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Endoleak type II after Endovascular Aneurysm Repair

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Dissertação de candidatura ao grau de Mestre em Medicina submetida ao
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RESUMO

Introdução: Os aneurismas da aorta abdominal (AAA) têm uma prevalência entre 0,7%[2] nas mulheres e 1,7%[2] nos homens com idade superior a 65 anos. O tratamento pode ser por EVAR ou por cirurgia aberta/laparoscópica. Os Endoleaks tipo II (ETII) são uma das principais complicações do EVAR e surgem em aproximadamente 9%[2] dos indivíduos. Consistem num fluxo de sangue persistente e retrógrado para o interior do saco aneurismático por vasos colaterais patentes (artéria mesentérica inferior e/ou artérias lombares). Desconhece-se ainda a sua história natural e não há consenso relativamente ao tratamento mais eficaz: conservadora ou intervenção (Tx). Dentro das técnicas endovasculares, as mais utilizadas são a Embolização Transarterial (TAE) e a Embolização Percutânea Direta do Saco aneurismático (DPSI). Nas últimas décadas, a embolização profilática peri-operativa também têm vindo a ganhar terreno na gestão de ETII. Em vários estudos comprovou-se que diminui a incidência de ETII após EVAR em indivíduos com fatores de risco para desenvolver ETII. A melhor abordagem aos ETII ainda hoje não é consensual e é motivo de discórdia entre a comunidade científica.

Objetivos: Face às incertezas relativas à gestão e tratamento do ETII, propomo-nos a realizar uma revisão sistemática com meta-análise das diferentes terapêuticas. Este artigo tem como objetivo avaliar se há benefício a curto e longo prazo de uma abordagem em detrimento de outra, qual a mais eficaz e a que tem associado menor risco de complicações.

Métodos e Resultados: A pesquisa dos artigos foi realizada na plataforma "PubMed" e a sua seleção foi realizada de acordo com a metodologia Prisma[3]. Dos 379 artigos, 11 foram selecionados tendo em conta os critérios de inclusão e exclusão pré-definidos. Foram criados 3 grupos de comparação: Conservador vs. Intervenção; Embolização Transarterial vs. Embolização Percutânea Direta do Saco e Tratamento Profilático vs. EVAR clássico. O outcome principal é a resolução de ETII durante o follow-up após tratamento primário /tratamento profilático. O outcome secundário consiste nas complicações diretamente associadas. De acordo com os resultados, o tratamento profilático (PT) diminui o risco de ETII (RR= 1,90; 95% CI [1,14;3,15]; Ztest=2,48 (P=0,01); I^2=91%). Não se verificou diferença na eficácia entre a abordagem conservadora e Tx, e DPSI tem 1,42 vezes mais probabilidade de resolver ETII comparativamente ao TAE (95% CI [0,83;2,43]; Ztest=1,29 (P=0,20); I^2=0%).

Conclusão: A embolização profilática tem um efeito positivo no prognóstico dos indivíduos submetidos a EVAR pois diminui o risco de ETII. Relativamente ao tratamento do ETII, serão necessários mais estudos para esclarecer qual a abordagem terapêutica mais eficaz e com melhores resultados.

Palavras-chave (*MeSH*): type II endoleak; EVAR; abdominal aorta; treatment and outcome

ABSTRACT

Introduction: Abdominal aortic aneurysms (AAA) have a prevalence of 1,7%[2] in men and 0,7%[2] in women over 65 years. They can be repaired either by endovascular- EVAR - or conventional surgery. The type II Endoleaks (ETII) are one of the main complications of EVAR and appear in approximately 9%[2] of individuals. They consist of persistent and retrograde blood flow into the aneurysmal sac through patent collateral vessels[2]. Currently, the natural evolution is not fully understood, and there is no consensus regarding the most effective therapy: conservative or treatment/intervention (Tx). The best approach of ETII is cause of disagreement within the scientific community.

Objectives: Given the uncertainties related to the management of ETII, a systematic review with a meta-analysis on the topic was accomplished. The aim was to assess whether there is a short- and long-term benefit of one approach over another, effectiveness, and low rate of complications.

Methods and Results: The search was conducted in the "PubMed" platform. Papers were selected according to the Prisma[3] method regarding the inclusion and exclusion criteria. Of the 379 articles, 11 were selected. The studies were separated into three comparison groups: Conservative vs. Intervention; Transarterial Embolization vs. Direct Percutaneous Sac Injection, and Prophylactic Treatment (PT) vs. EVAR classic (No PT). The main outcome was the resolution/absence of ETII during follow-up after primary treatment / prophylactic treatment. The secondary outcome consists of complications directly associated. According to the results, Prophylactic embolization decreases the risk of ETII (RR= 1,90; 95% CI [1,14;3,15]; Ztest=2,48 (P=0,01); I^2=91%). There was no difference in effectiveness between the conservative vs treatment approach, but when treated, Direct Percutaneous Sac Injection (DPSI) are 1.42 times more likely to resolve ETII compared to Transarterial Embolization (TAE) (95% CI [0,83;2,43]; Ztest=1,29 (P=0,20); I^2=0%).

Conclusion: Prophylactic embolization has a positive effect on the prognosis of individuals undergoing EVAR because it decreases the risk of ETII. Regarding the treatment of ETII, further studies are necessary to clarify which therapeutic approach is the most effective and with the best results.

Keywords (*MeSH)*: type II endoleak; EVAR; abdominal aorta; treatment and outcome

LIST of ABBREVIATIONS

AAA - Abdominal Aortic Aneurysms
CASP - Critical Appraisal Skills Program
CEUS - Contrast-enhanced ultrasound imaging
CI - Confidence Interval
CS - Clinical Success
CTA - Computed Tomography Angiography
DPSI - Direct Percutaneous Sac Injection
DUS - Duplex Ultrasound
ESVS - *European Society for Vascular Surgery*
ETII - Type II Endoleaks
EVAR - Endovascular Aneurysm Repair
IMA - Inferior Mesenteric Artery
LA - Lumbar Arteries
MeSH - Medical Subject Heading
NA - Not Applicable
NBCA - n-butyl-2-cyanoacrylate
NR - Not Reported
OS - Open/Laparoscopic Surgery
PT - Prophylactic Embolization
RD - Risk Difference
RR - Risk Ratio
SVS - *Society of Vascular Surgery*
TAE - Transarterial Embolization
Tx - Medical Intervention/treatment

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INTRODUCTION

Abdominal Aortic Aneurysms (AAA) are the most frequent aneurysms, defined as pathological dilations of 3cm or more (or a diameter greater than 50% of the expected) with fusiform or saccular shape[2]. Atherosclerosis is the primary cause, leading to erosion of the tunica media with rupture of the elastic fibers, resulting in the weakening of the wall and consequent dilation. The main risk factors for the growth and rupture of AAA are smoking and hypertension. Despite the aging population, its incidence has decreased by 20-50%[2] in developing countries in the last 20 years. Currently, the prevalence is 1,7%[2] in men and 0,7%[2] in women over 65 years. Before the age of 55-60, the incidence is virtually insignificant. At the time of diagnosis, about 75%[4] of AAA are asymptomatic and often diagnosed incidentally in complementary diagnostic tests requested for other purposes. Less often, they may manifest in the form of abdominal/lumbar pain or hemodynamic shock caused by aneurysm rupture. Tendentially AAA have a progressive growth, increased in 16%[2] if smoking habits are present. When they reach a diameter of 6cm, annual mortality increases to 50%[2]. Conservative care and periodic monitoring in asymptomatic individuals with a diameter <5mm or annual growth < 10mm are recommended[2]. Repair of AAA can be with one of two techniques: (1) open surgery or (2) endovascular surgery. Recently, Endovascular Aneurysm Repair (EVAR) is overcoming the conventional surgery, as has a lower morbidity and mortality rate and a faster recovery (in EVAR, the rate is about 1%[2], and in open surgery, 3-4 times higher[2]). But the greater need for long-term reintervention outweighs the EVAR's short-term benefits[5,6,8]. Endoleaks are one of the most common complications of EVAR (60%[9]), often associated with a larger sac diameter and the need for reintervention[2]. There are five types of endoleaks: type I, II, III, IV, and V[2]. This systematic review, with meta-analysis, will focus solely on type II. They are the most common form of endoleak and one of the most common causes of long-term complications following AAA endovascular repair.

Approximately 9%[10] of individuals undergoing EVAR develop type II endoleak (ETII). They consist of retrograde blood flow into the aneurysmal sac through collateral vessels[2]. This process contributes to a continuous increase in aneurismatic pressure, a resulting increase in its size, and the risk of rupture. The inferior mesenteric artery (IMA) and the lumbar arteries (LA) are the vessels mostly associated[9,10]. Patency and the diameter of these vessels are the major risk factors for developing short and long-term ETII[11]. The higher the number of patent vessels, the more likely to grow ETII[12]. Uncontrolled systolic pressures also favor faster endoleak growth[13].

