FLOW: Flow dysfunction of hemodialysis vascular access: a randomized controlled trial on the effectiveness of surveillance of arteriovenous fistulas and grafts

Zomer, B.; Ruiter, M.S.; Dekker, F.W.; Goertz, E.G.; Haan, M.W. de; Hemmelder, M.H.; ... ; FLOW Study Grp

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Bianca Zomer[1,2], Matthijs S Ruiter[3], Friedo W Dekker[4], Ellen GD Goertz[2], Michiel W de Haan[5], Marc HH Hemmelder[1], Mickaël JC Hiligsmann[6], Wanda S Konijn[7], Magda M van Loon[2], José MC Maessen[8], Barend ME Mees[2], Joris I Rotmans[9], Geert WH Schurink[2], Marie-José JPJ Vleugels[2] and Maarten GJ Snoeijs[2], on behalf of the FLOW study group

Abstract

Introduction: It is assumed that identification and correction of asymptomatic stenoses in the vascular access circuit will prevent thrombosis that would require urgent intervention to continue hemodialysis treatment. However, the evidence base for this assumption is limited. Recent international clinical practice guidelines reach different conclusions on the use of surveillance for vascular access flow dysfunction and recommend further research to inform clinical practice.

Methods: The FLOW trial is a double-blind, multicenter, randomized controlled trial with a 1:1 individual participant treatment allocation ratio over two study arms. In the intervention group, only symptomatic vascular access stenoses detected by clinical monitoring are treated, whereas in the comparison group asymptomatic stenoses detected by surveillance using monthly dilution flow measurements are treated as well. Hemodialysis patients with a functional arteriovenous vascular access are enrolled. The primary outcome is the access-related intervention rate that will be analyzed using a general linear model with Poisson distribution. Secondary outcomes include patient satisfaction, access-related serious adverse events, and quality of the surveillance process. A cost effectiveness analysis and budget impact analysis will also be conducted. The study requires 828 patient-years of follow-up in 417 participants to detect a difference of 0.25 access-related interventions per year between study groups.

Discussion: As one of the largest randomized controlled trials assessing the clinical impact of vascular access surveillance using a strong double-blinded study design, we believe the FLOW trial will provide much-needed evidence to improve vascular access care for hemodialysis patients.

Keywords

Vascular access, hemodialysis, follow up, surveillance, monitoring

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[1]Department of Internal Medicine, Division of Nephrology, Maastricht University Medical Centre, Maastricht, Limburg, The Netherlands
[2]Department of Vascular Surgery, Maastricht University Medical Centre, Maastricht, Limburg, The Netherlands
[3]Kennisinstituut, Federation Medical Specialists, Utrecht, The Netherlands
[4]Department of Clinical Epidemiology, Leids University Medical Centre, Leiden, The Netherlands
[5]Department of Radiology, Maastricht University Medical Centre, Maastricht, Limburg, The Netherlands
[6]Department of Health Services Research, CAPHRI Care and Public Health Research Institute, Maastricht University, Maastricht, Limburg, The Netherlands
[7]Nierpatienten Vereniging Nederland, Bussum, The Netherlands
[8]CAPHRI Care and Public Health Research Institute, Maastricht University, Maastricht, Limburg, The Netherlands
[9]Department of Internal Medicine, Division of Nephrology, Leids University Medical Centre, Leiden, The Netherlands

Corresponding author:
Bianca Zomer, Department of Internal Medicine, Division of Nephrology, Maastricht University Medical Centre, PO Box 5800, Maastricht, Limburg 6202 AZ, The Netherlands.
Email: bianca.zomer@mumc.nl

Introduction

Each year, a million interventions are performed worldwide to maintain the vascular access of patients with end-stage renal disease.[1] The vast majority of these procedures are percutaneous balloon angioplasties done to correct vascular access stenosis causing flow dysfunction. The angioplasties may be prompted either by clinical signs of flow dysfunction, such as the inability to achieve sufficient blood flow to the dialysis machine, or by hemodynamic evidence of stenosis without clinical signs, such as a reduction of blood flow through the vascular access. It is assumed that identification and correction of these asymptomatic stenoses will prevent access thrombosis that would require urgent intervention to continue hemodialysis treatment. However, the evidence for this assumption is limited. Recent international clinical practice guidelines reach different conclusions on the use of surveillance for vascular access flow dysfunction and recommend further research to inform clinical practice (Table 1).

Meta-analysis of randomized controlled trials on vascular access surveillance

Search strategy

In a Cochrane systematic review of randomized controlled trials on vascular access surveillance for hemodialysis patients, 14 trials with 1390 participants were identified.[2] The literature search for this review was done on October 15, 2015 and we updated this search using the same search strategy on February 9, 2020. We found 220 hits on CENTRAL, 1416 hits on EMBASE, and 523 hits on MEDLINE. After review of title and abstract, eight full text papers and three entries in clinical trial registries were included for further study. Of the full text papers, we found one randomized controlled trial that was published after the literature search for the Cochrane systematic review.[3] The guidelines from the European Renal Association also updated the Cochrane systematic review and found the same additional randomized controlled trial.[4]

