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Ana Isabel Bernardes Romeiro

Predictors of adverse events in uncomplicated type B Aortic Dissection: A Systematic Review with Meta-Analysis

Preditores de eventos adversos na Disseção Aórtica tipo B não complicada: uma Revisão Sistemática com Meta-Análise

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Ciências médicas e da saúde

TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

Predictors of adverse events in uncomplicated type B Aortic Dissection: A Systematic Review with Meta-Analysis

ORIENTADOR

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É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	[X]
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DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTE TRABALHO.	[ ]

Faculdade de Medicina da Universidade do Porto, 06 / 04 / 2021

Assinatura conforme cartão de identificação: Ana Isabel Bernardes Romeiro

Aos meus pais, pelo incentivo, paciência e amor infindáveis.
Ao meu irmão, que esteve sempre à distância a torcer por mim.
Ao Minorca, pela sua ternura infinita, e à Zelda, a minha parceira de passeios.

Aos meus avós, que recordo com carinho e saudade por terem moldado o início desta longa viagem.

Predictors of adverse events in uncomplicated type B Aortic Dissection: A Systematic Review with Meta-Analysis

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WHAT THIS PAPER ADDS:

This study is the first meta-analysis conducted in order to find the most important predictors of an unfavourable outcome in patients with uncomplicated TBAD.

Among risk factors analysed, aortic diameter ≥ 40 mm is the one with the greatest impact on adverse outcomes and it should encourage clinicians to opt for expedited TEVAR.

Despite recent efforts, standards of reporting for studies on TBAD are still lacking.

INTRODUCTION: Thoracic Endovascular Aortic Repair (TEVAR) has been selectively used for uncomplicated acute type B Aortic Dissection (TBAD); however, not all cases will benefit from TEVAR. A search for high risk clinical and radiographic predictors for complications is ongoing.

This systematic review and meta-analysis aimed to identify predictors of major adverse events during follow-up in uncomplicated TBAD, in order to identify who might benefit from elective TEVAR.

EVIDENCE ACQUISITION: A systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) statement.

EVIDENCE SYNTHESIS: 16 studies were included in a qualitative synthesis and 10 in the meta-analysis. Several risk factors associated to major adverse events have been described, including (1) aortic diameter ≥40 mm, (2) greater false lumen diameter (>22mm), (3) patent false lumen, (4) primary entry tear > 10mm, and (5) greater number of false lumen vessels origin. Quantitative synthesis identified an aortic diameter ≥40 mm significantly associated with major adverse events (HR=3.56; p<0.00001). Reporting of false lumen status, aortic diameters and growth, and demographic data was not always congruent with the most recent recommendations by Society for Vascular Surgery and Society of Thoracic Surgeons, published in 2020.

CONCLUSIONS: Acute and subacute TBAD patients with an aortic diameter ≥ 40 mm should be submitted to expedited TEVAR, as this risk factor had the greatest impact on adverse outcomes (HR). Remaining risk factors have weaker evidence. Additional standards of reporting for some risk factors, long-term outcomes and follow-up imaging are needed for better treatment selection.

Key Words: Aortic Dissection; Endovascular; TEVAR; Endoprosthesis; Prognostic factors

TEXT

INTRODUCTION

Acute aortic dissection is a clinical entity with an estimated incidence of 3.5 per 100,000 persons per year which has gradually increased over the last decade[1]. However, these values may underestimate the real magnitude of the problem[2].

Timely evaluation and management are crucial given its potentially life-threatening outcomes[3]. Up to 30% of all aortic dissections are Type B Aortic Dissections (TBAD)[1,4], with an in-hospital mortality estimated at 10.7%[5]. In-hospital mortality accounts for: (1) visceral and renal malperfusion, (2) spinal cord ischemia, (3) limb malperfusion, (4) coronary malperfusion and (5) aortic rupture, but also for (6) perioperative complications of aortic interventions[6].

Best medical treatment (BMT), including adequate antihypertensive therapy to reduce shear stress[7], is recommended for TBAD treatment, and generally, the sole treatment for uncomplicated TBAD. Thoracic Endovascular Aortic Repair (TEVAR) is considered first-line treatment for the management of complicated TBAD. However, in recent years, TEVAR has been increasingly used for the treatment of uncomplicated TBAD[8].

The rationale behind TEVAR in TBAD is the coverage of proximal aorta intimal tear, promoting false lumen exclusion and thrombosis, thus preventing aneurysm degeneration and rupture[9]. INSTEAD Trial (Investigation of Stent Grafts in Aortic Dissection Trial) was the first randomized controlled trial (RCT) to compare TEVAR with BMT alone in patients with uncomplicated subacute TBAD; Even though no survival improvement was attained within 2 years[10], after 5 years TEVAR was associated to reduced mortality, disease progression and aortic-specific events[11]. ADSORB trial, the only RCT to compare elective TEVAR with BMT alone on uncomplicated acute TBAD patients, was not sufficiently powered for mortality at 1 year follow up. This trial did, however, reveal higher rates of false lumen (FL) thrombosis in patients with acute TBAD randomized to TEVAR, which was associated with fewer late complications and increased aortic remodeling[12].

Several risk factors for aortic growth and unfavourable outcomes in patients with uncomplicated acute TBAD have already been advocated in the Literature[13]. Consensus has not been reached and their impact on patients with TBAD is not entirely known. As a consequence, there is still much debate about when to favour pre-emptive TEVAR over

BMT alone.

The aim of this Systematic Review and Meta-Analysis was to highlight which demographic characteristics and radiographic features might prompt for a combination of early TEVAR with BMT instead of BMT alone in uncomplicated TBAD, in order to prevent future complications and optimize patient outcome.

EVIDENCE ACQUISITION

This manuscript was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and guidelines[14].

Definitions: According to the Society for Vascular Surgery (SVS) and Society of Thoracic Surgeons (STS) reporting standards for type B aortic dissections published in 2020, acute TBAD can be defined in the time period from 1 to 14 days from onset of symptoms,[15]subacute TBAD from 15 to 90 days from onset of symptoms[15] and chronic TBAD after >90 days from onset of symptoms.[15]

Complicated acute TBAD can be defined as the presence of rapid aortic expansion, aortic rupture and/or hypotension/shock, visceral, renal, or limb ischaemia, paraplegia/paraparesis, peri-aortic haematoma, recurrent or refractory pain, and refractory hypertension despite adequate medical therapy.[16]

Information sources and search: An extensive search in two electronical databases (MEDLINE, EMBASE) was performed. Reference checking was also performed to scan for additional articles. The last search was performed on 27th September 2020. The following query was used: ((type B aortic dissection OR descending aorta dissection) AND acute AND uncomplicated AND (predictor OR factors)). Demonstration of the conduction of the search as proposed, using a PRISMA diagram, is demonstrated in Figure 1.

Eligibility criteria: Published studies reporting the relationship between radiographic findings in Computed Tomography Angiography (CTA) and the occurrence of major adverse events after uncomplicated TBAD (treated with BMT alone) were included; Major adverse events were defined as follows: additional unplanned interventions for the dissected aorta, rupture, ≥55mm dilatation of the dissected aorta, rapid dilatation of the dissected aorta (>5 mm), saccular aneurysm, aorta-related death, the occurrence of new

aortic dissection or rupture, or death. Minimal accepted follow-up was 14 days, the defined temporal cut off for defining acute TBAD[17]. Studies which identified predictors of major adverse events during the acute phase of the disease (first 14 days after onset)[17] and, therefore, had follow-up periods ≤14 days were not included.

Studies including patients with type A aortic dissections or complicated aortic dissections were excluded, as well as studies focused only on TEVAR outcomes or simply comparing TEVAR with BMT outcomes. Further exclusion criteria included case-reports, reviews, expert opinions, and editorials.

No exclusion criteria regarding year in which a study had been published, submitted or during which the studies participants had enrolled were used as exclusion criteria. Studies in languages other than English, Portuguese or German were also excluded.

