AJKD

Original Investigation

Preemptive Correction of Arteriovenous Access Stenosis: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Pietro Ravani, MD, PhD,[1,2] Robert R. Quinn, MD, PhD,[1,2] Matthew J. Oliver, MD,[3] Divya J. Karsanji, MSc,[2] Matthew T. James, MD, PhD,[1,2] Jennifer M. MacRae, MD, MSc,[1] Suetonia C. Palmer, MD, PhD,[4] and Giovanni F.M. Strippoli, MD, PhD[5,6,7,8,9]

Background: Preemptive correction of a stenosis in an arteriovenous (AV) access (fistula or graft) that is adequately providing hemodialysis (functional AV access) may prolong access survival as compared to waiting for signs of access dysfunction to intervene (deferred salvage). However, the evidence in support of preemptive intervention is controversial. We evaluated benefits and harms of preemptive versus deferred correction of AV access stenosis.

Study Design: Systematic review and meta-analysis of randomized controlled trials.

Setting & Population: Adults receiving hemodialysis by a functional AV access.

Selection Criteria for Studies: We searched the Cochrane Kidney and Transplant Specialised Register and EMBASE to October 15, 2015.

Intervention: Active access surveillance (flow measurement and Doppler or venous pressure) and preemptive correction of a newly identified stenosis versus routine clinical monitoring and deferred salvage, or preemptive correction of a known stenosis versus deferred salvage.

Outcomes: Access loss (primary outcome) and thrombosis (overall and by access type), infection, mortality, hospitalization, and access-related procedures.

Results: We included 14 trials (1,390 participants; follow-up, 6-38 months). Relative to deferred salvage, preemptive correction of AV access stenosis had a nonsignificant effect on risk for access loss (risk ratio [RR], 0.81; 95% CI, 0.65-1.02; $I^2 = 0\%$) and a significant effect on risk for thrombosis (RR, 0.79; 95% CI, 0.65-0.97; $I^2 = 30\%$). Treatment effects were larger in fistulas than in grafts for both risk for access loss (subgroup difference, $P = 0.05$) and risk for thrombosis (subgroup difference, $P = 0.002$). Results were heterogeneous or imprecise for mortality, rates of access-related infections or procedures, and hospitalization.

Limitations: Small number and size of primary studies limited analysis power.

Conclusions: Preemptive stenosis correction in a functional AV access does not improve access longevity. Although preemptive stenosis correction may be promising in fistulas, existing evidence is insufficient to guide clinical practice and health policy.

Am J Kidney Dis. ■(■):■-■.

INDEX WORDS: Hemodialysis access; vascular access; arteriovenous fistula; arteriovenous graft; access screening; access surveillance; access thrombosis; pre-emptive stenosis correction; access salvage; access angioplasty; access loss; patency; renal replacement therapy; systematic review.

A reliable access to the bloodstream by a vascular access is necessary for hemodialysis, the most common form of therapy for end-stage kidney failure. The native arteriovenous (AV) fistula (a direct link between an artery and a vein in the arm) is considered the best type of access, followed by the AV graft (in which graft material is used for the AV communication),[1,2] based on large studies showing associations with reduced risk for all-cause mortality, fatal infections, and cardiovascular events in people using an AV access compared with those using central venous catheters.[3] However, stenosis and thrombosis of the

From the [1]Department of Medicine and [2]Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary; [3]Department of Medicine, University of Toronto, Toronto, Canada; [4]Department of Medicine, University of Otago Christchurch, Christchurch, New Zealand; [5]Cochrane Kidney and Transplant, Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia; [6]Department of Emergency and Organ Transplantation, University of Bari; [7]Diaverum Academy, Bari, Italy; [8]Diaverum Medical Scientific Office, Lund, Sweden; and [9]Sydney School of Public Health, University of Sydney, Sydney, Australia.

Received August 15, 2015. Accepted in revised form November 23, 2015.

This review is excerpted from a Cochrane Review to be published in The Cochrane Library (www.thecochranelibrary.com). Cochrane Reviews are regularly updated at The Cochrane Library as new evidence emerges in response to comments and criticisms.

Address correspondence to Pietro Ravani, MD, PhD, Foothills Medical Centre, 1403 29th Street NW, Calgary, Alberta, T2N 2T9 Canada. E-mail: pravani@ucalgary.ca

0272-6386

http://dx.doi.org/10.1053/j.ajkd.2015.11.013

AV access are a leading cause of hospitalization and health care resource consumption among hemodialysis patients.[4] About 50% of fistulas require additional procedures in the year following creation (1.45-3.3 procedures/access-year) and revisions are often necessary in the long term to maintain patency (0.17-0.57 procedures/access-year).[5] Vascular access–related morbidity has profound social and psychological consequences for the patient.[6]

Optimal access function is routinely assessed during hemodialysis to ensure that the access is adequate to provide sufficient dialysis dose (functional access). Routine clinical monitoring involves examination of access thrill and bruit, hemostasis time after needle removal, and hemodialysis parameters, including hemodialysis circuit blood flow (Q_b), arterial and transmembrane pressures, or dialysis adequacy indexes. During clinical monitoring, evidence of access dysfunction (eg, reduced Q_b or prolonged bleeding upon needle removal) prompts access-related procedures to correct the underlying cause of access dysfunction (usually a stenosis or narrowing) and thereby prevent thrombosis and access loss (deferred salvage interventions). Because stenosis of the AV access reduces blood flow in the AV access (Q_a) and consequently increases the risk for access thrombosis, different noninvasive methods of active surveillance of Q_a have been proposed to determine earlier whether a functional access is at risk for dysfunction.[7,8] These involve direct measurements of Q_a; indirect measures, including dynamic or static venous dialysis pressure (venous pressure to systolic blood pressure ratio); and duplex ultrasound, which provides both blood flow and anatomical information. Guidelines recommend access imaging and preemptive correction of stenoses $>$ 50% when critical Q_a values are present regardless of the access ability to provide adequate hemodialysis (preemptive correction of access stenosis).[7-12] These guideline recommendations assume that a reduction in Q_a identifies a treatable stenosis before the access becomes dysfunctional, and that preemptive correction of the stenosis will maintain the functional AV access, prevent thrombosis, and prolong longevity of the access use as compared to deferred salvage. However, a previous systematic review found no benefits from access screening in grafts and uncertain benefits in fistulas.[13]

Because of the substantial morbidity associated with access complications, as well as the resource implications of both preemptive and deferred interventions and their unclear benefits and harms based on the limited power of previous knowledge synthesis,[13] we did a systematic review of randomized controlled trials (RCTs) comparing a strategy of preemptive correction of AV access stenosis versus a strategy of deferred salvage in people with a functional AV access.

METHODS

Study Design, Interventions, and Outcomes

We conducted a systematic review and meta-analysis of RCTs according to a published peer-reviewed protocol[14] and followed recommended guidelines for reporting.[15]

We included RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by predictable methods such as alternation, use of alternate medical records, or date of birth) evaluating the benefits and harms of a preemptive strategy to correct AV access stenosis in adults with end-stage kidney failure treated with hemodialysis, regardless of the duration of dialysis therapy. These studies could be of any follow-up duration and reported in any language. Participants had to have an AV access (either fistula or graft) that was adequately providing hemodialysis (functional AV access) without suspected or known stenoses (primary prophylaxis) or a functional AV access with a known or suspected stenosis (secondary prophylaxis). Studies of primary prophylaxis evaluated the effects of any method for measuring Q_a (flow measurement, Doppler, or venous pressure; active surveillance) to identify and preemptively correct stenosis (preemptive correction) in addition to or instead of a strategy for routine physical examination or monitoring of hemodialysis parameters (clinical monitoring) and interventions prompted by access dysfunction (deferred salvage). Studies of secondary prophylaxis evaluated the effects of preemptive correction of a documented stenosis in a functional access versus deferred salvage. We excluded studies in which participants used a central venous catheter for hemodialysis and studies comparing different approaches to treat a dysfunctional AV access (an access that was not adequately providing hemodialysis) or a clotted access.

