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THE FROZEN ELEPHANT TRUNK TECHNIQUE FOR THE TREATMENT OF COMPLEX AORTIC ARCH AND DESCENDING THORACIC AORTA PATHOLOGIES: LONG TERM OUTCOMES AND DISTAL REINTERVENTION

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Abstract

Background

The frozen elephant trunk(FET) technique is one of the last evolution in the treatment of complex pathologies of the aortic arch and the descending thoracic aorta. This technique has become a widely used approach for the treatment of thoracic aortic aneurysm(TAA), chronic aortic dissection(CAD) and acute aortic dissection(AAD).

Materials and methods

Between January 2007 and March 2021, a total of 396 patients (mean age=60.8±11.3 years, man=80%) underwent total aortic arch replacements with the FET technique at the Cardiac Surgery Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, University of Bologna. The FET prostheses used were Jotec E-vita open (Jotec Inc, Hechingen, Germany) (n=181,49.1%), and Vascutek Thoraflex-Hybrid (Vascutek, Inchinnan, Scotland) (n=188,50.9%). The main indications

were thoracic aortic aneurysm (n=104,28.2%), chronic aortic dissection (n=224,53.4%) and acute aortic dissection (n=68, 18.4%).

We divided the population in two groups according 2 factors: the position of the distal anastomosis (zone 2 vs zone 3) and the length of the stent graft (< 150 mm vs > 150 mm). The 2 groups analyzed were: conservative group (Zone 2 anastomosis + stent length < 150mm, n. 140 pts) and aggressive group (zone 3 anastomosis + stent length > 150mm, n. 141).

Data were analyzed with SPSS Statistics 24.0 (Statistical Package for Social Science, IBM, Armonk, NY, USA). All values are expressed as n.(%) and mean ± standard deviation or range. Categorical and continuous variables were compared using chi-square test and t-test respectively. Survival and freedom from aortic reintervention was analyzed with Kaplan Meyer method. For the risk factor analysis a Cox regression analysis was per performed.

Results

The overall 30-day mortality rate was 13% (48/369); the risk factor analysis showed that an aggressive approach was neither a risk factor for major complication (permanent dialysis, tracheostomy, bowel malperfusion and permanent paraplegia) neither for 30-day mortality. The survival rate at 1, 5,10 and 15 years was 87.7%, 75%, 61.3% and 58.4% respectively. During the follow up, 127 patients underwent a redo cardiac surgery; among these group, an aortic reintervention was performed in 122 patients (38%), 5 patients received a non-aortic cardiac surgery. Freedom from aortic reintervention at 1-, 5- and 10-year was 77%, 54% and 44% respectively. The freedom from aortic reintervention in the two subgroups was higher in the ‘aggressive’ group respect the ‘conservative’ group (62.5% vs 40.0% at 5 years, log rank=0.056). The Cox regression analysis revealed that an aggressive approach was not protective for aortic reintervention at follow up and for death at follow up.

Conclusions

The FET technique represents a feasible and efficient option in the treatment of complex thoracic aortic pathologies. An aortic reintervention after FET is very common and the decision-making approach should consider and balance the higher risk of an aggressive approach in terms of post-operative complication versus the higher risk of a second aortic reintervention at follow up.

Introduction

The Frozen Elephant Trunk Technique

The pathologies of the aortic arch and the descending thoracic aorta have always been hard to handle for cardiac surgeons. The treatment of these pathologies often requires multiple operations with high intra-and post-operative risks, with a significant rate of in-hospital mortality.[1] In 1983, Dr. Borst described the 2-stage elephant trunk technique in Hannover, Germany, which has greatly facilitated surgical treatment of this special pathologic entity.[2]

Among the years, several new techniques have been introduced to simplify the procedures with the aim to reduce the operative risks and the necessity of two major surgical procedures to achieve a complete repair of extensive aortic lesions in one single operation.[1,3]

The frozen elephant trunk (FET) technique was introduced in 1996 and is one of the last evolutions in this field, it requires the use of a pre-assembled hybrid prosthesis consisting of a standard Dacron vascular portion to replace the aortic arch and a stent graft (SG) component, which is placed anterogradely through the open aortic arch into the proximal descending thoracic aorta.[1] The FET approach fundamentally, represents the modern evolution of the Borst's technique, allowing the replacement of the whole arch in one stage with the option of a direct treatment of the proximal descending thoracic aorta based on the stent component. Furthermore, this creates a safe landing zone for the following endovascular treatment of the downstream aorta.[1,4]

Since the application of FET, this technique has become a widely used approach for the treatment of thoracic aortic aneurysm, TAA) as well as chronic aortic dissection (CAD) and acute aortic dissection (AAD). acute and post- dissection aneurysms as well as aneurysms of the thoracic aorta.[5,6]

Thus, the FET technique not only affects the stent-grafted segment but also the downstream aorta with positive effects on aortic remodeling.

It also enables subsequent procedures, either one or second stage (i.e., endovascular stent extension or open aortic repair).[7]

Several studies reported the benefits of the hybrid stent graft technique it has an immediate effect on the collapsed true lumen in case of aortic dissection and hence an improve in the perdusion and chronically it promotes the downstream aortic remodeling. [8,9]

Devices

During the last two decades the continuous development of technologies leads to the design of different FET devices in order to improve this one step procedure.[10–13] Some of them are following listed:

- Gianturco Z-stent (Cook®, Inc., Bloomington, USA).
- Chavan-Haverich Prosthesis (Curative GmbH, Dresden, Germany).
- E-Vita Open, E-Vita Open Plus, E-vita NEO® (Jotec® GmbH, Hechingen, Germany).

- CronusTM (MicroPort Medical Co., Ltd, Shanghai, China).
- ThoraflexTM Hybrid Prosthesis (Vascutek®, Terumo®, Inchinnan, Scotland, UK).
- J Graft FROZENIX (Japan Lifeline, Tokyo, Japan)
- Ascyrus Medical Dissection Stent (AMDS) Hybrid Prosthesis, Cryolife/Jotec, Hechingen, Germany)

The two hybrid prostheses currently available in Europe are the E-evita Open Plus/ NEO hybrid stent graft system provided by JOTEC (Hechingen, Germany) and the Thoraflex Hybrid provided by Vascutek (Inchinnan, Scotland).

E-Vita Open, E-Vita Open Plus and Evita Open Neo and Enovia

The E-Vita Open and its new version the E-Vita Open Plus was the first hybrid prosthesis available on the market. It consists of a proximal part in Dacron for the arch replacement invaginated inside the self-expandable stent graft for the descending thoracic aorta. It can be delivered anterogradely form the arch by an introducer. The vascular portion is sutured to the distal stump of the aorta using a collar then the arch prosthesis is released from the endovascular portion and used to replace the arch, with an 'island' reimplantation of the supra-aortic vessels. The Evita Open stent graft portion is available between 20- and 40-mm diameter ant 130-, 150- and 160-mm length.[14,15]

The E-vita Open NEO is a recent evolution of the Evita graft, it's available in tree versions with branches for the reimplantation of the supra-aortic vessels with a separated technique or debranching.[16,17]

Thoraflex Hybrid

The Thoraflex hybrid prostheses, available from 2012, is composed by a tetra-branched arch gelatin-coated vascular portion that allows the single reimplantation of the 3 supra-aortic vessels and a prompt reperfusion of the lower part of the body with the fourth branch once the distal anastomosis is completed; the stent portion is composed by a self-expanding stent-graft constructed of thin-walled polyester and nitinol ring stents. The endovascular part of these prostheses can be available in different diameters (28–40mm) and lengths (100 or 150 mm).[13,18,19]

Aortic Pathologies and Surgical Indications for Frozen Elephant Trunk

The frozen elephant trunk (FET) is nowadays in the aortic surgeons' armamentarium, it's use has grown significantly in recent years since this hybrid prostheses can be used for several aortic pathology, especially in case of complex thoracic aorta lesions (both acute and chronic).