Study Selection: Two reviewers (AIR, CN) independently performed an eligibility assessment of identified studies, using the search terms. The reviewers initially screened manuscripts by title and abstract. Further assessment of articles that potentially met inclusion criteria was performed using the full text. (Figure 1)

Authorship of the studies was not masked from the reviewers. Discrepancies between the reviewers during the search, selection, and quality assessment were resolved by consensus. In case of persisting disagreement, a third reviewer was consulted (AM). When duplicate analysis of the same cohort were found, the authors included only the latest published manuscript.

Data collection process and data items: A data extraction sheet based on the Cochrane Consumers and Communication Review Group's data extraction template was created and adapted to collect all relevant data from each included study[18]. Data was collected by two independent reviewers and disagreements between reviewers were resolved by consensus. In case of persisting disagreement, a third reviewer was consulted (AM).

Collected data included: Type of study; Funding source; Patient recruitment; Inclusion and exclusion criteria; Number of participants (n); Age; Sex; Median follow-up time; Cardiovascular Risk Factors; Imaging predictors for dismal outcome; Major adverse events as previously defined.

An analysis using IBM-SPSS Statistics Version 27 was performed to determine whether participants' demographics differed across studies; Kuskall-Wallis Test was used to calculate p value and a p value ≤0.05 was considered significant.

Risk of bias: Risk of bias was systematically assessed using the ROBINS-I tool ("Risk Of Bias In Non-randomized Studies of Intervention")[19].

Summary measures and synthesis of results: Hazard ratios (HR) reported with 95% confidence interval (CI) were extracted from each individual study and used as the effect measure.

All analyses were conducted using Review Manager version 5.4. For all outcomes considered, the Generic Inverse Variance method was used along with a Random Effects analysis model. For each individual study and outcome considered, the *lnHR* was calculated to estimate the intervention effect; additionally, standard error (SE) with 95% CI was calculated.

To estimate heterogeneity, the I2 statistic was used; a I2 greater than 50% indicates that differences identified are more probably due to the heterogeneity across studies than to chance.

EVIDENCE SYNTHESIS

Study selection: A total of 208 potential studies were initially identified through database searching and, after duplicates removal, a total of 128 studies titles and abstracts were skimmed. After application of the eligibility criteria a total of 33 studies were read in full and additionally four studies were included by backward citation. (Figure 1)

By the end of the selection process a total of 16 studies were included in the qualitative synthesis and a total of 10 studies were included in the meta-analysis.

Study characteristics: Table I depicts the main characteristics of each individual study included.

All included studies were retrospective, most of them single-centre (n=14), with two exceptions[20,21]. It is also noteworthy that 10 studies were set in Japan[21–30], whereas 6 took place in other geographic locations: China (N=1)[31], USA (N=4)[32–35] and Europe (N=1)[20].

A total of 2395 patients were included ranging from study inclusion in January 1983[22] to March 2018[21]; Pooled analysis revealed 60% of male participants, with a median follow-up period of 2.5 years, ranging from (2.66 ± 2.88 years[30] to 6.8 years[34]).

All patients were initially diagnosed with uncomplicated TBAD on enhanced computed tomography (CT) scan and initially managed conservatively[20,21,30–35,22–29]; Using

information from the initial CT scan and CT scans performed during follow-up, several radiographic features were assessed in order to understand whether they played a role in the development of an unfavourable outcome[20,21,30–35,22–29]; the definition of an "unfavourable outcome" slightly differed across studies. A notable exception is the study by *Xiang et al*, where the identification of predictors of major adverse events was a secondary, rather than a primary aim[31].

Table II depicts participants' demographics across studies.

Risk of bias: The ROBINS-I tool[19] was used to assess the risk of bias of each study.

A total of 6 studies were classified as having a low risk of bias[22–24,31,32,34] and 10 studies were classified as having a moderate risk of bias[20,21,25–30,33,35].

Table III shows the main bias domains identified in each study (with reasons) and the risk of bias for each study.

Risk Factors:

Table IV summarizes main findings regarding each risk factor analysed.

1. **Aortic Diameter ≥40 mm:**

A total of 10 studies agreed that an aortic diameter cut off ≥40 mm at the time of diagnosis was a significant predictor of major adverse events occurrence ($p<0.05$)[21,22,34,23–30]. (Table IV)

A single study reported a lower cut off at 35 mm[32] and two studies reported higher cut offs at 44 mm[33] and 45 mm[35].

The remaining studies (n=3) reported a relationship between thoracic aortic diameter and adverse outcomes, but did not establish a cut off value.[20,29,31]

2. **False lumen diameter:**

Data on false lumen diameter was heterogeneous with contradictory conclusions.

Ueki et al demonstrated that false lumen diameter (*per* 1mm increment) was not a significant predictor of major adverse events ($p=0.82$)[27].

On the other hand, for *Shimamoto et al* FL diameter (*per* 1mm increment) was a significant predictor of major adverse events ($p<0.0001$)[29]. *Also, Schwartz et al* revealed that a false lumen diameter > 20mm was predictive of major adverse events ($p=0.03$)[34], and for *Ray et al* a false lumen diameter > 22mm was a significant predictor of major

adverse events ($p<0.04$)[33].

In *Matsushita et al* study, a false lumen diameter greater than true lumen diameter was predictive of major adverse events ($p=0.004$)[28]. This group reached the same conclusion in 2020 ($p<0.001$)[21].

3. False lumen patency:

False lumen patency was analysed in most included studies (n=15) with one exception[33]. Of note, this predictor was often heterogeneously classified: some studies classified FL status as patent, partially thrombosed or completely thrombosed[20,22,26,27,29,31,35]; others classified it simply as patent or completely thrombosed[21,23–25,28,30,32,34].

Among studies classifying the FL status as patent, partially thrombosed or completely thrombosed, five concluded that FL status was not predictive of major adverse events[20,27,29,31,35], and two stated otherwise ($p<0.05$)[22,26].

Among studies classifying the FL status as patent or completely thrombosed, three concluded that FL status was not predictive of major adverse events[21,25,28]. However, the remaining five studies reached a different conclusion[23,24,30,32,34].

The influence of number of entry tears or presence of re-entry tears on FL status was not analysed in any of the included studies.

4. Location of the primary entry tear:

Primary entry tear location was only analysed in five studies.

Ueki et al reported a shorter distance between the primary entry tear and the left subclavian artery (<50mm) as a significant predictor of major adverse events ($p=0.002$)[27]; This conclusion was supported by two additional studies[31,35].

On the one hand, *Kato et al* concluded that location of primary entry tear (in thorax) was predictive of major adverse events ($p<0.001$)[22]. On the other hand, *Takahashi et al* established that primary entry tear location was not predictive of major adverse events ($p>0.05$)[25].

None of the included studies evaluated the risk of major adverse events between patients with an entry tear at the concavity versus convexity of the distal aortic arch.

5. Size of the entry tear:

Schwartz et al demonstrated that a primary entry tear > 10mm was predictive of major adverse events ($p=0.03$)[34]. However, *Codner et al* concluded that size of the primary entry

tear was not predictive of major adverse events[35].

6. Number of vessels originating from the false lumen:

Only *Kamman et al* analysed this predictor, demonstrating that increasing the number of vessels (from 0 to 3 vessels) originating from the FL was predictive of major adverse events (p=0.049)[20].

7. Cardiovascular Risk Factors

A total of 11 studies analysed hypertension[21,22,35,23–26,29,31,32,34], diabetes mellitus[21–25,29,31,32,34,35], dyslipidaemia[21,24,25,29,31,35] or smoking[24,26,31,35] as risk factors for major adverse events. All studies were concordant that these factors were not predictive of major adverse events (p>0.05), with the exception of a single study that concluded that smoking was predictive of major adverse events (p=0.02)[35]. (Table IV)

8. Age

All included studies (n=16) analysed this risk factor and 13 studies concluded that age was not predictive of major adverse events (p>0.05)[20,22,32,34,35,23–30]. In the remaining studies, *Ray et al*, stated that an admission age >60 as predictive of major adverse events (p<0.01)[33]; *Xiang et al* (p=0.013)[31] and *Matsushita et al* stated that an admission age ≥70 as predictive of major adverse events (p=0.009)[21].

