Master Programme in Endovascular Techniques

Medical School of National and Kapodistrian University of Athens and University of Milan, Bicocca

TITLE:

ANEURYSM SAC-FILLING.

A NEW APPROACH IN THE TREATMENT OF ABDOMINAL AORTIC ANEURYSM

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ΠΡΑΚΤΙΚΟ ΚΡΙΣΕΩΣ

ΤΗΣ ΣΥΝΕΔΡΙΑΣΗΣ ΤΗΣ ΤΡΙΜΕΛΟΥΣ ΕΞΕΤΑΣΤΙΚΗΣ ΕΠΙΤΡΟΠΗΣ ΓΙΑ ΤΗΝ ΑΞΙΟΛΟΓΗΣΗ ΤΗΣ ΔΙΠΛΩΜΑΤΙΚΗΣ ΕΡΓΑΣΙΑΣ

Του Μεταπτυχιακού Φοιτητή Γεωργίου Τσαπλέ

Εξεταστική Επιτροπή

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Η Τριμελής Εξεταστική Επιτροπή η οποία ορίσθηκε από την ΓΣΕΣ της Ιατρικής Σχολής του Παν. Αθηνών Συνεδρίαση της 13ης Ιανουαρίου 2010 για την αξιολόγηση και εξέταση του υποψηφίου κου Γεωργίου Τσαπλέ, συνεδρίασε σήμερα 16/01/2015

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Η εξεταστική επιτροπή αφού έλαβε υπ' όψιν το περιεχόμενο της εργασίας και τη συμβολή της στην επιστήμη, με ψήφους ..... προτείνει την απονομή στον παραπάνω Μεταπτυχιακό Φοιτητή την απονομή του Μεταπτυχιακού Διπλώματος Ειδίκευσης (Master's).

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ABSTRACT

Objective: To conduct a comprehensive review of the recent evidence on suggested approaches for the aneurysm sac filling as a treatment of abdominal aortic aneurysm (AAA).

Methods: A bibliographic search was performed between December 15th 2014 and December 29th 2014 using the Pubmed database. The search keywords included: 'aneurysm sac filling', 'abdominal aorta aneurysm sac filling', 'Nellix' and 'endovascular aneurysm sealing'. The detected articles were sorted based on the information provided in the title and the abstract. Studies written in English and relevant to the main objective of this study were considered eligible and included in the review.

Results: Pubmed results detected 350 articles in total; from those, 17 independent studies were eligible. Five studies referred to direct sac filling using elastomer or polymer materials (2 in vitro, 2 in vivo and 1 ex vivo, experimental studies) and 12 studies referred to indirect sac filling using the endovascular Nellix device (2 multicenter clinical trials, 2 non randomized prospective cohort studies, 1 commentary, 1 in vitro experimental study, 4 case reports, 1 abstract of 4-centers single reports and 1 review).

Conclusions: The current evidence on the recently suggested approaches for aneurysm sac filling for the treatment of AAA is very limited and relies only in few experimental studies and some early results in a small number of patients that have used the Nellix endovascular device in clinical practice. However, the findings from the first available studies are encouraging and suggest that sac filling, due to the secure fixation and sealing properties in various anatomies could be a new challenge in EVAR. The long term on progress results of the experimental and clinical studies along with the continuous multidisciplinary collaboration of medicine, biochemistry, bioengineering and computer science, guarantee the ability to give answers for the effectiveness of aneurysm sac filling as a safe, durable and cost-efficient method for EVAR, regarding the life threatening rate and the long term surveillance after EVAR.

ΠΕΡΙΛΗΨΗ

Σκοπός: Η διενέργεια ολοκληρωμένης ανασκόπησης των πρόσφατων στοιχείων της βιβλιογραφίας που αφορούν σε προσεγγίσεις πλήρωσης του ανευρυσματικού σάκου ως τρόπο θεραπείας των ανευρυσμάτων της κοιλιακής αορτής (ΑΚΑ).

Μεθοδολογία: Η βιβλιογραφική αναζήτηση διενεργήθει από τις 15 Δεκεμβρίου 2014 έως και 29 Δεκεμβρίου 2014 χρησιμοποιώντας τη βάση δεδομένων του Pubmed. Οι λέξεις κλειδιά που χρησιμοποιήθηκαν για την αναζήτηση, περιλάμβαναν τα ακόλουθα: 'Aneurysm sac filling', 'Abdominal aneurysm sac filling', 'Nellix' και 'Endovascular aneurysm sealing'. Τα αποτελέσματα των άρθρων που εντοπίστηκαν ταξινομήθηκαν βάσει των πληροφοριών που δίνονται στον τίτλο και την περίληψη. Στην ανασκόπηση επιλέχθηκαν οι μελέτες που ήταν στην Αγγλική γλώσσα και ήταν σχετικές με το βασικό αντικείμενο αυτής της μελέτης.

Αποτελέσματα: Στα αποτελέσματα του Pubmed εντοπίστηκαν συνολικά 350 άρθρα. Πέντε μελέτες αφορούσαν στον άμεσο τρόπο πλήρωσης του ανευρυσματικού σάκου με τη χρήση πολυμερών υλικών (2 in vitro, 2 in vivo και 1 ex vivo, εργαστηριακές μελέτες) και 12 μελέτες που αφορούσαν στον έμμεσο τρόπο πλήρωσης του σάκου μέσω της ενδαγγειακής συσκευής Nellix. (2 πολυκεντρικές κλινικές μελέτες, 2 μη τυχαιοποιημένες προοπτικές μελέτες, 1 σχόλιο, 1 in vitro ερευνητική μελέτη, 4 αναφορές κλινικών περιστατικών, 1 περίληψη 4 κέντρων με μεμονωμένες αναφορές και 1 ανασκόπηση)

Συμπεράσματα: Τα σύγχρονα στοιχεία των προτεινόμενων προσεγγίσεων για πλήρωση του ανευρυσματικού σάκου ως τρόπο θεραπείας του ΑΚΑ είναι περιορισμένα σε αριθμό και βασίζονται μόνο σε λίγες ερευνητικές μελέτες και στα πρώτα κλινικά αποτελέσματα μικρού αριθμού ασθενών, μετά από χρήση της ενδαγγειακής συσκευής Nellix. Παρόλα αυτά, τα αποτελέσματα των πρώτων διαθέσιμων μελετών είναι ενθαρρυντικά και παραθέτουν πως η πλήρωση του σάκου, λόγω των ιδιοτήτων της ασφαλούς στερέωσης και στεγανοποίησης σε ποικίλες ανατομίες, δύναται να αποτελέσει μια νέα πρόκληση στην ενδαγγειακή αντιμετώπιση των ΑΚΑ.

Τα μακροπρόθεσμα αποτελέσματα των ερευνητικών και κλινικών μελετών που είναι σε εξέλιξη καθώς και η συνέχιση της διεπιστημονικής συνεργασίας της ιατρικής, βιοχημείας, βιομηχανικής και επιστήμης υπολογιστών, δύνανται στο άμεσο

μέλλον να δώσουν απαντήσεις για την ασφάλεια και διάρκεια στο χρόνο, της νέας προσέγγισης στην ενδαγγειακή αποκατάσταση του ανευρύσματος της κοιλιακής αορτής μέσω πλήρωσης του αορτικού σάκου, δεδομένου του απειλητικού για τη ζωή ποσοστού και τη μακρόχρονη παρακολούθηση μετά από ενδαγγειακή αποκατάσταση ανευρύσματος κοιλιακής αορτής.

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1. INTRODUCTION

The rupture of abdominal aortic aneurysm (AAA), i.e. the abnormal dilatation of the abdominal aorta, is a severe condition associated with a high mortality rate leading to cessation in around 80% of all patients. From the patients who receive an intervention (i.e. two thirds of the patients suffering AAA), only the 50% will survive intervention and admission.[1] The natural history of the disease is ongoing expansion, with greater risk of rupture in cases with as aneurysm enlargement by >5,5cm in men and by >5,0cm in women. AAA of less diameter should be considered for repair treatment unless major contraindications exists.[2]

The elective management of AAA has traditionally depended on open surgical aneurysm repair (OR).[3] The first open AAA repair was performed in France by Charles Dubost in 1951.[4] Since then, significant improvements in operative techniques, anesthesia, and postoperative care have led to markedly lower morbidity and mortality from open AAA repair. Open repair, through an abdominal incision, results in the aneurysm being ablated, the sac clot removed and the aortic branches ligated and therefore a synthetic graft is placed for preserving the continuity of the blood stream to the lower limbs. In the early 90´s, Volodos in USSR[5] and Parodi in Buenos Aires[6] opened the era of the minimally invasive procedure of endovascular aneurysm repair (EVAR). EVAR aims at the positioning of an endovascular graft (EG) within the AAA sac using an over-the-wire technique either via surgical exposure of both common femoral arteries or totally percutaneously.

