ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΙΑΤΡΙΚΗ ΣΧΟΛΗ

ΚΟΙΝΟ ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

«ΕΝΔΑΓΓΕΙΑΚΕΣ ΤΕΧΝΙΚΕΣ»

ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ

ΙΑΤΡΙΚΗ ΣΧΟΛΗ ΣΕ ΣΥΝΕΡΓΑΣΙΑ ΜΕ ΤΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΤΟΥ ΜΙΛΑΝΟΥ-BICOCCA

ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

ΘΕΜΑ:

PRE-EMPTIVE EMBOLIZATION OF ANEURYSM SAC OR AORTIC SIDE BRANCHES IN ENDOVASCULAR ANEURYSM REPAIR: META-ANALYSIS AND TRIAL SEQUENTIAL ANALYSIS OF RANDOMIZED CONTROLLED TRIALS.

ΠΡΟΦΥΛΑΚΤΙΚΟΣ ΕΜΒΟΛΙΣΜΟΣ ΑΝΕΥΡΥΣΜΑΤΙΚΟΥ ΣΑΚΟΥ Η ΠΛΑΓΙΩΝ ΚΛΑΔΩΝ ΣΤΗΝ ΕΝΔΑΓΓΕΙΑΚΗ ΕΠΙΔΙΟΡΘΩΣΗ ΑΝΕΥΡΥΣΜΑΤΟΣ: ΜΕΤΑ-ΑΝΑΛΥΣΗ ΚΑΙ ΔΙΑΔΟΧΙΚΗ ΜΕΘΟΔΟΣ ΑΝΑΛΥΣΗΣ (TSA) ΤΥΧΑΙΟΠΟΙΗΜΕΝΩΝ ΜΕΛΕΤΩΝ.

ΜΕΤΑΠΤ. ΦΟΙΤΗΤΗΣ:

ΚΗΠΑΡΑΚΗΣ Ι. ΜΙΧΑΗΛ

ΑΘΗΝΑ

Ιούνιος, 2022

ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΙΑΤΡΙΚΗ ΣΧΟΛΗ

ΚΟΙΝΟ ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

«ΕΝΔΑΓΓΕΙΑΚΕΣ ΤΕΧΝΙΚΕΣ»

ΠΡΑΚΤΙΚΟ ΚΡΙΣΕΩΣ

ΤΗΣ ΣΥΝΕΔΡΙΑΣΗΣ ΤΗΣ ΤΡΙΜΕΛΟΥΣ ΕΞΕΤΑΣΤΙΚΗΣ ΕΠΙΤΡΟΠΗΣ ΓΙΑ ΤΗΝ ΑΞΙΟΛΟΓΗΣΗ ΤΗΣ ΔΙΠΛΩΜΑΤΙΚΗΣ ΕΡΓΑΣΙΑΣ
του Μεταπτυχιακού Φοιτητή ΚΗΠΑΡΑΚΗ ΜΙΧΑΗΛ

Εξεταστική Επιτροπή

- Καθηγητής Γεώργιος Γερουλάκος, Επιβλέπων
- Καθηγητής Ιωάννης Κακίσης
- Καθηγητής Αχιλλέας Χατζηϊωάννου

Η Τριμελής Εξεταστική Επιτροπή για την αξιολόγηση και εξέταση του υποψηφίου **κ. Κηπαράκη Μιχαήλ**., συνεδρίασε σήμερα 17/06/2022.

Η Επιτροπή **διαπίστωσε** ότι η Διπλωματική Εργασία του Κηπαράκη Μιχαήλ με τίτλο **«Pre-emptive embolization of aneurysm sac or aortic side branches in endovascular aneurysm repair - Meta-analysis and trial sequential analysis of randomized controlled trials»** είναι πρωτότυπη, επιστημονικά και τεχνικά άρτια και η βιβλιογραφική πληροφορία ολοκληρωμένη και εμπεριστατωμένη.

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

Στην ψηφοφορία για την βαθμολογία ο υποψήφιος έλαβε για τον βαθμό «ΑΡΙΣΤΑ» ψήφους ....., για τον βαθμό «ΛΙΑΝ ΚΑΛΩΣ» ψήφους ..... και για τον βαθμό «ΚΑΛΩΣ» ψήφους ..... Κατά συνέπεια, απονέμεται ο βαθμός «.....».

Τα Μέλη της Εξεταστικής Επιτροπής

- Καθηγητής Γεώργιος Γερουλάκος, Επιβλέπων (Υπογραφή) ——————
- Καθηγητής Ιωάννης Κακίσης (Υπογραφή) ——————
- Καθηγητής Αχιλλέας Χατζηϊωάννου (Υπογραφή) ——————

Αφιερωμένο στους

Γονείς μου

Ευχαριστίες προς:

- **κο Νικόλαο Κοντοπόδη,**

Επίκουρος Καθηγητής Αγγειοχειρουργικής, Ιατρική Σχολή, Πανεπιστήμιο Κρήτης, Πανεπιστημιακό Γενικό Νοσοκομείο Ηρακλείου

- **κο Γεώργιο Αντωνίου,**

Consultant Vascular Surgeon - MAHSC Honorary Clinical Chair, Manchester University NHS Foundation Trust - The University of Manchester · Department of Vascular & Endovascular Surgery

- **κο Γεώργιο Γερουλάκο,**

Καθηγητής Αγγειοχειρουργικής, Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών, Πανεπιστημιακό Νοσοκομείο «Αττικόν»

- **κο Χρήστο Ιωάννου**

Καθηγητής Αγγειοχειρουργικής, Ιατρική Σχολή, Πανεπιστήμιο Κρήτης, Πανεπιστημιακό Γενικό Νοσοκομείο Ηρακλείου

CONTENTS

Page

- **PART A. Introduction**…….1

  I. Abdominal aortic aneurysm…….....2

  II. Endovascular Aneurysm Repair……....11

  III. Endoleaks…….....19

- **PART B. Pre-emptive embolization of aneurysm sac or aortic side branches in endovascular aneurysm repair - Meta-analysis and trial sequential analysis of randomized controlled trials** ……..25

  1. Introduction……..……26
  2. Methods……27
  3. Results……..33
  4. Discussion……49
  5. Conclusions……..51
  6. Summary……..52
  7. Περίληψη.....53
  8. References…….....…….55
  9. Appendix.…….……64
  10. Keywords…….65

PART A. Introduction

I. Abdominal Aortic Aneurysm

Abdominal aortic aneurysm (AAA), which is a focal dilation 50 percent greater than the normal diameter of the aorta (Image 1), is a common but potentially life-threatening condition. AAAs are described as infrarenal, juxtarenal (pararenal), or suprarenal depending upon the involvement of the renal or visceral vessels.

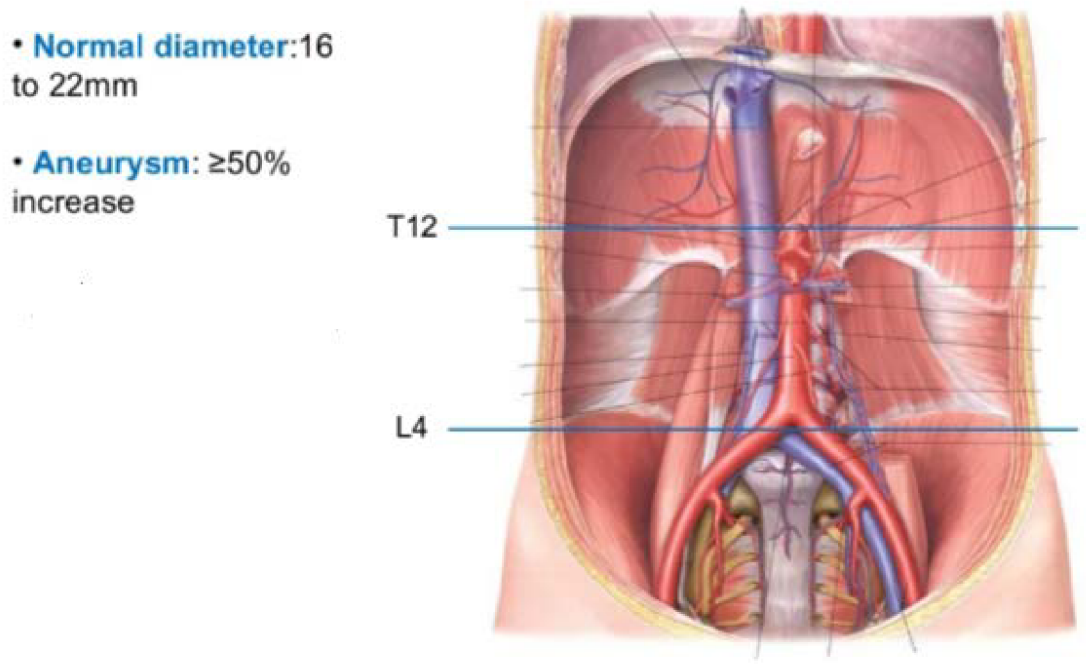


Image 1

- Infrarenal – aneurysm originates below the renal arteries
- Juxtarenal – aneurysm originates at the level of the renal arteries
- Suprarenal – aneurysm originates above the renal arteries

AAAs most often occur in the segment of aorta between the renal and inferior mesenteric arteries; approximately 5 percent involve the renal or visceral arteries (Image 2).

Up to 40 percent of AAAs are associated with iliac artery aneurysm(s).

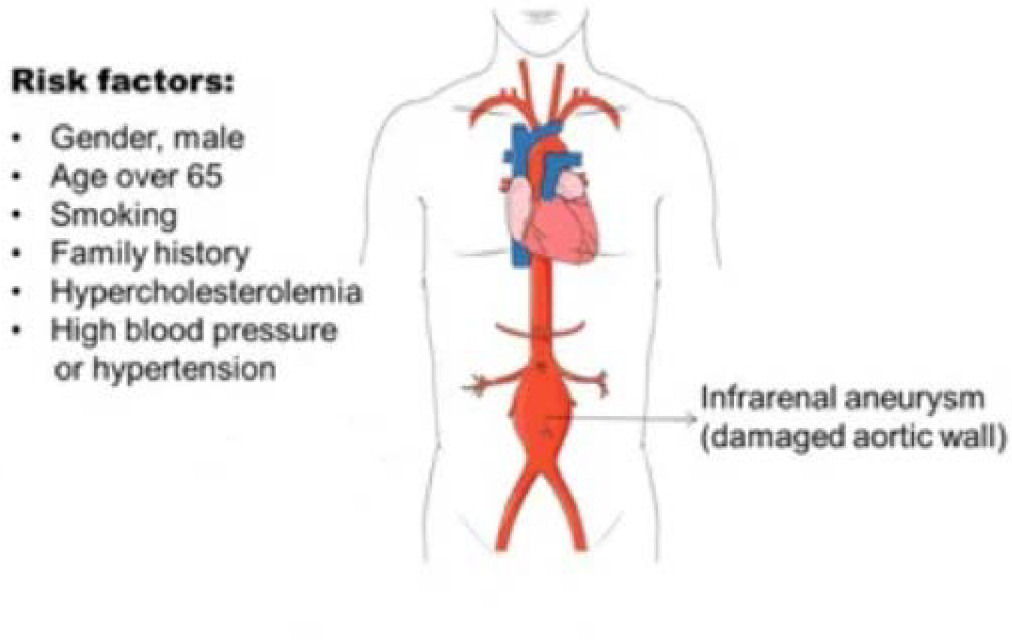


Image 2

Well-defined risk factors are associated with the development of AAA and include older age, male gender, Caucasian race, a positive family history, smoking, the presence of other large vessel aneurysms and atherosclerosis (Image 2).

Many pathogenic mechanisms have been proposed for the development, expansion, and rupture of AAA, however, the relative contribution of these mechanisms to AAA expansion and rupture in humans is unclear. Irrespective of the definition, the underlying problem in aneurysmal disease is weakening of the aortic wall, resulting in progressive dilatation and, left untreated, eventual aortic rupture. Less common complications include distal embolization, aortoenteric or aortocaval fistulae, and iliac vein compression resultant in deep vein thrombosis. As a result, AAA is estimated to be the tenth commonest cause of mortality (before COVID-era) and is responsible for ≈2% of all deaths.[1]

Ultrasound screening studies have shown that 4 to 8 percent of older men have an occult AAA.[2, 3]Abdominal aortic aneurysm occurs four to five times more commonly in men than women. Because the incidence of AAA rises sharply in individuals over 60 years of age, the future prevalence of AAA could increase substantially in association with the aging population. On the other hand, some suggest that a reduction in the prevalence of smoking could have the opposite effect.[4]

The annual incidence of AAA is difficult to measure. Screening studies in the United States and the United Kingdom have estimated the incidence of AAA in men over 50 to be 3.5 to 6.5 per 1000 person-years.[5] These studies also found that new AAAs develop in 2 to 2.6 percent of at-risk men 4 to 5.5 years after an initially normal study.

Aneurysmal degeneration of the abdominal aorta is a multifactorial, systemic process generally felt to be due to alterations in vascular wall biology leading to a loss of vascular structural proteins and wall strength.[6]

Although atherosclerotic changes frequently coexist with AAA, and the risk factors for aneurysmal and atherosclerotic aortic disease overlap to some extent, contemporary research suggests that atherosclerosis is not causal.[7] Aneurysmal degeneration of the aortic wall is pathologically distinguished from atherosclerosis. Whereas atherosclerotic changes are limited to inner layers of the aortic wall, AAAs are characterized by transmural inflammatory change, abnormal collagen remodeling and cross-linking, and loss of elastin and smooth muscle cells.[8, 9] These changes result in aortic wall thinning and progressive aortic expansion.

Chronic inflammation of the aortic wall likely mediates aortic wall elastin and collagen degradation through proteases, including plasmin (formed from plasminogen by urokinase plasminogen activator and tissue type plasminogen activator), matrix metalloproteinases (MMPs), and cathepsin S and K. These factors are derived from endothelial and smooth muscle cells and inflammatory cells infiltrating the media and adventitia (Image 3).[7]

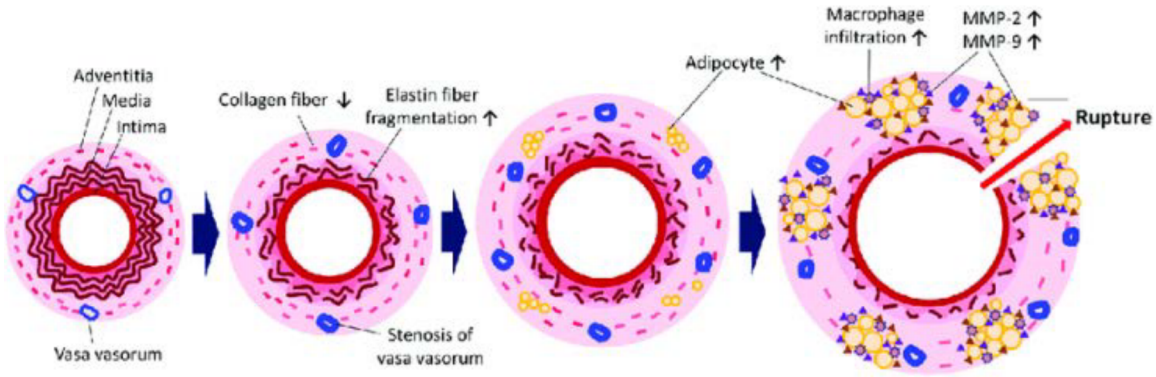


Image 3

The natural history of AAA is one of progressively increasing diameter; however, expansion rates vary. The main risk factors associated with AAA expansion and rupture include large aneurysm diameter, faster aortic expansion rate, current smoking, and female gender.