Presently, the natural evolution of the ETIIs is not fully understood by the scientific community. However, they are relatively benign entities[2] with a low risk of rupture (<1%[2]). Approximately 50%[10] solve spontaneously after six months[14]. The eligibility criteria for ETII treatment are not consensual. The most recent *Society of Vascular Surgery[4](SVS)* guidelines (2018) recommend surgical procedures when there is an aneurysmal sac growth >5mm, and/or an ETII that subsists for more than six months[4]. On the other hand, the current guidelines (2019) of the *European Society for Vascular Surgery (ESVS)[2]* recommend intervention of ETII with ≥10mm or with an enlargement of 1mm or more between follow-ups[2]. In symptomatic cases, most centers choose to treat the Endoleak. The options for ETII treatment are Transarterial Embolization (TAE), Direct Percutaneous Sac Injection (DPSI), transcaval embolization, and laparoscopic/open surgery for sacotomy and ligation of the nourishing arteries (OS)[2,4]. Within endovascular techniques, DPSI and TAE are the most popular.

There is no consensus on which is the best approach to ETII[8,10]. The decision between treating or monitoring depends on several factors: ETII characteristics (sac growth >5mm and/or duration > six months[4]), patient comorbidities, and vascular anatomy[8]. The literature describes postoperative complications in about 2-9%[15,16] of the individuals undergoing intervention: cardiac complications (atrial fibrillation, acute myocardial infarction), mesenteric ischemia, sepsis, vascular perforation. Endovascular procedures have lower morbimortality when compared with open/laparoscopic surgery in the short term. The latter is overly invasive and reserved for endovascular therapy failure (persistent ETII or progressive aneurysmatic expansion)[17]. However, in the long term, the endovascular intervention has a higher rate of therapeutic failure[9]. Almost 45%[9] of the individuals undergoing endovascular therapy require at least one reintervention due to ETT recurrence or therapeutic failure (a progressive increase of the sac)[9].

Within the most common endovascular techniques — TAE and DPSI — there is no consensus on the most effective with best outcome. In general, TAE is more frequently used. In cases of anatomical incompatibility, technical or clinical failure[7], most surgeons resort to DPSI as a second-line treatment. Despite the controversy, several studies demonstrate that DPSI has a higher technical and clinical success when compared to TAE[14,17,18]. Incomplete embolization of the vessel(s) responsible for the ETII and the inability/difficulty in reaching the patent vessel during TAE may be responsible for these results. The main complication of this technique is mesenteric ischemia and retroperitoneal hematoma caused by collateral vessel rupture. DPSI consists of a non-selective embolization of the aneurysmal sac by the percutaneous puncture[2]. This method has higher efficiency and lower risk of intestinal ischemia and retroperitoneal hematoma[7]. Despite the advantages, its safety and efficiency is dependent on the operator and vessel anatomy (puncture

path and adjacent structures[18]), and it can be impractical in some cases. In both techniques, the most-used embolization materials are coils and embolic glues[2,4].

Patients with occluded arteries have a lower incidence of ETII (13-19%[12] vs. 32-42%[12] with patent arteries). These results led several investigators to suggest the perioperative prophylactic embolization (PT) of these vessels as preventive measure. Studies demonstrated that this technique is associated with a lower risk of reinterventions. However, this procedure can carry complications[19]. Many authors have been trying to determine which patients benefit from prophylactic embolization and what anatomical features are associated with a greater risk of developing ETII. Despite the divergences, patency of the Inferior Mesenteric Artery (IMA) and/or Lumbar artery(ies) (LA) ≥2mm are high-risk factors unanimously accepted.

However, there are still many uncertainties related to when to treat and which method to choose. The aim of this study is to carry out a systematic review with meta-analysis of the different approaches to ETII, to assess whether there is a long-term benefit of one over the other.

MATERIALS AND METHODS

Database and Search Strategy

The following Systematic Review with Meta-analysis was performed according to the PRISMA[3] methodology (*Figure 1*) - "Preferred Reporting Items for Systematic Review and Meta-Analysis statement"- with search in the "PubMed" database. The last search was carried out on 1/10/2020 under the following search terms: ("type II" OR "type 2" OR "type IIa" OR "type 2a" OR "type IIb" OR "type 2b") AND ("endoleak") AND ("EVAR" OR "abdominal aortic aneurysm" OR "abdominal aneurysm") AND ("treatment" OR "repair" OR "correction" OR "management"). 381 articles were evaluated.

Selection of Studies and Eligibility Criteria

Randomized, non-randomized, cohort, and observational studies (with and without a control group) published in the last five years and in English language were included.

Inclusion criteria were: i) patients that developed ETII after EVAR; ii) patients who received perioperative prophylactic therapy; iii) papers with a population ≥ of five patients and extractable statistical data. Articles that include other types of endoleaks, different EVAR techniques, prophylactic embolization (PT), and intervention (Tx) in which it was possible to extract the intended outcome, were included.

Exclusion criteria were: i) bibliographic review articles or clinical cases; ii) studies carried out on an animal model; iii) unpublished articles; iv) studies that included treatment of aneurysms other than the infrarenal abdominal aorta; v) articles whose differentiation between types of endoleak was not comprehensible/possible; vi) articles that include variations of the EVAR technique (fEVAR and chEVAR); vii) articles that included preventive embolization techniques in vessels other than IMA or LA; viii) articles without extractable statistical data and/or without the statistical value.

Data Extraction and Outcomes

The extracted data included study type, study location, date, original cohort, demographics (total number of participants, age, sex, number of ETII), embolization material, pre-operatory, imaging technique, follow-up method, protocol, and extension. Concomitantly, the number of participants submitted to the different approaches to ETII (conservative vs. intervention vs. prophylactic) and the type of intervention (TAE vs. DPSI), when applicable, were accounted. The authors calculated the clinical success (considering the resolution/absence of ETII during follow-up) and screened the complications derived from the different approaches to ETII. The information retrieved from the text, tables, and images is in *Tables I* and *II*. *Table I* includes the studies of the different ETII treatment approaches. *Table II* comprehends the papers concerning prophylactic embolization in selected patients with high-risk factors for developing ETII. The abbreviation NR ("Non-Reported") identifies non-extractable data. The studies divide into three comparison groups:

- Prophylactic vs. Non-Prophylactic Treatment
- Conservative Management vs. Intervention
- Transarterial Embolization vs. Direct Percutaneous Sac Embolization

While structuring the article, the primary and secondary outcomes were determined.

The primary outcome is:

- ETII resolution after primary treatment / Absence of ETII during follow-up after prophylactic treatment.

The secondary outcome is:

- Complications directly related to the approach.

For assessing the primary outcome, cases not reported as a failure and/or recurrence were described as a success. The authors only reviewed the primary interventions. Statistical data related to reinterventions were excluded. Interventions executed after clinical failure were not numbered as primary treatments.

Only the complications directly related to the approach/technique used were acknowledged while assessing the secondary outcome. The authors considered "non-event" (absence of complications), in information absence.

Statistical Analysis

The data were entered in Microsoft Excel[20] (Microsoft Corporation, Redmond, Washington) by the author M.J.O.

To quantify the “Risk Ratio” and “Risk Difference”, the authors used RevMan® version 5.4 (Cochrane Collaboration Review Manager)[21,22]. The proportion was determined by using “Freeman-Tukey proportion”[23] (double arcsine proportion) and “Random Effects Model” in MedCalc®. The confidence interval (CI) is 95% and the level of significance is p = 0.05. The heterogeneity was calculated using the I^2 statistical test and classified (according to *Higgins and Thompson* [24]) as low (25%), moderate (50%), and high (75%). The “Chi2 statistical test” and the “df” were also calculated to assess the heterogeneity and sample error[25].

Statistical analysis for each outcome and between the different ETII management are independent.

The extracted data for the meta-analysis is discrete (discontinuous) and in the numeral.

For each type of approach, the clinical success (CS) was expressed as a percentage. The clinical success of PT was calculated as: no. of individuals without ETII who underwent PT / Total no. of individuals who underwent PT. To assess the CS of the different ETII management methods,

we used the following calculous: number of ETII resolved / total number of patients undergoing X, with X being the type of therapy under study.

To calculate the "Risk Ratio" (RR) and "Risk Difference", the statistical method used was the "Mantel-Haenszel" with " Random-Effects models"[22]. RR[25,26] was used to calculate the primary outcome. To evaluate the secondary outcome, the authors used the "Risk Difference" (RD)[25].

Risk of Bias

The global quality and risk of bias of the included papers were assessed with the "CASP Cohort Study Checklist"[1] . Nine out of the twelve original items were selected. The remaining three were excluded for not being adequate or for requiring an open answer - *Figure 2 and Table III*. Each topic was rated as high (Red (-)), unclear (Yellow(?)), and low (Green (-)) risk of bias. The overall bias of the studies was defined as High Risk (HR) if ≥2 topics classified as high risk (Red (-)) or >3 as unclear[27]. The further were classified as low risk (LR) of bias[27].

