Vascular Access Outcomes Reported in Maintenance Hemodialysis Trials: A Systematic Review

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Background: Many randomized controlled trials have been performed with the goal of improving outcomes related to hemodialysis vascular access. If the reported outcomes are relevant and measured consistently to allow comparison of interventions across trials, such trials can inform decision making. This study aimed to assess the scope and consistency of vascular access outcomes reported in contemporary hemodialysis trials.

Study Design: Systematic review.

Setting & Population: Adults requiring maintenance hemodialysis.

Selection Criteria: All randomized controlled trials and trial protocols reporting vascular access outcomes identified from ClinicalTrials.gov, Embase, MEDLINE, and the Cochrane Kidney and Transplant Specialized Register from January 2011 to June 2016.

Interventions: Any hemodialysis-related intervention.

Outcomes: The frequency and characteristics of vascular access outcome measures were analyzed and classified.

Results: From 168 relevant trials, 1,426 access-related outcome measures were extracted and classified into 23 different outcomes. The 3 most common outcomes were function (136 [81%] trials), infection (63 [38%]), and maturation (31 [18%]). Function was measured in 489 different ways, but most frequently reported as "mean access blood flow (mL/min)" (37 [27%] trials) and "number of thromboses" (30 [22%]). Infection was assessed in 136 different ways, with "number of access-related infections" being the most common measure. Maturation was assessed in 44 different ways at 15 different time points and most commonly characterized by vein diameter and blood flow. Patient-reported outcomes, including pain (19 [11%]) and quality of life (5 [3%]), were reported infrequently. Only a minority of trials used previously standardized outcome definitions.

Limitations: Restricted sampling frame for feasibility and focus on contemporary trials.

Conclusions: The reporting of access outcomes in hemodialysis trials is very heterogeneous, with limited patient-reported outcomes and infrequent use of standardized outcome measures. Efforts to standardize outcome reporting for vascular access are critical to optimizing the comparability, reliability, and value of trial evidence to improve outcomes for patients requiring hemodialysis.

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A reliably functioning vascular access is associated with improved health outcomes and overall well-being of patients treated by maintenance hemodialysis, but establishing and maintaining such a vascular access without major complications and the need for recurrent interventions remains challenging.[1-3] Vascular access–related complications account for ~20% of hospital admissions of patients with end-stage kidney disease annually and are associated with increased morbidity, mortality, and health care costs.[4,5] As such, vascular access is often referred to as both the "lifeline" and "Achilles' heel" of hemodialysis.[6] From a patient's perspective, the experience and anticipation of vascular access surgery and complications, particularly pain during cannulation, bleeding, and access failure, are key sources of stress and anxiety.[7,8] Improving vascular access outcomes is a high priority for patients, their caregivers, and health professionals.[9,10]

During the last 2 decades, numerous interventions have been trialed in an attempt to improve vascular access outcomes, with little success.[11-13] This is in the context of increasing recognition across many health conditions that outcomes used in clinical trials are measured inconsistently and may not be relevant to end-users, including patients, caregivers, and health professionals.[2,7,8,14,15] In addition, reporting bias due to selective publication of outcomes with favorable results makes interpretation and comparison of research output unreliable.[16,17] The lack of consensus on outcome selection (ie, what to measure, such as "infection" or "pain") and outcome measures (ie, how and when to measure the outcome, such as "number of access interventions within 12 months of access creation") has been identified as an additional source of research waste.[18-21] The comparability, value, and reliability of trial evidence are compromised by the selection of outcomes with limited clinical or policy relevance, under-reporting of patient-centered outcomes, and inconsistent use of outcome measures. There have been efforts to standardize outcome definitions for vascular access by various working

groups, with the most recent publication released in 2011.[22-25] However, these may not have been widely adopted.

This study aimed to describe the scope and consistency of vascular access outcomes and outcome measures used in contemporary hemodialysis trials and assess the use of previously published standardized outcome definitions. A secondary longer-term aim is to underpin strategies to prioritize outcomes, improve outcome reporting for vascular access complications, increase the value of future trials to inform evidence-based practice, and ultimately, help improve patient outcomes.

Methods

Selection Criteria

An electronic search using Embase, the Cochrane Kidney and Transplant Specialized Register, and MEDLINE databases without language restriction was conducted using search strategies developed in collaboration with a specialist information manager to identify trials reporting on vascular access outcomes in adult (aged ≥ 18 years) patients requiring maintenance hemodialysis (Table S1). Trials in patients with acute kidney injury undergoing temporary hemodialysis were excluded. All randomized controlled trials including protocols and post hoc analyses of randomized controlled trials published between January 1, 2011, and June 16, 2016, were included. This time frame was chosen to provide an assessment of contemporary outcome measures of recently published and ongoing trials allowing for implementation of previously published standardized outcome measures.[22-25] Systematic reviews and meta-analyses were screened to identify additional randomized controlled trials published within the same time frame. In addition, the ClinicalTrials.gov registry was searched for unpublished protocols of randomized controlled trials using the same inclusion criteria to ensure that current and ongoing trials were included. Trials of registered protocols that had completed recruitment before January 2011; terminated recruitment due to poor enrollment; been withdrawn, suspended, or published; or not yet started recruitment were excluded. Research ethics committee approval was not required for this study.

