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Original Article

Can blood flow surveillance and pre-emptive repair of subclinical stenosis prolong the useful life of arteriovenous fistulae? A randomized controlled study

Nicola Tessitore[1], Giovanni Lipari[2], Albino Poli[3], Valeria Bedogna[1], Elda Baggio[2], Carmelo Loschiavo[1], Giancarlo Mansueto[4] and Antonio Lupo[1]

[1]Divisione di Nefrologia, [2]Dipartimento di Scienze Chirurgiche, [3]Dipartimento di Medicina e Sanità Pubblica and [4]Istituto di Radiologia, Verona, Italy

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Abstract

Background. Stenosis is the main cause of arteriovenous fistula (AVF) failure. It is unclear, however, if surveillance for stenosis enhances AVF function and longevity and if there is an ideal time for intervention.
Methods. In a 5-year randomized, controlled, open trial we compared blood flow surveillance and pre-emptive repair of subclinical stenoses (one or both of angioplasty and open surgery) with standard monitoring and intervention based upon clinical criteria alone to determine if the former prolonged the longevity of mature forearm AVFs. Surveillance with blood pump flow (Qb) monitoring during dialysis sessions and quarterly shunt blood flow (Qa) or recirculation measurements identified 79 AVFs with angiographically proven, significant (>50%) stenosis. The AVFs were randomized to either a control group (intervention done in response to a decline in the delivered dialysis dose or thrombosis; $n = 36$) or to a pre-emptive treatment group ($n = 43$). To evaluate a possible relationship between outcome and haemodynamic status of the access, AVFs were divided into functional and failing subgroups, according to Qa values higher or lower than 350 ml/min or the absence or presence of recirculation.
Results. A Kaplan–Meier analysis showed that pre-emptive treatment reduced failure rate ($P = 0.003$) and the Cox hazards model identified treatment ($P = 0.009$) and higher baseline Qa ($P = 0.001$) as the only variables associated with favourable outcome. Primary patency rates were higher in treatment than in control AVFs in both functional ($P = 0.021$) and failing subgroups ($P = 0.005$). They were also higher in functional than in failing AVFs in both control ($P < 0.001$) and treatment groups ($P = 0.023$). Access survival was significantly higher in pre-emptively treated than in control AVFs ($P = 0.050$), a higher post-intervention Qa being the only variable associated with improved access longevity ($P = 0.044$). Secondary patency rates were similar in pre-emptively treated and control AVFs in both functional ($P = 0.059$) and failing subgroups ($P = 0.394$). They were also similar in functional and failing AVFs in controls ($P = 0.082$), but were higher in pre-emptively treated functional AVFs than in pre-emptively treated failing AVFs ($P = 0.033$) or in the entire control group ($P = 0.019$).
Conclusions. We provide evidence that active blood flow surveillance and pre-emptive repair of subclinical stenosis reduce the thrombosis rate and prolong the functional life of mature forearm AVFs. We also show that Qa is a crucial indicator of access patency and a Qa >350 ml/min portends a superior outcome with pre-emptive action in AVFs.

Keywords: access blood flow rate; angioplasty; arteriovenous fistula; stenosis; surgery; thrombosis

Introduction

Native forearm arteriovenous fistulae (AVF) provide the ideal vascular access for haemodialysis, because once they have fully matured they have few complications and excellent patency rates [1].

Mature AVF can become stenosed and, consequently, thrombosed; therefore, to increase access longevity, monitoring for stenoses and their correction prior to thrombosis have been advocated [1,2].

National Kidney Foundation-K/DOQI guidelines recommend elective stenosis repair in poorly

Correspondence and offprint requests to: Nicola Tessitore, Divisione di Nefrologia – Servizio Emodialisi Ospedale Policlinico, Università di Verona, Piazzale L.A. Scuro 10, Verona 37126, Italy. Email: nicola.tessitore@azosp.vr.it

functioning AVF (when significant haemodynamic dysfunction warns of inadequate delivery of dialysis and impending thrombosis). Elective repair is not warranted, however, in well-functioning AVF, since prospective studies on the efficacy of the repair are lacking [1] and early and aggressive treatment may be neither useful nor cost-effective in this type of access, which already has low thrombosis rates [3].

A recent prospective controlled trial showed, however, that the prophylactic angioplasty of stenoses reduces failure rates in functioning AVF [4]. In addition, it has been demonstrated recently that monitoring access blood flow (Qa) coupled with preventive intervention [5–7] halves thrombosis rates in AVF, though the drop in those rates was not consistently of statistical significance [7]. Despite some design drawbacks, such as lack of one or more of concurrent control groups [6], strict randomization [4] or short follow-up periods [5], these studies support a role for surveillance and the early detection and treatment of stenosis to reduce thrombosis rates in AVF. None, however, have addressed the issue of whether or not the useful life of AVF could also be prolonged, so it is unknown if surveillance and pre-emptive correction of stenosis can increase the longevity of AVF.

