. The median time between hemodialysis start and permanent access placement was 1 day after start (interquartile range, 1 week before start–1 month after).

Table 1. Characteristics of the participants according to their first permanent vascular access

Characteristic	All (*n*=7140)	Fistula (*n*=3352)	Graft (*n*=1432)	Catheter (*n*=2356)	*P* Value[a]
Age (yr)	63.3±15.0	62.2±14.7	64.4±14.2	64.3±15.7	<0.001[b]
Body mass index (kg/m^2)	25.8±6.0	25.1±5.3	27.2±6.9	26.1±6.2	<0.001
Male	58.8	67.8	45.3	54.0	<0.001
Smoking (%)					
Never	40.9	42.4	40.9	38.7	<0.001
Current	17.4	18.2	15.3	17.5	
Previous	20.5	22.1	16.2	20.7	
Unknown	17.9	14.3	24.3	19.3	
Race/ethnicity (%)					
White	71.8	73.7	61.6	75.2	<0.001
Black	15.7	7.9	30.5	18.0	
Asian	8.8	15.8	4.0	1.7	
Other	3.7	2.7	3.9	5.1	
Coronary artery disease	44.0	36.2	49.6	51.7	<0.001
Congestive heart failure	37.6	28.6	44.6	46.3	<0.001
Other cardiovascular diseases	28.1	25.1	27.5	32.7	<0.001
Hypertension	83.1	83.2	84.7	81.9	0.09
Cerebrovascular disease	16.0	13.6	18.4	18.1	<0.001
Peripheral vascular disease	24.5	20.5	25.4	29.5	<0.001
Diabetes	45.3	38.2	55.8	49.0	<0.001
Cancer	12.5	11.0	12.1	14.9	<0.001

Values expressed with a plus/minus sign are the mean ± SD.
[a]*P* value based on ANOVA for continuous variables and chi-square test for categorical variables, testing for any differences among the three access types.
[b]No significant difference in age between graft and catheter users.

Most patients started chronic hemodialysis with temporary catheters, and only 35% of the patients had their permanent access placed before hemodialysis start (Supplemental Table 2). During a median follow-up of 14 months (interquartile range, 7–22 months), 2642 patients received a second access, and 1050 received three or more accesses (Figure 1). A total of 1630 patients died during the study period.

Event Rates and Hazards

Rates of noninfectious complications were higher than those of infectious complications: A total of 10,452 noninfectious events (85% due to thrombosis) and 1131 infections occurred in 112,085 patient-months at risk. Infections consisted of 580 access infections and 551 septicemia or sepsis events (hereafter both referred to as sepsis events),[16] the most common forms of infection reported in the hospitalization and outpatient event files. Noninfectious events (and, to a lesser extent, also infections) tended to recur in the same access (Figure 1). For example, 45.5% (n=1585) of the patients who had at least one noninfectious complication of their first access (n=3481) had another noninfectious complication in the same access. We found that crude rates for infections were approximately 10 times lower than rates of noninfectious complications and that both types of complication tended to occur or recur less frequently over time in all access types (Table 2). In other words, the longer an access had remained complication-free after placement or after successful treatment of a complication, the lower the risk of this access developing that complication. This pattern was similar across countries or regions and patient characteristics (no significant interactions were found). Initial rates (*e.g.*, up to 1 month) were higher with catheters (22 noninfectious events and 2.7 infections per 1000 access-days) than with grafts (13.4 noninfectious events and 1.8 infections per 1000 access-days) and fistulas (9.6 noninfectious events and 1.0 infection per 1000 access-months).

The observed rates of complications tended to decline steadily over follow-up time for all access types and both complication types (Figure 2). We modeled the hazard function for each type of complication using Weibull regression and found that the predicted adjusted hazards (at the covariate

