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*Risk Factors, Incidence, and Clinical Impact of Intraluminal **T**hrombosis Following the F**R**ozen Eleph**A**nt Trunk (FET) Pro**C**edure and Thoracic Endovascular Repair (TEVAR): A multicenter r**E**trospective cohort study*

(Fattori di rischio, incidenza e impatto clinico della trombosi intraluminale dopo le procedure di Frozen Elephant Trunk (FET) e Riparazione Endovascolare Aortica Toracica (TEVAR): uno studio di coorte retrospettivo multicentrico)

Acronym: TRACE

Promoter: Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico,
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2. List of abbreviations

ILT – Intraluminal Thrombosis

FET – Frozen Elephant Trunk

TEVAR – Thoracic Endovascular Aortic Repair

CT – Computed Tomography

NYHA Classification – New York Heart Association Classification

COPD – Chronich Obstructive Pulmonary disease

3. Responsibilities (role of the promoter and collaborators)

The promoter of this clinical study is Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico.

The Principal Investigator (PI) of the study is Prof. Santi Trimarchi, *SC Chirurgia Vascolare* director, which is responsible of the clinical coordination of the study

At the same *SC Chirurgia Vascolare* belong different collaborators, which play various functions:

- *: investigator, patient screening and enrollment*
- *: investigator, patient screening and enrollment, data and imaging verification*
- *: investigator, data and imaging verification*
- *: data analysis*
- *i: study coordinator, eCRF RedCap desing, input and data verification*

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External collaborations

Institution	*Unit*	*Name*	*Role and functions in the study*
Università degli Studi di Milano	Dipartimento di Scienze Cliniche e di Comunità		Protocol review, statistical analysis, manuscript review
Università degli Studi di Milano	Dipartimento di Scienze Cliniche e di Comunità		Protocol review, statistical analysis, manuscript review

4. Amendments and other changes to the protocol

NA

5. Timelines

Study status	***Planning***
Start of the study and data collection	October 2025
End of the study and data collection	March 2026
Final report	May 2026

6. Rational and background

Intraluminal thrombosis (ILT) is a significant but underexplored complication in aortic interventions. It is defined as the formation of thrombosis, partially or totally obstructing the lumen, in the surgically treated, stented, or native aorta. In cases of Frozen Elephant Trunk interventions for which are performed regulary for type A dissections, or pathologies such as penetrating aorting ulcers or aneurysm of the distal arch or proximal descending, an ILT can occur early in the postoperative traject and have severe consequences. A recent systematic review and meta-analysis from our group (abstract attached as Annex 1; manuscript pending) analyzed data from 825 patients

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and estimated a pooled incidence of ILT of 8.6% [95% CI: 5.7-12.9]. The included studies reported ILT rates ranging from 6.2% to 16.8% (1-4). Patients with ILT had significantly higher risks of dialysis (43% vs. 16%) and mortality (25% vs. 8%). Risk factors included female gender, older age, and concomitant aortic valve replacement. Despite these findings, the underlying pathophysiology and management strategies for ILT in FET remain poorly defined

Intraluminal thrombosis (ILT) is a recognized but poorly studied complication following endovascular thoracic aortic repair (TEVAR). Case reports have described its occurrence, particularly in patients with blunt aortic trauma (5-14), and one study suggested a higher risk of intraluminal narrowing among female patients, associated with increased reoperation rates (15). However, no reliable data exist regarding the overall incidence, risk factors, or clinical outcomes of ILT following TEVAR.

A recent systematic review conducted by our group (abstract attached as Annex 2; manuscript pending) identified 10 case reports and three retrospective studies reporting highly variable ILT rates (5-14, 16-18). A study, focusing on blunt aortic trauma patients, found an ILT incidence of 20.6% in a cohort of 34 patients, while another study observed 2 cases in 97 patients (2.06%), and a third study reported 0 cases in 11 patients (0%). The lack of consistent epidemiological data highlights the necessity of a multicenter cohort study to establish a reliable incidence estimate and investigate potential risk factors and clinical outcomes.