9. Connective tissue disease

A total of 3 studies analysed this risk factor, 2 of which concluded that connective tissue disease (CTD) was not predictive of major adverse events (p>0.05)[32,34], while the study by *Ray et al* reported CTD as predictive of major adverse events (p<0.01)[33].

<u>Quantitative synthesis:</u>

With the information extracted from some of the previous studies, we ran a quantitative analysis of following relationships: (1) Aortic diameter ≥40mm (*versus* aortic diameter < 40mm) and the occurrence of major adverse events, (2) False lumen diameter (*per* 1mm increment) and the occurrence of major adverse events and (3) False lumen status (patent *versus* completely thrombosed false lumen) and the occurrence of major adverse events.

(1) Aortic diameter ≥40 mm

An aortic diameter ≥40 mm was significantly associated with an increased hazard of major adverse events during follow-up (HR=3.56; 95%CI=2.91- 4.35).

(2) False lumen diameter

False lumen diameter (*per* 1mm increment) was also associated with an increased hazard of major adverse events during follow-up, but results failed to reach significance (HR= 1.05; 95% CI= 0.99-1.11).

(3) False lumen status

A patent false lumen diameter was associated with an increased hazard of major adverse events, but results failed to reach significance (HR= 1.13; 95% CI= 0.79-1.60).

Standards for reporting: Recently, the Journal of Vascular Surgery published extensive guidelines of standards for reporting TBAD.

These guidelines recommend that false lumen patency status is documented as patent, partially thrombosed or completely thrombosed[15]. Reporting was not congruent with this recommendation in eight studies[21,23–25,28,30,32,34].

Aortic growth is also defined as a "≥5mm increase in maximal aortic diameter in any segment after any form of management"[15], yet some studies use a different cut-off for aortic growth[22,23,27–29,35].

It is also proposed that aortic diameters should be measured from outer aortic wall to outer aortic wall, perpendicular to the angle of blood flow (centerline technique). Most studies do not provide specific information on how these diameters were measured[22–25,27,31] or use multiplanar reconstruction techniques to obtain these measurements[29,32–35]; Aortic diameters were therefore calculated differently across studies.

Compliance of included studies with the aforementioned guidelines was also not always possible to analyse due to lack of data (particularly for the use of illicit drugs or CTD incidence).

CONCLUSIONS

To our knowledge, this manuscript is the first attempt to conduct a meta-analysis to find most important predictors of an unfavourable outcome in patients with uncomplicated

TBAD.

TBAD may present without complications in almost 50% of cases (uncomplicated TBAD). However, the prognosis under conservative management is not as benign as the name can imply. In-hospital mortality reaches 3-10%, and on the long term approximately 20-40% of patients with TBAD develop enlargement of the FL, needing treatment[23].

The risk for short and long term complications warrants further investigation of anatomic criteria that point towards increased risk for complications and re-intervention need.

In this meta-analysis, aortic diameter ≥40 mm at presentation was the strongest predictor of major adverse events during follow-up, with an HR of 3.56 (95%CI=2.91-4.35; I^2=11%).

FL diameter presented heterogeneous results. In our quantitative synthesis, a trend towards an increase in the hazard of major adverse events appears to exist *per* 1mm increment in FL diameter (HR=1.05), but it did not reach significance (95% CI= 0.99-1.11). Of note are the studies by *Schwartz et al* and *Ray et al*, where a FL diameter >20mm[34] and >22mm[33] respectively was significantly associated with an increased risk of major adverse events.

It is also difficult to conclude on the role FL patency plays in the outcome of patients with uncomplicated TBAD. A patent FL accounts for an increased HR of 1.13 for major adverse events; however, results failed to reach significance (95% CI= 0.79-1.60) and substantial heterogeneity between studies appears to exist (I^2=65%). This could be explained by the fact that FL status classification differs amongst included studies, as previously stated. When devaluing partially thrombosed FL and classifying it as patent, we risk misperceiving FLs status true effect, creating clinically relevant information bias. Indeed, some authors have proposed that patients with a partially thrombosed FL require more intensive surveillance and timely interventions than their patent or completely thrombosed counterparts, given that their aortic growth rate during follow-up is higher with poorer outcomes[36].

Again, no consensus was reached about primary entry tear location due to heterogeneity in the description of this radiographic feature.

Although admitting that false lumen diameter and location of primary entry tear may be high-risk radiographic features[15], recommendations on how these measurements should be reported are still lacking and heterogeneity among studies documenting these features exists. We would like to suggest that location of primary entry tear is reported according

to the zone from which it originates (illustrated in the SVS/STS new classification system)[15], further specifying whether it originates from the convexity or the concavity of the distal aortic arch[37,38], instead of measuring its distance from the left subclavian artery. When reporting on false lumen diameter, measurements should "be based on a single line bisecting the center of the intimal flap perpendicular to flow", so that true lumen and false lumen diameters add up to the total aortic diameter[15]; additionally: 1) special emphasis should be placed on measuring the FL diameter at the level of the main pulmonary artery, because this is the location where a 22mm cut off for defining high risk patients was first described[33], 2) authors should define cut off values for distinguishing high risk groups.
Recommendations regarding vessel wall inflammation on PET-scan also remain lacking. Although PET-scan is inadequate for diagnosing TBAD in an emergency setting, it has proved useful in predicting patients' outcomes, given that it is able to identify changes in the dissected aorta (not detectable by CTA) correlated with disease progression[36,39]. As it is, we propose that patients with TBAD are followed using not only multiphasic CTA, but also PET-scan with a 30-day, 3- or 6- month, and yearly schedule after the index dissection event or surgical intervention.[15]
Also these guidelines do not consider the need for surgical intervention a long-term outcome of TBAD[15] which is an outcome in many included studies[21,25,27–29,34,35], and in our opinion rightfully so.

Standards of reporting have been recently published and compliance with such standards could facilitate future data comparison and individualized patient data meta-analysis. However, recommendations are still lacking on how to report false lumen diameter, location of primary entry tear at the concavity versus convexity of the distal aortic arch[37,38] or vessel wall inflammation on PET-scan[36,39], even though these features have been reported as high-risk radiographic features[15].

Our study has some important limitations, the most important being the lack of RCT or large national registries on the subject. Included studies are mostly retrospective analysis of single centre studies (with 2 multicentric studies), with moderate quality of evidence[40]; most of them are comprised of Asian patients[21-31] and it is not certain whether results might be generalized to other ethnicities, due to lack of studies on how ethnical disparities affect the risk of major adverse events in TBAD. Indeed, some studies suggest that TBAD in African Americans occurs at a younger age and has a higher rate of reintervention than

in their white counterparts[41]; differences in dissection subtype by ethnicity have also been reported[15]. Risk of bias is therefore significant.

The available evidence supports that acute and subacute TBAD patients with an aortic diameter ≥ 40 mm should probably be submitted to expedited TEVAR, as this risk factor had the greatest impact on the risk for adverse outcomes (HR) in this meta-analysis. The remaining risk factors that have been studied in the literature have weaker evidence and need additional evidence. Clarification of the real impact of some of these risk factors would benefit from the development of standards of reporting, which even with recent efforts from SVS and STS are still ill-described.

A need for multicentre prospective studies, following a standardized protocol regarding outcomes definition, risk factors definition, and the impact measures used, still persist 18 years after the launch of the INSTEAD trial[42]. Additional granular data and standard reporting of risk factors in national based registries and in RCT´s will facilitate future data comparison and individualized patient data meta-analysis.

