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

ΚΟΙΝΟ ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
«ΕΝΔΑΓΓΕΙΑΚΕΣ ΤΕΧΝΙΚΕΣ»

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ΘΕΜΑ:

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ENDOVASCULAR VERSUS OPEN ABDOMINAL AORTIC ANEURYSM REPAIR IN YOUNG PATIENTS- A META-ANALYSIS

ΜΕΤΑΠΤ. ΦΟΙΤΗΤΡΙΑ:

ΑΙΚΑΤΕΡΙΝΗ Ν. ΓΑΒΑΛΑΚΗ

ΑΘΗΝΑ
Ιούνιος, 2022

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της Μεταπτυχιακής Φοιτήτριας Αικατερίνης Ν. Γαβαλάκη

Εξεταστική Επιτροπή

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

Η Τριμελής Εξεταστική Επιτροπή για την αξιολόγηση και εξέταση της υποψηφίου **κας. Αικατερίνης Ν. Γαβαλάκη** συνεδρίασε σήμερα -/-/2022.

Η Επιτροπή **διαπίστωσε** ότι η Διπλωματική Εργασία του/της Αικατερίνης Ν. Γαβαλάκη με τίτλο **«Endovascular versus open abdominal aortic aneurysm repair in young patients- A Meta-analysis»** 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

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CONTENTS

PART 1. Introduction

I. Abdominal Aortic Aneurysm (AAA)

An aneurysm is a permanent and irreversible localized dilatation of an artery. This abnormal dilatation involves all three layers of the vascular wall: the intima, the media and the adventitia. The abdominal aorta is the most common anatomic site of aortic aneurysm [1]. Abdominal aortic aneurysms (AAAs) are described relative to the involvement of the renal or visceral vessels. Infrarenal are the aneurysms originating below the renal arteries; juxtarenal originate at the level of the renal arteries but the aorta at the renal arteries is normal; pararenal involve the aorta at the level of the renal arteries, ie, the renal artery originates from an aneurysmal aorta; suprarenal originate above the renal arteries (Figure 1). The majority of AAAs are infrarenal. About 15 percent are juxtarenal [2]. Suprarenal aneurysms are uncommon, but may develop late following AAA repair [3].

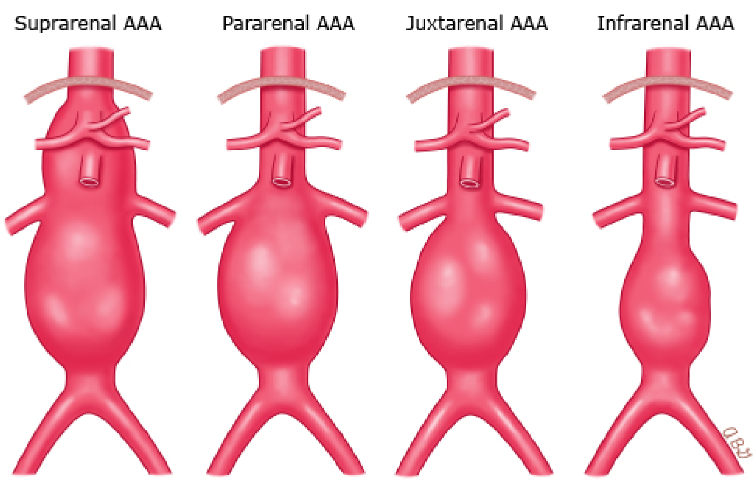

Figure 1. Anatomical classification of AAAs

There is no general agreement on AAA definition. According to the Society for Vascular Surgery and the International Society for Cardiovascular Surgery Ad Hoc Committee on Standards in Reporting, a dilatation of the aorta is an AAA if the diameter of the infrarenal aorta is 1.5 times the expected normal diameter [4]. Although “normal” diameter varies with age, gender, and body habitus, the average diameter of the human infrarenal aorta is about 2.0 cm; the upper limit of normal is typically <3.0 cm. In clinical practice, the infrarenal aorta is considered aneurysmal if the diameter is ≥30 mm [5]. However, this definition might not be appropriate for women, who have smaller in diameter arteries than men, or for individuals with arteriomegaly, a condition of generalized arterial dilatation. Therefore, when reporting a dilatation of the diameter of the infrarenal aorta in a patient, the diameter of the undilated adjacent aorta should be taken into consideration [6], concluding that an AAA should be diagnosed when the ratio of these diameters is ≥1.5. On the basis of the diameter of the aorta, AAA can be classified as small (not considered for repair, <55 mm) or large (≥55 mm), when repair should be considered [7].

Morphologically, AAAs can be fusiform, when the dialatation involves the whole circumference of the aorta, or saccular, when only part of its circumference is involved. The majority of aneurysms are fusiform. Saccular abdominal aortic aneurysms may be treated earlier, with a lower threshold for elective repair than for standard fusiform abdominal aortic aneurysms [7].

II. Epidemiology

Abdominal aortic aneurysm (AAA) is a potentially lethal condition. AAA prevalence and incidence rates have decreased over the last 20 years, which has been attributed partially to the decline in smoking [8-10]. Prevalence is negligible before the age of 55-60 years and thereafter prevalence increases steadily with age [8]. In Europe, population screening studies show 1.3-3.3% prevalence in older than 65 years men [11-13], while a program in the USA which only offers screening to smokers reports a prevalence of over 5% [14].

Most studies show that the prevalence is up to fourfold less in women than men. A recent systematic review of publications between 2000 and 2015 indicates that the pooled prevalence of AAA in women over 60 years was 0.7% [15].

Well-defined clinical risk factors are associated with the development of AAA. Smoking is a major risk factor for AAA. Smoking predicts a larger aortic diameter at presentation [16], and in screening studies, 18 to 52 percent of patients with small AAAs are current smokers [17]. Once an aneurysm has formed, active smoking is associated with the highest risk of aneurysm progression and rupture [18].

Other risk factors include age, atherosclerosis, hypertension, ethnicity, and family history of AAAs [19]. Unique twin registry studies from Sweden and Denmark suggest that the heritability may be as high as 70% [20-21].

The natural history of small AAA is progressive growth in the majority of patients. The mean reported growth rate of AAAs has varied widely, with the majority of reports noting an overall growth rate of smaller AAAs measuring between 3.0 and 5.5 cm to be approximately 0.2 to 0.3 cm per year [22]. Multiple studies have shown increased initial aortic diameter and female gender to be independent risk factors for aneurysm expansion [23]. Smoking seems to increase aneurysm growth rates by 0.35 mm/year (about 16%), and diabetes, although associated with atherosclerosis, was related to decreased aneurysm growth rates by 0.51 mm/year (approximately 25% reduction) [24].

Aneurysms rupture when the local wall stress exceeds the corresponding local wall strength. Laplace's law (wall tension = pressure x radius) is commonly referenced as the theoretical basis for the widely used maximum diameter criterion for predicting AAA rupture. Indeed, baseline aortic diameter is the most validated parameter associated with AAA, with annual rupture rates steadily rising with increased AAA diameter [25]. As reported by the Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery, the estimated annual rupture risk according to AAA diameter is featured in Table 1 [26].

AAA diameter (cm)	Annual rupture risk (%)
< 4.0	0
4.0–4.9	0.5–5
5.0–5.9	3–15
6.0–6.9	10–20
7.0–7.9	20–40
≥ 8.0	30–50

AAA, abdominal aortic aneurysm

Table I. Estimated annual risk of abdominal aortic aneurysm rupture [26]

Increased systemic arterial blood pressure appears to be associated with progression to AAA rupture as predicted by Laplace's law, although the association of hypertension and AAA expansion is not entirely clear [26].

Additional factors are likely to contribute to elevated peak aortic wall stress other than aneurysm diameter alone. In recent years, three-dimensional imaging modalities have been used to facilitate finite element analysis as a method to characterize wall stress distribution within an aneurysm based on a multitude of factors, including aneurysm geometry, mechanical properties of the aortic wall, aneurysm morphology, growth rate, diameter, blood pressure, and gender [27]. Using finite element analysis, aneurysms of similar size have been shown to have higher wall stress when arising from smaller aortas compared to larger native aortas.

In addition to being a dominant risk factor for the development and growth of AAAs, smoking has been associated with a twofold increase in the risk of aneurysm rupture [28]. Females are known to rupture with mean AAA diameters 5 mm to 10 mm smaller than those in males and their risk of death from rupture is up to four times higher compared to males with similar AAA diameters during surveillance [29]. Rapid aneurysm expansion, defined as growth of 5 mm or more over a six month period, is also an independent risk factor for AAA rupture [30].

Rupture of an abdominal aortic aneurysm (AAA) is often lethal, with a mortality of 85-90% [31]. It is estimated that ruptured AAA accounts for 1% of all deaths of men over age 65 and that 50% of patients with a ruptured AAA will die before reaching the hospital [32].

III. Management

Most AAAs do not produce any symptoms. An occult AAA may be discovered as a result of screening, on routine physical examination, or on imaging studies obtained to evaluate an unrelated condition. Symptomatic AAA refers to any of a number of symptoms (eg, abdominal pain, back pain, limb ischemia) that can be attributed to the aneurysm. Patients with ruptured AAA who are admitted to the emergency department usually present with abdominal pain. However, the classic triad of clinical signs (abdominal or back pain, hypotension or shock, and abdominal pulsatile mass) does not always lead to an accurate diagnosis of AAA, as only 25–50% of patients with ruptured AAA demonstrate all signs [33].

Management of an AAA depends on diameter, morphology and symptoms. A ruptured AAA is a surgical emergency, and immediate treatment is required.

Contemporary management of patients with ruptured AAAs can be performed either by endovascular or open surgical repair [7].

Patients who present with a symptomatic but non-ruptured AAA can also require prompt treatment. Optimal timing of treatment is debated. These aneurysms are thought to have a higher rupture risk than asymptomatic aneurysms, while emergency repair under less favourable circumstances is associated with a higher risk of peri- operative complications [34]. Some have suggested that delay in operative repair might improve outcome by allowing a more complete risk assessment, patient optimisation and avoiding out of hours operations by less experienced surgical and anaesthetic teams [34]. Therefore, the management of these cases should involve a brief period of rapid assessment and optimisation followed by delayed urgent repair under optimum conditions.

Patients with an asymptomatic fusiform AAA ≥5.5 cm in diameter should be considered for elective repair. Of note, elective repair is also recommended for patients with a saccular AAA, which generally has a smaller diameter than fusiform AAAs [7]. Early elective repair can occasionally be considered for patients with AAAs of small diameter (≤5.5 cm) but rapid expansion rate and for young and healthy patients, particularly women, with AAAs 5.0–5.4 cm. By contrast, in patients with AAAs ≥5.5 cm but of advanced age or with substantial comorbidities and risk factors, elective repair may be delayed or inappropriate [7].

The management of AAAs has improved substantially since the first resection was performed (Figure 2.). In a modern vascular service, two treatment options are available for elective repair: open surgery or endovascular aneurysm repair (EVAR). Several randomized controlled trials have analyzed the differences in long-term outcomes between EVAR and open repair surgery. Several factors, on different levels, influence the choice between the two procedures, including reimbursement issues and factors related to the hospital, surgeon and patient [33].

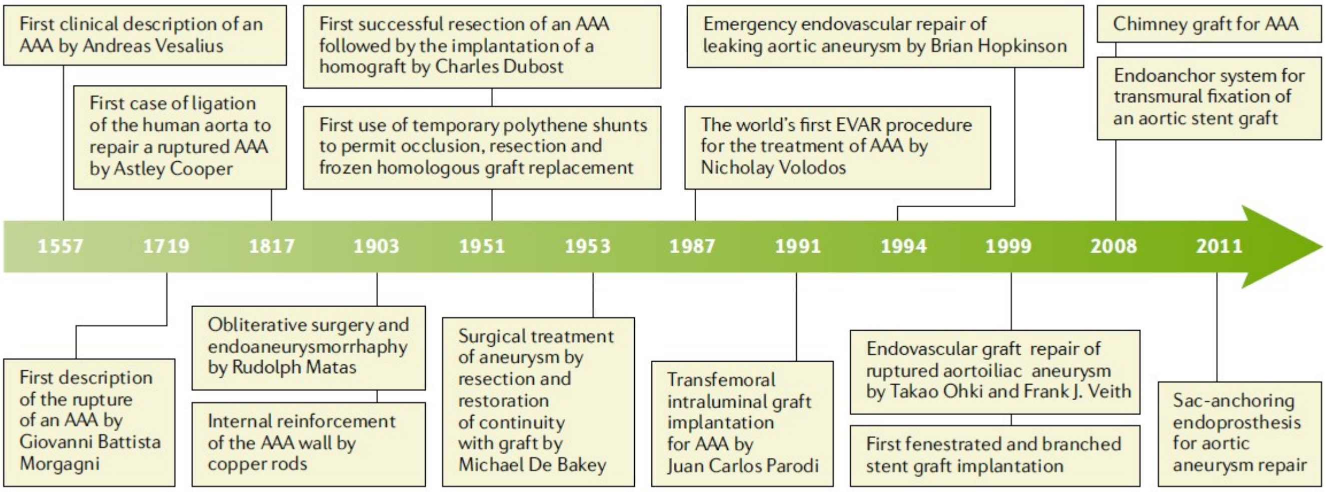

Figure 2. **History of the treatment of AAA** (obtained from *Sakalihasan N, Michel JB, Katsargyris A, Kuivaniemi H, Defraigne JO, Nchimi A, Powell JT, Yoshimura K, Hultgren R. Abdominal aortic aneurysms. Nat Rev Dis Primers. 2018 Oct 18;4(1):34*)

Open AAA repair requires direct aortic exposure via a transperitoneal or retroperitoneal approach and subsequent in situ reconstruction with either a tube or a bifurcated prosthetic graft (Figure 3.). It continues to be used for patients whose vascular anatomy is not suitable for EVAR (for example, with short sealing zones, multiple accessory renal arteries or no suitable access vessels). Open repair surgery may also be offered to young and healthy individuals who are also suitable for EVAR, given that open repair surgery is more likely to have better long-term durability and a reduced need for long-term surveillance and reinterventions compared with EVAR. Open repair surgery may also be required for the treatment of complications after EVAR (for example, persistent endoleak or aneurysmal sac growth) or for the treatment of a mycotic AAA or graft infection [7].

