Transatlantic Registry of Type A Aortic Dissection (TARTAAD)

Study reference
IRAS number: **363388**
Sponsor: Helsinki University Central Hospital (Finland)
Date and Version No: 01/05/25 n. 1.0b

Leicester (national leading) site
Principal Investigator: **Dr Giovanni Mariscalco** Hon Associate Professor of Cardiac Surgery Lead for Complex Aortic Surgery Head of Service for Cardiac Surgery Consultant Cardiothoracic Surgeon Leicester University Hospital NHS Trust Glenfield Hospital Groby Road Leicester, LE3 9QP Tel : 07754309530 Email: gm247@le.ac.uk Email: g.mariscalco@nhs.net

Other UK sites:

Liverpool Site	
Principal Investigator: **Mr Mark Field** Clinical Lead for Aortic Surgery Consultant Aortic and Cardiac Surgery Liverpool Heart and Chest Thomas Drive Liverpool, L14 3PE Email: Mark.Field@lhch.nhs.uk	**Co-Principal Investigator:** **Mr Manoj Kuduvalli** Associate Medical Director for Surgery Consultant Cardiothoracic Surgeon Liverpool Heart and Chest Thomas Drive Liverpool, L14 3PE Email: Manoj.Kuduvalli@lhch.nhs.uk
Papworth Site	
Principal Investigator: **Mr Ravi De Silva** Clinical Lead for Aortic Surgery Consultant Cardiothoracic Surgeon Royal Papworth Hospital NHS Foundation Trust Papworth Road Cambridge Biomedical Campus Cambridge CB2 0AY Email: ravidesilva@nhs.net	**Co-Principal Investigator:** **Mr Shakil Farid** Consultant Cardiac and Aortic Surgeon TPD, NHS East of England Royal Papworth Hospital NHS Foundation Trust Papworth Road Cambridge Biomedical Campus Cambridge CB2 0AY Email: shakil.farid@nhs.net

Southampton	London Site
Principal Investigator: **Mr Geoffrey Tsang** Clinical Lead for Aortic Surgery Consultant Cardiothoracic Surgeon University Hospital Southampton NHS Trust Tremona Road Southampton, SO16 6YD Email: geoff.tsang@uhs.nhs.uk	**Principal Investigator:** **Mr Michael M Sabetai** Chair UK-Aortic Society Consultant Cardiac and Aortic Surgeon Guy's and St Thomas' NHS Foundation Trust St Thomas' Hospital Westminster Bridge Road London SE1 7EH Email: michael.sabetai@icloud.com
Oxford Site	**Plymouth Site**
Principal Investigator: **Prof George Krasopoulos** Consultant Cardiac and Aortic Surgeon Oxford University Hospitals NHS Foundation Trust John Radcliffe Hospital Headley Way, Headington Oxford OX3 9DU Email: george.krasopoulos@ouh.nhs.uk	**Principal Investigator:** **Dr Mathias Ferrari** Senior Cardiothoracic Fellow University Hospitals Plymouth NHS Trust Derriford Road,Crownhill Plymouth Devon PL6 8DH Email: m.ferrari1@nhs.net

Confidentiality Statement

All information contained within this protocol is regarded as, and must be kept confidential. No part of it may be disclosed by any Receiving Party to any Third Party, at any time, or in any form without the express written permission from the Chief Author/Investigator and/or Sponsor.

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1. AMENDEMNT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

2. SUMMARY

This is an observational retrospective multicentre study registry aiming at evaluating the outcomes of patients affected by type A acute aortic dissection (TAAD) undergoing surgery.

Understanding the patient's conditions and treatment strategies which are associated with postoperative outcomes is essential for an appropriate management of acute TAAD. The analysis of this large multicentre registry will allow more conclusive results on the prognostic importance of critical preoperative conditions and the value of different treatment strategies to reduce the risk of early adverse events after surgery for acute TAAD. This registry will provide insights into the long-term durability of surgery for TAAD.

3. SYNOPSIS

Title of Study	Transatlantic Registry of Type A Aortic Dissection (TARTAAD)
Sponsor	University Hospital of Helsinki (Finland)
Study Hypothesis	• Primary Hypothesis: understanding the patient's conditions and treatment strategies which are associated with postoperative outcomes is essential for an appropriate management of acute TAAD
Study Objectives	• Primary objective: to identify the predictors influencing early and late mortality in TAAD patients undergoing open heart surgery • Secondary objectives: to elucidate and identify predictors of: 1) re-exploration for bleeding; 2) cerebrovascular accident 3) surgical site infection; 4) blood transfusion; 5) acute kidney injury; 6) length of intensive care unit (ICU) stay; 7) length of hospital stay and 8) reoperation after hospital discharge; 8) late survival; 9) rate of late re-intervention.
Study Design	Retrospective observational cohort study registry
Planned Sample Size	This study will use data from 32 high-volume aortic centers. It is anticipated that the final database will approximately contain clinical details for more than 10000 patients.
Subject Selection Criteria	Inclusion criteria: • Type A aortic dissection or intramural hematoma involving the aortic root/ascending aorta; • Patients aged > 18 years: • Symptoms started within 7 days from surgery; • Primary surgical repair of acute type A aortic dissection; • Any other major cardiac surgical procedure concomitant with surgery for type A aortic dissection
Intervention	This is a non-interventional study
Study period	1 January 2010 – 31 December 2024
Follow-up/End-study	31 December 2025
Primary Outcomes	• Mortality rate during the index hospital stay until last follow-up control • Cumulative incidence of reoperation on the aorta during the index hospital stay until last follow-up control (any surgical and endovascular procedure on any segment of the aorta for aortic dissection or its related complication)
Secondary Outcomes	1) Incidence of stroke; 2) Incidence of acute kidney injury; 3) Incidence of surgical site infection; 4) Incidence of reoperation for bleeding; 5) Incidence and amount of blood transfusion; 6) Length of stay in the intensive care unit; 7) Incidence of global brain ischemia; 8) Incidence of paraplegia/paraparesis; 8) late survival; 9) rate of late re-intervention
Statistical Considerations	Continuous variables will be reported as mean and standard deviation or median and interquartile range as needed. Dichotomous and nominal variables will be reported as counts and percentages. Univariate analysis will be performed using the Mann-Whitney U test, Student's t-test, Kruskall-Wallis test, Wilcoxon test, Fisher exact test, Chi-square test, Kaplan-Meier test. Multivariable analyses will be performed using logistic, classification tree, linear and ordinal regression methods. A Bayesian hierarchical approach will be used in case of significant between center variability.