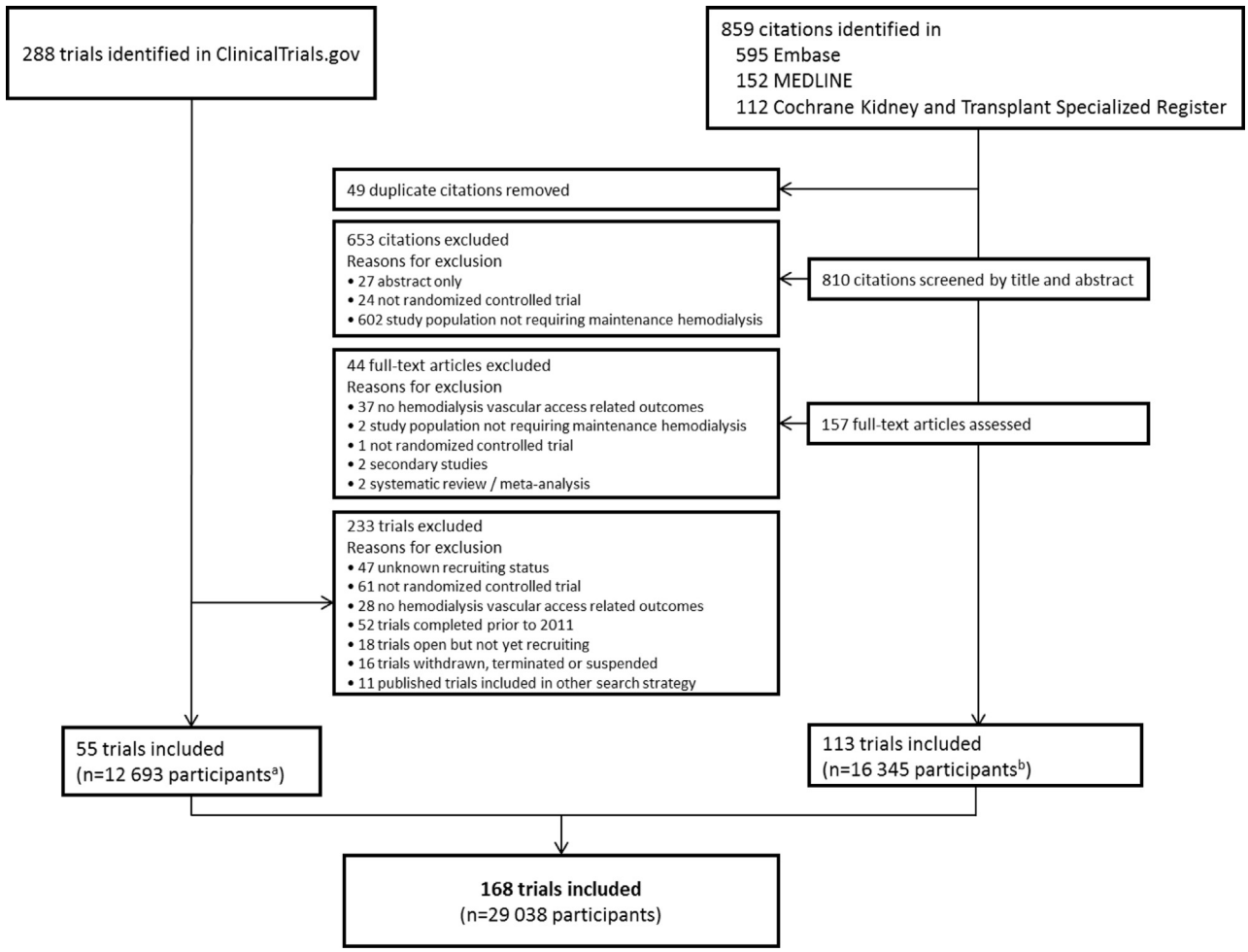


Figure 1. Search results. [a]Estimated number of enrollment. [b]Sample size unknown in 4 trials.

