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Can Failure of Vascular Access for Hemodialysis be Predicted by the Initial Blood Flow Measurement?

by

Felix Mauricio Monroy-Cuadros

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Abstract

Background: Clinical practice guidelines have supported vascular access surveillance programmes on the premise that the natural history of the vascular access will be altered by radiological or surgical interventions after vascular access dysfunction is detected. The primary objective of this study was to determine if the initial intra-access blood flow measurement predict the subsequent vascular access failure.

Methods: This was a retrospective study of all chronic hemodialysis patients followed by the Southern Alberta Renal Program (SARP) from January 1, 2002 to June 30, 2005. All patients had an initial intra-access blood flow measurement performed within two weeks after initial cannulation and successful use of the access for hemodialysis. All vascular access blood flow measurements were performed in a standardized fashion by using the ultrasound dilution technique. Mixed models were used to explore the relationship between initial blood flow and a group of independent variables, including age, sex, underlying disease, comorbidities, type and location of the procedure and surgeon.

Results: Eight hundred thirty one arteriovenous fistulae and three hundred fifty nine prosthetic grafts were available for evaluation. The primary failure was 10% for patients with fistulae and 30% for patients with prosthetic grafts. Multivariable analysis found that older age (>65 years OR 3.6, $p < 0.001$), history of diabetes (OR 2.3, $p = 0.007$), history of smoking (OR 4.3, $p < 0.001$), the presence of forearm fistulas (OR 4.0, $p < 0.001$), and low initial intra-access blood flow (<500 ml/min, OR 29, $p < 0.001$) were independently associated with vascular access failure in this cohort of patients. In patients with AVG a multivariable model found older age (>65 years OR 3.2, $p < 0.001$), history

of diabetes (OR 3.5, $p < 0.001$), history of peripheral vascular disease (OR 2.5, $p < 0.005$), and initial intra-access blood flow (< 650 ml/min, OR 31, $p < 0.001$) were independently associated with vascular access failure.

Conclusion: This study produced findings to help identify a group of patients at high risk of vascular access failure and for whom the current guidelines of access monitoring (monthly) should be followed given the high incidence of vascular access failure. However for the group of patients considered low risk these guidelines may be excessive. Identification of this set of high risk patients provides valuable information for physicians, patients and their families, and increased the efficacy of care in these high risk patients. Knowledge of the long term outcomes following vascular access placement in this high risk population has a great impact on health care. Also, health care system cost may decrease if minimal surveillance is provided for patients in the low risk

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List of Symbols, Abbreviations, and Nomenclature

Symbol	Definition
AVF	arteriovenous fistula
AVG	arteriovenous graft
CAPD	continuous ambulatory peritoneal dialysis
CKD	chronic kidney disease
CI	confidence interval
ESRD	end-stage renal disease
GFR	glomerular filtration rate
IABF	intra-access blood flow
NKF-DOQI	National Kidney Foundation Dialysis Outcomes Quality Initiative
NKF-K/DOQI	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
OR	odds ratio
PTFE	polytetrafluoroethylene
RRT	renal replacement therapy
SARP	Southern Alberta Renal Program
SD	standard deviation
VAF	vascular access failure

CHAPTER ONE: THE RESEARCH PROBLEM

1.1 Introduction

Chronic kidney disease (CKD) is the degree of irreversible loss of renal function that is incompatible with life. CKD is a worldwide public health problem with increasing prevalence, poor outcomes and high costs [1, 2]. During the last two decades, the United States Renal Data System has documented an epidemic of CKD in the United States, and similar increases in CKD incidence have been reported for other industrialized and developing countries [3-9]. The epidemic is illustrated by the United States population from 219 per million in 1991 to 334 per million persons in 2000, an increase of 51 % during the decade [10]. Individuals aged 75 years and older have experienced the greatest increase in incidence (98% over the last decade), attributable in part to improved survival of individuals with cardiovascular disease and diabetes mellitus and expanded access to renal replacement therapy (RRT) for older patients [11-13]. CKD incidence rates during the same period also increased among younger Americans by 1% for those aged less than 20 years, 27% for individuals 20 to 44 years, 47% for those 45 to 64 years, and 48% for those 65 to 74 years [10].

In patients with ESRD, death will occur without RRT. Hemodialysis is the most common form of continuous RRT. The most recent data from the Canadian Organ Replacement Register show that over 5000 new patients began RRT in 2004. This corresponds to an annual incidence of about 1.5 new cases per 10000 population, or 5 cases per 10000 km

of the total landmass [13]. In the Southern Alberta Renal Program (SARP), there were 590 patients (454 per million) receiving hemodialysis by the end of 2002. CKD and end-stage renal disease (ESRD) result from a large number of diseases that are either systemic and damage the kidney or are intrinsic to the kidney. The most common causes of ESRD are diabetes (44% of patients in 2004), hypertension (30%), and glomerulonephritis (12%).

Because hemodialysis involves extracorporeal passage of the blood through the dialysis equipment for 3-5 hours several times weekly, a critical requirement is repetitive, reliable access to the circulation [14-21]. Vascular access has been called the "Achilles heel" of hemodialysis [22], because construction of these accesses and the management of subsequent complications can be time-consuming and frustrating for both surgeons and patients and expensive for the health care system. Ideally, access to the circulation should meet three criteria: 1) it should be suitable for repeated use, 2) it should allow for a blood flow suitable to conduct modern high-efficiency dialysis, and 3) the complication rate should be minimal. Currently there are three types of hemodialysis vascular access: 1) native arteriovenous fistulas (AVFs) 2) arteriovenous grafts (AVGs) and 3) central venous catheters [14-21]. AVFs and AVGs are preferred over catheters for permanent vascular access. These vascular access devices do an excellent job performing the first two functions, but do have a substantial complication rate [14-17].

Complications of hemodialysis vascular access have emerged as a major cause of patient morbidity and major cost to the end-stage renal disease program. Health care

organizations planning for a capitated environment estimate as much as 25% of the total cost of the ESRD program may actually be spent on the maintenance of vascular access [23-25]. Thus, maintenance of access to the circulation has emerged not only as a major cause of patient morbidity, but is one of the single largest expenses in the care of ESRD

Hemodialysis access failure and morbidity have been carefully evaluated. The clinical practice guidelines of The National Kidney Foundation Dialysis Outcomes Quality Initiative (NKF-DOQI) [19, 26] support vascular access blood flow monitoring on the premise that the natural history of the access will be altered by radiological or surgical intervention if access dysfunction is detected.

The rationale for surveillance is grounded in what has been termed the “dysfunction hypothesis”, which states that stenosis causes access dysfunction and this dysfunction reliably precedes and accurately predicts vascular access failure [27]. Therefore, if a particular surveillance technique is to be successful at predicting access failure, several assumptions of this dysfunction hypothesis must be true. Specifically, the measurements must be reproducible, stenosis should progress slowly enough so that there is time to intervene before failure, and other factors outside of stenosis, such as hypercoagulability, should not abrogate or appreciably confound the surveillance technique’s prediction of thrombosis. An ideal access monitoring test would predict nearly all patients who will develop vascular access failure, with a low false positive result. Most monitoring techniques that have been developed rely on detecting hemodynamic dysfunction, usually a reduction in blood flow.

1.2 Gaps in the Knowledge

Although the intra-access blood flow (IABF) has been identified as a reliable indicator of short-term thrombosis and failure risk [17, 22], whether the initial blood flow measured after the first successful cannulation and use of the vascular access is predictive of failure has not been reported.

1.3 Purpose of the Study

The main objectives of this study are:

- To explore the association between vascular access failure and initial IABF in patients receiving chronic RRT with AVFs.
- To explore the association between vascular access failure and the initial IABF in patients receiving chronic RRT with AVGs.

Secondary objectives are:

- To determine patient characteristics associated with vascular access failure in patients with AVFs and AVGs.
- To determine vascular access characteristics associated with vascular access failure in patients with AVFs and AVGs

1.4 Research Question

This study was guided by the following research questions:

1. Can failure of vascular access for hemodialysis be predicted by the initial IABF measurement?
2. Can the measurement of baseline IABF predict the subsequent failure of AVFs or AVGs?

1.5 Significance of this Study

If the initial blood flow can be used as a predictor of access failure, then at-risk patients could be more closely monitored to allow for early detection of dysfunction and for rapid intervention. As well, patients not in the high risk group could be monitored less often, thus reducing medical costs and increasing patient quality of life.

CHAPTER TWO: LITERATURE REVIEW

A search of several bibliographic search engines, including MEDLINE, EMBASE, CINAHL, and PUBMED from their inception dates, was performed in January 2008 using the OVID interface. The search was done using the following MESH terms: kidney disease, dialysis, arteriovenous fistulae, arteriovenous grafts, vascular access, vascular access failure and thrombosis and access monitoring with the limitation of requiring an abstract. After the inspection of the abstracts, the articles written in either English or Spanish that seemed most relevant were selected for a more thorough examination. Recent review articles were used to identify relevant articles in the area of CKD, ESRD, hemodialysis vascular access, access failure and IABF measurement and monitoring. The reference list of relevant articles and reviews retrieved was scrutinized to identify additional studies.

2.1 Definition and Etiology of Chronic Kidney Disease

CKD is defined by the presence of sustained abnormalities of renal function and may terminate in ESRD [28]. CKD has two characteristics. First, there is chronicity because the kidney damage of CKD is rarely repaired and loss of function persists, unlike the course of acute kidney failure. Second, loss of kidney function generates even more kidney damage so that CKD progressively worsens, even if the disorder that caused it becomes inactive. CKD has an important clinical and societal consequence of reduced quality of life and reduced life expectancy.

CKD and ESRD result from a large number of diseases that are either systemic and damage the kidney or are intrinsic to the kidney (Table 2.1). In the last few decades, the distribution of the primary causes of ESRD has changed dramatically [28]. In 1980, 18% of ESRD was caused by hypertension, 16% by glomerulonephritis, and 15% by diabetes. In 2004, hypertension as a cause had almost doubled to 30% and diabetes had almost tripled to 44%. In contrast, glomerulonephritis had decreased to 12%. In view of the increasing prevalence of diabetes [29, 30], this disease will remain as the primary cause of ESRD in the future, and the prevalence of ESRD will continue to increase.

Table 2.1 Causes of Chronic Renal Failure

Diabetic glomerulosclerosis	
Hypertensive nephrosclerosis	
Glomerular disease	
	Glomerulonephritis
	Amyloidosis, light chain disease
	Systemic lupus erythematosus, Wegener's granulomatosis
Tubulointerstitial disease	
	Reflux nephropathy (chronic pyelonephritis)
	Analgesic nephropathy
	Obstructive nephropathy (stones, benign prostatic hypertrophy)
	Myeloma kidney
Vascular disease	
	Scleroderma
	Vasculitis
	Renovascular renal failure (ischemic nephropathy)
	Atheroembolic renal disease
Cystic diseases	
	Autosomal dominant polycystic kidney disease
	Medullary cystic kidney disease
(From [31], Table 131-1)	

2.2 Physiopathology of CKD Progression

Despite the many diseases that can initiate kidney injury, three common pathways are responsible for the progression of kidney disease [30]. First, as a consequence of the initial kidney injury, the remaining nephrons compensate for the reduction in nephron mass by increasing the single nephron filtration rate [30, 32-35]. Elevated glomerular pressures drive this hyperfiltration. Glomerular hyperfiltration has initial adaptive effects by maintaining the glomerular filtration rate (GFR), but may subsequently lead to progressive glomerular injury and ultimately ESRD. Second, abnormal glomerular permeability is common in glomerular disorders with proteinuria being the clinical consequence. Evidence has accumulated that proteinuria might be a factor in causing tubulointerstitial injury, which is a prime risk factor for subsequent progression in all forms of glomerular diseases studied [30, 36]. Third, a direct consequence of the renal injury is a syndrome characterized by hypertension, anemia, renal bone disease, nutritional impairment, neuropathy, impaired quality of life, and reduced life expectancy. At least some of these clinical consequences, such as hypertension, may further impair renal function.

2.3 Classification

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) proposed a definition and classification scheme for CDK in 2002 [28] that has since been widely adopted both within and outside of the United States and Canada [37-

41]. The NKF-K/DOQI guidelines define CKD on the basis of kidney damage and/or reduced kidney function. Kidney damage may be confirmed through a variety of methods including histologic evidence of kidney disease, abnormalities in the composition of blood or urine, or abnormal findings on renal imaging. Reduced kidney function is defined by a GFR below 60 ml/min/1.72 m^2 body surface area for at least 3 months [28] or by evidence of kidney damage with an abnormal GRF. A cutoff GFR of 60 ml/min/1.73 was selected because it represented a decrement of approximately half of normal renal function and because its use avoided the classification of many older individuals who may have a mild reduction in their GFR [42].

The NKF-K/DOQI classification defines five stages of CKD with increasing degree of impaired kidney function (Table 2.2). At each stage, patients can benefit from measures that delay or prevent the progressive loss of renal function, modification of medications with renal clearance, avoidance of nephrotoxins, and reduction of cardiovascular risk factors [43, 44]. Patients who advance to CKD stage 3 require increased attention to control hypertension, anemia, renal bone disease, and nutrition. Recognition and early referral of patients who advance to stage 4 and 5 is important for appropriate initiation of RRT [43, 45-59].

Table 2.2 Stages of CKD

Stage	Description	GFR (mL/min/1.73m²)
1	Kidney damage with normal or increased GFR	≥ 90
2	Kidney damage with mild decreased GFR	60 - 89
3	Moderate decreased GFR	30 - 59
4	Severe decreased GRF	15 - 29
5	Kidney failure	< 15 (or dialysis)

(From [31, 60, 61])

2.4 Prevalence of CKD

Using the NKF-K/DOQI schema, the estimated prevalence of each stage of CKD in the United States is stage 1, 3.3% (5.9 million individuals); stage 2, 3% (5.3 million); stage 3, 4.3% (7.6 million); and stage 4, 0.2% (4 million) [60, 62-64]. Canadian prevalence rates using this schema are not specifically available, but it is estimated that prevalence rates are about $1/10^{th}$ of rates in the United States (based on the size of the national populations). The prevalence of CKD increases with age and is higher among individuals with hypertension and diabetes and may be associated with the presence of cardiovascular disease.

2.5 Risk factor for progression of CKD to ESRD

There are a number of risk factors in patients with CKD that are considered to be a high risk for developing ESRD: 1) patients with hypertension, 2) patients with diabetes mellitus, 3) patients with cardiovascular disease, and 4) hyperlipidemia, 5) smoking, 6) obesity, 7) proteinuria/microalbuminuria and 8) family members of incident ESRD patients [65]. The first six risk factors may also be risk factors associated with vascular access failure in patients on hemodialysis.

2.5.1 Hypertension

Hypertension is the second most common cause of ESRD in the United States and Canada, accounting for 23% of incident ESRD patients between 1996 and 2000 [28].

Hypertension is also an important modifiable risk factor for progressive CKD, regardless of the initial cause of kidney injury. Observational studies have established that patients with hypertension are at high risk for progressive renal insufficiency, and this risk is not unique to patients with malignant or accelerated hypertension [65-69]. Evidence from clinical trials shows that blood pressure reduction reduces the rate of loss of renal function and progression to renal failure, and this information has been incorporated into clinical practice guidelines [70-78].

2.5.2 Diabetes mellitus

Diabetes mellitus is the most common cause of ESRD, accounting for nearly 45% of all new cases of ESRD between 1996 and 2000 [28, 64] Diabetes as a cause of ESRD is increasing at a 10% per year rate, and if sustained, the number of patients with diabetes-caused ESRD will double within 7 years. Strict control of hyperglycemia reduces the rate of loss of renal function and progression to renal failure among patients with both type 1 and type 2 diabetes mellitus [79-83].

2.5.3 Cardiovascular disease

Cardiovascular disease, being present at baseline in a Canadian cohort of patients in different stages of CKD, increased the probability of progression to ESRD by 50% [84]. Patients undergoing coronary angiography, patients treated with percutaneous coronary interventions and coronary artery bypass surgery, and participant in clinical trials of atherosclerotic disease are at increased risk of CKD [84-101]. Patients with heart failure have decreased kidney perfusion. Patients with atherosclerotic coronary artery disease

have a higher prevalence of renovascular atherosclerosis, and there is a correlation between extent of atherosclerosis and degree of glomerular scaring [102, 103]. The prevalence of glomerulosclerosis is higher in patients with moderate to severe atherosclerosis (15%) compared with individuals with mild disease (8%).

2.5.4 Hyperlipidemia

Hyperlipidemia has been associated with a two-fold increase risk of developing CKD, and may be associated with CKD progression [104-108]. Hyperlipidemia is also a risk factor for cardiovascular disease. Lipid-lowering therapy may be directly renoprotective or protective by modifying cardiovascular effects on renal function.

2.5.5 Smoking

Smoking is a risk factor for genitourinary disease, including cancer, proteinuria and CKD [109, 110]. Patients with previous or current history of smoking have three-fold increased risk of proteinuria [111, 112]. Recent observational studies have reported that smoking cessation is associated with reduced risk of progressive renal injury [111, 113].