In primary prophylaxis studies, the intervention could be any method for access surveillance followed by preemptive correction of a newly identified stenosis, including surgical or imaging-assisted procedures. In secondary prophylaxis studies, the intervention was any preemptive correction procedure. In primary prophylaxis studies, the comparator was either a strategy based on routine clinical monitoring and deferred correction of a stenosis (inactive comparator) or another active surveillance method for preemptive stenosis correction (active comparator). Deferred correction procedures included surgical interventions or imaging-assisted procedures. In secondary prophylaxis studies, the intervention was any deferred correction procedure.

The primary outcome was access loss (permanent loss of access patency leading to access abandonment). Secondary outcomes were AV access thrombosis (temporary loss of patency leading to access dysfunction, or inability to adequately provide hemodialysis, and prompting an access procedure), mortality, rates of infection, access-related procedures and hospitalization, health costs, and quality of life.

Study Searches, Selection, and Data Extraction

We searched the Cochrane Kidney and Transplant Specialised Register and EMBASE to October 15, 2015, without language restriction (Table S1, available as online supplementary material).

Two authors (P.R. and D.J.K.) independently screened the citations retrieved by searching by title and abstract, then by reviewing the full text, to identify studies that fulfilled the inclusion criteria. Any study considered potentially eligible by at least 1 reviewer was retrieved for further review.

The same 2 authors extracted data for study population characteristics, interventions, nonrandomized cointerventions, and risks of reporting bias into a purpose-built database. Each author double-checked data extraction and data entry independently, and

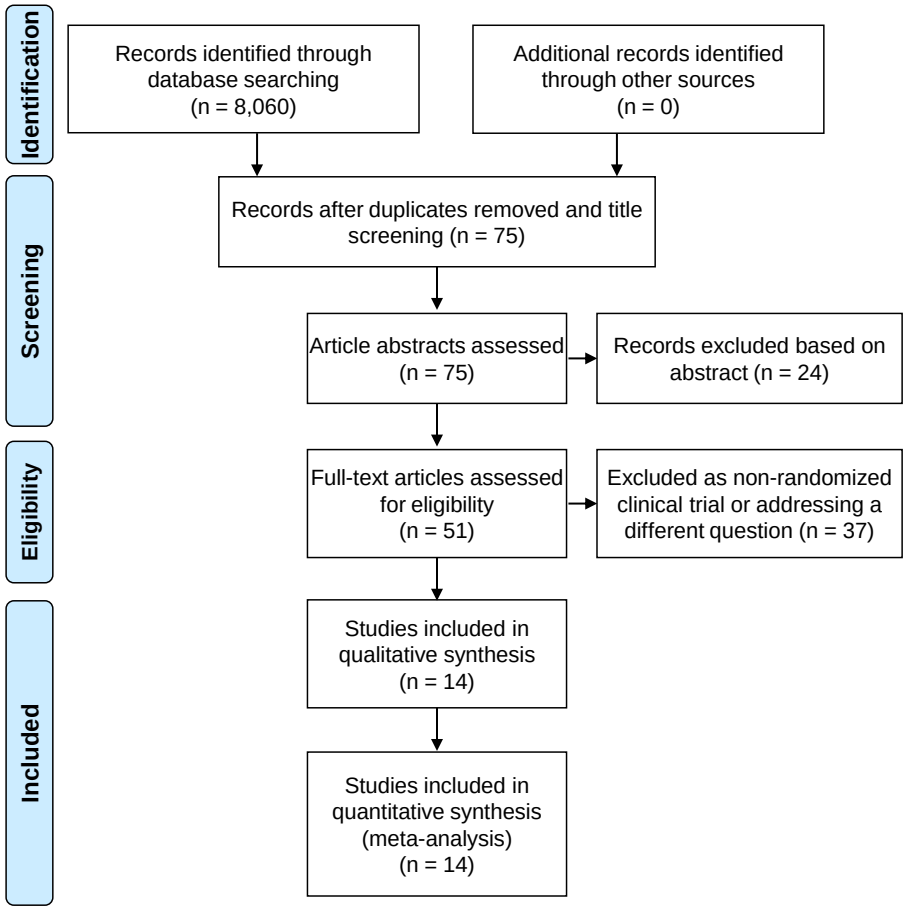

Figure 1. Flow chart shows number of citations retrieved by database searching and the trials included in this review.

any discrepancies between authors were resolved by discussion. When more than one publication of one study existed, we grouped the reports together.

Risk of Bias

Two authors (P.R. and D.J.K.) independently evaluated risk-of-bias items using the Cochrane risk of bias assessment tool (Table S2).[16]

Statistical Analysis

We summarized treatment effects as risk ratio (RR), hazard ratio, or incidence rate ratio and 95% confidence intervals (CIs) using a random-effects model. The unit of analysis was the access for access loss and thrombosis and the patient for death, infection, access-related procedures, and hospitalization. For all analyses, 2-tailed $P < 0.05$ indicated statistical significance. We conducted all analyses using R statistical software version 3.2.3 (R Foundation for Statistical Computing).

When only proportions were provided in the study report (rather than raw event data), we derived the number of events from the proportion and sample size. We assumed a Poisson distribution for count data to calculate the variance of the log-incidence rate ratio when a measure of precision was not reported. We included all relevant studies in the systematic review and included in the meta-analysis the data that they reported.[16] We sought additional information from the authors when reporting was unclear.

We used the Cochran Q, considering $P < 0.05$ to indicate evidence of statistical heterogeneity in treatment effects between studies. We then assessed the magnitude of variation between studies that could not be explained by random chances as the I^2 (with 95% CIs).[17] We considered I^2 values of 0% to 25%, 26% to 50%, 51% to 75%, and ≥76% to indicate low, moderate, considerable, and substantial levels of heterogeneity. We explored for potential sources of heterogeneity in subgroup analyses according to the following prespecified potential effect modifiers: type of access (fistula or graft), aim of the intervention (primary or secondary prophylaxis), and type of intervention in primary prophylaxis (Q_a- or pressure measurement–based surveillance, which provide only Q_a data, or ultrasound-based surveillance, which provides both Q_a and anatomical information about the access).

We performed sensitivity analyses by including and excluding studies according to the following criteria: participants assigned to the comparator arm received an additional screening (ie, measurement of dynamic or static pressure in addition to clinical monitoring), participants assigned to the intervention arm received an additional screening (ie, measurement of dynamic or static pressure in addition to Doppler ultrasound or flow measurement), participants assigned to the comparator arm did not receive clinical monitoring, and participants assigned to the intervention arm did not receive clinical monitoring.

