

Risk Equation Determining Unsuccessful Cannulation Events and Failure to Maturation in Arteriovenous Fistulas (REDUCE FTM I)

Charmaine E. Lok,* Michael Allon,[†] Louise Moist,[‡] Matthew J. Oliver,[§] Hemal Shah,* and Deborah Zimmerman^{||}

*University Health Network-Toronto General Hospital and the University of Toronto, and [§]Department of Nephrology, Sunnybrook Health Sciences Centre, Toronto, [‡]Department of Nephrology, University of Western Ontario, London, and ^{||}Nephrology, University of Ottawa, Ottawa, Ontario, Canada; and [†]Department of Nephrology, University of Alabama, Birmingham, Alabama

Fistulas are the preferred permanent hemodialysis vascular access but a significant obstacle to increasing their prevalence is the fistula's high "failure to mature" (FTM) rate. This study aimed to (1) identify preoperative clinical characteristics that are predictive of fistula FTM and (2) use these predictive factors to develop and validate a scoring system to stratify the patient's risk for FTM. From a derivation set of 422 patients who had a first fistula created, a prediction rule was created using multivariate stepwise logistic regression. The model was internally validated using split-half cross-validation and bootstrapping techniques. A simple scoring system was derived and externally validated on 445 different, prospective patients who received a new fistula at five large North American dialysis centers. The clinical predictors that were associated with FTM were aged ≥ 65 yr (odds ratio [OR] 2.23; 95% confidence interval [CI] 1.25 to 3.96), peripheral vascular disease (OR 2.97; 95% CI 1.34 to 6.57), coronary artery disease (OR 2.83; 95% CI 1.60 to 5.00), and white race (OR 0.43; 95% CI 0.24 to 0.75). The resulting scoring system, which was externally validated in 445 patients, had four risk categories for fistula FTM: low (24%), moderate (34%), high (50%), and very high (69%; trend $P < 0.0001$). A preoperative, clinical prediction rule to determine fistulas that are likely to fail maturation was created and rigorously validated. It was found to be simple and easily reproducible and applied to predictive risk categories. These categories predicted risk of FTM to be 24, 34, 50, and 69% and are dependent on age, coronary artery disease, peripheral vascular disease, and race. The clinical utility of these risk categories in increasing rates of permanent accesses requires further clinical evaluation.

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The ideal vascular access would provide long-term, reliable access to the blood circulation with minimal complications. Of all hemodialysis (HD) access types, the arteriovenous fistula (AVF) achieves this goal most successfully. If the AVF matures, then it has excellent long-term patency with low thrombosis and infection rates, few interventions, and low cost (1–3). This information is well established and recognized by nephrologists (4) and has been widely publicized by the Medicare "Fistula First Program" initiative (5). Despite this consensus, many North American dialysis centers have been unable to achieve the recommended targets for AVF use (6,7).

One obstacle to increasing fistula prevalence is the high "failure to mature" (FTM) rate. Failure of fistula maturation, also known as primary fistula failure, ranges from 9 to 70%

The use of the proposed risk equation to determine the likelihood of AV fistula failure in individual patients may permit more rational selection of dialysis patients for anticoagulant therapy, a topic reviewed by Bennett in this month's issue of CJASN (pp. 1357–1359).

(8–10). Patients with nonmaturing AVF require "temporary" dialysis catheter placement and an aggressive interventional strategy to develop fistula functionality. Despite such efforts, a substantial proportion of marginal fistulas never mature adequately to be used for dialysis. The clinical consequences of immature fistulas include prolonged dependence on "bridging catheters" with all of the attendant complications, patient inconvenience, need for further attempts at permanent access surgery, and risk for eventual patient refusal (8,11). Even in programs that use routine preoperative vascular mapping to guide the surgeon's choice of access type and location, primary failure still occurs in a subset of patients (12,13). In promoting fistula creation and use, it would be ideal to be able to predict which patients would benefit from an AVF that would mature successfully, without excessive intervention, and to tailor access placement accordingly. Patients with very low likelihood of fistula maturation despite salvage procedures might benefit from having an AV graft placed instead.

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Address correspondence to: Dr. Charmaine E. Lok, Department of Medicine, Division of Nephrology, The Toronto General Hospital, 8NU-844, 200 Elizabeth Street, Toronto, Ontario, M5G 2C4, Canada. Phone: 416-340-4140; Fax: 416-586-9827; E-mail: charmaine.lok@uhn.on.ca

Few studies have specifically examined factors that are associated with fistula FTM. More than a decade ago, Feldman *et al.* (14) summarized the state of the literature regarding this problem: “Despite a large risk of primary fistula failure, little is known about the specific surgical, comorbidity, or demographic factors predictive of primary fistula function. . . . A great challenge before the dialysis community is the identification of patients in whom an AVF is a viable vascular option so that shorter-lived synthetic (PTFE) vascular access grafts can be reserved for patients in whom an AVF is unlikely to mature successfully.” Indeed, studies that evaluate fistula use and failure often do not differentiate between early surgical failure (*e.g.*, as a result of thrombosis or technical complications) and failure to mature (15–18). A variety of patient demographics (*e.g.*, age, gender, cause of ESRD), access characteristics (*e.g.*, site, vessel morphology), and practice patterns (*e.g.*, timing of referral and placement) have been associated with nonspecific fistula use, adequacy, and failure. Specific studies relating to fistula FTM have uncovered factors that are beyond the nephrologist’s control, such as intraoperative influences and surgical technique (19).

