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A Meta-analysis of Randomized Clinical Trials Assessing Hemodialysis Access Thrombosis Based on Access Flow Monitoring: Where Do We Stand?

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ABSTRACT

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative recommends the routine use of hemodialysis arteriovenous (AV) access surveillance to detect hemodynamically significant stenoses and appropriately correct them to reduce the incidence of thrombosis and to improve accesses patency rates. Access blood flow monitoring is considered as one of the preferred surveillance method for both AV fistulas (AVF) and AV grafts (AVG); however, published studies have reported conflicting results of its utility that led healthcare professionals to doubt the benefits of this surveillance method. We performed a meta-analysis of the published randomized controlled trials (RCTs) of AV access surveillance using access blood flow monitoring. Our hypothesis was that access blood flow monitoring lowers the risk of AV access thrombosis and that the outcome differs between AVF and AVG. The estimated overall pooled risk ratio (RR) of thrombosis was 0.87 (95% confidence interval [CI], 0.67–1.13) favoring access blood flow monitoring. The pooled RR of thrombosis were 0.64 (95% CI, 0.41–1.01) and 1.06 (95% CI, 0.77–1.46) in the subgroups of only AVF and only AVG, respectively. Our results added to the uncertainty of access blood flow monitoring as a surveillance method of hemodialysis accesses.

Hemodialysis access thrombosis is a significant cause of access loss in hemodialysis patients and a cause of decreased secondary patency. Stenosis in the dialysis access is frequently the culprit of access thrombosis. The hallmark of stenosis is decreased flow in the access. About 80% of accesses fail because of thrombosis (1). The frequency of thrombosis is several fold lower in arteriovenous fistulas (AVF) than in arteriovenous grafts (AVG) (2). On average, the annual frequency of intervention (elective angioplasty, thrombectomy, or surgical revision) in mature accesses is approximately four-fold higher for AVG than for AVF (1,2).

A very promising surveillance method for predicting access stenosis and thrombosis is the monitoring of access blood flow (3). A noninvasive method implemented by a number of dialysis centers has been the ultrasound dilution method proposed initially by Krivitski (4–7), and shown to have robust accuracy for assessing access blood flow (6,8). To date, there have been several clinical trials of different sizes assessing the role of access blood flow monitoring and its impact on detecting stenosis and preventing thrombosis (9–15). However, such trials have shown conflicting results and have left many doubting the financial benefits of conducting access blood flow monitoring to lower the risk of access loss.

We, therefore, pooled the results of available randomized controlled trials (RCTs) published thus far that assessed the risk of access thrombosis using access blood flow monitoring. Our hypothesis was that hemodialysis access blood flow monitoring lowers the risk of thrombosis and that its impact on lowering that risk differed between AVG and AVF.

Methods

Data Sources, Searches, and Included Studies

We performed a systematic review of the available literature according to the Preferred Reporting

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Items for Systematic Reviews and Meta-Analyses (PRISMA (16)). An electronic search was conducted using the MEDLINE, EMBASE, and Cochrane Library databases from 1980 to 2014 for RCTs involving dialysis access blood flow measurement.

Our search terms included the following: (i) Surveillance of arteriovenous hemodialysis access and duplex and thrombosis; (ii) Hemodialysis access and RCT and flow; (iii) RCT and AVF and flow; (iv) RCT and hemodialysis access; and, (v) Hemodialysis access flow surveillance and randomized control and access flow or hemodialysis access flow surveillance or RCT of hemodialysis access flow surveillance and access flow or hemodialysis access thrombosis or surveillance and RCT. Three authors (TM, GC, and LS) also manually scanned the references in the relevant articles for cross-reference to other trials conducted, and also reviewed Clinicaltrials.gov. The eligibility criteria of studies included the following: (i) RCTs; (ii) English language; (iii) Access blood flow assessed either directly through ultrasound dilution or ultrasound Duplex methods; (iv) Hemodialysis access being a AVG or AVF, or both; (v) Thrombosis reported either as a primary or secondary outcome; and, (vi) Data available for extraction. Reviews, observational studies, and clinical trials that did not clearly define outcomes or that did not have thrombosis as an outcome were excluded.

