PROTOCOL_ASTUTE_OBSERVATIONAL_vers1.0

1. TITLE

Aorto-iliac occusion treatment with ShorT Unibody aorTic Endograft – ASTUTE study

NCT number ###

2. FUNDING

The study is physicians-sponsored. The medical device will be provided by the national health system. The clinical work-up, hospitalization, and operation costs will be delivered under the national health system without any additional cost compared to the standard care. A specific insurance for the patients being part of the study will not be required.

3. STUDYSTAFF

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PI will be responsible for funding. PI will supervise all clinical and research phases (enrollment, treatment, clinical follow-up, data collection, data analyses, validation of the results, and publication).

Investigators:

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Role: protocol writing, clinical screening, enrollment, treatment, data collection, clinical follow-up, data analyses, and publication. The Investigator will be part of the data monitoring.

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Role: protocol writing, clinical screening, enrollment, treatment, data collection, clinical follow-up, data analyses, and publication. The Investigator will be part of the data monitoring committee and the second data manager.

4. BACKGROUND

In the last two decades there was a general shift from conventional open surgery to endovascular mini-invasive interventions, particularly towards patients with iliac and aortic occlusive disease (AIOD). However, while iliac artery angioplasty and stenting increased of 8.5 fold from 1996 to 2000, aorto-bifemoral bypass fell by only 15%[1,2]. Indeed, according to ESVS/ESC guidelines open surgery remains the preferred choice for the most complex lesions to address by in endovascular fashion (TransAtlantic Inter-Society Consensus [TASC II] type C and D lesions)[3]. The reason is the good long-term patency of aorto-bi-iliac or aorto-bifemoral bypass among endovascular devices[4]. Surgery, however, is associated with a high burden of early and late morbidity and mortality, and this aggressive approach is limited by patient's age and comorbidity[3,4]. In 1991 the kissing stent technique emerged as an alternative for bilateral aortoiliac occlusive disease. Even if the reported technical success rates varied between 89% and 100% with a 1 year primary patency between 76% and 98%, outcomes may be worse in more complex lesions owing to radial size mismatch between stents and certain stent configurations within the distal aorta[5,6]. In addition, heavy calfidied or thrombus filled aorta could increase technical complexity and risk of limb and life-threatening procedural complications such as dissections, aortic rupture and peripherical emoblizations. Covered stents may increase patency rates in extensive disease, as shown by the COBEST trial and confirmed in various case series but did not address the problem of a potential radial size mismatch that can lead to re-circulation, turbulence, and stasis of blood, which in turn, may cause thrombus formation and intimal neohyperplasia[7,8]. Another endovascular procedure for the treatment of AIOD is the CERAB technique. A CERAB is defined as an endovascular reconstruction of the aortic bifurcation using at least one covered stent-graft for the

infrarenal aorta (flared proximally) and 2 stent-grafts deployed within the aortic stent and into the common iliac arteries.[9,10,11] This particular configuration leads to the reduction of the radial mismatch, which is defined as the discrepancy between the stented lumen and the vessel lumen after stent placement and, as a result, to more favorable flow conditions. In addition, it protects against potentially fatal aortoiliac rupture during dilatation of heavily calcified lesions. However, radial mismatch is increased if the limbs are placed higher than the nonflared aortic stent. In addition, while the CERAB technique does recreate the aortic bifurcation, future crossover interventions may be more difficult. This is similar to most bifurcated aortic stentgrafts where the angle of engagement at the flow divider makes up-and-over access more challenging. Finally, dead space outside the proximal aortic stent can result in cases of aortic diameters > 20 mm. The aortic stent is then left protruding mal-opposed in a dilated aorta. Hence, this technique may not be indicated in the setting of even mild proximal aortic dilation.