Grading of Recommendations Assessment, Development and Evaluation

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[18] approach to summarize

Table 1. Data Sources and Design

Study	Country	Funding	Start Year	End Year	F/U, mo	No. of Participants[a] (I:C)	Access Type	Prophylaxis	Inclusion Criteria	Exclusion Criteria
Polkinghorne[25] (2006)	AU	Public	2001	2003	18	137 (69:68)	Prevalent fistulas (some with previous procedures)	Primary	Age > 18 y; on HD for 3+ mo; Q_a > 500 mL/min	Home HD; waiting for living Tx
Malik[19] (2005)	CZ	Public	1999	2004	13	189 (97:92)	New grafts	Primary	New grafts	None specified
Mayer[20] (1993)	US	NR	NA	NA	21	70 (35:35)	Prevalent grafts (some with previous procedures)	Primary	NA	NA
Smits[24] (2001)	NL	Public	NA	NA	8	119 (27:24:37:31)[b]	Prevalent grafts (some with previous procedures)	Primary	NA	NA
Robbin[23] (2006)	US	Public	NA	NA	38	126 (65:61)	Prevalent grafts (some with previous procedures)	Primary	On HD for 3+ mo; outpatient	Poor prognosis; waiting for living Tx
Sands[27] (1999)	US	Public	NA	NA	6	103 (62:41)	Prevalent grafts and fistulas (some with previous procedures)	Primary	NA	NA
Moist[21] (2003)	CA	Public	2000	NA	12	112 (59:53)	Prevalent grafts (without previous procedures)	Primary	Q_a > 650 mL/min; no abnormalities	NA
Ram[22] (2003)	US	Private	1998	2001	24	101 (32:34:35)	Prevalent grafts (some with previous procedures)	Primary	Q_a measurement possible	NA
Scaffaro[26] (2009)	BR	NR	2005	NA	7.5	111 (53:58)[c]	Prevalent fistulas (some with previous procedures)	Primary	Nondysfunctional	NA
Lumsden[29] (1997)	US	Public	1993	NA	15	64 (32:32)	Prevalent grafts (some with previous procedures)	Secondary	>50% stenosis (Doppler ultrasound), nondysfunctional graft	Allergy to contrast
Dember[28] (2004)	US	Private	NA	NA	24	64 (32:32)	Prevalent grafts (some with previous procedures)	Secondary	[d]Static venous pressure to SBP ratio = 0.4+	Poor prognosis; anticipated change in RRT method; allergy to contrast
Tessitore[30] (2003)	IT	NR	1995	2001	15	60 (30:30)[e]	Prevalent fistulas (some with previous procedures)	Secondary	Kt/V > 1.2, mature, forearm, distal fistulas; angio-proven stenosis > 50%	Already revised/ salvaged fistulas
Tessitore[31] (2004)	IT	NR	1997	NA	30	79 (44:39)	Prevalent fistulas (without previous procedures)	Secondary	Kt/V > 1.2, mature, forearm, distal fistulas; angio-proven stenosis > 50%	Other clinical trials

(Continued)

Table 1 (Cont'd). Data Sources and Design

Study	Country	Funding	Start Year	End Year	F/U, mo	No. of Participants[a] (I:C)	Access Type	Prophylaxis	Inclusion Criteria	Exclusion Criteria
Tessitore[32] (2014)	IT	Public	2006	2013	30	58 (28:30)	Prevalent fistulas (no procedure in previous 3 mo)	Secondary	Kt/V > 1.2; fistula with suspected stenosis at screening (Q_a < 900 mL/min and/or physical signs or static venous pressure ratio > 0.5) that was confirmed as >50% stenosis at angiography	Access procedures in previous 3 mo

Note: The data source for all studies was academic, except Sands 1999, for which it was nonacademic. Tessitore 2014 was the only study with trial registration.

Abbreviations: AU, Australia; BR, Brazil; CA, Canada; CZ, Czech Republic; F/U, follow-up; HD, hemodialysis; I:C, no. in intervention:comparator groups; Q_a, flow in the access; IT, Italy; NA, not available; NL, Netherlands; NR, not reported; RRT, renal replacement therapy; SBP, systolic blood pressure; Tx, transplant; US, United States.

[a]In the studies by Ram and Sands, there was only 1 comparison group for 2 comparisons (I:I:C).

[b]There were 125 grafts in 119 participants (I:C:I:C: 2 intervention arms and 2 comparators).

[c]There were 111 accesses in 108 participants.

[d]Stenosis not documented with an imaging study at randomization (only increased static venous pressure ratio).

[e]There were 32 fistulas in 30 participants.

the confidence in the evidence. According to these criteria, evidence from RCTs is initially graded as high, but is downgraded in the presence of bias in the studies; inconsistency in the direction or magnitude of study findings; indirectness related to differences in populations, interventions, or outcomes between studies and the clinical context; imprecision of the estimated effects; and publication bias.

RESULTS

Search Results and Study Characteristics

Search results are summarized in Fig 1. We included 14 RCTs involving 1,390 adults in this review. Of these, 9 RCTs included 1,065 adults without access stenosis (primary prophylaxis): 6 included 717 participants using grafts,[19-24] 2 included 245 participants using fistulas,[25,26] and 1 included 103 participants with either a graft or a fistula.[27] Five RCTs enrolled 325 adults with a highly suspected stenosis (static venous pressure to systolic blood pressure ratio > 0.4)[28] or imaging-documented stenosis > 50%[29-32] in a functional access (secondary prophylaxis): 2 included 128 participants using grafts[28,29] and 3 included 197 participants using fistulas.[30-32]

All 14 studies included in the systematic review contributed to the qualitative and quantitative synthesis. Detailed information about the design, participants, intervention, comparator, and outcomes of the included studies are summarized in Tables 1 and 2. Two included studies[22,29] published additional data in a subsequent report.[33,34] In studies of primary prophylaxis, preemptive correction of a stenosis followed identification of the stenosis by means of an active surveillance strategy, involving in at least 1 of the intervention arms Doppler ultrasound,[19,20,22,23,26] direct Q_a measurement,[21,22,24,25,27] or an indirect measure of Q_a (venous pressure in the access).[21,24,27] Three studies reported 2 comparisons each.[22,24,27] In all RCTs, participants in both interventions and comparator arms received routine clinical monitoring, except in 3 studies.[20,27,29] In one of the studies of secondary prophylaxis, participants were randomly assigned to undergo angiography confirmation and correction of a stenosis (suspected on the basis of an increase in the static venous pressure to systolic blood pressure ratio) or to continue venous pressure monitoring of the access until it became dysfunctional.[28] In the other 4 RCTs of secondary prophylaxis, participants had an angiography-documented stenosis and were randomly assigned to undergo correction or continue clinical monitoring until the access became dysfunctional.[29-32]

Study characteristics and reported outcomes are summarized in Tables 3 and 4. Overall, included RCTs were small (58-189 participants) and of short duration (6-38 months). Participants' ages ranged from 55.7 to 64.6 years; the proportion of males, from 41% to 68%; and the proportion of diabetic patients,

Table 2. Description of the Interventions

Study	Intervention	Intervention Details	Comparator	Comparator Details	Radiologist Involved in Interpreting Angiography	Method of Stenosis Correction
Polkinghorne[25] (2006)	Q_a (screening) + control	Monthly Q_a (DUS); referred if $Q_a < 500$ or falls >20% once <1,000	Clinical (monitoring) + DVP	Clinical (referred if): DVP > 150, ↓arterial pressure; ↓Q_b, bleeding following needle removal, ↓URR	Reported	33% PTA, 66% SX
Malik[19] (2005)	DUS (screening) + control	DUS every 3 mo; referral if peak systolic velocity ratio >2 or >25% decrease	Clinical (monitoring) + DVP	Clinical + DVP or recirculation or Q_a	NA	94% PTA, 6% SX
Mayer[20] (1993)	DUS (screening); no control	DUS at 3 and 6 mo, then every 12 mo	Clinical (monitoring)	Clinical at 3 & 6 mo; then every 12 mo	NA	100% SX
Smits[24] (2001) (A)	Q_a (screening) every 2 mo	Q_a (referral if <600) + clinical	Clinical (monitoring) + S/DVP	Clinical + S/DVP (referral if DVP > 150; SVP ratio > 0.5)	NA	87% PTA, 13% SX
Smits[24] (2001) (B)	Q_a + S/DVP every 2 mo	Q_a (referral if <600) + S/DVP + clinical	Clinical (monitoring) + S/DVP	Clinical + S/DVP (referral if DVP > 150; SVP ratio > 0.5)	NA	89% PTA, 11% SX
Robbin[23] (2006)	DUS (screening) + control	DUS every 4 mo; referred if peak systolic velocity ratio = 2+	Clinical (monitoring)	Referral based on clinical signs	Reported	100% PTA
Sands[27] (1999) (A)	Q_a every mo + DUS screening every 6 mo	Referred if $Q_a < 600$ and DUS stenosis > 50%	DUS screening every 6 mo	Another screening method: no monitoring	NA	NA
Sands[27] (1999) (B)	Q_a every mo + DUS screening every 6 mo	Referred if $Q_a < 800$ and DUS stenosis > 50%	DUS screening every 6 mo	Another screening method: no monitoring	NA	NA
Sands[27] (1999) (C)	SVP every month + DUS screening every 6 mo	Referred if SVP = 0.5+ and DUS stenosis > 50%	DUS screening every 6 mo	Another screening method: no monitoring	NA	NA
Sands[27] (1999) (D)	SVP every month + DUS screening every 6 mo	Referred if SVP = 0.5+ and DUS stenosis > 50%	DUS screening every 6 mo	Another screening method: no monitoring	NA	NA
Moist[21] (2003)	Q_a + DVP (screening) + control	DVP > 125/140 + monthly Q_a; referral if $Q_a < 650$ or >20% decrease	Clinical (monitoring) + DVP	Referral for clinical signs	Reported	NA
Ram[22] (2003) (A)	Q_a every mo	Referred to angiography if $Q_a < 600$ or clinical criteria	Clinical (monitoring) + DVP	Criteria for angiography referral if Q_b not attained, >DVP, bleeding, swelling	NA	NA