Meta-analysis of randomized controlled trials

Of the 15 randomized controlled trials on the effectiveness of vascular access surveillance, five trials studied only patients with a hemodynamically significant vascular access stenosis diagnosed by duplex ultrasound or angiography. We excluded these trials because their study design does not address the question whether periodic follow-up to detect asymptomatic stenosis is effective in preventing access complications. We did a meta-analysis including the remaining 10 trials with 1281 patients (758 grafts and 523 fistulas) and studied vascular access thrombosis, vascular access loss, and intervention rate as relevant outcomes (Figures 1–3).[3,5–13] In a random effects model, the effect size differed between fistulas and grafts. For fistulas, vascular access surveillance reduced the risk of access loss (RR 0.50, 95% CI: 0.28–0.89; based on 46 events), with a trend toward reduced risk of access thrombosis (RR 0.57, 95% CI: 0.31–1.05; based on 61 events). For grafts, vascular access surveillance had no effect on access loss (RR 0.85, 95% CI: 0.65–1.11; based on 53 events) or access thrombosis (RR 0.96, 95% CI: 0.79–1.15; based on 231 events). Vascular access surveillance tended to increase the rate of access-related interventions 1.21 (95% CI: 0.95–1.54) times, with substantial statistical heterogeneity between the included studies.

Interpretation

The trials in the meta-analysis had important clinical heterogeneity, in particular with regards to the protocols for assessment of the vascular access and the threshold for referral to correct a suspected stenosis (Table 2). These protocols were not always applicable to international standards of care. For example, the finding that surveillance prevents fistula loss was based on two trials that both used duplex ultrasound examinations, whereas surveillance is often done with flow measurements using dilution techniques. Furthermore, in all but one trial some form of surveillance was done in the control group to detect and treat access stenosis without clinical signs of

Table 1. Summary of international guidelines.

Guideline	Fistula	Graft
European Society for Vascular Surgery[23]	Recommend to do periodic access flow measurements and suggest to take action when flow in arteriovenous fistulas is <500 mL/min	Advise against duplex ultrasound surveillance and pre-emptive correction of stenosis in arteriovenous grafts
European Renal Association[4]	Suggest that the evidence for surveillance of arteriovenous fistulas is inconclusive and requires more research	Suggest against surveillance of arteriovenous grafts unless it occurs in the context of a clinical study
US National Kidney Foundation (KDOQI)[22]	Inadequate evidence on routine surveillance of arteriovenous fistulas	Suggest against surveillance of arteriovenous grafts

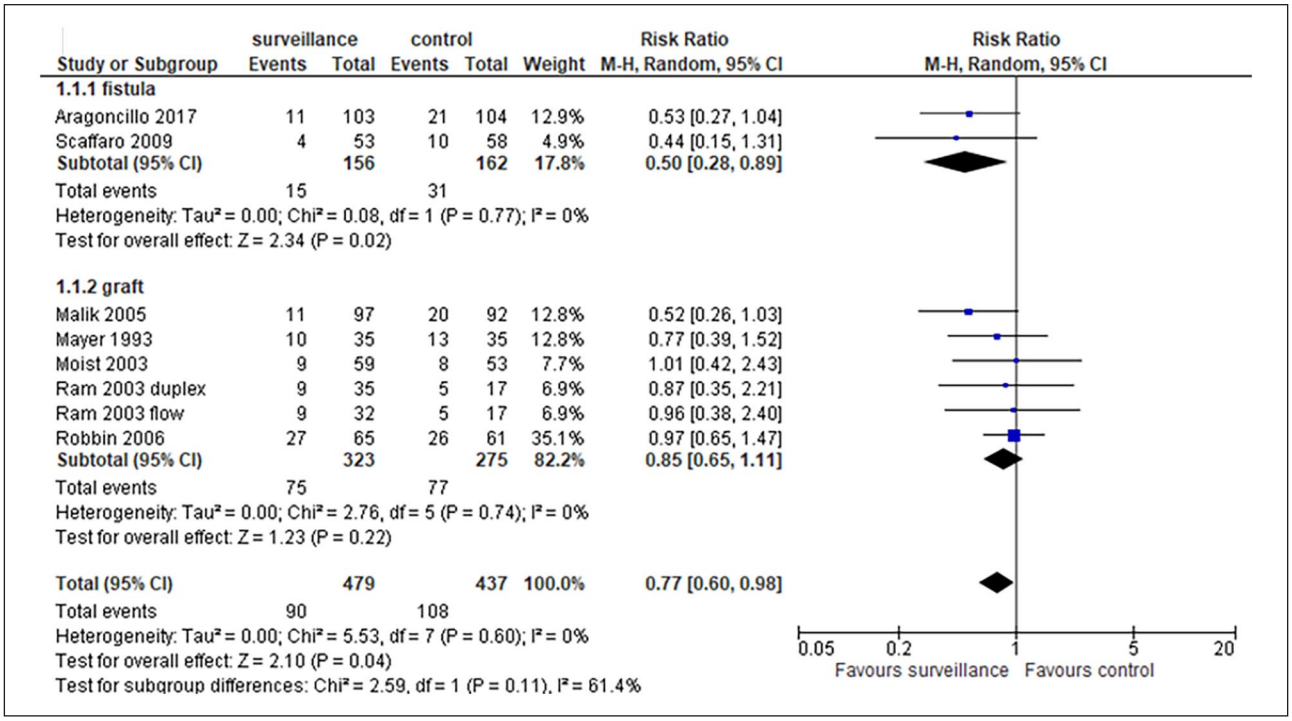

Figure 1. Vascular access loss with surveillance and pre-emptive correction versus treatment of stenosis based on clinical indicators.
Z: *p*-value of pooled effect; df: degrees of freedom; I^2: statistical heterogeneity; CI: confidence interval.
Mantel-Haenszel statistics, random effects model.