One potential alternative to treat disease of both the distal aorta and the iliac arteries is the use of unibody stent-grafts[1]. The Endologix AFX2 stent-graft is a unibody, low-profile endograft aimed to treat abdominal aortic aneurysms[12,13]. The particular configuration of this device and its so-called anatomical fixation make it potentially an optimal solution to overcome the issue reported before inherent to AIOD treatment[12,13]. This device presents a unique design with its long main body and two innate limbs and is designed to be deployed and sits on the native aortoiliac bifurcation and represents the only one-piece bifurcated endograft designed to use anatomical fixation for endograft stabilization. The AFX device consists of a main bifurcated body and a proximal aortic extension, which affix firmly to the aorta and provides sealing, while reducing the possibility of stent's migration at the same

time. The skeleton of the device is made of a cobalt-chromium alloy in a multilinked self-expanding unibody. External to the stent, the fabric is made of multilayer ePTFE material (STRATA). The stent is attached only to the proximal and distal ends at the proximal aortic extension and allows ePTFE to move independently and conform to abnormal surfaces, facilitating sealing of the sac.[14] According to published literature, the unibody device seems to represent a valid choice in the treatment of abdominal aortic aneurysms, but this particular device would seem to satisfactorily perform even in the treatment of occlusive pathologies.

Theoretical advantages of AFX are:

- Unibody design preserves aortic bifurcation, thank to its anatomical fixation, as described previously. Unlike kissing stents (covered or uncovered), which can often protrude into the native aorta, disrupting flow and functionally raising the aortic bifurcation, a unibody device sits on and preserves the native bifurcation. This makes future “up-and-over” interventions to the lower extremities less technically challenging. Compared to CERAB, by using fewer stents in the narrow aorta, this technique has the added advantage of minimizing potential flow disturbances introduced by multiple covered stents.
- Graft fabric reduces neointimal hyperplasia: there is some evidence, including the randomized COBEST trial, that covered stents may be less likely to restenose or occlude than bare metal stents, particularly in TASC C and D lesions.[7,8] This may be because the graft fabric represents a direct barrier to tissue ingrowth from neo-intimal hyperplasia.
- No limb competition in narrow bifurcation, thanks to its unibody design.
- Unibody stent-graft is protective in cases of potential rupture, such as in heavily calcified lesions.

- Coverage of the entire diseased aorta may reduce atheroembolic risk. Using this covered graft and positioning it proximal and distal to the limits of disease effectively traps atherosclerotic material that could potentially embolize during device deployment, reducing atheroembolic risk.

As with any new treatment alternative, this treatment strategy has limitations.

- Compared with the placement of kissing stents, or even the CERAB technique, the AFX device requires a larger profile sheath (17-Fr ipsilateral sheath, 9-Fr contralateral).
- Placing a stent-graft also has a higher potential for coverage of collateral vessels.
- The procedure is more time consuming and requires a higher level of endovascular technical skill.
- Finally, while cost-effectiveness cannot be evaluated without robust efficacy data and will fluctuate based upon local differences in costs, use of the AFX unibody stent-graft is likely to be more expensive than kissing stent placement.

5. STUDY AIM

BASIC RESEARCH

The aim of the study is to evaluate the patency rates, the safety, and the efficacy of the AFX unibody stent-graft for the treatment of aorto-iliac occlusive disease (AIOD), which may represents an additional technique in the endovascular treatment of this disease.

CLINICAL STUDY

To assess the real-world, in-vivo, clinical effectiveness of the use of Endologix AFX2 stent-graft to treat AIOD. The study population is subjects with AIOD eligible for endovascular treatment, of both sexes, aged 18> years with aorto-iliac occlusive lesions classified as TASC C and D involving aortic bifurcation and/or the first 5mm of one or both common iliacs with a calcium volume in target zone based on real lumen of less than 20% and absence of circumferential calcifications. The clinical intervention will be performed in the study participating centers and for our competence at the Unit of Vascular Surgery (Ospedale Civile di Baggiovara, Azienda Ospedaliero-Universitaria di Modena, Via Pietro Giardini, 1355, 41126 Baggiovara MO, Italy).

EXPECTED RESULTS AND RISK/BENEFIT CONSIDERATIONS

The results will demonstrate whether the Endologix AFX2 stent-graft is effective for the treatment of AIOD, in particular in more complex lesions (TASC C and D). The effectiveness will be evaluated in terms of patency (primary, assisted and secondary), technical success, clinical success, and quality of life improvement. Other objectives are the evaluation of procedure-related adverse events and re-interventions, as well as operative details.