Although expansion rates vary, the rate of aortic expansion is greater for larger compared with smaller diameter AAA.[10, 11] This pattern of differential expansion over time related to baseline AAA diameter was illustrated in an analysis from the United Kingdom Small Aneurysm Trial in which the following annual expansion rates were noted[10]

- 1.9 mm per year for aneurysms 2.8 to 3.9 cm in baseline diameter
- 2.7 mm per year for those 4.0 to 4.5 cm in baseline diameter
- 3.5 mm per year for those 4.6 to 8.5 cm in baseline diameter

The cumulative evidence from studies that prospectively followed the size of AAAs suggests that small and medium-sized AAAs (<5.5 cm) expand at an average rate of 2 to 3 mm/year, while larger aneurysms expand at about 3 to 4 mm per year.[11] Some aneurysms, for unclear reasons, remain relatively fixed in size for a period of time and then undergo rapid expansion, which is thought to increase the risk for rupture, and is defined as an increase in maximal aortic diameter ≥5 mm over a six-month period of time or >10 mm over a year.[12]

Aneurysm diameter is the most important factor predisposing to rupture, with risk increasing markedly at aneurysm diameters greater than 5.5 cm (Image 4).[13] In addition to diameter, a faster rate of expansion (highest in smokers), gender, and other factors play a role.[14]

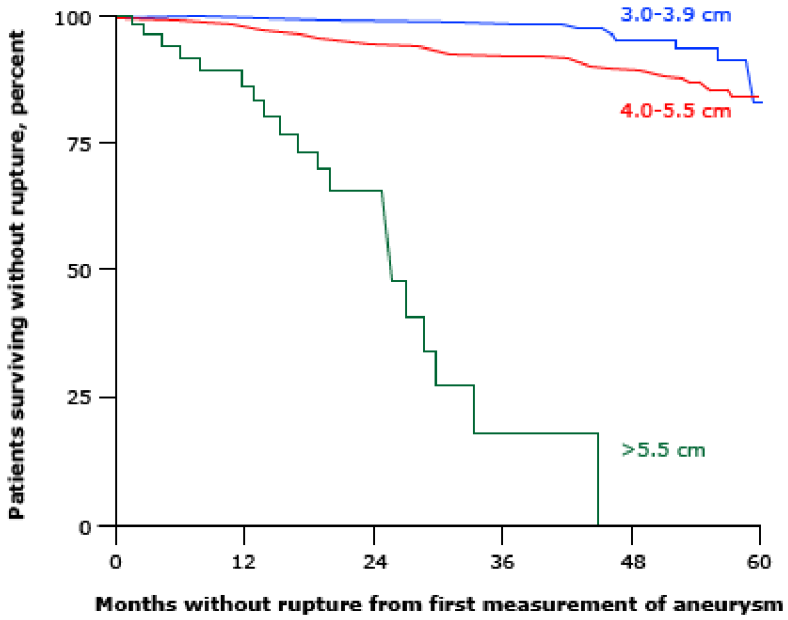


Image 4

The relationship of aneurysm diameter to aortic rupture was first demonstrated in a seminal study in which patients with aneurysms >6 cm had a much higher rate of rupture at five years compared with aneurysms <6.0 cm (43 versus 20 percent), and lower rate of survival (6 versus 48 percent). Virtually identical differences in survival rates have been noted in other series.[15]

A statement from the Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery estimated the annual rupture risk according to AAA diameter as follows[12, 14]

- Zero for AAA <4.0 cm in diameter
- 0.5 to 5 percent for AAA 4.0 to 4.9 cm in diameter
- 3 to 15 percent for AAA 5.0 to 5.9 cm in diameter
- 10 to 20 percent for AAA 6.0 to 6.9 cm in diameter
- 20 to 40 percent for AAA 7.0 to 7.9 cm in diameter
- 30 to 50 percent for AAA ≥8.0 cm in diameter

The rate of aneurysm expansion may also be an important determinant of rupture risk.[16] A small (<4.0 cm) or medium (4 to 5.5 cm) AAA that expands ≥0.5 cm over six months of follow-up is considered to be at high risk for rupture.[17]

For asymptomatic patients, elective repair of the aneurysm is the most effective management to prevent rupture. However, elective aortic surgery is also associated with risks, and thus, elective AAA repair is not recommended until the risk of rupture exceeds the risks associated with repair. For asymptomatic patients, the risk of AAA rupture generally exceeds the risk associated with elective AAA repair when aneurysm diameter exceeds 5.5 cm.[17] Other factors such as the patient's age, rate of aneurysm expansion, and the presence of coexistent peripheral artery disease or peripheral aneurysm are also important to consider when determining when to proceed with elective AAA repair.

For patients with asymptomatic AAA who do not have indications for elective repair, medical treatment is aimed at reducing cardiovascular risk in the event that AAA repair is needed, and limiting the rate of aortic expansion.

Two methods of aneurysm repair are currently available: open surgery and endovascular aneurysm repair (EVAR). The mortality of elective AAA repair is 3 to 5 percent for open AAA repair, but lower at 0.5 to 2 percent for EVAR.[18] When choosing the type of repair, it is important to take into account the patient's expected survival (short-term and long-term), which depends upon the patient's age and medical comorbidities.

Repair of AAA is generally indicated under the circumstances listed below.

- Asymptomatic AAA >5.5 cm
- Symptomatic (tenderness or abdominal or back pain, evidence for embolization, rupture)
- Rapidly expanding AAA
- AAA associated with peripheral arterial aneurysm (eg, iliac, popliteal) or peripheral artery disease (eg, iliac occlusive disease)

Open AAA repair – Open aneurysm repair involves replacement of the diseased aortic segment with a tube or bifurcated prosthetic graft (Image 5) through a midline abdominal

or retroperitoneal incision. With technical refinements for open AAA repair, complications such as acute renal failure, distal embolization, wound infection, colonic ischemia, false aneurysm formation, aorto-duodenal fistula, graft infection, and perioperative bleeding have become less common following routine elective surgery but remain significant issues following emergent open AAA repair.

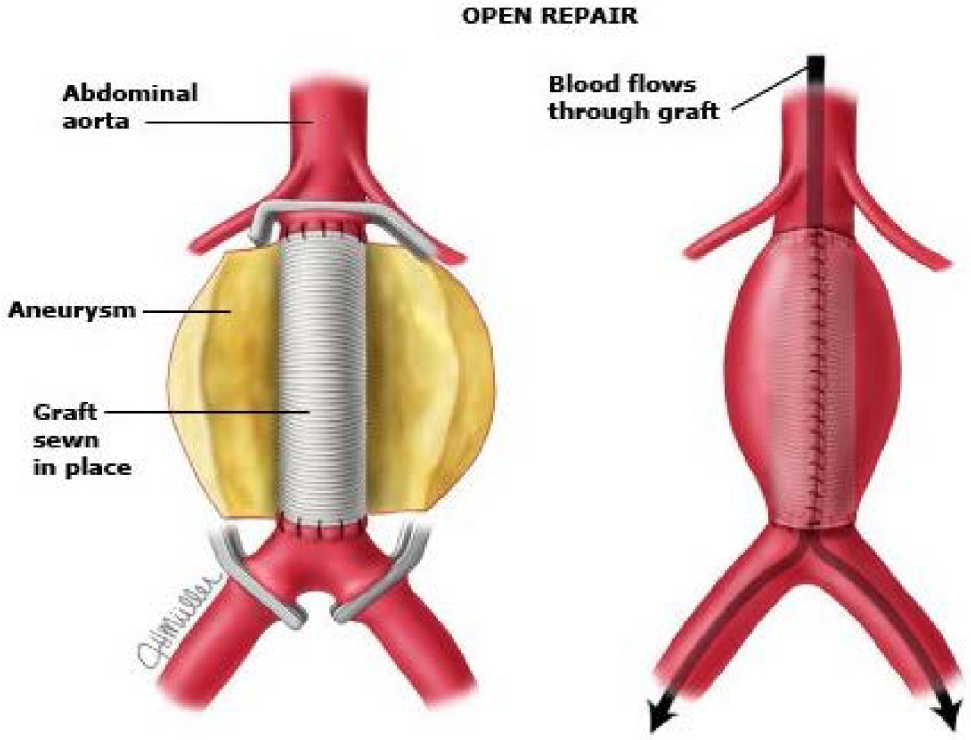


Image 5

EVAR – involves the placement of modular graft components delivered via the iliac or femoral arteries to line the aorta (Image 6) and exclude the aneurysm sac from the circulation. EVAR requires fulfillment of specific anatomic criteria. Up to 70 percent of patients are EVAR candidates. This percentage is expected to increase with the approval of specialized endograft designs that will allow the treatment of more challenging aortic aneurysm anatomy. Although EVAR is associated with lower perioperative mortality, late AAA rupture has been reported.

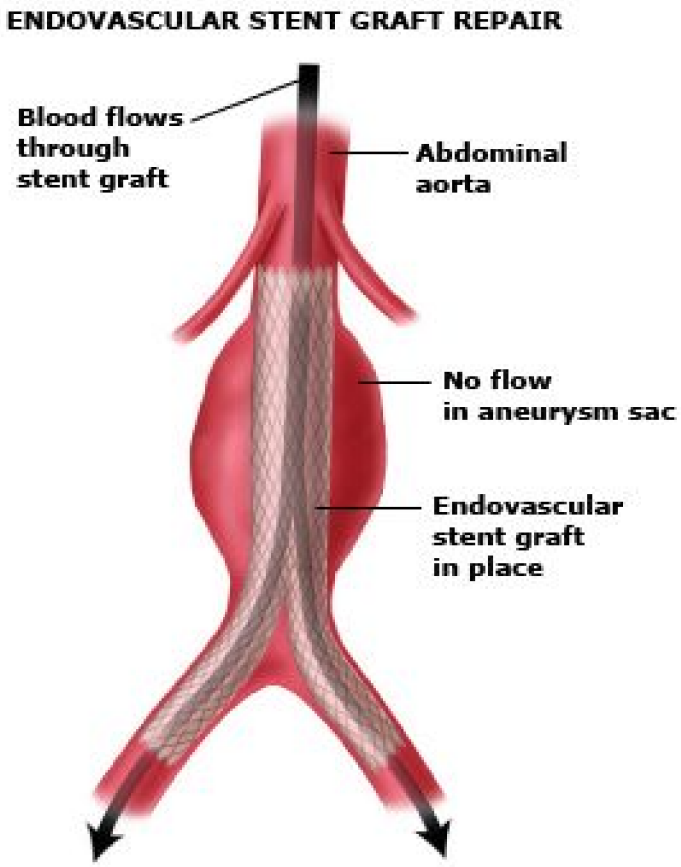


Image 6

When it has been determined that a patient should undergo AAA repair, the choice between open surgical or endovascular aneurysm repair is individualized based upon the patient's age, risk for perioperative morbidity and mortality, and aortoiliac anatomy.[17, 19] Given the need for lifelong surveillance with endovascular repair, younger patients with low operative risk may benefit more from open surgical repair, whereas older patients and those with high perioperative risk may benefit more from endovascular repair, provided their aortoiliac anatomy is appropriate for repair.

Randomized trials comparing open AAA repair with EVAR have found significantly improved short-term (30-day) morbidity and mortality for EVAR, but no significant differences in long-term outcomes.[20-24] A pooled analysis of these trials identified a 69 percent reduction in the risk for perioperative mortality for endovascular compared with open repair ([OR] .33, 95% CI 0.17-0.64).[24] EVAR appears to be associated with the need for more secondary procedures, and an ongoing future risk of aortic rupture.

In general:

- Open surgical repair may be preferred for younger patients who have a low or average perioperative risk.
- EVAR may be preferred in patients with favorable anatomy (as defined by the instructions for use [IFU] of a given device) who are at a high level of perioperative risk.
- EVAR may be appropriate in patients with favorable anatomy but who do not have a high surgical risk; however, the early perioperative benefit may not be sustained in the long-term.

II. Endovascular Aneurysm Repair

EVAR is an important advance in the treatment of AAA, is performed by inserting graft components folded and compressed within a delivery sheath through the lumen of an access vessel, usually the common femoral artery. Upon deployment, the endograft expands, contacting the aortic wall proximally and iliac vessels distally to exclude the aortic aneurysm sac from aortic blood flow and pressure.

Compared with open AAA repair, EVAR is associated with a significant reduction in perioperative mortality, primarily because EVAR does not require operative exposure of the aorta or aortic clamping. Concurrent with the increased use of EVAR, a decrease in the incidence of ruptured AAA and associated morbidity and mortality has been reported in the United States, likely due to the ability to offer EVAR to patients who would not otherwise be candidates for open surgical repair.[25]

Several aortic measurements are important for determining the feasibility of endovascular aneurysm repair and for endograft sizing. The definitions of important terms are as follows[26]

- Aortic neck diameter – The aortic diameter at the lowest renal artery.
- Aortic neck length – The distance from the lowest renal artery to the origin of the aneurysm.
- Aortic neck angulation – The angle formed between points connecting the lowest renal artery, the origin of the aneurysm, and the aortic bifurcation.
- Conical/reverse tapered aortic neck – A conical neck is present when the diameter of the aorta 15 mm below the lowest renal artery is ≥10 percent larger than the diameter of the aorta at the lowest renal artery.
- Infrarenal aortic length – The distance from the lowest renal artery to the aortic bifurcation.

Other measurements that are important for sizing endografts include the maximal common iliac artery diameter, minimum external iliac artery diameter, distance from the aortic neck to the iliac bifurcation, and maximal AAA sac diameter.

Prior to consideration for endovascular aneurysm repair, aortoiliac imaging is needed to define the anatomy, determine the feasibility of endovascular repair, and choose the size and configuration of endograft components. Computed tomography (CT) is typically used for elective AAA repair, but under urgent or emergent circumstances, endograft feasibility and sizing can be determined intraoperatively using arteriography.

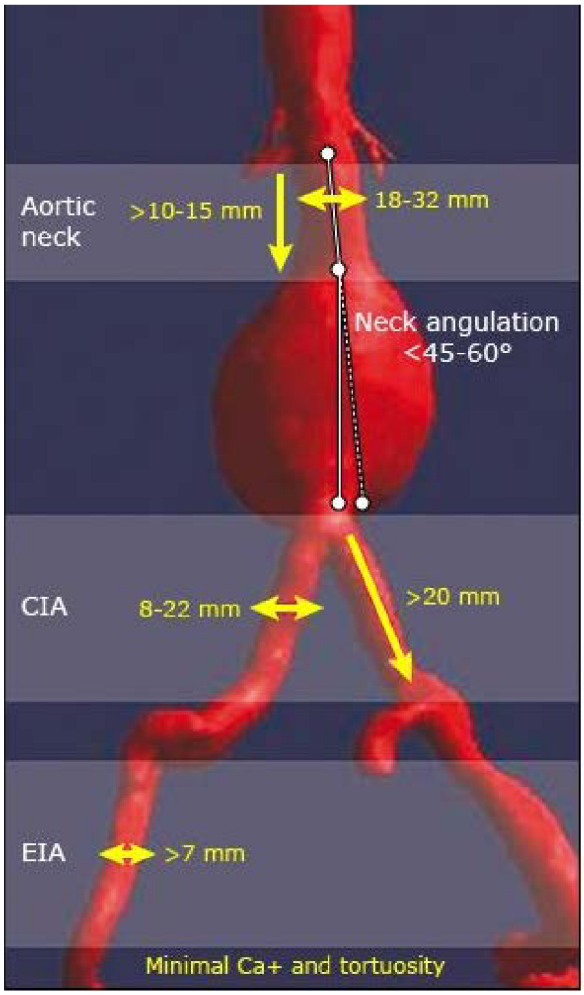


Image 7

Anatomic suitability is the most important determinant for successful EVAR in the long term. With early endograft designs, about 50 percent of patients were not candidates for EVAR because of the site, extent, or morphology of the aneurysm, or unsuitability of access vessels. The availability of devices that allow for shorter proximal seal zones and lower profile devices has expanded the use of EVAR to almost two-thirds of patients with an infrarenal AAA.

To exclude blood flow from the aneurysm sac, the endograft must provide an adequate seal where the endograft contacts the arterial wall proximally at the aortic neck and distally in each of the iliac arteries, otherwise known as the landing zones. The security of the repair relies solely upon the radial force generated by the graft at the landing zones since endografts do not have any suture-mediated stability. Thus, certain anatomic criteria must be fulfilled to perform EVAR (Image 7).

The specific criteria recommended for a specific device are given in the IFU that are published and packaged with each device used. Failure to follow device specifications increases the risk for complications.

The required endograft diameter is determined by measuring the aortic neck diameter (eg, 20 mm) and adding an additional 15 to 20 percent of the aortic neck diameter (20 mm + 3 to 4 mm = 23 to 24 mm). Under-sizing the diameter of the endograft will lead to an inadequate seal and failure to exclude the aneurysm. Over-sizing the endograft 15 to 20 percent over the measured aortic neck diameter should provide sufficient radial force to prevent device migration. Over-sizing the endograft may lead to kinking of the device, which can form a nidus for thrombus formation or endoleak and may result in incomplete expansion of the endograft with infolding and inadequate seal, and can also be associated with intermediate and long-term neck expansion.[27]

The aortic neck length should be at least 10 to 15 mm to provide an adequate proximal landing zone for endograft fixation. Qualitative assessment of the proximal neck is also important. Ideally, the proximal aorta should be normal in appearance, without significant thrombus or calcification. Although not an absolute contraindication for EVAR, large amounts of thrombus or calcification will interfere with fixation of the graft and increase the risk for graft migration or type I endoleak.