Pathologies that would require multiple-step surgical procedures can now be treated with a single step procedure and eventually treated with an endovascular 2nd step. [10]

According to current guidelines the FET procedure have a surgical indication in several aortic pathologies. We generally treat chronic aneurysms involving the ascending aorta, the aortic arch and the descending thoracic aorta such us thoracic aortic aneurysm and aortic dissections with the FET technique, Acute and chronic dissections involving all thoracic aorta and aneurysms affecting the distal aortic arch and proximal portion of the descending thoracic aorta. We have also extended the indication to all patients with acute aortic dissection of type A who present an intimal laceration in correspondence of the aortic arch f either in correspondence with the proximal portion of the descending thoracic aorta or in case of retrograde type A dissection with intimal laceration in the descending thoracic aorta and with retrograde propagation of the dissecting process. Another indication to the FET is the type B aortic dissection when endovascular treatment is not possible for anatomical reasons or when an aneurysm of the ascending aorta and/or aortic arch coexists.[20]

Thoracic aortic aneurysms

In case of thoracic aortic aneurysm involving several portions of the aorta, especially when two surgical steps are planned. If a distal sealing is achieved with the hybrid procedure, the FET procedure is definitive; in case of a not optimal distal sealing a second stage with TEVAR can be planned to reach a proper exclusion of the aneurysm, in selected case the second case can be either endovascular either surgical. The nitinol stent graft infact can be clamped or it can be a safe proximal landing zone for the following TEVAR. [12,21]

Acute type A aortic dissection

The FET can also be used successfully in case of acute aortic dissection, especially in case of dissection complicated by malperfusion it can lead to an expansion of the true lumen and with an extensive treatment of the DTA it can help to prevent the development of post-dissection aneurysm in the chronically dissected downstream aorta. On the other hand, the use of FET for the treatment of an acute aortic dissection must be carefully balanced, evaluating the higher surgical risk, especially in an emergency setting, and the mid-term benefits. Aortic morphology including an accurate evaluation of the entry tears and the origins of the visceral vessels is mandatory for a correct indication in an emergency situation.[22–24]

Post-dissection aneurysm after Type A dissection repair

Residual aortic dissection represents the most frequent indication for the use of the frozen elephant trunk.[25] The possibility to use FET depends on entry tear position and involvement of the thoraco-abdominal aorta including visceral branches. A careful evaluation of the origin of visceral branches is mandatory: a selective origin from the false lumen represents a possible contraindication to FET since the high risk of FL thrombosis and consequent malperfusion. The presence of an intimal tear in the descending thoracic aorta could call for a FET, an accurate measurement of the true lume aortic diameter is mandatory to achieve the best sealing on the distal landing zone.[26]

Acute type B aortic dissection

According to current guidelines, the medical therapy is the first line treatment in case of uncomplicated type B acute aortic syndrome. The endovascular treatment with TEVAR is the treatment of choice in patients with complicated acute type B aortic dissection.[27]

In selected cases of type B aortic dissection (or other type B aortic syndromes) the FET technique can be an alternative to the TEVAR; a complicated type B with a concomitant ascending aorta pathology or a dissection morphology with an high risk of retrograde extension can be an indication for FET in this cases. [28]

Penetrating atherosclerotic ulcers/intramural hematomas

As previously discussed, the FET technique find indication also in those acute or chronic aortic pathologies that involve several segments of the thoracic aorta including the arch and the descending thoracic aorta. For instance, patients with penetrating atherosclerotic ulcers (PAUs) with an increased risk of stroke and embolism could be candidates for the FET procedure. In patients with intra-mural hematoma of the entire thoracic aorta the frozen elephant trunk can be evaluated even in case of a suspect entry tear (incomplete dissection) in the distal aortic arch or the descending aorta. [29,30]

Materials and Methods

All data are reported according to the reporting standard in aortic surgery. [31]

Population

Between January 2007 and March 2022, a total of 369 consecutive patients underwent total aortic arch replacements with FET technique. Indications for the FET procedure were: degenerative aortic aneurysm (DAA) involving the aortic arch and the descending thoracic aorta (n=101, 27.4%); chronic aortic dissection (CAD, n=200, 54.2%), including residual type A, chronic type A and chronic type B dissections and acute aortic dissection (AAD) (n. 68, 18.4%), including acute type A dissection (n=49, 13.3%) and acute type B dissection (n=18, 4.9%).

All elective patients underwent routine preoperative examinations. coronary angiography or coronary angio computed tomography scan if aged < 50 years, echocardiography and aortic angio (CT) scans. In emergency cases surgery was performed after the diagnostic CT scan and echocardiography only.

We performed a descriptive analysis according to the different underlining pathology. Therefore, in order to investigate the impact of a more distal repair on outcomes (post-operative comorbidities, reintervention, early and late mortality) we divided the population in two groups according 2 factors: the position of the distal anastomosis (zone 2 vs zone 3) and the length of the stent graft (< 150 mm vs > 150 mm). The 2 groups analyzed were: conservative group (Zone 2 anastomosis + stent length < 150mm, n. 140 pts) and aggressive group (zone 3 anastomosis + stent length > 150mm, n. 141). The remaining patients (n.88) were excluded by this second analysis.

Peri-operative management

In all patients, near-infrared spectroscopy was used to monitor cerebral perfusion before, during and after the surgery. The cerebrospinal fluid (CSF) drain was routinely used to monitoring the spinal pressure with a target value below ca. 12 mmHg in all elective patients. In acute cases the drain was inserted in the ICU immediately after the operation if a spinal cord injury was suspected during the early neurological examination in the intensive care unit.

Surgical Technique

Our surgical technique provides a full sternotomy; after systemic heparinization, the cardiopulmonary bypass is instituted using the right axillary artery (directly or through a 8 mm Dacron graft interposition), femoral artery, innominate artery, or ascending aorta when feasible. Right atrial cannulation is usually used for venous drainage. A left ventricular drain is achieved with a vent inserted through the right superior pulmonary vein. Core cooling to a nasopharyngeal temperature of 25°C was then accomplished, and circulatory arrest was instituted.[32] Myocardial protection is performed with infusion of modified Bretschneider cardioplegia (Custodiol; Koehler Chemie, Alsbach- Haenlein, Germany). The cerebral protection is achieved with antegrade selective cerebral perfusion according Kazui technique.[33,34] The arch it opened and completely resected, and the disal stump of the aorta is prepared with external polytetrafluoroethylene felt fixed with 4 internal pledgeted U-stitches. The stent-graft system was then introduced in an antegrade fashion into the descending aorta over the previously positioned stiff guidewire and then released. The distal anastomosis is performed between the collar and the previously prepared native aorta at aortic zone 2 or 3.[35] The side branch was then cannulated, and the lower-body perfusion was restored. The supra-aortic vessels were reimplanted, starting from the left subclavian artery. In order to reduce the myocardial ischemia, the proximal repair is performed before the supra-aortic vessels that are usually reimplanted on beating heart during the rewarming.[13]

Follow-up

The follow-up was 100% complete and performed for all hospital survivor with outpatient clinic visits or phone call. Moreover, the radiological follow-up was performed with postoperative CT at 6 months from the discharge and yearly thereafter if a stability of the pathology was recorded. Multiplanar reconstruction in 3 dimensions was used to measure orthogonal aortic diameters and center line reconstructions were used to measure aortic length.

