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

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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; I² = 0%) and a significant effect on risk for thrombosis (RR, 0.79; 95% CI, 0.65-0.97; I² = 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.

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
AV access are a leading cause of hospitalization and health care resource consumption among hemodialysis patients. 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). Vascular access–related morbidity has profound social and psychological consequences for the patient.

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 (Qb), arterial and transmembrane pressures, or dialysis adequacy indexes. During clinical monitoring, evidence of access dysfunction (eg, reduced Qb 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 (deferral of salvage interventions). Because stenosis of the AV access reduces blood flow in the AV access (Qa) and consequently increases the risk for access thrombosis, different noninvasive methods of active surveillance of Qa have been proposed to determine earlier whether a functional access is at risk for dysfunction. These involve direct measurements of Qa, 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 Qa values are present regardless of the access ability to provide adequate hemodialysis (preemptive correction of access stenosis). These guideline recommendations assume that a reduction in Qa 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 as compared to deferred salvage. However, a previous systematic review found no benefits from access screening in grafts and uncertain benefits in fistulas.

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, 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 and followed recommended guidelines for reporting.

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 Qa (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...
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 I² (with 95% CIs).17 We considered I² 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 (Qa- or pressure measurement–based surveillance, which provides only Qa data, or ultrasound-based surveillance, which provides both Qa 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Funding</th>
<th>Start Year</th>
<th>End Year</th>
<th>F/U, mo</th>
<th>No. of Participants</th>
<th>Access Type</th>
<th>Prophylaxis</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polkinghorne</td>
<td>AU</td>
<td>Public</td>
<td>2001</td>
<td>2003</td>
<td>18</td>
<td>137 (69:68)</td>
<td>Primary</td>
<td>Prevalent fistulas (some with previous procedures)</td>
<td>Age &gt; 18 y; on HD for 3+ mo; Q_a &gt; 500 mL/min</td>
<td>Home HD; waiting for living Tx</td>
</tr>
<tr>
<td>Malik</td>
<td>CZ</td>
<td>Public</td>
<td>1999</td>
<td>2004</td>
<td>13</td>
<td>189 (97:92)</td>
<td>Primary</td>
<td>New grafts</td>
<td>Primary New grafts</td>
<td>None specified</td>
</tr>
<tr>
<td>Mayer</td>
<td>US</td>
<td>NR</td>
<td>NA</td>
<td>NA</td>
<td>21</td>
<td>70 (35:35)</td>
<td>Primary</td>
<td>Prevalent grafts (some with previous procedures)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Smits</td>
<td>NL</td>
<td>Public</td>
<td>NA</td>
<td>NA</td>
<td>8</td>
<td>119 (27:24:37:31)</td>
<td>Primary</td>
<td>Prevalent grafts (some with previous procedures)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Robbin</td>
<td>US</td>
<td>Public</td>
<td>NA</td>
<td>NA</td>
<td>38</td>
<td>126 (65:61)</td>
<td>Primary</td>
<td>Prevalent grafts (some with previous procedures)</td>
<td>Primary On HD for 3+ mo; outpatient</td>
<td>Poor prognosis; waiting for living Tx</td>
</tr>
<tr>
<td>Sands</td>
<td>US</td>
<td>Public</td>
<td>NA</td>
<td>NA</td>
<td>6</td>
<td>103 (62:41)</td>
<td>Primary NA</td>
<td>Prevalent grafts and fistulas (some with previous procedures)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Moist</td>
<td>CA</td>
<td>Public</td>
<td>2000</td>
<td>NA</td>
<td>12</td>
<td>112 (59:53)</td>
<td>Primary Q_a &gt; 650 mL/min; no abnormalities</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ram</td>
<td>US</td>
<td>Private</td>
<td>1998</td>
<td>2001</td>
<td>24</td>
<td>101 (32:34:35)</td>
<td>Primary Q_a measurement possible</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Scaffaro</td>
<td>BR</td>
<td>NR</td>
<td>2005</td>
<td>NA</td>
<td>7.5</td>
<td>111 (53:58)</td>
<td>Primary Nondysfunctional</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lumsden</td>
<td>US</td>
<td>Public</td>
<td>1993</td>
<td>NA</td>
<td>15</td>
<td>64 (32:32)</td>
<td>Secondary &gt;50% stenosis (Doppler ultrasound), nondysfunctional graft</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Dember</td>
<td>US</td>
<td>Private</td>
<td>NA</td>
<td>NA</td>
<td>24</td>
<td>64 (32:32)</td>
<td>Secondary Static venous pressure to SBP ratio = 0.4+</td>
<td>Poor prognosis; anticipated change in RRT method; allergy to contrast</td>
<td>Poor prognosis; anticipated change in RRT method; allergy to contrast</td>
<td>Poor prognosis; anticipated change in RRT method; allergy to contrast</td>
</tr>
<tr>
<td>Tessitore</td>
<td>IT</td>
<td>NR</td>
<td>1995</td>
<td>2001</td>
<td>15</td>
<td>60 (30:30)</td>
<td>Secondary Kt/V &gt; 1.2, mature, forearm, distal fistulas; angio-proven stenosis &gt; 50%</td>
<td>Already revised/salvaged fistulas</td>
<td>Already revised/salvaged fistulas</td>
<td></td>
</tr>
<tr>
<td>Tessitore</td>
<td>IT</td>
<td>NR</td>
<td>1997</td>
<td>NA</td>
<td>30</td>
<td>79 (44:39)</td>
<td>Secondary Kt/V &gt; 1.2, mature, forearm, distal fistulas; angio-proven stenosis &gt; 50%</td>
<td>Other clinical trials</td>
<td>Other clinical trials</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
the confidence in the evidence. According to these criteria, evi-
dence 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 compared to the clinical context; impre-
sicion of the estimated effects; and publi-
cation bias.

