Protocol

1. Introduction

The prevalence of Aortic Regurgitation (AR) is difficult to assess as it is well tolerated for a long period before symptoms emerge.[1] Results from the population based study in Framingham gave some insight: trace or mild AR was seen in 8.5% of women and in 13% of men.[2, 3] Within a hospital based cohort the Euro Heart Survey (EHS) program observed that 10.4% of the patients with valvular heart disease presented with moderate to severe AR (grade =2-4), of which 1.7% underwent aortic valve (AV) repair.[4] AV repair started three decades ago with valve sparing root replacement using either the reimplantation or remodeling technique.[5, 6] Both technique has evolved during the years.[7-11]
Recent analysis of the Society of Thoracic Surgeons (STS) database reported that 14% of patients with dystrophic bicuspid or tricuspid AR receive a valve-sparing procedure while 80% receive a composite graft-valve replacement (Bentall procedure). [12, 13] Some patients of the latter group could actually be candidates for repair.

In the current era, relative risk-adjusted mortality of valve sparing aortic root replacement appears comparable with composite graft-valve replacement in low- and high-risk subgroups.[14] A recent meta-analysis indicates that AV repair seems a safe and feasible alternative to AV replacement in selected patients with aortic root aneurysm with or without AR.[15, 16] However, generalization of published results is still hard due to the heterogeneity or inadequate description of the population studied. Furthermore, loss to follow-up and incomplete or inadequate reporting of valve-related events, makes interpretation of the results difficult. As a result, patients are treated according to guidelines based on 30 year old evidence.[17, 18]

To achieve a real breakthrough in treatment of AR, collaboration of cardiologists and surgeons is needed as they both treat the same patients at different time points during the course of the disease. Including the complete time span of AR from diagnosis through intervention till death within a longitudinal cohort is essential to investigate key epidemiological questions. Solid evidence based guidelines cannot do without complete and long-term follow- up. From here starts the international AVIATOR initiative.

2. Objectives

The main objectives are to enhance uniform scientific reporting, to optimize multidisciplinary patient care, to assess quality of care and to update and improve guidelines.

3. Study design

Longitudinal observational cohort study.

4. Study population

The AVIATOR initiative is enrolling patients with ascending aorta aneurysm and/or AR. Centers all over the world who are interested can participate. The registry contains two separate entities: 1). AVIATOR medical registry to evaluate the natural history of non-operated patients; 2). AVIATOR surgical registry to evaluate long term outcomes after surgical treatment. Both registries will have an adult and a pediatric counterpart (AVIATOR Kids). The adult surgical database is established and is enrolling patients. AVIATOR medical and AVIATOR kids are in progress and enrollment will follow in the near future.

Inclusion criteria

The AVIATOR registry includes all patients with AR and/or ascending aorta aneurysms (Figure 1). Patients with AR > grade 1 (mild AR) – inclusive congenital mixed aortic valve disease – and/or an aortic diameter = 40 mm are eligible for the medical registry. Patients who are operated on because of AR (including congenital mixed aortic valve disease) and/or aortic aneurysm (root or tubular ascending aorta) are eligible for the surgical database. Patient characteristics are leading and the performed intervention is secondary. This means that both patients who undergo AV repair including valve sparing root replacement as well as AV replacement – including composite valve graft replacement – are eligible. Centers without an AV repair program are encouraged to join the AVIATOR initiative as well. It is important to enroll all consecutive patients within a center, and not only the successful repairs. Isolated AV stenosis is excluded. Operative correction of an aneurysm of the ascending aorta can be either root and/or supra coronary aorta replacement. Patients operated for aortic dissection (Type A) are eligible as well.

