Scandinavian trial of Uncomplicated Aortic Dissection Therapy

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Primary Objective: The primary objective of the study is to determine the superiority of TEVAR versus SMT in reducing the incidence of all-cause mortality. Secondary Objectives: The secondary objectives of the study are:• To compare the risk of...

Ethical review	Approved WMO
Status	Pending
Health condition type	Aneurysms and artery dissections
Study type	Interventional

Summary

ID

NL-OMON56870

Source
ToetsingOnline

Brief title
SUNDAY

Condition

- Aneurysms and artery dissections

Synonym
aortic tear, Dissection, inner wall tear aorta

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Onderzoekers worden niet betaald.

Intervention

Keyword: Aortic dissection

Outcome measures

Primary outcome

The primary analysis will be based on the intention to treat principle using the full analysis set and all-cause mortality events as confirmed by the local investigator. The primary objective of the study is to determine the superiority of TEVAR versus SMT in reducing the incidence of all-cause mortality.

Secondary outcome

The endpoints will be collected from the electronic database and correlated, where relevant, with the individual national board of health registries

• Aortic-related mortality: Death as a result from aortic rupture or organ malperfusion, or death due to aortic intervention.

• Aortic intervention: Any open surgical or endovascular intervention performed in any anatomical location, performed for the following indications, which are related to the aortic pathology: aneurysmal degeneration, visceral ischemia, lower extremity ischemia, rupture, or any of the criteria listed above under the definition of a complicated TBAD. 1,28 Both the timing and indication for the aortic intervention should be recorded. Importantly, the decision for intervention is at the discretion of the treating physician and medical team.

• Neurological injury: These are divided into two categories: cerebrovascular accidents (CVA) and spinal cord ischemia (SCI). CVAs are defined according to the Society for Vascular Surgery reporting standards and classified as any

central neurological complication, ischemic and hemorrhagic. For this project, the modified Rankin scale will be used for classifying stroke severity.29
Spinal cord ischemia is defined as either ischemic or hemorrhagic resulting in paraparesis or paraplegia. The modified Tarlov scoring scale will be used for the grading of any spinal cord injuries.30 It is recommended, but not mandatory, that an independent neurologist be consulted for this purpose.
• Reintervention: Any open or endovascular intervention after the original TEVAR procedure that was related to the dissection. These should be categorized as either planned reintervention, e.g., a staged procedure, or unplanned, which indicates a complication from the original procedure, a failure of the device, or progression of disease.
• Quality of life: The quality of life will be assessed with the three following self-assessment forms:
1)The EuroQOL-5D-5L instrument from the EuroQol Group, comprised of five dimensions with five levels of scoring that can be combined into a five-digit number of description.
2)The Hospital and Anxiety Depression Score (HADS)
3)The 12-Item Short-Form (SF-12) Health Survey.

The economic evaluation will be performed from a payer/healthcare point of view, including resource use associated with healthcare, intervention and medication, whereas broader potential consequences for society, i.e., effects on productivity, will not be included. During the course of the trial, the accumulated costs will be measured per treatment arm from the participating

hospital*s administrative/controlling/billing systems. As far as possible, the following resource use items will be included and captured as accumulated costs from the hospital*s cost-per- subject system on all outpatient and inpatient visits:

• costs for healthcare staff
• subject -specific costs for primary and secondary endovascular and surgical procedures postoperative care unit costs
• costs of drugs during surgery and postoperative care
• costs of anaesthetic procedures and blood transfusions
• additional diagnostic procedures from the radiology and clinical physiology departments and from clinical chemistry.

The costs for healthcare staff will comprise the full wage costs, including costs for social security. Costs for each endovascular and surgical procedure will be retrieved individually, and, as far as possible, be based on the price per minute according to the hospital*s cost-per-subject systems.