RESULTS

Search Results and Study Characteristics

Search results are summarized in Fig 1. We
included 14 RCTs involving 1,390 adults in this re-
view. Of these, 9 RCTs included 1,065 adults without
access stenosis (primary prophylaxis): 6 included 717
participants using grafts, 19-24 2 included 245 partici-
pants using fistulas, 25,26 and 1 included 103 partici-
pants 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 syn-
thesis. Detailed information about the design, partic-
ipants, intervention, comparator, and outcomes of the
included studies are summarized in Tables 1 and 2.

Two included studies22,29 published additional data in
a subsequent report.33,34 In studies of primary pro-
phylaxis, 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
ultrasound,24,25,27 or an indirect measure of Qa (venous
pressure in the access).21,24,27

Three studies reported 2 comparisons each.22,24,27 In
all RCTs, participants in both intervention and
comparator arms received routine clinical monitoring,
except in 3 studies.22,29 In one of the studies of
fistula with suspected stenosis at screening (Qa
900 mL/min and/or physical signs or.

Table 1 (Cont’d): Data Sources and Design

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

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; Qa, 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.

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

<sup>b</sup>There were 125 grafts in 119 participants (I:C:I:C: 2 intervention arms and 2 comparators).

<sup>c</sup>There were 111 accesses in 108 participants.

<sup>d</sup>Stenosis not documented with an imaging study at randomization (only increased static venous pressure ratio).

<sup>e</sup>There were 32 fistulas in 30 participants.
Table 2. Description of the Interventions