Assessment of Quality and Data Extraction

We used the Consolidated Standards of Reporting Trials (CONSORT) check list to assess the quality of included trials (17). The quality of studies was based on the randomization, the blinding, the similarity of both groups at baseline, and eligibility criteria. The literature search yielded 879 articles. Initially, each abstract and when necessary each full article was reviewed for abstraction of RCTs by two authors (TM and GC). The interrater agreement was excellent with a kappa of 0.856. Disagreements on eligibility criteria for abstraction of a potential study were resolved by the consensus of three authors (TM, GC, and LS). Of those 879, 868 studies were not randomized or did not meet the inclusion criteria, which left 11 studies. However, four had no pertinent data. Thus, seven studies (9–15) were eligible for analysis (Fig. 1).

The study by Smits et al. (10) used access blood flow in two substudies (study A: venous pressure versus access blood flow; and study B: venous pressure versus access blood flow plus venous pressure) and consequently, it was separated in two studies. In the study by Ram et al. (11), the group that used ultrasound duplex without reporting the access blood flow was not included in the meta-analysis. All studies except Scaffaro et al. (15) used the ultrasound dilution method. Scaffaro et al. (15) estimated the access blood flow with the ultrasound duplex method applying the formula: $V = r^2 \times V_{\text{average}} \times 60$, where V indicated flow in milliliters per minute; r, ray of the segment; V_{average}, average of the velocity in centimeters per second; and 60, correction factor. All studies except Scaffaro et al. (15) had financial disclosures. Extracted data included type of access (AVG or AVF), the number of patients with thrombosis, and surveillance methods used for controls. We contacted authors of included studies to obtain unpublished data.

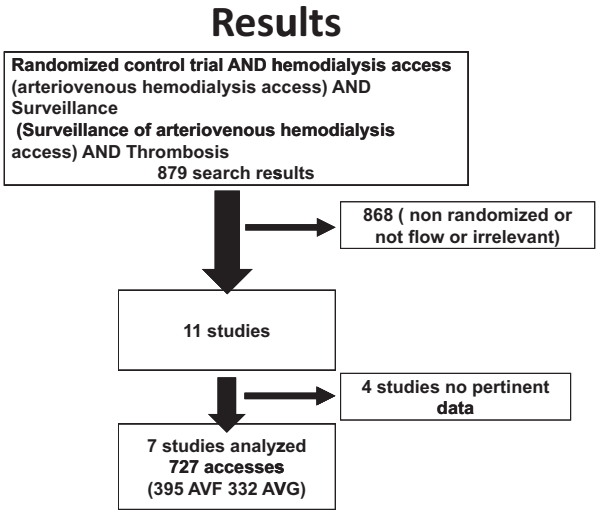

FIG. 1. Flow chart of the selection of studies.

Risk of Bias

The plan to minimize publication bias was to include also studies only published as abstracts; however, our search for abstracts of meetings did not provide any study with enough data for inclusion in this investigation. The extent to which the review of the MEDLINE, EMBASE, and Cochrane Library databases is free of bias and can draw a conclusion about the effect of hemodialysis access blood flow monitoring in the risk of thrombosis of AVG and AVF depends on whether the data and results from the included studies are valid.

Data Synthesis, Outcome, and Statistical Analysis

The outcome of interest was access thrombosis. Thrombosis could be either reported as the primary or secondary outcome in the studies. The control group was defined as the one that used clinical assessment (difficult cannulation, pulling clots during cannulation, prolonged bleeding after needle removal, aneurysm formation, extremity edema, recirculation, low urea reduction ratio or Kt/V), static venous pressure, or dynamic venous pressures of the access as surveillance methods. The access blood flow-monitoring group was defined as the one in which access blood flow measurements were additionally implemented using noninvasive ultrasound dilution or duplex methods.

We estimated the pooled risk ratio (RR) and the 95% confidence interval (CI) of thrombosis for the access blood flow-monitoring group compared to the control group. The statistical analysis was performed using both the fixed and random effects models; however, estimates were reported according to the effect quality test or the Cochran's Q test and the I^2 statistics that assessed for heterogeneity of studies gathered and estimate the percentage of variability across studies attributable to heterogeneity beyond chance (18). In a fixed-effects model, the assumption was made that there was one true effect size, which underlies all studies in the analysis and that differences in observed effects were due to sampling error. A random effects model assumes that the true effect varied from study to study, which makes the estimate of the pooled effect size more conservative (18). In a subgroup analysis, the pooled RR and 95% CI of thrombosis were estimated in subgroups or studies that either enrolled patients with only AVG or only AVF. Statistical analyses were done using the STATA 12.1 software package (StataCorp., College Station, TX, USA), and statistical significance was recorded with a p value < 0.05 or 95% CI that excluded 1.