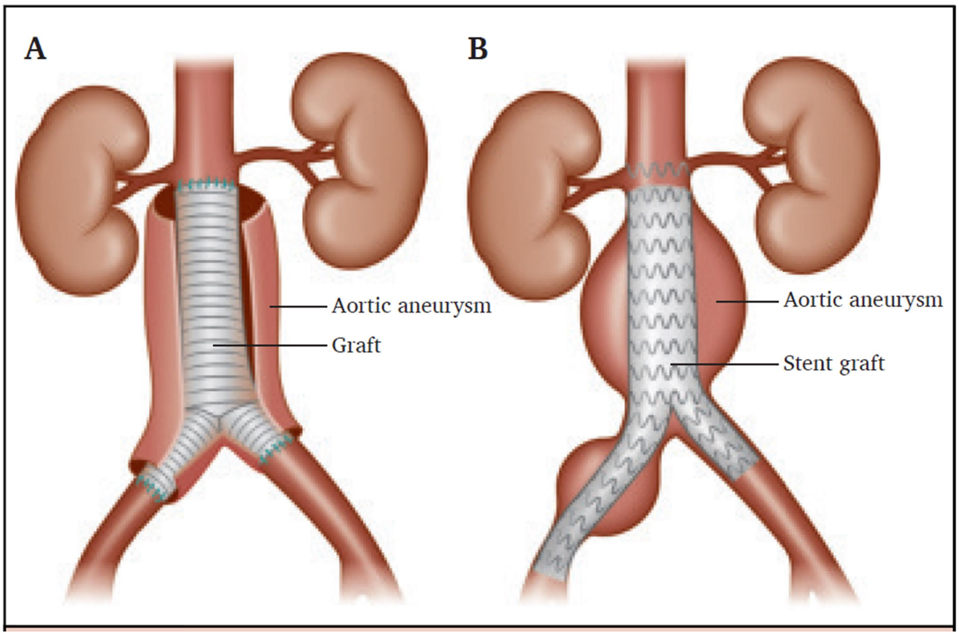

Figure 3. (A) Open surgery for an abdominal aortic aneurysm (open AAA repair). The affected segment of the aorta is replaced with a material graft stitched in place. (B) Endovascular AAA repair (EVAR). A stent graft is placed inside the aneurysm to reline the aorta and prevent the aneurysm rupture. [7]

EVAR consists of the implantation of a bifurcated graft via the femoral and iliac arteries; the graft is anchored with stents at the normal, non-aneurysmal aorta at the level of the renal and iliac arterial walls, and the aneurysmal sac is left in situ. EVAR aims to exclude the AAA from the systemic circulation instead of replacing the damaged aorta. Several factors must be considered when assessing the feasibility of EVAR. The access vessels should be of adequate quality to enable the introduction of the stent graft. Furthermore, to achieve complete sealing, healthy (non-aneurysmal) proximal and distal zones are required for anchoring of the stent graft. In cases of inadequate proximal anchoring zones below the renal arteries, the suprarenal part of the aorta can be used for sealing using advanced EVAR techniques, such as fenestrated grafts (stent grafts with fenestration-holes to accommodate the renal arteries and the superior mesenteric artery and coeliac trunk if needed) or the chimney technique [35]. Aortic morphology influences EVAR outcomes. The performance of EVAR in patients who do not have the necessary features for this procedure is associated with inferior long-term outcomes [36-37]. Thus, a strict indication should be followed to achieve safe long-term EVAR outcomes (Table 2). In cases of questionable anatomical suitability, alternative treatment strategies (for example, open repair surgery or advanced EVAR with fenestrated or chimney grafts) should be considered.

Anatomical parameter	Endurant	Excluder	Zenith
Neck length	≥10 mm[a]	≥15 mm	≥15 mm
Neck diameter	19–32	19–29	18–32
Suprarenal neck angulation (α-angle)	≤45°	–	<45°
Infrarenal neck angulation (β-angle)	≤60°	≤60°	<60°
Distal fixation site length	≥15 mm	≥10 mm	>10 mm
Distal fixation site diameter	8–25 mm	8–25 mm	7.5–20 mm
Additional criteria	No significant or circumferential calcification or thrombus in proximal and distal landing zones No conical neck shape (<2–3 mm increase in neck diameter for each centimetre of length) Adequate femoral access		

[a] ≥ 15 mm with >60° to ≤75° infrarenal and >45° to ≤60° suprarenal neck angulation.

Table 2. Anatomical requirements for the most commonly used stent grafts according to the latest instruction for use available to the authors [7].

IV. Endovascular versus open abdominal aortic aneurysm repair

Several randomized controlled trials (RCTs) have compared EVAR with open AAA repair surgery including the EVAR 1 trial, DREAM, OVER, and ACE trial [38-41]. The first RCT is UK EVAR 1 (UK Endovascular Aneurysm Repair 1) trial, which included a total of 1082 patients with aneurysm diameter ≥5.5 cm, randomized between 1999 and 2003 to receive elective EVAR or open surgical repair. It showed an early survival advantage for EVAR, with lower 30-day mortality (1.7% vs. 4.7%). However, secondary interventions were more frequent in that group (9.85% vs. 5.8%). At the 4-year follow-up aneurysm related mortality was increased in the EVAR. At 15 years of follow-up, EVAR was associated with lower survival than open repair surgery, mainly owing to increased secondary aneurysmal sac rupture (7.1% vs. 1%), as well as increased cancer mortality [38].

The DREAM trial enrolled 351 patients in the Netherlands and Belgium with an aneurysm diameter ≥5 cm, between 2000 and 2003. The study findings showed a benefit of EVAR compared with open repair surgery with regard to 30-day mortality (1.2% and 4.6%, respectively), complication rates (11.7% and 26.4%) and length of hospital stay (6 days and 13 days) [39]. EVAR was associated with higher re-intervention rates than open repair surgery during 6 years of follow-up (29.6% and 18.1%), but overall survival rate (EVAR 38.4% vs. open 41.7%), as well as aneurysm related mortality was similar after 12 years follow-up [42].

The OVER trial randomised 881 patients with an aneurysm diameter of ≥5 cm or more, between 2002 and 2008 in the USA. It showed low peri-operative mortality for both procedures, specifically lower for EVAR than OSR (0.5% vs.3%) [40]. After 14 years of follow up, no difference was observed between endovascular and open repair in the primary outcome of all-cause mortality. Secondary procedure were more in the EVAR group. The between-group difference in the numbers of procedures is significant (P=0.04), as is the between-group difference in the percentage of patients who underwent a secondary procedure (26.7% in the endovascular-repair group vs. 19.8% in the open-repair group). Among patients younger than 70 years of age, overall survival appeared, surprisingly, to be higher in the endovascular-repair group than in the open-repair group, but the difference was not significant (hazard ratio for death, 0.81; 95% CI, 0.62 to 1.05; P=0.10) [43].

In France, the ACE trial randomised 316 patients with an aneurysm diameter of ≥5 cm, suitable for EVAR and at low to intermediate risk of OSR, between 2003 and 2008. After a median follow up of three years, no difference was found in the cumulative survival free of death or major events rates between OSR and EVAR (95.9% vs. 93.2% at one year and 85.1% vs. 82.4% at three years, respectively). The re-intervention rate was higher in the EVAR group (16%, vs. 2.4% p < 0.0001) and there was a trend towards a higher aneurysm related mortality in the EVAR group (4%; vs. 0.7% p=0.12) [41].

A recent meta-analysis30 of individual patient data, reported data on mortality, aneurysm related mortality, and re-intervention considering the four RCTs of EVAR versus OSR mentioned aboveThese four randomized trials, in Europe and the USA, provide the best evidence for the early survival advantage offered by EVAR rather than open repair. In terms of aneurysm related mortality, there was no difference between EVAR and OSR after 30 days and up to three years of follow up, but after three years the number of deaths was higher in the EVAR group (3 vs. 19 deaths). The re-intervention rate was higher in the EVAR group but not all trials reported incision related complication after OSR. When taking incisional hernias, bowel obstructions, and other laparotomy based complications into account, as was done in the OVER trial, the difference in secondary interventions between groups appear much less significant than that observed in the EVAR1 or DREAM trials. Further investigations focused on whether the early survival advantage was either maintained or lost in subgroups of patients categorized by preoperative characteristics. Over a 5-year time horizon, there was no convincing evidence that being randomized to EVAR or open repair resulted in differential survival between any subgroups of the population. This does not support the suggestion that younger and fitter patients with aortic morphology suitable for EVAR are likely to benefit from open repair over 5 years [44].

There have been substantial improvements in stent graft technology that may have a positive effect on EVAR durability. Materials have been improved (for example, grafts have lower permeability and stent designs are more flexible), and deployment mechanisms have also been revised to enable more-precise proximal deployment. Consequently, the long-term outcomes of EVAR with current stent graft technology may improve compared with those reported in the existing studies evaluating EVAR with previous-generation stent grafts. Therefore, the above mentioned results are not entirely relevant for today's situation.

V. Endovascular versus open abdominal aortic aneurysm repair in young patients

The choice of AAA repair technique should be discussed with the patient, while multiple factors should be considered when constructing a patient's treatment plan. These include anatomical suitability for EVAR, physiological reserves and fitness for surgery, life expectancy, patient preferences, needs and expectations, including the importance of sexual function, and anticipated compliance with frequent lifelong surveillance and follow up [45]. Therefore the decision is extremely complex, with multiple variables for consideration, concluding that it is important to allow some degree of freedom for individualized decision making (Figure 4.).

In patients with long life expectancy, open abdominal aortic aneurysm repair should be considered as the preferred treatment modality [7]. This is the latest recommendation from the European Society for Vascular Surgeons, referring to younger patients. However, it is a Class IIa recommendation with a level of evidence B. In the long term, the higher mortality but good durability associated with open repair surgery has to be balanced against the lower early mortality but questionable durability of EVAR [33].

There are several retrospective, few randomized trials and some meta-analyses examining the outcomes of EVAR in younger patients [46-50]. Although data on 30-day mortality and peri-operative morbidity indicated that EVAR may be advantageous in young patients, re-interventions rate is still higher in that group. Concurrently, most of the studies lack results regarding long-term outcomes. There is need for more randomized trials, recent, where up-to-date technology in EVAR is utilized, in order to confirm the long term advantage EVAR could offer in younger patients.

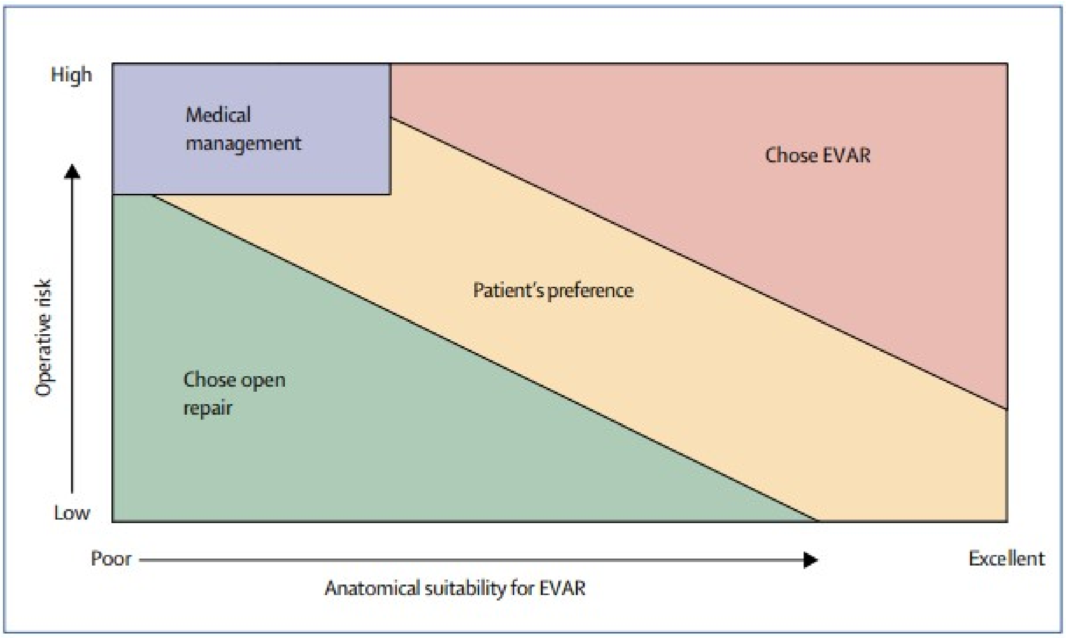

Figure 4. Choosing the best management of abdominal aortic aneurysm for individual patients. Obtained from *Cronenwett JL. Endovascular aneurysm repair: important mid-term results. Lancet. 2005 Jun 25-Jul 1;365(9478):2156-8.*

PART 2. Endovascular versus open abdominal aortic aneurysm repair in young patients- A Meta-analysis

I. Introduction- Purpose

The surgical management of abdominal aortic aneurysms (AAA) aims to prevent aortic rupture. Rupture of an AAA is often lethal, with a mortality of 85-90% [31]. There are two main surgical strategies for patients with asymptomatic AAA: open surgical repair (OSR) and endovascular repair (EVAR). EVAR has revolutionized the treatment of abdominal aortic aneurysm (AAA) disease, currently accounting for almost 74% of all procedures performed on patients with AAA in the United States [51].