4. ABBREVIATIONS

CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
E-CABG	European Coronary Artery Bypass Grafting registry
EKFC	European Kidney Function Consortium
ERTAAD	European Registry of Type A Aortic Dissection
KDIGO	Kidney Disease: Improving Global Outcomes
RBC	Red Blood Cell
TAAD	Type A Aortic Dissection

5. BACKGROUND AND RATIONALE

5.1. Background

Acute Stanford type A aortic dissection (TAAD) is a life-threatening condition. Surgery is usually performed as a salvage procedure and is associated with increased postoperative early mortality and morbidity (1). Although early mortality has declined during the last years (2), the recent The Nordic Consortium for Acute Type A Aortic Dissection registry including 1189 patients operated from 2005 to 2015 in 8 centers showed that 30-day mortality after surgery for acute TAAD was 18% (3). The multicentre, prospective German Registry for Acute Aortic Dissection Type A including 2137 TAAD patients operated from 2006 and 2010 documented a 30-day mortality of 16.9% (4). A more recent analysis of the Society of Thoracic Surgeon database including 7353 patients operated from 2014 and 2017 for acute TAAD reported a 30-day mortality of 17% (5). Furthermore, surgery for TAAD is often complicated by major adverse events such as stroke (5) and acute kidney failure (6), which may have a significant impact on late survival. In this scenario of significant postoperative mortality and morbidity, surgeon faces the controversial issue of the extent of surgical repair for acute TAAD by avoiding a major surgical repair with its possible increased risk of early adverse event. At the same time, the surgeon would need to decide on whether to resect aortic segments which may expose the patient to the risk of late complications at the level of the aortic root (7) as well as of the aortic arch or distal to it (8). Understanding the balance between the patient's conditions which may not allow extensive procedure and those treatment strategies which may limit the risk of late adverse events in patients who remain alive long after the surgery is essential for an appropriate management of TAAD. We aim to create the present multicenter European registry of surgery for acute TAAD (ERTAAD) to evaluate the contemporary early outcomes and late durability of different surgical strategies for acute TAAD in a large study population within a long follow-up period.

5.2. Rationale of the Study

The analysis of this multicentre registry will allow more conclusive results on the prognostic importance of critical preoperative conditions and the value of different treatment strategies to reduce the risk of early adverse events after surgery for acute TAAD. This registry will provide insights into the long-term durability of surgery for TAAD.

6. AIMS AND OBJECTIVES

6.1. Primary hypothesis

Understanding the patient's conditions and treatment strategies which are associated with postoperative outcomes is essential for an appropriate management of acute TAAD.

6.2. Objectives

The primary objective of this retrospective study is to identify the predictors influencing the mortality rate during the index hospital stay until last follow-up control, and the cumulative incidence of reoperation on the aorta during the index hospital stay until last follow-up control. Secondary objectives include: 1) incidence of stroke; 2) incidence of acute kidney injury; 3) incidence of surgical site infection; 4) incidence of reoperation for bleeding; 5) incidence and amount of blood transfusion; 6) length of stay in the intensive care unit; 7) incidence of global brain ischemia; 8) incidence of paraplegia/paraparesis

7. STUDY DESIGN AND METHODS

7.1. Study Design

The ERTAAD is an observational registry, and its data will be retrospectively collected from 20 centers of cardiac surgery of university hospitals located in eight European countries (Belgium, Czech Republic, Finland, France, Germany, Italy, Nederland, Spain, United Kingdom and USA).