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TABLES

Table I. – Studies characteristics

First author (year)	Aim	Nº of participants	Median follow-up: duration in years ± SD (IQR)	Outcome
Kato (1995)[22]	To determine the indications for surgical treatment of acute TBAD by studying chronic-phase enlargements of aortic dissections in patients treated successfully with medical hypotensive therapy during the acute phase.	41	3.2 (0.33-11.67)	Aortic enlargement (maximum diameter of the dissected aorta ≥60mm, rapid enlargement of the dissected aorta >10mm/year, or rupture of the dissected aorta).
Marui (1999)[23]	To predict the acute-phase factors that may affect chronic-phase aortic enlargement by studying chronic- phase enlargement of dissections in patients without complications during the acute phase.	101	4.9 (0.17-10.42)	Aortic enlargement (maximum diameter of the dissected aorta ≥60 mm, rapid enlargement of the dissected aorta >10 mm/year, rupture of the dissected aorta, and rapid enlargement of ulcer-like projection by >5 mm/year).
Onitsuka (2004)[24]	To examine the long-term outcome and the prognostic predictors related to the development of complications associated with acute TBAD.	76	4.37 ± 2.99 (0.26-10.06)	Aortic events (dissection-related death, rupture or impeding rupture, visceral ischemia, lower limb ischemia, increase in the maximum aortic diameter >50mm, and a mean aortic enlargement rate >5mm *per* year).
Takahashi (2008)[25]	To identify the most prognostic predictor of Stanford type B aortic dissection at admission.	43	4.24 ± 0.44	Dissection-related events (need for aortic surgery, aortic rupture, dissection-related death, mean aortic enlargement greater than 5 mm in diameter per year, and death from unknown causes).
Kudo (2014)[26]	To elucidate the factors predicting late aortic events in patients treated conservatively for acute type B dissections.	117	5.1 ± 4.1	Late aortic events (malperfusion or progressive aortic pathologic features, including rupture and expansion).
Ueki (2014)[27]	To detect prognostic factors in patients with uncomplicated acute type B aortic dissection.	228	3.2 ± 2.6	Aortic event (dissection-related death, surgical intervention, aortic enlargement of greater than 60 mm, or occurrence of type A aortic dissection).
Durham (2015)[32]	To evaluate the rate of aneurysmal degeneration in a contemporary series of patients with acute type B aortic dissection who were initially treated with medical therapy alone and to identify factors associated with aortic growth.	200	5.3 (0.1-14.7)	Aortic growth (increase of ≥5 mm in the maximal aortic diameter on subsequent imaging compared with the initial imaging study, rapid degeneration - early growth ≥5 mm occurring ≤14 days of initiation of medical therapy).
Ray (2016)[33]	To determine the predictors of intervention and mortality in patients with uncomplicated acute TBAD.	156	3.7 (2.1-6.9)	All-cause death
Kamman (2017)[20]	To better understand which uncomplicated TBAD patients are at risk of aortic dilatation, we investigated BMT patients from the ADSORB database, with and without aortic growth, to determine clinical and radiologic predictors of aortic dilatation	21	2.83	False lumen growth (increase >0.0 mm).
Matsushita (2018)[28]	To evaluate the outcomes of patients with uncomplicated ATBAD and identify the risk factors for major adverse events.	134	3.9 (2.08-6.33)	Major adverse events (aortic related mortality, late operation for dissected aorta, and indication of operation for dissected aorta -rupture or impending rupture of the aorta, dilatation of the aorta - >55 mm-, rapid dilatation of the aorta - >10mm *per* year - and saccular aneurysm).
Schwartz (2018)[34]	To identify clinical and anatomic factors that are associated with the need for subsequent aortic intervention in patients who present with uncomplicated TBAD.	254	6.8 (0.1-13.6)	Need for aortic intervention (development of malperfusion syndrome, aneurysmal degeneration of the thoracic aorta - increase in the total aortic diameter of >5.5 cm or growth of ≥0.5 cm in a 6-month period - and death).
Shimamoto (2018)[29]	To describe the reliable prognostic factors of mortality and subsequent aortic events during the follow-up of uncomplicated type B acute aortic dissection.	255	4.58 ± 0.5	Aortic event (aorta-related death, surgical or endovascular intervention, aortic enlargement greater than 55 mm, or occurrence of new aortic dissection or rupture).
Nakamura (2018)[30]	To investigate risk factors associated with the aortic enlargement in medically treated patients.	104	2.66 ± 2.88 (0.08-11.9)	Aortic diameter enlargement (> 40 mm during the observation period or >5mm during a 6-month period) and death.
Codner (2019)[35]	To identify radiographic predictors of acute uncomplicated TBAD patients who will fail to respond to BMT.	121	3.25 ± 2.83 (no growth group) and 2.25 ±2.25 (growth group)	Aortic growth (thoracic aortic growth ≥10 mm during the study period or underwent surgical intervention for rapid aneurysmal growth).
Xiang (2019)[31]	The purpose of this retrospective study was to further assess the early and mid-term outcomes of TEVAR in patients with acute uncomplicated TBAD compared with those receiving BMT.	357	3.2 (1.9-4.2) in TEVAR group. 3.8 (1.3-5.6) in BMT group	All-cause death.
Matsushita (2020)[21]	To build a risk prediction score model for late aortic events in patients with UTBAD and validate it using large-size clinical data with a high follow-up rate.	187	3.42 (1.33-6)	Late aortic events (late intervention for the dissected aorta after discharge from initial diagnosis and medical management, rupture, or impending rupture, ≥55-mm dilatation of the dissected aorta, rapid dilatation of the dissected aorta - >5 mm/6 month -, and saccular aneurysm).

Table note: SD – Standard Deviation; IQR – Interquartile Range

Table II. – Participants' demographics

First author (year)	N° of male participants (%)		Age (mean ± SD)		HT (%)		DM (%)		RI (%)		Dyslipidaemia (%)		Smokers (%)		Connective tissue disease (%)	
	E	NE	E	NE	E	NE	E	NE	E	NE	E	NE	E	NE	E	NE
Kato (1995)[22]	11 (73.3)	18 (69.2)	64±9	63± 12	12 (80)	19 (73.1)	3 (20)	4 (15.4)	3 (20)	0	NR		NR		0	0
Marui (1999)[23]	31 (72.1)	38 (65.5)	66±12		36 (83.7)	42 (72.4)	8 (18.6)	6 (10.3)	4 (9.3)	2 (3.4)	NR		NR		0	0
Onitsuka (2004)[24]	20 (80)	35 (69)	65.5 ±10. 9	64.9 ±9.5	76%		3%		4%		1%		14 (56)	36 (71)	0	0
Takahashi (2008)[25]	15 (83.3)	14 (56)	71.2 ±2.6	67.7 ±2.4	9 (50)	15 (60)	2 (11.1)	1 (4)	7.3%		1 (5.6)	1 (4)	NR		0	0
Kudo (2014)[26]	81 (69.3%)		68.9 ± 11.3		82.9%		NR		NR		NR		63.2%		NR	
Ueki (2014)[27]	153 (67.1%)		70.4 ± 11.8		NR		NR		NR		NR		NR		0.9%	
Durham (2015)[32]	63 (67.7)	59 (55.1)	62± 16.1	64.6 ±14. 3	73.6%	79.4%	18.3%	16.8%	2.2%	8.4%	NR		NR		5.4%	3.7%
Ray (2016)[33]	94 (60%)		60.6 ± 13.6		NR		17.3%		5.8%		NR		NR		4.5%	
Kamman (2017)[20]	13 (92.9)	5 (71.4)	55.3 ±15. 6	62.3 ±9.4	11 (78.6)	5 (71.4)	0	1 (14.3)	1 (7.1)	0	4 (28.6)	2 (28.6)	9 (64.3)	2 (28.6)	Excluded	
Matsushita (2018)[28]	98 (73.1%)		67 ± 12.2		100%		11.2%		3%		20.9%		NR		NR	
Schwartz (2018)[34]	68 (69.8)	99 (62.7)	66.6 ±14. 8	67.3 ±15. 9	82%	85%	27%	28%	7%	4%	NR		NR		4%	6%
Shimamoto (2018)[29]	185 (72.5%)		70.7 ± 11.5		91.4%		12.9%		NR		38%		NR		Excluded	
Nakamura (2018)[30]	24 (67)	42 (62)	70± 11	70± 13	NR		NR		NR		NR		NR		1.9%	
Codner (2019)[35]	55 (76)	26 (53)	52± 11	55± 11	72 (100)	48 (98)	8 (11)	12 (24)	6(8)	11(22)	22 (31)	16 (33)	19 (27)	13 (27)	4.1%	
Xiang (2019)[31]	226 (63.3%)		54.3 ± 10 in TEVAR group. 54.9 ± 10.8 in BMT group.		51.8%		3.9%		3.4%		3.9%		33.6%		Excluded	
Matsushita (2020)[21]	60 (80)	70 (62.5)	66.2 ±12	67.3 ±12. 2	75 (100)	110 (98.2)	7 (9.3)	10 (8.9)	1 (1.3)	4 (3.6)	14 (18.7)	29 (25.9)	NR		0	0
***p* Value**	0.437	0.437	0.43 3	0.43 3	0.429	0.429	0.429	0.429	0.423	0.423	0.392	0.392	0.368	0.368	0.423	0.423

Table note: SD – standard deviation; HT -Hypertension; DM – Diabetes mellitus; RI – Renal insufficiency; E – major adverse events group; NE – no major adverse events group; NR – not reported Kuskall-Wallis Test was used to calculate *p* value; $p \leq 0.05$ was considered significant.