The advantages of EVAR over OSR are well described, regarding lower peri-operative morbidity and mortality, reduced length of stay and earlier recovery [38-41]. In patients with long life expectancy, open abdominal aortic aneurysm repair should be considered as the preferred treatment modality [7]. This is the latest recommendation from the European Society for Vascular Surgeons, referring to younger patients. However, it is a Class IIa recommendation with a level of evidence B.

In the long term, the lower overall mortality associated with open surgical repair has to be balanced against the lower early mortality but questionable durability of EVAR [33]. This fact, along with the higher need for re-interventions, creates controversy on whether EVAR is a suitable technique in younger patients. Since the initial randomised trials were accomplished, accumulated experience, rapid technological improvement, newer devices, and better patient selection have taken place, rendering their results outdated [52].

On this assumption, a systematic review and meta-analysis of available data was performed, addressing the results of EVAR versus OSR in young patients.

II. Patients and Methods

The objectives and methodology of our review were prespecified in a protocol, which was registered in PROSPERO (CRD42022325051). The review was developed in line with principles described in the Cochrane Handbook for

Systematic Reviews of Interventions [53]. Reporting of the review complied with the updated 2020 PRISMA guidelines [54].

Eligibility criteria

Types of studies

Studies which reported comparative outcomes of standard EVAR versus open surgical repair in young patients electively treated for AAA were considered. The design of the studies was not used as an exclusion criterion (i.e. observational or randomized trials). No time restrictions were applied (i.e. study recruitment period or publication date). Only studies published in English language were considered. Small case series studies reporting <10 cases were excluded, as were case reports and review articles. Additionally studies including patients with ruptured AAAs or those with complex aortic disease were excluded. For the purposes of meta-analyses, we used the definition of "young" that was applied in individual studies, but only definitions <70 years were accepted.

Types of participants

Eligible participants were male or female young patients undergoing elective AAA treatment with either EVAR or open surgery.

Types of intervention and prognostic factor

The intervention of interest was standard EVAR with a bifurcated device and the comparator intervention was open surgical repair.

Information sources

Search strategy

The literature search strategy was developed by the review author team. 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 Cochrane Central Register of Controlled Trials (CENTRAL) was also searched for eligible studies. 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 30 March 2022. Search syntaxes are presented in Appendix 1. A second level search was conducted by interrogating the bibliographic list of articles that qualified for inclusion in this review.

Selection process

Two review authors conducted the prespecified literature searches and evaluated the eligibility of studies against the inclusion criteria independently. When disagreement arose, a third review author acted as an arbitrator. Articles published in a non-English were discarded.

Data collection process

Data to be collected from individual studies were prespecified 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 extracted data from the selected studies and these were then crosschecked by a third review author. 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

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, definition of “young” patients, number of patients in each group, length of follow-up and type of outcome measures.
- Individual study population data: gender, age, maximum AAA diameter.

- ➢ Data pertaining to risk of bias assessment.
- ➢ Outcome data, as outlined here:

-Primary outcomes:

- Perioperative mortality, defined as death occurring within 30days from surgery or during the hospital stay.
- All-cause mortality, defined as any death occurring from the initiation of the surgical procedure (or the time that intervention was considered for patients managed non-operatively) to the end of follow-up.
- Overall re-intervention rate

-Secondary outcomes were:

- Length of hospital stay
- Need for transfer in the ICU
- Length of stay in the ICU
- Peri-procedural re-intervention rate
- Complication regarding cardiac, renal, respiratory and bleeding morbidity.

Study risk of bias assessment and evidence appraisal

The Newcastle-Ottawa scale (NOS) was applied to assess the methodological quality of observational cohort studies [55]. Two review authors assessed the studies independently. When disagreement arose, consensus was reached with discussion.

The quality of evidence for the primary intervention/prognostic factor was graded using the system developed by the GRADE (Grading of Recommendation, Assessment, Development, and Evaluation) working group, and a summary of findings table was generated using software [56, 57].

Effect measures and Synthesis methods

For binary outcomes, the effect measure used in the synthesis was the odds ratio (OR) and 95% confidence interval (CI). 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 RevMan computer 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 [58].

Sensitivity analysis

To explore robustness of the results, the analysis was repeated after excluding

- Studies of low methodological quality (NOS < 7stars)
- Studies published before 2010

Assessment of heterogeneity

In-between study heterogeneity was examined with the Cochrane's Q ($\chi 2$) test. 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 [59].

III. Results

Results of the literature search

From electronic literature searches 19,381 reports were retrieved. Fifteen studies were deemed suitable for inclusion in qualitative and quantitative syntheses [46-49, 60-70]. The literature flow diagram is presented in Figure 1.

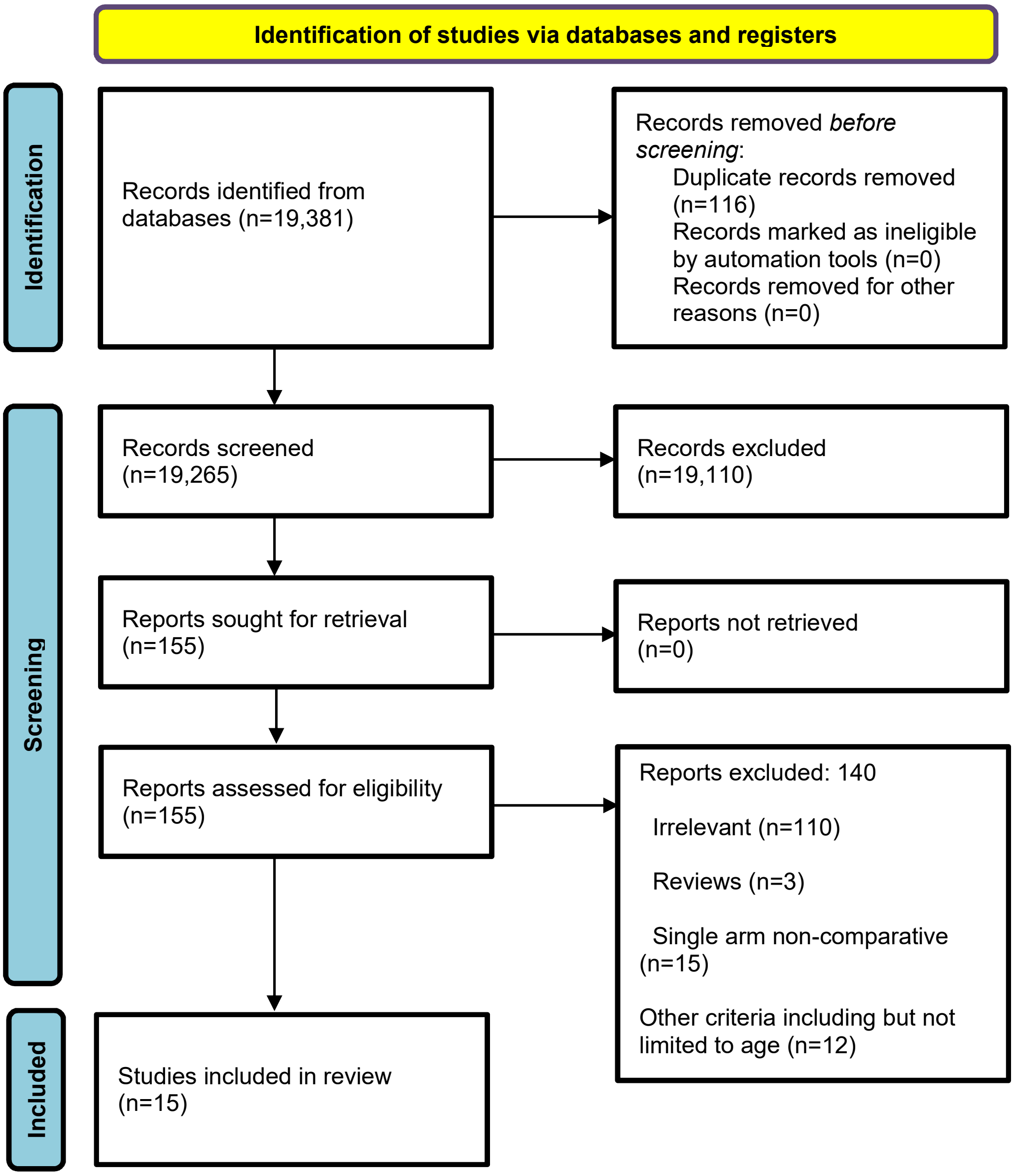

Figure 1. Literature flow diagram generated using a Shiny App available at https://www.eshackathon.org/software/PRISMA2020.html.

Study characteristics

Among the studies, included in the analysis, there were nine observational retrospective studies (8 single-center and 1 multi-center), five administrative databases and one RCT, that reported comparative data on EVAR versus open surgery in young patients [46-49, 60-70]. The studies were published between 2008 and 2022, and the study recruitment period spanned from 1994 to 2018.

The studies reported a total population of 44,658 young patients undergoing AAA treatment, among which 22,361 received open surgery and 22,297 received EVAR. The individual study characteristics are summarized in **Table 1**.

The definition of a young patient was not consistent among the included studies. Various criteria were used for age ranging from 60 to 70 years. The thresholds were 70 years in 4 studies, 65 years in 5 studies, and 60 years in 3 studies. The duration of follow-up ranged between 30 days and 124 months. Baseline characteristics of young patients undergoing EVAR or OSR were specifically mentioned in 11 of 15 studies [46-49, 63-70]. These results are summarized in **Table 2.**

Table 1. Main characteristics of the studies included in the analysis

Author Journal Year	Country	Study design	Age	Enrollment period	# Patients OSR	# Patients EVAR	Follow-up period	Endpoints
Diehm 2008[47]	USA-Switzerland	Retrospective Single center	<65	1994-2007	25	25	EVAR 7.1y OSR 5.9 y	30-d M&M, ICU, LOS, LT Mortality, RI
Schermerhorn 2008[61]	USA	Registry (MEDICARE)	67-69	2001-2004	3173	3173	NA	30-d Mortality
Schwarze 2009[61]	USA	Registry (NIS)	50-64	2001-2006	14067	12783	30 d	30-d M&M, LOS, Discharge to home
Giles 2011[62]	USA	Registry (MEDICARE)	67-69	2001-2004	3173	3173	3-7y	Overall RI
Lederle 2012[63]	USA	RCT	<70	2002-2006	188	218	5.2y	LT mortality
Gupta 2012[49]	USA	Registry–(NSQIP)	<60	2007-2009	282	369	30 d	30-d M&M, LOS
Altaf 2013[46]	UK	Retrospective Single Center	<65	1994-2011	68	97	77 m EVAR 44 OSR 89	30-d mortality, LT mortality, RI
Sandford 2013[48]	UK	Retrospective Single center	<65	2000-2010	99	59	75.5 months EVAR 35 OSR 93	30-d M&M, LOS, ICU, Early and overall RI
Lee 2015[64]	Canada	Retrospective Single Center	<60	2000-2013	119	50	EVAR 62.5 m OSR 78.2m	30-d mortality, Early and overall RI, Overall mortality
Sirignano 2016[65]	Italy	Retrospective Multi center	<60	2005-2014	70	49	Mean 56.8 ± 42.7m	30-d mortality, RI, Overall mortality, Overall RI
Liang 2019[66]	USA	Registry(VQI)	<65	2003-2014	713	1928	Median 401d	30-d mortality, Overall mortality, RI rate, Adj overall mort, LOS
Gallito 2019[67]	France Italy	Retrospective-Single center	<65	2005-2013	57	58	Mean 86 ± 38m	ICU, Transfusion, LOS, 30-d mortality, 30-d RI, Overall RI, Overall survival
Reitz 2020[68]	USA	Retrospective-Single center	<70	2003-2013	49	204	Median 4.5y	30-d mortality LOS, Overall mortality, overall RI rate,
Byun 2021[69]	Korea	Retrospective-Single center	<70	2012-2016	53	37	52 m	30-d mortality, Overall mortality, aneurysm related mortality, Cost effectiveness, QOL
Gibello 2022[70]	Italy	Retrospective-Single center	<70	2010-2018	157	34	71 m	30-d mortality, Overall mortality, LOS, Perioperative RI, Overall RI