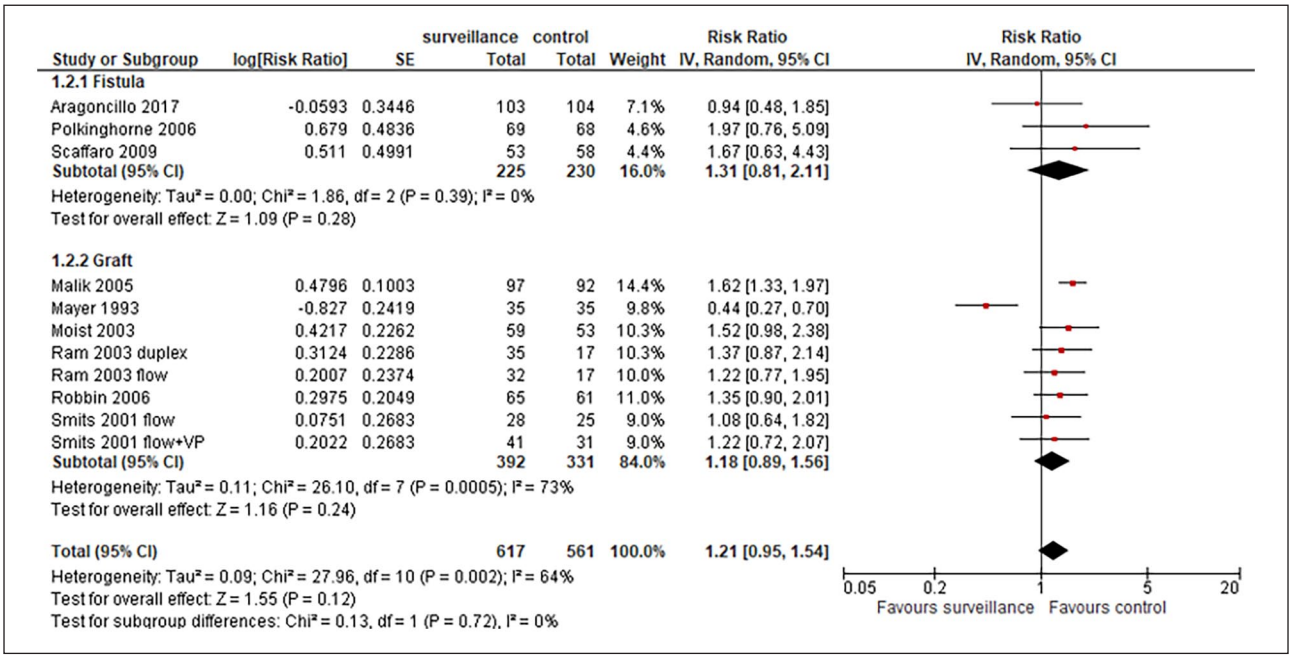

Figure 2. Intervention rate with surveillance and pre-emptive correction versus treatment of stenosis based on clinical indicators.
Z: *p*-value of pooled effect; df: degrees of freedom; I^2: statistical heterogeneity; CI: confidence interval; SE: standard error.
Inverse Variance statistics, random effects model.