Although initially EVAR was offered only to patients deemed unfit to undergo open repair, it gradually became a secure and widely used under certain conditions technique, as it associates with significantly lower perioperative morbidity and mortality compared to open repair. Three randomised trials, DREAM, EVAR1 and OVER have demonstrated significantly lower operative mortality of EVAR compared to open repair, but also created concerns relevant to the long term sustainability and effectiveness of the endovascular method.[7] Early and late complications, such as EG migration, endoleaks and material failure demand from the patients long term surveillance and a respectful number of secondary interventions and furthermore are critical as the may lead to the reexposure of the AAA wall to pulsatile blood pressure and sac enlargement with excessive wall stress and thus, potential rupture.[8-10]

In 2011, Schanzer et al using data from a large multicenter cohort suggested that patients who had hostile aneurysm anatomy were more prone to complications leading to AAA sac enlargement.[11]These anatomical limitations on the aortic neck morphology (length, diameter, angulation, thrombus, calcification), the iliac arteries morphology (length, diameter, tortuosity, aneurysm presence, calcification) and the size of the aneurysm have led to exclusion of almost the 40% of patients with AAA from the endovascular treatment.[12] Therefore, the design of the current endovascular devices has focused on the strength of proximal and distal fixation attending to reduce the longitudinal migration forces and thus, to achieve secure exclusion of the aneurysm sac by sealing the attachment zones and in the same time introduce more flexible endovascular devices for better conformation to the angulated aortic necks and the tortuosity of the iliac arteries.[47,56,57,69] The importance of proximal fixation, especially when the landing surface is a short aortic neck has been considered one of the major anatomical limitations for EVAR.[46] Additionally, the long-term results from randomized trials may no longer accurately represent contemporary EVAR. Through procedure centralization and accumulated experience, centers of excellence have now traversed a steep EVAR-related learning curve, currently allying improved technical execution to better patient selection, factors that may greatly influence long-term outcomes, thus reducing aneurysm-related adverse events

Due to the persistent reintervention rate and the limited applicability of standard EVAR, a new approach has been proposed for the improvement of a more secure and durable aneurysm sac exclusion. This new approach do not rely in the use of a proximal and distal fixation system, but rather recommend the secure sac exclusion with its own filling, through catheter injection of biocompatible substances directly in the aneurysm sac around endovascular balloons or current endografts or through polymer-filled endobags indirectly with the Nellix technology. The aneurysm sac, that remains untreated with the current endovascular devices, leaves a large space where blood flow may continue with potential endoleaks from proximal or distal fixation zones. In addition, the untreated aneurysm sac space provides an opportunity for lateral movement of the endograft within the aneurysm sac, resulting in angulation and dislodgement of the proximal and distal fixation zones and leading to new endoleaks and stent graft migration. The endograft receives resultant forces, as studied with computational analysis, from the pulsatile blood flow and tends to lateral movement inside the aneurysm sac over time[44, 45]. It is also remarkable to mention

that the shrinkage of the sac, that is marked as success treatment after EVAR, acts with biomechanical forces on the proximal attachment zone of the currently used endografts over time and results in a type I or type III after component separation endoleaks[58].

The endovascular aneurysm sac filling, provides a variety of potentials regarding the durable and safe sealing of the aneurysm, the increased proximal, distal and lateral support of the endograft, the anatomical variations that can be customized, the ability to conform and cure the aneurysm sac, and to minimize the adverse events due to the remodeling of the aneurysm.

Given the high mortality rate linked to the rupture of AAA shown also in patients that receive a surgical intervention, the critical for AAA secondary interventions following EVAR, and the high number of patients that are excluded from EVAR due to a deviant aneurysm morphology, future research on the evolution and improvement of the currently available techniques is considered critical. Therefore, the aim of this study was to comprehensively review the recent state of evidence on suggested approaches for the sac-filling of the AAA as a treatment and provide insights into a more efficient treatment of AAA in the future.

2. METHODS

A Pubmed search was conducted between December 15th 2014 and December 29th 2014. The keywords used were: 'aneurysm sac filling', 'abdominal aorta aneurysm sac filling' and 'Nellix', 'endovascular aneurysm sealing'. Each keyword resulted to a certain number of scientific articles. Pubmed results were sorted based on the information provided in the title and the abstract of the articles. Studies written in English and relevant to the main objective of this study were considered eligible and were included in the review. The eligible studies were classified into two groups according to two different ways of inserting the filling material into the aneurysm sac. The first group of studies included those referring to a direct sac filling for treatment of the AAA. Those studies have performed the injection of a biocompatible polymer directly inside the sac around a balloon catheter. The second group of studies included those referring to an indirect sac filling of the AAA using the Nellix device. The sac filling in these studies is performed indirectly through the polymer-filled endobags of the Nellix device, not allowing the polymer come in direct touch with the blood. This endovascular indirect sac filling is commonly mentioned in the literature as Endovascular Aneurysm Sealing (EVAS).

3. RESULTS

3.1 LITERATURE SEARCH RESULTS

The Pubmed search resulted to a total of 350 scientific articles (*Figure 1*). From those, 333 articles were excluded because they were written in a language other than English or were duplicates of articles detected using the different keywords and/or were irrelevant to the main objective of this review. A total of 17 independent studies were finally included in the review. From those, 5 experimental studies referred to direct sac filling treatment approaches (2 in vitro, 2 in vivo and 1 ex vivo studies) and 12 referred to indirect sac filling treatment using the Nellix device and EVAS (2 multicenter clinical trials, 2 non randomized prospective cohort studies, 1 commentary, 1 in vitro experimental study, 3 case reports, 1 abstract, 1 review).

3.2 EVIDENCE ON DIRECT SAC FILLING OF AAA

The studies related to the direct sac filling of AAA are summarized in *Table 1*. Uflacker and Brothers (2006)[13] from the Medical University of South Carolina, Charleston, have investigated the direct polymer sac filling as a new technique for the treatment of AAA. In their study they aimed to obliterate the sac in a swine AAA model, using the injection of deacetylated-poly-N-acetyl glucosamine (DEAC-poly-N-acetyl glucosamine) around a stent-graft. Eleven Yucatan pigs were used to create an AAA with a Dacron pouch implanted surgically and left for 2 weeks to mature. Two weeks after a 13 mm × 5,5cm straight tube Aneurx stent graft (Medtronic Santa Clara CA) was placed to exclude the aneurysm and a Kumpe catheter (Cook Inc. Bloomington IN) was used for the DEAC – glucosamine sac filling. Procedures performed and outcomes are summarized in *Table 2*. The AAA creation and aneurysm sac filling was successful in all animals. An organized thrombus layer of about 2 mm in thickness was observed in all subjects along the Dacron aneurysm wall. All aneurysms were angiographically patent at the time of treatment, but fresher thrombus within the sac was seen in 4 subjects before the polymer injection. The stent-graft placement excluded the AAA sac and the polymer injection filled all AAA sacs. The AAA sac had acquired a firm rubbery consistency at the time of necropsy. There was mild inflammatory reaction to the Dacron material in the surrounding tissues and within the sac, to a lesser extent. Two animals developed paralysis of the hind limbs following treatment, most likely related to spinal ischemia, and were used

as acute subjects. DEAC-glucosamine injection was easy in all cases. There was no recanalization of the aneurysm sac, during the follow-up time, ranging from 1 to 24 weeks in the treatment animals (n=8) or in the control animals (n=2). To the contrary there was 25% of shrinkage in the AAA sac at 6th, 40% at 12th week and 75% by the 24th week. The 2 control subjects showed shrinkage of less than 25% at 6 and 12 weeks. There was replacement of the polymer/thrombus complex by connective tissue and fat tissue with capillary neovascularization in the treated subjects. Fibrosis and calcifications were also detected within the sac, mostly around the stent-graft and in contact with the aortic wall starting at 4 weeks. Control subjects did not show replacement of the thrombus by connective tissue or neovascularization. The histologic findings and adverse events are summarized in *Table 3*.

Bosman et al (2010) in the Netherlands devised Aortic Customize, an alternative method for endovascular aneurysm repair, in which a non-polymerized, biocompatible elastomer, polydimethylsiloxane (PDMS) is injected to fill the aneurysm sac around a balloon catheter. An endoluminal mold obliterates the aneurysm sac after in situ polymerization and with the deflation of the balloon a noncompliant elastomer cuff with a patent lumen is created. Four experimental studies took place, 2 in vitro, 1 in vivo and 1 ex vivo.

The first in vitro study aimed to investigate the extent of aneurysmal wall stress reduction by the presence of the noncompliant elastomer cuff.[14] A thin walled fusiform latex aneurysm model (inner radius of the aneurysm: 18,25 mm; inner radius of the proximal and distal aorta: 8mm; and latex aneurysm wall thickness: 0,8 mm) equipped with 12 tantalum markers (placed in three planes of four markers on the proximal M1-4, the distal neck M9-12 and on the middle part M5-8 of the aneurysm), were attached to an in vitro circulation model. Fluoroscopic roentgenographic stereo photogrammetric analysis (FRSA) was used to measure marker movement during six cardiac cycles of 70 bpm, with different pressure settings of 60/40, 80/60, 90/60, 120/80, 150/100 and 220/140mmHg. The radius of circles-rings drawn through the markers was measured before and after the direct sac filling. Wall stress was then measured at different systemic pressures using the type: $\sigma = pr/2t$. The systolic, diastolic and mean pressure (p; n/cm2; 1mmHg = 0,0133 N/cm2) were known from the pressure measurements, the radius (r;cm) was calculated from the FRSA measurements and the thickness of the aneurysm (t) was known from fabrication (0,08cm). The mean compliance (C) of the aneurysm calculated by measuring the

volume (δV) needed to obtain a pressure increase (δP) in the isolated aneurysm as C = δV/δP was 0,41ml/mmHg (0,15ml/mmHg – 0,91mm/Hg) in the pressure range of 30mmHg – 90mmHg because the thin latex aneurysm nearly ruptured at pressures higher than 90mmHg, as wall stress nearly exceeded wall strength. The FRSA measurements showed an increase in average radius of the proximal, middle and distal rings with increasing systemic pressure, before the sac filling. (3,3% - 184,3%). After sac filling with the elastomer there was a little change in the radius of the rings. (0,7% - 8,8%) (*Table 4*). The wall stress calculation before sac filling ranged from 7,5 – 13,3 N/cm^2, while after sac filling markedly reduced to 0,5 – 1,2 N/cm^2.

