Should current criteria for detecting and repairing arteriovenous fistula stenosis be reconsidered? Interim analysis of a randomized controlled trial

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ABSTRACT

Background. The vascular access guidelines recommend that arteriovenous fistulas (AVFs) with access dysfunction and an access blood flow (Qa) < 300–500 mL/min be referred for stenosis imaging and treatment [1–4]. Significant (>50%) stenosis may be detected in a well-functioning AVF with a Qa > 500 mL/min as well, but whether it should be corrected or not remains to be seen.

Methods. In October 2006, we began an open randomized controlled trial enrolling patients with an AVF with subclinical stenosis and Qa > 500 mL/min, to see how elective stenosis repair [treatment group (TX)] influenced access failure (thrombosis or impending thrombosis requiring access revision), or loss and the related cost compared with stenosis correction according to the guidelines, i.e. after the onset of access dysfunction or a Qa < 400 mL/min [control group (C)]. An interim analysis was performed in July 2012, by which time the trial had enrolled 58 patients (30 C and 28 TX).

Results. TX led to a relative risk of 0.47 [95% confidence interval (CI): 0.17–1.15] for access failure (P = 0.090), 0.37 [95% CI: 0.12–0.97] for thrombosis (P = 0.033) and 0.36 [95% CI: 0.09–0.99] for access loss (P = 0.041). In the setting of our study (in which all surgery was performed as in patient procedure) no significant differences in costs emerged between the two strategies. The mean incremental cost-effectiveness ratio for TX was €282 or €321 to avoid one episode of thrombosis or access loss, respectively.

Conclusions. Our interim analysis showed that elective repair of subclinical stenosis in AVFs with Qa > 500 mL/min cost-effectively reduces the risk of thrombosis and access loss in comparison with the approach of the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, raising the question of whether the currently recommended criteria for assessing and treating stenosis should be reconsidered.

INTRODUCTION

The vascular access guidelines recommend that arteriovenous fistulas (AVFs) with access dysfunction and/or an access blood flow (Qa) < 300–500 mL/min be referred for stenosis imaging and treatment [1–4]. Significant (>50%) stenosis may be detected in a well-functioning AVF with Qa > 500 mL/min as well, but whether it should be corrected or not is still not
clear, due to the shortage of good-quality studies addressing this issue.

Many experts believe that no action is warranted in such AVFs as the stenosis is not haemodynamically significant (i.e. a stenosis exceeding 50% of the vessel’s diameter and associated with a low access flow or a high pressure or a change in access flow or pressure) [1], judging its treatment is pointless since the access can deliver an adequate dialysis and is at low risk of failure [8,10]. Treatment could even be harmful in some patients, because unnecessary angioplasty (PTA) for stable or slowly growing stenoses may impair access survival by prompting an aggressive restenosis due to accelerated neointimal hyperplasia [1,11,12].

On the other hand, some observational and randomized studies have found that higher baseline and post-intervention Qa values were major determinants of a lower thrombosis rate and improved access longevity [13,14], suggesting a benefit of repairing stenosis at higher Qa values than those recommended by the current guidelines.

To test this hypothesis, we conducted an open randomized controlled trial to see whether elective repair of subclinical stenosis (i.e. a stenosis detected by our screening programme in an access showing no signs of dysfunction during dialysis)—such as persistent cannulation difficulties, excessive post-dialysis bleeding or high dialysis pressures preventing the target dialysis blood pump flow (Qb) from being achieved—and capable of delivering an spKt/V > 1.2 [15]) in AVFs with a Qa > 500 mL/min could reduce the risk of access failure (thrombosis or evidence of impending thrombosis [6]), extend access longevity and prove cost-effective in comparison with the strategy recommended in the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines [1], for correcting only haemodynamically significant stenosis showing signs of access dysfunction detected during dialysis or a Qa < 400 mL/min.