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Intervention Details</th>
<th>Comparator</th>
<th>Comparator Details</th>
<th>Radiologist Involved in Interpreting Angiography</th>
<th>Method of Stenosis Correction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polkinghorne</td>
<td>$Q_a$ (screening) + control</td>
<td>Monthly $Q_a$ (DUS); referred if $Q_a &lt; 500$ or falls $&gt;20%$ once $&lt;1,000$</td>
<td>Clinical (monitoring) + DVP</td>
<td>Clinical (referred if): DVP $&gt;150$, arterial pressure; $\downarrow Q_a$, bleeding following needle removal, $\downarrow URR$</td>
<td>Reported</td>
<td>33% PTA, 66% SX</td>
</tr>
<tr>
<td>Malik</td>
<td>DUS (screening) + control</td>
<td>DUS every 3 mo; referral if peak systolic velocity ratio $&gt;2$ or $&gt;25%$ decrease</td>
<td>Clinical (monitoring) + DVP</td>
<td>Clinical + DVP or recirculation or $Q_a$</td>
<td>NA</td>
<td>94% PTA, 6% SX</td>
</tr>
<tr>
<td>Mayer</td>
<td>DUS (screening); no control</td>
<td>DUS at 3 and 6 mo, then every 12 mo</td>
<td>Clinical (monitoring)</td>
<td>Clinical at 3 &amp; 6 mo; then every 12 mo</td>
<td>NA</td>
<td>100% SX</td>
</tr>
<tr>
<td>Smits</td>
<td>$Q_a$ (screening) every 2 mo</td>
<td>$Q_a$ (referral if $&lt;600$) + clinical</td>
<td>Clinical (monitoring) + S/DVP</td>
<td>Clinical + S/DVP (referral if DVP $&gt;150$; SVP ratio $&gt;0.5$)</td>
<td>NA</td>
<td>87% PTA, 13% SX</td>
</tr>
<tr>
<td>Smits</td>
<td>$Q_a$ + S/DVP every 2 mo</td>
<td>$Q_a$ (referral if $&lt;600$) + S/DVP + clinical</td>
<td>Clinical (monitoring) + S/DVP</td>
<td>Clinical + S/DVP (referral if DVP $&gt;150$; SVP ratio $&gt;0.5$)</td>
<td>NA</td>
<td>89% PTA, 11% SX</td>
</tr>
<tr>
<td>Robbin</td>
<td>DUS (screening) + control</td>
<td>DUS every 4 mo; referred if peak systolic velocity ratio $= 2+$</td>
<td>Clinical (monitoring)</td>
<td>Referral based on clinical signs</td>
<td>Reported</td>
<td>100% PTA</td>
</tr>
<tr>
<td>Sands</td>
<td>$Q_a$ every mo + DUS screening every 6 mo</td>
<td>Referred if $Q_a &lt; 600$ and DUS stenosis $&gt;50%$</td>
<td>DUS screening every 6 mo</td>
<td>Another screening method: no monitoring</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sands</td>
<td>$Q_a$ every mo + DUS screening every 6 mo</td>
<td>Referred if $Q_a &lt; 800$ and DUS stenosis $&gt;50%$</td>
<td>DUS screening every 6 mo</td>
<td>Another screening method: no monitoring</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sands</td>
<td>SVP every month + DUS screening every 6 mo</td>
<td>Referred if SVP $= 0.5+$ and DUS stenosis $&gt;50%$</td>
<td>DUS screening every 6 mo</td>
<td>Another screening method: no monitoring</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sands</td>
<td>SVP every month + DUS screening every 6 mo</td>
<td>Referred if SVP $= 0.5+$ and DUS stenosis $&gt;50%$</td>
<td>DUS screening every 6 mo</td>
<td>Another screening method: no monitoring</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Moist</td>
<td>$Q_a$ + DVP (screening) + control</td>
<td>DVP $&gt;125/140$ + monthly $Q_a$; referral if $Q_a &lt; 650$ or $&gt;20%$ decrease</td>
<td>Clinical (monitoring) + DVP</td>
<td>Referral for clinical signs</td>
<td>Reported</td>
<td>NA</td>
</tr>
<tr>
<td>Ram</td>
<td>$Q_a$ every mo</td>
<td>Referred to angiography if $Q_a &lt; 600$ or clinical criteria</td>
<td>Clinical (monitoring) + DVP</td>
<td>Criteria for angiography referral if $Q_a$ not attained; $&gt;DVP$, bleeding, swelling</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