On the other hand, a recent retrospective study showed that outcomes were similar after declotting or prospective dilatation of dysfunctional forearm AVF [8]. This finding, coupled with recent reports of high success rates obtained with percutaneous declotting followed by the correction of the underlying stenoses [9–12] raises the question of whether surveillance and prophylactic stenosis correction is at all useful in AVF.

In short, both the role of surveillance and the value of pre-emptive stenosis repair in AVF remain controversial.

We performed a prospective, randomized, controlled, open trial to determine if blood flow surveillance and pre-emptive repair of subclinical [13] stenosis, using a combination of balloon angioplasty (PTA) and surgical revision ('spare' surgery), reduce thrombosis rates and improve the useful life of native, mature, forearm, radio-cephalic AVF compared with the more traditional approach of monitoring and intervention based on clinical criteria alone, e.g. the measurement of dialysis adequacy. The secondary aims of the study were to identify the optimal timing of stenosis correction and to evaluate the relationship between the haemodynamic characteristics of the access and outcomes.

Subjects and methods

This study, a prospective, randomized, controlled, open interventional trial, was performed between November 1997 and June 2003 at two haemodialysis units, Ospedale Policlinico (Unit A) and Ospedale Civile Maggiore (Unit B), in Verona, Italy.

All subjects gave their informed consent to the study protocol, which was approved by the local Ethical Committee.

Study design

Based on the reports of Schwab *et al.* [14] and Sands and Miranda [2], we hypothesized that stenosis treatment should provide at least a 3-fold reduction in AVF failure rates and in computing sample size we considered a hazard risk of 3.0. On this basis, projecting a study duration of 60 months and an enrolment period of 36 months, we calculated that the study needed at least 75 subjects, equally distributed between the treatment and control arms.

Of the 320 patients on dialysis during the study period, 191 had native, mature, well-functioning forearm AVF (i.e. clinically normal accesses delivering adequate dialysis, spKt/V >1.2) with no history of surgical and angioplastic procedures and, therefore, were eligible for the study.

Access surveillance. All eligible patients joined the surveillance programme, which consisted of direct ultrasound dilution (UD)-based Qa measurements and surrogate Qa markers, such as monitoring Qb during dialysis and measuring access recirculation. Qb monitoring was done during each haemodialysis session throughout the study, while urea-based access recirculation (Ru) was measured quarterly until the UD technology became available.

Direct UD-based Qa measurements, routinely available since July 1998 in Unit A and since November 1999 in Unit B, were performed quarterly.

The prescribed Qb ranged from 300 to 350 ml/min; the negative arterial pre-pump pressure (NAP) alarm was set at −250 mmHg and any decrease of >40 ml/min in the prescribed Qb (dQb) triggered the need for dialysis as a consequence of the high NAP recorded. Within a week of any documented dQb, Ru or Qa measurements were also taken.

Ru was evaluated using the two-needle slow-flow technique and Qa was measured with a Transonic HD01 monitor (Transonic System Inc., Ithaca, NY, USA), as described elsewhere [15]. When serial Qa measurements were available, changes of Qa over time were also computed and expressed as a percentage decrease in Qa (dQa) [15].

Every 6 weeks, spKt/V was evaluated according to the procedure of Daugirdas [16].

In all, 118 AVF were referred for fistulography: 22 because of dQb >40 ml/min in at least two consecutive haemodialysis sessions; six because of Ru >5%; and 90 because of Qa <750 ml/min or a decrease in Qa over time >25%.

The flow parameters in our surveillance programme were chosen based on the early NKF-DOQI guidelines [17] for dQa and on the results obtained in our preliminary trial showing that the most accurate threshold for detecting stenosis in fistulae was a Qa of <700 ml/min [18]. Given the relatively high variability of the assay, however, a threshold Qa of <750 ml/min was preferred to ensure high sensitivity.

Fistulography. Angiography was performed before dialysis, as explained elsewhere [15], and it identified 101 AVF, from 101 subjects, with significant stenosis (>50% reduction in luminal diameter compared with an adjacent non-stenosed segment). Stenosis was always subclinical [13], since none of the AVF included in the study had clinically evident dysfunction [inadequate delivery of dialysis (all subjects had spKt/V ≥1.20 within a 4 h haemodialysis session), difficulty in cannulation or abnormal physical findings]. Therefore, stenoses were detected only as a result of our surveillance programme.

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Subject allocation. Because they were enrolled in a different trial, evaluating the effect of PTA on AVF failure rate, 18 AVF were excluded from the study [4].

The remaining 83 stenotic AVF were included in our present study and were randomly assigned by tossing a coin to either the control group, in which action was taken in response to clinically evident access dysfunction (defined by inability to sustain adequate dialysis) or following thrombosis, or to the treatment group, in which action was taken pre-emptively within 3 weeks of the diagnosis of stenosis. The control group ended up with 39 AVF and the treatment group with 44.