Abbreviations: d, days; EVAR, endovascular aneurysm repair; ICU, intensive care unit; LOS, length of stay; LT, long-term; m, months; M&M, mortality and morbidity; NA, not available; NIS, National Inpatient Sample; NSQIP, National Surgical Quality Improvement Program; OSR, open surgical repair; RCT, randomized controlled trial. RI, re-interventions; VQI, Vascular Quality Initiative; y, years

Table 2. Main Baseline Characteristics of Patients Retrieved From the Included Studies

Author Journal Year		n	Age	Male sex	Aneurysm Diameter	Hypertension	Smoking	COPD
Diehm [47]	EVAR	25	62± 2.8 (mean ± SD)	23	49.6 (mean max)	14	23	6
	OSR	25	59±3.9	23	54.9 (mean max)	19	20	6
Gupta [49]	EVAR	369	56 (mean)	335	NA	280	231	59
	OSR	282	56	227	NA	215	202	37
Altaf [46]	EVAR	97	63 (61-65) (median + IQR)	NA	NA	61	72	43
	OSR	68	63 (60-64)	NA	NA	34	30	6
Sandford[48]	EVAR	59	61 (37-65) (median + range)	93	64 (mean)	34	51	NA
	OSR	99	62 (43-65)	56	66 (mean)	45	66	NA
Lee[64]	EVAR	50	57.1 (mean)	46	56.4 (max)	43	41	12
	OSR	119	56.6	109	63.7 (max)	82	107	17
Sirignano[65]	EVAR	49	57.4±2.75	47	54.45 (mean max)	29	33	7
	OSR	70	(mean, SD) 56±3.25	68	55.36 (mean max)	51	56	8
Liang[66]	EVAR	1928	62 (59-64) (median + IQR)	1696	54 (max)	1556	NA	NA
	OSR	713	61 (58-64)	608	55 (max)	566	NA	NA
Gallito[77]	EVAR	58	60 (mean)	56	58.5 (mean)	44	34	20
	OSR	57	62	57	66 (mean)	49	31	26
Reitz[68]	EVAR	204	66 (median)	173	56 (mean)	147	175	36
	OSR	49	65	41	59 (mean)	44	46	17
Byun[69]	EVAR	37	66 (63-68) (median, IQR)	34	57.8 (mean max)	16	14	4
	OSR	53	63 (58.5-65)	49	59.2 (mean max)	32	23	4
Gibello[70]	EVAR	34	66±4 (mean, SD)	32	57 (mean)	24	27	8
	OSR	157	65±4	154	55 (mean)	115	137	26

Abbreviations: COPD, chronic obstructive pulmonary disease; EVAR, endovascular aneurysm repair; NA, not available; OSR, open surgical repair

Results of the risk of bias assessment and evidence appraisal

Mean number of stars allocated to the included studies was 7 (Range 4-9). In general, studies reporting information derived from administrative databases were judged to be of lower methodological quality mainly due to limitations in the "Selection" domain, as presented in **Table 3**.

The results of the GRADE assessment are presented in **Table 4**. The level of evidence was very low for nearly all outcomes, with the exception of Transfer to the ICU and Respiratory complications for which it was low. Downgrading of the evidence was mainly due to high risk of bias of included studies and inconsistency resulting from significant heterogeneity and different definitions of outcomes across studies.

Table 3. The Quality of Observational Studies Assessed Using the Newcastle-Ottawa Scale

Study,year	Definition adequate	Representativeness	Selection	Definition of controls	Comparability	Ascertainment of exposure	Same method	Non response rate	Total
Diehm, 2008	*	*	*	*	*	*	*	*	8
Schwartze, 2009				*		*	*	*	4
Gupta, 2012	*			*	*	*	*	*	5
Altaf, 2013	*	*	*	*	*	*	*	*	8
Sandford, 2013	*	*	*	*	*	*	*	*	8
Schermerhom, 2008				*		*	*	*	4
Giles, 2011				*		*	*	*	4
Lee, 2015	*	*	*	*	**	*	*	*	9
Sirignano, 2016	*	*	*	*	**	*	*	*	9
Liang, 2018				*	*	*	*	*	5
Reitz, 2019	*	*	*	*	**	*	*	*	9
Byun, 2021	*	*	*	*	*	*	*	*	8
Gallito, 2020	*	*	*	*	*	*	*	*	8
Gibello, 2022	*	*	*	*	**	*	*	*	9

Table 4. GRADE Assessment

EVAR versus OSR for young patients

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects: Risk with Control	Anticipated absolute effects: Risk difference with EVAR versus OSR (95% CI)
30-Day Mortality	37741 (13 studies)	⊕⊖⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, inconsistency, large effect	**OR 0.24** (0.16 to 0.34)	**Study population**	
				14 per 1000	**11 fewer per 1000** (from 9 fewer to 12 fewer)
				Moderate	
				10 per 1000	**8 fewer per 1000** (from 7 fewer to 8 fewer)
LOS	30718 (7 studies)	⊕⊖⊖⊖ **VERY LOW**[1,4] due to risk of bias, inconsistency			The mean los in the intervention groups was **4.44 lower** (4.79 to 4.09 lower)
Long-Term Mortality	1130 (7 studies)	⊕⊖⊖⊖ **VERY LOW**[1,4,5] due to risk of bias, inconsistency, imprecision	**OR 1** (0.41 to 2.44)	**Study population**	
				177 per 1000	**0 fewer per 1000** (from 96 fewer to 167 more)
				Moderate	
				155 per 1000	**0 fewer per 1000** (from 85 fewer to 154 more)
Overall Reinterventions	7596 (10 studies)	⊕⊖⊖⊖ **VERY LOW**[1,4,5] due to risk of bias, inconsistency, imprecision	**OR 1.62** (0.9 to 2.94)	**Study population**	
				65 per 1000	**36 more per 1000** (from 6 fewer to 105 more)
				Moderate	
				99 per 1000	**52 more per 1000** (from 9 fewer to 145 more)
Peri-operative reinterventions	1055 (7 studies)	⊕⊖⊖⊖ **VERY LOW**[1,4,5] due to risk of bias, inconsistency, imprecision	**OR 0.67** (0.12 to 3.87)	**Study population**	
				28 per 1000	**9 fewer per 1000** (from 25 fewer to 72 more)
				Moderate	
				14 per 1000	**5 fewer per 1000** (from 12 fewer to 38 more)
Transfer to the ICU	526 (3 studies)	⊕⊕⊖⊖ **LOW**[1,4,6] due to risk of bias, inconsistency, large effect	**OR 0.02** (0.01 to 0.1)	**Study population**	
				849 per 1000	**748 fewer per 1000** (from 489 fewer to 796 fewer)
				Moderate	
				790 per 1000	**720 fewer per 1000** (from 517 fewer to 754 fewer)
LOS in the ICU	2944 (3 studies)	⊕⊖⊖⊖ **VERY LOW**[1,4] due to risk of bias, inconsistency			The mean los in the icu in the intervention groups was **1.06 lower** (1.76 to 0.35 lower)
Renal Complications	30541 (6 studies)	⊕⊖⊖⊖ **VERY LOW**[1,2,4,5] due to risk of bias, inconsistency, imprecision	**OR 0.5** (0.15 to 1.68)	**Study population**	
				46 per 1000	**22 fewer per 1000** (from 39 fewer to 29 more)
				Moderate	
				31 per 1000	**15 fewer per 1000** (from 26 fewer to 20 more)

Cardiac Complications	30744 (6 studies)	⊕⊖⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, inconsistency, large effect	**OR 0.22** (0.13 to 0.35)	**Study population**	
				63 per 1000	**48 fewer per 1000** (from 40 fewer to 54 fewer)
				Moderate	
				60 per 1000	**46 fewer per 1000** (from 38 fewer to 52 fewer)
Respiratory Complications	30744 (6 studies)	⊕⊕⊖⊖ **LOW**[1,2,6] due to risk of bias, inconsistency, large effect	**OR 0.17** (0.11 to 0.26)	**Study population**	
				124 per 1000	**100 fewer per 1000** (from 88 fewer to 108 fewer)
				Moderate	
				82 per 1000	**67 fewer per 1000** (from 59 fewer to 72 fewer)
Bleeding Complications	30541 (6 studies)	⊕⊖⊖⊖ **VERY LOW**[1,2,3,4] due to risk of bias, inconsistency, large effect	**OR 0.26** (0.11 to 0.64)	**Study population**	
				88 per 1000	**64 fewer per 1000** (from 30 fewer to 78 fewer)
				Moderate	
				43 per 1000	**31 fewer per 1000** (from 15 fewer to 38 fewer)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] High risk of bias of included studies
[2] Different definitions used across studies
[3] OR < 0.5
[4] Considerable heterogeneity between studies
[5] 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both 1) no effect and 2) appreciable benefit or appreciable harm.
[6] OR < 0.2

Effects of interventions

- Perioperative mortality

Comparative perioperative mortality data for young patients undergoing OSR or EVAR were reported in 13 studies [46-49, 60-61, 64-70] with a total of 37,741 patients (18,932 patients that received surgery and 18,809 that received EVAR) (Figure 2). There were 266 events in the surgical and 58 in the endovascular group for pooled perioperative mortality of 1.4% and 0.3% respectively. There was a statistical significant difference in favor of EVAR for this outcome (OR 0.24, 95% CI 0.16 – 0.34; P<0.00001). The between-study heterogeneity was not important (P=0.35, I^2=10%).

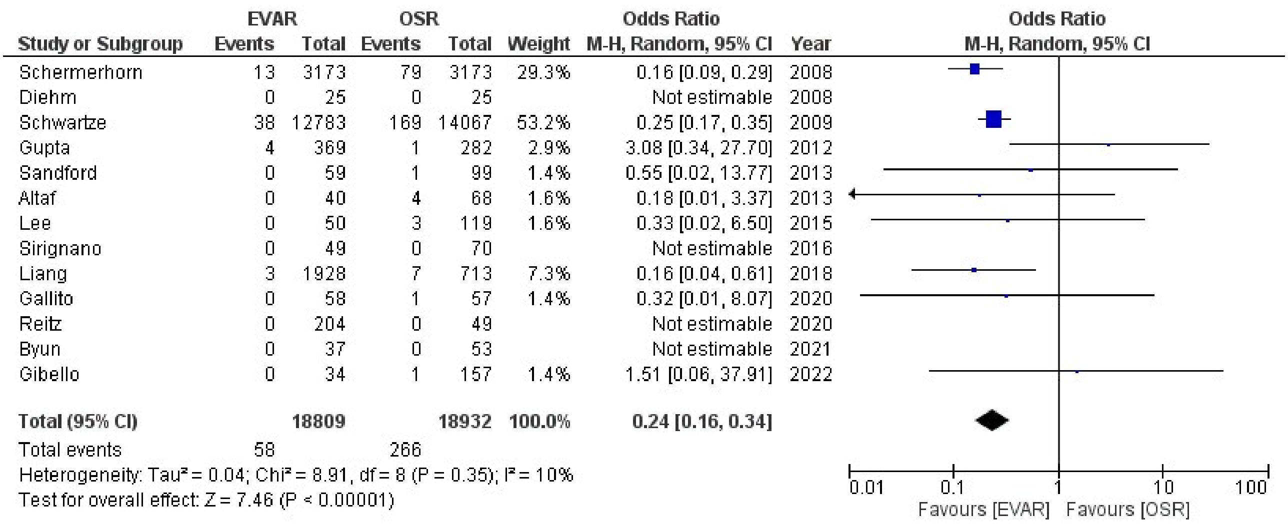

Figure 2. Forest plot of pooled odds ratios for 30-day mortality after endovascular versus open repair of abdominal aortic aneurysm in young patients.

- Long-term mortality

Number of events for long term mortality were reported by seven studies [46-47, 63-65, 69-70] including a total of 677 patients undergoing open surgery (120 events; 17.7%) and 453 patients undergoing EVAR (76 events; 16,7%). Long term mortality was not significantly different between the two treatment groups (OR 1.00, 95% CI 0.41 – 2.44; P=1.00). The between-study heterogeneity was considerable (P<0.0001, I^2=80%) (Figure 3).

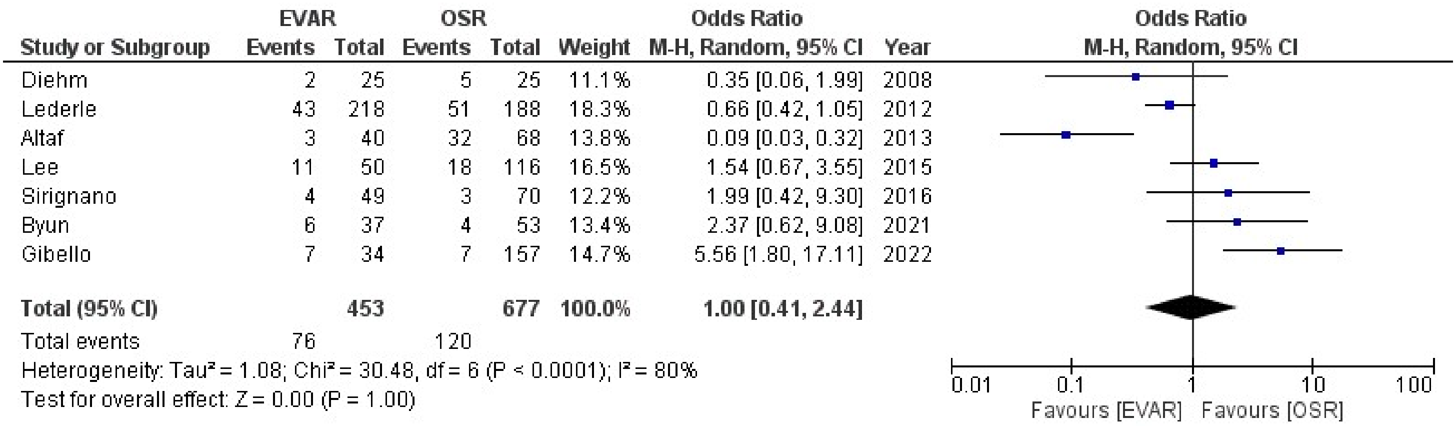

Figure 3. Forest plot of pooled odds ratios for long-term mortality after endovascular versus open repair of abdominal aortic aneurysm in young patients.