(Continued)
Table 2 (Cont’d). Description of the Interventions

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Intervention Details</th>
<th>Comparator</th>
<th>Comparator Details</th>
<th>Radiologist Involved in Interpreting Angiography</th>
<th>Method of Stenosis Correction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ram²² (2003) (B)</td>
<td>DUS every mo</td>
<td>Referred to angiography if &gt;50% stenosis or clinical criteria</td>
<td>Clinical (monitoring) + DVP</td>
<td>Criteria for angiography referral were Qₑ not attained, &gt;DVP, bleeding, swelling</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Scaffaro²⁶ (2009)</td>
<td>DUS every 3 mo + control</td>
<td>DUS every 3 mo</td>
<td>Clinical (monitoring)</td>
<td>Clinical + hemodynamic assessment</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lumsden²⁹ (1997)</td>
<td>PTA</td>
<td>Randomly assigned to preemptive correction of stenosis; DUS every 2 mo</td>
<td>Observation</td>
<td>Recirculation &gt; 15%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Dember²⁸ (2004)</td>
<td>Referred to angiography</td>
<td>Repair if &gt;50% stenosis (at angiography)</td>
<td>Continued SVP monitoring if nondysfunctional</td>
<td>Repair if dysfunction/thrombosis (clinical)</td>
<td>NA</td>
<td>88% PTA, 12% SX</td>
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<tr>
<td>Tessitore³⁰ (2003)</td>
<td>Preemptive PTA (within 3 wk)</td>
<td>Randomly assigned to preemptive correction of stenosis (referral was Qₐ &lt; 850)</td>
<td>Deferred PTA</td>
<td>Correction of stenosis if Qₑ reduction &gt; 30; or recirculation &gt; 5%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Tessitore³¹ (2004)</td>
<td>Preemptive PTA/ surgery (within 3 wk)</td>
<td>Randomly assigned to preemptive correction of stenosis (referral was Qₐ &lt; 750)</td>
<td>Deferred PTA/SX</td>
<td>Correction of stenosis if Qₑ reduction &gt; 40; or recirculation &gt; 5%</td>
<td>Reported</td>
<td>79% PTA, 21% SX</td>
</tr>
<tr>
<td>Tessitore³² (2014)</td>
<td>Preemptive angioplasty or surgery within 3 wk of randomization</td>
<td>Preemptive correction of stenosis at baseline and repeated during follow-up if Qₐ &lt; 750 or Qₐ dropped by &gt;25%</td>
<td>Deferred salvage procedures (angioplasty or SX)</td>
<td>Elective repair allowed if Qₑ &lt; 400 (but 300+)</td>
<td>Reported</td>
<td>72% PTA, 28% SX</td>
</tr>
</tbody>
</table>