Changes in health status will be assessed in terms of quality-adjusted life-years (QALYs), which combine the time spent in a specific health state with the corresponding self-assessed health-related quality of life (HRQoL), as derived from the EuroQOL EQ-5D-5L questionnaire. Time is measured in years and the HRQoL is measured on an index scale ranging from 0 (equivalent to being dead) to 1 (best possible health state). The total number of QALYs will be

calculated by multiplying the HRQoL index score (QALY weight) by the time spent in each health state. Group differences in total costs will be calculated and divided by the difference in QALYs in the interval from baseline until end of study, and the incremental cost-effectiveness ratio will be calculated as follows:

(CostTEVAR *CostSMT)/(QALYsTEVAR * QALYsSMT)=ΔCost/ΔQALY.

Study description

Background summary

An acute aorta dissection (AD) is the sudden tearing of the inner layer of the aorta and, depending on its location and severity, can lead to frank rupture or often times to splitting of the aorta into several lumens, typically two, a true and a false lumen. There is a timeframe for ADs, that is, they are classified according to their chronicity: acute, <= 14 days, subacute, 15-90 days, and chronic,> 90 days.

For the sake of simplicity, there are essentially three types of ADs. Dissections more proximal, or closer to the heart and proximal to the left subclavian artery are termed Type A dissections, and these almost always require immediate open surgery. There are then two types of dissections in the descending aorta, which are labelled Type B aorta dissection (TBAD), which are divided into either complicated (cTBAD) or uncomplicated (uTBAD). According to the European Society of Vascular Surgery, a complication is defined as the presence of one or more of the following: rupture, hypotension/shock, organ malperfusion, rapid aortic expansion, paraplegia/paraparesis, or intractable pain or hypertension.1,2 As these cTBADs pose an immediate threat to survival, prompt intervention, either open surgery or endovascular (minimally invasive-catheter-based) treatment, is also necessary. The final group of dissections, the uTBADs, invoke a more varying and unpredictable clinical trajectory. These individuals have traditionally been treated conservatively with medication and *watchful waiting*, and there is currently no high level of evidence regarding the best treatment. This paradigm may need changes, based on some of the findings described below.

The incidence of TBADs is estimated at 3.9 - 6.0 per 100,000 person years, although this may be an underestimate. 1,3,4 Approximately 50-60% of these are uncomplicated. The average age in a recent analysis was approximately 57 years,

although ranges have been reported from 36 to 97 years. 5,6 The ratio of men to women is approximately 1.5 :1,6 while the mortality of ADs varies depending on its type, acuity, and method of repair (more below). The economic burden on healthcare systems and the psychological impact are considerable. It has been shown that the median and total yearly costs to treat ADs have increased beyond the rate of inflation, while rehabilitation constitutes a significant portion of these costs. 7 Meanwhile, individuals surviving an AD have reported poorer levels of mental health and sexual function. 8

Open aortic surgery has previously played a role in TBAD treatment, but its dismal outcomes, particularly when compared to medical treatment, were what led to a more conservative strategy of medical therapy and watching waiting, as mentioned above. 9-11 The use of medical therapy includes blood pressure lowering medicine, typically β -blockers, in order to mitigate the stress on the aorta and the potential pressure on the various false lumens, as well as pain relief and anti-anxiety medications. 1, 12

The introduction of TEVAR, a minimally invasive and catheter-based technique for placing a stent graft across the aortic tear, has radically changed the treatment of aortic disease, and is now the recommended therapy for many aortic pathologies.13, 14 Its use in the treatment of uTBADs, however, is uncertain. The dilemma centers around the balance of the relatively satisfactory short-term outcomes with medical therapy, against the subsequent relatively poorer long-term outcomes. That is, in-hospital survival for those treated with medical therapy is reported at 90%.15 In contrast, the survival at five years has been reported at 79.3%, and approximately 30% of the surviving cohort ultimately require treatment at some point which, notably often becomes more technically challenging with increased risks.16, 17 Indeed, some experts have commented that the term *uncomplicated* is a blatant misnomer, and that the complication is really, in effect, just waiting to happen.16 The counterproposal is that early TEVAR treatment confers prompt aortic remodeling and avoids the inevitable progression to complex aortic disease, rupture, and death. The benefit of TEVAR, however, comes with associated up-front risks of an invasive procedure, which are not benign. The risks of TEVAR include inadvertent rupture, paraplegia, further operations, and death, among others.18,19