Statistical Analysis

Data were analyzed with SPSS Statistics 24.0 (Statistical Package for Social Science, IBM, Armonk, NY, USA). All values are expressed as n. (%) and mean ± standard deviation or range. Categorical and continuous variables were compared using chi-square test and t-test respectively. The incidence of post-operative complications in both groups of patients was assessed using the Mantel– Haenszel $\chi 2$ test.

Death at follow-up and freedom from reintervention were analyzed with the Kaplan–Meier method. We perform a Cox proportional-hazard risk analysis to identify if a more aggressive approach was a risk factor for early complication and/or 30-day mortality.

All the analysis were performed with SPSS 26.0 (SPSS Inc, Chicago, Ill).

Results

Mean age at the time of aortic arch repair was 60.7±11.4 years with a significant difference between groups: patients operated for degenerative aneurysm were significantly older. Two-hundred ninety-eight patients (80.8%) were male, with higher prevalence in chronic aortic dissection group respect to the others two groups. The 52.8% of patients underwent a previous cardiac operation (n=195). All pre-operative details are presented in Table 1. Two different FET prostheses were used: the Jotec E-vita open (Jotec Inc, Hechingen, Germany) (n=181, 49.1%), and the Vascutek Thoraflex-Hybrid (Vascutek, Inchinnan, Scotland) (n=188, 50.9%).

Operative Data

Operative and post-operative data are given in Tables 2 and 3. All patients were operated through a median sternotomy. Arterial cannulation was achieved through the brachiocephalic trunk in 120 pts (32.5), the axillary artery in 109 (29.5%), the femoral artery and the ascending aorta respectively in 14.9 and 14.6 %; left carotid artery was used in 30 patients (8.1%). Mean cardiopulmonary bypass time and aortic cross-clamp time were 230.8±67.7 and 144.8±52.3 minutes, respectively.

A concomitant cardiac procedure was performed in 161 patients (43.6%), an aortic root repair (Bentall procedure or valve- sparing aortic root repair) was necessary in 91 patients (24.7%). The David procedure was more frequently used in patients operated for acute aortic dissection (p-value=0.033).

The supra-aortic vessels were reimplanted with selective reimplantation in 268 patients (72.6%), in the remaining patients the island technique was performed. Separate grafting of arch vessels was utilized significantly more frequently in the acute aortic dissection group (85.1%) respect to other groups: 59.4% in degenerative aortic aneurysm vs 75.1% in the chronic aortic dissection group (p-value <0.001).

Mean endovascular stent diameter was 30.9 ±4.5 mm, the stent diameter was significantly larger in the DAA group (33.8 ±4.6) respect to the AAD (28.0 ±3.1) and the CAD groups (30.4 ±3.9, p-value <0.001). Other operative data including the stent length and the others types of concomitant procedure are reported in table 2.

Early Outcomes

Re-exploration for bleeding was performed in 13% of patients (48/369). Respiratory failure requiring tracheostomy assessed at 10.3% (n=38). The incidence of permanent neurological events was 16.5% (61/269 pts); we observed an incidence of spine malperfusion of 10.6% with only 16 patients (4.3%) that suffered of permanent spinal cord injury with persistent paraplegia and positive spine MRI. The incidence of spinal cord injury was comparable between the three groups (p-value=0.99). Overall renal malperfusion occurred in 21.1% of patients;

44 (11.9%) patients depended on dialysis at discharge (permanent dialysis).

The overall 30-day mortality rate was 13% (48/369 pts); there was a statistically significant different between patients with degenerative aneurysm, acute dissection and chronic dissection: 14.9% (n= 15) vs 22% (n= 15) and 9% (n=18) respectively (p-value=0.015).

Causes of death were multiorgan failure in 4.9% (n=18), low cardiac output in 4.3% (n=16), irreversible neurological damage in 1.6% (n=6) and aortic rupture in 2.2% (n=8). Postoperative data are reported in table 3.

The risk factor analysis showed that an aggressive approach was neither a risk factor for major complication (permanent dialysis, tracheostomy, bowel malperfusion and permanent paraplegia) neither for 30-day mortality.

Late Outcomes and Reintervention

All 321 survivors were followed up for a mean follow up time of 60.2 ± 50.7 months. The survival rate at 1, 5,10 and 15 years was 87.7%, 75%, 61.3% and 58.4% respectively. Figure 1.

The subgroup analysis revealed that the incidence of death at follow up was significantly higher in the patients that received an aggressive approach, similarly the survival rate at five years was significantly lower in patient that received a more extensive approach respect the ones received a conservative one: 70.9% vs 82.6 respectively, log-rank=0.05) Figure 2.

During the follow up, 127 patients underwent a redo cardiac surgery; among these group, an aortic reintervention was performed in 122 patients (38%), 5 patients received a non-aortic cardiac surgery.

Freedom from aortic reintervention at 1-, 5- and 10-year was 77%, 54% and 44% respectively with a mean interval time to aortic reintervention of 22.6 ± 28.6 months (Figure 3).

One hundred four-teen patients (35.5%) received a second endovascular stage while an open thoracic, thoracoabdominal aortic, or abdominal aortic replacement was performed in 8 patients (2.5%).

Among the patients received an endovascular treatment, the vast majority (49 patients; 43%) were operated for distal stent induced new entry (dSINE) or distal landing zone degeneration. Thirty-six patients (31.1) required an aortic reintervention for a pathology progression (i.e., aortic diameter enlargement), in the remaining 29 patients (25.4) the indication for endovascular re-operation was an endoleak.

Open thoracic, thoracoabdominal aortic, or abdominal aortic repairwere performed in 7 patients (20%). Detailed informations on distal intervention are depicted in Table 4.

The freedom from aortic reintervention in the two subgroups was higher in the 'aggressive' group respect the 'conservative' group (62.5% vs 40.0% at 5 years, log rank=0.056; figure 4).

The Cox regression analysis revealed that an aggressive approach was not a risk factor for aortic reintervention at follow up and for death at follow up (table 5).

Discussions

The frozen elephant trunk technique is nowadays widely used for complex thoracic aortic disease since it allows the aortic arch replacement and the descending thoracic aorta coverage in a single step procedure facilitating a positive remodeling of the downstream aortic segments. In the last period we assisted to a ‘proximalization’ of the technique with a more proximal distal suture line and the use of shorter stent graft with the aim to reduce the incidence of post-operative malperfusion and particularly spinal cord malperfusion. On the other hand, a more conservative approach may expose to a higher rate of reintervention.

Our peri-operative results are satisfactory with an acceptable 30 day - mortality considering the complexity of the pathology, similar to other studies performed by other European cardiac surgery units. Similarly, the long-term survival at 5-, 10- and 15-years were comparable to previous studies.[9,15,19]

Our analysis showed that a more aggressive approach is burdened by a higher incidence of post-operative complication; despite this, at the risk factor analysis, a more aggressive approach did not result a significant risk factor for early post-operative comorbidities and 30-day mortality.

Looking at the longer-term outcomes our analysis showed that patients that received an 'aggressive approach' had a significant lower survival at follow up compared to the conservative group.

In our series the rate of aortic reintervention assessed at 38%. The subgroup analysis showed that patients treated with an aggressive approach had also a lower rate of aortic reintervention during the follow up, even if the risk factor analysis did not identify any independent predictors for aortic reintervention.

Conclusions

The FET technique represents a feasible and efficient option in the treatment of complex thoracic aortic pathologies. An aortic reintervention after FET is very common and the decision-making approach should consider and balance the higher risk of an aggressive approach in terms of post-operative complication versus the higher risk of a second aortic reintervention at follow up.