Ideally, the aortic neck angle should be less than 60º. Angles that are greater lead to difficulties in implantation, kinking, endoleak, and the potential for distal device migration. Severe angulation (>60°) is generally considered to be a contraindication to EVAR. However, the ability to place a device in aneurysms with significant angulation at the neck

is ultimately determined by the conformability of the specific device type and its delivery characteristics.

Suitable iliac artery morphology is also required for endograft placement. The iliac arteries should have a minimal amount of calcification and tortuosity, and no significant stenosis or mural thrombus should be present in the distal graft landing zones. The common iliac artery is the preferred distal attachment site, but the external iliac artery can also be used. When the external iliac artery is used for distal fixation (eg, common iliac artery aneurysm), the origin of the hypogastric artery (ie, internal iliac artery) is covered by the endograft. Thus, prior to endograft placement, the hypogastric artery will need to be embolized to prevent back-bleeding into the aneurysm sac, unless there is severe stenosis at its origin. A minimal external iliac artery diameter of 7 mm is needed to allow safe passage of the endograft delivery sheath. The common iliac artery diameter should measure between 8 and 22 mm, and the length of normal diameter common iliac artery into which the limbs of the endograft will be fixed should measure at least 15 to 20 mm to achieve an adequate seal. Aneurysmal iliac arteries (>22 mm) are treated by excluding them.

Endovascular repair of AAA is contraindicated in patients who do not meet the anatomic criteria required to place any of the available endografts. Adverse anatomic features include suprarenal or juxtarenal AAA, small caliber vessels, circumferential aortic calcification, and extensive tortuosity. Depending upon the location of the main and accessory renal arteries, endovascular repair may also be contraindicated for the management of AAA associated with horseshoe kidney. A variety of next-generation devices are being developed to treat suprarenal and juxtarenal abdominal aortic aneurysms.

A relative contraindication to EVAR is the inability to comply with the required post-EVAR surveillance.

Whether younger patients (<60 years of age) who are not at high risk for open surgery should undergo open surgical repair versus EVAR remains controversial. Surveillance over an extended period of time exposes the patient to greater levels of cumulative radiation, and EVAR does not completely eliminate the risk of future aortic rupture. Guidelines from major medical and surgical societies emphasize an individualized approach when choosing

endovascular repair, taking into account the patient's age and risk factors for perioperative morbidity and mortality.[17, 19]

Although EVAR is associated with lower perioperative morbidity and mortality compared with open surgical repair, there is a small risk that the endovascular repair may need to be converted to an open repair, and thus, patients should be evaluated and prepared as if undergoing an open surgical repair. Coronary artery disease (CAD) is the leading cause of early and late mortality following AAA repair, and other comorbidities such as chronic obstructive pulmonary disease (COPD) and renal insufficiency also increase perioperative morbidity and mortality. There is agreement with the Society for Vascular Surgery and other societies that recommend a comprehensive assessment of medical comorbidities prior to EVAR including cardiac, pulmonary, and renal evaluation, also taking into account hypertension and patient age as relevant risk factors for morbidity and mortality.[28, 29]

The technical success rate for abdominal aortic endografting is high, and the overall rate of severe perioperative complications is lower compared with open surgical repair; however, the endograft remains a dynamic entity and late complications are more likely. Complications associated with endovascular abdominal aortic repair are usually related to some technical aspect of endograft placement such as problems with vascular access, or due to the structural integrity and stability of the endograft such as endoleak, endograft migration, or endograft collapse.

Endograft complications rarely lead to a need to convert to open surgery at the time of placement, and when they occur late, can usually be managed using endovascular means.[30] Device-related complications are the main reason for re-intervention (including late conversion), which is required in up to 30 percent of patients. The overall incidence of conversion is about two percent.[31] Ischemic complications are often related to embolism, but may also be due to positioning the endograft and can affect the extremities, intestine, pelvic organs, spinal cord, or kidneys. Renal insufficiency can also be caused by the administration of intravenous contrast (eg, allergic reaction, contrast-induced nephropathy). The risk of ischemic complications increases with more complex endovascular repairs.

Although the technical success rate for abdominal aortic endografting is high (99 percent), endograft-related complications are common with an incidence that ranges from 11 to 30 percent.[32, 33] The incidence of complications at initial repair appears to be higher with larger diameter aneurysms.[34] Technical complications associated with endografts include vascular injury (eg, iliac, femoral) during access or device deployment; endoleak from inadequate fixation, sealing of the graft to the vessel wall, or breakdown of the graft material; stent fractures; component separations; and endograft collapse. These problems occur with varying frequency and timing relative to endograft placement. Their occurrence depends upon many factors, including anatomic suitability for endograft placement, graft choice, and proper measurement for the specific device chosen.

An analysis of 22,830 matched Medicare beneficiaries who underwent open or endovascular aneurysm repair showed that re-intervention related to aneurysm was significantly more likely with endovascular compared with open repair (9.0 versus 1.7 percent).[35]

The importance of strict adherence to anatomic suitability in preventing complications during endovascular repair of EVAR was evaluated in a series of 10,228 patients treated with a variety of endografts who underwent pre-EVAR and at least one post-EVAR CT scan.[36] This multicenter observational study found a low compliance with manufacturer's instructions for device use and a high rate of post-EVAR aneurysm sac enlargement, raising concern for an increased long-term risk of aneurysm rupture when adherence to device-specific criteria is not strict. The manufacturer's most conservative indications for anatomic suitability were met in 42 percent of patients, but 31 percent did not meet the manufacturer's most liberal criteria. The rate of aortic sac enlargement was 41 percent at five-year follow-up. Independent predictors of AAA sac enlargement included endoleak, age ≥80 years, aortic neck diameter ≥28 mm, aortic neck angle >60°, and common iliac artery diameter >20 mm.

Immediate problems during endograft placement are common and are often not predictable. In most cases, these issues are corrected at the initial procedure and initial technical success rates are high.

Following endovascular aortic aneurysm repair, the aneurysm sac typically thromboses and approximately 50 percent of aneurysm sacs have decreased in diameter at one-year of follow-up. However, the endograft remains a dynamic entity and may respond to the new mechanical stresses and the changing configuration of the aorta. Late endograft complications develop and require re-intervention in up to 30 percent of cases. As examples, changes in the aneurysm sac may lead to endograft angulation, kinking, migration, or thrombosis.

Changes in endograft configuration can be easily evaluated with abdominal plain films. The identification of any abnormalities should prompt follow-up evaluation with CT.[37] The importance of ongoing surveillance following endograft placement to detect and correct endograft problems cannot be overstressed.

The most common complications of EVAR are

- Access site complications
- Endoleaks
- Device migration
- Component separation
- Limb kinking and occlusion
- Endograft infection
- Systemic complications (Intravenous contrast complications, cardiopulmonary complications, Ischemic complications, etc.)

Despite advances in endovascular salvage techniques for endograft failures, certain circumstances (eg, persistent endoleak, late rupture) require conversion to open abdominal aneurysm repair.

When open conversion is performed, suprarenal or supraceliac aortic control is often needed depending upon the location of the endograft and whether or not the graft has suprarenal fixation. Replacement of the clamp to an infrarenal position is performed as soon as possible to reduce complications related to intestinal and renal ischemia.

Explantation of the endograft, complete or partial, with in-situ aortic replacement is performed. The degree to which the graft is adherent to surrounding structures determines if complete or partial removal of the endograft is undertaken. Portions of the graft that are adherent to surrounding structures are best left in place. A poorly adherent graft may be infected.

The perioperative morbidity and mortality associated with elective conversion of endovascular to open AAA repair appears to be increased, particularly if the patient was originally deemed high risk for open surgery. In retrospective reviews, the mortality rate for open conversion is 10 to 13 percent.[38] However, others have reported lower mortality rates comparable to open AAA repair.[39] The mortality rates for emergent conversion related to ruptured aneurysm are similar to open repair of ruptured AAA not related to endograft conversion at about 50 percent.[40] Open conversion is performed using standard open aneurysm surgical techniques via a transperitoneal or retroperitoneal approach. The overall incidence of conversion (early or late) is about 2 percent.

The indications for conversion included the following (in descending order of frequency), in a study that followed patients over a seven-year period[39]

- Type I endoleak
- Graft migration with aneurysm expansion
- New aneurysm in the visceral segment
- Type II endoleak with aneurysm expansion
- Aortic rupture
- Aortic infection

III. Endoleaks

Endoleak is defined as persistent flow of blood into the aneurysm sac after device placement and indicates a failure to completely exclude the aneurysm.[41] Five types of endoleak are described. Endoleak is associated with a continued risk for aneurysm expansion or rupture. The most common types of endoleak (I and II) are usually managed successfully with the placement of additional stents or embolization techniques, but sometimes surgery is needed.

Following completed endovascular repair, the diagnosis of endoleak is made on follow-up imaging, usually CT that demonstrates blood outside the bounds of the endograft. For some types of endoleak, the source can be difficult to determine. For type II endoleak, the aneurysm sac fills through a collateral network and the endoleak may not be seen on the arterial phase of CT scanning, and thus, delayed imaging is required. Color flow duplex or selective arteriography may be needed to establish the diagnosis.

Type I endoleak (Image 8) is due to an incompetent seal at the proximal (IA), distal (IB) or side branch (IC) attachment sites. It occurs in 0 to 10 percent of endovascular aortic aneurysm repairs.[42]

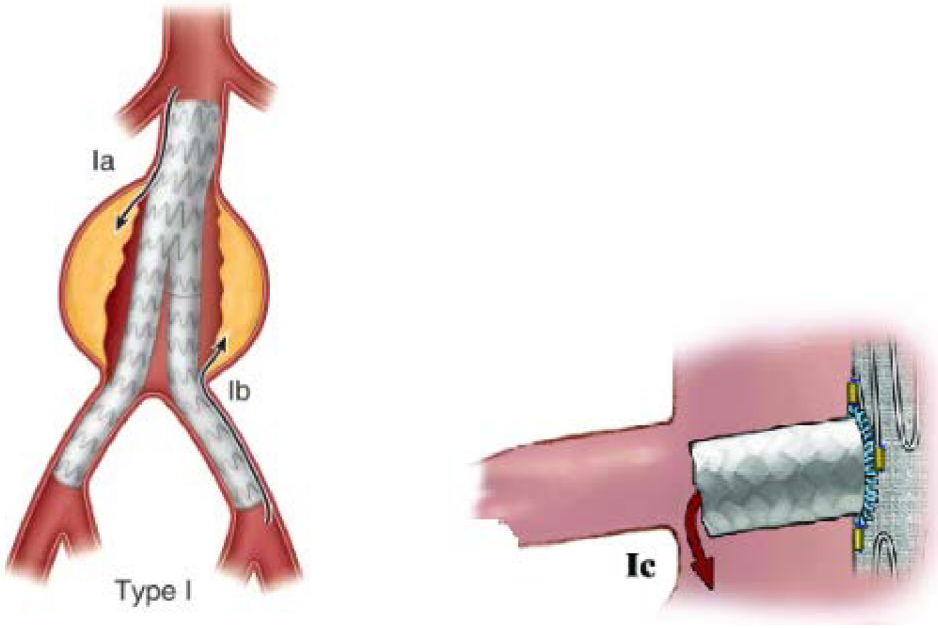


Image 8

Type I leak can occur immediately after device placement or can develop over time. Immediate proximal type I endoleak is typically due to incomplete apposition of the stent-graft to the aortic neck. Contributing factors include mural thrombus, aortic neck calcification, angulation, a short aortic neck, reverse tapering of the neck, and incorrect device sizing. Immediate distal type I endoleak is usually due to incorrect sizing of the iliac limbs, or inadvertent deployment of the endograft limb, often because of excessive iliac tortuosity, within the more proximal, larger iliac vessel. Late type I endoleaks can develop as a result of aneurysmal degeneration of the aortic neck or iliac arteries, severe angulation at the fixation sites or graft migration.[42, 43]

Type I endoleaks are repaired as soon as they are discovered because the aneurysm sac remains exposed to systemic pressure leading to aneurysm growth and rupture.[44] Spontaneous closure of the type I endoleak is uncommon.

Measures to prevent type I endoleak include correcting radiologic parallax during positioning to ensure correct placement and appropriate balloon inflation of the attachment sites once the device is correctly deployed. When a type I endoleak is identified at the time of endograft placement, the initial approach consists of re-ballooning the fixation sites and possibly the reversal of anticoagulation. For proximal type I endoleaks that persist after re-ballooning, the placement of additional aortic cuffs, or a balloon-expandable stent increases the radial force exerted by the proximal graft and maximizes apposition of the graft to the aortic wall.

For distal type I endoleaks that persist after balloon angioplasty of the distal attachment site, iliac limb extensions are used. If the iliac limb has been undersized, a flared iliac extension limb can be placed to exclude the endoleak. If the distal common iliac artery does not have an adequate length to provide a proper seal, coil embolization of the origin of the hypogastric artery and placement of a limb extension into the external iliac artery may be needed. It is important to maintain pelvic perfusion through the contralateral hypogastric artery to minimize the risk of pelvic ischemia.

Conversion to an open surgical repair may be needed in the rare situation in which a type I leak is refractory to percutaneous treatment.

Type II endoleak (Image 9) is due to a patent inferior mesenteric artery or patent lumbar artery branches that allow retrograde flow into the aneurysm sac. Type II endoleaks are the most prevalent type, occurring with all device types in about 15 percent of patients at one month following endograft placement.[44] The incidence of type II endoleak has been correlated with the number of patent aortic branches prior to endovascular repair of the aneurysm.[45] There are two types, IIA when there is single causative vessel and IIB if there is multiple involved vessels.

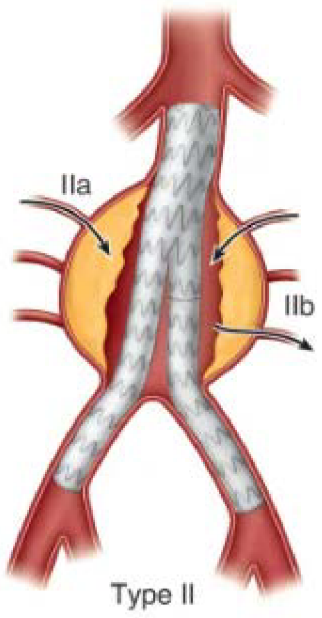


Image 9

The significance and management of type II endoleaks are controversial. Most investigators argue that careful follow-up imaging to detect changes in aneurysm sac volume and morphology is preferred, since spontaneous resolution occurs in many cases.[44] If an increase in the volume of the aneurysm is detected, the endoleak should be repaired. Repair is also indicated for persistent endoleaks (>6 to 12 months duration), because the natural history is not completely benign.[46] However, there is no consensus regarding treatment of type II endoleaks that are not associated with aneurysm sac enlargement.

The approach to the repair of type II endoleaks is most commonly endovascular, consisting of embolization of the feeding vessels or aneurysm sac.[43] Other approaches include laparoscopic clipping of the involved branch vessels, or surgical conversion.

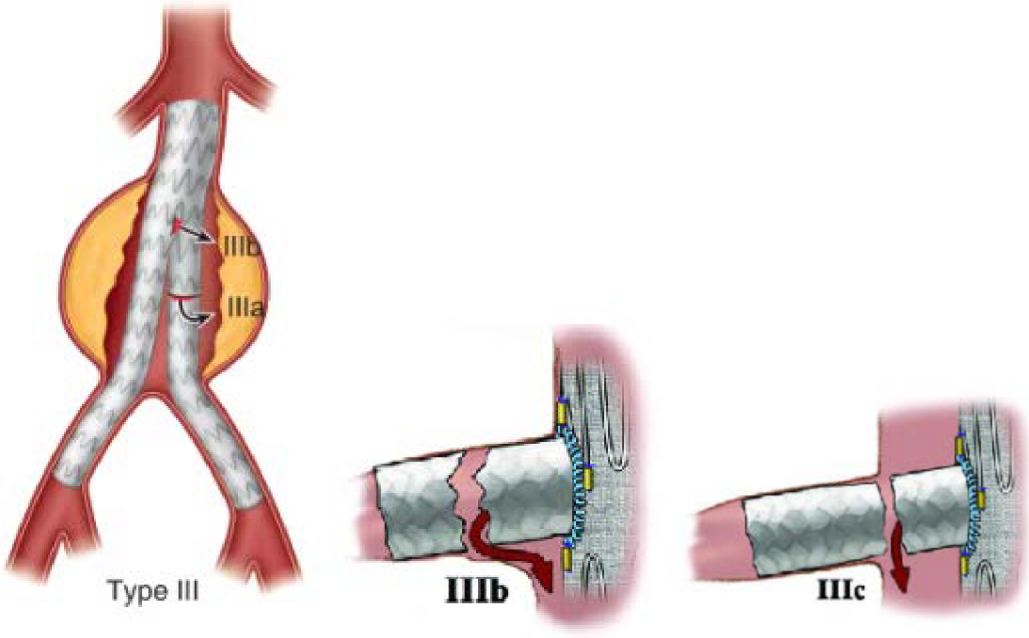


Image 10

Type III endoleaks (Image 10) are due to a junctional leak or disconnect of the endograft components (IIIA) or holes in the endograft fabric (IIIB) or side branch-side branch component (IIIC).[47] Type III endoleak is as serious as type I endoleak because it pressurizes the aneurysm sac. Type III leak is treated to prevent aortic rupture typically by deploying additional stent-graft components to seal the fabric defect or bridge the disconnected components.