All authors had full access to the data. All authors were responsible for the decision to submit the manuscript for publication.

Results

All studies combined included a total of 727 patients with hemodialysis vascular access of whom 395 had AVF and 332 had AVG. Sample size ranged from 51 to 137 patients in studies. Three studies consisted of only AVF and three consisted of only AVG, while one consisted of both type of accesses. Two studies (9,11) were done in the United States, one in Canada (12), one in Australia (14), one in Brazil (15), one in Italy (13), and one in the Netherlands (10).

All studies used clinical assessment during every dialysis treatment in both active and control groups. In the active group, the surveillance method of the access blood flow in six studies was ultrasound dilution (9–14), and one study used ultrasound duplex (15). In the control group, the surveillance method of the access in two studies was static pressure (9,10), two studies used dynamic venous pressure (10,12), and one study measured the velocity by ultrasound duplex (9). Table 1 included other important patient demographics such as age, sex, and history of diabetes.

Seventy six of 347 (21.9%) and 90 of 380 (23.7%) patients had hemodialysis access thrombosis in the access blood flow-monitoring and the control groups, respectively (Table 2). The estimated overall pooled RR of thrombosis was 0.87 (95% CI, 0.67–1.13) favoring access blood flow monitoring (Fig. 2). There was no significant heterogeneity (Q test χ^2 of 8.91 with 7 degrees of freedom $p = 0.26$) among studies that had mild variability (I^2 of 21.5%). The study by Tessitore et al. (13) had the highest fixed effect weight of 20.26% with the RR of 0.42 (95% CI, 0.20–0.86). In that study, the access blood flow-monitoring group compared to the control group had a significantly lower frequency of thrombosis (18.6% versus 44.4%, respectively). Overall, five studies showed benefit of access blood flow-monitoring versus control (9,10,12,13,15). The benefit was noted in three studies involving AVG (9,10,12) (Fig. 3) and in three studies involving AVF (9,13,15) (Fig. 4). In the subgroup of AVG, 52 of 163 (31.9%) and 51 of 169 (30.2%) patients had thrombosis in the access blood flow-monitoring and the control groups, respectively. In the subgroup of AVF, 24 of 184 (13%) and 39 of 211 (18.5%) patients had thrombosis in the access blood flow-monitoring and the control groups, respectively. The pooled RR of thrombosis were 1.06 (95% CI, 0.77–1.46) and 0.64 (95% CI, 0.41–1.01) in the subgroups of only AVG and only AVF, respectively. There was no significant heterogeneity among studies pooled in the AVG (Q test χ^2 of 1.64 with 4 degrees of freedom $p = 0.80$; I^2 of 0%) or AVF (Q test χ^2 of 3.23 with 3 degrees of freedom $p = 0.36$; I^2 of 7.2%) subgroups.

Discussion

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative recommends that access blood flow with ultrasound dilution be monitored monthly (3). In this meta-analysis, results showed that surveillance of hemodialysis vascular access with the additional use of access blood flow monitoring had a 13% lower risk of thrombosis, although its effect was not statistically significant (95% CI included 1). In the subgroup analysis, access blood flow-monitoring impact on the risk of thrombosis differed between AVG and AVF. In ESRD patients with AVG, the risk of thrombosis was 6% higher in those assigned to the access blood flow group compared to controls. In ESRD patients with AVF, the risk of thrombosis was 36% lower in those assigned to the access blood flow group compared to controls. However, these associations were not statistically significant. Subgroup analyses were in both cases underpowered and should be viewed cautiously and only as hypothesis-generating for future research.

The actual beneficial effect of access blood flow monitoring on the risk of thrombosis was smaller than the one predicted in the RCTs that clearly defined a beneficial effect with power calculations (10,12,13). Smits et al. (10) and Moist et al. (12) predicted that by measuring AVG blood flow, the expected risk of thrombosis would be 25–60%