**MATERIALS AND METHODS**

An ongoing prospective, randomized, controlled, open trial was started in October 2006 at the Haemodialysis Unit of the Policlinico Borgo Roma in Verona (Italy). All subjects gave their informed consent to the study protocol, which complies with the principles of the Helsinki Declaration and was approved by the local Ethical Committee (Project CE No. 1331). The study was registered under the Current Controlled Trial No. ISRCTN69115386. In July 2012, we found an >2-fold difference in access loss between the two arms of the trial, and performed an interim analysis, the results of which are the basis of the present paper.

**Study design**

Based on the results of a subgroup analysis in a randomized controlled trial performed at our institution [14] showing that elective stenosis revision in functional AVFs with a Qa > 350 mL/min was associated with a 4-fold reduction in the risk of access loss in comparison with intervention following access dysfunction, we hypothesized that electively treating stenosis should achieve at least a 3-fold reduction in the rate of access failure/loss in our sample. In calculating our sample size, we considered a hazard ratio of 3.0 and, on this basis, assuming that the study would last 4 years, with a 40% drop-out rate, an enrolment period of 3 years, an α-value of 0.05 and a β-value of 0.80, we calculated that the study needed to enrol at least 76 subjects, equally distributed between the control and treatment arms.

By the time of our interim analysis in July 2012, 58 AVFs with angiographically proven significant subclinical stenosis (>50% reduction in vessel diameter compared with the adjacent segment at biplanar angiography [15]) and a Qa > 500 mL/min had been identified by means of a screening programme based on highly sensitive criteria for detecting stenosis, i.e. the combination of a positive physical examination (PE), a Qa < 900 mL/min or a derived static venous pressure (VAPR) > 0.5. Qa was measured using the ultrasound dilution method with the HD03 monitor (Transonic, Inc., Ithaca, NY) within 30–150 min after starting dialysis, in a dialysis session with no haemodynamic cardiovascular instability. The arterial needle was placed in the main trunk of the draining vein, proximal to any collateral veins either facing the incoming blood flow or the shoulder, and the venous needle always was placed facing the shoulder, either in the main stream of the access or one of its branches [6]. The Qa values were the mean of measurements taken in triplicates and the VAPR values the mean of five measurements taken during a single dialysis session [9]. None of these AVF had undergone any surgical and/or endovascular treatment in the 3 months prior to our assessment and were consequently eligible for the study. The AVFs were randomly assigned [using the sealed envelope method, handled by one of the investigators (A.P.) uninvolved in the patients’ clinical care to ensure allocation concealment] to a control group (C), managed according to the current guidelines (i.e. treating stenosis in the event of access dysfunction or a Qa < 400 mL/min [1]), or a treatment group (TX), in which stenoses were corrected electively within 2 weeks of randomization. All AVFs were cannulated using the rope-ladder technique, using 15-G needles with the arterial needle placed in the initial portion of the draining vein at least 3–4 cm apart from the anastomosis. During the follow-up, the dialysis dose delivered was assessed every 6 weeks (according to Daugirdas [17]) and all AVFs were monitored at every dialysis session (recording any cannulation difficulties, dialysis pressures and Qb), and surveilled by taking Qa and recirculation measurements every 3–4 months. The frequency of Qa measurement was based on an observed 10th–90th percentile time to restenosis of 7–31 months after elective surgery, and 3–24 months after PTA, in our experience [18]. AVF’s underwent imaging for restenosis [by angiography or duplex ultrasound (DU)] and repair in the event of access dysfunction, clinically detectable during dialysis or a Qa ≤400 mL/min in C, and a Qa < 750 mL/min or a drop in Qa > 25% in TX, given the high sensitivity value of these criteria in predicting stenosis [95% [95% confidence interval (CI): 85–99]], in our experience [6] (Figure 1).