RESULTS

Included Studies

The detailed selection strategy of the articles is in the diagram in *Figure 1*. There were 379 articles after excluding the duplicates. First, the selection was based on abstract and title. 61 papers were included in the first phase. After full reading, only 11 articles[7,8,11,28-35] were eligible for inclusion in this review with meta-analysis. The reasons for excluding the 50 articles are detailed in the diagram in *Figure 1.*

Study Characteristics and Demographic Data

The 11 articles were published between 2016 and 2020. Three resulted from a multicentric collaboration[11,30,32], and the remaining eight were conducted in a single center. Most studies consist in a retrospective analysis. The ETII ratio after EVAR (included in the study) is 54.27% (95% CI [38,38;69,71]; I2= 96,41%, P <0,0001). The mean age ranged from 70.1 to 86 years. From the studies

in which it was possible to extract information about the gender of the participants, there is a clear preponderance of males - *Table I and II*

A complete description of the included studies will be conducted in more detail within the different comparison groups (to better interpret the results).

I. Prophylactic vs. Non-Prophylactic Treatment

To evaluate the primary and secondary outcome in the prophylactic embolization comparison group, the authors selected six articles[11,28,29,32-34] conducted between 2007 and 2019 (*Table II*). The demographic data (age, sex, comorbidities) was not statistically different between the compared groups. The group not submitted to prophylactic embolization is composed of a historical cohort.

In five papers - *Mascoli et al[28], Piazza et al[11], Dosluoglu et al[32], Aoki et al[29]* and *Vaillant et al[33]* - the PT group includes individuals with high-risk factors and eligibility criteria to undergo prophylactic embolization. Despite few differences, the inferior mesenteric artery patency ≥2mm from and/or ≥1 patent lumbar artery are transversal eligibility criteria (*Table II*). The group not submitted to prophylactic embolization is composed of a historical cohort. It includes individuals with the same risk factors/eligibility criteria subjected to EVAR before preventive embolization implementation in the center(s) in question.

The literature describes different endovascular techniques: non-selective embolization of the sac and/or selective embolization of the patent vessels. In all studies, endovascular access was via femoral approach - *Table II.*

The follow-up method and protocol were different (*Table II*). The average follow-up time varied between 6.5 and 57 months, except for *Aoki et al[29]*, in which the average follow-up time was seven days (until hospital discharge).

Clinical success (CS) was defined as the absence of ETII or no need for post-EVAR re-intervention (due to ETII) during the follow-up, in most cases.

The studies are similar to each other except for *Ohba et al[34],* which only included patients who underwent urgent EVAR due to aneurysm rupture. There is no definition of risk factors/eligibility criteria, and the execution of PT depended on the surgeon's experience and familiarity with the technique. In *Ohba et al[34]*, the clinical success depended on hemodynamic stability and the absence of ETII after EVAR.

II. Conservative Management vs. Intervention

To compare the conservative approach vs. intervention, the authors used statistical data from five studies[7,8,31,32,35] (*Table I*).

This comparison group is composed of 364 individuals with ETII. Patients who did not respect the follow-up protocol predefined by the center were excluded. In *Haq et al*[8], exclusion criteria are not described. The demographics of the comparison groups (conservative vs. intervention) did not differ statistically from each other in all the articles included. The average age of the individuals (who developed ETII) varies between 70.1 and 79.5 years. It was impossible to calculate the proportion of male/female due to missing data (*Table I*).

The eligibility criteria for ETII intervention are described in *Table I*.

The evaluated therapies were intervention (TAE, DPSI, and open/laparoscopic surgery) and the conservative approach. In most cases[7,8,32,35], TAE was the most widely used endovascular technique.

Ribé et al[31] was the only study in which the embolization material used were the same for all patients. On the others, it is not explicit which materials and under what circumstances were used at the expense of others.

The average surveillance period ranged between 19 and 48 months. The follow-up protocol and the imaging methods used are detailed in *Table I*. *Haq et al*[8] does not characterize the follow-up protocol.

In several studies, the outcome is screened at a different time in the follow-up, depending on the ETII approach. These variations can cause heterogeneity and variability in outcome values.

In *Pineda et al*[35], an aneurysmal sac rupture was described in a conservatively managed ETII. The remaining studies did not report other complications.

III. TAE vs. DPSI

To assess the outcome, the authors selected patients with eligibility criteria for ETII intervention who underwent primary TAE or DPSI. The comparison group includes three studies (*Carrafiello et al*[7], *Haq et al*[8] and *Moulakakis et al*[30]) conducted between 2006 and 2015. *Moulakakis et al*[30] is the only multicenter study. Demographic data and the original cohort are shown in *Table*

I. The demographic and clinical characteristics of the compared groups did not show statistically significant differences between them in all the items included.

In *Moulakakis et al*[30] and *Haq et al*[8], the eligibility criteria are reported. In the first, asymptomatic individuals with a sac extension > of 5 mm or with symptomatic ETII are submitted to endovascular repair. In *Haq et al*[8], an aneurismatic growth ≥5mm is the only intervention criteria described (*Table I*).

The follow-up imaging technique and the protocol are described in *Table I*. The mean follow-up time was 31.2-37.2 months.

The first-line endovascular technique varied between studies. In *Carrafiello et al*[7] and *Haq et al*[8], the first line technique was TAE. DPSI was performed only in cases of technical or clinical failure. In *Moulakakis et al*[30], the embolization technique depended on the vessel nourishing the ETII: (1) if the IMA was at the origin of the ETII, TAE was chosen; (2) if LA(s) were responsible for ETII, the surgeons opted for DPSI, except if high proximity between vena cava and the puncture site. On these occasions, they opted for TAE. Most patients were asymptomatic at the time of the endovascular intervention.

The definition of CS- the absence of ETII during follow-up - was similar between studies and is consistent with the outcome defined in this meta-analysis.

Moulakakis et al[30] reported a self-limited psoas hematoma after TAE, that resolved spontaneously. There were no other described complications.

Primary Outcome - Results

I. Prophylactic vs. Non-Prophylactic Treatment

The comparison group between PT vs. EVAR Classic (No PT) includes seven studies[11,28,29,32-34,36] and 414 patients. Of these, 178 underwent PT, and 79% did not develop ETII during the follow-up. In comparison, 50% of individuals who did not undergo prophylactic embolization developed ETII during the surveillance period. After a preliminary analysis of the studies, the following results were obtained: RR of 1.90 (95% CI [1.14; 3.15]; Ztest = 2.48 (P = 0.01); I2 = 91%; Chi2 = 56.55 (P <0.05)), which translates into a 90% decrease in the probability of developing ETII during surveillance. We can then say prophylactic embolization has a protective effect compared to the classic EVAR – *Figure 3.*

Taking into consideration the high heterogeneity (I^2=91%; Chi^2=56,55 (P<0,05)) and the results obtained, the authors did a sensitivity analyzes and a division into subgroups.

A sensitivity analysis was conducted to assess the follow-up impact on the prophylactic embolization efficacy. In *Piazza et al*[11], the outcome was considered only 24 months after PT, so it was excluded. In this case, PT has a worse prognosis when compared to the group not submitted to prophylactic embolization. In the remaining studies (outcome <24 months), RR = 2.18 (95% CI [1,80;2,62]; Ztest=8,11 (P<0,05); I^2=0%; Chi^2=2,66 (P=0,62)). According to this result, PT has a superior advantage over the classic EVAR, which is similar the global analysis result – *Figure 3* and *4*.

The different embolization techniques and their impact on the outcome were also explored. The papers were split into three subgroups: (1) non-selective embolization of the aneurysmal sac (*Piazza et al*[11], *Dosluoglu et al*[32] and *Ohba et al*[34]); (2) selective embolization of the patent arteries (*Aoki et al*[29] and *Vaillant et al*[33]) and (3) both techniques (*Mascoli et al*[28]) - *Figure 5.* When RRs are compared to each other, the most successful procedure consists of combining both techniques (RR= 2,93; 95% CI [1,74;4,94], Z test= 4,05). When applied individually, the selective embolization of IMA and/or LA (RR= 2,20; 95% CI [1,73;2,81], Z test= 6,38; P<0,05; I^2=0%; Chi^2=0,28 (P=0,59) has a better prognosis than the non-selective one (RR= 1,36; 95% CI [0,75;2,49], Z test= 1,01; P<0,05; I^2=82%; Chi^2=11,03 (P=0,04)) - *Figure 5*. None of the techniques presented an absolute higher risk of complications in any of the outcomes (primary or secondary).

II. Conservative Management vs. Intervention

98 (26.9%) of the 364 primary ETII underwent intervention, and the further 266 (73.1%) resolved conservatively. 57.1% of the ETII intervened had resolved. Of the ETII managed conservatively, 62.8% resolved spontaneously. The following results were obtained after meta-analysis: RR = 1.00 (95% CI [0.72;1,38]; I^2= 69%; Chi^2=12,87 (P=0,01) Z test= 0 (P=1,00)). The RR (resolution of ETII) is not statistically significant (P>0,05)[22,25] and the heterogeneity is considerable (I^2= 69%) – *Figure 6.* Thus, we cannot prove that one approach is better when compared to the other.