Table 1. Characteristics of Included Trials

Trial Characteristic	No. of Trials
Year of publication	
2011-2012	45 (27%)
2013-2014	45 (27%)
2015-2016	23 (14%)
Unpublished (ongoing or completed trial)	55 (33%)
Country	
Not stated/not reported[a]	55 (33%)
United States	17 (10%)
Iran	17 (10%)
Canada	10 (6%)
United Kingdom	8 (5%)
Taiwan	7 (4%)
Italy	6 (4%)
Turkey	5 (3%)
Greece	4 (2%)
Spain	4 (2%)
Australia	3 (2%)
China	3 (2%)
Multinational studies	10 (6%)
Other[b]	19 (11%)
Sample size[c]	
1-50	35 (21%)
51-100	54 (32%)
101-150	22 (13%)
151-200	15 (9%)
>200	38 (23%)
Not reported	4 (2%)
Duration of trial, mo	
≤3	40 (24%)
>3-6	32 (19%)
>6-9	2 (1%)
>9-12	48 (29%)
>12	37 (22%)
Not reported	9 (5%)
Intervention type	
Pharmacologic	79 (47%)
Radiologic	11 (7%)
Catheter type	11 (7%)
Surgical	9 (5%)
Radiologic/pharmacologic combined	9 (5%)
Graft material	7 (4%)
Anesthetic	7 (4%)
Cannulation technique	7 (4%)
Dialysis delivery	5 (3%)
Radiation	5 (3%)
Exercise	3 (2%)
Other[d]	15 (9%)
No. of outcome measures reported in each trial	
1-5	97 (58%)
6-10	31 (18%)
11-15	23 (14%)
>16	17 (10%)
Access type	
AVF	69 (41%)
CVC	53 (32%)
AVG	17 (10%)
All	14 (8%)
AVF and AVG	14 (8%)
CVC and AVF	1 (1%)

Note: n = 168. Values are given as count (percentage).
Abbreviations: AVF, arteriovenous fistula; AVG, arteriovenous graft; CVC, central venous catheter.
[a]Trials only registered with ClinicalTrial.gov did not report countries (n=55).
[b]Asia (n = 1), Belgium (n = 2), Brazil (n = 1), Egypt (n = 1), France (n = 1), Georgia (n = 1), Germany (n = 2), India (n = 1), Israel (n = 1), Japan (n = 2), Korea (n = 1), Pakistan (n = 1), Poland (n = 2), and United Arab Emirates (n=2).
[c]Including estimated numbers for trial protocols according to latest update on ClinicalTrials.gov (June 2016).
[d]Access location (n = 2), access planning (n = 1), algorithm (n = 3), behavioral (n = 2), biological (n = 1), education (n = 1), surgical/interventional combined (n = 1), surveillance (n = 1), and ultrasound (n = 3).

Data Extraction

For each trial, one reviewer (AV) extracted the following trial characteristics if available: first author, year of publication (for published trials) and year of registration with ClinicalTrials.gov (for unpublished trials), participating countries, sample size, study duration, intervention type, access type, and all vascular access–related outcomes. All levels of specification of outcome measures were collected if reported by 1 reviewer (AV): outcome (eg, infection or cannulation problems), specific measurement (eg, catheter-related bacteremia or successful cannulation at first attempt), specific metric (ie, time to event, change from baseline, or milliliters per minute), method of aggregation (ie, mean, median, or proportion), and time point of measurement in line with previously published tools.[19,26]

Analysis

Two reviewers independently grouped individual outcome measures assessing a similar aspect of vascular access complications into outcomes. Discrepancies were discussed to reach agreement (AV and BS). The list of outcomes was reviewed and agreed on by 4 additional reviewers (AT, CH, EO, and JC). Reviewer AV assigned all outcomes to 3 categories based on the majority of outcome measures: clinical (a "direct" medical end point based on clinician assessment or diagnosis that in itself represents or characterizes a meaningful outcome), surrogate (a laboratory, imaging-based, or physical sign that is used as a substitute for a clinically meaningful end point), and patient-reported (outcomes reported by the patients usually relating to quality of life or symptoms) using standard definitions.[27,28] The classification was agreed on by 2 reviewers (AT and JC).

Results

Trial Characteristics

We identified 168 relevant trials involving 29,038 participants (Fig 1). Two-thirds of trials were published and one-third were registered trial protocols (Table 1).