2.5.6 Obesity

The emergence of obesity as a growing public health problem has led to its investigation as a risk factor for kidney disease. Obesity, defined as body mass index >30 kg/m^2, is associated with higher risk for the development of proteinuria and reduced kidney function [114, 115]. Obesity also appears to predispose the development of focal

segmental glomerulosclerosis [116]. Several studies have suggested a benefit of weight loss on preserving kidney function in obese patients [117-121].

2.5.7 Proteinuria/microalbuminuria

There is abundant evidence in support of a strong and independent association between microalbuminuria and cardiovascular disease. The presence and degree of proteinuria are strong risk factors for progressive kidney disease in both diabetic and non-diabetic kidney disease patients [122-125]. Higher levels of urine protein excretion increase the risk of progressive kidney disease by nearly six-fold for each 1 g/d higher protein excretion [125].

2.5.8 Family history

Family history was first reported as a risk factor for ESRD by Ferguson et al. [126], who noted that a family history of first-or second-degree relative with CKD was reported by 26% of prevalent ESRD patients compared to 11% of community controls. There are several hereditary kidney diseases that follow specific inheritance patterns and are due to single gene mutations. Although the majority of kidney diseases are not associated with identifiable genetic defects, the presence of familial aggregation of kidney disease suggests a multi-factorial etiology involving a genetic component with regard to susceptibility [127-129]

2.6 Impact of Chronic Kidney Disease on Patient Survival

According to the United States Renal Data System report, once RRT is initiated, the range of the expected remaining life span is 7 to 11 years (varies with race) for dialysis patients aged 40 to 44, and 4 to 6 years for those 60 to 64 years of age [130, 131]. These values are only slightly better than those for patients with lung cancer and are much worse than in the general population (30 to 40 years for those aged 40 to 44, and 15 to 23 years for individuals aged 60 to 64).

It is well established that inadequate dialysis is a contributor to lower overall survival. This has important implications because more intensive dialysis, particularly above a certain threshold value, may improve survival.

2.7 Causes of Death

For patients undergoing dialysis cardiac causes combined account for 48% of all deaths. Infection, cerebrovascular disease, and malignancy account for 15%, 6% and 4% respectively [132-135]. The predominant cause of cardiac death was sudden death, accounting for 39% of all deaths, followed by acute myocardial infarction (24%), cardiomyopathy (10%), and atherosclerotic heart disease (9%). The high prevalence of both coronary artery disease and left ventricular hypertrophy contributed to these cardiac deaths.

Disruption of the skin barrier by the vascular access in hemodialysis patients and the peritoneal catheter in peritoneal dialysis patients are factors which are partly responsible for the high risk of death due to infection. Septicemia due to the vascular access and peritonitis is responsible for 8% of the deaths [135]. In addition, there is evidence that patients with ESRD have defects in cellular immunity, neutrophil function, and complement activation.

2.8 Treatment of Irreversible Renal Insufficiency

Unlike other forms of end-stage organ failure, ESRD is unique in having three modalities of therapy: 1) hemodialysis, 2) peritoneal dialysis, and 3) renal transplantation. Each form of RRT has its unique risks and benefits. All three modalities of RRT have evolved significantly over the last four decades. Although this thesis will focus on patients receiving hemodialysis, for completeness, a short review of the other major modality of dialysis is included.

2.8.1 Peritoneal dialysis

This procedure uses the patient's own peritoneal membrane for removal of waste products and fluid. During peritoneal dialysis, 2 to 3 L of dialysate solution, containing electrolytes in physiologic concentrations and varying concentrations of glucose, is instilled into the peritoneal cavity via a peritoneal catheter. After a specified dwell time, varying between 3 and 6 hours per exchange, the fluid is drained and the process is repeated. The removal of solute from the body depends on the development of a

concentration gradient between the blood and peritoneal fluid and occurs by diffusion across the peritoneal membrane. Osmotic ultrafiltration is achieved by the addition of increasing concentrations of glucose to the dialysate solution. The osmotic pressure generated by the glucose draws water from the extra-cellular fluid and tissues into the peritoneal fluid. More than 20% of patients with ESRD in the United States and more than 50% in the United Kingdom are receiving continuous ambulatory peritoneal dialysis (CAPD). CAPD offers a number of potential advantages: 1) there is no need for vascular access, a major challenge in diabetic patients, young children, and patients with severe vascular disease; 2) it can be performed without anticoagulation, decreasing the potential risk of bleeding; 3) because it is a slow, continuous process, it avoids the marked hemodynamic and osmotic shifts associated with hemodialysis; and 4) there are quality of life advantages because of independence from hemodialysis machines.

Despite these advantages, there are disadvantages to CAPD, of which infection is the most important and represents the most frequent cause for discontinuation of therapy. Other complications include mechanical problems including catheter malfunction, catheter migration, and abdominal hernias due to increased intra-abdominal pressure with large volumes of dialysate. A number of metabolic complications may also occur, including hyperglycemia and hypertriglyceridemia from high glucose loads, weight gain, and protein loss.

2.8.2 Hemodialysis

Hemodialysis is the most common form of RRT used in the SARP for ESRD. Kolff first employed hemodialysis in the late 1940s for the treatment of acute renal failure. The development of vascular access by Scribner in the early 1960s enabled the use of hemodialysis as an ongoing therapy for ESRD. However, it was not until 1973, when the United States Congress recognized ESRD as a catastrophic illness and approved Medicare funding for hemodialysis patients, that hemodialysis achieved widespread availability. In the United States, more than 200,000 individuals are on hemodialysis, a point of prevalence of 731 subjects per million population. Because hemodialysis involves extracorporeal passage of the blood through the dialysis equipment for 3-5 hours, several times weekly, a critical requirement is repetitive, reliable access to the circulation [20, 21, 136-140].

Vascular access has been called the “Achilles heel” of hemodialysis [137, 141], because construction of these accesses and the management of subsequent complications can be time-consuming, frustrating for both surgeons and patients, and costly for the health care system. Ideally, access to the circulation should meet three criteria: 1) it should be suitable for repeated cannulation, 2) it should allow for a blood flow suitable to conduct modern high-efficiency dialysis, and 3) the complication rate should be minimal.

2.9 Vascular Access

2.9.1 History of vascular access

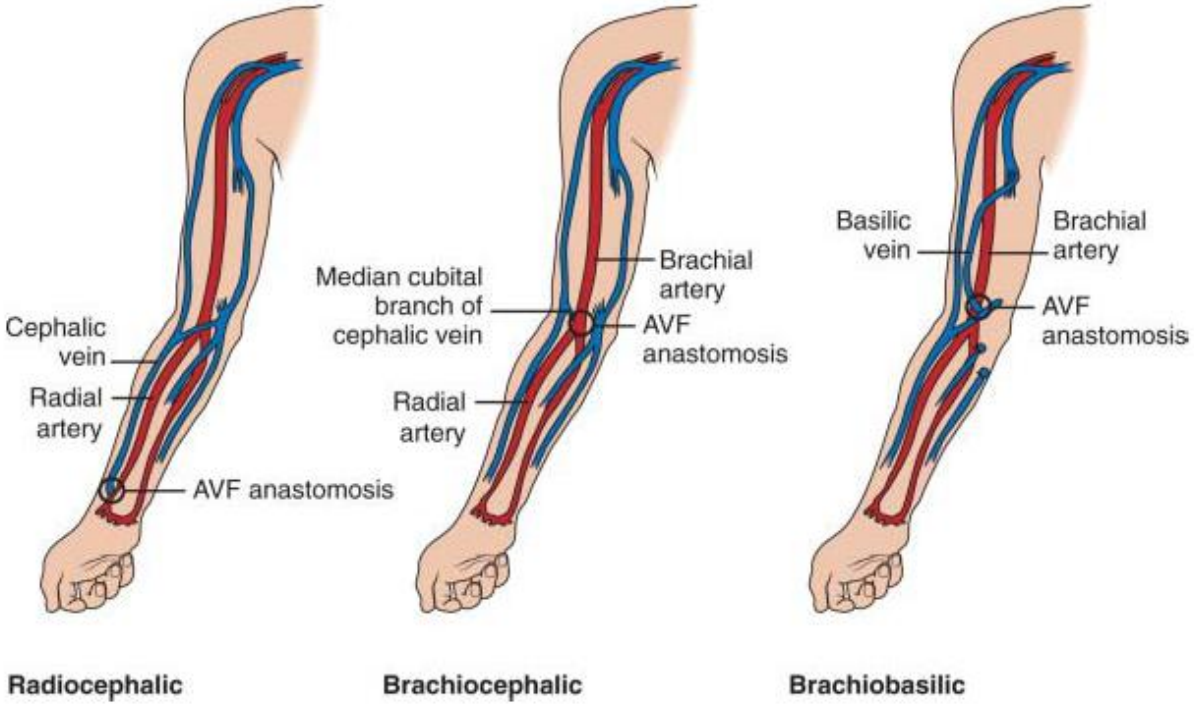
"As we did not know at all how our first patient would react to the dialysis we started with repeatedly dialyzing small proportions of blood. In the end we succeeded in keeping the percentage of urea at the same level for 26 days, after that no serviceable veins were available" [142]. The 29-year-old female patient suffering from malignant hypertension died 1 week after her last dialysis treatment. This text fragment by Willem Kolff and co-workers, published in 1944, was not only part of the first report of successful hemodialysis treatment in humans, it also describe the crucial importance of an adequate access to the blood circuit that is required for chronic hemodialysis.

It took another 16 years before Quinton and Scribner introduced the first permanent vascular access: the Scribner shunt [143]. This device consisted of 2 Teflon tubes connecting the patient to the dialyser; one tube was inserted into a suitable peripheral artery and one into a suitable vein. After treatment, the circulatory access was kept open by connecting the two tubes outside the body using a small U-shaped Silastic device over a stainless steel plate. The major disadvantages of Scribner shunts were high thrombosis rate and infection rates, resulting in a limited shunt and hence patient life span.

In 1966, Brescia and Cimino solved the blood access problem with a surgically created AVF between the radial artery and a vein [144]. This new vascular access was able to deliver flow rates of 250-300 mL/min for unlimited intervals. Results were satisfactory:

13 AVFs (87%) functioned without any complication and two failed before cannulation. The patients were relatively young, and all but one had chronic glomerulonephritis as primary diagnosis for renal failure [144]. Nowadays, the Brescia-Cimino (radio-cephalic) AVF is still the preferred type of vascular access [139, 140]. Other common native variations are brachio-cephalic, brachio-basilic, and perforating vein AVFs in the elbow and upperarm [138, 140].

Fig. 2.1 Types of autogenous arteriovenous fistulas

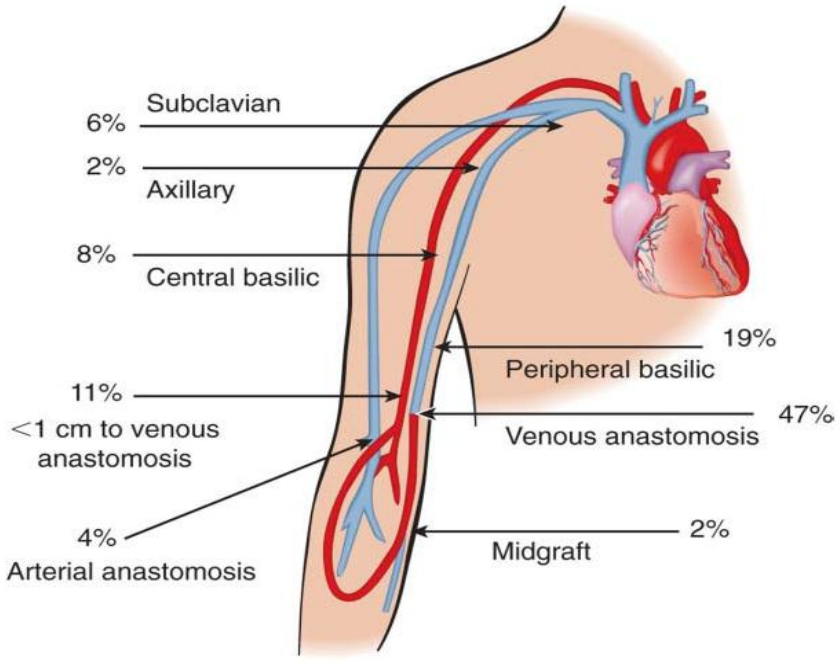


(From [145], p. 344)

Due to inclusion of overweight and obese ESRD patients as well as ESRD patients with insufficiently sized or stenotic vessels, AVF creation did not always result in a vascular

access with sufficient access blood flow for efficient hemodialysis treatment. Hence, the AVG was introduced in order to create an artificial conduit for cannulation. Saphenous vein grafts, bovine heterografts, homologous vein grafts and human umbilical vein grafts have all been used for hemodialysis purposes in the past [146]. However, the expanded polytetrafluoroethylene (PTFE) graft, introduced in 1973 [147], is the most widely used graft today [146]. Alternative synthetic materials such as plasma tetrafluoroethylene or polyurethane have not proven to be superior to PTFE [146]. The 2006 NKF-DOQI working group recommended a graft either of synthetic or biological material [140]. The graft can be straight or looped with a diameter ranges between 4 and 8 mm. Grafts can be modified to be tapered [148], thin walled [149], and reinforced [150].

Fig. 2.2 Upperarm Loop graft



(Modified from [151])

Common graft locations are straight forearm (radial artery to cephalic vein), looped forearm (brachial artery to cephalic vein), straight upper arm (brachial artery to axillary vein), or looped upper arm (axillary artery to axillary vein). The 2006 NKF-DOQI working group prefers a forearm loop graft, rather that a straight configuration [140]. Leg grafts, looped chest grafts, axillary-axillary (necklace), and axillary-atrial grafts have also been constructed [152]. In the 2005 Canadian and 2006 United States guidelines, the recommended permanent vascular access are, in order of preference, the wrist (radio-cephalic) fistula [139, 140], the elbow (brachio-cephalic) fistula, the transposed brachial-basilic fistula [140], followed by forearm loop grafts, upper arm grafts or, if all upper arm sites are exhausted, chest wall or leg grafts [140]. Use of long term central venous catheters is discouraged.

Tunneled cuffed catheters are dual lumen catheters usually composed of silicone or polyurethane composites. The composites are softer than polyurethane, but are stronger than silicone. These catheters are most commonly placed in the internal jugular vein with the tip in the right atrium, and then tunneled superficially to exit on the upper anterior chest. Right-sided catheters malfunction less than left-sided catheters, and subclavian catheters are avoided to prevent subclavian stenosis [140]. AVFs and AVGs are preferred over catheters for permanent vascular access. Catheters are often used as temporary access while awaiting surgical construction or modification of a fistula or graft, or as a permanent access if surgical accesses are not possible.

2.9.2 Comparison of fistulae and grafts

Fistulae and grafts differ according to failure rates, determination of access maturity, patency, complications, and peri-operative morbidity. Fistulas are preferred to grafts because of higher long-term patency rates, and lower rate of complications [140].

2.9.3 Determination of access maturity

Although some fistulas mature within weeks, others require up to 6 months before they provide reliable hemodialysis access. One empiric measure of maturity, the time to first cannulation, appears to vary significantly by country, with nearly 30 days being the median period for Japan and Italy, and almost 100 days for the United States and United Kingdom [153-155]. Grafts can be cannulated for hemodialysis earlier than fistulas. Grafts can usually be cannulated within weeks, and some centers have successfully cannulated grafts within days of surgery [156].

2.9.4 Patency/primary and secondary failure

Fistulas are more likely than grafts to experience primary failure, defined as an access that does not provide reliable hemodialysis. The primary failure rates of radio-cephalic, brachio-cephalic, and brachio-basilic fistulas are approximately 24-35%, 9-12% and 29-36%, respectively [153, 154]. The risk of primary failure is increased in wrist fistulae and in patients who are older, obese, nonwhite, female, diabetic, and/or have peripheral vascular or cardiovascular disease [153, 154].The primary failure rates are 0-13% and 0-3% for forearm and upperarm grafts, respectively [157, 158]. The lower risk of primary

failure with grafts is offset by the increased risk of complications and secondary failure over time.

Although native fistulas have a high rate of primary failure, their long-term patency is superior because the risk of secondary failure is low. A radio-cephalic fistula that matures may function for up to 20 years. The 5-year and 10–year cumulative patencies for radio-cephalic fistulas are reported to be 53% and 45%, respectively [153, 159]. By comparison, cumulative patency for PTFE grafts at one, two, and four years is approximately 67%, 50% and 43%, respectively [160]. In general, PTFE forearm grafts have lower cumulative patency than upper arm grafts.