Below the list and location of participating centres:

	Participating hospitals	Contact persons	E-mail addresses
1	Heart and Lung Center, Helsinki University Hospital, University of Helsinki, Helsinki, Finland	Fausto Biancari Tatu Juvonen Emily Pan Mikko Jormalainen Timo Mäkikallio	tatu.juvonen@hus.fi; mikko.jormalainen@hus.fi; xiapan@utu.fi; timo.makikallio@sydankeskus.com
2	Department of Cardiac Surgery, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK	George Krasopoulos Sarvananthan Sajiram	george.krasopoulos@ouh.nhs.uk sarvananthan.sajiram@ouh.nhs.uk
3	Department of Cardiovascular Surgery University Heart and Vascular Center Hamburg, Hamburg, Germany	Till Demal	t.demal@uke.de
4	Erasmus Medical Center, Rotterdam, Holland	Jolanda Kluin	j.kluin@erasmusmc.nl
5	Department of Cardiothoracic Surgery, University Hospital Cologne, Cologne, Germany	Lenard Conradi Maximilian Luehr Anastasiia Alokhina	lenard.conradi@uk-koeln.de maximilian.luehr@uk-koeln.de anastasiia.alokhina@uk-koeln.de
6	Department of Cardiovascular Surgery, Glenfield Hospital, Leicester, UK	Giovanni Mariscalco Zein El-Dean	giovannimariscalco@yahoo.it zein.eldean@hotmail.co.uk
7	Department of Cardiovascular Surgery, University of Liverpool, Liverpool, UK	Mark Field Manoj Kuduvalli Amer Harky	mark.field@lhch.nhs.uk; manoj.kuduvalli@lhch.nhs.uk; ameralihasan.harky@lhch.nhs.uk
8	Department of Cardiovascular and Thoracic Surgery, Cabrol University Hospital, Reims, France	Giovanni Vito Ruggieri	vgruggieri@chu-reims.fr
9	Department of Cardiac Surgery, University of Dijon, Dijon, France	Andrea Perrotti Olivier Bouchot	a.perrotti@hotmail.it olivier.bouchot@chu-dijon.fr
10	Department of Cardiac Surgery, Varese Hospital, Varese, Italy	Dario Di Perna	dariodiperna@gmail.com

11	Department of Cardiac Surgery, Martin Luther University Halle-Wittenberg, Halle, Germany	Angelo M. Dell'Aquila	am.dellaquila@gmail.com
12	Department of Cardiac Surgery, LMU University Hospital, Ludwig Maximilian University, Munich, Germany	Sven Peterss	sven.peterss@med.uni-muenchen.de joscha.buech@med.uni-muenchen.de
13	Department of Cardiovascular Surgery, Hospital Clínic de Barcelona, University of Barcelona, Spain	Eduard Quintana Robert Pruna	equintan@clinic.cat pruna@clinic.cat
14	Department of Cardiac Surgery, Charles University and University Hospital Kralovske Vinohrady, Prague, Czech Republic	Petr Kacer Jan Roček	petr.kacer@fnkv.cz jan.rocek@fnkv.cz
15	Division of Cardiac Surgery, Cardiothoracic and Vascular Department, Azienda Sanitaria Universitaria Giuliano Isontina, Trieste, Italy	Giuseppe Gatti	gius.gatti@gmail.com
16	Department of Cardiac Surgery, Masarykova nemocnice, Ústí nad Labem, Czech Republic	Marek Pol	pol.marek@email.cz
17	Department of Cardiothoracic Surgery, University Hospital Muenster, Muenster, Germany	Konrad Wisniewski	konrad.wisniewski@ukmuenster.de
18	Cardiovascular Surgery Department, University Hospital Gregorio Marañón, Madrid, Spain	Javier Rodríguez Lega Ángel González Pinto	jrl2003@gmail.com angel.g.pinto@gmail.com
19	Department of Cardiothoracic Surgery, Kuopio University Hospital, Kuopio, Finland	Antti Valtola	antti.valtola@pshyvinvointialue.fi
20	Heart Center, Turku University Hospital, Turku, Finland	Vesa Antila	vesa.anttila@tyks.fi
21	Department of Cardiac Surgery, University Hospital Southampton NHS Foundation Trust, Southampton, UK	Geoffrey Tsang	geoff.tsang@uhs.nhs.uk
22	Department of Cardiac Surgery, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA	Cristiano Spadaccio	cristianospadaccio@gmail.com
23	Division of Cardiothoracic Surgery, Department of Surgery, Westchester Medical Center, Valhalla, NY, USA	David Spielvogel Corazon De La Pena	spielvogeld@wcmc.com corazon.delapena@wmchealth.org
24	Department of Cardiothoracic Surgery, University Hospitals Plymouth, Plymouth, UK	Matthias Ferrari	m.ferrari1@nhs.net
25	Division of Vascular Surgery, Henry Ford Hospital, Detroit, USA	Loay Kabbani	lkabban1@hfhs.org
26	Division of Cardiac Surgery, University of Verona Medical School, Verona, Italy	Giovanni Battista Luciani	giovanni.luciani@univr.it
27	Cardiac Surgery Unit, Cardiovascular Department, Cliniques Universitaire Saint Luc, Brussel, Belgium	Matteo Pettinari	matteo.pettinari@gmail.com
28	Department of Cardiothoracic Surgery, Maastricht University Medical Centre (MUMC+), Netherlands	Samuel Heuts Elham Bidar	sam.heuts@mumc.nl elham.bidar@mumc.nl
29	University Hospital Puerta de Hierro Majadahonda, Madrid, Spain	Carlos Esteban Marin	carlosestebanmartin@hotmail.com
30	Department of Cardiovascular Surgery, University Medical Center Mainz, Mainz, Germany	Philipp Pfeiffer	philipp.pfeiffer@unimedizin-mainz.de
31	Daepartment of Cardiac Surgery Royal Papworth Hospital NHS Foundation Trust	Ravi De Silva Shakil Farid	ravidesilva@nhs.net shakil.farid@nhs.net
32	Department of Cardiac Surgery, St Thomas' Hospital	Michael.Sabetai@icloud.com	michael.sabetai@icloud.com