This study aims to fill the knowledge gap through a multicenter analysis involving patients treated with FET and TEVAR. By identifying risk factors for ILT, describing related outcomes, and evaluating management strategies, the ultimate goal is to improve clinical care and outcomes for patients undergoing these procedures.

7. Research question and objectives

Question 1 – What is the incidence of ILT in patients undergoing FET or TEVAR?

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Question 2 – What are the risk factors for the onset of ILT after FET or TEVAR?

Question 3 – How does ILT modify the outcome of FET or TEVAR?

Primary objective: evaluate the incidence of ILT in patients undergoing FET or TEVAR.

Secondary objective:

1 – search for any preoperative or perioperative risk factors, for the onset of postoperative ILT in patients undergoing FET or TEVAR

2 – evaluation of outcomes (mortality, renal complication, organs and limbs malperfusion, prolonged hospitalization and ICU lenght of stay) in patients with or without postoperative ILT after receiving FET or TEVAR

8. Methods

8.1 Study design

International, multicenter, non pharmacological, retrospective, observational, cohort clinical study.

8.1.1 Primary endpoint

Incidence (percentage on total case) of postoperative ILT in patients undergoing FET or TEVAR

8.1.2 Secondary endpoint

1 – calculation of the possible correlation (pvalue, t-test and chi-test for risk factors) between perioperative factors and the occurrence of postoperative ILT in patients undergoing FET or TEVAR

2 – calculation of the possible correlation (pvalue, t-test and chi-test for risk factors) between postoperative ILT in patients undergoing FET or TEVAR, and postoperative complications

8.2 Setting

The patients examined will be those who have undergone FET or TEVAR procedures in the enrolling centers from January 2010 to June 2025. No further investigations will be performed other

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than those that are commonly performed, particularly during the postoperative follow-up (CT angiography).

8.2.1 Study population

Adult patients undergoing elective and emergency FET and TEVAR procedures between Jan 2010 and June 2025.

8.2.2 Inclusion criteria

Patients who simultaneously meet the following criteria will be included:

- age ≥18 years
- males and females
- presence of pre- and post-operative CT imaging

8.2.3 Exclusion criteria

Patients will be excluded if they meet at least one of the following criteria:

- Patients previously treated with TEVAR or FET

8.3 Variables

Demographic variables: age, sex, BMI,

Anamnestic clinical variables: comorbidities (hypertension, diabetes, hypercolesterlomia, hystory of stroke, NYHA Classification, atrial fibrillation, previous coronary disease, peripheral artery disease, COPD, liver disfunction, connective tissue disease, histroy of venous thrombosis, renal impairement, dialysis dependant, previous open or endovascular surgery)

Preoperative imaging correlated variables: type of aortic pathology, maximum aortic diameter

Perioperative and postoperative variables: type of prosthesis (diameter, length, type), intraoperative complications, number of transfusions, mortality, renal failure requiring dialysis, visceral ischemia, stroke, spinal cord injury, reoperations, aorto-related complications, prosthesis-related complications, ICU lenght of stay, total lenght of hospitalization, postoperative

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antithrombotic therapy,

Post operative imaging correlated variables: days form intervention, aortic diameter, presence of ILT, location of ILT, presence of endoleak

-Variables for primary endpoint: presence of ILT at postoperative CT angiography

-Variables for secondary endpoint 1 – age, sex, comorbidities, type of aortic pathology, type of prosthesis (diameter, length, type), intraoperative complications, number of transfusions

- Variables for secondary endpoint 2 – mortality, renal failure requiring dialysis, visceral ischemia, stroke, spinal cord injury, reoperations, aorto-related complications, prosthesis-related complications

8.4 Source documents

Eletronic Medical Records, CT scan imaging both stored according to clinical practice in the departments/archives

8.5 Sample size

For patients treated with FET, an estimated incidence of 8.6% requires a sample size of approximately 400 patients to reach a 95% confidence interval with a margin of error of ±3%.