Nowadays, kissing stenting technique and CERAB technique are considered the standard of care in the endovascular treatment of AIOD. However, patency rates and clinical success of the endovascular treatment, especially in the mid- and long- term, are still lower than the classic aorto-femoral bypass. Many aspects like the preservation of the aortic bifurcation, neointimal hyperplasia, limb competition, potential rupture and atheroembolic risk are challenging problems that the endovascular surgeon has to face to improve the outcomes of the endovascular treatment. In vitro studies has investigated hemodynamic aspects[15] but only three other groups have previously discussed their experience with this technique[1,16,17] showing encouraging early- and mid-term results.

Comparing to other endovascular procedures, AFX unibody endograft shows many risks and disadvantages:

- It is a more invasive procedure with larger introducer (19F+7F), which may need a surgical access
- The cost of the procedure is higher if compared to KS (but similar to CERAB)
- The endograft has a risk of fabric laceration with high calcium volume
- Very low chronic outward force (COF) of the Elgiloy stent

6. STUDY DESIGN

This study is multi-center non-randomized prospective observational cohort study which aim to evaluate early-, mid- and long-term patency results in patients affected by AIOD and treated using AFX unibody stent-graft. Patients were followed for 5 years from the moment of the intervention. Inclusion/exclusion criteria were reported above.

7. METHODS

Setting

Patients affected by AIOD classified as TASC B, C or D involving aortic bifurcation and or the first 5mm of one of both common iliacs with indication to endovascular treatment will be prospectively enrolled at the Unit of Vascular Surgery of the Ospedale Civile di Baggiovara (Azienda Ospedaliero-Universitaria di Modena). The Investigators (3 experts Vascular surgeons) will screen the patients for inclusion. Once the patient's eligibility will be stated, informed consent will be collected and the study could take place.

Inclusion criteria:

- Age >18;
- Both sex;
- Preoperative 2.5mm CTA available;
- Written informed consent;
- Patients affected by AIOD classified as TASC B (with aortic involvement) C or D involving aortic bifurcation and or the first 5mm of one of both common iliacs;
- Treated in the coordinator center or in one of the study's participating center's;
- With a calcium volume in target zone based on real lumen of less than 20% and absence of circumferential calcifications;
- Minimum follow-up requested: 3-months, 12-18 months and 5-years CTA; clinical and DUS examination at 6- and 12- and 36-months after the intervention and yearly thereafter.

Exclusion criteria:

- Age<18;
- No preoperative 2.5mm CTA available;
- Refused to sign the informed consent;
- Treated outside the coordinator centers or in one of the study's participating centers;
- Refusal to adhere to the requested follow-up;
- Patients affected by AIOD classified as TASC A or not involving aortic bifurcation or the first 5mm of one of both common iliacs;
- With a calcium volume in target zone based on real lumen of more than 20% and presence of circumferential calcifications;

Pre-operative work-up

The subjects will undergo a complete clinical examination, including pathological and pharmacological anamnesis. Clinical data like Rutherford's stage, WIfI score, ABI will be collected. A complete doppler ultrasound examination will be performed before admission to the ward.

High-quality CTA scans (6th rib to feet and 1-mm slice thickness) not older than 6 months from the scheduled intervention is mandatory for every included patient.

The mentioned CTA will be carefully evaluated independently by two vascular surgeon experts in endovascular aortic and peripheral procedures. Multiplanar and curved reconstructions were obtained for each CTA in a dedicated workstation plugged with Therenva Endosize reconstruction software (Therenva, Rennes, France). All the measures were based on the orthogonal centerline reconstruction. Calcium and thrombus volumes were calculated in percentage respect of the total valles lumen volume.

The measurements taken were reported above:

- Diameters – measured intima-intima. The measures were taken at different levels: aortic diameter just above the lower renal artery (D1), aortic diameter just above the inferior mesenteric artery (D2) maximum aortic diameter above renal arteries (D3), aortic bifurcation (D4), right and left common iliac arteries diameters at level of their bifurcations (D5 and D6 respectively). Diameter of the arteries used for delivery system insertion
- Lengths – total aortic length from lower renal artery to aortic bifurcation (L4), distance between the inferior mesenteric artery to the aortic bifurcation (L2), common iliac arteries lengths (L5 and L6 for right and left respectively), length of stenosis/occlusions.
- Other – Calcium and thrombus volume compared to the total vessel lumen volumes; maximum percentage of stenosis at iliac and, if present, aortic level.