(Continued)

Table 2 (Cont'd). Description of the Interventions

Study	Intervention	Intervention Details	Comparator	Comparator Details	Radiologist Involved in Interpreting Angiography	Method of Stenosis Correction
Ram[22] (2003) (B)	DUS every mo	Referred to angiography if >50% stenosis or clinical criteria	Clinical (monitoring) + DVP	Criteria for angiography referral were Q_b not attained, >DVP, bleeding, swelling	NA	NA
Scaffaro[26] (2009)	DUS every 3 mo + control	DUS every 3 mo	Clinical (monitoring)	Clinical + hemodynamic assessment	NA	NA
Lumsden[29] (1997)	PTA	Randomly assigned to preemptive correction of stenosis; DUS every 2 mo	Observation	Recirculation > 15%	NA	NA
Dember[28] (2004)	Referred to angiography	Repair if >50% stenosis (at angiography)	Continued SVP monitoring if nondysfunctional	Repair if dysfunction/thrombosis (clinical)	NA	88% PTA, 12% SX
Tessitore[30] (2003)	Preemptive PTA (within 3 wk)	Randomly assigned to preemptive correction of stenosis (referral was Q_a < 850)	Deferred PTA	Correction of stenosis if Q_b reduction > 30; or recirculation > 5%	NA	NA
Tessitore[31] (2004)	Preemptive PTA/ surgery (within 3 wk)	Randomly assigned to preemptive correction of stenosis (referral was Q_a < 750)	Deferred PTA/SX	Correction of stenosis if Q_b reduction > 40; or recirculation > 5%	Reported	79% PTA, 21% SX
Tessitore[32] (2014)	Preemptive angioplasty or surgery within 3 wk of randomization	Preemptive correction of stenosis at baseline and repeated during follow-up if Q_a < 750 or Q_a dropped by >25%	Deferred salvage procedures (angioplasty or SX)	Elective repair allowed if Q_a < 400 (but 300+)	Reported	72% PTA, 28% SX

Note: Letters A, B, C, and D for the same study indicate different arms within the same study (Smits, Sands, and Ram). Stenosis defined was >50% for all studies, except for Malik 2005, for which definition was not provided.

Abbreviations: DUS, Doppler ultrasound; DVP, dynamic venous pressure; NA, not available; PTA, percutaneous angioplasty interventions; Q_a, blood flow in access (mL/min); Q_b, hemodialysis blood pump speed (mL/min); SVP, static venous pressure ratio (SVP over systolic blood pressure); SX, surgical intervention; URR, urea reduction ratio.

Table 3. Study Characteristics

Study	Age, y	Male, %	DM, %	Dialysis Vintage, y	Intervention		Comparator		Additional Data on Drug Use[a]
					Access Location; Mean Access Age	Mean Baseline Q_a; Previous Access Procedures	Access Location; Access Age	Mean Baseline Q_a; Previous Access Procedures	
Polkinghorne[25] (2006)	58	68	31	2.17	61% distal, 36% proximal, 3% others; 23 mo (median)	1,243 mL/min; NA	62% forearm, 34% upper arm, 4% others; 29 mo (median)	1,145 mL/min; NA	Reported
Malik[19] (2005)	58	44	48	0	78% forearm, 20% upper arm, 2% subclavian; NA	769 mL/min; >0%	78% forearm, 20% upper arm, 2% subclavian; NA	NA; >0%	NA
Mayer[20] (1993)	NA	NA	NA	0	57% forearm, 43% upper arm; NA	NA; NA	46% forearm, 54% upper arm; NA	NA; NA	NA
Smits[24] (2001)	61	49	20	2.5	A: 93% forearm, 7% upper arm; 8 mo B: 90% forearm, 10% upper arm; 16 mo	NA; NA	A: 92% forearm, 8% upper arm; 13 mo B: 100% forearm; 18 mo	NA; NA	NA
Robbin[23] (2006)	57.5	41	61	0.75	17% forearm, 83% upper arm; 9 mo	NA; 48%	30% forearm, 70% upper arm; 9 mo	NA; 57%	NA
Sands[27] (1999)	57.3	NA	27.5	2	NA; 18 mo	NA; NA	NA; 28 mo	NA; NA	NA
Moist[21] (2003)	64.6	50.2	37.7	2	68% forearm, 24% upper arm, 8% leg; 21 mo	1,116 mL/min; >0%	76% forearm, 24% upper arm; 24 mo	1,100 mL/min; >0%	Reported
Ram[22] (2003)	55.7	41.6	47.5	1.5	NA; 16 and 14 mo	1,219 and 1,253 mL/min; 41% and 26%	NA; 9 mo	1,333 mL/min; 35%	NA
Scaffaro[26] (2009)	55.7	55.8	36.9	NA	NA; 64% > 6 mo	NA; 58%	NA; 62% > 6 mo	NA; 57%	NA
Lumsden[29] (1997)	57	48	39.5	NA	25% forearm, 72% upper arm, 3% leg; NA	1,716 mL/min; >0%	28% forearm, 72% upper arm; NA	1,886 mL/min; >0%	NA
Dember[28] (2004)	59	64	55	1	34% forearm; 11 mo	NA; 34%	53% forearm; 12 mo	NA; 28%	Reported
Tessitore[30] (2003)	59.4	63	25	1	100% forearm; 10 mo (median)	451 mL/min; NA	100% forearm; 16 mo (median)	473 mL/min; 0%	NA
Tessitore[31] (2004)	59.8	55	23	18	100% forearm; 17 mo	445 mL/min; 0%	100% forearm; 22 mo	438 mL/min; 0%	NA
Tessitore[32] (2014)	63.6	58.6	30.9	NA	17/28 forearm; 21 mo	720 mL/min; 0% (last 3 mo)	22/30 forearm; 27 mo	792 mL/min; 0% (last 3 mo)	NA

Abbreviations: DM, diabetes mellitus; NA, not available; Q_a, blood flow in access.
[a]Antiplatelets or anticoagulant.