Limitation

Main limitations of this study are its retrospective nature and the single-center experience.

Bibliography

1. Kato M, Ohnishi K, Kaneko M, et al. New graft-implanting method for thoracic aortic aneurysm or dissection with a stented graft. *Circulation*. 1996;94(9 Suppl):II188-93.

2. Borst HG, Walterbusch G, Schaps D. Extensive aortic replacement using “elephant trunk” prosthesis. *Thorac Cardiovasc Surg*. 1983;31(1):37-40. doi:10.1055/s-2007-1020290

3. Suto Y, Yasuda K, Shiiya N, et al. Stented elephant trunk procedure for an extensive aneurysm involving distal aortic arch and descending aorta. *J Thorac Cardiovasc Surg*. 1996;112(5):1389-1390. doi:https://doi.org/10.1016/S0022-5223(96)70157-5

4. Karck M, Chavan A, Hagl C, Friedrich H, Galanski M, Haverich A. The frozen elephant trunk technique: a new treatment for

thoracic aortic aneurysms. *J Thorac Cardiovasc Surg*. 2003;125(6):1550-1553. doi:10.1016/s0022-5223(03)00045-x

5. Shrestha M, Martens A, Kaufeld T, et al. Single-centre experience with the frozen elephant trunk technique in 251 patients over 15 years. *Eur J Cardiothorac Surg*. 2017;52(5):858-866. doi:10.1093/ejcts/ezx218

6. di Bartolomeo R, Pantaleo A, Berretta P, et al. Frozen elephant trunk surgery in acute aortic dissection. *Journal of Thoracic and Cardiovascular Surgery*. 2015;149(2):S105-S109. doi:10.1016/j.jtcvs.2014.07.098

7. Usai MV, Ibrahim A, Oberhuber A, et al. Quantification of volume changes in the descending aorta after frozen elephant trunk procedure using the Thoraflex hybrid prosthesis for type A aortic dissection. *J Thorac Dis*. 2021;13(1):60.

8. Dohle DS, Tsagakis K, Janosi RA, et al. Aortic remodelling in aortic dissection after frozen elephant trunk. *European Journal of*

Cardio-thoracic Surgery. Published online 2016. doi:10.1093/ejcts/ezv045

9. Ius F, Fleissner F, Pichlmaier M, et al. Total aortic arch replacement with the frozen elephant trunk technique: 10-year follow-up single-centre experience †. Published online 2013. doi:10.1093/ejcts/ezt229

10. Mariani C, Murana G, Leone A, di Marco L, Pacini D. Frozen Elephant Trunk in Aortic Arch Disease: Different Devices for Different Pathologies. *Medicina (Kaunas)*. 2021;57(10). doi:10.3390/medicina57101090

11. di Bartolomeo R, Pellicciari G, Cefarelli M, di Eusanio M. Frozen elephant trunk surgery using the E-vita open plus prosthesis. *Ann Cardiothorac Surg*. 2013;2(5):656-659. doi:10.3978/j.issn.2225-319X.2013.09.01

12. Karck M, Chavan A, Hagl C, Friedrich H, Galanski M, Haverich A. The frozen elephant trunk technique: a new treatment for

thoracic aortic aneurysms. *J Thorac Cardiovasc Surg*. 2003;125(6):1550-1553.

13. di Marco L, Pacini D, Murana G, Mariani C, Amodio C, di Bartolomeo R. Total aortic arch replacement with frozen elephant trunk (Thoraflex). *Ann Cardiothorac Surg*. 2018;7(3):454-456. doi:10.21037/acs.2018.04.05

14. Tsagakis K, Dohle D, Benedik J, Lieder H, Jakob H. Overall Essen's experience with the E-vita open hybrid stent graft system and evolution of the surgical technique. *Ann Cardiothorac Surg*. 2013;2(5):612.

15. Jakob H, Dohle D, Benedik J, et al. Long-term experience with the E-vita Open hybrid graft in complex thoracic aortic disease. *European Journal of Cardio-thoracic Surgery*. 2017;51(2):329-338. doi:10.1093/ejcts/ezw340

16. Rorris FP, Antonopoulos CN, Gissis I, Tsagakis K, Kokotsakis J. E-Vita OPEN NEO Hybrid Stent Graft: A New Frontier for Total Arch Replacement. *Ann Vasc Surg*. Published online 2022.

17. Jakob H, Idhrees M, Bashir M. From E-VITA open plus to E-VITA NEO and E-NOVIA. *J Card Surg*. 2021;36(5):1814-1817.

18. Harky A, Bashir M, Wisniewski K, et al. Single-Center Experience With the Thoraflex TM Hybrid Prosthesis: Indications, Implantation Technique and Results. *Frontiers in Cardiovascular Medicine | www.frontiersin.org*. 2022;1:924838. doi:10.3389/fcvm.2022.924838

19. Shrestha M, Pichlmaier M, Martens A, Hagl C, Khaladj N, Haverich A. Total aortic arch replacement with a novel four-branched frozen elephant trunk graft: First-in-man results. *European Journal of Cardio-thoracic Surgery*. 2013;43(2):406-410. doi:10.1093/ejcts/ezs296

20. Shrestha M, Bachet J, Bavaria J, et al. Current status and recommendations for use of the frozen elephant trunk technique: A position paper by the Vascular Domain of EACTS. *European Journal of Cardio-thoracic Surgery*. 2015;47(5):759-769. doi:10.1093/ejcts/ezv085

21. Baraki H, Hagl C, Khaladj N, et al. The frozen elephant trunk technique for treatment of thoracic aortic aneurysms. *Ann Thorac Surg*. 2007;83(2). doi:10.1016/J.ATHORACSUR.2006.10.083

22. Katayama A, Uchida N, Katayama K, Arakawa M, Sueda T. The frozen elephant trunk technique for acute type A aortic dissection: Results from 15 years of experience. *European Journal of Cardio-thoracic Surgery*. 2014;47(2):355-360. doi:10.1093/ejcts/ezu173

23. Shrestha M, Haverich A, Martens A. Total aortic arch replacement with the frozen elephant trunk procedure in acute DeBakey type I aortic dissections. *European Journal of Cardio-thoracic Surgery*. 2017;51:i29-i34. doi:10.1093/ejcts/ezw341

24. Leone A, Murana G, di Marco L, et al. Current status in decision making to treat acute type a dissection: limited versus extended repair. The Bologna approach. *Journal of Cardiovascular Surgery*. 2020;61(3):272-277. doi:10.23736/S0021-9509.20.11229-1

25. Mariani C, Botta L, Leone A, et al. Visceral malperfusion after Frozen Elephant Trunk in chronic aortic dissection: post-operative predictors and outcomes. *Int J Cardiol*. 2021;335:26-31. doi:10.1016/j.ijcard.2021.04.004

26. Roselli EE, Bakaeen FG, Johnston DR, Soltesz EG, Tong MZ. Role of the frozen elephant trunk procedure for chronic aortic dissection. *European Journal of Cardio-thoracic Surgery*. Published online 2017. doi:10.1093/ejcts/ezw338

27. Erbel R, Aboyans V, Boileau C, et al. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the

thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European. *Eur Heart J*. 2014;35(41):2873-2926. doi:10.1093/eurheartj/ehu281

28. Qi RD, Zhu JM, Liu YM, et al. Frozen Elephant Trunk for Acute Type B Dissection Involving the Distal Arch in the Hybrid Repair Era. *Ann Thorac Surg*. 2018;106(4):1182-1188. doi:10.1016/j.athoracsur.2018.04.011

29. di Marco L, Murana G, Leone A, et al. Use of the frozen elephant trunk technique for type A intramural hematoma. *Ann Cardiothorac Surg*. 2019;8(5):574-576. doi:10.21037/acs.2019.08.04