The second in vitro study measured the influence of aneurysm sac filling with PDMS on the strength of the proximal fixation of different EVAR grafts.[15] The proximal part of three different stent grafts was inserted in a bovine artery (19,5 mm) with an attached latex aneurysm and fixated with the inflation of a Reliant endovascular balloon (Medtronic) of 30mm diameter. The graft was connected to a tensile testing machine, applying force to the proximal fixation, while the artery with the aneurysm was fixated to the set up. An Excluder AAA Endoprothesis (WL Gore and Associates, Inc, Flagstaff, Ariz), an Anaconda AAA Endovascular Graft (Vascutek, Inchinnan, Scotland), and an Endurant AAA Stent Graft (Medtronic, Minneapolis, Minn) were used in this study, all with a diameter of 23mm each. The force to obtain graft dislodgement (DF) from the aorta was recorded in Newtons (N) and three different proximal seal lengths (5, 10, 15 mm) were evaluated. The test was repeated five times for each type of graft at each length of proximal seal before and after the sac filling with the biocompatible elastomer. The Anaconda was only tested for the 10 and 15 mm proximal seal, as its fixation rings and hooks take more than 5 mm of the proximal side of the graft when positioned in the aorta. This study found that for a proximal seal length of 5, 10 and 15mm, the mean dislodgement forces of all grafts without sac filling , were 4,4 ± 3,1 N, 12,2 ± 10,6N and 15,1 ± 6,9N. After elastomer sac filling, the DF increased significantly to 20,9 ± 3,8N, 31,8 ± 9,8N and 36,0 ± 14,1N, respectively. The sac filling was associated with an increase in the fixation strength by percentages of 376%, 161% and 139%, respectively (*Figure 2* and *Table 5*).

The third study aimed to test the feasibility of a percutaneous technique for aneurysm sac filling with PDMS in an in vivo porcine model.[16] Three in vivo porcine experiments were conducted. A porcine aorta was ligated and replaced by a handmade

polyester aneurysm. After placing the aneurysm, a fill catheter 7-French (Boston Scientific, Natick, USA) was placed, through an arteriotomy in the left femoral artery, in the aneurysm sac and a control angiogram was made, showing no leakages from the sac or the attachment sites. Through the contralateral femoral artery a 7-Fr catheter with an endovascular balloon (Cordis Corporation, New Brunswick, USA) was inserted and placed in the aneurysm just below the renal arteries. The inflation of the balloon excluded the aneurysm from the circulation and the elastomer was pumped through the catheter to fill the excluded aneurysm sac. ± 6.1ml of elastomer were injected [(volume aneurysm sac – volume of the balloon) + 5%]. The elastomer was given 5 minutes to cure, after which the balloon was deflated and circulation was restored with a patent lumen at the place of the balloon. Dissection of the aneurysms, after euthanisation of the animals, showed that the sac was completely filled by the elastomer, with a patent lumen at the site of the balloon in all animals.

The fourth study compared the thrombogenicity of PDMS to expanded polytetrafluoroethylene (ePTFE) in a human ex vivo model.[17] Non antigulated blood was drawn from the antecubital veins of 10 healthy donors with a 19 gauge needle. It was drawn through elastomer and through e-PTFE Gore Tex vascular grafts, both 60 cm long and with an inner diameter of 3mm. Fibrinopeptide A (FPA) and P – selectin expression measurements were done from blood samples collected at the end of the grafts. The deposition of platelets and fibrin onto the grafts was then visualized by scanning electron microscopy. Findings of this study suggested that the production of FPA increased over time for both the elastomer and e-PTFE grafts and no significant differences were shown in FPA levels between the two grafts. The secretion of P – Selectin was not shown to increase in either the elastomer graft or the e-PTFE graft. By scanning electron microscopy, numerous platelets aggregates were observed on the e – PTFE graft whereas just a few adhered platelets and no aggregates were observed in the elastomer graft.

3.3 EVIDENCE ON INDIRECT SAC FILLING USING NELLIX SAC ANCHORING ENDOPROSTHESIS

The Nellix device (www.endologix.com) is a fillable, sac-anchoring, low profile endovascular device that was designed to provide aneurysm exclusion and long term device stability and durability through the indirect sac filling through the polymer-filled endobags. The device consists of two flow channels supported by

bilateral e-PTFE covered (Cobalt Chromium) balloon expandable stents, with surrounding nonporous e-PTFE Endobags that are filled with a biocompatible, nonbiodegradable, polyethylene glycol-based solution, mixed with a radiopaque contrast agent that is visible under fluoroscopy and cures to a solid in less than 5 minutes at 37^{o} C . The polymer filling step is performed under pressure monitoring until the Endobags expand and occupy the blood lumen space within the aneurysm sac allowing sealing of side branch flow.

The studies related to the indirect sac filling of AAA with the Nellix Sac Anchoring Endoprosthesis (Endologix) are summarized in *Table 6.* One prospective multicenter trial study aimed to evaluate the performance of the Nellix endoprosthesis.[18] The study was conducted at four clinical sites (Latvia, New Zealand, Venezuela and Colombia) from 2008 to 2010. All patients were deemed to be appropriate candidates for open aortic aneurysm repair with suitable anatomy for endovascular repair using the sac anchoring endoprosthesis. Data from 21 patients were collected. This study was updated a few months later, with a change to the initial protocol by including patients with shorter aortic lengths (≥5mm), and was published as a review of worldwide clinical experience with Core Lab evaluation.[19] A total of 34 patients were enrolled and treated from 2008 to 2010. Patients included 31 (91%) men and 3 (9%) women with a mean age of 71 ± 8 years (range 53-84 years). Patient comorbidities and aneurysm characteristics are shown in *Table 7* and *Table 8*, respectively. The aortic neck length was <10 mm in eight patients (24%); the mean aortic length in these patients was 6,6 mm. The aortic neck angulation was >60 degrees in three patients (9%). The common iliac diameter was >23 mm in one or both iliac arteries in 13 patients (38%); four patients had common iliac aneurysms >30 mm in diameter and six patients had bilateral iliac enlargement. A total of 17 patients (50%) had one or more adverse anatomic features, while six patients (18%) had two or more adverse anatomic features. Technical success with successful deployment and implantation was achieved in all patients (n=34). Clinical procedural data are summarized in *Table 9* and mortality and clinical outcomes are shown in *Table 10*. One patient died during the postoperative period of multisystem organ failure. This was the first clinical implant using the device, and the endoframe balloon expanders were kept inflated throughout the endobag inflation and the prefill and polymer filling procedure, resulting in a prolonged aortic occlusion time. The implant procedure was modified after this case by the immediate deflation of the endoframe

balloons after full endoframe expansion with an aortic occlusion time <2min. This death was not device related, as evidenced by post-procedure CT scan and post-mortem examination of the aneurysm and device. Aneurysm related mortality was 1/34 (2,9%). In addition, one patient died at ten months due to congestive heart failure. Two patients were noted with type I endoleak. The first had a proximal type I endoleak that was fully resolved without intervention at 60 days. The other patient had a distal type I endoleak and an elective secondary endovascular procedure was performed at 15 months resulting in complete resolution of the endoleak. During a mean follow-up of 15 ± 6 months (range 7-27 months), no aneurysm ruptures, no conversions to surgery, no device migration, no aneurysm enlargement and no new endoleaks were noticed. Results of quantitative morphologic analysis of follow-up CT scans revealed no change in aneurysm diameter or circumference 2 years of follow up compared with baseline, nor device position relative to the reference points of superficial mesenteric artery (longitudinal movement) and the vertebral body (lateral movement).

Kisis et al (2012)[20] conducted a cohort study from 2008 to 2011 with the aim to compare the quality of life (QOL) of patients after AAA repair with either the endovascular method using the Nellix device or open surgery. Each group comprised 20 patients, and the QOL evaluation was performed using the SF-36 questionnaire before operation, at 1 month and at 1 year after operation. The improvement of QOL in the EVAR group was higher for the first month and the difference almost diminished 1 year after (*Tables 13-15*). The study had poorly documented data about the sac behavior.

The proportion of patients with AAA, from January 2004 until June 2012, that were morphologically suitable for treatment with Nellix instructions for use(*Table 12),* was investigated with quantification of pre-operative morphology using three-dimensional computed tomography according to a validated protocol, in two vascular units in the United Kingdom.[21] A total of 776 patients were identified, with mean age 75 ± 9 years (*Table 11*). Of those, 730 (94,1%) had undergone infrarenal EVAR, 6 (0,8%) open repair, 27 (35%) fenestrated EVAR (FEVAR) and 13 (1,7%) had been managed non-operatively. The AAA, in 544 (70,1%) of all AAA were morphologically suitable for Nellix. Out of all patients, 533(73%) of patients who had undergone infrarenal EVAR were compliant with Nellix IFU (Instructions For Use) compared to 497 (68,1%) with Medtronic Endurant, 379 (51,9%) with Cook Zenith

and 214 (29,3%) with Gore C3 Excluder (*Table 12*). Three patients (50%) of the open repair group, 2 (7,4%) with FEVAR and 6 (46,2%) of the no repair group were compliant with Nellix (*Figures 3-5*).