Table 4. Measures of Reported Outcomes

Study	Access Loss	Thrombosis	Angiography	PTA	SX	PTA or SX	Need for CVC	Infection	Hospital Admission	Death
Polkinghorne[25] (2006)		RR	RR	RR	RR					
Malik[19] (2005)	HR; RR					IRR[a]				
Mayer[20] (1993)	RR	RR; HR[b]				RR; IRR				RR
Smits[24] (2001)		RR; IRR; HR[b]	RR; IRR	RR; IRR	RR; IRR	IRR				
Robbin[23] (2006)	HR; RR	HR; RR		RR; IRR	RR; IRR			RR		RR
Sands[27] (1999)		RR		RR						
Moist[21] (2003)	RR; HR[b]	RR; HR[b]	RR; IRR	RR; IRR		RR				
Ram[22] (2003)	RR[c]; HR[b]	IRR; RR; HR[b]	RR; IRR	RR; IRR			RR; IRR		RR; IRR	
Scaffaro[26] (2009)	RR	RR		RR			RR; HR			
Lumsden[29] (1997)		RR[c]; HR[b]								RR
Dember[28] (2004)	RR; HR	RR; HR	RR; IRR			IRR	IRR	IRR; RR; HR		RR
Tessitore[30] (2003)	IRR; RR	IRR; RR; HR			RR; IRR		IRR; RR; HR		IRR; RR; HR	RR
Tessitore[31] (2004)	RR; HR	RR; HR								
Tessitore[32] (2014)	RR; HR; IRR	RR; HR; IRR					IRR	IRR	IRR	

Abbreviations: CVC, central venous catheter; HR, hazard ratio (time-to-event data); IRR, incidence rate ratio (from rate data); PTA, percutaneous angioplasty; RR, risk ratio; SX, surgical intervention.

[a]Rates and follow-up reported.

[b]Log(HR)s (and their standard errors) were not reported by authors but were estimated from survival plots (or tables) using methods proposed by Parmar et al.[37]

[c]Events from survival plots.

from 20% to 61%. Four studies were published after 2005,[23,25,26,32] and only one[32] had evidence of registration within a trial registry. No study reported information about authorship and/or involvement of the study sponsor in data collection, analysis, and interpretation.

Risk of Bias

Risks of reporting bias are summarized in Fig 2 and Table S3. In general, risk of bias was high for at least one of the domains we assessed in 12 of 14 studies and unclear or high in all studies.

Treatment Effects

Main Analyses

Preemptive correction of an AV access stenosis had a nonsignificant effect on risk for access loss (primary outcome: 11 studies, 972 participants; RR, 0.81; 95% CI, 0.65-1.02; $I^2 = 0\%$; Fig 3) and a modest but significant effect on risk for thrombosis (18 studies, 1,212 participants; RR, 0.79; 95% CI, 0.65-0.97; $I^2 = 30\%$; Fig 4). Preemptive stenosis correction had imprecise effects on mortality (5 studies, 386 participants; RR, 1.38; 95% CI, 0.91-2.11; $I^2 = 0\%$; Fig 5) and infection rates (3 studies, 248 participants; RR, 1.74; 95% CI, 0.78-3.91; $I^2 = 0\%$; Fig 6) and significantly increased rates of diagnostic angiograms (5 studies, 539 participants; RR, 1.78; 95% CI, 1.18-2.67; $I^2 = 62.4\%$; Fig 6) and reduced rates of hospitalization (3 studies, 219 participants; RR, 0.54; 95% CI, 0.31-0.93; $I^2 = 66.6\%$; Fig 6). However, given the considerable heterogeneity in these analyses, effects on these outcomes are uncertain. Preemptive correction of an AV access stenosis reduced rates of catheter use and had nonsignificant effects on rates of angioplasties or surgical procedures (Fig S1). One study of secondary prophylaxis in people with fistulas did not find differences in costs between preemptive and deferred correction of stenosis.[32] None of the RCTs reported data for quality of life.

Subgroup Analyses

We found borderline-significant differences in treatment effects on risk for access loss by access type (4 studies in fistulas [310 participants; RR, 0.50; 95% CI, 0.29-0.86; $I^2 = 0\%$] and 7 studies in grafts [662 participants; RR, 0.90; 95% CI, 0.71-1.15; $I^2 = 0\%$]; subgroup differences, $P = 0.05$). Three of the 4 studies reporting access loss data in fistulas (n = 199) were conducted in the same center and reported by the same authors.[30-32] There were no significant subgroup differences by prevention aim ($P = 0.6$) or surveillance method in primary prophylaxis ($P = 0.6$). We found significant differences in treatment effects on risk for thrombosis by access type (7 studies in fistulas [515 participants; RR, 0.50; 95% CI, 0.35-0.71;

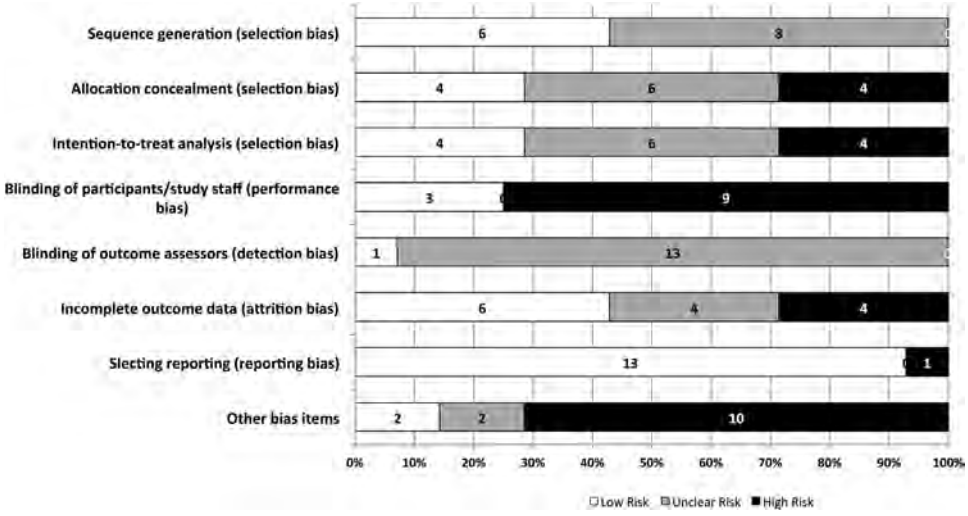

Figure 2. Risk of bias in included studies (details of quality assessment are in Table S3).

$I^2 = 0\%$] and 11 studies in grafts [697 participants; RR, 0.95; 95% CI, 0.80-1.12; $I^2 = 0\%$]; subgroup differences, $P = 0.002$) and in prevention aim (13 studies of primary prophylaxis [885 participants; RR, 0.94; 95% CI, 0.78-1.12; $I^2 = 0\%$] and 5 studies of secondary prophylaxis [327 participants; RR, 0.53; 95% CI, 0.32-0.87; $I^2 = 59\%$]; subgroup differences, $P = 0.04$). There were no significant subgroup differences by surveillance method in primary prophylaxis ($P = 0.2$).