Published studies that have evaluated predictors of a successful fistula have varied in study end points and their definitions, study design and size, patient population, and clinical factors considered. These discrepancies make it difficult for a clinician to determine the relative importance of these potential risk factors and to determine which clinical variables to apply in assessing the likelihood of achieving a mature fistula in patients who are referred for a permanent access. Preoperative algorithms that are based on noninvasive and invasive radiologic procedures have been proposed (20–22), but their widespread use may be limited by the expense and time requirement.

We aimed to develop a simple, inexpensive, clinically practical, and user-friendly scoring system to predict which AVF are likely to fail to mature. The first study objective was to identify clinical characteristics that are predictive of fistula FTM. The second objective was to use these predictive factors to develop and validate a risk equation determining unsuccessful cannulation events and failure to maturation of arteriovenous fistulas (REDUCE FTM I) that could be applied to patients to stratify their risk for FTM.

Materials and Methods

Patients and Accesses

The University Health Network HD program currently treats approximately 350 HD patients per year and has incorporated a multidisciplinary approach to access management (23). Since January 1, 1995, baseline demographic information has been collected into a computerized database, including age, gender, race, cause of renal failure, and comorbidities. Comorbidities were defined as follows: (1) Coronary artery disease (CAD; documented coronary stenosis by angiography or history of myocardial infarction or previous coronary revascularization by angioplasty, stenting, or bypass surgery); (2) peripheral vascular disease (PVD; history of lower extremity revascularization or digit or extremity amputation or history of claudication and ischemic extremity changes or gangrene); (3) cerebrovascular disease (a stroke or transient ischemic attack documented by computed tomography scan, magnetic

resonance imaging, or classical clinical signs and symptoms and confirmed by a neurologist or when the diagnosis had been noted in the medical records at least twice by two different physicians); (4) heart failure (classic signs and symptoms and either documentation by echocardiography or chest x-ray or complete symptom resolution with ultrafiltration); and (5) diabetes (if a patient had ever required hypoglycemic agents or insulin or when the diagnosis had been noted in the medical records at least twice by two different physicians). The definition of hyperlipidemia conformed to our Canadian guideline definitions (24,25). Patients were defined as overweight when their body mass index was ≥ 30 , consistent with the World Health Organization definition (26). Access characteristics that were ascertained include access type and anatomic location, dates of creation and loss, and reason for loss. The access coordinator also prospectively tracked the intra-access flow measurements using ultrasound dilution technique and the number of angiograms, angioplasties, surgical revisions, and thrombectomies of each AVF created.

Using this prospective clinical database, we identified 422 patients who received a first AVF between January 1, 1995, and January 1, 2004 (“derivation set” of patients). Of note, all surgeons shared a common goal of creating AVF as an initial access whenever possible (approximately 75% of all first permanent accesses in this period were AVF). However, each surgeon’s clinical and/or radiologic evaluation of the patient’s suitability for an AVF varied and was left to his or her own discretion. All clinical variables regarding these patients were verified independently by the vascular access coordinator and an investigator (H.S.). Once the prediction rule had been developed, it was applied prospectively to 461 patients who received new AVF (first or subsequent fistula) in the external validation of the prediction model. This “validation set” of patients consisted of 95 patients within University Health Network who had their AVF created after January 1, 2004, and 366 patients from other dialysis centers. The four other large Canadian and American university-based HD centers involved included Sunnybrook Health Sciences center (Toronto, ON), London Health Sciences Centre Renal Program (London, ON), the Ottawa Hospital (Ottawa, ON), and the University of Alabama at Birmingham (Birmingham, AL). In total, these four centers care for approximately 2200 HD patients.

Outcome Definition

The primary outcome was AVF FTM. This was defined as a fistula that was used for HD and was unable to provide prescribed dialysis *via* two-needle cannulation consistently (*i.e.*, must use two-needle cannulation for two thirds or more of all dialysis runs) for 1 mo within 6 mo of its creation, despite interventions to facilitate maturation. A typical dialysis prescription would be a frequency of 3 times per wk for a duration of 3.5 to 4.5 h, blood flow rates of 300 to 450 ml/min, and dialysate flows of 500 to 800 ml/min. The blood flow rates, duration, and frequency may vary to achieve a target sp-KT/V of 1.2. This definition does not pertain to patients who had fistulas created and did not initiate dialysis within 6 mo; these fistulas were excluded from the study. Facilitative interventions were determined at the discretion of the treating nephrologists, interventional radiologists, or surgeons. They most commonly included angioplasty of stenotic lesions and embolization or surgical ligation of competing veins. In defining FTM, early technical failures (intraoperative thrombosis or other complications that required return to the operating room or abandonment of the newly created AVF) were excluded. This contrasts with our definition of fistula *primary failure* (PF) that shares the same criteria as fistula FTM except that early technical failures also were included. PF was used in sensitivity analysis.

