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Patency and Complication Rates of the Arteriovenous Fistula: A Systematic Review

Ahmed A. Al-Jaishi
The University of Western Ontario

Supervisor
Dr. Louise Moist
The University of Western Ontario

Graduate Program in Epidemiology and Biostatistics

A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

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(Thesis format: Integrated Article)

by

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The School of Graduate and Postdoctoral Studies
The University of Western Ontario
London, Ontario, Canada

Abstract

Advantages of fistulas, which include long patency and low complication rates, were ascertained over two decades ago and may not apply to the contemporary dialysis population. We conducted a systematic review to summarize the patency and complication rates of fistulas from literature published after 1999. We screened 7,008 citations and 62 articles met our criteria. The risk of primary failure was 27% (95% confidence interval (CI): 23–32%). When primary failures were included, the primary and secondary patency rates were 59% (CI 53–64%) and 66% (CI 58–74%) at one year, respectively. The median rates of infection, ischemic steal syndrome, and thrombosis were 0.11 (range 0.01–1.0), 0.05 (range 0.0–0.1), and 0.27 (range 0.04–0.68) events per 1000 patient-days. When considering the fistula as the preferred option, the initial high risk of primary failure and complication rates should be considered alongside the long-term benefits of using this access.

Keywords

arteriovenous fistula, fistula, hemodialysis, infection, ischemic steal syndrome, meta-analysis, patency, primary failure, rates, steal syndrome, systematic review, thrombosis, vascular access

Co-Authorship Statement

Chapter 3 co-authorship:

Al-Jaishi AA, MSc (c); Oliver M, MD; Thomas SM, MSc (c); Lok CE, MD, MSc; Zhang JC, MD (c); Garg AX, MD, PhD; Quinn RR, MD; Kosa SD, MSc (c); Moist LM, MD, MSc.

Chapter 4 co-authorship:

Al-Jaishi AA, MSc (c); Lok CE, MD, MSc; Oliver M, MD; Zhang JC, MD (c); Thomas SM, MSc (c); Garg AX, MD, PhD; Quinn RR, MD; Kosa SD, MSc (c); Moist LM, MD, MSc.

The concept of conducting a systematic review on patency and complication rates of the arteriovenous fistula was conceived by Drs. Oliver and Louise Moist. Drs. Moist, Oliver, Lok, and Garg aided with the building of the literature search strategy. Ms Thomas, Zhang, and Kosa acted as the second reviewer for data extraction and classification. All co-authors provided critical revisions, intellectual content and gave final approval of the manuscript. Dr. Moist was responsible for study co- supervision. There were multiple authors for Chapters 3 and 4, with my contributions cited below.

Contributions for Chapter 2 & 3: I was primarily responsible for the review supervision, concept and design of the study. I coordinated the acquisition of the data, analyzed and interpreted the data, drafted the manuscript, and incorporated author comments during the revision stages.

Contributions for Chapter 3 and 4 are explicitly outlined in **Appendix E** and **Appendix I**, respectively.

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List of Abbreviations

Arteriovenous Access: Arteriovenous fistula or Arteriovenous graft

AV-Graft: Arteriovenous graft

CI: 95% Confidence Interval

CSN: Canadian Society of Nephrology

DOPPS: Dialysis Outcomes and Practice Patterns Study

eGFR: Estimated glomerular filtration rate

ESKD: End-Stage Kidney Disease

HR: Hazard Ratio

IQR: Inter-Quartile Range

MOOSE: Meta-analysis of Observational Studies in Epidemiology

NKF/KDOQI: National Kidney Foundation Kidney Disease Outcomes Quality Initiative

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

QALY: Quality-Adjusted Life-Years

RR: Relative Risk

USRDS: United States Renal Data System

Chapter 1 : Introduction

1 Introduction

Chronic hemodialysis is a form of renal replacement therapy that involves a dialysis machine which replaces or supplements the blood filtration and fluid removal role of the kidneys for patients with end-stage kidney disease (ESKD). Prior to starting hemodialysis, patients must have a vascular access inserted or created in the form of an arteriovenous fistula (fistula), arteriovenous graft (AV-graft), or central venous catheter (catheter). A vascular access provides the connection between the patient's bloodstream and the hemodialysis machine.

A complication-free, functioning vascular access continues to be the Achilles' heel of hemodialysis therapy. The fistula is the preferred type of vascular access due to its longer patency or survival rate and lower complication rates.[1–4] Use of a fistula is also associated with lower mortality compared to the AV-graft and catheter.[1–4] However, the advantages of the fistulas were ascertained over two decades ago and may not apply to the contemporary hemodialysis population.

To describe fistula outcomes in the last decade we conducted two studies: 1) A systematic review, meta-analysis and meta-regression of the risk of primary fistula failure, primary fistula patency rate, and secondary fistula patency rate; and 2) A systematic review of fistula complication rates including infection, ischemic steal syndrome, and thrombosis. Our objectives were to efficiently summarize literature published between January 2000 and June 2012 on the fistula patency or survival and complication rates, as well as to identify existing knowledge gaps.

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Chapter 2

2 Literature Review

2.1 End-Stage Kidney Disease

End-stage kidney disease (ESKD) occurs when the kidneys are no longer able to function at a level needed for day-to-day life.[1] The burden of ESKD in Canada is growing; since 1990, the incidence has increased by 58% and recently stabilized, while the prevalence has increased more than 200% and continues to grow.[2] Patients with ESKD have a reduced health related quality of life and a five-year mortality rate of less than 50%.[3–6] The treatment of ESKD is renal replacement therapy by means of a kidney transplant or dialysis (peritoneal dialysis or hemodialysis).

The care of patients with ESKD is resource intense and places a heavy burden on the patient, family, and the healthcare system.[7–10] For example, patients with ESKD represent 0.11% of the Canadian population, however, Manns et al.[8] reported 1.2% of all Canadian public health expenditure in 2002 was directed towards ESKD treatment.[6] Using estimates from the Ontario Renal Network, the cost of hemodialysis management is approximately $500 million per year for approximately 11,000 patients.[11] In 2009, the annual average Canadian cost of hemodialysis treatment was $60,000 per patient.[12] It should be noted that this cost did not incorporate the cost of managing or diagnosing hemodialysis complications, surveillance of vascular access complications, and hemodialysis related-hospitalizations.

Each patient with ESKD is uniquely affected by the burden attributed to social and economic changes. Similar to chronic diseases such as cancer and HIV, the number and severity of symptoms experienced by patients with ESKD contribute significantly to the patient's quality of life.[13,14] However, there are unique aspects related to hemodialysis,

that can affect the patient's perception of his or her quality of life. For example, once on hemodialysis, patients have significant diet and fluid restrictions. Additionally, due to symptoms and time spent on hemodialysis, patients may experience changes in their employment status, recreational activities, and social roles. Being on hemodialysis may be financially burdensome to the patient and their families because of potential loss of income due time taken off work, travel to and from the dialysis facility, time spent on hemodialysis, as well as dialysis related transportation costs. Further, a family member or a friend may be needed to help prepare the patient for dialysis, drive the patient to the dialysis facility, and help deliver them home safely, exerting a greater burden. In a cohort of patients (n=101 patients) at the London Health Science Center, Diamant et al.[15] found that patients had to travel an average of 82 minutes to get to the dialysis facility and spent $42 per week on transportation. Furthermore, 86% of patients required an additional person (family/friend or other) to drive them to the dialysis facility.

2.2 Modalities of Renal Replacement Therapy

2.2.1 Kidney Transplantation

Kidney transplantation is the preferred treatment option for ESKD. Approximately 40% of patients with ESKD in Canada have a pre-emptive transplant, and 3.5% of patients starting renal replacement therapy begin with this type of treatment.[6] Transplantation is associated with improved patient quality of life, morbidity, mortality and reduced burden on the healthcare system.[12,16] Kidney allograft survival is approximately 94% at one year and 89% at two years when the organ is procured from a living donor.[17,18] When the kidney is procured from a cadaveric donor, the allograft survival is 83% at one year and 77% at two years.[17,18] Compared to dialysis patients, individuals who receive a kidney

transplant have a 70% risk reduction in mortality and a dramatic improvement in quality of life.[16,17] An economic analysis of patients with Type 1 diabetes and ESKD found that kidney transplantation was associated with 10.29 quality-adjusted life-years (QALY), whereas dialysis was associated with 4.52 QALY.[19] Furthermore, patients will, on average, live 10 to 15 years longer with a kidney transplant compared to those on dialysis.[16,19] However, not all patients are eligible or able to receive a kidney transplant.

Currently, the number of kidney donations does not meet the demand for organs.[20] In 2005, transplant waitlists were increasing at a rate of 233 per million population in the United States, and 85 per million population in Canada.[20] The corresponding transplant rates for the United States and Canada were 51 and 32 per million population, respectively.[20] As a result, a large proportion of patients must undergo dialysis to replace kidney function.

2.2.2 Dialysis

Chronic dialysis is a form of renal replacement therapy that uses an internal or external non-kidney semi-permeable membrane filter that replaces or supplements the blood filtration and fluid removal role of the kidneys for patients with end-stage kidney disease. There are two types of dialysis: peritoneal dialysis and hemodialysis.

2.2.2.1 Peritoneal Dialysis

Approximately 10% of patients with ESKD in Canada are on peritoneal dialysis, and 17% of patients starting renal replacement therapy begin with this type of treatment.[6] In peritoneal dialysis, the non-kidney filter is the peritoneal membrane (an internal filter). An external catheter (hollow tube) is inserted into the abdominal cavity (peritoneum) and is used to fill the abdomen with dialysis solution (dialysate). The peritoneal membrane

filters waste products and extra fluid from the blood to the dialysate, which is then removed by drainage through the catheter. Peritoneal dialysis is usually performed in the home, but can be performed at work or in other environments, and offers patients the advantage of control and independence over the timing, duration and location of dialysis treatment. Utilization of peritoneal dialysis, however, may not be feasible in a proportion of patients due to medical and/or social contraindications.[21] An increasing majority of frail and/or elderly patients are encountering barriers to self-care peritoneal dialysis.[22–25] Physical barriers include failing strength to lift peritoneal dialysis solution bags, poor vision, as well as immobility which are present in 37%, 25%, and 20% of the peritoneal dialysis population, respectively.[26] As a result, such patients would require support from a family member and/or home care assistance to aid with peritoneal dialysis treatment. Physical and/or cognitive barriers and absence of an appropriate support system are important determinants of peritoneal dialysis eligibility.

2.2.2.2 Hemodialysis

Hemodialysis is the most common treatment modality for Canadian patients with ESKD. Approximately 50% of patients with ESKD in Canada are on hemodialysis, and 80% of patients starting renal replacement therapy begin with this type of treatment.[6] Hemodialysis removes waste products and excess fluid by passing blood through an external semi-permeable membrane within a hemodialysis machine. The hemodialysis machine consists of the filter "dialyzer", dialysate solution, and a blood circuit which connects to the patient's vascular access.

Chronic hemodialysis is provided either in the home or in a dialysis facility (which may be attached to or independent of a hospital). In conventional hemodialysis, the patient

receives hemodialysis three to four times per week, for approximately three to five hours per session. For some patients, hemodialysis is prescribed five or six times per week for 2 to 3 hours per session (frequent hemodialysis). Other patients are prescribed hemodialysis overnight for 6 to 8 hours per session (nocturnal hemodialysis) at a frequency of five to six times weekly. Regardless of the type of hemodialysis, the patient's blood circulation must be connected to a dialysis machine via a vascular access. There are three traditional types of vascular access utilized, fistulas, AV-grafts, and catheters.

2.3 Vascular Access

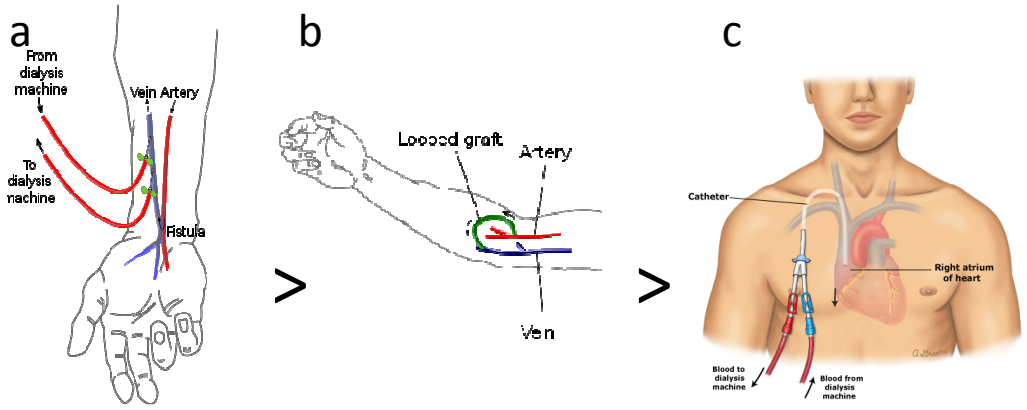
2.3.1 Types of Vascular Access

Arterio-venous (AV) fistulas are surgically created, typically in the patient's non-dominant forearm or upper arm by connecting an artery directly to a vein (**Figure 1a**). This anastomosis allows for higher blood flow directly from the artery through the vein. As a result, the vein distends and thickens over time (matures) allowing for repeated needle cannulations for hemodialysis treatment. Thus, creation of a fistula requires advance planning because it can take up to six months to mature and be used for hemodialysis.

AV-grafts are also surgically created by using a synthetic tube to connect the arterial and venous circulations (**Figure 1b**). The AV-graft becomes an artificial vein that can be used for repeated cannulation and blood access for hemodialysis. Unlike the fistula, the AV-graft does not need to mature. However, traditional AV-grafts require two to three weeks for swelling and bruising to subside before use.

Catheters are inserted into the patient's internal jugular, subclavian, or femoral vein. The most common placement is the internal jugular vein in the neck (**Figure 1c**). Catheters

are indicated for same day placement and immediate use for hemodialysis. Furthermore, hemodialysis patients who are not suitable for creation of an arteriovenous access (fistula or AV-graft) will use a catheter.



Source: From Google

Figure 1. Types of vascular access: a) arteriovenous fistula [fistula] b) arteriovenous graft [AV-graft], and c) central venous catheter [catheter]

2.3.2 Burden of Vascular Access

Vascular access and its associated complications are significant contributors to rising morbidity, mortality, reduced patient quality of life, and burden on the healthcare system.[10,20,27,28] Complications such as thrombosis (blood clots in the vascular access), and infections account for nearly 30% of hospital admissions in hemodialysis patients.[9,27,29] These complications consume a significant proportion of outpatient resources including vascular access monitoring and diagnostic radiology.[9,27,29] Manns et al.[10] reported the mean cost of access care during the first year of dialysis per patient-year at risk was $7,989 for a fistula, $11,685 for an AV-graft, and $9,180 for a catheter. These costs included cost of surgery, radiology, hospitalization for access complications,

physician services, management of outpatient bacteremia, and vascular access monitoring.

2.3.3 Comparing Outcomes of Patients Receiving Hemodialysis by Vascular Access Type

Clinical practice guidelines strongly advocate for the fistula as the preferred vascular access.[30–32] Fistula use has been associated with lower morbidity and mortality compared to both AV-grafts and catheters. The preferred vascular access placement (in order of preference) is radiocephalic fistula (at the wrist), brachiocephalic fistula (at the elbow), transposed brachiobasilic fistula (upper arm), followed by a forearm loop AV-graft, upper arm AV-graft, lower extremity AV-graft, and finally with catheters being least preferred option.[30–32] In **Section 2.3.3.1** to **Section 2.3.3.3**, we compare the risk of patient mortality and hospitalization between each type of vascular access.

2.3.3.1 Catheters versus fistulas

<u>Mortality</u>

In a study of 4,196 incident patients (number of patients: fistula=626; catheter=3,570), Wasse et al.[33] found that there was a statistically significant decrease in the all-cause mortality comparing patients using a fistula to those using a catheter. Patients who used a fistula had a 29% hazard reduction (HR=0.71; 95% CI 0.62 to 0.82) in all-cause mortality compared to patients who used a catheter. Using Canadian data, Moist et al.[34] found that there was a 37% (RR=0.63; 95% CI 0.57 to 0.69) risk reduction in all-cause mortality when comparing patients using a fistula or AV- graft to initiate dialysis compared to those using a catheter. Examining cardiovascular-related mortality, the adjusted (for age, sex, race, and co-morbidities) hazard ratio was 0.69 (CI 0.56 to 0.84) for patients who used a fistula compared to those who used a catheter at 90 days after initiating dialysis. In

a propensity score matched cohort (n=1,479), Polkinghorne et al.[35] reported an all-cause mortality rate of 115 per 1000 person-years ([CI 94 to 142; 90 deaths) in patients with fistulas and 242 per 1000 person-years (CI 211 to 277; 209 deaths) in patients using a catheter. Results from a systematic review and meta-analysis from 62 studies (n=586,337 patients) collected between 1985 and 2011, Ravani et al.[36] reported a 53% risk increase (RR=1.53; CI 1.41 to 1.67) in all-cause mortality comparing patients using catheter to those using a fistula.

Hospitalization

Catheter use is associated with an increased risk of infection-related complications, RR=2.77 (CI 1.83 to 4.21) and vascular access-related hospitalization, RR=3.10 (CI 2.05 to 4.68) when compared to fistula use.[37] Patients using a catheter had a rate of 38.8 (35 to 44) hospitalizations per 100 person-years, while patients using a fistula had a rate of 23.8 (CI 17 to 32) hospitalizations per 100 person-years.[37] This relation of increased risk of hospitalization is also consistent across facilities with higher catheter use. Facilities with higher catheter use have been shown to be an independent predictor of hospitalization risk, even after adjusting for patient demographics, laboratory values, and comorbidities.[38,39] Data from the Dialysis Outcomes and Practices Patterns Study (DOPPS) show that facilities with >21% of patients using a catheter had a 1.6 fold increased risk of hospitalization as a result of infections compared facilities with ≤7% of patients using catheters.[38] In a meta-analysis, Ravani et al.[36] found a 68%increased risk (RR=1.68; CI 1.33 to 2.12) of hospitalization comparing patients using a catheter to those using a fistula. Furthermore, patients who dialyzed using a catheter spent on average 1.7 to 3.7 times longer period in a hospital compared to those who used a fistula.[40]

2.3.3.2 Catheters versus AV-grafts

Mortality

Polkinghorne et al.[35] investigated the risk of mortality between prevalent catheter and AV-graft use in the Australian and New Zealand Dialysis and Transplant Association (ANZDATA) registry data. Polkinghorne et al.[35] reported a 67% (RR=1.67; CI 1.15 to 2.43) risk increase in all-cause mortality comparing those using a catheters versus AV-grafts. The crude rate of all-cause mortality was 261 (CI 233 to 293) deaths per 1000 person years for catheters, and 146 (CI 115 to 185) deaths per 1000 person-years for AV-grafts.[35] When examining only diabetic patients, two studies reported different results in regards to the risk of all-cause mortality between those using catheters versus AV-grafts. Allon et al.[41] reported a relative risk of all-cause mortality of 3.11 (CI 2.31 to 4.19), while Dhingra et al.,[28] reported a RR of 1.09 (CI 0.77 to 1.54) for all-cause mortality comparing diabetic patients using a catheter versus an AV-graft. In a meta-analysis comparing catheters to AV-grafts, Ravani et al. reported a 38% risk increase (RR=1.38; 1.25 to 1.52) in all-cause mortality.