Other Analyses

Insufficient data were available to assess the effects of 2 surveillance methods versus 1 method

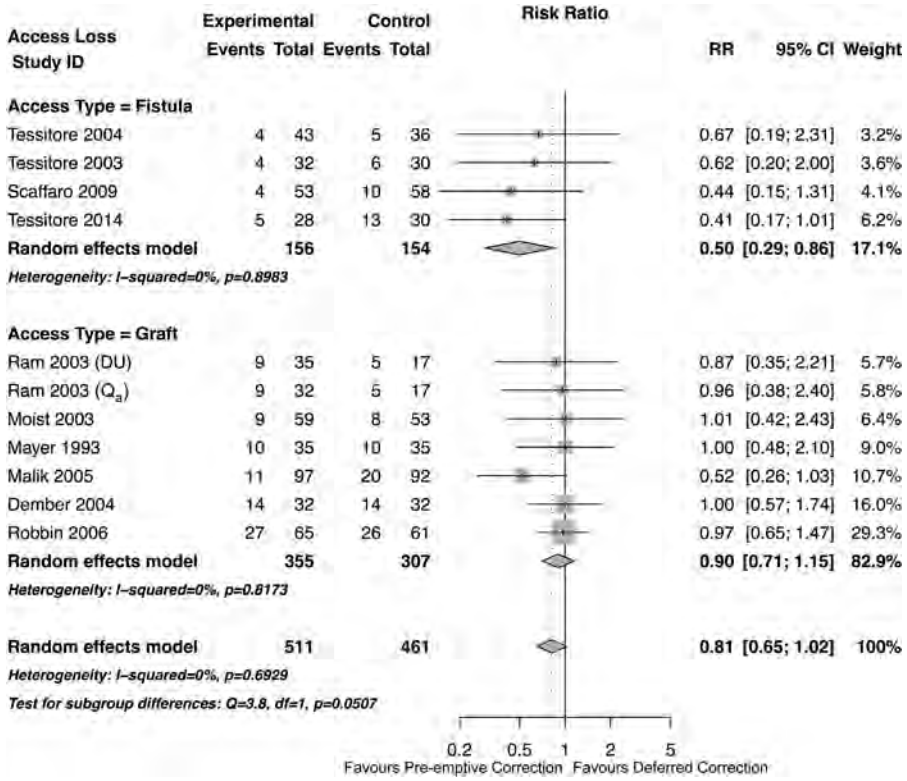

Figure 3. Meta-analysis of access loss, overall and by access type. Alternative analytical approaches are reported in Item S1. Abbreviations: CI, confidence interval; DU, doppler ultrasound; Q_a, blood flow in access; RR, risk ratio.

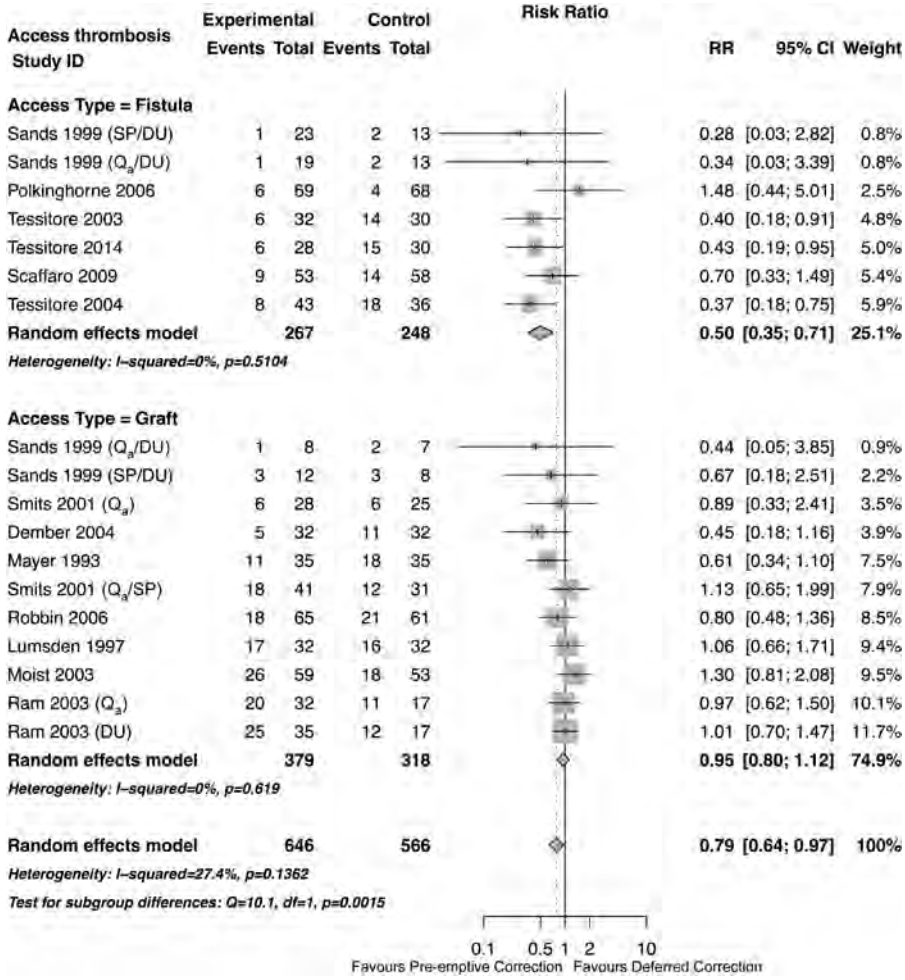

Figure 4. Meta-analysis of access thrombosis, overall and by access type. Alternative analytical approaches are reported in Item S1. Abbreviations: CI, confidence interval; DU, doppler ultrasound; Q_a, blood flow in access; RR, risk ratio; SP, static pressure measurement.

or to compare 2 different surveillance methods head to head. Results were the same in several sensitivity analyses we conducted by including and excluding studies of 2 surveillance methods, studies in which venous pressure was measured in the intervention arm and/or in the comparator arm, and studies in which clinical monitoring was or was not a cointervention. Results using different analytical approaches are reported in tables *a-c* of Item S1.

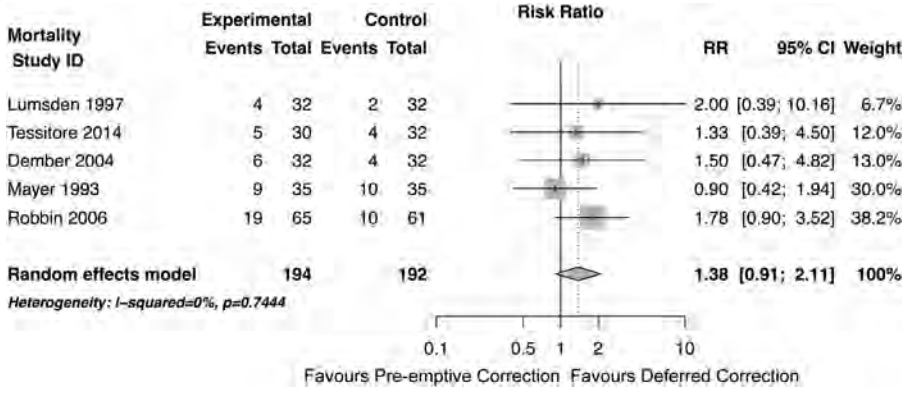

Figure 5. Meta-analysis of mortality data. Alternative analytical approaches are reported in Item S1. Abbreviations: CI, confidence interval; RR, risk ratio.