2.9.5 Complications of the vascular access

Neither fistulas nor grafts are physiological. The vascular remodeling and adaptation to high-flow conditions, as well as the effects of repeated cannulation, play a pivotal role in causing complications such as thrombosis, aneurysm formation, infection, ischemic changes, venous hypertension, neuropathy, and cardiovascular problems [136, 161]. Complications of hemodialysis vascular access have emerged as both a major cause of patient morbidity and as a major cost to ESRD programs, the latter accounting for up to 25% of all hospital stays and up to 50% of the first year hemodialysis cost. In its latest report, the United States Renal Data System estimated that the cost for access morbidity approaches US$ 8000 per patient per year. Health care organizations planning for a capitated environment estimate that as much as 25% of the total cost of the ESRD program may actually be spent on the maintenance of vascular access. Problems with

vascular access are also a major contributor to inadequate hemodialysis [15, 16]. In an analysis of North American dialysis patients in the year 2000, approximately 14% did not receive adequate dialysis, mostly because of low flow rates from access dysfunction. Inadequate dialysis leads to increased morbidity and mortality, decreased quality of life, and increased healthcare costs, with extended dialysis times. Thus, maintenance of access to the circulation has emerged as a major cause of patient morbidity, and as one of the single largest expenses in the American and Canadian ESRD systems.

Chronic hemodialysis access complications include thrombosis, infection, aneurysm and pseudo-aneurysm formation, distal ischemia, venous hypertension, heart failure, median nerve injury, and seroma formation. Thrombosis, infection, and seromas appear to occur more frequently with grafts than with fistulas.

Thrombosis is the most common complication of permanent vascular access, and when not correctable, accounts for 80-85% of AV access loss. The Dialysis Outcomes and Practice Patterns Study found that grafts are 3.8 times more likely to require a thrombectomy and 3.0 times more likely to require access intervention than native fistula [72]. The major predisposing factor for thrombosis is anatomic venous stenosis, responsible for 80-85% of thromboses [20, 21]. Other causes of thrombosis include arterial stenoses and non-anatomic problems, such as excessive post-dialysis fistula compression, hypotension, increased hematocrit levels, hypovolemia, and hypercoagulable states [18, 20, 21, 162, 163].

Vascular access stenosis is initiated by endothelial cell injury, which leads to the up-regulation of adhesion molecules on the endothelial cell surface. Subsequent leukocyte adherence to damaged and activated endothelium causes the release of chemotactic and mitogenic factors for vascular smooth muscle cells, thereby enhancing smooth muscle cell migration and proliferation [164-166].

Additional factors that contribute to the myointimal proliferation and fibromuscular hyperplasia include shear stress generated by the turbulent blood flow [167, 168] and the mismatch in elastic properties around the anastomosis, leading to excessive mechanical stretch [169]. Activated platelets and inflammatory cells also secrete oxidants and other toxins that directly injure the vessel wall [170].

In AVFs, about 50% of all stenoses leading to reduced flow are close to the AV anastomosis along the first venous segment. This is probably caused by the devascularization of the venous wall during dissection. More centrally located stenoses are observed within cannulation areas or venous segments in the upper arm. In AVGs, stenoses along the inflow tract and the graft itself are rarely seen. Predominantly, stenoses are seen in the outflow tract, usually as graft-vein stenosis.

Treatment of venous stenosis is important clinically because it preserves the access sites for future use. Treating vascular access thrombosis involves both removal of the thrombotic material and correction of the underlying venous or, more rarely, arterial stenosis. Performing a thrombectomy alone without correcting any underlying stenosis

will result in an inevitable recurrence within a short period of time. In native AVFs, thrombectomy should be performed as early as possible, usually within days. Waiting for revision often causes an appositional growth of the thrombus and a substantial loss of venous capital. In AVGs, thrombectomy can be done successfully even after a couple of months. However, an immediate procedure is preferred.

Infection accounts for approximately 20% of vascular access loss. The risk of infection for grafts averages 10%, while the risk for transposed fistulas is 5%, and less than 2% for non-transposed fistulas [158, 171-174]. The vascular access is the source of the majority of bacteremia in hemodialysis patients. *Staphylococcus aureus*, and less commonly *Staphylococcus epidermidis*, are the predominant pathogens [160, 175]. Predisposing factors to infection include pseudoaneurysms or perifistular hematomas, often due to inappropriate graft cannulation, severe pruritus over needle sites, the use of hemodialysis fistulas for intravenous drug abuse, and manipulation of the access via secondary surgical procedures [176]. Bacteremia frequently occurs during cannulation without actual fistula infection. Infection occurring in native fistulas can usually be treated with intravenous antibiotics and, if necessary, surgical drainage [140, 177]. Graft infection may require complete excision to eradicate the infection, which results in loss of the access [178].

Aneurysms and pseudoaneurysms are relatively infrequent complications of vascular access that usually result from repeated cannulation in the same area of the access. True aneurysms and pseudoaneurysms occur in up to 5% and 3% of grafts and fistulas, respectively. Pseudoaneurysms are a particular problem with PTFE grafts, occurring as

the graft material deteriorates with prolonged use. Initial fears that the current movement toward daily hemodialysis would lead to accelerated graft loss have not been borne out [177].

Placement of an AV access can result in distal hypoperfusion of the extremity in patients with severe peripheral vascular disease due to shunting ("steal") of arterial blood flow into the fistula. Symptomatic steal occurs in approximately 1-20% of patients receiving an upper extremity access [179, 180]. Acute ischemic symptoms characterized by an absent pulse or a cold extremity, warrant immediate surgical correction to prevent the development of permanent injury. These severe complications may be more common among diabetics and the elderly [177-181]. More commonly, less severe symptoms and signs, such as paresthesias, and a sense of coolness with retained pulses, usually improve over a period of weeks with the development of collateral blood flow. Careful, frequent observations and an alert nursing staff are required in this setting. Hand ischemia from steal may require intervention (e.g. distal revascularization interval ligation) or complete ligation in severe cases.

Venous hypertension occurs in approximately 3% of fistulas and grafts [158, 159, 172, 182] and is usually related to central vein stenosis [173]. This can cause severe upper limb edema, skin discoloration, access dysfunction, and peripheral ischemia with resultant fingertip ulceration. In most cases, the underlying venous pathology follows ipsilateral central venous catheter placement with consequent venous stenosis. While arm swelling is common following access surgery, an underlying venous outflow problem

will be present in a quarter of cases if it persists beyond two weeks. Venous duplex ultrasound is usually sensitive enough to demonstrate dilated central veins with possible reversal of flow, although, in some cases, upper limb venography is required. Treatment is aimed at correcting the underlying vascular problem, either via a percutaneous or direct surgical approach.

Vascular access-related cardiac decompensation is a rare complication (<1%), even in patients with underlying cardiac dysfunction [159, 179, 183]. Patients with an AVF do not have higher rates of heart failure than patients with an AVG or catheter [184], but they may experience an increase in preexisting left ventricular hypertrophy following the creation of the fistula [185].

Median nerve dysfunction in long-term dialysis patients is most often due to local amyloid deposition, leading to carpal tunnel syndrome. The vascular access also may contribute to this problem in some cases via compression of the median nerve (due to the extravasation of blood or fluid) or via ischemic injury by a vascular steal effect [181, 186, 187].

Ultra-filtration of plasma across a PTFE graft ("weeping syndrome") occurs occasionally, forming a pocket of serous fluid that can become firm and gelatinous over time [188]. Seromas typically form at the arterial end of the graft where intraluminal pressure is higher, although the same process can occur at the distal end if there is significant central venous obstruction [189]. Seromas usually form slowly, beginning within 30 days after

implantation of the graft. However, a more acute presentation mimicking a hematoma has been reported.

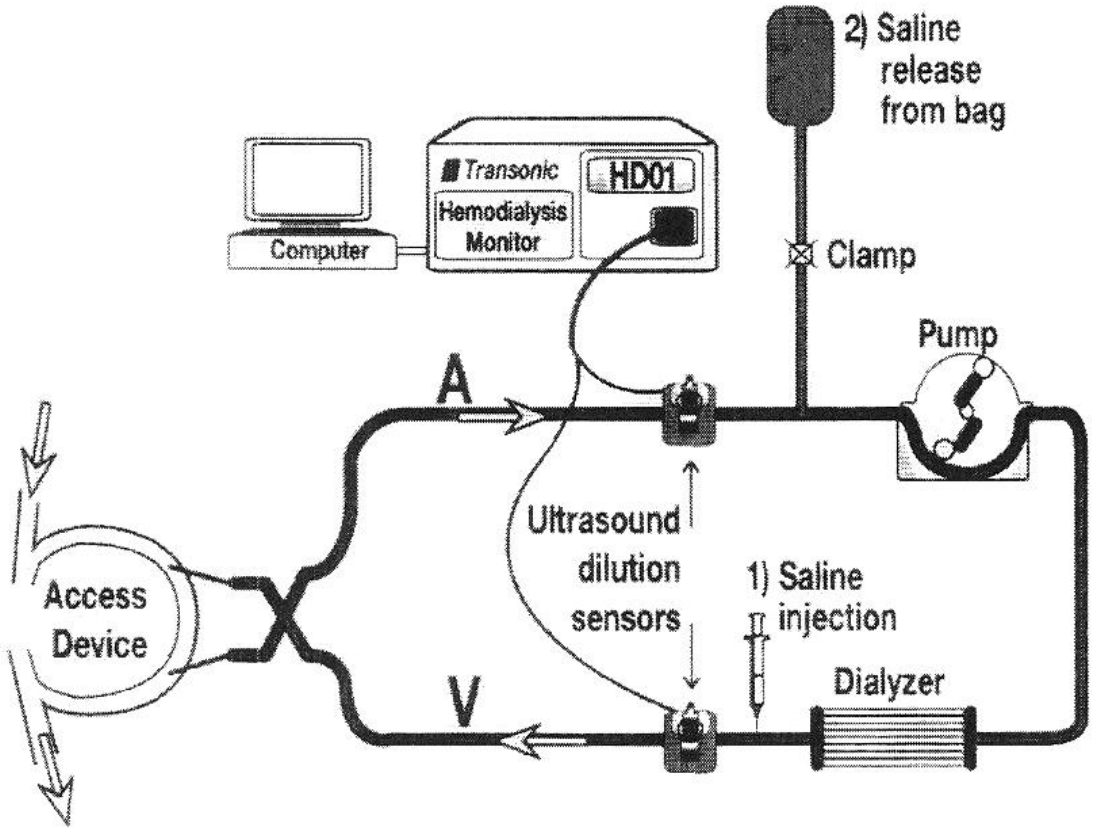
2.10 Access Monitoring

Since the introduction of vascular access for use in hemodialysis, multiple approaches have been developed to estimate and monitor access blood flow. The first method used dye dilution [190], which was followed by the use of isotopes [191], and then video-densitometry [192]. Color Doppler was first used to estimate flow and structure by Forseberg et al. [193] in 1980. More sophisticated technologies such as magnetic resonance imaging were introduced by Oudenhoven et al. [194] in 1994. Of the many approaches developed, none found routine use in the clinics because they were expensive, difficult to use, had significant inter-observer variations, and were not widely available. In 1995, a method of reversed-line velocity dilution using ultrasound was describe for vascular access blood flow measurement [195]. This method allowed for routine, operator-independent measurements to be made by a nurse and required only 3-5 minutes to perform. This development initiated widespread use of access flow measurements in hemodialysis clinics. Since 1995, more than 100 papers have been published addressing the accuracy, prognostic value, and economic impact of ultrasound velocity dilution technology [196].

With this method, patients need to have two needles in the access, one facing the arterial anastomosis in countercurrent orientation (dialyzer blood inlet) and the other facing the

venous anastomosis. To measure the access flow rate, the dialyzer lines are reversed from normal: the arterial inlet is downstream to the venous outlet, and the outlet then faces the access stream (Fig. 2.1). The purpose of line reversal is to enable delivery of indicator into the venous dialyzer outflow line upstream of the access, and then be able to sample downstream of the access (after the indicator has mixed) in the withdrawal arterial line. A flow sensor is clipped on the arterial line to measure the dialyzer flow rate and for recording ultrasound dilution caused by saline injections. An additional identical flow sensor is clipped on the venous line downstream from the place of the saline injection. The indicator injected into the venous line can serve both to calibrate the sensor and to measure access flow. To measure access blood flow, 10 mL of isotonic saline is injected into the venous line. The indicator is mixed with the blood flowing in the access. The fraction of the indicator detected by the sensor on the arterial line is determined by the ratio between flows in the extracorporeal circuit and the access. Knowing the blood flow rate in the extracorporeal circuit, the access flow rate can be calculated from this ratio [197]. Flow determination consisted of three single measurements, which are averaged. All measurements are done during a fixed dialyzer pump speed, usually 250 mL/min. The ultrafiltration rate is usually turned off 3 minutes before the start of measurements. After the flow-rate measurements are done, the dialyzer lines are reversed back to normal.

Fig. 2.3 Transonic System Monitor Setup



Transonic System HD01 Monitor Setup showing one ultrasound sensor applied to each blood line. To measure access flow, a 10 mL bolus of normal saline is injected proximal to or into the venous bubble trap (1) or normal saline is released from a saline bag into the arterial line (2).

The most often used formula to calculate access flow utilizes the relationship between access blood flow (Qa) and the access recirculation (R) introduced by line reversal [197]:

$$Qa = Qb (1/R-1)$$

Where Qb represents pump flow. Use of this formula assumes that delivery of pump flow upstream of the access does not change the initial access inflow. Any technology that

measures recirculation can be used to measure access flow with the reversed-line position [197]. All such technologies use formulas that are mathematically equivalent to the previous equation.

Over the process of developing this techniques, it has become clear that there are many factors that affect the accuracy of access flow measurement and may have clinical implications: 1) the quality of mixing of indicator with access flow between the introduction and recording sites; 2) second pass of the indicator through the cardiopulmonary system; 3) distortion of initial access flow by line reversal, indicator introduction, or indicator withdrawal; and 4) indicator loss.

2.11 Access Monitoring and Vascular Access Failure

The high cost of vascular access failure demands a closer look at strategies that may prevent it occurring. Comparison of a variety of prospective monitoring tools indicates that measurement of access blood flow may provide the best prediction of future access failure [16, 17]. Current recommendations [22, 23] have supported such monitoring on the premise that the natural history of the access will be altered by radiological or surgical intervention if access dysfunction is detected. This facilitates the change from emergent inpatient procedures to outpatient procedures, reduces total procedure rates and the need for catheters. Recently, however, the effectiveness of access monitoring in predicting future failure has become controversial. A meta-analysis and a prospective trial demonstrate that access flow measurement was only approximately 80% sensitive

and 80% specific for identifying future access thrombosis. [197]. Others reported that neither dynamic nor static venous pressures are predictive of access thrombosis [198, 199]. Thrombosis rates in access flow monitoring programs have been demonstrated to be 0.1-0.3/patient-year in AVFs and 0.25-0.40/patient-year in AVGs. This compares to baseline thrombosis rates of 0.25-0.40/patient-year in AVFs and 0.8-1.2/patient-year in AVGs without monitoring [200-204]. For these reasons, NKF-DOQI continues to recommend monthly access monitoring for all patients with vascular access. Unfortunately, there are few randomized controlled trials from which to draw conclusions about the benefit of surveillance with subsequent intervention to prevent thrombosis. Also, there are no randomized controlled trials to date that compare a control group receiving no monitoring with an intervention group that receives a particular method of surveillance. As well, there may be many patient- and population-dependant variables that influence access thrombosis and access blood flow. Finally, the duration of the follow-up period for any surveillance technique will have a profound influence on the predictive accuracy of monitoring.

The rationale for surveillance is grounded in what has been termed the “dysfunction hypothesis”, which states that stenosis causes access dysfunction, and that this dysfunction reliably precedes, and accurately predicts, thrombosis [27]. Therefore, if a particular surveillance technique is to be able to predict vascular access thrombosis, several assumptions of this dysfunction hypothesis must be true. Specifically, the measurements must be reproducible, stenosis should progress slowly enough so that there is time to intervene before thrombosis, and other factors outside of stenosis, such as

hypercoagulability, should not abrogate or appreciably confound the surveillance technique's prediction of thrombosis. An ideal access monitoring test would predict nearly all patients who will experience thrombosis without falsely predicting thrombosis in those who do not have access dysfunction. Most monitoring techniques that have been developed rely on detecting hemodynamic dysfunction, usually a reduction in blood flow that results from an access stenosis, rather than detecting the stenosis itself.

Observational studies suggest that monitoring and surveillance can lead to pre-emptive and elective surgical and/or interventional revision of a dysfunctional AVF or AVG. For example, it has been observed that if a moderate stenosis can be detected in a timely fashion, then it can be widened by concentrating cannulations exactly to the venous segment, resulting in relative dilation that can correct the underlying stenosis [205]. Other studies have found that correction of hemodynamically significant graft stenosis with angioplasty appears to substantially reduce the frequency of access thrombosis [206-209]. These results suggest that noninvasive surveillance methods can be used on an ongoing basis to screen for hemodynamically significant stenosis, permitting timely referral for a fistulogram. However, this has not been tested with rigorous clinical trials. Nevertheless, the NKF guidelines, as well as many researchers and clinicians, have advocated access surveillance as a means to improve patient care and reduce access-related costs.