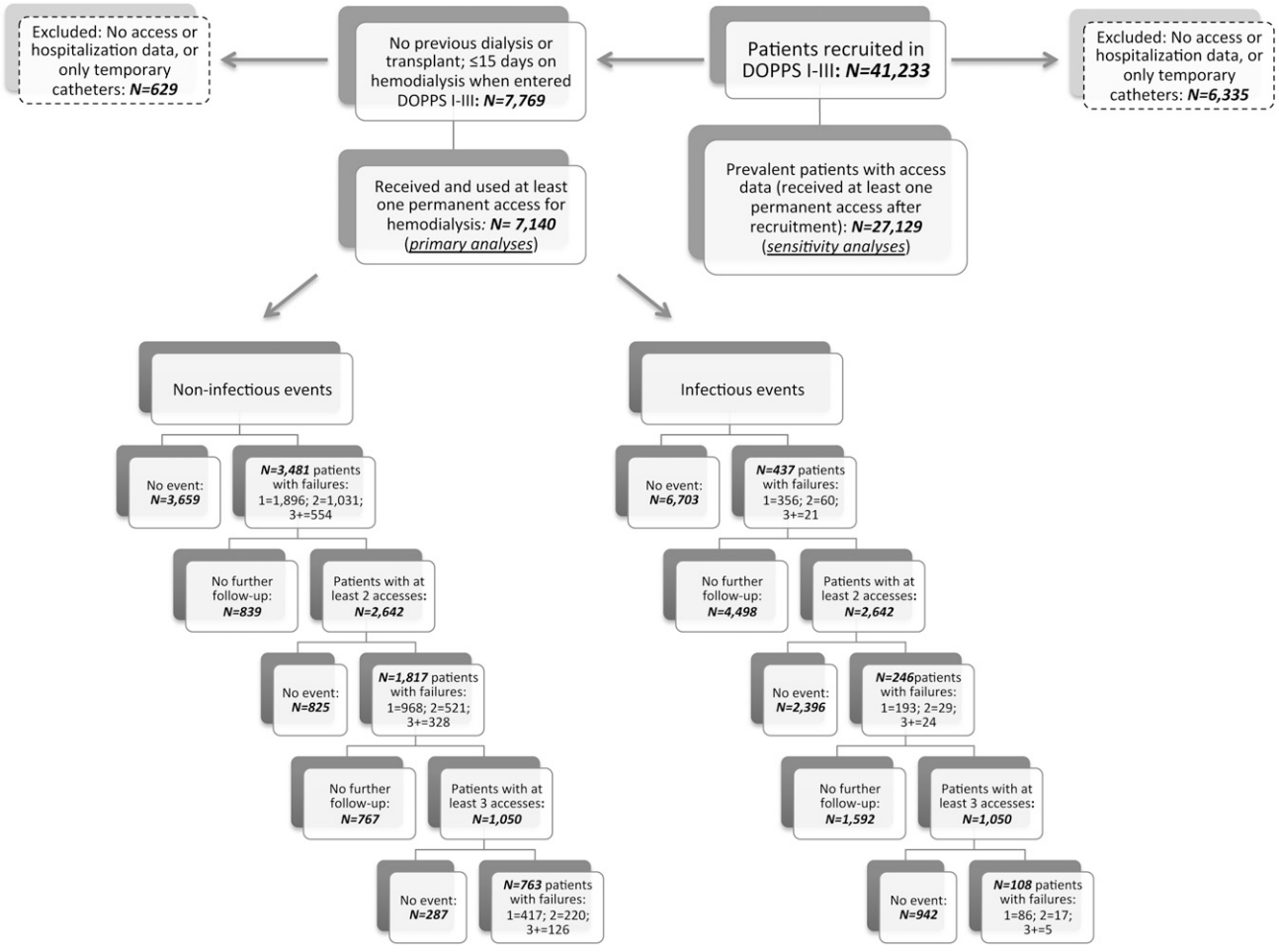

Figure 1. Derivation of the incident and prevalent cohorts, and distribution of the noninfectious and infectious events.