Table III. – Risk of bias

First author (year)	Bias domain			Risk of Bias
	Bias due to confounding	Bias in classification of predictors	Bias due to missing data	
Kato (1995)[22]	x	x	x	Low
Marui (1999)[23]	x	x	x	Low
Onitsuka (2004)[24]	x	x	x	Low
Takahashi (2008)[25]	x	Yes - lack of patients with a completely thrombosed FL in the group which developed major adverse events	x	Moderate
Kudo (2014)[26]	x	x	Yes - 29.1% of patients were lost to follow-up	Moderate
Ueki (2014)[27]	x	x	Yes – Study population poorly characterized (lack of information regarding cardiovascular risk factors)	Moderate
Durham (2015)[32]	x	x	x	Low
Ray (2016)[33]	x	x	Yes - 120 patients were not included because their CT scans were no longer available[33]	Moderate
Kamman (2017)[20]	x	Yes - "One of the limitations was varying scan quality and slice thickness that sometimes hindered assessment of radiologic parameters"	Yes - some patients were not included because their CT scans were no longer available	Moderate
Matsushita (2018)[28]	x	Yes - it was not possible to distinguish between intramural hematoma and aortic dissection with a completely thrombosed FL	x	Moderate
Schwartz (2018)[34]	x	x	x	Low
Shimamoto (2018)[29]	Yes - some known risk factors for major adverse events, namely the existence of ulcer-like projections, were not taken into account and these could influence the effect size	x	x	Moderate
Nakamura (2018)[30]	Yes - important confounders such as smoking, and hypertension were not controlled	x	Yes - 11% of patients were lost to follow-up	Moderate
Codner (2019)[35]	Yes - inadequate blood pressure control and antihypertensive therapy could have affected the results	x	Yes - Yes - some patients were not included because their CT scans were no longer available	Moderate
Xiang (2019)[31]	x	x	x	Low
Matsushita (2020)[21]	x	Yes - it was not possible to distinguish between intramural hematoma and aortic dissection with a completely thrombosed FL	x	Moderate

Table IV. – Risk factors of major adverse events analysed in the included studies

	Risk Factor											
First author (year)	**Aortic Diameter ≥40 mm**	**FL diameter**	**FL patency**	**Location of PET**	**Size of PET**	**Number of vessels originating from the FL**	**HT**	**DM**	**Dyslipidaemia**	**Smoking**	**Age**	**Connective tissue disease**
Kato (1995)[22]	HR=8.83	NR	*p*=0.018	*p*<0.01	NR	NR	*p*=0.362	*p*=0.315	NR	NR	*p*=0.169	NR
Marui (1999)[23]	HR=3.97	NR	HR=2.09	NR	NR	NR	*p*>0.05	*p*>0.05	NR	NR	*p*>0.05	NR
Onitsuka (2004)[24]	HR=3.88	NR	HR=7.57	NR	NR	NR	*p*=0.07			*p*=0.2	*p*=0.78	NR
Takahashi (2008)[25]	HR=3.13	NR	*p*=0.22	*p*=0.732	NR	NR	*p*=0.550	*p*=0.562	*p*=0.999	NR	*p*=0.325	NR
Kudo (2014)[26]	HR=4.072	NR	*p*<0.0001	NR	NR	NR	*p*=0.979	NR	NR	*p*=0.144	*p*=0.604	NR
Ueki (2014)[27]	HR=3.95	*p*=0.82	*p*=0.37	2.90‡	NR	NR	NR	NR	NR	NR	*p*=0.22	NR
Durham (2015)[32]	HR=2.54 (used a 35mm cut off)	NR	*p*<0.01	NR	NR	NR	*p*=0.34	*p*=0.79	NR	NR	*p*=0.22	*p*=0.58
Ray (2016)[33]	*p*<0.01 (used a 44 mm cut off)	*p*=0.04 (used a 22 mm cutoff)	NR	NR	NR	NR	NR	NR	NR	NR	*p*<0.01	HR=2.3
Kamman (2017)[20]	HR=1.06 (no established cut off value	NR	*p*=0.066	NR	NR	HR=22.1	NR	NR	NR	NR	*p*=0.0502	NR
Matsushita (2018)[28]	HR=3.735	HR=3.411	*p*=0.102	NR	NR	NR	NR	NR	NR	NR	*p*=0.379	NR
Schwartz (2018)[34]	HR=2.2	HR=1.8	*p*≤0.05	NR	HR=2.1	NR	*p*=0.45	*p*=0.55	NR	NR	*p*=0.35	*p*=0.12
Shimamoto (2018)[29]	No established cut off value	HR=1.07	*p*=0.31	NR	NR	NR	*p*=0.48	*p*=0.5	*p*=0.76	NR	*p*=0.4	NR
Nakamura (2018)[30]	HR=1.116	NR	HR=0.617	NR	NR	NR	NR	NR	NR	NR	*p*=0.965	NR
Codner (2019)[35]	HR=2.36 (used a 45mm cut off)	NR	*p*>0.05	HR=0.995*	*p*=0.73	NR	*p*=0.4	*p*=0.06	*p*=0.33	HR=1.89	*p*=0.61	NR
Xiang (2019)[31]	No established cut off value	NR	*p*>0.05	HR=2.30 Δ	NR	NR	*p*=0.408	*p*=0.799	*p*=0.214	*p*=0.686	HR=1.04	NR
Matsushita (2020)[21]	HR=4.108	HR=4.207	*p*=0.197	NR	NR	NR	*p*>0.05	*p*>0.05	*p*>0.05	NR	HR=1.918	NR

Table note: FL – false lumen; PET – primary entry tear; HT -Hypertension; DM – Diabetes mellitus; NR – not reported. Where statistically significant results were obtained ($p \leq 0.05$) and when available, HR were reported.

‡ Primary entry tear <5 cm from Left Subclavian artery; *Primary entry tear in zone 3; ΔPrimary entry tear <2 cm from Left Subclavian artery

TITLES OF FIGURES

Figure 1. – PRISMA Flow Diagram.

Figure 2. - Forest plot: aortic diameter ≥40 mm *versus* aortic diameter < 40mm and the occurrence of major adverse events.

Figure 3. – Forest plot of the relationship between false lumen thickness and the occurrence of major adverse events.

Figure 4. – Forest plot: patent false lumen *versus* completely thrombosed false lumen and the occurrence of major adverse events.

FIGURES

Figure 1. – PRISMA Flow Diagram.