Statistical Analyses

From the derivation set of 422 patients, the following variables were identified, *a priori*, to be clinically important predictors of fistula FTM: Age, gender, race (categorized as white *versus* other), diabetic status, CAD, PVD, cerebrovascular disease, heart failure, hyperlipidemia, body mass index, location of fistula (upper arm or forearm), smoking status (ever *versus* never), and cause of ESRD. Univariate analyses of continuous variables by *t* test and of categorical variables by χ^2 test were performed to determine which of these risk factors differed significantly between fistulas with FTM and fistulas that achieved adequacy for dialysis. A parsimonious model then was developed using multivariate stepwise backward logistic regression to select, from the identified candidate variables, a subset of variables that were independent predictors of fistula FTM. The referent variable was always opposite the variable of interest (*e.g.*, if “white” was the variable of interest, then the referent group would be “nonwhite”). The criterion for a variable to enter the model was $P < 0.25$, whereas the criterion for eliminating a variable from a model was $P > 0.025$. The model discrimination was assessed by the concordance or C-index (equivalent to the area under the receiver operating characteristic curve) and its calibration by the Hosmer and Lemeshow goodness of fit test. The model then was validated internally using two methods: The split-half cross-validation and bootstrapping. In the split-half cross-validation, the model is developed on a randomly drawn half and tested on the other and *vice versa* (27). Bootstrapping replicates the process of sample generation from an underlying population by drawing samples with replacement from the original data set of the same size as the original data set (28). Bootstrap resampling was fitted to the logistic model in a bootstrap sample of 422 patients. Performance measures were evaluated twice on 1000 repetitions (*i.e.*, 1000 bootstraps \times 2). Once a final model was derived, it was converted into a clinical prediction score by conversion of resultant odds ratios. As a sensitivity analysis, conversion using the β -parameter estimates or regression coefficients was performed. The external validation of this clinical prediction scoring system then was applied to a validation set of 445 patients and analyzed by Mantel-Haenszel χ^2 trend test. Sensitivity analysis was performed using PF as the outcome. Analysis was performed using SAS (version 8.2; SAS Institute Inc., Cary, NC).

Results

Risk Factors and the FTM Prediction Model

Prospective analysis of the derivation set of 422 first AVF that were created between January 1995 and January 2004 revealed a FTM rate of 14% ($n = 58$). Access characteristics and univariate analysis of clinical variables are shown in Table 1. Univariate analysis found the following variables to be associated with FTM (Table 1): Age ≥ 65 yr (odds ratio [OR] 2.23; 95% confidence interval [CI] 1.25 to 3.96), PVD (OR 2.97; 95% CI 1.34 to 6.57), CAD (OR 2.83; 95% CI 1.60 to 5.00), and hyperlipidemia (OR 2.02; 95% CI 1.08 to 3.79). Having diabetes was borderline ($P = 0.05$; OR 1.77; 95% CI 0.98 to 3.17). Male gender (OR 0.54; 95% CI 0.30 to 0.96) and white race (OR 0.43; 95% CI 0.24 to 0.75) were associated with a decreased risk for FTM.

When these candidate variables were placed into a multivariate logistic regression model, the following prediction equation was derived: $-\log$ odds of failure of fistula maturation $[\log/(1 - P)] = -2.0809 + 0.6907 \times (\text{age} \geq 65) + 0.9821 \times (\text{PVD}) + 0.8576 \times (\text{CAD}) - 1.0496 \times (\text{white})$. There was good calibration as indicated by the Hosmer and Lemeshow goodness of fit test ($P = 0.90$); the C-statistic was 0.76.

In a sensitivity analysis, the exit criteria for the model allowed variables to remain when $P < 0.05$, and all variables of clinical interest were included irrespective of univariate results. Female gender had a $P = 0.042$ but was not statistically significant in the internal cross-validation model and did not contribute to the external validation; therefore, it was not included in the resultant score.

Independent External Validation and Development of Predicted Risk Categories

Using the above prediction model, the following clinically user-friendly scoring system was derived: Prediction score = $3 + 2 \times (\text{age} \geq 65) + 3 \times (\text{PVD}) + 2.5 \times (\text{CAD}) - 3 \times (\text{white})$. The possible range of scores is 0.0 to 10.5. Although this was derived from conversion of OR, the identical proportionate result was achieved with conversion of regression coefficients; however, the multiplication factor resulted in less user-friendly values (*e.g.*, 0 to 35.5). The scores then were categorized into probability risks for FTM as follows: Score < 2.0 , low risk; 2.0 to 3.0, moderate risk; 3.1 to 7.9, high risk; and > 8.0 , very high risk ($P < 0.0001$). The prediction rule and “FTM predicted risk categories” were applied to the external validation set that consisted of 461 patients. Sixteen patients were predialysis and were excluded, leaving 445 patients for analysis. Eleven patients had early technical failures and were excluded from the FTM analysis but kept in the PF sensitivity analysis. Basic characteristics of this validation set of patients are shown in Table 2. A total of 170 (39%) of these patients had fistulas that failed to mature. Twenty-four percent of patients who scored in the low-risk category had fistulas that failed to mature (Figure 1), 34% failed to mature in the moderate risk category, 50% failed to mature in the high risk category, and 69% failed to mature in the very-high-risk category (Mantel-Haenszel χ^2 for trend $P < 0.0001$; Figure 1). When the score was applied to PF ($n = 445$), 25% were low risk, 35% were moderate risk, 52% were high risk, and 71% were very high risk (Mantel-Haenszel χ^2 for trend $P < 0.0001$). The score was found to be efficient and easy to use by nephrologists, vascular access coordinators, and study coordinators who collected the data. For example, a 75-yr-old black patient who had no CAD but had PVD would have a score of 8 with a predicted very high risk for PF of 71% or for FTM of 69% (Table 3).

Discussion

A total of 39% of fistulas in a current, independent, external validation cohort of patients failed to mature, and 41% had PF. These findings are consistent with study of Feldman *et al.* (14), in which the FTM rate in 348 patients was 44.5%. Although the rate is high, it is not unexpected given the fistula’s history of problematic maturation and how the dialysis population has evolved. When the radiocephalic fistula first was described in 1966 by Cimino and Brescia (29), the patients’ average age was 43 yr, almost all had chronic glomerulonephritis, and blood flows were 250 to 300 ml/min. The FTM rate was 11%. Today’s patients with ESRD are quite different. In 2003, a large and increasing proportion of people who started dialysis were 75 yr or older (30,31) with the greatest growth in patients who were

Table 1. Access characteristics and univariate analysis of clinical risk factors for FTM^a