Four subjects (three from control and one from treatment) were lost to follow-up, because they transferred to other facilities ($n = 3$) or were transplanted ($n = 1$) within 3 months of enrolment. Therefore, only 79 AVFs were included in the final analysis (36 in the control and 43 in the treatment groups).

The AVF were located at the wrist in 62 patients and in the mid-forearm in 17, because either the vascular surgeons' clinical judgment had determined that more distal vessels were unsuitable due to calcified and atherosclerotic arteries or because of the lack of superficial veins or both ($n = 10$), or because a more distal AVF had failed to mature ($n = 4$) or had been unable to provide adequate dialysis once mature ($n = 3$).

The AVF were then divided in two subgroups according to their haemodynamic status and following Sidawy *et al*. [19]. AVF with Qa >350 ml/min or no access recirculation (when direct Qa measurement was unavailable) were defined as functional; those with Qa equal to or less than 350 ml/min or Ru >5% were considered as failing.

The thresholds of Qa <350 ml/min and Ru >5% were chosen because of their excellent accuracy in detecting fistulae at risk of incipient thrombosis, with 100% and 67% sensitivity and 90% and 92% specificity, respectively [15].

Treatment for stenosis

The interventions were PTA and open 'spare' surgery, with the goals of preserving the matured venous capital available for cannulation and saving more proximal vessels for future access procedures.

Angioplasties of stenotic segments were performed as described elsewhere [4]. An angiogram was performed immediately after PTA and the procedure was considered anatomically successful if the residual stenosis was <30%.

Surgery consisted of either the creation of a new anastomosis a few cm above the lesion (neoanastomosis) or the insertion of a short (4–7 cm) PTFE arterial–venous interposition graft, 4–6 mm in diameter between the feeding artery and the non-stenotic draining vein, to bypass the stenotic segment (graft interposition).

The indications for surgery were the presence of lesions that the radiologist considered unlikely to be amenable to PTA, such as multiple or critical (>90%) perianastomotic (artery or vein) stenoses, lesions >2.5 cm in length or lesions refractory to PTA (i.e. >30% residual anatomic stenosis or <20% increase in Qa or both) and stenoses with repeated early recurrence after dilatation (Figure 1).

Clotted AVF were treated by surgical thrombectomy followed by the correction of the underlying stenosis either by PTA or surgery within 72 h of onset.

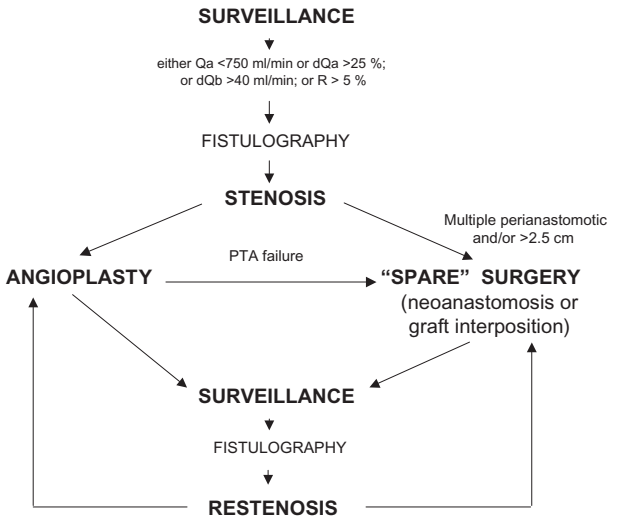

Fig. 1. Stenosis surveillance and treatment algorithm.

Outcomes

AVF patency rates were evaluated and defined according to the criteria of Sidawy *et al*. [19]. In the control group, the primary patency was defined as the interval from the diagnosis of stenosis to access failure as a consequence of either thrombosis or the abandonment of the access due to the inability to sustain adequate dialysis (inability to provide a spKt/V >1.0 within a 4 h haemodialysis session). In the treatment group, the assisted primary patency was considered to have ended when the AVF thrombosed or was abandoned and it included all surgical or endovascular measures designed to preserve access function.

The secondary patency rate was based on the interval from the diagnosis of stenosis to access loss, including all intervening actions to maintain or restore access function after an episode of thrombosis.

Subjects were censored because of death, transplantation or if they ended the study with a functional access [19].

Our study was not blinded, because thrombosis is an easily identifiable event and dialysis adequacy (as an indicator of whether or not to abandon the access) was evaluated by the investigators.

Statistical analyses

Data are reported as percentages, means ± SD, mean [95% confidence interval (CI)] or median (10th–90th percentile), as appropriate. Normally distributed data were analysed using the non-paired *t*-test and skewed data were analysed using the Mann–Whitney *U*-test.

Patency rates were calculated according to the Kaplan–Meier method [20] and different patency curves were compared using the log-rank test.

Cox's multivariate proportional hazards model was used to evaluate whether or not subjects or AVF characteristics other than the investigated variables might influence outcome [21].