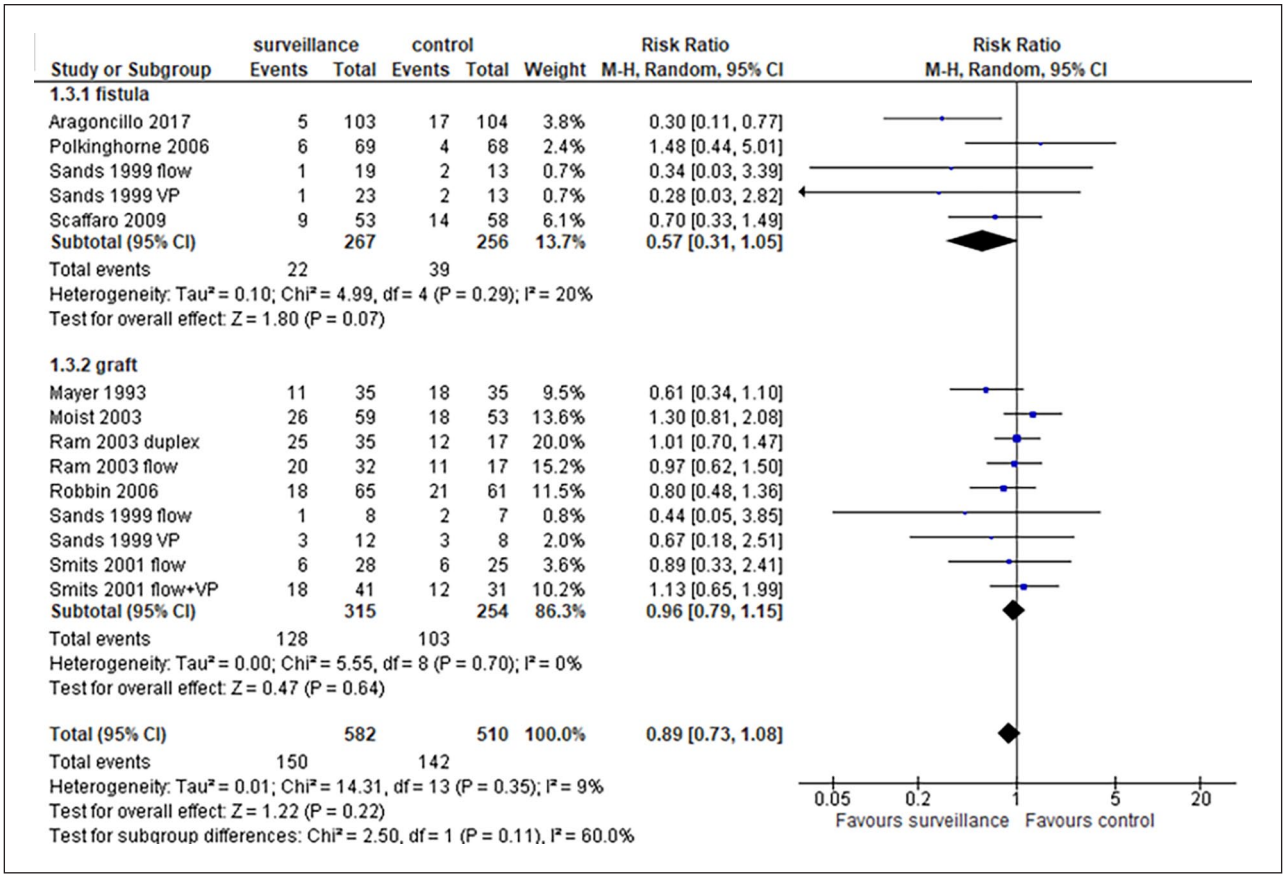

Figure 3. Thrombosis with surveillance and pre-emptive correction versus treatment of stenosis based on clinical indicators.
Z: *p*-value of pooled effect; df: degrees of freedom; I^2: statistical heterogeneity; CI: confidence interval.
Mantel-Haenszel statistics, random effects model.

flow dysfunction. This approach may well have reduced any beneficial effects of vascular access surveillance in the intervention group. We conclude that the currently published randomized controlled trials provide insufficient evidence for the effectiveness of vascular access surveillance by flow measurements using dilution techniques. This conclusion is in line with the findings of the largest observational study on vascular access surveillance that reported similar vascular access survival in patients who were or were not referred for angioplasty based on access flow measurements (HR 1.02, 95% CI: 0.96–1.08) with some patient subgroups having positive effects and other subgroups having negative effects of preemptive correction of vascular access stenosis.[14]

Rationale

The FLOW trial aims to define the best the vascular access follow-up strategy. In current clinical care, vascular access flow is periodically assessed to detect and treat asymptomatic stenosis. The FLOW trial will determine whether it is safe to abandon this practice of active surveillance. Vascular access stenosis will then be treated only when clinical problems of flow dysfunction occur during hemodialysis. This would reduce access-related interventions and lower health care costs.

Diagnostic performance of surveillance strategies may vary according to vascular access type and stenosis location.[15] We chose vascular access flow measurements using ultrasound dilution as the surveillance strategy because it can be conveniently measured during hemodialysis sessions and because flow reductions occur independently of the stenosis location. Surveillance based on dynamic or static blood pressure in the vascular access will only detect venous outflow stenosis,[15] whereas flow measurements using duplex ultrasound are typically done in the vascular laboratory outside the dialysis unit.

Methods

Study design

We conduct a double-blind, multicenter randomized controlled trial with a superiority framework and a 1:1 individual participant treatment allocation ratio over two study arms (Figure 4). In the intervention group, only symptomatic vascular access stenosis detected by clinical monitoring is treated, whereas in the comparison group asymptomatic

Table 2. Summary of randomized controlled trials on vascular access surveillance.