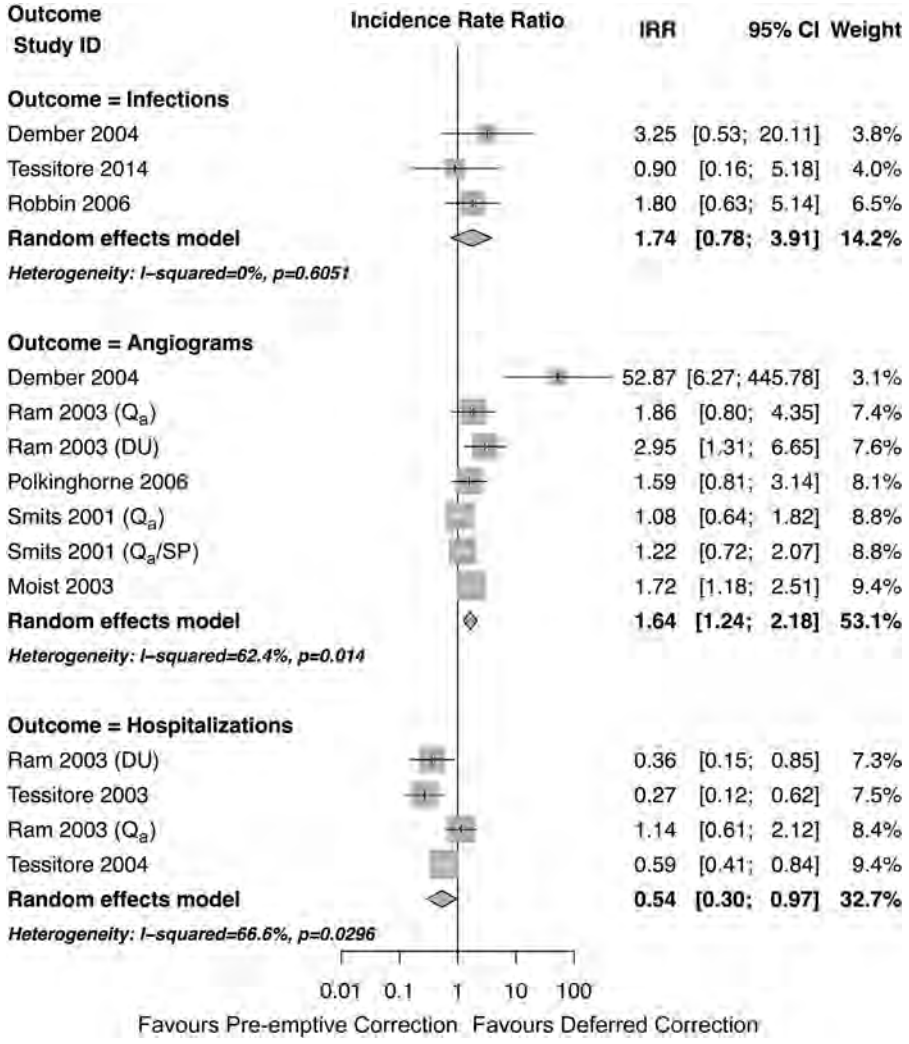

Figure 6. Meta-analysis of secondary outcomes: infection (reported as access infections), access-related procedures, and hospitalization. Abbreviations: CI, confidence interval; DU, doppler ultrasound; IRR, incidence rate ratio; Q_a, blood flow in access; SP, static pressure measurement.

Evidence Grading

The evidence profile for the effects of preemptive correction of AV access stenosis is summarized in Table S4. In absolute numbers, preemptive correction of AV access stenosis in 1,000 people using either a graft or fistula for 1 year might prevent the occurrence of thrombosis in 94 on average, but may require additional access-related procedures in 234 and does not prevent the loss of the AV access. Assuming treatment effects vary by access type (subgroup analyses, $P = 0.05$), a strategy for preemptive correction of stenosis in 1,000 people using a fistula can prevent thrombosis in 200 and access loss in 50. Given the low to moderate level of evidence, further research is very likely or likely to have an important impact on our confidence in these estimates and change these estimates.

DISCUSSION

We found that preemptive correction of an AV access stenosis may reduce the risk for thrombosis but not the risk for access loss, the most important outcome. We also found that this strategy has uncertain benefits in terms of hospitalization and potential harms in terms of number of procedures, infections, and mortality. Although in prespecified subgroup analyses, preemptive stenosis correction may decrease the risk for access loss in fistulas, these differences by access type were nonsignificant. Considering the low quality of existing studies in fistulas, additional placebo-controlled trials may alter the confidence in the size and direction of the treatment estimates we detected.

A previous systematic review found that Q_a screening does not prevent thrombosis or access graft loss, may prevent thrombosis in fistulas, but may not

prevent access loss in fistulas or extent of resource use.[13] As compared to this earlier study, we made a distinction between primary and secondary prophylaxis and assessed patient outcomes. Despite the inclusion of 3 additional studies in our review,[26,28,32] the estimate of the effects of preemptive correction of AV access stenosis on important clinical outcomes (access loss in fistulas, infection, and mortality) remains imprecise. Considering the high risk for access complications and the morbidity burden and high cost associated with the effort to maintain a functional AV access, the finding that only 2 RCTs[26,32] were published since this previous review[13] raises several concerns about the reasons and consequences of the decreasing interest in this topic, which is relevant to patients and the health care system, as shown in a recent survey of patients, researchers, and health care providers.[35]

Our review has strengths because it is based on a peer-reviewed protocol and performed with methods developed by Cochrane. However, the review has some limitations, which might be considered when interpreting the results, principally due to the quality of the data in contributing studies, including lack of protocol publication in most studies and inability to assess reporting bias. First, our analyses included studies with relatively few participants overall and may have lacked sufficient power to detect treatment effects. Second, based on GRADE assessments, due to study limitations, there was low confidence in the summary effects. Additional trials may change the overall treatment effects estimated in existing studies. Third, the majority of data were from studies in people using grafts, a type of access used in $<10\%$ of the hemodialysis population in most countries, and limited information is available for fistulas, the preferred AV access for hemodialysis therapy. Fourth, the interventions were complex, yet insufficient information was available for important factors that might have been responsible for potential benefits on fistula outcomes, including algorithms for referral for intervention or intervention strategies. Finally, resource use and patient outcomes such as infections and mortality were under-reported and little information was available about the cost of access surveillance programs and patient perspective or quality of life, which are needed to inform policy decisions.

In terms of clinical practice, although available evidence does not support surveillance for preemptive stenosis correction in people using grafts, there is some promising but insufficient information about potential benefits and harms of access-related procedures to support this practice in people using fistulas. Reported benefits in terms of fistula loss are based on low-quality evidence from only 4 studies,[26,30-32] 3 of which are single-center studies conducted in the same institution and reported by the same investigators.[30-32] Until more and stronger data are available, any prevention strategy should be weighed against a potential increased number of invasive procedures, procedure-related adverse events, and use of health resources. Considering the potential harms and inconvenience associated with these procedures, patients' involvement in decision making is key to determine the management strategy that is more consistent with their preferences and values.

In terms of future research, considering that in people using grafts, estimates of RR for thrombosis and access loss between treatment arms are close to unity in both main and secondary analyses and that bias tends to overestimate treatment effects, additional RCTs of preemptive stenosis correction are unlikely to change the confidence in the size and direction of the effect we found in grafts. In grafts, research focus should shift to the development of materials less prone to complications and new interventions to prevent stenosis or reduce the risk for restenosis after a salvage procedure.[13] In fistulas, considering the signal of benefit we observed, particularly in secondary prophylaxis, a large secondary prophylaxis RCT with fistula loss as the main outcome is warranted. Based on the findings of our review, we estimated that an RCT of about 1,000 participants per arm recruited over 1 year and followed up for 3 years will have power of 90% to detect as significant at a 2-sided $P = 0.01$ a 30% (or greater) reduction in hazard ratio for access loss, assuming a baseline risk of 10% per year and withdrawal rate of 10%. Ideally, this RCT should include also patient-centered outcomes (quality of life, infections, and mortality) and data for health resource use (including resources necessary to run a surveillance program) and cost as secondary outcomes. Finally, data for patient preferences and views about expected benefits and potential harms of access surveillance and preemptive correction of access stenosis should be included in future research if we want to promote patient-centered care in this area. These data will allow the development of decision aids and incorporation of patient perspectives and informed decisions into a truly shared decision-making process at the bedside.[36]

ACKNOWLEDGEMENTS

We acknowledge the assistance of Ruth Mitchell, Trials Search Coordinator; Narelle Willis (former Managing Editor); and Ann Jones (current Managing Editor) from the Cochrane Renal Group; the referees for their comments; and Drs N. Tessitore, G. Bacchini, and P. Roy-Chaudhury for providing additional data.

Support: The study received no specific external funding. No funding body had any role in study design; collection, analysis, and interpretation of data; writing the report; or the decision to submit the report for publication.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Contributions: Research idea and study design: PR, GFMS; data acquisition: PR, DJK; data analysis/interpretation: PR, RRQ, MJO, DJK, MTJ, JMM, SCP, GFMS; statistical analysis: PR; supervision or mentorship: GFMS. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. PR takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Peer Review: Evaluated by 3 external peer reviewers, a Statistical Editor, the Deputy Editor, and the Editor-in-Chief.