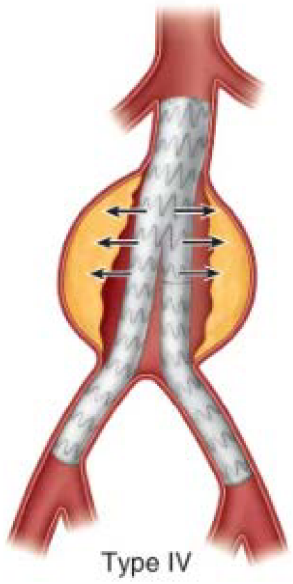


Image 11

Type IV endoleak (Image 11) is associated with graft porosity and is self-limited, typically resolving in 24 hours. It has not been associated with any long-term adverse events and does not require treatment. Type IV leak can obscure more serious type I or III leaks and can be quite disconcerting to see at completion angiography.

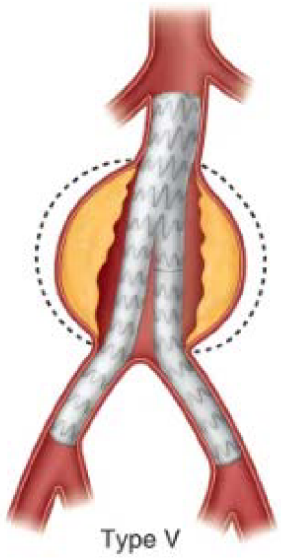


Image 12

Type V endoleak (Image 12), also referred to as endotension, is defined as continued aneurysm sac expansion without a demonstrable endoleak on any imaging modality.[44] The phenomenon is poorly understood. It was more commonly associated with semiporous graft materials (first generation expanded polytetrafluoroethylene [ePTFE] endografts), in which sac enlargement was associated with exudation of a protein rich material across the wall of the endograft. A change in the graft design appears to have resolved this problem, confirming the source of this type of endoleak. Treatment consisted of relining the existing endograft with a newer, lower porosity graft, or explantation of the graft.

PART B.

PRE-EMPTIVE EMBOLIZATION OF ANEURYSM SAC OR AORTIC SIDE BRANCHES IN ENDOVASCULAR ANEURYSM REPAIR: META-ANALYSIS AND TRIAL SEQUENTIAL ANALYSIS OF RANDOMIZED CONTROLLED TRIALS.

1.INTRODUCTION

Endovascular repair is the mainstay of treatment for AAA.[48] With the accumulated clinical experience and technological advancements, a broader range of aortic anatomies can be treated inside the instructions for use of newer generation devices.[49-51] Despite such advances, type II endoleak remains a common occurrence after EVAR. Even though it is been considered a benign condition, it requires close follow-up and has the potential of causing severe late complications.[52] Indeed, a type II endoleak may cause the aneurysm sac to expand as result of continuous sac pressurization, in which case treatment is required to avoid adverse sequela, such as graft migration, type I or III endoleak, and ultimately rupture. In case of sac expansion caused by a type II endoleak, the first-line treatment is embolization of the culprit vessel or aneurysm sac via the transarterial or translumbar route. Despite high rates of technical success, such procedures may be technically challenging.[53] Reports have shown that the clinical success is achieved in less than a third of the patients treated, and recurrence of endoleak is commonly observed.[54, 55] Open surgical repair is an option in case of failure of endovascular treatment strategies and continuing sac expansion.

Emerging evidence suggests that preventive embolization of aortic side branches or the aneurysm sac itself during the index EVAR procedure may be safe and result in lower rates of type II endoleak and secondary interventions, and a higher rate of sac regression.[56, 57] There is currently no meta-analysis of all published randomized controlled trials (RCT) comparing embolization with standard EVAR. We sought to investigate whether pre-emptive aortic branch or aneurysm sac embolization performed at the same time as the standard EVAR confers improved clinical outcomes compared to standard EVAR alone.

2.METHODS

Review design and protocol registration

The objectives and methodology of our review were pre-specified in a protocol, which was registered in PROSPERO (international prospective register of systematic reviews) under the registration number CRD42022311333. No amendments to the review protocol were made during the review conduct. The review was developed in line with principles and methodology described in the Cochrane Handbook for Systematic Reviews of Interventions.[58] Reporting of the review complied with the updated Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[59] The PRISMA 2020 checklist was generated using a Shiny App available at https://prisma.shinyapps.io/checklist/ (Appendix 1), and the flow diagram using a Shiny App available at https://www.eshackathon.org/software/PRISMA2020.html.

Eligibility criteria

Types of studies

Only RCTs were eligible for this review.

Types of participants

Eligible participants were male or female patients of any age who underwent standard endovascular repair for intact infra-renal AAA with or without preventive embolization of aortic side branches or the aneurysm sac.

Types of intervention

The intervention of interest was preventive embolization of patent aortic side branches arising from the AAA sac, such as the lumbar arteries or the inferior mesenteric artery (IMA), and/or preventive embolization of the AAA sac. Such interventions could have been performed with coils, glue, or plugs. Embolization of aortic side branches could have

been performed either at the same time as the index EVAR or in a different setting but within three months prior to the EVAR. No restriction to size, number, or type of embolized branch(es) was applied. The control intervention was standard EVAR without pre-emptive embolization.

Types of outcome measures

Primary outcomes were:

- Aneurysm-related mortality.
- All-cause mortality.
- Aneurysm rupture.

Secondary outcomes were:

- Type II endoleak.
- Type II endoleak-related re-intervention.
- Procedure and fluoroscopy time.
- Aneurysm sac expansion.

Studies should report at least one primary or secondary outcome to be eligible for this review. No other study eligibility criteria were applied, e.g. language or recruitment period.

Information sources and search strategy

The literature search strategy was developed by a review author (GA) with experience in outreach, knowledge, and evidence search. The PICO (patient, intervention, comparison, outcome) approach was used to form search strategies. Access to healthcare databases was via online sources of institutional library services. MEDLINE (Medical Literature Analysis

and Retrieval System Online) and EMBASE (ExcerptaMedica Database) were searched using the Ovid interface. The following limits were applied: ″humans”, "year 2000 to current", and "all adult (19 plus years)". The Cochrane Central Register of Controlled Trials (CENTRAL) was also searched for eligible RCT. A combination of controlled vocabulary (subject headings) and free text terms was used to search electronic literature sources. Subject headings/thesaurus trees, search operators, and search limits in each of the above databases were adapted accordingly. Electronic searches were last run in March 2022. A second level search was conducted by interrogating the bibliographic list of articles that qualified for inclusion in this review.

Study selection and data collection process

Two review authors (NG, MK) conducted the pre-specified literature searches and evaluated the eligibility of studies against the inclusion criteria independently. When disagreement arose, a third review author (NK) acted as an arbitrator. Articles published in a non-English language were translated to determine eligibility, assess the risk of bias, and extract relevant data.

Data to be collected from individual studies were pre-specified during the development of the review protocol. Additional relevant data identified during the data collection process were extracted and entered into a Microsoft Excel spreadsheet. Two independent review authors (NG, MK) extracted data from the selected studies. The collected data were then cross-checked by a third review author (NK). Data were extracted from the main text, figures, and tables of the original publications. Only published material was considered, and no study investigators were contacted to obtain or confirm relevant information. Data items were grouped as follows:

- Study level data: first author, journal where the study was published, year of publication, study period, country where the study was conducted, single or multi-centre study, inclusion criteria for participant enrolment, information on the

intervention interest (embolization), number of patients in each group, technical success, complications, length of follow-up.

- Individual study population data: male gender, age, maximum AAA diameter.
- Data pertaining to risk of bias assessment.
- Outcome data, as outlined in the "Eligibility criteria" section.

Study risk of bias assessment and evidence appraisal

Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) was used to assess the risk of bias in RCT included in this review.[60] The tool, that is outcome-based, is structured into five domains through which bias might be introduced into the result: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. The tool gives the option for an overall predicted direction of bias for a specific outcome. An Excel tool was used to implement RoB 2. Two review authors (NG, NK) assessed the risk of bias in studies independently; a third review author (MK) acted as an arbitrator in case of disagreement.

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework was used to appraise the certainty of the body of evidence for specific outcomes.[61, 62] The GRADE approach results in an assessment of the quality of a body of evidence in one of four grades: high, moderate, low, very low. Factors determining the quality of evidence are: limitations in study design or execution, inconsistency of results, indirectness of evidence, imprecision, publication bias, magnitude of effect, plausible confounding, and dose-response gradient. Summary of findings tables were generated using an online platform (https://gdt.gradepro.org/app/).

Synthesis methods

For binary outcomes, the effect measure used in the synthesis was the odds ratio (OR) or risk difference (RD) and 95% confidence interval (CI). The RD was calculated when no events were reported in either group.[63] For continuous outcomes, the effect measure used was the mean difference (MD) and 95% CI.

All studies reporting the primary and secondary outcomes were eligible for data synthesis. Numbers of events and total numbers of patients in each group for dichotomous outcomes, and means values, corresponding standard deviations (SD), and total number of patients in each group were inputted into the RevMancomputer program (Version 5.4, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020). Effect estimates for binary outcomes were calculated using the Mantel-Haenszel statistical method, and those for continuous outcomes were calculated using the inverse variance method. A forest plot was generated for graphical presentation of meta-analysis for each outcome.

Because of the anticipated between-study heterogeneity, e.g. different methods of embolization, random-effects models proposed by DerSimonian and Laird were used for all meta-analyses.[64] The extent and impact of between-study heterogeneity were assessed by inspecting the forest plots and by calculating the tau-squared and the I-squared statistics, respectively. Inconsistency was quantified and interpreted with the following guide: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% may represent considerable heterogeneity.[65] To explore possible causes of heterogeneity, a subgroup analysis was conducted for patients who had aortic side branch embolization versus those who had aneurysm sac embolization.

Sensitivity analyses were conducted to explore the robustness of the meta-analyses by excluding studies that were deemed to be of high risk of bias. Furthermore, the analyses were repeated after removing one study at a time to examine the impact of each study on the overall meta-analysis.

To assess risk of bias due to missing results in a synthesis arising from reporting biases, the effect by the inverse of its standard error would be plotted for each study and the possibility of publication bias would be assessed both visually evaluating the symmetry of the funnel plot and mathematically using the Egger′s regression intercept had more than 10 studies reported data for specified outcomes.[66]

Trial sequential analysis was used to quantify the statistical reliability of data in the cumulative meta-analysis adjusting significance levels for sparse data and repetitive testing on accumulating data.[67, 68] To control for type I error, the thresholds for statistical significance were adjusted using the O′Brien-Fleming α-spending function to account for the elevated risk of random error, when the required information size was not surpassed. Furthermore, the test statistic itself was penalized in congruence with the strength of the available evidence. To control for type II error, adjusted thresholds for non-superiority and non-inferiority were constructed using the β-spending function and futility boundaries. The information size was estimated based on 80% power and 5% type 1 error. The incidence in the intervention and control arm was calculated with the Comprehensive Meta-Analysis software (Biostat, Englewood, NJ, USA) by pooling the incidence rates of type II endoleak reported in the included trials in a proportion meta-analysis. The trial sequential analysis was conducted using an open-source software: Trial Sequential Analysis (TSA) [Computer program]. Version 0.9.5.10 Beta. The Copenhagen Trial Unit, Centre for Clinical Intervention Research, The Capital Region, Copenhagen University Hospital – Rigshospitalet, 2021.

3.RESULTS

Results of the literature search and characteristics of included studies

Electronic literature searches retrieved 2,238 reports. Four RCT were eligible for inclusion in this review.[69-72] The PRISMA flow diagram is presented in Figure 1.

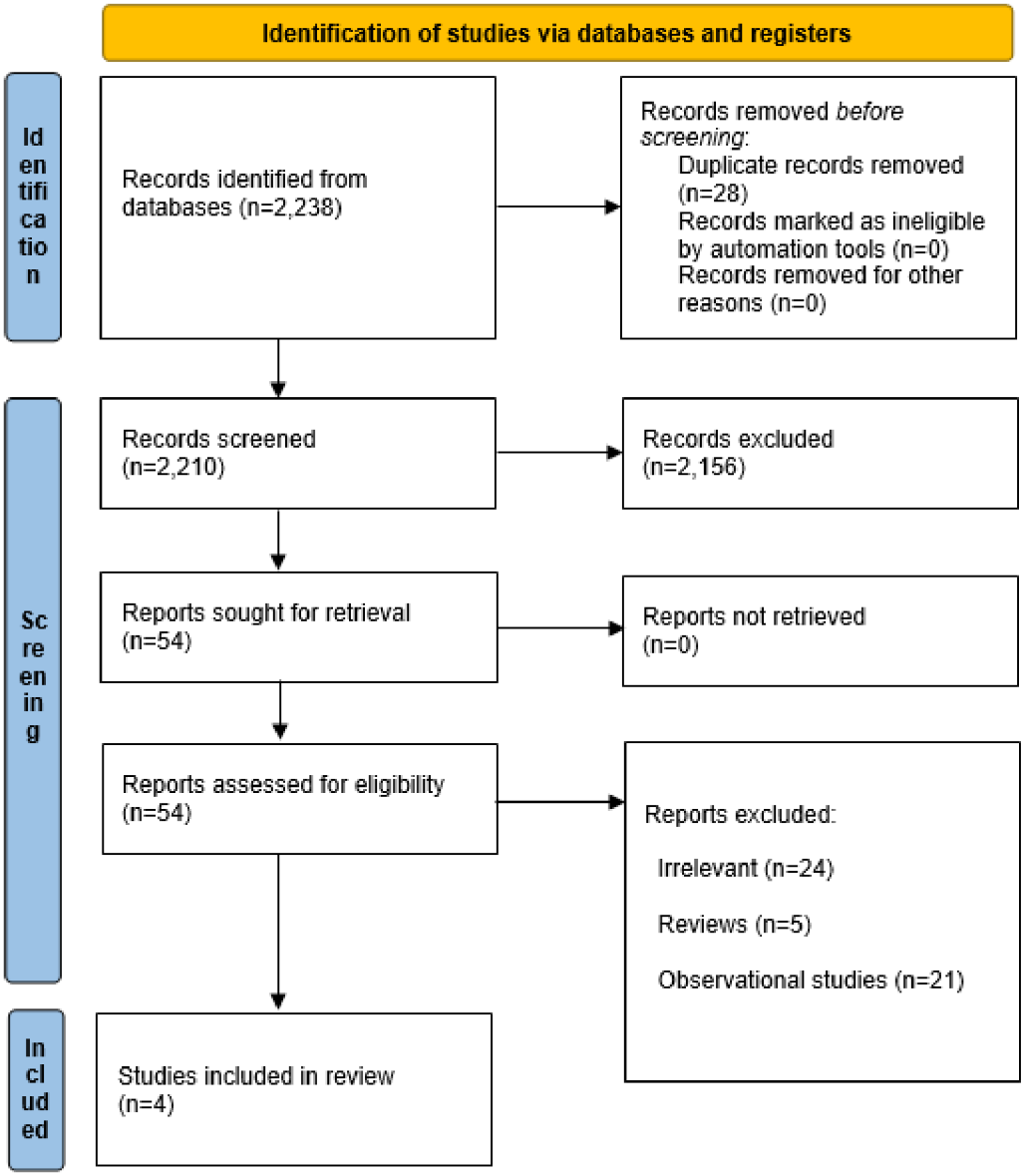


Figure 1. Literature flow diagram generated using a Shiny App available at https://www.eshackathon.org/software/PRISMA2020.html.