In order to treat more complex aortic neck anatomies, Nellix endoprosthesis and the compliance of its endobag have been investigated for parallel graft (snorkel, chimney) repair of juxta-renal aneurysms. In one in vitro experimental juxta-renal aneurysm model, W.Niepoth et al (2013) investigated the feasibility of Nellix Sac-Sealing Endoprosthesis in a double chimney graft configuration.[22] A self-expanding (SE) Viabahn stent graft and a balloon expandable (BE) Advanta V-12 stent graft, were used in the pressurized silicone juxta-renal flow model. Two consecutive experiments took place, the first including whether the balloons were inflated at the beginning of the procedure and the second to simulate varying renal ischemic times half way through the injection of the sac-sealing polymer into the Nellix endobags. Chimney graft compression exceeded 50% if the balloons were inflated half way through polymer injection, while in the initial experiment compression was 22% for the SE stent graft and 42% for the BE. The patency did not change appreciably after 24 hours of flow.

Nellix endoprosthesis with chimney grafts for the treatment of juxta-renal aneurysms has been used in clinical practice but only single case reports have been published so far. Two men aged 83 and 81 years with a juxtarenal abdominal aortic aneurysm (66 and 69 mm, respectively) have been studied.[23] Both were considered for open surgery as well as custom-made fenestrated stent-graft but deemed unsuitable for both options. They were both treated using the Nellix endoprosthesis in combination with chimney grafts to preserve the renal arteries. Technical success was achieved in both cases, with successful aneurysm exclusion and target vessel preservation (the right renal artery in the first case and both renal arteries in the second). At 6 months, duplex ultrasound and computed tomographic angiography of the first patient showed no signs of endoleak and patent renal arteries. The second patient developed a right retroperitoneal hematoma with minor extravasation near the lower pole of the right kidney for which coil embolization was necessary. The subsequent clinical sequelae led to respiratory insufficiency and ultimately death.

In another study, a 79-year-old woman was diagnosed with a 6-cm juxtarenal aneurysm.[24] Standard endovascular aneurysm repair was not possible due to lack of an adequate infrarenal landing zone, and poor iliac access and angulated

visceral aortic branches precluded a custom-made fenestrated solution. The patient was not a suitable candidate for open surgery due to significant comorbidity, so she underwent successful endovascular aneurysm repair with the Nellix EVAS system and a renal chimney stent. Follow-up imaging at 6 months showed a sealed aneurysm sac and patent renal chimney stent.

Single case studies have been reported in four European vascular centers using the Nellix off-IFU, addressing technical aspects as well as patient selection criterias.[25] Recent preliminary clinical experience using Nellix outside of the IFU in challenging neck anatomies proves early feasibility and efficacy in patients being excluded for open repair (OR) and also for EVAR and FEVAR within OR. Short-term results are promising. Migration, renal artery occlusions or type II endoleaks were not observed. One type Ia endoleak was observed but was temporary and resolved. Feasibility has been proven in single cases. A case report of intervention for type I endoleak post-Nellix EVAS in a woman has been also recently published.[26] A 82-year old man underwent Nellix EVAR for an 8,2cm infrarenal aortic aneurysm. A routine postoperative US duplex at 4 days suggested a possible proximal type I endoleaks and CT angiography (CTA) was performed in the same day and showed a 10mm focus of high density adjacent to the proximal end of the graft. A further CTA was performed 6 days later that showed an increase in the area of high density to 16mm. a proximal type I endoleaks was diagnosed and angiography with a view to embolization with Onyx (Covidien, Irvine, California, USA). The procedure was complicated by reflux of Onyx into one of the graft limbs causing significant stenosis, which was successfully treated by placement of a covered within the Nellix graft restoring patency.

4. DISCUSSION

4.1 SUMMARY OF MAIN FINDINGS

The endovascular aneurysm sac filling concept seeks to overcome many of the problems relating to endovascular aneurysm repair such as endoleaks, migration and aneurysm configuration demands. This review detected 17 studies in total that focuses on the recently proposed treatment approach of AAA using direct and indirect sac filling. Findings from the experimental studies related to the direct sac filling suggest that the method can be performed percutaneously with the use of a 7 Fr catheter and sheath and that the filling of the aneurysm sac with an elastomer (PDMS) almost diminishes the wall movement and the consequent wall stress by molding the sac cavity. Therefore the sac filling with PDMS enhances the proximal fixation of an EG and can be used as a complementary procedure around an EG and as standalone procedure regarding the PDMS elastomer biocompatible features and its low thrombogenicity . The sac filling with DEAC-glucosamine seems to be feasible in achieving complete exclusion of the aneurysm sac and promote shrinkage of the aneurysm size following EVAR. However, direct sac filling approaches has not yet been tested in clinical settings.

On the other hand, the indirect method of sac-filling with the Nellix device was recently introduced and is currently used in clinical settings. The early results of the multicenter clinical trial of 34 patients on a 2-year follow-up period are encouraging. Two patients (5,9%) needed an intervention, the first had an exploratory laparotomy for renal insufficiency with no conversion and the second with coil embolization and stent insertion for distal type I endoleak. Core laboratory evaluations of CT scans showed absence of aneurysm ruptures, no conversions to open repair surgery, stability of the device and no migration, no aneurysm enlargement, no limb occlusion, no stent fracture, no endobag failure nor type II endoleaks. The high morphological applicability, in particular 70,1% of 776 patients with AAA were compliant with the IFU for Nellix in various anatomic profiles and the potential feasibility of use in juxta-renal aneurysms with parallel chimney grafts, may increase the number of patients with hostile anatomy for EVAR. Thus, the first case reports available on the EVAR approach suggest that this may be a promising method for a more accurate treatment of AAA.

4.2 THE ROLE OF THE FILLING MATERIALS IN THE ANEURYSM SAC

In 1864, Moore inserted and left length of silver wire in a thoracic aneurysm to induce clot formation. [27] Few years later, Corradi passed a galvanic current through the wire and few decades after Blakemore and King devised an accurate means of electrothermic coagulation of aortic aneurysms.[27] These previous works have contributed importantly in the breakthrough idea of acting inside the aneurysm sac as an alternative treatment approach of the AAA. The aneurysm sac after EVAR is the source for incoming complications like endoleaks, especially type II endoleaks due to uncontrolled aortic side branches[61-63]. The most common techniques in the management of type II endoleaks, for prevention or treatment, involve insertion of coils, thrombin, or liquid embolic agents like cyanoacrylate or Onyx by intra-arterial catheter directed embolization or by percutaneous direct aneurysm sac puncture.[28] Unfortunately these procedures have proven to be time consuming, expensive and permanent solutions of the endoleaks without promoting long term sac shrinkage.[29,61,62] Experimental studies using in vitro aneurysm models have investigated biocompatible and biodegradable radiopaque hydrogels like Embogel and Ultragel[30] while animal studies have used small intestinal submucosal sponges and sheet pieces for sac embolization and prevention of endoleaks after an endograft placement.[31] The results are promising and may be used as a treatment or prevention of endoleaks type II after EVAR, but due to their biodegradable features[32,33] , a recanalization of the sac potentially could happen.

4.2.1 DEAC-glucosamine

In the study DEAC-glucosamine, a polysaccharide polymer that can be isolated from cultures of marine micro algae, which is a fully biocompatible material[34,35] showed to be reliable in sealing and excluding the aneurysm sac in the animal model and therefore prevent persistent endoleaks that is considered by some to have similar risks of rupture of the untreated AAA[64]. The potential of the insertion of the gel inside inside the aortic branches (L5) was common for the specific animal model, as all the AAAs were created in the L5 level. In addition the hind paralysis observed in the swine model, is likely to be transient and full recover may be expected in some animals. Although this scenario is less likely to occur in humans, the animal complication only underscore the need to be aware of the potentials risks of the

injection in sac-filling. The gel has the viscosity of honey and its handling was safe and the injection easy. It does not spread within the aneurysm cavity and tends to stay were injected. Degradation can be manipulated at wish according the application. Addition of sulphate to the mixture will change the rate of absorption. When used intravascular, DEAC-glucosamine immediately precipitates and recruits inflammatory cells leading to complete replacement of the vessels lumen by connective tissue. Eventually, the study shows that the gel after 6 weeks from injection in the aneurysm sac, gradually reabsorbs and tends to be replaced by connective tissue with presence of neovascularization and the residual mixture of clot and polymer develops into an organized and fibrotic tissue. The maximum shrinkage of the sac in the 24th week (75%) shows the potentials of the gel for sac occlusion, but therefore leaves questions for long term results regarding the neovascularization and its progress.

4.2.2 PDMS AORTIC CUSTOMIZE

The formulation used in the experiments consisted of a two component room temperature addition-cure liquid silicone formulation obtained from Viazym BV (Viazym BV; Delft, the Netherlands). Silicone-based elastomers meet the requirements of blood compatibility and have been successfully used in intravascular applications.[36-39] The material is non-toxic and cross links isothermically in the presence of blood, without the release of toxic by-products. The viscosity of the compound may allow infusion rates of up to 2mL/sec using a standard angiographic pump with an injection pressure of up to 1200 pounds per square inch. The average polymerization time was ~ 5min and after curing, the material had a yield stress of~ 400 kilopascal (kPa), failing at >20% elongation. Fatigue tests at 21 cycles/sec with stresses compared to those in the human aorta revealed no signs of material failure over one month observation, which is theoretically comparable to an exposure of 18 years in a circulation with a mean frequency of 70 beats /min.