	N	Access	Inclusion	Exclusion	Referral criteria in surveillance group	Referral criteria in control group
Mayer, 1993	70	Graft			Duplex at 3, 6, 18 months	Clinical examination at 3, 6, 18 months
Sands, 1999	15/32	Graft/Fistula			Flow volume <750 mL/min measured every month, or duplex	Duplex every 6 months with referral at >50% stenosis and flow volume <800 mL/min for
	20/36	Graft/Fistula			Static venous pressure ratio >0.5 measured every month, or duplex	AVG and <600 mL/min for AVF or >25% decrease
Smits, 2001	53	Graft			Flow volume <600 mL/min every 2 months (every month with flow volume 600–800 mL/min)	Dynamic venous pressure >150 mmHg and/or static venous pressure to MAP ratio >0.5 at three consecutive sessions measured
	72	Graft			Flow volume <600 mL/min every 2 months (every month with flow volume 600–800 mL/min), or venous pressures	Every week
Moist, 2003	112	Graft	Flow volume >650 mL/min	Clinical or functional abnormality	Flow volume <650 mL/min or >20% decrease from baseline measured every month, or clinical signs	Clinical signs: abnormal physical examination or dynamic venous pressure >125 mmHg for Baxter and >140 mmHg for Gambro machines at three consecutive sessions
Ram, 2003	49	Graft			Flow volume <600 mL/min measured every month, or clinical signs	Clinical signs: circuit flow not attained, excessive bleeding, arm swelling, or high
	52	Graft			Duplex with >50% diameter reduction measured every 3 months, or clinical signs	dynamic venous pressure
Malik, 2005	189	Graft	Newly implanted grafts		Duplex with PSV-ratio >2 or >25%decrease flow volume, or <2 mm luminal diameter measured every 3 months (4–6 weeks with indeterminate findings and 4 months with normal findings)	Physical signs; dynamic venous pressure >140 mmHg or increasing trend; abnormal recirculation; unexplained reduction in dialysis dose; of flow volume <600 mL/min or >25% decrease
Robbin, 2006	126	Graft	>3 months dialysis; AVG 1–24 months old	Waiting for living kidney transplantation; severe or unstable medical illness; intervention in previous month of planned intervention	Duplex with PSV-ratio >2 measured every 4 months, or clinical signs	Clinical signs: physical examination (absent thrill, abnormal auscultation, or edema); abnormalities during dialysis (difficulty in cannulation, aspiration of cloths, inability to achieve circuit flow, or bleeding >30 min); or sustained fall in Kt/V > 0.2
Polkinghorne, 2006	137	Graft	>3 months dialysis; flow volume >500 mL/min; adults	Waiting for living kidney transplantation; home hemodialysis	Flow volume <500 mL/min or >20% decrease below 1 L/min measured every month, or clinical signs	Clinical signs: stenosis at clinical examination, dynamic venous pressure >150 mmHg, reduced circuit flow, excessive bleeding, reduction in urea reduction ratio
Scaffaro, 2009	111	Fistula		Clinical or functional abnormality	Duplex with >50%diameter reduction or <500 mL/min measured every 3 months, or clinical signs	Clinical signs (referral when two signs present): reduces thrill; extensive hematoma formation or edema for 3 weeks; dialysis circuit flow volume <300 mL/min during three consecutive sessions; dynamic venous pressure >150 mmHg during three consecutive sessions
Aragoncillo, 2017	207	Fistula	>3 months functional access	Coagulopathy or hemoglobinopathy; hospitalization in last month; access complications or dysfunction in last 3 months	Flow volume <500 mL/min or >25% reduction compared to previous measurement or duplex with >50% diameter reduction and PSV >400 cm/s or PSV-ratio >3 measured every 3 months, or clinical signs	Clinical signs; dynamic venous pressure >25% increase; dialysis circuit flow volume >25% decrease; Kt/V >0.2 decrease; recirculation >10%; prolonged bleeding or cannulation problems in three consecutive sessions

stenosis detected by surveillance is treated as well (current standard of care in the Netherlands). Hemodialysis patients with a functional arteriovenous vascular access are eligible to participate in the trial. Inclusion and exclusion criteria are listed in Table 3. Patients will be followed for a minimum of 2 years and a maximum of 3 years (follow-up will end for all participants when the last included patient will reach a 2 year follow-up period) and will be censored when their mode of renal replacement therapy is changed to kidney transplantation, peritoneal dialysis, or conservative treatment. The study will be conducted according to the principles of the Declaration of Helsinki (Brazil 2013) and has been approved by the institutional review board (METC azM/UM 21-004). The Dutch Renal Patients Society was involved in the study design.

Vascular access monitoring

Dialysis nurses routinely perform a physical examination including inspection, palpation, and auscultation of the vascular access before cannulation and report their findings along with details on the dialysis session in standardized electronic patient records. Patients with clinical signs of flow dysfunction (Table 4) are discussed within the vascular access team and referred for correction of the underlying stenosis on a weekly basis. Electronic patient records are uploaded to the study database once weekly and notifications are sent to remind dialysis nurses when clinical signs of flow dysfunctions have been reported.

Vascular access surveillance and maintenance of double-blind study design

In both study groups, vascular access blood flow will be measured by ultrasound dilution using the HD03 Hemodialysis Monitor (Transonic Inc., Ithaca, NY) by dialysis nurses every month. Measurements will be done according to the instructions for use, that is, with needle tips placed more than 6 cm apart and the arterial cannula preferably in retrograde position, with 10 mL saline injected in 3–5 s at dialysis circuit flow volumes of 250–350 mL/min, and with measurements done in triplicate in the first hour of the dialysis session. We chose monthly intervals because vascular access stenosis tends to progress rapidly,[16] and we set the threshold to trigger referral for angioplasty at a vascular access flow of 500 mL/min. Although surveillance protocols vary substantially between dialysis units, this surveillance frequency and intervention threshold is commonly used.

The software of the HD03 Hemodialysis Monitor is adjusted to allow blinded measurements that will be sent to the trial coordinator as encrypted data; patients, health care providers, and trial coordinators remain unaware of surveillance findings. Because low flow may be caused by accidental hemodynamic instability or poor needle positioning, dialysis nurses will be automatically notified to repeat measurements of access flow below 500 mL/min at the next dialysis session. Another patient with normal vascular access flow will be randomly selected for a repeat flow measurement to maintain blinding. For patients randomized to the surveillance group, dialysis nurses will be notified when the repeated measurement confirms vascular access flow below 500 mL/min. For patients randomized to the intervention group, vascular access flow will not be disclosed and therefore will not be used for clinical decision-making.