CHAPTER THREE: METHODS

Sections 3.1 and 3.2 of this chapter describe the study design and the population studied with the inclusion and exclusion criteria. The next sections focus on the data management and analysis plan, and the final section discusses the ethical considerations for implementation of this study. Appendix 1 gives definitions for terms used in this study.

3.1 Study design

The study was conducted using a retrospective cohort design. The cohort was all patients in Southern Alberta with chronic renal disease receiving chronic RRT with a vascular access created for dialysis between January 1, 2002 to June 30, 2005 that were follow by SARP.

3.2 Study population and sample

Patients were recruited from SARP, which provides hemodialysis at facilities located throughout southern Alberta. SARP manages between 600 and 700 hemodialysis patients. Since 2002, SARP has used a multidisciplinary approach to vascular access management, including a full-time vascular access coordinator, a nurse who is responsible for Transonic monitoring, a group of interventional radiologists, several nephrologists, and full-time dedicated vascular access surgeons. For a patient to be included in the study sample, first and foremost their vascular access must have been considered mature. This

means that the surgery was successful, and the patient proceeded to have at least one successful functional cannulation for the purposes of dialysis; this usually occurs in 95% of both grafts and fistula. (The numerical value of 95% refers to the initial maturation of the vascular access, not the primary patency. Primary patency of a vascular access is the first failure at any time of an access from a starting point of its surgical creation including those that fail prior to maturation.) Successful functional cannulation of a vascular access is defined as affording an extracorporeal blood flow of at least 300 ml per minute, for at least 3 hours. The reason for restricting the study sample as such was the concern that interventions performed prior to the initial cannulation would change the biology of the access. With this restriction of defining the study population, the study sample was selected using the following inclusion and exclusion criteria.

3.2.1 Inclusion criteria

1. Patients 18 years of age or older.
2. All patients with a functioning and mature AVF or AVG created by a SARP affiliated vascular surgeon.
3. Only upper extremity vascular accesses were considered.
4. First cannulation of the access and adequate dialysis achieved.

3.2.2 Exclusion criteria

1. Patients receiving peritoneal dialysis as their only method of RRT
2. A central line catheter as the method of vascular access.
3. Access located in any part of body other than the upper extremities.

4. Any intervention, either surgical or radiological, performed before initial intra-access blood flow measurement.
5. First cannulation was attempted but adequate dialysis was not achieved.

3.3 Data Collection

Study data was collected from two electronic, in-house database systems: SARP and ALTRAbase. SARP records demographic and clinical variables on all patients in Southern Alberta with chronic renal disease receiving chronic RRT [210]. Data from the SARP database is then linked to an electronic surgical record (ALTRAbase data system), which captures data on all vascular access surgeries. Following each access surgery, the responsible surgeon enters an electronic standardized record with the details of the surgical procedures such as artery and vein used and whether it was a fistula or graft. Other data recorded included a unique surgery number, patient identification number, the date of the surgery, and the contemporary dialysis modality. Subsequently, the access coordinator recorded IABF rates (described below) and complications including access failure using a standardized instrument (Appendix 2).

A deterministic linkage process between the SARP and ALTRAbase database was performed. Variables used for this linkage included the Alberta personal health number, sex, date of birth, surname, and given name. Data was exported from the source databases and linked using Microsoft Excel 2003 (Microsoft Corp., Redmond WA). As dialysis services are exclusively provided by SARP, linkage was expected to be and was complete. String variables were changed to numeric form. “Yes” and “No” categories

were coded as “1” and “0” respectively. Clinical variables from both databases were collected on all sample participants. Demographics included age, sex, and race. The etiology of renal insufficiency (diabetes, glomerulonephritis, ischemia/hypertension, interstitial nephritis, polycystic kidney disease and unknown) were determined. Specific co-morbidities included diabetes, hypertension, peripheral vascular disease, and smoking (currently smoking or self-classified as a regular smoker within the past 5 years). This clinical information was collected by the predialysis clinic nurses on all patients starting dialysis to enable calculation of the Charlson comorbidity index [211], which has been validated for use in the ESRD population [212].

3.4 Variables of Interest

Information was collected on the following categories of variables:

- Outcome Variable
- Exposure Variable
- Independent Variables

3.4.1 Outcome variable – Vascular access failure

The primary outcome of interest was vascular access failure. Access failure was defined as any event of thrombosis, the need for surgical or endovascular revision with angioplasty, or the abandonment of the access site, whichever came first following initial cannulation and achievement of adequate dialysis. Vascular access outcomes were followed until the primary outcome occurred or for maximum of 6 months, following the

initial baseline blood flow measurement. The variable was dichotomized into “Yes” and “No” categories. “Yes” indicated that the patient experience a vascular access failure; “No” indicted that the patient did not experience a vascular failure during the time of the study. All categorical variables were coded as “1” (yes) and “0” (no).

3.4.2 Exposure variable – Initial IABF

All patients had an initial IABF measurement performed within 2 weeks after initial cannulation and successful use of the access for hemodialysis. All vascular access blood flow measurements were performed in a standardized fashion using the ultrasound dilution technique (HD01 Monitor, Transonic Systems, INC., Ithaca N.Y., USA). This technique has been extensively validated both *in vivo and in vitro* [196]. The ultrasound dilution technique was performed as follows: two ultrasonic sensors were attached to the lines of the hemodialysis tubing, one to the arterial, and another to the venous line, 2-6 inches from the connection to the access cannulation needles. Blood recirculation was checked while the blood lines were in the normal position. Then, the blood lines were reversed and ultra-filtration was turned off. The blood pump flow was set at 300 mL/min. A bolus of saline (10 mL) was released into the venous line, diluting the flow of blood in the access and resulting in changes of sound velocity, measured by the transducers. The Doppler shift in velocity was determined and then the vascular access blood flow (mL/min) was calculated. All access flow measurements were done in the first hour of the hemodialysis treatment as these results are reproducible and unaffected by changes in cardiac output associated with ultra-filtration. Blood flow measurements were not performed during periods of clinically significant hypotension (at the discretion of the

dialysis unit nurses). All access blood flow measurements were performed in duplicate and subsequently averaged. If a measurement differed by more than 10%, a third measurement was taken and the average of the measurements was calculated. After the measurements were performed, the data were recorded and enter into the SARP database. Based on previous research studies initial IABF was stratified in two categories: higher than 500 ml/min and lower or equal than 500 ml/min for AVFs and higher than 650 ml/min and lower or equal than 650 ml/min for AVGs.

3.4.3 Socio-demographic variables

Demographics included age, sex and race. The variable age was considered at the time the surgical procedure was performed. Based on previous research, age was stratified as patients equal to or younger than 65 years, and those older than 65 years. Patients included in the study were classified as either males or females; this variable was changed to numeric form. “Female” and Male” categories were code as “0” and “1” respectively. Race was classified in two categories: (1) Caucasian, (2) Other. In the other category were included the following races: Chinese, South Asian, Black, Aboriginal peoples of North America, West Indian, Filipino, South East Asian, Latin American, Japanese and Korean.

3.4.4 Clinical variables

Clinical variables include both continuous and discrete variables were obtained from the SARP and ALTRAbase databases. These clinical variables are defined as follows:

- **Time on dialysis:** This was defined as the time since the patient start receiving chronic replacement therapy until the first successful cannulation of the vascular access was performed. For the purpose of the study, this continuous variable was measured in days.
- **Successful access cannulation**: Successful use of a vascular access is defined as affording an extracorporeal blood flow of at least 300 ml per minute, for at least 3 hours, using an arterial and venous needles placed in the vascular access. This continuous variable was measured in days from the surgery to first cannulation.
- **Diabetes mellitus:** This is a chronic condition associated with abnormally high levels of glucose (sugar) in the blood. The two types of diabetes are referred to as insulin-dependent (type I) and non-insulin dependent (type II). Type I diabetes results from a lack of adequate insulin secretion by the pancreas. Type II diabetes (also known as adult-onset diabetes) is characterized by an insensitivity of the tissues of the body to insulin secreted by the pancreas (insulin resistance). For the purpose of the study, patients were classified as having or not the disease. No stratification was done between patients with diabetes type I or type II diabetes.
- **Hypertension:** High blood pressure is defined as a systolic blood pressure greater than 140 mm Hg and/or diastolic blood pressure greater than 90 mm Hg.
- **Glomerulonephritis:** This is a disease of the kidneys in which the glomeruli, the tiny filters in the kidneys that help to clean the blood, become inflamed or damaged. This allows protein and red blood cells to pass into the urine. If glomerulonephritis does not respond to treatment, the glomeruli may slowly be destroyed and the kidneys may lose their ability to clean the blood.

- **Interstitial nephritis:** This is a form of nephritis affecting the interstitium of the kidneys surrounding the tubules. This disease can be either acute, which means it occurs suddenly or chronic, meaning it is ongoing and eventually ending in kidney failure.
- **Polycystic kidney disease:** This is a progressive, genetic disorder of the kidneys, characterized by the presence of multiple cysts (hence, "polycystic") in both kidneys. The disease can also damage the liver, pancreas, and rarely, the heart and brain.
- **Peripheral vascular disease**: Diseases of the vessels of the extremities such as atherosclerosis, resulting in diminished circulation, pain (claudication), or a blood clot.
- **Smoking:** Subjects were defined as a current smoker or a non-smoker based on self-reported current smoking status.
- **Anticoagulation**: This refers to use of a group of medications that prevent blood from clotting (ASA, Coumadin, Heparin).

3.4.5 Vascular access characteristics

The clinical characteristics of all vascular accesses were obtained from the ALTRAbase database. The unique descriptors of the accesses included: 1) location (forearm, upper arm, right or left, dominant or non-dominant), 2) type (native fistula or graft), 3) the surgeon of record (A, B, C, D). The surgeon of record was made anonymous prior to data extraction from the database.

3.5 Data Analysis

This section describes the data analysis employed in this study under the following headings: initial data analysis, descriptive analysis, and analytical analysis. Analysis was performed using Stata version 9.0 (Stata Corp, College Station, TX).

3.5.1 Initial data analysis

In this phase of the data analysis all abstracted data forms were reviewed prior to entry into the study database in order to ensure consistency of application of study definitions and diagnosis. The aim was to detect errors and out-of rage values. To avoid assessment of multiple outcomes for a single patient, only the first access surgery associated with vascular access failure was analyzed for patients with multiple access procedures. In the event of missing data for a particular variable that was not available after review of the SARP or ALTRAbase database, the data were not replaced.

3.5.2 Descriptive analysis

All variables were assessed for underlying distribution qualitatively using histograms or box plots. Normally or near normally distributed variables were reported as means with standard deviations (SD) and were compared using the appropriate Student's t test. Categorical data were reported as proportions and compared using the Chi-square Test. Levels of significance were not adjusted for multiple testing, and two-side p-values of <0.05 were considered statistically significant for all comparisons.

3.5.3 Hypothesis testing

The particular steps in this section were undertaken to address the objectives of the study and are describe in the next three sub-sections.

The primary outcome of interest in the study was vascular access failure. The outcome was stratified by type of vascular access (AVF or AVG). Differences in demographic or clinical variables between those with, and without, vascular access failure were explored using classical descriptive analysis (measures of central tendency and dispersion) and compared using the appropriate parametric or non-parametric test for continuous variables, or Chi-square test for proportions.

A univariate logistic analysis was performed on each of the independent variables to identify variables associated with an increased risk of vascular access failure. Estimated odds ratios (ORs) and corresponding 95% confidence intervals were computed. Generally, the estimated ORs were considered significant at p-values less than 0.05. In a few instances, however, variables were considered for further analysis in the absence of significant p-value. This was the case for variables that have been shown in the literature to be significant predictors of vascular access failure or if the 95% confidence interval associated with the OR was very close to the null value (close to 1). The particular variables that fit in this category are indicated in the relevant Results section.

Stratified analysis was performed to explore whether selected independent variables may have been confounders or effect modifiers. This analysis was performed by exploring whether the crude OR of the relationship between vascular access failure and initial IABF

was affected by stratification on the third independent variable. Estimated ORs in the different strata of each variable were then compared to each other and to the estimated crude odds ratio. Based on the results of the comparison, a judgment was made whether that variable acted as a confounder, an effect modifier, or neither. The criteria used for confounding were that the stratum specified ORs were similar but different from the crude, while the criteria for effect of modification were that the stratum specific ORs were different and different from the crude.

A multivariable analysis using logistic regression was performed to determine the potential contribution of independent variables including age, sex, race, time on dialysis, primary renal disease, co-morbidities (diabetes, hypertension, peripheral vascular disease, smoking), access location (dominant or non-dominant extremity), type of procedure (forearm fistula vs. upperarm fistula/ forearm loop graft vs. upperarm C-graft), surgeon (identified as surgeon A, B, C, D), use of medications (aspirin, anticoagulants, angiotensin-converting enzyme inhibitors), and initial IABF with the dependant variable of vascular access failure. Multiple logistic regression allows the use of both discrete and continuous independent variables in a regression model to simultaneously assess the effects of each on a discrete dependant variable. Variables that were clinically relevant with $p < 0.25$ were entered simultaneously into the initial model. Variables were removed using a backward elimination process, leaving only variables with $p < 0.05$ in the final model. First-order interactions were also assessed by testing the significance of the product terms generated between various independent variables.

3.6 Ethical Concerns

This study involved the review of existing data from clinical and administrative databases, and the review of patients' medical records. Following the data linkage between databases, the participants in the final study sample were assigned a unique identifier, followed by removal of all patient specific identifiers. Data is presented in aggregate only (minimum cell value of 5 participants), and therefore identification of individuals by unique isolated outcomes should not be possible. Prior to data acquisition, ethical review and approval was obtained from the Research Ethics Board of the University of Calgary and the Calgary Health Region.

CHAPTER FOUR: RESULTS

This chapter provides information on the primary research question – the association between vascular access failure and initial IABF measurement in patients with AVFs and AVGs. Estimates are made of effect of modification or confounding of this association due to various socio-demographic and clinical variables. In an effort to explore this association further, logistic regression models were developed in the last part of the chapter.

During the 42-month study period from January 2002 to June 2005, a total of 1510 vascular access procedures were performed at the Foothills Hospital in Calgary. The numbers and types of procedures are shown in Table 4.1. Data from those patients whose accesses matured properly (831 AVFs and 359 AVGs) are included for analysis.

Table 4.1 Numbers and types of procedures performed from January 2002 to June 2005

Procedure	Number	Number maturing (included in thesis)
AVF	867	831
AVG	379	359
Peritoneal dialysis catheter	264	Not included
Total	1510	1190

All patients included in the study were on renal replacement therapy at the time of the first access cannulation. The majority of these patients had been on hemodialysis for a period ranging from 6 to 18 months. Table 4.2 describes characteristics of the patient

sample including age, sex, ethnicity, months on dialysis, underlying disease, co-morbidities, surgeon, location of access, and type of procedure for patients who received these two types of vascular access. The mean (± SD) age of all participants was 69 ± 15 years (range: 20-97). The cohort consisted of approximately 58% men; 77% of patients were Caucasian; and diabetes mellitus and hypertension were the most common underlying cause of renal failure in 43% and 15% of the cases, respectively.

During the study period, death occurred in 64 out of the total cohort of 1510 patients: 25 with AVFs and 39 with AVGs. Data were included for those patients who reached the primary outcome of vascular access failure before death (12 patients with AVFs and 30 patients with AVGs). Data were not included for those patients who died with a functional access (13 with AVFs and 9 with AVGs).

4.1 AVFs

Seventy percent of the total vascular accesses placed were fistulas. Of these fistulas, about 30% were radio-cephalic fistulas in the forearm and 70% were brachio-cephalic fistulas in the upper arm. No brachio-basilic fistulas were placed during the study time. The most common underlying disease causing renal insufficiency was diabetes, present in 43% of the cases. Other causes included hypertensive nephropathy (15%), glomerulonephritis (12%), interstitial nephritis (4%), and polycystic kidney disease (4%). In 22% of the patients, no definite etiological factor was identified (Table 4.2).