**Access imaging and intervention procedures**

Imaging for stenosis involved angiography or DU. Biplanar angiography was performed before dialysis using the ‘arterial’
needle for contrast medium injection. The AVF was then visualized in its entirety, inverting flow in the venous limb with an inflated sphygmomanometer [6]. On the few occasions when it was impossible to visualize the anastomosis, either a DU or a fistulogram by puncturing the brachial artery were obtained on a nondialysis day. The DU was performed by one of the investigators with expertise in this area [G.L.] using the Logiq 7 device (General Electric, Milwaukee, WI) with an L12-5 broadband linear array transducer. Greyscale images were taken after optimizing the device for superficial vessels, while the colour images were taken using the B-flow colour technology (General Electric, Milwaukee, WI), allowing for high spatial resolution, high frame rate and no overlay displaying blood and tissue together. Standard techniques were used for flow velocimetry, aligning the cursor parallel to the vessel wall, obtaining spectral waveforms using a sample volume placed in the centre of the flow, on the basis of colour DU, making any effort to maintain an insonating angle at 60°. The examinations were performed in both longitudinal and transverse planes. Vein diameters were always measured using an electronic caliper. All components of the AVF were assessed for stenosis, from the feeding artery to the subclavian vein. The primary criterion for significant stenosis was the degree of narrowing of the internal diameter of the access by >50% on greyscale or B-flow colour imaging. In the few cases with a measured degree of stenosis around a value of 50% and in which we were uncertain of the findings of the imaging procedures, we also used Doppler velocimetry and considered a stenosis as significant if the peak systolic velocity was >375 cm/s [19]. Stenosis was repaired electively by PTA or surgery; the choice of intervention was made case by case at discretion of and depending on the availability of the radiologist and the vascular surgeon with the goal of correcting stenosis without any major reduction in the venous capital available for puncture [18]. PTA of stenotic segments was performed under light anaesthesia, puncturing the AVF according to the Seldinger technique. An intravenous dose of 5000 IU of heparin was administered before angioplasty. Balloons 6–9 mm in size were used, and their diameter was oversized by 1 mm in comparison with the size of the adjacent non-stenotic vessel. Balloons were inflated to a pressure of 12 atmospheres for 60–90 s. Dilation-resistant lesions sequentially underwent multiple dilatations at up to 20 atmospheres for 3 min. An angiogram was performed immediately after PTA, and the procedure was considered anatomically successful if a <30% residual stenosis was recorded. Lesions with elastic recoil and early restenosis underwent intravascular stent placement. The stents deployed were the self-expanding Wallstent-unii stent (Bostonic Scientific Medi-Tech, Natick, MA) or polytetrafluoroethylene (PTFE) Viabahn stent-graft (W.L. Gore, Flagstaff, AZ). Stent size approximated the angioplasty balloon size and ranged from 6 to 10 mm in diameter. The length of the stent dependent on the length of the lesion to cover, allowing for the edge of the stent to overlap the normal-appearing vessel by ~10 mm. Preemptive surgery was performed under axillary plexus anaesthesia and involved either creating a more proximal re-anastomosis a few centimetres above the stenotic venous segment (neo-anastomosis) or inserting a short interposition PTFE arteriovenous graft to replace the stenosed venous segment (interposition graft).

Thrombectomy was performed depending on the availability of the attending radiologist and vascular surgeon by manual catheter-directed thrombo-aspiration [20] or surgical revision, with the aim of declotting thrombosed AVFs within 48 h of their detection [21]. Manual thrombo-aspiration was performed after placing two introducer-sheaths in a criss-cross fashion to gain access to the venous outflow and to the anastomosis. The venous outflow was accessed first in order to check the proximal extent of the thrombosis. Heparin and antibiotics were injected systemically. A similar manoeuvre was then performed in the direction of the anastomosis. A 7–9-F aspiration catheter was pushed through the ‘venous’ introducer, while aspirating manually through a 50 mL syringe and gradually removing the catheter; this manoeuvre was repeated as often as necessary to remove all of the thrombus. The aspiration catheter was then pushed through the ‘arterial’ introducer down to the anastomosis to aspirate the thrombus located between the tip of the introducer and the anastomosis. Then dilatation of any stenoses identified was done with high-pressure balloons. Surgical thrombectomy was performed through a small incision near the anastomosis, removing the clot with Fogarty catheters and correcting the underlying stenosis by means of a more proximal neo-anastomosis or a PTFE interposition graft. Recovery of the access flow after endovascular and surgical thrombectomy was assessed intraoperatively by PE.