Hospitalization

Among patients who were hospitalized for any reason, those using a catheter spend on average 6.9 (CI 0 to 24) days in the hospital compared to 6.6 (CI 0 to 25) days for patients using an AV-graft.[37] Catheters are at high risk of vascular access-related infections and infection-related hospitalization. For example, there is a 40% increase in the risk of hospitalization for patients using catheters compared to those using an AV-graft.[37] Patients dialyzing with a catheter at baseline experience a hospitalization incident rate of 170 per 100 person-years (CI 160 to 180) compared to 121 per 100 person-years for AV-grafts (CI 108 to 136).[42] Ravani et al.[36] reported a pooled relative risk of 1.51 (CI

1.30 to 1.75) in all-cause hospitalization comparing patients using a catheter to those using an AV-graft.

2.3.3.3 AV-grafts versus fistulas

Mortality

There is conflicting results on all-cause mortality when comparing AV-grafts to fistulas. Polkinghorne et al.[35] reported a crude all-cause mortality of 86 (CI 76 to 98) deaths per 1000 person-years for fistulas compared to 146 (CI 115 to 185) for AV-grafts. After adjusting for morbid conditions and propensity score, there was a 1.55 (CI 1.15 to 2.07) hazard ratio for all-cause mortality comparing AV-grafts to fistulas.[35] The authors stratified on the presence of coronary artery disease and adjusted for age, gender, late referral, peripheral vascular disease, and cerebral vascular disease. Similarly, in a study of 25,226 patients, Xue et al.[43] reported a significant increase in the risk (RR=1.16; CI 1.08 to 1.24) of all-cause mortality when comparing patients using AV-grafts and fistulas. However, we identified five studies that found no association between type of arteriovenous access (fistula or AV-graft) used and all-cause mortality.[28,33,41,44,45] Although there is a lack of consensus across studies, there is a consistent trend towards a higher risk of all-cause mortality comparing patients using an AV-graft versus a fistula. In a meta-analysis, Ravani et al.[36] found an 18% (RR=1.18; CI 1.07 to 1.27) increase in the risk of all-cause mortality when comparing individuals using an AV-graft to those using a fistula.

Hospitalization

Using a random sample of 2635 incident patients from the United States, patients using an AV-graft at baseline experienced a hospitalization incidence rate of 121 (CI 108 to

136) compared to 104 (CI 90.5 to 118) per 100 person-years for patients using a fistula.[37] When comparing AV-grafts and fistulas within the first six months of hemodialysis start, there was no difference in the risk all-cause hospitalizations (RR=1.15; CI 0.94-1.40). However, when exploring risk of specific hospitalizations, AV-grafts had a 91% increased risk of vascular access-related hospitalizations compared to patients using a fistula.[37] Indeed, these results were further supported by Pisoni et al.[39] using facility data collected by DOPPS. The authors reported a 10% greater risk (RR=1.10; CI 1.02 to 1.19) in all-cause hospitalizations for every 20% greater facility use of AV-grafts. As expected, the authors also found a substantially greater risk of vascular access-related hospitalizations among facilities with greater use of AV-grafts.[39] Pooling results of all-cause hospitalizations in a meta-analysis, Ravani et al.[36] found that individuals using an AV-graft had a 26% increase (RR=1.26; CI 1.13 to 1.40) in the risk of all-cause hospitalization compared to those using a fistula. The increased risk of hospitalization is postulated to be due to the higher risk of thrombosis, as well as vascular access-related infections associated with AV-grafts.

2.3.3.4 Limitations of Studies Included Above

Studies comparing vascular access types are generally observational in nature and susceptible to high risk of bias and confounding by indication. Ravani et al.[36] found that among studies reporting on vascular access, the description of methods was generally incomplete and all studies were at moderate or high risk of bias, especially selection bias. To assess study quality, Ravani and colleagues addressed two questions for each quality domain to define the risk of bias. The risk of bias for each domain was defined as low if the answer was ‘Low Risk of Bias’ for both questions; moderate if only one was ‘Low

risk of bias' and the other 'High risk of bias' or 'unclear'; and high if neither was 'Low risk of bias' (i.e. both answers were 'High risk of bias' or 'unclear'). Furthermore, the current evidence for vascular access must be interpreted with caution due to the high degree of heterogeneity between studies. There are a number of factors that may contribute to this heterogeneity including variability in monitoring, vascular access care, and patient case mix. Currently, there are no randomized control trials that evaluate the benefits and harms of hemodialysis vascular access.[36] Therefore, the current vascular access literature provides low-quality observational evidence that is vulnerable to confounding by measured and unmeasured variables.

2.3.4 Vascular Access Trends

Placement of the appropriate vascular access for each patient is a key priority in order to minimize complications, thereby reducing associated costs, morbidity and mortality. Vascular access clinical performance measures,[46] and initiatives such as the "Fistula First"[47] all share the common goal of optimizing management of vascular access and increasing the appropriate creation and subsequent use of fistulas. These initiatives aim to increase fistula use to >60-65% among prevalent patients.[30,47] Globally, Canada has consistently had one of the lowest rates of fistula use.[48] In 2010, Canadian registry data revealed that only 17% of incident and 46% of prevalent hemodialysis patients dialyzed using a fistula (**Figure 2 and 3**). The use of AV-grafts was 1% among incident and 4% among prevalent patients (**Figure 2 and 3**). The low fistula and AV-graft incident use has remained unchanged since 2001. However, the prevalent use continues to progressively decline, despite the recommendations from the clinical practice guidelines.

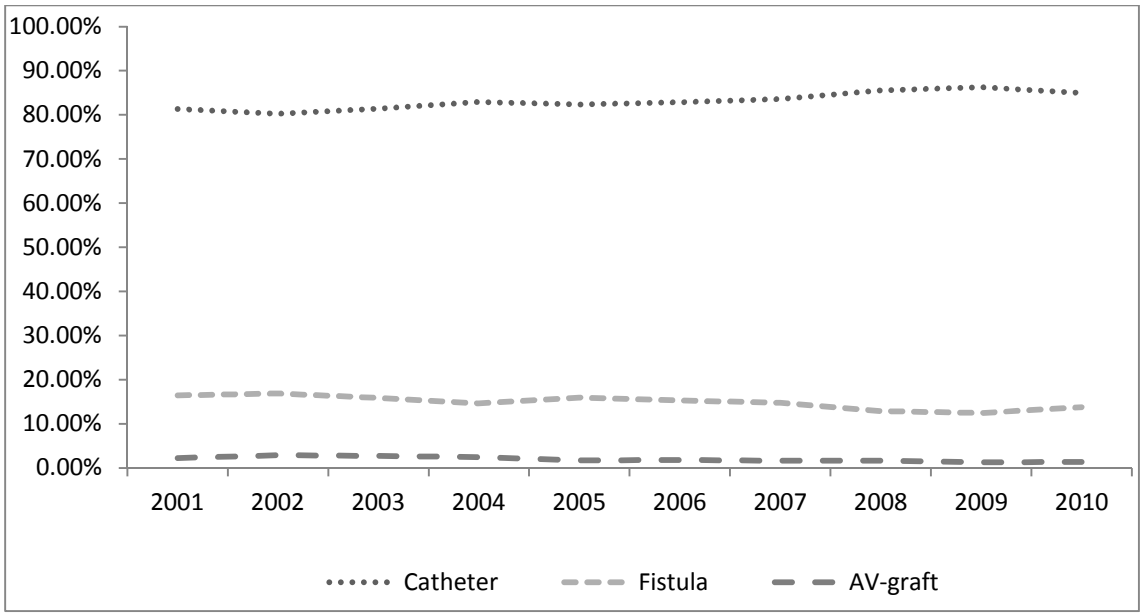


Figure 2. Incident vascular access use among Canadian adult patients ≥18 years.[6]

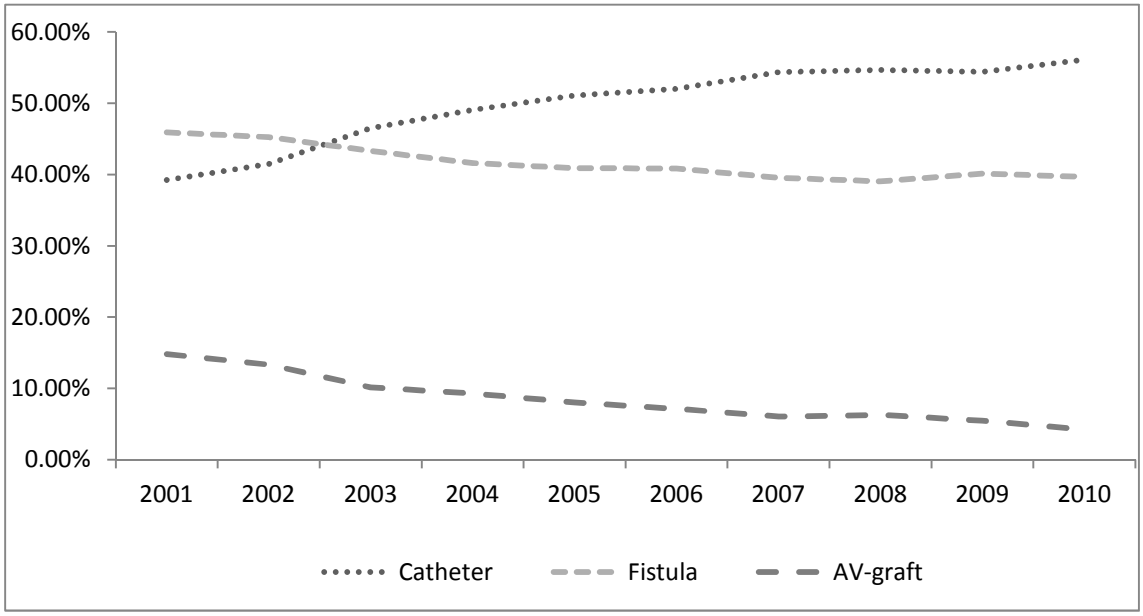


Figure 3. Prevalent vascular access use among Canadian adult patients ≥18 years.[6]

2.3.5 Barriers to Optimal Vascular Access Creation and Use

2.3.5.1 Aging hemodialysis population with increasing numbers and complexities of comorbidities

Older age and increased comorbidities are important determinants in the use of an arteriovenous access. There is a large body of literature associating low rates of fistula use among the elderly (age >65), females, Caucasians, and those patients with diabetes, peripheral vascular disease, and coronary artery disease.[48–51] It makes pathophysiologic sense for older age and co-morbid conditions to impact fistula use because adequate blood inflow and output are required for fistula maturation and would be hampered by diseased vasculature and poor cardiac output.[52] The changing patient demographics and the increasing proportion of frail and/or elderly patients in the recent decade may further decrease fistula creation and performance. Indeed, 58% of Canadian patients starting hemodialysis were ≥ 65 years of age in 2011, compared to 33% in 1990.[53] Given the aging hemodialysis population and the increase in accompanying complexities of comorbidities, it would not be surprising to see arteriovenous access creation, performance or use decrease overtime.

2.3.5.2 Difficulty predicting the rate of kidney loss and when to initiate hemodialysis, as such, the optimal timing for arteriovenous access creation is challenging

It is difficult to accurately determine the optimal timing of vascular access creation as timing of dialysis initiation is difficult to predict. In fact, hemodialysis initiation is unplanned in up to 50% of patients, primarily because of late ESKD diagnosis, urgent medical indications, or acute inter-current illnesses in a patient with chronic kidney disease.[54–57] Patients with unplanned dialysis starts usually initiate dialysis with a catheter. Additionally, the competing risk of death exceeds the rate of progression to

ESKD among the elderly with chronic kidney disease.[58] Thus, if a vascular access was created in all patients at a certain level of kidney function, a significant number of patients would die before starting dialysis. This utilizes limited resources that could otherwise be used for patients who might benefit. Therefore, in the elderly, one has to estimate the risk of dying compared to the risk of starting dialysis. For example, data from Veterans affairs estimates that if all patients over age of 80 years had an access created at a estimated glomerular filtration rate <25 ml/min/1.73m^2, only one patient out of six would in fact use their vascular access for dialysis.[59] In an Ontario study, 9% of patients who had an arteriovenous access created during the pre-dialysis period died before needing hemodialysis and another 10% never required dialysis after a follow-up of 39 months.[60] This means 19% of arteriovenous accesses were created too early in the course of chronic kidney disease progression and were unnecessary procedures.

2.3.5.3 Late nephrology referral or urgent hemodialysis starts

Late nephrology referral (<3 months of nephrology care prior to dialysis start) is associated with unplanned dialysis starts, higher catheter use, and adverse health outcomes.[61–64] This is not surprising as fistulas may take up to 6 months to mature. Thus, late nephrology care limits the planning and preparation time to creating an arteriovenous access. In contrast, adequate pre-dialysis care takes months to years in order to prepare the patient for living with chronic kidney disease and help the patient decide on modality choice (pre-emptive kidney transplant versus peritoneal dialysis versus hemodialysis) before a patient can be appropriately referred for dialysis access assessment. Beyond this process, time is required for surgical consultation, operation room booking, and unexpected cancellations. Appropriate pre-dialysis care and arteriovenous access

placement has been shown to reduce risk of mortality. However, the benefit of early nephrology care is negated by initiating hemodialysis using a catheter.[65]

2.3.5.4 Suboptimal pre-dialysis care, including lack of process to assist patient decision makings, identifying suitable patients for an arteriovenous access, and a shortage of surgical and radiological expertise and resources

Although 60% to 70% of new patients with ESKD in Canada are seen by a nephrologist ≥12 months before starting hemodialysis,[51] only 20% of patients initiate hemodialysis using an arteriovenous access. Barriers to arteriovenous access creation exist at the health care organizational, institutional, provider, and patient levels. These barriers of vascular access creation even exist among those under a nephrologist's care in the chronic kidney disease clinic. At the patient level, patients with chronic kidney disease face many decisions about the type of dialysis modality they want (hemodialysis, peritoneal dialysis or transplant), and other pressing issues as they start dialysis, often delaying the process in arteriovenous access creation.[66–68]

Patient delays and sub-optimal process of arteriovenous access creation is further complicated by lack of resources and access to timely radiological and surgical care.[51,69] In a Canadian study, system/resource limitations had the greatest influence on catheter use within the first six months of hemodialysis.[69] Compared to Europe and the United States, Canada has fewer vascular access surgeons per 100 hemodialysis-patients, and consequently less hours devoted to vascular access surgery.[51]

Canadian nephrologists were asked to identify barriers to arteriovenous access use among incident and prevalent patients.[70] The majority of nephrologists felt patient delays in decision making, patient refusal of arteriovenous access creation, and long wait times for

surgical and radiological care contributed substantially to barriers achieving a functional arteriovenous access. Studies suggest that having a defined care pathway that includes dialysis modality education (**Figure 4**), higher estimated glomerular filtration rate thresholds for surgical referral, and a patient tracking database can lead to timely vascular access placement and improve patient outcomes.[71] In contrast, the tension with the unnecessary procedures and cost, and other studies indicating lack of significant benefit of long term follow-up in pre-dialysis with regards to initiating dialysis with an arteriovenous access, highlights the need to study specific process gaps, failures and successes in a rigorous manner.

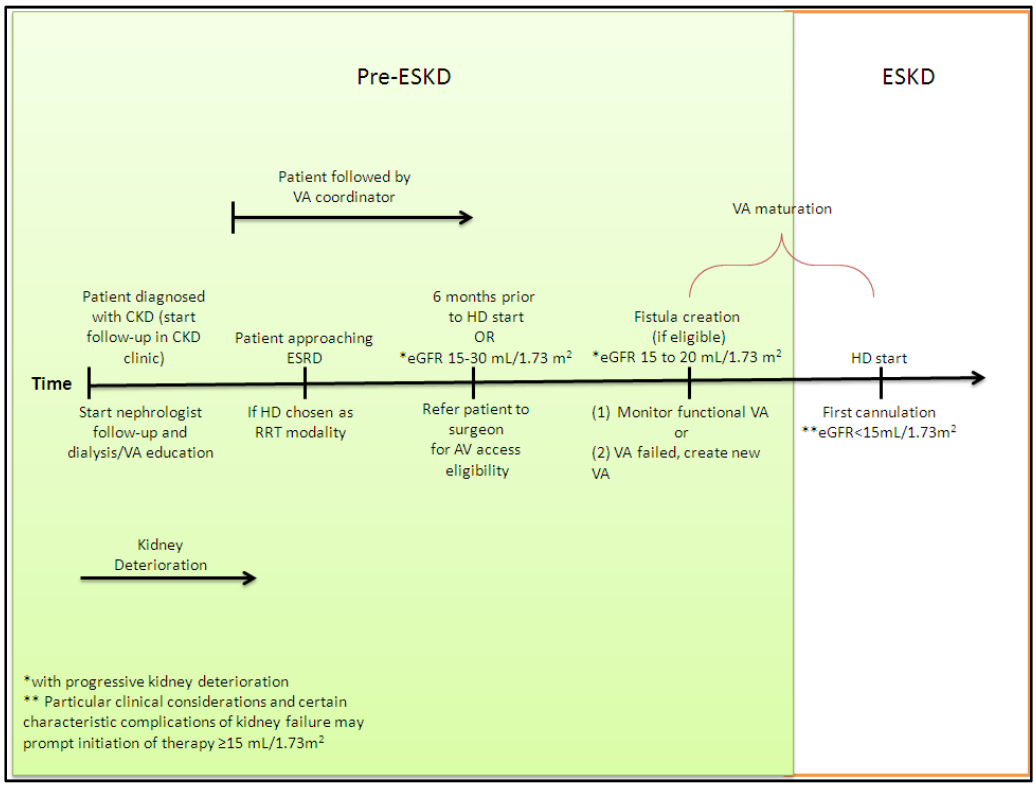


Figure 4. Defined care pathway that includes dialysis modality education, higher eGFR (estimated glomerular filtration rate) thresholds for surgical referral and fistula placement. AV=Arteriovenous; CKD= Chronic Kidney Disease; ESRD=End-stage Renal Disease; ESKD=End-Stage Kidney Disease; HD=Hemodialysis; RRT=Renal Replacement Therapy; VA=Vascular Access

2.3.5.5 High rates of arteriovenous access failure and non-suitability for dialysis once created

As defined by a previous study,[52] several decades ago, fistulas had acceptable risk of primary failure ranging between 10% to 24%[72–75] and 1-year primary and secondary patency rates between 65% to 94%[74,76–78] and 85% to 90%, respectively.[79] Compared to data published prior to 2000, there has been a significant decrease in the performance of fistulas over time, with current data suggesting primary failure rates of 24% to 60%.[80–88] The 1-year primary and secondary patency rates from recent published literature range between 43% to 87% and 52% to 89% respectively.[81,82,85,86,88–92] Older age (>65 years), coronary artery disease, and peripheral vascular disease are some of the clinical factors that are consistently associated with the increase risk of arteriovenous access failure and as a result lead to catheter use.[49,71,93]

2.3.5.6 Variability of practice patterns

Both surgical creation and nursing cannulation experience and skill set independently impacts arteriovenous access creation, dialysis suitability, and maintenance. However, there is a wide variation in practice patterns that exist between regions and individual dialysis programs in terms of emphasis on types of vascular access placement and care.