III. TAE vs. DPSI

The comparison group juxtaposing the two endovascular techniques - TAE and DPSI - has three studies[7,8,30]. It includes 50 individuals, of which 30 underwent TAE. The further 20 submitted to DPSI. Of the ETII repaired by TAE, 33.3% resolved after the first intervention. In addition, DPSI (first intervention) clinical success rate was 50%. The RR (ETII resolution) was 1.42 (95% CI [0,83;2,43]; Ztest=1,29 (P=0,20); I^2=0%; Chi^2=1,74 (P=0,42)). According to the result, patients undergoing DPSI are 1.42 times more likely to resolve ETII and have a better prognosis when compared to TAE[25]. The RR is not statistically significant (P> 0.05) and the comparison group has no heterogeneity (I^2=0%; Chi^2=1,74 (P=0,42)) – *Figure 7.*

Secondary Outcome - Results

There were no significant differences in the absolute risk of complications between the approaches in the three comparison groups. None is objectively safer than the other, and the risk of complications is not a criterion for differentiation and a viable choice parameter.

In the three groups, RDs are not statistically significant, and the studies are homogeneous between each other - *Figure 8,9* and *10.*

Risk of Bias

Overall, the risk of bias was high – *Figure 2.*

The principal source of bias was the follow-up time. Two of the selected articles[8,34] did not report a surveillance protocol, and four[7,33-35] had different follow-up times between the compared therapies. *Aoki et al[29]* has a specially short follow-up time compared to the others (7 days). The difference in follow-up techniques and protocols also increased the risk of bias – *Figure 2.*

The primary outcome was not assessed at the same point of the follow-up in all papers, which can be a predominant cause of heterogeneity. In two studies[28,33], the absence of ETII was estimated 12 months after PT. In another[29], were accounted for after 7 days of follow-up, and in *Piazza et al[11]* 24 months after PT. In the others, the outcome was rated at the end of the follow-up - *Tables I and II*.

In some cases, eligibility criteria for the different types of interventions were not clear. Between studies, the techniques held performance by distinct doctors in various hospitals, which is relevant to highlight. The same was true, sometimes, within the same article.

The vast majority of articles described confounding factors (as materials, techniques, anatomy, ...). However, the statistical impact of these in the many approaches has not always been made explicit.

In the studies in *Table II*, except for *Ohba et al*[34], the comparison groups (PT vs. not submitted to PT) correspond to different chronological periods, which may raise the bias of results.

DISCUSSION

Despite the arising research in the area, the impact of ETII in the short and long term is not fully understood[28]. Studies have shown that ETII predispose to EVAR failure and the need for reintervention[29,37]. Although there are some guidelines for ETII treatment, the optimized management of this pathology is not consensual[38]. Thus, is necessary to create a treatment algorithm with the best response rate.

To achieve the most favorable long-term prognosis, several authors suggest ETII prophylactic embolization[29,39]. According to the current literature, PT has a higher efficacy rate (significant reduction in ETII and the need for intervention during follow-up[32]) when compared with classic EVAR[40]. However, this technique was not supported by the scientific community as expected. It occurred due to several factors: (1) procedure risks and lack of experience; (2) extended intraoperative time; (3) extra intraoperative contrast volume; (4) added costs to EVAR; (5) technical failure (the main vessel is not detected and embolized)[40].

The results suggest that PT positively influences the prognosis in patients with risk factors for developing ETII (patent IMA ≥2mm and/or ≥1 patent LA) with a 90% decrease (95% CI [1,14;3,15]; Ztest=2,48 (P=0,01); I^2=91%; Chi^2=56,55 (P<0,05)) of the risk of developing ETII during follow-up (with no increase in associated complications), in the studied cohort. However, this trend does not occur uniformly during the follow-up. *Piazza et al*[11] (outcome calculated 24 months after PT), prophylactic embolization showed no clinical benefit (absence of ETII), and the results favored, though lightly, the classic EVAR – *Figure 4*. These results suggest that the therapy may retard, but not prevent, the onset of ETII. Further studies are needed in the area to prove this theory.

Non-selective prophylactic embolization (uniform distribution of coils within the sac) is less complex and less expensive than the selective embolization of the nourishing arteries (LA and IMA)[28,41]. After subgroup analysis, the latter proved larger effectiveness when compared to the first one. However, in *Vaillant et al*[33], the patent LA(s) submitted to prophylactic embolization originated ETII, which goes against the data obtained in the present meta-analysis.

A significant disadvantage of this procedure is the artifacts detected in the follow-up Computed Tomography Angiography (CTA) (created due to prophylactic embolization), described throughout some of the studies[11,28,32,34]. These decrease the image quality and increase the number of false negatives in ETII surveillance. In addition, they constitute a significant risk of bias that should not be neglected.

The exclusive inclusion of patients with risk factors for ETII in the study of the efficacy of PT is the main limitation of this comparison group. We must note that the difference in the follow-up time between the groups submitted to PT and the classic EVAR (No PT), and the comparison of a more recent cohort with a historical group are bias factors that should not remain omitted.

Regarding the management of already established ETII, the main question is when to treat or maintain surveillance. Some authors propose that ETII should follow its natural course and solve spontaneously. Others, considering the minimal risk (<1%[39]), support medical action to prevent late complications[38]. In *Dosluoglu et al*[32], ETIIs that appeared in the first year after EVAR were more likely to resolve spontaneously. On the contrary, late ETII (>1 year) often met the eligibility criteria (*Table I*) for intervention. According to the findings of the other included articles (*Table I*) and the current guidelines[2,4], aneurysmatic sacs with a growth >5mm should be treated (in the ESVS with an increase ≥ of 10mm). We enhance that the intervention does not always show satisfactory results. It is not explicit whether the procedures are less effective than conservative management or whether the ETII with aneurysmal growth ≥5mm, due to its more aggressive nature, has a higher risk of recurrence. High reintervention rates (72%)[42,43] are reported after treatment, with high costs resulting from multiple procedures[42,43]. In the included studies (*Table I*), the clinical success rate for Tx was over 50%, except in *Haq et al*[8], which was around 18%. Overall, the CS reached values of 57.1%. In conservative management, the overall clinical effectiveness was approximately 62.8%, and the lowest value was 33%.

The conducted meta-analysis does not support the advantages and benefits of the conservative method when compared with Tx, even though many authors defend it[8]. The RR (RR = 1,00; 95% CI [0.72;1,38]; I^2 =69%; P=1,00) concludes that none of the approaches (Tx vs. conservative) has a significant advantage over another, both in terms of prognosis and in terms of

complications. However, the results are not statistically significant and cannot be assumed in the general population. The main limitations in this comparison group were: (1) the heterogeneity between the studies; (2) retrospective analysis including techniques and devices from different generations; (3) different follow-up protocol and duration, and different imaging technique; (4) different embolization materials; (5) unclear ETII management algorithm in a few studies.

When candidate for treatment, there is no consensus on the most suitable technique: TAE or DPSI. According to the existing literature, none has reached decisive efficacy[8], and TAE is still used preferentially as the first line in most centers[7,8,30]. According to the meta-analysis recently conducted by *Guo et al*[44], DPSI is more effective in resolving ETII compared to TAE and has no increased risk of complications. Although not statistically significant, the results demonstrated that the overall clinical success of DPSI and TAE were 50% and 33.3%, respectively, and are in line with those obtained in the present meta-analysis. The RR was 1.42 (95% CI [0,83;2,43]; P=0,20; I^2=0%). Thus, DPSI is 42% more likely to resolve ETII compared to TAE. Unsuccessful TAE is usually due to the recanalization of collateral vessels. These results can be due to incomplete embolization of the vessel(s) and inability/difficulty in reaching the vessel evident in the TAE. Performing DPSI has several advantages when compared to TAE: (1) a lower risk of anatomical incompatibility; (2) shorter full-length intraoperative, and less ionizing radiation exposure, (3) lower risk of non-target vessel embolization (for example, the inferior mesenteric artery)[44]. *Guo et al*[44] demonstrated that the technical failure of the first procedure is a predictive source of failure in subsequent procedures and that after two failed attempts, we should proceed to laparoscopic/open surgery (greater morbidity and associated mortality). Some authors[44,45] recommend Onyx® and coils (embolization material) because these may reduce the risk of complications and recanalization of the vessels responsible for ETII. However, it was not possible to extract results with statistical significance in this meta-analysis, and further studies will be needed to confirm this premise. In most studies, the description of the ETII management algorithm was unclear. DPSI was performed only in cases of incompatibility or technical failure of TAE. These were the main limitations in this comparison group.

Regarding the present meta-analysis results and the current literature, we suggest: (1) conservative treatment in individuals without eligibility criteria (mainly in patients with frailty and comorbidity); (2) DPSI as 1st line in ETII with eligibility criteria where total occlusion of the AAA nidus (studied in preoperative CTA) is possible, as suggested in *Marcelin et al*[45]. Otherwise, we recommend TAE as the first option. To conclude, we may acknowledge that: (1) only 20%[28] of the patients submitted to EVAR develop ETII, and (2) most of the statistical data derived from cohort studies that only compare individuals with morphological risk factors to develop ETII.