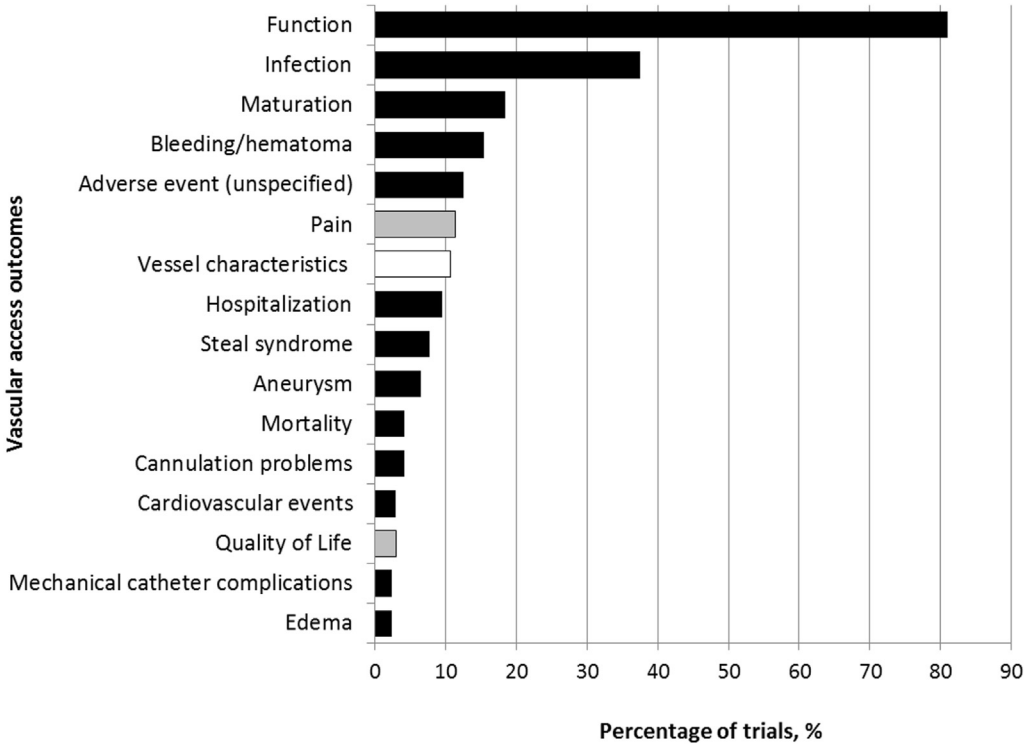


Figure 2. Percentage of trials reporting each vascular access outcome (total 168 trials, 23 outcomes). Outcome categories: clinical (black), patient-reported (grey), and surrogate (white). Outcomes reported in <2% of trials: venous hypertension (surrogate), procedure-related complications (clinical), patient satisfaction (patient-reported), erythema (clinical), needle phobia/fear (patient-reported), vascular access location (surrogate), and inflammation (surrogate).