- Perioperative re-interventions rate

Perioperative re-interventions were reported by 7 studies [47-48, 64-65, 67-68, 70] including 536 patients undergoing open surgical repair and 519 patients treated with EVAR. The difference between the two treatment groups was not significantly different (OR 0.67, 95% CI 0.12 – 3.87; P=0.65). The between-study heterogeneity was important (P=0.05, I^2=58%) (Figure 4).

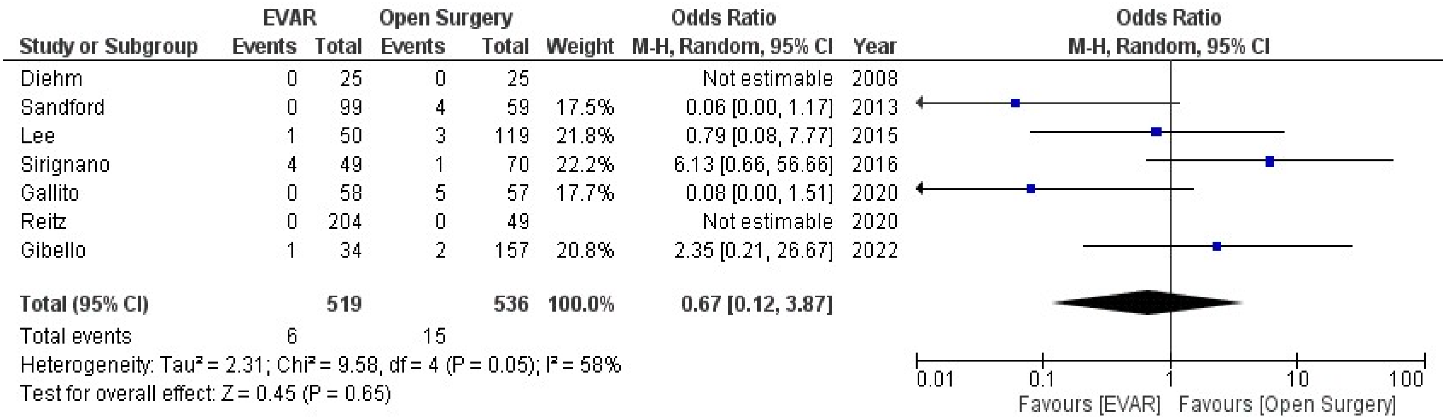

Figure 4. Forest plot of pooled odds ratios for perioperative re-interventions rate.

- Overall re-intervention rate

Events of overall re-interventions were reported by 10 studies [46-48, 62, 63-65, 67-70] including a total of 3,867 patients (253 events; 6.5%) that received open surgery and 3,729 patients (273 events; 7.3%). Overall re-interventions were more common among EVAR patients but the difference was not statistically significant (OR 1.64, 95% CI 0.90 – 2.94; P=0.11). The between-study heterogeneity was significant (P<0.0001, I^2=75%) (Figure 5).

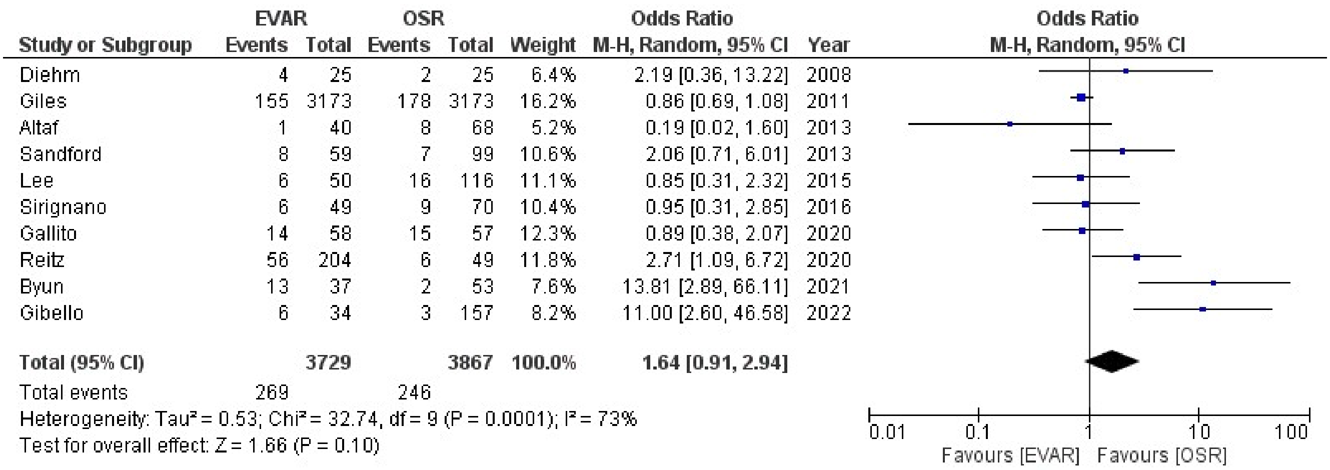

Figure 5. Forest plot of pooled odds ratios for overall re-interventions rate.

- Length of Stay

Length of hospital stay was reported by 7 studies [46-48, 61, 66-68] including a total of 15,292 patients in the open surgical and 15,426 in the EVAR group. Patients undergoing EVAR had a significantly shorter hospitalization compared to those undergoing open surgery (MD -4.44 days, 95% CI 4.79 – 4.09; P<0.00001). The between-study heterogeneity was considerable (P<0.00001, I^2=93%) (Figure 6).

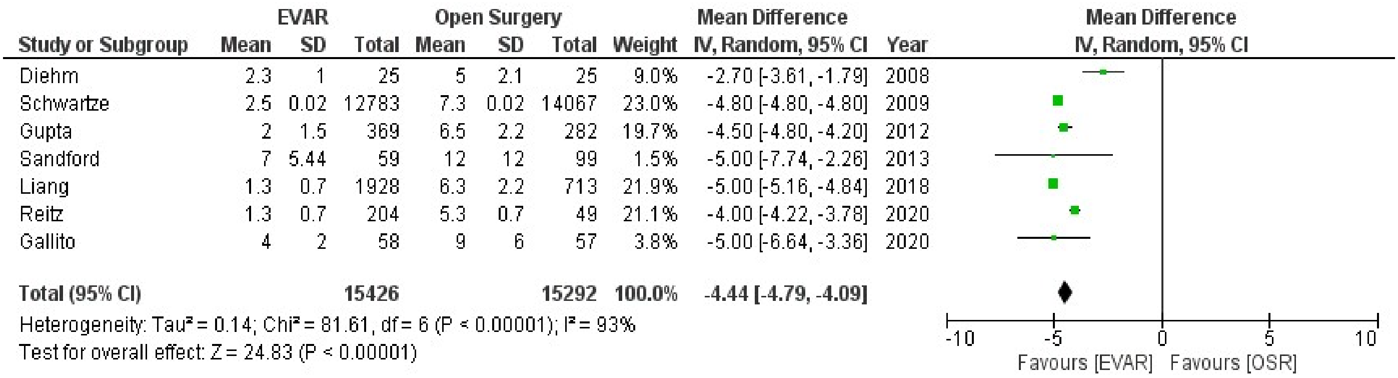

Figure 6. Forest plot of pooled mean differencies for length of stay in hospital.

- Need for ICU

The need to transfer patients in the ICU after AAA treatment was reported by 3 studies [48, 67-68] including 321 patients undergoing EVAR and 205 receiving open surgery. Need for ICU was significantly more common among patients in the latter group (85% versus 10%), (OR 0.02, 95% CI 0.01 – 0.10; P<0.00001). The between-study heterogeneity was significant (P=0.03, I^2=73%) (Figure 7).

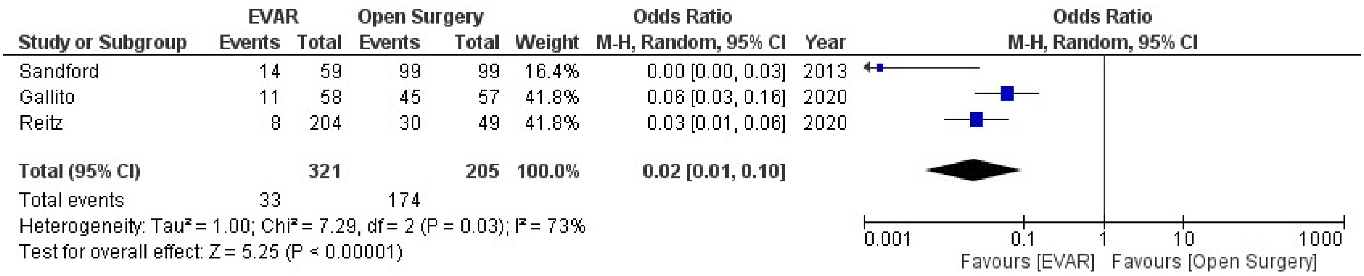

Figure 7. Forest plot of pooled odds ratios for need for ICU.

- Length of ICU stay

Length of ICU stay was reported by 3 studies [47, 66, 68] including 2,157 and 787 patients that received EVAR and open surgical repair respectively with a significantly shorter ICU stay among EVAR cases (MD -1.06 days, 95% CI -1.76 – -0.35; P=0.003). The between-study heterogeneity was significant (P<0.00001, I^2=97%) (Figure 8).

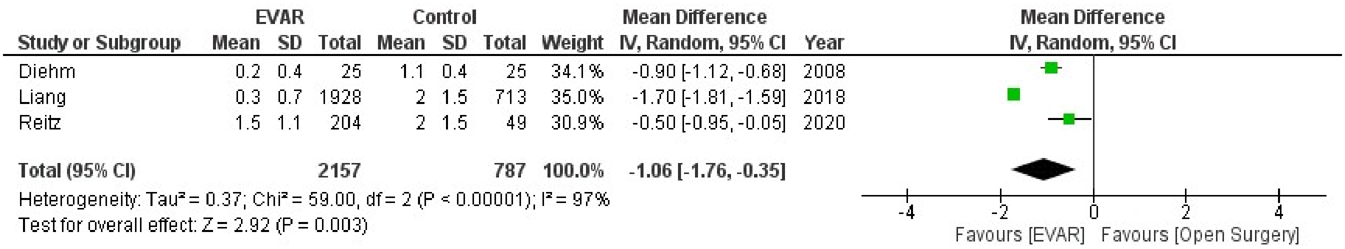

Figure 8. Forest plot of pooled mean differencies for ICU length of stay.

- Peri-operative complications

During the perioperative period, cardiac, respiratory and bleeding complications were significantly more common among patients in the open surgery group compared to those in the EVAR group. Renal complications were similar among the two treatment groups.