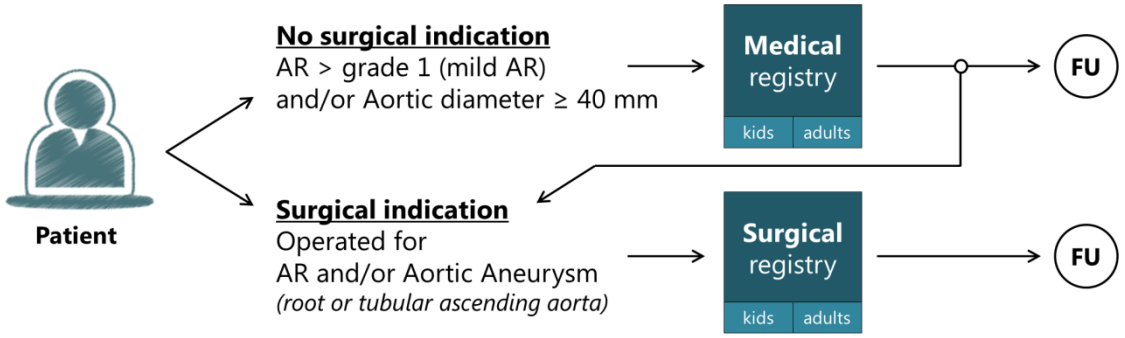

Figure 1. Inclusion flowchart

5. Methods

Study parameters/endpoints

The following information regards the adult surgical database, as this part is open for patient enrollment since January 2013. However, patients operated before can be uploaded retrospectively, and follow-up will be continued prospectively according to AVIATOR standards. Collected data includes: baseline patient characteristics, procedural information, in-hospital outcomes, longitudinal measurement of echo parameters and (valve related) events during at least yearly follow-up.

Baseline data

Baseline data are collected prospectively before surgery. Upon inclusion, the following patient characteristics are gathered: demographics, reason for referral, grade of AR, connective tissue disease, potential risk factors for operative mortality (EuroSCORE) and echocardiographic valve parameters.

Procedural information

Procedural variables include: date of surgery, AV anatomy, intra-operative cusp analysis, AV repair or replacement details, additional cardiac procedures. Each clamp session will be registered individually. In case of an additional clamp session, the reason plus procedural information of the additional session should be entered.

Outcomes

Surgical outcome data during hospitalization include: AV related reoperation, reoperation for another reason, stroke, pacemaker implantation, rhythm at discharge and all-cause mortality. Annual follow-up includes: grade of AR, AV or aorta related reoperation, AV endocarditis, thrombosis, stroke, major bleeding, pacemaker implantation and survival according to the guidelines of reporting mortality and morbidity after cardiac valve interventions.[19] In addition, echo parameters are registered yearly.

Echo parameters

During hospitalization for surgery the echo parameters are collected at four time points: preoperatively at time of diagnosis or referral to surgical center, intra-operative pre-repair/replacement, intra-operative post-repair/replacement and at discharge. The echo parameters include left ventricular ejection fraction, left ventricular end diastolic dimension (LVEDD), left ventricular end systolic dimension (LVESD), grade of AR, coaptation height/length, effective height, AV mean gradient and the dimensions of the annulus, sinus, sino-tubular-junction (STJ) and tubular aorta.

6. Statistical analysis

Data ownership and online analysis

The AVIATOR registry is the property of the Heart Valve Society (HVS) which therefore endorse the responsibility of the database, including any multi center publication originated from it (validated by the scientific committee). Each individual center is the owner of its own submitted data and is responsible

for their content. Online extractions can be performed whenever desired. Within the online application, reports and graphs will be developed. Individual center data are not visible for any other center. In a report with summary statistics single center data will be presented aside with aggregated results of the entire database. Data of centers other than your own are only visible for the central data management group for the purpose of data validation to enhance data quality.

Single center analysis

Each center can extract his own submitted data for local analysis. One is asked to mention the AVIATOR project when single center results based on this registry are presented or published. For analysis of multi center data a scientific research proposal is needed. Applications should be submitted to the Scientific Committee.