For patients treated with TEVAR, no reliable incidence data for ILT exist. Our systematic review identified small retrospective studies with highly variable ILT rates in heterogenic cohorts, which did not allow the pooling of data. The largest study, including 97 patients, reported an incidence of 2.06%, while another study with 11 patients found 0 ILT cases. A separate study found 20.6% ILT, but this was in blunt aortic trauma patients, a highly specific subgroup that is not representative of the broader TEVAR population. Therefore, this cohort was excluded from sample size estimation.

Based on the 2.06% incidence, approximately 87 patients would be required to achieve a 95% confidence interval with a margin of error of ±3%. However, given the small sample sizes and

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uncertainty surrounding the true incidence, a conservative target of 300-400 patients is proposed to ensure sufficient statistical power. A *post-hoc power analysis* will be conducted once enough data have been collected.

8.6 Data Management

Each participant, at the time of enrollment, will be assigned a unique code. The de-identification of the data will be done in such a way that people accessing the database will not be able to trace the identity of the subjects in any way. Only local investigators will be able to trace the identity of the enrolled subjects.

The data necessary for the study will be recorded in a specific eCRF in a Data Management System validated according to national regulations, provided by the Scientific Direction of the Foundation. The platform used will be RedCap (Research Electronic Data Capture).

The REDCap Consortium is composed of >1000 institutional partners worldwide (research institutions, universities, ministries, etc.). The consortium supports a secure web application (REDCap) designed exclusively to support the acquisition of data for research studies. The REDCap application allows users to create and manage online databases quickly and securely, and is currently in use for more than 110,000 projects with approximately 150,000 users covering numerous areas of research interest across the consortium.

Through REDCap, for this study the following will be implemented: a) user-level identification, with specific restrictions based on role in the study b) real-time data validation and integrity control c) patient de-identification prior to data export d) centralized data storage with daily backup, a secure server within the Foundation's IT structure.

The Study Manager guarantees that the data of patients enrolled during the study will be stored, archived and processed in full compliance with the privacy regulations pursuant to art. 13 of Regulation no. 2016/679/EU and the current national privacy legislation, the Code of Ethics regarding the processing of data for statistical-scientific purposes and the "Guidelines for the processing of personal data in the context of clinical trials of medicinal products" published in the Official Journal no. 190 of 14 August 2008.

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Patient data will be collected in pseudonymized form and will be accessible only to internal and external personnel specifically appointed and bound by an obligation of confidentiality in relation to any information learned during the study.

The Study Manager also guarantees that he has implemented the minimum security measures prescribed by the aforementioned legislation for the processing of data using electronic and non-electronic tools, in order to avoid unlawful data processing.

8.7 Data analysis

Continuous variables will be expressed as mean with standard deviation or median with a range. Categorical variables will be presented as frequencies and percentages. Comparative univariate analyses will use Chi-square or Fisher exact tests for categorical variables and Mann-Whitney U test or t-tests for continuous variables to analyze any correlations between groups with versus without postoperative ILT.

8.7.1 Primary endpoint - analysis

The primary endpoints for analysis are the incidences of ILT following FET and TEVAR. For the primary outcome no statistical analysis will be performed, the incidence will be reported as a percentage of the total cohort in a descriptive manner.

8.7.2 Secondary endpoint - analysis

A secondary endpoint for analysis is to identify risk-factors for ILT formation after FET and TEVAR. For this purpose demographic and intraoperative variables will be compared between patients who developed an ILT and those wo did not. For continious data the Shapiro-Wilk test will be used to assess the distribution of. Depending on the normality of distribution either the t-test (normal distribution) or Mann Whitney U test (non-normal distribution) will be used. For categorical variables either the Chi-square test or the Fisher's exact test. The Chi-square test will be applied when all expected cell counts in the contingency table are ≥ 5. However, if one or more expected cell counts are < 5, Fisher's exact test will be used instead. A p-value below 0.05 will be considered statistically significant. Outcomes in terms of complications and mortality between

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patients devoloping ILT and those who do not, both in FET and TEVAR patients will be compared in the same manner.