The generalized linear model-Poisson loglinear statistical procedure was used to test for associations between thrombosis, loss and restenosis rates in the study groups.

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All tests of significance were two-sided and differences were considered significant when P was ≤ 0.05.

The sample size and the generalized linear model-Poisson loglinear procedure were computed using EGRET SIZ Version 6-027 and EGRET Version 1.02.10 (SERC Corporation, Seattle, WA, USA), respectively. All other statistical analyses were performed using SPSS software, version 11.0 (SPSS Inc., Chicago, IL, USA).

Results

The characteristics of the subjects and AVF included in the study are shown in Tables 1 and 2, respectively. The control and treatment groups were well matched for prognostic factors associated with AVF survival, as well as for the haemodynamic status of shunts and for number, degree, distribution and length of stenoses.

The characteristics of functional and failing AVF are shown in Table 3 and were similar for the two subgroups, except for the degrees of stenosis, which was significantly higher in failing than in functional AVF ($P = 0.001$).

Table 1. Subjects' characteristics

	Control	Treatment	*P*-value
Number of patients	36	43	
Age (years)	61.9 ± 13.0	58.1 ± 14.9	NS
Gender (male/female)	21/15	23/20	NS
Proportion of elderly (>65 years) (%)	42.8	34.9	NS
Proportion of diabetics (%)	22.8	23.2	NS
Proportion with cardiovascular disease (%)	48.5	39.5	NS
spKt/V	1.29 ± 0.07	1.30 ± 0.08	NS

Table 2. AVF characteristics

	Control	Treatment	*P*-value
Number of AVF	36	43	
AVF age (months)	22.1 ± 20.5	17.4 ± 13.9	NS
Site of anastomosis (wrist/mid-forearm)	29/7	33/10	NS
Degree of stenosis (%)	77 ± 9	82 ± 7	NS
Proportion of multiple stenoses (%)	25.7	37.2	NS
Proportion of stenoses >2.5 cm (%)	11.4	9.3	NS
Location of stenoses (%)			NS
Arterial	2.9	4.7	
Venous perianastomotic (initial 4 cm)	83.3	88.3	
Venous distal (past the initial 4 cm)	13.8	7.0	
Proportion of recirculation >5% (%)	16.7	11.6	NS
Decrease in Qb to continue dialysis (ml/min)	47 ± 37	40 ± 35	NS
Access blood flow rate (ml/min)	438 ± 197 ($n = 29$)	445 ± 157 ($n = 36$)	NS
Proportion of failing AVF (%)	36.1	30.2	NS

Table 3. Characteristics of functional and failing AVF

	Functional	Failing	*P*-value
Number of AVF	53	26	
AVF age (months)	21.5 ± 18.3	15.1 ± 10.9	NS
Site of anastomosis (wrist/mid-forearm)	41/12	21/5	NS
Degree of stenosis (%)	76 ± 6	83 ± 7	<0.001
Proportion of multiple stenoses (%)	26.4	46.1	NS
Location of stenoses (%)			
Arterial	1.9	7.7	NS
Venous	98.1	92.3	NS
Proportion of subjects with peripheral or cerebral vascular disease or both (%)	24.5	23.2	NS

PTA was the initial treatment modality in 31 AVF and open surgery in 12 (five by neoanastomosis and seven by graft interposition). The radiologist and surgeons determined the need for surgery. The indications adopted by them for surgery were stenoses longer than 2.5 cm in four AVF, multiple perianastomotic stenoses in six cases and critical isolated perianastomotic stenoses in two.

Restenosis was a frequent event after initial stenosis correction by either treatment modality. The percentage of restenosed AVF, the restenosis rate and the median time to restenosis were similar after PTA or surgery, being 64.5% *vs* 50.0%, 42.1% *vs* 24.2% per year at risk and 11.5 (10th–90th percentile: 2.0–33.0) *vs* 9.0 (10th–90th percentile: 3.0–40.0) months, respectively (P = NS). The restenosis rates were also similar in functional and failing AVF (25.9% *vs* 54.1% per year at risk, respectively; P = NS).

During follow-up, 31 additional PTAs and four surgical operations (two neoanastomoses and two jump grafts) were needed in 24 AVF. The indications for these operations were PTA failure in two AVF and early restenosis after PTA in the remaining two.

The anatomical success rate was 96.7% for PTA; the early clinical success rate, i.e. immediate adequacy of the access for dialysis, was 100% for both treatment modalities. No major complications were observed after treatment.

The correction of stenosis led to an immediate improvement of haemodynamic status. Within 1 week of the procedure, Qb returned to baseline values, Ru was abolished in all but two AVF and Qa significantly increased in both subgroups ($P < 0.001$), as shown in Figure 2. The mean increase of Qa was 381 ± 226 ml/min in functional and 402 ± 161 ml/min in failing AVF (P = NS). Post-treatment Qa was significantly higher in functional than in failing AVF ($P = 0.005$).