TABLE 1. Important characteristics of included studies

Studies	Number of patients	Female/Male Number (%)	Diabetics Number (%)	Mean follow-up Days	Access blood flow cut off point ml/min and/or % change	Degree of stenosis for indication of percutaneous transcutaneous angioplasty	Methods and frequency of surveillance	
							Access flow group	Control group
Sands (9)	103	–	28	204–192	<750/20%	>50%	Clinical assessment every dialysis, ultrasound dilution monthly and ultrasound duplex every 6 months	Clinical assessment every dialysis, static venous pressure monthly, and ultrasound duplex every 6 months
Moist (12)	112	56/56	30	450	<650/20%	>50%	Clinical assessment and Ultrasound dilution monthly	Clinical assessment and dynamic venous pressure every dialysis
Ram (11)	66	42/24	31	450	<600/20%	>50%	Clinical assessment and ultrasound dilution monthly and ultrasound duplex every 3 months	Clinical assessment every dialysis
Polkinghorne (14)	137	44/93	43	660	<500/20%	>50%	Clinical assessment every dialysis and ultrasound dilution monthly	Clinical assessment every dialysis
Tessitore (13)	79	35/44	18	1800	<750/25%	>50%	Clinical assessment every dialysis and ultrasound dilution every 3 months	Clinical assessment every dialysis
Smits-study A (10)	51	24/27	11	225–312	<600/15%	>50%	Clinical assessment every dialysis and ultrasound dilution every 2 months	Clinical assessment every dialysis, dynamic and static venous pressures weekly
Scaffaro (15)	111	59/62	41	365	<500	>50%	Clinical assessment every dialysis and ultrasound duplex every 3 months	Clinical assessment every dialysis
Smits-study B (10)	68	37/31	11	186–252	<750/25%	>50%	Clinical assessment every dialysis, dynamic and static venous pressure weekly, and ultrasound dilution every 2 months	Clinical assessment every dialysis, dynamic and static venous pressures weekly

TABLE 2. Number of patients with events and thrombosis proportions stratifying by access blood flow-monitoring and control groups

	Access blood flow group		Control group	
All studies	Number with events/*N*	Thrombosis %	Number with events/*N*	Thrombosis %
Moist (12)	14/59	23.7	13/53	24.5
Ram (11)	17/32	53.1	16/34	47.1
Polkinghorne (14)	6/69	8.7	4/68	5.9
Tessitore (13)	8/43	18.6	16/36	44.4
Smits-study A (10)	4/27	14.8	4/24	16.7
Scaffaro (15)	9/53	17	14/58	24.1
Smits-study B (10)	16/37	43.2	10/31	32.3
Sands (9)	2/27	7.4	13/76	17.1
Sands subgroups[a]				
Sands only graft (9)	1/8	12.5	8/27	29.6
Sands only fistula (9)	1/19	5.3	5/49	10.2

[a]Sands' study included patients with both fistula and graft. *N* = number of patients used in denominator to calculated proportion of patients with thrombosis.