Clinical Characteristics	<i>n</i> (<i>N</i> = 422)	% Total	% FTM	OR for FTM (95% CI)	<i>P</i>
Age (mean [SD]; range)					<0.01
total: 58 (17.5; 17 to 90)	422				
≥65: 74 (5.8; 65 to 90)	184	43.6	18.5	2.23 (1.25 to 3.96)	
<65: 45.5 (12.4; 17 to 64)	238	56.4	9.2		
Gender					0.03
male	286	67.8	10.8	0.54 (0.30 to 0.96)	
female	136	32.2	18.4		
Race					0.003 ^g
white	278	65.8	9.7	0.43 (0.24 to 0.75)	
black	35	8.3	20.1		
other	109	25.9	20.2		
Cause of ESRD					
hypertension	102	24.2	12.8	0.94 (0.48 to 1.83)	0.86
diabetes	104	24.6	16.4	1.40 (0.75 to 2.59)	0.29
glomerulonephritis	111	26.3	9.9	0.65 (0.32 to 1.31)	0.22
interstitial nephritis	16	3.8	18.8	1.54 (0.42 to 5.57)	0.51
other/unknown	89	21.1	13.5	1.02 (0.52 to 2.03)	0.95
Vintage on dialysis					
≤6 mo	337	79.9	13.6	1.18 (0.57 to 2.45)	0.65
6 to 12 mo	34	8.0	11.8	0.86 (0.29 to 2.55)	0.79
1 to 5 yr	27	6.4	14.8	1.15 (0.38 to 3.46)	0.80
>5 yr	24	5.7	8.3	0.58 (0.13 to 2.54)	0.47
Comorbidities					
diabetes ^b	120	28.4	18.3	1.77 (0.98 to 3.17)	0.05
hypertension	321	76.0	14.6	1.75 (0.83 to 3.72)	0.14
CAD	136	32.2	22.1	2.83 (1.60 to 5.00)	<0.01
PVD	35	8.3	28.6	2.97 (1.34 to 6.57)	<0.01
cerebrovascular disease ^c	38	9.0	10.5	0.75 (0.26 to 2.20)	0.60
congestive heart failure ^d	87	16.0	18.4	1.66 (0.88 to 3.14)	0.11
dyslipidemia ^e	82	19.4	20.7	2.02 (1.08 to 3.79)	0.03
active smoker	124	29.4	12.9	0.96 (0.51 to 1.72)	0.89
overweight ^f	56	13.3	20.0	1.80 (0.89 to 3.66)	0.10
Access placement					
previous catheter use	214	50.8	16.3	1.73 (0.97 to 3.09)	0.06
upper arm	163	38.6	11.0	0.73 (0.40 to 1.34)	0.31
Surgeon (individual surgeon not shown)	N/A	N/A			0.73
Anatomic configuration					
radiocephalic	256	60.7			N/A
brachiocephalic	145	34.4			N/A
transposed brachiocephalic	18	4.2			N/A
femoral-saphenous	3	0.7			N/A
Side					
right	112	26.5			N/A
left	310	73.5			N/A

^aCAD, coronary artery disease; CI, confidence interval; FTM, failure to mature; OR, odds ratio; PVD, peripheral vascular disease.

^bDefined when a patient had ever required hypoglycemic agents or insulin or when the diagnosis had been noted in the medical records at least twice by two different physicians; it includes those with diabetes as cause of ESRD.

^cDefined as a stroke or transient ischemic attack documented by computed tomography scan, magnetic resonance imaging, or classical clinical signs and symptoms and confirmed by a neurologist or when the diagnosis had been noted in the medical records at least twice by two different physicians.

^dDefined by classical signs and symptoms and either documentation by echocardiography or chest X-ray or complete symptom resolution with ultrafiltration.

^eHyperlipidemia conformed to our Canadian guideline definitions (24,25).

^fBody mass index ≥30, consistent with the World Health Organization definition (26).

^gWhite *versus* nonwhite.

Table 2. Summarized patient characteristics of the external validation set ($n = 445$) compared with the original derivation set ($n = 422$)

Variable	Derivation Set (Original from UHN)	Validation Set		
		UHN	Non-UHN	Total
<i>N</i>	422	95	350	445
Age ≥ 65 yr	184 (43.6%)	24 (25.3%)	147 (42.0%)	171 (38.4%)
PVD	36 (8.3%)	7 (7.4%)	63 (18.0%)	70 (15.7%)
CAD	136 (32.2%)	28 (29.5%)	128 (36.6%)	156 (35.1%)
White	278 (65.8%)	58 (61.1%)	178 (50.9%)	236 (53.0%)
Previous graft	5 (1.2%)	3 (3.3%)	2 (<1%)	5 (1.1%)
Previous catheter	214 (50.7%)	54 (56.3%)	122 (35.1%)	176 (39.6%)
Prehemodialysis	194 (46.0%)	20 (20.8%)	125 (35.9%)	145 (32.6%)
Mean score	3.0 (± 2.4)	2.6 (± 2.6)	3.8 (± 2.4)	3.5 (± 2.5)

^aTwice the proportion of patients had PVD and 1.42 times more were nonwhite in the validation set compared with the derivation set. UHN, University Health Network.