Unadjusted primary and assisted primary patency rates are shown in Figure 3. Pre-emptive stenosis correction significantly improved failure-free AVF survival rates compared with controls ($P = 0.003$).

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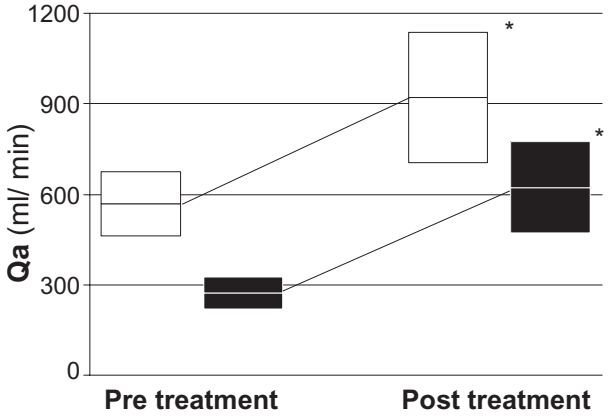
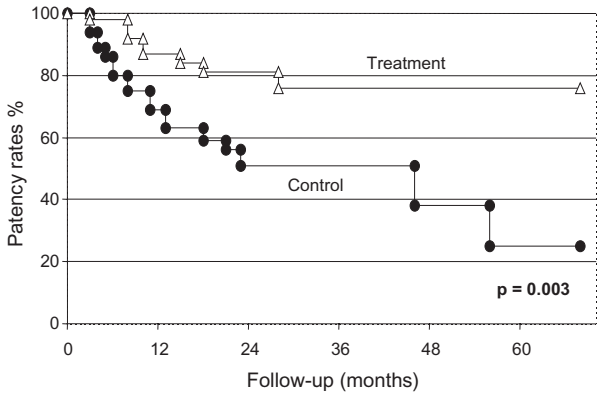


Fig. 2. Mean (95% CI) blood flow rates before and after pre-emptive treatment in functional (pre-treatment Qa >350 ml/min, white rectangles; $n=22$) and failing (pre-treatment Qa ≤350 ml/min, black rectangles; $n=11$) AVF. *$P<0.001$ *vs* pre-treatment.



AVFs at risk :

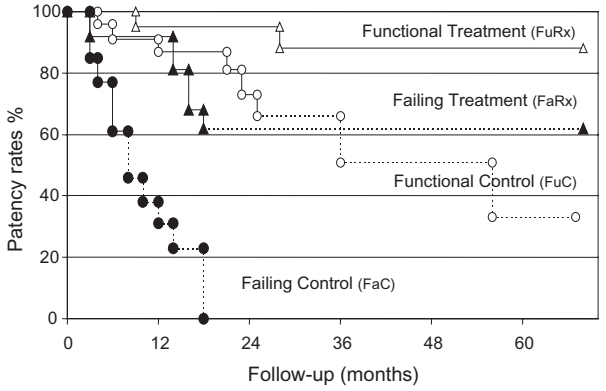
Treatment	43	31	21	17	13	11
Control	36	23	9	5	5	2

Fig. 3. Unadjusted primary patency rates of controls (closed circles) compared with unadjusted assisted primary patency rates in the treatment group (open triangles).

In the control group, 18 AVF failed (16 thrombosed and two were abandoned), as opposed to eight thrombosed AVF in the treatment group. The relative risk (RR) of AVF failure in controls was 3.35 (95% CI: 1.44–7.78; $P=0.003$).

Cox's multivariate proportional hazards analysis identified treatment and baseline Qa as the only variables significantly associated with outcome; the highest failure rates were associated with non-utilization of pre-emptive treatment (control group) [RR 3.933 (95% CI: 1.415–10.933; p=0.009); $P=0.009$] and the lowest Qa values [1.005 (RR 95% CI 1.002–1.008); $P=0.001$]. All other variables included in the model (age of subjects and AVF, gender, comorbidities and location of anastomosis) were not statistically significant.

To elucidate the relationship between the outcome and the haemodynamic status of the access, unadjusted primary patency rates were evaluated in the functional



AVFs at risk :

Fu Rx	30	23	16	13	9	8
Fu C	23	19	10	4	3	1
Fa Rx	13	8	5	4	4	3
Fa C	13	4				

Fig. 4. Unadjusted primary patency rates and access haemodynamic status. Open triangles, pre-emptive intervention in functional AVF (functional treatment, Fu Rx); open circles, intervention reactive to thrombosis in functional AVF (functional control, Fu C); closed triangles, pre-emptive intervention in failing AVF (failing treatment, Fa Rx); closed circles, intervention reactive to thrombosis in failing AVF (failing controls, Fa C). Patency rates of the treatment group differed significantly from those of the control in both functional ($P=0.021$) and failing AVF ($P=0.005$) and those of functional AVF differed significantly from those of failing AVF in both treatment ($P=0.023$) and control groups ($P<0.001$).

and failing AVF subgroups, in both the control and the treatment groups (Figure 4).