Multi center analysis

The Scientific Committee (SC) will facilitate initiatives for multi-center analysis. The objective of the SC is: 1). Transparency and 2). Facilitate high quality output from AVIATOR. To achieve these goals the following bylaw is formulated: Multi-center analysis is open for all active participants. Research proposal submission to the SC is possible twice a year (e.g. a month before the Annual Meeting of the HVS and the European Association for Cardio-Thoracic Surgery (EACTS). The SC will review the proposal to assess the validity of the research question and proper use of the data. Submitted proposals will be discussed in detail during the AVIATOR meeting at the Annual Meeting of HVS, EACTS and AATS (or aortic symposium). Proposals are validated when the majority of the participants during the meeting agree. Each center which can participate in the study will be notified about the accepted proposals and their data will be used automatically (Non-opposition Procedure). If a center does not agree, his opposition should be justified to the SC. The research team will receive an anonymous data set, without patient and center identifying variables. After data extraction, the team will be given a deadline of 6 months to perform the analysis and write a draft publication that should be presented at the next meeting. When the deadline is exceeded, the topic can be passed on to another group. First and second authorship is for the person who did the job (ideally young investigators). Last authorship is for the PI of the proposal. Authors in between are those who contributed to the data analysis and/or included data to the specific research question. Data selection from the entire database will take into account data completeness. It will be measured in sub modalities, like hospitalization data, clinical follow-up and echo follow-up. Follow-Up completeness will be represented with the C* ratio: the total observed follow-up years divided by the total potential follow-up years (taking the observed death rate into account).[20] Each selected center can propose at least one author for the studies using its data. Authors will be listed based on their ranking in data completeness divided by 100 and multiplied by volume (from high to low). The number of authors will depend on journal requirements. Ideally, all participating centers in the research dataset will be represented. In case there is limit, centers with the highest ‘data quality *volume factor’ will come first.

7. Data safety

Data are entered on a web-based Case Report Form (CRF) through a secure data-entry system. Telemedicine technologies hosts the database application (CleanWebTM) in Paris, France.[21] The data system is set up according to Good Clinical practice (GCP) guidelines, is United States Food and Drug Administration (FDA) compliant (21 CFR part 11) and meets the criteria of European legislation (EU Directive 2001/20/EC/Directive 2005/28/EC, Annex 11, cGMP).

Patient Identifiable Data

CleanWEB offers the availability to enter Patient Identifiable Data like the last and first name of a patient for practical use in clinic. Each center can decide if it wishes to use this feature or not, and should inform their Institutional Review Board before enrolling patients. The patient name is subject to special protection regulations. It is the responsibility of the owner of the collected data to justify why such identifying data are needed. The online database CleanWEB is compliant with the most demanding requirements. This includes the following: 1). The Patient Identifiable Data is stored encrypted 2). It is saved on a separate server than the medical parameters. 3). Differentiation of access rights enables to fully control the access to the Patient Identifiable Data and allow such access only to relevant personnel (within the own site only). 4). For other personnel (such as CRA, Data Manager, Project Manager, Principal Investigator) the corresponding data fields will be displayed in the user interface but their value will be set to *****. The term "User Interface" shall also include all dashboards and all printable material that may be generated using CleanWEB. 5). Patient Identifiable Data cannot be included in the extraction files.

8. Organizational structure

The AVIATOR project is officially declared as a Valve Research Network of the HVS. AVIATOR organization consists of a technical support group of the database, functional support group of the project, a SC and the Network members. The latter includes all participants of the registry, who are welcome to join the Network meetings. The AVIATOR group follows the HVS policies and regulations. This allows any HVS member to join the AVIATOR freely. At least one member of each center should be member of the HVS.

HVS Aortic Valve Repair Research Network

The members form the heart of the Aortic Valve Repair Research Network which aim to gather cardiologist, surgeon and scientist interested in the field of dystrophic AR and AV repair. There is a tri-annual meeting of the project during the annual meeting of the HVS and EACTS and AATS (including aortic symposium) to which all participants are invited. A project update is given at this meetings as well as the outcome of research and/or audit originating from the Registry.

Scientific committee

The SC consists of 7 members, including at least 2 cardiologists, 2 surgeons and 2 scientists. Members of the committee will serve for 3 years. After their term they have to wait 3 years before they can apply again. The SC reviews research proposals and scientific papers originating from the registry, it deals with financial issues, interacts with other HVS working groups and advises the HVS board.

9. Ethical considerations

Regulation statement

The study will be conducted according to the principles of the World Medical Association (WMA) Declaration of Helsinki on *Ethical Principles for Medical Research Involving Human Subjects* (19 October 2013) and the WMA Declaration of Taipei on *Ethical Considerations regarding Health Databases and Biobanks* (October 2016). See for more details the WMA website: www.wma.net.

10. References

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