Cardiac complications were reported by 6 studies [48-49, 61, 66, 68, 70] including a total of 15,377 EVAR patients and 15,367 open surgery patients (OR 0.22, 95% CI 0.13 – -0.35; P<0.00001, I^2=50%) (Figure 9A). Respiratory complications were reported by 6 studies [48-49, 61, 66, 68, 70] including 15,377 patients undergoing EVAR and 15,367 patients undergoing open surgery (OR 0.17, 95% CI 0.11 – 0.26; P<0.00001, I^2=40%) (Figure 9B). Bleeding complications were reported by 6 studies [47-49, 61, 66, 70] including 15,198 patients undergoing EVAR and 15,343 undergoing open surgery (OR 0.26, 95% CI 0.11 – -0.64; P=0.003, I^2=77%) (Figure 9C). Renal complication were reported by 6 [47-49, 61, 66, 70] studies including 15,198 patients undergoing EVAR and 15,343 undergoing open surgery (OR 0.50, 95% CI 0.15 – -1.68; P=0.26, I^2=82%) (Figure 9D). Regarding complications, studies reported various definitions of them [47-49, 61, 66, 68, 70], summarized in **Table 5.**

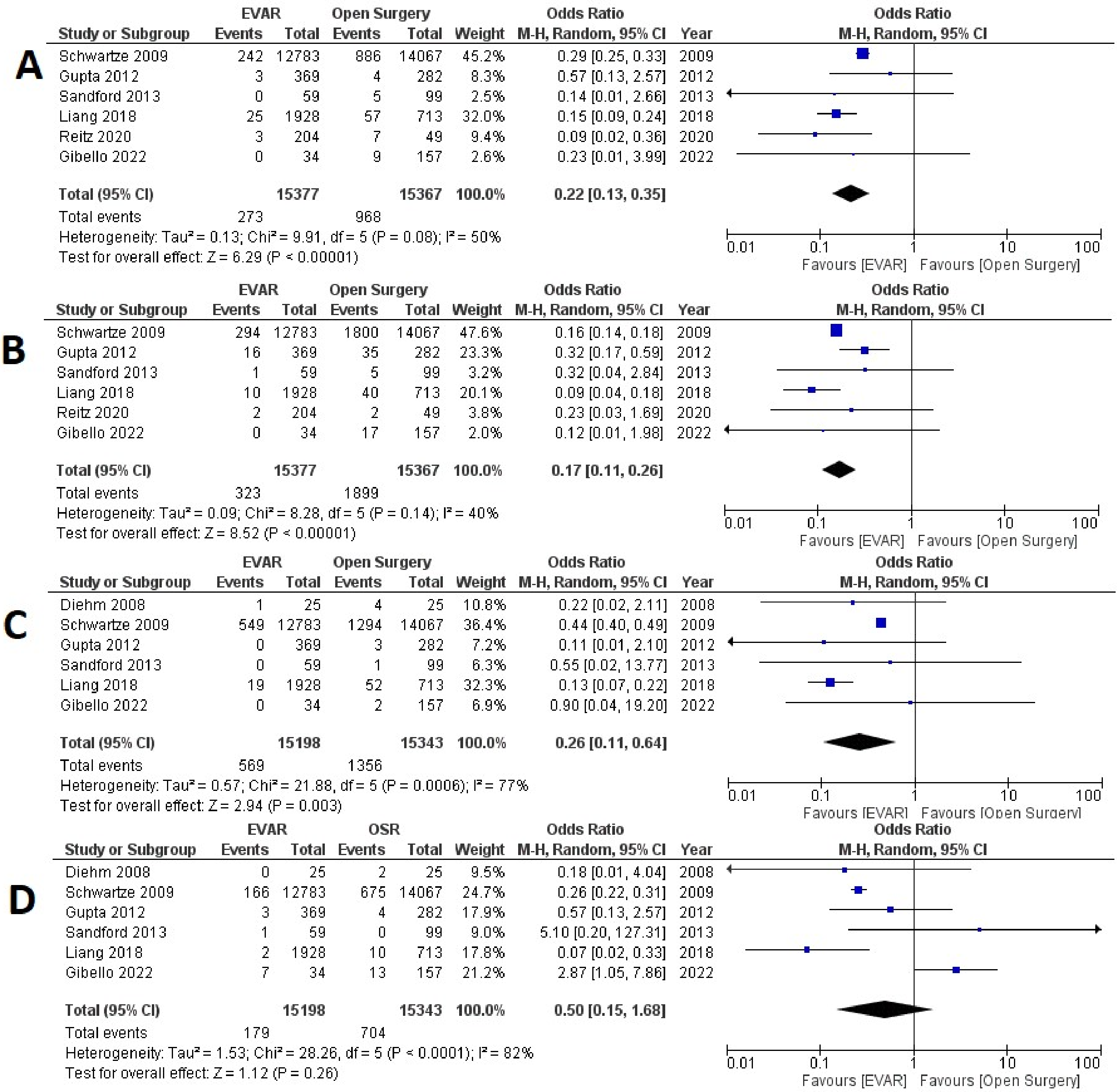

Figure 9. Forest plots of pooled odds ratios for (A) cardiac complications, (B) respiratory complications, (C) bleeding complications, (D) renal complications

Table 5. Clarification of complication definitions in each study [47-49, 61, 66, 68, 70]

Author	Renal Complications	Bleeding Complications	Cardiac Complications	Pulmonary Complications
Diehm	Renal failure	N of patients need for transfusion	NR	NR
Schwarze	Acute renal failure	Bleeding events	Cardiovascular	Pulmonary complications
Gupta	Acute renal failure Renal insufficiency	Postoperative PRBC transfusion > 4 Units	Cardiac arrest, Myocardial infarction	Pneumonia Reintubation Ventilator > 48 h
Sandford	Renal failure	Hemorrhage events	Acute coronary syndrome, Cardiac arrhythmia	Chest infection
Liang	Renal failure	N of patients need for transfusion	Myocardial infarction, Dysrhythmia	Respiratory failure
Reitz	NR	NR	Myocardial infarction, Dysrhythmia	Respiratory failure
Gibello	Acute renal insufficiency	Major bleeding events	Acute myocardial infarction, Atrial fibrillation	Pulmonary complications

Sensitivity analysis

Sensitivity analysis excluding studies of low methodological quality did not result in changes in the direction of effect for any of the outcomes examined, but statistical significance was lost for peri-operative mortality (OR 0.42, 95% CI 0.10 – 1.68; P=0.22) and rate of bleeding complications (OR 0.40, 95% CI 0.08 – 1.96; P=0.26). Exclusion of studies published before 2010, did not change the direction of effect or the statistical significance in any of the outcomes examined.

IV. Discussion

Since the first successful EVAR in the 1990s, EVAR procedures for AAA management have steadily increased [71]. This is a result of the numerous studies including EVAR 1, DREAM, OVER, and ACE [38-41], demonstrating favorable perioperative and short-term outcomes for EVAR compared with those for OSR. Despite the early survival benefit of EVAR over OSR; long-term results were depreciated by a higher risk of both the re-intervention and AAA rupture rate [72]. In the OVER trial, the outcomes of OSR and EVAR were stratified according to age (<70 years) with no difference between OSR and EVAR [40]. In other studies, procedure durability, long life expectancy, and re-intervention rates were considered critical issues for younger patients [73-75]. With the development of AAA screening, an increase of young patients eligible for AAA repair would occur. The main limitation in recommending EVAR in young patients is the risk of stent graft-related complication due to their longer life expectancy.

The systematic literature search highlighted a lack of high-quality evidence on a subgroup of young patients in whom the endovascular approach may confer significant benefit. Data on 30-day mortality indicated that EVAR is advantageous in young patients. The duration of hospital stay varied significantly among reports; however, it was constantly in favor of the endovascular approach, which may be attributed to different discharge policies among hospitals and the lower invasiveness of EVAR. ICU transfer and length of stay in most studies wasn't reported. Despite the small sample, analysis of three studies showed significantly lower number of EVAR patients, who needed ICU, as well as significantly shorter length of stay.

Analysis of the long-term mortality was based on significantly fewer subjects since the larger studies did not provide such information. No statistically significant difference was found, while secondary intervention rates were in favor of OSR groups, without, however, reaching statistical significance.

Peri-operative complications were more common in OSR group, apart from renal complications, which seem to be similar. Peri-operative re-interventions rate analysis, also, showed no statistically significant difference.

The present results may seem paradoxical in the light of previous RCTs that indicated higher complication and re-intervention rates for the EVAR group in follow-up [38-39, 41]. However, in the EVAR-1 trial, secondary procedures beyond 30 days after open surgery were not recorded, and access-related complications, such as hernia and bowel obstruction, were not included [38]. The OVER study [40] compensated for this oversight; 13.5% of patients in the OSR group underwent secondary surgical procedures for hernia or bowel obstruction. Sanford et al. [48] in a retrospective review of patients undergoing elective aneurysm repair at the age of 65 years or younger showed similar 30-day mortality (0 vs. 1%), complications (12% vs. 15%), and re-interventions (14% vs. 7%) in EVAR and OSR groups, with significantly higher rates of cardiac and respiratory complications in the OSR group. Among the OSR group, the complications were generally of a more significant nature including hemorrhage, myocardial infarction, and limb and mesenteric ischemia. Even if EVAR requires more frequent late revisions, those are mainly minimally invasive endovascular outpatient procedures under local anesthesia. On the opposite, OSR-related re-interventions often require general anesthesia and redo-laparotomy particularly for incisional abdominal hernias [60].

There is only one study, among those included in the analysis, which refers to post-operative sexual dysfunction. Talking about younger patients, this is also an important issue. Gallito et al. [67] reported postoperative sexual dysfunction occurred in 37 (32%) patients (EVAR: n =15, 30% vs. OSR: n=22, 49%; P=0.09). There was no difference between EVAR and OSR in terms of erectile dysfunction (EVAR: n=14, 26% vs. OSR: n=8, 18%; P=0.44), but patients with OSR had a statistically significant, higher rate of retrograde ejaculation (EVAR: n=1, 2% vs. OSR: n =14, 31%; P=0.001).

Sirignano et al. [65] suggested that, in an unselected young patient population undergoing elective AAA repair, OSR and EVAR can be performed safely with similar immediate and long-term outcomes. Kontopodis et al. [50] in a large meta-analysis, reported no outcome differences in OSR and EVAR in patients aged 65 years and concluded that age was not the only factor to be considered. The early presentation of the aortic aneurysm may be a marker of aggressive vascular disease [73]. Young patients have also many other comorbidities, pulmonary or cardiovascular. Age is only one of the multiple factors used for risk stratification in

AAA patients. Therefore, it would be reasonable to offer EVAR to this subgroup of patients.

Independent of age, previous work has demonstrated that failure to comply with device Instructions for Use (IFU) is associated with the need for re-intervention following EVAR [76]. A proportion of the studies, analyzed, have reported application of EVAR in cases outside these instructions. Therefore, especially for younger patients who have a low perioperative morbidity and mortality with either EVAR or OSR, strict adherence to device IFU for appropriate aortic neck anatomy may help to minimize the number of patients, who require re-intervention following EVAR.

Among the studies, included in the analysis, there is heterogeneity between the technologies used for EVAR procedure. The use of first-generation stent grafts and early experience of EVAR are significant factors that have resulted in some of the complications reported in EVAR 1, DREAM, and OVER. Technical improvements of EVAR securing the sealing zone more precisely and decreasing stent graft-related complications, call into question the use of these results nowadays [77].

The choice of surgical technique should be discussed with the patient, and multiple factors should be considered when individualizing a treatment plan. These include anatomical suitability for EVAR, physiological reserves and fitness for surgery, life expectancy, patient preference, including sexual function, and anticipated compliance to lifelong surveillance and follow-up. Young patients are usually asking for a quick return to a normal active life. However, they should be informed of the key role of anatomy for long-term success after EVAR.

The current findings should be interpreted in the context of certain limitations. The observational retrospective design of all but one study included in the present review, may introduce risk of bias such as selection bias, recall bias, confounding etc and naturally limits applicability of the results, as displayed in the “very low quality of evidence” obtained for nearly all outcomes. Additionally, different definitions that were used to identify eligible participants across the studies and variability in reporting outcomes, has resulted in the significant heterogeneity observed for most outcomes.

V. Conclusion

Emerging evidence supports beneficial short-term and similar long-term outcomes of EVAR for AAA as compared with OSR in young patients, setting it as a safe alternative, on, however, strict terms. Future randomized trials are necessary, providing separate data on young patients, following strictly the indications for use, regarding EVAR, in order to elucidate the comparative effect of EVAR and OSR in this subgroup of patients.

SUMMARY

Introduction

The advantages of endovascular repair (EVAR) of abdominal aortic aneurysm (AAA) over open surgical repair (OSR) are well described, regarding lower peri-operative morbidity and mortality, reduced length of stay and earlier recovery. In the long term, the low overall mortality associated with open repair surgery has to be balanced against the lower early mortality but questionable durability of EVAR. This fact, along with the higher need for re-interventions, creates controversy on whether EVAR is a suitable technique in younger patients. However, accumulated experience, rapid technological improvement, newer devices, and better patient selection reinforce the assumption that long-term outcomes of EVAR should be improved and at least, similar to OSR. In this study, clinical data on younger patients were analyzed to investigate the results of EVAR versus OSR in younger patients with AAA.

Patients and Methods

The MEDLINE, CENTRAL, and EMBASE databases were searched from January 2000 to March 2022. Peri-operative (30-day mortality and morbidity, length of hospitalization) and long-term outcomes (long-term mortality, re-intervention rate) were compared between young patients undergoing EVAR and OSR. For the meta-analysis of comparative studies, the random effects model was used to calculate combined overall effect sizes of pooled data. Nine observational retrospective studies (8 single-center and 1 multi-center), five administrative databases and one randomized control trial were included in the analysis. Data are presented as the odds ratio (OR) or mean difference (MD) with 95% confidence interval (CI).

Results

EVAR was associated with a decreased risk of 30-day mortality (OR 0.24, 95% CI 0.16 – 0.34; P<0.00001, shorter length of hospitalization (MD -4.44 days, 95% CI 4.79 – 4.09; P<0.00001), significantly lower need of intensive care unit (ICU) (OR 0.02, 95% CI 0.01 – 0.10; P<0.00001) and shorter stay in the ICU (MD -1.06 days, 95% CI -1.76 – -0.35; P=0.003). Moreover, a potential long-term survival benefit of either the procedures failed to reach statistically significant difference (OR 1.00,

95% CI 0.41 – 2.44; P=1.00), whereas the overall re-interventions were more common among EVAR patients but the difference was not statistically significant (OR 1.64, 95% CI 0.90 – 2.94; P=0.11).

Conclusion

Emerging evidence supports beneficial short-term and similar long-term outcomes of EVAR for AAA as compared with OSR in young patients, setting it as a safe alternative, on, however, strict anatomical terms. Future randomized trials are necessary, providing separate data on young patients, following strictly the indications for use, regarding EVAR, in order to elucidate the comparative effect of EVAR and OSR in this subgroup of patients.