All the measurements were used to plan the interventions and to choose the appropriate device and eventually the distal stent. The device description and characteristics were detailed above.

All supra-mentioned data were collected in a dedicated eCRF.

According to our standard clinical practice all the patients were admitted to ward the evening before surgery day to exclude possible acuity.

Device description

The AFX stent-graft (Endologix, Inc, Irvine, CA, USA) was described in different papers.[18] It is a unibody endograft based on the concept of anatomical fixation. Its proximal extension seals into the aortic neck via exertion of radial force. The cobalt-chromium endoskeleton of the AFX device consists of interconnected stents along the entire length, attached only at the proximal and distal ends of the inner surface of the graft. The stents can slide onto each other and adapt a range of accommodations, allowing flexibility and optimal apposition of the polytetrafluoroethylene (PTFE) material in cases of angulated and curved geometries. Thus, the AFX can accommodate onto the irregularities of the aortic neck (angulation, calcification, thrombus) where an inflexible material might fail to do. Furthermore, the flexibility of the non-attached PTFE fabric can efficiently conform to the wall irregular-shaped necks since it moves independently from the stent under a pressure gradient between the aorta and excluded sac, thus extending the effective seal zone beyond the burdens of the neck's straight segment ("ActiveSeal" mechanism). Notably, in 2014 the PTFE material changed from "Strata" to "Duraply" referring to a highly dense, helical wrap of 20 layers of PTFE providing impermeability and maximum longitudinal and transverse strength.

The diameter of the main unibody comes in 22, 25 and 28mm. The unibody bifurcate comes in variety of lengths (all with increments of 10mm) from 60mm to 90mm for the 22mm size and extending to 120mm for the 25- and 28mm sizes. The iliac limbs of the unibody bifurcate come in diameters of 13, 16 and 20mm in lengths of 30mm and 40mm or even 55mm specifically for the 16mm-diameter limb. The proximal sealing extension (VELA) is available in diameters of 25, 28mm and 34mm and lengths of 75, 80, 95 and 100mm. The VELA segment is responsible for the infrarenal sealing and can be available with stent for suprarenal fixation.

The 25, 28 and 34mm VELA extension is adjusted to the 22, 25 and 28mm of the unibody, respectively.

The iliac limb cylindrical extensions come in 16- and 20mm diameters with accordant 55 and 88mm length, the tapered (20-to-13mm) extensions are available in 70 and 88mm length whereas the stepped fashion comes in 20/25mm of central/distal diameter, respectively, in 55mm and 65mm lengths. Finally, the device is delivered with a 17F introducer system while an 8F sheath can be used contralaterally.

The deployment of the usual Nitinol-based bifurcated endografts is based on the cranial navigation of the device to the level of the renal arteries, deployment of the mainbody with consequent sealing and release of the top cap to disengage the central stent with hooks and/or barbs to achieve fixation. Accordingly, the catheterization of the contralateral limb gate follows; several maneuvers have been described to ensure the proper cannulation of the latter in dubious cases where excessive iliac tortuosity or improper orientation of the limbs' radiopaque markers hinder the discrimination between the ipsilateral and contralateral iliac gate.

On the contrary, the deployment of the unibody bifurcated AFX platform follows a different philosophy. Basically, an integrated contralateral 0.014'' guidewire is advanced through the AFX-introducer from the ipsilateral side, then its floppy end is snared at the aortic bifurcation and withdrawn out of the contralateral sheath while being simultaneously advanced up from the ipsilateral side. The AFX delivery system is advanced until its handle docks into the hemostatic valve. Then the inner core of the delivery device is advanced to transfer the stent-graft though the AFX-introducer. Once the base of the radiopaque tip is aligned with the radiopaque marker-band of the AFX-introducer, the parallel-to-the-contralateral side position of the 0.014'' wire is ensured. Further advancement of the inner core of the delivery system

completes the transfer of the stent-graft which exits the AFX-introducer. It is only then that the proper orientation of the contralateral limb can be checked and adjusted -if needed- by rotating the inner core of the delivery system. Next, the inner core and the contralateral wire are pulled down simultaneously until the stent graft is seated tightly on the aortic bifurcation. The inner core Y-connector is withdrawn to deploy the main-body followed by the removal of the cover of the contralateral limb until it is fully deployed. The contralateral wire lock at the tip of the delivery system is disengaged via advancing a catheter to the aforementioned site and withdrawing the wire through the catheter. Accordingly, the inner core is withdrawn to deploy the ipsilateral limb within the AFX-introducer, whose sequential withdrawn releases fully the deployed ipsilateral limb. Finally, the advancement, deployment and molding ballooning of the central segment (VELA) complete the AAA endovascular treatment with the AFX platform.