The authors believe that there is not enough information to conclude that prophylactic embolization is advantageous when systematically applied to all patients, despite not adding complications - *Figure 3* and *8*. We reiterate that it may have a high degree of utility in selected individuals, despite the lack of data to state that it prevents ETII in the long term (most have average follow-up periods of less than 24 months). In conclusion, selective embolization is more effective in preventing ETII than non-selective embolization. Although, the latter has less associated costs and is easier to perform. Thus, more data is needed to state with a high degree of certainty which technique to recommend.

It is not credible to apply the conclusions regarding the best ETII management in the medical community since the results are not statistically significant (P> 0.05) and have considerable heterogeneity. These may be due to the following factors: 1) small cohorts; (2) retrospective analysis with different generations techniques and devices; (3) non-standardized time and follow-up protocol as the imaging technique; (4) diverse embolization materials, (5) unclear patient management algorithm and (6) different treatment criteria between articles. Only the comparison group between PT and the classic EVAR regarding the primary outcome had statistically significant (P <0.05) results, which allow more precision conclusions.

In future studies, to acquire high-quality data, we recommend (1) eligibility criteria with a clear definition; (2) studies with follow-up over 24 months; (3) comparison between the different approaches through randomized case-control studies (possible ethical limitations).

CONCLUSION

In conclusion, the results suggest that prophylactic embolization is advantageous in selected individuals (with high risk factors). However, it is impossible to conclude whether the benefit persist in the long term (>24 months). Regarding ETII management, there was no quantifiable superiority between conservative management and intervention. The latter should only be employed in patients with eligibility criteria described in the current guidelines. We also suggest DPSI as the first line treatment in ETII instead of TAE, when anatomically possible. It appears that no approach presented a higher absolute risk of complications. The lack of statistical significance in the ETII treatment comparison groups and the high overlapping heterogeneity make it necessary to conduct further studies with larger samples and follow-up

APPENDIX

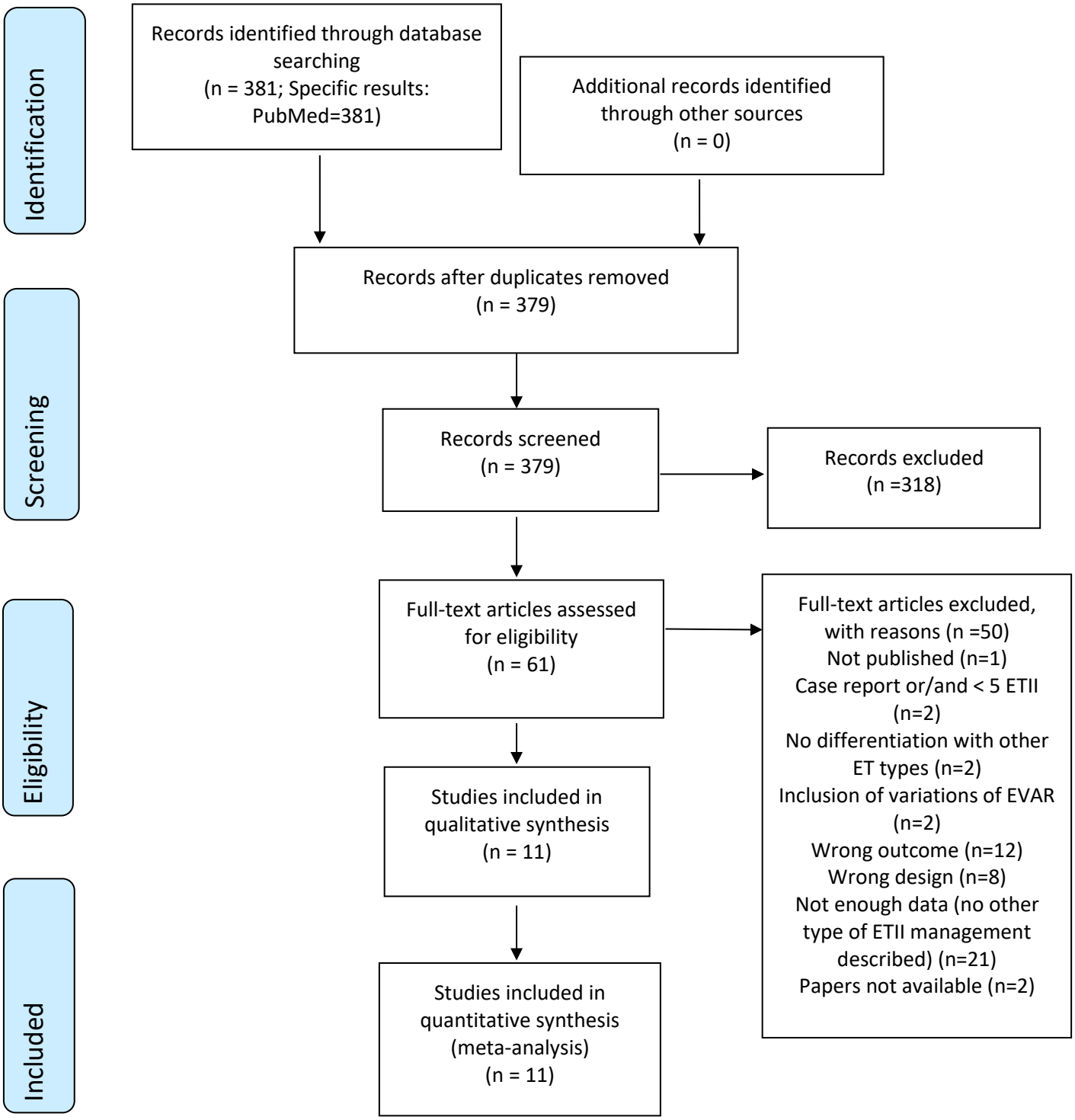

Figure 1- Preferred Reporting Items of Systematic Reviews and Meta-analysis Diagram.

Table I. Study Details.

Study	*Type of Study*	*Year*	*Location*	*Cohort origin*	*Eligibility criteria for ETII intervention*	*Method of treatment*	*Embolization material*	*Clinical Success Definition*	*Follow-up Method*
Carrafiello et al, 2016[7]	Cohort Retrospective study	2007/ 2014	Insubria Hospital, Varese, VA, Italy	Patients underwent EVAR of AAA with ETII during follow-up	Sac diameter increase during follow- up	TAE / DPSI/ Conservative	Glue/Onyx/Coils	No recurrent endoleak during follow-up /stability of the sac diameter	CTA (1 m) + DUS (6m) + CTA (12 m and annually)[c]
Haq et al, 2017[8]	Cohort Retrospective study	2006/ 2015	University College Hospital, London, UK	Patients underwent elective and emergency EVAR	Aneurysm growth >5 mm or more[a]	TAE/DPSI/ Conservative	Coils/ other	No endoleak detectable	CTA (protocol NR)
Moulakakis et al, 2017[30]	Cohort Retrospective study	2010/ 2015	University General Hospital "Attikon" and "Laikon", Athens, Greece	Asymptomatic ETII with expanding sac > 5mm in follow-up CTA scan **or** symptomatic with sac expansion **or** aneurysm rupture	Asymptomatic ETII with expanding sac > 5mm in follow-up CTA scan **or** symptomatic with sac expansion **or** aneurysm rupture	OS/TAE/DPSI	Glubran® +/-coils	No endoleak detectable	CTA (1 m); DUS/ CTA (every 6m)
Ribé et al, 2017[31]	Cohort Retrospective study	2005/ 2012	St Mary's Hospital, London, Uk	Patients underwent EVAR for AAA	ETII >3m and/or aneurysm sac growth> 5 mm	TAE / Conservative	Onyx 18®	No recurrent endoleak during follow-up / stability of the sac diameter	CTA (6m, 12m, annually)
Pineda et al, 2018[35]	Cohort Retrospective study	1998/ 2015	Pennsylvania Hospital, Philadelphia, USA	Patients underwent EVAR for AAA	ETII with sac growth >5 mm	TAE/DPSI/Conservative	TAE: coils or glue; DPSI: NR	Absence of endoleak during follow-up / stability or decrease in sac size	DUS (1m,6m than annually) +/- CTA[d]
Dosluoglu et al, 2019[32]	Cohort Retrospective study	2007/ 2015	Western NY Healthcare System, New York, USA	Patients who underwent elective EVAR [b]	ETII with >5mm increase in sac diameter	TAE/DPSI/Conservative	Coils +/- NBCA	No endoleak detectable during follow-up/ stable sac	CTA (6m than annually) +/- DUS [c,e]

AAA- Abdominal Aortic Aneurysm; CTA- Computed Tomography Angiography; DPSI- Direct Percutaneous Sac Injection; DUS- Duplex Ultrasound; EVAR- Endovascular Abdominal Aortic Aneurysm Repair; ETII- Type II Endoleak; OS- Open/Laparoscopic Surgery; TAE - Transarterial Embolization; NBCA- n-butyl-2-cyanoacrylate; NR- Not Reported; ([a]) Depends on the comorbidities and rate of success; ([b]) With and without risk factors for ETII; ([c]) Reviewed by the same experienced radiologist; ([d]) If an increase>5 mm of the aneurysmatic sac is observed in DUS; ([e]) If an increase>5 mm of the aneurysmatic sac is observed in CTA

Table I (cont.) - Study Data.