Failure-free survival rates were significantly higher in pre-emptively treated than in control AVF in both the functional ($P=0.021$) and failing subgroups ($P=0.005$). Functional AVF had failure-free rates significantly higher than failing AVF in both the control ($P<0.001$) and treatment groups ($P=0.023$). The thrombosis rate was 3.7% per year at risk in the pre-emptively treated functional AVF and it was significantly lower than the thrombosis rate of 13.9% in functional controls (RR: 0.23; 95% CI: 0.06–0.77; $P=0.033$) and of 17.8% in the pre-emptively treated failing AVF (RR: 0.21; 95% CI: 0.05–0.99; $P=0.050$), whose thrombosis rate was significantly lower than the thrombosis rate of 100% in failing controls (RR: 0.23; 95% CI: 0.07–0.71; $P=0.011$).

Clotted AVF were treated by surgical thrombectomy followed by the correction of the underlying stenosis and the technical and functional success rate, defined as the re-establishment of patency and flow with the resumption of adequate dialysis within 24 h, was 70.8% [13/16 AVF (81.2%) in controls and 4/8 AVF (50.0%) in the treatment group]. Stenosis was corrected by PTA in two, by neoanastomosis in eight and by jump graft interposition in seven AVF. Due to extensive organization of the thrombus, the large volume of clots or inadequate forearm veins, seven AVF were considered unsalvageable.

A Kaplan–Meier analysis showed that unadjusted secondary patency rates were significantly higher in

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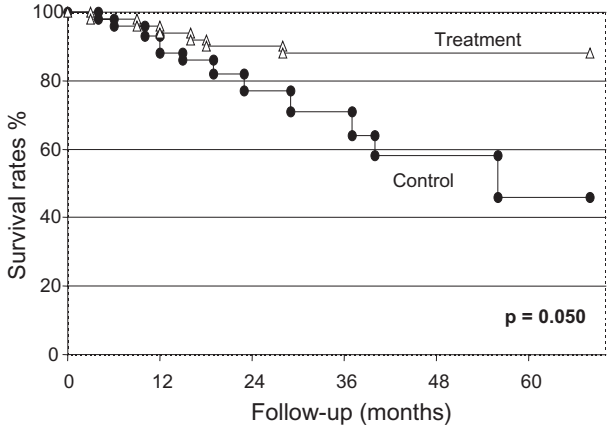
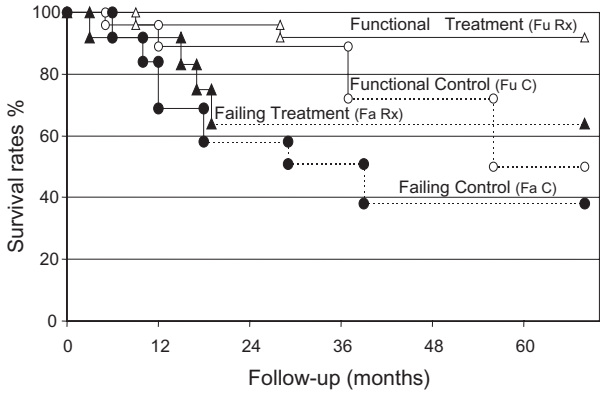


AVFs at risk :

Treatment	43	35	25	20	16	12
Control	36	31	24	13	8	3

Fig. 5. Unadjusted secondary patency rates in the control group (closed circles) compared with unadjusted assisted secondary patency rates in the treatment group (open triangles).



AVFs at risk :

Fu Rx	30	24	18	14	10	9
Fu C	23	21	16	8	5	2
Fa Rx	13	11	7	6	6	3
Fa C	13	10	7	5	3	1

Fig. 6. Unadjusted secondary patency rates and access haemodynamic status. Open triangles, pre-emptive intervention in functional AVF (functional treatment, Fu Rx); open circles, intervention reactive to thrombosis in functional AVF (functional control, Fu C); closed triangles, pre-emptive intervention in failing AVF (failing treatment, Fa Rx); closed circles, intervention reactive to thrombosis in failing AVF (failing controls, Fa C). Patency rates of treatment did not differ significantly from those of the control group in functional ($P = 0.059$) and in failing AVF ($P = 0.394$) but those of functional AVF differed significantly from those of failing AVF in the treatment group ($P = 0.033$) but not in the control group ($P = 0.079$).

the treatment than in the control group ($P = 0.050$; Figure 5). Loss rates were 15.6% per year at risk in controls and 5.1% in the pre-emptively treated. The RR of AVF loss for controls was 2.66 (95% CI: 0.98–6.85; $P = 0.055$).