Surgical procedure

All the procedure will be carried out in a standard operating room equipped with a mobile C-Arm, or in a Hybrid theater under local sedation. General anesthesia was used in the case of additional procedures. A bilateral percutaneous access was obtained, even if on the basis of the specific case a cut down and contralateral percutaneous access is possible. Hemostasis was achieved using the Proglide/Prostyle (Abbott Vascular, Abbott Park, IL, USA) if a percutaneous access was used. Intraoperative heparin dosing varied by center. However, generally, heparin was administered so as to maintain an activated clotting time >250 seconds, when possible. Techniques for delivery and deployment of the AFX device have been well described when treating AAAs, but in this specific setting there are some tricks to

mention. Normally an exclusive femoral access was used, although a brachial approach can be useful for crossing total occlusions. For TASC B and C lesions, predilatation of the iliac lesions is advisable, while for TASC D lesions it is mandatory. In case of total aortic occlusions, the procedure demands that recanalization of the distal aorta occurs as close as possible to the bifurcation. This will ensure that the AFX device sits directly on the aortic bifurcation and that it is not wedged on aortic debris. The key technique is to recanalize from one common iliac artery into the opposing snaring the wire to create a femoral-femoral crossover. The femoral-femoral wire is then replaced with a MPA catheter; the SurePass wire attached to the contralateral limb is then passed through the catheter. The sheath can be placed within 5 cm of the aortic bifurcation, and the AFX can be delivered through the common iliac and aortic occlusion. Predilatation were performed with bilateral 6-8 mm x 150 mm balloons and or progressive dilatators. Adjunctive stenting of the common iliac or distal aorta could be used in relation on the degree of compression or calcification visualized intraoperatively on completion angiogram and/or intravascular ultrasound. According to our standard of care patients are discharged in the first post-operative day on either aspirin or clopidogrel, if not already on one of these medications.

Follow-up

The first clinical evaluation (before surgery) was performed before discharge primarily to check the femoral access; ABI, Rutherford classification and WIfI score were then collectted All the patients will be assessed clinically and with a high-quality CTA (from 6th rib to groin) within 3 months from surgery and yearly for 5 years thereafter for a total of seven evaluations. DUS and clinical examination will be performed within 3 months from the procedure and yearly thereafter. All the visits will be performed by Investigators.

The patients will be followed up via telephone call to strictly adhere to the present scheme. A telephone number of the Vascular Surgery Unit will be daily available for any patient's clinical issue during the study period. The clinical and radiological follow-up will continue regularly as a standard practice also in case of patients' voluntary withdrawal.

Endpoints

Primary endpoint: short-, mid- and long-term patency rate (primary, assisted and secondary). Restenosis was defined as > 50% diameter reduction (peak systolic velocity [PSV] ratio 2.5-4 and/or PSV of > 180 cm/second) or 75% area reduction on axial imaging. Patency was defined according to suggested Society for Vascular Surgery standards.[19]

Primary patency was defined as uninterrupted flow in the treated aortoiliac segment without occlusion or reintervention. Primary-assisted patency was defined as uninterrupted flow in the treated segment, allowing for reintervention for hemodynamically significant lesions in order to prevent occlusion. Secondary patency was defined as patency of the treated allowing for reintervention for occlusion.

Patency is defined as follows:

- Demonstrably patent graft by an accepted vascular imaging technique, such as arteriography, duplex ultrasound color-flow scan, or magnetic resonance imaging.
- The presence of a palpable pulse, or the recording of a biphasic or triphasic Doppler wave form at two points directly over a superficially placed graft.
- Maintenance of the achieved improvement in the appropriate segmental limb pressure index, that is, not more than 0.10 below the highest postoperative index. Although a greater reduction in pressure index may occur and the graft or re-opened segment may still be patent, imaging proof is required in these instances or any other doubtful or marginal circumstances

covered under criteria 2, 3, or 4. To avoid the confusing effects of distal runoff disease, the most appropriate pressure index for this purpose is at the hext level beyond the revascularized segment or distal anastomosis (see comment below).