Table 2. Crude complication rates per 1000 access-days by vascular access type

Time (mo)	Fistula (*n*=4,733)		Graft (*n*=2,756)		Catheter (*n*=4,207)	
	Noninfectious	Infectious	Noninfectious	Infectious	Noninfectious	Infectious
0–1	9.6 (9.1 to 10.2)	1.0 (0.8 to 1.2)	13.4 (12.5 to 14.2)	1.8 (1.4 to 2.2)	21.9 (20.9 to 23)	2.7 (2.3 to 3.1)
1–3	3.0 (2.8 to 3.2)	0.3 (0.2 to 0.4)	4.9 (4.6 to 5.4)	0.6 (0.5 to 0.8)	6.1 (5.6 to 6.5)	0.8 (0.7 to 1.0)
3–6	1.7 (1.5 to 1.8)	0.2 (0.1 to 0.2)	3.0 (2.7 to 3.3)	0.3 (0.3 to 0.5)	4.7 (4.4 to 5.2)	0.6 (0.5 to 0.8)
6–12	0.9 (0.85 to 1.1)	0.07 (0.05 to 0.1)	2.1 (1.9 to 2.3)	0.3 (0.2 to 0.4)	3.1 (2.8 to 3.4)	0.4 (0.3 to 0.6)
>12	0.6 (0.5 to 0.7)	0.04 (0.02 to 0.1)	1.3 (1.1 to 1.6)	0.2 (0.1 to 0.2)	2.1 (1.7 to 2.5)	0.4 (0.3 to 0.6)

Values in parentheses are 95% confidence intervals.

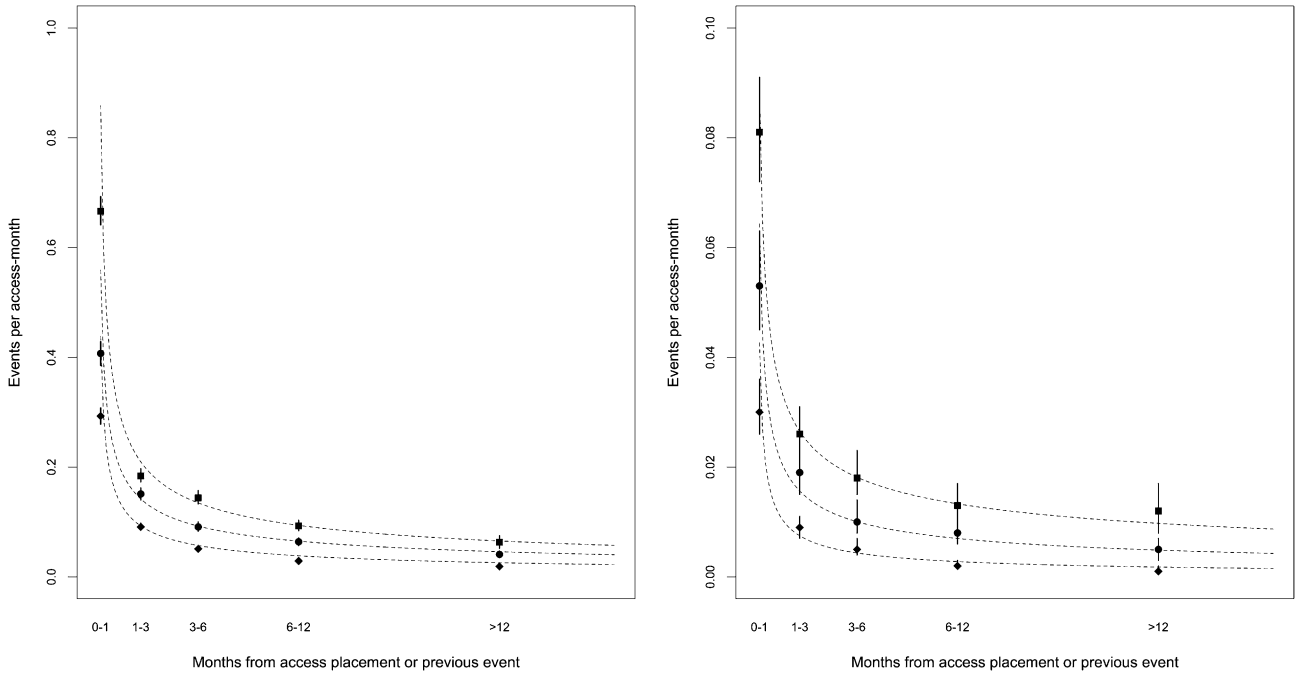

Figure 2. Crude rates and modeled hazards for noninfectious (left) and infectious events (right) in fistulas (diamond), grafts (circles), and catheters (squares). Dots with 95% confidence interval whiskers represent crude rates of complications per access-month plotted at the mid-point of the time interval. Dashed lines represent the hazard estimates from the Weibull models (models 1; Table 3). There were 1401 incident patients at risk at 24 months, 695 at 30 months, and 332 at 36 months.

means) were consistent with observed rates. Temporal risk profiles were similar in prevalent patients (Supplemental Figure 1).