Even though the results are quite preliminary and currently supported by a limited number of studies (n=5) the idea of aneurysm sac-filling with an elastomer, that molds the entire sac cavity and customizes itself to the form of the AAA sac by diffusing into all irregularities and side holes, presents a lot of potential advantages compared to the current EVAR techniques. The non-porous and low thrombogenicity material is suggested to diminish the risk for type II endoleaks as it may occlude the aortic branches as well as the aneurysm sac. No type III and IV endoleaks are

expected as there is no graft material to tear in the standalone procedure. Its feasibility of percutaneous use may overcome hostile anatomies that are excluded from EVAR due to the iliac arteries tortuosity and occlusion. When endovascular balloons will be available in different kinds of form and configuration, hypothetically, all AAA with a deviant anatomy would be treatable, as it could overcome the important and dangerous anatomic limitations of the short length and severe angulation of the aortic neck.[40-42] The ability of the PDMS to be used also as an adjuvant procedure around an endovascular stent-graft, may give solutions for the treatment of type II and IV endoleaks[43] and for increased proximal and distal fixation and sealing, protection over the lateral movement of the stent-graft and thus elimination of the lateral and longitudinal migration, the endoleaks and kinking of the stent-graft that follow the migration and finally protect the aneurysm sac from eventual rupture.[44-48]

Despite the potential benefits, the treatment option may have other shortcomings. The set ups of the experiments even though are different with the conditions inside the human aorta, regarding the blood pressure, the anatomic features like the angulation of the aortic neck, the non-spherical shape of the aneurysm and the presence of thrombus and calcification, they are validated methods that are used to investigate physiological questions concerning aneurysm repair[49-52] and fixation of EVAR grafts.[53-55] When working with arterial embolic agents there is always the risk of developing an embolus that could embolize the lumbar arteries or the inferior mesenteric artery and lead to paraplegia or colonic ischemia[74]. The amount of elastomer that has to be used can be preoperatively calculated with computerized tomography scan volume measurements and thus, the potential of sac overfilling that may lead to leakage can be prevented. In nonthrombosed infrarenal aneurysms the needed volume of elastomer can be up to 400mL-500mL. Theoretically, this might cause shear forces at the borders of the native aorta/common iliac arteries and the elastomer lump and might increase the risk of kinking and obstruction. It is though that due to the lower density of the elastomer compared to the density of blood and thrombus the shear forces before and after the use of the elastomer should be in the same range. One more disadvantage could be the overpressure filling of the sac that may lead to rupture. The curing process of the elastomer could potentially cure the rupture, however this for the moment is just a speculation, as clinical studies evaluating this possibility are currently not available. More experimental evidence is

much needed to reaffirm the safety and efficacy of PDMS in the treatment of AAA before the method is tested in the clinical setting.

4.3 NELLIX SAC-FILLING ENDOPROSTHESIS

The safe sealing and exclusion of the aneurysm sac from blood flow is the main gold standard for the treatment of AAA. The aneurysm sac and its shrinkage or enlargement may declare the success or fail of the procedure of the endovascular treatment. It should be delineated that endovascular treatment of AAA is not an instant fixation of an EVG in the aortic lumen, but rather an ongoing process of conformational changes in the aortic EG during the post-EVAR shrinkage process of the sac, changing its geometry and thus, putting increased axial strain and altering the distribution stress patterns on the different components of an EG.[58] The aneurysm sac is the source of potential endoleaks after EVAR, from its side branches (type II), the distal-proximal fixation zones (type I) and the endograft itself (type III,IV). The endograft receives resultant forces, as studied with computational analysis, from the pulsatile blood flow and tends to lateral movement inside the aneurysm over time.[44,45] It is also worthy to note that the shrinkage of the sac, that predicts the successful treatment after EVAR, acts with biomechanical forces on the proximal attachment zone of the currently used endografts over time and may result in a type I or type III after component separation endoleaks.[44]

The Nellix device uses a technology of ePTFE polymer-filled endobags that fills the aneurysm sac and conforms perioperatively to the specific shape of the aortic and also the iliac aneurysm, cures the aneurysm sac and provide aneurysm exclusion and long term proximal, distal and lateral device stability and large sealing surface area, without the help of proximal and distal fixation systems, such as suprarenal fixation and infrarenal fixation with the use of hooks, barbs, self-expanding radial force, columnar fixation, even the use of endoanchors or polymer filled rings in which the current and lately used endografts rely their safety[70-73,76-78]. The reduction or elimination of remodeling of the aneurysm with the Nellix device seems to have a positive impact on long term durability and reduction of endoleaks, regarding also the group of patients with angulated aortic necks and tortuous aneurysms that are more prone to endograft migration[11,68].. Another feature of the device is that it is not a bifurcated endograft and thus, the deployment is simplified without cannulating and deploying the contralateral iliac limb. Moreover, the critical accurate device placement demands the physicians training with the device. This is particularly

important as when the cure has started, there is no way back. The reductions in the angulation and tortuosity of the endografts, due to the independent limbs of the device self-select of optimum pathway through the aneurysm sac and the raise of the bifurcation aortic flow to the level of the renal arteries may reduce iliac limb kinking and therefore improve the hemodynamic performance of the device. However, longer clinical and hemodynamic studies are currently needed.[58,45] The enhanced morphological applicability demonstrated by Karthikesalingam et al[21] shows that 73% of a total of the 776 patients were compatible with the IFU of Nellix, a rate that was significantly higher compared with that within the IFU for the most common devices currently used in clinical practice. Almost half of the patients managed non-operatively were also compliant for the IFU of Nellix, but this may be due to other reasons than the aneurysm morphology itself.[59] However, the challenge for increasing the morphological applicability of Nellix in more patients, are the juxta-renal aneurysms.

Initially reported as a bailout technique for inadvertent renal artery coverage during EVAR, the placement of a parallel conduit to the main endograft to allow perfusion of collateral vessels has been used to treat AAAs with short proximal necks to elongate the proximal seal zone. More accurate method for such anatomies seems to be the fenestrated EVAR[80]. The use of chimney parallel stents with Nellix although has been presented as a feasible procedure with a small number of case reported clinical uses[23-25], on the other hand demands from the physicians excellent training, due to the critical complication of the procedure. Further research is needed in this field. Despite the potential suitability for treatment within the Nellix IFU of many patients who currently undergo EVAR outside the IFU, the experience with Nellix in the clinical setting is limited at the presence. Larger studies with a more longitudinal follow-up period and a careful clinical and technical assessment are much needed to elucidate whether potentially enlarged indications go parallel with safety and effectiveness of the current endovascular technology[60].

The design features of the device raise new challenges and questions in regards to the methodology of EVAR. The ability of the device to be precustomized for every patient's anatomy including the preservation of the IMA and the internal iliac artery is critical, especially for the patients that have internal iliac aneurysms and are prone to colon and pelvic ischemia after EVAR, more commonly due to microembolization[74,81]. Pelvic ischemia often results from atheroembolization despite

preservation of hypogastric arterial circulation. Colonic and spinal ischemia are associated with higher morbidity and mortality[65]. Future modification of the Nellix iliac extenders are designed for being able to treat internal iliac aneurysms without occluding the flow lumen. Future redundant fill system designs are under investigation, so that patients with large aneurysms and true aortic lumen of more than 60mm can be treated safely. By lowering the secondary intervention rate there will be an adequate decrease in the CT surveillance of the patients that could be continued with follow-up by duplex ultrasound and as consequence, the cost effectiveness of EVAR and patients discomfort could be minimized[7].

Despite being promising, some limitations remain to be solved with this technology. Although Nellix was designed to broaden the range of patients who are anatomically suitable for EVAR, neck-related IFUs are similar to "common" devices.[21] Additionally, endobag filling may produce hazardous effects on the aneurysm wall, as the transmitted pressure may potentially cause intraoperative aneurysm rupture or thrombus dislodgement, with a risk of renal embolization. Furthermore, treatment of ruptured AAAs, when an integrate wall is absent, can lead to endobag prolapse throughout the rupture site with inadequate aneurysm seal and compression of the neighboring structures. As for the remaining stent grafts, accurate device positioning still remains of paramount importance, particularly in challenging proximal neck anatomy to avoid unintended endobag prolapse into the lumen. Proximal type I endoleaks in patients treated with the Nellix system cannot be addressed the same way as patients treated with other endografts. Finally, the effect on long-term sac dynamics is uncertain as thrombus reabsorption may leave the patient at risk of developing late endoleaks. Long term remodeling of the aneurysm and mural thrombus, stability of the polymer-filled endobags and the potential for late endoleaks in the space between the endobag and aneurysm wall must be evaluated.

The first clinical results rely on studies with up to 2 years of follow-up (n=5) period that have evaluated the device properties. The successful device deployment in all patients, the fact that 50% of the patients treated out of the current devices IFU, the lack of changes in device position, elimination of endoleaks type II and III and IV that are not applicable to Nellix by design and the low secondary intervention rate, are promising early results. However, there is a need for longer term evaluation and surveillance regarding any potential unpredictable remodeling of the aneurysm over time, due to the natural progression of the disease.