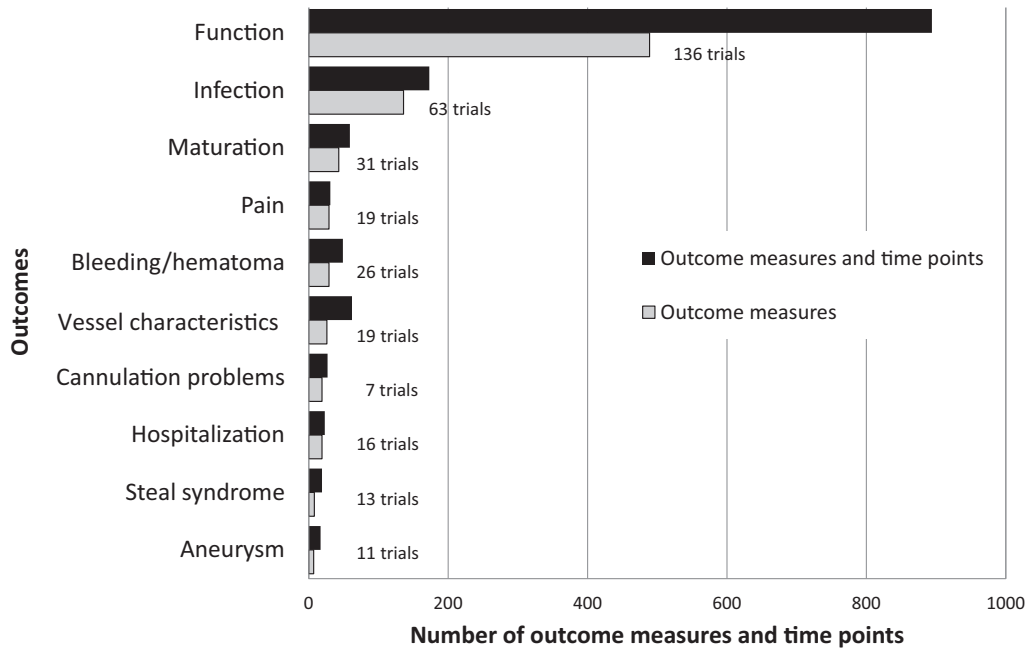
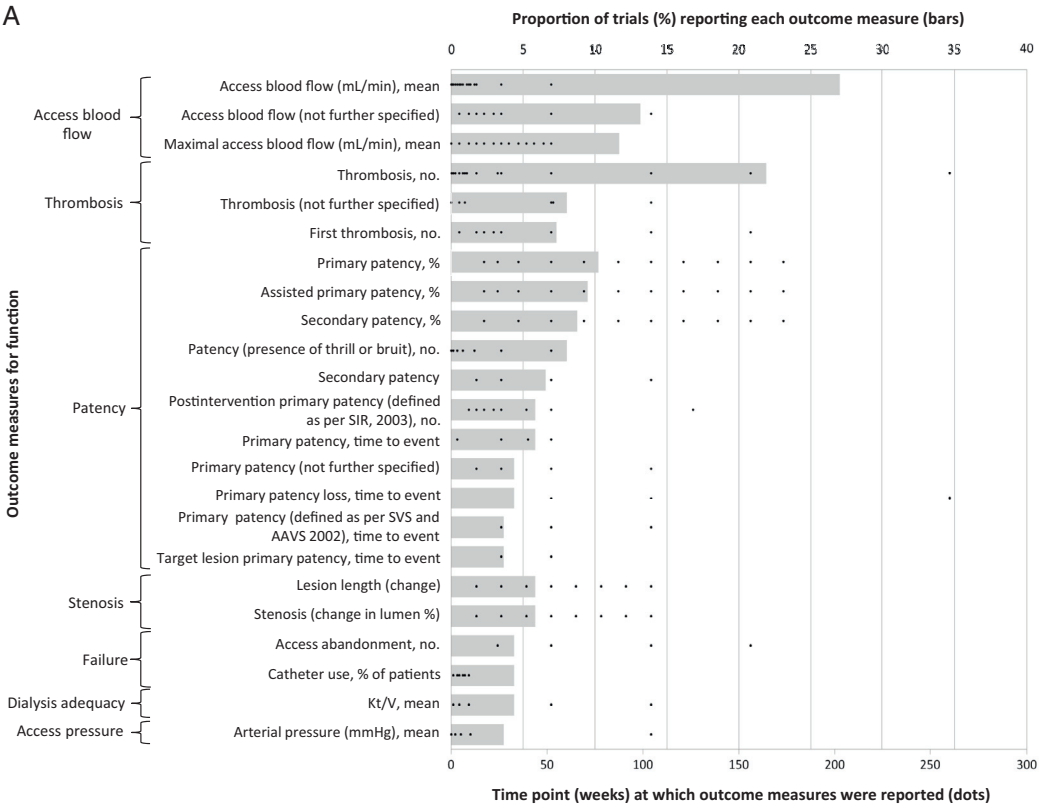
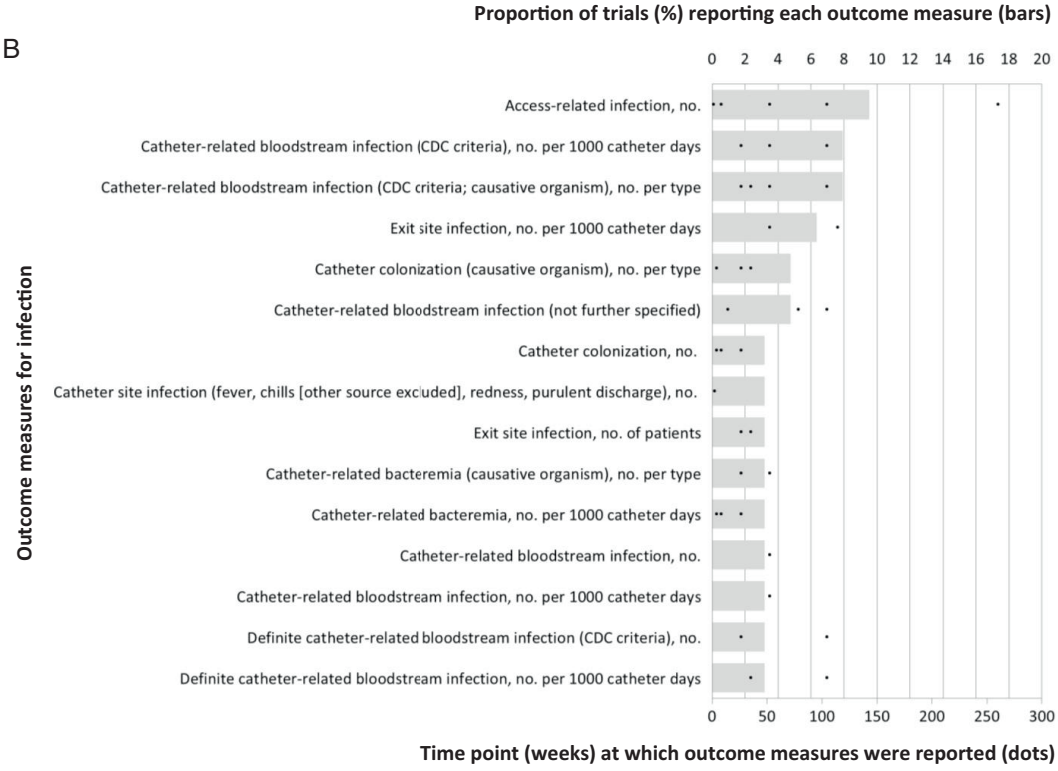


Figure 3. Number of outcome measures (with and without time points) for the 10 most frequently reported specified vascular access outcomes.