7.2. Inclusion criteria

- TAAD or intramural hematoma involving the aortic root/ascending aorta
- Patients aged > 18 years
- Symptoms started within 7 days from surgery
- Primary surgical repair of acute TAAD
- Any other major cardiac surgical procedure concomitant with surgery for TAAD

7.3. Exclusion criteria

- Patients aged < 18 years
- Onset of symptoms > 7 days from surgery
- Prior procedure for TAAD
- Retrograde TAAD (with primary tear located in descending aorta)
- Concomitant endocarditis
- TAAD secondary to blunt or penetrating chest trauma

7.4. Ethics and Informed Consent

Permission to conduct this study will be requested from institutional or national review boards according to local legislation. Informed consent will be waived since this is a retrospective study and only anonymised data will be collected.

7.5. Schedule

Only TAAD patients undergoing open heart surgery between 1 January 2010 and 31 December 2024 will be retrospectively retrieved and enrolled in the study. Deadline for submission of data is set up for 31 December 2021.

7.6. Source of Data

Source documents are original documents, data, and records at Glenfield Hospital (University Hospitals of Leicester NHS Trust). These include hospital records, clinical and office charts, laboratory and pharmacy records, and imaging test results. No hospital documents will be stored or retained.

7.7. Variables to be Collected and Definitions

Variables to be collected are defined according to relevant literature and definition provided below:

▪ *Onset of symptoms to surgery*

It refers to the time (in hours) between the onset of symptoms associated with TAAD and the start of surgery.

▪ *Estimated distance to hospital*

Distance (in km) between the place where patients experience onset of symptoms associated with TAAD and the hospital where primary surgery was performed.

▪ *Nighttime surgery*

It refers to a procedure which started between 20:00-08:00.

▪ *Preoperative laboratory parameters*

Data on preoperative levels of creatinine (in micromol/L), hemoglobin (in g/L), platelet count (x10/L) and arterial lactate (in mmol/L) as measured immediately before the start of surgery.

▪ *Preoperative parameters of myocardial ischemia*

Coronary malperfusion will be defined according to preoperative increased levels of troponin/CK-MB and/or ECG changes of myocardial ischemia. When cardiac biomarkers are measured, this information will be gathered.

▪ *Renal function*

Baseline renal function will be classified according to the estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (9) and the European Kidney Function Consortium (EKFC) equation (10). The severity of renal failure will be classified in different stages as listed in Table 1.

Table 1. Stages of chronic kidney disease.

Stages	**eGFR (mL/min/1.73 m^2)**
1	≥90
2	60-89
3	45-59
4	30-44
5	15-29
6	<15 or dialysis

Abbreviation: eGFR, estimated glomerular filtration rate.

▪ *Genetic syndromes*

Genetic syndromes may lead to aortopathies and TAAD (11). Information on any specific genetic syndrome associated with TAAD will be collected in this registry.

▪ *Family history of aortic dissection and aneurysm*

It refers to dissection and/or aneurysm involving any segment of the aorta in first or second-degree relatives.

▪ *Prior aortic surgery*

Any open surgery or endovascular repair on any segment of the aorta. Details on the type of procedure will be collected.

▪ *Iatrogenic TAAD*

TAAD secondary to any surgical or endovascular procedure performed within a week before surgery. Details on the timing and type of procedure will be collected.

▪ *Preoperative antithrombotic drugs*

Exposure to any of the following antithrombotic drugs within 2 days from surgery: aspirin, clopidogrel, ticagrelor, prasugrel, ticlopidine, low-molecular weight heparin, unfractionated heparin, fondaparinux, direct oral anticoagulants and/or warfarin. When data on preoperative antithrombotic drugs were not available, this will be reported in the datasheet.

▪ *Arterial hypertension*

Systemic arterial pressure > 150/80 mmHg or use of antihypertensive drugs.

▪ *Diabetes*

Hyperglycemia requiring treatment with insulin or oral drugs.

▪ *Prior stroke*

Any preoperative focal or global neurological syndrome caused by ischemia or hemorrhage not resolving within 24 h. It refers to a neurological event occurring any time, but excluding those acute neurological events related to TAAD.

▪ *Prior transient ischemic attack*

Any preoperative focal or global neurological syndrome caused by ischemia or hemorrhage resolving within 24 h. It refers to a neurological event occurring any time, but excluding those acute neurological events related to TAAD.

▪ *Pulmonary disease*

Use of bronchodilators and/or steroids for lung diseases (12).

▪ *Extracardiac arteriopathy*

One or more of the following: lower limb claudication, critical limb ischemia, carotid occlusion or >50 % stenosis, major amputation for arterial disease, previous or planned intervention on the abdominal aorta or on the extremities or carotid arteries (12).

▪ *Prior myocardial infarction*

History of myocardial infarction excluding to those events (coronary malperfusion) related to TAAD.

▪ *Prior percutaneous coronary intervention*

History of percutaneous coronary intervention any time before surgery excluding those procedures resulting in iatrogenic TAAD.

▪ *Critical preoperative state*

Critical preoperative state will be defined as one of the following conditions: 1) preoperative external cardiac massage any time before surgery, 2) cardiogenic shock requiring inotropes any time before surgery, 3) preoperative invasive mechanical ventilation before admission to the anesthetic/operating room and 4) preoperative acute renal failure (anuria or oliguria <10ml/hr) (12). Data on each of these conditions will be collected.