Table 3 summarizes the results of Weibull regression models of noninfectious and infectious complications in incident patients (details are in Supplemental Table 3). The Weibull distribution has two parameters: the scale parameter, which captures the covariate effects in terms of hazard ratios (HRs), and the shape parameter, which estimates the rate of change of the hazard over time. For example, in the noninfectious model 1 (Table 3), the hazard for fistulas declined from 0.27 noninfectious event per month immediately after placement to 0.06 per month at 3 months (value obtained by inserting the model estimates into the Weibull hazard function [h] at time=3: $h(3)=0.27\times0.43\times3^{[0.43-1]}$). Although the hazard for both complications declined more quickly with fistulas than with grafts and catheters ($P<0.001$), the differences by access type in the shape parameter estimates were relatively small, such that the model coefficients (and goodness of fit) remained similar when one single shape parameter was assumed for all access types (models 2 and 3; Table 3). During model building we found that access-specific hazards were greater in the second and subsequent accesses than in the first access (Supplemental Figure 2). When we included in these models the current access number for the patient, we found increased risks in the second and subsequent accesses compared with the initial access for both noninfectious complications (from 35% to 58%) and infectious complications (from 51% to 85%; Supplemental Table 4). The scale and shape parameters for vascular access type in models 1–3 were similar to those of the final models reported in Table 3.

Within the first 2–3 years from access placement or from a remedial access complication, the hazards of noninfectious and infectious events quickly declined over time. In models

Table 3. Models for time to vascular access complications using Weibull regression

Variable	Model 1: Robust		Model 2: Robust		Model 3: Frailty	
	Hazard (95% CI)	HR (95% CI)	Hazard (95% CI)	HR (95% CI)	Hazard (95% CI)	HR (95% CI)
Noninfectious model						
Fistula	0.27 (0.26 to 0.29)	Reference	0.25 (0.24 to 0.27)	Reference	0.23 (0.22 to 0.25)	Reference
Graft	0.35 (0.31 to 0.40)	1.29 (1.20 to 1.37)	0.37 (0.33 to 0.42)	1.46 (1.37 to 1.55)	0.32 (0.28 to 0.36)	1.37 (1.29 to 1.45)
Catheter	0.53 (0.48 to 0.61)	1.97 (1.85 to 2.09)	0.54 (0.49 to 0.62)	2.16 (2.04 to 2.29)	0.46 (0.42 to 0.53)	1.99 (1.89 to 2.11)
Shape parameter						
Fistula	0.43 (0.42 to 0.44)	—	0.47 (0.46 to 0.47)	—	0.50 (0.49 to 0.51)	—
Graft	0.49 (0.48 to 0.51)					
Catheter	0.48 (0.47 to 0.49)					
Infectious model						
Fistula	0.027 (0.021 to 0.034)	Reference	0.023 (0.018 to 0.029)	Reference	0.024 (0.019 to 0.029)	Reference
Graft	0.040 (0.024 to 0.065)	1.49 (1.16 to 1.90)	0.041 (0.026 to 0.063)	1.77 (1.44 to 2.17)	0.035 (0.022 to 0.052)	1.45 (1.18 to 1.79)
Catheter	0.057 (0.037 to 0.088)	2.12 (1.74 to 2.58)	0.061 (0.04 to 0.092)	2.66 (2.24 to 3.17)	0.046 (0.030 to 0.066)	1.90 (1.57 to 2.29)
Shape parameter						
Fistula	0.36 (0.32 to 0.41)	—	0.46 (0.44 to 0.48)	—	0.53 (0.50 to 0.55)	—
Graft	0.48 (0.42 to 0.54)					
Catheter	0.55 (0.50 to 0.60)					

