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REVIEW

Arteriovenous Fistulae for Haemodialysis: A Systematic Review and Meta-analysis of Efficacy and Safety Outcomes

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WHAT THIS PAPER ADDS

This systematic review and meta-analysis summarizes arteriovenous fistula patency, maturation, infection, and abandonment. Fistulae were characterized by low rates of infection but also high risk of abandonment and failure to mature, which should be taken into consideration when selecting a vascular access modality.

Background: Arteriovenous fistulae are the currently recommended gold standard vascular access modality for haemodialysis because of their prolonged patency, improved durability, and low risk of infection for those that mature. However, notable disadvantages are observed in terms of protracted maturation time, associated high rates of catheter use, and substantial abandonment rates. The aim of this study was to quantitatively summarize the outcomes of fistula patency, infection, maturation, and abandonment published in the scientific literature.
Methods: This was a systematic review and meta-analyses of studies evaluating fistula outcomes. Literature searches were conducted in multiple databases to identify observational and interventional studies of mean fistula patency rates at 1 year, infection risk, maturation time, and abandonment. Digitisation software was used to simulate individual patient level data from Kaplan–Meier survival plots.
Results: Over 8000 studies were reviewed, and from these, 318 studies were included comprising 62,712 accesses. For fistulas the primary unassisted, primary assisted, and secondary patency rates at one year were 64%, 73% and 79% respectively, however not all fistulas reported as patent could be confirmed as being clinically useful for dialysis (i.e. functional patency). For fistulas that were reported as mature, mean time to maturation was 3.5 months, however only 26% of created fistulas were reported as mature at 6 months and 21% of fistulas were abandoned without use. Overall risk of infection in fistula patients was 4.1% and the overall rate per 100 access days was 0.018.
Conclusions: Reported fistula patency rates may overstate their potential clinical utility when time to maturation, maturation rate, abandonment and infection are considered. Protracted maturation times, abandonment and infection all have a significant impact on evaluating the clinical utility of fistula creation. A rigorous and consistent set of outcomes definitions for hemodialysis access are necessary to clarify factors contributing to fistula success and the clinical consequence of fistula failure.

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INTRODUCTION

The use of chronic haemodialysis (HD) as renal replacement therapy (RRT) in patients with end stage renal disease (ESRD) is a prevalent practice worldwide and in the USA, and HD accounts for approximately 63% of RRT.[1] The US Renal Data System estimated that there were 120,688 incident and 678,383 prevalent cases of ESRD in the USA in 2014.[1] The three modalities of vascular access used for chronic HD are central venous catheters (CVC), arteriovenous grafts (AVG), and autologous arteriovenous fistulae (AVF). Although AVF had been recommended since 1997, in 2003, the National Kidney Foundation (NKF) set forth the Fistula First Breakthrough Initiative (FFBI), recommending fistula rates of $\geq$50% for incident (first placed access), and $\geq$40% for prevalent (patient had previous surgically created

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accesses) patients undergoing HD. The current goal for fistula use among prevalent patients is 68%.[2] In the USA, 80% of patients initiate HD using a catheter, which has gone unchanged for nearly a decade, and only 16.9% initiate dialysis with an AVF. However, at 1 year post-HD initiation, 65% of patients dialyse exclusively using an AVF.[1]

The NKF recommends that AVF be placed at least 6 months prior to initiation of HD treatment to allow sufficient time for access creation and evaluation, vein maturation, and if necessary, maturation enhancing interventions prior to cannulation. It is therefore recommended that chronic kidney disease (CKD) patients in the fourth or fifth stages be educated on vascular access modalities to allow sufficient time for access placement.[3] While this is a noble goal, it has been difficult to implement because of the unpredictability of renal failure progression, patient referral patterns, and financial disincentives for early fistula creation. It is common for patients to progress to ESRD and initiate HD before the fistula has either been created or matured. In such cases a CVC is commonly placed to be used for vascular access, placing patients at high risk of complications and infection, resulting in increased patient costs and burden,[4] and resulting in a mentality of both "fistula first" and "catheter last."[5]

The use of AVFs as vascular accesses for haemodialysis has independent risks. Not all patients are candidates for AVF and many of the studies that highlighted the advantages of autologous access discounted and/or did not acknowledge the unacceptable rate of early failure and fistula non-maturation.[6] The FFBI inadvertently exposed the disadvantages of autologous access and the related cascade of unintended consequences from early AVF failure or prolonged catheter exposure because of the need for several maturation enhancing procedures. The resulting undesired situation (high AVF placement and low initial AVF HD rates) is the result of high levels of primary fistula failure, either non-maturation caused by early thrombosis or insufficient dilation to support repetitive cannulation. Fistula non-maturation rates ranging from 20% to 60% have been reported.[6,7]

The objectives of this study were: 1) to perform a systematic literature review of AVF among adults in developed nations including the outcomes of patency, maturation, infection, and abandonment; 2) to digitize available Kaplan—Meier curves and simulate individual patient level data; 3) to meta-analytically combine estimates for the outcomes of interest; and 4) to evaluate the summary estimates by various potential confounding or modifying factors.

METHODS

Study design

This systematic review and meta-analysis was conducted in accordance with PRISMA guidelines[8] (the protocol was filed with PROSPERO register [registration number CRD42016040010] on 6/7/2016). The study population consisted of patients with CKD or ESRD either preparing for or on chronic HD treatment with an autologous AVF. Included studies were published in the English language with no lower date limit. Studies with outcomes of primary unassisted patency, primary assisted patency, secondary patency, infection rates, fistula maturation, access abandonment, and bridging catheter time were included. Randomised controlled trial and observational study designs were included. To generalise the analyses to outcomes of vascular accesses in developed nations, only studies conducted in countries classified as "developed" by the United Nations were included.[9] After discussion with the clinical team (SMG and JHL), South Africa, Brazil, and Argentina were added to this list given that the level of dialysis health care that ESRD patients in those countries are likely to receive is comparable with that of the "developed" nations. Only standard of care methods were included in this review to produce the most generalisable results to other vascular access methods. The clinical team provided input as to the methods and interventions considered to be "standard of care."