A
Proportion of trials (%) reporting each outcome measure (bars)
0 5 10 15 20 25 30 35 40
Outcome measures for function
Access blood flow
Access blood flow (mL/min), mean
Access blood flow (not further specified)
Maximal access blood flow (mL/min), mean
Thrombosis
Thrombosis, no.
Thrombosis (not further specified)
First thrombosis, no.
Patency
Primary patency, %
Assisted primary patency, %
Secondary patency, %
Patency (presence of thrill or bruit), no.
Secondary patency
Postintervention primary patency (defined as per SIR, 2003), no.
Primary patency, time to event
Primary patency (not further specified)
Primary patency loss, time to event
Primary patency (defined as per SVS and AAVS 2002), time to event
Target lesion primary patency, time to event
Stenosis
Lesion length (change)
Stenosis (change in lumen %)
Failure
Access abandonment, no.
Catheter use, % of patients
Dialysis adequacy
Kt/V, mean
Access pressure
Arterial pressure (mmHg), mean
0 50 100 150 200 250 300
Time point (weeks) at which outcome measures were reported (dots)


B
Proportion of trials (%) reporting each outcome measure (bars)
0 2 4 6 8 10 12 14 16 18 20
Outcome measures for infection
Access-related infection, no.
Catheter-related bloodstream infection (CDC criteria), no. per 1000 catheter days
Catheter-related bloodstream infection (CDC criteria; causative organism), no. per type
Exit site infection, no. per 1000 catheter days
Catheter colonization (causative organism), no. per type
Catheter-related bloodstream infection (not further specified)
Catheter colonization, no.
Catheter site infection (fever, chills [other source excluded], redness, purulent discharge), no.
Exit site infection, no. of patients
Catheter-related bacteremia (causative organism), no. per type
Catheter-related bacteremia, no. per 1000 catheter days
Catheter-related bloodstream infection, no.
Catheter-related bloodstream infection, no. per 1000 catheter days
Definite catheter-related bloodstream infection (CDC criteria), no.
Definite catheter-related bloodstream infection, no. per 1000 catheter days
0 50 100 150 200 250 300
Time point (weeks) at which outcome measures were reported (dots)

Published trials were conducted across 39 countries from North America, Latin America, Europe, Middle East, Asia, and Oceania. Median trial duration was 12 (interquartile range [IQR], 6-24) months, and median sample size was 96 (IQR, 61-196) participants. The most commonly studied type of intervention was pharmacologic (47%). Forty-one percent of trials investigated vascular access outcomes in arteriovenous fistulas alone; 32%, in central venous catheters; 10%, in arteriovenous grafts; and 17% of studies included various combinations of access types.

Outcomes

In total, 1,426 outcome measures were identified (defined by the measurement, metric, method of aggregation, and time point of measurement), which could be grouped into 23 outcomes, of which 15 (65%) were predominantly clinical, 4 (17%) were surrogate, and 4 (17%) were patient-reported. The 3 most frequent outcomes were function (136 [81%] trials), infection (63 [38%] trials), and maturation (31 [18%] trials). Pain was the most common patient-reported outcome and was assessed in 19 (11%) trials. Less than 5% of trials reported quality of life (5 [3%] trials), satisfaction with the vascular access (2 [1%]), or needle phobia (1 [<1%]). Nineteen (11%) trials measured vessel characteristics, which was the most commonly reported surrogate outcome (Fig 2).

Outcome Measures

The number of outcome measures of the 10 most frequently reported specified vascular access outcomes are presented in Figure 3.

Function

Function was measured in 489 different ways and at 46 different time points. Function was the most heterogeneous outcome due to the variety of ways it can be assessed (Fig S1). The most frequently used outcome measures for assessing the function of a vascular access included mean access blood flow in milliliters per minute (37 trials [27%]) and number of thromboses (30 trials [22%]; Fig 4A). Approximately one-third of outcome measures described patency, thrombosis, or stenosis (Fig S1). Of the 134 patency measures reported across 64 trials, 17 (13%) were consistent with 1 or more of the patency definitions as proposed by the Society for Vascular Surgery and the American Association for Vascular Surgery, the Society of Interventional Radiology Technology Assessment, or the North American and Australian Vascular Access Consortium.[22-24]

Infection

Infection was reported in 136 different ways (not including variation in time points) and at 20 different time points, with 30 (22%) consistent with criteria used by the US Centers for Disease Control and Prevention (CDC) and/or other published definitions.[29-32] Number of access-related infections was the most commonly used outcome measure (10% of trials; Fig 4B). Ninety different outcome measures were used to assess catheter-related infections (excluding time points), of which 64 referred specifically to systemic catheter-related infection; 11, to exit-site infection; and 4, to tunnel infection. The rate (number per 1,000 catheter-days) and type (causative organism) of catheter-related bloodstream infection, as defined by the CDC,[32] were the most frequently used catheter-related outcome measures, and each was reported in only 8% of trials.