**Outcomes**

The primary outcomes were (i) access failure, i.e. thrombosis or preemptive intervention triggered by signs of impending thrombosis (Qa < 300 mL/min, access recirculation or a >60 mL/min drop in the prescribed Qb) [6], and (ii) access loss because patency was impossible to restore after a thrombotic episode (if the access was considered unsalvageable due to unsuitable veins or extensive thrombus organization, or if thrombectomy was unsuccessful), or a patent access was unsuitable for cannulation or unable to provide an adequate Qb to support a spKt/V ≥ 1.0 (access malfunction).

Primary outcomes were measured as population rates (expressed as event/AVF-year), and patency rates, assessed

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**FIGURE 1:** Study design algorithm.

**Outcome of AVF subclinical stenosis repair**
according to the criteria in Sidawy et al. [22]. The primary patency period was defined as the time elapsing from randomization to access failure, including all surgical and endovascular measures designed to maintain access function; the secondary patency was defined as the time elapsing from randomization to access abandonment, including all intervening actions to maintain and restore access patency following a thrombotic episode. Subjects were censored in the event of death, transplantation, transfer to another dialysis unit, access abandonment or if they still had a functional access when the study came to an end.

Secondary study outcomes were elective stenosis repair (endovascular or surgical), temporary central venous catheter (CVC) placement, CVC-related infection (one or the other of bloodstream or tunnel/exit-site infection), hospitalization and direct stenosis treatment-related costs, expressed as population rates per AVF-year.

**Cost analysis**

The direct cost of access treatment and maintenance was estimated, including all expenses incurred for surveillance and imaging during the follow-up, elective endovascular and surgical intervention, thrombectomy, placement of a new access or a cuffed or uncuffed temporary CVC and hospitalization. Procedural costs included the actual cost of personnel, the surgical and endovascular suite, equipment and materials. PTA and endovascular thrombectomy were performed as day-hospital procedures and all surgery as in patient procedures (because it can only be scheduled as in hospital procedure at our institution). For each endovascular procedure, we included the day-hospital cost (€180), while costs for hospital stay were based on an average cost in surgical wards (€550 per day). These costs were established from the Azienda Ospedaliera Universitaria Integrata Verona financial data system as at the year 2011, in Euros.

The incremental cost-effectiveness ratio (ICER) for TX was calculated as follows [23]:

\[
\Delta \text{Cost}/\Delta \text{Rate} = (\text{Cost}_{\text{TX}} - \text{Cost}_{\text{C}})/(\text{Rate}_{\text{C}} - \text{Rate}_{\text{TX}}),
\]

where Cost refers to the cost for all patients divided by the years of the follow-up and Rate to the number of events divided by the years of the follow-up for both arms.

**Statistical analysis**

Data are given as means ± standard deviation or 95% CI or ranges, or percentages, as appropriate. Patency rates were analysed using the Kaplan–Meier method and differences between groups with the log-rank test. Cox’s analysis was used to identify predictors of access failure, thrombosis and loss.

Population rates were calculated by dividing the total number of events or costs by the total number of years of the follow-up. Poisson’s analysis was used to estimate differences in rates. The relative effect of treatment was assessed in terms of the incidence rate ratio (IRR), derived from the event rate (the total number of events divided by the sum of AVF-years of the follow-up) for TX divided by the event rate for C [24]. All tests were two sided, and differences were considered significant at P < 0.05. All statistical analyses were performed using the SPSS software, version 17 (SPSS, Chicago, IL).

**RESULTS**

As of July 2012, our C included 30 AVFs and the TX 28. The characteristics of the patients and their AVF are given in Table 1. The two groups were similar, apart from a more severe degree of stenosis in TX (a difference that is likely to be clinically insignificant).

Stenoses were identified on the strength of a Qa < 900 mL/min combined with a positive PE in 24 AVFs (13 C, 11 TX); a Qa < 900 mL/min in 21 (9 C, 12 TX); a positive PE in seven (five C, two TX); a positive PE combined with a VAPR > 0.5 in six (three each in C and TX).