8.8 Quality control

To ensure adequate quality control of the study, the investigator will, if requested, allow direct access to all relevant documentation and dedicate part of his/her time to discuss the results of the study. In addition, Regulatory Authorities may carry out inspections. In this case, the investigator must allow the inspector direct access to all relevant documentation, and dedicate part of his/her time and personnel to the inspector to discuss the monitoring results and any other aspects of the study. If applicable, all manual data entry must be performed by two operators to avoid any errors.

8.9 Study limitations

- The retrospective nature of the study could represent a structural bias.
- Since ILT is a relatively rare complication after FET or TEVAR, the data at our disposal may not reach a statistically significant measure.

9. Protection of the subjects enrolled

The study will be conducted in accordance with the Rules of Good Clinical Practice, the ethical principles deriving from the Declaration of Helsinki and the current regulations on observational studies.

The observational study and the related documentation will be submitted to the competent Ethics Committee of each center. The study will only begin after receiving the required authorizations according to the institution's internal procedures. The Ethics Committee must also approve any modification to the protocol and the advertising used to recruit subjects for the study, according to local regulations.

9.1 Information note to the subject and consent form for the processing of personal data

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Given the nature of Scientific Hospitalization and Treatment Institutes of the Policlinico, promoter of the study, in compliance with the current legislation on the protection of personal data (EU Regulation 679/2016) and Legislative Decree 196/2003 (Privacy Code) as amended by Legislative Decree 101/2018, for the data collected and processed within the scope of the study it will not be mandatory to ask participants for consent to the use of their personal data for the conduct of the study itself.

In compliance with the provisions of art. 110 bis paragraph IV of the amended Legislative Decree 196/2003, due to the instrumental nature that the healthcare activity assumes with respect to research at the Scientific Hospitalization and Treatment Institutes, the processing, for research purposes, of personal data already collected for clinical activity, including the anonymization of the same, does not constitute further processing.

As provided by the Authority for the protection of personal data, the aforementioned provision applies to any type of medical research (prospective and retrospective) promoted by IRCCS, even of a multi-center nature that involves the participation of entities that do not have the same nature.

Therefore, the aforementioned legal basis also extends to all other centers participating in the study that do not have the nature of IRCCS.

The IRCCS, as the Study Promoter, will be responsible for drafting an Impact Assessment to be published on its website and communicated to the Authority for the protection of personal data.

9.2 Insurance Coverage

Given the observational nature of the proposed studies, no additional insurance policies are necessary other than those already provided for normal clinical practice.

10. Dissemination and communication plan for study results

The scientific director of the study will undertake to draft a final report and to make the results public at the end of the study. The data will be made public anonymously and presented in aggregate form as requested.

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11. Publications and Intellectual Property Rights on the Results of the Study

Pubblications:

The Foundation, as Promoter, will guarantee the dissemination and publication of the study results, even in the event of negative results, without any constraints and guaranteeing the collaborating center visibility proportional to the actual participation.

Each scientific journal or publication containing the results and data of the study must indicate the role and participation of the Centers and the Foundation, in a manner proportional to the actual contribution made to the study and the role covered by each party. The data will be published in aggregate form or in any case anonymized, so as not to allow in any way the identification of the interested party to whom the data refers.

Intellectual property rights:

The Parties acknowledge that for the conduct of the collaboration within the scope of the study, data, information, know-how, inventions (patentable or not) owned by each party may be used and shared, which remains the exclusive owner even if it grants the other a right of access and use, non-exclusive and free of charge, for the sole purpose of carrying out the activities covered by the study and limited to the duration of the study. It is understood that this right of use does not include the right to sublicense to third parties.

In accordance with current legislation, the data and results generated within the scope of the Study will be owned by the Promoter, except for specific agreements between the Promoter and the Centers.