Study	*Patients n*	*Mean Age, Y*	*Men n (%)*	*ETII (n)*	*Conservative n (%)*	*1st TX n (%)*	*Clinical Success, n (%)*	*Complications, (n)*	*Follow-up Mean (m)*
Carrafiello et al, 2016[7]	480	NR	NR	94	75 (79,8%)	Tx= 19 (19,1%) TAE = 14 (73,7%) DPSI = 4 (28,16%)	Tx=10 (55,5%) DPSI= 4(100%) TAE=10 Conservative=25 (33,3%);	0	Tx= 36 m; Conservative= 28m
Haq et al, 2017[8]	386	79,5[a]	64 (79%)[a]	81	53 (65,4%)	Tx= 28 (34,6%) TAE=17 (60,7%) DPSI= 11 (39,3%)	Tx=5 (17.9%) TAE =2 (11.8%) DPSI=3 (27.3%) Conservative = 25 (47.2%)	0	37,2[a]
Moulakakis et al, 2017[30]	29[b]	77	29 (100%)	29	NA	TAE = 6 (20,7%) DPSI= 4 (20,7%) OS= 19 (65,5%)	TAE=3 (75%) DPSI= 4 (66,7%) OS=19 (100%)	TAE= 1 DPSI=0	31,2[a]
Ribé et al, 2017[31]	600	79	14 (78%)	92	56 (60,9%)	Tx= 36(39,1%) TAE= 18 (50%)	TAE= 18 (100%); Conservative= 56 (100%)	0	19[a]
Pineda et all, 2018[35]	462	Early ETII: 74; Delayed ETII:75,6	69 (72%)[a]	96	74 (77,1%)	Tx=22 (22,9%)	Tx= 15 (68,2%); Conservative= 58 (78,4%)	Conservative= 1; Tx= 0	Early ETII= 48,5 m; Delayed ETII= 52,4 m
Dosluoglu et al, 2019[32]	266	70,1[a]	211 (99,5%)[a]	20	8 (40%)	Tx=12 (60%) TAE+ DPSI= 11 (55%)	TAE+DPSI= 8 (72,7%); Conservative= 3 (37,5%)	0	44[a]

ETII- Type II Endoleak; DPSI- Direct Percutaneous Sac Injection; TAE - Transarterial Embolization; Tx-Intervention /treatment; NA- Not Applicable; NR- Not Reported; n- number; m- month; ([a])- total number of ETII; ([b]) ETII eligible for treatment.

Table II- Study Details (PT).

Study	*Type of Study*[e]	*Years*	*Location*	*Cohort origin*	*Criteria for PT*	*Pré-PT study*	*Method of treatment (PT)*	*Embolization material (PT)*	*Clinical Success*	*Follow-up Method*
Mascoli et al, 2016[28]	Cohort study	2008/ 2013	Policlinico Sant'Orsola-Malpigh (University of Bologna)	Patients with high morphological risk of ETII	Patency of > 6 EPV and/or VR % < 40% on the pre-operative CTA	CTA	Non-selective embolization of the AAA + efferent vessels [a]	coils	Freedom from ETII during the follow up	DUS (6m) + CEUS (12m) +/- CTA[d]
Piazza et al, 2016[11]	Cohort study	2012 / 2014	Padova University/ NS HV Institute, Atlanta	Patients with high morphological risk of ETII	Patency of IMA >3 mm; Patency of ≥ 3 pairs of LA; 2 pairs of LA + SA/ARA/Patent IMA	CTA	Non-selective embolization of the AAA [a]	coils + fibrin/ glue	EII and related reintervention freedom/ No sac volume variation	CTA (3m,6m,12m than annually)
Aoki et al, 2017[29]	Cohort study	2009/ 2016	Showa University, (Tokyo, Japan)	Patients with patent IMA and/or LA [b]	Patency of IMA and all LAs patent by ≥2 mm	CTA	Direct embolization of the patent arteries [a]	coils	Freedom from ETII in the first CTA (after 7 days)	CTA (7 days)
Dosluoglu et al, 2019[32]	Cohort study	2007/ 2015	Western NY Healthcare System, New York, USA	Patients who underwent elective EVAR	≥ 4 patent LAS **or** patent IMA >3 mm + flow lumen diameter >30 mm	CTA	Non-selective embolization of the AAA [a]	coils	No ETII and reinterventions during the follow-up	CTA (6m than annually) +/- DUS (if ETII suspicious)
Vaillant et al, 2019[33]	Cohort study	?/2016	"La Timone" Hospital, Marseille, France	IMA > 3 mm + pre-op embolization **and** asymptomatic AAA + IMA > 3 mm (no stenosis) **and** IMA > 3 mm+ pre-op embolization	Permeable IMA > 3 mm w/ no stenosis **or** w/ no ostial occlusion	CTA	Direct embolization of the patent arteries [a]	Coils (IMA<5Mmm e/ou anatomia desfavorável); vascular plug (IMA >5mm na favorable anatomy)	No ETII + no reinterventions during the follow-up	CTA (3m than annually) +/- DUS/CEUS [c]
Ohba et al, 2020[34]	Cohort study [f]	2012/ 2019	University Graduate School of Medical Sciences, Nagoya, Japan	Patients underwent emergency EVAR	NR - discretion of the operators	CTA	Non-selective embolization of the AAA [a]	NBCA	Hemodynamic stabilization without evidence of further bleeding	CTA (NR protocol)

CG- Control group; AAA- Abdominal Aortic Aneurysm; IMA - inferior mesenteric artery; LA- lumbar arteries; NBCA- n-butyl-2-cyanoacrylate;PT- Prophylactic Treatment; VR- Vessels patency [(a)]- femoral access; [(b)] elective EVAR; [(c)] In case of suspicion of ETII (increase in AA diameter> 5mm), DUS / CEUS was performed for confirmation; [(d)] In case of an increase in the diameter of AA> 5mm, an additional CTA was performed for preoperative study; [(e)] "control" group composed by historical cohort except ; [(f)] no comparison group; * Individuals with and without risk factors for EII were included.

Table II (cont.) - Study Data (PT).

Study	*Patients, n.*	*Mean Age, Y*	*Men n (%)[d]*	*N. patients PT*	*Clinical Sucess n (%)*	*Complications, n*	*Follow-up Mean (m)*
Mascoli et al, 2016[28]	70	73[d]	67(95,7%)	25	20 (80%)[a]	0	12
Piazza et al, 2016[11]	107	Case:74,8 Control: 75,9	100 (93,4%)	52	45 (87%)[b]	0	16
Aoki et al, 2017[29]	80	Case= 76,0 Control =77,5	58 (72,5%)	24	23 (95,8%)[c] (7 days)	0	0,25
Dosluoglu et al, 2019[32]	266	70,1[d]	211 (99,5%)	16	15 (93,8%)[c]	2	44
Vaillant et al, 2019[33]	82	Case= 73,78 Control= 76,73	81 (98,8%)	37	32 (86,5%)[a]	0	Case= 21,5 Control=57
Ohba et al, 2020[34]	29	Case: 77,5 Control: 88	24(82,8%)	22	4 (18,2%)[c]	0	Case=14 Control= 6,5

m- months; n- number; [(a)] 12 months after PT; [(b)] 24 months after PT; [(c)] at the end of the follow-up;[(d)] calculated taking account the total number of patients.

Table III- Risk of Bias using CASP cohort study check list[1].

Original CASP itens	Adapted CASP itens	Reasons for downgrading
1.Did the study address a clearly focused issue?	1.Did the study address a clearly focused issue?	
2.Was the cohort recruited in an acceptable way?	2.Was the cohort recruited in an acceptable way?	Not included all the patients and not excluded all the patients with exclusion criteria; Not clearly reported the cohort (unclear); Wrong outcome/ wrong cohort (red).
3.Was the exposure accurately measured to reduce bias?	3.Was the exposure accurately measured to reduce bias?	No clear explanation of how the diagnosis was obtained (unclear); No explanation (red).
4.Was the outcome accurately measured to reduce bias?	4.Was the outcome accurately measured to reduce bias?	No clear explanation of the follow-up method (unclear); No explanation of the follow-up or/and different follow up times (red).
5. (a) Have the authors identified all important confounding factors?	5. (a) Have the authors identified all important confounding factors?	The risk factors for bias (different types of material, intervention, etc.) was not reported and/or description of the cohort was not reported (age, sex, etc.) (red); Not clearly described (unclear).
5. (b) Have they take account of the confounding factors in the design and/or analysis?	5. (b) Have they take account of the confounding factors in the design and/or analysis?	Not clear adjustment between comparison groups and/or no adjustment have been made for this risk factors (unclear).
6. (a) Was the follow up of subjects complete enough?	6. (a) Was the follow up of subjects complete enough (1M,6M, 1Y)?	No follow-up method description (red). Follow-up is not complete enough (unclear).
6. (b) Was the follow up of subjects long enough?	6. (b) Was the follow up of subjects long enough?	Follow up less than 12 months (red).
7. What are the results of this study?	Not used- not applicable (open question format)	
8. How precise are the results?	Not used- not applicable (open question format)	
9. Do you believe the results?	9. Do you believe the results?	No clear definition of clinical success and/or not stratified way to choose the management and/or different techniques (unclear); No definition of the outcome (red).
10. Can the results be applied to the local population?	10. Can the results be applied to the local population?	The cohort is not valid or adequate for the outcome
11. Do the results of this study fit with other available evidence?	11. Do the results of this study fit with other available evidence?	The results are in concordance with some aspects with the overall data (unclear); the results are not in concordance with the overall available data regarding ETII management (red).
12. What are the implications of this study for practice?	Not used- not applicable (open question format)	

Risk of Bias using CASP cohort study check list[1]. This tool was adapted from the "CASP cohort study checklist", from which 9 of the 12 original items were used. The following table shows the changes made and what was considered a reason to increase the risk of bias.