30. Evangelista A, Czerny M, Nienaber C, et al. Interdisciplinary expert consensus on management of type B intramural haematoma and penetrating aortic ulcer. *Eur J Cardiothorac Surg*. 2015;47(2):209-217. doi:10.1093/ejcts/ezu386

31. Rylski B, Pacini D, Beyersdorf F, et al. Standards of reporting in open and endovascular aortic surgery (STORAGE guidelines). *European Journal of Cardio-Thoracic Surgery*. 2019;56(1):10-20. doi:10.1093/ejcts/ezz145

32. Pacini D, Pantaleo A, di Marco L, et al. Visceral organ protection in aortic arch surgery: safety of moderate hypothermia. *Eur J Cardiothorac Surg*. 2014;46(3):438-443. doi:10.1093/ejcts/ezt665

33. Kazui T, Inoue N, Yamada O, Komatsu S. Selective cerebral perfusion during operation for aneurysms of the aortic arch: a reassessment. *Ann Thorac Surg*. 1992;53(1):109-114. doi:10.1016/0003-4975(92)90767-x

34. di Bartolomeo R, Pacini D, di Eusanio M, Pierangeli A. Antegrade selective cerebral perfusion during operations on the thoracic aorta: our experience. *Ann Thorac Surg*. 2000;70(1):10-16. doi:10.1016/s0003-4975(00)01400-4

35. Leone A, di Marco L, Coppola G, et al. Open distal anastomosis in the frozen elephant trunk technique: Initial experiences and preliminary results of arch zone 2 versus arch zone 3. *European Journal of Cardio-thoracic Surgery*. 2019;56(3). doi:10.1093/ejcts/ezz103