ΠΕΡΙΛΗΨΗ

Εισαγωγή- Σκοπός

Τα πλεονεκτήματα της ενδαγγειακής αποκατάστασης (EVAR) του ανευρύσματος κοιλιακής αορτής έναντι της ανοιχτής χειρουργικής αποκατάστασης (OSR), όσον αφορά τη χαμηλότερη περιεγχειρητική νοσηρότητα και θνησιμότητα, τη μειωμένη διάρκεια παραμονής στο νοσοκομείο και την πρώιμη ανάρρωση, έχουν περιγραφεί στη βιβλιογραφία. Μακροπρόθεσμα, η χαμηλή συνολική θνησιμότητα, που σχετίζεται με την ανοιχτή χειρουργική επέμβαση αποκατάστασης πρέπει να εξισορροπηθεί έναντι της χαμηλότερης πρώιμης θνησιμότητας, μεν, αλλά αμφισβητήσιμης αντοχής της ενδαγγειακής επιδιόρθωσης. Το γεγονός αυτό, μαζί με την υψηλότερη ανάγκη για επανεπεμβάσεις, δημιουργεί διαμάχη για το εάν η ενδαγγειακή αποκατάσταση αποτελεί κατάλληλη τεχνική σε νεότερους ασθενείς. Ωστόσο, η συσσωρευμένη εμπειρία, η ταχεία τεχνολογική ανάπτυξη, οι πλέον σύγχρονες συσκευές και η καλύτερη επιλογή ασθενών ενισχύουν την υπόθεση ότι τα μακροπρόθεσμα αποτελέσματα του EVAR θα πρέπει να είναι πλέον βελτιωμένα, και τουλάχιστον παρόμοια με το OSR. Σε αυτή τη μελέτη, αναλύθηκαν κλινικά δεδομένα για νεότερους ασθενείς, με σκοπό τη σύγκριση της βραχυ- και μακροπρόθεσμης έκβασης του EVAR έναντι του OSR σε νέους ασθενείς με ανεύρυσμα κοιλιακής αορτής.

Υλικό και μεθοδολογία

Οι βάσεις δεδομένων MEDLINE, CENTRAL και EMBASE ερευνήθηκαν από τον Ιανουάριο του 2000 έως τον Μάρτιο του 2022. Συγκρίθηκαν τα περιεγχειρητικά (θνησιμότητα και νοσηρότητα 30 ημερών, διάρκεια νοσηλείας) και τα μακροπρόθεσμα αποτελέσματα (μακροχρόνια θνησιμότητα, ποσοστό επανεπέμβασης) μεταξύ νεαρών ασθενών που υπεβλήθησαν σε ενδαγγειακή (EVAR) και ανοικτή χειρουργική αποκατάσταση (OSR) ανευρύσματος κοιλιακής αορτής. Για τη μετα-ανάλυση συγκριτικών μελετών, χρησιμοποιήθηκε το μοντέλο τυχαίων επιδράσεων για τον υπολογισμό των συνδυασμένων συνολικών μεγεθών των ομαδοποιημένων δεδομένων. Εννέα αναδρομικές μελέτες παρατήρησης (8 μονοκεντρικές και 1 πολυκεντρική), πέντε βάσεις δεδομένων και μία τυχαιοποιημένη μελέτη συμπεριλήφθησαν στην ανάλυση. Τα δεδομένα

παρουσιάζονται ως λόγος πιθανοτήτων (OR) ή μέση διαφορά (MD) με διάστημα εμπιστοσύνης 95% (CI).

Αποτελέσματα

Το EVAR συσχετίστηκε με μειωμένη περιεγχειρητική θνητότητα (εντός 30 ημερών) (OR 0,24, 95% CI 0,16 – 0,34, P<0,00001, μικρότερη διάρκεια νοσηλείας (MD -4,44 ημέρες, 95% CI 4,79 – 4,09, P<0,0000), σημαντικά χαμηλότερη ανάγκη για μονάδα εντατικής θεραπείας (ΜΕΘ) (OR 0,02, 95% CI 0,01 – 0,10; P<0,00001) και μικρότερη παραμονή στη ΜΕΘ (MD -1,06 ημέρες, 95% CI -1,76 – -0,35, P=0,003). Επιπλέον, ένα πιθανό όφελος μακροπρόθεσμης επιβίωσης μεταξύ των δύο επεμβάσεων απέτυχε να φτάσει σε στατιστικά σημαντική διαφορά (OR 1,00, 95% CI 0,41 – 2,44, P=1,00), ενώ οι συνολικές επανεπεμβάσεις ήταν πιο συχνές μεταξύ των ασθενών με EVAR αλλά η διαφορά δεν ήταν στατιστικά σημαντική (OR 1,64, 95% CI 0,90 – 2,94, P=0,11).

Συμπέρασμα

Τα αναδυόμενα στοιχεία υποστηρίζουν καλύτερα βραχυπρόθεσμα και παρόμοια μακροπρόθεσμα αποτελέσματα του EVAR για AAA σε σύγκριση με το OSR σε νέους ασθενείς, θέτοντας το ως μια ασφαλή εναλλακτική, ωστόσο, υπό αυστηρούς, ανατομικούς όρους. Είναι απαραίτητες μελλοντικές τυχαιοποιημένες μελέτες, οι οποίες θα παρέχουν ξεχωριστά δεδομένα για νέους ασθενείς, ακολουθώντας αυστηρά τις ενδείξεις χρήσης των συσκευών (IFU), σχετικά με το EVAR, προκειμένου να διευκρινιστεί η συγκριτική έκβαση του EVAR έναντι του OSR σε αυτή την υποομάδα ασθενών.

References

1. *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.*
2. *Jongkind V, Yeung KK, Akkersdijk GJ, et al. Juxtarenal aortic aneurysm repair. J Vasc Surg 2010; 52:760.*
3. *Martin GH, O'Hara PJ, Hertzer NR, et al. Surgical repair of aneurysms involving the suprarenal, visceral, and lower thoracic aortic segments: early results and late outcome. J Vasc Surg 2000; 31:851.*
4. *Johnston KW, Rutherford RB, Tilson MD, Shah DM, Hollier L, Stanley JC. 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 Mar;13(3):452-8.*
5. *McGregor JC, Pollock JG, Anton HC. The value of ultrasonography in the diagnosis of abdominal aortic aneurysm. Scott Med J. 1975 May;20(3):133-7*
6. *Wanhainen A. How to define an abdominal aortic aneurysm--influence on epidemiology and clinical practice. Scand J Surg. 2008;97(2):105-9; discussion 109.*
7. *Wanhainen A, Verzini F, Van Herzeele I, Allaire E, Bown M, Cohnert T, Dick F, van Herwaarden J, Karkos C, Koelemay M, Kölbel T, Loftus I, Mani K, Melissano G, Powell J, Szeberin Z, Esvs Guidelines Committee, de Borst GJ, Chakfe N, Debus S, Hinchliffe R, Kakkos S, Koncar I, Kolh P, Lindholt JS, de Vega M, Vermassen F, Document Reviewers, Björck M, Cheng S, Dalman R, Davidovic L, Donas K, Earnshaw J, Eckstein HH, Golledge J, Haulon S, Mastracci T, Naylor R, Ricco JB, Verhagen H. Editor's Choice - European Society for Vascular Surgery (ESVS) 2019 Clinical Practice Guidelines on the Management of Abdominal Aorto-iliac Artery Aneurysms. Eur J Vasc Endovasc Surg. 2019 Jan;57(1):8-93.*

8. *Sampson A, Norman PE, Fowkes GR, Aboyans V, Song Y, Harrell Jr FE, et al. Estimation of global and regional incidence and prevalence of abdominal aortic aneurysms 1990 to 2010. Glob Heart 2014;9:159e70.*
9. *Sidloff D, Stather P, Dattani N, Bown M, Thompson J, Sayers R, et al. Aneurysm global epidemiology study: public health measures can further reduce abdominal aortic aneurysm mortality. Circulation 2014;129:747-53.*
10. *Svensjö S, Björck M, Gürtelschmid M, Djavani Gidlund K, Hellberg A, Wanhainen A. Low prevalence of abdominal aortic aneurysm among 65-year-old Swedish men indicates a change in the epidemiology of the disease. Circulation 2011;124:1118-23.*
11. *Jacomelli J, Summers L, Stevenson A, Lees T, Earnshaw JJ. Impact of the first 5 years of a national aneurysm screening programme. Br J Surg 2016;103:1125-31.*
12. *Jacomelli J, Summers L, Stevenson A, Lees T, Earnshaw JJ. Results of the first five years of the NHS abdominal aortic aneurysm screening programme in England. Br J Surg 2016;103:1125-31.*
13. *Grondal N, Sogaard R, Lindholt JS. Baseline prevalence of abdominal aortic aneurysm, peripheral arterial disease and hypertension in men aged 65-74 years from a population screening study (VIVA trial). Br J Surg 2015;102:902-6.*
14. *Lee ES, Pickett E, Hedayati N, Dawson DL, Pevec WC. Implementation of an aortic screening program in clinical practice: implications for the screen for abdominal aortic aneurysms very efficiently (SAAAVE) act. J Vasc Surg 2009;49:1107-11*
15. *Ulug P, Powell JT, Sweeting MJ, Bown MJ, Thompson SG. Metaanalysis of the current prevalence of screen-detected abdominal aortic aneurysm in women. Br J Surg 2016;103:1097-104.*
16. *Lederle FA, Johnson GR, Wilson SE, et al. Relationship of age, gender, race, and body size to infrarenal aortic diameter. The Aneurysm Detection and Management (ADAM) Veterans Affairs Cooperative Study Investigators. J Vasc Surg 1997; 26:595*
17. *Lederle FA, Nelson DB, Joseph AM. Smokers' relative risk for aortic aneurysm compared with other smoking-related diseases: a systematic review. J Vasc Surg 2003; 38:329.*

18. *Lederle FA, Johnson GR, Wilson SE, et al. The aneurysm detection and management study screening program: validation cohort and final results. Aneurysm Detection and Management Veterans Affairs Cooperative Study Investigators. Arch Intern Med 2000; 160:1425.*
19. *Jahangir E, Lipworth L, Edwards TL, Kabagambe EK, Mumma MT, Mensah GA, et al. Smoking, sex, risk factors and abdominal aortic aneurysms: a prospective study of 18 782 persons aged above 65 years in the Southern Community Cohort Study. J Epidemiol Comm Health 2015;69:481-8.*
20. *Wahlgren CM, Larsson E, Magnusson PK, Hultgren R, Swedenborg J. Genetic and environmental contributions to abdominal aortic aneurysm development in a twin population. J Vasc Surg 2010;51:3-7.*
21. *Joergensen TM, Christensen K, Lindholt JS, Larsen LA, Green A, Houlind K. Editor's choice e high heritability of liability to abdominal aortic aneurysms: a population based twin study. Eur J Vasc Endovasc Surg 2016 Jul;52:41-6.*
22. *Brady AR, Thompson SG, Fowkes FG, Greenhalgh RM, Powell JT; UK Small Aneurysm Trial Participants. Abdominal aortic aneurysm expansion: risk factors and time intervals for surveillance. Circulation. 2004 Jul 6;110(1):16-21.*
23. *Solberg S, Singh K, Wilsgaard T, Jacobsen BK. Increased growth rate of abdominal aortic aneurysms in women. The Tromsø study. Eur J Vasc Endovasc Surg. 2005 Feb;29(2):145-9.*
24. *Oliver-Williams C, Sweeting MJ, Turton G, Parkin D, Cooper D, Rodd C, et al. Lessons learned about prevalence and growth rates of abdominal aortic aneurysms from a 25-year ultrasound population screening programme. Br J Surg 2018;105:68-74.*
25. *Ullery BW, Hallett RL, Fleischmann D. Epidemiology and contemporary management of abdominal aortic aneurysms. Abdom Radiol (NY). 2018 May;43(5):1032-1043.*
26. *Brewster DC, Cronenwett JL, Hallett JW Jr, Johnston KW, Krupski WC, Matsumura JS; Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery. 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 May;37(5):1106-17.

27. *Gasser TC, Nchimi A, Swedenborg J, Roy J, Sakalihasan N, Böckler D, Hyhlik-Dürr A. A novel strategy to translate the biomechanical rupture risk of abdominal aortic aneurysms to their equivalent diameter risk: method and retrospective validation. Eur J Vasc Endovasc Surg. 2014 Mar;47(3):288-95.*
28. *Rabkin SW. The Effect of Nicotine and Tobacco on Aortic Matrix Metalloproteinases in the Production of Aortic Aneurysm. Curr Vasc Pharmacol. 2016;14(6):514-522.*
29. *Smart CJ, Fisher RK. Influence of sex on expansion rate of abdominal aortic aneurysms (Br J Surg 2007; 94: 310-314). Br J Surg. 2007 Aug;94(8):1041-2*
30. *Powell JT, Greenhalgh RM. Clinical practice. Small abdominal aortic aneurysms. N Engl J Med. 2003 May 8;348(19):1895-901.*
31. *Kent KC. Clinical practice. Abdominal aortic aneurysms. N Engl J Med. 2014 Nov 27;371(22):2101-8.*
32. *Howard DP, Banerjee A, Fairhead JF, Handa A, Silver LE, Rothwell PM; Oxford Vascular Study. Age-specific incidence, risk factors and outcome of acute abdominal aortic aneurysms in a defined population. Br J Surg. 2015 Jul;102(8):907-15.*
33. *Sakalihasan N, Michel JB, Katsargyris A, Kuivaniemi H, Defraigne JO, Nchimi A, Powell JT, Yoshimura K, Hultgren R. Abdominal aortic aneurysms. Nat Rev Dis Primers. 2018 Oct 18;4(1):34.*
34. *De Martino RR, Nolan BW, Goodney PP, Chang CK, Schanzer A, Cambria R, et al. Outcomes of symptomatic abdominal aortic aneurysm repair. J Vasc Surg 2010;52:5-12.*
35. *Williamson AJ, Babrowski T. Current endovascular management of complex pararenal aneurysms. J Cardiovasc Surg (Torino). 2018 Jun;59(3):336-341.*
36. *Katsargyris A, Verhoeven EL. Endovascular strategies for infrarenal aneurysms with short necks. J Cardiovasc Surg (Torino). 2013 Feb;54(1 Suppl 1):21-6.*
37. *AbuRahma AF, Yacoub M, Mousa AY, Abu-Halimah S, Hass SM, Kazil J, AbuRahma ZT, Srivastava M, Dean LS, Stone PA. Aortic Neck Anatomic*

Features and Predictors of Outcomes in Endovascular Repair of Abdominal Aortic Aneurysms Following vs Not Following Instructions for Use. J Am Coll Surg. 2016 Apr;222(4):579-89.