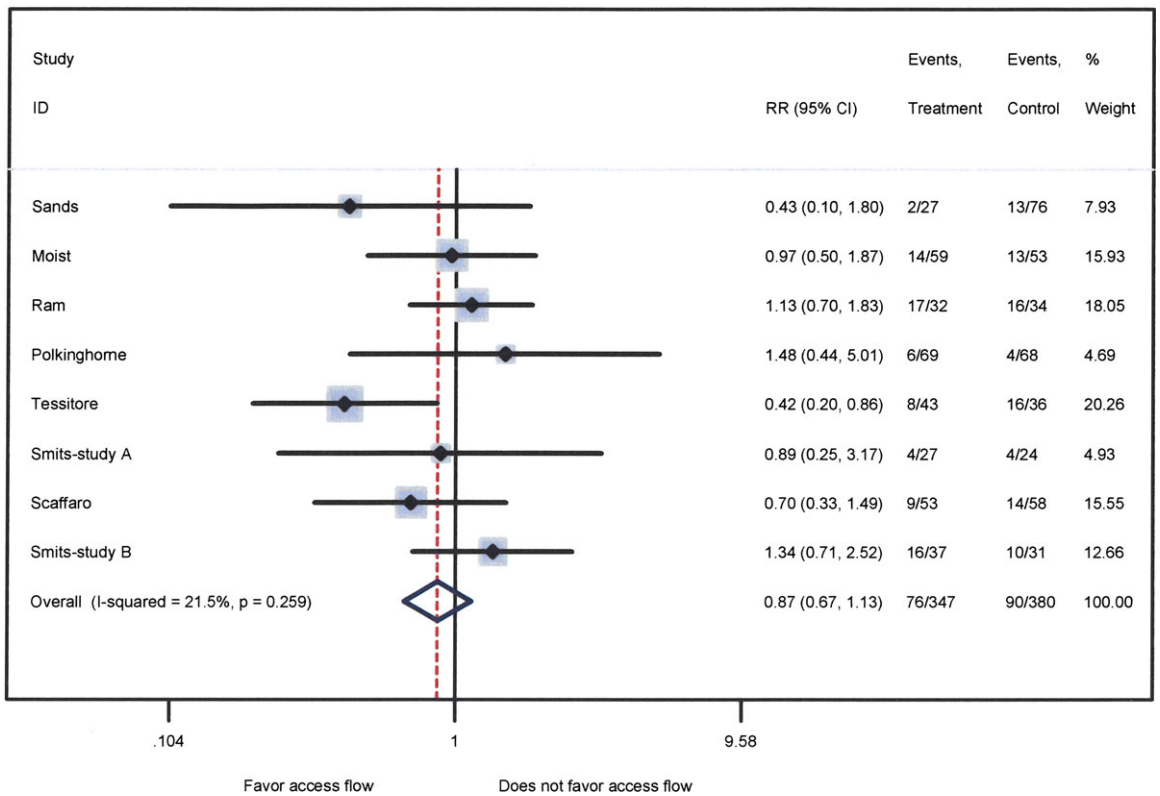

FIG. 2. The use of access blood flow monitoring and the risk of thrombosis in hemodialysis ESRD patients with graft or fistulas.

lower compared to controls monitored by measuring the dynamic and/or static venous pressures; however, the actual risk of thrombosis were 3% and 11% lower in the AVG blood flow group compared to controls group of the Smits-study A and Moist study, respectively (see Table 2). By contrast, the risk of thrombosis was 34% higher in the AVG blood flow group compared to controls of the Smits-study B (see Table 2). Tessitore et al. (13) predicted that with the measuring of AVF blood flow, the risk of thrombosis would be at least 200% lower compared to controls monitored by only clinical assessment; however, the actual risk of thrombosis was only 58% lower in the AVF blood flow group compared to controls (see Table 2).

There were important differences among the studies included in this meta-analysis. Trials had substantial discrepancy in the sample size; however, size did not appear to influence the result. It is notable that the only study that showed a significantly lower risk of thrombosis monitoring the access blood flow was the one with the smallest sample size (13). Among the two studies with the largest sample size, one showed a lower (12) but the other a higher (14) risk of thrombosis (both