Table 4.2 Demographics and co-morbid variables in AVFs or AVGs cohorts

Variable	All Patients	AVFs	AVGs
No. of Patients: n (%)	1190 (100)	831 (70)	359 (30)
Age: mean ± SD years	69 ± 15	68 ± 15	70 ± 12
Sex: Male, n (%)	696 (58)	511 (62)	185 (52)
Ethnicity: n (%)			
• ***Caucasian***	916 (77)	648 (78)	259 (72)
• ***Other***	274 (23)	183 (22)	100 (28)
Primary Renal Disease: n (%)			
• ***Diabetes***	511 (43)	363 (44)	148 (41)
• ***Glomerulonephritis***	148 (12)	103 (12)	45 (12)
• ***Ischemic/Hypertension***	181 (15)	120 (14)	61 (17)
• ***Interstitial nephritis***	47 (4)	30 (4)	17 (5)
• ***Polycystic kidney disease***	45 (4)	32 (4)	13 (4)
• ***Unknown/Other***	258 (22)	183 (22)	75 (21)
Co-morbidities: n (%)			
• ***Diabetes***	602 (51)	404 (49)	198 (55)
• ***Hypertension***	745 (63)	496 (60)	249 (69)
• ***Peripheral vascular disease***	430 (36)	274 (33)	156 (43)
• ***Smoking***	585 (49)	378 (46)	207 (58)
• ***Medications***	130 (11)	65 (8)	65 (18)
Surgeon: n (%)			
• ***A***	365 (31)	250 (30)	115 (32)
• ***B***	428 (36)	298 (36)	130 (36)
• ***C***	356 (30)	248 (30)	108 (30)
• ***D***	41 (3)	35 (4)	6 (2)
Location: n (%)			
• ***Right***	308 (26)	222 (27)	86 (24)
• ***Left***	882 (74)	609 (73)	273 (76)
Procedure: n (%)			
• ***Forearm AVF***	255 (22)	255 (31)	
• ***Upper arm AVF***	576 (48)	576 (69)	
• ***Forearm AVG***	264 (22)		264 (74)
• ***Upper arm AVG***	95 (8)		95 (26)
Vascular access failure: n (%)	188 (16)	81 (10)	107 (30)
• ***Thrombosis***	139 (95)	66 (81)	73 (68)
• ***Surgical intervention***	11 (1)	4 (5)	7 (7)
• ***Angioplasty***	27 (3)	9 (11)	18 (17)
• ***Abandonment***	11 (1)	2 (3)	9 (8)
Initial IABF: mean ± SD ml/min	885 ± 490	936 ± 515	759 ± 409

Table 4.3 Baseline demographics and co-morbid variables in patients with AVF failure compared with patients without failure

Variable	AVFs without failure	AVFs with failure	All AVFs	P Value
No. of Patients: n (%)	750 (90)	81 (10)	831 (100)	
Age: mean ± SD	67 ± 15	72 ± 11	68 ± 15	0.0098 [a]
Gender: Male, n (%)	464 (62)	47 (58)	511 (62)	0.49 [b]
Ethnicity: n (%)				0.3 [b]
• ***Caucasian***	550 (73)	53 (65)	604 (72)	
• ***Other***	220 (27)	28 (35)	227 (28)	
Primary Renal Disease: n (%)				0.4 [b]
• ***Diabetes***	331 (44)	32 (40)	363 (44)	
• ***Glomerulonephritis***	91 (12)	12 (15)	103 (12)	
• ***Ischemic/Hypertension***	109 (15)	11 (14)	120 (14)	
• ***Interstitial nephritis***	29 (4)	1 (1)	30 (4)	
• ***Polycystic kidney disease***	26 (3)	6 (7)	32 (4)	
• ***Unknown/Other***	164 (22)	19 (23)	183 (22)	
Comorbidities: n (%)				
• ***Diabetes***	347 (46)	57 (70)	404 (49)	< 0.001 [b]
• ***Hypertension***	432 (58)	64 (79)	496 (60)	< 0.001 [b]
• ***Peripheral vascular disease***	230 (31)	44 (54)	274 (33)	
• ***Smoking***	317 (42)	61 (75)	378 (45)	< 0.001 [b]
• ***Medications***	58 (8)	7 (9)	65 (8)	< 0.001 [b]
				0.77 [b]
Surgeon: n (%)				0.6 [b]
• ***A***	221 (30)	29 (36)	250 (30)	
• ***B***	269 (36)	29 (36)	298 (36)	
• ***C***	227 (30)	21 (26)	248 (30)	
• ***D***	33(4)	2 (3)	35 (4)	
Location: n (%)				0.48 [b]
• ***Right***	203 (27)	19 (24)	222 (27)	
• ***Left***	547 (73)	62 (76)	609 (73)	
Procedure: n (%)				< 0.001 [b]
• ***Forearm AVF***	207 (28)	48 (59)	255 (31)	
• ***Upper arm AVF***	543 (72)	33 (41)	576 (69)	
Initial IABF:				
• ***mean ± SD ml/min***	992 ± 510	421 ± 138	936 ± 515	< 0.001 [a]

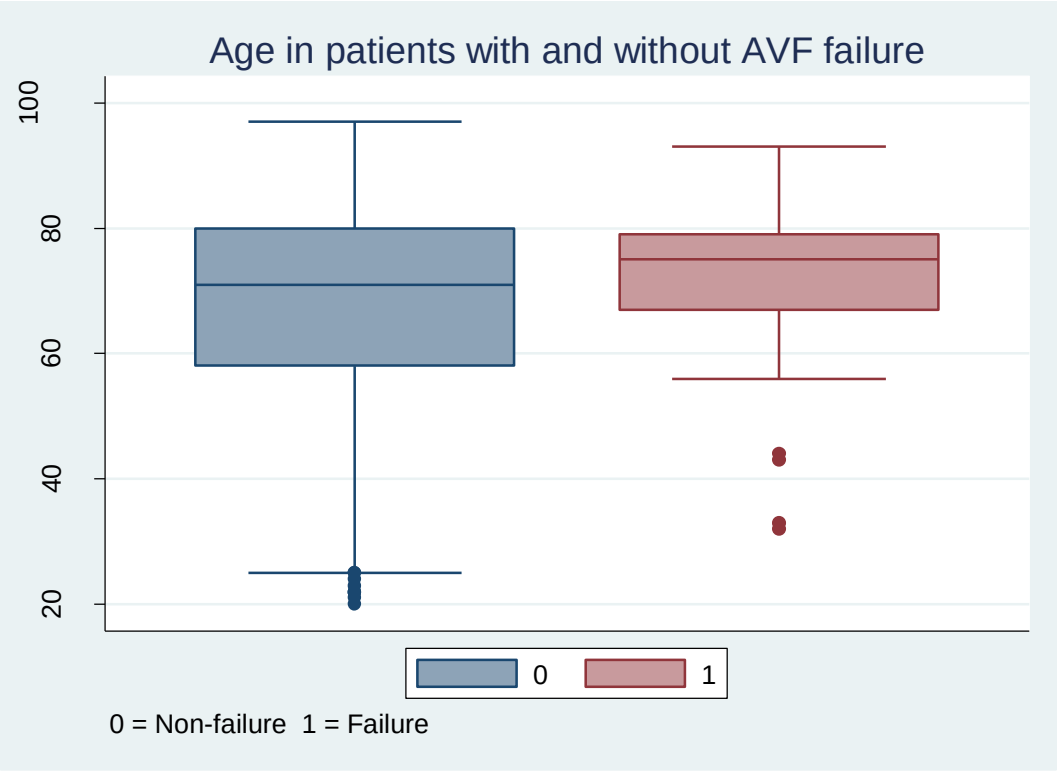
[a] P values for continuous variables are based on two sample test.
[b] P values for categorical variables are based Chi^2 test of two samples

4.1.1 Vascular access failure

The primary outcome of interest in the study was vascular access failure defined as any event of thrombosis, the need for surgical or endovascular revision with angioplasty, or the abandonment of the access site, whichever came first following initial cannulation and achievement of adequate dialysis within 6 months following first use. Primary failure of the AVF occurred in 81 (10%) of cases. Sixty-six patients (81%) had thrombosis as a cause, 9 patients (11%) had radiological intervention with angioplasty, 4 patients (5%) required surgery, and 2 patients (3%) had the vascular access abandoned (Table 4.2). The median time from first cannulation to vascular access failure was 48 days (IQR: 12 – 95). Baseline demographics and co-morbid variables of patients who developed vascular access failure are compared to patients without AVF failure in Table 4.3.

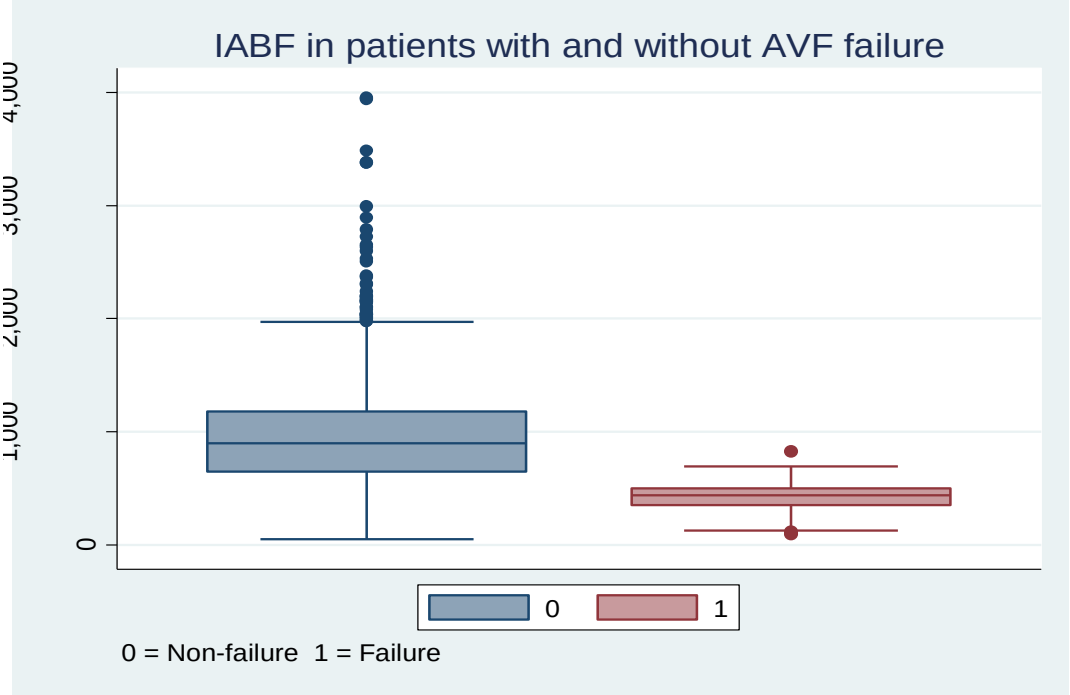
Patients with access failure were significantly more likely to have a current co-morbid diagnosis of diabetes, hypertension, peripheral vascular disease, or smoking. Additionally, patients with primary failure of the vascular access fistula were significantly older than those without AVF failure (Fig. 4.1), and were significantly more likely to have a forearm fistula or an initial IABF of less than 500 ml/min (Fig. 4.2). No differences in sex, ethnicity, underlying primary kidney disease, medications, surgeons, or location of the access were demonstrated between those with, and without, AVF failure (Table 4.3).

Fig. 4.1 Age of patients with and without AVF failure



Upper horizontal line of box, 75th percentile; lower horizontal line of box, 25th percentile; horizontal bar within box, median; upper horizontal bar outside box, 90th percentile; lower horizontal bar outside box, 10th percentile. Open circles (O) represent values more than 1.5 box-lengths from 75th percentile (outliers). Asterisks (*) represent values more than 3 box-lengths from 75th percentile (extremes).

Fig. 4.2 Initial IABF in patients with and without AVF failure



Upper horizontal line of box, 75th percentile; lower horizontal line of box, 25th percentile; horizontal bar within box, median; upper horizontal bar outside box, 90th percentile; lower horizontal bar outside box, 10th percentile. Open circles (O) represent values more than 1.5 box-lengths from 75th percentile (outliers). Asterisks (*) represent values more than 3 box-lengths from 75th percentile (extremes).

4.1.2 Relative risk for vascular access failure

Relative risk calculations of the patient characteristic variables showed that patients with initial IABF less than 500 ml/min were 16 times more likely to experience vascular access failure, smokers were 3.7 times more likely, those with forearm fistulas were 3.3 times more likely, and those older than 65, those with a history of diabetes, hypertension, or peripheral vascular disease were about 2.5 times more likely to experience vascular

access failure from any cause as those without these characteristics (Table 4.4). The relative risks based on sex, ethnicity, medications, or AVF location were not significant.

Table 4.4 Relative risk of vascular access failure (VAF) from any cause in patients with AVFs

Variable	No. with characteristic: % (ratio)	Incidence of VAF among patients with characteristic: % (ratio)	Incidence of VAF among patients without characteristic: % (ratio)	Relative Risk: (95% CI)
Age ≥ 65	64 (537/831)	12(66/537))	5(15/294)	2.4 (1.4 to 4.1) [a]
Diabetes	49 (404/831)	14 (57/404)	5 (24/427)	2.5 (1.6 to 4.0) [a]
Hypertension	60 (496/831)	13 (64/496)	5 (17/335)	2.5 (1.5 to 4.3) [a]
Peripheral vascular disease	33 (274/831)	16 (44/274)	7 (37/557)	2.4 (1.6 to 3.6) [a]
Smoking	46 (378/831)	16 (61/378)	4 (20/453)	3.7 (2.2 to 5.9) [a]
Procedure (forearm)	31 (255/831)	19 (48/255)	6 (33/576)	3.3 (2.2 to 5.0) [a]
Initial IABF (< 500 ml/min)	14 (116/831)	51 (59/116)	3 (22/715)	16 (11 to 26) [a]

[a] *P<0.001; variables with no significant p value are not shown in table.*

When relative risk was calculated for the subset of patients whose access failed as a result of thrombosis, similar results were obtained as for those patients with vascular access failure from any cause. Table 4.5 shows that showed that patients with initial IABF less than 500 ml/min were over 19 times more likely to experience vascular access failure, those older than 65 were 4.5 times more likely, smokers were 3.5 times more likely, those

with forearm fistulas were 3 times more likely, and those with a history of diabetes, hypertension, or peripheral vascular disease were about 2.5 times more likely to experience vascular access failure from thrombosis as those without these characteristics.

Table 4.5 Relative risk of vascular access failure (VAF) secondary to thrombosis in patients with AVFs

Variable	No. with characteristic: % (ratio)	Incidence of VAF among patients with characteristic % (ratio)	Incidence of VAF among patients without characteristic % (ratio)	Relative Risk: (95% CI)
Age ≥ 65	65 (530/816)	11 (59/530)	2 (7/286)	4.5 (2.1 to 9.8) [a]
Diabetes	49 (404/816)	14 (53/485)	4 (13/331)	2.8 (1.5 to 5.0) [a]
Hypertension	59 (485/816)	11 (53/485)	4 (13/331)	2.8 (1.5 to 5.0) [a]
Peripheral vascular disease	32 (265/816)	13 (35/265)	5 (31/551)	2.3 (1.4 to 3.7) [a]
Smoking	41 (336/816)	15 (49/336)	4 (17/450)	3.5 (2.0 to 6.0) [a]
Procedure (forearm)	30 (244/816)	15 (37/244)	5 (29/572)	3.0 (1.8 to 4.7) [a]
Initial IABF (< 500 ml/min)	13 (106/816)	46 (49/106)	2 (17/710)	19 (11 to 32) [a]

[a] *P<0.001; variables with no significant p value are not shown in table*

4.1.3 Stratified analysis

The stratified analysis aimed to investigate whether the crude association between vascular access failure and initial IABF measurement was confounded or modified by selected socio-demographic and clinical variables. Confounding occurs when the apparent association between a risk factor and an outcome is affected by the relationship of a third variable to the risk factor and the outcome; the third variable is called a

confounder. For a variable to be a confounder, the variable must be independently associated with the risk factor and outcome, but not be in the causal pathway between risk factor and outcome. To assess for confounding, a series of models with and without subsets of the potential confounders: age, sex, ethnicity, diabetes, hypertension, peripheral vascular disease, history of smoking, medications, IABF, and type of procedure were compared. The fully adjusted model containing all the variables listed above is referred to by Kleinbaum and Klein [213] as the "gold standard model", all "reduced" models are compared to the "gold standard model".

The estimated crude OR for the relationship between vascular access failure and initial IABF in patients with AVFs was OR 32, (95% CI 18-49). The crude association between the vascular access failure and the initial IABF remained unchanged after stratification on each of the socio-demographic characteristics including age, sex, and ethnicity.

The association between vascular access failure and initial IABF was also assessed after stratification by the following clinical variables: diabetes mellitus, hypertension, peripheral vascular disease, smoking, medications, IABF, and type of surgical procedure. With the exception of smoking, the stratum-specific estimates were similar to each other and similar to the crude estimates OR. Only in the model of smoking (OR 42, 95% CI 21-70), the fully adjusted estimates were different from those obtained from the reduced model. The 95% CIs of the estimates for the reduced model were extremely wide and therefore it is difficult to determine whether in fact smoking was a confounder. Because

of this difficulty the fully adjusted "gold standard model" will be the final model of choice.

4.1.4 Multivariable modeling

One objectives of this study was to construct a statistical model identifying factors that are associated with vascular access failure in patients on hemodialysis with AVFs. Addressing this objective, a stepwise logistic modeling procedure was employed in order to produce a parsimonious model of factors that are associated with vascular access failure. Modeling was also used to assess whether main effects of various independent variables were confounded when a new variable was added to the model.