Case series with fewer than 20 patients, opinion pieces and editorials, guidelines and recommendations, articles without original data, and conference abstracts were excluded from the review. AVFs placed anywhere other than the arm were excluded as they are not considered standard of care. Publications from the same cohort that contained unique study populations or analyses were included in the review.

Literature search

Literature searches were conducted in April 2016 in multiple scientific databases including Medline, Embase, Cochrane Library, and Clinicaltrials.gov. A flow diagram of the study selection and inclusion process is shown in Fig. 1. The included search terms used in each database are found in Table S1 (supplementary information). Studies were screened for eligibility by two reviewers at the levels of abstract and full text.

Statistical analysis

Meta-analyses were conducted using random effects models in the statistical software packages of either STATA (StataCorp LP, V.14.1) or Comprehensive Meta-Analysis (Biostat, v.3.0). Individual study weights were created using the inverse of the variance using the method proposed by DerSimonian and Laird.[10] Stratified analyses were also performed on variables selected *a priori* to potentially affect the outcomes of interest, such as gender, age, race, diabetes status, obesity, cardiovascular disease status, access location, time on dialysis, access placed before or after dialysis began, incident or prevalent AVF patients, primary cause of renal failure, and whether vein transposition was involved in access construction.[11] Evolving clinical practice patterns of enhanced fistula maturation meant that outcomes by studies conducted before and after 2005 were stratified, as surgical interventions used to prolong patency underwent a pivotal shift toward more aggressive

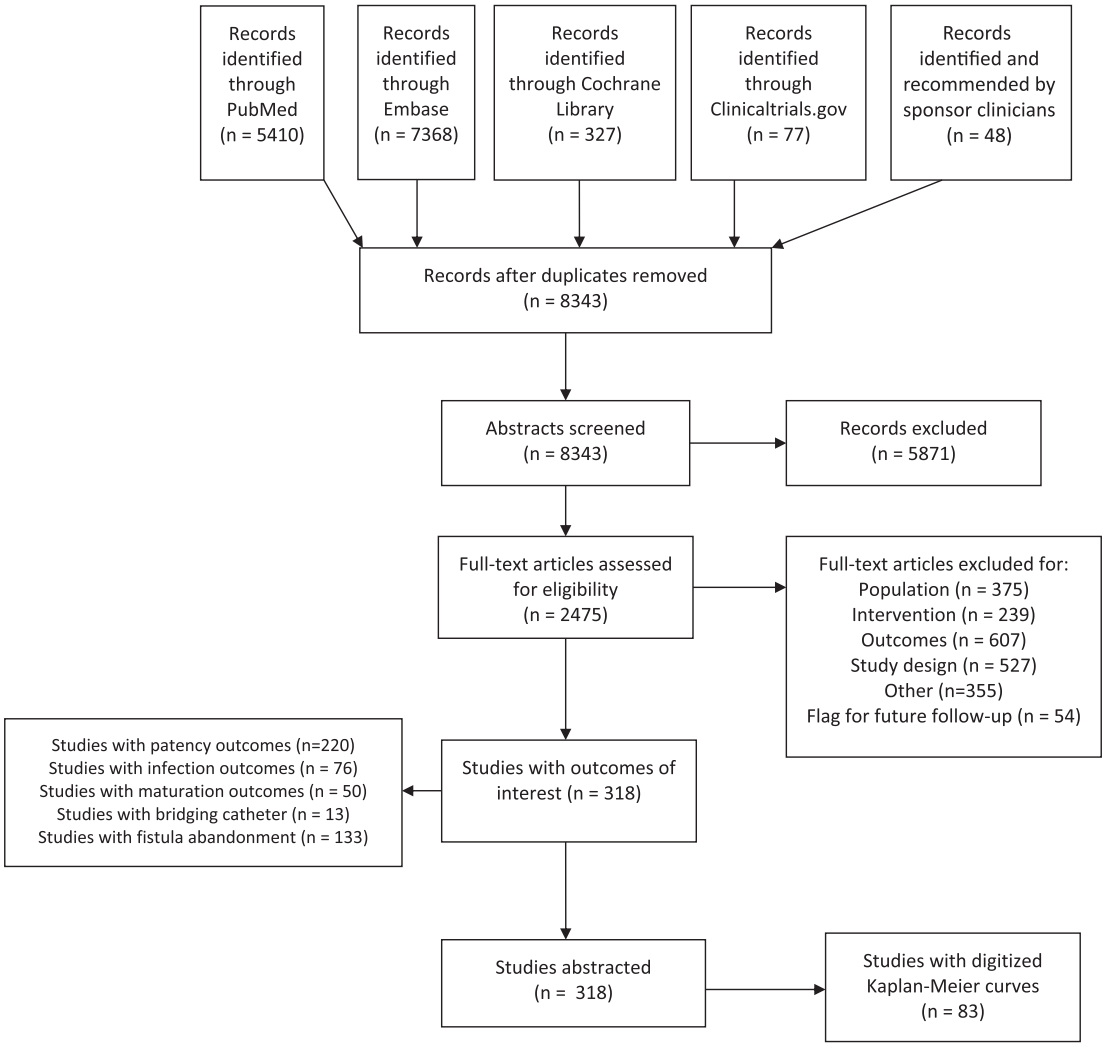


Figure 1. Flow diagram of study inclusion.

endovascular interventions, which may have contributed to improvement of patency during this time period. Subgroup analyses were performed for outcomes reported in three or more studies.

For many outcomes, the included studies used time to event analysis and published survival curves using the Kaplan—Meier method.[12] As the gold standard for meta-analyzing time to event data is individual patient level data (IPD), a published algorithm[13] was used and DigitizeIt software to reproduce IPD. The software identified each line in a Kaplan—Meier curve and the resulting output was used, in coordination with the study's reported life tables, to estimate survival summary statistics for each study including patency at 1 and 2 years, mean and median patency time, and standard errors, which were then entered into the meta-analyses. If outcome estimates were both reported in the text as well as published in survival curves, the originally reported in-text data were used, provided that a measure of variance was included. Comparisons were made between the digitisation output and the original reported outcomes on a sample of papers with survival curves and in-text data as a quality control measure for the digitisation software. Some curves could not be digitized because of lack of numbers at risk or poor digital quality of the publication; others were not compatible with the algorithm and could not be included.