This clinical dilemma is perhaps well-reflected by a recent international survey of cardiovascular specialists regarding the preferred treatment of uTBADs. When asked regarding their preferred strategy, 54.8% of respondents answered that they do not routinely use TEVAR, while 37.4% were in favor of routine TEVAR treatment. Moreover, 88.6% of respondents agreed that equipoise, or perhaps an agreement to disagree, was present and that an RCT was warranted.20

Thus, it would appear logical that a(n) RCT would resolve this issue. There are, in fact, two industry-affiliated studies assessing early TEVAR in uTBAD.

The statistically underpowered Acute Dissection: Stent graft OR Best medical therapy (ADSORB) trial randomized a total of 61 individuals from 17 European centres. As noted, it was underpowered to discern differences in survival, but they found that TEVAR was associated with improved remodeling of the aorta, which many believe is reason enough to offer this treatment.21 The Investigation of Stent Grafts in Aortic Dissection (INSTEAD) trial included 140 uTBAD participants and was primarily powered for analysis of two-year outcomes,22 later extended to a five-year analysis. The overall survival at two years was statistically equivalent, while the five-year analysis showed a non-significant absolute reduction in all-cause mortality of 8.2% for those who underwent TEVAR. Interestingly, they also showed that 26.5% of the cohort randomized to medical therapy ultimately crossed-over to the intervention of TEVAR.

There are several TEVAR stents on the market, while only three are used in Scandinavia. Despite minor design and structural differences, the underlying principle of construction is the same, as are the associated risks.
Importantly, all devices used in Scandinavia and in this trial are currently CE-marked for the pathology indicated and treated in this project. According to the EU regulation, Article 103 (2017/745), endorsed by the Medical Device Coordination Group (MDCG), all of the stent grafts used in this trial are categorized as Class III.

The TEVAR stent grafts used in this trial are designed for the endovascular repair of lesions in the descending thoracic aorta. When placed, the stent graft provides an alternative conduit for blood flow within the vasculature by excluding the lesion from blood flow and pressure. They may be used as a single device or in multiple device combinations to accommodate the intended treatment site. All of the devices used in this trial are composed of two components: an implantable stent graft and a disposable delivery system. The stent graft is preloaded into the delivery system, which is inserted endoluminally via the femoral or iliac artery and tracked through the vascular system to deliver the stent graft at the target site.

This project aims to answer whether or not standard medical therapy (SMT) and early TEVAR treatment for participants with an uncomplicated Type B aortic dissection (uTBAD) is superior to SMT alone. Survival at five years is the primary outcome for analysis. Secondary outcomes include aortic-related mortality, neurological events, hospital readmissions, reinterventions, and an economic analysis in conjunction with quality of life.
The impact of these findings, irrespective of various benefits or not, will have a major impact on future care. Multiple scenarios are possible, each of which will better inform us as to the health of the participant and the economic resources req

Study objective

Primary Objective: The primary objective of the study is to determine the superiority of TEVAR versus SMT in reducing the incidence of all-cause mortality.

Secondary Objectives: The secondary objectives of the study are:
• To compare the risk of aortic-related mortality.
• To compare the risk of neurological injury, including stroke or paraplegia.
• To compare the proportion and indication of subjects who underwent an aortic intervention within 5 years due to development of an aortic complication.
• To compare the number of disease-related readmissions during follow-up. To compare, based on subgroup analyses, whether extent of TEVAR is associated with either improved survival or neurological injury.
• To compare the associated risk of reinterventions, including those subjects who were initially randomized to SMT and subsequently required an aortic intervention.
• To compare the associated changes in quality-of-life.
• To compare the 10-year overall survival and aortic-related mortality.
• To compare the costs.