Data from the DOPPS show marked variation in the number of vascular accesses created and emphasis on vascular access education among surgical training programs.[94] There were marked differences across countries regarding number of vascular access surgeons per hemodialysis unit, number of vascular access placed during surgical training, and number/type of vascular access creations per surgeon in the preceding 12 months. A greater number of fistula placement during surgical training was an independent predictor

for patients receiving a functional access in practice. Surgeons who created at least 25 fistulas during their surgical training had a 34% lower risk of creating fistulas that had a primary failure compared with those with <25 fistula creations.[94]

In addition to surgical expertise, nursing cannulation skills and experience with arteriovenous access care has a paramount influence on vascular access-related outcomes. Cannulation skill and the level of vascular access care provided by the dialysis nurse affects the risk of complications and have a vital role in patient satisfaction.[95] A deficit in nursing experience can cause an increase patient dissatisfaction, pain during needling, prolonged vascular access bleeding, as well as clotting and infections.[95] It is well established that procedural skills require a minimal set time per week of performing the skill to maintain its proficiency.[96] In an environment where ≥80% of patients initiate dialysis with a catheter, nurses are likely to lose their cannulation skills, resulting in damaged arteriovenous accesses and a further prolonged dependence on catheters.

2.3.6 Factors Affecting Long-term Fistula Outcomes

The natural development of the fistula includes remodelling of the vein once the arteriovenous anastomosis has been created and as a result may favour stenosis and eventually thrombosis. During the process of maturation, there is a significant increase of blood flow. Initial blood flow rate within the radial artery increases from 20-30 ml/min before fistula creation to 200-300 ml/min immediately after surgical creation of the fistula.[97] This flow rate increases to 600-1200 ml/min in a few weeks after surgery, provided there are no complications and the blood vessels are healthy.[97,98] In a series of 17 radiocephalic fistulas, Lemonte et al.[99] reported that blood flow through the brachial artery to the fistula was >480 mL/min at 28 days post-surgical fistula creation. This

suggests that a clinical assessment of fistula development can be made at 4 to 6 weeks after creation.[100] In fact, there are programs that evaluate fistula maturation as early as one month post-surgical construction.[101] Fistulas failing to achieve adequate (>500 mL/min) flow rates by 6 to 8 weeks will likely require surgical/radiological interventions or perhaps a creation of a second permanent access in the event the fistula is not salvageable.[30]

Not surprisingly, fistula failure can be expected to occur when the vessel wall is either not ready to be used (non-maturation), is damaged (due to poor surgical creation, as well as early and/or unskilled cannulation), becomes abnormal (atherosclerosis, calcification, and/or fibrosis/stenosis), and/or when the blood and/or the vessel walls contain coagulating factors favouring fibrin formation and platelet aggregation.[98] As discussed above (**Section 2.3.5.5**), several clinicopathological risk factors have emerged from observational studies that can be incorporated in assessment for risk of fistula failure.[49] Although inconsistent results have been observed, gender, age, diabetes, and cancer, for example, are associated with higher risk of fistula failure.[93,102–104] Conversely, cardiovascular disease, late referral to nephrologist, and previous radiological intervention of the fistula or catheter use are consistently associated with shortened fistula patency even after adjusting for co-morbid conditions and other prognostic factors.[105,106] These factors shed light on the importance of referring patients early to a nephrologist for timely assessment and placement of a permanent vascular. Additionally, these factors become increasingly important when screening for eligible patients for fistula creation.

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Chapter 3

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3 Patency Rates of the Arteriovenous Fistula for Hemodialysis: A Systematic Review and Meta-Analysis

3.1 Introduction

Hemodialysis clinical practice guidelines endorse the arteriovenous fistula (fistula) as the preferred form of vascular access. Its use is associated with fewer complications, improved access survival, and lower risk of mortality compared to an arteriovenous graft or central venous catheter.[1–3] However, the fistula has a high risk of primary failure due to early thrombosis and maturation failure.[4,5] The changing patient demographics and the increasing proportion of frail, elderly patients in recent decade, may further decrease fistula performance. Indeed, 58% of Canadian patients starting hemodialysis were ≥ 65 years of age in 2011, compared to 33% in 1990.[6] Estimates of primary fistula failure, as well as primary and secondary patency vary considerably in the literature (standardized definitions of these outcomes are presented in **Box 1**). Recent reports estimate primary fistula failure and 1-year primary patency to range between 30% to 70% and 40% to 70%, respectively.[7–11]

Knowledge of fistula performance not only informs patient consent and quality improvement initiatives but more importantly guides patient and clinician decision-making. A better understanding of fistula performance can help explain the discrepancy in fistula use between best practice recommendations and current practice, and help re-evaluate standards for what is deemed "best practice".[12] In the present study, we conducted a systematic review and pooled estimates of primary failure, as well as primary and secondary patency rates (1 and 2-year) from prospectively collected data published between January 2000 and June 2012. We aimed to improve the precision of

fistula performance estimates, as well as explore the influence of study and patient characteristics on the overall parameter estimates. In subgroup analyses, we examined the effect of fistula location (lower vs. upper arm), age (elderly vs. non-elderly), and location of study (North America vs. Europe) on primary failure, primary patency, and secondary patency rates.

3.2 Methods

We conducted and reported this systematic review according to published guidelines using a pre-specified protocol (MOOSE Checklist: **Appendix A**).[13,14]

3.2.1 Studies Eligible for Review

We formulated study inclusion and exclusion criteria a priori. We included any study that collected data prospectively (observational cohort studies or randomized control trials) and followed patients for at least 3 months. We only deemed studies eligible if they described ≥100 fistulas in patients with chronic kidney disease. We included only full-text English-language articles published after December 31st, 1999. Studies must have reported information on one or more of the following: a) primary failure; b) primary patency (1 and/or 2-year); c) secondary patency (1 and/or 2-year). We excluded studies of peritoneal dialysis and pediatric patients (<18 years).

3.2.2 Study Definitions

Unless otherwise specified, all vascular access definitions were in accordance with the Society of Vascular Surgery and the American Association of Vascular Surgery and the North American Vascular Access Consortium (NAVAC) (**Box 1**).[4,15] When definitions were not in agreement between the two documents, we used the NAVAC definitions.

When an outcome definition was unclear, not reported, or different from the above definitions it was documented within our tables.

Box 1: Outcome Definitions

- **Primary failure:** immediate failure of fistula within 72 hours of surgery, early dialysis suitability failure, or late dialysis suitability failure.[4]
  - *Early dialysis suitability failure:* This is an access that, despite radiological or surgical intervention, cannot be used successfully for dialysis by the third month following its creation.
  - *Late dialysis suitability failure:* This is an access that, despite radiological or surgical intervention, cannot be used successfully for dialysis by the sixth month following its creation.
- **Primary patency:** the interval from the time of access creation until first access thrombosis, or any intervention to maintain or restore blood flow.[4,15]
- **Functional primary patency:** the time from the first successful two-needle cannulation until first intervention or access failure.[4,15]
- **Secondary (cumulative) patency:** the time from access creation until access abandonment. Secondary patency was not terminated by surgical or interventional radiology procedures to maintain or restore patency.[4,15]
- **Functional secondary patency:** the interval from first successful two-needle cannulation for hemodialysis treatment to access abandonment.[4,15]

3.2.3 Data Sources and Study Selection

We designed and implemented a systematic literature search to identify all relevant published reports in Medline (OVID and Pubmed) from January 1st 2000 to June 30th 2012. The search strategy included a combination of key and MeSH words (**Appendix B**). We also used related articles features in PubMed. One investigator (A.A.) screened all titles and abstracts obtained through the search syntax to identify potentially relevant articles. We retrieved the full-text of these articles to further assess their suitability for inclusion in this review. Bibliographies of selected articles were searched manually to identify any additional relevant studies.

3.2.4 Data Extraction and Quality Assessment

Two reviewers (A.A. and either J.C.Z., S.D.K., or S.M.T.) independently extracted data using a standardized form. This was done in duplicate to increase accuracy and reduce measurement bias. If extracted data differed between the two reviewers, we resolved disagreement by consensus or with the help of a third reviewer (J.C.Z or S.M.T). We extracted data on the following: a) study characteristics including the year of publication, country, study design, and number of fistulas; b) methodological characteristics such as outcome definitions, follow-up period, and loss to follow-up; c) patient characteristics including location of upper extremity fistulas, mean age, mean time between fistula creation and two-needle cannulation, as well as proportion of men, Caucasians, patients with peripheral vascular disease, diabetes, and upper arm fistulas; d) assessed risk of bias among included studies, exploring participation, patient selection, attrition, exposure and outcome measurements, and confounding using a previously validated method;[16] and e) primary failure and/or patency rates as defined above (**Box 1**) [Note: The term “rate”

reported here is not a true rate {i.e. event per person-time} but used because of convention in the literature]. Most studies reported patency rates using life tables or in the text of the article, as opposed to Kaplan-Meier curves. When patency rates were only reported using Kaplan-Meier plot, we estimated the patency rate from the curve.

3.2.5 Data Analysis

The primary outcomes were rates of primary failure, primary patency, and secondary patency. Secondary outcomes were rates of functional primary patency and functional secondary patency. We calculated the 95% confidence interval (CI) for each study estimate using the Wilson Score method.[17] The Wilson Score interval has been shown to provide excellent coverage and has better performance than the standard Wald interval.[18,19]

We pooled the rates of primary failure, as well as rates of primary and secondary patency using a random effects model. We used the I^2 statistic to test for heterogeneity in risk estimates across studies.[20] We recorded and analyzed estimates separately for clinically important subgroups. We calculated the pooled estimate for pre-specified subgroups including fistula location (lower vs. upper arm), age (elderly vs. non-elderly as defined in the selected study), as well as study location (North America vs. Europe). We performed the analysis using SAS 9.2 (SAS Institute Inc., Cary, NC, USA) PROC MIXED procedure. This method allowed us to specify covariates in random effects univariable meta-regression. We explored heterogeneity between risk estimates according to the mean patient age, proportions of men, diabetic patients, and patients with peripheral vascular disease, number of fistulas, proportion of upper arm fistulas, country study was performed, recruitment start date, and publication year. In sensitivity analysis, we

excluded studies that were published after 2000 but recruited patients prior to 2000, sample size was <100 fistulas, studies that asked study question after data collection (i.e. retrospective design). We performed additional sensitivity analyses for patency rate and excluded studies that did not report if primary failures were included/excluded in the patency calculation. In order to justify our analyses, we required at least three independent estimates per subgroup. We used a two-sided p-value and considered a p-value <0.05 to be statistically significant.

3.3 Results

3.3.1 Included Studies

We screened 7,008 citations and retrieved 459 full-text articles to assess for eligibility. Forty-two articles met our criteria for review; however, two studies were excluded due to insufficient information on study design.[22,23] Three eligible articles were published using data from United States Renal Data System Dialysis Mortality and Morbidity Wave II (USRDS); however, since study patients among these articles significantly overlapped, we only included results from the study with the largest sample of fistulas.[24–26] Details of the study selection are shown in **Figure 5**. We identified five additional studies through manual search of bibliographies of selected articles. Thus, we included 43 articles (41 studies) reporting on 61 cohorts (59 unique cohorts; n=11 868 fistulas), published after January 1st 2000 with patient recruitment between 1985 and 2008. The characteristics of each article are described in **Table 1** and **Table 2**. Seventeen studies reported outcomes from the United States, five from each of Italy and United Kingdom, four from each of Canada and Netherlands, three from Turkey, and one each from Croatia, Saudi Arabia, and Slovenia. One additional article by the Dialysis Outcomes and Practice Patterns

Study (DOPPS) examined fistula outcomes from European countries in DOPPS.[27] Follow-up was not reported for 30 cohorts. In the remaining 31 cohorts; the median loss to follow-up was 3% (range 0% to 22%; interquartile range [IQR] =8%).

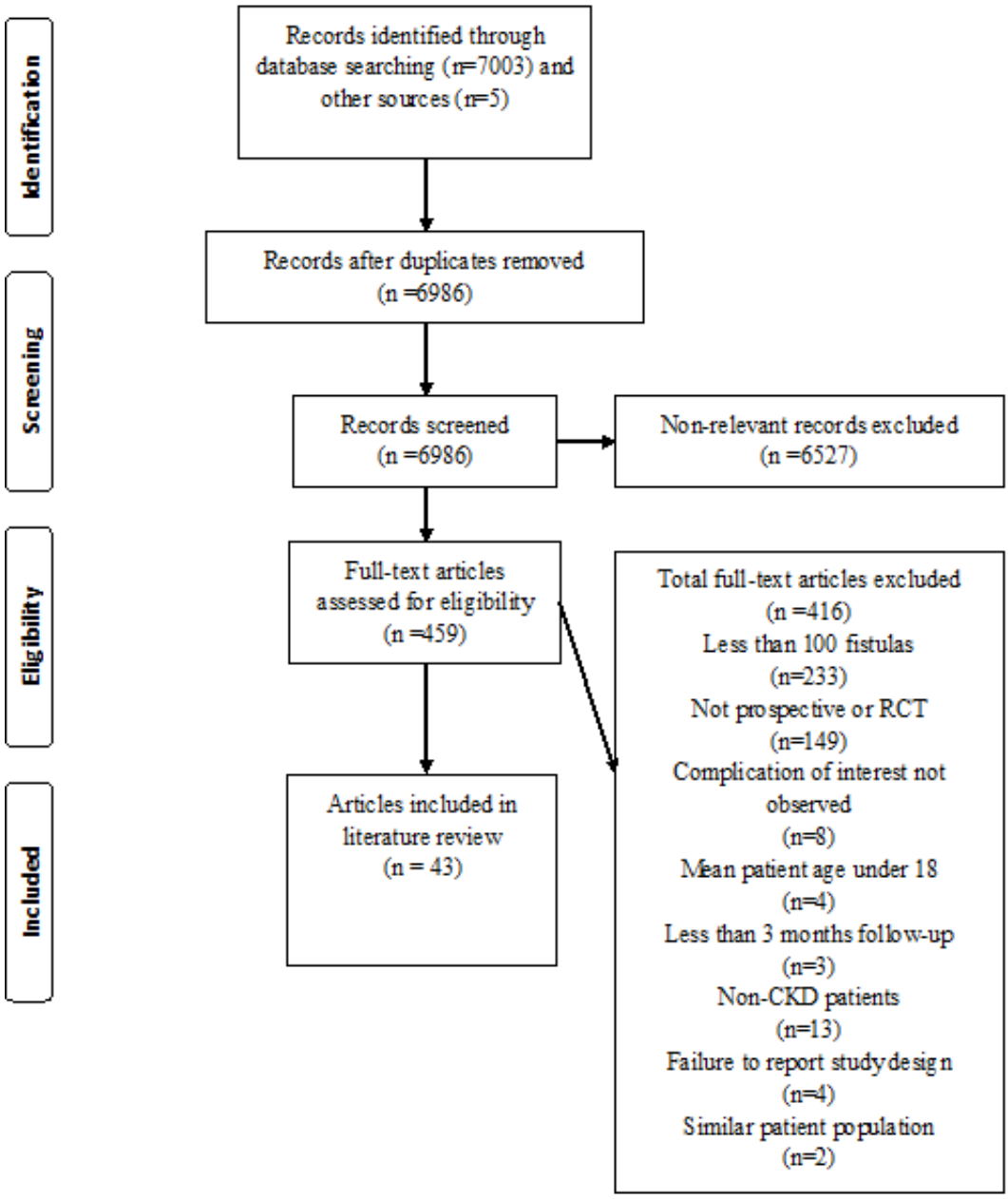


Figure 5. Flow diagram of study eligibility and inclusion. CKD= Chronic Kidney Disease; RCT=randomized controlled trial.

Table 1. Study Characteristics

Author	Year	Country	Recruitment Start	Cohort Characteristics	Follow-up (Mths)	Number of Access	Upper Arm* (%)	Age (years)	Male (%)	White (%)	DM (%)	PVD** (%)
Quintaliani et al.[41]	2000	Italy	.	Lower Arm	41	124	0%	57.5	56%	.	0%	.
Wolowczyk et al.[42]	2000	UK	1985	Lower Arm	.	208	0%	63.0	55%	.	14%	.
Allon et al.[9]	2001	USA	1998	All	.	138	46%	.	64%	40%	54%	.
Gibson et al.[43]	2001	USA	1996	All	11	492	.	66.0	53%	66%	54%	.
Dixon et al.[10]	2002	USA	1992	Lower Arm	.	88	0%	52.0	82%	95%	45%	15%
Dixon et al.[10]	2002	USA	1992	Upper Arm	.	117	100%	59.0	55%	54%	52%	28%
Huber et al.[44]	2002	USA	1999	All	.	117	75%	53.0	51%	60%	49%	.
Malovrh[45]	2002	Slovenia	1993	All	3	116	.	51.4	47%	.	.	.
Pisoni et al.[27]	2002	USA	1996	USA	.	177	.	60.5	53%	62%°	46%	23%
Pisoni et al.[27]	2002	Europe	1998	Europe	.	429	.	60.7	57%	99%°	22%	19%
Puskar et al.[46]	2002	Croatia	1992	All	.	463	5%	.	58%	.	6%	.
Ravani et al.[47]	2002	Italy	1995	All	20	197	19%	65.7	59%	.	22%	.
Feldman et al.[48]	2003	USA	1994	All	.	237	.	56.0	68%	.	34%	.
Bonforte et al.[49]	2004	Italy	1991	Lower Arm	27	112	0%	71	50%	.	22%	.
Perera et al.[50]	2004	USA	1999	All	.	100	50%	55.0	75%	.	50%	.
Ravani et al.[51]	2004	Italy	1997	All	42	513	.	66.3	58%	98%	27%	.
Zeebregts et al.[52]	2004	NLD	2000	Clip	15	51	0%	58.9	69%	.	19%	.
Zeebregts et al.[52]	2004	NLD	2000	Suture	11	56	0%	58.9	69%	.	19%	.
Lok et al.[53]	2005	Canada	1995	Elderly	.	196	53%	74.0	69%	69%	30%	10%
Lok et al.[53]	2005	Canada	1995	Non-elderly	.	248	43%	46.0	65%	63%	29%	8%
Manns et al.[54]	2005	Canada	1999	All	.	157	40%	63.6	72%	.	48%	22%
Vernaglione et al.[55]	2005	Italy	1995	Lower Arm	42	105	0%	63.8	52%	100%	23%	19%
Wells et al.[56]	2005	UK	2002	All	.	136	28%	.	70%	.	17%	.
Zeebregts et al.[57]	2005	NLD	1999	Upper Arm	20	100	100%	59.2	59%	.	24%	.
Elsharawy[58]	2006	Saudi Arabia	2003	All	.	126	69%	36.0	64%	.	41%	.
Erkut et al.[59]	2006	Turkey	1995	Lower Arm	47	298	0%	45.0	75%	.	12%	.
Lok et al.[7]	2006	Canada	1995	Derivation Cohort	6	422	39%	.	.	.	.	16%
Lok et al.[7]	2006	Canada	2004	Validation Cohort	6	445	.	58.0	68%	66%	18%	8%