The trials were published between 2010 and 2020.The recruitment period across all four RCT spanned from 2008 to 2019. Three RCT were single center.[69-71] Three RCT reported embolization of the AAA sac[69, 70, 72], one reported embolization of a patent IMA.[71]

The four RCT reported a total of 393 patients, of whom 194 were allocated to the intervention group and 199 to the control group. Three hundred-eighty-two patients received the treatment they were assigned to (197 standard EVAR and 185 preemptive embolization). Three of the studies included only patients who were deemed high risk for type II endoleak. Eligibility criteria for participant inclusion in the individual studies and definitions for high risk for type II endoleak are presented in Table 1. Various agents were used for sac or side branch embolization, such as coils, fibrin glue, and plugs. The technical success rate of embolization ranged across the trials from 89% to 100%. No perioperative complications resulting from sac or branch embolization were reported. The follow-up period ranged across the studies from 16 to 24 months. Two trials reported separate outcomes for a third group of patients, who were considered low risk for type II endoleak.[70, 71] The study characteristics of are summarized in Table 1.

1st author	Journal	Country	Single/multicentre	Publication year	Recruitment period	Eligibility criteria	Intervention	No of patients (embolization EVAR/standard EVAR)	Technical success	Length of follow-up in months
Sedivý [22]	Rozhl Chir	Czech Republic	Single	2010	2008-2009	Consecutive patients scheduled for EVAR	Sac embolization with coils	86 (42/44)	NR	NR
Piazza [23]	J Vasc Surg	Italy	Single	2016	2012-2014	High risk for development of type II endoleak[a]	Sac embolization with volume-dependent dose of fibrin glue and coils	107 (52/55)	100%[d]	Embolization EVAR: 16.4±10.7; standard EVAR: 15.9±9.9[f]
Samura [24]	Ann Surg	Japan	Single	2019	2014-2018	High risk for development of type II endoleak[b]	IMA embolization mainly using the Amplatzer vascular plug	106 (53/53)	88.7%[e]	Embolization EVAR: 22.5±11.5; standard EVAR: 22.4±11.6[f]
Fabre [25]	Eur J Vasc Endovasc Surg	France	Multi	2020	2014-2019	High risk for development of type II endoleak[c]	Sac embolization with volume-dependent number of coils	94 (47/47)	100%[d]	24[g]

[a] Defined as patent IMA and ≥2 pairs of lumbar arteries.
[b] Defined as patent IMA ≥3 mm, lumbar artery ≥2 mm, or aorto-iliac aneurysm.
[c] Defined as patent IMA with a luminal diameter at its origin >3 mm, ≥3 pairs of patent lumbar arteries, or 2 pairs of lumbar arteries and a median sacral artery or an accessory renal artery.
[d] Not specifically defined but refers to both control and intervention groups.
[e] Defined as successful IMA embolization.
[f] Mean and SD.
[g] Target follow-up period for the study population.

Table 1. Characteristics of included studies. EVAR, endovascular aneurysm repair; IMA, inferior mesenteric artery; NR, not reported; SD, standard deviation.

Baseline demographics are presented in Table 2.

	Male sex	Age	Maximal AAA diameter in mm
Sedivý [21]	95% vs 86%	73.2 vs 76.3	68.6 vs 67
Piazza [22]	96% vs 94%	74.8 vs 75.9	56 vs 53
Samura [23]	90% vs 73%	75.5 vs 77.5	53.2 vs 50.5
Fabre [24]	89% vs 93%	72 vs 73	NR

Table 2. Baseline demographics and maximal AAA diameter. Data are presented as embolization EVAR versus standard EVAR. Age and maximal AAA diameter are reported as mean values. AAA, abdominal aortic aneurysm; EVAR, endovascular aneurysm repair; NR, not reported.

A summary of methods used to describe changes in AAA size is provided in Supplementary Table 1.

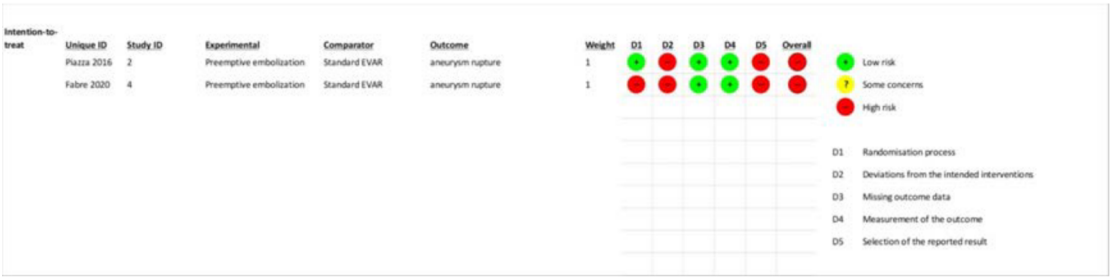
Study	AAA sac size measurements in each study	Comparisons of changes in AAA sac volume	Comparisons of diameter changes
Sedivý et al [22]	1. Absolute differences in diameter 2. Stable vs increased vs decreased diameter	NR	Standard EVAR: -4.9mm; embolization EVAR: -4.7mm Standard EVAR: 2 increased sac, 19 stable sac, 23 decreased sac; embolization EVAR: 1 increased sac, 18 stable sac, 23 decreased sac
Piazza et al [23]	1. Absolute differences in volume	At 24 months Standard EVAR: -4.6 ± 25.9 cm^3; embolization EVAR: -27.3 ± 24.7 cm^3 (P=0.008)	NR
Samura et al [24]	1. Absolute differences in diameter 2. Increase vs stable/ decrease diameter	NR	Mean follow-up of 22.5 months Standard EVAR: -2.9 ± 6.7 mm; embolization EVAR: -6.3 ± 7.5 mm (P=0.021) Standard EVAR: 17.6% increase >2mm; embolization EVAR: 2.2% increase >2mm (P=0.017)
Fabre et al [25]	1. Absolute values of volume at different time points 2. Stable vs decreased diameter	At 24 months Standard EVAR: 54.5 cm^3 (IQR 37.7-70.1); embolization EVAR: 27.6 cm^3 (IQR 18-41.1) (P=0.001) (similar baseline values)	At 24 months Standard EVAR: 43% decreased sac, 57% stable sac; embolization EVAR: 64% decreased sac, 36% stable sac (P=0.18)

Supplementary Table 1. A summary of variables that were used by included studies to express changes in AAA size. AAA, abdominal aortic aneurysm; EVAR, endovascular aneurysm repair; IQR, interquartile range.

Data on sac growth were explicitly reported in two studies.[69, 71] In the other two, data of sac expansion were extracted from the number of re-interventions, since the authors reported that secondary interventions were indicated in case of AAA sac enlargement.[70, 72] One study defined sac expansion as an increase in maximum diameter >2mm[71], two studies defined it as an expansion >5mm[70, 72], and one study failed to define sac expansion.[69] None of the trials provided definitions for sac regression.

Results of data synthesis, risk of bias assessment, and certainty of evidence appraisal

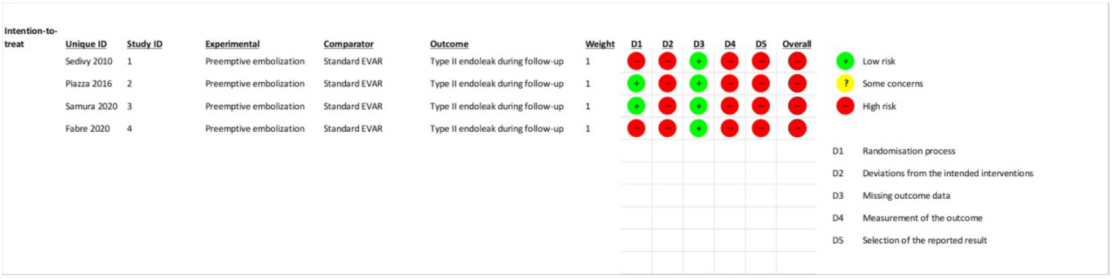
The results of risk of bias assessment for the individual outcomes using the Cochrane Rob 2 tool are presented.



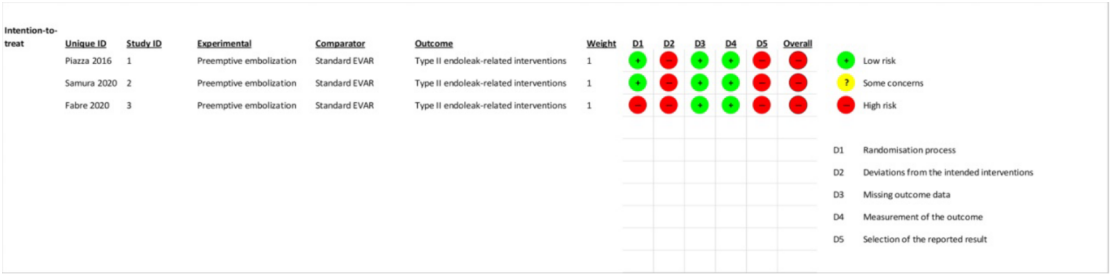
a. Aneurysm-related mortality

b. Overall mortality

c. Aneurysm rupture

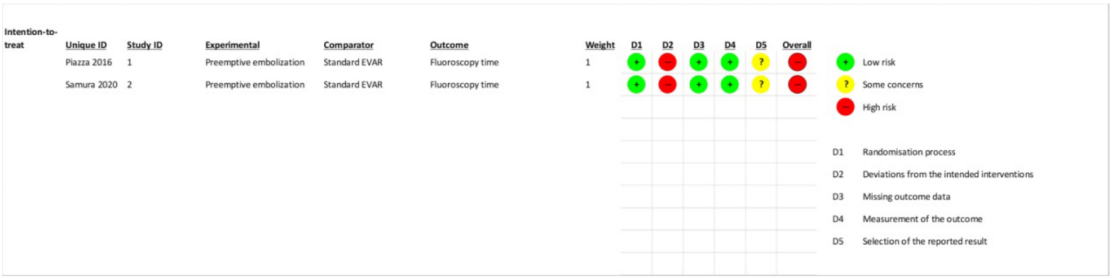


d. Type II endoleak



e. Type II endoleak related re-intervention

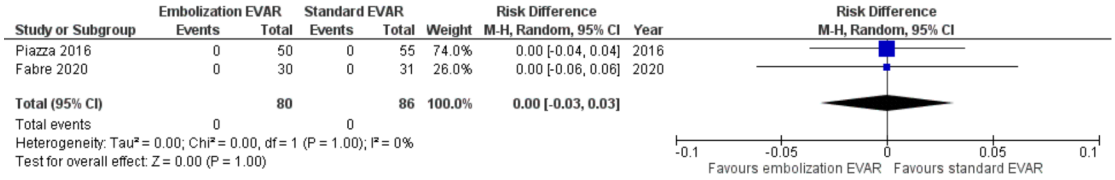
f. Procedure duration



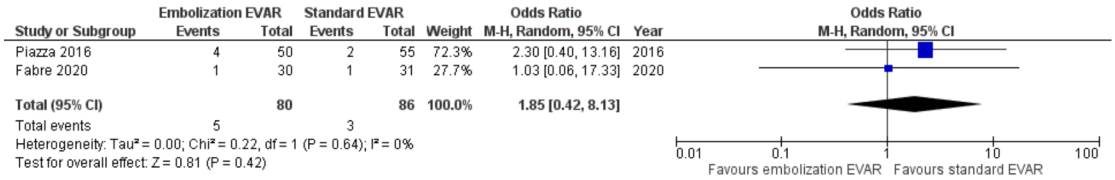
g. Fluoroscopy time

h. Aneurysm sac expansion

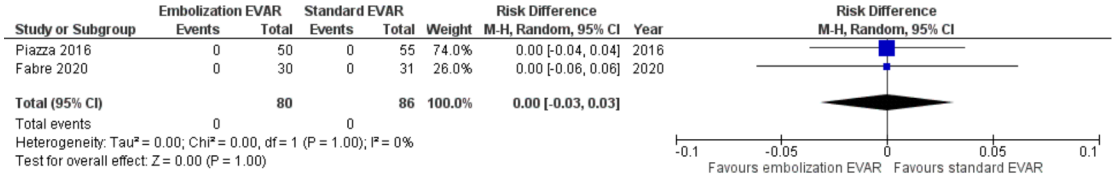
The forest plots for the primary and secondary outcomes are presented in Figure 3.



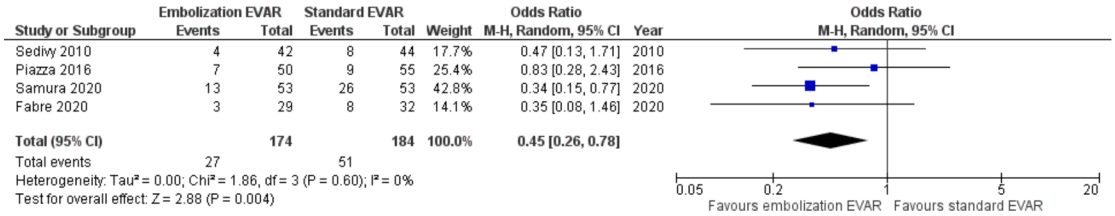
a. Aneurysm-related mortality



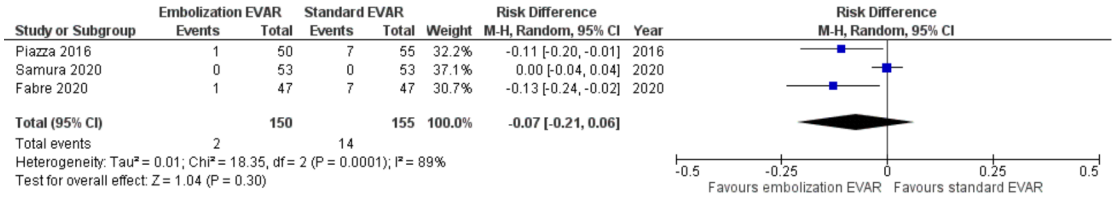
b. Overall mortality



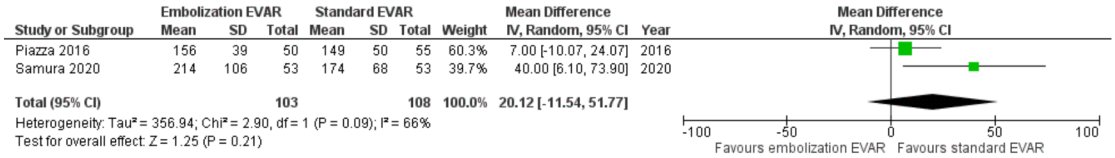
c. Aneurysm rupture



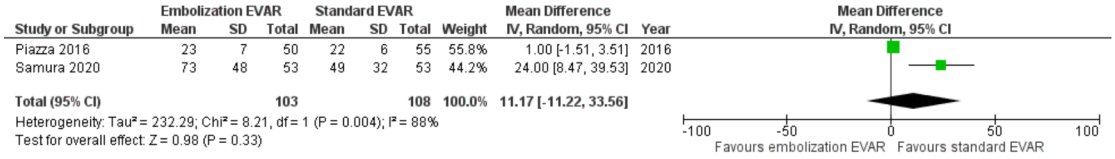
d. Type II endoleak



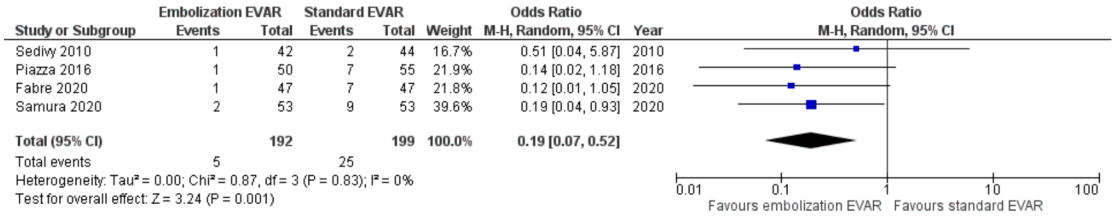
e. Type II endoleak-related reintervention



f. Procedure duration



g. Fluoroscopy time



h. Sac expansion

Figure 3. Forest plots for the comparison embolization versus standard EVAR. The solid squares denote the odds ratios, risk differences, or mean differences, the horizontal lines represent the 95% confidence intervals, and the diamonds denote the pooled odds ratios, risk differences, or mean differences. CI, confidence interval; EVAR, endovascular aneurysm repair; IV, inverse variance; M-H, Mantel–Haenszel; SD, standard deviation.

The results of the GRADE assessment for the individual outcomes are summarized in Table 3.