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; Qₑ, blood flow in access (mL/min); Qₐ, hemodialysis blood pump speed (mL/min); SVP, static venous pressure ratio (SVP over systolic blood pressure); SX, surgical intervention; URR, urea reduction ratio.
<table>
<thead>
<tr>
<th>Study</th>
<th>Age, y</th>
<th>Male, %</th>
<th>DM, %</th>
<th>Dialysis Vintage, y</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Additional Data on Drug Usea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polkinghorne25 (2006)</td>
<td>58</td>
<td>68</td>
<td>31</td>
<td>2.17</td>
<td>61% distal, 36% proximal, 3% others; 23 mo (median)</td>
<td>1,243 mL/min; NA</td>
<td>62% forearm, 34% upper arm, 4% others; 29 mo (median)</td>
</tr>
<tr>
<td>Malik19 (2005)</td>
<td>58</td>
<td>44</td>
<td>48</td>
<td>0</td>
<td>78% forearm, 20% upper arm, 2% subclavian; NA</td>
<td>769 mL/min; &gt;0%</td>
<td>78% forearm, 20% upper arm, 2% subclavian; NA</td>
</tr>
<tr>
<td>Mayer20 (1993)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>57% forearm, 43% upper arm; NA</td>
<td>NA; NA</td>
<td>46% forearm, 54% upper arm; NA</td>
</tr>
<tr>
<td>Smits24 (2001)</td>
<td>61</td>
<td>49</td>
<td>20</td>
<td>2.5</td>
<td>A: 93% forearm, 7% upper arm; 8 mo</td>
<td>NA; NA</td>
<td>A: 92% forearm, 8% upper arm; 13 mo</td>
</tr>
<tr>
<td>Polkinghorne25 (2006)</td>
<td>58</td>
<td>68</td>
<td>31</td>
<td>2.17</td>
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<td>A: 93% forearm, 7% upper arm; 8 mo</td>
<td>NA; NA</td>
<td>A: 92% forearm, 8% upper arm; 13 mo</td>
</tr>
<tr>
<td>Robbin23 (2006)</td>
<td>57.5</td>
<td>41</td>
<td>61</td>
<td>0.75</td>
<td>17% forearm, 83% upper arm; 9 mo</td>
<td>NA; 48%</td>
<td>30% forearm, 70% upper arm; 9 mo</td>
</tr>
<tr>
<td>Sands27 (1999)</td>
<td>57.3</td>
<td>NA</td>
<td>27.5</td>
<td>2</td>
<td>NA; 18 mo</td>
<td>NA; NA</td>
<td>28% NA; NA</td>
</tr>
<tr>
<td>Moist26 (2003)</td>
<td>64.6</td>
<td>50.2</td>
<td>37.7</td>
<td>2</td>
<td>68% forearm, 24% upper arm, 8% leg; 21 mo</td>
<td>1,116 mL/min; &gt;0%</td>
<td>1,100 mL/min; &gt;0%</td>
</tr>
<tr>
<td>Ram25 (2003)</td>
<td>55.7</td>
<td>41.6</td>
<td>47.5</td>
<td>1.5</td>
<td>NA; 16 and 14 mo</td>
<td>1,219 and 1,253 mL/min; 41% and 26%</td>
<td>NA; 9 mo</td>
</tr>
<tr>
<td>Scarpino25 (2000)</td>
<td>55.7</td>
<td>55.8</td>
<td>36.9</td>
<td>NA</td>
<td>NA; 64% &gt; 6 mo</td>
<td>NA; 58%</td>
<td>NA; 62% &gt; 6 mo</td>
</tr>
<tr>
<td>Lumosden29 (1997)</td>
<td>57</td>
<td>48</td>
<td>39.5</td>
<td>NA</td>
<td>25% forearm, 72% upper arm, 3% leg; NA</td>
<td>1,716 mL/min; &gt;0%</td>
<td>28% forearm, 72% upper arm; 1,886 mL/min; &gt;0%</td>
</tr>
<tr>
<td>Denman28 (2004)</td>
<td>59</td>
<td>64</td>
<td>55</td>
<td>1</td>
<td>34% forearm; 11 mo</td>
<td>NA; 34%</td>
<td>53% forearm; 12 mo</td>
</tr>
<tr>
<td>Tessitore30 (2003)</td>
<td>59.4</td>
<td>63</td>
<td>25</td>
<td>1</td>
<td>100% forearm; 10 mo (median)</td>
<td>451 mL/min; NA</td>
<td>100% forearm; 16 mo (median)</td>
</tr>
<tr>
<td>Tessitore31 (2004)</td>
<td>59.8</td>
<td>55</td>
<td>23</td>
<td>18</td>
<td>100% forearm; 17 mo</td>
<td>445 mL/min; 0%</td>
<td>100% forearm; 22 mo</td>
</tr>
<tr>
<td>Tessitore32 (2014)</td>
<td>63.6</td>
<td>56.6</td>
<td>30.9</td>
<td>NA</td>
<td>17/28 forearm; 21 mo</td>
<td>720 mL/min; 0% (last 3 mo)</td>
<td>22/30 forearm; 27 mo</td>
</tr>
</tbody>
</table>

Abbreviations: DM, diabetes mellitus; NA, not available; Qa, blood flow in access.

\(^a\)Antiplatelets or anticoagulant.
from 20% to 61%. Four studies were published after 2005, and only one 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, 0.74; 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. 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. 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;
I² = 0%] and 11 studies in grafts [697 participants; RR, 0.95; 95% CI, 0.80-1.12; I² = 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; I² = 0%] and 5 studies of secondary prophylaxis [327 participants; RR, 0.53; 95% CI, 0.32-0.87; I² = 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.
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 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; Qa, blood flow in access; RR, risk ratio; SP, static pressure measurement.

Figure 5. Meta-analysis of mortality data. Alternative analytical approaches are reported in Item S1. Abbreviations: CI, confidence interval; RR, risk ratio.
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 stenosis correction 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\textsubscript{s} 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. 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, 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 were published since this previous review 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.

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, 3 of which are single-center studies conducted in the same institution and reported by the same investigators. 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. 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 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.

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**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

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