Table 1. Continued

Author	Year	Country	Recruitment Start	Cohort Characteristics	Follow-up (Mths)	Number of Access	Upper Arm* (%)	Age (years)	Male (%)	White (%)	DM (%)	PVD (%)
Korten et al.[60]	2007	NLD	2000	Lower Arm	.	148	0%	65.0	55%	.	31%	.
Chan et al.[24]	2008	USA	1996	All	.	318	.	62.2	53%	58%	53%	22%
Dember et al.[61]	2008	USA	2003	Clopidogrel	6	385	47%	52.7	62%	50%	49%	4%
Dember et al.[61]	2008	USA	2003	Placebo	6	373	45%	54.5	63%	54%	47%	3%
Field et al.[62]	2008	UK	2003	Lower Arm	.	210	0%	61.7	59%	94%	33%	31%
Field et al.[62]	2008	UK	2003	Upper Arm	.	79	100%	61.0	34%	94%	43%	47%
Huijbregts et al.[63]	2008	NLD	2004	All	11	491	40%	64.6	62%	78%	33%	10%
Peterson et al.[64]	2008	USA	2001	All	.	205	55%	.	60%	14%$^{\circ}$	52%	15%
Pflederer et al.[65]	2008	USA	2004	All	.	321	37%	64.5	65%	.	43%	.
Pflederer et al.[65]	2008	USA	2004	AVF-T	.	161	97%	63.3	61%	.	45%	.
Koksoy et al.[66]	2009	Turkey	2003	AVF-T	28	50	100%	54.7	52%	.	32%	.
Koksoy et al.[66]	2009	Turkey	2003	Upper Arm	28	50	100%	54.8	60%	.	24%	.
Maya et al.[67]	2009	USA	2000	AVF-T	.	67	100%	56.0	52%	16%	58%	12%
Maya et al.[67]	2009	USA	2000	Upper Arm	.	322	100%	56.0	48%	23%	53%	16%
Weber et al.[68]	2009	Canada	2003	All	.	125	54%	66.0	58%	54%	44%	.
Ferring et al.[69]	2010	UK	2006	Clinical	.	101	37%	.	66%	67%	34%	22%
Ferring et al.[69]	2010	UK	2006	Ultrasound	.	107	41%	.	62%	71%	43%	14%
Gonzalez et al.[70]	2010	USA	2007	AVF-T	11	33	100%	54.5	46%	70%	81%	6%
Gonzalez et al.[70]	2010	USA	2007	Lower Arm	11	75	0%	54.3	52%	72%	56%	4%
Gonzalez et al.[70]	2010	USA	2007	Upper Arm	11	35	100%	50.2	51%	75%	68%	3%
Korkut & Kosem[71]	2010	Turkey	2004	AVF-T	48	350	100%	57.8	44%	.	51%	30%
Paul et al.[72]	2010	USA	2003	AVF-T	18	176	100%	61.0	34%	.	52%	.
Pisoni et al.[73]	2010	USA	2000	No Statin	.	218	100%	55.0	52%	23%$^{\circ}$	44%	16%
Pisoni et al.[73]	2010	USA	2000	On Statin	.	99	100%	58.0	39%	22%$^{\circ}$	75%	16%
Ravani et al.[74]	2010	Italy	1997	All	42	473	18%	66.3	58%	98%	27%	.
Schenk[75]	2010	USA	2008	All	.	131	83%	.	.	.	.	.
Jennings et al.[76]	2011	USA	2003	Elderly	17	461	38%	73.0	49%	.	60%$^{\times\times}$	.
Jennings et al.[76]	2011	USA	2003	Non-Elderly	.	618	.	53.0	52%	.	56%$^{\times\times}$	.
Lee et al.[77]	2011	USA	2005	One[1]	.	54	70%	.	70%	30%	56%	13%
Lee et al.[77]	2011	USA	2005	≥Two[1]	.	23	61%	.	52%	13%	70%	39%
Lee et al.[77]	2011	USA	2005	Zero[1]	.	96	69%	.	82%	26%	43%	19%
Swindlehurst et al.[78]	2011	UK	2000	Elderly	25	246	71%	74.0	62%	62%	41%	.
Swindlehurst et al.[78]	2011	UK	2000	Non-elderly	28	89	71%	49.0	55%	47%	29%	.

Legend: *Upper Arm (%) refers to the percentage of upper arm fistulas in each cohort; DM= Diabetes; PVD= Peripheral Vascular Disease; ^Under Group column, “All” refers to the entire study cohort; °Percentage Caucasian was estimated based on 78% of the patient population being African-American (i.e. not Black); ××Percentage of patients whose diabetes was the cause of renal failure. The actual proportion of diabetic patients in this cohort is likely higher than reported here. NLD=Netherlands; USA=United States.

[1]Number of interventions conducted for each group

Table 2. Data extracted for each study

Author	Year	Incident/ Prevalent	Data Collection*	Table/ Curve**	Outcome								
						1-Year				2-Year			
					PF	PP	SP	FPP	FSP	PP	SP	FPP	FSP
Quintaliani et al.[41]	2000	Prevalent	No	C	.	.	.	.	Y	.	.	.	.
Wolowczyk et al.[42]	2000	Incident	Yes	T	Y	Y-	.	.	.	Y-	.	.	.
Allon et al.[9]	2001	Incident	No	C	Y	Y	Y	.	.	.	.	.	.
Gibson et al.[43]	2001	Incident	No	T	.	Y	Y	.	.	Y	Y	.	.
Dixon et al.[10]	2002	Incident	No	T	Y	Y	Y	.	.	Y	Y	.	.
Huber et al.[44]	2002	Incident	Yes	.	Y	.	.	.	.	.	.	.	.
Malovrh[45]	2002	Incident	Yes	.	Y	.	.	.	.	.	.	.	.
Pisoni et al.[27]	2002	Both	No	T	.	.	.	Y	.	.	.	.	.
Puskar et al.[46]	2002	Incident	Yes	C	Y	Y	.	.	.	Y	.	.	.
Ravani et al.[47]	2002	Incident	Yes	T	Y-	Y	Y	.	.	Y	Y	.	.
Feldman et al.[48]	2003	Incident	Yes	.	Y-	.	.	.	.	.	.	.	.
Bonforte et al.[49]	2004	Incident	Yes	C	.	Y-	.	.	.	Y-	.	.	.
Perera et al.[50]	2004	Incident	No	T	Y	Y-	Y-	.	.	Y-	Y-	.	.
Ravani et al.[51]	2004	Incident	No	C	.	.	.	Y	.	.	.	Y	.
Zeebregts et al.[52]	2004	Incident	Yes	C	.	Y	Y	.	.	.	.	.	.
Lok et al.[53]	2005	Incident	No	T	Y	Y	Y	.	.	Y	Y	.	.
Manns et al.[54]	2005	Incident	No	.	Y-	.	.	.	.	.	.	.	.
Vernaglione et al.[55]	2005	Incident	Yes	C	.	Y-	.	.	.	Y-	.	.	.
Wells et al.[56]	2005	Incident	Yes	T	Y-	Y-	.	.	.	.	.	.	.
Zeebregts et al.[57]	2005	Incident	Yes	T	.	Y	Y	.	.	Y	Y	.	.
Elsharawy et al.[58]	2006	Incident	yes	.	Y	.	.	.	.	.	.	.	.
Erkut et al.[59]	2006	Incident	No	T	.	Y-	.	.	.	Y-	.	.	.
Korten et al.[60]	2006	Incident	No	T	Y-	Y	.	.	.	.	Y	.	.
Lok et al.[7]	2006	Incident	No	.	Y	.	.	.	.	.	.	.	.
Huijbregts et al.[63]	2007	Incident	Yes	T	Y	Y	Y	Y	Y	.	.	.	.
Chan et al.[24]	2008	Incident	No	.	Y-	.	.	.	.	.	.	.	.
Dember et al.[61]	2008	Incident	Yes	.	Y	.	.	.	.	.	.	.	.

Table 2. Continued

Author	Year	Incident/ Prevalent	Data Collection*	Table/ Curve**	Outcome								
						1-Year				2-Year			
					PF	PP	SP	FPP	FSP	PP	SP	FPP	FSP
Field et al.[62]	2008	Incident	No	T	.	Y	.	.	.	Y	.	.	.
Peterson et al.[64]	2008	Incident	No	.	Y	.	.	.	.	.	.	.	.
Pflederer et al.[65]	2008	Incident	No	T	Y-	Y	Y	.	.	Y	Y	.	.
Koksoy et al.[66]	2009	Incident	Yes	T	.	.	.	Y	Y	.	.	.	.
Maya et al.[67]	2009	Incident	No	C	Y	.	Y	.	Y	.	Y	.	Y
Weber et al.[68]	2009	Incident	Yes	.	Y	.	.	.	.	.	.	.	.
Ferring et al.[69]	2010	Incident	Yes	C	Y	Y	.	.	.	.	.	.	.
Gonzalez et al.[70]	2010	Incident	No	.	Y-	.	.	.	.	.	.	.	.
Korkut & Kosem[71]	2010	Incident	Yes	T	Y-	.	Y	Y	.	.	Y	Y	.
Paul et al.[72]	2010	Incident	No	T	.	Y	Y	.	.	Y	Y	.	.
Pisoni et al.[73]	2010	Incident	No	C	Y	.	Y	.	.	.	Y	.	.
Ravani et al.[74]	2010	Incident	No	C	.	Y	.	.	.	Y	.	.	.
Schenk[75]	2010	Incident	Yes	.	Y-	.	.	.	.	.	.	.	.
Jennings et al.[76]	2011	Incident	No	T	.	Y-	Y	.	.	Y-	Y	.	.
Lee et al.[77]	2011	Incident	No	T	Y-	.	.	.	Y	.	.	.	Y
Swindlehurst et al.[78]	2011	Incident	No	T	T	Y	Y	.	.	.	.	.	.

Legend: *Was data collected prior to conception of study question?; **Patency reported within text or table format (T) vs. in a Kaplan-Meier curve (C); PP: Primary Patency; SP: Secondary Patency; FPP: Functional Primary Patency; FSP: Functional Secondary Patency; Y- refers to a study that reported the outcome of interest, however, the author(s) did not report a definition or the definition was not in accordance with our pre-specified definitions.

3.3.2 Patient population

Patient demographic data, co-morbid conditions, and site of fistula creation were not always reported in the selected studies. However, when reported, the median age was 58.9 years (range 36 to 74 years; IQR=9.2 years). The median proportion of men was 58% (range 34 to 82%; IQR=13%). Within selected studies, the median proportion of patients with diabetes and peripheral vascular disease was 43% (range 0 to 81%; IQR=25%) and 16% (range 3 to 47%; IQR=12%), respectively.

3.3.3 Risk of bias

Many studies reported methods inadequately and definitions were inconsistent across studies. **Appendix C** lists definitions of primary failure reported in the included studies. When calculating the primary patency rate, fourteen studies included primary failures, six studies excluded primary failures, and eight studies did not report whether primary failures were included or excluded in their definition. Similarly, when calculating secondary patency, twelve studies included primary failures, six studies excluded primary failures, and five studies did not report the exclusion or inclusion of primary failures. When studies did not report the inclusion or exclusion of primary failure in the calculation of the patency rate, we assumed that primary failures were excluded. In sensitivity analyses, there were no differences in estimate of patency rates when we excluded studies that that did not report inclusion of primary failures. All studies were at moderate or high risk of bias in all domains assessed. The distribution of the components that described study quality is summarized in **Table 3**.

Table 3. Distribution of components describing study quality

Component	Number of Studies (%)
Participation Bias	
How were participants recruited?	
Consecutive	30 (70%)
Random	4 (9%)
Stratified method	6 (14%)
Not reported	3 (7%)
Was enrolment based on pre-specified eligibility criteria?	
Yes	26 (61%)
No	16 (37%)
Not reported	1 (2%)
Selection Bias	
Did follow-up begin at fistula creation or was fistula being used prior to study start?	
Fistula in place prior to the study start	4 (10%)
Follow-up began at fistula creation	38 (88%)
Not reported	1 (2%)
Is it reported whether participants were eligible to different forms of fistulas?	
Yes	22 (51%)
No	21 (49%)
Attrition Bias	
Was loss-to-follow-up treated as censored observations (as opposed to missing)?	
Censored	28 (65%)
Missing	6 (14%)
Not reported	9 (21%)
*Was loss-to-follow-up reported for each cohort?**	
Yes	30 (51%)
No	29 (49%)
*Proportion lost to follow-up**	
≤10%	22 (37%)
>10%	8 (14%)
Not reported	29 (49%)

Table 3. Continued

Component	Number of Studies(%)
Measurement Bias	
Was the outcome definition based on published standardized definition[4]?	
Primary Failure	
Yes	18 (62%)
No	11 (38%)
Primary patency	
Yes	17 (71%)
No	7 (29%)
Secondary Patency	
Yes	15 (94%)
No	1 (6%)
Confounding	
Were at least age, sex, diabetes, and PVD considered or reported?	
Yes	20 (47%)
No	23 (53%)

Legend: *The number of cohorts reported rather than the number of studies. PVD=Peripheral vascular disease.

3.3.4 Meta-Analysis

3.3.4.1 Primary Failure

The pooled estimate for primary failure among all studies was 27% (CI 23% to 32%) (**Figure 6**). This estimate must be interpreted cautiously given the high degree of heterogeneity (I^2= 97%) amongst the studies. In subgroup analyses, the risk of primary failure was 28% (CI 20% to 37%) for lower arm and 26% (CI 19% to 34%) for upper arm fistulas. The risk of primary failure was 43% (CI 18% to 68%) among elderly and 32% (CI 13% to 51%) for non-elderly patients. The risk of primary failure was 30% (CI 24% to 36%) for North American and 23% (CI 17% to 28%) for European studies. When sources of heterogeneity were explored in meta-regression, we noted a trend towards an increase in the risk of primary failure among studies with a higher proportion of diabetic patients (p-value [p]=0.06).

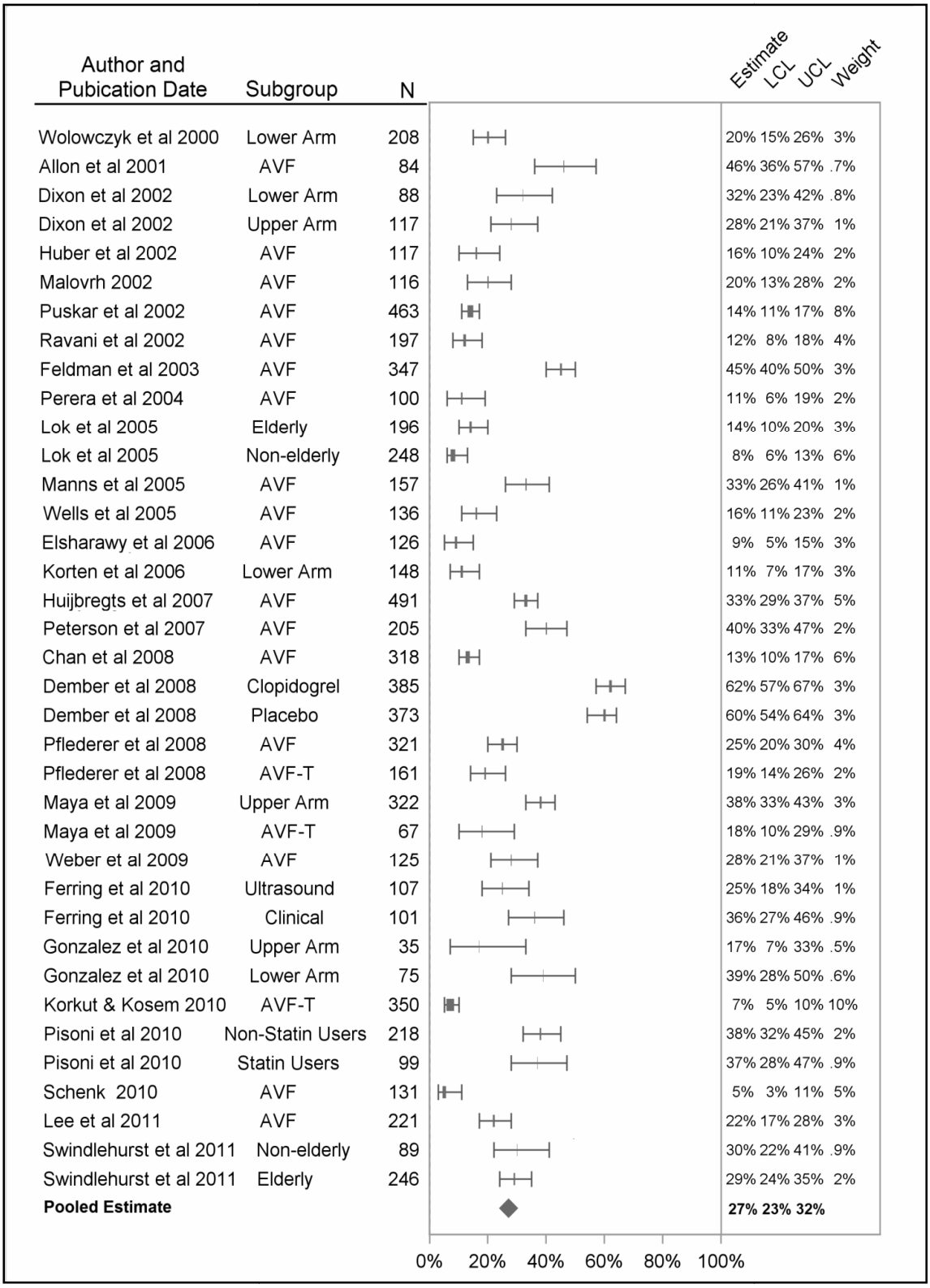
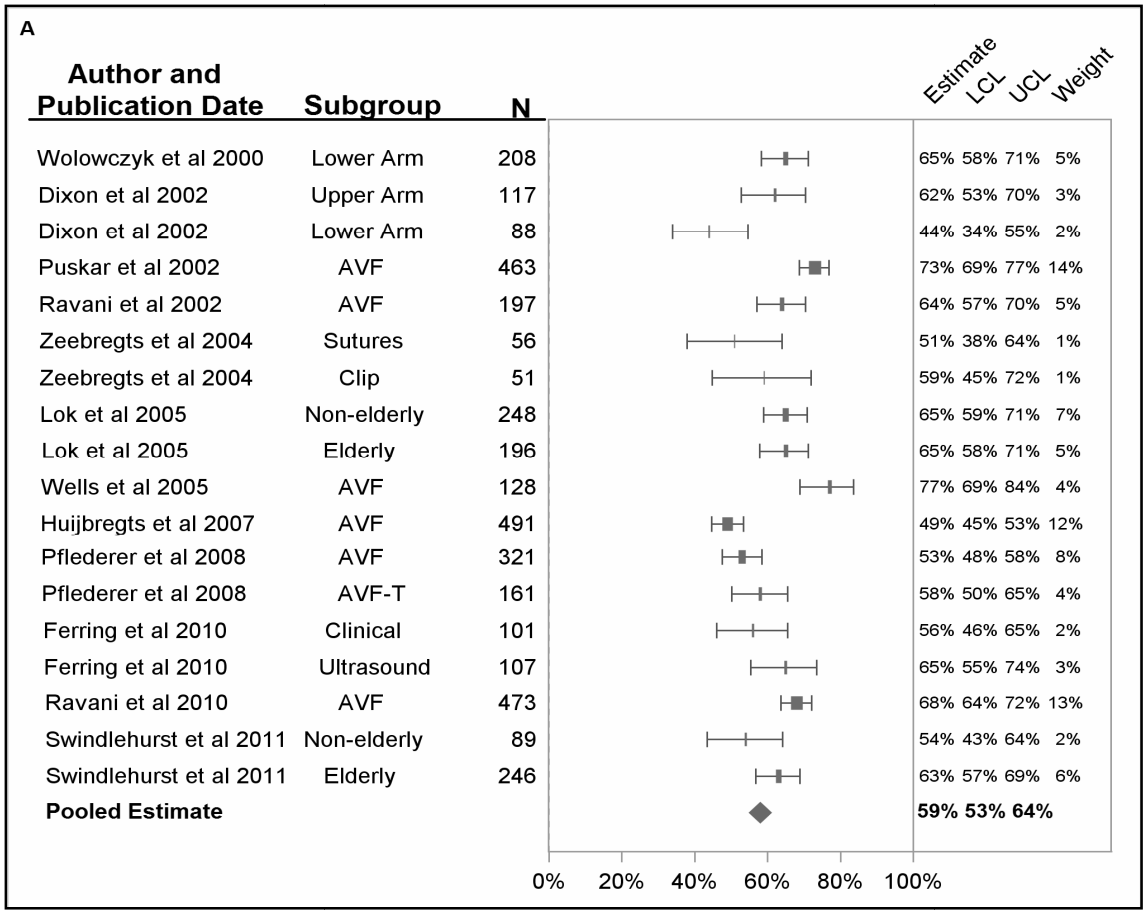


Figure 6. Rates of primary fistula failure. Studies are ordered by ascending publication date. AVF= all types of fistulas; AVF-T= transposed arteriovenous fistula; LCL= lower confidence limit; UCL= upper confidence limit.