Outcome	No of participants	Quality of Evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard EVAR	Risk with embolization EVAR (95% CI)
Aneurysm-related mortality	166 (2 studies)	⊕⊖⊖⊖ VERY LOW[1,3,6,11] due to risk of bias, inconsistency, imprecision	RD 0.00 (-0.03 – 0.03)	NA	NA
Overall mortality	166 (2 studies)	⊕⊖⊖⊖ VERY LOW[1,6,11] due to risk of bias, inconsistency, imprecision	OR 1.85 (0.42 to 8.13)	35 per 1000	28 more per 1000 (from 20 fewer to 192 more)
Aneurysm rupture	166 (2 studies)	⊕⊖⊖⊖ VERY LOW[1,3,6,11] due to risk of bias, inconsistency, imprecision	RD 0.00 (-0.03 – 0.03)	NA	NA
Type II endoleak	358 (4 studies)	⊕⊕⊖⊖ LOW[1,2,3,4] due to risk of bias, inconsistency, imprecision, large effect	OR 0.45 (0.26 to 0.78)	277 per 1000	130 fewer per 1000 (from 47 fewer to 187 fewer)
Type II endoleak-related re-intervention	305 (3 studies)	⊕⊖⊖⊖ VERY LOW[1,2,3,5,6] due to risk of bias, inconsistency, imprecision	OR 0.45 (0.26 to 0.78)	90 per 1000	74 fewer per 1000 (from 210 fewer to 60 more)
Procedure time	211 (2 studies)	⊕⊖⊖⊖ VERY LOW[1,2,7] due to risk of bias, inconsistency, imprecision	MD 20.12 (-11.54 to 51.77)	-	The mean procedure time in the intervention groups was 20.12 higher (11.54 lower to 51.77 higher)
Fluoroscopy time	211 (2 studies)	⊕⊖⊖⊖ VERY LOW[1,2,3,5] due to risk of bias, inconsistency, imprecision	MD 11.17 (-11.22 to 33.56)	-	The mean fluoroscopy time in the intervention groups was 11.17 higher (11.22 lower to 33.56 higher)
Aneurysm sac expansion	391 (4 studies)	⊕⊖⊖⊖ VERY LOW[1,2,4,8,9] due to risk of bias, inconsistency, indirectness, large effect	OR 0.19 (0.07 to 0.52)	126 per 1000	99 fewer per 1000 (from 56 fewer to 116 fewer)

1 High risk of bias.
2 Different types of interventions (aneurysm sac or side branch embolization).
3 Small sample size and small number of events.
4 OR <0.5.
5 Between-study heterogeneity.
6 CI includes both no effect and appreciable benefit or appreciable harm.
7 Small number of patients.
8 Different definitions used by primary studies.

9 Some of the studies did not provide direct information on sac expansion; such data were extracted indirectly through secondary interventions.
10 No definition of sac regression.
11 Wide variance of point estimates.

Table 3. Summary of findings table for the comparison of embolization versus standard EVAR. CI, confidence interval; EVAR, endovascular aneurysm repair; MD, mean difference; NA, not applicable; OR, odds ratio; RD, risk difference.

Primary analyses

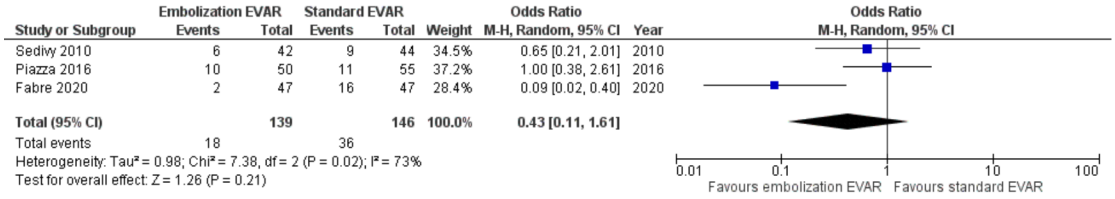
Aneurysm-related mortality: Data on aneurysm-related mortality were reported in two studies[70, 72], with a total of 166 patients (80 in the pre-emptive embolization group and 86 in the control group). No aneurysm-related death occurred in either treatment arm (RD 0.00, 95%CI -0.03 – 0.03, P=1; test for heterogeneity: P=1.0, I^2=0%). The overall risk of bias was high, and the quality of evidence was very low.

Overall mortality: Data on overall mortality were reported in two study[70, 72], with a total of 166 patients (80 in the pre-emptive embolization group and 86 in the control group). Meta-analysis showed no statistically significant difference in overall mortality between the treatment arms (OR 1.85, 95%CI 0.42 – 8.13, P=0.42; test for heterogeneity: P=0.64, I^2=0%). The overall risk of bias was high, and the quality of evidence was very low.

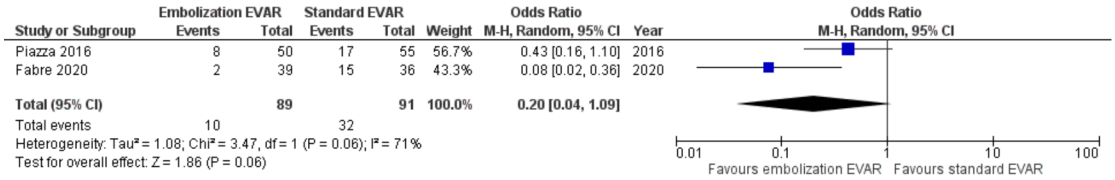
Aneurysm-rupture: Data on aneurysm rupture were reported in two studies[70, 72], with a total of 166 patients (80 in the pre-emptive embolization group and 86 in the control group). No rupture occurred in either treatment arm (RD 0.00, 95%CI -0.03 – 0.03, P=1; test for heterogeneity: P=1.0, I^2=0%). The overall risk of bias was high, and the quality of evidence was very low.

Type II endoleak: Data on type II endoleak were reported in all trials[69-72], with a total of 358 patients (174 in the pre-emptive embolization group and 184 in the control group). The odds of type II endoleak were lower in patients who underwent pre-emptive embolization with the difference being statistically significant (OR 0.45, 95% CI 0.26 – 0.78; P=0.004; test for heterogeneity: P=0.60, I^2=0%). The overall risk of bias was high, and the quality

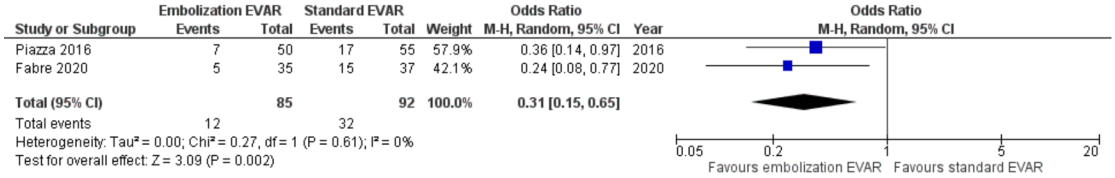
of evidence was low. Meta-analyses for type II endoleak at different time points are presented in Supplementary Figure 1.



a. Early type II endoleak (within 30 days)



b. Type II endoleak at 6 months



c. Type II endoleak at 12 months

Supplementary Figure 1: Forest plots for the comparison embolization versus standard EVAR for type II endoleak at different time points. The solid squares denote the odds ratios, the horizontal lines represent the 95% confidence intervals, and the diamonds denote the pooled odds ratios. CI, confidence interval; EVAR, endovascular aneurysm repair; M-H, Mantel–Haenszel.

Type II endoleak-related re-intervention: Data on type II endoleak-related re-intervention were reported in three studies[70-72], with a total of 305 patients (150 in the pre-emptive embolization group and 155 in the control group). Meta-analysis showed no statistically significant difference in the odds of type II endoleak-related re-intervention between the treatment arms (RD -0.07, 95% CI -0.21 – 0.06, P=0.30; test for heterogeneity: P=0.0001, I^2=89%). The overall risk of bias was high, and the quality of evidence was very low.

Procedure time: Data on procedural time were reported in two studies[70, 71], with a total of 211 patients (103 in the pre-emptive embolization group and 108 in the control group). Meta-analysis showed no statistically significant difference in the duration of the procedure between the treatment arms (MD 20.12, 95% CI -11.54 – 51.77; P=0.21; test for heterogeneity: P=0.09, I^2=66%). The overall risk of bias was high, and the quality of evidence was very low.

Fluoroscopy time: Data on fluoroscopy time were reported in two studies[70, 71], with a total of 211 patients (103 in the pre-emptive embolization group and 108 in the control group). The difference in fluoroscopy time between the groups was not statistically significant (MD 11.17, 95% CI -11.22 – 33.56; P=0.33; test for heterogeneity: P=0.004, I^2=88%). The overall risk of bias was high, and the quality of evidence was very low.

Aneurysm sac expansion: A total of 391patients (192 in the pre-emptive embolization group and 199 in the control group) were included meta-analysis for sac expansion. The odds of sac expansion were significantly lower in patients with pre-emptive embolization (OR 0.19, 95% CI 0.07 – 0.52; P=0.001; test for heterogeneity: P=0.83, I^2=0%). The overall risk of bias was high, and the quality of evidence was very low.

Subgroup and sensitivity analyses

Subgroup analyses for method of embolization (aneurysm sac versus side branch) showed that the direction of the effect estimate was not affected for any of the outcomes. Meta-analyses of studies that used sac embolization, thus excluding the study that reported side branch embolization, affected the significance of effect estimates as follows:

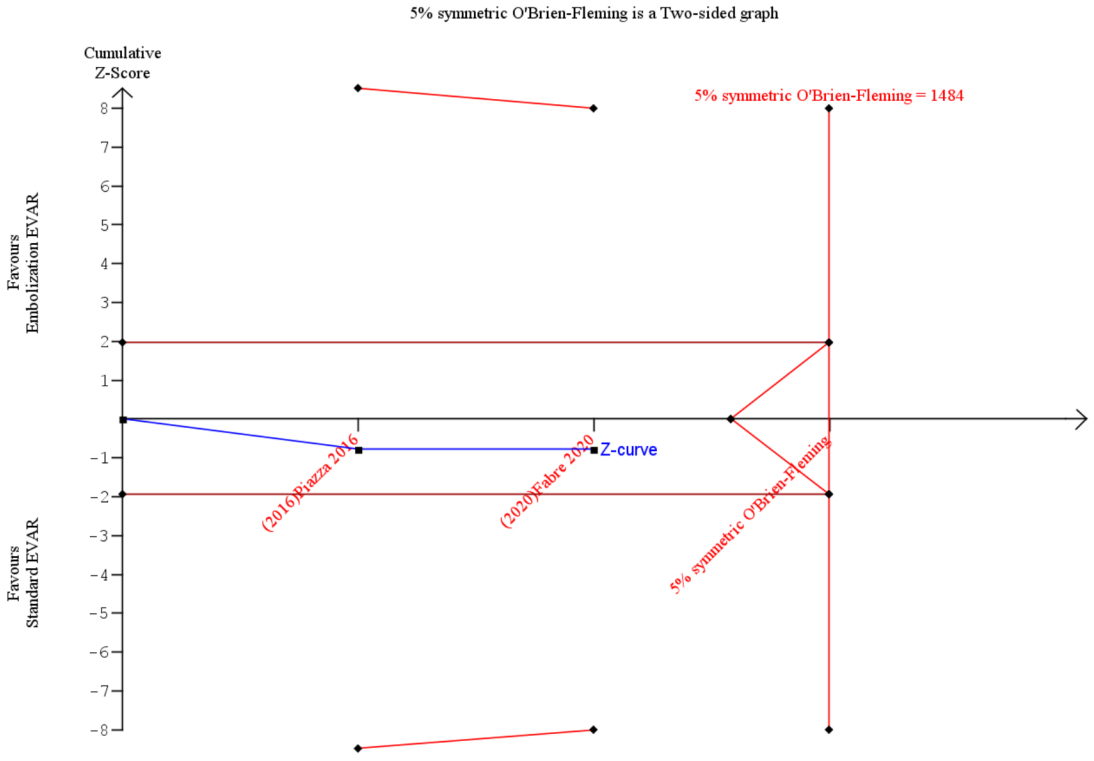
1. The difference in type II endoleak became non-significant (OR 0.56 95% CI 0.28-1.15, P=0.11; heterogeneity: P=0.60, I^2=0%).

2. The difference in type II endoleak-related re-interventions became statistically significant in favour of pre-emptive sac embolization (RD -0.12 95% CI -0.19 - 0.04, P=0.002; heterogeneity: P=0.78, I^2=0%).

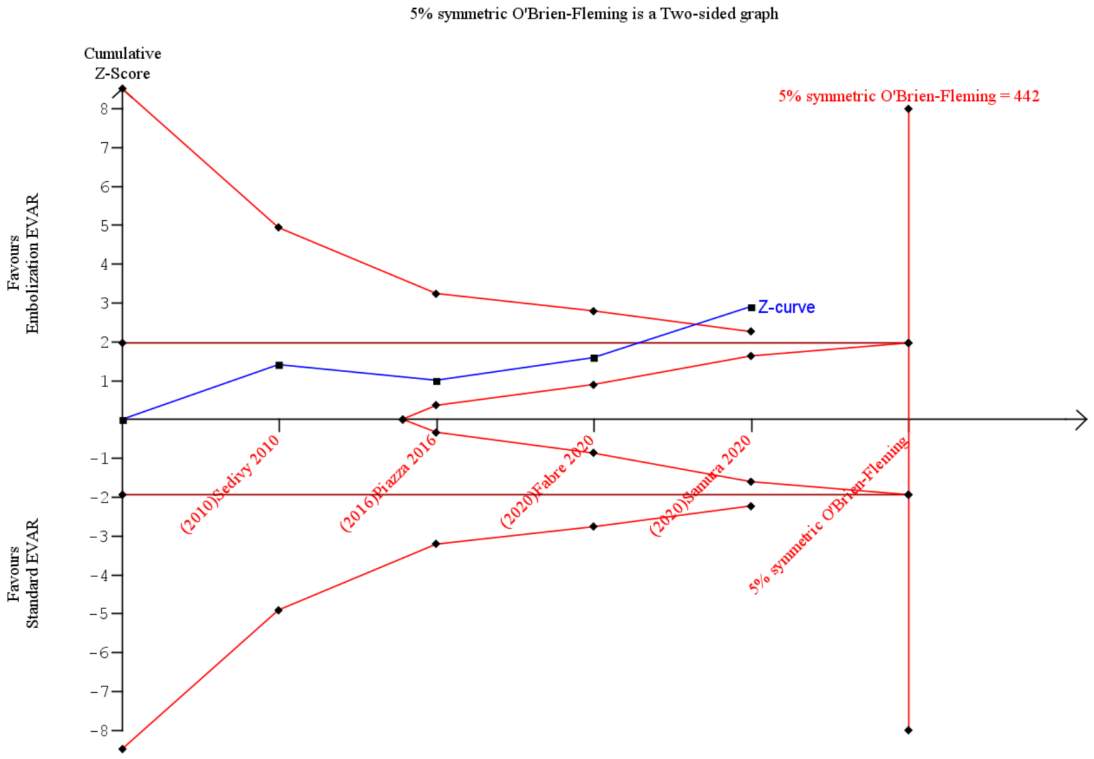
Pre-specified sensitivity analyses did not affect the direction or statistical significance of effect estimate for any of the outcomes.

Trial sequential analysis

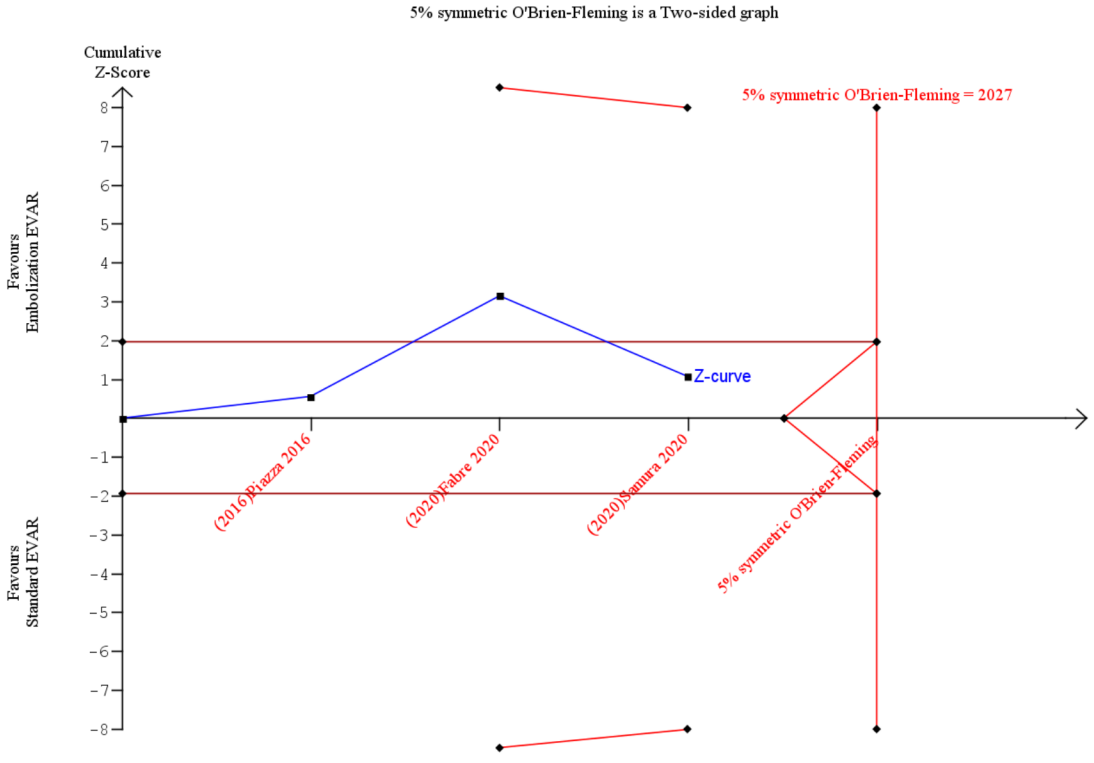
A graphical presentation of the results of trial sequential analyses is presented.