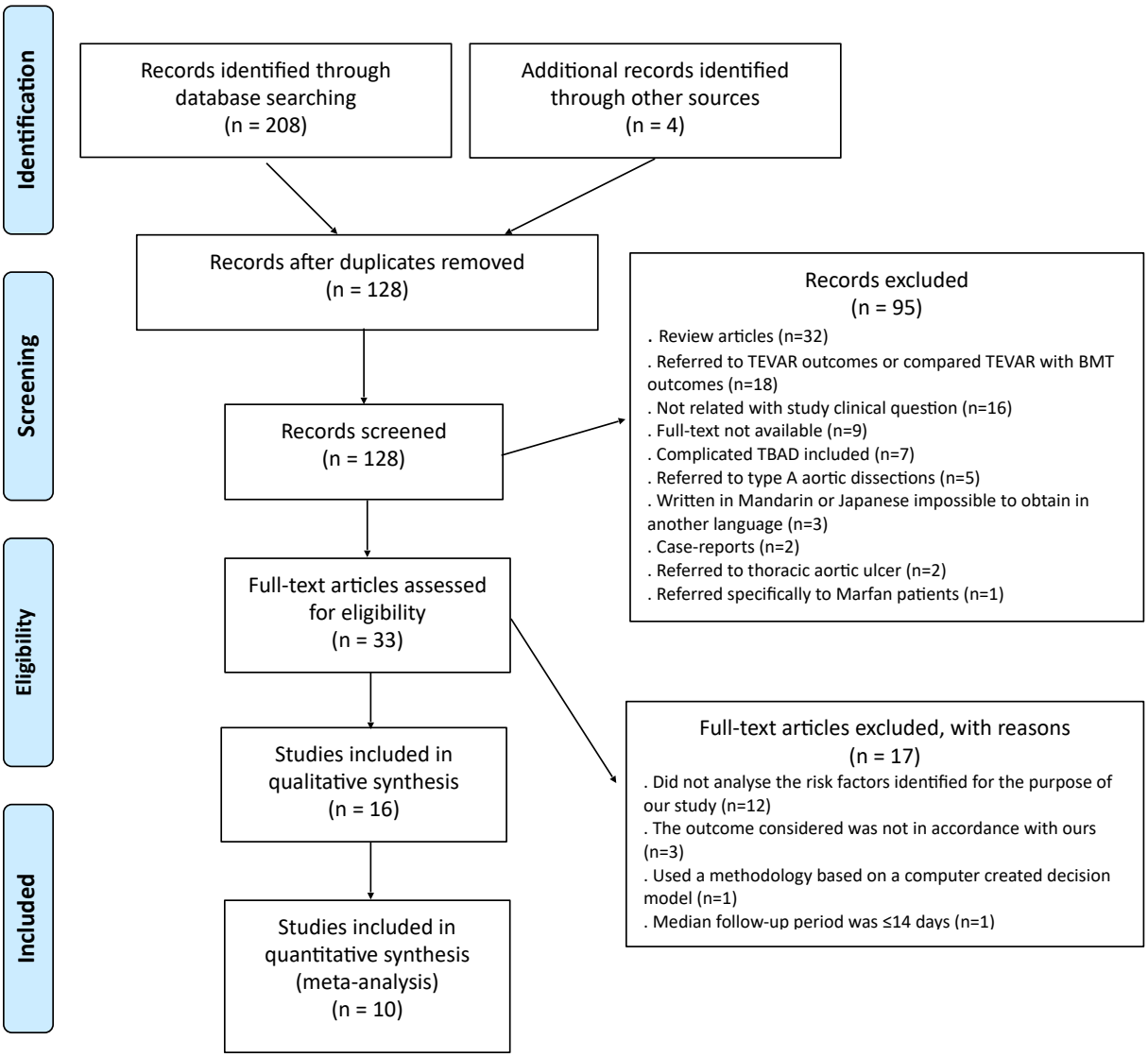


Figure 2. - Forest plot: aortic diameter ≥40 mm *versus* aortic diameter < 40mm and the occurrence of major adverse events.

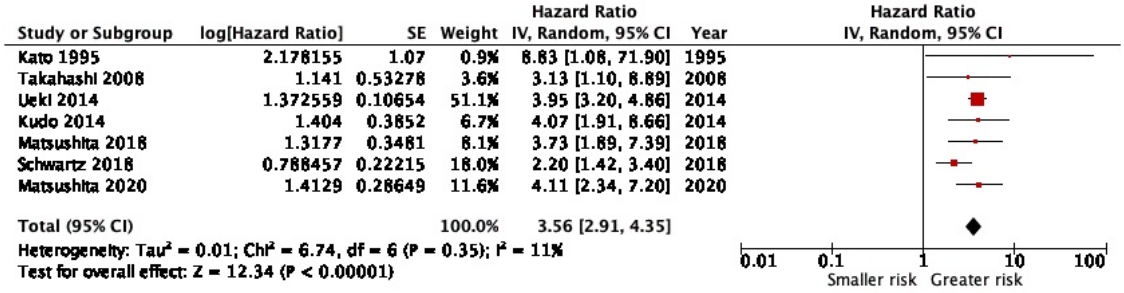


Figure 3. – Forest plot of the relationship between false lumen thickness and the occurrence of major adverse events.

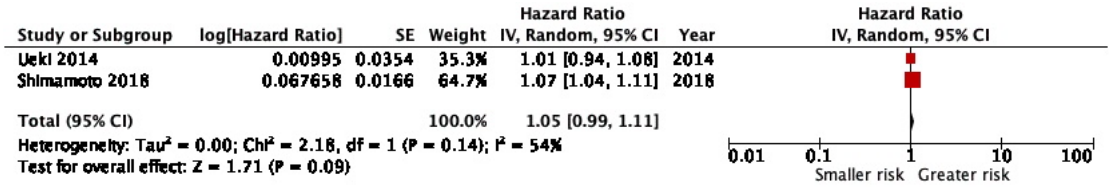
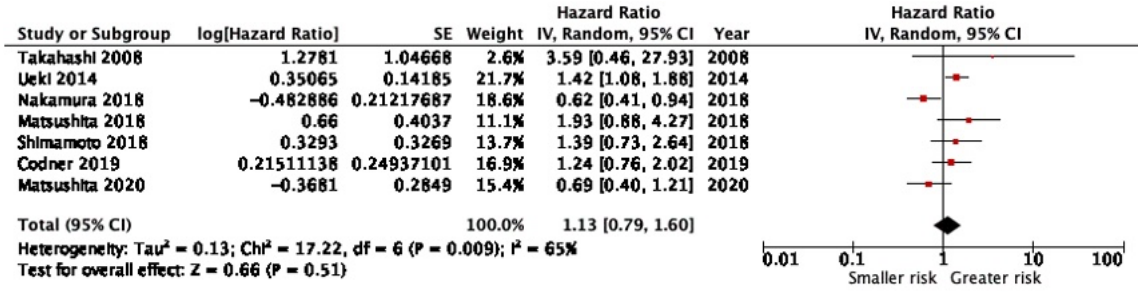


Figure 4. – Forest plot: patent false lumen *versus* completely thrombosed false lumen and the occurrence of major adverse events.



Anexo(s)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page and paragraph/ table #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both. **- MANDATÓRIO**	**Page 1:** "Predictors of adverse events in uncomplicated type B Aortic Dissection: A Systematic Review with Meta-Analysis"
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. **– SEGUIR RECOMENDAÇÕES DA REVISTA**	**Page 2:** "INTRODUCTION: Thoracic Endovascular Aortic Repair (TEVAR) has been selectively used for uncomplicated acute type B Aortic Dissection (TBAD); however, not all cases will benefit from TEVAR. A search for high risk clinical and radiographic predictors for complications is ongoing. This systematic review and meta-analysis aimed to identify predictors of major adverse events during follow-up in uncomplicated TBAD, in order to identify who might benefit from elective TEVAR. EVIDENCE ACQUISITION: A systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) statement. EVIDENCE SYNTHESIS: 16 studies were included in a qualitative synthesis and 10 in the meta-analysis. Several risk factors associated to major adverse events have been described, including (1) aortic diameter ≥40 mm, (2) greater false lumen diameter (>22mm), (3) patent false lumen, (4) primary entry tear > 10mm, and (5) greater number of false lumen vessels origin. Quantitative synthesis identified an aortic diameter ≥40 mm significantly associated with major adverse events (HR=3.56; p<0.00001). Reporting of false lumen status, aortic diameters and growth, and demographic data was not always congruent with the most recent recommendations by Society for Vascular Surgery and Society of Thoracic Surgeons, published in 2020. CONCLUSIONS: Acute and subacute TBAD patients with an aortic diameter □ 40 mm should be submitted to expedited TEVAR, as this risk factor had the greatest impact on adverse outcomes (HR). Remaining risk factors have weaker evidence. Additional standards of reporting for some risk factors, long-term outcomes and follow-up imaging are needed for better treatment selection."
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. **– MANDATÓRIO** ***O rationale corresponde à justificação da importância da revisão sistemática***	**Pages 3 and 4:** "Several risk factors for aortic growth and unfavourable outcomes in patients with uncomplicated acute TBAD have already been advocated in the Literature13. Consensus has not been reached and their impact on patients with TBAD is not entirely known. As a consequence, there is still much debate about when to favour pre-emptive