▪ Urgency of the procedure

Urgency of the procedure will be classified in five categories whose definition criteria are summarized in Table 2.

Table 2. Urgency of the procedure.

Urgency	Definition
Urgent	Scheduled procedure performed in a patient with stable conditions during the index hospitalization
Emergency grade 1	Emergency procedure performed in a patient with stable conditions before the beginning of the next working day after decision to operate
Emergency grade 2	Emergency procedure performed for hemodynamic instability requiring inotropes before the beginning of the next working day after decision to operate – no cardiopulmonary resuscitation with external cardiac massage
Salvage grade 1	Salvage procedure: patients requiring cardiopulmonary resuscitation with cardiac massage between induction of anesthesia and initiation of cardiopulmonary bypass
Salvage grade 2	Salvage procedure: patients requiring cardiopulmonary resuscitation with external cardiac massage en route to the operating theatre or prior to induction of anesthesia

▪ *Penn Classification*

The Penn Class of each patient will be derived considering the components of this risk classification (15).

▪ *Neurological status immediately before procedure*

Data on derangements of neurological status such as unconsciousness before sedation, hemiplegia/hemiparesis, paraplegia/paraparesis, dysarthria/aphasia, vision disturbances, visuospatial neglect (individual fails to detect stimuli on a space that is contralateral to a hemispheric lesion), severe confusion, or intubated/sedated at arrival will be reported as separate variables.

▪ *Malperfusion*

Malperfusion refers to acute organ ischemia secondary to aortic branch vessel hypoperfusion. This severe condition is usually classified based on clinical signs and symptoms (15,16). Herein, myocardial malperfusion will be defined as any changes in ST level in electrocardiogram and/or an increase in cardiac enzymes. Cerebral malperfusion will be defined as signs and symptoms related to acute preoperative stroke or cerebral hypoperfusion. Spinal malperfusion will be defined as acute paraparesis/paraplegia. Mesenteric malperfusion will be as sudden, mild-to-severe abdominal pain with or without nausea and vomiting, which is accompanied by rectal bleeding or bloody diarrhea in case of colon ischemia (17). Renal malperfusion will be defined as anuria/oliguria. Peripheral malperfusion will be defined as loss of pulse with or without sensory or motor deficits of any limb.

▪ *Preoperative computed tomography findings*

Preoperative computed tomography scans will be reviewed for evaluation of the extent of aortic dissection/intramural hematoma in different segments of the aorta and its branches. Dissection of the aortic branches will be defined as any intimal flap at the origin of the artery causing stenosis of any severity. This applies also to aortic branches perfused through the false lumen.

Data on maximal diameter of the aortic root, ascending aorta, aortic arch, descending aorta and abdominal aorta will be collected.

▪ *Intramural hematoma*

Intramural hematoma is defined as a contained aortic wall hematoma within the media, but without intimal flap formation. Patients with intramural hematoma and concomitant intimal flap in any segment of the aorta will be classified as having typical aortic dissection.

▪ *Heart valve status and left ventricular function*

Data from preoperative echocardiographic evaluation of the aortic valve, mitral valve and left ventricular function will be collected.

▪ *Arterial and venous cannulation sites*

It refers to the primary cannulation sites. Any switch to other cannulation site before initiation of cardioplegia will be described.

▪ *Intraoperative findings*

Data on the intraoperative findings of the pericardium, ascending aorta and aortic arch will be collected. The extent of aortic dissection at the level of the Valsalva sinuses and morphology of the aortic valve will be described. Injury of the coronary ostia will be classified as spontaneous when related only to dissection or iatrogenic when related to the procedure. Injury of the coronary ostia can be both spontaneous and iatrogenic.

▪ *Surgical repair*

Data on the type of aortic root/ascending aorta and aortic arch surgical repair will be collected along with data on any major concomitant cardiac surgery procedure. Details of the level of aortic anastomosis and suture techniques will be documented.

▪ *Cardiopulmonary bypass parameters*

Data on duration of myocardial ischemia, cardiopulmonary bypass, hypothermic circulatory arrest and retrograde or antegrade cerebral perfusion will be collected. When multiple periods of perfusion or organ ischemia have occurred, the total length of these periods will be reported. The lowest temperature during hypothermic circulatory arrest will be documented. Hypothermic circulatory arrest will be defined as the duration of discontinuation of systemic perfusion independently of the use and duration of antegrade or retrograde cerebral perfusion. Many colleagues may not agree with this definition criterion. However, this definition may be helpful from a statistical point of view to identify different perfusion strategies. The use and duration of antegrade or retrograde cerebral perfusion will be of help to further identify different strategies used at each participating center.

▪ *Outcomes and Their Definition Criteria*

▪ *Intraoperative death*

Death occurred in the operating room at the end of the index procedure.

▪ *Hospital death*

All-cause death having occurred during the index hospitalization, i.e., at the institution where surgery for TAAD was performed.

▪ *Stroke*

Acute episode of a focal or global neurological deficit with at least one of the following: change in the

level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke duration of a focal or global neurological deficit ≥ 24 h; OR <24 h if available neuroimaging documents a new brain hemorrhage or infarct; OR the neurological deficit results in death (17). Stroke will be classified as ischemic, hemorrhagic or both.