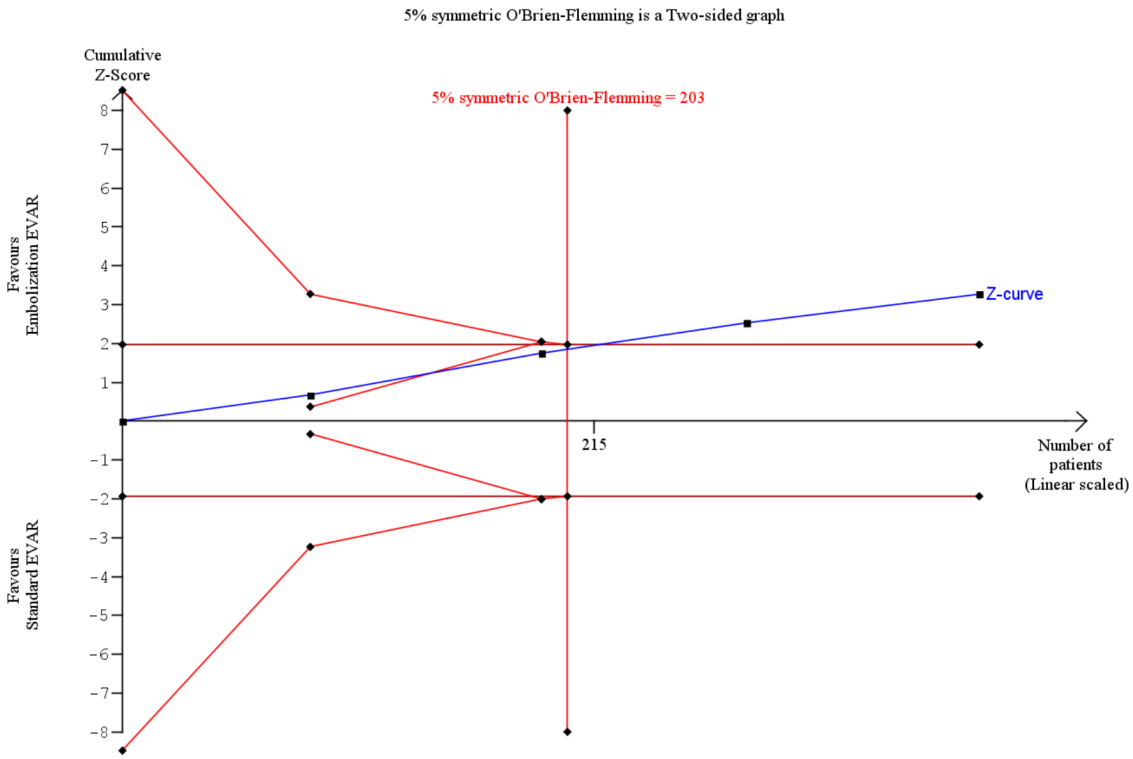
a. Overall mortality



b. Type II endoleak



c. Type II endoleak-related reintervention



d. Aneurysm sac expansion

Analysis of embolization EVAR versus standard EVAR for overall mortality showed that the information size has not been reached and the meta-analysis result is inconclusive with the cumulative Z-curve crossing neither the conventional significance threshold nor the O′Brien-Fleming boundaries. More trials are needed to confidently conclude on potential effects of pre-emptive embolization on overall mortality.

For type II endoleak, trial sequential analysis showed significant benefit of pre-emptive embolization; the cumulative Z-score reaches significance by crossing both the conventional boundary as well as the O′Brian-Fleming boundaries. It can be inferred that pre-emptive embolization is superior to standard EVAR without embolization, and no further trials are required.

The cumulative Z-curve for type II endoleak-related re-intervention crosses neither the conventional significance boundaries nor the O′Brien-Fleming boundaries, and the information size has not been reached, meaning that the meta-analysis result is inconclusive and more trials are required to make inferences for this outcome.

For aneurysm sac expansion, the information size has been reached, and no more trials are required to confirm the benefit of pre-emptive embolization for this outcome.

4. DISCUSSION

We found no significant difference for any of the primary outcomes, namely aneurysm-related mortality, overall mortality, and aneurysm rupture, between EVAR with pre-emptive embolization and standard EVAR without. No events were recorded for aneurysm-related mortality and aneurysm rupture, reflecting the underpowered trials and/or short follow-up. The risk of type II endoleak was reduced with pre-emptive embolization of the aneurysm sac or aortic side branches, but such benefit did not translate into a reduction of type II endoleak-related re-intervention. Pre-emptive embolization was not shown to prolong the procedural or the fluoroscopy time and was found to be associated with a reduced risk of sac expansion. Trial sequential analyses confirmed a true positive finding for type II endoleak and aneurysm sac expansion but showed inconclusive results for overall mortality and type II endoleak-related re-intervention. The absence of embolization-related complications and the high technical success rates reflect the safety of the procedure in the context of EVAR.

Type II endoleaks are not always benign. They have been reported to be associated with sac expansion and, commonly, require secondary interventions.[73-76] This is important, particularly in light of recent research, which has shown that not only sac expansion, but failure of the aneurysm sac to regress may result in a higher risk of death.[77] Deery et al have shown that patients with type II endoleak have a relative risk of 3 for sac expansion and a relative risk of 0.2 for sac regression, which was independently associated with mortality.[78] All trials included in this review reported size-related outcomes. The trials found a reduction in both aneurysm sac volume and diameter in the embolization group. Such reductions in size did not translate in improvements in important clinical outcomes, such as aneurysm rupture and mortality.

Previous research has also shown that complications following type II endoleaks are significantly more common in persistent endoleaks or those that appear late.[76, 79] Our analysis showed similar rates of type II endoleak early after the index EVAR, but a significant reduction in the medium term.

Of the three previously published systematic reviews examining the effect of pre-emptive embolization in EVAR, only one distinguishes between early and late type II endoleaks.[80-82] These reviews included mainly observational studies, which contaminate the results because of selection bias and limit their applicability. The review of Yu et al[81] examined the effect of aortic side branch embolization and included no RCT; that of Li et al[80] investigated outcomes of both side branch and aneurysm sac embolization and included only one RCT.[70] The most recent meta-analysis[82] reported outcomes of aortic side branch embolization and include done RCT.[71] Our study adds to the evidence base with four RCT, two of which were published recently.[71, 72] Our results are in accordance with those of the previous studies.

The certainty of evidence was judged to be very low the critical outcomes, mainly due to limited data and high risk of bias in the trials. Similarly, the level of evidence was judged to be very low for all secondary outcomes, except for type II endoleak, for which the level of evidence was low. Rates of secondary interventions for type II endoleak varied across the studies, which may reflect different indications and thresholds for treatment. Samura et al[71] did not undertake re-interventions for type II endoleak in any of the trial participants, even though the rate of sac expansion was significantly higher in the control group. Fabre et al[72] and Piazza et al[70] reported a higher re-intervention rate in the non-embolization group.[70-72]

Our findings should be viewed and interpreted in the context of limitations. Only patients at high risk for type II endoleak were eligible for inclusion in three of the trials, which may limit the external validity of our findings to the general EVAR population. The meta-analysis population and the number of events was low resulting in imprecision and downgrading the certainty of evidence. No events were recorded for the primary outcomes, which indicates that the trials are underpowered. The optimal information size was reached for none of the outcomes except for sac expansion, and the CI around both relative and absolute estimates of effect include both appreciable benefit and appreciable harm. Furthermore, outcome reporting was not consistent across the trials not allowing inclusion in statistical comparisons. Considerable heterogeneity between the trials was noted; plausible explanations include different eligibility criteria for participant enrollment,

different definitions (e.g. sac expansion), and different indications and thresholds for secondary interventions.

5.CONCLUSIONS

The evidence base on potential benefits of pre-emptive embolization as an adjunct to EVAR is limited. Available data suggest that such treatment may not confer a survival advantage compared with standard EVAR without aneurysms sac or aortic side branch embolization. However, pre-emptive embolization may reduce the risk of type II endoleak in the medium term, such benefit is not translated in reduction of re-intervention, aneurysm rupture, or aneurysm-related mortality. The optimal information size has not been reached, and underpowered studies may explain the absence of tangible benefits. None of the trials investigated patient-reported outcomes. Trial sequential analyses confirmed the meta-analysis result is inconclusive for critical outcomes. Further large studies with longer follow-up are required to provide more information on appreciable benefits and risks of the procedure and make inferences about potential benefits of pre-emptive embolization in EVAR.

6.SUMMARY

Objectives: To investigate outcomes of pre-emptive embolization of the aneurysm sac or aortic side branches in EVAR.

Data sources: Bibliographic sources (MEDLINE, EMBASE, and CENTRAL) were searched using subject headings and free text terms.

Review methods: The review was reported according to PRISMA 2020 with a preregistered protocol. Randomized controlled trials (RCT) comparing EVAR with versus without embolization were included. Pooled estimates of dichotomous outcomes were calculated using odds ratio (OR) or risk difference (RD) and 95% confidence interval (CI) applying the Mantel-Haenszel method. Continuous outcomes were summarized using mean difference (MD) and 95%CI applying the inverse variance method. The certainty of evidence was appraised with the GRADE framework. Version 2 of the Cochrane tool was used to assess the risk of bias. Trial sequential analysis assumed an alpha=5% and power=80%.

Results: Four RCT reporting a total of 393 patients were included. No significant difference was found in aneurysm-related mortality (RD 0.00, 95%CI -0.03 – 0.03), overall mortality (OR 1.85, 95%CI 0.42 – 8.13), aneurysm rupture (RD 0.00, 95%CI -0.03 – 0.03), type II endoleak-related re-intervention (RD -0.07, 95% CI -0.21 – 0.06), procedure time (MD 20.12, 95% CI -11.54 – 51.77), or fluoroscopy time (MD 11.17, 95% CI -11.22 – 33.56). Patients with pre-emptive embolization had significantly lower odds of developing type II endoleak (OR 0.45, 95% CI 0.26 – 0.78) and sac expansion (OR 0.19, 95% CI 0.07 – 0.52). The risk of bias was high for all outcomes. The certainty of evidence was very low for all outcomes, except for type II endoleak, for which it was low. Trial sequential analysis showed an inconclusive result for overall mortality and type II endoleak-related re-intervention but confirmed the advantage of embolization in reducing type II endoleak and sac expansion.

Conclusions: Limited, low certainty data suggest pre-emptive embolization confers no clinical benefits in EVAR.

7.ΠΕΡΙΛΗΨΗ

Στόχοι: Διερεύνηση αποτελεσμάτων προληπτικού εμβολισμού του σάκου του ανευρύσματος ή των πλευρικών κλάδων της αορτής στην ενδαγγειακή αποκατάσταση ανευρύσματος (EVAR).

Πηγές δεδομένων: Οι βιβλιογραφικές πηγές (MEDLINE, EMBASE και CENTRAL) αναζητήθηκαν χρησιμοποιώντας επικεφαλίδες θεμάτων και ελεύθερους όρους.

Μέθοδοι ανασκόπησης: Η ανασκόπηση αναφέρθηκε σύμφωνα με το PRISMA 2020 με προκαταχωρημένο πρωτόκολλο. Συμπεριλήφθηκαν τυχαιοποιημένες ελεγχόμενες δοκιμές (RCT) που συνέκριναν το EVAR με ή χωρίς εμβολισμό. Οι συγκεντρωτικές εκτιμήσεις των διχοτόμων υπολογίστηκαν χρησιμοποιώντας αναλογία πιθανοτήτων (OR) ή διαφορά κινδύνου (RD) και 95% διάστημα εμπιστοσύνης (CI) χρησιμοποιώντας τη μέθοδο Mantel-Haenszel. Τα συνεχή αποτελέσματα συνοψίστηκαν χρησιμοποιώντας τη μέση διαφορά (MD) και 95% CI με εφαρμογή της μεθόδου της αντίστροφης διακύμανσης. Η βεβαιότητα των αποδεικτικών στοιχείων εκτιμήθηκε με το πλαίσιο GRADE. Η έκδοση 2 του εργαλείου Cochrane χρησιμοποιήθηκε για την αξιολόγηση του κινδύνου μεροληψίας. Η διαδοχική μέθοδος ανάλυσης υπέθεσε άλφα=5% και ισχύ=80%.

Αποτελέσματα: Συμπεριλήφθηκαν τέσσερις RCT που ανέφεραν συνολικά 393 ασθενείς. Δεν βρέθηκε σημαντική διαφορά στη θνησιμότητα που σχετίζεται με το ανεύρυσμα (RD 0,00, 95%CI -0,03 – 0,03), τη συνολική θνησιμότητα (OR 1,85, 95%CI 0,42 – 8,13), τη ρήξη ανευρύσματος (RD 0,00, 95%CI -0,03 – 0,0.), επανεπέμβαση σχετιζόμενη με ενδοδιαφυγή τύπου II (RD -0,07, 95% CI -0,21 – 0,06), συνολικός χρόνος επέμβασης (MD 20,12, 95% CI -11,54 – 51,77) ή χρονικό διάστημα ακτινοσκόπησης (MD 11,17, 95% CI - 11.22 – 33.56). Οι ασθενείς με προληπτικό εμβολισμό είχαν σημαντικά χαμηλότερες πιθανότητες εμφάνισης ενδοδιαφυγής τύπου II (OR 0,45, 95% CI 0,26 – 0,78) και διόγκωσης του σάκου (OR 0,19, 95% CI 0,07 – 0,52). Ο κίνδυνος μεροληψίας ήταν υψηλός για όλα τα αποτελέσματα. Η βεβαιότητα των αποδεικτικών στοιχείων ήταν πολύ χαμηλή για όλα τα αποτελέσματα, εκτός από την ενδοδιαφυγή τύπου II, για την οποία ήταν χαμηλή. Η διαδοχική μέθοδος ανάλυσης έδειξε ένα ασαφές αποτέλεσμα για τη συνολική θνησιμότητα και την επανεπέμβαση που σχετίζεται με ενδοδιαφυγή τύπου II, αλλά

επιβεβαίωσε το πλεονέκτημα του εμβολισμού στη μείωση της ενδοδιαφυγής τύπου ΙΙ και της αύξησης διαστάσεων του σάκου.

Συμπεράσματα: Περιορισμένα δεδομένα χαμηλής βεβαιότητας υποδηλώνουν ότι ο προληπτικός εμβολισμός δεν προσφέρει κλινικά οφέλη στο EVAR.