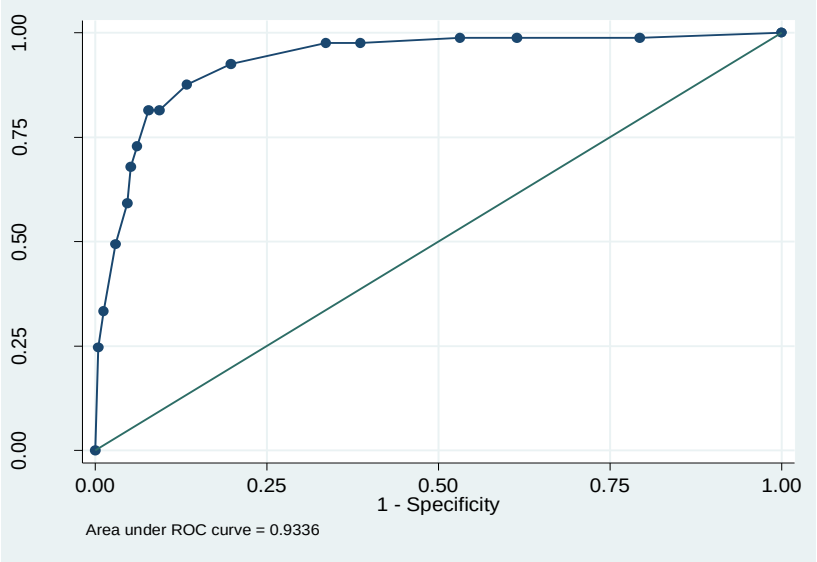
The stratified analysis did not indicate that any variable acted as a confounder or effect modifier of the association between vascular access failure and initial IABF. The only variables chosen for inclusion in the multivariable logistic regression analysis were those found in the univariate analysis to be significantly correlated with vascular access failure. Variables with a p value of <0.25 were selected for multiple regression modeling as suggested by Hosmer and Lemeshow [214]. Variables that met those criteria were age ($\geq$ 65), presence of diabetes, hypertension, peripheral vascular disease, history of smoking, having a forearm AVF, and having an initial IABF less than 500 ml/min. Sex was not significant in this analysis ($p = 0.5$); however in previous research, being female has been associated with a higher incidence of vascular access failure hypothesized due to smaller vascular structures in women [215]. Therefore, sex was included in the multiple regression model despite its lack of statistical significance.

At the multivariable modeling stage of the analysis, assessment for interaction was done. An interaction occurs when the impact of a risk factor on outcome is changed by the value of another variable. All possible pairwise interactions were tested and none were found to be statistically significant. Higher order (three-way) interaction terms, for instance sex by age by diabetes mellitus, were not considered.

4.1.5 Final model

This analysis yielded a model that included age, history of diabetes, history of smoking, type of procedure, and initial IABF dichotomized at 500 ml/min. Assessment of the model fit using the Hosmer-Lemeshow goodness of fit test yielded high p-values (c=14.80, p=0.19). This model was found to have excellent discrimination as determined by the area under the Receiver Operator Characteristics curve of 0.93 (Fig. 4.3).

Fig. 4.3 Area under the Receiver Operating Characteristic Curve: Association of vascular access failure and initial IABF for patients with AVFs



The final regression model demonstrates that all selected variables remain statistically significant (Table 4.6). The odds of experiencing vascular access failure occurred in those patients with initial IABF of less than 500 ml/min (OR=29 and 95% CI 15-52), adjusting for all other covariates. A history of smoking, being older than 65, having a forearm fistula, and a history of diabetes produced ORs between 4.2 and 2.3 (Table 4.6), adjusting for all the other covariates. The calculated coefficients allowed for the elaboration of a regression equation to predict the occurrence of vascular access failure. The equation may be applied using the variables selected according to the following regression significance criteria:

Logit *p* = - 6.3 + [3.4 × IABF (ml/min)] + [1.3 × Age (<65 years = 0, ≥65 years = 1)] + [0.9 × Diabetes (no = 0, yes = 1)] + [1.4 × Smoking (no = 0, yes = 1)] + [1.4 × Procedure (upperarm fistula = 0, forearm fistula = 1)]

All variables are associated with an increase risk of vascular access failure. In our cohort, the baseline probability of access failure was 0.2% (IABF >500 ml/min, younger than 65 years of age, non-smoker, no diabetes, and with upperarm fistula). The most significant variable associated with an increase risk was an initial IABF lower than 500 ml/min. From previous analysis, a patient with an initial IABF <500 ml/min with no other risk factors had a probability of 16% risk of vascular access failure. A probability of failure of 16% is practically significant and suggest that all patients with an initial IABF less than 500 ml/min should have either and intervention or repeat monitoring. Individuals with initial IABF >500 ml/min have an extremely low probability of subsequent access failure.

We decided to examine in this subgroup in an exploratory manner to determine if there were any risk factors associated with an increased risk of failure: if so, this might suggest an area of future study, or practically, a population of patients who might benefit from repeat monitoring. The same steps used in the creation of the previous model were applied for this second model, and yielded only smoking as important covariate (Table 4.7).

Logit p = - 6.0 + [2.6 × Smoking (no = 0, yes = 1)]

Table 4.6 Final multiple logistic regression model: Retained dichotomized variables for vascular access failure in patients with AVFs [a]

Variable	Coefficient	OR	95 % Confidence Interval	P value
IABF_500 [b]	3.4	29	15 – 52	< 0.001
Age_65 [c]	1.3	3.6	1.7 – 7.7	0.001
Diabetes	0.9	2.3	1.3 – 4.5	0.007
Smoking	1.4	4.3	2.2 – 8.3	< 0.001
Procedure	1.4	4.0	2.1 – 7.4	< 0.001

[a] *Adjusted for age, diabetes, history of smoking and access type.*
[b] *Initial IABF dichotomized at 500 ml/min.*
[c] *Age dichotomized at 65 years.*

Table 4.7 Logistic regression stratified on initial IABF > 500 ml/min

Variable	Coefficient	OR	95 % Confidence Interval	P value
Smoking	2.6	13	3.1 – 56	0.001

The odds of experiencing vascular access failure were 13 times greater in smokers than non-smokers. Stated another way, in our cohort, smokers with an initial IABF > 500 ml/min had a probability of subsequent access failure of 3.5%. The implication of this result is that routine monitoring in patients with an initial IABF > 500 ml/min and no other covariates should be questioned. There may be utility in monitoring patients with initial IABF > 500 ml/min and history of smoking.

We did examine further multivariable models to examine if an outcome of thrombosis was different than the other outcomes. The results of these models was similar to the results from the classical analysis presented in Table 4.5, and is not presented here.

4.2 AVGs

Thirty percent of the total vascular accesses placed were prosthetic grafts. Of these grafts, approximately 74% were forearm loop grafts and 26% were upperarm C-grafts. No tight grafts were included on the study. The most common underlying disease causing renal insufficiency was diabetes, present in 41% of the cases. Other causes included hypertensive nephropathy (17%), glomerulonephritis (12%), interstitial nephritis (5%), and polycystic kidney disease (4%). In 21% of the patients, no definite etiological factor was identified (Table 4.2).

The primary outcome of interest in the study was vascular access failure defined as any event of thrombosis, the need for surgical or endovascular revision with angioplasty, or

the abandonment of the access site, within 6 months following first use, whichever came first following initial cannulation and achievement of adequate dialysis. Primary failure of the AVG occurred in 107 (30%) of cases. Seventy-three patients (68%) had thrombosis as a cause of the vascular access failure, 7 patients (7%) had surgery, 8 patients (18%) had radiological intervention with angioplasty, and 9 patients (8%) had the vascular access abandoned. The median time to vascular access failure was 61 days (IQR: 48 – 110). Baseline demographics and co-morbid variables of patients who developed vascular access failure are compared to patients without AVG failure in Table 4.8.

4.2.1 Vascular access failure

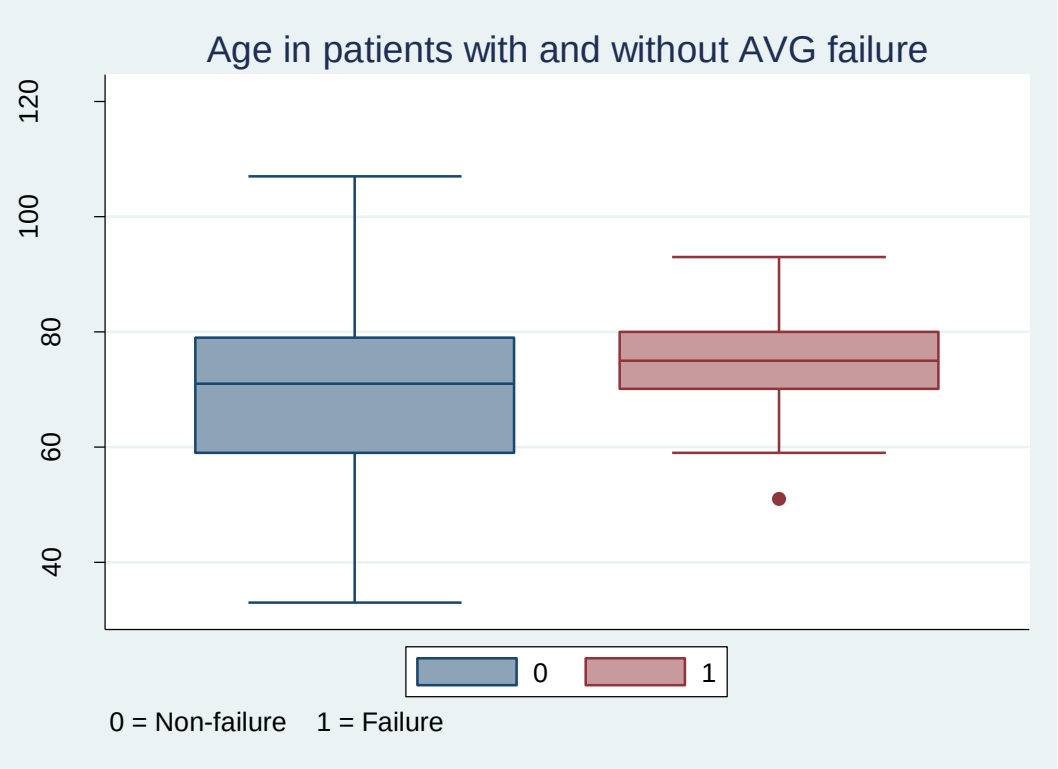
Patients with access failure were significantly more likely to have a current co-morbid diagnosis of diabetes, hypertension, peripheral vascular disease, or smoking. Additionally, patients with primary failure of the vascular access grafts were significantly older than those without AVG failure (Fig. 4.4) and were male or an initial IABF of less than 650 ml/min (Fig. 4.5). No differences in ethnicity, underlying primary kidney disease, medications, surgeons, or location of the access were demonstrated between those with and without AVG failure (Table 4.8).

Table 4.8 Baseline demographics and co-morbid variables in patients with AVG failure compared with patients without failure

Variables	AVGs without failure	AVGs with failure	All AVGs	P Value
No. of Patients: n (%)	252 (70)	107 (30)	359 (100)	
Age: mean ± SD	68 ± 13	74 ± 8	70 (12)	< 0.001[a]
Gender, Male n, (%)	121 (48)	64 (60)	185 (52)	0.027 [b]
Ethnicity, n (%)				0.07 [b]
• ***Caucasian***	189 (75)	70 (65)	259 (72)	
• ***Other***	63 (25)	37 (35)	100 (28)	
Primary Renal Disease: n (%)				0.3 [b]
• ***Diabetes***	97 (39)	51 (48)	148 (41)	
• ***Glomerulonephritis***	31 (12)	14 (13)	45 (13)	
• ***Ischemic/Hypertension***	44 (18)	17 (16)	61 (17)	
• ***Interstitial nephritis***	15 (6)	2 (1)	17 (5)	
• ***Polycystic kidney disease***	8 (3)	5 (5)	13 (3)	
• ***Unknown/Other***	57 (23)	18 (17)	75 (21)	
Comorbidities: n, (%)				
• ***Diabetes***	114 (45)	84 (79)	198 (55)	< 0.001
• ***Hypertension***	168 (67)	81 (76)	249 (69)	0.09
• ***Peripheral vascular disease***	96 (38)	60 (56)	156 (43)	0.01
• ***Smoking***	135 (54)	72 (67)	207 (58)	0.01
• ***Medications***	48 (19)	17 (16)	65 (18)	0.47
Surgeon: n (%)				0.8 [b]
• ***A***	78 (31)	37 (35)	115 (32)	
• ***B***	91 (36)	39 (36)	130 (36)	
• ***C***	78 (31)	30 (28)	108 (30)	
• ***D***	5 (2)	1 (1)	6 (2)	
Location: n (%)				0.08 [b]
• ***Right***	51 (20)	35 (33)	86 (24)	
• ***Left***	201 (80)	72 (67)	273 (76)	
Procedure: n, (%)				0.5 [b]
• ***Forearm AVG***	187 (74)	77 (72)	264 (74)	
• ***Upperarm AVG***	65 (26)	30 (28)	95 (26)	
Initial IABF	916 ± 388	421 ± 131	769 ± 402	0.000 [a]
• ***mean ± SD ml/min***				

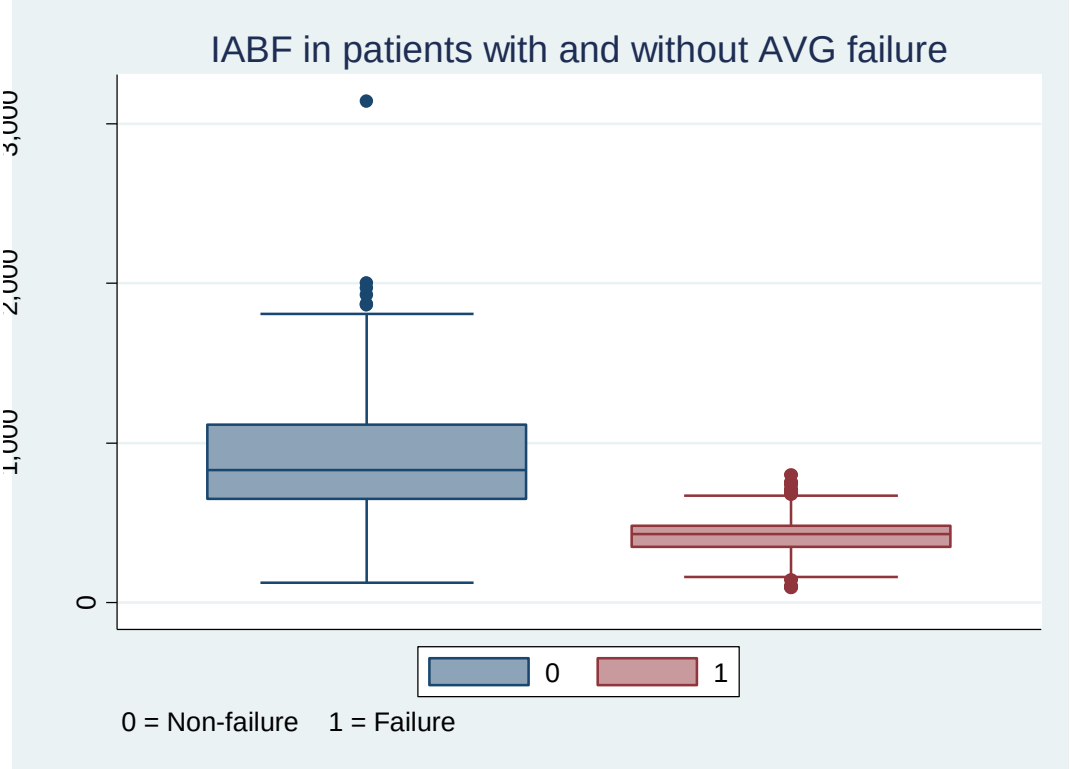
[a] P values for continuous variables are based on two sample test
[b] P values for categorical variables are based Chi^2 test of two sample proportions

Fig. 4.4 Age of patients with and without AVG failure



Upper horizontal line of box, 75th percentile; lower horizontal line of box, 25th percentile; horizontal bar within box, median; upper horizontal bar outside box, 90th percentile; lower horizontal bar outside box, 10th percentile. Open circles (O) represent values more than 1.5 box-lengths from 75th percentile (outliers). Asterisks (*) represent values more than 3 box-lengths from 75th percentile (extremes).

Fig. 4.5 Initial IABF in patients with and without AVG failure



Upper horizontal line of box, 75th percentile; lower horizontal line of box, 25th percentile; horizontal bar within box, median; upper horizontal bar outside box, 90th percentile; lower horizontal bar outside box, 10th percentile. Open circles (O) represent values more than 1.5 box-lengths from 75th percentile (outliers). Asterisks (*) represent values more than 3 box-lengths from 75th percentile (extremes).

4.2.2 Relative risk for vascular access failure

Relative risk calculations of the patient characteristic variables showed that patients with initial IABF less than 650 ml/min were over 14 times more likely to experience vascular access failure, those older than 65 years, those with a history of diabetes were 3 times more likely, and those with a history of hypertension, or peripheral vascular disease or smoking were about 1.5 times more likely to experience vascular access failure as those

without these characteristics (Table 4.9). The relative risks based on sex, ethnicity, medications, or AVG location were not significant.