Endpoints and definitions

The patency analysis was categorized using the definitions provided by Sidawy.[14] "Primary unassisted patency" is the interval from access placement until any intervention designed to maintain or re-establish patency, access thrombosis, or the time of measurement of patency. "Primary assisted patency" is the interval from access placement until access thrombosis or the time of measurement of patency, including intervening manipulations (surgical or endovascular interventions) designed to *maintain* the functionality of a patent access. "Secondary patency" is the interval from access placement until access abandonment, thrombosis, or the time of patency measurement including intervening manipulations (surgical or endovascular interventions) designed to *re-establish* functionality in thrombosed access. These definitions, with the inclusion of the "functionality" modifier, intend to take into

consideration clinical usefulness of the access for hemodialysis (i.e. functional patency), but it was apparent that approximately half of reports focused simply on the patency aspect of the definition (i.e., any blood flow through the access) in their patency definition, and were therefore ambiguous as to the clinical utility of the accesses analyzed.

Patency rates at 1 year were meta-analysed in STATA using a log transformation. Mean patency times were meta-analysed in Comprehensive Meta-Analysis v3. As a sensitivity analysis, studies were excluded that did not use access placement as the beginning of patency (i.e. assessments began after cannulation) and studies that excluded some patients from the patency analyses (i.e. primary failures). The analyses labelled "restricted overall" include only the studies that used a consistent definition of patency beginning at the time of access placement with an intent to treat analysis.

Overall risk and rate of infections reported in fistula patients were abstracted. Although the intention was to use the Centers for Disease Control and Prevention (CDC) definitions of vascular access related infections,[15] many reported definitions could not be incorporated into these categories. Therefore, infection was analysed overall, as infection not otherwise specified, access site infection, bacteremia/bloodstream infection, and access related bacteremia/bloodstream infection. Infection was harmonised across studies to a rate per 100 access days.

For maturation outcomes, percent mature (unassisted and assisted) at various time points, time to maturation, percent requiring catheter dialysis before maturation, amount of time on a catheter before maturation, percent abandoned without use, and percent abandoned at various time points were abstracted. Unassisted maturation is the time before suitability for dialysis that was not interrupted by surgical or endovascular procedures. Assisted maturation is the time before suitability for dialysis inclusive of any surgical or endovascular procedures used to promote maturation. The variability of maturation definitions and outcomes reported among the included studies meant that maturation was evaluated using two outcomes: rate of maturation at 6 months and mean time to maturation. Rate of maturation at 6 months was analysed using studies that published a time to maturation Kaplan—Meier curve, as none of the included studies provided a 95% CI with the reported rate of maturation at 6 months. Mean time to maturation was analysed using data derived from the Kaplan—Meier curves as well as mean estimates reported in text with a measure of standard error or standard deviation. None of the studies in the meta-analysis of mean time to maturation specified that the maturation was assisted or unassisted. The proportion of AVF abandoned without use was meta-analysed using in text data only. Studies that reported an outcome of "primary failure" or "immediate post-operative failure" were also included in this analysis.

Table 1. Meta-analyses of primary unassisted patency in arteriovenous fistulae.

Analysis	1 year rate				Mean in months			
	n[a]	n[b]	Rate (95% CI)	I^2; p-Het	n[a]	n[b]	Mean (95% CI)	I^2; p-Het
Overall	59	11,433	0.64 (0.59—0.68)	94.6%; <.001	52	10,735	20.09 (17.65—22.54)	99.53%; <.001
Overall restricted	43	7919	0.63 (0.58—0.67)	93.1%; <.001	37	7221	20.71 (17.82—23.60)	99.51%; <.001
USA	18	3379	0.57 (0.49—0.64)	93.7%; <.001	18	3379	18.23 (14.33—22.13)	98.93%; <.001
Other countries	41	8054	0.66 (0.61—0.71)	94.8%; <.001	34	7356	21.17 (17.99—24.34)	99.64%; <.001
<65 years old	7	1373	0.63 (0.51—0.72)	93.4%; <.001	3	936	16.41 (9.09—23.74)	98.14%; <.001
65+ years old	10	1194	0.60 (0.52—0.68)	85.5%; <.001	6	883	19.10 (13.48—24.73)	97.82%; <.001
Diabetic	7	377	0.67 (0.60—0.73)	25.4%; .235	4	251	28.78 (19.3—38.26)	92.77%; <.001
Non-diabetic	6	848	0.72 (0.61—0.80)	88.3%; <.001	3	331	27.06 (9.34—44.77)	98.97%; <.001
Incident access	14	3688	0.69 (0.57—0.77)	96.8%; <.001	6	2807	15.49 (8.91—22.06)	99.69%; <.001
Prevalent access	4	183	0.57 (0.42—0.70)	58.1%; .067	4	183	13.34 (9.93—16.76)	78.51%; .003
Access created post-initiation of dialysis	3	199	0.54 (0.46—0.61)	0.0%; .379	3	199	9.00 (0.85—17.16)	99.08%; <.001
Location: upper arm	4	401	0.69 (0.37—0.87)	95.9%; <.001	4	401	23.89 (12.36—35.43)	98.74%; <.001
Location: forearm/wrist (RCAVF, snuffbox, ulnaris)	15	1718	0.55 (0.46—0.63)	89.9%; <.001	22	1768	21.14 (18.09—24.20)	98.76%; <.001
Location: mixed arm	18	4262	0.52 (0.46—0.58)	92.3%; <.001	16	4472	15.51 (13.07—18.55)	98.47%; <.001
Location: brachiocephalic only	10	996	0.52 (0.41—0.61)	87.1%; <.001	10	996	16.12 (12.28—19.95)	97.32%; <.001
Location: brachiobasilic and/or brachiobrachial only	16	1264	0.55 (0.47—0.63)	82.6%; <.001	16	1264	17.52 (13.77—21.26)	96.88%; <.001
Basilic vein transposition	17	1237	0.57 (0.49—0.65)	83.5%; <.001	17	1237	18.51 (14.93—22.08)	96.71%; <.001
No superficialisation	17	2329	0.61 (0.54—0.68)	86.7%; <.001	22	2379	17.91 (15.45—20.38)	98.27%; <.001
Mixed superficialisation	15	3376	0.59 (0.49—0.67)	95.8%; <.001	15	3376	19.58 (14.91—24.24)	99.13%; <.001
Studies conducted pre-2005	19	3375	0.71 (0.63—0.77)	93.5%; <.001	11	3026	20.30 (15.27—25.33)	99.29%; <.001
Mixed years (pre- and post-2005)	18	4785	0.62 (0.56—0.68)	94.0%; <.001	18	4789	22.43 (17.76—27.10)	99.23%; <.001
Studies conducted post-2005	17	2603	0.54 (0.44—0.63)	94.9%; <.001	18	2653	18.73 (15.56—21.89)	99.24%; <.001