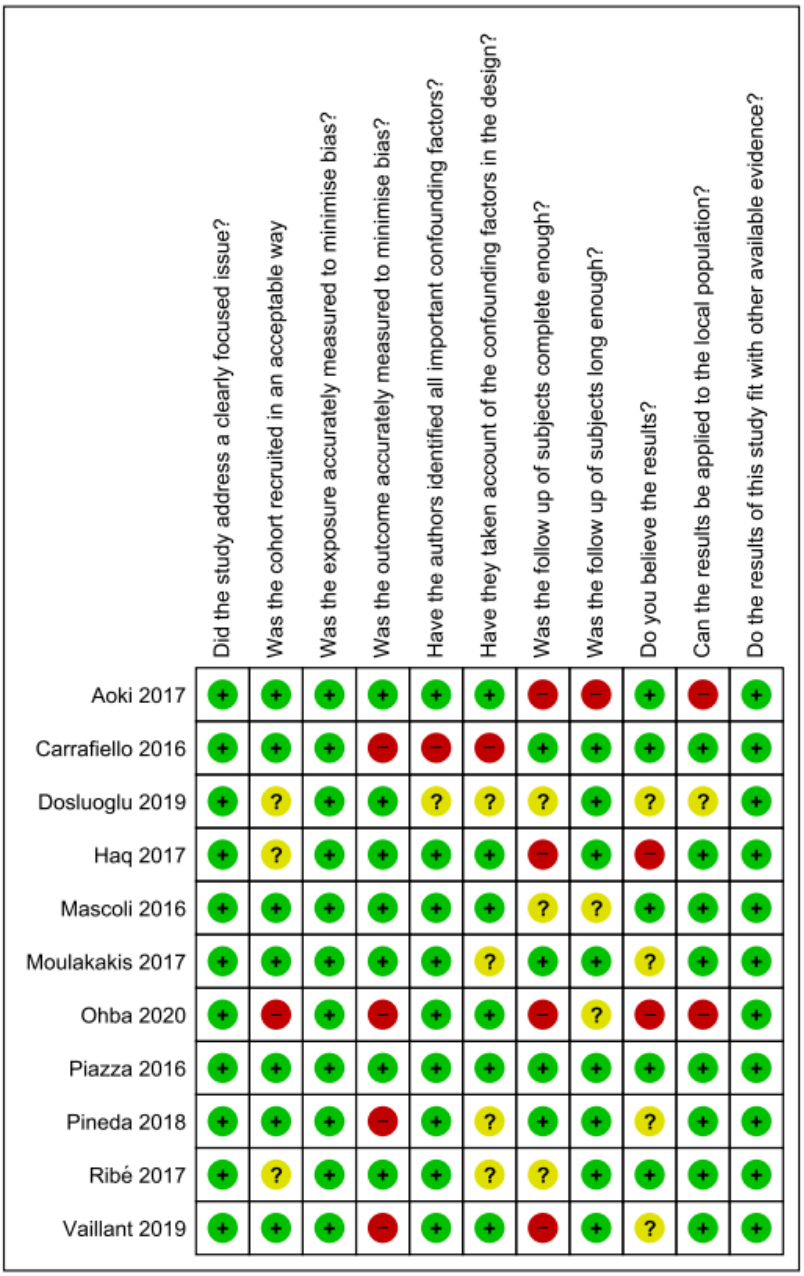

Figure 2- Risk of Bias: CASP cohort study checklist[1].

Risk of Bias using CASP cohort study checklist[1]. Red (-): High Risk of Bias; Yellow (?): Unclear Risk of Bias; Green (+): Low risk of Bias.

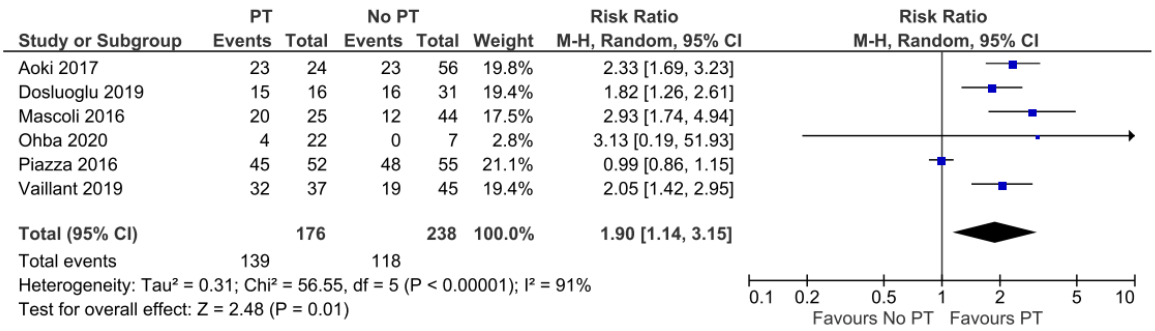

Figure 3- Forest Plot analyzing the RR of not developing ETII between PT and No PT.

PT indicates Prophylactic Therapy. The subgroup named "Favors PT" is composed by the studies in which PT has a better prognosis than "No PT". The events represent the absence of ETII during follow-up after treatment. RR mean "Risk Ratio".

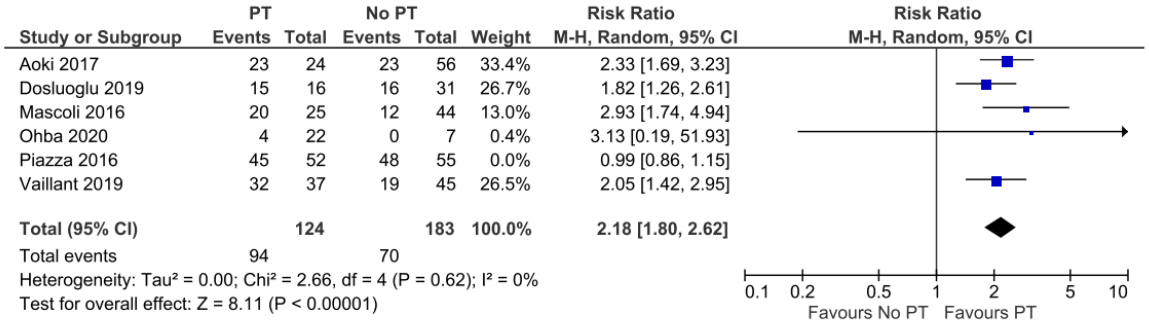

Figure 4- Forest Plot analyzing the follow-up impact in the PT efficacy.

PT indicates Prophylactic Therapy. The subgroup named "Favors PT" is composed by the studies in which PT has a better prognosis than "No PT". The events represent the absence of ETII during follow-up after treatment. RR mean "Risk Ratio".