The third generation of the Nellix device is now on the way for the FDA approval. The reported use of Nellix until now brings some encouraging messages for diminishing the risk for endoleaks and migration that may result, if not treated into the AAA rupture. However, the current state of evidence is still relying on few studies, most of which has a reduced number of patients. However, in the past two years since Nellix received the CE Mark[67] and the device became commercial available in Europe, many vascular centers have been using it in patients suffering from AAA, thus more findings on its applicability, safety and efficacy are expected to be reported in the near future. The EVAS FORWARD Global registry is on progress and the early results of this multicenter trial with 300 patients from Europe and New Zealand, were recently presented as an oral communication in the Veith Symposium 2014 in New York[67].

In conclusion, the evidence on the recently suggested approaches for direct and indirect aneurysm sac filling for the treatment of AAA is very limited. The available studies on direct filling techniques include only few experimental studies, while those focusing on the direct filling using the Nellix device include further some first case reports from clinical settings. Despite the gap in the current state of evidence, findings from the first available studies are encouraging and suggest that sac filling could be a promising approach for the treatment of AAA. Future research is needed to define a standardized surgical approach for sac filling and determine the most cost-efficient material to be used in the procedure. The multidisciplinary collaboration between the scientific fields of medicine, physics, biochemistry, bioengineering, computer science, and statistics, guarantees the ability of succeeding in it. Given the high mortality rate linked to the rupture of AAA shown also in patients that receive a surgical intervention, future research on the evolution and improvement of the currently available approaches is considered critical.

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TABLES

TABLE 1. Summary of studies on direct sac filling included in the review

AUTHOR	STUDY DESIGN	OBJECTIVE	MAIN FINDINGS
Bosman et al 2010 Aortic Customize	IN VITRO	WALL STRESS EXTENSION AFTER PDMS	DIMINISH OF WALL STRESS
Bosman et al 2010 Aortic Customize	IN VITRO	PDMS ON THE STRENGTH OF PROXIMAL FIXATION OF EVAR GRAFTS	SIGNIFICANCE INCREASE OF GRAFTS PROXIMAL FIXATION
Bosman et al 2010 Aortic Customize	IN VIVO	FEASIBILITY OF PERCUTANEOUS TECHNIQUE WITH PDMS	FEASIBLE STANDALONE OR ADJUVANT PROCEDURE
R.Uflacker ; T. Brothers 2006	IN VIVO	DEAC-GLUCOSAMINE FOLLOWING STENT GRAFT REPAIR	SCHRINKAGE OF THE SAC CONNECTIVE TISSUE BIODEGRADABLE FEATURES NEOVASCULARIZATION
Van der Steenhoven et al. 2012	EX VIVO HUMAN MODEL	THROMBOGENICITY OF PDMS VS EPTFE	EQUAL THROMBOGENICITY LESS ADHERED PLATELETS FOR PDMS

TABLE 2. Summary of DEAC-glucosamine study. Procedures performed and outcomes

MODEL DEVELOPMENT	CREATION AA	GLUCOSAMINE INJECTION	FOLLOW UP AORTOGRAM	EUTHANASIA	AUTOPSY	HISTOLOGY	AAA SHRINKAGE	ENDOLEAK TYPE	GEL IN L5
PIG#1	YES	NO	YES	24H	NO	NO	N/A	N/A	N/A
ACUTE STUDY PIG#4	YES	YES	YES	6H	YES	YES	N/A	NO	YES
PIG#5	YES	YES	YES	6H	YES	YES	N/A	TYPE I	NO
CHRONIC STUDY PIG#9	YES	YES	YES	1W	YES	YES	NO	NO	NO
PIG#8	YES	YES	YES	2W	YES	YES	NO	TYPE I	NO
PIG#2	YES	YES	YES	4W	YES	YES	NO	TYPE I	YES
PIG#7	YES	YES	YES	6W	YES	YES	25%	TYPE I	NO
PIG#6	YES	YES	YES	12W	YES	YES	45%	TYPE I	NO
PIG#3	YES	YES	YES	24W	YES	YES	75%	TYPE I	NO
CONTROL STUDY PIG#10	YES	NO	YES	6W	YES	YES	NO	NO	N/A
PIG#11	YES	NO	YES	12W	YES	YES	>25%	NO	N/A
N/A: Not Applicable									

TABLE 3 Histological findings and outcomes of DEAC-glucosamine study

MODEL DEVELOPMENT	GLUCOSAMINE INJECTION	FOLLOW UP	HISTOLOGY within AAA	Organized thrombus along wall	GEL IN L5	Adverse events
PIG#1	NO	24H	N/a	No	No	None
ACUTE STUDY PIG#4	YES	6H	Polymer mixed with clot	Yes 2mm	YES	Paralysis
PIG#5	YES	6H	Polymer mixed with clot	Yes 2mm	NO	Paralysis left iliac ligated

CHRONIC STUDY PIG#9	YES	1W	Fibrin with red cells, granulation tissue Inflammatory response with intimal proliferation	Yes 2mm w/granulation tissue	NO	left iliac ligated

PIG#8	YES	2W	Fibrin with red cells. Fresh clot within graft, dark artifacts within AAA. Large clear area of polymer mixed with red cells	Yes 2mm	NO	
PIG#2	YES	4W	Polymer mixed with broken down red cells displacing organized clots within AAA. Fibrin and connective tissue	Yes 2mm	YES	None
PIG#7	YES	6W	Retraction of the polymer. Mixture of the polymer with red cells and artifacts. Fibrosis and organization along the wall thrombus. Connective tissue with some vessels	Yes 1,5mm w/retraction	NO	left iliac ligated
PIG#6	YES	12W	Well organized thrombus within AAA with retraction of wall thrombus and calcifications at the suture areas with fibrous tissue. Polymer with few red cells within. Multiple artifacts	Yes 2mm w/retraction	NO	Incisional hernia repair
PIG#3	YES	24W	Well organized thrombus retracted thrombus within AAA. Partial reabsorption and replacement of the polymer by connective tissue, fat tissue and small capillary vessels within the sac. Calcification at sutures. Breakdown of the polymer with isolated particles	Yes 2mm w/retraction and disintegration	NO	None
CONTROL STUDY PIG#10	NO	6W	Layers of organized thrombus within AAA sac with some retraction. Areas with serum. Calcification at sutures.	Yes 2mm	NO	Aortic and bilateral iliac thrombosis
PIG#11	NO	12W	Layered thrombus with center of serum. Scar tissue and fibrosis around stent graft. Retraction	Yes 2mm w/retraction	NO	None

TABLE 4. Increase of radius of the aneurysm sac in the study of Bosman W et al.

	Proximal ring		Middle ring		Distal ring	
	r (mm)	%	r (mm)	%	r (mm)	%
Before						
60/40mmHg	0,7	7,8	0,6	3,3	0,9	10,5
80/60mmhg	2,9	33,5	2,5	13,3	3,8	43,4
90/60mmHg	1,8	20,2	4,8	25,2	16,1	184,3
After						
90/60mmHg	0,6	7,1	0,1	0,7	0,5	5,3
120/80mmHg	0,7	7,6	0,1	0,8	0,5	5,6
150/100mmHg	0,6	6,8	0,1	0,7	0,5	5,2
220/140mmHg	0,8	8,8	0,2	1,1	0,6	6,7

TABLE 5. Dislodgement force (DF) before and after elastomer injection in the study of Bosman W et al

	DF (Graft only)			DF (Elastomer)			
Graft	**Proximal seal**	**Mean**	**SD**	**Mean**	**SD**	**P**	**% Gain**
All grafts	5 mm	4.39	3.10	20.89	3.82	<0.01	376
	10 mm	12.16	10.59	31.77	9.75	<0.01	161
	15 mm	15.08	6.99	35.98	14.10	<0.01	139
Excluder	5 mm	1.62	0.03	18.08	1.44	<0.01	1015
	10 mm	5.58	1.02	19.51	0.86	<0.01	250
	15 mm	11.40	0.79	22.45	0.78	<0.01	97
Anaconda	10 mm	22.50	13.07	39.71	5.50	.039	76
	15 mm	23.38	6.35	53.05	8.58	<0.01	127
Endurant	5 mm	7.15	1.60	23.69	3.34	<0.01	231
	10 mm	8.42	3.90	36.10	3.45	<0.01	329
	15 mm	10.46	0.63	32.43	3.55	<0.01	210

*Independent sample t tests were used to compare the dislodgement forces. The percentage that the fixation at that proximal seal length was increased is shown under the header % gain.The % gain was obtained by the following equation: (DFafter – DFbefore) / DFbefore*100.*

TABLE 6. Summary of studies on Nellix sac filling endoprosthesis included in the review