RCAVF = radiocephalic arteriovenous fistula.

[a] Number of studies.

[b] Number of accesses.

Table 2. Meta-analyses of primary assisted patency in arteriovenous fistulae.

Analysis	1 year rate				Mean in months			
	n^a	n^b	Rate (95% CI)	I^2; p-Het	n^a	n^b	Mean (95% CI)	I^2; p-Het
Overall	23	4000	0.73 (0.65—0.80)	95.2%; <.001	21	3496	23.06 (17.53—28.59)	99.46%; <.001
Overall restricted	18	3279	0.72 (0.62—0.80)	96.0%; <.001	16	2688	23.76 (16.34—31.21)	99.54%; <.001
USA only	9	1927	0.73 (0.52—0.86)	96.9%; <.001	9	1827	23.29 (11.19—35.39)	99.56%; <.001
Non-USA only	14	2073	0.73 (0.64—0.80)	92.5%; <.001	13	1582	22.83 (17.57—28.08)	99.18%; <.001
Prevalent access	3	135	0.69 (0.33—0.88)	91.7%; .004	3	135	16.00 (11.17—20.84)	87.97%; <.001
Access created post-initiation of dialysis	3	548	0.64 (0.51—0.74)	77.6%; .011	3	548	14.87 (12.13—17.61)	89.94%; <.001
Location: forearm	—	—	—	—	3	486	11.14 (6.50—15.77)	92.95%; <.001
Location: mixed arm	8	2226	0.78 (0.60—0.89)	97.8%; <.001	9	2226	29.57 (15.87—43.28)	99.7%; <.001
Location: brachiocephalic only	4	278	0.69 (0.51—0.82)	83.9%; <.001	5	313	16.93 (10.28—23.59)	96.22%; <.001
Location: brachiobasilic and/or brachiobrachial only	10	792	0.76 (0.64—0.85)	88.8%; <.001	11	825	18.74 (14.46—23.02)	98.08%; <.001
Basilic vein transposition	10	792	0.76 (0.64—0.85)	88.8%; <.001	11	825	18.74 (14.46—23.02)	98.08%; <.001
No superficialisation	5	689	0.61 (0.46—0.72)	89.6%; <.001	7	799	14.63 (1051—18.74)	96.74%; <.001
Mixed superficialisation	6	1991	0.69 (0.45—0.84)	98.1%; <.001	7	1991	22.61 (8.5—36.72)	99.73%; <.001
Studies conducted pre-2005	7	674	0.66 (0.55—0.74)	73.0%; .001	6	574	18.14 (14.95—21.33)	9.12%; <.001
Mixed years (pre- and post-2005)	11	2876	0.79 (0.68—0.87)	97.0%; <.001	10	2385	30.65 (19.31—41.98)	99.74%; <.001
Studies conducted post-2005	4	395	0.72 (0.43—0.88)	95.0%; <.001	4	395	18.98 (10.73—27.23)	98.67%; <.001

RCAVF = radiocephalic arteriovenous fistula.
[a] Number of studies.
[b] Number of accesses.

Table 3. Meta-analyses of secondary patency in arteriovenous fistulae.