SUPPLEMENTARY MATERIAL

Table S1: Search strategy.

Table S2: Quality assessment.

Table S3: Review authors' judgments about each risk-of-bias item for each included study.

Table S4: Summary of findings

Figure S1: Other outcomes.

Item S1: Other sensitivity analyses.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2015.11.013) is available at www.ajkd.org

REFERENCES

1. Allon M, Robbin ML. Resolved: fistulas are preferred to grafts as initial vascular access for dialysis. Con. *J Am Soc Nephrol*. 2008;19:1632-1633.

2. Besarab A. Resolved: fistulas are preferred to grafts as initial vascular access for dialysis. *Pro. J Am Soc Nephrol*. 2008;19:1629-1631.

3. Ravani P, Palmer SC, Oliver MJ, et al. Associations between hemodialysis access type and clinical outcomes: a systematic review. *J Am Soc Nephrol*. 2013;24:465-473.

4. Manns B, Tonelli M, Yilmaz S, et al. Establishment and maintenance of vascular access in incident hemodialysis patients: a prospective cost analysis. *J Am Soc Nephrol*. 2005;16:201-209.

5. Lok CE. Fistula first initiative: advantages and pitfalls. *Clin J Am Soc Nephrol*. 2007;2:1043-1053.

6. Casey JR, Hanson CS, Winkelmayer WC, et al. Patients' perspectives on hemodialysis vascular access: a systematic review of qualitative studies. *Am J Kidney Dis*. 2014;64:937-953.

7. Vascular Access Work Group. Clinical practice guidelines for vascular access. *Am J Kidney Dis*. 2006;48(suppl 1):S248-S273.

8. Vascular Access Work Group. Clinical practice guidelines for vascular access. *Am J Kidney Dis*. 2006;48(suppl 1):S176-S247.

9. Jindal K, Chan CT, Deziel C, et al; Canadian Society of Nephrology Committee for Clinical Practice. Hemodialysis clinical practice guidelines for the Canadian Society of Nephrology. *J Am Soc Nephrol*. 2006;17(3)(suppl 1):S1-S27.

10. Polkinghorne K. Caring for Australians With Renal Impairment. The CARI guidelines. Vascular access surveillance. *Nephrology (Carlton)*. 2008;13(suppl 2):S1-S11.

11. Renal Association. Vascular access guidelines - update 2011. http://www.renal.org/guidelines/. Accessed December 21, 2015.

12. Tordoir J, Canaud B, Haage P, et al. EBPG on vascular access. *Nephrol Dial Transplant*. 2007;22(suppl 2):ii88-ii117.

13. Tonelli M, James M, Wiebe N, Jindal K, Hemmelgarn B; Alberta Kidney Disease Network. Ultrasound monitoring to detect access stenosis in hemodialysis patients: a systematic review. *Am J Kidney Dis*. 2008;51:630-640.

14. Ravani PJ, James MT, MacRae JM, Palmer SC, Quinn RR, Oliver MJ, Strippoli GFM. Pre-emptive correction for haemodialysis arteriovenous access stenosis. *The Cochrane Library,* 8. 2013. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010709/abstract. Accessed December 19, 2015.

15. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6:e1000100.

16. Higgins JPG, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. http://handbook.cochrane.org/. Accessed December 19, 2015.

17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.

18. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924-926.

19. Malik J, Slavikova M, Svobodova J, Tuka V. Regular ultrasonographic screening significantly prolongs patency of PTFE grafts. *Kidney Int*. 2005;67:1554-1558.

20. Mayer DA, Zingale RG, Tsapogas MJ. Duplex scanning of expanded polytetrafluoroethylene dialysis shunts: impact on patient management and graft survival. *Vasc Endovasc Surg*. 1993;27:647-658.

21. Moist LM, Churchill DN, House AA, et al. Regular monitoring of access flow compared with monitoring of venous pressure fails to improve graft survival. *J Am Soc Nephrol*. 2003;14:2645-2653.

22. Ram SJ, Work J, Caldito GC, Eason JM, Pervez A, Paulson WD. A randomized controlled trial of blood flow and stenosis surveillance of hemodialysis grafts. *Kidney Int*. 2003;64:272-280.

23. Robbin ML, Oser RF, Lee JY, Heudebert GR, Mennemeyer ST, Allon M. Randomized comparison of ultrasound surveillance and clinical monitoring on arteriovenous graft outcomes. *Kidney Int*. 2006;69:730-735.

24. Smits JH, van der Linden J, Hagen EC, et al. Graft surveillance: venous pressure, access flow, or the combination? *Kidney Int*. 2001;59:1551-1558.

25. Polkinghorne KR, Lau KK, Saunder A, Atkins RC, Kerr PG. Does monthly native arteriovenous fistula blood-flow surveillance detect significant stenosis–a randomized controlled trial. *Nephrol Dial Transplant*. 2006;21:2498-2506.

26. Scaffaro LA, Bettio JA, Cavazzola SA, et al. Maintenance of hemodialysis arteriovenous fistulas by an interventional strategy: clinical and duplex ultrasonographic surveillance followed by transluminal angioplasty. *J Ultrasound Med*. 2009;28:1159-1165.

27. Sands JJ, Jabyac PA, Miranda CL, Kapsick BJ. Intervention based on monthly monitoring decreases hemodialysis access thrombosis. *ASAIO J*. 1999;45:147-150.

28. Dember LM, Holmberg EF, Kaufman JS. Randomized controlled trial of prophylactic repair of hemodialysis arteriovenous graft stenosis. *Kidney Int*. 2004;66:390-398.

29. Lumsden AB, MacDonald MJ, Kikeri D, Cotsonis GA, Harker LA, Martin LG. Prophylactic balloon angioplasty fails to prolong the patency of expanded polytetrafluoroethylene arteriovenous grafts: results of a prospective randomized study. *J Vasc Surg*. 1997;26:382-390; discussion 390-382.

30. Tessitore N, Mansueto G, Bedogna V, et al. A prospective controlled trial on effect of percutaneous transluminal angioplasty

on functioning arteriovenous fistulae survival. *J Am Soc Nephrol*. 2003;14:1623-1627.

31. Tessitore N, Lipari G, Poli A, et al. Can blood flow surveillance and pre-emptive repair of subclinical stenosis prolong the useful life of arteriovenous fistulae? A randomized controlled study. *Nephrol Dial Transplant*. 2004;19:2325-2333.

32. Tessitore N, Bedogna V, Poli A, et al. Should current criteria for detecting and repairing arteriovenous fistula stenosis be reconsidered? Interim analysis of a randomized controlled trial. *Nephrol Dial Transplant*. 2014;29:179-187.

33. Dossabhoy NR, Ram SJ, Nassar R, Work J, Eason JM, Paulson WD. Stenosis surveillance of hemodialysis grafts by duplex ultrasound reduces hospitalizations and cost of care. *Semin Dial*. 2005;18:550-557.

34. Martin LG, MacDonald MJ, Kikeri D, Cotsonis GA, Harker LA, Lumsden AB. Prophylactic angioplasty reduces thrombosis in virgin ePTFE arteriovenous dialysis grafts with greater than 50% stenosis: subset analysis of a prospectively randomized study. *J Vasc Interv Radiol*. 1999;10:389-396.

35. Manns B, Hemmelgarn B, Lillie E, et al. Setting research priorities for patients on or nearing dialysis. *Clin J Am Soc Nephrol*. 2014;9:1813-1821.

36. Barry MJ, Edgman-Levitan S. Shared decision making–pinnacle of patient-centered care. *N Engl J Med*. 2012;366:780-781.

37. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med*. 1998;17(24):2815-2834.