▪ *Global brain ischemia*

Diffuse hypoxic damage as diagnosed at brain imaging and electroencephalography.

▪ *Paraplegia/paraparesis*

Bilateral weakness and/or multimodality sensory disturbance below the level of the ischemic spinal lesion.

▪ *Mesenteric ischemia*

Abdominal pain with or without nausea and vomiting and rectal bleeding or bloody diarrhea (18). Diagnosis is made at imaging, endoscopy and/or surgery.

▪ *Sepsis*

Sepsis is defined as severe systemic infection diagnosed in blood cultures, which may lead to life-threatening organ dysfunction.

▪ *Deep sternal wound infection/mediastinitis*

Proven infection involving deep sternal wound tissues and/or mediastinum.

▪ *Acute Heart failure*

Acute heart failure requiring prolonged postoperative treatment with inotropes (>24 hours) and/or mechanical circulatory support.

▪ *Mechanical circulatory support*

The use of intra-aortic balloon pump (IABP) and/or venoarterial extracorporeal membrane oxygenation (VA-ECMO) for postoperative acute heart failure unresponsive to medical treatment. The configuration and duration of treatment of these salvage therapies will be documented.

▪ *Postoperative peak level of creatinine, dialysis and acute kidney injury*

It will be defined according to postoperative change in serum creatinine levels and its severity will be stratified according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria (19) (Tab. 3). However, in view of the prolonged hospital treatment of TAAD patients, changes in serum

creatinine level will be evaluated as occurring during the index hospitalization. We recognize that acute kidney injury can also be diagnosed according to urine output measure, however, this method is not feasible in retrospectively gathered data and this will not be considered in the present study. Dialysis will be defined as temporary when discontinued and permanent if continued at the time of discharge from the institution where the index surgery was performed.

Table 3. Definition criteria of postoperative acute kidney injury.*

Stages	Serum creatinine
1	1.5-1.9 times baseline OR ≥0.3 mg/dL (≥26.5 micromol/L) increase
2	2-2.9 times baseline
3	≥3.0 times baseline OR Increase to ≥4 mg/dL (≥353.6 micromol/L) OR Initiation of renal replacement therapy

*Changes in serum creatinine level occurring during the index hospitalization.

▪ *Perioperative bleeding*

Data on the number of transfused units of red blood cell will be collected. The E-CABG bleeding classification has been proposed as a simple classification of perioperative bleeding (20) and it has been shown to be comparable to the Universal Definition of Perioperative Bleeding (21) in predicting early mortality (22). Herein we will adopt a simplified version of the E-CABG perioperative classification, which defines severe bleeding as reoperation for excessive intrathoracic bleeding and/or transfusion of more than 4 units of red blood cells (Table 4). The number of transfused units of red blood cells will be considered as the overall number of transfused units during the index hospitalization (both during the stay in the intensive care unit and in the ward).

Table 4. Simplified E-CABG perioperative bleeding classification (20).

Grades	Intervention for treatment of bleeding
0	No RBC transfusion or transfusion of 1 unit of RBCs
1	Transfusion of 2-4 units of RBCs
2	Transfusion of 5-10 units of RBCs
3	Transfusion of >10 units of RBCs

Abbreviation: RBC, red blood cell.

▪ *Reoperation for bleeding*

Chest reopening for excessive bleeding. It qualifies as a reoperation for bleeding also any reoperation for hemostasis in patients in whom the sternum was left open. Chest reopening for hemodynamic instability without excessive bleeding, pericardial/pleural puncture or chest drain insertion for retained blood syndrome do not qualify as reoperation for bleeding.

▪ *Postoperative lowest level of hemoglobin*

The lowest level of hemoglobin will be recorded as a further measure of perioperative bleeding.

▪ *Laryngeal nerve palsy*

Injury of the recurrent laryngeal nerve injuries resulting in vocal cord paresis and in voice changes or hoarseness.

▪ *Tracheostomy*

Tracheostomy performed any time during the index hospitalization.

▪ *Procedures for vascular complications*

Any vascular and endovascular procedure for ischemic or bleeding complications.

These complications will encompass neurologic complications, mesenteric ischemia, upper and lower limb ischemia as well as bleeding from the aorta and its branches.

▪ *Length of stay in the intensive care unit*

Overall length of treatment in the intensive care unit, including readmissions, at the institution where the primary surgery for TAAD was performed, i.e. during the index hospitalization.

▪ *Last follow-up date*

It refers to the last date when the patient was reportedly alive or the date of her/his death.

▪ *Patients lost to follow-up*

Patient will be considered lost to follow-up when no information is available on her/his survival status within the last 3 months of the date of data collection.

▪ *Reoperation data*

Data on any surgical and/or endovascular reoperation on any segment of the aorta and/or aortic valve will be collected. Information on the aortic segments treated during reoperation/s will be collected along with the indication for repeated aortic procedure.

Noteworthy, aortic reoperation will be classified as a prophylactic procedure when it was performed for completion of the primary procedure for aortic remodeling without evidence of TAAD-related complications.

8. Statistical Analysis

8.1. Number of Participants

An estimated number of 20-25 patients affected by TAAD and undergoing open heart surgery are usually admitted in mid/high-volume aortic centres (1). Therefore, it is estimated that the registry will encompass more than 5000 patients in total. Locally, the number of patients admitted to Glenfield Hospital (University Hospitals of Leicester NHS Trust) fulfilling the inclusion criteria between 1 January 2010 and 31 December 2025 is (average) 15-20 per year.