The initial hazard (failure rate) per unit time (month) is given for each access type, as well as the hazard ratios for grafts and catheters compared with fistulas. Different shape parameters were allowed in models 1; the significantly smaller shape parameter for fistulas indicates a faster decline in the rate of complications over time. A common shape parameter was assumed in models 2 and 3. All models take into account the correlation in the data due to repeated observations within patient (using robust variance or frailty method) and are adjusted for the effects of sex, race, and diabetes (scale effects). See Supplemental Table 3 for details. The hazards reported above can be seen as the initial hazard values in the curves in Figure 2. The shape parameter reflects the change in the hazard over time; when shape=1 the hazard is constant (exponential model); when shape>1 the hazard increases over time; when shape<1 the hazard declines over time (as in the case for all estimates above). In both models 1, which allow access-specific shape parameters, the hazard ratios are not constant over time. The hazard ratio estimates presented above correspond to the ratios of hazard functions at initial time (t=3 days), after which the hazard ratios increase over time as a result of the differences in the hazard shapes (in this case because the shape parameter of fistulas [reference category] is the smallest). HR, hazard ratio; CI, confidence interval.

Table 4. Median times (ranges) to complication by access type and individual frailty category

Variable	Time to Noninfectious Events (Range) (mo)		Time to Infectious Events (Range) (mo)	
	Median (Range)	25th Percentile	Median	25th Percentile
Fistula (*n*=4733)	8.7 (4.7–23.6)	1.51 (0.82–4.1)	586.0 (184.1–7047.9)	110 (35–1329)
Graft (*n*=2756)	3.8 (2.5–12.6)	0.67 (0.44–2.2)	136.9 (90.4–3459.9)	26 (17–652)
Catheter (*n*=4207)	1.8 (1.2–5.9)	0.31 (0.21–1.03)	82.4 (54.4–2083.5)	16 (10–393)

Median times are based on predictions from model 3 (Table 3; frailty models). A median time to complication was calculated for each patient on the basis of his or her covariate values. The median values and ranges reported above are the median values and ranges of those median times; thus, the range reflects covariate variability. Frailty models are used in situations when some individuals are more or less prone to experience the event of interest due to some shared (but unmeasured) characteristics. We used frailty models to study repeated outcomes occurring in the same individuals over time, and individuals are more or less prone to fail. Frailty models are survival models that take into account the correlation in the data (risks are more similar within patients than between patients) using random effects. The above predictions are calculated for an average frailty of 1.[26]

incorporating individual frailties (a patient's tendency to have a complication), both the average patient-specific hazard functions and the overall population hazard function declined over time (Supplemental Figure 3). Although the shapes of the average individual hazard and the population hazard were similar, the average individual hazard tended to decline more slowly with grafts and catheters than with fistulas for both noninfectious and infectious complications.

Predicted Survival Times

Table 4 summarizes for each type of hemodialysis access the median and the 25th percentile times to complication (times at which 50% and 75% of the sample, respectively, are still event free). For noninfectious events, median times to complication were 8.7 months with fistulas, 3.8 months with grafts, and 1.8 months with catheters. Although hazard ratios for infectious and noninfectious complication models were similar (Table 3), estimated median infection-free times were extremely long in infection models because of the low rates of sepsis and access infections. Twenty-fifth percentile times to an infection complication were 110, 26, and 16 months with fistulas, grafts, and catheters, respectively.

Sensitivity Analyses

Analyses of sepsis events provided results similar to those seen with analyses including both access infections and sepsis (Supplemental Table 5). Results were similar when we modeled time to the first event of each access (unassisted survival) or time to the final event of each access irrespective of the number of procedures necessary to maintain the patency of that access (assisted survival). Results did not materially change when we considered the first use date instead of the access placement date as time 0 in the Weibull models (not shown). Treating death as a competing event or including in the models the use of temporary catheters at hemodialysis start did not substantially change results (Supplemental Table 6).

DISCUSSION

In a large international cohort of patients commencing hemodialysis therapy, we found that the risk of noninfectious complications leading to access-related procedures and the risk of sepsis or access infection requiring medical intervention were both high during the first 3–6 months after access placement or a previous access complication. Risk quickly declined over time in all forms of hemodialysis access. These risks were higher with catheters and grafts than with fistulas, and the rates of decline over time were independent of individual comorbid conditions, countries, or regions. The rates of potentially serious access-related infections were approximately 10 times lower than the rates for noninfectious complications. Beyond 3 months after access placement or a remedial access complication, these rates were lower than 0.2, 0.3, and 0.6 per 1000 access days with fistulas, grafts, and catheters, respectively, leading to extremely long estimated median time to infectious complications.