When dialysis nurses are notified of vascular access flows below 500 mL/min, patients and health care providers may become aware of treatment assignment to the surveillance group. To solve this methodological problem, patients will be randomized anew following an intervention for flow dysfunction, as soon as the indicator for vascular access intervention has been resolved and vascular access function has been restored. In case these criteria are not met, patients will remain in the same study group. This trial design maintains blinding during vascular access follow-up and results in a hybrid parallel-crossover design with a proportion of patients contributing follow-up time to both study groups.[17]

Treatment of vascular access stenosis

In both study groups, correction of vascular access stenosis will take place according to local practice at the study site. This strategy may include preoperative confirmation and localization of the stenosis (defined as $>$50% lumen diameter reduction and peak systolic velocity ratio $>$2 in the venous outflow and $>$3 at the arteriovenous anastomosis) by duplex ultrasound examination. However, flow measurements using ultrasound dilution and clinical signs of flow dysfunction continue to guide the decision to intervene. Alternatively, patients may be referred for diagnostic angiography with immediate treatment of vascular access stenosis by balloon angioplasty. Vascular access stenosis should be corrected within 1 week of its detection to reduce the risk of thrombosis while awaiting treatment. Vascular access flow will be measured to confirm the hemodynamic effects of the intervention within 1 week after correction of the stenosis.

Primary endpoint

The primary outcome is the access-related intervention rate, in line with the recently accepted core outcome measure for hemodialysis vascular access.[18] This core outcome measure includes all endovascular interventions, open surgical procedures, and central venous catheter interventions. Interventions that are done under general anesthesia or that require hospital admission of more than 1 day are scored as major interventions,

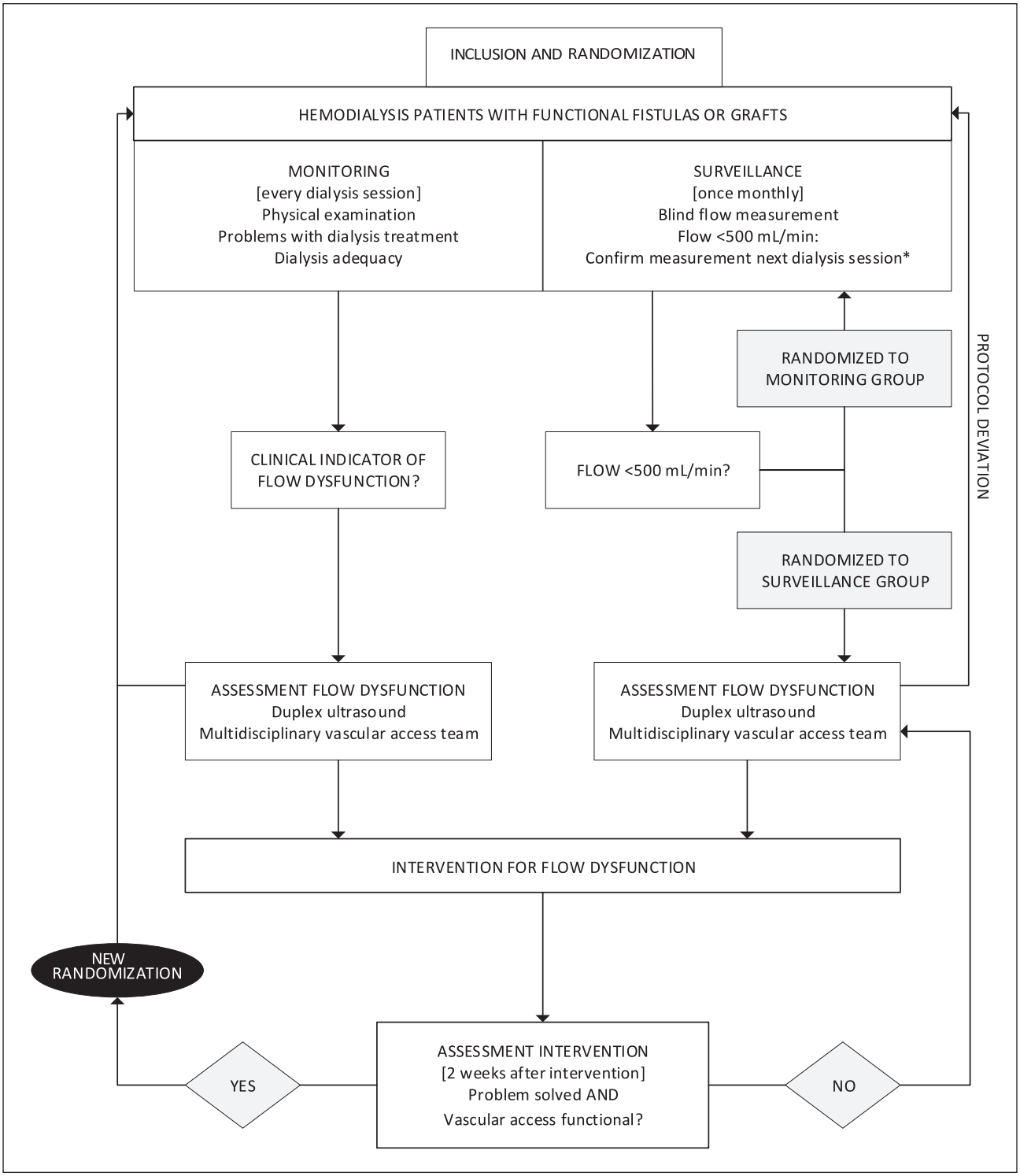

Figure 4. Flowchart.
* For each repeat measurement, an additional patient with flow >500 mL/min is randomly selected for a repeat measurement to maintain the blind.

whereas interventions under local or locoregional anesthesia as day-case or office procedures are scored as minor interventions. Access-related complications that are resolved using conservative or pharmacological treatment are not considered as interventions.