Analysis	1 year rate				Mean in months			
	n^a	n^b	Rate (95% CI)	I^2; p-Het	n^a	n^b	Mean (95% CI)	I^2; p-Het
Overall	65	13,261	0.79 (0.76—0.83)	94.8%; <.001	63	12,784	28.01 (25.28—30.74)	99.58%; <.001
Overall restricted	56	12,021	0.79 (0.75—0.82)	95.1%; <.001	51	11,163	28.84 (25.60—32.08)	99.63%; <.001
Males	4	949	0.82 (0.68—0.90)	82.0%; .001	7	845	31.92 (19.65—44.20)	98.32%; <.001
Females	6	848	0.83 (0.66—0.92)	87.6%; <.001	3	573	33.54 (7.27—59.80)	98.86%; <.001
USA only	15	3271	0.81 (0.73—0.87)	92.7%; <.001	19	3227	28.59 (20.98—36.21)	99.62%; <.001
Non-USA only	50	9990	0.79 (0.75—0.82)	94.7%; <.001	44	9028	27.67 (24.76—30.58)	99.54%; <.001
<65 years old	6	1396	0.88 (0.67—0.96)	96.6%; <.001	3	1057	56.5 (19.29—93.70)	99.76%; <.001
65+ years old	9	1482	0.88 (0.78—0.93)	89.3%; <.001	6	937	44.73 (18.27—71.19)	99.79%; <.001
Diabetic	7	363	0.82 (0.71—0.89)	68.9%; .004	6	591	35.59 (20.35—50.83)	98.45%; <.001
Non-diabetic	7	838	0.90 (0.78—0.96)	92.7%; <.001	5	658	34.58 (14.56—54.59)	99.49%; <.001
Incident access	15	3172	0.85 (0.77—0.90)	94.4%; <.001	9	2160	34.55 (26.47—42.63)	99.55%; <.001
Prevalent access	4	168	0.71 (0.56—0.81)	53.4%; .092	6	168	22.38 (16.52—28.24)	91.67%; <.001
Access created prior to dialysis initiation	5	1451	0.83 (0.71—0.90)	92.2%; <.001	7	1451	41.61 (24.79—58.42)	98.97%; <.001
Access created post-initiation of dialysis	4	941	0.75 (0.61—0.84)	87.3%; <.001	6	941	25.26 (18.47—32.05)	98.17%; <.001
Location: upper arm	6	880	0.67 (0.53—0.77)	91.4%; <.001	6	880	29.09 (17.6—40.59)	98.74%; <.001
Location: forearm/wrist (RCAVF, snuffbox, ulnaris)	15	3160	0.71 (0.65—0.77)	89%; <.001	21	2608	25.90 (22.26—29.54)	99.40%; <.001
Location: mixed arm	22	7973	0.82 (0.75—0.86)	97.6%; <.001	25	7755	36.58 (30.49—42.66)	99.73%; <.001
Location: brachiocephalic only	8	1105	0.74 (0.63—0.83)	91.2%; <.001	8	1072	29.81 (22.15—37.47)	98.58%; <.001
Location: brachiobasilic and/or brachiobrachial only	15	1250	0.75 (0.67—0.82)	83.7%; <.001	15	1150	22.71 (18.44—26.97)	98.25%; <.001
Basilic vein transposition	16	1230	0.76 (0.69—0.82)	83.4%; <.001	16	1180	23.32 (19.12—27.51)	98.21%; <.001
No superficialisation	16	3261	0.73 (0.66—0.79)	91.2%; <.001	17	2709	26.33 (22.07—30.58)	99.42%; <.001
Mixed superficialisation	17	5759	0.79 (0.72—0.85)	95.8%; <.001	17	5379	36.74 (26.11—47.36)	99.74%; <.001
Studies conducted pre-2005	21	3171	0.81 (0.75—0.86)	89.9%; <.001	14	2495	27.45 (22.56—32.34)	98.37%; <.001
Mixed years (pre- and post-2005)	22	6975	0.82 (0.75—0.87)	97.3%; <.001	21	6875	35.63 (29.20—42.06)	99.74%; <.001
Studies conducted post-2005	18	2813	0.75 (0.68—0.80)	90.5%; <.001	18	2583	23.27 (19.24—27.30)	99.54%; <.001

RCAVF = radiocephalic arteriovenous fistula.
[a] Number of studies.
[b] Number of accesses.

The proportion of AVF requiring a bridging catheter while awaiting maturation was also meta-analysed.

Ethics approval

All data were obtained from published scientific articles. No ethics approval was necessary.

RESULTS

A total of 318 studies including 62,712 accesses were identified for these meta-analyses. The included studies and their characteristics are listed in Table S2. The results of the overall patency analyses are demonstrated in Tables 1—3. For each patency outcome, the overall and overall restricted analyses were very similar, often within 1% (1 year rate) or 1 month (mean patency) and the 95% CI between analyses overlapped for each outcome. For this reason, the full analytic group of studies included in the overall analysis was used for the subgroup analyses to maximise the number of studies. As expected, AVF patency improved from primary unassisted (Fig. 2; 1 year rate 0.64; mean 20.1 months) to primary assisted (1 year rate 0.73; mean 23.1 months) to secondary patency (Fig. 3; 1 year rate 0.79; mean 28.0 months). Statistical heterogeneity was present in all of the patency analyses.

The stratified patency analyses revealed a number of interesting disparities among subgroups, although none was

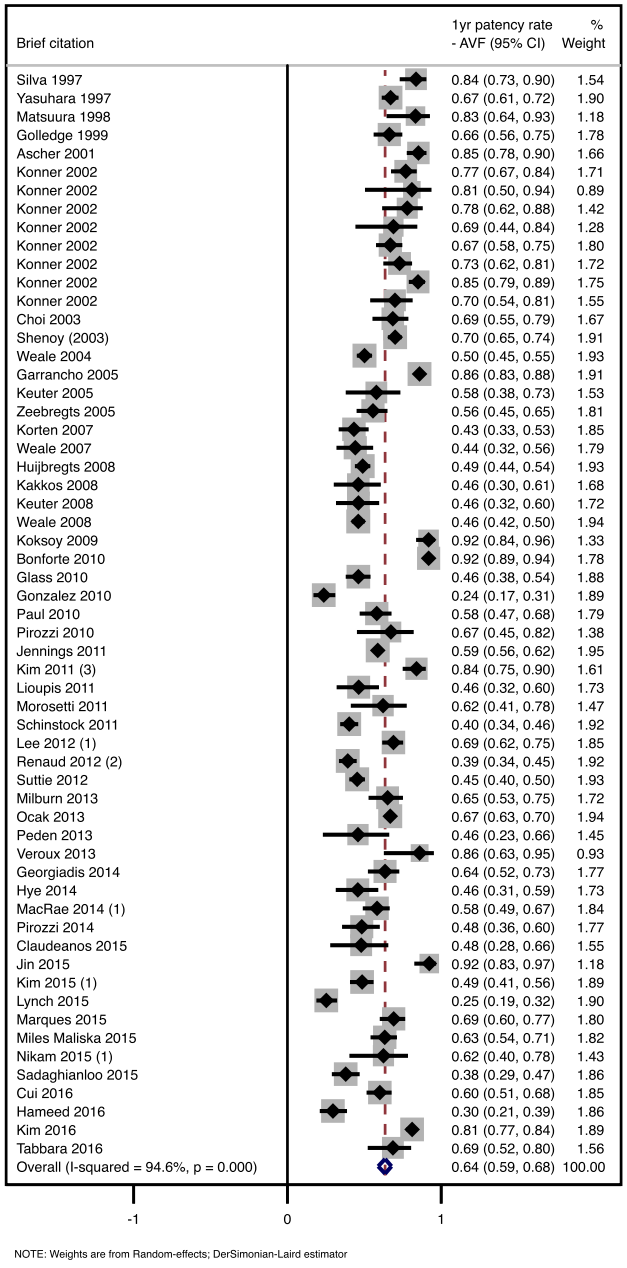


Figure 2. Meta-analysis of overall primary unassisted patency at 1 year (*n*=59).