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			TEVAR over BMT alone."
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). - **MANDATÓRIO**	**Page 4:** "The aim of this Systematic Review and Meta-Analysis was to highlight which demographic characteristics and radiographic features might prompt for a combination of early TEVAR with BMT instead of BMT alone in uncomplicated TBAD, in order to prevent future complications and optimize patient outcome."
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. – **FACULTATIVO**	Não aplicável.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. – **MANDATÓRIO** ***É altamente recomendado, de acordo com as boas práticas da Cochrane, que não sejam aplicados critérios de exclusão baseados na língua e/ou data de publicação dos estudos.***	**Pages 4 and 5:** "Published studies reporting the relationship between radiographic findings in Computed Tomography Angiography (CTA) and the occurrence of major adverse events after uncomplicated TBAD (treated with BMT alone) were included; Major adverse events were defined as follows: additional unplanned interventions for the dissected aorta, rupture, ≥55mm dilatation of the dissected aorta, rapid dilatation of the dissected aorta (>5 mm), saccular aneurysm, aorta-related death, the occurrence of new aortic dissection or rupture, or death. Minimal accepted follow-up was 14 days, the defined temporal cut off for defining acute TBAD17. Studies which identified predictors of major adverse events during the acute phase of the disease (first 14 days after onset)17 and, therefore, had follow-up periods □14 days were not included. Studies including patients with type A aortic dissections or complicated aortic dissections were excluded, as well as studies focused only on TEVAR outcomes or simply comparing TEVAR with BMT outcomes. Further exclusion criteria included case-reports, reviews, expert opinions, and editorials. No exclusion criteria regarding year in which a study had been published, submitted or during which the studies participants had enrolled were used as exclusion criteria. Studies in languages other than English, Portuguese or German were also excluded."
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. – **MANDATÓRIO** ***Em consonância com as boas práticas da Cochrane, é mandatório que se verifique pesquisa em pelo menos duas bases de pesquisa bibliográfica (idealmente, deverão ser pesquisadas duas bases generalistas e uma específica da área). No caso de revisões sistemáticas de estudos***	**Page 4: "**An extensive search in two electronical databases (MEDLINE, EMBASE) was performed. Reference checking was also performed to scan for additional articles. The last search was performed on 27th September 2020."

		experimentais/ensaios clínicos aleatorizados, é altamente recomendado que uma das bases pesquisadas corresponda à CENTRAL ou a bases de ensaios clínicos como a ClinicalTrials.gov. ***Estudos de revisão da literatura em que a pesquisa decorra numa única base de dados não serão classificados como revisões sistemáticas.***	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. **– MANDATÓRIO** ***A query de pesquisa deve ser obrigatoriamente disponibilizada. A utilização de filtros de pesquisa da InterTASC é altamente recomendada (https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home)***	**Pages 4 and 23:** "The following query was used: ((type B aortic dissection OR descending aorta dissection) AND acute AND uncomplicated AND (predictor OR factors)). Demonstration of the conduction of the search as proposed, using a PRISMA diagram, is demonstrated in Figure 1."
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). **– MANDATÓRIO** ***As fases de selecção dos estudos primários devem ser descritas. Em consonância com as boas práticas da Cochrane, é mandatório que o processo de selecção envolva duas fases (fase de rastreio, em que os registos são seleccionados por título e abstract, e fase de inclusão, na qual se procede à leitura integral dos full texts). Em cada uma destas fases, o processo de selecção deve mandatoriamente envolver dois investigadores actuando de forma independente.***	**Pages 5 and 23: "**Two reviewers (AIR, CN) independently performed an eligibility assessment of identified studies, using the search terms. The reviewers initially screened manuscripts by title and abstract. Further assessment of articles that potentially met inclusion criteria was performed using the full text. (Figure 1) Authorship of the studies was not masked from the reviewers. Discrepancies between the reviewers during the search, selection, and quality assessment were resolved by consensus. In case of persisting disagreement, a third reviewer was consulted (AM). When duplicate analysis of the same cohort were found, the authors included only the latest published manuscript."
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. **– MANDATÓRIO** ***Trata-se de descrever de que forma se procedeu à extracção de dados dos estudos primários. Em consonância com as boas práticas da Cochrane, tal processo deverá envolver dois investigadores de forma independente.***	**Page 5: "**A data extraction sheet based on the Cochrane Consumers and Communication Review Group's data extraction template was created and adapted to collect all relevant data from each included study18. Data was collected by two independent reviewers and disagreements between reviewers were resolved by consensus. In case of persisting disagreement, a third reviewer was consulted (AM) (…) An analysis using IBM-SPSS Statistics Version 27 was performed to determine whether participants' demographics differed across studies; Kuskall-Wallis Test was used to calculate p value and a p value ≥0.05 was considered significant."
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and	**Page 5:** "Collected data included: Type of study; Funding source; Patient recruitment; Inclusion and exclusion criteria; Number of participants (n); Age; Sex; Median follow-up time;

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		simplifications made. **– MANDATÓRIO** ***Trata-se de descrever as variáveis para as quais foi obtida informação.***	Cardiovascular Risk Factors; Imaging predictors for dismal outcome; Major adverse events as previously defined."
Risk of bias in individual studies / Risk of bias across studies	12/ 15	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. **– MANDATÓRIO** ***Em todas as revisões sistemáticas, deverá existir um processo de avaliação da qualidade dos estudos primários. No caso de revisões sistemáticas de estudos experimentais/ensaios clínicos aleatorizados, a aplicação dos critérios de risco de viés (Risk of Bias) da Cochrane é altamente recomendada. No caso de revisões sistemáticas de estudos observacionais, poderão ser seguidos os critérios ROBINS ou os critérios dos National Institutes of Health (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).***	**Page 6: "**Risk of bias was systematically assessed using the ROBINS-I tool ("Risk Of Bias In Non-randomized Studies of Intervention")[19]."
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). **– FACULTATIVO. APENAS NECESSÁRIO SE FOR FEITA META-ANÁLISE**	**Page 6: "**Hazard ratios (HR) reported with 95% confidence interval (CI) were extracted from each individual study and used as the effect measure."
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis. **– FACULTATIVO. APENAS NECESSÁRIO SE FOR FEITA META-ANÁLISE**	**Page 6:** "All analyses were conducted using Review Manager version 5.4. For all outcomes considered, the Generic Inverse Variance method was used along with a Random Effects analysis model. For each individual study and outcome considered, the lnHR was calculated to estimate the intervention effect; additionally, standard error (SE) with 95% CI was calculated. To estimate heterogeneity, the I2 statistic was used; a I2 greater than 50% indicates that differences identified are more probably due to the heterogeneity across studies than to chance."
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. **– FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE**	Embora tenha sido realizada uma análise de sensibilidade para uma das variáveis em estudo (diâmetro aórtico ≥40mm), esta não foi incluída no manuscrito final, uma vez que os resultados não sofreram alteração. Paralelamente, o número de estudos incluídos na meta-análise das outras duas variáveis era insuficiente para permitir análises adicionais.
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. **– MANDATÓRIO**	**Pages 6 and 23:** "A total of 208 potential studies were initially identified through database searching and, after duplicates removal, a total of 128 studies titles and abstracts were skimmed. After application of the eligibility criteria a total of 33 studies were read in full and