- Maintenance of a plethysmographic tracing distal to the reconstruction that is at least 50% or 5 mm greater in magnitude than the preoperative value and close to the postoperative value. (This is the weakest criterion and acceptable only when accurate pressures cannot be measured, as with calcific arteritis in a diabetic patient. However, even in such cases, stronger evidence of patency, in the form of imaging, is clearly preferred.)
- Direct observation of patency at operation or postmortem examination.

Secondary endpoints:

- Technical success, defined as insertion of the endograft with flow into both iliac arteries at the conclusion of the procedure.
- Short-, mid- and long-term clinical success. Ankle brachial indices (ABI) were measured at all follow-up time points. Clinical improvement was assessed using the Rutherford classification (RC) of chronic limb ischemia.
- Freedom from procedure related Adverse events. Adverse events are defined as any systemic or local complication directly related to the procedure. Adverse events that occurred in the first 30-day were considered procedure-related, unless differently demonstrated.
- Freedom from procedure related re-interventtion. Any surgical, open, or endovascular, procedure aimed to address adverse events was named re-intervention.
- Quality of life improvement;
- Analysis of anatomical and preoperative factors afflicting the primary outcomes.

The secondary endpoints represent specific technical aspects related to the procedure and the endograft.

Treatment-related adverse events and re-interventions are important to state the safety of the procedure over time and its external reproducibility.

Timeline

Months 1-3 Organization and logistic set-up.

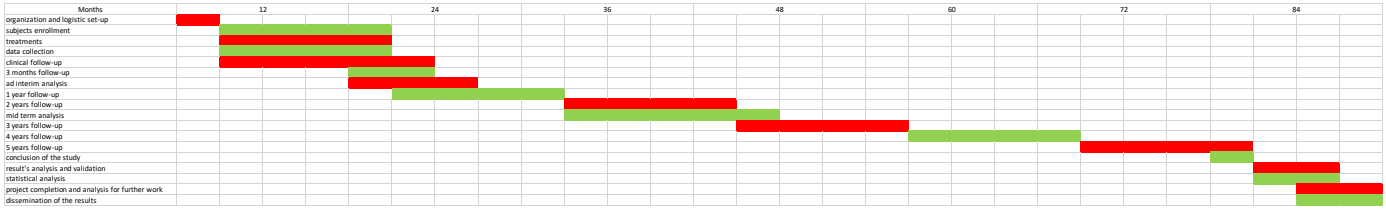
Months 3-15 Subjects enrollment, data collection, treatments, clinical follow-up.

Months 15-18 Conclusion of recruitment, first (3 months) follow-up end for every patient, ad-interim analysis

Month 15-36 12-months follow-up end, mid-term analysis

Month 63-75 Conclusion of the follow-up, analysis of the results and their validation, statistical analysis, project completion and analysis for further work, dissemination of the results

Gannt chart:



Sample size

No statistical analysis of the sample size was carried out. Considering the number of AIOD responding to the inclusion criteria treated in the participating centers and the enrollment period (1 year) a sample size of 100 patients was estimated. This number should be sufficient to evaluate the endpoints reported above.

Recruitment

All patients affected by AIOD responding criteria for endovascular treatment were evaluated at the Vascular Surgery Unit of the Azienda Ospedaliero Universitaria di Modena and the other participating centers. Those meeting the inclusion criteria will be singularly recruited. Taking into account a mean of 100 endovascular procedures for the treatment of complex AIOD (TASC C and D lesions involving aortic bifurcation and or the first 5mm of one of both common iliacs) a safety 12-month recruitment should be considered. The entire Medical staff of the department is informed about the present project and will refer the potential subjects to the Investigators.

8. MANAGEMENT OF THE DATA

The collected data will be managed into a dedicated electronic dedicated case report form (eCRF). Only the Investigators will have access to the data with a personal password to enter in the eCRF. . Only the PI and the first data manager will be able to see all the data, while the other investigators will have permission to manage only the data of the patients enrolled in their center.