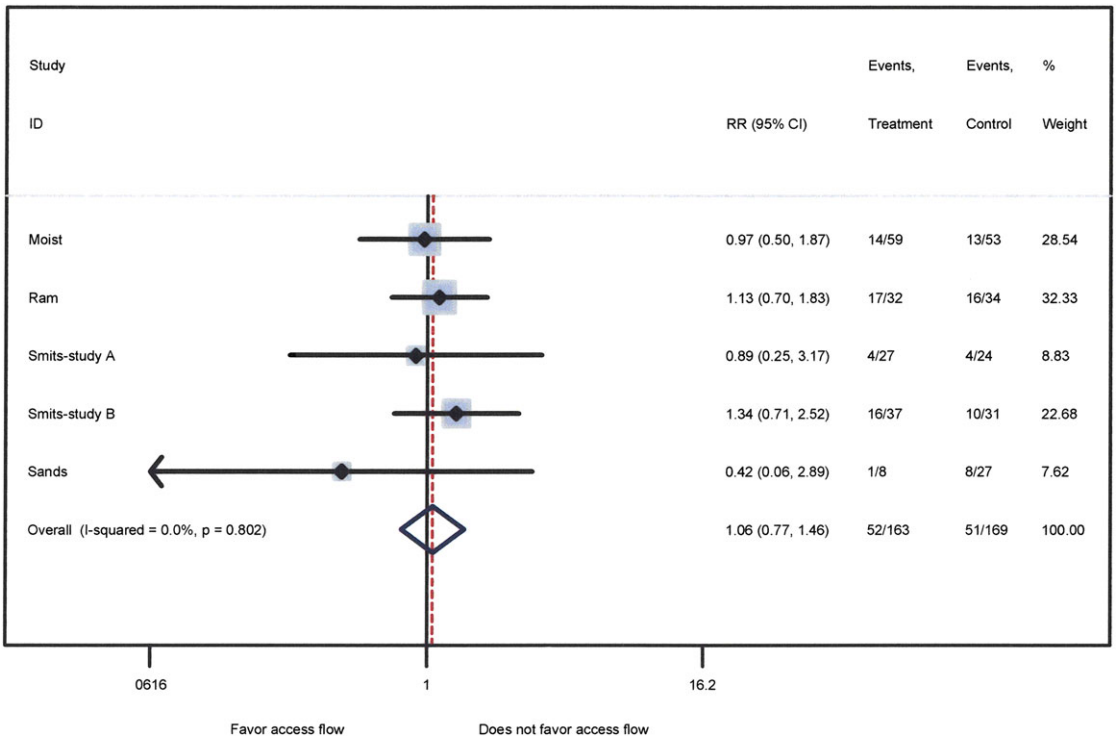

FIG. 3. The use of access blood flow monitoring and the risk of thrombosis in hemodialysis ESRD patients with grafts.

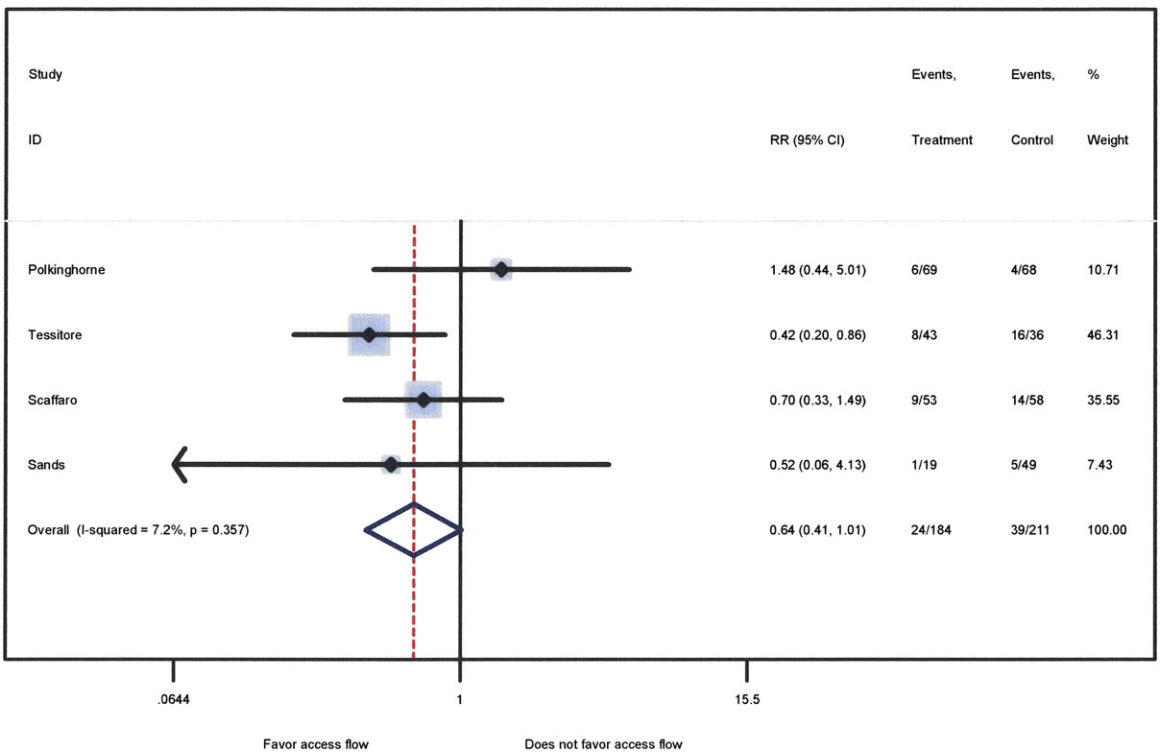

FIG. 4. The use of access blood flow monitoring and the risk of thrombosis in hemodialysis ESRD patients with fistulas.

nonsignificant effect) in the access blood flow group compared to controls. The proportion of thrombosis varied substantially between 5.3% and 53.1% among trials. The only appreciable association with thrombosis was a lower proportion in patients with AVF compared to those with AVG. It is important to also highlight that the frequency of the access blood flow monitoring varied from monthly to

thrice monthly among the trials (see Table 1). In only four studies (9,11,12,14), the access blood flow was monitored monthly as recommended by the Kidney Disease Outcomes Quality Initiative guidelines (3).