Maturation

Maturation was measured in 43 different ways and at 15 different time points (Fig S2), with one-quarter of trials referring to previously published criteria.[29,33] Maturation was most commonly defined as number of fistulas with a vein diameter of 6 mm and blood flow > 600 mL/min[29] and/or vein diameter of 4 mm and blood flow of at least 500 mL/min[33] or as time to first cannulation (n = 2 [6%] trials for each outcome measure).

Figure 4 (previous page). (A) Most frequently reported outcome measures (definitions and time points) to assess vascular access function (136 trials, 23 of 489 outcome measures). The proportion of trials reporting each outcome measure (bars) and the different time points the outcome measure has been reported at (dots). Definitions: Postintervention primary patency as defined by the Society of Interventional Radiology (SIR)[24]: interval following intervention until the next access thrombosis or repeated intervention. Primary patency as defined by the Society of Vascular Surgery (SVS) and American Association for Vascular Surgery (AAVS) 2002[23]: the interval from the time of access placement until any intervention designed to maintain or re-establish patency, access thrombosis, or the time of measurement of patency. (B) Most frequently reported outcomes measures (definitions and time points) to assess infection (63 trials, 15 of 136 outcomes measures). The proportion of trials reporting each outcome measure (bars) and the different time points the outcome measure has been reported at (dots). Definitions: Centers for Disease Control and Prevention (CDC) criteria[31,32]: bacteremia/fungemia in a patient with an intravascular catheter with at least 1 positive blood culture obtained from a peripheral vein, clinical manifestations of infections (ie, fever, chills, and/or hypotension), and no apparent source for the bloodstream infection except the catheter. Definite bloodstream infection: isolation of the same organism from a peripheral-blood sample and catheter-derived blood sample of a symptomatic patient (fever, chills, hypotension, or mental confusion) when there is no other probable source of infection. Probable bloodstream infection: infectious symptoms disappear after catheter removal when either blood cultures or culture of the catheter tip, but not both, confirm infection in a symptomatic patient in the absence of another suspicious source of infection. Possible bloodstream infection: disappearance of infectious symptoms in a symptomatic patient with negative blood and catheter tip cultures after catheter removal when there is no other probable source of infection.[45]

Pain

The patient-reported outcome pain was assessed in 19 trials using 29 different outcome measures. Two (10%) studies measured procedural pain, but the majority of studies (n = 15 [79%]) assessed pain during cannulation using 1 of 11 different methods to quantify pain (Fig S3).

Bleeding/Hematoma

Access-related hematomas or the occurrence of bleeding from the access site were recorded in 26 trials and measured in 29 different ways at 24 different time points (Fig S4). Number of hematomas was the most frequently used outcome measure and was recorded by more than a quarter of trials (n = 7), followed by number of access-related bleeding episodes (n = 4 [15%]). Bleeding after removal of dialysis needles was assessed in 7 different ways, including bleeding time, number or proportion of bleeding episodes following removal of the dialysis needles, and number of prolonged bleeding episodes (defined as >10 minutes' duration or unspecified).

The surrogate outcome, vessel characteristics, included measurements of vessel diameter, depth, and wall thickness and was evaluated in 26 different ways (Fig S5). Outcome measures for cannulation problems, steal syndrome, aneurysms, and vascular access–related hospitalization provided in Figures S6 to S9 were heterogeneous, as highlighted by the fact that the majority of outcome measures were only used in 1 or 2 trials.

Discussion

The vascular access outcomes reported in clinical trials of adult patients requiring hemodialysis were most frequently clinical, such as function, infection, and maturation. Patient-reported outcomes, including pain, quality of life, satisfaction with the vascular access, and fear of cannulation, were rarely reported. The outcome measures used were extremely numerous and heterogeneous at every level; measurement, metric, method of aggregation, and time point of measurement, making it very difficult to reliably evaluate the comparative effectiveness of different interventions designed to improve the lives of people receiving hemodialysis. Attempts to standardize definitions appear to have been only partially successful, with a minority of trials using such definitions.

This study highlights the plethora and broad heterogeneity of vascular access outcome measures across trials in hemodialysis, with 1,426 outcome measures used to assess 23 different outcomes. This inconsistency was observed at all levels of an outcome measure.[26] Consequently, comparative assessments of vascular access outcomes across trials to guide evidence-based clinical practice (ie, meta-analyses) are likely to be problematic. The need for standardizing outcome measures for vascular access complications has been recognized and several proposals have been published by expert committees and societies over the past 2 decades.[22-24,30-32,34] However, as demonstrated in this study, implementation of standardized outcome measures into recent clinical trials and trial protocols is infrequent. Major barriers to global implementation of standardized outcome measures may be the limited engagement of stakeholders from all relevant clinical specialties (ie, vascular access surgery, interventional radiology, and nephrology), different types of health professionals (eg, nurses and physicians), regulatory bodies and policy makers, and patients. Feasibility and relevance may also be issues, with selected outcome measures being cumbersome to collect and regarded as of limited clinical utility for daily practice and quality improvement.