12. Financing

NA

13. Bibliography

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Annex 1. Abstract

Incidence and Clinical Importance of Intraluminal Thrombosis Following Frozen Elephant Trunk: A Systematic Review

Nesar A. Hasami[1,2,3], Michiel Been[1], Jasper F. de Kort[1,3], Guillaume S.C. Geuzebroek[2], Guido Gelpi[4], Carlo de Vincentiis[5], Himanshu J. Patel[6], Martin Czerny[7,8], Robin H. Heijmen[2], Joost A. van Herwaarden[3], Santi Trimarchi[1,9]

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Abstract

Objectives

The frozen elephant trunk procedure can treat aneurysms of both the arch and descending aorta. Although being a single stage treatment, it is associated with certain deleterious complications. Among these, intraluminal thrombosis is a relatively underrecognized but clinically significant

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complication. This systematic review and meta-analysis aimed to determine the incidence and clinical impact of intraluminal thrombosis.

Methods

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. PubMed, Web of Science, and SCOPUS databases were searched for relevant studies. Quality was assessed using the Risk of Bias in Non-Randomized Studies of Interventions tool. Evidence certainty was evaluated with Grading of Recommendations Assessment, Development, and Evaluation analysis. The primary outcome was the incidence of intraluminal thrombus (both partial and total). Meta-analysis was performed to calculate pooled proportions and weighted means with 95% confidence intervals. Additionally, patients with and without intraluminal thrombosis were compared to identify differences in clinical characteristics and outcomes.

Results

Four studies with 825 patients were included. The pooled incidence of intraluminal thrombosis was 8.6% [95% confidence interval: 5.7–12.9]. Patients with intraluminal thrombosis were older, more often female, and more likely to present with an aneurysm than a dissection. They also had higher rates of dialysis (43% versus 16%) and mortality (25% versus 8%) compared to patients without intraluminal thrombosis.

Conclusion

Intraluminal thrombosis after frozen elephant trunk procedure is not uncommon and is associated with increased mortality. These findings highlight the need for awareness, further research on risk factors, and development of preventive strategies.

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Annex 2. Abstract

Incidence and Clinical Importance of Intraluminal Thrombosis Following Frozen Elephant Trunk: A Systematic Review

Nesar A. Hasami[1,2,3], Jasper F. de Kort[1,3], Guillaume S.C. Geuzebroek[2], Constantijn E.V.B. Hazenberg[3], Robin H. Heijmen[2], Joost A. van Herwaarden[3], Santi Trimarchi[1,4]

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Abstract

Objectives

Thoracic endovascular aortic repair has expanded as a treatment for various aortic diseases, but complications such as intraluminal thrombosis remain poorly understood. This systematic review evaluates the available literature on intraluminal thrombosis after thoracic endovascular aortic repair, its incidence, and management strategies.

Methods

A systematic search of PubMed, Web of Science, and SCOPUS identified studies reporting intraluminal thrombosis following thoracic endovascular aortic repair. Retrospective cohort studies and case reports were included. Risk of bias was assessed using the Risk of Bias in Non-

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randomized Studies of Interventions tool for cohort studies and the Joanna Briggs Institute checklist for case reports. Due to study heterogeneity, findings were synthesized narratively.

Results

A total of three retrospective cohort studies and ten case reports were included. The overall incidence of intraluminal thrombosis remains unclear but appears low, except in blunt aortic trauma, where one study reported an incidence of 20.6%. Quality assessment showed a critical risk of bias in all retrospective studies, primarily due to confounding. Case reports were of moderate to good quality. In nine out of ten case reports, intervention was required, with seven patients undergoing open surgical repair. Thrombus recurrence occurred after endovascular relining in one case.

Conclusion

The literature on intraluminal thrombosis after thoracic endovascular aortic repair is scarce and of limited quality. Although the overall incidence appears low, patients treated for blunt aortic trauma may be at higher risk and require careful follow-up. Treatment should be individualized, as anticoagulation alone may not always suffice. Both open and endovascular reinterventions may provide a solution.