8.2. Sample Size Calculation

The impact of total aortic arch repair compared to more limited aortic resection on the early and late outcomes will be one of the main topics of research from this registry. Therefore, in the light of the expected limited frequency of this surgical strategy, we performed a sample size analysis considering the extent of distal aortic resection. Despite the limitation of a pooled analysis which did not take in to account the cumulative incidences from competing risk analysis and the segment of repeat operation, Poon et al. (24) estimated a pooled hazard ratio on 0.73 (95%CI 0.56-1.18) of freedom from any late aortic reoperation for total arch replacement. Based on this hazard ratio, a sample size of 163 patients per study groups would be enough to reject the null hypothesis (alpha 0.05, power 0.80). Pan et al. (25) reported a freedom from distal reoperation after ascending aortic resection at 8 years of 95.3% which was not statistically different from that of hemiarch or total aortic arch repair (92.4%, p=0.22). For the sample size calculation of a non-inferiority trial, we assumed a freedom rate from distal aortic reoperation of 95% and we considered that a difference in the reoperation rate as large as 10% in favor of a total aortic arch repair still allow the less extensive repair to be non-inferior (delta=0.1, power 0.90, one-sided confidence 97.5%), the required sample size would be 100 patients per each group. We assume that about 5% of patients have undergone total arch repair in this collaborative registry and therefore a study population of 4000 patients would be enough to investigate the impact of total aortic arch repair in preventing late aortic reoperation in patients with acute TAAD.

8.3. Statistical Analysis

Statistical analyses will be conducted using Stata v. 15.1 (StataCorp LLC, Texas, USA) and SPSS v. 29.0 (IBM Corporation, Armonk, NY, USA) statistical softwares. Continuous variables and outcomes will be summarized as mean and standard deviation as well as median and interquartile range. Categorical variables and outcomes will be reported as counts and percentages. A $p<0.05$ will be set for statistical significance. Differences between the study groups will be evaluated using the Fisher's exact test, the Chi-square test, the linear-by-linear association test, the Mann-Whitney test and the Kruskal-Wallis test. The McNemar test and paired samples T-test will be used in case of

analysis of paired groups. Propensity score matching will be performed to balance treatment strategies for baseline differences. A propensity score will be estimated using a non-parsimonious multilevel mixed-effects logistic regression considering the cluster effect of the participating centers whose results may be affected by the referral pathway, surgical techniques and perioperative care. Multilevel mixed-effects logistic regression model will include all available baseline variables. One-to-one propensity score matching will be performed using a caliper width of 0.2 of the standard deviation of the estimated logit. Standardized differences <0.10 will be considered an acceptable imbalance between the matched cohorts. The estimated propensity score will be also included into regression models to adjust for multiple confounders or for analysis within its strata.

Logistic and linear regression analyses will be employed to identify independent risk factors for early adverse events with and without a stepwise approach. For the purpose of developing a risk scoring method from this registry, the study cohort will be randomly divided into two datasets, i.e. the derivation data set (75.0% of patients) and the validation data set (25.0% of patients). Univariate analysis will be performed on all candidate covariates of the derivation dataset to identify predictors of in-hospital mortality. Multiple logistic regression analysis will be then performed using the derivation dataset. A stepwise procedure with a bootstrap approach will be used, and 100 samples will be extracted with a size of 70% of the derivation dataset. A stepwise procedure will be applied to each sample (probability to stay = 0.05; probability to entry = 0.1). Variables selected in at least 50% of the stepwise procedures will be included in the regression model. Additional covariates were selected using a forward selection comparing the Akaike information criterion for the models with and without each covariate. The model with the lowest Akaike information criterion will be selected for each forward step, until the inclusion of a new covariate determined an increase in the Akaike information criterion value. The model will be tested in the validation data set for calibration, using the Hosmer–Lemeshow test, and for discrimination using the receiver-operating characteristic curve analysis. A comparison of the predictive ability of the new score with the current risk scoring methods for prediction of in-hospital mortality will be performed in the overall dataset as well as in the validation dataset using the DeLong test. The improvement of discrimination of the new score will be estimated by calculating the net reclassification index and the integrated discrimination improvement.

Interinstitutional and between-surgeons differences in terms of early outcomes will be evaluated using logistic regression. The risk-adjusted rate of adverse binary events at each center will be estimated by dividing the observed number of adverse events by the expected number of adverse events, and by multiplying this ratio by the average event rate of the overall series. The expected numbers of adverse events will be calculated with logistic regression. The estimated risk-adjusted rates of adverse events will be summarized as odds ratios and their 95% confidence intervals in caterpillar plots with the x-axis ordered for increasing adjusted rates.

8.3. Measures Taken to Avoid Bias

All necessary steps will be taken to reduce the risk of bias. A preliminary validation and checking of collected variables will be performed by the second local PI. Transcriptional discrepancies will be harmonized, and clinical and temporal conflicts and extreme values will be highlighted by the data master and re-sent for final corrections. No attempt to replace missing values will be made.

8.4. Frequency of Analysis

Statistical analyses and sub-group study analyses will be performed after the end of recruitment data (31 December 2025).