AUTHOR	STUDY DESIGN	OBJECTIVE	MAIN FINDINGS
DONAYRE ET AL 2011	MULTICENTRE CLINICAL TRIAL	INITIAL CLINICAL TRIAL WITH NELLIX	➢ 100% technical success ➢ 2/21 deaths non device related ➢ 0 ruptures ➢ 0migrations ➢ 1 early type I(12month control) ➢ No interventions
KRIEVINS ET AL 2011	MULTICENTRE CLINICAL TRIAL	CLINICAL TRIAL NELLIX AND ADVERSE ANATOMY	Table 10
KISIS ET AL 2012	PROSPECTIVE STUDY	QOL NELLIX VS OR	Advantage for EVAR the first 30d Almost equal with open repair after a year
KARTHIKESALINGAM ET AL 2013	PROSPECTIVE STUDY	MORPHOLOGICALLY APPLICABILITY OF NELLIX	733/776 (73,0%) Compatible with Nellix IFU
TSOMBA ET AL	COMMENTARY	COMMENTARY	
NIEPOTH ET AL	IN VITRO	NELLIX AND CHIMNEY GRAFTS	Feasible Chimney graft compression >50% Inflation halfway through polymer injection
DIJKSTRA ET AL	CASE REPORT	NELLIX AND CHIMNEY GRAFTS	N=2 6months follow up: 1. Ok 2. Retroperitoneal hematoma and death
BOECKLER ET AL	4 CENTERS SINGLE CASE REPORTS	Out-IFU Juxta-renal	100% technical success 1 typeIa ,contemporary No migration, No typeII Feasibility of chEVAR, patent renals
MALKAWI ET AL	CASE REPORT	NELLIX AND CHIMNEY GRAFTS	N=1 chEVAR 6 months patent renal chim/stent Sealed sac
AMELI-RENANE ET AL	CASE REPORT	TYPE Ia ENDOLEAK AFTER NELLIX	Post Nellix typeIa Onyx embolization and reflux in one of the graft limbs->stenosis
THOMPSON	REVIEW	EVAS	

TABLE 7. Patient's demographics and comorbidities in the study of Krievins D et al

Number		%	Range
Total # Patients	34		
Age	71		53 - 84
Gender			
Male	31	91	
Female	3	9	
Comorbidities			
Hypertension	23	68	
CAD (MI/stent)	19	56	
CABG	6	18	
Renal insufficiency (creatinine>2,0 mg/dl)	1[a]	3	
Diabetes	4	12	
Smoking	17	50	
MI	9	27	
Abdominal surgery / trauma	2	6	
PVD	7	21	

[a] Following enrolment of this one subject, this criterion was changed to require serum creatinine ≤ 2mmg/dl.

TABLE 8. Summary of aneurysm characteristics in the study of Krievins D et al

Characteristics	Mean	Range
AAA diameter (cm)	5,8	4,3-7,6
AAA volume (cc)	177,8	67,5-362,7
AAA lumen diameter (mm)	42,3	30,3-60,4
Aortic neck length (mm)	22,1	5,0-50,0
Aortic neck vessel diameter (mm)	23,5	17,5-31,0
Aortic neck lumen diameter (mm)	20,3	16,0-25,0
Aortic neck angulation (^{o})	37,4	9,1-72,0
[a] The measurements identified in this table are provided by the Core Lab. Measurements may differ slightly from those made by the clinical site at the time of enrolment.		

TABLE 9. Clinical procedure data in the study of Krievins D et al

Clinical procedure data	Mean	Std.dev.	Range
Nellix indwelling time (min)	70	32	33-150
Fluoroscope time (min)	33	17	17-71
Contrast volume (min)	180	81	110-350
Amount of polymer infused (ml)	73	33	18-168
Estimated blood loss (ml)	165	107	35-400
Hospital stay (days)	3,8	2,2	1-9

TABLE 10. Summarize of clinical outcomes in the study of Krievins D et al

Event	30 days (0-30 days) (n = 34)	6 months (31-182days) (n=33)	1 year (183-365 days) (n=32)	2 years (366-730 days (n=5)	Total (n=34)
Mortality	2,9% (1)[a]	0,0% (0)	3,1% (1)	0% (0)	5,9% (2)
Aneurysm-related mortality	2,9% (1)[a]	0% (0)	0% (0)	0% (0)	2,9% (1)
Rupture	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
Conversion to surgery	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
Device migration	NA	0% (0)	0% (0)	0% (0)	0% (0)
AAA sac enlargement [b]	NA	0% (0)	0% (0)	0% (0)	0% (0)
Any endoleaks	5,9% (2)	3,2% (1)	3,1% (1)	0% (0)	5,9% (2)
Secondary interventions	2,9% (1)	0% (0)	0% (0)	20% (1)	5,9% (2)

[a] These events occurred in the same subject; the death is considered aneurysm related as this occurred within the 30 days following the intervention.

[b] Sac enlargement is defined as change greater than 5 mm.

TABLE 11. Demographics of patients treated by EVAR in the study of Karthikesalingam et al

	Infrarenal EVR	OR	FEVR	Non-operative
Male, n (%)	649 (88.9)	6 (100)	24 (88.9)	7 (53.8)
Mean age, n (%)	74.7 ± 9.04	72.7 ± 7.97	73.5 ± 7.73	80.1 ± 7.20
Smoking:				
Non-smoker, n (%)	156 (21.4)	0 (0)	5 (18.5)	1 (0.77)
Current smoker, n (%)	350 (47.9)	3 (50.0)	7 (25.9)	5 (38.5)
Ex-smoker, n (%)	224 (30.7)	3 (50.0)	15 (55.5)	7 (53.8)
Hypertension, n (%)	495 (67.8)	5 (83.3)	22 (81.5)	12 (92.3)
IHD, n (%)	336 (46.0)	2 (33.3)	17 (62.9)	8 (61.5)
COPD, n (%)	183 (25.1	1 (8.3)	7 (25.9)	5 (38.5)
Dyslipidaemia, n (%)	459 (62.9)	4 (66.7)	21 (77.8)	10 (76.9)
Diabetes, n (%)	104 (14.2)	0 (0)	0 (0)	1 (0.8)
Maximum patent AAA lumen diameter (mm)	48.74 ± 17.65	46.07 ± 11.15	43.43 ± 11.02	48.69 ± 11.86
Neck length (mm)	32.40 ± 15.28	15.03 ± 14.16	2.63 ± 4.76	15.61 ± 18.83
Neck diameter (mm)	25.89 ± 4.32	29.40 ± 4.67	38.51 ± 9.12	31.04 ± 8.15
Maximum CIA diameter (mm)	21.22 ± 12.30	17.10 ± 2.95	17.32 ± 5.58	21.48 ± 7.08

AAA =abdominal aortic aneurysm;CIA =common iliac artery; COPD = chronic obstructive pulmonary disease; EVR = endovascular aortic repair; FEVR = fenestrated endovascular repair; IHD = ischaemic heart disease; OR = open repair.

TABLE 12. Instructions for use for Nellix and contemporary endovascular aortic repair devices.

	Nellix	Cook Zenith	Medtronic	Gore
Non-aneurysmal AN length	≥10 mm	≥15 mm	≥10 mm	≥15 mm
Non-aneurysmal AN diameter	18-32 mm	18-32 mm	19-32 mm	19-29 mm
Maximum aortic blood flow lumen diameter	≤60 mm	-	-	-
Maximum common iliac artery diameter	8-35 mm	7.5-20 mm	8-25 mm	8-18.5 mm
Angle from neck to sac	<60	<45	If AN length 10-15 mm then ≤45 If AN length >15 mm, then ≤60	-
Angle from suprarenal aorta to neck	-	<60	If AN length 10-15 mm, then ≤60 If AN length >15 mm, then ≤75	≤60

AN= aortic neck.

TABLE 13. Comparison of Patients in Endovascular and Open Surgery Groups Before Treatment (Kisis et al)

Characteristic	EVAR Group	OS Group	P
Gender, n			
Men	17	16	NS
Women	3	4	
Age at surgery, mean (range), years	70 (53–80)	67 (55–77)	NS
Coronary heart disease	50	40	NS
Peripheral vascular diseases	40	35	NS
Transient ischemic attacks	5	0	NS
Chronic heart failure at least functional class II according to NYHA	20	35	NS
Permanent atrial fibrillation	15	10	NS
Primary arterial hypertension	50	35	NS
Aneurismal widening of other blood vessels	20	0	<0.05
Chronic venous insufficiency	10	10	NS
Chronic obstructive pulmonary disease	0	10	NS
Chronic renal failure	5	10	NS
Benign prostatic hyperplasia	20	5	<0.05
Prostate cancer	5	0	NS
Condition after urinary bladder extirpation	5	5	NS
Type 2 diabetes mellitus	15	10	NS
Chronic gastritis	5	5	NS
Inflammatory bowel disease	0	5	NS
Abdominal surgeries	5	0	NS
Obesity	10	15	NS

Joint pain	30	25	NS
Sleep disorders	10	15	NS

Values are percentage unless otherwise indicated.

EVAR, endovascular aneurysms repair; OS, open surgery;

NYHA, New York Heart Association; NS, not significant.

TABLE 14. Comparison of Indicators Affecting Patients' Well-Being in Endovascular **and Open Surgery Groups (Kisis et al)**

Variable	EVAR Group n=20	OS Group n=20	P
Duration of epidural analgesia, hours	25 (5)	50 (23)	0.002
Gastrointestinal disorders, %	10	60	<0.001
Duration of postoperative urinary catheterization, hours	24 (3)	29 (18)	0.024
Stay in ICU, hours	24 (5)	30 (13)	0.035
Length of hospital stay after surgery, days	2.9 (0.8)	8 (2)	0.021

Values are mean (standard deviation) unless otherwise indicated.

EVAR, endovascular aneurysms repair; OS, open surgery.