To ensure the correct data collection two Investigators will perform the clinical and radiological assessment at each follow-up visit. Before the conclusion of the visit, a double-check will be performed by the Investigators. The CRF will be completed at the time of enrollment and each follow-up visit thereafter.

A personal code will be generated at the enrollment. The CRF will be filled anonymously. The following anamnestic data: age, sex, comorbidities (hypertension, cardiopathy, hyperlipidemia, peripheral arterial disease, previous surgery, etc). Procedure planning details were detailed previously. The procedure details: planned and unplanned adjunctive procedure, the adverse events, the skin-to-skin time, the fluoroscopy time and DAP, the type of anesthesia, the dose, and characteristics of CM used. Primary and secondary endpoints will be registered as defined previously.

The following indicators will also be collected: time of recovery from the intervention and the number of an hour passed in the Intensive Care Unit if needed.

In case of the patient's voluntary withdrawal, the CRF will be discontinued. The patient will undergo standard clinical practice follow-up.

In case of device-related adverse-events, a detailed description of the event will be performed to inform the regulatory authority. The clinical follow-up and the CRF proceed as stated.

In case of death, the study personnel will investigate the cause and any eventual relation with the treatment or device will be declared to the regulatory authority and carefully reported on the eCRF.

Statistical methods

Continuous variables are expressed as mean, and standard deviation and differences were tested with the two-sided t-test or the Mann–Whitney U-test, if appropriate. Categorical variables are expressed as counts and percentages and the chi-square test or Fisher's exact test was used for analysis. All data were entered into the logistic regression model if they had a univariable P-value of <0.05. Data resulted significative in this model were put in a multivariate one. In the multivariable analyses, clinical factors or potential confounding variables were expressed as odds ratio with 95% confidence interval (CI). The goodness of fit of the logistic regression models has been assessed calculating the C-statistic. Patency rate and freedom from adverse events were assessed through the Kaplan-Meier analysis with their relative 95% CI. The analysis was carried out using STATA 15.1 (StataCorp College Station, Texas, USA).

9. MONITORING

The monitoring committee will be composed by the Investigators. The PIs will supervise the committee. The committee will monthly revise the data until the end of the study. The committee will collectively resolve any issues during related to the data collection.

The committee will produce ad interim analyses. Eventual adverse events (mild and/or severe) will be internally investigated by the monitoring committee and externally communicated according to the local regulatory authority disposition. The auditing process will be independent.

The study will be stopped in case of early signs for benefit or arm. The PIs will decide the early interruption. The PIs will communicate the decision within 15-day as the local regulatory authority advice (DM 21.12.2007). The interruption will be conducted under the local regulatory authority.

The Investigators will diffuse the data even in case of early interruption.

10. ETHICAL ASPECTS AND DISSEMINATION

The study will require registration in Clinicaltrial.gov. The study will be conducted under the principles of the Helsinki Declaration and the Local Ethics Committee approval (CE AVEN, Comitato Etico dell'Area Vasta Emilia-Nord). The Investigators will promptly communicate to the CE AVEN any changes to present protocol. The CE AVEN will decide on ad interim modification. The patients' enrollment will require informed consent collection. The consent could be provided by legal guardian. The Investigators will be responsible for the signed document collection. The informed consent will specify the possibility to receive autologous fat harvesting and grafting treatment, basic research analyses on the residual adipose tissue, and clinical follow-up adherence. The study data will be managed anonymously. The data will be kept at the Vascular Surgery unit in a locked room. Only the Investigators will have access to the data. The electronically gathered data will be depersonalized aiming anonymous analysis and interpretation. All Investigators have no disclosure to declare. All Investigators will have access to the final database as well as the regulatory authorities on reasonable request. The study will not provide a specific insurance. Eventual clinical complication will be managed under the national health insurance. Results of the study will be disseminated by scientific publications, congress presentations and medical meetings. The dissemination will proceed to the general audience through general journals, hospital and university websites. The dissemination will be anonymous. The authorship will be defined by the PIs based on each publication. The Investigators will be included amongst authors of the scientific publications. Medical writer it is not expected. The dataset will be shared in a data repository according to the journals requirements for publication.

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