Our study has limitations worth mentioning. This meta-analysis is limited to only seven trials and the sample size limited the power to detect small differences, particularly in the subgroup comparisons. We only screened trials published in the English language which might have limited our access to other studies published in other languages. We limited our analysis to assessing the risk of thrombosis without assessing the risk of stenosis when comparing different vascular access surveillance methods; however, thrombosis is a "hard" outcome that is free of ascertainment bias or diagnostic interpretation as stenosis may be. Our meta-analysis is also limited by the strength of included studies; however, we only included RCTs, excluding observational studies of lower strength and a higher chance of overestimating the true effect.

Conclusion

The benefit of AV access surveillance using access blood flow monitoring to lower the risk of thrombosis is uncertain and varies substantially between AVG and AVF. No consensus can be reached regarding the utility of access blood flow monitoring to predict stenosis of hemodialysis vascular accesses. With vascular access-related morbidity accounting for up to 50% of total dialysis patient costs (19,20), it will be important to conduct well-powered multicenter randomized trials that compare the different methods of surveillance to lower the risk of vascular access stenosis and thrombosis, preventing hemodialysis access loss.

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References

1. Allon M: Current management of vascular access. *Clin J Am Soc Nephrol* 2:786–800, 2007
2. Allon M, Robbin ML: Increasing arteriovenous fistulas in hemodialysis patients: problems and solutions. *Kidney Int* 62:1109–1124, 2002
3. Clinical practice guidelines for vascular access: *Am J Kidney Dis* 48 (Suppl 1):S176–S247, 2006
4. Krivitski NM: Theory and validation of access flow measurement by dilution technique during hemodialysis. *Kidney Int* 48:244–250, 1995
5. Krivitski NM: Novel method to measure access flow during hemodialysis by ultrasound velocity dilution technique. *ASAIO J* 41: M741–M745, 1995
6. Krivitski NM, MacGibbon D, Gleed RD, Dobson A: Accuracy of dilution techniques for access flow measurement during hemodialysis. *Am J Kidney Dis* 31:502–508, 1998
7. Krivitski NM, Starostin D, Smith TL: Extracorporeal recording of mouse hemodynamic parameters by ultrasound velocity dilution. *ASAIO J* 45:32–36, 1999
8. Lindsay RM, Bradfield E, Rothera C, Kianfar C, Malek P, Blake PG: A comparison of methods for the measurement of hemodialysis access recirculation and access blood flow rate. *ASAIO J* 44:62–67, 1998
9. Sands JJ, Jabyac PA, Miranda CL, Kapsick BJ: Intervention based on monthly monitoring decreases hemodialysis access thrombosis. *ASAIO J* 45:147–150, 1999
10. Smits JH, van der Linden J, Hagen EC, Modderkolk-Cammeraat EC, Feith GW, Koomans HA, van den Dorpel MA, Blankestijn PJ: Graft surveillance: venous pressure, access flow, or the combination? *Kidney Int* 59:1551–1558, 2001
11. 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* 64:272–280, 2003
12. Moist LM, Churchill DN, House AA, Millward SF, Elliott JE, Kribs SW, DeYoung WJ, Blythe L, Stitt LW, Lindsay RM: Regular monitoring of access flow compared with monitoring of venous pressure fails to improve graft survival. *J Am Soc Nephrol* 14:2645–2653, 2003
13. Tessitore N, Lipari G, Poli A, Bedogna V, Baggio E, Loschiavo C, Mansueto G, Lupo A: 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* 19:2325–2333, 2004
14. 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* 21:2498–2506, 2006
15. Scaffaro LA, Bettio JA, Cavazzola SA, Campos BT, Burmeister JE, Pereira RM, Barcellos CS, Caramori P: Maintenance of hemodialysis arteriovenous fistulas by an interventional strategy: clinical and duplex ultrasonographic surveillance followed by transluminal angioplasty. *J Ultrasound Med* 28:1159–1165, 2009
16. Moher D, Liberati A, Tetzlaff J, Altman DG: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 151: 264–269; w264, 2009
17. Schulz KF, Altman DG, Moher D: CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 340: c332, 2010
18. Higgins JPT, Thompson SG, Deeks JJ, Altman DG: Measuring inconsistency in meta-analyses. *BMJ* 327:557–560, 2003
19. McCarley P, Wingard RL, Shyr Y, Pettus W, Hakim RM, Ikizler TA: Vascular access blood flow monitoring reduces access morbidity and costs. *Kidney Int* 60:1164–1172, 2001
20. Besarab A: Access monitoring is worthwhile and valuable. *Blood Purif* 24:77–89, 2006