Secondary endpoints

- All access-related complications that require pharmacological treatment, including blood transfusions and central venous catheter thrombolysis.

Table 3. Eligibility criteria.

Inclusion criteria	Exclusion criteria
Adult patients aged 18 years or older	History of thrombosis of the current vascular access in the past year
End-stage renal disease with unlikely recovery of kidney function according to the attending nephrologist	Planned access-related intervention
Arteriovenous fistula or arteriovenous graft as hemodialysis vascular access that fulfils both of the following criteria at the time of trial enrollment: • Access flow volume of at least 500 mL/min; and • Functional: the vascular access was cannulated with two needles and achieved the prescribed access circuit flow in at least six dialysis sessions over the past 30 days. Patients who have single needle hemodialysis for reasons other than vascular access dysfunction (e.g. for nocturnal hemodialysis) but who can be cannulated with two needles for flow measurements and fulfill the other requirements for a functional vascular access can be enrolled as well.	Arteriovenous fistulas with multiple venous outflow paths upstream of the cannulation sites, that are not suitable for flow volume measurements using dilution techniques (e.g. Gracz fistulas and Ellipsys or WavelinQ endovascular fistulas)
Planning to remain in one of the participating dialysis centers for at least 1 year	Home hemodialysis
	Living donor kidney transplantation, switch to peritoneal dialysis, or switch to home hemodialysis planned within 6 months
	Life expectancy of less than 6 months, in the opinion of the attending nephrologist
	Unable to provide informed consent

Table 4. Clinical signs of flow dysfunction.

Physical signs	Weak and/or discontinuous thrill with only a systolic component
	High pitched and/or discontinuous bruit with only a systolic component
	Hyperpulsatile vascular access without venous collapse on arm elevation
	Weak vascular access with poor pulse augmentation at venous outflow compression
	New difficulty with cannulation when previously not a problem
Recurrent problems during dialysis (occurring in at least two dialysis sessions within 2 weeks)	Inability to achieve the target dialysis blood flow at a minimal arterial pressure of −250 mmHg and/or a maximal venous pressure of +250 mmHg when using 16 G or larger needles
	Prolonged bleeding beyond usual for that patient from the needle puncture sites
Unexplained, sustained fall in dialysis adequacy	eKt/V $<$1.2 or a decline $>$0.2 (measured every 3 months, with confirmation in the week after measuring a fall in dialysis adequacy; or, when using online clearance monitoring, measured in at least 2 dialysis sessions within 2 weeks)
	Urea reduction ratio $<$65% or decline $>$15% (measured every month, with confirmation in the week after measuring a fall in dialysis adequacy)

- Access-related health costs. Medical costs will be derived from hospital registration systems at the individual participant level and a study-specific adaptation of the Medical Consumption Questionnaire (MCQ). The Productivity Cost Questionnaire (PCQ) will be used to capture the societal costs.
- Patient-reported outcome measures. Short-Form Vascular Access Questionnaire (SF-VAQ) and 5-Level EuroQol 5-Dimensional questionnaire (EQ-5D-5L) are used. SF-VAQ was developed to measure hemodialysis patients' satisfaction with their vascular access.[19] EQ-5D-5L was developed to measure health-state utility values. All questionnaires are filled out at baseline and every 3 months during the follow-up period.
- Quality of the surveillance program by assessing repeatability and reproducibility of vascular access flow measurements using ultrasound dilution, diagnostic accuracy of vascular access flow measurements to predict clinical signs of flow dysfunction and access thrombosis within 1 month in the intervention group, the proportion of percutaneous balloon angioplasties resulting in technical success (residual stenosis $<$30%) and clinical success

(increase in vascular access flow to >500 mL/min, restoration of vascular access function, and resolution of any clinical signs of flow dysfunction), vascular access patency after balloon angioplasty, and adherence to the study protocols for vascular access follow-up and referral to correct vascular access stenosis.

Sample size estimation

The FLOW trial aims to detect an absolute difference in intervention rate of 0.25 per year between study groups in a superiority analysis. This difference is associated with the economically relevant effect of saving approximately 1 million euros per year at a 75% implementation rate in the Netherlands. The minimal clinically relevant difference in the intervention rate remains to be defined for this core outcome measure, but will likely be greater than 0.25 per year. Assuming an average of 1.77 interventions per patient-year[1] and a drop-out rate of 20% per year due to death or kidney transplantation, a total follow-up time of 828 patient-years (414 patient-years in each treatment arm) achieves 80% power to detect a 0.25 decrease in the intervention rate between the study groups using a two-sided, large-samples z-test of the Poisson event-rate difference at a significance level of 0.05.[20] With a variable follow-up time of a minimum of 2 years and a maximum of 3 years, we expect to achieve this follow-up time with 417 participants.