A potential strategy to overcome these barriers may be the implementation of a "core outcome set" incorporating a consensus-based "minimum set of outcomes that should be measured and reported in all clinical trials of a specific disease or trial population."[18(p. 2)] This would ensure that results can be compared across trials and that all trials contribute relevant and usable information.[18] The Outcome Measures in Rheumatology (OMERACT) initiative was the first to establish core outcomes for clinical trials and has led to improvements in the reporting and relevance of outcomes in rheumatology.[35] A recent analysis demonstrated that reporting and homogeneity of outcomes were better in registered trial protocols for rheumatology compared to those for nephrology.[19] There have been increasing efforts to identify and establish core outcomes in nephrology, as evident from recent work via the Standardized Outcomes in Nephrology (SONG) initiative.[10,36,37] Based on the shared priorities of patients and their caregivers, clinicians, researchers, and policy makers, vascular access has been identified as a core outcome domain in hemodialysis. This study, led by the SONG Hemodialysis Vascular Access Expert Working Group,[38] further informs the process of establishing and implementing a core outcome measure for vascular access that is: (1) considered important and relevant by all relevant stakeholders, (2) feasible across different clinical settings without adding additional burden to clinicians or patients, (3) inexpensive, and (4) relevant to clinical decision making and quality improvement.

Function was the most commonly reported vascular access outcome in hemodialysis trials. Although thrombosis and access flow were the most frequently used outcome measures to assess function, these outcomes may not capture all relevant contributing aspects of function and dysfunction of a vascular access and may therefore lack content validity.[18] For example, using thromboses as an outcome measure may not adequately assess whether an intervention improves the function and usability of a vascular access. Results from the largest interventional vascular access trial to date showed that despite clopidogrel leading to a reduction in early thrombosis rates, this did not translate into a

simultaneous improvement in the usability of fistulas for hemodialysis,[39] suggesting that other unmeasured outcomes may play a greater role.

There is increasing interest in using outcome measures considered important by patients. This study showed that patient-reported vascular access problems were measured infrequently in hemodialysis trials and therefore the effect of many interventions on patients' comfort and satisfaction with their vascular accesses remains uncertain. Pain during cannulation has been identified as the most commonly reported problem by patients,[8] yet was assessed in only 11% of trials. Cosmetic and lifestyle considerations such as restrictions on showering and swimming with a catheter, free time lost to frequent appointments for access procedures, and fear of a potentially life-threatening hemorrhage of an aneurysmal access are also important to patients, but these outcomes were not reported in any of the studies included in our systematic review.[7,40]

This study addresses an evidence gap by providing a detailed analysis of the scope and consistency of vascular access outcome measures and of the implementation of previously published standardized outcome definitions across a large selection of contemporary hemodialysis trials. Limitations of this study include the sampling frame that was restricted to recently published (since January 2011) and ongoing trials, which may have introduced selection bias. However, attempts were made to provide a contemporary assessment of outcomes and outcome measures and assess the use of previously published outcome definitions with the most recent publication released in 2011.[22] It is likely that including older trials would only have increased the heterogeneity of outcome measures due to less consistency with existing outcome definitions, only strengthening the study's key findings. The quality or risk of bias of included trials was not assessed, such that it was not possible to evaluate the association between the reliability of trial results and the outcomes reported.

In conclusion, there is substantial variability and inconsistency in vascular access outcomes and outcome measures reported in hemodialysis trials, with very little focus on patient-reported outcomes, making it difficult for clinicians, patients, and policy makers to make informed decisions. Clinicians are encouraged to judge current trial outcomes and measures based on the relevance to their patients and clinical practice. To improve the relevance and consistency of vascular access outcome measures used in clinical trials and day-to-day clinical practice, we recommend implementation of trial end points tailored to the different types of vascular access and time points of their life cycle. These were recently published by the Dialysis Vascular Access group of the American Society of Nephrology Kidney Health Initiative.[41-43] Complementing the Kidney Health Initiative, the international SONG initiative has established a core outcome set for hemodialysis that includes vascular access as 1 of 4 core outcome domains based on the shared priorities of patients and health professionals.[10,36,44]

Supplementary Material

Table S1. Search terms.

Figure S1. Categories of outcome measures used to assess function.

Figure S2. Outcome measures (frequency and time points) used to assess maturation.

Figure S3. Outcome measures (frequency and time points) used to assess pain.

Figure S4. Outcome measures (frequency and time points) used to assess bleeding/hematoma.

Figure S5. Outcome measures (frequency and time points) used to assess vessel characteristics.

Figure S6. Outcome measures (frequency and time points) used to assess cannulation problems.

Figure S7. Outcome measures (frequency and time points) used to assess vascular access related hospitalization.

Figure S8. Outcome measures (frequency and time points) used to assess steal syndrome.

Figure S9. Outcome measures (frequency and time points) used to assess aneurysms and/or pseudoaneurysms.

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