8.5. Data Management

The dataset will be anonymized and will not be shared between the participating centers to avoid any infringement of current privacy policies. Indeed, the Access datasheet was chosen for data collection to protect each institution's data avoiding gathering all the data into a web cloud. Data management and analysis will be conducted by the investigators of the Helsinki University Hospital, Finland. Investigators from other centers who are willing to accomplish their own studies for the TARTAAD will get the results of statistical analysis from the sponsor.

9. DATA HANDLING AND RECORD KEEPING

9.1. Data Protection

The name and any other identifying detail will NOT be included in any study data electronic file. Data will be collected and retained in accordance with the General Data Protection Regulation.

9.2. Data Handling, Storage and Sharing

Data will be entered onto a purposely-designed Excel encrypted database (Microsoft, Redmond, WA) obtained from the master Access database. The database file will be retained in a secure location (hard-drive computer in the University Hospitals of Leicester NHS Trust-Glenfield Hospital site). In compliance with the MRC Policy on Data Preservation, the anonymised dataset, a separate secure electronic 'key' with a unique patient identifier, will be retained in electronic form for potential controls. The final database version to be sent to the sponsor for merging will be completely anonymised. Please see the detailed "Database management" attachment.

9.3. Dissemination of Findings

The findings will be disseminated by usual academic channels, i.e. presentation at international

meetings, as well as by peer-reviewed publications and through patient organisations and newsletters to patients, where available.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, host institution, and the regulatory authorities to permit trial-related monitoring, audits and inspections.

11. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, relevant regulations and standard operating procedures.

12. STUDY GOVERNANCE

12.1. Sponsor Approval

This clinical trial will be sponsored by the Helsinki University Central Hospital and will be conducted in accordance with:

• International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines

• Research Governance Framework for Health and Social Care, the European Union Directive 2001/20/EC on clinical trials

• General Data Protection Regulation

• Human Tissue Act 2004

Any amendments to the trial documents must be approved by the sponsor prior to submission to the REC and/or implementation.

12.2. NHS Approval

Approval from University Hospitals Leicester NHS Trust will be obtained prior to the start of the trial. Any amendments to the trial documents will be submitted to the Trust for information or approval as required.

12.3. Investigators' Responsibilities

The investigators will be required to ensure that the local research approvals have been obtained. Investigators will be required to ensure compliance to the protocol. Investigators will be required to allow access to study documentation or source data on request for monitoring visits and audits

performed by any regulatory authorities.

12.4. Clinical Trial Authorisation

This is not a randomised trial of an Investigational Medicinal Product and as such a Clinical Trial Authorisation from the MHRA is not required.

12.5. End of the study

The study will be concluded with the end of patient recruitment: 31-Dec-2025. This will represent also the end of follow-up and data collection.

13. FUTURE DEVELOPMENT

13.1. Implications for the Treatment of TAAD Patients

Analysis of the data from this collaborative registry will allow analysis of contemporary results of a large number of TAAD patients with a lengthy follow-up period. We expect that the multicentre nature of this registry will allow reduction in the risk of bias related to institutional volume and surgical experience. In fact, all the participating centers have an annually rate of at least 25 procedures for acute TAAD and have an aortic surgery program which would facilitate an adequate follow-up and management of possible late aortic events after primary repair of TAAD. Therefore, we expect to gather data which will provide important insights into the assessment of the operative risk of patients with acute TAAD and conclusive results on the value of different surgical and perfusion strategies for this emergency condition.

13.2 Limitations

The retrospective nature is the main limitation of this registry. However, our aim is to investigate the long-term outcome (>10 years) of these patients and this may not be feasible with a prospective registry. Second, the prognostic impact of different treatment strategies will be analyzed using several statistical methods to adjust for baseline differences. However, the lack of randomization does not prevent the effects of confounding variables. Third, perioperative care may significantly vary between institutions as well as individual surgeons and their effects should be considered in all analyses.

13.3. Strengths

This registry will include detailed data on patients' characteristics, operative strategies and outcomes from centers with large volume of cardiac surgery and significant experience in the

treatment of acute and chronic aortic diseases. This may reduce the risk of bias related to limited experience in the surgical treatment of aortic diseases. This multicenter registry will allow recruiting of more than 10000 patients, which is expected to decrease the risk of type II errors. The long follow-up of this study will allow reliable analysis of the durability of different surgical repair strategies.

13.4. Conclusions

The ERTAAD is expected to recruit a large number of patients who underwent surgery for acute TAAD. This multicenter study will allow the identification of risk factors associated with major adverse events and of strategies for adequate end-organ protection. The rather long follow-up of this registry will provide solid data on the durability of different types of aortic repair strategies.

14. PUBLICATION POLICY

A summary of study findings will be available to participants on request. We intend to disseminate any findings from our research in peer-reviewed journals. All clinicians and researchers involved in the project will be acknowledged in written papers. For each output, a writing team will be convened from the study group and any external collaborators necessary. Authorship will be decided on a paper-by-paper basis.

Each center participating in the TARTAAD will be represented by two coauthors in the main coauthors' list of each article. The investigators who will accomplish their own study will have the right to list up to four coauthors from their Institution.

The TARTAAD is expected to provide data accomplish 42 studies. These studies will be submitted for publication in peer-review international journals in the fields of surgery and cardiology.

15. COMPETING INTERESTS

The participants/authors do not have any conflict of interest related to this study.

16. FUNDING

This study will be performed without external financial support.

17. CONFLICT OF INTERST

The principal investigators of the TARTAAD do not have any conflicts of interest related to the topic of these studies.

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