The reasons for the observed temporal risk profiles for access complications are not entirely clear, especially for grafts and catheters. Although the risk of infection may be high immediately after the surgical creation of an arteriovenous access or the insertion of a central venous catheter, persistent presence of a foreign material in the vascular system (a prosthetic graft or a catheter) may be expected to predispose to increasing rather than decreasing risk of infections.[12] However, our data show that the risk of infection declines with all access forms, including grafts and catheters, and in both incident and prevalent patients. Similarly, the risk of access dysfunction due to thrombosis declines over time with all forms of access, although more quickly with fistulas than with grafts and catheters. This finding is consistent with the known high rate of primary failure in fistulas.[14] Alternatively, the decline of the risk for access complications over time may be related to patient rather than access factors. Dialysis initiation represents a critical transition period for patients with ESRD. Comorbid conditions accelerating the progression of kidney disease or cardiovascular disease may put more frail individuals at risk for different clinical events, including vascular access complications.

Rates of noninfectious and infectious complications of the hemodialysis access have been reported previously with the assumption that they were constant over a relatively long study period; these rates are difficult to compare with the hazard rate functions over time from our study. For example, in a small trial

of brachial-antecubital forearm loop grafts and brachial-basilic fistulas in patients in whom cephalic fistulas failed, the intervention rate was 7.4 interventions per 1000 patient-days in patients with a graft and 4.6 in those with a fistula.[17] In another study of less complex patients, the incidence of thrombotic episodes was 1.5 episodes per 1000 patient-days with grafts and 0.5 with fistulas.[18] Both these studies report average rates over 1-year follow-up. Reports from shorter studies are more consistent with our findings. A 6-month trial of catheter locking solutions reported 3.91 dysfunction events per 1000 access-days in the standard heparin therapy group,[13] a rate similar to the 6-month rate in our cohort. Despite different definitions used for infectious events, the rates of catheter-related infections, ranging from 0.6 to 6 events per 1000 access-days in clinical trials,[19] are consistent with our findings at 6 months. However, all these studies reported rates as if they were constant over the study period, an assumption that our study does not support.

Our findings have important implications for clinical practice. Because the risk of recurrent complications is particularly high immediately after access placement or a previous access event, the first 3–6 months of the life of an access or after an access procedure is the period that should be targeted for preventive strategies. Referral to the access clinic after an arteriovenous creation or a salvage procedure in predialysis patients and access monitoring or surveillance for patients receiving hemodialysis therapy may be part of this strategy. New catheter locking solutions may be considered in newly placed catheters or after successful treatment of a previous event. Our data also have implications for future research in prevention of complications. Because outcomes are much more common early during the life of an access or immediately after an access-related procedure, enrollment of study participants immediately after a new access has been placed or treated will reduce sample size requirements. This applies to both incident and prevalent patients. For example, to demonstrate a relative risk reduction of 30% with a two-sided significance level of 5% and a power of 80%, 30 participants per group are required if the baseline rate is 8 per 1000 access-days; 400 are necessary if the baseline rate is 0.4 per 1000 access-days. Short follow-up duration, measurement of recurrent events, and consideration of the temporal risk profile (*i.e.*, declining hazard) are important to maximize the efficiency of a trial of hemodialysis access.

Our study has strengths, including rigorous methods and study design, a large international sample of practices and participants, consistency of the associations in several sensitivity analyses, and relevance to nephrology practice and clinical research. In particular the findings of decreasing individual hazard functions in prevalent patients at different hemodialysis vintages (times since hemodialysis start) are consistent with the results of the analyses in the incident cohort. In addition, results were the same when death was treated as a competing event rather than as censored.

However, our study has also important limitations, primarily due to the level of detail of the primary source data. First, we defined infections as diagnosis of sepsis or access infections requiring medical intervention. Although bacteremia may remain undetected in the absence of screening protocols,[12] the lack of a specific code for bacteremia in the DOPPS may have led to inclusion of bacteremia cases among sepsis events and therefore overestimation of the rates of sepsis. Our analysis excluded access complications that did not require medical procedures, and therefore, our results may underestimate the total morbidity burden associated with each access type. It is reasonable to expect that this exclusion is limited only to less clinically relevant events handled in an outpatient fashion. Second, it is possible that the rates of infection could have been artificially inflated when permanent access failures required temporary catheter placement immediately before the event. To address this concern, we reanalyzed the data and attributed each event to the access in place 7 days before the event as opposed to the access in use the day before the event and found no material changes in any of our results.