Table 4.9 Relative risk of vascular access failure (VAF) from any cause in patients with AVGs

Variable	No.(%) with characteristic: % (ratio)	Incidence of VAF among patients with characteristic: % (ratio)	Incidence of VAF among patients without characteristic: % (ratio)	Relative Risk: (95% CI)
Age > 65	72(257/359)	38 (97/257)	9 (10/102)	3.8 (2.1 to 7.1) [a]
Diabetes	55(198/359)	42 (84/198)	14 (23/161)	3.0 (2.0 to 4.5) [a]
Peripheral vascular disease	43(156/359)	38 (60/156)	23 (47/203)	1.7 (1.2 to 2.3) [a]
Smoking	58(207/359)	35 (72/207)	23 (35/152)	1.5 (1.1 to 2.1) [a]
Initial IABF (< 650 ml/min)	43(155/359)	63 (98/155)	5 (9/204)	14 (7.5 to 27) [a]

[a] *P<0.001; variables with no significant p value are not shown in table.*

When relative risk was calculated for the subset of patients whose access failed as a result of thrombosis, similar results were obtained as for those patients with vascular access failure from any cause. Table 4.9 shows that showed that patients with initial IABF less than 650 ml/min were over 14 times more likely, those older than 65 were 3.8 times more likely, those with history of diabetes were 3 times more likely, smokers were 1.5 times more likely, and those with a history of peripheral vascular disease were about 1.7 times more likely to experience vascular access failure from thrombosis as those without these characteristics. (Table 4.10)

Table 4.10 Relative risk of vascular access failure (VAF) secondary to thrombosis in patients with AVGs

Variable	No. with characteristic: % (ratio)	Incidence of VAF among patients with characteristic % (ratio)	Incidence of VAF among patients without characteristic % (ratio)	Relative Risk: (95% CI)
Age ≥ 65	70 (238/338)	32 (78/238)	8 (8/100)	4.0 (2.0 to 8.1) [a]
Diabetes	53 (182/338)	137 (68/182)	11 (18/156)	3.2 (2.0 to 5.1) [a]
Peripheral vascular disease	42 (144/338)	33 (48/144)	19 (38/194)	1.7 (1.2 to 2.4) [a]
Smoking	57 (191/338)	29 (56/191)	20 (30/147)	1.5 (1.2 to 2.4) [a]
Initial IABF (< 500 ml/min)	40 (135/338)	57 (78/135)	4 (8/203)	15 (7.3 to 29) [a]

4.2.3 Stratified analysis

The stratified analysis aimed to investigate whether the crude association between vascular access failure and initial IABF measurement was confounded or modified by selected socio-demographic and clinical variables. Confounding occurs when the apparent association between a risk factor and an outcome is affected by the relationship of a third variable to the risk factor and the outcome; the third variable is called a confounder. For a variable to be a confounder, the variable must be independently associated with the risk factor and outcome, but not be in the causal pathway between risk factor and outcome. To assess for confounding, a series of models with and without subsets of the potential confounders: age, sex, ethnicity, diabetes, hypertension, peripheral vascular disease, history of smoking, medications, IABF, and type of

procedure were compared. The fully adjusted model containing all the variables listed above is referred to by Kleinbaum and Klein [213] as the "gold standard model", all "reduced" models are compared to the "gold standard model".

The estimated crude OR for the relationship between vascular access failure and initial IABF in patients with AVGs was OR 32, (95% CI 18-49). The crude association between the vascular access failure and the initial IABF remained unchanged after stratification on each of the socio-demographic (age, sex, and ethnicity) and clinical variables (diabetes mellitus, hypertension, peripheral vascular disease, history of smoking, medication, initial IABF, and type of surgical procedure).

4.2.4 Multivariable modeling

One objectives of this study was to construct a statistical model identifying factors that are associated with vascular access failure in patients on hemodialysis with AVGs. Addressing this objective, a stepwise logistic modeling procedure was employed in order to produce a parsimonious model of factors that are associated with vascular access failure. Modeling was also used to assess whether main effects of various independent variables were confounded when a new variable was added to the model.

The stratified analysis did not indicate that any variable acted as a confounder or effect modifier of the association between vascular access failure and initial IABF. The only variables chosen for inclusion in the multivariable logistic regression analysis were those found in the univariate analysis to be significantly correlated with vascular access failure.

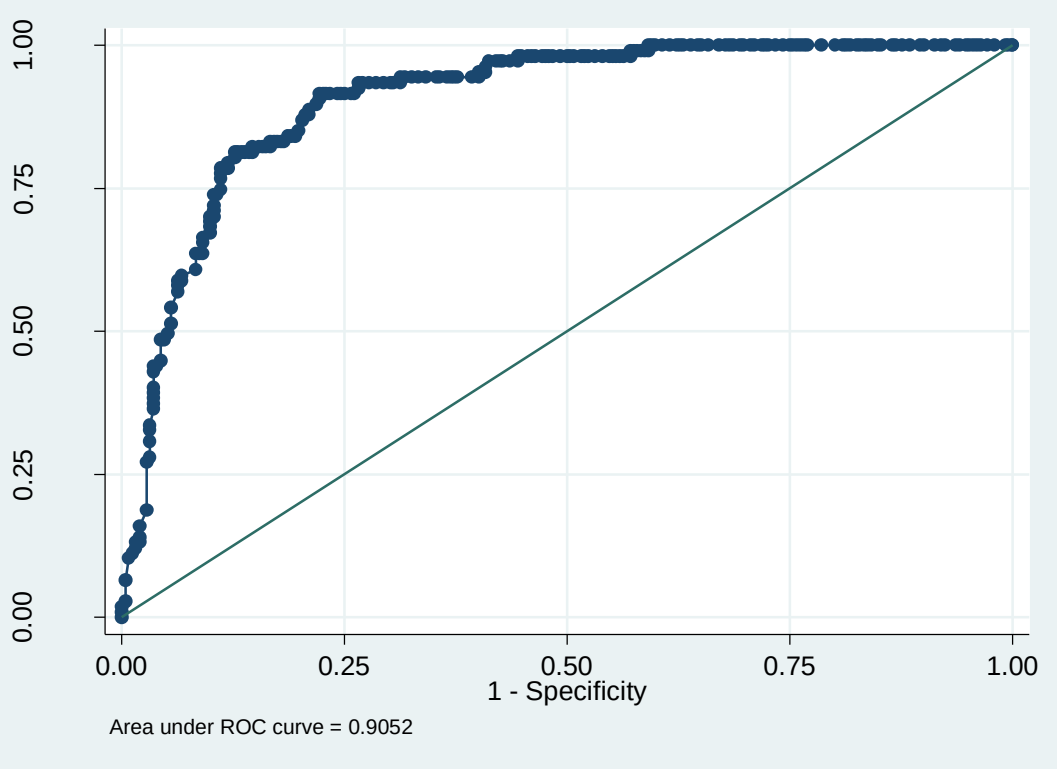
Variables with a p value of <0.25 were selected for multiple regression modeling as suggested by Hosmer and Lemeshow [214]. Variables that met those criteria were age (≥ 65), presence of diabetes, hypertension, peripheral vascular disease, history of smoking, having a forearm AVG, and having an initial IABF less than 650 ml/min. Sex was not significant in this analysis (p = 0.5); however in previous research, being female has been associated with a higher incidence of vascular access failure hypothesized due to smaller vascular structures in women [215]. Therefore, sex was included in the multiple regression model despite its lack of statistical significance.

At the multivariable modeling stage of the analysis, assessment for interaction was done. An interaction occurs when the impact of a risk factor on outcome is changed by the value of another variable. All possible pairwise interactions were tested and none were found to be statistically significant. Higher order (three-way) interaction terms, for instance sex by age by diabetes mellitus, were not considered.

4.2.5 Final model

This analysis yielded a model that includes age, history of diabetes, history of peripheral vascular disease, and IABF dichotomized at 650 ml/min. Assessment of the model fit using the Hosmer-Lemeshow goodness of fit test yielded exceptionally high p-values (p=018). This model was found to have excellent discrimination as determined by the area under the Receiver Operator Characteristics curve of 0.90 (Fig. 4.6)

Fig. 4.6 **Area under the Receiver Operating Characteristic Curve: Association of vascular access failure and initial IABF for patients with AVGs**



The final regression model demonstrates that all selected variables, remain statistically significant (Table 4.11). The odds of experiencing vascular access failure occurred in those patients with initial IABF of less than 650 ml/min (OR=31 and 95% CI 14-68), adjusting for all other covariates. A history of diabetes, being older than 65, and a history of peripheral vascular disease produced odds ratios between 3.5 and 2.5 (Table 4.11), adjusting for all the other covariates. The calculated coefficients allowed for the elaboration of a regression equation to predict the occurrence of vascular access failure. The equation may be applied using the variables selected according to the following regression significance criteria:

Logit *p* = - 5.1 + [3.4 × IABF (ml/min) (≥650 ml/min = 0, < 650 ml/min = 1)] + [1.2 × Age (<65 years = 0, ≥65 years = 1)] + [1.3 × Diabetes (no = 0, yes = 1)] + [0.9 × Peripheral Vascular Disease (no = 0, yes = 1)] .

Table 4.11 Final multiple logistic regression model: Retained dichotomized variables for vascular access failure in patients with AVGs [a]

Variable	Coefficient	OR	95 % Confidence Interval	P value
IABF_650 [b]	3.4	31	14 - 68	< 0.001
Age_65 [c]	1.2	3.2	1.3 – 7.9	< 0.001
Diabetes	1.3	3.5	1.8 – 7.0	< 0.001
PVD	0.9	2.5	1.3 – 4.8	0.005

[a] *Adjusted for age, diabetes, and peripheral vascular disease.*
[b] *Initial IABF dichotomized at 650 ml/min.*
[c] *Age dichotomized at 65 years.*

We did examine further multivariable models to examine if an outcome of thrombosis was different than the other outcomes. The results of these models was similar to the results from the classical analysis presented in Table 4.10, and is not presented here.

CHAPTER FIVE: DISCUSSION

Among the greatest challenges facing physicians and other health care professionals who care for patients with chronic renal failure is the preservation of vascular access for hemodialysis. Vascular access failure is a cause of considerable morbidity, discomfort, inconvenience and cost. Approximately 20-30% of all hospital admissions for patients with ESRD are related to complications of vascular access for hemodialysis. In order to decrease the incidence of vascular access failure and other access-related complications, the NKF-DOQI guidelines recommend that all vascular accesses undergo regular monitoring and measurement of the IABF for identification of dynamically significant dysfunction. Although following these guidelines leads to the identification of access dysfunction in both AVFs and AVGs, there remains considerable room for improvement in surveillance. The main objective of this study was to explore the association between vascular access failure and initial IABF in patients receiving chronic RRT with AVFs or AVGs.

5.1 Initial IABF

It is clear from our data that the initial IABF is quite different between patients who develop vascular access failure and those who do not, both for patients with AVFs or AVGs. Patients who developed access failure had substantially lower IABF values than patients without vascular failure.

In fact, our results show that AVF patients with initial IABF less than 500 mL/min, even without any additional risk factors, have a 16 % risk of subsequent vascular access failure and, therefore, should be routinely monitored.

5.2 Patient Characteristics

A secondary objective of this work was to determine patient characteristics associated with vascular access failure in patients with AVFs and AVGs. In the group of patients with AVFs, no difference was found between the proportion of those with and without access failure when categorized by ethnicity, sex, underlying disease, hypertension, peripheral vascular disease, use of medications, or surgeon. Therefore, these variables are unlikely to explain the association observed between low initial IABF <500 ml/min) and vascular access failure. Among these patients, a significant difference in time to access failure was found between the specific subgroups, including patients older than 65 years, patients with a history of diabetes, patients who smoke or with a history of smoking, and patients with a fistula located in the forearm.

In the group of patients with AVGs, no difference was found between the proportion of those with and without vascular access failure when categorized by ethnicity, sex, underlying disease, hypertension, smoking, use of medication, surgeon, or type of procedure. Therefore, these variables are unlikely to explain the association observed between low initial IABF <650 ml/min and the presence of vascular access failure. Among these patients, a significant difference in time to access failure was found

between the specific subgroups, including patients older than 65 years and patients with history of diabetes or peripheral vascular disease. These patient characteristics are discussed in more detail below.

5.2.1 Age

In Canada, the number of elderly people on hemodialysis continues to steadily increase. For the past 30 years, treatment of elderly patients with chronic renal insufficiency with hemodialysis has changed from being the exception (less than 10% of the patients older than 65 years in 1997) to becoming one of the largest age group represented in dialysis units (more than 49% of the prevalent patients on hemodialysis in 2001). This increase is due to both greater survival of the dialysis patient within the last few decades and to the increase in inclusion of elderly patients. The mean age at which dialysis commences has now reached 64.7 years, and the overall age of the dialysis population has risen to 62.2 years [216].

In elderly people, systemic vascular diseases, especially cardiovascular and cerebrovascular diseases, are common. As far as could be determined, while there is much published material dealing with vascular access and other hemodialysis-associated problems in general, there is little published work dealing with age as a risk factor for vascular access failure or other hemodialysis associated problems. Some studies used 65 years of age as a cut-off point for the elderly group [217-219], while other studies adopted 67 years of age [220], 70 years of age [221], or other ages. In the present study, an age cut-off of 65 years was chosen based on the literature [217-219] and the clinical

experience of surgeons doing the procedures in the Calgary Health Region. In contrast to previous studies [217, 222-224], in which there no significant difference was noticed between patient age and risk of vascular access failure, our results indicated that for patients undergoing vascular access creation, age was a risk factor for the vascular access failure in patients older than 65 years of age in both the AVF and AVG groups. Windus et al. [224] also found that older age predicted lower vascular access survival. This suggests that patients who start hemodialysis therapy after 65 years of age need special attention in order to maintain their vascular access patency, given the fact that the ORs for access failure were significantly higher in this patient population compared with patients under 65 years age.

5.2.2 Gender

The present study did not show a significant association between gender and the risk of vascular access failure. These results were consistent after adjusting for age, presence of diabetes mellitus, hypertension, history of peripheral vascular disease, smoking history and type of procedure. An association of female gender with a greater risk for access-related failure has been reported in two large studies [225, 226], although neither study investigated the results by access type. Prischl et al.[227] found no significant differences in access survival between 80 men and 43 women on hemodialysis therapy with a first AVF. Aman et al.[228] found no gender differences in access failure or complication rates in 91 patients with PTFE grafts. Feldman et al.[225] suggested that differences in vessel diameter may account for the increased access-related morbidity experienced by women in their study. In a report on surgical placement of AV fistulae. Reilly et al [229]

found that vein size was a significant predictor of subsequent fistula survival, although gender was not. A more recent European study also found that small vessel size predicted fistula failure in the first 3 months after surgery [230].

5.2.3 Co-morbid illnesses

Our study also evaluated the association of co-morbid illnesses with vascular access failure. For both the AVF and AVG groups, there was a significant difference in vascular access failure between patients with diabetes and those without, consistent with a previous report [224].

The present study also confirms an earlier report [231] of a significant association between a history of peripheral vascular disease and subsequent access failures in patients with AVGs. This association is not surprising, because the condition of the native vasculature is likely a determinant of the adequacy of any access created. The pathophysiological characteristics of peripheral vascular disease and vascular access complications may also be similar. It has been postulated that peripheral vascular disease may compromise blood flow in the access, producing a greater risk for thrombosis [232]. In the present study, the association of peripheral vascular disease and access failure was present only for patients with AVGs — patients in which the vascular anatomy did not permit the construction of a native AVF. In the present study, the decision of placing a fistula versus a graft was made directly by the surgeon intraoperatively.

5.2.4 Smoking

Smoking history has been examined in a few studies of vascular access morbidity, with inconsistent results [223, 229, 233]. In the present study, current or previous smoking was associated with an OR of 6 (95% CI, 3 to 12) for subsequent vascular access failure in the AVF group of patients. Previous peripheral vascular damage in both former and active smokers, leading to acute access thrombosis, may partially explain this observation. In patients with initial IABF greater than 500 ml/min, smoking is associated with an increase risk of vascular access failure of approximately 3.5%, suggesting that these patients should have routine vascular access monitoring. The utility of routine vascular access monitoring in patients with IABF greater than 500 ml/min and no history of smoking should be questioned.

5.3 Vascular Access Characteristics

Another secondary objective of this work was to determine vascular access characteristics associated with vascular access failure in patients with AVFs and AVGs.