Cox's multivariate proportional hazards analysis identified post-intervention Qa as the only variable significantly associated with outcome [RR: 0.995 (95%: CI 0.990–0.999); $P = 0.044$], the highest loss rates being associated with the lowest post-intervention Qa levels.

Unadjusted secondary patency rates in the subgroups of functional and failing AVF in the control and treatment groups are shown in Figure 6. Pre-emptive treatment was associated with higher survival rates compared with controls, but the difference was not statistically significant in either failing ($P = 0.394$) or functional AVF ($P = 0.059$) (though in the latter it approached statistical significance). Survival rates were significantly higher in functional than in failing AVF in the treatment arm ($P = 0.033$), while no significant difference in survival was observed between the functional and failing AVF in controls ($P = 0.079$).

AVF were lost at a rate of 2.4% and 9.7% per year at risk in the pre-emptively treated and control functional AVF (RR: 0.23; 95% CI: 0.04–1.07; $P = 0.069$) and of 13.2% and 23.3% in the pre-emptively treated and control failing AVF (RR: 0.59; 95% CI: 0.17–2.04; $P = 0.404$), respectively. Loss rates in functional AVF were significantly lower than in failing AVF in the treatment group (RR: 0.19; 95% CI: 0.03–1.00; $P = 0.050$), but similar between functional and failing AVF in controls (RR: 0.43; 95% CI: 0.13–1.36; $P = 0.150$).

To determine if the timing of intervention, pre-emptively in AVFs with moderate or advanced haemodynamic impairment *vs* in reaction to a thrombotic episode or inadequate dialysis delivery, would affect the useful life of the access, secondary patency rates in the entire control group were compared with those in the two subgroups of pre-emptively treated functional and failing AVF. In this analysis, the control group was considered in its entirety, since intervention was reactive to access thrombosis or functional failure independent of baseline haemodynamic status and functional and failing AVF had similar survival rates in controls.

A Kaplan–Meier analysis showed that unadjusted secondary patency rates in controls were significantly lower than in pre-emptively treated functional AVF ($P = 0.019$), but similar to those observed in pre-emptively treated failing AVF ($P = 0.968$) (data not shown).

The loss of access rate in controls was significantly higher than in pre-emptively treated functional AVF (RR: 4.16; 95% CI: 1.24–27.53; $P = 0.034$), but similar to that in pre-emptively treated failing AVF (RR: 0.83; 95% CI: 0.59–1.41; $P = 0.976$). As previously reported, the loss of access rate in pre-emptively treated functional AVF was significantly lower than in pre-emptively treated failing AVF (RR: 0.19; 95% CI: 0.03–1.00; $P = 0.050$).

Discussion

Stenosis is a major cause of morbidity and malfunction in AVF and existing guidelines recommend its surveillance and prospective correction mainly in poorly functioning AVF, to increase their longevity [1]. This

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suggestion, however, is generally supported by studies that have been considered methodologically inadequate, since they often are retrospective or prospective with historical controls. Moreover, recent studies provide conflicting information. Some support a role for early stenosis detection and punctual repair in reducing AVF thrombosis rates [4–7], while others suggest that the outcome is much the same if the stenosis is corrected only as needed in dysfunctional AVF, such as after a thrombotic episode [8]. These studies also have their drawbacks, so it remains to be seen if surveillance for pre-emptive stenosis treatment can reduce thrombosis rates and significantly prolong AVF survival and if there is an ideal time for intervention.

Our prospective, randomized, controlled, open trial shows that Qa surveillance and pre-emptive correction of subclinical stenosis (those in fistulae adequate for dialysis and without any clinically evident abnormalities) reduce failure rates and prolong an access's useful life when compared with the more traditional approach, which involves monitoring and intervention based upon clinical criteria alone. Our results also suggest that the timing of intervention, i.e. pre-emptively in AVF with Qa >350 ml/min, is crucial to provide the lowest failure rate and the highest access longevity.

It is reasonable to surmise that our surveillance of clinically normal AVF enabled the early and accurate diagnosis of a stenosis, since, in our experience, the combination of Qa <750 ml/min and dQa >25%, which was the main criterion for fistulography in the study, had excellent diagnostic accuracy with a 95% sensitivity and 86% specificity [15].

Both treatment modalities, endovascular and surgical, proved safe and highly successful; no major complications were observed, shunt cannulation and adequate dialysis delivery were always possible immediately after successful treatment and a stenosis could be corrected with little or no reduction in the venous capital.

However, restenosis was a frequent event after the initial treatment and restenosis rates and time to restenosis varied considerably, with no apparent differences after PTA and surgery. This last observation, however, should be considered with caution, since indications for treatment were different for the two techniques and our study may be underpowered to detect differences in restenosis rates.

Our study confirms the results of previous ones [4–6] and provides convincing evidence that a strategy involving regular blood flow surveillance and pre-emptive repair of stenosis in well-functioning AVF is safe and effective and allows a 3-fold reduction in the risk of thrombosis. Furthermore, it shows that immediate intervention is warranted in AVF when Qa drops below 350 ml/min or access recirculation appears to be preventing incipient thrombosis.