In summary, the risks for noninfectious and infectious complications are highest immediately after placement of a permanent hemodialysis access or following an access procedure, and decline over time in all types of access and similarly in incident and prevalent patients. The risk of access infections and sepsis is 10 times lower than the risk of noninfectious complications in any access type, including tunneled catheters. Prevention strategies should target the first 6 months after placement of an access or an access-related procedure in a hemodialysis patient.

CONCISE METHODS

Data Source and Participants

We used data from DOPPS I (1996–2001), II (2002–2004), and III (2005–2008). DOPPS, an international cohort study of patients receiving chronic in-center hemodialysis, was designed to evaluate the association of practice patterns and selected patient outcomes, including mortality, hospitalization, and vascular access outcomes. For participation in DOPPS, 20–40 hemodialysis patients aged 18 years or older were randomly selected from 308 dialysis facilities in DOPPS I (n=17,034 patients from France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States), 322 dialysis facilities in DOPPS II (n=12,839 patients from the same countries plus Australia, Belgium, Canada, New Zealand, and Sweden), and 300 facilities in DOPPS III (n=11,361 from the same countries as in DOPPS II).[20,21] In DOPPS I, patients who left the study because of death, modality change or transfer to another facility were replaced every 4 months, by randomly selected new patients. In DOPPS II replacement was not performed, but the cohort was supplemented with up to 15 consecutive patients per facility initiating hemodialysis within 30 days of study entry. In DOPPS III patient replacement occurred annually, drawing from patients who joined the study unit during the prior year.

We included only incident patients in the primary analysis and considered multiple procedures per access and multiple permanent vascular accesses per patient. Incident patients were defined as those new to ESRD and receiving hemodialysis therapy for 15 days or less at DOPPS study entry.[22] We excluded participants with history of peritoneal dialysis or kidney transplantation, individuals who never received a permanent vascular access (fistula, graft, or tunneled catheter), and those for whom vascular access data were not reported. We used data from prevalent patients for sensitivity analyses in examining study outcomes for permanent vascular accesses created during the study.

Outcomes

We used longitudinal information about complications of vascular accesses categorized as related or unrelated to infections. Available data included date of first use after access placement and first use after a salvage procedure, primary and secondary diagnoses at discharge from hospital (including clotted access, dysfunctional access, skin infection, and sepsis), use of antibiotics, and access-related procedures (new creation, surgical or medical revision, angioplasty, type of surgical or radiologic repair, access removal, and fibrin disruption), and updated access status (functioning, not used/abandoned, infected, or removed) every 4 months.

Noninfectious complications were defined in two ways: (*1*) "remediable access failure" due to any noninfectious cause (thrombosis of the access, fibrin material within or around a catheter, catheter migration, central vein stenosis or thrombosis) requiring a revision procedure to maintain patency or improve access performance (*i.e.*, thrombolysis, angioplasty, or surgical correction) in an inpatient or outpatient setting or (*2*) "irremediable access failure" (*i.e.*, access removal or abandonment with creation of a new access that was not due to an access-related infection). We used these definitions to conduct unassisted (time to the first event in each access, either irremediable or remediable) and assisted survival analyses (time to irremediable failure irrespective of the number of procedures necessary to maintain patency of the same access).

Infectious complications were defined as any documented diagnosis of access infection requiring medical intervention (managed in an outpatient or inpatient setting) or sepsis as diagnosis in the hospitalization file whether access related or not. Codes for infections were available in the outpatient file (access infection) and in the hospitalization file (sepsis and access infection). Analysis was performed with the event defined as access infection or sepsis, and as sepsis only.