Study outcomes and elective interventions are reported in Figure 2. In TX, Qa increased significantly from 720 ± 220 to 1078 ± 250 mL/min (P < 0.001) very soon after the initial elective stenosis repair (within 2 weeks).

Two electively treated AVF rapidly restenosed after initial PTA (one thrombosed and one was abandoned) and one required repeat PTAs to maintain patency, supporting the concern that early stenosis repair by PTA may be harmless in some AVF [1, 11, 12, 25]. The mean Qa measurement per year was 3.4 [95% CI: 3.2–3.6] in C and 3.3 [95% CI: 3.0–3.6] in TX (P = 0.763). In three TX patients restenoses were treated by PTA and stent deployment (one Wallstent-uni stent and two Viabhan stent-grafts). Four patients (one in C and three in TX) underwent surgery if restenoses occurred after PTA or vice versa; in addition, one patient in TX underwent immediate surgical revision of the access after a failed PTA.

The success rate for stenosis repair in dysfunctional but patent AVF in C was 100% (3/3 for PTA and 2/2 for surgery) and it was 94% (45/48) for elective stenosis repair in TX (38/41 for PTA and 7/7 for surgery). A total of nine clotted AVFs (seven in C and two in TX) were considered unsalvageable: this was because one patient was dying (in C), and due to an extensive organization of the thrombus (a large thrombus burden or a thrombus adhering to the vessel wall) or to inadequate veins in the remaining cases. Eight thrombectomies were performed in C, and four in TX: overall, (excluding one patients who was dying) only 8/20 (40%) thrombosed AVFs were declotted and remained suitable for use [5/14 (36%) in C and 3/6 (50%) in TX, P = 0.631].

Unadjusted primary patency, thrombosis-free survival and secondary patency rates are shown in Figures 3 and 4.

Cox’s multivariate analysis identified no significant predictors of access failure (after adjusting for diabetes, baseline Qa and treatment). TX was the only significant predictor of a lower occurrence of thrombosis [β 0.223 (95% CI: 0.067–0.736), P = 0.014]; but when the Qa value immediately before thrombosis or censoring with a patent access (i.e. the latest available Qa measured during the follow-up) was included in the model, this variable became the only significant predictor of a lower risk of thrombosis [β 0.80 (95% CI: 0.70–1.00) for each 100 mL/min, P = 0.029], while TX was no longer associated with thrombosis. TX and the absence of thrombosis
were independent predictors of greater access longevity [β 3.52 (95% CI: 1.08–11.51), P = 0.037 and β 13.52 (95% CI: 3.53–51.75), P < 0.0001, respectively].

Table 2 shows the rates of elective stenosis repair, access failure, thrombosis and loss, temporary CVC placement, CVC-related infections (all involving the tunnel/exit-site) and hospitalization. Figure 5 shows the relative risk ratios (IRRs) of access failure, thrombosis and access loss.

Table 3 shows that there were no statistically significant differences between the groups in terms of mean total annual costs for stenosis repair and maintenance (P = 0.933). The mean ICER for TX was €282 to avoid one episode of thrombosis and €321 to avoid one access loss.

**Post hoc analyses**

Since the guidelines prefer Qa to VAPR surveillance in AVFs [1–4], and because we were still unaware that measuring VAPR was more useful than Qa in detecting outflow stenosis [9] at the time when our study was designed, intervention in our study was based entirely on measuring Qa and its surrogate measures, despite the fact that ~20% of the AVFs enrolled had outflow stenosis (which may be better to surveil by means of VAPR) and the data needed to calculate VAPR were routinely available during the follow-up. In fact, access thrombosis and/or loss was preceded in three AVFs (two in C and one in TX) by an increased VAPR, with no drop in Qa. To see whether conducting VAPR surveillance could change our patient outcomes, we performed a sensitivity analysis considering the above AVFs as uneventful: Kaplan–Meier analysis confirmed that TX significantly reduced the risk of access thrombosis (P = 0.041) and improved access survival (P = 0.017) (data not shown).

To see whether our cost analysis could be generalizable (given that surgery on AVF is performed as an outpatient procedure in many health-care settings, whereas it is always an in-hospital procedure at our institution), we recalculated the costs after substituting the cost of hospital stay with the cost of 1 day at the day hospital for each surgical procedure. Under these conditions.