Tables

Figures

Figure 1. Overall Survival

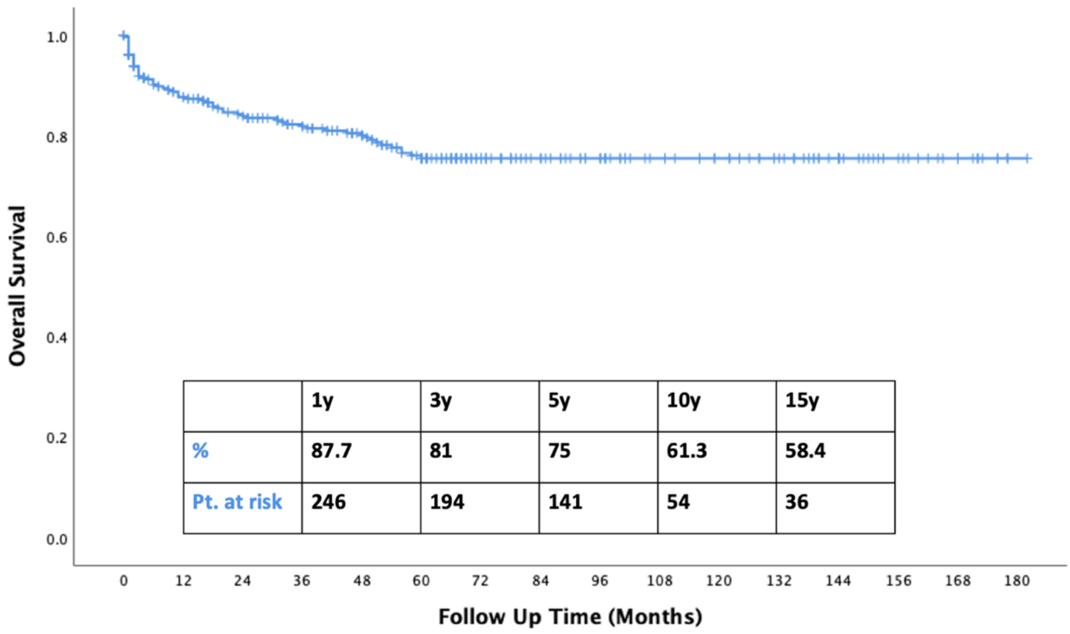


Figure 2. Overall Survival Aggressive vs Conservative

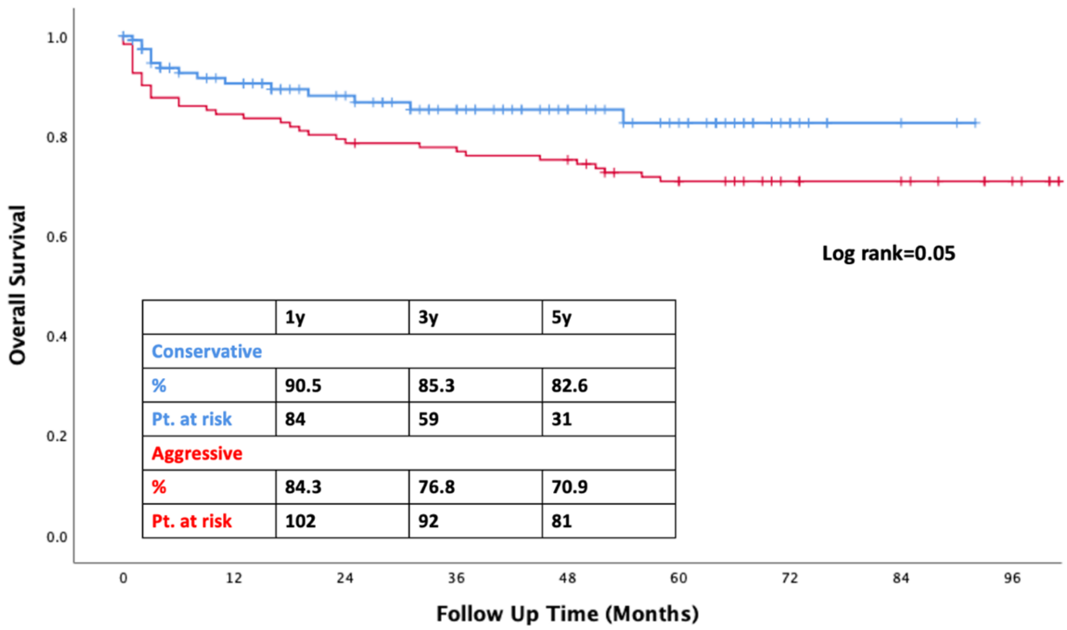


Figure 3. Freedom from Aortic Reintervention

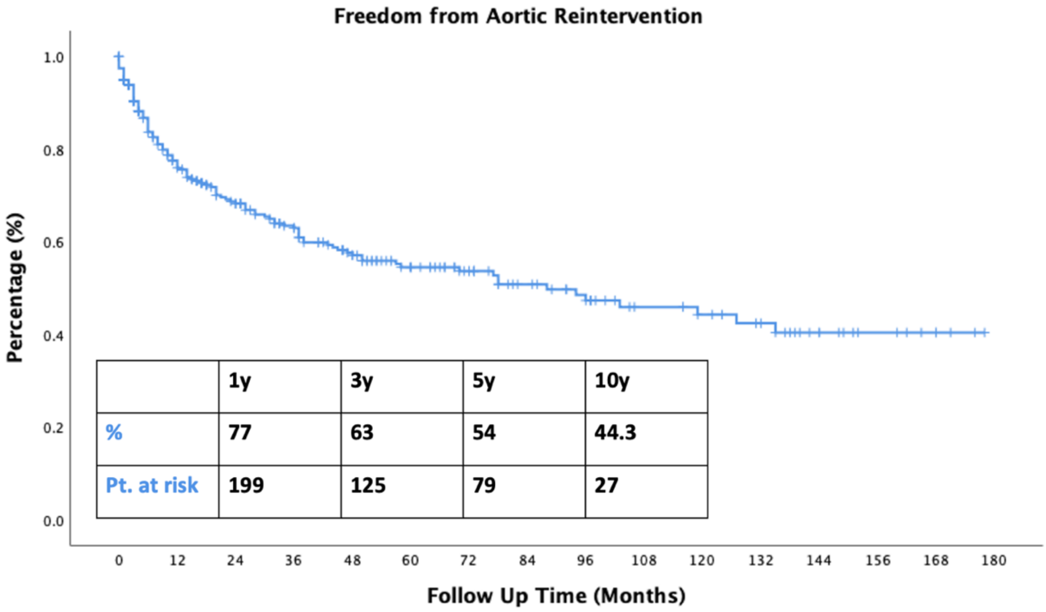
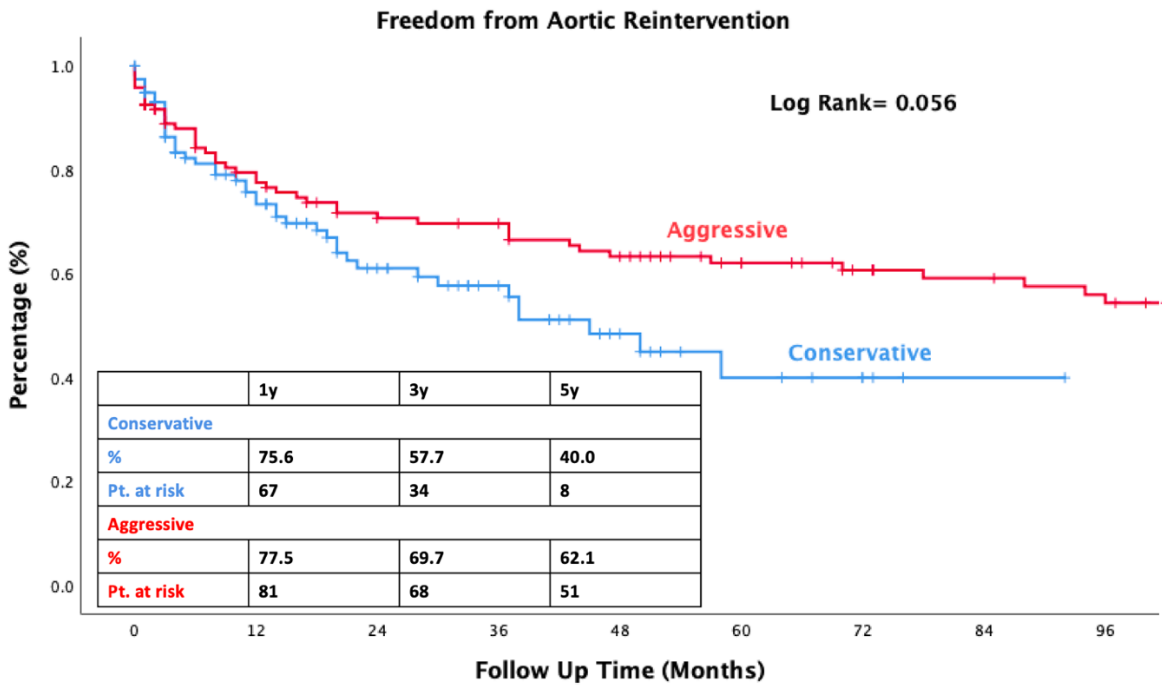


Figure 4. Freedom from Aortic Reintervention Aggressive vs Conservative



Tables

Table 1 Preoperative patient characteristics					
Characteristics	**All**	**Degenerative Aneurysm**	**Acute Dissection**	**Chronic Dissection**	**P-value**
Number of patients	369	101 (27.4)	67 (18.4)	201 (54.2)	
Age (years)	60.7 ± 11.4	64.5 ± 11.9	58.2 ± 11.1	59.6 ± 10.8	**<0.001**
Sex, male	298 (80.8)	78 (26.2)	56 (18.8)	164 (55)	0.57
BMI (kg/m2)	26.6 ± 4.4	25.9 ± 4.1	28.2 ± 5.3	26.4 ± 4.1	**0.003**
Hypertension	305 (82.7)	82 (26.9)	50 (16.4)	173 (56.7)	0.18
Smoking	162 (43.9)	58 (35.8)	31 (19.1)	73 (45.1)	**0.01**
COPD	40 (10.8)	22 (55)	5 (12.5)	13 (32.5)	**0.001**
Marfan Snd	26 (7)	2 (7.7)	4 (15.4)	20 (76.9)	0.11
Renal failure	18 (4.9)	7 (38.9)	2 (11.1)	9 (50)	0.55
Diabetes	18 (4.9)	8 (44.4)	3 (16.7)	7 (38.9)	0.47
Redo surgery	195 (52.8)	3 (1.5)	31 (15.9)	161 (82.6)	**<0.001**
Acute malperfusion	20 (28.6)				
Cerebral MPS	8 (11.4)				
Spine MPS	6 88.6)				
Bowel/Visceral MPS	3 (4.3)				
Renal MPS	9 (12.9)				
Lower limb MPS	6 (8.6)				

Table 2. Operative data					
Variable	**All**	**An**	**AD**	**CD**	**P value**
Number of patients	369	101 (27.4)	68 (18.4)	200 (54.2)	
Cannulation site					
Axillary artery	109 (29.5)	31 (30.7)	12 (17.9)	66 (32.8)	0.065
femoral artery	55 (14.9)	12 (11.9)	19 (28.4)	24 (11.9)	**0.014**
Ascending aorta	55 (14.6)	20 (19.8)	15 (20.9)	20 (10)	0.074
Brachiocephalic trunk	120 (32.5)	32 (31.7)	17 (25.4)	71 (35.3)	0.31
Left carotid artery	30 (8.1)	6 (5.9)	5 (7.5)	19 (9.5)	0.56
Bypass time (min)	230.8±67.7	199.9±46.3	245.7±67.9	241.3±72	**<0.001**
Myocardial ischemia time (min)	144.8±52.3	124.5±41.5	150.6±51.0	153.1±54.9	**<0.001**
Antegrade selective cerebral perfusion (min)	96.6±37.4	88.6 ±32.6	105.1±48.1	97.8±35.0	**0.017**
Lower body ischemia time (min)	51.6±19.6	52.4±21.5	49.2±17.3	52.1±19.3	0.520
distal aortic anostomosis zone 2	149 (40.4)	36 (35.6)	38 (56.7)	75 (37.3)	**0.010**
distal aortic anostomosis zone 3	220(59.6)	65 (64.4)	29 (43.3)	126 (62.7)	**0.010**
Separate supra-aortic vessels reimplantation	268 (72.6)	60 (59.4)	57 (85.1)	151 (75.1)	**0.001**
Stent diameter (mm)	30.9±4.5	33.8±4.6	28.0±3.1	30.4±3.9	**<0.001**
Stent lenght (mm)					**<0.001**
100	181 (49.1)	35 (34.7)	44 (65.7)	102 (50.7)	
130	37 (10)	20 (19.8)	9 (13.4)	8 (4)	
140	1 (0.3)	0 (0)	0 (0)	1 (0.5)	
150	83 (22.5)	14 (13.9)	11 (16.4)	58 (28.9)	
160	67 (18.2)	32 (31.7)	3 (4.5)	32 (15.9)	
Concomitant procedures	161 (43.6)	39 (38.6)	30 (44.8)	92 (45.8)	0.48
Bentall procedure	83 (22.5)	9 (8.9)	17 (25.4)	57 (28.4)	**0.001**
David Procedure	8 (2.2)	0 (0)	4 (6)	4 (2)	**0.033**
AV repair	10 (2.7)	1 (0.3)	3 (0.8)	6 (1.6)	0.37
AV replacement	31 (8.4)	9 (8.9)	6 (9)	16 (8)	0.94
CABG	34 (9.2)	17 (16.8)	15 (7.5)	2 (3)	**0.004**
Mitral valve surgery	4 (1.1)	0 (0)	0 (0)	4 (2)	0.18