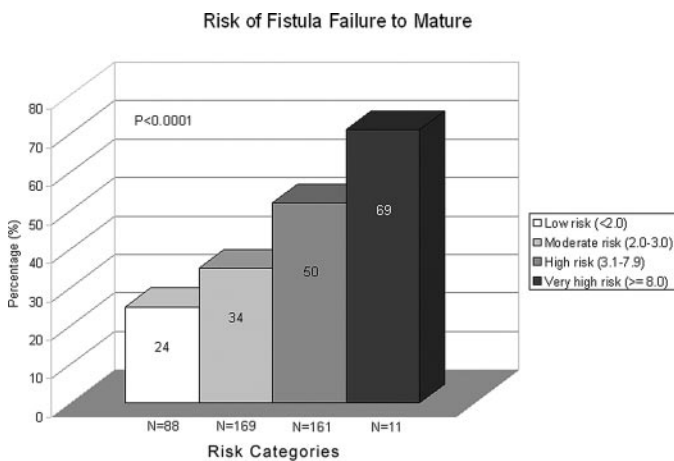


Figure 1. The percentage of primary failure (PF) in each risk category were as follows: Low risk, 25%; moderate risk, 35%; high risk, 52%; and very high risk, 71% ($P < 0.0001$, trend). The risks in each category for each outcome are *not* additive (e.g., low risk is not 24 + 25%; it is either 24% with failure to mature or 25% with PF).

>85 yr of age. Three quarters of them had five or more comorbidities, with 90% having cardiovascular disease (31). Overall, >50% of North American dialysis patients had diabetes, and approximately one half and one third had CAD and PVD, respectively (30–32). European patients tend to have less diabetes but still have substantial comorbidity (32). In addition, the average blood pump speed is much higher: 350 to 450 ml/min. Not surprising, achieving functional fistulas in today's population is more challenging than ever.

For a fistula to mature, there must be sufficient delivery of intra-access blood flow and pressure, dependent on adequate cardiac output/systemic BP and a good-quality feeding (arterial) vessel that will be able to transmit this high pressure to an accepting, unrestricted (*i.e.*, no anastomotic stenosis), compliant, and distensible outflow (venous) vessel. It is not surprising, then, that both CAD and PVD were predictors of FTM, each

indicating diseased inflow and outflow in reference to the anastomosis, respectively. Our data are consistent with other studies in which PVD was associated with poor AVF outcomes (33,34). This also was true in black patients, in whom PVD was associated with failed fistula adequacy (34). Perhaps as a result of the close relationship between predictive factors and pathophysiology, the location of the fistula in the lower or upper arm did not factor into our prediction rule because adequate inflow and outflow are required irrespective of fistula location. This is consistent with some studies (18,22), whereas others found improved maturation in upper arm fistulas (12,35). This same reasoning may be applied to gender. Whereas some studies found female gender to be associated with FTM (20,22,36,37), our study did not after multivariate adjustment. Our finding is consistent with other studies that evaluated factors that are associated with fistula adequacy or patency (13,19,38–40). Whether gender is an independent risk factor for FTM/PF remains an open question, given the roughly equal number of conflicting studies and with the variability that was found in our primary and sensitivity analysis; the answer likely will require a large-scale prospective study.

Our study demonstrated that being white was protective of FTM. In the HEMO study, 64% of study patients were black, but only 28% of them used an AVF (41). Although reasons for the lower prevalence was not stated, it is known that greater complications occur in AVF that are created in black patients (14). In a study of AVF in black patients, 45% were inadequate for cannulation (34); the primary patency reported was 49% at 6 mo and 33% at 12 mo. A few studies did not find an association between race and fistula adequacy (13,35).

The association between increasing age and greater risk for FTM is consistent with the underlying need for adequate vessels, which deteriorate with the normal aging process and are damaged by concurrent disease; this finding is supported by other studies (19,35). Diabetes affects the micro- and macrovasculature, but, after multivariate adjustment, we did not find it a predictor of FTM. Although this is consistent with Feldman's and other studies (13,19,34,40), it contrasts with others (12,35).

Table 3. Clinical use of the scoring system^a

Variable	Points	Score	Variable Definitions
Age \geq 65 yr	+2		Age at time of fistula creation
PVD	+3		Documented lower extremity revascularization, digit or extremity amputation, history of claudication and ischemic extremity changes or gangrene
CAD	+2.5		Documented coronary stenosis by angiography or history of myocardial infarction or previous coronary revascularization by angioplasty, stenting, or bypass surgery
White	-3		Not of black, Asian, aboriginal, or other non-European descent
Baseline score		+3	All patients are given baseline score of 3
Total			Sum of scores

^aThe total score could range from 0 to 10.5.

However, other studies may not have included variables such as CAD and PVD or had as strict of a definition as we had. CAD and PVD are significant comorbidities that likely incorporate and predominate the effects of diabetes; therefore, it consequently falls out of the final equation. Indeed, diabetes association with suboptimal veins that lead to poor fistula adequacy was described previously (22). In a study that evaluated fistula adequacy in black patients, diabetes was not associated with greater failure, but PVD was. In their population, patients with diabetes were more likely to have PVD ($P < 0.0001$).

The FTM predicted risk categories are intended to provide the nephrologist and the vascular surgeon another estimate along with other considered factors on which to guide their access management strategy. An example is provided in Table 4. Our example is guided by our own experience and that of the literature. For example, the suggestion to place an AVF (with or without imaging) if a patient is in a low-risk category (<25%) is based on the finding that when preoperative physical examination can be performed accurately, it can have good predictive value in determining which patients will have successful fistulas. Maturation rates of 80% have been reported in patients who were evaluated preoperatively solely by good physical examination (13). Indeed, vessels that are visible and palpable on

examination may be inherently different from those that require detection *via* radiologic imaging. Greater risks may involve the implementation of preoperative imaging protocols (*e.g.*, routine venous duplex ultrasonography scanning) in conjunction with selective venography and arteriography, because some studies have found their use to be associated with an increase in AVF prevalence (20,42–44).