Table 1. Characteristics of patients and AVF

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>TX</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No patients/AVF</td>
<td>30</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>16/14</td>
<td>18/10</td>
<td>0.435</td>
</tr>
<tr>
<td>Patients age (years)</td>
<td>67 ± 14</td>
<td>60 ± 17</td>
<td>0.103</td>
</tr>
<tr>
<td>Proportion with diabetes (%)</td>
<td>29</td>
<td>33</td>
<td>0.780</td>
</tr>
<tr>
<td>Proportion with cardiovascular disease (%)</td>
<td>50</td>
<td>46</td>
<td>0.798</td>
</tr>
<tr>
<td>AVF age (months)</td>
<td>27 ± 21</td>
<td>21 ± 19</td>
<td>0.271</td>
</tr>
<tr>
<td>Anastomosis site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>distal (lower third of the forearm)</td>
<td>22</td>
<td>17</td>
<td>0.404</td>
</tr>
<tr>
<td>proximal (upper 2/3 of the forearm/upper arm)</td>
<td>8</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Proportion of virgin AVF a (%)</td>
<td>83</td>
<td>86</td>
<td>1.000</td>
</tr>
<tr>
<td>Degree of stenosis (%)</td>
<td>72 ± 8</td>
<td>76 ± 8</td>
<td>0.046</td>
</tr>
<tr>
<td>Site of stenosis b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeding artery</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Anastomosis</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Juxta-anastomotic segment</td>
<td>21</td>
<td>19</td>
<td>0.593</td>
</tr>
<tr>
<td>Cannulation segment</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Outflow segment</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Juxta-anastomotic and outflow segment</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Baseline Qa (mL/min)</td>
<td>792 ± 322</td>
<td>720 ± 220</td>
<td>0.241</td>
</tr>
<tr>
<td>Length of follow-up (months)</td>
<td>27.9 ± 17.6</td>
<td>32.2 ± 19.8</td>
<td>0.376</td>
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</tbody>
</table>

a AVF with no previous surgical or endovascular procedure.
bAnastomosis: includes 1 cm of vessel length on both sites of the anastomosis/juxta-anastomotic segment: the 2–5 cm of the draining vein cranial to the anastomosis/cannulation segment: needling area/outflow segment: draining vein downstream from the needling area (including central veins)/juxta-anastomotic and outflow segment: indicates the presence of multiple stenoses at the different sites of the access.
conditions, the cost was significantly higher for TX than for C \( [841.3 \text{ (95\% CI: 414.6–5899.4)} \text{ versus } 563.2 \text{ (95\% CI: 201.5–1538.4)} \text{ €/AVF-year, } P = 0.012] \) and the mean ICER for TX was €2045 for thrombosis and €2317 for access loss.

**DISCUSSION**

The main finding of this interim analysis on our randomized controlled trial is that elective repair of subclinical stenosis in
AVFs with a $Q_a > 500$ mL/min (i.e. fistulas considered adequate for the purpose of dialysis and at low risk of failure) achieves a significant 3-fold reduction in the risk of thrombosis and access loss in comparison with taking action only once the stenosis has become haemodynamically significant, as recommended in the KDOQI guidelines [1]. We also found that under our study conditions (where all elective surgical procedures and thrombectomies were performed as inpatient procedures) the two strategies share much the same cost profile.

Our study also confirms that revising asymptomatic stenosis may exacerbate stenosis and trigger thrombosis, supporting concerns that early PTA may even be harmful [1, 11, 12, 25]. This unwanted effect was limited in our series, however, and it did not influence the beneficial effect of the strategy devised for our treatment arm (i.e. elective correction of subclinical stenosis and aggressive restenosis identification and repair) on outcomes important to patients. In theory, another unwanted effect of electively correcting stenosis in AVFs with a ‘high’ $Q_a$ may be the onset of high-output heart failure [26]. This should not be a major concern in our study, however, because the $Q_a$ after the elective treatment in our TX arm was always lower than the critical threshold associated with high-output heart failure, i.e. $Q_a > 2000$ mL/min [26]. Moreover, none of the patients in the TX group developed signs of high-output cardiac failure during the follow-up.