Data analysis plan

The intervention group will be compared to the control group. Analyses will be stratified for treatment center and for vascular access type (graft vs fistula) and will be based on the intention to treat population. A comparison of included and excluded patients is done to provide insight into the external validity of the clinical trial. The primary outcome (access-related intervention rate) will be analyzed using a general linear model with Poisson distribution and identity link, and with time as off-set variable. Subgroup analysis will be done for patient with arteriovenous fistulas and grafts.

An interim analysis for safety will be done when 72 access-related serious adverse events (including vascular access thrombosis) have taken place. This would lead to sufficient power to show non-inferiority with regards to access-related serious adverse events at a margin of 0.5 events per patient-year with a power of 90%. The rate of access-related serious adverse events will be analyzed using general linear models with Poisson distribution, and mortality will be analyzed using Cox regression. The interim analysis will be used by the Data Safety Monitoring Board to issue recommendations with regards to study continuation.

Health economic evaluation

A cost effectiveness analysis and a budget impact analysis will be done to gain insight into the health economics impact when vascular access surveillance programs for hemodialysis patients are abandoned. For the trial-based cost effectiveness analysis, we will consider sphere societal perspective in line with the Dutch guideline for economic evaluation, and results will be presented in costs per quality-adjusted life years (QALY) gained, derived from the EQ-5D-5L questionnaire. One way sensitivity and bootstrapping will be conducted to characterize (sampling) uncertainty.

A budget impact analysis will also be performed to estimate the financial consequences of the different follow-up strategies for the Dutch national healthcare budget. The perspectives that will be included in the analysis are the wider societal perspective including productivity losses, the narrower perspective of the public, and the perspective of healthcare providers and health insurance companies. Several scenarios will be included to assess the impact of different reimbursement options.

Discussion

The FLOW trial started in November 2021, and 239 patients from 11 study sites have been enrolled on June 2023. After completion of the trial (which is expected on October 2025), the results will be disseminated among nephrologists, vascular surgeons, interventional radiologists, and dialysis nurses through international peer-reviewed publications in medical journals and presentations at scientific meetings. The findings will be included in the national clinical practice guidelines with an expedited review process. Patients will be informed through local and national patient organizations. Implementation into clinical practice will be refined with strategies tailored to the specific circumstances based on a process evaluation. This evaluation will include the prospective registration of reasons for not participating in the study, adherence to the follow-up protocol, and study protocol violations. Any protocol violations will trigger interviews with the health care providers to clarify their reasons for not adhering to the study protocol. Furthermore, we will have periodic semi-structured interviews with nephrologists and dialysis nurses at all study sites and with a sounding board of trial participants to identify practical issues and attitudes toward the vascular access follow-up protocols of the FLOW trial.

After applying for funding for the FLOW trial, the Hemodialysis Access Surveillance Evaluation (HASE) cluster randomized controlled trial has been published.[21] This study compared vascular access surveillance with flow measurements and correction of asymptomatic stenosis to vascular access monitoring and correction of symptomatic stenosis only in a general hemodialysis

population using mostly arteriovenous fistulas. Although the design of the HASE trial has some similarities to our research protocol, important differences between the studies maintain the validity of our trial. Physical examination of the vascular access was done only once per month in the HASE trial, which may have led to late detection of clinically relevant stenoses. In the FLOW trial, the vascular access will be formally examined by dialysis nurses before every dialysis treatment, as recommended in current clinical guidelines.[22] Furthermore, the HASE trial applied a liberal threshold for referral to correct underlying stenoses (vascular access flow <500 mL/min or $>25\%$ reduction to <1000 mL/min within 4 months) that has been abandoned in current clinical guidelines.[22] In the FLOW trial, a restrictive threshold of vascular access flow <500 mL/min is used in line with the current ESVS guidelines.[23] In addition, the HASE trial reported no data on critical outcomes including permanent loss of vascular access, patient-reported outcomes, and health care costs, and presented the data on vascular access thrombosis in a way that precluded inclusion in our meta-analysis. Finally, the statistical analysis used in the HASE trial did not account for its cluster randomized trial design which may have resulted in overestimated statistical significance levels. Taken together, we consider the FLOW trial has maintained its clinical relevance for hemodialysis patients.

Besides being one of the largest randomized controlled trials assessing the clinical impact of vascular access surveillance, the FLOW trial has the major strength of having a double-blinded study design. Although blinding is not typically considered in comparative effectiveness research, we believe it is useful to increase the credibility of the study findings because it will minimize possible bias in patient management. Since assessment of the vascular access for signs of flow dysfunction is subject to clinical judgment, patient referral for interventions based on this assessment could easily be influenced by knowledge of the assigned treatment group. Furthermore, patients and physicians may decide to withdraw from the study selectively when they have knowledge of treatment assignment. With these advances over previous studies comparing follow-up strategies for vascular access, we believe the FLOW trial will provide much-needed evidence to improve clinical care for hemodialysis patients.

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Declaration of conflicting interests

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Ethical approval

This study is approved by the institutional review board (METC azM/UM 21-004).

Trial registration information

Netherlands Trial Registry: NL9165. URL: https://trialsearch.who.int/

ORCID iDs

Bianca Zomer https://orcid.org/0000-0002-5427-7123
Matthijs S Ruiter https://orcid.org/0000-0002-4834-4561
Joris I Rotmans https://orcid.org/0000-0001-9682-6234
Maarten GJ Snoeijs https://orcid.org/0000-0002-4551-2451

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