38. *Greenhalgh RM, Brown LC, Kwong GP, Powell JT, Thompson SG, EVAR trial participants. Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1), 30-day operative mortality results: randomised controlled trial. Lancet 2004;364:843e8.*
39. *Blankensteijn JD, de Jong SE, Prinssen M, van der Ham AC, Buth J, van Sterkenburg SM, et al. Dutch Randomized Endovascular Aneurysm Management (DREAM) Trial Group. Twoyear outcomes after conventional or endovascular repair of abdominal aortic aneurysms. N Engl J Med 2005;352:2398e405.*
40. *Lederle FA, Freischlag JA, Kyriakides TC, Padberg Jr FT, Matsumura JS, Kohler TR, et al. Outcomes following endovascular vs open repair of abdominal aortic aneurysm: a randomized trial. JAMA 2009;302:1535e42.*
41. *Becquemin JP, Pillet JC, Lescalie F, Sapoval M, Goueffic Y, Lermusiaux P, et al. ACE trialists. A randomized controlled trial of endovascular aneurysm repair versus open surgery for abdominal aortic aneurysms in low-to-moderate-risk patients. J Vasc Surg 2011;53:1167e73*
42. *Blankensteijn, de Bruin J, Grobbee R, Prinssen M, van Sambeek M, van Schaik TG, et al. Very long-term follow-up (12-15 Years) of the Dutch randomized endovascular aneurysm repair management (DREAM) trial. J Vasc Surg 2016;63. 6S Abstracts 143S.*
43. *Lederle FA, Kyriakides TC, Stroupe KT, Freischlag JA, Padberg FT Jr, Matsumura JS, Huo Z, Johnson GR; OVER Veterans Affairs Cooperative Study Group. Open versus Endovascular Repair of Abdominal Aortic Aneurysm. N Engl J Med. 2019 May 30;380(22):2126-2135.*
44. *Powell JT, Sweeting MJ, Ulug P, Blankensteijn JD, Lederle FA, Becquemin JP, et al. Meta-analysis of individual-patient data from EVAR-1, DREAM, OVER and ACE trials comparing outcomes of endovascular or open repair for abdominal aortic aneurysm over 5 years. Br J Surg 2017;104:166-78.*
45. *Cronenwett JL. Endovascular aneurysm repair: important mid-term results. Lancet. 2005 Jun 25-Jul 1;365(9478):2156-8.*

46. *Altaf N, Abisi S, Yong Y, et al. Mid-term results of endovascular aortic aneurysm repair in the young. Eur J Vasc Endovas Surg 2013; 46: 315–319.*
47. *Diehm N, Tsoukas AI, Katzen BT, et al. Matched-pair analysis of endovascular versus open surgical repair of abdominal aortic aneurysms in young patients at low risk. J Vasc Interv Radiol 2008; 19: 645–651.*
48. *Sandford RM, Choke E, Bown MJ, et al. What is the best option for elective repair of an abdominal aortic aneurysm in a young fit patient? Eur J Vasc Endovas Surg 2014; 47: 13–18.*
49. *Gupta PK, Natarajan B, Fang X, et al. Endovascular repair of abdominal aortic aneurysm does not improve survival versus open repair in patients sixty years or younger. J Vasc Surg 2011; 54: 1540.*
50. *Kontopodis N, Antoniou SA, Georgakarakos E, Ioannou CV. Endovascular vs Open Aneurysm Repair in the Young: Systematic Review and Meta-analysis. J Endovasc Ther. 2015 Dec;22(6):897-904.*
51. *Dua A, Kuy S, Lee CJ, et al. Epidemiology of aortic aneurysm repair in the United States from 2000 to 2010. J Vasc Surg 2014; 59: 1512–1517.*
52. *Torella F. Effect of improved endograft design on outcome of endovascular aneurysms repair. J Vasc Surg. 2004;40:216–221.*
53. *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.*
54. *Antoniou GA, Antoniou SA, Mani K.Enhancing the reporting of systematic reviews and meta-Analyses in vascular surgery: PRISMA 2020. Eur J Vasc Endovasc Surg. 2021;62:664-666.*
55. *(http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).*
56. *https://gdt.gradepro.org/app/. Accessed 8 April 2021 12.*
57. *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.*
58. *DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.*
59. *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.*

60. *Schermerhorn ML, O'Malley AJ, Jhaveri A, Cotterill P, Pomposelli F, Landon BE. Endovascular vs. open repair of abdominal aortic aneurysms in the Medicare population. N Engl J Med. 2008 Jan 31;358(5):464-74.*
61. *Schwarze ML, Shen Y, Hemmerich J, Dale W. Age-related trends in utilization and outcome of open and endovascular repair for abdominal aortic aneurysm in the United States, 2001-2006. J Vasc Surg. 2009 Oct;50(4):722-729.e2.*
62. *Giles KA, Landon BE, Cotterill P, O'Malley AJ, Pomposelli FB, Schermerhorn ML. Thirty-day mortality and late survival with reinterventions and readmissions after open and endovascular aortic aneurysm repair in Medicare beneficiaries. J Vasc Surg. 2011 Jan;53(1):6-12,13.e1.*
63. *Lederle FA, Freischlag JA, Kyriakides TC, Matsumura JS, Padberg FT Jr, Kohler TR, Kougias P, Jean-Claude JM, Cikrit DF, Swanson KM; OVER Veterans Affairs Cooperative Study Group. Long-term comparison of endovascular and open repair of abdominal aortic aneurysm. N Engl J Med. 2012 Nov 22;367(21):1988-97.*
64. *Lee K, Tang E, Dubois L, Power AH, DeRose G, Forbes TL. Durability and survival are similar after elective endovascular and open repair of abdominal aortic aneurysms in younger patients. J Vasc Surg. 2015 Mar;61(3):636-41. doi: 10.1016/j.jvs.2014.10.012.*
65. *Sirignano P, Speziale F, Montelione N, Pranteda C, Galzerano G, Mansour W, Sbarigia E, Setacci C. Abdominal Aortic Aneurysm Repair: Results from a Series of Young Patients. Biomed Res Int. 2016;2016:7893413.*
66. *Liang NL, Reitz KM, Makaroun MS, Malas MB, Tzeng E. Comparable perioperative mortality outcomes in younger patients undergoing elective open and endovascular abdominal aortic aneurysm repair. J Vasc Surg. 2018 May;67(5):1404-1409.e2.*
67. *Gallitto E, Faggioli G, Mascoli C, Spath P, Pini R, Ricco JB, Logiacco A, Sonetto A, Gargiulo M. Long-term Efficacy of EVAR in Patients Aged Less Than 65 Years with an Infrarenal Abdominal Aortic Aneurysm and Favorable Anatomy. Ann Vasc Surg. 2020 Aug;67:283-292.*
68. *Reitz KM, Liang NL, Xie B, Makaroun M, Tzeng E. Inferior Mid-term Durability with Comparable Survival for Younger Patients Undergoing*

Elective Endovascular Infrarenal versus Open Abdominal Aortic Aneurysm Repair. Ann Vasc Surg. 2020 Apr;64:143-150.e1.

69. *Byun E, Kwon TW, Kim H, Cho YP, Han Y, Ko GY, Jeong MJ. Quality-adjusted life year comparison at medium term follow-up of endovascular versus open surgical repair for abdominal aortic aneurysm in young patients. PLoS One. 2021 Dec 2;16(12):e0260690.*
70. *Gibello L, Verzini F, Spalla F, Frola E, Porro L, Peluttiero I, Ripepi M, Boero M, Varetto G. Long-Term Outcomes of Open and Endovascular Abdominal Aortic Repair in Younger Patients. Ann Vasc Surg. 2022 Mar 8:S0890-5096(22)00112-1.*
71. *Lilja F, Mani K, Wanhainen A. Editor's Choice—Trend-break in Abdominal Aortic Aneurysm Repair With Decreasing Surgical Workload. Eur J Vasc Endovasc Surg. 2017; 53(6):811–9.*
72. *Patel R, Sweeting MJ, Powell JT, et al. EVAR trial investigators. Endovascular versus open repair of abdominal aortic aneurysm in 15-years' follow-up of the UK endovascular aneurysm repair trial 1 (EVAR trial 1): a randomized controlled trial. Lancet 2016; 12:2366-74.*
73. *Vallabhaneni R, Farber MA. Part one: for the motion. Young patients with good risk factors should be treated with EVAR. Eur J Vasc Endovasc Surg 2013; 46:614-7.*
74. *Schneider F, Ricco JB. Part two: against the motion. Young patients with good risk factors should not be treated with EVAR. Eur J Vasc Endovasc Surg 2013; 46:618-21.*
75. *Ricco JB, Forbes TL. Trans-atlantic debate: should young patients with good risk factors be treated with EVAR? Eur J Vasc Endovasc Surg 2013; 46:622-3.*
76. *Herman CR, Charbonneau P, Hongku K, Dubois L, Hossain S, Lee K, et al. Any nonadherence to instructions for use predicts graft-related adverse events in patients undergoing elective endovascular aneurysm repair. J Vasc Surg 2018;67:126–33*
77. *Böckler D, Power AH, Bouwman LH, van Sterkenburg S, Bosiers M, Peeters P, Teijink JA, Verhagen HJ; ENGAGE investigators. Improvements in patient outcomes with next generation endovascular aortic repair devices in*

*the ENGAGE Global Registry and the EVAR-1 clinical trial. J Cardiovasc Surg (Torino). 2020 Oct;61(5):604-60*9.

Appendix 1. Search Strategy

Database: Ovid MEDLINE(R) ALL <1946 to April 01, 2022> (9080 items)

Search Strategy:

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1 endovascular aneurysm repair.mp. or exp Endovascular Procedures/ (139171)

2 exp Endovascular Procedures/ or EVAR.mp. (139367)

3 exp Endovascular Procedures/ or endovascular repair.mp. (140954)

4 1 or 2 or 3 (142825)

5 abdominal aortic aneurysm.mp. or exp Aortic Aneurysm, Abdominal/ (25786)

6 AAA.mp. or Aortic Aneurysm, Abdominal/ or exp AAA Domain/ (29037)

7 aortic aneurysm.mp. or exp Aortic Aneurysm/ (65115)

8 5 or 6 or 7 (71569)

9 young*.mp. (1632204)

10 younger.mp. (235635)

11 young patient*.mp. (32580)

12 younger patient*.mp. (29663)

13 65 year*.mp. (98540)

14 70 year*.mp. (54482)

15 60 year*.mp. (80877)

16 age*.mp. (12672757)

17 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (12912011)

18 4 and 8 and 17 (9809)

19 limit 18 to yr="2000 -Current" (9530)

20 limit 19 to (english language and yr="2000 -Current") (9080)

Database: Embase <1974 to 2022 April 07> (10089 items)

Search Strategy:

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1 endovascular aneurysm repair.mp. or exp endovascular aneurysm repair/ or endovascular surgery/ (46009)

2 endovascular aneurysm repair/ or EVAR.mp. (20321)

3 1 or 2 (47374)

4 abdominal aortic aneurysm.mp. or exp abdominal aorta aneurysm/ or exp abdominal aortic aneurysm/ (24851)

5 AAA.mp. (21435)

6 aortic aneurysm.mp. or exp abdominal aorta aneurysm/ or exp aortic aneurysm/ or exp aorta aneurysm/ (51765)

7 4 or 5 or 6 (62245)

8 young*.mp. (1390155)

9 young patient*.mp. (49180)

10 younger patient*.mp. (47287)

11 65 year*.mp. (156643)

12 70 year*.mp. (86982)

13 60 year*.mp. (125320)

14 exp age/ or age*.mp. (11569569)

15 8 or 9 or 10 or 11 or 12 or 13 or 14 (12058903)

16 3 and 7 and 15 (10611)

17 limit 16 to yr="2000 -Current" (10474)

18 limit 17 to (english language and yr="2000 -Current") (10089)

CENTRAL (212 items)

(abdominal aortic aneurysm) AND (open surgical repair OR endovascular repair) AND (young patients OR (60 OR 65 OR 70) years).