Study design

The trial is a randomized, open label, clinical trial with parallel assignment of participants in multiple clinical centres in Denmark, Sweden, Norway, Iceland, Finland and the Netherlands. Recruited participants will be randomized to either SMT exclusively or TEVAR + SMT.

Intervention

Contemporary standard medical therapy for TBAD consists of antihypertensive agents and pain relief. The choice of the specific agents will be left to the discretion of the individual treatment sites/surgical team, based on the individual subject*s prior and current therapy and tolerance to various medical regimens. While the goal is to reduce the systolic blood pressure to between 100 - 120 mm Hg and the pulse rate below 60 beats/minute in the acute phase, the advocated first-line therapy consists of intravenous β-blockade, with calcium channel antagonists and/or renin-angiotensin inhibitors as alternatives. Pain relief is furthermore critical in order to mitigate activation of the sympathetic nervous system and resultant tachycardia and blood pressure elevation. Anxiolytic medication may also be used in this role.

Long-term SMT is essential and, although not evaluated in any clinical trials, the target blood pressure is 120/80 mmHg.15 All subjects will be equipped with a home blood pressure apparatus in order to measure and record their values. As detailed below, these measurements will be recorded in the electronic database for all subjects at follow-up consultations.

Clearly, medical therapy for aortic dissection is a complex and unresolved research topic in and of itself, and individual-specific therapy can only be supported by guidelines from the European Society of Vascular Surgery and the European Society of Cardiology. Consideration in the trial was given to the connotations of *best* or *optimal* medical therapy, as well as kindred RCT protocols, e.g. Asymptomatic Carotid Surgery Trial-1 (ACST-1), 24 and the ramifications of these definitions vis-à-vis endpoint determination. Because of the recognized local differences in medical therapy and the interest in maintaining the pragmatic nature of this trial, it was determined that the terminology of *standard medical therapy* is most appropriate.

To that end, all sites, investigators, and subjects will be informed of the blood pressure target-oriented nature of this treatment and the following recommendations from the European Society of Vascular Surgery: Initial therapy consists of β-blockers. In subjects who do not respond to β-blockers or who do not tolerate the drug, calcium channel antagonists and/or renin-angiotensin inhibitors can be used as alternatives.1 In addition to these recommendations for hypertension, efforts should be made to alter and improve lifestyle and cardiovascular risk profiles, including smoking cessation, weight control, and potential treatment of other comorbidities such as diabetes mellitus and ischemic heart disease.

Subjects randomized to TEVAR therapy will undergo placement of an endovascular stentgraft in the descending thoracic aorta. When placed, the stent graft provides an alternative conduit for blood flow within the vasculature by excluding the lesion from blood flow and pressure. They may be used as a single device or in multiple device combinations to accommodate the intended treatment site. All of the devices used in this trial are composed of two components: an implantable stent graft and a disposable delivery system. The stent graft is preloaded into the delivery system, which is inserted endoluminally via the femoral or iliac artery and tracked through the vascular system to deliver the stent graft at the target site.

Each device is supplied with an instructions-for-use (IFU), wherein specifications of device material, contraindications, warnings and precautions, and imaging safety information are provided.
Importantly, all devices used in this trial are currently CE-marked for the pathology indicated and treated in this project.

The selection of the stent graft is left to the discretion of the treating physicians. While the implicit goal of TEVAR in dissection treatment is to treat the primary tear, certain adjunct proximal and/or distal procedures are often required, e.g., coverage of the left subclavian artery with or without a supplementary left subclavian artery revascularization, e.g., left carotid artery-to-left subclavian artery bypass/transposition or fenestration to left subclavian artery. Any or all adjunct procedures deemed necessary or beneficial by the treating physicians and subjects are allowable under the allocation to

the TEVAR subject cohort, as this reflects real-world considerations and the question at hand based on analysis of an intention-to-treat. This includes distal or proximal aortic sealing, as well as Provisional Extension To Induce Complete Attachment (PETTICOAT) or Stent-Assisted Balloon-Induced Intimal Disruption and Relamination in Aortic Dissection Repair (STABILISE). 25, 26