3.3.4.2 Primary Patency

When including primary failure in the calculation for patency rate, the pooled primary patency rate was 59% (CI 53% to 64%) at one year and 47% (CI 39% to 55%) at two years (**Figure 7**). These estimates must again be interpreted cautiously given the high degree of heterogeneity amongst studies (I^2>96%). In subgroup analyses (**Table 4**), there was no difference in the primary patency among fistula location (lower vs. upper arm) and study location (North America vs. Europe). We were unable to pool estimates of primary failure for the elderly and non-elderly due to insufficient number of observations. When sources of heterogeneity were explored in meta-regression, we noted a statistically significant decrease in the 1-year and 2-year patency rate among studies with a higher proportion of diabetic patients (p=0.006 and p=0.0004, respectively). We also noted a statistically significant decrease in the 2-year primary patency rate in studies which started recruitment in more recent years (p=0.05) and had a higher proportion of patients with upper arm fistulas (p=0.03).

When the primary failure was not reported or excluded from the calculation of the patency rate, the pooled primary patency rate was 61% (CI 54% to 69%) at one year and 46% (CI 38% to 55%) at two years. The pooled estimate for functional primary patency was 78% (CI 69% to 87%) at one year and 70% (CI 46% to 93%) at two years. Heterogeneity between studies was high (I^2>95%). We noted a statistically significant decrease in the one- and two-year primary patency rate among studies with a higher proportion of diabetic patients (p=0.01 and 0.001, respectively) and more recent recruitment start date (p=0.001 and p=0.002, respectively).



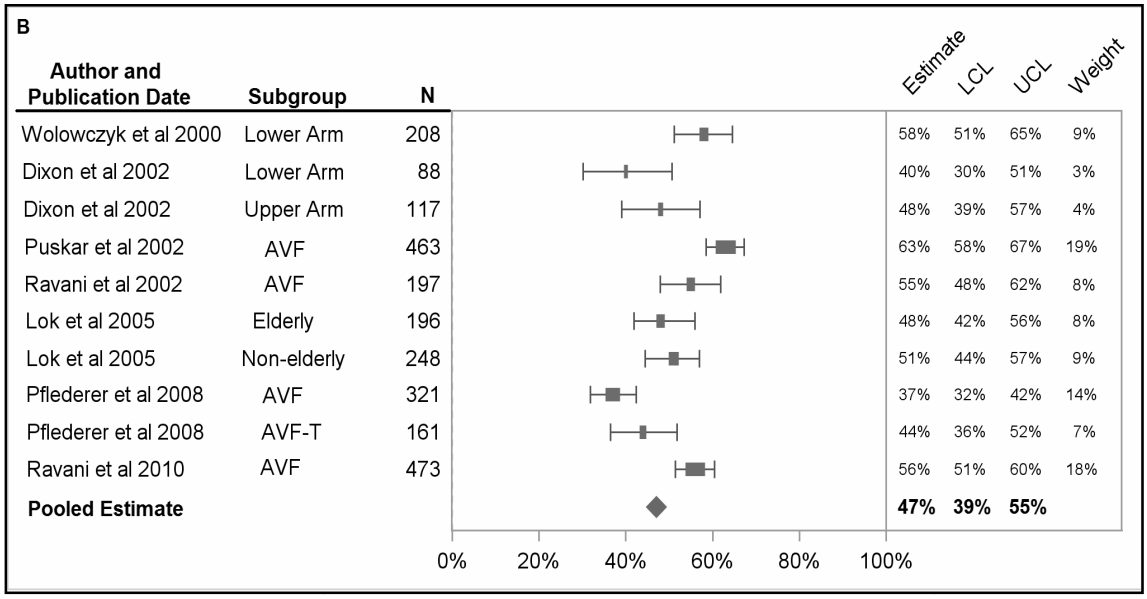


Figure 7. Primary patency rates at one (a) and two (b) years for fistulas. Primary failures were included in the calculation of patency rate. Studies are ordered by ascending publication date. "AVF= all types of fistulas; AVF-T= transposed arteriovenous fistula; LCL= lower confidence limit; UCL= upper confidence limit.

3.3.5 Secondary Patency

When including the primary failure in the calculation of the patency rate, the pooled secondary patency rate was 66% (CI 58% to 74%) at one year and 58% (CI 49% to 68%) at two years (**Figure 8**). In subgroup analyses (**Table 4**), we found no difference in secondary patency rate among fistula location and study location. Once again, there was not an insufficient number of observations reporting on the elderly and non-elderly patients. Heterogeneity between studies was high (I^2>97%). We noted a decrease in the 1-year and 2-year secondary patency rate as the proportion of patients with diabetes increased (p=0.02 and p=0.02, respectively).

When the primary failure was not reported or excluded from the calculation of the patency rate, the pooled secondary patency rate was 82% (CI 75% to 90%) at one year and 73% (CI 64% to 82%) at two years. The pooled functional secondary patency was 78% (CI 69% to 87%) at one year and 70% (CI 60% to 81%) at two years. Heterogeneity between studies was high (I^2>98%). In meta-regression analyses, we noted a statistically significant decrease in the 1-year secondary patency rates among studies with a higher proportion of men (p=0.01). However, there was a statistically significant increase in the 1-year and 2-year secondary patency among studies with more recent recruitment start dates (p=0.001 and p=0.003, respectively).

3.3.6 Sensitivity Analyses

Our estimates of primary failure were unchanged when we analyzed cohorts that had ≥100 number of fistulas, recruitment date ≥2000, and when the study question was asked before data collection (i.e. prospective design). **Appendix D** shows sensitivity analyses for estimates of primary and secondary patency rates.

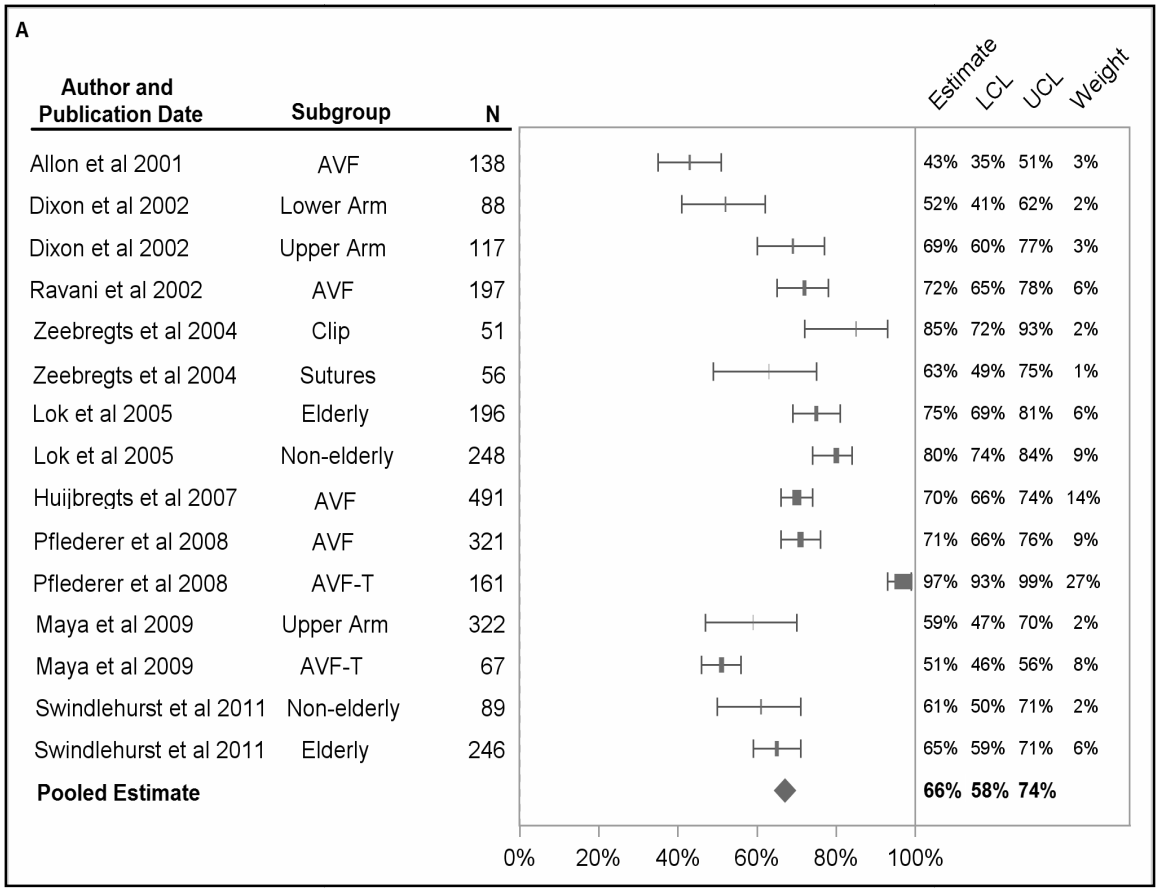


Figure 8. Secondary patency rates at one (a) and two (b) years for fistulas. Primary failures were included in the calculation of patency rate. Studies are ordered by ascending publication date. AVF= all types of fistulas; AVF-T= transposed arteriovenous fistula; LCL= lower confidence limit; UCL= upper confidence limit.

Table 4. Subgroup analyses

Outcome	Pooled Estimates			
	1-Year	95% CI	2-Year	95% CI
Primary Patency Rate- Primary failures included				
Lower Arm	55%	48% to 62%	45%	32% to 57%
Upper Arm	59%	46% to 71%	43%^	31% to 56%
North America	55%	45% to 65%	41%	31% to 51%
Europe	61%	56% to 67%	58%	53% to 63%
Primary Patency Rate-Primary failures excluded or not reported				
Lower Arm	63%	44% to 81%	53%	31% to 75%
Upper Arm	58%	44% to 73%	42%	24% to 60%
North America	57%	50% to 64%	36%	29% to 42%
Europe	61%	46% to 77%	50%	34% to 67%
Secondary Patency Rate-Primary failures included				
Lower Arm	70%	59% to 81%	62%	49% to 76%
Upper Arm	65%	56% to 74%	59%	48% to 69%
North America	64%	53% to 76%	58%	47% to 69%
Europe	69%	59% to 80%	.	.
Secondary Patency Rate-Primary failures excluded or not reported				
Lower Arm	.	.	.	.
Upper Arm	84%	76% to 93%	71%	61% to 82%
North America	82%	72% to 92%	72%	60% to 85%
Europe	.	.	.	.

Legend: CI=Confidence interval; North America refers to studies conducted in Canada or United States; Europe refers to studies conducted in Croatia, England, Italy, Netherlands, or Slovenia; There was not sufficient number of cohorts to pool estimates for elderly and non-elderly patients. ^Fixed effects model was used to estimate patency rate.

3.4 Discussion

We conducted a comprehensive review of recent studies of hemodialysis fistula describing rates of primary failure, primary patency and secondary patency according to standardized definitions. There were two key findings: 1) approximately a quarter to one-third of created fistulas failed to ever be used with an even higher risk in the elderly (>65 years); and 2) by one year, over half of all fistulas failed or required at least one intervention (radiological or surgical). Indeed, we found a lower primary failure rate than previously reported for the contemporary patient population (previous literature has reported the primary failure to range between 30% and 70%).

Prior to 2000, fistulas tended to have acceptable risk of primary failure ranging between 10% to 24%[28–31] and one-year primary and secondary patency rates between 65% to 94%[30,32–34] and 85% to 90%[35] respectively. Using data from 1970 and 2002, Rooijens et al.[36] reported a primary failure risk of 15% (CI 13% to 18%), a 62.5% (CI 54 to 70%) primary patency, and 66% (CI 58% to 73%) secondary patency rate at one year for radiocephalic (lower arm) fistulas. We obtained a higher risk of primary failure, as well as lower primary and secondary patency rates among lower arm fistulas (when primary failures were included). However, when we excluded primary failures from the calculation of patency rate, we obtained a similar pooled estimate for one-year primary patency. Compared to Rooijens et al., we examined all fistula locations and included only prospectively collected data. Our results show a significant decrease in fistula performance over time, with more current data highlighting a higher risk of primary failure and low to moderate primary and secondary patency rates.

Given the significant heterogeneity in the study results, the pooled estimates must be applied judiciously to different types of patients and fistula procedures. We conducted meta-regression to examine the sources of heterogeneity, and found parameter estimates depended significantly on the proportion of diabetic patients and study recruitment date. At the study level, we could not attribute study differences in fistula outcomes to patient factors (age, sex, peripheral vascular disease). There may be other important factors not available in our data sources, such as vessel diameter and quality, surgical expertise, and differences in vascular access practices across programs, which may account for some of the differences.[37–39]

This review serves as a call to action to improve several key factors that impact vascular access choice, evaluation and management. First, the quality of reporting in future studies in this theme requires refinement and consistent application of standardized definitions. We found inconsistent reporting of definitions across studies and a high risk of potential bias. Study definitions, however, did not only suffer from inconsistent reporting, but also a lack of an objective definition that is easily benchmarked across studies and programs. For example, the exact time point of fistula use was not clearly defined across studies. Many definitions are used for defining successful fistula use, including single-needle versus two-needle cannulation, consistency of cannulation (e.g. three successive cannulations), having greater than 350 mL/min blood flow, and catheter removal. The "zero-time" for fistula use is not represented by a specific point in time. Since one objective of using a fistula is to avoid catheter use, the success of a fistula could be indicated by the time the catheter is removed or by not using a catheter at hemodialysis start.[4] However, there are limitations in the precision of even this definition, as catheter removal may depend on other factors, such as available resources, which then potentially falsely lengthens the time of catheter dependence and delays the fistula use time. Our study highlights the importance of coming to a consensus amongst disciplines using an objective standard definition that can be used across studies to allow comparison of fistula outcomes.

Our review has a number of strengths including rigorous methodology, consistency of one and two-year parameter estimates for patency rates, and it's relevance to current practice and informing practice guidelines. Our review does have limitations. The screening of articles was conducted by a single individual, possibly contributing to study

selection bias. We only searched Medline and may be missing relevant studies only captured in Embase and/or Google Scholar. While we restricted this review to articles published in English, whether this introduced some bias is controversial.[40]

In conclusion, we report a high risk of primary failure and low to moderate primary and secondary patency rates. There has been a significant decrease in fistula performance over time. These results may in part explain the decrease in fistula use in some countries. However, these results should be used judiciously because the quality of evidence for fistula performance is low and susceptible to bias.

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Chapter 4

Co-Authorship:

Al-Jaishi AA, Lok CE, Oliver MJ, Zhang JC, Thomas SM, Garg AX, Quinn RR, Kosa SD, Moist LM.

4 Complication Rates of the Arteriovenous Fistula: A Systematic Review

4.1 Introduction

Previous studies have demonstrated the arteriovenous fistula (fistula) to be the preferred type of vascular access.[1–3] Once established, the fistula has longer patency and lower rates of complications compared to an arteriovenous grafts and catheters.[4,5] However, with the increasing proportion of elderly and frail patients, the rate of failure to mature has increased with a decrease in patency rates.[6–10] Other complications, related to vascular access, also deserve consideration to individualize patient risk, assist in providing informed consent, and to develop appropriate prevention and monitoring strategies. Complications are associated with morbidity, mortality, and high economic burden.[11–14] To our knowledge, no published systematic review has evaluated fistula complication rates in terms of infections, ischemic steal syndrome and thrombosis rates in the contemporary hemodialysis population between 2000 and 2012. We conducted this systematic review to efficiently summarize current published information on the rates for abovementioned complications, as well as identify knowledge gaps in the existing literature.

4.2 Methods

We conducted and reported this systematic review according to published guidelines using a pre-specified protocol (PRISMA Checklist: **Appendix G**).[15,16] Description of studies eligible for review, data sources, study selection, data abstraction and quality assessment used for this review have been reported elsewhere (**Chapter 3:** Methods).

Briefly, we included English-language studies indexed in MEDLINE that followed patients prospectively (observational cohort, randomized control trials, or surveillance programs) for a period of at least three months. We excluded any study that reported on less than 100 fistulas, or published results prior to January 1st 2000. Two blinded and independent reviewers (A.A. and either J.C.Z., S.D.K., or S.M.T.) abstracted data from selected studies using a standardized form with a third reviewer adjudicating discrepancies. We assessed risk of bias using previously validated methods,[17] and abstracted data on study methodology and cohort characteristics. All studies must have reported on at least one outcome of interest: a) rate of infection; b) rate of ischemic steal syndrome c) rate of thrombosis among incident and/or prevalent hemodialysis patients using a fistula.

4.2.1 Study Definitions

We used outcome definitions in accordance with the Society of Vascular Surgery and the American Association of Vascular Surgery document as well as the North American Vascular Access Consortium (NAVAC) document (**below**).[18,19] When definitions were not in agreement between the two documents, we used the NAVAC definitions. When the study definition was not in accordance with previously published definitions, we noted the differences in our tables.

4.2.1.1 Outcome Definitions

Infections: Definite or probable local vascular access infections, vascular access-related sepsis, bacteremia or a composite of these infections.

Ischemic steal syndrome: One or more clinical manifestations of: pain, ischemic neuropathy, ulceration, and gangrene felt to be related to a fistula diverting blood from the distal circulation resulting in a zone of arterial insufficiency in the tissues distal to the fistula.[18]

Thrombosis: Absence of bruit or thrill, using auscultation and palpation, throughout systole and diastole at least 8 cm proximal to the arteriovenous anastomosis.[18,19]

4.2.2 Summary Statistics

We report the median and range for the event rate (per 1000 patient-days) of an outcome. Due to differences in sampled populations, outcome definitions, prevalence of co-morbid conditions, and variable sample selection criteria, it was not appropriate to calculate a summary statistic based on the weighted average. When the rates were not reported, we calculated the overall follow-up time (denominator) by multiplying the mean follow-up time by the number of patients. We used the overall follow-up time to calculate the event rate per 1000 patient-days. It is important to note that in using this method; we assumed that the hazard rate of developing a particular outcome was constant across individuals and over time.