Polytetrafluoroethylene (PTFE) dialysis grafts have decreased longevity compared with native arteriovenous fistulas [217, 220, 221] and are more prone to recurrent stenosis, thrombosis and infection [217]. Recognizing the superiority of fistulas over grafts, the NKF-DOQI guidelines on vascular access recommend an aggressive approach to the creation of fistulas. AVGs should be reserved for patients whose vascular anatomy does not permit the construction of a native AVF. Of all vascular accesses evaluated in this

study, 831 (70 %) were AVFs, and 30% were AVGs. The AVF utilization in this study (70 %) is higher than in the USA (32 %) and similar to that in Europe (74 %) [228, 234]. According to the Canadian Organ Replacement Registry the prevalence of AVFs and AVGs in the Canadian population is 53% and 14% respectively, compared with our cohort population that showed a significant number AVFs, superseding the goal of 50% recommended in the NKF-DOQI guidelines. This high percentage of fistulae in the Southern Alberta Renal Program reflects an aggressive division policy in terms of vascular access placement.

5.4 Study Strengths

There is limited information in the literature on the relationship between initial IABF and vascular access failure in patients with chronic renal failure receiving chronic replacement therapy. To our knowledge, this is the largest study of patients with fistulas and grafts in which initial IABF measurement was obtained for evaluation of its impact on vascular access failure. In addition, baseline co-morbid and demographic data were collected in a comprehensive, detailed, validated manner which enabled us to investigate the effect of these variables on failure of vascular access, the outcome of interest.

The present study was a population-based retrospective cohort study of prospectively collected patient data. This design reduced the impact of selection bias, because all incident hemodialysis patients with a mature access(either AVF or AVG)—meaning at least one successful functional cannulation for the purposes of dialysis affording an

extracorporeal blood flow of at least 300 ml per minute, for at least 3 hours—were included in the study sample. Cohort studies sometimes lose subjects at follow-up, In this study, 98% (1190) patients had complete follow-up and 2% (22) had incomplete follow-up (their data were excluded). The patients that were excluded were only those that died who had not reached the primary outcome i.e. it was less than 6 months, and their vascular access had not failed. Patients who had a vascular access failure within the first 6 months, and then subsequently died, were included as they met the primary outcome definition for the study. Patients excluded were so as the longevity of that access could not be determined. Loss to follow-up bias can occur when there are differences in completeness of follow-up between comparison groups. However, when comparing baseline patients and access characteristics between those who were lost to follow-up and those who completed the study, we found that the two groups were very similar. Patients who were excluded likely suffered a cardiovascular event as their cause of death. Cardiovascular events are the leading cause of death in patients with ESRD on dialysis. If so, these patients may have had both diminished IABF (through impaired cardiac performance) and would have had an increased risk of vascular access failure due to their vascular disease. By excluding these patients, our results may have underestimated the association of IABF with vascular access failure.

Patient data was abstracted electronically from two patient care databases, SARP and ALTRA. Staff in the Department of Nephrology and Transplantation maintains these databases, and data quality is assured by the staff. Thus, information bias, due to data abstraction, or data entry is considered to be unlikely. Measurement bias can arise from

the choice of tools one uses to measure. In this study, measurement of the IABF (exposure) was done in duplicate by trained nurses using the same technique, factors that reduced the variability and therefore the measurement bias. Any misclassification of baseline data was most likely of the non-differential variety, as the outcome was unknown at the time of the collection. Similarly, differential misclassification of the outcome was unlikely, as the exposure was unknown by the access nurses at the time the outcome occurred. Thus, the misclassification of outcome or exposure was not likely to be dependent on the exposure or outcome, respectively.

5.5 Study Limitations

In any study, it is important to assess whether the results cold have been influenced by any sources of bias. Bias can be introduced through the measurement of information (information bias), the methods used to identify and recruit subjects (selection bias), or through confounding.

Regarding measurement bias, as databases were reviewed to collect the information on the study variables, the accuracy of the results depends upon the quality of the information recorded in these databases. These databases are maintained for administrative and research purposes. The information on certain important variables may not have been recorded or may have been recorded casually or incompletely. For example, information on the amount smoked or number of years smoking could not be collected, as this information was frequently missed or appeared incorrect. Similarly,

thrombolytic agents have been shown to extend the longevity of the access by reduction of thrombosis, but we did not have information on the use of this therapy.

Selection bias is error due to systematic differences in characteristics between those who are selected for a study and those who are not. A potential source of selection bias in the study is the fact that patients who required angioplasty to correct an immature access or failure before the first successful cannulation were not included in the study. The rationale for exclusion was that this type of procedure changes the hemodynamics of the vascular access, making it difficult to determine the real value of the initial intra-access blood flow as a predictor of failure.

Our study definition of vascular access failure (primary outcome) was defined as any event of thrombosis, the need for surgical or endovascular revision with angioplasty, or the abandonment of the access site, whichever came first following initial cannulation and achievement of adequate dialysis. Defining angioplasty as primary outcome may have introduced another source of selection bias. This is because the guidelines of vascular access surveillance recommend angiogram/angioplasty for vascular access with intra-access blood flow less than 500 ml/min for AVFs and 650 ml/min for AVGs. Patients with intra-access flows less than the numbers mentioned above would be more likely to have an angiogram and detection of vascular access dysfunction to be treated with angioplasty, thus satisfying the definition of primary outcome used in this study. On the other hand, patients with intra-access blood flow greater than the guideline numbers would be unlikely to be sent for angiography, and the presence of potential

arterial/venous stenosis as a cause of the vascular access dysfunction may not be diagnosed. Therefore, guidelines and clinical practice during the interval that patients were recruited, might have affected the use of radiological tests to evaluate for the presence of stenosis, and resulted in differential use of angioplasty. This effect may have been a systematic differential effect between groups: being higher in the cohort with low access flow, and present in both strata (AVF's and AVG's).

Another potential threat to the internal validity of this study is the inability to measure all confounding variables. Although the data collected from the two databases were very rich and generally of high quality, there is a possibility that some variables that confound the relationships we tried to explore may not have been included. For example, a stenosis or abnormalities of the central veins, secondary to previous jugular or subclavian catheters prior to the creation of a permanent access in the extremities, could have an impact on the risk of vascular access. Likewise, thrombolytic agents, have been shown to extend the longevity of the access by reduction of thrombosis, but we did not have access to data on this use of this therapy.

Using the cut-off values of 65 years of age and IABF at 500 ml/min and 650 ml/min for AVF and AVG respectively may lead to a loss of information and consequently obscure associations that may be present in the data. Further analysis of the data could include an exploratory analysis of the data with both age and IABF examined as continuous variables.

Another limitation of the study is the short time to follow-up: only 6 months. It is well known that many vascular access failures can occur after this time frame. Early vascular access failure is more common in AVFs than AVGs and is due in part to adventitial bands, a traumatized vein, twisted veins, and veins with proximal stenosis or sclerosis from previous phlebitis or venipunctures. The primary patency of a surgically created vascular access—the initial failure of any access, whether it has matured or not (i.e. been successfully cannulated and used for dialysis), starting from the operative procedure—is approximately 60%. As many as 30% of newly placed AVFs will fail within the first three months of initial successful cannulation. On the other hand, if the AVF continues to be functional beyond this point, it has lower long-term complications and failure rates than any other alternative long term vascular access. AVGs have a lower incidence of early vascular access failure than AVFs because they are anastomosed to more proximal vessels in the forearm; the incidence of failure may increase after 6 months. However, it is the practical experience of the local surgical group, that identifying failure within a 6 month time period is clinically important.

Finally, when generalizing the study results to other hemodialysis populations, it is important to take into account the eligibility criteria of the study. The population of interest was chronic hemodialysis patients within the Southern Alberta Renal Program, and a primary criterion for study eligibility was that the patient had a vascular access (AVF/AVG) with first cannulation of the access and adequate dialysis achieved. Therefore the results of this study may be generalized to chronic hemodialysis patients

with similar characteristics undergoing similar treatment in other health regions in Canada.

5.6 Conclusions and Recommendations

Vascular access failure remains a cause of frequent and costly morbidity in patients receiving chronic hemodialysis. Investigation of determinants of vascular access failure in both AVF and AVG patients will have direct implications for patient care. First, it will allow us to potentially identify subgroups of patients at higher risk of vascular access failure and to consider modifying our surveillance of fistulas and grafts accordingly. Given that there is a subgroup of patients at higher risk, efforts need to be directed toward to finding ways for early prediction and prevention of vascular access failure in this population. Second, increased surveillance of high risk patients may identify a greater number of patients that can under go fistula/graft rescue therapy with balloon angioplasty to prevent total fistula/graft failure. Third, a modification of surveillance systems according to risk group, may result in cost savings for the health care system.

This study produced findings to help identify a group of patients at high risk of vascular access failure and for whom the current guidelines of access monitoring (monthly) should be followed given the high incidence of vascular access failure. The results demonstrated that the initial IABF was indeed a powerful predictor of vascular access failure. Additionally, the study identified other risk factors in patients with AVFs (age ≥65 years, history of diabetes and smoking, and the presence of forearm arteriovenous fistula) and in

patients with AVGs (age ≥65 years, history of diabetes, and peripheral vascular disease). Thus, to improve patency rates, the focus should be on this high-risk group of patients. However for the group of patients considered low risk, the guidelines of monthly monitoring may be excessive. Also, health care system cost may decrease if minimal surveillance is provided for patients in the low risk group.

The findings of our study suggest that for many hemodialysis patients (diabetics, or patients older than 65 years), the likelihood of vascular access failure is high, and that they will very likely require a second dialysis access procedure. Miller et al [235] reported similar results. Thus, in these subsets of patients, it might be reasonable to construct the initial fistula in the upper arm rather than the forearm, despite the NKF-DOQI guidelines recommend creating a forearm fistula in preference to an upper arm fistula. Such a strategy would maximize the probability that the first fistula constructed would be usable for dialysis. This would not only improve outcomes but would also decrease cost.

Current guidelines aimed to prevent vascular access failure are resource intensive, and based on ongoing surveillance of all patients with early intervention in those with evidence of vascular access dysfunction. The results of our study offer novel findings and a more directive approach to surveillance techniques. Specifically we have identified a set of clinical risk factors and vascular access characteristics that identify hemodialysis patients with low initial intra-access blood flow most at risk of developing vascular access failure. These clinical risk factors can be used to guide a more directive approach

and development of a vascular access screening protocol. Further work is required to confirm these initial findings, and to translate this work into meaningful clinical practice. Here are 2 examples of projects which are reasonable extensions of our results, and work which would reasonably follow our initial results. The first project might be to examine the utility of an intensive ongoing screening program with versus an initial measurement of IABF only in patients with no other identified risk factors. If the results of our research are correct, we would hypothesize that patients with normal initial IABF and no other risk factors would have a very low probably of vascular access failure, and therefore, no regular monitoring is required. Therefore, normal clinical practice would dictate that all patients will have an initial IABF measurement. In patients with normal IABF and no other risk factors, we could randomize them into 2 groups: an ongoing intensive monitoring program, and no monitoring, with an outcome of vascular access failure (at 6 months, 1 year, et cetera). If our hypothesis was correct, there might be a significant cost-savings to no longer monitoring patients who are at low risk, freeing up nurses for either more intensive monitoring of patients at high risk, or for other tasks. An example of a second project might be to target patients at higher risk for vascular access failure, with a modifiable risk factor: for example, smoking. A reasonable research study might be to randomize patients to a smoking cessation program—stratified by IABF measurement—to see if such a program either affects subsequent changes in IABF and also changes the subsequent probability of vascular access failure. In summary, our results are suggestive of further research which might assist in modifying vascular access monitoring methods, identifying treatment interventions which might modify the risk of vascular access failure, and examine the most cost-effective method of delivering this technology.

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APPENDIX 1: STUDY DEFINITIONS

Access failure: Any event of thrombosis, the need for surgical revision, endovascular intervention, or the abandonment of the access site, whichever came first.

Anticoagulation: A group of medications used to prevent blood from clotting. (ASA, Coumadin, Heparin).

Diabetes mellitus: A chronic condition associated with abnormally high levels of glucose (sugar) in the blood. Type I (insulin-dependent) diabetes results from a lack of adequate insulin secretion by the pancreas. Type II diabetes (non-insulin-dependent adult-onset diabetes) is characterized by an insensitivity of the tissues of the body to insulin secreted by the pancreas (insulin resistance).

End-stage renal disease (ESRD): An irreversible state where kidney function is less than 10-15% and renal replacement therapy (dialysis or transplantation) is required to sustain life.

Fistula (AVF): A large vein that has been attached to a nearby artery. Because it carries arterial blood under high pressure, its walls thicken (arterialize) and its lumen dilates to accommodate the increased blood flow. This process takes several weeks before the vein can have two needles inserted to provide an exit and return conduit for blood flow during dialysis.

Glomerulonephritis: A disease of the kidneys in which the glomeruli, the tiny filters in the kidneys that help to clean the blood, become inflamed or damaged. This allows protein and red blood cells to pass into the urine. If glomerulonephritis does not respond to treatment, the glomeruli may slowly be destroyed and the kidneys may lose their ability to clean the blood.

Graft (AVG): A hollow cylindrical synthetic tube that the surgeon attaches between an artery and a vein, and superficially places under the skin of the upper extremity. At the start of each dialysis session, the hemodialysis nurse attaches the arterial needle to an extracorporeal plastic tube through which the patient's blood flows, passes through the dialysis membrane, and then returns through another plastic tube to the patient via the "venous" needle.

Hemodialysis: A form of dialysis that is performed in hospital, an outpatient dialysis unit, or the patient's home. It involves sitting in a chair for 3-4 hours while the patient's blood is circulated through tubing and through a special membrane for cleansing. The patient's blood circulates from a vein in the arm or neck, through a membrane, and back to the vein repetitively during the course of dialysis session. The hemodialysis nurse has to access the venous blood by placing two needles in an arm vein or arm graft. Alternatively, the nurse accesses the internal jugular neck vein through a double lumen plastic catheter previously placed by a doctor.

Hypertension: High blood pressure, defined as a systolic blood pressure greater than 140 mm Hg and/or diastolic blood pressure greater than 90 mm Hg.

Interstitial nephritis: A form of nephritis affecting the interstitium of the kidneys surrounding the tubules. This disease can be either acute, which means it occurs suddenly, or chronic, meaning it is ongoing and eventually ends in kidney failure.

Peripheral vascular disease: Diseases of the vessels of the extremities such as atherosclerosis, resulting in diminished circulation, pain (claudication), or a blood clot.

Peritoneal dialysis: A form of dialysis that is accomplished by instilling a glucose solution through a permanent tube (the placement requires a short surgery) into the abdominal cavity and leaving the fluid in place for a period of 1 to 6 hours before it is drained out. The drainage is immediately followed by instillation of fresh fluid. This procedure is manually by the patient or automatically by a machine (usually in the patient's home) and needs to be repeated several times per day.

Polycystic kidney disease: A progressive, genetic disorder of the kidneys characterized by the presence of multiple cysts (hence, "polycystic") in both kidneys. The disease can also damage the liver, pancreas, and rarely, the heart and brain.

Smoker: A person currently smoking or self-classified as a regular smoker within the past 5 years.

Successful access cannulation: Successful use of a vascular access affording an extracorporeal blood flow of at least 300 ml per minute for at least 3 hours, using an arterial and venous needle placed in the vascular access.

Transplants: A kidney transplant is a treatment option for many people with ESRD. With advances in transplantation and improved success rates, it is now widely considered the best way of treating kidney failure. However, not all patients can have a transplant and often an organ is not available. There are two types of kidney transplants: a living donor transplant and a deceased donor transplant

APPENDIX 2: ACCESS INFORMATION ABSTRACTION FORM

1. Name (Last name, first name) _____

2. Health Care Number _____ Surgery number _____

3. Age _____

4. Gender (Male) (Female)

5. Primary cause of chronic kidney disease

Diabetes Mellitus	_____
Glomerulonephritis	_____
Ischemia/HTN	_____
Interstitial Nephritis	_____
PKD	_____
Unknown/Other	_____

6. Comorbidities

Diabetes Mellitus	(Y)	(N)
Hypertension	(Y)	(N)
PVD	(Y)	(N)
Smoking	(Y)	(N)
Anticoagulation	(Y)	(N)

7. Access Creation Date _____ (yy/mm/dd)

8. Surgeon

A	_____
B	_____
C	_____
D	_____

9. Type of Access AVF ____ AVG ____

10. Location of the access

AVF Forearm Fistula _____
AVF Upperarm Fistula _____
AVG Forearm loop graft _____
AVG Upperarm C-graft _____

11. AVF Access used

YES
NO (Access malfunction surgical/radiologic revision)

NO (death)
NO (changed to PD)
NO (transplant)
NO (other reason _____)
UNKNOWN _____

12. Initial intra-access blood flow _____ mls/min

13. Date of the initial blood measurement_____(yy/mm/dd)

14. AVG Access used

YES
NO (Access malfunction)
NO (not 6 months yet)
NO (death)
NO (changed to PD)
NO (transplant)
NO (other reason _____)
UNKNOWN (_____)

15. Confirmed access failure YES / NO (Total abandonment)

16. Date of access failure _____ (month/day/year)

17. Reason for access failure

a) Thrombosis
b) Surgical Revision
c) Radiological Intervention
d) Other _____