			additionally four studies were included by backward citation. (Figure 1) By the end of the selection process a total of 16 studies were included in the qualitative synthesis and a total of 10 studies were included in the meta-analysis."
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. **– MANDATÓRIO**	**Pages 6, 7, 18 and 19: "**Table I depicts the main characteristics of each individual study included. All included studies were retrospective, most of them single-centre (n=14), with two exceptions[20,21]. It is also noteworthy that 10 studies were set in Japan[21–30], whereas 6 took place in other geographic locations: China (N=1)[31], USA (N=4)[32–35] and Europe (N=1)[20]. A total of 2395 patients were included ranging from study inclusion in January 1983[22] to March 2018[21]; Pooled analysis revealed 60% of male participants, with a median follow-up period of 2.5 years, ranging from (2.66 ± 2.88 years[30] to 6.8 years[34]). All patients were initially diagnosed with uncomplicated TBAD on enhanced computed tomography (CT) scan and initially managed conservatively[20,21,30–35,22–29]; Using information from the initial CT scan and CT scans performed during follow-up, several radiographic features were assessed in order to understand whether they played a role in the development of an unfavourable outcome[20,21,30–35,22–29]; the definition of an "unfavourable outcome" slightly differed across studies. A notable exception is the study by *Xiang et al*, where the identification of predictors of major adverse events was a secondary, rather than a primary aim[31]. Table II depicts participants' demographics across studies."
Risk of bias within and across studies	19/ 22	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). **– MANDATÓRIO**	**Pages 7 and 20: "**The ROBINS-I tool[19] was used to assess the risk of bias of each study. A total of 6 studies were classified as having a low risk of bias[22–24,31,32,34] and 10 studies were classified as having a moderate risk of bias[20,21,25–30,33,35]. Table III shows the main bias domains identified in each study (with reasons) and the risk of bias for each study."
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. **– FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE**	**Pages 7,8, 9, 10 and 21: "**Table IV summarizes main findings regarding each risk factor analysed (…)while the study by *Ray et al* reported CTD as predictive of major adverse events ($p<0.01$)[33]."
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency. **– FACULTATIVO. MANDATÓRIO APENAS SE FOR FEITA META-ANÁLISE**	**Pages 9, 10 and 24:** "With the information extracted from some of the previous studies, we ran a quantitative analysis of following relationships: (…) but results failed to reach significance (HR= 1.13; 95% CI= 0.79-1.60)."
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). **– FACULTATIVO. APLICÁVEL APENAS SE**	Não realizado pelos motivos previamente expostos no item 16.

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		FOR FEITA META-ANÁLISE	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). **– MANDATÓRIO**	**Pages 11 and 12: "**In this meta-analysis, aortic diameter ≥40 mm at presentation was the strongest predictor of major adverse events during follow-up (…) even though these features have been reported as high-risk radiographic features[15]."
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). **– MANDATÓRIO**	**Pages 12 and 13:** "Our study has some important limitations, the most important being the lack of RCT or large national registries on the subject. Included studies are mostly retrospective analysis of single centre studies (with 2 multicentric studies), with moderate quality of evidence[40]; most of them are comprised of Asian patients[21-31] and it is not certain whether results might be generalized to other ethnicities, due to lack of studies on how ethnical disparities affect the risk of major adverse events in TBAD. Indeed, some studies suggest that TBAD in African Americans occurs at a younger age and has a higher rate of reintervention than in their white counterparts[41]; differences in dissection subtype by ethnicity have also been reported[15]. Risk of bias is therefore significant."
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research. **– MANDATÓRIO**	**Page 13:** "The available evidence supports that acute and subacute TBAD patients with an aortic diameter ≥ 40 mm should probably be submitted to expedited TEVAR, as this risk factor had the greatest impact on the risk for adverse outcomes (HR) in this meta-analysis. The remaining risk factors that have been studied in the literature have weaker evidence and need additional evidence. Clarification of the real impact of some of these risk factors would benefit from the development of standards of reporting, which even with recent efforts from SVS and STS are still ill-described. A need for multicentre prospective studies, following a standardized protocol regarding outcomes definition, risk factors definition, and the impact measures used, still persist 18 years after the launch of the INSTEAD trial[42]. Additional granular data and standard reporting of risk factors in national based registries and in RCT´s will facilitate future data comparison and individualized patient data meta-analysis."
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. **– SEGUIR RECOMENDAÇÕES DA REVISTA**	**Page 17:** *"Funding.* — The authors report no involvement in the research by the sponsor that could have influenced the outcome of this work."

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Original articles. These should be original contributions to the subject. The text should be 3000-5500 words (8 to 16 typed, double-spaced pages) not including references, tables, figures. No more than 50 references will be accepted. The article must be subdivided into the following sections: introduction, materials (patients) and methods, results, discussion, conclusions. The introduction should describe the theoretical background, the aim of the study and the hypothesis to be tested. The materials and methods section should describe in a logical sequence how the study was designed and carried out, how the data were analyzed (what hypothesis was tested, what type of study was carried out, how randomization was done, how the subjects were recruited and chosen, provide accurate details of the main features of treatment, of the materials used, of drug dosages, of unusual equipments, of the statistical method ...). In the results section the answers to the questions posed in the introduction should be given. The results should be reported fully, clearly and concisely supported, if necessary, by figures, graphs and tables. The discussion section should sum up the main results, critically analyze the methods used, compare the results obtained with other published data and discuss the implications of the results. The conclusions should briefly sum up the significance of the study and its future implications. For randomised controlled trials it is suggested to the authors to conform the structure of their paper to the checklist requirements of the following guidelines reported by the CONSORT statement: **http://www.consort-statement.org**.

Review articles. These articles are commissioned by the Editor in Chief or the Managing Editor. They should discuss a topic of current interest, outline current knowledge of the subject, analyze different opinions regarding the problem discussed, be up-to-date on the latest data in the literature. Systematic reviews and meta-analyses must be subdivided into the following sections: introduction, evidence acquisition, evidence synthesis, conclusions. For systematic reviews and meta-analyses it is suggested to the authors to conform the structure of their paper to the checklist requirements of the following guidelines reported by the PRISMA statement: **http://www.prisma-statement.org**. The text should be 6000-12000 words (17 to 34 typed, double-spaced pages) not including references, tables, figures. No more than 100 references will be accepted.

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Short title, with no abbreviations. First name in full, middle name's initial, surname of the authors. Collective name, if any, as last author. Corresponding author marked with an asterisk. Affiliation (section, department and institution) of each author. Name, address, e-mail of the corresponding author.

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Articles should include an abstract of between 200 and 250 words. For original articles, the abstract should be structured as follows: background (what is already known about the subject and what the study intends to examine), methods (experimental design, patients and interventions), results (what was found), conclusions (meaning of the study). For systematic reviews and meta-analyses, the abstract should be structured as follows: introduction, evidence acquisition, evidence synthesis, conclusions. Key words should refer to the terms from Medical Subject Headings (MeSH) of MEDLINE/PubMed. No abstracts are required for editorials or letters to the Editor.

Text

Identify methodologies, equipment (give name and address of manufacturer in brackets) and procedures in sufficient detail to allow other researchers to reproduce results. Specify well-known methods including statistical procedures; mention and provide a brief description of published methods which are not yet well known; describe new or modified methods at length; justify their use and evaluate their limits. For each drug generic name, dosage and administration routes should be given. Brand names for drugs should be given in brackets. Units of measurement, symbols and abbreviations must conform to international standards. Measurements of length, height, weight and volume should be given in metric units (meter, kilogram, liter) or their decimal multiples. Temperatures must be expressed in degrees Celsius. Blood pressure must be expressed in millimeters of mercury. All clinical chemistry measurements should be expressed in metric units using the International System of Units (SI). The use of unusual symbols or abbreviations is strongly discouraged. The first time an abbreviation appears in the text, it should be preceded by the words for which it stands.

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- Standard article.

Sutherland DE, Simmons RL, Howard RJ. Intracapsular technique of transplant nephrectomy. Surg Gynecol Obstet 1978;146:951-2.

- Organization as author

International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Ann Int Med 1988;108:258-65.

- Issue with supplement

Payne DK, Sullivan MD, Massie MJ. Women's psychological reactions to breast cancer. Semin Oncol 1996;23(1 Suppl 2):89-97.

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Rossi G. Manual of Otorhinolaryngology. Turin: Edizioni Minerva Medica; 1987.

- Chapter from book

De Meester TR. Gastroesophageal reflux disease. In: Moody FG, Carey LC, Scott Jones R, Ketly KA, Nahrwold

DL, Skinner DB, editors. Surgical treatment of digestive diseases. Chicago: Year Book Medical Publishers; 1986. p. 132-58.
- Congress proceedings
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