4.3 Results

The literature search yielded 7,006 citations. All citations were screened and 459 full-text articles were assessed for eligibility. Twenty-six articles met eligibility criteria; however, three studies were excluded due to insufficient information on study design.[20–22] Details of the study selection are shown in **Figure 9**. Three additional studies were identified through manual search of bibliographies of selected articles.[23] Thus, 26 studies (34

unique cohorts; n≥ 6577 fistulas) were included from ten countries. Nine articles reported outcomes from the United States, five from Italy, three from Canada, and one each from Australia, Belgium, Iran, Israel, Jordan, Netherlands, Saudi Arabia, and Turkey. One study reported outcomes of interest across European countries.[24] All studies were published between 2001 and 2011 with patient recruitment beginning between 1991 and 2006. The characteristics of each study are described in **Table 5**.

4.3.1 Patient population

Patient demographic data, co-morbid conditions, and site of fistula creation were not always reported. However, when the data was reported, the median age was 61 years (range 48 to 73 years; IQR=7 years). The median proportion of men and patients with diabetes was 57% (range 27% to 71%; IQR=10%) and 35% (range 14% to 60%; IQR=21%), respectively. The median proportion of patients who had an upper arm fistula was 38% (range 0% to 100%; IQR=41%). The median proportion of patients who were Caucasian was 84% (range 62% to 100%; IQR=23%).

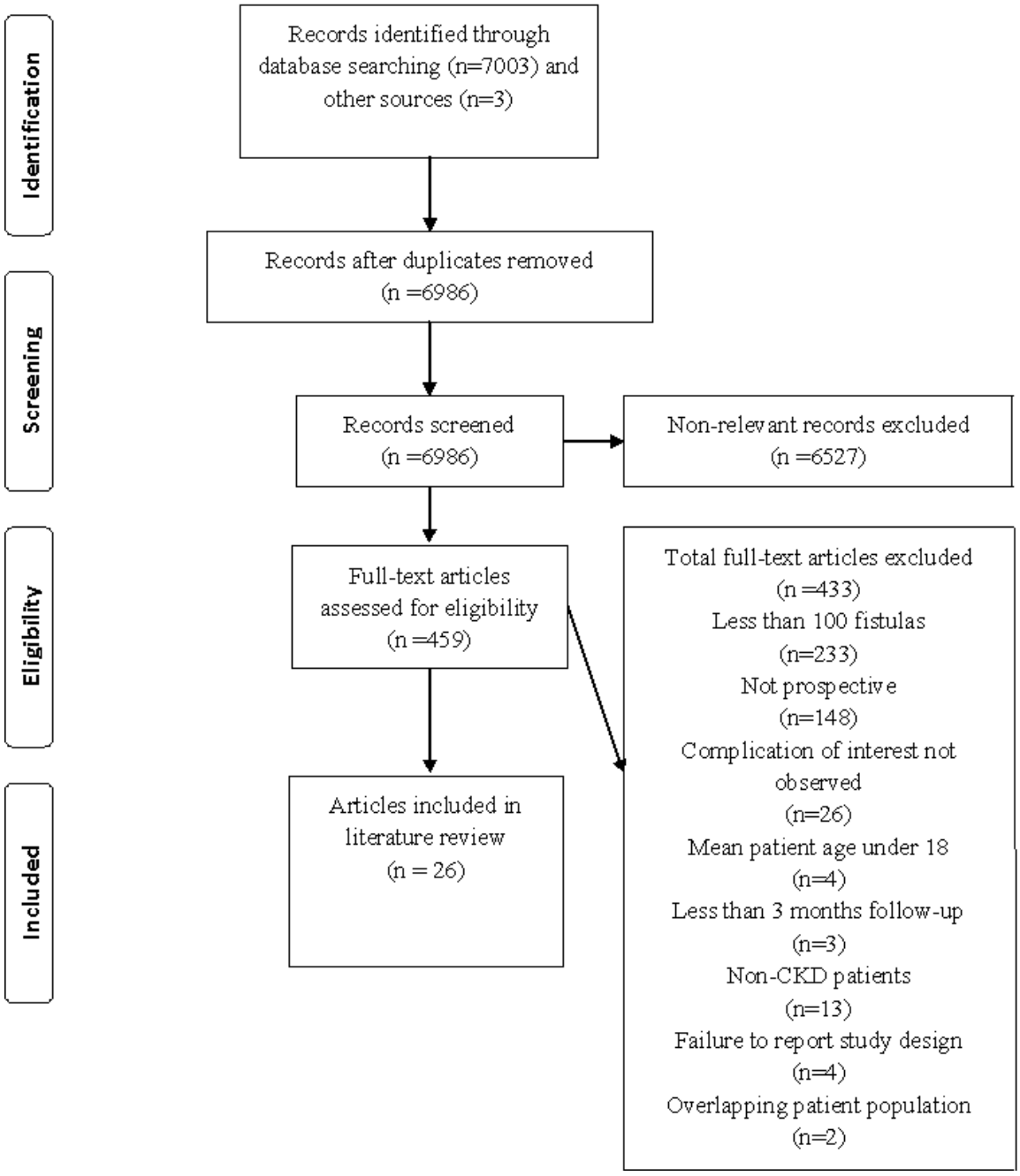

Figure 9. Flow diagram of study eligibility and inclusion. CKD= Chronic Kidney Disease

Table 5. Study Characteristics

Author	Year	Country	Recruitment Start	Cohort Characteristics	Follow-up (Mths)	Number of Fistulas	Upper Arm* (%)	Age (years)	Male (%)	White (%)	DM (%)	PVD (%)
Bonforte et al.[25]	2004	Italy	1991	Lower Arm	27	112	0%	71	50%	.	22%	.
[1]Elseviers et al.[24]	2003	Europe	2003	All	12	1049	.	.	56%	92%	.	.
[1]Gilad et al.[26]	2005	Israel	2002	All	.	143-161**	.	63.5	55%	.	48%	.
Huijbregts et al.[5]	2008	NLD	2004	All	11	491	40%	64.6	62%	78%	33%	10%
Jennings et al.[27]	2011	USA	2003	≥65 Years	17	461	38%	73	49%	.	60%[xx]	.
Jennings et al.[27]	2011	USA	2003	≤65 Years	18	618	.	53	52%	.	56%[xx]	.
Korkut & Kosem[28]	2010	Turkey	2004	AVF-T	48	350	100%	57.8	44%	.	51%	30%
Labriola et al.[29]	2011	Belgium	2001	All	75	193	.	70.4	66%	.	33%	.
Lok et al[30]	2003	Canada	1997	All	12	189	30%	57.5	71%	62%	22%[xx]	.
Mallamaci[31]	2005	Italy	.	All	33	205	5%	59.4	57%	100%	14%	.
[1]McCarley et al.[32]	2001	USA	1996	NM	11	39	.	55.3	51%	71%	36%[xx]	.
[1]McCarley et al.[32]	2001	USA	1996	DVPM	12	41	.	56.6	54%	70%	36%[xx]	.
[1]McCarley et al.[32]	2001	USA	1997	VABFM	10	43	.	56.1	59%	68%	34%[xx]	.
Paul et al.[33]	2010	USA	2006	endo/AVF-T	14	98	100%	60	40%	.	52%	.
Paul et al.[33]	2010	USA	2003	open/AVF-T	18	78	100%	62	27%	.	56%	.
Pflederer et al.[7]	2008	USA	2004	All	.	321	37%	64.5	65%	.	43%	.
Pflederer et al.[7]	2008	USA	2004	AVF-T	.	161	97%	63.3	61%	.	45%	.
[2]Polkinghorne et al.[34]	2006	Australia	2001	No Monitoring	16	68	34%	56.4	71%	97%	28%	7%
[2]Polkinghorne et al.[34]	2006	Australia	2001	Monitoring	17	69	36%	60	65%	89%	35%	13%
Qasaimeh et al.[35]	2008	Jordan	2004	All	7.6	105	.	.	.	.	.	.
Ravani et al.[36]	2002	Italy	1995	All	20	197	19%	65.7	59%	.	22%	.
Roozbeh et al.[37]	2006	Iran	.	All	23[£]	171	57%	53	68%	.	27%[xx]	.
[1]Saxena et al.[38]	2003	Saudi Arabia	1997	All	6	102	.	47.5	54%	.	.	.
[3]Shahin et al.[39]	2005	USA	1992	No Monitoring	21	146	51%	54.9	58%	93%	49%	39%
[4]Shahin et al.[39]	2005	USA	1999	Monitoring	19	76	61%	57.6	59%	90%	57%	53%

Table 5. Continued

Author	Year	Country	Recruitment Start	Cohort Characteristics	Follow-up (Mths)	Number of Fistulas	Upper Arm* (%)	Age (years)	Male (%)	White (%)	DM (%)	PVD (%)
Taylor et al.[40]	2002	Canada	1998	All	6	>100	.	.	.	.	.	.
[1]Taylor et al.[41]	2004	Canada	1998	All	6	>100	.	.	.	.	34%	.
Tessitore et al.[42]	2003	Italy	1998	All	7	120	0%	62.1	64%	.	23%	.
[5]Tessitore et al.[43] **(A)**	2008	Italy	2002	All	.	97	18%	65.1	64%	.	19%	.
[5]Tessitore et al.[43] **(B)**	2008	Italy	2002	All	.	62	21%	63.4	55%	.	31%	.
Tokars et al.[44]	2001	USA	1997	All	6	130	.	.	.	.	.	.
Tokars et al.[45]	2002	USA	1999	All	.	>100	.	.	.	.	.	.
Zasuwa et al.[46]▪	2010	USA	2003	All	6	104	.	.	.	.	.	.

PVD= Peripheral vascular disease; All=all fistula locations; NLD=Netherlands; Lower arm= A cohort consisting of patients only fistulas located in the lower arm; NM=No monitoring; DVPM=Dynamic venous pressure monitoring; VABFM=vascular access blood flow monitoring; endo/AVF-T= A transposed arteriovenous fistula (AVF-T) created using an endoscopic procedure; open/AVF-T=A transposed arteriovenous fistula (AVF-T) created using a long open incision technique (open/AVF-T)

[1]Note: Baseline characteristics were not provided specifically for patients with fistula. This information pertains to all types of accesses in the cohort.

[2] This is a randomized control trial comparing blood-flow surveillance by ultrasound dilution to standard clinical care.

[3]Patients that did not receive access flow monitoring.

[4]Patients who received regular access flow monitoring.

[5]Tessitore et al. collected data in 159 haemodialysis patients with mature fistulas, 97 followed by unsystematic clinical monitoring (A) and 62 by adding Qa surveillance to monitoring (B).

▪Only patients from postintervention group (0-6 months) were included here.

**There were between 199 and 224 HD patients dialyzing at the author's centre with seventy-two percent of the follow-up time being contributed by those using a fistula.

[xx]Percentage of patients whose diabetes was the cause of renal failure.

^Number of patients is estimated from patient-year-at-risk or dialysis-run-per-year from two studies.

£ Roozbeh et al. reported a study period of 14-months, however, provided a mean follow-up time of 23 months.

4.3.2 Study Quality Assessment

Methods were inadequately reported and definitions were inconsistent across studies. Definitions were not reported for five out of thirteen studies reporting infections, all studies reporting ischemic steal syndrome, and eight out of thirteen studies on thrombosis (**Figure 10**). **Appendix H** lists definitions of infections and thrombosis amongst the included studies. Loss to follow-up was not reported in 17 out of 34 cohorts; however, when reported, the median loss to follow-up was 5% (range 0% to 17%; interquartile range [IQR]=6%). All studies were at moderate or high risk of bias in all domains assessed. The distribution of the components that described study quality is summarized in **Table 6**.

From the studies that reported on infection: six reported on blood stream infections, four on all types of infections, four on vascular access-related infections, one on wound infection in the early post-operative period, one on infections requiring vascular access removal, and one on vascular access-related septicemia. Six out of the thirteen studies were prospective surveillance studies and generally did not report baseline characteristics specific to patients using a fistula.

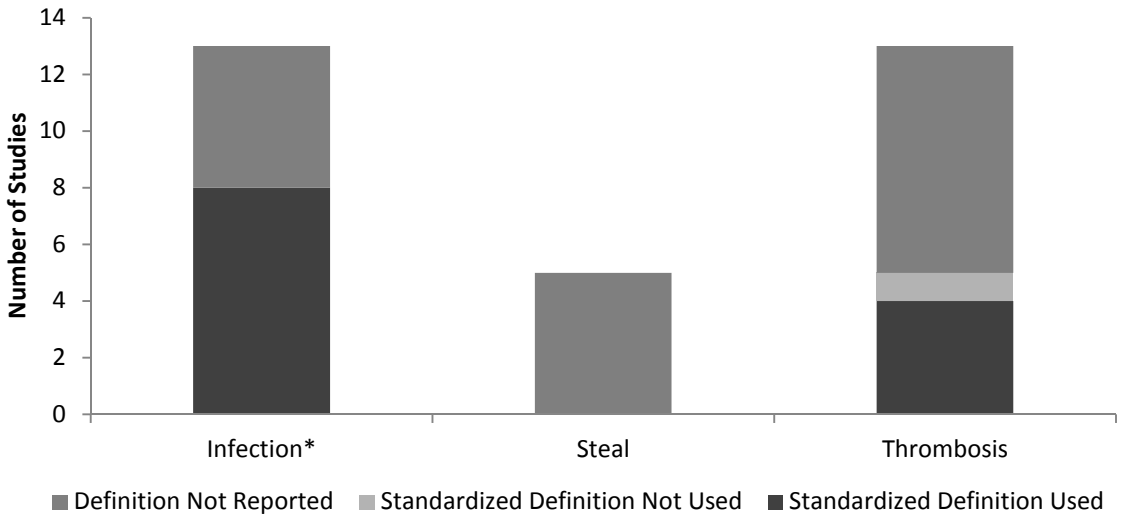

Figure 10. Number of studies that used a standardized definition

*We aggregated various types of infections; hence, it was not possible to use a standardized definition. However, eight out of ten studies provided a definition of infection.

Table 6. Distribution of components describing study quality

Component	Number of Studies (%)
Participation Bias	
How were participants recruited?	
Consecutive	16 (62%)
Stratified method	4 (15%)
Not reported	6 (23%)
Was enrolment based on pre-specified eligibility criteria?	
Yes	11 (42%)
No	15 (58%)
Selection Bias	
Did follow-up begin at fistula creation or was fistula being used prior to study start?	
Fistula in place prior to the study start	19 (73%)
Follow-up began at fistula creation	7 (27%)
Is it reported whether participants were eligible to different forms of fistulas?	
Yes	5 (19%)
No	21 (81%)
Attrition Bias	
*Was loss-to-follow-up reported for each cohort?**	
Yes	17 (50%)
No	17 (50%)
*Proportion lost to follow-up**	
≤10%	13 (38%)
>10%	4 (12%)
Not reported	17 (50%)
Measurement Bias	
Was the outcome definition similar to published standardized definition[18,19]?	
Infection**	
Yes	8 (61%)
No	5 (39%)
Ischemic Steal Syndrome	
Yes	0 (0%)
No	5 (100%)
Thrombosis	
Yes	4 (31%)
No	9 (69%)
Confounding	
Were at least age, sex, diabetes, and PVD considered or reported?	
Yes	4 (15%)
No	22 (85%)

*The number of cohorts reported rather than the number of studies.

**We aggregated various types of infections; hence, it was not possible to use a standardized definition. However, eight out of the thirteen studies provided a definition of infection.

4.3.3 Incidence of Outcomes

4.3.3.1 Infection:

Thirteen studies reported the rate of infection for fourteen unique cohorts (**Table 7**). Among the four studies that examined all infections together, the median rate was 0.17 infections per 1000 patient-days (ranged 0.06 and 0.39; IQR=0.12).[7,23,24] The median rate for bloodstream infection was 0.09 events per 1000 patient-days (range 0.05 and 0.21; IQR=0.04) among six unique cohorts.[23,26,29,40,41,45] The median rate for vascular access site infections was 0.4 events per 1000-patient days (range 0.02 to 1; IQR=0.55). When we aggregated all types of infections (i.e. composite infection rate), the median rate was 0.11 infections per 1000 patient-days (range 0.01 to 1.0; IQR=0.13).

4.3.3.2 Ischemic Steal Syndrome

Five studies reported event rates of ischemic steal syndrome for seven unique cohorts (**Table 7**). The median rate of ischemic steal syndrome was 0.05 events per 1000 patient-days (range 0 to 0.1; IQR= 0.03 events per 1000 patient-days). One study reported a rate of 0.1 events for elderly (>65 years) and 0.08 events per 1000 patient-days for non-elderly individuals and found no difference in the event rate between the two groups (p-value>0.05).[27] Similarly, Lok et al.[47] found no statistical difference (p-value=0.2) between the elderly and non elderly for ligation of fistula due to severe steal syndrome. Paul et al.[33] compared the incident rate of steal syndrome in transposed fistula (AVF-T) created using an endoscopic procedure versus a long open incision. The authors reported an incident rate of zero and 0.05 events per 1000 patient-days for the two groups, respectively.

4.3.3.3 Thrombosis:

Thirteen studies reported event rates of thrombosis in eighteen unique cohorts (**Table 7**). The median thrombosis rate was 0.27 events per 1000 patient-days (range 0.04 to 0.68; IQR=0.24). From the fifteen cohorts included, thirteen included only prevalent patients (patients already on

Table 7. Infection, ischemic steal syndrome, and thrombosis rates per 1000 patient-days

Author	Site	Incident/ Prevalent	Number of Accesses	Infection Rate**	Steal Syndrome**	Thrombosis Rate**
Bonforte et al.[25]	Single	Incident	112	.	0.02	0.14
Elseviers et al.[24]	Multi	Prevalent	1049	0.06•	.	0.14
Gilad et al.[26]	Single	Prevalent	143-161**	0.05◊	.	.
Gilad et al.[26]	Single	Prevalent	143-161**	0.02□	.	.
Huijbregts et al.[5]	Multi	Incident	491	.	.	0.38
Jennings et al.[27]	Single	Incident	461	.	0.1	.
Jennings et al.[27]	Single	Incident	618	.	0.08	.
Korkut & Kosem[28]	Single	Incident	350	0.04^	0.05	0.37
Labriola et al.[29]	Single	Prevalent	193	0.13◊	.	.
Lok et al[30]	Single	Both	189	.	.	0.33
Mallamaci[31]	Multi	Prevalent	205	.	.	0.39
McCarley et al.[32]	Multi	Prevalent	39	.	.	0.38
McCarley et al.[32]	Multi	Prevalent	41	.	.	0.41
McCarley et al.[32]	Multi	Prevalent	43	.	.	0.19
Paul et al.[33]	Single	Incident	98	.	0	.
Paul et al.[33]	Single	Incident	78	.	0.05	.
Pflederer et al.[7]	Single	Incident	321	0.14•	.	.
Pflederer et al.[7]	Single	Incident	161	0.19•	.	.
[1]Polkinghorne et al.[34]	Single	Prevalent	68	.	.	0.12
[2]Polkinghorne et al.[34]	Single	Prevalent	69	.	.	0.17
Qasaimeh et al.[35]	Multi	Prevalent	105	1□	.	.
Ravani et al.[36]	Single	Incident	197	0.01£	0.05	.
Roozbeh et al.[37]	Multi	Prevalent	171	.	.	0.31
Saxena et al.	Single	Prevalent	102	0.06□	.	.
[3]Shahin et al.[39]	Single	Incident	76	.	.	0.30
[4]Shahin et al.[39]	Single	Incident	146	.	.	0.25
Stevenson et al.[23]	Multi	Prevalent	238^	0.39•	.	.
Stevenson et al.[23]	Multi	Prevalent	238^	0.09◊	.	.
Taylor et al.[40]	Multi	Prevalent	>100	0.09◊	.	.
Taylor et al.[41]	Multi	Both	>100	0.21◊	.	.
Tessitore et al.[42]	Multi	Prevalent	120	.	.	0.19

Tessitore et al.[43] **(A)**	Multi	Prevalent	97	.	.	0.10
Tessitore et al.[43] **(B)**	Multi	Prevalent	62			0.04
Tokars et al.[44]	Multi	Prevalent	130	0.60	.	.
Tokars et al.[45]	Multi	Prevalent	>100	0.19	.	.
Tokars et al.[45]	Multi	Prevalent	>100	0.08◊	.	.
Zasuwa et al.[46]▪	Single	Prevalent	104	.	.	0.68

**Rates are per 1000 patient-days; • Any infection; ◊ Bloodstream infections; Vascular access site infection; ^ Wound infection in the early post-operative period; £ Infections requiring vascular access removal; VA-related septicemia

[1] Blood-flow surveillance by standard clinical care. Additional data was provided by author.