The preoperatively determined FTM predicted risk categories also can be used to guide postoperative management. For example, in the highest risk patients (>50%), close postoperative surveillance and identification of a fistula that is failing to mature is crucial. Whether the fistula will be successful may be obvious within 6 wk, but it often is clear much sooner (16). If a fistula is deemed inadequate at 4 to 8 wk, then it is unlikely to be adequate at a later date (22,45), especially without intervention. Early identification of fistula adequacy may be assisted by ultrasonography, which has predictive value when both anatomic and functional parameters are used (22). Should an inadequate AVF be found, aggressive facilitation and salvage (15,46) are required. The intent of using a prediction scoring system is to stratify risk (*i.e.*, define high- and low-risk patients) to guide decision making for patient-tailored optimal access creation and use. This should streamline process, optimize

Table 4. An example use of the FTM predicted risk categories^a

Score	Risk Category ^b	Clinical Application ^c
<2.0	Low risk: 25%	PE ^d \pm duplex ultrasound; create AVF
2.0 to 3.0	Moderate risk: 35%	PE, ^d duplex ultrasound \pm venogram; create AVF
3.1 to 6.9	High risk: 50%	Arteriogram + venogram and appropriate preoperative intervention as necessary; create AVF with very close postoperative monitoring (<i>e.g.</i> , weekly or biweekly), and anticipate the need for aggressive intervention to facilitate maturation
\geq 7.0	Very high risk: 70%	Consider another form of permanent access (<i>e.g.</i> , graft); continue to avoid catheter use

^aAll patients with risk factors for central vein stenosis should have a venogram regardless of score. AVF, arteriovenous fistula; PE, physical examination.

^bBecause of the similarity in risks for patients who have fistula primary failure and those that fail to mature (see Figure 1), the risks have been rounded for ease of use.

^cThese are untested possible applications that will require prospective trial evaluation.

^dPhysical exam.

resource allocation, and reduce costs. The goal is to increase the number of functional permanent accesses and reduce catheter use and their associated complications.

There are several limitations to our study. The creation of the prediction rule was based on 422 fistulas that were placed in a single Canadian center. The prevalence of diabetes in the derivation set was only 28% and may not be representative of the North American dialysis population, for whom the current prevalence is closer to 50% (47). Patients with diabetes also are more likely to have other comorbidities, such as PVD. Indeed, the derivation set of patients had a low prevalence of PVD (8.3%) and few black patients (<10%). In contrast, the validation set had almost double the prevalence of PVD and 1.5 times more nonwhite patients. These two variables contributed the greatest weighting in the scoring system (Table 2). In the derivation set, surgery was performed by experienced surgeons who were accustomed to creating fistulas (48). These surgeons had a unified goal to increase fistulas despite variations in preoperative evaluation and intervention. They also were highly experienced, with the majority of them performing the surgery themselves (rather than training residents); there was minimal staff turnover during the 9 yr in which the fistulas were created. Even with extensive case-mix adjustments seen in previous studies, unmeasurable factors, such as surgical approaches and philosophies of care, may be important (49). Furthermore, the institution in which a fistula is created was shown previously to affect fistula survival (50). These differences and biases may account for the difference in FTM rates between the derivation and validation patients. Nevertheless, the prediction score performed well in a heterogeneous validation cohort with different surgeons. Also, we did not consider surgical factors (*e.g.*, intraoperative heparin [19]) or evaluate the effect of preoperative imaging (44). Because such factors were demonstrated previously to affect fistula maturation, this study attempted to determine to which patients it might be most appropriate to offer these interventions, particularly in the climate of cost containment and limited resources. In many cases, the nephrologist or the surgeon cannot alter the known risk factors, such as vessel size or quality (*e.g.*, compressibility), or intraoperative flow (51). These fistulas were the patient's first fistulas; therefore, the prediction rule could not account for the effect of previously failed fistulas. Previous studies demonstrated that fistulas that were placed in patients with previous accesses had better success than first fistulas (19). However, our prediction scores performed well in the external validation of fistulas that involved Canadian and American patients who had previously failed fistulas.

Although the external validation of North American patients was representative of today's dialysis patients with a good case mix and size ($n = 445$), the validation was of the prediction rule and did not examine the clinical suggestions that were associated with the FTM predicted risk categories (Table 4). Indeed, because of the positive relationship between scores and likelihood of fistula failure, the score categorization was based on practicality (*e.g.*, easy to remember and use) and "clinical sensibility." For example, a wider range of patients in a high-risk category might encourage more aggressive and careful fol-

low-up of fistulas to prevent failure. The upper value for "very high risk" was to ensure capture of truly high-risk patients (*e.g.*, multiple previous failures), for whom careful consideration of an alternative permanent access (*e.g.*, graft) might be appropriate. However, the optimal strategy is unknown. The risks and benefits of repeated fistula attempts and failures *versus* either graft creation or prolonged catheter insertion and their associated complications are unknown. Work is ongoing to develop and implement the proper evaluation of the FTM predicted risk categories, taking these issues into consideration, and to determine whether its application will lead to a greater number of fistulas that mature and, overall, a greater number of functional permanent accesses.

Conclusion

A preoperative, clinical prediction rule to determine fistulas that are likely to fail to mature was created and validated rigorously. It was found to be simple and easily reproducible and applied to predictive risk categories. These categories predicted risk for FTM to be 24, 34, 50, and 69% and are dependent on age, CAD, PVD, and race. The clinical utility of these risk categories in increasing rates of permanent accesses requires further evaluation in a prospective, randomized, clinical trial.