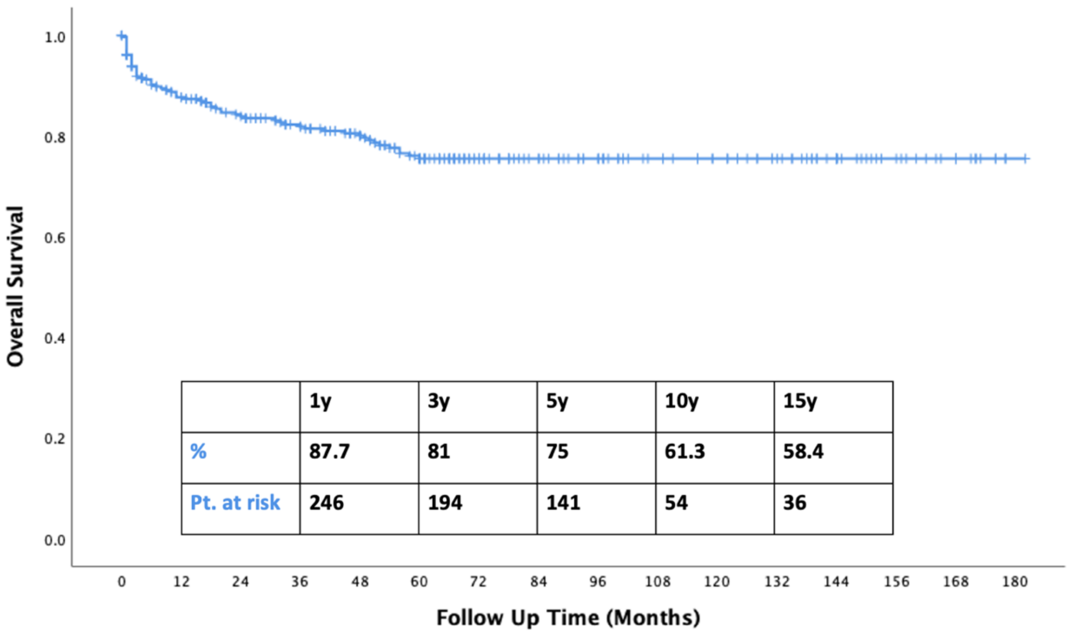
Table 3. Postoperative data					
Characteristics	**All**	**Degenerative Aneurysm**	**Acute Dissection**	**Chronic Dissection**	**P-value**
Number of patients	369	101 (27.4)	68 (18.4)	200 (54.2)	
Number of patients	369	101 (27.4)	68 (18.4)	200 (54.2)	
Prolonged ventilation with tracheostomy	38 (10.3)	13 (12.9)	9 (13.4)	16 (8)	0.269
Rethoracotomy for bleeding	48 (13)	8 (7.9)	15 (22.4)	25 (12.4)	0.084
Recurrent nerve palsy	41 (11.1)	15 (14.9)	4 (6)	22 (10.9)	0.424
Permanent Neurological Malperfusion	61 (16.5)	22 (21.8)	11 (16.4)	28 (13.9)	0.319
Spine Malperfusion	39 (10.6)	11 (10.9)	7 (10.4)	21 (10.4)	0.99
Permanent Paraplegia	16 (4.3)	5 (5)	6 (9)	5 (2.5)	0.074
Renal Malperfusion	78 (21.1)	22 (21.8)	18 (26.9)	38 (18.9)	0.721
Permanent Dialysis	44 (11.9)	17 (16.8)	10 (14.9)	17 (8.5)	0.201
Bowel malperfusion	23 (6.2)	6 (5.9)	6 (9)	11 (5.5)	0.830
30-day mortality	48 (13)	15 (14.9)	15 (22.4)	18 (9)	**0.015**

Table 4. Follow up data and reintervention					
Characteristics	All	Degenerative Aneurysm	Acute Dissection	Chronic Dissection	P-value
Survival patients	321 (100)	86 (23.3)	52 (14.1)	183 (49.6)	**0.015**
Follow-up time (months)	60.2 ± 50.7	41.9±35.9	55.2±38.1	70±56	**0.001**
Aortic reoperation	122 (38)	23 (26.7)	13 (25)	86 (47)	**0.001**
Other Cardiac Surgery	5 (1.6)	1 (1.2)	2 (3.8)	2 (1.1)	**0.009**
Time to aortic reintervention (months)	22.6 ± 28.6	14.7 ± 18.5	24.5 ± 28.7	24.4 ± 30.7	0.330
Type of aortic reintervention and indication					
Thoracic Endovascular Repair	114 (35.5)	21 (24.4)	13 (25)	80 (43.7)	
EL	29 (25.4)	8 (38.1)	3 (23.1)	18 (22.5)	
dSine/Distal LZ degeneration	49 (43)	4 (19)	8 (16.3)	37 (46.3)	
Pathology Progression	36 (31.3)	9 (42)	2 (5.6)	25 (31.3)	
Open Aortic Repair	8 (2.5)	2 (2.3)	6 (3.3)	0 (0)	
Pathology Progression	6 (75)	1 (50)	0	5 (83.3)	
EL	2 (25)	1 (50)	0	1 (16.7)	

Table 5. Subgroups analysis and Risk factor analysis				
	All	**Condervative**	**Aggressive**	**p-value**
Type of Pathology				0.001
Degenerative Aneurysm	72	31 (22)	41 (29.1)	
Chronic Aortic dissection	157	71 (50.7)	86 (61)	
Acute aortic dissection	52	38 (27.1)	14 (9.9)	
Permanent Paraplegia	13	4 (2.9)	9 (6.4)	0.159
Permanent Dialisis	36	14 (10)	22 (15.6)	0.08
Bowel Malperfusion	18	6 (4.3)	12 (8.5)	0.351
30 day mortality	39	21 (15)	18 (12.8)	0.58
Death at FU	69	18 (12.9)	51 (36.2)	**<0.001**
Aortic reintervention	93	44 (31.4)	49 (34.8)	0.77
Thoracic Endovascular Repair	86	42 (30)	44(31.2)	
EL	18	11 (26.2))	7 (15.9)	
dSine/Distal LZ degeneration	37	19 (13.6)	18 (12.8)	
Pathology Progression	31	12(28.6)	19 (43.2)	
Open Aortic Repair	7	2 (1.4)	5(3.5)	
Pathology Progression	5	2 (100)	3 (60)	
EL	2	0 (0)	2 (40)	
Risk factor analysis Aggressive approach *				
Variable	**p-value**	**Exp (B)**	**CI 95%**	
30 day mortality	0.588	0.829	0.421	1.634
permantent paraplegia	0.170	2.318	0.697	7.711
permanent dialisis	0.184	1.624	0.794	3.323
Prolonged ventilation with tracheostomy	0.332	0.688	0.323	1.465
Bowel malperfusion	0.155	2.079	0.757	5.709
Aortic Reintervention at FU	0.060	1.516	0.982	2.340
Death at FU	0.271	0.724	0.407	1.287