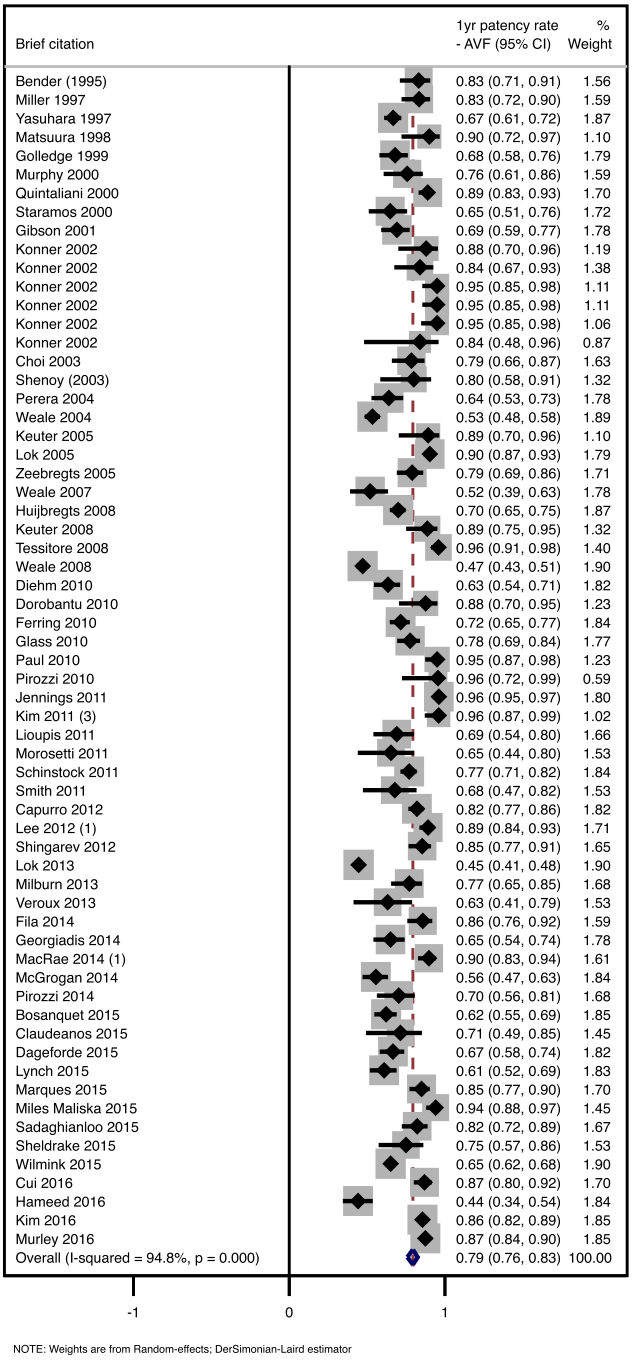


Figure 3. Meta-analysis of secondary patency rate at 1 year (*n*=65).

statistically significant. Studies conducted within the USA had poorer primary unassisted patency than studies conducted outside the USA (0.57 [95% CI 0.49—0.64] vs. 0.66 [95% CI: 0.61—0.71] at 1 year), although the primary assisted and secondary patency analyses were very similar between the two groups (0.73 vs. 0.73; 0.81 vs. 0.79, respectively, at 1 year). Incident AVF had improved primary unassisted and secondary patency when compared with prevalent AVF (0.69 vs. 0.57; 0.85 vs. 0.71, respectively, at 1 year). Secondary patency was also increased for accesses created prior to haemodialysis initiation when compared with those created post-initiation (0.83 [95% CI 0.71—0.90] vs. 0.75 [95% CI 0.61—0.84] at 1 year). Studies conducted pre-2005 had better primary unassisted patency and secondary patency than those conducted post-2005 (0.71 vs. 0.54; 0.81 vs. 0.75 at 1 year), although this trend was reversed for primary assisted patency (0.66 vs. 0.72 at 1 year).

A total of 76 studies with an outcome of infection were identified and abstracted. The overall risk of infection over the study period was 0.041 and the overall rate per 100 access days was 0.018 (Table 4). While few differences were noted between infection types for risk of infection, the rate of bacteremia was slightly higher than the overall infection rate.

The mean time to maturation for AVF was reported in text in 34 studies and was calculated from the Kaplan—Meier curve in two studies. The overall mean time to maturation was 3.49 months (95% CI 3.17—3.81) (Fig. 4). The meta-analyses of maturation cannot be classified as "unassisted" or "assisted" maturation, as the included studies did not specify this designation. Studies that reported time intervals for unassisted or assisted maturation did not provide a measure of variance and could not be meta-analysed.

Three studies provided Kaplan—Meier curves of time to maturation and were included in a meta-analysis of maturation rate at 6 months, resulting in a rate of 0.26 (95% CI 0.23—0.29), although this was based on three studies (n=1502 accesses).[16—18] There was not significant heterogeneity present in this analysis (I^2: 0%; p-Het: .787). Although it was not possible to identify sufficient studies for an analysis of mean time on a catheter while awaiting AVF maturation, 19 studies were identified that reported the proportion of AVF requiring a bridging catheter while maturing. The summary rate was 0.66 (95% CI 0.57—0.75).

In the meta-analysis of AVF abandoned without use, a summary rate of 0.21 (95% CI: 0.19—0.24) was calculated among 164 included populations from 133 different publications. The large number of studies made it possible to stratify the analysis by a number of subgroups of interest (Table 5). AVF placed in females were abandoned at a higher rate than those placed in males (0.43 vs. 0.22), and AVF placed in the USA were abandoned more often than those placed outside the USA (0.27 vs. 0.16). Regarding location of fistula placement, accesses placed in the upper arm were abandoned at a lower rate than accesses placed in the forearm (0.16 vs. 0.23).