TABLE 15. Results of the SF-36 (Kisis et al)

Component	Before procedure			One month after procedure			One year after procedure		
	OS n=20	EVAR n=20	P	OS n=20	EVAR n=20	P	OS n=20	EVAR n=20	P
Physical functioning	71 (8)	76 (10)	NS	43 (9)	70 (7)	<0.001	59 (9)	68 (10)	0.016
Role-physical	66 (12)	66 (12)	NS	34 (12)	60 (13)	<0.001	57 (11)	65 (13)	NS
Bodily pain	63 (8)	61 (8)	NS	28 (10)	60 (10)	<0.001	27 (8)	60 (11)	<0.001
General health	65 (10)	64 (10)	NS	60 (13)	63 (11)	NS	65 (8)	68 (10)	NS
Vitality	59 (11)	59 (11)	NS	30 (10)	52 (5)	<0.001	54 (8)	58 (10)	NS
Social functioning	66 (10)	66 (10	NS	36 (11)	61 (9)	<0.001	45 (6)	54 (10)	0.007
Role-emotional	63 (10)	63 (10)	NS	35 (7)	58 (15)	<0.001	42 (15)	57 (15)	0.009
Mental health	64 (10)	63 (6)	NS	53 (13)	65 (10)	0.002	51 (10)	54 (9)	NS
PCS	48 (3)	48 (4)	NS	38 (3)	47 (3)	<0.001	42 (3)	48 (4)	<0.001
MCS	45 (3)	44 (3)	NS	37 (3)	44 (14)	<0.001	39 (4)	40 (4)	NS

PCS, physical component summary; MCS, mental component summary; EVAR, endovascular aneurysms repair; OS, open surgery

FIGURES

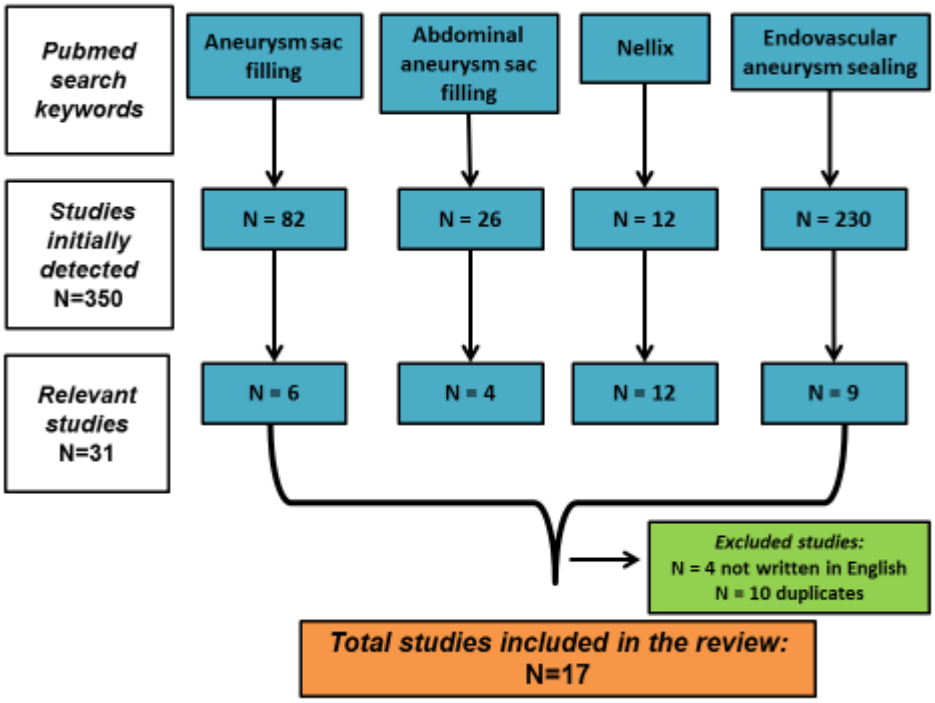

Figure 1. Flowchart of Pubmed search results

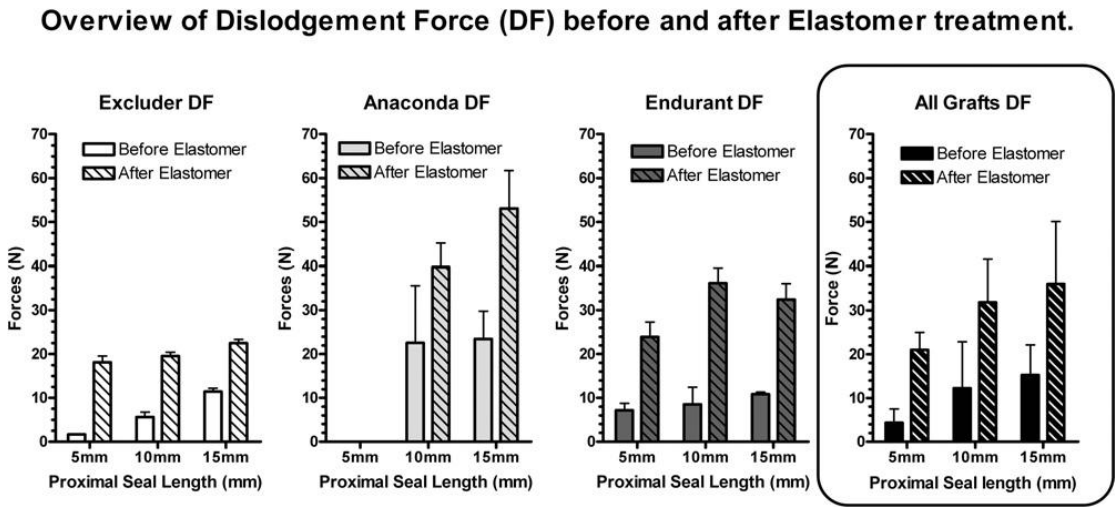

Figure 2. The dislodgement forces (DF) for the different kinds of stent grafts. The bars show mean dislodgement force (n _ 5) for the seal length, while the error bars depict the standard deviation (SD). The empty bars show the force needed to dislodge the graft when the aneurysm sac was empty; the striped bars show the forces needed after filling the sac with elastomer. The graph at the right shows that all grafts benefit from the elastomer augmentation.

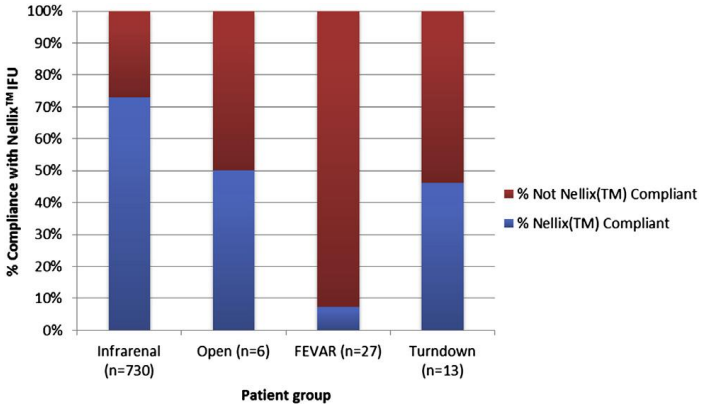

Figure 3. Differing suitability for Nellix among four groups of patients. FEVR = fenestrated endovascular repair

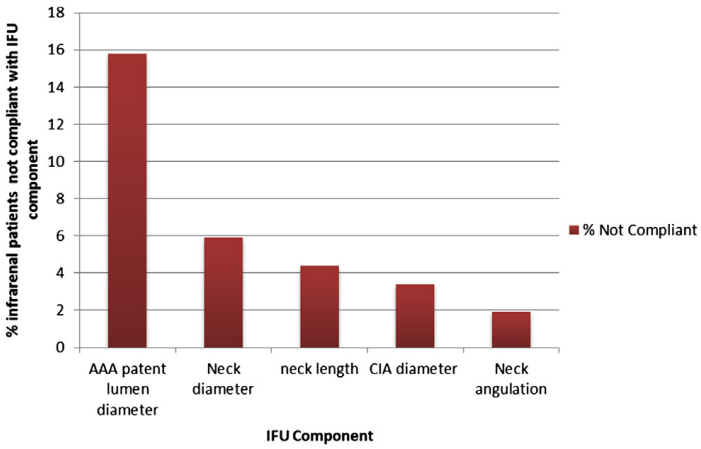

Figure 4. Limitations of each component of Nellix instructions for use (IFU) in patients undergoing endovascular aortic repair (EVR). AAA = abdominal aortic aneurysm; CIA = common iliac artery.

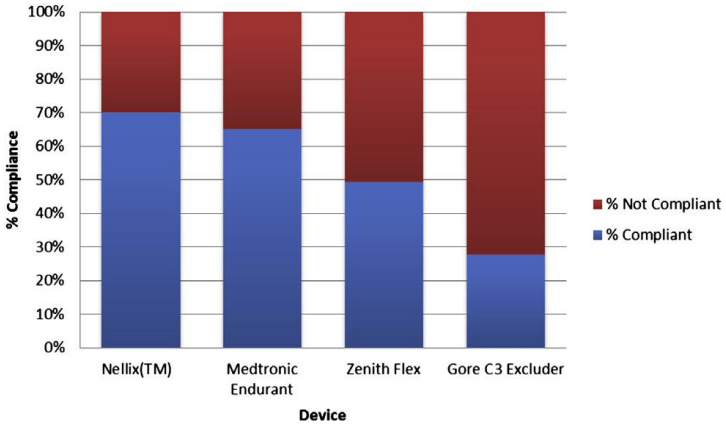

Figure 5. Nellix instructions for use (IFU) compliance compared with current endovascular aortic repair (EVR) devices in patients from all four groups (n = 776). FEVR = fenestrated endovascular repair.

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