Early treatment was no longer a significant predictor of thrombosis when $Q_a$ during the follow-up was included in the Cox analysis, suggesting that its beneficial effect is mediated by the maintenance of higher $Q_a$ levels.

Treatment and thrombosis were independent predictors of access loss, indicating that access longevity can be improved by a strategy of early identification and correction of stenosis, and also by preventing thrombosis (although this may relate to our relatively low declotting success rate).

Our cost analysis revealed no significant differences between the two strategies, because the higher costs incurred for elective stenosis repair in the TX arm were offset by the lower costs for thrombectomies, hospitalizations and the placement of new accesses.

Our study confirms the results of a previous economic analysis showing that the cost of $Q_a$ surveillance in AVFs is much the

FIGURE 4: Unadjusted secondary patency rate (access survival). Access survival was significantly higher in TX (dotted line) than in C (continuous line) ($P = 0.012$). Survival curves were truncated at the 60-month follow-up.

FIGURE 5: The relative risk of events for TX versus C was assessed with the IRR. Circles indicate the IRR and horizontal lines its 95% CI.

Table 2. Outcome rates

<table>
<thead>
<tr>
<th></th>
<th>C mean [95% CI]</th>
<th>TX mean [95% CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure rate (event/AVF-year)</td>
<td>0.271 [0.158–0.334]</td>
<td>0.162 [0.075–0.288]</td>
<td>0.164</td>
</tr>
<tr>
<td>Thrombosis rate (event/AVF-year)</td>
<td>0.215 [0.120–0.354]</td>
<td>0.080 [0.029–0.174]</td>
<td>0.033</td>
</tr>
<tr>
<td>Access loss rate (event/AVF-year)</td>
<td>0.186 [0.099–0.318]</td>
<td>0.066 [0.022–0.155]</td>
<td>0.041</td>
</tr>
<tr>
<td>Elective stenosis repair (event/AVF-year)</td>
<td>0.115 [0.049–0.226]</td>
<td>0.665 [0.494–0.877]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Temporary CVC rate (event/AVF-year)a</td>
<td>0.143 [0.069–0.263]</td>
<td>0.066 [0.022–0.155]</td>
<td>0.202</td>
</tr>
<tr>
<td>Temporary CVC infection rate (event/AVF-year)</td>
<td>0.029 [0.004–0.103]</td>
<td>0.026 [0.003–0.096]</td>
<td>0.941</td>
</tr>
<tr>
<td>Days in hospital (day/AVF-year)</td>
<td>1.12 [0.88–1.39]</td>
<td>0.66 [0.49–0.88]</td>
<td>0.004</td>
</tr>
</tbody>
</table>

aMean number of temporary CVC days was 30 [95% CI: 20–39] in C and 28 [95% CI: 8–48] in TX ($P = 0.844$).
same whatever the threshold used [27], but—at variance with the assumption made by Tonelli et al. [27]—adopting a higher Qa threshold is economically more attractive than a lower one, because it is associated with a mean extra cost of just €828 for thrombosis and €321 for access loss, in comparison with a mean cost of €3500 (range 2219–4465) for thrombectomy and €3800 (856–5877) for the placement of a new access.

Our results support the usefulness of highly sensitive AVF stenosis monitoring/surveillance programmes [e.g. combining PE, a high Qa threshold and VAPR measurements: sensitivity 98% (95% CI: 91–100), in our experience] [16] as opposed to strategies based on programmes with a high positive predictive value [like the one recommended by the KDOQI guidelines: PPV 87% (95% CI: 66–97), in our experience] [9], although the former approach has the drawback of prompting more unnecessary imaging procedures [false positives 38% (95% CI: 25–63) versus 6% (95% CI: 2–14), in our experience] [9] and screening costs.

Based on the results of this interim analysis, we judged it unethical to continue our trial, which was consequently terminated.