The novel information emerging from this study is that the greatest benefit of the pre-emptive correction of subclinical stenosis is obtained when action is taken on AVF with less advanced haemodynamic impairments.

The thrombosis rate of 3.7% per year at risk obtained in our stenotic functional AVF is comparable with the remarkably low thrombosis rate reported by Konner *et al.* [22] in a general population of forearm AVF that included both stenotic and non-stenotic fistulae. If we extrapolate the results of our study to a general population of forearm AVF, bearing in mind that the prevalence of stenosis in our study is ~50% and non-stenotic fistulae very seldom clot [1], our approach should result in thrombosis rates as low as 2.0% per year at risk.

To our knowledge, this is the first randomized controlled trial that has studied the influence of Qa surveillance and pre-emptive stenosis repair on the overall functional life of AVF. It shows that a strategy of continuous Qa surveillance and repeat prophylactic treatments of stenoses can increase access longevity when action is taken early on in still well-functioning AVF, when that strategy is compared with the traditional approach of correcting stenoses when their dysfunction is clinically evident or waiting until thrombosis occurs. Our results suggest that pre-emptive treatment should be preferentially undertaken in AVF with Qa >350 ml/min or no access recirculation to optimize survival. In fact, we found that pre-emptive treatment in functional AVF was associated with significantly higher survival rates than pre-emptive intervention in failing AVF or correction of stenosis after thrombosis. This conclusion, however, should be considered with caution since the difference in rates of access loss between the pre-emptively treated functional AVF and their matched controls was not significant. This, however, is most likely the consequence of an underpowered sample size for detecting significant differences among subgroups. Moreover, the observed RR of access loss in pre-emptively treated AVF of 0.23 and its 95% CI support the notion that pre-emptive intervention is effective in reducing access loss rates in functional AVF, despite the lack of statistical significance [23]. Obviously, larger controlled randomized trials are needed to fully evaluate whether or not correcting stenoses in AVF with low risks of failure and thrombosis is beneficial.

We also recognize that our findings on the effect of pre-emptive treatment on patency rates may be biased by an overestimation of the treatment effect, resulting from the lack of blinding [24].

Conversely, pre-emptive stenosis correction in failing AVF had much the same outcome in our study as stenosis correction after declotting, a finding consistent with that of a large retrospective study on forearm AVF [8].

This observation should be considered with caution, since our study probably is not powerful enough to detect significant differences in outcome between pre-emptive stenosis treatment in dysfunctional AVF and treatment after declotting.

Although our results confirm that thrombosis is not necessarily detrimental to AVF survival [8], they should

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not be an excuse for complacency, since treating thrombosed AVF may take longer and be more difficult and less successful than prophylactic treatment.

In our experience, the success rate of surgical stenosis treatment following declotting was only 71%. This outcome is inferior to those obtained by other investigators, who report success rates of ≥90% after percutaneous and thrombolytic treatment of clotted AVF [8–12] and, thus, suggest that thrombosed AVF should be treated preferentially by interventional radiologists.

This study also emphasizes the crucial role of haemodynamic status in AVF patency and treatment outcome, suggesting that correcting stenosis reduces thrombosis rate and improves AVF survival, because it increases shunt blood flow rate.

Several lines of evidence support this conclusion. First, pre-emptive treatment in functional AVFs, those with baseline Qa >350 ml/min or no access recirculation, produced a 4-fold reduction of thrombosis rates and a 3-fold increase in AVF survival rates compared with pre-emptive correction in AVF with lower baseline Qa or presence of recirculation. Second, stenosis correction was associated with an improvement of the haemodynamic status of the shunt and a significant increase in Qa, the highest post-treatment Qa values being observed in the AVF with the highest patency rates. Third, Cox's hazards analyses identified higher baseline Qa and higher post-intervention Qa (the combined result of treatment and the pre-treatment Qa) as major determinants of a longer failure-free interval and AVF useful life, respectively.

In addition, the critical role of haemodynamic status in determining patency was emphasized by the finding that failure rates in the control group were higher in the AVF with lower Qa.

In conclusion, our study provides evidence that, in a well-functioning shunt, the early detection of stenosis by Qa surveillance and its pre-emptive correction (by PTA or open surgery) reduces failure rate and prolongs the useful life of native, mature forearm AVF compared with the standard approach of waiting until dysfunction is clinically evident before repairing stenosis.

Our study also suggests that the best outcome can be obtained when pre-emptive action is taken in AVF with lesser haemodynamic impairments (Qa >350 ml/min and absence of access recirculation), while elective treatment in AVF with Qa <350 ml/min or presence of access recirculation may provide no substantial benefit over stenosis correction in response to thrombosis. Finally, our study confirms the crucial role of Qa in determining patency and treatment outcome in AVF.

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