DISCUSSION

In this review, a wide body of scientific literature was identified on patency, infection, maturation, and abandonment in arteriovenous fistulae used for haemodialysis, and published estimates were meta-analytically combined to calculate summary outcome measures. The strengths of this analysis include the comprehensive literature covered and the variety of subgroups that were evaluated in stratified analyses. Also, software was used to simulate IPD from published Kaplan—Meier curves, allowing inclusion of patency data that were not published in the included studies. A potential limitation of this study may be uncontrolled confounding or other small biases not noted explicitly in the individual studies, as a full methodological assessment of each study was not conducted. Analytically, the influence of arbitrary patency definitions was evaluated by removing these studies, and no statistical effect was found on overall patency.

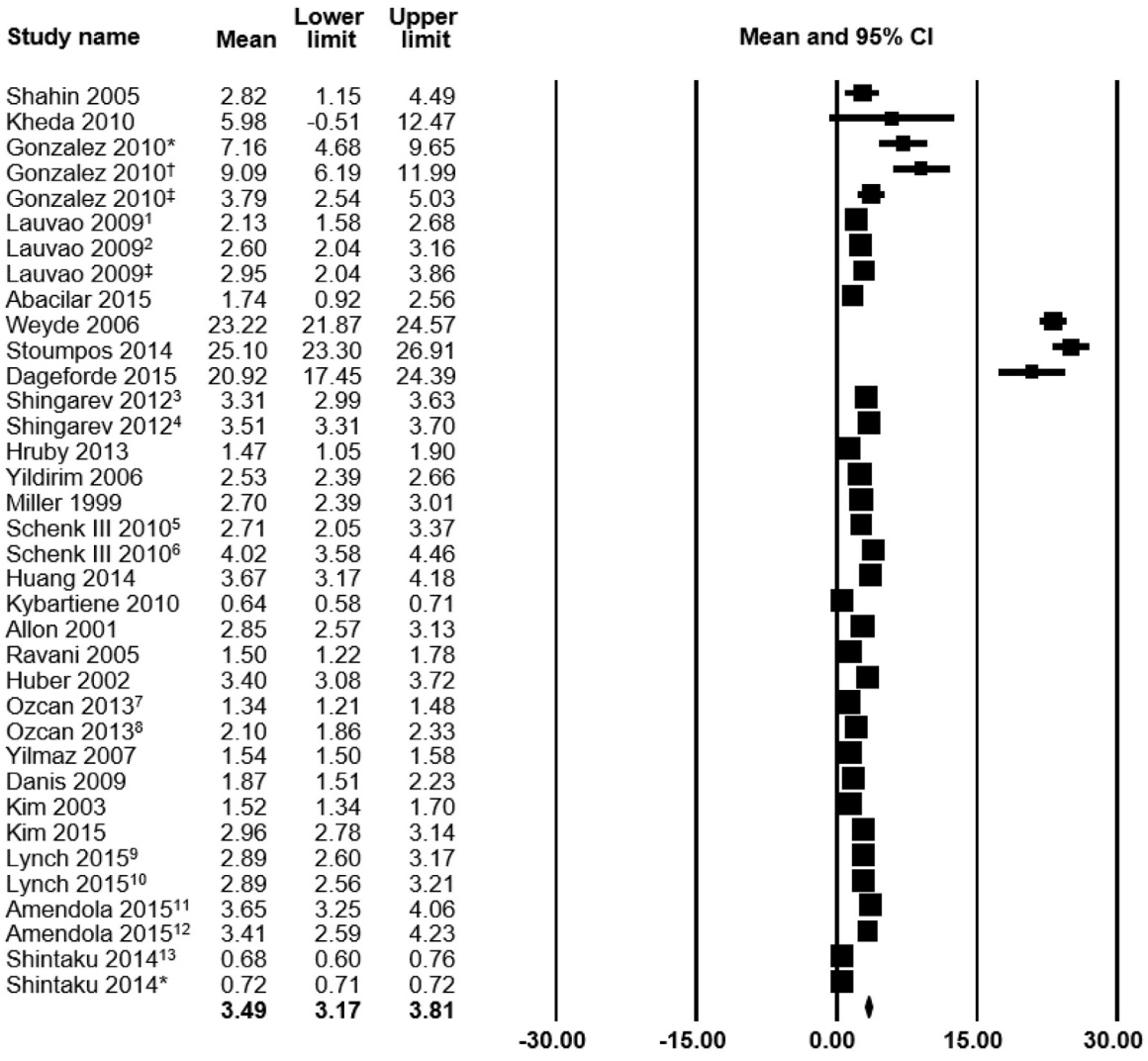
While conducting this study, a new systematic review and meta-analysis was published[19] evaluating primary unassisted patency and secondary patency rates at 2 years as well as overall infection rates. Therefore, AVF patency rates were analysed at 2 years in the present study for comparison with the new study. The present patency rates were similar to those reported in the new study, with a primary unassisted patency at 2 years of 0.51 (Almasri: 0.55) and a secondary patency rate of 0.70 (Almasri: 0.63). However, the present infection risk was twice the rate reported in the new study (0.04 vs. 0.02).

Many of the present meta-analyses were stratified by factors chosen *a priori* to potentially affect the outcome. Fistulae created in incident patients were consistently superior to those placed in prevalent patients across multiple outcomes. Additionally, accesses created prior to HD initiation were found to have improved patency and decreased abandonment versus those created after HD initiation, a

Table 4. Risk of infection over study period and rate per 100 access days.

Infection type	Risk of infection (95% CI)	Rate of infection per 100 access-days (95% CI)
Total infection (all types)	0.041 (0.032—0.053) N=75; I^2: 61.11%; p<.001	0.018 (0.011—0.043) N=34; I^2: 72.05%; p<.001
Infection not otherwise specified	0.043 (0.031—0.061) N=37; I^2: 36.78%; p=.015	0.016 (0.007—0.035) N=7; I^2: 0%; p=.642
Access site infection	0.037 (0.024—0.055) N=31; I^2: 66.06%; p<.001	0.020 (0.006—0.062) N=13; I^2: 85.80%; p<.001
Bacteremia/BSI	0.039 (0.015—0.099) N=5; I^2: 83.12%; p<.001	0.025 (0.017—0.038) N=12; I^2: 10.3%; p=.344

BSI = blood stream infection.