We are aware that our study has its limitations. First, it is single-centre study with a small sample size, and unblinded, and this could lead to an overestimation of the effect of treatment. Secondly, we did not consider changes in VAPR as a criterion for intervention, although 20% of our AVFs had outflow stenosis; on the other hand, our sensitivity analysis suggests that the lack of VAPR surveillance did not affect the study outcomes. A third limitation lies in the fact that our cost analysis may not be generalizable, because surgery was performed as an inpatient procedure (whereas it is performed as an outpatient procedure elsewhere). In fact, when we replaced the cost of the hospital stay with the cost of a day spent at a day hospital for each surgical procedure, our early treatment strategy coincided with a significantly higher costs and and a mean ICER of €2045 to avoid one episode of thrombosis and €2317 for avoid losing an access, which is still a relatively modest increase in cost in comparison with a mean cost of €1463 (range 1173–1996) for thrombectomy and €1597 (range 306–2367) for the placement of a new access in this scenario.

Finally, our results only apply to the approach considered in our study (regular monitoring and Qa measurements every 3–4 months, elective stenosis repair by PTA and surgery, unaggressive thrombectomy) and the success rate of the intervention procedures (which was high for elective stenosis revision, but low for thrombosed AVF). We are well aware that the results of our study might have been different had our Qa surveillance been more aggressive (with monthly measurements, as suggested in the KDOQI guidelines [1]), as this would probably have enabled a more timely identification of AVFs at risk of failure in the control arm, before they thrombosed. On the other hand, our study design may have the strength of being more representative of the practice patterns of a busy haemodialysis unit such as ours, where surveillance at very frequent intervals is often unfeasible.

In conclusion, this interim analysis of our randomized controlled trial shows that electively repairing subclinical stenosis in AVF with Qa > 500 mL/min significantly reduces the risk of thrombosis and access loss, and may be cost-effective in comparison with the approach of the KDOQI guidelines, which refers patients for assessment and treatment only if an AVF reveals hemodynamically significant stenosis. This raises the question of whether the currently-recommended criteria should be reconsidered, especially in health-care settings where it is difficult or impossible to screen AVFs for stenosis as frequently as the guidelines suggest.

### CONFLICT OF INTEREST STATEMENT

None declared.

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**Table 3. Cost analysis**

<table>
<thead>
<tr>
<th></th>
<th>Unitary cost (€)</th>
<th>C</th>
<th>TX</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qa measurement</td>
<td>23</td>
<td>82.3 [72.4–93.1]</td>
<td>75.2 [66.0–85.3]</td>
<td>0.937</td>
</tr>
<tr>
<td>Access imaging</td>
<td>41–100</td>
<td>12.5 [4.8–27.1]</td>
<td>40.2 [25.6–61.5]</td>
<td>0.023</td>
</tr>
<tr>
<td>Elective stenosis repair (PTA ± stenting/neo-anastomosis/interposition graft)</td>
<td>844–2924</td>
<td>70.3 [13.8–245.8]</td>
<td>592.9 [289.4–5285.0]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Thrombectomy (endovascular/surgical)</td>
<td>993–1690</td>
<td>170.1 [33.7–595.6]</td>
<td>40.8 [4.3–176.5]</td>
<td>0.106</td>
</tr>
<tr>
<td>Placement of new permanent access (AVF/PTFE graft/permanent CVC)</td>
<td>308–2061</td>
<td>155.8 [34.7–460.8]</td>
<td>34.5 [3.0–168.2]</td>
<td>0.214</td>
</tr>
<tr>
<td>Temporary CVC (cuffed or uncuffed)</td>
<td>308–716</td>
<td>18.0 [8.6–33.2]</td>
<td>16.9 [2.7–57.7]</td>
<td>0.913</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>550</td>
<td>616.0 [484.0–764.6]</td>
<td>363.0 [269.5–484.0]</td>
<td>0.004</td>
</tr>
<tr>
<td>Total cost (€/AVF-year)</td>
<td>1125.0 [652.0–2220.2]</td>
<td>1163.5 [660.5–6318.2]</td>
<td></td>
<td>0.993</td>
</tr>
</tbody>
</table>
REFERENCES


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