[2] Blood-flow surveillance by ultrasound dilution. Additional data was provided by author.

[3]Patients that did not receive access flow monitoring.

[4]Patients who received regular access flow monitoring.

hemodialysis) and therefore excluded thrombotic events that may have occurred during the fistula maturation period. Lok et al.[47] compared the proportion of incident elderly and non-elderly patients who lost their access due thrombosis. The authors found no difference (p-value=0.7) in the proportion of patients who lost their fistula due to thrombosis between the two groups.

4.4 Discussion

Our review identified 34 unique cohorts that reported on the rate of infections, steal syndrome or thrombosis among patients using a fistula. We identified two important findings: 1) the contemporary rates of complications in the fistula; 2) the critical need for consistent reporting of complication rates to allow evaluation of these outcomes across studies. Despite the burden of vascular access complications on the healthcare system, there remains a poor consensus on the incidence rate and risk factors associated with fistula complications.

The clinical practice guidelines for the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) and Canadian Society of Nephrology (CSN) recommends that the infection rate should not exceed 0.01 events per patient-year (0.027

per 1000 patient-days).[1,2] Based on the evidence from the current literature, the rate of infection was higher for 15 out of 17 cohorts compared to recommended rates proposed by practice guidelines. Compared to AV-grafts and catheters, fistulas have lower rates of infection and thrombotic events. Previous studies have shown that the rate of catheter infection can range between 0.05 to 0.18 per patient-year and depends on the duration of the catheter use.[48,49] Similarly, AV-grafts are at high risk for infection.[2,50] The rate of local and bacteremic infections for AV-grafts can range between 0.11 and 0.20 per patient-year. [51–54]

Ischemic steal syndrome is an important complication of fistulas; with significant implications including pain and loss of access function. Non-symptomatic physiological steal is common and can occur in 70% for lower arm fistulas to 90% for upper arm fistulas.[55,56] The NKF/KDOQI and CSN has no recommendations for target rates of ischemic steal syndrome. Previous studies have reported symptomatic ischemic steal occurrence to range between 1% to 2% for lower arm fistulas and 5% to 10% among patients using an upper arm fistula.[57–62] We found that the rate of ischemic steal syndrome was similar to estimates reported in the NKF/KDOQI guideline (1% to 4% of patients) and other studies.[2] When comparing the fistula to the AV-graft, it has been shown that there is a lower risk of ischemic steal syndrome. Previous reports have shown a two-fold lower risk of developing ischemic steal syndrome when comparing fistulas to AV-grafts.[2,50,63]

Thrombosis is a common complication and it is a recognized cause of fistula loss. The current NKF/KDOQI and CSN guidelines recommend that center specific thrombosis rate for the fistula should not exceed 0.25 events per patient-year (0.69 per 1000 patient-

days).[64] Among studies included in our review, the thrombosis rates observed were generally lower than the target rates recommended by practice guidelines. Furthermore, the rates of thrombosis observed in studies prior to 2000 were also comparable to rates reported in our study.[65,66] Compared to AV-grafts, fistulas have lower rates of thrombotic events. Previous reports have reported AV-graft thrombosis to exceeded 0.8 events per patient-year (2.2 events per 1000 patient-days).[67–69]

Studies included in our review varied substantially in quality, outcome definitions, and characteristics of patient population. Accordingly, the rate of fistula complications varied and may reflect selection bias of study participants, differences in clinical practice, variable vascular access care and monitoring or surveillance across facilities, and variable case definitions. Despite published recommendations for standardized vascular access reporting,[18,19] a number of studies failed to report definition of outcomes and only a smaller number of studies used published standardized definitions.

This information on complication rates is critical to informing patient-physician decision making, patient consent, and guiding resource allocation for vascular access monitoring/surveillance. Having accurate information on fistula complications and patients at highest risk is important in making informed decisions and choosing the appropriate vascular access based on the risks. Furthermore, identifying the risk factors and patients at highest risk for a complication, appropriate resources and monitoring can be allocated for these individuals. For example, the elderly and patients with history of hypertension, peripheral vascular disease, and diabetes are at high risk of developing ischemic steal syndrome and thrombosis. Special emphasis should be placed on closely monitoring these patients. The importance of this type of surveillance will increase as the

demographic changes in the dialysis population and there is a higher prevalence of frail patients. Delay in treatment of complications can lead the patient experiencing pain, vascular access loss, catheter dependence, and increased patient morbidity and hospitalizations.

Our review has a number of strengths compared to prior narrative reviews on this topic. We conducted a comprehensive search of the literature and systematically identified relevant studies in accordance with published guidelines and a pre-specified protocol. To our knowledge, this is the first review that has examined the rates of fistula complications in the contemporary dialysis population. Previous narrative reviews have included studies from the 1970's whose patients are different from current dialysis population. Furthermore, previous reviews limited their focus to upper arm fistulas and reported the risks of infections, ischemic steal syndrome, and thrombosis as opposed to the event rate.[70–72]

Our study does have limitations. The screening of articles was conducted by a single individual, possibly contributing to study selection bias. Methodological differences between studies precluded a precise estimate of complication rates and the pooling of risk factors; it has been suggested that pooling results when not warranted may lead to misleading conclusions.[73] We restricted this review to articles published in English and whether this introduced some bias is controversial.[74] Our review focused on infection, ischemic steal, and thrombosis. Although we observed similar rates of ischemic steal and thrombosis practice guidelines, it should be noted that the majority of included studies utilized prevalent patients and therefore reported outcomes for functional fistulas. Fistulas that were lost due to primary failure from thrombosis were excluded (therefore

non-functional fistulas), potentially biasing the ischemic steal and thrombosis rates to a lower rate. Although there are a number of other fistula complications such as aneurysms, venous hypertension, bleeding, etc., we were unable to capture these complications due to poor reporting of these complications in the literature. Finally, when calculating event rates, we assumed a constant hazard ratio; however, it has been shown that the hazard ratio of fistula outcomes can vary over time, with higher hazard rates being observed within the first six months of dialysis.[75] We attempted to stratify complication rates per time period (e.g. 0-6 months of access placement, 7-12 months of access placement, etc); however, such granular data was not available within selected studies.

The quality of primary studies inherently limits the conclusions that can be drawn from this review. Risk factors for fistula complications which include patient comorbidities, vessel characteristics, surgeon's experience, and nursing experience with cannulation were generally not reported. Additionally, factors on timing between fistula creation and fistula use, timing of vascular access interventions, and clinical monitoring/surveillance practices were also not reported. These variables may have explained some of the heterogeneity in the estimates of complication rates. The paucity in reporting of risk factors impairs our ability to identify patients at highest risk for complications.

Based on knowledge gaps identified in our review, we make the following recommendations for future studies. First, we recommend studies report infection events by type of infection (e.g. bloodstream versus local access site infection). This will help quantify the true burden of specific types of infection among those using a fistula. For example, a local fistula infection should not be treated the same as a vascular access-related bacteremia resulting in sepsis and hospitalization. Second, an understanding of the

incidence of infection, steal syndrome, and thrombosis is needed to guide sample size calculations in future clinical trials to ensure that they have adequate statistical power. For example, in a systematic review of clinical trials testing the efficacy of blood flow surveillance in reducing risk of access loss, the biggest limitation in current trials was inadequate statistical power to detect a difference between the intervention group and control group among prevalent patients.[76] Third, there is a need for longer and larger cohort studies that reflect the contemporary dialysis population. Although we included large scale national surveillance studies, a major limitation was the absence of patient characteristics for those using a fistula. This limited our ability to compare the effect of patient characteristics on the complication rates of the fistula. Finally, to advance the quality of vascular access information, future studies need to utilize consistent definitions and reporting methods in accordance to accepted published standards.[19,77] This will permit comparison of fistula outcomes across studies to provide better insight on the burden of fistula complications.

4.5 Conclusions

We found that the rate of thrombosis and ischemic steal was similar to rates in published reports and those recommended by NKF/KDOQI. However, the infections rate was much higher than the range recommended by NKF/KDOQI guidelines. We found marked variability in complications rates in part due to the poor quality of studies, significant heterogeneity of study populations, and inconsistent definitions. There is an urgent need to standardize methods for reporting outcomes and complications of vascular access in future clinical studies to get better insight on the rates of complications and estimate the burden of vascular access complications.

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Chapter 5

5 Conclusions and Future Directions

5.1 Overview

This thesis explores the performance of arteriovenous fistulas using prospective data published between 2000 and 2012. We conducted two systematic reviews to summarize patency and complication rates of the arteriovenous fistula, as well as assessed the data quality and identified knowledge gaps in the existing literature.

5.2 Outcomes of the fistula

Chapters 3 and 4 of this thesis examined the primary failure, patency rate, and complication rates among chronic hemodialysis patients using the fistula. In Chapter 3, we conducted a systematic review and meta-analysis that suggested fistulas had a high risk of primary failures, with approximately a quarter of all fistulas failing prior to starting hemodialysis. Furthermore, we found that fistulas had moderate to good primary and secondary patency rates at one and two years. There was high heterogeneity across studies in part explained by the proportion of patients with diabetes and recruitment start date of each study.

Studies with a higher proportion of patients with diabetes tended to have decreased fistula performance in terms of primary failure, primary patency and secondary patency. Furthermore, we found that the primary patency or time from fistula creation to need for intervention or failure has decreased with time. We identified an era effect with better patency rates in patients recruited to studies at the start of the 1990's compared to 2005-2011. This could be partly explained by the increase in the proportion of elderly patients who are more likely to be frail and have a number of co-morbidities. Unlike primary patency, secondary patency rates tended to increase as study recruitment dates progressed

closer to 2012. This is likely attributed to the advances in intervention (radiological and surgical) techniques, as well as an increase in the proportion of programs conducting vascular access blood flow surveillance for vascular access thrombosis and early intervention for this complication.

In Chapter 4, we examined the rates of infection, ischemic steal syndrome, and thrombosis among studies published between 2001 and 2012. We found that fistula complication rates were generally low. Thrombotic events were the most common fistula complications, followed by infection, and finally the occurrence of ischemic steal syndrome was rare. Our median estimate of thrombosis rate was approximately 3.5 times higher than the infection rate and 7.6 times higher than the rate of ischemic steal syndrome complications.

5.3 Limitations and Knowledge gaps in the Current Literature

As discussed in Chapters 3 and 4, the quality of evidence in the selected studies was generally low to moderate. There was a high risk of bias, especially selection bias and confounding by indication. This thesis highlights that data for fistula outcomes are substantially biased by pre-specified eligibility criteria. Individuals who receive fistulas that mature sufficiently for dialysis are likely to be different from individuals for whom a fistula cannot be established before dialysis initiation.[1] These differences may in part be attributed to insufficient pre-dialysis planning or exposure to pre-dialysis care, unsuitable vascular anatomy for access creation, or limited patient life expectancy.[1,2] Furthermore, study populations were heterogeneous and reporting of potential confounders and study definitions were not always complete. Therefore it was not possible to adjust for known

confounders. The low quality of data limits our confidence in reporting complication rates and accurately estimating the burden of fistula complications.

Lastly, one is left questioning if the small change in the patency (after excluding primary failure) and complication rates is just due to a change in the population at risk, with the patients at higher risks of complications dying early leaving a healthier population with a lower risk of complications. Although not discussed in the primary articles, the risk of death is likely to be highest around the initial period of starting dialysis (first 6 months).[3] This was not addressed in the primary studies; therefore, we were unable to account for the competing risk of death and observing the outcome of interest.

5.4 Future Work

Future epidemiologic and health services research can examine indicators that impact fistula creation and use (separately). Without this necessary information, the modification of other downstream factors will not yield change in the proportion of patients starting dialysis using the appropriate vascular access. There is an urgent need for large cohort studies that identify groups of patients who are eligible for fistula creation and patients with whom fistula creation should not be attempted. This knowledge can inform approaches/tactics to guide resource allocation and alter dialysis initiation practices.

Future work in vascular access research should examine clinical and health system variables that are associated with fistula creation and use. Linked registry and health care databases in Ontario can be leveraged for the purpose of this research. These data sources can be used to assess the rates of fistula creation among hemodialysis patients using a fistula compared to those not using a fistula. Furthermore, these data sources can be used to assess the association between arteriovenous access creation and use with variables

including patient co-morbid conditions, number of surgical/radiological interventions required for first use, duration of pre-dialysis nephrology care, as well as dialysis facility size (number of patients), location (urban vs. rural) and type (community vs. hospital). Observing an association between clinical and facility level factors on fistula creations and subsequent use can play a critical role in establishing patient selection criteria, providing informed consent, follow-up of patients, and addressing short falls within the process of care.

The Ontario Renal Network (ORN) has identified vascular access as a priority program and its main objective is to increase the rate of functioning complication-free vascular access.[4] It is reasonable to leverage the rich existing health care databases in the province of Ontario for vascular access research. The large samples reflect routine clinical practice compared to existing small cohort studies. Linkage between billing and registry databases can enable accurate assessment of key exposures of interest and vascular access creation and use.

5.5 Conclusion

Rather than the fistula as the first choice, patient and center variables should be considered to ensure the choice of the appropriate vascular access for each patient. When considering the fistula, the initial high risk of maturation failure and complication rates should be considered alongside the long-term benefit of using this access. Given the high risk of primary failure, vascular access programs and policy makers should consider allocating sufficient resources and target preventive strategies around the timing of fistula creation and dialysis initiation period.

It is important for nephrologists and healthcare stakeholders to recognize the performance and complication rates of the fistula. This information is critical for doctor-patient decision making and can be used for clinical trials to determine the appropriate sample size calculations. However, these data should be used with caution because the current vascular access literature on fistula outcomes is comprised of low quality evidence.

5.6 References

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Appendix 1

Appendix A. MOOSE Checklist

Criteria		Brief description of how the criteria were handled in the meta-analysis
Reporting of background should include		
√	Problem definition	**Chapter 3 Introduction, Paragraph 1 and 2:** Fistula use is associated with fewer complications, improved vascular access survival, and lower risk of mortality compared to an arteriovenous graft (AV-graft) or central venous catheter (catheter).
√	Hypothesis statement	**Chapter 3 Introduction, Paragraph 1:** Fistulas are associated with a high risk of primary failure and low primary and secondary patency.
√	Description of study outcomes	**Chapter 3 Introduction, Paragraph 2:** Primary failure, primary patency (1- and/or 2-year), and secondary patency (1- and/or 2-year).
√	Type of exposure or intervention used	Fistula use
√	Type of study designs used	**Chapter 3 Introduction, Paragraph 2:** We included cohort studies that collected data prospectively (the study question could be derived prior to or after data collection).
√	Study population	Mean age ≥18 years in chronic kidney disease or end-stage kidney disease patients.
Reporting of search strategy should include		
√	Qualifications of searchers	The credentials of the investigators (AA, LM, MO, AG, CL) who devised the search strategy is indicated in the author list.
√	Search strategy, including time period included in the synthesis and keywords	**Chapter 3 Methods:** PubMed was searched from January 2000 to June 2012
√	Databases and registries searched	**Chapter 3 Methods:** PubMed
√	Search software used, name and version, including special features	We did not employ a search software. Reference Manager was used to merge retrieved citations and eliminate duplications
√	Use of hand searching	**Chapter 3 Methods:** We hand-searched bibliographies of retrieved papers for additional references.
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart (**Figure 1**). The citation list is available upon request
√	Method of addressing articles published in languages other than English	**Chapter 3 Methods**: **Eligibility Criteria** Only English-language articles were included.

√	Method of handling abstracts and unpublished studies	We did not search gray literature
√	Description of any contact with authors	We did not contact any authors
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	**Chapter 3 Methods**: **Eligibility Criteria** Detailed inclusion and exclusion criteria were described in the methods section.
√	Rationale for the selection and coding of data	**Chapter 3 Methods**: **Data Extraction and Quality Assessment** Data extracted from each of the studies were relevant to the population characteristics, study design, exposure, outcome, and possible confounders.
√	Assessment of confounding	Restricted the analysis to studies published after 2000. Conducted subgroup analyses based on location of fistulas and American vs. European countries. We also conducted sensitivity analyses by eliminating studies that recruited patients before the year 2000, had less than 100 fistulas in any one group, and those that collected data before derivation of study question.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	**See Table 3**
√	Assessment of heterogeneity	Heterogeneity of the studies were explored using I^2 statistic which provides the relative amount of variance of the summary effect due to the between-study heterogeneity.
√	Description of statistical methods in sufficient detail to be replicated	**Chapter 3 Methods: Data Analysis** Description of methods of meta-analyses, sensitivity analyses, meta-regression and assessment of publication bias are described in the methods.
√	Provision of appropriate tables and graphics	**Table 1.** Study Characteristics **Table 2.** Data extracted for each study **Table 3.** Distribution of components describing study quality **Table 4.** Subgroup analyses **Figure 5.** Flow diagram of study eligibility and inclusion **Figure 6 to 8.** Forest Plots of our three outcomes **Appendix B.** Search strategy (OVID) **Appendix C.** Reported definition of primary access failures.