Exposure and Covariates

The exposure of interest was vascular access type. A given patient could be represented in the data more than once, with more than one access type and/or more than one access of the same type. Covariates included country, demographic and clinical characteristics at study entry (age, sex, history of heart failure, coronary artery disease, peripheral artery disease, cerebrovascular disease, neoplasm, current/past smoking habit, chronic lung or systemic diseases). Throughout follow-up, we abstracted updated treatment, including location (outpatient versus inpatient) and type of treatment (angioplasty versus surgery for noninfectious complications), and laboratory data from patient records at 4-month intervals, which allowed the use of time-varying covariates.

Ethics Approval

The DOPPS study received institutional review board approval, and patient consent was obtained as required by local medical research ethics committees.

Statistical Analyses

We studied the effects of the access type on the profiles of risk (*i.e.*, the shape of the hazard function over time since access placement or previous event) for infectious and noninfectious complications. We also estimated hazard ratios for each complication by access type. We considered repeated complications across multiple accesses per patient, resetting the "risk clock" to 0 after each failure (*i.e.*, gap-time risk set).[23] According to this approach, observations continue after a remediable failure in the same access, and also continue after an irremediable failure into the period of a new access in the same patient. However, after each failure the survival time is reset to 0. We censored observations at the date of death, transplant, loss to follow-up, transfer to peritoneal dialysis, transfer to another center, or end of study observation.

We explored how the hazard functions for each event type (noninfectious and infectious complications) changed over time by plotting the crude hazard rates for time intervals 0–1, 1–3, 3–6, 6–12, and >12 months, and overlaying nonparametric (smoothed) estimates of these functions (analytical steps are summarized in Supplemental Table 7). On the basis of the monotonic risk decline observed in these crude hazard estimates, we tested the fit of parametric survival models nested in the three-parameter gamma family and found that the Weibull model provided the best fit. We compared parametric survival models using formal tests (including testing the parameters of nested gamma models) and by graphical assessment of the goodness of fit.[14] Because the chosen Weibull model is a proportional hazards model, during model building we checked that the hazard ratios (scale effects) were the same as those from the corresponding Cox model for conditional (stratified by access number) repeated events.[23]

We considered all covariates described above during model building and monitored variations of the exposure regression coefficients (scale and shape parameters associated with access type) to identify variables that could be manually removed as nonconfounders or nonmodifiers (absolute parameter change >0.1). We tested the effect of access number on both Weibull scale and shape parameters and found only significant hazard scale differences between second and subsequent accesses versus the first. We checked model specification, assumptions, and overall fit using formal and graphical tests based on residuals. We accounted for the correlation in the data due to repeated infection or noninfectious events in the same patient using robust variance or random effects (shared frailties).[24] The robust variance takes into account the clustering between repeated events within a person using the sandwich estimator method.[25] These dependencies are instead modeled as random effects in frailty models, which allow estimation of the person-specific frailty (*e.g.*,

an individual's tendency to experience an access complication) assuming a gamma frailty distribution.[26] The levels of correlation due to center or country were of substantially smaller magnitude. We hypothesized that the hazard function declines over time both at the population level (as expected in a frailty context) and at the individual level (where the hazard function may have any form). We therefore compared the shape of the population hazard function with the average individual hazard function (frailty effect) using unshared frailty models (gamma frailty) of time to the first event in the initial access. We did this to remove the effect of cluster size and have a population defined by patients rather than access observations.[26]

In sensitivity analyses, we studied time to the first event of each access (unassisted survival), and time to the final event of each access irrespective of the number of procedures necessary to maintain the patency of that access (assisted survival). In analyses of time to the first complication of the initial access, we examined the effect of the use of temporary catheters to start hemodialysis and compared the results of Weibull regression and Cox regression models in which death was treated as censored with those from models in which death was treated as competing event.[27] We also considered the first use date[22] as opposed to the access placement date as time zero because survival from placement without use may confer an advantage to fistulas and grafts versus catheters. In another sensitivity analysis we reanalyzed the data attributing each event to the access in place 7 days before the event as opposed to the access in use 1 day before the event.[28] In addition, we repeated the models considering only vascular access complications resulting in a patient being hospitalized.[28] We repeated all these analyses in prevalent patients who had at least one permanent access for hemodialysis created during the study period. We did all analyses using Stata software (www.stata.com) and R software (http://cran.r-project.org/).

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DISCLOSURES

None.

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See related editorial, "The Upfront Risks of Vascular Access Complications," on pages 1509–1511.

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