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References

1. Manns B, Tonelli M, Yilmaz S, Lee H, Laupland K, Klarenbach S, Radkevich V, Murphy B: Establishment and maintenance of vascular access in incident hemodialysis patients: A prospective cost analysis. *J Am Soc Nephrol* 16: 201–209, 2005
2. Churchill DN, Taylor DW, Cook RJ, LaPlante P, Barre P, Cartier P, Fay WP, Goldstein MB, Jindal K, Mandin H, *et al.*: Canadian Hemodialysis Morbidity Study. *Am J Kidney Dis* 19: 214–234, 1992
3. Kherlakian GM, Roedersheimer LR, Arbaugh JJ, Newmark KJ, King LR: Comparison of autogenous fistula versus expanded polytetrafluoroethylene graft fistula for angioaccess in hemodialysis. *Am J Surg* 152: 238–243, 1986
4. National Kidney Foundation: NKF K/DOQI clinical practice guidelines for vascular access: Update 2000. *Am J Kidney Dis* 37[Suppl 1]: S137–S181, 2001
5. Tonnessen BH, Money SR: Embracing the fistula first national vascular access improvement initiative. *J Vasc Surg* 42: 585–586, 2005
6. Rayner HC, Besarab A, Brown WW, Disney A, Saito A, Pisoni RL: Vascular access results from the Dialysis Outcomes and Practice Patterns Study (DOPPS): Performance against Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines. *Am J Kidney Dis* 44: 22–26, 2004
7. Reddan D, Klassen P, Frankenfield DL, Szczech L, Schwab S, Coladonato J, Rocco M, Lowrie EG, Owen WF Jr: Na-

- tional profile of practice patterns for hemodialysis vascular access in the United States. *J Am Soc Nephrol* 13: 2117–2124, 2002
8. Allon M, Robbin ML: Increasing arteriovenous fistulas in hemodialysis patients: Problems and solutions. *Kidney Int* 62: 1109–1124, 2002
 9. Lok CE, Oliver MJ: Overcoming barriers to arteriovenous fistula creation and use. *Semin Dial* 16: 189–196, 2003
 10. Hakaim AG, Nalbandian M, Scott T: Superior maturation and patency of primary brachiocephalic and transposed basilic vein arteriovenous fistulae in patients with diabetes. *J Vasc Surg* 27: 154–157, 1998
 11. Lee T, Barker J, Allon M: Tunneled catheters in hemodialysis patients: Reasons and subsequent outcomes. *Am J Kidney Dis* 46: 501–508, 2005
 12. Hernandez T, Saudan P, Berney T, Merminod T, Bednarkiewicz M, Martin PY: Risk factors for early failure of native arteriovenous fistulas. *Nephron* 101: c39–c44, 2005
 13. Patel ST, Hughes J, Mills JL Sr: Failure of arteriovenous fistula maturation: An unintended consequence of exceeding Dialysis Outcome Quality Initiative guidelines for hemodialysis access. *J Vasc Surg* 38: 439–445; discussion 445, 2003
 14. Feldman HI, Held PJ, Hutchinson JT, Stoiber E, Hartigan MF, Berlin JA: Hemodialysis vascular access morbidity in the United States. *Kidney Int* 43: 1091–1096, 1993
 15. Beathard GA, Arnold P, Jackson J, Litchfield T; Physician Operators Forum of RMS Lifeline: Aggressive treatment of early fistula failure. *Kidney Int* 64: 1487–1494, 2003
 16. Beathard GA: An algorithm for the physical examination of early fistula failure. *Semin Dial* 18: 331–335, 2005
 17. Rayner HC, Pisoni RL, Gillespie BW, Goodkin DA, Akiba T, Akizawa T, Saito A, Young EW, Port FK: Creation, cannulation and survival of arteriovenous fistulae: Data from the Dialysis Outcomes and Practice Patterns Study. *Kidney Int* 63: 323–330, 2003
 18. Saran R, Dykstra DM, Pisoni RL, Akiba T, Akizawa T, Canaud B, Chen K, Piera L, Saito A, Young EW: Timing of first cannulation and vascular access failure in haemodialysis: An analysis of practice patterns at dialysis facilities in the DOPPS. *Nephrol Dial Transplant* 19: 2334–2340, 2004
 19. Feldman HI, Joffe M, Rosas SE, Burns JE, Knauss J, Brayman K: Predictors of successful arteriovenous fistula maturation. *Am J Kidney Dis* 42: 1000–1012, 2003
 20. Huber TS, Ozaki CK, Flynn TC, Lee WA, Berceci SA, Hirneise CM, Carlton LM, Carter JW, Ross EA, Seeger JM: Prospective validation of an algorithm to maximize native arteriovenous fistulae for chronic hemodialysis access. *J Vasc Surg* 36: 452–459, 2002
 21. Rooijens PP, Burgmans JP, Yo TI, Hop WC, de Smet AA, van den Dorpel MA, Fritschy WM, de Groot HG, Burger H, Tordoir JH: Autogenous radial-cephalic or prosthetic brachial-antecubital forearm loop AVF in patients with compromised vessels? A randomized, multicenter study of the patency of primary hemodialysis access. *J Vasc Surg* 42: 481–486; discussions 487, 2005
 22. Robbin ML, Chamberlain NE, Lockhart ME, Gallichio MH, Young CJ, Deierhoi MH, Allon M: Hemodialysis arteriovenous fistula maturity: US evaluation. *Radiology* 225: 59–64, 2002
 23. Kalman PG, Pope M, Bhola C, Richardson R, Sniderman KW: A practical approach to vascular access for hemodialysis and predictors of success. *J Vasc Surg* 30: 727–733, 1999
 24. Fodor JG, Frohlich JJ, Genest JJ Jr, McPherson PR: Recommendations for the management and treatment of dyslipidemia. Report of the Working Group on Hypercholesterolemia and Other Dyslipidemias. *CMAJ* 162: 1441–1447, 2000
 25. Genest J, Frohlich J, Fodor G, McPherson R: Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: Summary of the 2003 update. *CMAJ* 169: 921–924, 2003
 26. Hubbard VS: Defining overweight and obesity: What are the issues? *Am J Clin Nutr* 72: 1067–1068, 2000
 27. Picard RR, Berk KN: Data splitting. *Am Stat* 44: 140–147, 1990
 28. Efron B, Tibshirani R: *An Introduction to the Bootstrap. Monographs on Statistics and Applied Probability*, New York, Chapman & Hall, 1993
 29. Brescia MJ, Cimino JE, Appel K, Hurwicz BJ: Chronic hemodialysis using venipuncture and a surgically created arteriovenous fistula. *N Engl J Med* 275: 1089–1092, 1966
 30. *Treatment of End-Stage Organ Failure in Canada. Canadian Organ Replacement Register*, Ottawa, Canadian Institute for Health Information, 2005
 31. US Renal Data System: *USRDS 2005 Annual Data Report: Atlas of Endstage Renal Disease in the United States. Incidence and Prevalence; Patient Characteristics*, Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2005
 32. Mendelssohn DC, Ethier J, Elder SJ, Saran R, Port FK, Pisoni RL: Haemodialysis vascular access problems in Canada: Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS II). *Nephrol Dial Transplant* 21: 721–728, 2005
 33. Woods JD, Turenne MN, Strawderman RL, Young EW, Hirth RA, Port FK, Held PJ: Vascular access survival among incident hemodialysis patients in the United States. *Am J Kidney Dis* 30: 50–57, 1997
 34. Obialo CI, Tagoe AT, Martin PC, Asche-Crowe PE: Adequacy and survival of autogenous arteriovenous fistula in African American hemodialysis patients. *ASAIO J* 49: 435–439, 2003
 35. Miller PE, Tolwani A, Luscyc CP, Deierhoi MH, Bailey R, Redden DT, Allon M: Predictors of adequacy of arteriovenous fistulas in hemodialysis patients. *Kidney Int* 56: 275–280, 1999
 36. Kinnaert P, Vereerstraeten P, Toussaint C, Van Geertruyden J: Nine years' experience with internal arteriovenous fistulas for haemodialysis: A study of some factors influencing the results. *Br J Surg* 64: 242–246, 1977
 37. Thomsen MB, Deurell SI, Elfstrom J, Alm A: What causes the failures in surgically constructed arteriovenous fistulas? *Acta Chir Scand* 149: 371–376, 1983
 38. Solomonson MD, Johnson ME, Ilstrup D: Risk factors in patients having surgery to create an arteriovenous fistula. *Anesth Analg* 79: 694–700, 1994
 39. Prischl FC, Kirchgatterer A, Brandstatter E, Wallner M, Baldinger C, Roithinger FX, Kramar R: Parameters of prognostic relevance to the patency of vascular access in hemodialysis patients. *J Am Soc Nephrol* 6: 1613–1618, 1995
 40. Wolford HY, Hsu J, Rhodes JM, Shortell CK, Davies MG, Bakhru A, Illig KA: Outcome after autogenous brachial-