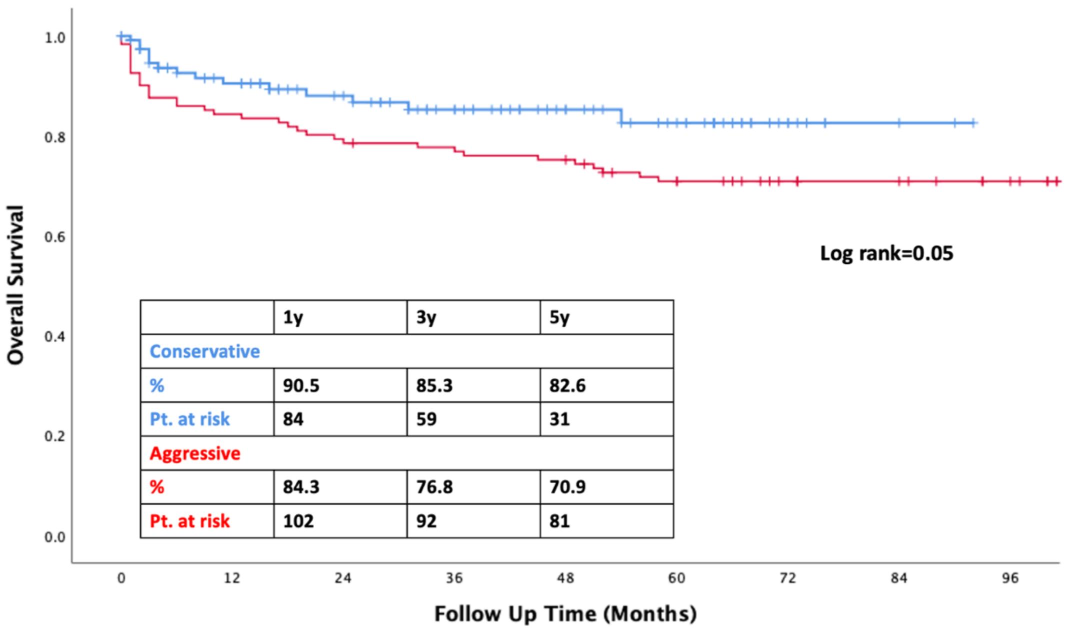
Figures

Figure 1. Overall Survival



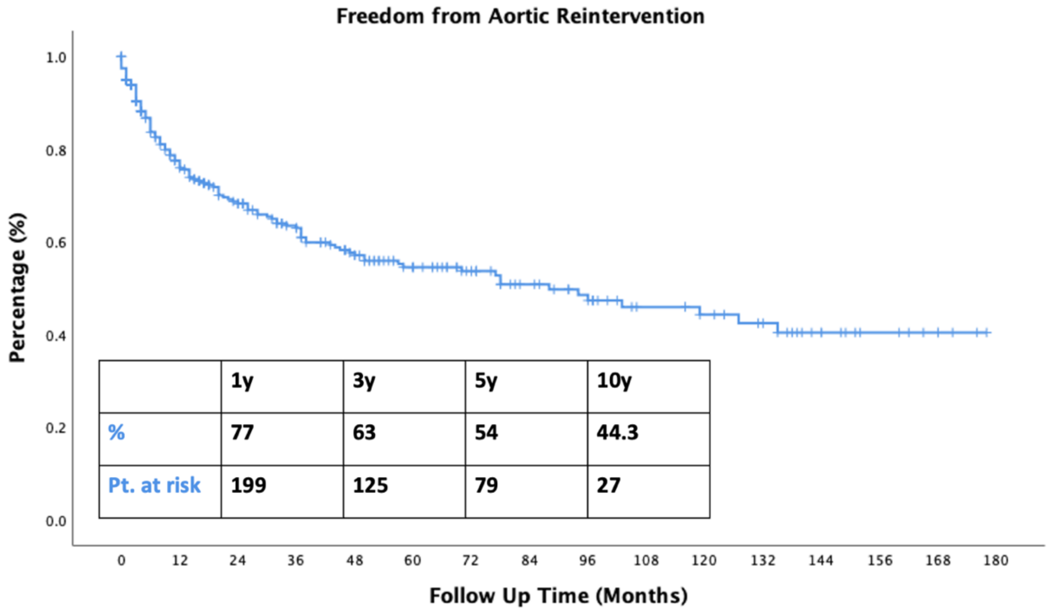
	1y	3y	5y	10y	15y
%	87.7	81	75	61.3	58.4
Pt. at risk	246	194	141	54	36

Figure 2. Overall Survival Aggressive vs Conservative



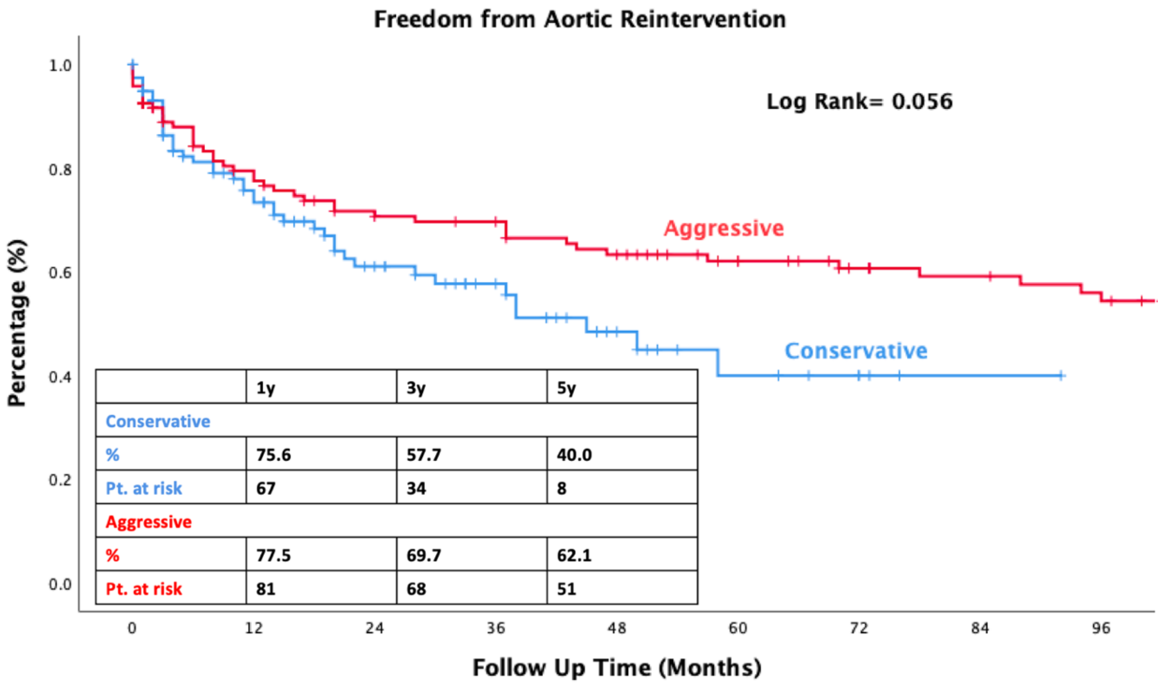
	1y	3y	5y
Conservative			
%	90.5	85.3	82.6
Pt. at risk	84	59	31
Aggressive			
%	84.3	76.8	70.9
Pt. at risk	102	92	81

Figure 3. Freedom from Aortic Reintervention



	1y	3y	5y	10y
%	77	63	54	44.3
Pt. at risk	199	125	79	27

Figure 4. Freedom from Aortic Reintervention Aggressive vs Conservative



	1y	3y	5y
Conservative			
%	75.6	57.7	40.0
Pt. at risk	67	34	8
Aggressive			
%	77.5	69.7	62.1
Pt. at risk	81	68	51