8. REFERENCES

1. *Johnston KW, Rutherford RB, Tilson MD, et al. Suggested standards for reporting on arterial aneurysms. Subcommittee on Reporting Standards for Arterial Aneurysms, Ad Hoc Committee on Reporting Standards, Society for Vascular Surgery and North American Chapter, International Society for Cardiovascular Surgery. J Vasc Surg 1991; 13:452.*
2. *Scott RA, Ashton HA, Kay DN. Abdominal aortic aneurysm in 4237 screened patients: prevalence, development and management over 6 years. Br J Surg 1991; 78:1122.*
3. *Boll AP, Verbeek AL, van de Lisdonk EH, van der Vliet JA. High prevalence of abdominal aortic aneurysm in a primary care screening programme. Br J Surg 1998; 85:1090.*
4. *Lederle FA. The rise and fall of abdominal aortic aneurysm. Circulation 2011; 124:1097.*
5. *Wilmink AB, Hubbard CS, Day NE, Quick CR. The incidence of small abdominal aortic aneurysms and the change in normal infrarenal aortic diameter: implications for screening. Eur J Vasc Endovasc Surg 2001; 21:165*
6. *Wassef M, Baxter BT, Chisholm RL, et al. Pathogenesis of abdominal aortic aneurysms: a multidisciplinary research program supported by the National Heart, Lung, and Blood Institute. J Vasc Surg 2001; 34:730.*
7. *MacSweeney ST, Powell JT, Greenhalgh RM. Pathogenesis of abdominal aortic aneurysm. Br J Surg 1994; 81:935.*
8. *Miller FJ Jr, Sharp WJ, Fang X, et al. Oxidative stress in human abdominal aortic aneurysms: a potential mediator of aneurysmal remodeling. Arterioscler Thromb Vasc Biol 2002; 22:560.*
9. *López-Candales A, Holmes DR, Liao S, et al. Decreased vascular smooth muscle cell density in medial degeneration of human abdominal aortic aneurysms. Am J Pathol 1997; 150:993.*
10. *Brady AR, Thompson SG, Fowkes FG, et al. Abdominal aortic aneurysm expansion: risk factors and time intervals for surveillance. Circulation 2004; 110:16.*

11. *Vega de Céniga M, Gómez R, Estallo L, et al. Growth rate and associated factors in small abdominal aortic aneurysms. Eur J Vasc Endovasc Surg 2006; 31:231.*
12. *Chaikof EL, Brewster DC, Dalman RL, et al. SVS practice guidelines for the care of patients with an abdominal aortic aneurysm: executive summary. J Vasc Surg 2009; 50:880.*
13. *Nevitt MP, Ballard DJ, Hallett JW Jr. Prognosis of abdominal aortic aneurysms. A population-based study. N Engl J Med 1989; 321:1009.*
14. *Brewster DC, Cronenwett JL, Hallett JW Jr, et al. Guidelines for the treatment of abdominal aortic aneurysms. Report of a subcommittee of the Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery. J Vasc Surg 2003; 37:1106.*
15. *Lederle FA, Johnson GR, Wilson SE, et al. Rupture rate of large abdominal aortic aneurysms in patients refusing or unfit for elective repair. JAMA 2002; 287:2968.*
16. *Bengtsson H, Bergqvist D, Ekberg O, Ranstam J. Expansion pattern and risk of rupture of abdominal aortic aneurysms that were not operated on. Eur J Surg 1993; 159:461.*
17. *Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation 2006; 113:e463.*
18. *Lee WA, Carter JW, Upchurch G, et al. Perioperative outcomes after open and endovascular repair of intact abdominal aortic aneurysms in the United States during 2001. J Vasc Surg 2004; 39:491.*

19. *Chaikof EL, Brewster DC, Dalman RL, et al. The care of patients with an abdominal aortic aneurysm: the Society for Vascular Surgery practice guidelines. J Vasc Surg 2009; 50:S2.*
20. *United Kingdom EVAR Trial Investigators, Greenhalgh RM, Brown LC, et al. Endovascular versus open repair of abdominal aortic aneurysm. N Engl J Med 2010; 362:1863.*
21. *Blankensteijn JD, de Jong SE, Prinssen M, et al. Two-year outcomes after conventional or endovascular repair of abdominal aortic aneurysms. N Engl J Med 2005; 352:2398.*
22. *EVAR trial participants. Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm (EVAR trial 1): randomised controlled trial. Lancet 2005; 365:2179.*
23. *Lederle FA, Freischlag JA, Kyriakides TC, et al. Long-term comparison of endovascular and open repair of abdominal aortic aneurysm. N Engl J Med 2012; 367:1988.*
24. *Karthikesalingam A, Thompson MM. Vascular disease: Repair of infrarenal aortic aneurysm--the debate is OVER. Nat Rev Cardiol 2013; 10:122.*
25. *Giles KA, Pomposelli F, Hamdan A, et al. Decrease in total aneurysm-related deaths in the era of endovascular aneurysm repair. J Vasc Surg 2009; 49:543.*
26. *Schanzer A, Greenberg RK, Hevelone N, et al. Predictors of abdominal aortic aneurysm sac enlargement after endovascular repair. Circulation 2011; 123:2848.*
27. *Mohan IV, Laheij RJ, Harris PL, EUROSTAR COLLABORATORS. Risk factors for endoleak and the evidence for stent-graft oversizing in patients undergoing endovascular aneurysm repair. Eur J Vasc Endovasc Surg 2001; 21:344.*
28. *Chaikof EL, Blankensteijn JD, Harris PL, et al. Reporting standards for endovascular aortic aneurysm repair. J Vasc Surg 2002; 35:1048.*
29. *Moll FL, Powell JT, Fraedrich G, et al. Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. Eur J Vasc Endovasc Surg 2011; 41 Suppl 1:S1.*

30. *Gabrielli L, Baudo A, Molinari A, Domanin M. Early complications in endovascular treatment of abdominal aortic aneurysm. Acta Chir Belg 2004; 104:519.*
31. *Moulakakis KG, Dalainas I, Mylonas S, et al. Conversion to open repair after endografting for abdominal aortic aneurysm: a review of causes, incidence, results, and surgical techniques of reconstruction. J Endovasc Ther 2010; 17:694.*
32. *Brown LC, Greenhalgh RM, Powell JT, et al. Use of baseline factors to predict complications and reinterventions after endovascular repair of abdominal aortic aneurysm. Br J Surg 2010; 97:1207*
33. *Drury D, Michaels JA, Jones L, Ayiku L. Systematic review of recent evidence for the safety and efficacy of elective endovascular repair in the management of infrarenal abdominal aortic aneurysm. Br J Surg 2005; 92:937.*
34. *Peppelenbosch N, Buth J, Harris PL, et al. Diameter of abdominal aortic aneurysm and outcome of endovascular aneurysm repair: does size matter? A report from EUROSTAR. J Vasc Surg 2004; 39:288.*
35. *Schermerhorn ML, O'Malley AJ, Jhaveri A, et al. Endovascular vs. open repair of abdominal aortic aneurysms in the Medicare population. N Engl J Med 2008; 358:464.*
36. *Schanzer A, Greenberg RK, Hevelone N, et al. Predictors of abdominal aortic aneurysm sac enlargement after endovascular repair. Circulation 2011; 123:2848.*
37. *Blankensteijn JD, Prinssen M. Does fresh clot shrink faster than preexistent mural thrombus after endovascular AAA repair? J Endovasc Ther 2002; 9:458.*
38. *Phade SV, Keldahl ML, Morasch MD, et al. Late abdominal aortic endograft explants: indications and outcomes. Surgery 2011; 150:788.*
39. *Brinster CJ, Fairman RM, Woo EY, et al. Late open conversion and explantation of abdominal aortic stent grafts. J Vasc Surg 2011; 54:42.*
40. *Brewster DC, Jones JE, Chung TK, et al. Long-term outcomes after endovascular abdominal aortic aneurysm repair: the first decade. Ann Surg 2006; 244:426*
41. *Görich J, Rilinger N, Sokiranski R, et al. Treatment of leaks after endovascular repair of aortic aneurysms. Radiology 2000; 215:414.*

42. *Veith FJ, Baum RA, Ohki T, et al. Nature and significance of endoleaks and endotension: summary of opinions expressed at an international conference. J Vasc Surg 2002; 35:1029.*
43. *Mehta M, Sternbach Y, Taggert JB, et al. Long-term outcomes of secondary procedures after endovascular aneurysm repair. J Vasc Surg 2010; 52:1442.*
44. *Veith FJ, Baum RA, Ohki T, et al. Nature and significance of endoleaks and endotension: summary of opinions expressed at an international conference. J Vasc Surg 2002; 35:1029.*
45. *Abularrage CJ, Crawford RS, Conrad MF, et al. Preoperative variables predict persistent type 2 endoleak after endovascular aneurysm repair. J Vasc Surg 2010; 52:19.*
46. *Jones JE, Atkins MD, Brewster DC, et al. Persistent type 2 endoleak after endovascular repair of abdominal aortic aneurysm is associated with adverse late outcomes. J Vasc Surg 2007; 46:1*
47. *White GH, May J, Waugh RC, et al. Type III and type IV endoleak: toward a complete definition of blood flow in the sac after endoluminal AAA repair. J Endovasc Surg 1998; 5:305.*
48. *Wanhainen A, Verzini F, Van Herzeele I, Allaire E, Bown M, Cohnert T, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2019 clinical practice guidelines on the management of abdominal aorto-iliac artery aneurysms. Eur J VascEndovasc Surg. 2019;57:8-93.*
49. *Witheford M, Brandsma A, Lane R, Prent A, Mastracci TM. Survival and durability after endovascular aneurysm repair reflect era-related surgical judgement. J Vasc Surg. 2022;75:552-560.e2.*
50. *Swerdlow NJ, Lyden SP, Verhagen HJM, Schermerhorn ML. Five-year results of endovascular abdominal aortic aneurysm repair with the Ovation abdominal stent graft. J Vasc Surg. 2020;71:1528-1537.e2.*
51. *Kontopodis N, Galanakis N, Tzartzalou I, Tavlas E, Georgakarakos E, Dimopoulos I, et al. An update on the improvement of patient eligibility with the use of new*

generation endografts for the treatment of abdominal aortic aneurysms. Expert Rev Med Devices. 2020;17:1231-1238.

52. *Guo Q, Du X, Zhao J, Ma Y, Huang B, Yuan D, et al. Prevalence and risk factors of type II endoleaks after endovascular aneurysm repair: A meta-analysis. PLoS One. 2017;12:e0170600.*

53. *Moulakakis KG, Klonaris C, Kakisis J, Antonopoulos CN, Lazaris A, Sfyroeras GS, et al. Treatment of type II endoleak and aneurysm expansion after EVAR. Ann Vasc Surg. 2017;39:56-66.*

54. *Ultee KHJ, Büttner S, Huurman R, Bastos Gonçalves F, Hoeks SE, Bramer WM, et al. Editor's Choice - Systematic review and meta-analysis of the outcome of treatment for type II endoleakfollowing endovascular aneurysm repair. Eur J VascEndovasc Surg. 2018;56:794-807.*

55. *Guo Q, Zhao J, Ma Y, Huang B, Yuan D, Yang Y, et al. A meta-analysis of translumbar embolization versus transarterial embolization for type II endoleak after endovascular repair of abdominal aortic aneurysm. J Vasc Surg. 2020;71:1029-1034.e1.*

56. *Manunga JM, Cragg A, Garberich R, Urbach JA, Skeik N, Alexander J, et al. Preoperative inferior mesenteric artery embolization: A valid method to reduce the rate of type II endoleak after EVAR? Ann Vasc Surg. 2017;39:40-47.*

57. *Burbelko M, Kalinowski M, Heverhagen JT, Piechowiak E, Kiessling A, Figiel J, et al. Prevention of type II endoleak using the AMPLATZER vascular plug before endovascular aneurysm repair. Eur J VascEndovasc Surg. 2014;47:28-36.*

58. *Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane Handbook for Systematic Reviews of Interventions, version 6.0 (updated July 2019). London, UK: Cochrane; 2019.*

59. *Antoniou GA, Antoniou SA, Mani K.Enhancing the reporting of systematic reviews and meta-Analyses in vascular surgery: PRISMA 2020. Eur J VascEndovasc Surg. 2021;62:664-666.*

60. *Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021).*

61. *https://gdt.gradepro.org/app/handbook/handbook.html (last accessed in March 2022).*

62. *Antoniou SA, Antoniou GA. The GRADE approach to appraising the evidence or how to increase the credibility of your research. Am J Surg. 2020;220:290-293.*

63. *https://training.cochrane.org/handbook/current/ chapter-06 .*

64. *DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.*

65. *Langan D, Higgins JPT, Jackson D, Bowden J, Veroniki AA, Kontopantelis E, et al. A comparison of heterogeneity variance estimators in simulated random-effects meta-analyses. Res Synth Methods 2019;10:83–98.*

66. *Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002.*

67. *Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. J Clin Epidemiol. 2008;61:64-75.*

68. *Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. User manual for trial sequential analysis (TSA). Copenhagen Trial Unit, Centre for Clinical*

Intervention Research, Copenhagen, Denmark. 2011. p. 1-115. Available from www.ctu.dk/tsa.

69. *Sedivý P, El Samman K, Bartík K, Mach T, Slais M, Stádler P, et al. Prevention of type II endoleak using postoperative coiling of the abdominal aortic aneurysm sac during stent graft implantation. RozhlChir. 2010;89:18-23.*

70. *Piazza M, Squizzato F, Zavatta M, Menegolo M, Ricotta JJ 2nd, Lepidi S, et al. Outcomes of endovascular aneurysm repair with contemporary volume-dependent sac embolization in patients at risk for type II endoleak. J Vasc Surg. 2016;63:32-8.*

71. *Samura M, Morikage N, Otsuka R, Mizoguchi T, Takeuchi Y, Nagase T, et al. Endovascular aneurysm repair with inferior mesenteric artery embolization for preventing type II endoleak: A prospective randomized controlled trial. Ann Surg. 2020;271:238-244.*

72. *Fabre D, Mougin J, Mitilian D, Cochennec F, Garcia Alonso C, Becquemin JP, et al. Prospective, randomised two Centre trial of endovascular repair of abdominal aortic aneurysm with or without sac embolisation. Eur J VascEndovasc Surg. 2021;61:201-209.*

73. *Jones JE, Atkins MD, Brewster DC, Chung TK, Kwolek CJ, LaMuraglia GM, et al. Persistent type 2 endoleak after endovascular repair of abdominal aortic aneurysm is associated with adverse late outcomes. J Vasc Surg. 2007;46:1-8.*

74. *El Batti S, Cochennec F, Roudot-Thoraval F, Becquemin JP. Type II endoleaks after endovascular repair of abdominal aortic aneurysm are not always a benign condition. J Vasc Surg. 2013;57:1291-7.*

75. *Cieri E, De Rango P, Isernia G, Simonte G, Ciucci A, Parlani G, et al. Type II endoleak is an enigmatic and unpredictable marker of worse outcome after endovascular aneurysm repair. J Vasc Surg. 2014;59:930-7.*

76. *Lo RC, Buck DB, Herrmann J, Hamdan AD, Wyers M, Patel VI, et al; Vascular Study Group of New England. Risk factors and consequences of persistent type II endoleaks. J Vasc Surg. 2016;63:895-901.*

77. *O'Donnell TFX, Deery SE, Boitano LT, Siracuse JJ, Schermerhorn ML, Scali ST, et al. Aneurysm sac failure to regress after endovascular aneurysm repair is associated with lower long-term survival. J Vasc Surg. 2019;69:414-422.*

78. *Deery SE, Ergul EA, Schermerhorn ML, Siracuse JJ, Schanzer A, Goodney PP, et al; Vascular Study Group of New England. Aneurysm sac expansion is independently associated with late mortality in patients treated with endovascular aneurysm repair. J Vasc Surg. 2018;67:157-164.*

79. *Pineda DM, Calligaro KD, Tyagi S, Troutman DA, Dougherty MJ. Late type II endoleaks after endovascular aneurysm repair require intervention more frequently than early type II endoleaks. J Vasc Surg. 2018;67:449-452.*

80. *Li Q, Hou P. Sac embolization and side branch embolization for preventing type II endoleaksafter endovascular aneurysm repair: A meta-analysis. J Endovasc Ther. 2020;27:109-116.*

81. *Yu HYH, Lindström D, Wanhainen A, Tegler G, Hassan B, Mani K. Systematic review and meta-analysis of prophylactic aortic side branch embolization to prevent type II endoleaks. J Vasc Surg. 2020;72:1783-1792.e1.*

82. *Zhang H, Yang Y, Kou L, Sun H, Chen Z. Effectiveness of collateral arteries embolization before endovascular aneurysm repair to prevent type II endoleaks: A systematic review and meta-analysis. Vascular. doi: 10.1177/17085381211032764.*

9.APPENDIX

AAA	Abdominal Aortic Aneurysm
CAD	Coronary Artery Disease
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence Interval
CIA	Common Iliac Artery
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed Tomography
EIA	External Iliac Artery
EMBASE	ExcerptaMedica Database
ePTFE	Polytetrafluoroethylene
EVAR	Endovascular Aneurysm Repair
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
IFU	Instructions for Use
IMA	Inferior Mesenteric Artery
IQR	Interquartile Range
IV	Inverse Variance
MD	Mean Difference
MEDLINE	Medical Literature Analysis and Retrieval System Online
M-H	Mantel-Haenszel
MMPs	Matrix Metalloproteinases
NA	Not Applicable
NR	Not Reported
OR	Odds Ratio
PICO	Patient, Intervention, Comparison, Outcome
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
RCT	Randomized Controlled Trials
RD	Risk Difference
RoB 2	Version 2 of the Cochrane risk-of-bias
SD	Standard Deviations
TSA	Trial Sequential Analysis

10. KEYWORDS

Endovascular repair

EVAR

Endoleak type II

Pre-emptive

Embolism

Aortic sac

Aortic side branch

Meta-analysis

Abdominal aortic aneurysm