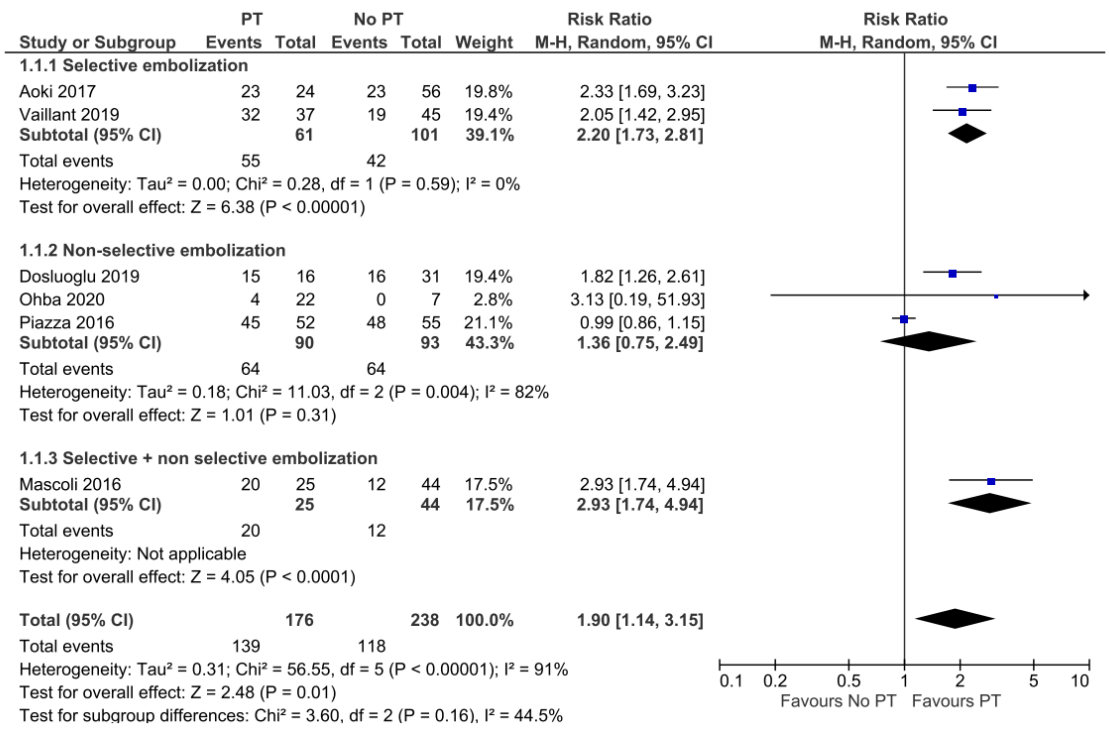

Figure 5- Forest Plot analyzing the effect of the different PT techniques.

PT indicates Prophylactic Therapy. The subgroup named "Favors PT" is composed by the studies in which PT has a better prognosis than "No PT". The events represent the absence of ETII during follow-up after treatment. RR mean "Risk Ratio".

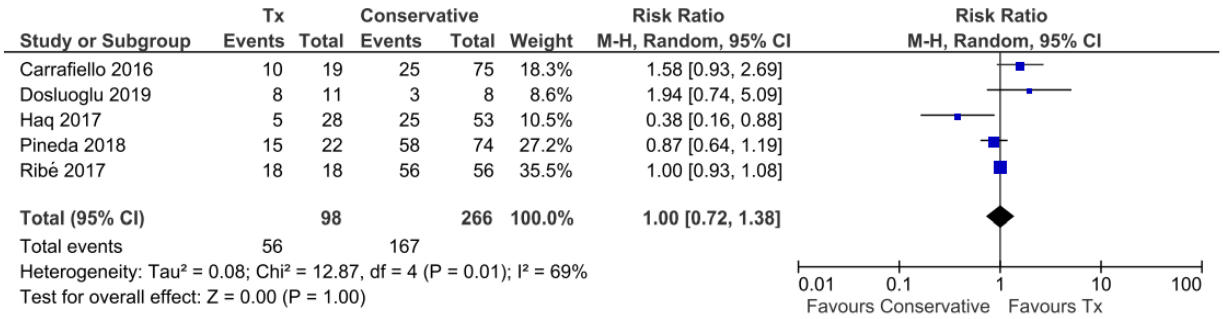

Figure 6- Forest Plot analyzing the RR of ETII resolution between Conservative and Tx.

The events represent the absence of ETII during follow-up after treatment. Tx indicates the Total number of ETII submitted to Intervention. The subgroup named "Favors Tx" is composed by studies in which "Tx" has a better prognosis than conservative approach. RR means "Risk Ratio".

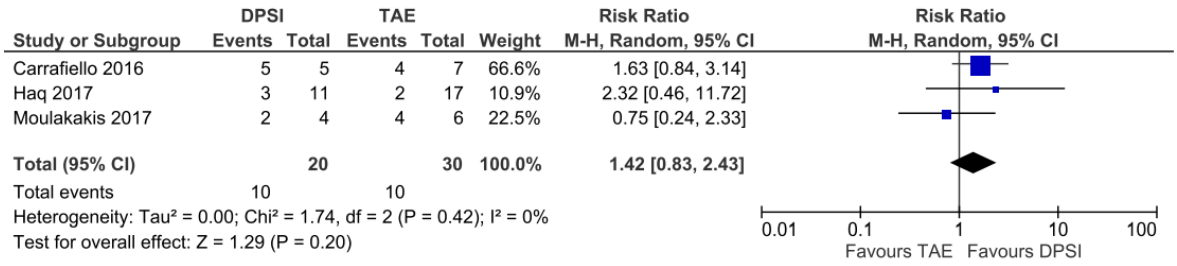

Figure 7- Forest Plot analyzing the RR of ETII resolution between DPSI and TAE.

The events represent the absence of ETII during follow-up after treatment. DSPI indicates Direct Percutaneous Sac Injection and TAE indicates Transarterial Embolization. The subgroup named "Favors DPSI" is composed by studies in which DPSI has a better prognosis than TAE. RR means "Risk Ratio".

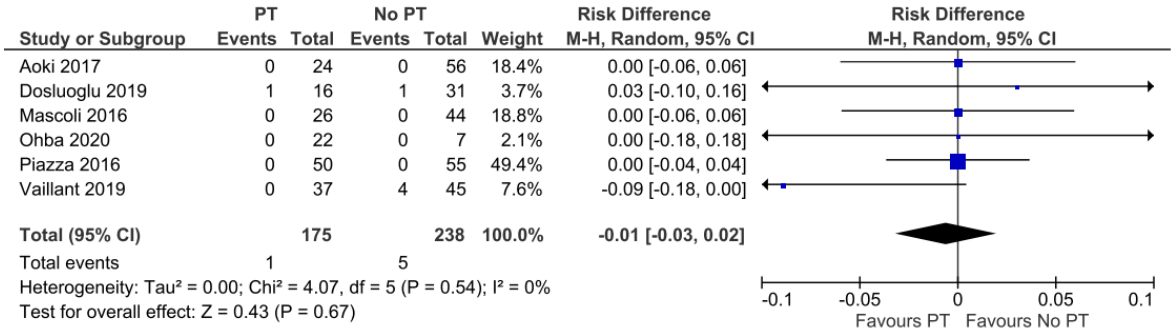

Figure 8- Forest Plot analyzing the RD of complications between PT and No PT.

The events represent the complications associated with the different approaches. PT indicates Prophylactic Therapy. The subgroup named "Favors PT" is composed by the studies in which PT as a better prognosis than "No PT". RD mean "Risk Difference".

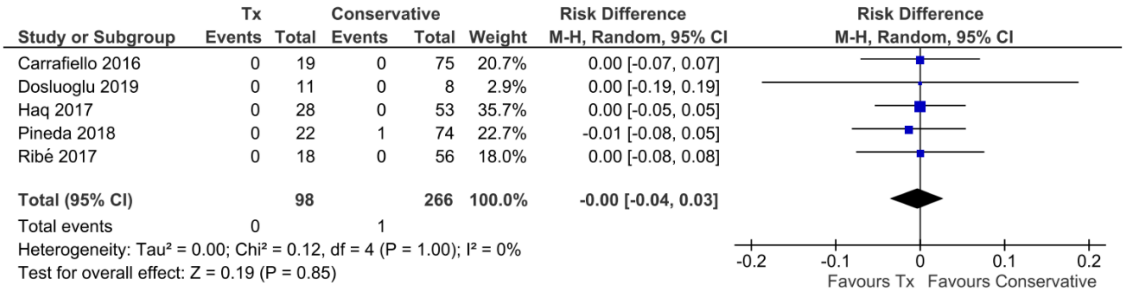

Figure 9-Forest Plot analyzing the RD of complications between Conservative and Tx.

Tx indicates the Total number of ETII submitted to Intervention. The events represent the complications associated with the different approaches. The subgroup named "Favors Tx" is composed by studies in which "Tx" has a better prognosis than conservative approach. RD indicates "Risk Difference".

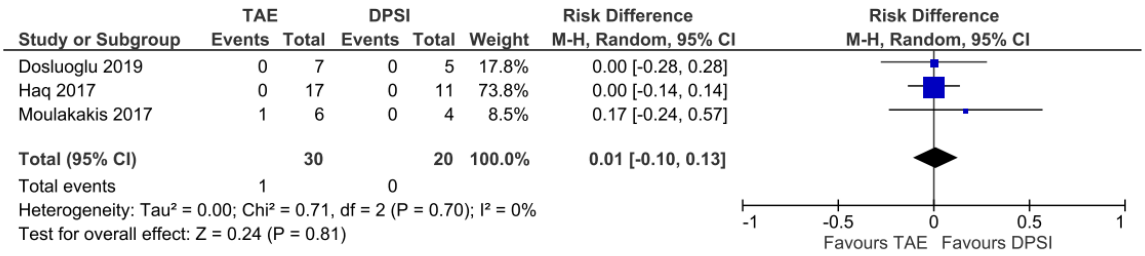

Figure 10- Forest Plot analyzing the RD of complications between DPSI and TAE.

The events represent the complications associated with the different approaches. DSPI indicates Direct Percutaneous Sac Injection and TAE indicates Transarterial Embolization. The subgroup named "Favors DPSI" is composed by studies in which DPSI has a better prognosis than TAE. RD indicates "Risk Difference".

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