		Appendix D. Sensitivity analyses
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	**Figure 6 to Figure 8**
√	Table giving descriptive information for each study included	**Table 1 and Table 2**
√	Results of sensitivity testing	**Appendix D**
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates and sensitivity analyses.
Reporting of discussion should include		
√	Quantitative assessment of bias	Sensitivity analyses indicate heterogeneity in strengths of the association due to most common biases in observational studies.
√	Justification for exclusion	We excluded non-English language articles, studies that reported on <100 fistulas, and published prior to 2000. Those studies that were excluded to improve study quality and provide fistula estimates on current dialysis population.
√	Assessment of quality of included studies	We discussed the results of the sensitivity analyses, and potential reasons for the observed heterogeneity.
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	We discussed potential unmeasured confounders, such as condition of vasculature, which may have caused residual confounding. We noted that the variations in the strengths of association may be due to true population differences, residual confounding, or to differences in quality of studies.
√	Generalization of the conclusions	The present review can only be used to provide important insight on rates of fistula outcomes. However, actual estimates of fistula outcomes are likely to vary between centers. The majority of studies included were from the United States, and there were a minimal number of studies from Asia.
√	Guidelines for future research	Our study emphasizes the need for consistent reporting and the use of standardized objective definitions in future clinical studies.
√	Disclosure of funding source	No funding was obtained for the undertaking of this systematic review and meta-analysis.

Appendix B. Search strategy (OVID)

1. exp renal dialysis/ or exp hemodiafiltration/ or exp hemodialysis, home/ or exp hemofiltration/
2. Kidney Failure, Chronic/ or *Aged/ or Renal Dialysis/ or *Adult/ or haemodialysis.mp. or *Middle Aged/ or exp Hemodialysis, Home/
3. Chronic Kidney Disease/ or renal dialysis/ or renal dialysis/ or renal dialysis/ or renal insufficiency/ or Dialysis Solutions/ or exp Renal Dialysis/ or Dialysis/ or dialysis.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
4. Hemodialysis.mp.
5. exp renal replacement therapy/ or exp renal dialysis/ or hemodiafiltration/ or hemodialysis, home/
6. 1 or 2 or 3 or 4 or 5
7. vascular malformations/ or arteriovenous malformations/ or arteriovenous fistula/ or exp vascular fistula/
8. exp Arteriovenous Fistula/ or AVF.mp.
9. exp Kidney Failure, Chronic/ or exp Renal Dialysis/ or AV-Fistula.mp.
10. fistula.mp. or Arteriovenous Fistula/ or Arterio-Arterial Fistula/ or Brachial Fistula/ or Fistula/ or Vascular Fistula/
11. 7 or 8 or 9 or 10
12. (epidemiology or (Staphylococcus aureus or Anti-Bacterial Agents)).mp. or exp infection/ or sepsis/ or exp bacteremia/ or shock, septic/ or wound infection/ or surgical wound infection/ or septicemia.mp. or exp sepsis/ or Enterococcus*.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
13. Subclavian Steal Syndrome/ or Coronary-Subclavian Steal Syndrome/ or steal.mp.
14. exp thrombosis/ or coronary thrombosis/ or exp thromboembolism/ or exp venous thrombosis/ or exp thrombophlebitis/ or upper extremity deep vein thrombosis/
15. exp Thrombosis/ or thrombosis.mp. or Cavernous Sinus Thrombosis/ or Carotid Artery Thrombosis/ or Upper Extremity Deep Vein Thrombosis/ or Venous Thrombosis/ or Coronary Thrombosis/
16. Vascular patency.mp. or exp Vascular Patency/
17. Vascular Patency/ or Ischemia/ or Graft Occlusion, Vascular/ or Primary patency.mp.
18. secondary patency.mp.
19. Arteriovenous shunt, surgical/mo or arteriovenous shunt, surgical/ae or arteriovenous shunt, surgical/sn or arteriovenous shunt, surgical/ or Vascular Patency/ or assisted patency.mp.
20. Vascular Surgical Procedures/ or loss of patency.mp.
21. 16 or 17 or 18 or 19 or 20
22. 14 or 15
23. 6 and 11 and 12
24. 6 and 11 and 13
25. 6 and 11 and 22
26. 6 and 11 and 21
27. 23 or 24 or 25 or 26
28. limit 27 to (English language and yr="2000 - 2012")

Appendix C. Reported definition of primary access failures.

Author	Definition	Comment
Allon et al. 2001[1]	An access that never achieved adequacy for dialysis. Fistula adequacy was defined prospectively as the ability to sustain hemodialysis with two needles and a blood flow of at least 350 mL/min on at least six dialysis sessions in one month.	Patients were only followed for one month compared to our definition of 3 months.
Chan et al. 2008[2]	Failure to mature: fistula inadequate for hemodialysis use	Did not define inadequacy. This definition includes immediate, early and late failures
Dember et al. 2008[3]	Fistula suitability was defined as the ability to use the fistula for dialysis with 2 needles and maintain a dialysis machine blood flow rate adequate for optimal dialysis (300 mL/min) during 8 of 12 dialysis sessions occurring during a 30-day suitability ascertainment period.	Examined early failures within one month
Dixon et al. 2002[4]	A fistula that failed before starting dialysis therapy, or if the patient started on dialysis therapy, had a catheter in place for dialysis for all but 7 days of the cumulative life of the access.	This definition captures immediate, early and late failures
Elsharawy et al. 2006[5]	Fistula thrombosis or an inability to cannulate both atrial and venous needles or to obtain sufficient dialysis blood flow (> 350 mL/min) within 8 weeks after fistula creation	This definition captures immediate and early failures within two months of access creation
Feldman et al. 2003[6]	Not able to use the access for dialysis more than 6 occasions for hemodialysis	It was not clear if patients who never progressed to dialysis were considered as having an access failure. This definition captures immediate, early and late access failures.
Ferring et al. 2010[7]	A fistula that was never adequate for hemodialysis after initial surgical formation, including immediate failure on the day of surgery, early thrombosis, and failure to mature	This definition captures immediate, early and late access failures.

Appendix C. Continued		
Author	**Definition**	**Comment**
Gonzalez et al. 2010[8]	Failed adequate maturation for initiation of dialysis	Did not define inadequacy. This definition likely captures immediate, early and late access failures.
Huber et al. 2002[9]	Fistula that had not dilated significantly for cannulation despite remedial interventions were declared "failures" at 6 months even if they were still patent	This definition captures immediate, early and late access failures.
Huijbregts et al. 2008[10]	A fistula that did not develop to maintain dialysis or thrombosed before the first successful cannulation for hemodialysis treatment, regardless of eventual AVF abandonment.	This definition captures immediate, early and late access failures.
Korkut & Kosem. 2010[11]	Not reported	No definition was reported
Korten et al. 2007[12]	Primary failure was defined as thrombosis of the radiocephalic or inadequate maturation, which resulted in inadequate dialysis access at 6 weeks after surgery.	This definition captures immediate and early failures within 6 weeks of access creation
Lee et al. 2011[13]	Not reported	No definition was reported
Lok et al. 2005[14]	Fistulas that FTM were defined as those that met the following criteria: (*1*) did not develop enough by six months after creation to provide consistent dialysis for one month, and (*2*) this failure persisted despite efforts to facilitate its maturation (e.g., collateral vessel ligation) up to and including six months after creation.	
Lok et al. 2006[15]	Fistula that was used for HD and was unable to provide prescribed dialysis via two-needle cannulation consistently for 1 month within 6 months of its creation despite interventions to facilitate maturation. This definition excludes technical failures.	Excludes Immediate access failures

Table C. Continued		
Author	**Definition**	**Comment**
Malovrh. 2002[16]	Failed fistula function either immediately after construction or in the first 24 hours.	Only immediate access failures were included within 24 hours of access creation
Manns et al. 2004[17]	Failing to cannulate the fistula with two needles on three consecutive runs with blood flow 300 ml/min	Required three successive cannulations. This definition includes immediate, early and late failures.
Maya et al. 2009[18]	Inability to use the access successfully for dialysis, due to either early thrombosis or if it could be cannulated reproducibly for dialysis with two needles with a blood flow 300 ml/min for at least 1 month.	This definition captures immediate and early failures within one month of access creation.
Perera et al. 2004[19]	Early failure within the first 90 days from the time of operation. Most of the failures were secondary to failure of the autogenous access to mature.	This definition captures immediate and early failures within one month of access creation.
Peterson et al. 2008[20]	A fistula was considered mature when it could be cannulated reproducibly for dialysis, using two needles and achieving a dialysis blood flow 300 ml/min, within 6 months of its creation. Failure to mature (primary failure) was defined as the inability to meet this goal.	This definition captures immediate, early and late access failure.
Pflederer et al. 2008[21]	Abandonment of access before being used for dialysis	A person with a functional fistula and not requiring dialysis would have been included in primary failures. This definition captures immediate, early and late failures.
Pisoni et al. 2010[22]	The inability to use the fistula successfully for dialysis because of early thrombosis or failure to mature	Maya et al. used the same patient population and had expanded definition. This definition captures immediate and early failures within one month of access creation.

Appendix C. Continued		
Author	**Definition**	**Comment**
Puskar et al. 2002[23]	Failure of the arteriovenous fistula function within a month from its creation was considered an early arteriovenous fistula failure and after that period a late arteriovenous fistula failure.	Did not define what failure of fistula entailed.
Ravani et al. 2002[24]	Fistula failure was defined as definitive clotting or malfunction caused by stenosis or partial thrombosis, usually suspected on the basis of inflow monitoring and dynamic pressure measurements and ascertained by recirculation studies, echo-power-Doppler, and fistulography, if necessary. This was the primary end point of the study, and if it occurred during the first 7 days after VA creation, it was considered an early failure. Failure to mature in the absence of these complications also was considered an early failure.	It is unclear how the authors defined failure to mature. Also, the authors only captured early failures within 7 days of access creation
Schenk. 2010[25]	Primary failure was defined as occlusion or abandonment of a fistula before its successful entry into use for dialysis.	A person with a functional fistula and not requiring dialysis would have been included in primary failures
Swindlehurst et al. 2011[26]	Immediate failure of fistula , early thrombosis, or failure to mature	Authors used definition as reported by Sidawy et al.[27]
Weber et al. 2009[28]	The fistula did not matured in 3 months by clinical examination or thrombosed prior to dialysis start	This definition captures immediate and early failure
Wells et al. 2005[29]	Immediate failure of fistula or failure to mature. Successful maturation was achieved when the fistula was used on three successive occasions with adequate dialysis exchange	Required three successive cannulations. This definition includes immediate, early and late failures.
Wolowczyk et al.[30] 2000	Primary Failure was defined as: 1) an access that failed within 24 hours of fistula creation; 2) an early failure within 6 weeks, before the fistula could be used for hemodialysis; and 3) a late failure that was patent but never developed adequately to be used for hemodialysis by 6 weeks.	A six week period may not be a sufficient period of time for all fistulas to mature. Authors did not define “adequately” used for dialysis.

Appendix D. Sensitivity analyses

Subgroup	One Year			Two Year		
Primary Patency	**Estimate**	**Lower 95% CI**	**Upper 95% CI**	**Estimate**	**Lower 95% CI**	**Upper 95% CI**
Primary Failure Included						
Number of fistulas ≥100	63%	60%	67%	51%	46%	57%
Question derived *before* data collection	62%	54%	70%	60%	42%	78%
Patients recruited ≥2000	55%	48%	63%	32%	11%	54%
Primary Failure Excluded						
Number of fistulas ≥100	63%	55%	72%	49%	38%	60%
Question derived *before* data collection	69%	46%	92%	56%	35%	78%
Patients recruited ≥2000	52%	47%	57%	36%	29%	44%
Secondary Patency						
Primary Failure Included						
Number of fistulas ≥100	69%	60%	79%	63%	51%	75%
Question derived *before* data collection	75%	61%	89%	-	-	-
Patients recruited ≥2000	67%	55%	78%	50%	33%	67%
Primary Failure Excluded						
Number of fistulas ≥100	85%	75%	94%	75%	65%	86%
Question derived *before* data collection	-	-	-	-	-	-
Patients recruited ≥2000	87%	79%	95%	77%	67%	88%

CI= Confidence Interval; "-" refers to estimate unable to be calculated due to insufficient number of observations.

Appendix E. Contributions Chapter 3

Al-Jaishi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Al-Jaishi, Moist, Oliver, Lok, and Garg;

Literature search and articles retrieval: Al-Jaishi, Moist, Oliver, Lok, and Garg;

Data extraction and classification: Al-Jaishi, Thomas, Zhang, Kosa;

Data analyses and interpretation: Al-Jaishi, Moist, Thomas;

Manuscript drafting: Al-Jaishi and Moist;

Critical revision of the manuscript for important intellectual content and final approval: Al-Jaishi, Moist, Oliver, Thomas, Lok, Zhang, Garg, and Quinn;

Study supervision: Al-Jaishi and Moist had full access to all of the data and had the final responsibility to submit the manuscript for publication.

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Appendix 2

Appendix G.PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 71
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	N/A
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 71
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 71
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 71,72
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 71,72
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix B
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 39-41, 71,72
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 41,42
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 41,42
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 41,42

Section/topic	#	Checklist item	Reported on page #
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 73
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 73
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 72
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	None conducted
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 73, 74
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 74
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Not reported
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 76,77
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 81-83
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 78-80
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	None Conducted
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 84-88
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 86,87
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 88

Section/topic	#	Checklist item	Reported on page #
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	No Funding

Appendix H. Reported definition for infection and thrombosis by study.

Author	Year	Infection Rate**	Thrombosis Rate**
Bonforte et al.[1]	2004	.	Not reported
Elseviers et al.[2]	2003	Not reported	Not reported
Gilad et al.[3]	2005	Centers for Disease Control definition	.
Huijbregts et al.[4]	2008	.	Not reported
Jennings et al.[5]	2011	.	.
Korkut & Kosem[6]	2010	Wound infection in the early post-operative period. Authors did not report how infection was defined.	Not reported
Labriola et al.[7]	2011	Infectious events included both unexplained bacteremia caused by skin bacteria and/or local fistula infection. Local fistula infection was defined as nonallergic erythema, pain or tenderness close to cannulation sites, necrotic scabs, or drainage from cannulation site(s)	.
Lok et al[8]	2003	.	Fistulas that demonstrated evidence of stenosis by two of three criteria (abnormal physical exam, elevated venous pressures or abnormal monthly recirculation studies) were referred for a Duplex US exam. If the Duplex US study of either an fistula found a severe stenosis, indicating a lesion of >50%, a referral for an angiogram was made.
Mallamaci[9]	2005	.	A sudden cessation of function of the fistula, rendering hemodialysis impossible and requiring thromboctemy, thrombolysis, or acute placement of another hemodialysis access.
McCarley et al.[10]	2001	.	Not reported
Paul et al.[11]	2010	.	.
Pflederer et al.[12]	2008	Not reported	.
[1]Polkinghorne et al.[13]	2006	.	Not reported

Qasaimeh et al.[14]	2008	Infection of the VA was considered positive when the access site became red, hot, tender and swollen, with or without discharge, or when the patient presented with fever or chills and the condition necessitated giving antibiotics, and ended in cure or cessation of use of the access. Signs could be in the blood stream resulting in fever and chills. Infection in fistula was wither an initial placement wound infection, a late localized puncture site infection, a declot wound infection, or a systemic bacteremia.	.
Ravani et al.[15]	2002	Not reported	.
Roozbeh et al.[16]	2006	.	Complete vascular access occlusion
Saxena et al.	2003	Not reported	.
[3]Shahin et al.[17]	2005	.	A fistula was determined to have thrombosed if it failed without other explanation (e.g., ligation for ischemia) or if a procedure was needed to remove thrombus at the time of access intervention.
Stevenson et al.[18]	2002	CDC definition	.
Taylor et al.[19]	2002	Health Canada Definition	.
Taylor et al.[20]	2004	Health Canada Definition	.
Tessitore et al.[21]	2003	.	Not reported
Tessitore et al.[22] **(A)**	2008	.	Not reported
Tokars et al.[23]	2001	Local signs of pus or redness at the vascular access site or a positive blood culture with no known source other than the vascular access, and hospitalization or receipt of an IV antimicrobial	.
Tokars et al.[24]	2002	Centers for Disease Control definition	.
Zasuwa et al.[25]	2010	.	Clinical staff documenting the inability to conduct hemodialysis by failure to obtain sufficient blood flow and confirmed by physical examination or endovascular evaluation

"." Indicate that the study did not report this complication. "Not reported" indicates that the study reported the complication but not the definition.

Appendix I. Contributions Chapter 4

Al-Jaishi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Al-Jaishi, Moist, Oliver, Lok, and Garg;

Literature search and articles retrieval: Al-Jaishi, Moist, Oliver, Lok, and Garg;

Data extraction and classification: Al-Jaishi, Thomas, Zhang, Kosa;

Data analyses and interpretation: Al-Jaishi, Moist;

Manuscript drafting: Al-Jaishi and Moist;

Critical revision of the manuscript for important intellectual content and final approval: Al-Jaishi, Moist, Oliver, Thomas, Lok, Zhang, Garg, and Quinn;

Study supervision: Al-Jaishi and Moist had full access to all of the data.

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Curriculum Vitae

Name:	Ahmed Al-Jaishi
Post-secondary Education and Degrees:	Western University London, Ontario, Canada 2011 – 2013 M.Sc. University of Guelph Guelph, Ontario, Canada 2006 – 2010 B.Sc.
Honours and Awards:	Schulich Graduate Scholarshop 2011-2013 Carol Buck Scholarship, Finalist 2012
Related Work Experience	Graduate Research Assistant Kidney Clinical Research Unit London Health Sciences Centre 2011-2013

Publications:

Moist LM, Lok CE, Vachharajani TJ, Xi W, **Al-Jaishi A**, Polkinghorne KR, Vazquez M, Lee TC. Optimal Hemodialysis Vascular Access in the Elderly Patient. *Semin Dial*, 2013, 25(6): 640-648. **Published**

Moist LM, Lee TC, Lok CE, **Al-Jaishi A**, Xi W, Campbell V, Graham J, Wilson B, Vachharajani TJ. Education in Vascular Access. *Semin Dial,* 2013, 26(2): 148-153. **Published**

Moist LM, **Al-Jaishi AA**. The Upfront Risks of Vascular Access Complications. *J Am Soc Nephrol* 24: 2013. **In Press**

Al-Jaishi AA, Oliver MJ, Thomas SM, Lok CE, Zhang JC, Garg AX, Quinn RR, Kosa SD, Moist LM. Patency Rates of the Arteriovenous Fistula for Hemodialysis: A Systematic Review and Meta-Analysis. *Am J Kidney Dis*. **Accepted**

Peer Reviewed Abstracts

2013 Failure and Patency of the Arteriovenous Fistulas: A Systematic Review and Meta-analysis, World Congress of Nephrology, Hong Kong, China, **Lead Author**

2013 Failure and Patency of the Arteriovenous Fistulas: A Systematic Review and Meta-analysis, World Congress of Nephrology, Montreal, Quebec, Canada, **Presenter**

2012 Patency and Complications of Arteriovenous Fistulas, London Health Research Day, London, Ontario, Canada, **Presenter**

Non-Peer Reviewed Presentations

2012 Eighth Annual Renal Research Day, Patency and Complications of Arteriovenous Fistulas: A Systematic Review, London, Ontario, Canada, **Presenter**

Teaching Activities

Coordinator- Research Methods Seminar

2012-Presents London Health Sciences Centre, Victoria Hospital, Department of Medicine, London, Ontario, Canada

Seminar Leader- Epidemiology and Biostatistics

2011-2012 London Health Sciences Centre, Victoria Hospital, Department of Medicine, London, Ontario, Canada

Mentoring- Mathematics Peer Mentor

2009-2010 University of Guelph, Department of Mathematics and Statistics, Guelph, Ontario, Canada