*RCAVF, †BCAVF, ‡BBAVF, [1]Posterior RCAVF, [2]Wrist RCAVF, [3]Ipsilateral catheter, [4]Contralateral catheter, [5]Recruited AVF, [6]Planned AVF, [7]One-stage BVT, [8]Two-stage BVT, [9]No routine preoperative US, [10]Routine preoperative US, [11]Incident AVF, [12]Prevalent AVF, [13]Ulnar-basilic AVF

Figure 4. Mean time to maturation in months (n=34).

pattern that was observed in prior literature.[20,21] Some of the present subgroup analyses were limited by a lack of published data, including race, length of time on dialysis, and relevant comorbidities such as cardiovascular disease and obesity. Furthermore, there was insufficient detail in the studies to perform a subgroup analysis by pre -operative vessel assessment, which is recommended by the NKF to improve AVF outcomes and may have influenced patency, maturation, or abandonment rates.[3] Most studies also did not specify whether a catheter was present when evaluating risk of infection. Given the known risk of infection on catheters, this information would better inform meta-analyses of infection in AVF.

The results of the present study highlight the strengths of AVF and also emphasize their limitations. It was found that nearly two thirds of AVF required the use of a bridging catheter while awaiting maturation, placing patients at increased risk of infection, and that approximately 20% of AVF were abandoned without use. A review of AVF studies conducted between 2000 and 2012 observed a similar primary failure rate of 23%.[22] This is notable in terms of healthcare resource use and patient risk, where patients are subjected to a surgical procedure and associated prolonged catheter time with a 21% failure rate. These patients have essentially failed operations and yet accrue significant costs of surgery, follow-up, and postsurgical interventions and/or revisions. The advantages of AVF compared with other access modalities are only achieved for accesses that mature or do not fail before use.[23]

This analysis was limited by the definitions of patency and maturation reported in the included studies. It is recommended that future studies use the Sidawy[14] or Lee[24]

Table 5. Stratified analyses of proportion of fistulae abandoned without use.

Analysis	n^a	n^b	Rate (95% CI)	I^2; *p*-Het
Overall	164	31,588	0.21 (0.19−0.24)	94.91%; <.001
Males	8	1289	0.33 (0.22−0.46)	91.93%; <.001
Females	7	732	0.43 (0.30−0.58)	87.18%; <.001
USA only	79	11,590	0.27 (0.24−0.30)	92.15%; <.001
Non-USA only	81	18,712	0.16 (0.14−0.20)	95.56%; <.001
65+ years of age	14	1948	0.29 (0.20−0.40)	94.12%; <.001
Diabetic	13	589	0.26 (0.18−0.36)	78.0%; <.001
Non-diabetic	6	349	0.25 (0.17−0.35)	63.82%; .017
Incident access	32	8800	0.26 (0.21−0.31)	93.72%; <.001
Prevalent access	9	488	0.19 (0.10−0.34)	87.07%; <.001
Length of time on dialysis <1 year	8	2806	0.25 (0.17−0.35)	95.64%; <.001
Access created prior to HD initiation	17	4265	0.19 (0.14−0.25)	91.19%; <.001
Access created post HD initiation	17	2232	0.30 (0.24−0.37)	86.66%; <.001
Location: upper arm	4	725	0.16 (0.09−0.29)	86.91%; <.001
Location: forearm/wrist (RCAVF, snuffbox, ulnaris)	44	10,197	0.23 (0.17−0.29)	96.17%; <.001
Location: brachiocephalic	17	2392	0.20 (0.14−0.26)	9.16%; <.001
Location: brachiobasilic and/or brachiobrachial	30	2229	0.19 (0.16−0.22)	70.1%; <.001
Location: mixed arm	72	18,282	0.23 (0.19−0.26)	95.19%; <.001
Location: other specific site	4	770	0.11 (0.02−0.46)	97.49%; <.001
Basilic vein transposition	34	2450	0.17 (0.14−0.21)	70.92%; <.001
No superficialisation	51	8232	0.22 (0.18−0.26)	92.57%; <.001
Mixed superficialisation	50	15,947	0.20 (0.17−0.24)	93.76%; <.001

HD = haemodialysis; RCAVF = radiocephalic arteriovenous fistula.
[a] Number of studies.
[b] Number of accesses.

patency definitions. Lee et al. uses similar patency definitions, but provides an expanded and more contemporary set of standardised haemodialysis vascular access definitions. The National Institutes of Health sponsored Haemodialysis Fistula Maturation Study Group provided a definition of "clinical maturation," which stipulates a defined ascertainment period of successful needle cannulations in addition to achievement of prescribed dialysis treatment (i.e. functional patency).[25] The differences in maturation definitions likely contributed to the incongruence between the two maturation analyses detailed in this study (mean time to maturation 3.49 months; maturation rate at 6 months 0.26). Additionally, one of the three studies included in the 6 month rate analysis only included patients that had one previously failed access,[17] and another included a unique maturation definition.[16] Clarity of reporting is paramount to understanding the true value of AVF as an access modality. The challenges of inconsistent or unclear outcomes terminology underscore the importance of applying a consistent set of definitions and nomenclature for specific fields. Using standardised definitions for patency and maturation in future publications will assist in combining and comparing fistula outcomes.

CONCLUSIONS

Although the mean full lifespan of AVFs that mature and are used for dialysis is over 2 years and infection rates are low, this vascular access modality is plagued by a high abandonment rate and a prolonged maturation period often requiring the use of a bridging catheter. Fistulae placed in incident AVF patients had a longer lifespan than those placed in prevalent AVF patients, but further research is necessary to better evaluate additional factors contributing to both fistula success and failure.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejvs.2017.06.024.

CONFLICT OF INTEREST

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