Study burden and risks

The benefits of TEVAR treatment for a participant with an uTBAD are based on the previously discussed RCTs above, the ADSORB and INSTEAD-XL trials, in addition to several retrospective studies.21, 22 There are two main benefits: first, it is well-documented that TEVAR treatment improves aortic remodeling and delays the progression of disease. While SMT may be sufficient to maintain early overall survival, the transformation of an acute/sub-acute dissection to a chronic dissection entails a new pathological entity, i.e., a thoracoabdominal aorta aneurysm, which is technically more challenging to treat with increased associated risks. TEVAR intervention, on the other hand, delays this process, thus reducing the yearly risk of rupture, which increases to approximately 12.5-18.8% once the aortic diameter reaches a diameter of 6.0 cm.36

The second benefit is overall survival. The INSTEAD-XL trial demonstrated this, using their prespecified use of a Landmark analysis for mortality. Between two and five years, the survival for TEVAR participants was 100% versus 83.1% for the SMT cohort.16 Their test for interaction between treatment effect and time was moreover significant, suggesting a late survival benefit for TEVAR. The use of the Landmark statistical analysis has had limited impact in altering international guidelines regarding treatment of uTBADs, hence the need for the present proposed trial.

The risk of TEVAR intervention is implicit in the very analysis performed in the INSTEAD-XL trial, revealed when the Landmark analysis is replaced by the standard Kaplan-Meier analysis, i.e., the starting point is moved back to day zero. When this analysis is performed, the overall survival still appears to benefit TEVAR participants, but the statistical p-value was nonsignificant. In other words, there were *up-front* risks of death within the first year, although none of these events were documented as periprocedural. Within one year, there were five deaths (7.5%) in the TEVAR cohort and two deaths (3.0%) in the SMT cohort, p=0.44. In addition to the risk of death, there were three cases of neurological injury documented (1 paraplegia, 1 major stroke, and 1 transient paraparesis).

These risks must also be considered for those individuals initially treated with SMT who ultimately cross over to TEVAR (26.5% within five years). Indeed, the risk of rupture, or aorta-specific mortality, is significantly greater for those on SMT, and any potential indication for aortic intervention may be associated with increased risks, particularly in cases of acuity.

It is in this light that the benefit-risk rationale supports the potential benefit of preemptive TEVAR treatment. Based on prior clinical research, there appear to be both advantages and disadvantages for both treatment arms (the control and intervention groups). However, these advantages and disadvantages cannot be directly compared, leading to a potential bias towards one of the groups. In summary, the intervention group entails perioperative risks, which may be offset by better long-term survival and fewer subsequent aorta-related interventions. This tension provides a solid foundation for conducting this randomized study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Patients aged 18 or greater at the time of informed consent signature

- Patients with an acute (< 14 days) or subacute (<90 days) uncomplicated type B dissection.

Exclusion criteria

·Patients with no signed informed consent.
·Patients presenting with a complicated type B aortic dissection according to the above definition.
·Patients previously treated in their descending aorta, either open surgery or TEVAR.
·Patients with pre-existing thoracoabdominal aortic aneurysm.
· Subjects with other aortic pathology with an indication for intervention that requires TEVAR.
· Patients with traumatic aortic dissections.
· Patients with an established connective tissue disease at the time of randomization, including but not limited to Marfans and Loeys-Dietz syndrome.
- Patients with a clinically estimated life expectancy < 2 years.
- Patients with dementia.
·Pregnant or nursing participants.
- Patients with current sepsis.
- Patients currently participating in other clinical interventional trials.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-06-2024
Enrollment:	255

Type:	Anticipated

Ethics review

Approved WMO Date:	08-07-2024
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	24-02-2025
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT05215587
CCMO	NL86347.058.24