- basilic upper arm transpositions in the post-National Kidney Foundation Dialysis Outcomes Quality Initiative era. *J Vasc Surg* 42: 951–956, 2005
41. Allon M, Ornt DB, Schwab SJ, Rasmussen C, Delmez JA, Greene T, Kusek JW, Martin AA, Minda S: Factors associated with the prevalence of arteriovenous fistulas in hemodialysis patients in the HEMO study. Hemodialysis (HEMO) Study Group. *Kidney Int* 58: 2178–2185, 2000
 42. Silva MBJ, Hobson RW 2nd, Pappas PJ, Jamil Z, Araki CT, Goldberg MC, Gwertzman G, Padberg FT Jr: A strategy for increasing use of autogenous hemodialysis access procedures: Impact of preoperative noninvasive evaluation. *J Vasc Surg* 27: 302–307, 1998
 43. Parmley MC, Broughan TA, Jennings WC: Vascular ultrasonography prior to dialysis access surgery. *Am J Surg* 184: 568–572, 2002
 44. Robbin ML, Gallichio MH, Deierhoi MH, Young CJ, Weber TM, Allon M: US vascular mapping before hemodialysis access placement. *Radiology* 217: 83–88, 2000
 45. Kian K, Vassalotti JA: The new arteriovenous fistula: The need for earlier evaluation and intervention. *Semin Dial* 18: 3–7, 2005
 46. Beathard GA, Settle SM, Shields MW: Salvage of the nonfunctioning arteriovenous fistula. *Am J Kidney Dis* 33: 910–916, 1999
 47. Lok CE, Oliver MJ, Rothwell DM, Hux JE: The growing volume of diabetes-related dialysis: A population based study. *Nephrol Dial Transplant* 19: 3098–3103, 2004
 48. Lok CE, OM, Su J, Bhola C, Hannigan N, Jassal SV: Arteriovenous fistula outcomes in the era of the elderly dialysis population. *Kidney Int* 67: 2462–2469, 2005
 49. Pisoni RL, Young EW, Dykstra DM, Greenwood RN, Hecking E, Gillespie B, Wolfe RA, Goodkin DA, Held PJ: Vascular access use in Europe and the United States: Results from the DOPPS. *Kidney Int* 61: 305–316, 2002
 50. Puskar D, Pasini J, Savic I, Bedalov G, Sonicki Z: Survival of primary arteriovenous fistula in 463 patients on chronic hemodialysis. *Croat Med J* 43: 306–311, 2002
 51. Wong V, Ward R, Taylor J, Selvakumar S, How TV, Bakran A: Factors associated with early failure of arteriovenous fistulae for haemodialysis access. *Eur J Vasc Endovasc Surg* 12: 207–213, 1996

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